Omics-Based Nanomedicine: the Future of Personalized Medicine

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Think different - Innovation

- Creativity
- Motivation
- Persistent
How do we solve problems?
Breaking the Cycle
Until today – “Blockbuster drugs” – everyone gets the same drug
Efficacy?
~ 15-20% of patients at most – will benefit

New area – Make it Personal
The ability to sequence the Genome (DNA), Transcriptom (RNA) and to edit Genes
Precision Medicine

Price in 1994: ~ $1B / One human Genome
Price in 2014: ~ $2000 / One human Genome
Each person react differently to drugs

1. Genome (genes)
2. Environment
What can we do with all the information from sequencing?

Sequence patients with a particular disease (e.g. Cancer)

↓

Learn about the mutations and genes that are overexpressed

↓

Design and synthesis new drugs based on RNA that fits the patient profile

↓

Design and synthesis of new delivery systems
Can make any target “druggable” •
“Playing” GOD with genes—silence genes, up regulating gene expression and editing
RNA / DNA technologies is ready to go BUT the DELIVERY of these molecules into specific cells types is not.
Targeted(Delivery(to(Tumors(
We need to have **3 components**: 

**The drug**: RNA sequence  
**The delivery system** that can package the drug  
**The targeting moiety**: provide an address to the delivery system (work like GPS) and bring it into the diseased cell
Laboratory of NanoMedicine

Exome / transcriptome analysis and Target Discovery & Validation

Delivery systems and protein engineering

February 3, 2016
Landscape of cancer genomics analyses

Tailored medicine
Localized RNAi Therapeutics of Chemoresistant Grade IV Glioma Using Hyaluronan-Grafted Lipid-Based Nanoparticles

Collaboration with Dept. of Neurosurgery, Sheba Hospital
Dr. Zvi R. Cohen
Looking for Glioma unique surface markers that can be used as GPS-like system

A

![Graphs showing CD44 expression in different glioma cell lines](image1)

B

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>CD 44 expression</th>
<th>Pathology</th>
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</thead>
<tbody>
<tr>
<td>9558/10</td>
<td>+++</td>
<td>GBM</td>
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<tr>
<td>3970/10</td>
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<td>20888/10</td>
<td>++/++++</td>
<td>GBM</td>
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<tr>
<td>22712/10</td>
<td>+++</td>
<td>GBM</td>
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</table>

Pathology images showing tumor tissue.
Microfluidics Enables Exquisite Control Over Manufacturing Process – CMC of Nanoparticles packaging RNA molecules

- Laminar fluid flow
- Controlled, time invariant mixing
- Rapid mixing (3 ms⁻¹): Timeₘᵢₓ < Timeₚₚ
- Reaction volumes ~ 14 nL
- Low energy input
- Total flow rates from 4 mL/min to 20 mL/min
- Parallelized mixers enable seamless scale-up
Choosing the appropriate therapeutic target (the drug): PLK1- cell cycle regulator
Therapeutic gene silencing prolongs the survival of GBM-bearing mice.

A

% Gene Silencing of PLK1

Mock treated HA-LNPs - siLuci HA-LNPs - siPLK1

B

Percent survival

Saline siControl siPLK1

Time (days)
How do we progress into the clinic?

Sequence glioma patients (DNA and RNA)

↓

Learn about the mutations and genes that are overexpressed

↓

Design and synthesis new drugs based on RNA that fits the patient profile

↓

Scale up the production of Nanoparticles with RNAs
Targeting Mantle Cell Lymphoma with Nanomedicines

Aggressive form of B-cell malignancy.

Low Incidence: 1-2/100,000 per year (6%-9% out of total malignant lymphomas).

Rate of men to women - 3:1

Median age: 60
Genetic characterization of Mantle Cell Lymphoma (MCL)

A chromosomal translocation - t(11;14)(q13;q32) •
Cyclin D1 overexpression

Conventional Therapy:
Chemotherapy cocktails •
anti-CD20 mAb (Rituximab) •
Proteasome and BCR pathway inhibitors •

siRNA-mediated gene silencing highlights Cyclin D1 as a potential therapeutic target for MCL.

Screening - 510 sequences that targets both long and short transcripts. Bioinformatics, chemistry and electroporation

Cyclin D1 silencing

Cell cycle arrest

Apoptosis

Lipid Nanoparticle assembly

LNP Formulation

<table>
<thead>
<tr>
<th>Component</th>
<th>% molar</th>
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<tbody>
<tr>
<td>Ionizable MC</td>
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</tr>
<tr>
<td>Cholesterol</td>
<td>38%</td>
</tr>
<tr>
<td>DSPC</td>
<td>10%</td>
</tr>
<tr>
<td>PEG-DMG</td>
<td>1.95%</td>
</tr>
<tr>
<td>PEG-Maleimide</td>
<td>0.05%</td>
</tr>
</tbody>
</table>

Ramishetti, Kedmi et al. *ACS Nano* 2015

NanoAssembler™

siRNA
pH 4

Lipids (EtOH)

Channel Dimensions:
~100 µm

Rapid & Controlled Mixing

Mixer design by:
Stroock et al., *Science* 2002

Peer Lab
Precision Nanomedicine

February 3, 2016
Mouse model of MCL

Weinstein et al. PNAS 2016
αCD38-LNPs-siCyD1 induce therapeutic gene silencing in MCL model

Double blinded experiments were performed at CRO (Charles River)

Weinstein S. et al., PNAS 2016
Duchenne Muscular Dystrophy - DMD

An X linked neuromuscular disease characterised by rapidly progressing muscle weakness and wasting, (WHO, 2013).

Lack of one protein names Dystrophin
DMD affects mostly males at a rate of 1 in 3,500 births

DMD is the most severe and common type of muscular dystrophy

Four phases

Early phase (<6 yrs): clumsy, fall frequently, difficulty jumping or running, enlarged muscles, contractures

Transitional Phase (ages 6-9): Trunk weakness, muscle weakness, heart problems, fatigue

Loss of ambulation (ages 10-14): by 12 yrs most boys use a powered wheelchair. Scoliosis due to constant sitting and back weakness

Late stage (15+): life threatening heart and respiratory problems more prevalent, dyspnea, oedema of the LL’s. Average age of death is 19 yrs in untreated DMD but due to improvements in clinical care in many centres the average age of death is the late twenties or beyond
Potential solution: modified mRNA
Bring in the missing protein

Normal Translation

Incomplete Translation

Ataluren-Facilitated Translation

Functioning Protein

Incomplete Protein

Ataluren-Facilitated Functioning Protein
Take home message

Its all personal

Its all in the message (mRNA)