CLINICAL IMAGING

Drug-Based Optical Agents: Infiltrating Clinics at Lower Risk

Werner Scheuer,[1] Gooitzen M. van Dam,[2] Michael Dobosz,[1] Markus Schwaiger,[3] Vasilis Ntziachristos[4]*

Fluorescent agents with specificity to cellular and subcellular moieties present promise for enhancing diagnostics and theranostics, yet challenges associated with regulatory approvals of experimental agents stifle the clinical translation. As a result, targeted fluorescent agents have remained predominantly as preclinical imaging tools. We discuss the potential of using optically labeled drugs to accelerate the clinical acceptance of optical and optoacoustic agents, in analogy to nuclear medicine approaches. This strategy, corroborated with microdosing studies, outlines a promising approach for overcoming bottlenecks and advancing photonic clinical imaging.

TROUBLE WITH TRANSLATION

Advances in optical imaging bring diagnostic and theranostic potential that is unavailable to conventional visual inspection. Optical coherence tomography (OCT), narrow band imaging (NBI), fiber-based confocal microscopy, or hyperspectral autofluorescence imaging, for example, can offer subsurface visualization in vivo and enhance anatomical, functional, and biochemical information (*1*). To improve target detection over intrinsic tissue contrast, contrast enhancement can be further imparted by optical agents that recognize otherwise-invisible disease biomarkers (*2*, *3*). The development of optical and optoacoustic agents with molecular specificity has seen substantial growth in the past decade. Optical agents targeting specific disease moieties promise to improve disease detection over the use of intrinsic tissue contrast or nonspecific fluorescent organic dyes, such as indocyanine green (ICG) (*2*).

In animals, fluorescent and optoacoustic agents have been successfully used to target cancer, cardiovascular disease, neurodegenerative disease, and bacterial infections, among others (*4*–*7*). However, the clinical translation of novel optical imaging agents requires overcoming regulatory barriers set by the U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMA). This often implies high-risk industrial or academic investments owing to the time and cost associated with the clinical translation of a new agent. Consequently, there has been little showcased ability to bring novel fluorescent agents to use in humans. Clinical fluorescence imaging therefore still relates to the use of ICG or fluorescein—agents approved several decades ago, primarily for resolving anatomical or physiological features. ICG, for example, has been used clinically for eye angiography, hepatic clearance studies, and visualization of the lymphatic system (*8*, *9*). Nevertheless, ICG and other nonspecific fluorescent dyes have not been found particularly useful in many other clinical application areas—for example, in cancer detection—owing to the lack of specificity.

The clinical propagation of novel agents engineered to be disease-specific has two levels of associated challenges. The first and more straightforward regards the toxicity and stability studies that are required for obtaining human use approvals. The primary limitation in clinical translation, however, comes from the second challenge: the risk associated with the efficacy of the agent. Preclinical (animal) studies do not accurately predict human efficacy of a new agent. Instead, a stepwise process from phase I to phase III clinical studies is required to establish the usefulness of a novel imaging agent. These translational studies constitute a leap in the resources required in terms of cost, time, skill, and critical mass over the original development and demonstration of a novel agent in animal studies. The added cost associated with clinical translation is typically the primary reason why targeted optical agents for clinical use are unavailable, despite the high expectations set by demonstration of these agents in animals. Yet, at the heart of the translational difficulty are not the additional resources required for translation, but the certainty associated with the imaging performance of a given optical agent in humans. In other words, if an agent would be certain to offer suitable imaging accuracy in humans—if the risks were removed—then it would be straightforward to secure the resources for clinically translating it from public funding sources or the industry.

Translation of fluorescent probes to medical applications can therefore be expedited by minimizing the uncertainty of their clinical imaging performance. Here, we discuss how the use of optical agents based on approved drugs, or on drugs already being explored therapeutically in late-phase clinical trials, may minimize the translational risk compared with novel optical agents that are based on molecules never administered to humans. We further discuss the use of optical imaging at microdosing amounts as a strategy to further accelerate the clinical translation of fluorescence molecular imaging. Lastly, we explain why accurate fluorescence imaging technology is required in clinical studies and in successful regulatory approval.

DRUGS DOUBLE AS IMAGING AGENTS

Analogous to radioisotopes in nuclear imaging, various optical tags, such as fluorescent dyes, can be used to label drugs and create agents that retain the targeting properties of the drug while providing optical contrast. Compared with optical agents based on molecules with undocumented biodistribution and targeting profiles in humans, the consideration of known drugs labeled with a fluorescent dye comes with advantages that can accelerate the clinical translation of the optical agent. First, a wide portfolio of drug molecules is available for doubling as optical imaging agents. Already, antibody- or antibody fragment–based agents as well as nonpeptidic small molecules considered originally for therapeutics have shown potent imaging performance in animal studies (*2*, *3*). Many additional agents can be potentially derived from approved or late-phase clinical trial drugs (Table 1). Second, each of the drugs considered comes with knowledge of the pharmacokinetics and targeting efficiency and specificity in humans—data that were

[1]Pharma Research and Early Development, Discovery Oncology, Roche Diagnostics GmbH, Penzberg 82377, Germany. [2]University Medical Center Groningen, Department of Surgery, 9700 RB Groningen, Netherlands. [3]Nuclear Medicine, Klinikum Rechts der Isar, Technische Universität München 81675, Germany. [4]Biological and Medical Imaging, Technische Universität München and Helmholtz Zentrum, München 81675, Germany.

*Corresponding author. E-mail: v.ntziachristos@tum.de

Table 1. Examples of clinically approved or investigated drugs that target established cancer-related biomarkers. These drugs could be considered for use as optical imaging agents for microdosing studies.

Drug	Type	Biomarker
Cetuximab	Chimeric monoclonal antibody	EGFR
Nimotuzumab	Chimeric monoclonal antibody	EGFR
Panitumumab	Chimeric monoclonal antibody	EGFR
Necitumumab	Monoclonal antibody	EGFR
Zalutumumab	Human monoclonal antibody	EGFR
Bevacizumab	Humanized monoclonal antibody	VEGF
Ranibizumab	Monoclonal antibody fragment	VEGF
Pazopanib	Small molecule	VEGF receptor (VEGFR)
Ramucirumab	Human monoclonal antibody	VEGFR
Etaracizumab	Humanized monoclonal antibody	$\alpha_v\beta_3$ integrin
Volociximab	Chimeric monoclonal antibody	$\alpha_5\beta_1$ integrin
Pertuzumab	Humanized monoclonal antibody	HER2
Trastuzumab	Humanized monoclonal antibody	HER2
Adecatumumab	Recombinant human monoclonal antibody	Epithelial cell adhesion molecule (EpCAM)
Farletuzumab	Monoclonal antibody	Folate binding protein

obtained during clinical trials. Third, each drug comes with corresponding information on possible side effects to humans, which can refine the selection process toward minimizing safety risks. When it comes to side effects, an advantage of an imaging session over a therapeutic protocol is that a labeled drug considered for optical imaging will be typically administered once in quantities that are much smaller than the total dose administered over a treatment protocol.

REDUCING TRANSLATIONAL RISK

Despite these advantages, a labeled drug is considered a new molecule in regulatory approvals for human use. Therefore, even for pilot clinical trials a labeled drug needs to undergo toxicity studies in an identical manner to new imaging agents—in other words, agents based on new molecules without previous experience on humans. At first impression, it would appear that there is no practical benefit when selecting a labeled drug over a new optical agent. Yet, the major challenge in the clinical translation process is not the investment associated with the toxicity study itself but the overall performance of the agent during phase I to III clinical trials. Although many new optical imaging agents appear promising for human use on the basis of preclinical animal data, animal studies do not always predict performance in humans. Then, the key question of new imaging agents tested only on animal models relates to the overall performance in humans.

A labeled drug comes with a different question at hand: Does the labeling process change the performance of the active molecule, which has already been characterized in vivo in humans? Confirmation that active sites of the drug-based agent are not blocked by optical labeling can be performed easily in the laboratory. Similarly, animals and pilot human examinations can quickly reject probes with altered biodistribution or pharmacokinetic profiles resulting from labeling. Nuclear imaging data may also be available as part of the drug development process, which could corroborate the biodistribution studies.

In contrast, the clinical translation of a new imaging probe requires information on broader questions that include the targeting ability, pharmacokinetics, and side effects of the new molecule in humans, which are typically only conclusively addressed after the completion of phase III clinical trials. Eventually, both labeled drugs and new imaging agents will undergo phase II and phase III clinical trials for approval in clinical use. However, a promising imaging agent based on a molecule that has already successfully undergone phase III trials may come under these conditions at higher performance certainty (reduced risk) as compared with those of new imaging agents, so as to justify the investment required for clinical translation.

FEATURES OF A LABELED DRUG

With the above assumptions, it is clear that risk management is an important criterion in accelerating the clinical propagation of fluorescence molecular imaging. From several optical imaging agents described in the literature (*2*, *3*), a narrowed selection that will, with high probability, lead to a successful outcome is important to help boost the field and reach patients faster. Risk management could be achieved by using not only labeled drugs for optical imaging but also molecules that were discontinued from the clinical translation pipeline owing to unsatisfactory therapeutic efficacy. Even a change in a drug's strategic priority, especially if targeted to disease-specific moieties, would also affect risk management.

Many drugs may not be ideal imaging agents. Besides favorable biodistribution to disease, an imaging agent also needs to generate a strong signal and high contrast within acceptable time frames. Accumulation and binding patterns will also play a vital role in the success of a drug as an imaging agent. For example, trastuzumab labels specific cancer cells and may be ideal for margin delineation of a subset of tumors expressing human epidermal growth factor receptor 2 (HER2) (Fig. 1, A and B), whereas bevacizumab preferentially accumulates in the stroma and may be better as a generic tumor marker (Fig. 1, C and D). Therefore, a careful selection from a long list of therapeutic molecules, such as those in Table 1, can lead to optimal disease imaging.

MICRODOSING

Microdosing is a tool developed to accelerate the discovery of new drugs by allowing fast regulatory approval of pharmacokinetic studies of a new molecule when administered in very low, nonpharmacologically active doses. Under the EMA Safety Working Party Position paper (*10*) and the FDA exploratory investigational new drug (IND) application guidelines (*11*), a microdose is defined as the administration of 100 μg of a small-molecule ligand or 1% of the pharmacological dose determined on animal data to yield a pharmacological effect, whichever is the lesser (*12*). Because of

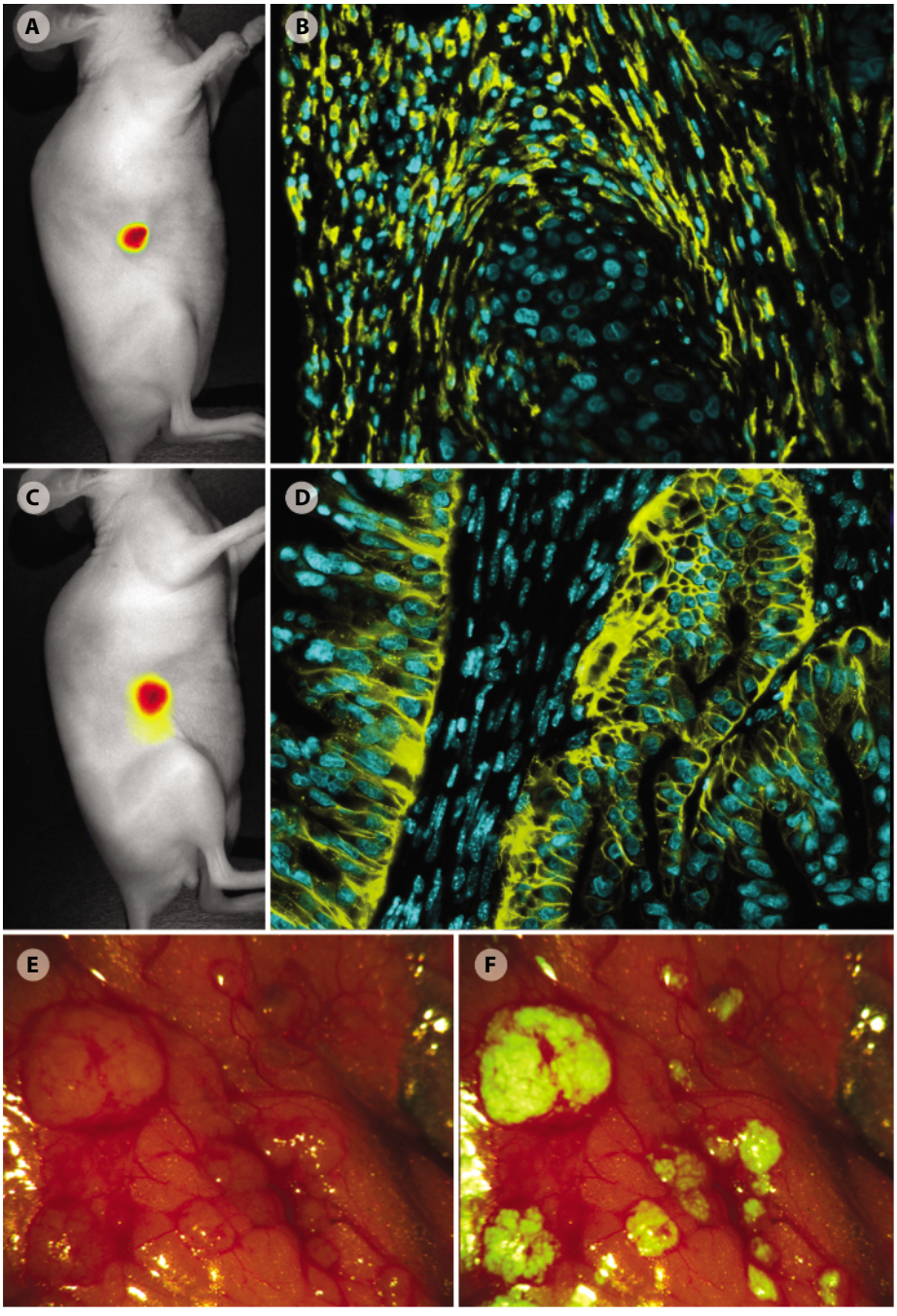

Fig. 1. Anticancer drugs double as imaging agents. (A to D) Macroscopic imaging of a human breast cancer xenograft overexpressing HER2 (A, C) and histological confirmation of excised tumor (B, D) confirms in vivo tagging in mice. Cy5-labeled trastuzumab (yellow) preferentially targets tumor cells (cyan) (B); whereas Cy5-labeled bevacizumab (yellow) accumulated in the tumor stroma (cyan) (D). (**E** and **F**) Color (E) and hybrid (F) imaging of an ovarian cancer patient imaged intraoperatively after the injection of a fluorescence probe targeting the folate-α receptor. The images were obtained with permission from (*13*).

the larger molecular weight, the maximum dose considered for protein products is ≤30 nanomoles (*11*).

Administration of an optical agent at microdosing (tracer) amounts is a strategy that can mitigate the clinical translation of optical agents. This is because regulatory guidelines accept the use of a single mammalian species to showcase safety in support of single-dose studies in humans. The selection of small animals (typically rodents) for toxicity demonstration and the availability of complete pharmacological and dosing profiles of the active molecule, obtained through the drug discovery process of the active molecule, lead to straightforward design and implementation of phase 0/I human clinical trials. Conversely, administration of an agent at doses above the microdosing limits typically requires studies on at least two species before translation to humans. One species is selected to be a small animal, such as a rat, and the second species is a larger animal (dog or monkey) (*11*). The use of large animals and the corresponding production of the agent at larger doses, to account for the larger animal weight over rodents, adds to the cost and time investment required.

Microdosing is another strategy to lower the translational barrier of new imaging agents (*11*), as it can reduce the cost and accelerate early studies investigating the clinical performance of optical agents. The combination of labeled drugs with microdosing has synergistic effects toward risk minimization because it may quickly address the issue of labeled versus unlabeled drug similarity, providing evidence for further investing in phase II and III trials.

Collecting early clinical imaging efficacy data, as facilitated by microdosing, is an important first step for the clinical translation of fluorescence molecular imaging. Similarly to nuclear imaging that can detect microdosing amounts from tissues, optical methods offer very sensitive detection of agents when imaging superficial activity from tissues—for example, in surgical procedures or gastrointestinal endoscopic inspection. Typically, tens of organic fluorescent dye femptomoles (or less) can be detected with sensitive charge-coupled device (CCD) cameras in vivo. One clinical study using targeted fluorescent agents for enhancing surgical vision (*13*) used ~6 to 7 mg of agent, which is more than the accepted microdosing amounts of 100 μg in this case. The fluorescence system used in the study operated in the visible range (480 to 530 nm), a spectral region that required narrow-band optical filtering leading to reduced detection sensitivity (Fig. 1, E and F). Operation in the near-infrared part of the spectrum (700 to 900 nm) combined with wider-band filtering can lead to substantial sensitivity gains to bring imaging of tracer fluorescent agent amounts (microdosing amounts) within reach.

POTENT TARGETS AND DRUGS

Successful imaging requires the selection of specific molecules against biomarkers (physiological or molecular characteristics of the target disease). The prevalence and specificity of the biomarker in the group of patients imaged will play a central role in the selection process. Selection criteria for imaging biomarkers have been suggested recently (*14*). Some validated cancer biomarkers are summarized in Table 1, as well as corresponding drugs considered for clinical use that target them, which can be applied as optical or optoacoustic imaging agents.

The ultimate clinical application will also define requirements for the imaging molecule used. Theranostic applications, such as surgical guidance, may choose an optical agent that can best delineate tumor margins or microscopic residual disease. For many cancer patients, tissue microarray confirmation of expression markers can be performed on tumor biopsies to select prominent targets present in the individual patient. In this case, agent specificity becomes important. Conversely, diagnostic applications focus on the ability to more generically identify disease, and thus the selection of an imaging agent may benefit from a broader targeting profile.

Many antibodies, antibody fragments, and small molecules developed for therapeutic purposes have shown good potential as imaging agents in nuclear imaging in animals and humans or in fluorescence imaging studies in animals (*3*, *14*). Popular targets include proteins involved in tumor growth, extracellular matrix invasion, cell adhesion and migration, and tumor cell signaling. Cetuximab, nimotuzumab, and panitumumab have been developed for targeting the epithelial growth factor receptor (EGFR), which has been implicated in cancer growth and migration, with high prevalence in several different tumor types (Table 1) (*14*). Such drugs already have been considered as nuclear (*15*, *16*) or optical agents (*17*). The monoclonal antibody bevacizumab and the derived fragment ranibizumab have been developed to bind the vascular epithelial growth factor A (VEGF-A), which has already been considered as a clinical imaging target in nuclear medicine applications (*18*, *19*). Although VEGF is only partly membrane-bound, imaging studies using radio-labeled drugs have been able to identify areas of neovascularization. The ability to use bevacizumab as an optical imaging agent is showcased in Figure 1, C and D. Similarly, labeled trastuzumab (Herceptin) has shown good binding and signal strength characteristics in the case of HER2-positive tumors (Fig. 1, A and B). Etaracizumab, Mpab, and other nonpeptide-based small molecules can also be considered for targeting and imaging integrins (Table 1). Despite their overall widespread distribution and varied functions, certain integrins, such as $\alpha_v\beta_3$, are closely associated with angiogenesis and metastasis and have been investigated as imaging targets for cancer using positron emission tomography (PET) (*20*).

Overall, small molecules may exert better tumor penetration and nonbinding fraction and are typically cleared faster from the circulation than are antibody-based agents, resulting in a better plasma-to-tumor ratio. Conversely, the impact of labeling on the biodistribution and clearance of an agent should be studied closely as the size of the active small molecule becomes comparable in size with the fluorescent label. Moreover, antibodies and their fragments generally have functional groups available for conjugation with fluorescent dyes, but small-molecule drugs may not have such groups existing in their structures and thus might require some structural modification. A new molecular structure, however, may introduce targeting, biodistribution, and clearance differences over the original molecule, qualifying the new probe as a new agent and increasing the risk of translation.

IMAGING TECHNOLOGY

The optical imaging technology used can also play an important role in the concept of risk minimization and the success of clinical translation. The use of accurate and sensitive detection systems, in combination with bright optical labels, is crucial for achieving reliable operation at micro-dosing conditions. Unfortunately, the intensity captured in epi-illumination (photographic) fluorescence imaging does not represent true fluorescence biodistribution because it depends not only on the underlying fluorochrome concentration but also on the local tissue optical properties and the fluorochrome's depth (*1*, *21*). The selection of optical imaging technology for clinical use should therefore offer operating characteristics that yield accurate fluorescent readings that are independent of tissue discolorations or light illumination patterns and shadows while offering real-time video operation. Such technology is not generally available because most systems offered for fluorescence imaging operate with simple photographic principles. Data standardization is a common topic in radiological imaging studies, especially when multicenter clinical trials are considered. Because visible and near-infrared photons have a strong nonlinear dependence on the geometrical and optical parameters of tissue, the issue of data standardization is a particularly important topic in optical imaging applications. Therefore, the use of optical imaging technology that yields accurate tissue- and system-independent measurements is important for ensuring data of quality and accuracy standards that are sufficient for regulatory and clinical approvals (*13*, *21*).

MINIMIZING RISK, MAXIMIZING TRANSLATION

A major bottleneck in performing early-phase clinical studies is not the cost or the effort involved in the regulatory process, but the risk of long-term clinical failure. With costs of preclinical validation and toxicity of an agent, including good manufacturing practices for clinical-grade production, being relatively low (<0.5 to 1 million euros), the main barrier for generating phase I clinical data is the overall certainty of how well an agent will perform during phase II and III clinical trials—studies that require a larger investment in time and cost (>1 million euros). Therefore, the selection of molecules that reduce the risk of clinical failure can accelerate the application of fluorescence molecular imaging to humans. Molecules of known performance in humans offer a potent way to risk minimization. Combined with the possibility of micro-dosing studies, such molecules can expedite building evidence on imaging efficacy for justifying investments into navigating the agent approval process. This example can follow the paradigm of nuclear imaging, which uses microdosing studies to accelerate the development of a clinical agent portfolio, and potentially benefit from the clinical experience using radio-labeled agents (*22*). Furthermore, accurate imaging technology and the establishment of data standardization concepts will be beneficial for ensuring the generation of high-quality multicenter clinical trial data. Besides camera-based fluorescence imaging methods, advanced photonic approaches including multispectral optoacoustic tomography (*4*) or fiber-based confocal methods can further improve the theranostic and diagnostic potential of clinical optical molecular imaging.

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