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Consiglio Nazionale delle Ricerche

IRGB
Istituto di Ricerca Genetica e Biomedica

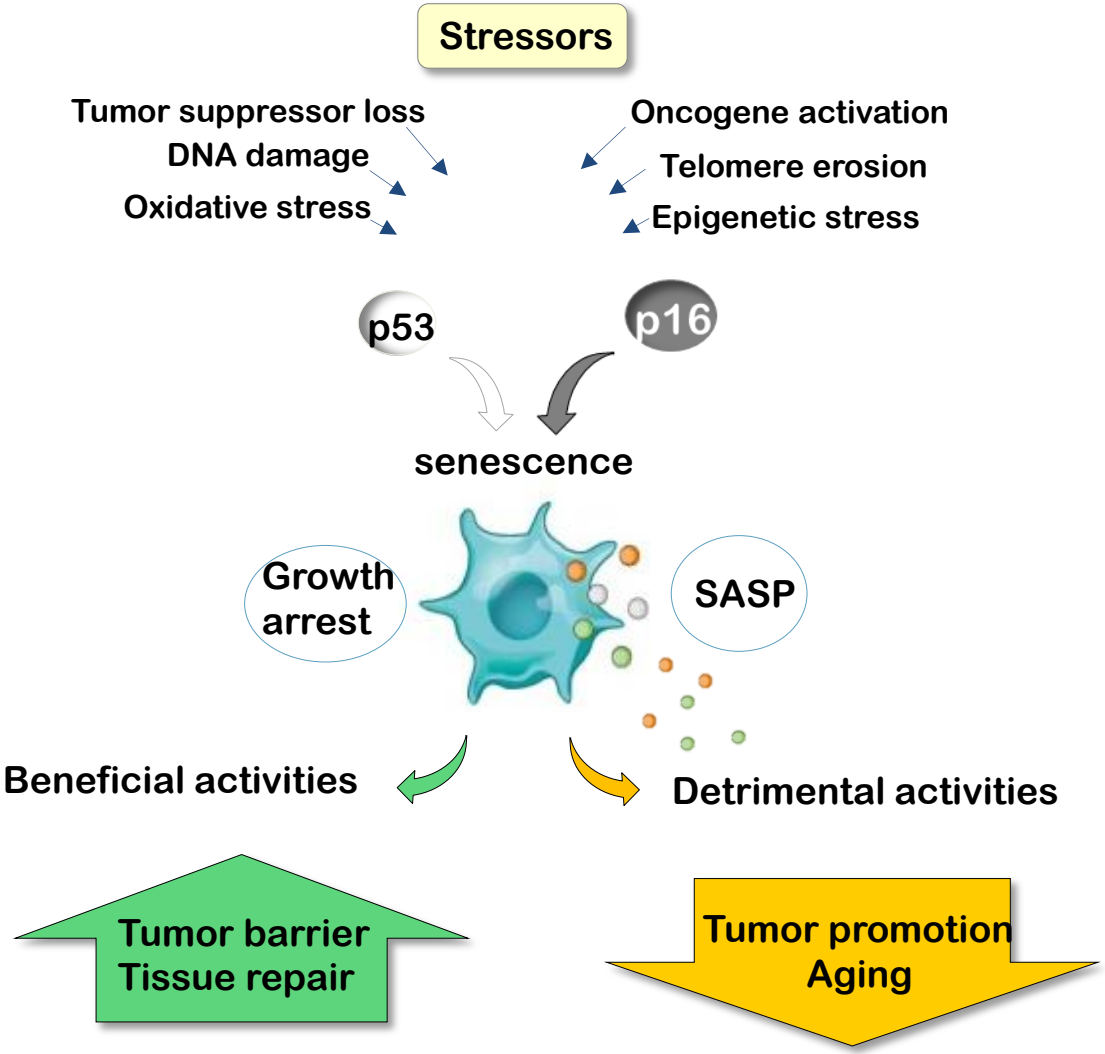
UOS di Milano

Cellular senescence:

The good and bad sides of a novel therapeutic target

Pavia, February 29th, 2016
Francesca Faggioli, PhD

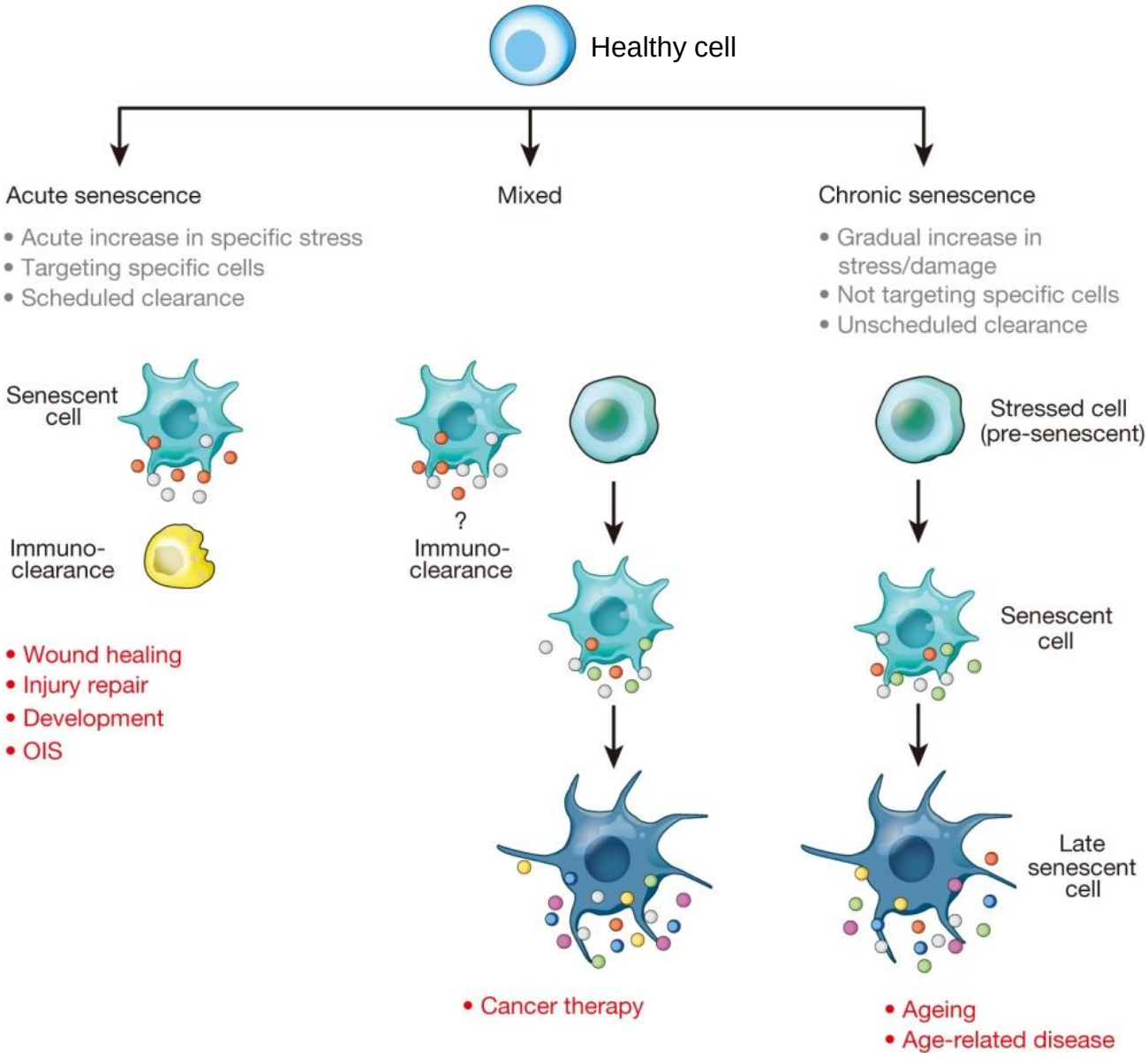
Cellular senescence



SASP, senescence associated inflammatory phenotype

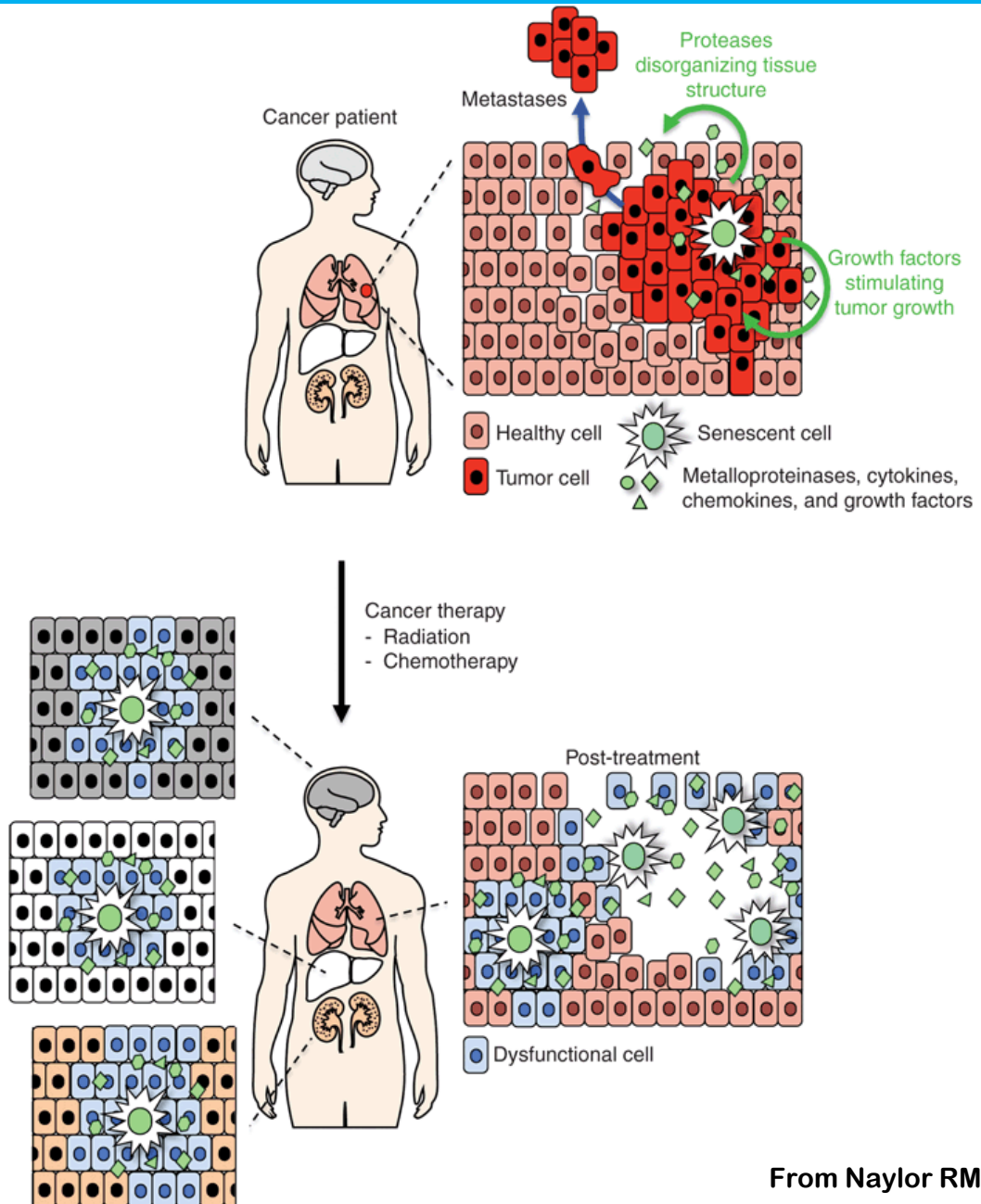
Adapted from JM van Deursen *Nature* **509**, 439-446 (2014) doi:10.1038/nature13193

Acute versus Chronic senescence cells



JM van Deursen *Nature* **509**, 439-446 (2014) doi:10.1038/nature13193

Therapy induced senescence, TIS



- ↑ susceptibility to severe or life-threatening health condition
- Secondary cancer
- developing of other disease (i.e. cerebrovascular disease etc.)

From Naylor RM, et al., Clin Pharmacol Ther. 2013 Jan;93(1):105-16.

Aging Cell (2010) **9,** pp398–409 Doi: 10.1111/j.1474-9726.2010.00567.x

Ionizing radiation-induced long-term expression of senescence markers in mice is independent of p53 and immune status

Oanh N. L. Le,[1] Francis Rodier,[2,3] Francois Fontaine,[1] Jean-Philippe Coppe,[2] Judith Campisi,[3] James DeGregori,[4] Caroline Laverdière,[1] Victor Kokta,[1] Elie Haddad[1,5] and Christian M. Beauséjour [1,6]

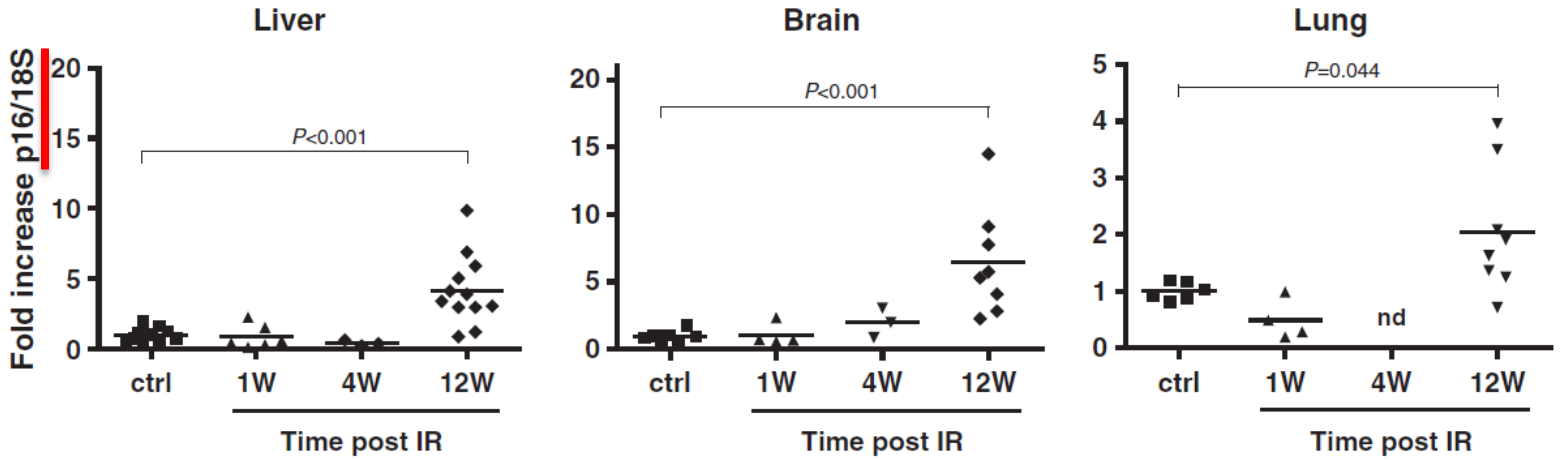
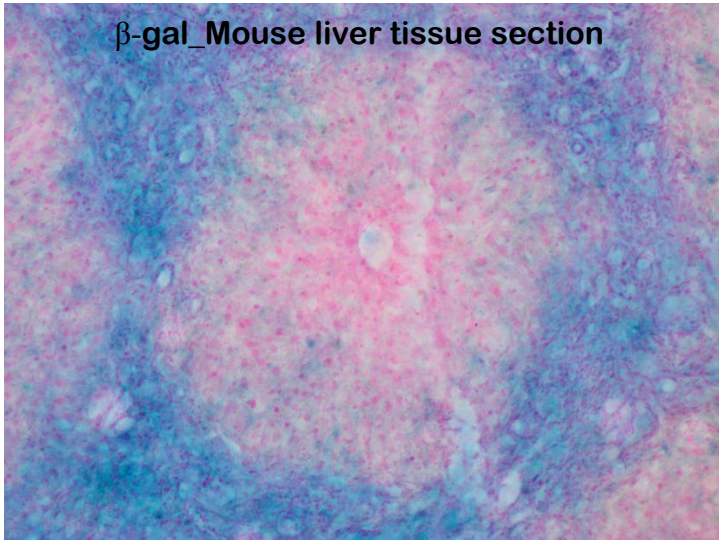


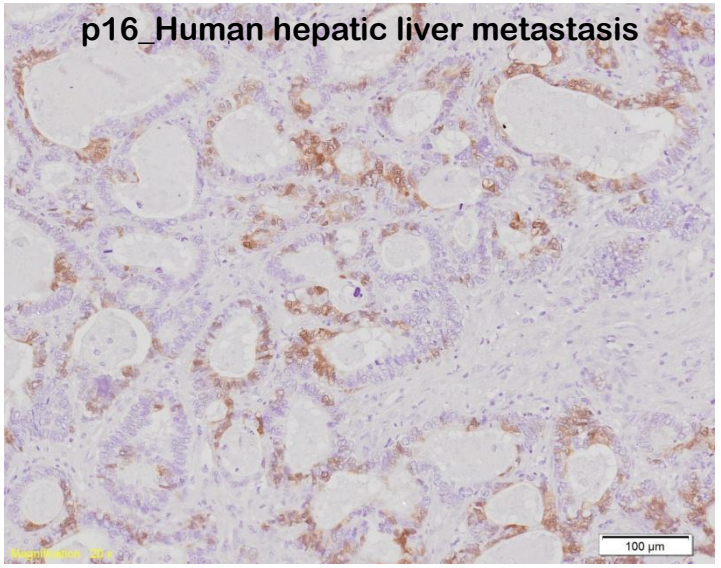
Fig. 2 Exposure to IR induces delayed p16^{INK4a} expression in mouse tissues. RNA was isolated from homogenized liver, brain, and lung tissues collected from control (ctrl) and from irradiated (8 Gy TBI) C57BL/6 mice killed at the indicated time in weeks (W) post IR. RNA was then used to determined p16^{INK4a} expression by quantitative real-time PCR (n = 3–12, each symbol representing an individual mouse). P values were obtained by performing a Student's t-test relative to control. nd = not determined.

Identification of senescent cells

In vitro

- increased cell size
- SA-β-galactosidase activity
  (lysosomal hydrolase)
- SAHF
  (senescence associated heterocromatin foci)
- CDKi expression (i.e. p21, p16 etc.)
- markers of proliferation (ki67, BrdU)
- SASP factors
  (inflammatory chemokines and cytokines ,
  matrix remodelling proteases;
  growth factors)
- resistance to apoptosis


β-gal_Mouse liver tissue section



p16_Human hepatic liver metastasis

Identification of senescent cells

In vivo

To tag or to kill senescent cells is essential for testing their biological effects

- **To check whether senescence is present and in what cell type, included immune cell types** Although the damage causing senescence may be random, some cell types are more vulnerable than others. (β-gal staining etc.)

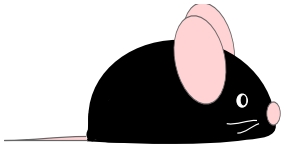
- **To assess SASP factors and CDKi expression across the biological contexts, through isolation of senescent cells.**

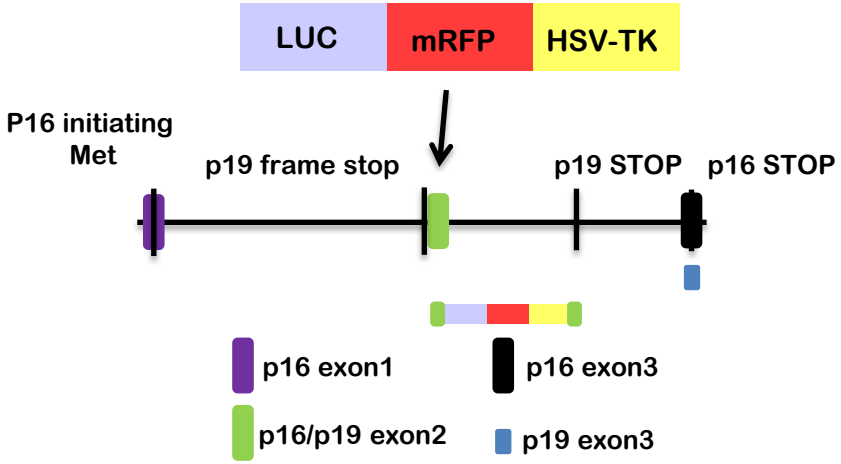
- **To check for the general fitness and for the onset of accelerated aging before and after clearance of senescent cells.**
  (Incidence of sarcopenia, lordokyphosis, cataracts, loss of adipose tissue, exercise ability; body and fat depot weights; dermis and subdermal adipose layer thickness etc.)

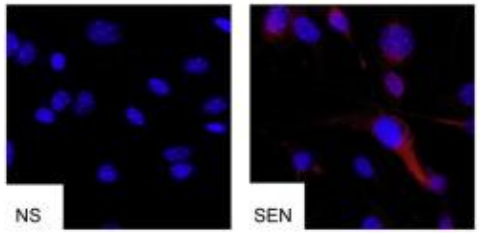
- **To check for reduction of progenitors cells in proliferative pools.**

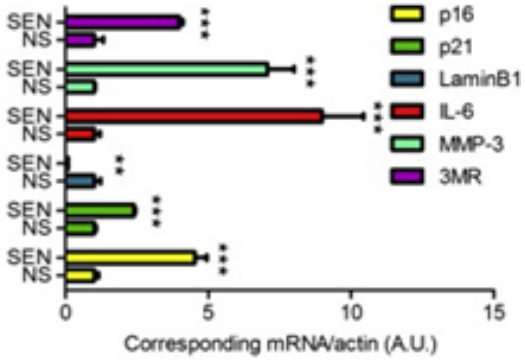
Senescent cell reporter systems in mice

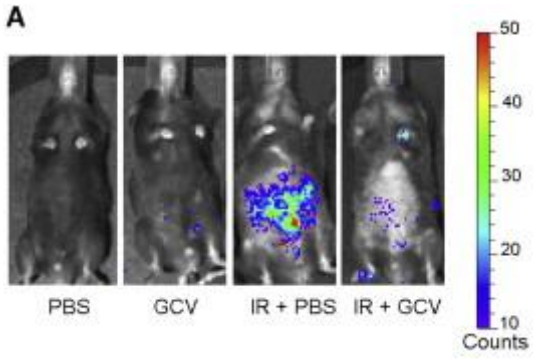
p16-3MR mouse GCV sensitive







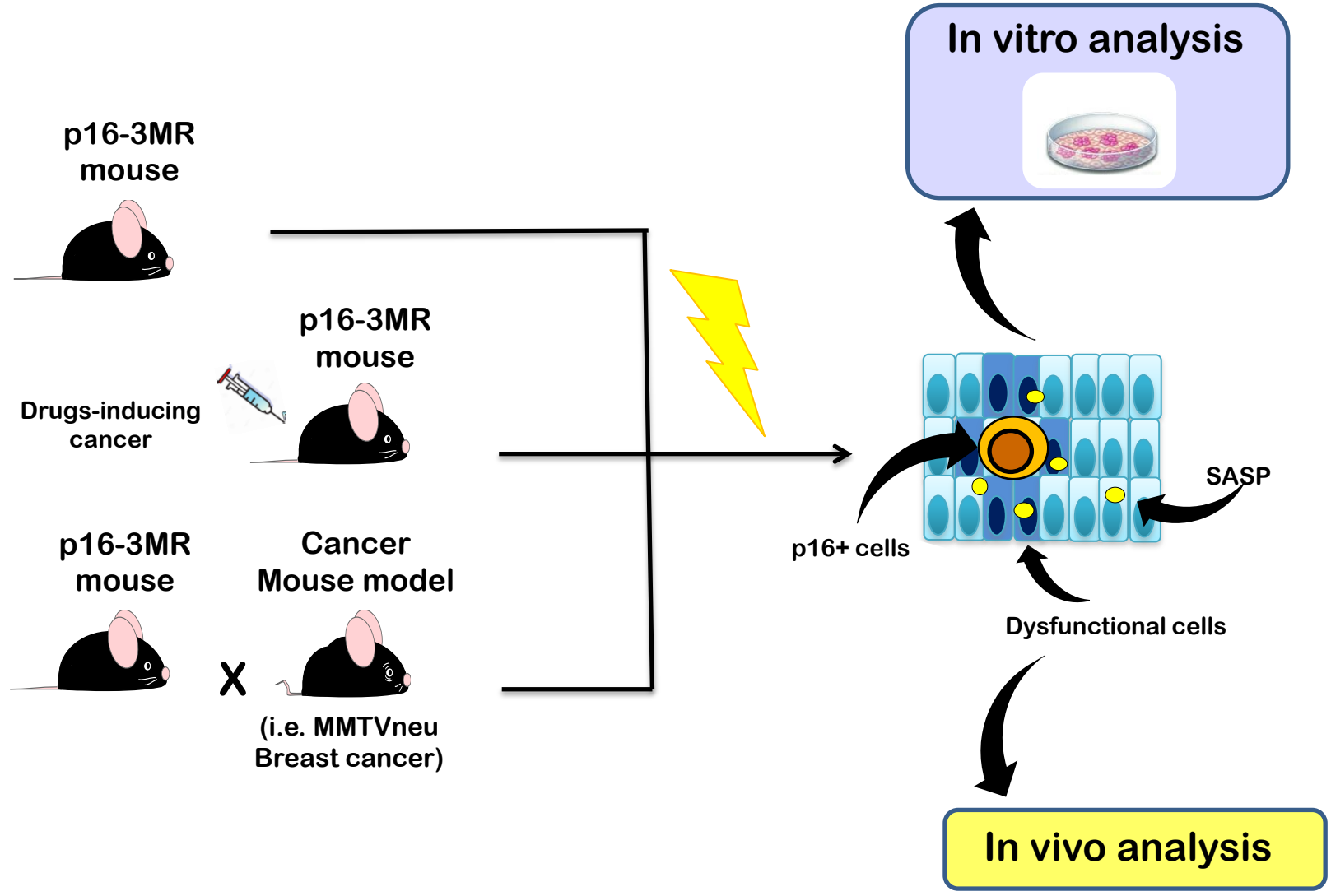




A gift, kindly provided by Prof. J. Campisi

Adapted from M Demaria *Developmental Cell* **31**, 722-733 (2014) doi:10.1016/j.devcel.2014.11.012

Hypothetical workflow



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THANK YOU

FOR YOUR

ATTENTION