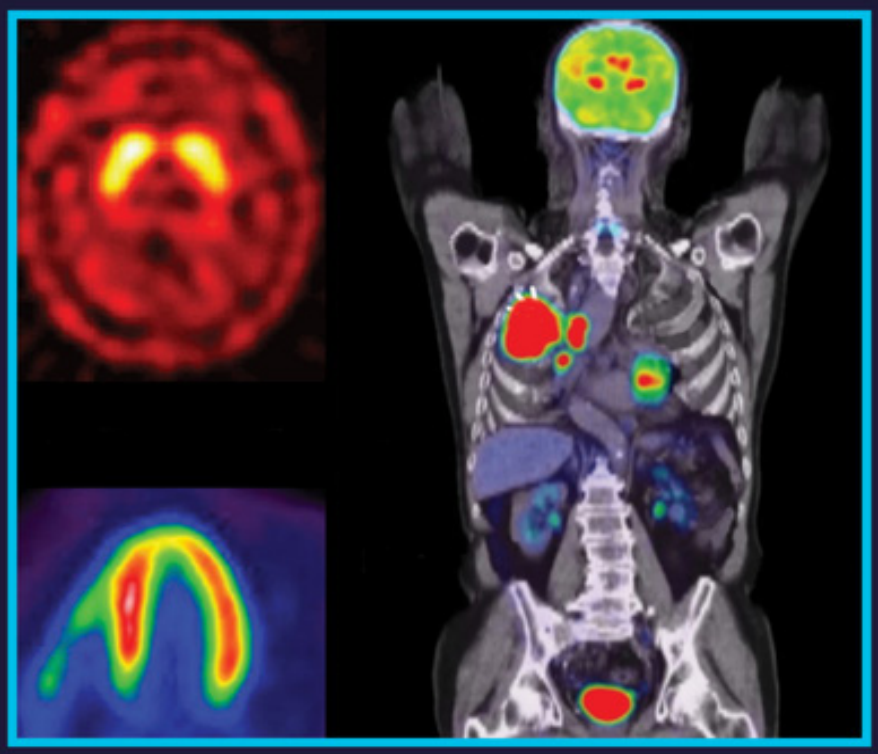
Second Edition

Handbook of Radiopharmaceuticals

Methodology and Applications



Edited by
Michael R. Kilbourn
Peter J. H. Scott

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HANDBOOK OF RADIOPHARMACEUTICALS:

METHODOLOGY AND APPLICATIONS

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Foreword

When Mike Welch and Carol Redvanly edited the first edition of the *Handbook of Radiopharmaceuticals* in 2003, the field of radiopharmaceutical sciences was undergoing a number of important changes. [^{18}F]Fludeoxyglucose ([^{18}F]FDG) had been recently approved by the US Food and Drug Administration (**FDA**), and reimbursement coverage was in place from the US Centers for Medicare and Medicaid Services. This was creating a burgeoning market for commercial production and distribution of [^{18}F]FDG, which in turn drove innovation in both radiopharmaceutical manufacture and clinical scanner technology. At the same time, increasing numbers of radiochemistry facilities were stimulating the development of many different radiopharmaceuticals for research applications.

This innovation and research have continued over the intervening years, and as we complete this new edition at the start of the *Roaring Twenties,* we have been reflecting that it is another exciting and transformative time in the fields of nuclear medicine and radiopharmaceutical sciences! New radiopharmaceuticals continue to be approved by the FDA, including PET radiotracers for brain and cancer imaging and theranostics for cancer treatment. These radiopharmaceuticals are transforming the lives of the patients we diagnose and treat in our clinicals every day. Coupled with lobbying efforts by the Society of Nuclear Medicine and Molecular Imaging (**SNMMI**) and others to inform reimbursement policy, significant efforts by industrial partners to develop the radiochemistry and PET imaging suites of the future, initiatives by academic colleagues to standardize the nomenclature of our science,[1] and the expected impact of artificial intelligence on our discipline, nuclear medicine has been invigorated and is transforming from a research technique into a powerful standard of care.

This growth in nuclear medicine is apparent in day-to-day operations around the world. In an established market like the United States, over 1.5 million clinical PET scans currently occur, and yet we have been impressed to see the number of clinical PET scans taking place at the University of Michigan double between 2014 and 2019. There is also substantial growth occurring in developing markets, and at the 2019 International Symposium of Radiopharmaceutical Sciences (**ISRS**) that took place in Beijing, it was remarked that a new PET scanner is being installed in China every two weeks! The concomitant growth in the use of radiotherapeutics means that innovation in the radiopharmaceutical sciences to meet these new demands is as important today as when the first edition of the *Handbook* was published.

[1] See Coenen et al., *Nucl Med Biol*. 2017;55:v-xi, doi: 10.1016/j.nucmedbio.2017.09.004.

We were both attracted to the fields of nuclear medicine and radiopharmaceutical sciences early in our careers for a number of reasons. First, radiopharmaceutical sciences is an exciting application of basic science with immediate impact on patient care; second, the translational aspect of the research is appealing; and finally, we thoroughly enjoy the diverse and multidisciplinary nature of the work. Our field exists at the intersection of medicine, biology, chemistry, physics, and engineering, and, with the exception of Antarctica, research applications and clinical uses of nuclear medicine are occurring on every continent.

The articles in the new edition of the *Handbook* demonstrate that the field of radiopharmaceutical sciences remains as multidisciplinary as ever. We have tried to keep this new edition faithful to the format of the original and asked authors to provide knowledge updates in their various sub-disciplines (radionuclide production, radiochemistry, applications of radiopharmaceuticals) that have occurred since the first edition was published. However, the evolution of the radiopharmaceutical sciences since that time, particularly in regards to current Good Manufacturing Practice (**cGMP**), regulatory oversight, and novel approaches to quality control, have necessitated the addition of new chapters in these areas.

We look forward to how our field continues to develop in the next 20 years, as we witness new technology and applications in the radiopharmaceutical sciences that might find their way into a future edition of the *Handbook* and continue the legacy of Mike Welch and the other visionaries who started our field.

Michael R. Kilbourn
Peter J.H. Scott
June 2020
Ann Arbor MI, USA

Preface

The first edition of the *Handbook of Radiopharmaceuticals* was published near the start of the twenty-first century. Dedicated by Michael J. Welch and Carol Redvanly to the memory of Alfred P. Wolf, that volume provided students and researchers with a comprehensive review of the field of radiochemistry and its growing importance in medicine.

This second edition of the *Handbook* is dedicated to the memories of Michael Welch and the many other notable scientists and physicians that the field has lost in recent years, many of whom served as mentors or colleagues of the contributing authors to this edition. The radiochemical sciences and medical imaging have grown tremendously just in the past two decades, and as we enter the third decade of the twenty-first century, there is the expectation that the future holds untold important and impactful advances. In this edition of the *Handbook*, we have emphasized chapters that bring the reader up to date on the exciting developments of recent years. We thank the editorial team at John Wiley & Sons as well as all of the authors, the majority of whom are new contributors, for their valuable time and effort in bringing this new edition of the *Handbook* to reality.

Michael R. Kilbourn
Peter J.H. Scott
June 2020
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Abbreviations

5-HT1A	serotonin 1A receptor
ACh	acetylcholine
AChE	acetylcholinesterase
AcOH	acetic acid
ACPC	1-aminocyclopentanecarboxylic acid
AD	Alzheimer's disease
ADC	antibody drug conjugate
ADM	s-adenosyl-L-methionine
AI	artificial intelligence
ALARA	as low as reasonably achievable
AMDP	aminomethylenediphosphonate
AMT	α-Methyl-L-tryptophan
ATP	adenosine triphosphate
ATTR	amyloid transthyretin
BACE	beta-secretase
BAT	brown adipose tissue
BBB	blood-brain barrier
B_{max}	maximum concentration of target binding sites
BOx	benzoxazole
BP	binding potential
BP	British Pharmacopeia
Bq	becquerel
BTA	aryl-benzothiazole
BZD	benzodiazepine
CAD	coronary artery disease
cAMP	cyclic adenosine monophosphate
CBF	cerebral blood flow
CBS	compton backscattered
[^{11}C]ACHC	aminocyclohexanecarboxylic acid
[^{11}C]DASB	[^{11}C]3-amino-4-(2-dimethylaminomethylphenylsulfanyl)-benzonitrile
[^{11}C]DOPA	[^{11}C dihydroxyphenylalanine
[^{11}C]DTBZ	[^{11}C]Dihydrotetrabenazine
[^{11}C]HED	[^{11}C]hydroxyephedrine
[^{11}C]PiB	[^{11}C]Pittsburgh compound B (PIB ([N-methyl-^{11}C]6-Me-BTA-1)
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practice
Ci	curie
ClogD	calculated distribution coefficient at pH 7.4
ClogP	calculated partition coefficient
CMC	chemistry, manufacturing, and controls

CMO	contract manufacturing organization
CNS	central nervous system
COMT	catecholamine O-methyl transferase
CSF	cerebrospinal fluid
CT	computed tomography
CTA	clinical trial application
CV	cardiovascular
CXCR4	CXC-chemokine receptor-4
Da	daltons
DAT	dopamine transporter
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDD	drug discovery and development
DIPE	di-isopropyl ether
DMA	*N,N*-dimethylacetamide
DMF	*N,N*-dimethylformamide
DMF	drug master file
DMSO	dimethyl sulfoxide
DNA	deoxyribose nucleic acid
DOTA	1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid
DPA	dipicolylamine
DPzA	dipyrazolylamine
Dx	dextran
EANM	European Association of Nuclear Medicine
EC	electron capture
ECD	[^{99m}Tc]ethylcysteine dimer
eCTD	electronic common technical document
EGFR	epidermal growth factor receptor
eLINACS	electron linear accelerators
EMA	European Medicines Agency
EOB	end-of-bombardment
EOS	end-of-synthesis
EP	European Pharmacopeia
EPI	epinephrine
EtOH	ethanol
EU	European Union
eV	electron volt
FA	fatty acid
FAAH	fatty acid amide hydrolase
[^{18}F]FACBC	1-amino-3-[^{18}F]fluorocyclobutanecarboxylic acid (Fluciclovine, Axumin)
FDA	Food and Drug Administration
[^{18}F]FDG	2-deoxy-2-[^{18}F]fluoro-D-glucose
FDH	formate dehydrogenase
[^{18}F]FDOPA	6-[^{18}F]fluorodihydroxyphenylalanine
[^{18}F]FES	[^{18}F]fluoroestradiol
[^{18}F]FET	2-[^{18}F]fluoroethyl)-L-tyrosine
[^{18}F]FMISO	[^{18}F]fluoromisonidazole

[^{18}F]FMT	[^{18}F]fluoromethyltyrosine
[^{18}F]FPEB	[^{18}F]3-fluoro-5-(pyridin-2- ylethynyl)benzonitrile
[^{18}F]FSPG	(S-4-(3-[^{18}F]fluoropropyl)-L-glutamic acid
g	gram
GABA	gamma amino butyric acid
GC	gas chromatography
GIST	gastrointestinal stromal tumors
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HBED	*N,N'*-bis(2-hydroxybenzyl)ethylendiamine-*N,N'*-diacetic acid
HDA	hexadecanoic acid
HER	human epidermal growth factor receptor
HEU	highly enriched uranium
HITS	high-throughput screening
HIV/AIDS	human immunodeficiency virus/ acquired immunodeficiency syndrome
HMPAO	[^{99m}Tc]hexamethylpropyleneamine oxime
HMR	heart mediastinal ratio
HPLC	high-performance liquid chromatography
HSA	human serum albumin
HYNIC	hydrazinonicotinamide
IAEA	International Atomic Energy Agency
IB	investigators brochure
IBZM	iodobenzamide
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ID	injected dose
ID/g	injected dose per gram
IHC	immunohistochemistry
IMPD	investigational medicinal product dossier
IMZ	iomazenil
IND	investigational new drug
iNOS	inducible nitric oxide synthase
IVS	interventricular septum
K_d	equilibrium dissociation constant, affinity of ligand toward the target
LAF	laminar air flow
LET	linear energy transfer
LV	left ventricular
MAA	macroaggregated albumin
mAb	monoclonal antibody
MAO	monoamine oxidase
MCA	multi-channel analyzer
MCNPX	Monte Carlo N-Particle eXtended
MCP-1	monocyte chemoattractant protein-1
mCRPC	metastatic castration resistant prostate cancer
MDP	methylenediphosphonate
MeV	mega electron volt

MIBG	meta-iodobenzylguanidine
Min	minutes
mmol	millimoles
MMP	matrix metalloproteinases
µmol	micromoles
MPI	myocardial perfusion imaging
MPI	myocardial perfusion reserve
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRI	magnetic resonance imaging
MR2	muscarinic receptor 2
NA	natural abundance
NDA	new drug application
NE	norepinephrine
NET	neuroendocrine tumors
NK-1	neurokinin-1 receptor
nM	nanomolar
NOS	nitric oxide synthase
NOTA	1,4,7-triazacyclononane-triacetic acid
NPH	normal pressure hydrocephalus
NPs	nanoparticles
OCT	organic cation transporter
PBR	peripheral benzodiazepine receptor
PC	prostate cancer
PD	pharmacodynamics
PD-L1	program death ligand 1 receptor
PET	positron emission tomography
Pgp	p-glycoprotein
PHEN	phenylephrine
p.i.	post-injection
PiB	Pittsburgh Compound B
PIDA	phenyliodonium diacetate
PK	pharmacokinetics
pKa	acid dissociation constant
PRRT	peptide receptor radionuclide therapy
PSMA	prostate-specific membrane antigen
PTFE	polytetrafluoroethane
QA	quality assurance
QC	quality control
QMA	quaternary methyl ammonium
QNB	quiniclidinyl benzilate
R&D	research and development
RBA	relative binding affinity
RCY	radiochemical yield
RDRC	Radioactive Drug Research Committee
RGD	arginine-glycine-aspartic acid
RIT	radioimmunotherapy

RLD	reference listed drug
RLT	radioligand therapy
RV	right ventricular
SERT	serotonin transporter
S_NAr	nucleophilic aromatic substitution
SPE	solid phase extraction
SPECT	single photon emission computed tomography
SSRIs	selective serotonin reuptake inhibitors
SSTR-2	somatostatin receptor 2
SUV	standardized uptake value
TACN	triazamacrocycle 1,4,7-triazacyclononane
TAT	targeted alpha therapy
TATE	(Tyr^3-Thr^6)-octreotide
TBA	tetrabutylammonium
TBAF	tetra-*n*-butylammonium fluoride
TCEP	tris(2-carboxyethyl)phosphine
Tf	triflate
THF	tetrahydrofuran
TNBC	triple-negative breast cancer
TOC	(Tyr^3)-octreotide
TSPO	translocator protein, 18 kDa
TTR	transthyretin
USP	United States Pharmacopeia
UV	ultraviolet
VA	ventriculo-atrial
VAChT	vesicular transporter for acetylcholine
VMAT2	vesicular monoamine transporter type 2
VP	ventriculo-peritoneal
WHO	World Health Organization

PART I

Introduction to Radiopharmaceuticals

Chapter 1

Targeted Diagnostic Radiopharmaceuticals: Design Options for Small-Molecule Radiotracers

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1.1 INTRODUCTION

The field of nuclear medicine has seen many important technical developments in the past seven decades, including improved radionuclide availability, new techniques for radiopharmaceutical synthesis, better imaging devices, and novel methods for image reconstruction and analysis. The importance of radiolabeled compounds used in nuclear medicine imaging is perhaps embodied in the proposal by Haberkorn et al. [1] that "Molecules are the future of nuclear medicine." Many established radiopharmaceuticals currently in routine clinical care are used to image general physiological properties of organs (flow, volume, clearance, and metabolism), and research efforts have not stopped in that area, as represented by such radiopharmaceuticals as [^{18}F]fluoromisonidazole [2] for hypoxia, [^{18}F]flurpiridaz [3] for cardiac blood flow, and [^{18}F]FROStrace for reactive oxygen species [4]. The emphasis in radiotracer design has more recently shifted to what

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are now termed "targeted" radiopharmaceuticals, in which radiolabeled compounds are designed specifically to indicate the presence or function of a single specific biochemical target, most often a particular macromolecule (e.g. protein, lipid, nucleic acid) whose numbers or functions have been identified as altered in pathological conditions.

The use of radiolabeled molecules for specific biochemical targets is, of course, not new and not limited to in vivo nuclear medicine imaging. In vitro studies of receptor binding or enzyme action have extensively used compounds labeled with longer-lived tritium, carbon-14, or iodine radionuclides. The steady improvements of imaging instrumentation (SPECT/computed tomography [**CT**], PET/CT, and PET/magnetic resonance imaging [**MRI**]) and their more widespread availability have spurred the continued development of small molecules as potential in vivo diagnostic radiopharmaceuticals. Adopting the concept of targeted radiotracer development for in vivo imaging is easy, but as noted in 1982 by Fowler and Wolf [5], "The site-specific delivery or targeting of radiotracers which probe particular aspects of the metabolism and function of a target organ or tissue is a particularly challenging aspect of radiotracer development."

The processes for the development of new radiotracers are as varied as the investigators involved, but the early steps are usually very similar, as represented in Figure 1.1. All radiopharmaceutical development starts with the goal of imaging a specific biochemical process and then begins the search for appropriate chemical matter to radiolabel. There are several general requirements that apply to targeted radiotracers for any tissue. First and most obvious is that the molecules chosen must be amenable to radiolabeling, through isotopic substitution, addition of or substitution by small radionuclide-bearing groups, or attachment of a radionuclide-bearing pendant group in a manner that does not interfere with the desired properties of the molecule (e.g. affinity or specificity). The molecules chosen for radiolabeling should be specific or at least predominantly selective for the target to provide sufficient target-to-background distributions for in vivo imaging. The labeled compounds must be chemically stable and not easily metabolized to form radiolabeled species that would interfere with the interpretation of the radioactivity distribution after intravenous injection. Some consideration must be given to avoiding compounds that are clearly excluded from

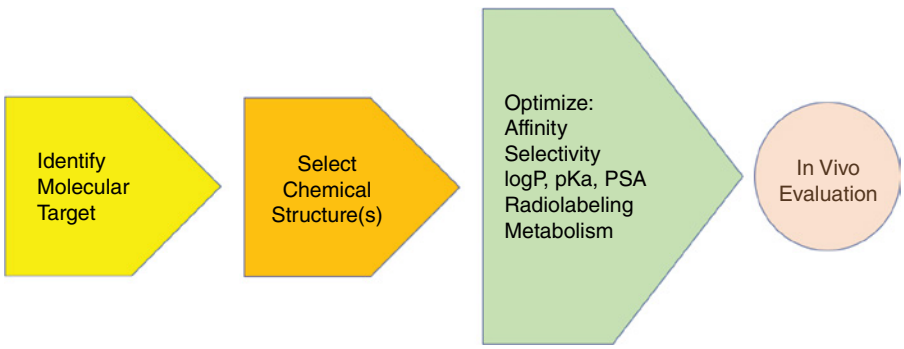

Figure 1.1 Radiopharmaceutical development pathway.