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Organizing Committee

Assaf Zinger

Avi Schroeder's lab, Faculty of Chemical Engineering, Technion

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31 years old, was born and raised in Safed. Assaf is married to Noa and they are expecting their first daughter.

Assaf's research deals with a new way to perform surgery without a knife, specifically, using enzymes that degrade tissue with molecular accuracy, thereby enhancing recovery and reducing pain.

Organizing Committee

Maya Bar-Zeev

Yoav Livney's lab, Faculty of Biotechnology and Food Engineering, Technion

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Maya received her B.Sc (*Summa cum laude*) in Pharmaceutical Engineering from the Jerusalem College of Engineering (2011). She joined Prof. Livney's group in 2011. Maya is currently a PhD direct track student of the Norman Seiden international multidisciplinary graduate program of nanoscience and nanotechnology. Her research is done under the co-supervision of Prof. Yehuda Assaraf, PI of the Fred Wyszkowski Cancer Research Laboratory and dean of the Biology Faculty. Maya's research focuses on the development of milk protein based nano-vehicles for oral delivery of targeted chemotherapeutic combinations to overcome multidrug resistance in cancer.

Organizing Committee

Zvi Yaari

Avi Schroeder's lab, Faculty of Chemical Engineering, Technion

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Zvi Yaari received his B.Sc. in Biochemical Engineering from the Technion – Israel Institute of Technology in 2012. Zvi joined the group of Prof. Avi Schroeder in the Department of Chemical Engineering. Currently, he is performing his Ph.D. research in the fields of nanotechnology and personalized cancer care. By fabricating Theranostic Barcoded Nanoparticles, Zvi aims to screen multiple drugs inside the patient's body to find the most potent drug.

Organizing Committee

Tsuf Croitoru-Sadger

Boaz Mizrahi's lab, Faculty of Biotechnology and Food Engineering, Technion

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Tsuf received her B.Sc. in Chemical Engineering in 2014 and her M.Sc in Biotechnology and Food Engineering in 2016, both from the Technion – Israel Institute of Technology.

She joined the laboratory for biomaterials under the supervision of Prof. Mizrahi on March 2014. Currently, she is a Ph.D. student. Her research interest focused on 3D printer, using unique printing technics, which includes injections of liquid bio-polymers in order to create novel type of scaffolds.

Organizing Committee

Michal Shevach

Tal Dvir's lab, Faculty of Life Sciences and the Center for Nanoscience and Nanotechnology,
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Michal received her B.Sc (*summa cum laude*) from the Technion Biomedical Engineering faculty in 2009. In 2010, Michal joined Dr. Dvir's lab for tissue engineering and regenerative medicine. She is in the final year of her Ph.D studies in the direct Ph.D program. Michal develops novel "smart" biomaterials for regeneration of cardiac and neural tissues.

Plenary Lecture

Dr. Alon Seri-Levy, CEO, Sol-Gel Technologies

TURNING CONTROL RELEASE TECHNOLOGY INTO PRODUCTS: THE STORY OF SOL-GEL

Sol-Gel is an Israeli pharmaceutical company that develops and commercializes innovative and generic topical skin medications, some based on proprietary microencapsulation controlled release technology for more effective treatment and better patient adherence and outcomes. The journey of Sol-Gel from innovation of a controlled release technology to products on the market will be told.

Plenary Lecture

Prof. Dan Peer, Laboratory of Precision Nanomedicine,

ICRS President, Tel-Aviv University

FROM A CONCEPT IDEA TO A NOVEL CLINICAL MODALITY

The traditional "one treatment fits all" paradigm disregards the heterogeneity between patients, and within a particular disease, thus limit the success of common treatments. Moreover, current treatment lacks specificity and therefore most of the drugs induce some types of adverse effects. Personalized medicine aims to individualize therapeutic interventions, based on the growing knowledge of the human multiple '-oms' (e.g. genome, epigenome, transcriptome, proteome and metabolome), which has led to the discovery of various biomarkers that can be used to detect for example, early stage cancers and predict tumor progression, drug response, and clinical outcome. Nanomedicine, the application of nanotechnology to healthcare, holds great promise for revolutionizing disease management such as drug delivery, molecular imaging, reduced adverse effects and the ability to contain both therapeutic and diagnostic modalities simultaneously termed theranostics. Personalized nanomedicine has the power of combining nanomedicine with clinical and molecular biomarkers ("OMICS" data) achieving improve prognosis and disease management as well as individualized drug selection and dosage profiling to ensure maximal efficacy and safety. In this presentation I will discuss the immense potential of combining the best of these two worlds, nanomedicine and high throughput OMICS technologies to pave the way towards personalized medicine. Examples will be given from the fields of inflammatory bowel diseases, cancer and rare genetic diseases.

Presenters

Stav Shamir, Ben-Gurion University - shamir.stav@gmail.com

BIO-INSPIRED ANIONIC NANOPARTICLES FOR DELIVERY OF PLASMID DNA

Stav Shamir, Efrat Forti, Matan Goldstein, Smadar Cohen

Gene therapy is a promising strategy for the treatment of many diseases including cancer and various genetic disorders by target-specific delivery of therapeutic genes. We are developing a novel anionic nanoparticle (NP) for targeted delivery of plasmid DNA (pDNA). The NPs are assembled by the electrostatic interactions of a modified natural polysaccharide, alginate sulfate (AlgS), with pDNA, mediated by interactions with calcium ion. Characterization of the NPs by dynamic light scattering (DLS) and zeta potential measurements showed an average size of 103±2.8 nm (SEM, n=5) and a mild negative surface charge of -5.8±0.3 (SEM, n=9). Encapsulation efficiently was estimated by ethidium bromide exclusion assay and found to be 62.2% ± 0.8% (SEM, n=9). The pDNA NPs did not affect cell viability, and efficient cellular uptake of fluorescently-labeled anionic pDNA NPs was observed (95%) in the human breast cancer cell line MDA-MB 231 by imaging flow cytometry. Collectively, anionic pDNA NPs show a promise to be an efficient and cytocompatible delivery system for pDNA.

Presenters

Hadas Gibori, Tel-Aviv University - hadas.gibori@gmail.com

TARGETING PANCREATIC DUCTAL ADENOCARCINOMA WITH A POLYMERIC NANOCARRIER AND AN ANTICANCER MICRORNA POLYPLEX

Hadas Gibori, Shay Eliyahu, Adva krivitsky, Ronit Satchi-Fainaro

Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive malignancy and currently the fourth leading cause of cancer death in the United States. The high mortality and poor prognosis are due to extensive metastasis and lack of early diagnostic markers and symptoms. In spite of advances in chemo therapies, the 5-year survival rate is still less than 5%, indicating the ineffectiveness of current approaches to treatment.

MicroRNAs, after being demonstrated as deregulated in cancer, are now being explored as therapeutic targets for cancer treatment. Reversion of miRNA expression to normal levels can restore perturbed cellular homeostasis. Importantly, the heterogeneity and complexity of cancer suggests that the only way to successful treatment might lie with the simultaneous targeting of multiple genes, further emphasizing the therapeutic potential of miRNAs. miR-34a, a master regulator of tumor suppression, is downregulated in numerous cancers including PDAC and inhibits malignant growth by repressing oncogenic genes.

Efficient delivery of miRNA for therapeutic purposes is extremely challenging due to low cellular uptake, RNases degradation and rapid renal clearance. Therefore, we synthesized a novel polymeric nanocarrier to deliver microRNAs to tumors and their vasculature. Our nanocarrier was able to complex electrostatically with miR-34a and form therapeutically active nano-scaled polyplexes. The polymer enhanced the internalization of miR-34a in its active form into human PDAC cells, as the miR was capable of downregulating four of its direct target genes. miR-34a delivered by the nanocarrier could also inhibit growth, clonogenicity and cell cycle of PDAC cells. Systemic administration of polymer-siRNA nanoplexes to orthotopically-inoculated pancreatic tumors showed no toxicity and accumulated selectively at the tumor site warranting its potential as a novel therapeutic for PDAC.

Presenters

Ranit Kedmi, Tel-Aviv University - ranit.kedmi@gmail.com

SYSTEMIC GENE SILENCING IN PRIMARY T LYMPHOCYTES USING TARGETED LIPID NANOPARTICLES

Ranit Kedmi, Srinivas Ramishetti, Meir Goldsmith, Fransisca Leonard, Andrew G. Sprague, Biana Godin, Michael Gozin, Pieter R. Cullis, Derek M. Dykxhoorn, Dan Peer

Modulating T cell function by down-regulating specific genes using RNA interference (RNAi) holds tremendous potential in advancing targeted therapies in many immune-related disorders including cancer, inflammation, autoimmunity, and viral infections. Hematopoietic cells, in general, and primary T lymphocytes, in particular, are notoriously hard to transfect with small interfering RNAs (siRNAs). Herein, we describe a novel strategy to specifically deliver siRNAs to murine CD4þ T cells using targeted lipid nanoparticles (tLNPs). To increase the efficacy of siRNA delivery, these tLNPs have been formulated with several lipids designed to improve the stability and efficacy of siRNA delivery. The tLNPs were surface-functionalized with anti-CD4 monoclonal antibody to permit delivery of the siRNAs specifically to CD4þ T lymphocytes. Ex vivo, tLNPs demonstrated specificity by targeting only primary CD4þ T lymphocytes and no other cell types. Systemic intravenous administration of these particles led to efficient binding and uptake into CD4þ T lymphocytes in several anatomical sites including the spleen, inguinal lymph nodes, blood, and the bone marrow. Silencing by tLNPs occurs in a subset of circulating and resting CD4þ T lymphocytes. Interestingly, we show that tLNP internalization and not endosome escape is a fundamental event that takes place as early as 1 h after systemic administration and determines tLNPs efficacy. Taken together, these results suggest that tLNPs may open new avenues for the manipulation of T cell functionality and may help to establish RNAi as a therapeutic modality in leukocyte-associated diseases.

Presenters

Efrat Forti, Ben-Gurion University - efrat.forti@gmail.com

SIRNA DELIVERY PLATFORM BASED ON CO-ASSEMBLING ANIONIC NANOPARTICLES OF SIRNA AND HYALURONAN SULFATE VIA CALCIUM BRIDGES

Efrat Forti, Olga Kryukov, Edan Elovic, Matan Goldstein, Efrat Korin, Gal Margolis, Felder Shani, Emil Ruvinov, Smadar Cohen

Therapeutic implementation of gene silencing using small interfering RNA (siRNA) relies on the critical need for a safe and effective carrier for siRNA protection, capable of strong but reversible complexation, cellular uptake, and cytoplasmatic unloading of its cargo. We developed anionic siRNA nanoparticles (NPs) co-assembled by the electrostatic interactions of the semi-synthetic polysaccharide hyaluronan-sulfate (HAS), with siRNA, mediated by calcium ion bridges. Physical characterization of the HAS-Ca2+-siRNA NPs, using high resolution microscopy and dynamic light scattering (DLS), showed the formation of stable nanosized complexes ~130 nm in diameter, bearing mild (~−10 mV) negative surface charge. 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 extremely stable in physiological-relevant environments and were cytocompatible, not affecting cell viability or homeostasis. The anionic siRNA NPs, successfully induced potent gene silencing (>80%) across multiple cell types, including murine primary peritoneal macrophages, human hepatocellular carcinoma cells, and human breast cancer cells. The potential toxic effects of anionic NP formulation were tested in mice, following single intravenous injection (IV) of HAS-Ca2+-siRNA. Results showed that acute administration of the HAS-Ca2+-siRNA NPs at a dose of 3.3 mg/kg siRNA via the intravenous (IV) route was not associated with toxic risk. Collectively, the developed anionic NPs were shown to be an efficient and cytocompatible platform for enhancing the therapeutic efficiency of siRNA.

Presenters

Hagit Shalom, Technion - hagitsh@campus.technion.ac.il

INVESTIGATING THE DISTRIBUTION OF MODIFIED NANO-GHOSTS FOR CANCER THERAPY AND USING FLUORESCENT DYES FOR THEIR LOCALIZATION

Hagit Shalom, Yael Lupu, Marcelle Machluf

The ultimate goal in cancer drug-delivery is producing a selective targeted system for cancer. Targeted drug-delivery systems are designed to reach the tumor, and thus reduce side-effects and improve efficacy. These targeted systems are usually engineered by conjugating them with moieties that improve their selectivity. In our lab we developed a novel targeted delivery system for cancer therapy, which is based on cell-derived nano-vesicles termed Nano-Ghosts (NGs) produced from the plasma membrane of human Mesenchymal Stem Cells (hMSCs). These NGs benefit the surface molecules of the MSCs and thus may preserve their unique targeting capabilities toward cancer, which are responsible for cell-cell and cell-matrix interactions. In this work we aim to elucidate the mechanism of interactions between the NGs and cancer cells, by characterization and modification of the NGs delivery-system. This approach may not only yield crucial information on MSCs involvement in cancer and metastasis progression, but may also provide means to increase the tumor targeting properties of the NGs. We discovered that stimulation of the MSCs with cytokines or cancer conditioned growth media prior to NGs production affect cellular uptake. Furthermore, in order to better localize and identify the NGs in vitro and in vivo, without harming the functionality of this unique delivery system, we loaded the NGs successfully with Dylight 488®. The Dylight 488® was loaded passively through the NGs' preparation process and also by electroporation post preparation. Loading the NGs with fluorescent dyes may overcome the drawbacks associated with labeling tracers.

Presenters

Marina Buzhor, Tel-Aviv University - marinabu@mail.tau.ac.il

SPECTRALLY ACTIVE MICELLAR NANOCARRIERS

Marina Buzhor, Roey J. Amir

The need for new imaging probes and delivery platforms requires the development of advanced smart systems that change their structure and spectral properties in response to external stimuli, which allows specific monitoring. To address this challenge we present a new molecular design of labeled enzyme-responsive amphiphilic hybrids that are composed of a linear hydrophilic polyethyleneglycol (PEG) block and an enzymatically responsive dendron as a hydrophobic block. We examine two different imaging approaches by simply changing the labeling moiety of the system either with a fluorescent marker [1] or with a fluorinated group (19F MR). In aqueous solution, the labeled PEG-dendron hybrids self-assemble into micelles and exhibit an "OFF" signal due to intermolecular dye-dye interactions or the low mobility of the 19F probes. Enzymatic cleavage of the hydrophobic end-groups increases the hydrophilicity of the hybrids, leading to disassembly of the micelles. This enzymatically induced structural change is translated into an "ON" signal of the fluorescent response due to the elimination of the dye-dye interactions or of the 19F MR caused by increase in the mobility of the 19F moieties. This highly modular approach enables generation of customized spectral activities in response to enzymatic activation of non-responsive labeling dyes.

Presenters

Gadi Slor, Tel-Aviv University - gadis@mail.tau.ac.il

DUAL STIMULI-RESPONSIVE POLYMERIC MICELLES AS A MODULAR PLATFORM FOR CONTROLLED DELIVERY

Gadi Slor, Assaf Harnoy, Roey Amir

Stimuli responsive micelles are highly attractive platforms for encapsulation of hydrophobic drugs or dyes, which can be loaded into the hydrophobic core of the micelles and released upon specific stimuli. Most reported systems showed that different types of stimuli such as pH changes, light and temperature could cause the disassembly of the micelles. More recently, others and we have reported the utilization of enzymatic stimuli to induce the disassembly of enzyme-responsive micelles. In this work, we demonstrate the incorporation of two different responsive groups that can respond to two different types of stimuli. Combining two stimuli can lead to higher degree of activation and to increase the efficiency of the drug delivery system. Furthermore, the utilization of two different responsive groups can open the way for greater control over the release profile of the delivery system.

Presenters

Hen Popilski, Ben-Gurion University - popilski@post.bgu.ac.il

INCORPORATION OF PENETRATION ENHANCERS INTO INTRA-TUMORAL BIODEGRADABLE POLYMERIC IMPLANTS AND THEIR EFFECT ON ANTICANCER DRUG DISPOSITION

Hen Popilski, David Stepensky

Anti-cancer drug delivery systems (DDSs) are designed to target chemotherapeutic drugs to their site of action in solid tumors, enhance their efficiency and reduce the incidence of adverse events. Unfortunately, currently available anti-cancer DDSs possess extremely low targeting efficiency and thereby present limited pharmacological effect and poor safety profile. Even following intra-tumoral (I.T.) administration of DDS, only a thin layer of the tumor cells that surround the implant are exposed to the therapeutic concentrations of anti-cancer drug.

We hypothesize that modulation of intra-tumoral drug distribution by penetration enhancers will increase the exposure of the tumor cells to the chemotherapeutic drugs and will increase the efficiency of the anti-cancer treatment.

We are investigating anti-cancer effects of intra-tumoral DDSs that encapsulate paclitaxel and specific penetration enhancers in the 4T1-Luc orthotropic breast cancer model in BALB/c mice. The experimental results demonstrate improved response to paclitaxel, significant decrease in tumor mass and reduced number of lung metastases in tumor mice treated with polymers containing various penetration enhancers. We aim to identify the optimal DDS formulation composition that would maximize the anti-cancer effects in the tumor that will be devoid of systemic adverse effects. To this end, we apply detailed histological and imaging tools to determine the effect of penetration enhancers on the intratumoral disposition and anti-cancer effects of the chemotherapeutic agent.

Presenters

Michal Rosenberg, Technion - michirosros@gmail.com

NANOSTRUCTURED POROUS SILICON FOR DELIVERY OF NERVE GROWTH FACTOR

Michal Rosenberg, Neta Zilony, Liran Holtzman, Orit Shefi, Ester Segal

Nerve growth factor (NGF) has been well characterized for its essential role in the development and maintenance of neurons both in the peripheral and central nervous systems. Potential therapeutic applications of this protein have been demonstrated in several models of neurodegenerative diseases, including Alzheimer's and Parkinson's. In particular, external administration of NGF exhibits protective properties for injured neurons and stimulates axonal regeneration. However, NGF effectiveness in therapeutics is limited by its short biological half-life due to rapid enzymatic degradation in vivo. Therefore, there is an immense need for delivery systems that will allow for sustained release of NGF. Nanostructured porous silicon (PSi) is characterized by several particularly appealing tunable properties predestining it for design of drug delivery systems, including high surface area, biocompatibility and ability to degrade completely in physiological environment. Our work aims to develop new PSi-based carriers for NGF delivery as an approach to prolong its bioavailability and promote neuronal differentiation. Different PSi nanostructures are fabricated by anodic electrochemical etching of single-crystalline Si wafers and the synthesis conditions are adjusted to allow efficient protein loading by physical adsorption. We demonstrate that NGF entrapment within the PSi carriers increases the protein stability while allowing for its sustained release to promote differentiation and neurite outgrowth of PC12 cells over a period of 14 days, within a single administration.

Presenters

Ron Feiner, Tel-Aviv University - feineron@gmail.com

ENGINEERED FREE-STANDING CARDIAC PATCHES WITH BUILT-IN ELECTRONICS FOR ON-LINE MONITORING AND REGULATION OF TISSUE FUNCTION

Ron Feiner, Leeya Engel, Sharon Fleischer, Maayan Malki, Assaf Shapira, Yosi Shacham-Diamand, Tal Dvir

Cardiac tissue engineering is envisioned as a regenerative therapy to treat myocardial infarction. In this approach cardiac cells are seeded within three-dimensional (3D) porous scaffolds to create functional cardiac patches. Despite the incremental improvements in the field, no technology is currently available that can provide on-line monitoring and reporting of the engineered tissue performance, and if needed, interfere to deliver signals for activating it, or enable its integration with the host. Here, we addressed this challenge by integrating flexible, free-standing electronics with a 3D nanocomposite scaffold and cardiac cells, to create a microelectronic engineered cardiac patch. The hybrid patch exhibited robust electronic properties enabling multiplexed recording of cellular electrical activities and when needed provided electrical stimulation for synchronizing cell contraction. Moreover, electroactive polymers containing biofactors were deposited on designated electrodes within the electronics, and provided on-demand drug release in the patch microenvironment. We expect that integration of such complex electronics within a cardiac patch will provide control and regulation of its function, significantly enhancing its therapeutic value.

Presenters

Lena Neufeld, Technion - yeli2006@gmail.com

DESIGNING A BIOCOMPATIBLE HYDROGEL FOR THE DELIVERY OF MESALAMINE

Lena Neufeld, Havazelet Bianco-Peled

Mesalamine is being used extensively for long-term maintenance therapy of Crohn's disease and colitis and may provide protection against the development of colorectal cancer. A new design for nanocomposite hydrogels based on cross-linked chitosan for the delivery of mesalamine is presented. To enhance drug loading in chitosan, the mineral montmorillonite was incorporated into the matrix. The exfoliated silica montmorillonite nanosheets form interactions with both chitosan and mesalamine, thus affecting the hydrogel's drug release mechanism and swelling properties.
The impact of montmorillonite and glutaraldehyde concentrations on the hydrogel properties was investigated. In vitro drug-release studies detected slower release at short times when Montmorillonite was combined. This study is the first to evaluate the influence of pH during mixing and mixing duration. It was shown that lowering the pH during mixing delayed the release since the positively charged drug was better introduced between the Montmorillonite layers, as confirmed by Differential Scanning Calorimetry (DSC) and Fourier Transform Infra-red spectroscopy (FTIR) analysis. All hydrogels showed prolonged sustained release of mesalamine over 24 h in simulated colonic fluid (pH 7.4). When modeled, the mesalamine release profile suggests a complex release mechanism, involving adsorption of the drug to the montmorillonite and diffusion. The results imply that chitosan-montmorillonite hydrogels can serve as potential drug carriers for controlled-release applications.

Presenters

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GELATIN-ALGINATE SURGICAL SEALANT LOADED WITH HEMOSTATIC AGENTS

Oded Pinkas, Meital Zilberman

The purpose of this study is to investigate the ability of natural-polymers solutions crosslinked by carbodiimides for biocompatible and hemostatic surgical sealant application. Our novel surgical sealants are based on the natural polymers gelatin and alginate, crosslinked by carbodiimide. Two types of hemostatic agents with a layer silicates structure, montmorillonite (MMT) and kaolin were loaded in order to improve the sealing ability in a hemorrhagic environment. The effect of the sealant's components on the in vitro burst strength was studied according to ASTM F2392, the physical properties (swelling ratio, degradation, viscosity, curing time) and cytotoxicity were investigated as well. A formulation based on 400 mg/ml gelatin, 10 mg/ml alginate and 15 mg/ml EDC was found as an optimal one, combining high burst strength together with no cytotoxicity. Incorporation of kaolin only slightly affected the sealant physical properties. When the maximal kaolin concentration of 50 mg/ml was used the burst strength was increased in 38% compared to unloaded sealant. In contrast, incorporation of MMT significantly affected the crosslinked polymeric system and improved the sealants properties. Loading of 5 and 20 mg/ml MMT increase the in vitro burst strength in 43% and 108%, in respectively. Unloaded sealant and kaolin/MMT Loaded sealants didn't show any cytotoxicity effects. The curing time of all sealant formulations was in the range of 5-10 seconds, which is suitable for surgical sealants. This research clearly shows that our novel formulations of gelatin-alginate crosslinked by carbodiimide have a promising potential to be used in surgical sealing applications. Furthermore, the incorporation of kaolin and MMT in gelatin-alginate surgical sealants is a very promising novel approach for improving the bonding strength and physical properties of the surgical sealants for use in hemorrhagic environments.

Presenters

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EXTRACELLULAR MATRIX- BASED GELS FOR MYOCARDIAL INFARCTION TRATMENT

Yael Efraim, Hadar Sarig, Marcelle Machluf

Injectable scaffolds were suggested in the recent years as a minimally invasive platform for cardiac tissue engineering. We have developed new injectable biomaterials, which are based on porcine cardiac extracellular matrix (pcECM), and gel upon injection into the myocardium. Our pcECM-based gel formulations were demonstrated to support the viability and proliferation of mesenchymal stem cells (MSCs) as well as human induced pluripotent stem cells (hiPSCs). Furthermore, the pcECM-based gels were shown to affect cell morphology and to enhance differentiation towards the cardiac linage. In addition, the gel's biocompatibility was comprehensively demonstrated in vitro and in vivo in mice model. Most importantly, the therapeutic efficacy of this injectable scaffold was demonstrated both in acute and chronic MI rat models. In these models, our pcECM-based gels remarkably enabled not only preservation, but also improvement in cardiac function. Altogether, our findings clearly point at these biomaterials as prospective scaffolds for the treatment of end-stage heart failure.

Presenters

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DEVELOPING CELL-DERIVED NANO-VESICLES AS A DRUG DELIVERY VEHICLE FOR LIPOPHILIC DRUGS

Alexandra Ereskovsky, Tomer Bronshtein Marcelle Machluf

Many of the most potent drugs used for cancer therapy, such as Paclitaxel (PTX), Docetaxel, and Cediranib, are water insoluble, which limits their bioavailability. Furthermore, these cytotoxic drugs affect non-malignant tissues leading to severe side effects. Drug delivery systems have been developed to increase the drugs bioavailability, decrease their toxicity, and hopefully increase their selectivity by active or passive targeting. Nano-ghosts (NGs) are liposome-like vesicles produced from the cytoplasmic membrane of human mesenchymal stem cells (hMSCs), which retain the surface proteins that allow MSCs' to specifically target a variety of tumors. NGs, unlike synthetic liposomes, cannot be loaded with hydrophobic compounds by simple thin film hydration. Therefore, using the NGs to deliver water insoluble drugs will require the development of novel approaches for the loading of such drugs without damaging the NGs integrity and disrupting the natural MSC-borne targeting capabilities. Our results so far show that PTX complexation with an amphiphilic polymer (PMB30W) allows its passive loading during the NGs production. Interestingly, we found that NGs could be also loaded by proxy by fusing them with cationic synthetic liposomes that were preloaded with PTX. PTX loaded NGs' led to a significant cytotoxic effect on breast cancer cells compared to no effect by empty NGs. Our collective results hint at the potential of the NGs' as an effective naturally targeted carrier of not only water soluble drugs, as demonstrated in our previous studies, but hydrophobic ones as well covering a wide range of applications.

Presenters

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NEW APPLICATIONS OF ORGANIC NANOPARTICLES: VECTORISATION OF MIX THROUGH THE SKIN AND DEVELOPMENT OF IN VITRO ASSAY FOR THE DIAGNOSIS OF FRAGRANCE ALLERGY

A. Cortial, M. Vocanson, J.F. Nicolas, S. Briancon

The aim of this work was to develop and optimize methods for fragrance mix I (FMI) encapsulation into nanoparticles (NPs) of two types of nanoparticles (NPs) : polymeric NPs (poly-ε-caprolactone, PCL) and solid lipid NPs (SLNs) (prepared with petrolatum, shea butter, candelilla wax, C10-18 triglycerides, or cetyl palmitate). Then, these new NPss were evaluated as vectors through a pig skin to analyze the distribution of the FMI molecules in the different skin layers. In parallel, NPs have also been applied as solubilizers for the development of a new in vitro test for the diagnosis of fragrance allergy. Our results show that (i) NPs polymers, mainly anionic NPs, are the most suitable vectors to promote trans-epidermal penetration of fragrance. On the contrary, SLNs were found in the stratum corneum, leading to an accumulation of fragrance in this layer; (ii) whatever the type of NPs, the penetration of the FMI molecules in the deeper layers of the skin depends on their intrinsic partition coefficient; (iii) PCL-NPs significantly increase the FMI solubilization in conventional culture media and, allowing a robust reactivation of circulating specific T cells in patients with allergy to fragrances. All of these results confirm the potential of organic NPs for the development of future strategies (for the skin delivery of several actives in the different skin layers). These new vectors further offer a promising alternative to improve the diagnosis of contact dermatitis induced by fragrances and more generally by hydrophobic allergens.

Presenters

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DESIGN AND CHARACTERIZATION OF NANOPARTICLES LOADED WITH A LIPOPHILIC Pt(IV) PRODRUG FOR THE DELIVERY OF OXALIPLATIN IN SOLID TUMORS

Aiman Abu Ammar, Raji Raveendran, Taher Nassar, Dan Gibson, Simon Benita

Platinum (Pt) anticancer drugs constitute a cornerstone for the treatment of various solid tumors but their therapeutic outcome is limited not only by serious side effects, but also by acquired resistance of cancer cells. Modification of oxaliplatin (OXA) into lipophilic Pt(IV) molecule namely OPA, containing both lipophilic and hydrophilic axial ligands, was applied for the purpose of improving performance and facilitating their incorporation into polymeric nanoparticles (NPs). OPA exhibited a unique potency against a panel of cancer cells, including cisplatin-resistant tumor cells. OPA NPs were prepared and characterized. The mean particle diameter of the NPs was 146 nm with optimal encapsulation yields of OPA (>95%). OPA and respective NPs showed enhanced in vitro cellular Pt accumulation and DNA platination, and a substantially anti-proliferative effect compared to OXA. Furthermore, three in vivo efficacy studies were carried out using a xenograft subcutaneous model of pancreatic (BxPC-3) and colon (HCT-116) tumors, and an orthotopic intraperitoneal model of metastatic ovarian cancer (SKOV-3) in SCID-bg mice. The antitumor activity of OPA and OPA NPs indicated significantly decreased tumor growth rates compared to the control and OXA treatment groups. The overall results support the hypothesis of this work, due to high potency of OPA and OPA NPs over the native molecule against solid tumors, illustrating the therapeutic potential of this compound for improved treatment of cancer. Consequently, these findings warrant further development towards up-scaling and clinical translation.

Presenters

Assaf J. Harnoy, Tel-Aviv University - asi.harnoy@gmail.com

ENZYME-RESPONSIVE POLYMERIC MICELLES AS A PLATFORM FOR CONTROLLED DELIVERY

Assaf J. Harnoy, Ido Rosenbaum, Roey J. Amir

Stimuli-responsive amphiphilic block copolymers have attracted considerable attention in recent years due to their ability to self-assemble in aqueous media into nano-sized polymeric micelles. Such micelles can encapsulate within their hydrophobic cores small guest molecules (e. g. hydrophobic drugs or dyes) and release them on cue. Therefore, polymeric micelles are interesting candidates to act as nanocarriers for controlled delivery and in vivo diagnostics. To this end, there have been many reports of polymeric micelles that can respond to various types of stimuli such as pH, irradiated light, temperature or their combinations. However, polymeric micelles that can respond to variations in enzymatic activity are not as prominent in the literature. Utilization of enzymes as triggers for micellar disassembly might be considerably advantageous due to the catalytic efficiency and high selectivity of the activating enzymes towards their substrates. Furthermore, common occurring imbalances in enzymatic activities are often associated with many diseases, and may be picked up by cleverly designed polymeric micelles to induce a site-specific release of molecular payload. In this talk, I will present an innovative and simple synthetic approach for preparation of amphiphilic PEG-dendron hybrids, which can self-assemble in aqueous media into enzyme-responsive polymeric micelles. I will demonstrate how each part of the hybrid can be altered in order to adjust the stability of the formed micelles and their disassembly rates in response to the enzymatic trigger. This approach might assist in future design of enzyme-responsive platforms for controlled delivery of poorly soluble drugs.

Presenters

Tom Givaty, Technion - tomgivaty@gmail.com

ENCAPSULATION OF GLUCOCORTICOIDS IN CELL DERIVED NANO-GHOSTS

Tom Givaty, Marcelle Machluf

Targeted drug delivery systems have been the focus of many studies in recent years in the hope to overcome obstacles associated with conventional drugs. A novel delivery platform based on cell derived nano-ghosts (NGs) was used in this research. Produced from the cytoplasmic membranes of MSCs, the NGs platform exploits the unique characteristics and targeting capabilities of MSCs to inflamed tissues, without the risk of tumorigenesis or other safety issues. The main goal of this study was to optimize the NGs system to encapsulate Prednisolone sodium phosphate (PSP), a synthetic glucocorticoid that is used for the treatment of inflammatory and auto-immune diseases, such as Rheumatoid Arthritis, Ulcerative Colitis and Multiple Sclerosis. With the search of an optimal encapsulation method, sonication, electroporation and incubation with the drug were compared. Incubation exhibited the highest encapsulation efficiency (about 5%) with a drugs-to-lipids ratio of 591 (w/w). NGs loaded with PSP were found to be at least effective in vitro as the free drug. These preliminary results have revealed that the NG drug delivery system displays a great potential for treatment of inflammatory diseases, and therefore need to be further tested in vivo.

Presenters

Yogita Patil, Hebrew University - yogita.udps@gmail.com

INTRACELLULAR ACTIVATION AND ENHANCED CYTOTOXICITY OF PEGYLATED LIPOSOMAL MITOMYCIN-C PRODRUG TARGETED TO THE FOLATE RECEPTOR OF CANCER CELLS

Yogita Patil, Yasmine Amitay, Patricia Ohana, Hilary Shmeeda, Alberto Gabizon

Mitomycin C (MMC) is a powerful anti-tumor antibiotic, often active against multidrug resistant cells. Despite a broad spectrum of antitumor activity, MMC clinical use is relatively limited due to its fast clearance and dose-limiting toxicity. To exploit the potential antitumor activity of MMC and reduce its toxicity we have previously developed a formulation of pegylated liposomes with a lipophilic prodrug of MMC (PL-MLP). In vitro, PL-MLP has minimal cytotoxicity unless reducing agents are added to the cell culture to activate the prodrug. In the present study, we hypothesized that targeting PL-MLP via folate receptors will facilitate intracellular activation of prodrug and enhance cytotoxicity without added reducing agents. We prepared folate targeted liposomes (FT-PL-MLP) and examined in vitro cell uptake and cytotoxicity in cancer cells with high folate receptors (HiFR). 3H-cholesterol-hexadecyl ether (3H-Chol)-radiolabeled liposomes were prepared to study liposome-cell binding in parallel to cellular uptake of prodrug MLP. 3H-Chol and MLP cell uptake levels were greater in KB HiFR cells when FT-PL-MLP is compared to PL-MLP liposomes. The cytotoxicity of FT- PL-MLP liposomes was significantly increased compared with PL-MLP in all tested HiFR cells. In vivo, no significant differences in pharmacokinetics were observed when PL-MLP was compared to FT-PL-MLP by the intravenous route. However, when liposomes were directly injected into the peritoneal cavity of mice with malignant ascites of J6456 HiFR lymphoma cells, the MLP levels were significantly greater with the FT-PL-MLP. Thus, folate targeting enhances liposome uptake by tumor cells enabling intracellular activation of prodrug, and leading to increased cytotoxicity. These results may be particularly relevant to the application of folate-targeted PL-MLP in intracavitary or intravesical treatment of cancer.

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PROTEIN PRODUCING PARTICLES FOR ONSITE DRUG DELIVERY

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Proteins have great therapeutic importance, however, in many cases lack of an efficient drug delivery system limits wider clinical implementation. Here we utilize liposomes as miniature bio-reactors for onsite autonomous protein production and delivery.

We developed liposomes that act as artificial cells, capable of producing proteins autonomously in response to a physical trigger. These liposomes can be injected into the body and then triggered to produce a protein of interest onsite. We demonstrate that this platform is effective for producing a variety of proteins; fluorescent protein, enzyme and therapeutic proteins were successfully produced using this system. In addition, we present the toxicity of cell-free produced Pseudomonas exotoxin A, an extremely potent protein which has been investigated as a treatment for cancer, towards 4T1 cancer cells.

Developing autonomous protein producing particles with responsive and therapeutic capabilities has promise to address a wide range of fundamental questions associated with protein synthesis in nature, as well as applicative protein delivery needs.

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NANO-GHOSTS FOR SELECTIVE DRUG DELIVERY TO AND ACROSS THE BLOOD BRAIN BARRIER

Noa Cohen Anavy, Marcelle Machluf

The central nervous system (CNS) is protected by the blood–brain barrier (BBB). The BBB, which is formed by impermeable tight junctions between Brain Capillary Endothelial cells (BCEC), serves as a selective barrier regulating the homeostasis of the brain and protecting it from toxic substances. Unfortunately, the high selectivity of the BBB also hampers the passage of drugs. Despite the rapid development of drugs with well-established activity in the brain, many disorders such as Alzheimer's disease, brain tumors and Multiple Sclerosis (MS) remain severely undertreated. In order to overcome these limitations, we aim to modify our mesenchymal stem cell (MSC) nano-ghosts (NGs) drug delivery system to allow transport across the BBB. The NGs are nano-vesicles produced from the plasma membrane of human mesenchymal stem cells which possess membrane-associated targeting and migratory abilities to and through the BBB, and towards sites of inflammation. The NGs are expected to retain the cells' surface moieties and encompass their unique targeting capabilities, and therefore may serve as an effective drug delivery system for targeting neurological disorders. Our primary hypothesis is therefore that brain targeting of a healthy or diseased BBB can be accomplished by NGs. The hypothesis will be tested both in vitro, using a 3D model of the BBB, which is composed of a co-culture of rat glial cells and bovine Brain Capillary Endothelial Cells (BCEC), and in vivo, using experimental autoimmune encephalomyelitis (EAE) mice, a mice model closely reflecting aspects of MS, and mice with glioblastoma multiforme (GBM)—an aggressive brain tumor.

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A NOVEL TARGETED CYTOTOXIC TREATMENT BY RGD-MODIFIED PROTEIN IN CUTANEOUS MELANOMA

Avraham Dayan, Osnat Ashur-Fabian, Gideon Fleminger

Dihydrolipoamide dehydrogenase (DLDH) is a mitochondrial enzyme which is critical for energy and redox balance in the cell and generates Reactive Oxygen Species (ROS) in the cell. In addition, bioinformatics analysis has suggested that DLDH is a homologue of Apoptosis-Inducing Factor (AIF) a central player in caspase-independent apoptosis. Cutaneous Melanoma (CM) is the most aggressive and deadliest form of skin cancer worldwide. CM cancer cells overexpress the cell surface integrin receptor (e.g. $\alpha v\beta 3$), which interacts with proteins of the Extra Cellular Matrix (ECM) through an RGD (Arg-Gly-Asp) recognition site. We bio-engineered the human DLDH with RGD tails on both sides (DLDH-RGD2), thus generating a cytotoxic protein with selectively binds to integrins on cancer cells surface. In-vitro studies show increasing amount of ROS production (Cyt C assay) with increased DLDH-RGD2 concentrations and incubation times. Tissue cultures studies of FACS analysis and confocal images have shown an in-situ apoptosis: Incubation of B16F10 melanoma cells (100,000 per 200µl) with DLDH-RGD2 (5µm) for up to 24 hr led to destruction, while normal kidney cells (HEK293), which express much less integrins on their surface, remain unharmed. When the same system (DLDH-RGD2, 5µm) was tested with $\alpha v\beta 3$ integrin transfected HEK293 cells (HEK293$\beta 3$) cell death was induced. In a control study intact DLDH (without RGD) has been shown to penetrate to B16F10 cells slower than the RGD-protein complex. In addition free RGD (1mM) inhibited DLDH-RGD2 penetration to the cells. *This system has been submitted as a patent provisional.

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TAGGING THE UNTAGGABLE: NEW OPENNING FOR BIOCONJUGATION CHEMISTRY

Samer Gnaim, Anna Scomparin, Ronit Satchi-Fainaro, Doron Shabat

Bioconjugation is typically implemented through chemoselective modification of native functional groups of the target molecule. This process of derivatization often involves “click” chemistry, such as azide–alkyne cycloaddition, amines through amide linkages, and carbonyl groups through oxime ligation. Although many medicinal agents include traditional “taggable” functional groups such as heteroatom−H bonds, some compounds present the challenge of not having any apparent chemical handles. This presentation describes the synthesis of a new difluoroalkyl ketone sulfinate reagent that enables the direct tagging of unactivated C−H bonds in untagged bioactive heteroarenes for use in bioconjugation. Tagged drug molecules bearing a carbonyl group can then be simply conjugated to a targeting moiety through the labile hydrazone linkage. The developed reagent was applied for direct incorporation of difluoroalkyl ketone handle onto substrate molecules (e.g., camptothecin-CPT, temozolomide-TMZ and Methotrexate-MTX). In vitro biological efficacy study clearly indicates that the designed ketone handle can completely maintain the original activity of a biologically relevant molecule when it is tagged with difluoropentyl ketone at the appropriate position. Bioconjugation of the "tagged" CPT drug molecules with folic acid via acid-sensitive semicarbazone linkage was evaluated. Similar In vitro antitumor effect of the CPT-bioconjugate on KB cells compared to that of the free drug was observed. Such chemistries, i.e. tagging and bioconjugation, represent a promising strategy to grant targeting features to small "untaggable" drug molecules.

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ENZYME-RESPONSIVE NANOCARRIERS WITH TUNABLE RELESE RATES

Merav Segal, Roey J. Amir

Enzymes show great promise as triggers for disassembly of nanocarriers thanks to their over expression in diseased states tissue. Herein we show a highly modular design of amphiphilic linear-dendron hybrids block copolymers. These amphiphilic hybrids are composed of linear hydrophilic polyethyleneglycol (PEG) block and the hydrophobic block is an enzyme-responsive dendron with cleavable lipophilic chains as end-groups. These hybrids can spontaneously self-assemble into nano-size micelles that can disassemble and release its encapsulated cargo upon enzymatic hydrolysis of the hydrophobic end-groups. Taking advantage of this modular system, we show that small changes in the hydrophobic dendron building block can lead to dramatic changes of the assembled nanoparticle size and its rate of disassembly. This molecular study can potentially be applied to create smart drug delivery platform with tunable sizes and release rates.

References: Rosenbaum, I.; Harnoy, A. J.; Tirosh, E.; Buzhor, M.; Segal, M.; Frid, L.; Shaharabani, R.; Avinery, R.; Beck, R.; Amir, R. J. "Encapsulation and Covalent Binding of Molecular Payload in Enzymatically Activated Micellar Nanocarriers" J. Am. Chem. Soc. 137, 6.

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NANOMETRIC MUCOADHESIVE CARRIERS FOR LOW MOLECULAR WEIGHT HEPARIN DELIVERY

Shaked Eliyahu, Havazelet Bianco-Peled

One of the known mucoadhesive polymers used as a drug carrier is chitosan (CS). It exhibits low toxicity and biocompatibility. Chitosan nanoparticles (NPs) are widely used as carriers for drug delivery systems. Heparin is a natural polysaccharide used as an anticoagulant for treatment of thromboembolic disorders and demonstrates no oral bioavailability. Heparin can be administrated only via parenteral route. Compared to unfractionated heparin, Low Molecular Weight Heparin (LMWH) has better subcutaneous bioavailability and longer half-life, therefore, LMWH is commercially used. Non-invasive drug delivery systems are being developed to further improve the bioavailability of LMWH in an attempt to avoid the inconvenience as well as the side effects associated with injections. Our group has previously developed the concept of acrylated polymers, and showed that molecules carrying unsaturated polyehtylene glycol di-acrylate (PEGDA) side chains have the ability to interact covalently with mucin. In this study we intend to use acrylated chitosan that may be a suitable candidate for mucoadhesive drug delivery system for LMWH.

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IMPROVED ORAL ABSORPTION OF EXENATIDE USING AN ORIGINAL NANOENCAPSULATION AND MICROENCAPSULATION APPROACH

Liat Soudry-Kochavi, Natalya Naraykin, Taher Nassar, Simon Benita

Oral delivery is the most convenient and favorable route for chronic administration of peptides and proteins to patients. However, many obstacles are faced when developing such a delivery route. Nanoparticles (NPs) are among the leading innovative solutions for delivery of these drugs. Exenatide is a peptidic drug administered subcutaneously twice a day chronically as an add-on therapy for the world wide pandemic disease, diabetes. Many attempts to develop oral nanocarriers for this drug have been unsuccessful due to the inability to retain this hydrophilic macromolecule under sink conditions or to find a suitable cross-linker which does not harm the chemical integrity of the peptide. In this study, we report about an original oral delivery solution based on a mixture of albumin and dextran NPs cross-linked using sodium trimetaphosphate. Moreover, we suggest a second defense line of gastro-resistant microparticles composed of an appropriate ratio of Eudragit® L100-55 and hydroxypropylmethylcellulose, for additional protection to these NPs presumably allowing them to be absorbed in the intestine intact. Our results demonstrate that such a system indeed improves the relative oral bioavailability of exenatide to a level of about 77% compared to subcutaneous injection due to the presence of dextran in the coating wall of the NPs which apparently promotes the lymphatic uptake in the enterocytes. This technology may be a milestone on the way to deliver other peptides and proteins orally.

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LAMININE DERIVED PEPTIDE POLYMER DRUG CONJUGATE FOR TARGETING CD44 OVEREXPRESSING CANCER CELLS

Michal Zaiden, Ayelet David

CD44 is a transmembrane adhesion glycoprotein and part of the extracellular matrix [ECM]. It is expressed in many cell types and involved in cell-cell and cell-ECM adhesion, cell migration and differentiation, and signal transmission from the cell surface in, leading for apoptosis or survival and proliferation. More than 20 known isoforms of CD44 have been identified to date. Overexpression of CD44v6 was detected in metastatic malignancies but was not found in non-metastatic tumors and the corresponding benign tissues. The laminin-derived A5G27 peptide (primary sequence RLVSYNGIIFFLK), binds to CD44 and its variants CD44v3 and CD44V6 via its heparin-like and chondroitin sulfate GAG side chains and blocks FGF2 activity by binding to heparin sulfate side chain. Thus, when attached to polymeric carrier A5G27 can be utilized both as therapeutic agent as well as a targeting peptide in order to navigate polymer-bound drugs directly to the areas of malignancy, and inhibit tumor progression. Among the variety of polymeric drug carriers, N-(2-hydroxypropyl)-methacrylamide (HPMA) copolymer is an excellent anticancer drug carrier owing to its good water solubility, enhanced tumor accumulation, reduced non-specific toxicity, low immunogenicity and easy for conjugation. In this work we propose to develop a novel CD44-targeted polymer drug conjugates composed of a conventional chemotherapeutic drug (Paclitaxe or Docetaxel) and A5G27 peptide as a targeting moiety and potential therapeutic agent to inhibit cell migration, invasion and metastasis.

HPMA-based precursor copolymer carrying fluorescein-isothiocyanate (FITC) and active ester (p-nitrophenyl, ONp) groups (designated as P-(GG-ONp)-FITC) was synthesized by random radical precipitation copolymerization and characterized by FPLC and UV-spectrophotometry. A5G27 was first attached to the precursor copolymer via ONp aminolysis, to give the CD44-targeted P-(A5G27)-FITC. Our primary FACS in-vitro result shows good correlation between CD44 levels to the binding and uptake of P-(A5G27)-FITC by PC3, 4T1 and LNCaP cells. Binding and uptake of P-(A5G27)-FITC was higher than that of the non-targeted control

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CALCIUM-SIRNA NANOCOMPLEXES: MECHANISM OF CELLULAR UPTAKE AND ENDOSOMAL RELEASE

Matan Goldshtein, Smadar Cohen

Small interfering RNA (siRNA) represents a promising type of therapeutics exploiting the mechanism of RNA interference for silencing target genes. Yet, the clinical translation of siRNA has been limited due to delivery challenges. We recently described a novel Ca2+- siRNA nanocomplex capable of strong but reversible complexation, siRNA protection, cellular uptake, and cytoplasmatic unloading of its cargo. Here, we investigated the importance of Ca2+compared to other bi- or tri-valent cations in creating these nanocomplexes, and the cytocompatibility of the various nanocomplexes. Further, we elucidated cellular entry and endosome release mechanisms of Ca2+-siRNA nanocomplexes. The nanocomplexes were prepared by incubating siRNA (50 nM final) with either Ca2+, Mg2+, Zn2+, Ba2+, Mn2+, Fe2+ or Fe3+ ions (5 mM for divalent, 3.33mM for Fe3+). Of these nanocomplexes, only those prepared with Ca2+, Mg2+, Ba2+ and Fe3+ were cytocompatible as judged by PrestoBlue® for cell viability. Effective eGFP silencing (~80%) in GFP expressing mouse colon carcinoma CT26 cells was achieved only with Ca2+-siRNA nanocomplexes. Cell uptake studies (using confocal microscopy) and silencing experiments (using flow-cytometry), were performed using different inhibitors of several possible entry mechanisms: Dynasore, Pitstop2®, EIPA, Nifedipine, Cadmium and Genistein. We revealed that the major endocytic pathways involved in the entry of Ca2+-siRNA nanocomplexes are clathrin and dynamin-dependent. Treatment with Bafilomycin, which inhibits endosome acidification after Ca2+ entry to endosomes, completely abolished siRNA-mediated silencing indicating that Ca2+ is critical for the endosomal unloading through a “proton sponge” effect. In conclusion, Ca2+ is a critical component for particle assembly, uptake and endosomal escape.

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ENHANCING THE STABILITY AND SELECTIVITY OF NANOCARRIERS BY DIMERIZATION OF THEIR BUILDING BLOCKS

Ido Rosenbaum, Roey J. Amir

Enzyme-responsive micelles have great potential as drug delivery platforms due to the high selectivity and overexpression of disease-associated enzymes. Recently we have reported on enzyme-responsive amphiphilic block copolymers composed of a hydrophilic PEG block and a dendron with enzymatically cleavable lipophilic end-groups as the hydrophobic block. These amphiphilic hybrids formed micellar structures in aqueous environment which were disassembled upon enzymatic activation. When examining the properties of micelles, it is clear that one of the biggest challenges is the risk of their fast dilution and disassembly in the body. Reversible cross-linking of the micelles could increase their stability and prevent their spontaneous disassembly in the body. Furthermore, the cross-linking allows the introduction of a second types of stimuli-responsive groups, resulting in nanocarriers that require activation by both types of stimuli. Such smart amphiphilic hybrids are promising materials for the design of advanced nanocarriers with increased stability and selectivity for biomedical delivery applications.

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