One common view of aging:
A gradual general decline of multiple cellular systems in our bodies
The Premature Aging Disease
Hutchinson Gilford Progeria Syndrome
(HGPS, progeria)

Suggests a more nuanced view:
Alterations in particular pathways can change the rate of aging

Early onset diseases can point to particularly vulnerable components in a system
A to Z:
Lamin A cleavage by the ZMPSTE24 protease

Prelamin A

ZMPSTE24

Mature Lamin A

ZMPSTE24 cleavage is critical for health
Defective lamin A processing results in the premature aging disease HGPS

Mutations either in Lamin A or ZMPSTE24 cause related progeroid diseases
Lamin A

- Structural scaffold for the nuclear envelope
- Interact with DNA, regulates gene expression

Early on, there was no connection between lamin A, ZMPSTE24, and progeria.
HGPS

First described by Dr. Jonathan Hutchinson (1886) and Dr. Hastings Gilford (1897)

Rare disease (1 in 4 million)
Accelerated aging:
• Thin skin
• Growth failure
• Loss of body fat, hair
• Joint and bone defects
• Blood vessel defect—early onset atherosclerosis

Fatal (death ~age 13) from heart attack or stroke

The key advance: HGPS maps to the LMNA gene encoding Lamin A
(F. Collins and N. Levy labs, 2003)

Brought disparate fields together and galvanized progress
Processing of farnesylated prelamin A

Permanently farnesylated prelamin A is the “culprit” that causes disease

Hypothesis: farnesyl transferase inhibitor (FTI), could be re-purposed to treat progeria
FTI Blocks Nuclear Defects of Progeria

From Bench to Bedside
Clinical trials with FTI’s show improved healthspan and lifespan for progeria children

Our current studies continue a focus on fundamental ZMPSTE24 mechanism

- New insights into premature aging
- New insights into normal physiological aging
ZMPSTE24 is a Novel Protease

Our recent studies suggest potential new treatment strategies for patients with certain mutations.

Disease mutations -> Basic Mechanism -> Personalized Medicine
Atherosclerosis timeline

• Aging is the greatest risk factor for atherosclerosis

• In progeria onset of atherosclerosis is accelerated, in the absence of known risk factors like high cholesterol levels

• Progeria may reveal a specific vulnerability in vessels? Understanding this vulnerability in molecular terms, could lead to more healthy vascular aging for all of us.
Research takes a village!!

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Collaborators
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Stephen Young, UCLA
Liz Carpenter, SGC, Oxford, England
Maya Schuldiner, Weizmann, Israel
Dan Berkowitz, Johns Hopkins
A “humanized yeast” system to study prelamin A processing

Catalytic and MAD-B Disease Mutants (blue are unstable)
Blocking degradation of P248L restores prelamin A cleavage

Doa10 is a yeast ubiquitin E3 ligase involved in ERAD

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Sparing ZMPSTE24 degradation may have therapeutic value for some, but not all MAD-B patients