Molecular imaging as a de-risking tool: coming into focus?

Molecular imaging is already engrained in early-stage trials for central nervous system disorders, but used infrequently in other therapeutic areas. What will it take to make it standard practice across the pipeline?

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When Endocyte and Merck & Co. asked for European approval for vintafolide in ovarian cancer late last year, the submission package included a novel feature: a molecular imaging companion diagnostic. Endocyte started work on the radiolabelled etarfolatide, which lights up folate-receptor-positive tumours in patients, even before it started developing the accompanying folate-receptor-targeted chemotherapeutic. This unusual approach, which could deliver the first coupled *in vivo* diagnostic–therapeutic duo, underscores the increasing interest in molecular imaging as a drug development tool.

The field's pioneers are working hard to showcase how their visualization technology can drive drug development programmes at a fundamental level: "This is really the ultimate way of de-risking early-stage projects," says Chris Behrenbruch, CEO of biologic imaging biotech company ImaginAb.

And if uncertainty equals risk, there is no doubt that drug developers continue to carry too much of it into mid-stage trials. Pfizer couldn't conclude whether its candidates' mechanisms of action had been tested properly in 43% of its Phase II failures, it reported last year, making 'go'/'no go' decisions difficult (*Drug Discov. Today* **17**, 419–424; 2012). Against this backdrop, molecular imaging could be a game changer. Beyond its ability to help identify likely responders (as per Endocyte's etarfolatide), it can show where drug candidates go in the body, whether they engage their targets and how they affect downstream physiology — all in first-in-human studies.

"I think it is well established that these techniques are wonderful research tools. But in the business sense, what does it mean for the advancement of your therapy for approval?" asks Matt Silva, Director of Imaging Research at inviCRO, an imaging contract research organization. "That is ultimately the equation that pharma has to solve."

Small molecules, big problems

As yet, only central nervous system (CNS) small-molecule drug developers — operating in the riskiest indications — have truly cracked the calculus. GlaxoSmithKline (GSK), Pfizer and Lundbeck all incorporate molecular imaging into their early-stage clinical CNS programmes whenever possible. At the simplest level, by synthesizing candidates or competitive binders with the radiolabel Carbon-11 (^{11}C), they track drug biodistribution to ensure their candidates cross the blood–brain barrier (BBB) in humans.

But they can also do much more, says Paul Matthews, head of Imperial College London's Division of Brain Sciences, in London, UK, and Vice President of Medicines Discovery and Development at GSK. In his favourite case study, GSK dosed volunteers first with ^{11}C-carfentanil, a potent radiolabelled opioid, and then treated them with GSK1521498, a candidate μ-opioid receptor inverse agonist. Using positron emission tomography (PET) to monitor ^{11}C-carfentanil displacement, the researchers showed that GSK1521498 crosses the BBB, charted the relationship between plasma concentration levels and target occupancy and determined optimal dosing levels. By looking at the effects of GSK1521498 on functional magnetic resonance imaging (fMRI) activation versus the response induced by a generic active comparator, they built the business case for advancing their candidate (*Mol. Psychiatry* **16**, 826–835; 2011).

"This was done in one joined up experiment. It was a really great poster child of what can happen under the best circumstances," says Matthews. (GSK1521498 was tested in Phase II overeating disorder trials, but is currently waylaid for commercial and other reasons.)

Despite the potential benefits, few groups are systematically using early-stage molecular imaging beyond the CNS. Oncology is an obvious potential beneficiary, given the ability to look at the biodistribution of agents in tumours *in vivo*. But with the exception of the use of ^{18}F-fluorodeoxyglucose (FDG)–PET, oncology holds only a distant second to CNS, say many in the field. "We've used it a couple of times, but it is not baked into the fabric of the oncology development paradigm," says Tim McCarthy, Pfizer's Head of Clinical and Translational Imaging and past president of the Society of Non-Invasive Imaging in Drug Development.

With fierce competition and hundreds of clinical anticancer candidates, many firms won't stomach a delay of up to a year while their chemists radiolabel early-stage candidates. In terms of understanding target engagement, the challenge is equally compelling; "Whether it is right or wrong, the current view is that there is a really strong marker of response — tumour shrinkage," says Matthews.

Coupled with these problems is a concern that just as target-based drug screening overlooks agents with pleiotropic activity, so too early-stage proof-of-mechanism validation could lead to discontinuation of candidates with unintended but beneficial broader activity. "I get asked about this all the time," says the US National Cancer Institute's James Doroshow, a proponent of using pilot clinical studies to better de-risk programmes. "But there are so many hundreds of molecules and not enough money to get them all into patients. I'm willing to take this risk."

Investment in other therapeutic areas is even worse. "I would be surprised if it's an even measurable amount," says Silva. Not that there is any lack of opportunity. Matthews points to respiratory indications and a paucity of data on the biodistribution of inhaled drugs as areas that are ready for exploration. McCarthy holds up cardiovascular and metabolic indications as therapeutic areas in need of imaging probes.

Incremental advances on several fronts may be levelling the playing field. More hospitals are building PET centres, driving down imaging costs. Microfluidics could help chemists to quickly test reaction conditions and facilitate bespoke ^{11}C-labelling of lead compounds. And non-radioactivity-based imaging modalities are coming online: molecularly targeted microbubbles could make ultrasound amenable to molecular imaging; and the spectroscopic resolution of high-Tesla MRI machines offers better assessment of *in vivo* chemical composition, including the ability to compare levels of glutamate and glutamine in the brain.

Drug developers are also hunting for imaging probes that can be used across programmes, like Lilly/Avid's approved amyloid-imaging agent florbetapir F18, a potentially invaluable tool for Alzheimer's disease clinical trials. The investment into bespoke versus multipurpose imaging agents currently lies at around 50/50, says McCarthy. But a shift towards re-usable probe discovery could lead to an increase in molecular imaging's return on investment.

Although florbetapir F18's future in the commercial diagnostic market remains uncertain (experts are sceptical about whether it will change health outcomes), it is clear that imaging agents can deliver value — often by helping to kill programmes early on — even if they won't ever generate stand-alone

revenue streams. "I think that companies are increasingly investing in imaging agents that they don't intend to commercialize," says Silva.

Labelling antibodies

Biotech companies, meanwhile, are gaining ground with the molecular imaging of monoclonal antibodies (mAbs) and antibody–drug conjugates (ADCs).

"There is huge interest in labelling biologics," says Matthews.

In some ways, mAbs make ideal imaging fodder. Whereas chemists may need to go to heroic lengths to radiolabel small molecules with ^{11}C, antibody engineers can tag mAbs relatively easily with various labels. "Most of the time it's like bolting a barnacle on to a supertanker, and it doesn't really change the kinetics or the behaviour of the mAb," says Behrenbruch. And given the high target specificity of mAbs, understanding where they go in the body is key.

But although the FDA approved the first radiolabelled antibody diagnostic 20 years ago (Cytogen's Tag-72-binding Indium satumomab pendetide), the long half-life and slow clearance of radiolabelled mAbs have held up their use in pilot clinical trials. Because of the short half-life of PET radionuclides, researchers have had to image patients at early time points when the antibody is still largely present in the blood pool and has yet to distribute to target tissues.

The rise of Zirconium-89 (^{89}Zr) helps to address these issues. With a half-life of 78 hours, the isotope decays in line with the clearance and tissue uptake of many mAbs. It can also be used at a radioactivity dose for which the safety burden is comparable to common FDG–PET/CT (computed tomography). "We like ^{89}Zr," says Jan Marik, a scientist in Genentech's biomedical imaging department. "It works."

In October last year, Genentech signed a supply agreement with NCM USA to ensure access to the radioisotope. "We are exploring the scope and possibilities the technology can give us," says Marik. This includes using ^{89}Zr in the clinic to look at mAb biodistribution and at dosing levels, which are particularly crucial for mAbs versus small molecules given the higher cost of mAb materials. Data on target expression may provide patient-selection and indication-scouting capabilities. As for pharmacodynamic biomarkers, says Marik, small-molecule imaging tools and other physiological end points guide decision making.

A less traditional but exciting possibility could be to advance several biologics against the same target into the clinic simultaneously, and then use imaging biodistribution and clearance data to decide which agent to advance.

mAb derivatives, too, are opening up new avenues of research. ImaginAb is going against the grain of therapeutic antibody engineers by reducing the immunogenicity, functionality and half-life of its partners' mAbs to generate inert, short-lived radioactive fragments that can be used as tracers. "We've become a chop shop for antibodies," says Behrenbruch.

The biotech company has already teamed up with 15 biopharma partners who hope these fast-clearing tissue-penetrating products can shed light on mAb biodistribution and inform patient-selection strategies. Other biotech companies are working with different types of fragments, peptides and small proteins with the same aims.

But not everyone agrees that advances in the small-molecule and biologic worlds alone will be enough to deliver on imaging's promise. "The problems that remain are more than mindset and more than pragmatic," says Silva. "If we look critically, there are just too few examples in the public domain of imaging agents transforming the drug development process — saving time, reducing costs and increasing approval rates." If success stories and tales of projects killed by imaging results are locked up in pharma's vaults, the final focus could come from setting these free.