NEW HORIZONS IN NANOMEDICINE

WEDNESDAY–THURSDAY
24–25 JUNE
2015
Dear Friends and Colleagues

It is our great pleasure to welcome all of you to the New Horizon in Nanomedicine Symposium that is taking place in Beit Hatfusot, Tel Aviv University.

We are honored to be hosting high-level experts in a range of topics of scientific interest.

Topics range from supramolecular architectures for drug delivery, targeted platforms for drugs and RNA inhibitory, antibody-drug conjugates, stem cells, bioengineering and theranostic imaging probes - all of which represent the vast research, technical challenges and achievements of scientists working in the immense fields of drug delivery and biomaterials in our hyper-connected world.

Tel Aviv University endorses the broad range of science, technology and international cooperation that forms the basis of this conference. Our interdisciplinary approach in matters of research, our researchers, and our innovative endeavors are critical in ensuring continual flow of knowledge, innovation and talent.

The ICRS Scientific executive committee and the The Center for NanoScience and Nanotechnology, would like to thank The Marian Gertner Institute for Medical Nanosystems for the generous support that enabled us to organize this conference.

The successful organization of this event required the devoted commitment and time of the organizers, to all of whom I would like to extend my grateful thanks including Mickey Shenhar and Dr. Inbal Hazan-Halevi.

On behalf of the ICRS Scientific executive committee we wish you all enjoyment and benefit from the conference, and look forward to continuing this cooperative endeavor for many years.

Sincerely Yours,

Prof. Dan Peer
ICRS President
JUNE 24TH, 2015 – DAY 1

08:20 – 09:00  Morning Coffee

09:00 – 09:05  Opening Ceremony (Chair: Dan Peer)
09:05 – 09:10  Yossi Klafter – President – TAU
09:10 – 09:15  Yael Hanein – Director, Gertner Institute for Medical Nanosystems
09:15 – 09:20  Dan Peer – President, ICRS

Session 1: Morning Session – mAbs, ADCs in Cancer and Inflammation

09:30 – 10:20  Plenary Peter Senter (Seattle Genetics)
Potent Antibody-Based Conjugates for Cancer Therapy: From Early Stage Research to a Clinically Approved Drug

10:20 – 10:50  Itai Benhar (TAU)
Targeted Antifungal Phage Nanomedicines

10:50 – 11:20  Coffee Break

11:20 – 11:50  Ayelet David (BGU)
Inhibition of Primary and Metastatic Tumors in Mice by Vascular-Targeted Polymer-Drug Conjugates

11:50 – 12:20  Ester Segeal (Technion)
Nanostructured Silicon for Drug Delivery and Diagnostics

12:20 – 12:50  Roy Weinstain (TAU)
meso-Methylhydroxy BODIPY: a Scaffold for Photo-Labile Protecting Groups

12:50 – 14:00  Lunch

Session 2: Afternoon Session – Stem Cells, Tissue Engineering and Regenerative Medicine

14:00 – 14:50  Plenary Jeff Karp (Harvard Medical School)
An Inflammation Responsive Platform for Controlled Drug Delivery

14:50 – 15:20  Tal Dvir (TAU)
Advanced Biomaterials for Mending Broken Hearts

15:20 – 15:40  Coffee Break

15:40 – 16:10  Rachela Popovtzer (BIU)
Nanomedicine for Cancer Immunotherapy: Tracking Cancer-Specific T-cells in vivo

16:10 – 16:40  Marcele Machluf (Technion)
Cancer gets spooked by nano-ghosts targeted delivery system

16:40 – 17:10  Rimona Margalit (TAU)
Mechanism and Efficacy of Macrophage-Targeted Drug-Encapsulating Liposomes in Cardiovascular Repair and in Cancer
Session 3: Morning Session – Theranostics in Cancer

08:20 – 09:00 Morning Coffee

09:00 – 09:50 Plenary Twan Lammers (Achen University)
Nanomedicines and Theranostics

09:50 – 10:20 Ronit Satchi-Fainaro (TAU)
Novel Cancer Models-Based Identification of Targets for the Rational
Design of Precision Theranostic Nanomedicines

10:20 – 10:50 Coffee Break

10:50 – 11:20 Smadar Cohen (BGU)
A Bridge To Silencing: Co-Assembling Anionic Nanoparticles Of siRNA
And Hyaluronan Sulfate Via Calcium Bridges

11:20 – 11:50 Abraham Rubinstein (HUJI)
Multimodal Targeted Platforms for in Situ Screening of Colonic Malignancy

11:50 – 12:20 Ofra Benny (HUJI)
A Rational Drug-Delivery Approach to Overcoming Tumor Resistance in
Anti-Angiogenic Therapy

12:20 – 13:20 Lunch

Session 4: Afternoon Session – New Delivery Concepts and Integrated Material Sciences

13:20 – 14:00 Plenary Yanjun Zhao (Tianjin University)
Polymeric Conjugate Micelles for On-Demand Drug Delivery

14:00 – 14:30 Yechezkel (Chezy) Barenholz (HUJI)
Liposomes’ Based Steroidal Nano-Drug Prevents Cerebral Malaria

14:30 – 15:00 Simon Benita (HUJI)
An Innovative Nano-Delivery System for Duchenne Muscular Dystrophy
Potential Improved Treatment

15:00 – 15:30 Coffee Break

15:30 – 16:00 Boaz Mizrahi (Technion)
Liquid Polymers for Drug Delivery and Regenerative Medicine

16:00 – 16:30 Roey Amir (TAU)
Enzyme Responsive Micellar Nano-Carriers

16:30 – 16:55 Avi Schroeder (Technion)
Personalized Programmed Nanomedicines

16:55 – 17:05 Closing – Dan Peer
Potent Antibody-Based Conjugates for Cancer Therapy: From Early Stage Research to a Clinically Approved Drug

Peter Senter
Seattle Genetics, 21823 30th Dr. SE, Bothell WA
Email: psenter@seagen.com

Monoclonal antibodies (mAbs) have played a major role in cancer medicine, with active drugs such as trastuzumab (Herceptin), cetuximab (Erbitux), bevacizumab (Avastin) and rituximab (Rituxan) in a wide range of therapeutic applications. The mechanism of activity of these agents once they bind to tumor associated antigens may involve direct signaling, interactions with Fcg receptor positive cells on effector cells, and complement fixation. Several approaches have been explored to improve antibody-based therapies for cancer treatment by optimizing these activities and by using antibodies as delivery agents for highly potent cytotoxic drugs. These areas have advanced significantly in the past few years, leading to the approval of two antibody drug conjugates (ADCs) and a glyco-engineered antibody with enhanced binding to endogenous natural killer cells.

New insights into how ADCs can be effectively developed have been gained through studies on cancer antigen targets and their expression on normal tissues, drug potency and mechanism, and linker stability and conditional drug release. Adcetris (brentuximab vedotin, SGN-35, approved in 2011 for use in relapsed or refractory Hodgkin lymphoma and systemic anaplastic large cell lymphoma) is an example an ADC designed with these parameters in mind. Since then, significant developments have been made many areas of ADC technology, include antigen targets, high potency drugs, linker technologies, and alternative carriers. An overview and progress surrounding new generation ADCs will be provided.
In cancer therapy, several attempts have been made to target chemotherapeutic drugs and nanomedicines directly to the endothelial cells of tumor-specific blood vessels. In this lecture I will describe the design of two novel HPMA copolymer-drug conjugates that actively bind either E-selectin – an adhesion molecule expressed exclusively on endothelial cells of inflamed and angiogenic blood vessels, or vascular endothelial growth factor receptor (VEGFR)-1 – that is expressed on various cell types of the tumor microenvironment, including endothelial cells, stromal cells, tumor associated macrophages, and on many human cancer cells of diverse tumor origin. The anticancer activity and selectivity of the new polymer-drug conjugates was assessed in primary tumors of Lewis lung carcinoma (3LL), and further tested for their ability to reduce the overall number of B16-F10 melanoma foci in murine model of experimental lung-metastases. The results demonstrate that the growth of an established 3LL tumors and B16-F10 lung metastases can be inhibited by a single intravenous injection of the E-selectin- and VEGFR-1-targeted copolymer-doxorubicin conjugate, and the percentage of mice surviving increased with increasing doses and with dosing frequency. The E-selectin-targeted system can further control the spread of cancer and inhibit the development of metastases. Our research thus highlights both E-selectin and VEGFR-1 as an effective potential targets for nanomedicines used to treat primary and metastatic tumors.
Nanostructured Silicon for Drug Delivery and Diagnostics

Ester Segal
Department of Biotechnology and Food Engineering
The Russell Berrie Nanotechnology Institute,
Technion – Israel Institute of Technology, Haifa 32000, Israel
Email: esegal@tx.technion.ac.il

Nanostructured porous Si (PSi) emerges as a promising platform for drug delivery as well as for in-vitro and in-vivo diagnostics owing to its low toxicity, high surface area, tunable pore sizes and volumes and versatile surface chemistry. The potential impact of PSi on future healthcare is evident by the current assessment of various PSi devices for medical applications in clinical trials.

Detection of biologically relevant targets such as microorganisms, DNA, proteins, or small molecules at low concentrations is important for applications in medical diagnostics. Of particular interest are point-of-care biosensing systems that can allow clinicians to provide rapid diagnoses at the time and location of care. Our work is focused on the design of label-free biosensing schemes which employ nanostructured porous silicon, as the optical transducer element, interfaced with a relevant capture probe (e.g., antibody, aptamer, and enzyme). We demonstrate rapid and sensitive detection of a wide variety of common environmental pollutants, ranging from disease causing bacteria to cancer biomarkers. Importantly, we show that our biosensors can identify their targets in complex biological fluids. Thus, these systems offer the possibility of designing highly stable and specific label-free biosensors, holding immense potential for application in detection of a broad range of targets, in a simple yet reliable manner.
meso-Methylhydroxy BODIPY: a Scaffold for Photo-Labile Protecting Groups

Naama Rubinstein,¹ Pei Liu,² Evan W. Miller,²,³,⁴ and Roy Weinstain¹

¹Department of Molecular Biology and Ecology of Plants, Life Sciences Faculty, Tel Aviv University, Ramat Aviv, Tel Aviv 6997801, Israel. ²Department of Chemistry, ³Molecular and Cell Biology, and ⁴Helen Wills Neuroscience Institute, University of California, Berkeley, CA, 94720 USA.

Email: royweinstain@post.tau.ac.il

Photochemically labile protecting groups enable precise control over the spatial and temporal release of bioactive molecules with light. The vast majority of commonly used photocages rely on high energy photons with wavelengths in the UV to near-UV range that limit many applications due to high scattering, tissue damage and autofluorescence. Therefore, a need exists for new photocages that operate by one photon in the visible spectrum. Here, we show that meso-methylhydroxyboron dipyrrromethene (m&m-BODIPY) scaffold, can be straightforwardly applied to cage a variety of biologically relevant functional groups, including phenols, amines, anilines, and carboxylic acids, and efficiently uncage them in response to green light. To demonstrate the utility of this novel BODIPY scaffold for controlling biological activity with green light, we caged two biogenic amines, histamine and dopamine, and showed delivery of these amines to cultured HeLa cells and neurons in a light-dependent fashion. Taken together, these data highlight the potential of m&m-BODIPY as a versatile platform for photochemical caging.
An Inflammation Responsive Platform for Controlled Drug Delivery

Jeff M. Karp
Brigham and Women’s Hospital, Harvard Medical School, USA
Email: jeffkarp@mit.edu

We have developed an autonomous delivery system that titrates the amount of drug released in response to the level of inflammation, ensuring the drug is released only when needed at a therapeutically relevant concentration. Translation of such technology would represent a paradigm shift in the treatment of inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease which has characteristic flares followed by periods of lower disease activity. We have evaluated its ability to release drugs in response to enzymes that are abundant in human synovial fluid and ulcerated gut tissue using a series of in vitro and in vivo experiments.
The heart is a non-regenerating organ. Consequently, the loss of cardiac cells and formation of scar tissue after extensive myocardial infarction frequently leads to congestive heart failure. Given the scarcity of cardiac donors, a potential approach to treat the infarcted heart is to repopulate the ‘dead zone’ with cells capable of spontaneous contraction. Cellular therapy evolved to introduce cells into diseased areas and regain function. However, two main drawbacks of this approach are the lack of control of cell accumulation site after injection, and cell death before forming cell-cell or cell-matrix interactions. These shortfalls motivated the development of the tissue engineering concept, where 3-dimensional (3D) biomaterials serve as extracellular matrix-like scaffolds to the cells, enabling the cells to assemble into effective tissue substitutes, that may restore tissue or organ function. After transplantation the scaffolds either degrade or metabolize, eventually leaving a vital tissue instead of the defected tissue. In this talk I will describe cutting-edge technologies for engineering functional cardiac tissues, focusing on the design of new biomaterials mimicking the natural microenvironment of the heart, and the use of inorganic nanostructures and devices for actuating and monitoring tissue performances in vitro and in vivo.
Nanomedicine for Cancer Immunotherapy: Tracking Cancer-Specific T-cells in vivo

Rachela Popovtzer
Faculty of Engineering and the Institute of Nanotechnology and Advanced Materials, Bar-Ilan University
Email: rachela.popovtzer@gmail.com

Cell-based therapy offers a promising solution for the treatment of diseases and injuries that conventional medicines and therapies cannot cure effectively, and thus comprises an encouraging arena for future medical breakthroughs. The development of an accurate and quantitative non-invasive cell tracking technique is a highly challenging task, which could help in evaluating the effectiveness of the treatment. Moreover, cell tracking could elucidate essential knowledge regarding fundamental trafficking patterns and poorly-understood mechanisms underlying the success or failure of cell therapy. This talk will focus on gold nanoparticles (GNPs), which provide cells with 'visibility' in a variety of imaging modalities for stem cell therapy, immune cell therapy and cancer treatment. Current challenges and future prospects relating to the use of GNPs in such roles are discussed.
The ultimate goal in cancer drug- and gene delivery is a ‘magic-bullet’ that provides a versatile platform for site-specific targeting of multiple cancers, implemented in a clinically relevant and non-toxic design. We have designed a novel delivery platform, which is based on unique cell-derived nano-ghosts (NGs) produced from whole cell membranes of mesenchymal stem cells (MSCs). MSC are well known for their natural targeting of multiple cancers and hypo-immunogenicity. Encompassing MSC surface proteins and armed with their unique targeting capabilities, the MSC-NGs may be loaded with various drugs and nucleic acids and can be selectively targeted against multiple cancers. Such a universal targeting platform can meet the three major prerequisites for an ideal delivery system: biocompatibility, long circulation time, and selectivity. It also represents a much more clinically relevant approach than conventional delivery systems as it avoids the elaborate production and incorporation of targeting moieties into delivery vehicles. Demonstrating its efficacy on tumors, we will elaborate on its specificity and the wide range of applications, which such platform can clinically address. The NGs platform can also contribute to our understanding of cancer progression and can readily be extended to cancer imaging and diagnostics, paving the way to possible treatments of other diseases, manifested by the expression of unique targetable.
Mechanism and Efficacy of Macrophage-Targeted Drug-Encapsulating Liposomes in Cardiovascular Repair

Rimona Margalit¹ and Jonathan Leor²

¹Department of Biochemistry and Molecular Biology, The George S. Wise Faculty of Life Sciences, Tel Aviv University, Tel Aviv, Israel. ²Neufeld Cardiac Research Institute, Tel Aviv University, Sheba Center for regenerative Medicine, Stem Cells, and Tissue Engineering, Israel, Tamman Cardiovascular research Institute Tel-Hashomer, Israel.

Email: rimona@tauex.tau.ac.il

Myocardial infarction (MI) is the most common cause of acute heart injury. The role macrophages have in controlling the post-MI progression and resolution of inflammation makes them an attractive therapeutic target, aiming at modulation of the pro-inflammatory macrophages (M1), switching them to the anti-inflammatory, reparative macrophages (M2). Based on its reported potential for M1 to M2 modulation, we focused on hemin (the iron-porphyrin complex) as a drug candidate for the treatment of MI patients. Hemin is thought to exert its anti-inflammatory effect through its involvement with the intracellular enzyme heme oxygenase 1 (HO-1), for which hemin is both an inducer and a substrate. Free hemin is prone to the well-known deficiencies of treatment with free drugs, that frequently result in poor therapeutic responses and treatment failures. To address this situation we formulated hemin in a special type of liposomes that we have previously shown to be macrophage-targeted - liposomes that have hyaluronan bound covalently to their surface (denoted HA-LP). Hemin/HA-LP induced significant anti-inflammatory activity in mouse and on human macrophage cell lines, whereas the same doses of free hemin had no effect. Administering HA-LP to mice that have undergone MI showed significant in vivo active targeting, namely extensive liposome accumulation in the infarcted heart and little or no accumulation elsewhere. Equi-doses of free and of liposomal hemin (Hemin/LP) were administered (iv injection to the tail vein) to MI mice. Hemin/HA-LP outperformed free hemin and generated a significant increase in the M2/M1 ratio for both peritoneal and heart macrophages, as well as improved heart function and enhanced healing and repair. Insight into the operating mechanism were pursued by following the impact of free and liposomal hemin on intracellular levels of active HO-1. The studies showed that the differences between the free and liposomal hemin is quantitative rather than qualitative, with a minor positive role for the HA-LP themselves. In summary, hemin in the macrophage-targeted liposomes is a novel strategy for treatment post MI, switching macrophages into an anti-inflammatory phenotype, elevating HO-1 expression and improving cardiac remodeling and dysfunction.
Nanomedicines are 1-100 nm-sized carrier materials designed to improve the pharmacokinetics and the biodistribution of low-molecular-weight (chemo-) therapeutic agents. By delivering drug molecules more efficiently to pathological sites, and by preventing them from accumulating in potentially endangered healthy tissues, nanomedicines are able to improve the balance between efficacy and toxicity. Nanomedicines rely on the Enhanced Permeability and Retention (EPR) effect, which is notoriously known to be highly variable, in particular in patients. To overcome this high variability, several strategies have been envisaged to improve EPR-based nanomedicine treatments, including enhancement, combination, avoidance and imaging. In the present lecture, I will highlight several of these approaches. In addition, I will provide some recent evidence showing that image-guided nanomedicines can be used to target metastatic cancer lesions, to treat inflammatory disorders and to facilitate drug delivery to the brain.
Novel Cancer Models-Based Identification of Targets for the Rational Design of Precision Theranostic Nanomedicines

Ronit Satchi-Fainaro
Department of Physiology and Pharmacology, Sackler School of Medicine, Tel Aviv University, Tel Aviv 6997801, Israel.
Email: ronitsf@post.tau.ac.il

Tumor progression is dependent on a number of sequential steps, including initial tumor-vascular interactions and recruitment of blood vessels (i.e., the “angiogenic switch”), as well as an established interaction of tumor cells with their surrounding microenvironment and its different immune, endothelial and connective cellular and extra-cellular components. Failure of a microscopic tumor, either primary, recurrent or metastatic, to complete one or more of these early stages may lead to delayed clinical manifestation of the cancer (i.e., tumor dormancy). Micrometastasis, dormant tumors, and residual tumor cells – referred to as minimal residual disease, contribute to the occurrence of relapse, and constitute fundamental clinical manifestations of tumor dormancy that together are responsible for the vast majority of cancer deaths. However, although the tumor dormancy phenomenon has critical implications for early detection and treatment of cancer, it is one of the most neglected areas in cancer research and the associated biological mechanisms are still mostly unknown.

We have created several models of patient-derived xenografts mimicking pairs of dormant vs fast-growing, primary vs metastatic and drug-sensitive vs resistant cancers. We investigated the molecular and cellular changes in tumor-host interactions that govern tumor dormancy. Those led to the discovery of novel targets and provided important tools for cancer theraistics (therapy and diagnostics). Based on the acquired knowledge, we designed a new strategy to improve treatment outcomes of patients with bone neoplasms, glioblastoma, brain metastases, melanoma, breast and prostate cancers. We have identified molecular signatures that, following selective delivery into their target cells, can potentially induce a dormant-like phenotype. This goal was achieved by utilizing polymeric nanomedicines and guidance by high resolution, intravital non-invasive imaging techniques.

A better understanding of tumor dormancy and the availability of relevant markers will most likely change the way we diagnose and treat the disease using novel combined theranostic nanomedicines.
A Bridge to Silencing: Co-Assembling Anionic Nanoparticles of siRNA and Hyaluronan Sulfate via Calcium Bridges

Efrat Forti¹, Olga Kryukov¹, Edan Elovic¹, Matan Goldstein¹, Efrat Korin¹, Gal Margolis¹, Emil Ruvinov¹, Smadar Cohen¹⁻³

¹Avram and Stella Goldstein-Goren Department of Biotechnology Engineering,
²Regenerative Medicine and Stem Cell (RMSC) Research Center,
³The Ilse Katz Institute for Nanoscale Science and Technology,
Ben-Gurion University of the Negev, Beer-Sheva, Israel

Email: scohen@bgu.ac.il

Synthetic small interfering RNA (siRNA) molecules have emerged as a promising therapeutic, effectively suppressing specific gene expression at mRNA level. Yet, the clinical translation of siRNA therapeutics is limited due to delivery challenges. In my talk, I will introduce the features of anionic siRNA nanoparticles (NPs) co-assembled by the electrostatic interactions of semi-synthetic polysaccharide hyaluronan-sulfate (HAS), with siRNA, mediated by calcium ion bridges. The NPs have an average size of 130 nm and a mild (-10 mV) negative surface charge. Transmission electron microscopy (TEM) using gold-labeled components and X-ray photoelectron spectroscopy (XPS) demonstrated the spatial organization of siRNA molecules in the particle core, surrounded by a layer of HAS. The anionic NPs efficiently encapsulated siRNA, were stable in physiological-relevant environments and were cytocompatible. Efficient cellular uptake of the anionic siRNA NPs, associated with potent gene silencing (>80%), was observed across multiple cell types, including murine primary peritoneal macrophages and human hepatocellular carcinoma cells. In a clinically-relevant model of acute inflammatory response in IL-6-stimulated human hepatocytes, STAT3 silencing induced by HAS-Ca²⁺-siRNA NPs resulted in marked decrease in the total and activated STAT3 protein levels, as well as in the expression levels of downstream acute phase response genes. Collectively, anionic NPs prove to be an efficient and cytocompatible delivery system for siRNA.
A Rational Drug Delivery Approach Against Tumor Resistance to Anti-Angiogenic Therapy

Karsh-Bluman A., Schwob O., Shoval H. Benny O.

Institute for Drug Research, The School of Pharmacy, Faculty of Medicine, Ein Karem Medical Center The Hebrew University of Jerusalem
Email: OfraB@ekmd.huji.ac.il

At the recent years anti-angiogenic drugs that aim to suppress blood vessel formation are in clinical use as first or second line therapy in cancer. Despite indications of benefit in certain types of cancers, usually in combination therapy, the great promise of anti-angiogenic therapy as demonstrated in numerous pre-clinical studies is yet to be fulfilled. The clinical efficacy of these drugs – particularly as monotherapies – remains relatively modest and in practice anti-angiogenic treatment becomes less effective at inhibiting tumor growth over time.

We now propose a potential mechanism that may contribute to tumor evasion in prolonged anti-angiogenic therapy based on modification of the tumor microenvironment. One of the clinical outcomes of long term anti-angiogenic therapy is the accelerated necrosis induced by hypoxia and metabolic stress. Although tissue necrosis is an overall positive outcome of treatment it also plays as a double edge sword; we found that necrotic signals which belong to the Damage-associated molecular pattern molecules (DAMP), and particularly one of the member protein, High Mobility Group Box 1 (HMGB1), acts as pro-angiogenic factor that contribute to revascularization of tumors leading to tumor evasion. Based on our finding we propose to introduce a rational combination therapy of anti-angiogenic drug coupled with antagonists of necrotic signals to achieve a durable therapeutic effect. This strategy may offers a novel platform for combinatory therapy with reduced tumor resistance which can be broaden to cytotoxic therapies.
Polymeric Conjugate Nanocarriers for On-Demand Drug Delivery

Yanjun Zhao
School of Pharmaceutical Science & Technology, Tianjin University, 92 Weiin Road, Nankai District, Tianjin 300072, China.
Email: zhaoyj@tju.edu.cn

Nanomedicine has been gaining increasing interests for enhanced therapeutic outcomes in managing intractable diseases (e.g. cancer). Engineered polymeric conjugate plays a unique role in nanomedicine as a versatile nano-platform for efficient drug delivery. For example, amphiphilic Polymeric conjugate micellar nanocarriers could integrate various benefits including enhanced aqueous solubility & stability, coupled passive and active targeting, sufficient cargo loading, ease of co-delivery, abundance of biocompatible building blocks available, and tunable particle size, shape and surface chemistry (Fig. 1).

The first part of this presentation explores a multi-targeting pleiotropic agent, curcumin and monovalent linear poly(ethylene glycol)-co-poly(lactic acid) as the model drug and polymer, respectively. Different types of stimuli-responsive conjugate nanocarriers are introduced and compared. The role of conjugate architecture, residue analysis, and sufficient loading in determining drug delivery efficiency is discussed [1-3]. The second part describes a special polymeric conjugate, surface-engineered dendrimers for on-demand drug delivery. The low molecular weight polyethylenimine-conjugated poly(amido amine) dendritic conjugate shows comparable gene delivery efficiency with reduced toxicity [4]. A dendritic nano-system containing tailor-made periphery moiety can achieve both controlled intracellular drug release, and facilitated endosomal escape [5, 6]. Finally, a self-triggered pressurized nanofoam topical delivery system is presented to address the dilemma of premature and on-demand drug release regarding topical nano-formulations [7, 8].

![Figure 1. Amphiphilic polymeric conjugate containing functional moieties, and its self-assembly into multifunctional micellar nanocarriers.](image_url)

References
The field of medicine is taking its first steps towards patient-specific care. Our research is aimed at tailoring treatments to address each person’s individualized needs and unique disease presentation. Specifically, we are developing nanoparticles that target sites of cancer where they help predict which medication is most suitable for each patient.

Metastasis is the cause of 90% of cancer deaths. In many cases, by the time a primary tumor is detected, subsets of malignant cells have already disseminated to other locations in the body seeding the spread of the disease. Nanoparticles have many potential benefits for treating metastatic cancer, including the ability to transport complex molecular cargoes, as well as targeting to specific cell populations.

The talk will describe principles for developing lipid nanoparticles that can be remotely triggered to perform a programmed therapeutic task in a disease site. Specifically, these systems utilize molecular-machines to synthesize therapeutic proteins onsite. The promise of such systems for treating metastatic cancer will be addressed.
Proteins, peptides, oligonucleotides, and small interfering RNA duplex (siRNAs) typically exhibit poor membrane permeability and high sensitivity to heat, pH, and enzymatic degradation. Furthermore, these hydrophilic biomacromolecules suffer from short biological half-lives and rapid clearance limiting their clinical applications. Most of the drawbacks can be overcome by incorporating such active macromolecules in adequate nanocarriers which can prolong their blood circulation and intracellular delivery into targeted pathological tissues. Antisense oligonucleotides (ASOs) with great potential for the treatment of Duchenne Muscular Dystrophy (DMD) caused by mutated pre-mRNA are currently the most promising therapy for DMD patients. It is expected that soon two new ASO drugs will enter the market, Sarepta Therapeutics’ eteplirsen and BioMarin/Prosensa’s drisapersen. The issue of limited dosage (mostly due to nephrotoxicity and hepatotoxicity) hampers their potential activity and still needs to be addressed. The objective of the present study was to develop novel nanodelivery systems that will double-encapsulate ASOs and provide protection, sustained release, and improved cells uptake and therapy, compared to their parenteral administration in solution following administration of much lower doses, avoiding or minimizing possible side effects and renal toxicities. The first line of protection is achieved by loading the ASO into primary nanoparticles (PNPs ~100 nm) made from crosslinked human serum albumin (HSA), containing the cationic lipid DOTAP (1,2-dioleoyl-3-trimethylammonium-propane), to increase loading of the negatively-charged ASO molecules and to further facilitate endosomal escape following cell internalization. The second line of stability is obtained by further encapsulating the PNPs into sub-micron capsules (i.e. nanocapsules or DNCs <1µm), made from PLGA (Poly D,L-lactic-co-glycolic acid), with or without PEG moieties, using a novel technique of nano spray drying (launched by Buchi in 2009). The main findings up to now are that a weekly administration of PNPs up to 2 mg/mouse (loaded with 100µg of active ASO) was well tolerated by the mice (n=3). Pathology of the spleen, liver, kidney, lungs, heart and brain found all examined tissues to be within normal range. New formation of dystrophin was observed in quadriceps muscles, already at the low dosage (1 mg/mouse), with significantly more positive dystrophin fibers formation in the mice treated with 2 mg/mouse. It should be emphasized that a weekly administration of up to 3 mg/mouse, was well tolerated for blank DNCs but not for active DNCs (loaded with 60µg ASO) whereas a weekly administration of active DNCs 1.5mg/mouse (30µg ASO), produced modest positive dystrophin fibers.

To the best of our knowledge, this work is the first attempt to produce double-nanocarriers using the nano spray-drying technique. The main advantage of the platform developed in this project is the preparation of the final product in the form of a dry powder easily dispersed prior to injection. Encouraging results were achieved in terms of loading capacity, drug content, extended in vitro drug release without a burst effect, cellular uptake, and preliminary efficacy results in animal models.
Injectable materials often have shortcomings in mechanical and drug-eluting properties that are attributable to their high water contents. For example, tissue adhesives such as cross-linked hydrogels adhere very weakly to tissues while polymersomes are often impermeable to many small organic molecules and as a result show a limited or slow release rate. These drawbacks are related in part to the high molecular weight of currently used biomaterials, that are solid in their basic form and therefore require a high solvent content in order to be administrated. In this presentation I will discuss new strategies for designing neat (without solvent) biomaterials for medicine and biotechnology as well as new concepts in drug delivery and tissue reconstruction. These biomaterials possess the following advantages: (a) they are liquid at room temperature and, therefore, can be applied without the need of solvent; (b) although they have low viscosity at room temperature, they can rapidly harden when crosslinked; (c) they possess a higher number of potentially reactive end groups per molecule compared to high molecular weight polymers of similar molecular weight; and (d) they have low immunogenicity and toxicity.
Enzyme Responsive Micellar Nano-Carriers

Assaf J. Harnoy, Ido Rosenbaum, Liat Frid, Marina Buzhor, Merav Segal, Yael Cohen, Gadi Slor, Natalya Weber and Roey J. Amir

Department of Organic Chemistry, School of Chemistry, Faculty of Exact Sciences, and the Tel Aviv University Center for Nanoscience and Nanotechnology, Tel Aviv University, Tel Aviv 6997801, Israel

Email: amirroey@post.tau.ac.il

Stimuli-responsive polymers have emerged as attractive candidates for the fabrication of smart micellar nanocarriers that can release their molecular payload only at the target tissue. Such micelles are designed to disassemble and release their encapsulated cargo upon external stimuli, such as changes in pH, temperature or irradiated light. Among the various types of stimuli, enzymes are especially attractive for the activation of biomedical carriers due to their overexpression in various diseases. In this talk we will present a highly modular design for the simple and efficient synthesis of amphiphilic block copolymer hybrids based on a linear hydrophilic polyethyleneglycol (PEG) and an enzyme-responsive hydrophobic dendron. These amphiphilic hybrids self-assembled in water into smart micelles that could disassemble and release their encapsulated molecular cargo upon enzymatic activation. The high modularity of these PEG-dendron hybrids offers great control over the disassembly rates of the formed micelles by simply tuning the length of the PEG. Further control over the release rate can be obtained by adjusting the loading approach: while non-covalent encapsulation allowed faster release, covalent-binding of the molecular cargo resulted in higher loading capacity and significantly slower release rates. These enzyme-responsive amphiphilic hybrids could potentially be applied in the future as nanocarriers with adjustable release rates for biomedical delivery applications.

References
Liposomes’ Based Steroidal Nano-Drug Prevents Cerebral Malaria

Jacob Golenser¹, , Judith H. Waknine-Grinberg¹,², and Yechezkel (Chezy) Barenholz².

¹Laboratory of Membrane and Liposome Research, Department of Biochemistry, Institute for Medical Research–Israel-Canada (IMRIC), The Hebrew University – Hadassah Medical School, Jerusalem, Israel. ²Department of Microbiology and Molecular Genetics, The Kuvin Center for the Study of Infectious and Tropical Diseases, The Hebrew University – Hadassah Medical School, Jerusalem, Israel

Email: chezyb1@gmail.com

Cerebral malaria (CM) is the most severe complication of Plasmodium falciparum infection, and a leading cause of death and long term cognitive damage in children under the age of five in malaria-endemic areas. We report high therapeutic efficacy of a novel formulation of liposome-encapsulated water-soluble glucocorticoid prodrugs, and in particular the novel pro-drug β-methasone hemisuccinate (BMS), for treatment of experimental cerebral malaria (ECM). BMS is a novel derivative of the potent steroid β-methasone which is an amphiphatic weak acid, and was specially synthesized to enable remote loading by trans membrane calcium acetate gradient into nano-sterically stabilized liposomes (nSSL), to form nSSL-BMS¹ also referred to as BMS-nano-drug. This novel BMS-nano-drug, composed of nSSL remotely loaded with BMS by trans membrane calcium acetate gradient, dramatically improves drug efficacy and abolishes the high toxicity seen upon administration of free BMS². nSSL-BMS reduces ECM rates in a dose-dependent manner and creates a survival time-window, enabling administration of an anti-plasmodial drug, such as artemisone. Administration of artemisone after treatment with the nSSL-BMS results in complete cure of the malaria. Treatment with BMS leads to lower levels of cerebral inflammation, demonstrated by changes in: cell markers cytokines and chemokines levels (in both mRNA² and the proteins³), as well as diminished hemorrhage and edema, correlating with reduced clinical score². Administration of the BMS nano-drug results in accumulation of BMS in the brains of sick mice but not of healthy mice. Free BMS did not reach the brain in measurable values. This steroidal nano-drug effectively eliminates the adverse effects of the cerebral syndrome even when the treatment is started at late stages of disease, in which disruption of the blood-brain barrier has occurred and mice show clear signs of neurological impairment. Overall, combined treatment with nSSL-BMS and artemisone may be an efficacious and well-tolerated therapy modality for prevention of CM, elimination of parasites, and prevention of long-term cognitive damage.

References
