Chapter 8
Choice of Radionuclides and Radiolabelling Techniques

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Summary Considerations on the choice of type of radionuclide suitable for tumour therapy are given. The physical properties of the radionuclides in relation to the therapy conditions are discussed as well as production and availability. Labelling methods are described in terms of direct versus indirect methods and also in terms of radioactive halogens versus radioactive metals. The influence of labelling method on the binding affinity and cellular processing of the targeting agent is discussed. Emphasis is also given to the influence of the labelling method on cellular radionuclide retention and biodistribution.

Introduction

Success in the multidisciplinary area of radionuclide therapy is dependent on good collaboration between scientists specialized in different fields such as radiochemistry, biochemistry, biotechnology, immunology, oncology, pathology, haematology, radiation physics (e.g. dosimetry) and nuclear medicine. Radiochemistry is of crucial importance since the choice of radionuclide and labelling method is as important as the choice of the targeting protein or peptide. This imposes high requirements on the radiochemists, prompting these persons not only to select the best methods for stable attachment of a given nuclide to a given protein or peptide, but also to take into account a variety of biological and pharmacological factors. These factors determine selection of the most suitable radionuclide for the considered application, and the selection of the labelling method, which provide delivery of a high radiation dose to the malignant cells while sparing healthy organs and tissues.
Choice of Radionuclides for Therapy

General Considerations

The main precondition for a successful radionuclide therapy is delivery of a high local radiation dose to the tumour cells and a low dose to healthy tissues. This defines the main requirement to a radionuclide: the energy emitted during its decay should be mainly deposited locally, while whole body irradiation must be as small as possible. To meet these requirements, the general demands for the physical properties of radionuclides should be (modified from [1]):

- The radionuclide should emit particulate radiation: alpha- or beta-particles, Auger and/or conversion electrons in sufficient abundance to exert cytotoxic action.
- High abundance of high-energy gamma components is undesirable since it gives whole-body irradiation, however, low abundance photons (100–200 keV) might be of advantage for imaging (e.g. dosimetry) and therapy monitoring.
- A physical half-life of 1 to 14 days, depending on in vivo pharmacokinetics of the targeting agent, seems to be optimal.
- Possibility to produce the radionuclide with a high enough amount of radioactivity with a suitable specific radioactivity.
- Possibility to produce the radionuclide in a cost-efficient way.
- The chemical properties of the radionuclide should enable high-yield labelling of proteins and peptides during relatively mild conditions and provide a conjugate, which is stable in the blood circulation.
- The radiocatabolites should be quickly excreted from the body, without too much accumulation in normal organs or tissues.

Physical Properties

The physical half-life of the radionuclide should match the biological half-life of the targeting protein. One cannot expect an efficient therapy effect on a solid tumour, if a full-length antibody, which has slow tumour penetration and long residence time in the circulation, is labelled with a nuclide with a too short half life. The main part of the radionuclides would then decay when the targeting conjugate is still outside the tumour, and possibly contribute to irradiation of healthy tissues, e.g. bone marrow. Moreover, theoretical calculations suggest that long half-life of the radionuclide is more favourable for radionuclide therapy [2], since for a given anti-tumour effect long-lived nuclides are more lenient to bone marrow. Still, considerations of logistics, costs and availability might suggest the use of rather short-lived therapeutic radionuclides for small proteins and peptides with a rapid blood clearance. Such decision should include careful dosimetric evaluations.