



Normal tissue tolerance to re-irradiation

Role of the stem cells and partial volume irradiation

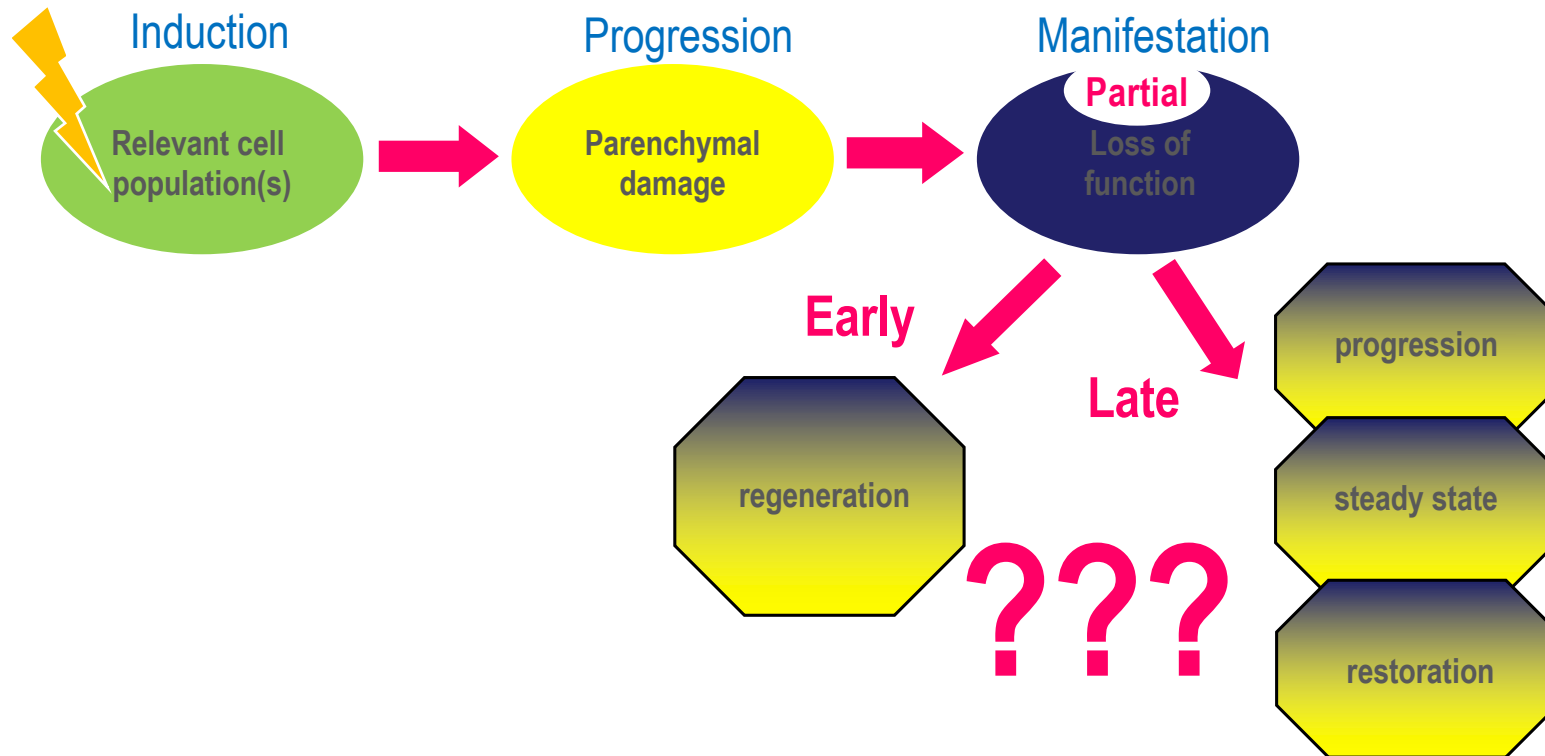
Rob Coppes

Departments of Radiation Oncology & Cell Biology
University Medical Center Groningen
University of Groningen
Groningen
The Netherlands

Workshop: Current challenges of patient re-irradiation
6-7 September 2018, Stockholm, Sweden



Pathogenesis of normal tissue radiation effects



Courtesy of W. Dörr



When retreatment?

No further treatment

- If the **radiation tolerance** within a given volume or organ has already been **exceeded** during the first treatment
- And **function** is **lost** (or loss is to be expected)

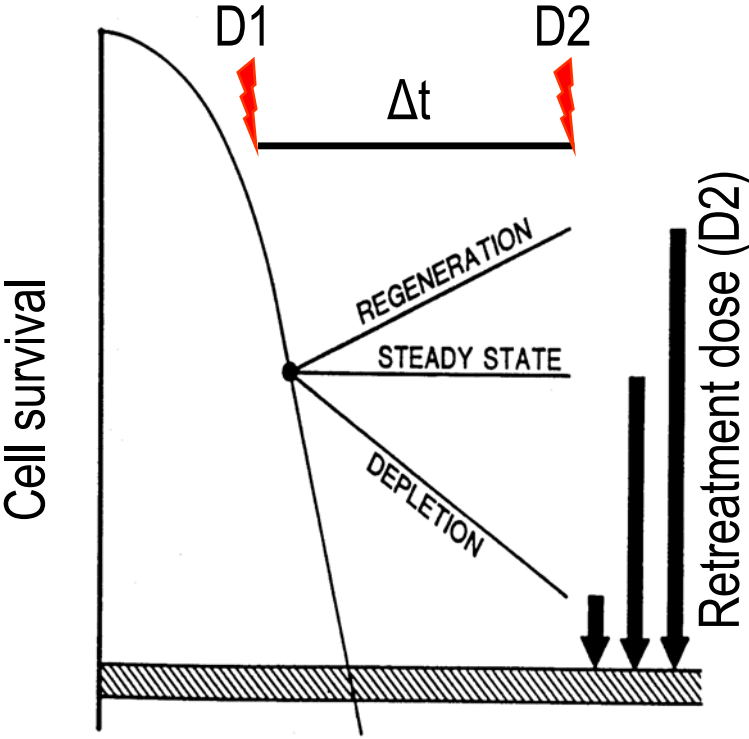
Retreatment possible

- If initial **radiation** treatment was in **subtolerance dose range**
- With the induction of only **subclinical or minimal damage**
- And with **possible long-term recovery** or **potential residual damage after longer periods**

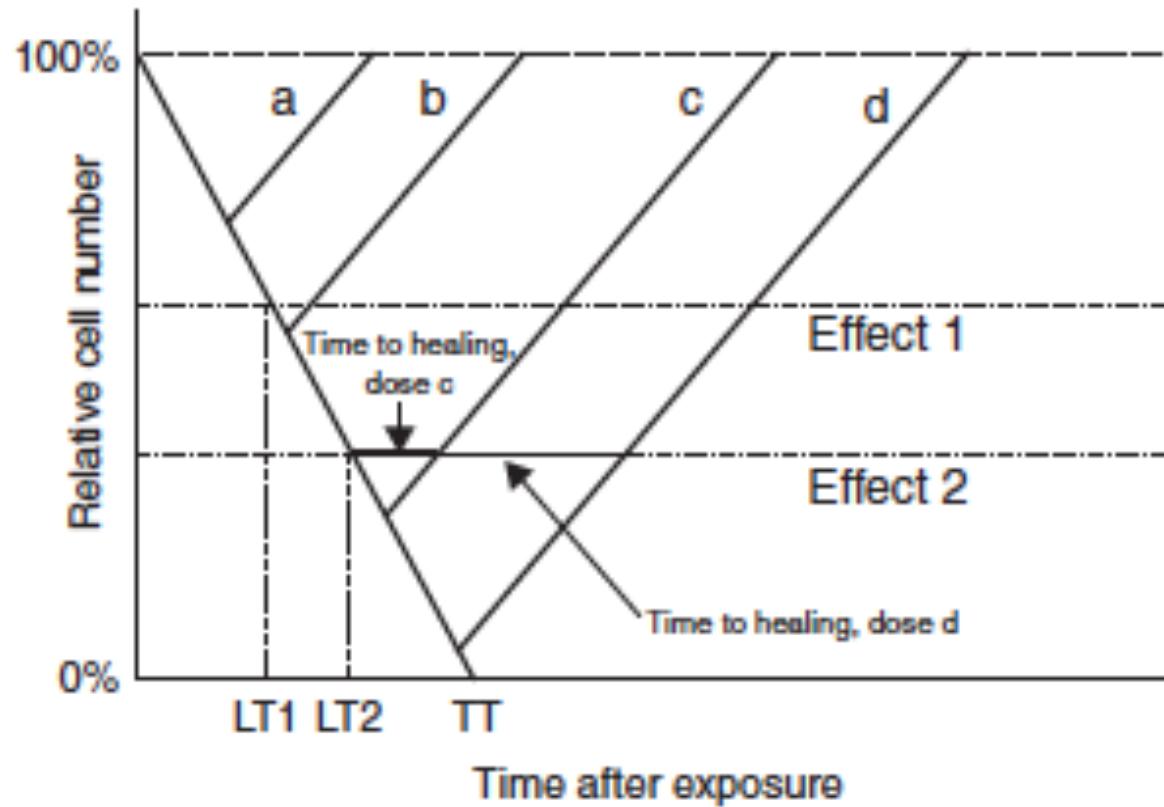
Retreatment tolerance depends on the level of cell kill and regeneration



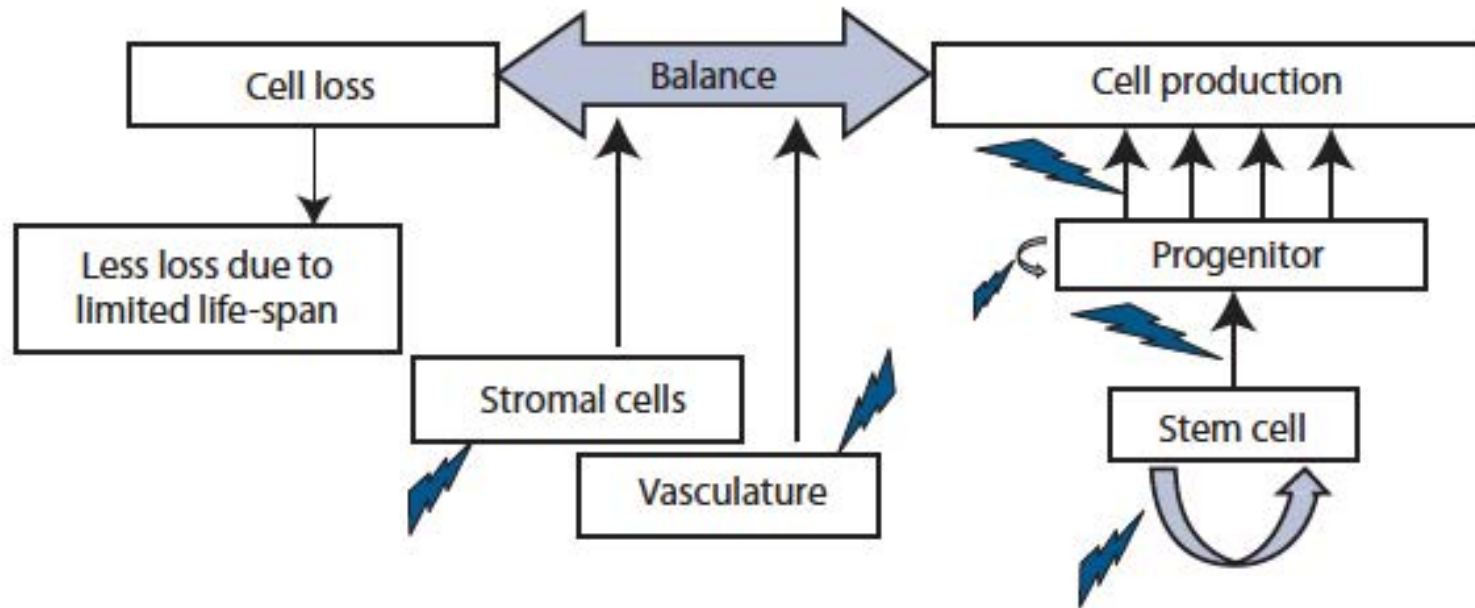
“E”
Level of cell kill
for tissue damage



Regeneration kinetics



Stem Cells and Radiation Response



Basic Clinical Radiobiology, 5th Edition,
Eds Joiner and Albert van der Kogel, Chpt
15, Stem Cells in Radiotherapy
Coppes et al. In press

What is a stem cell?

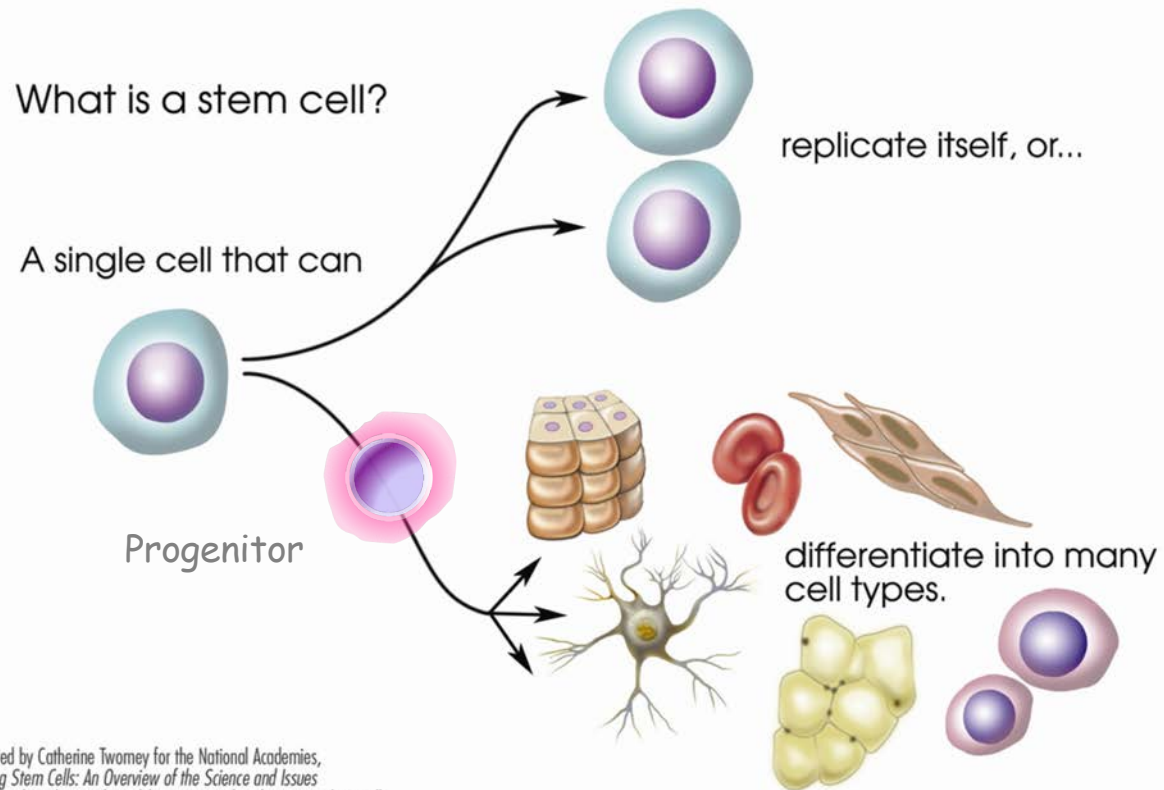
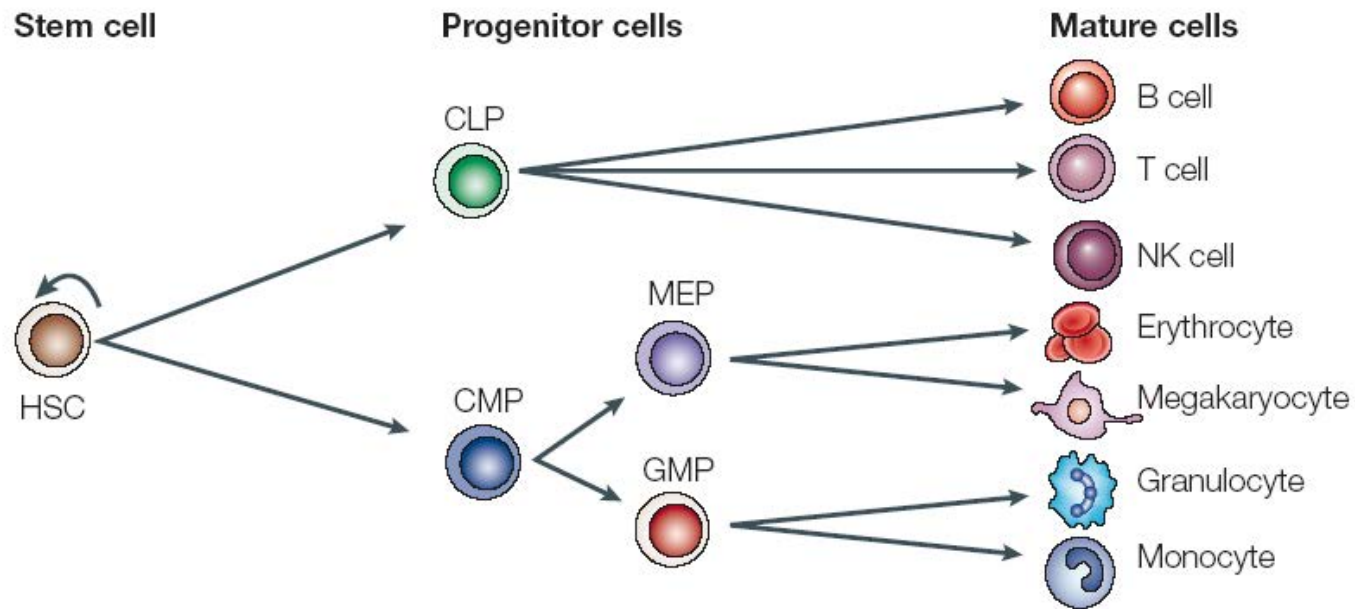


Image prepared by Catherine Twomey for the National Academies, *Understanding Stem Cells: An Overview of the Science and Issues* from the National Academies, <http://www.nationalacademies.org/stemcells>. Academic noncommercial use is permitted.

Hematopoietic Stem Cell Hierarchy

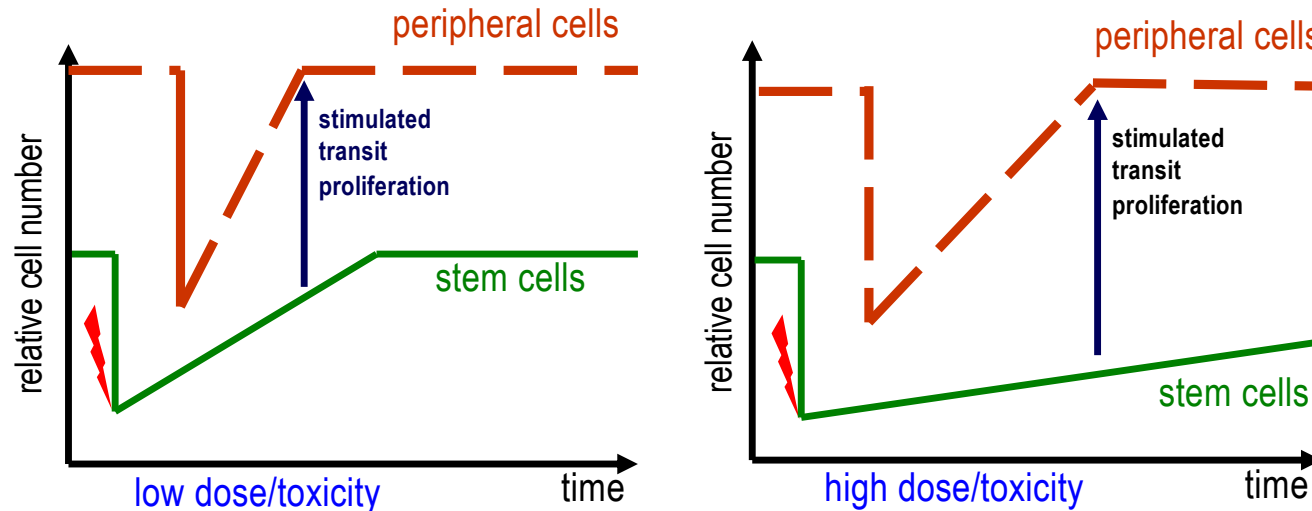


Bone marrow

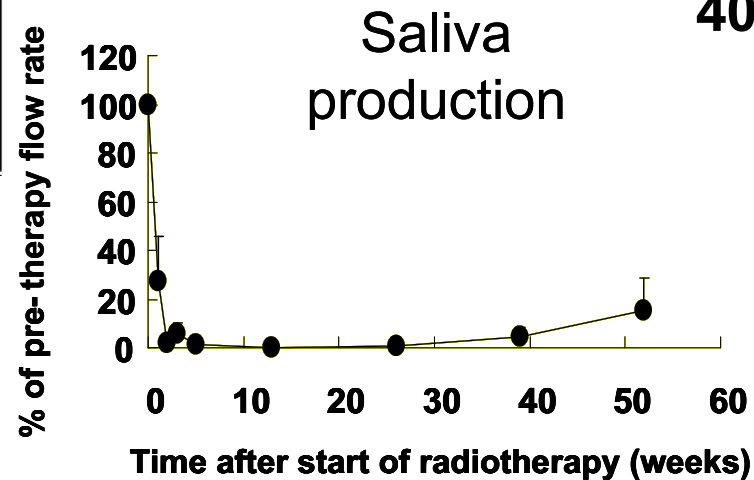
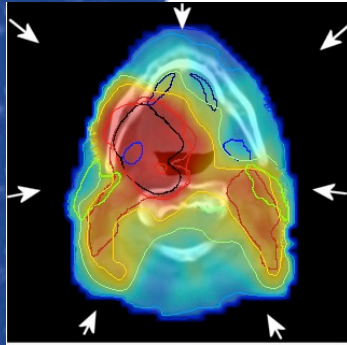


- Toxicity of initial treatment must be considered, independently of blood cell counts that may be misleading!

Earlier recovery of peripheral cell number does not reflect recovery of stem cell population (*i.e.* restoration of radiation tolerance)



Damage to salivary glands during radiotherapy of head & neck tumours



40% patients develop xerostomia

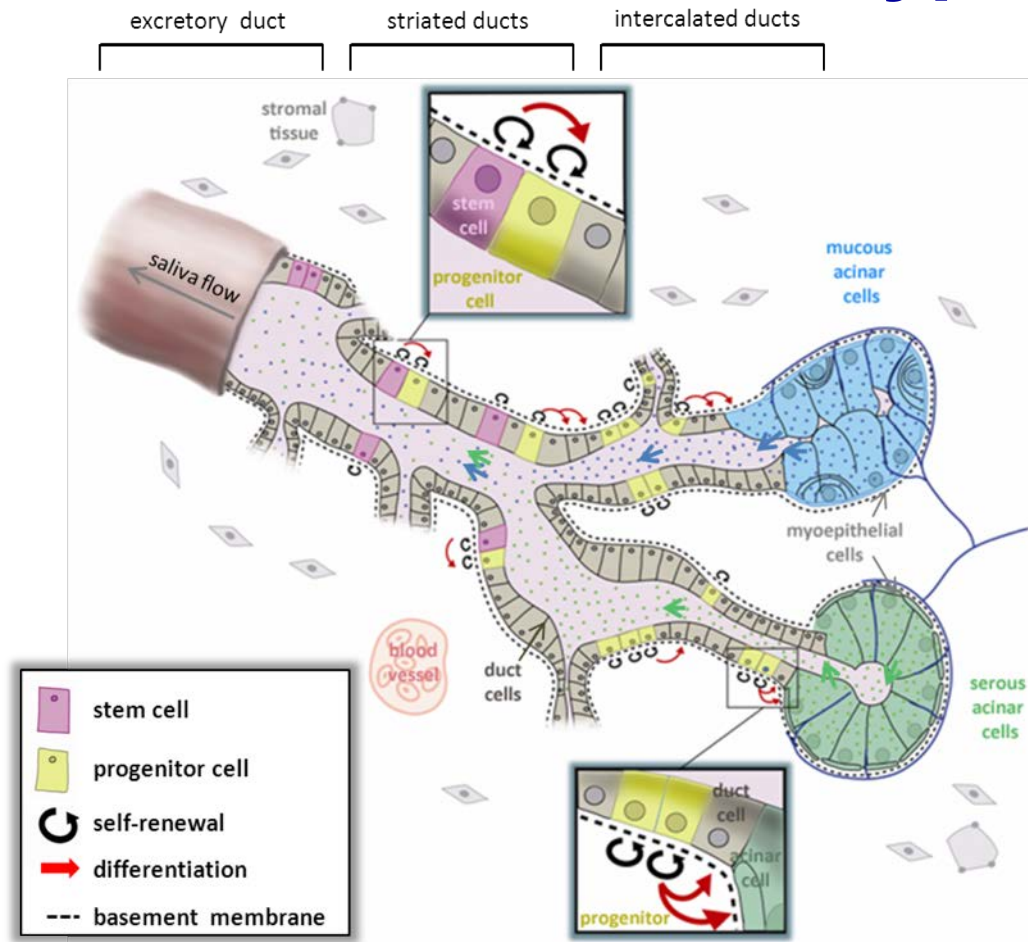
- Dryness of the mouth
- Periodontal disease
- Sleeplessness
- Continuous thirst
- Speaking difficulties
- Eating difficulties

Severe loss of quality of life

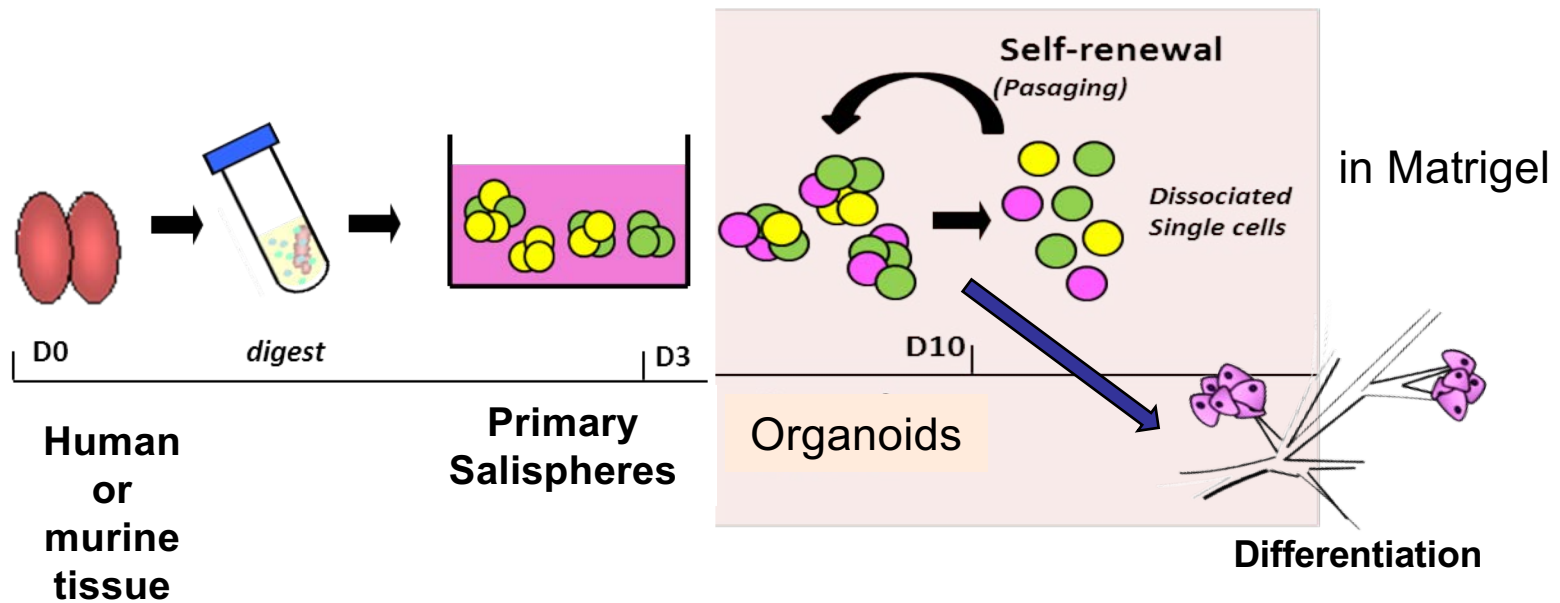
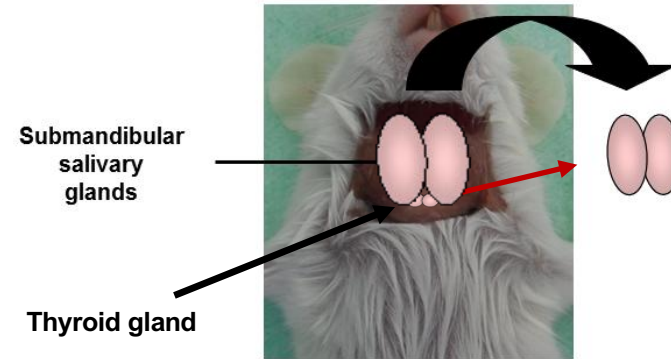
Burlage et al 2001



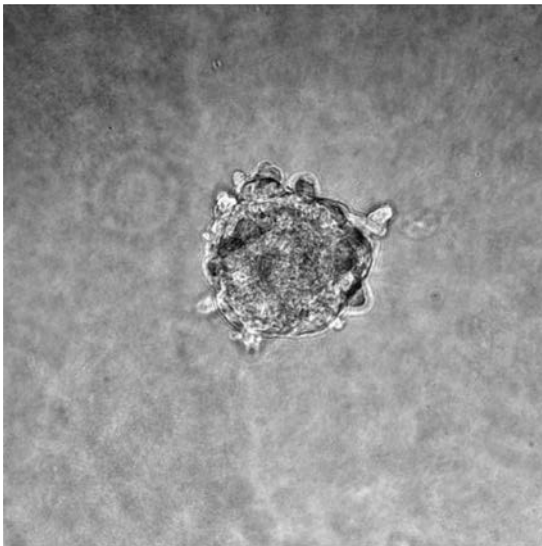
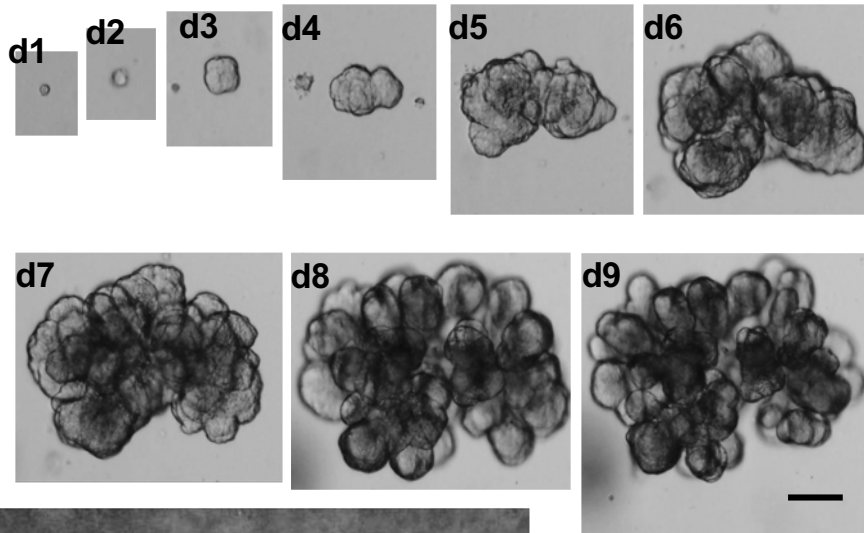
Simplified model of salivary gland and its various cell types



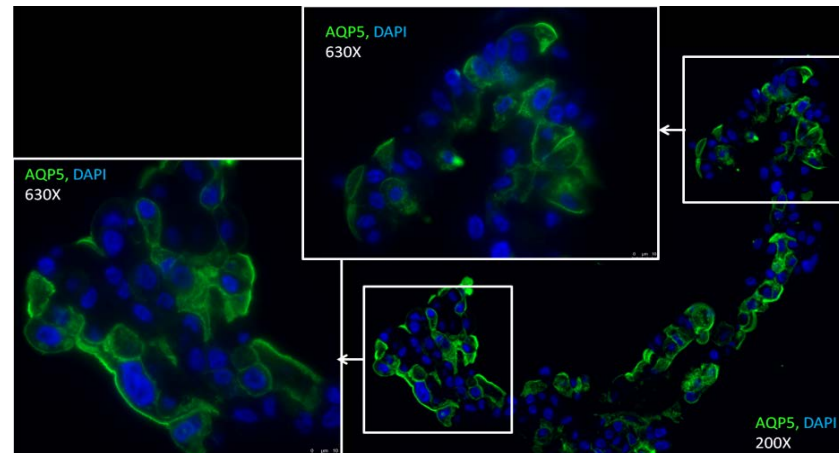
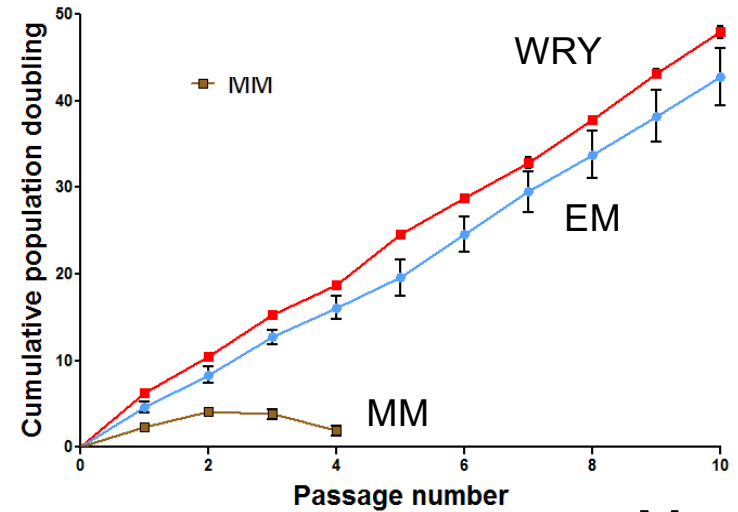
Glandular stem cell cultures



Salivary gland organoids



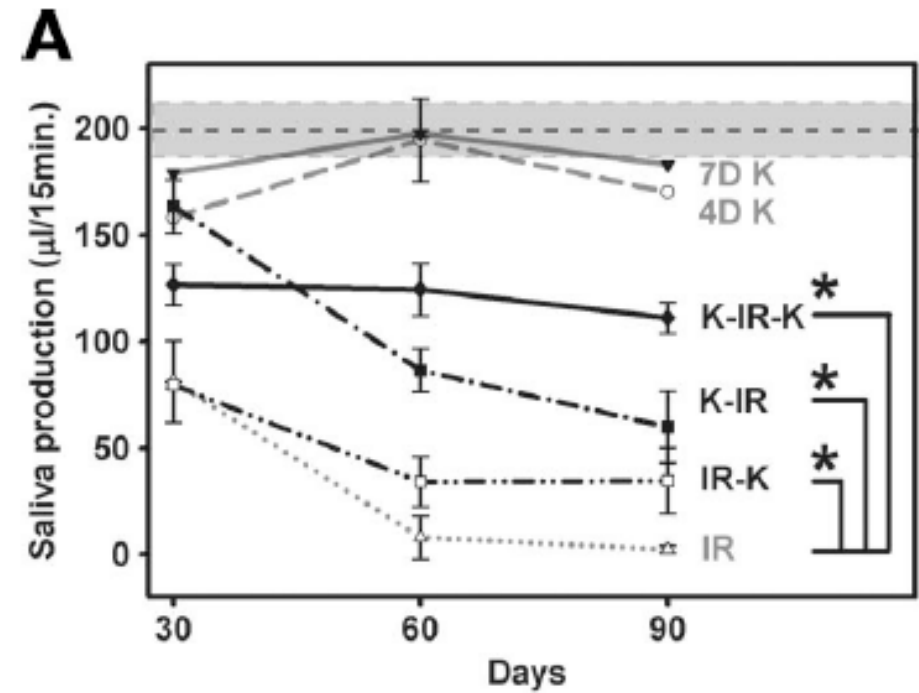
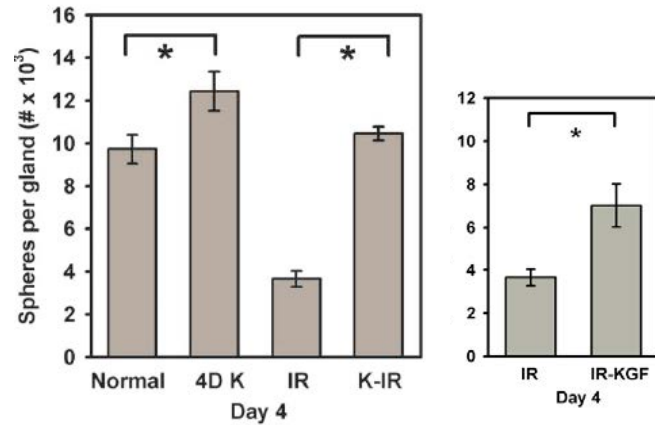
Johan de Rooij, UU



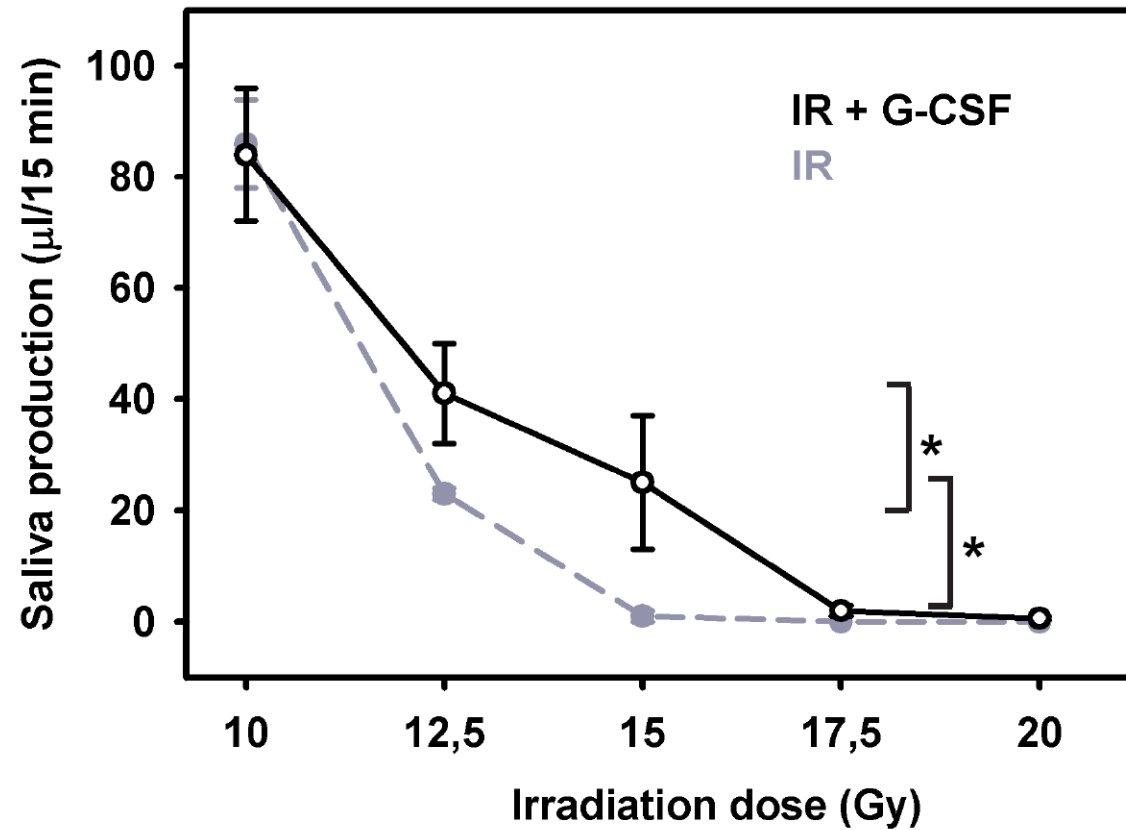
Ijsbrand Vermeu

Martti Maimets et al Stem Cell Reports 2016

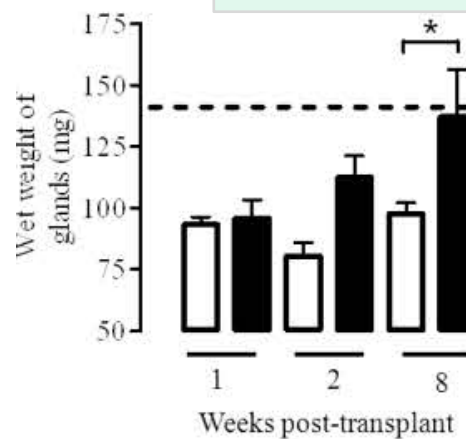
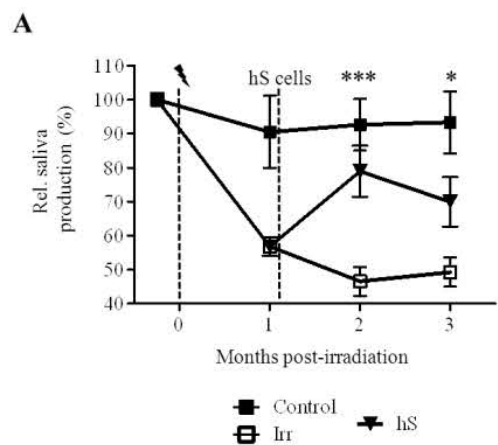
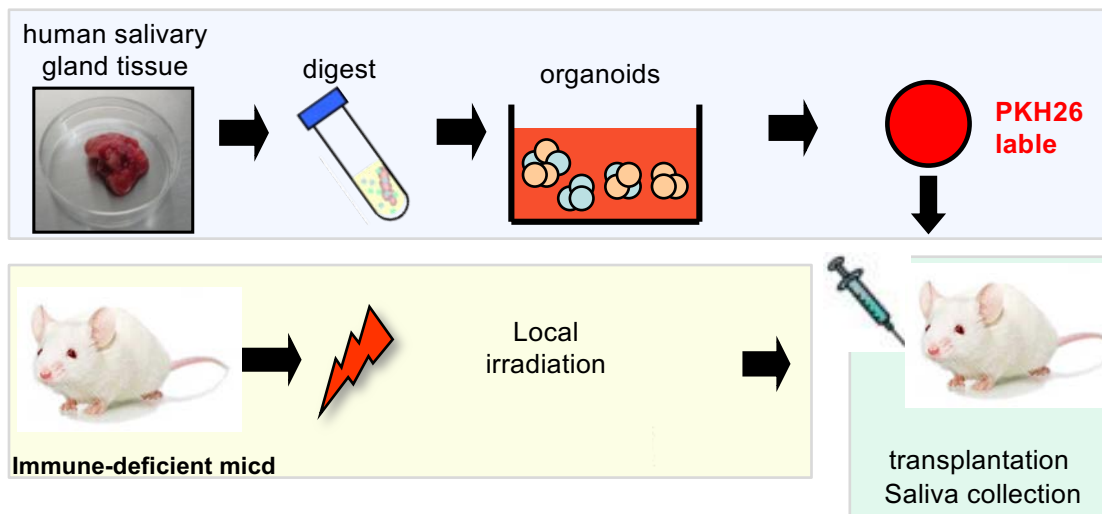
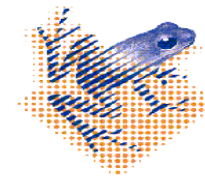
Stimulation of stem cell number using KGF (FGF7)



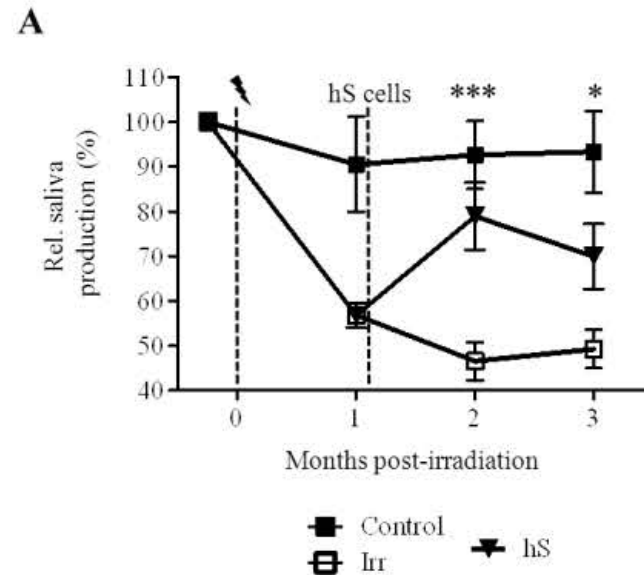
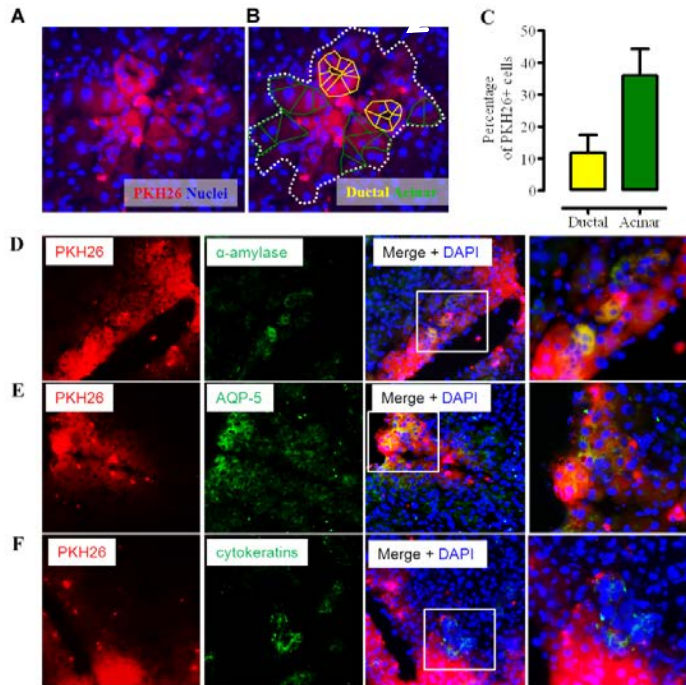
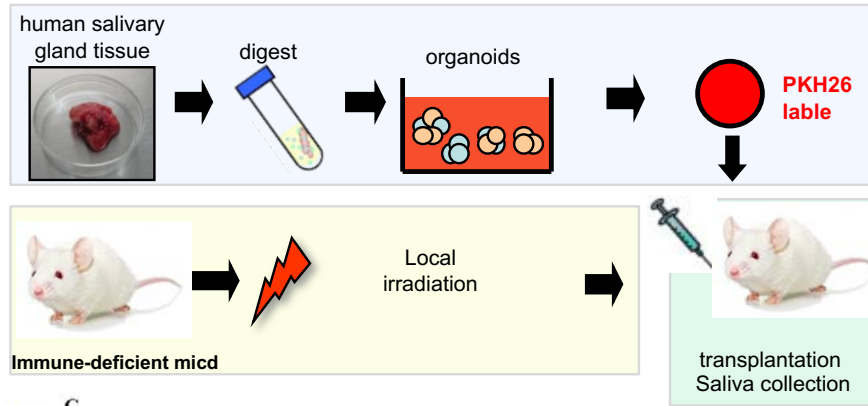
Remaining Stem cells are necessary



Xeno-transplantatie

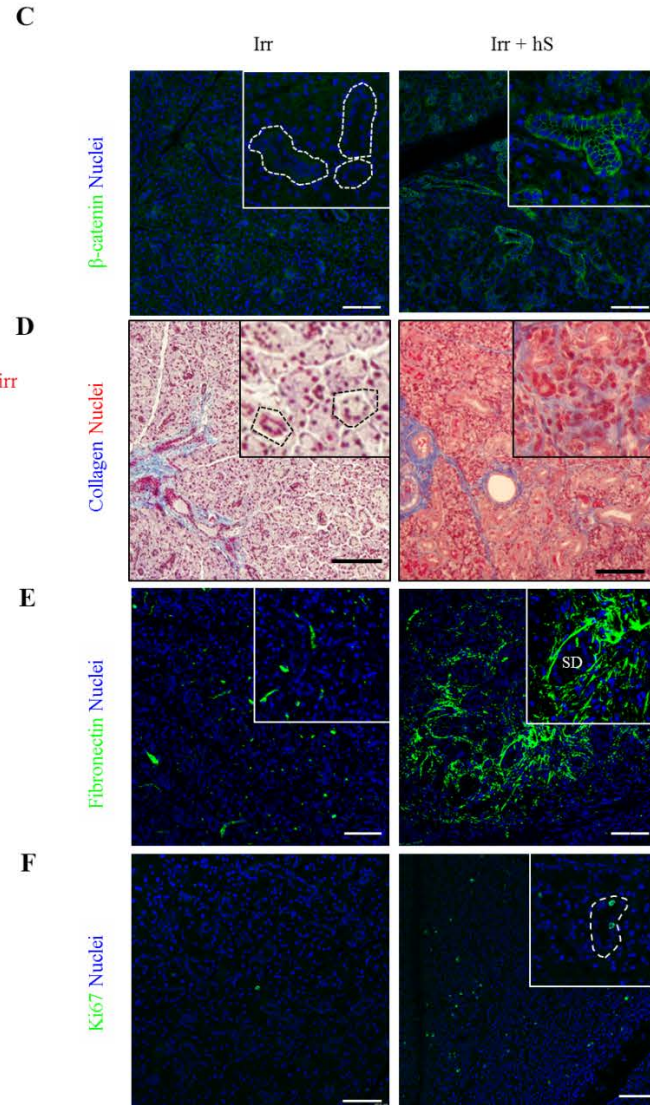
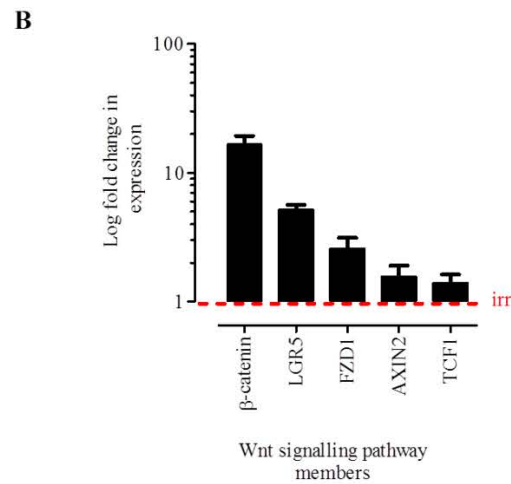
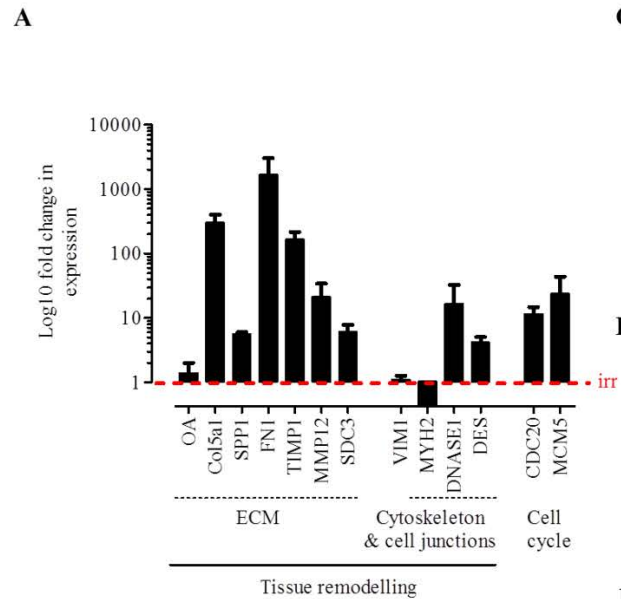


Human organoid cells restore tissue

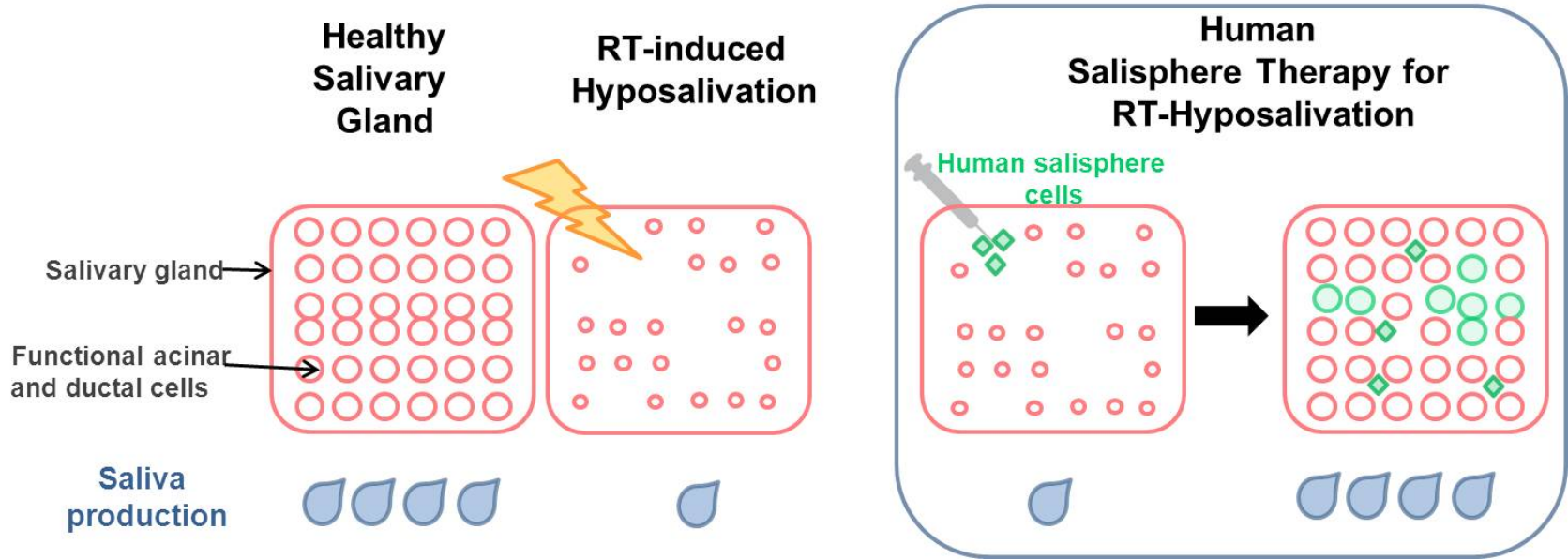




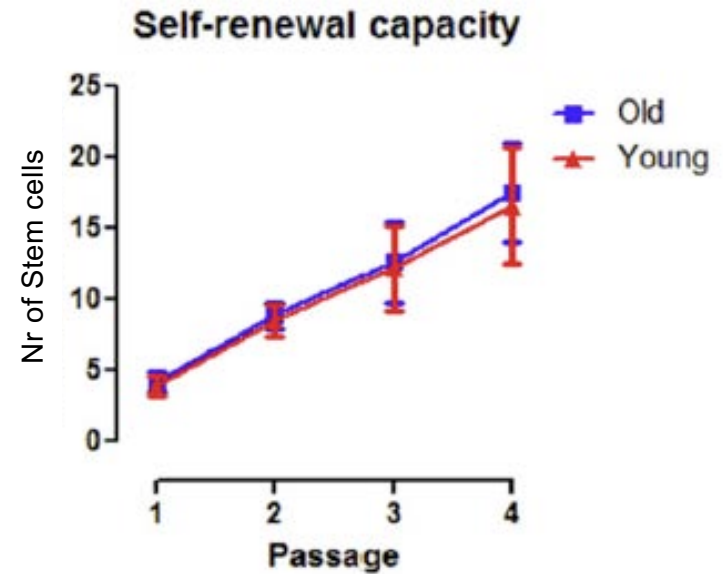
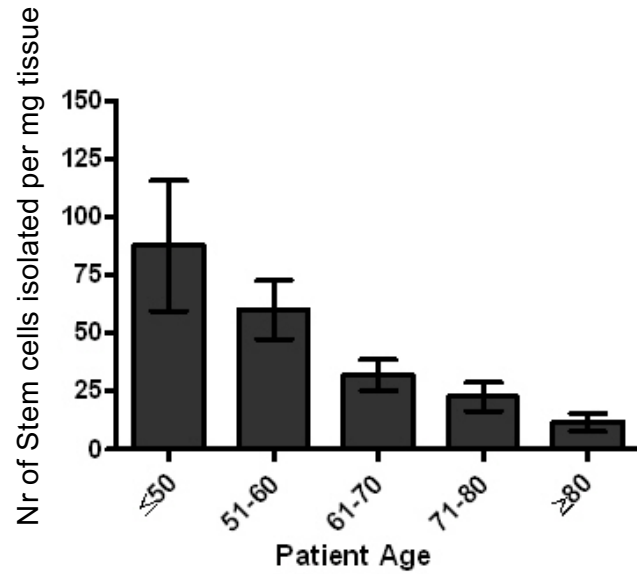
Remodeling of irradiated tissue after stem cell transplantation



Remodeling of irradiated tissue after stem cell transplantation



Stem cell number reduces with age



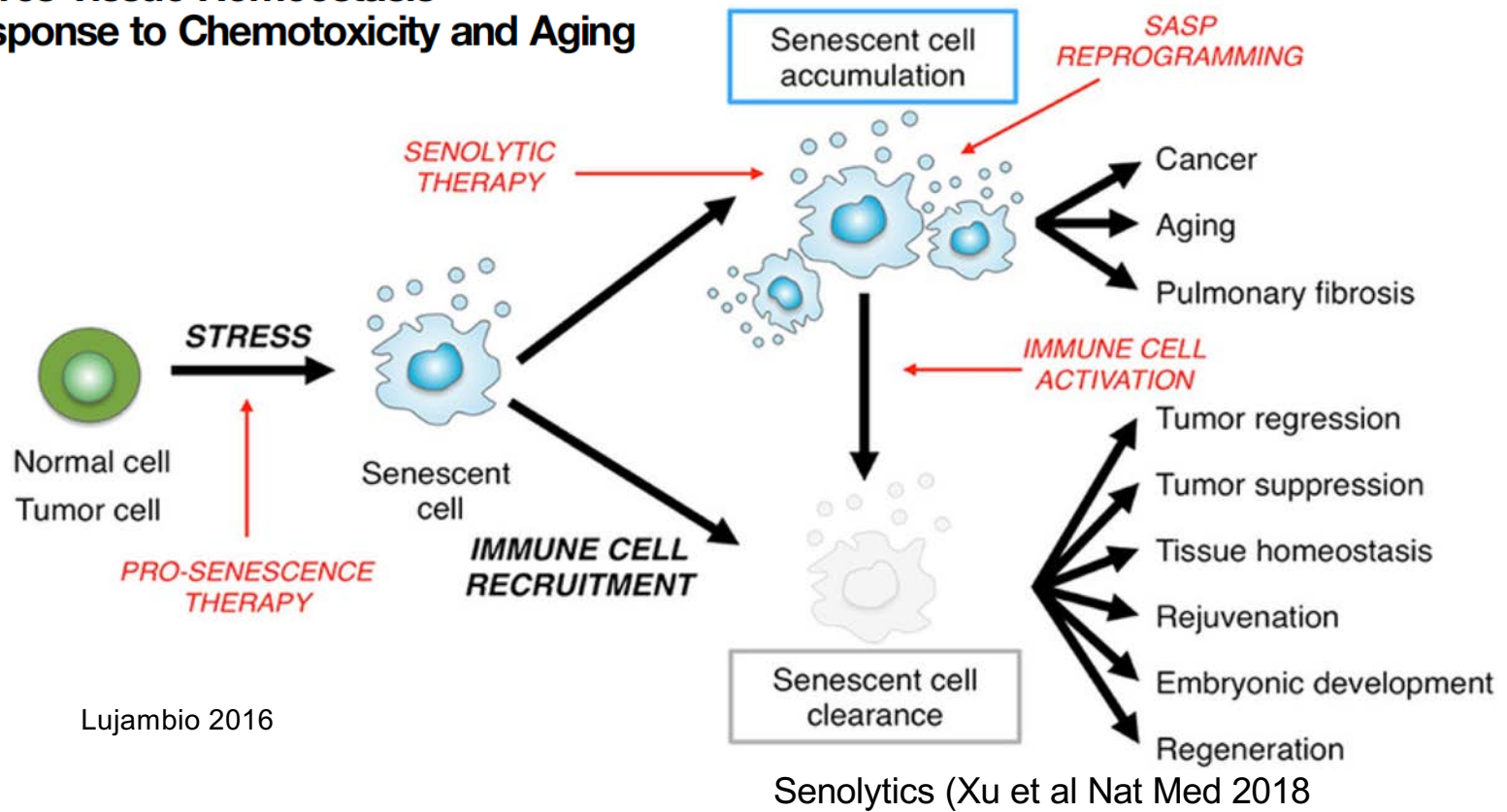
Senescence?

Removal of senescence cells expands life span

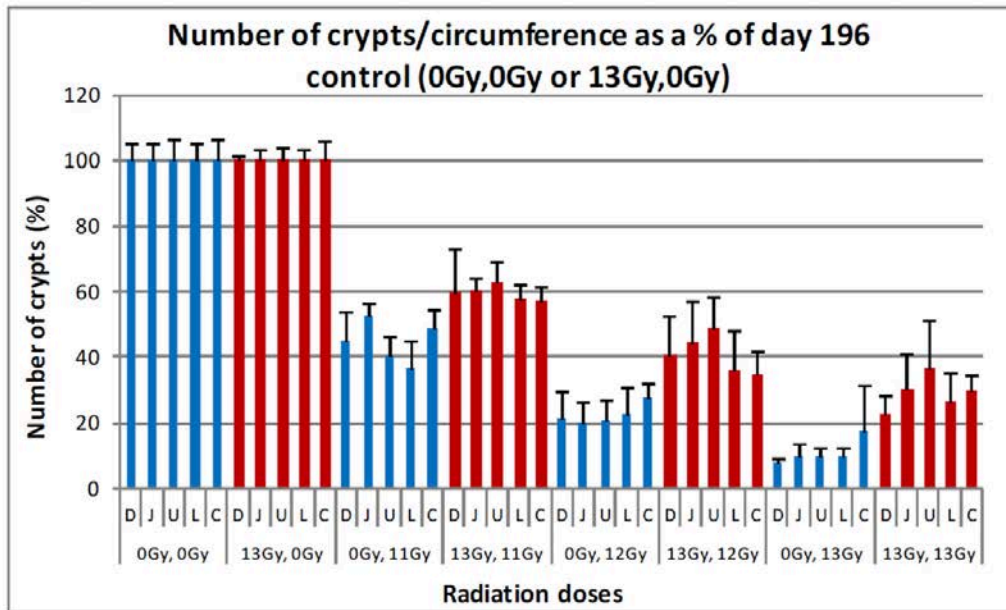
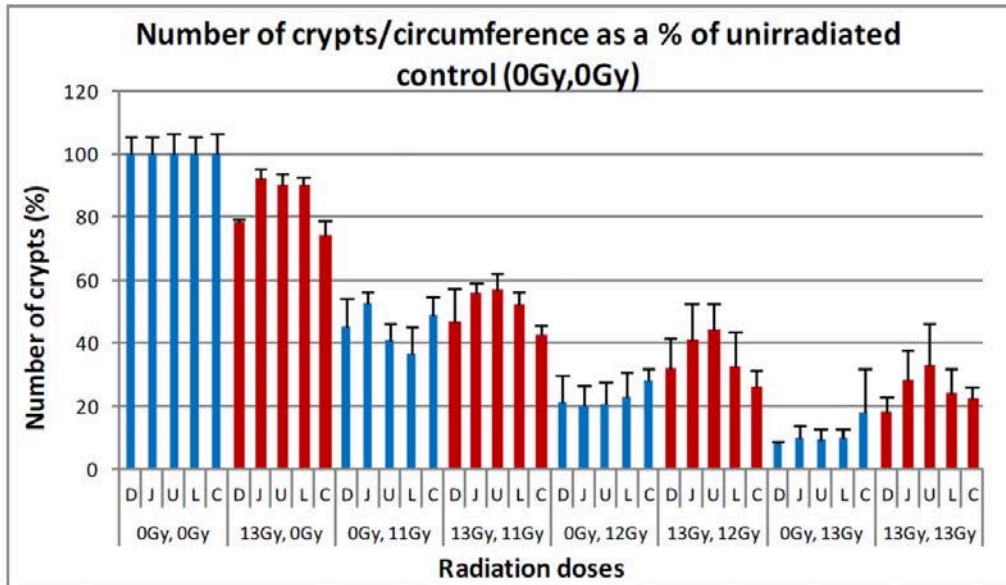
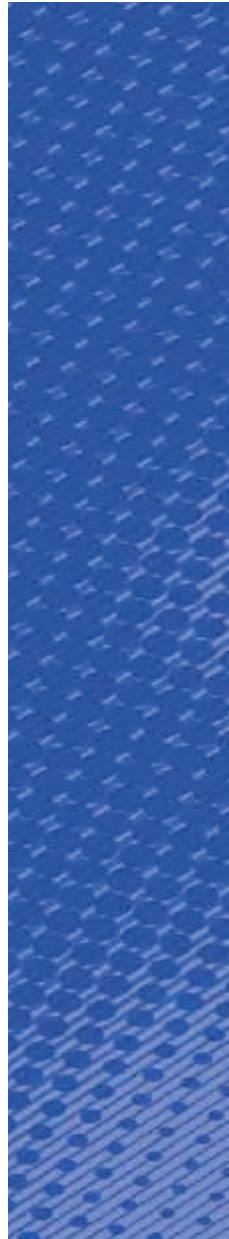


Targeted Apoptosis of Senescent Cells Restores Tissue Homeostasis in Response to Chemotoxicity and Aging

Baar et al. Cell 169, 132–147, March 23, 2017



Lujambio 2016

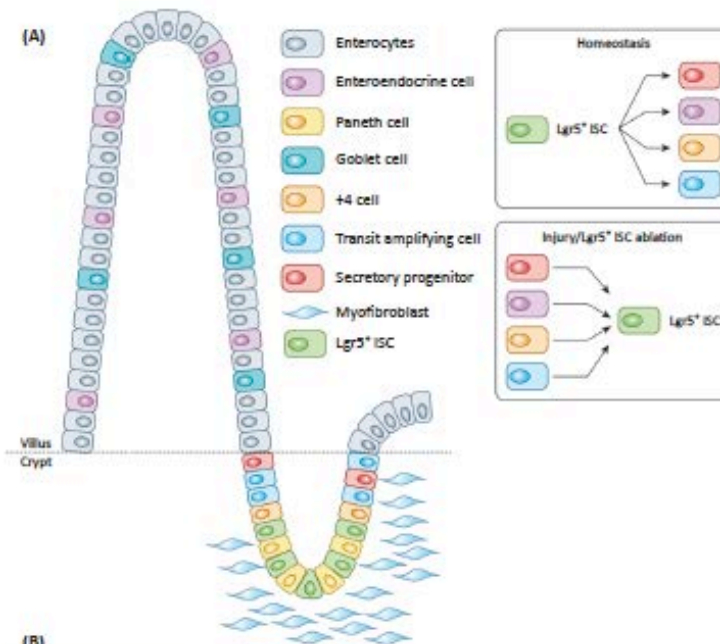


Intestinal RERT

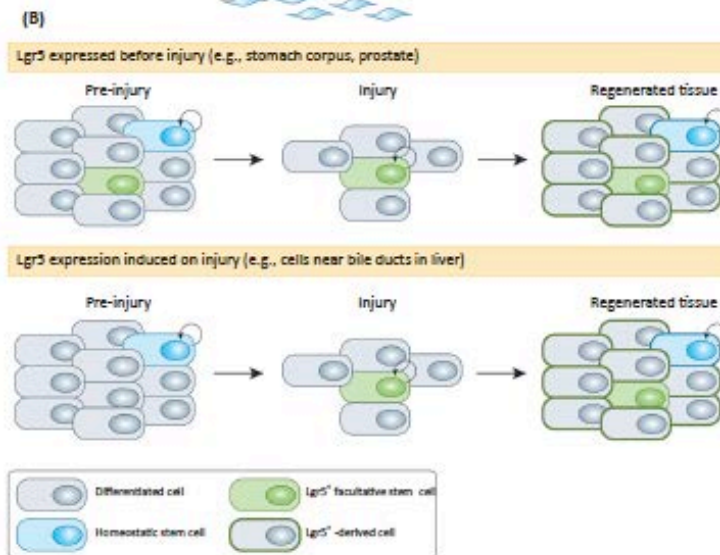


More stem cells after previous IR
or
Stem Cells become more resistant

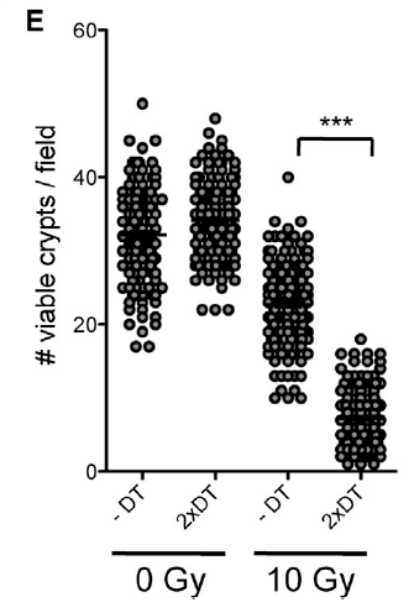
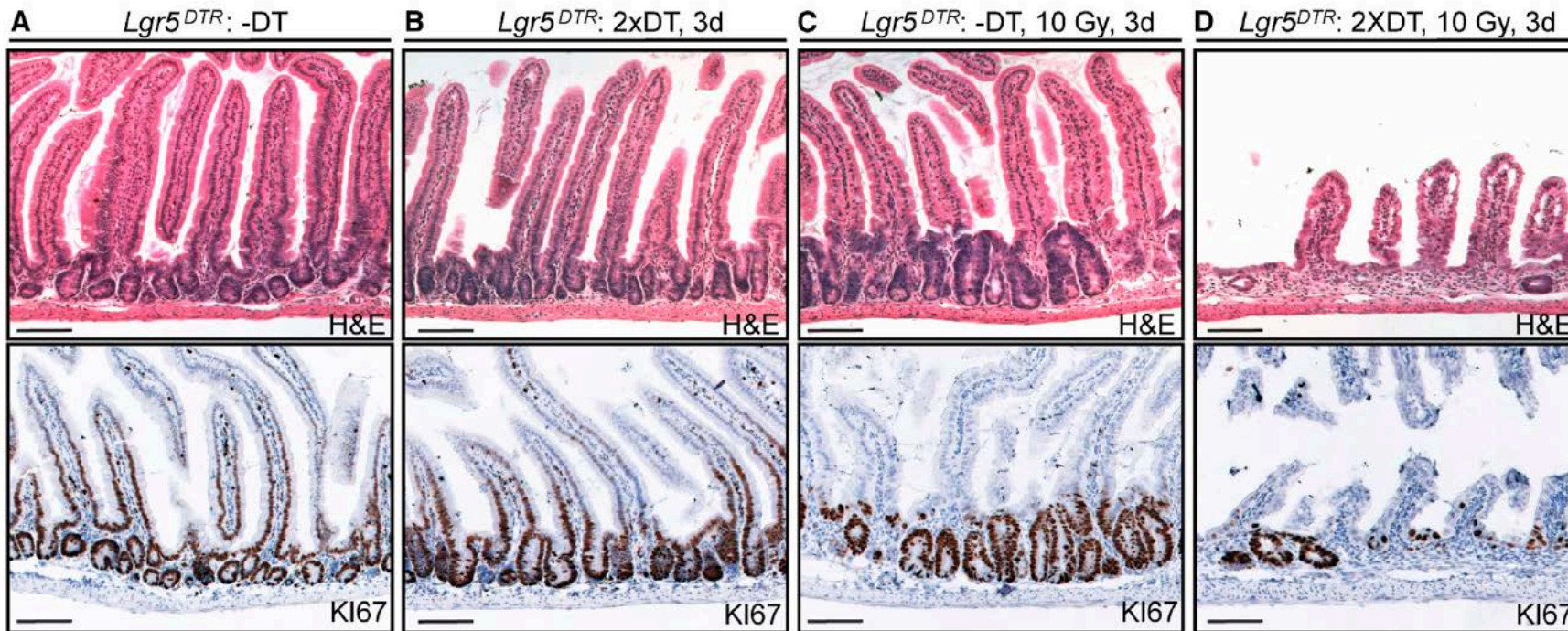
Or vasculature?



Damage dependent regeneration



Role of stem cells in homeostasis and post IR regeneration

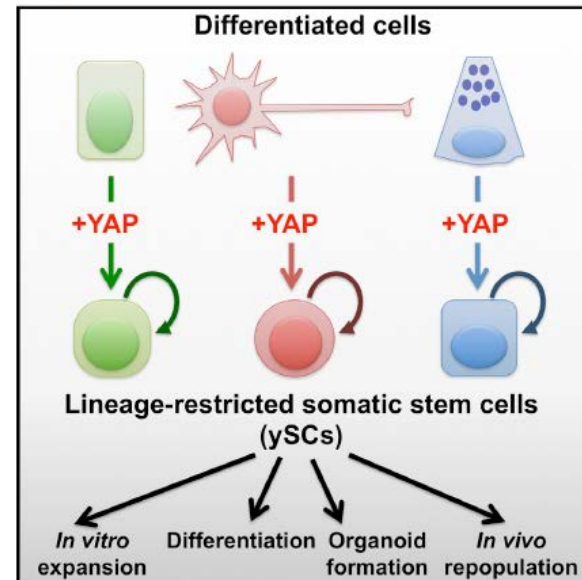




Cell Stem Cell

Induction of Expandable Tissue-Specific Stem/Progenitor Cells through Transient Expression of YAP/TAZ

Graphical Abstract



Highlights

- YAP/TAZ expression turns differentiated mammary gland cells into mammary stem cells
- YAP-induced MaSCs form organoids and have reconstitution capacity
- Induction of YAP in differentiated fetal neurons yields tripotent neural stem cells
- Pancreatic exocrine cells are also converted to progenitors by YAP expression

Authors

Tito Panciera, Luca Azzolin, Atsushi Fujimura, ..., Antonio Rosato, Michelangelo Cordenosi, Stefano Piccolo

Correspondence

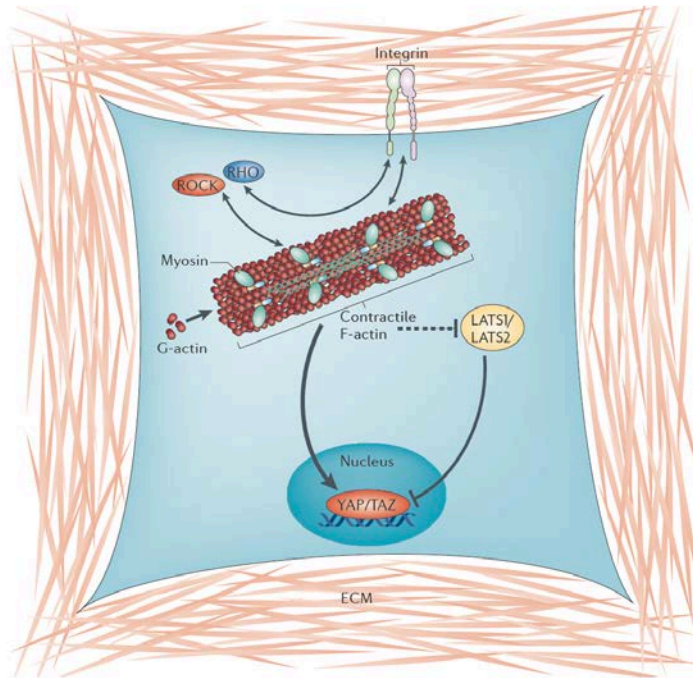
piccolo@bio.unipd.it

In Brief

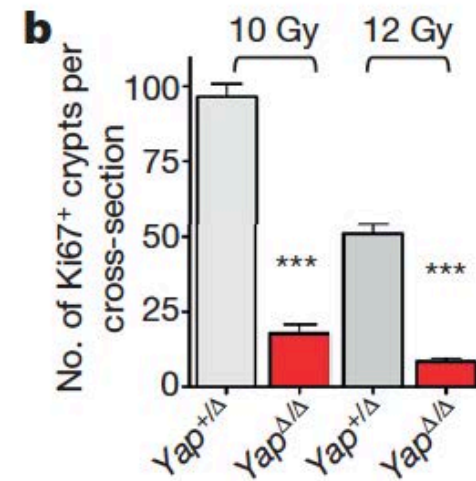
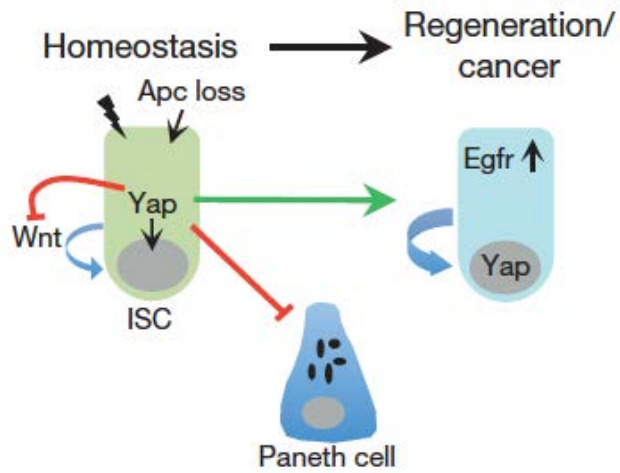
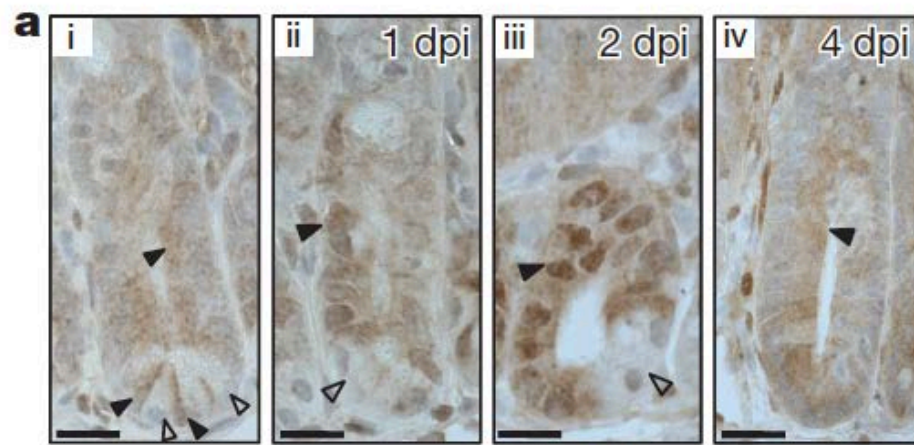
Reprogramming and lineage conversions have highlighted the plasticity of differentiated cell states. Here Panciera et al. build on these principles by showing that expression of YAP/TAZ can convert a range of differentiated cells into somatic stem cells of the same tissue, respecting lineage restrictions.

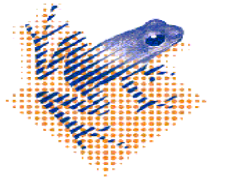
Accession Numbers

GSE70174



From Halder, Dupont, Piccolo 2012

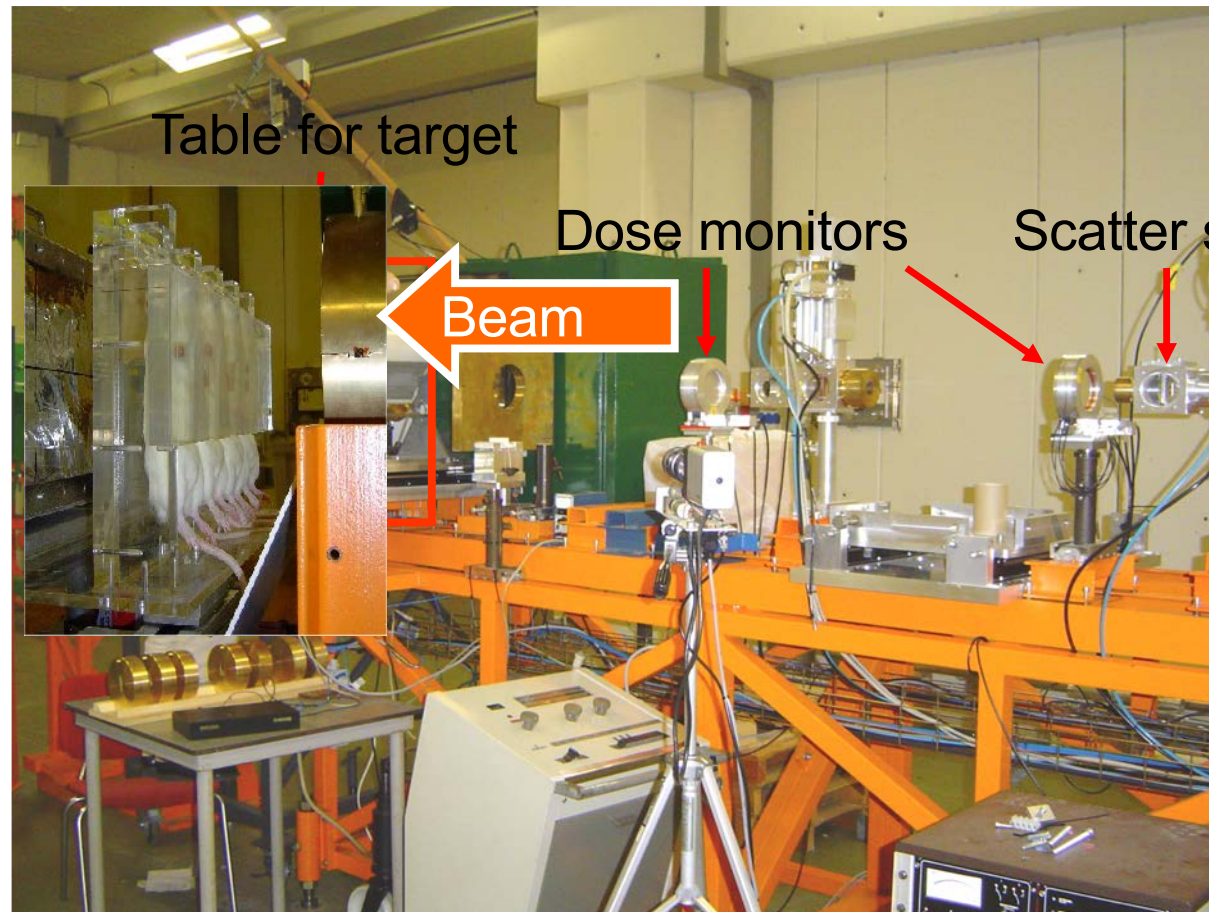




Some thoughts about post-IR regeneration

Role of inhomogenous dose deliveries and subtolerance doses

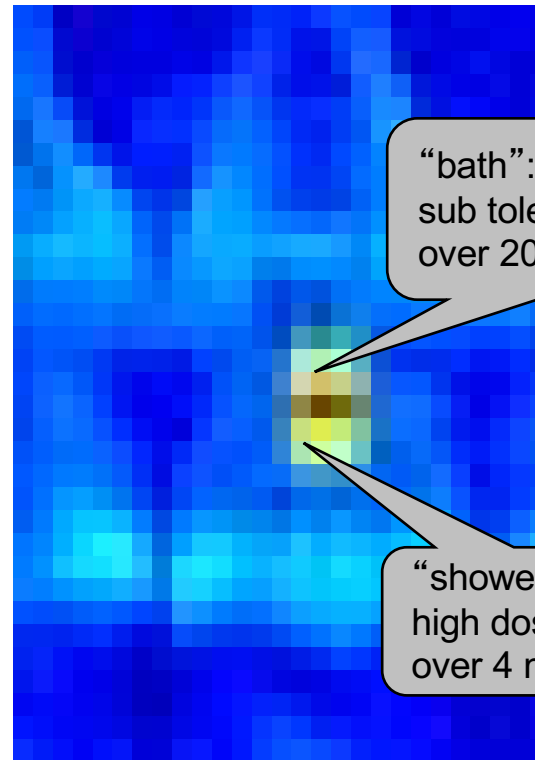
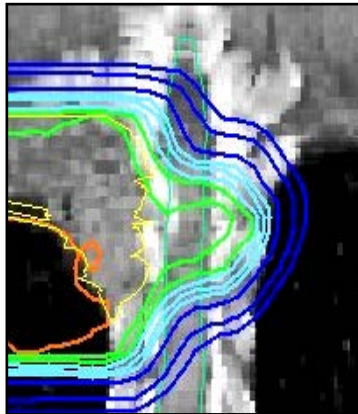
Proton irradiation setup at KVI-CART Groningen



Inhomogeneity in dose distributions *spinal cord*



jan 2000, 20 mm+4 mm field superimposed on picture



20 mm alone =
21 Gy

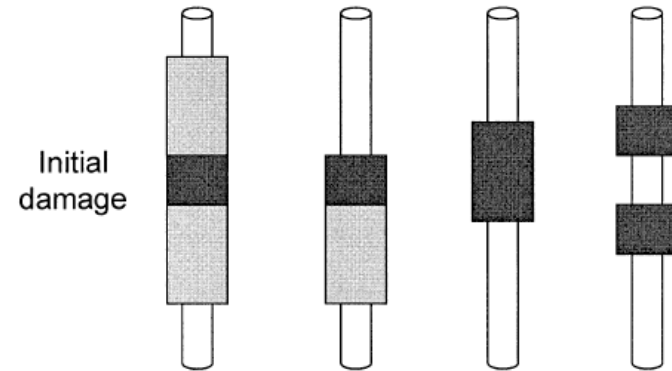
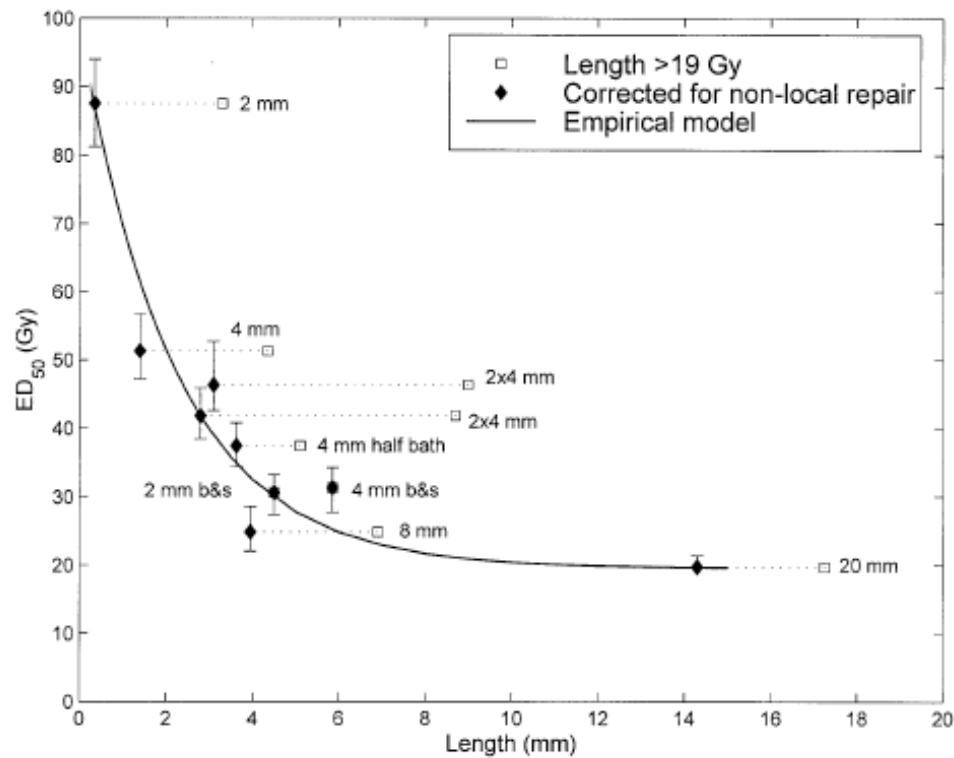
“bath”:
sub tolerance dose
over 20 mm

4 mm + subtolerance
“bath” dose = 31 Gy

“shower”:
high dose
over 4 mm

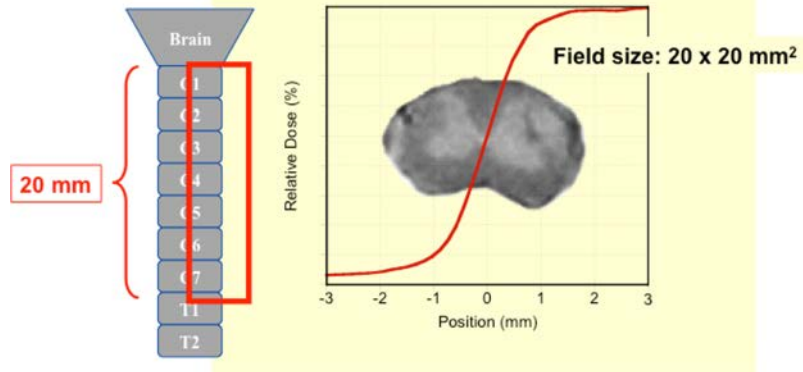
4 mm alone = 53 Gy

Regeneration also depends on volume of below thresholds doses

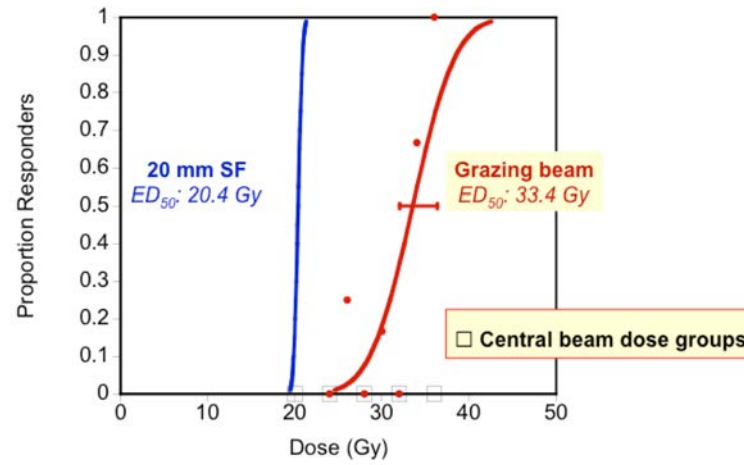
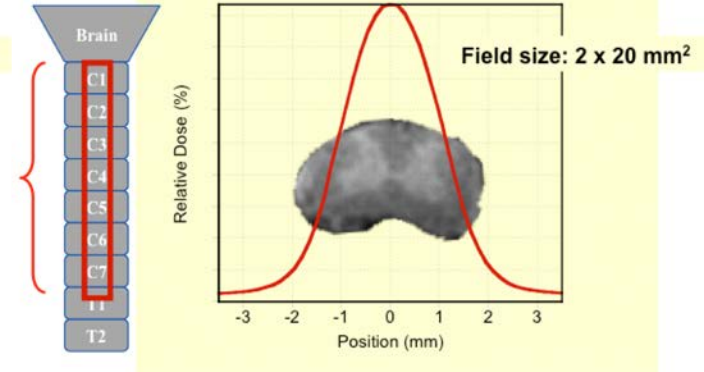




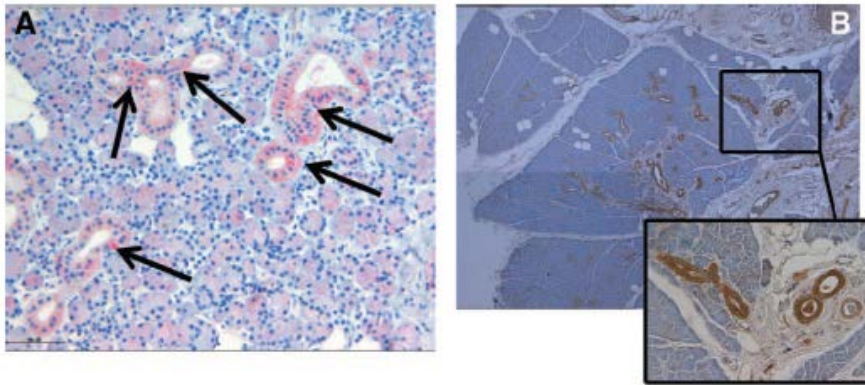
- High precision proton beam (150 MeV)
- Type 1: Grazing beam (20-40 Gy)



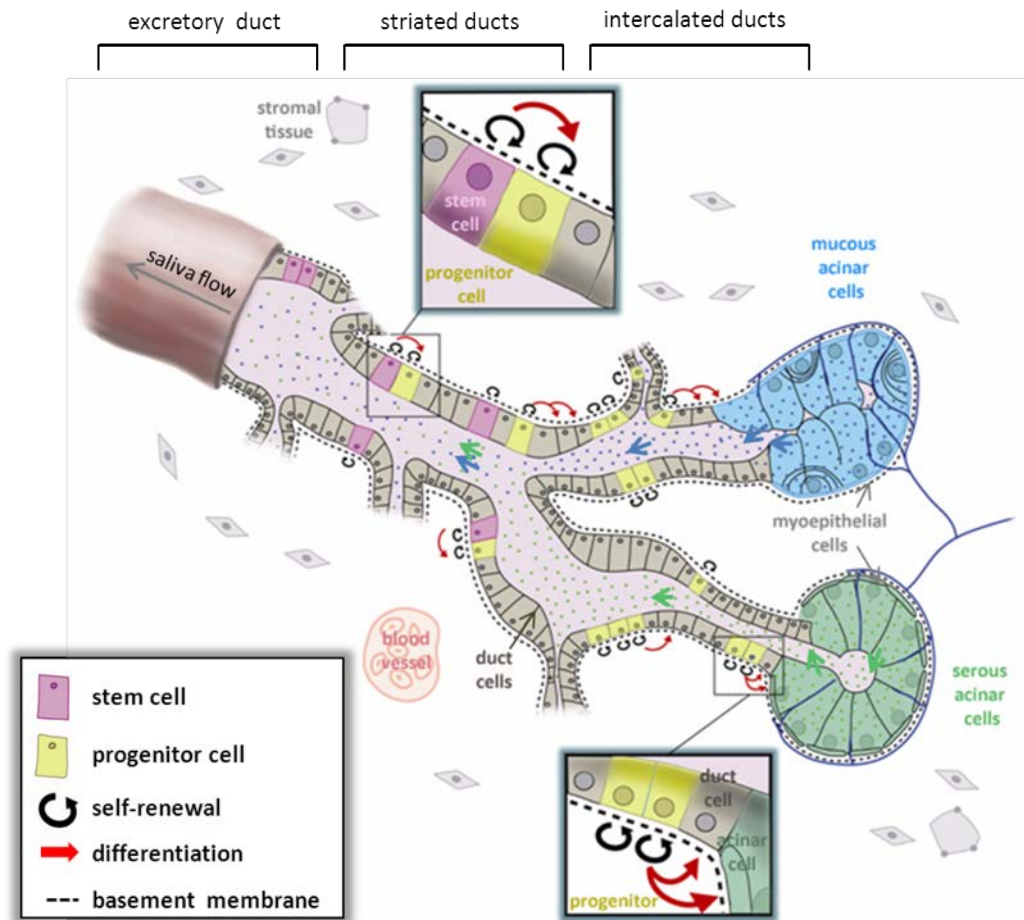
- Type 2: Central beam (20-36 Gy)



Role of stem cells in salivary gland radiation response

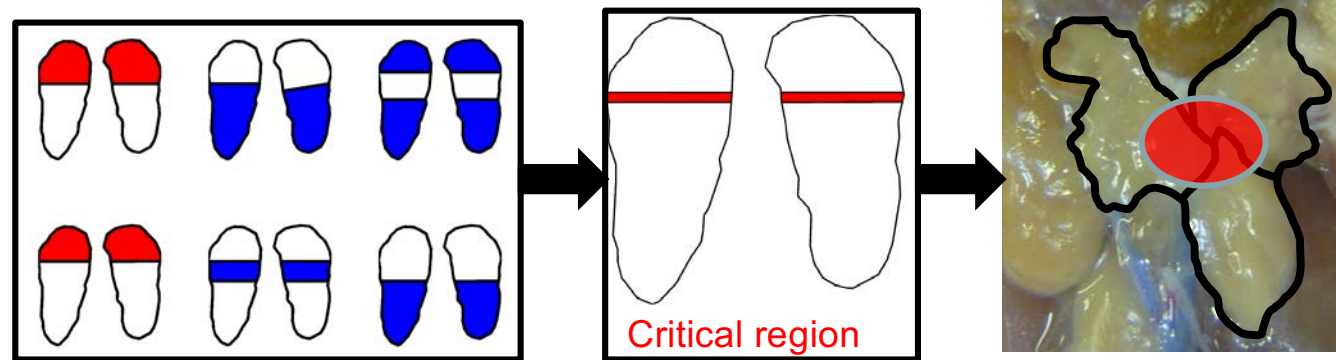
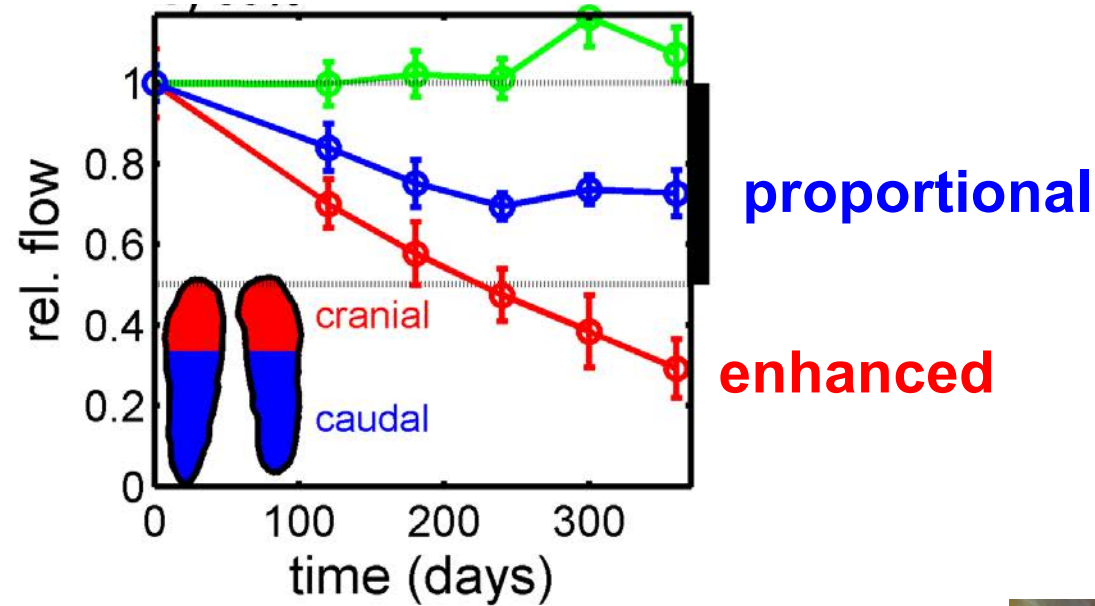


Van Luijk et al Science Translational Medicine 2015



Pringle et al., Stem Cells 2013

Stem cell localization



Rat morphology



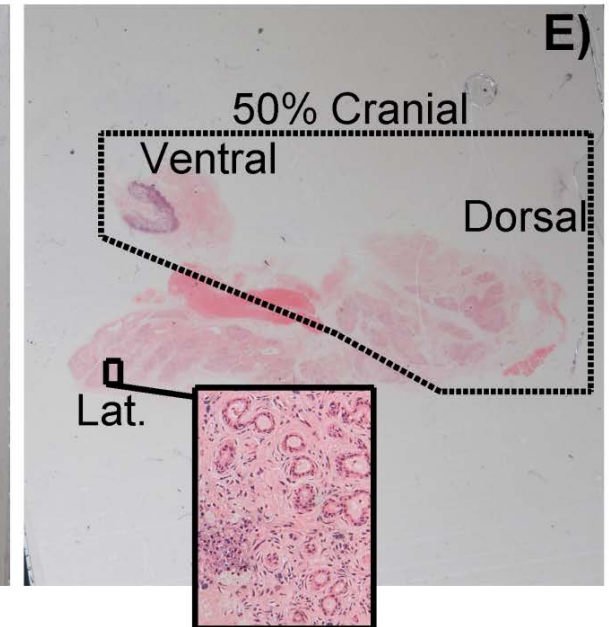
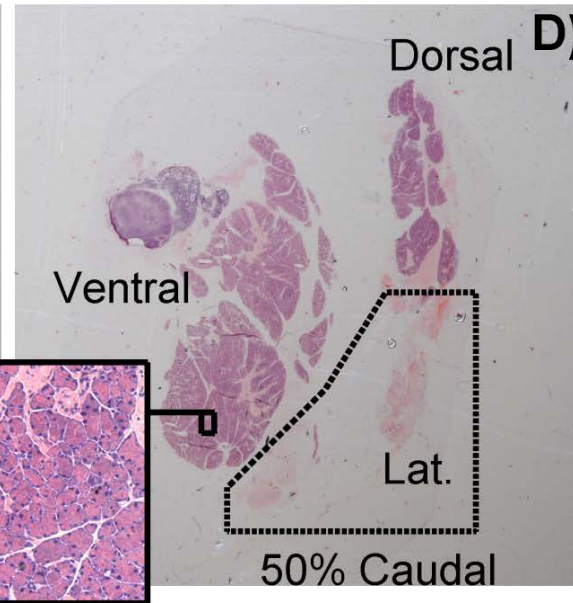
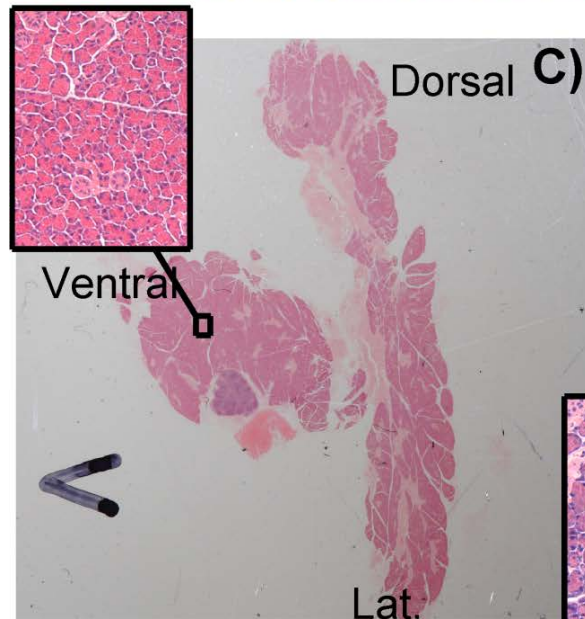
Control

50% Caudal

50% Cranial

spare critical region

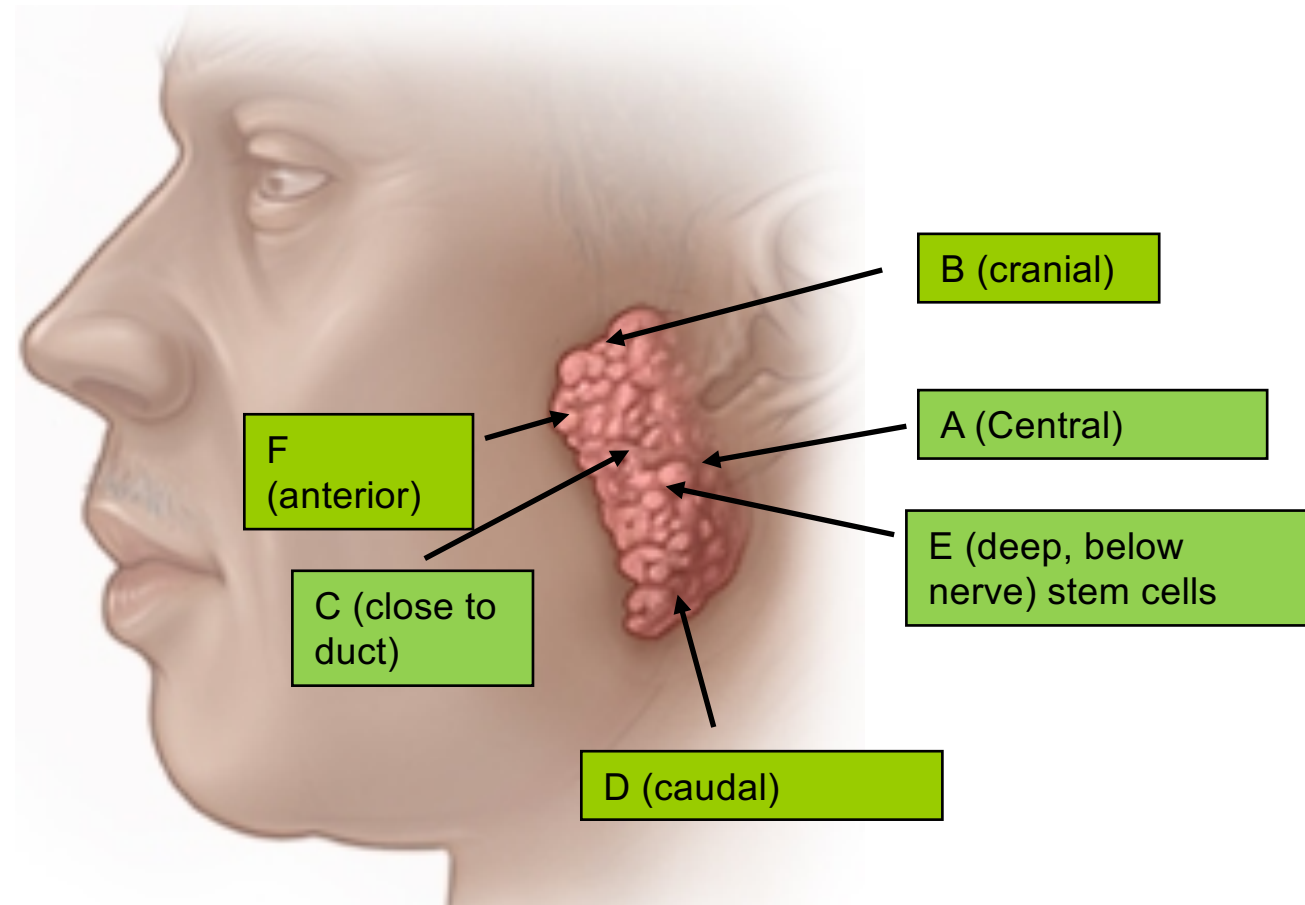
irradiate critical region



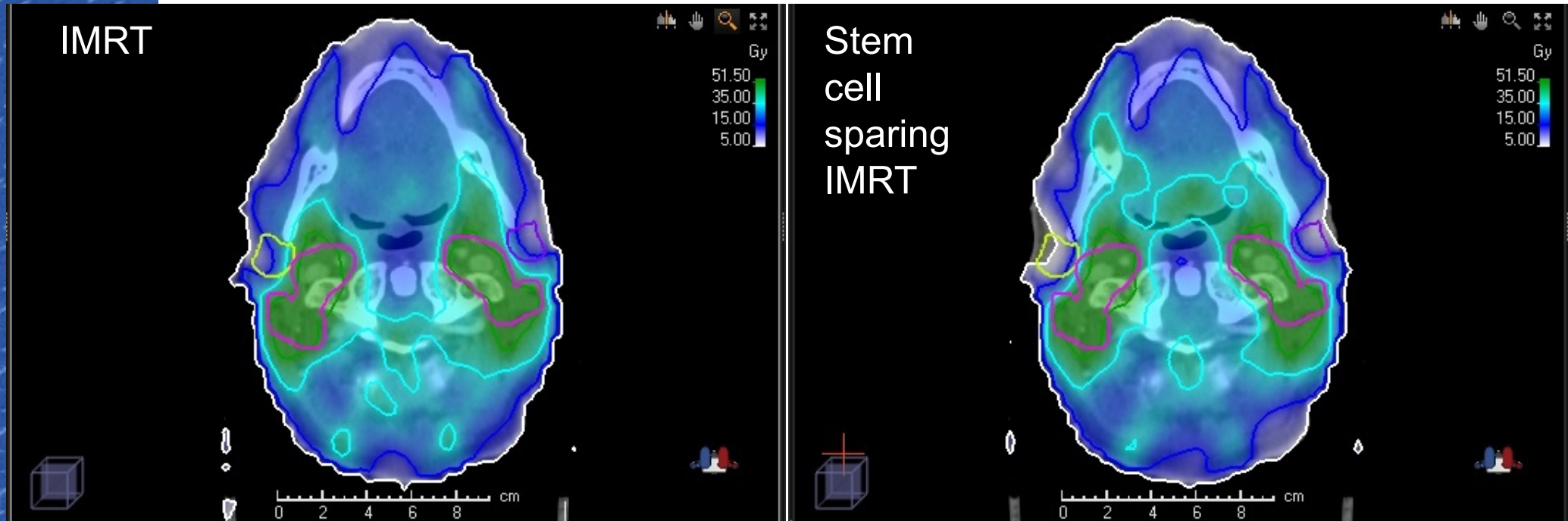
Local damage
irradiated tissue

Global
degeneration entire
gland

Parotid samples from different locations

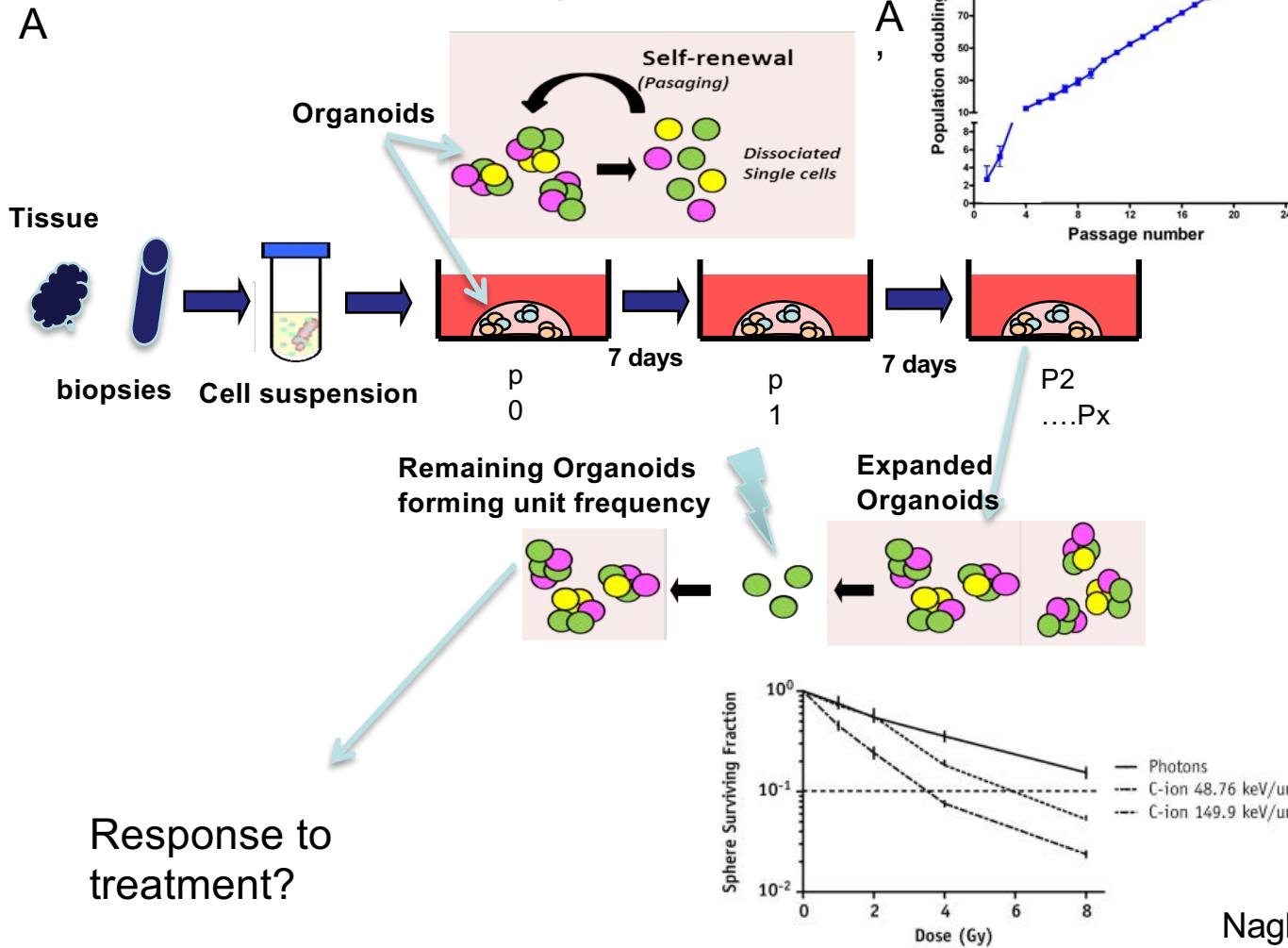


Stem Cell Sparing IMRT

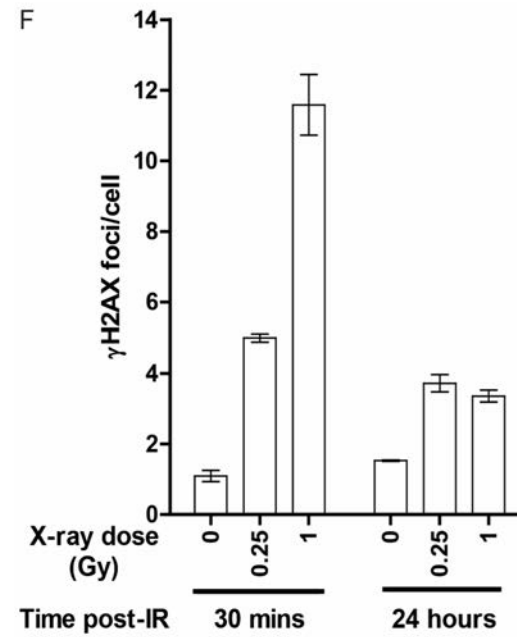
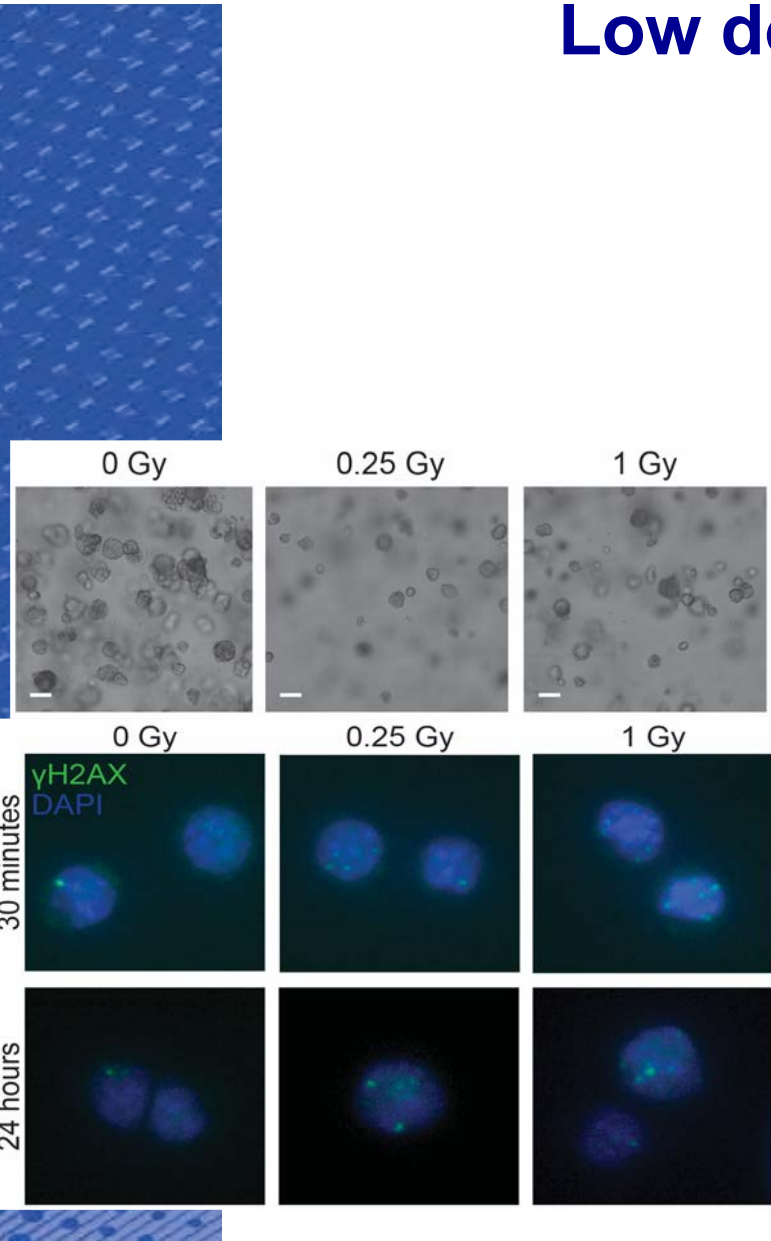
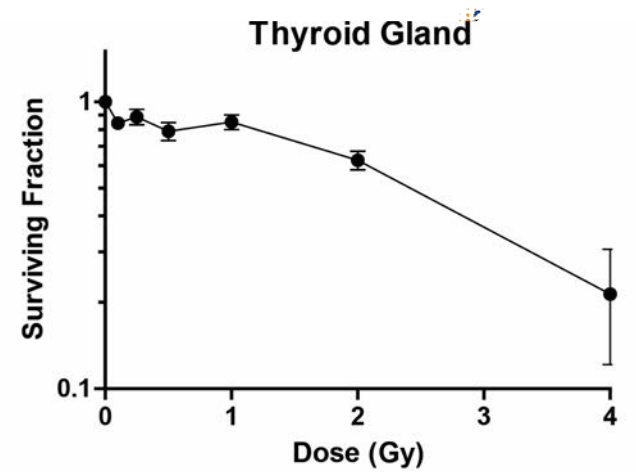
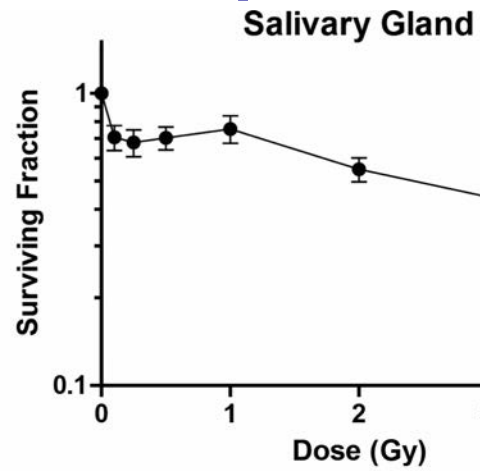


<https://clinicaltrials.gov/ct2/show/NCT01955239>

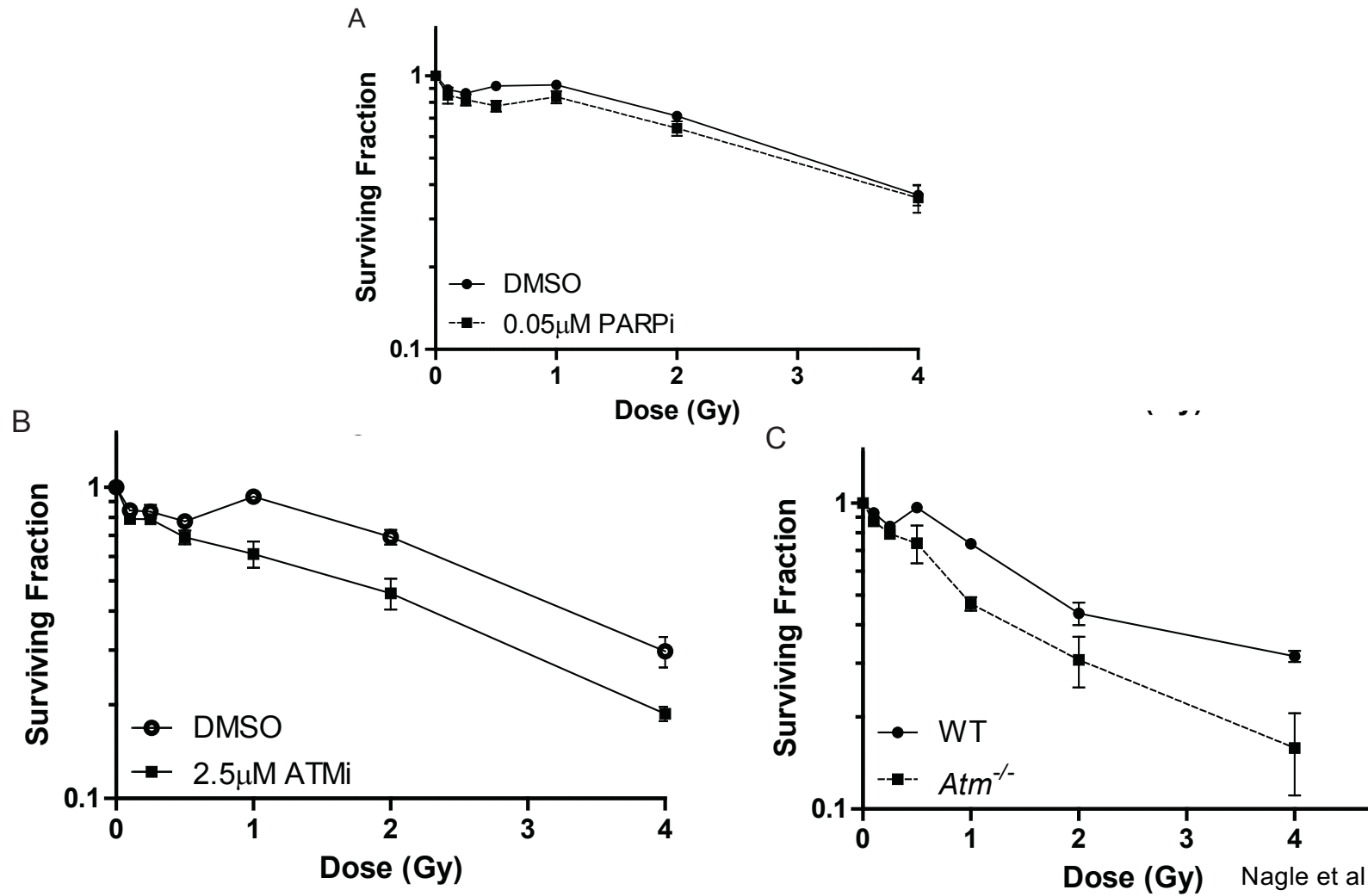
Radiation response of stem cells using organoids



Low dose response of stem cells

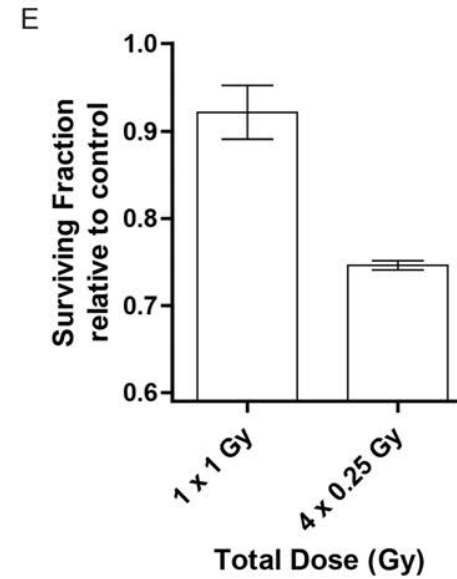
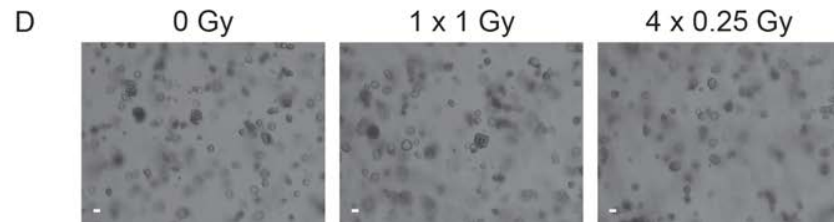
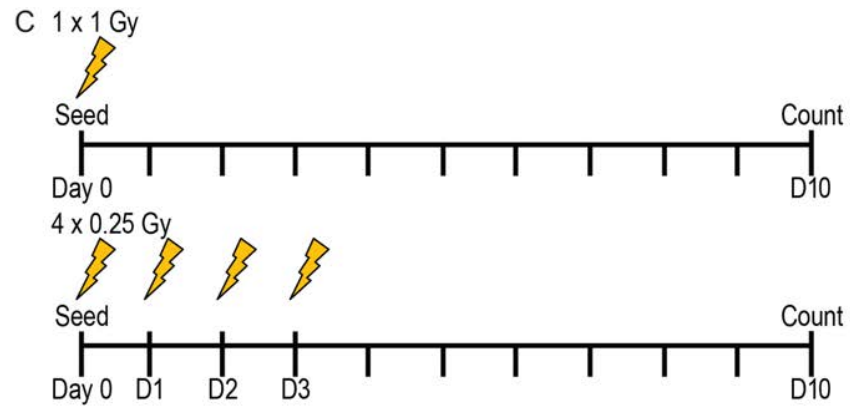
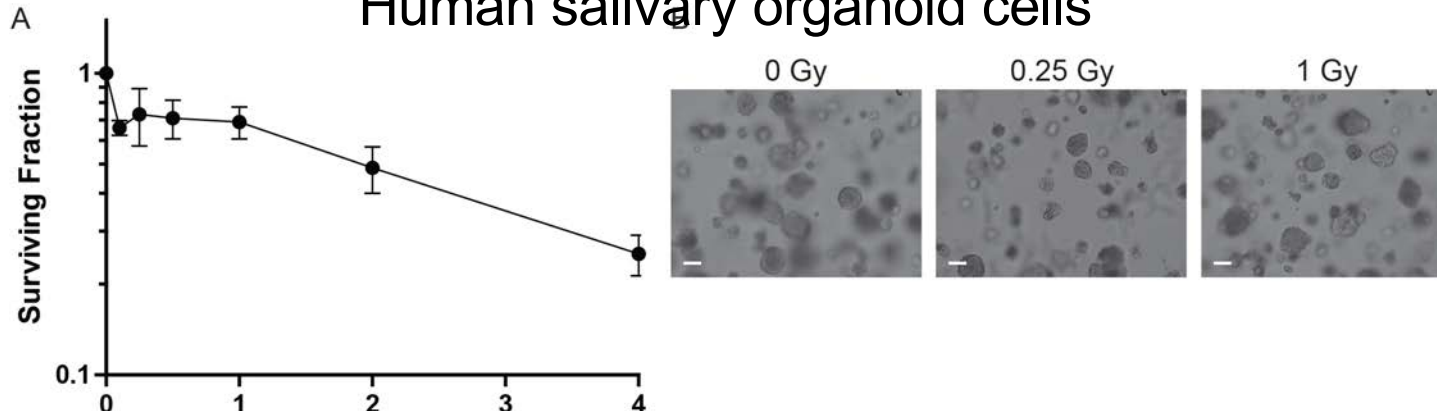


Induced repair of stem cells reduced upon DDR inhibition.

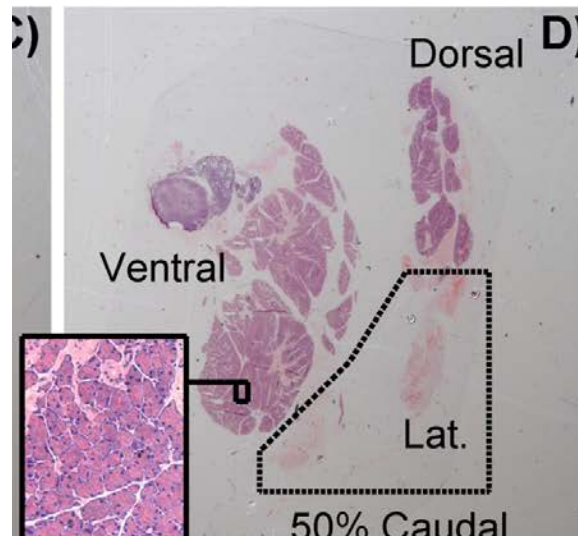
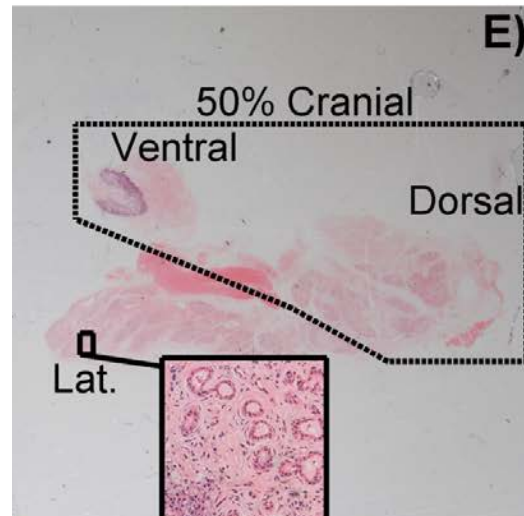
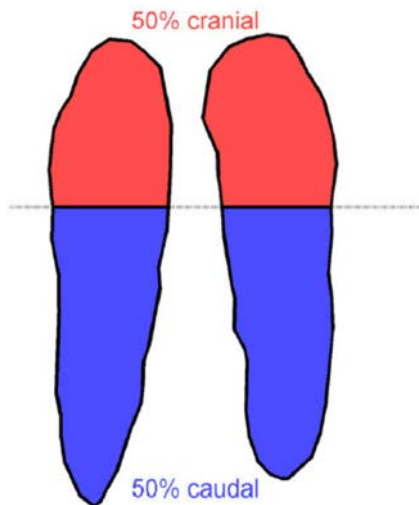
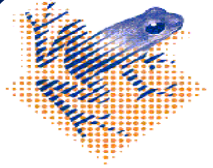


Clinical relevance?

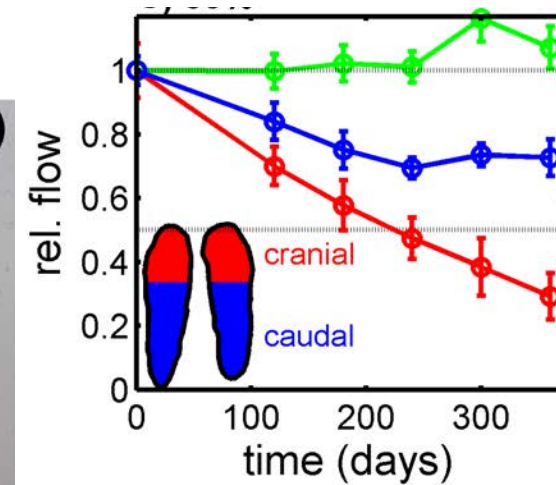
Human salivary organoid cells



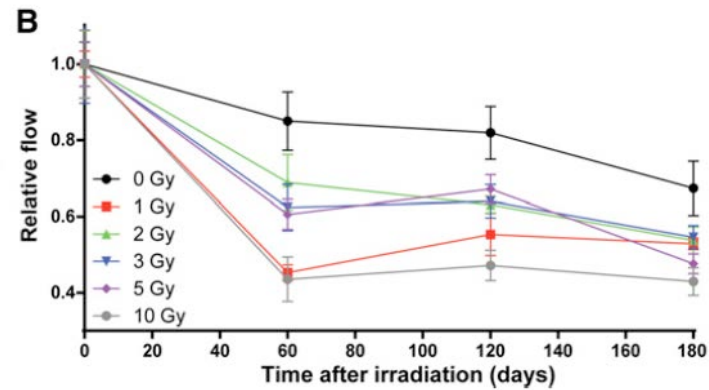
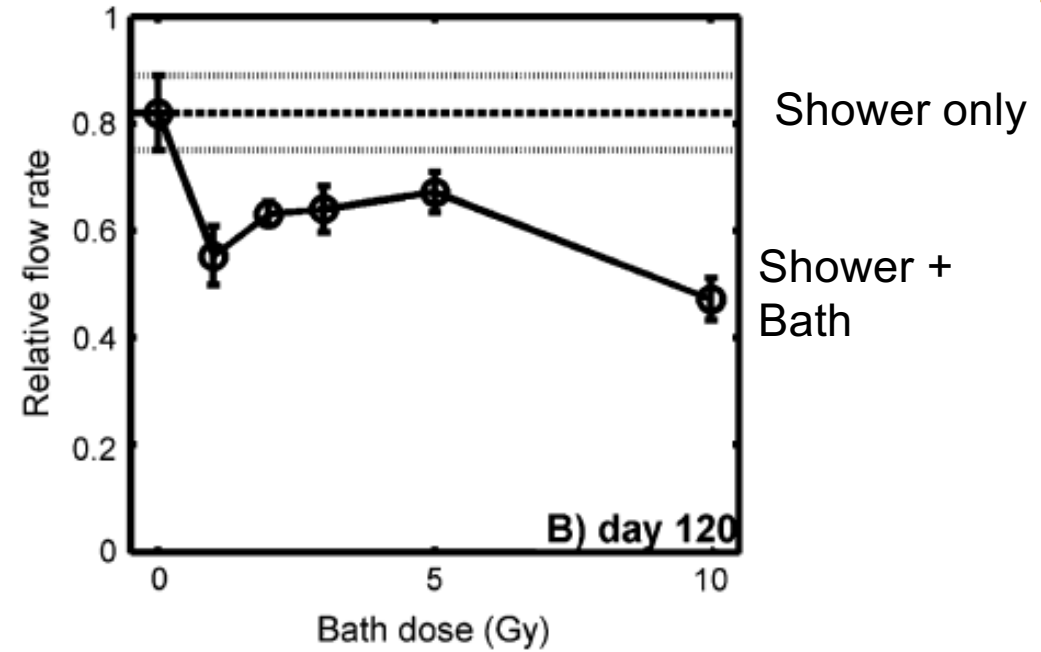
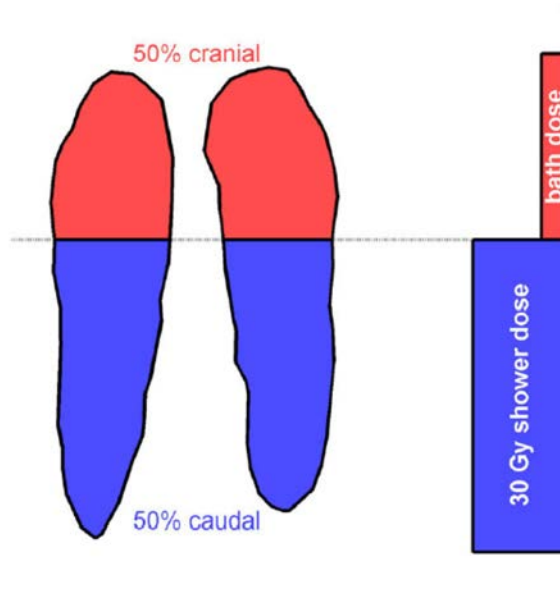
Does low dose hypersensitivity matter?



Stem cells are in cranial 50%



Does low dose hypersensitivity matter?



Conclusions:



- A lot to a little may be better than a little to a lot
- Not only volume is important but also what volume is irradiated (stem cell localization)
- The irradiated environment may influence stem cell potential

Hypothesis:

Healthy and (radiation) senescence cell interact and may provide novel avenues to improve post-irradiation regeneration and subsequent retreatment tolerance.



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