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Meeting Abstracts

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Plenary Symposia

An Approach to Cancer from Nanoscale to Patient

Opportunities for Nanosystems to Minimize Regimen-Related Toxicities in the Treatment of Cancer

Stephen T. Sonis[1,2]

[1]*Brigham and Women's Hospital and the Dana-Farber Cancer Institute, USA*
[2]*Biomodels, LLC, USA*

Abstract

Regimen-related toxicities are common, often painful, disruptive and dose-limiting complications of many forms of chemo- and radiation therapy used for the treatment of cancer. In addition to their symptomatic and physiologic consequences, cancer treatment toxicities significantly increase the use of health resources and the overall cost of care. Despite their frequency and impact on outcome, the overall prevention and management of such side effects is inadequate. The biological basis for toxicities generally is driven by two major factors: indiscriminant clonogenic cell death of dividing normal cells and the activation of a cascade of biological pathways–both culminate in damage, apoptosis and death of the stem cells responsible for the replenishment of normal tissue. The application of nanotechnology to the management of malignancies provides at least three opportunities to minimize toxicities, prevent or treat them and assess their course and severity. Coupling nano-delivery systems to chemotherapy or radiosensitizers could provide an opportunity for more tumor-directed treatment, while simultaneously reducing the risk of collateral damage to non-tumor tissue. Likewise, innovative nano-radiation delivery systems applied to or around tumors might minimize the need for broader radiation fields to achieve comparable levels of tumor kill. Since chemo- or radiation therapy damages epithelial tight junctions, tissue permeability increases providing an opportunity for nano-formulated agents to enhance trans-epithelial drug delivery. Such formulations would result in high local concentrations, but minimize the probability of significant systemic levels. Finally, the application of microfluidic analytics provides a platform for the implementation of biomarkers as practical means to assess the trajectory of many toxicities.

Voices and Vision from Stem Cells: Mutant Vibrations for Regenerative Medicine

Carlo Ventura

Stem Wave Institute for Tissue Healing (SWITH), Gruppo Villa Maria (GVM) Care & Research - Ettore Sansavini Health Science Foundation, Italy

Abstract

For decades Scientists have used Chemistry to affect cell behavior. It is now evident that cells produce and sense electromagnetic fields and nanomechanical vibrations, affording major changes in their dynamics. Here, we investigated whether exposure to these physical energies may affect stem cell fate and senescence patterning. We found that asymmetrically conveyed radio electric fields (ACREF) were able to transform mouse embryonic stem cells and human adipose-derived stem cells (hADSCs) into cardiac myocytes, neurons, skeletal muscle, and endothelial cells. Moreover, ACREF acted as a sort of "time machine", reprogramming human adult non-stem somatic cells, like skin fibroblasts, into cell types in which these cells would never otherwise appear, including myocardial, neural, and skeletal muscle cells. Intriguingly, hADSC exposure to ACREF reversed stem cell senescence *in vitro*, acting at the level of both telomerase-dependent and -independent pathways.

Consonant with these observations is our discovery that cells can produce acoustic vibrations, and express "vibrational" signatures of their health/differentiating potential. hADSCs exposure to acoustic vibrations derived from the human heartbeat was found to resume the expression of pluripotency genes, including Nanog, SOX-2 and Oct-4. This effect was associated with an increase in the transcription of cardiogenic and vasculogenic genes, ultimately leading to the commitment to myocardial and endothelial lineages. The present data demonstrate that stem cell fate can be remarkably modulated by physical energies. This discovery prompts a deeper understanding of the interconnections between the physical universe and the living world in the attempt to further approach the information of Life.

A Novel Nanoparticle Approach for Translation of Tolerogenic and Anti-Inflammatory Therapies for Auto (Immune) Diseases

Stephen D. Miller

Northwestern University Medical School, USA

Abstract

Ag-specific tolerance is the desired therapy for immune-mediated diseases. Our recent Phase I trial demonstrated that infusion of myelin peptide-coupled autologous apoptotic PBMCs induces dose-dependent regulation of myelin-specific T cell responses in MS patients. Antigen-coupled apoptotic leukocytes accumulate in the splenic marginal zone (MZ) and are engulfed by F4/80+ MZ macrophages and CD8+ DCs inducing upregulation of PD-L1 in an IL-10-dependent manner. Tolerance results from the combined effects of PD-L1/PD-1-dependent T cell anergy and activation of Tregs recapitulating how tolerance is normally maintained in the hematopoietic compartment in response to uptake of senescing blood cells.

To speed clinical translation of tolerogenic therapies, we showed that long-lasting tolerance is inducible by i.v. administration of (auto)antigens covalently linked to or encapsulated within 500 nm carboxylated poly(lactide-co-glycolide) (PLG) nanoparticles (Ag-NP) abrogating development of Th1/Th17-mediated autoimmune disease (EAE, T1D and celiac disease) and Th2-mediated allergic airway disease when used prophylactically or therapeutically. Ag-NP tolerance is mediated by the combined effects of cell-intrinsic anergy and Treg activation and is dependent on route of administration, particle size and charge, and uptake by MZ macrophages via the MARCO scavenger receptor. Additionally, we have shown that i.v. infusion of 'naked' carboxylated PLG NP targets inflammatory monocytes/macrophages in a MARCO-dependent fashion leading to their sequestration in the spleen and eventual apoptosis and is a potent therapy for ameliorating acute inflammatory diseases, including myocardial infarction, peritonitis, and virus encephalitis. Ag-NP are a novel, safe and cost-effective means for inducing antigen-specific tolerance for therapy of (auto)immune-mediated diseases using an FDA-approved, GMP-manufacturable biomaterial.

Cell-Free Synthetic Biology for Medicine

Shaorong (Ron) Chong[1,*], Haruichi Asahara[1], Huidan Zhang[2], John Heyman[2] and Dave Weitz[2]

[1]*New England Biolabs, USA*
[2]*School of Applied Physics and Engineering, Harvard University, USA*

Abstract

The biological information of normal and diseased cells is largely recorded as DNA sequences. The next generation sequencing technologies have dramatically revealed genetic mutations that may hold the keys to curing a variety of human diseases. However, the overwhelming amount of such genetic information has completely outpaced the biologists ability to understand them with conventional experimental approaches. We are developing synthetic cell-free biological systems to allow high-throughput investigation of gene functions and screening of novel gene functions and small-molecule modulators. Using our systems, we can rapidly translate gene sequences into peptides or proteins and test their functions in microliter microplate wells and picoliter microfluidic drops or nanowells. This game-changing platform can potentially accelerate our understanding of genome functions and lead to discovery of novel therapeutics.

Doxil®— The First FDA-Approved Nano-Drug: Lessons Learned

Yechezkel (Chezy) Barenholz

The Hebrew University-Hadassah Medical School, Israel

Abstract

Doxil®, the first FDA-approved nano-drug (1995), is based on four unrelated principles: (i) prolonged drug circulation time and avoidance of the RES due to the use of PEGylated nano-liposomes; (ii) nano-size which enable to benefit from the enhanced permeability and retention (EPR) effect which enable passive targeting of Doxil to tumors; (iii) high and stable remote

loading of doxorubicin driven by a transmembrane ammonium sulfate gradient, which also benefit from the nano-volume of the liposomes. This remote loading method also allows for drug release at the tumor; which is induced by the relatively large concentration of ammonia produced by the unique tumor cells glutaminolysis; (iv) having the liposome lipid bilayer in a "liquid ordered" phase composed of the high-Tm (53 ºC) phosphatidylcholine, and cholesterol. Due to the EPR effect, Doxil is "passively targeted" to tumors and its doxorubicin is released and becomes available to tumor cells by as yet unknown means. This presentation summarizes historical and scientific perspectives of Doxil development and lessons learned from its development, and 25 years of its use and new findings that describes high resolution structure of Doxil, its unique thermotropic behavior and the role of doxorubicin intra-liposome nano-rod crystal in Doxil performance. The success story of Doxil demonstrates the obligatory need for applying and understanding of the cross talk between physicochemical, nano-technological, and biological principles. It also paved the road for the development of other liposomes based nano drug including an improved (over Doxil) pegylated liposomal doxorubicin (PLD) formulation.

Organic Photovoltaics: the Ultimate Green Energy Solution or a Distant Dream

Bernard Kippelen

Center for Organic Photonics and Electronics, School of Electrical and Computer Engineering, Georgia Institute of Technology, USA

Abstract

Organic photovoltaic devices have reached power conversion efficiencies above 10% in small area laboratory cells. However, manufacturing such devices on a large scale and at low cost remains a challenge due to the complexity of the device architecture. In this talk, we will discuss the results of recent studies aimed at developing new strategies for collecting the photogenerated holes and electrons efficiently in devices with a simplified architecture and increased stability. We will also focus on the modeling of organic solar cells using engineering-inspired equivalent-circuit models and discuss how parasitic resistance effects influence the shape of their current-voltage characteristics. In particular, we will show that when these effects are properly mitigated, organic solar cells can be modeled with a simple Shockley diode equation and they can exhibit low dark current densities in reverse bias that can yield high performance photodetectors. We will show that the electrical properties measured in the dark are controlled by the strength of the charge-transfer complex or the donor-like and acceptor-like materials in the bulk heterojunction. If organic photovoltaics are to become the ultimate low-cost energy solution, a full lifecycle assessment must be conducted and strategies must be developed to minimize their overall environmental footprint. As a small step in the right direction we will discuss organic solar cells fabricated on nanocellulose substrates that can be easily recycled.

Protein Structure at Atomic Scale by Synchrotron, CRYOEM and XFEL

Deterministic Delivery of Ultrasmall Volumes of Biological Materials

Christian Riekel

The European Synchrotron, France

Abstract

Technical progress in the field of X-ray micro- and nanobeam scattering on biological samples is dominated by the development of more and more brilliant X-ray sources based on undulator insertion devices allowing recording structural data from increasingly smaller samples in a shorter time. The recent introduction of X-ray free electron laser (XFEL) sources with femtosecond X-ray flashes has been a driving factor in the projected upgrade of existing 3rd generation synchrotron radiation (SR) sources -such as The European Synchrotron (ESRF)- into 4th generation, emittance-limited SR-sources. The impact of XFELs can also be seen in experimental approaches emerging at SR sources. Indeed, serial protein microcrystallography involving thousands of crystallites -developed at the LCLS XFEL source- is also starting to get used at SR-sources. Reduction of sample volumes of biological materials in X-ray scattering experiments is, however, a general challenge and requires new approaches in sample environments. Indeed, manipulating and positioning of individual biological objects at predetermined positions allows a considerable reduction of sample consumption when using raster-scan diffraction. I will discuss several methods for reducing sample volumes by deterministically delivering single particles or droplets into micro- or nanobeams using nanotechnology approaches. Replacing continuous flow microfluidics by droplet-based "digital" microfluidics allows also reducing sample consumption and time-scales for kinetic experiments. I will discuss possible applications of these approaches at XFEL and SR sources.

LB Nanotemplate as Optimal Nanotechnology for SR, EM and XFEL

Eugenia Pechkova[1,2]

[1]*Laboratories of Biophysics and Nanotechnology, Department of Experimental Medicine, University of Genova, Italy*
[2]*Fondazione ELBA-Nicolini, Italy*

Abstract

The methods of 3D protein structure resolution had significant progress in the recent years. However, many protein structures of high industrial, pharmaceutical and fundamental life science interest are still unsolved. Protein X-ray crystallography still remain the most powerful method to obtain the protein 3D atomic structures in foreseeable future. With the new generation of synchrotrons and microfocus beamlines the great progress can be achieved – microcrystals before unusable for 3D structure determination can be utilized. However, the production of the protein crystal as well as its quality (order, intensity of diffraction, radiation stability) remains the major problem. The determination of protein crystal structures is hampered by the need for macroscopic crystals. X-ray free-electron lasers (XFELs) provide extremely intense pulses of femtosecond duration, which allow data collection from nanometer to micrometer-sized crystals. Serial femtosecond crystallography will become an important tool for the structure determination of proteins that are difficult to crystallize, such as membrane proteins, if the problems such as low hit rate and high quantity protein nanocrystals needed will be solved. Cryo-Electron Microscopy (Cryo-EM) is a structural molecular and cellular biology technique that has experienced major advances in recent years. Technological developments in image recording by direct detectors as well as in processing software make possible to obtain 3D reconstructions of macromolecular assemblies at near-atomic resolution that were formerly obtained only by X-ray crystallography or NMR spectroscopy.

A common problem to all these advanced techniques is both radiation damage and difficult sample preparation. Langmuir-Blodgett (LB) protein nanotechnology is a novel approach for highly ordered and radiation stable protein sample preparation for all above methods of analysis. The numerous nanocrystallographic studies confirm exceptional radiation stability and quality of the crystals grown by homologous protein LB nanotemplate, including those failed to be obtain by classical methods. Moreover, highly ordered LB protein multilayer can bypass the bottleneck of protein crystallization. Thereby the property of the LB nanocrystals and LB multilayers can be used in all three frontier methods of analysis aiming to optimal protein 3D atomic structure resolution by Monte Carlo integration of high-quality diffraction intensities from which experimental phases could be determined, resulting in an experimental electron density map good enough for automated building of the novel protein structures, including those membrane, and the structures of protein complexes. Monte Carlo and Molecular Dynamics simulations can be also used to evaluate the obtained structures, including radiation damage effect.

Do Protein Crystal Structures Always Reveal Function? the Case of *Helicobacter pylori*

Giuseppe Zanotti

Department of Biomedical Sciences, University of Padua, Italy

Abstract

The bacterium *Helicobacter pylori* colonizes the stomach of more than half of the world's population, with the highest rates in developing countries, making it one of the most successful bacterial pathogens. Although the infection is mostly asymptomatic, *H. pylori* is responsible of severe gastroduodenal pathologies, including gastritis, ulcer and eventually gastric adenocarcinoma and MALT lymphoma. *H. pylori* has become an important target for research in the last thirty years, both from the medical and from the biological point of view. Despite the identification of the bacterium dating back to 1984, its pathogenesis remains poorly understood at the molecular level. Indeed, it is estimated that the function of approximately 40%-50% among the about 1550 genes encoded within its genome is only hypothetical or completely unknown. In our laboratory we are working on the structural characterization of proteins of the bacterium relevant for pathogenesis or host colonization. In this communication we will focus on some secreted proteins, whose function was unknown or undefined, and we will show how the crystal structure, combined with other experimental evidences, can provide clues about the physiological function of the protein.

Chimeric Proteins: Selective Evolution to Increase Pharmaceutical Potency

Howard Seeherman

Bioventus Surgical, USA

Nanomaterials, Nano Devices and Systems

Introductory Lecture

Anilkumar P. Thakoor
Jet Propulsion Laboratory, NASA, USA

Access to Space: Trends and Opportunities Deriving from Lower Cost Launch Systems

Davide Nicolini
European Space Agency, France

Abstract

The presentation outlines how the US Commercial Space Launch Act has changed the global landscape of access to space and paved the way for new opportunities in the economic development in space or of space related applications. Starts with brief history of commercial space transportation from the early days of government backed systems up to today's constantly evolving commercial market.

Printing of Carbon Nanotube-based Sensor Platform for Physiological Monitoring and Pathogen Detection

Ahmed Busnaina, Hobin Jeong, Ju-Kyung Lee, Cihan Yilmaz, Nimet Yildirim and April Gu
NSF Nanoscale Science and Engineering Center for High-rate Nanomanufacturing (CHN), Northeastern University, USA

Abstract

We have developed a novel, flexible s-SWCNT conductance based sensor platform for instantaneous measurement of pathogens in the environment and for monitoring physiological parameters of human body for applications in the wearable electronic skin and environmental monitoring. These two terminal sensor comprises of highly sensitive and selectively functionalized s-SWCNTs serving as the channel with an active area of < 10 μm^2. s-SWCNTs channels were fabricated using a novel offset printing process while the electrodes were made using conventional lithography process. The selective functionalization is conducted employing an in-house developed enzyme-immobilization technique. The choice of functionalization molecule is determined by the chemo- bio analyte that is to be detected. We show that D-glucose, L-lactate, Urea, Oxytetracycline (OTC), *E. coli*, and Adenovirus were detected with very high sensitivity, selectivity, stability and repeatability. This developed biosensor platform detects D-glucose, L-lactate, Urea, Oxytetracycline (OTC), *E. coli*, and Adenovirus over a wide range (0~300 µM, 0~100 mM, 0~100 mg/dL, 0-150 µg/L, 0-107 cfu/ml, and 0-107 pfu/ml respectively) in less than 5 seconds making them suitable for various applications.

Nanomanufacturing of Flexible Polymer Structures for Applications in Bio-devices, Sensors and Coatings

Joey Mead and Carol Barry
University of Massachusetts, USA

Abstract

Polymeric materials are attractive for many nano and micro-structured products because of their fabrication ease, cost effectiveness, and wide property range. Thus, we anticipate polymers based products to play a large role in advanced manufacturing for lightweight structures. This work presents novel manufacturing approaches for the incorporation of nano/microscale functionality that are environmentally friendly (melt-based) and industrially relevant. Nano or micro-structured surfaces with patterns of different polymers or nanoparticles can be made with directed assembly and transfer to a polymer substrate in a continuous or roll to roll printing approach. The integration of the printing in a continuous roll to roll process provides a method to prepare unique structures for flexible electronic devices, metamaterials, structural nanocomposites, icephobic surfaces or biocompatible materials. The work will present printing of conducting nanoelements, the fabrication of metamaterials for near-IR and microwave, and preparation of icephobic surfaces. This process can be coupled with nanoscale embossing using a two-stage roll to roll line. Substrate materials can include designer nanocomposites (thermoplastic polymers with nanoclays,

CNTs, silver nanoparticles, etc.) fabricated by continuous, melt based twin-screw extrusion, then used as substrates in a roll to roll process. Multi-layer films for optical structures and elastomer materials for improved traction and barrier properties can also be fabricated by high rate polymer processing. Issues for end of life, such as recycling and exposure monitoring of thermoplastic nanocomposites will also be discussed.

Nanoelectronic Sensor Arrays for Chemical Sensing

Sameer Sonkusale

Electrical and Computer Engineering, Tufts University, USA

Abstract

This talk will feature recent research activities on making chemical sensors based on heterogeneous integration of diverse nanomaterials on a single chip. The approach utilizes bottom up fabricated CMOS chips as functional substrates for assembly of different nanomaterials in a high throughput manner. Our recent results on making an electronic.

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