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Nanotechnology applications in medical diagnosis, imaging, and therapy

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Invited Seminar Presentation at the 2016 ECI Conference - Nanotechnology in Medicine: From Molecules to Humans - Hernstein, Austria
Monday, July 4th, 2016

Translational Nano-Medicine:

Targeted Delivery Systems for Cancer and Inflammatory Diseases

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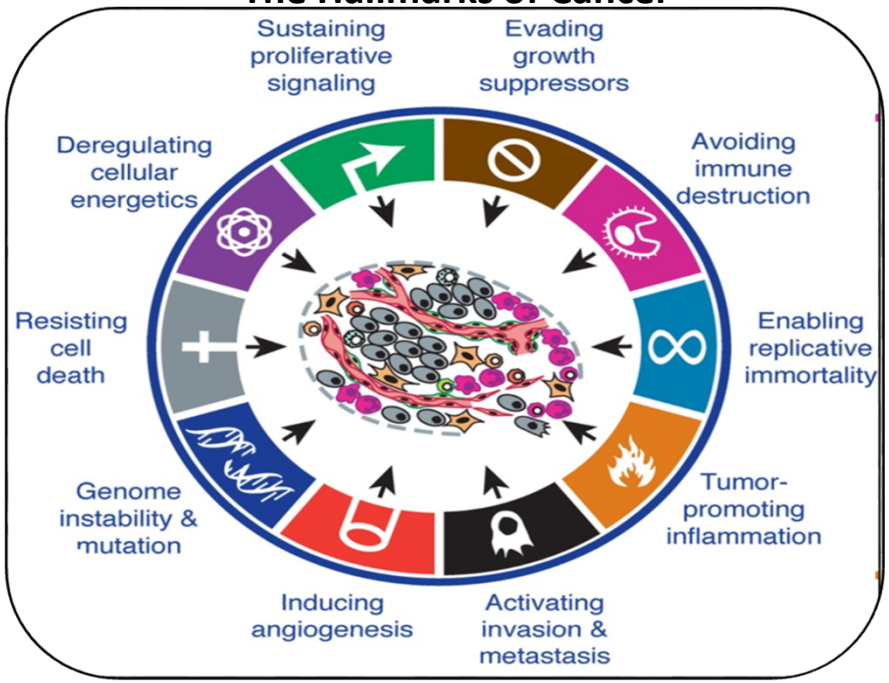
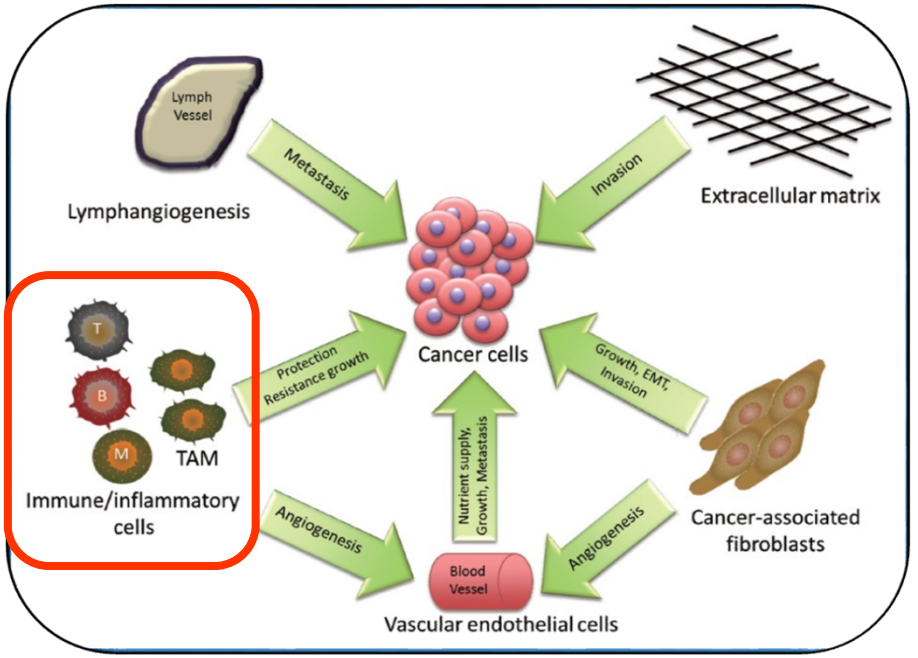
The Tumor Microenvironment

The Hallmarks of Cancer



Ref: D. Hanahan and R.A. Weinberg. *Cell*; **144:** 646-674 (2011).

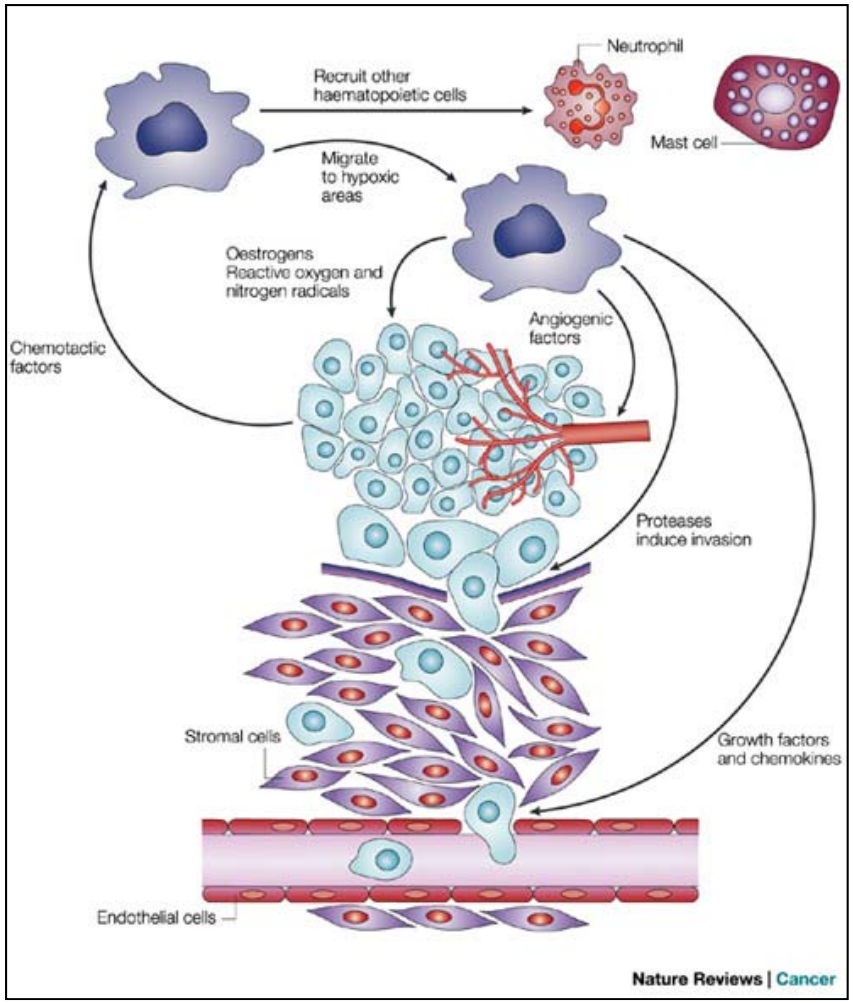
Cells of the TME



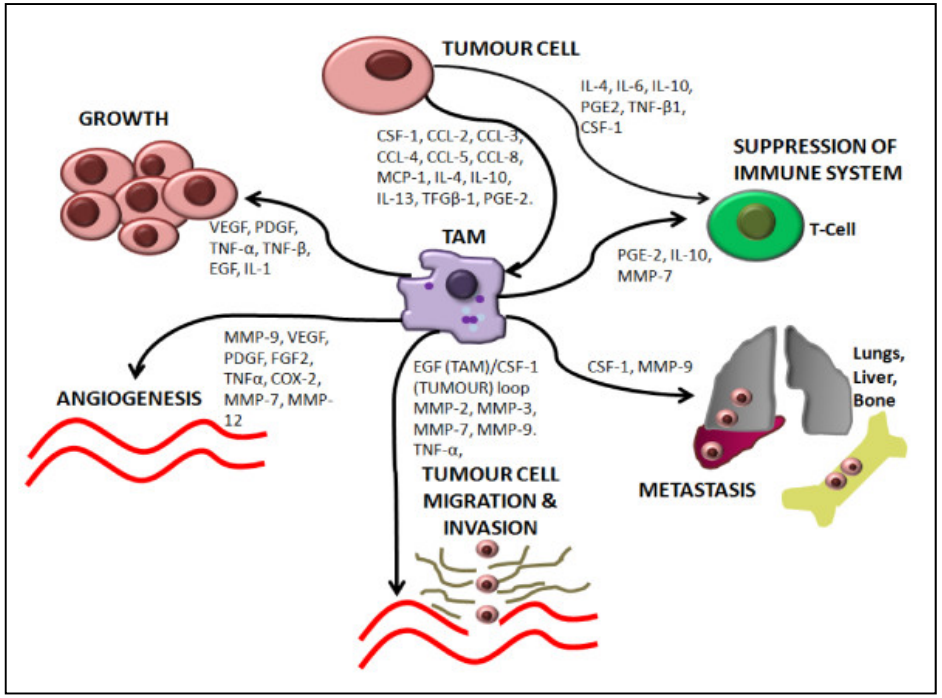
Ref. D. Leyva-Illades, et al., *Transl Gastrointest Cancer;* **1:** 71-80 (2012).

Tumors are composite of many different cellular and non-cellular constituents that surround the malignant cancer cells harboring activating mutations in oncogenes or loss of tumor suppressors that drive tumor growth. **A variety of infiltrating immune cells, cancer-associated fibroblasts, and angiogenic endothelial cells play expanding and critical functions in sustaining cell proliferation, evading growth suppressors, promoting survival, activating invasion and metastasis, and reprogramming energy metabolism.**

Tumor-Associated Macrophages



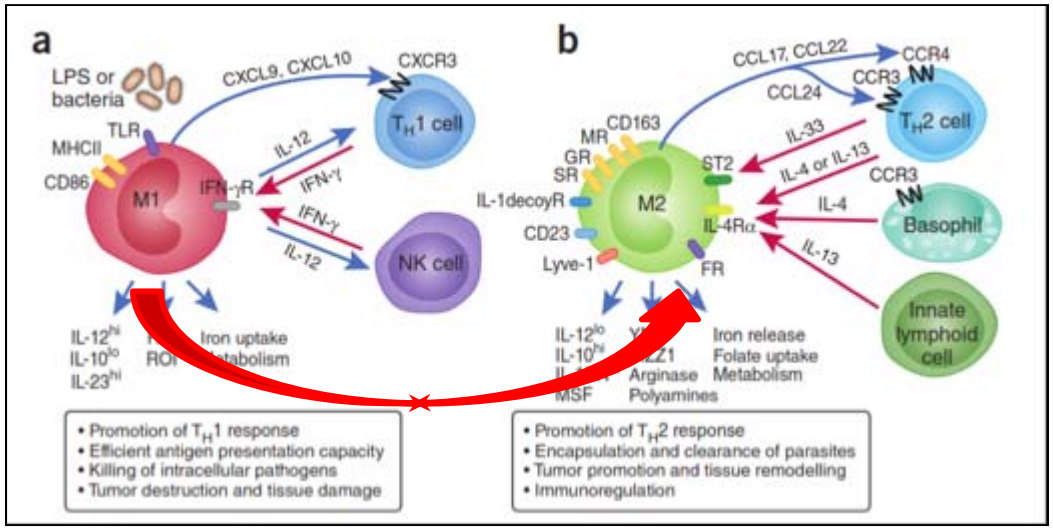
Ref. J.W. Pollard. *Nat Revs Cancer,* **4**, 71-78 (2004)



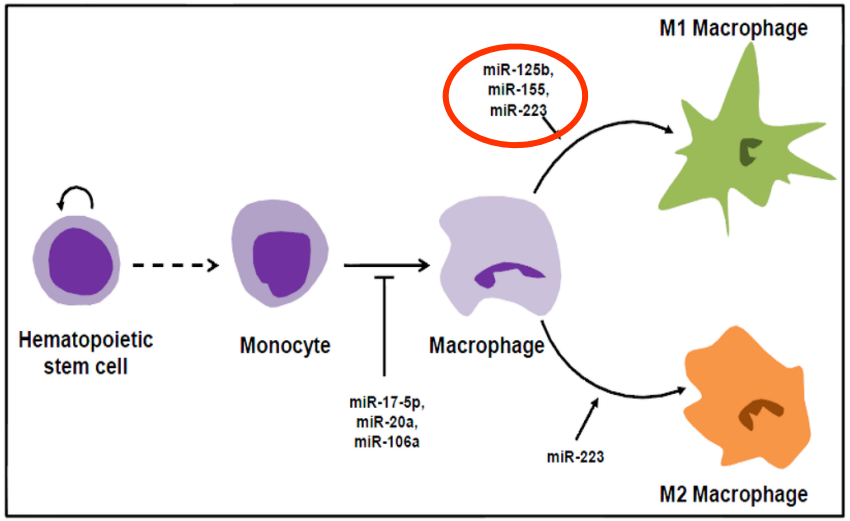
Ref. T.L. Rogers and I. Holen. *J Translational Med,* **9:**177 (2011)

Tumor-associated macrophages (TAMs), **which are predominantly M2 polarized**, affect virtually all aspects of tumor growth and progression, including stem cells, metabolism, angiogenesis, invasion, metastasis, and therapeutic resistance. **Communication between tumor cells and macrophages is critical for tumor malignancy.**

TAM Repolarization from M2 to M1



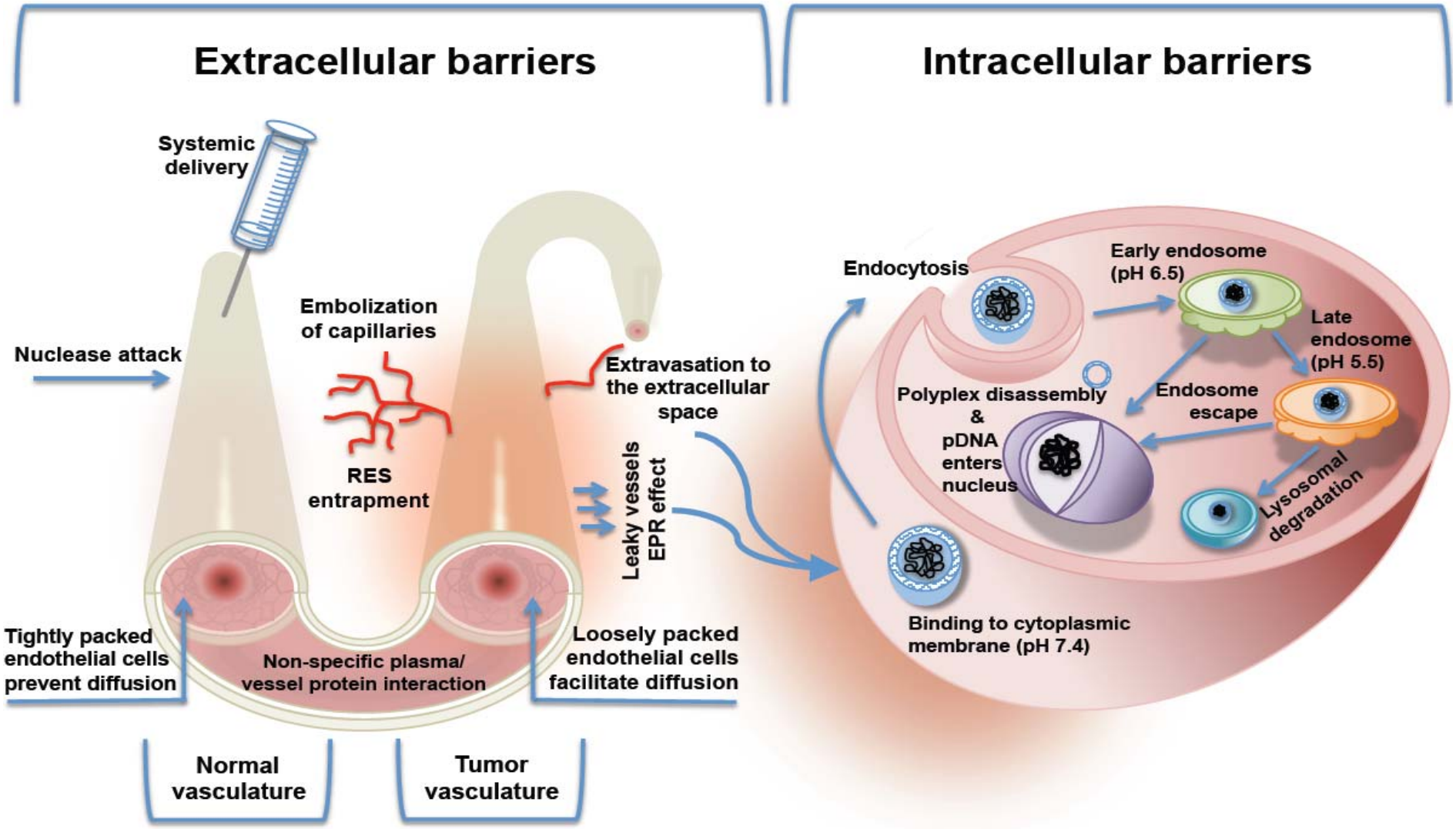
Ref. S.K. Biswas & A. Montovani, *Nat Immunol.,* **11:** 889-896 (2010).



Ref. R.C. Chang, *et al., Cells,* **3**(3): 702-712 (2014).

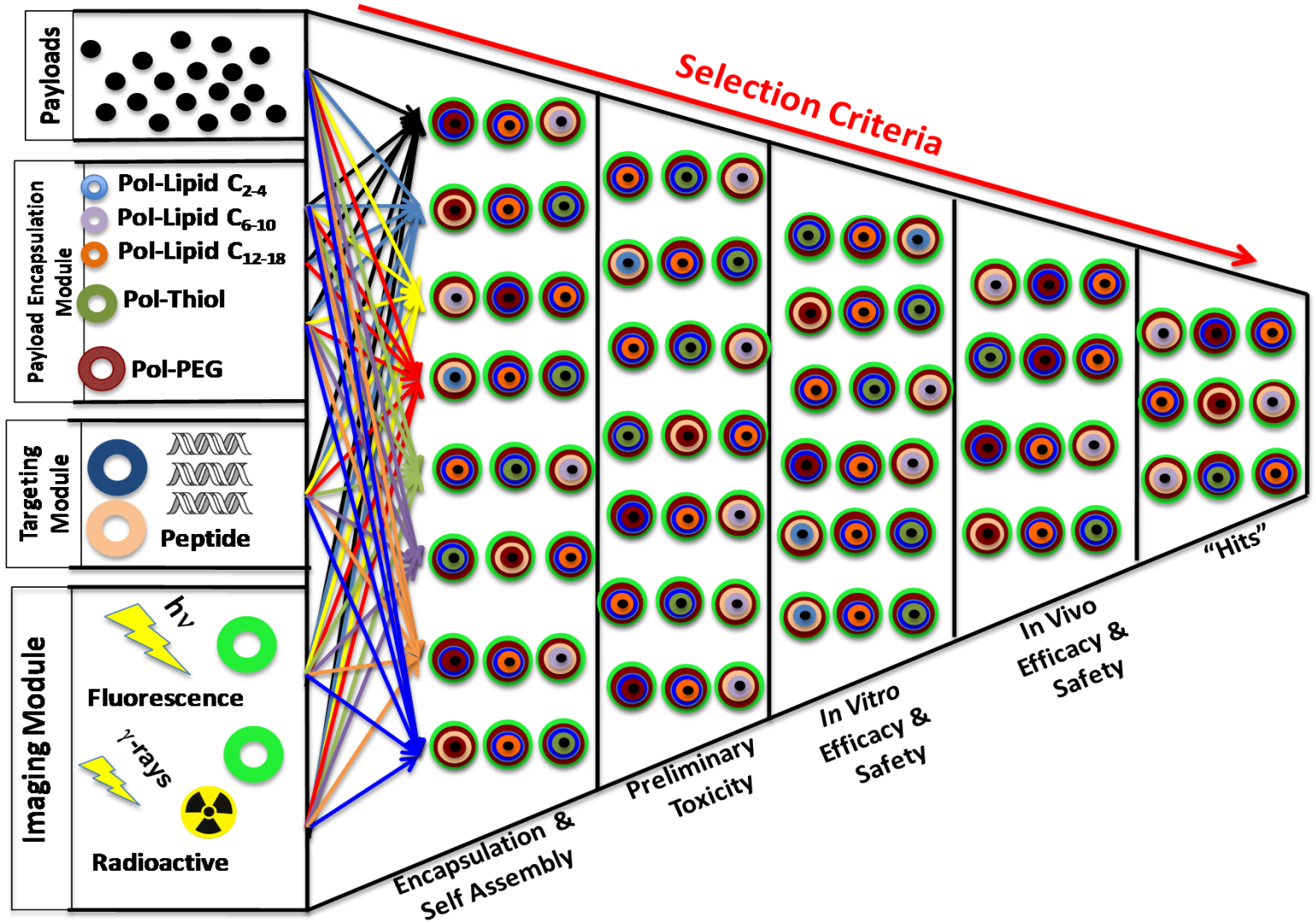
- Reprogramming TAMs from a predominant M2 to M1 phenotype would provide an opportunity for anti-tumor response and potentially improve cancer immunotherapy.
- Several microRNA's (e.g., miR-155 and miR-125b) have shown to change macrophage polarity from M2 to M1.

Barriers to Delivery of Nucleic Acids



Ref. *http://http://www.intechopen.com/books/gene-therapy-tools-and-potential-applications/cancer-gene-therapy-key-biological-concepts-in-the-design-of-multifunctional-non-viral-delivery-syst*

Combinatorial-Designed Nano-Assemblies



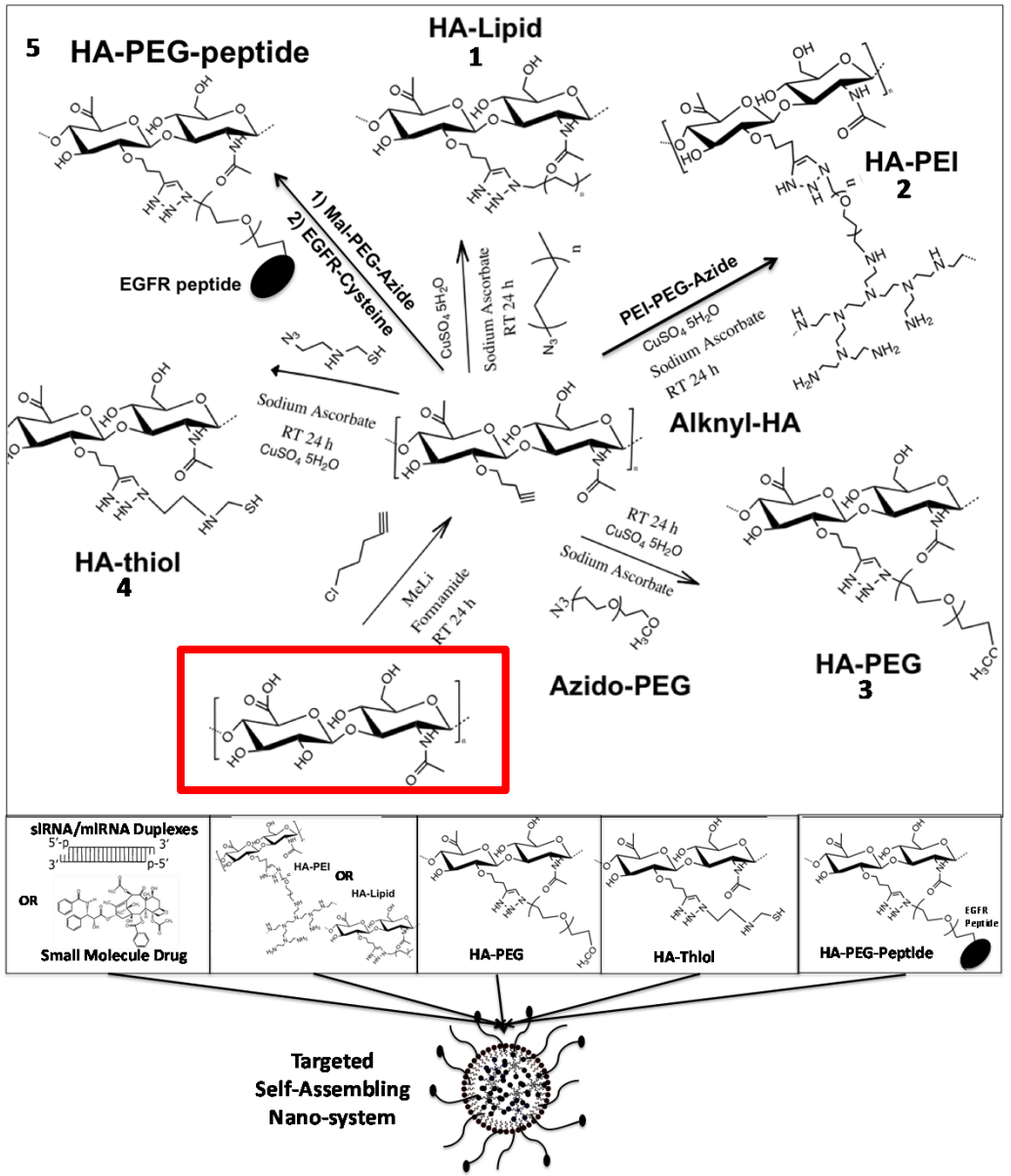
Shanthi Ganesh

Arun Iyer

Amit Singh

Hyaluronic Acid Derivatives

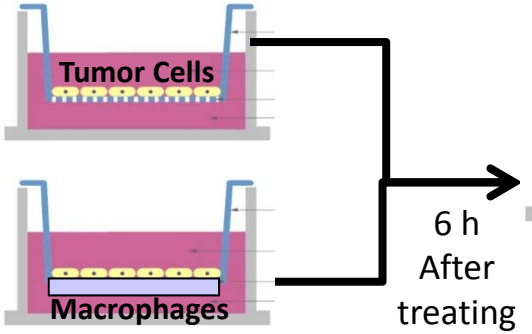
- Hyaluronic acid (HA) is a natural, biocompatible, and biodegradable polymer
- Long history of safe use in clinical applications (e.g., for visco-supplementation therapy in arthritis)
- Intrinsic targeting to CD44 receptors over-expressed on tumor cells (e.g., cancer stem cells) and macrophages
- Modular HA nanoparticle platform synthesized using different functional substitutions (EDC coupling or "click" chemical cojugation)
- Combinatorial library of formed nanoparticles by self-assembly of the constituents at specific weight ratios of each (i.e., LEGO blocks)



Exosome Transfer from Human Pancreatic Tumor Cells to Macrophages using a Co-Culture System

Mei-Ju Su

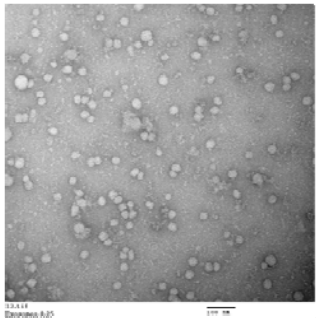
Transwell® Co-Culture System



6 h After treating LPS/IFN-γ

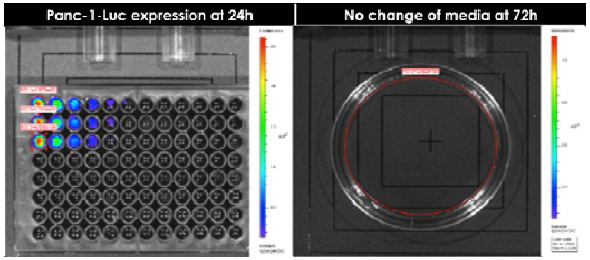
48h & 72h

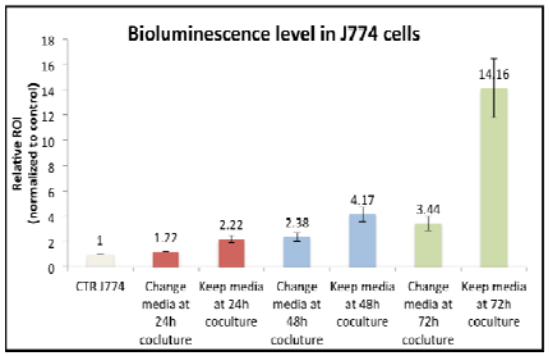
Microscopy and RT-PCR Analysis of Exosome-Mediated Macrophage Polarization



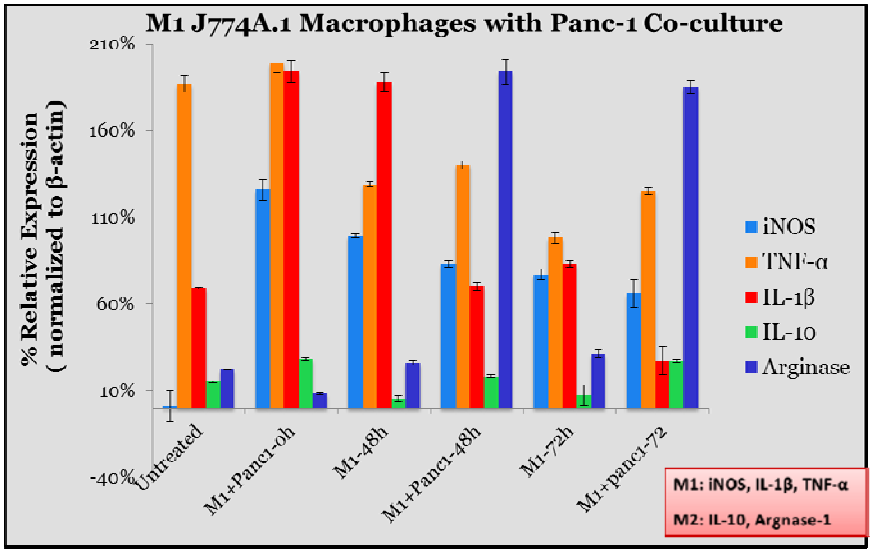
TEM image of Panc-1 Exosomes

Luciferase Expressing Panc-1 Cells



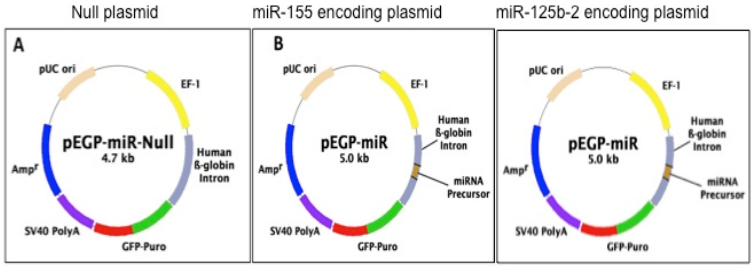


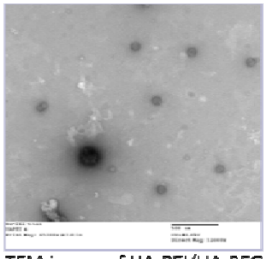
RT-PCR Analysis of M1/M2 Macrophage Polarization Markers



Ref. M.J. Su, *et al., Scientific Reports,* (In press).

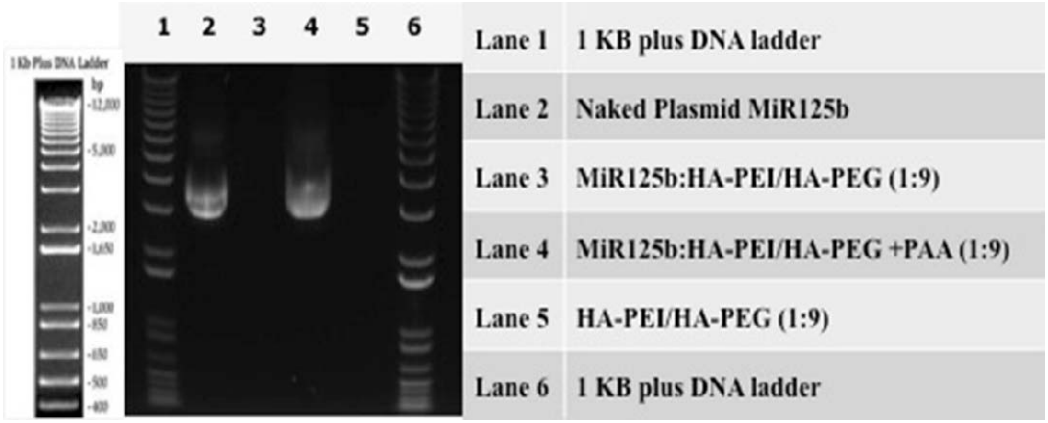
MicroRNAs 155 and 125b Transfection in Panc-1 Cells with HA-PEI/HA-PEG Nanoparticles



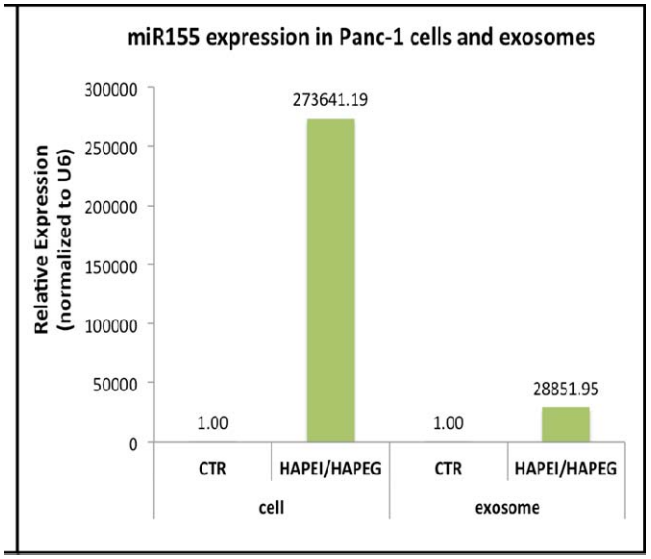


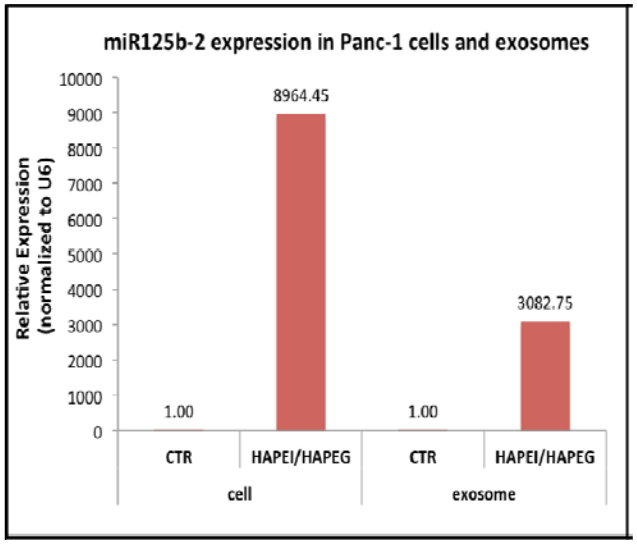
TEM image of HA-PEI/HA-PEG Nanoparticles

Agarose gel electrophoresis analysis of plasmid encapsulation in HA-PEI/HA-PEG nanoparticles



Lane 1	1 KB plus DNA ladder
Lane 2	Naked Plasmid MiR125b
Lane 3	MiR125b:HA-PEI/HA-PEG (1:9)
Lane 4	MiR125b:HA-PEI/HA-PEG +PAA (1:9)
Lane 5	HA-PEI/HA-PEG (1:9)
Lane 6	1 KB plus DNA ladder

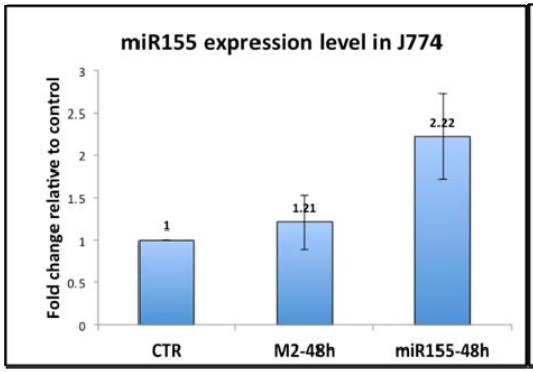


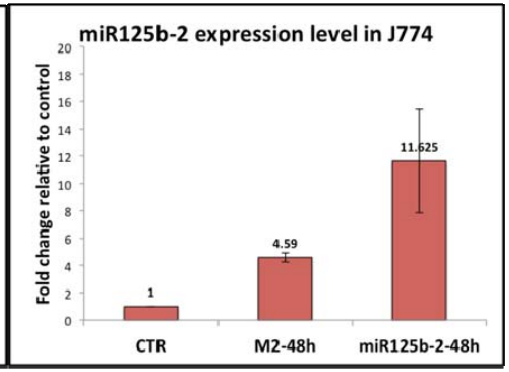


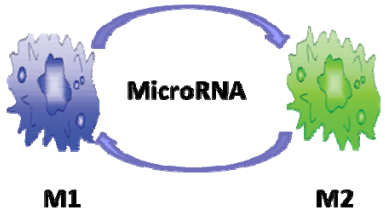
Human pancreatic cancer cells (Panc-1) transfected with plasmid DNA expressing miR-155 and miR-125b and the levels of expression in cells relative to control were measured using PCR. The plasmid dose was 20 μg per 200,000 cells.

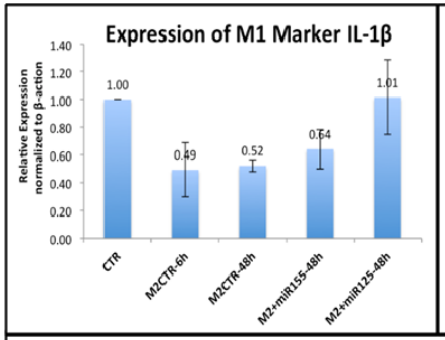
Ref. M.J. Su, *et al., Scientific Reports,* (In press).

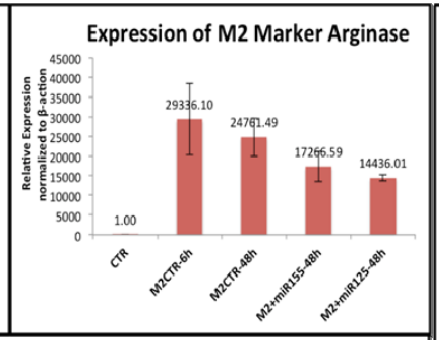
Change in Macrophage Polarization from M2 to M1 with Exosome-Mediated Transfer of MicroRNAs 155 and 125b

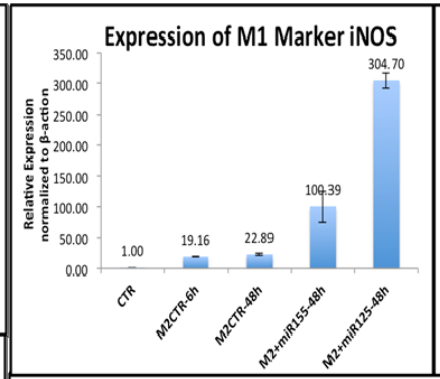


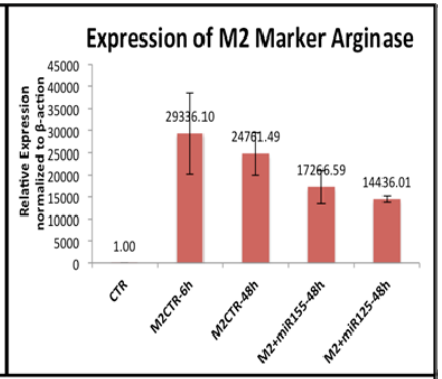


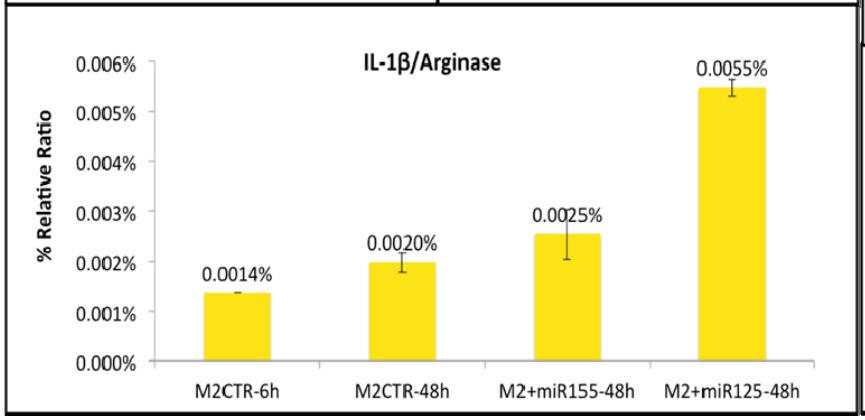


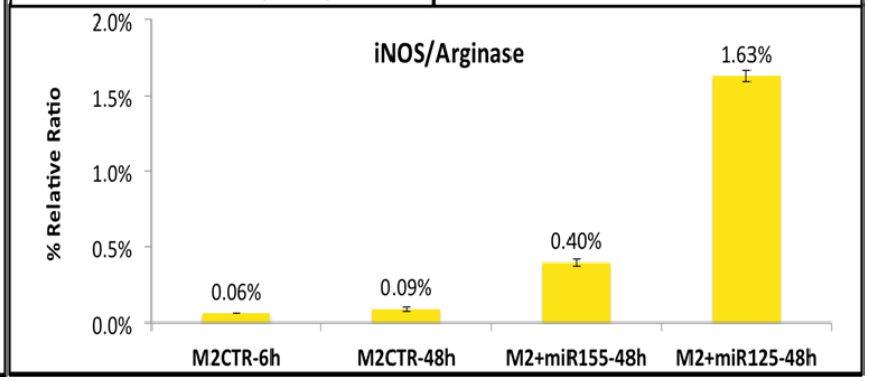








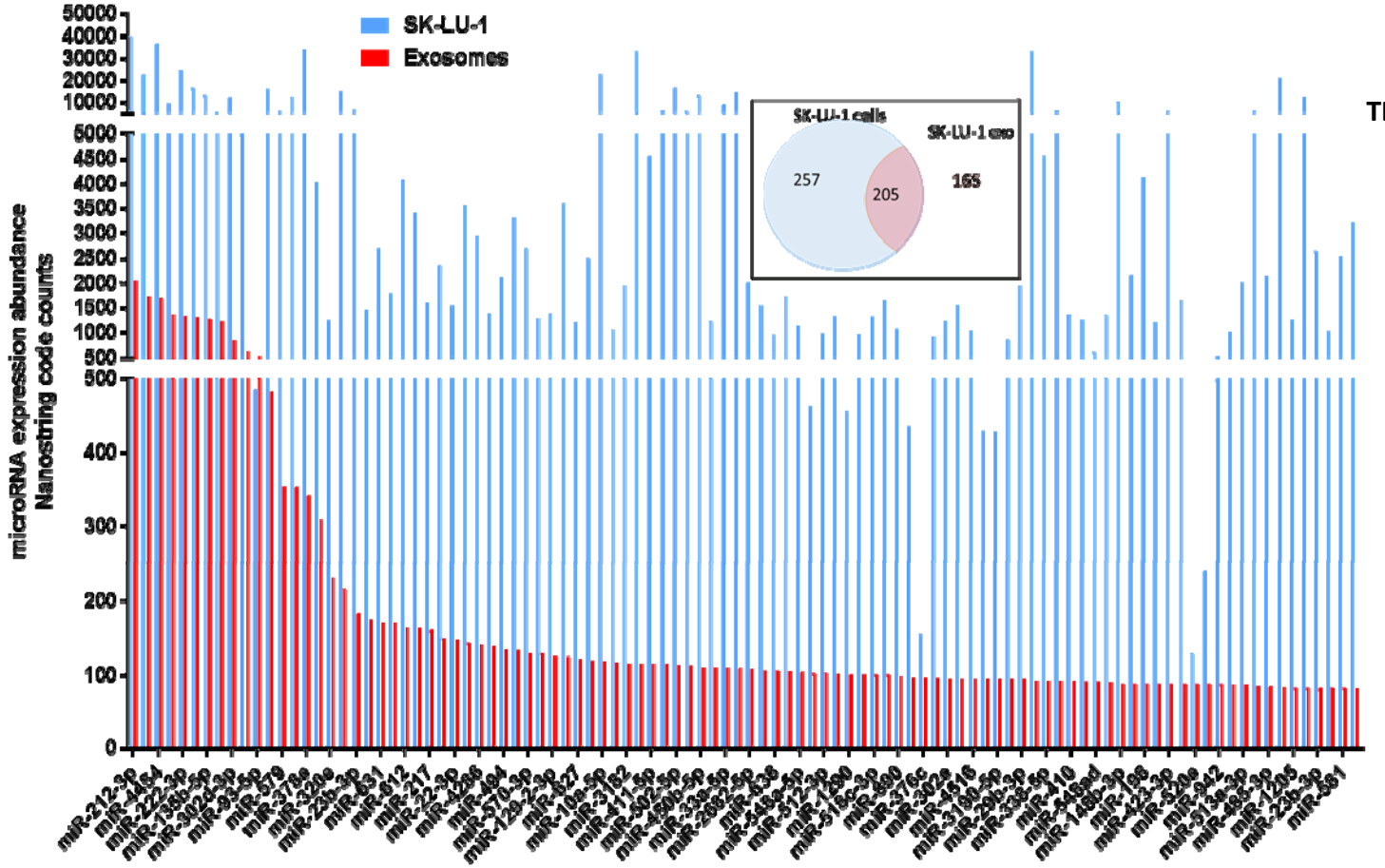




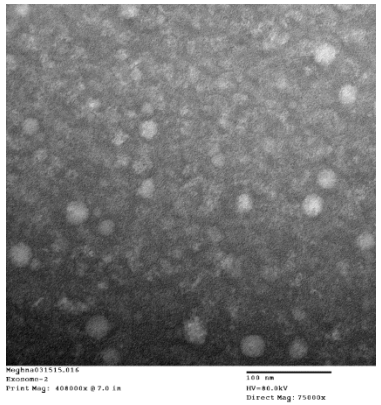
Ref. M.J. Su, *et al., Scientific Reports,* (In press).

MicroRNA Profiling in Cytosol and Exosomes in SK-LU1 Non-Small Cell Lung Cancer Cells

Malav Trivedi



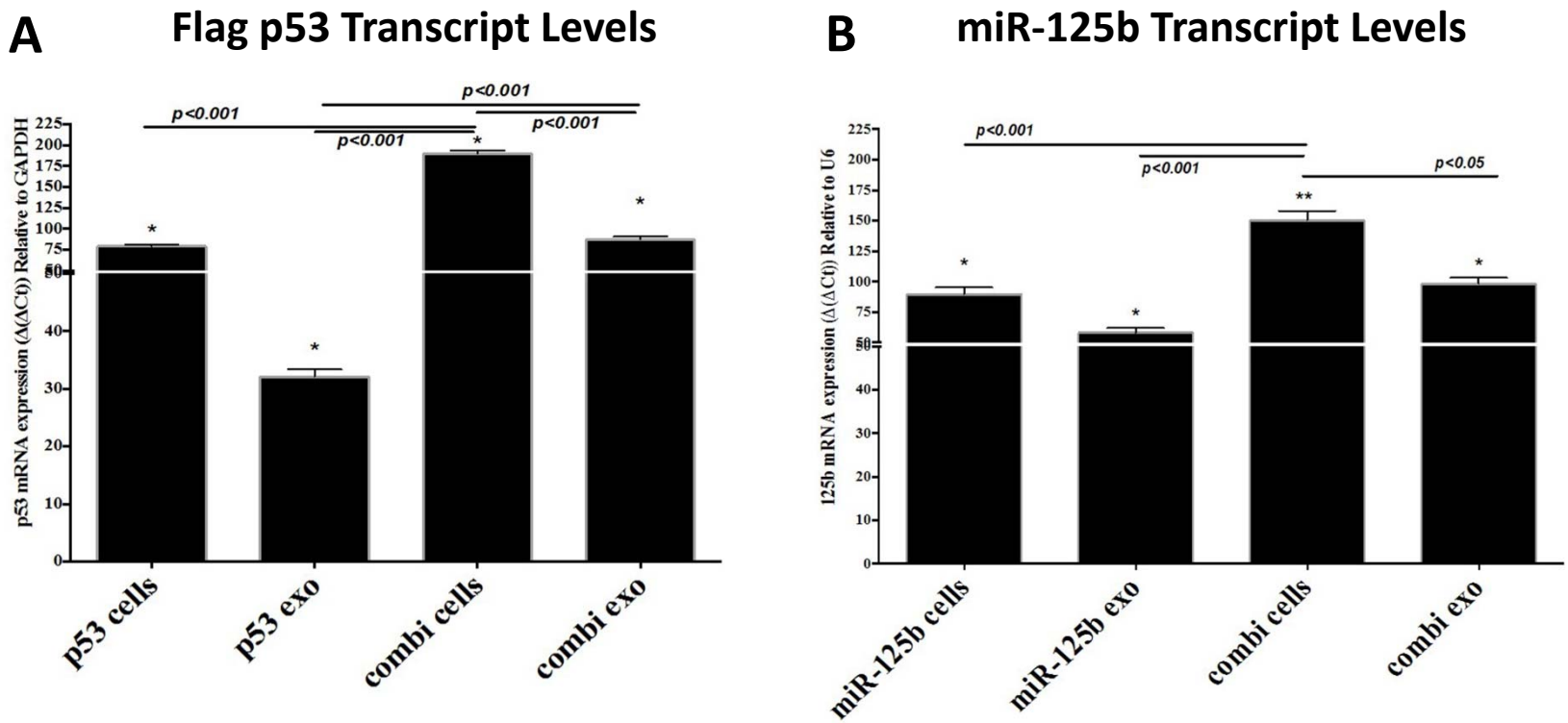
TEM image of SK-LU1 exosomes



Meghna Talekar

Ref. M. Trivedi, *et al., Oncogenesis,* (In press)

Changes in wt-p53 and miR-125b Levels in Cytosol and Exosomes upon Transfection with HA-Based Nanoparticles

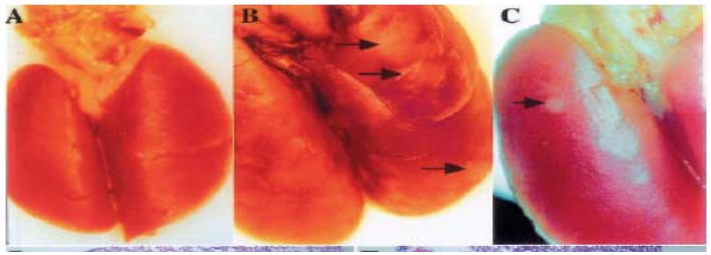


(A) Quantitative qRT-PCR analysis of expression of wt-p53 in cells (p53/cells) and in exosomes (p53/exo) when transfected with wt-p53 expressing plasmid DNA alone or in combination with miRNA-125b expressing plasmid DNA in cells (combi/cells) and in exosomes (combi/exo) after 18 hours of incubation. **(B)** Quantitative qRT-PCR analysis of expression of miR-125b expression in cells (miR-125b/cells) and in exosomes (miR-125b /exo) when transfected with miRNA-125b expressing plasmid DNA alone or in combination with wt-p53 expressing plasmid DNA in cells (combi/cells) and in exosomes (combi/exo) after 18 hours of incubation.

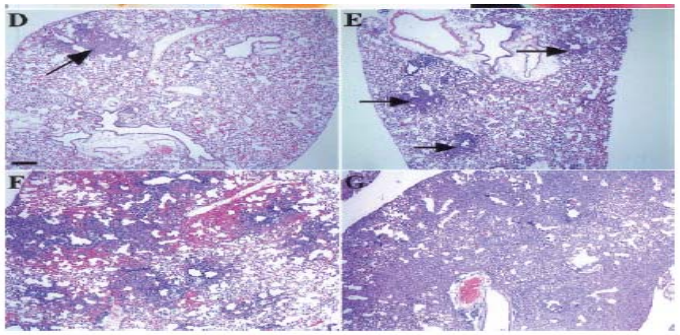
Ref. M. Trivedi, *et al., Oncogenesis,* (In press).

Establishment of KRAS/p53 Mutant Genetically-Engineered Mouse Model of Non-Small Cell Lung Cancer

Wild type lungs **Mutant 4 wks** **Mutant 10 wks***



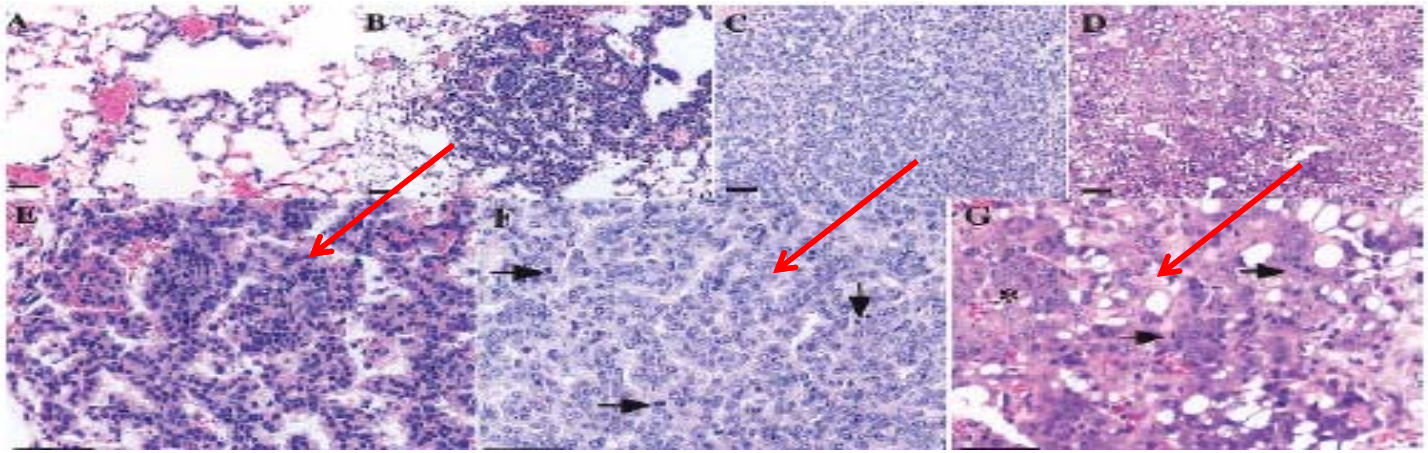
6 weeks post AdeCre dosing – variable viral dose



Time course analysis of stages of tumor progression in Lox-K-ras-G12D mice

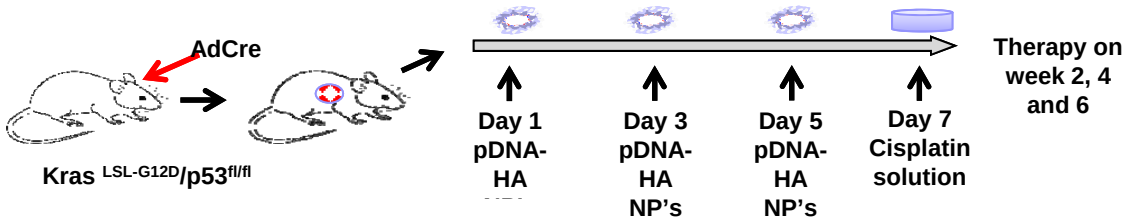
Papillary adenoma 6 weeks **Large adenoma 12 weeks** **Adenocarcinoma 16 weeks**

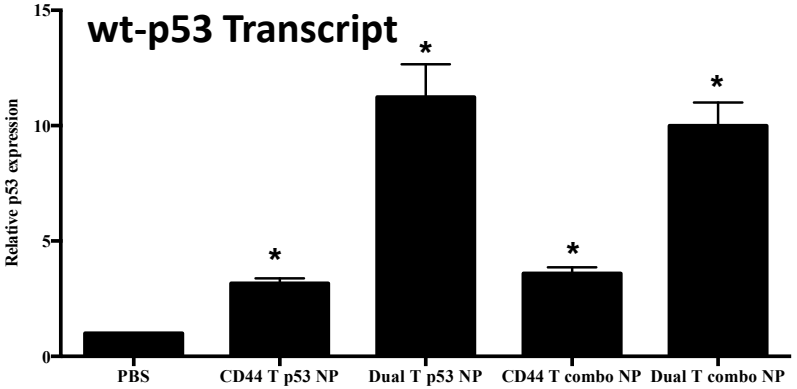
Atypical adenomatous hyperplasia 2 weeks

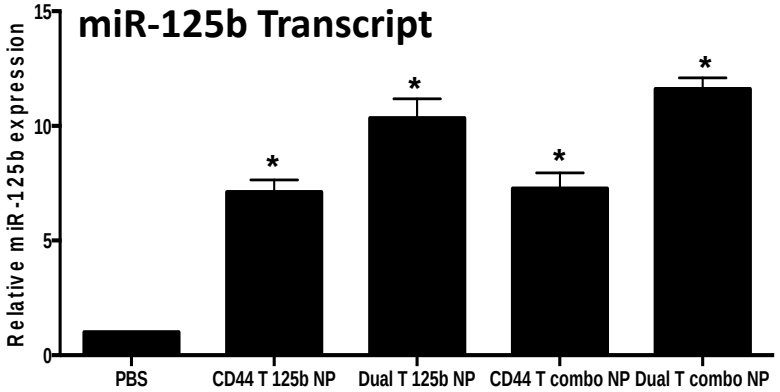


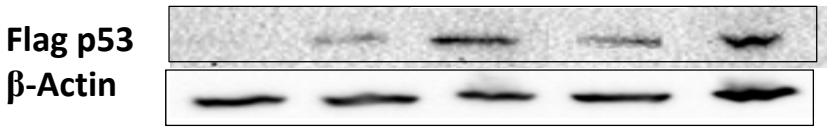
Ref. M. Talekar, *et al., Molecular Therapy,* **24(4):** 759–769 (2016).

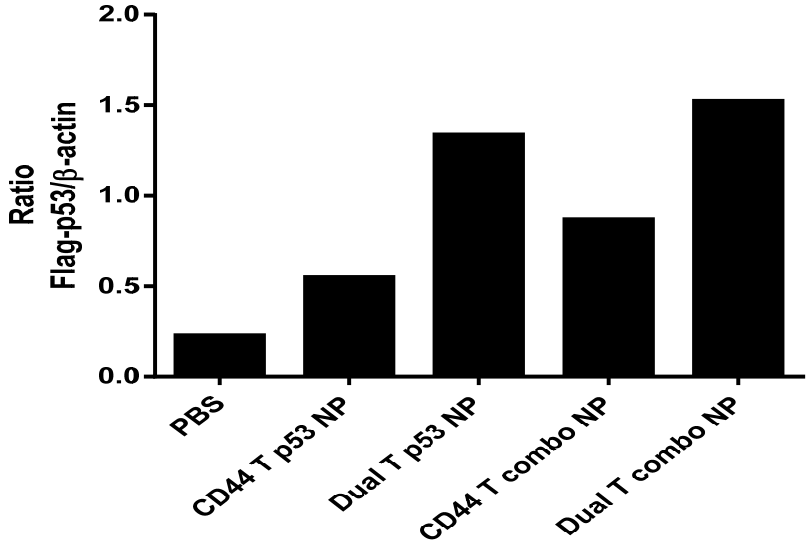
In Vivo wt-p53 and miR-125b Transfection in Lung Tumor Tissues in the KRAS/p53 GEM Models





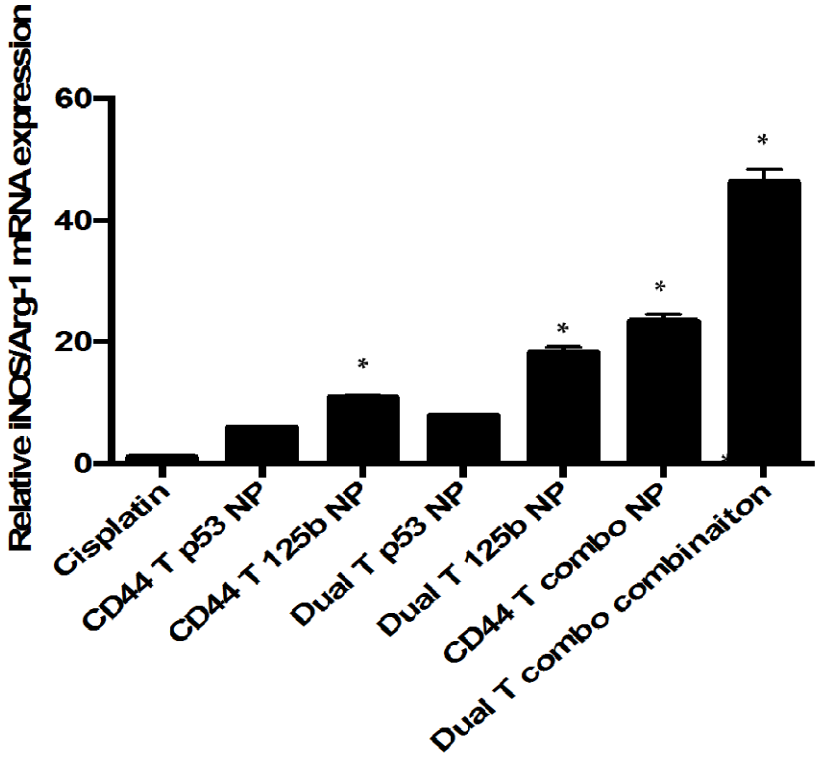


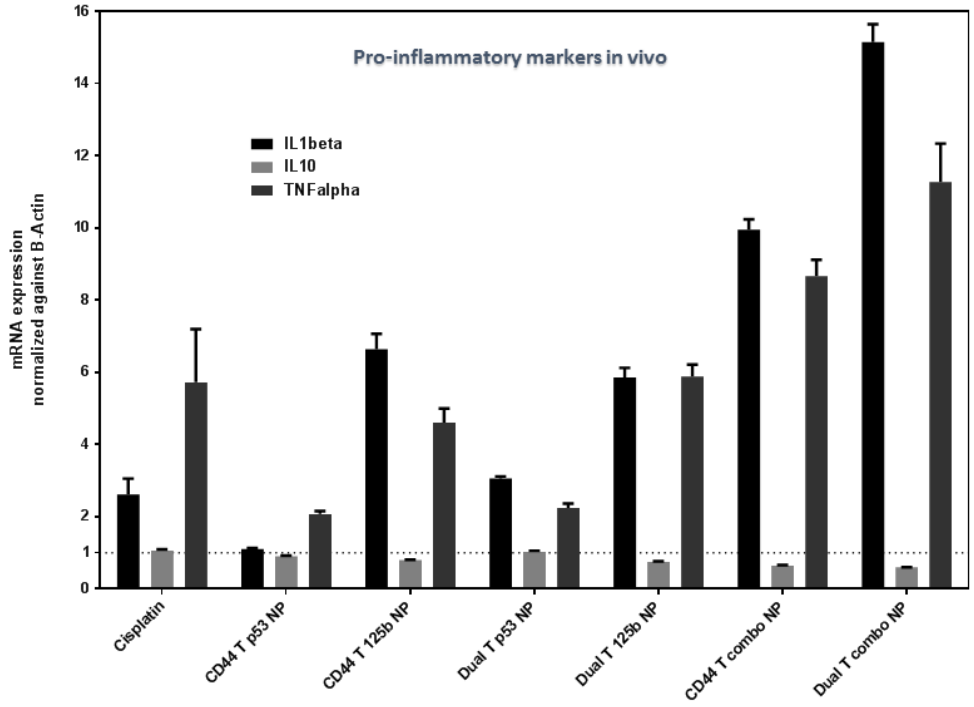




Ref. M. Talekar, *et al., Molecular Therapy,* **24(4):** 759–769 (2016).

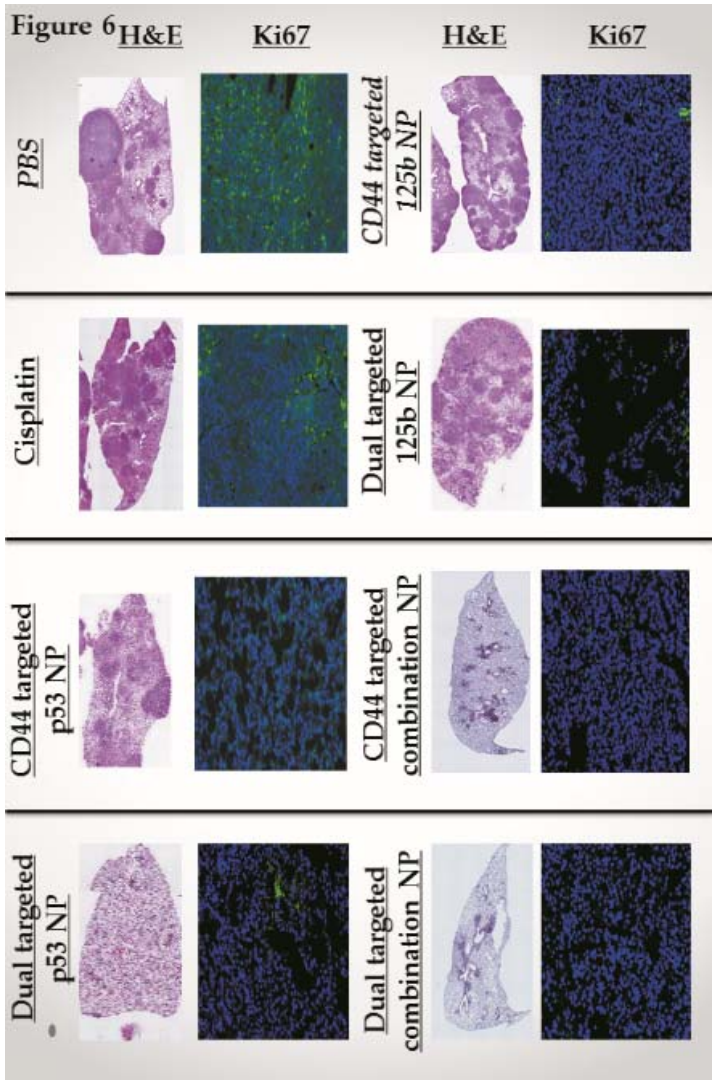
Changes in the M1/M2 Macrophage Markers and Inflammatory Cytokine Levels in Tumor Tissues

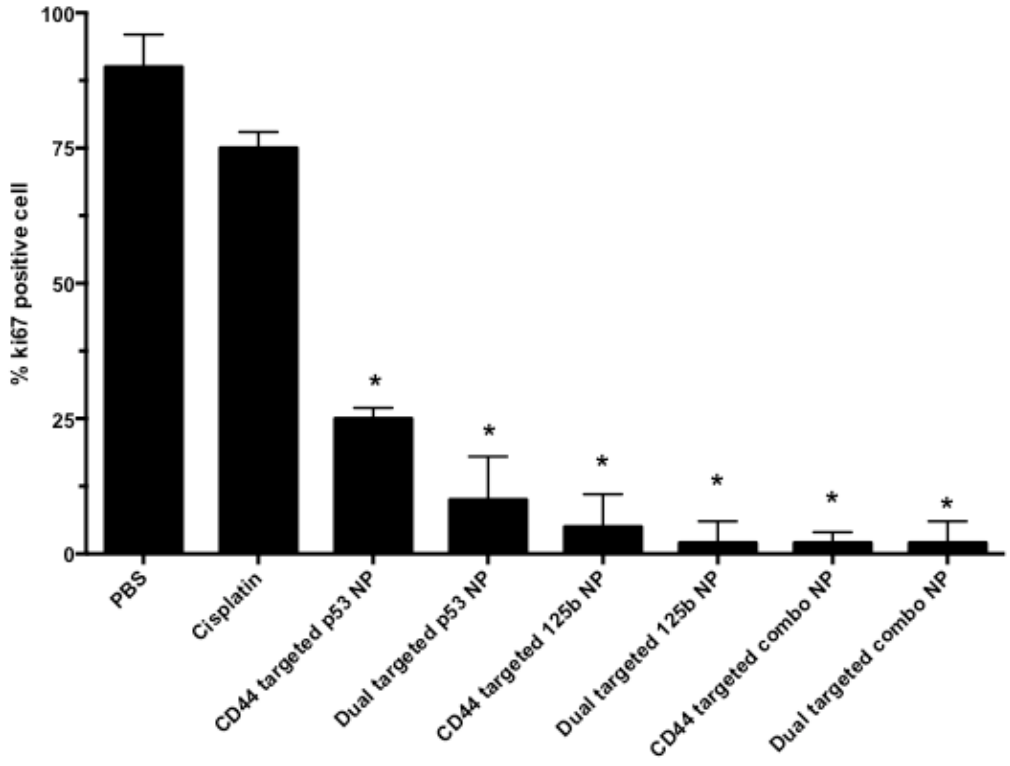




Ref. M. Talekar, *et al., Molecular Therapy,* **24(4):** 759–769 (2016).

Changes in the Ki-67 Expression Profile in Tumor Tissues upon Transfection with wt-p53 and miR-125b

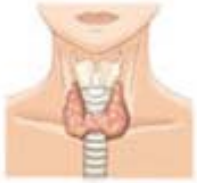




Ref. M. Talekar, *et al., Molecular Therapy,* **24(4):** 759–769 (2016).

Chronic Inflammatory Diseases

Brain
Multiple Sclerosis
Guillaun-Barre Syndrome
Autism

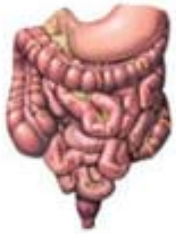


Thyroid
Thyroiditis
Hashimoto's Disease
Graves' Disease

Blood
Leukemia
Lupus Erythematosus
Hemolytic Dysglycemia

Bones
Rheumatoid Arthritis
Ankylosing Spondylitis
Polymyalgia Rheumatica

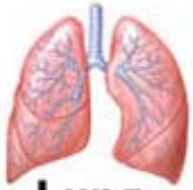
GI Tract
Celiac's Disease
Crohn's Disease
Ulceratic Colitis
Diabetes Type I



>100 Autoimmune Diseases

Muscles
Muscular Dystrophy
Fibromyalgia

Nerves
Peripheral Neuropathy
Diabetic Neuropathy

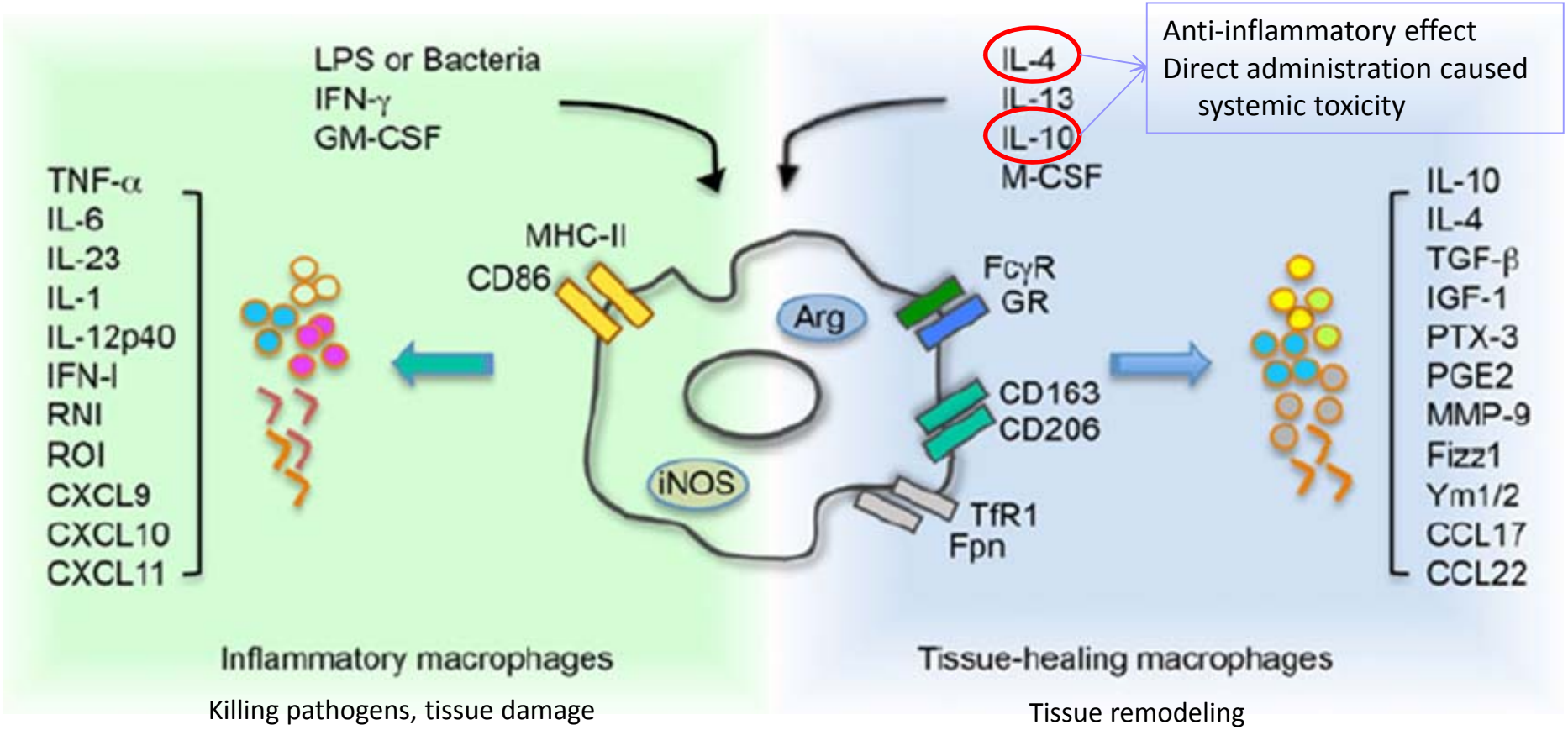


Lung
Fibromyalgia
Wegener's Granulomatosis

Skin
Psoriasis
Vitiligo
Eczema
Scleroderma

Macrophage Functional Polarization

Macrophages: Cells of the immune system involving in phagocytosis, antigen-presentation, and modulation of the immune response



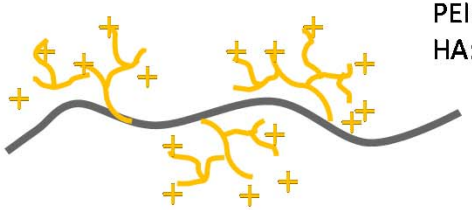
M1 macrophages **M2 macrophages**

Ref. L. Bosurgi, *et al., Frontiers in Immunol.,* **2:** 62 (2011).

Encapsulation and Delivery of Nucleic Acid Constructs in HA-PEI Nanoparticles

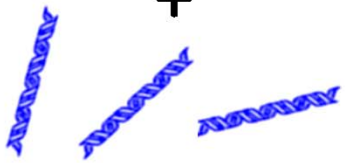
Huyen Tran

PEI: complexation with nucleic acid
HA: targeting CD44, mask toxicity of PEI



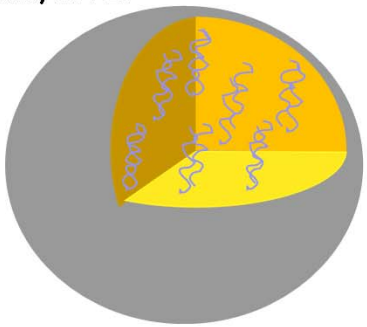
HA-PEI

+

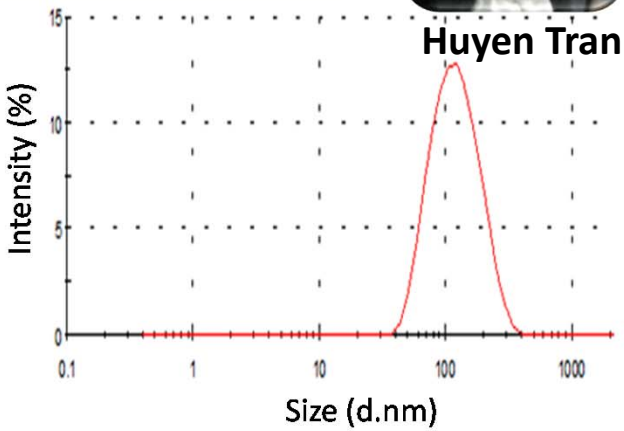


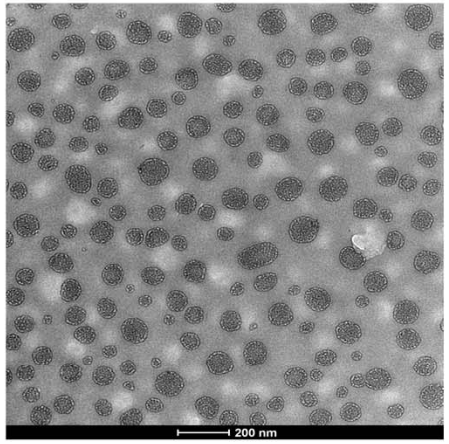
pDNA-IL4/IL10
or miR-223

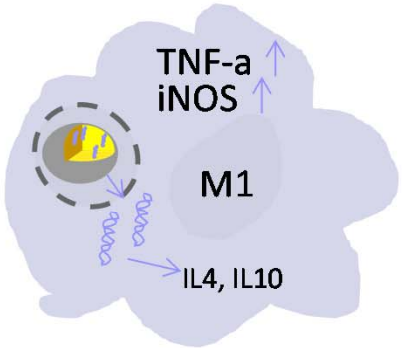
Self-assembly
Aqueous media



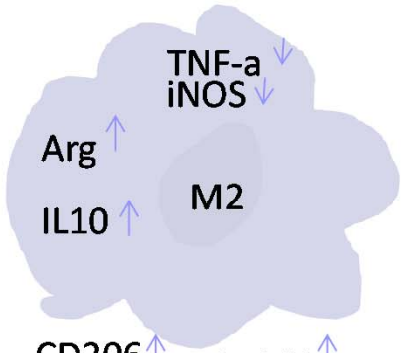
HA-PEI/pDNA
nanoparticles





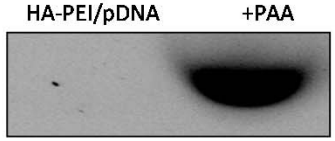


Re-polarization



CD80
Pro-inflammatory
M1 macrophages

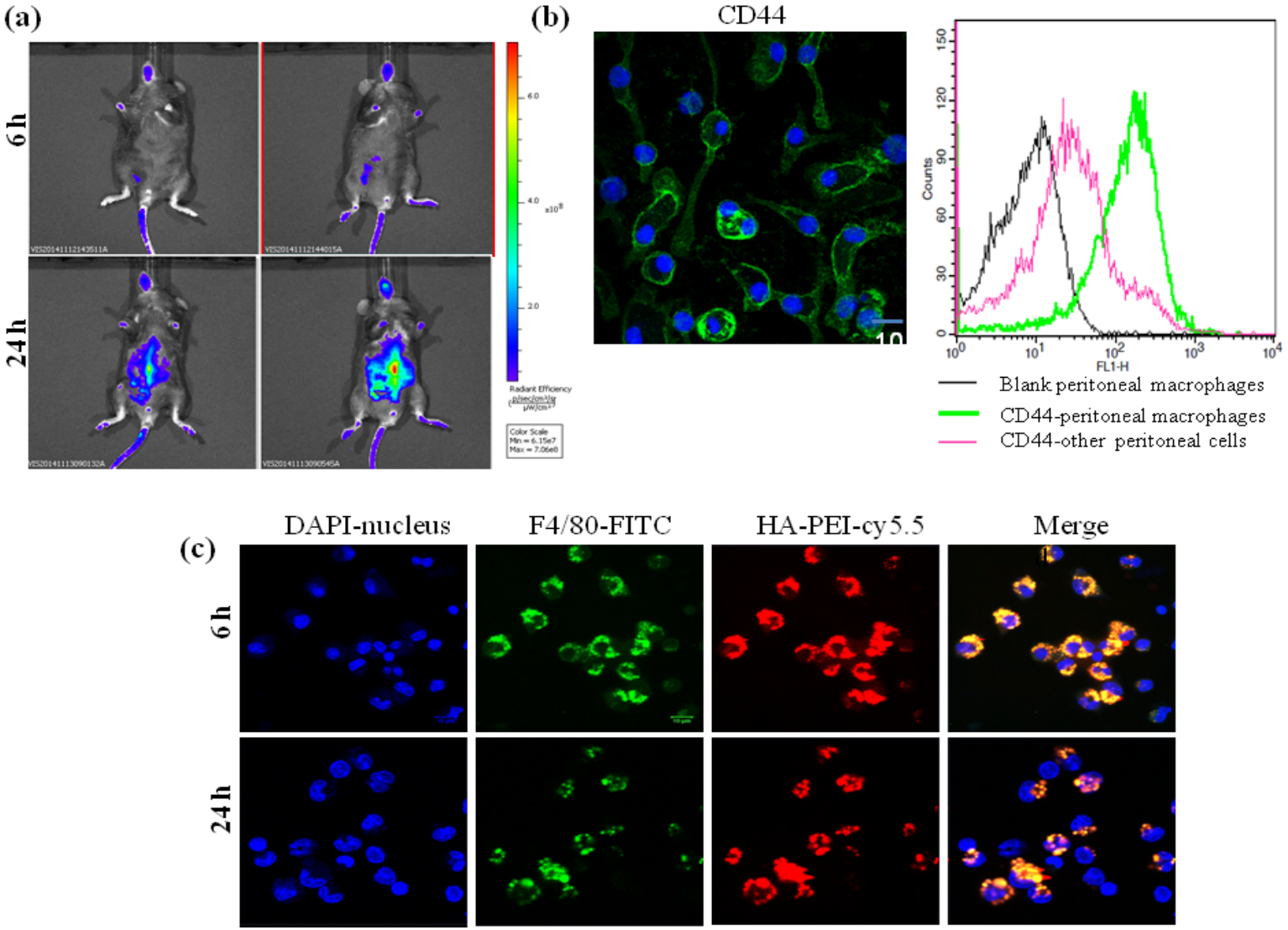
CD206 CD163
Anti-inflammatory M2
macrophages



Gel retardation showing
100% pDNA encapsulation

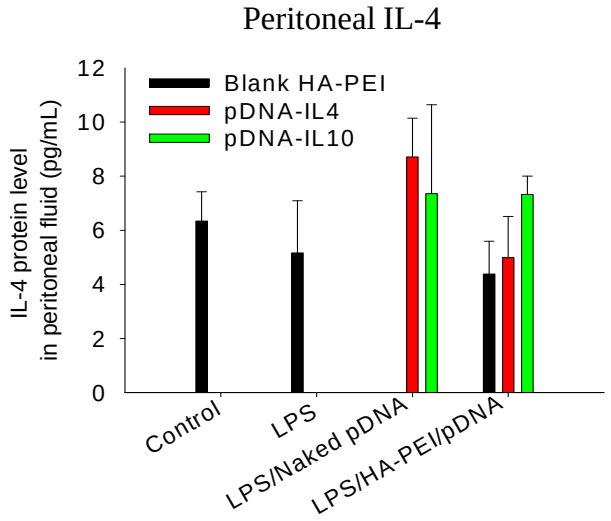
Ref. T.H. Tran, *et al., Scientific Reports,* **5:** 16632 (2015).

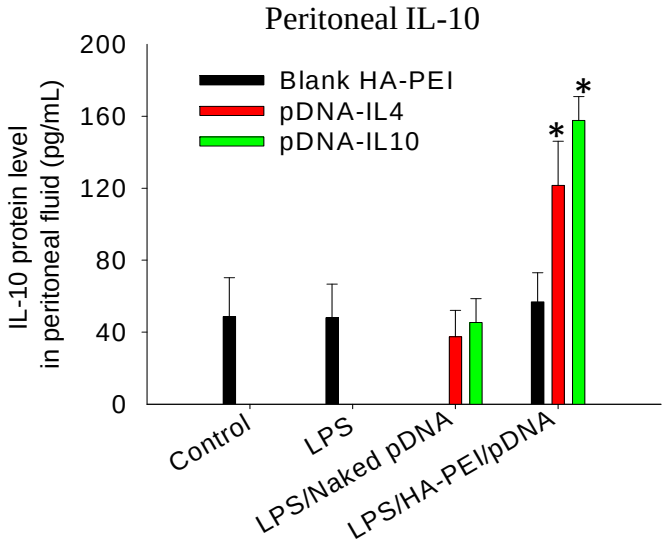
In Vivo CD44-Specific Targeted Delivery in Peritoneal Macrophages upon IP Administration

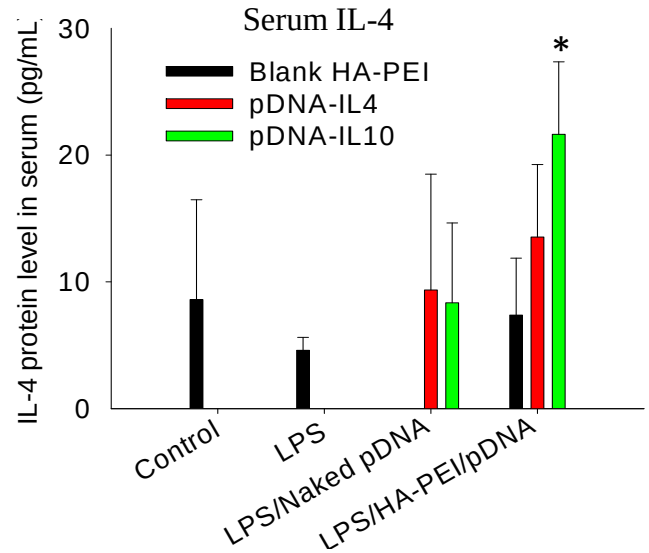


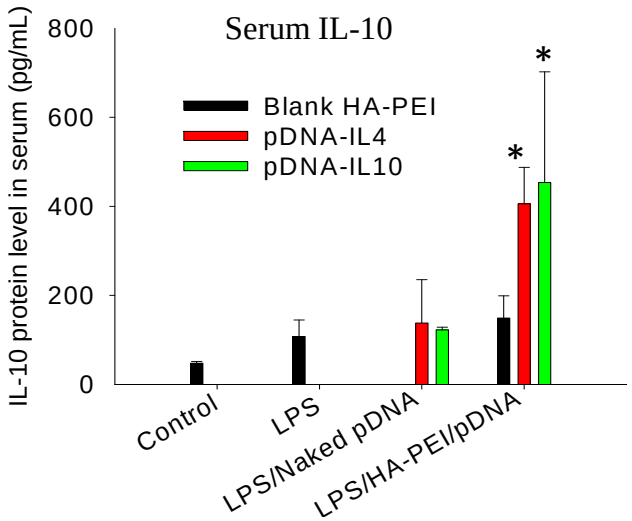
Ref. T.H. Tran, *et al., Scientific Reports,* **5:** 16632 (2015).

In Vivo Transfection with IL4 and IL10 Plasmid DNA using HA-PEI Nanoparticles



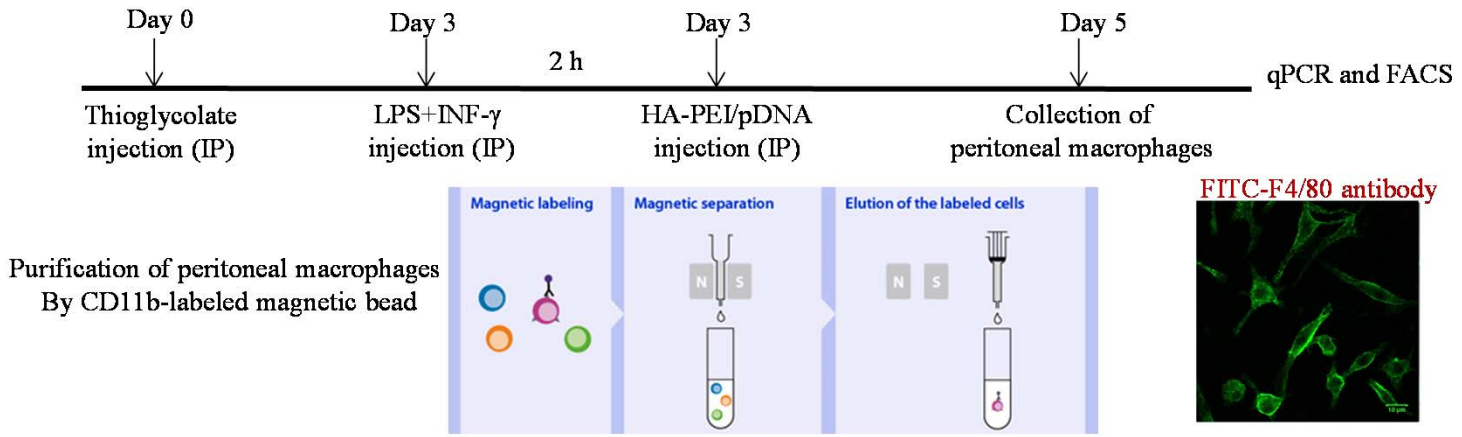


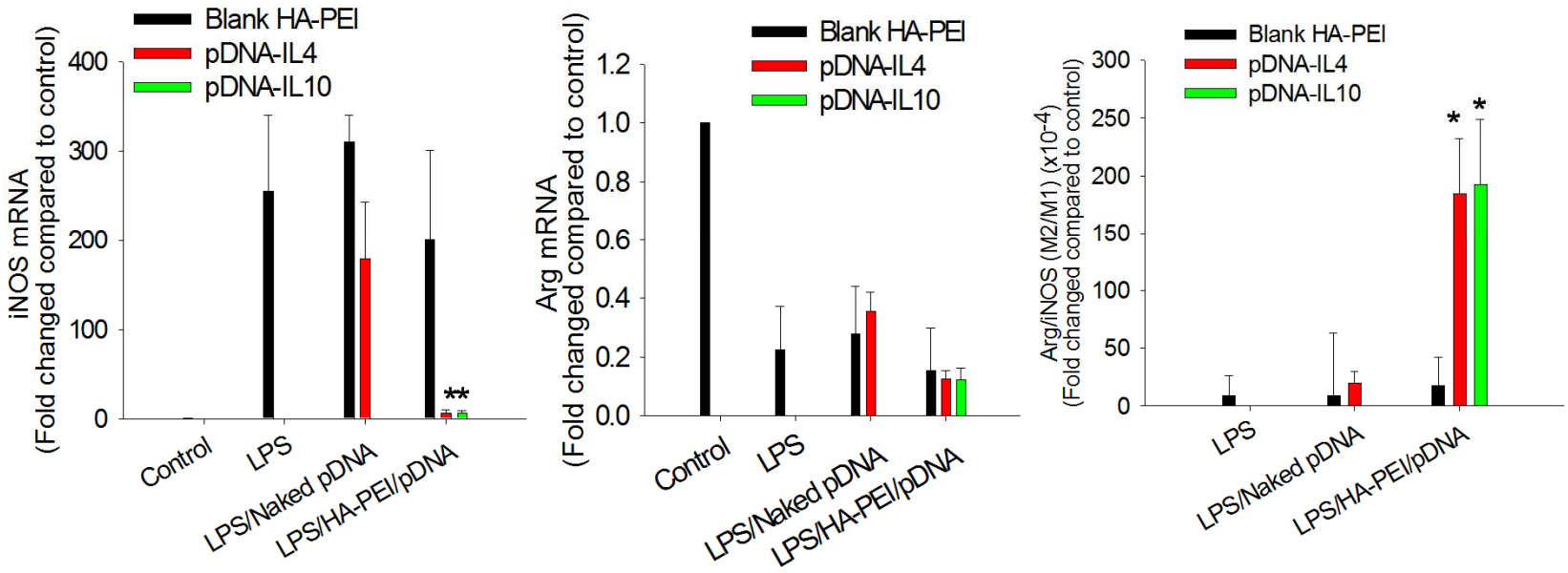




Ref. T.H. Tran, *et al., Scientific Reports,* **5:** 16632 (2015).

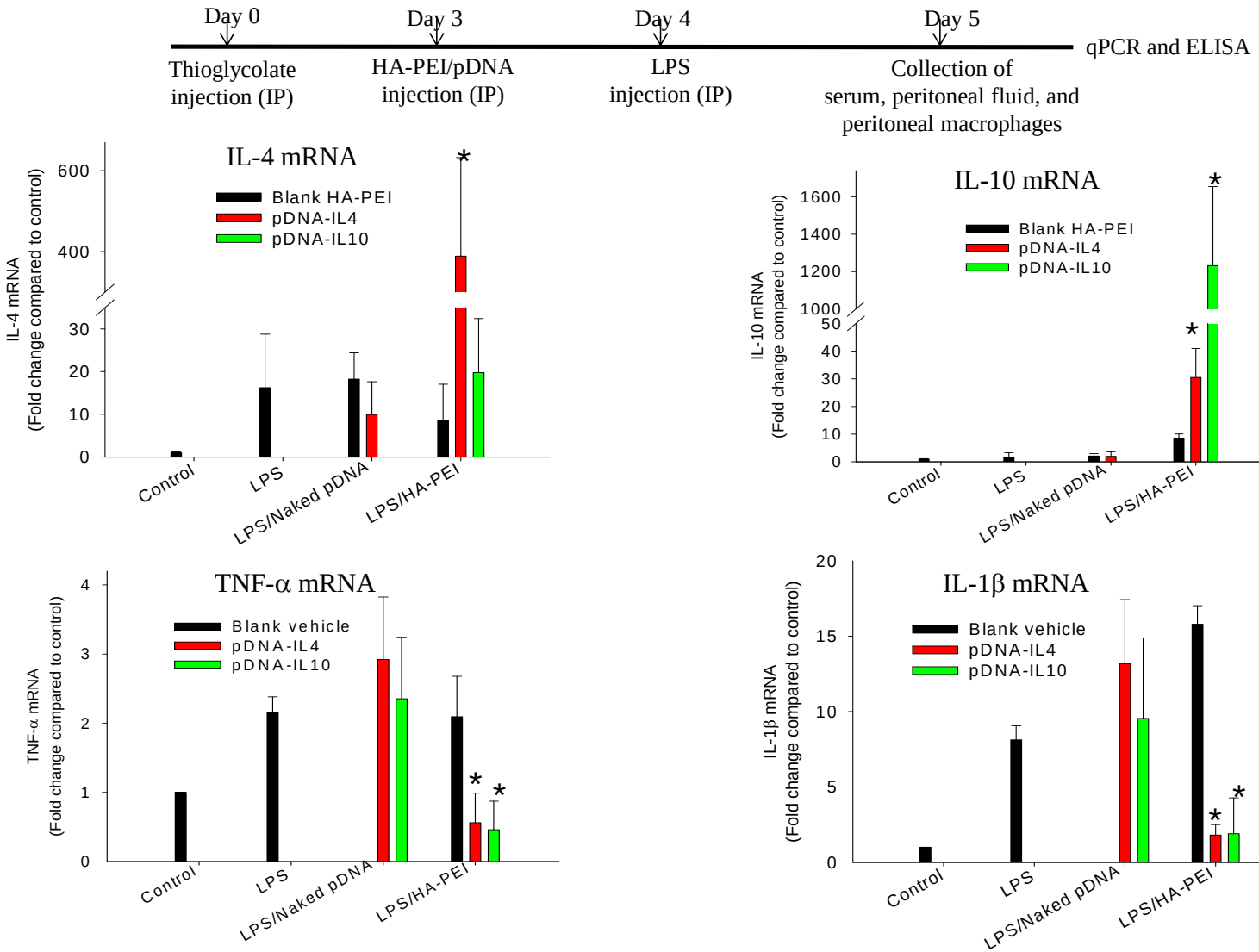
In Vivo Repolarization of Peritoneal Macrophages using IL4/IL10 Plasmid DNA Transfected in HA-PEI Nanoparticles





Ref. T.H. Tran, *et al., Scientific Reports,* **5:** 16632 (2015).

In Vivo Pro- and Anti-Inflammatory Cytokine Levels in Serum After IL4/IL10 Transfection with HA-PEI Nanoparticles



Ref. T.H. Tran, *et al., Scientific Reports,* **5:** 16632 (2015).

Summary

- There is a significant need to facilitate clinical translation of advances in molecular medicine into effective disease diagnosis and therapeutic strategies.
- Nanotechnology has an important role to play in disease diagnosis, imaging, and therapy and potentially may advance personalized medicine.
- In cancer, we are interested in reprogramming with exosome-mediated tumor microenvironment with genetic therapies using combinatorial-designed hyaluronic acid-based nanoparticles platform.
- For anti-inflammatory therapy, we are evaluating macrophage repolarization approaches and have evaluated IL-10 and microRNA-223 delivery and transfection using CD44 targeting hyaluronic acid nanoparticles.
- For each example, our focus is on solving important medical problems with innovative solutions that use inexpensive and safe materials, as well as, scalable fabrication methods so that these promising experimental technologies are realized in the clinic in the near future.