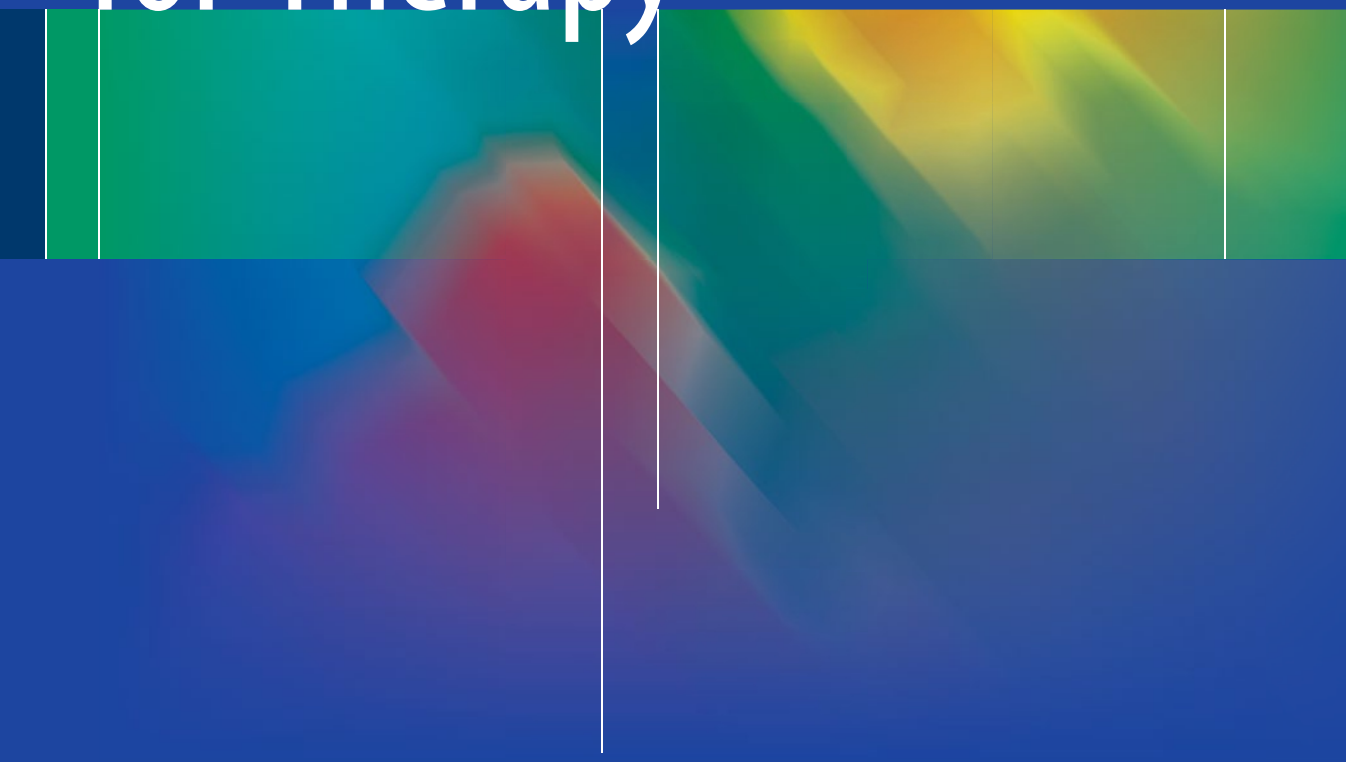
F.F. (Russ) Knapp
Ashutosh Dash

# Radiopharmaceuticals for Therapy



Springer

# Radiopharmaceuticals for Therapy

F.F. (Russ) Knapp • Ashutosh Dash

# Radiopharmaceuticals for Therapy

Springer

F.F. (Russ) Knapp
Nuclear Security and Isotope Division
Oak Ridge National Laboratory
OAK RIDGE
USA

Ashutosh Dash
Isotope Production and
Applications Division
Bhabha Atomic Research Centre
Mumbai
India

ISBN 978-81-322-2606-2 ISBN 978-81-322-2607-9 (eBook)
DOI 10.1007/978-81-322-2607-9

Library of Congress Control Number: 2015960843

Springer New Delhi Heidelberg New York Dordrecht London


Printed on acid-free paper

Springer (India) Pvt. Ltd. is part of Springer Science+Business Media (www.springer.com)

*The authors dedicate this book to their families, mentors, and colleagues who have so strongly affected their professional careers. Russ Knapp offers his dedication to his parents, who inspired and supported a strong interest in science at an early age; to his wife and best friend Toni, who for over 50 years encouraged and, even in many cases, tolerated his professional work; and to their children Michael and Gina, who have made his more important personal life such a joy. He also expresses his personal thanks to his deceased important friend, Mr. A. P. Callahan, who as a mentor and colleague had taught him so much about science and life. Ashutosh Dash gives his dedication to his wife Sarita and son Shaswat, who stood by him through thick and thin, lifted him up when he was low, pushed him forward at difficult times, and never complained at all when times were difficult. Through lonely and difficult times, they gave him strength and encouraged him. He also expresses his personal thanks to Dr. Russ Knapp for believing, encouraging, understanding, and tolerating through the whole process of completing this book.*

# Foreword

The use of radioactivity for treatment of disease is more than a century old and began with the use of naturally occurring radium-226 in the early part of the twentieth century. However, the field of radionuclide therapy (RNT) had not progressed as rapidly as probably anticipated due to the early failure due to absence of suitable targeting mechanisms. The use of artificially produced phosphorus-32 for the treatment of *polycythemia vera* beginning in the 1930s was a positive step which had stimulated the growth of this field. The major breakthrough for RNT, however, was the use of iodine-131 for the treatment of thyroid cancer which began in 1946. The uptake of radioactive iodide anions is governed by a well-defined mechanism involving the sodium iodide symporter protein and is the most basic and finest example of molecular nuclear medicine. Normal thyroid tissue takes up around 30 % of ingested iodine, which represents the highest targeting that a drug can achieve. Iodine-131 continues to be widely used post surgically for the ablation of remnant cancer cells. Although a variety of radiopharmaceuticals were subsequently introduced in later years for treatment of some types of cancer and for palliation of pain due to bone metastases, widespread/routine use has not yet gained broad acceptability. Generally, the majority of the patients who have undergone unsuccessful treatment by alternative nonradioactive strategies who have few other options for success are often referred for nuclear medicine RNT as a last resort and mainly for palliative therapy. In fact, none of the other therapeutic radiopharmaceuticals introduced in the last century have been anywhere nearly successful like the use of iodine-131 for the treatment of thyroid cancer.

In this regard, introduction of peptide receptor radionuclide therapy (PRRNT) in the beginning of the current millennium for the treatment of neuroendocrine tumors (NETs) with beta-emitting is an important seminal exception. PRRNT utilizes low molecular weight radiolabeled peptides targeting to specific cell surface receptors which are very often upregulated on cancer cells. Although several radioisotopes have been identified that are used for PRRNT, lutetium-177 and yttrium-90 are two key examples as radionuclides used for both PRRNT and radioactive antibody targeting. Currently, PRRNT using somatostatin analog peptides is the most efficacious mode of therapy for the treatment of inoperable NETs. However, NETs are tumors with relatively low incidence, and hence the total number of patients benefitted is still very small. Another important developing theme is the use of alpha-emitting radioisotopes for therapy, and the commercialization and

routine clinical introduction of the Xofigo® (radium-223 chloride) for the treatment of castration-resistant prostate cancer is an important advance for the therapeutic arena.

However, the real success of PRRNT, as an example, will be demonstrated when suitable radiopharmaceuticals are developed for the treatment for major cancer entities, and success in this direction is already on the horizon. The pharmacophore, N-acetyl aspartyl glutamate (NAAG), radiolabeled with $^{68}$Ga, for instance, is providing excellent PET images of patients presenting with prostate cancer. Adenocarcinoma of the prostate gland overexpresses prostate-specific membrane antigen (PSMA) which is targeted by NAAG. Because this is a small peptide, the radioactivity not attached to the targeted cancer cells is rapidly excreted, thereby providing excellent PET images of the cancer-affected areas. Lutetium-177-labeled NAAG is also under evaluation for the treatment of prostate cancer, and the male patient population who can benefit from this PET technology is very large and is expected to dramatically change the trajectory of targeted therapy.

Growth in the development of therapeutic radiopharmaceuticals is linked to advances in many related disciplines, and molecular biology identifies suitable targets for different types of cancer. An in-depth understanding of the biochemical reactions occurring within the body is important to provide information which will help identify new targets. Once suitable target-seeking molecules are identified, subsequent detailed research is required to develop a successful therapeutic radiopharmaceutical. These efforts include an evaluation for modification of the target-seeking pharmacophore to provide suitable radiolabeling without compromising the affinity to the target. In addition, both in vitro and in vivo biological studies are required to demonstrate the targeting property, and preclinical evaluation and finally the demonstration of the clinical efficacy must be established. A major goal which presents these challenges is the subsequent use in humans. Current regulations in most countries mandate that a radiopharmaceutical undergoes the same phase 0, I, II, and III studies before its market introduction as a product. Compliance with these regulatory requirements is difficult for a commercial radiopharmaceutical manufacturer to justify, since the modest market volume for therapeutic radiopharmaceuticals will often not qualify the high investment required for a clinical trial. The usual short shelf lives of radiopharmaceuticals do not allow large-scale manufacturing, and it is difficult for patent holders to overcome the competition of use of generic radiopharmaceutical products. Hence, most discoveries in the therapeutic radiopharmaceutical arena are not used to the most effective extent for the benefit of mankind. Nevertheless, the scientists working in this area put forth extensive efforts to develop new therapeutic radiopharmaceuticals.

There are many young colleagues who wish to work in the fascinating multidisciplinary field of therapeutic radiopharmaceuticals, which, by nature, requires broad knowledge in many fields, which includes radioisotope production, chemistry, radiochemistry, and biology and physiology. There is extensive literature available on therapeutic radiopharmaceuticals; however, a primary source which will provide basic knowledge is highly useful, not only for new investigators in this area but also for those scientists, physicians, and

other professionals already working in the field of nuclear medicine. For these reasons this book on "radiopharmaceuticals for therapy" authored by Prof. F. F. (Russ) Knapp and Dr. A. Dash is expected to fill an important niche in the literature. The 17 chapters span all key aspects describing the development and use of therapeutic radiopharmaceuticals. The expertise and extensive experience of these authors are reflected in the appropriate selection of chapters and their contents. This book will be highly useful to scientists and nuclear medicine physicians working in this fascinating field, and I am honored to have been given the opportunity to provide the Foreword to *Therapeutic Radiopharmaceuticals*.

Cochin, India M.R.A. Pillai, PhD, DSc

# Acknowledgments

The authors extend their sincere appreciation to Dr. M. R. A. Pillai, Ph.D., D.Sc., for his vision in conceiving the important need for a book on therapeutic radiopharmaceuticals and for providing the *Foreword*. He had initially recommended this book to Springer Verlag and had encouraged the authors to move forward. The authors also thank their families for their patience and their colleagues who have helped in many different ways and who had provided information and insights which encouraged the authors. Special thanks are also extended to Mr. Mark Dickey, a senior member of the ORNL technical library staff, for his enthusiastic assistance in identifying and obtaining reference and reprint materials.

# Contents

**Part I Radiopharmaceuticals**

**1 Introduction: Radiopharmaceuticals Play an Important Role in Both Diagnostic and Therapeutic Nuclear Medicine** . . . . . 3
1.1 Introduction: Use of Radioisotopes in Nuclear Medicine . . . 3
1.2 Key Examples of Nuclear Medicine. . . . . 4
1.2.1 Nuclear Medicine Imaging . . . . . 4
1.2.2 Molecular Imaging . . . . . 4
1.2.3 In Vivo Function Tests. . . . . 6
1.2.4 Nuclear Medicine Therapy . . . . . 6
1.3 Radiopharmaceuticals. . . . . 6
1.3.1 Diagnostic Radiopharmaceuticals. . . . . 8
1.3.2 Nuclear Medicine Imaging . . . . . 9
1.4 Therapeutic Radiopharmaceuticals . . . . . 13
1.4.1 Traditional Applications of Therapeutic Radiopharmaceuticals. . . . . 14
1.4.2 Current and New Therapeutic Applications . . . . . 15
1.5 Historical Timeline of Nuclear Medicine. . . . . 17
1.6 Summary. . . . . 20
References. . . . . 21

**2 Therapeutic Radionuclides Decay with Particle Emission for Therapeutic Applications**. . . . . 25
2.1 Introduction . . . . . 25
2.2 Criteria for Selection of Therapeutic Radionuclides . . . . . 27
2.2.1 Particle Emission. . . . . 27
2.2.2 Tissue Treatment Morphology . . . . . 28
2.2.3 Radionuclide Half-Life . . . . . 28
2.2.4 Radionuclide Decay Products . . . . . 28
2.2.5 Radionuclide Purity. . . . . 28
2.2.6 Gamma Emissions. . . . . 28
2.2.7 Radiolabeling Chemistry. . . . . 29
2.2.8 Economic Factors . . . . . 29
2.3 Beta-Particle-Emitting Radionuclides . . . . . 29
2.4 Alpha-Particle-Emitting Radionuclides . . . . . 29
2.5 Low-Energy Electron Emitters. . . . . 30
2.6 Radionuclide Production . . . . . 30

2.6.1 Targets for Irradiation . . . . . 32
2.6.2 Production of Therapeutic Radionuclides . . . . . 33
2.6.3 Auger Electron-Emitting Radionuclides . . . . . 33
2.6.4 Alpha-Particle-Emitting Radionuclides . . . . . 33
References . . . . . 34

**3 Alpha Radionuclide Therapy** . . . . . 37
3.1 Introduction . . . . . 37
3.2 Alpha Particles . . . . . 38
3.2.1 Energy Dissipation of Alpha Particles in a Medium . . 38
3.2.2 Linear Energy Transfer (LET) . . . . . 38
3.2.3 Relative Biological Effectiveness (RBE) . . . . . 39
3.2.4 Interaction of Alpha Particles in a Biological System . . . . . 40
3.2.5 Basis of Alpha Radionuclide Therapy . . . . . 40
3.2.6 Dosimetry . . . . . 41
3.3 Alpha-Particle-Emitting Radionuclides for Radiotherapy . . . 42
3.3.1 Astatine-211 . . . . . 42
3.3.2 Terbium-149 . . . . . 47
3.3.3 Actinium-225 . . . . . 47
3.3.4 Bismuth-213 . . . . . 50
3.3.5 Bismuth-212 . . . . . 51
3.3.6 Radium-223 . . . . . 51
3.3.7 Radium-224 . . . . . 52
3.3.8 Thorium-227 . . . . . 52
3.4 Summary: Future Prospects of Alpha Radionuclide Therapy . . . . . 53
References . . . . . 53

**4 Auger Electron-Based Radionuclide Therapy** . . . . . 57
4.1 Introduction: Cancer Treatment with Radioisotopes . . . . . 57
4.2 Particle Emission . . . . . 57
4.3 The Auger Process . . . . . 58
4.4 Cell Killing with Auger Electron Emitters . . . . . 58
4.5 The Importance of Auger Electron-Emitting Radionuclides for Cancer Therapy . . . . . 60
4.6 Key Auger Emitters . . . . . 61
4.6.1 Iodine-125 . . . . . 61
4.6.2 Platinum-195m . . . . . 61
4.6.3 Rhodium-103m . . . . . 62
4.6.4 Holmium-161 . . . . . 63
4.7 Dosimetry . . . . . 63
4.7.1 Electron Transport Evaluation and Dosimetry Assessment . . . . . 64
4.7.2 Auger Electron Spectra . . . . . 64
4.7.3 Energy Loss by Auger Electrons . . . . . 64
4.7.4 Dosimetry Issues . . . . . 65
4.8 Summary . . . . . 65
References . . . . . 65