

LONG-TERM BENEFITS FROM RESEARCH INTO *STREPTOMYCES* BACTERIA

*Many of the most important antibiotics used in hospitals around the world come from *Streptomyces* bacteria. Recent discoveries have shown that *Streptomyces* could also be the source of new antibiotics needed to fight MRSA and other infections that are resistant to commonly-used medicines. The bacteria could provide new anti-fungal and anti-parasite drugs for people and livestock, as well as compounds used to fight cancer and during transplant operations.*

*Much of our current understanding of *Streptomyces* biology, and its potential for innovative new medicines and other products, stems from research supported in whole or in part by the Biotechnology and Biological Sciences Research Council (BBSRC).*

As a result, BBSRC investment in *Streptomyces* genetics research since the 1960s has made and continues to make a significant impact on the UK economy and on human and animal health.

It has enabled the creation of five spinout companies founded by *Streptomyces* researchers, including one that was sold for \$190m (~£120m) and another which established a \$195m (~£123m) licensing deal.

BBSRC funding also supported a highly skilled workforce in the UK and internationally, allowing researchers to gain new knowledge and skills. For instance, many of those who worked on *Streptomyces* at the John Innes Centre have since moved on to senior positions in companies and academic institutions around the world.

Streptomyces research continues to support the pharmaceuticals industry. When the *Streptomyces* genome was decoded in 2001 it revealed that there were many previously-unknown potentially bioactive substances and novel pathways such as new antibiotics. According to an independent study, these could be worth around £240 million per year to UK industry. Such new drugs are needed to help doctors treat people with life-threatening MRSA and other 'super-bug' infections.

New discoveries and innovative techniques from research into *Streptomyces* are helping to improve industrial processes. Even a one per cent improvement in productivity could save the UK pharmaceutical industry around £45m annually in research and development costs.

What are *Streptomyces*?

Streptomyces are microscopic bacteria. They commonly form long thin filaments in soil and decaying vegetation. There are over 500 known species of *Streptomyces* bacteria.

They are valued by scientists because they produce a variety of 'secondary metabolites' – chemicals that help the bacteria prosper by inhibiting rivals.

Many of these secondary metabolites have been found to have useful properties, providing us with new antibiotics and other medicines.

TRAINED RESEARCHERS FOR INDUSTRY

BBSRC investments in *Streptomyces* research began with work conducted at the John Innes Centre in Norwich, UK, in the 1960s¹. Since then, continued support for *Streptomyces* research at the institute has provided training for large number of scientists at PhD and post doctoral level, as well as sabbatical and other visiting researchers. Many of these people now occupy senior industrial or academic positions.

These include senior scientists at companies such as Novacta Biosystems, GenWay Biotech, and Cubist Pharmaceuticals, the Head of Infectious Diseases at Merck, and the co-founders of Kosan Biosciences and Acera Biosciences.

When such people move from academia to industry, they take with them knowledge of the latest scientific research and the ability and training to use the latest techniques². In particular, this allows companies to harness the latest methods and results from *Streptomyces* research to develop new products and improve their processes, potentially saving millions of pounds. For example, a report produced by DTZ for BBSRC suggested that even a one per cent increase in productivity for the pharmaceutical industrial as a result of new or improved processes arising from *Streptomyces* research could save around £45m in research and development costs annually³.

¹ For more information, see the report 'BBSRC meeting on the history of Streptomyces science and the sequencing of the *S. coelicolor* genome' [web link tbc]

² For more about the impacts of training through basic research, see: Salter, A.J. & Martin, B.R. (2001). The economic benefits of publicly funded basic research: a critical review. *Research Policy*. 30, p 509-532.

³ Figures from DTZ report: Economic Impact of Streptomyces Genetics Research [web link tbc].

Assuming a 1% cost saving on £4.4billion spent on R&D annually:

<http://www.ons.gov.uk/ons/rel/rdit1/bus-ent-res-and-dev/2009-edition/business-enterprise-research-and-development.pdf>

HISTORY OF UK *STREPTOMYCES* RESEARCH – PART ONE

1940s: 'Golden Age' of antibiotic discovery, with international efforts to find and exploit medicines from *Streptomyces* and other microorganisms.

1950s: Dr David Hopwood develops chromosomal linkage maps in *Streptomyces coelicolor*, a technique which underpinned much future work.

1968: BBSRC's predecessor ARC begins funding *Streptomyces* genetics research at the John Innes Centre (JIC) in Norwich, establishing the Norwich *Streptomyces* group led by Hopwood.

1970s: Researchers at JIC discover that antibiotic genes are clustered, so easier to manipulate.

1970s: Working with others around the world, the JIC *Streptomyces* group pioneers protoplast fusion, used to improve strains of *Streptomyces* for antibiotics, and protoplast transformation, a genetic engineering technique.

Over this period, Hopwood creates an industry club at JIC to aid collaboration and harness industrial funding.

1980s: The group at JIC, and partners, successfully clone a complete set of antibiotic genes from *Streptomyces*.

NEW SPIN-OUT COMPANIES

Streptomyces research supported by BBSRC at the John Innes Centre and universities in the UK has already led to the creation of five spin-out companies.

Kosan Biosciences was founded in 1995 to exploit patents arising from research started at JIC and continued at Stanford. The company aimed to exploit the newly invented field of combinatorial biosynthesis to produce novel antimicrobials and anti-cancer drugs. In 2006, at its peak as a public company, Kosan had 130 employees in California. Kosan was bought by Bristol Myers Squibb for \$190 million in May 2008⁴.

Biotica Technology was co-founded in 1996 by two academics at the University of Cambridge⁵ (who had received substantial BBSRC funding for their work on natural product biosynthesis). The company focuses on the discovery and development of novel therapeutics for cancer and inflammatory diseases, and has established preclinical partnerships and licensing agreements to accelerate commercialisation. For example, in 2006 it signed a licensing deal with Wyeth worth up to \$195 million⁶ focussing on the discovery, development and commercialization of drugs similar to rapamycin, used to prevent rejection of transplanted organs, which target several different types of disease.

Novacta Biosystems was founded as a John Innes Centre spin-out company in 2003, based on a series of JIC patents⁷. It is focused on the discovery and development of potential treatments for infectious diseases, particularly those caused by drug-resistant bacteria. For instance, Novacta's lead product, known as NVB302, is designed to treat *Clostridium difficile* infections. It is currently undergoing phase I clinical trials. *Clostridium difficile* was involved in 2,704 deaths in the UK in 2010⁸. Novacta has recently spun out its industrial biotechnology work, including biocatalysis, metabolic pathway engineering and fermentation, into a new company, BioSyntha Technology.

⁴ http://www.bms.com/news/press_releases/pages/default.aspx

⁵ <http://www.biotica.com/index.php/biotica/page/5/>

⁶ http://www.biotica.com/index.php/biotica/news_article/biotica_enters_into_a_research_and_license_agreement_with_wyeth/

⁷ <http://www.novactabio.com/>

⁸ <http://www.ons.gov.uk/ons/rel/subnational-health2/deaths-involving-clostridium-difficile/2006-to-2010/statistical-bulletin.html>

HISTORY OF UK STREPTOMYCES RESEARCH – PART TWO

1980s: The *Streptomyces* Group at the John Innes Centre engineer the first hybrid antibiotic.

1990s: Researchers develop combinatorial biosynthesis – a technique to create new natural products from existing antibodies.

1997: BBSRC invests £1.5m to sequence the genome of one strain of *Streptomyces*, which was followed by £0.9m from the Wellcome Trust. It was one of the largest genomes to be sequenced at the time.

2002: *Nature* published the results of the genome sequencing project.

2003: Researchers examining the genome sequence discover many previously-unknown gene clusters for secondary metabolites.

The discovery shows there are many more natural products to be discovered, beginning a new era of drug discovery in *Streptomyces*, with enormous economic potential.

2003 Onwards: Groups around the world use genetic engineering to create a variety of new antibiotics from *Streptomyces*.

Procarta Biosystems was spun out from the John Innes Centre and Plant Biosciences Limited in March 2008. Its main focus is on the development of a novel approach to combating antibiotic resistant pathogens – an approach first developed using *Streptomyces coelicolor* as a model system⁹. For his role in developing the Procarta technologies, Dr Michael McArthur was awarded the BBSRC ‘Most Promising Innovator of the Year’ for 2010¹⁰.

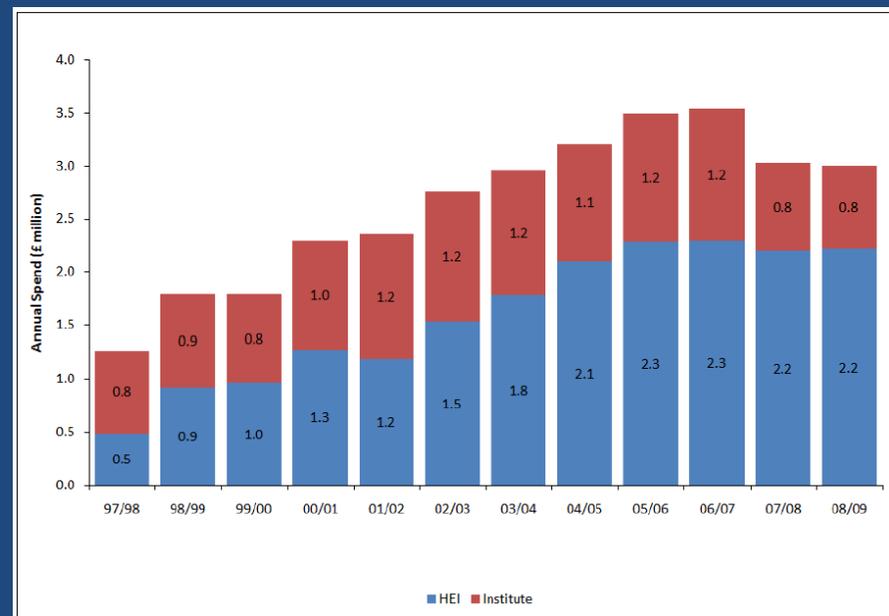
Mycobics is a Dutch company founded in 2006 and developed by former members of the JIC *Streptomyces* group. The two objectives of the company are to discover novel antibiotics through genomics approaches, and to use genetic engineering to modify the growth habit of filamentous microorganisms such as actinomycetes (the group of bacteria to which *Streptomyces* belong) to improve their utility in fermentation.

BUILDING INDUSTRY COLLABORATIONS

During the 1980s and 1990s the John Innes Centre *Streptomyces* group also established strong links with industry, which helped to forge new collaborations and bring in additional research funding through the JIC *Streptomyces* Club. The club allowed member companies to contribute towards a research fund in return for (non-exclusive) access to expert advice and research materials. The fund, which held more than £570,000 in the early 1990s, helped to support graduate students, post-doctoral fellows and visitors, strengthening the department and its research.

BBSRC FUNDING FOR STREPTOMYCES RESEARCH 1997 – 2009

BBSRC funding for *Streptomyces* research was around £1.3m in 1997/98. This peaked at £3.5m in 2006/07 before falling slightly to £3m in 2008/09.



Key: Blue – funding to HEIs. Red – funding to institutes (mostly JIC).

⁹ <http://www.procartabio.com/company.php>

¹⁰ <http://www.bbsrc.ac.uk/news/policy/2010/101019-f-innovators-innovation-pt3-macarthur.aspx>

THE FUTURE IMPACT OF *STREPTOMYCES* RESEARCH ON THE PHARMACEUTICAL INDUSTRY

Much of the impact of research into *Streptomyces*, including the publication of the complete genome sequence of one strain of *Streptomyces*, will continue to be through the creation of new antibiotics and other drugs. DTZ produced a report for BBSRC which estimated that new products from *Streptomyces*, enabled by BBSRC funding for genomics research, could conservatively be worth as much as £240m per year¹¹. New antibiotics are vital to help hospitals tackle infections such as MRSA, which have developed resistance to many existing antibiotics. In 2010 MRSA caused 485 deaths in UK hospitals¹².

Between 1997 and 2002 BBSRC and the Wellcome Trust funded researchers to decode the genome – the full set of genes – of one species of *Streptomyces*. This revealed that there were previously-undiscovered clusters of genes that could produce commercially-valuable and potentially life-saving medicines and other products. Before the genome was sequenced, many pharmaceutical companies had switched to chemical approaches to create and identify new drugs, with mixed success. The *Streptomyces* genome showed that there were many new natural products awaiting discovery.

As well as new classes of antibiotics, other previously unknown secondary metabolites from *Streptomyces* might also be used as anti-cancer drugs and immunosuppressants. Assuming these now anti-cancer compounds and other drugs are as effective as existing medications, global annual sales could exceed £120m per year¹³.

Drugs from *Streptomyces* also have a role in animal health. For instance, Ivermectin, a drug used by the livestock industry to treat a wide range of animal parasites, was developed from a secondary metabolite in *Streptomyces*. Ivermectin generates annual revenues of around \$10billion. Any new drugs that could be used in livestock and other animals could be worth £millions in annual sales; even replicating just ten per cent of Ivermectin's success could result in £60million of sales every year.

¹¹ Calculated as 1% of total antibacterial market of \$37billion (<http://www.visiongain.com/Report/431/The-World-Antibacterial-Treatments-Market-2010-2024>), of which antibiotics from actinomycetes (the group of bacteria to which *Streptomyces* belongs) account for around 30%.

¹² See: <http://www.ons.gov.uk/ons/rel/subnational-health2/deaths-involving-mrsa/2006-to-2010/statistical-bulletin.html>

¹³ See DTZ report: Economic Impact of *Streptomyces* Genetics Research