



# AULA VIRTUAL de RADIOFARMACIA

Plataforma Virtual de Formación Continuada en Radiofarmacia

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## INFORMA

# Alfa Radiofármacos (II)

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### Targeted Alpha Therapy – Part II

*Jorgen Elgqvist*

As already mentioned in Part I of these two hot-topic issues for Targeted Alpha Therapy (TAT), 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. As discussed in Part I, this concept now seems feasible partly due to the use of highly specific protein targeting constructs (Olafsen et al., *Curr. Radiopharm.*, 2011, 4(3), 197-213), and refined radiochemical labeling techniques (Wilbur, *Curr. Radiopharm.*, 2011, 4(3), 214-247, and Lindegren et al., *Curr. Radiopharm.*, 2011, 4(3), 248- 260). In Part I the production of radionuclides suitable for TAT was also discussed (Zalutsky et al., *Curr. Radiopharm.*, 2011, 4(3), 177-185, and Haddad et al., *Curr. Radiopharm.*, 2011, 4(3), 186-196) as well as some dosimetric aspects of alpha( $\alpha$ )- particles (Sgouros et al., *Curr. Radiopharm.*, 2011, 4(3), 261-265, and Chouin et al., *Curr. Radiopharm.*, 2011, 4(3), 266-280).

The use of  $\alpha$ -particles, having a linear energy transfer (LET) typically of about 100 keV/ $\mu$ m and, therefore, a high probability of causing double strand breaks (DSB) and hence killing cells along its track, is very promising. The short range of the  $\alpha$ - particles (maximum  $\sim$ 80  $\mu$ m in tissue) makes them even more interesting by minimizes unwanted irradiation of normal tissue surrounding the targeted cancer cells, assuming high specificity of the targeting construct and good stability of the chemical bonds between the targeting construct and the  $\alpha$ -particle emitter. If specificity or penetration of the radioimmunoconjugate into tumor tissue is not good enough though, heterogeneous distribution of the



radioimmunoconjugates will occur (and hence a heterogeneous absorbed dose distribution) and the short range of the  $\alpha$ -particles will be a drawback. The need for developing targeting constructs with high specificity must therefore be emphasized, although the bystander effect potentially could decrease the unwanted effect of heterogeneous cancer cell killing in a tumor to some degree. The importance of improving the specific activity of the injected solution should also not be underestimated, especially important when treating low antigen-expressing cancer cells.

It is very encouraging to see an increasing clinical experience with TAT, although the pace with which it does could preferably be higher. The clinical experience includes gliomas, ovarian cancer, metastatic melanoma, metastatic prostate cancer, lymphoma, and acute myeloid leukemia. Further clinical trials, e.g. phase II trials, are to a large extent dependent on governmental support and funding, and one of the aims of these two hot-topic issues is therefore to summarize and to show the potential of TAT for the relevant authorities.

In this issue, the last of these two hot-topic issues for TAT, articles discuss the recent developments in the applications of  $^{211}\text{At}$ ,  $^{223}\text{Ra}$ ,  $^{213}\text{Bi}$ , and  $^{225}\text{Ac}$ , the toxicity of  $\alpha$ -particle emitting radioimmunoconjugates, patient specific  $\alpha$ -particle dosimetry, and the future prospects for TAT. In the first article, Vaidyanathan et al. discusses  $^{211}\text{At}$  and  $^{223}\text{Ra}$  and their applications in TAT. The authors say that  $^{211}\text{At}$  probably is the most versatile based on its half life, decay scheme and chemistry. But for targeting bone metastases, they indicate that  $^{223}\text{Ra}$  is the ideal radionuclide because simple cationic radium can be used for this purpose. The second article by Morgenstern et al. discusses the applications of  $^{213}\text{Bi}$  in TAT and describes methods for the production of  $^{225}\text{Ac}$  and  $^{225}\text{Ac}/^{213}\text{Bi}$  radionuclide generators. The article gives an overview of selected preclinical studies and summarizes the current clinical experience with  $^{213}\text{Bi}$ . Scheinberg et al. presents different therapeutic applications of  $^{225}\text{Ac}$  and mentions for example that it has been developed into potent targeting drug constructs and is in clinical use against acute myelogenous leukemia. The fourth article, by Dahle et al., discusses the normal tissue toxicity and relative biological effectiveness (RBE) of  $\alpha$ -emitting radioimmunoconjugates, and conclude by for example saying that RBE is useful preclinical information that should be taken into consideration when designing clinical trials of TAT. In the article by Palm et al. the patient dosimetry related to TAT is discussed. Similarities and differences compared to conventional therapies using  $\beta$ -particle emitters are mentioned, and the specific challenges of establishing accurate dosimetry for  $\alpha$ -particles in the individual patient are presented. In the concluding article by Barry Allen the future prospects of TAT are presented. The strengths and weaknesses of TAT are examined and the way forward for clinical acceptance is discussed. For example, tumor antivascular  $\alpha$ -therapy (TAVAT) for solid tumors is mentioned by the author as one way to extend the promise of TAT.....



## **Applications of $^{211}\text{At}$ and $^{223}\text{Ra}$ in Targeted Alpha-Particle Radiotherapy**

*Ganesan Vaidyanathan and Michael R. Zalutsky*

Targeted radiotherapy using agents tagged with  $\alpha$ -emitting radionuclides is gaining traction with several clinical trials already undertaken or ongoing, and others in the advanced planning stage. The most commonly used  $\alpha$ -emitting radionuclides are  $^{213}\text{Bi}$ ,  $^{211}\text{At}$ ,  $^{223}\text{Ra}$  and  $^{225}\text{Ac}$ . While each one of these has pros and cons, it can be argued that  $^{211}\text{At}$  probably is the most versatile based on its half life, decay scheme and chemistry. On the other hand, for targeting bone metastases,  $^{223}\text{Ra}$  is the ideal radionuclide because simple cationic radium can be used for this purpose. In this review, we will discuss the recent developments taken place in the application of  $^{211}\text{At}$ -labeled radiopharmaceuticals and give an overview of the current status of  $^{223}\text{Ra}$  for targeted  $\alpha$ -particle radiotherapy.

## **Targeted Alpha Therapy with $^{213}\text{Bi}$**

*Alfred Morgenstern, Frank Bruchertseifer and Christos Apostolidis*

The potential of targeted therapy with the alpha emitter  $^{213}\text{Bi}$  has been successfully demonstrated in a large number of preclinical studies and several clinical trials have provided evidence for its feasibility, safety and therapeutic efficacy. This review describes methods for the production of  $^{225}\text{Ac}$  and  $^{225}\text{Ac}/^{213}\text{Bi}$  radionuclide generators, gives an overview of selected preclinical studies and summarizes the current clinical experience with  $^{213}\text{Bi}$ .

## **Actinium-225 in Targeted Alpha-Particle Therapeutic Applications**

*David A. Scheinberg and Michael R. McDevitt*

Alpha particle-emitting isotopes are being investigated in radioimmunotherapeutic applications because of their unparalleled cytotoxicity when targeted to cancer and their relative lack of toxicity towards untargeted normal tissue. Actinium- 225 has been developed into potent targeting drug constructs and is in clinical use against acute myelogenous leukemia. The key properties of the alpha particles generated by  $^{225}\text{Ac}$  are the following: i) limited range in tissue of a few cell diameters; ii) high linear energy transfer leading to dense radiation damage along each alpha track; iii) a 10 day half-life; and iv) four net alpha particles emitted per decay. Targeting  $^{225}\text{Ac}$ -drug constructs have potential in the treatment of cancer.



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## **Toxicity and Relative Biological Effectiveness of Alpha Emitting Radioimmunoconjugates**

*Jostein Dahle, Nasir Abbas, Oyvind S. Bruland and Roy H. Larsen*

Radioimmunotherapy based on  $\alpha$ -particle emitters has excellent properties as a treatment against micrometastatic and disseminated cancers because of the short path length (50 – 80  $\mu\text{m}$ ) and high linear energy transfer ( $\sim 100 \text{ keV}/\mu\text{m}$ ). Alpha-particles produce clustered DNA double-strand breaks and highly reactive hydroxyl radicals when hitting biological tissue. Hence, targeted  $\alpha$ -particle therapy offers the potential of selective tumor cell killing with low damage to surrounding normal tissue. The ideal applications for targeted  $\alpha$ -therapy are in treating neoplastic cells in circulation or when cancer cells are present as free-floating cells or spread along compartment walls. This review will provide a brief overview of the most promising radionuclides for targeted  $\alpha$ -therapy and compare their relative biological effectiveness (RBE) and normal tissue toxicity.

## **Patient-Specific Alpha-Particle Dosimetry**

*Stig Palm, Jorgen Elgqvist and Lars Jacobsson*

Alpha-particle therapy has received increased attention during the last few years because of the development of new targeting constructs and new labeling techniques and the availability of suitable  $\alpha$ -particle – emitting radionuclides. This work provides an overview of methods that have been used in clinical trials in estimating the absorbed dose to tumors and healthy tissue in patients following such  $\alpha$ -particle therapy. Similarities and differences compared to conventional therapies using  $\beta^-$ -particle emitters are presented. The specific challenges of establishing accurate dosimetry for  $\alpha$ - particles in the individual patient are also discussed, as is the effect that improved patient-specific dosimetry might have on the overall efficacy of this type of therapy.

## **Future Prospects for Targeted Alpha Therapy**

*Barry J. Allen*

The objectives in the application of targeted alpha therapy (TAT) for cancer therapy are reviewed. These relate to elimination of isolated cancer cells, cell clusters and tumors. Requirements for isolated cancer cells are good cellular targeting, high specific activity, and very short range. The regression of cell clusters in the peri-vascular space requires high capillary permeability and short range cross fire whereas for developed tumors, good bioavailability and anti-capillary activity are essential.

Current sources of alpha radiation are reviewed and the prospects for commercial sources for clinical application are discussed. The Ac:Bi generator



is the most practical alpha source, bringing therapy to Nuclear Medicine with the same practicality as the Mo:Tc generator has for imaging.

The status quo of TAT is briefly reviewed with respect to dose normalization, real time microdosimetry and biological dosimetry for deterministic and stochastic effects and toxicity. The role of Monte Carlo calculations is emphasized. The strengths and weaknesses of TAT are examined and the way forward for clinical acceptance is discussed.

## **Microwave Accelerated Labeling Methods in the Synthesis of Radioligands for Positron Emission Tomography Imaging**

*Amy E. Kallmerten, Abigail Alexander, Krista M. Wager and Graham B. Jones*

Nuclear imaging using positron emission tomography [PET] is a powerful technique with clinical applications which include oncology, cardiovascular disease and CNS disorders. Conventional chemical syntheses of the short half-life radionuclides used in the process however imposes numerous limitations on scope of available ligands. By utilizing microwave assisted synthesis methods many of these limitations can be overcome, paving the way for the design of diverse families of agents with defined cellular targets. This review will survey recent developments in the field with emphasis on the period 2006-2011.

Positron emission tomography [PET] has become one of the most powerful in vivo imaging modalities, capable of delivering mm<sup>3</sup> resolution of radiotracer distribution and metabolism [1]. When combined with anatomic imaging methods (MRI, CT) co-registered multimode images offer the potential to track metabolic and physiologic events in diseased states and guide and accelerate clinical trials of investigational new drugs. Also, this same methodology can be used to evaluate first pass pharmacokinetics/pharmacodynamics in early stage drug discovery. Though powerful as a technique only a limited number of drugs have seen clinical use and to date only one drug 2-fluoro-deoxy-D-glucose (FDG) has received FDA approval [2]. One of the drawbacks of PET imaging is the need for tracers labeled with an appropriate nuclide and the half-lives of these agents places special constraints on the chemical synthesis. Among the most popular are <sup>11</sup>C ( $t_{1/2} = 20.4$  min) and <sup>18</sup>F ( $t_{1/2} = 109.8$  min) labeled compounds and this has resulted in a resurgence of interest in practical application of their chemistries [3,4]. This review will focus on microwave mediated methods of acceleration of organic reactions used for the production of labeled PET image contrast agents, with emphasis on the five year period 2006 to 2011.



## **Preparation and Primary Bioevaluation of $^{99m}\text{Tc}$ -labeled-1-thio- $\beta$ -D-Glucose as Melanoma Targeting Agent**

*Romina Castelli, Marcelo Fernandez, Williams Porcal, Juan Pablo Gambini, Omar Alonso, Alejandro Chabalgoity, Maria Moreno and Pablo Cabral*

The development of specific radiolabeled probes towards molecular markers *in vivo* has gained interest as targeted imaging agents for a more accurate detection of diseases. The aim of this study was to evaluate early detection of melanoma tumor based on 1-thio- $\beta$ -D-glucose (1-TG) radiolabeled with technetium-99m.  $^{99m}\text{Tc}$ -1-TG has been synthesized and evaluated *in vitro* and *in vivo* for melanoma uptake.

Tumor-cell uptake of the  $^{99m}\text{Tc}$  complex was performed with cultured B16F1 murine melanoma cells which were also used for the *in vivo* studies. The methodology consisted in radiopharmaceutical synthesis followed by intravenous administration of  $^{99m}\text{Tc}$ -1-TG in melanoma bearing mice and scintigraphic imaging.

1-thio- $\beta$ -D-glucose was labeled with  $^{99m}\text{Tc}$  under reductive conditions using  $\text{SnCl}_2$ . Radiolabeling efficiency was  $> 96\%$ .  $^{99m}\text{Tc}$ -1-TG showed high melanoma uptake *in vitro*. This was confirmed *in vivo* since a significant difference of  $^{99m}\text{Tc}$ -1-TG uptake between melanoma model and the control joint was observed. General biodistribution showed renal uptake. The scintigraphic images showed tumor selective uptake of the 1-TG labeled, in tumor-bearing mice

This study indicates effective labeling of 1-thio- $\beta$ -D-glucose with  $^{99m}\text{Tc}$  that shows potential as a new type of specific probe for melanoma detection.

## **Nitroimidazole Radiopharmaceuticals in Bioimaging: I: Synthesis and Imaging Applications**

*Rakesh Sharma*

The paper is review on synthesis of nitroimidazole radiosensitizers useful in imaging of tumor cells. Nitroimidazole compounds are radiolabeled probes for specific use in imaging such as  $^{18}\text{F}$  for positron emission tomography;  $^{99m}\text{Tc}$  for single photon emission computed tomography;  $^{123}\text{I}$ , or  $^{131}\text{I}$  for computer assisted tomography and  $^{19}\text{F}$  for magnetic resonance imaging. In synthesis of radiopharmaceutical compounds, parent nitroimidazole is modified to thiopyranosyl nucleosides, neuraminic acid derivatives followed by nitro group deprotection-substitution and radiolabeling by specific isotopes. Commercial attempts have been made to radiolabel the nitroimidazole by [ $^{18}\text{F}$ ]fluorine, [ $^{131}\text{I}$ ] or [ $^{123}\text{I}$ ]iodine, [ $^{99m}\text{Tc}$ ]technetium and [ $^{64}\text{Cu}$ ]copper on modified side chain of nitroimidazole compounds to design multimodal and multifunctional imaging



techniques to detect and monitor the tumor hypoxia by measuring distribution of radiolabel or radiation. Nitroimidazole initially showed poor diffusion and poor stability in tissues with neurotoxicity concern limited its use as radiosensitizer. In last decade, several nitroimidazole derivatives were developed as potent less toxic and highly stable radiopharmaceuticals with optimized radiolabel concentration with high detectability of tumor oxygen or hypoxia. Currently, nitroimidazole based radiopharmaceuticals have emerged as multimodal and multifunctional hypoxia reporters with antitumor, anti-ischemic, anti-inflammatory and tumor targeting properties. In conclusion, nitroimidazole based radiopharmaceuticals are a new generation hypoxia biosensors for localized theradiagnostic utility in clinical medicine.

## **Nitroimidazole Radiopharmaceuticals in Hypoxia: Part II Cytotoxicity and Radiosensitization Applications**

*Rakesh Sharma*

Feasibility paper explores the cytotoxicity of nitroimidazole on tumor cells and liver cells to establish the 2'-nitroimidazole as radiosensitizer in cancer therapy and hypoxia monitoring. Hypothesis is that the presence of substituted nitro group on 2' position of imidazole ring is more enzyme sensitive and determinant of biochemical cytotoxicity as hypoxia reporter in isolated tumor cells or tumor tissues. Radiolabeling of nitroimidazole imparts tracer properties to locate the distribution (radiosensitizer) of nitroimidazole in the body. A 'theradiagnostic criteria of hypoxia' using nitroimidazole radiosensitizer is proposed based on tumor killing by enhanced tumor oxygen tension (therapeutics) and altered metabolizing enzymes (diagnostics) due to cytotoxicity of radiosensitizer. Both properties of nitroimidazole cytotoxicity and oxygen sensitivity place the nitroimidazole compounds in the class of tumor therapy and hypoxia detection. Initially nitroimidazole cytotoxicity was reported as antiparasitic drug. Now radiolabeled 2'-nitroimidazole is potential radiosensitizer in hypoxia treatment and monitoring in last two decades. Hydrophilic double radiolabel groups on imidazole ring offer multimodal imaging and active nitro- or imidazole ring in nitroimidazoles interact with intracellular metabolism in liver by biotransformation and biooxidation to cause cytotoxicity as biomarker of hypoxia. Nitroimidazole metabolizing and xenobiotic enzymes showed regulatory role to excrete out nitroimidazole from the body and reduced stay time in tissue. Nitroimidazoles showed physicochemical properties with poor tissue diffusion, less antioxidant redox potential and long retention time in tissue making them poor choice of hypoxia markers. Key of success is achieving 2'-Nitroimidazole based multimodal radiopharmaceuticals as less cytotoxic, more tumor oxygen specific multifunctional reporters of apoptosis, proliferation, and hypoxia in theradiagnostics and radiation oncology.



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