UK BioIndustry Association

Celebrating UK bioscience

unravelling the stories behind UK bioscience success

Executive summary

Bioscience is a fundamentally important sector for the UK's health and wealth.

The sector is thriving. Recent figures[1] show that the life sciences sector in the UK employs approximately 183,000 people; generates an estimated turnover of £56 billion and comprises an estimated 4,398 companies and their sites developing, manufacturing and marketing products and services to the UK and global markets.

However, more often than not, when this sector comes into focus – whether through media headlines or even through its own internal lens – it is often for the deals done, cash made or lost and the locus of the investment globally. Whilst securing funding for the bioscience sector is crucial and ensuring the right incentives are in place for investments to be made and kept here in the UK is paramount, at times this focus detracts from the positive patient benefit that results from the combination of UK scientific excellence and its commercial exploitation by the UK bioscience sector.

Bioscience may also seem to hide its success under a bushel because of the nature of the business. Developing therapies and technologies takes a long time, the science behind developments is complicated, and multiple parties are often involved along the way. Adding to this the early focus on development over communication and the fact that there is rarely a single hero scientist or entrepreneur in a product's story, the net effect is that there is a lack of awareness of how successful UK bioscience has been – and is at present – in developing and delivering the astonishing new innovations and therapies to benefit patients and the public.

With this in mind, the UK BioIndustry Association (BIA) is delighted to publish this report that aims to unravel the stories behind just some examples of UK bioscience success. These are only a snapshot of the full spectrum of UK bioscience successes, past or ongoing, but help illuminate where UK bioscience is shaping scientific innovation and is delivering benefits to humanity:

- We commence with **Humira**, the world's top-selling medicine that helps almost half a million people across the world to live with a range of debilitating and often painful conditions, including **rheumatoid arthritis** and **Crohn's disease**. Humira was the first ever "fully human monoclonal antibody" treatment and it was conceived at the heart of UK bioscience.
- The antibody-humanising technologies developed in the UK and which were the foundation of Humira's success have also been used in the development of over half of marketed antibody therapies today, including **multiple sclerosis** drug **Lemtrada**, featured in this document.
- Harnessing the power of the immune system to target cancer, in the field commonly known as **cancer immunotherapy** is also another area where the UK has taken a leading role. One of the most promising advances in this field has been the development of "checkpoint inhibitors", drugs designed to scupper cancer cells' clever methods of hiding from the body's immune system. Here we feature the story behind cancer drug **Keytruda**.
- The UK has also been at the heart of a new generation of **personalised medicines** aimed at patients with specific genetic mutations that mean they're most likely to benefit from treatment. The story included here, of the background to the **first PARP inhibitor**, demonstrates the effective collaboration between academics, funders and the public and private sector to effect this innovation.
- UK bioscience also excels in creating innovative technology. Here we explain the background to the **StaR® technology**, key to unlocking the potential of drug discovery through targeting GPCRs, **potentially a hugely important target family in the human genome**.
- We close with the story behind **Oxitec's genetically engineered mosquitoes** and how they are battling **mosquito-borne diseases** around the world.

[1]Strength and Opportunity 2014, HM Government https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/427769/BIS-15-224-BIS-strength-opp-2014.pdf

These case studies help to illuminate a wider UK bioscience success story. Large parts of the global innovation in modern drug development are rooted in the UK. The core development of many key blockbuster drugs changing patients' lives today happened in the UK. Looking forward, the UK is at the heart of the development of a new generation of genetically targeted personalised medicines and cancer immunotherapy, as well as the science tools and platforms underpinning these game-changing therapies.

The UK excels at bioscience and working in partnership with companies across the globe we can deliver the benefits of this sector for the world – building a high value, high wage export sector of the UK economy as we change the course of human disease.

However, without our world-leading science base, the right levers in place to effect translation of core science into commercial application and a broader environment that nurtures investment, human capital and take-up of outputs into our National Health Service, then this benefit cannot be realised.

That is why the BIA calls on the new Parliament and Government of 2015 to support UK bioscience with a conducive policy environment that allows this important sector to reach its fullest potential and secure not only the wealth of the nation, but also its health.

Consistent focus and support must be maintained to realise this potential. The BIA believes that this can be achieved through:

1. A **policy and funding environment that continues to support our world-leading universities and the research funders** that are critical to UK bioscience. This foundation is crucial to a thriving commercial UK bioscience sector.

2. Continued **focus of the Government's strategically important technologies** – including regenerative medicine and synthetic biology – with great potential to benefit UK economy and society.

3. A **supportive tax and finance environment**. Ensuring existing provisions such as the Biomedical Catalyst, R&D Tax Credits and the Patent Box continue and flourish is vital to a successful life sciences sector that can continue to invest in and develop products that benefit society.

4. **Flexible routes for licensing, evaluation, uptake and reimbursement** will be essential to ensure that patients can access the latest medical advances. We maintain that for the Early Access to Medicines Scheme to fully benefit patients, it must be centrally funded and reimbursed.

We hope you find this report helpful, informative and most of all inspiring.

It is right to celebrate success. In doing so, we can provide hope for patients and their families, inspiration for the next generation of scientists and entrepreneurs, and confidence for the country.

In telling the stories behind UK bioscience success we can raise overall awareness of how this sector is impacting on lives and how with continued and additional support it can only go further in delivering such benefits for humanity.

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Humira: the world's top-selling medicine and its UK heritage

Humira (adalimumab) is the world's top-selling medicine. The treatment helps almost half a million patients across the world to live with a range of debilitating and often painful conditions, including rheumatoid arthritis (RA) and Crohn's disease.

Humira's target is tumour necrosis factor alpha (TNF-α), a protein that can cause excessive inflammation associated with auto-immune diseases like RA. In 2003 Humira became the first "fully human monoclonal antibody" to gain approval. To place this in context:

- Antibodies are proteins produced by the body's immune system to fight off disease
- Monoclonal antibody therapies mimic these disease-fighting molecules, but are designed in a laboratory to recognise and attach to a particular, specific target
- Monocolonal antibodies can be produced in useful quantities in species such as mice or rats, but this species difference can cause unwanted reactions (and inactivation) in human patients. Therefore techniques to create "humanised" (more human) or "fully human" monoclonal antibodies have led to improved therapies that are as close as possible to human antibodies.

In the 1990s, TNF, and its potential as a drug target, were well understood. The issue was how to avoid the toxicity drawbacks of antibodies that were produced using non-human cell lines. The story behind how this challenge was overcome is a showcase for UK scientific excellence.

A NEW TECHNOLOGY FOR MAKING MEDICINES

Working at the Medical Research Council (MRC)'s Laboratory of Molecular Biology in Cambridge during the 1980s, UK antibody pioneer and prize-winning scientist Sir Greg Winter and fellow scientist John McCafferty invented new techniques including "phage display" and "CDR grafting" (see p.7-8 for further background on CDR grafting) to create and isolate humanised and fully human antibodies for therapeutic use.

Key to Humira's discovery was the "phage display" method. This uses special viruses called bacteriophages as vehicles to display proteins of interest (e.g. human antibody fragments) on their outside, so they can be screened for interactions with other proteins or molecules. Antibody "libraries" containing millions of different human antibody fragments displayed on phages are thereby used to isolate very targeted, specific leads with therapeutic potential. These fragments are then used to build full-sized antibodies using humanisation technologies.

Sir Greg and John McCafferty co-founded Cambridge Antibody Technology (CAT) in 1989, along with David Chiswell, to allow the phage display technology to be fully exploited to create new medicines.

THE PARTNERSHIP THAT CREATED HUMIRA

Meanwhile, with phage display poised to revolutionise antibody drug discovery in the early 1990s, a group of scientists at BASF Bioresearch Corporation (BBC) (part of what was then the pharmaceuticals division of Germany's BASF) in Worcester, Massachusetts, were looking for ways to produce fully human antibodies to TNF. They knew the target well, had lots of it, and already had a murine (mouse-derived) antibody to this target in clinical tests.

In 1993, BBC partnered with CAT to access its phage display technology. The group had investigated several alternative antibody design systems, including mouse-based methods. ***"CAT's method was proven, it was patent protected, and we felt it was most likely to generate what we needed,"*** **recalls a former senior executive at BBC**.

Thus began Humira's gestation – first as clinical candidate D2E7 from early 1995, then, as the compound approached commercialisation, as Humira – HUman Monoclonal antibody In Rheumatoid Arthritis.

OVERCOMING THE ODDS: HUMIRA'S PATH TO MARKET

Humira's journey from the CAT laboratories to a multi-billion dollar global blockbuster wasn't a straightforward one. Few drug development stories are.

The research collaboration between the CAT team in Cambridge, UK and BBC in the US worked very well. Yet BASF was primarily a chemicals conglomerate and was not particularly interested in pursuing this compound developed by a research offshoot on the other side of the Atlantic. BBC's clinical development budget was already squeezed; it had had to make sacrifices to fund D2E7. So at the very end of 2000, after a flurry of almost-deals with other players, BASF's pharmaceuticals division, known as Knoll, was sold to Abbott Laboratories in a virtual auction. Abbott paid $6.9 billion in cash.

By that time, D2E7 was already in the final stages of clinical development. Abbott's management understood the compound's potential value. Three years later, the regulators, too, saw what Humira could offer patients suffering from inflammatory disease – the drug was approved six months earlier than expected, without debate. Humira was a rare good news story for an industry often beleaguered by regulatory delay and clinical failure. **Humira** ***"is the most important drug launch in our 115-year history,"*** **said Jeffrey Leiden, MD, PhD**, then Abbott's chief scientific officer and executive vice president of its pharmaceuticals division.

A patient self injecting a dose of Humira

As sales took off, CAT and Abbott became embroiled in a fierce royalty dispute, but CAT held its ground. This UK biotech's technology and expertise had been validated to an extraordinary degree. In 2005, AstraZeneca bought CAT for £702 million. Following Abbott's decision in 2011 to separate into two publically traded companies, Humira is now manufactured and sold by AbbVie.

HELPING PATIENTS AND IMPROVING LIVES ACROSS MULTIPLE CONDITIONS

Humira's approval timeline by indication

2003	Rheumatoid arthritis: a long-term condition that causes pain, swelling and stiffness in the joints
2005	Psoriatic arthritis: joint pain and stiffness and often associated with a scaly skin condition called psoriasis
2006	Ankylosing spondylitis: a chronic condition causing inflammatory back pain
2007	Crohn's disease: a chronic inflammation of the gastro-intestinal tract with few alternative treatment options and no surgical or medical cure
2008	Plaque psoriasis: painful and itchy skin lesions, where Humira has cleared up to 75% of lesions in some cases; and also juvenile idiopathic arthritis, an inflammatory condition in under 16s with no known cause
2012	Ulcerative colitis: a long-term condition, where the colon and rectum become inflamed
2014	Paediatric Crohn's disease

Humira's full potential is still unfolding: AbbVie is testing the drug in a rare, painful chronic skin condition called hidradenitis suppurativa (sometimes referred to as 'acne inversa'), for which there is no approved treatment or cure, and in uveitis, inflammation of the eye.

In 2014 Humira's sales reached almost £12 billion and they are still growing. Humira's success; and that of anti-TNF therapies more broadly, has also led to a deeper understanding of the inflammatory process, in turn helping create other therapies for inflammatory joint diseases – and further choices for patients.

Two decades after CAT helped create Humira, this drug continues to improve lives and break records.

The story of Lemtrada: improving the lives of those living with Multiple Sclerosis (MS)

Lemtrada (alemtuzumab), previously known as CAMPATH, is a humanised monoclonal antibody whose target is CD52, a protein found on mature lymphocytes (a type of immune system cell). It was originally developed for use with bone marrow and solid organ transplantation and in leukaemia and is still used, under the CAMPATH name, for these conditions. However, it has a new role under the name Lemtrada, as a treatment for multiple sclerosis (MS), which was approved in May 2014 by the National Institute for Health and Care Excellence (NICE). Clinical trials, published in The Lancet in 2012, revealed that Lemtrada is making a real impact in the treatment of this difficult and disabling condition.

These publications, and ongoing research, are the culmination of many years of effort by scientists in the UK and elsewhere. Indeed, according to the co-discoverer of the CAMPATH family of antibodies, Geoff Hale, over 2,000 people (from researchers and clinicians to patent lawyers) have been involved in the development of this important treatment. He also acknowledges the invaluable contribution of the patients who took part in early clinical trials of what was, at the time, a very experimental drug.

FROM THE LAB TO THE CLINIC

The origins of CAMPATH-1 lay in the need for a treatment for graft-versus-host disease (GvHD), a complication of bone marrow transplantation. In 1979, Herman Waldman and Geoff Hale at the Department of Pathology at Cambridge University, funded by the MRC, isolated monoclonal antibodies from rats, which could eliminate donor T lymphocyte ("T") cells from bone marrow prior to transplantation. It is the attack of these donor T cells on the recipient that causes GvHD. One of these antibodies, CAMPATH-1M, gave virtually complete elimination of the T cells and was selected for further development.

The first bone marrow transplant using CAMPATH-1M for T cell depletion was carried out at Hammersmith Hospital in 1982 on a patient with severe aplastic anaemia (inability to produce mature blood cells). Soon after, it was trialled on a small group of patients with leukaemia and findings were published in The Lancet in 1984. This study was confirmed by other trials in Europe, leading to the establishment of the international CAMPATH users group, which sparked many clinical collaborations over the following 15 years.

The Cambridge lab then came up with another antibody, called CAMPATH-1G. This gave good results in two leukaemia patients and pointed the way to a new direction in this research – the need for a humanised version of the CAMPATH antibody.

As it happened, (see p. 3-4) Michael Neuberger and Greg Winter at the MRC Laboratory of Molecular Biology (just over the road from the pathology labs in Cambridge) were working on producing fully humanised monoclonal antibodies as an important step up from the rat or mouse versions. The two teams worked together to develop humanised CAMPATH (CAMPATH-1H).

The first patient to be treated with CAMPATH-1H was a woman suffering from non-Hodgkins lymphoma. The treatment shrank her tumour-affected spleen from 4.5kg to 0.6kg. Moreover, there were no tumour cells detectable in her blood or bone marrow. This patient still had tumour cells in her spleen, however, and required further treatment with CAMPATH-1H. She did, unfortunately, relapse again and died shortly afterwards. But much had been learned about CAMPATH-1H and how it works. The second patient to be treated fared better, with complete remission of his lymphoma and, over the years, he and his family were very active in fund-raising to support the research.

It was difficult to produce enough of the CAMPATH antibodies to meet growing demand from the research community. Therefore, in 1990, the Therapeutic Antibody Centre (TAC) was set up to take care of large scale antibody production.

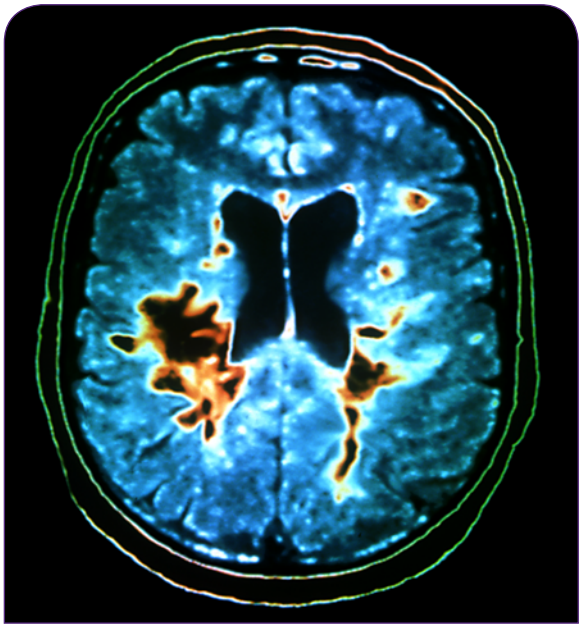
Shortly after the TAC opened, Waldman and Hale were approached about a young woman with a rare autoimmune disease, with a view to trying CAMPATH-1H, as no other treatment had worked for her. After just a short course of the antibody, the patient responded with complete remission. She also produced a very strong immune response to CAMPATH-1H which meant that her blood samples proved very valuable in the further study of the antibody. This **patient, Nicola Cole, has contributed a great deal over the years to the development of CAMPATH, so it was highly appropriate that she was the one to open the new TAC in Oxford in 1995**. This was the start of the development of CAMPATH-1H for other autoimmune diseases, including rheumatoid arthritis and, later, multiple sclerosis.

Commercial development of the CAMPATH family

- In 1985, the British Technology Group (BTG, which handled tech transfer for the MRC) licensed CAMPATH-1M to Wellcome Biotech for application in bone marrow transplant.
- CAMPATH-1G and CAMPATH-1H were also licensed to Wellcome Biotech as these looked more promising for clinical applications – including organ transplantation and autoimmune disease.
- Eventually Wellcome (the parent company, into which Wellcome Biotech was absorbed) dropped CAMPATH-1H and BTG licensed it in 1997 to LeukoSite, a small US biotech company, which was later purchased by Millennium, who continued the development of CAMPATH-1H with ILEX Oncology.
- In 2001, the antibody was first licensed for the treatment of chronic lymphocytic leukaemia. Genzyme acquired ILEX from Millennium and began to develop CAMPATH-1H for multiple sclerosis.
- In 2011, Sanofi acquired Genzyme and clinical development of Lemtrada continues.

LEMTRADA IN MULTIPLE SCLEROSIS

In 1991, Alastair Compston's group at the Department of Neurology in Cambridge, was contacted about CAMPATH-1H by a middle-aged patient with MS. She went, within a few months, from being confined to a wheelchair to being able to ski. Magnetic resonance imaging (MRI) scans showed a reduction in the inflammation that is one of the hallmarks of MS. The researchers began a pilot trial and, by 1998, 29 patients had been treated with CAMPATH-1H.



A coloured MRI scan of the brain of a patient suffering from MS. The black/orange lesions highlight the destruction of the myelin sheaths around the axon nerve fibres of the brain and spinal cord which cause MS. Lemtrada has been shown to slow down this damage to the brain tissue.

Further research followed, culminating in two Phase III trials. In the CARE-MS 1 trial, Lemtrada was compared with Rebif (interferon beta-1a, a signalling protein) in people with relapsing remitting MS not previously on treatment. Those on Lemtrada were around 55% less likely to experience a relapse over the next two years. The CARE-MS 2 trial compared Lemtrada with Rebif in people with relapsing remitting MS who had experienced at least one relapse when on Rebif or Copaxone (glatiramer – a protein which mimics the nerve cell coating myelin that is lost in MS). Those on Lemtrada were around 50% less likely to have a relapse and 42% less likely to experience disability over the next two years.

In 2014, NICE recommended Lemtrada as treatment for relapsing-remitting MS. The antibody is given by infusion once a year, for five days in the first year and three days in the second. For the patient, this compares favourably with other treatments, which involve oral tablets or weekly injections. Recently, Genzyme announced magnetic resonance imaging data that show that Lemtrada is associated with a slowing of brain atrophy (loss of neurons and connections) in MS.

30 years on from its beginnings in the lab, Lemtrada's benefits for patients continue to grow.

Keytruda: a first-in-class cancer therapy

Harnessing the immune system to target cancer offers a new, powerful approach to tackling the disease, beyond the traditional methods of directly destroying cancer cells. One of the most promising recent advances in cancer immunotherapy, and indeed in cancer drug development more broadly, has been the emergence of "checkpoint inhibitors". These therapies are designed to scupper cancer cells' clever methods of hiding from the body's immune system. Cancer cells exploit checkpoints within the immune system that are designed to prevent it from going into overdrive, effectively dampening the immune response. Checkpoint inhibitors release these immune system "brakes", allowing the body's defence network to spot and attack invasive tumour cells.

Keytruda, recently approved for the treatment of life threatening forms of skin cancer, is a leading example of this new class of therapies. Not only does UK science and its exploitation form a key part of its development, but it is one example of a number of emerging therapies coming out of UK bioscience that are changing the face of future cancer treatment.

ACCELERATED APPROVAL FOR FIRST-IN-CLASS DRUG

In September 2014, Keytruda (pembrolizumab) became the first in a new class of checkpoint inhibitors to receive US regulatory approval. This antibody targets the programmed death-1 (PD-1) pathway – a checkpoint normally involved in preventing tissue damage during chronic inflammation. Keytruda was shown in trials to shrink tumours, sometimes for six months or more, in almost a quarter of patients suffering from advanced, life threatening forms of skin cancer.

The benefits Keytruda offers for these patients, who have few other treatment options, prompted the US regulator, the Food and Drug Administration (FDA) to approve the drug almost two months earlier than expected, via an accelerated review process reserved for breakthrough therapies. European approval followed in May 2015, though the drug was made available to UK patients two months earlier. It was the **first product to receive a "positive Scientific Opinion" from the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK's Early Access to Medicines (EAMS) scheme**, aimed to speed up access to treatments for patients with life threatening or seriously debilitating conditions.

THE PIVOTAL ROLE OF UK SCIENCE IN KEYTRUDA'S DEVELOPMENT

Keytruda is sold by Merck & Co. Inc., and has changed hands several times during its path to market. But a key step in the drug's early development occurred at the UK medical research charity MRC Technology (MRCT). In 2006, MRCT applied an antibody humanisation technology, conceived by Sir Greg Winter and his team at the MRC's Laboratory of Molecular Biology (see p. 3-4), to a compound belonging to Dutch pharmaceuticals group Organon.

The technique, known as CDR grafting, involved identifying and then inserting the coding sequences responsible for the antibody's desired binding properties – e.g. to PD-1 in this case – into a human antibody scaffold. CDR grafting has now been used to humanise over 55 antibodies, including three further marketed therapies. Multiple sclerosis treatment Tysabri (natalizumab), rheumatoid arthritis drug Actemra (tocilizumab) and Entyvio (vedolizumab), sold for ulcerative colitis and Crohn's disease, are all examples of treatments that are available thanks in part to UK bioscience.

Organon was attracted to MRCT's technology and to what was already a highly experienced and well-established antibody engineering group. Under a licensing contract signed in 2006, the Dutch group agreed to pay milestones, as well as small royalties on sales of any resulting therapy. In 2008, MRCT delivered to its partner the humanised antibody that would become Keytruda.

By then, though, the first of the two multi-billion dollar deals on Keytruda's path to market had already occurred. Organon was acquired by Schering Plough in March 2007 for $14.4 billion. Two years later, in November 2009, Merck bought Schering Plough for $41.1 billion. Both deals were driven in part by the buyers' need to access biotechnology expertise, as big drug firms (until then focused on chemistry-based, small molecule pharmaceutical drugs) began to wake up to the promise of large molecule biological therapies like antibodies and other proteins.

KEYTRUDA AND ITS POTENTIAL TO FIGHT MULTIPLE CANCERS

Keytruda's story is only just beginning. Its contribution to the fight against cancer – like that of checkpoint inhibitors more broadly – has much further to go. It has been filed in the US for an advanced form of lung cancer, and is in trials for bladder, head and neck and gastric cancers. The benefit that it offers some patients in slowing disease progression even after multiple other treatments have failed, has led some oncologists to describe it as a "game changer".

Merck is working to find possible biomarkers or gene-expression signatures that could help identify patients most likely to respond to anti-PD-1 therapies. If successful, this would help both patients and payers, allowing treatment with the drug to be given to those most likely to benefit.

Keytruda highlights the potential of mobilising patients' own immune systems to fight cancer. So do other drugs in the same class, such as Bristol-Myers Squibb's Opdivo (nivolumab), another marketed PD-1 inhibitor, approved for the same skin cancer indication just three months after Keytruda, also via the FDA's breakthrough therapy programme. Opdivo is also approved for metastatic lung cancer, having shown not just improved progression-free survival, but better overall survival among patients with previously-treated forms of this disease.

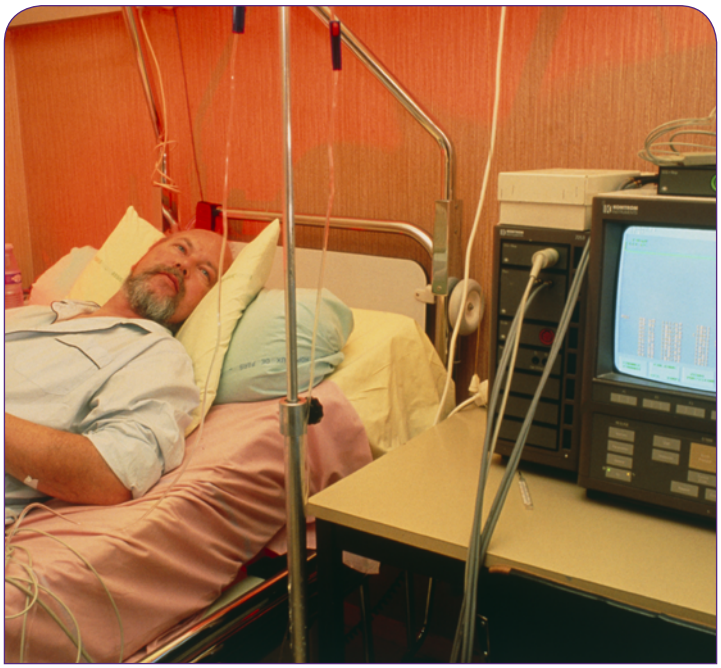
Keytruda was not the first checkpoint inhibitor. That accolade belongs to Bristol Myers Squibb's Yervoy (ipilimumab), approved in the US in 2011 for advanced melanoma. Keytruda has shown better efficacy than Yervoy, which targets a different checkpoint, cytotoxic T-lymphocyte antigen 4 (CTLA-4). But these drugs may be most effective in combination.

TREATMENT COMBINATIONS ARE KEY

Cancer treatment is increasingly about combining a variety of therapeutic approaches in what amounts to a multi-pronged attack. Checkpoint inhibition and other immunotherapies may offer more potent and durable effects than older therapies that block cancer cell growth or kill cells directly, but both contribute to the growing toolbox available to fight the disease.

PD-1 inhibitors like Keytruda will be used alongside other targeted and cytotoxic (cell destroying) therapies, including checkpoint inhibitors that hit one or both of the protein "ligands" (PD-L1 or PD-L2) that bind to PD-1 to regulate the immune system.

These PD-1/PD-L1 duos were once again the hot topic at the American Society of Clinical Oncology's annual gathering in Chicago in May/June 2015. Credit Suisse analysts predict that the market for these promising drug classes will, over time, be worth over $35 billion.



A patient receiving immunotherapy cancer treatment

The UK biotech sector continues to contribute to cutting edge research around checkpoint inhibition and other novel approaches to fighting cancer. One example is Oxford-based PsiOxus Therapeutics Ltd. This company is using an oncolytic (cancer destroying) vaccine technology platform to design and develop cancer-targeting viruses. A recent funding round will allow the start-up to test whether its oncolytic virus, in combination with a checkpoint inhibitor, may provide some hope for patients with metastatic colorectal cancer.

As we head into a new frontier of cancer treatment, UK bioscience is helping drive game-changing cancer treatments.

The first PARP Inhibitor: the promise of personalised medicine and the UK's role in its exploitation

The story of AstraZeneca's newly approved first-in-class Lynparza (olaparib) for ovarian cancer showcases the critical role played by the UK bioscience sector in the development of cutting edge therapies. It also highlights the promise of personalised medicine.

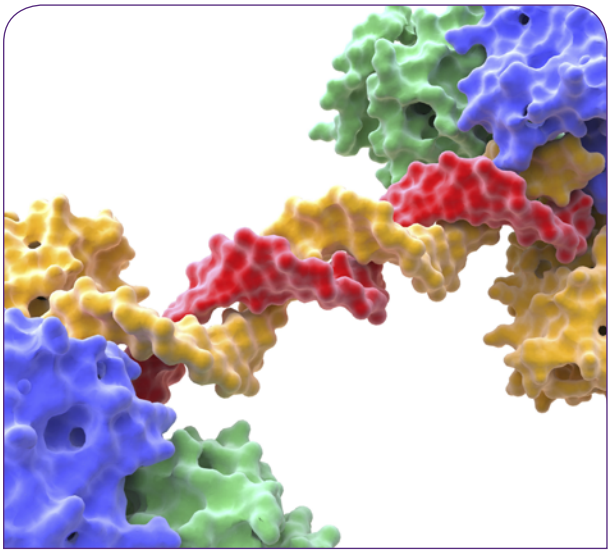
Lynparza is one of a new generation of targeted medicines aimed at patients with specific genetic mutations that mean they're most likely to benefit from treatment. The drug is approved for women suffering from ovarian cancer thanks to expertise and partnerships spanning the entire UK bioscience sector: from academic research excellence at University of Cambridge, through funding and support from cancer research charity Cancer Research UK (CRUK), biotech entrepreneurship and UK venture capital backing at KuDOS Pharmaceuticals Ltd., and the clinical development expertise and resources of UK drugs giant AstraZeneca.

KNOCKING OUT CANCER'S REPAIR MECHANISM

Lynparza's approval in December 2014 for patients with advanced, pre-treated ovarian cancer offered a much-needed treatment option for many patients suffering from this relatively rare disease. Lynparza was shown in trials to prolong survival for six months or more among women with advanced, BRCA-mutated ovarian cancer.

The drug is a poly ADP-ribose polymerase (PARP) inhibitor, which kills cancer cells by knocking out their ability to repair damaged DNA. Cancer cells displaying mutations in the BRCA1 and BRCA2 genes are thought to be particularly vulnerable to this form of attack. Crucially, inhibiting PARP – an important DNA repair signalling molecule - doesn't appear to affect healthy cells, unlike traditional treatments that directly attack cells, such as chemo- or radiotherapy.

Lynparza's mechanism of action means it has potential across a wide range of tumour types whose cells have DNA repair deficiencies. AstraZeneca is testing the treatment in gastric cancer, pancreatic cancer and some breast cancers, and also recently announced promising Phase II trial results in prostate cancer. It's not alone: competitors are hot on its heels with clinical stage PARP inhibitors of their own, including AbbVie's veliparib in Phase III trials for breast cancer and Tesaro's niraparib, in late-stage testing in ovarian and breast cancer.



A PARP enzyme bound to a DNA double strand break. A PARP inhibitor kills cancer cells by knocking out their ability to repair damaged DNA.

THE CHALLENGE IN VALIDATING THIS INNOVATIVE APPROACH

Lynparza and the wider PARP inhibitor family have however faced various challenges. Olaparib's development came to a halt during Phase II trials in 2011, before it was clear which patients would benefit from the treatment. AstraZeneca was also struggling to formulate the drug into a manageable dosing schedule. Fortunately, genomics came to the rescue. Scientists analysed a subset of patients from the Phase II trial showing the BRCA mutation – roughly 10-20% of ovarian cancer sufferers. Efficacy among this group looked far more promising, so the programme was resumed, with pivotal trials starting in 2013.

That same year, the PARP inhibitor field suffered a further knock when Sanofi dropped development of its candidate, iniparib, after failed trials in breast, lung and ovarian cancer. Better patient sub-typing may have helped, but the compound was also found to be far less potent in its binding to PARP than others in the family.

Lynparza's approval has re-ignited interest in this drug class. It also provides a reminder of the challenge of drug development, and the perseverance required to bring new therapies to market.

A TEAM EFFORT FROM ACROSS UK BIOSCIENCE

Lynparza emerged from work in the 1990s by Professor Stephen Jackson and his team at the University of Cambridge. With research funding from CRUK (then known as Cancer Research Campaign), Professor Jackson's group was looking at the role of various DNA repair proteins in cancer cells that help these cells survive. As the potential of such proteins as targets for drug therapy became clearer, Professor Jackson set up KuDOS Pharmaceuticals Ltd., initially within his Cambridge labs, in 1997. CRUK's technology transfer arm, known today as Cancer Research Technology (CRT), provided seed funding. Two years later, the company attracted a combined £5 million from Advent Venture Partners, Schroder Ventures Life Sciences, and 3i Group. The start-up more than trebled its head-count and moved into new laboratories at the Cambridge Science Park. KuDOS continued to collaborate with Professor Jackson at Cambridge University.

In 2005, KU59436 – the precursor to olaparib – was only in Phase I trials, a relatively early phase of development. But AstraZeneca was engaged in a flurry of pipeline-enhancing dealmaking. It liked KuDOS' DNA repair platform and the early clinical candidate. In December that year, AstraZeneca paid over £120 million to buy the company outright.

The collaboration with CRT continued and has further evolved since. In 2010, AstraZeneca and CRT allied to discover drugs targeting cancer metabolism – how cancer cells use energy to grow – and expanded this alliance in 2013 for a further two years. Indeed, **Professor Jackson pointed out on the day of Lynparza's approval in 2014 that the achievement** ***"...shows how, by collaborating with a partner such as AstraZeneca, basic academic research, such as that carried out by the research team at the University of Cambridge, can lead to major medical developments."***

AstraZeneca has further deepened its partnership with UK academic expertise, setting up a joint research facility with the MRC, the AstraZeneca MRC UK Centre for Lead Discovery, in Cambridge. That Centre is working with CRUK to screen for new cancer medicines in a five-year collaboration that provides CRUK scientists with access to over two million compounds from AstraZeneca libraries.

ANOTHER TOOL AGAINST CANCER, MULTIPLE NEW RESEARCH AVENUES

Scientists' understanding of the potential of PARP inhibitors in treating cancer has much further to go. There may be several other mutations, as yet unidentified, that mark out patients likely to benefit most from this type of treatment. The combination treatment options are also growing exponentially as new therapies are approved. PARP inhibitors used with chemo- or radiotherapy may together offer a compelling one-two punch, with chemo damaging the cancer cell DNA, and PARP inhibition then preventing recovery (though in practice such treatment regimen is challenging).

There are also further challenges, even after approval, to ensure that Lynparza and related targeted treatments are accessible to those who need them. In June 2015 NICE opened its consultation on draft guidance on olaparib for ovarian, fallopian tube and peritoneal cancer and at the time of publication it has not recommended funding the drug on the NHS. **Professor Peter Johnson, Cancer Research UK's chief clinician, commented saying,** ***"NICE's provisional decision is hard to understand. This is a great example of a personalised medicine which offers a new treatment for a type of cancer where we have made little progress in the last decade and where there is a clear need for different approaches. The NHS can't afford to ignore important innovations like this***".

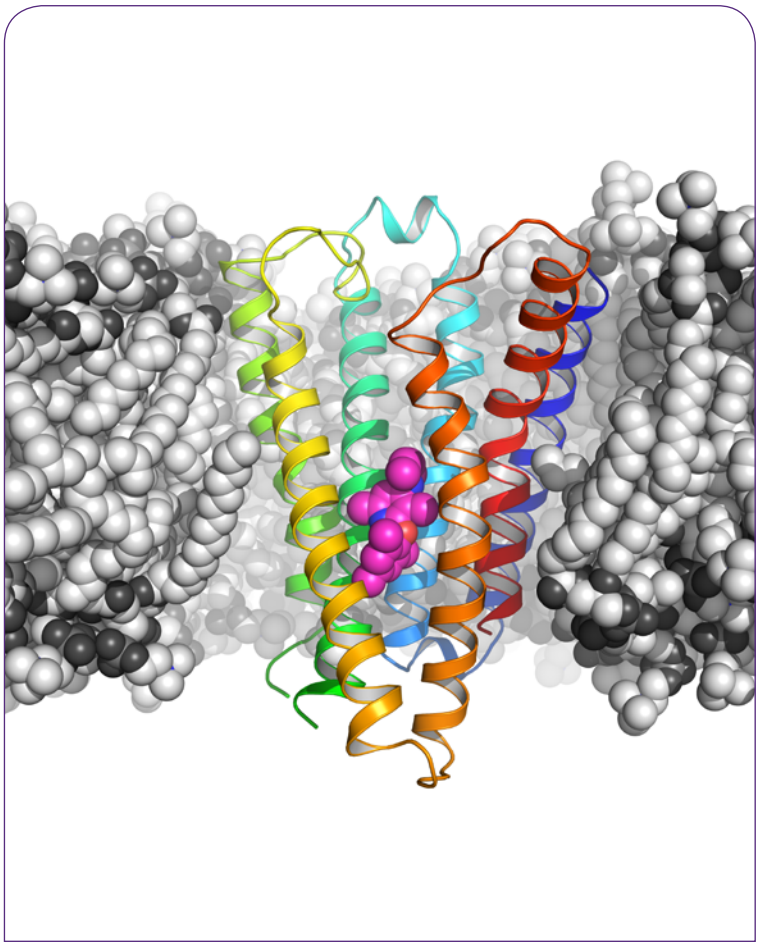
Unlocking the potential of GPCR drug targets: the UK's contribution

As well as developing therapies, UK bioscience also develops, builds and commercialises the tools that Research and Development (R&D) scientists need to do their research. These platform businesses sell their techniques, kits and services to R&D labs in universities and competing global corporations. One example is the work developed by Heptares Therapeutics to unlock the potential of GPCR drug targets and the scientific research that has underpinned this.

G protein-coupled receptors (GPCRs) are proteins found embedded in the cell membrane. They act as a bridge between the interior and exterior environment of the cell. As such, they can transfer information in the form of biochemical signals. They play a role in many physiological and biological processes, including taste, vision, smell, autonomic nervous system function, mood, behaviour, immunity and tumour growth. GPCRs are, therefore, important drug targets and many of today's current drugs target a GPCR, contributing to treatments for patients across a wide range of conditions, including asthma, high blood pressure, schizophrenia, migraine and leukaemia.

THE CHALLENGE AND THE OPPORTUNITY

The challenge surrounding GPCRs is that, like all membrane-bound proteins, GPCRs are very unstable outside of the membrane environment and are hard to crystallise. Drug discovery and development relies heavily on solving the 3-D structure of a target through x-ray crystallography, which then allows structure-based drug design (SBDD) to open the door to small molecule drugs that are safer, more potent and can become best or first in class in a therapeutic area.



A cross-section through a membrane showing a GPCR's 7 transmembrane helices and a drug molecule (pink) binding in the middle

GPCRs represent a major class of targets, many of which are clinically validated, but which are currently not optimally 'drugged' - for existing compounds have limited potency and selectivity. There are also metabolic, safety and delivery issues around some of the GPCR drugs currently on the market.

Thus, not only is there room for development of best in class, there are also many high value GPCR targets which remain unexplored, so there are opportunities for first in class too, particularly in areas such as the central nervous system (CNS), metabolic diseases and cancer. Examples include the muscarinic receptor family, where "selective agonists" of the M_1 and M_4 receptors (drugs which bind to and activate those receptors), developed by Heptares, could treat cognitive impairment and psychosis (both significant symptoms of Alzheimer's disease), respectively.

Another high value GPCR target is the adenosine A_{2A} receptor, which plays a key role in dampening down the natural immune response to cancer. By blocking this process, A_{2A} receptor antagonists (blockers) could be the basis of a novel approach to cancer immunotherapy.

THE ROLE OF UK SCIENCE IN UNDERSTANDING AND EXPLOITING GPCRs

Scientists funded by the UK's MRC and the pharmaceutical industry worked for many years to try to overcome the barriers to solving GPCR structures, taking key steps towards developing new treatments for patient benefit. Dr Christopher Tate, and colleagues, developed a groundbreaking technology which uses mutagenesis to stabilise GPCRs, and other membrane proteins, in a specific conformation or shape. In this original version of the technology, each amino acid residue in the GPCR is altered in turn and the thermostability of the resulting mutant protein is measured. The best mutations, i.e. most thermostable, are then combined to create a stable GPCR.

This technique was optimised by Heptares to create its StaR® technology. The stabilised GPCRs, or StaR® proteins, are purified and crystallised for x-ray crystallography. Importantly, the StaR® technology greatly improves the thermostability of a GPCR without disrupting its pharmacological properties, so that studies on it are still relevant to the drug discovery process. What's more, the thermostabilised receptors can be crystallised in several different detergents and also with many different inhibitors or activators bound, so that the function of these receptors can be studied. SBDD can be started by the virtual screening of libraries of molecules to generate a number of hits which are then optimised using knowledge of the protein and ligand structures.

In 2007 Malcolm Weir and Fiona Marshall formed Heptares, as a spinout from the MRC Laboratory of Molecular Biology in order to further develop and commercialise the StaR® technology. The StaR® technology has been used to stabilise many GPCRs in all three main families (A, B and C) and to date has enabled Heptares to elucidate the x-ray structures of more than 10 GPCRs. Furthermore, the technology has potential beyond GPCRs and can open up other membrane proteins, such as the ion channels, to SBDD and the development of new, more effective and safer medicines.

Heptares Therapeutics, which is now a wholly owned subsidiary of Sosei Group Corporation, has an impressive pipeline and a number of collaborations within the pharmaceutical industry. Highlights include:

- The world's first selective M_1 agonist for improving learning and memory in Alzheimer's disease and schizophrenia.
- A_{2A} receptor antagonists with potential to be non-stimulant medications for Attention Deficit Hyperactivity Disorder (ADHD) and as a novel approach to cancer immunotherapy.
- Biologics (antibodies) targeting GPCRs, which are being developed in partnership with MedImmune and MorphoSys.

"Heptares technology is the key to unlocking the potential of drug discovery targeting GPCRs, the most important target family in the human genome," *says Dr Malcolm Weir, Heptares CEO and Co-founder.* ***"Our StaR® technology enables, for the first time, powerful structure-based approaches to be applied to discovering and precisely engineering novel small molecules that modulate GPCRs, while also providing stable protein for therapeutic antibody development. The successful creation of new medicines targeting GPCRs, given their crucial role in the body, has the potential to improve the treatment of severe and debilitating conditions that affect many millions of people around the world."***

Oxitec's genetically engineered mosquitoes and how they are battling mosquito-borne diseases

THE DANGER OF THE STATUS QUO – WHY WE NEED NEW INTERVENTIONS TO BATTLE MOSQUITO-BORNE DISEASES

Mosquitoes are the most dangerous creature in the world. They kill one person every 12 seconds and infect hundreds of millions of people each year with serious diseases. *Aedes aegypti* is a particularly harmful species because it mainly bites people and it lives in and around homes. The tendency of the biting females to hide in nooks and crannies around the home makes it remarkably difficult to reach those hiding places. This mosquito is also developing resistance to the chemicals used to kill it.

Ae. aegypti can carry serious diseases including dengue, chikungunya and Zika viruses, so without more effective ways to control these mosquitoes, the public health implications are stark. Even world-leading mosquito control groups with fleets of planes and helicopters can only reduce *Ae. aegypti* by about 50%. With that many disease vectors still around, it is possible for these serious diseases to be introduced and reintroduced at any time. With no cure or available vaccine for either dengue fever or chikungunya, the World Health Organisation recommends controlling the mosquito itself[2].

HOW OXITEC'S MOSQUITOES ARE PROVIDING A NEW WAY FORWARD

The battle against mosquito-borne diseases can be fought on multiple fronts. Companies are racing to find working vaccines and to test them in clinical trials to determine whether they will work. But viruses mutate and new strains appear. A compatible but different approach is to reduce the numbers of mosquitoes spreading the disease below the transmission threshold[3], so that whatever the virus does, there simply aren't enough mosquitoes around to spread it.

UK biotech company Oxitec, which was spun out of Oxford University in 2002, does exactly that by using genetically engineered mosquitoes to control their own species. Oxitec mosquitoes are genetically engineered so their offspring die before they can reproduce and before they can become transmitters of disease. It's an approach similar to the Sterile Insect Technique (SIT) where male insects are sterilised by radiation and released to mate with pest females. With successive releases there are fewer offspring each generation and the pest population crashes. SIT has been used worldwide for more than 50 years and has been successful in tackling pests such as New World Screw Worm[4].

The Oxitec mosquito is inspired by the SIT approach but doesn't rely on radiation, which can affect many genes and the insect's competitiveness. Instead, Oxitec uses just one gene to induce 'sterility' and a colour marker gene for monitoring the results. Like SIT, this approach requires successive releases, but there are major environmental benefits such as the disappearance of the engineered insects and their genes from the environment once releases are stopped. The approach is also species-specific, controlling only the non-native *Ae. aegypti*, so other native species can flourish.

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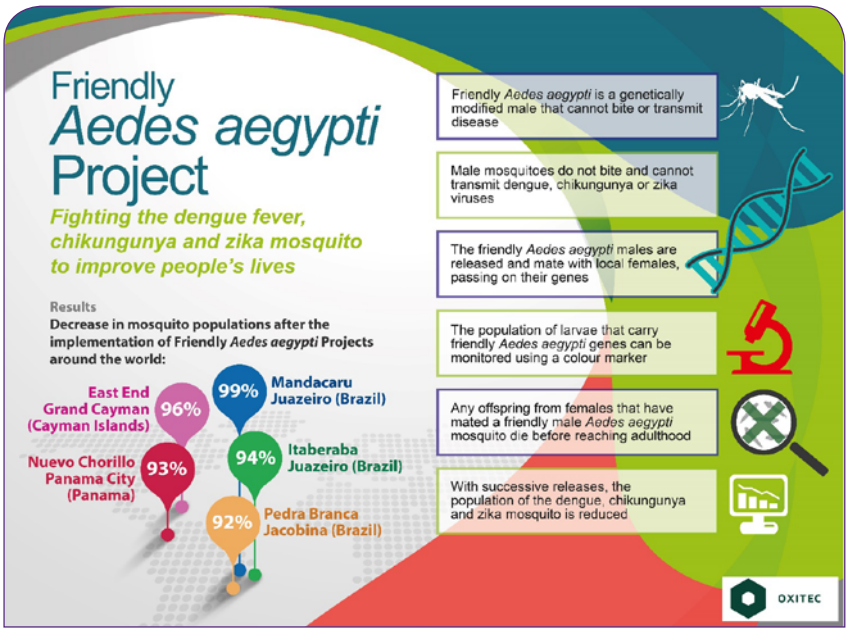
[2]World Health Organization Dengue and Severe Dengue Factsheet www.who.int/mediacentre/factsheets/fs117/en/

[3]Focks et al. 2000. Transmission thresholds for dengue in terms of Aedes aegypti pupae per person with discussion of their utility in source reduction efforts. www.ncbi.nlm.nih.gov/pubmed/10761719

[4]www.oxitec.com/SIT

Since trials started in 2009, Oxitec has reduced target *Ae. aegypti* populations by more than 90%. This is an unprecedented level of control and is a key reason why mosquito control groups around the world are keen to evaluate it for use in their countries. Another reason is its light ecological footprint because it's a highly targeted control method that is non-toxic and pesticide-free.



SUCCESS TO DATE AND AMBITIONS FOR THE FUTURE

Children putting their hands inside a cage of Oxitec male mosquitoes, which don't bite.

Since 2009, mosquito trials have been completed in Cayman, Malaysia, Brazil and Panama, without adverse effects on people or the environment, and more projects are being planned. The Oxitec mosquito has been rigorously evaluated both scientifically and by regulators in multiple countries with laboratory studies, cage studies, and field studies of increasing size[5].

This evaluation process for new control methods is vital to progress in the war against mosquitoes, and an important consideration for such evaluations is weighing the potential risks of a new intervention against the risks of maintaining the status quo.

In Brazil, the dengue burden is so great that they've called in the army to help educate people on how to fight the *Ae. aegypti* mosquito. Brazil has a lot of experience and expertise in tackling dengue and recognises the need for new approaches to complement and improve on current methods. This forward thinking has led to the first municipal project of genetically engineered mosquito control following approval by the national biosafety group (CTNBio) for release of Oxitec mosquitoes throughout the country. The city leading the way is Piracicaba, in São Paulo state[6].

The lead inventor of the Oxitec mosquito was also the UK's sole nominee for a prestigious international award for this biotechnology breakthrough in battling disease-carrying mosquitoes[7].

The hope is to build on the success of the Oxitec mosquito to tackle the mosquitoes that transmit malaria next. Named one of the top 20 European inventors, award nominee, Dr Luke Alphey, also hopes to inspire the next generation of scientists to carry on this important work, and join in the fight against vector-borne disease.

[5] www.oxitec.com/publications

[6] www.cctv-america.com/2015/05/03/biotech-firm-experiments-with-mosquitoes-to-fight-dengue-fever-in-brazil

[7] www.epo.org/news-issues/press/releases/archive/2015/20150421a.html http://edition.pagesuite-professional.co.uk/Launch.aspx?EID=ca405540-3c0d-4c23-88b2-a43edb8f57a6&pnum=83

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