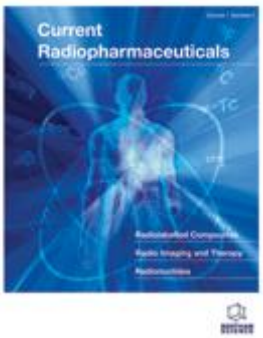
AULA VIRTUAL de RADIOFARMACIA

Plataforma Virtual de Formación Continuada en Radiofarmacia
(www.aulavirtualradiofarmacia.es)

Recomendamos la lectura del número de Julio de 2011 de Current Radiopharmaceuticals sobre α-Radiofármacos



Current Radiopharmaceuticals

Volume 4, Number 3, July 2011

Editorial **Targeted Alpha Therapy – Part I (Guest Editor: Jorgen Elgqvist)]** Pp. 176-176
Jorgen Elgqvist

Astatine-211: Production and Availability Pp. 177-185
Michael R. Zalutsky and Marek Pruszynski

The ARRONAX Project Pp. 186-196
Ferid Haddad, Jacques Barbet and Jean-Francois Chatal

Protein Targeting Constructs in Alpha Therapy Pp. 197-213
Tove Olafsen, Jorgen Elgqvist and Anna M. Wu

Chemical and Radiochemical Considerations in Radiolabeling with α-Emitting Radionuclides Pp. 214-247
D. Scott Wilbur

Pretargeted Radioimmunotherapy with α-Particle Emitting Radionuclides Pp. 248-260
Sture Lindegren and Sofia H.L. Frost

Modelling and Dosimetry for Alpha-Particle Therapy Pp. 261-265
George Sgouros, Robert F. Hobbs and Hong Song

Alpha-Particle Microdosimetry Pp. 266-280
Nicolas Chouin and Manuel Bardies

Abstracts

Editorial [Hot Topic: Targeted Alpha Therapy – Part I (Guest Editor: Jorgen Elgqvist)]

Jorgen Elgqvist

The Magic-Bullet: Moving the Concept Towards Reality – Part I

The possibility of pinpointing biological targets, and thereby potentially targeting and eradicating small tumors or even single cancer cells, is a tantalizing concept that has been discussed since the magic-bullet concept was first presented by Paul Erlich in the beginning of the 20th century in connection with his work on tissue staining for histological examinations and the work by Kohler and Milstein on antibody production published in 1975. This concept now seems feasible through the use of highly specific targeting constructs, chemical labeling of radioactive substances to these targeting constructs that results in high specific activities, radioimmunocomplexes with good stability even after injection, and the use of radionuclides emitting alpha(α)-particles having exceedingly high ionizing density and, therefore, a high probability of killing cells along its track in tissue. The short range of the emitted α-particles makes them even more interesting by minimizing unwanted irradiation of normal tissue surrounding the targeted cancer cells of interest, assuming high specificity of the targeting construct and good stability of the chemical bonds between the targeting construct and the α-particle emitter.

Targeted Alpha Therapy (TAT), in which an α-particle emitting radionuclide is specifically directed to the biological target, is gaining more attention as new targets, targeting constructs, chemical labeling techniques, and α-particle emitters are, respectively, identified, constructed, developed, and made available. Results and improvements are now being published at an increasing rate and the number of conceivable applications is expanding, especially in the field of cancer treatment. Therefore, it is of utmost importance to provide an overview of the overall progress in the research field of TAT on a regular basis. However, problems such as limited or delayed diffusion of the α-radioimmunocomplex and inhomogeneous activity distributions in the targeted tumors, resulting in inhomogeneous absorbed dose distributions, are challenges that need to be addressed. These challenges need to be overcome before TAT becomes a standard treatment for diseases such as micrometastatic cancer. Hopefully, when enough funding will be provided and, hence, more treatment strategies of TAT will reach the clinical level the importance to conduct controlled, randomized trials with sufficient patient numbers, enabling statistical significance to occur must be emphasized in order to be able to properly compare and evaluate different approaches.

In this issue, of the two hot-topic issues for targeted alpha therapy, articles discuss the recent developments in radionuclide availability, biomolecular targeting, labeling chemistry, and dosimetry for the most promising α-particle emitters. In the first article, Zalutsky et al. discuss the possibilities and limitations of using the promising α-particle emitter, 211At, and emphasize the need for funding new cyclotrons and prioritizing beam-times of already existing cyclotrons to improve the availability of 211At. Haddad et al. describe the status of the ARRONAX project through which a number of important nuclear medicine radionuclides will be produced, including some of those suitable for TAT. Relevant targeting constructs and their associated antigens used today and candidates for use in the future are discussed by Olafsen et al. in the third article. The next article, by Scott Wilbur, discusses chemical and radiochemical issues of radiolabeling using α-particle emitting radionuclides, e.g. factors that are important in selecting chelation or bonding reagents during the development of α-particle emitting radiopharmaceuticals. Lindegren at al. continue the discussion of chemical considerations in the following article, but focuses on pre-targeting techniques, which will hopefully enhance both the activity distribution in the targeted tumor and the tumor-to-normal tissue absorbed dose ratio. The two final articles discuss different aspects of the dosimetry related to α-particles. The article by Sgouros et al. discusses how knowledge of the microscopic distribution of α-particle emitters is necessary to perform correct dosimetry, as well as the importance of the translation of activity distributions obtained in pre-clinical studies to the human situation, which requires micro-scale models of the source-target geometry at human dimensions according to the authors. Chouin et al. focus in the following article on the microdosimetry of α-particles. The authors present basic concepts and some applications of the microdosimetry for TAT, and conclude microdosimetry should only be considered when alternative approaches fail to provide an account of a given biological endpoint.

The intention of this particular hot-topic issue is to present an up-to-date overview of key areas in the research field of TAT, i.e. radionuclides available, targeting constructs, labeling chemistry, and dosimetry. This issue will hopefully be followed by similar ones jointly produced by contributions from the research community active in the field, of which most researchers are participating in these two particular issues, i.e. Targeted Alpha Therapy – Part I and II.

Astatine-211: Production and Availability

Michael R. Zalutsky and Marek Pruszynski

The 7.2-h half life radiohalogen 211At offers many potential advantages for targeted α-particle therapy; however, its use for this purpose is constrained by its limited availability. Astatine-211 can be produced in reasonable yield from natural bismuth targets via the 209Bi(α,2n)211At nuclear reaction utilizing straightforward methods. There is some debate as to the best incident α-particle energy for maximizing 211At production while minimizing production of 210At, which is problematic because of its 138.4-day half life α-particle emitting daughter, 210Po. The intrinsic cost for producing 211At is reasonably modest and comparable to that of commercially available 123I. The major impediment to 211At availability is attributed to the need for a medium energy α-particle beam for its production. On the other hand, there are about 30 cyclotrons in the world that have the beam characteristics required for 211At production.

The ARRONAX Project

Ferid Haddad, Jacques Barbet and Jean-Francois Chatal

A new high-energy and high-intensity cyclotron, ARRONAX, has been set into operation in 2010. ARRONAX can accelerate both negative ions (H- and D-) and positive ions (He++ and HH+). Protons can be accelerated from 30 MeV up to 70 MeV with a maximum beam intensity of 2 × 375 μAe whereas He++ can be accelerated at 68 MeV with a maximum beam current of 70 μAe. The main fields of application of ARRONAX are radionuclide production for nuclear medicine and irradiation of inert or living materials for radiolysis and radiobiology studies. A large part of the beam time will be used to produce radionuclides for targeted radionuclide therapy (copper-67, scandium-47 and astatine-211) as well as for PET imaging (scandium-44, copper-64, strontium-82 for rubidium-82 generators and germanium-68 for gallium-68 generators). Since the beginning of the project a particular interest has been devoted to alpha-radionuclide therapy using complex ligands like antibodies and astatine-211 has been selected as a radionuclide of choice for such type of applications. Associated with appropriate carriers, all these radionuclides will respond to a maximum of unmet clinical needs.

Protein Targeting Constructs in Alpha Therapy

Tove Olafsen, Jorgen Elgqvist and Anna M. Wu

The progress in the field of targeted α-particle therapy (TAT) has to a great extent been enhanced by developments in both recombinant DNA technology and radionuclide labeling chemistry. Advances in genomics and proteomics have promoted an increase in the identification of novel targets and molecules that can define different diseases, such as cancer. In radioimmunotherapy (RIT), the primary goal is to improve delivery to and therapeutic efficacy of the cancer cells, whilst minimizing toxicity. Different approaches have been investigated to achieve this, such as reducing the size of the carrier, pretargeting, multidosing, locoregional administration and using a cocktail of radiolabeled monoclonal antibodies for targeting multiple antigens simultaneously. Some of these approaches have been encouraging, but translation of TAT into the clinic has been slow, in part because of the limited availability and the short physical half-lives of some of the available α-particle emitters. The clinical studies carried out to date have been promising, although many challenges remain in order to make TAT safe and economically feasible. In this paper a number of different targeting constructs used hitherto that may be promising carriers for TAT in the future are presented and discussed. The constructs include enzymatic cleaved antibody fragments (Fab and F(ab˙)2 fragments); genetically engineered antibody fragments (scFv monomer, dimer (i.e. diabody) and tetramer, CH2 domain deleted antibody fragments); other protein targeting constructs such as affibodies and peptides as well as liposomal delivery.

Chemical and Radiochemical Considerations in Radiolabeling with α-Emitting Radionuclides

D. Scott Wilbur

A review of chemical and radiochemical factors that must be considered when radiolabeling targeting agents with radionuclides is presented. The review discusses factors that are important in choice of radionuclide and choice of chelation or bonding reagents to use in the development of an α-emitting radiopharmaceutical. Chemical parameters, such as physical properties and pendant groups for radiolabeling, are reviewed. A major portion of the review outlines the development of chelates and labeling conditions for radiometals, and application of these reagents/conditions to radiometals. Acyclic and macrocyclic chelates containing amine and carboxylic acid coordination groups are highlighted, with examples of bifunctional chelates for biomolecule conjugation. Information is presented on over 60 radiometal-binding chelates. 211At radiolabeling is separated from that of radiometals, and the various reagents used for radiolabeling have been reviewed. Although not all 211At-labeling reagents are reviewed (due to another recent review), nearly 50 reagents studied in the development of pendant groups for labeling with 211At are described. The review also discusses how therapeutic doses of α-emitting radiopharmaceuticals can be affected by the radionuclide used and how radiation damage to the radiopharmaceutical can be minimized.

Pretargeted Radioimmunotherapy with α-Particle Emitting Radionuclides
Sture Lindegren and Sofia H.L. Frost

Alpha-particle emitting radionuclides are attractive for targeted cancer therapies due to their physicochemical properties. Their high linear energy transfer (LET) and short particle range makes them particularly toxic at a microscopic level, which is ideal for treating disseminated micrometastases. However, their cytotoxic properties also place special demands on the pharmacokinetics of the tumor specific carrier vector, where high tumor-to-normal-tissue ratios are a prerequisite. Tumor specific antibodies are perhaps the most common vector for targeted therapy, but due to pharmacokinetics considerations antibodies will generally not meet the standard for α-particle radioimmunotherapy. However, the tumor specificity of monoclonal antibodies may be used in pretargeting techniques, strategies used to increase the selectivity of the radioactivity. The basic concept of pretargeting relies on a separate administration of a modified antibody and a radioactive ligand. The modified antibody is first injected and allowed to localize on the tumor. Then, the radiolabeled ligand is injected, which is a small molecule that rapidly localizes the modified antibody on tumor cells while non-localized ligand rapidly clears from the circulation, preferably through renal filtration. Several pretargeting strategies have been developed, in particular the avidin-biotin system and bispecific antibodies. Approaches under evaluation are the use of complementary DNA, morpholinos, and the use of infinite antigen binding. Preclinical and clinical studies of pretargeting have shown that favorable distribution of the radioactivity can be achieved, which may increase dose to the tumor as compared with the dose from directly labeled antibodies, and most important decrease the dose to normal tissues. This survey describes different pretargeting strategies, and includes a review of pretargeting with α emitting radionuclides.

Modelling and Dosimetry for Alpha-Particle Therapy

George Sgouros, Robert F. Hobbs and Hong Song

As a consequence of the high potency and short range of alpha-particles, radiopharmaceutical therapy with alpha- particle emitting radionuclides is a promising treatment approach that is under active pre-clinical and clinical investigation. To understand and predict the biological effects of alpha-particle radiopharmaceuticals, dosimetry is required at the micro or multi-cellular scale level. At such a scale, highly non-uniform irradiation of the target volume may be expected and the utility of a single absorbed dose value to predict biological effects comes into question. It is not currently possible to measure the pharmacokinetic input required for micro scale dosimetry in humans. Accordingly, pre-clinical studies are required to provide the pharmacokinetic data for dosimetry calculations. The translation of animal data to the human requires a pharmacokinetic model that links macro- and micro-scale pharmacokinetics thereby enabling the extrapolation of micro-scale kinetics from macroscopic measurements. These considerations along with a discussion of the appropriate physical quantity and related units for alpha-particle radiopharmaceutical therapy are examined in this review.

Alpha-Particle Microdosimetry

Nicolas Chouin and Manuel Bardies

With the increasing availability of alpha emitters, targeted α-particle therapy has emerged as a solution of choice to treat haematological cancers and micrometastatic and minimal residual diseases. Alpha-particles are highly cytotoxic because of their high linear energy transfer (LET) and have a short range of a few cell diameters in tissue, assuring good treatment specificity. These radiologic features make conventional dosimetry less relevant for that context. Stochastic variations in the energy deposited in cell nuclei are important because of the microscopic target size, low number of α- particle traversals, and variation in LET along the α-particle track. Microdosimetry provides a conceptual framework that aims at a systematic analysis of the stochastic distribution of energy deposits in irradiated matter. The different quantities of microdosimetry and the different methods of microdosimetric calculations were described in the early eighties. Since then, numerous models have been published through the years and applied to analyse experimental data or to model realistic therapeutic situations. Major results have been an accurate description of the high toxicity of α-particles, and the description of the predominant effect of activity distribution at the cellular scale on toxicity or efficacy of potential targeted α-particle therapies. This last factor represents a major limitation to the use of microdosimetry in vivo because determination of

the source – target distribution is complicated. The future contributions of microdosimetry in targeted α-particle therapy research will certainly depend on the ability to develop high-resolution detectors and on the implementation of pharmaco-kinetic models at the tumour microenvironment scale.

Colabora con Farmacéuticos Mundi (**FarmaMundi**) (http://www.farmaceuticosmundi.org/)