The Young Who Die Old: Understanding The Premature Aging Disease Progeria and its Link to Normal Aging

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JHMI Science Writers' Boot Camp

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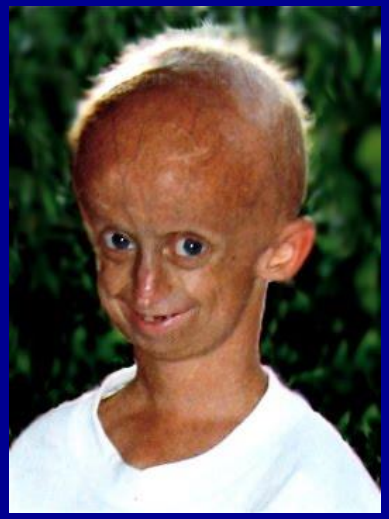
One common view of aging:

A gradual general decline of multiple cellular systems in our bodies

Nicholas Nixon
Brown Sisters

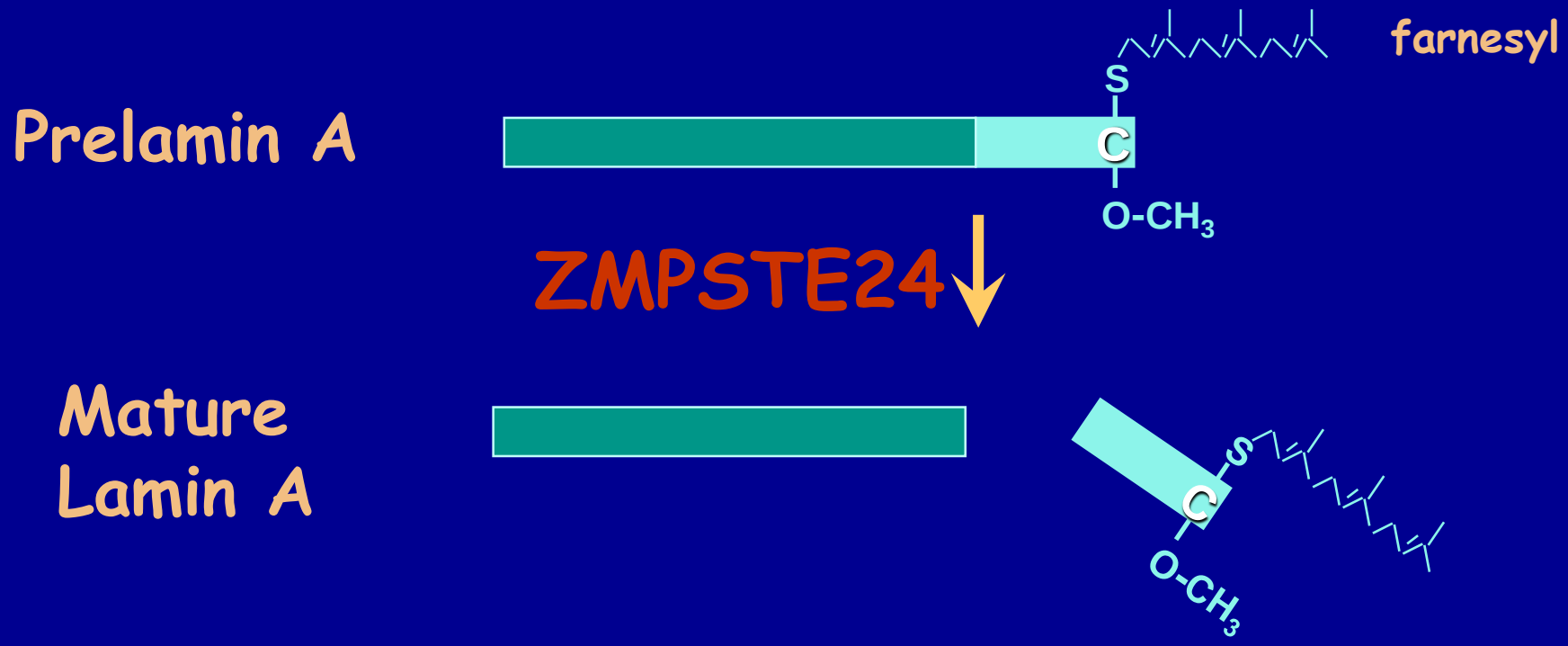
The Premature Aging Disease Hutchinson Gilford Progeria Syndrome (HGPS, progeria)

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



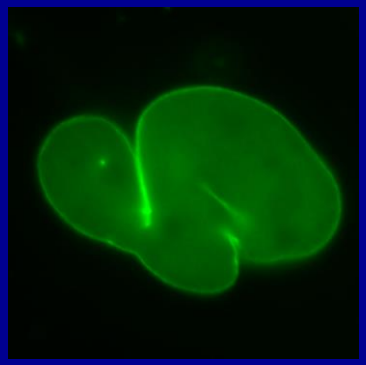
Early onset diseases can point to particularly vulnerable components in a system

A to Z:
Lamin A cleavage
by the ZMPSTE24 protease



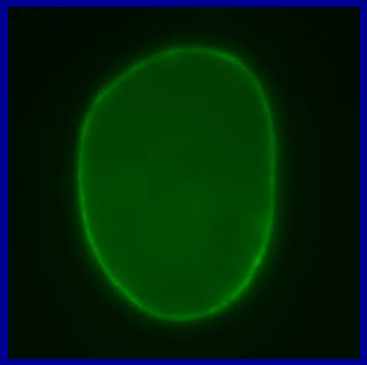
ZMPSTE24 cleavage is critical for health

Defective lamin A processing results in the premature aging disease HGPS



Sam Sam's Mom

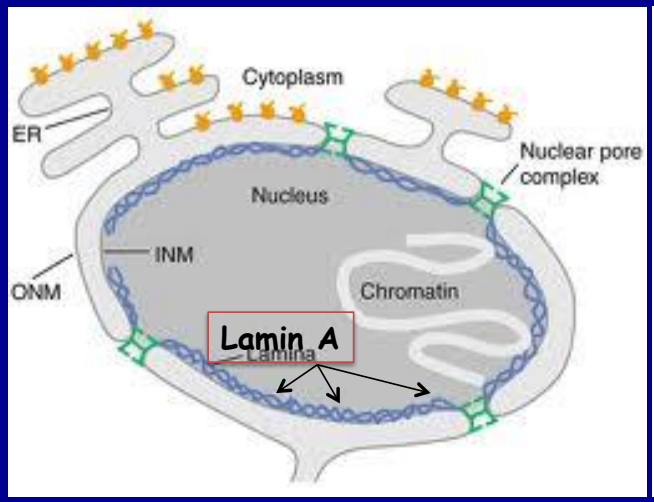
Sam Berns TEDx talk 2013
"My Philosophy for a Happy Life"
>29 million views

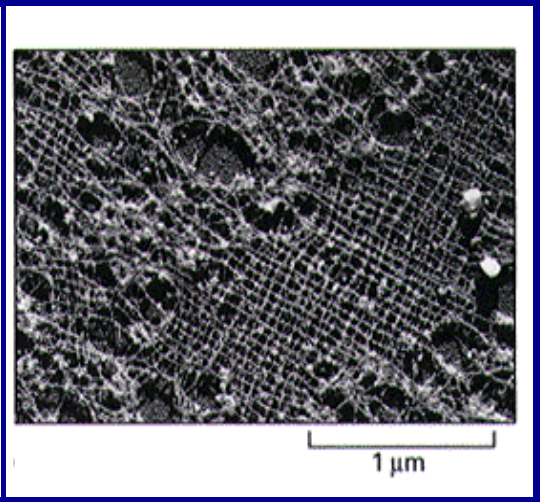


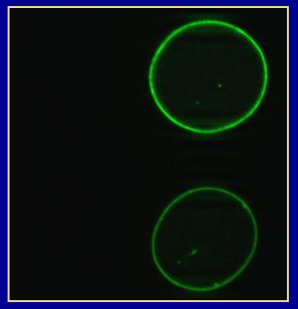
Mutations either in Lamin A or ZMPSTE24 cause related progeroid diseases

Lamin A

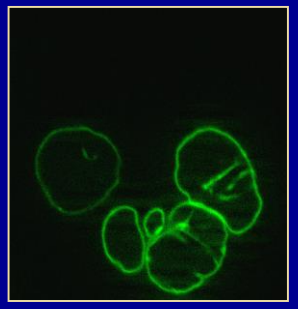
- Structural scaffold for the nuclear envelope
- Interact with DNA, regulates gene expression



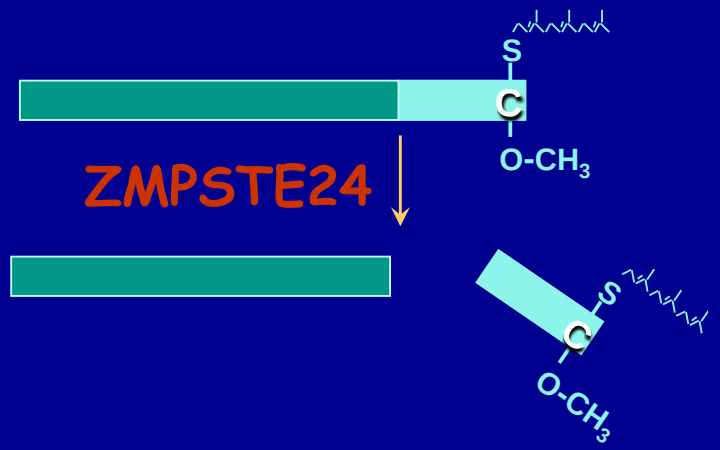




WT



progeria



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

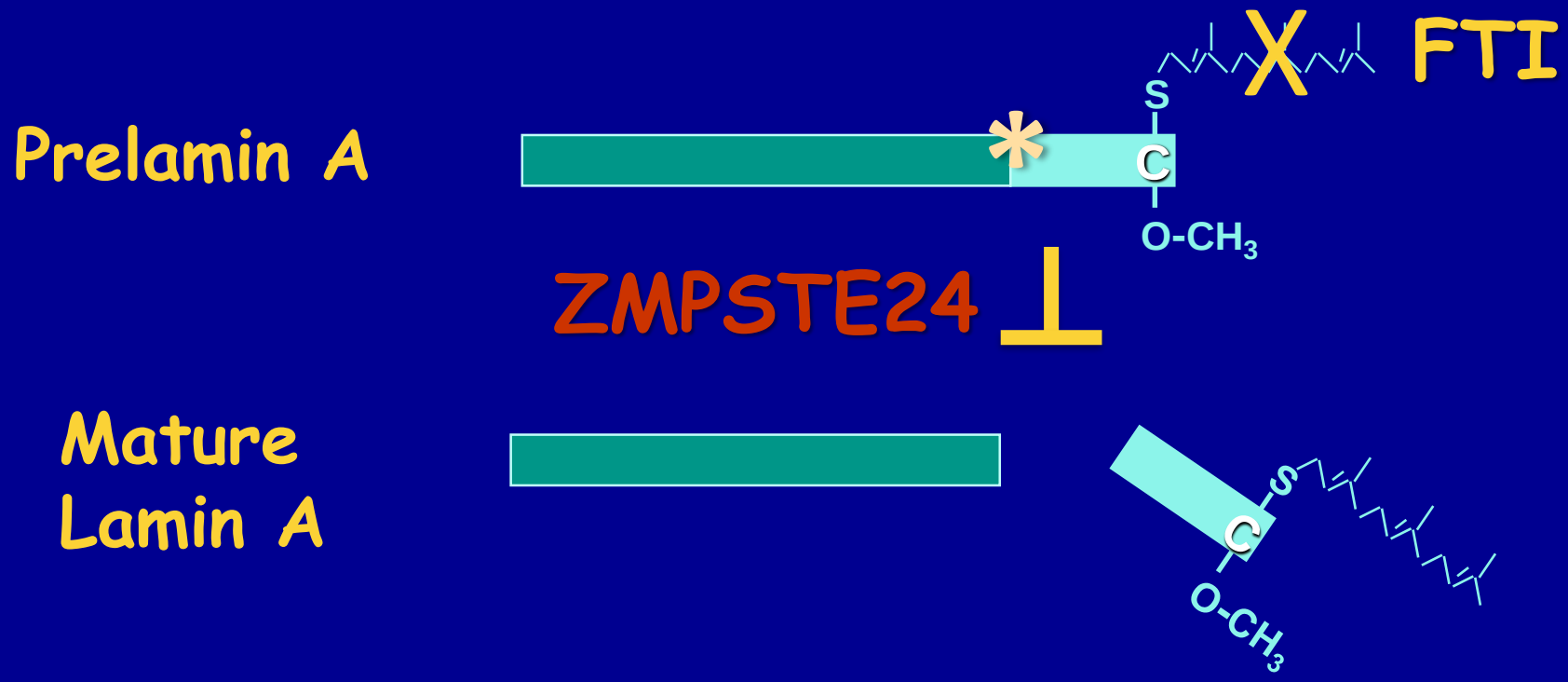
Fatal (death ~age 13) from heart attack or stroke

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

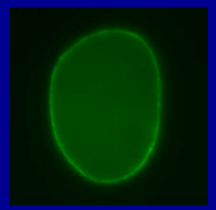
Permanently farnesylated prelamin A is the "culprit" that causes disease



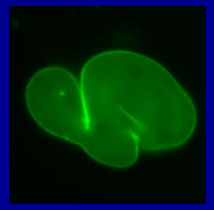
Hypothesis: farnesyl transferase inhibitor (FTI), could be re-purposed to treat progeria

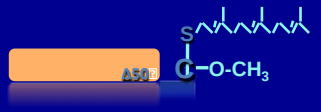
FTI Blocks Nuclear Defects of Progeria

Lamin A

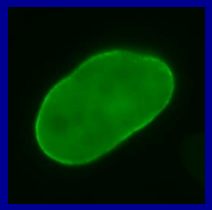


Progerin





Progerin
+
FTI



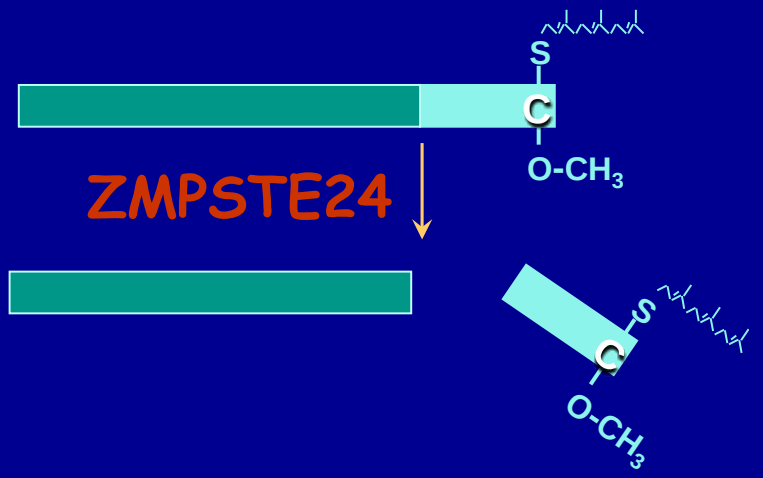
From Bench to Bedside

Clinical trials with FTI's show improved healthspan and lifespan for progeria children

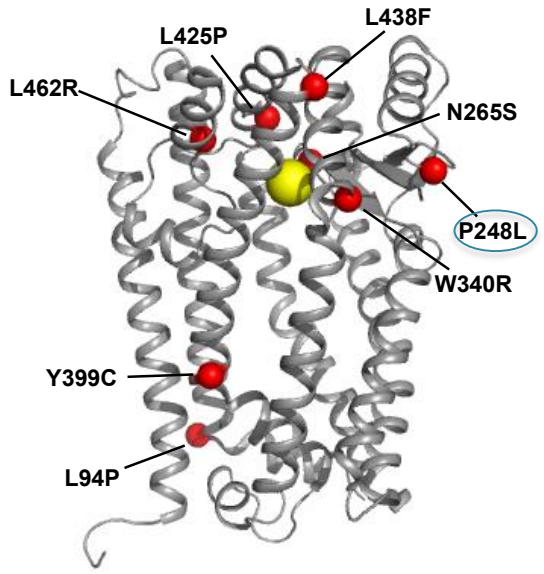
Gordon et al. PNAS (2012), Gordon et al. JAMA (2018)

Our current studies continue a focus on fundamental ZMPSTE24 mechanism

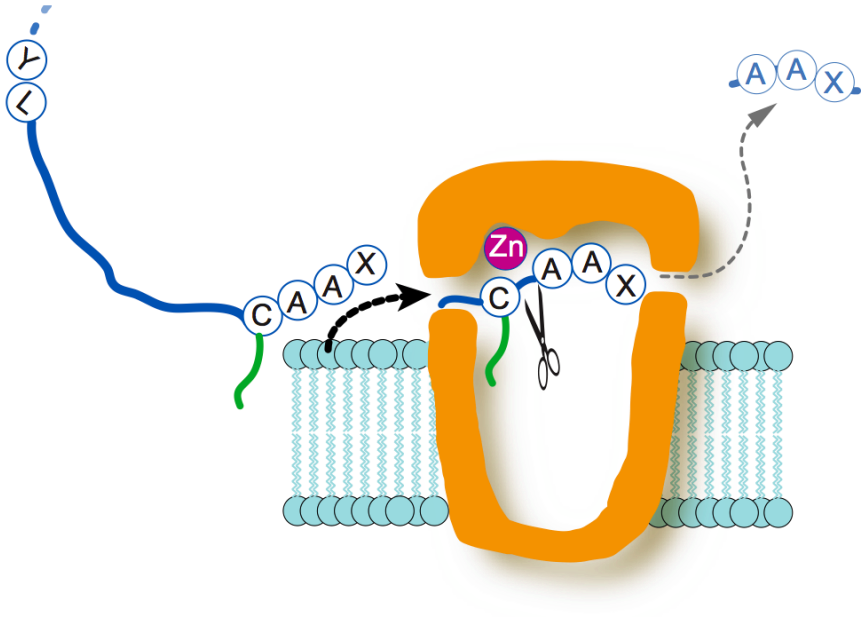
- New insights into premature aging
- New insights into normal physiological aging



ZMPSTE24 is a Novel Protease



ZMPSTE24 Progeria Mutations



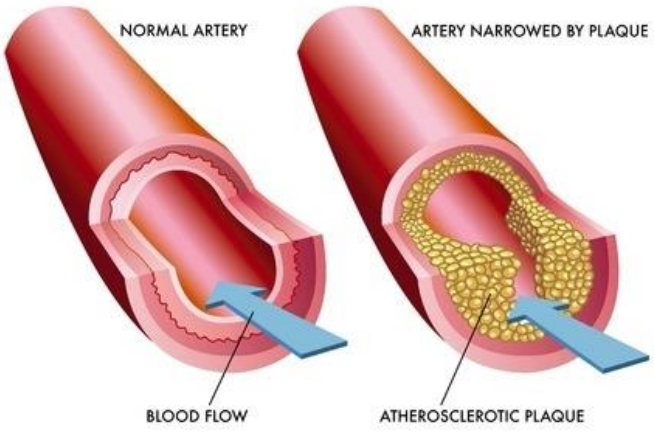
ZMPSTE24

Disease mutations -> Basic Mechanism -> Personalized Medicine

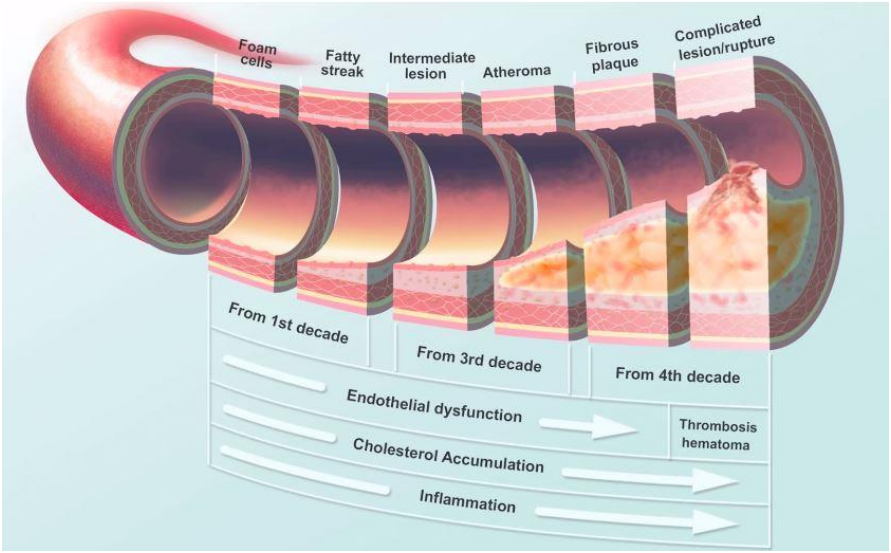
Our recent studies suggest potential new treatment strategies for patients with certain mutations

Progeria will likely provide insights into the Atherosclerosis of Normal Aging

Atherosclerosis



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!!

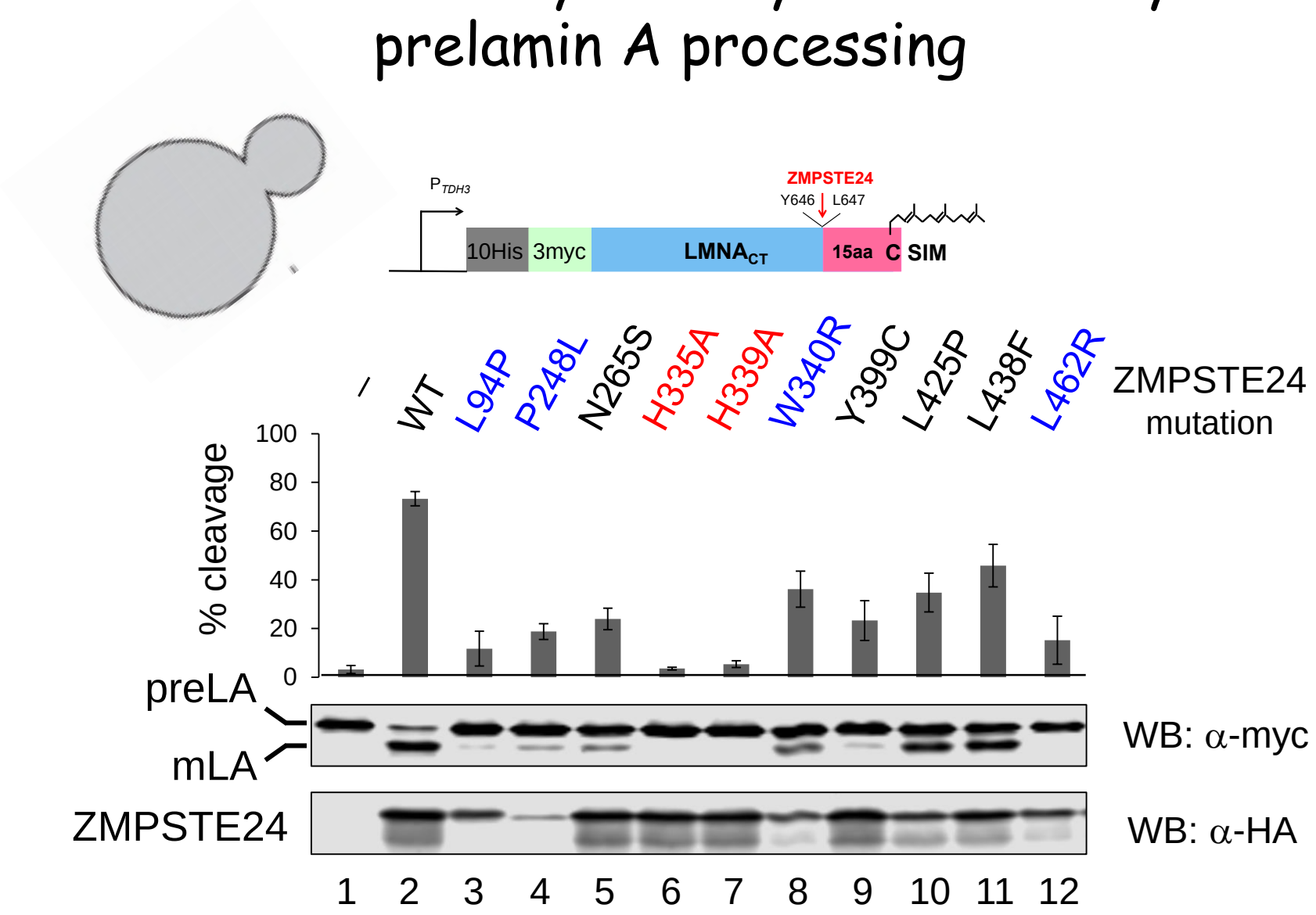
Michaelis Lab

Eric Spear
Khurts Shilgardi
Tim Babatz
Kaiti Wood
Otto Mossberg

Collaborators

Christine Hrycyna, Purdue
Stephen Young, UCLA
Liz Carpenter, SGC, Oxford, England
Maya Schuldiner, Weizmann, Israel
Dan Berkowitz, Johns Hopkins

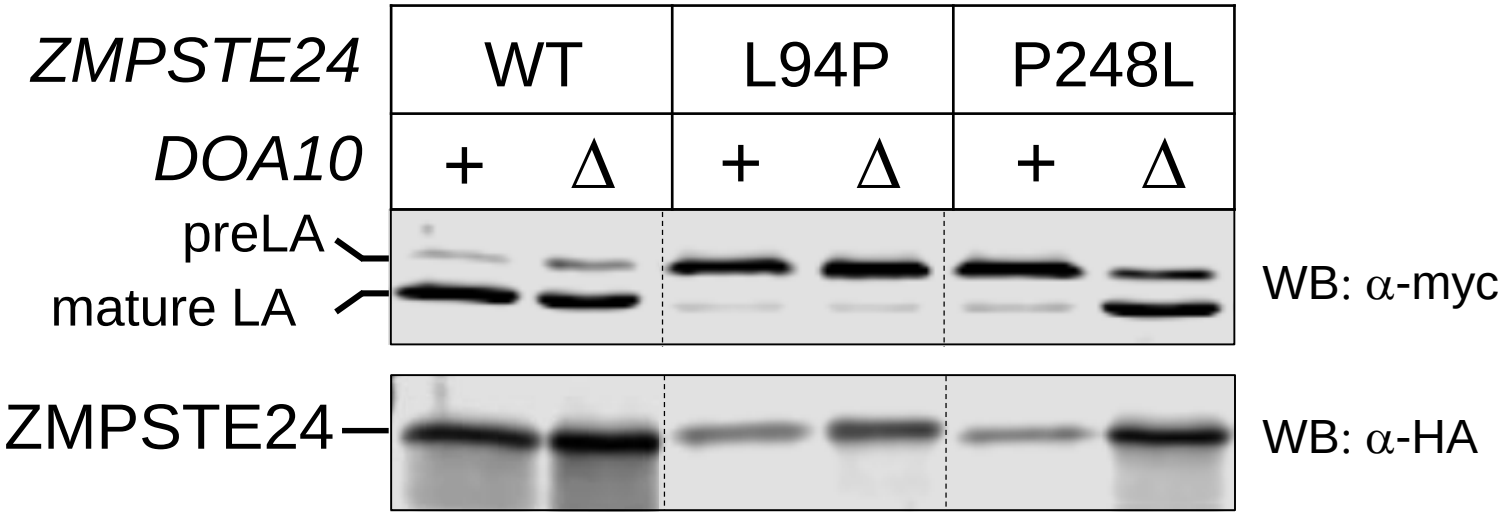
A "humanized yeast" system to study prelamin A processing



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



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