Nanotechnology applications in medical diagnosis, imaging, and therapy

Mansoor M. Amiji

*University Distinguished Professor, Department of Pharmaceutical Sciences, School of Pharmacy, Northeastern University, USA, m.amiji@neu.edu*

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Translational Nano-Medicine: Targeted Delivery Systems for Cancer and Inflammatory Diseases

Mansoor M. Amiji, PhD

University Distinguished Professor
Department of Pharmaceutical Sciences and the Nanomedicine Education and Research Consortium (NERC)
Northeastern University
140 The Fenway Building
Boston, MA 02115
Website: http://www.northeastern.edu/amijilab
The Tumor Microenvironment

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

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.

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

Extracellular barriers

- Systemic delivery
- Embolization of capillaries
- RES entrapment
- Nuclease attack
- Tightly packed endothelial cells prevent diffusion
- Non-specific plasma/vessel protein interaction
- Loosely packed endothelial cells facilitate diffusion

Intracellular barriers

- Extravasation to the extracellular space
- Early endosome (pH 6.5)
- Late endosome (pH 5.5)
- Lysosomal degradation
- Endosome escape
- Polypelex disassembly & pDNA enters nucleus
- Endocytosis
- Binding to cytoplasmic membrane (pH 7.4)

Combinatorial-Designed Nano-Assemblies

Selection Criteria

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 conjugation).
- 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

Transwell® Co-Culture System

Tumor Cells

Macrophages

6 h After treating LPS/IFN-γ

48h & 72h Microscopy and RT-PCR Analysis of Exosome-Mediated Macrophage Polarization

Luciferase Expressing Panc-1 Cells

RT-PCR Analysis of M1/M2 Macrophage Polarization Markers

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

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.

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

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

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.

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

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

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

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

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

Chronic Inflammatory Diseases

Brain
- Multiple Sclerosis
- Guillain-Barre Syndrome
- Autism

Blood
- Leukemia
- Lupus Erythematosus
- Hemolytic Dysglycemia

Thyroid
- Thyroiditis
- Hashimoto’s Disease
- Graves’ Disease

GI Tract
- Celiac’s Disease
- Crohn’s Disease
- Ulcerative Colitis
- Diabetes Type I

Bones
- Rheumatoid Arthritis
- Ankylosing Spondylitis
- Polymyalgia Rheumatica

Muscles
- Muscular Dystrophy
- Fibromyalgia

Skin
- Psoriasis
- Vitiligo
- Eczema
- Scleroderma

Nerves
- Peripheral Neuropathy
- Diabetic Neuropathy

Lung
- Fibromyalgia
- Wegener’s Granulomatosis

>100 Autoimmune Diseases

we are 50 million
Macrophage Functional Polarization

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

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

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

Self-assembly
Aqueous media

HA-PEI/pDNA nanoparticles


Gel retardation showing 100% pDNA encapsulation
In Vivo CD44-Specific Targeted Delivery in Peritoneal Macrophages upon IP Administration

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

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

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

<table>
<thead>
<tr>
<th>Day 0</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thioglycolate injection (IP)</td>
<td>LPS/HA-PEI/pDNA injection (IP)</td>
<td>LPS injection (IP)</td>
<td>Collection of serum, peritoneal fluid, and peritoneal macrophages</td>
</tr>
</tbody>
</table>

**qPCR and ELISA**

**IL-4 mRNA**
- Blank HA-PEI
- pDNA-IL4
- pDNA-IL10

**IL-10 mRNA**
- Blank HA-PEI
- pDNA-IL4
- pDNA-IL10

**TNF-α mRNA**
- Blank vehicle
- pDNA-IL4
- pDNA-IL10

**IL-1β mRNA**
- Blank vehicle
- pDNA-IL4
- pDNA-IL10

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.