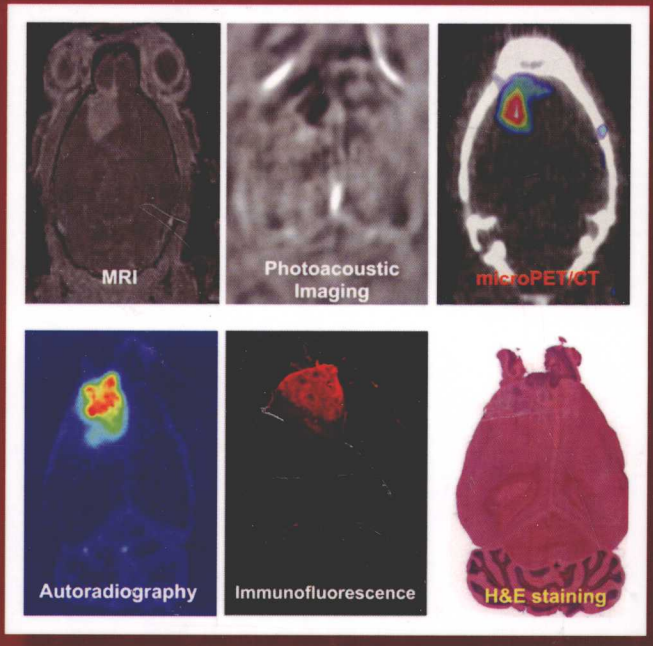
Drug Delivery Applications of Noninvasive Imaging

Validation from Biodistribution to Sites of Action



Edited by

Chun Li · Mei Tian

WILEY

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Published by John Wiley & Sons, Inc., Hoboken, New Jersey
Published simultaneously in Canada

Library of Congress Cataloging-in-Publication Data:

Drug delivery applications of noninvasive imaging : validation from biodistribution to sites of action / edited by Chun Li, Mei Tian.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-0-470-63347-2 (cloth)
I. Li, Chun, 1963– II. Tian, Mei.
[DNLM: 1. Drug Delivery Systems. 2. Diagnostic Imaging. QV 785]
RS431.R34
615.1′9–dc23

2013014002

Printed in the United States of America

ISBN: 9780470633472

10 9 8 7 6 5 4 3 2 1

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PREFACE

Modern imaging technologies offer high-sensitivity and high-resolution visualization of imaging probes. In the last decade, in vivo imaging has been gradually growing in importance as an aid for the development of new drug delivery systems and approaches to controlled dosage release. These two fields are powerful in their own right, but together they can generate considerable new knowledge in a cost-effective manner with regard to the pharmacokinetics, biodistribution, bioavailability, local concentration, and clearance of drug substances for the treatment of a variety of diseases including, in particular, the treatment of cancer. In the pharmaceutical industry, controlled release formulations are widely used, and become increasingly popular for reasons of improving patient compliance, reducing side effects, and extending patent protection. Noninvasive imaging techniques allow rapid, repetitive (and thus potentially high throughput) assessment of the drug deposition in various tissues in the body, which can vastly facilitate the eventual translation of novel dosage forms into the clinic. Giving the popularity and importance of both imaging and drug delivery fields, we are extremely pleased to present to you this book entitled *Drug Delivery Applications of Noninvasive Imaging: Validation from Biodistribution to Sites of Action*.

The book starts with an introduction to molecular imaging. Chapters 2–4 focus on *in vivo* imaging techniques including PET, SPECT, and optical imaging. Given the importance of quantitative analysis on the basis of imaging data, a whole chapter (Chapter 5) is dedicated to quantitative analysis. Chapters 6–13 highlight imaging drugs and drug carriers at the sites of action. These therapeutic agents include small-molecular weight radiopharmaceuticals, peptide and proteins, siRNA, cells, and nanoparticles. Many different types of nanoparticles with new and improved diagnostic and therapeutic effects have been developed over the last 20 years. A more broad-based nanotechnology application will come from a better understanding of how nanoparticles interact with biological systems and how multiple functions, including imaging and therapeutic functions, can be integrated into a single nanoplatform. This volume has attempted to represent several major classes of nanoparticles that are being developed for image-guided therapy (theranostics), such as liposomes (Chapter 11), polymeric micelles (Chapter 12), perfluorocarbon nanoparticles (Chapter 13), and gold nanoparticles (Chapter 14). The next two chapters (Chapters 14, 15) highlight the applications of imaging techniques in routes of administration other than intravenous injection, including pulmonary and oral delivery. Finally, no comprehensive volume of imaging and drug delivery would be complete without

translational research towards clinical applications. Chapter 16 offers valuable information on imaging drug delivery in large animal models. Chapters 18–20 provide examples on clinical applications of imaging techniques in guiding drug development and drug delivery.

Thanks to excellent contributors and the Wiley publication team, this book has turned out to be the only one of its kind bringing synergy between imaging and drug delivery. With 20 authoritative chapters highlighting the contemporary use of imaging in preclinical and clinical evaluation of drug and drug delivery systems, we have no doubt that this book will be extremely helpful for a broad spectrum of readers ranging from students, teachers, practitioners, and followers of pharmaceutics and drug delivery.

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CONTENTS

CHAPTER 1

INTRODUCTION TO MOLECULAR IMAGING

VIKAS KUNDRA

Molecular imaging may be defined as the imaging of molecules either delivered to the body or already present in the body. Generally, this refers to *in vivo* imaging, that is, imaging within a living multicellular organism. The process requires an imaging instrument, a subject, and, commonly, an imaging agent. These tools enable longitudinal assessment of delivered materials, specific targets, mechanisms of action, and biological processes. Molecular imaging has already found utility in the clinic.

An example of a clinically useful molecular imaging system is positron emission tomography (PET) imaging using ^{18}F-fluorodeoxyglucose (^{18}F-FDG). The agent is a glucose analogue labeled with a radioactive substance, ^{18}F, with known decay characteristics. Glucose is the primary source of energy in animals. Most foods that we ingest are broken down to or converted to glucose. This sugar enters the bloodstream and then cells via one of several specific transporters, known as GLUT transporters. Once inside the cell, glucose is phosphorylated by hexokinase into glucose-6-phosphate. This is then isomerized by phosphoglucose isomerase to fructose-6-phosphate and continues along the path for energy generation. Fluorodeoxyglucose (FDG) mimics glucose and also enters the cell via GLUT transporters and is phosphorylated by hexokinase; but once inside the cell, it is a poor substrate for phosphoglucose isomerase and for glucose-6-phosphatase and remains phosphorylated. This adds a negative charge to ^{18}F-FDG, which prevents the molecule from crossing the cell membrane and entraps it inside the cell.

Cells with greater metabolic demand require more glucose and therefore entrap more ^{18}F-FDG. Cells can use glucose to generate more ATP, usable energy within the cell, using oxidative phosphorylation rather than using anaerobic respiration. Because cancer cells are constantly reproducing, they have high energy demand; however, they are also inefficient at energy production and behave as though they are in an oxygen-poor environment. They tend to use the less efficient anaerobic pathway, and thus, require more glucose. In turn, in the presence of the glucose analogue, cancer cells tend to accumulate more ^{18}F-FDG than normal cells.

Drug Delivery Applications of Noninvasive Imaging: Validation from Biodistribution to Sites of Action, First Edition. Edited by Chun Li and Mei Tian.

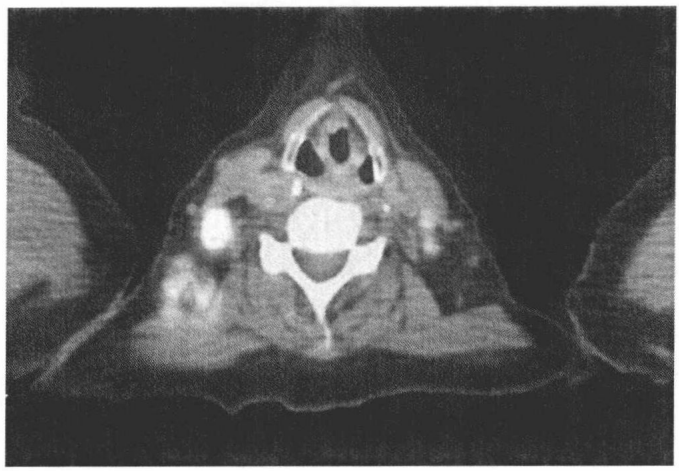

FIGURE 1.1 ^{18}F-FDG PET/CT. Axial view of the neck demonstrates increased uptake (orange) of ^{18}F-FDG in lymph nodes signifying involvement by lymphoma. For color details, please see color plate section.

In this imaging agent, the FDG provides specificity by mimicking glucose rather than another sugar such as sucrose. ^{18}F enables imaging. The known decay of ^{18}F can be imaged using a PET camera sensitive to the positron decay that is employed by ^{18}F to come to a more stable atomic state. ^{18}F-FDG enables one to study a basic biological process, cellular metabolism, that is used to identify and characterize disease. Clinically, ^{18}F-FDG imaging (Fig. 1.1) is used to identify, localize, and stage many types of cancer, such as breast cancer and lymphoma. It is also used to assess response to therapy. More recently, it has been used to predict response to certain therapies and to assess durability of response at the end of therapy [1, 2]. It has also had a significant impact in cardiology, primarily for assessing ischemia and infarction, and in neurology for locating a seizure focus.

1.1 ASSESSING THE TARGET DIRECTLY VERSUS DOWNSTREAM EFFECTS

Systems may be designed to image the target itself versus downstream effects. For example, one may image a receptor or the downstream effect of signaling pathways elicited by the receptor. Practically, one may first want to know if the target is present and how it is distributed within a site of disease and within normal tissues. If the target is present, the drug created against it may be effective. On the other hand, if the target is not present, the targeted therapy is not likely to be effective by the expected mechanism of action. Clinically, although target presence may be evaluated by biopsy, it is not without risk and patient compliance issues may arise if biopsies need to be performed in multiple locations and/or longitudinally. Biopsy samples a small portion of the tissue of interest. By imaging, heterogeneity of target expression may be assessed, for example, within a tumor. Without bystander effect, areas of tumor without target expression may not respond to the targeted

drug. Likewise, heterogeneity of target expression in different metastases may be assessed. If expression is present in some metastases, but not others, there may be a mixed response to the therapy. Longitudinal imaging may be used to assess change in target expression, which may change secondary to the targeted or other therapy that is given to the subject. Reduction in target expression may make the therapeutic less effective.

With targeted imaging used in conjunction with targeted therapy, careful interpretation is necessary. The timing of delivering the imaging agent versus the therapeutic is important since the two may compete. This may be advantageous because one can use it to assess if the therapeutic can displace binding of the imaging agent to the target. On the other hand, the imaging agent may bind to a site separate to that bound by the therapeutic agent; therefore, the imaging agent may not reflect the binding site of the therapeutic agent. Moreover, the imaging agent may bind, but not inhibit function, such as that of a tyrosine kinase domain, whereas the therapeutic agent needs to bind and inhibit function in order to be effective. A caveat for delivery is that to be effective, a therapeutic agent may not need as favorable a biodistribution in terms of signal to background noise as is needed for imaging. Another potential outcome is that the imaging identifies the target and the drug inhibits target function, yet the tumor grows, that is, the drug is not efficacious. This may be because the primary growth/maintenance signaling pathway for the tumor was not targeted or was not adequately suppressed, or secondary/redundant pathways supported growth.

One example of targeted imaging is using ^{111}In-octreotide to image somatostatin receptors. Identifying the presence of this receptor predicts response to octreotide therapy for suppressing carcinoid syndrome, which is associated with neuroendocrine tumors [3]. Another example is ^{18}F-fluoroestradiol (^{18}F-FES). PET imaging with this agent correlates with estrogen receptor (ER) expression and predicts response to tamoxifen [4]. With targeted imaging, the imaging system commonly requires development of a particular contrast agent/radiopharmaceutical for each target; this provides specificity but may limit its utility to a few relevant applications/diseases.

Signaling induced by receptors may activate a variety of downstream pathways that regulate a few critical cellular functions such as growth and metabolism. Processes at the tissue level also represent central processes that may play a key role in normal physiology and diseases. These may be less specific, but because many interesting targets affect them, these downstream effects represent an opportunity for understanding a variety of normal and pathological processes. For example, one may image alterations in glucose metabolism by ^{18}F-FDG PET or changes in the function of the vasculature by dynamic contrast-enhanced magnetic resonance (MR) imaging [5–9] by a number of drugs. Because the process being imaged may be affected by various pathways, a variety of targeted therapeutic agents may be tested using a similar readout. Care must be taken since the downstream readout may not be due to the predicted mechanism of action of the targeted therapeutic. Even so, such a readout may prove practically useful and hypothesis generating. Imaging of downstream effects has the potential for wider applicability than specifically targeted agents, which would be an advantage for clinical translation.

1.2 IMAGING METHODS

Physical properties such as radioactive decay; absorbance or reflectance of light, sound, or X-rays; and behavior in a magnetic field are used to generate images. Machines sensitive to such physical changes are used to create images (Table 1.1). These require appropriate tissue and spatial resolution. If the imaging is performed from one angle, a two-dimensional (2D) image is generated. If the imaging is performed at multiple angles, with appropriate mathematical algorithms and the speed of modern computers, three-dimensional (3D) images can be created.

In vivo imaging may consist of superficial imaging such as that of skin and lumens like the epithelium of the bowel. In such situations, light-based imaging may be applied since one is not as limited by depth of penetration. Due to scatter, light-based imaging is currently limited to a few millimeters or centimeters, thus is not applicable to percutaneous imaging of deep structures. However, for small animals, this is less of an issue since their entire width may fall within this range. Light may be generated from within the animal itself, for example, using an enzyme such as luciferase that converts a substrate such as luciferin into light. Fluorescence may also be exploited in which a certain wavelength of light is input and output of a second wavelength is separated from scatter using a filter and then measured by a camera. Currently, most cameras are cooled charge-coupled device (CCD) chips of the type found in digital cameras.

Due to high sensitivity, light-based imaging is commonly used in small animal imaging, particularly of mice. Luciferase-based imaging in particular has enjoyed a large amount of success since it can be placed into vectors and delivered to cells, enabling a range of molecular biology techniques such as studying promoter function. Fluorescent proteins have the advantage that they can be seen in tissues and cells without a substrate, thus can be followed *in vitro*, *in vivo*, and often *ex vivo*.

TABLE 1.1 Imaging Modalities

Light-based imaging
Primarily CCD-based cameras
White light
With filters: fluorescence, near infrared, infrared
Raman spectroscopy
Penetration depth limited: external cameras, internal cameras such as endoscopes
Nuclear medicine
Gamma camera-based imaging
PET
Magnetization
MR
Sound
Ultrasound
Photoacoustic imaging (light input, sound output)
Thermoacoustic imaging (radiofrequency input, light output)
X-rays
Radiography
CT