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Brussels RadioTheranostics Platform “BRTP”

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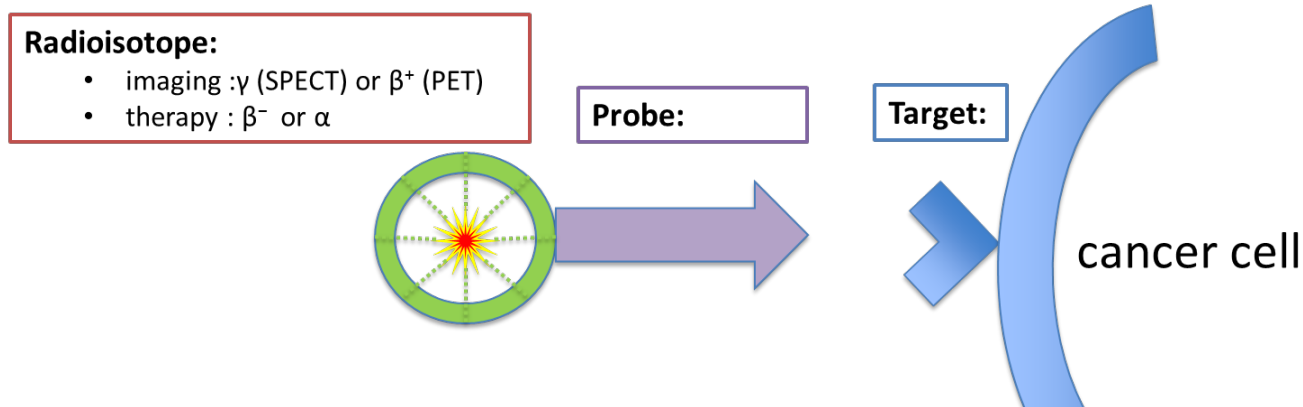
Nuclear Medicine/Radiopharmacy

Institut Jules Bordet

Université Libre de Bruxelles (U.L.B.)

Introduction

- ♦ **Personalized medicine** => core paradigm in modern oncology
- ♦ **“Theranostics concept”**: Nuclear Medicine unique opportunity
 - ♦ Tumor specific probe used both for **imaging** and **therapy** (**Radionuclide pairs**/cold drug)
 - ♦ radioactive payload to the tumor but also detected with nuclear imaging



- ♦ **Institut Jules Bordet (IJB) has been a major protagonist of the “radiotheranostic approach”:**
 - ♦ $^{68}\text{Ga}/^{177}\text{Lu}$ -octreotide for neuroendocrine tumors
 - ♦ $^{99\text{m}}\text{Tc}$ -MAA/ ^{90}Y -microspheres for radioembolization of liver tumors
 - ♦ $^{89}\text{Zr}/^{90}\text{Y}$ -rituximab for CD-20 positive lymphomas
 - ♦ $^{68}\text{Ga}/^{177}\text{Lu}$ -PSMA (under development) for therapy of prostate cancer
- ♦ **VUB is at the forefront of innovative vectors based on single domain fragments (sdAbs)**
 - ♦ first-in-human clinical trial with radiolabeled sdAbs:
 - ♦ safe in humans, very low systemic radiation
 - ♦ cleared very rapidly, mostly through the renal route
 - ♦ good targeting and high contrast.

Brussels RadioTheranostics Platform “B RTP”

What?:

- ♦ **State of the art infrastructures:** research facilities & clinics in Brussels
- ♦ Prelude: **Brussels Imaging Pharmacy “BIP”:**
 - ♦ 3 partners: Institut Jules Bordet, Hôpital Erasme, and UZ Brussel
 - ♦ **cyclotron** based diagnostic radiotracers **GMP** production for the PET units

Objectives:

1. **Generation of innovative radiotheranostics**
 - ♦ Increase access to existing products for cancer patients
 - ♦ Innovative radiotheranostics → translate them into the clinic
 - ♦ Focus on both α and β -emitting cancer drugs
2. **Radiobiology of radiotheranostics**
 - ♦ Explore fundamental and applied aspects of radiobiology

How?:

1. **Generation of innovative radiotheranostics**
2. **Radiobiology of radiotheranostics**

Target

Probe

Radiolabeling

Design

Development of a
radiotheranostic
in oncology

QC

Physico-chemical
evaluation

In vitro

Preclinical
evaluation

In vivo

GMP

Clinical
Production

In patients

Clinical evaluation



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Target

Design

Probe

Radiolabeling

Development of a
radiotheranostic
in oncology

Design (1)

What?:

R&D of new radiotheranostics

Objectives:

- Develop new radiotracers for the targeted delivery of α and β
- Optimization of precursors and reference production
- pre-GMP radiolabeling developments

How?:

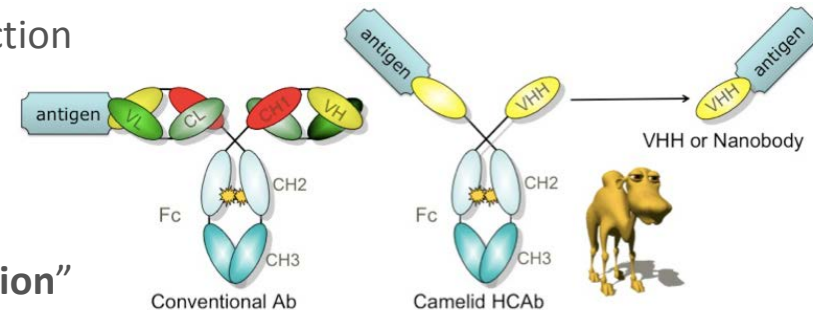
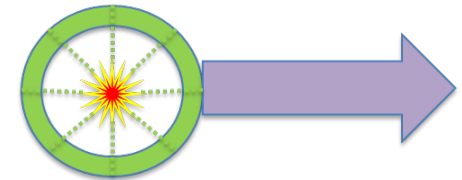
1. Vector Research & Development : “Cold production”

- Synthesis of non-radioactive probes
- Specific compounds directed at the desired (oncological) target
 - Single-domain antibodies (sdAbs, VHH, nanobodies):
 - as derivatives from unique single-chain antibodies of the Camelidae family
 - Small (10-14 kDa), monodispersity, low immunogenicity, stability, and versatility
 - can be generated to strongly and specifically bind to virtually any protein epitope of interest
 - Small chemical molecules and other peptides

Radioisotope:

- imaging : γ (SPECT) or β^+ (PET)
- therapy : β^- or α

Probe:



Design (2)

What?:

R&D of new radiotheranostics

Objectives:

- ◆ Develop new radiotracers for the targeted delivery of α and β
- ◆ Optimization of precursors and reference production
- ◆ pre-GMP radiolabeling developments

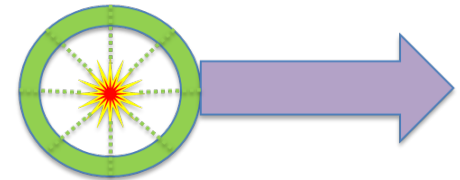
How?:

1. **Vector Research & Development : “Cold production”**
2. **“hot production”:** Radiolabeling of the designed molecules
 - ◆ radiolabeling with the radionuclide of choice γ , $\beta^{-/+}$ and α
 - ◆ Alpha Therapy Lab – ATL
 - research lab only focusing on the development and evaluation of targeted alpha therapy (TAT) probes.
 - development of automated radiochemistry methods for α radiolabeling
 - proof-of-concept

Radioisotope:

- imaging : γ (SPECT) or β^+ (PET)
- therapy : β^- or α

Probe:



Target

Design

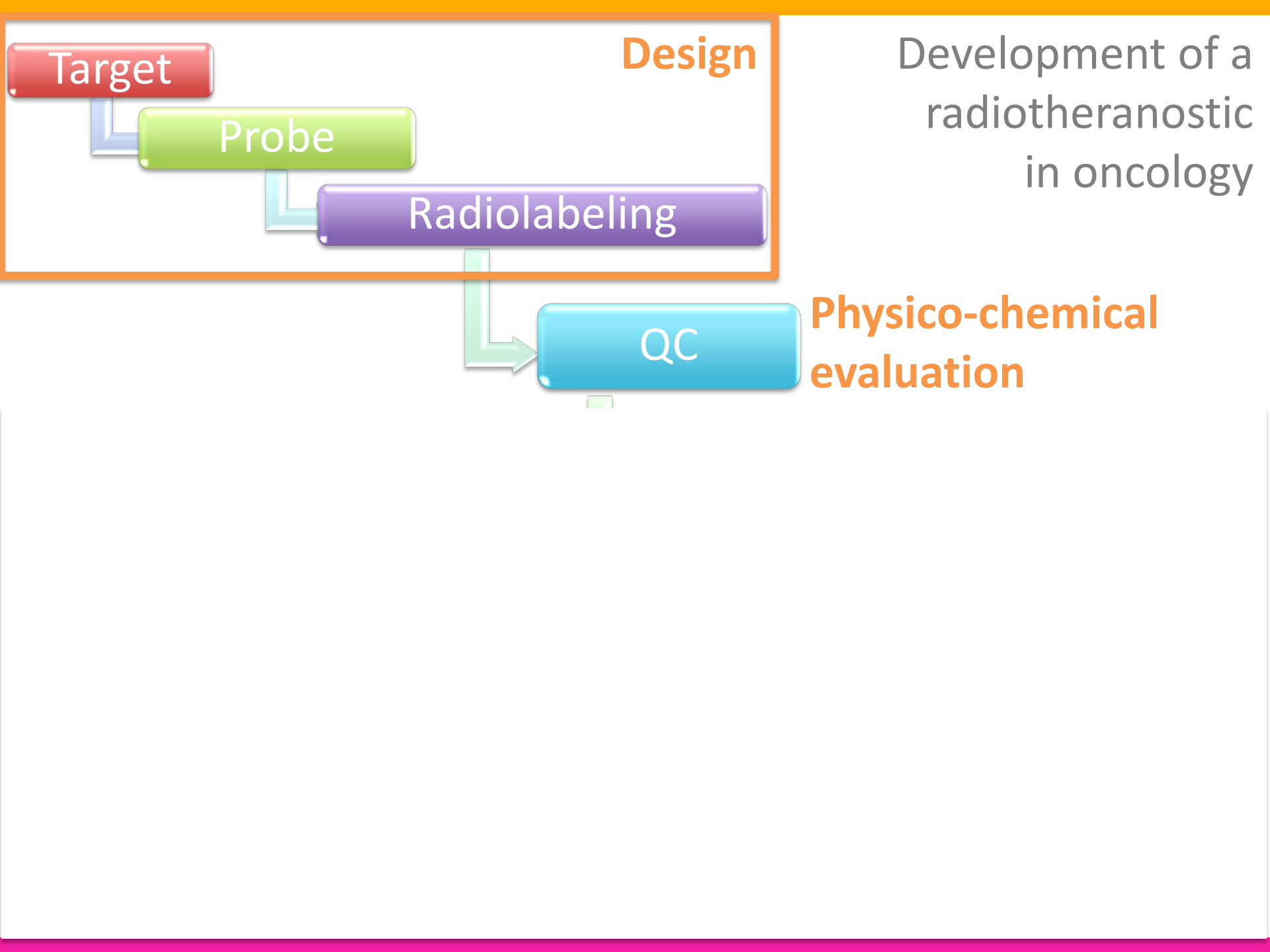
Probe

Radiolabeling

QC

Development of a
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Physico-chemical
evaluation



Physico-chemical evaluation

What?:

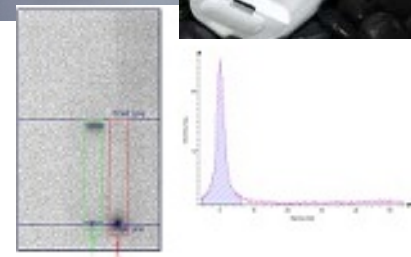
- ♦ Quality control and chemical characterization

Objectives :

- ♦ Knowledge on physical and chemical properties
- ♦ High quality radiotheranostics
- ♦ pre-GMP radiolabeling developments validation (RCY)

How?:

- ♦ appearance, pH, stability and the different types of purity



Type of purity	Definition	methods
Radionuclidic	radioactivity desired radionuclide / the total radioactivity of the source	Dose Calibrator/ Multichannel Analyzer
Chemical	stated chemical form/the total mass present	Colorimetric or HPLC
Radiochemical	desired radiolabelled species/total radioactivity	TLC or radio-HPLC
Bacteriological	No Bacterial presence	Bacterial culture
Serological	No Viral presence	RT-PCR

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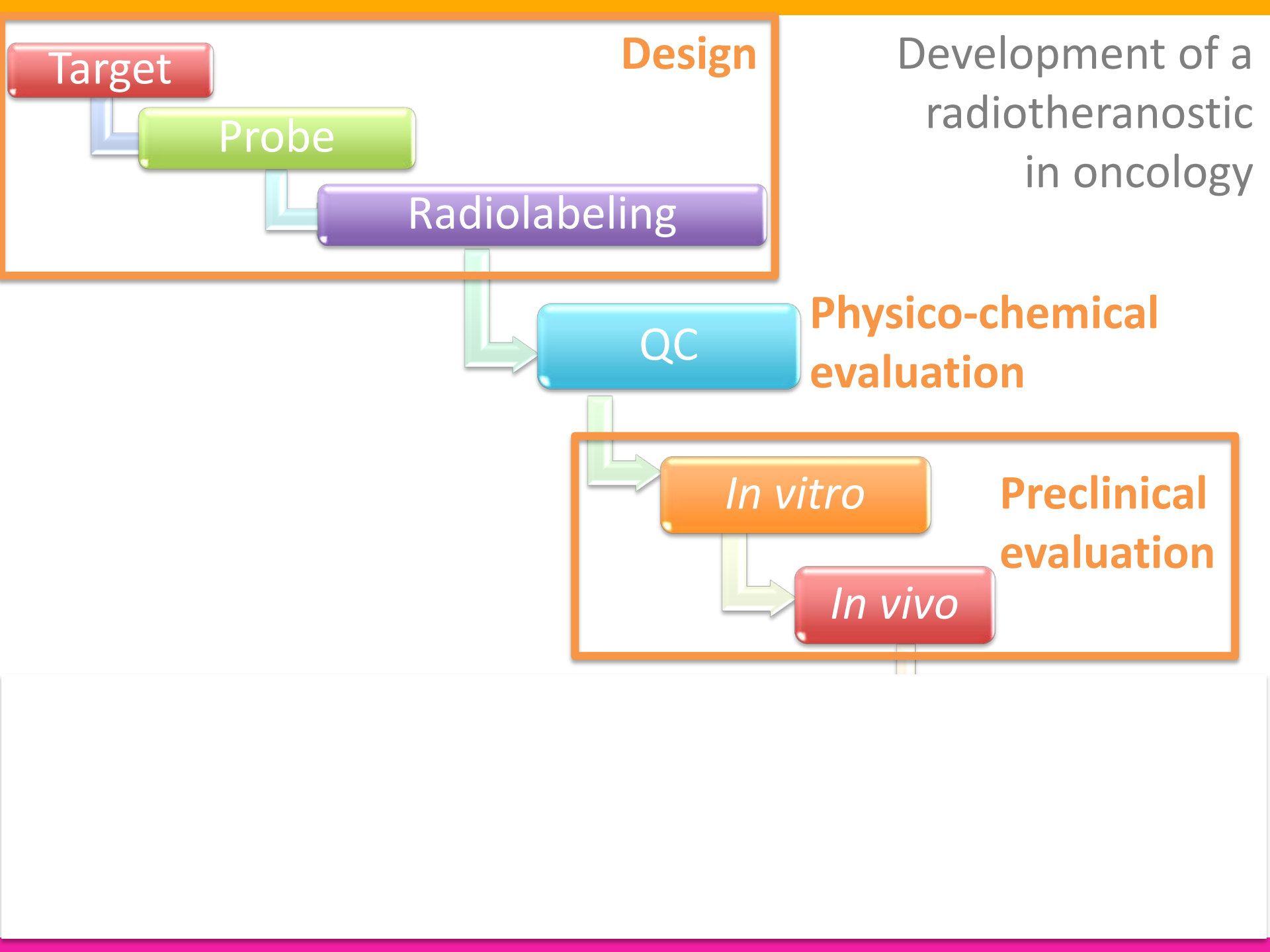
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Preclinical
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In vivo



Preclinical & Radiobiological Evaluation

What?:

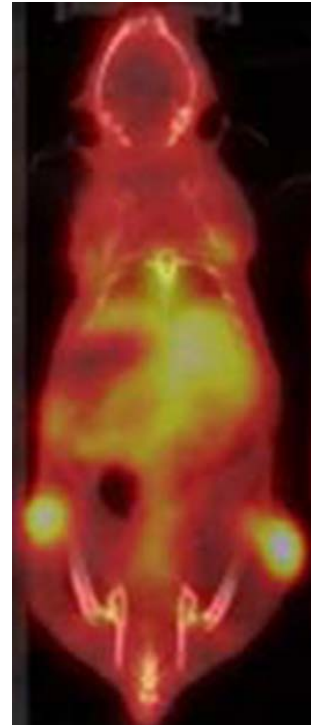
- ♦ (Radio)biological characterization of the radiotracer **in vitro, in vivo and ex vivo**

Objectives:

- ♦ **General preclinical biological properties** of the radiotheranostic:
 - ♦ after radiolabeling the compounds has retained its biological properties
- ♦ **Specific radiation research:**
 - ♦ Radiobiological effects of the radiotheranostics and (comparison with) EBRT

How?:

- ♦ General preclinical biological properties of the theranostic:
 - ♦ In vitro: binding, uptake, specificity, affinity, ...
 - ♦ In vivo: biodistribution, pharmacokinetic, tumor accumulation, specificity, affinity
- ♦ Radiobiology of radiotheranostics and EBRT:
 - ♦ Radiotoxicity : effect of radiation on survival, proliferation, cell death
 - ♦ Radioresistance: molecular markers, hypoxia, DNA repair, ROS scavenger,...
 - ♦ Radiosensitization: combination studies with other therapies



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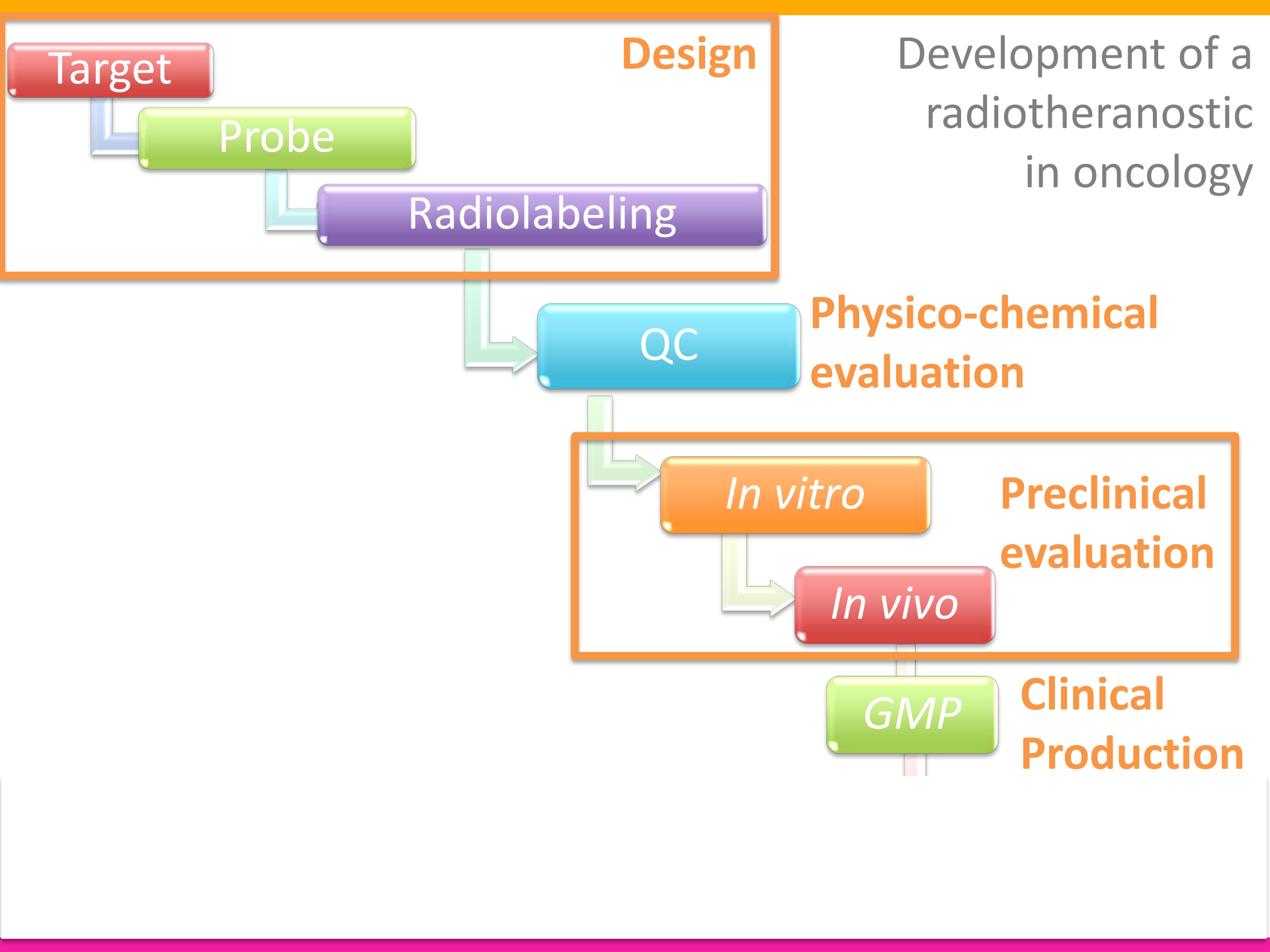
In vitro

Preclinical
evaluation

In vivo

GMP

Clinical
Production



Clinical Production (GMP)

What?:

Production lab to clinically translate theranostics in the best conditions

Objectives:

Manufacture Radiopharmaceuticals in accordance with the principles of good manufacturing practices (GMP) (according to ruling regulations; Eudralex Volume 4 Annex 3)

How?:

- ♦ GMP premises (environmental, rooms, ...)
- ♦ GMP Production (Hotcells, Isolator, Modules, ...)
- ♦ GMP Quality Control
- ♦ GMP Quality Assurance (management system (software, monitoring...) & validation (Documents and validation))



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Clinical evaluation

What? :

In patient evaluation of the radiotheranostic
Ultimate quality test of a radiotheranostic

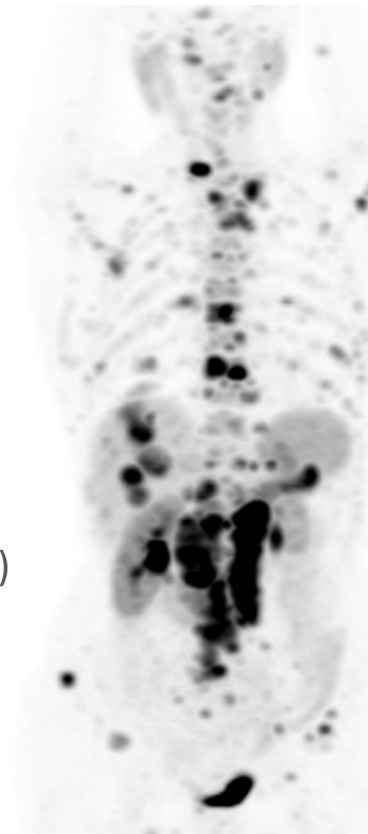
Objectives:

- ♦ Patient selection: imaging of target expression
- ♦ prediction of efficacy/toxicity
 - ♦ Personalized dosimetry
 - ♦ Pre-therapeutic simulation
 - ♦ Pharmacokinetics and distribution
- ♦ Patient treatment optimization

How?:

- ♦ Clinical trials
- ♦ Regulatory steps: (FAMHP & FANC, ethical committee)
- ♦ In vivo imaging studies : PET/CT and SPECT/CT
- ♦ Blood samples
- ♦ Radiobiological effects on (Liquid) Biopsies

Imaging
 ^{68}Ga -DOTATATE PET



Therapy
 ^{177}Lu -DOTATATE (SPECT)



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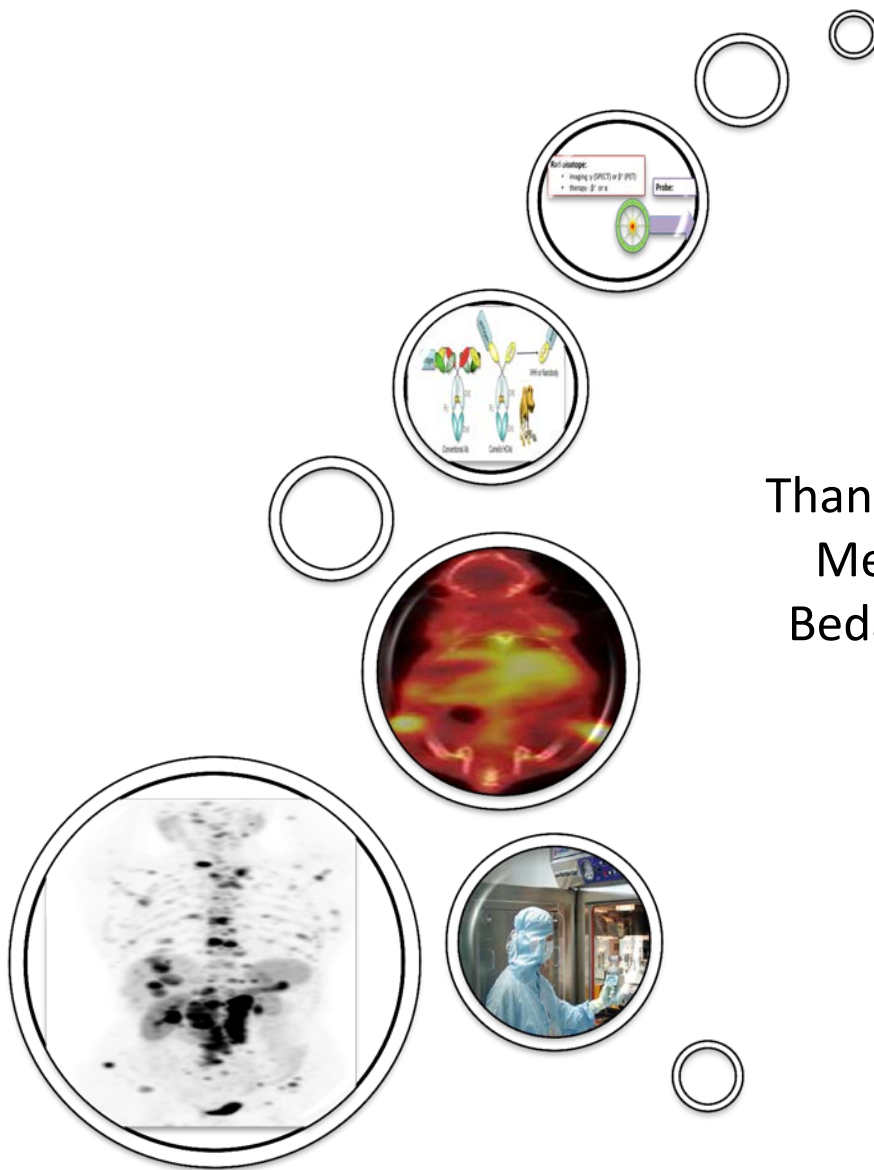
Summary and conclusion

- ♦ Generation of innovative radiotheranostics
 - ♦ R&D of radiotheranostics for molecular diagnosis and therapy
 - ♦ follows a strict development process (Requires a dedicated research infrastructure)
 - ♦ Translation to patient
- ♦ Radiobiology of radiotheranostics
 - ♦ identify relevant radioresistance biomarkers
 - ♦ study the radiobiological dynamics
 - ♦ Cancer cells in vitro, animal models in vivo and translationally on biological specimens

B RTP

- ♦ Network of **scientist and clinicians** in Brussels region (IJB, VUB, Erasme)
- ♦ **Exchanges and collaborations** : NM physicians, medical physicists, radiopharmacists, radiochemists, radiobiologist, medical and radiation oncologists, together with clinical research professionals
- ♦ **Complete chain** : Bench to bedside
- ♦ B RTP +BIP: Premier position at Belgian level

➔ Radiotheranostics to the forefront of oncology research



Thank you
 Merci
 Bedankt