

NEWS FEATURE

A Wellcome experiment in seeding drug discovery

Take UK£91 million, plant it into 30 drug discovery projects in academic institutes and in industry, and fertilize regularly with expert advice. What do you get? Bethan Hughes investigates.

When the Wellcome Trust launched its 5-year Seeding Drug Discovery Initiative (SDDI) in October 2005 they set out to facilitate the development of drug-like small molecules that address unmet medical needs.

“We consider projects in all disease areas, from any originating environment,” says Richard Davis, the business development manager at the Trust, who is responsible for the day-to-day management of the SDDI based in London, UK. “A project could be from an academic institution, a spin-out company or even an established pharmaceutical company because we ultimately base the decision [to grant an award] on the excellence of the science.”

Four years into the initiative, the Trust’s Board of Governors is considering the programme’s future. Those that have been fortunate enough to receive an award obviously hope that the initiative will continue. “The SDDI is a good complement to R&D funding sources elsewhere,” says David Payne, Vice President of the Antibacterial Discovery Performance Unit in the Infectious Diseases Center of Excellence for Drug Discovery at GlaxoSmithKline (GSK), USA. Payne’s group has received two awards to develop novel antibacterials. “The SDDI’s focus on areas in which there is a high unmet medical need, but less than a critical mass of R&D in industry, is a great thing for them to do. I hope they will continue,” he adds.

Gaining funding from external sources is an important addition to GSK’s internal antibacterial research because of the extent of the challenges in antibacterial drug discovery (*Nature Rev. Drug Discov.* 6, 29–40; 2007). “We approached Wellcome to accelerate our internal programmes because the challenges are so tough that we need larger chemistry and biology teams to increase our probability of success,” Payne explains.

Funding commitments

Since its inception, the SDDI has committed £80.4 million to 30 awards (in 19 academic institutions and 11 companies) covering a wide range of therapeutic areas. With the exception of GSK, the companies receiving SDDI awards are spin-out or small biotech companies navigating the currently particularly challenging capital-raising environment. It is essential therefore that the SDDI aims for “projects to progress to a stage whereby there is sufficient evidence to make the project results, intellectual property and outcomes attractive to follow-on developers or investors who may be from the commercial or not-for-profit sectors.” This goal also appeals to the self-selecting academics that want to do this research, says Davis. “They really have a drive to understand this process and to ultimately develop compounds that can be taken into the clinic.”

One such researcher is Professor Steve Bloom at Imperial College, London, UK, who received an award to develop novel analogues of the satiety hormone pancreatic polypeptide for the treatment of obesity. For Bloom, funding from the Trust came at a time when venture capital (VC) funding is particularly hard to obtain. He had previously been successful at raising VC funds for his spin-out company Thiakis, a biopharmaceutical company developing oxyntomodulin peptide technology for the treatment of obesity and associated conditions. Thiakis was acquired by Wyeth (now part of Pfizer) in December 2008 for an upfront fee of US\$30 million and potential milestone payments of up to \$120 million. However, acquiring funding to develop the pancreatic

polypeptide analogue was more difficult. “We found that every VC company we visited wanted to fund drugs that had already been shown to be efficacious and safe in humans. The appetite for investing in biotechnology has diminished such that it is now very difficult to get funding for anything other than a tried and tested pill,” says Bloom.

Access to experts

Apart from the availability of funds from the Trust, Bloom appreciated the scientific expertise provided by the SDDI team. “The Trust has an enormous depth of scientific understanding and they have a very large cadre of experts who are willing to work hard on their behalf. They are in a position to choose genuine winners, and they are in the position to fund them properly.”

John Hollway, Vice President of Business Development at Achaogen, a company that received an award to complete a Phase I clinical trial in healthy volunteers of the neoglycoside antibiotic ACHN-490, agrees that access to expert advice makes the Wellcome Trust an attractive partner. “Our relationship is more than financial



engineering. The award is coupled to the resources and pragmatism of the Trust, as well as access to global thought leaders in drug discovery," he says.

Gaining expert advice from the SDDI and independent advisors also had the impact of cost-saving, says Bloom, "One can always get access to experience, but you have to pay for it. For Thiakis we employed a Chief Executive Officer. He did a good job but his salary was quite significant. With the SDDI we gained additional intellectual input and experience, which was genuinely useful, but which was not a drain on our budget."

Importantly, Bloom also notes that basing the work at a university helped reduce financial overheads. "If you create a VC-funded spin-out company you have to pay for everything — the rent, business rates and salaries. Whereas, basing the work at a university means that you don't have to pay the salaries or hire laboratory space. You can do it for at least half the price and this makes all the difference to the risk benefit ratio," he explains.

The application process

When applicants apply for SDDI awards they have to provide "compelling evidence that a small molecule ligand can yield a therapeutic benefit in the disease indication under investigation." They also have to demonstrate that their project complements drug discovery R&D elsewhere. Once applications have been shortlisted, the SDDI science team and its independent advisors do full 'due diligence' on each programme to determine how each project fits into the competitive landscape, says Davis.

Before the final projects are selected, the shortlisted applicants receive feedback on their full proposals from an independent advisory panel. "The comments we received were thoughtful, realistic and forward-looking in terms of questions we could answer now that would help us to make the right decisions in the future. It really was an impressive assemblage of talent that they had gathered to provide us with useful feedback on the programme, whether or not we ended up being funded by the Trust," says Hollway.

Ultimately, the decision to make an SDDI award is based on the science, so it is possible that an academic group applying for an award may have little or no prior experience in drug development. "If they have a good idea then we should be able to support them and build a team around them to realize the benefit of their insight," says Davis.

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Another research organization that has recognized the benefit of academic research exploring potential new drug targets is the London-based charity Cancer Research UK (CR-UK). "For the initial stage of building confidence in new targets through target validation, a process that often requires a small-molecule compound, academia has a niche where it performs that role really well," says Julian Blagg, Head of Medicinal Chemistry in the CR-UK Centre for Cancer Therapeutics at The Institute of Cancer Research, who previously worked for 19 years at Pfizer. "Small molecules that act against targets such as cytochrome P450 17 α -hydroxylase/C₁₇₋₂₀ lyase, heat shock protein 90 and phosphoinositide 3-kinase have emerged from our centre. These are examples in which there were significant risks that made the pharmaceutical industry initially wary of heavily resourcing research into these targets. Once academia had proven that the risks were not as substantial as first thought, investment flowed into these targets," he says.

Team-building

To ensure that researchers with good drug development ideas would not be penalized for their lack of pharmaceutical expertise, when a project is selected the SDDI team determines how much support each group needs to accomplish their goals. A common element is that each project is supported by a research steering committee that includes a business development manager from the Trust, as well as independent advisors.

For Achaogen, this support was invaluable. "In our case, the steering committee was small, consisting of Richard Davis, who is a fantastic asset to the Trust, and John Powers [a former lead medical officer for antimicrobial drug development and resistance initiatives in the Office of Antimicrobial Products, Center for Drug Evaluation and Research at the US FDA]. For a company looking to do clinical development of a novel antibacterial, to have access to that sort of thought, in a friendly, non-adversarial way is a great asset," says

Hollway. Davis adds, "We are generalists rather than specialists and so we take advice when we need to. It is very much a partnership."

In addition to the research steering committee, teams based in academic institutions are also eligible for a feasibility grant of £20,000. "The money is used so they can seek expert independent advice to put together their development programme," says Davis, adding that the advice received helps to build the team's confidence in the drug development decisions that they make at a later date.

Outsourced support

Access to independent advice is also important when contract research organizations (CROs) are approached to conduct part of the drug development programme. "The ultimate rule is that you should only outsource to a CRO what you actually understand. So, the best way to ensure that a CRO is delivering the right work is to have an independent advisor," says Davis.

In agreement with this, Payne explains that it is very important to have expertise in a research team to guide the work of external collaborators. For example, he says: "We have good chemists at GSK, but we work externally with other chemists too. That interaction requires good chemists to drive what the external chemists do. You can't just press a button and expect everything to work, it takes a lot of expertise to formulate what those additional chemists should make."

The SDDI encourages the use of CROs because it means that the Trust does not have to build infrastructure, such as screening facilities, for every project. "It also allows us to access the expertise and technology as and when needed," says Davis. This is particularly important because the awards are set up so that the teams have to meet milestones along a previously agreed research path. The use of CROs enables the SDDI to halt a programme if the milestone is not met. "You need to show progress because your future funding is dependent on meeting those milestones," says Payne, "I think it is a good, healthy tension to have." Since the SDDI has been set up, three full awards have been terminated; all at the first milestone stage.

A challenge associated with the milestone-based funding of projects is that there is not a portfolio of options to switch to if a programme is not successful. "It is an all or nothing approach, which creates a situation in which a team is betting everything on one programme. This approach has a high attrition rate, which needs to be understood from the start," says Davis.

Progress so far

The successes to date include ~£48 million in additional funds that have been raised for active programmes, and the completion of a Phase I clinical trial of ACHN-490 in healthy volunteers. Two Phase I clinical trial applications are also in process: one for Bloom's pancreatic polypeptide analogue and the other for a novel 11 β -hydroxysteroid dehydrogenase inhibitor. In addition, the Oxford University spin-out company Prolysis was acquired by Biota Holdings, and 12 patents have been filed overall. Just one more opportunity to apply for funding in the 5-year pilot programme remains; the closing date for applications is 21 May 2010 (<http://www.wellcome.ac.uk/Funding/Technology-transfer/Awards/Seeding-Drug-Discovery/index.htm>).

When the SDDI recently conducted a review of the programme, a key need for medicinal chemistry expertise became apparent. Blagg thinks that a resource that would benefit all researchers aiming to address unmet medical needs is a quality screening file comparable to those held at pharmaceutical companies. "It is possible to collaborate to access a commercial partner's

compound file, but if academics had access to a state-of-the-art compound screening file, that would enable everybody," he says.

A step in the right direction was the Trust's £4.7 million award to the European Molecular Biology Laboratory's European Bioinformatics Institute to transfer chemogenomics data from the publicly listed company Galapagos (*Nature Rev. Drug Discov.* **7**, 789–790; 2008). The resulting database, ChEMBLdb (<http://www.ebi.ac.uk/chemblpdb>) was launched on 18 January 2010. "Essentially, it contains all of the medicinal chemistry and structure–activity relationships against targets that are in the public domain. It is a window into a world that big pharma has had for more than 10 years that is now in the academic domain. I see it as a really key enabler," says Blagg.

With ongoing discussion considering the future of the SDDI, a key question is what changes would be made if the initiative continues? "We would make only minor modifications to how we run the programme," says Davis. "We do need to ensure that we don't become too risk averse. But our focus on the best science, irrespective of where it comes from, will continue because it has kept our minds open to the best ideas."