Unraveling mechanisms of salivary gland toxicity after PSMA-TRT

Nathalie Heynickx[1,2] **Promotor: Prof. Sarah Baatout**[1,2] **Co-promotor: Dr. Koen Vermeulen**[1], **Dr. An Aerts**[1]
[1]Radiobiology Unit; Interdisciplinary Biosciences; Institute for Environment, Health and Safety; Belgian Nuclear Research Centre (SCK•CEN), Mol, Belgium
[2]Department of Molecular Biotechnology; Ghent University, Ghent, Belgium
nathalie.heynickx@sckcen.be

Background

- Prostate cancer remains a significant **health burden**
- **PSMA-targeted radionuclide therapy** (PSMA-TRT) is emerging as a new treatment modality
- Uptake of PSMA-targeting compounds in healthy tissues results in **healthy organ toxicity**
- **Salivary glands** show high uptake
  → Salivary gland hypofunction and **xerostomia**
  = extremely uncomfortable side effect

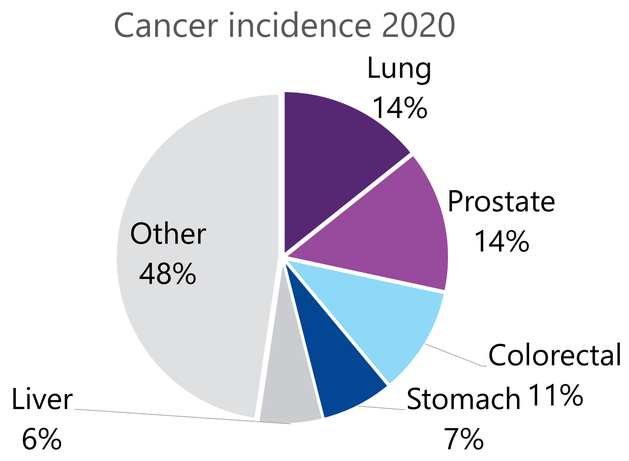


Figure 1: Overview cancer incidence in 2020

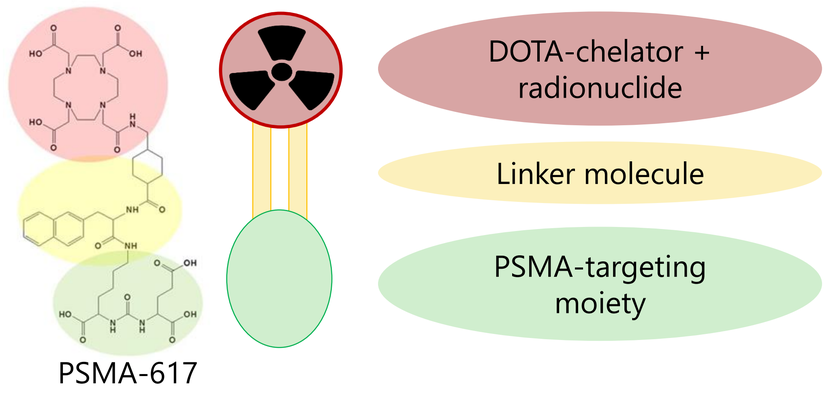
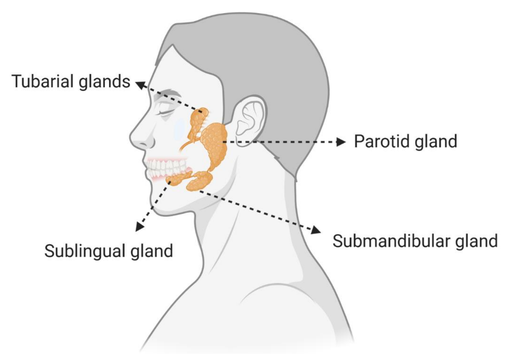


Figure 2: Overview of the compound PSMA-617 and its schematic representation



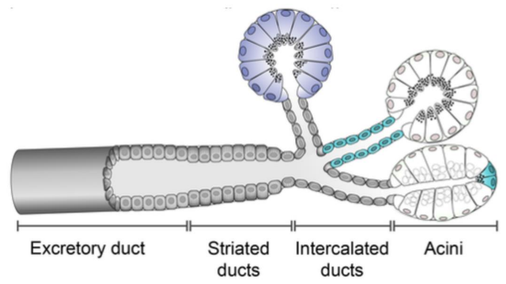


Figure 3: Overview of the human salivary glands and their histological structure

Goal

- Increase understanding of **salivary gland uptake** of PSMA-targeting compounds
- Gain knowledge on **how salivary gland toxicity** after PSMA-TRT arises
- Test different compounds for **preventive value** of salivary gland toxicity

Contribute to making PSMA-TRT safer for patients

Innovation?

- PSMA-TRT is used in clinic, but no extensive preclinical investigation of salivary gland uptake
- Little understanding of mechanisms underlying salivary gland toxicity
  → Help to find preventive strategies

Results

- Decreased survival with increasing doses of ^{177}Lu-PSMA-617
- PSMA-positive (PC3-PIP & LNCaP): specific uptake
- PSMA-negative cells (PC3-Flu): no specific uptake
- A253 salivary gland cells: minor specific uptake

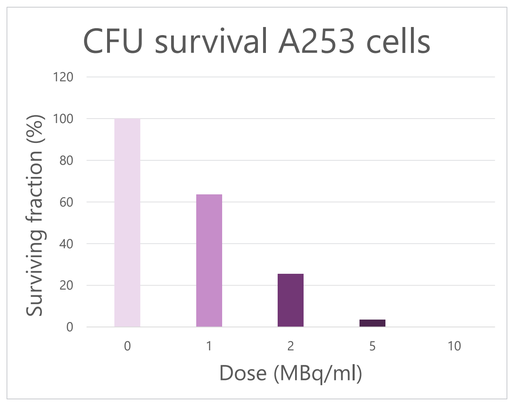


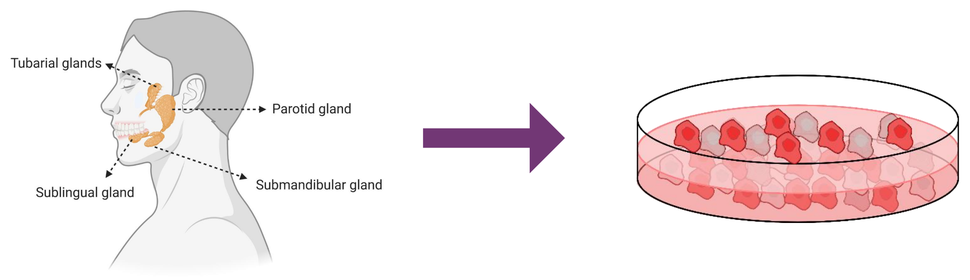
Figure 4: CFU Survival fraction of A253 cells after treatment with different doses of ^{177}Lu-PSMA-617

Average blocking %		
	Low block 10x excess	High block 1000x excess
PC3-PIP	37,9	93,5
PC3-Flu	No block	No block
A253	6,9	18,6
LNCaP	13,8	77,5

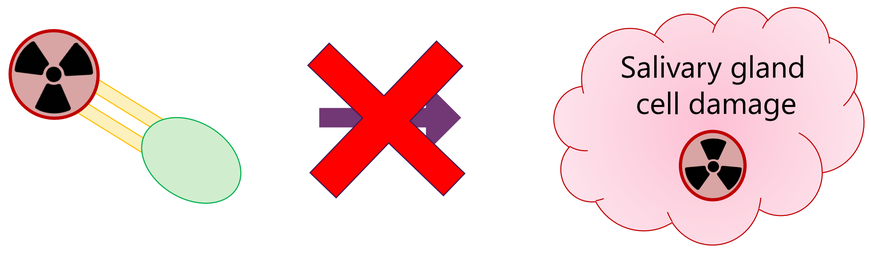
Table 1: Results of blocking experiments. Cells were treated with 5nM ^{177}Lu-PSMA-617. Cells were blocked using vehicle (medium with milli-Q), 50 nM 2-PMPA or 5 µM 2-PMPA

Challenges

- *In vitro* representation of human salivary glands



- Lack of compounds and methods for preventing salivary gland toxicity



Exploring a better tomorrow
www.sckcen.be