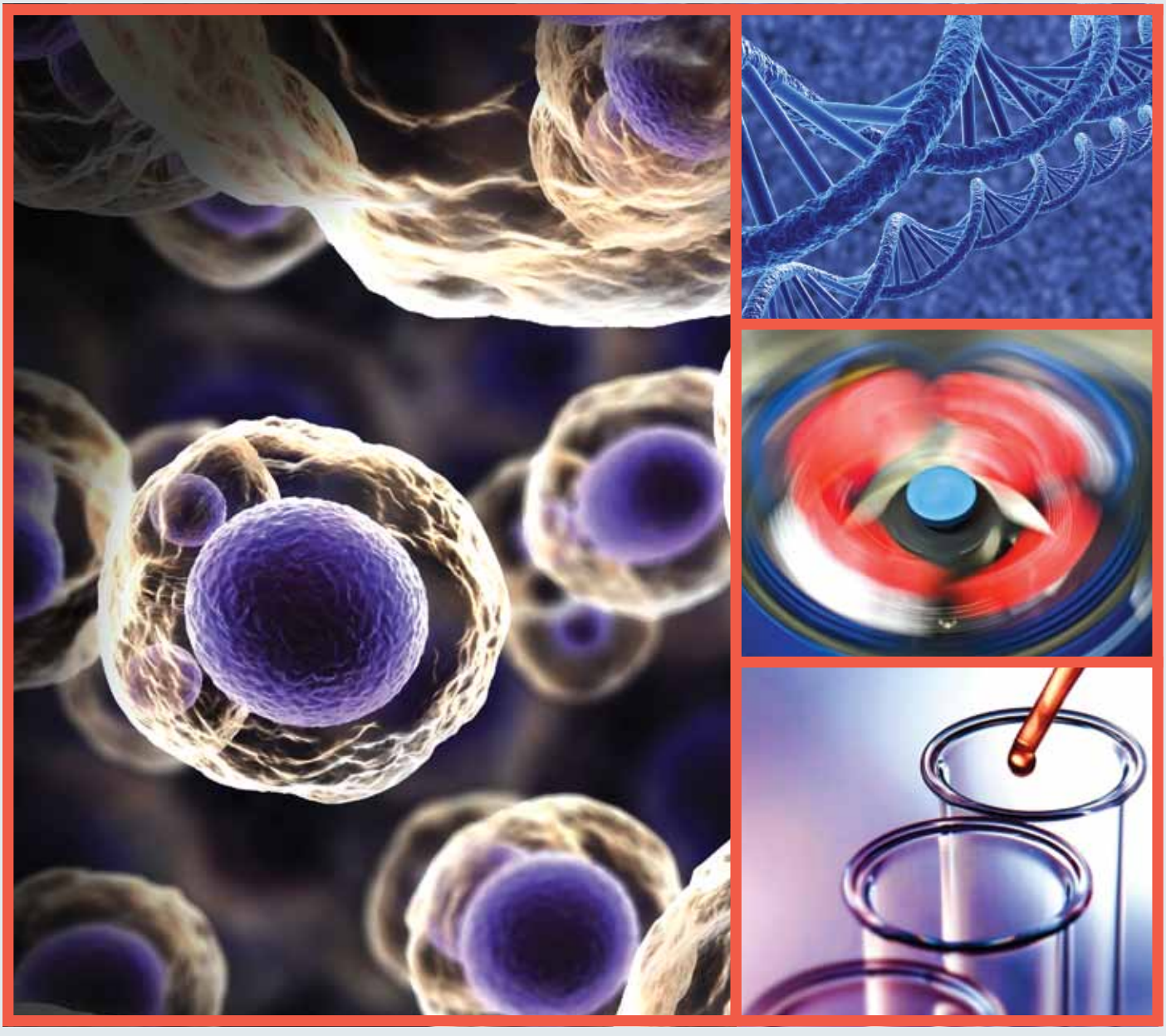
SBE's 6th International Conference on Bioengineering and Nanotechnology

ICBN 2012



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Society for Biological Engineering
An AIChE Technological Community

Institute of Bioengineering and Nanotechnology
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University of California, Berkeley Campus

June 24 – 27, 2012

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ICBN 2012

Program Overview

Sunday, June 24		
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6:30 – 6:40 PM	**Welcome by Matthew Tirrell and Luke Lee**	Claremont Hotel
6:40 – 7:40 PM	**Keynote Address – Shuming Nie (Georgia Institute of Technology)**	Claremont Hotel
7:40 – 9:00 PM	Dinner	Claremont Hotel
Monday, June 25		
7:30 AM – 3:00 PM	**Registration**	First Floor Atrium
8:00 – 8:30 AM	Breakfast	B1 Atrium
8:30 – 9:30 AM	**Keynote Address – Joe DeSimmone (University of North Carolina)**	105 Stanley Hall Aud.
9:30 – 11:00 AM	**Session 1: Drug, Protein and Gene Delivery Systems**	105 Stanley Hall Aud.
11:00 – 11:30 AM	Coffee Break	B1 Atrium
11:30 AM – 1:00 PM	**Session 1: Drug, Protein and Gene Delivery Systems**	105 Stanley Hall Aud.
1:00 – 2:00 PM	Lunch	B1 Atrium
2:00 – 3:30 PM	**Session 2: Nanoparticles, Nanocomposites and Nanoporous Materials for Bio-Applications**	105 Stanley Hall Aud.
3:30 PM – 4:00 PM	Coffee Break	B1 Atrium
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7:30 AM – 1:00 PM	**Registration**	First Floor Atrium
8:00 – 8:30 AM	Breakfast	B1 Atrium
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Wednesday, June 27		
7:30 – 10:00 AM	**Registration**	First Floor Atrium
8:00 – 8:30 AM	Breakfast	B1 Atrium
8:30 – 9:30 AM	**Keynote Address – Ali Khademhosseini (Harvard University)**	105 Stanley Hall Aud.
9:30 – 11:00 AM	**Session 5: Cell and Tissue Engineering**	105 Stanley Hall Aud.
11:00 – 11:30 AM	Coffee Break	B1 Atrium
11:30 AM – 1:00 PM	**Session 5: Cell and Tissue Engineering**	105 Stanley Hall Aud.
1:00 – 2:00 PM	**Keynote Address and Lunch – Mark Saltzman (Yale University)**	105 Stanley Hall Aud.
2:00 – 2:15 PM	Awards and Closing Remarks	B1 Atrium

Welcome Letter

Greetings!

It is a pleasure to welcome you to Berkeley, California for the Society for Biological Engineering's Sixth International Conference on Bioengineering and Nanotechnology (ICBN)! This year's conference is co-organized by the Institute of Bioengineering (IBN) and the Nanoscale Science Engineering Forum (NSEF). The meeting, titled "Bionanoscience and Bioengineering for Translational Medicine" will foster greater knowledge exchange and collaboration in the areas of bioengineering and nanotechnology — two interdisciplinary fields that cut across and integrate different areas in science, engineering, and medicine to create breakthroughs in biomedical research.

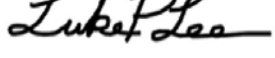
This meeting features 35 speakers and 44 posters to be presented from Sunday June 24th to Wednesday June 27th at the Berkeley campus. We hope that you will be able to take time to enjoy all of the speakers during the next three days and actively participate in the poster sessions. We have arranged to make all of the posters available for viewing during the entire meeting with the hope that it will allow you to thoroughly view each of them during the coffee and lunch breaks during the meeting.

We trust that you will also enjoy the social and networking events that we have scheduled in Berkeley. We hope you will be able to join us for our reception on Sunday evening, June 24th at the Claremont Hotel. The conference dinner will be held following the keynote address by Shuming Nie on Sunday.

We would like to thank all the keynote and invited speakers, contributed talks, poster presenters, sponsors, organizers, and people who made this conference possible. In addition, we would like to thank the NSF for their committed support of student travel grants.

On behalf of the Organizing Committee,

Matthew Tirrell
Co-Chair



Luke Lee
Co-Chair

Organizing Committee

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Organizing Society and Poster Instuctions

The Society for Biological Engineering (SBE), an AIChE Technological Community, is a global organization of leading engineers and scientists dedicated to advancing the integration of biology with engineering. The mission of SBE is to promote the integration of biology with engineering and realize its benefits through bioprocessing, biomedical and biomolecular applications by connecting people, cultivating knowledge, and catalyzing the future.

SBE PROVIDES:

- An international professional network
- Discounts on leading biological engineering conferences
- News that is relevant
- Access to academic and industrial experts
- A voice in education, employment and technology advancement.
- Free live and archived webinars

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SBE is governed by a Managing Board of industrial and academic leaders, which sets the course for the society.

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PRESENTATION INSTRUCTIONS

SPEAKERS

Speakers should plan to meet the session chair at least 15 minutes prior to the session. Please sit in the front of the room during your session. Your presentation must be uploaded to the conference computer at least 30 minutes before the session. The presentation needs to be in either PowerPoint or PDF format. It is the job of the speakers and session chairs to ensure that all talks are ready for presentation. Speakers will have 15 minutes for their talk, including questions. Please help us remain on time.

POSTER PRESENTERS

Please set up your poster in the **First Floor Atrium in Stanley Hall** before the sessions begin on Monday. Posters may be left up until Wednesday morning at 9 AM.

IMPORTANT ADDRESSES

SBE staff will be available at the Registration Booth in the Prefunction Area outside of Stanley Hall at the following times:

Sunday, June 24, 4 pm - 5:30 pm
Monday, June 25, 7:30 am - 3 pm
Tuesday, June 26, 7:30 am - 1 pm
Wednesday, June 27, 7:30 am - 10 am

Following the conference, you may reach SBE by email at bio@aiche.org.

Technical Program

Sunday, June 24	Event and Speaker
5:30 – 6:30 PM	**Reception**
6:30 – 6:40 PM	**Welcome by Matthew Tirrell (*University of Chicago*) and Luke Lee (*University of California, Berkeley*)**
6:40 – 7:40 PM	**KEYNOTE ADDRESS – Shuming Nie (*Georgia Institute of Technology*) – Nanotechnology for Intraoperative Tumor Detection and Image-Guided Surgery**
7:40 – 9:00 PM	Dinner
Monday, June 25	
7:30 AM – 3:00 PM	Registration
8:00 – 8:30 AM	Breakfast
9:30 – 9:30 AM	**KEYNOTE ADDRESS – Joe DeSimmone (*University of North Carolina*) – Co-opting Moore's Law: The Cost-effective Design of Vaccines and Therapeutics**
9:30 – 11:00 AM	**Session 1: Drug, Protein and Gene Delivery Systems**
	Chairs: Tejal Desai *(University of California, Berkeley)* and Zev Gartner *(University of California, San Francisco)*
9:30 – 10:10 AM	Theresa Reineke *(University of Minnesota)* – Carbohydrate-Based Block Copolymers Designed for the Delivery of Drugs and Nucleic Acids
10:10 – 10:35 AM	Harry Bermudez *(University of Massachusetts, Amherst)* – DNA-Based Vehicles for the Delivery of Functional Nucleic Acids and Proteins
10:35 – 11:00 AM	Richard W. Roberts *(University of Southern California)* – Directed Evolution of Stable, Orally Bioavailable S-U-P-R Peptides
11:00 – 11:30 AM	Coffee Break
11:30 AM – 1:00 PM	**Session 1: Drug, Protein and Gene Delivery Systems**
11:30 AM – 12:10 PM	Tatiana Segura *(UCLA)* - Bionanotechnology to Guide Vessel Sprouting
12:10 – 12:35 PM	David V. Schaffer *(University of California, Berkeley)* – Directed Evolution of New Viruses for Therapeutic Gene Delivery
12:35 – 1:00 PM	Divya Chandra *(Rensselaer Polytechnic Institute)* – Targeted Drug Delivery to the Brain Using Transferrin-Binding Peptides
1:00 – 2:00 PM	Lunch
2:00 – 3:30 PM	**Session 2: Nanoparticles, Nanocomposites and Nanoporous Materials for Bio-Applications**
	Chairs: Jessica Winter *(The Ohio State University)* and Seung Wuk Lee *(University of California, Berkeley)*
2:00 – 2:40 PM	Warren Chan *(University of Toronto)* – The Complexities of Nanoparticle Tumor Targeting
2:40 – 3:05 PM	Jessica O. Winter *(The Ohio State University)* – Magnetic Quantum Dots and Magnetic Microarrays for Cell and Molecular Detection
3:05 – 3:30 PM	Bahman Anvari *(University of California, Riverside)* – Nano-Constructs Fabricated From a Genome-Depleted Plant Virus and Indocyanine Green for near Infrared Imaging and Phototherapy
3:30 – 4:00 PM	Coffee Break
4:00 – 5:30 PM	**Session 2: Nanoparticles, Nanocomposites and Nanoporous Materials for Bio-Applications**
4:00 – 4:40 PM	**Jinwoo Cheon *(Yonsei University)* – Magnetic Nanoparticles for Imaging and Therapeutics**
4:40 – 5:05 PM	Noah Malmstadt *(University of Southern California)* – Mechanical Deformation of Synthetic Cell Membranes by Nanoparticle Interactions
5:05 – 5:30 PM	Ling Ching Wong *(Imperial College London)* – Polymer Foam Nanocomposites Synthesised Via Nanoparticle Stabilised Emulsions
5:30 – 6:30 PM	**Poster Session**
Tuesday, June 26	
7:30 AM – 1:00 PM	**Registration**
8:00 – 8:30 AM	Breakfast
8:30 – 9:30 AM	**KEYNOTE ADDRESS – Christina Smolke *(Stanford University)* – Designing Synthetic Regulatory RNAs: New languages for Programming Biological Systems**
9:30 – 11:00 AM	**Session 3: Synthetic Biology**
	Chair: David Schaffer *(University of California, Berkeley)*
9:30 – 10:10 AM	Drew Endy *(Stanford University)* – Finally! A Workable Abstraction Hierarchy for Engineering Integrated Gene Expression Systems

10:10 – 10:35 AM	Sai T. Reddy *(University of Texas Austin)* – Systems Immunology Approach for Antibody Discovery and B Cell Repertoire Analysis
10:35 – 11:00 AM	Lei Qi *(University of California, Berkeley)* – Developing Versatile RNA-Based Genetic Programs
11:00 – 11:30 AM	Coffee Break
11:30 AM – 1:00 PM	**Session 3: Synthetic Biology**
11:30 AM – 12:10 PM	**Andre Levchenko *(Johns Hopkins University)* – From Wires to Grooves: Nano-Engineering of Cell Behavior**
12:10 – 12:35 PM	Joshua P. Ferreira *(Stanford University)* – Synthetic Optimization of the MAPK and PI3K Pathways for Cell Proliferation and Survival
12:35 – 1:00 PM	Patrick Benitez *(Stanford University)* – Nanofibrous Elastin-Like Protein As a Biomimetic Platform for Multifactorial Control of Cell-Matrix Interactions
1:00 – 2:00 PM	Lunch
2:00 – 3:30 PM	**Session 4: Biological Devices/Biosensors and Molecular Diagnostics**
	Chairs: Tom Soh *(University of California, Santa Barbara)* and Lydia Sohn *(University of California, Santa Barbara)*
2:00 – 2:40 PM	**Amy Herr *(University of California, Berkeley)* – Talking about a Revolution: Microfluidic Integration for Next-Generation Protein Analysis**
2:40 – 3:05 PM	Xiaoxia Nina Lin *(University of Michigan, Ann Arbor*) – A Microfluidic Platform for Droplet-Enabled Co-Cultivation of Microbial Communities
3:05 – 3:30 PM	Niren Murthy *(University of California, Berkeley)* – Maltodextrins Image Early Stage Bacterial Infections and Drug Resistance by Positron Emission Tomography
3:30 – 4:00 PM	Coffee Break
4:00 – 5:30 PM	**Session 4: Biological Devices/Biosensors and Molecular Diagnostics**
4:00 – 4:40 PM	**Seung-Hun Hong *(Seoul National University)* – Hybrid Nanobio-Devices Based on Carbon Nanostructures and Biomolecules**
4:40 – 5:05 PM	Karthik Balakrishnan *(University of California, Berkeley)* – Multimarker Cellular Screening Using Variable Cross-Section Pores
5:05 – 5:30 PM	H. Tom Soh *(University of California, Santa Barbara)* – Rapid Directed Evolution of Molecules In Microfluidic Systems
5:30 – 6:30 PM	**Poster Session**
Wednesday, June 27	
7:30 – 10:00 AM	**Registration**
8:00 – 8:30 AM	Breakfast
8:30 – 9:30 AM	**KEYNOTE ADDRESS – Ali Khademhosseini (*Harvard University)* – Microengineered Hydrogels for Stem Cell Bioengineering and Tissue Regeneration**
9:30 – 11:00 AM	**Session 5: Cell and Tissue Engineering**
	Chairs: Sanjay Kumar *(University of California, San Francisco)* and Song Li *(University of California, Berkeley)*
9:30 – 10:10 AM	**Jason Burdick *(University of Pennsylvania)* – Engineering Hydrogel Structure and Degradation for Cardiac Repair**
10:10 – 10:35 AM	Widya Mulyasasmita *(Stanford University)* – Injectable Protein-Engineered Hydrogels to Improve Cell Transplantation
10:35 – 11:00 AM	Joanna Mackay *(University of California, Berkeley)* – Genetically Engineering Cellular Mechanobiology Through RhoA and Mlck
11:00 – 11:30 AM	Coffee Break
11:30 AM – 1:00 PM	**Session 5: Cell and Tissue Engineering**
11:30 AM – 12:10 PM	**Yasuyuki Sakai *(University of Tokyo)* – Microtechnologies and Chemical Engineering for Organization of Liver Tissue**
12:10 – 12:35 PM	Christina Chan *(Michigan State University)* – Signaling Molecules Induced by cAMP and the Mechanical Environment On MSC Morphology and Function
12:35 – 1:00 PM	Andrew E. Rodda *(Monash University)* – Nano-Bottlebrush Electrospun Fibres for Investigation of Cell-Substrate Interactions
1:00 – 2:00 PM	**KEYNOTE ADDRESS AND LUNCH – Mark Saltzman *(Yale University)* – Systemically Delivered Polymer Nanoparticles Mediate Site-Specific Genome Editing in Human Hematopoietic Cells**
2:00 – 2:15 PM	Awards and Closing Remarks

Speaker Biographies

Conference Chairs

Luke Lee

University of California, Berkeley

Luke P. Lee is a 2010 Ho-Am Laureate. He is Arnold and Barbara Silverman Distinguished Professor of Bioengineering at UC Berkeley, the Director of the Biomedical Institute of Global Healthcare Research & Technology (BIGHEART) and a Co-Director of the Berkeley Sensor & Actuator Center. He was Chair Professor in Systems Nanobiology at the Swiss Federal Institute of Technology (ETH, Zurich). He received his B.A. in Biophysics and Ph.D. in Applied Science & Technology: Applied Physics (major) / Bioengineering (minor) from UC Berkeley. He has more than ten years of industrial experience in integrated optoelectronics, Superconducting Quantum Interference Devices (SQUIDs), and biomagnetic assays. His current research interests are bionanoscience, nanomedicine for global healthcare and personalized medicine, and Bioinspired Photonics-Optofluidics-Electronics Technology and Science (BioPOETS) for green building with living skin. Prof. Lee has authored and co-authored over 250 papers on bionanophotonics, microfluidics, single cell biology, quantitative biomedicine, molecular diagnostics, optofluidics, BioMEMS, biosensors, SQUIDs, SERS, and nanogap junction biosensor for label-free biomolecule detection.

Matthew Tirrell

University of Chicago

Matthew Tirrell, a pioneering researcher in the fields of biomolecular engineering and nanotechnology, is the founding Pritzker Director of the Institute for Molecular Engineering. Tirrell specializes in the manipulation and measurement of the surface properties of polymers, materials that consist of long, flexible, chain molecules. His work combines microscopic measurements of intermolecular forces with creation of new structures. His work has provided new insight into polymer properties, especially surface phenomena such as adhesion, friction, and biocompatibility, and new materials based on self-assembly of synthetic and bio-inspired materials.

Keynote Speakers

Joseph M. DeSimone

University of North Carolina at Chapel Hill
North Carolina State University

Joseph DeSimone is the Chancellor's Eminent Professor of Chemistry at the University of North Carolina at Chapel Hill and William R. Kenan Jr. Professor of Chemical Engineering at North Carolina State University. DeSimone is also an Adjunct Member at Memorial Sloan-Kettering Cancer Center in New York. DeSimone has published over 280 scientific articles and has 120 issued patents in his name with over 120 patents pending. In 2005 DeSimone was elected into the National Academy of Engineering and the American Academy of Arts and Sciences.

DeSimone has received over 40 major awards and recognitions including the 2012 Walston Chubb Award for Innovation by Sigma Xi, 2011 Mendel Medal from Villanova, 2010 AAAS Mentor Award, the 2009 NIH Director's Pioneer Award, the 2009 North Carolina Award, and the 2008 Lemelson-MIT Prize for Invention and Innovation. In 2002 DeSimone, along with Dr. Richard Stack (Duke University) and Dr. Robert Langer (MIT), co-founded Bioabsorbable Vascular Solutions (BVS) to commercialize a fully bioabsorbable, drug-eluting stent. The stent achieved CE Mark approval in Europe in 2011 and is being further evaluated in a series of international clinical trials led by Abbott for the treatment of coronary artery disease.

DeSimone's group is now heavily focused on harnessing the fabrication technologies from the semiconductor industry to design high-performance, cost-effective vaccines and medicines. DeSimone and his team have developed a roll-to-roll particle fabrication technology called PRINT (Particle Replication in Non-wetting Templates). They are exploiting the advantages of PRINT to generate "calibration quality" nano-tools to define the geometric (size, shape), surface (zeta potential, stealthing ligands), and deformability limitations for the effective delivery of drugs and vaccines. DeSimone recently launched Liquidia Technologies (www.liquidia.com), which employs roughly 60 people in Research Triangle Park, North Carolina and has raised over $60 million in venture financing, including the first ever equity investment by the Bill and Melinda Gates Foundation in a for-profit biotech company. Liquidia has converted PRINT into a GMP compliant process and has recently brought its first product, a seasonal influenza vaccine based on PRINT particles, into its first clinical trial. DeSimone received his BS in Chemistry in 1986 from Ursinus College in Collegeville, PA and his Ph.D. in Chemistry in 1990 from Virginia Tech.

Ali Khademhosseini

Harvard University

Dr. Ali Khademhosseini is an internationally recognized bioengineer regarded for his contributions and research in the area of biomaterials and tissue engineering. Currently he is an associate professor at Harvard University and holds appointments at the Harvard-MIT Division

of Health Sciences Technology, Brigham & Women's Hospital and Tohoku University. He has published more than170 refereed publications and 35 book chapter. He holds numerous awards and distinctions, including the Presidential Early Career Award for Scientists and Engineers as well as the young investigator awards in the fields of chemical engineering, mechanical engineering, electrical engineering, tissue engineering, and biomaterials science.

Shuming Nie

Georgia Institute of Technology

Professor Nie received his BS degree from Nankai University (China) in 1983, earned his MS and PhD degrees from Northwestern University (1984-1990), and did postdoctoral research at both Georgia Institute of Technology and Stanford University (1990-1994). He is currently the Wallace H. Coulter Distinguished Chair Professor in Biomedical Engineering at Emory University and the Georgia Institute of Technology, with joint appointments in chemistry, materials science and engineering, and hematology and oncology. His research is broadly in the areas of molecular engineering and nanotechnology, with a focus on bioconjugated nanoparticles for cancer molecular imaging, molecular profiling, and targeted therapy. His major academic achievements include the discovery of colloidal metal nanoparticles that are able to amplify the efficiencies of surface-enhanced Raman scattering (SERS) by 14-15 orders of magnitude, his pioneering work on water-soluble semiconductor quantum dots, and his breakthrough work in developing multifunctional smart nanoparticles for integrated biomedical imaging and therapy, including image-guided surgery of breast and lung tumors. Professor Nie has published over 290 papers, patents, and book chapters, and his scholarly work has been cited more than 26,000 times (Google Scholar). In recognition of his work, Professor Nie has received many awards and honors including a Special Achievement Award in Nanomedicine (Nature Symposium, 2012); "Deal of the Year" Award in Technology Licensing (Emory University, 2012); the NIH Director's Transformative R01 Award (2011); "Innovation of the Year" Award (Emory University, 2010); the "MilliPub" Award (for 4 publications that have each been cited over 1000 times (2010); the Merck Award in Analytical Chemistry (2007); the Georgia Cancer Coalition (GCC) Special Achievement Award (2007); Elected Fellow of the American Institute of Biological and Medical Engineering (2006); the Cheung Kong Professorship (The Ministry of Education of China, 2006); the Rank Prize in Optoelectronics (London, UK, 2005); the Georgia Distinguished Cancer Scholar Award (Georgia Cancer Coalition, 2002-2007); the Beckman Young Investigator Award; the National Collegiate Inventors Award; and the Chinese Natural Science Foundation Young Scholar Award.

W. Mark Saltzman

Yale University

W. Mark Saltzman's research interests include controlled drug delivery, materials for drug delivery, and tissue engineering. He has published over 200 research papers, 3 books, 2 edited books, and 15 patents in these fields. He graduated with distinction from Iowa State University, in 1981with a B.S. in chemical engineering and pursued graduate studies at the Massachusetts Institute of Technology, where he earned an M.S. in chemical engineering in 1984 and a Ph.D. in medical engineering in 1987. He joined the faculty at Johns Hopkins University in 1987 as assistant professor of chemical engineering through the ranks, becoming a tenured full professor in 1995. In 1996, he became professor of chemical engineering at Cornell University and, in 2001, he was named the first holder of the BP Amoco/H. Laurance Fuller Chair in Chemical Engineering.

Dr. Saltzman moved to Yale University as the Goizueta Foundation Professor of Chemical and Biomedical Engineering in July of 2002. In 2003, he became the founding chair of the Yale's Department of Biomedical Engineering. Dr. Saltzman's honors and awards include: Camille and Henry Dreyfus Foundation Teacher-Scholar Award (1990); Allan C. Davis Medal as Maryland's Outstanding Young Engineer (1995); the Controlled Release Society Young Investigator Award (1996); Fellow of the American Institute of Biological and Medical Engineers (1997); Professional Progress in Engineering Award from Iowa State University (2000); Britton Chance Distinguished Lecturer in Engineering and Medicine at the University of Pennsylvania (2000); Distinguished Lecturer of the Biomedical Engineering Society (2004); Fellow of the Biomedical Engineering Society (2010); and Member of the Connecticut Academy of Science & Engineering (2012).

Invited Speakers

Jason Burdick

University of Pennsylvania

Jason A. Burdick, PhD is an Associate Professor of Bioengineering at the University of Pennsylvania in Philadelphia, PA, USA. Jason has his PhD in Chemical Engineering from the University of Colorado working with Dr. Kristi Anseth and was a postdoc at MIT under Dr. Bob Langer. Dr. Burdick's research involves the development of photopolymerizable and degradable

biomaterials for various biological applications and his laboratory is specifically interested in understanding and controlling polymers on a molecular level to control overall macroscopic properties. The applications of his research range from controlling stem cell differentiation through material cues to fabricating scaffolding for regenerative medicine. Jason currently has over 100 peer-reviewed publications and has been awarded a K22 Scholar Development and Career Transition Award through the National Institutes of Health, an Early Career Award through the Coulter Foundation, a National Science Foundation CAREER award, and a Packard Fellowship in Science and Engineering.

Warren Chan

University of Toronto

Dr. Chan is currently an Associate Professor in the Institute of Biomaterials and Biomedical Engineering at the University of Toronto. He also holds the Canadian Research Chair in Bionanotechnology and is affiliated with the Department of Materials Science and Engineering, the Terrence Donnelly Center for Cellular and Biomolecular Research Chemistry, Chemistry and Chemical Engineering. His research interest is in the development of nano and microtechnology for cancer and infectious disease diagnosis. He has received the BF Goodrich Young Inventors Award, Lord Rank Prize Fund award in Optoelectronics (England), and Dennis Gabor Award (Hungary). Dr. Chan received his B.S. degree from the University of Illinois in 1996 and Ph.D. degree from Indiana University in 2001. He did his post-doctoral training at the University of California (San Diego).

Jinwoo Cheon

Yonsei University

Jinwoo Cheon is a Horace Underwood Professor of Chemistry at Yonsei University in Korea and the director of National Center for Evolutionary Nanoparticles. He graduated from Yonsei University with his B.S. and received his Ph.D. from University of Illinois, Urbana. He is a recipient of awards including Inchon Prize, Song-gok Award, and National Science Prize for Junior Faculty. Currently, he is a senior editor of Accounts of Chemical Research and an editorial board member of Nano Letters and the Journal of the Materials Chemistry. His research interests include “rational design” of inorganic nanocrystalline materials and their applications for biomedical and energy related sciences.

Drew Endy

Stanford University

Drew Endy and his Stanford research team are pursuing one byte of programmable genetically encoded data storage. He co-founded the BioBricks Foundation as a public-benefit charity that supports the open development of free-to-use standards and technology that enable the engineering of biology. Endy also co-organized what has become the International Genetically Engineered Machines (iGEM) competition and the BIOFAB International Open Facility Advancing Biotechnology (BIOFAB). Prior to coming to Stanford, he helped launch the biological engineering major at MIT. In 2008, Esquire named Endy one of the “75 Most Influential People of the 21st Century.”

Amy Herr

University of California, Berkeley

Amy E. Herr received her BS degree from Caltech and her MS (1999) and PhD (2002) degrees from Stanford in Mechanical Engineering. From 2002-2007, Dr. Herr was a Biosystems Research staff member at Sandia National Laboratories (Livermore). At UC Berkeley since 2007, Prof. Herr’s research focuses on instrumentation innovation to advance quantitation in life sciences and clinical problems – impact spans from tools for fundamental research (cell signaling) to near-patient disease diagnostics. Her major awards include the NIH New Innovator Award (2010-15), the NSF CAREER Award (2011-16), the Eli Lilly & Co. New Investigator Award in analytical chemistry, the Alfred P. Sloan Research Fellowship (2010-12, chemistry), the DARPA Young Faculty Award (2009-11), and the 2012 Association for Women in Science (AWIS) Ellen Weaver Award. In 2012, she was recognized by the UC Berkeley Bioengineering Honor Society as Outstanding Instructor and in 2007 as an Outstanding Mentor by Sandia National Labs. She Chaired (2009) & Vice-chaired (2007) the Gordon Research Conference (GRC) on the Physics & Chemistry of Microfluidics, has served on the technical program committee for several international conferences and is on the Editorial Board of the peer-reviewed international journal Electrophoresis.

Seunghun Hong

Seoul National University

Dr. Seunghun Hong is a professor of physics, biophysics, and chemical biology at Seoul National University. He received his Ph.D from Purdue University in physics.

Andre Levchenko

Johns Hopkins University

Andre Levchenko was born in the former Soviet Union and grew up in Siberia. He obtained BS and MS degrees from the Moscow Institute of Physics and Technology, and his PhD at Columbia University. He then moved to Caltech for his postdoctoral work in genetics and computer science. He was appointed to a faculty position at Johns Hopkins University in 2001, where he is now professor of Biomedical Engineering. His lab is interested in using engineering approaches to understand cell signaling and decision making. Andre is on editorial boards of Science Signaling, PLoS Biology, Biophysical Journal and other publication venues.

Theresa Reineke

University of Minnesota

Theresa M. Reineke, Ph.D. joined the University of Minnesota's Department of Chemistry as a professor with tenure in September 2011. With expertise in polymer science and gene therapy and diagnostics, Reineke is a world leader in the area of polymer/deoxyribonucleic acid (DNA) nanostructures for medical applications.

Yasuyuki Sakai

University of Tokyo

Yasuyuki SAKAI is a Professor in Organs and Biosystems Engineering Laboratory at the Institute of Industrial Science (IIS), University of Tokyo since 2008. His current research topics are engineering of implantable 3D tissues/organs for clinical applications and development of advanced in vitro micro-tissue/organ models for cell-based pharmacological or toxicological assays. He has been placing particular importance on simultaneous realization of good mass transfers and 3D organization of cells together with various micro-technologies. He is supervising graduate school students both in Department of Chemical System Engineering and Department of Bioengineering, Graduate School of Engineering.

Dr. Sakai received the Ph.D. degree in chemical engineering from University of Tokyo in 1993. From 1997-1998, he stayed in University of Rochester, US, as a visiting scientist investigating 3D culture of bone marrow cells (Prof. David Wu's Lab). From 2003-2008, he worked as an associate professor of Regenerative Medical Engineering Laboratory at the Center for Disease Biology and Integrative Medicine (CDBIM), Graduate School of Medicine, University of Tokyo. During his research carrier, he got several scientific awards such as young investigator award of Society of Chemical Engineers, Japan, publication awards of Society for Bioscience and Bioengineering, Japan and Japanese Society for Alternatives to Animal Experiments. He recently became an AIMBE fellow.

Tatiana Segura

University of California, Los Angeles

Professor Tatiana Segura received her Bachelor's of Science degree from the University of California Berkeley and her doctorate from Northwestern University. She pursued post-doctoral training at the Swiss Federal Institute of Technology, Lausanne. Professor Segura's Laboratory studies hydrogel materials for stem cell culture and drug/gene delivery. On this topic she has published over 20 peered reviewed publications. She has been recognized with the Outstanding Young Investigator Award from the American Society of Gene and Cell Therapy, the American Heart Association National Scientist Development Grant, and the CAREER award from National Science Foundation.

Keynote Address

Nanotechnology for Intraoperative Tumor Detection and Image-Guided Surgery

Shuming Nie
Georgia Institute of Technology

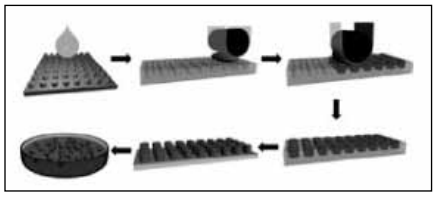
The development of biocompatible nanoparticles for in-vivo molecular imaging and targeted therapy is an area of considerable current interest across a number of science, engineering, and biomedical disciplines. The basic rationale is that nanometer-sized particles have functional and structural properties that are not available from either discrete molecules or bulk materials. When conjugated with biomolecular targeting ligands such as monoclonal antibodies, peptides or small molecules, these nanoparticles can be used to target malignant tumors with high specificity and affinity. In the "mesoscopic" size range of 10-100 nm diameter, nanoparticles also have large surface areas for conjugating to multiple diagnostic (e.g., optical, radioisotopic, or magnetic) and therapeutic (e.g., anticancer) agents. Recent advances have led to the development of biodegradable nanostructures for drug delivery, iron oxide nanocrystals for magnetic resonance imaging (MRI), quantum dots (QDs) for multiplexed molecular diagnosis and in-vivo imaging, and nanoscale carriers for short-interfering RNA (siRNA) delivery. We have developed biocompatible and nontoxic nanoparticles for in-vivo tumor targeting and detection based on self-assembled nanostructures and pegylated colloidal gold. In particular, colloidal gold has been safely used to treat rheumatoid arthritis for 50 years, and has recently been found to amplify the efficiency of Raman scattering by 14-15 orders of magnitude. Here we show that large optical enhancements can be achieved under in-vivo conditions for tumor detection in live animals. A major finding is that small-molecule Raman reporters such as organic dyes are not displaced but are stabilized by thiol-modified polyethylene glycols. These pegylated SERS nanoparticles are considerably brighter than semiconductor quantum dots with light emission in the near-infrared window. When conjugated to tumor targeting ligands such as single chain variable fragment (ScFv) antibodies, the conjugated nanoparticles are able to target tumor biomarkers such as epidermal growth factor receptors (EGFR) on human cancer cells and in xenograft tumor models.

Keynote Address

Co-opting Moore's Law: The Cost-effective Design of Vaccines and Therapeutics

Joe DeSimone
University of North Carolina

In 1965, Gordon Moore, co-founder of Intel, described the trend that the number of components in integrated circuits had doubled every year since 1958. This trend has continued to today, enabled by advances in photolithography which has taken the minimum feature size of transistors down from about 10 microns in 1970 to 0.045 microns (45 nm) today. In biological terms, this corresponds to going from the size of a red blood cell to the size of a single virus particle! As such, this top-down nano-fabrication technology from the semiconductor industry is, for the first time, in the size range to be relevant for the design of medicines, vaccines and interfacially active Janus particles. This lecture will describe the design, synthesis and efficacy of organic nano- and micro-particles using a top-down nano-fabrication technique we developed called PRINT (Particle Replication in Non-wetting Templates). PRINT is a continuous, roll-to-roll, high resolution molding technique that allows the fabrication of precisely defined micro- and nano-particles in a continuous manner with control over chemical composition, size, shape, deformability and surface chemistry. With these 'nanotools', we are establishing definitive biodistribution maps to elucidate the interdependent roles that size, shape, deformability and surface chemistry play on particle distribution as a function of different dosage forms (IV, IP, inhaled, subcutaneous, intramuscular, etc). This information is setting the stage for the design of highly effective chemotherapeutics, respiratory therapeutics and vaccines which will be described.



Session 1: Drug, Protein and Gene Delivery Systems

Invited Speaker

Carbohydrate-Based Block Copolymers Designed for the Delivery of Drugs and Nucleic Acids

Theresa Reineke
University of Minnesota

The targeted delivery of drugs and nucleic acids offers promise for revolutionizing drug development. We have developed a library of novel carbohydrate-containing polymers that form core-shell nanostructures that encapsulate polynucleotides (pDNA and siRNA) into polyplexes that facilitate highly efficient intracellular delivery without toxicity. We have utilized step growth polymerization

techniques to yield a comprehensive series of polycations that contain various mono-, di-, and oligosaccharide moieties copolymerized with ethyleneamine units. In addition, we have recently created analogs of these polymers via RAFT polymerization methods, allowing us to create a variety of block copolymer architectures with saccharides and a variety of cationic units in a highly controlled manner. A number of these polymer systems have revealed high efficacy for both pDNA and siRNA delivery *in vitro* and *in vivo*. In addition, our group has also recently developed a series of amphiphilic diblock terpolymers for the delivery of small molecule drugs that have the structure poly(ethylene-alt-propylene)– poly[(N,N-dimethylacrylamide)- grad-(2-methacrylamido glucopyranose)] by combining anionic and RAFT polymerization techniques. These structures form micelles in aqueous media that are colloidally stable in physiological salt and serum conditions. To examine the intracellular mechanisms and kinetics of delivery for these vehicles, three dimensional confocal microscopy imaging techniques have been also been developed that has allowed us to examine intracellular trafficking in 3D space and time.

Oral Presentation

DNA-Based Vehicles for the Delivery of Functional Nucleic Acids and Proteins

Jung-Won Keum[1], Phapanin Charoenphol[2] and **Harry Bermudez[2]**
[1]Chemical Engineering, University of Massachusetts, Amherst, MA
[2]Polymer Science and Engineering, University of Massachusetts, Amherst, MA

The ability of DNA to form predictable nanostructures through sequence-directed hybridization has allowed the design of complex supramolecular materials. Our discovery of the nuclease resistance of DNA nanostructures has led us to explore their potential as delivery vehicles, and we have successfully demonstrated their ability to delivery functional antisense *in vitro*. More recently, we have pursued non-canonical Watson-Crick base pairing as an in situ approach for achieving actuation through sensitivity to solution conditions. By designing a DNA pyramid containing i-motif elements, we have shown that these i-motifs can be used to regulate nanostructure assembly / disassembly as well as the release of protein cargo. Importantly, disassembly is triggered with physiologically relevant acidification, making the present DNA pyramids an important step towards synthetic mimics of viruses. We are currently exploring the incorporation of aptamer sequences into our pyramids to achieve both targeting and uptake without the need for transfection reagents.

Oral Presentation

Directed Evolution of Stable, Orally Bioavailable S-U-P-R Peptides

Richard W. Roberts
University of Southern California

Peptides have poor biostability and natural sequences cannot readily be converted into drug-like molecules. We have adapted mRNA display to evolve highly stabilized versions of peptides while retaining function toward their intended target. To do this, we incorporated an unnatural 21st amino acid in a combinatorial scanning library and subjected this pool to proteolysis prior to selection for function. These experiments have resulted several new dramatically stabilized “SUPR peptides” (scanning unnatural protease resistant) that show half lives in human serum of several days to one week. One utility of these SUPR peptides is that it may be adapted to give an in vivo half-life of >18 hours in the mouse and an oral bioavailability of >10%. Experiments to analyze the structure and function of these peptides will be discussed.

Invited Speaker

Bionanotechnology to Guide Vessel Sprouting

Tatiana Segura
University of California, Los Angeles

Vascular endothelial growth factor (VEGF) is known to activate proliferation, migration, and survival pathways in endothelial cells through phosphorylation of VEGF receptor-2 (VEGFR-2). VEGF has been incorporated into biomaterials through encapsulation, electrostatic sequestration, and covalent attachment, but the effect of these presentation strategies on VEGF signaling and endothelial cell sprouting has not been thoroughly investigated. In our laboratory, we investigate if the manner in which VEGF is presented from a scaffold to endothelial cells influences the phosphorylation of VEGFR-2 and the architecture of the blood vessels formed. We used three different VEGF presentations to study their role of VEGFR-2 signaling and vessel sprouting: covalently bound (Vc), covalently bound and clustered (cVc), and sustained release from nanocapsules (nV). We covalently bound VEGF to either self-assembled monolayers on gold to make Vc or to polymeric nanoparticles to make cVc. To make nV we used in situ polymerization to polymerize a plasmin degradable nanogel around the protein. We found that covalently bound VEGF (Vc) is able to phosphorylate VEGFR-2 (VR-2) to the same extent as soluble VEGF (Vs) in endothelial cells (EC), but that the mode of VEGF presentation alters the tyrosine residues that are phosphorylated, the time course of phosphorylation, and the resulting downstream

signaling. Using cVc and an EC branching assay or CAM assay we found that VEGF clusters led to an increase in EC sprout branching, thickness, and total vessel network length compared to soluble VEGF or less clustered VEGF. Last, sustained released VEGF from nV resulted in sustain receptor phosphorylation and enhanced EC branching without VEGF replenishing.

Oral Presentation

Directed Evolution of New Viruses for Therapeutic Gene Delivery

David V. Schaffer
University of California, Berkeley

Strong basic and translational efforts in the gene therapy field have culminated in successes in an increasing number of human trials, including for Leber's congenital amaurosis, severe combined immunodeficiencies, hemophila, and X-linked adrenoleukodystrophy. These studies have established that certain viral vectors are capable of efficient, safe, and therapeutic gene delivery to numerous target cells and tissues. Vectors based on adeno-associated virus and lentivirus thus have considerable promise; however, numerous challenges can limit the applicability of these biological nanoparticles, such as anti-vector humoral and cellular immunity, low transduction of some therapeutically relevant cells *in vitro* or *in vivo*, difficulty in overcoming cellular and physical barriers within complex tissue structures, and an inability for targeted delivery to specific cells. These challenges are not surprising, as nature did not evolve viruses for use as human therapeutics. Rational design has made progress in engineering viral variants to address several such shortcomings; however, in many situations there is insufficient mechanistic knowledge of underlying virus structure-function relationships to effectively empower rational design with the capacity to improve a vector. As an alternative, directed evolution has been emerging as a strategy to engineer novel viral variants that meet specific biomedical needs.

We have been developing directed evolution and library selection approaches to address a number of problems with adeno-associated viral (AAV) and retro/lentiviral vectors for a decade. Directed evolution – which emulates the natural evolution process – is the iterative genetic diversification of components of a viral genome and functional selection for desired properties. In the case of adeno-associated virus, genetic diversification has included the random diversification of peptide sequences at defined locations in the viral capsid structure, random point mutagenesis of the cap gene, and recombination of cap genes from a number of parental serotypes to create random chimeras. By iterative selection and further diversification of such libraries, the receptor specificity, tropism, biodistribution, and antigenicity of the viral particles can be fundamentally shifted. As one example, it would be desirable to develop non-invasive means to deliver genes to the retina; however, natural AAV variants can only transduce cell types involved in retinal degeneration (photoreceptors and retinal pigment epithelium) with an invasive subretinal injection, which in many cases can further damage an already degenerating tissue. We evolved AAV for the capacity to mediate high efficiency gene delivery to photoreceptors upon a simple injection into the vitreous humor of the eye, and this ability to traverse a formidable tissue barrier may have implications for treating retinal degenerations that cause blindness. We have also recently applied directed evolution to create vector variants that evade human neutralizing antibodies or mediate gene delivery and gene targeting in stem cells, attractive targets for basic and applied studies.

In summary, natural variants of viruses are suitable for a number of therapeutic applications; however, in many situations these "off the shelf" products of nature do not meet urgent biomedical needs. Continuing the process of evolution, but changing the trajectory towards functions and properties that are useful in medical rather than natural settings, is therefore a promising approach to create designer viral nanoparticles to meet specific human therapeutic needs.

Oral Presentation

Targeted Drug Delivery to the Brain Using Transferrin-Binding Peptides

Divya Chandra and Pankaj Karande
Rensselaer Polytechnic Institute

Drug-delivery to the brain is a significant challenge due to the presence of the formidable blood-brain barrier (BBB). Current therapeutic interventions to treat brain disorders include surgical implants or catheters, both of which are highly invasive and carry the risk of long term neurological damage. A treatment strategy that is non-invasive provides uniform distribution of the drug in the brain at therapeutically relevant concentrations, and carries a low risk of neurological damage is highly desirable but not clinically available. We are focusing on a specific pathway called receptor-mediated transcytosis (RMT) that is facilitated by proteins expressed on the surface of endothelial cells that form the BBB and are dedicated for ferrying transport proteins across the BBB. This pathway has previously shown great promise for transport of antibodies and drug conjugates of transport proteins like transferrin (Tf), insulin etc. We are developing a novel drug delivery strategy based on short peptides as drug carriers to the brain, whereby

these peptides will bind to human Tf (hTf) and deliver the attached drug via the RMT pathway of hTf. The transferrin receptor (hTfR) is of particular importance here as it is over expressed on brain capillaries and is involved in the transfer of iron-carrying hTf to the brain. Given the high circulation half-life (~8 days) of hTf, designing peptides that enable drugs to stay conjugated to hTf increases the in vivoresidence time and efficacy of the drugs as well as reduces their required dosage and side effects. This addresses another major challenge of obtaining desirable pharmacokinetics when designing therapeutics for brain diseases. High abundance (1-3 mg/ml) of hTf in blood also facilitates high drug dosing. Additionally, chaperone peptides eliminate the need for covalent conjugation of drugs to hTf outside the body and can be tailored to improve solubility and stability of drugs in circulation.

In order to design high-affinity hTf–binding peptides that can act as drug chaperones we adopted a rational design approach that relied on naturally occurring receptors for Tf. It is known that several bacterial species have evolved surface proteins that bind to hTf in serum. These proteins, called transferrin binding proteins (Tfbp) enable the pathogens to scavenge iron from circulating hTf and use it for their own metabolic requirements. The binding interfaces of Tfbps on different pathogens do not bear any significant structural or sequence similarity to hTfR and therefore are expected not to interfere with binding of hTf to hTfR. Thus, they offer a potential search space for designing short peptides that bind to hTf with a high-affinity and enable the delivery of a drug cargo across the BBB.

Using high-throughput peptide synthesis and microarray screening, several potential peptide candidates that mimic Tfbps have been identified from an initial library of ~1000 peptides. These peptides show very high affinity (1-10nM) for hTf in the presence of physiologically relevant concentrations of human serum albumin (HSA) – the most abundant protein in human serum. This ensures that the peptides not only have high affinity but also high selectivity for hTf. As a first step, while peptides have been identified that bind to hTf, the future validation of this drug delivery strategy *in vivo* in a mouse model would require peptides that bind to mouse Tf (msTf). Keeping this in mind, the entire library has also been screened with msTf in the presence of HSA in order to select peptides that bind to msTf with high affinity and selectivity. A set of candidates that bind to both hTf and msTf has been selected for *in vitro* and in vivostudies.

We are currently testing a subset of these peptides in an in vitro BBB cell culture model. This, followed by studies in an animal model would further validate the lead peptide candidates as drug carriers. Finally, the fact that these peptides come from a non-human protein and therefore less likely to compete with hTfR-hTf interaction will have a significant impact on designing better peptide chaperones for drug delivery to the brain.

Session 2: Nanoparticles, Nanocomposites and Nanoporous Materials for Bio-Applications

Invited Speaker

The Complexities of Nanoparticle Tumor Targeting

Warren Chan
University of Toronto

Nanoparticles of different sizes, shapes and material properties have many applications in biomedical imaging, clinical diagnostics and therapeutics. Strategies that can reproducibly prepare colloidal nanoparticles of a wide range of geometries with a tight size distribution have been achieved and unique size and shape dependent optical, magnetic, electrical, and biological properties have been discovered. A broad of range of applications of nanoparticles have been demonstrated. In spite of what has been achieved so far, a complete understanding of how cells and animals interact with nanoparticles of well-defined sizes remains poorly understood. This has led to the inability to rationally design nanoparticles for cancer applications or has led to the inability to establish a definitive conclusion on the toxicity of nanomaterials. This presentation will focus the effect of nanoparticle parameters on cellular interaction and tumor targeting. We will also describe how the outcomes of these fundamental studies have led to the engineering of artificial nanoparticle-targets to improve tumor targeting. The findings presented here may assist in the design of nanoscale delivery and therapeutic systems and provide insights into nanotoxicity.

Oral Presentation

Magnetic Quantum Dots and Magnetic Microarrays for Cell and Molecular Detection

Kalpesh D. Mahajan[1], Greg Vieira[2], Gang Ruan[1], Jeffrey J. Chalmers[1], R. Sooryakumar[2], and **Jessica O. Winter[1]**
[1]Deptartment of Chemical and Biomolecular Engineering, The Ohio State University, Columbus, OH
[2]Department of Physics, Ohio State University, Columbus, OH

Biomarker detection, whether of soluble biomolecules or surface expressed proteins, is critical to disease diagnosis

and treatment. Nanotechnology has made a tremendous impact in ultrasensitive detection because of its size similarity to biomolecules and the unique properties conferred at the nanoscale. However, the majority of nanodetection schemes fail to isolate the molecules of interest in a non-destructive method that permits their subsequent downstream use. Here, we describe a lab-on-a-chip nanomagnetic conveyer belt scheme for the detection, quantification, and isolation of cells and biomolecules. This platform consists of magnetic quantum dots targeted to the molecules of interest that are manipulated by mobile magnetic disk or nanowire trap arrays controlled with external electromagnetic fields. We have used this technology to isolate single leucocytes via their CD45 receptors and have also quantified the number of expressed CD45 receptors in situ via quantum dot fluorescence. Additionally, we have detected and isolated avidin and short sequence p53 DNA from 10-10 M solutions both individually and in multiplexed configurations. This corresponds to the ability to isolate ~60 copies of RNA/DNA per cell from samples of as few as 100 cells without the use of the polymerase chain reaction (PCR). Further, all of these experiments were accomplished using extremely small samples volumes (~ 5 µl). We are currently adapting this technology for the isolation of circulating tumor cells and PCR-less detection of their miRNA profiles. This technology thus has tremendous potential for clinical diagnostic applications.

Oral Presentation

Nano-Constructs Fabricated From a Genome-Depleted Plant Virus and Indocyanine Green for near Infrared Imaging and Phototherapy

Bahman Anvari[1], Yadir Guerrero[1], Bongsu Jung[1], Baharak Bahmani[1], Ayala L. N. Rao[2], Sheela Singh[3], Valentine I. Vullev[1] and Vikas Kundra[3]
[1]Bioengineering, University of California, Riverside, Riverside, CA
[2]Plant Pathology and Microbiology, University of California, Riverside, Riverside, CA
[3]Diagnostic Radiology, The University of Texas MD Anderson Cancer Center, Houston, TX

We have constructed a new type of an optical nano-material composed of genome-depleted plant infecting brome mosaic virus (BMV) doped with FDA-approved near infrared (NIR) chromophore, indocyanine green (ICG). We refer to these constructs as optical viral ghosts (OVGs) since only the capsid protein (CP) subunits of the BMV remain to encapsulate ICG. The abundance of naturally present amines on the CP shell of the OVGs provide addressable sites for covalent attachment of targeting moieties such as antibodies using a simple method based on reductive amination. OVGs can serve as a theranostic construct since the same chromophore (ICG) may be used for both imaging and phototherapy. One of our areas of interest for biomedical applications of OVGs is in their potential use for real-time intraoperative NIR fluorescence imaging and photodestruction of small peritoneal ovarian tumor nodules. In this presentation, we will provide results associated with physical characterization of OVGs, and their ability to target and image ovarian cancer cells *in-vitro*.

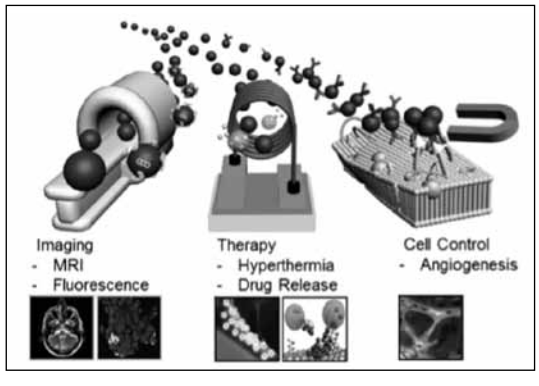
Acknowledgement: NSF grant CBET-1144237.

Invited Speaker

Magnetic Nanoparticles for Imaging and Therapeutics

Jinwoo Cheon
Yonsei University

One of the important trends of next-generation nanomedicine is theranostics that is defined by the combination of therapeutics and diagnostics on a single platform. Magnetic nanoparticles are among one of the most essential platforms for targeted imaging, therapy, and simultaneous monitoring of therapeutic efficacy. In this talk, I will discuss magnetic nanoparticles as a core platform material for theranostics and add a variety of functionalities such as drug, targeting moiety, and gene to enhance their performance. Their unique utilization in highly accurate dual-modal MR imaging[1], therapeutic hyperthermia of cancer cells[2], controlled drug release[3], gene delivery[4], and molecular level cell signaling and cell fate control[5] will be discussed.



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Oral Presentation

Mechanical Deformation of Synthetic Cell Membranes by Nanoparticle Interactions

Noah Malmstadt
University of Southern California

While there has been significant attention paid to potential applications of nanoparticulate materials, the potential environmental health implications of the widespread adaptation of nanoparticle systems are not yet fully understood. Several researchers have shown that nanoparticles with multivalent surface charges are readily trafficked across cell membranes, and that they can even pass through layers of epithelial cells, entering systemic circulation. This trafficking process is passive, general, and seems to involve damage to the cell membrane.

Here, we investigate the mechanism of cell membrane damage by charged nanoparticles. Using a synthetic lipid bilayer vesicle system, we show that multivalent cationic polymer particles with diameters in the range of ~20 nm bind tightly to membranes composed of neutral lipids. This binding is electrostatically mediated, and can be shielded at high ionic strengths. There is no membrane compositional dependence to the binding process; it occurs regardless of the particular neutral lipid species present.

Upon binding, the particles aggregate with the lipids in the membrane, drawing membrane area into micron-scale aggregates. As a consequence, the vesicle diameter shrinks as tension on the vesicle increases. At increasing vesicle tension, pores are formed in the membrane, allowing high-molecular-weight species to leak from the vesicles. By controlling the molecular weight of fluorescently labeled dextran species inside the vesicles, we are able to identify the size range of the pores formed; they are between 20 and 50 nm in diameter. As nanoparticles continue to bind the membrane, the vesicle ruptures.

These observations of membrane-nanoparticle interactions have significant implications for the physiological properties of nanoparticles. The potential of multivalently charged nanoparticles to aggregate with lipids species and induce membrane poration suggests that they are potentially hazardous to human health. From an engineering perspective, however, it also suggests that they can be tools for controlled membrane permeabilization and drug delivery.

Oral Presentation

Polymer Foam Nanocomposites Synthesised Via Nanoparticle Stabilised Emulsions

Ling Ching Wong[1], Suelen Barg[2], Angelika Menner[1], Alexander Bismarck[1] and Eduardo Saiz[2]
[1]Department of Chemical Engineering, Polymer and Composite Engineering Group, Imperial College London, London, United Kingdom
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Polymer foams are an important class of materials in tissue engineering as they are highly porous, interconnected and have high surface areas. This makes them excellent candidates as scaffolds for tissue engineering. Emulsion templating is a viable method to prepare polymer foams with such qualities, which would make suitable scaffolds for cell proliferation. This versatile technique is quickly gaining interest as it is a straightforward method that affords the user good control over the porosity and pore morphology of resulting polymer foams. Besides being in an injectable liquid form, a range of porosities and pore morphologies can also be achieved by varying the composition of the emulsion templates.

We report on the synthesis of electrically conducting polymer foams synthesised from graphene oxide-stabilised emulsion templates. By polymerising water-in-oil emulsions stabilised by functionalised graphene oxide, open-celled polymer foams with high porosities of above 80% and average pore diameters ranging from 100 mm to 300 mm were obtained. Functionalised graphene oxide platelets adsorb at the oil-water interface during emulsification and on polymerisation formed a 3D network spanning the entire polymer foam, making it electrically conducting. Such porous materials could be especially interesting as scaffolds for the directional differentiation of stem cells by applying an external electrical stimulus.

Keynote Address

Designing Synthetic Regulatory RNAs: New Languages for Programming Biological Systems

Christina Smolke
Stanford University

Advances in synthetic biology are transforming our ability to design and build synthetic biological systems. While progress has been made in the design of complex genetic circuits, capabilities for constructing large genetic systems currently surpass our ability to design such systems. This growing ‘design gap’ has highlighted the need to develop methods that support the generation of new functional

biological components and scalable design strategies for complex genetic circuits that will lay the foundation for integrated biological devices and systems.

As examples of functional RNA molecules playing key roles in the behavior of natural biological systems have grown over the past decade, there has been growing interest in the design and implementation of synthetic counterparts. Researchers are taking advantage of the relative ease with which RNA molecules can be modeled and designed to engineer functional RNA molecules that act as diverse components including sensors, regulators, controllers (ligand-responsive RNA regulators), and scaffolds. These synthetic regulatory RNAs are providing new tools for temporal and spatial control in biological systems. I will describe recent work in the design of RNA controllers and advances in addressing challenges faced in their broad implementation as user-programmed control systems in living cells. In particular, I will describe the development of high-throughput cell-based screens for rapidly generating synthetic regulatory RNAs with specified quantitative properties. In addition, I will discuss how such RNA controllers can be implemented as sensitive biosensors providing a noninvasive readout of target metabolites supporting the development of high-throughput screening strategies for enzyme and metabolic pathway engineering. Finally, I will address how the application of synthetic regulatory RNAs as controllers in different biological pathways are leading to the elucidation of integrated systems design strategies and new languages for programming genetic systems.

Session 3: Synthetic Biology

Invited Speaker

Finally! A Workable Abstraction Hierarchy for Engineering Integrated Gene Expression Systems

Drew Endy
Stanford University

We proposed roughly 10 years ago that abstraction, a la' computer science and engineering, would be a useful tool for managing complexity during the process of engineering genetic systems. Although interesting as an idea, in practice abstraction of biological functions across a hierarchy of complexity had never been made true. However, very recently we have demonstrated how to make reliably reusable transcription and translation control elements, that can precisely program protein synthesis rates regardless of variation in expressed coding sequences. When combined with earlier work to establish POlymerase Per Second (PoPS) as a common signal carrier for composing integrated genetic devices, and ongoing work to decouple design of genetic sequences from their physical fabrication, we have now established a practically operational 3(++) layer stack supporting the forward engineering of integrated genetic systems. Much more work needs to be done to establish reference standards and signal levels that support still more reliable composition. But, practically, researchers can now begin to consider the forward design of up to 6-10 gene systems prior to first experimental testing for expression failure.

Oral Presentation

Systems Immunology Approach for Antibody Discovery and B Cell Repertoire Analysis

Sai T. Reddy
University of Texas, Austin

Isolation of antigen-specific monoclonal antibodies (mAbs) and antibody fragments relies on high-throughput screening of immortalized B cells or recombinant antibody libraries. We bypassed the screening step by using high-throughput DNA sequencing and bioinformatic analysis to mine antibody variable region (V)-gene repertoires from bone marrow plasma cells (BMPC) of immunized mice. BMPCs, which cannot be immortalized, produce the vast majority of circulating antibodies. We found that the V-gene repertoire of BMPCs becomes highly polarized after immunization, with the most abundant sequences represented at frequencies between ~1% and >10% of the total repertoire. We paired the most abundant variable heavy (VH) and variable light (VL) genes based on their relative frequencies, reconstructed them using automated gene synthesis, and expressed recombinant antibodies in bacteria or mammalian cells. Antibodies generated in this manner from six mice, each immunized with one of three antigens were overwhelmingly antigen specific (21/27 or 78%). Those generated from a mouse with high serum titers had nanomolar binding affinities.

In an ongoing study, we performed a systems immunology analysis of the humoral response in mice, focusing on the molecular, cellular, and physiological diversity of plasma cell responses. Specifically, we used high-throughput repertoire analysis to quantify the immunoglobulin diversity in plasma cells located in the various lymphoid organs of mice following immunization with a protein antigen. For example, we were able to quantify junctional clonal diversity and frequency across multiple lymphoid organs (based on VH complementarity determining region 3 (CDRH3)). Moreover, we used clustering analysis to identify clonal correlations, therefore gaining insight into the overlap of repertoires in different lymphoid compartments. Importantly, we discovered that mice with high serum antigen-specific antibody titers converged to the same highly abundant plasma cell

IgG VH clones, suggesting immunoglobulin equilibration across lymphoid organs may be correlated to the strength of the immune response.

Oral Presentation

Developing Versatile RNA-Based Genetic Programs

Lei Qi and Adam Arkin
University of California, Berkeley

RNA molecules are key regulators of cellular networks in all organisms. Recently, non-coding RNA (ncRNA) regulators have been used in the programming of complex genetic systems. However, it remains a major challenge in the field of RNA synthetic biology to create multiple orthogonally acting ncRNAs and to assemble them into useful regulatory networks. Here we demonstrate a systemic approach from designing ncRNA regulators (parts) to assembling them into higher-order circuits (circuitry). On the parts level, we rationally mutated the natural RNA regulators to create orthogonally acting ncRNAs. Two primary types of ncRNAs that could control either transcription elongation (pT181) or translation initiation (IS10) have been engineered. For the translational ncRNA, we further developed a computer-aided algorithm that predicts the specificity of RNA-RNA interactions and allows us to design more orthogonal ncRNAs. The engineered ncRNAs could also be fused to RNA aptamers as chimeras that could sense small molecules or proteins. We discuss the principles for designing such allosteric chimera molecules. On the circuitry level, we combined multiple ncRNA regulators into higher-order functions. We demonstrate that multiple ncRNAs could form useful circuits that independently control a large number of genes in a single cell, perform logic computation of cellular inputs, and propagate signals along transcriptional cascades. Together, our work demonstrated ncRNAs as useful and powerful genetic tools that can be rationally created *in vitro*, *in vivo*, and *in silico*, and combined into complex circuits useful for therapeutic and manufacturing applications.

Invited Speaker

From Wires to Grooves: Nano-Engineering of Cell Behavior

Andre Levchenko
Johns Hopkins University

Single live fells are exquisitely sensitive to extracellular cues, including those presented to them on very small spatial scales. In this talk, I will highlight our recent work to develop and use methods and tools to control cell collective and single cell behavior on micro- and nano-scales. I will discuss in particular the unexpected insights into cell biology arising from this research.

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Kim et al., PNAS, 2010

Oral Presentation

Synthetic Optimization of the MAPK and PI3K Pathways for Cell Proliferation and Survival

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To fully characterize the effects of gene expression on cellular phenotypes, a range of expression levels needs to be explored. Variable gene expression has typically been achieved at the level of transcription through the use of inducible transcription systems or varying strength synthetic promoters. As an alternate approach, we employed a system that would control protein amount at the level of translation through the engineering of the Kozak sequence immediately preceding a gene of interest. By using a GFP reporter, we established a translation initiation sequence (TIS) library exhibiting over a 200-fold range in GFP intensity with a high degree of consistency across five cell lines. We then utilized the TIS library to determine the optimal contributions from the MAPK (mitogen-activated protein kinase) and PI3K (phosphatidylinositol 3-kinase) pathways towards survival through the overexpression of oncogenic H-Ras variants in heterogeneous culture.

Constitutively-active mutants of the GTPase H-Ras, are potent oncogenes that are involved in signal transduction down multiple cellular pathways. Two of these pathways, the MAPK and PI3K pathways, are especially important in cellular transformation and have well defined downstream targets that allows for measurement of the signaling through that pathway. We used our translation initiation sequence (TIS) library to translate (i) oncogenic H-RasG12V and (ii) mutant versions of H-RasG12V that are only able to signal down the MAPK branch (an H-RasG12V T35S mutant) or the PI3K branch (an H-RasG12V Y40C mutant). Each transgene is fused to a fluorescent protein to enable quantitative analysis at the single-cell level by flow cytometry. The TIS library allowed us to maintain a heterogeneous culture that contains cells translating our transgene over several orders of magnitude (i.e., inputs to the system). Next we performed a population competition experiment. By allowing this mixed culture to grow over time, optimal gene dosage levels become evident as cells expressing protein at an optimal level begin to outcompete the cells expressing sub-optimal levels (i.e., outputs from the system). Here we report the optimization of the MAPK and PI3K signaling pathways in an antibody-producing murine plasmacytoma line, MPC-11. We envision utilizing the TIS system in conjunction with engineered het-

ereogeneous cell culture to overexpress multiple genes in lymphocytes or CHO cells and to engineer pathways for optimal cell proliferation and/or antibody production.

Oral Presentation

Nanofibrous Elastin-like Protein as a Biomimetic Platform for Multifactorial Control of Cell-Matrix Interactions

Patrick Benitez[1], Jeffrey Sweet[2] and Sarah C. Heilshorn[2]
[1]*Bioengineering, Stanford University, Stanford, CA,* [2]*Materials Science and Engineering, Stanford University, Stanford, CA*

To produce physiologically relevant results, engineered extracellular matrices (eECMs) for in vitro studies of cell-matrix interactions must mimic the inherently nanoscale architecture, mechanics, and biochemistry of the native extracellular matrix (ECM). Given that cells sense the nanoscale articulation of each of these features, ideal eECMs must offer not only a multifactorial design space but also a broadly mimetic microevironmental context. Here, to begin to meet this need, we electrospin a highly mimetic family of elastin-like proteins (ELPs) into a nanofibrous, stable, and broadly mimetic eECM. On the molecular level, ELPs have been engineered to mimic essential ECM proteins, combining a sequence derived from elastin, which confers native-like mechanical properties, with an extended sequence from fibronectin's arginine-glycine-aspartic acid (RGD) ligand that enables specific adhesion. With limited self-assembly, though, ELPs require further processing to mimic the protein nanofibers that characterize the ECM: hence, electrospinning. To stabilize ELP nanofibers, we develop a crosslinking protocol that respects sequence specificity. Further characterization is done to demonstrate that relevant mechanics are achieved and specific signaling from the matrix is preserved during electrospinning and crosslinking.

Session 4: Biological Devices/Biosensors and Molecular Diagnostics

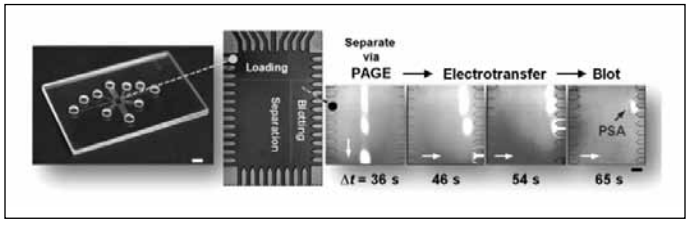
Invited Speaker

Talking about a Revolution: Microfluidic Integration for Next-Generation Protein Analysis

Amy Herr
University of California, Berkeley

Technology advances have driven a genomics revolution with sweeping impact on our understanding of life processes. Nevertheless, the arguably more important "proteomics revolution" remains unrealized. Proteins are complex; meaning that multiple physicochemical properties must be assayed. Consequently, proteomic studies are resource intensive and 'data limited'. To drive a bold transformation of biomedicine, engineering innovation in proteomics instrumentation is needed.

While microfluidic technology has advanced separations science, progress lags in the multi-stage separations that are a hallmark of proteomics. This talk will summarize new microengineering design strategies for critical multi-stage protein assays. Specifically, I will introduce our tunable photopatterned materials for switchable function, microfluidic architectures for seamless integration of discrete stages, and multiplexed readouts for quantitation. In a translational example, I will detail assay and design advances from our two highly integrated Western blotting platforms. Focus will center on next-generation confirmatory HIV diagnostics. In a life sciences example, I will highlight our recent contributions to protein isoform measurements, here for new prognostic cancer biomarkers and biospecimen repository monitoring. Performance and operational gains will be discussed, including quantitation capability, total assay automation, integration of sample preparation, and workflows that require minutes not days. Ultimately, we aim to infuse engineering advances into the biological and biomedical sciences – collaboration that promises to address a range of unmet scientific, biomedical, & societal needs.



Microfluidic integration strategies advance automated, quantitative proteomics. *(left) Glass microfluidic device. Scale bar: 2 mm (middle) Photopatterned polymers in 1 x 1.5 mm2 chamber (right) A 1-minute automated Western blot of prostate specific antigen (PAGE: polyacrylamide gel electrophoreses). Scale bar: 250 um.*

Oral Presentation

A Microfluidic Platform for Droplet-Enabled Co-Cultivation of Microbial Communities

Jihyang Park and **Xiaoxia Nina Lin**
University of Michigan, Ann Arbor

The majority of existing microbial species, in particular bacteria living in synergistic communities, have not been cultured in the laboratory with conventional pure-culture oriented methods. This severely limits the characterization and understanding of various microbial systems, includ-

ing those closely related to the human health. To address this issue, we have developed a microfluidic co-cultivation platform to expand the repertoire of cultivable species from natural microbial communities and to characterize co-cultivated communities. We fabricated a microfluidic device that could readily encapsulate and co-cultivate subsets of a community, using highly parallel nano-liter aqueous droplets dispersed in a continuous oil phase. To demonstrate the effectiveness of this approach in discovering synergistic microbial interactions, a synthetic model system consisting of cross-feeding E. coli mutants was co-cultivated. Our device was able to detect pair-wise symbiotic relationship when one partner accounted for as low as 1% of the total population or each symbiont was about 3% of the artificial community.

Different microbial species have different level of oxygen tolerance and preference. To further enhance the likelihood of cultivating diverse species from a community, we have combined droplet co-cultivation and oxygen gradient to provide both the environment for microbial interactions and the optimal oxygen condition. Our prototype device is composed of two glass layers with fluid channels separated by a thin PDMS membrane. A linear oxygen gradient, covering the range of strictly anaerobic to fully aerobic conditions, is established and maintained via a tree-shaped channel mixing humidified nitrogen and air. The gradient is then transferred through the porous PDMS membrane to the chambers in the liquid channel incubating droplets. A murine fecal microbial sample, of which the bacteria lived with limited oxygen concentration in their native environment, was cultivated and different species were enriched in chambers featuring different oxygen conditions.

Oral Presentation

Maltodextrins Image Early Stage Bacterial Infections and Drug Resistance by Positron Emission Tomography

Niren Murthy and Xinghai Ning
University of California, Berkeley

Bacterial infections are a central cause of mortality in the world and affect all areas of medicine ranging from cardiology to oncology. Bacterial infections remain a major health problem despite the availability of effective antibiotics, because their diagnosis is challenging and because they are frequently treated with ineffective antibiotics, due to the widespread rise of bacterial drug resistance. In this report, we present a new PET contrast agent, composed of F-18 conjugated to maltohexaose (18F-MH), which can for the first time image bacteria in vivo with the specificity and sensitivity needed to detect early stage infections and measure drug resistance *in vivo*. We show here that 18F-MH can detect as few as 105 E.coli colony forming units (CFUs) in rats, which is 3-4 orders magnitude higher in sensitivity than FDG, the current clinically used bacterial infection contrast agent. In addition, we demonstrate that 18F-MH can distinguish bacterial infections from inflammation, and has a specificity that is 2-3 orders of magnitude higher than FDG, giving it the potential to identify infections clinically without a biopsy. Finally, we demonstrate that 18F-MH can monitor treatment efficacy in vivo and can identify beta lactam resistance in E.coli in real time, thus providing physicians with a powerful tool for guiding antibiotic selection. We anticipate numerous clinical applications of 18F-MH given the widespread use of PET and the pervasiveness of infections in medicine.

Invited Speaker

Hybrid Nanobio-Devices Based on Carbon Nanostructures and Biomolecules

Seung-Hun Hong
Seoul National University

Recently, various new nanostructures (e.g. nanoparticles, carbon nanotubes, protein motors, graphene etc) have been utilized as a component for advanced functional devices. However, a major stumbling block holding back their practical applications is a difficulty in massive assembly of such devices. In this talk, we will first present a strategy to mass-produce nanostructure-based hybrid devices, where molecular patterns on solid substrates are utilized to direct the adsorption and alignment of nanostructures to form a desired device structures. Then, we will discuss how this simple strategy can be utilized to fabricate various new hybrid nanobio-devices for bio- and medical applications such as taste receptor protein-based bioelectronic tongues, canine olfactory receptor-based artificial noses, and carbon nanostructure-based substrates for stem cell control.

Oral Presentation

Multimarker Cellular Screening Using Variable Cross-Section Pores

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Multimarker screening is a useful tool for disease diagnosis, as cell characterization is essential for understanding and dealing with pathologic conditions. Existing techniques suffer from drawbacks as they require advanced preparation, including labeling cells, which increases time for incubation steps and can change cellular properties. This presents issues if cells are to be used for post-screening analysis. Microfluidic pores have emerged as versatile tools capable of probing the properties of proteins and nucleic acids.[1,2] Recent work[3,4] has shown that pore functionalization can result in slower translocation rates of a particle due to particle-pore interactions, thereby providing chemical specificity for detection of single molecules and cells. Because functionalization with only one type of organic species limits the effectiveness of these pores, we have developed a novel pore device that can characterize multiple surface markers of a cell in a single measurement.

Our novel device utilizes standard photolithography to define a single pore into variable cross-section regions. Individual transit times within the pore are easily extracted, providing a means to determine transient binding events within each region of the pore.[5] By functionalizing different regions of the pore with different antibodies and by comparing transit times with controls, we are able to determine the presence of different markers on the surface of a cell in a single measurement. Our screening method is label-free, as the labels (i.e. antibodies) are incorporated in the device directly. Furthermore, our variable cross-section pores can be used to create unique electronic signatures that can improve real-time analysis capabilities.

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Oral Presentation

Rapid Directed Evolution of Molecules In Microfluidic Systems

H. Tom Soh
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Current techniques in high performance bioseparations are limited by the inherent coupling among three competing parameters: throughput, purity, and recovery of rare species. Our work utilizes unique advantages of microfluidics technology to decouple these competing parameters by precise and reproducible generation of separation forces that are not accessible in conventional, macroscopic systems. In this work, we will first discuss novel methods of generating ultrahigh magnetic field gradients in microchannels for high purity molecular separations. Then we describe our recent work in utilizing this technique for directed evolution of molecules, such that affinity reagents based on nucleic acids (aptamers) and proteins (monobodies) can be generated with unprecedented efficiencies. We provide the theoretical framework behind the selection efficiencies, and present our recent results in using deep sequencing to identify optimal molecules using bioinformatics. Finally, we present innovative methods of evolving molecules that are capable of performing complex functions including binding-induced structure switching.

Keynote Address

Microengineered Hydrogels for Stem Cell Bioengineering and Tissue Regeneration

Ali Khademhosseini
Harvard University

Micro- and nanoscale technologies are emerging as powerful tools for controlling the interaction between cells and their surroundings for biological studies, tissue engineering, and cell-based screening. In addition, hydrogel biomaterials have been increasingly used in various tissue engineering applications since they provide cells with a hydrated 3D microenvironment that mimics the native extracellular matrix. In our lab we have developed various approaches to merge microscale techniques with hydrogel biomaterials for directing stem cell differentiation and generating complex 3D tissues. In this talk, I will outline our work in controlling the cell-microenvironment interactions by using patterned hydrogels to direct the differentiation of stem cells. In addition, I will describe the fabrication and the use of microscale hydrogels for tissue engineering by using a 'bottom-up' and a 'top-down' approach. Top-down approaches for fabricating complex engineered tissues involve the use of miniaturization techniques to control cell-cell interactions or to recreate biomimetic microvascular networks within mesoscale hydrogels. Our group has also pioneered bottom-up approaches to generate tissues by the assembly of shape-controlled cell-laden microgels (i.e. tissue building blocks), that resemble functional tissue units. In this approach, microgels were fabricated and seeded with different cell types and induced to self assemble to generate 3D tissue structures with controlled microarchitecture and cell-cell interactions.

Session 5: Cell and Tissue Engineering

Invited Speaker

Engineering Hydrogel Structure and Degradation for Cardiac Repair

Jason Burdick
University of Pennsylvania

Heart disease is a major clinical problem in the United States and post myocardial infarction (MI), left ventricular (LV) remodeling ensues and leads to geometric changes that result in dilation and thinning of the myocardial wall. This increases stress in the infarct and healthy tissue and can ultimately result in heart failure. Injectable biomaterials are being investigated to address this clinical problem, including to alter stresses in the infarct region when injected as an array and to deliver biologics, such as stem cells and biomolecules. We are interested in a class of hydrogels based on the molecule hyaluronic acid (HA). HA is found in native cardiac extracellular matrix and is involved in numerous biological functions, such as morphogenesis and wound healing, and importantly, can be modified with reactive groups (e.g., methacrylates) to form hydrogels. We have synthesized variations of HA macromers that form hydrogels with a range of mechanical properties and degradation (from a few weeks to stable over many months) and that form hydrogels through either photoinitiated or red-dox initiated radical polymerizations. This tunability in properties allows us to investigate how material properties (e.g., mechanics and degradation) influence the ability of injectable HA hydrogels to alter stress profiles and LV remodeling and to deliver therapeutic molecules. Examples will be provided that include in vivo assessment in an ovine model of MI over a range of hydrogel properties and the delivery of biomolecules such as stromal-derived factor 1- and TIMP-3, to alter progenitor cell homing to and matrix remodeling within infarcts, respectively. Our ability to design materials with controlled properties and degradation is allowing us to investigate how engineered hydrogels can be used to alter cardiac outcomes by adjusting endogenous signals. Overall, these advanced HA hydrogels provide us the opportunity to investigate diverse and controlled material properties for a range of biomedical applications.

Oral Presentation

Injectable Protein-Engineered Hydrogels to Improve Cell Transplantation

Widya Mulyasasmita[1], Andreina Parisi-Amon[1], Cindy Chung[2] and Sarah C. Heilshorn[2]
[1]Bioengineering, Stanford University
[2]Materials Science and Engineering, Stanford University

Low post-transplantation cell viability presents a major roadblock in the success of cell therapy, as functional recovery is correlated with donor cell survival at the therapy site. While deemed minimally invasive, cell delivery by direct injection still result in significant cell death (<5% survival rate), owing to harsh mechanical forces during injection and hostile biochemical environment at the delivery site. Thixotropic hydrogels, characterized by the ability to undergo shearthinning and rapid post-shear recovery, have been used as cell carriers to rescue viability during injection.

We describe the design and characterization of mixing-induced two-component hydrogels (MITCH), which comprise two recombinant protein block copolymers with complementary peptide binding domains. Unlike common hydrogels that require extreme shifts in temperature, pH, or ionic strength for gelation, these physical hydrogels form by a simple mixing procedure, thereby enabling cell encapsulation at constant physiological conditions. Taking advantage of the specific and stoichiometric interactions between the peptide domains, hydrogels with predictable mechanical stiffness can be formed through systematic variation of component concentration and stoichiometric ratio. Crosslinked by reversible physical interactions, MITCH also exhibit thixotropic properties, thus promoting suitability as hand-injectable cell carriers.

Live cell tracking by bioluminescence imaging (BLI) revealed an immediate 1.5-fold improvement in *in vitro* post-injection viability when luciferase-positive rat mesenchymal stem cells were injected in MITCH, relative to saline. The protective effect of cell encapsulation and injection in MI TCH was also evaluated *in vivo* against saline, as well as alginate and collagen biomatrices by tracking the viability of luciferase-positive cells injected subcutaneously to the dorsum of athymic mice. Normalized to day 1 BLI signal, the retention of viable donor cells was significantly higher in MITCH throughout the two-week course of the experiment (3.4-fold improvement over alginate at day 3; 2-fold improvement over collagen at day 14). Work is currently underway to assess the ability of MITCH-delivered human iPS-derived endothelial cells to restore blood perfusion in a murine hindlimb ischemia injury model.

The constant physiological conditions under which cells are encapsulated in MITCH also allow peptide and protein drugs to be encapsulated and released in their native, bioactive state. The possibility of simultaneous cell and drug delivery to a therapy site further highlights MITCH as a versatile material for injectable therapy.

Oral Presentation

Genetically Engineering Cellular Mechanobiology Through RhoA and Mlck

Joanna MacKay, Albert J. Keung, and Sanja Kumar
University of California, Berkeley

The structural and mechanical properties of cells such as cell size, shape, and stiffness have recently been recognized as important regulators of cell behavior. For example, cells cultured on small areas of adhesive extracellular matrix (ECM) grow slowly and apoptose more frequently than cells spread on large areas (Chen et al., 1997 Science 276: 1425-1428), and cells confined to one-dimensional lines of ECM elongate their cell bodies and can migrate faster than cells cultured on standard unconfined two-dimensional substrates (Doyle et al., 2009 J Cell Biol. 184: 481-490). Others have shown that both ECM patterning and changes in ECM stiffness can alter stem cell self renewal and differentiation. While there are many strategies to indirectly control cell behavior through manipulation of the extracellular environment, there is a marked lack of strategies for controlling these mechanotransductive signaling systems in more direct and precise ways. Such strategies could offer a powerful means with which to control cell behavior at cell-material interfaces. To address this unmet need, we have developed a synthetic biology-inspired strategy for directly tuning the mechanical properties of cells. Specifically, we have placed constitutively active (CA) mutants of two intracellular mechanotransductive signaling proteins: RhoA GTPase and myosin light chain kinase (MLCK) under a tetracycline-repressible promoter and introduced a single copy of these constructs into human glioblastoma cells using viral gene delivery (Fig. 1a). RhoA and MLCK are both known to activate non-muscle myosin II, which is the motor protein responsible for cellular force generation. By expressing these proteins from a tetracycline-repressible promoter, we can vary their activity in a graded fashion by simply changing the concentration of tetracycline in the cell culture medium. This strategy could thus provide a unique opportunity to dynamically alter the mechanical properties and behaviors of cells independently from properties of the ECM.

In this study, we first show that modest expression of CA RhoA from the tetracycline-repressible promoter (only 23% over endogenous RhoA, Fig. 1b) increases the overall activity of RhoA by fivefold. We also evaluate the kinetics of the system by placing a GFP reporter behind the same tetracycline-repressible promoter and measuring intracellular fluorescence following tetracycline withdrawal, which reveals initiation of gene expression within 12 hours and complete expression within 48 hours. Maximal expression of CA RhoA induced by complete withdrawal of tetracycline causes a dramatic increase in the assembly of stress fibers, focal adhesions, and cell-cell adhesions (Fig. 1c). These effects can be modulated in a graded fashion by varying the concentration of tetracycline and are not accompanied by significant changes in expression of key adhesive and motor proteins such as beta-1 integrin, alpha-actinin, vinculin, and myosin II. We then demonstrate that by varying the expression level of either CA RhoA or CA MLCK, we can engineer graded changes in both the cortical stiffness of cells and the traction forces that these cells exert on their surroundings, as measured by atomic and traction force microscopy, respectively. By culturing cells on defined-stiffness matrices, systematically varying tetracycline concentration, and measuring random cell migration, we find that CA RhoA expression inhibits cell migration and that cells are most sensitive to increased RhoA activity when cultured on soft ECMs. Moreover, by reversibly switching expression of CA RhoA on and off over time (by adding and removing tetracycline), we can dynamically control cell spreading, migration, and ECM remodeling. Finally, we show that this strategy offers significantly superior performance to standard pharmacological agents used to activate RhoA; for example, the effects

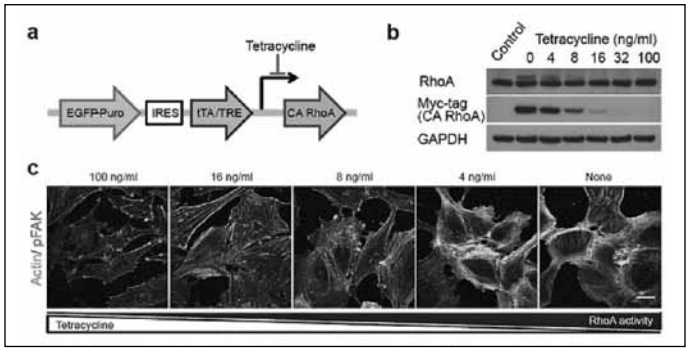

Figure 1. a) Schematic of genetic construct. **b)** Western blot showing graded expression of constitutively active (CA) RhoA with varying tetracycline concentrations. **c)** Immunostaining showing a graded increase in stress fiber formation with RhoA activity.

of lysophosphatidic acid are short-lived and the molecule is poorly soluble in water, and the Rac GTPase inhibitor NSC23766 is toxic at the dosages needed to produce clear and sustained effects on cell morphology.

We believe that this genetic strategy for varying the activity of mechanotransductive proteins could serve as a valuable tool for directly controlling how cells physically interact with their microenvironment and could potentially allow one to “re-engineer” how cells respond to ECM properties. In addition, this strategy would be useful for developing quantitative relationships between intracellular signaling pathways, cellular physical properties, and complex cell behaviors. For example, most direct manipulations of mechanotransductive signaling in living cells have focused only on turning specific proteins “on” or

"off", and the relationships describing how cellular properties vary quantitatively with specific signaling proteins is largely unknown. Thus, exploring the effects of more measured changes in the activity of proteins like RhoA and MLCK would advance our quantitative understanding of mechanotransductive signaling and could reveal important nonlinear relationships (such as an optimal level of protein activity for cell migration).

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Invited Speaker

Microtechnologies and Chemical Engineering for Organization of Liver Tissue

Yasuyuki Sakai
Institute of Industrial Science, University of Tokyo

In order to organize artificial liver tissues for regenerative medicine or cell-based assays, optimization of 3D cellular organization and mass transfer is very important to get highly-functional tissues *in vitro*. Integration of various microtechnologies and chemical engineering-based tissue design should be a good approach to achieve the goals [1]. In this presentation, first, we introduce special 3D macroporous scaffolds having a blanching/joining macro-scale flow channel network. For the design of the scaffolds, we proposed a criterion based on oxygen diffusion-consumption around a flow channel in the 3D scaffolds, fabricated them, and evaluated their efficacy/limitation in perfusion culture of liver cells [2]. Second, we introduce growth of thick seudo-3D sheet-like tissue using direct oxygenation through highly oxygen-permeable polydimethylsiloxane (PDMS) membranes to solve completely the limitation of oxygen supply in static culture [3]. In particular, we stress that meeting the cellular oxygen demand at appropriate physiological concentrations enables highly-efficient aerobic respiration of the cells with less oxidative stresses, leading to spontaneous 3D cellular organizations that have never been observed before in vitro [4]. Third, as examples of 2D micropatterning with direct oxygenation, we introduce highly efficient tissue element formation of liver cells and pancreatic beta cells in PDMS microwells and bile acid recovery from small hepatocyte colonies formed in micropatterned collagen gel with direct oxygenation [5]. As such, optimization of oxygen supply to the cells should give a firm basis for the design of culture systems together with 3D cellular organization with microtechnologies for various applications.

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Oral Presentation

Signaling Molecules Induced by cAMP and the Mechanical Environment On MSC Morphology and Function

Christina Chan and Seungik Baek
Michigan State University

Stem cells residing in tissue-specific niches that contain the necessary cues for differentiation can regenerate tissue upon injury or disease. Before stem cells can realize their therapeutic promise as a cell source for the clinical regeneration of aged, injured, and disease tissues, several challenges must be overcome. Specifically, to control the fate of stem cells, one must understand the intertwined roles of internal cues (e.g., genes, proteins) and external cues (e.g., biochemical (soluble) factors, matrix elasticity and anisotropy) in determining the fate of stem cells, and in particular, the signaling imparted. Understanding the signaling processes that will enhance the maturation of stem cell cultures for cell replacement therapies, and in particular stem cell-derived neurons, could facilitate the development of novel therapies for treating diseases such as Alzheimer's and Parkinson's diseases. Towards this challenge, the overall goal of this study is to elucidate the interaction between soluble factors (namely, the induction of cyclic adenosine monophosphate, cAMP) and mechanical properties (matrix elasticity and anisotropy) in mediating cell fate decision, that is associated with both function and morphology. A critical step in neuronal development is the formation of axon/ dendrite polarity. Recent studies in cortical and hippocampal neurons have shown that local elevation of cAMP and protein kinase A (PKA) activity is a critical early event in axon initiation, to promote axon differentiation and growth. However, we found cAMP, a soluble cue used either alone or in combination with other factors to induce neural differentiation of MSCs, promoted neural function but produced only transient neural-like morphology. In contrast, low modulus surfaces produced neural-like morphology but the cells were not functional. In this study we identified signaling molecules, i.e. SMURF1, regulated by CREB1 (which is activated by cAMP) that could be modulating maturation of MSCs to the neuronal phenotype, both function and morphology. We will discuss how mechanical stimuli, anisotropy in addition to modulus, affect or cross-talk with the signaling imparted by cAMP to affect differentiation.

Oral Presentation

Nano-Bottlebrush Electrospun Fibres for Investigation of Cell-Substrate Interactions

Andrew E. Rodda[1,2,3,4], David R. Nisbet[5], Laurence Meagher[2,3], Francesca Ercole[1], Justin C. St John[4], Kevin E. Healy[6] and John S. Forsythe[1,3]
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Cells respond to many environmental signals, including biological signals (such as adhesion proteins, growth factors and small peptide analogs) and physical features such as topography and mechanical properties. Variation of multiple, concurrently presented signals can lead to a change in cell response that is not easily predictable from investigations of individual signals. Investigation of these non-linear responses requires a culture platform where both physical and biochemical signals can be varied independently of each other.

While these systems exist for flat substrates and hydrogels, we have developed a platform that utilises electrospun fibres, whose fibrous morphology can mimic that of the native extracellular matrix (ECM). These are produced from poly(styrene-co-vinylbenzyl chloride), where the VBC monomer subunits allow for the subsequent grafting of polymer brushes onto the fibres via atom transfer radical polymerisation (ATRP) without requiring further chemical activation. This process creates a bottlebrush-like core-shell structure. Polymer brush layers containing poly(ethylene glycol) can provide a low protein fouling background, and can be co-grafted with other functional monomers. This has allowed the creation of low-fouling electrospun fibres that contain reactive groups, such as alkynes. When combined with azide-modified peptides, this allows for oriented, chemically orthogonal covalent attachment of these peptides via click-chemistry. At the same time, the physical properties of the material can be altered easily through optimisation of the electrospinning and grafting conditions, independently of changes in peptide attachment. This type of material can provide a highly controlled 3D nanofibre substrate within which cell-substrate interactions may in the future be investigated and optimised.

Keynote Address

Systemically Delivered Polymer Nanoparticles Mediate Site-Specific Genome Editing in Human Hematopoietic Cells

W. Mark Saltzman[1], Nicole A. McNeer[1], Erica B. Schleifman[2], Amy Cuthbert[4], Michael Brehm[4], Andrew Jackson[5], Christopher Cheng[1], Kavitha Anandalingam[1], Priti Kumar[5], Leonard D. Shultz[6], Dale L. Greiner[4], Peter M. Glazer[2,3]
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Site-specific gene modification has the potential to produce permanent changes in genomic DNA to correct genetic defects or to enhance cellular function. But delivery of the molecular tools for site-specific editing *in vivo* is a major hurdle. In recent years, we have shown that degradable nanoparticles of PLGA can be engineered into surprisingly versatile systems for intracellular delivery of plasmid DNA, siRNA, and a variety of synthetic oligonucleotides. Further, we have established several methods for engineering the particle surface to allow for targeting. Now, we have applied this technology to the problem of genome editing, by synthesizing degradable polymer nanoparticles that are loaded with triplex-forming peptide nucleic acids (PNAs) and single-stranded donor DNA molecules. These nanoparticles produce site-specific gene editing of human cells in vivo in hematopoietic stem cell-engrafted NOD-scid IL2r null mice. Comparison studies have demonstrated greater efficacy of nanoparticles containing PNA/DNA together over PNA-alone or DNA-alone nanoparticles. Intravenous injection of particles containing PNA and DNA produced modification of the human CCR5 gene in hematolymphoid cells throughout the mice, including CD4+ T cells in the spleen, CD34+ hematopoietic stem/progenitor cells (HSPCs) in the bone marrow, colony-forming hematopoietic progenitors, and true hematopoietic stem cells capable of engraftment in a secondary recipient mouse. We also induced specific modification of the human ß-globin gene using nanoparticles carrying ß-globin-specific targeting molecules, demonstrating this method's versatility. Direct *in vivo* gene modification, such as we demonstrate here, eliminates the need for cell harvest, providing a mechanism by which to perform gene therapy in systemic diseases or in cells that cannot be manipulated *ex vivo*.

Poster Authors

Name	Paper Title	Poster No.
Mohammad Alcheikh Ali	Production and Functionalization of Chitosan Films Fortified with Quinones As Anti-Microbial Bio-Bandages	1
Joakim M Andersen	Prebiotic Utilization by Lactobacillus Acidophilus Ncfm and Framework for Protein Discover	2
Sekhar Bhattacharjee	Nanokinetic STUDIES On SYNTHESIS of Gold Particles by Classical Citrate REDUCTION METHOD	3
Basar Bilgicer	Engineering Multifunctional Nanoparticles to Selectively Target Multiple Myeloma Cells and Overcome Cell Adhesion Mediated Drug Resistance	4
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Production and Functionalization of Chitosan Films Fortified with Quinones as Anti-Microbial Bio-Bandages

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Conventional bandages used in many pharmaceutical industries have lots of disadvantages caused by their composition, they are made from such materials that negatively impact on general health in addition to environmental concerns because they degrade under highly cost conditions and human efforts. Furthermore, they may be contagious and conduct infections due to their direct adhesiveness onto wounds, burns and ulcers which pollutes the bandage that does not have anti-bacterial activity and does not help in wound healing.

Since conventional bandages have above mentioned disadvantages, we have fabricated new wound dressings from organic abundant biodegradable material from marine crustaceans in Syrian fisheries and marine food restaurants such as Shrimp shells that had been used as wound dressings by ancient chineses warriors since centuries, this material is called chitosan. The chitosan have had strong anti-microbial activity, natural bio-adhesive properties, permeability to oxygen and water vapor, non-inflammatory and accelerate wound healing. Conventional bandages may isolate wounds from microbes but, my bio-bandages have anti-microbial effects, help in wound healing by accelerating wound recovery. in addition to that , they do stimulate immunological responses against pathogenic agents. Throughout the ages, Olive tree has got historical, economical and social importance in Syria and Syrian Ebla city in Idleb is considered the first home for olive tree in the world and The cultivation of olive in Syria composes 12% of the total cultivated area and 65% of the total area of fruit trees and thus constitute a rich source of natural phenolesthat can be used to strengthen and improve the bio- bandages characteristics.

Prebiotic utilization by *Lactobacillus acidophilus* NCFM and framework for protein discovery.

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Probiotic bacteria have been shown to positively modulate human chronic bowel disorders, immunity and life-style diseases. Carbohydrate utilization has been identified as an important determinant of probiotic action. Utilization of non-digestible oligosaccharides (prebiotics) can selectively stimulate probiotics in the gastrointestinal tract. However, only few carbohydrates are classified as prebiotics mainly due to limited experimental knowledge of *in vivo* studies and molecular understanding of their selective utilization.

The aim of the work was to use an array of omics technologies to provide a comprehensive and molecular understanding of prebiotic utilization, represented by the commercial *Lactobacillus acidophilus* NCFM.

Here we demonstrate the versatility of this approach by discerning the molecular basis of uptake and catabolism of galacto-oligosaccharides containing α - ß or ß-linkages. Transcriptional analysis led to the discovery of the first ß-galacto-oligosaccharide transporter within the Lactobacillus genus[1] which displayed extensive substrate specificity with respect to oligosaccharide size and composition. This work was integrated with the proteomic reference map and DIGE-proteomics of *L. acidophilus* NCFM, to reveal the catabolic pathways of potential galactoside prebiotics and identified the upregulated specific glycoside hydrolases of GH families 2, 42. Additionally transcriptional and functional genomics analysis of ß-galacto-oligosaccharides identified a key catabolic ß-galactosidase which was biochemically and structurally characterized, highlighting the specificity of this enzyme towards raffinose family oligosaccharides. Sequence motifs and other structural elements important for the molecular architecture were identified allowing us to propose a subdivision of GH36[3] which differentiated sub-specificities within the family.

This work provides a more detailed view of key mechanisms underlying utilization of prebiotic galactosides within probiotic lactobacilli.

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Nanokinetic Studies on Synthesis of Gold Particles by Classical Citrate Reduction Method

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Although vast information on preparation of metal nanoparticles and their applications in bioimaging, biosensors, nanomedicines and diagnostic products has been reported in recent past, experimental data on the fundamental parameters of reaction kinetics or process engineering of metal nanoparticle synthesis are not available till date. In this paper we present a novel approach to study the reaction kinetics and the dynamics of surface morphology during synthesis of metal nanoparticles. Synthesis of gold nanoparticles (GnPs) by reduction of chloroauric acid with trisodium citrate (Turkevitch method) was selected as the model reaction where the citrate acted as a reducing agent and stabilizer. The reduction reaction proceeded through rapid color changes due to change in surface plasmon resonance (SPR) of the colloidal gold solution. Our objectives were to determine the reaction order and kinetic rate constants for the pseudo-homogeneous reduction reaction and to study the effects of process operating conditions on the GnP morphology during the nucleation and maturing stages. Influences of the process parameters- molar ratio of reactants (0.33-5.3), temperature (333-373 K) and pH (3-7) of the reaction medium on the kinetic parameters and GnP morphology were investigated for identification of optimal reaction conditions and suitability of mature GnPs for biomedical applications.

Engineering Multifunctional Nanoparticles to Selectively Target Multiple Myeloma Cells and Overcome Cell Adhesion Mediated Drug Resistance

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In the continuing search for effective treatments for cancer, here we report the rational engineering of a novel multifunctional nanoparticle that combines traditional chemotherapy with cell targeting and anti-cellular-adhesion functionalities to selectively target multiple myeloma (MM) cells and overcome cell adhesion-mediated drug resistance (CAM-DR). Anti-cellular-adhesion evolves as a promising target in oncology. VLA-4-mediated adhesion to the bone marrow extracellular matrix and stromal cells confers MM cells with CAM-DR. In our design, we used micellar nanoparticles as dynamic self-assembling scaffolds to present VLA-4-antagonist peptides and doxorubicin conjugates simultaneously to selectively target MM cells and to overcome CAM-DR. Doxorubicin was conjugated to the nanoparticles through an pH-sensitive hydrazone bond to prevent premature release and thus non-specific toxicity. Peptides were conjugated via a multifaceted synthetic procedure for generating precisely controlled number of targeting functionalities per nanoparticle. The nanoparticles, which exhibited a size of ~20nm, were efficiently internalized by MM cells with an optimal peptide valency of 20 per micelle, and induced cytotoxicity to MM cells. Mechanistic studies revealed that nanoparticles induced DNA double strand breaks as evidenced by H2AX phosphorylation, and triggered apoptosis, which was associated with PARP and caspase-8 cleavage. Importantly, multifunctional nanoparticles were more efficacious than doxorubicin in the presence of fibronectin (IC_{50}=0.15±0.04 μM and 0.42±0.09 μM, respectively), and overcame CAM-DR induced by adherence of MM cells to fibronectin. Finally, in a MM xenograft model, nanoparticles preferentially homed to MM tumors, with a ~10 fold more drug accumulation when compared to doxorubicin, and demonstrated dramatic tumor growth inhibition with much reduced overall systemic toxicity. Taken together, we demonstrate the disease-driven engineering of a nanoparticle-based drug delivery system, enabling the model of an integrative approach in the treatment of MM.

In silico Examination of the Structure of Closed Naked DNA and Protein/DNA Complexes

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We created a user-friendly application, called 3DNAdesigner, that allows a user to construct minimum-energy configurations of open linear and spatially confined DNA molecules. Comprehension of DNA and protein/drug-bound DNA in biological processes, such as transcription, requires an understanding of their structure. When analyzing large DNA systems the complexity of the molecular dynamics in such structures makes it necessary to simplify models of the molecules due to the vast computational requirements of all-atom based simulations. Our model consists of two primary simplifications. First, it focuses on the interactions between adjoining base pairs, not all atoms. Second, the base pairs are modeled as rectangular slabs that are subject to small

elastic deformations. These assumptions allow the use of a base-pair level theory of DNA elasticity.

3DNAdesigner enables a wider audience to build models of superhelical DNA. In order to address this need we identified a core set of input variables needed to generate meaningful models, without requiring the user to modify the source code, and to satisfy a wide range of interests. The resulting set of input data include (i) the sequence of the structure, (ii) the spatial boundary conditions placed on the ends of the molecule, (iii) the decision of whether or not to bind one or more proteins or drugs to sites along the sequence, and (iv) the identities of the latter proteins or drugs. In order to create the most straightforward and user-friendly experience possible with our new modeling package, we decided to capture the capabilities of our equilibrium configuration application in a graphical user interface, or GUI.

3DNAdesigner, expertly guides the users through the process of inputting the details required to generate a meaningful model by presenting them with a series of wizards that take them through the process step by step. Once the user has provided the proper input, the model is generated. However, in order to create a structure with the ends held in a particular spatial arrangement, such as a closed circle or protein-mediated loop, initial values of moments and forces are applied to one of the ends. This set of moments and forces is and initial guess needed to kickoff the iterations of the Newton-Raphson based minimum-energy calculations, which tries to find a stable configuration.

The output of 3DNAdesigner includes the coordinates of the constituent base-pairs (in the form of the origins and local coordinate axes of each pair) and detailed data on the topology (Twist, Wr, Lk), the total elastic energy E_{Total} of the fragment, and the six base-pair-step parameters (Shift, Slide, Rise, Tilt, Roll, Twist). 3DNAdesigner also provides the user with a three-dimensional visualization of the resulting structure so that (s)he can investigate it in greater detail. Also included in the output is a new definition of the twist that we developed for DNA base-pair steps called the twist of supercoiling, Tw^{SC}. Tw^{SC} is related to the overall folding of the DNA molecule and is a new contribution to the field of DNA topology.

The software was used to create minimum-energy configuration of DNA mini-circles and DNA/protein complexes. The stabilities of all converged configurations are calculated and quantified through the examination of the elastic energies. We found that the binding of EcoRV endonuclease protein affected the overall fold of the DNA mini-circles and changed the Lk and energy from that of the naked structure. This type of result might be of interest to a lab performing in vitro studies of their sequences. We also found numerous minimum-energy configurations of the Lac operon bound to the Lac repressor and compared them to being in the presence of the architectural prokaryotic protein called HU.

Biomimetic Self-Templating: A Biomimetic Approach to Synthesis of Biological and Optical Materials

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A fundamental challenge in nanotechnology research is to simultaneously synthesize high performance nanomaterials and to assemble them into well-defined, large-scale devices in a cost-effective manner. One approach to tackle this challenge is to learn from and adopt nature's strategies (biomimetics) to design innovative engineering materials. Nature is a potent source for inspiration because, through millions of years of evolution, remarkably effective and efficient hierarchical structures have emerged to meet a variety of functions. Surprisingly, a single type of helical macromolecule (e.g., collagen) is often found to form diverse, functional structures (e.g., cornea, skin, and bone) when self-templated under different conditions. Based on this observation, in this study, we present an innovative biomimetic approach to synthesis of functional hierarchical structures based on directed evolution and self-templating. We utilize the bacterial virus M13 phage as a model helical macromolecule. First, we demonstrate a single-step process to create long-range-ordered supramolecular film showing multiple levels of hierarchical organization and helical twist. Both chiral liquid crystalline phase transitions and competing interfacial forces at the interface are found to be critical factors in determining the morphology of the structures during assembly. The resulting materials show potentials as optical materials (e.g., optical filters, structural color matrices) and biological materials (e.g., soft and hard tissue guiding scaffolds). This self-templating approach provides insight into the complexities of hierarchical assembly in nature and could be expanded to other chiral molecules for further engineering of sophisticated functional structures.

A Nanoporous, Biodegradable Thin-Film Polymer Device for Sustained-Release Delivery of Biopharmaceuticals to the Eye

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The traditional dosage forms of ocular drug delivery, such as eye drops and ointments, are widely used to treat a variety of ophthalmic disorders, but they have several limitations. They often require frequent daily administration, commonly three of four times a day, and are difficult to self-administer, especially for elderly patients. Importantly, they also provide little to no penetration into the vitreous and retina and are thus ineffective in treating diseases affecting the posterior segment of the eye. Retinal diseases are therefore most commonly treated using intraocular injection. A prime example is the intravitreal administration of ranibizumab (LucentisÓ, Roche, Inc.) used for the treatment of age-related macular degeneration (AMD), a disease affecting more than two million people in the United States alone.

While intraocular injection can effectively deliver drug to the retinal tissue, this method has limitations as well. The drug is often cleared rapidly from the eye (i.e. 9 day half-life for ranibizumab), reducing the time that the drug concentration stays within the therapeutic window. Additionally, there is potential for rare but serious complications associated with the injection, including endophthalmitis and retinal detachment. Consequently, minimizing the frequency of intraocular injection is an important objective in patient care. However, a number of therapies require repeated injections, including AMD treatment, which requires monthly injections of ranizibumab often lasting for several years. The risk and cost associated with such frequent injections has resulted in reduced compliance with the recommended treatment regimen limiting therapeutic response. Improvements in drug delivery technology to more effectively deliver drugs to the retina while reducing the risk of complication are sorely needed and actively being investigated.

Modeling of Effects of Lipids On Dissolution of Poorly Water-Soluble Drugs

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Despite the recognized capability of ingested lipids to impact several processes associated with the overall oral absorption of poorly water-soluble drugs, the fate of co-administered drugs remains unclear and unpredictable. The aim of this study is to quantitatively investigate and model the effects of ingested lipids and lipid digestion on dissolution and partitioning of hydrophobic drugs orally delivered in simulated intestinal fluids by means of in vitrolipolysis models.

An updated in vitro digestion model – comprising a bio-relevant medium, soybean oil as lipid substrate, and lipase/colipase enzymes – was designed to closely mimic fed state intestinal conditions. The paramagnetic compound TEMPOL benzoate (TB) was selected as a model for poorly water-soluble moderately lipophilic drug (log P = 2.46). Digestion kinetics were investigated by acid-base titration and correlated to dissolution tests. Kinetics of drug partitioning between colloidal phases (oil, micellar, aqueous) formed during in vitro digestion was tracked by electron paramagnetic resonance (EPR). A model considering pseudo-equilibrium micelle partitioning, interfacial-barrier driven oil partitioning, and oil digestion kinetics was developed and compared to experimental results.

A film-equilibrium model, in the form of Noyes-Whitney expression, was developed and utilized to predict drug dissolution kinetics in the simulated intestinal fluids with and without lipids. In the model, the influence of interacting colloids on transport rates was explicitly taken into account, and drug partitioning with micelles was considered as a pseudo-equilibrium process. The impact of lipids and their digestion on dissolution was evaluated based on EPR measurements pre- and during in vitro lipolysis simulations. EPR provided real-time compound tracking measurements being able to quantify the amount of drug present in each phase related to the lipolysis process. After the addition of soybean oil into the bio-relevant medium, EPR spectra of pre-lipolysis samples showed an increasing partitioning of TB into the oil phase up to 30%, over a time scale similar to that of lipid digestion (3 hours), suggesting an interfacial-barrier driven process rather than pure diffusion of drug into the oil phase.

Drug dissolution, partitioning coefficients, and digestion kinetics of digestion were correlated in system-based model enabling prediction of the fate of orally administered drugs during the lipid digestion process and providing insight into their anticipated overall effect on oral absorption.

Rationally Designing Peptide Amphiphile Micelles for Use As Targeted Drug Delivery Vehicles

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Peptide amphiphile micelles provide a modular design platform for the creation of targeted drug delivery vehicles. Peptide amphiphiles are formed by conjugating a hydrophilic peptide headgroup to a hydrophobic lipid tail. The peptides used in the formation of these peptide amphiphiles are designed to target specific sites of interest in the body. Our approach is to use two peptides that can target both early stage inflammation markers of atherosclerosis as well as late stage markers of atherosclerotic plaques. Atherosclerosis, characterized by the formation of a plaque in the artery wall, can lead to heart disease, the leading cause of death in the United States. The formation of a targeted vehicle that can selectively deliver a therapeutic agent at the site of plaque formation is thus highly desirable as such targeted therapeutics are not currently available. In order to develop such a therapeutic delivery agent, however, it is first necessary to determine how the specific components of the peptide amphiphile micelle, namely the hydrophilic head group and hydrophobic tail, affect the size, shape, and stability of the micelle formed. We will thus discuss how changing the peptide targeting agent and the hydrophobic tail affect the dissociation kinetics of the micelle and how we can increase the micelle's half life *in vitro*. In addition, we will present both dynamic light scattering (DLS) data and transmission electron microscopy (TEM) images to show the size and shape micelles that are formed. Both spherical micelles with a diameter on the order of 10-20 nm and cylindrical micelles will be discussed. The critical micelle concentration (CMC), or the concentration at which micelles begin to form, provides insight into the stability of micelles. The ability to tailor the CMC based upon the hydrophobic tail will also be discussed. Enzymes play an important role in degrading peptides in vivo, and we will thus discuss how the formation of micelles affects the degradation of peptides in the corona as compared to a peptide control. Finally, we will show the in vitro binding capabilities of micelles formed from these early and late stage targeting peptides.

A Novel Method for Fabrication of Chemically Heterogeneous 3D Nanofibers Scaffold for Tissue Engineering Applications

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The aim of the tissue engineer to develop functional scaffold with adequate close mimic of highly heterogeneous physical (topography) and chemical (functional groups and molecules like proteins etc.) features of natural extracellular matrices (ECM) to encourage cells for regeneration of the specific functional tissues, is obligatory and challenging. Most of the current scaffold fabrication techniques have been focused to mimic the physical structure of natural ECM (i.e., topological features) in the scaffold. Conversely to introduce the chemical feature into the scaffold, most common post chemical modification of fabricated scaffold has been used. In this process it is difficult to introduce multi chemical functionality into a scaffold. Thus the current scaffold fabrication methods have limitation in fabrication of 3D scaffold having both physical and heterogeneous chemical features in a scaffold. We have developed a novel fabrication technique of nanofiber-pocket 3D scaffold where each fibers pocket (>100 μm) in 3D can have different physical and chemical signatures. This technique has four distinct process steps; nanofibers preparation, chemical modification of the nanofibers, protection of the fiber by encapsulation into NaCl crystal, and arranging the fibers in 3D and unprotected the fibers. The nanofibers are encapsulated into the NaCl crystal to protect from solvents and the encapsulated fiber-NaCls crystals are used for 3D scaffold fabrication by salt-leached techniques. The NaCl crystals protect nanofibers from array of organic solvents and preserving their physical and chemical signature during the scaffold processing and carry into the 3D scaffold. This is a generic technique that allows us to fabricate a 3D nanofibers scaffold of single or multiples polymers systems with chemical heterogeneity (encapsulated/immobilized growth factors, proteins and biomolecuels for specific cell functions and fate) in 3D. The scaffold prepared in our technique has superior mechanical and cell penetration properties than the conventional electrospun nanofiber scaffold. Using this technique we prepared scaffold with specific chemical functionality in 3D for particular cellular function such as targeting the stem cell to specific site of scaffold in 3D.

Stabilization of Proteins by Nanoencapsulation in Sugar-Glass for Drug Delivery and Tissue Engineering Applications

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There is a need in regenerative medicine to develop next generation 'smart scaffolds' that will mimic extracellular matrix (ECM) in providing appropriate physical and chemical environmental cues for cell growth and differentiation. Such scaffolds will incorporate cytokines to direct cell behaviour. Proteins and other biomolecules sequestered in and delivered from polymeric tissue scaffolds and other delivery vehicles undergo several process and storage-related stresses throughout the life

of the product that can result in significant degradation, loss of bioactivity and elevated safety risk. The stresses include exposure to hydrophobic surface (polymer and organic solvents), mechanical agitation, and elevated temperature etc[1]. A number of approaches have been developed to ameliorate the impact of individual processing stresses, but no single approach has been available heretofore which would protect against all these stresses. Far from meeting this ideal, many approaches for improving one aspect of performance are neutral or deleterious to others.

We have developed a novel Sugar-Glass-nanoparticle (SGnP) system to stabilizing proteins that is nearly ideal in that the single approach yields excellent protection from process-related stresses, very good encapsulation efficiency and storage stability, as well as giving burst-free sustained release for essentially any protein and polymer system.

Electrochemical Detection of the P. Aeruginosa Virulence Factor Pyocyanin Using Nanochannel Devices

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Nearly one in ten hospital-acquired infections is caused by *Pseudomonas aeruginosa*, a versatile bacterium that is found in nearly every environment on earth. Clinical identification of *P. aeruginosa* is often carried out by observation of bluish-green colonies after culturing samples overnight at 42 degrees Celsius. The unique bluish-green color of these bacteria is caused by pyocyanin, a virulence factor that causes oxidative stress in cells. We have developed a device that integrates both a working and reference electrode inside of a nanoscale constriction and used it to measure pyocyanin produced by *P. aeruginosa* in growth media. By utilizing square wave voltammetry, micromolar concentrations of pyocyanin were selectively detected in a complex liquid solution.

Differential Epitope Targeting of Iron Oxide Nanoparticles Enhances Her2+ Cellular Specificity In vitro and Tumor Uptake In vivo – 13

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Magnetic nanoparticles (mNP) have shown broad utility as MRI contrast agents, and the capacity to remotely energize some mNP designs using high frequency alternating magnetic fields forms the basis of magnetic hyperthermia for cancer therapy. The engineering of increasingly complex nanoparticle constructs has resulted in versatile, multifunctional "theranostic" platforms that extend the inherent utility of mNP by incorporating optical imaging agents, chemotherapeutics, siRNA's, and gene therapies. The ultimate clinical utility of any such platform is, however, dependent upon efficient and specific localization to cancerous cells. In cases where direct injection into tumor masses is not a viable option, passive targeting, via mechanisms such as enhanced permeability and retention, is unlikely to achieve adequate mNP concentrations at sites of malignancy. To facilitate cancer-specific accumulation of mNP, nanotechnologists have begun examining molecular targeting via antibodies, peptides, aptamers, and other biological moieties. Employing a systematic and rigorous molecular engineering approach, we have recently developed mNP bearing Fab antibody fragments that selectively target the Her2 receptor, commonly up regulated in breast and ovarian cancers. We show that the affinity and specificity of Fab targeting moieties is unaltered by conjugation to the mNP surface, and in vitro experiments with cell lines having varied Her2 expression levels demonstrate the preferential targeting of Her2+ cells by Fab-functionalized mNP, relative to non-targeted controls. The efficiency of Her2+ cell targeting is shown to be dependent upon the identity and epitope specificity of the Fab fragment, and up to two orders of magnitude enhanced accumulation can be achieved in vitro with appropriately designed mNP constructs. Moreover, we demonstrate that cellular internalization of mNP, a key determinant of prospective therapeutic efficacy, can be enhanced by Fab targeting of the Her2 receptor. To assess in vivo targeting efficiency, A2780 (Her2+) human ovarian tumors were developed IP in Rag1 deficient mice. The tumor specificity of IP-administered mNP is enhanced by Fab functionalization, and analogous to our in vitro results, the epitope specificity of the Fab-targeting moiety appears to influence tumor selectivity and biodistribution. The implications of these targeting studies will be discussed within the broader context of the Dartmouth Center of Cancer Nanotechnology Excellence and its translational objectives.

Magnetic Resonance Imaging Parameters Are Indicative of Malignant Transformation in Low Grade Gliomas

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Gliomas are heterogeneous, infiltrating tumors of the central nervous system that include astrocytomas, oligodendrogliomas, and mixed oligoastrocytomas. The prognosis for these patients can vary significantly depending on the grade of malignancy and histological characteristics, as defined by the World Health Organization (WHO) (1). Although patients with low grade glioma (grade II) generally live much longer than their high-grade counterparts (grades III and IV), there is substantial heterogeneity in outcome, even for individuals with the same initial diagnosis. Primary treatment is maximal safe resection, followed by radiation and/or chemotherapy at the time of progression. Many patients with tumors that are initially diagnosed as low-grade will upgrade to higher grade lesion at the time of recurrence. Previous studies have shown that *ex vivo* spectroscopy can discriminate between upgraded and non-upgraded lesions (2), but there are significant limitations that remain in the assessment of malignant transformation using conventional MR imaging methods. This study has applied advanced *in vivo* magnetic resonance imaging and spectroscopy techniques to characterize parameters that are associated with malignant transformation.

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Formulation of PLGA Nanoparticles for Anticancer Drug-Doxorubicin and Sustained Release Studies of the Drug In Simulated Buffer Systems

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Since anticancer drugs lack specificity, are highly toxic and have to be administered for long durations, drug delivery systems seem promising for such treatments by modifying the bio-distribution and pharmacokinetics of the drug *in vivo*. Polymer based sustained release of these drugs from nanoparticles (NP) will lead to maintenance of drug levels within desirable range with much lower doses, reducing the toxicity, number of administrations and better patient compliance. Polylactic acid (PLA) and polyglycolic acid (PGA) copolymer, PLGA has been suitable because of its excellent biocompatibility and biodegradability Here, we report the studies done on encapsulation and *in vitro* release of the chemotherapeutic drug doxorubicin from poly(lactic-co-glycolic acid) nanoparticles under *in vitro* simulated conditions.

Synthesis of Biocompatible Photoluminescent Hybrid Particles

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Quantum dot nanoparticles have gathered wide attention for their narrow emission spectrum, intense luminescence and high stability against photobleaching compared with organic dyes. A drawback remains that quantum dot is highly toxic and needs to be modified before being used for biological applications. This study presents a method to easily fabricate biocompatible photoluminescent hybrid particles using quantum dots. Silica@QD@Silica particles are synthesized in organic solvent phase which is then transferred to aqueous phase. The synthesized hybrid particles have a silica surface for a wide range of surface modification, excellent biocompatibility, and higher photoluminescence efficiency compared to water soluble quantum dots. Another merit of the hybrid particles is the size controllability, allowing for various applications with different sizes while preserving the particle properties.

Bio-Nano Platform for Cell-Cell Communication

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We have developed a novel microfluidic device for space- and time-resolved visualization of intracellular events when a cell surface is partially exposed to external stimuli. The device, fabricated using 3D rotational inclined UV lithography of photoresist SU-8, consists of a cell-containing chamber and a flow channel separated by a thin vertical wall having a lateral micrometer aperture smaller than a cell. A cell is first immobilized on the aperture by suction from the flow channel using

a syringe pump, and a chemical stimulant is then fed to the channel so that only the cell surface bounded by the aperture is subjected to the stimulus without leakage to other part of the cell surface. The subsequent lateral signal propagation inside the cell can be visualized using high-speed fluorescence confocal microscopy. As an experimental demonstration of the device, 2-NBDG (fluorescence glucose analog) intake into a mouse insulinoma cell, MIN6m9, was visualized in 4D resolution.

And to measure the cell-cell communication of the MIN6m9, we developed the double layered micro fluidic channel with micro orifice to stimulate the target cell. The cell are immobilized on the micro orifice and the target cell is stimulated by the high glucose solution by the micro cannel which is designed only target cell is stimulated. The micro-channels and micro-orifices are simultaneously fabricated by using inclined UV lithography. And the cytosolic Ca2+ concentration of immobilized cells is measured.

Neuroprotective Effect of Clitorea Ternatea Extract On 6-Hydroxydopamine Induced Parkinsonism In Aged Rats

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Parkinson's disease (PD) is one of the commonest neurodegenerative diseases, and oxidative stress has been evidenced to play a vital role. The present study was designed to delineate the neuroprotective effect of Clitorea ternatea extract (CTE) enriched with bioflavanoids on lipidperoxidation (LPO), antioxidant-status and repairing enzymes of 6-hydroxydopamine (6-OHDA)-induced neurotoxicity and DNA content in the discrete regions of brain associated with Parkinsonism in aged rat brain.

A Bioresponsive and Bioinstructive Protein-Engineered Hydrogel for 3D Cell Encapsulation and Neurite Growth

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Neural regeneration within the central nervous system (CNS) is a critical unmet challenge as brain and CNS disorders continue to be the leading cause of disability nationwide. Common tissue engineering goals seek to customize cell-biomaterial interactions and guide cell behavior. Here we have developed a material that is both cell instructive and cell responsive, creating a dynamic interplay between cells and their engineered extracellular matrix (ECM). Using recombinant protein technology, we engineered a family of elastin-like protein hydrogels with multiple independently tunable properties. With these materials we can investigate individual and synergistic effects of elastic modulus, degradation rate, and cell adhesivity on cell behavior in a tunable microenvironment. Unlike natural matrices, the concentration of adhesive ligands such as the fibronectin-derived sequence RGD can be precisely controlled without altering the mechanical properties of the hydrogel. When dorsal root ganglion neurons were cultured in 3D in these gels, RGD ligands at 1.9 x 10^7 ligands/μm^3 promoted neuron-specific growth, and more than doubled the rate of neurite extension compared to hydrogels without the adhesive sequence. Crosslinking density was tuned to create scaffolds with elastic moduli from 0.5-2.1 kPa with constant adhesive site densities. The most compliant gels led to the greatest outgrowth from encapsulated DRGs with neurites extending over 1800 μm by day 7. In contrast, the stiffest gels permitted far fewer extensions and limited outgrowth to a maximum of 600 μm over the same time frame.

We have designed the proteins with a second set of bioactive sequences that specifically respond to changes in cell phenotype. Neural stem cells (NSCs) undergoing differentiation may change their production of the protease urokinase plasminogen activator (uPA), which has previously been found at the growth cones of extending neurites. By incorporating cell-mediated degradable subunits into the elastin-like proteins, we are able to mimic the natural remodeling of the ECM. We engineered multiple uPA target sites with different degradation kinetics into the elastin-like protein to allow neural cell-mediated control of the scaffold degradation dynamics. These crosslinked scaffolds are useful for directing the growth and differentiation of multiple cell types including clinically relevant NSCs. Adult murine NSCs were capable of proliferation and differentiation into neurons and glia when seeded on top of RGD-containing scaffolds.

This cell-regulated strategy was also used to enhance the functionality of the polymer by controlling delivery of multiple molecules with distinct release kinetics. One molecule was tethered to the matrix via a fast-degrading uPA-responsive sequence and fully released in 48 hours, while another molecule tethered by a more slowly degrading uPA-responsive sequence was continually released for more than 240 hours.

These tunable scaffolds are responsive to neural cells

which may be able to specifically self-modulate the release of multiple bioactive factors while undergoing differentiation. This work demonstrates the versatility and responsiveness of our modularly-designed protein hydrogels for neural cell culture and encourages continued development as a biomaterial tissue construct for treating spinal cord injury.

Assessment of the Myc Dose Response In An Abl-Transformed Pre-B Cell Line

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The Myc transcription factor is a complex proto-oncogene known to both stimulate proliferation of cells while blocking terminal differentiation and trigger apoptosis in certain contexts. In addition, Myc has been found to be deregulated in human cancers, most frequently in colon, breast, and prostate cancers. Such phenomena indicate the possibility of a dose-dependent effect of Myc expression on the crucial cellular decisions between survival and death, or proliferation and differentiation. Here we have created a tamoxifen-inducible MYC fusion with GFP and cloned it into a library of viral constructs, each with a distinct level of expression. This estrogen responsive (ER) domain prevents Myc localization to the nucleus until tamoxifen is added. We have transduced this construct into PD31 cells, a v-Abl immortalized pre-B cell line and have demonstrated a range of Myc expression using flow cytometry and qPCR. Upon tamoxifen induction, we have measured the effect of Myc dosage on the cell line's proliferation rate under decreasing amounts of serum, a condition known to decrease endogenous Myc expression using a fluorescence-based dye and flow cytometry. Transduced, tamoxifen-treated cells were shown to express downstream Myc targets such as Npm1 in response to ectopic Myc expression. The ability to express an active, inducible, fluorescent Myc fusion over a range of expression levels may prove useful in tandem with another gene of interest, e.g., the Ras oncongene; such an experiment could yield insight on how Myc interacts with other oncoproteins at the signaling and phenotypic levels over a broad 2-D expression space.

Virus-Based Piezoelectric Materials for Energy Generation

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The future growing energy demands ask for new ways to generate, store, and utilize energy. Piezoelectric devices can be utilized in the future as clean energy generators by scavenging the ubiquitous, mechanical energy and converting it to electrical energy. However, the synthesis of piezoelectric devices often requires the utilization of harmful materials, harsh conditions, and/or complex procedures. Here, we demonstrate electrical energy production utilizing a novel piezoelectric material based on M13 bacteriophage (phage). We characterized the structure-dependent piezoelectric properties of the self-assembled phage thin films. We also showed that their piezoelectric properties can be tuned by modulating their dipole strength through genetic engineering of their major coat proteins. The phage films showed piezoelectric strengths of ~7.8 pm/V and the devices could produce 6 nA of current and 400 mV of potential, enough to operate liquid crystal displays. The self-replication and self-assembly of the phage allows for simple and environmentally friendly production of piezoelectric materials that may be used for energy harvesting and transduction in future miniature scale devices.

Incorporation of Sacrificial Fibers Increases Cell Infiltration and Influences Synovial Stem Cell Behavior

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Neural crest-like synovial stem cells (NCL-SSCs) are isolated, maintained, and characterized. In addition, electrospinning is used to fabricate nanofibrous scaffold containing sacrificial polyglycolic acid (PGA) fibers to improve porosity and enhance cell infiltration. Preliminary studies to assess the effect of increased cell infiltration on NCL-SSCs are presented.

Recent studies have demonstrated that bioactive scaffolds can be used to regenerate cartilage by local cell homing. However, the specific types of cells participating in regeneration are not fully understood. In this study, we identified a novel type of neural crest-like synovial stem cell (NCL-SSC) residing within the synovial membrane, which possesses several important characteristics distinct from previously identified stem cells. Protein marker screening revealed that NCL-SSCs homogeneously expressed neural crest stem cell markers, such as Sox1, Sox10, Snail and Vimentin. In addition, differentiation assays showed that NCL-SSCs can be not only induced into cells of mesenchymal

lineages, including osteoblasts, adipocytes, and chondrocytes, but also differentiated into peripheral neurons and Schwann cells. Furthermore, we found that the combination of chick embryo extract and basic fibroblast growth factor can maintain the multipotency and maker expression of NCL-SSCs. Cloning assay showed that the average plating efficiency of NCL-SSCs is about 10% and the cloned colonies retained the marker expression and multipotency. Lastly, NCL-SSCs can form neurosphere-like aggregates when cultured in ultra-low attachment culture dishes.

Novel Quantitative FRET Assays for the Sumoylation Pathway Analysis

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Förster resonance energy transfer (FRET) is a widely used method that determines molecular distance of 1-10nm which fits well with biomolecular interactions and conformational changes. FRET has been widely used in biological and biomedical research in vitro and in vivo. We recently developed a novel quantitative FRET analysis methodology and applied this method to determine protein interaction affinities and protease kinetics in the SUMOylation cascade. The novel methodology is based on the quantitative analysis of the FRET signal from the total fluorescent signal at acceptor emission wavelength, which consists of three components: donor emission, acceptor emission and FRET signal. SUMOylation is an important protein post-translational modification, which is carried out by multi-step enzymatic cascade reactions for peptide activation and substrate conjugation, and plays critical roles in diverse physiological processes, including transcriptional regulation, signal transduction, cell survival and death and DNA damage response. We developed a new theoretical and experimental procedure for protein interaction K_d determination of SUMO1 and its E2 ligase, Ubc9, and individual interaction in the full SUMOylation cascade by FRET assay. The K_d values (~0.3mM) are in good agreement with those determined with other traditional approaches, such as surface plasmon resonance(SPR) (0.35mM) and isothermal titration calorimetry(ITC)(0.25mM). We have applied the same strategy to develop a novel quantitative FRET-based protease assay for SENP kinetics parameter determination. SENP is a family of proteases that are responsible for SUMO maturation from precursor and removal from conjugated substrates. The novel theoretical and experimental procedures to determine the kinetics parameters, K_{cat}, K_M and catalytic efficiency ($k_{cat}/K_M = 2.49 \times 10^7\ M^{-1}s^{-1}$) that is superior than traditional biochemical assays. We have applied this novel methodology for K_d determinations of entire SUMOylation cascade and SENP proteases. These developments represent a novel methodology of biosensor based on FRET for systems kinetics analysis, which can be used in other biosystems and applied for drug discoveries.

Statistical Distribution of Microparticle Trapping in Hydrodynamic Tweezer Arrays for Single-Cells Analysis

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Steady streaming microeddies can be useful for trapping microparticles or single-cells in isolation.[1-3] Tuning the fluid oscillation frequency and amplitude allows these microeddy devices to trap a variety of objects such as micro-bubbles, T-cells, macrophage, and motile phytoplankton.[1,4] Microeddies can be arrayed for high throughput trapping. Here we examine the statistics of trapping in microeddy arrays in order to combine tools for single particle analysis with population analysis. We present a method to rapidly determine overall cell counts and analyze sub-populations based on low resolution imaging the statistical behavior of trapping.

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Development of a Biocompatible Conductive Platform to Measure Cell Traction Forces

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Changes in the mechanical properties of mammalian cells are indicators for cell health and can provide better understanding towards disease diagnosis. While routine cancer cell detection methods rely mainly on diagnosis through morphological analysis, it can be inconclusive or

unreliable for certain cell lines. Mechanical factors such as cell exertion of traction forces on a surface are instrumental in biological processes such as cell migration, extracellular matrix formation, and cell signaling. Several researchers have investigated methods to calculate the traction forces exerted by cells, which may provide a more accurate method to diagnose cancer cells. While some of these methods, which involve micropillars, microneedles, and nanowire arrays, are able to isolate the mechanical force of a cell, the process to make these platforms is laborious and exhibits an interface which is not biocompatible or characteristic of a native cell environment. In this work, we investigated the use of single-walled carbon nanotubes (SWNTs), and by utilizing various deposition techniques, we developed a facile technique to manufacture a platform that is both biocompatible and a conductive source for quantitative analysis of the mechanical behavior of cell traction forces. Due to their excellent electrical characteristics for uses in organic electronic applications including thin film transistors, conducting electrodes, and biosensors, SWNTs were chosen as the material to provide a conductive platform. Previous studies were able to adsorb SWNTs for film deposition by drop casting, airbrush spray coating, spin coating, vacuum filtration, electrophoretic deposition, and Langmuir-Blodgett deposition. Furthermore, researchers have found that when surfaces are covalently functionalized with primary amines, they selectively adsorb semiconducting SWNTs. However, this and similar techniques are dependent upon environmentally sensitive surface modification techniques. To address this issue, we explored a range of substrates modified with physisorbed polymers, poly(L-lysine) (PLL), as an alternative methodology. In this work, we detail a number of methods for depositing SWNTs onto various substrate materials using amine-rich PLL and other methods of covalently functionalizing the surface with primary amines. We constructed devices using these methods and used them to observe if cell movement on the surface would elicit changes in the device performance. SWNT adsorption and alignment were characterized by atomic force microscopy (AFM), which revealed that the surface density was strongly dependent upon the adsorbed concentration of PLL on the surface, spin coating speed, and SWNT solution concentration. We also demonstrated the biocompatibility of PLL as an adhesion layer with cells. Results from examining mitochondrial hydrogenase activity and Live/Dead fluorescence assay suggest that the PLL SWNTs spin-coat devices exhibited higher biocompatibility with NIH-3T3 fibroblast cells than the drop-cast SWNTs devices, possibly due to differences of substrate surface roughness. To further elucidate the effect of SWNT roughness on biocompatibility, cell morphology was observed on substrate surfaces of varying SWNT network density using a spray coating method. We envision these conducting biocompatible SWNT networks could be used as biosensors to investigate cell adhesion mechanics or disease diagnosis.

Nanoliter Droplet Viscometer with Additive-Free Operation

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Measurement of the viscosity of a sample solution is an important analytic technique for medical diagnosis, pharmaceutical development, and industrial processing, among other applications. The use of droplet-based «digital» microfluidic operation allows nanoliter-scale sample volumes, much smaller than those in continuous-phase microfluidics. By observing the flow rate of a sample plug through a drastic constriction, we achieve accurate and precise measurement of the plug viscosity without addition of labels or tracers. Sample plugs in our device geometry had a volume of ~30 nL, and measurements had an average error of 7.2% ± 6.2%, with an average relative standard deviation of 2.65% ± 4.08%. We tested glycerol-based samples with viscosities as high as 101 mPa*s, with the only limitation on samples being that their viscosity should be higher than that of the continuous oil phase.

Synthetic, Extracellular Matrix Mimicking Hydrogel to Promote Spreading, Migration, and Proliferation of Schwann Cells

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Peptide amphiphiles, short peptide sequences attached to a fatty acid tails, can self assemble into extended cylindrical micelles which entangle giving rise to a flexible hydrogel. The modular nature of peptide amphiphiles allows incorporation of features which can stabilize extended micelle structures, and add a variety of bioactive modalities. Here we present a peptide amphiphile system where hydrogen bonding of the peptide headgroup was studied as a method of stabilizing the self assembled micelle structure and thus increasing the modulus. Initially the solution behaves as a weak gel at acidic conditions, and then effectively crosslinks through

amino acid side chain hydrogen bonding to form very stiff gels at physiological pH. Tuning of the modulus was accomplished by increasing the concentration and is able to span a range of G'= 100-10,000 Pa. Stiffness of the bulk material was also tuned independently of fiber density by changing the linker chemistry of the peptide headgroup. Using this versatile 3D system we were able to study a variety of applications where stiffness and ligand presentation must be tuned independently. One such application, nerve tissue regeneration, will be discussed where Schwann cells, a cell type involved in nerve tissue regeneration, are shown to sense stiffness changes in the underlying matrix, as evidence by changes in proliferation, spreading and migration.

Dual Mode Iron Oxide Nanoparticles for Bio-Distribution Studies in Life Sciences

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Assessing bio-distribution and pharmacokinetic (PK) properties are key steps in designing drug delivery vehicles. With this in mind, we have synthesized water soluble, ^{14}C ($t_{1/2}$=5730 years) labeled, magnetic iron oxide nanoparticles (~10nm) with differing surface functional groups (carboxylic acid or amine) to assess how surface properties affect bio-distribution in vivo. The radiolabeling reaction schemes were highly flexible and the degree of radiolabeling was controllably varied from 0.1[2] nCi/mg to 0.1 mCi/mg without any increase in reaction times. The reaction schemes involved converting silano-organic moieties on the nanoparticle, to carboxylic acid (-COOH) functional groups using substitution chemistry or to amine (-NH_3) functional groups using polymer chemistry. The bio-distribution and PK properties were determined using Accelerator Mass Spectroscopy (AMS), an ultrasensitive (10^{-18} moles) spectrometric technique that allows quantitation of ^{14}C in small amounts of sample. The radio-labeling approach used in these studies was significant as the radio-labeled probes had the same chemical properties as the non-labeled probes they were meant to mimic, which provides for a comparable set of data. Furthermore, the use of a magnetic core as the nano-carrier for the radiolabels allows for dual detection schemes, which will increase the accuracy of the bio-distribution data. The synthesized particles in this work have implications for use in many biological applications aside from drug delivery.

Highly Selective Bioinspired Colorimetric Sensor Using Genetically Engineered M13 Virus

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In nature, evolution creates numerous nanomaterials, of which only the best are chosen and propagated through generations in the form of proteins and genes. Proteins and genes mutually orchestrate spatial and temporal control over the synthesis of organic and inorganic nanomaterials, commonly resulting in hierarchical structures with specific functions. During natural selection, the ability of manipulation of light to further modify these structures for more adaptive functions has been a critical component of evolutionary pressure. For examples, using an array of inorganic calcite lenses, brittle star collects more light in the abyss; using flickering photonic color from periodic layers of cuticles, Morpho butterfly communicates to each other in long distances; and using hierarchical protein structures in skins or feathers, many birds (i.e, turkeys and ostriches) express tempers. Various inorganic and organic nanomaterial-based photonic crystals have been developed to mimic biological functions through top-down and bottom-up processes. Self-assembled colloidal nanoparticles combined with atomic layer deposition process have been utilized to recapitulate the optical function of the complex butterfly wing characteristics. Magnetic nanoparticles fixed in curable polymer matrices have been used to rapidly create arbitrary shapes and colors. These biomimetic approaches for color manipulation have demonstrated great promises to develop the sensing applications; however, a common limitation of such sensors is their general lack of chemical selectivity, which makes differentiation among similar compounds, due to the difficulty of tailoring their specific functions and performances. Here, we show high selective bio-inspired colorimetric sensors with tunable functions by self-assembly process and directed evolution of a basic building block, M13 phage. We fabricated multi-color matrices using phage through self-assembly processes. The resulting colorimetric phage matrices composed of quasi-ordered phage bundle structures which can exhibit distinct colors in coherent scattering. Colorimetric phage matrices swelled with different rates depending on the initial phage-bundle structures (different colored phage matrices), which can specifically respond to water and various organic solvents in a sensitive manner. Through directed evolution, we imparted trinitrotoluene (TNT) recognition receptors on the phage and induced the specific response of the colorimetric phage matrices to TNT. Using the commonly used handheld device (iPhone) and automated colorimetric image analysis, we could detect the target TNT molecules in 300 ppb scales in a selective manner. Our sensitive and

selective colorimetric phage-based sensors promise to establish a rapid, portable, simple but effective detection of various harmful chemical and biological toxins, an initiative step towards the protection of human health and national security.

Directional Migration of Melanoma Cells on Post Gradient Density Arrays

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Melanoma encounters severed extracellular matrix (ECM) by proteolysis and initiates metastasis. During this process, the inhomogeneous texture of in vivo ECM architecture is exposed and this affects cell migration. We investigate melanoma cell migration on this inhomogeneity with post gradient density array (GPDA). Malignant melanoma, 1205Lu migrates from denser to sparser post arrays preferentially to higher ECM contact by more wrapping posts on sparser than denser arrays. This directional migration is reversed by the inhibition of PI3K activity to control the protrusion of infiltration. Moreover, the biased translocations of PI3K toward sparser post array and, in turn, reduced intercellular tensions on sparser zone of GPDA are consistent with the directions of 1205Lu migration. Conversely, benign melanoma, Scbl2 that have less PI3K activity exhibits the reversed migration on high ECM density coated GPDA. Reduced PI3K activity induces the enhancement of intercellular tension by increased MLCK, which impede the vertical protrusion of pseudopods for cells to confine the top of posts. This allows cells to contact more area from denser post arrays, which cause translocation of PI3K toward denser arrays and, thus, increased intercellular tension on sparser ones. This reversed migration of Scbl2 on GPDA is re-reversed by the inhibition of MLCK. These data demonstrate PI3K determines distinctive directional migrations of melanoma cells on inhomogeneous ECM structure in metastasis.

Synthesis and Characterization of Gold Nanostars Functionalized to Target Cancer Cells

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Directly or indirectly, cancer affects the lives of most people, regardless of sex, social status or age. Each year millions of people die from this disease, in addition it causes pain and suffering, substantially affecting the quality of life of patients and their families, because of very long periods of hospitalization, recovery, and financial costs. Since first half of the twentieth century began to use different anti-cancer treatments that combine surgery with radiation and chemotherapy, achieving a tremendous progress in the fight against this disease. Anti-cancer agents can be as diverse as drugs, liposomes, natural products, therapeutic antibodies, cell growth inhibitors, angiogenesis inhibitors and apoptosis-inducing compounds. The introduction of new technologies has had a major impact on how cancer is treated and diagnosed. Specially with the identification of specific cancer biomarkers and the development of methods for early detection and monitoring, development of non-invasive diagnostic methods, alternative techniques to obtain and processing of biopsies, development of new contrast agents for imaging, revolutionary surgical procedures for removal of tumors and metastases, and the modification of compounds with anti-cancer activity to achieve tissue-specific delivery and reduce side effects. The recent advances in nanotechnology provide new alternatives to diagnose and treat cancer. It is possible to perform synthesis of inorganic materials with high precision and control at the nanoscale (1-100 nm), coupled with availability of functionalization/bioconjugation techniques to modify the surface of nanomaterials to achieve the development of smart devices based on functional nanoparticles for biomedical applications. Use of hybrid nanoparticles as nanomedicines requires a precise control of different properties like size, shape, morphology, charge, and physicochemical parameters to ensure biocompatibility and specificity for cancer cells. Obtaining smart nanodevices with advanced properties to be used for cancer therapy and diagnostics.

Photo-Activated Micro-RNA Osteogenic and Angiogenic Differentiation of Human ASC

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Heterotopic ossification (HO), the mineralization of soft tissue also known as osseous metaplasia, is often associated with diffusible therapies such as bone morphogenic protein (BMP) used in repair of bone defect. Maintenance of appropriate osteogenic concentrations with such short half-life diffusible factors at the site of

bone repair requires high doses, resulting in a gradient of the bioactive compound in the surrounding soft tissue that can result in ectopic bone formation. In cases where it is associated with joint or spinal tissue, the clinical complications of HO can be serious and costly for health care providers to correct. Attempts to mediate the delivery of diffusible factors through localized injection and controlled release substrates have met with only limited success as control and localization of the dose remain problematic. Several other studies have examined gene delivery, using viral vectors or infected/transfected stem cells as an alternative to improve localization of osteogenic factors. Direct viral vector delivery as a means of driving osteogenesis remains hampered by imprecise control over which cells are infected and levels of protein expression post infection. Injection of infected/transfected cells provides an effective means of localization but safety concerns related to levels of osteogenic protein expression and temporal control (i.e. when expression is turned on/off) limits enthusiasm for this technique.

Protein Immobilization On the Surface Using Sortase-Mediated Ligation

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The immobilization of proteins on surfaces is of great importance in molecular diagnostics and biosensors. An enzymatic approach has distinct advantages compared to chemical methods since such immobilization can be achieved covalently and site-specifically in mild conditions compatible with protein structure and function. Sortase A is a transpeptidase that can sequence-specifically bind proteins or peptides to each other or to a surface. Staphylococcus aureus sortase A recognizes a LPXTG sequence tag at the C-terminus of a protein and cleaves between threonine and glycine to yield an acyl-enzyme intermediate; this intermediate is resolved by nucleophilic attack from a gly_n (n>2) tag at the N-terminus of a second protein to link the two proteins through LPXT-$G_{n>2}$. By extension, a recombinant protein tagged with LPETG can be ligated in the desired orientation to a gly_n -functionalized surface. We have used sortase A to site-specifically bind recombinant eGFP (green fluorescent protein)-LPETG to a gold surface functionalized with triglycine using a cysteinyl linker. Fluorescence and atomic force microscopy show that protein immobilization is sortase A-mediated and tag-specific. We also patterned eGFP on glass functionalized with Gly_n using a Ni-NTA- PDMS stamp to capture his-tagged SrtA. Contact of the SrtA–loaded, patterned, stamp with the surface in the presence of eGFP-LPETG, produced patterned eGFP on the glass. As the next step toward creating well-defined “molecular print-boards,” we made layers of eGFP using a bifunctional eGFP with an LPETG sequence at the C-terminus and a GGG sequence immediately following a cleavable peptidic (genetically encoded) protecting group at the N-terminus. Sequential deprotection-ligation steps enabled cyclic deposition of monomeric units in a manner analogous to other solid-phase synthesis applications, such as peptide or oligonucleotide synthesis. Thus, layer-by-layer assembly of surface-attached, oriented molecular wires can be accomplished in a controlled manner.

Dispensable Lab On Chips - to Estimate the Biochemical State of Blood

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This paper presents a novel idea of interpreting micro fluidic MEMS sensor used in analyzing the amount of chemical mixtures present in the blood, precisely defined as lab on chips. The fatal amount of time required for a doctor diagnosing disease are majorly due to the late arrival of test results leading to a prolong discomfort and increase in severity of disease , by the time the doctors gets the right test and right diagnosis the disease exacerbate to the peak. Thus this novel concept is to establish a LOC which is capable of providing the test results of blood bio chemistry in the door steps without the need of posting a visit to the medical lab. The dispensable LOC is capable of analyzing the patient’s blood sample through the channelled assembly of micro fluidic channels, micro pump , bio sensors , bio readout transducer and wireless module which in turn communicates the results immediately to the medicos ,thus helping him in his pre- diagnosing process .

Tether: A Modular Synthesis Strategy for I norganic Nanomaterials Using Biomolecules

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Natural systems often utilize a single protein to perform multiple functions. Control over functional specificity is achieved through interactions with other proteins at well-defined epitope binding sites to form a variety of functional co-assembled structures. Inspired by the biological use of epitope recognition to perform diverse

yet specific functions, we present Template Engineering Through Epitope Recognition (TEThER), a strategy that takes advantage of noncovalent, molecular recognition between different components to achieve functional versatility from a single protein template.

Engineered TEThER peptides are designed to serve as molecular bridges between protein epitope binding sites and the surrounding environment in a localized, specific, and versatile manner. The peptides discussed in this work are bifunctional sequences that span the biologic-inorganic interface by noncovalently binding to specific recognition sites on the protein scaffold and serving as sites for localized bio-enabled nucleation and growth of inorganic nanomaterials.

Clathrin, a protein that plays a key role in the dynamic remodeling of the cell membrane during endocytosis, provides a framework that offers access to a variety of architectures outside of a cell, such as cages, barrels, tetrahedra, and cubes. This structural diversity makes clathrin an attractive candidate for use as a versatile protein scaffold. Formation of these architectures is achieved by modulating environmental conditions to induce self-assembly (pH, concentration, ionic strength). We have begun a systematic study of these environmental conditions to gain an understanding of the kinetic and thermodynamic principles of self-assembly and predictive, controllable structuring of clathrin.

We functionalized self-assembled clathrin protein cages at specific sites through co-assembly with designer TEThER peptides to achieve three diverse functions: the bio-enabled synthesis of gold, cobalt oxide, and anatase titanium dioxide nanoparticles in aqueous solvents at room temperature and ambient pressure. Compared with previous demonstrations of site-specific bio-enabled inorganic synthesis, the TEThER strategy relies solely on defined, noncovalent interactions without requiring any genetic or chemical modifications to the protein template. Therefore, this design strategy represents a mix-and-match, biomimetic approach to achieve versatile and site-specific functionalization that can be broadly applied to other protein templates to generate structures with a range of functionalities.

Nanoporous Gold for Neuroengineering Applications

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Nanostructured materials have made a significant impact on the development of advanced functional materials. Nanoporous gold (np-Au), produced by a nano-scale self-assembly process, is a relatively new material and has mostly attracted attention for sensor and catalyst applications due to its high effective surface area, electrical conductivity, and ease of surface functionalization. Surprisingly, the biomedical potential of this material has remained largely untapped. We report on our research efforts to control nano-/micro-scale properties of np-Au and the application of micropatterning techniques for fabricating high-sensitivity multiple electrode arrays for neural electrophysiology studies. In the context of biocompatibility of such devices, we will discuss how tunable properties of np-Au may be utilized to alleviate adverse biological response to sensor coatings. We will specifically focus on drug delivery from np-Au coatings for *in situ* modulation of neuronal cell behavior. We expect these results to benefit the development of multifunctional devices for neuroengineering applications.

Identification and Targeting of Prostate Cancer Cells Via Molecular Recognition Elements

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Among males in the United States, prostate cancer is the most-diagnosed cancer and is the second leading cause of cancer-related deaths. Current detection and therapeutic methods are not specific for the disease. The current standard in detection, prostate specific antigen (PSA) levels in the blood, was recently given a “D” grade by the U.S. Preventative Services Task Force. Therefore, it is no longer recommended for use. To address this problem, molecular recognition elements (MREs) that specifically bind to prostate cancer cells and not benign prostate cells have been selected. This was done through the Selective Evolution of Ligands by Exponential Enrichment (SELEX). Using this in vitro selection process, a library of 10^9 yeast-displayed antibody fragments were exposed to a prostate cancer cell line. Antibody fragments that bound to those cells were then amplified and incubated with benign prostate cells. Those antibody fragments that did not bind to these cells were amplified. Seven rounds of positive and negative selection were completed and a small number of antibody fragment MREs have been identified.

Nanostructures for Stem Cell Engineering

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Biomaterials incorporating inorganic components such as bone and dental replacements have proven to be mechanically stable and, in addition, exhibit unique physicochemical properties that can modulate biological pathways such as the blood clotting cascade and stem cell differentiations. Synthetic organic nanostructures such as liposome and micelles, on the other hand, have great utility as multifunctional theranostic, bioimaging, and delivery systems that can be mass-produced in a reproducible manner. Various dynamic cellular-level processes such as cell mobility and biosynthesis often work in concert with the immediate surroundings and associated biological pathways that are essentially hierarchical systems and the stem cell self-renewal and differentiation processes are no exception. Thus, it will be ideal to construct hierarchically structured nanomaterials that incorporate modular organic components for stem cell engineering. In an attempt to facilitate the hybrid materials' development, two different classes of synthetic materials that show different bioactivities towards human neural stem cells (hNSCs) will be discussed. Engineered peptide amphiphiles (PAs) that self-assemble into fibrous micellar (high-aspect ratio) structures show a spectrum of responses from hNSCs based on concentration and surface engineering properties while nanostructured inorganic particles and extended surfaces do not. Physicochemical and biological characterization of both platforms of biomaterials will be presented interfaced to hNSCs and their potential utility in biomedical applications will be further discussed.

Self Assembling Peptide Amphiphes As An Alternate Aproach to Immunotherapy

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Peptides are capable of stimulating an immune response but are generally weak immunogens on their own and require strong adjuvants to be effective, prohibiting their use in clinical applications. Peptide amphiphiles (PAs), which consist of a hydrophilic peptide conjugated to a hydrophobic lipid or fatty acid tail, self assemble into micelles that we propose have distinct advantages for a safe and effective antigen delivery system. PA micelles display a high density of peptide antigen and can be efficiently taken up by immune cells. Multiple functionalities can be incorporated into the micelles in a modular fashion by simple mixing of the different molecules, alleviating the need for complex chemistries to covalently link different components. Two different PA vaccines have been developed to evaluate the potential of PA micelles to serve as a platform for immunotherapy. PAs containing a cytotoxic T-cell (T_c-cell) epitope derived from the model tumor antigen ovalbumin stimulate a T_c-cell response, providing protection in mice against tumor growth. Other PAs incorporating an antigenic sequence found in Group A Streptococcus induce a potent antibody response in mice. The antibody response was further enhanced by using amphiphilic Toll-like receptor agonists to make mixed micelles. The design and physical characterization of the PA micelles will be discussed, along with details regarding their *in vivo* immunogenicity.

Engineer Bioactive Vascular Grafts to Recruit Endogenous Progenitor Cells for In Situ Regeneration of Blood Vessels

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Small-diameter synthetic vascular grafts have high failure rate due to thrombogenic responses. In addition, the lack of endothelialization in synthetic grafts results in low patency rate in the long-term. In the past decade, significant progress has been made to construct tissue-engineered blood vessels (TEBV) in vitro by using vascular cells with or without scaffolds. However, constructing cellular grafts involves extensive manipulation of cells in vitroand is time consuming, which limits the application to individualized and non-urgent therapies. Stromal cell–derived factor-1 (SDF-1) is a potent factor for endothelial progenitor cell (EPC) homing as well as neovascularization. In this study, we investigated the effects of immobilized SDF-1 on the recruitment of EPCs and smooth muscle progenitor cells (SMPCs) to vascular grafts. We propose an in situ tissue engineering approach that recruits two types of endogenous progenitor cells for the regeneration of blood vessels.

Photoresponsive Dispersion and Acutation of Graphene-Elastin Hybrid Materials

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In the field of bioengineering, graphene-derivatives (GDs) have emerged as promising nanomaterials for incopora-

tion into sensors, therapeutics, and biomaterials due to their mechanical strength, thermal/electrical conductivity, optical properties, and low cost. However, as a consequence of their poor colloidal stability and lack of inherent specificity towards specific targets, GDs generally require covalent or non-covalent modifications before they can function in biological systems. Here we describe the one-step non-covalent functionalization of GDs, i.e. graphene oxide (GO), and reduced graphene oxide (rGO) with a genetically engineered, protein-based polymer. Specifically, we utilzed elastin-like polypeptides (ELPs) due to their tunable thermoresponsiveness (reversible aggregation above a critical temperature), biocompatibility, and mechanical properties. ELPs genetically engineered to display a phage-display derived graphene-binding petpide motif were shown to bind to both GO and rGO and stabilize their dipersion in aqueous and organic solvents. The ELP-GD hybrids retained a stimuli-responsive behavior both in solution, and when incorporated into hydrogels resulting in reversible aggregation/dispersion and swelling/deswelling, respectively. Furthermore, these responses could be induced remotely by infrared light illumination as a result of the GDs› ability to convert IR to heat. In the case of hydrogels, local IR stimulation allowed for controlled actuation due to non-uniform deswelling. Finally, we demonstrated that further engineering of ELP-GDs with integrin-binding motifs allows for efficient cell adhesion onto GD surfaces. GD functionalization with genetically engineered ELPs provides a facile and tunable method for imparting multiple functions and stimuli-responsiveness. This strategy can be utilized in the future for theranostics, sensing, and tissue engineering, as well as be adapted for use with other nanoparticles.

Enhanced Islet Survival and Function On Extracellular Matrix Protein-Coated Scaffolds

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Islet transplantation offers the potential to improve glycemic control and reduce insulin dependence in patients with type 1 diabetes mellitus (T1DM), an autoimmune disease that affects over 1.5 million Americans. We have successfully employed biodegradable, microporous scaffolds fabricated from poly(lactide-co-glycolide) (PLG) for islet transplantation. These have been shown to provide a three-dimensional matrix that supports islet attachment following isolation, which resulted in improved islet function and viability. However, the process required to isolate islets severs critical vascular connections and disrupts interactions between the islet cells and their extracellular matrix (ECM). In a previous report, we demonstrated that adsorption of ECM proteins found in the native islet microenvironment to the scaffold surface resulted in enhanced islet function in vivo and significantly decreased the amount of time required to reverse hyperglycemia in a mouse model of T1DM. The current studies extend this work by examining the role of ECM proteins in enhancing islet survival and function, independent from other effects these proteins may mediate in the diabetic recipient, such as promoting host cell infiltration and islet revascularization.

Engineering Multi-Functional Antigen Carriers for the Treatment of Autoimmune Diseases and Allergies

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The current challenge in the treatment of autoimmune diseases is the development of therapies that induce antigen-specific immunological tolerance, which would in turn circumvent the present need for generalized immunosuppression that results in increased susceptibilities to potentially life-threatening infections and the development of neoplasia.

We had previously shown that antigen (Ag) coupled to apoptotic splenocytes was capable of inducing Ag-specific immunological tolerance that ultimately resulted in the prevention and treatment of both relapsing-remitting experimental autoimmune encephalomyelitis (R-EAE) and allergic airway inflammation (AAI). This approach is the focus of a Phase I/IIa clinical trial examining the effects of immunological tolerance using multiple myelin peptides coupled to autologous peripheral blood leuko-

cytes in early relapsing-remitting multiple sclerosis (MS) patients.

Iron Oxide Nanotubes for Magnetically Guided Delivery and pH Activated Release of Insoluble Anticancer Drugs

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Magnetic delivery system has gained significant attention in anticancer therapy. Traditionally, magnetic nanoparticles are encapsulated into other polymer particles, acting as functional material for target delivery. However, these complexes are still associated with poor drug loading efficiency, especially for insoluble anticancer drugs, which are the major component of new chemical entities generated for anticancer use.

Herein, we attempt to develop an iron oxide nanoparticle-based multifunctional system. To screen for appropriate ship, we perform PEG coating and compare the feasibility of spherical and rod-like iron oxide nanoparticles in a view of carcinoma cellular uptake; rod-like nanoparticles attracted our interest since they could be quickly and massively internalized. For insoluble anticancer drug paclitaxel (PTX) loading, we next transform the nanorods into a tube structure by a hydrothermal method. The results show that drug crystals can be successfully loaded in the inner voids of these nanotubes (PMNTs) by controlling the crystallization process of PTX. The acquired nanocomplexes not only escape phagocytosis of macrophage cells by a PEG stealth effect, but also exhibit an increased cellular uptake with magnetic field exposure. In addition, this iron oxide-based drug carrier possesses a low pH-activated release profile, which would accelerate drug release in the carcinoma cells and minimize non-specific drug release. Owing to these advantages, PMNTs promote the anticancer efficacy of PTX and clearly exhibit promising potential for using as high-efficiency insoluble drug delivery system in clinical applications.

Strong Surface-Enhanced Raman Scattering Signals From Nanoconjugate Comprised of Popcorn-Shaped Gold Nanoparticles and Semiconductor Quantum Dots and the Application In Protein Detection

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Strong surface-enhanced Raman scattering (SERS) signals of 4-mercaptobenzoic acid (4-MBA) are detected from nanoconjugates comprised of popcorn-shaped gold nanoparticles (PS-AuNP) and CdSe\ZnS core\shell quantum dots (QDs). The presence of QD, which is bond to PS-AuNP via an amide bond, is important for the large enhancement factor of the Raman signals. According to finite-difference time-domain (FDTD) simulation, the electromagnetic field enhancement factor near the surface of PS-AuNP can be as high as 400, which means the theoretical Raman signal enhancement due to the electromagnetism enhancement could be 10^{10}, Electrodynamics calculation confirms that the presence of the QD near a spherical gold particle can generate much higher electromagnetic field enhancement compared with the situation when just spherical gold particle alone in an electromagnetic field. Protein conjugation detection was also applied based on biotin-avidin interaction using the PS-AuNP-QD nanoconjugates. The SERS spectrum illustrated rich molecular vibration information of the conjugated avidin. The new PS-AuNP-QD nanoconjugate can be employed as a single particle SERS platform, which has potential application in biomolecular detection.

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