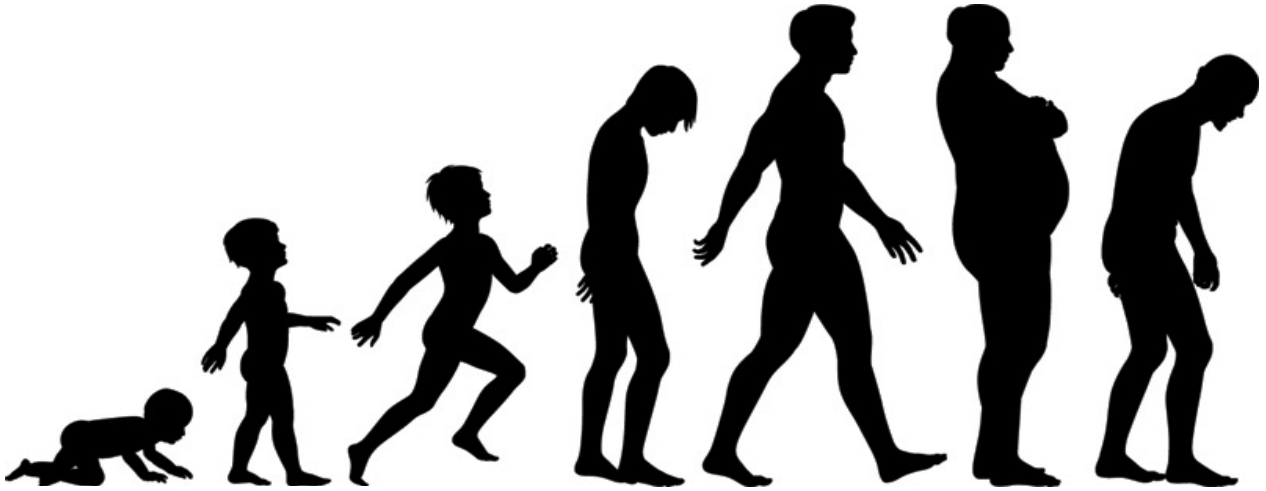
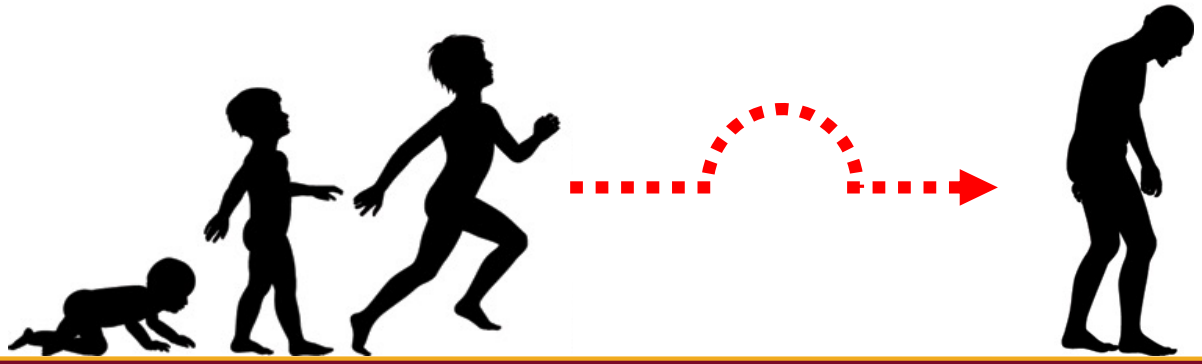


Progeroid syndromes



Keck School of Medicine of USC

Lucio Comai

Davis School of Gerontology of USC

Segmental progeroid syndromes (SPS): a group of disorders characterized by signs of premature aging in more than one organ or tissue.

Unimodal progeroid: premature aging is limited to one organ or one tissue.

Typical signs of premature aging in SPS is the premature onset of the following symptoms:

Graying/loss of hair
Hearing loss
Cataract
Scleroderma-like skin changes
Type 2 diabetes mellitus
Osteoporosis
Atherosclerosis and coronary heart disease
Various malignant tumors

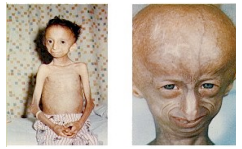
Syndrome	Inheritance	Mean life-span	Mutations
Werner	autosomal recessive	47-50	*WRN* (RECQL2) gene
Hutchinson-Gilford	autosomal dominant	12-15	*LMNA* gene
Cockayne	autosomal recessive	20-25	*CSA (ERCC8)* gene
Ataxia telangiectasia	autosomal recessive	20-25	*ATM* gene
Wiedemann–Rautenstrauch	autosomal recessive	Variable (<1; 20-25)	*POLR3A* gene
Myotonic dystrophy type 1	autosomal dominant	48-55	Trinucleotide repeat expansion in DMPK gene

Hallmarks of WS

Incidence= 1:500,000 - 1:1,000,000
Most tissues and organs are affected.
Pathology: short stature, graying and loss of hair, cataracts, bone deformities, lack of subcutaneous fat.
Diabetes, atherosclerosis, osteoporosis, malignancies.

Cause of death: myocardial infarction.

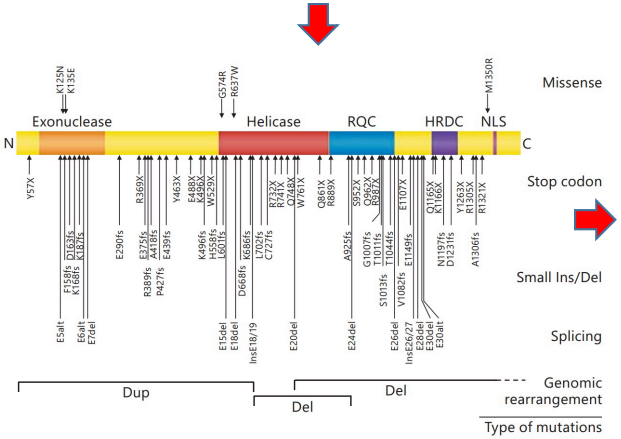
Hallmarks of HGPS



Incidence: 1:6,000,000.
Most tissues and organs are affected.
Pathology: dwarfism wrinkled/aged-looking skin, baldness, and a pinched nose.
Respiratory, cardiovascular, and arthritic conditions.

Cause of death: myocardial infarction.

Spectrum of mutations in the WRN gene

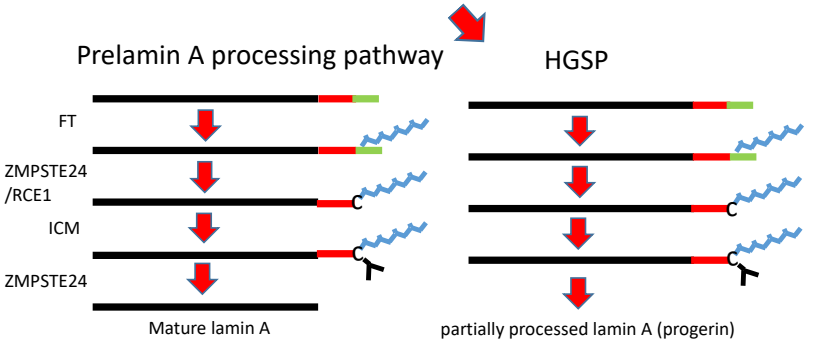


nonsense mediated mRNA decay

Loss of WRN protein

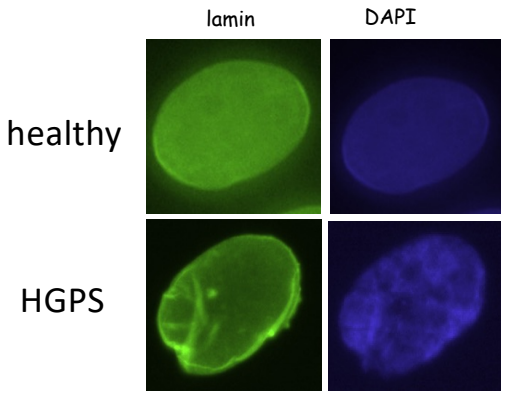
De-novo mutation in the LMNA gene

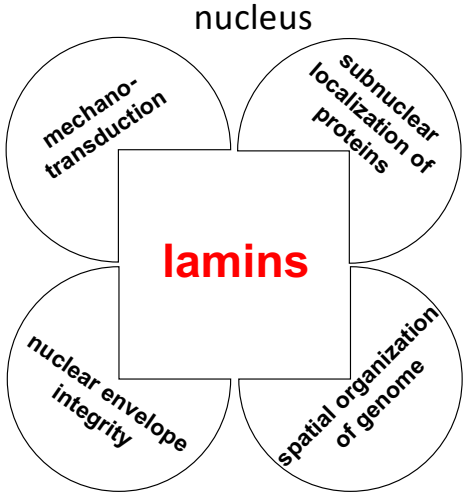
Activation of a cryptic splice site



HGSP: deregulation of nuclear functions

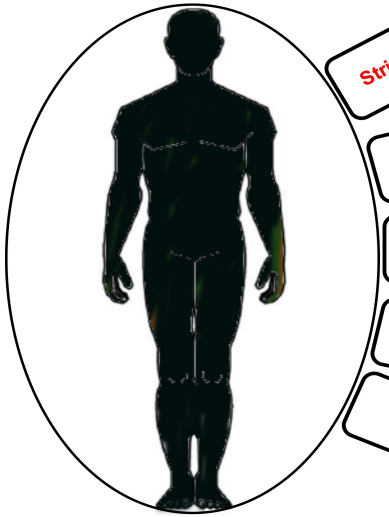
Lamin A contribute to the regulation of cell structure and function





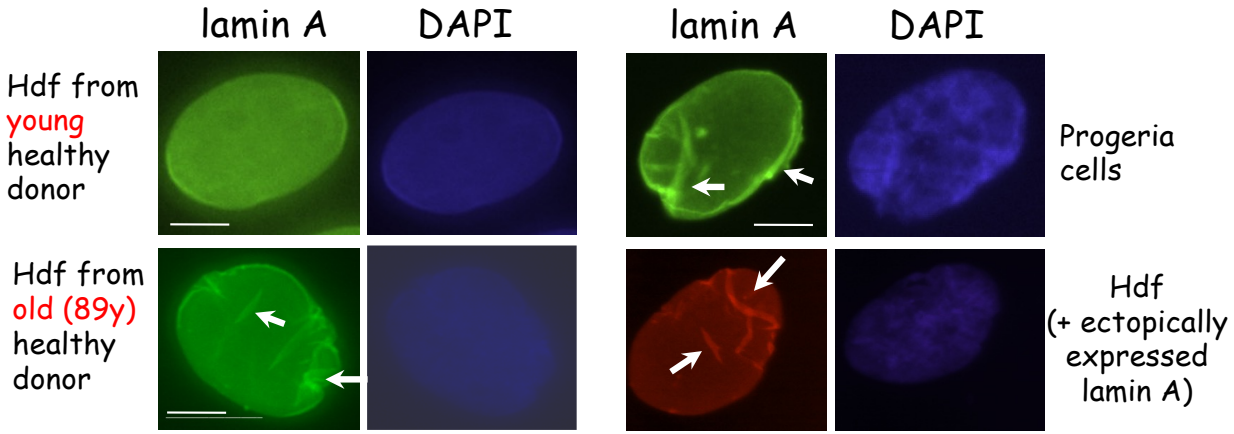
- chromatin organization
- DNA damage response
- telomere length homeostasis
- nucleocytoplasmic transport
- antioxidant response
- DNA replication
- Gene expression

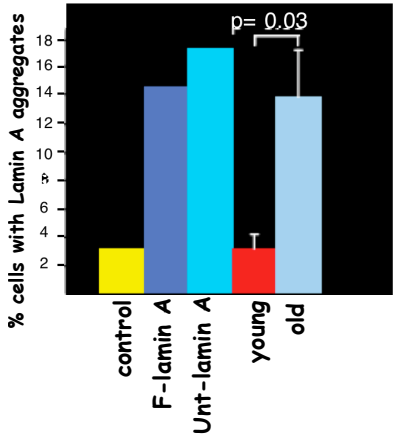
Lamin A mutations and disease: laminopathies

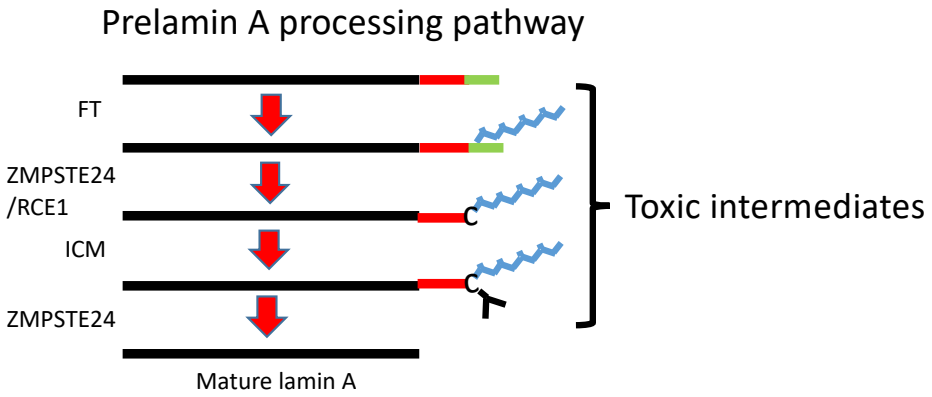


disorder	dominant	recessive
EDMD2/3	✓	✓(rare)
LGMD1B	✓	
CMD1A	✓	
MDC	✓	
H-HS	✓	
CMT2A	✓(rare)	✓
FPLD2	✓	
ADLD	✓	
MADA	✓	✓
HGPS		✓
AWS		✓
RD		

Lamin A maturation pathway: a biomarker of biological aging?

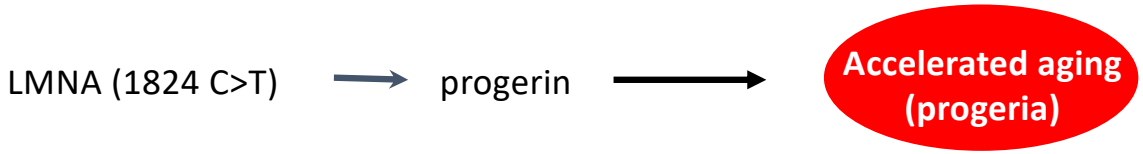




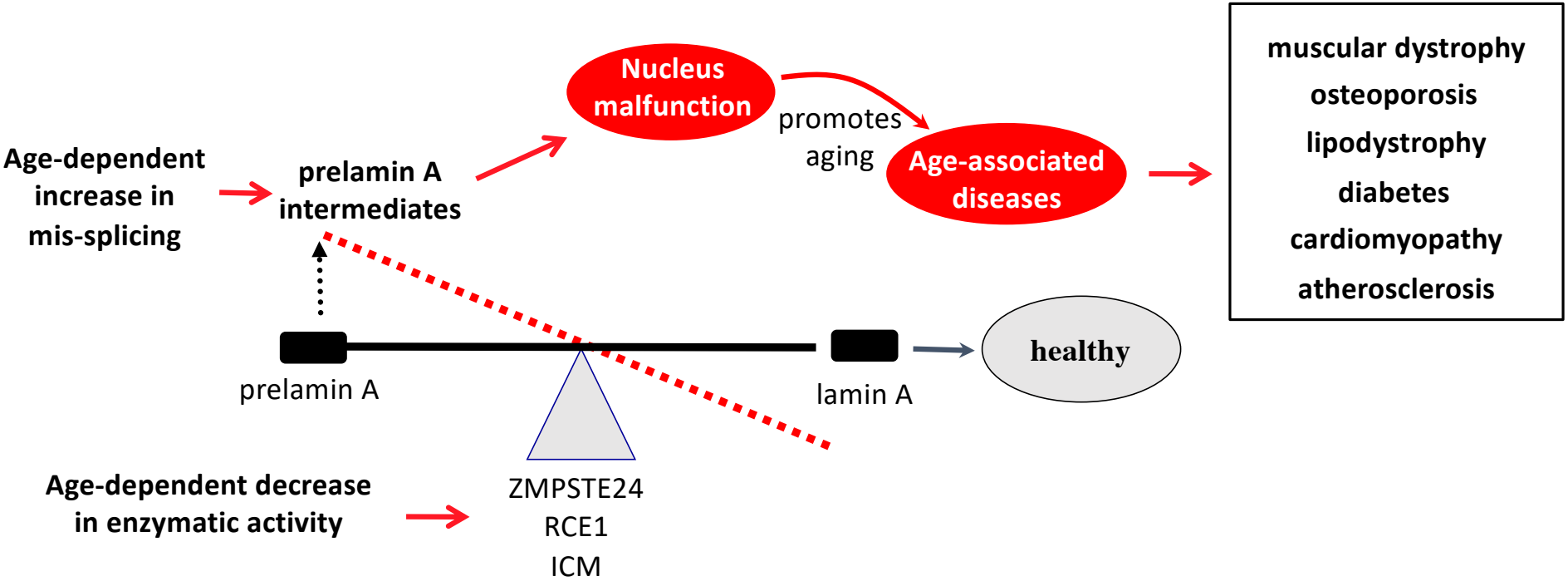


Lamin A maturation pathway: a therapeutic target for physiological aging?

1. Disease-linked mutation



2. Perturbation of normal prelamin A metabolism in physiological aging



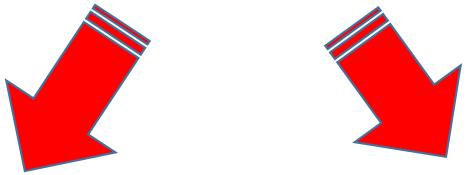
Werner syndrome
(adult onset progeria)

loss-of function mutations in the Werner syndrome gene, which encodes for a protein with helicase and exonuclease activities (WRN)

(DNA repair, transcription ?)

DNA replication: lagging strand synthesis

Genetic instability



telomeres

Other genomic loci?

- Prolonged S-phase of the cell cycle.
- Genetic instability-chromosome deletions and translocation (variegated translocation mosaicism).
- Altered telomere length homeostasis.
- WRN deficiency results in the loss of telomeres replicated by lagging strand synthesis and the formation of extrachromosomal telomeric circles.

Three motifs are the most common sequence features enriched in WRN ChIP peaks

Human cells

↓

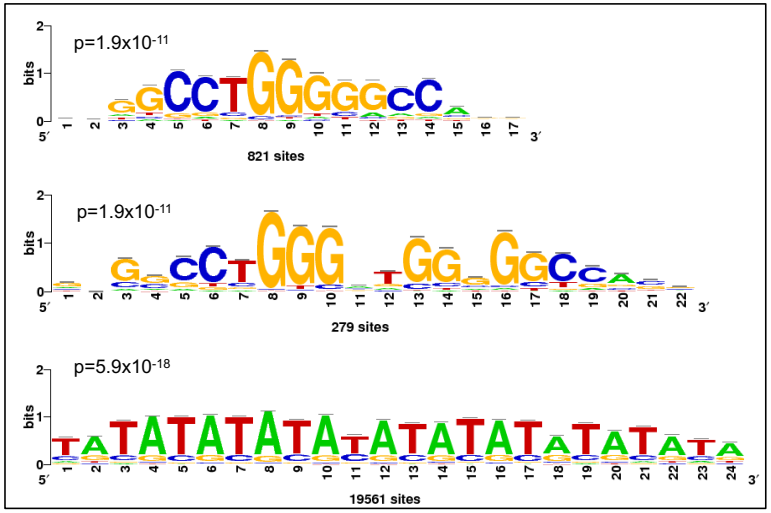
Chromatin IP using WRN antibody

↓

High-throughput sequencing

↓

Data analysis



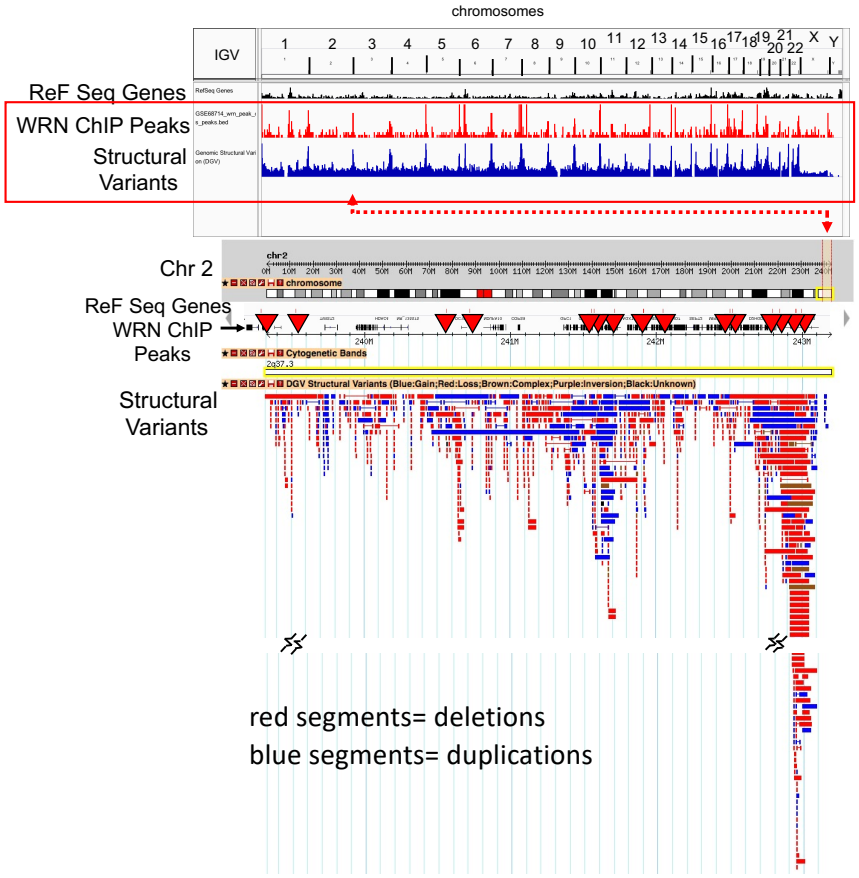
Gosal et al. unpublished

- WRN binding sites are repetitive elements/low-complexity motifs.
- Repetitive DNA sequences are a major threat to genome stability often driving chromosome rearrangements and disease.
- Repetitive sequences represent a challenge to the replication machinery because they are prone to form stable secondary (non-canonical) structures.
- Maintaining the stability of loci with repetitive sequences is critical to overall cellular fitness and lifespan, but this weakness be exploited to generate replication catastrophe in cancer cells.

WRN was discovered as a completely novel selective vulnerability in Microsatellite Instability (MSI) cancer (Chan EM et al., Nature 2019; Lieb S et al., eLife 2019; Kategaya L et al., iScience 2019; Behan FM et al., Nature 2019).

In MSI cancer cells, WRN is required for DNA replication through (TA) n dinucleotide repeats scattered throughout the genome (van Wietmarschen N et al., Nature 2020)

WRN binding sites correlate with structural variants in the human genome



- Structural variants (SV) include cytogenetically detectable and submicroscopic Copy Number Variants (CNVs; deletions, duplications and insertions rearrangements, such as inversions and interchromosomal and intrachromosomal translocations).

- SVs are present in every human genome and can affect molecular and cellular processes, regulatory functions, 3D structure and gene expression.

Progeroid syndromes: a window into biological aging

- Lamins regulate many fundamental nuclear processes thereby playing a critical role in cell homeostasis.
- Prelamin A processing pathway is tightly regulated, and small perturbations can alter the balance between health and disease.
- WRN contributes to telomere length homeostasis, thereby affecting the onset of replicative senescence.
- WRN maintains the stability of repetitive elements across the human genome, thus influencing phenotypic variation and disease.

Acknowledgments: all members of the Comai lab; funding by: NIH, ACS, Progeria Foundation