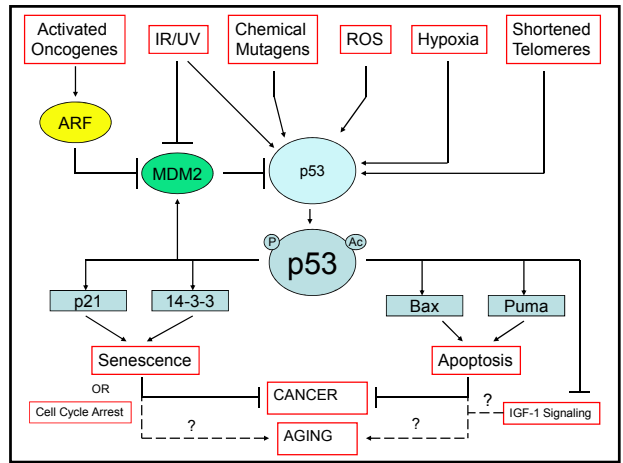
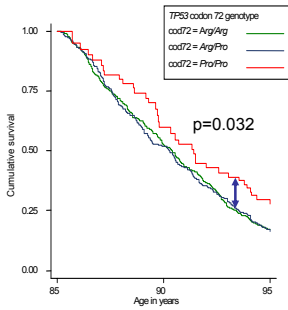


# Insights into stem cells and aging provided by a P53 mutant mouse

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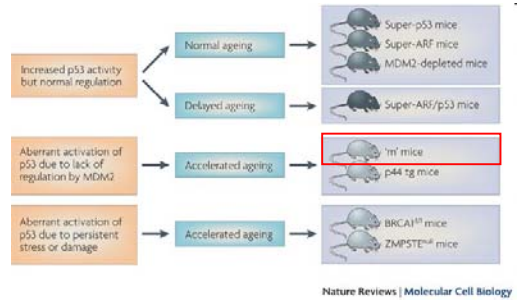
## A human p53 polymorphism may confer extended longevity



- Humans carry a p53 polymorphism (R72P) with decreased apoptotic potential
- Although P/P people are more tumor prone, they exhibit reduced mortality
- Indicative of reduction in p53 activity may enhance survival

van Heemst et al. *Exp Gerontology* (2005)

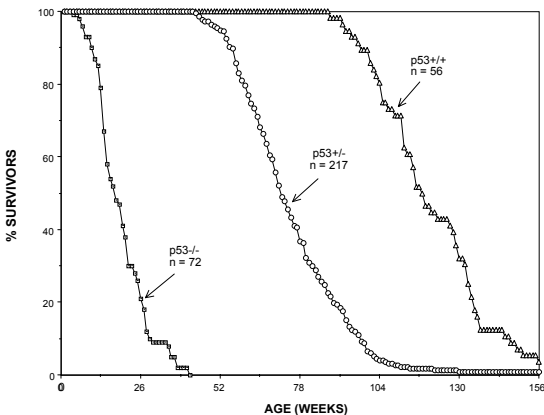
## Different p53 mouse models show different effects on longevity and cancer



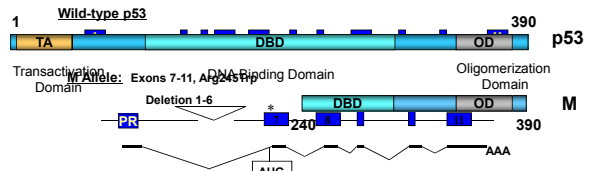
Nature Reviews | Molecular Cell Biology

From Serrano and Blasco, 2007

## p53 is a Longevity Assurance Gene (Formal Proof)

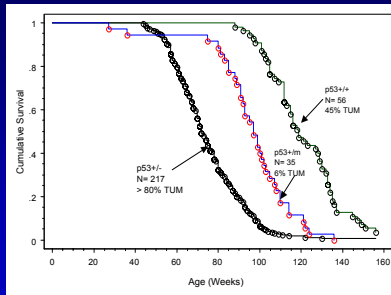


## The p53 M Allele



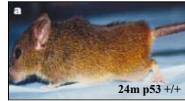
- Mutant (m) Allele
  - Encodes truncated C-terminal p53 fragment
  - Missing Transactivation domain
  - Missing majority of DNA binding domain
  - Interacts with WT p53
  - Drives WT p53 into the nucleus

## p53 +/m mice have reduced longevity



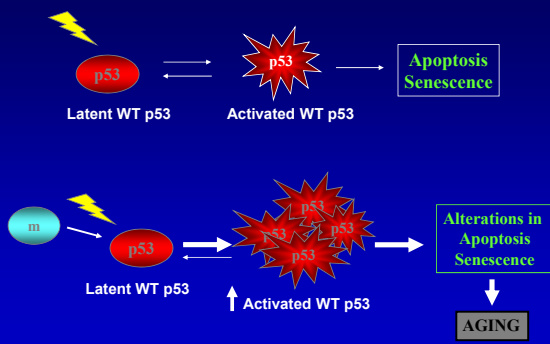
+/m median lifespan = 96 weeks  
+/+ median lifespan = 118 weeks

## The p53+/m mouse: An Accelerated Aging Model

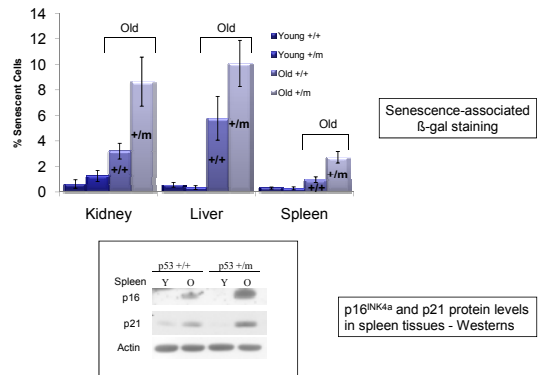


- **Highly Tumor Resistant**
- **Reduced Longevity**
- **Accelerated Aging Phenotypes**
  - Reduced body weight
  - Osteoporosis
  - Lordokyphosis
  - Organ atrophy
  - Decreased regeneration
  - Reduced stress tolerance
  - Muscle atrophy
  - Increased senescence with age
- Mice appear normal until 12 months, overt phenotype by 16-18 months

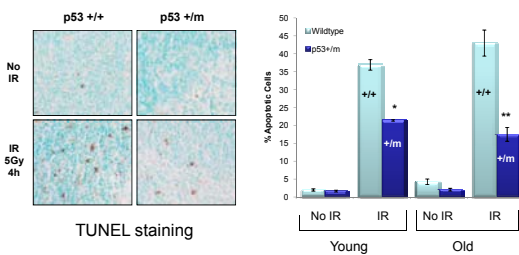
## Proposed model of m function: p53 Hyperactivity



## Senescence markers are elevated in aged p53+/m tissues

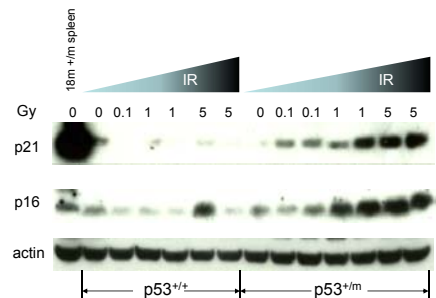


## p53+/m tissues exhibit attenuated IR-induced apoptosis



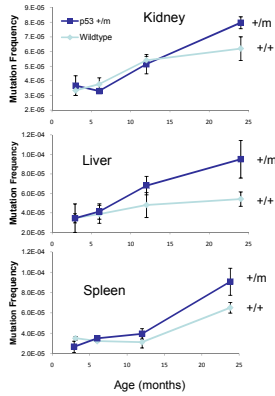
Spleen sections  
5 Gy IR  
4 hr post IR

## p53+/m tissues show prolonged DNA damage response



1 week post IR  
Spleen cells  
3 month old mice

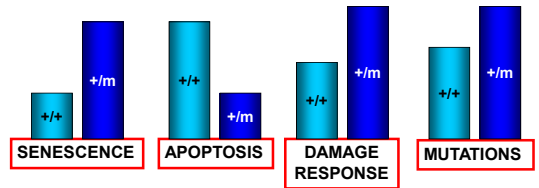
p53+/m mice exhibit increased age-associated mutation rates



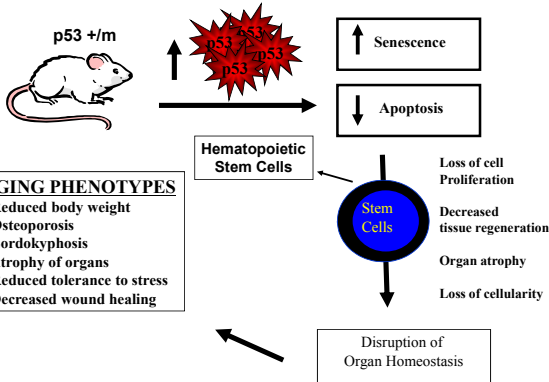
Big Blue mouse mutation assay (lambda cl1 transgene)

p53+/m tissues display:

- (1) Increased age-associated senescence
- (2) Decreased damage-induced apoptosis
- (3) Enhanced and prolonged DNA damage response
- (4) Higher age-associated mutation rates

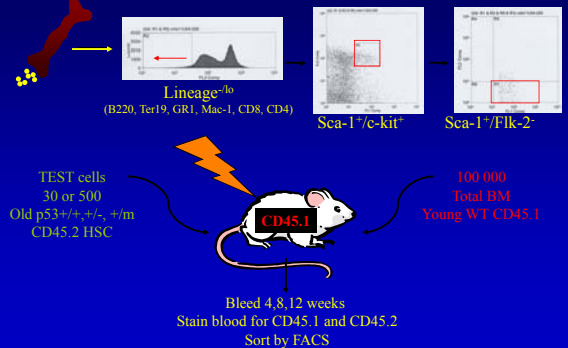


### Aging and the m Allele

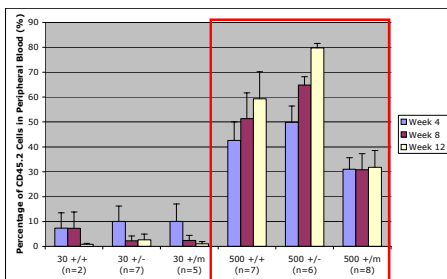


### Limiting Dilution Old HSC Transplants

2 test cell doses: 30 and 500 cells



### Limiting Dilution - Old HSC Transplant Results



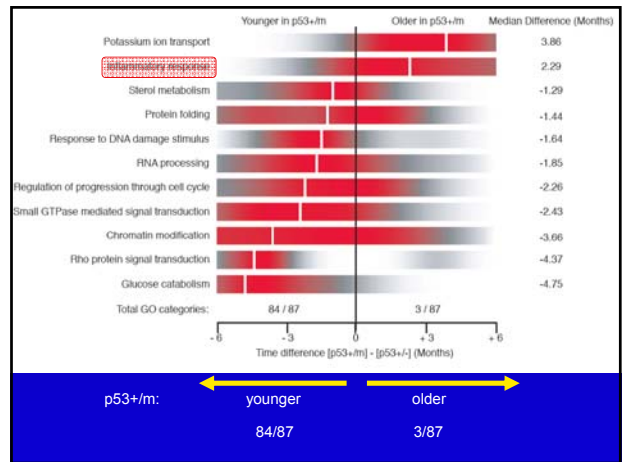
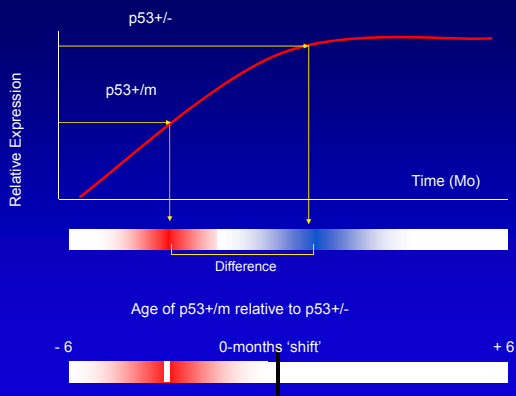
- 30 cells: - very little engraftment and contribution to peripheral blood.  
- no difference seen between genotypes.
- 500 cells: - p53+/m HSC contribute less to blood than WT or p53+/-.  
- no increase in p53+/m cell contribution with time.

### p53+/m and p53+/- mice

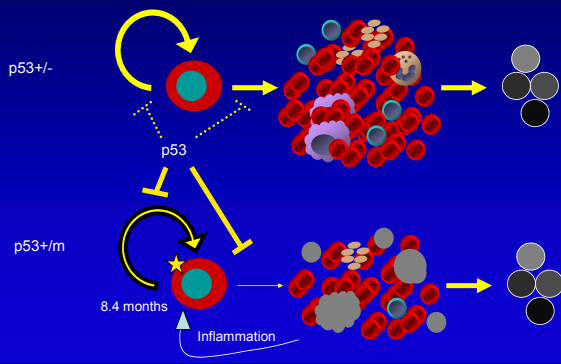
- p53+/m (hypermorph) "+/m"
- p53+/- (hypomorph) "het"
- \* 12 month old \*



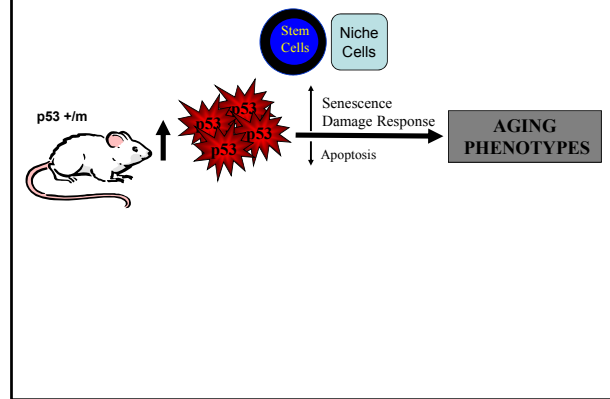
## Convert expression into time



## p53 model (12 Mo)



## Effects of the m Allele



## Overall Conclusions

- p53+/m mice exhibit enhanced cancer resistance and accelerated aging phenotypes
- p53+/m mouse tissues display:
  - enhanced and prolonged p53-mediated DNA damage response
  - increased age-associated senescence
  - increased age-associated mutation rates
  - reduced apoptosis
- Aged p53+/m HSCs show reduced reconstitutive function
- p53+/m HSCs by array profiling appear "younger", suggesting reduced self-renewal potential

## Acknowledgements

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