nanoDDS

13th INTERNATIONAL NANOMEDICINE & DRUG DELIVERY SYMPOSIUM

Program & Abstract Book

September 16 - 18, 2015

University of Washington, Seattle, USA

nanoDDS 2015 Chairs:	Patrick Stayton and Suzie Pun, University of Washington
Symposium Location:	Kane Hall Auditorium 210
Lunch Location:	By George Café, Odegaard Undergraduate Library Ground Floor on Red Square
Poster Session Location:	Kane Hall Walker-Ames Room
Dinner Pickup Location:	George Washington Statue on Red Square (in front of By George Café)

All destinations are within walking distance (see campus map at end of program). Shuttles to and from Watertown Hotel and Silver Cloud Inn may be available. Check with nanoDDS or hotel front desk staff for details.

Wireless Network: University of Washington
UW NetID: event0583 password: 5S4e/6K3u/4M2j

www.nanodds15.org

Symposium Agenda

Welcome to the 13th International Nanomedicine and Drug Delivery Symposium at the University of Washington! All events take place in Kane Hall Auditorium 210 unless otherwise indicated.

Wednesday, September 16

8:00 – 9:00	Registration and Continental Breakfast (Second Floor Lobby)

Session I: Biological-Based Targeting and DDS

Allan Hoffman, Chair

9:00 – 9:15	Welcome and Opening Remarks Suzie Pun and Patrick Stayton, University of Washington
9:15 – 10:00	Keynote Talk: *Engineering Protein Nanocarriers: Design of Protein Interaction Inhibitors and Self Assembling Nanocages* David Baker, University of Washington, USA
10:00 – 10:30	*Potent Antibody-Based Conjugates for Cancer Therapy: From Early Stage Research to a Clinically Approved Drug* Peter Senter, Seattle Genetics, USA
10:30 – 10:50	Break (Second Floor Lobby)
10:50 – 11:20	*Tumor Targeting: Wishful Thinking v. Reality* K. Dane Wittrup, MIT, USA
11:20 – 11:50	*Shaping Plant Virus-Based Nanomaterials for Applications in Medicine* Nicole Steinmetz, Case Western Reserve University, USA
11:50 – 12:00	*Demonstrating the Uptake Mechanism of Cisplatin in Cells by Single Cell ICP-MS* Stan Smith, PerkinElmer, USA
12:00 – 1:00	Lunch (By George Café)

Session II: Nucleic Acid Delivery DDS

Tatiana Bronich and David Oupicky, Chairs

1:00 – 1:30 *Drug Delivery with Nanoparticles for Cancer Stem Cell Therapy*

Jun Wang, University of Science and Technology, China

1:30 – 2:00 *Polymeric Nanomaterials for Gene and Vaccine Delivery*

Chun Wang, University of Minnesota, USA

2:00 – 2:30 *Challenges and Opportunities in the Clinical Translation of Nucleic Acid Nanomedicines*

Paul Burke, Burke Bioventures, USA

2:30 – 3:00 Break (Second Floor Lobby)

3:00 – 3:30 *Drug Delivery through the Ultrasound-Induced Opening of the Blood-Brain Barrier*

Elisa Konofagou, Columbia University, USA

3:30 – 4:20 Rapid Fire Poster Presentations

Intracellular Trafficking and Endosomal Escape of Nanoparticles for mRNA Delivery (Poster Session 1, # 49)

Gaurav Sahay, Oregon State University, USA

Syndecan-1 Conjugated Mesoporous Silica-Coated Gold Nanorods Act as Optoacoustic Signal Amplifiers for Detection of Orthotopic Pancreatic Tumors in Vivo Via Multispectral Optoacoustic Tomography (Poster Session 2, # 22)

Lacey McNally, University of Louisville, USA

Chemotherapeutic Caterpillar Conjugates (Poster Session 2, #36)

Anthony Convertine, University of Washington, USA

Neutrophil-mediated Drug Delivery (Poster Session 2, #15)

Zhenjia Wang, Washington State University, USA

Self-Assembled Cholesteryl Albumin Nanoparticles Enhance Tumor Accumulation of Paclitaxel (Poster Session 1, #13)

Gantumur Battogtokh, Gachon University, Korea

4:20 – 4:30	*Quidel Specialty Products Group* Julie Garrels, Quidel, USA
4:30 – 5:00	*Stimuli-Responsive Nanoparticles for Smart Drug and Gene Delivery* Won Jong Kim, POSTECH, Korea
5:00 – 6:30	Poster Session 1 (Walker-Ames Room)

Thursday, September 17

8:00 – 9:00	Continental Breakfast (Walker Ames Room)

Session III: Polymer DDS

Sonke Svenson and Wim Hennik, Chairs

9:00 – 9:45	Keynote Talk: *Self-Assembled Supramolecular Smart Nanosystems for Targeted Drug Delivery* Kazunori Kataoka, University of Tokyo, Japan
9:45 – 10:15	*Exploring the Use of Light in Drug Delivery Science* Stefaan De Smedt, University of Ghent, Belgium
10:15 – 10:45	Break (Walker-Ames Room)
10:45 – 11:15	*Nanogel-Incorporated Physical and Chemical Gels for Highly Effective Chemo-Protein Combination Therapy* Xuesi Chen, Changchun Institute of Applied Chemistry, China
11:15 – 11:45	*Self-Assembled Glycopolymers for the Delivery of Drugs* Martina Stenzel, University of New South Wales, Australia
11:45 –11:55	*Well-defined Polymers for Biomedical Applications and Their Confirmation by MALDI-TOF* Nicolynn E. Davis, Sigma Aldrich, USA
12:00 – 1:00	Lunch (By George Café)

Session IV: Imaging and Image-Guided Therapy

Sasha Kabanov and Rachel Johns, Chairs

1:00 – 1:30	*Determinants of Efficacy of a Heat-activated Thermosensitive Liposome Formulation of Cisplatin in Models of Cervical, Breast and Lung Cancer* Christine Allen, University of Toronto, Canada
1:30 – 2:00	*Nanomedicine and Theranostics* Twan Lammers, University Hospital Aachen, Germany
2:00 – 2:30	*Ultrasound-Assisted Drug Delivery Systems* Tyrone Porter, Boston University, USA
2:30 – 3:00	*Imaging with Multi-Functional Nanoparticles* Xiaohu Gao, University of Washington, USA
3:00 – 3:10	*Medical Grade Carbon Nanotubes* Herschel Watkins, Bio-Pact, USA
3:10 – 3:20	*Advancing Nanomedicine Development through Precise and Accurate Characterization of Drug Delivery Nanoparticles Using TRPS* Subhash Kalluri, Izon Inc., USA
3:20 – 3:30	Announcement of Poster Competition Winners
3:30 – 5:00	Poster Session 2 (Walker-Ames Room)
5:30	Shuttle to UW Waterfront Activities Center (Meet at the George Washington Statue)
6:00	Conference Dinner Banquet and Cruise for Registered Participants (UW Waterfront Activities Center Dock)
9:30	Shuttle Back to Conference Hotels from UW Waterfront Activities Center

Friday, September 18

8:00 – 9:00 Continental Breakfast (Walker-Ames Room)

Session V: Immunotherapy DDS

Honggang Cui and Lacey McNally, Chairs

9:00 – 9:30 *Structured Polymers for Vaccine Delivery*

Almar Postma, CSIRO Melbourne, Australia

9:30 – 10:00 *Engineering Immunity with Hitchhiking Therapeutics*

Darrell Irvine, MIT, USA

10:00 – 10:30 *Orchestrating the Immune Response Using Modular Nanomaterials for Autoimmunity and cancer immunotherapy*

Tarek Fahmy, Yale University, USA

10:30 – 10:45 Break (Walker-Ames Room)

10:45 – 11:15 *High-throughput Polymer Screening for Biological Delivery: From Discovery to Design*

Theresa Reineke, University of Minnesota, USA

11:15 – 11:45 *Intelligent Tailor-Made Adenovirus Using Nanocarriers for Cancer Gene Therapy*

Chae-Ok Yun, Hanyang University, Korea

11:45 – 11:55 *The NanoAssemblr™ Platform: Microfluidic Manufacture of Liposomes and Nanoparticles*

Gesine Heuck, Precision NanoSystems

11:55 – 12:00 Closing Remarks

Suzie Pun and Patrick Stayton, University of Washington

Poster Sesssion 1: Wednesday, September 16, 5:00 - 6:30 pm

Biological-Based Targeting and DDS			
1	*Protein Polymer Architecture Modulates Drug Entrapment and Release*	*Jugal Dhandhukia*	*University of Southern California*
2	*Super-resolution imaging and quantitative analysis of membrane protein/lipid raft clustering mediated by cell surface self-assembly of hybrid nanoconjugates*	*Jonathan Hartley*	*University of Utah*
3	*Nano-formulation of BDNF: A Potential Therapy for Rett syndrome*	*Yuhang Jiang*	*University of North Carolina at Chapel Hill*
4	*Targeted delivery of antibody-conjugated ferritin nanocages directed to pulmonary endothelium*	*Makan Khoshnejad*	*University of Pennsylvania*
5	*Optimizing PolySTAT: Varying Peptide Content to Maximize Fibrin Crosslinking*	*Robert Lamm*	*University of Washington*
6	*Identifying peptide ligands by phage display and next-generation sequencing: a retrospective approach*	*Gary Liu*	*University of Washington*
7	*Development of a model system to gain insights into active nanoparticle targeting*	*Janni Mirosevich*	*Intezyne*
8	*Clustering of receptors enables lysosomal delivery of therapeutic proteins and degradation of oncogenic receptors*	*Paul Moody*	*Cardiff University*
9	*Targeted PEGylated Nanoparticles for Maternal Pulmonary Delivery during Pregnancy*	*Sanaalarab Al-Enazy*	*University of Texas Medical Branch*
10	*In vitro and in vivo characterization of Raw 264.7 macrophages-derived exosomes as brain delivery nanovectors*	*Dongfen Yuan*	*University of North Carolina at Chapel Hill*
Formulation and Characterization			
11	*Effect of Cryo-Protectants on Size Stability and Preservation of Coated and Uncoated Chitosan Nanoparticles after lyophilization.*	*Ibrahim Alradwan*	*King Abdulaziz City for Science and Technology (KACST)*
12	*Measuring The Unique Absorbance/Scattering Characteristics Of Metallic Nanoparticles*	*Toby Astill*	*PerkinElmer*
13	*Self-Assembled Cholesteryl Albumin Nanoparticles Enhance Tumor Accumulation of Paclitaxel*	*Gantumur Battogtokh*	*Gachon University*
14	*Lung Targeting of Angiotensin Receptor Blockers for COPD Lung Injury*	*Jane Chisholm*	*Johns Hopkins University*
15	*Wearable Microprojection Array Skin Patches for Improved Biomarker Sampling from Skin*	*Jacob Coffey*	*University of Queensland*
16	*Evaluating the Role of Particle Surface Properties on their Distribution and Cellular Association Following Pulmonary Delivery*	*Catherine Fromen*	*University of Michigan*
17	*Microdialysis method to determine delivery rates from programmable carbon nanotube membrane-based transdermal delivery device*	*Gaurav Gulati*	*University of Washington*
18	*Use of AF4-MALS to prove the mechanism of action of the silver-nanolipid complex*	*Wafa Hassouneh*	*Wyatt Technology Corp.*
19	*Radiosensitization effects of cisplatin-conjugated gold nanoparticles in triple negative breast cancer*	*Sohyoung Her*	*University of Toronto*
20	*Nanoparticle Formulation of Orlistat Improves Drug Stability and Cytotoxicity Against Human Cancer Cell Lines*	*Tanner Hill*	*University of Nebraska Medical Center*
21	*Physicochemical characterization, in vivo evaluation, and hepatoprotective activity of silymarin-loaded solid nanoparticle*	*Duhyeong Hwang*	*University of North Carolina at Chapel Hill*
22	*Synthesis of heterogeneous gold nanoparticle clusters in aqueous media using electrostatic attraction and controlled steric interactions.*	*Ryan Kastilani*	*University of Washington*

23	*PEGylation of BSA-drug nanoparticles and site elucidation of PEGylation on BSA-drug nanoparticle using LC-MS*	*Achyut Kathuria*	*Campbell University*
24	*Characterisation and potential applications of Chitosan–lignosulfonates sono-chemically prepared nanoparticles*	*Suyeon Kim*	*Pontificia Universidad Católica del Perú*
25	*Polymer functionalized and surface modified Quantum Dots as Hybrid Systems for Biomedical Studies*	*Redouane Krini*	*Johannes-Gutenberg-University Mainz*
26	*Preparation and characterisation of SmarCrystals of aprepitant and ibuprofen by combinative method*	*Gupta Koteshwara Kunnatur Balasundara*	*Manipal College of Pharmaceutical Sciences*
27	*Recanilization of blood clots using amphiphilic gold nanoparticle stabilized Pickering emulsions*	*Yi-Ting Lee*	*University of Washington*
28	*Coenzyme Q10 Adsorption on Carbon Aerogels*	*Sandeep Manandhar*	*University of Washington*
29	*Formation Of Phytosome Containing Silymarin Using Thin Layer-Hydration Technique Aimed For Oral Delivery*	*Wina Maryana*	*Institut Teknologi Bandung*
30	*Preparation, characterization, in vitro and in vivo evaluation of nanoparticles of erlotinib*	*Chander Parkash*	*NIPER, S.A.S. Nagar, India*
31	*Light responsive nanocarriers for light controlled gene therapy*	*Rishav Shrestha*	*National University of Singapore, Grad School for Integrative Sciences and Engineering*
Lipid DDS			
32	*Liposome Based Vectors for Cytosolic Delivery of Macromolecules*	*Anna Brown*	*Oregon State University*
33	*Transcription in nanoliposomes that can be endocytosed by human platelets*	*Vivienne Chan*	*University of British Columbia*
34	*Development and characterization of lipidic nanoparticles for an antiepileptic drug*	*Silki Kumar*	*University Institute of Pharmaceutical Sciences, Panjab University*
35	*Fusogenic targeted liposomes as next-generation nanomedicines for Prostate Cancer*	*Jihane Mriouah*	*University of Alberta*
36	*Development of lipid nanoparticles for treatment of osteoporosis*	*Mina Ordobadi*	*University of British Columbia*
37	*Development and characterization of liposomal drug delivery system for prodrugs of vinca alkaloids.*	*Vidhi Shah*	*Oregon State University*
38	*Mixed lipid/peptide vesicles bearing stealth and targeting motifs: a biomimetic delivery system tailored to cancer therapy*	*Giovanni Signore*	*CNI@NEST Istituto Italiano di Tecnologia*
Nucleic Acid Delivery			
39	*Fibrillar nanocarbon-mediated delivery of siRNA prevents acute kidney injury*	*Simone Alidori*	*Memorial Sloan Kettering Cancer Center*
40	*Sunflower pDMAEMA-based polycations as effective gene transfer vehicles*	*Yilong Cheng*	*University of Washington*
41	*Polypept(o)ides as novel non-viral Vectors for Gene Therapy*	*Philipp Heller*	*Institute of Organic Chemistry, Johannes Gutenberg University Mainz*
42	*Porous Silicon Nanoparticles for Targeted Delivery of siRNA*	*Jinmyoung Joo*	*University of California, San Diego*
43	*Development of Targeted "Smart" Particles for Silencing Breast Cancer Metastases*	*Neha Kausal*	*University of Michigan*
44	*Microfluidic synthesis of helper-lipid-enhanced lipid nanoparticles for intracellular delivery of plasmid-DNA*	*Jayesh Kulkarni*	*University of British Columbia*
45	*Nanocarriers for Gene Therapy: Recent approches*	*Tariq Mahmood*	*University of Central Punjab*
46	*Engineering platelets for the delivery of mRNA*	*Stefanie Novakowski*	*University of British Columbia*
47	*Enhanced Gene Delivery to a Kidney-derived Cell Line with Gentamicin-conjugated PEI-based Nanoparticles*	*Fatemeh Oroojalian*	*University of Minnesota*

48	*Lipid Nanoparticles Encapsulating siRNAs Against the Androgen Receptor to Treat Advanced Prostate Cancer*	*Joslyn Quick*	*University of British Columbia*
49	*Intracellular Trafficking and Endosomal Escape of Nanoparticles for mRNA Delivery*	*Gaurav Sahay and Anna Lorenz*	*Oregon State University*
50	*A Combinatorial Approach for the Treatment of Ovarian Cancer Using Gene and Chemotherapies*	*Canan Schumann*	*Oregon State University*
51	*Microbubbles and Ultrasound Improve Polymeric Gene Delivery to the Brain*	*James-Kevin Tan*	*University of Washington*
52	*Tracking the Transport of Intact DNA in Gene Delivery using FRET Labeled Beacons*	*Sriram Vaidyanathan*	*University of Michigan*
53	*Niemann-Pick C1 inhibitor enhances intracellular retention and gene silencing capability of lipid nanoparticle formulations of siRNA*	*Haitang Wang*	*University of British Columbia*
54	*Evaluation of Tween 85 Modified Polyethylenimines for Antisense oligomer Delivery*	*Mingxing Wang*	*Carolinas Medical Center*

Poster Sesssion 2: Thursday, September 17, 3:30 - 5:00 pm

Immunotherapy DDS			
1	*Nanostructured glycopolymer-functional liposomes to elucidate carbohydrate receptor mediated targeting*	*Jasmin Chen*	*University of Washington*
2	*Development of a drug delivery system based on surface modifications for efficient lymphatic uptake to treat metastatic melanoma*	*Bhuvana Doddapaneni*	*Oregon State University*
3	*Development of dual functional nanoparticles to orally deliver siRNA for treatment of Inflammatory Bowel Disease*	*Shrey Kanvinde*	*University of Nebraska Medical Center*
4	*Biodegradable PEG Nanocarriers Build from PEG-Acetal-Dimethacrylates for Specific Immunotherapy*	*Hannah Koehring*	*Institute of Organic Chemistry, University of Mainz*
5	*Multivalent M2pep for improving selective toxicity to M2-like tumor associated macrophages*	*Chayanon Ngambenjawong*	*University of Washington*
6	*Nanoparticle functionalized biodegradable polymer for immune-mediated enhancement of wound healing*	*Emeka Okeke*	*University of Manitoba*
7	*Development of Anti-Inflammatory Nanoparticles for Inflammatory Diseases*	*Hong Yang*	*Child & Family Research Institute, University of British Columbia*
8	*Improved local delivery of HIV nanotherapies to the colorectum*	*Taarika Babu*	*Johns Hopkins School of Medicine*
9	*Lipid-coated PLGA nanoparticles conjugated with a dual-function antibody for targeted delivery of ARVs to $\alpha 4\beta 7$ expressing T cells*	*Shijie Cao*	*University of Washington*
10	*Nanoparticles of immune-tolerant elastin-like polypeptide (iTEPs) for delivering CTL vaccine*	*Shuyun Dong*	*University of Utah*
11	*A Potent Anti-inflammatory Agent Targeting Toll-Like Receptor Signaling Identified from Marine Sponge Extracts*	*Shan-Yu Fung*	*University of British Columbia, Child & Family Research Institute*
12	*Dendritic cell presentation of class II antigen delivered by PLG nanoparticles favors immune tolerance*	*Robert Kuo*	*University of Michigan, Ann Arbor*
13	*Antibodies/Peg-Protein A Complex As A New Targeted Drug Delivery System*	*Gianfranco Pasut*	*University of Padova*
14	*Polymeric CXCR4 Antagonists for Inhibiting Breast Cancer Growth and Metastasis*	*Zheng-Hong Peng*	*University of Nebraska Medical Center*
15	*Neutrophil-mediated Drug Delivery*	*Zhenjia Wang*	*Department of Pharmaceutical Sciences, Washington State University*
Imaging and Image-Guided DDS			
16	*Magnet-Optical nanoparticles for Magnetomotive Photoacoustic Imaging*	*Junwei Li*	*University of Washington*
17	*Development of Next Generation Magnetic Nanohybrids for Theranostics*	*Souvik Biswas*	*Life Sciences Institute, University of British Columbia*
18	*Indocyanine Green-Loaded Nanoparticles Improve Tumor Contrast for Image-Guided Surgery*	*Tanner Hill*	*University of Nebraska Medical Center*
19	*Radiation-Sensitized Nanocarriers for Triggered Drug Delivery and Radiation Dose Monitoring*	*Marc Kai*	*Oregon State University*
20	*A Nanotheranostic System for delivery of Tumor Site "Turn-on" Imaging Agent*	*Xiaoning Li*	*Oregon State University*
21	*Targeted polymeric micelles facilitate detection of ovarian cancer using multispectral optoacoustic tomography*	*Lacey McNally*	*University of Louisville*
22	*Syndecan-1 conjugated mesoporous silica-coated gold nanorods act as optoacoustic signal amplifiers for detection of orthotopic pancreatic tumors in vivo via multispectral optoacoustic tomography*	*Lacey McNally*	*University of Louisville*

23	*Poly(2-oxazoline) based magnetic fields-responsive hybrid nanoclusters for taxane delivery*	*Youngee Seo*	*Eshelman School of Pharmacy, University of North Carolina*
24	*A Multifunctional Theranostic Nanoplatform for Cancer Treatment*	*Oleh Taratula*	*Oregon State*
25	*Development of Antibody-Conjugated Iron Oxide Nanoworms for Targeting HER2 Positive Breast Cancer Cells and Endothelial Cells*	*Guankui Wang*	*University of Colorado Denver | Anschutz Medical Campus*
26	*Single-cell mRNA and protein profiling with quantum dots*	*Pavel Zrazhevskiy*	*University of Washington*
27	*Nanodroplet Mediated Histotripsy (NMH) Cell Ablation on 3D Prostate Cancer Models*	*Omer Aydin*	*University of Michigan*
Polymer DDS			
28	*Development of "Smart" Targeted Micelles for Triggered Release of Chemotherapeutic Cargo in Metastatic Prostate Cancer Lesion in Bone*	*Omer Aydin*	*University of Michigan*
29	*Raltegravir Prodrugs for Improved Nanoparticle Delivery*	*Wilma E. Afunugo*	*Seattle University*
30	*pH-sensitive stealth coating of polymeric nanoparticles by polydopamine polymerization*	*Sara Ahmed*	*Industrial and Physical Pharmacy Department- College of Pharmacy- Purdue University*
31	*Folate receptor-targeted transplacental delivery of digoxin for the treatment of fetal arrhythmia*	*Norah Albekairi*	*University of Texas Medical Branch*
32	*Transplacental transfer of paclitaxel-loaded nanoparticles in the dually perfused human placental cotyledon*	*Shariq Ali*	*University of Texas Medical Branch*
33	*Nanocarrier based Amphotericin B delivery system for treatment of Visceral Leishmaniasis: an in-vivo assessment*	*Madhusudan Bhat*	*All India Institute of Medical Sciences*
34	*Polymeric Nanocarriers for Drug Delivery: Improving physicochemical parameters by a nanoprecipitation approach*	*Johanna Catalan-Figueroa*	*University of Chile*
35	*iTEP Nanoparticle-Delivered Salinomycin Displays an Enhanced Antitumor and Anti-Metastasis Efficiency in Orthotopic Breast Tumors*	*Mingnan Chen*	*University of Utah*
36	*Chemotherapeutic Caterpillar Conjugates*	*Anthony Convertine*	*University of Washington*
37	*Oxidation-Responsive Polymers: Tailored Sensitivity to Reactive Oxygen Species for Drug Delivery Purposes*	*Richard d'Arcy*	*University of Manchester*
38	*Polymeric Prodrug Therapy for Respiratory Infections Involving Burkholderia Pseudomallei*	*Debobrato Das*	*University of Washington*
39	*Performance-programmable clustered nanoassembly for biological stimuli-responsive multistage cancer chemotherapy*	*Jinzhi Du*	*Emory Univeristy*
40	*Design of Polymer Nanoreactors with Triggered Activity for Medicine and Biosensing Applications*	*Tomaz Einfalt*	*University of Basel*
41	*Hemocompatible Biohybrid Structures Made by Non-Covalent Conjugation of Glycopolymers and Proteins. Synthesis, Characterization and Purification Strategies.*	*Johannes Fingernagel*	*Leibniz Institute of Polymer Research Dresden*
42	*Cathepsin B-cleavable polymer-peptide conjugates for the intracellular delivery of a proapoptotic peptide in cancer*	*Hanna Kern*	*University of Washington*
43	*PeptoMicelles: A Novel Platform For Drug Delivery*	*Kristina Klinker*	*Johannes Gutenberg University, Mainz*
44	*Development of Targeted, Enzyme-Activated Nano-conjugates for Hepatic Cancer Therapy*	*Sibu Kuruvilla*	*University of Michigan*
45	*RAFT micelles for selective drug delivery to macrophages*	*Kate Montgomery*	*Imperial College London*
46	*Cheminformatics-driven selection of drugs for solubilization by poly(2-oxazoline) polymeric micelles to improve their delivery*	*Eugene Muratov*	*University of North Carolina at Chapel Hill, Chapel Hill, NC*
47	*Host cell surface-mimicking polymersomes (nanomimics) to trap and expose malaria parasites*	*Adrian Najer*	*University of Basel and Swiss Tropical and Public Health Institute*

48	*Polyvalerolactone Hydrogel for Sustained Delivery of Tacrolimus*	*Duc Nguyen*	*Oregon State University College of Pharmacy*
49	*Functional Polymers using RAFT for Drug Delivery Applications*	*Gangadhar Panambur*	*Sigma Aldrich Incorporated*
50	*Acid-sensitive oxidative stress generating polymeric micelles as anticancer therapeutic agents*	*Hoyeon Park*	*Chonbuk National University, Korea*
51	*Passive Tumor Targeting of PRINT Nanoparticles: A Function of Particle Size, Shape, and Tumor Model*	*Jillian Perry*	*University of North Carolina at Chapel Hill*
52	*Carbamazepine stimulates mTOR-independent autophagic killing of drug-resistant Mycobacterium tuberculosis*	*Mark Schiebler*	*Cambridge Nanoscience Centre*
53	*Primaquine-polymer prodrug model as potential antimalarial for liver targeting*	*Selvi Srinivasan*	*University of Washington*
54	*Bioactive polymeric nanocarriers for intracellular antibiotic delivery for the treatment and prevention of pulmonary infection*	*Fang-Yi Su*	*University of Washington*
55	*Poly(2-oxazoline) Micellar Formulation of Single Drug and Combinatin for Cancer Therapy*	*Xiaomeng Wan*	*University of North Carolina at Chapel Hill*
56	*Development of Sunflower Polymers for Tumor-Targeted Drug Delivery*	*Christine Wang*	*University of Washington*
57	*Nanomedicine for the prevention of corneal neovascularization*	*Qingguo Xu*	*Johns Hopkins School of Medicine*
58	*Dequalinium-coated Poly(lactide-co-glycolide) Nanoparticles to Overcome Paclitaxel Resistance in Ovarian Cancer cells*	*Venkata Yellepeddi*	*Roseman University of Health Sciences*
59	*Inflammation-responsive polymeric prodrug nanoparticles for the treatment of inflammatory liver diseases*	*Donghyuck Yoo*	*Chonbuk National University, Korea*
60	*Dendrimer Based Systemic Therapies for the Treatment of Glioblastoma*	*Fan Zhang*	*Johns Hopkins University*
61	*Defining Essential Considerations to Achieve Optimal, Local Nanocarrier Delivery to the Brain*	*Clark Zhang*	*Johns Hopkins University School of Medicine*

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Session 1: Biological-Based Targeting and DDS
Session II: Nucleic Acid Drug Delivery DDS
Session III: Polymer DDS Session
Session IV: Imaging and Image-Guided Therapy
Session V: Immunotherapy DDS

Speakers

Name	Institution	Email
Christine Allen	University of Toronto	cj.allen@utoronto.ca
David Baker	University of Washington	dabaker@uw.edu
Paul Burke	Burke Bioventures	paul@burkebio.com
Xuesi Chen	Changchun Institute of Applied Chemistry	xschen@ciac.ac.cn
Nicolynn Davis	Sigma-Aldrich	nicolynn.davis@sial.com
Stefaan De Smedt	University of Ghent	Stefaan.Desmedt@Ugent.be
Tarek Fahmy	Yale University	tarek.fahmy@yale.edu
Xiaohu Gao	University of Washington	xgao@uw.edu
Julie Garrels	Quidel	jgarrels@quidel.com
Gesine Heuck	Precision Nanosystems	gheuck@precision-nano.com
Darrell Irvine	MIT	djirvine@mit.edu
Subhash Kalluri	Izon Inc.	bhargava.kalluri@izon.com
Kazunori Kataoka	The University of Tokyo	kataoka@bmw.t.u-tokyo.ac.jp
Won Jong Kim	Pohang University of Science and Technology	wjkim@postech.ac.kr
Elisa Konofagou	Columbia University	ek2191@columbia.edu
Twan Lammers	University Hospital Aachen	tlammers@ukaachen.de
Tyrone Porter	Boston University	tmp@bu.edu
Almar Postma	CSIRO Melbourne	almar.postma@csiro.au
Theresa M. Reineke	University of Minnesota	treineke@umn.edu
Peter Senter	Seattle Genetics	psenter@seagen.com
Stan Smith	PerkinElmer	stan.smith@perkinelmer.com
Nicole Steinmetz	Case Western Reserve University	nicole.steinmetz@case.edu
Martina Stenzel	University of New South Wales	m.stenzel@unsw.edu.au
Chun Wang	University of Minnesota	wangx504@umn.edu
Jun Wang	University of Science and Technology	jwang699@ustc.edu.cn
Herschel Watkins	Lead Scientist, Bio-Pact	inquiries@bio-pact.com
K. Dane Wittrup	MIT & Koch Institute	wittrup@mit.edu
Chae-Ok Yun	Hanyang University	chaeok@hanyang.ac.kr

Rapid Fire Poster Presenters

Jump to: Rapid Fire Presentations

Name	Institution	Email	Session	Poster
Gantumur Battogtokh	Gachon University	gantumur.b24@gmail.com	1	13
Anthony Convertine	University of Washington	aconv@uw.edu	2	36
Lacey McNally	University of Louisville	lacey_mcnally@hotmail.com	2	22
Gaurav Sahay	Oregon State University	sahay@OHSU.edu	1	49
Zhenjia Wang	Washington State University	zhenjia.wang@wsu.edu	2	15

Poster Presenters

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Name	Institution	Email	Session	Poster
Wilma E. Afunugo	Seattle University	afunugow@seattleu.edu	2	29
Sara Ahmed	Purdue University	sabouelm@purdue.edu	2	30
Sanaalarab Al-Enazy	University of Texas Medical Branch	saalenaz@utmb.edu	1	9
Norah Albekairi	University of Texas Medical Branch	naalbeka@utmb.edu	2	31
Shariq Ali	University of Texas Medical Branch	sh2ali@utmb.edu	2	32
Simone Alidori	Memorial Sloan Kettering Cancer Center	alidoris@mskcc.org	1	39
Ibrahim Alradwan	King Abdulaziz City for Science and Technology	ialradwan@kacst.edu.sa	1	11
Toby Astill	PerkinElmer	Toby.Astill@perkinelmer.com	1	12
Omer Aydin	University of Michigan	biomer@umich.edu	2	27-28
Taarika Babu	Johns Hopkins School of Medicine	tbabu1@jhmi.edu	2	8
Gantumur Battogtokh	Gachon University	gantumur.b24@gmail.com	1	13
Madhusudan Bhat	All India Institute of Medical Sciences	bhat.madhusudan86@gmail.com	2	33
Souvik Biswas	University of British Columbia	souvik87@mail.ubc.ca	2	17
Anna Brown	Oregon State University	broanna@ohsu.edu	1	32
Shijie Cao	University of Washington	sjcao@uw.edu	2	9
Johanna Catalan-Figueroa	University of Chile	joh.catalan@ug.uchile.cl	2	34
Vivienne Chan	University of British Columbia	vivienne.vc@gmail.com	1	33
Jasmin Chen	University of Washington	jbrchen@uw.edu	2	1
Mingnan Chen	University of Utah	mingnan.chen@utah.edu	2	35
Yilong Cheng	University of Washington	ylcheng@uw.edu	1	40
Jane Chisholm	Johns Hopkins University	jchisho3@jhu.edu	1	14
Jacob Coffey	University of Queensland	j.coffey@uq.edu.au	1	15

Anthony Convertine	University of Washington	aconv@uw.edu	2	36
Richard d'Arcy	University of Manchester	richard.darcy@manchester.ac.uk	2	37
Debobrato Das	University of Washington	debobrato.das08@gmail.com	2	38
Jugal Dhandhukia	University of Southern California	dhandhuk@usc.edu	1	1
Bhuvana Doddapaneni	Oregon State University	bhuvanshyam@gmail.com	2	2
Shuyun Dong	University of Utah	shuyun.dong@utah.edu	2	10
Jinzhi Du	Emory University	jdu24@emory.edu	2	39
Tomaz Einfalt	University of Basel	tomaz.einfalt@unibas.ch	2	40
Johannes Fingernagel	Leibniz Institute of Polymer Research Dresden	fingernagel@ipfdd.de	2	41
Catherine Fromen	University of Michigan	cfromen@umich.edu	1	16
Shan-Yu Fung	University of British Columbia	shanefung@gmail.com	2	11
Gaurav Gulati	University of Washington	ggulati@uw.edu	1	17
Jonathan Hartley	University of Utah	jonathanmhartley@gmail.com	1	2
Wafa Hassouneh	Wyatt Technology Corp.	whassouneh@wyatt.com	1	18
Philipp Heller	Johannes Gutenberg University Mainz	heller@uni-mainz.de	1	41
Sohyoung Her	University of Toronto	sohyoung.her@utoronto.ca	1	19
Tanner Hill	University of Nebraska Medical Center	tanner.hill@unmc.edu	1	20
			2	18
Duhyeong Hwang	University of North Carolina at Chapel Hill	dhhwang@email.unc.edu	1	21
Yuhang Jiang	University of North Carolina at Chapel Hill	yuhang.jiang@unc.edu	1	3
Jinmyoung Joo	University of California, San Diego	jinmyoung@ucsd.edu	1	42
Marc Kai	Oregon State University	kaim@oregonstate.edu	2	19
Shrey Kanvinde	University of Nebraska Medical Center	shrey.kanvinde@unmc.edu	2	3
Ryan Kastilani	University of Washington	rkas@uw.edu	1	22
Achyut Kathuria	Campbell University	a_kathuria0804@email.campbell.edu	1	23
Neha Kausal	University of Michigan	nkaus@umich.edu	1	43
Hanna Kern	University of Washington	kernh@uw.edu	2	42
Makan Khoshnejad	University of Pennsylvania	makank@mail.med.upenn.edu	1	4
Suyeon Kim	Pontificia Universidad Católica del Perú	skim@pucp.pe	1	24
Kristina Klinker	Johannes Gutenberg University Mainz	kklinker@uni-mainz.de	2	43
Hannah Koehring	University of Mainz	h.koehring@uni-mainz.de	2	4
Redouane Krini	Johannes-Gutenberg-University Mainz	rkrini@students.uni-mainz.de	1	25
Jayesh Kulkarni	University of British Columbia	jaykul91@gmail.com	1	44
Silki Kumar	Panjab University	silky.walia7@gmail.com	1	34
Gupta Koteshwara Kunnatur Balasundara	Manipal College of Pharmaceutical Sciences	kb.koteshwara@manipal.edu	1	26
Robert Kuo	University of Michigan, Ann Arbor	robrtkuo@umich.edu	2	12
Sibu Kuruvilla	University of Michigan	skuruvi@umich.edu	2	44

Robert Lamm	University of Washington	rjlamm@uw.edu	1	5
Yi-Ting Lee	University of Washington	ytlee@uw.edu	1	27
Anna Lorenz	Oregon State University	lorenz@OHSU.edu	1	49
Hoyeon Park	Chonbuk National University, Korea	pphyy123@naver.com	2	50
Junwei Li	University of Washington	ljw1209@uw.edu	2	16
Xiaoning Li	Oregon State University	lixiaon@onid.oregonstate.edu	2	20
Gary Liu	University of Washington	garywliu@uw.edu	1	6
Tariq Mahmood	University of Central Punjab	tariqmahmood750@gmail.com	1	45
Sandeep Manandhar	University of Washington	xandeep@uw.edu	1	28
Wina Maryana	Institut Teknologi Bandung	winamaryana@hotmail.com	1	29
Lacey McNally	University of Louisville	lacey_mcnally@hotmail.com	2	21-22
Janni Mirosevich	Intezyne	Janni.Mirosevich@intezyne.com	1	7
Kate Montgomery	Imperial College London	km412@ic.ac.uk	2	45
Paul Moody	Cardiff University	moodyp2@cardiff.ac.uk	1	8
Jihane Mriouah	University of Alberta	mriouah@ualberta.ca	1	35
Eugene Muratov	University of North Carolina at Chapel Hill	murik@email.unc.edu	2	46
Adrian Najer	University of Basel and Swiss Tropical and Public Health Institute	adrian.najer@unibas.ch	2	47
Chayanon Ngambenjawong	University of Washington	ngamc@uw.edu	2	5
Duc Nguyen	Oregon State University College of Pharmacy	nguyend@onid.orst.edu	2	48
Stefanie Novakowski	University of British Columbia	s.novakowski@gmail.com	1	46
Emeka Okeke	University of Manitoba	umokeke@myumanitoba.ca	2	6
Mina Ordobadi	University of British Columbia	mina@alumni.ubc.ca	1	36
Fatemeh Oroojalian	University of Minnesota	orooj002@umn.edu	1	47
Gangadhar Panambur	Sigma Aldrich Incorporated	gangadhar.panambur@sial.com	2	49
Chander Parkash	NIPER, S.A.S. Nagar, India	chanddora@gmail.com	1	30
Gianfranco Pasut	University of Padova	gianfranco.pasut@unipd.it	2	13
Zheng-Hong Peng	University of Nebraska Medical Center	josephpenguu@gmail.com	2	14
Jillian Perry	University of North Carolina at Chapel Hill	perryjl@email.unc.edu	2	51
Joslyn Quick	University of British Columbia	joslynquick@alumni.ubc.ca	1	48
Gaurav Sahay	Oregon State University	sahay@OHSU.edu	1	49
Mark Schiebler	Cambridge Nanoscience Centre	mss58@cam.ac.uk	2	52
Canan Schumann	Oregon State University	schumanc@onid.orst.edu	1	50
Youngee Seo	University of North Carolina at Chapel Hill	seoy@email.unc.edu	2	23
Vidhi Shah	Oregon State University	shahv@onid.oregonstate.edu	1	37
Rishav Shrestha	National University of Singapore	rishav@u.nus.edu	1	31
Giovanni Signore	CNI@NEST Istituto Italiano di Tecnologia	giovanni.signore@iit.it	1	38

Selvi Srinivasan	University of Washington	selvis@uw.edu	2	53
Fang-Yi Su	University of Washington	fysutw@uw.edu	2	54
James-Kevin Tan	University of Washington	jkyt@uw.edu	1	51
Oleh Taratula	Oregon State University	Oleh.Taratula@oregonstate.edu	2	24
Sriram Vaidyanathan	University of Michigan	svaidy@umich.edu	1	52
Xiaomeng Wan	University of North Carolina at Chapel Hill	xiaomengwan@unc.edu	2	55
Haitang Wang	University of British Columbia	Haitangw@mail.ubc.ca	1	53
Mingxing Wang	Carolinas Medical Center	mingxing.wang@carolinashealthcare.org	1	54
Zhenjia Wang	Washington State University	zhenjia.wang@wsu.edu	2	15
Guankui Wang	University of Colorado Denver	Guankui.Wang@ucdenver.edu	2	25
Christine Wang	University of Washington	cewang@uw.edu	2	56
Qingguo Xu	Johns Hopkins School of Medicine	qxu15@jhmi.edu	2	57
Hong Yang	University of British Columbia	hongyang36@gmail.com	2	7
Venkata Yellepeddi	Roseman University of Health Sciences	vyellepeddi@roseman.edu	2	58
Donghyuck Yoo	Chonbuk National University, Korea	Hyuck@jbnu.ac.kr	2	59
Dongfen Yuan	University of North Carolina at Chapel Hill	dyuan@email.unc.edu	1	10
Fan Zhang	Johns Hopkins University	zfan.eng@gmail.com	2	60
Clark Zhang	Johns Hopkins University School of Medicine	czhang30@jhmi.edu	2	61
Pavel Zrazhevskiy	University of Washington	pavelz@uw.edu	2	26

Session 1: Biological-Based Targeting and DDS

David Baker
Professor, University of Washington

Keynote Talk
Design of protein interaction inhibitors and self assembling nanocages

I will describe recent progress in computational protein design that now allows the design of high affinity inhibitors of protein interactions and of customizable self assembling nanoparticles for targeted delivery.

Peter Senter
Vice President, Seattle Genetics

Potent Antibody-Based Conjugates for Cancer Therapy: From Early Stage Research to a Clinically Approved Drug

Monoclonal antibodies (mAbs) have played a major role in cancer medicine, with active drugs such as trastuzumab (Herceptin), cetuximab (Erbitux), bevacizumab (Avastin) and rituximab (Rituxan) in a wide range of therapeutic applications. The mechanisms of these agents involve such activities as direct signaling, interactions with Fcγ receptors on effector cells, and complement fixation. Several approaches have been explored to improve antibody-based therapies for cancer treatment by optimizing such activities and by conscripting their selectivity profiles for the delivery of high potency cytotoxic drugs. This latter area has advanced significantly in the past few years, with the approval of antibody drug conjugates such as Adcetris (brentuximab vedotin, SGN-35) for the treatment of relapsed Hodgkin lymphoma and anaplastic large cell lymphoma. This presentation will describe how Adcetris was discovered and developed, and will also overview how antibody drug conjugate technology for cancer therapy is being extended to include new antigen targets, new drugs, and new conditionally-labile linkers.

K. Dane Wittrup
Professor, MIT & Koch Institute

Tumor Targeting: Wishful Thinking v. Reality

Cytokine therapy can activate potent, sustained antitumor responses, but collateral toxicity often limits dosages. Although antibody-cytokine fusions (immunocytokines) have been designed with the intent to localize cytokine activity, systemic dose-limiting side effects are not fully ameliorated by attempted tumor targeting. Using the s.c. B16F10 melanoma model, we found that a nontoxic dose of IL-2 immunocytokine synergized with tumor-specific antibody to significantly enhance therapeutic outcomes compared with immunocytokine monotherapy, concomitant with increased tumor saturation and intratumoral cytokine responses. Examination of cell subset biodistribution showed that the immunocytokine associated mainly with IL-2R-expressing innate immune cells, with more bound immunocytokine present in systemic organs than the tumor microenvironment. More surprisingly, immunocytokine antigen specificity and Fcγ receptor interactions did not seem necessary for therapeutic efficacy or biodistribution patterns because immunocytokines with irrelevant specificity and/or inactive mutant Fc domains behaved similarly to tumor-specific immunocytokine. IL-2-IL-2R interactions, rather than antibody-antigen targeting, dictated immunocytokine localization; however, the lack of tumor targeting did not preclude successful antibody combination therapy. Mathematical modeling revealed immunocytokine size as another driver of antigen targeting efficiency. This work presents a safe, straightforward strategy for augmenting immunocytokine efficacy by supplementary antibody dosing and explores underappreciated factors that can subvert efforts to purposefully alter cytokine biodistribution.

Nicole Steinmetz
Assistant Professor, Case Western Reserve University

Shaping plant virus-based nanomaterials for applications in medicine

Sizing and shaping of nanostructured features with temporal and spatial control is a key opportunity to produce the next-generation biomaterials with diverse applications in medicine. Nanoscale self-assembly is a technique that Nature masters with atomic precision; genetic programming provides the highest achievable reproducibility. Therefore we turned toward the study and application of Nature's nanomaterials, specifically the structures formed by plant viruses. Plant viruses come in many shapes and sizes but most species form highly uniform structures. The nanomanufacturing and bioengineering design of plant virus-based materials is highly scalable and economic through molecular farming in plants. Viruses have naturally evolved to deliver cargos to specific cells and tissues; and the medical research thrust in my laboratory is aimed at understanding these natural properties for effectively tailoring tissue-specificity for applications in molecular imaging and therapeutic interventions. In this presentation, I will discuss our efforts focused on the shape-engineering of molecularly targeted plant virus-based carriers for applications in molecular magnetic resonance imaging and drug delivery, as well as highlight our recent developments in cancer vaccines and immunotherapeutic approaches targeting oncological and cardiovascular diseases.

Stan Smith
Senior Researcher, Perkin Elmer

Demonstrating the Uptake Mechanism of Cisplatin in Cells by Single Cell ICP-MS

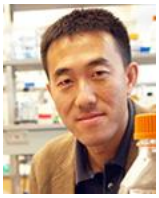
Cisplatin, carboplatin, and oxaliplatin are the most widely used class of anticancer agents used to treat many types of cancer. The mechanism of action for these platinum compounds is DNA damage resulting in cell death. Initially, patients respond well to this treatment but would later relapse and display resistance to the platinum compounds. Resistance to platinum compounds is mediated by the following mechanisms: decreased drug uptake, increase drug export, increased DNA repair, and cytosolic inactivation. This work focuses on the use of a Single Cell Inductively Coupled Plasma- Mass Spectrometry (SC-ICP-MS) technique which explores the uptake mechanism of cisplatin in cells based on individual cells. Experiments were performed using the A2780 cisplatin- sensitive ovarian carcinoma cell line and the corresponding cisplatin-resistant cell line, A2780-CP70. Cells were treated with 3 μM of cisplatin and uptake was analyzed by a time course experiment 1, 2, 4, and 8 hours post-cisplatin exposure. Prior to harvesting, drug-containing media was removed and cells were rinsed three times with PBS. Cells were counted on a hemocytometer and resuspended to a final concentration of 50,000 cells/ml in cell media. Whole cell cisplatin levels were measured using the PerkinElmer NexION 350 ICP-MS. Total cellular cisplatin was measured analyzing the platinum 195 isotope and calculated using the Syngistix Nano Application software. The Syngistix Nano software allows the determination of platinum within each cell and creates a histogram of cisplatin uptake. The uptake of cisplatin differed between the cisplatin-sensitive A2780 cell line in comparison to the A2780-CP70 cisplatin resistant cell line. Additionally, we observed a heterogeneous distribution of cisplatin uptake in both cell lines, reflecting that drug uptake within cancer cells differs from cell to cell. Traditionally, cisplatin uptake is measured by digesting an entire cell population with nitric acid and quantitating the total platinum content by ICP-MS or other analytical technique. The downfall of this approach is it does not reflect the distribution and individual cellular variation of cisplatin uptake. Single cell analysis allows the real time uptake of cells, reflecting in more detail what is observed within tumor. This may yield the possibility to determine resistance status for these cells. Additionally, SC-ICP-MS allows for the development of experimental models to determine drug delivery and efficacy translating to a better response in the clinic.

Session II: Nucleic Acid Delivery DDS

Jun Wang
Professor, University of Science and Technology of China

Drug Delivery with Nanoparticles for Cancer Stem Cell Therapy

Cancer stem cells (CSCs), also called tumor-initiating cells or cancer stem-like cells, are known to be resistant to chemotherapy and radiotherapy, associated with tumor metastasis and recurrence after treatments, which attracts increasing attentions by developing advanced therapeutic methods in recent years. The possible therapeutic strategies that can eliminate CSCs generally include inhibiting their self-renewal pathway, differentiating CSCs, or targeting the CSCs niche. Practically, delivery of drug into the rare population of CSCs in tumor tissue is challenging. Herein, we introduce nanoparticle delivery system-based therapy for eliminating both the bulk tumor cells and the rare CSCs.



Chun Wang
Associate Professor, University of Minnesota

Polymeric Nanomaterials for Gene and Vaccine Delivery

Since the last decade, much progress has been made toward designing cationic polymeric gene carriers with high transfection efficiency and low cytotoxicity and in elucidating the relationship between polymer structure and gene delivery performance. However, delivery of gene-based vaccine to improve antigen presentation and immune activation poses unique challenges that have yet been fully addressed. Using well-defined copolymers of 2-aminoethyl methacrylate (PAEM) as models, we have shown that a chemically simple cationic polymer can have surprisingly high efficiency in transfecting dendritic cells (DCs), leading to antigen-presentation and T cell activation, but the mechanism behind in vitro and in vivo delivery is rather complex. Further, cellular stress responses (including apoptosis and autophagy) provoked by polyplexes and the timing of phenotypic maturation of DCs may be manipulated to improve transgene expression and cross-presentation of antigen. In addition to serving as models, the PAEM polymers may have the potential to be practically useful carriers of DNA vaccine in preventing and treating diseases. To facilitate formulation and delivery of multi-component cancer vaccines, we have recently developed a new class of biodegradable semi-solid polymers (named Caproxamers®) that allows easy loading and controlled release of both hydrophobic and hydrophilic cargos. Subcutaneous injection of antigens and adjuvants formulated in an ortho-ester-containing Caproxamer induced antigen-specific antibody and T cell responses and showed therapeutic benefit in mice with orthotopic brain tumor. Combining simplicity in synthesis with versatility in properties, the potential use of the Caproxamers may go beyond vaccine delivery to include other drug delivery applications.

Paul Burke, PhD
Principal, Burke Bioventures

Challenges and opportunities in the clinical translation of nucleic acid nanomedicines

New biology—ranging from advances in the understanding of the role of RNA to new approaches to genome editing—presents an explosion of opportunity for therapeutic intervention. Realizing this potential involves traversing biological barriers at the cellular, tissue, and organismal levels. In addition, the commercial hurdles associated with the clinical translation of novel technologies must be overcome. Recent progress, particularly in RNAi and antisense, illustrates the sometimes arduous path from biological discovery to compelling pharmaceutical products. Increased safety margins and delivery approaches for a broader range of targets exemplify some of the remaining hurdles to nucleic acid therapies becoming competitive against established alternative therapeutic modalities. Interdisciplinary approaches to addressing these hurdles—based on the nexus of advanced biological tools and molecular engineering—comprise a new frontier of exploration, with unprecedented potential for positive impact to human health.

Elisa Konofagou
Professor, Columbia University

Drug delivery through the ultrasound-induced opening of the blood-brain barrier

Current treatments of neurological and neurodegenerative diseases are limited due to the lack of a truly non-invasive, transient, and regionally selective brain drug delivery method. The brain is particularly difficult to deliver drugs to because of the blood-brain barrier (BBB). The impermeability of the BBB is due to the tight junctions connecting adjacent endothelial cells and highly regulatory transport systems of the endothelial cell membranes. The main function of the BBB is ion and volume regulation to ensure conditions necessary for proper synaptic and axonal signaling. However, the same permeability properties that keep the brain healthy also constitute the cause of the tremendous obstacles posed in its pharmacological treatment. The BBB prevents most neurologically active drugs from entering the brain and, as a result, has been isolated as the rate-limiting factor in brain drug delivery. Until a solution to the trans-BBB delivery problem is found, treatments of neurological diseases will remain impeded. Over the past decade, methods that combine Focused Ultrasound (FUS) and microbubbles have been shown to offer the unique capability of noninvasively, locally and transiently open the BBB so as to treat central nervous system (CNS) diseases. Four of the main challenges that have been taken on by our group and discussed in this paper are: 1) assess its safety profile, 2) unveil the mechanism by which the BBB opens and closes, 3) control and predict the opened BBB properties and duration of the opening and 4) assess its potential in neurotherapeutics. All these challenges will be discussed, findings in both small (mice) and large (non-human primates) animals will be shown as well as its clinical potential.

Session II: Rapid Fire Poster Presentations

Gaurav Sahay
Assistant Professor, Oregon State University

Intracellular Trafficking and Endosomal Escape of Nanoparticles for mRNA Delivery (Poster Session 1, #49)

RNA therapeutics represents a new class of modern medicine for targets considered undruggable (1). Nanoparticle based platforms remain the most advanced in clinical trials for RNA based drugs (2). Yet, the lack of mechanistic insights into the cellular trafficking and endosomal escape of nanoparticles has become a major hurdle for efficient intracellular delivery (3). Nanoparticles enter cells through highly dynamic endocytic pathways that are routed towards lysosomes for degradation (4,5).

This study aims to 1) Dissect the gateways of cellular entry and subsequent itinerary of lipid nanoparticles that deliver messenger RNA (mRNA) inside cells through the use of state of the art microscopy techniques like super-resolution imaging, high content screening, spinning disk confocal microscopy in combination with different markers of endocytosis and/or inhibitors of select trafficking pathways 2) Identify small molecules that potentiate endosomal escape through disruption of key steps in endocytic trafficking. We have identified the key features that are involved in the entry and endosomal escape of mRNA to the cytosol. Unlocking the mechanisms of intracellular transport will guide in the development of novel nanoparticles that can efficiently delivery mRNA inside cells for therapeutic production of proteins for the treatment of wide variety of diseases.

Acknowledgements: We would like to thank Dr. Robbie Allen and Dylan Nelson for support within the high throughput facility at Oregon Translation Research and Development Institute (OTRADI). This work was supported by the College of Pharmacy OTRADI grant and start up funds of G.S.

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Lacey McNally
Assistant Professor, University of Louisville

Syndecan-1 conjugated mesoporous silica-coated gold nanorods act as optoacoustic signal amplifiers for detection of orthotopic pancreatic tumors in vivo via multispectral optoacoustic tomography (Poster Session 2, #22)

Early detection of pancreatic cancer cells is difficult due to poor spatial resolution and shallow depth penetration, low sensitivity, and specificity of traditional imaging modalities. Multispectral optoacoustic tomography (MSOT) overcomes these limitations due to its hybrid modality, but is hindered by lack of tumor-specific contrast agents. Therefore, we constructed highly stable nano-contrast agents by encapsulating gold nanorods (GNRs) having aspect ratio 3:1 in polyacrylic acid (PAA) with shell thickness (1.5 $\pm$ 0.5 nm), and amine-functionalized mesoporous silica (MS) with shell thickness (6.25 $\pm$ 0.25 nm), respectively. Syndecan-1 targeting ligand was conjugated on the surface of amine-functionalized mesoporous silica coated gold nanorods (MS-GNRs) or polyacrylic acid coated gold nanorods (PAA-GNRs) to examine optoacoustic (OA) signal enhancing effect in MSOT and tumor targeting using flow cytometry. The Syndecan-MS-GNRs gave 10X higher OA signal than Syndecan-PAA-GNRs in S2VP10L cell lines, positive for insulin like growth factor1 receptor (IGF1-R), and minimum binding in MiaPaca-2 cell lines, negative for IGF1-R. Thus, Syndecan-MS-GNRs were iv injected into orthotopic pancreatic cancer-bearing nude mice prior to MSOT imaging. In vivo, Syndecan-MS-GNRs significantly accumulated in tumors with peak accumulation occurring at slice 49.3 mm containing 175.4 MSOT a.u. at four hours post-injection with minimal accumulation in the liver. For the first time, we report the combination of MSOT with targeted nano-contrast agents (Syndecan-MS-GNRs) provide a high-resolution signal amplifier by minimizing off-target effect for successful detection of orthotopic pancreatic cancer cells in vivo.

Zhenjia Wang
Assistant Professor, Washington State University

Neutrophil-mediated Drug Delivery (Poster Session 2, #15)

Endothelial cells form a monolayer in lumen of blood vessels presenting a great barrier to delivery of therapeutic nanoparticles into extravascular sites where most diseases occur, such as inflammation disorders and infection. Here we report the development of a novel strategy to deliver therapeutic nanoparticles across this blood vessel barrier via the neutrophil transmigration pathway. Using intravital microscopy of TNF-α-induced inflammation of mouse cremaster venules and a mouse model of acute lung inflammation, we demonstrated that intravenously infused nanoparticles made from denatured albumin were specifically internalized by activated neutrophils, and subsequently the neutrophils migrated across blood vessels and deposited nanoparticles into inflammatory tissues. Furthermore, nanoparticle internalization did not affect neutrophil mobility and functions. Using albumin nanoparticles we were able to deliver anti-inflammatory drugs or antibiotics to inflammatory or infected lungs, dramatically mitigating the lung inflammation induced by LPS (lipopolysaccharide) or infection by P. aeruginosa bacteria. Our results illustrate that neutrophils can be exploited as novel vehicles to mediate the transport of therapeutic nanoparticles across blood vessel barrier, and using this approach we could significantly improve current treatments of acute inflammatory diseases and infection.

Anthony Convertine
Research Assistant Professor, University of Washington

Chemotherapeutic Caterpillar Conjugates (Poster Session 2, #36)

Reversible addition-fragmentation chain transfer (RAFT) polymerization was used to prepare dense polyethylene glycol methacrylate brushes containing the potent chemotherapeutic agents camptothecin and dasatinib. These caterpillar-like copolymer drug conjugates incorporated the therapeutic agent into the polymeric scaffold using either a conjugation strategy or by direct polymerization of the prodrug monomers. In the conjugation approach anhydride residues distributed throughout the polymer backbone were reacted with hydroxyl-functional drugs using DMAP catalyzed carbodiimide chemistry. The reactive anhydride residues were also employed to react near IR dyes for live animal imaging as well as antibody targeting groups. In the second approach polymerizable methacrylate-based prodrug monomers were synthesized and subsequently polymerized via RAFT to yield copolymers with controllable drug compositions. In both cases the ester-linked drugs were shown to release in human serum with rates dependent on both the nature of the ester linkage (i.e. aliphatic vs. benzoic) as well as the type of covalently linked drug. Polymer morphology was also shown to play a key role in drug release rates with copolymers distributed within a hydrophilic copolymer segment showing higher rates than materials where the hydrophobic drug molecules were localized in discreet hydrophobic blocks. The latter materials were shown to self assemble into nanoparticles where the drug block was separated from the aqueous phase. Cytotoxicity measurements conducted in a variety of cell lines (i.e. lymphoma, breast, ovarian, and leukemia) demonstrated ability of the caterpillar conjugates to release the covalently linked rugs in an active form.

Gantumur Battogtokh
Postdoctoral Fellow, Gachon University

Self-Assembled Cholesteryl Albumin Nanoparticles Enhance Tumor Accumulation of Paclitaxel (Poster Session 1, #13)

The objective of this study was to develop an albumin nanoparticle with improved stability and drug loading capacity. The cholesteryl bovine serum albumin conjugate (Chol-BSA) was synthesized with 16% degree of substitution. PTX-Chol-BSA nanoparticle was then prepared using Chol-BSA by self-assembly with the mean hydrodynamic diameter and zeta potential of 147.6 ± 1.6 nm and -20.47 ± 3.5 mV, respectively. The loading efficiency and loading capacity of PTX-Chol-BSA were 94.8 and 37.9%, respectively. PTX-Chol-BSA showed much higher colloidal stability than a simple complex of PTX and BSA (PTX-BSA). An in vitro release study indicated that around 30% PTX was released from PTX-Chol-BSA over an 8-h period, which was around 2-fold slower than PTX-BSA. PTX-Chol-BSA nanoparticles showed greater cellular uptake and higher cytotoxicity in B16F10 and MCF-7 cancer cell lines, as compared with PTX in Cremophor EL/ethanol (PTX-Cre/EtOH) and PTX-BSA formulations. A pharmacokinetic study in tumor-bearing mice showed that the area under the concentration-time curve (AUC0 8 h) following administration of PTX-Chol-BSA was 8177.03 ± 303.06 ng/mL•h, 2-fold higher than those following administration of PTX-BSA or PTX-Cre/EtOH. In addition, the tumor AUC0 8 h of PTX-Chol-BSA was 100.53 ± 9.88, compared with 57.03 ± 2.64 for PTX-BSA. Furthermore, in vivo antitumor efficacy was evaluated in tumor-bearing mice and the results revealed that PTX-Chol-BSA nanoparticles have greater antitumor efficacy. In conclusion, we demonstrated the potential of PTX-Chol-BSA nanoparticles for anti-tumor chemotherapy, with enhanced in vitro and in vivo behaviors, as compared to PTX-BSA and PTX-Cre/EtOH.

Julie Garrels
Sr. Account Manager, Quidel

Quidel Specialty Products Group

The complement system plays and increasingly important role in nanopharmaceutical development. Testing for complement activation can determine if a nanomaterial will cause an adverse patient reaction. Quidel's Specialty Products Group can help assess the safety of nanomaterials in all stages of preclinical development and clinical testing.

Won Jong Kim
Professor, Pohang University of Science and Technology (POSTECH), Korea

Stimuli-responsive nanoparticles for smart drug and gene delivery

Jihoon Kim, Jinhwan Kim, In-San Kim, Byung-Heon Lee, Allan S. Hoffman, Won Jong Kim

Herein, we designed self-assembled nanoparticles for Paclitaxel (PTX) delivery toward tumor cell. Self-assembled nanoparticles were constructed through host-guest chemistry between PTX and β-cyclodextrin (β-CD). CD and PTX are covalently conjugated with poly maleic anhydrides via ester linkage that provide higher solubility of nanoparticles. This inclusion complex forms a stable nano-sized particles, in which hydrophilic polymers cover outside nanoparticle and the inclusion complex of CD/PTX is located inside nanoparticle. It was revealed that this nanoparticle effectively inhibited the tumor growth in vivo by delivering PTX into tumor site. We also present a pH-responsive dynamic DNA nanocluster based on gold nanoparticles with highly packed nucleic acid assembly and evaluate its potential as a drug delivery vehicle with tumor-specific accumulation. Our size-tunable clustered nucleic acid-grafted gold nanoparticles provide tumor homing in the blood circulation and are thus a potential multifunctional therapeutic agent in vivo as well as in vitro.

Session III: Polymer DDS

Kazunori Kataoka
Professor, The University of Tokyo

Keynote Talk
Self-Assembled Supramolecular Smart Nanosystems for Targeted Drug Delivery

Nanotechnology-based medicine (Nanomedicine) has received progressive interest for the treatment of intractable diseases, such as cancer, as well as for the non-invasive diagnosis through various imaging modalities. Engineered polymeric nanosystems with smart functions play a key role in nanomedicine as drug carriers, gene vectors, and imaging probes. This presentation focuses present status and future trend of the development of polymeric micelles with distinctive core-shell architecture as self-assembled nanosystems with 10 to 100 nm in size prepared by the programmed self-assembly of block copolymers in aqueous entity. Several micellar formulations of antitumor drugs have been intensively studied in preclinical and clinical trials, and their utility has been demonstrated [1]. Critical features of the polymeric micelles as drug carriers, including particle size, stability, and loading capacity and release kinetics of drugs, can be modulated by the structures and physicochemical properties of the constituent block copolymers [2,3]. The development of smart polymeric micelles that dynamically change their properties due to sensitivity to chemical or physical stimuli is the most promising trend toward nanomedicines, directing to the targeting therapy with high efficacy and ensured safety. Notable anti-tumor efficacy against intractable cancer, including pancreatic cancer, of antitumor drug-incorporated polymeric micelles with pH-responding property was demonstrated to emphasize a promising utility of the nanosystems for the treatment of intractable diseases.

References

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Stefaan De Smedt
Professor, Department of Pharmaceutics of Ghent University

Exploring the Use of Light in Drug Delivery Science

S.C. De Smedt, K. Braeckmans and J. Demeester

Obtaining a better insight into the biophysical behavior of the nanoparticles during the various phases of the delivery process is required to achieve efficient optimization of their structure and composition.

For more than 10 years, we have been exploring the use of advanced fluorescence microscopy methods for this purpose. This lecture will overview what we learnt regarding the use of light based methods (like FRAP, FCS, fluorescence Single Particle Tracking-fSPT) for the characterization of the behavior of nanomaterials in complex biological fluids like blood, sera, eye vitreous, lung mucus. Special emphasis will be on a recently developed light based method which seems successful in a challenging application for which no alternative technique is currently available, namely the determination of the extent of vascular permeability which is an important parameter in the extravasation of nanomaterials from blood into the tissues.

Besides the use of light to measure critical steps in the delivery of drugs from nanomaterials we got a recent interest in the use of light to deliver compounds. Laser-induced photoporation, especially in combination with gold nanoparticles, is a method that is receiving increasing attention for delivering macromolecules in cells. By allowing gold nanoparticles to bind to the cell membrane, nanosized pores can be created upon pulsed laser illumination. Depending on the laser energy, pores are created through either direct heating of the AuNPs or by vapour nanobubbles (VNBs) that can emerge around the AuNPs.

Xuesi Chen

Professor, Key Laboratory of Polymer Ecomaterials, Changchun Institute of Applied Chemistry, Chinese Academy of Sciences

Nanogel-incorporated physical and chemical gels for highly effective chemo-protein combination therapy

Chemotherapies and protein therapeutics have emerged as two common treatments for malignant tumors, but they have limited therapeutic efficacy due to the dose-dependent significant toxicity and inactivation of protein drugs stemming from their poor stabilities. To overcome the barriers and minimize dosing frequency, here a self-assembled amphiphilic nanogel-crosslinked physical and chemical glycopeptide gels (nPCGs) were reported for the coadministration of doxorubicin (DOX), protein cytokines recombinant human interleukin-2 (IL-2) and recombinant human interferon-gamma (IFN-Î³). The syringe-injectable nPCGs, using self-assembled nanogels of periodate-oxidized cholesterol-bearing dextran (OCDEX) as cross-linkers, were fabricated based on covalent bonds and ionic crosslinking between synthetic poly(amino acids) and modified natural polysaccharides. Dynamic rheological measurements and in vitro degradation exhibited that the doubly cross-linked nPCGs improved the mechanical strength and stability of gels. The combining activities of IL-2, IFN-γ and DOX (IID) incorporated in nPCGs were better maintained than in OCDEX nanogels solely. IID released from nPCGs inhibited the proliferation of human lung carcinoma cell line A549 and induced apoptosis involving two classical apoptotic pathways, which are associated with the JAK/STAT and mitochondrial pathways. As compared to either single-agent regimen, the cooperative treatment of IID significantly suppressed A549 xenograft tumors in vivo. The well-defined nPCGs offer new revelation for improving the efficacy of chemotherapy and biologic-based anti-cancer therapy.

Martina Stenzel

Professor, University of New South Wales

Self-assembled glycopolymers for the delivery of drugs

Glycopolymers are synthetic polymeric backbones featuring pendant and/or terminal saccharide moieties. Due to their excellent biocompatibility and bioactivity, glycopolymers have received considerable attention in chemistry, material science and nanomedicine. We have developed a range of self-assembled micelles and other aggregates based on glycopolymer diblock copolymers and ABC triblock terpolymers. Besides investigating glycopolymers based on mannose, we have focused our attention to less explored glycopolymers, namely, the ones based on fructose and fucose. The interest in frucose and fucose stem from their ability to recognize cancer cells: Fructose transporter GLUT5 is overexpressed in breast cancer cell lines, but not in healthy tissue. Furthermore, fucosylated proteins are overexpressed on the surfaces of multiple types of cancer cells. We have therefore prepared micelles carrying fucose and fructose. By adjusting the size of the polymers, various aggregates such as micelles, vesicles and cylindrical micelles were obtained. Cell uptake studies could show the targeted delivery of drugs such as curcumin and platinum drugs to cancer cells. Furthermore, the size and shape of these micelles also affected their movement in multicellular cancer models.

Nicolynn Davis

Materials Science Research & Development, Sigma-Aldrich

Well-defined polymers for biomedical applications and their confirmation by MALDI-TOF

Nicolynn E. Davis1*, Philip Dimitrov1, Gangadhar Panambur1, Karolina Kosakowska2, Scott Grayson2, Viktor Balema1

Innovative polymerization techniques have enabled the synthesis of many new highly diverse, complex polymers for biomedical applications. This includes biodegradable polymers (polylactides, polyglycolides, and polycaprolactones), functionalized polymers for bioconjugation (PEGs, polyoxazolines), and smart polymers such as poly(N-isopropylacrylamide). Many of these polymers take advantage of advanced synthesis techniques, such as ionic, ring opening, and RAFT polymerization, to obtain well-defined polymers of low dispersity with diverse functional groups. High-quality characterization is essential to confirm the true structure and end-functionalization of these advanced polymer architectures, but in many cases, polymer characterization is still dominated by basic analysis techniques such as GPC and NMR. Improvements in matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) spectroscopy now allow for the confirmation of the structure and purity of complex polymer structures. Aldrich Materials Science has collaborated with academic partners to characterize a number of polymer materials using MALDI-TOF. In this talk, we will highlight the results of our internal polymer development program and academic collaborations for characterization and application testing for biomedical applications.

1 Materials Science R&D, Sigma-Aldrich, Milwaukee, WI 53209, United States
2 Department of Chemistry, Tulane University, New Orleans, Louisiana 70118, United States

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Session IV: Imaging and Image-Guided Therapy

Christine Allen
Professor and GSK Chair in Pharmaceutics and Drug Delivery, University of Toronto

Determinants of Efficacy of a Heat-activated Thermosensitive Liposome Formulation of Cisplatin in Models of Cervical, Breast and Lung Cancer

Liposomes are one of the few drug delivery platforms that have resulted in clinically approved products in oncology. Notwithstanding this success, the approved liposome formulations largely result in improvements in the toxicity profile of drug with limited to no enhancements in efficacy. In addition, a number of drugs relying on formulation in liposomes have failed in clinical development. The many pre-clinical and clinical studies that have been conducted on liposomes have revealed a number of limitations associated with this technology. These include variability in tumor accumulation due to clinical heterogeneity in the enhanced permeability and retention (EPR) effect as well as poor tumor penetration, and in some cases, limited drug release once at the tumor site. Thermosensitive liposomes have the potential to address these issues, in particular, when they are designed to provide largely intravascular release of drug within the tumor region. Our laboratory has designed a thermosensitive liposome formulation of cisplatin that provides triggered drug release in response to temperatures in the mild hyperthermia range. This presentation will review our data obtained to date with this formulation in combination with mild hyperthermia in a series of tumor xenograft models of human cervical, lung and breast cancers. The factors that impact the effect of this therapeutic strategy will be discussed including tumor microenvironment parameters such as microvessel density, degree of hypoxia, stromal content, cell sensitivity to drug and heat shock protein expression.

Twan Lammers
Professor, RWTH Aachen

Nanomedicine and Theranostics

Nanomedicines are 1-100(0) nm-sized carrier materials designed to improve the pharmacokinetics and the biodistribution of low-molecular-weight (chemo-) therapeutic agents. By delivering drug molecules more efficiently to pathological sites, and by preventing them from accumulating in potentially endangered healthy tissues, nanomedicines are able to improve the balance between efficacy and toxicity. Nanomedicines rely on the Enhanced Permeability and Retention (EPR) effect, which is notoriously known to be highly variable, in particular in patients. To overcome this high variability, several strategies have been envisaged to improve EPR-based nanomedicine treatments, including enhancement, combination, avoidance and imaging. In the present lecture, I will highlight several of these approaches. In addition, I will provide some recent evidence showing that image-guided nanomedicines can be used to target metastatic cancer lesions, to treat inflammatory disorders and to facilitate drug delivery to the brain.

Tyrone Porter
Associate Professor, Boston University

Ultrasound-assisted drug delivery systems

Ultrasound is a very attractive tool for a variety of biomedical applications. While the technology has been developed more fully for diagnostic applications, ultrasound has shown tremendous potential for facilitating drug delivery. In this talk, I will present three projects centered around the concept of applying ultrasound to increase the permeability of intact barriers. The first project involves the use of ultrasound to locally heat thermosensitive liposome for triggered release of encapsulated chemotherapy. In the second project, perfluorocarbon nanodroplets are used to nucleate cavitation and cavitation-mediated delivery of siRNA across cell membranes. Lastly, I will discuss opening the blood-brain/tumor barrier with ultrasound and its implications for delivery of free and encapsulated therapeutic agents.

Xiaohu Gao
Associate Professor, University of Washington

Multifunctional nanoparticles for cancer molecular imaging

Nanoparticles in the 1-10 nm size range are of considerable current interest, not only because of their unique size-dependent properties but also their dimensional similarities with biological macromolecules (e.g., nucleic acids and proteins). These similarities could allow an integration of nanotechnology and biology, leading to major advances in medical diagnostics, prognostics, and targeted therapeutics. In this talk, I will present recent development of multifunctional nanostructures for ultrasensitive detection and characterization of cancer cells.

Herschel Watkins
Lead Scientist, Bio-Pact

Medical grade carbon nanotubes

Carbon nanotubes have many valuable physical properties including excellent structural, and electrical, thermal, and optical properties. The many and varied medical applications of carbon nanotubes have been known for decades; but no commercial products have lived up to the hype. This is due, in large part, to the challenge of producing large quantities of discrete, functionalized carbon nanotubes of defined length devoid of toxic metals. Biopact has developed the first truly medical grade, nontoxic carbon nanotubes with the chemical and physical properties necessary to be used in a wide variety of medical application.

This reimagined nanotube is known as Medical Grade Molecular Rebar, or MGMR, and it marks a complete departure from the dirty, tangled micron bundles that have frustrated medical researchers for years. Less than a micron in length, MGMR is composed of discrete, multi-walled carbon nanotubes designed specifically for targeted drug delivery, diagnostics and devices. Multiple studies by independent groups have demonstrated it is non-cytotoxic. The potential applications of MGMR include: drug delivery, gene delivery, diagnostics, imaging, structural enhancements, etc.

Subhash Kalluri
Sales Scientist, Izon Inc.

Advancing Nanomedicine development through precise and accurate characterization of Drug Delivery nanoparticles using the TRPS Technology

Precise measurements, with particle-by-particle details, of a range of engineered and biological particles, is necessary to understand physical and surface properties of nanoparticles as they play a major role in the biodistribution, toxicity and pharmacokinetics of nanoparticles inside the body.

TRPS's ability to characterize on individual particle basis allows one to determine particle concentration (particles/mL), accurate size distribution, aggregation levels and particle-by-particle zeta-potential. In this talk, we address the Nanomedicine field's characterization needs with examples using TRPS technology.

Session V: Immunotherapy DDS

Almar Postma
Senior Research Scientist, CSIRO – Manufacturing, Australia

Polymer Architectures for Vaccine Delivery

Protein-based vaccines offer a number of important advantages over organism-based vaccines but generally elicit poor CD8+ T cell responses. We have previously demonstrated that pH-responsive, endosomolytic polymers can enhance protein antigen delivery to major histocompatibility complex class I (MHC-I) antigen presentation pathways thereby augmenting CD8+ T cell responses following immunization. Here, we describe a new family of nanocarriers for protein antigen delivery assembled using architecturally distinct pH-responsive polymers. RAFT polymerization was used to synthesize linear, hyperbranched, and core-crosslinked copolymers of 2-(N,N-diethylamino)ethyl methacrylate (DEAEMA) and butyl methacrylate (BMA) that were subsequently chain extended with a hydrophilic N,N-dimethylacrylamide (DMA) segment copolymerized with thiol-reactive pyridyl disulfide (PDS) groups.

In aqueous solution, polymer chains assembled into 25 nm micellar nanoparticles and enabled efficient and reducible conjugation of a thiolated protein antigen, ovalbumin. Polymers demonstrated pH-dependent membrane-destabilizing activity in an erythrocyte lysis assay, with the hyperbranched and cross-linked polymer architectures exhibiting significantly higher hemolysis at pH≤7.0 than the linear diblock. Antigen delivery with the hyperbranched and cross-linked polymer architecture enhanced in vitro MHC-I antigen presentation relative to free antigen, whereas the linear construct did not have a discernible effect. The hyperbranched system elicited a 4- to 5-fold increase in MHC-I presentation relative to the cross-linked architecture, demonstrating the superior capacity of the hyperbranched architecture in enhancing MHC-I presentation. This work demonstrates that the architecture of pH-responsive, endosomolytic polymers can have dramatic effects on intracellular antigen del! ivery, and offers a promising strategy for enhancing CD8+ T cell responses to protein-based vaccines.

Darrell J. Irvine
Professor, MIT

Engineering immunity with hitchhiking therapeutics

We describe engineering strategies to enhanced vaccines and immunotherapy based on two different approaches to the design of “hitchhiking” therapeutics: First, an approach to enhance adoptive cell therapy (ACT) for cancer will be described. ACT using patient-derived tumor-specific T-cells is a promising approach for cancer treatment, but strategies to enhance ACT T-cell functionality in vivo are needed. We developed a strategy combining nanomedicine with ACT, based on the chemical conjugation of drug-loaded nanoparticles (NPs) to the surfaces of live lymphocytes for ACT. ACT T-cells carrying cytokine-loaded NPs (to permit pseudo-autocrine self-stimulation following transfer into tumor-bearing hosts) are capable of massive in vivo expansion and robust anti-tumor responses, enabled by minimal doses of cytokines that by comparison have no therapeutic effect when given in a soluble form systemically. Second, we describe a novel strategy for targeting antigens and immunostimulatory agents to lymph nodes. Lymph node targeting is achieved clinically is sentinel lymph node mapping in cancer patients, where small-molecule dyes are efficiently delivered to lymph nodes by binding to serum albumin. To mimic this process in vaccine delivery, we synthesized amphiphiles designed to non-covalently bind vaccine antigens and adjuvants to endogenous albumin. These “albumin-hitchhiking” amphiphiles were efficiently delivered to lymph nodes following injection, leading to as much as 30-fold amplified cellular immune responses and anti-tumor immunity. These examples illustrate the power of bioengineering approaches in shaping the immune response and studying immune cell biology, and provide concepts that may be of utility in regenerative medicine and other related biomedical applications.

Tarek M. Fahmy
Associate Professor, Yale University

Orchestrating the Immune Response using Modular Nanomaterials for Autoimmunity and Cancer Immunotherapy

The immune system is made up of a complex network of molecules and cells that can screen its own components, protect itself, and attack invaders such as bacteria and viruses. Immune system malfunction can lead to the pathogenesis of many common chronic and autoimmune disease, and even progression of cancer. A particularly challenging case is the tumor microenvironment, which thwarts conventional immunotherapy through multiple immunologic mechanisms. Another challenging case is induction of tolerance against sites of immune invasion.

Nanomaterials can be engineered in ways that can overcome the immunoinhibitory nature of the tumor microenvironment, provide a paradigm for new vaccines or induce immune tolerance in areas where immune responses are too active. An attractive feature of these synthetic systems is that they can be 'tuned' in predictable, designable ways to optimize immune function; ultimately orchestrating the magnitude and direction of an immune response. Here we discuss novel nanotechnologies and biomaterials that work interface with immune system cells (T cells, Antigen-presenting cells) facilitating novel and effective means for induction of therapeutic immune responses in cancer and autoimmunity. Interestingly, the same systems can be appropriately tailored with diagnostic agents to report on the progress of the immune response inside the body. This talk will focus on four examples that discuss the power of Immunoengineering and why it makes sense that biomaterials will play a significant role in the development of newer generations of immunotherapeutics.

Theresa Reineke
Professor, University of Minnesota

High-throughput Polymer Screening for Biological Delivery: From Discovery to Design

Synthetic and natural polymers hold tremendous potential to improve therapeutic potency, bioavailability, stability, and safety through aiding the solubility of lipophilic drug candidates that may otherwise be clinically inaccessible. For the leading pharmaceutical delivery method (oral administration), one such approach involves maintaining drugs in an amorphous, nonequilibrium state using spray-dried dispersions (SDDs). Spray-dried dispersions are fascinating polymer–drug mixtures that exploit the amorphous state of a hydrophobic drug to dramatically elevate its aqueous solubility above equilibrium for oral administration. However, these materials have limited fundamental understanding of what polymeric attributes prolong drug supersaturation and combat crystallization in solution. We present an automated protocol to combinatorially explore a vast architectural parameter space for five polymer platforms and elucidate how specific microstructures dictate drug dissolution. Over 60 reversible addition-fragmentation chain transfer (RAFT) polymerizations were conducted in three high-throughput experiments, varying constituent properties such as polymer amphilicity, thermoresponsive phase behavior, and hydrogen bonding capability. The intermolecular interactions of well–defined lead compounds with model drug phenytoin were screened and studied in vitro. This study reports the first results of a polymer–focused screening assay that successfully solubilized an otherwise-intractable drug for oral delivery. Our results show the utility of high throughput synthesis and screening to design polymer excipient platforms. These delivery vehicles can be precisely tuned via monomer selection and functionality, as direct handles for elucidating important structure−property relationships in oral delivery.

Chae-Ok Yun
Professor, Hanyang University, Seoul, Korea

Intelligent tailor-made adenovirus using nanocarriers for cancer gene therapy

An important issue in adenovirus (Ad)-mediated cancer gene therapy that has thus far received little attention is the limited capacity for effective systemic delivery. Although primary tumors are treated effectively with intralesional injection of conventional Ad vectors, systemic metastasis is difficult to cure with this method. Systemic administration of conventional naked Ads leads to the acute accumulation of Ad particles in the liver, induction of neutralizing antibody, short blood circulation half-life, nonspecific biodistribution in undesired organs, and low selective accumulation in the target disease site. Versatile strategies involving the modification of viral surfaces with polymers and nanomaterials have been designed to maximize Ad antitumor activity and specificity by systemic administration. Modification of the Ad surface allows Ad to circulate in the bloodstream for a longer time, to be not targeted to the liver, and to passively accumulate in tumor sites via enhanced permeation and retention effects. The addition of affinity tags results in active targeting and high efficacy. Strategies including addition of polymer complexes, chemical modifications, and targeting moieties for the development of systemically injectable Ad gene therapeutic carriers will be discussed.

Gesine Heuck
Drug Formulation, MITACS Fellow, Precision Nanosystems

The NanoAssemblr™ Platform : Microfluidic Manufacture of Liposomes and Nanoparticles

Traditional methods for producing nanomedicines are labor-intensive, inconsistent and difficult to scale up. Here, we describe the NanoAssemblrâ„¢ Platform: a scalable, microfluidics-based system for the development and manufacture of liposomes and nanoparticles for drug delivery applications, such as genomic studies, cancer targeting, etc.

The NanoAssemblrâ„¢ Platform uses custom engineered microfluidic cartridges to perform nanoprecipitation within milliseconds and nanoliter reaction volumes. This enables well controlled, bottom-up self-assembly of nanoparticles and liposomes tunable sizes and low polydispersity in a single step with. Full automization of the system allows for high reproducibility of batches and excellent transferability of protocols between users and facilities.

The NanoAssemblrTM Benchtop Instrument facilitates rapid formulation screening at volumes between 1-15mL making it ideal for low-cost formulation and process development. Prototype formulations are easily scaled-up with the NanoAssemblrTM Scale Up Device, which uses parallel microfluidic mixers. Incorporating multiple mixers into a single microfluidic chip increases the throughput while maintaining identical reaction conditions. This technique allows for massive parallelization to achieve production scales from milliliters to liters.

Poster Session 1: Wednesday, September 16 at 5:00 – 6:30 pm

1.

Protein Polymer Architecture Modulates Drug Entrapment and Release

Jugal Dhandhukia, University of Southern California, dhandhuk@usc.edu

Pu Shi, University of Southern California, pushi@usc.edu

John Andrew MacKay, University of Southern California, jamackay@pharmacy.usc.edu

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'Protein polymers' are macromolecules that can be fused to functional peptides and proteins at high fidelity using genetic engineering. One class of 'protein polymers' is the elastin-like polypeptide (ELP), which was bioinspired by human tropoelastin. ELPs are water soluble macromolecules that can be produced well in excess of the renal filtration cutoff. In addition, they can be tuned to phase separate in response to heating, which can drive their assembly of nanoparticles and drug depots. Recent advances suggest these biodegradable materials make attractive therapeutic scaffolds for cancer, autoimmune diseases, diabetes, dry eye disease, and age-related macular degeneration. As they are peptide-based, they facilitate precision strategies using protein domains as drug carriers. Our group explores their ability to modulate drug binding and release for a potent anti-proliferative macrolide known as rapamycin. We recently reported that an ELP fusion to FK506-binding protein 12 (FKBP) binds strongly to rapamycin. When decorated with FKBP, ELP nanoparticles exhibit slow drug release that correlates with in vivo efficacy in models of breast cancer and the autoimmune disease known as Sjogren's Syndrome. In this abstract, we describe two ongoing studies: i) the effect of co-assembling FKBP and the RGD tripeptide onto a mixed micelle to target to integrins expressed within breast cancer; and ii) the influence of attaching multiple FKBP domains to a non-assembling monomeric ELP formulation. We observe that FKBP-ELP and RGD-ELP co-assemble into mixed micelles of approximately 25 nm in radius; furthermore, these nanoparticles delay tumor growth at a three fold lower dose than for an untargeted nanoparticle in a human xenograft model. To study the effects of monomeric FKBP-ELP fusions, drug release was monitored using dialysis and RP-HPLC. Interestingly, we report that the fusion of two copies of FKBP protein to a non-assembling ELP slowed the rate of terminal drug release from a half-life of 19 hour for a single FKBP domain to approximately 170 hours for attachment of two FKBP domains. Both polymers were approximately the same size as their parent ELP, ranging between 8 and 10 nm in radius. In comparison FKBP-ELP nanoparticles release drug with a half-life of 60 hours. The effects of the bivalent FKBP species on tumor regression remains to be determined; however, biodistribution and pharmacokinetic studies suggest that the lower hydrodynamic radius will facilitate added tumor penetration and reduced hepatic accumulation. If successful, these carriers are intended to facilitate long duration parenteral delivery via a non-intravenous route, such as intra-muscular, intra-peritoneal, or sub-cutaneous administration.

2.

Super-resolution imaging and quantitative analysis of membrane protein/lipid raft clustering mediated by cell surface self-assembly of hybrid nanoconjugates

Jonathan Hartley, University of Utah, jonathanmhartley@gmail.com

Mr. Te-Wei Chu, University of Utah, tewei.chu@utah.edu

Dr. Eric Peterson, University of Utah, emp@chem.utah.edu

Dr. Rui Zhang, University of Utah, zhangruiyantai@hotmail.com

Dr. Jiyuan Yang, University of Utah, jiyuan.yang@utah.edu

Dr. Joel Harris, University of Utah, harrisj@chem.utah.edu

Dr. Jindrich Kopeček, University of Utah, jindrich.kopecek@utah.edu

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We used direct stochastic optical reconstruction microscopy (dSTORM) and pair-correlation analysis to study how a nanomedicine redistributes proteins in the plasma membrane of Raji B cells. The nanomedicine binds to CD20 expressed on the surface of B cells, and after crosslinking the proteins, initiates apoptosis. The clinical use of anti-CD20 therapy using monoclonal antibodies such as Rituximab has been successful for the treatment of Non-Hodgkin's lymphoma (NHL); however, ~50% of patients with NHL don not respond to treatment so new medicines are needed. This clinical need prompted us to design a new class of nanomedicine. The nanomedicine comprises two conjugates: 1) an anti-CD20 antibody fragment (Fab') bound to one of two complementary oligonucleotides (Fab'-MORF1); 2) a biocompatible nanopolymer backbone bound to multiple copies of the second oligonucleotide (P-MORF2). The first nanoconjugate, Fab'-MORF1, binds to CD20 on the surface of B cells, then the second conjugate, P-MORF2, binds and crosslinks the bound Fab'-MORF1 on the surface of the cell, thereby initiating apoptosis. We showed that lipid raft aggregation is required for initiation of apoptosis. Using pair-correlation analysis the size of lipid raft clusters needed was >200 nm in diameter. Cholesterol and cortical actin provide lipid raft stability and their extraction or destabilization precludes apoptosis signaling. Nanoconjugate self-assembly and hypercrosslinking of CD20 indirectly induced apoptosis through lipid raft clustering. dSTORM images showed unclustered lipid rafts when the cells were pretreated with methyl-β-cyclodextrin, which extracts plasma membrane cholesterol or Latrunculin B, which disrupts cortical actin.

3.

Nano-formulation of BDNF: A Potential Therapy for Rett syndrome

Yuhang Jiang, University of North Carolina at Chapel Hill, yuhang.jiang@unc.edu

William A. Banks, University of Washington, Seattle, wabanks1@u.washington.edu

Xiang Yi, UNC Chapel Hill, xiang_yi@unc.edu

Alexander V. Kabanov, UNC Chapel Hill, akabanov@email.unc.edu

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Bain derived neurotrophic factor (BDNF) has been recognized as a potential therapeutic agent for Rett syndrome (RTT), a unique developmental disorder that is first recognized in infancy and seen almost always in girls. However, to hold promise in clinical development, exogenous BDNF must be delivered to the brain in sufficient amounts via feasible administration routes. Brain delivery of protein therapeutics is a well-known challenge because of their poor serum bioavailability and limited capacity to cross the blood-brain barrier (BBB). To address this critical challenge in the delivery of BDNF to the brain, we propose a novel delivery system for BDNF composed of safe and biocompatible polymers that entrap the BDNF molecule in a nanoscale complex, named nano-BDNF. We show that formulating BDNF into this Nano-BDNF particle significantly prevents BDNF aggregation and results in a stable and narrowly distributed nanoparticle. lmportantly, this Nano-BDNF demonstrates 1) simil! ar serum clearance as BDNF (t1/2 6.6 min vs. 7.1 min); 2) greater blood to brain penetration in comparison to BDNF that is rapidly effluxed from brain to blood; and 3) that the % of the injected dose taken up by the brain (%lnj/g) exceeds that of BDNF. By the first 10 min, the area under the curve (AUC) for nano-BDNF is ~6 times higher than that of BDNF (2.96 vs 0.54). Together, we develop a novel, safe and stable nano-formulation of BDNF and provide preclinical pharmacokinetic evidence that systemically administered BDNF in this nano-formulation enters the brain in a greater amount than native BDNF. Therefore, continuous development of nano-BDNF as a potential therapy for RTT will be of great interest.

4.

Targeted delivery of antibody-conjugated ferritin nanocages directed to pulmonary endothelium

Makan Khoshnejad, University of Pennsylvania, makank@mail.med.upenn.edu

Colin Greineder, University of Pennsylvania, Colin.Greineder@uphs.upenn.edu

Vladimir Shuvaev, University of Pennsylvania, shuvaevv@mail.med.upenn.edu

Vladimir Muzykantov, University of Pennsylvania, muzykant@mail.med.upenn.edu

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Development of an effective and safe targeted therapeutic delivery system to pulmonary endothelium could help immensely in treatment of oxidative and inflammatory conditions such as acute lung injury, pulmonary hypertension, edema, and other pathologic conditions. Ferritin with its small size, high stability, and biocompatibility provides a great therapeutic and imaging delivery platform with great potential for clinical translation. Here, we report on targeted delivery of ferritin nanocages using 390scFv (mPECAM), YN1mAb (mICAM), and MECA32mAb (mPV1) antibodies to pulmonary endothelium. Targeted ferritin nanocages were characterized by electron microscope and DLS particle size measurements, showing the antibody-conjugated ferritin to be uniform and homogeneous in the 20nm range. Targeted ferritin nanocages demonstrated selective binding and pulmonary uptake. Biodistribution to the lung were 160.9 $\pm$ 6.5 % ID/g with YN1mAb, 71.1 $\pm$ 1.8 % ID/g with MECA32 mAb, and 27.7 $\pm$ 2.8 %ID/g with 390 scFv coated nanocages. Various therapeutic proteins and small molecules as well as imaging agents could be delivered utilizing the targeted ferritin delivery platform. Ferritin-based therapeutics have great application for clinical translation due to their small size, high stability, and biocompatibility.

5.

Optimizing PolySTAT: Varying Peptide Content to Maximize Fibrin Crosslinking

Robert Lamm, University of Washington, rjlamm@uw.edu

Leslie W. Chan, University of Washington, lwchan@uw.edu

Nathan J. White, , University of Washington, whiten4@uw.edu

Suzie H. Pun, University of Washington, spun@uw.edu

Injectable hemostats have the potential to improve patient outcomes in the event of hemorrhage by shortening clotting time, increasing clot strength, and decreasing clot lysis. These materials combat coagulopathy, or depletion of clotting factors, by performing functions normally fulfilled by the body's natural clotting factors. PolySTAT, a peptide-polymer conjugate, comprises fibrin-binding peptide (FBP) and a poly(hydroxyethyl methacrylate) backbone. This elegant structure inspired by the activity of factor XIIIa results in crosslinking of fibrin in the forming clot. Previous work with PolySTAT showed treatment with the material leads to improved clotting parameters in vitro and increased survival in a rat femoral artery injury model. While the material had a strong performance in these studies, PolySTAT was previously optimized only for its degree of polymerization. Further optimization of the material is necessary for ultimate translation. This report is focused on optimization of the peptide content of PolySTAT. Understanding the trend for varying peptide content is the difference between increasing crosslinks between fibrin fibers and saturating the potential binding sites for FBP. Conjugates with varying FBPs per polymer were synthesized and characterized for peptide content. The effect of varying peptide content was studied by rotational thromboelastometry (ROTEM). Improved clotting parameters were observed with an increase in peptide per polymer. The observations in this study will inform the design of the next-generation PolySTAT, a material which, upon translation, holds the potential to significantly decrease hemorrhage-related death.

6.

Identifying peptide ligands by phage display and next-generation sequencing: a retrospective approach

Gary Liu, University of Washington, garywliu@uw.edu and Brynn R. Livesay (co-first author), University of Washington, livesb4@uw.edu

Nataly A. Kacherovsky, University of Washington, artom@uw.edu

Maryelise Cieslewicz, University of Washington, mcieslew@uw.edu

Emi Lutz, University of Washington, emilutz@uw.edu

Adam Waalkes, University of Washington, waalkes@u.washington.edu

Michael C. Jensen, Ben Towne Center for Childhood Cancer, michael.jensen@seattlechildrens.org

Stephen J. Salipante, University of Washington, stevesal@u.washington.edu

Suzie H. Pun, University of Washington, Department of Bioengineering, spun@uw.edu

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Introduction. Phage display enables high-throughput screening of peptide and antibody fragment libraries for binding ligands to targets of interest in drug discovery. However, the current method of identifying ligand sequences, Sanger sequencing, is low-throughput and provides a limited perspective of the complete sequence space. To expand this perspective, we employed next-generation Illumina sequencing to couple high-throughput screening with high-throughput sequencing. To characterize the effectiveness of Illumina sequencing analysis for ligand identification, we sequenced phage libraries screened against macrophage polarized to the M2 (anti-inflammatory) phenotype. As our group has previously identified a murine M2 macrophage-binding sequence, M2pep, this study characterized how M2pep is represented in high-throughput sequencing readouts. This retrospective study aims to define the "hallmarks" of binding sequences in Illumina sequencing analysis for identifying target-binding sequences in prospective approaches. Methods. Peptide phage display was conducted using the New England BioLabs Ph.D.-12 linear 12-mer library. Negative and positive selection was performed on murine M1 and M2 macrophages, respectively. After three subtractive rounds, phage libraries were sequenced by Sanger and Illumina sequencing. Results. We identified multiple M2 macrophage-binding peptides using Illumina sequencing. Within Illumina sequencing data, the hallmarks of binding sequences were (1) consistency across biological replicates; (2) an unselected library amplified the same number of times enabled filtering of "parasitic sequences"; and (3) multiple unique sequences contain the same binding motif. Conclusions. Here, phage libraries panned for M2 macrophage-binding sequences were used to define the "hallmarks" of binding sequences in Illumina sequencing data. Moreover, multiple novel M2 macrophage-binding peptides were identified.

7.

Development of a model system to gain insights into active nanoparticle targeting

Janni Mirosevich, Intezyne, Janni.Mirosevich@intezyne.com

Siddharth Patel, Intezyne, Siddharth.Patel@intezyne.com

Tomas Vojkovsky, Intezyne, Tomas.Vojkovsky@intezyne.com

Rick Crouse, Intezyne, Rick.Crouse@intezyne.com

Tara Costich, Intezyne, Tara.Costich@intezyne.com

Taylor Buley, Intezyne, Taylor.Buley@intezyne.com

Adam Carie, Intezyne, Adam.Carie@intezyne.com

Kevin Sill, Intezyne, Kevin.Sill@intezyne.com

Habib Skaff, Intezyne, Habib.Skaff@intezyne.com

Active targeting has long been proposed as a way to improve nanoparticle drug delivery to diseased tissues and cells. Yet, despite numerous publications, only a handful of actively targeted technologies have reached clinical trials. The number and scope of core nanotechnologies has made evaluation and comparison of targeted systems difficult. Therefore, we sought to develop a model nanoparticle delivery system to evaluate active targeting. Commercially available QDots and PEG reagents were used to create PEGylated-QDot nanoparticles of various sizes. PEG-QDot nanoparticles were characterized and evaluated for stability and delivery kinetics both in vitro and in vivo. Subsequently, actively targeted nanoparticles were created by further modifying PEG-QDot nanoparticles to include the transferrin protein as the targeting moiety. Comparison of 2, 5, 10 and 20k PEG revealed that greater than 10k PEG was necessary for sufficient PEG coverage to inhibit QDot cell binding and entry, in vitro. Greater than 10k PEG also provided sufficient QDot coverage for improved serum stability, and to avoid protein adsorption. In vivo, 10 and 20k PEGs provided better QDot PK and biodistribution results. Addition of transferrin protein as targeting moiety on the PEG-QDot surface demonstrated cell specific uptake of QDots via receptor mediated endocytosis. It was determined that 20-30% transferrin coverage was optimal for cell binding and entry. The QDot model system we have developed is easy to manipulate, analyze and reproducible. As such, this model system should prove useful for evaluating other targeting moieties and therefore, help advancement of active targeting in the nanotechnology field.

8.

Clustering of receptors enables lysosomal delivery of therapeutic proteins and degradation of oncogenic receptors

Paul Moody, Cardiff University, moodyp2@cardiff.ac.uk

Edward J. Sayers, Cardiff University, SayersEJ@cardiff.ac.uk

Paola Borri , Cardiff University, BorriP@cardiff.ac.uk

Peter Watson, Cardiff University, WatsonPD@cardiff.ac.uk

Cameron Alexander, University of Nottingham, cameron.alexander@nottingham.ac.uk

Arwyn T. Jones, Cardiff University, JonesAT@cardiff.ac.uk

Subcellular trafficking of biopharmaceuticals to lysosomes strongly modifies their therapeutic potency. On one hand, therapeutic entities such as siRNA/DNA are degraded within lysosomes, reducing their bioavailablity. On the other hand, lysosomes are the target organelle for many enzyme replacement therapies (ERTs) and some anti-cancer antibodies. It is thus critical to understand the mechanisms that mediate endocytic delivery to lysosomes, so that entry of biotherapeutics to this organelle can avoided or improved.

Cancer cells often overexpress oncogenic receptors, which generate aberrant signals that drive growth and spread of tumours. Some antibodies can cause these receptors to internalise and traffic to lysosomes, resulting in degradation of the receptor and thus reduced oncogenic signalling. For antibody-drug conjugates ("ADCs"), degradation of ADC:receptor complexes also enables release of a conjugated cytotoxin, which becomes free to bind its intracellular target.

We investigated internalisation and endolysosomal delivery of three different biotinylated protein ligands, namely Herceptin, Transferrin and an anti-[MHC class I] antibody. Lysosomes and biotinylated protein ligands were both fluorescently labelled, and endocytosis was evaluated in live cells by confocal microscopy. For each [protein ligand]:receptor complex, lysosomal delivery was significantly increased by addition of streptavidin to cluster these complexes. Additionally, streptavidin:Herceptin complexes significantly increased degradation of the target receptor Her2, compared with Herceptin alone. The reproducibility of streptavidin-induced lysosomal delivery raises the possibility that the majority of plasma membrane receptors can be internalised and trafficked to lysosomes by clustering. This may have wide implications in receptor-mediated drug delivery, and may be exploited for degradation of antibody:receptor complexes.

9.

Targeted PEGylated Nanoparticles for Maternal Pulmonary Delivery during Pregnancy

Sanaalarab Al-Enazy, University of Texas Medical Branch, saalenaz@utmb.edu

Erik Rytting, University of Texas Medical Branch, erik.rytting@utmb.edu

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Purpose:

Targeted peptide-conjugated, prednisolone-loaded, PEGylated PLGA nanoparticles may improve therapy for asthma during pregnancy. cLABL and gamma-3 targeting peptides were selected based on previous reports of binding to ICAM-1, which is upregulated in asthmatic pulmonary endothelium. The feasibility of this approach was investigated by quantifying the peptide conjugation efficiency, nanoencapsulation of prednisolone, and drug release kinetics.

Methods:

Prednisolone-loaded PEGylated PLGA nanoparticles were prepared by nanoprecipitation. Drug concentrations were quantified at various time points by HPLC for the determination of encapsulation efficiency and drug release under sink conditions at 37°C. cLABL and gamma-3 peptides were conjugated to blank nanoparticles containing maleimide. Peptide conjugation efficiency was determined by microBCA assay or fluorescence. Cytotoxicity was assessed by the WST-1 assay.

Results:

The Z-average size of the prednisolone-loaded nanoparticles was 182 $\pm$ 3.0 nm (polydispersity index = 0.10, zeta potential = -33$\pm$ 0.8 mV). Up to 96.4% encapsulation efficiency was achieved, and the in vitro release profile showed minimal burst release. Gamma-3-conjugated nanoparticles had an average size of 198 $\pm$ 4.0 nm (PDI = 0.20, zeta potential = –42 $\pm$ 1.5 mV, conjugation efficiency = 70 $\pm$ 6%). cLABL-conjugated nanoparticles had an average size of 217 $\pm$ 4.1 nm (PDI = 0.20, zeta potential = –43.0 $\pm$ 4.2 mV, conjugation efficiency = 83 $\pm$ 7%). Unloaded nanoparticles showed no significant cytotoxicity in A549 and BeWo cell lines.

Conclusion:

These results highlight the feasibility of prednisolone encapsulation in targeted, peptide-conjugated nanoparticles. This novel approach may lead to improved control of asthma during pregnancy.

10.

In vitro and in vivo characterization of Raw 264.7 macrophages-derived exosomes as brain delivery nanovectors

Dongfen Yuan, University of North Carolina at Chapel Hill, dyuan@email.unc.edu

Xiang Yi, University of North Carolina at Chapel Hill, xiang_yi@unc.edu

Daria Alakhova, University of North Carolina at Chapel Hill, alakhova.daria@unc.edu

Alexander Kabanov, University of North Carolina at Chapel Hill, M.V. Lomonosov Moscow State University, kabanov@email.unc.edu

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Exosomes are 40-150 nm natural membrane-bounded vesicles that carry proteins and RNAs for intercellular communication. We are interested in the potential use of exosomes derived from Raw 264.7 macrophages as brain delivery nanovectors. Herein, we report the physical chemical properties of these exosomes, their cellular uptake and endocytosis mechanisms within brain endothelial cells, and brain pharmacokinetics in mice.

Raw 264.7 macrophages derived exosomes were 130 nm, negatively charged, spherical nanoparticles as characterized by dynamic light scattering, nanoparticle tracking analysis and transmission electron microscopy. Using western blot we confirmed Alix and Tsg 101, two exosomal markers expressed in the exosomes. To study the cellular uptake and endocytosis mechanisms, exosomes were fluorescently labeled and incubated with human brain endothelial cells (hCMEC/D3) for flow cytometry and confocal microscopy analysis. Exosomes were actively internalized in a saturable manner via clathrin-/caveolin- mediated endocytosis and macropinocytosis, and associated with exosomal surface integrin (LFA-1) and carbohydrate moieties. Upon internalization, exosomes were sorted to endo/lysosomes and endoplasmic reticulum. Following intravenous injection to CD-1 mice, iodinated exosomes circulated in bloodstream as long as albumin, and accumulated in brain better than albumin. Exosomes were mainly distributed in liver and spleen followed by lung and kidney.

In conclusion, Raw 264.7 macrophages derived exosomes had appropriate size and charge as drug delivery nanovectors. They were actively internalized and interacted with brain endothelial cells. The long serum circulation and accumulation in brain endothelial cells present the potential of macrophages derived exosomes as natural nanovectors to deliver therapeutics for treatment of brain diseases.

Funding: NIH grant RO1 NS36229-07.

11.

Effect of Cryo-Protectants on Size Stability and Preservation of Coated and Uncoated Chitosan Nanoparticles after lyophilization.

IbrahimAlradwan, King Abdulaziz City for Science and Technology (KACST), ialradwan@kacst.edu.sa

Abdulaziz Almalik, King Abdulaziz City for Science and Technology (KACST), aalmalik@kacst.edu.sa.

1- Purpose: to determine the effect of different cryo-protectants on the physicochemical properties and characterization of HA, Alg caoted, and uncoated chitosan nanoparticles after freeze-drying. In addition, to look for the optimum cryo-protectant type and concentration those prevent particles aggregation during freeze-drying processes.

2- Methods: Nanoparticles synthesized by the ionic gelation method. Six different types of cryo-protectant were investigated in the experiment (Sucrose, Glucose, Trehalose, mannitol and polyethylene-glycol 2,000, and polyethylene-glycol 10,000), and were used at different concentrations (5%, 10%, 20%, and 50%).

3- Results: As a novel result, coatings of nanoparticles with hyaluronic acid along with using higher concentrations of cryo-protectants provided particle size stability and distribution that is the most relative to the size of freshly synthesized nanoparticles. NP`s were stored for 3 months. Samples that were freeze-dried without cryo-protectants resulted in an increase in average size due to aggregation and agglomerations. All cryo-protectants with the different concentrations provided some sort of size stability for the NP`s except for the PEG 10,000 which had no protective effect at higher concentrations. Sucrose and trehalose sugars had the greatest protective effect with HA coated and uncoated NP`s.

4- Conclusion: the utilization of cryo-protectants along with NP`s coatings can lead to the achievement of storing nanoparticles with the desired physico-chemical size characteristics for long periods of times.

12.

Measuring The Unique Absorbance/Scattering Characteristics Of Metallic Nanoparticles

Toby Astill, PerkinElmer, Toby.Astill@PERKINELMER.COM

Chady Stephan, PerkinElmer, Chady.Stephan@PERKINELMER.COM

Jeff Taylor, PerkinElmer, jeffrey.taylor@perkinelmer.com

Angular resolved scattering measurements are a key analytical tool for the characterization of many types of nanomaterials that may be involved in the health care industry. While goniometric spectroscopy can yield detailed information on size and shape of nanostructures, it can be a costly and time consuming technique for survey work. The procedure presented here, total integrated scatter spectroscopy, utilizes a less expensive 150 mm integrating sphere with center mount to quickly characterize scatter from a wide variety of nanomaterials with just several spectra. The methodology can be used on a wide variety of samples such as suspensions, solids, liquids, creams, and gels. Since many metallic nanoparticles used in medical applications tend to be highly reactive or unstable to aggregation, this methodology represents an excellency survey methodology to follow those changes. In addition, it would be appropriate for quality control and aging studies of nanomaterials, as well as a screening technique to select appropriate candidates for more intensive angular resolves scatter characterization.

13.

Self-Assembled Cholesteryl Albumin Nanoparticles Enhance Tumor Accumulation of Paclitaxel

Gantumur Battogtokh, Gachon University, gantumur.b24@gmail.com

Ji Hee Kang, Ph. D. Candidate, Gachon University, kkangjh@gmail.com

Gantumur Battogtokh, PostDoc, Gachon Univesrsity, b_ganiron@yahoo.com

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The objective of this study was to develop an albumin nanoparticle with improved stability and drug loading capacity. The cholesteryl bovine serum albumin conjugate (Chol-BSA) was synthesized with 16% degree of substitution. PTX-Chol-BSA nanoparticle was then prepared using Chol-BSA by self-assembly with the mean hydrodynamic diameter and zeta potential of 147.6 ± 1.6 nm and -20.47 ± 3.5 mV, respectively. The loading efficiency and loading capacity of PTX-Chol-BSA were 94.8 and 37.9%, respectively. PTX-Chol-BSA showed much higher colloidal stability than a simple complex of PTX and BSA (PTX-BSA). An in vitro release study indicated that around 30% PTX was released from PTX-Chol-BSA over an 8-h period, which was around 2-fold slower than PTX-BSA. PTX-Chol-BSA nanoparticles showed greater cellular uptake and higher cytotoxicity in B16F10 and MCF-7 cancer cell lines, as compared with PTX in Cremophor EL/ethanol (PTX-Cre/EtOH) and PTX-BSA formulations. A pharmacokinetic study in tumor-bearing mice showed that the area under the concentration-time curve (AUC0 8 h) following administration of PTX-Chol-BSA was 8177.03 ± 303.06 ng/mL•h, 2-fold higher than those following administration of PTX-BSA or PTX-Cre/EtOH. In addition, the tumor AUC0 8 h of PTX-Chol-BSA was 100.53 ± 9.88, compared with 57.03 ± 2.64 for PTX-BSA. Furthermore, in vivo antitumor efficacy was evaluated in tumor-bearing mice and the results revealed that PTX-Chol-BSA nanoparticles have greater antitumor efficacy. In conclusion, we demonstrated the potential of PTX-Chol-BSA nanoparticles for anti-tumor chemotherapy, with enhanced in vitro and in vivo behaviors, as compared to PTX-BSA and PTX-Cre/EtOH.

14.

Lung Targeting of Angiotensin Receptor Blockers for COPD Lung Injury

Jane Chisholm, Johns Hopkins University, jchisho3@jhu.edu

Jung Soo Suk, Johns Hopkins University, jsuk@jhmi.edu

Enid Neptune, Johns Hopkins University, eneptune@jhmi.edu

Justin Hanes, Johns Hopkins University, hanes@jhmi.edu

Chronic obstructive pulmonary disease (COPD) is currently the third leading cause of death in the United States. Currently available treatments for COPD only reduce symptoms, but none arrests or reverses deterioration in lung function and architecture that accompanies moderate to severe COPD diseases. Abundant genetic, biochemical and histological evidence strongly implicate elevated transforming growth factor (TGF)-□ signaling as a key contributor to COPD development and progression, thus making the TGF-□ pathway an especially attractive target. We previously showed that an orally administered angiotensin receptor blocker (ARB) protected against airspace damage in animal models of COPD via TFG-□ antagonism. Based on these findings, we sought to develop nano-based ARB formulations suitable for the most relevant delivery modality to treat lung diseases, inhalation. Inhaled delivery would provide improved drug distribution and persistence at the site of disease following inhalation while minimizing unwanted systemic side effects observed with oral ARB administration. Here we have engineered a drug nanocrystal (NC) formulation based on the ARB telmisartan (TEL) possessing bio-inert surface coatings that minimize aggregation, mucus entrapment and macrophage uptake, solely based on FDA-approved materials without introducing any new chemical entities. We demonstrate that the inhaled delivery of telmisartan nanocrystals (TEL-NC) provide protective intervention and/or therapeutic resolution of COPD disease pathogenesis in two widely explored animal models relevant to COPD, specifically an acute cigarette smoke-induced lung injury model and the tight-skin transgenic emphysema model. These findings suggest that inhaled TEL-NC can prevent and/or reverse COPD-related disease manifestation caused by enhanced TGF-□ signaling.

15.

Wearable Microprojection Array Skin Patches for Improved Biomarker Sampling from Skin

Jacob Coffey, University of Queensland, j.coffey@uq.edu.au

Simon Corrie, University of Queensland, s.corrie1@uq.edu.au

Mark Kendall, University of Queensland, m.kendall@uq.edu.au

Surface functionalised microprojection arrays (MPAs) capture circulating biomarkers from the skin as a needle-free alternative to traditional blood sampling.1,2 The microprojections penetrate the outer layers of the skin where the functionalised surface selectively binds target biomarkers from skin fluid with minimal invasiveness. Using this approach we have previously demonstrated capture of antigen specific IgG, dengue NS1 protein, and malaria HRP2 protein in mouse models. Understanding the factors which contribute to protein capture and how to increase this within the confines of the skin environment are critical to increase MPA diagnostic sensitivity and realise their full potential.

We have previously characterised the effect of microprojection array design (length, density, array size) on biomarker capture and demonstrated that biomarker capture increases with the surface area of the MPAs. We recently investigated the effect of MPA design on biomarker extravasation from skin vasculature and the concentration of biomarkers in skin. MPA insertion induces biomarker extravasation which may play a key role in accessing circulating biomarkers, synergistically increasing the capture of biomarkers onto the microprojections in vivo. Complementary approaches to induce extravasation, in addition to MPA induced extravasation, were observed to further improve MPA capture. Combining this with our optimal MPA design we demonstrate MPAs rapidly, reliably and reproducibly sample biomarkers for immunoassays within 2 min – currently the best reported diagnostic sensitivity using microprojections.

1 Coffey JW, Corrie SR, Kendall MAF.Biomaterials 2013, 34, 9572-83.

2 Corrie SR, Fernando GJP, Crichton ML, Brunck MEG, Anderson CD, Kendall MAF. Lab on a Chip 2010,10, 2655-8.

16.

Evaluating the Role of Particle Surface Properties on their Distribution and Cellular Association Following Pulmonary Delivery

Catherine Fromen, University of Michigan, cfromen@umich.edu

Catherine A. Fromen, PhD. University of Michigan, Ann Arbor, cfromen@umich.edu.

Tammy W. Shen, PhD. University of North Carolina at Chapel Hill, twshen@unc.edu.

Tojan B. Rahhal. University of North Carolina at Chapel Hill, rahhal@email.unc.edu.

Marc P. Kai, PhD. North Carolina State University, mpkai@ncsu.edu.

Gregory R. Robbins, PhD. University of North Carolina at Chapel Hill, grrobbin@email.unc.edu.

J. Christopher Luft, PhD. University of North Carolina at Chapel Hill,. jluft@email.unc.edu.

Joseph M. DeSimone, PhD. University of North Carolina at Chapel Hill, and North Carolina State University, desimone@unc.edu.

Engineered nano- and microparticle drug delivery vehicles have the potential to expand the breadth of pulmonary therapeutics. Understanding how particle properties, such as size, shape, and surface chemistry, can interact with key lung cells will lead to more effective pulmonary drug delivery vehicles. However, optimal particle properties have not been identified for many applications, such as mucosal vaccines or controlled-release lung depots. Using the nano-molding technique Particle Replication In Non-wetting Templates (PRINT), we investigated the role of particle surface properties to increase residence times and alter the cellular fate of nano- and microparticles delivered to the lung. Various sizes of PRINT hydrogel particles, including 80x320 nm, 1.5 and 6 um donuts, were fabricated with varied surface properties, including cationic, anionic, PEGylated, and antigen-loaded surfaces. Broncheoalveolar lavage fluid, whole lungs, and draining lymph nodes were evaluated for inflammatory cytokines, histopathology, cellular populations, and particulate uptake through flow cytometry, ELISAs, and fluorescent imaging. PEGylation was found to increase lung residence times of all sizes of particles tested, with the largest increase in residence time observed for smaller 80x320 nn particles. Interestingly, unPEGylated cationic nanoparticles preferentially associated with two important lung DC populations, supporting their ability to produce more potent antigen presenting cells and enhanced systemic and lung antibody titers upon pulmonary vaccination. Thus, surface modification of engineered particles was found to significantly affect uptake kinetics by key cell populations in the lung and can direct future particle formulations for cell-specific targeted delivery of pulmonary therapeutics.

17.

Microdialysis method to determine delivery rates from programmable carbon nanotube membrane-based transdermal delivery device

Gaurav Gulati, University of Washington, ggulati@uw.edu

Tao Chen, University of Kentucky, tao.chen@uky.edu

Bruce Jackson Hinds, University of Washington, bjhinds@uw.edu

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Transdermal nicotine patches have low success rates in smoking cessation therapy due to the need for variable flux/dose for treatment and relapse events. Ideal is to have a low power switchable nicotine delivery device that can couple psychological counseling over a wireless device to enhance counseling and mitigate relapse events. Switchable carbon nanotube (CNT) membrane devices for transdermal nicotine delivery have been successfully demonstrated in an in-vivo study, but did not directly measure nicotine due to its rapid conversion to cotinine making long-term switching studies impossible. By using a microdialysis analysis system in which nicotine that passes through the skin barrier goes directly into a microdialysis membrane probe for analysis, such studies can be enabled. In-vitro nicotine transdemal delivery (TDD) through CNT membrane was carried out using flow cell geometry with microdialysis membrane directly under dermatomed skin. Nicotine flux measured by the microdialysis membrane probe was proportional to total flux into the flow cell allowing microdialysis to predict blood circulation level of nicotine with switchable devices. Cumulative nicotine release for 3 days were 0.29±0.16 μmoles for CNT membranes verses 0.16 μmoles using commercially available nicoderm patch calibration, indicating therapeutically useful doses. The CNT membrane TDD system had 6-9 times increase in delivery rate when turned from passive delivery to active delivery states. This method can be applied a broad range of switchable transdermal delivery devices. These blue-tooth enabled switchable TDD devices, along with smart phone app-based tools for behavioral support and disease self-management, are highly promising for smoking cessation therapy.

18.

Use of AF4-MALS to prove the mechanism of action of the silver-nanolipid complex

Wafa Hassouneh, Wyatt Technology Corp., whassouneh@wyatt.com

Dierk Roessner, Wyatt Technology Europe GmbH, droessner@wyatt.eu

Roger Scherrers, Wyatt Technology Europe GmbH, rscherrers@wyatt.eu

Thomas Jocks, Wyatt Technology Europe GmbH, tjocks@wyatt.eu

Horst Seidel, Fachhochschule Kaiserslautern - University of Applied Sciences, Pirmasens, Germany

Cornelia M. Keck, Fachhochschule Kaiserslautern - University of Applied Sciences, Pirmasens, Germany

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Microsilver shows anti-microbial activity due to the oligodynamic effect. Upon dermal application, Nanostructured Lipid Carriers (NLC) increase skin hydration and re-enforce the natural lipid barrier of the skin. The combination of silver and NLC leads to the formation of a silver–nanolipid-complex, originally developed as a cosmetic product for sensitive skin and later found active against atopic dermatitis.

The proposed mechanism of action includes the assumptions that:

1. Silver acts as an electrode by releasing positively charged ions.

2. Positive silver ions adsorb to the negatively charged NLC surface, forming the silver-nanolipid complex.

3. NLCs promotes adhesion to surfaces, i.e. after dermal application the microsilver remains longer on membranes such as skin or bacteria than in the absence of NLCs and exhibits increased activity.

Mechanistic proof of this concept has been difficult, since standard methods such as zeta potential and dynamic light scattering size measurements fail to prove the adsorption of silver ions onto the surface of the NLC. By utilizing asymmetric-flow field-flow fractionation coupled to multi-angle light scattering (AF4-MALS) we show clearly the increase in size associated with microsilver adsorption onto nanolipids, and the dependence of adsorption on preparative conditions. The data are sensitive and robust, providing detailed size distributions with excellent repeatability.

19.

Radiosensitization effects of cisplatin-conjugated gold nanoparticles in triple negative breast cancer

Sohyoung Her, University of Toronto, sohyoung.her@utoronto.ca

Lei Cui, Ms. (1), David A. Jaffray, Prof., Ph.D. (2,3,4), Christine Allen, Prof., Ph.D. (1)

Lei Cui, University of Toronto, lei.cui@mail.utoronto.ca

David A. Jaffray, Ph.D., , University of Toronto, david.jaffray@rmp.uhn.on.ca

Christine Allen, Ph.D., University of Toronto cj.allen@utoronto.ca

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Triple negative breast cancer (TNBC) is an aggressive form of cancer that is commonly associated with high rates of recurrence and poor survival. Despite the improvements in the treatment of breast cancer, TNBC remains one of the major clinical challenges. Unfortunately, there is no targeted therapy that is specific to TNBC, which highlights the need for an innovative strategy to improve the outcomes of TNBC. Here, we present a novel nanotechnology-based approach to enhance the therapeutic efficacy of TNBC by using gold nanoparticles as a radiosensitizer. Gold nanoparticles have demonstrated great potential as a radiosensitizer owing to their tunable physico-chemical properties and the high X-ray absorption cross-section. Taking advantage of the physical dose enhancements achieved with gold nanoparticles, a potential strategy to further improve the radiosensitization effects is to combine gold nanoparticles with cisplatin, a gold standard radiosensitizer, that target an alternate biological pathway of radiosensitization.

In this study, we developed cisplatin-conjugated gold nanoparticles and evaluated their radiosensitization effects in a panel of human TNBC cell lines (MDA-MB-231, MDA-MB-468, MDA-MB-436). These nanoparticles are approximately 5 nm in core diameter, and are stabilized with a layer of poly(ethylene glycol), and labelled with a peptide that targets receptor-mediated endocytosis to enhance cellular uptake. In vitro clonogenic survival data revealed that the conjugation of cisplatin to gold nanoparticles resulted in increased radiosensitization in comparison to gold nanoparticles alone, suggesting that the co-delivery of gold nanoparticles and cisplatin represents a promising strategy for enhancing radiotherapy for the treatment of TNBC.

20.

Nanoparticle Formulation of Orlistat Improves Drug Stability and Cytotoxicity Against Human Cancer Cell Lines

Tanner Hill, University of Nebraska Medical Center, tanner.hill@unmc.edu

Amanda L. Davis, Wake Forest University Health Sciences, amadavis@wakehealth.edu

Frances B. Wheeler, Wake Forest University Health Sciences, fwheeler@wakehealth.edu

Sneha S. Kelkar, PhD, Wake Forest University Health Sciences, skelkar@wakehealth.edu

Erica C. Freund, Wake Forest University, efreuec11@wfu.edu

W. Todd Lowther, PhD, Wake Forest University Health Sciences, tlowther@wakehealth.edu

Steven J. Kridel, PhD, Wake Forest University Health Sciences, skridel@wakehealth.edu

Aaron M. Mohs, PhD, University of Nebraska Medical Center, aaron.mohs@unmc.edu

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Fatty acid synthase (FASN) is an oncogene commonly used by cancer cells for the de novo synthesis of fatty acids used in cell membranes. Orlistat is an FDA-approved gastric lipase inhibitor, which also inhibits FASN. However, oral delivery of Orlistat leads to very low absorption and its high hydrophobicity is not optimal for systemic delivery. This study examines the development of a nanoparticle formulation of Orlistat using conjugates of hyaluronic acid, termed Nano-ORL. Orlistat was loaded up to 20 wt% into nanoparticles with a 97% loading efficiency. Nanoparticle size had a linear relationship with Orlistat content; diameters ranged from 300-600 nm. Free Orlistat and Nano-ORL inhibited recombinant FASN similarly, and this inhibition translated to reduced incorporation of 14C-acetate into membrane lipids in PC3 cells. The cytotoxicity, as measured by dehydrogenase activity, of Nano-ORL was higher than Orlistat in prostate (PC3), breast (MDA-MB-231), brain (U87mg), and colon (RKO) cancer cell lines. The increased cytotoxicity toxicity is attributed to improved formulation stability of Nano-ORL. Orlistat pre-incubated for 24 h prior to cell exposure was significantly less cytotoxic than Nano-ORL that was pre-incubated. Further, Nano-ORL disrupted mitochondrial function by reducing ATP turnover in MDA-MB-231 and LNCaP cells as efficiently as Orlistat.

21.

Physicochemical characterization, in vivo evaluation, and hepatoprotective activity of silymarin-loaded solid nanoparticle

Duhyeong Hwang, University of North Carolina at Chapel Hill, dhhwang@email.unc.edu

Kwan Yeol Yang, Dong Wuk Kim, Young-Jun Shin, Jong Oh Kim, Chul Soon Yong, Han-Gon Choi

College of Pharmacy, Yeungnam University, Dae-dong, Gyongsan, South Korea

College of Pharmacy and Institute of Pharmaceutical Science and Technology, Hanyang University, Sangnok-gu, Ansan, South Korea

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Background: This study was aimed to develop a novel silymarin-loaded solid nanoparticle system with enhanced oral bioavailability and an ability to provide excellent hepatic protection using Shirasu porous glass (SPG) membrane emulsification and a spray-drying technique.

Methods: A silymarin-loaded liquid nanoemulsion was formulated by applying the SPG mem¬brane emulsification technique. This was further converted into solid state nanosized particles by the spray-drying technique. The physicochemical characteristics of these nanoparticles were determined by scanning electron microscopy, differential scanning calorimetry, and powder X-ray diffraction. Their dissolution, bioavailability, and hepatoprotective activity in rats were assessed by comparison with a commercially available silymarin-loaded product.

Results: Formulation of a silymarin-loaded nanoemulsion was accomplished using an SPG membrane emulsification technique. This resulted in generation of comparatively uniform emulsion globules with a narrow size distribution. Moreover, the solid nanoparticles improved about 1,300-fold drug solubility and retained a mean size of about 210 nm. Silymarin was located in unaltered crystalline form in the nanoparticles. The drug dissolved rapidly from the nanopar¬ticles, reaching nearly 80% within 15 minutes, indicating three-fold better dissolution than that of the commercial product. Further, the area under the concentration-time curve of the drug provided by the nanoparticles was approximately 1.3-fold greater than that of the commercial product. In addition, the nanoparticles significantly reduced CCl4-induced hepatotoxicity, indicating improved bioactivity compared with the commercial product.

Conclusion: Silymarin-loaded nanoparticles developed using SPG membrane emulsification and spray-drying techniques could be a useful system for delivery of poorly water-soluble silymarin while affording excellent hepatic protection.

22.

Synthesis of heterogeneous gold nanoparticle clusters in aqueous media using electrostatic attraction and controlled steric interactions.

Ryan Kastilani, University of Washington, rkas@uw.edu

Lilo D. Pozzo, University of Washington, dpozzo@uw.edu

Gold nanoparticles has been a topic of great interest in the biomedical community in the last several years due to their wide range of potential applications. In particular, previous works have shown that gold nanoparticles are promising drug delivery vehicles. Tuning these vehicles requires robust control of the gold nanoparticle structure. In this work, we present a new method to synthesize gold nanoparticles that can readily self-assemble into complex plasmonic nano-structures. The technique relies on carefully balancing attractive electrostatic forces with repulsive steric hindrance that is provided by surface-grafted polyethylene glycol (PEG). First, gold nanoparticles with diameter 14 nm and 4 nm are synthesized using the Turkevich method and the method proposed by Martin, respectively. A controlled amount of PEG is added to both the larger and smaller particles while ensuring that the surface of the particles is not saturated with polymer. The larger particles are subsequently functionalized with anionic thiol groups (e.g. 8-mercaptooctanoic acid), while the smaller particles are functionalized with cationic thiols. When combined together, these oppositely charged particles self-assemble into stable colloidal structures (i.e. nanoclusters) whose structure depends strongly on the surface concentration of PEG and the relative concentration of the particles. Smaller structures are obtained as the PEG surface concentration increases because steric hindrance dominates and prevents uncontrolled aggregation. The complex nanoparticle structures are analyzed with small angle X-ray scattering (SAXS), dynamic light scattering (DLS), UV-vis spectroscopy, and transmission electron microscopy (TEM).

23.

PEGylation of BSA-drug nanoparticles and site elucidation of PEGylation on BSA-drug nanoparticle using LC-MS

Achyut Kathuria, Campbell University, a_kathuria0804@email.campbell.edu

Qinfeng (Sarah) Liu, Campbell University, liuq@campbell.edu

Purpose: The Project aims at formulation and PEGylation of BSA-drug nanoparticle and at finding the effects on size and stability of BSA-drug nanoparticles by PEGylation. The extent and PEGylation site on BSA-drug nanoparticles will be elucidated by LC-MS. The purpose of the PEGylation of the BSA-drug nanoparticles is to increase the residence time and decrease the toxicity of the drug.

Results: The nanoparticles formulation was done by homogenization-emulsification method. The SDS-PAGE showed that PEGylation of the protein or BSA-drug nanoparticle have difference in mass when compared to non-PEGylated protein or nanoparticles. Different ratio of PEG to BSA showed different extent of PEGylation which lead to difference in mass change. The zeta-potential of the BSA-drug nanoparticles was measured, of the PEG: BSA-drug nanoparticles in different ratio. The LC-MS of the PEGylated BSA-drug nanoparticles showed PEGylation is dependent on the ratio of PEG to BSA-drug nanoparticles and site elucidation was achieved for the same.

Conclusion: The drugs-BSA nanoparticles were achieved with model drug reserpine. PEGylation made change in the molecular weight of BSA and drug-BSA nanoparticles. PEGylation reduces the zeta potential of the BSA-drug nanoparticles. PEGylation sites on BSA were identified using LC-MS of tryptic BSA purified from BSA-drug NP. Formation of nanoparticles reduced accessibility of lysine at positions of 36, 140,401,495,544, which might be buried inside of nanoparticles.

24.

Characterisation and potential applications of Chitosan–lignosulfonates sono-chemically prepared nanoparticles

SUYEON KIM, Pontificia Universidad Católica del Perú, skim@pucp.pe

Margarida M. Fernandesa, PhD, Universitat Politecnica de Catalunya, margarida.fernandes@upc.edu

Teresa Matamá, PhD, University of Minho, teresamatama@gmail.com

Andreia C. Gomes, PhD/Professor. University of Minho, agomes@bio.uminho.pt

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Due to their recognized properties of biocompatibility, biodegradability and sustainability, chitosan nanoparticles have a huge potential as new delivery systems. In this work, nanoparticles comprising chitosan-lignosulfonate complex were developed for the first time aiming cosmetic and medical applications. Several conditions for particles preparation were tested and the resulting nanoparticles were thoroughly characterized by measuring particle size, zeta potential, and polydispersity index. The pH of chitosan solution and sonication time were determinant factors on the development of smaller particles with low polydispersity index in the presence of proper surfactant, poloxamer 407 (an average particle size of 230nm was obtained at pH5 after eight minutes of sonication). A full characterization was performed in order to assess the beneficial effects of lignosulfonate complexation with chitosan nanoparticles. Lignosulfonates induced high stability against enzymatic degradation with lysosyme after one hour of incubation. A higher stability in the presence of PBS was also observed after one hour or even after one week demonstrating the stability improvement of chitosan-lignosulfonate nanoparticles at physiological environment. These particles were further able to incorporate a hydrophilic model protein - RNase A. The protein release in the presence of lysosyme was evaluated. An improvement of antimicrobial activity was also detected upon LS incorporation into CS nanoparticles.

25.

Polymer functionalized and surface modified Quantum Dots as Hybrid Systems for Biomedical Studies

Redouane Krini, Johannes-Gutenberg-University Mainz, rkrini@students.uni-mainz.de

Lutz Nuhn, Johannes Gutenberg University Mainz, Lutz.Nuhn@UGent.be

Rudolf Zentel, Johannes Gutenberg University Mainz, zentel@uni-mainz.de

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Understanding of interactions between nanoparticles and biological systems is of a huge interest in the biomedical research field. We developed a synthetic strategy of polymer functionalized nanoparticles for biomedical studies to obtain hybrid systems of QDs and biocompatible copolymers with a strong binding network (core crosslinked) in an inner shell and which can be modified in the end through their poly(ethylene glycol) functionalized outer shell. These hybrid systems can be used as models for investigation of cell penetration and drug delivery by using measurements combination between CryoTEM and fluorescence studies.

26.

Preparation and characterisation of SmarCrystals of aprepitant and ibuprofen by combinative method

Gupta Koteshwara Kunnatur Balasundara, Manipal College of Pharmaceutical Sciences, kb.koteshwara@manipal.edu

Zenab Attari, Manpal College of Pharmaceutical Sciences, znbattari2008@gmail.com

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SmartCrystals are the second generation nanocrystals with increased stability and solubility of drug and drug product with a particle size of less than 100 nm. An attempt was made to use the combinative methods for the preparation of SmartCrystals so as reduce the processing time and particle size of the drug. The objective of the study was to prepare nanosuspensions of aprepitant and ibuprofen using two pretreatment methods, precipitation and ball milling in combination of high pressure homogenisation (HPH). Ball milling and precipitation resulted in nanosuspensions with a particle size less than 1 micron, which were subjected to HPH. HPH further led to a reduction in the particle size to a nano size range. Solubility of aprepitant SmartCrystals was several times more as compared to pure drug.

27.

Recanilization of blood clots using amphiphilic gold nanoparticle stabilized Pickering emulsions

Yi-Ting Lee, University of Washington, ytlee@uw.edu

Lilo D. Pozzo, University of Washington, dpozzo@uw.edu

This work details the synthesis of stable Pickering emulsions of amphiphilic gold nanoparticles and perfluorinated oils that capable of producing photoacoustic and ultrasound signals. These emulsions have potential application in biomedical imaging, drug delivery, and in the mechanical re-canalization of blood clots with non-invasive methods. Amphiphilic gold nanoparticle clusters are synthesized by sequentially functionalizing gold nanoparticles with controlled amounts of hydrophilic thiol-terminated poly(ethelene glycol) methyl ether (PEG) and hydrophobic alkane thiols. Control over the PEG surface concentration, PEG molecular weight and the alkane thiol chain length is used to manipulate the aggregation number of the gold nanparticle clusters. Pickering emulsions are then prepared by applying ultrasound fields to dispersions of amphiphilic gold nanoparticle clusters in the presence of oil. Perfluoropentane and perfluorohexane are chosen for the oil phase due to their low boiling point and their negligible solubility in water. Emulsions are characterized by ultraviolet-visible spectroscopy (UV-VIS), dynamic light scattering (DLS), small x-ray scattering (SAXS), and transmission electron microscopy (TEM). Our results shows that the size of the Pickering emulsions is still small enough to possibly penetrate through the blood clot fibers. It is also shown that NIR laser irradiation and ultrasound excitation can lead to reversible emulsion expansion and mechanical breakup the fibrin clot fibers.

28.

Coenzyme Q10 Adsorption on Carbon Aerogels

Sandeep Manandhar, University of Washington, xandeep@uw.edu

Jennifer L. Hanson, University of Washington, jlh87@uw.edu

Paden B. Roder, University of Washington, roderpad@uw.edu

Xuezhe Zhou, University of Washington, xuezhe@uw.edu

D. Scott Wilbur, University of Washington, dswilbur@u.washington.edu

Peter J. Pauzauskie, University of Washington, peterpz@uw.edu

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Silica aerogels have demonstrated properties that make them attractive for use in a drug delivery system, because drug loading and crystallinity can be controlled. The crystalline state of drug is important as it has been shown to affect the release kinetics of the drug from the aerogel. However loading of crystalline drugs into a silica aerogel using supercritical CO2 can limit the amount of drug loaded due to low drug solubility in that supercritical solvent. This limitation cannot be circumvented as supercritical CO2 is required for maintaining the fragile porous aerogel structure while loading the drug, but it does provide a means to achieve a crystalline phase of the drug in the aerogel. In this work we demonstrate a simple method of loading and controlling crystallinity of a model drug (Coenzyme Q10) in pyrolyzed carbon aerogels. Our studies showed that the chemical microstructures of aerogels can be varied to control the crystallinity of the loaded drug, and that the microstructure can have an impact on the loading kinetics of the drug.

29.

FORMATION OF PHYTOSOME CONTAINING SILYMARIN USING THIN LAYER-HYDRATION TECHNIQUE AIMED FOR ORAL DELIVERY

Wina Maryana, Institut Teknologi Bandung, winamaryana@hotmail.com

Heni Rachmawati, Institut Teknologi Bandung, h_rachmawati@fa.itb.ac.id

Diky Mudhakir, Institut Teknologi Bandung, mudhakir@fa.itb.ac.id

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Silymarin is a unique flavonoid complex isolated from milk thistle (Silybum marianum) and has been widely used as hepatoprotective agent. Orally administered silymarin will be absorbed rapidly and only 20-50% of silymarin will be absorbed through gastrointestinal tract, resulting on its low bioavailability. Those limitations are due to its poorly soluble either in water and oil and its low intestinal permeability. This study was aimed to develop silymarin-loaded phytosomes to improve silymarin bioavailability with sufficient safety and stability. This system consists of silymarin-phospholipid complex prepared by solvent evaporation method, which was incorporated to formed phytosome shape vesicles using thin layer method with various concentration and molar ratio of silymarin and phospholipid. Phytosome vesicles size was reduced using probe sonication. The result demonstrated that formula with 2% silymarin-phospholipid complex and molar ratio of 1:5 showed the best physical properties with mean vesicle diameter of 133.53 $\pm$ 8.76 nm, polidispersity index of 0.34 $\pm$ 0.08, entrapment efficiency of 97.17 $\pm$ 2.41 %, loading capacity of 12.18 $\pm$ 0.30%, and good stability after freeze thaw stability test. Analysis of FTIR spectroscopy and DSC was confirmed the presence of physical and chemical interactions between silymarin and phospholipid complex. Well formed and discrete vesicles of phytosome were revealed by Transmission Electron Microscopy, drug content, and freeze thaw stability test.

30.

Preparation, characterization, in vitro and in vivo evaluation of nanoparticles of erlotinib

Chander Parkash, NIPER, S.A.S. Nagar, India, chanddora@gmail.com

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The present study was envisaged to evaluate the effect of erlotinib β-cyclodextrin nanosponge (ERL-NS) on the solubility, dissolution, in vitro cytotoxicity and in vivo pharmacokinetics of erlotinib (ERL).

Initially, β-cyclodextrin nanosponge was synthesized by pyromellitic dianhydride linker, and later ERL was loaded. The complexation phenomenon was confirmed by DSC, SEM, PXRD, FTIR, and TEM studies. In vitro release profile of ERL and ERL-NS was established and In vivo pharmacokinetics study was performed using Sprague Dawley rats. In vitro cell line cytotoxicity study was studied with pancreatic cancer cell lines, viz. MIA PaCa-2 and PANC-1.

ERL formed nanosponge complex at the ratio of 1:4 w/w of ERL:NS with 372±31 nm size, narrow size distribution (0.21±0.07 PDI) and high zeta potential (-32.07±4.58 mV). In vitro dissolution studies revealed increased dissolution rate (2-folds) with ERL-NS in comparison to ERL. In vitro cytotoxicity study in cancer cell lines indicates the increased toxicity of ERL-NS, which further showed 1.8 fold higher Cmax (78.98±6.2 vs. 42.36±1.75 µg/ml), and ~2 fold AUC0-∞ (1079.95±41.38 vs. 580.43±71.91), in comparison to pure ERL.

Therefore, we conclude the formation of β-cyclodextrin based nanoparticles with ERL is a successful approach to increase its solubility, dissolution and oral bioavailability which may ultimately result in reduction in dose and dose related side-effects.

31.

Light responsive nanocarriers for light controlled gene therapy

Rishav Shrestha, National University of Singapore, rishav@u.nus.edu

Yong Zhang, Professor, National University of Singapore, biezy@nus.edu.sg

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Light responsive nanocarriers demonstrate features suitable for deployment as engineered vectors for light-controlled gene therapy. Core-shell upconversion nanocarrier (UCNs) excited by deeply penetrating 980nm Near-Infrared (NIR) light and emitting in the UV-visible-NIR range were synthesized. They were further coated with a known transfection agent, Generation 4 Polyamidoamine (PAMAM) dendrimers through a facile ligand exchange method for conferring biocompatibility and for attachment of nucleic acids.

Next, nucleic acids (Plasmid GFP and ERα siRNA) were covalently bound to the coumarin photocage 6-bromo-4-diazomethyl-7-hydroxycoumarin (Bhc-diazo) rendering them inactive. Such photoinactivated nucleic acids were then loaded onto the biocompatible PAMAM-coated-UCNs.

The prepared complex was then used for delivery and highly controlled release of nucleic acids through photoactivation in MCF-7 Breast cancer cells for the expression of GFP and the silencing of ERα nuclear receptor that is involved in tumorigenesis in the breast tissue. Simultaneously, the UCNs were used for background free imaging of the breast cancer cells. UCNs excited by NIR has the potential for a controlled, safe and convenient tool in gene therapy and imaging.

32.

Liposome Based Vectors for Cytosolic Delivery of Macromolecules

Anna Brown, Oregon State University, broanna@ohsu.edu

Conroy Sun, Oregon State University, sunc@OHSU.edu

Niemann-pick type C (NPC) is a rare autosomal recessive lipid storage disorder, that is characterized by buildup of cholesterol in late endosomes/early lysosomes. The inability to clear cholesterol through normal endosomal processing leads to hepatic and pulmonary dysfunction and neurodegeneration. This disorder is always fatal, often before age 10. Clearance of cholesterol using 2-propyl-β-cyclodextrin (HPβCD), which is well biologically tolerated, has been shown to be an effective strategy for treatment of pre-clinical animal models of NPC1 disorder (Vite et al. Sci Transl Med. 2015 Feb 25;*7*(276). However, extremely high concentrations of HPβCD are necessary to achieve therapeutic effects, and to alleviate neurodegeneration, direct brain injections are necessary. We hypothesized that liposomes based formulation of HPβCD will be taken into the cell through endosomal processing and deliver HPβCD specifically into the late endosome/lysosomes, thereby improving efficacy of the drug. We have developed liposome formulations that can package water soluble cyclodextrin and demonstrate a significant reduction in the effective dose of HPβCD required for sequestration of cholesterol from NPC1 deficient cells. Future studies will focus on formulating nanoparticles with ligands that can traverse the blood brain barrier to deliver HPβCD into the brain of NPC1 deficient animal models.

33.

Transcription in nanoliposomes that can be endocytosed by human platelets

Vivienne Chan, University of British Columbia, vivienne.vc@gmail.com

Stefanie Novakowski, University of British Columbia, s.novakowski@gmail.com

Simon Law, University of British Columbia, hello@lawsimon.com

Christian Kastrup, University of British Columbia, ckastrup@mail.ubc.ca

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Transcribing exogenous RNA in eukaryotic cells requires efficient gene delivery to the nuclei of cells and changing their genome, limiting the potential scope of gene therapy and synthetic biology. Manipulating gene expression in anucleate cells is particularly challenging. We hypothesize that these challenges can be overcome by co-delivering components necessary for transcription along with exogenous DNA to cells, allowing for extranucleate transcription. Previously, protocells have been developed for transcription to occur in liposomes without nuclei, but their use in modifying gene expression of eukaryotic cells has not been explored. We adapted these protocells to co-encapsulate a reporter DNA template, T7 RNA polymerase, and ribonucleotides within 170nm liposomes, and delivered these to ex vivo human platelets, a model of anucleate eukaryotic cells. This led to the internalization of nanoliposomes and accumulation of functional reporter mRNA within platelets. Internalization of RNA-transcription liposomes was measured using various techniques, including flow cytometry, fluorescence microscopy, and quantitative PCR. This initial proof-of-concept study represents a method to alter eukaryotic gene expression without gene delivery to nuclei. To our knowledge, this is the first report of direct delivery of mRNA to human platelets, which may have important applications in studying platelet biology and for therapeutic use. Future studies will explore the use of therapeutically relevant gene targets, as well as external stimuli to controllably initiate transcription and modify gene expression in human platelets and in other eukaryotic cells.

34.

Development and characterization of lipidic nanoparticles for an antiepileptic drug

Silki Kumar, University Institute of Pharmaceutical Sciences, Panjab University, silky.walia7@gmail.com

V R Sinha, University Institute of Pharmaceutical Sciences, Panjab University, sinha_vr@rediffmail.com

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Epilepsy has been existent for years and still continues to affect approximately 50 million individuals worldwide. Carbamazepine is one of the most widely used drug in treatment of epilepsy, however, its low bioavailability attributed to poor aqueous solubility has always been a limitation. It has also been reported that food enhances the bioavailability of carbamazepine. Such issues of low and variable bioavailability can be resolved by formulating the drug in the form of solid lipid nanoparticles (SLN). Drug loaded SLN can enhance the bioavailability thereby making the drug more efficacious leading to better drug utilization. Incorporation of the drug in solid lipid nanoparticles would also be apt to reduce fed and fasting variability by alleviating the solubility problems. The present research work is aimed at preparation of carbamazepine loaded solid lipid nanoparticles. Compritol® (COM) and glyceryl monostearate (GM) have been used as the lipids with Tween 80 and soya lecithin as the stabilizers. SLNs were prepared by solvent diffusion evaporation method combined. Prepared SLNs were characterized for drug: lipid compatibility, particle size and morphology, percent entrapment efficiency, solid state characterization and in-vitro release profile. The release mechanism was confirmed by analyzing fitness of data into various release kinetic models and determining correlation coefficients.

35.

Fusogenic targeted liposomes as next-generation nanomedicines for Prostate Cancer

Jihane Mriouah, University of Alberta, mriouah@ualberta.ca

R.L. Nesbitt, Entos Pharmaceuticals, Edmonton, AB, raelynnnesbitt@gmail.com

D. Pink, University of Alberta, Entos Pharmaceuticals, Edmonton, AB, desmond.pink@ualberta.ca

R. Duncan, Dalhousie University, Halifax, NS, roy.duncan@dal.ca

A. Zijlstra, Entos Pharmaceuticals, Edmonton, AB, Vanderbilt University School of Medicine, andries.zijlstra@vanderbilt.edu

J.D. Lewis, University of Alberta, Entos Pharmaceuticals, Edmonton, AB, jdlewis@ualberta.ca

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Chemotherapies for advanced prostate cancer have extended survival, but their efficacy is limited by dose-limiting toxicities due to suboptimal biodistribution. We address the lack of specificity and accumulation in Castrate Resistant Prostate Cancer (CRPC) by developing a unique nano-carrier for drug delivery: targeted fusogenic liposomes.

We have developed a platform whereby liposomes are formulated with fusion associated small transmembrane protein p14 displaying targeting ligands. The p14 protein catalyzes mixing of the liposomal bilayer with cell membranes to deliver the cargo directly into the cytoplasm, while the targeting ligand, bombesin, allows for targeting to the Gastrin-releasing Peptide (GRPR) that is overexpressed in prostate cancer.

We hypothesized that this novel targeted fusogenic liposome formulation would significantly improve the biodistribution and efficacy of chemotherapy.

A clinical liposomal doxorubicin formulation (DOXIL) was modified it to incorporate targeted fusogenic p14 protein. Resulting nanoparticle size (100nm) and drug encapsulation were unchanged.

We then evaluated the efficacy and biodistribution of these new formulations using in vitro and in vivo models of CRPC. In PC3 cells, compared to conventional liposomes, intracellular levels of doxorubicin are increased by 15 and 25 times when p14 or p14-bombesin liposomes are used. Additionally,the, the IC50 is reduced from 21mM to 2mnM. In mice bearing PC3 tumors treated with targeted fusogenic liposomal doxorubicin, we observed tumor growth inhibition of 57% (vs control).

This establishes a proof of concept for an innovative targeted drug delivery system that may improve the outcome of patients with CRPC by enhancing the effect of approved drugs.

36.

Development of lipid nanoparticles for treatment of osteoporosis

Mina Ordobadi, University of British Columbia, mina@alumni.ubc.ca

Pieter Cullis, University of British Columbia, pieterc@mail.ubc.ca

Robert Young, Simon Fraser University, roberty@sfu.ca

Marion Thevenin, marion.thevenin@hotmail.fr

Anabolic drugs are a family of compounds that induce bone growth in order to treat osteoporosis. Most anabolic agents are hampered with unpleasant side effects and dose dependent toxicity. We hypothesize that through associating anabolic agents with lipid nanoparticles (LNP), the unpleasant side effects can be minimized leading to higher therapeutic indices.

We are currently pursuing encapsulation of a number of novel agents that have been proven to induce significant anabolic response in vivo. Our LNP systems can enhance the permeability and retention of these agents. Using microfluidic mixing techniques, we have recently formulated a potential therapeutic that exerts its anabolic effect through the prostanoid receptor EP4. Taking advantage of cationic lipids, a prodrug version of this small molecule drug is efficiently encapsulated and retained within the LNP. The prodrug version of the compound consists of a bone targeting moiety which improve delivery efficiency. We are currently investigating the pharmacokinetics and biodistribution profiles of the formulation as well as in vivo efficacy of the EP4 receptor agonist-associated LNP. The data generated through this study will lead to new development of highly potent and safe nanomedicine therapeutics for bone diseases such as osteoporosis.

37.

Development and characterization of liposomal drug delivery system for prodrugs of vinca alkaloids.

Vidhi Shah, Oregon State University, shahv@onid.oregonstate.edu

Duc Nguyen, Oregon State University, nguyend@onid.oregonstate.edu

Adam W.G. Alani , Oregon State University, adam.alani@onid.oregonstate.edu

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Introduction

Vinca alkaloids, known antimitotic agents, are limited in their use due to their inherent toxicity. Recently, prodrugs of two Vinca alkaloids have been synthesized,CPD100 and CPD101 to overcome these limitations. To further improve their pharmacokinetic profiles we have developed and characterized liposomal formulations for each of these prodrugs.

Method

CPD100 & CPD101 were loaded into 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC):Cholesterol (55:45) liposomes by transmembrane pH gradient or passive loading method respectively. The resulting multilamellar vesicles were extruded through a 0.1 µm polycarbonate filter to generate large unilamellar vesicles (LUV). The LUVs were characterized for size by dynamic light scattering, drug loading and retention by reverse-phase HPLC (RP-HPLC). Prodrug release from LUVs was evaluated by dialysis under sink conditions and quantified by RP-HPLC. All experiments were done in triplicate.

Results & Conclusions

CPD100 and CPD101 liposomal formulations were successfully loaded into LUVs at 4 mg/mL and 3.3 mg/mL respectively. Size of the LUVs ranged from 120 – 150 nm and no change was seen over 48 hours. Drug loading and retention studies indicated the LUVs maintained concentrations for 48 hours. Release studies are ongoing. Initial studies indicate that LUVs offer a viable, therapeutically relevant drug delivery system for the CPD100 and CPD101 and offer the potential for prolonged circulation with limited adverse side effects.

38.

Mixed lipid/peptide vesicles bearing stealth and targeting motifs: a biomimetic delivery system tailored to cancer therapy

Giovanni Signore, CNI@NEST Istituto Italiano di Tecnologia, giovanni.signore@iit.it

Luigi Capriotti CNI@NEST Istituto Italiano di Tecnologia

Alessandro Ranalli NEST, Scuola Normale Superiore

Melissa Santi NEST, Scuola Normale Superiore

Dr. Claudia Boccardi CNI@NEST Istituto Italiano di Tecnologia

Dr. Vincenzo Piazza CNI@NEST Istituto Italiano di Tecnologia

Prof. Fabio Beltram NEST, Scuola Normale Superiore

PEGylated liposomes are extensively employed as carriers for small drug in cancer therapy, owing to their minimal aspecific protein adsorption (opsonization) and good passive –and active- targeting capability. However, their therapeutic efficiency markedly decreases upon repeated administrations due to the presence of unnatural PEG chains, which leads to the formation of anti-PEG antibodies, and hence to faster body clearance. Thus, it is nowadays accepted that a paradigm shift from PEG-based structures to biomimetic sequences is required.

Starting from a reported stealth sequence (EKEKEKE), we synthesized a lipopeptide which can be mixed with lipids commonly used in liposomal formulations in percentages ranging from 10% to 60% w/w. The resulting vesicles are thermally and chemically stable, and have negative surface charge (-20 to -50 mV). Furthermore, the peptide coating completely abolishes serum protein adsorption even upon prolonged (5 hours) incubation in pure serum at physiological temperature. The extent of protein adsorption depends on the percentage of stealth lipopeptide in the nanostructure, and compares favorably with benchmark PEGylated liposomes.

We shall show that addition at low concentration (<5%) of lipid-modified targeting sequences against transferrin receptor (TfR) allows effective and specific interaction with cell expressing TfR. Given the known overexpression of TfR in most solid tumors and on the blood-brain barrier, this feature could lead to targetable nanodevices for tumor treatment. Finally, we will present our results on nanoparticles loading with a chemotherapeutic agent (doxorubicin) and we shall discuss their internalization efficiency and cytotoxicity in target and control cell lines.

39.

Fibrillar nanocarbon-mediated delivery of siRNA prevents acute kidney injury

Simone Alidori, Departments of Radiology, Memorial Sloan Kettering Cancer Center, alidoris@mskcc.org

Nima Akhavein, Molecular Pharmacology Program, Memorial Sloan Kettering Cancer Center, nima.akhavein@gmail.com

Daniel L.J. Thorek, Department of Radiology and Radiological Sciences, Johns Hopkins School of Medicine, dthorek1@jhmi.edu

David A. Scheinberg, Memorial Sloan Kettering Cancer Center, scheinbd@mskcc.org

Michael R. McDevitt, Memorial Sloan Kettering Cancer Center, m-mcdevitt@ski.mskcc.org

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The therapeutic potential of systemic RNAi remains unrealized in part from an inability to target specific cells of interest and degradation in vivo. An ideal transport platform is expected to be biocompatible, non-immunogenic and capable of releasing the RNAi cargo after crossing the membrane of target cells. Several nanoformulations have entered clinical trials, including lipid nanoparticles and cyclodextrins. However, these agents have undesirable pharmacokinetic and targeting profiles, which preclude RNAi delivery to organs such as the kidneys. Acute kidney injury (AKI) is a consequence of numerous standard of care treatments which result in off-target damage to the nephron. Kidney damage from common medical intervention presents a considerable medical and socioeconomic burden, as the acute injury and subsequent deterioration of renal function results in high morbidity. Furthermore, AKI limits the effective application of current treatment approaches in oncology, infection and surgery as the dose of these medicines must be reduced in order to avoid AKI. No therapeutic intervention is available to mitigate the initial damage and the progressive deterioration of the kidney. In this work, we demonstrated the rapid and selective transport of siRNA to renal proximal tubule cells (PTC) using fibrillar ammonium-functionalized carbon nanotubes (fCNT). Our approach achieves a 10-fold increase in cell-specific renal uptake of the RNAi and in the effective knockdown of several genes and proteins within the PTC following systemic administration. We used co-morbid mice as a model to evaluate the therapeutic potential of fCNT to deliver siRNA directed against genes that regulate the pathogenesis of renal injury. We achieved prophylaxis by systemic administration of a fCNT/siRNA complex designed to target two key genes in the PTC. The fCNT delivery platform improved progression-free survival, reduced fibrosis, and decreased immune cell infiltration compared to controls. This work demonstrates that fibrillar nanocarbon-mediated delivery of RNAi can be used as preventive therapy for AKI in anticipation of a nephrotoxic or ischemic medical intervention and as a precision tool to study PTC biology.

40.

Sunflower pDMAEMA-based polycations as effective gene transfer vehicles

Yilong Cheng, University of Washington, ylcheng@uw.edu

Hua Wei, Lanzhou University, weih@lzu.edu.cn

James-Kevin Y. Tan, University of Washington, jkyt@uw.edu

Suzie H. Pun, University of Washington, spun@uw.edu

Polycations as nucleic acid carriers show promising potentials treating a myriad of inherited and acquired affliction. Until now, diverse polycations have been exploited and intensively studied for in vitro and in vivo gene delivery. In this work, a new polycation, "sunflower" poly(2-dimethyl amino)ethyl methacrylate) (pDMAEMA)-based polymers were prepared by atom transfer radical polymerization (ATRP) and employed as nucleic acid carrier compared to linear pDMAEMA homopolymer and comb pDMAEMA. The sunflower pDMAEMAs showed higher IC50 and greater buffer capacity than comb pDMAEMAs. All the polymers could condense pDNA into nanoparticles with positive charged surface, while sunflower polymers showed enhanced pDNA condensation capability. Moreover, sunflower polymers mediated higher transfection efficiency than comb and linear polymers, even better than bPEI (25 kDa) in the complete growth medium. The high in vitro delivery efficiency of sunflower pDMAEMAs in the presence of serum suggests these architetures may be more efficienct than current options for polymeric gene transfer in vitro. This work might give valuable insights into the effect of the architecture of polycations on gene transfection and biocompatibility.

41.

Polypept(o)ides as novel non-viral Vectors for Gene Therapy

Philipp Heller, Institute of Organic Chemistry, Johannes Gutenberg University Mainz, heller@uni-mainz.de

Benjamin Weber, Institute of Organic Chemistry, Johannes Gutenberg University Mainz, b.weber@uni-mainz.de

Nicole Mohr, Institute of Organic Chemistry, Johannes Gutenberg University Mainz, nicolemohr@uni-mainz.de

Jiajia Zhou, Institute of Physics, Johannes Gutenberg University Mainz, zhou@uni-mainz.de

Dominika Hobernik, Department of Dermatology, University Medical Center Mainz, dhoberni@uni-mainz.de

Matthias Bros, Department of Dermatology, University Medical Center Mainz, mbros@uni-mainz.de

Matthias Barz, Institute of Organic Chemistry, Johannes Gutenberg University Mainz, barz@uni-mainz.de

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Gene therapy offers great potential for the treatment of various diseases. It appears particularly promising for immune therapies where only a small number of cells need to be transfected, e.g. antigen-presenting cells.[1] To reach the full therapeutic potential, however, it is essential to engineer efficient, biocompatible delivery systems for DNA/mRNA which can overcome biological barriers while displaying minor off-target effects.

PeptoPlexes are built of plasmid DNA and polypept(o)ides which consist exclusively of endogenous amino acids, such as sarcosine, lysine, histidine and cysteine. While the hydrophilic polysarcosine block provides stealth-like properties, the amino acid segments enable efficient complexation of DNA, reversible crosslinking by disulfide formation and endosomal penetration.

Sequential NCA polymerization combined with suitable protecting group chemistry allows for the synthesis of diblock and triblock copolypept(o)ides with adjustable block length ratios, block reactivity and functionality.[2–4] Functional initiators such as amine-bearing mannose derivatives, azide or alkine groups can be easily incorporated.[5]

PeptoPlexes are characterized by light scattering with respect to applied block copolymers. These studies, together with computer simulations, elucidate the structure-property relationships between polymer architecture, PeptoPlex formation and transfection efficiency.

PeptoPlexes prove to be successful for the transfection of different cell lines while showing no detectable cytotoxicity which makes them promising candidates for further studies.

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42.

Porous Silicon Nanoparticles for Targeted Delivery of siRNA

Jinmyoung Joo, University of California, San Diego, jinmyoung@ucsd.edu

Michael J. Sailor, University of California, San Diego, msailor@ucsd.edu

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Gene silencing by RNA interference (RNAi) is limited by extracellular nucleolytic degradation and by inefficient delivery into the cytoplasm of target cells. Here we report the synthesis, characterization, and in vitro assessment of a nanoparticle-based RNAi delivery platform that protects an siRNA payload and efficiently delivers it to cells. The nanosystem is based on biodegradable mesoporous silicon nanoparticles (pSiNPs), where siRNA is loaded into the voids of the nanoparticles which are then coated with graphene oxide nanosheets. The graphene oxide encapsulant delays release of the oligonucleotide payload in vitro by a factor of 3. The nanocarriers also efficiently protect the siRNA payloads against nuclease-induced degradation. Under nucleolytic conditions that completely degrade free siRNA, siRNA loaded into pSiNPs retains 50% activity, and siRNA loaded into GO-pSiNPs retains 80% activity. When conjugated to a targeting peptide derived from the rabies virus glycoprotein (RVG), the nanoparticles show greater cellular uptake and they increase silencing of the peptidylprolyl isomerase B (PPIB) gene in acetylcholine receptor-positive Neuro2a cells in vitro. Furthermore, administration of the RVG-targeted GO-pSiNPs containing dye-labeled siRNA into brain-injured mice by intravenous administration results in significant accumulation of the label specifically at the injury site of the brain.

43.

Development of Targeted "Smart" Particles for Silencing Breast Cancer Metastases

Neha Kausal, University of Michigan, NKAUS@UMICH.EDU

The morbidity and mortality associated with breast cancer is linked to their metastatic spread to distant organs, caused by the overexpression of RhoC-GTPase protein in the cytoplasm of metastatic cells making them a potential therapeutic target. Prior research showed that anti-RhoC siRNA suppressed RhoC expression at the mRNA and protein levels, that inhibited breast cancer cell proliferation, migration, and invasion in vitro and tumor growth and angiogenesis in vivo. However, the systemic delivery of siRNA molecules require carrier vectors that can transform this promising anti-RhoC siRNA into an effective and clinically-viable therapy to suppress metastatic breast cancer cells. We reported the synthesis of pH-sensitive, membrane-destabilizing polymers using β-cyclodextrin (β-CD) as the carrier core, which proved to suppress GAPDH gene expression both at the mRNA and protein levels. We used these β-CD carriers to deliver anti-RhoC siRNA (100nM) into SUM149 and MDA-MB-231 breast cancer cells. We report a 100% reduction in the RhoC gene expression at the protein and the mRNA levels in SUM149 cells using our "smart" particles encapsulating anti-RhoC siRNA in vitro, which caused a 60% reduction in cell invasion and migration. Using this amphiphilic graft composition, we developed asymmetric targeted, PEGylated particles that could render stealth-like conformation to successfully deliver our therapeutic cargo into the cytoplasm of cancer cells in vivo. These particles show hemocompatibility, selective internalization via receptor-mediated endocytosis, and 70% reduction in migration and invasion phenotypes at low anti-RhoC siRNA (25nM) concentrations. Successful development of these "smart" particles will offer a platform technology for delivery of a range of therapeutic nucleic acids into the cytoplasm of targeted cancer cells.

44.

Microfluidic synthesis of helper-lipid-enhanced lipid nanoparticles for intracellular delivery of plasmid-DNA

Jayesh Kulkarni, University of British Columbia, jaykul91@gmail.com

Layne Myhre, Sam Chen, Chris Tam, Adrian Danescu, Joy Richman, and Pieter Cullis

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Lipid Nanoparticles (LNPs) have rapidly gained prominence for their ability to effectively delivery macromolecular structures such as short interfering RNA (siRNA) to the cytosol of target cells. While these particles have been developed for the delivery of siRNA, little effort has been expended in re-engineering LNPs for other applications. Initial studies suggest that the most potent gene-silencing LNPs perform poorly in the delivery of plasmid-DNA. We have leveraged microfluidics technology to generate helper-lipid-enhanced LNPs capable of achieving high transfection efficiency. Through the incorporation of helper lipids such dioleoyl-phosphatidylcholine into LNPs, the expression maximum can be increased four-fold. Similarly, through the use of pKa-optimized ionizable amino lipids (such as DLin-KC2-DMA) the transfection can be further improved. The result of helper-lipid-enhanced LNPs containing pKa-optimized ionizable lipids is a 16-fold improvement in transfection efficiency for plasmid-DNA.

45.

Nanocarriers for Gene Therapy: Recent approches

Tariq Mahmood, University of Central Punjab, tariqmahmood750@gmail.com

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Biodegradable polymeric nanoparticles have the potential to be safer alternatives to viruses for gene delivery; however, their use has been limited by poor efficacy in vivo. Several approaches are being anticipated for fabrication of polymeric gene delivery nanoparticles and to evaluate their efficacy. Various techniques of synthesizing polymeric nanoparticles are discussed in this article with special focus on anticancer therapeutics. Emerging platform for cancer therapy like block copolymers, cyclodextrins, copolypeptides, charged lipids, and cholesterol-modified small interfering RNA (siRNA) via lipoprotein-based advanced Nanocarriers with an ability to successfully deliver siRNA into target cells, are major focus of this article.

46.

Engineering platelets for the delivery of mRNA

Stefanie Novakowski, University of British Columbia, s.novakowski@gmail.com

Vivienne Chan, University of British Columbia, vivienne.vc@gmail.com

Simon Law, University of British Columbia, hello@lawsimon.com

Christian Kastrup, University of British Columbia, ckastrup@mail.ubc.ca

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There is a large research effort to develop materials that controllably deliver therapeutics and nucleic acids to specific areas of disease. Within the bloodstream platelets naturally perform this function by releasing small molecules and biological macromolecules at sites of vascular injury. This includes the release and transfer of RNA-containing microparticles, leading to altered protein expression in nearby cells. The natural role of platelets as delivery vehicles provides strong motivation for utilizing these cells as carriers of RNA-based therapeutic agents. Previous work has shown that platelets can be transfected with synthetic miRNA, however direct genetic modification of platelets with messenger RNA (mRNA) has not yet been achieved. My project aims to develop ways to directly introduce mRNA for use in platelets and for the release and delivery to other cells following platelet activation. To complete this aim, in vitro transcribed RNA was encapsulated within nanoliposomes and incubated with platelets ex vivo to allow for delivery. Using this approach, I have shown that exogenous mRNA encapsulated within these nanoliposomes can be delivered to platelets via endocytosis, and this mRNA is controllably released following activation of platelets with specific agonists. Future work will focus on testing whether this mRNA can either be translated by platelets, or transferred to and utilized in the target cells. This is a novel approach for the delivery of RNA to platelets, with many potential long-term applications in drug delivery.

47.

Enhanced Gene Delivery to a Kidney-derived Cell Line with Gentamicin-conjugated PEI-based Nanoparticles

Fatemeh Oroojalian, Department of Medicinal Chemistry,College of Pharmacy, University of Minnesota,8-101 Weaver-Densford Hall 308 Harvard St. SE, Minneapolis, USA., orooj002@umn.edu

F. Oroojalian1,2,3, W. T. Shier2*, A. H. Rezayan1, M. Ramezani3*

1 Department of Life Science Engineering, Faculty of New Sciences and Technologies, University of Tehran, Tehran, P.O. Box 14395-1561, Iran.orooj002@umn.edu

2 Department of Medicinal Chemistry, College of Pharmacy, Minneapolis, University of Minnesota, USA. shier001@umn.edu

3 Research Center, Department of Pharmaceutical Biotechnology, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, P.O. Box 91775-1365, Iran. RamezaniM@mums.ac.ir

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Gene therapy holds great promise as a treatment modality for kidney disease. To be useful, the gene therapy technique must be cell-type specific. Of particular interest are therapies targeting proximal tubule cells, which are known to express some relatively specific markers, including megalin, which contains several binding motifs including one for oligocations like gentamicin and neomycin. As a strategy for targeting megalin-expressing cells, we undertook the preparation of PEI-gentamicin conjugates and their evaluation as gene delivery agents with a kidney-derived cell type, Madin-Darby Canine Kidney (MDCK) cells. Polyethyleneimines (PEI, 10 and 25 kDa) were derivatized at a range of levels by alkylation with 6-bromohexanoic acid to yield alkylcarboxylate-PEIs that were then conjugated to various amounts of gentamicin by forming amide linkages using the water-soluble carbodiimide, ECDI. Ethidium bromide-DNA exclusion assays showed the conjugates retained full DNA-binding ability. Modified PEIs were complexed with enhanced green fluorescent protein (EGFP) plasmid DNA and the particle size and zeta potential of the polyplexes determined by Dynamic Light Scattering (DLS) and Laser Doppler Velocimetry (LDV), which showed that the modified PEIs effectively condense plasmid DNA and form 80-160 nm nanoparticles. Gentamicin-conjugated polyplexes exhibited low cytotoxicity with MDCK cells using the MTT assay. Transfection activity of gentamicin-conjugated polyplexes measured using flow cytometry was significantly increased (2.5-3 fold) relative to unmodified PEI. Thus, modifying vectors by gentamicin conjugation appeared to be an effective strategy for a kidney-derived cell line, MDCK.

48.

Lipid Nanoparticles Encapsulating siRNAs Against the Androgen Receptor to Treat Advanced Prostate Cancer

Joslyn Quick, University of British Columbia, joslynquick@alumni.ubc.ca

Kaixin Zhang, Vancouver Prostate Centre, kaixinkevin.zhang@vch.ca

Yuen Yi C Tam, Department of Biochemistry and Molecular Biology at the University of British Columbia, tam7@mail.ubc.ca

Paul S Rennie, Vancouver Prostate Centre, prennie@prostatecentre.com

Pieter R Cullis, University of British Columbia, pieterc@mail.ubc.ca

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The androgen receptor (AR) regulates the growth and viability of the prostate gland, and plays a critical role in the progression of prostate cancer (PCa). Our lab has developed a long-circulating lipid nanoparticle (LNP) formulation of small-interfering RNA (siRNA), specifically targeted to the prostate-specific membrane antigen, to silence AR. With this system, we have achieved almost 50% knockdown of AR mRNA 14 days after i.v. administration in mice bearing human PCa xenograft tumours.

In these past studies, we have focused on silencing the full-length AR using siRNA (siAR-fl) against a region encoding the C-terminal ligand-binding domain. However, as PCa progresses there is increased expression of constitutively active AR splice-variants that lack the whole ligand-binding domain, and mediate resistance to current available therapies.

SiRNA sequences have been designed for binding the N-terminal-encoding region of AR mRNA, and screened for silencing in vitro in PCa cells expressing both full-length and variant AR. An optimal siRNA sequence (siAR-v) has been taken forward and shown to have specific silencing effects in vitro in five additional PCa cell lines. In addition to silencing both full-length and variant AR, cell treatment with LNP-siAR-v also results in improved silencing of an AR target gene, prostate specific antigen (PSA), as well as reduced cell proliferation, as compared to LNP-siAR-fl and untreated controls. Future studies will focus on testing siAR-v efficacy in vivo using our targeted, long-circulating LNP, as well as the optimization of an siRNA and small-molecule combination therapy utilizing siAR-v and a LNP-loadable docetaxel derivative.

49.

Intracellular Trafficking and Endosomal Escape of Nanoparticles for mRNA Delivery

Gaurav Sahay, Oregon State University, sahay@OHSU.edu and Anna Brown, Oregon State University, broanna@ohsu.edu

Marc Kai, PostDoctoral Fellow, Oregon State University, kai@OHSU.edu

Conroy Sun, Assistant Professor, Oregon State University, sunc@OHSU.edu

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RNA therapeutics represents a new class of modern medicine for targets considered undruggable (1). Nanoparticle based platforms remain the most advanced in clinical trials for RNA based drugs (2). Yet, the lack of mechanistic insights into the cellular trafficking and endosomal escape of nanoparticles has become a major hurdle for efficient intracellular delivery (3). Nanoparticles enter cells through highly dynamic endocytic pathways that are routed towards lysosomes for degradation (4,5).

This study aims to 1) Dissect the gateways of cellular entry and subsequent itinerary of lipid nanoparticles that deliver messenger RNA (mRNA) inside cells through the use of state of the art microscopy techniques like super-resolution imaging, high content screening, spinning disk confocal microscopy in combination with different markers of endocytosis and/or inhibitors of select trafficking pathways 2) Identify small molecules that potentiate endosomal escape through disruption of key steps in endocytic trafficking. We have identified the key features that are involved in the entry and endosomal escape of mRNA to the cytosol. Unlocking the mechanisms of intracellular transport will guide in the development of novel nanoparticles that can efficiently delivery mRNA inside cells for therapeutic production of proteins for the treatment of wide variety of diseases.

Acknowledgements: We would like to thank Dr. Robbie Allen and Dylan Nelson for support within the high throughput facility at Oregon Translation Research and Development Institute (OTRADI). This work was supported by the College of Pharmacy OTRADI grant and start up funds of G.S.

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50.

A Combinatorial Approach for the Treatment of Ovarian Cancer Using Gene and Chemotherapies

Canan Schumann, Oregon State University, schumanc@onid.orst.edu

Olena Taratula, Oregon State University, olena.taratula@oregonstate.edu

Cesar Escalante, Oregon State University, escalanc@onid.orst.edu

Oleh Taratula, Oregon State University, oleh.taratula@oregonstate.edu

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We have developed a combinatorial synergistic approach for the treatment of ovarian cancer using a tumor targeted siRNA drug delivery system DDS and the first line chemotherapy agent cisplatin. We have synthesized a targeted DDS using a generation 4 poly(propylene imine) dendrimer (PPIG4) as the nanoplatform. The PPIG4 was chosen because the distal ends of the polymer consist of primary amines which at physiological pH are protonate yielding a highly positively charged surface that can complex, through electrostatic interactions, the negatively charged phosphate backbone of the siRNA molecule. After siRNA complexation the DDS is conjugated with a bifunctional polyethylene glycol (PEG), and final modification with the LHRH targeting moiety at the PEG's distal ends. This DDS was designed to deliver DJ-1 targeted siRNA to an ovarian cancer cell model where it suppresses DJ-1 a key protein that is upregulated and responsible for an increased antioxidant stress response, proliferation, as well as the overall survival of ovarian carcinomas. After 24hr siRNA suppression the cells were then treated with cisplatin and showed an overall decrease in proliferation in vivo and in vitro, as well as an increase in apoptosis leading to dramatic decrease in cell viability. Both treatments alone work well but when combined into a combinatorial modality shows superior synergy over each of the treatments alone. It is our goal to use gene therapy in combination with chemotherapy to 1.) Decrease the amount of chemotherapy needed thereby decreasing overall chemotherapeutic side effects and 2.) Increase chemotherapy efficacy thereby reducing 5 year patient survival mortality.

51.

Microbubbles and Ultrasound Improve Polymeric Gene Delivery to the Brain

James-Kevin Tan, University of Washington, jkyt@uw.edu

Drew Sellers, University of Washington

Don Maris, University of Washington

Nathaniel Coulson, University of Washington

Binhan Pham, University of Washington

Pierre Mourad, University of Washington

Phil Horner, UW, phorner@uw.edu

Suzie Pun, UW, spun@uw.edu

The human body has natural mechanisms to regenerate neurons in the brain after neural death; however, proliferation and differentiation of neural progenitor cells (NPCs) and neural stem cells (NSCs) in the subventricular zone (SVZ) is not enough to restore function. Gene therapy has emerged as a promising strategy to enhance the differentiation of NPCs and NSCs to neurons. Our promising polyplex, composed of nucleic acids and a PCL-SS-p(GMA-TEPA)-co-OEGMA) polymer, has demonstrated effective gene transfer in the brain after intraventricular injection. Nevertheless, the choroid plexus epithelium that surrounds the SVZ remains a major obstacle and prevents the penetration of vectors into the brain. Recently, transient disruption of the blood-brain barrier by microbubble (MB)-enhanced ultrasound (US) has allowed the permeation of macromolecules into the brain with minimal safety concerns. In this work, custom slightly cationic (SCat) MBs were prepared and compared to commercially available Definity® (Def) MBs in their ability to temporarily permeabilize murine choroid plexus epithelium in vitro and after intraventricular injection in vivo. Both MBs had similar diameters but differed in surface charge. In transwell assays with choroid plexus monolayers, sonoporation by the MBs and US increased the permeation of dextrans across the transwell. When coupled with luciferase-encoding polyplexes and administered in vivo, the SCat MBs and US increased the transfection of brain cells better than the Def MBs with US by over 3-fold. Enhanced permeation into the SVZ by MB and US application is a viable method for increasing gene transfer in the brain and merits more investigation.

52.

Tracking the Transport of Intact DNA in Gene Delivery using FRET Labeled Beacons

Sriram Vaidyanathan, University of Michigan, svaidy@umich.edu

Junjie Chen, University of Michigan, Ann Arbor

Bradford G. Orr, University of Michigan, Ann Arbor

Mark M. Banaszak Holl, University of Michigan, Ann Arbor

Our limited understanding of how polymer-DNA complexes, termed polyplexes, are internalized into cells, transported to the cell's nucleus and then translated into functional proteins hinders the development of new non-viral vectors. It is well known that gene expression is due to a small fraction of the delivered DNA. A major limitation with present imaging techniques is that they cannot distinguish functional intact DNA from degraded DNA. We use a DNA nucleotide labeled with a dye pair that exhibit Forester Resonance Energy Transfer (FRET). This two color DNA construct emits with greater intensity in the red region when intact and emits with greater intensity in the green region when cleaved. Two color molecular beacon oligonucleotides containing are delivered using various polycationic polymers. Flow cytometry and confocal microscopy are used to quantify the intracellular degradation of the beacon.

53.

Niemann-Pick C1 inhibitor enhances intracellular retention and gene silencing capability of lipid nanoparticle formulations of siRNA

Haitang Wang, University of British Columbia, Haitangw@mail.ubc.ca

Yuen Yi C. Tam, University of British Columbia, christam@gmail.com

Sam Chen, University of British Columbia, s.chen@alumni.ubc.ca

Josh Zaifman, University of British Columbia, jzaifman@chem.ubc.ca

Pieter R. Cullis, University of British Columbia, pieterc@mail.ubc.ca

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A recent study has reported that approximately 70% of internalized siRNA is recycled to the extracellular media. Thus, lowering siRNA recycling to the extracellular space appears to be a promising strategy to improve the intracellular amount of siRNA and subsequently gene silencing. Niemann-Pick type C 1 (NPC1) is a membrane protein implicated in the intracellular transport of cholesterol in mammals. It has been reported that NPC1-deficient cells show enhanced cellular retention of siRNA and increased gene silencing. NPC1-B, a small molecule inhibitor of NPC1, has been demonstrated to effectively block Ebola virus infection by interfering viral glycoprotein binding to NPC1. Here, we assess the effects of NPC1-B in lipid nanoparticle (LNP)-mediated siRNA delivery and gene silencing. Our results showed that NPC1-B increases intracellular accumulation of LNP-siRNA and gene silencing of a marker gene GAPDH by four folds. In addition, NPC1-B does not neutralize any acidic organelles, suggesting that the effect of NPC1-B in gene silencing may be different from pH-raising agents, such as bafilomycin and chloroquine. The recycling test showed that NPC1-B significantly delays siRNA recycling to the extracellular media. Furthermore, co-localization microscopy confirmed that NPC1-B causes more LNP-siRNA to reside in late endosomes/lysosomes, leading to a slow and controlled release of siRNA into the cytosol. These findings reveal a role of NPC1-B in delaying LNP-siRNA recycling and enhancing LNP-mediated siRNA delivery and gene silencing.

54.

Evaluation of Tween 85 Modified Polyethylenimines for Antisense oligomer Delivery

Mingxing Wang, Carolinas Medical Center, mingxing.wang@carolinashealthcare.org

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A series of Tween 85 modified low molecular weight polyethylenimine copolymers (Zs) has been investigated for their potential to enhance delivery of an antisense oligomer (AOs)in vitro and in dystrophic mdx mice. Z polymers significantly enhanced AO-induced exon-skipping in a GFP reporter-based myoblast culture system. Application of optimized formulations of Zs with AO targeted to dystrophin exon 23 demonstrated a significant increase in exon-skipping efficiency in dystrophic mdx mice. Consistent with our observations in vitro, optimization of molecular size and the HLB of plymers are important factors to achieve enhanced AO delivery in vivo. Observed cytotoxicity of the Zs was lower than Endo-porter and PEI 25K. Tissue toxicity of Zs in muscle was not clearly detected with the concentrations used, indicating the potential of the Zs as effective and safe AO carriers for treating diseases such as muscular dystrophy.

Poster Session 2: Thursday, September 17 at 3:30 – 5:00 pm

1.

Nanostructured glycopolymer-functional liposomes to elucidate carbohydrate receptor mediated targeting

Jasmin Chen, University of Washington, jbrchen@uw.edu

Hye-Nam Son, University of Washington, hyenam77@gmail.com

Patrick Stayton, University of Washington, stayton@uw.edu

John Hill, University of Washington, hilljb@uw.edu

Anthony Convertine, University of Washington, convertine@gmail.com

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Carbohydrates play an essential role in a myriad of biological processes, including cellular adhesion and migration, organismal development, infectious disease, and the immune response. One key aspect of interest is the high specificity of carbohydrate-protein interactions for the targeting of glycans to receptors on cells and tissues. A prime example of carbohydrate receptor-mediated targeting in nature can be seen in the alveolar macrophage, a resident cell of the lung that serves as a predominant effector of the pulmonary innate immune response. Alveolar macrophage express carbohydrate receptors that enable them to recognize microbial-associated markers, localize and isolate infectious events, and trigger adaptive immunity. The macrophage's ability to bind and internalize microorganisms via endocytosis and phagocytosis in the absence of opsonins makes them favorable not only for host defense, but paradoxically for pathogen inhabitation and infection. Therefore, understand the nuances of receptor-mediated uptake pathways is critical to improve delivery and therapeutic applications involving host effector cells, such as the macrophage.

Well-defined glycopolymers can by synthesized utilizing reversible addition-fragmentation chain transfer (RAFT) polymerization and subsequently incorporated into delivery vehicles aimed at targeting cell surface receptors via multivalent binding. In this study, we synthesized and formulated mannose and galactose glycopolymers copolymerized with a cholesterol methacrylate, enabling the polymers to be incorporated into liposomes to elucidate receptor-mediated uptake in various macrophage cell lines. The significance of this study is to elaborate the contribution of carbohydrate receptors in cell targeting and leverage this knowledge to enhance drug delivery applications in receptor- targeted drug delivery strategies.

2.

Development of a drug delivery system based on surface modifications for efficient lymphatic uptake to treat metastatic melanoma

Bhuvana Doddapaneni, Oregon State University, bhuvanshyam@gmail.com

Sergiy Kyryachenko, Universite de pierre, skyryachenko@gmail.com

Sharmin Chagani, Oregon State University, chaganis@onid.oregonstate.edu

Deepa A. Rao, Pacific University, deeparao@pacificu.edu

Arup K. Indra, Oregon State University, arup.indra@oregonstate.edu

Adam W. G. Alani, Oregon State University, adam.alani@oregonstate.edu

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Purpose

The goal of this project is to develop a combinatorial drug delivery system using three chemotherapeutic drugs Docetaxel(DTX), Everolimus(EVR) and LY294002(LY) for the treatment of metastatic melanoma by modifying the surface properties of the delivery system for efficient lymphatic uptake.

Methods

(DTX+EVR+LY) combination nanoparticles were prepared using poly(ethylene glycol)-block-poly(caprolactone) mPEG-b-PCL and hoocPEG-b-PCL polymers using the solvent evaporation method. Nanoparticles were characterized for size and drug loading using DLS & HPLC techniques. Neutral (100%mPEG), slightly charged (60%mPEG+ 40%hoocPEG), and highly charged (100%hoocPEG) combination nanoparticles were prepared for evaluating their lymphatic uptake and ability to treat metastatic melanoma. The prepared nanoparticles were injected subcutaneously once a week for 3 weeks into wild type(TyrNRasRXRL2/L2) and mutant(TyrNRasRXRep-/-) metastatic melanoma mice near the inguinal lymph nodes at 20mg/kg of each drug. Inguinal and axillary lymph nodes were collected and analyzed using Fontana Masson staining after 4 weeks to evaluate efficacy and loss in mice body weight was monitored to evaluate toxicity.

Results

The prepared nanoparticles had a size of around 46nm and could solubilize up to 2mg/mL of each drug. The (60%mPEG+40%hoocPEG)combination nanoparticles were highly effective in reducing the proliferation of melanocytes at both axillary and inguinal lymph nodes in both metastatic mice models, while the 100%mPEG nanoparticles were effective only at the site of injection (Inguinal nodes).

Conclusion

We have developed an effective nanoparticle system that has preferential accumulation in the lymphatic system based on its surface properties for treating metastatic melanoma.

3.

Development of dual functional nanoparticles to orally deliver siRNA for treatment of Inflammatory Bowel Disease

Shrey Kanvinde, University of Nebraska Medical Center, shrey.kanvinde@unmc.edu

Suthida Boonsith, University of Nebraska Medical Center, boonsith.suthida@unmc.edu

Jing Li, University of Nebraska Medical Center, jing.li@unmc.edu

David Oupicky, University of Nebraska Medical Center, david.oupicky@unmc.edu

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Purpose:

Inflammatory Bowel Disease (IBD) is a chronic inflammation of the gastrointestinal tract. The etiology for IBD is thought to be a complex combination of genetic and environmental factors as a consequence of abnormal mucosal immune response to gut microbiota. Upregulation of pro-inflammatory cytokines like TNFα, IL-6 is a hallmark of IBD. Systemically administered TNFα antibodies are the mainstay of IBD therapy. However, they cause systemic immunosuppression exposing patients to opportunistic infections. Recently, blockade of chemokine receptor CXCR4 has been implicated in ameliorating murine IBD. The purpose of this study is to develop an oral system that can simultaneously deliver CXCR4 antagonist and TNFα siRNA locally to the inflamed colon.

Methods:

Polymeric CXCR4 antagonist (PCXA) was synthesized using Michael addition of CXCR4 antagonist Plexirafor and bisacrylamide crosslinker. Mixed nanoparticles containing chitosan, PCXA and siRNA were formulated. siRNA complexation was analyzed using agarose gel electrophoresis. CXCR4 inhibition was determined using CXCR4 redistribution assay. siRNA protecting ability against RNase, simulated gastric and colonic fluids was assessed by agarose gel electrophoresis. siRNA delivery to mouse macrophages in vitro was investigated using flow cytometry and confocal microscopy.

Results:

Our data demonstrates that formulating PCXA as nanoparticles with chitosan improved its properties as an oral delivery vehicle without hampering its CXCR4 antagonist activity. Mixed nanoparticles showed better siRNA protection and delivered more siRNA as compared to PCXA only formulations.

Conclusion:

Mixed nanoparticles show good properties as an oral delivery system in vitro. The results obtained make these nanoparticles a promising candidate for treating IBD in vivo.

4.

Biodegradable PEG Nanocarriers Build from PEG-Acetal-Dimethacrylates for Specific Immunotherapy

Hannah Koehring, Institute of Organic Chemistry, University of Mainz, Germany and Department of Dermatology, University Medical Center Mainz, Germany, h.koehring@uni-mainz.de

Iris Bellinghausen, Department of Dermatology, University Medical Center Mainz, Germany

Joachim Saloga, Department of Dermatology, University Medical Center Mainz, Germany

Holger Frey, Institute of Organic Chemistry, University of Mainz, Germany

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During the last decades, the number of allergic patients has increased dramatically (about 300 Mio patients worldwide). The only available causal oriented therapy is the specific immunotherapy (SIT). SIT reduces the allergic symptoms, but also exhibits some disadvantages, i.e., it is a long-lasting procedure, and in a few cases severe side effects like an anaphylactic shock can occur. In this work we have developed a method to encapsulate the allergen used during specific immunotherapy into nanoparticles to avoid severe side effects during treatment.

We have synthesized a novel type of difunctional, water soluble poly(ethylene glycol) dimethacrylate macromonomer with acetal-sites that degrade at acidic pH. The allergen and the macromonomer were entrapped inside liposomes as templates that were produced by dual centrifugation. Radical polymerization of the methacrylate groups inside the liposomes generated PEG-nanocarriers. The allergen-loaded nanocarriers were approximately 150-200 nm in size and showed low polydispersity indices. In-vitro studies demonstrated that dendritic cells (DCs) internalize the protein-loaded, non-toxic PEG-nanocarriers. Furthermore, we demonstrate that the nanocarriers effectively shield the allergen cargo from detection by immunoglobulins on the surface of basophilic leucocytes, which is supported by cellular antigen stimulation tests. Uptake of nanocarriers into DCs does not lead to cell maturation; however, the released allergen was capable of inducing immune responses.

5.

Multivalent M2pep for improving selective toxicity to M2-like tumor associated macrophages

Chayanon Ngambenjawong, University of Washington, ngamc@uw.edu

Maryelise Cieslewicz, Univerisity of Washington, mcieslew@uw.edu

Joan G. Schellinger, PhD, University of Washington, jschellinger@sandiego.edu

Suzie H. Pun, PhD, University of Washington, spun@uw.edu

Targeted depletion of M2-like tumor associated macrophages is a promising strategy for improving therapeutic outcome in various types of cancer. In this study, multivalent display of M2 macrophage-targeting peptide (M2pep) and pro-apoptotic peptide (KLA) was investigated in terms of potency and selectivity to M2 macrophages over M1 macrophages. Monovalent, divalent and tetravalent M2pep were first synthesized and investigated for binding activity. Divalent M2pep exhibited the best M2 macrophage-binding activity and selectivity. Surprisingly, divalent and tetravalent M2pep also showed selective toxicity to M2 macrophages even in the absence of cargo. To investigate the effect of targeting peptide-to-cargo ratio on toxicity selectivity to M2 macrophages, M2pepKLA, [M2pep]2[KLA] and [M2pep]2[KLA]2 were synthesized. Among the three constructs tested, [M2pep]2[KLA] was the most potent and also had the best selectivity to M2 macrophages over M1 macrophages. Together, this study suggests the possibility of using multivalent display of M2pep to improve M2 macrophage-selective toxicity.

6.

Nanoparticle functionalized biodegradable polymer for immune-mediated enhancement of wound healing

Emeka Okeke, University of Manitoba, umokeke@myumanitoba.ca

A major priority following injury to the skin is the prevention of bacterial infection. Injury to the skin through burns and lacerations is a common occurrence and the development of septic wounds is a major problem in the clinic. We recently showed that a subset of CD4+ T cells called regulatory T cells (Tregs) ameliorate inflammation in bacterial infection (Okeke et al, J. Immunol. 2014; 193: 655-662). Previous reports revealed that Tregs express the chemokine receptor CCR4 and are highly responsive to the chemokine CCL22 (Iellem et al, J. Exp. Med. 2001; 194: 847-853). Hyaluronic acid (HA) is a linear polysaccharide found in the extracellular matrix of higher animals. HA is an attractive building block for biocompatible polymers and can easily be modified for particular application (Ossipov et al, Macromolecules 2013; 46:4105-4113). Additionally, HA is also important in wound healing and is therefore a suitable delivery agent for wound dressing. Herein, we will investigate the use of a HA-based hydrogel for the sustained release of the chemokine CCL22 for the preferential induction of Tregs to sites of skin injury. HA will be cross-linked with a suitable polymer for the formation of a hydrogel incorporating the chemokine CCL22. Additionally, hydrogel incorporation of antibacterial nanoparticles can accelerate wound healing. Since HA is biologically relevant in wound healing, a hydrogel film based on HA has great potential for use in wound dressing and the sustained release of the chemokine CCL22 can induce preferential trafficking of Tregs to wound sites and accelerate wound healing.

7.

Development of Anti-Inflammatory Nanoparticles for Inflammatory Diseases

Hong Yang, Child & Family Research Institute; University of British Columbia, hongyang36@gmail.com

Mingyao Liu, Latner Thoracic Surgery Research Laboratories, University Health Network, Toronto General Research Institute; Department of Surgery, Faculty of Medicine, University of Toronto, Canada, mingyao.liu@utoronto.ca

Stuart Turvey, BC Children's Hospital and Child & Family Research Institute; Department of Pediatrics, University of British Columbia, Canada, sturvey@cfri.ca

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Manipulation of immune responsiveness using nano-devices provides a new strategy to treat human diseases. Toll-like receptor (TLR) signaling plays a central role in the pathophysiology of many acute and chronic human inflammatory diseases, and pharmacological regulation of TLR responses is anticipated to be beneficial in many of these inflammatory conditions. In seeking nanoparticles that potently inhibit TLR signaling, we screened a library of physiologically stable peptide-gold nanoparticle hybrids and discovered a unique class of nanoparticles which exhibit a broad inhibitory activity on TLR signaling, inhibiting signaling through TLRs 2, 3, 4, and 5. As exemplified using TLR4, the nanoparticles were found to inhibit both arms of TLR4 signaling cascade triggered by the prototypical ligand, lipopolysaccharide (LPS). Further mechanistic studies showed that the inhibitory activity of the nanoparticles was through blocking the activation of two pro-inflammatory transcription factors, the nuclear transcription factor kappa B (NF-kB) and interferon regulatory factor 3 (IRF3), triggered by LPS. This inhibitory activity was further confirmed in human peripheral blood mononuclear cells (PBMCs). Through structure-activity relationship studies, we identified the key chemical components of the hybrids that contribute to their immunomodulatory activity. Specifically, the hydrophobicity and aromatic ring structure of the amino acids on the peptides were essential for modulating TLR4 responses. This work enhances our fundamental understanding of the role of nanoparticle surface chemistry in regulating innate immune signaling, and identifies specific nanoparticle hybrids that may represent a novel class of anti-inflammatory therapeutics for human inflammatory diseases.

8.

Improved local delivery of HIV nanotherapies to the colorectum

Taarika Babu, Johns Hopkins School of Medicine, tbabu1@jhmi.edu

Katharina Maisel, University of Chicago, katha.maisel@gmail.com

Abhijit Date, Johns Hopkins School of Medicine, abhijitdatecnm@gmail.com

Craig Hendrix, Johns Hopkins School of Medicine, chendrix@jhmi.edu

Richard Cone, Johns Hopkins University, cone@jhu.edu

Laura Ensign, Johns Hopkins School of Medicine, lensign@jhmi.edu

Justin Hanes, Johns Hopkins School of Medicine, hanes@jhmi.edu

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Every year, 2-3 million people worldwide are infected with HIV. Receptive anal intercourse is the cause for a significant number of these infections, particularly in the United States, as rates of HIV transmission per sexual act are 20-fold higher in the colorectum than in the vagina. Approaches for HIV pre-exposure prophylaxis (PrEP) to prevent colorectal HIV infection include orals pills and rectal gels. Oral drug administration can lead to undesired systemic drug exposure and relatively low drug concentrations locally in the colorectal tissue. Topical gel formulations are limited by their high osmolality, which can cause toxicity and fluid secretion that drives expulsion, and high viscosity, which limits distribution into the colorectal folds. Furthermore, drugs with low water solubility are typically micronized in these formulations, which we have found further limits their colorectal distribution. We have found that drug formulations need to be both non-adhesive and smaller than the colorectal mucus mesh, which acts as a steric and adhesive barrier to drug delivery in the colorectum. Here, we demonstrate that muco-inert drug-loaded nanoparticles and nanocrystals administered in a hypotonic enema vehicle can effectively penetrate the mucus barrier, leading to improved local colorectal distribution with minimal toxicity. Such a formulation may improve colorectal HIV PrEP while minimizing adherence issues.

9.

Lipid-coated PLGA nanoparticles conjugated with a dual-function antibody for targeted delivery of ARVs to α4β7 expressing T cells

Shijie Cao, Department of Bioengineering, University of Washington, sjcao@uw.edu

Yonghou Jiang, University of Washington, yhj@uw.edu

Kim A. Woodrow, University of Washington, woodrow@uw.edu

A reservoir of latently infected CD4+ T remains a barrier to achieving complete HIV-1 eradication and cure. These latently infected cells are found primarily in the gut-associated lymphoid tissue (GALT). Gut CD4+ T cells typically express α4β7 integrin, which mediates cell migration to the GALT and also serves as a HIV-1 binding site. It has been shown that an anti-α4β7 antibody could target gut T cells, as well as block HIV-1 binding to uninfected T cells. However, the antibody alone can neither eliminate HIV-1 infected cells nor stop virus production. Here, we conjugated anti-α4β7 antibodies to lipid-coated PLGA nanoparticles (A4B7-LPNPs) loaded with protease inhibitors. LPNPs were synthesized by an optimized single-emulsion method and the antibodies were conjugated at 30% efficiency to LPNPs. Tipranavir (TPV) and atazanavir (ATV) were encapsulated individually into the LPNPs with the average drug loading of 8.0% (TPV) or 1.3% (ATV), respectively. We found that up to 40% of the antibodies shed from LPNPs in PBS within 48 hours. In vitro studies showed antibody specific binding of A4B7-LPNPs to HUT-78 T cells, which highly express α4β7, but showed no binding to a HeLa cell line. These A4B7-LPNPs will be administered in vivo to assess biodistribution and used in vitro and ex vivo models to measure antiviral activity. We expect our PI loaded A4B7-LPNPs to target latently infected gut T cells, where the delivered PIs could block infected cells from producing new virions and the delaminated antibodies could protect uninfected T cells by blocking virus binding to α4β7.

10.

Nanoparticles of immune-tolerant elastin-like polypeptide (iTEPs) for delivering CTL vaccine

Shuyun Dong, University of Utah, shuyun.dong@utah.edu

Kristin Parent, Michigan State University, kparent@msu.edu

Mingnan Chen, University of Utah, mingnan.chen@utah.edu

Vaccines that induce cytotoxic T lymphocyte (CTL) responses are important prophylactic and therapeutic treatments against cancer and infections. Vaccine carriers are known to enhance CTL responses induced by vaccines but a search for more effective carriers is warranted. Elastin-like polypeptides (ELPs) possess features appealing to CTL vaccine delivery. However, they have not yet been reported as CTL vaccine carriers. Because humorally immunogenic carriers jeopardize the potency of their CTL vaccine payloads, in this study, we created immune tolerant ELPs, termed iTEPs, and then explored the iTEPs as CTL vaccine carriers to improve vaccine-induced responses. Four sets of iTEPs having novel monomer motifs were designed and generated as recombinant proteins. These iTEPs were confirmed to be non-immunogenic in mice and their phase transition properties were characterized. An iTEP nanoparticle (NP) was assembled from an amphiphilic iTEP copolymer with a CTL peptide vaccine, SIINFEKL. The NP promoted epitope presentation by dendritic cells and enhanced the vaccine-induced CTL responses in vivo. Furthermore, by modulating the stability of iTEP NPs, we revealed an intriguing relationship between carrier stability and CTL vaccine-induced responses. In conclusion, our non-canonical ELPs (iTEPs) broadened our understanding about the ELP sequence motif. We also demonstrated that ELPs can be used as vaccine carriers that enhance CTL responses, a very important but previously untested medical application. Finally, thanks to the precisely tunable nature of iTEPs, we created a spectrum of CTL vaccine delivery NPs with varied stability and revealed that the most effective carrier should have a dynamic, environment-responsive stability.

11.

A Potent Anti-inflammatory Agent Targeting Toll-Like Receptor Signaling Identified from Marine Sponge Extracts

Shan-Yu Fung, University of British Columbia, Child & Family Research Institute, shanefung@gmail.com

Vladimir Sofiyev, Kate Woods, Raymond J. Andersen, University of British Columbia, Vancouver, British Columbia, Canada

Julia Schneiderman, Aaron F. Hirschfeld, Rachel E. Victor, Department of Pediatrics, British Columbia Children's Hospital and Child & Family Research Institute, Vancouver, British Columbia, Canada

Nicole J. de Voogd, Netherlands Centre for Biodiversity Naturalis, Leiden, The Netherlands

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While Toll-like receptors (TLRs) play a critical role in innate immunity, activation of TLR signaling pathways is also associated with many harmful inflammatory diseases. Identification of novel anti-inflammatory molecules targeting TLR signaling pathways is anticipated to empower the development of new treatment approaches for acute and chronic inflammation.

We performed high throughput screening to isolate TLR inhibitors from crude marine sponge extracts and we identified girolline. The top hits were validated by looking at their cytotoxicity and dose-dependent activity. After several cycles of screening and validation, the leading compound girolline was identified. We demonstrated that girolline inhibits signaling through both MyD88-dependent and–independent TLRs (i.e., TLR2, 3, 4, 5 and 7), in variety of relevant cell types, including human peripheral blood mononuclear cells (PBMCs) and macrophages. It also significantly lowers the cytokines (IL8 and IL6) production induced by flagellin (TLR5 ligand). The molecular target of girolline was determined to be downstream in the TLR signaling cascade, distal to TRAF6, but not directly affecting NF-kappaB activation. In addition, the structure-activity analysis indicated that the whole chemical structure of girolline is necessary for its bio-activity. Together these data identify the sponge natural product girolline as a potent inhibitor of TLR signaling.

12.

Dendritic cell presentation of class II antigen delivered by PLG nanoparticles favors immune tolerance

Robert Kuo, University of Michigan, Ann Arbor, robrtkuo@umich.edu

Eiji Saito, University of Michigan, Ann Arbor, esaito@umich.edu

Lonnie D. Shea, Professor, University of Michigan, Ann Arbor, ldshea@umich.edu

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Autoreactive T cells play major roles in the occurrence of autoimmune diseases. In experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis, disease can be initiated by adoptive transfer of T cells from mice immunized against myelin. Interestingly, we have demonstrated that administration of poly(lactide-co-glycolide) (PLG) nanoparticles loaded with class II myelin antigen were able to limit the peak severity of EAE clinical score. To investigate the immune tolerance mechanism, PLG nanoparticles were loaded with either ovalbumin (257-264), a class I antigen, or Ealpha (52-68), a class II antigen. Murine bone marrow-derived dendritic cells were treated with antigen-loaded nanoparticles for 24 hours, followed by analysis of antigen presentation and co-stimulatory expression using flow cytometry. Dendritic cells treated with nanoparticles carrying class I antigen resulted in low efficiency of antigen presentation compared to soluble antigen delivery. In addition, the majority of dendritic cells presenting antigen also expressed positive co-stimulatory molecules (CD86, CD80, CD40), providing the necessary inputs for T cell activation. Conversely, dendritic cells treated with nanoparticles carrying class II antigen were very efficient for antigen presentation, at times exceeding levels of antigen presentation resulting from soluble antigen delivery. Moreover, at the highest tested nanoparticle concentration, nearly half the population of dendritic cells presenting antigen lacked expression of positive co-stimulatory molecules while expressing the negative co-stimulatory molecule, PD-L1, providing the necessary inputs to induce T cell anergy. These studies indicate a likely mechanism of EAE abrogation resulting from administration of myelin-loaded PLG nanoparticles.

13.

ANTIBODIES/PEG-PROTEIN A COMPLEX AS A NEW TARGETED DRUG DELIVERY SYSTEM

Gianfranco Pasut, University of Padova, gianfranco.pasut@unipd.it

Katia Maso, University of Padova, katia.maso@studenti.unipd.it

Antonella Grilletto, PhD, University of Padova, antonella.grigoletto@unipd.it

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The positive clinical performances of antibody–drug conjugates (ADCs) have exemplified the promise of targeted oncology therapy. However, there are technical challenges associated with drug conjugation to antibodies, primarily due to heterogeneous degrees and conjugation sites and the conjugate stability. Here a new approach of ADC is presented. Antibodies mediate the delivery of drugs in a non-covalent manner using protein A as drug carrier and antibody chelator. Protein A is able to bind the Fc portion of immunoglobulins, especially IgGs, with an high affinity (Ka= 107-108 M-1). The immunogenicity of protein A was reduced by site-selective PEGylation, which allowed the carrying of the drug at the other side of the polymer end. Protein A PEGylation was based on two different strategies: an enzymatic approach based on Transglutaminase for Gln selective conjugation and N-terminal conjugation with PEG-aldehyde. The two conjugates preserved the secondary structure as determined by CD analysis. DLS and ITC were used to study the stoichiometry of binding and the affinity of the conjugates for Bevacizumab and Rituzimab in comparison to native protein A. The results demonstrated that while the stoichiometry of binding was unchanged, the complex affinity was 10 fold lower for PEG-Gln-Protein A conjugates and unmodified for the PEG-Nter-protein A conjugate. The last was further investigated by FACS. The binding properties of the complex Cy5.5-PEG-Nter-Protein A / Rituximab, was investigated in cell lines with different expression level of CD20. The results showed a high affinity of the complex for the cell-line with the greater expression of CD20.

14.

Polymeric CXCR4 Antagonists for Inhibiting Breast Cancer Growth and Metastasis

Zheng-Hong Peng, University of Nebraska Medical Center, josephpenguu@gmail.com

Jing Li, University of Nebraska Medical Center(jing.li@unmc.edu);

James E. Talmadge, University of Nebraska Medical Center, (jtalmadg@unmc.edu);

Yan Wang, University of Nebraska Medical Center(yan.wang@unmc.edu);

Fei, Yu, University of Nebraska Medical Center(fei.yu@unmc.edu);

Ying Xie, University of Nebraska Medical Center(ying.xie@unmc.edu);

Yi Chen, University of Nebraska Medical Center,(y.chen@unmc.edu) ;

Jindrich Kopecek, University of Utah(jindrich.kopecek@utah.edu);

David Oupicky, University of Nebraska Medical Center, (david.oupicky@unmc.edu).

Breast cancer is one of the most common malignant cancers and the second leading cause of cancer-related death among women in the United States. More than 200,000 women are diagnosed with breast cancer every year, and more than 40,000 are estimated to die of the disease in 2015. In these patients, the cause of death is generally not the primary tumor, but instead metastases to distant organs. The 5-year survival of Stage IV breast cancer is only about 22% . Many studies have highlighted the critical role of chemokine receptor CXCR4 along with its ligand CXCL12 in breast cancer growth and metastases. Silencing CXCR4 expression in breast cancer cells using RNA interference or blocking the CXCL12/CXCR4 interactions by anti-CXCR4 antibody or antagonists significantly impaired the breast cancer metastasis. BKT140 peptide is one of the most potent CXCR4 antagonists due to its high binding affinity (1 nM) towards CXCR4 and its satisfactory safety profile in vivo. However, the intrinsic characteristics of peptides (e.g. short half-life) considerably limit the in vivo application of free BKT140. Our studies aim to improve the plasma residence time and therapeutic efficacy of BKT140 by conjugating the peptide to a biocompatible and water-soluble polymer HPMA using Reversible Addition-fragmentation Chain Transfer (RAFT) polymerization. Our results show that the HPMA copolymers containing BKT140 significantly enhance the inhibition of both primary breast tumor growth and metastasis compared with free peptide in an orthotopic mouse breast cancer model.

15.

Neutrophil-mediated Drug Delivery

Zhenjia Wang, Department of Pharmaceutical Sciences, Washington State University, zhenjia.wang@wsu.edu

Dafeng Chu, Jin Gao

Endothelial cells form a monolayer in lumen of blood vessels presenting a great barrier to delivery of therapeutic nanoparticles into extravascular sites where most diseases occur, such as inflammation disorders and infection. Here we report the development of a novel strategy to deliver therapeutic nanoparticles across this blood vessel barrier via the neutrophil transmigration pathway. Using intravital microscopy of TNF-α-induced inflammation of mouse cremaster venules and a mouse model of acute lung inflammation, we demonstrated that intravenously infused nanoparticles made from denatured albumin were specifically internalized by activated neutrophils, and subsequently the neutrophils migrated across blood vessels and deposited nanoparticles into inflammatory tissues. Furthermore, nanoparticle internalization did not affect neutrophil mobility and functions. Using albumin nanoparticles we were able to deliver anti-inflammatory drugs or antibiotics to inflammatory or infected lungs, dramatically mitigating the lung inflammation induced by LPS (lipopolysaccharide) or infection by P. aeruginosa bacteria. Our results illustrate that neutrophils can be exploited as novel vehicles to mediate the transport of therapeutic nanoparticles across blood vessel barrier, and using this approach we could significantly improve current treatments of acute inflammatory diseases and infection.

16.

Magnet-Optical nanoparticles for Magnetomotive Photoacoustic Imaging

Junwei Li, University of Washington, ljw1209@uw.edu

Bastien Arnal, University of Washington, barnal@uw.edu

Chenwei Wei, University of Washington, cwwei28@uw.edu

Matt O'Donnell, University of Washington, odonnel@uw.edu

Xiaohu Gao, University of Washington, xgao@uw.edu

Photoacoustic imaging has emerged as a highly promising tool to diagnose tumor lesion site with deep tissue penetration. However, image contrast under in vivo conditions is far from optimal due to background signals from tissue. We have previously developed the new concept of magnetomotive photoacoustic (mmPA) imaging, which is capable of dramatically reducing the influence of background signals and producing high-contrast images. Here we addressed two significant advances toward clinical translation of this technology. First, we prepared a new class of compact, uniform, magneto-optically coupled core-shell nanoparticles through localized copolymerization of polypyrrole (PPy) on an iron oxide nanoparticle surface. The resulting multifunctional nanoparticles solve the photo-instability and small-scale synthesis problems previously encountered by the gold coating approach. In parallel, we developed a new generation of mmPA imaging featuring cyclic magnetic motion and ultrasound speckle tracking (USST), whose imaging capture frame rate is several hundred times faster than the photoacoustic speckle tracking (PAST) method we demonstrated previously. These advances enable robust artifact elimination caused by physiologic motions and first application of the mmPA technology in vivo for sensitive solid tumor imaging.

17.

Development of Next Generation Magnetic Nanohybrids for Theranostics

Souvik Biswas, Life Sciences Institute, University of British Columbia, souvik87@mail.ubc.ca

Jayesh A. Kulkarni; Life Sciences Institute, University of British Columbia, Vancouver, BC, Canada, jaykul91@gmail.com

Chris Y. Y. Tam; Life Sciences Institute, University of British Columbia, Vancouver, BC, Canada, tam7@mail.ubc.ca

Sam Chen; Life Sciences Institute, University of British Columbia, Vancouver, BC, Canada, s.chen@alumni.ubc.ca

Ying K. Tam, Life Sciences Institute, University of British Columbia, Vancouver, BC, Canada, yingtam@mail.ubc.ca

Pieter R. Cullis; Life Sciences Institute, University of British Columbia, Vancouver, BC, Canada, pieterc@mail.ubc.ca

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Bio-imageable nanoscale assemblies that can be activated and controlled through external stimuli represent the next generation multifunctional theranostics (therapeutics + diagnostics). MRI contrast agents such as iron oxide nanoparticles, which generate thermal energy by an external AC magnetic field, can be effectively used to induce localized hyperthermia or heat-triggered drug release when co-encapsulated with drugs in lipid nanoparticles (LNP). We have developed well defined, reproducible, easy to scale up, and size controllable (from 30 nm to 100 nm) magnetic nanohybrid systems that consist of either hydrophobic or hydrophilic magnetic nanoparticles encapsulated in various lipid components. We herein present their synthesis and biophysical characterization, as well as their effects in in vitro/in vivo MRI imaging and AC magnetic field-induced drug release.

18.

Indocyanine Green-Loaded Nanoparticles Improve Tumor Contrast for Image-Guided Surgery

Tanner Hill, Department of Pharmaceutical Sciences, University of Nebraska Medical Center, tanner.hill@unmc.edu

Asem Abdulahad, PhD, Virginia Tech, aabdula6@vt.edu

Sneha S. Kelkar, PhD, Wake Forest University Health Sciences, skelkar@wakehealth.edu

Frank C. Marini, PhD, Wake Forest University Health Sciences, fmarini@wakehealth.edu

Timothy E. Long, PhD, Virginia Tech, telong@vt.edu

James M. Provenzale, MD, Duke University, james.provenzale@duke.edu

Aaron M. Mohs, PhD, University of Nebraska Medical Center, aaron.mohs@unmc.edu

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Detection of positive margins, local metastases, and sentinel lymph nodes during tumor resection is critical for long-term patient survival. Near infrared image-guided tumor surgery is a potential method that provides surgeons with visual feedback to facilitate detection of diseased lesions. In this work, we develop hyaluronic acid derived nanoparticles which entrap the near infrared dye indocyanine green, termed NanoICG, for improved delivery of the dye to tumors. Nanoparticles were synthesized by conjugation of a hydrophobic ligand, aminopropyl-1-pyrenebutanamide, to drive self-assembly and loading of ICG in aqueous solution. MDA-MB-231 breast tumor xenografts were established in female nude mice. The contrast agents, free ICG or NanoICG, were delivered intravenously and mice were euthanized at 4 or 24 hours post-injection. Whole-animal imaging showed strong correlation between tumor location and contrast agent fluorescence, and identification of a positive margin was confirmed in one tumor with extracapsular extension. Ex vivo examination showed strong fluorescent enhancement and improved contrast in Nano-ICG treated mice at 24 hours compared to free ICG treated mice, while no differences were observed at 4 hours. A reduction in signal variance was observed between 4 and 24 hours for both free ICG and NanoICG. Further analysis showed that total fluorescent signal was dependent on tumor size, while average volumetric signal was not, indicating similar levels of contrast for both large and small tumors.

19.

Radiation-Sensitized Nanocarriers for Triggered Drug Delivery and Radiation Dose Monitoring

Marc Kai, Oregon State University, kaim@oregonstate.edu

Anna Brown, Oregon State University broanna@ohsu.edu

Anna Lorenz, Oregon State University, lorenzan@oregonstate.edu

Conroy Sun, Oregon State University, sunco@onid.oregonstate.edu

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Nanoparticle-based carriers offer several advantages in therapeutic delivery applications. One such improvement over single molecule dosage forms is by virtue of the "many-to-one" property: the ability of one particle to deliver a large number of drug moieties. This property also extends to alternative cargo, such as imaging agents, thereby improving the multifunctional capability of a nano-delivery platform. When incorporated into a stimulus-responsive matrix, these theranostic particles can release their payload in specific locations, improving efficacy and mitigating toxicity. Additionally, the sensitivity to externally applied stimuli, such as x-rays, can lend to advancements in image guidance and treatment monitoring when combined with radiation therapy. In the realm of oncology, this translates to a potential improvement in tumor detection and treatment.

Here we capitalize on these advantages offered by nanotechnology through the development of a particle platform consisting of magnetic resonance imaging (MRI) contrast agents and a chemotherapeutic, cisplatin, encapsulated in a cross-linked alginate matrix. Upon exposure to x-rays, we observed degradation of the particles, resulting in controlled release of the cargo. In vitro assays revealed effective cytotoxicity in several human and murine cancer cell lines. In vivo work is being pursued to measure the pharmacokinetics, toxicity, and efficacy in a variety of cancer models. Furthermore, the presence of both T1- and T2-contrast agents allows for unique applications in imaging and radiation dose monitoring with newly available combined MRI-linear accelerators providing unique methods for tracking therapy in real-time. Overall, the platform has the potential to augment current treatments, as well as provide valuable new information to personalize therapy.

20.

A Nanotheranostic System for delivery of Tumor Site "Turn-on" Imaging Agent

Xiaoning Li, Oregon State University, lixiaon@onid.oregonstate.edu

Olena Taratula, College of Pharmacy, Oregon State University, Olena.Taratula@oregonstate.edu

Oleh Taratula, College of Pharmacy, Oregon State University, Oleh.Taratula@oregonstate.edu

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Advances in diagnostic medicine have provided promising future for early diagnosis and treatment of tumor. However, certain types of tumor remain a challenge due to the indolent symptoms at early stage. Thus, the difficulties in diagnosis of such tumor types limit the treatment options to only the conventional strategy, involving debulking surgery and chemotherapy. In this approach, the surgical removal of tumor is a critical step. Optical imaging guided surgical approaches have been shown to yield great benefit for success in cancer debulking surgeries. Among these approaches, fluorescence imaging using agents that can be activated by light in the region of 700-900 nm, known as the "near infrared (NIR) spectral window", have become particular attractive due to the advantages of deep tissue penetration and minimal tissue autofluorescence and light scattering. Even with tumor-targeted moiety on the NIR imaging agent delivery systems, it is difficult to realize localized fluorescence at tumor site. Therefore, to eliminate possible non-specific fluoresce observed in normal tissues, we have designed a system that turns on the fluorescence at tumor site. A NIR dye is modified to be nonfluorescent at physiological condition and tumor site responsive. Once the nano delivery system reaches tumor site, the dye becomes fluorescent and serve as imaging agent.

21.

Targeted polymeric micelles facilitate detection of ovarian cancer using multispectral optoacoustic tomography

Lacey McNally, University of Louisville, lacey_mcnally@hotmail.com

Peter Frederick, Roswell Park Cancer Institute, Peter.Frederick@RoswellPark.org

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Early detection and treatment of ovarian cancer cell is challenging due to limitations in both traditional imaging techniques (shallow depth penetration, low sensitivity and specificity, or the use of ionizing radiation) and insufficient efficacy of conventional chemotherapy in vivo. Here in, we constructed pH dependent tumor specific theranostic nanoparticle, which binds $\alpha 5\beta 3$ integrin and releases contents in the presence of an acidic tumor microenvironment to enhance tumor detection via MSOT. The cRGD-pH responsive micelles were spherical in size (176 ± 10 nm) at pH 7.4 and were stable over the pH range of non-malignant tissue at pH 7.0-7.4, but dissociate in the acidic environment (pH 6.8) due to protonation. The paclitaxel (PTX) loading efficiency was 70% in cRGD-pH responsive micelles and released at the rate constant of 0.05 h-1 and 0.19 h^{-1} at pH 7.4 and pH 6.5, respectively. Cytotoxicity measurements revealed that PTX loaded cRGD-pH responsive micelles effectively killed ovarian cancer cells in vitro >92% at extracellular pH of 6.8 and >98% at 6.5, but < 10% at pH 7.4 by induction of apoptosis. In vivo, dye encapsulated cRGD-pH responsive micelles significantly accumulated in tumors at two hours post-injection as detected using multispectral optoacoustic tomography. cRGD-pH responsive micelles were observed in tumor vasculature and in areas of hypoxia. We reported for the first time that targeted theranostic cRGD-pH responsive micelles facilitate MSOT detection of ovarian cancer in vivo .

22.

Syndecan-1 conjugated mesoporous silica-coated gold nanorods act as optoacoustic signal amplifiers for detection of orthotopic pancreatic tumors in vivo via multispectral optoacoustic tomography

Lacey McNally, University of Louisville, lacey_mcnally@hotmail.com

Matthew Zeiderman, University of Louisville, mzeid89@gmail.com

Nichola Garbett, University of Louisville, nichola.garbett@louisville.edu

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Early detection of pancreatic cancer cells is difficult due to poor spatial resolution and shallow depth penetration, low sensitivity, and specificity of traditional imaging modalities. Multispectral optoacoustic tomography (MSOT) overcomes these limitations due to its hybrid modality, but is hindered by lack of tumor-specific contrast agents. Therefore, we constructed highly stable nano-contrast agents by encapsulating gold nanorods (GNRs) having aspect ratio 3:1 in polyacrylic acid (PAA) with shell thickness (1.5 ± 0.5 nm), and amine-functionalized mesoporous silica (MS) with shell thickness (6.25 ± 0.25 nm), respectively. Syndecan-1 targeting ligand was conjugated on the surface of amine-functionalized mesoporous silica coated gold nanorods (MS-GNRs) or polyacrylic acid coated gold nanorods (PAA-GNRs) to examine optoacoustic (OA) signal enhancing effect in MSOT and tumor targeting using flow cytometry. The Syndecan-MS-GNRs gave 10X higher OA signal than Syndecan-PAA-GNRs in S2VP10L cell lines, positive for insulin like growth factor1 receptor (IGF1-R), and minimum binding in MiaPaca-2 cell lines, negative for IGF1-R. Thus, Syndecan-MS-GNRs were iv injected into orthotopic pancreatic cancer-bearing nude mice prior to MSOT imaging. In vivo, Syndecan-MS-GNRs significantly accumulated in tumors with peak accumulation occurring at slice 49.3 mm containing 175.4 MSOT a.u. at four hours post-injection with minimal accumulation in the liver. For the first time, we report the combination of MSOT with targeted nano-contrast agents (Syndecan-MS-GNRs) provide a high-resolution signal amplifier by minimizing off-target effect for successful detection of orthotopic pancreatic cancer cells in vivo.

23.

Poly(2-oxazoline) based magnetic fields-responsive hybrid nanoclusters for taxane delivery

Youngee Seo, Eshelman School of Pharmacy, University of North Carolina, seoy@email.unc.edu

Hemant Vishwasrao 2, Alyssa Master 1, Marina Sokolsky 1, Alexander V. Kabanov 1,3 .

1 Center for Nanotechnology in Drug Delivery and Division of Molecular Pharmaceutics, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-7362, USA enter for Drug Delivery and Nanomedicine, Department of Pharmaceutical Sciences, University of Nebraska Medical Center, Omaha, NE, USA

3 Laboratory of Chemical Design of Bionanomaterials, Faculty of Chemistry, M.V. Lomonosov Moscow State University, Moscow 119992, Russia

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We have previously reported poly(2-oxazoline) polymeric micelles system that displayed an extremely high taxane loading capacity (>40 %) with particle size below 50 nm [1]. As the pattern of drug release is beyond the control, it is necessary to design remotely actuated nanocarriers for the control of time and place of release. Among various internal and external triggers, such as pH, temperature, and magnetic field, we designed magnetic fields-responsive organic-inorganic nanoclusters (NanoFerrogels) to control the release and delivery of taxanes, especially paclitaxel (PTX). The two main components of NanoFerrogels – Superparamagnetic iron oxide nanoparticles (MNPs) and poly(2-oxazoline)-based polymeric micelles - were connected to each other by various anchors. We posit that under an applied magnetic field, magnetic nanoparticles (MNPs) in the NanoFerrogels realign along the field, causing the release of drug from the polymeric micelles. PTX-loaded NanoFerrogels sizes were about 150 nm depending on media types, such as DI water, Saline, and PBS and were stable for at least 24 hours regardless of the media. The PTX loading capacity is 11 %, and MNP content in NanoFerrogels was 15 % w/w as measured by TGA and ICP-MS. PTX-loaded NanoFerrogels releases PTX steadily without any burst release. Following 20 minutes exposure to 50 Hz radiofrequency alternative current (RFAC) field with 50 kA/m, PTX-NanoFerrogels released twice higher amount of PTX compared to no field exposure (20.8±5.8 % and 9.1±3.6 %, respectively). Furthermore, PTX-NanoFerrogels showed high toxicity against cancer cell lines. Taken together, these results underscore the potential of PTX-NanoFerrogels as a platform for remotely controlled taxane delivery.

24.

A Multifunctional Theranostic Nanoplatform for Cancer Treatment

Oleh Taratula, Oregon State, Oleh.Taratula@oregonstate.edu

Olena Taratula, Oregon State University, College of Pharmacy, Olena.Taratula@oregonstate.edu

Canan Schumann, Oregon State University, College of Pharmacy, schumanc@onid.orst.edu

Tony Duong, Oregon State University, College of Pharmacy, duongton@onid.oregonstate.edu

Karmin L. Taylor, Oregon State University, College of Pharmacy, taylorka@onid.oregonstate.edu

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Currently, only optimal surgical resection of all disease sites can improve survival of ovarian cancer patients. Even with the best microsurgical techniques, however, palpation and visual inspection for malignant tissue identification can result in microscopic tumors being left behind that lead to cancer relapse. We developed a single agent-based nanoplatform (NP) that can be used concurrently for two purposes: (1) tumor delineation with real-time near infrared (NIR) fluorescence signal and (2) intraoperative targeted treatment to further eliminate unresected cancer cells by non-toxic combinatorial phototherapy with dual photothermal (PTT) and photodynamic (PDT) therapeutic mechanisms. The main building block of the nanoplatform is naphthalocyanine (SiNc) that can generate a strong NIR fluorescence signal, required for eliminating autofluorescence from healthy tissue. Potential clinical application of SiNc, however, is currently limited by low water solubility and aggregation. The developed encapsulation strategy offers the possibility of separating the SiNc molecules thus decreasing their aggregation, preserving their NIR fluorescence signal, stabilizing their PDT and PTT properties and enhancing their water solubility. Furthermore, SiNc-NP exhibits minimal dark cytotoxicity and remarkable combinatorial phototherapeutic effects on ovarian cancer in vitro and in vivo, through its cytotoxic effects that cause a high production of ROS and heat without releasing the photoactive agent from the nanoplatform. Finally, the potential of SiNc-NP as an NIR imaging agent was confirmed by recording the strong fluorescence signal in the tumor area. We anticipate that the developed theranostic nanoplatform can be potentially applied for NIR fluorescence image-guided surgery and intraoperative cancer treatment.

25.

Development of Antibody-Conjugated Iron Oxide Nanoworms for Targeting HER2 Positive Breast Cancer Cells and Endothelial Cells

Guankui Wang, University of Colorado Denver | Anschutz Medical Campus, Guankui.Wang@ucdenver.edu

Dmitri Simberg, Department of Pharmaceutical Sciences, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado Denver | Anschutz Medical Campus, Dmitri.Simberg@ucdenver.edu

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Superparamagnetic Iron oxide nanoparticles have been under extensive investigation as T2-negative contrast agents for tumor magnetic resonance imaging (MRI), from laboratory research into clinical practice. We have recently reported a two-step modification method to crosslink dextran coated iron oxide nanoworms (CLIO NWs). In the present study, we explored the targeting ability of CLIO NWs conjugated with antibodies. We modified the NWs with Herceptin® antibody that targets human epidermal growth factor receptor-2 (HER2) positive breast cancers or with antibody that targets human vascular endothelial growth factor receptor 2 (VEGFR2). Antibody conjugated NWs were characterized using dynamic light scattering and transmission electron microscopy for size measurement. The transverse relaxivity measurements of NWs were performed using an MRI scanner. The antibody conjugation and complement component 3 (C3) binding measurements were performed using immuno-dot blot assay. The cellular uptake of the NWs by breast cancer SK-BR-3 cells, human umbilical vein endothelial cells (HUVECs) and macrophages was studied using Prussian blue staining and cell imaging. The efficiency of uptake was quantified using iron assay and MRI. Only a few antibodies attached per NW were needed to achieve highly effective uptake of NWs by SK-BR-3 cells and HUVECs. There was minimal mouse C3 binding to NWs and minimal uptake of NWs by macrophages. In conclusion, CLIO NW is a promising imaging and drug delivery platform for specific targeting of HER2 positive breast cancers and VEGFR2 positive angiogenic endothelium. Our future studies will focus on in vivo targeting, imaging and drug delivery using CLIO NWs.

26.

Single-cell mRNA and protein profiling with quantum dots

Pavel Zrazhevskiy, University of Washington, pavelz@uw.edu

Xiaohu Gao, University of Washington, xgao@uw.edu

Comprehensive molecular profiling of individual cells within the context of microenvironment promises to provide a powerful tool for addressing phenotypic heterogeneity of biological specimens, opening access to studying low-abundance events often masked or completely erased by batch processing, and elucidating disease biomarker signatures for accurate diagnosis and targeted therapy. To achieve this objective we have developed a versatile quantum dot-based imaging technology capable of ex vivo single-cell molecular profiling in cultured cells and tissue sections via multicolor fluorescence microscopy. Many fundamental limitations of existing methods are resolved by employing an innovative target labeling strategy via DNA encoding and taking advantage of molecular self-assembly mechanisms for the straightforward probe preparation. As a result, multiple protein and mRNA targets can now be labeled simultaneously with unique quantum dot tags and analyzed in a multiplexed quantitative manner. A fine balance of technical simplicity and analytical power featured by this technology should prove instrumental in achieving demanding objectives of single-cell analysis and facilitating further technology translation into biomedical research and clinical diagnostics.

27.

Nanodroplet Mediated Histotripsy (NMH) Cell Ablation on 3D Prostate Cancer Models

Omer Aydin, University of Michigan, biomer@umich.edu

Eli Vlaisavljevich, University of Michigan, evlaisav@umich.edu

Yasemin Y. Durmaz, Medipol University, ydurmaz@medipol.edu.tr

Zhen Xu, University of Michigan, zhenx@umich.edu

Mohamed ElSayed, University of Michigan, melsayed@umich.edu

Focal prostate cancer therapy is an approach that successfully eradicated the single tumor lesion. However, the focal therapy approaches have limitations on high-volume and multi-modal tumor lesions, and the success of focal prostate cancer therapy depends on the ability to selectively ablate cancer lesions. To address current therapeutic limitations, we have developed nanodroplets (average diameter<500nm) encapsulating perfluorocarbons(PFC), which can rapidly expand reaching >500µm in <1µsecond when exposed to therapeutic ultrasound before they collapse, which proved to mechanically fractionate neighboring cells with the significantly reduced cavitation threshold. To test the tumor ablation efficiency of the different PFCs(PFP or PFH)-encapsulated nanodroplets, we developed 3D-prostate cancer spheroids from PC-3 and C4-2B cancer cells with using aqueous-two-phase-system (ATPS). First the spheroids were treated w/o PFP/PFH-loaded nanodroplets in the tube filling with PBS under low-pressure ultrasound signal(10 MPa) with the control of no ND and US. Afterwards, resazurin viability assay was employed. Based on the results we did not observe any significant ablation with only low-pressure ultrasound comparing to the control for both 3D models. However, once NDs were inserted to the tube upon exposure to 1-cycle of histotripsy(9.0 MPa) with the pulse repetition frequency of 500 kHz, more than 60% of the cells of both PC-3 and C4-2B spheroids were killed with PFP/PFH loaded-nanodroplets. Further, we developed agarose 3D tumor phantom model that mimicked the cells inside a tissue extracellular-matrix. The applied treatment groups were no ND with low-pressure(13 MPa), no ND with high-pressure(28 MPa), with PFP-loaded NDs with low-pressure (13 MPa), and with PFH-loaded NDs with low-pressure(13 MPa). During the treatments such high-pressure and low-pressure with nanodroplets, cavitation bubbles were observed at the transducer focus and cells were observed to be mechanically ruptured. After the treatments, the ablated area of the spheroids was calculated. No nanodroplets low-pressure could ablate less than 20% area for both cell lines. However, no nanodroplets with high-pressure ablated around 80% of the spheroids. Whereas, with low-pressure, PFP-nanodroplets destroyed 40% of the spheroids, and PFH-nanodroplets could ablate almost 80% of the spheroids. These results indicate PFC-loaded nanodroplets significantly reduce the histotripsy threshold, and PFH-loaded nanodroplets with low-pressure can destroy the cells as efficient as high-pressure.

Funding: OA is supported by the Republic of Turkey the Ministry of National Education (1416).

28.

Development of "Smart" Targeted Micelles for Triggered Release of Chemotherapeutic Cargo in Metastatic Prostate Cancer Lesion in Bone

Omer Aydin, University of Michigan, biomer@umich.edu

Harsha Ramaraju, University of Michigan, sramara@umich.edu

Omer Aydin, University of Michigan, biomer@umich.edu

Gopinath Tiruchinapally, University of Michigan, gtiruchi@umich.edu,

Yasemin Y. Durmaz, Medipol University, ydurmaz@medipol.edu.tr

Kenneth Kozloff, University of Michigan, kenkoz@umich.edu

David Kohn, University of Michigan, dhkohn@umich.edu

Mohamed ElSayed, University of Michigan, melsayed@umich.edu

Prostate cancer (PC) is the 2nd leading cause of cancer related deaths in U.S. men. The reason of prostate cancer mortality is not from the primary cancer but spread of the primary cancer cells to distant organs, especially bone. The current bone metastases therapy modalities are not efficient to cure bone metastasis because of the inability to deliver therapeutic concentrations of anticancer-agents (Cabazitaxel; CTX) to PC lesions in bone. To address the limitations, we synthesized a bone targeted amphiphilic triblock copolymer, pVTK-poly(ethylene)-b-poly(acrylic acid)-b-poly(methyl methacrylate), which self-assembles in aqueous medium forming nano-sized micelles that can encapsulate CTX in the hydrophobic core. Cross-linkage of the PAA blocks using a ketal-linker forms an acid-labile shell, which stabilizes the formed micelles at physiologic pH but allows selective release of the loaded cargo in acidic environments. The average size of the particles was around 100 nm. Further, we investigated the optimum bone binding mole percent of 0.32 nmol of pVTK (0, 5, 10%) in the particles using HA-disc, bone powder, and bone-chip relying on FITC fluorescence of the peptide. The percent of bound of 5% and 10% pVTK micelles on HA-discs were 58 and 61, respectively, while the same formulations binding percentage on rat bone powder were 42 and 38, respectively. On the other hand, the binding tests of 5 and 10% pVTK-micelles on bone-slice were 9% and 17%, respectively. Furthermore, the CTX loading efficiency of 5 and 10% pVTK-micelles were around 26.0 and 18.8%, respectively. Based on the cytotoxicity results of the particles, pVTK-micelles (0, 5, 10%) did not have any cytotoxic effect on PC cells. Meanwhile, the anti-cancer activity of CTX-encapsulated 5-10%-pVTK-micelles was investigated with comparing to non-targeted micelles and as well as free CTX on PC-3 cells. The IC50 values of CTX-loaded non-targeted, 5%, and 10% pVTK-micelles were 0.76, 2.46, 0.37 nM, respectively with the control of 0.60 nM free CTX. Current investigation focuses on anti-cancer activity of the particles on bone and C4-2B cell lines as well as these cell lines particle uptake. These results indicate pH-sensitive, CTX-loaded, bone-targeted pVTK-micelles can preferentially bind to bone and achieve tunable CTX release in tumor lesion, which can selectively kill tumor cells while limiting systemic side effects.

* I.A.Y., H.R., and O.A. have equal contributions to this study.

Funding: I.A.Y. is supported by a Fellowship from the Ministry of Higher Education of Arab Republic of Egypt, O. A. recognizes the Fellowship from the National Ministry of Education of Republic of Turkey. Sanofi-Aventis.

29.

Raltegravir Prodrugs for Improved Nanoparticle Delivery

Wilma E. Afunugo, Seattle University, afunugow@seattleu.edu

Mikaela E. Ebner, Seattle University, ebnerm@seattleu.edu

Yonghou Jiang, University of Washington, yhj@uw.edu

Shijie Cao, University of Washington, sjcao@uw.edu

Kim A. Woodrow, University of Washington, woodrow@uw.edu

Pre-exposure prophylaxis (PrEP) is an emerging HIV prevention strategy that employs approved antiretroviral drugs (ARVs) to inhibit sexual transmission in high-risk populations. The use of polymeric nanoparticles to deliver ARVs for PrEP has a number of potential advantages, including decreased toxicity through ARV localization to the site of infection, increased duration of protection through sustained drug release, and the simultaneous delivery of potent ARV combinations that are difficult to co-formulate by traditional methods. One challenge in the synthesis of ARV-loaded nanoparticles is the large dependence of drug loading on the physicochemical properties of the drug. We have observed low drug loading in poly(lactide-co-glycolide) (PLGA) nanoparticles incorporating raltegravir (RAL), an ionizable HIV integrase inhibitor that is predicted to exhibit advantageous drug synergies with a number of hydrophobic ARVs. To address these challenges we have developed a prodrug strategy to increase the loading efficiency of RAL while maintaining its activity. Our results suggest that simple ester analogs of RAL dramatically improve nanoparticle loading and are readily cleaved intracellularly, producing levels of HIV inhibition identical to the parent compound. We anticipate similar strategies will improve nanoparticle formulation of several approved ARVs and expand the number of ARV combinations accessible in the development of topical microbicides.

30.

pH-sensitive stealth coating of polymeric nanoparticles by polydopamine polymerization

Sara Ahmed, Industrial and Physical Pharmacy Department- College of Pharmacy- Purdue University, sabouelm@purdue.edu

Youn Jin Ku, College of Pharmacy- Purdue University, yku@purdue.edu

Yoon Yeo, Industrial and Physical Pharmacy Department, College of Pharmacy- Purdue University, yyeo@purdue.edu

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Low molecular weight chitosan (LMWC) can function as a hydrophilic pH-sensitive stealth coating for nanoparticulate drug delivery systems. The LMWC-coated nanoparticles (NPs) were previously made with a conjugate of poly(lactide-co-glycolic) acid (PLGA) and LMWC (PLGA-LMWC) and showed pH-sensitive surface charge profiles. However, this preparation method has disadvantages such as production complexity and difficulty in drug encapsulation. We used an alternative surface modification method based on dopamine polymerization, which formed a layer of polydopamine (pD) on NP surface into polydopamine (pD) allowing for simple conjugation of LMWC to the preformed NP cores. By decoupling the NP formation and surface modification, this method enabled flexible control of paclitaxel (PTX) release kinetics. The presence of LMWC on the surface of NPs mediated the electrostatic interactions between the NPs and SKOV-3 cells only at mildly acidic pH, which translated to enhanced cellular uptake of NPs and selective PTX delivery to SKOV-3 cancer cells in acidic microenvironment such as solid tumors.

31.

Folate receptor-targeted transplacental delivery of digoxin for the treatment of fetal arrhythmia

Norah Albekairi, University of Texas Medical Branch, naalbeka@utmb.edu

Shariq Ali, University of Texas Medical Branch, sh2ali@utmb.edu

Sanaalarab Al-Enazy, Univesity of Texas Medical Branch, saalenaz@utmb.edu

Erik Rytting, University of Texas Medical Branch, erik.rytting@utmb.edu

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Background:

Fetal tachyarrhythmias can cause fetal congestive heart failure and may lead to hydrops fetalis. Digoxin (first-line treatment) transport across the placenta is limited by P-glycoprotein efflux. In this study, we targeted digoxin-loaded polymeric nanoparticles to folate receptors present on the placenta to increase transplacental delivery by receptor-mediated endocytosis.

Methods:

A folate-terminated biocompatible block copolymer, folate-PEG-PLGA, was synthesized by coupling carboxylic acid-terminated PLGA (17 kDa) and amine-terminated folate-PEG (3.4 kDa) by carbodiimide chemistry. Folate-PEG-PLGA was used to prepare digoxin-loaded folate-targeted nanoparticles (10% drug loading) by a modified solvent displacement method. A transport study in BeWo cells (an in vitro model of human placental trophoblast) was performed comparing folate-targeted digoxin-loaded nanoparticles (with and without excess folate) to non-targeted digoxin-loaded PEG-PLGA nanoparticles and free digoxin (with and without blank PEG-PLGA nanoparticles).

Results:

Synthesis of folate-PEG-PLGA was confirmed by gel permeation chromatography and folate absorbance at 365 nm (65% conjugation yield). All nanoparticles were between 100 and 115 nm with narrow polydispersity. The apparent permeability values (Pe) for free digoxin, free digoxin with blank nanoparticles, non-targeted digoxin nanoparticles, folate-targeted digoxin nanoparticles, and folate-targeted digoxin nanoparticles with excess folate across BeWo cells were 1.45 $\pm$ 0.45E-5, 1.28 $\pm$ 0.35E-5, 2.01 $\pm$ 1.49E-5, 2.43 $\pm$ 1.53E-5, and 1.62 $\pm$ 0.52E-5 cm/s, respectively.

Conclusion:

The folate-targeted nanoparticles displayed a trend towards increased digoxin delivery across the placenta by receptor-mediated endocytosis. This represents a novel treatment strategy for fetal tachyarrhythmias which may improve maternal and fetal outcomes.

32.

Transplacental transfer of paclitaxel-loaded nanoparticles in the dually perfused human placental cotyledon

Shariq Ali, University of Texas Medical Branch, sh2ali@utmb.edu

Norah A Albekairi, University of Texas Medical Branch, naalbeka@utmb.edu

Tatiana N Nanovskaya, University of Texas Medical Branch, tnnanovs@utmb.edu

Svetlana Patrikeeva, University of Texas Medical Branch, svpatrik@utmb.edu

Mahmoud S Ahmed, University of Texas Medical Branch, maahmed@utmb.edu

Erik Rytting, University of Texas Medical Branch, erik.rytting@utmb.edu

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Background

Taxol® (paclitaxel in Cremophor®-EL) is administered during pregnancy for the treatment of breast and ovarian cancers. Paclitaxel is a substrate of the efflux transporter P-glycoprotein, which is highly expressed in human placenta and limits transfer of paclitaxel to the fetus. Nevertheless, paclitaxel can cause fetal morbidity. It is known that nanoencapsulation of drugs can alter their transplacental transfer. Therefore, the purpose of this study was to determine the transplacental transfer of paclitaxel in albumin nanoparticle (Abraxane®) and polymeric micelle (Genexol®-PM) formulations.

Methods

Transplacental transfer of Abraxane, Genexol-PM, and Taxol was determined using the dually perfused human placental cotyledon model. Medium containing physiological albumin concentration (30 mg/mL) was perfused in term placentas obtained from uncomplicated pregnancies (according to a protocol approved by the Institutional Review Board). The initial maternal concentration of paclitaxel was 20 μg/mL for all formulations. A freely diffusing marker (antipyrine) was co-administered to normalize paclitaxel transfer and eliminate interplacental variability. Drug concentrations were determined in maternal and fetal circulations during the four hours of perfusion by HPLC.

Results

Fetal transfer rates of Genexol-PM (n=3), Abraxane (n=3), and Taxol (n=2) were 18.9 ± 0.9%, 16.3 ± 4.4%, and 9.7 ± 1.3% respectively. The clearance indices were 0.40 ± 0.02, 0.35 ± 0.04, and 0.23 ± 0.02, respectively.

Conclusion

Both Abraxane and Genexol-PM had significantly higher transplacental transfer than Taxol. Mechanisms behind these differences may involve various endocytosis pathways, as well as shielding from P-glycoprotein efflux. It may therefore be necessary to avoid these formulations when treating pregnancy-associated malignancies.

33.

Nanocarrier based Amphotericin B delivery system for treatment of Visceral Leishmaniasis: an in-vivo assessment

Madhusudan Bhat, ALL INDIA INSTITUTE OF MEDICAL SCIENCES, bhat.madhusudan86@gmail.com

Amit Ranjan Maity, Department of Pathology, All India Institute of Medical Sciences, New Delhi, armchem@gmail.com

Susmita Mitra, Amity Institute of Nanotechnology, Amity University, Noida, susm58@yahoo.com

Amit Kumar Dinda, Department of Pathology, All India Institute of Medical Sciences, New Delhi, amit_dinda@yahoo.com

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The objective of the following investigation was to develop a cost-effective nano-delivery system of AmB within chitosan grafted co-polymer with a hydrophobic core consitute by cholesterol (AC-CMA). Average size of the nanoparticles was 180±7nm (TEM) with surface charge of -3.7±1.2mV. HPLC analysis revealed 70±1% drug loading efficiency. Rapid uptake of the drug loaded NPs by the macrophage cells were noted starting from 2 minutes with a immobilization of intracellular parasite (L. donovani) within 3 hours and their lysis by 6 hours within the infected macrophage cells. Flow cytometric study with GFP expressing L. donovani also confirmed high parasitocidal activity. Pharmacokinetic study in rats revealed the disapperance of AmB from the plasma within 3 hours and availability upto 36 hours in the vital organs like spleen, liver. Anti-leishmanial activity was assessed in vivo in L. donovani infected hamster by comparing the parasite load after administration every day for 5 days in one study (n=6) and alternate day administration for 5 days in another (n=6) using AmBisome and AC-CMA having 1mg/kg, 500µg/kg, 250 µg/kg equivalent AmB. Alternative day administration of 500µg/kg was found to be more efficient in reducing the parasitic load, with increased safety. The parasitic clearance in the splenic tissue with AC-CMA was significantly more than AmBisome (95.32% vs 82.14%) and the suppression of parasite replication in the spleen was also found to be significant (97.18% vs 87.17%). The present nanocarrier is stable, low cost and has a high efficacy against Leishmania infection suggesting it high translational potential.

34.

Polymeric Nanocarriers for Drug Delivery: Improving physicochemical parameters by a nanoprecipitation approach

Johanna Catalan-Figueroa, Department of Pharmaceutical Science and Technology, School of Chemical and Pharmaceutical Sciences. University of Chile, joh.catalan@ug.uchile.cl

Miguel O. Jara. Department of Pharmaceutical Science and Technology, School of Chemical and Pharmaceutical Sciences, University of Chile, jaritamiguel@hotmail.com

Ulises Gajardo-Lopez. Department of Pharmaceutical Science and Technology, School of Chemical and Pharmaceutical Sciences, University of Chile, ulises.gajardo@yahoo.es

Javier O. Morales. Principal Investigator. Department of Pharmaceutical Science and Technology, School of Chemical and Pharmaceutical Sciences, University of Chile. Advanced Center for Chronic Diseases (ACCDiS), Santiago, Chile.

Purpose: To develop a nanocarrier system based on the nanoprecipitation of Eudragit polymers RS (ERS) or RL (ERL), for hydrophobic drug encapsulation, achieving narrow size distributions.

Methods: Loperamide and curcumin were selected as model drugs. Nanoparticles were fabricated by nanoprecipitation of an acetone-based organic phase, containing the polymer and the model drug, into an aqueous solution containing either poloxamer 188 (P188) or 407 (P407) at 0.5 w/v. Curcumin was quantified by UV-Vis at 420 nm, and loperamide by RP-HPLC/UV-Vis detected at 220 nm. Size, polydispersity index (PdI), and zeta potential (ZP) were determined in a Malvern Zetasizer Nano ZS. Nanoparticles were visualized by SEM.

Results: The smallest nanoparticles obtained resulted from nanoprecipitating ERL in a P407 aqueous phase (size 47.2±0.9 nm; PdI 0.215±0.009). Conversely, ERS in P407 allowed for the narrowest size distribution (PdI 0.167±0.010; size 74.9±0.9 nm). All formulations showed ZP above 40 mV. SEM images confirmed the size range and revealed the spherical nature of nanoparticles. Loading efficiency was under 5% for both drugs.

Conclusions: Both polymers resulted in small and narrowly distributed nanoparticles by nanoprecipitation. Although encapsulation efficiency was low, curcumin loading was enough to visualize nanoparticles and loperamide encapsulation was possible with both polymers. These systems may be used for nanoparticle tracking and for hydrophobic drug delivery to target tissues.

Acknowledgements: The authors thank FONDECYT 11130235, FONDAP 15130011 and CONICYT 21120192.

35.

iTEP NANOPARTICLE-DELIVERED SALINOMYCIN DISPLAYS AN ENHANCED ANTITUMOR AND ANTI-METASTASIS EFFICIENCY IN ORTHOTOPIC BREAST TUMORS

Mingnan Chen, University of Utah, mingnan.chen@utah.edu

Guiquan Xia, Key Laboratory of Combinatorial Biosynthesis and Drug Discovery (Wuhan University), Ministry of Education, and Wuhan University School of Pharmaceutical Sciences, Wuhan 430071 (China)

Shuyun Dong, Department of Pharmaceutics and Pharmaceutical Chemistry, The University of Utah, 30S 2000E, Salt Lake City, Utah 84112, United States

Zhaong-Xing Jiang, Key Laboratory of Combinatorial Biosynthesis and Drug Discovery (Wuhan University), Ministry of Education, and Wuhan University School of Pharmaceutical Sciences, Wuhan 430071 (China)

Mingnan Chen, Department of Pharmaceutics and Pharmaceutical Chemistry, The University of Utah, 30S 2000E, Salt Lake City, Utah 84112, United States

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Salinomycin (Sali) is a selective inhibitor to cancer stem cells (CSCs) and potentially inhibits cancer metastasis given role of CSCs in the metastasis. Previously, we engineered an immune-tolerant, elastin-like polypeptide (iTEP)-based nanoparticle (NP) to deliver Sali in an encapsulated form. We found that the encapsulated Sali was more potent than free Sali in reducing CSCs in murine orthotopic breast tumors but failed to inhibit the tumor growth. In this study, a nanoparticle that is capable of an intracellular release of Sali was engineered through a cleavable and covalent hydrazone bond. This releasable conjugate improves the pharmacokinetics profile and tumor accumulation of Sali and enhances its metastasis-inhibition effect. Sali was conjugated to an iTEP that we recently invented, in order to obtain a desired biocompatibility and stability of nanoparticles formed. Sali after modified by ABA ((4-(1,3-dioxolan-2-yl)phenyl)methanamine) was conjugated to iTEP through a pH-sensitive hydrazone bond. iTEP-Sali conjugates self-assembled into a NP, named Sali-NP. Sali was released from the Sali-NP in a controlled manner, and the NP maintained the CSC-selective toxicity of Sali. Sali delivered by the NP had a prolonged pharmacokinetics and a greater tumor accumulation than free Sali. Although Sali-NP only inhibited the growth of primary 4T1 tumors modestly, it significantly inhibited the metastasis of the tumors better than free Sali, which was evidenced by a longer metastasis-free survival period of the Sali-NP-treated mice. All these improvements in the efficacy over Sali may be attributed to the NP carrier and the effective drug release mechanisms. To complement the therapeutic effect of the Sali-NP, we combined Sali-NP with a Paclitaxel-loaded NP (PTX-NP. The combinational therapy demonstrated a long-lasting primary tumor growth inhibition effect. Most importantly, the combination therapy brought induced an enhanced metastasis-inhibition effect over Sali-NP alone, resulting more than 80 days of metastasis-free time in mice receiving the combinational therapy. iTEP NP enabled Sali to effectively inhibiting metastasis. The combinational therapy consisting of Sali and PTX resulted in a long-lasting metastasis inhibition.

36.

Chemotherapeutic Caterpillar Conjugates

Anthony Convertine, University of Washington, aconv@uw.edu

Hye-Nam Son, Selvi Srinivasan, Yhee J Young, Debobrato Das, Maria C Palanca-Wessels, Bridget Daugherty, Geoffrey Y Berguig, Garrett Booth, Daniel D. Lane, Menko P Ypma, Oliver W Press, Patrick S Stayton, and Anthony J Convertine

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Reversible addition-fragmentation chain transfer (RAFT) polymerization was used to prepare dense polyethylene glycol methacrylate brushes containing the potent chemotherapeutic agents camptothecin and dasatinib. These caterpillar-like copolymer drug conjugates incorporated the therapeutic agent into the polymeric scaffold using either a conjugation strategy or by direct polymerization of the prodrug monomers. In the conjugation approach anhydride residues distributed throughout the polymer backbone were reacted with hydroxyl-functional drugs using DMAP catalyzed carbodiimide chemistry. The reactive anhydride residues were also employed to react near IR dyes for live animal imaging as well as antibody targeting groups. In the second approach polymerizable methacrylate-based prodrug monomers were synthesized and subsequently polymerized via RAFT to yield copolymers with controllable drug compositions. In both cases the ester-linked drugs were shown to release in human serum with rates dependent on both the nature of the ester linkage (i.e. aliphatic vs. benzoic) as well as the type of covalently linked drug. Polymer morphology was also shown to play a key role in drug release rates with copolymers distributed within a hydrophilic copolymer segment showing higher rates than materials where the hydrophobic drug molecules were localized in discreet hydrophobic blocks. The latter materials were shown to self assemble into nanoparticles where the drug block was separated from the aqueous phase. Cytotoxicity measurements conducted in a variety of cell lines (i.e. lymphoma, breast, ovarian, and leukemia) demonstrated ability of the caterpillar conjugates to release the covalently linked rugs in an active form.

37.

Oxidation-Responsive Polymers: Tailored Sensitivity to Reactive Oxygen Species for Drug Delivery Purposes

Richard d'Arcy, University of Manchester, richard.darcy@manchester.ac.uk

Nicola Tirelli, University of Manchester, Nicola.Tirelli@manchester.ac.uk

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Many of today's prevailing diseases have a pathology associated with inflammation, these include Alzheimer's, Parkinson's, cirrhosis, diabetes, atherosclerosis and cancer, all of which have been heavily linked with the presence of reactive oxygen species (ROS)1.

In this context, materials responsive to ROS have since been developed; these include ferrocene-cyclodexrin derivatives, boronic esters, thioketals and the focus of this research, polysulfides to name but a few2. Polysulfides are sulfur (II)-composing organic polymers which can be oxidized by ROS to the higher oxidation state sulfoxides or sulfones resulting in a large increase in polarity and a hydrophobic to hydrophilic transition; accordingly, this transition can and has been exploited to release a drug payload in response to ROS2. In the present study, we focused on the development of star polysulfides; these branched materials allow the preparation of unimolecular micelles, which are advantageous due to their insensitivity against dilution (virtually no critical micellar concentration)3.

Polysulfides with a star morphology and a variable number of arms (linear, 4, 6 or 8) were synthesized as the hydrophobic core, thus varying the packing density of polymer chains. The polysulfide chains were also varied with respect to the propylene sulfide/ethylene sulfide copolymer ratio in order to assess the effect of chemical composition on oxidation kinetics. A poly(ethylene glycol)-vinyl sulfone was used to end-cap the chains in order to endow water solubility.

The aim of this study was therefore to determine the effect of macromolecular architecture (degree of branching, packing density, accessibility of sulphur atoms) and composition (ethylene sulfide content) on the responsiveness to ROS.

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38.

Polymeric Prodrug Therapy for Respiratory Infections Involving Burkholderia Pseudomallei

Debobrato Das, University of Washington, debobrato.das08@gmail.com

Abby M. Kelly, M.S., University of Washington, abbymichellekelly@gmail.com

David Chiu, Ph.D., University of Washington, chiudys@gmail.com

Selvi Srinivasan, Ph.D., University of Washington, selvis@uw.edu

Anthony Convertine, Ph.D., University of Washington, aconv@uw.edu

Daniel Ratner, Ph.D., University of Washington, dratner@uw.edu

Patrick Stayton, Ph.D., University of Washington, stayton@uw.edu

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There is an urgent need to develop new drug nanocarriers for pre-and post-exposure therapy against suspected airborne exposure to potentially fatal and infectious biothreats, specifically Burkholderia pseudomallei. The current standard of care for respiratory Burkholderia sp. is an exhaustive intravenous and oral antimicrobial regimen consisting of potent drug cocktails over prolong periods of time. Systemic complications and poor drug biodistribution and pharmacokinetics in the lung serves as strong motivation, and accordingly necessitates for the engineering of novel polymeric prodrugs as a biodynamic and bioactive drug delivery platform that improves on these limitations and provides prophylactic and therapeutic drug delivery to prevent and treat pulmonary Burkholderia sp. Using clinically relevant Ciprofloxacin as a model drug, various polymeric prodrug architectures have been created to understand materials and functional properties such as drug release kinetics, toxicity, and in vitro bioactivity. Current efforts have been focused towards engineering and evaluating different drug linkages to modulate and provide sustained drug release behavior, and demonstrate antimicrobial efficacy in an appropriate bacterial co-culture model. Our results suggest that drug linkage chemistry plays an important role in not only imparting construct stability, but also controlling efficacy in either a prophylactic or therapeutic manner.

39.

Performance-programmable clustered nanoassembly for biological stimuli-responsive multistage cancer chemotherapy

Jinzhi Du, **Emory Univeristy**, **jdu24@emory.edu**

Hongjun Li, Univerisity of Science and Technology of China, lihomjun@mail.ustc.edu.cn

Xiaojiao Du, Univerisity of Science and Technology of China, dxj1121@ustc.edu.cn

Congfei Xu, Univerisity of Science and Technology of China, smxcf@mail.ustc.edu.cn

Chunyang Sun, Univerisity of Science and Technology of China, chysun@mail.ustc.edu.cn

Shuming Nie, Emory University, snie@emory.edu

Jun Wang, Univerisity of Science and Technology of China, jwang699@ustc.edu.cn

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A major goal for nanomedicine in cancer therapy is to deliver therapeutics effectively to tumour tissues and cells. However, there is a series of sequential barriers in the body that hamper the nanocarriers from reaching the targets. Here, we present the development of a performance-programmable multistage nanoassembly to systematically overcome these barriers by adapting its properties (e.g. size, zeta potential, and drug release rate) to biological stimuli of the tumour microenvironment. The nanoassembly achieves superior antitumour effects in several different xenograft models. Our results demonstrate that the crucial step for its effectiveness is attributed to the enhanced tumour penetration caused by tumour extracellular pH triggered release of smaller PAMAM dendrimer from the nanoassembly. Our study provides a new strategy to dictate the performance of nanomedicine in the complex biological environment.

40.

Design of polymer nanoreactors with triggered activity for medicine and biosensing applications

Tomaz Einfalt, University of Basel, tomaz.einfalt@unibas.ch

Roland Goers, roland.goers@unibas.ch,

Adrian Dinu, adrian.dinu@unibas.ch Adrian.najer@unibas.ch

Cornelia Palivan, Cornelia.palivan@unibas.ch

Development of pH-triggered platforms plays a pivotal role in various scientific fields, ranging from nanomedicine to biosensing applications. As an example the pH, temperature and reduction potential in the body often varies, which is especially noticeable in the case of inflamed or cancerous tissue. These differences in cell conditions can be exploited by therapeutic or diagnostic systems that are responsive to the local changes in environment. Here, we introduce polymer nanoreactors with pH and reduction triggered activity. These nanoreactors are based on polymer vesicles, whose membrane permeability is controlled by insertion of channel proteins acting as "gates". The previous concept of nanoreactors, where active compounds are encapsulated inside polymer compartments (proteins, enzymes, mimics) and are able to act in situ, is extended by chemically modification of the membrane protein such to serve as an responsive gate. Only in certain conditions the gate is opened (by releasing its cap in specific conditions) and the enzymatic substrate can penetrate the vesicular membrane. Through this the substrate can enter inside the cavity where the enzymatic reaction takes place: the subsequent products of the reaction are released in the nanoreactors environment. Through encapsulation of different enzymes, the nanoreactors can be tailored for purposes of therapy or biosensing.

41.

Hemocompatible Biohybrid Structures Made by Non-Covalent Conjugation of Glycopolymers and Proteins. Synthesis, Characterization and Purification Strategies.

Johannes Fingernagel, Leibniz Institute of Polymer Research Dresden, fingernagel@ipfdd.de

Susanne Boye, Leibniz Institute of Polymer Research Dresden, boye@ipfdd.de

Jan Malý, J. E. Purkinje University, malyjalga@seznam.cz

Brigitte Voit, Leibniz Institute of Polymer Research Dresden, voit@ipfdd.de

Dietmar Appelhans, Leibniz Institute of Polymer Research Dresden, applhans@ipfdd.de

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Hemocompatible biohybrid materials in nano-sized range with bioactive functionalities are highly promising in the field of biomedical applications. These materials combine properties of natural and synthetic components to aim desired biological activities. To avoid unnecessary side reactions during the fabrication, the conjugation of these structures is preferentially motivated by the use of non-covalently directed conjugation steps. Therefore, different non-covalent interactions, biotin-(strept)avidin[1] and the nickel(II)-nitrilotriacetic acid-(Ni(II)-NTA)-histidine[2] interactions, have been studied for the fabrication of defined biohybrid structures based on ligand-modified dendritic glycopolymers. In this context dendritic glycopolymers also provide very promising biological properties for in-vitro and in-vivo applications [2-4].

Here, we present the synthesis of ligand-modified dendritic glycopolymers to assemble biohybrid structures made of biotin-streptavidin interactions. To improve blood circulation time and biocompatibility we include protein-protein interactions to serum proteins (HSA) by using a streptococcal albumin binding domain (ABD) attached to streptavidin. These structures were characterized by various methods and could be purified by hollow fiber filtration (HFF). A quantification of the conjugation efficiency was done by asymmetric flow field flow fractionation (AF4), including the determination of molecular parameters of these nanostructures.

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[2] Hauptmann et al., Biomacromolecules 2014, 15, 957.

[3] Höbel et al., J. Controlled Release 2011, 149, 146.

[4] Gutsch et al., Mol. Pharmaceutics 2013, 10 (12), 4666.

[5] Klementieva et al., Biomacromolecules 2013, 14, 3570.

42.

Cathepsin B-cleavable polymer-peptide conjugates for the intracellular delivery of a proapoptotic peptide in cancer

Hanna Kern, University of Washington, kernh@uw.edu

Anthony Convertine, University of Washington, convertine@gmail.com

Selvi Srinivasan, University of Washington, selvis@uw.edu

DPatrick Stayton, University of Washington, stayton@uw.edu

Peptide antagonists of the pro-survival B-cell lymphoma 2 (Bcl-2) proteins induce apoptosis and present a promising strategy for treating cancer. Unfortunately, the therapeutic efficacy of these peptides is limited by delivery barriers including poor stability and intracellular delivery. This work describes a novel diblock copolymer carrier that incorporates an enzyme-labile peptide macromonomer for the intracellular delivery and release of the pro-apoptotic peptide BIM. The peptide macromonomer consists of the BIM peptide motif caped with a cathepsin B substrate, phe-lys-phe-leu (FKFL), and functionalized on its N-terminus with methacrylamide. This design facilitates the stable integration of BIM into the polymer backbone and its specific release within endo/lysosomal compartments where cathepsin B functions. RAFT polymerization was employed to synthesize a peptide-containing diblock copolymer with precise molecular weight and low polydispersity. The first polymer block, designed for solubility and stability, was composed of poly(ethylene glycol) methyl ether methacrylate (Mn 300) and peptide. The second block consisted of a pH-responsive formulation, 60% N,N-diethylaminoethyl methacrylate (DEAEMA) and 40% butyl methacrylate (BMA), known to facilitate endosomal escape. In a red blood cell hemolysis assay, the diblock copolymer exhibited pH-dependent membrane destabilizing activity. Incubation with cathepsin B cleaved peptide monomers at the FKFL linker and released BIM peptide from the polymer. In SKOV3 ovarian cancer cells, the polymer activated the apoptotic pathway and lead to a decrease in cell viability. These results demonstrate the promise of this novel multifunctional carrier for enhancing the stability, delivery and activity of peptide therapeutics with intracellular targets.

43.

PeptoMicelles: A Novel Platform For Drug Delivery

Kristina Klinker, Johannes Gutenberg University Mainz, kklinker@uni-mainz.de

David Huesmann, Johannes Gutenberg University Mainz, d.huesmann@uni-mainz.de

Olga Schäfer, Johannes Gutenberg University Mainz, olga.schaefer@uni-mainz.de

Marilena Gimnich, Johannes Gutenberg University Mainz, mgimnich@students.uni-mainz.de

Matthias Barz, Johannes Gutenberg University Mainz, barz@uni-mainz.de

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PeptoMicelles are based on amphiphilic polypept(o)ides[1] and can be stabilized by chemoselective core cross-linking.[2] Polypept(o)ides combine the multifunctionality of polypeptides with the PEG-like properties of the polypeptoid polysarcosine (poly(N-methyl glycine)), e.g., hydrophilicity, reduced protein binding and non-immunogenic character. Unlike many other materials currently under evaluation for drug delivery applications, these systems are not only biocompatible but also intrinsically degradable and completely based on endogenous amino acids.

Block copolypept(o)ides are easily synthesized by sequential ring-opening polymerization of α-amino acid N-carboxyanhydrides (NCAs).[2,3] Amphiphilic block copolypept(o)ides consisting of a novel reactive cysteine polymer block[4] and polysarcosine self-assemble in aqueous solution into micellar core-shell structures (60-100 nm). The hydrophilic polysarcosine block can expose targeting moieties, which are easily introduced by highly selective ligation techniques[5] and shields the active pharmaceutical ingredient (API). The API can be either physically entrapped in or covalently attached to the hydrophobic core. PeptoMicelles are core cross-linked by disulfide bond formation using dithiols. Disulfides are particularly attractive for core cross-linked polymeric micelles (CCPMs) since they are stable in the blood stream but degraded inside the cell. This enables controlled degradation of the carrier using natural differences in redox potential. Thus, one block copolymer can be converted into a library of functional CCPMs in a simple but precisely controlled fashion.

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[2] A. Birke et al., Biomacromolecules, 2014, 15, 548–57.

[3] P. Heller et al., Macromol Biosci, 2014, 14, 1380–95.

[4] European patent application EP14167291.5

[5] K. Klinker et al., submitted.

44.

Development of Targeted, Enzyme-Activated Nano-conjugates for Hepatic Cancer Therapy

Sibu Kuruvilla, University of Michigan, skuruvi@umich.edu

Gopinath Tiruchinapally, Ph.D., University of Michigan, gtiruchi@umich.edu

Mohamed ElSayed, Ph.D., University of Michigan, melsayed@umich.edu

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Liver (i.e. hepatic) cancer is currently the 3rd leading cause of cancer-related deaths worldwide, and continues to lack an effective therapy. The current work involves developing a therapeutic drug delivery system targeted to hepatic cancer cells (HCC) that is able to release a loaded drug controllably within those cells. Specifically, a chemotherapeutic agent, doxorobucin (DOX), is conjugated to generation 5 (G5) polyamido-amine (PAMAM) dendrimers via different aromatic azo-linkers that exhibit a controllable release profile of DOX within HCC. We have previously shown that the display of N-acetylgalactosamine (NAcGal) ligands on G5 dendrimers through a poly(ethylene-glycol) (PEG) brush results in selective recognition and internalization of the nanoparticles into HCC via the highly expressed asialoglycoprotein receptor. The present work details the successful synthesis and characterization of NAcGal-cPEG-G5-L(x)-DOX nano-conjugates. Further, we have established that the nano-conjugates are able to selectively target and internalize into HCC (e.g. HepG2 and Hep3B cell lines) more efficiently than free DOX controls, via flow cytometry. This internalization correlated with cytotoxicity profiles that show NAcGal-cPEG-G5-L(x)-DOX nano-conjugates to have comparably toxic effects towards HCC when compared to the free drug, and this toxicity can be tailored based on the linkage chemistry. These promising results indicate the ability for the nano-conjugates to target and controllably kill hepatic cancer cells, and thus offer significant potential as a novel drug delivery system able to achieve a high local dose of chemotherapeutic agents to tumor tissue in vivo for hepatic cancer therapy.

45.

RAFT micelles for selective drug delivery to macrophages

Kate Montgomery, Imperial College London, km412@ic.ac.uk

Susan Nilsson, CSIRO, Melbourne, Australia

John Chiefari, CSIRO, Melbourne, Australia

Greg Simpson, CSIRO, Melbourne, Australia

Ben Cao, CSIRO, Melbourne, Australia

Brenda Williams CSIRO, Melbourne, Australia

Matthew Fuchter, Imperial College London, London, England

RAFT polymerisation is a versatile and flexible technique which allows for excellent control over the polymers produced.(1) In this work, we aimed to develop a series of polymeric micelle particles for application to selective drug delivery purposes, specifically to tumour associated macrophages. RAFT polymerisation was applied to the synthesis of amphiphilic block copolymers and we subsequently studied the self-assembly of our polymer samples into micelle particles under aqueous conditions. Since previous studies have shown that the size of the particle is crucial for selective phagocytosis by macrophages, a series of micelles of different sizes were prepared by altering the polymer composition and chain length.(2) The size of the particles synthesised ranged from 15 nm to nearly 200 nm. We additionally developed conditions to fluorescently label the particles as well as to crosslink them to increase their stability in vivo, and have also successfully encapsulated a fluorescent dye inside the particles. Cellular studies comparing macrophage and non-macrophage uptake have been carried out to determine the most promising candidates for selective drug delivery to macrophages. We believe that the particle's efficient uptake by macrophages, their ability to deliver an encapsulated cargo and their high stability makes them ideal for drug delivery to tumour associated macrophages.

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(2) Ahsan, F., Rivas, I. P., Khan, M. A., Torres Suarez, A. I., J. Controlled Release, 2002, 29-40

46.

Cheminformatics-driven selection of drugs for solubilization by poly(2-oxazoline) polymeric micelles to improve their delivery

Eugene Muratov, University of North Carolina at Chapel Hill, Chapel Hill, NC, murik@email.unc.edu

Ekaterina Varlamova,Federal University of Goias, Goiania, Brazil, silver.varlam@mail.ru

Marina Sokolsky, Center for Nanotechnology in Drug Delivery and Division of Molecular Therapeutics, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, msokolsk@email.unc.edu

Alexander Tropsha, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, alex_tropsha@unc.edu

Alexander Kabanov, Center for Nanotechnology in Drug Delivery and Division of Molecular Therapeutics, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, kabanov@email.unc.edu

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Poor solubility of drug candidates severely restricts the types of molecules that can be developed into marketed drugs. Use of novel biocompatible poly(2-oxazoline) (POx) polymeric micelles could greatly enhance the solubility of many hydrophobic active pharmaceutical ingredients. The ultimate goal of this project is to develop a versatile, cheminformatics-aided high throughput and high capacity Pox-based nano-formulation platform for rapid screening, selection, and successful solubilization of water insoluble or poorly water-soluble drugs. To this end, we have rationally selected a diverse chemical library of poorly soluble compounds for solubilization by poly(2-oxazoline) polymeric micelles. The dataset contained 114 combinations of 6 polymers and 12 drugs including the following: (i) 94 Polymer + Drug combinations; (ii) 18 Polymer + 2 drugs combinations; and (iii) 2 combinations Polymer + 3 drugs. We have developed special Simplex Representation of Molecular Structure (SiRMS) descriptors for polymers and modified SiRMS descriptors for mixtures to deal with drug-polymer complexes of any composition (2 polymers – 1 drug, 1 polymer – 2 drugs, 2 polymers – 3 drugs, etc.). We have developed binary models to predict drug loading capacity and loading efficiency using the developed descriptors and several machine learning techniques. These models were used for virtual screening of the Selleck library of FDA-approved drugs to prioritize the selection of new drug-polymer complexes with improved delivery properties. This pilot study helps establish a novel approach to computer-aided design of novel drug delivery systems.

47.

Host cell surface-mimicking polymersomes (nanomimics) to trap and expose malaria parasites

Adrian Najer, University of Basel and Swiss Tropical and Public Health Institute, adrian.najer@unibas.ch

Cornelia G. Palivan, University of Basel, cornelia.palivan@unibas.ch

Hans-Peter Beck, Swiss Tropical and Public Health Institute, hans-peter.beck@unibas.ch

Wolfgang Meier, University of Basel, wolfgang.meier@unibas.ch

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Infectious diseases are one of the biggest threats to public health today; they are the cause of approximately a quarter of total annual deaths worldwide. Malaria, caused by the protozoan species Plasmodium spp., is one devastating infectious disease, being responsible annually for about 600'000 reported deaths. Plasmodium parasites are an example of pathogens that utilize host heparan sulfate proteoglycan for initial attachment to host cells, which also applies to a huge variety of other pathogens including viruses, bacteria and parasites [1]. Challenges in finding an efficacious vaccine for malaria and the threat of a spread of drug resistance, motivated us to develop an alternative, nanotechnological approach, which aims for a drug- and "vaccine-like" dual action against malaria and possibly other infectious diseases [2,3].

Polymer-based vesicles (polymersomes) – possessing diameters of about 130 $\pm$ 30 nm – were successfully synthesized to mimic the outer membrane of host red blood cells (RBCs) by exposing a polysaccharide chain (heparin) of a known parasite receptor (heparan sulfate) on the surface of polymersomes (nanomimics). When added to cultured malaria parasites and human RBCs, our nanomimics very efficiently captured egressing parasites and subsequently inhibited reinvasion of fresh RBCs (drug action). This inhibitory effect was much more potent (10'000 fold) when using nanomimics compared to soluble receptors, due to multivalent interactions of nanomimics with parasites [2]. Inhibiting parasite invasion of RBCs by nanomimics also keeps a huge number of parasites extracellular, which could induce a beneficial immune response in vivo ("vaccine-like" action).

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[2] A. Najer et al. ACS Nano. 2014, 8(12), 12560–12571.

[3] A. Najer et al. Patent Application: EP14188354.6. 2014.

48.

Polyvalerolactone Hydrogel for Sustained Delivery of Tacrolimus

Duc Nguyen, Oregon State University College of Pharmacy, nguyend@onid.orst.edu

Reid Kinser, Oregon State University, kinserre@onid.orst.edu

Bhuvana S. Doddapaneni, Oregon State University College of Pharmacy, doddapab@onid.orst.edu

Adam Alani, Oregon State University College of Pharmacy, adam.alani@oregonstate.edu

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Introduction:

Tacrolimus (TAC), a common immunosuppressant used following kidney transplantation, though effective requires daily dosing to maintain a level within therapeutic window. In adolescents and young adults receiving TAC following kidney transplant, non-adherence to medication intake results in kidney rejection. In this study, we have prepared and evaluated two hydrogel formulations of TAC intended for weekly dosing in vivo model as an initial step to resolve this problem.

Methods:

Two formulations, one a TAC solution in ethanol or TAC-loaded nanoparticles each loaded into a 25% (w/v) polyvalerolactone (PVL) hydrogel solution at 1 mg/mL. The polyethylene glycol-b-polycapralactone TAC nanoparticles were prepared using solvent evaporation method. Each formulation was injected subcutaneously into 8 groups (n=32, 4/group) of mice. The volume of injection was kept between 0.5-0.75 mL and the dose was set at 16.7 mg/Kg to achieve therapeutically relevant concentrations (5 - 15 ng/mL). On days 1, 3, 5, 7, 10, 14, 21, and 28, whole blood was collected by cardiac puncture and analyzed by LC-MS/MS for TAC and creatinine concentrations. Weights, grooming and feeding behaviors were monitored on a daily basis after injection.

Results & Conclusion:

TAC-nanoparticle hydrogel formulation maintained clinically relevant TAC concentrations up to 14 days. Creatinine elevation was statistically lower in the TAC-nanoparticle hydrogel as compared to the TAC in hydrogel formulation. Overall, both formulations showed no significant toxicity in term of weight loss or change in animal behavior. PVL-based TAC-nanoparticle hydrogel formulation has a potential as a sustained delivery system for the prevention of graft rejection.

49.

Functional Polymers using RAFT for Drug Delivery Applications

Gangadhar Panambur, Sigma Aldrich Incorporated, gangadhar.panambur@sial.com

Shahinur Rehman, Sigma Aldrich Incorporated, shahinur.rahman@sial.com

Donghun Koo, Sigma Aldrich Incorporated, Donghun.Koo@sial.com

Philip Dimitrov, Sigma Aldrich Incorporated, Philip.Dimitrov@sial.com

Viktor Balema, Sigma Aldrich Incorporated, Viktor.Balema@sial.com

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Polymers represent the leading and versatile type of biomaterials being extensively applied in bio-medical applications such as drug delivery, tissue engineering, nano-medicine, medical devices etc. The versatility of polymers is attributed to the relative ease with which polymers can be designed with a range of architecture, functionality and appropriate physical, chemical and biological properties.

At Sigma-Aldrich, we are focusing on synthesizing and evaluating novel well defined synthetic polymers for Drug Delivery researches. Several classes of polymers including functional polymers, biodegradable polymers, amphiphilic polymers, hydrophilic polymers, and stimuli responsive polymers have been prepared and characterized by using advanced techniques.

In this poster presentation novel strategies for the synthesis of functional polymers for biomedical applications such as bioconjugation, drug delivery, gene transfection etc. using RAFT technology will be discussed. Amphiphilic, biodegradable and smart polymers with various functionalities will be presented.

50.

Acid-sensitive oxidative stress generating polymeric micelles as anticancer therapeutic agents

Hoyeon Park, Department of BIN Convergence Technology, Chonbuk National University, Korea, pphyy123@naver.com

Gyun Kwon, enhanced_4leaf@hanmail.net, Department of BIN Convergence Technology, Chonbuk National University , Korea

Jinsub Kim, look1206@naver.com, Department of BIN Convergence Technology, Chonbuk National University , Korea

Donghyuck Yoo, hyuck@jbnu.ac.kr, Department of BIN Convergence Technology, Chonbuk National University , Korea

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"Oxidation therapy" has arisen as a promising anticancer strategy, which can be achieved by inducing the generation of cytotoxic level of reactive oxygen species (ROS) or inhibiting the antioxidant systems in tumor cells. Cinnamaldehyde, a major active compound of cinnamon, is known to induce apoptotic cell death in numerous human cancer cells. However, its clinical uses have been limited by poor bioavailability and low therapeutic efficacy. In order to overcome these limitation of cinnamaldehyde, we have developed dual acid-responsive polymeric micelle-forming cinnamaldehyde prodrugs, poly[(3-phenylprop-2-ene-1,1-diyl)bis(oxy)bis(ethane-2,1-diyl)diacrylate]-co-4,4'(trimethylene dipiperidine)-co-poly (ethylene glycol), termed PCAE copolymers. PCAE is designed to incorporate cinnamaldehyde via acid-cleavable acetal linkages in its pH-sensitive hydrophobic backbone and self-assemble to form stable micelles which can encapsulate common anticancer drugs such as camptothetcin and antioxidant scavenging drugs. PCAE could self-assemble to form micelles which release drug payloads and cinnamaldehyde in pH-dependent manners. PCAE micelles induce apoptotic cell death through the generation of intracellular reactive oxygen species (ROS) and exert synergistic anticancer effects with a payload in vitro and in vivo model of tumor xenografts. We anticipate that dual acid-sensitive micelle-forming PCAE with intrinsic anticancer activities has enormous potential as novel anticancer therapeutics.

51.

Passive Tumor Targeting of PRINT Nanoparticles: A Function of Particle Size, Shape, and Tumor Model

Jillian Perry, University of North Carolina at Chapel Hill, perryjl@email.unc.edu

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Persistence in blood circulation is one of the main hurdles in the development of nanocarriers for cancer therapy. In this account, we have fabricated long circulating polymeric hydrogels of various sizes and shapes using the PRINT (Particle Replication In Non-wetting Templates) platform. Pharmacokinetics and biodistribution of these nanoparticles were explored in xenograft and allograft tumor models, in either orthotopic or heterotopic locations, and compared to naïve mice. Interestingly, we found that tumor accumulation was not only dependent on particle size, but also on tumor model and disease site. Developing a deeper understanding how disease dictates particle sequestration at the target-site will help establish what types of cancer are most suited for nanoparticle-based drug delivery. In our future work, we will explore the potential of particle based therapeutics.

52.

Carbamazepine stimulates mTOR-independent autophagic killing of drug-resistant Mycobacterium tuberculosis

Mark Schiebler, Cambridge Nanoscience Centre, mss58@cam.ac.uk

Mark Schiebler, Karen Brown, Krisztina Hegyi, Sandra M. Newton, Myriam Ouberai9, Maurizio Renna, Lucy Hepburn, Catherine Klappholz, Sarah Coulter, Andres Obregón-Henao, Marcela Henao Tamayo, Randy Basaraba, Beate Kampmann, Katherine M. Henry, Joseph Burgon, Stephen A. Renshaw, Angie Fleming, Karen E. Anderson, Phillip T. Hawkins, Diane J. Ordway, Mark Welland, David C. Rubinsztein & R. Andres Floto

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Mycobacterium tuberculosis (MTB) remains a major challenge to global health made worse by the spread of multi-drug resistance driven by difficulties in treatment. Antibiotic regimens for MTB infection require long durations of therapy with multiple drugs and are associated with significant side effects and a high pill burden, contributing to poor adherence, treatment failure and hence the development of drug resistance. Currently, the efficacy and safety of antibiotic regimens is limited by difficulties in achieving and sustaining antibiotic concentrations above the minimum inhibitory concentration (MIC) for MTB in tissue. There is therefore a clear unmet clinical need to improve the delivery of MTB therapy.

A drug screening approach on FDA-approved drugs used for non-infectious indications identified several autophagy enhancers. We determined that one of the hits, CBZ, had in vitro and in vivo efficacy against drug-resistant MTB (Schiebler et al, 2014). We characterised the mechanism of autophagy activation, identifying a new mTOR-independent autophagy pathway, with several potential downstream therapeutic targets. To try and improve macrophage-specific drug delivery, we have engineered polymeric nanoparticles (NP) to encapsulate the novel autophagy enhancer carbamazepine within FDA approved polymeric particles. These particles result in enhanced intracellular drug concentration and uptake into infected primary human macrophages. These results indicate that nanoparticle treatment of MTB remains an exciting prospect for enhancing the efficacy of novel host-directed drug therapy.

53.

Primaquine-polymer prodrug model as potential antimalarial for liver targeting

Selvi Srinivasan, University of Washington, selvis@uw.edu

Hye-Nam, Son, University of Washington, hyenam@uw.edu

Anthony J. Convertine, University of Washington, convertine@gmail.com

Patrick S. Stayton, University of Washington, stayton@uw.edu

Primaquine (PQ) is a widely used antimalarial for treating both liver stage infection and blood parasites, and is the only clinically validated medication against hypnozoites of P. vivax and P. ovale in the liver. However, higher drug administration necessitated by its short half-life (5~7 h) induces serious complications such as methaemoglobinemia, and hemolysis in groups with glucose-6-phosphate 1-dehydrogenase (G6PD) deficiency. In an attempt to reduce the mass drug administration and associated toxicity, we have designed a prodrug polymer system carrying PQ and targeting ligand N-acetylgalactosamine (GalNAc) for site selective delivery that can release the drug in liver tissue and maintain sustained levels of drug by enzymatic hydrolysis. As a first step, we have prepared a monomer by conjugating PQ to mono-2-(methacryloyloxy)ethylsuccinate through benzyl carbamate linkage capable of undergoing enzymatic hydrolysis followed by rapid 1,6-β-elimination to release the free drug PQ. A copolymer was successfully made by incorporating this monomer along with polypegma using reversible addition fragmentation chain transfer (RAFT) technique. Release of PQ from the copolymer was evaluated in mouse liver microsomes as well as in human serum at 37 ^{0}C by HPLC. Percentage of PQ released by microsomes was 40 % in 3 h, and serum required more than 24 h to release the same dose of PQ. The faster hydrolysis kinetics by liver microsomes compared to serum suggest that this system is sufficiently stable in serum prior to bioactivation, and could be a promising material for further modification with targeting GalNAc to act against liver stage malarial parasites.

54.

Bioactive polymeric nanocarriers for intracellular antibiotic delivery for the treatment and prevention of pulmonary infection

Fang-Yi Su, University of Washington, fysutw@uw.edu

Anthony Convertine, University of Washington, Department of Bioengineering, aconv@uw.edu

Jasmin Chen, University of Washington, Department of Bioengineering, jasminchen33@gmail.com

Abby Kelly, University of Washington, Department of Bioengineering, abbymichellekelly@gmail.com

David Chiu, PhDepartment of Bioengineering, chiudys@gmail.com

Daniel Ratner, University of Washington, Department of Bioengineering, dratner@uw.edu

Patrick Stayton, University of Washington, stayton@uw.edu (corresponding author)

Pulmonary infections caused by Francisella tularensis and Burkholderia pseudomallei (tularemia and melioidosis, respectively) are highly lethal in untreated patients. The intracellular compartmentalization of these bacteria within alveolar macrophages presents a challenging barrier to bacterial clearance and contributes to their associated morbidity and mortality. Current treatments against these bacterial pathogens rely on oral delivery and intravenous injection of antibiotics, which entail drawbacks such as systemic toxicity, limited bioavailability to the infection sites, and high rate of relapse. Herein, two novel "smart" polymeric nanocarrier systems, polymersomes and polymer-augmented liposomes, have been developed to provide prophylactic and therapeutic antibiotic delivery to prevent and/or treat presymptomatic tularemia and melioidosis. The polymers endow these antibiotic delivery systems with biocompatibility, transport stability, and minimize off-target cell uptake and toxicity. Additionally, these antibiotic carriers have pH-sensing functionalities to mediate nanoparticle disassembly and to destabilize the endosomal membrane for rapid cytosolic delivery of hydrophilic antibiotics. The pH-responsive characteristics of the two delivery systems have been shown in dynamic light scattering measurements and a red blood cell hemolysis assay, which demonstrate their pH-dependent disintegration and the ability to enhance intracellular drug release. The therapeutic efficacy of antibiotic-loaded polymersomes against intracellular infections has been confirmed using a bacteria-macrophage co-culture study using Raw 264.7 macrophages and B. thailandensis, an in vitro model for B. pseudomallei infection. These results demonstrate the potential of the polymeric drug delivery systems as potent antibiotic drug carriers capable of reaching persistent intracellular bacteria.

55.

Poly(2-oxazoline) Micellar Formulation of Single Drug and Combinatin for Cancer Therapy

Xiaomeng Wan, University of North Carolina at Chapel Hill, xiaomengwan@unc.edu

Yuanzeng Min, Department of Radiation Oncology, Lineberger Comprehensive Cancer Center, Carolina Center for Cancer Nanotechnology Excellence, University of North Carolina at Chapel Hill, yuanzeng_min@med.unc.edu

Zhijian He, Center for Nanotechnology in Drug Delivery and Division of Molecular Pharmaceutics, Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, jimmyhe@email.unc.edu

Marina Sokolsky, Center for Nanotechnology in Drug Delivery and Division of Molecular Pharmaceutics, Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, msokolsk@email.unc.edu

Rainer Jordan, Professur für Makromolekulare Chemie, Department Chemie, Technische Universität Dresden,

Alexander Kabanov, Center for Nanotechnology in Drug Delivery and Division of Molecular Pharmaceutics, Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, kabanov@email.unc.edu

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PURPOSE:

Paclitaxel (PTX) is an anticancer drug with very little aqueous solubility and require significant amount of excipients to solubilize, such as Cremophor-based paclitaxel using a Cremophor EL/ethanol vehicle, which cause toxicity and limit maximum tolerated doses. Poly (2-oxazoline) micelle is a new platform for higher PTX loading and better effect of tumor inhibition.

METHODS:

We use tri-block poly (2-oxazoline)s (POx) polymer to make micellar formulation of paclitaxel as a high capacity delivery strategy for cancer therapy. Maximum tolerate dosage is tested on female nude mice. Xenograft model of A2780 human ovarian cancer cells on nude mice and T11 orthotopic syngeneic transplants (OST) breast cancer models are used for evaluation of anti-tumor activity. Taxol and Abraxane are used as control. Pharmacokinetics and biodistribution of the formulation are studied on A2780 tumor bearing mice.

RESULTS AND CONCLUSION:

Tri-block POx micelle is able to incorporate paclitaxel (PTX) with high loading capacities up to 50 wt.% in the final formulation. The formulation is stable in size (50nm) and drug loading for at least 2 weeks. The maximum tolerate dosage (MTD) of PTX loaded POx micelle is 150mg/kg, which is much improved comparing to Taxol (20mg/kg) and Abraxane (90mg/kg) receiving an every four days four-time in total tail vein injections (q4dX4). On the xenograft model on nude mice with the MTD injections, PTX loaded POx micellar formulation shrink the tumor, and the formulation shows better tumor inhibition effect than Taxol on T-11 OST model. In conclusion, PTX loaded POx micelles provide a high drug loading, stable and effective platform of anticancer therapeutics.

56.

Development of Sunflower Polymers for Tumor-Targeted Drug Delivery

Christine Wang, University of Washington, cewang@uw.edu and Hua Wei, Lanzhou University, China, weih@lzu.edu.cn (equally contributing author)

Nicholas Tan, University of Washington, nicktzr@uw.edu

Roma Yumul, University of Washington, ryumul@uw.edu

Andrew J. Boydston, University of Washington, boydston@chem.washington.edu

Suzie H. Pun, University of Washington, spun@uw.edu

Polymeric drug carriers have been widely investigated for the delivery of chemotherapy drugs, due to their prolonged circulation time relative to free drug and greater accumulation in tumors via the "enhanced permeability and retention" (EPR) effect. For clinical translation, carriers must be able to penetrate into tumors and release drug preferentially in the tumor microenvironment, as well as be scalable in manufacturing. Recent advances in controlled radical polymerization have made it possible to synthesize polymers with increasingly complex nanostructures, such as comb, star, and cyclic polymers. In this work, we have developed polymers with a sunflower-like architecture by controlled polymerization. Sunflower polymers can be synthesized with low polydispersity and good control over particle size based on polymerization time. Polymers were targeted to cancer cells by conjugation of folate to the "petal" termini; folate-modified constructs exhibited receptor-mediated uptake in folate receptor-positive KB cells. Finally, doxorubicin (Dox) was used as a model chemotherapy drug and conjugated to the polymer core via a pH-sensitive linker. Targeted Dox-loaded sunflower polymers demonstrated intracellular release of active drug leading to cytotoxicity in KB cells.

57.

Nanomedicine for the prevention of corneal neovascularization

Qingguo Xu, Johns Hopkins School of Medicine, qxu15@jhmi.edu

Bing Wang, Johns Hopkins School of Medicine, bwang9@jhu.edu

Yating Tang, Johns Hopkins School of Medicine, ytang30@jhu.edu

Baiwei Chen, Johns Hopkins School of Medicine, baiweichen5@gmail.com

Yumin Oh, Johns Hopkins School of Medicine, yoh11@jhmi.edu

Nicholas Lamb, Johns Hopkins School of Medicine, nicklamb88@me.com

Shiyu Xia, Johns Hopkins University, shiyu@jhu.edu

Zheng Ding, Johns Hopkins University, zding5@jhu.edu

David Emmert, Johns Hopkins School of Medicine, demmert@jhmi.edu

María J. Suárez, Johns Hopkins School of Medicine, mariajose1621@gmail.com

Charles G. Eberhart, Johns Hopkins School of Medicine, ceberha@jhmi.edu

Walter J. Stark, Johns Hopkins School of Medicine, wstark@jhmi.edu

Justin Hanes, Johns Hopkins School of Medicine, hanes@jhmi.edu

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The cornea is avascular and transparent. Various pathological conditions can induce the corneal neovascularization, which consequently can compromise visual acuity, increase the risk of corneal graft rejection and eventually lead to complete vision loss. Current mainstay treatments for corneal neovascularization include topical corticosteroids and non-steroid anti-inflammatory medications. However, eye drops undergo rapid ocular clearance, thus very frequent administration is required. Here we developed nanoparticles (NP) loaded with corticosteroids to inhibit the corneal neovascularization in a rat model. Dexamethasone sodium phosphate (DSP) was co-encapsulated with zinc into poly(lactic-co-glycolic acid) (PLGA) nanoparticles (DSP-NP). Corneal neovascularization was induced by suturing the cornea. After the placement of sutures, the animals were randomly divided into 3 groups undertaking one single 50 μL subconjunctival injection: 1) saline, 2) free drug (6mg DSP/ml) and 3) DSP-NP (6mg DSP/ml). Nanoparticles exhibit a diameter of 200 nm, high drug loading of 8wt% and controlled drug release profile over 15 days. Subconjunctival administration of DSP-NP to rat eyes prevented corneal neovascularization up to 2 weeks without new blood vessel growth to the cornea. In comparison, control groups of either saline or free drug solution, new blood vessels started to grow from day 3 and intensive new blood vessels covered the whole suture area within 7 days. VEGF, MMPs, bFGF and TNF-α mRNA expressions were down-regulated in the corneas undertaken the DSP-NP treatment. DSP-NP did not induce increased IOP. This corticosteroid nanoparticle treatment strategy effectively inhibited the corneal neovascularization, and may improve patient compliance through reducing the administration frequency.

58.

Dequalinium-coated Poly(lactide-co-glycolide) Nanoparticles to Overcome Paclitaxel Resistance in Ovarian Cancer cells

Venkata Yellepeddi, Roseman University of Health Sciences, vyellepeddi@roseman.edu

KyungMi Kim, Roseman University of Health Sciences, kkim4@student.roseman.edu

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Dequalinium (DQA) is an antimicrobial agent which has a unique ability to preferentially accumulate in mitochondria. Therefore, mitochondrial-targeting property of DQA has been exploited for intracellular delivery of various chemotherapeutic agents, macromolecules and genes.

Paclitaxel (Taxol®) is an anticancer agent widely used as an effective agent in the treatment of various solid tumors including ovarian, breast and non-small cell lung cancers. However, development of resistance due to p-glycoprotein mediated efflux is one of the major drawbacks associated with paclitaxel therapy. In the present study, DQA-coated poly (lactide-co-glycolide) nanoparticles (NP's) loaded with paclitaxel were prepared and their ability to overcome paclitaxel resistance in ovarian cancer cells was investigated in vitro.

DQA-coated PLGA NP's loaded with paclitaxel were prepared by modified solvent diffusion technique and their physicochemical properties such as size, zeta potential, encapsulation efficiency etc. were characterized. The in vitro cytotoxicity of DQA-coated PLGA NPs was evaluated in paclitaxel-sensitive (OVCAR-3) and paclitaxel-resistant (NCI/ADR-RES) ovarian cancer cells. The in vitro cellular uptake of paclitaxel in both cell lines was also evaluated using high performance liquid chromatography (HPLC).

The IC50 of DQA-coated PLGA-paclitaxel NPs was approximately 17-fold lower in paclitaxel-resistant NCI/ADR-RES cells when compared to paclitaxel alone. However, there was only 3-fold decrease in IC50 of paclitaxel in paclitaxel-sensitive OVCAR-3 cells. The in vitro cellular uptake studies showed that in both cell lines DQA-coated PLGA NPs were able to enhance cellular uptake and reduce efflux. Therefore, DQA-coated PLGA NPs can be potentially used as nanocarriers to overcome paclitaxel resistance in ovarian cancers.

59.

Inflammation-responsive polymeric prodrug nanoparticles for the treatment of inflammatory liver diseases

Donghyuck Yoo, Department of BIN Convergence Technology, Chonbuk National University, Korea, Hyuck@jbnu.ac.kr

Gyun Kwon, enhanced_4leaf@hanmail.net, Department of BIN Convergence Technology, Chonbuk National University , Korea

Jinsub Kim, look1206@naver.com, Department of BIN Convergence Technology, Chonbuk National University , Korea

Hoyeon Park, pphyy123@naver.com, Department of BIN Convergence Technology, Chonbuk National University , Korea

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Overproduction of ROS (reactive oxygen species) such as hydrogen peroxide (H2O2) leads to oxidative stress, causing inflammation and cellular death. H2O2 is one of the most stable and abundant ROS and H2O2-mediated oxidative stress is a key mediator of cellular damages during various inflammatory diseases. Therefore, H2O2 could hold tremendous potential as a therapeutic target for oxidative stress-associated inflammatory conditions such as ischemia-reperfusion (I/R) injury and acute liver failure. Vanillin, a major component of natural vanilla, has potent antioxidant and anti-inflammatory activities. We developed a novel inflammation-responsive antioxidant polymeric prodrug of vanillin, poly(vanillin oxalate) (PVO). In design, PVO incorporates H2O2-reacting peroxalate ester bonds and bioactive vanillin via acid-responsive acetal linkages in its backbone. In cells undergoing damages by oxidative stress, PVO readily degraded into three nontoxic components, one of which is antioxidant and anti-inflammatory vanillin. Therapeutic efficacy of PVO nanoparticles was evaluated using cell culture models and mouse models of hepatic I/R and acute liver failure. PVO nanoparticles significantly suppressed the liver damages during hepatic I/R and acute liver failure, by scavenging ROS and inhibiting inflammation and apoptosis. We therefore, anticipate that PVO nanoparticles have great potential as novel antioxidant therapeutics and drug delivery systems for ROS-associated inflammatory diseases.

60.

DENDRIMER BASED SYSTEMIC THERAPIES FOR THE TREATMENT OF GLIOBLASTOMA

Fan Zhang, Johns Hopkins University, zfan.eng@gmail.com

Zhang Fan, Mastorakos Panagiotis, Mishra Manoj, Mangraviti Antonella, Zhou Jinyuan, Hanes Justin, Brem Henry, Olivi Alessandro, Tyler Betty, Kannan Rangaramanujam

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Malignant glioma is the most common and most aggressive primary brain tumor. Despite the advances in treatment, the median survival remains at 16.4 months. Recent advances in nanotechnology have offered multiple novel platforms for targeted, sustained and controlled delivery of therapeutics in order to overcome the limitations of traditional small molecule drugs. However, the small 'cut off size' of the brain tumor microvasculature pores, the relatively large and heterogeneous intervascular distances in combination with the tortuous and dense extracellular matrix, impose serious limitations in the ability of nanoparticles to reach target cells. Hydroxyl-terminated poly(amidoamine) (PAMAM) dendrimers, with their small size, near-neutral surface charge, and safety profile may offer new opportunities to address these challenges. In addition, dendrimers have demonstrated promising results in targeting neuroinflammation, promising their potential to be taken-up by tumor associated macrophage (TAM). In this study we show systemically delivered hydroxyl terminated PAMAM dendrimer uniformly and selectively distributed through the entire solid tumor and peritumoral area 15 min after injection with subsequent co-localization and retention in TAM even at 48 hours post injection. The rapid clearance of systemically administered dendrimers from major organs promises minimal off-target adverse effects of conjugated drugs. This comprehensive study of the pharmacokinetics and biodistribution of dendrimers in a rodent gliosarcoma model provides crucial information for the design and engineering of dendrimer-drug conjugates for effective treatment of glioblastoma.

61.

Defining Essential Considerations to Achieve Optimal, Local Nanocarrier Delivery to the Brain

Clark Zhang, Johns Hopkins University School of Medicine, czhang30@jhmi.edu

Panagiotis Mastorakos, MD, Johns Hopkins University School of Medicine, panagiotis.mastorakos@gmail.com

Miguel Sobral, Johns Hopkins University School of Medicine, msobral1@jhu.edu

Sneha Berry, Johns Hopkins University School of Medicine, sberry14@jhu.edu

Eric Song, Johns Hopkins University School of Medicine, ericsong@jhu.edu

Elizabeth Nance, PhD, Johns Hopkins University School of Medicine, enance2@jhu.edu

Jung Soo Suk, PhD, Johns Hopkins University School of Medicine, jsuk@jhmi.edu

Justin Hanes, PhD, Johns Hopkins University School of Medicine, hanes@jhmi.edu

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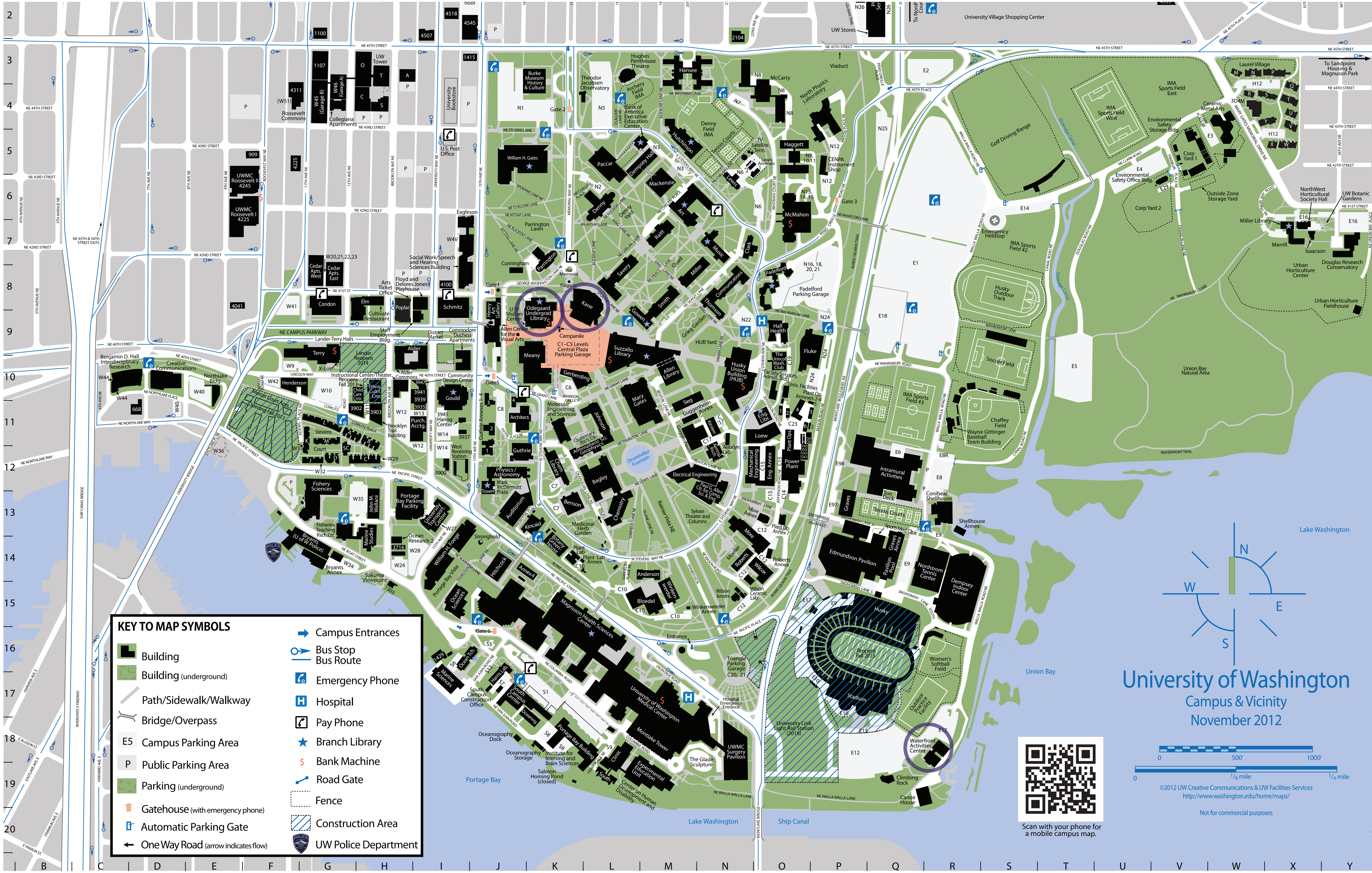
Local administration of therapeutics into the central nervous system using convection enhanced delivery (CED) is a promising strategy as it avoids the highly selective blood brain barrier and utilizes a pressure driven flow to drive therapeutics to far distances away from the administration site. However, numerous clinical trials employing CED have failed, likely due to poor therapeutic distribution that arises as a result of anatomical barriers such as components of the brain extracellular matrix and the low-resistance perivascular spaces that serve as a sink. These revelations have limited the translational applicability of CED as an administration method. To understand and further address these barriers, we use probe nanoparticles to identify the necessary conditions that improve nanocarrier distribution within the rodent striatum following CED. More specifically, our strategy entails delivering nanoparticles possessing non-adhesive surfaces via CED in a hyperosmolar infusate solution. This combined approach minimizes the hindrances imposed by the brain extracellular matrix and reduces the therapeutic sequesteration that occurs within perivascular spaces, thereby enabling significantly improved therapeutic distribution within the extracellular spaces of the brain parenchyma. These findings provide a strategy to overcome several key limitations of CED that have been previously observed in clinical trials, potentially offering a breakthrough for the treatment of neurological diseases using CED.



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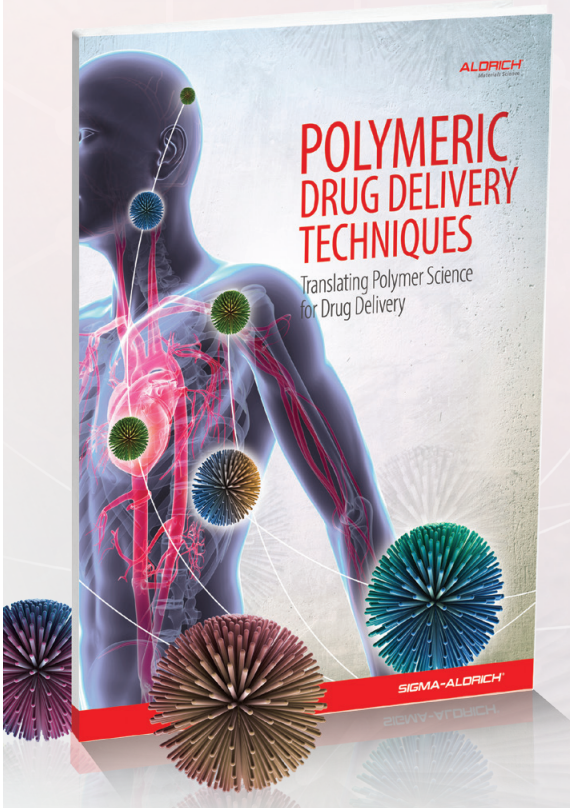

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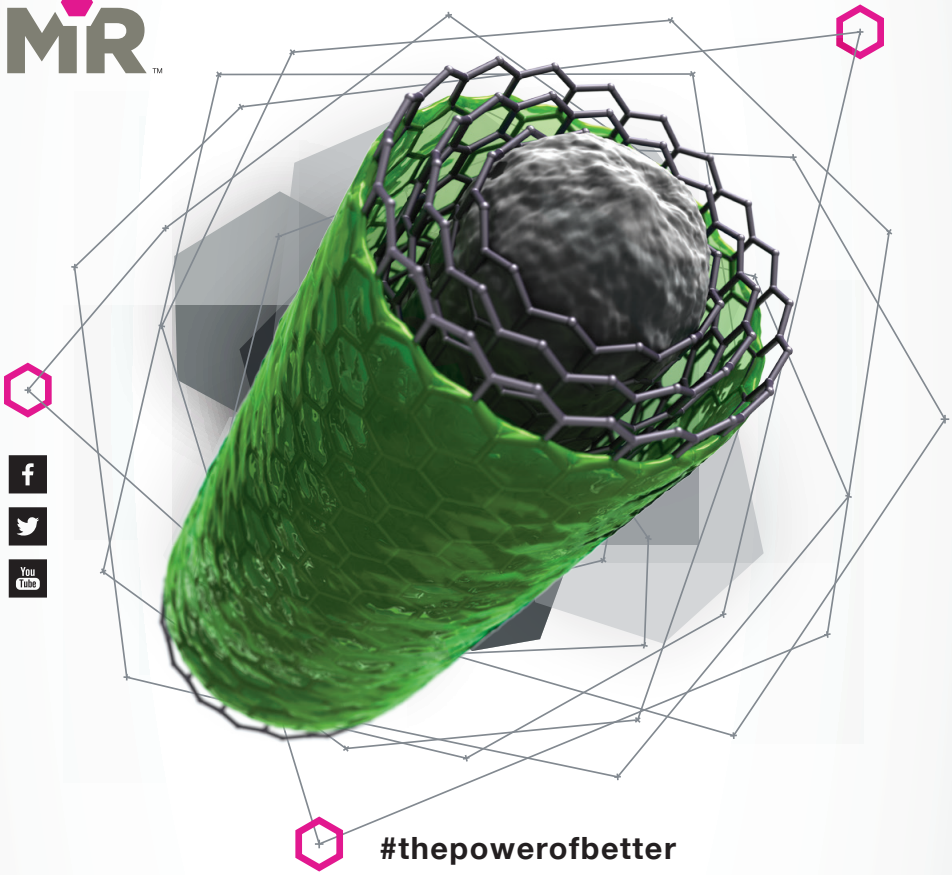

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