

**A** fourteen-year partnership between The Babraham Institute and AstraZeneca has contributed to the development of new drugs to treat cancer and new clinical practices in the use of anti-cancer drug combinations.

Researchers at The Babraham Institute, which receives strategic funding from BBSRC, have used their expertise in the signalling pathways that control cell survival and cell division to help AstraZeneca<sup>1</sup> (AZ) develop anti-cancer drugs targeting these pathways. This was made possible by BBSRC's award of a rolling programme of grants to Babraham for fundamental biology research and infrastructure.

By testing the efficacy and selectivity of potential drugs, Dr Simon Cook<sup>2</sup> and his team at Babraham have allowed AZ to make decisions at an early stage about which drugs to develop<sup>3</sup>, saving the company valuable time and money. This process has supported the development of selumetinib, an anti-cancer drug which is now in phase III clinical trials<sup>4</sup>.

"These signalling pathways are very interesting and important from a basic biology perspective, but also very

important from a cancer drug discovery perspective," says Cook. "Whilst we don't carry out cancer research at Babraham, our understanding of these pathways and how they are controlled has obviously proved attractive to companies like AstraZeneca."

### Tackling drug resistance

An important issue for AZ is the resistance of tumours to their drugs. In collaboration with AZ, researchers at Babraham discovered the mechanisms underlying tumours' resistance to certain medications. This allowed AZ to anticipate potential problems with their drugs, make decisions regarding their best use and identify ways in which different anti-cancer medications could be combined to overcome the problems of resistance.

"Through our work with Babraham, we are increasingly recognising that understanding the potential mechanisms of resistance to our oncology agents as early as possible, i.e. preclinically, can inform our thinking on patient selection and drug combination options," says Dr Teresa Klinowska, Principal Scientist in Oncology at AZ.

For example, a collaborative research project at Babraham investigated how cells adapt and acquire resistance to particular drugs over time, including selumetinib<sup>5</sup>. This was one of a number of studies that validated the use of two anti-cancer drugs in combination: a BRAF inhibitor and a MEK1/2 inhibitor, for patients with BRAF mutant melanoma, a type of melanoma that quickly acquires resistance to a single drug on its own. This drug combination is now the standard treatment for patients with this type of tumour.

## IMPACT SUMMARY

### Babraham Institute – Astra Zeneca partnerships:

- **Contributed to anti-cancer drug development: Selumetinib is now in phase III clinical trials**
- **Informed clinical practice regarding anti-cancer drug combinations**
- **Increased AstraZeneca's competitiveness in the £46.7Bn (\$77.4Bn) global anti-cancer treatment market**
- **Secured substantial industry funding for health research**
- **Trained project managers for UK industry**

## THE BABRAHAM INSTITUTE

The Babraham Institute, based on the Babraham Research Campus near Cambridge, UK, receives strategic funding from BBSRC for research into the biology of lifelong health and wellbeing<sup>11</sup>.

In 2013/14 the Babraham Institute received £28.8M<sup>12</sup> from BBSRC, consisting of Institute Strategic Programme Grants (ISPGs) and Campus Capability Grants (CCGs), capital and other funding. The ISPGs and CCGs from BBSRC provide strategic funding to help deliver the Council's priorities<sup>13</sup>. They enable the Institute to leverage funding from other sources, including industry. Support from BBSRC is complemented by funding from other Research Councils, especially the MRC, and medical charities such as Cancer Research UK.

The Institute plays an important role in the broader life science research community around Cambridge. Babraham researchers have established close links with local biotechnology companies, including those on the Babraham Research Campus. They also work with colleagues at the University of Cambridge, Addenbrooke's Hospital and the Wellcome Trust Genome Campus, amongst others.

These case studies illustrate the impact of major scientific breakthroughs at the Institute, and the development of the Institute's infrastructure and capability. Professor Michael Wakelam, Director of the Babraham Institute, says, "Long-term support from BBSRC has and continues to enable world-class bioscience at Babraham, which is leading to a wide range of current and future impacts from the Institute's research such as those outlined in these case studies."

“Our research, together with that of others, raised the possibility of using two drugs to hit the same pathway at different steps, to increase efficacy and delay or overcome resistance,” says Cook. “This was an important advance in modern drug discovery, and our results contributed to it.”

Another Babraham-AZ study validated the use of a different combination of anti-cancer drugs: a MEK1/2 inhibitor and a PI3K or PKB inhibitor, to combat the intrinsic resistance of certain tumours to MEK1/2 inhibitors<sup>6</sup>.

This research contributed to the decision by AZ to enter into a joint clinical trial with major pharmaceutical company Merck, targeting tumours using the combination of AZ’s MEK inhibitor and Merck’s PKB inhibitor. For two large

## KEY MILESTONES

- 2000** – AstraZeneca (AZ) initiates a collaboration with The Babraham Institute
- 2007** – A Babraham-AZ research project is launched anticipating the problem of acquired drug resistance in tumours
- 2009** – Babraham-AZ research validates the use of two anti-cancer drugs in combination to combat intrinsic drug resistance of tumours. This contributes to a decision by AZ to run a joint clinical trial with Merck
- 2011** – A Babraham-AZ study is one of several that validates the use of two anti-cancer drugs (BRAF and MEK inhibitors) in combination; this is now the standard treatment for a specific type of melanoma
- 2013** – AZ announce plans to relocate their global HQ and UK Research Centre to Cambridge

pharmaceutical companies to run a joint clinical trial such as this was, at the time, unprecedented.

## An increasing problem

Cancer is on the increase, reflecting in part the ageing population. With one in three people in the UK developing it at some point in their lives<sup>7</sup>, this creates a growing need for new treatments.

The global anti-cancer treatment market is one of the largest and fastest growing areas for new drug development, and is estimated to rise from £46.7Bn (\$77.4Bn) to £86.7Bn (\$143.7Bn) by 2023<sup>8</sup>.

Collaboration with Babraham has been of significant strategic value to AZ in increasing their competitiveness in this market. In 2011 AZ contributed £3.8Bn total Gross Value Added to the UK economy, and in 2012 accounted for 1.8% of total UK goods exports<sup>9</sup>.

## Two-way benefits

However, the benefits of the collaboration have not been one-sided. Over the past 14 years, AZ has funded four postdoctoral researchers at Babraham, supported six BBSRC CASE PhD students (students who receive collaborative training with a partner organisation), and co-funded a BBSRC Industrial Partnership Award. Researchers at Babraham have also had access to AZ’s unique drugs and other substances for their own research into the basic biology of ageing, which involves some of the same signalling pathways in cells as those involved in tumour growth.

The aim of this research is to better understand how we can maintain good health in old age. The ageing population is increasing, and the average spending on NHS services



for retired households is nearly double that for non-retired households<sup>10</sup>, placing a large burden on the UK economy. “I feel that my basic research has benefited enormously from the collaboration with AZ,” says Cook. “The information flow and the exchange were two-way.”

“We got access to the most specific inhibitors of that pathway that were available at the time – and in many cases we got them before other labs – which meant we could do great cell biology, and AZ got our expertise which helped them determine which of their inhibitors had potential as anti-cancer drugs.”

“The basic cell biology we’ve done here is not only giving new insights to AZ with regards to cancer, it’s also teaching us a lot about how these pathways may be controlling ageing at the cellular level. So it very much shows that research doesn’t just flow from basic to translational, it’s a two-way process.”

## Training the new generation

The postgraduate and postdoctoral researchers at Babraham also benefited from working with AZ, with many going on to become project managers in industry. Former Babraham researchers are now working for businesses ranging from Horizon Discovery and MedImmune, local biotechnology companies, to Novartis, a leading player in the global pharmaceutical industry.

“So we’re not just exchanging knowledge,” says Cook, “we’re actually exchanging training, and we are training the workforce that is now doing drug discovery in UK biotech and UK pharma.”

## The future

AZ have recently announced plans to relocate their global headquarters and UK research centre to Cambridge. This opens up the possibility of even closer collaboration with Babraham in the future. Indeed, collaborations with AZ have now expanded to include at least six research team leaders at Babraham. This includes Len Stephens, Phillip Hawkins and Klaus Okkenhaug studying the PI3-kinase enzymes and Michael Wakelam studying the regulation of lipid metabolism. These are both areas for which Babraham is world renowned.

“I think one can claim that Babraham are now significant partners with AZ in several of their key projects,” says Cook, “and I think this is one of many reasons why AZ made the decision to relocate to Cambridge, because of the outstanding laboratories in the Cambridge area, including Babraham.”

## AGEING RESEARCH AND ANTI-CANCER DRUGS: THE LINK

Researchers at the BBSRC-funded Babraham Institute are world renowned for their work on signalling pathways inside cells. These pathways are activated by external cues and control cell behaviour, including cell survival, cell division and cell movement.

Babraham researchers study the normal function of these pathways, which are vital for lifelong maintenance of health; indeed some of these signalling pathways control aspects of normal ageing.

These same pathways are also inappropriately activated in a variety of diseases, including those often associated

with old age such as infection, inflammation, metabolic diseases like type 2 diabetes, and cancer.

In many forms of cancer, the genes that code for the receptors and enzymes controlling these pathways are mutated. These mutations cause the pathway to be over-active, leading to inappropriate cell division and survival, which creates tumours.

Using their expertise, Babraham researchers can help pharmaceutical companies such as AstraZeneca develop drugs that fight cancer by inhibiting the actions of the malfunctioning enzymes in these pathways.

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