Chapter 3
Team Sciences and Core Resources within the NTR

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3.1 Introduction

The fact that translation of biomedical optical imaging modalities is relatively untraversed territory from start to finish is a major theme of this book. Despite the lack of translational activity by the optical imaging community, the translational pathway is far from uncharted. The 21 CFR (Code of Federal Regulations) governs procedures and actions to be taken by individuals and institutions interested in commercializing drugs or medical devices within the United States. These regulations apply to all biomedical optical device technologies and therefore represent fixed markers along the pathway to translation for any emerging biomedical imaging technology. While these regulations are in place for the researchers to follow, their main purpose is to protect the consumer. As a result, the total array of regulatory signposts is often confusing and burdensome to the researchers, creating more of a barrier than a pathway for translational research. As mentioned in the previous chapter, the NTR was formed in 2008 as a team approach to test academic methods to navigate these barriers in an attempt to bring new biomedical imaging technologies closer to the endpoint of FDA approval and product commercialization.

As a part of the networking process, the four centers of the NTR have shared best practices as well as translational mistakes to create a pathway for others to follow. Within the Network, core groups were formed to promote resource sharing and to expedite transmission of pertinent information among the centers. Five Research Support Cores were originally created within the network to focus on issues that were thought to be specific to optical imaging and common to all the research centers. Their goal was to develop the technical consensus and expertise necessary for the translation process. These core groups were organized to be external to the individual research centers, each with its own goals and organization. Membership of the cores was drawn from researchers from each of the centers. The original cores addressed problems in (1) Standards and Compliance, (2) Instrumentation and Industrial Relations, (3) Chemistry Probes and Guided Therapies, (4) Information Technologies, and (5) Validation and Clinical Studies. The purpose of the core concept was to

collect and communicate information pertinent to translation-related technological and regulatory needs of the centers in each of the focus areas. The cores built on strengths such as pre-existing expertise of some core members, e.g., regulatory/compliance and information technology specialists, and gathered information when needed from industrial partners, FDA guidance documents, and experimentation. Efforts by the individual cores, as well as essential information for optical imaging modality translational development collected by the cores, are described in the following sections.

While the Standards and Compliance and the Validation and Clinical Studies Cores had separate missions early in the NTR program, they were eventually merged as the goals of the first core were met. All of the cores conducted monthly teleconferences, led by chairpersons who each served a one-year term.

3.2 Validation/Clinical Studies Core

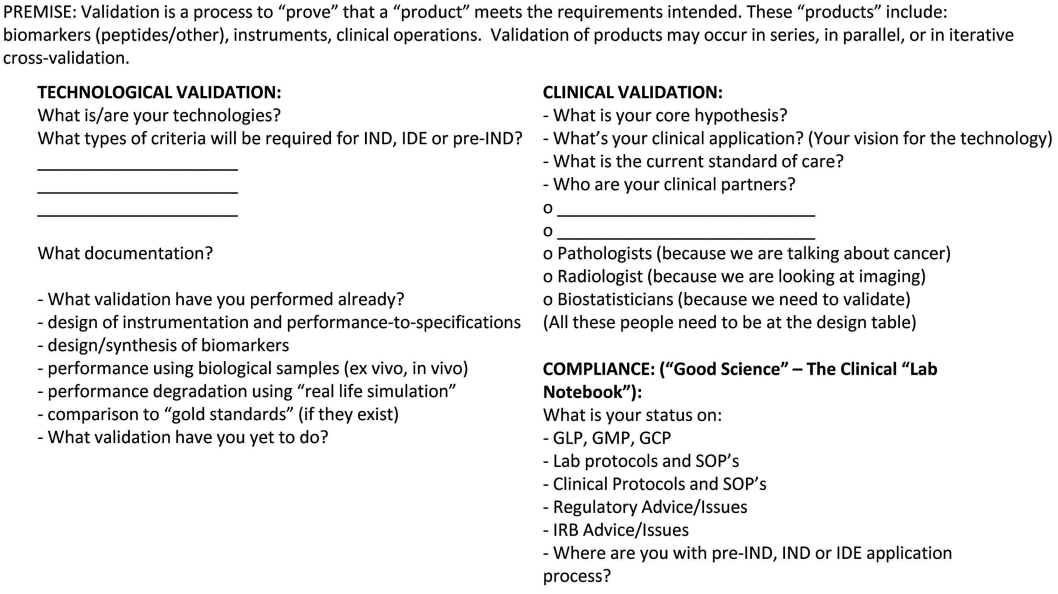
The Validation and Clinical Studies Core merged with the Standards and Compliance Core in year three of the five-year NTR program. This was in part due to significant overlap of responsibilities and duplication of background knowledge in FDA compliance issues within the two cores, and also because goals of the Standards and Compliance Core were met early in the program with the creation of a compliance Handbook, provided in this book as an appendix. The NTR centers were uncharacteristically well represented by individuals with knowledge of 21 CFR compliance issues. This is commonly encountered in industry, not in academic settings. Before the merger, the Validation and Clinical Studies Core began with a definition of what *validation* means within the context of translational research and to distinguish it from *verification*, an easily confused concept. Validation is described in an FDA guidance document[1] as follows:

> "Validation involves documenting, through the use of specific laboratory investigations, that the performance characteristics of the method [or agent or instrument] are suitable and reliable for the intended analytical applications."

Verification, on the other hand, is the process of establishing that an agent or device performs as it was designed to perform, e.g., a camera capturing images at the specified resolution. Validation can be described by the query "Are you building the correct device?," and verification by "Are you building the device correctly?"[2] Of course, these definitions also apply to research focused on drug or image contrast agent development. These concepts are developed further in the next section of this chapter.

The Validation and Clinical Studies Core found that, within the context of translational research, validation is a continual process, rather than a set of procedures that come at the end of a research process. Validation is necessary throughout the development, production, and testing of agents or devices, and requires many iterations and revisions. The core developed a self-assessment tool in the form of a survey, as shown in Fig. 3.1, for researchers to use to determine what specific validation needs are required. The survey asked what, if any, validation actions were completed or underway, what documentation was needed, GLP/GMP/GCP (good clinical practice) status, the intended clinical application for the agents/devices, and other pertinent questions. The answers to some of these questions come from information within the knowledge-base of the researcher, such as an understanding of needed device performance specifications or drug requirements, user qualifications and clinical needs, and which imaging technologies or accompanying imaging agent pathways are suitable for the problem. Other answers, however, are needed to satisfy regulatory questions that stand as milestones in the translational road.

The Validation and Clinical Studies Core also determined that validation requirements exist at several levels during research. For instance, some validation duties require only accurate recording of experimental details and results (GLP), while other validation efforts require a higher level of validation effort, including a great deal of planning and design, such as proving whether or not a device actually detects cancer. Examples of these different levels are detailed below.



PREMISE: Validation is a process to "prove" that a "product" meets the requirements intended. These "products" include: biomarkers (peptides/other), instruments, clinical operations. Validation of products may occur in series, in parallel, or in iterative cross-validation.

TECHNOLOGICAL VALIDATION:
What is/are your technologies?
What types of criteria will be required for IND, IDE or pre-IND?
_____
_____
_____

What documentation?

- What validation have you performed already?
- design of instrumentation and performance-to-specifications
- design/synthesis of biomarkers
- performance using biological samples (ex vivo, in vivo)
- performance degradation using "real life simulation"
- comparison to "gold standards" (if they exist)
- What validation have you yet to do?

CLINICAL VALIDATION:
- What is your core hypothesis?
- What's your clinical application? (Your vision for the technology)
- What is the current standard of care?
- Who are your clinical partners?
o _____
o _____
o Pathologists (because we are talking about cancer)
o Radiologist (because we are looking at imaging)
o Biostatisticians (because we need to validate)
(All these people need to be at the design table)

COMPLIANCE: ("Good Science" – The Clinical "Lab Notebook"):
What is your status on:
- GLP, GMP, GCP
- Lab protocols and SOP's
- Clinical Protocols and SOP's
- Regulatory Advice/Issues
- IRB Advice/Issues
- Where are you with pre-IND, IND or IDE application process?

Figure 3.1 Validation self-assessment tool.

Validation at the lower levels simply requires knowing what is required in the code of regulations along with the proper format and controls. The details of this are left for the next chapter. For optical imaging devices, diligent recording of bench research results, clinical studies forms, and documentation showing that the research workplace is compliant with FDA expectations all constitute lower-level validation requirements. The NTR centers found that most of the validation needs at this level could be met using the software tool SciPort, developed by Siemens Healthcare.[3,4] This software consists of templates that investigators can use to develop, store, and share many of the written records needed to document compliance with FDA procedures in the translational process. Records such as standard operating procedures (SOPs), GLP logs, equipment logs, batch release records, manufacturing logs, installation quality/operational quality (IQ/OQ) records, personnel training records, consent forms, case report forms, and other documents needed in optical imaging translational research can be generated and updated using Sciport. As electronic data capture (EDC) becomes increasingly accepted and even required in clinical trials,[5] an integrated tool such as SciPort to collect and store relevant data will help to streamline the translation process and provide an all-important audit trail. Using 21 CFR Part 11-compliant software security adds assurance that recorded data is tamper-proof and protected from unauthorized access.

Batch release is a low-to-mid-level validation requirement that deserves specific emphasis because this concept is not familiar to most academic scientists and because early batch release validation efforts by researchers are crucial. Batch release is the final approval to release a product to a study, clinical trial, or market. The decision is ultimately made by a Quality Control person. Batch release is essentially a guarantee of identity, strength, quality, and purity. Acceptable criteria for batch release of an optical imaging agent or device can be determined at a pre-IND meeting with the FDA prior to IND application submission. Paperwork needed for batch release includes: (1) SOPs for sterility, pyrogenicity, purity, biological activity, and stability assays (for molecular imaging agents), (2) worksheets with blanks for initialing, dating, and adding notes to use during assay performance, (3) labels for supplies and batches of products, and (4) reports for FDA folders. Researchers have to follow specific rules for labels: final-product labels must be printed on separate pages from intermediate-product labels, and all labels must contain agent identity, concentration, storage specifications, batch number and date, and expiration date. Retention samples must be labeled and kept for one year to test for stability/shelf life/storage conditions, or as long as evaluable, if stability is less than one year. Batch release requirements become important to optical imaging researchers before preclinical trials

and therefore should be integrated into agent and device development efforts at an early stage.

Batch release as part of the validation of optical imaging modalities requires a number of mid-level supporting validation efforts. These requirements vary, depending on the particular device or imaging agent, and specific needs are determined at pre-IDE or pre-IND meetings with the FDA. These needs include proving that molecular imaging agents are adequately pure, sterile, nonpyrogenic, nonimmunogenic, specific, sensitive, stable, and nontoxic, or that molecular devices are reliable, or that software performs reliably, accurately, and securely. Meeting some of these needs can be accomplished by following existing guidelines contained in FDA guidance documents, U.S. Pharmacopeia (USP) documents, or industrial group guidelines. A number of such resources are listed in the appendix to this book.

Some validation requirements have no existing guidance available, and for these, researchers may need to design and produce a specific validation. Several NTR members published papers that described validation of optical imaging agent purity, agent immunogenicity, agent toxicity, and integrity of an imaging data analysis software tool.[6–9] For these papers, the investigators followed a general scheme for validation development that is illustrated in Fig. 3.2. After first determining the purpose or use of the assay, such as validating imaging agent purity, investigators should also determine the assay

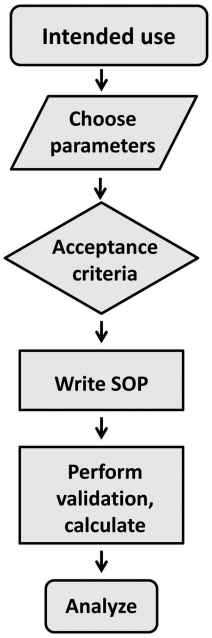


Figure 3.2 General scheme for validation development.

parameters to be used, such as precision, accuracy, and detection limits. Setting acceptance criteria, i.e., less than 20% coefficient of variance, and writing the detailed SOP are then followed by performance of the assay, calculations of precision, accuracy, or other parameters, and analysis. This process can be used to create a validation procedure whenever a literature search produces no appropriate paper or guidance for any required validation parameter. For example, proving the stability of a molecular imaging agent could entail documenting the chemical characteristics of the agent after storage in human serum. The validation could require repeating the tests a number of times, with a specified limit to the variation (i.e., less than a 20% coefficient of variation, which is standard deviation/average $\times$ 100%). Determining the number of repeats and limits necessary can be accomplished by adapting a published validation or guidance for a similar or similar-use agent, such as a radiolabeled imaging agent.

A number of terms are perhaps unfamiliar to academic researchers, yet important to validation efforts; most of these that are necessary for optical imaging validation are given in the Glossary of Terms (Section 3.11), where, e.g., *lower limit of detection* (LLOD), *precision*, *accuracy*, and *selectivity* are defined, as understanding these validation attributes and terms is necessary for designing and conducting appropriate mid-level validations.

Higher-level validation activities have been described in several papers produced by NTR investigators. Several of these studies validated the usefulness of an optical imaging modality for discerning whether therapeutic treatments were efficacious.[10,11] Other papers described validation of tomography or tumor margin determination.[12,13] Another paper described sensitive and specific labeling of tumors and metastases in a murine model of prostate cancer, using fluorophore-producing cancer cells and a dual-labeled molecular agent.[14] The agent contained a radioactive element as well as an optical component, allowing direct comparison of the optical results to the standard-of-care radioactive tracer, along with direct tumor localization using genetically fluorescent-labeled (dsRed) tumor cells and pathology. Higher-level validations should ultimately include studies to determine tumor margins, assess cost effectiveness, and evaluate comparisons to pathology, which is treated as the "gold standard," yet is limited due to the amount of tissue that can be sampled.[15] Clinical management should be the ultimate standard, yet defining its relationship to optical imaging and pathology may present challenges.

There are several validation and clinical study concerns that emerging optical imaging modalities will have to tackle and that the core did not fully address. For example, a pathology image database could be useful for unifying and standardizing pathology readings of tumor margins and characterization. Some core members began efforts to validate imaging agent

binding to cancer cells by comparing optical images to histology results (image registration). Correlative optical image databases would greatly strengthen the usefulness of these comparisons. Distinguishing dysplasia, hyperplasia, and normal tissue with optical modalities will require standardization of image reading and analysis.

Standardized phantoms (in the case of research within the NTR, a set of fluorescent standards of varying intensity) as well as the Air Force chart standard resolution test used for resolution standardization, could help to compare technologies and describe optical read capabilities. Several NTR members developed and used optical phantoms during the course of research.[16] These phantoms consisted of fluorescent lipid solutions, fluorescent bead-embedded polymer blocks, gels, dye and gel mixtures in microchannels etched into glass substrates, quantum beads mixed with polyurethane, and even a fluorescence mouse solid phantom. The use of standardized phantoms is especially important if clinical trials using optical imaging devices will be conducted at multiple sites, as inconsistencies between the sites in collecting, interpreting, or analyzing imaging data could jeopardize a study. In fact, in some studies, inter- and intraobserver variability has been documented to be as high as 100%.[17,18] These problems apply to existing imaging modalities (e.g., CT, MR, x-ray, PET, etc.), so it can be speculated that these same concerns will also apply to optical methods when they finally make it to the clinic. Agreement on image analysis algorithms, training for observers, tissue sampling percentages/locations/orientation, cutoffs for positives and negatives, use of scales from 1 to 10 versus yes/no grading, and use of contralateral versus healthy control tissue will all be necessary considerations when designing validation assays.

Unifying image reading proficiency could entail including imaging analytics experts to generate effective image analysis algorithms to meet study needs, since universal software that provides do-it-yourself image analysis capabilities may not suffice. These professionals would have postdoctoral experience with biomedical imaging and computer science and software engineering. The University of Michigan Center designed an image registration model, using histological, fluorescent, and MRI images of mouse colonic adenoma. The complete development of this or an analogous model could equip optical imaging researchers with an important tool for standardizing and validating optical images.

Another higher-level validation need has arisen from the changing landscape in health care: cost accountability. Review by the CMS will now determine whether or not a new optical imaging modality will be reimbursed by these agencies. If not, often private insurers, such as Blue Cross/Blue Shield (BCBS), will also refuse coverage. Such refusal is a "death sentence" to new drugs and devices. Thus, new drugs and devices must be validated to be not only as safe and more effective than existing treatments, but also more cost

effective. This task may seem insurmountable for academic researchers, but several published studies can be used as prototypes for relatively easy cost-effectiveness research. For example, one study compared the cost and effectiveness of substituting MRI and PET imaging for sentinel lymph node biopsy.[19] NTR researchers could conduct similar studies by gathering procedure cost and specificity/sensitivity data for optical imaging methods from published literature or estimates using comparable modalities, designing a chart to represent procedural flow, and using software such as Microsoft® Excel to calculate potential costs and quality-of-life parameters.

The translational research efforts could benefit greatly from direct interaction with the CMS because several cost-related topics need to be considered early in the translational process. For example, the target market for a new device may be smaller than the number of patients with the relevant condition because CMS may require initial use of conservative, existing therapy before approving payment for a new device.[20] So, the researchers could use CMS input for determining where the cutoff for exhausting the use of existing technology lies. If there will be a professional (i.e., physician) fee associated with the use of the device, then a code will be needed to determine this cost for use in cost-effectiveness validation. This code is determined using an editorial panel [Current Procedural Terminology (CPT)], consisting of members from CMS, BCBS, the American Medical Association (AMA), and the American Hospital Association. If a hospital will receive payment, then a Healthcare Common Procedure Coding System (HCPCS) code is an extremely important part of the reimbursement process for a new medical device. CMS has the authority to distribute these codes, and unanimous consent from a panel from CMS, BCBS, and America's Health Insurance Plans is required for changes to these codes. Finally, hospital administrators have a say in whether or not to purchase devices. Charges for inpatient products and services are not individually reimbursed. Hospitals are given a flat amount of money to cover all expenses for an inpatient hospitalization. So, there is no mechanism for separately paying for a device that is an adjunct to inpatient treatment. New medical devices, then, need to demonstrate value, such as decreased hospital stay, intensive care unit (ICU) stay, or healthcare personnel. Thus, input from hospital administrators for determining under what conditions hospitals would purchase an imaging modality is needed. Yet another type of code, Medicare Severity-Adjusted Diagnosis-Related Group (MS-DRG) code, is assigned weight, upon which payment to the hospital is based. Thus, NTR could benefit from information from CMS on the availability of needed codes to calculate cost effectiveness.

If CMS approval is largely based on cost, and the cost of a new optical imaging modality significantly decreases with time (as seen with DVD players or color televisions), is it fair to deny approval based on initial costs? Perhaps

some reasonable estimate of future cost decreases could be incorporated into approval decisions. This is yet another issue that needs CMS interaction.

The Validation and Clinical Studies Core also assisted researchers in the NTR to develop clinical protocols. The core provided references for IND/IDE applications for combination drug/device products and provided guidance for the development of case report forms and SOPs. For any research effort where a clinical endpoint of drug or device is the goal, it is necessary to embrace the concept of validation. While many researchers may shy away from the validation process because it seems mundane compared to the excitement of discovery, validation is a very necessary task for translation and occupies a central place. Proper validation can reduce overall translation/development costs, improve product safety, and may very well make or break FDA approval of a device or drug/device combination. Effective validation is crucial during the development of an imaging modality because that modality may then be used in other studies to prove/disprove efficacy of treatment regimens or treatments using another device.[21] While some validation duties were handled by NTR industrial partners, the centers primarily relied on internal efforts. The Validation and Clinical Studies Core leaves behind a validation section of the NTR Handbook, including a design plan, along with a number of validation papers produced by NTR members for use by other investigators performing and designing validation work for optical imaging translation.

3.3 Instrumentation and Industrial Relations Core

As part of the NTR, the Instrumentation and Industrial Relations Core members have been exploring, evaluating, and defining specific approaches for validation and verification (V&V) of multimodal molecular imaging devices, through a collaborative program that includes academics, industry, and regulatory institutions. While the terms *validation* and *verification* are frequently used interchangeably, each has a distinct definition within the Quality System Regulations (Federal Code of Regulations, 21 CFR 820). Validation is defined as "confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use can be consistently fulfilled" [21 CFR 820.3(z)]. For medical imaging devices, validation includes confirming that an imaging system provides the intended clinical decision-making capabilities. For example, in the case of cancer-targeted imaging, the validation of the system's clinical sensitivity and specificity will generally require comparison to "gold standard" assays of cancer such as histology. While clinical sensitivity and specificity may be the ultimate validation test required for emerging molecular imaging methods, intermediate validation steps are also needed, as the previous section discussed, to provide faster feedback for technology development in

early stages of research, including feasibility, Phase I, and Phase II clinical studies. These earlier validation efforts are challenging due to the technological complexities of molecular imaging modalities, which often include both a new device and new imaging agents. Thus, validation is required for the combination of both components, coupling what would normally be separated in the validation process and regulatory approval process. The same can hold true for multimodal imaging, where the combined images taken by both conventional and emerging modalities need to be validated. With multimodal imaging, however, it is possible that the established clinical imaging modality itself can be used to support the validation efforts of the emerging modality, depending on the eventual interaction of the two approaches.

Verification is defined as the "confirmation by examination and provision of objective evidence that specified requirements have been fulfilled" [21 CFR 820.3(aa)]. The process of confirming that an imaging system has been constructed to specifications also has inherent challenges for molecular and multimodal imaging. For instance, while x-ray imaging can be verified with relatively simple tissue-simulating phantoms of anatomical contrast, molecular imaging may require dynamic phantoms, possibly with biological processes. Molecular-level contrasts are by definition more biologically derived than x-ray or other anatomical imaging modalities; hence, their verification becomes more complex. Issues such as reproducibility, generalization, and traceability become considerably more challenging for biological phantoms compared to static inorganic phantoms. Due to this increased complexity, while V&V standards are well developed for x-ray imaging and other mature imaging modalities, there are few established approaches and little community consensus for molecular-level imaging, hindering progress toward clinical use.

An additional barrier for the translation of biomedical imaging modalities is the frequent disconnect between the development phase of an academic prototype and the commercially viable medical imaging system it might become. Typically, academic prototypes are one-of-a-kind devices, used to acquire specific data in a specific way to demonstrate the technical principle for which it was constructed. As such, they are not designed nor intended to be commercially viable devices. In academia, the final users of the device are typically part of the team developing the device, so user-interface design and fail-safe devices are minimal. The primary objective of the research and discovery is a successful demonstration of the principles involved. The device is merely a vehicle to demonstrate the underlying principle. Ultimately, the goal is publication of data in papers.

Due to the continual design modification and tweaking common with research prototypes, it is often difficult to establish and standardize V&V procedures. Furthermore, because only one or, at most, a few systems will

ever be built, thorough V&V activities are usually considered to be unwarranted. Cost of parts, serviceability, user-friendliness, regulatory approval and even operator and patient safety are addressed as needed on fairly small and generally uneconomical scales. By industrial standards, academic research prototypes are considered a financial high-risk. It is possible that the FDA may begin asking for documentation of GLP for ancillary data coming from academic labs and/or for standardized phantoms for imaging data obtained in multicenter academic clinical trials and submitted with a commercial device application. To facilitate the translation of their prototypes, academics should understand and plan early in the development process for the design needs of future industrial collaborations. Indeed, early collaborations with industrial and regulatory partners may be advantageous in terms of facilitating rapid commercialization.

The main goal of industry is to maximize profits by developing commercially viable products that meet well-defined consumer needs. Commercial devices or drugs in the biomedical arena are required to have fully documented V&V procedures. This is an example of the milestones established by 21 CFR through translational research. Knowledge of these regulations and an understanding of when they will become necessary is important for keeping translational research moving forward at a rapid pace. As such, it is not uncommon to have whole divisions in industry devoted to the development, marketing, sales, distribution, and service of the device. Industry's need to minimize and mitigate the development and commercialization risks of new devices coupled with the creativity and innovation of academia leads to a natural and strong synergy between academic and industrial institutions. When the roles, constraints, and goals of each of the players have been clearly and transparently defined and communicated as early as possible, industry and academic partnerships have proven in the past to be very effective at bringing new imaging devices to market.

To accelerate bench-to-bedside translation of emerging modalities, there is a need for academics to begin incorporating V&V practices earlier in the development process. Generally, the limitations to overcome are lack of knowledge regarding V&V practices and lack of knowledge about the associated regulatory rules and procedures. These can be mitigated by early-stage involvement of industrial partners in the development of promising devices, early-stage feedback from regulatory agencies including the FDA, and CMS, and establishment of a project management framework within academic research efforts that follow standardized V&V guidelines.

3.3.1 V&V process during device design

From the point of view of the medical device industry, an imaging device product lifecycle typically has five phases: (1) design, (2) regulatory clearance and approval, (3) early adoption, (4) reimbursement, and (5) full adoption.[22]

Each phase of the commercialization process has distinct needs for clinical evidence, and it is this need that often can be fulfilled best by an academic or clinical collaborator.

During the design phase, the unmet clinical imaging needs or clinical indications that the new imaging device is targeting must be clearly defined. This is emphasized by several of the questions in the self-assessment tool of Fig. 3.1. Within the context of product development, these ideas are collected through *user requirements*. As part of the design phase, the concern of "Will this new imaging device do what we think it will do?" can be mitigated by building one or a few prototypes and gathering clinical evidence to either mitigate the risk or terminate the project. Just like in early drug development, terminating unpromising new imaging devices as early as possible in the development cycle will save substantial subsequent development costs. Should the level of risk be found acceptable, then the new device will move into the new product development process at a company.

All device documentation and development cascade from user requirements through a process development model called the V Model as shown in Fig. 3.3. The left side of the V Model denotes the specifications, which become more detailed as they descend toward the bottom of the V. The right side of the V Model specifies the testing for the V&V of the design at various levels of specification. Therefore, tests done on the right side of the V must trace back to a requirement on the left side of the V. The interaction between the left and right sides create a *traceability matrix*. Many of the documents produced by the V&V process are stored in a *device history file*, as described below. It is these types of processes and documentation that regulatory agencies [e.g., the FDA and International Organization for

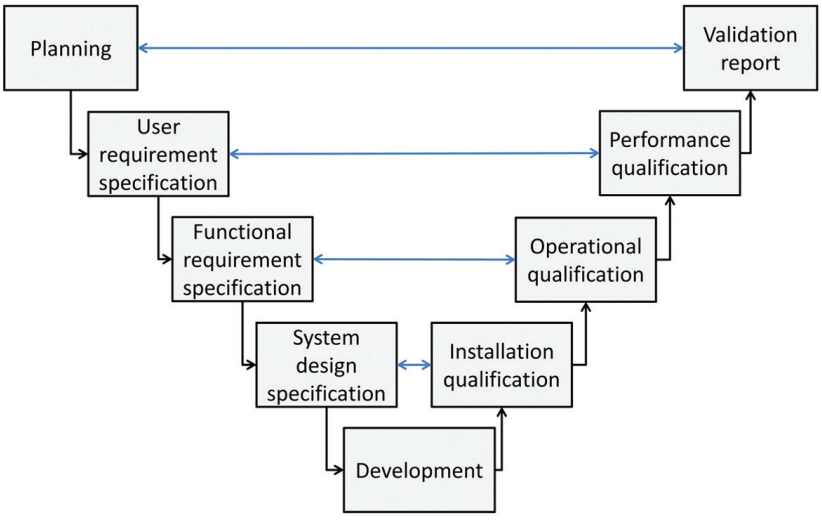


Figure 3.3 The industry standard V Model of device development and testing.

Standardization (ISO)] use to evaluate the safety and efficacy of a new product. In Fig. 3.3 verification is the testing of the functional requirements specifications, whereas validation is the testing of the user requirement specifications. Several books have been written on the design process of medical devices.[23,24]

For the other four phases of a device's lifecycle (regulatory clearance and approval, early adoption, reimbursement, and full adoption), industry relies heavily on relevant clinical data acquired from collaborating academic and clinical sites, as well as the regulatory agencies. *Care and proper oversight, including proper documentation and tracking of the data, analysis, equipment used to generate the data, service records of the equipment, etc., are critical aspects of these phases and should not be underestimated.* For example, academic and clinical research centers typically do not have the tools for managing this massive amount of information in an efficient way and hence need a robust, low-cost scientific data management, collaboration and document tracking system. For this reason, SciPort, a platform for scientific data management and integration,[3,4] was adopted by the NTR sites.

To summarize, synergistic and effective academic–industrial collaborations that include positive and transparent working relationships with government funding and regulatory agencies can significantly reduce the financial risk in bringing new multimodality molecular imaging devices to market. Establishing a community consensus on good practices for V&V at the academic prototype level would help industry achieve their goal of reducing this risk and reduce product-to-market times.

3.3.2 Phantoms

Another integral component of the V&V process for medical imaging is development of appropriate phantoms that enable the testing and validation of the imaging device. Phantoms are artificial constructs that mimic a set of properties of biological tissue.[25] Optical tissue phantoms can play a key role at various steps of the development of a new optical biomedical imaging device. Although they will never replace the ultimate validation provided by a clinical trial, they can provide valuable information during device development and later for quality control.

The usefulness of tissue phantoms extends well beyond instrument development and validation trials, yet they are not generally introduced alongside the new modalities. Though imaging technologies such as PET have made it through clinical acceptance without a generally recognized standard phantom, standardized phantoms facilitate data comparison across multi-institutional studies. A well-established phantom platform trusted by the user community can be used to standardize the instrumentation coming from different vendors and benefit and accelerate the development and acceptance of new protocols based on novel imaging technology.

The ideal phantom should be stable and reproducible, should accurately mimic all physiological features relevant to the intended application, and its properties of interest should be accurately characterized in a way that is traceable to international standards, if applicable. This long list of phantom qualities will be discussed in more depth when describing the different uses of phantoms. It is very challenging, if not impossible, to meet all of these requirements with a single phantom platform, especially in the case of multimodal imaging systems. Often a subset of the desired qualities must be selected depending on the V&V role of the phantoms. Therefore, it is very important to identify the goal of the phantom experiment to be conducted, and to derive the phantom requirements based on that goal.

Three general classes of phantoms use can be defined: calibration phantoms, development phantoms, and verification phantoms. Although calibration phantoms are used during both system development and for final system verification, they are treated herein as a separate class to highlight their specific requirements.

3.3.2.1 Calibration phantoms

A calibration phantom is a material standard used to transfer the accuracy of its characterization to another instrument. The ultimate goal of this transfer should be to achieve traceability to the international system of units.[26] Traceability to the international system of units is key to ensuring that measurements taken at any point in space and time will be comparable to any other measurement taken at any other point in space and time. This is the best way to ensure long-term integrity of data produced by any instrumentation. SI (International System of Units abbreviated SI from French: Le Système International) traceability requires that measurements of the phantom property of interest are derived from secondary measurements (optical power, length, time delay) taken with calibrated instrumentation. This ensures an unbroken chain of comparison from the unit definitions themselves to the final measurement. Each comparison must have a stated and documented uncertainty.

Another possible way of ensuring long-term measurement repeatability and consistency is to reference measurements against a standard material produced with a controlled fabrication process and for which the user community has agreed to assign a conventionally true value to its physical properties of interest. In the field of diffuse optics, some research groups are currently considering the use of injectable fat emulsion as calibration standards.[27]

A calibration phantom should focus on accuracy, traceability, and stability. Good calibration phantoms can provide value at every stage of the translational path, from academic research to commercialization, by providing ground truth that will help reduce intersystem and interlaboratory variability.

3.3.2.2 Development phantom

Development phantoms are phantoms used as inanimate test subjects during the iterative R&D process that are needed to bring a concept into a working prototype capable of acquiring human data to demonstrate potential. The key characteristics of development phantoms may vary greatly, depending on the technical issue addressed. In very early stages, the phantom design may emphasize adequately reproducing the challenges of the intended application, with little regard to stability, accuracy or even reproducibility. The rigors of true traceability are usually not required. A typical application of such a phantom would be to perform a proof-of-concept experiment to generate preliminary data required to obtain research funding. A very complex phantom with inhomogeneity and dynamics could be used to acquire a dataset aimed at developing reconstruction algorithms, without any strict requirement for this phantom to be either stable in the long term or traceable to international standards. Development phantoms can even be assembled from biological tissue.[28] As the R&D process evolves, other issues such as repeatability and accuracy may become more important than having a structure representative of the targeted organ.

3.3.2.3 Verification phantom

In the rigorous context of V&V of new medical devices seeking commercialization approval, tissue phantoms should be seen as verification tools, material artifacts of *a priori* known characteristics that are used for verifying that a specific performance requirement (design input) is met by a prototype or a production unit of a medical device (design output; see Fig. 3.3). The key objective here is to ensure that every future production unit of the device will produce data that is consistent with that of the very first few units used during the validation clinical trials. In this context, the validation phantom's key requirements are traceability, accuracy, stability, and reproducibility. A homogeneous block of phantom material could be perfectly suitable to ensure device-to-device consistency, even if that device normally acquires data from an inhomogeneous organ.

Calibration and verification phantoms, although they may be physically identical, have very distinct roles. Verification phantoms are used for translating the raw output of a device into clinically meaningful traceable quantities. They are therefore an integral part of the device manufacturing or servicing process. Calibration phantoms, on the other hand, are meant to be independent quality control tools to ensure instrument-to-instrument consistency. So, wouldn't calibration phantoms also be an integral part of device manufacturing and servicing?

Thus, development of new imaging modalities can benefit from synergistic industry–academic collaboration, taking into consideration industry's goals and academic and clinical partners' strengths. Using the V model of device

development and testing with diligent documentation throughout the process is crucial. Careful consideration of the requirements for developmental, calibration, and verification phantoms will enable consistency in manufacturing as well as meaningful comparison of results from multisite clinical studies.

3.4 Chemistry Probes and Guided Therapies Core

The NTR Chemistry Probes and Guided Therapies Core focused primarily on the development and validation of new targeted probes for clinical translation using multimodal imaging techniques. The four research centers of the NTR each had specific requirements for imaging probes based on the type of optical imaging technology selected. Some were best administered systemically, while for others, a topical application was chosen. Furthermore, because each center was required to create a multimodal imaging platform by combining optical imaging with a clinical imaging method, the combination of probes (dual labeling or separate application) was also unique to each center. For these reasons, the technical challenges, and even the validation requirements, were distinct among the teams. Although each team was equipped with a distinct research direction, an open science model was used in the core discussions to stimulate dialogue and share knowledge, experiences, and infrastructure to ultimately expedite the translational development of new probes.[29]

3.5 Center 1: Washington University

The NTR center from Washington University worked toward clinical use of photoacoustic tomography (PAT), a hybrid of optical and ultrasound imaging.[30] PAT is a relatively new optical imaging modality that has great potential for diagnostic application in many diseases. In contrast to fluorescence imaging, PAT relies on ultrasound waves resulting from instantaneous thermal expansion upon molecular absorption of modulated light. Hemoglobin and melanin are intrinsic absorbers naturally present at high concentrations in mammalian tissue and provide exceptional PAT contrast for blood vessels and melanomas, respectively.[30,31] Contrast can also be achieved by using highly absorbing dyes and nanomaterials that have low spectral overlap with hemoglobin, such as those active in near-infrared (NIR) wavelengths. Small-molecule contrast agents include methylene blue (MB) and indocyanine green (ICG),[30,32] which are approved for use in humans, with many more being developed. Nanomaterial platforms are also being developed for photoacoustic imaging.[33] The details of the research and the translational challenges faced are presented in Chapter 5 of this book.

The strategy for this center was to validate PAT as an imaging modality with clinically available contrast agents, creating standards for future multi-institutional clinical trials. Upon successful validation of PAT as a clinical

imaging modality and development of standardized methods, molecular imaging agents based on clinically approved components will be tested. Following these standards, molecular imaging contrast agents can be efficiently evaluated for faster translation. For initial translation of this technology, the center initiated a clinical trial to detect the sentinel lymph node (SLN), a major determinant of the next course of treatment in patients diagnosed with breast cancer. For this purpose, contrast agents can be injected peritumorally, and the agents then collect in regional lymph nodes, the first of which are the SLNs.

Contrast in PAT is achieved by absorption of light as opposed to fluorescence emission. Therefore, exogenous contrast agents for PAT have focused on organic dyes with high molar extinction coefficients, e.g., MB ($\epsilon_{670\text{nm}} > 70{,}000\ \text{cm}^{-1}\text{M}^{-1}$) and ICG ($\epsilon_{800\text{nm}} = 180{,}000\ \text{cm}^{-1}\text{M}^{-1}$). ICG is approved for use in humans but does not have functional groups for attaching to targeting agents and molecular imaging. Direct iodination of MB produced a multimodal contrast agent for SLN mapping that uses single-photon emission computed tomography (SPECT) and PAT in rats with a real-time PAT/US system developed for clinical applications.[32,34] Cypate is a near-infrared fluorescence (NIRF) dye very close in structure to ICG, but with carboxylic acid groups for functionalization. This agent has been used in many preclinical studies with and without targeting groups, and with no adverse effects detected.[35] A new multimodal contrast agent, cypate-DOTA, was developed by this NTR center by conjugating a chelating agent for radiometal incorporation to cypate. This multimodal contrast agent was also used for SLN mapping using a novel handheld video-rate diffuse optical tomography device that is being developed for deep-tissue fluorescence imaging.[36]

Another approach taken by this center during this program was the development of nanoparticle agents with large payload capacity and effective concentration of signal for PAT contrast. This avenue of research emphasizes that, although the overall goals of the center are translational, there is still opportunity to explore areas that may not have immediate translational capability. As a class of imaging agents, nanoparticles require extensive basic and preclinical research before they are ready for clinical testing. Examples of biocompatible nanomaterial contrast agents include dye-loaded polymeric[37] and perfluorocarbon nanoparticles, gold nanobeacons,[38–40] colloidal gold,[41,42] gold nanocages,[43] and copper neodecanoate nanoparticles.[44] Most nanomaterials were formulated using components with a history of safe use in humans (e.g., gold and perfluorocarbon), but this does not mean that the resulting material is safe or effective.

Nanomaterials offer significant advantages in contrast capabilities for PAT but face barriers to translation due to size, reproducibility of production, and validation of selective targeting. The insight gained through participation

in the NTR program played a key part in planning the early stages of the approval process, such as choice of pathway (academic versus traditional), early communication with regulatory agencies, and establishment of teams to optimize chances of success.

In the end, each agent will need to be fully tested before approval for use in humans. Without doubt, translation of this nascent PAT technology into the clinic is essential to drive the market for further advances in contrast agents. It is evident that academic laboratories will play an active role in bringing diagnostic agents to clinical utility and that, to do so, the laboratories will need to increase their understanding and acceptance of translational regulatory matters.

3.6 Center 2: The University of Texas Health Science Center at Houston

The overall objective of the chemistry group within the University of Texas Health Science Center at Houston (UTHealth) NTR center has been to develop molecular imaging agents to enhance diagnostic capabilities and support personalized health initiatives. (The details of the research and the translational challenges faced are presented in Chapter 6 of this book.) A highlight of this study that differentiated it from the other NTR chemistry probe studies was the need for dual-labeling (NIR for optical measurements and radioactive for nuclear imaging). To accomplish this, the team focused on a multimodal imaging approach with antibody-based agents to detect primary and metastatic lesions in an orthotopic prostate cancer model. A hybrid approach was employed using targeting compounds that were dual-labeled with radioactive and NIRF contrast to permit whole-body and intraoperative imaging from a single-agent administration. Given the relative infancy of translational NIRF imaging at the beginning of the NTR program, it was necessary to gain a more comprehensive understanding of the optical properties of NIRF dyes through comparative studies, particularly in light of the growing interest in dual-labeling approaches that combined NIRF and radioactive labels for hybrid imaging but that failed to assess the impact of the radioactivity on optical properties. Thus, to optimize the dual-labeling approach, this center focused initial studies on determining the suitability of commercially available NIRF dyes for dual labeling and published the first report that systematically compared the optical properties of a panel of NIRF dyes in response to increasing amounts of radioactivity.[45] The data showed a dose-dependent reduction in relative brightness for each dye, with IRDye 800 having the lowest percentage decrease in response to higher radioactive amounts. These data indicate the enhanced optical stability of IRDye 800 and suggest that it may be an ideal NIRF dye for future dual-labeling studies.

To achieve tumor-specific delivery of the diagnostic payload epithelial cell adhesion molecule (EpCAM), a nearly universal tumor marker that is expressed on the surface of virtually all epithelial cancers was selected as a target, based on its widespread utility for identifying cancer positivity in resected tissues by immunohistochemical analysis. Developing an EpCAM-targeted agent that could be used for noninvasive imaging required conjugating a chelating agent to a commercially available monoclonal antibody (mAb) to permit radiolabeling with Copper-64 (^{64}Cu; $t_{1/2} = 12.7$ h) for PET imaging, and attaching a NIRF dye for intraoperative use. To ensure that the two-step conjugation process did not alter the biological activity of the mAb, flow cytometry analysis and ELISAs were conducted as part of the batch release criteria needed to initiate *in vivo* studies. The dual-labeling approach capitalized on the comparable detection sensitivities of NIRF and nuclear imaging and was able to detect tumors in an orthotopic prostate cancer animal model that was transfected with the gene reporter DsRed.[14]

The abundance of therapeutic mAbs on the market provides a seemingly simple and straightforward path for development of mAb-based conjugates for diagnostic use. However, key properties of a therapeutic mAb, which include attenuated target affinity and prolonged circulation time, are not ideally suited for imaging. Thus, significant optimization efforts are needed in order to develop immunoconjugates for diagnostic imaging. To improve the specificity of EpCAM and reduce off-target signal, the UTHealth core collaborated with the Division of Applied Biologics at UTHealth to employ surface plasmon resonance (SPR) to screen a library of in-house mAbs and selected two candidates with the highest affinity for EpCAM for *in vivo* characterization. The resulting animal studies indicated higher accuracy for tumor detection with the optimized anti-EpCAM mAbs and demonstrated the impact of affinity on efficacy for tumor detection.[46]

Due to the inability to perform site-specific chemical modifications on many commercially available chelating agents, dual labeling of mAbs generally occurs in a random, two-step process. In addition to preventing batch-to-batch reproducibility, this approach could result in overmodification of a mAb and subsequent loss of potency. The UTHealth core implemented a novel dual-labeling approach that used synthetic chemistry to combine a NIRF dye and radiometal chelator into a single moiety. Studies confirmed that radiolabeling efficiency and optical properties were comparable to unmodified chelating and NIRF reagents, respectively, and enabled reduction of the conjugation footprint on the mAb.[47] Studies to further enhance the resulting multimodality chelator (MMC) to permit regiospecific conjugation to partially reduced interchain disulfides have begun to ensure that the dual-labeling process does not interact with the pharmacophore of the mAb. Using the experience gained in developing dual-labeled mAbs, the center has evaluated the potential use of reagents developed during the NTR period for

use with peptide-based agents to overcome the limitations of existing dual-labeling technologies.

The NTR-wide focus on validation guided the chemistry group in this center in standardizing agent production protocols and putting forth acceptance criteria for characterizing dual-labeled agents. In addition, the GMP facility that was established at this facility has provided full capabilities for sterile fill and preparation of imaging agent kits, radiolabeling, and quality control/assurance (QC/QA) under aseptic conditions to support the planned clinical translation of the anti-EpCAM targeting agent. Using SOPs for immunoconjugate synthesis, labeling, and QC that were developed as part of the NTR, the core is assembling the Chemistry, Manufacturing, and Controls (CMC) section for an IND submission and will benefit from the experiences of the Validation/Clinical Studies Core and colleagues from the University of Michigan who have already translated a peptide-based fluorescent imaging agent into patients. Given the growing interest in dual-labeled agents, the proactive role of the NTR in building a bridge between the nuclear and optical imaging communities may lead to new opportunities for collaborative research and help define translational pathways for new NIRF agents.

3.7 Center 3: University of Michigan

The University of Michigan chemistry probes group performed probe discovery in the area of peptide, peptide heterodimer, and multimers for targeted imaging of flat and depressed colonic neoplasia and high-grade dysplasia (HGD) in the esophagus using multimodal imaging approaches.[48,49] The group identified ligands that specifically recognize the overexpressed cell surface targets. In particular, short peptides were developed for molecular recognition because of their superior biocompatibility, low immunogenicity, good solubility, and easy synthesis. The group used the technique of phage display, a powerful method for the rapid identification of peptide ligands for a variety of cell-surface receptors. Methods were successfully developed to identify these specific peptide ligands for binding with overexpressed cell-surface targets in human and mouse models of colorectal cancer using *ex vivo* and *in vivo* biopanning methods. Either human cell lines / purified proteins or the genetically engineered CPC;Apc mice model for spontaneous colorectal cancer were used as the panning substrate.[50] Using these technologies, several peptide ligands were isolated that home to cancer cells and malignant and premalignant tissues. The synthesis and labeling of these peptides was accomplished by means of solid phase synthesis using the well-established Fmoc chemistry. The details of the research and the translational challenges faced are presented in Chapter 7 of this book.

Peptides are diverse molecules, and each sequence is unique with regard to its chemical and physical properties. The optimal strategy of synthesis

applicable on all scales should be determined before preclinical use. While some peptides are difficult to synthesize, many peptides are relatively straightforward to produce but may still be difficult to purify after synthesis. The chemistry group from this center successfully outlined the scheme for design, synthesis, and validation of various peptides for translation into the clinic. Before moving to the clinical trial, they performed extensive validation to determine if the peptide was safe for human testing with one or more optimized peptides. They then carried out *in vitro* and *in vivo* tests to characterize the peptide binding properties and the safety profile.

The FDA requires thorough testing before a candidate drug can be studied in humans. During this stage, the group determined how to produce sufficient quantities of the peptide for clinical trials under GMP conditions. During this process, they were provided support from the other NTR research centers and cores through the networking process for (1) sharing information related to FDA requirements, (2) providing guidelines for translating molecular probes from small animals to humans (Standards and Compliance Core), and (3) designing and verifying the imaging instrument to match the imaging probes (Instrumentation and Industry Relations Core). The impact of networking was also evident during preclinical probe development, where the chemistry probes team from this center faced technical challenges in identifying a suitable fluorophore that could be efficiently conjugated to their targeting moiety and be chemically compatible with the available optical imaging instrumentation. Through the NTR, they successfully established a collaboration with Professor Eric Seibel's group at the University of Washington to successfully perform *in vivo* multispectral imaging in a spontaneous mouse model of colorectal cancer.[51] The chemistry probes team then built upon their preclinical findings by partnering with Olympus Medical System Corporation and completing a Phase I clinical trial with peptides developed for detection of dysplastic lesions in esophagus and colon.[52]

In optical imaging, the area of highest translational impact lies in the NIR window (650–900 nm), where light is able to penetrate most deeply into tissue. Moreover, tissue autofluorescence is reduced in this spectral regime in comparison to that of the visible range. Imaging in this window requires the targeting abilities of the probe to accumulate specifically in diseased cells while being cleared from surrounding normal tissues, using bright fluorophores absorbing and emitting in the NIR range.

3.8 Center 4: Stanford University

Detection of early-stage cancer or of chronically inflamed tissue remains an important clinical challenge, leading to an ongoing search for specific imaging-relevant biomarkers for these conditions. Cyclooxygenase-2 (COX-2) mRNA and protein are detectable in a significant percentage of inflammatory

and premalignant lesions and an even higher percentage of malignant tumors.[53–55] In fact, studies have shown that COX-2 expression is an early event in carcinogenesis.[56] Therefore, COX-2 is a potentially useful target for detection of inflammation and many cancers using fluorescent or radiolabelled COX-2 inhibitors. To develop COX-2-targeted optical imaging probes, the Stanford University center, along with researchers from Vanderbilt University, faced a major challenge involving the construction of fluorescent COX-2 inhibitors. To solve this problem, the team employed a conjugate chemistry approach. They constructed molecules comprising one of several scaffolds based on a known COX-2 inhibitor attached through a variety of linker groups to one of a series of fluorescent dyes. This design was based on the discovery that certain carboxylic-acid-containing inhibitors of both COX-2 and its isoform, COX-1, can be transformed into highly potent and selective COX-2 inhibitors by converting the carboxylic acid moiety into an ester or amide function.[57] Using this strategy, the group generated more than 200 fluorescent compounds,[58] each of which was tested for its ability to inhibit COX-1 and COX-2 in a purified protein assay. The COX-2-selective compounds were then tested for inhibition of the enzyme in cell lines, and active molecules were further evaluated in animal models of cancer and inflammation. Of the large number of compounds tested, only two showed promising results in both *in vitro* and *in vivo* settings. These compounds, containing indomethacin as the scaffold tethered through a butylenediamine linker to the carboxy-X-rhodamine fluorophore, have been designated fluorocoxibs. A number of animal models were used to evaluate the fluorocoxibs.[59] For example, imaging detected selective accumulation of fluorocoxib B in the inflamed but not the control footpad of mice after intraperitoneal injection of the fluorophore. Studies in tumor xenografts revealed specific uptake of fluorocoxib A in COX-2-positive tumors. Finally, utilization of fluorocoxib A for the early detection of carcinogenesis in the APC^{Min+}(Min) mouse model of intestinal polyposis showed a remarkable 50- to 75-fold higher uptake in polyps compared to the surrounding normal tissues, and indicated the broader applicability of fluorocoxibs for early detection at hard-to-reach sites. The details of the research and the translational challenges faced are presented in Chapter 8 of this book.

The lessons learned while developing fluorocoxibs are: (1) Among the carboxylic acid-containing COX inhibitors evaluated (indomethacin, celecoxib, flurbiprofen, ketoprofen), indomethacin affords the best COX-2-selective conjugates. (2) An *n*-butyl tether is optimal for conjugation with fluorophore functional groups. (3) Zwitterionic fluorophores provide the best binding efficiency, as seen with carboxy-X-rhodamines. (4) Metal or halide salts, such as IRDye800 or NIR667, are not suitable for binding. (5) Highly polar polycarboxylic acids, such as lanthanide chelators, are not suitable for COX-2-targeted molecular probe development. (6) COX-2-targeted *in vivo* imaging of inflammation and cancer is possible using fluorescently labeled

indomethacin derivatives, the fluorocoxibs. This strategy enables adoption within or outside the NTR chemistry core of the development of a range of new and useful molecular probes for early diagnosis of inflammatory and neoplastic diseases.

The probe development program in this center effectively utilized the NTR framework in several ways. First, they applied expertise in developing pertinent animal models for agent characterization, validated COX-2 as a new imaging target, and demonstrated the utility of fluorocoxibs for optical imaging. Second, they supported NTR initiatives by commercializing the fluorocoxibs and making their novel reagents accessible to the research community. Third, the core collaborated with the Standards and Compliance Core and completed the necessary steps to initiate first-in-humans studies. Finally, based on interactions with members of the NTR Chemistry Core, the core proposed new applications with the fluorocoxib platform that include the development of chemocoxibs, COX-2-targeted NSAID or COXIB-toxin conjugates that selectively deliver chemotherapy into neoplastic cells.

3.9 Information Technologies Core

The mission of the Information Technology (IT) Core was to support the NTR website and the other research cores. The IT Core worked to develop and deploy an infrastructure to support validation of the performance of the imaging technologies developed by the Network, and to permit sharing of data, information, and software pertinent to the overall NTR mission. The IT Core also worked to engage National Institute of Standards and Technology (NIST), FDA, CMS, and industry partners to develop imaging standards. Additionally, the core worked to allow adoption of several of the NCI cancer Biomedical Informatics Grid® (caBIG®) tools and standards by researcher institutions, scientific societies [such as the American Association of Physicists in Medicine (AAPM), Society of Nuclear Medicine (SNM), International Society for Magnetic Resonance in Medicine (ISMRM), SPIE, IEEE, Radiological Society of North America (RSNA), and Quantative Imaging Biomarkers Alliance (QIBA)], and the imaging industry.

The IT Core set up the nuts-and-bolts mechanisms that allowed the NTR to conduct internal business. The core created and maintained a wiki site that was available to the NTR, in order to allow intra-NTR information sharing. Each NTR center created its specific program website that was linked to the wiki. The cores were able to post teleconference and face-to-face meeting proceedings on the wiki, and the wiki contained a HELP function to provide guidance on wiki-page editing and contributions.

The major focus of the IT Core was the launch of SciPort, a caBIG-compatible, web-based platform, designed for scientific data management and integration.[3,4] A demonstration site for SciPort, accessible from the wiki, was

created to allow the NTR centers to become familiar with SciPort. The IT Core also enabled WebEx and Centra services to supplement audio teleconference meetings, allowing document and presentation sharing among centers within the NTR.

The IT Core also enabled sharing between NTR and research groups outside the network. For example, the core established a liaison between NTR and another NCI-supported imaging network called the Quantitative Imaging Network (QIN), enabling collaboration in software validation and information exchange. The IT Core supported the Cancer UK cooperative agreement for the NTR to share data and tools, as well as supporting the NCI caBIG leadership through the Imaging Workspace. A group of academic pathologists worked with the IT Core to establish an image database/registry to allow comparison and standardization of image reading. This registry of images allowed image reading uniformity for modality comparisons and standardization, as well as synchronization for multisite clinical trials.

The greatest contribution of the IT Core to the NTR program was the establishment of the software package Sciport to handle the documentation control and other translational issues for the four centers. The core worked with Siemens Corporate Research to provide each of the NTR centers and each of the universities a personal, nonexclusive, nontransferable, royalty-free, fully paid (subject to each of the universities fulfilling their payment obligation) right and license to use Sciport for NTR work. SciPort was partially funded by caBIG, a former NCI program focused on informatics and connectivity. Sciport is a flexible database/program that was designed for translational researchers in academia and allows hierarchical organization of data/images and sharing among academic sites. Importantly, the program enables easy facilitation of GLP, current GMP (cGMP), and GCP compliance. Through customized data structures, web forms for clinical data, and a security infrastructure to guard clinical subject-specific (HIPAA-protected), as well as proprietary, information, the program can make trials easier and less risky. SciPort includes an interface to the National Biomedical Imaging Archive (NBIA), which was developed for more conventional Digital Imaging and Communications in Medicine (DICOM) imaging modalities.

Sciport provides a user-friendly method to develop document templates for bench research and clinical trial data input, workflow design, and compliance oversight of laboratory and clinical staff. The software allows easy creation of SOPs and clinical study source documents, and accurate and secure data recording. The software maintains an audit trail for study evaluation and is 21 CFR Part 11-compliant. SciPort enables batch upload of all data file types, as well as easy data mining. Documents can be electronically signed by researchers. Manufacturing logs, IQ/OQ of equipment, batch release data,

and preclinical safety, pharmacokinetics, and toxicity findings can all be stored and tracked in SciPort. The use of templates allows easy revision of SOPs or clinical case report forms that may be needed as preclinical and clinical studies progress.

A most important function of the IT Core was the validation, verification, and qualification of SciPort. The definitions of these terms, relative to SciPort software, are proving that the software will accomplish what it was designed to do (verification), proving that the software addresses the clinical/biological needs it was designed to address (validation), and providing consistent evidence to demonstrate that the measurement or technique reliably answers preclinical or clinical questions (qualification).

The IT Core created a NTR Verification and Validation Survey for all NTR centers in order to understand what IT could do to support V&V plans. The core worked with Siemens Corporate Research on an academic–industrial partnership grant to allow use of SciPort in all the NTR centers. Siemens provided one NTR center with an advanced 3D rendering and image analysis package (OMIRAD, Optical & Multimodal Imaging for Research, Assessment, and Diagnosis). The software package was designed to allow data fusion between optics and other modalities, such as US, compliant with DICOM standards. The core worked to connect OMIRAD and caBIG to "publish" data for other researchers to use.

A major validation goal of the core was to enable the mapping of histology images (the gold standard) back to *in vivo* images produced by the modalities developed by the NTR centers. This goal could be achieved by successful image processing and registration, including aligning the white-light and fluorescence images collected from nuclear, endoscopic, and microscopic imaging systems. The *in vivo* images could then also be registered with images from tissue specimens excised *en bloc* for pathology histological validation. "Virtual slides," produced using standardized imaging formats, could then provide cohesiveness among image readers and pathologists. Registration between pathology and optical imaging images, and linkage of both domains to caBIG, particularly the In Vivo Imaging Workspace and Tissue Banks and Pathology Tools Workspace within caBIG, was a major goal. The IT Core considered incorporating caBIG's cache of radiographic images, the National Cancer Imaging Archive (NCIA).

Some NTR members worked to establish a digital archive for the NCI Office of Biospecimens and Biorepositories (OBBR). The IT Core discussed ways to use such archives and establish a continuum of image analysis algorithms for radiographic, ultrasonographic, and optical images to work with standardized pathology digital imaging rules. The core worked to extend DICOM to support the different NTR data types, such as visible, SPECT, and US, and to include image mosaicking. In order to use caBIG optimally, the core worked to adopt DICOM WG 23 application hosting (a plug-in

interface for software applications). The core also suggested a XIP (eXtensible Imaging Platform, NCI's open space workstation) extension to launch Matlab® applications, and for developing an appropriate environment for XIP development.

3.10 Summary

While each core focused on different needs of translational researchers, the cores provided cohesive progress toward the common goals of the four centers. The cores allowed participation of researchers with a wide variety of talent and expertise to derive the best practices needed to translate optical imaging agents and devices. The outputs of the NTR cores include a handbook, numerous validation papers, an electronic data entry and management tool, phantoms, and the start of image registration. These products should allow for smoother transition of optical modalities through the "Valley of Death" on the way to FDA approval, and, ultimately, market presence of important tools for improving health.

3.11 Glossary of Terms

Accuracy: The degree of closeness of the determined value to the nominal or known true value under prescribed conditions. This is sometimes termed *trueness*.

Biological matrix: A discrete material of biological origin that can be sampled and processed in a reproducible manner. Examples are blood, serum, plasma, urine, feces, saliva, sputum, and various discrete tissues.

Limit of detection (LOD): The lowest concentration of an analyte in a sample that the bioanalytical procedure can reliably differentiate from background noise.

Lower limit of quantification (LLOQ): The lowest amount of an analyte in a sample that can be quantitatively determined with suitable precision and accuracy.

Precision: The closeness of agreement (degree of scatter) between a series of measurements obtained from multiple samplings of the same homogenous sample under the prescribed conditions.

Process validation: Collection and evaluation of data—from the process design stage through production—that establishes scientific evidence that a process is capable of consistently delivering quality products.

Quantification range: The range of concentration—including ULOQ and LLOQ—that can be reliably and reproducibly quantified with accuracy and precision through the use of a concentration–response relationship.

Selectivity: The ability of the bioanalytical method to measure and differentiate the analytes in the presence of components that may be expected to be present. These could include metabolites, impurities, degradants, or matrix components.

Stability: The chemical stability of an analyte in a given matrix under specific conditions for given time intervals.

Upper limit of quantification (ULOQ): The highest amount of an analyte in a sample that can be quantitatively determined with precision and accuracy.

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References

1. U.S. Food and Drug Administration Guidelines on General Principles of Process Validation (1987).

2. https://en.wikipedia.org/wiki/Verification_and_validation.
3. F. Wang, P. Hussels, and P. Liu, "Securely and flexibly sharing a biomedical data management system," *Proc. SPIE* **7264**, 726492 (2009) [doi: 10.1117/12.811716].
4. F. Wang, F. Thiel, D. Furrer, C. Vergara-Niedermayr, C. Qin, G. Hackenberg, P. E. Bourgue, D. Kaltschmidt, and M. Wang, "An adaptable XML based approach for scientific data management and integration," *Proc. SPIE* **6919**, 69190K (2008) [doi: 10.1117/12.773154].
5. C. Garritty and K. El Emam, "Who's using PDAs? Estimates of PDA use by health care providers: a systematic review of surveys," *J. Medical Internet Research* **8**(2), e7 (2006).
6. M. B. Marshall, D. Draney, E. M. Sevick-Muraca, and D. M. Olive, "Single-dose intravenous toxicity study of IRDye800 CW in Spraque-Dawley rats," *Molecular Imaging and Biology* **12**(6), 583–94 (2010).
7. M. B. Aldrich, X. Wang, A. Hart, S. Kwon, L. Sampath, M. V. Marshall, and E. M. Sevick-Muraca, "Assessment of free dye in solutions of dual-labeled antibody conjugates for *in vivo* molecular imaging," *Molecular Imaging and Biology* **13**(1), 32–42(2011).
8. M. A. Hall, M. B. Aldrich, A. Azhdarinia, P. A. Lachance, H. Robinson, A. Hazen, D. L. Haviland, and E. M. Sevick-Muraca, "Quantifying multimodal contrast agent biological activity using near-infrared flow cytometry," *Contrast Media and Molecular Imaging* **7**(3), 338–45 (2012).
9. J. Zhang, S. K. Zhou, X. Xiang, M. L. Bautista, B. A. Niccum, G. S. Dickinson, I. C. Tan, W. Chan, E. M. Sevick-Muraca, and J. C. Rasmussen, "Automated analysis of investigational near-infrared fluorescence lymphatic imaging in humans," *Biomedical Optics Express* **3**, 1713–23 (2012).
10. I. C. Tan, E. A. Maus, J. C. Rasmussen, M. V. Marshall, K. E. Adams, C. E. Fife, L. A. Smith, W. Chan, and E. M. Sevick-Muraca, "Assessment of lymphatic contractile function after manual lymphatic drainage using near-infrared fluorescence imaging," *Archives Physical Medicine and Rehabilitation* **92**, 756–764 (2011).
11. K. E. Adams, J. C. Rasmussen, C. Darne, I. C. Tan, M. B. Aldrich, M. V. Marshall, C. E. Fife, E. A. Maus, L. A. Smith, R. Guilloid, S. Hoy, and E. M. Sevick-Muraca, "Direct evidence of lymphatic function improvement after advanced pneumatic compression device treatment of lymphedema," *Biomedical Optics Express* **1**, 114–125 (2010).
12. B. Zhu, G. Wu, H. Robinson, N. Wilganowski, M. A. Hall, S. C. Ghosh, K. L. Pinkston, A. Azhdarinia, B. R. Harvey, and E. M. Sevick-Muraca, "Tumor margin detection using quantitative NIRF molecular imaging targeting EpCAM validated by far-red gene reporter iRFP," *Molecular Imaging and Biology* **15**(5), 560–568 (2013).

13. Y. Lu, C. D. Darne, I. C. Tan, G. Wu, N. Wilganowski, H. Robinson, A. Azhdarinia, B. Zhu, J. C. Rasmussen, and E. M. Sevick-Muraca, "*In vivo* imaging of orthotopic prostate cancer with far-red gene reporter fluorescence tomography and *in vivo* and *ex vivo* validation," *J. Biomedical Optics* **18**(10), 101305 (2013) [doi: 10.1117/1.JBO.18.10.101305].
14. M. A. Hall, S. Kwon, H. Robinson, P. A. Lachance, A. Azhdarinia, R. Ranganathan, R. E. Price, W. Chan, and E. M. Sevick-Muraca, "Imaging prostate cancer lymph node metastases with a multimodality contrast agent," *Prostate* **72**, 129–46 (2012).
15. T. M. Bydlon, W. T. Barry, S. A. Kennedy, J. Q. Brown, J. E. Gallagher, L. G. Wilke, J. Geradts, and N. Ramanujam, "Advancing optical imaging for breast margin assessment: an analysis of excisional time, cautery, and patent blue dye on underlying sources of contrast," *PLoS One* **7**, e51418 (2012).
16. B. Zhu, I.-C.Tan, J. C. Rasmussen, and E. M. Sevick-Muraca, "Validating the sensitivity and performance of near-infrared fluorescence imaging and tomography devices using a novel solid phantom and measurement approach," *Techniques in Cancer Research and Treatment* **11**, 95–104 (2012).
17. A. Vasanji and B. A. Hoover, "Art & science of imaging analytics," *Applied Clinical Trials* **22**(3), 38–45 (2013).
18. K. Borradaile, R. Ford, M. O'Neal, and K. Byrne, "Discordance between BICR readers: understanding the causes and implementing processes to mitigate preventable source of discordance," *Applied Clinical Trials* (supplement), September 2010, pp. 14–20.
19. Y. Meng, S. Ward, K. Cooper, S. Haman, and L. Wyld, "Cost-effectiveness of MRI and PET imaging for the evaluation of axillary lymph node metastases in early stage breast cancer," *European J. Surgical Oncology* **37**, 40–46 (2011).
20. B. Keagy and D. Levin, "Medical device trials," *Applied Clinical Trials*, May 2012, pp. 36–41.
21. E. Ashton and M. Henning, "Maximizing oncology imaging data," *Applied Clinical Trials* (Oncology Clinical Trials insert), May 2013, pp. 2–3.
22. R. A. Frank, D. W. Rucker, M. A. Ferguson, and T. J. Sweeney, "Evidence requirements for innovative imaging devices: from concept to adoption," *J. American College of Radiology* **8**, 124–131 (2011).
23. S. S. Mehta, *Commercializing Successful Biomedical Technologies: Basic Principles for the Development of Drugs, Diagnostics and Devices*, Cambridge University Press, Cambridge (2008).

24. B. Berenbach, D. Paulish, J. Kazmeier, and A. Rudorfer, *Software & Systems Requirements Engineering: In Practice*, McGraw-Hill Osborne Media, New York (2009).
25. B. W. Pogue and M. S. Patterson, "Review of tissue simulating phantoms for optical spectroscopy, imaging and dosimetry," *J. Biomedical Optics* **11**(4), 041102 (2006) [doi: 10.1117/1.2335429].
26. J.-P. Bouchard, I. Veilleux, I. Noiseux, and O. Mermut, "Accurately characterized optical tissue phantoms: How, why and when?" *Proc. SPIE* **7906**, 79060K (2011) [doi: 10.1117/12.875400].
27. P. D. Ninni, F. Martelli, and G. Zaccanti, "Intralipid: Towards a diffusive reference standard for optical tissue phantoms," *Physics in Medicine and Biology* **56**, N21–N28 (2011).
28. J. Xia, C.-W. Wei, L. Huang, I. M. Pelivanov, and M. O'Donnell, "Comparison of PA imaging by narrow beam scanning and one-shot broad beam excitation," *Proc. SPIE* **7899**, 78991L (2011) [doi: 10.1117/12.975879].
29. E. M. Sevick-Muraca, W. J. Akers, B. P. Joshi, G. D. Luker, C. S. Cutler, L. J. Marnett, C. H. Contag, T. D. Wang, and A. Azhdarinia, "Advancing the translation of optical imaging agents for clinical imaging," *Biomedical Optics Express* **4**, 160–70 (2013).
30. C. Kim, C. Favazza, and L. V. Wang, "In vivo photoacoustic tomography of chemicals: high-resolution functional and molecular optical imaging at new depths," *Chemical Reviews* **110**, 2756–82 (2010).
31. L. V. Wang, "Prospects of photoacoustic tomography," *Medical Physics* **35**, 5758–67 (2008).
32. C. Kim, T. N. Erpelding, K. Maslov, L. Jankovic, W. J. Akers, L. Song, S. Achilefu, J. A. Margenthaler, M. D. Pashley, and L. V. Wang, "Handheld array-based photoacoustic probe for guiding needle biopsy of sentinel lymph nodes," *J. Biomedical Optics* **15**, 046010 (2010) [doi: 10.1117/1.3469829].
33. D. Pan, B. Kim, L. V. Wang, and G. M. Lanza, "A brief account of nanoparticle contrast agents for photoacoustic imaging," *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology* **5**, 517–43 (2013).
34. W. J. Akers, W. B. Edwards, C. Kim, B. Xu, T. N. Erpelding, L. V. Wang, and S. Achilefu, "Multimodal sentinel lymph node mapping with single-photon emission computed tomography (SPECT)/computed tomography (CT) and photoacoustic tomography," *Translational Research* **159**, 175–81 (2012).
35. S. Achilefu, "Lighting up tumors with receptor-specific optical molecular probes," *Technology in Cancer Research & Treatment* **3**, 393–409 (2004).

36. M. Solomon, B. R. White, R. E. Nothdruft, W. Akers, G. Sudlow, A. T. Eggebrecht, S. Achilefu, and J. P. Culver, "Video-rate fluorescence diffuse optical tomography for in vivo sentinel lymph node imaging," *Biomedical Optics Express* **2**, 3267–77 (2011).

37. D. Pan, X. Cai, B. Kim, A. J. Stacy, L. V. Wang, and G. M. Lanza, "Rapid synthesis of near infrared polymeric micelles for real-time sentinel lymph node imaging," *Advanced Healthcare Materials* **1**, 582–9 (2012).

38. D. Pan, M. Pramanik, A. Senpan, J. S. Allen, H. Zhang, S. A. Wickline, L. V. Wang, and G. M. Lanza, "Molecular photoacoustic imaging of angiogenesis with integrin-targeted gold nanobeacons," *The FASEB J.* **25**, 875–82 (2011).

39. D. Pan, M. Pramanik, A. Senpan, S. Ghosh, S. A. Wickline, L. V. Wang, and G. M. Lanza, "Near infrared photoacoustic detection of sentinel lymph nodes with gold nanobeacons," *Biomaterials* **31**, 4088–93 (2010).

40. W. J. Akers, C. Kim, M. Berezin, K. Guo, R. Fuhrhop, G. M. Lanza, G. M. Fischer, E. Daltrozzo, A. Zumbusch, X. Cai, L. V. Wang, and S. Achilefu, "Noninvasive photoacoustic and fluorescence sentinel lymph node identification using dye-loaded perfluorocarbon nanoparticles," *ACS Nano* **5**, 173–82 (2011).

41. D. Pan, M. Pramanik, S. A. Wickline, L. V. Wang, and G. M. Lanza, "Recent advances in colloidal gold nanobeacons for molecular photoacoustic imaging," *Contrast Media and Molecular Imaging* **6**, 378–88 (2011).

42. D. Pan, M. Pramanik, A. Senpan, X. Yang, K. H. Song, M. J. Scott, H. Zhang, P. J. Gaffney, S. A. Wickline, L. V. Wang, and G. M. Lanza, "Molecular photoacoustic tomography with colloidal nanobeacons," *Angewandt Chemie International Edition in English* **48**, 4170–3 (2009).

43. W. Li, P. K. Brown, L. V. Wang, and Y. Xia, "Gold nanocages as contrast agents for photoacoustic imaging," *Contrast Media and Molecular Imaging* **6**, 370–7 (2011).

44. D. Pan, X. Cai, C. Yalaz, A. Senpan, K. Omanakuttan, S. A. Wickline, L. V. Wang, and G. M. Lanza, "Photoacoustic sentinel lymph node imaging with self-assembled copper neodecanoate nanoparticles," *ACS Nano* **6**, 1260–7 (2012).

45. A. Azhdarinia, P. Ghosh, S. Ghosh, N. Wilganowski, and E. M. Sevick-Muraca, "Dual-labeling strategies for nuclear and fluorescence molecular imaging: a review and analysis," *Molecular Imaging and Biology* **14**, 261–76 (2012).

46. M. A. Hall, K. L. Pinkston, N. Wilganowski, H. Robinson, P. Ghosh, A. Azhdarinia, K. Vazquez-Arreguin, A. M. Kolonin, B. R. Harvey, and E. M. Sevick-Muraca, "Comparison of mAbs targeting epithelial cell

adhesion molecule for the detection of prostate cancer lymph node metastases with multimodal contrast agents: quantitative small-animal PET/CT and NIRF," *J. Nuclear Medicine* **53**, 1427–37 (2012).

47. S. C. Ghosh, P. Ghosh, N. Wilganowski, H. Robinson, M. A. Hall, G. Dickinson, K. L. Pinkston, B. R. Harvey, E. M. Sevick-Muraca, and A. Azhdarinia, "Multimodal chelation platform for near-infrared fluorescence/nuclear imaging," *J. Medicinal Chemistry* **56**, 406–16 (2013).
48. M. B. Sturm, B. P. Joshi, S. Lu, C. Piraka, S. Khondee, B. J. Elmunzer, R. S. Kwon, D. G. Beer, H. D. Appelman, D. K. Turgeon, and T. D. Wang, "Targeted imaging of esophageal neoplasia with a fluorescently labeled peptide: first-in-human results," *Science Translational Medicine* **5**, 184ra61 (2013).
49. B. P. Joshi, Z. Liu, S. F. Elahi, H. D. Appelman, and T. D. Wang, "Near-infrared-labeled peptide multimer functions as phage mimic for high affinity, specific targeting of colonic adenomas in vivo," *Gastrointestinal Endoscopy* **76**, 1197–206 (2012).
50. S. J. Miller, B. P. Joshi, Y. Feng, A. Gaustad, E. R. Fearon, and T. D. Wang, "In vivo fluorescence-based endoscopic detection of colon dysplasia in the mouse using a novel peptide probe," *PLoS One* **6**, e17384 (2011).
51. B. P. Joshi, S. J. Miller, C. M. Lee, E. J. Seibel, and T. D. Wang, "Multispectral endoscopic imaging of colorectal dysplasia in vivo," *Gastroenterology* **143**, 1435–7 (2012).
52. C. R. Piraka, Y. Chen, X. Duan, R. B. J. Elmunzer, R. S. Kwon, H. D. Apelman, S. R. Owens, D. K. Turgeon, and T. D. Wang, "Quantitative targeted wide area in vivo imaging of neoplasia in Barrett's esophagus," *Gastroenterology* **144**, S-117 (2013).
53. G. Li, T. Yang, and J. Yan, "Cyclooxygenase-2 increased the angiogenic and metastatic potential of tumor cells," *Biochemical and Biophysical Research Communications* **299**, 886–90 (2002).
54. M. M. Taketo, "COX-2 and colon cancer," *Inflammation Research* **47** Supplement 2, S112–6 (1998).
55. S. I. Abdalla, P. Lao-Sirieix, M. R. Novelli, L. B. Lovat, I. R. Sanderson, and R. C. Fitzgerald, "Gastrin-induced cyclooxygenase-2 expression in Barrett's carcinogenesis," *Clinical Cancer Research* **10**, 4784–92 (2004).
56. M. M. Taketo, "Cyclooxygenase-2 inhibitors in tumorigenesis: Part II," *J. National Cancer Institute* **90**, 1609–20 (1998).
57. A. S. Kalgutkar, B. C. Crews, S. W. Rowlinson, A. B. Marnett, K. R. Kozak, R. P. Remmel, and L. J. Marnett, "Biochemically based design of cyclooxygenase-2 (COX-2) inhibitors: facile conversion of nonsteroidal

antiinflammatory drugs to potent and highly selective COX-2 inhibitors," *Proc. National Academy of Sciences USA* **97**, 925–30 (2000).

58. M. J. Uddin, B. C. Crews, K. Ghebreselasie, and L. J. Marnett, "Design, synthesis, and structure-activity relationship studies of fluorescent inhibitors of cycloxygenase-2 as targeted optical imaging agents," *Bioconjugate Chemistry* **24**, 712–23 (2013).
59. M. J. Uddin, B. C. Crews, A. L. Blobaum, P. J. Kingsley, D. L. Gorden, J. O. McIntyre, L. M. Matrisian, K. Subbaramaiah, A. J. Dannenberg, D. W. Piston, and J. L. Marnett, "Selective visualization of cyclooxygenase-2 in inflammation and cancer by targeted fluorescent imaging agents," *Cancer Research* **70**, 3618–27 (2010).

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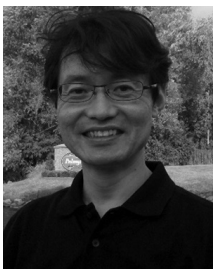

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