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Theranostic and nanotheranostic probes in nuclear medicine

Natascha Drude [a,b,*], Lena Tienken [a,c], Felix M. Mottaghy [a,d]

[a] Department of Nuclear Medicine, Uniklinik RWTH Aachen University, Germany
[b] Leibniz Institute for Interactive Materials – DWI, RWTH Aachen University, Germany
[c] Institute of Inorganic Chemistry, RWTH Aachen University, Germany
[d] Department of Nuclear Medicine, Maastricht University Medical Center, The Netherlands

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ABSTRACT

In nuclear medicine, a theranostic probe describes a substance that combines diagnostic and therapeutic capabilities by radiolabeling it with different radionuclides. Next to a brief description of the different emitters (α, β^+, β^-, γ) used for imaging and/or therapy, the aim of this review is to summarize the most commonly used theranostic probes in nuclear medicine. Another goal is to give an idea which chemical requirements need to be fulfilled for radiolabeling with either therapeutic and/or diagnostic relevant nuclides. Furthermore, a perspective is given into the field of nanotheranostics which is gaining more and more attention in nuclear medicine. The combination has been called radionanomedicine and is a very proliferative field with an enormous potential.

Contents

* Corresponding author at: Department of Nuclear Medicine, Uniklinik RWTH Aachen University, Germany.
E-mail address: ndrude@ukaachen.de (N. Drude).

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1. Introduction

1.1. Theranostic

The term theranostics was recently introduced in 2002 by Funkhouser et al. and was defined as single compounds that combine diagnostic imaging and therapy [1]. However, in nuclear medicine this concept has already been employed for almost 80 years using Indium isotopes for diagnosis and therapy in thyroid diseases [2]. The significance of the theranostic concept is indisputable and settled with the initial allocation of *Theranostics* (Ivyspring International) in 2011 and was given an additional direction with the first edition of *Nanotheranostics* (Ivyspring International) in January 2017. The theranostic system assembles diagnostic imaging to detect whether a molecular target for an intended treatment is present and whether the therapy with the theranostic agent leads to improved clinical symptomatology [3]. Thus, a theranostic substance can be used for both visualization and treatment of a specific disease. Imaging with the same chemical compound that can also be used for therapy provides the opportunity to select patients that are more likely to benefit from the treatment as well as to predict therapeutic impact on the tumor with individual biodistribution. Hence, the dose for each individual state of disease can be individualized, enabling personalized therapy. As Hicks summarized "*If you can see it you can treat it*" [4] However, if you can see it you can not only select, but also learn about the biodistribution and potential side effects of a given molecule. Nuclear imaging can be described like *in vivo* immunohistochemistry and in doing so providing non-invasive biomarkers [5]. To design a theranostic probe in nuclear medicine, it is first necessary to identify the target, and afterwards chemically design a tracer for specifically targeted radiolabeling for diagnostic and therapeutic application (Fig. 1). With the tracer concept, it is not only possible to trace down and image the potential target but also to follow the probe itself gaining insights on the materials biodistribution especially with respect to healthy organs.

1.2. Decay properties of diagnostic and therapeutic radionuclides

1.2.1. Diagnosis

For nuclear imaging either gamma emitters or positron emitters (β^+) are mandatory for detection and visualization with a gamma camera (single photon emission computed tomography (SPECT)) and positron emission tomography (PET), respectively. Those non-invasive molecular imaging techniques are used for the diagnosis as well as monitoring of therapy efficiency. The radionuclides most commonly used for SPECT are Tc-99m, In-111 and I-123/125. The radionuclides most commonly used for PET are Ga-68, F-18, I-124, Zr-89, Y-86 and Cu-64 (see also Table 1).

As a generator nuclide, Ga-68 is accessible for most radiochemistry labs and thus an attractive alternative to cyclotron produced positron emitters like F-18, I-124 (26% β^+ probability), Cu-64 (19% β^+ yield) and Zr-89 (23% β^+ yield). F-18, with the highest probability of positron decay (97%), still remains the most important radionuclide and a lot of effort has been made regarding fluorination of established tracers former labeled with radiometals, e.g. ligands to address the prostate specific membrane antigen (PSMA). The half-life of 110 min allows for shipping of the probe and higher activity can be produced to diagnose more patients with one batch compared to the Ga-68 product. Compared to F-18 with the highest probability of positron decay (97%), Ga-68 has only 89% positron branching. Ga-68, with a positron energy of 740 keV, still results in sufficient spatial resolution for PET imaging. Cu-64 is an attractive positron emitting nuclide with favorable decay characteristics with a half-life ($t_{1/2}$ = 12.7 h) that allows for monitoring up to 48 h post injection. Additional decay by electron capture (EC) and β^--particle emission is followed by emission of auger electrons increasing cytotoxic potential of Cu-64 as a theranostic nuclide itself; whereas Zr-89, with a half-life of more than three days, is especially interesting for long-term studies and biokinetic profiling (e.g. antibodies). Despite a higher resolution as a nuclide suitable for PET, I-124 has a half-life of 4.2 days and can give insights regarding long term side effects that could be expected for I-131 therapy analogues. Using the γ-emitting I-123 ($t_{1/2}$ = 13 h), those long term biodistribution information could not be assessed.

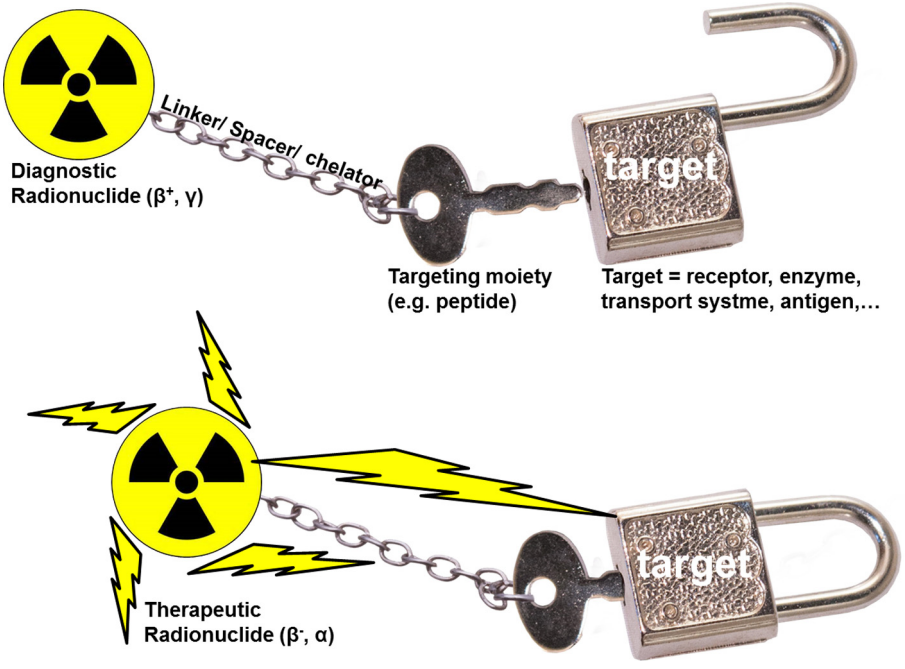

Fig. 1. Tracer concept for a theranostic probe in nuclear medicine.