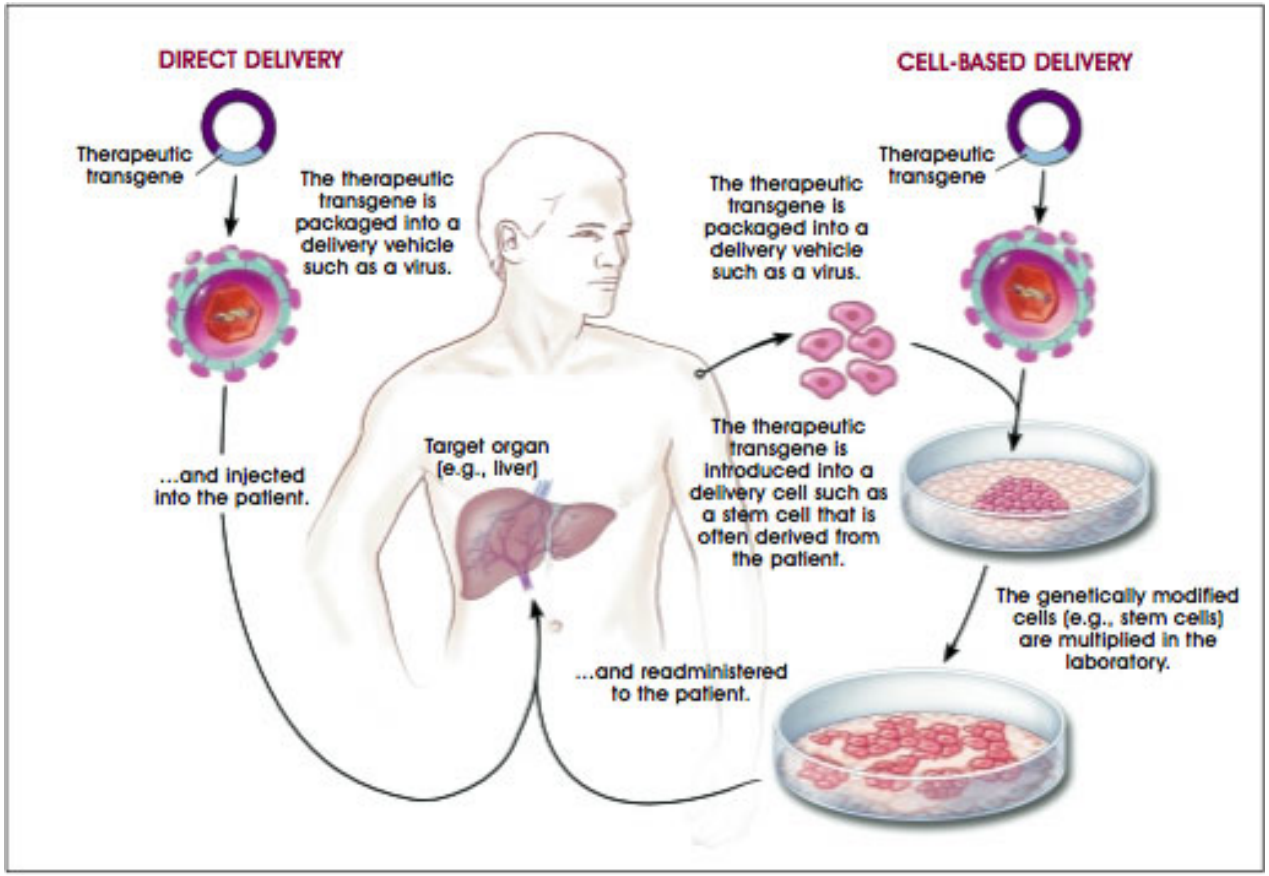
Treatment of Genetic Disorders

Hal Dietz, MD
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


BEIJING
LOS
ANGELES

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)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adenovirus-Associated Virus Vector–Mediated Gene Transfer in Hemophilia B

Amit C. Nathwani, M.B., Ch.B., Ph.D., Edward G.D. Tuddenham, M.B., B.S., M.D., Savita Rangarajan, M.B., B.S., Cecilia Rosales, Ph.D., Jenny McIntosh, Ph.D., David C. Linch, M.B., B.Chir., Pratima Chowdary, M.B., B.S., Anne Riddell, B.Sc., Arnulfo Jaquilmac Pie, B.S.N., Chris Harrington, B.S.N., James O'Beirne, M.B., B.S., M.D., Keith Smith, M.Sc., John Pasi, M.D., Bertil Glader, M.D., Ph.D., Pradip Rustagi, M.D., Catherine Y.C. Ng, M.S., Mark A. Kay, M.D., Ph.D., Junfang Zhou, M.D., Yunyu Spence, Ph.D., Christopher L. Morton, B.S., James Allay, Ph.D., John Coleman, M.S., Susan Sleep, Ph.D., John M. Cunningham, M.D., Deokumar Srivastava, Ph.D., Etiena Basner-Tschakarjan, M.D., Federico Mingozzi, Ph.D., Katherine A. High, M.D., John T. Gray, Ph.D., Ulrike M. Reiss, M.D., Arthur W. Nienhuis, M.D., and Andrew M. Davidoff, M.D.

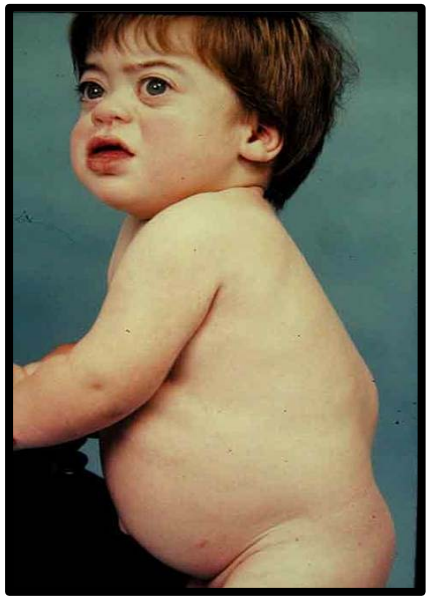
N Engl J Med 2011; 365:2357-2365 | December 22, 2011

Kenneth S. Shindler, M.D., Ph.D., Maureen G. Maguire, Ph.D., J. Fraser Wright, Ph.D., Nicholas J. Volpe, M.D., Jennifer Wellman McDonnell, M.S., Alberto Auricchio, M.D., Katherine A. High, M.D., and Jean Bennett, M.D., Ph.D.

Basic tenet: It takes a village.

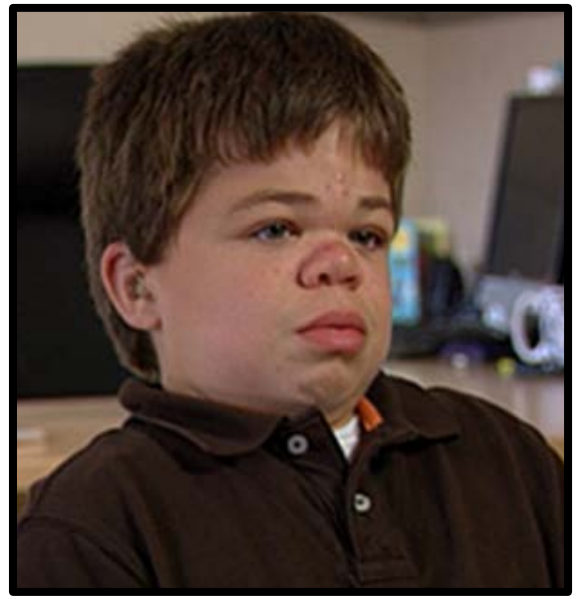
A confluence of…and synergy between… the basic and clinical sciences is needed to develop a full mechanistic understanding of a disease process and, in that manner, to derive novel and rationale therapeutic strategies.

Hurler Disease

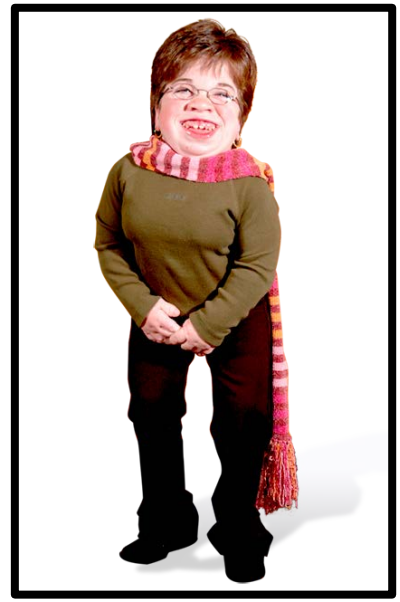


Hurler-Scheie

Hunter Disease

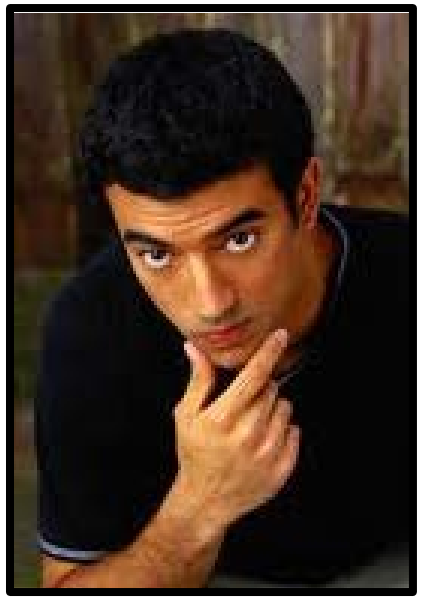


Maroteaux-Lamy



Pompe Disease

Fabry Disease



Gaucher Disease

Lysosomal Storage Diseases (LSDs)

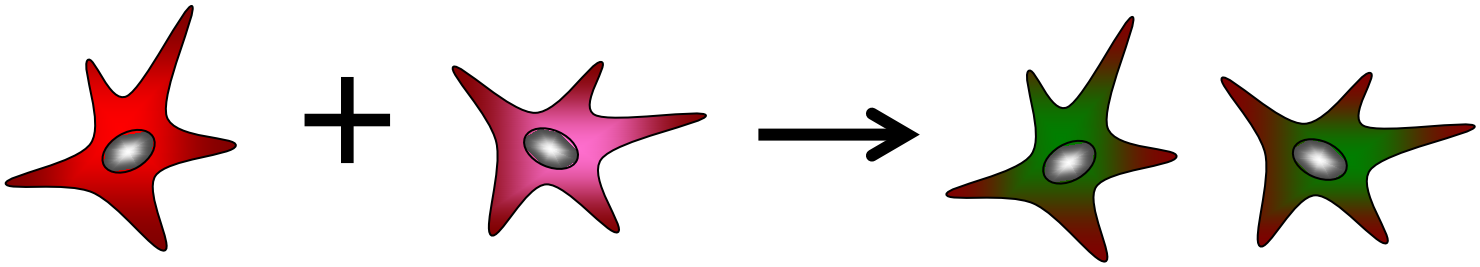
Unified by the toxic accumulation of lysosomal substrates due to lysosomal enzyme deficiencies.

Complementation in Lysosomal Storage Diseases

Normal Enzymes
And Function

No Enzyme A
LSD1

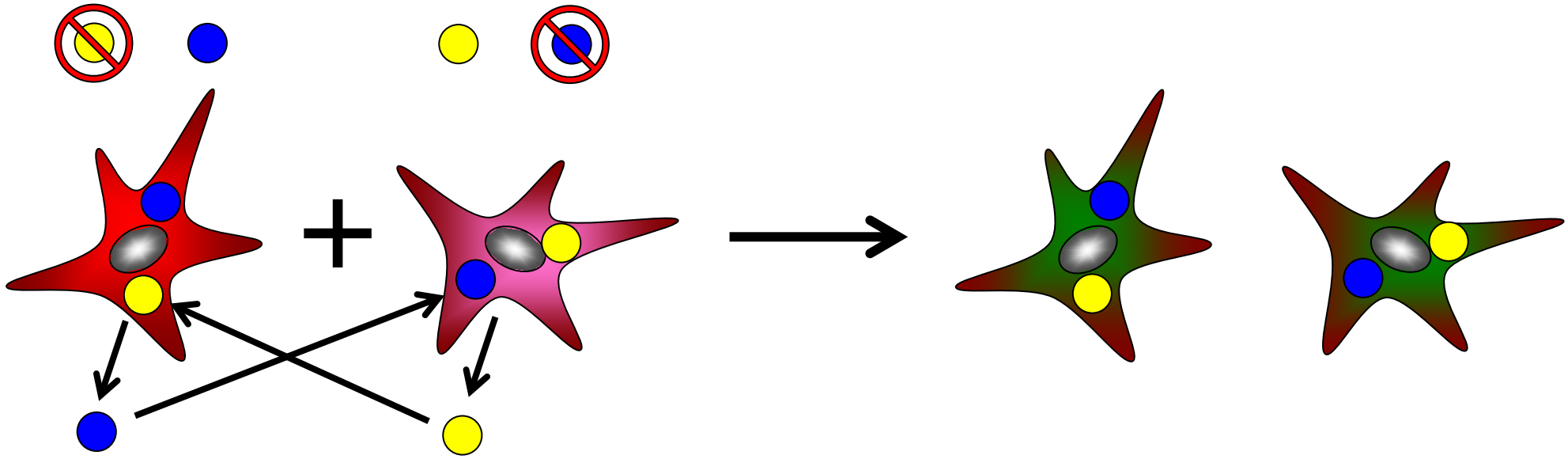
No Enzyme B
LSD2



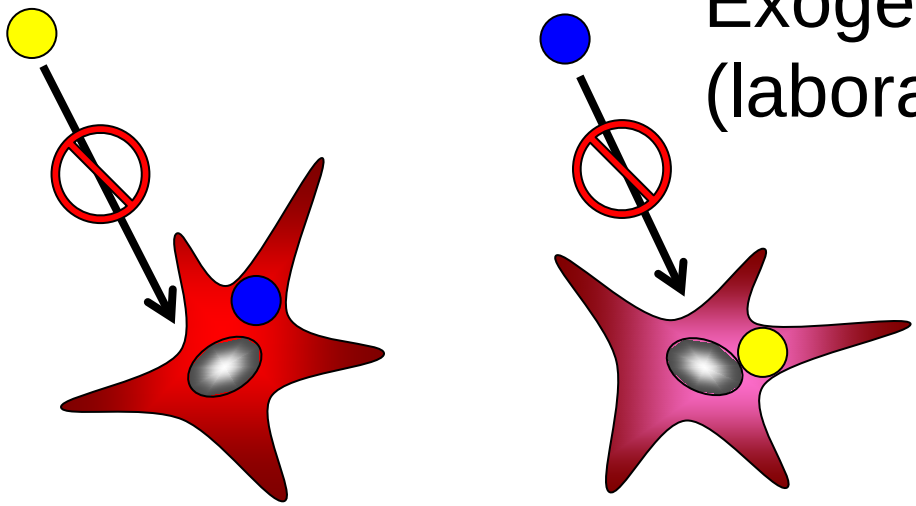
Corrected function
in both

Liz Neufeld

One cell type
“complemented”
the other



The prospect of enzyme replacement therapies (ERTs).

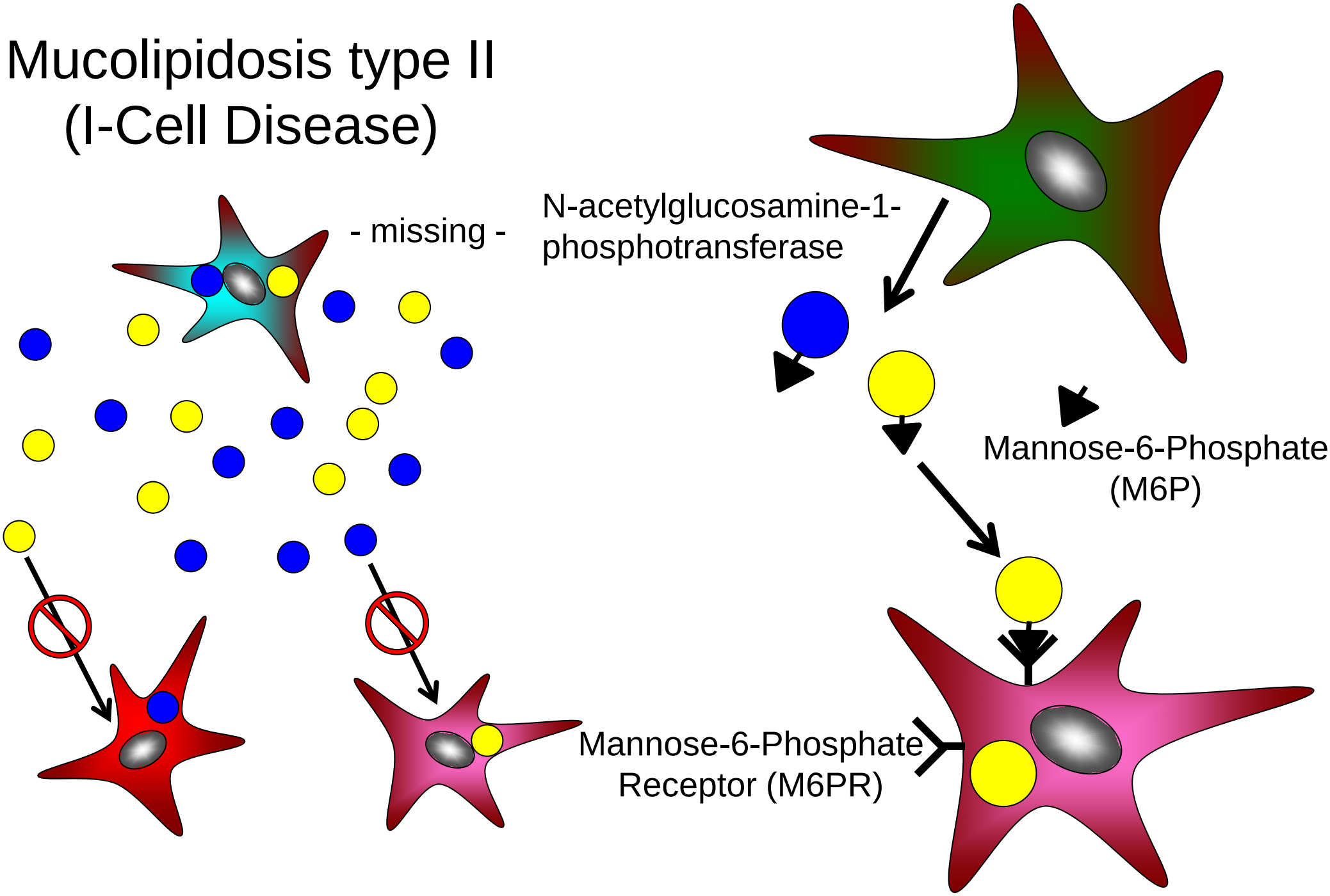


Exogenous enzyme
(laboratory-made)

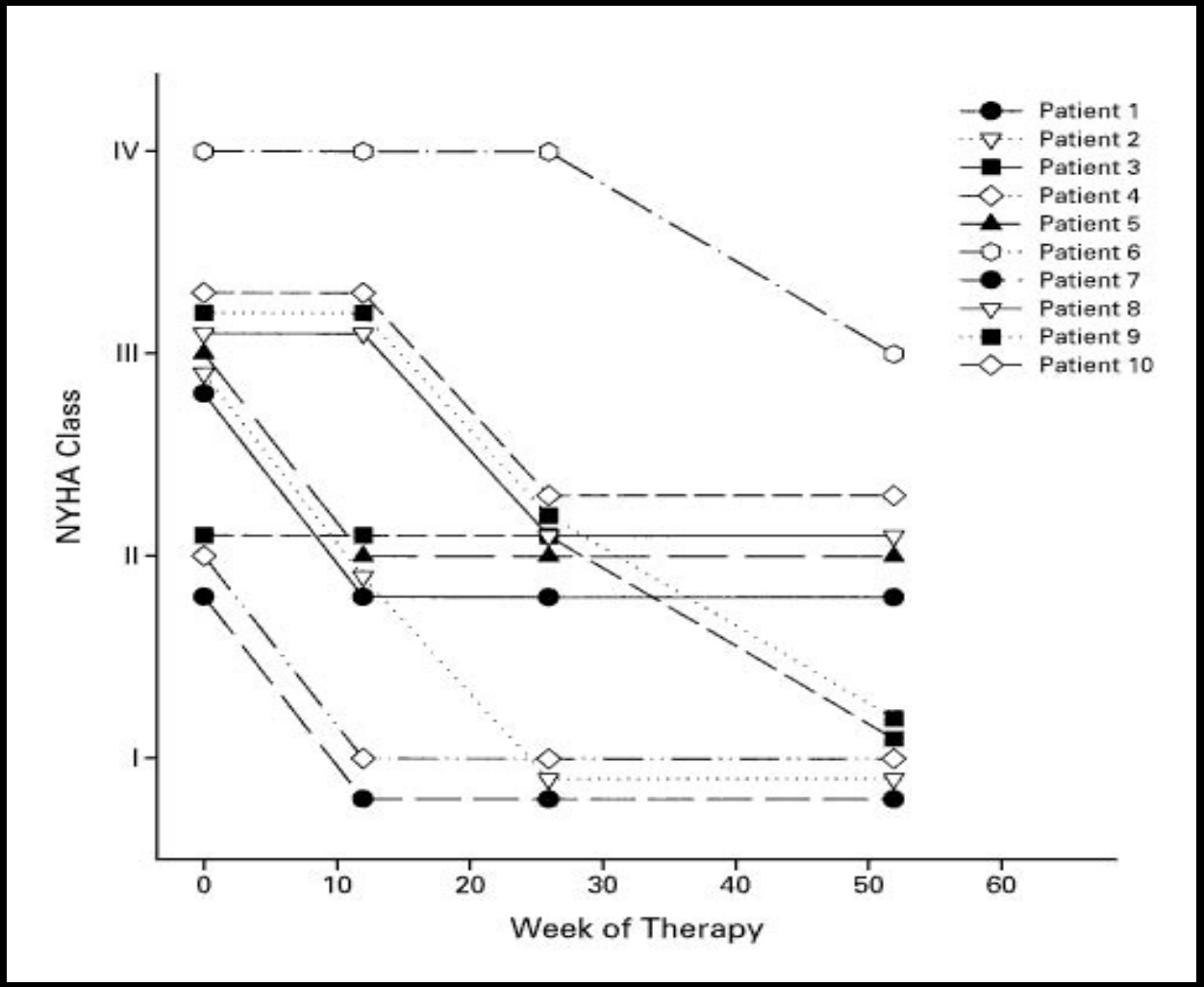
No Rescue of Function

Why?

Mucolipidosis type II (I-Cell Disease)



Treatment of Hurler Syndrome (MPS I) with α-l-Iduronidase Therapy



Kakkis ED et al. N Engl J Med 2001;344:182-188.

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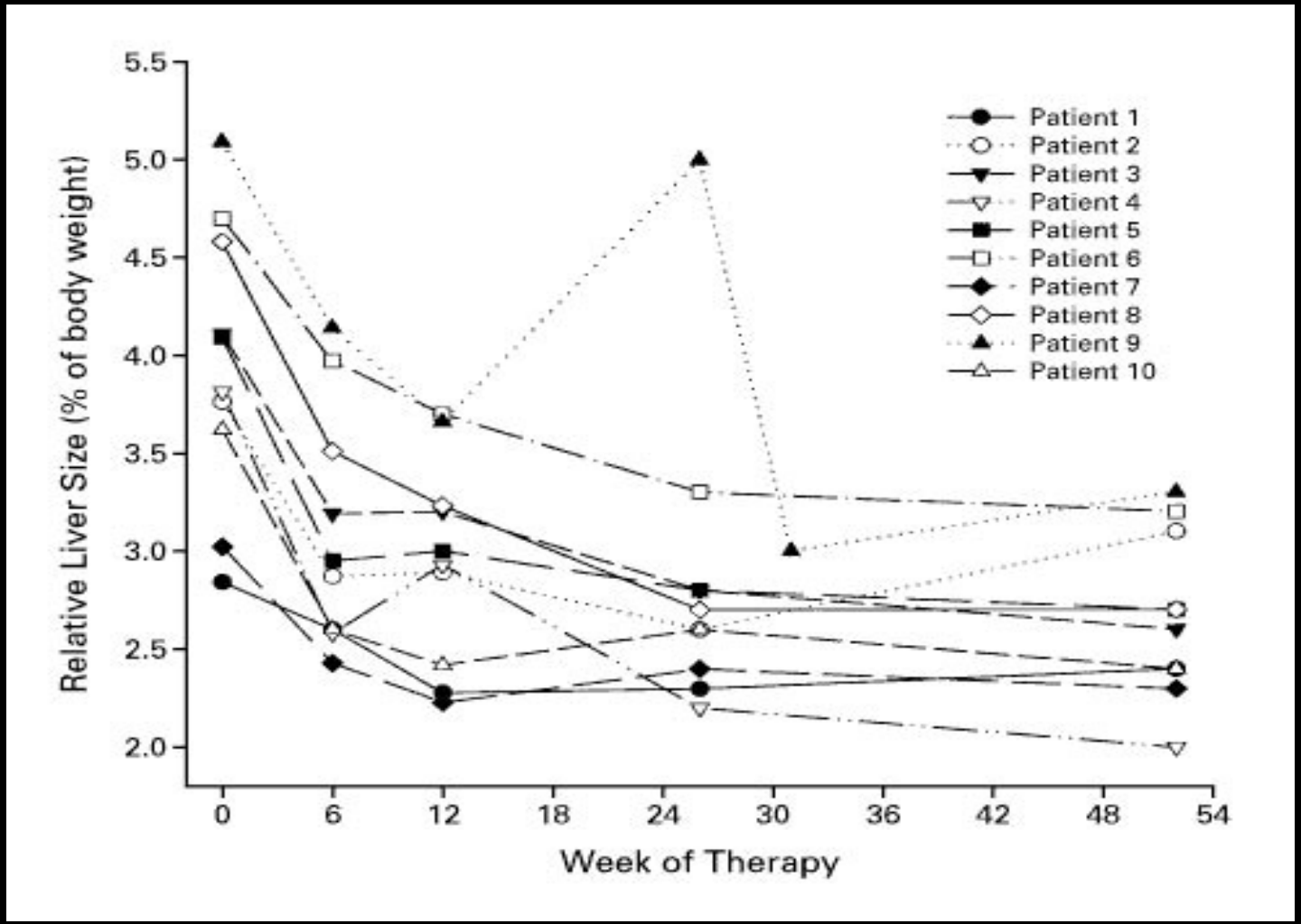
Changes in Liver Size in Patients with Mucopolysaccharidosis I during α-l-Iduronidase Therapy.



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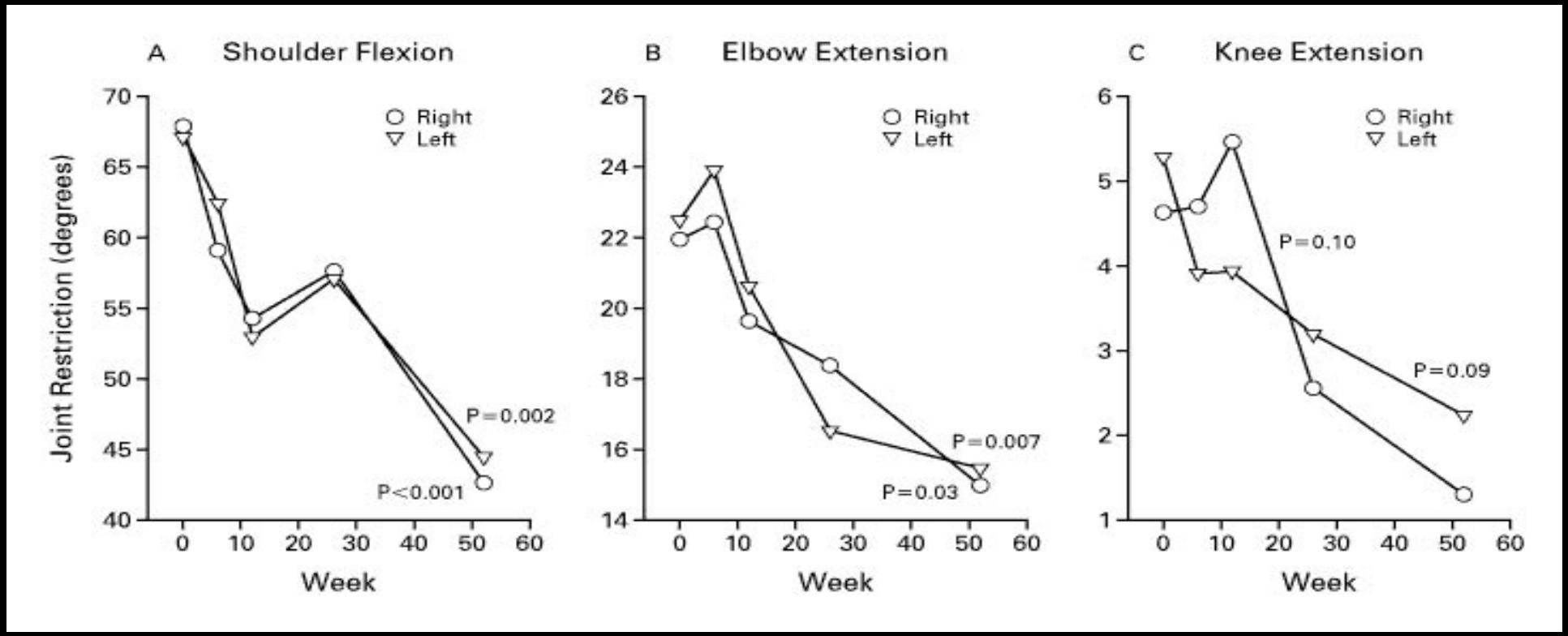
Mean Changes in the Restriction of Range of Motion of Shoulder Flexion (Panel A), Elbow Extension (Panel B), and Knee Extension (Panel C) in Patients with Mucopolysaccharidosis I during α-l-Iduronidase Therapy.



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Established and Investigational Therapies for Lysosomal Storage Diseases

Table 1. Established and Investigational Therapies for Lysosomal Storage Diseases.*

Disease	Enzyme Replaced or Targeted	Therapeutic Agent†	Manufacturer	Indication	Status of Agent
Commercially available therapies					
Gaucher's disease type 1	Glucocerebrosidase	Imiglucerase (Cerezyme)	Genzyme	ERT	FDA approved
Gaucher's disease type 1	Glucocerebrosidase	Miglustat (Zavesca)	Actelion	SRT	FDA approved
Fabry's disease	α-Galactosidase A	Agalsidase beta (Fabrazyme)	Genzyme	ERT	FDA approved
Pompe's disease	α-Glucosidase	Alglucosidase alfa (Myozyme)	Genzyme	ERT	FDA approved
MPS II (Hunter's syndrome)	Iduronate-2-sulfatase	Idursulfase (Elaprase)	Shire	ERT	FDA approved
MPS VI (Maroteaux–Lamy syndrome)	Arylsulfatase B	Galsulfase (Naglazyme)	BioMarin	ERT	FDA approved
MPS I (Hurler's syndrome or the Hurler–Scheie syndrome)	α-L-iduronidase	Laronidase (Aldurazyme)	BioMarin–Genzyme	ERT	FDA approved
Gaucher's disease type 1	Glucocerebrosidase	Velaglucerase alfa	Shire	ERT	FDA approved
Investigational therapies					
Gaucher's disease type 1	Glucocerebrosidase	Taliglucerase alfa (Uplyso)	Protalix	ERT	In phase 3 study
Gaucher's disease type 1	Glucocerebrosidase	Isofagomine tartrate (Plicera)	Amicus	Pharmacologic chaperone	In phase 2 study
Fabry's disease	α-Galactosidase A	Migalastat hydrochloride (Amigal)	Amicus	Pharmacologic chaperone	In phase 2 study
Fabry's disease	α-Galactosidase A	Agalsidase alfa (Replagal)	Shire	ERT	In phase 3 study (approved in EU)
Pompe's disease	α-Glucosidase	AT2220	Amicus	Pharmacologic chaperone	In phase 2 study
Niemann–Pick disease type C	Sphingomyelinase	Miglustat (Zavesca)	Actelion	SRT	In phase 2 study (approved in EU)
Tay–Sachs disease	Hexosaminidase A	Miglustat (Zavesca)	Actelion	SRT	In phase 2 study

* 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.

Dietz HC. N Engl J Med 2010;363:852-863

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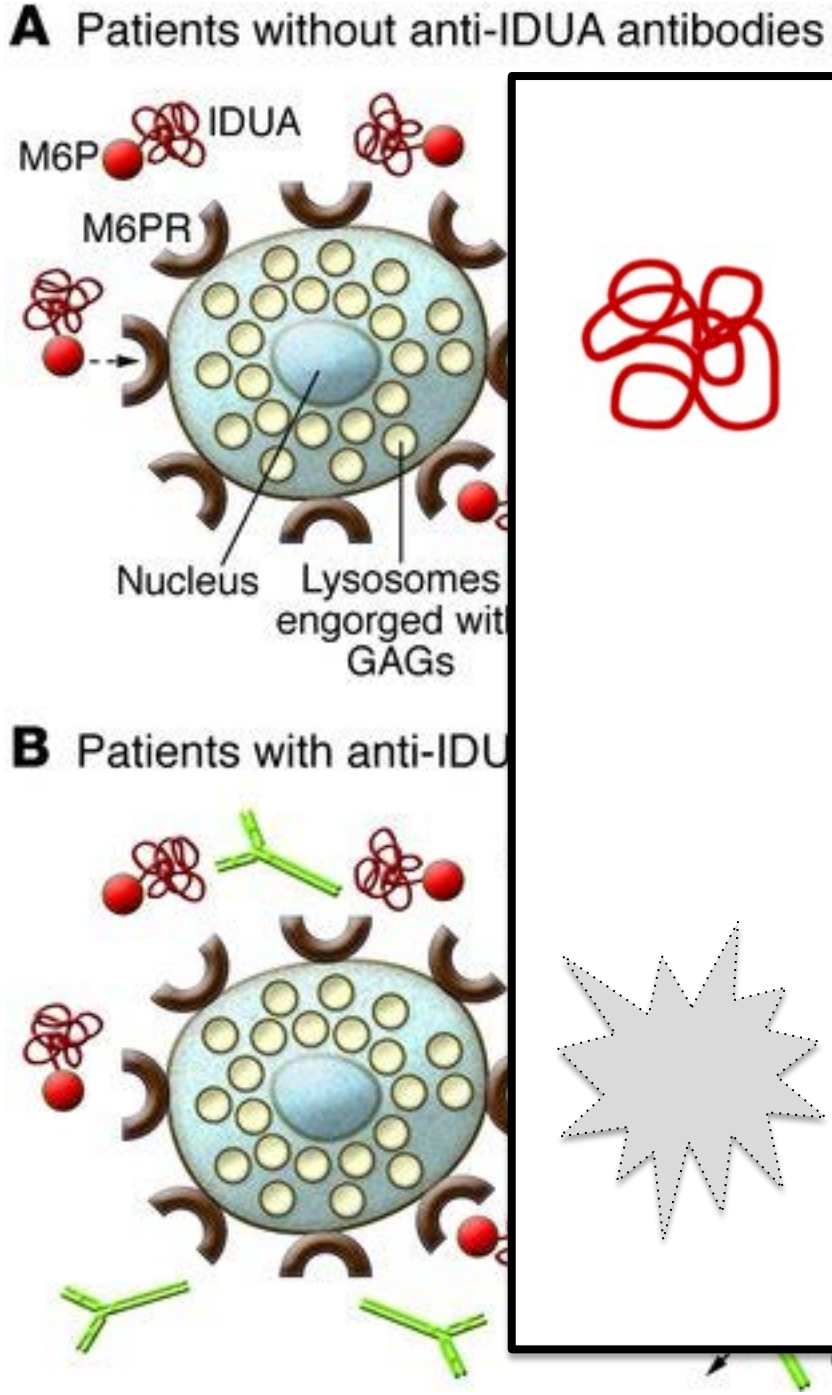
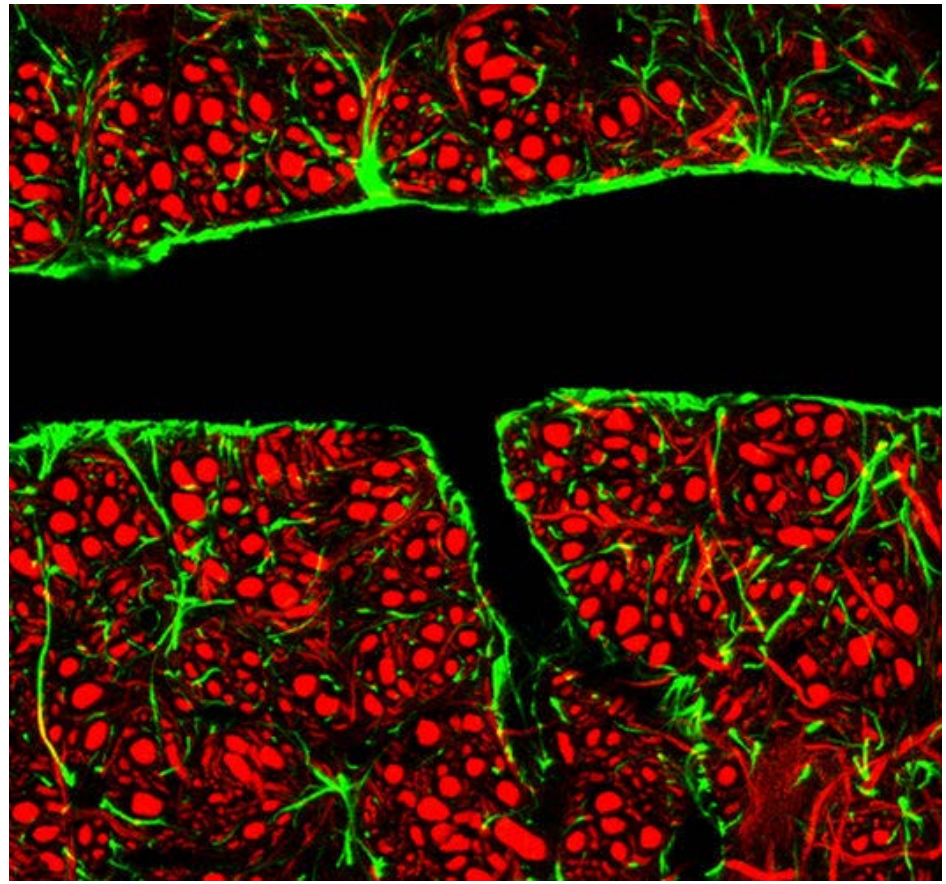


Some endogenous enzyme
Promotes “tolerance” to ERT

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)

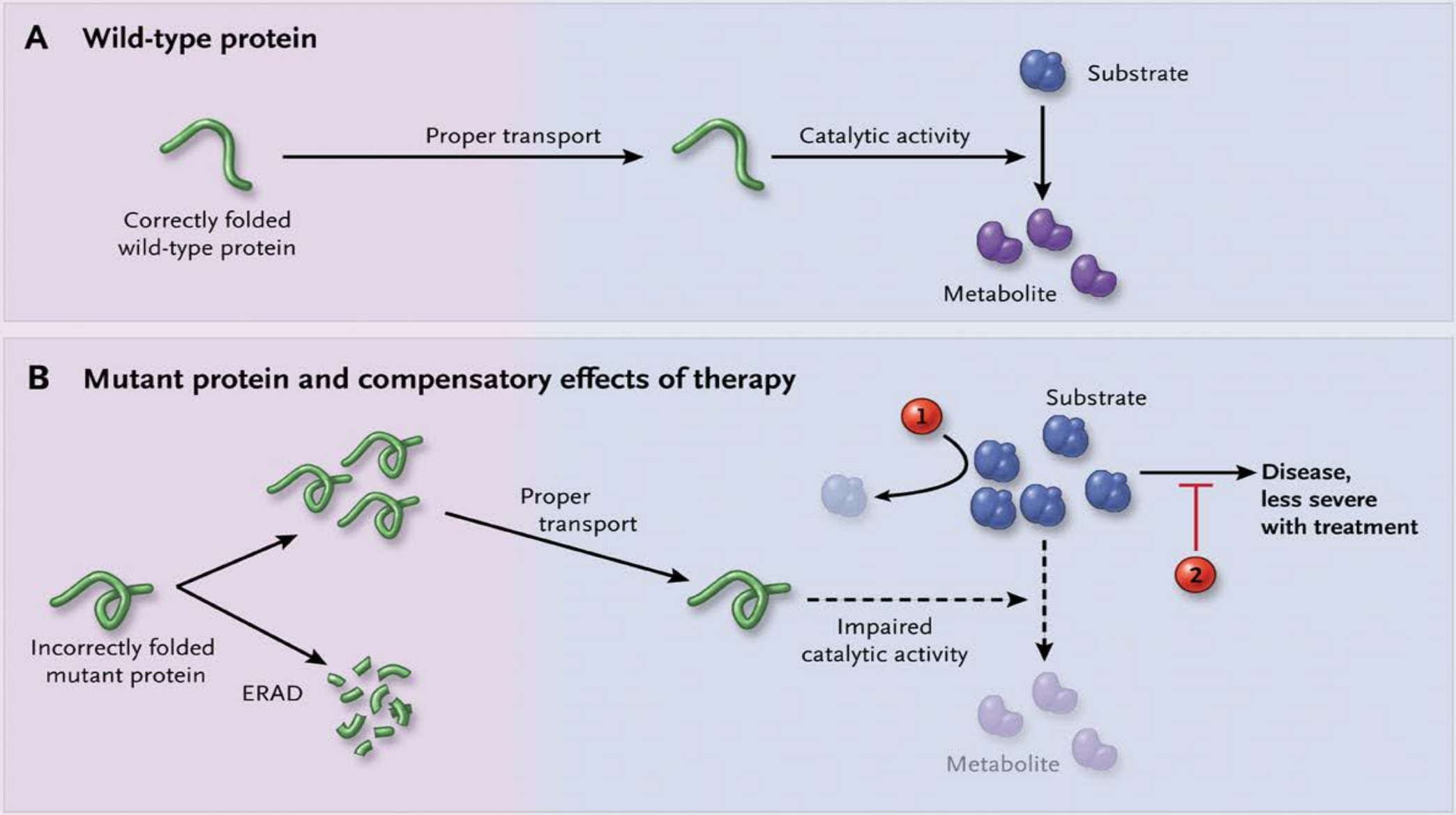
Potential Solutions:

- 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



1. Substrate reduction

2. Pathogenic modulator

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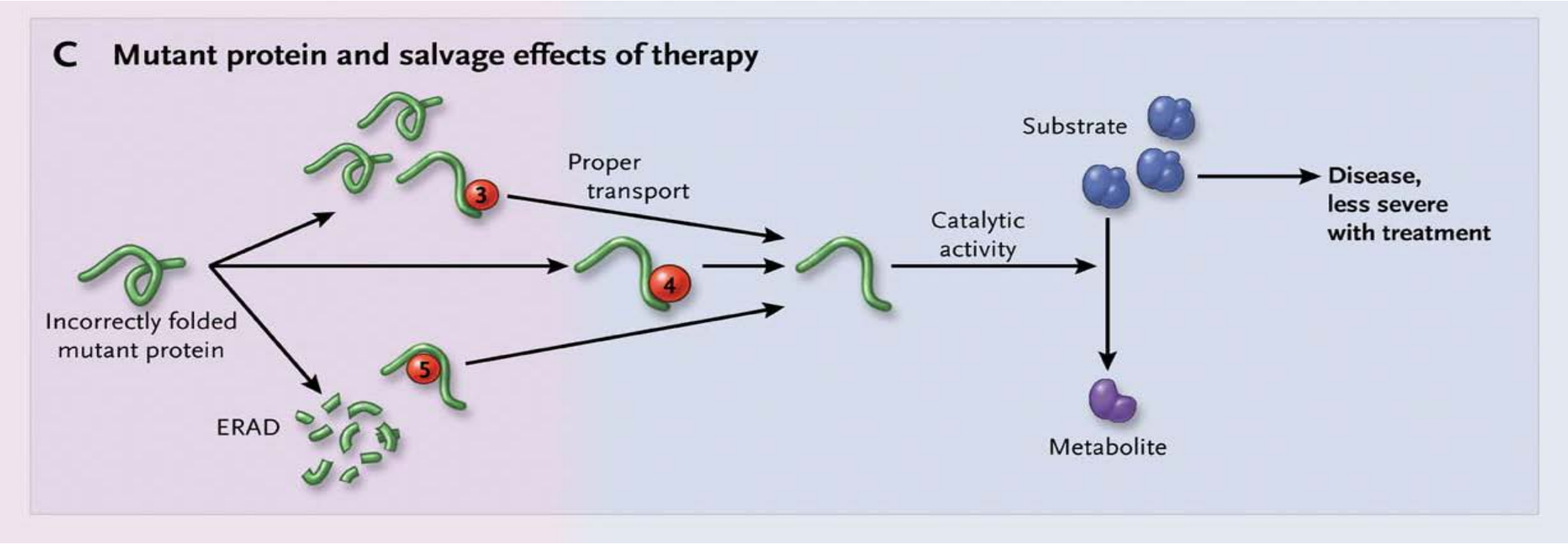
Compensatory and Salvage Therapeutic Agents



3. Corrector
 - corrects folding/trafficking

4. Potentiator
 - corrects folding/activity

5. Stabilizer
 - corrects stability

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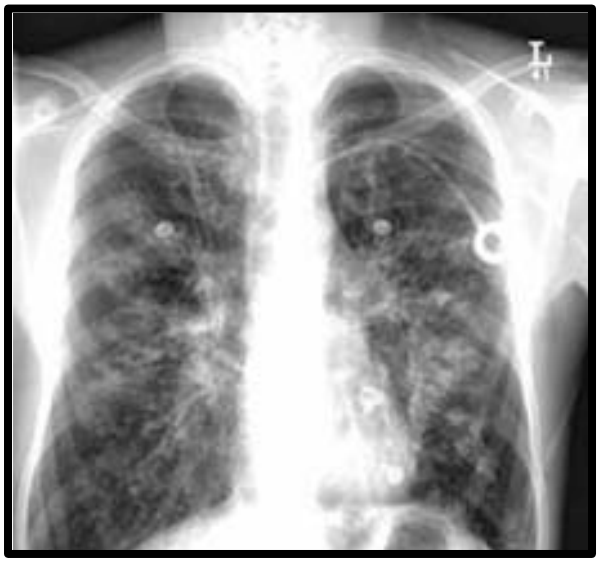
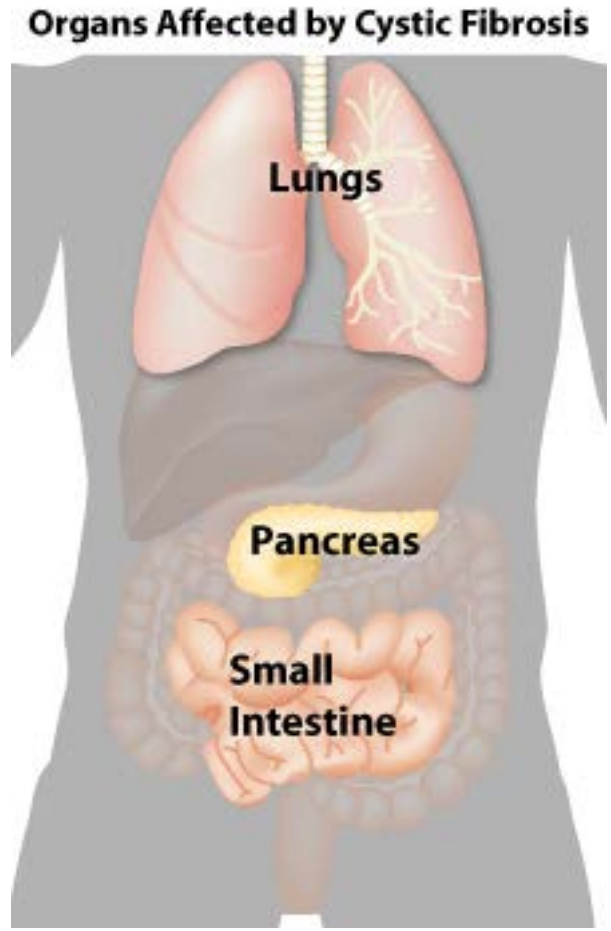
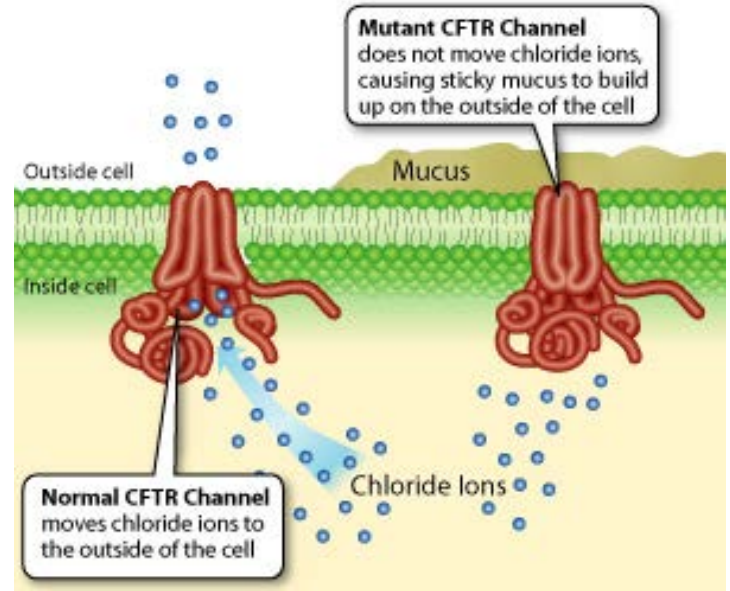
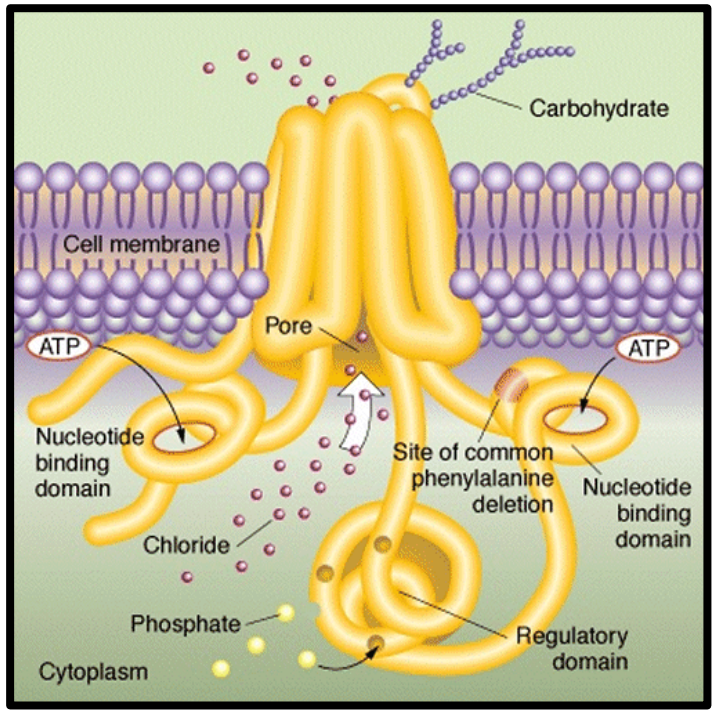
Cystic Fibrosis:





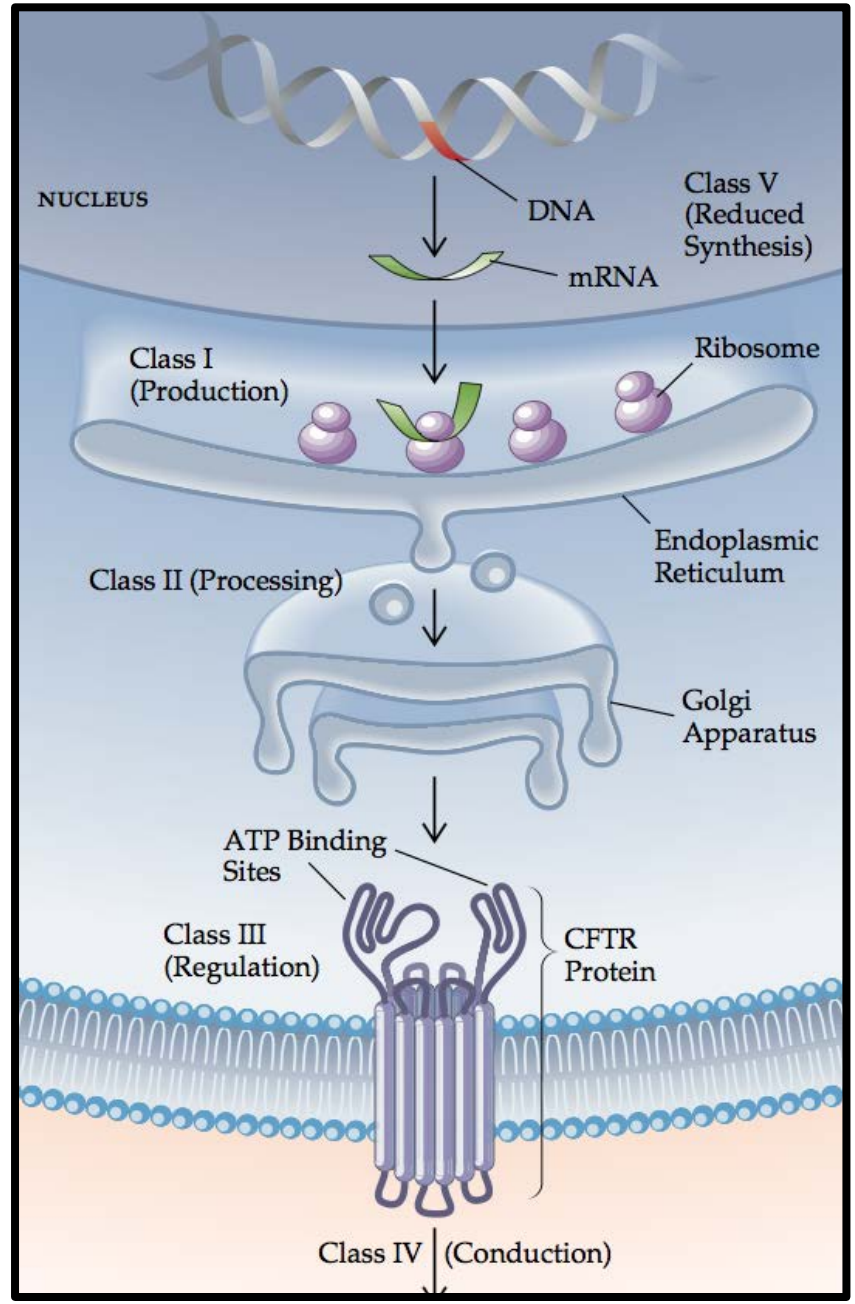


Anatomy of a vulnerable channel (CFTR)



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.



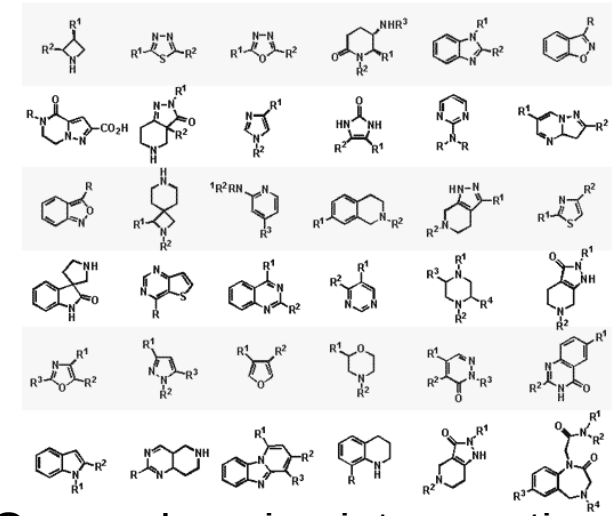
Why so narrow?

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

- By definintion, 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.

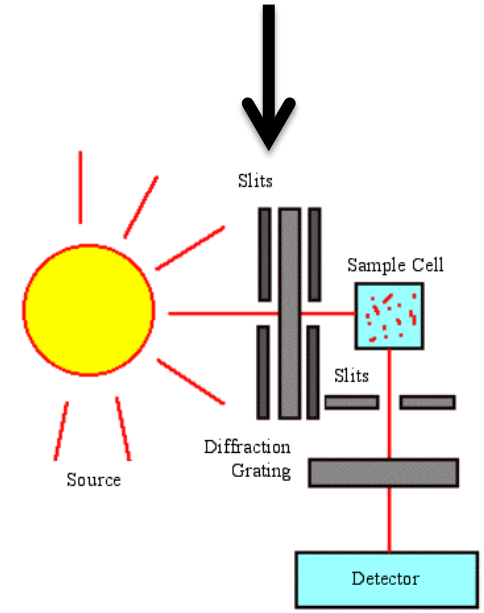
Combine deficient cells and an indicator for desired activity (e.g fluorescent marker that is activated by restored chloride conductance).



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

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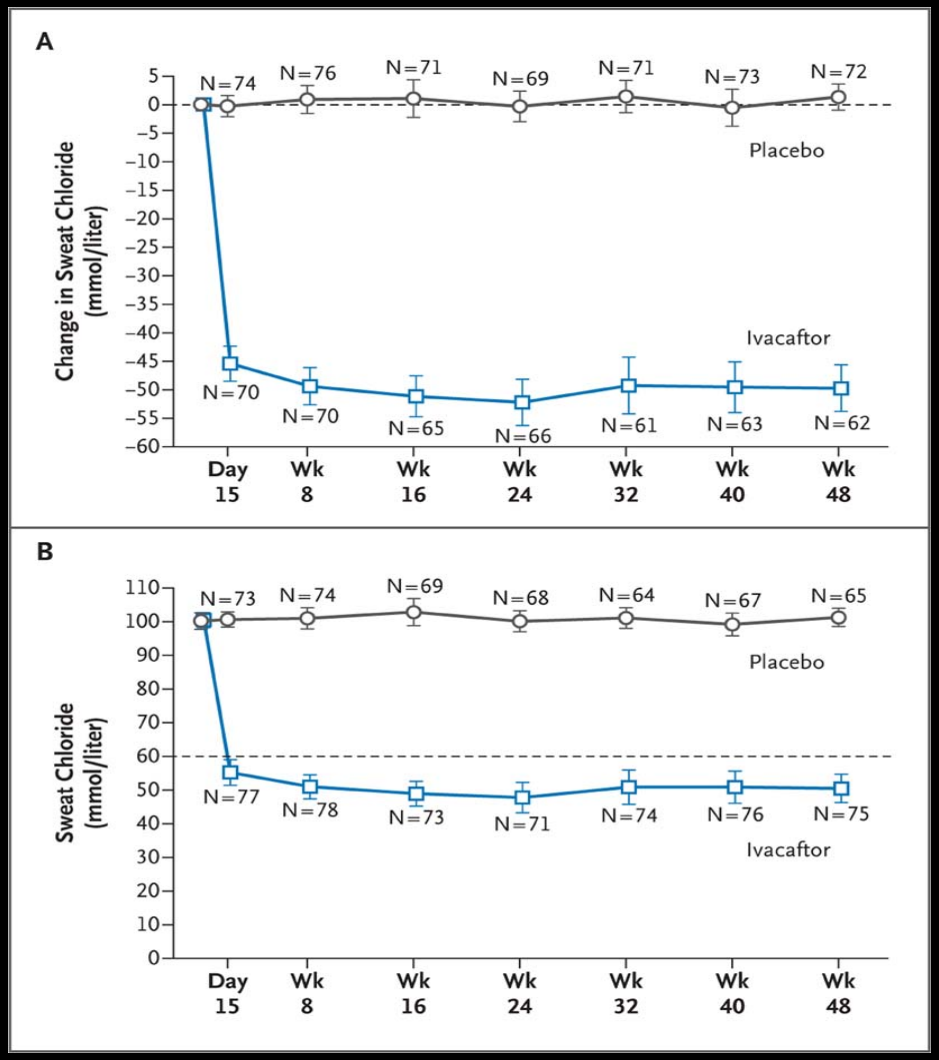
Changes from Baseline through Week 48 in Sweat Chloride, According to Study Group.



Ramsey BW et al. N Engl J Med 2011;365:1663-1672

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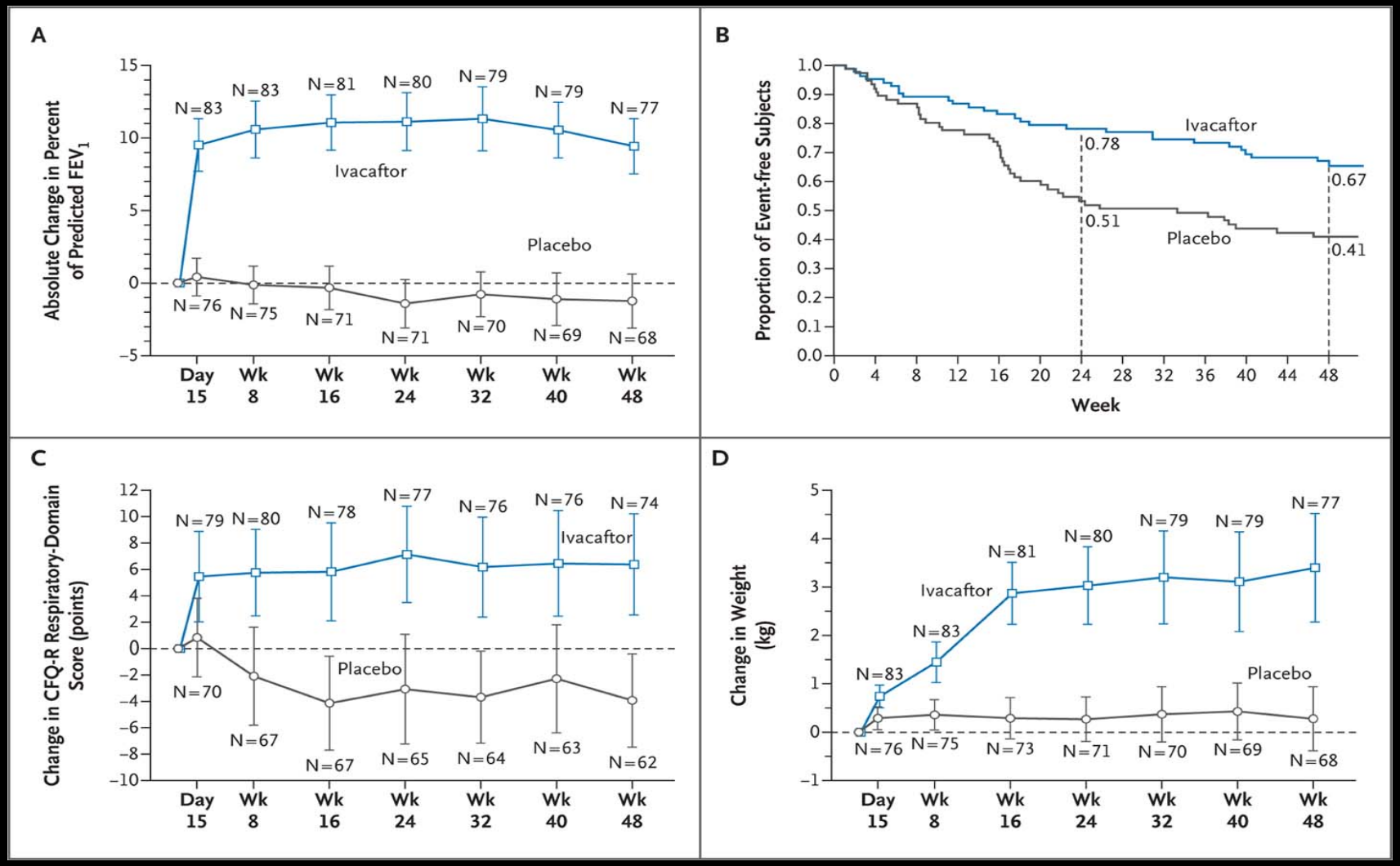
Changes from Baseline in Percent of Predicted FEV_1, Respiratory Symptoms, and Weight, and Time to the First Pulmonary Exacerbation, According to Study Group.

FEV1

Resp. Score



No Events

Weight

Ramsey BW et al. N Engl J Med 2011;365:1663-1672

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Treatment Effect of Ivacaftor with Respect to the Change from Baseline through Week 48 in the Percent of Predicted FEV_1, According to Subgroups.

Table 2. Treatment Effect of Ivacaftor with Respect to the Change from Baseline through Week 48 in the Percent of Predicted FEV_1, According to Subgroups.*

Subgroup	Treatment Effect	P Value
Baseline % of predicted FEV_1		
<70%	10.6	<0.001
≥70%	10.3	<0.001
Geographic region		
North America	9.0	<0.001
Europe	9.9	<0.001
Australia	11.9	0.008
Sex		
Male	11.0	<0.001
Female	11.6	<0.001
Age		
<18 yr	11.4	0.005
≥18 yr	9.9	<0.001

* 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_1.

Works irrespective of:

Severity

Location

Gender

Age

Ramsey BW et al. N Engl J Med 2011;365:1663-1672

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Adverse Events.

Table 3. Adverse Events.

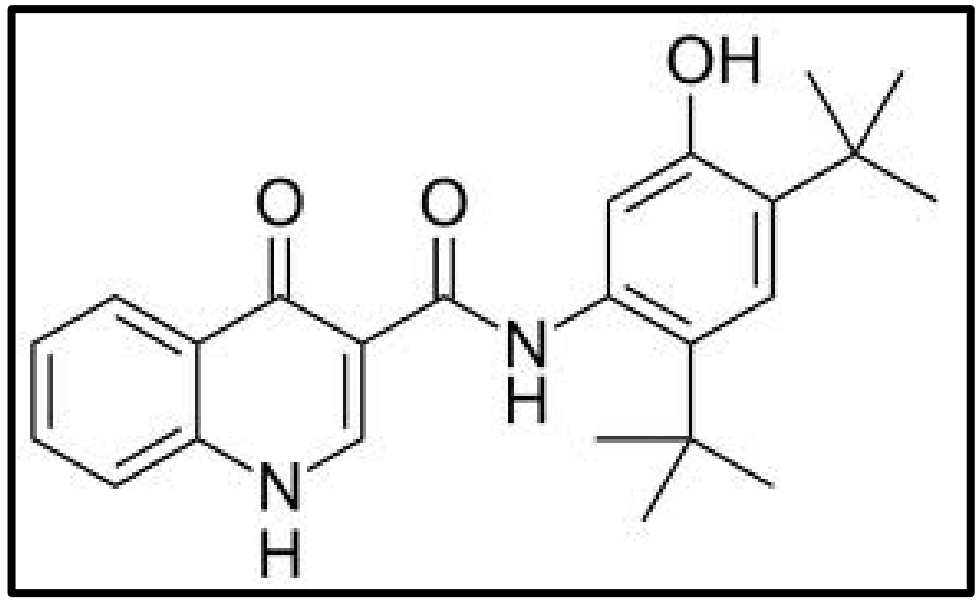
Adverse Event	Placebo (N=78)	Ivacaftor (N=83)
	no. of subjects (%)	
Any adverse event	78 (100)	82 (99)
Serious adverse event*	33 (42)	20 (24)
Pulmonary exacerbation	26 (33)	11 (13)
Hemoptysis	4 (5)	1 (1)
Hypoglycemia	0	2 (2)
Adverse event leading to study-drug interruption	5 (6)	11 (13)
Adverse event leading to study-drug discontinuation	4 (5)	1 (1)

* Included are serious adverse events that occurred in more than one subject per group.

Ramsey BW et al. N Engl J Med 2011;365:1663-1672

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).

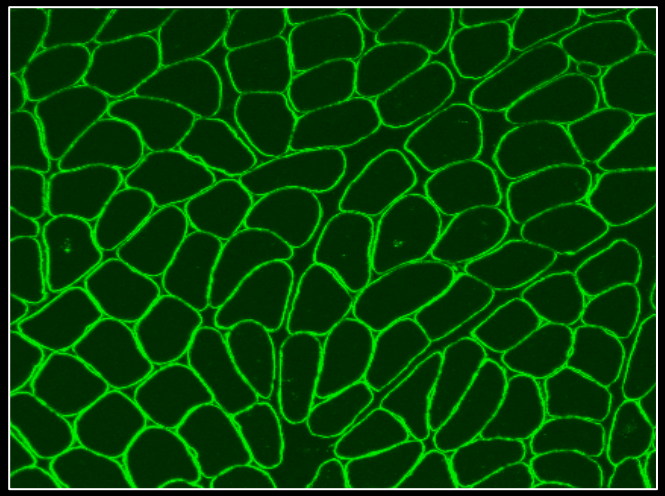
January 31, 2012

	Duchenne Muscular Dystrophy (DMD)	Becker Muscular Dystrophy (BMD)
		
Diagnosis	4.6	teens
Wheelchair	teens	adult
Death	young adult (onward)	4^{th}-5^{th} decade

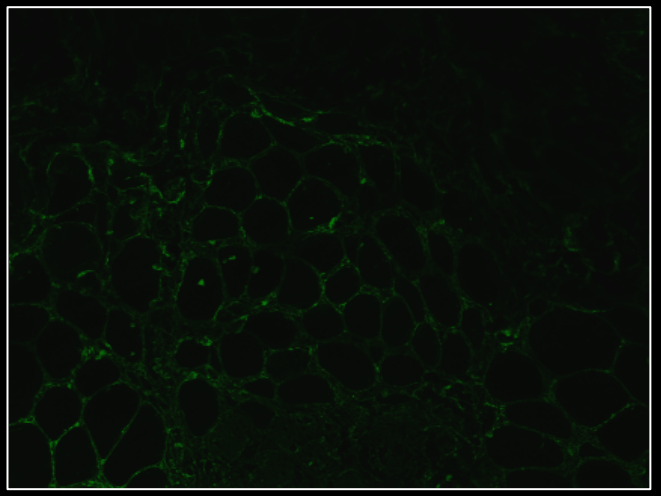
Both caused by mutations in the *DMD* gene encoding dystrophin.

DMD/BMD

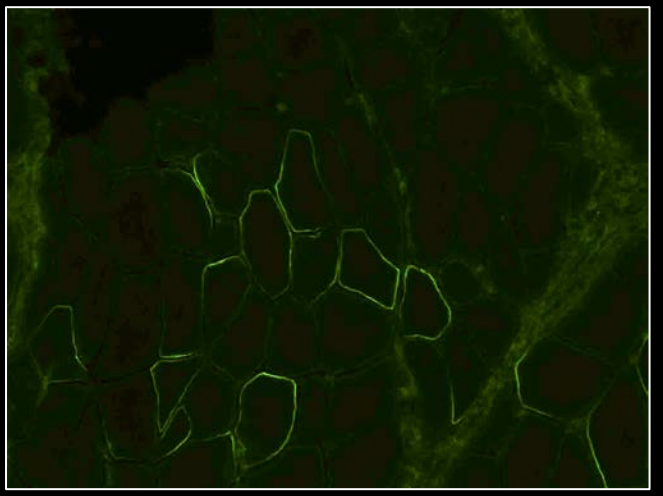
Dystrophin Staining



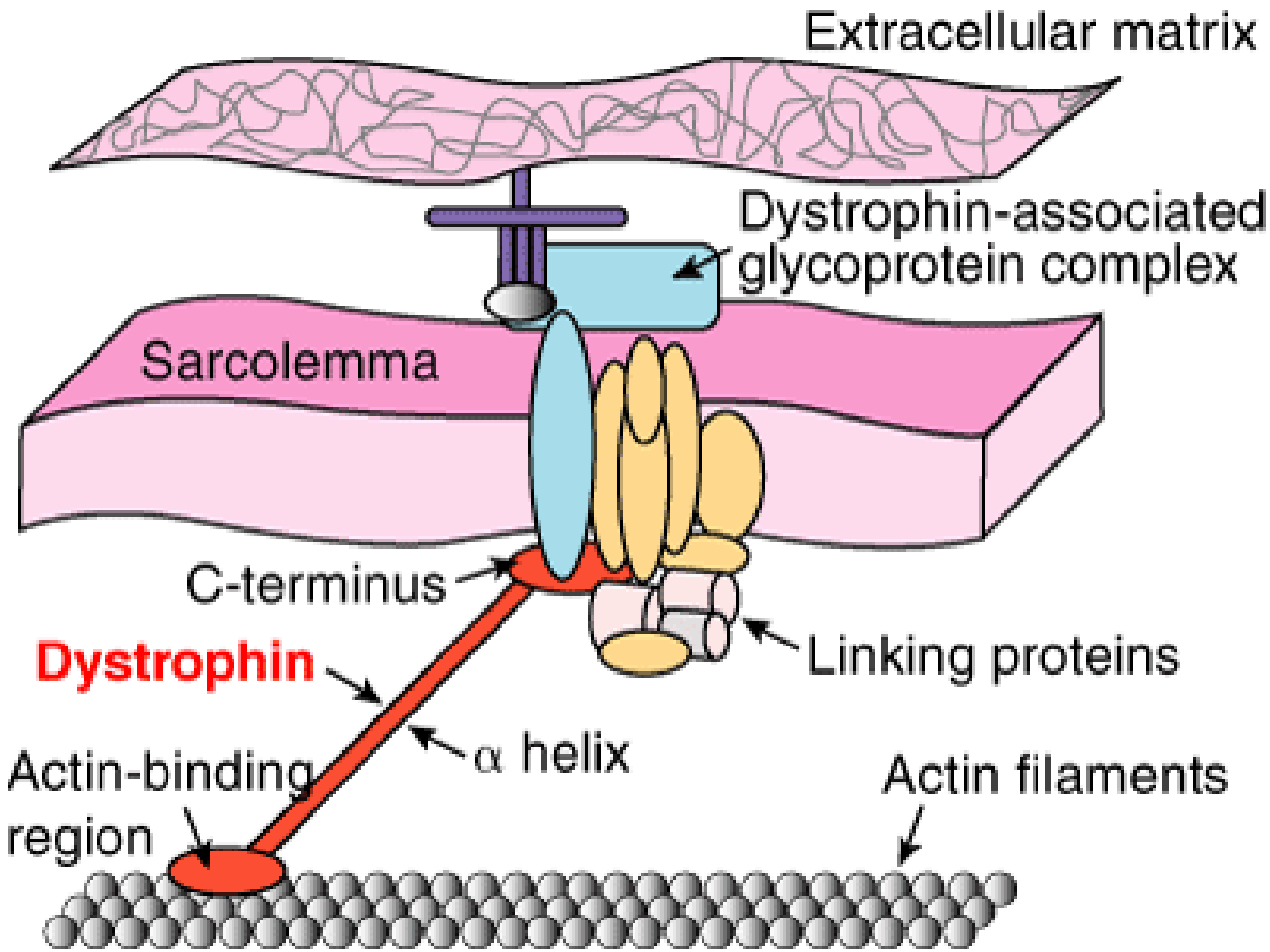
Control

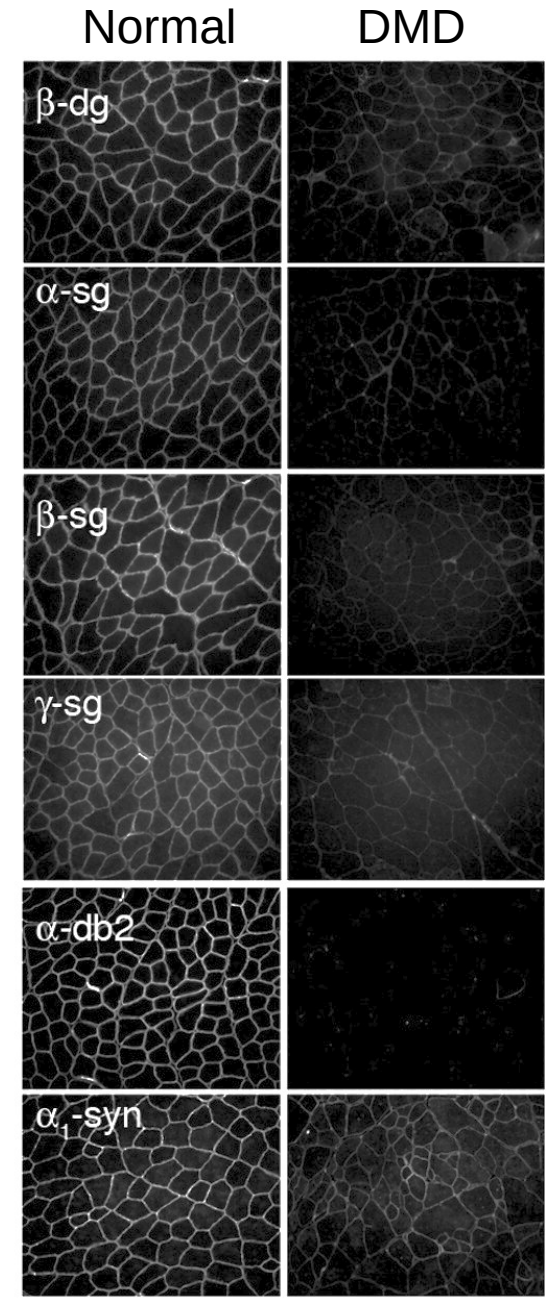


DMD



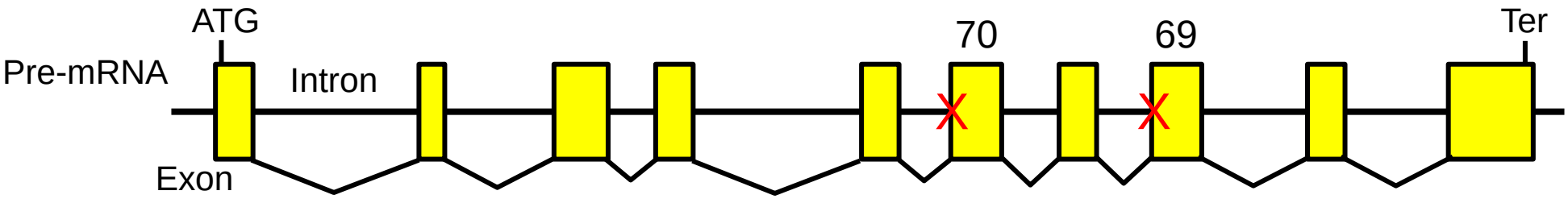
BMD





Dystrophin needs its head and its tail – but perhaps not all of its middle???

Judge L M et al. J Cell Sci 2006;119:1537-1546

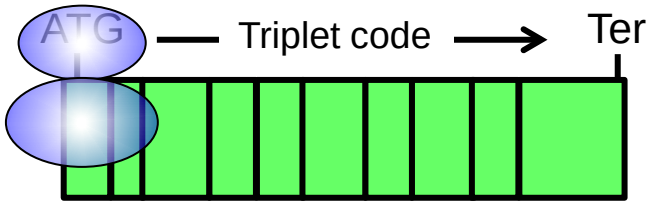


Normal pre-mRNA splicing

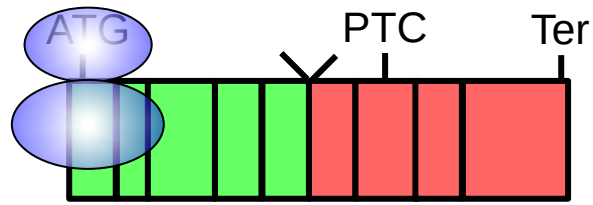
Exon skipping
(Not even multiple of 3 nt.)

Exon skipping
(Even multiple of 3 nt.)

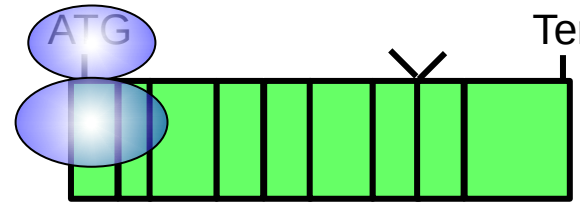
Mature mRNA



“Open Reading Frame”

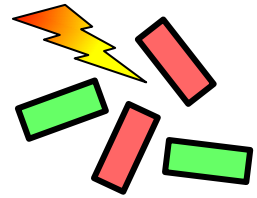


“Frameshift leading to a
Premature Termination Codon”



“Open Reading Frame”

Full length dystrophin protein
with full function



Nonsense-mediated
mRNA decay (NMD)

Truncated protein
with no function

Centrally-deleted protein
with partial function

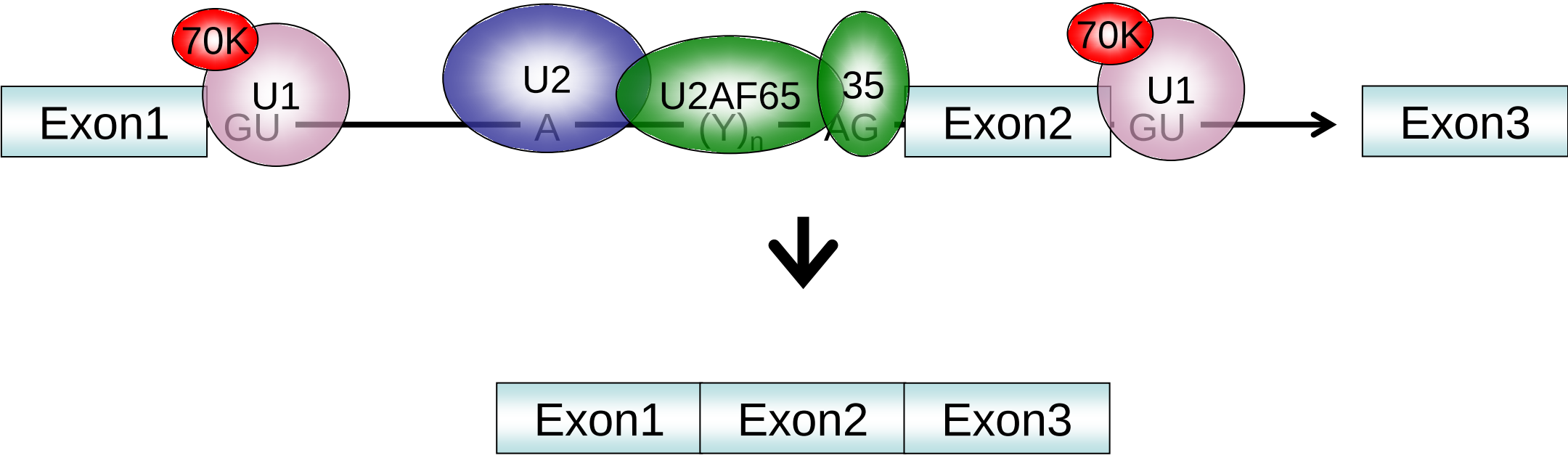
Normal
Phenotype

Duchenne
Muscular
Dystrophy

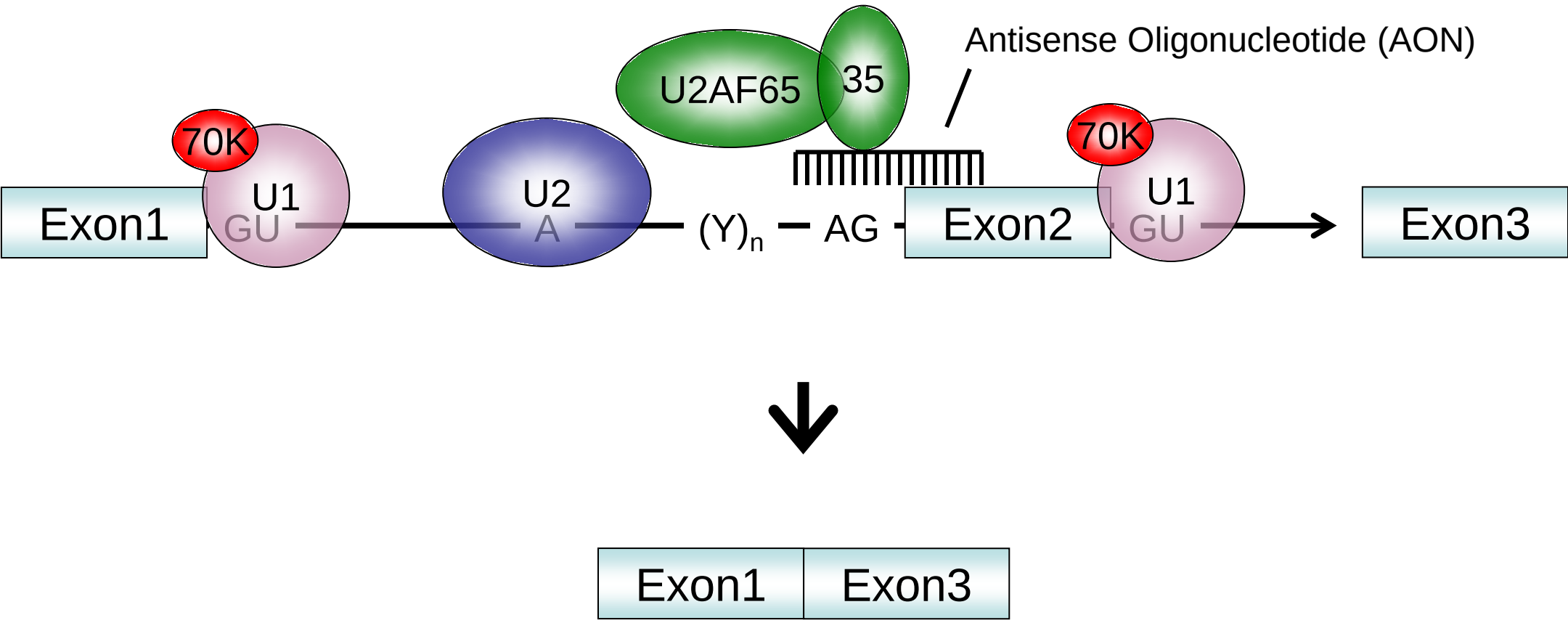
?

Becker
Muscular
Dystrophy

The mechanics of pre-mRNA splicing



Spliced mRNA



Spliced mRNA
(with targeted exon skipping)

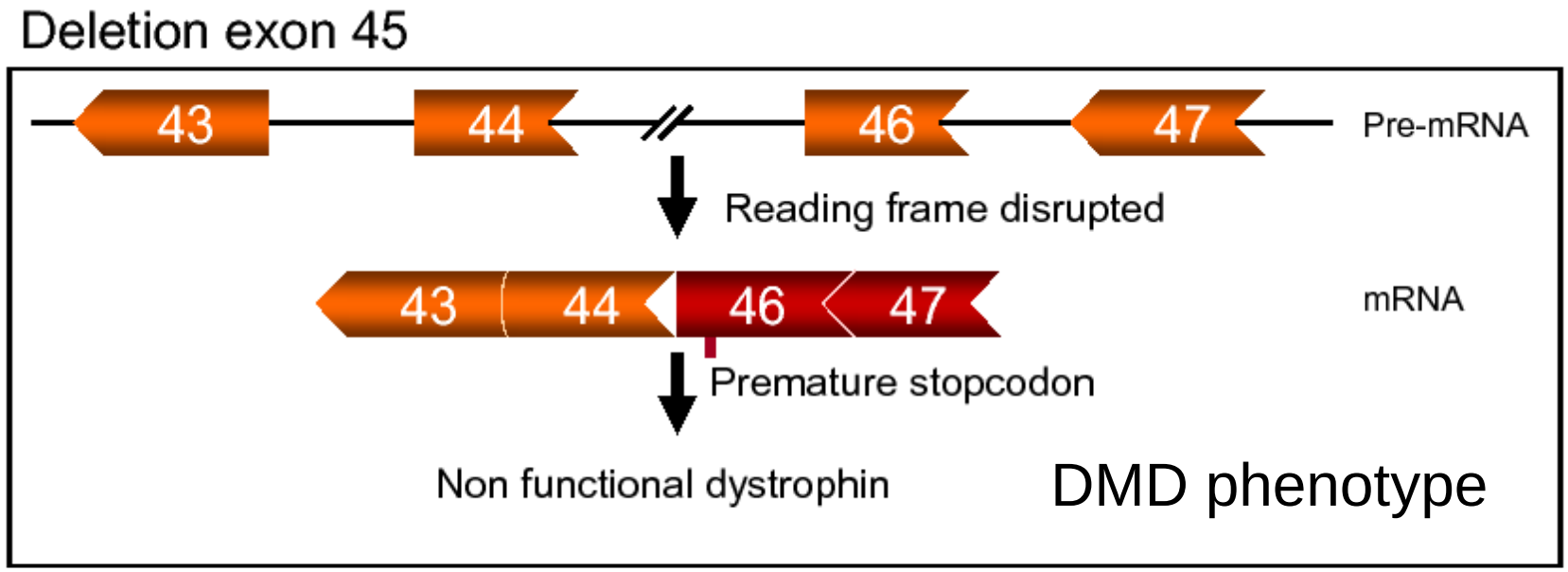
Pre-mRNA

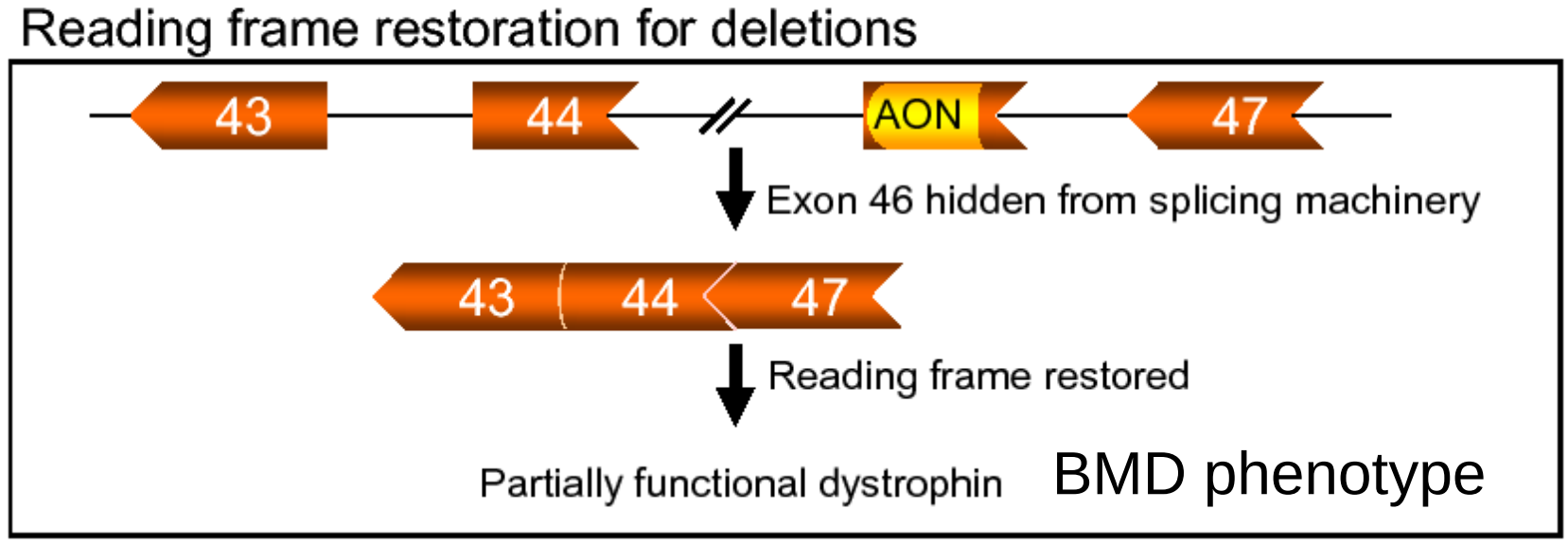
Splicing

Mature mRNA with
Open Reading Frame

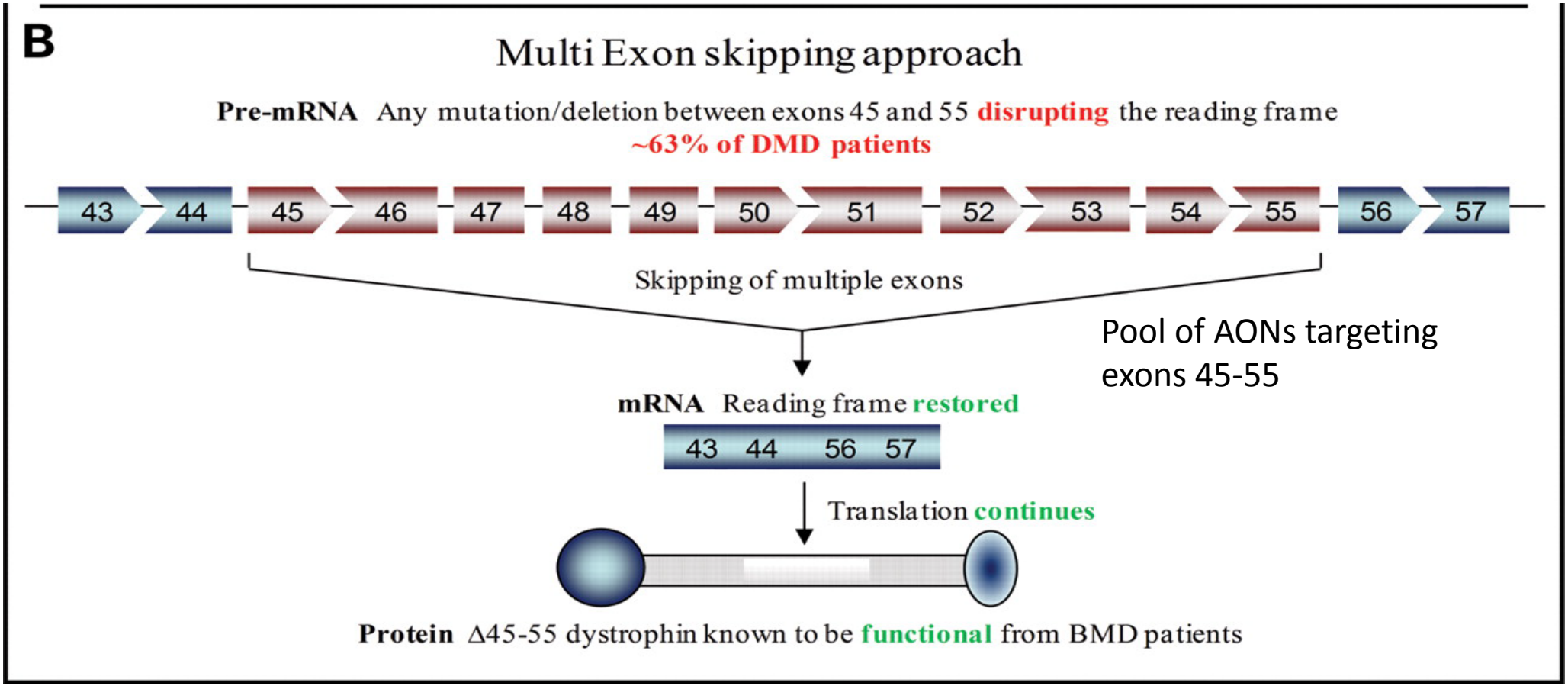
Protein

Antisense-mediated exon skipping rationale for DMD



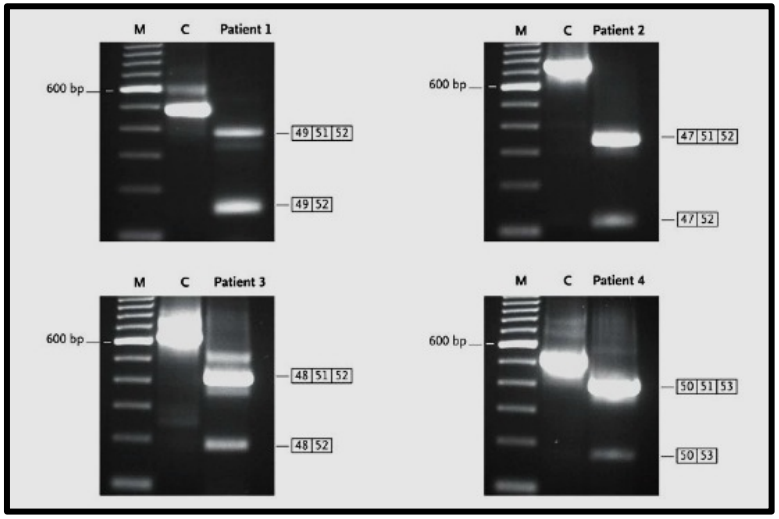


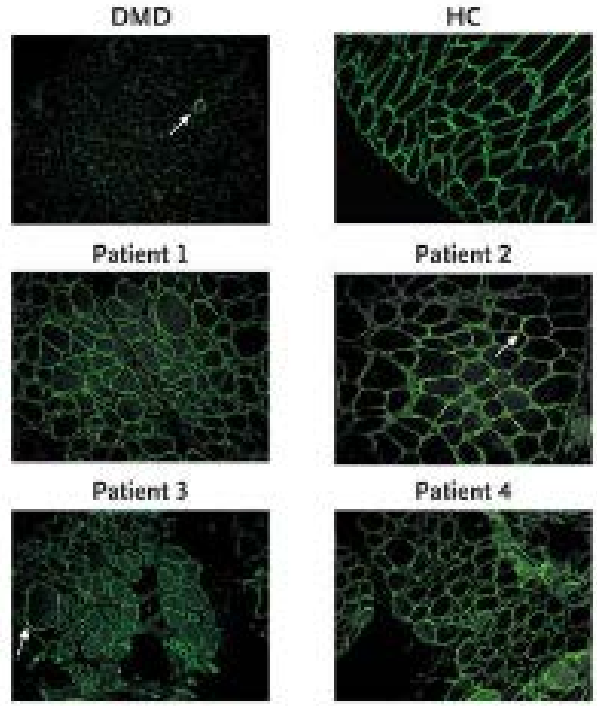
Dr. Annemieke Aartsma-Rus

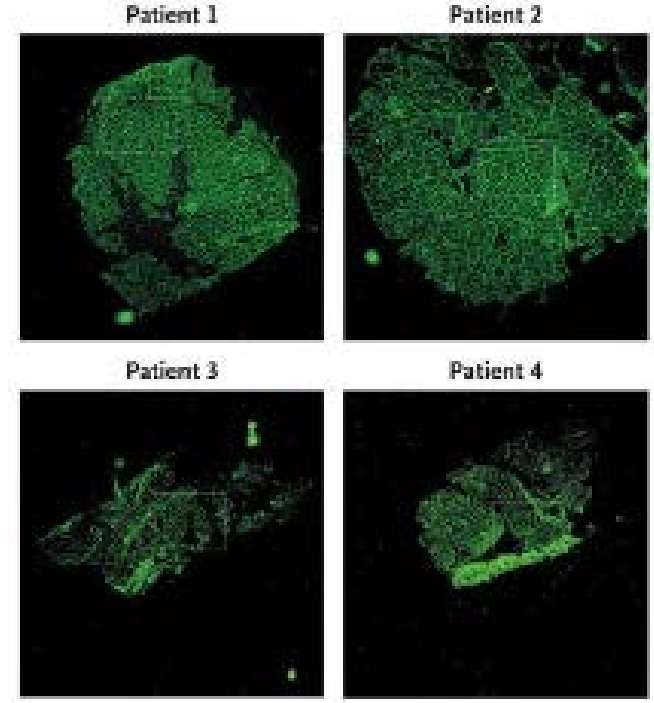


Goyenvalle A et al. Hum. Mol. Genet. 2011;20:R69-R78

Dystrophin expression after local delivery of antisense oligonucleotide

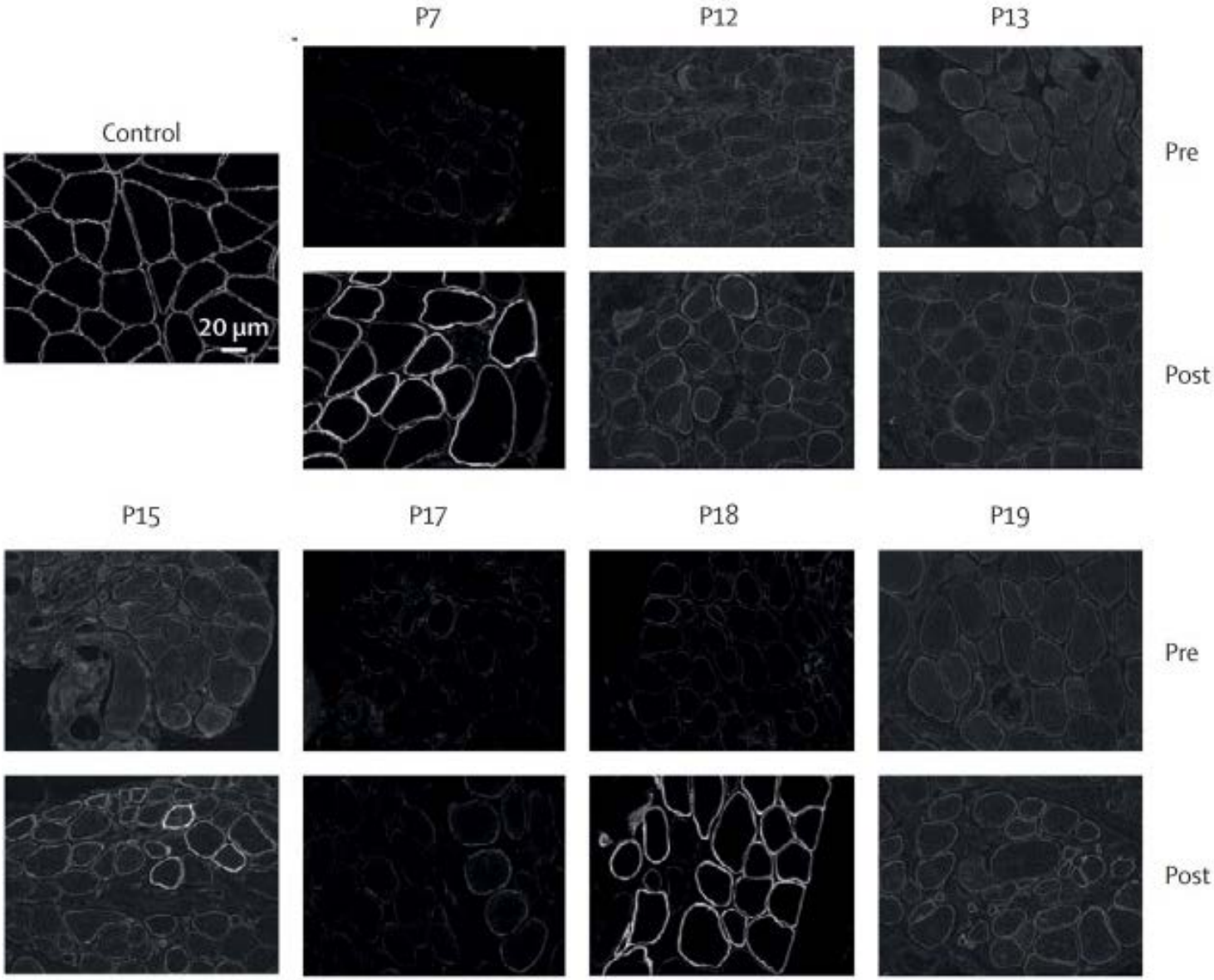






Von Deutekom NEJM, 2007

Dystrophin expression after systemic delivery of antisense oligonucleotide



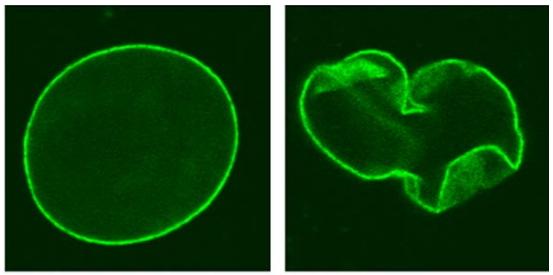
7/19 responders

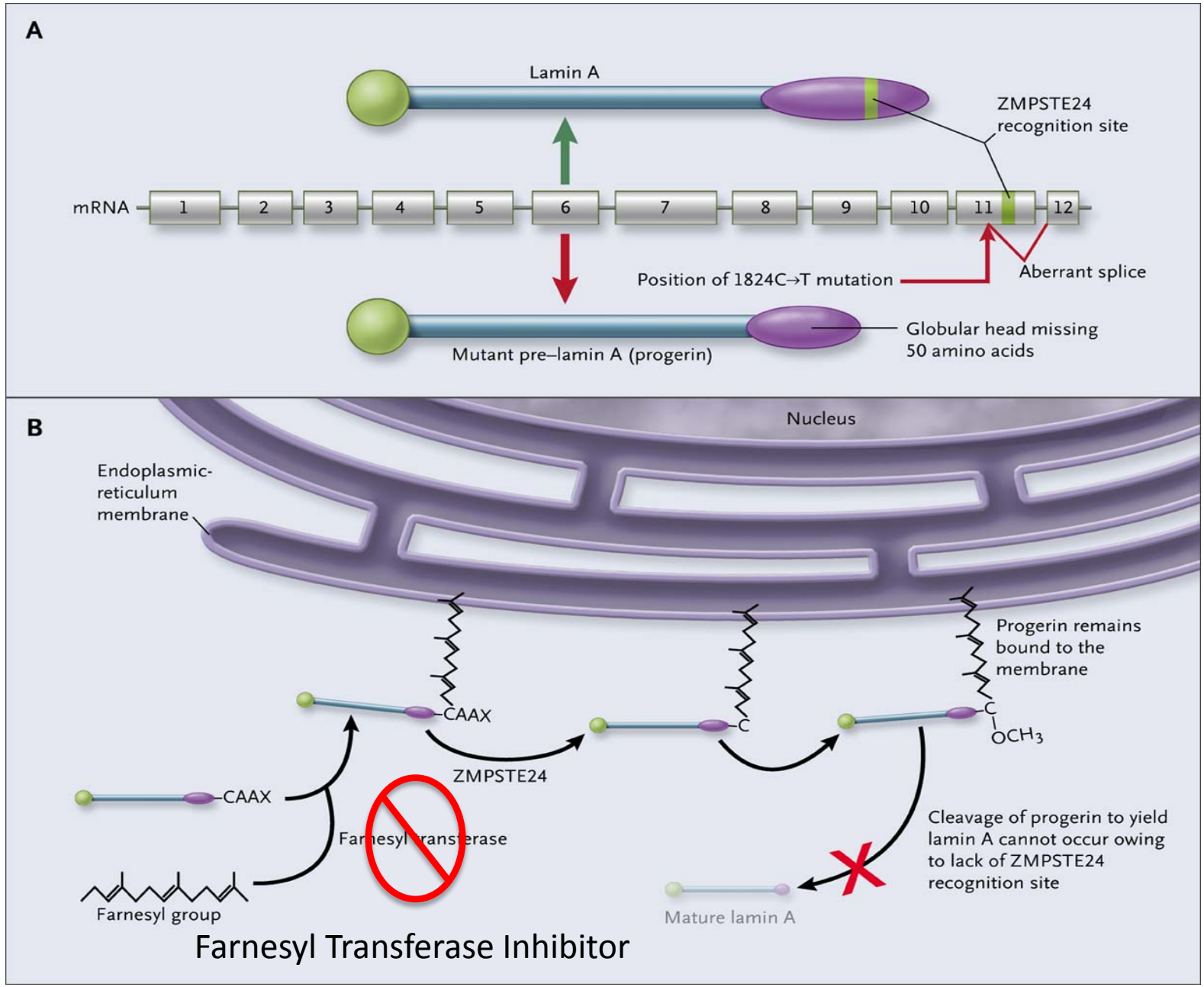
- delivery
- stability

Cirak et al. Lancet, 2011

Proposed Pathogenesis of the Hutchinson–Gilford Progeria

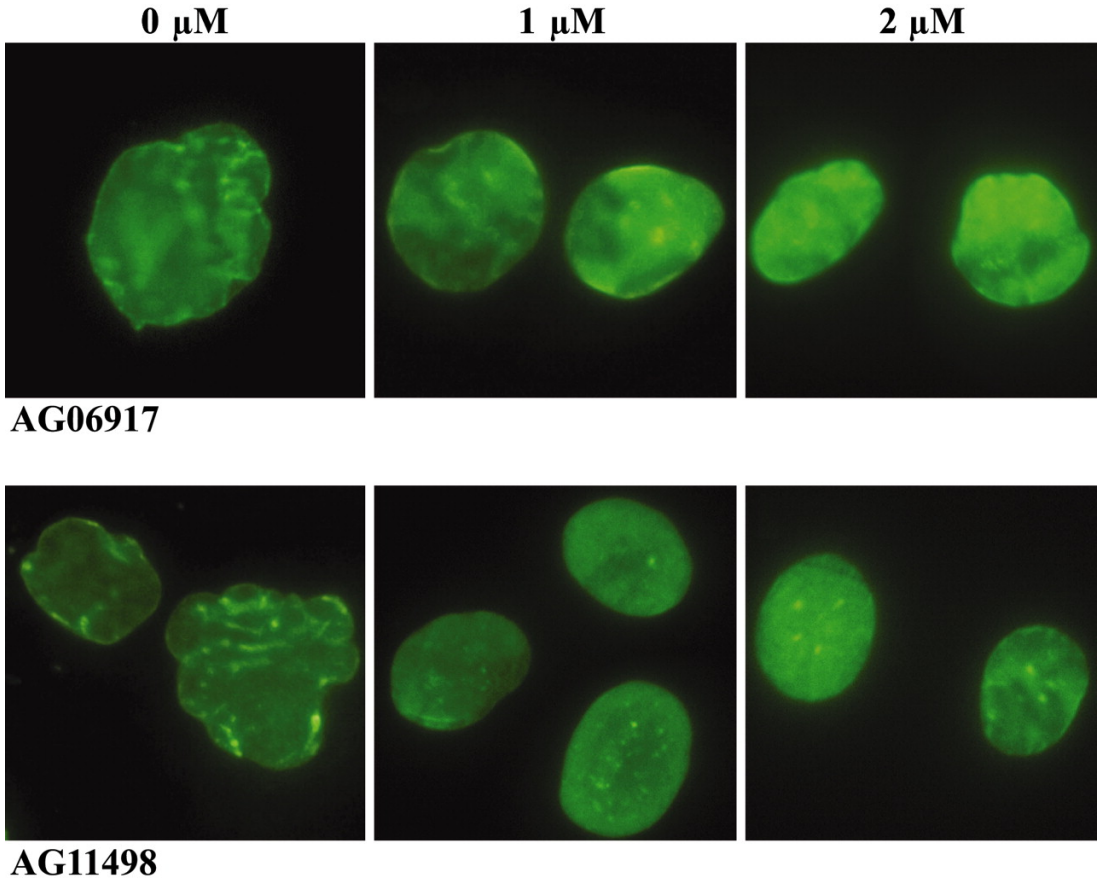
Nuclear Blebbing

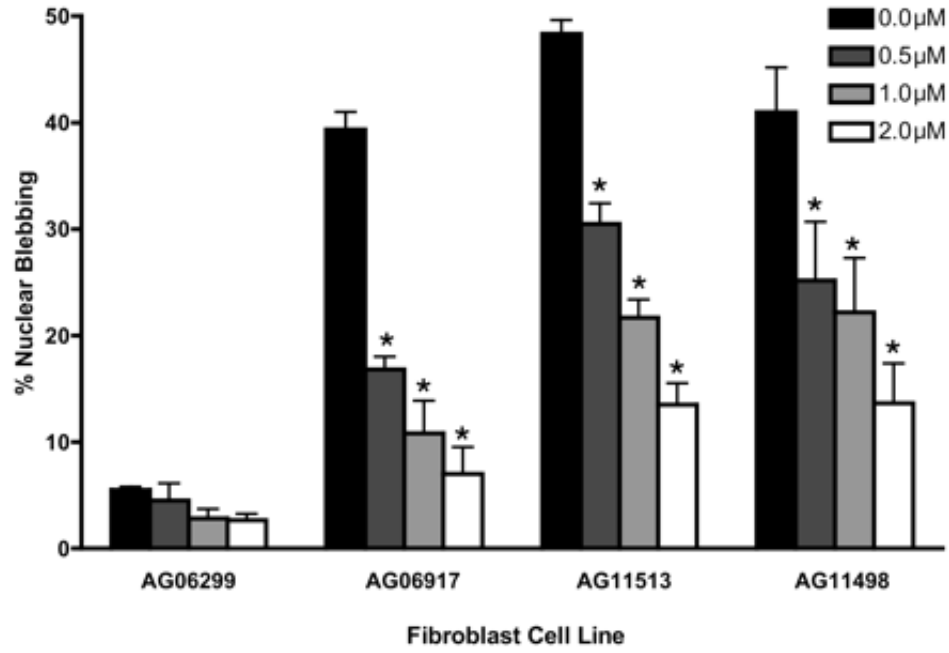




Dietz HC. N Engl J Med 2010;363:852-863

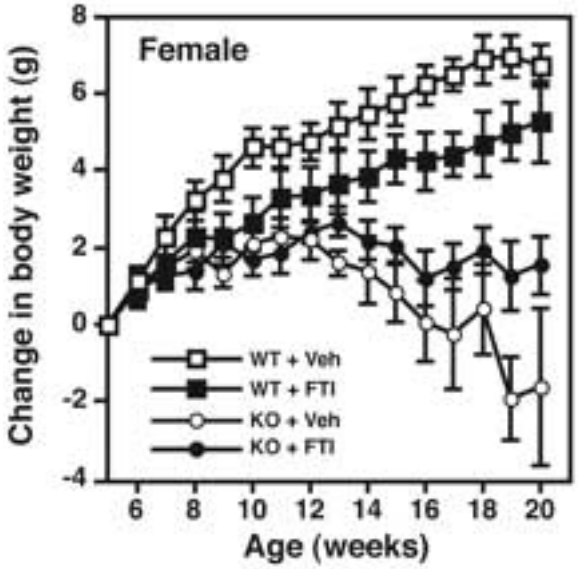
FTI treatment causes reversion of the nuclear blebbing in two different progerin-expressing HGPS human fibroblasts.

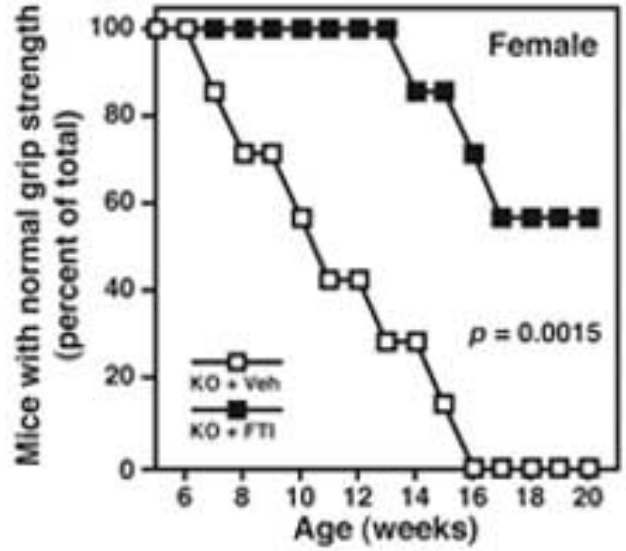


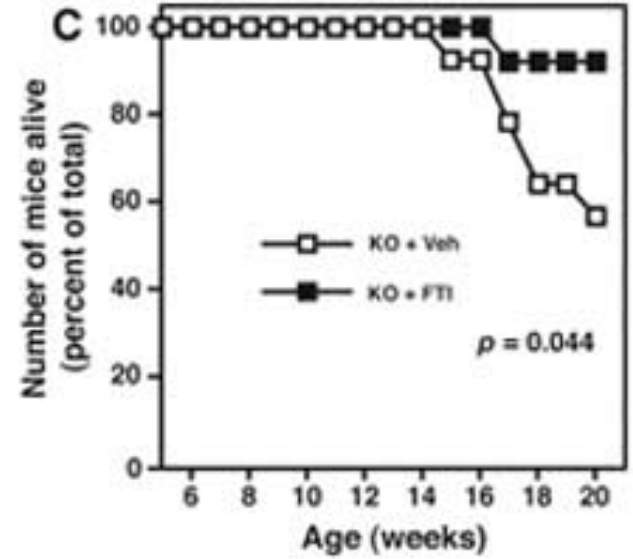


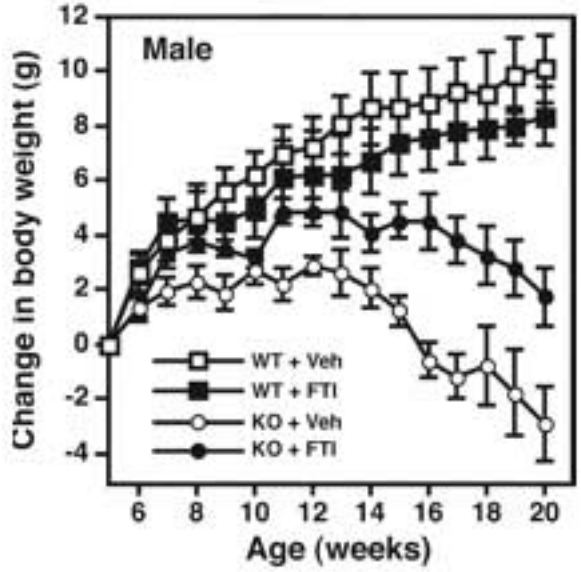
Capell B C et al. PNAS 2005;102:12879-12884

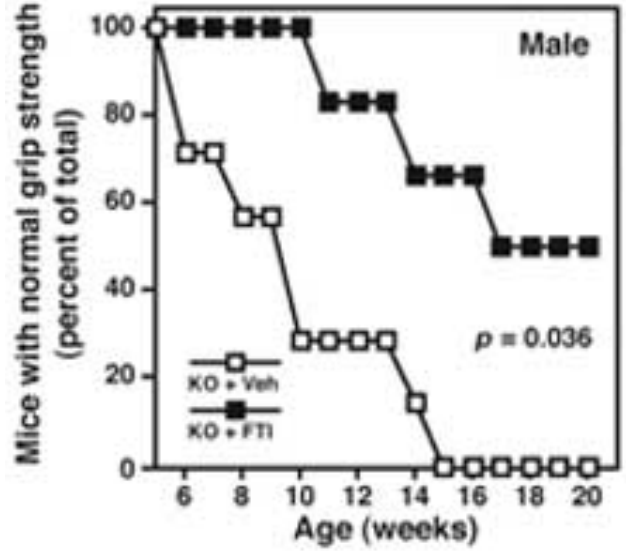
Treatment of a Mouse Model of Progeria with a FTI

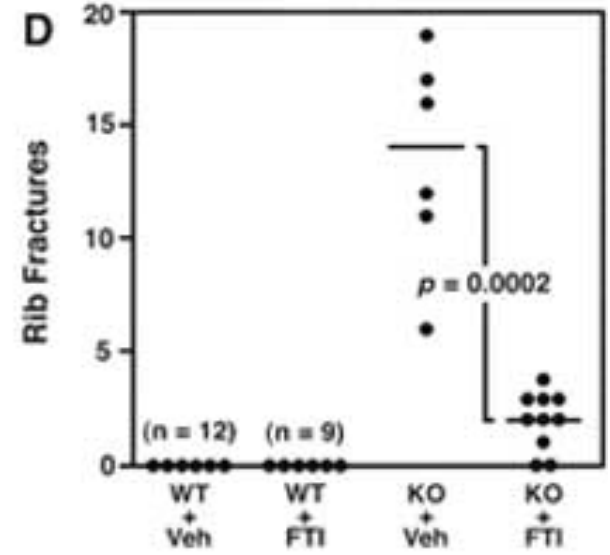






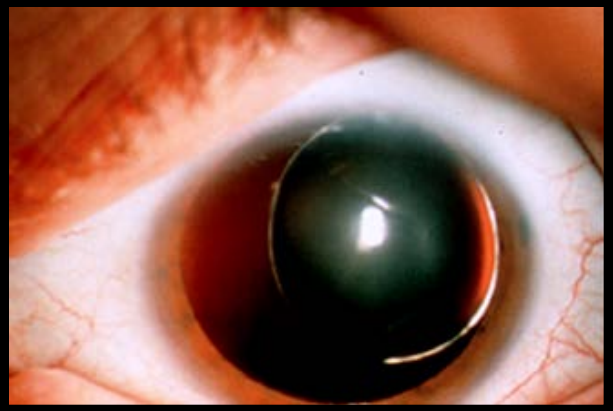


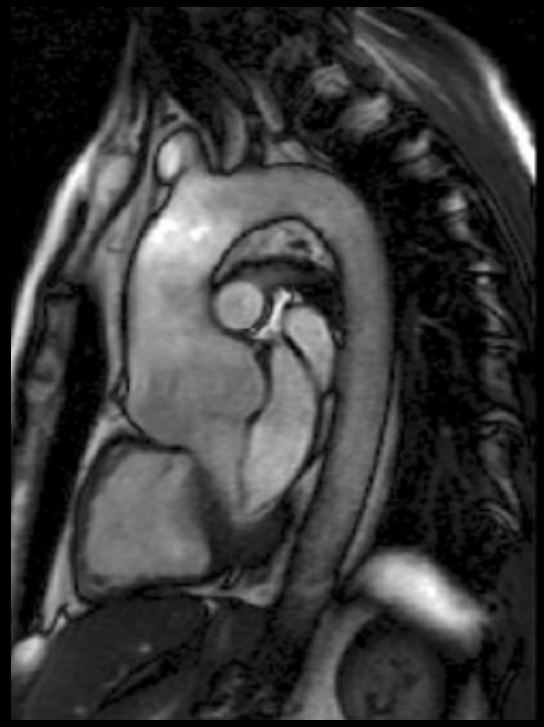


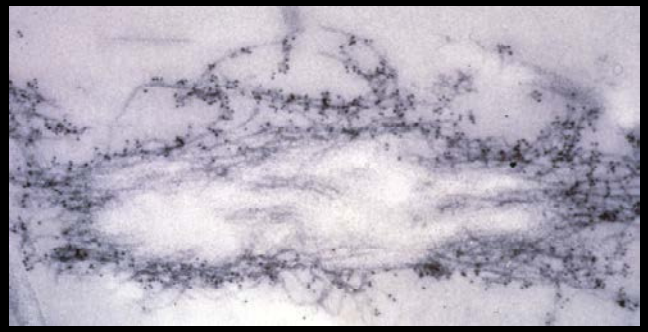


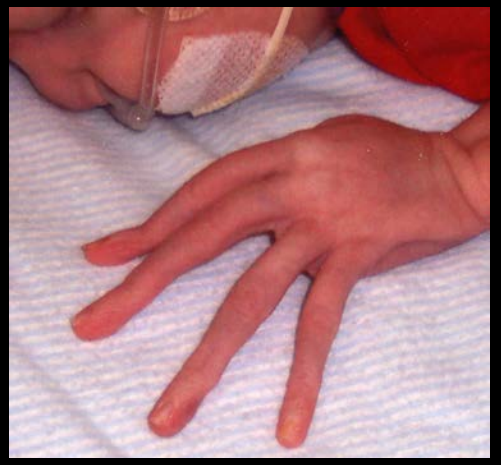
Fong LG, et al. Science, 2006

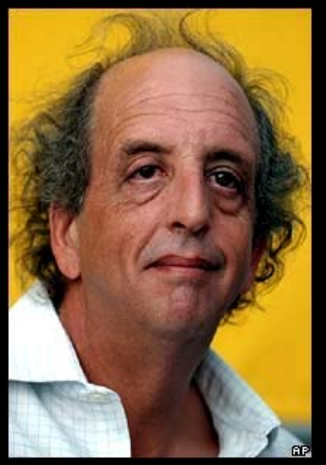
Marfan syndrome



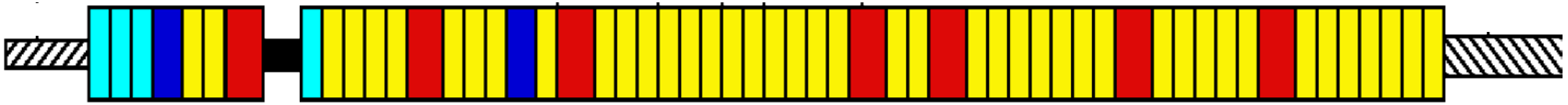








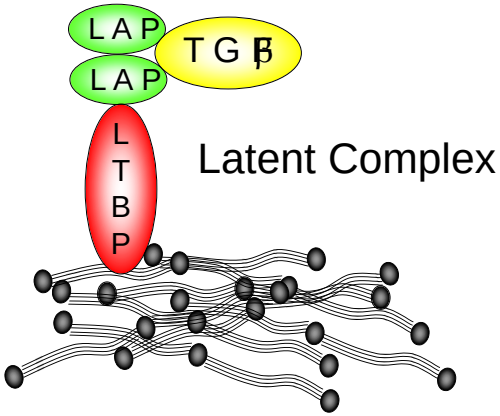
Fibrillin-1



Dietz…and Francomano Nature, 1991

Fibrillin-1 Mutations Lead to Excess TGF□Activation in MFS

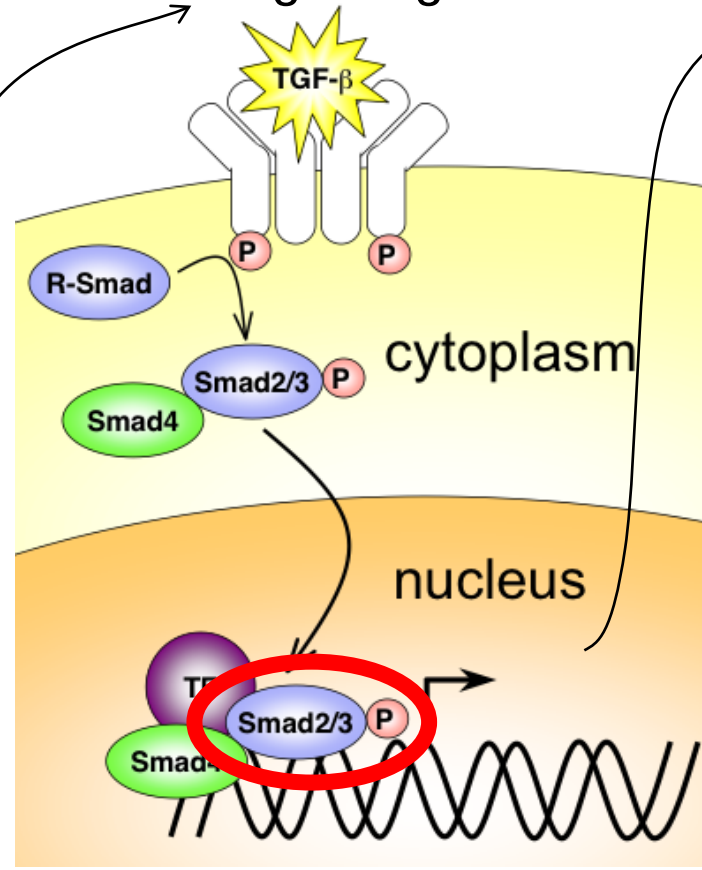
Excess TGFβ Activation



Latent Complex

Microfibrils composed of Fibrillin-1

Excess TGFβ Signaling



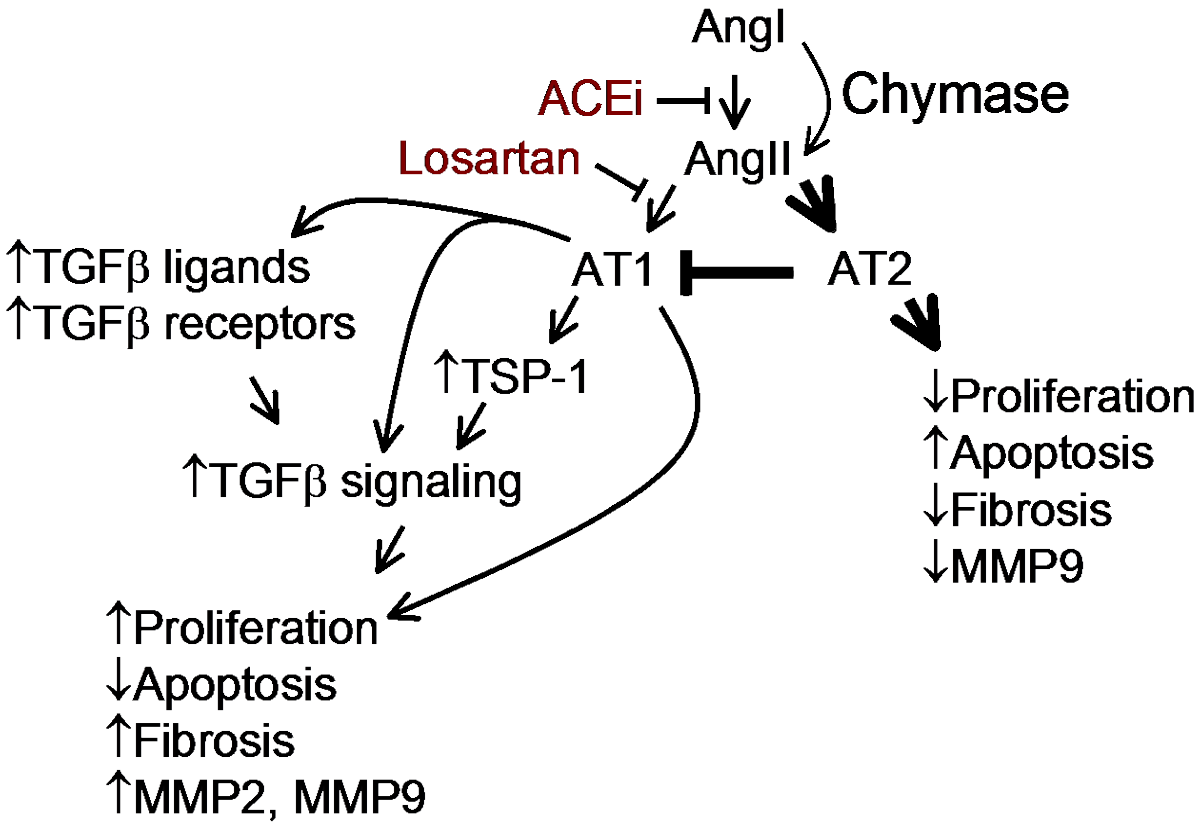
Phenotypic Consequences

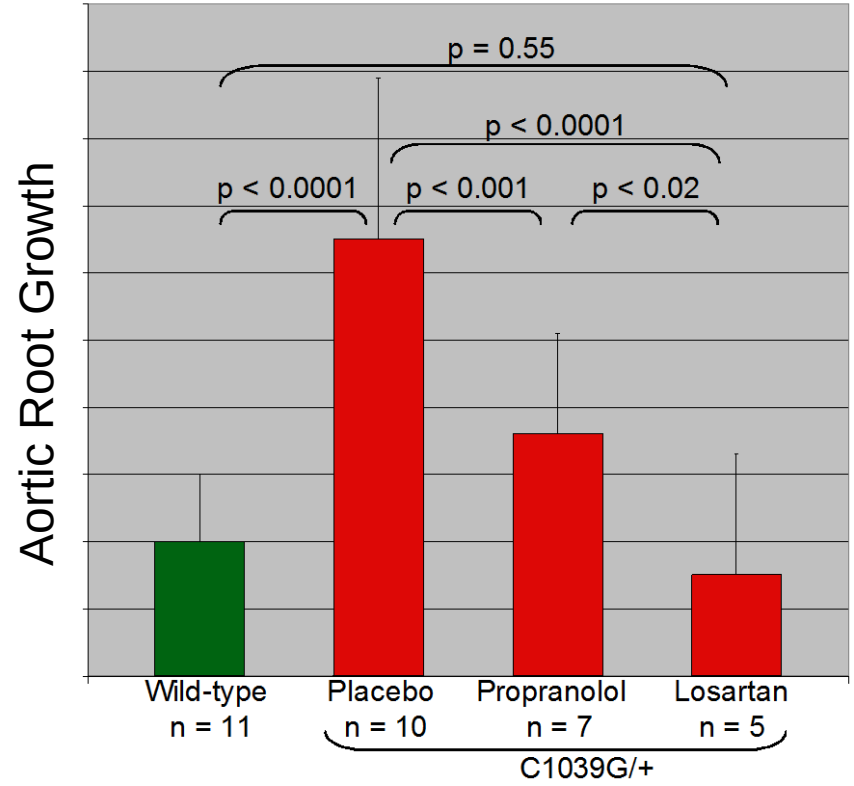
Emphysema
Mitral Valve Prolapse
Aortic Aneurysm
Myopathy

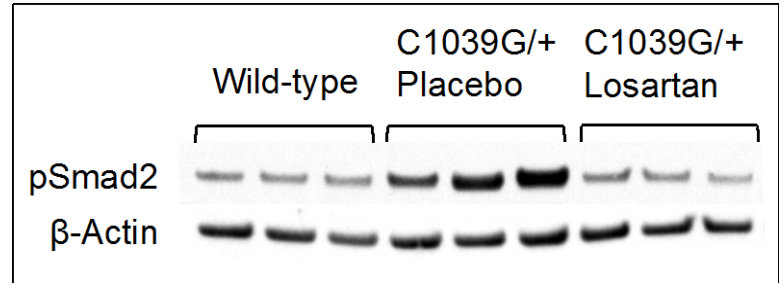
(All rescued by TGFβ-neutralizing antibody)

Neptune, *Nature Genetics*, 2003
Judge, *JCI*, 2004
Ng, *JCI*, 2004
Habashi, *Science*, 2006
Cohn, *Nature Medicine*, 2007

The Angiotensin II Type 1 Receptor Blocker (ARB) Losartan

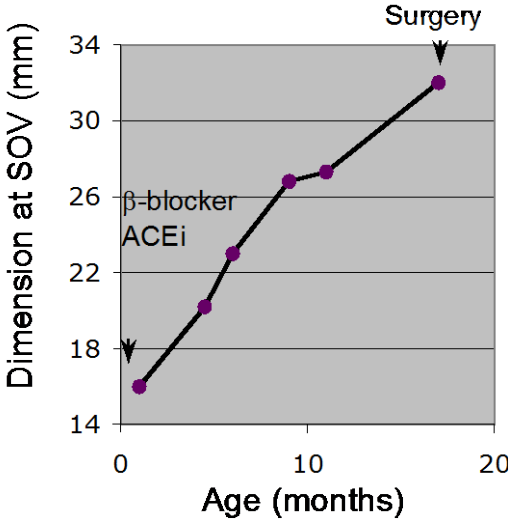


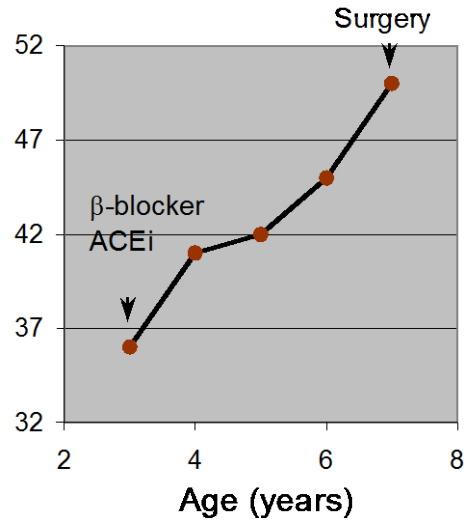


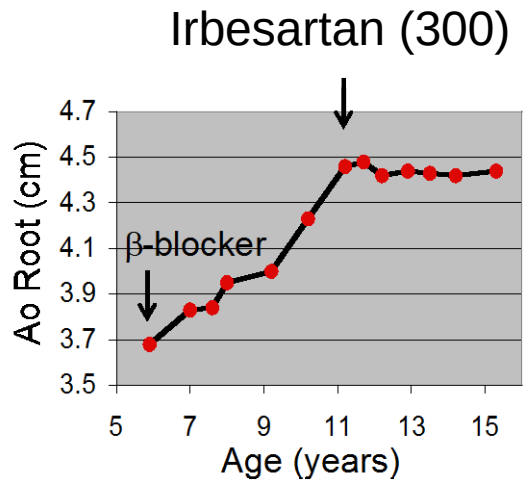


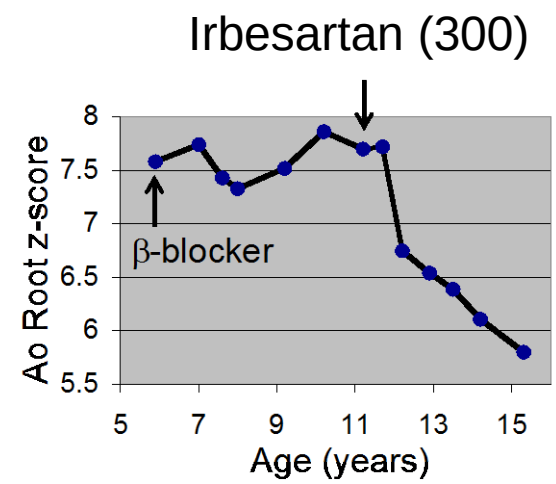
Habashi…and Dietz, *Science*, 2006

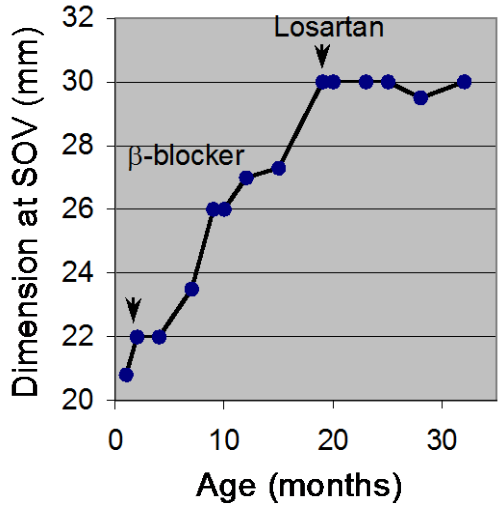
Therapeutic Response to ARBs

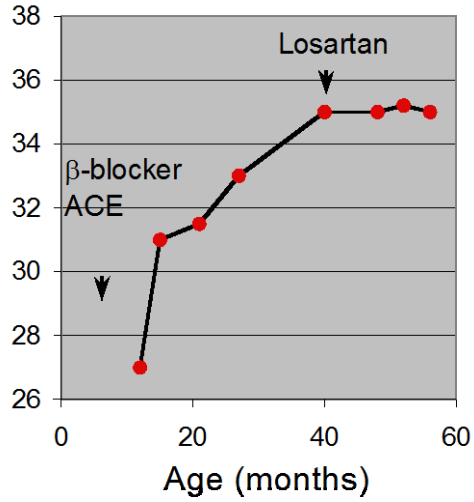


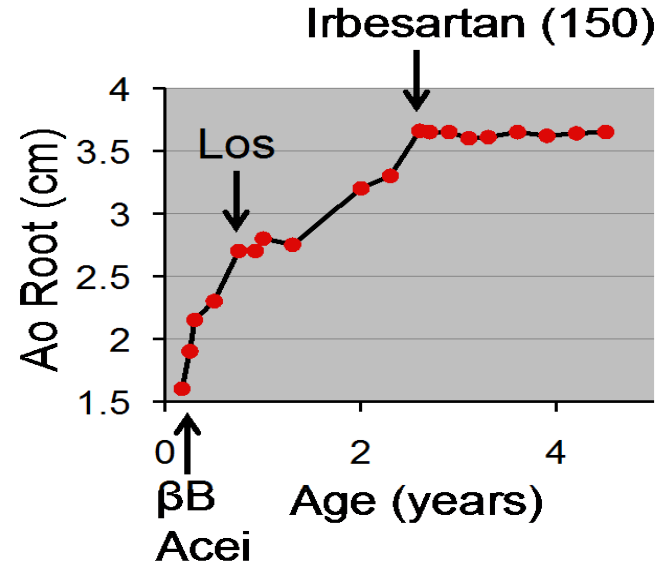




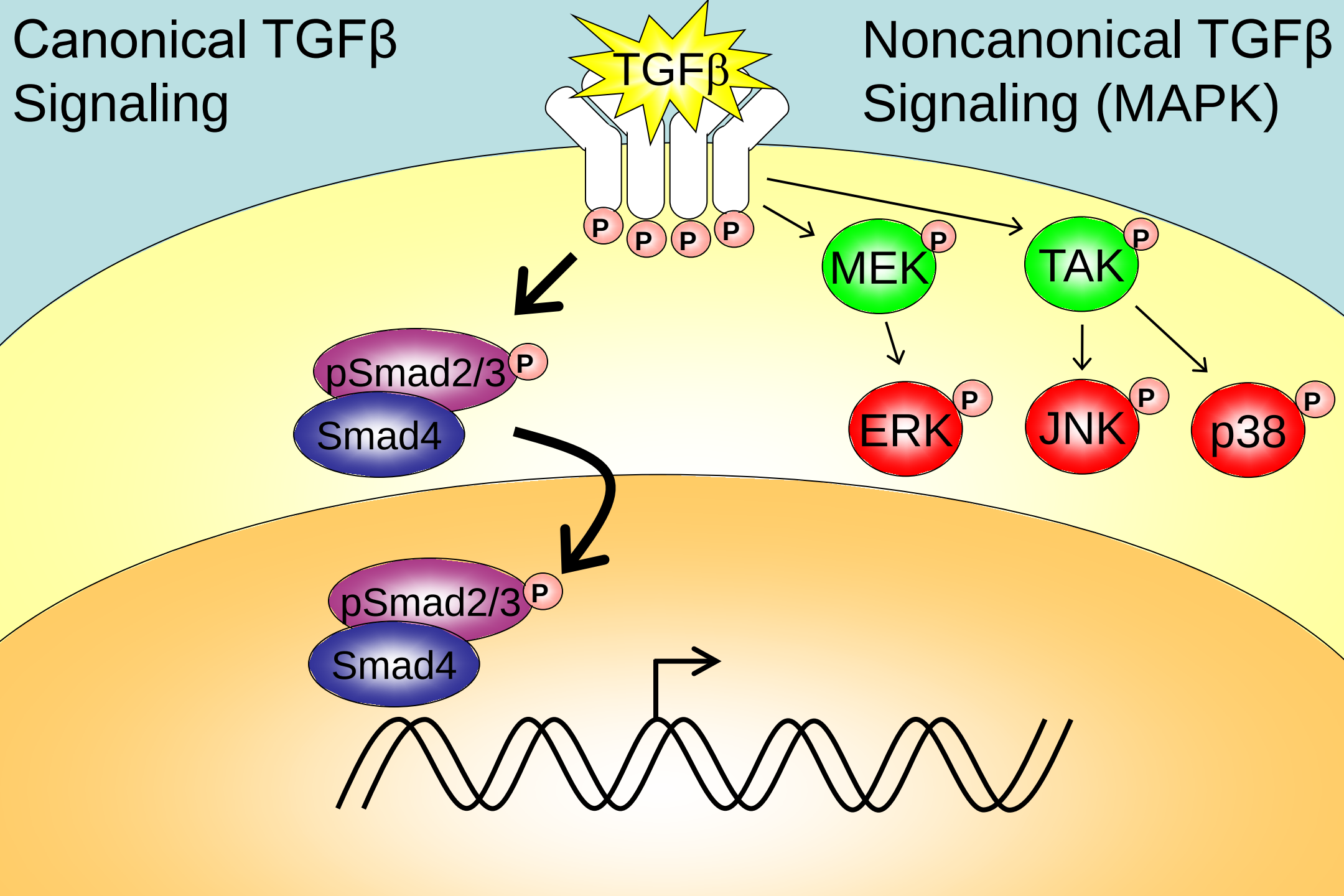




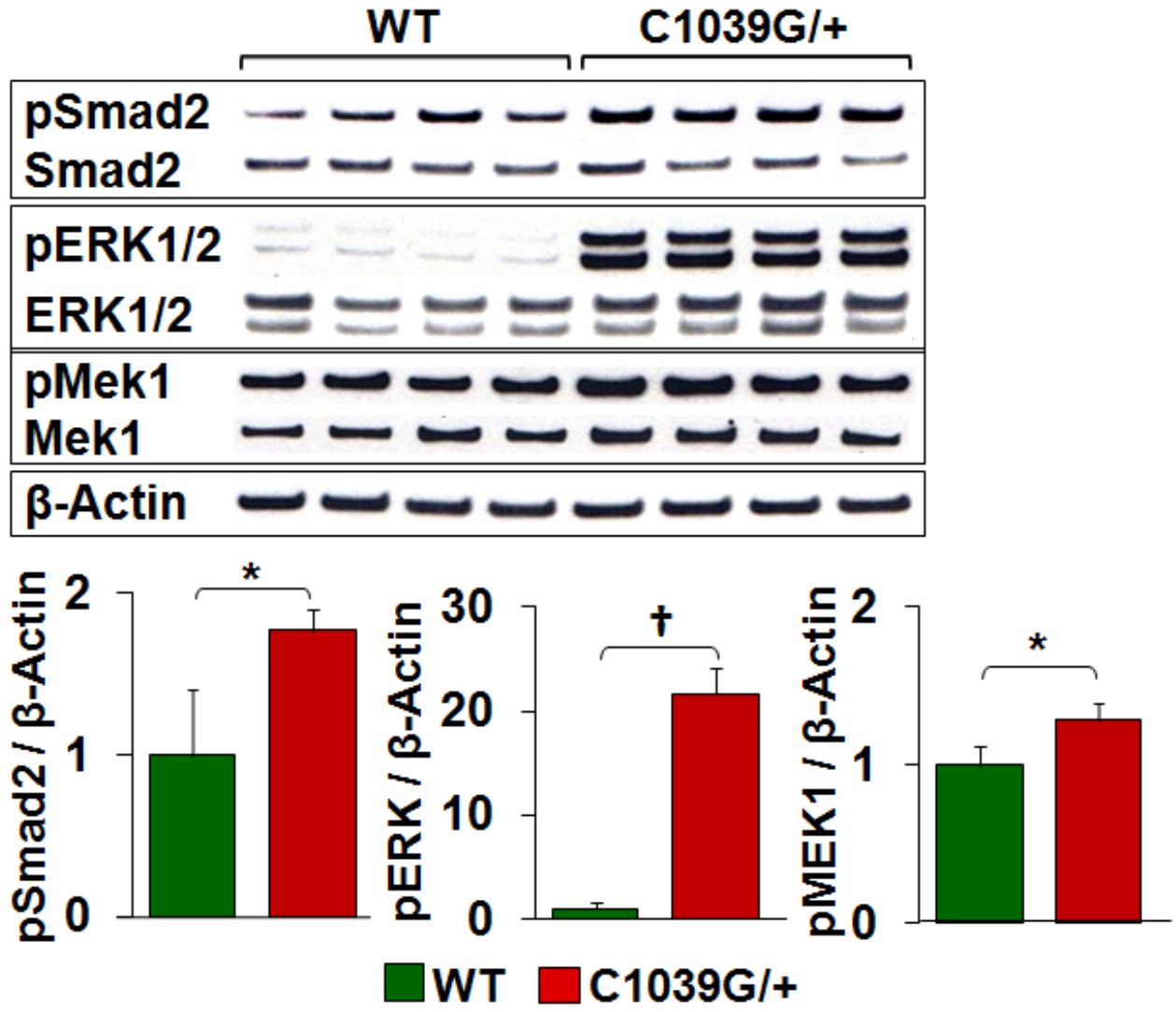




Brooke et al., *New Engl J Med*, 2008

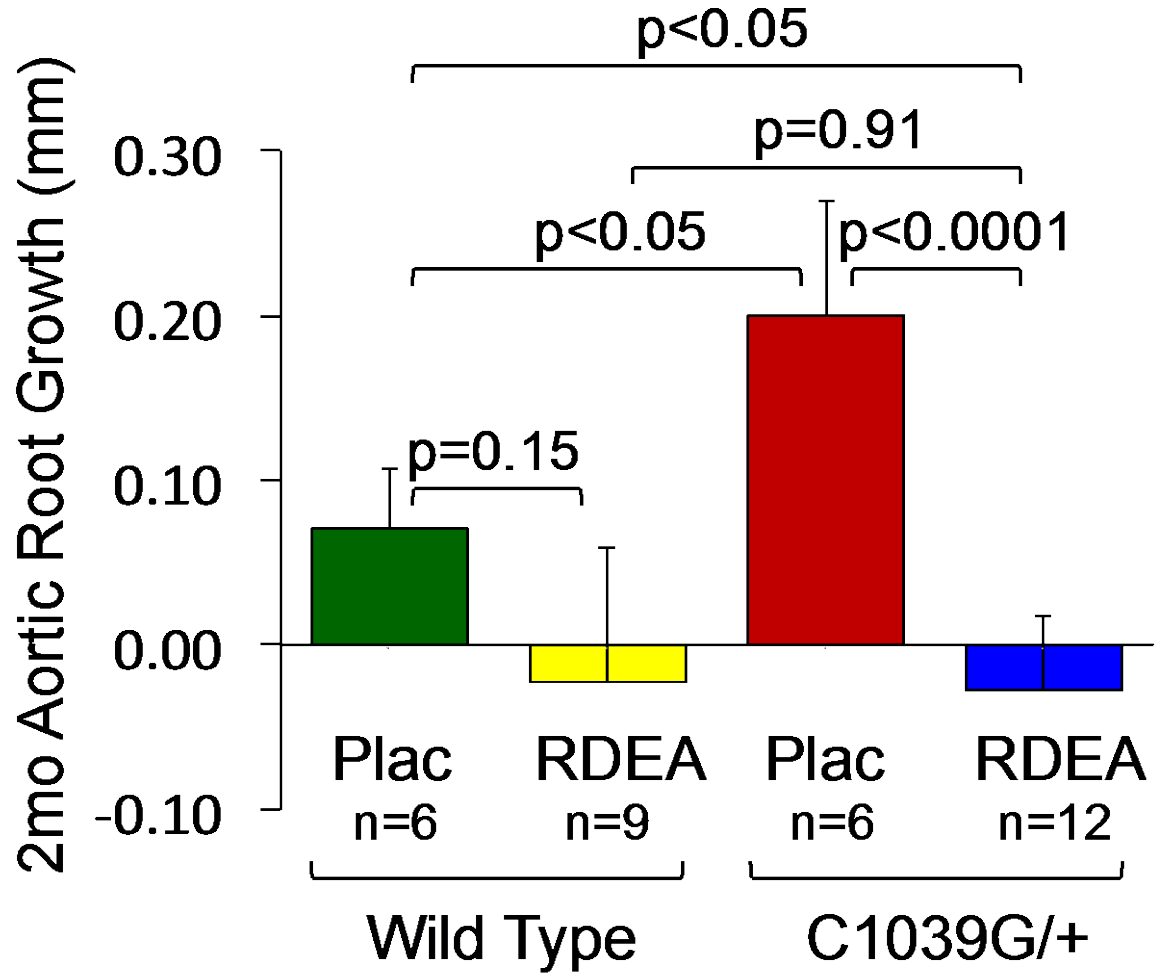

Canonical TGFβ Signaling
TGFβ
Noncanonical TGFβ Signaling (MAPK)
P
P
P
P
MEK
P
TAK
P
pSmad2/3
P
Smad4
ERK
P
JNK
P
p38
P
pSmad2/3
P
Smad4

Selective Activation of ERK MAPK in Marfan Mice



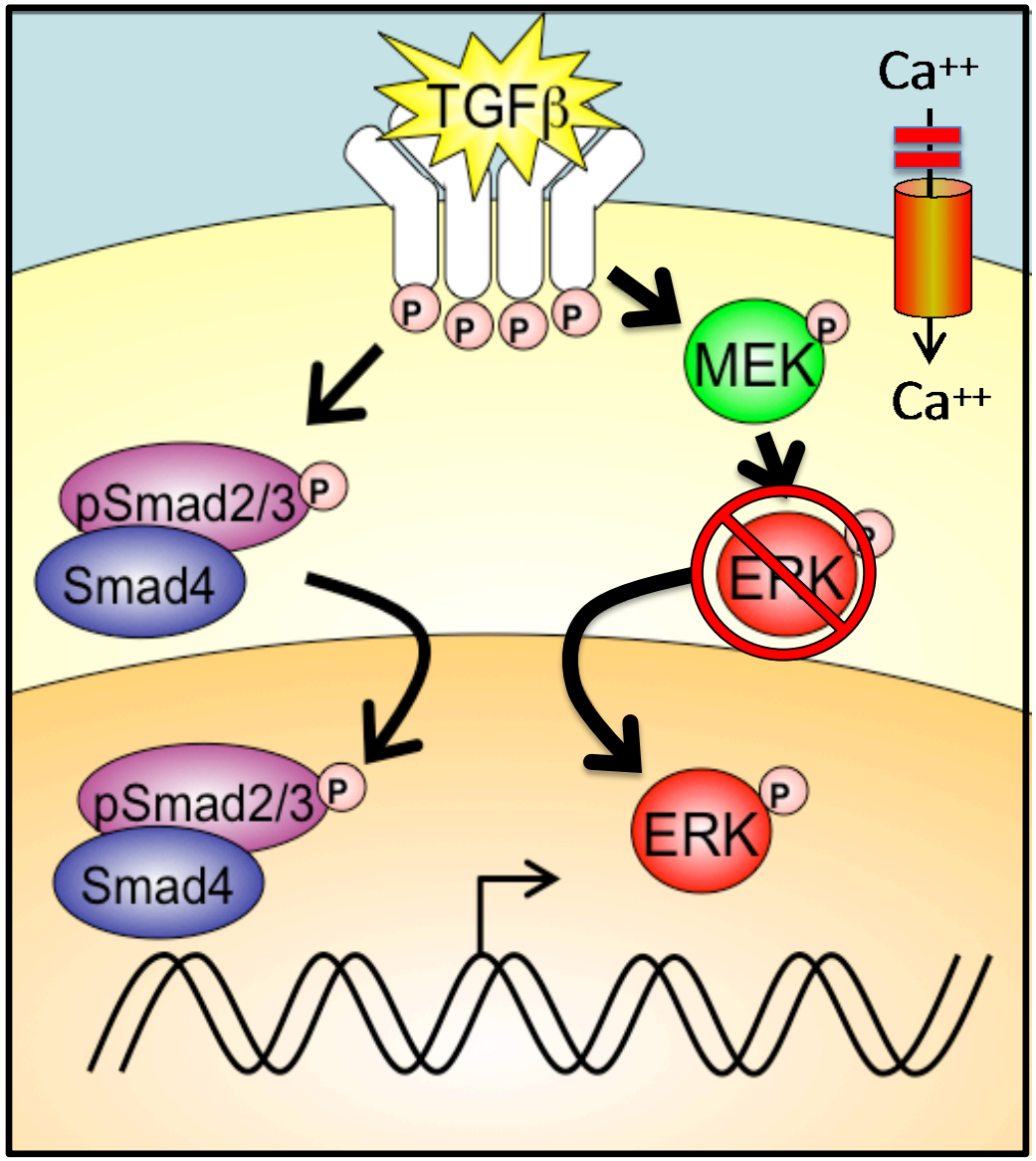
Holm…and Dietz, *Science*, 2011

ERK1/2 Antagonist RDEA-119 Arrests Aortic Root Growth in a Mouse Model of MFS



Holm…and Dietz; Science, 2011

Calcium Channel Blocker Trial in MFS Mice



- 2nd line antihypertensive agents in MFS patients unable to tolerate β-blockers

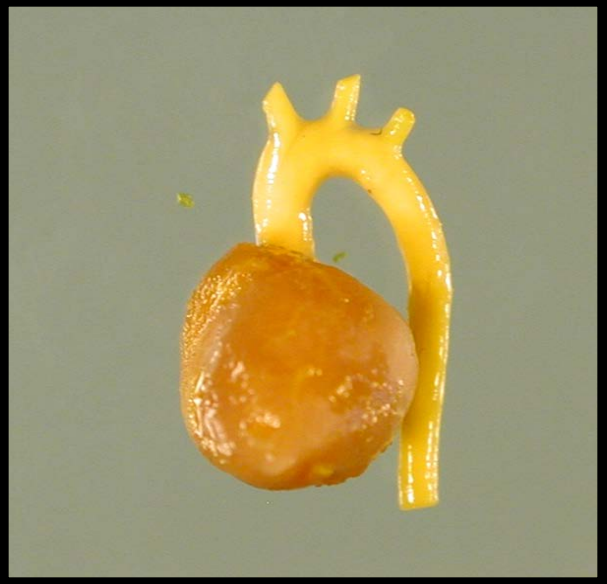
- Azelnidipine reduces ERK activation in synergy with olmesartan in murine arterial injury model (Jinno *et al*., 2004)

- Amlodipine dose: 15mg/kg/day
- Echocardiogram: 2, 6 & 10mo

Doyle and Dietz, unpublished

WT

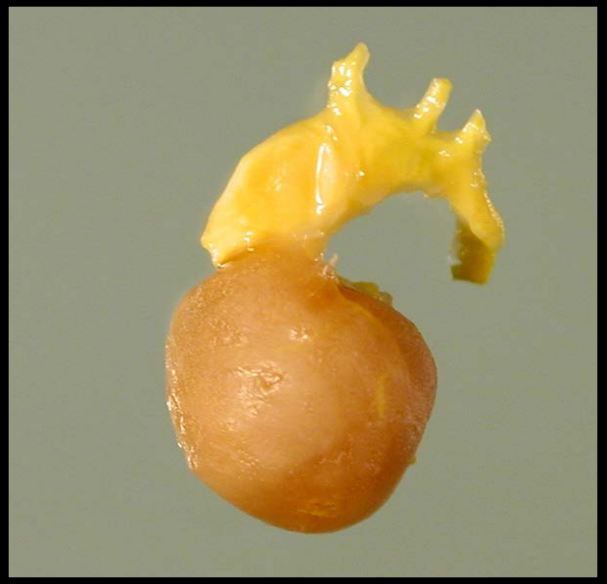
C1039G/+



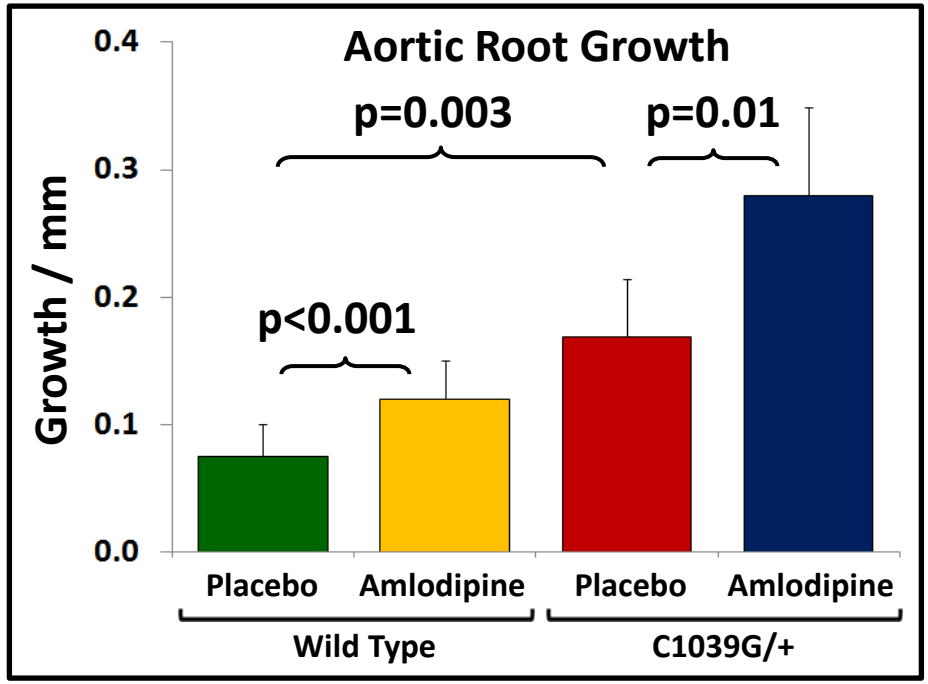
WT Amlod

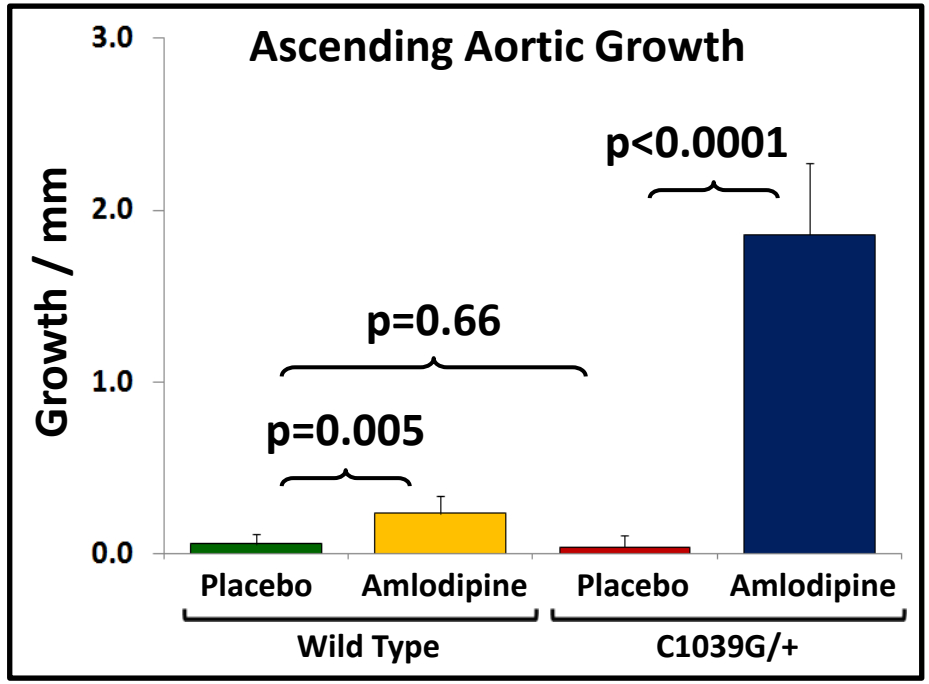
C1039G/+ Amlod

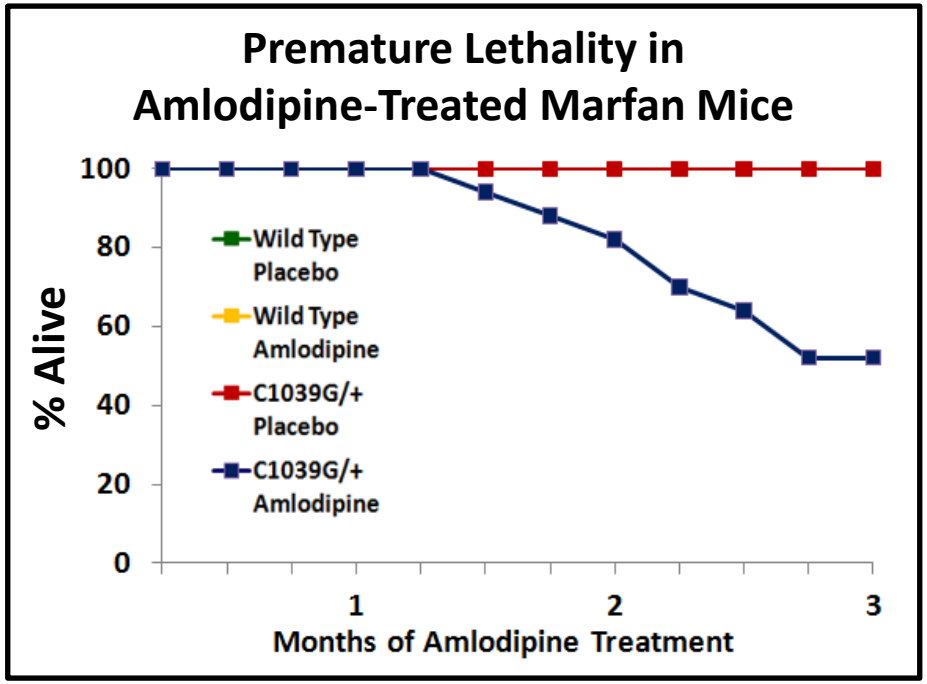
C1039G/+ Amlod

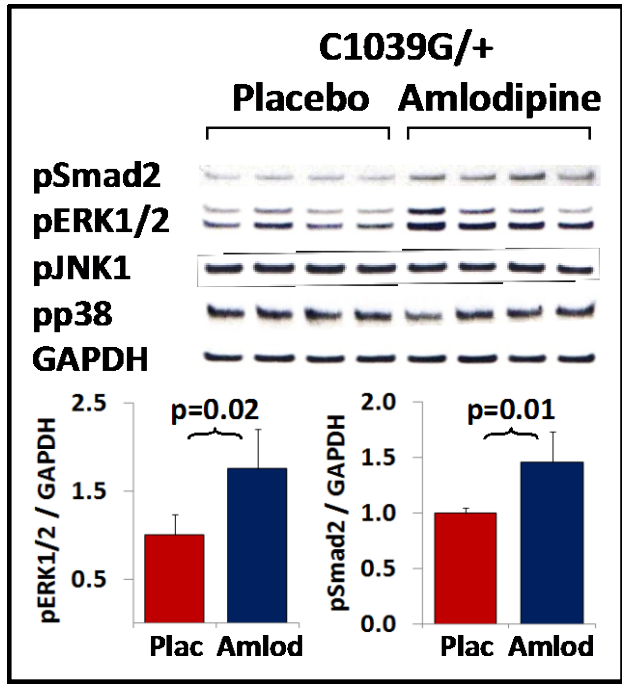


C1039G/+ Amlod





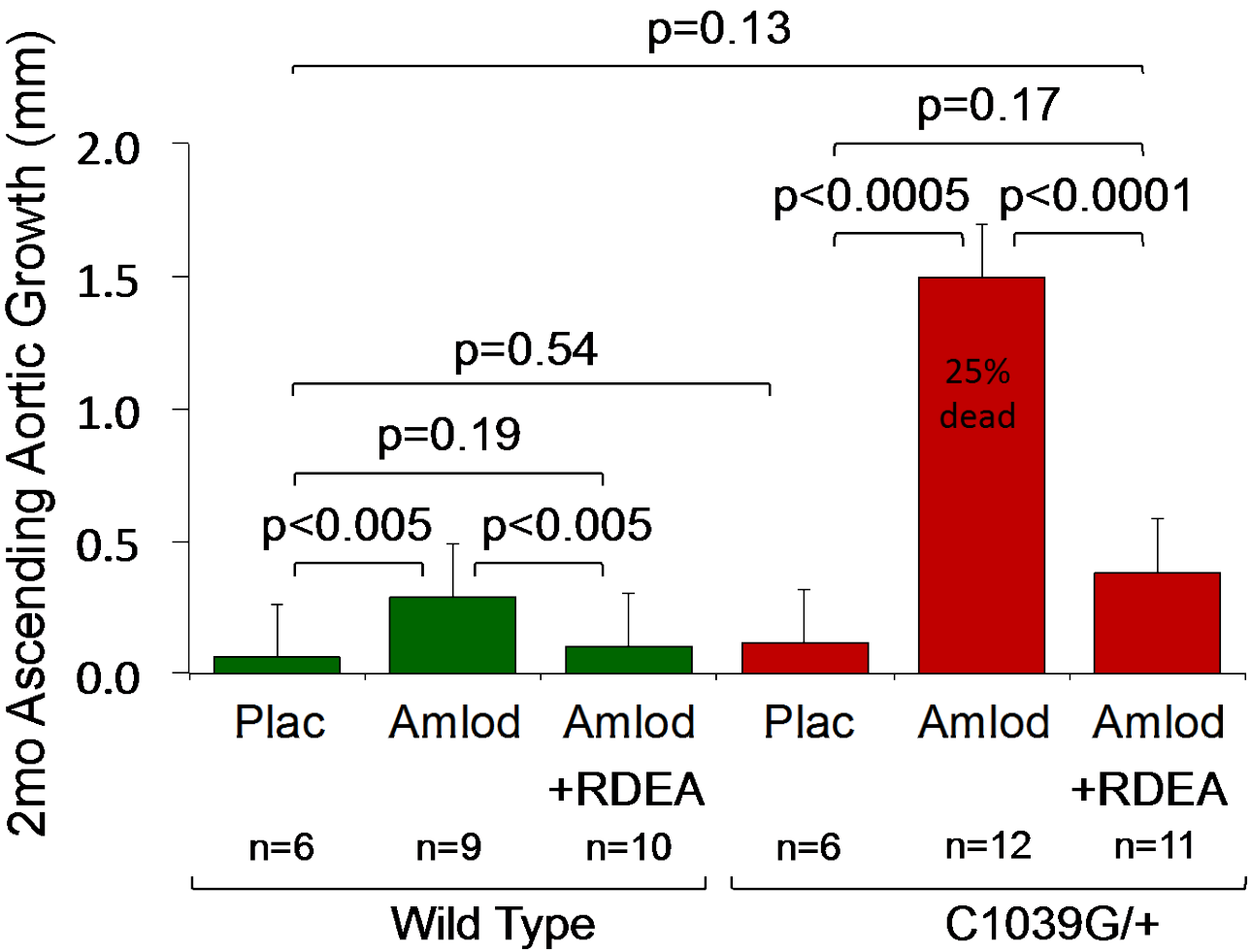


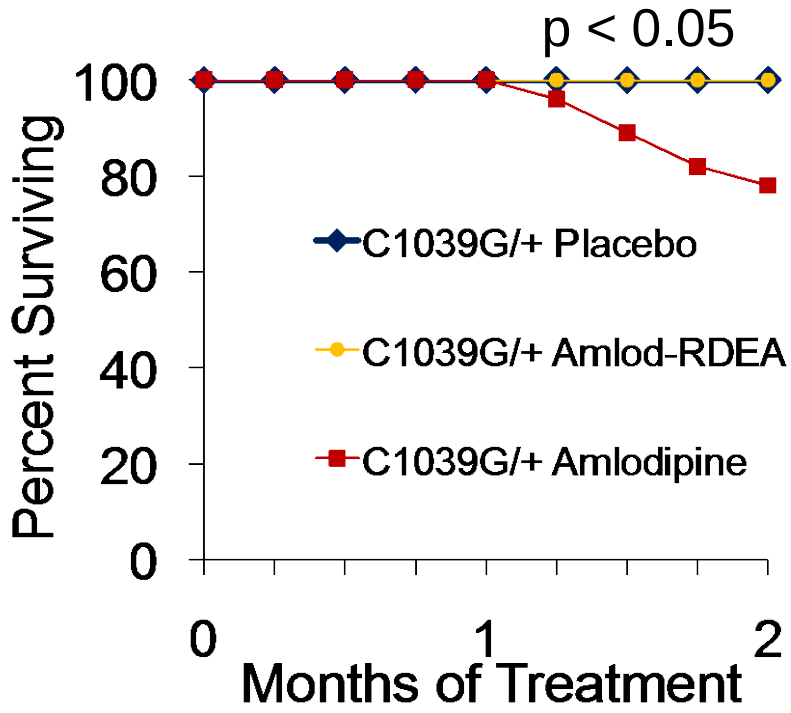


Identical results for non-dihydropyridine calcium channel blockers such as verapamil.

Doyle and Dietz, unpublished

ERK Inhibitor RDEA-119 Abrogates the Deleterious Gene-by-Environment Interaction Imposed by Calcium Channel Blockers





Doyle and Dietz, unpublished

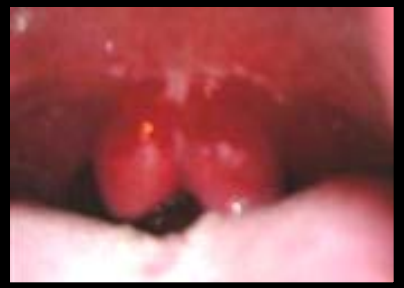
Pessimistic model for disease pathogenesis

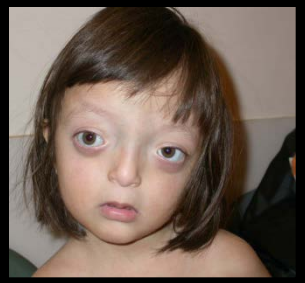
↓Fibrillin-1 ⟶ Tissue Failure

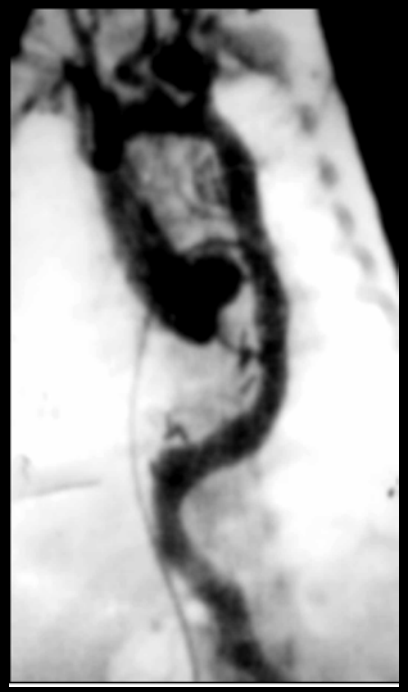
Losartan (ARBs)
TGFβ-neutralizing antibody
AT2 agonist
RDEA-119 (ERK antagonists)
SP600125 (JNK antagonist)
Hydralazine
β1-integrin agonist
β3-integrin antagonist

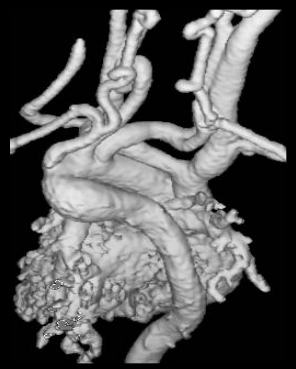
(Caution with calcium channel blockers)

A New Aortic Aneurysm Syndrome









(> 200 families)

Like Marfan syndrome:

- curvature of spine
- chest wall deformity
- long fingers
- aortic root aneurysm

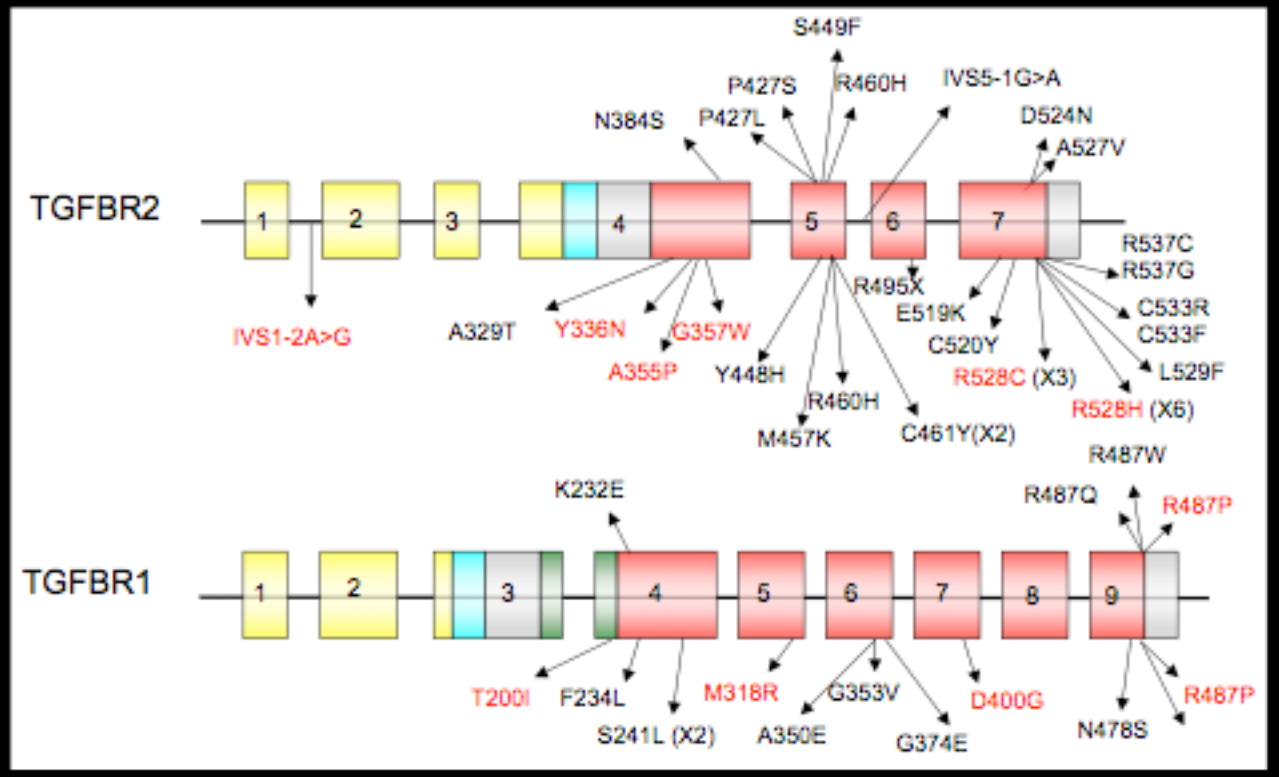
Unique:

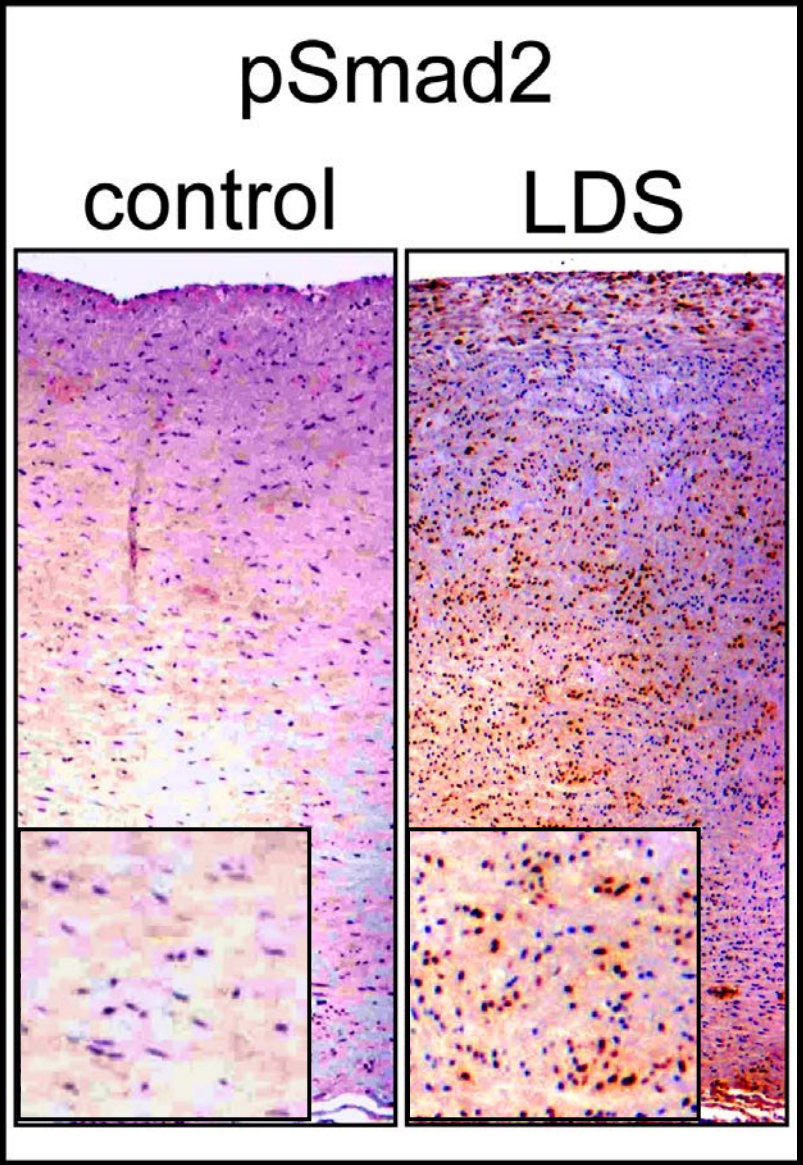
- widely-spaced eyes
- cleft palate/bifid uvula
- premature skull fusion
- club foot deformity
- congenital heart disease (PDA, BAV, ASD)
- arterial tortuosity
- diffuse aneurysms
- rupture / death
  - young age
  - small dimensions

Loeys-Dietz syndrome (LDS)

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

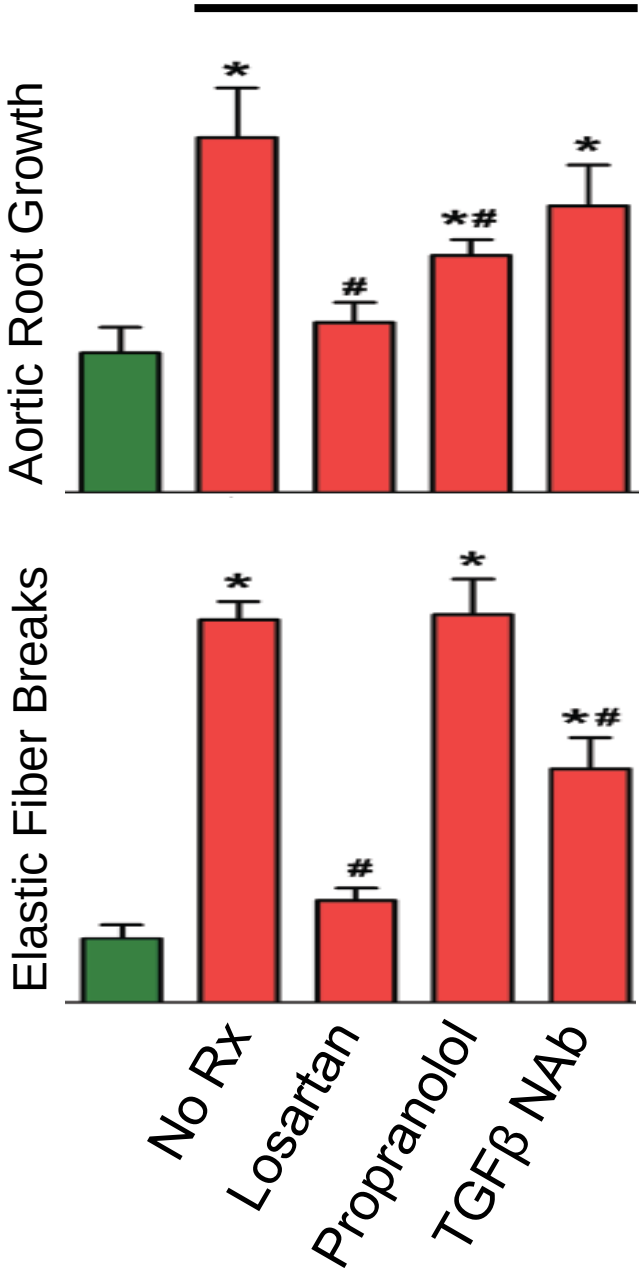
Mutations in the TGFβ receptor cause Loeys-Dietz syndrome

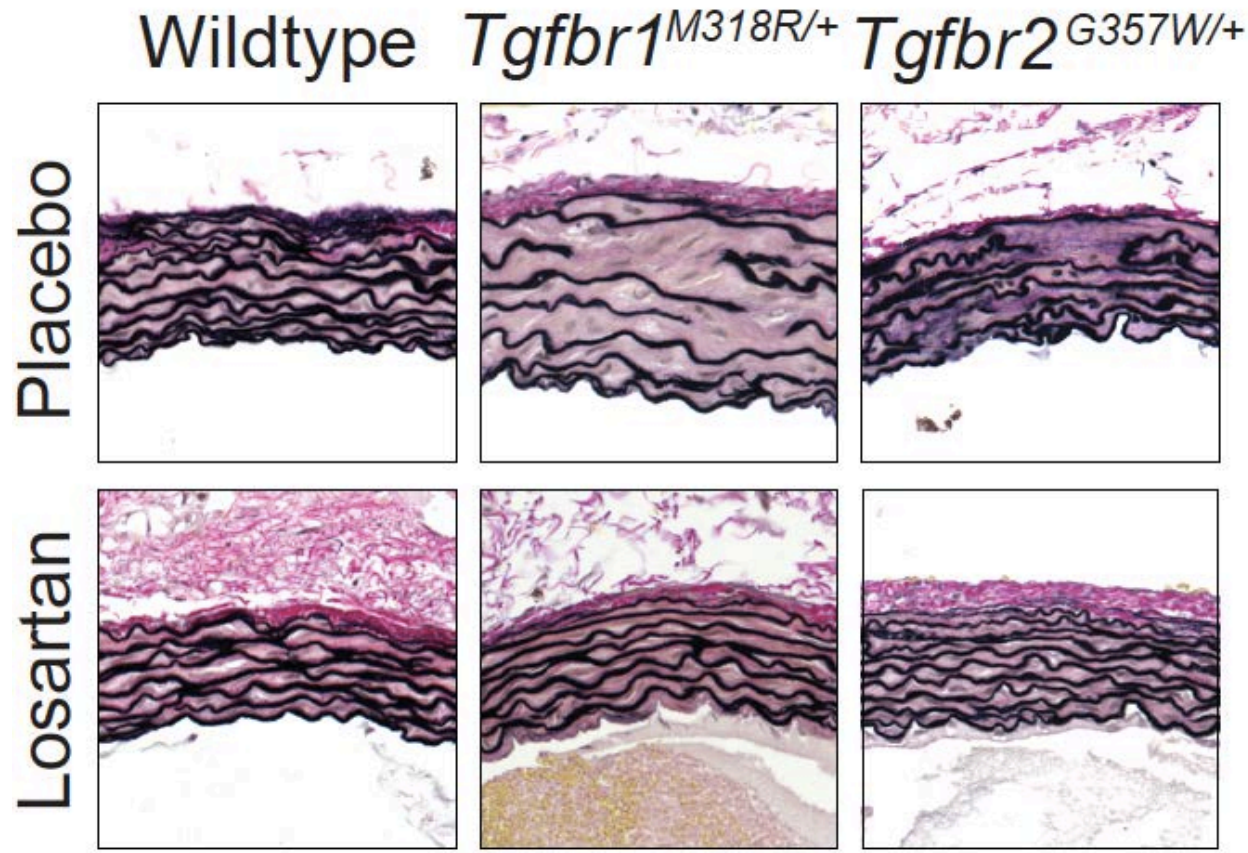




LDS-like conditions also observed in patients with mutations in the *SMAD3* or *TGFB2* genes.

Loeys et al., *Nature Genetics*, 2005; *New Engl J Med*, 2006; Lindsay et al. *Nature*, 2011





Loch, Gallo and Dietz, unpublished

The TGFβ Vasculopathies

Marfan Syndrome (*FBN1*)

Loeys-Dietz Syndrome (*TGFBR1/2*)

Loeys-Dietz-Osteoarthritis Syndrome (*SMAD3*)

Loeys-Dietz-like Syndrome (*TGFB2*)

Recessive Cutis Laxa (*FBLN4*)

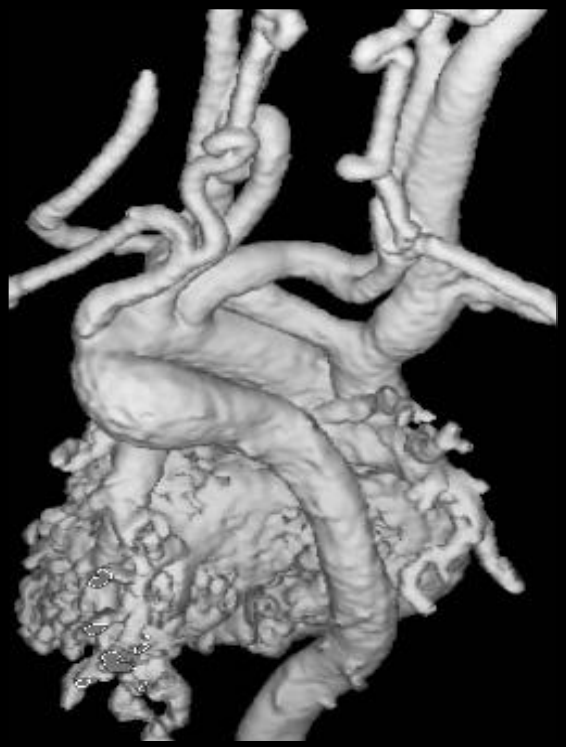
Vascular EDS (*COL3A1*)

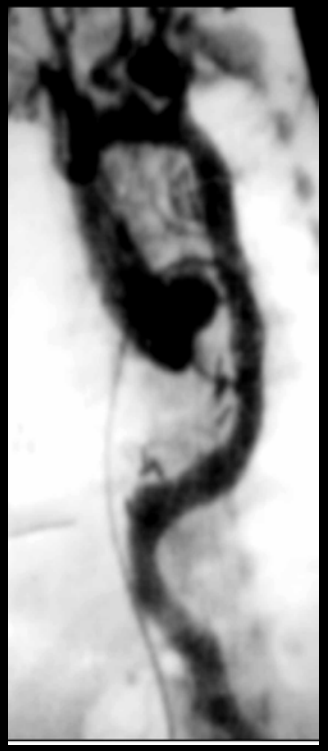
Bicuspid Aortic Valve/Asc AA

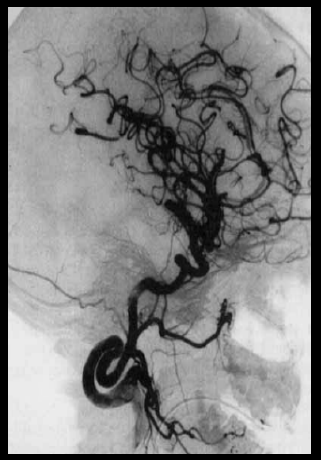
Arterial Tortuosity Syndrome (*GLUT10*)

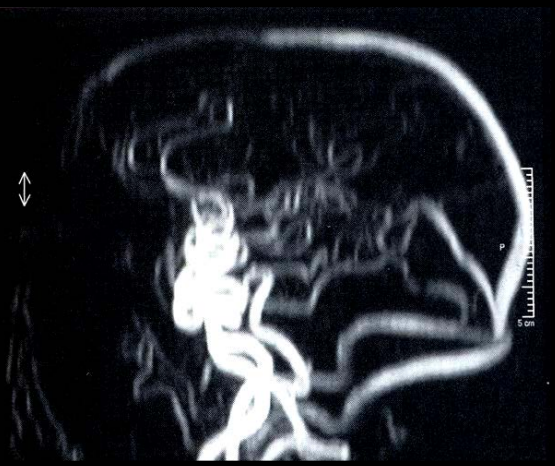
Familial Thoracic Aortic Aneurysm (*MYH11, ACTA2*)

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.

Dietz lab:

Hamza Aziz
Ben Brooke
Ronni Cohn
Sara Cooke
Tim Cooper
Jef Doyle
Pam Frischmeyer
Elena Gallo
Elizabeth Gerber
Jennifer Habashi
Mark Halushka
Tammy Holm
Dan Judge
K.C. Kent
David Kim
Mark Lindsay
David Loch
Bart Loeys
Peter Matt
Loretha Myers
Enid Neptune
Connie Ng
Nishant Patel
Rosanne Rouf
Florian Schoenhoff
Christel van Erp

Jennifer van Eyk

Dave Huso

Checco Ramirez
Jason Cooke

Dan Rifkin

Lynn Sakai
Doug Keene

Elaine Davis

Anne De Paepe
Julie De Backer

Ken Chien

GenTAC Investigators

HHMI

National Heart Lung and Blood Institute

William S. Smilow Center For Marfan Syndrome Research

Loeys·Dietz Syndrome Foundation

NIAMS

NMF

Sarnoff Cardiovascular Research Foundation

GenTAC