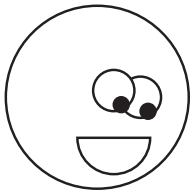
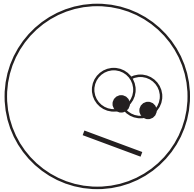
oncogene-induced senescence

Franziska Witzel

Computational Modelling in Medicine



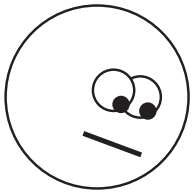
dividing cell



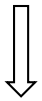
non-dividing cell

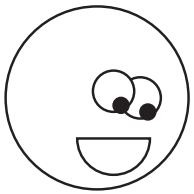
non-cancer cell

cancer cell



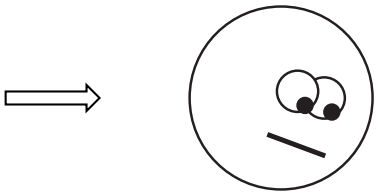
growth factor



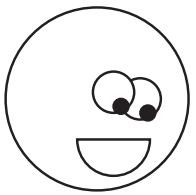


quiescence

reversible
cell cycle exit



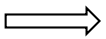
growth factor

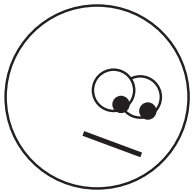


quiescence

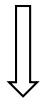
reversible
cell cycle exit

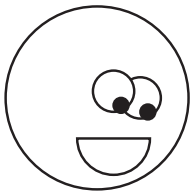
- anti-mitogenic signals
- starvation
  (depriving cells
  of growth factors)
- contact inhibition





growth factor

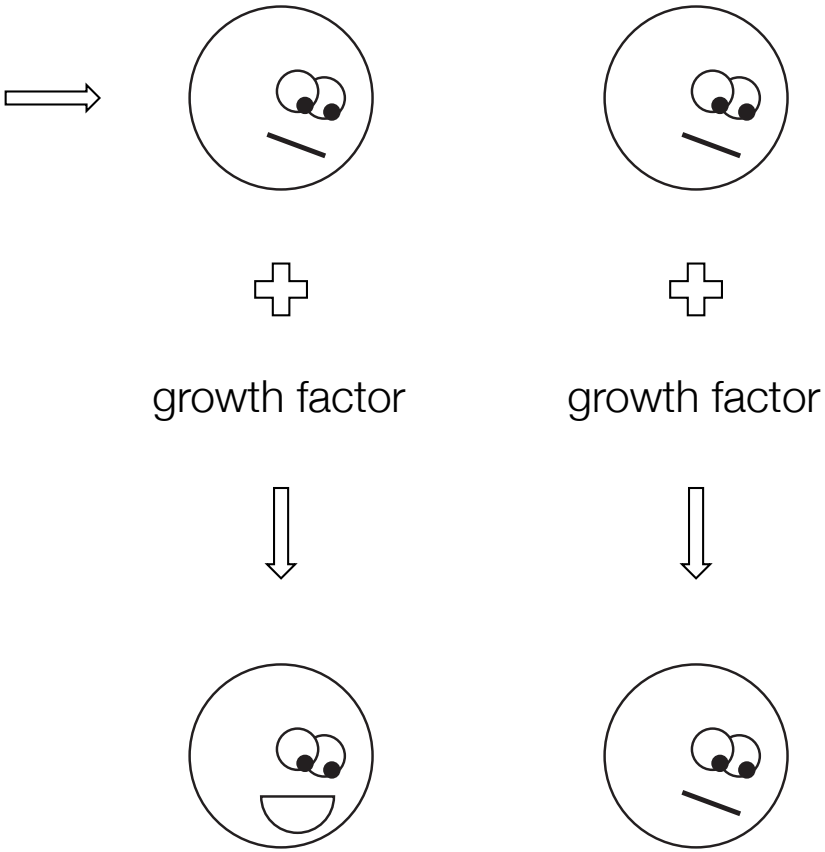




quiescence

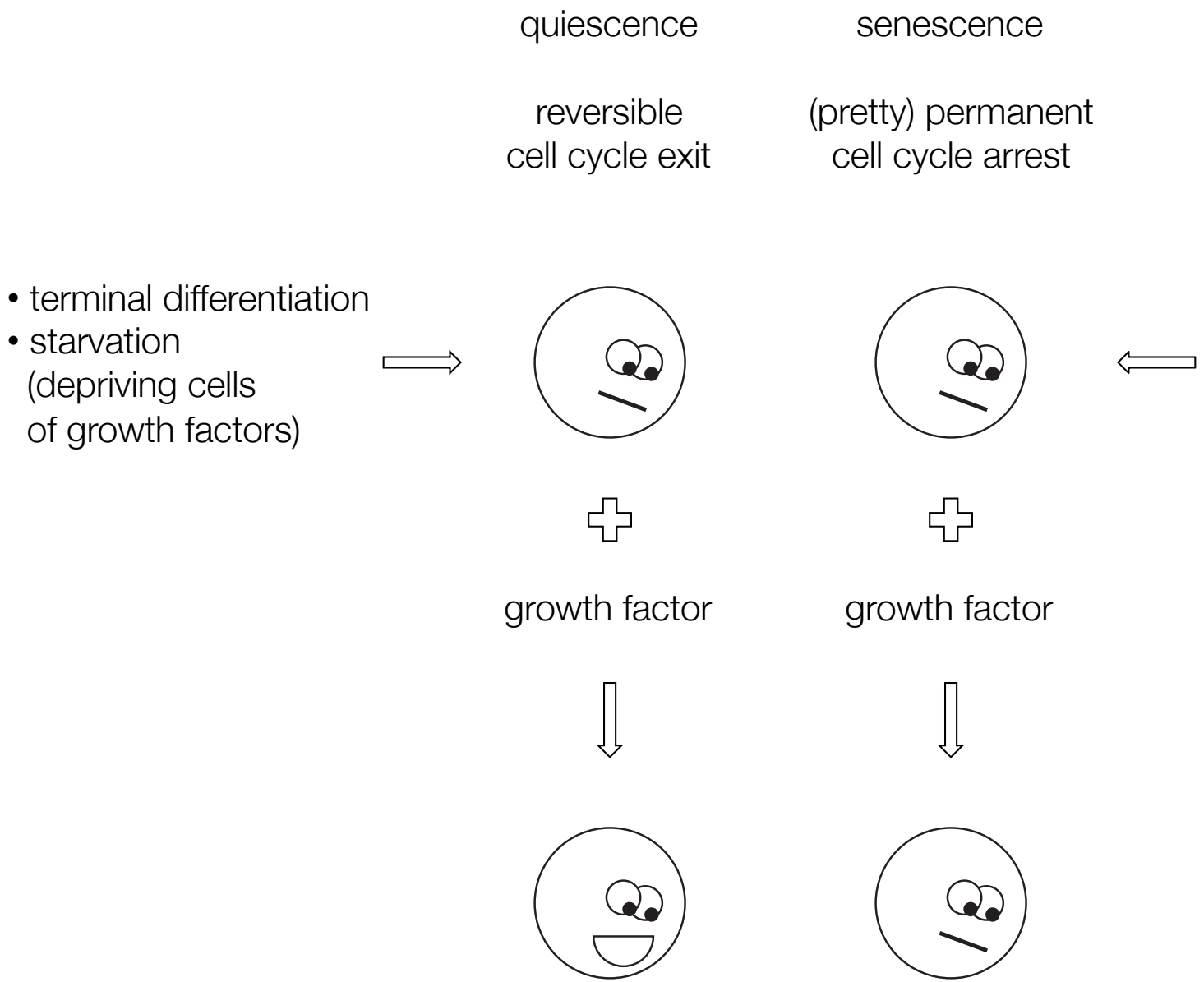
reversible
cell cycle exit

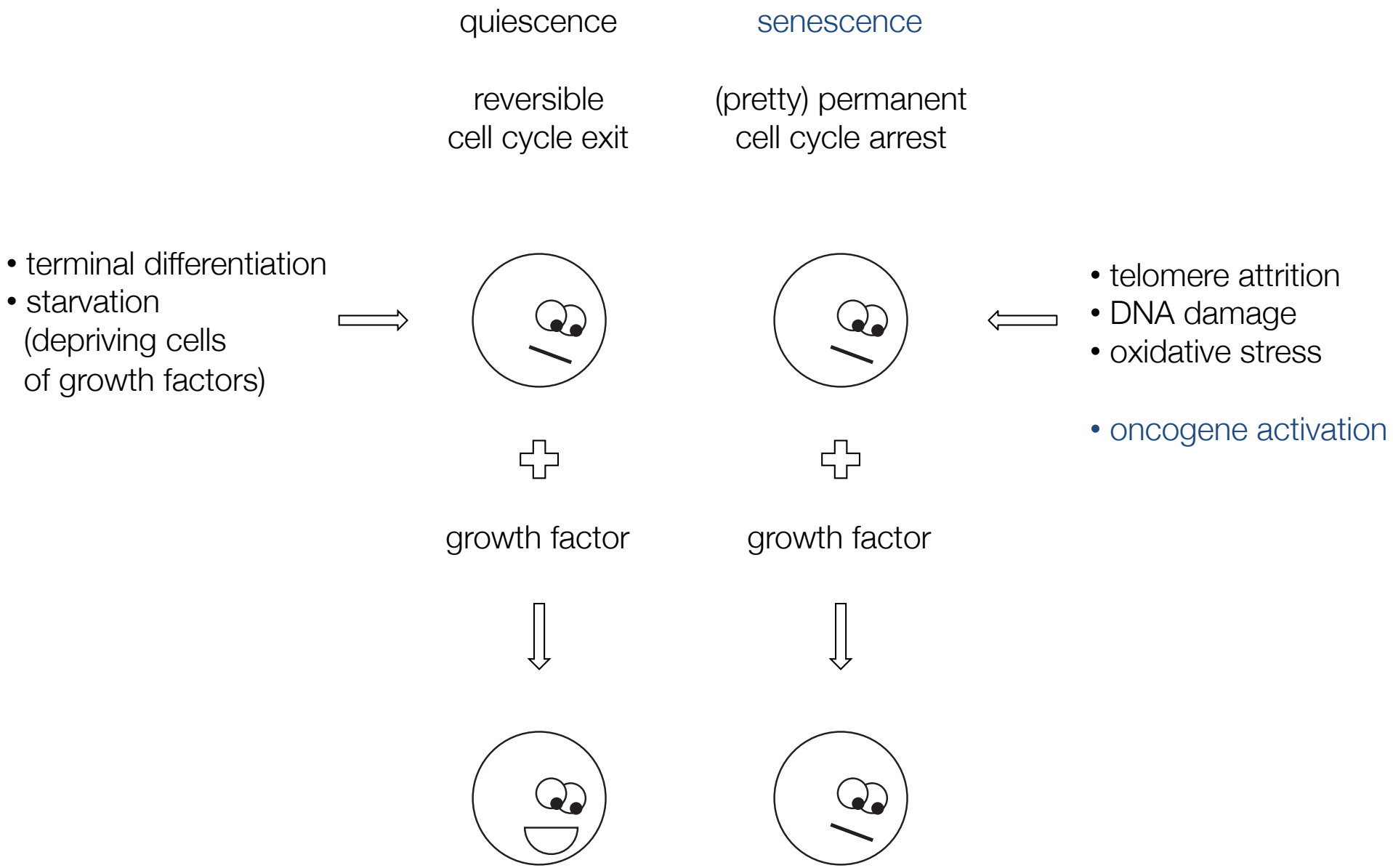
- terminal differentiation
- starvation
  (depriving cells
  of growth factors)

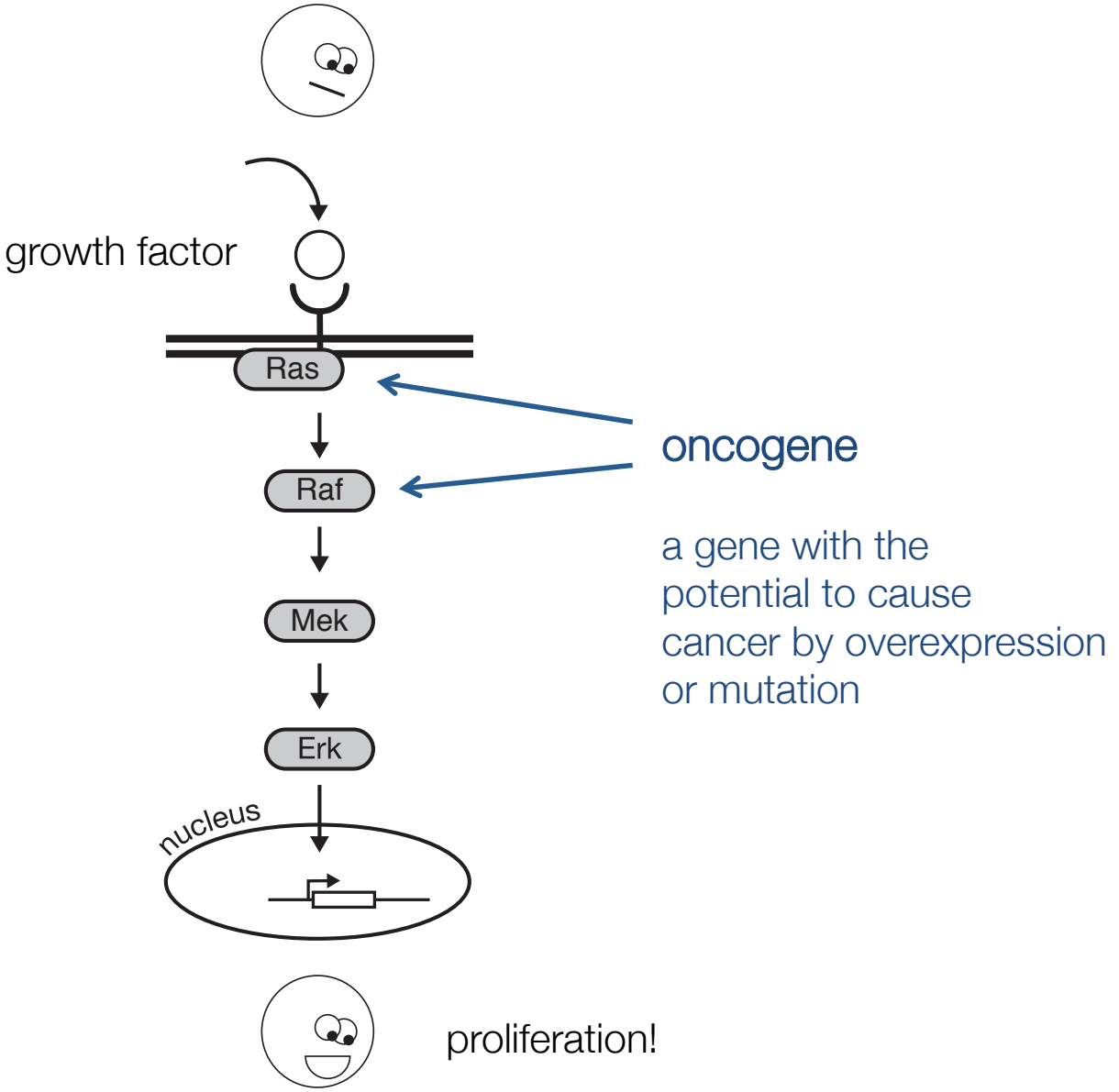


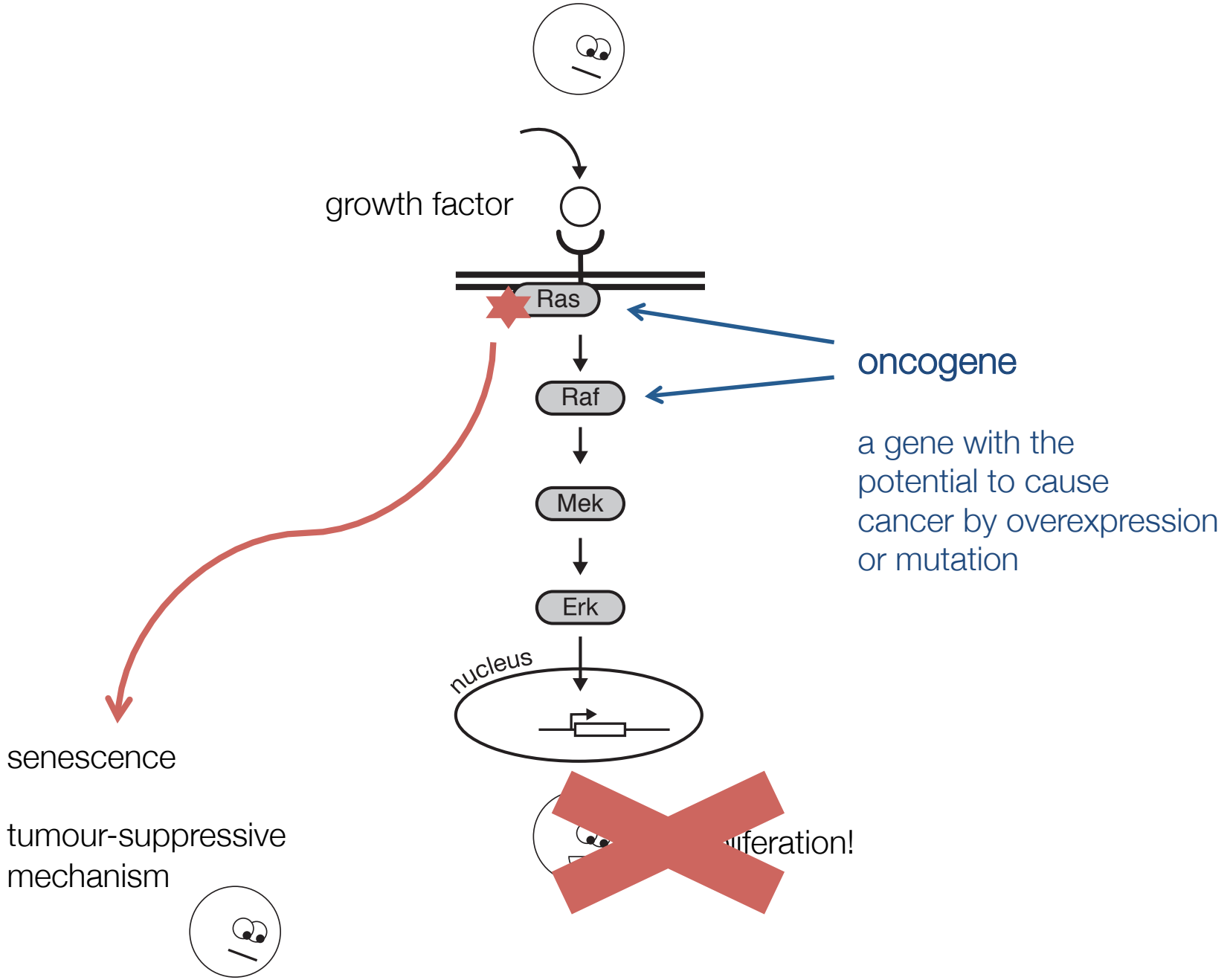
growth factor

growth factor


quiescence
reversible
cell cycle exit
senescence
(pretty) permanent
cell cycle arrest
• terminal differentiation
• starvation
(depriving cells
of growth factors)
growth factor
growth factor

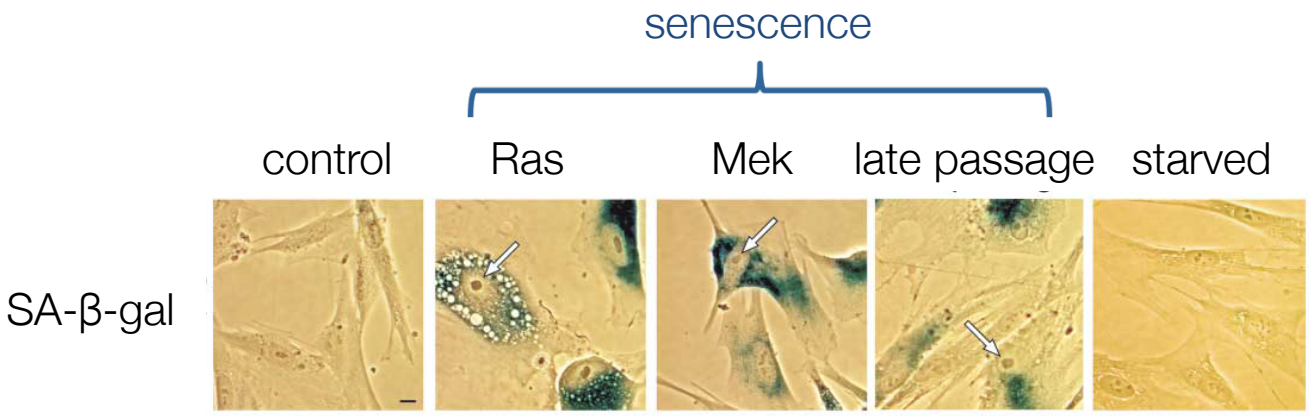

quiescence
senescence
reversible
cell cycle exit
(pretty) permanent
cell cycle arrest
• terminal differentiation
• starvation
(depriving cells
of growth factors)
• telomere attrition
• DNA damage
• oxidative stress
• oncogene activation
growth factor
growth factor

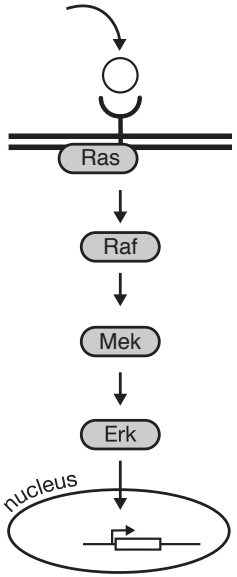

growth factor
Ras
Raf
Mek
Erk
nucleus
proliferation!
oncogene
a gene with the
potential to cause
cancer by overexpression
or mutation


growth factor
Ras
Raf
Mek
Erk
nucleus
oncogene
a gene with the potential to cause cancer by overexpression or mutation
senescence
tumour-suppressive mechanism
iferation!

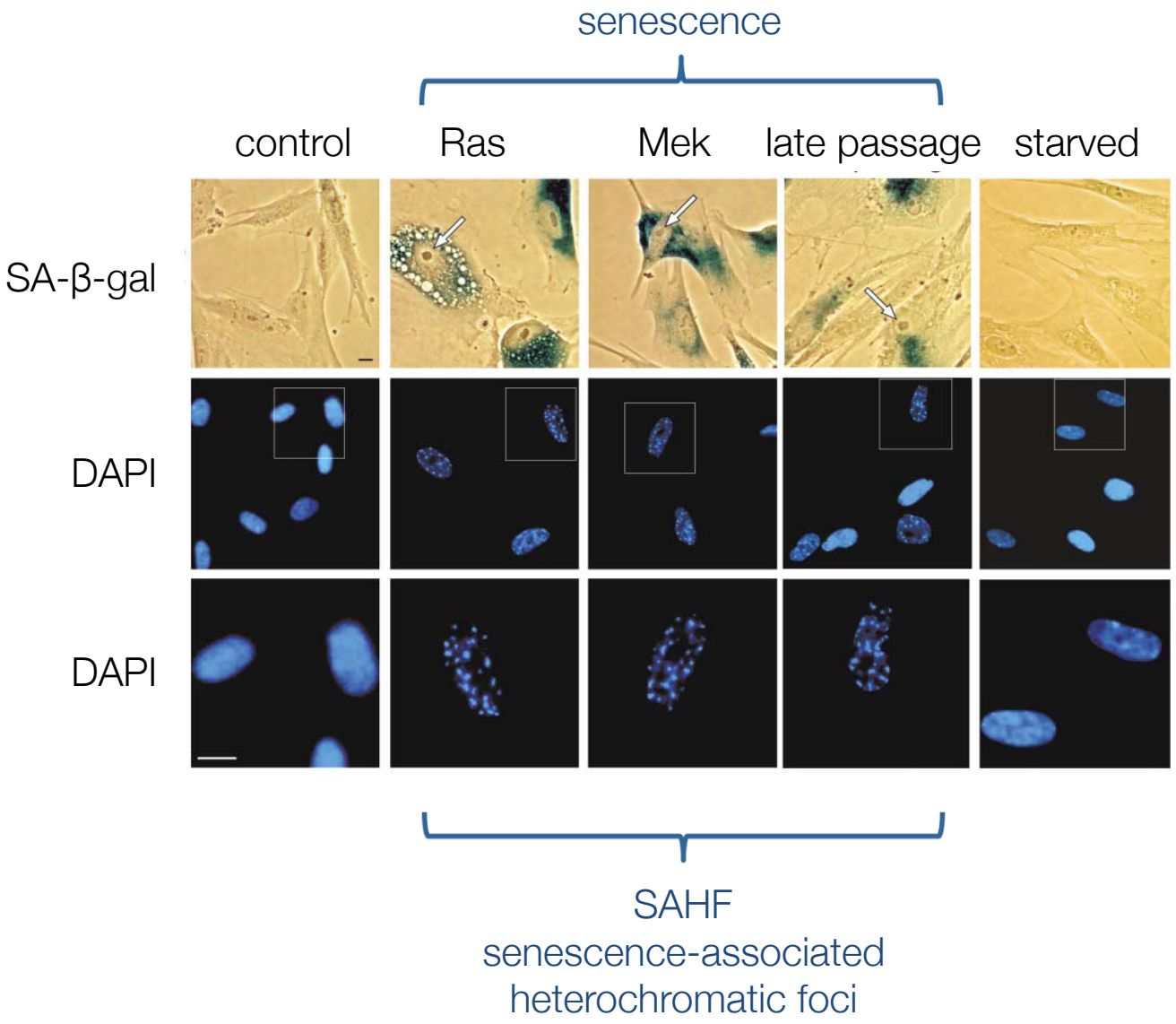
1. Why is the senescent state so stable?
   (how to create a permanent cell cycle exit)

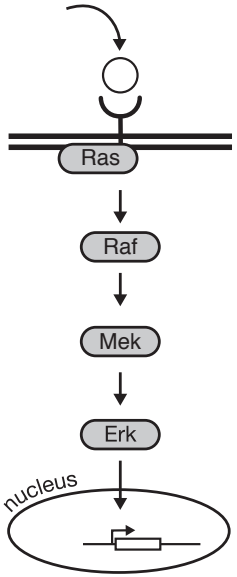
2. Why do we still get cancer?



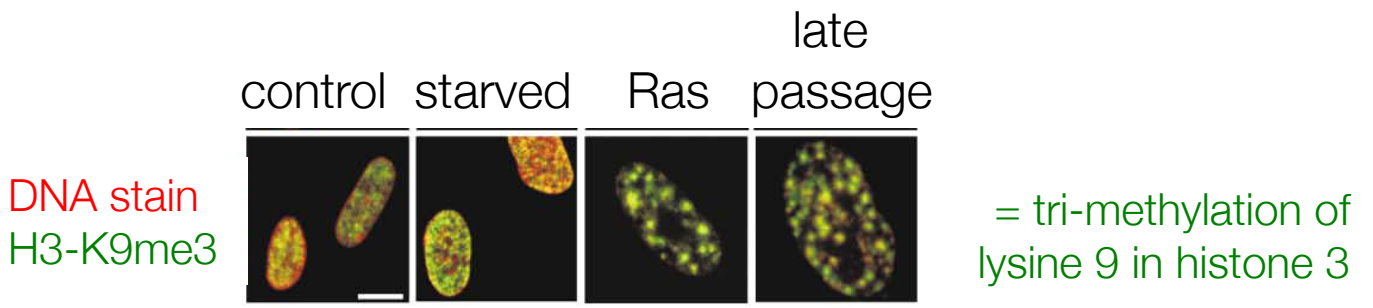


Masashi Narita et al.,Cell, 2003



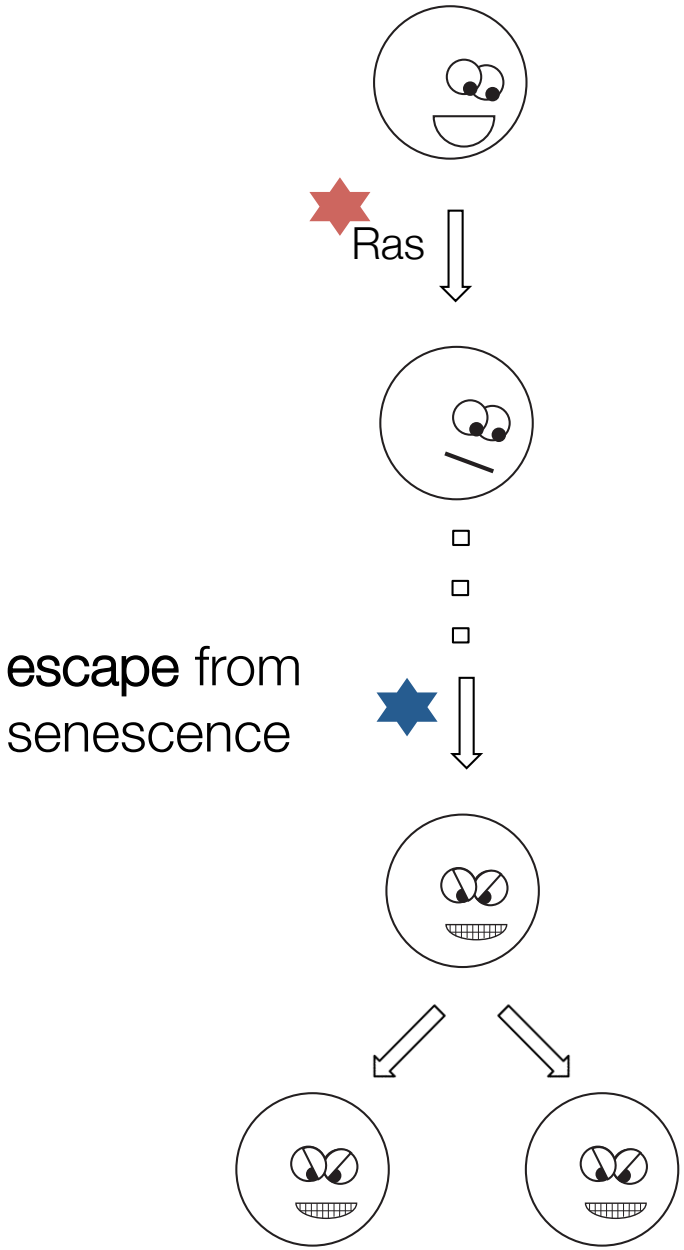


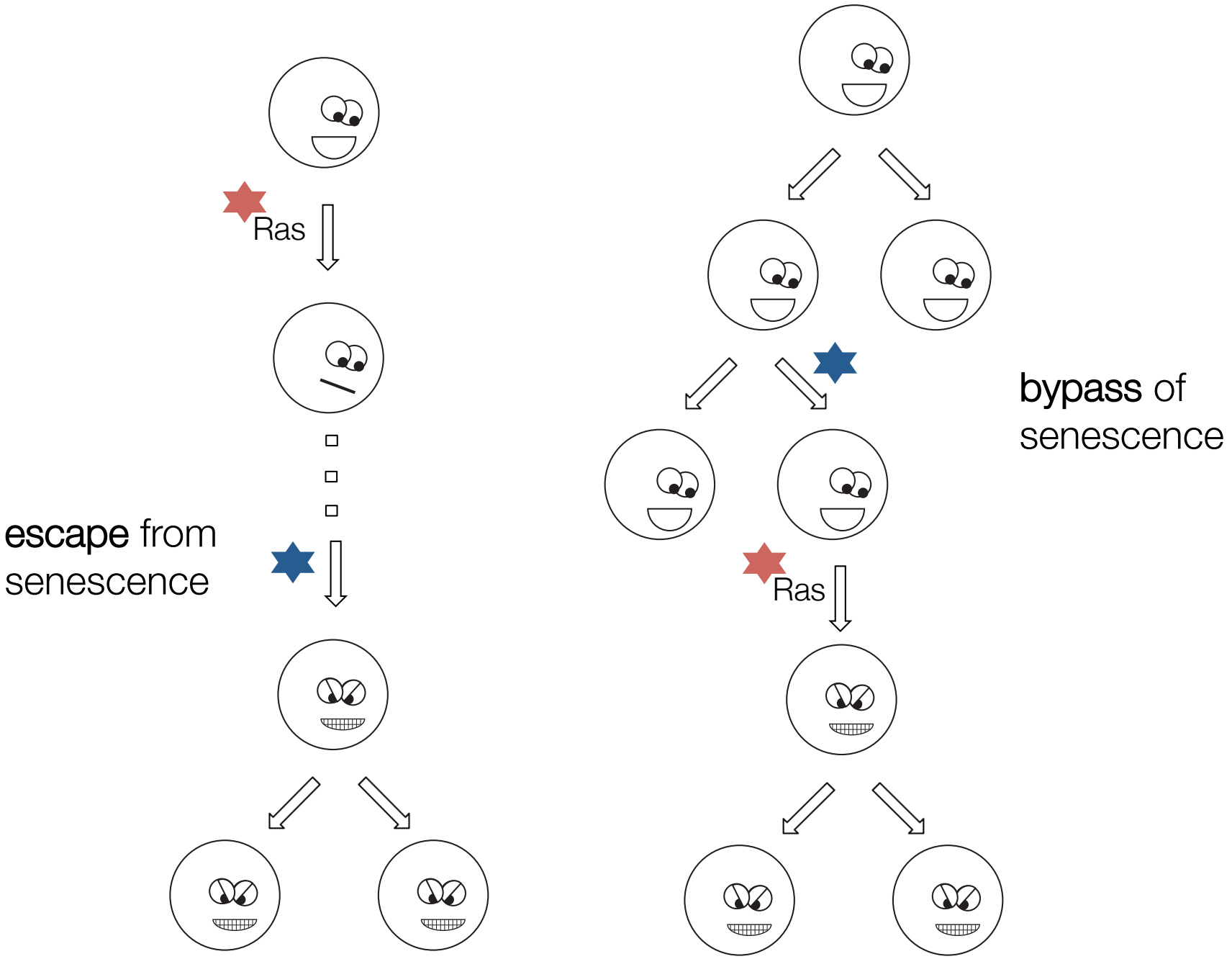
Masashi Narita et al.,Cell, 2003

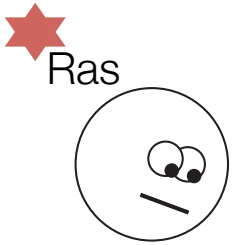


- epigenetic marks specific for senescent state
- silencing of genes required for proliferation
- methylation competes with acetylation

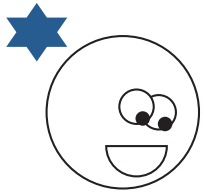
unfortunately, creating and maintaining these epigenetic marks requires other genes ...


Ras
escape from
senescence

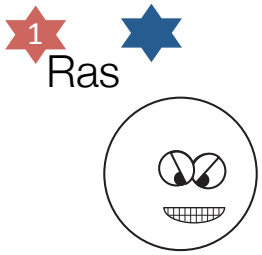

Ras
escape from senescence
Ras
bypass of senescence



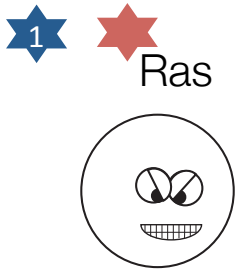
senescence



KDM4C



senescence escape



senescence bypass

RNAseq data

collaboration with
Bin Yue
from
Clemens Schmitt lab

oncogene-induced senescence ...

... is a tumour-suppressive mechanism that can be hacked