Personalized Medicine or Precision Medicine

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**Personalized Verses Precision Medicine- NRC Report**

Precision Medicine- tailoring medical treatment to characteristics of each patient- not creation of drugs unique to a patient

—challenge: create a drug for a patient?

Recent advances in Spinal Muscular Atrophy (SMA)

One SMN1 (telomeric) and several SMN2 (centromeric)\(^1\)

95–98% of patients with SMA have a homozygous disruption of SMN1

SMN2 encodes a truncated mRNA isoform\(^1\)
- A critical nucleotide transition in SMN2 mRNA results in a nonfunctional protein

About 10% of SMN2 pre-mRNA is translated into full-length SMN protein\(^3\)

The severity of the SMA phenotype is correlated with the number of SMN2 gene copies \(^1\)

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Summary of the genetics of SMA

- One SMN1 (telomeric) and several SMN2 (centromeric)\(^1\)
- 95–98% of patients with SMA have a homozygous disruption of SMN1
- SMN2 encodes a truncated mRNA isoform\(^1\)
  - A critical nucleotide transition in SMN2 mRNA results in a nonfunctional protein
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- The severity of the SMA phenotype is correlated with the number of SMN2 gene copies \(^1\)

ASOs can modify splicing of SMN2

- Screening of ASOs showed that targeting ISS-N1 in intron 7 can increase inclusion of exon 7
- These ASOs compete with hnRNP A1/2 for binding to the ISS-N1 site
- ASOs with certain chemical modifications promoted inclusion of exon 7 in the final transcript

Full-length SMN2 mRNA in thoracic spinal cord in nusinersen-treated infants with SMA compared with untreated infants with SMA

RT-PCR analysis

% full-length SMN2 by group
- Healthy infants / untreated SMA = 15-26
- Nusinersen-treated SMA = 50-69 ➤ 2.6-fold increase
Development of (the anti-sense oligonucleotide) Spinraza for treatment of SMA

1. Adrian Krainer (CSHL) collaborated with Frank Bennett of Ionis (2008)

2. Ionis Pharmaceutical developed the anti-sense oligonucleotide, founded by Stanley Crooke in 1989


Francis Crick and James Watson
(Molecular Genetics, G.S. Stent, 1971)
The original operon model of Jacob and Monod, as proposed for the regulation of the lac genes of *E. coli* in 1961

DNA mRNA Protein
Inactive repressor Active repressor

Galactosidase Permease Transacetylase


EM of RNA/DNA hybrid of hexon mRNA/genome - 3 loops
EST evidence has demonstrated several modes of variation for transcripts coming from a single locus

- Standard transcriptional activation
- Alternative promoter usage
- Exon inclusion/exclusion
- 3’ UTR utilization
- All of the above

EST evidence has demonstrated several modes of variation for transcripts coming from a single locus

- Oligonucleotide specific for exon included in splicing pattern (1) inhibits expression of function encoded by (1) isoform but not (2) isoform.
- Gene sequence leads directly to design of oligonucleotide for treatment.
Technology behind biotechnology

1) Recombinant DNA (1972)
2) DNA sequencing (1977)
3) Chemical DNA synthesis
Cluster of high tech companies near MIT

Cambridge transformed from candy to biotechnology- Novartis International Research Center

Courtesy of MIT Entrepreneurship Initiative

Courtesy of MIT Tech Review
RNA Biology and new Therapeutics?

Celebrating the Nobel Prize for RNAi
Drs. Andrew Fire and Craig Mello

nature collections. 2004 December.
1. ~3,000 Mendelian disease genes known

2. ~8% of live births—genetic disorder by early adulthood

3. Estimated—each child with genetic disorder costs ~$5,000,000

4. Diagnostic rate of genetic disorders: children ~11%, adults ~34%

Human genetic-disease genes


Potential Conflicts of Interest


2. Alnylam founded (2002)—research expenditures $1.5B

3. Co-founder, Board of Directors, Chair SAB
Therapeutic gene silencing

RNA interference (siRNA) targets mRNA from a gene

Therapeutic gene silencing

Proteins
Receptors
Enzymes
Antibodies
Small Molecules
Nucleic acid delivery

- Importance and challenges
- Viral vs. non-viral
- Standard reagents are ineffective


Tissue and Cellular Uptake
Targeting the liver: ASGPR and GalNAc

GalNAc-siRNA Conjugate
- GalNAc ligand conjugated to chemically modified siRNA to mediate targeted delivery
- Trivalent GalNAc carbohydrate cluster has nM affinity for ASGPR
- Administered subcutaneously (SC)

Optimizing chemistry improves stability, PK, potency and duration of effect

Metabolic profiling in liver

Standard Template Chemistry (STC)

Enhanced Stabilization Chemistry (ESC)

Liver Exposure

Dramatic increase in efficacy of siRNA delivery to hepatocytes in vivo

Data from R. Meyers
Hemophilia and Rare Bleeding Disorders

Genetic deficiency resulting in inability to generate thrombin and stop bleeding

1. Highest need is prophylaxis for inhibitor patients and to avoid inhibitor formation in all patients

2. Global need due to frequent IV infusions, ability to manufacture, and cold chain

PATIENT POPULATION*
Hemophilia A and B
200,000 worldwide
~4,000 with inhibitors


Fitusiran for Hemophilia- siRNA inhibitors of Anti-thrombin (AT)
Potential to Restore Hemostasis in Hemophilia

Genetically validated, liver-expressed target gene → Biomarker for POC → Path to approval

Fitusiran Phase 1 results: Pasi et al., WFH, July 2016

Photo courtesy of Guy Young, M.D. Director, Hemostasis & Thrombosis Center at Children’s Hospital Los Angeles and Professor of Pediatrics, USC Keck School of Medicine
Other emerging liver targets

- Suppression of hemolysis in Paroxysmal Nocturnal Hemoglobinuria (PNH) patients
- Suppression of Hepatitis B replication
- Potential therapeutic for primary hyperoxaluria
- Potential treatment for hypercholesterolemia—PCSK9 target

Treatment effect is prolonged allowing dosing every 6 months

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean (SEM) % PCSK9 Knockdown (Change from Baseline)</th>
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<tbody>
<tr>
<td>Placebo</td>
<td></td>
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<tr>
<td>100 mg</td>
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<tr>
<td>300 mg</td>
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1990-2003

Broad Institute (2003) large collaborative multidisciplinary science

Draft: (90%) Feb 2001
Finished: (99.3%) Apr 2003

Convergence timeline

Timeline: The three revolutions

1953: Discovery of DNA Structure
1960: Salvador Luria, theorist of molecular biology, awarded Nobel Prize
1976: Biotech sector emerges with founding of Genentech
mid-2000s: Academic sectors start exploring convergence
2009: NAS releases A New Biology report
2001: Human Genome Project, Celera publish working draft of human genome

Image and info credits (clockwise from top-left): DNAmazing.com, Gene.com, Bshl.stanford.edu, qb3.org, mit.edu/ki, nlp.edu, sciencemag.org, nature.com, nlm.nih.gov
"Physicists gave engineers the electron and they created the IT revolution. Biologists gave engineers the gene and together they will create the future."

- Susan Hockfield

Convergence is a blueprint for innovation.

Advances in information technology, materials, imaging, nanotechnology, optics, and quantum physics, coupled with advances in computing, modeling, and simulation, have already transformed physical science. They are now beginning to transform life science as well.
Revolutions in engineering

1) Information technology
2) Storage and processing of large sets of data
3) Synthesis of composites of nanoscale
4) Micro-fabrication - tooling at nanoscale
5) Sensitive and quantitative measuring devices including imaging
6) Control technologies - dynamics

Information science for medical care- Kendall Square

Courtesy of MIT Tech Review
White House Priorities - Brain Initiative

Agencies should give priority to R&D investments...[including] research at the interfaces of biology, physical sciences, and engineering.

Agencies should also give priority to the President's BRAIN (Basic Research through Advancing Innovative Neurotechnologies) Initiative.


The Koch Institute: A New Model for Cancer Research

Integration and Collaboration
Discoveries and Solutions
Institutions that combine a broad range of scientific and engineering disciplines in biosciences research.
From Convergence to Confluence

Thank you for the opportunity to present this lecture.
- Phil Sharp