Accelerating drug discovery: natural products as guides

Dr Mark Moloney of Oxford University and Galapagos NV have developed an industrial – academic collaboration to exploit the potential of natural products for anti-infective drug development. Their partnership has successfully demonstrated the utility of using a natural product guided approach to direct drug discovery in a rapid and cost-efficient way.

New drugs from natural sources

The global antiinfectives market is estimated to be around €45 bn p.a. with a strong clinical need for new drugs due to resistance and emerging diseases. Natural products often have excellent potential as drugs but their development can be difficult and costly as they are complex in structure and not easy to make or change in the laboratory. New approaches are needed to overcome these technical hurdles.

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Background

Dr Mark Moloney has a long-standing interest in the use of natural products for antiinfectives and considered a modern take on the approach of reducing natural products to their core functionalities in order to rebuild the molecules in a medicinal chemistry friendly way. This approach was used 50 years ago during the development of the penicillins but had been largely forgotten in more recent times.

Moloney's work at Oxford University focused on using the tetramates class, as these compounds possessed good bioactivity, and provided a space with no existing clinical drugs and a clear IP landscape. Drug discovery is an interdisciplinary effort and it soon became apparent that a partner for the biological assays was necessary for the successful development of this programme. He spent over 5 years in a fruitless search for academic partners with both the necessary competency and an interest in collaborating.

Galapagos is a mid-size biotechnology company with operations in the US and Europe, including the Argenta and BioFocus service divisions in the UK, and specialises in the discovery and development of small molecule and antibody therapies with novel modes-of-action. It has an active portfolio of risk/reward-sharing alliances with major pharmaceutical partners and is progressing one of the largest pipelines in biotech.

The formation of a research collaboration

Graham Dixon, Galapagos' SVP Drug Discovery and Mark Moloney met at a Natural Products Exploitation Workshop run by the KTN, the link was followed up and ideas for a simple feasibility or "look-see" early study were agreed. This early no-risk study demonstrated that the natural product analogues retained activity as determined by Galapagos' bioassays and so a negotiation began for future collaborative work on the validated strategy.

This next phase of the relationship was difficult and frustrating for the participants as progress was slow, by industrial timeframes, and aligning the wishes, best interests and expectations of the various protagonists proved challenging.Fortunately, the parties

Industry need for Knowledge Transfer opportunities:

"One of the biggest challenges for us is getting to know about the expertise within academic groups which is complementary to our own research. There's a real need for forums for universities to talk about their research and look for opportunities"

Phil Dudfield (VP Alliances and Informatics, Galapagos)

Galápagos

reached agreement on a framework that allowed innovation to flourish while meeting industry timelines.

What's in it for us?

Dr Phil Dudfield, VP Alliances and Informatics, outlines the immediate benefits to Galapagos the industrial partner as:

- *Access to top class chemistry*
- *Alternative view of approaching problem*
- *Introduction to research area that would not be obvious route without academic guidance*
- *Direct access to novel compounds with an elevated likelihood of finding actives*

The academic partner benefits as suggested by Dr Moloney include:

- *Partnership retains confidentiality and IP issues are clearly decided*
- *Contribution to genuine drug discovery effort with associated expertise*
- *Excellent opportunity for rapid progress of technology development*
- *Great learning experience for academics and chance to gain wider perspective*

Perhaps not too surprisingly the major benefits of the collaborative experience seem to lie in the chance to access complementary skills, opinions or systems in a clearly delineated relationship.

What are the downsides?

Both Galapagos and Oxford University admit that there are downsides to working in an industrial-academic partnership but interestingly both indicate that even these have in some ways turned out to be quite positive!

The academic group have had to make adjustments to their working practices to fit with industry protocols and information expectations. In particular the transfer and management of large amounts of electronic data have provided challenges for the Oxford team. The terms of the commercial contract are also quite demanding but in some ways this uncertainty provides an excellent point of focus and helps to prioritise research activities on successful outcomes. Publication could be an issue for post-doctoral workers' career progression but again a good working compromise has been achieved.

For Galapagos the relative complexity of negotiations and time taken to achieve a working agreement with the University administration was frustrating and costly compared with other EU states. At times working with an academic partner has provided administrative challenges as processes tend to be more ordered with in-house working, although this disruption is sometimes welcome as internal processes can become too routine and stifle innovation.

What makes this collaboration work?

Any real collaboration is based on mutual advantage for the participants and an acceptable risk/reward ratio for the individual partners. However on a practical level the collaborators identified the following as key factors for success:

- Regular communications
- Flexibility from participants
- Good mix of personalities
- Clear and easy process for IP capture

Outcomes to date

The collaborative programme has delivered a viable, accelerated process for production of natural product leads, providing Dr Moloney's group with the proof of principle required. Galapagos has benefitted strategically by its pharma partner's acceptance of the validated approach and commercially with earlier access to novel, natural product chemistries.

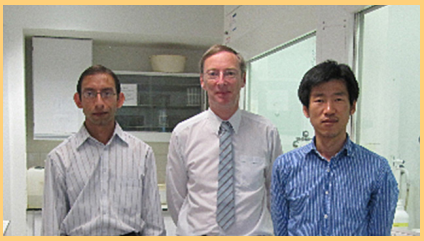
Importantly, there have been additional outputs from the collaboration, Galapagos have been pleasantly surprised by the positive effects of the programme and are now more amenable to working with other university-based groups.

New projects outside of the original scope and using new approaches such as molecular modelling, have also developed between the partners as a result of their good working relationships and the synergies within the collaborative group. Overall, significant progress from a timely idea has been brought about by meeting the right partner in the right environment.

Mark Moloney on Galapagos and their collaboration:

"real eye-opener for post doctoral workers"

"example of truly synergistic partnership"



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