Treatment of Genetic Disorders

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Victor A. McKusick Professor of Medicine and Genetics
Director
Departments of Pediatrics and Medicine
Investigator, Howard Hughes Medical Institute
Johns Hopkins University School of Medicine
Gene Therapy (and its obvious appeal...and obstacles)

- Immune response to viral proteins

- Disruption of essential genes upon viral integration into host DNA (e.g. causing leukemia)
Adenovirus-Associated Virus Vector–Mediated Gene Transfer in Hemophilia B


Basic tenet: It takes a village.

A confluence of...and synergy between... the basic and clinical sciences is needed to develop a full mechanistic understanding of a disease process and, in that manner, to derive novel and rationale therapeutic strategies.
Hurler Disease  
Hurler-Scheie  
Hunter Disease  
Maroteaux-Lamy  
Pompe Disease  
Fabry Disease  
Gaucher Disease  
Lysosomal Storage Diseases (LSDs)

Unified by the toxic accumulation of lysosomal substrates due to lysosomal enzyme deficiencies.
Complementation in Lysosomal Storage Diseases

Normal Enzymes And Function

No Enzyme A
LSD1

No Enzyme B
LSD2

Corrected function in both

One cell type “complemented” the other

Liz Neufeld
The prospect of enzyme replacement therapies (ERTs).

Exogenous enzyme (laboratory-made)

No Rescue of Function

Why?
Mucolipidosis type II (I-Cell Disease)

- missing -

N-acetylglucosamine-1-phosphotransferase

Mannose-6-Phosphate (M6P)

Mannose-6-Phosphate Receptor (M6PR)
Treatment of Hurler Syndrome (MPS I) with α-L-Iduronidase Therapy

Changes in Liver Size in Patients with Mucopolysaccharidosis I during α-l-Iduronidase Therapy.

Mean Changes in the Restriction of Range of Motion of Shoulder Flexion (Panel A), Elbow Extension (Panel B), and Knee Extension (Panel C) in Patients with Mucopolysaccharidosis I during α-l-Iduronidase Therapy.

Established and Investigational Therapies for Lysosomal Storage Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Enzyme Replaced or Targeted</th>
<th>Therapeutic Agent†</th>
<th>Manufacturer</th>
<th>Indication</th>
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Investigational therapies

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* ERT denotes enzyme-replacement therapy, EU European Union, FDA Food and Drug Administration, MPS mucopolysaccharidosis, and SRT substrate-reduction therapy.
† Therapeutic agents are listed by their U.S. adopted name followed by the trade name (if any) in parentheses.

Some endogenous enzyme
Promotes “tolerance” to ERT

No endogenous enzyme
ERT recognized as “foreign” by immune system
The specialized anatomy of the cerebral microvasculature creates a functional “Blood Brain Barrier” that selectively restricts transport of selected substances from the circulation into brain tissues…

…including all enzyme replacement therapeutics.
Excellent utility of ERT in Maroteaux-Lamy (no CNS manifestations)
Limited utility of ERT in Gaucher disease type 2 or 3 (severe CNS manifestations)
Potential Solutions:

- Immunologic tolerance regimens

- Alternative targeting procedures

- Complementary therapeutic regimens that utilize small molecules capable of crossing the blood-brain barrier.
Compensatory and Salvage Therapeutic Agents

A  Wild-type protein
Correctly folded wild-type protein

Proper transport → Catalytic activity → Metabolite

B  Mutant protein and compensatory effects of therapy

Incorrectly folded mutant protein

Proper transport → ERAD

1. Substrate reduction

2. Pathogenic modulator

Compensatory and Salvage Therapeutic Agents

C Mutant protein and salvage effects of therapy

3. Corrector - corrects folding/trafficking
4. Potentiator - corrects folding/activity
5. Stabilizer - corrects stability

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Cystic Fibrosis:
A public-corporate partnership between the CF Foundation and Vertex Pharmaceuticals set its sights high (but focus narrow).

Develop a drug therapy for people with the Class III G551D mutation.
Why so narrow?

- The chance of finding a drug that can address all potential problems in CFTR biogenesis, trafficking and function is slim.

- By definition, a drug that “potentiates” the function of G551D CFTR binds to and influences the folding of CFTR. It therefore might influence the structure and function of other mutant forms.

- At a minimum, a drug for G551D would address the ~4% of CF patients who carry at least one copy of this allele.
Combine deficient cells and an indicator for desired activity (e.g. fluorescent marker that is activated by restored chloride conductance).

Comprehensive interrogation of molecule (or known drug) library.

Compound optimization (e.g. medicinal chemistry) and iterative screening.

Compound scoring.

Signal detection.
Original Article

A CFTR Potentiator in Patients with Cystic Fibrosis and the G551D Mutation

Bonnie W. Ramsey, M.D., Jane Davies, M.D., M.B., Ch.B., N. Gerard McElvaney, M.D., Elizabeth Tullis, M.D., Scott C. Bell, M.B., B.S., M.D., Pavel Dřevínek, M.D., Matthias Griese, M.D., Edward F. McKone, M.D., Claire E. Wainwright, M.D., M.B., B.S., Michael W. Konstan, M.D., Richard Moss, M.D., Felix Ratjen, M.D., Ph.D., Isabelle Sermet-Gaudelus, M.D., Ph.D., Steven M. Rowe, M.D., M.S.P.H., Qunming Dong, Ph.D., Sally Rodriguez, Ph.D., Karl Yen, M.D., Claudia Ordoñez, M.D., J. Stuart Elborn, M.D., for the VX08-770-102 Study Group

N Engl J Med
Volume 365(18):1663-1672
November 3, 2011
Changes from Baseline through Week 48 in Sweat Chloride, According to Study Group.

Changes from Baseline in Percent of Predicted FEV$_1$, Respiratory Symptoms, and Weight, and Time to the First Pulmonary Exacerbation, According to Study Group.

Treatment Effect of Ivacaftor with Respect to the Change from Baseline through Week 48 in the Percent of Predicted FEV\textsubscript{1}, According to Subgroups.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Treatment Effect</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline % of predicted FEV\textsubscript{1}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;70%</td>
<td>10.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥70%</td>
<td>10.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Geographic region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>9.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Europe</td>
<td>9.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Australia</td>
<td>11.9</td>
<td>0.008</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>11.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>11.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18 yr</td>
<td>11.4</td>
<td>0.005</td>
</tr>
<tr>
<td>≥18 yr</td>
<td>9.9</td>
<td>&lt;0.001</td>
</tr>
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* The treatment effect represents the difference between the ivacaftor group and the placebo group with respect to the absolute change from baseline through week 48 in the percent of predicted FEV\textsubscript{1}.


Works irrespective of:

Severity
Location
Gender
Age
### Table 3. Adverse Events.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (N=78)</th>
<th>Ivacaftor (N=83)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>no. of subjects (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any adverse event</td>
<td>78 (100)</td>
<td>82 (99)</td>
</tr>
<tr>
<td>Serious adverse event*</td>
<td>33 (42)</td>
<td>20 (24)</td>
</tr>
<tr>
<td>Pulmonary exacerbation</td>
<td>26 (33)</td>
<td>11 (13)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>4 (5)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>0</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Adverse event leading to study-drug interruption</td>
<td>5 (6)</td>
<td>11 (13)</td>
</tr>
<tr>
<td>Adverse event leading to study-drug discontinuation</td>
<td>4 (5)</td>
<td>1 (1)</td>
</tr>
</tbody>
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* Included are serious adverse events that occurred in more than one subject per group.

Conclusions

• Ivacaftor was associated with improvements in lung function at 2 weeks that were sustained through 48 weeks.

• Substantial improvements were also observed in the risk of pulmonary exacerbations, patient-reported respiratory symptoms, weight, and concentration of sweat chloride.

• Ivacaftor was not associated with an increased incidence of adverse events when compared to placebo.
Kalydeco (ivacaftor) – the first and only drug that is FDA-approved for the treatment of cystic fibrosis (in children older than 6 years with the G551D mutation).

January 31, 2012
Duchenne Muscular Dystrophy (DMD) and Becker Muscular Dystrophy (BMD) are both caused by mutations in the DMD gene encoding dystrophin.

- **Diagnosis**: 4.6 teens
- **Wheelchair**: teens
- **Death**: young adult (onward) for Duchenne, 4th-5th decade for Becker
- **Both**: caused by mutations in the DMD gene encoding dystrophin.
DMD/BMD

Dystrophin Staining

Control  DMD  BMD
Dystrophin needs its head and its tail – but perhaps not all of its middle???
ATG Ter

Truncated protein with no function

Duchenne Muscular Dystrophy

Centrally-deleted protein with partial function

Becker Muscular Dystrophy

ATG Ter

Triplet code

"Open Reading Frame"

Pre-mRNA

Intron

Exon

Normal pre-mRNA splicing

Mature mRNA

ATG

Triplet code

Ter

“Open Reading Frame”

Normal Phenotype

Full length dystrophin protein with full function

Nonsense-mediated mRNA decay (NMD)

Truncated protein with no function

Centrally-deleted protein with partial function

"Open Reading Frame"

Exon skipping (Even multiple of 3 nt.)

"Frameshift leading to a Premature Termination Codon"

Exon skipping (Not even multiple of 3 nt.)

"Open Reading Frame"

Full length dystrophin protein with full function

Duchenne Muscular Dystrophy

Becker Muscular Dystrophy

?
The mechanics of pre-mRNA splicing

Exon1  U1  GU  
\[70K\]  U2  A  U2AF65  35  AG  Exon2  U1  GU  
\[70K\]  Exon3

Exon1  Exon2  Exon3

Spliced mRNA
Exon1

U1 GU

70K

U2 A

(Y)_n AG

Exon2

U1 GU

70K

Exon3

U2AF65 35

Antisense Oligonucleotide (AON)

↓

Exon1  Exon3

Spliced mRNA
(with targeted exon skipping)
Pre-mRNA

Splicing

Mature mRNA with Open Reading Frame

Protein
Antisense-mediated exon skipping rationale for DMD

Deletion exon 45

Pre-mRNA

Reading frame disrupted

mRNA

Premature stop codon

Non functional dystrophin

DMD phenotype

Reading frame restoration for deletions

Exon 46 hidden from splicing machinery

Reading frame restored

Partially functional dystrophin

BMD phenotype

Dr. Annemieke Aartsma-Rus
Multi Exon skipping approach

Pre-mRNA  Any mutation/deletion between exons 45 and 55 disrupting the reading frame

~63% of DMD patients

Skipping of multiple exons

mRNA  Reading frame restored

Pool of AONs targeting exons 45-55

Translation continues

Protein \(\Delta 45-55\) dystrophin known to be functional from BMD patients

Dystrophin expression after local delivery of antisense oligonucleotide
Dystrophin expression after systemic delivery of antisense oligonucleotide

7/19 responders
- delivery
- stability

Cirak et al. Lancet, 2011
Proposed Pathogenesis of the Hutchinson–Gilford Progeria Syndrome


Nuclear Blebbing

Farnesyl Transferase Inhibitor
FTI treatment causes reversion of the nuclear blebbing in two different progerin-expressing HGPS human fibroblasts.

Capell B C et al. PNAS 2005;102:12879-12884
Treatment of a Mouse Model of Progeria with a FTI

Marfan syndrome

Fibrillin-1

Dietz...and Francomano Nature, 1991
Fibrillin-1 Mutations Lead to Excess TGFβ Activation in MFS

- Excess TGFβ Activation
- Excess TGFβ Signaling
- Phenotypic Consequences
  - Emphysema
  - Mitral Valve Prolapse
  - Aortic Aneurysm
  - Myopathy

Microfibrils composed of Fibrillin-1

(Judge, *JCI*, 2004)
(Ng, *JCI*, 2004)
(Cohn, *Nature Medicine*, 2007)
The Angiotensin II Type 1 Receptor Blocker (ARB) Losartan

Habashi...and Dietz, Science, 2006
Therapeutic Response to ARBs

Canonical TGFβ Signaling

Noncanonical TGFβ Signaling (MAPK)

- pSmad2/3
- Smad4
- MEK
- ERK
- JNK
- p38
- TAK
Selective Activation of ERK MAPK in Marfan Mice

Holm…and Dietz, Science, 2011
ERK1/2 Antagonist RDEA-119 Arrests Aortic Root Growth in a Mouse Model of MFS

TGFβ → MEK1 → RDEA-119 → pERK1/2 → EMT → MMP2/9

![Graph showing aortic root growth comparison between placebo (Plac) and RDEA-119 in wild type and C1039G/+ mice.]

- Wild Type:
  - Placebo (n=6)
  - RDEA-119 (n=9)

- C1039G/+:
  - Placebo (n=6)
  - RDEA-119 (n=12)

Significance levels:
- p<0.05
- p=0.91
- p<0.05
- p<0.0001
- p=0.15

Holm…and Dietz; Science, 2011
2nd line antihypertensive agents in MFS patients unable to tolerate β-blockers

Azelnidipine reduces ERK activation in synergy with olmesartan in murine arterial injury model (Jinno et al., 2004)

Amlodipine dose: 15mg/kg/day

Echocardiogram: 2, 6 & 10mo

Doyle and Dietz, unpublished
Identical results for non-dihydropyridine calcium channel blockers such as verapamil.

Doyle and Dietz, unpublished
ERK Inhibitor RDEA-119 Abrogates the Deleterious Gene-by-Environment Interaction Imposed by Calcium Channel Blockers

Doyle and Dietz, unpublished

p < 0.05

2mo Ascending Aortic Growth (mm)

Plac Amlod Amlod +RDEA Plac Amlod Amlod +RDEA
n=6 n=9 n=10 n=6 n=12 n=11

Wild Type C1039G/+ Placebo C1039G/+ Amlod-RDEA C1039G/+ Amlodipine

p=0.13

p=0.17

p<0.0005 p<0.0001

p=0.54

p=0.19

p<0.005 p<0.005

25% dead

Percent Surviving

p < 0.05

0 1 2

Months of Treatment

Doyle and Dietz, unpublished
Pessimistic model for disease pathogenesis

↓ Fibrillin-1 → Tissue Failure

Losartan (ARBs)
TGFβ-neutralizing antibody
AT2 agonist
RDEA-119 (ERK antagonists)
SP600125 (JNK antagonist)
Hydralazine
β1-integrin agonist
β3-integrin antagonist

(Caution with calcium channel blockers)
A New Aortic Aneurysm Syndrome

Like Marfan syndrome:
- curvature of spine
- chest wall deformity
- long fingers
- aortic root aneurysm

Unique:
- widely-spaced eyes
- cleft palate/bifid uvula
- premature skull fusion
- club foot deformity
- congenital heart disease (PDA, BAV, ASD)
- arterial tortuosity
- diffuse aneurysms
- rupture / death
- young age
- small dimensions

Loeys-Dietz syndrome (LDS)

Loeys et al., *Nature Genetics*, 2005
Loeys et al., *NEJM*, 2006

(> 200 families)
Mutations in the TGFβ receptor cause Loeys-Dietz syndrome


LDS-like conditions also observed in patients with mutations in the SMAD3 or TGFB2 genes.
WT  LDS  Tgfbr2^{M318R/+}

Aortic Root Growth

Elastic Fiber Breaks

No RX  Losartan  Propranolol  TGFβ NAb

Wildtype  Tgfbr1^{M318R/+}  Tgfbr2^{G357W/+}

Placebo

Losartan

Loch, Gallo and Dietz, unpublished
Marfan Syndrome (*FBN1*)

Loeys-Dietz Syndrome (*TGFBR1/2*)

Loeys-Dietz-Osteoarthritis Syndrome (*SMAD3*)

Loeys-Dietz-like Syndrome (*TGFB2*)

Recessive Cutis Laxa (*FBLN4*)

Vascular EDS (*COL3A1*)

Bicuspid Aortic Valve/Asc AA

Arterial Tortuosity Syndrome (*GLUT10*)

Familial Thoracic Aortic Aneurysm (*MYH11, ACTA2*)

These data suggest that altered TGFβ signaling is a common pathway to aneurysm formation and that treatments for MFS may find broad application.
The study of rare Mendelian disorders represents both an obligation and an opportunity.

The obligation:
- While individually rare, these conditions are personally burdensome and collectively common.
- Patients with rare genetic disorders have disproportionately fueled progress in molecular therapeutics, often at real personal cost despite a remote chance of personal advantage.

The opportunity:
- The single gene basis of the defect implies genes and pathways that are sufficient to cause diseases of interest and that are therefore inherently attractive therapeutic targets.
- Such therapies can then be explored in more common but complex presentations of the same phenotype.