Understanding the radiobiology of therapeutic medical radionuclides (UNRANU)

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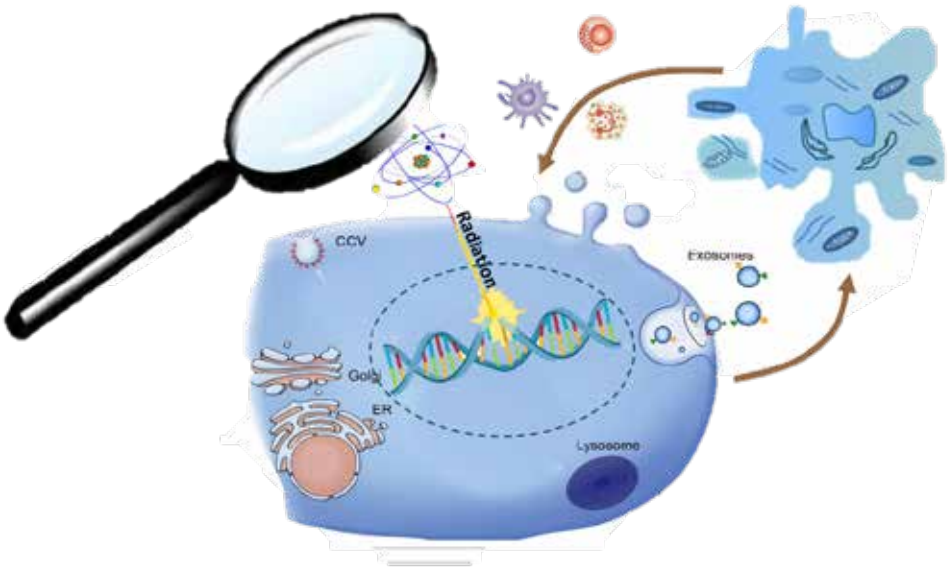

Introduction

December 14th, 2022, the UNRANU research proposal was awarded by the Dutch Research Council (NWO) within the *Perspectief* program. This *Perspectief* funding instrument supports projects that contribute to the creation of economic opportunities within the societal challenges and key technologies of the Mission-driven Innovation Policy of NWO. Within UNRANU, we aim to improve the radiobiological knowledge and accessibility of therapeutic isotopes for radionuclide therapy (RNT). Ultimately, this would improve the availability of RNT, contribute to more rationalized treatment selection and/or treatment planning, with the final goal to help more cancer patients with a better disease outcome.

The consortium

UNRANU is a Dutch consortium consisting of the initiators Frank Nijsen, Sandra Heskamp (Radboudumc), Antonia Denkova (TU Delft) and Julie Nonnekens (Erasmus MC) and various industry partners, peripheral hospitals, patient associations and knowledge institutes. Eight researchers (post-docs and PhD students) will be allocated across Radboudumc, TU Delft and Erasmus MC. The other participating institutions are Oncode, RIVM, Meander Medisch Centrum, Nederlandse Leverpatiënten Vereniging, Nederlandse Vereniging van Nucleaire Geneeskunde, Prostaatkanker Stichting, Reinier de Graaf Ziekenhuis, Stichting Darmkanker, Wetenschapsknooppunt. The involved companies are AlfaRIM, HUB Organoids, MILabs, NRG, PALLAS, Quirem Medical (Terumo), RTM, Siemens Healthineers, TerThera, URENCO, Von Gahlen and VSL. A multidisciplinary advisory board consisting of Prof. Dr. F. Verburg, Dr. J. Nagarajah, Prof. Dr. J. Bussink, Dr. R. de Blois, Prof. Dr. A. Glaudemans, and Prof. Dr. J. Zeevaart has been established, which ensures up-to-date knowledge, critical thinking and analysis of the project and its results. The project will run for 5 years starting in Q4 2023.

Project background and scientific challenge

Cancer is a major challenge in healthcare and leading cause of death worldwide, accounting for nearly 10 million deaths in 2020. Despite numerous developments, most patients with metastasized disease cannot be cured. Successful clinical trials such as NETTER-1 and VISION have shown that RNT can significantly improve survival of cancer patients. NETTER-1 showed that [^{177}Lu]Lu-DOTATATE (Luthatera, Novartis) significantly improves overall survival of patients with somatostatin receptor (SSTR) positive neuroendocrine tumors, while VISION demonstrated that [^{177}Lu]Lu-PSMA-617 (Pluvicto, Novartis) improves outcome of castrate-resistant metastatic prostate cancer patients (1,2) These studies led to the FDA approval of Luthatera and Pluvicto for the afore mentioned patient populations. In addition to systemic applications, RNT has been successfully applied locally, for example through transarterial radioembolization (TARE) with

radioactive labelled microspheres with yttrium-90 or holmium-166 (3,4). Despite these initial successes, most patients cannot be cured with the current treatment regimen and the application of RNT in clinical practice is still limited to a few cancer types and small cohorts of patients, thereby not fully exploiting its potential. This outcome can be explained by the fact that the choice of radionuclides and RNT schedule are currently suboptimal, due to limited fundamental knowledge of the biological effects of different radionuclides, resulting in inferior therapeutic efficacy. Furthermore, for many patients RNT is not fully accessible yet, and therefore it is only applied in selected patient populations.

In the UNRANU program we have defined three main objectives:

1) To determine the radiobiological and immunological effects of therapeutic radionuclides with different physical properties in vitro and in vivo.

2) To improve the availability of selected radionuclides by developing new or improving existing production routes.

3) To transfer this knowledge to clinicians, society, patients, industry, and policy makers.

For objective 1, we will tighten the knowledge gap on the biological responses of tumors when treated with different radionuclides. Current scientific developments in RNT are typically related to research on new targeting agents to achieve high tumor uptake with little accumulation in non-target tissues. However, seeing that results are still far from optimal, it is essential to implement additional research strategies. High tumor uptake of the targeting agent is important, but it does not guarantee tumor elimination. Tumor cell killing efficiency also depends on other factors including the radionuclides' distribution within the tumor, the type of radiation, and tissue range and dose rate of the particles. In this respect, dosimetry is key to accurately determine the tumor-absorbed dose and relate this to the biological effects of the therapeutic radionuclides and specific tumor characteristics (e.g. size, perfusion, immunological status). In patients, (pre-treatment) dosimetry can also play a key role in optimal selection and planning of RNT for individual patients. However, in order to apply this correctly, more knowledge on the dose-biological effect relationship is essential, and this will therefore be studied in detail in UNRANU.

For objective 2 and 3, we aim to improve the accessibility of RNT. Currently, RNT applications are mostly limited to academic hospitals to a selected group of patients with a specific oncological indication. This is a drawback compared to more general treatment modalities such as external beam radiation therapy (EBRT) or chemotherapy. There are several reasons for the limited accessibility. First, many clinicians and patients are not fully aware of the potential of RNT, which challenges rapid developments and clinical implementation. Second, not all therapeutic radionuclides can be regularly supplied at sufficient amounts or quality. In UNRANU we aim to improve all aspects involved in making RNT accessible to larger cohorts of cancer patients, from target production to its application in the clinic (figure 1).

Work packages

UNRANU is divided in 5 Work Packages (WP), which will focus on a selection of 6 different clinically relevant radionuclides: lutetium-177 (^{177}Lu), terbium-161 (^{161}Tb), holmium-166 (^{166}Ho), yttrium-90 (^{90}Y), actinium-225 (^{225}Ac) and lead-212 (^{212}Pb). These radionuclides have been selected as representative for a panel of radionuclides with varying characteristics such as half-life, dose rate, energy disposition. The first 4 radionuclides are beta-emitters and the last 2 radionuclides are alpha-emitters (see table 1 for

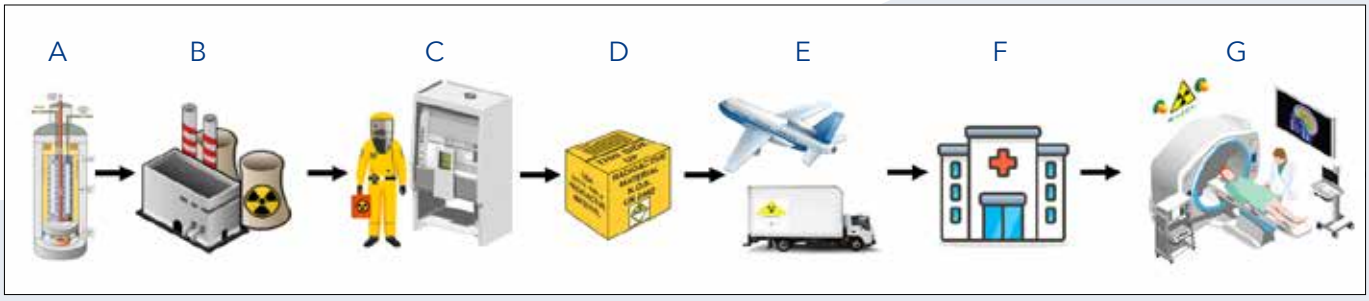

Figure 1. Nuclear industry value chain. Examples of companies/institutes that are partners in this proposal: A) enriching target material (URENCO), B) neutron activation to produce medical isotopes (NRG, Pallas, RTM, AlfaRIM, TerThera), C) Handling & production: Shielding, production laboratory (Von Gahlen, Fieldlab NRG, Quirem Medical), D) Packaging, E) Transport, F) Hospitals (Radboudumc, Erasmus MC), G) Imaging apparatus (MILabs, VSL, Siemens).

characteristics). ^{177}Lu and ^{161}Tb have comparable, but not the same physical characteristics, i.e., ^{161}Tb also emits Auger electrons. ^{177}Lu is frequency used in clinical practice, while ^{161}Tb application is under development, but it could potentially serve as replacement of ^{177}Lu when this radionuclide would become scarce. ^{177}Lu and ^{161}Tb have a relative long half-life of approximately 1 week, while ^{166}Ho and ^{90}Y have a much shorter half-life of a few days. In addition, ^{166}Ho and ^{90}Y have different physical characteristics, including a longer range. Both ^{166}Ho and ^{90}Y are being used in clinical practice, but it is unknown whether they can be exchanged, since they have different dose-rate. Besides the use of beta-emitters, alpha-emitters are used in the clinic, of which ^{225}Ac has shown great results. ^{225}Ac has a long half-life of 10 days and decays via several daughter radionuclides emitting four alpha particles in total. ^{212}Pb is an alpha-emitter with a half-life of 2 days, emitting one alpha particle.

In WP1, we will improve the availability and specific activity of therapeutic radionuclides, by developing new or improving existing production routes. In WP2-4, we will determine the radiobiological effects of radionuclides with different physical properties on tumor cell survival in monolayer settings (WP2) and 3D tumor structures (WP3), and unravel the radiobiological and immunological effects in animal models (WP4). In figure 2 an overview of the models used is given, illustrating their characteristics in relation to the complexity, relevance and multiplexing capacity. Finally, we will transfer the obtained knowledge to society and commercial and care industry in WP5 Program management, communication and utilization.

Expected outcome

At the end of the project, we expect to have a more detailed fundamental understanding of the biological effects of therapeutic radionuclides,

Table 1. Overview of the different radionuclides used in UNRANU and their physical properties.

Radionuclide	Main type of therapeutic dec	Half-life	Energy (E_{max})	Penetration in soft tissue
Lutetium-177	β- particles	6.7 days	0.497 MeV	Maximum 1.7 mm
Terbium-161	β- particles Auger electrons	6.9 days	0.593 MeV	<2 mm (β-) <1 µm (Auger)
Holmium-166	β- particles	27 hours	1.855 MeV	Maximum 8.7 mm
Yttrium-90	β- particles	64 hours	2.280 MeV	Maximum 1.1 cm
Actinium-225	Four Alpha particles	10.0 days	5.935 MeV	<10 µm
Lead-212	One Alpha particle	10.6 hours	6.207 MeV	<10 µm

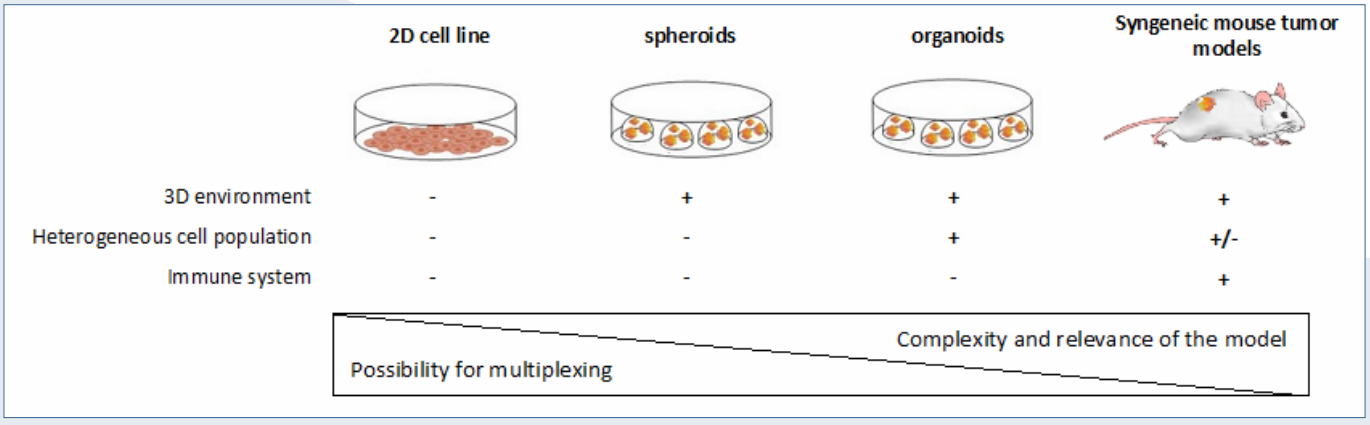

Figure 2. Overview of the models used in WP 2, 3 and 4 illustrating their characteristics in relation to the complexity, relevance and multiplexing capacity.

which will result in better informed decisions which radionuclides are most effective to treat a certain type of tumors. Furthermore, we will have contributed to a more reliable and sustainable supply of therapeutic radionuclides leading to better accessibility and therefore eventually the project is expected to have high societal impact not only in the Netherlands but worldwide.

Disclosure
J.F.W. Nijsen is co-founder of Quirem Medical which has been acquired by Terumo Europe NV in July 2020. Nijsen has a scientific advisory role and is entitled to certain milestone payments from Terumo which are related to Quirem's financial, operational and regulatory performance in the future. Furthermore, Nijsen is inventor on the patents related to radioactive microspheres that are assigned to University Medical Center Utrecht Holding BV, Quirem Medical or BASF Corp. The activities of J.F.W. Nijsen within Quirem Medical are approved and supported by the Board of Directors of the Radboudumc.

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