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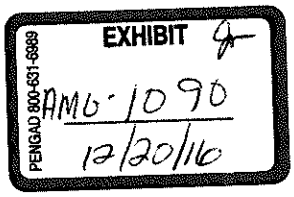

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Abiraterone: a story of scientific innovation and commercial partnership

Abiraterone is one of the ICR's biggest success stories – the first treatment shown to be effective in men with advanced prostate cancer. In 2012 it was made available on the NHS, at a stroke transforming the options available for the 10,000 men each year diagnosed with aggressive forms of prostate cancer. In the current financial year alone, abiraterone is forecast to earn the ICR £10m in royalties, all of which will be ploughed back into our research.

But the road from abiraterone's initial concept to today's life-extending treatment was not always smooth and highlights the importance of maintaining focus on a critical stage in the ICR's work – the commercialisation of the cancer drugs we discover. Without commercialisation, we would fail in an essential part of the ICR's mission, in delivering new cancer treatments to patients.

This article details the key stages in abiraterone's almost 20-year history from initial idea to cancer drug in the clinic. It draws out some of the key learning points from its discovery and development, so that the ICR can not only reproduce the success of abiraterone, but can speed the journey from our next major discovery to the clinic.

The initial idea

Abiraterone's journey began in the 1990s, when a team of ICR scientists began to look for ways of shutting off production of male androgen sex hormones. Prostate cancer relies on testosterone to grow, so one of the main ways doctors treat the disease is by blocking its action. Over time most patients' cancers stop responding to standard hormone treatments and many scientists believed the cancers had learned how to grow without testosterone. The ICR's Professor Mike Jarman, and colleagues Dr Elaine Barrie and Professor Gerry Potter, began investigating an alternative theory – that these prostate cancers were using testosterone from elsewhere in body to grow, and might therefore still be treated by disrupting testosterone synthesis.

The team, working in what is now the Cancer Research UK Cancer Therapeutics Unit, started with a drug called ketoconazole, which they noticed prevented the growth of prostate cancer cells. The drug worked by inhibiting an enzyme called CYP17, which is important in the production of male sex hormones. Ketoconazole proved to be not very potent, not sufficiently specific and quickly broken down by the body, so the team set out to design new more effective inhibitors of the CYP17 enzyme.

Dr Barrie assessed compounds made within Professor Jarman's team to work out how successfully and selectively they would inhibit CYP17. They were aided by three-dimensional models created by Professor Stephen Neidle, Dr Charles Laughton and colleagues.

The search was rewarded when Professor Potter and Dr Barrie designed and evaluated a chemical called CB7598, which they called abiraterone. The drug specifically and irreversibly blocked CYP17, and prevented testosterone being made anywhere in the body.

Patenting and early commercialisation

The ICR team filed the first of its patents on abiraterone in 1992, on the usefulness of the compound as a potential cancer treatment, and followed that with a second patent the following year covering its synthesis. A year later the team published the first paper describing the drug, its rationale as a cancer treatment and how it was synthesised.

The decision to patent and its timing were key to the abiraterone success story, and opened the door to the drug's commercialisation. The ICR assigned rights for the development of abiraterone to British Technology Group, an international specialist healthcare company. Jennifer Hodgson, Business Development Manager in the ICR's Enterprise Unit, explains: "The critical step in commercialisation of abiraterone was the filing of the two patents from this initial research. A key role for the ICR's Enterprise Unit is in deciding when to file a patent. Patents only last for 20 years. If we file too early we reduce the number of years we can receive royalties because it takes a while for commercialisation to occur. It is because of these initial patents that we are now entitled to royalties from abiraterone. Protecting our intellectual property for licensing is one of the most important roles of the Enterprise Unit and we encourage researchers doing work with commercial implications to get in touch at an early stage."

Early studies

The next step for the ICR team was to turn the chemical they had designed into a medicine that could be taken by patients. Professor Mitch Dowsett, Dr Barrie and others showed in animal and cancer cell models that the drug worked as expected, blocking synthesis of androgens and reducing their levels in the body and the size of androgen-dependent organs. These and other early studies were important as they demonstrated the drug was safe, effective and ready to be evaluated in patients. Professor Potter and Dr Ian Hardcastle then scaled up the small amounts of the drug used in the lab into a quantity and purity suitable for patient use.

In 1996 BTG out-licensed abiraterone to the German pharmaceutical company Boehringer Ingelheim, and initial Phase I clinical trials began. Early-stage clinical trials in prostate cancer led by Professor Ian Judson, with pharmacodynamic studies carried out by Dr Florence Raynaud, showed that abiraterone did hit the correct target and lower levels of male hormones. However, early in the drug's development concerns were raised about the possible side-effects of blocking CYP17 – in particular about the risk of adrenal insufficiency, a potentially life-threatening complication. The developmental progress was further hampered by a lack of interest in hormone treatments for prostate cancer. Part of the problem lay in the name of late-stage prostate cancer, which was often referred to as 'refractory' disease, implying the cancer became resistant to androgens and could progress without them. Many scientists and clinicians argued that blocking androgen production at this late stage would be ineffective. These concerns led to Boehringer withdrawing from the development of abiraterone, with the licence returning to BCG.

But the scepticism surrounding the drug was challenged when Professor Johann de Bono joined the ICR from San Antonio, Texas, in 2003. Professor de Bono recognised the potential of abiraterone as a treatment for men with advanced prostate cancer, and reasoned that late-stage prostate cancer was not 'hormone refractory' but 'castration resistant', meaning that the tumour was still dependent on testosterone but was able to progress because it could get androgens from elsewhere – perhaps even from the prostate cancer itself. He also reasoned that adrendal insufficiency would not be an issue with abiraterone, since children born with inherited deficiency of CYP17 do not suffer from it. The ICR was ready to take abiraterone back into clinical trials.

Licensing and clinical trials

In 2004, BTG licensed abiraterone to Ortho Biotech Oncology Research and Development, a unit of Cougar Biotechnology Inc., granting worldwide exclusive rights to develop and commercialise abiraterone. In doing so the ICR gained the financial backing it needed to run the clinical trials now required to prove the drug's efficacy and safety.

"Licensing is a critical step in the commercialisation process," explains Toby Richardson, Senior Business Development Manager in the Enterprise Unit. "Licensing gives a company permission to own our property. Our number one goal is to ensure patients benefit as quickly as possible from our innovations. The Enterprise Unit has good links with a range of companies and has cover 40 years of collective experience and expertise in negotiating. Collaborations can take a long time but the ICR has strong record of success.

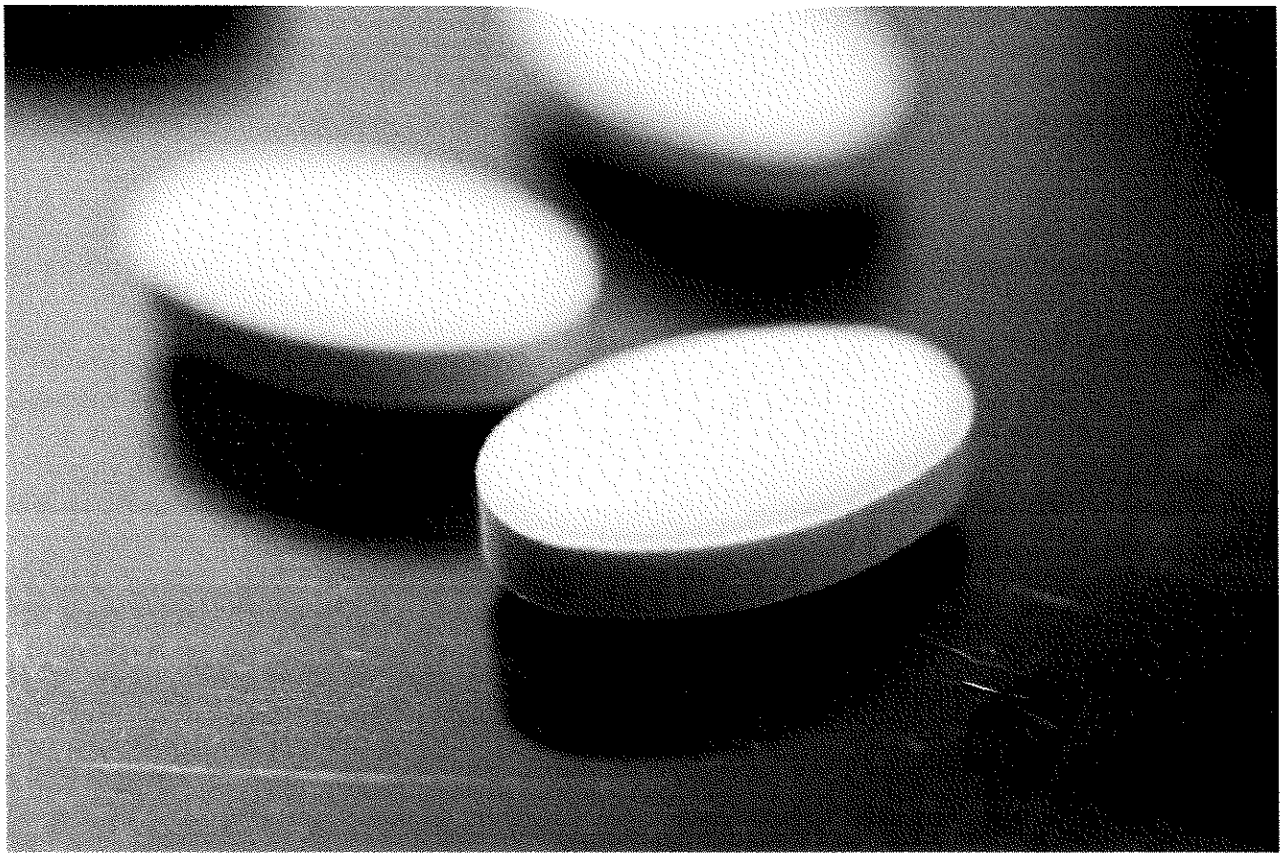
"The ICR has the highest amount of invention income per faculty head in the UK – more than twice the organisation in second place. But it's not only the ICR who benefits. The Rewards for Innovators Scheme means that the researchers involved in the development of abiraterone are also entitled to a share of the royalties.

With support from Cougar, Professor de Bono, Dr Gert Attard and colleagues began phase I clinical trials to test abiraterone's safety and anti-tumour activity.

The first phase I study of abiraterone in patients with advanced prostate cancer was run by the ICR and The Royal Marsden. The small study involved 21 men and found that the drug appeared safe in humans and that the majority of patients who took it experienced both significant tumour shrinkage and dramatic falls in PSA levels.

Less than a year later, the results of a larger phase I/II study were reported. This study of 54 patients confirmed the phase I results, and showed that up to 70 per cent of men responded to abiraterone. These men experienced significant benefits for an average of eight months, with scans showing their tumours decreased in size and their PSA levels dropped substantially.

Following these very positive results, the giant US pharmaceutical company Johnson & Johnson agreed to buy Cougar for just under £600million, gaining access to the drug as it progressed through phase III evaluation. And in 2010, a pivotal phase III trial showed that patients given abiraterone lived on average 15.8 months longer, compared with 11.2 months for men taking a placebo. This part of abiraterone's story is an exemplar of how basic molecular studies, followed by collaborations between researchers, doctors and industry, can lead to the successful development of effective drugs that can transform lives.



Approval and acceptance by NICE

There was now strong clinical trial evidence for the effectiveness of abiraterone, but there remained some significant hurdles in gaining regulatory approval for the drug. The ICR had to play an active role in the regulatory process to make sure abiraterone was made available to as many patients as possible.

The first step was the submission to a new drug application to the US Food and Drug Administration, leading to the approval of abiraterone in the US.

Hodgson says: "Approval in the US was a significant step in abiraterone's development. Both the ICR and BTG received a milestone payment, together with the royalties that followed on worldwide sales of abiraterone."

Later in 2011, the European Medicines Authority also licensed abiraterone. That opened the door to the drug being made available in the UK, but accessing it on the NHS continued to rely on local decisions by primary care trusts, or access via the Government's new NHS Cancer Drugs Fund. Abiraterone became one of the most requested drugs on the Cancer Drugs Fund, as anticipation grew that it would shortly be accepted by NICE.

However, in February 2012, NICE announced that it was minded to reject abiraterone on cost grounds unless more data were forthcoming or a better price was offered. The decision came as a significant blow to the ICR and to men with prostate cancer across the UK. We responded to the NICE appraisal consultation document highlighting our concerns about certain aspects of the process underling the NICE decision, and asking it to reconsider its position. The ICR called for NICE to re-examine fully the potential for abiraterone to be cost-effective in a subgroup of patients for whom it appeared to be particularly effective, and to follow its own 'end-of-life criteria' for deciding whether drugs should be made available.

The end-of-life criteria are more lenient guidelines, developed by NICE, which should be followed when reviewing treatments which may extend the lives of patients who are terminally ill. The guidelines cover drugs which would normally be deemed too expensive for standard NHS use and which are licensed for a terminal illness affecting a small number of patients with less than two years to live. Cancer Research UK estimated 7,000 men would be eligible for abiraterone and thought this number low enough for the drug to be assessed under the end-of-life guidance.

In May 2012, NICE and Janssen finally reached an agreement over cost, and the drug was made available on the NHS in England, Wales and Northern Ireland. Since then, abiraterone has gained a further licence for the treatment of prostate cancer before chemotherapy, opening up the prospect that it will be made available for even more men.

The path from abiraterone's discovery to its commercialisation was long and winding, but it was ultimately a major success story for the ICR demonstrating how partnership with industry can deliver real benefits for patients.

We know that patented drugs have huge and increasing price tags. However no one ever explains why? Is the drug difficult to manufacture? Does a month's supply of the drug cost something close to $7,000 to manufacture? Or is it $700, or even $70? The drug manufacturers would never say and would argue that, in addition to manufacturing and distribution, the money is needed to pay for the high cost of clinical trials and research.

The drug company argument is at least partially valid. Clinical trials and other startup costs are expensive, though in more and more cases the actual research is paid for by government agencies like the NCI in the US and ICR in the UK, from taxes on all of us. But drug companies, like computer companies and car companies and all other commercial companies, are in business to make money - which requires charging the highest price that the market will bear. This is normal capitalism and it works well for computers and cars, but it doesn't work so well when the product is not something that people can elect to buy or not, or to buy from this vendor or that. What is being sold is life. The alternative is death.

I think that in the US, UK, and other capitalist countries we need a new model for regulated drug pricing. It should be one that ensures that drug companies can do their job of developing drugs, but also ensures that public health needs are served. I don't have a plan

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