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ABSTRACTS

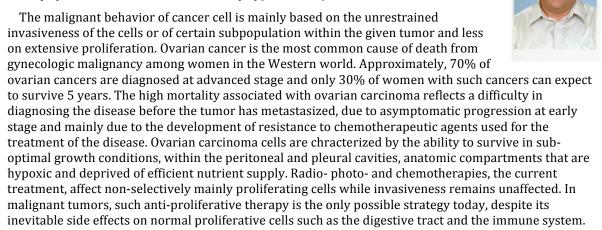
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Approaches to Eradicate Ovarian Carcinoma

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Our laboratory in involved in illuminating the process involved in the progression of this devastating disease and in the development of novel potential therapeutically approaches towards essential target molecules dominating this disease. Our efforts are directed *to identify essential molecular targets* along tumor progression and to develop novel anti-metastatic drugs.

Tumor cell invasiveness and subsequent angiogenesis and secondary tumor growth have been shown to be dependent on enzymes called matrix metalloproteinases (MMPs). Inhibiting MMPs would hold at stall the disseminating tumor cells without considerable toxic side effects and thus turning acute metastatic disease to a chronic surgically treatable condition. *The inhibition of MMPs is, therefore, an important therapeutic target*, which has stimulated considerable activity in pharmaceutical research laboratories. Yet, due to toxic side effects, no compound has reached marketing so far, except for a tetracycline analog for "external use" as a mouthwash in sub-antimicrobial concentration to treat periodontal disease.

We have recently developed potent in vivo active *MMP inhibitors based on the carbamoylphosphonate (CPO) group*. Our unique inhibitors overcome the obstacles that caused the failures of the previously synthesized molecules and offer new hope for developing this promising area. Our results showed *that specific CPO inhibitors are active in vivo in a murine melanoma model, without showing any toxicity even at doses ten times higher than those required for the biological activity.*

The objectives of our overall program involving MMPs are as follows: (1) To further optimize CPO based MMP inhibitors by synthesizing more potent and longer acting compounds. (2) To evaluate the newly synthesized compounds in vitro, in order to determine their potency, selectivity and specificity. (3) To examine the best of the newly synthesized inhibitors in vivo in order to determine their efficacy and toxicity, first in animals and eventually in patients.

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Novel Platinum Based Anticancer Agents

Dan Gibson

The Laboratory of Platinum Anticancer Agents, School of Pharmacy, The Institute for Drug Research, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel



Cisplatin is an important, widely used, anticancer drug that was able to completely cure Lance Armstrong from a severe case of testicular cancer and allowed him to win the Tour de France 7 times. Yet, this drug suffers from acquired resistance which means that if tumors that were treated with cisplatin reappear, they are no longer eradicated by cisplatin. Therefore it is important to have other Platinum anticancer drugs that work in a mechanism that is significantly different than cisplatin.

We have been developing novel classes of platinum anticancer agents that are able to overcome cisplatin resistance and act by a completely different mechanism of action These new compounds (patented by us) have less undesirable side effects in mice than cisplatin and are effective in extending the life span of tumor bearing mice. We are trying to improve upon the delivery and biological properties of these compounds in the hope that they will turn out to be promising anticancer agents.

Platinum anticancer agents are believed to work by entering the cell, binding to the nuclear DNA, distorting it and triggering cellular processes that lead to cell death. Only a small fraction of the cellular platinum ends up on the DNA. Most of the platinum reacts with other cellular components causing undesirable side effects. We have developed new methods for studying the cellular interactions of platinum anticancer agents and are currently trying to identify the major cellular targets of platinum drugs by using two dimensional NMR spectroscopy and mass spectrometry.

We are also engaged in understanding the cellular transformation of Pt(IV) prodrugs that are currently under intensive investigation as new generation platinum anticancer agents.

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Integrating Biochemistry and Biomechanics to Understand Endothelial Cell - Basement Membrane Interaction

Alisa Morss-Clyne

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Endothelial cell injury is considered the initiating event in cardiovascular

disease, a leading cause of mortality worldwide. In a healthy blood vessel, endothelial cells regulate vascular function in a complex three-dimensional environment. Cells dynamically integrate biochemical and mechanical stimulation from the flowing blood at their apical surface and the basement membrane at their basolateral surface. Disruptions in the biochemical environment, such as elevated glucose, and disturbances in the mechanical environment, such as low shear stress, contribute to endothelial cell dysfunction and subsequent cardiovascular disease. People with diabetes develop accelerated atherosclerosis at low shear stress locations, suggesting that biochemistry and biomechanics may interact through common signaling pathways.

Our laboratory investigates integrated biochemical and biomechanical interactions within the endothelial cell – basement membrane co-regulatory unit. We develop quantitative relationships describing how growth factors are regulated in mechanical conditions, how basement membrane properties are altered by shear stress and high glucose, and how these basement membrane changes affect the endothelial cell mechanical response.

This new knowledge is then used to develop targeted pharmaceutical therapies that decrease cardiovascular morbidity and mortality.

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Nanoparticles for Immunomodulation: Development and Clinical Studies

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Therapeutic efficacy and reduced side effects all markedly improved by encapsulation of drugs in nano-particulated dosage forms. The rapid elimination from the blood by the mononuclear phagocytic systems (MPS), a major drawback of particulated delivery systems, was utilized as a pharmacological means for the immunomodulation and therapy of certain inflammatory disorders.

We hypothesized that monocytes play a key role in the inflammation cascade of restenosis and endometriosis. Intimal hyperplasia is a universal response of the arterial wall to mechanical injury and is the major cause of restenosis following angioplasty and stent deployment. Macrophage recruitment is associated with endometriosis; characterized by the deposition of endometrial cells in areas outside the uterine cavity. We validated the hypothesis that systemic and transient depletion of monocytes inhibits the inflammatory cascade. Monocytes/macrophage depletion was achieved with a systemic injection of nanoparticulated dosage forms (PLGA-based NP and liposomes) containing bisphosphonates (BP) formulated for effective phagocytosis. Following phagocytosis the vesicles discharge their encapsulated drug like a Trojan Horses, inactivating the cell without any effect on non-phagocytic cells.

We investigated the effect of different BP, NP type (polymeric or liposomal), and size on the formulation properties and biodistribution. Bioactivity and mechanism were examined in tissue cultures, and in animal models of restenosis and endometriosis. Partial and transient depletion of blood monocytes following NP systemic injection correlated with the therapeutic effect. **Phase I clinical studies confirmed the safety and potential efficacy of the nanoparticulate delivery system leading to ongoing Phase II clinical studies in stented patients**.

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Harnessing the Action of Natural and Synthetic Bioactive Agents through Controlled/Targeted Delivery

Margaret Wheatley

School of Biomedical Engineering, Science & Health Systems (BIOMED), Drexel University, Philadelphia, USA



Systemic delivery of chemotherapeutics is fraught with problems of adverse side effects due to the need to administer high doses in order for a therapeutic dose to reach the intended site. This exposes healthy tissue to the effects of highly toxic drugs. Controlled and targeted drug delivery has become an aggressively pursued alternative. To target solid tumors, researchers are investigating various approaches, including active targeting by drug microencapsulation followed by attachment of specific targeting ligands, and passive targeting taking advantage of the aberrant vascular physiology present in tumors which allows nanoparticles to exit the blood stream through enlarged pores. The nanoparticles reside in the tumor interstitium due to the lack of a lymph system to drain the area (EPR effect).

In our lab we take advantage of both these mechanisms. Targeting is by virtue of the fact that we encapsulate the drug in an echogenic particle. Ultrasound is used to image the tumor, and locate the drug-loaded particles. The particles are designed to be resonant at the imaging frequency, and this resonance causes the particles to shatter into nano-sized fragments. These fragments are propelled by ultrasound radiation forces through the vasculature to lodge in the tumor interstitium where they degrade by a controlled hydrolysis and deliver drug in situ.

This session will investigate shared goals and potential collaboration in the area of controlled/targeted drug delivery; we will discuss *cancer therapy* (my area) and open up the discussion to all areas impacted by *controlled release technology including delivery of factors such as growth factors in regenerative medicine, facilitating spinal cord repair, lineage direction of stem cells and more.*

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Pain: Mechanisms, Biomarkers and Therapeutics

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Philadelphia, PA, USA

This presentation will provide an overview of research efforts within the Department as well as with collaborators that focus on the experimental approaches to pain mechanisms as well as therapeutics. We are focused on neuropathic, inflammatory and cancer pain with a view towards identifying target-based mechanisms, determining mechanisms of CNS plasticity involved in central and chronic pain after CNS or peripheral

determining mechanisms of CNS plasticity involved in central and chronic pain after CNS or peripheral nerve injury, and in developing microRNA biomarkers to 'fingerprint' various types of pain as potential diagnostics as well as to identify regulatory mechanisms. In addition, our efforts in the pain area also include the use of optogenetics to control pain and to validate certain targets and pharmacological approaches. Finally, we are incorporating epigenetic analyses into these research programs as a way of gaining further insight into pain and therapeutic interventions.

These efforts integrate molecular, pharmacological, neuroanatomical and behavioral disciplines with a goal of identifying new targets and developing novel therapeutics.

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Delivery Systems for Improved Diagnostic and Therapeutic Applications

Simon Benita

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Aspiration is a major cause of lung disease in infants and young children. As the



symptoms and signs of aspiration are not specific, the diagnosis is delayed due to a low index of suspicion and low sensitivity and specificity of the available diagnostic tests. In our studies we evaluated the utility of microspheres composed of the degradable polymer, polylactic glycolic acid (PLGA), which acts as a marker to diagnose aspiration in hamsters. PLGA microspheres were easily identified under light microscopy inside the alveolar macrophages obtained from whole-lung lavage in all PLGA-instilled animals. The number and size of PLGA microspheres within the alveolar macrophages decreased gradually with time with a 90% rate of disappearance by day 36. From these results we deduced that PLGA microspheres have the potential to be considered sensitive and specific markers for aspiration in hamsters. The benefits of this test should be further evaluated and it is our intention to develop a simpler and more quantitative technique which can be easily performed by hospital laboratories and will diagnose aspiration in humans.

There has been considerable interest in developing biodegradable and biocompatible nanoparticles (NPs) conjugated to monoclonal antibodies (INPs) which would be used for targeted therapy. Such systems would significantly improve the therapeutic index of chemotherapeutic drugs while greatly reducing their side effects. We have designed NP delivery systems with the potential to improve the chemotherapeutic drug performance in oncology using systemic (iv) or local (pulmonary) administration. We examined the safety of pulmonary-delivered blank NPs and more recently of INPs in healthy mice. We are further evaluating the activity of pegylated poly(lactic acid) NPs loaded with paclitaxel-palmitate (pcpl) conjugated to an antibody that recognizes the epithelial cell adhesion (EpCAM) molecule in a transgenic mouse model of lung cancer (NSCLC) following pulmonary delivery. In another iv study, trastuzumab was conjugated to pegylated polylactic NPs containing pcpl. Cell culture binding/uptake, and pharmacokinetic experiments showed that these INPs enhanced drug internalization into the desired cells. This was confirmed in a pharmacological model of metastatic prostate cancer in SCID/Bg mice where pcpl-loaded INPs inhibited the tumor growth much more than the pcpl NPs and solution. With further development, *these INPs may lead to a promising potential modality for an efficient targeted treatment of various malignancies.*

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Controlled Delivery and Optical Methods of Assessing Treatment Effectiveness

Elisabeth S. Papazoglou

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The objective of our work is to identify optimal drug delivery vehicles to solve specific problems of drug actives and to develop non-invasive optical methods of assessing their efficacy. Our research focuses on skin damage and healing where we are developing optimal nanosomes encapsulating in the same particle



hydrophobic and hydrophilic vitamins to enhance synergy of their effects. Similar approaches are being investigated for delivery of nitric oxide to wounds. Effectiveness of the delivery vehicle is evaluated by both non-invasive optics and histology/biochemical assays.

The concept that size and particle viscoelastic properties affect the interactions with tissue is being further explored by using ultrasound to deliver the nanosomes. The concept that size affects interaction dynamics of drugs / receptors and can have beneficial effects is being explored in our research where gold-nanoparticle-peptide conjugates are synthesized to study the dynamics of HIV inhibition peptides.

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Characterization of the Intestinal Drug Absorption Mechanism for Optimizing the Oral Delivery System

Amnon Hoffman

MOTEC

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The oral route is the most preferred mode of drug administration due to its convenience and patient compliance. For many drugs there is a need for a special delivery system to overcome the limited bioavailability following oral administration. In specific cases certain modifications have to be made in the chemistry of the active compound.

In our lab we are developing gastro-retentive dosage forms, based on polymeric blends, that retain in the stomach and release the drug in a controlled manner into the upper part of the intestine. This is done both for extended absorption of drugs characterized by narrow absorption window, and for prolonged activation of luminal receptors within the intestine.

For lipophilic drugs we are developing nanoemulsion formulations that improve both the solubilization as well as presystemic metabolism in the intestinal wall, leading to improved oral bioavailability of problematic and highly variable drugs.

Since peptides are involved in many pathologic conditions, there is a great potential to utilize active peptides as therapeutic agents. However, peptides are degraded rapidly by peptidases in the blood and in the intestinal tract. Using a unique cyclization, named backbone cyclization, we convert active peptide to become metabolically stable. In this approach, by using restricted library of confirmationally diverse analogs, we search for the most active/selective compound that also has the best intestinal permeability properties, thus yielding novel orally available drugs.

We are currently utilizing this approach for the treatment of obesity, diabetes, chronic pain, psychiatric disorders, atherosclerosis and AIDS.

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Treatment of Solid Malignant Tumors with Microwave Balloon Ablation Catheters and Localized Chemotherapy

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Despite important advances in the treatment of cancer with surgery, radiation therapy, and chemotherapy, and despite the introduction of newer anticancer therapies such as, for example, hyperthermia and monoclonal antibodies, there still remains an urgent need for additional new therapies to help the numerous cancer patients that are failing currently available therapies.

In this research the tumors are thermally ablated with minimally invasive microwave balloon catheters, and the cavities created in the tumors by the balloon catheters are filled with anticancer agents that can be forced through the ablated malignant tissues to the margins of the tumors in order to destroy any remaining viable tumor cells. In vivo and in vitro experiments are described that illustrate the ability of microwave balloon ablation catheters to rapidly ablate large volumes of tissues, to create reservoirs for anticancer agents in the ablated (necrosed) tissues, and to force substances with large molecular weights that are introduced into these reservoirs through the ablated tissues to the margins of the ablation.

In this approach solid tumors are first thermally ablated (necrosed) with minimally invasive microwave balloon catheters that can produce lesions that conform to the shapes of the tumors. Next the cavities that are created by the balloon catheter in the necrosed tumor tissues are filled with anti-cancer agents that are forced by applied pressure through the necrosed tumor tissues to the margins of the tumors where they can act against any remaining viable malignant cells that, if not destroyed, could lead to recurrences of the cancer. These agents can be heated to enhance their anti-cancer efficacy. If immunotherapeutic agents are introduced into the cavities it might also be possible to stimulate systemic anticancer effects against distant metastasis.

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Non-Invasive MRI Methods to Estimate Tumor Cellular Dynamics

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Understanding tumor dynamics, i.e. how it develops and/or responds to treatment, requires measuring the cellular changes which proceed morphological and global tissue changes. Such follow up will assist in design of new therapeutic approaches and could be used for early prediction of treatment response.

Combining two independent magnetic resonance strategists; apparent diffusion coefficient (ADC) imaging and magnetization transfer (MT) imaging, we propose a non-invasive method to estimate changes in tumor cellular level. While ADC is strongly affected by the extra cellular space and thus can be used to map tumor necrotic regions, MT is affected by the extra- and intra- cellular morphological structure thus can be used to identify abnormal cells as in the early stages of apoptosis. A careful combination of both methods is therefore proposed. Two tumor types, a GL261 mouse brain tumor and malignant sarcoma applied on rat's hind limb, were used to show differences in ADC and MT distributions. In comparison to histology, ADC was shown to map necrotic regions while MT identified regions suspected to be in early apoptotic stage. Use for early response to treatment will be discussed.

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Piezoelectric Biosensors: Recent Advances and Applications

Ryszard M. Lec

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Modern biosensors developed with advanced microfabrication and signal

processing techniques are becoming inexpensive, accurate, and reliable. Increasing miniaturization of biosensors leads to realization of complex analytical systems such as Bio-Chem-Lab-on-a-Chip. This rapid progress in miniature devices and instrumentation development will significantly impact the practice of medical care as well as future advances in the chemical, pharmaceutical and environmental industries. In this presentation emerging piezoelectric biosensors technologies and applications are discussed and the challenges facing biosensor developers in the coming decade are outlined.

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Mast cells and Eosinophils: the Main Players of Allergy - Are They the Main Targets for Therapy?

Francesca Levi-Schaffer

NOTEC

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Allergic inflammation (AI) is a complex phenomenon consisting usually of two main phases, the early and late one. Mast cells have been historically ascribed a central role in the acute-early phase while eosinophils have been described as the effector cells of the late phase and when the reaction becomes chronic. However these cells co-exist in high numbers in the late and chronic stages. We have therefore postulated and demonstrated in vitro the existence of a mast cell-eosinophil cross-talk ("The Allergic Effector Unit" (AEU)) able to up-regulate via soluble and physical interactions each other's cell function. We therefore believe that the AEU might also be able to modulate in vivo the allergic inflammatory reaction. Moreover both mast cells and eosinophils not only act on each other but also influence structural cells such as fibroblasts and endothelial cells carrying out reparative/fibrotic responses. Therefore mast cells and eosinophils appear to be the main cells appropriate to be targeted in an attempt to down-regulate allergy and its consequences.

We have lately concentrated our efforts in the search of specific activating and/or inhibitory receptors on these cells as suitable immune-pharmacological targets, the first one to be inhibited and the second one to be activated. In this framework, we have defined the CD48 receptor, a member of the CD2 family, as a main activating receptor on both mast cells and eosinophils. CD48 ligation on eosinophils by antibodies (Abs) leads to eosinophil degranulation and production of cytokines. Importantly CD48 expression is enhanced on eosinophils from asthmatic patients. In two asthma models in mice (induced by OVA or Aspergillus fumigatus) CD48 was also found to be upregulated on the eosinophils and its neutralization abrogated lung inflammation and mucus production.

We next described the presence and functional activity on mast cells and eosinophils of CD300a, an inhibitory receptor belonging to the Ig superfamily. Its activation by the specific abs led to inhibition of both mast cell and eosinophils survival and activation. When bispecific antibodies directed against CD300a and IgE on mast cells, or against CD300a and CCR3 on eosinophils were administered to an OVA model of acute and chronic murine asthma, the lung inflammatory responses were completely abrogated.

In summary, we have demonstrated that mast cells and eosinophils are the main effector cells of allergic inflammation acting both by themselves and in the context of the AEU. Moreover it has been shown that selective down-regulation of these cells by targeting either activating or inhibitory receptors can abrogate the allergic response in vivo mode of experimental asthma. We therefore believe that *mast cells and eosinophils are not only the main players of allergy but also that they should be the main target for anti-allergic therapy.*

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Diversity Is Key - Using Repertoire Signatures to Determine Immune Health

Uri Hershberg

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Due to the diversity of its B cell receptor repertoire the immune system can adapt to nearly any pathogen it encounters. This ability protects from recurrent infections, helps guard against rapidly mutating pathogens and is the basis for vaccines. Following infection, the B cell repertoire undergoes affinity maturation, a process by which rare mutants, with higher affinity for the immunizing antigen, are expanded through a cycle of hyper-mutation, proliferation and cell-death.

In previous work I have shown how in immune systems the germ line repertoire of B cells has evolved to strike the correct balance between mutation-induced change and genetic stability to create viable diversity. Thus, affinity maturation of B cells is a process of diversification and selection. I therefore hypothesize that beyond the selection of affinity in specific B cell, there is a network of affinities that creates a structure to the diversity of B cell repertoires. This structure is maintained throughout the lifetime of healthy immune systems in different species. Understanding the structure of repertoire diversity could greatly enhance our ability to design specific antigens and adjuvants that will be effective in much lower doses as they will be tailored to the specific diversity of affinities of a an individual immune system. Furthermore, I predict that changes from the overall patterns of B cell repertoire diversity will be correlated to specific malfunctions of the immune system and could represent a tendency for negative immune interactions such as allergy, autoimmunity and cancer.

Recent advances in sequencing provide us, for the first time the ability to generate measurements of the full repertoire diversity in healthy and pathological status. Such measurements can be used to systematically investigate the rules governing the diversity of B-cell repertoires. This type of research cannot be done at the level of a single receptor but must involve the repertoire as a whole. I therefore propose to use sophisticated statistical analysis techniques and computational modeling to study the germ line and functional repertoires in different healthy and diseased immune systems.

Defining the nature of diversity, the relationship between specific B cell affinities and the overall related affinities of the repertoire will enable us to determine the potential to malfunction of an individual's immune system and how it may react to specific antigens in vaccines and anti allergy treatments.

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Investigation and Systems Modeling of Stress Responses in Aging

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Aging is characterized not only by accumulating damage and dysfunction but also by stress-responsive and adaptive mechanisms at the cellular level. Two specific pathways known to modulate the aging process are NF-kB and mTOR. For instance, cells from older humans demonstrate higher NF-kB DNA binding activity accompanied by an inflammatory gene expression profile. While the role of NF-kB and mTOR pathways is initially adaptive and protective, chronic elevated high levels are characteristic markers of age related diseases including cancer, diabetes and dementias. Therefore it is important to decipher the behavior of these pathways during aging and to predict the potential outcome of interventions with the goal to extend health span. Since our work is inspired by a system biology approach, the experimental investigations with respect to cell phenotypes and molecular cell states are complemented by a computer based cell modeling. Computer simulations are particularly desirable due to the slow progression of aging in humans and difficulties to emulate aging experimentally in cells within reasonable timeframes.

Our computational approach is based on a whole cell network graph representing the connectivity of key cellular mechanisms structured into positive and negative feedback loop motifs centrally important for aging. The network is casted into a fuzzy-logic, hybrid-intelligent framework based on interaction rules assembled from experimental and a prior knowledge. Time-lapse simulations of the adaptive response model uncover how transcriptional and translational changes, mediated by stress sensors NF-kB and mTOR, counteract accumulating damage and dysfunction by modulating mitochondrial respiration, metabolic fluxes, biosynthesis, and autophagy, crucial for cellular survival. The model allows consideration of lifespan optimization scenarios with respect to fitness criteria using a sensitivity analysis. It also supports the generation of hypotheses about chronic elevation of NF-kB and mTOR activities. *Therefore, our work establishes a novel extendable and scalable approach capable to connect tractable molecular mechanisms and interventions with cellular network dynamics underlying aging and age-related disease phenotypes.*

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Non-Invasive Optical Imaging of Cysteine Proteases Activity using Near Infrared Fluorescent Activity Based Probes

Galia Blum

Laboratory of Bio Imaging, The School of Pharmacy, The Institute for Drug Research, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel

Cysteine proteases play a pivotal role in normal and pathological processes and have been shown to be highly expressed in active forms during tumorigenesis and other diseases. The cysteine cathepsin proteases therefore serve as good markers for cancer detection. However, most enzymatic proteins such as proteases are tightly regulated by a series of post-translational mechanisms thereby making simple measurement of protein levels a poor indicator of function.

We previously developed fluorescently quenched activity based probes (ABPs) for cysteine proteases that allow real time imaging in living cells as well as non-invasive imaging of protease activity in subcutaneous cancer models. These cell permeable small molecules bind to cathepsin B, L and S through a highly selective enzyme-catalyzed chemical reaction within the active site. This allows direct visualization of cathepsin activity in live cells and in tumors of live mice using simple optical detection methods.

Here, we describe an *in vivo* comparison of fluorescently labeled ABPs with commercially available substrate-based probes. Using a Fluorescence Molecular Tomography (FMT) imaging system that detects fluorescent signal deep in the body, we show the advantages of the small molecule probes in terms of the kinetics of labeling, absolute signal, and reduction in background signal compared to the substrate probes. Furthermore, we show our attempts to imaging atherosclerosis non-invasively.

Therefore, the technology of optical imaging based on ABP provides a novel platform for translational medicine diagnostic activity.

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Functional Optical Brain Monitor [fNIR]

Kurtulus Izzetoglu

School of Biomedical Engineering, Science & Health Systems (BIOMED), Drexel University, Philadelphia, USA

Near-infrared spectroscopy (NIRS) has been widely used in functional brain studies as a noninvasive tool to study changes in the concentration of oxygenated hemoglobin (oxy-Hb) and deoxygenated hemoglobin (deoxy-Hb). Based on the NIRS technique, Drexel University's Optical Brain Imaging team has developed a functional brain monitoring system (fNIR) to assess cognitive activity of healthy subjects and patients. The fNIR is a portable, safe, affordable and negligibly intrusive monitoring system which enables the study of cortical activation-related hemodynamic changes under various field conditions.

This presentation will focus on select applications of the fNIR including human performance assessment, training and learning, and depth of anesthesia monitoring. The audience will be introduced to the Cognitive Neuroengineering and Quantitative Experimental Research (CONQUER).

Collaborative which hosts the Optical Brain Imaging team and welcomes all regional, national and international partners dedicated to the research, development, integration, translation and commercialization of functional imaging techniques to monitor human brain activation.

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Imaging of Colorectal Tumors Using Near Infrared Epidermal Growth Factor

Shimon Lecht, Dana Stoler, Gadi Cohen, Hadar Arien-Zakay and <u>Philip</u> Lazarovici

The Laboratory of Neuropharmacology, Neuro-Oncology and Neural Engineering, School of Pharmacy, The Institute for Drug Research, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel

Major clinical applications for molecular imaging offer improvement of disease detection through increased image contrast between normal and diseased tissue and generation of an early measurement of the likelihood of successful response to specific therapies. The biological concentration of target for imaging is a critical point for successful development of novel diagnostic tools. Several types of cell surface receptors undergo over-expression in the course of disease development. They can help achieve the broad clinical goals of detection, characterization, and therapy response assessment sooner and more accurately than current standard-of care imaging techniques that rely largely on anatomic appearance. Fluorescence emission wavelengths in the near infrared (NIR) (700–900 nm) have several relative advantages over visible fluorescence emission in terms of optical molecular imaging: less auto fluorescence, full-color imaging of the tissue for anatomic analysis, and provide a simultaneous selective molecular signal and permits deeper penetration of the tissue for whole body imaging. Over-expression of epidermal growth factor receptor (EGFR) and its oncogenic forms is associated with many types of cancers including colorectal carcinoma (CRC). Therefore it is of great importance to image noninvasively the EGFR expression *in vivo*.

In this study, we used EGF labeled with a NIR dye (IRDye800CW) and investigated receptor imaging: i) in vitro - using a panel of CRC cell culture models specifically designed for imaging purposes, with and without anti-EGFR antibody or EGF pretreatment; ii) in vivo - in mouse orthotopic CRC tumor models as well as iii) ex-vivo – in CRC human biopsies. The results indicate that EGF-IRDye800CW was specifically bound and taken up by EGFR-overexpressing A431 cells. The photo-optic signal obtained from measuring tumor EGRF-positive cells was 15-fold higher compared with EGF-negative normal enterocytes. In vivo imaging showed a time dependent pharmacokinetic accumulation of the EGF-NIR probe. The A431 orthotopic tumor were observed as early as 4h post-injection and a significant optical signal could be monitored for up to 72 hrs. Time course after study indicated that the highest signal ratio between tumor and normal surrounding tissue was achieved 48 hrs post-injection. Images of dissected tissue sections demonstrated that the accumulation of EGF- IRDye800CW in addition to the tumor was in the kidney, liver, testis or ovaries (known to express EGFR). In human ex-vivo CRC biopsies EGF-NIR probe identified specifically the tumors overexpressing EGFR as was validated using Western blotting. In conclusion, EGF-IRDve800CW is a promising molecular imaging agent for EGFRpositive CRC tumors. Additional studies are performed in our laboratory to further characterize this probe as a tool for diagnostic use in terms of mechanism of cell labeling, stability and modes of delivery.

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Bi-Additive Process for Cell Printing

Wei Sun

Department of Mechanical Engineering and Mechanics, College of Engineering, Drexel University, Philadelphia, PA, USA

In the new paradigm of tissue science and engineering, living cells and biomolecules are used as basic building blocks for bio-fabrication of cell-integrated medical therapeutic products and/or non-medical biological systems with applications found as tissue substitutes, 3D cell and organ biological models, micro-fluidic biochips and biosensors, and tissue models for study of disease pathogenesis, drug discovery and toxicity testing.



This presentation will introduce our recent research in the emerging field of cell printing and report our work on using additive technology for direct cell writing for construction of 3D cell assemble and tissue structures. Presentation topic will include: 1) introduction of direct cell writing process; 2) effect of the process parameters on cell survivability; 3) characterization of biological responses of various cells to the printing process; and 4) applications to the field of tissue science and engineering.

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LCL - Vascular Grafts*

Foundation.

Peter I. Lelkes¹, Anat Perets¹, Ari Brooks², Robert Levy³, Russell Composto⁴

¹Drexel School of Biomedical Engineering, Science, and Health Systems (BIOMED), ²Drexel University College of Medicine (DUCOM), ³Children's Hospital of Pennsylvania (CHOP), ⁴University of Pennsylvania (UPenn), Philadelphia, PA, USA

One of the major research areas in our "Integrated Center for Tissue Engineering and Regenerative Medicine" (*i*CTERM) is to advance the development and preclinical testing of proprietary nanofibrous scaffolds with the aim of rapidly advancing translational research and commercialization of a portfolio of thematically related nano-bio products for tissue engineering and regenerative medicine, specifically focusing on vascular grafts, acellular dressings/skin substitutes for wound healing and mineralized scaffolds for the repair of bone defects.

In this short presentation we will focus on the LCL-graft technology aimed at generating a novel small diameter vascular graft and utilizing this technology for other cardiovascular applications, as well. The LCL technology is based on a combination of IP-protected approaches towards a) synthesizing unique biocompatible biomaterials and b) a complex, the electrospinning-based manufacturing process of for generating micro-textured highly compliant small diameter vascular grafts. The inter-university IP issues have been resolved ahead of time using the model developed through the Nanotechnology Institute of Southeastern Pennsylvania (NTI). Following successful trials *in vitro* and some *in vivo* studies in a porcine model, further, long-term animal studies are being prepared to test patency and biocompatibility for up to one year.

In addition to the originally intended use as vascular grafts the technology, future applications of the LCL technology include improvement of tissue integration and healing by incorporation of drug-eluting, slow release modalities and generating compliant non-thrombogenic surfaces on other vascular devices, such as stents.

*We gratefully acknowledge support through grants from NIH, NSF, NTI and the Coulter



Biodegradable Polymers for Regional Therapy

Abraham J. Domb

delivery.

BioPolymers Laboratory, School of Pharmacy, The Institute for Drug Research, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel

Biodegradable polymers have been used as carriers for extended drug delivery and as implantable temporary devices. Applications of biodegradable polymers synthesized in our laboratory will be demonstrated by the development of injectable polymers for regional drug therapy, tissue augmentation, and radiation protection devices.

Localized chemotherapy provides high drug loading in the solid tumor with minimal drug distribution to healthy tissues which both improves drug effectiveness and reduces side effects associated with systemic chemotherapy. Injectable polymeric formulations that deliver effective doses of anticancer agents within a tumor for a few weeks while being eliminated were developed. Biodegradable polymers derived from castor oil were synthesized and used for the delivery of paclitaxel and cisplatin to animals bearing solid tumors. These polymer formulations gel to a pasty material which releases the incorporated drugs for about 4 weeks while degrading and eliminating from the body within 10 weeks. The concept of polymeric regional therapy has been expanded to deliver antibiotics, anesthetics, peptides and nucleic acids.

Prostate Cancer is commonly treated by localized radiation, an external-beam source or brachytherapy. Radiotherapy side effects which decrease patient's quality of life include, erectile dysfunction, rectal irritation bleeding, and urinary frequency. The adverse effects are a result of prostate proximity to rectum wall and nearby innervations, which are permanently damaged along to malignant tissue eradication. Since radiation intensity rapidly decays away from radiation focus, displacing irradiated prostate out of the most sensitive normal tissues, mainly the rectum wall and nearby innervations, changes radiation damage from a permanent status to temporal one. A biodegradable balloon inserted between the rectum wall and prostate gland that distances the two organs by about 10 mm was developed. The balloon is inserted rolled up through the perineum using a minimally invasive catheter, to be placed between the organs and inflated with buffer saline. Balloons are designed to serve throughout patient's radiation sessions for nearly two months. Animal studies confirmed balloon's biocompatibility and effectiveness.

These studies demonstrate the use of biodegradable materials for temporary devices and drug

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Injectable Hydrogels for Nucleous Pulposus Replacement

Anthony Lowman

Department of Chemical and Biological Engineering, College of Engineering, Drexel University, Philadelphia, PA, USA

Degenerative Disc Disease (DDD) is caused by the damage or dehydration of the nucleus pulposus, which reduces the hydrostatic pressure on the internal surface of the annulus fibrosis. These results in abnormal compressive stress on the intervertebral disc, causing tears, cracks and fissures in the annular tissues



after repeated loads. This can manifest in back pain as the result of the nucleus migrating through the annulus and impinging on nerve roots. The current treatments for DDD provide only temporary relief of back pain with no restoration of biomechanical function. Investigators have begun to realize the potential benefits of replacing the damaged or dehydrated nucleus with a synthetic material, such as a hydrogel. Using an in situ forming hydrogel could have important clinical consequences because it can be injected non-invasively using a small gage needle. One way to achieve in situ gel formation is using a thermo-responsive polymer that forms a free flowing solution in water at ambient temperatures and a gel at body temperature, such as N-isopropylacrylamide (PNIPAAm). Below the PNIPAAm LCST (ranging from 29-34°C), PNIPAAm is hydrophilic, allowing it to form a miscible solution with water. Above this transition temperature, the polymer becomes hydrophobic, so the water and polymer separate, forming a compact gel. PNIPAAm-PEG copolymers that were either all branched or all tethered indicated trends toward higher swelling ratios and showed static mechanical behavior in the range suitable for restoring biomechanical function.

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Acute Mechanisms of Axonal Injury and Repair

Kenneth Barbee

School of Biomedical Engineering, Science & Health Systems (BIOMED), Drexel University, Philadelphia, PA, USA

Diffuse axonal injury (DAI) is a manifestation of microstructural cellular trauma and various ensuing neurochemical reactions that lead to secondary neuronal death. The mechanisms by which mechanical trauma leads to the observed axonal pathology are poorly understood. Our *in vitro* model using cultured primary chick forebrain neurons reproduces important features of *in vivo* DAI such as



membrane permeability changes, focal disruption of microtubules, impaired axonal transport, and focal accumulation of organelles. These changes were dependent on the influx of extracellular calcium and the activation of the proteolytic enzyme, calpain. To test the hypothesis that mechanical disruption of the plasma membrane is responsible for initiating these pathological processes, we tested the effect of Poloxamer 188 (P188), a tri-block co-polymer that is known to promote resealing membrane pores. Post-injury P188 treatment prevented trauma-induced membrane permeability changes and reduced axonal beading and associated cytoskeletal disruption to control levels. Beading could also be prevented by removal of extracellular calcium, intracellular buffering of calcium, and direct inhibition of calpain. These results indicate that acute mechanoporation of axons in response to injury is a necessary condition for subsequent axonal pathology, suggesting that membrane integrity is a potential target for therapeutic interventions. P188 provides neuroprotection via resealing the plasma membrane following injury and prevents focal disruption of microtubules and axonal bead formation.

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Designing Multifunctional Scaffolds for Repair of Spinal Cord Injury

11. Fischer, 2A. Lowman, 3P. Lelkes

¹Department of Neurobiology and Anatomy, Drexel University College of Medicine, ²Department of Chemical and Biological Engineering, ³School of Biomedical Engineering, Science & Health Systems (BIOMED), Drexel University, Philadelphia, PA, USA



Investigators at the Spinal Cord Research Center at the Drexel University
College of Medicine are studying the pathophysiology of spinal cord injury (SCI) with respect to
neuroprotection and regeneration as well as developing repair strategies that include cell
transplantation, drug therapy, physical rehabilitation, and robotics. My laboratory has been working on
the therapeutic potential of various stem cells with particular interest in neural stem cells and adult
stem cells. Some of the challenges associated with grafting these cells in models of SCI include cell
survival, neural differentiation and combination treatments that allow cell transplantation together with
delivery of therapeutic factors. The use of multifunctional scaffolds in spinal cord injury presents a
promising approach that addresses these issues. We have therefore developed two important
collaborations that employ different strategies for the design and application multifunctional scaffolds.

1. Injectable scaffolds combined with microspheres (Dr. Anthony Lowman).

The project utilizes a thermosensitive hydrogel (PNIPAA and PEG) that allows for minimally invasive injection of the hydrogel together with the cell graft into the injury together with controlled delivery of neurotrophic factors (BDNF) by either the hydrogel alone or by microspheres. Our results have shown that *the injectable hydrogel fills the injury site without eliciting a major inflammatory response and the inclusion of BDNF promotes axonal growth.* Future experiments are designed to optimize the mechanical and chemical properties of the hydrogel with respect to the injury environment and the neural cells, and to prepare microspheres with an appropriate release profile to maximize neuroprotection and repair.

2. Scaffold with guided channels combined with endothelial cells (Dr. Peter Lelkes).

The project utilizes a permissive nanofibrous scaffold with guided channels that will be implanted with endothelial cells and grafted into a model of SCI. This therapeutic approach is designed to provide a bridge across the injury site that will guide axonal growth and promote connectivity through the channels and the aligned endothelial cells. In addition it will promote recovery through angiogenesis by the formation of blood vessels that facilitate the repair process. Preliminary data have shown that *the scaffold is compatible with neural cells and that it can be implanted at the injury site with the appropriate orientation.* Future experiments are designed to include endothelial cells in the grafting experiments, to analyze the effects on the injury site, and to evaluate recovery of function.

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An Experimental Model of Traumatic Brain Injury for Evaluation of Candidate Drugs: Studies of Neurobehavioral, Cognitive and Neurochemical Changes

Esther Shohami

Laboratory for Research on Traumatic Brain Injury (TBI), The School of Pharmacy, The Institute for Drug Research, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel

Traumatic brain injury (TBI) represents a major health care problem with ~ 1.5 million patients affected each year, and mortality of severe TBI of 35%-40%. Yet, despite advances in basic and clinical research there are no pharmacological treatment modalities to TBI. Understanding of the cellular and molecular mechanisms underlying the pathophysiological events after TBI has resulted in the identification of new potential therapeutic targets. Nevertheless, the extrapolation from basic research data to clinical application in TBI patients has invariably failed, and results from prospective clinical trials are disappointing.

We have developed a rodent model that mimics the clinical TBI and induces closed head injury (CHI) by a standardized weight-drop device creating a focal blunt injury. The resulting impact triggers a profound neuropathological response with high consistency and reproducibility, leading to neurological impairment, edema and breakdown of the blood-brain barrier. This model allows not only to study the pathophysiology of TBI, but also to evaluate the effects of drugs and genetic manipulations on relevant outcome measures. This model is of great relevance as a pre-clinical platform for evaluation of drugs for TBI.

In our CHI model we have established the dual role of the inflammatory response after TBI, mechanisms by which oxidative stress is involved in the pathophysiology of TBI and a role for the endocannabinoid system. In addition, our findings on the temporal changes in the NMDA receptors led us to a novel approach towards treatment of TBI. We showed that NMDA agonists rather than antagonists are beneficial, and thus led to a paradigm shift, explaining why NMDA antagonists not only failed in the clinic, but were detrimental.

Chronic exposure to moderate environmental heat (30 days at $34\pm1^{\circ}\text{C}$) induces a conserved adaptive response known as heat acclimation (HA). This physiological process confers a wide-scale protective effect against various types of stress including TBI. Thus, mice subjected to TBI after HA were more resistant and displayed less cell death TBI. We studied the mechanisms underlying HA-induced cross tolerance and have identified some cellular and molecular pathways which are activated during the period of heat acclimation, as part of the organism's adaptive capacity. These include activation of HIF1 α and the p-Akt, lower levels of pro-inflammatory cytokines, higher levels of erythropoietin signaling and of the neurotrophic factor BDNF.

These findings may lead to the development of new strategies toward treatment of TBI patients.

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Human Umbilical Cord Blood Stem Cells, Potential Neuroprotectors for Ischemic Brain Injury*

 $\underline{Hadar\ Arien-Zakay^{1,2}}$, Shimon Lecht 1 , Marian M Bercu 1 , Esther Shohami 1 , Arnon Nagler 2 and Philip Lazarovici 1

¹The Laboratory of Neuropharmacology, Neuro-Oncology and Neural Engineering, School of Pharmacy, The Institute for Drug Research, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem and ²Division of Hematology and Cord Blood Bank, Chaim Sheba Medical Center, Tel-Hashomer, Israel



Stem cell-based regenerative medicine is an emerging new concept for treating diseases of the central nervous system. Among variety of proposed procedures, one of the most promising is the refilling of damaged cavities of injured brain parenchyma with artificial neural tissue. Recent studies in rodents have revealed that allogenic transplantation of tissue-engineered scaffolds may be efficient in the repair of hypoxic/ischemic brain injuries. Lately, human umbilical cord blood (CB) has been recognized as a feasible, efficient and uncontroversial source of neural stem cells. CB has also established itself as a legitimate source for hematopoietic stem cell transplantation. It is also considered an accessible and less immunogenic source for mesenchymal, unrestricted somatic and for other stem cells with pluri/multipotency properties, which are capable of differentiating into a wide variety of cell types including neural. We describe a novel technology for the isolation of a unique population of progenitor cells from the CB termed HUCBNP, using their collagen adherent properties and positive expression of alpha1 and alpha2 collagen-receptors. Microarray gene expression analysis indicates that HUCBNP are negative for common hematopoietic markers and positive for common mesenchymal markers. Our approach to induce differentiation towards a neuronal phenotype is based on supplementation of growth factors, mainly of nerve growth factor and interferon-gamma. The cells differentiation was evaluated by the activation of the MAPK intracellular signaling as well as the expression of a wide range of neural markers. Our results indicate that a three-dimensional environment facilitates maturation and long term maintenance of HUCBNP, suggesting a more suitable environmental structure for the use of CB cells in regenerative medicine. The neuroprotective potential of HUCBNP was evaluated using a neuronal ischemic *in vitro* model, which was adjusted to measure cell-cell induced neuroprotection. We found that HUCBNP release antioxidants and angioneurins, supporting a "bystander" neuroprotective mechanism. CB neuroprotective effects in vivo were evaluated using a closed head injury model in mice. Upon intra-cerebral administration of CB cells, many of the physical and behavioral deficits associated with this disease were ameliorated. Furthermore, an improvement in the neurological score was achieved upon cell implantation of 1 and 7 days after injury. *These results* indicate a wide range of translational clinical applications for ischemic brain injuries such as stroke and brain trauma.

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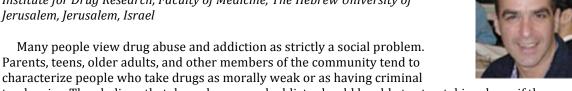
*We gratefully acknowledge support through grants from the Israel Ministry of Science and Technology.



Drug Addiction

Rami Yaka

Laboratory of Neurobiology of Drug Addiction, The School of Pharmacy, The Institute for Drug Research, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel



tendencies. They believe that drug abusers and addicts should be able to stop taking drugs if they are willing to change their behavior. These myths have not only stereotyped those with drug-related problems, but also their families, their communities, and the health care professionals who work with them. Drug abuse and addiction comprise a public health problem that affects many people and has wide ranging social consequences. Addiction is a chronic, relapsing, and treatable disease.

Our research is focused on the changes in the brain that occurs following withdrawal from drug intake. We found that prolonged withdrawal from cocaine increases the expression of glutamate receptors in the Nucleus Accumbens, a brain region that responsible for reward. This increase underlies the amplification of the behavioral response to drugs or drugs associated cues following prolonged abstinence. We are currently developing specific blockers to reverse these changes which will hopefully lead to prevent the relapse to drug use following withdrawal.

One of the ways by which drugs of abuse, such as cocaine, affect our brain function is by cytotoxicity and oxidative damage. We have recently showed that treatment with antioxidants can reduce the oxidative stress induced by cocaine in the brain reward system. We also showed that antioxidants can reduce cocaine's addictive/behavioral effects. Based on these novel and striking findings, we are currently examining the ability of different antioxidants which are in use in the clinic, to reduce the addictive properties of drugs of abuse.

If successful, these studies will lead to a novel strategies and immediate treatment for drug addiction.

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Targeting the Action of Amphetamines on Serotonin and Dopamine Transporters

Ole Valente Mortensen

Department of Pharmacology and Physiology, Drexel University College of Medicine, Philadelphia, PA, USA

I have a long standing interest in understanding the molecular determinants of serotonin (SERT) and dopamine transporter (DAT) function and regulation. DAT and SERT serve a pivotal role in limiting monoamine-mediated neurotransmission. Whereas the psychostimulant cocaine achieves its effect by direct inhibition of DAT, amphetamine and MDMA (Ecstasy) have a more complex mechanism of action as, in addition, they cause the release (efflux) of intracellular dopamine and serotonin. Enhancing our understanding of the mechanism of transporter-elicited efflux is therefore essential for a more complete understanding of how this process contributes to substance abuse and may be employed for developing novel therapeutic strategies for treating human drug addiction.

We have recently isolated SERT and DAT cDNAs from the human parasite *Schistosoma mansoni* and determined that these transporters take up their endogenous substrates in a manner very similar to their mammalian counterparts. In the parasite SERT, however, unlike in its mammalian counterparts, only serotonin but not other substrates including amphetamine and MDMA induce serotonin efflux. This opens up the intriguing possibility that the efflux process can be therapeutically targeted without interfering with the uptake process. We are using the parasite transporters as tools to identify important structural regions within the transporter that determines if the transporter will elicit amphetamine induced efflux. We intend to ultimately pursue the specific role of DAT and SERT in amphetamine and MDMA addiction and neurotoxicity by using this structural information to produce novel animal models in which the DAT and SERT has been rendered insensitive to amphetamine-like molecules.

We believe these data may lead to important insights into novel methods of regulating transporter action and, as a consequence, new targets for drug discovery and development in behavioral, psychiatric and substance abuse disorders.

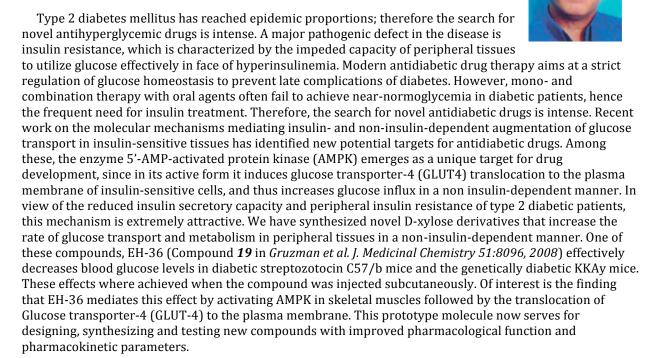
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Development of Novel Classes of Antidiabetic Drugs

Shlomo Sasson

Laboratory of Molecular and Pharmacological Diabetes Research, School of Pharmacy, The Institute for Drug Research, The Hebrew University of Jerusalem, Jerusalem, Israel



In addition, we have recently discovered another compound that increases the rate of glucose uptake to skeletal muscles by augmenting the intrinsic activity of GLUT-4. This is an original discovery, and hitherto no molecules that augment the intrinsic activity of the transporter have been reported. We use this discovery as a platform for designing, synthesizing and testing novel derivatives to obtain prototype lipophilic molecules that increase the intrinsic activity of GLUT-4 at pharmacologically relevant concentrations. Such compounds may represent a unique class of potential antidiabetic drugs.

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Identification and Characterization of APP Metabolism Regulators: Therapeutic Insights into Alzheimer's disease

Aleister Saunders

Department of Biology, College of Arts and Sciences, Drexel University, Philadelphia, PA, USA

Alzheimer's disease is the leading cause of dementia in the developed world and currently there is no effective therapy. APP metabolism plays a central role in the pathogenesis of Alzheimer's disease. Using a cell-based functional genetic screen we have identified numerous genes that regulate APP metabolism. We confirmed the ability of these genes to regulate APP metabolism in vivo.



Using a novel transgenic Alzheimer's model we have demonstrated that genetic or pharmacologic manipulation of these genes can improve the neuropathological and cognitive defects associated with this AD model.

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A Drexel Translational Cross-Campus Grant Group Investigating Mechanism and Prevention of HIV-1 Host Cell Entry

<u>1Irwin Chaiken</u>, <u>1</u>Jeffery Jacobson, <u>1</u>Michele Kutzler, <u>2</u>Cameron Abrams and <u>3</u>Elisabeth Papazoglou

¹Department of Biochemistry and Molecular Biology, Drexel University College of Medicine (DUCOM), ²Department of Chemical and Biological Engineering, ³School of Biomedical Engineering, Science, and Health Systems (BIOMED), Drexel University, Philadelphia, PA, USA



HIV-1 infection is initiated by entry of the virus into host cells. The entry process depends on initial attachment of virus with host, and the molecular components of this attachment process are known. HIV-1 cell recognition occurs through envelope proteins on the viral spike, a heterotrimer of the gp120/gp41 complex. The interactions between gp120 and cell receptors appear to play the central role in viral entry. Host cell recognition by envelope gp120 occurs through both CD4 and a co-receptor, most commonly one of the chemokine receptors CCR5 or CXCR4. These interactions lead to rearrangements in gp120-gp41 organization, exposing structural components of gp41 for virus-host cell fusion. The multimolecular interactions of HIV-1 envelope gp120 with cell receptors have become targets to inhibit viral infection and suppress the pathogenesis of AIDS. Env gp120 is also a major target for protective vaccine immunogen development.

Work in the Chaiken Lab at Drexel explores design and mechanism of action investigations of gp120 antagonists. In one path of work, a peptide-based strategy has led to identification of a dual receptor site inhibitor lead, HNG-156, which strongly suppresses virus cell infection, can be structurally minimized, is potency-enhanced by nanoparticle conjugation and appears to function through conformational entrapment of gp120.

This work has stimulated translational research in a cross-campus group at Drexel/Drexelmed to deepen understanding of mechanisms of action at the molecular, virus spike and cellular levels and to seek methods to use these agents for therapeutic, microbicide and vaccine development. Synergistic cross-disciplinary collaborations to strengthen and expand the above efforts would be welcomed. This could include synthetic and computational design, formulation of active agents, determining how inhibitors alter the viral envelope spike, recombinant immunogen construction and models for pre-clinical testing. Some looming future challenges include peptide-to-drug design and learning how inhibitors affect virus spike structure at high resolution.

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ADDITIONAL ABSTRACT

ADDITIONAL ABSTRACT:

Drug Transporters - Focus on the Blood-Brain Barrier and the Placenta

Sara Eyal

Clinical Pharmacy Division, The School of Pharmacy, The Institute for Drug Research, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel

Neurological diseases affect millions of people worldwide. Optimizing pharmacotherapy for patients with such diseases is complicated by variability among individuals in drug response. Whereas major drugs are effective in less than half of the patients with neurological disorders such as migraine, Alzheimer's disease, and epilepsy, toxic drug effects are often observed. A key factor in rational therapeutics of neurological disorders is therefore enhanced understanding of the causes and consequences of variability in response to medications. Crucial to this understanding is the question of how drugs gain access to their CNS (and other) targets.

My studies focus on the impact of pharmacogenetics, physiological and environmental factors on drug transporters at the blood-brain barrier as well as at other blood-tissue barriers and their clinical significance in terms of dosing requirements, treatment success or failure, and adverse drug reactions. For example, our positron emission tomography imaging studies in non-human primates indicate that drug transport across the blood-brain barrier and the placenta is altered during pregnancy. Based on our results, my future research projects include characterizing the role of uptake and efflux transporters in the disposition and response to CNS drugs and the inter-relationships between pregnancy and CNS drugs disposition, response and toxicity.

To do so, I will use translational research to convert clinical information from patients with neurological diseases into basic science (e.g., rodent models) and then translate the results back to clinic. Beyond traditional methods for analysis of gene expression and protein function, the nature of such studies calls for the use of novel imaging technologies, including those developed and utilized by researchers from Drexel University.

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ROUNDTABLE DISCUSSION

Roundtable: Translational Biomedical Research - From Bench to Bedside

Moderator: Israel Ringel / Mike Edwards

Presenters: *Itzik Goldwaser* (Yissum): Yissum concept

Giora Feuerstein (FARMCON LLC.): A new business model

Anthony Green (BFTP/Nanotechnology Institute): Unique models for multi-institutional

commercialization partnerships

Banu Onaral (BIOMED, DU): Coulter Foundation / Philadelphia Health

Alliance

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Yissum - Research Development Company of The Hebrew University of Jerusalem

- We are charged with protecting Hebrew University's (HU) inventions, products, and technologies developed by the Universities faculty, staff, and researchers.
- We are an active partner with HU's researchers. Using our extensive knowledge of industries and markets, we seek appropriate businesses with which to partner.
- Our commercialization strategies -- licensing, establishing a company, joint ventures, and collaborative research -- enhance the market value and performance of HU's discoveries and increase their availability to a broad global marketplace.

About Yissum

Yissum Research Development Company of the Hebrew University of Jerusalem Ltd. was founded in 1964 to protect and commercialize the Hebrew University's intellectual property. Ranked among the top technology transfer companies in the world, Yissum has registered over 6,100 patents covering 1,750 inventions; has licensed out 480 technologies and has spun-off 68 companies. Yissum's business partners span the globe and include companies such as Novartis, Johnson & Johnson, Roche, Merck, Teva, Intel, IBM, Phillips, Sygenta, Vilmorin, Monsanto and many more.

Yissum's commercialization successes are in various fields including biotechnology, drugs and drug delivery, agriculture, hi-tech, nanotechnology, cleantech and many more. In 2009, 138 new inventions were received, 140 new patents applied for and 67 new patents were granted (based on patent applications from previous years). Biotechnology and life sciences remain the major field of innovation at the Hebrew University, however other scientific fields such as material, agriculture and computer sciences are rapidly growing in percentage.

Israel is a world leader in technology transfer, and Israeli experts – including Yissum's top management – are proud to assist governments, universities and other organizations around the world in maximizing the potential of their academic research.

Case Studies - Samples of Yissum's Success Stories

DOXIL®, the only cancer medication of Israeli origin currently on the world market, was developed by Hebrew University researcher Prof Yechezkel Barenholz and his colleague Prof Alberto Gabizon, currently Head of Oncology at Shaarei Tzedek Medical Centre in Jerusalem. The Doxorubicin HCI liposome injection is Alza's lead







product for oncology and provides relief to many ovarian and breast cancer patients around the world. 2009 sales were ~\$500 million.

Exelon®, a cholinesterase inhibitor developed by Prof. Marta Weinstock-Rosin of the Hebrew University's department of Pharmacology, treats the symptoms of Alzheimer's disease and other dementias. Licensed to world leader Novartis, 2009 sales were \$954 million. A new once-a-day patch formulation is now being launched around the world, providing further relief to patients and caretakers.

About the IDR:

The Institute for Drug Research (IDR), operating within the Hebrew University's School of Pharmacy, was established in 2009 to meet the complexity and versatility facing today's drug research and development.

Training the new generation of leading scientists in the field of drug research is a national mission. The IDR encourages formation of multi-disciplinary research groups to advance scientific excellence and convenes special multi-disciplinary teams to solve complex problems. IDR researchers partner with the pharmaceutical industry in new initiatives, contributing their unique and invaluable experience and knowledge.

As teams and individuals, the institute's researchers have discovered new drugs and invented novel drug-delivery platforms for the treatment of a variety of clinical disorders. These pathologies include allergies, cancer, age-related and neurological diseases, brain trauma, diabetes and drug addiction.

Over the years, 13 start-up companies have been established based on research of the institute's current research staff. Collectively, the institute's scientists have registered more than 200 patents, totaling more than 25% of all approved patent applications of the Hebrew University.

Today, four novel drugs, developed by the institute's researchers and commercialized by Yissum, the Research and Development Company of the Hebrew University, are in the market. The most well-known is Exelon, a drug which delays the onset of the symptoms of Alzheimer's disease. In the year 2009 alone, income from this drug – which is marketed worldwide by Novartis was US\$954 million. Several other drugs are currently in various stages of development, including clinical and preclinical trials.



ROUNDTABLE DISCUSSION

Unique Models for Multi-Institutional Commercialization Partnerships

Anthony Green

Ben Franklin Technology Partners of Southeastern Pennsylvania

The Nanotechnology Institute (NTI), which will celebrate its 10th anniversary this fall, is a novel example of a partnership that enables and accelerates the commercialization of innovative research. Created in 2000, the NTI's founders, Ben Franklin Technology Partners of Southeastern PA, Drexel University, and the University of Pennsylvania, recognized that overcoming these barriers to innovation and entrepreneurship in the 21st century required completely new thinking and new structures. The NTI's innovative structure, groundbreaking IP



sharing agreement and revenue return formula result in tangible commercial payoffs for regional economical development. The NTI model has now become the framework for many other regional proposals for technology commercialization. It was the impetus for the creation of the Energy Commercialization Institute (ECI) by the State of PA in 2009 and the unique inter-organizational agreements and structure of the NTI are core elements in the recently announced \$122 million DOE, NIST, EDA, and SBA award to create Greater Philadelphia Regional Innovation Cluster for Energy Efficient Buildings (GPIC) at the Philadelphia Navy Yard.

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Moderator:

ROUNDTABLE DISCUSSION

Public Roundtable: Cardiovascular Regenerative Engineering

Cem Bozkurt

Presenters: Abraham J. Domb, Gershon Golomb, Peter Lelkes, Cem Bozkurt NOTES: