# December 13th, 2022

Yaglom Hall, Senate building, Tel Aviv University

# The 3rd Meeting of the Young Israeli Controlled Release Society

## Opening Remarks

**Prof. Avi Schroeder**
ICRS President
Technion

## Keynote Speakers

**Prof. Ronit Satchi-Fainaro**
Director, Cancer Biology Research Center
Tel Aviv University

**Prof. Rachela Popovtzer**
Vice Dean of the Faculty of Engineering
Bar-Ilan University

## Mentoring Panel:
## Academy and Industry Perspectives
## Questions You Have Never Dared to Ask

**Moderator**

**Dr. Assaf Zinger**
Technion

**Dr. Dana Bar-On**
Specialty R&D at Teva Pharmaceuticals

**Prof. Dan Peer**
VP for R&D at Tel Aviv University

**Prof. Asya Rolls**
Full Professor at the Technion

**Dr. Tomer Bronshtein**
VP Business Development at Bonus BioGroup

Young ICRS

## The organizing committee

Gal Chen
Ofri Vizenblit
Ron Kleiner
Riccardo Rampado

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## Program

Young ICRS

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|---|---|
| 08:45 - 09:15 | Welcome & Light Breakfast |
| 09:15 - 09:30 | Opening remarkss |
| 09:30 - 09:40 | YICRS committee |
| 09:40 - 09:45 | ICRS president, Prof. Avi Schroeder |
| 09:30- 10:40 | Keynote talks<br>Moderators: Ron Kleiner & Riccardo Rampado |
| 09:30 - 10:05 | Prof. Ronit Satchi-Fainaro |
| 10:05 - 10:40 | Prof. Rachela Popovtzer |
| 10:40 - 11:20 | Student talks - Session 1 (10 min + 3 min Q&A)<br>Moderator: Gal Chen<br>Dana Tarab-Ravski<br>Shani Hamias |
| 11:05 - 11:20 | Coffee break |
| 11:20 - 13:10 | Student talks - Session 2 (10 min + 3 min Q&A)<br>Moderator: Aviram Avital<br>Patricia Mora Raimundo<br>Si Naftaly Kiros<br>Danna Niezni<br>Arnon Fluksman<br>Edo Kon<br>Michal Skitel-Moshe<br>Daniel Rodriguez Ajamil<br>Ofer Prinz Setter |
| 13:10- 13:15 | Group photo |
| 13:15- 13:45 | Lunch break & Networking |
| 13:45 - 14:40 | Poster session |
| 14:40 - 15:40 | Mentoring panel: Academy & Industry Perspectives<br>Moderator: Dr. Assaf Zinger<br>Dr. Dana Bar-On, Prof. Dan Peer, Prof. Asya Rolls, and Dr. Tomer Bronshtein |
| 15:40 - 16:00 | Closing remarks & Prizes |

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# Student Talks - Session 1


## Dana Tarab-Ravski

**Ph.D. student at Prof. Dan Peer's lab, Tel Aviv University**


### RNA-based therapy using lipid nanoparticles as a novel therapeutic approach for multiple myeloma


Multiple myeloma (MM) is the second most common hematological malignancy, and it arises from differentiated malignant plasma cells accumulating in the bone marrow (BM). Despite the recent approval of several drugs for MM, most patients eventually relapse, and the disease is considered incurable. RNA-based therapies are an appealing therapeutic approach for cancer, as they hold the potential to manipulate the genetic expression of any gene and cell. However, clinical implementation of RNA therapy is limited due to inefficient systemic delivery of ribonucleotides to cells outside the liver. We aim to generate a novel RNA-based therapy for MM by silencing the expression of crucial genes in myeloma cells and lead to the alleviation of the disease. We used siRNA to block the expression of CKAP5, a protein that regulates centrosomal organization during mitosis. For this, we designed targeted lipid nanoparticles (tLNPs) coated with an anti-CD38 antibody to allow specific delivery to myeloma cells. Our data show that silencing the expression of CKAP5 results in ~90% and ~60% decrease in cell viability of MM cell lines and primary MM cells, respectively. Moreover, we established a novel xenograft MM mouse model with high engraftment to the BM and high resemblance to the human disease. Using this model, we showed the specific delivery of aCD38-tLNPs to myeloma cells in the BM and the therapeutic effect of our aCD38-tLNPs-siRNA-CKAP5 in vivo. These results highlight the potential of RNA therapy for treatment of MM and open new therapeutic opportunities for treating hematological malignancies with tLNPs.

# Shani Hamias

## Ph.D. student at Prof. Marcelle Machluf's lab, Technion


## Nano-ghosts for drug transport across the blood-brain barrier

Introduction: The Blood-Brain Barrier high selectivity (BBB) restrict the delivery of an adequate amount of drugs to the brain in case of illness such as Glioblastoma (GBM). To overcome this obstacle our lab developed a novel delivery system, Nano-Ghosts (NG). The NGs are Nano-vesicles produced from the plasma membrane of human Mesenchymal Stem Cells (hMSCs). In this study, we aim to utilize the NGs as an effective drug delivery system for the treatment of GBM as it can overcome the natural barrier and specifically target the tumor site.
Results: in-vivo studies with U87 intracranial model injection showed the NGs penetrate to the brain and particularly colocalize in the tumor site after NGs IV injection. This result was repeated in a mouse model of intracranial 005 cells injection that was done with the collaboration of Dr. Dinorah Fridman-Morvinski from Tel-Aviv university. Furthermore, we loaded Gboxin inside the NGs and the bioactivity of Gboxin-NGs was tested in-vivo. Gboxin-NGs significantly reduce the tumor size and prolong animal survival compared to free drug. In addition, we armed the NGs surface by engineering NGs to present PD-1 protein on the membranes as an immune checkpoint blockade. By disrupting the PD-1/PD-L1 to boost the immune system response. PD-1 NGS reduces tumor size and improves animal survival.
Conclusion: We successfully proved NGs effectiveness as a versatile targeted drug-delivery system for the treatment of GBM.

# Student Talks - Session 2

## Dr. Patricia Mora Raimundo

**Post-Doc. student at Prof. Avi Schroeder's lab, Technion**

### Brain-targeted transferrin liposomes loaded with anti-alpha-synuclein monoclonal antibody for targeting Parkinson's disease in its early stages

Parkinson's disease (PD) is one of the most common neurodegenerative diseases with limited treatment options. The disease is characterized by the loss of dopaminergic neurons and abnormal accumulation and propagation of the neuronal protein alpha-synuclein. An anti-alpha-synuclein antibody (SynO4) has previously shown a high affinity to alpha-synuclein aggregates in PD human brains, suggesting that it can be used as a therapeutic agent to slow down the disease progression. However, SynO4 has a short half-life; being necessary to increase the drug dosage, which can generate toxic effects. To overcome this challenge the designed of a delivery system is required. In this study, we developed a brain-targeted drug delivery system by loading the SynO4 in transferrin modified lipid nanoparticles. Transferrin liposomes loaded with SynO4 antibody (TF-SynO4-lipo) demonstrated an enhanced penetration across the blood-brain barrier (BBB) in vitro model and significantly higher cellular uptake efficiency than the free SynO4 in PD neurons culture. We emphasized the importance of the PEG-lipid paring effect in the design of the nanocarriers, which highlights the necessity of selecting PEG lipids of an appropriate length. In addition, in vivo studies revealed that transferrin-targeted liposomes efficiently crossed the BBB and were safely delivered to damaged neuronal cells in an AAV-based PD mouse model. Intravenous administration of TF-SynO4-lipo showed improved therapeutic efficacy in the PD mice brain, including reduced alpha-synuclein aggregation and slowing the degeneration of dopaminergic neurons. Taken together, TF-SynO4-lipo represents a promising therapeutic approach for treating Parkinson's disease.

## Si Naftaly Kiros

**Ph.D. student at Asst. Prof. Assaf Zinger's lab, Technion**


# Breast milk biomimetic nano-particles as a versatile, non-invasive, oral drug delivery tool

Oral delivery of therapeutic agents is the most patient-preferred route of administration because it is painless and convenient. Still, every day, millions of patients across the globe are subjected to injections of vaccines and multiple other drugs. The main reason for it is that most of the therapeutic agents are large molecules, such as messenger RNA and proteins, that cannot be delivered orally, mainly because of enzymatic degradation and extreme physiological condition in the gastrointestinal (GI) tract and the impermeability of the intestine. Surprisingly, although the cells are thousand-fold bigger than these large molecules, during breastfeeding, breast milk cells successfully survive the extreme conditions in the GI tract, and they are able to cross the intestinal barrier into the blood circulation. Understanding this phenomenon of cells that cross the GI tract into our body, can facilitate the development of a novel tool for the oral delivery of therapeutic agents. Herein, we will identify the exact cell populations that cross the GI tract and engineer human breast milk biomimetic phospho-lipid nanoparticle (NP), MILKOSOME, to deliver drugs orally into the body. We already developed the first ever MILKOSOMES, and demonstrated their in-vitro stability in GI tract physiological conditions using simulated gastric fluids and ex-vivo ability to cross the intestine barrier using murine intestine samples. Our findings will increase our fundamental understanding of cellular and NP trafficking through the GI tract and lay the foundations for designing a next-generation and non-invasive nano-biomimetic oral drug delivery technology that may affect public health worldwide.

# Danna Niezni

## Ph.D. student at Prof. Yosi Shamay's lab, Technion


## Polydopamine copolymers for stable drug nanoprecipitation


Polydopamine (PDA), a biomaterial inspired from marine mussels, has attracted interest in cancer nanomedicine due to its photothermal properties, nanoparticle coating, and pi-pi stacking-based drug encapsulation abilities. Despite numerous one-pot and post-polymerization modifications, PDA copolymers have not been studied in the context of stabilizing drug nanoprecipitation. In this study, we tested combinatorial panels of co-monomers with PDA in order to optimize drug loading efficiency, particle size and stability of nano formulations made with drug nanoprecipitation. We identified a novel co-monomer and optimized the conditions for its incorporation in PDA copolymers used for drug nanoprecipitation. Surprisingly, it was superior to polyethylene glycol (PEG) modifications in every aspect. The leading copolymer was scaled up, characterized and tested in-vitro. It showed long term stability, high encapsulation efficiency, low toxicity and antitumor efficacy in colon cancer cells in-vitro. Nanoprecipitation of hydrophobic drugs can be greatly enhanced by the use of these PDA copolymers, which are safe, easy-to-prepare and highly effective stabilizers.

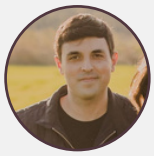
## Arnon Fluksman

**Ph.D. student at Prof. Ofra Benny's lab, Hebrew University**


# Externally controlled multifunctional iron magneto-plasmonic nanocapsules for tumor eradication


Multifunctional polymeric-metal nanoparticles (NPs) attract increasing attention in the field of drug delivery due to their potential to combine various mode of actions and response to physical or biochemical stimuli, in addition to drugs activity. With the aim to locally enhance the efficacy of cancer nanotherapies, here we present an iron based magnetoplasmonic drug-loaded nanocapsules (MAPSULES) merging powerful external magnetic concentration in the tumor and efficient photothermal actuation to locally boost the drug therapeutic action at ultralow drug concentrations. The MAPSULES are composed of paclitaxel-loaded poly-lactic-co-glycolic-acid (PLGA) nanoparticles partially coated by a nanodome shape iron/silica semi-shell. The iron semi-shell has been designed to present a ferromagnetic vortex for incorporating a large quantity of ferromagnetic material while maintaining high colloidal stability. The large iron semi-shell provides very strong magnetic manipulation via magnetophoretic forces, exhibits highly damped plasmonic behavior, yielding intense broadband absorbance in the near infrared biological windows and photothermal efficiency similar to the best plasmonic nanoheaters. The in vivo therapeutic assays in a mouse xenograft tumor model show a high amplification of the therapeutic effects by combining magnetic concentration and photothermal actuation in the tumor, leading to a complete eradication of the tumors at ultralow nanoparticle and drug concentration (equivalent to only 1 mg/kg PLGA nanoparticles containing 8 g/kg of paclitaxel). These results highlight the strength of this externally controlled and amplified therapeutic approach, which could be applied to locally boost a wide variety of drugs for different diseases.

## Edo Kon



**Ph.D. student at Prof. Dan Peer's lab, Tel Aviv University**


# Development of an effective mRNA-LNP Vaccine against a highly lethal bacterium


Lipid nanoparticle (LNP) mRNA vaccines have recently emerged as an extremely effective vaccination strategy. Although currently applied towards numerous viral pathogens, data concerning the platform's effectiveness against bacterial pathogens is very limited. Here, we demonstrate how we developed an effective mRNA-LNP vaccine against a lethal bacterial pathogen by optimizing the mRNA payload GC content and antigen design. We designed a nucleoside-modified mRNA-LNP vaccine based on the bacterial F1 capsule antigen, a major protective component of Yersinia pestis, the etiological agent of plague. Plague is a rapidly deteriorating contagious disease that has killed millions of people during the history of humankind. Currently, the disease is treated effectively with antibiotics, however, in the case of an outbreak caused by a multiple-antibiotic-resistant strain, alternative countermeasures are required. Our mRNA-LNP vaccine elicited both humoral and cellular immunological responses and conferred rapid and full protection against lethal Yersinia pestis infection after a single dose. The data presented in the current study opens new avenues for effective anti-bacterial vaccines, which are urgently needed, given the looming threat of antibiotic resistance.

# Michal Skitel-Moshe

**Ph.D. student at Prof. Marcelle Machluf's lab, Technion**


## A pancreatic ECM-based microencapsulation as a novel insulin delivery system for diabetes therapy


Pancreatic islets microencapsulation has been studied as a diabetes therapy, thus isolating and supporting the encapsulated islets post-transplantation. The material used for microcapsules fabrication, however, has a crucial role in mimicking the natural tissue and granting the islets a structural, biological, and mechanical support. Therefore, we developed a microencapsulation platform based on the biocompatible bioactive porcine pancreatic extracellular matrix (ppECM), thus hypothesizing that it will provide the islet a natural pancreatic niche.

Following the encapsulation of rat pancreatic islets within ppECM microcapsules, the islets remained viable for at least 14 days. The islets demonstrate proper function, expressing insulin and glucagon. Moreover, their insulin secretion was shown to be glucose-responsive and on day 14 post-encapsulation, it was significantly higher than control-encapsulated islets. Furthermore, cells in the ppECM and the control-encapsulated islets, expressed Pdx1, which is required for their maintenance and survival in the mature pancreas. The preservation of the islet structural integrity was demonstrated by the expression of Collagen IV. Surprisingly, Collagen I, which exists in the pancreatic ECM, was only observed in ppECM encapsulated islets but not in the control. The protective effect of the ppECM in hypoxic conditions was shown through their complete recovery 1 week after hypoxia induction. The microcapsules biocompatibility was demonstrated in-vivo, showing similar profile of complete blood count to controls 1 and 4 weeks post transplantation with no significant inflammatory reaction. Altogether, these findings demonstrate the potential of ppECM-based microencapsulation as a prospective insulin delivery system for the treatment of diabetes.

## Daniel Rodriguez Ajamil

**Ph.D. student at Prof. Ronit-Satchi-Fainaro's lab, Tel Aviv University**


# Design of targeted PLGA-SO3 Nanoparticles encapsulating PARP and PD-L1 Inhibitors for BRCA-mutated breast cancer therapy


Breast cancer (BC) is the most frequently diagnosed cancer and the second most common cause of cancer mortality in women worldwide. Approximately 15% of all BC are triple negative (TNBC), among them, 30% are BRCA1- or BRCA2- mutated. These tumors are highly aggressive and invasive. Recently, inhibition of poly(ADP-ribose)polymerase-1 (PARP1), a DNA repair enzyme, was shown to induce synthetic lethality in BRCA-mutated cancer cells. Despite their promise, resistance mechanisms to PARPi often develop. Moreover, PARPi have been shown to have an impact on cancer-associated immunity, and their combination with immune checkpoint therapy (ICT) has been explored in clinical trials. Therefore, we aimed to rationally design a nanomedicine combining PARPi with a programmed death-ligand 1 (PD-L1) inhibitor. We postulated that co-delivery of these therapeutic agents would result in enhanced therapeutic efficacy in BRCA-mutated cancers and will also help to overcome PARPi resistance. We first, assessed the anti-proliferative effect of several PARPi and selected Talazoparib, as it was shown to be the most potent. In addition, we observed increased expression of PD-L1 following treatments with Talazoparib on EMT6, murine BRCA-mutated BC cell line. This was subsequently abrogated following treatment with our PD-L1i small molecule. Furthermore, our PD-L1i small molecule limited EMT6 spheroids growth when were in coculture with activated splenocytes. Talazoparib and PD-L1i were co-encapsulated within PLGA NPs. We synthesized three targeted NPs with sulfonated moieties that actively target the P-Selectin, an adhesion molecule expressed in our 3D EMT6 spheroids models. We found the targeted PLGA-PEG-Gly-SO3 NPs to internalize better inside the EMT6 spheroids. Thus, we propose PLGA-PEG-Gly-SO3 NPs co-encapsulating PARPi and PD-L1i to selectively target and treat this aggressive BRCA-mutated BC while reducing the side effects.

## Ofer Prinz Setter

**Ph.D. student at Prof. Ester Segal's lab, Technion**


### How to fight pathogens with porcelain: Natural nanocaly for targeted delivery of antimicrobials


Targeted delivery of drugs to animal cells is extensively investigated, but what about targeted delivery to bacteria? Selective antibacterial solutions can minimize the harm caused to beneficial bacterial populations, and assist against antibiotic-resistant strains. We endeavor to utilize natural nanoclay, called Halloysite nanotubes (HNTs), for the task. These abundant mesoporous particles are composed of alternating layers of silica and alumina geologically rolled into 600-900 nm-long tubes with characteristic outer and inner diameters of 50 and 15 nm, respectively. HNTs have emerged as superb carriers for various active compounds, including drugs and antibiotics, due to their high porosity and adsorptive surface area. In our work the targeted delivery of the antibacterial payload was realized by immobilizing antibodies onto the HNTs surface. Two separate antimicrobial cargoes were studied: (1) the potent antibiotic ciprofloxacin to be gradually released near the target bacteria or (2) plasmonic gold nanorods to be activated by near-infrared radiation for a local photothermal effect. The selective binding of the Ab-functionalized HNTs to their target bacteria is confirmed by fluorescence and electron microscopy along with high-throughput imaging flow cytometry. Selective-medium plate count and live/dead staining indicate the enhanced and specific antibacterial effect in a challenging heterogeneous culture. In addition, the biocompatibility of the multifunctional clay is studied towards a physiologically relevant co-culture of human colon epithelial cells (Caco-2 / HT29) and the localization of the particles after administration is discussed. We believe this work signifies the potential of easily obtainable natural nanomaterials to open new avenues for biomedical applications.

# Poster Session

**Poster Number, Title & Presenter Name**

**#1** Active Targeting of Nanoparticles to The Brain For Treating Parkinson's Disease - **Mor Sela**

**#2** Energy Pathways in Synthetic Cells - **Shanny Ackerman**

**#3** Personalized Nanomedicine for Osteosarcoma -**Orr Bar Natan**

**#4** Foliar Delivery of Siran Particles for Treating Viral Infections in Agricultural Grapevines - **Aviram Avital**

**#5** Jellyfish-Based Smart Wound Dressing Containing Porous Silicon Nanoparticles Loaded with Antibiotics for Drug Release Applications - **Hagar Elizur**

**#6** Single-Chain Polymer Nanoparticles (SCPNs) As Potential Carriers - **Nasreen Nasser**

**#7** Nanostructured Porus Silicon Growth Factor Delivery Integrated Osteoinductive 3D-Printed Polymeric Scaffold for Bone Regeneration - **Yuexi Lin**

**#8** Insights into the Pleiotrpic Relationships Between Chronic Back Pain and Inflammation-Related Musculoskeletal Conditions: Rheumatoid Arthritis and Osteoporotic Abnormalities - **Melody Kasher**

**#9** Studying the Effect of Polymer Architecture on Reaction Rate in Organometallic Micellar Nanoreactors - **Krishna Vippala**

**#10** The Role of c-MYC in Resistance to Immunotherapy - **Ortal Harush**

**#11** Development of personalized skin regenerative therapy based on porcine skin ECM - **Yehonatan Zur**

**#12** Nano-Ghosts: A Drug Delivery Platform for Inflamed Cardiac Tissue - **Anastasia Brandis**

**#13** Combined Novel Immunotherapies Improve Anti-Cancer Immune Response in Glioblastoma - **Opal Avramoff**

# Poster Session

**Poster Number, Title & Presenter Name**

**#14** Development of Liposomes Encapsulating mRNA-MECP2 for Treating Rett Syndrome - **Sivan Barash Shahar**

**#15** Synthesis and Characterization of Positively Charged Starch-based Carriers for siRNA in the in-vitro Treatment of Melanoma - **Amir Regev**

**#16** Biodegradable Polyesters-Based Green Renewable Materials for Drug Delivery Applications - **Reem Hogerat**

**#17** Functionalized Polymers for Long-Term and Controlled Release of Small Disinfectant Molecules - **Eid Nassar-Marjiya**

**#18** Enhancing HNSCC Therapeutic Efficiency by Overcoming Cetuximab Resistance Using Modified Q-Starch/siRNA Particles Decorated with Cetuximab as a Targeting Agent - **Chen Benafsha**

**#19** MCP-1/CCR2 axis Inhibition in Combination with Nanovaccine Against MART-1 Sensitizes the Brain Microenvironment Against Melanoma Brain Metastasis Progression - **Sabina Pozzi**

**#20** Stimuli-Induced Architectural Transition as a Tool for Controlling the Enzymatic Degradability of Polymeric Micelles - **Shahar Tevet**

**#21** Glucose-Functionalized Liposomes for Reducing False Positives in Cancer Diagnosis - **Chen Tzror-Azankot**

**#22** The Effect of Antibodies-Gold Nanoparticles Conjugation methods on their characterizations and functionality - **Adi Anaki**

**#23** Topical Delivery of High Molecular Weight Hyaluronic Acid Using Polysaccharide Carrier and Ultrasound - **Leah Shimonov**

**#24** Transdermal Delivery of Q-starch/PIP3 Complexes Incorporated into 3D Bioprinted Hydrogel for Wound Healing - **Yossi Blitsman**

**#25** CKAP5 Down-Regulation Leads to Lethality in Genetically Unstable Cancer Cells - **Sushmita Chatterje**

# Poster Session

**Poster Number, Title & Presenter Name**

**#26** Non-Invasive Treatment for Melanoma Using Topical Gene Therapy and Ultrasound - **Shir Elkabetz Harel**

**#27** Automated Discovery of Nanomaterials Via Drug Aggregation Induced Emmition - **Yuval Harris**

**#28** Ethinyl-Estradiol Anchored Stealth Liposomes as a Nanomodule for the Combination Therapy of Breast Cancer - **Sunny Rathee**

**#29** Development of a Spheroid Model to Simulate Drug Penetration in Cancer Tumors - **Maytal Avrashami**

**#30** Nanoparticle-Based System for Targeted Delivery of Therapeutic Agents Against Glioblastoma - **Alina Brosque**

**#31** Investigating and Developing a New Method for Drug Crystallization - **Edwar Odeh**

**#32** Novel Analgesic Drug Eluting Soy Protein Films as Wound Dressing: An *In Vivo* and *In Vitro* Study - **Daniella Goder Orbach**

**#33** Development of Phytosterol Oleogel-Based Emulsions for Enhancement of Oral Bioavailability of Hydrophobic Molecules - **Areen Ashkar-Abu `Uksa**

**#33** Preventing Skin Toxicites Induced by EGFR Inhibitors by Topically Opically Blocking Drug-Receptor Interaction - **Nehtanel Friedman**

**#34** Breast Milk Biomimetic Nano-Particles as a Versatile, Non-Invasive, Oral Drug Delivery Tool - **Si Naftaly Kiros**

**#35** RNA-Based Therapy Using Lipid Nanoparticles as a Novel Therapeutic Approach for Multiple Myeloma - **Dana Tarab-Ravski**

# The YICRS 2022 Organizing Committee

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**We would like to thank our mentors, Prof. Avi Schroeder, Prof. Dan Peer, Prof. Ronit Satchi-Fainaro, and especially Dr. Assaf Zinger for his excellent guidance.**

**A special thanks to Prof. Rosa Azhari for her tremendous support.**

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