Institution: University of Strathclyde		
Unit of Assessment: A3 Allied Health Professions, Dentistry, Nursing and Pharmacy		
Title of case study: A new class of anti-infective drugs from DNA Minor Groove Binders		
Period when the underpinning research was undertaken: 2000 - 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Iain Hunter	Professor	01/01/1995 – 31/07/2014
Katharine Carter	Senior Lecturer	01/08/1986 – present
Nicholas Tucker	Senior Lecturer	01/09/2009 – present
Period when the claimed impact occurred: August 2013 – December 2020		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

An outstanding, novel anti-infective drug discovered at Strathclyde is reaching the final stages of clinical trials. In the class known as DNA minor groove binders (S-MGBs), it completed Phase-IIa clinical trials in 2020, achieving total cures for the treatment of *Clostridioides difficile* infections, out-performing the existing benchmark (vancomycin), and is now approved for a Phase-III trial. Its novel multi-target mode of action explains why, to date, antibiotic-resistance is not seen. MGB Biopharma, a new biotechnology company formed to develop the drug and sponsor the clinical trials, has raised over GBP11,000,000 in equity and public funding. MGB Biopharma expects the drug to be fully licensed and commercialised in 2024/5.

2. Underpinning research

'Antimicrobial resistance' (AMR) is a current global issue. The 2016 O'Neill report on Antimicrobial Resistance highlighted 0.5M global-deaths annually due to drug-resistant infections. Without action, 50M people could die annually by 2050. Discovery of novel antibiotics to treat resistant infections is therefore a priority.

Since 2000, a multidisciplinary team of chemists and biologists at Strathclyde has developed a novel class of compounds, originally distinguished by their ability to bind to the minor groove of DNA (MGBs). From their library of 'Strathclyde-MGBs' (S-MGBs), compounds with anti-infective activity were characterised by defining/refining the specificity of binding to nucleic acids, demonstrating selectivity in interrupting cellular processes in pathogens. The compounds form a family of putative anti-infective agents with a number of clinical applications. To realise this potential, the Strathclyde research team has partnered with a new company (MGB-Biopharma) to translate their research to the clinic.

Key research findings

The S-MGB library:

The initial design of the S-MGBs was based loosely on the structure of distamycin. The key initial discovery was design of a novel S-MGB that demonstrated exceptionally high antibacterial activity [**R1**]. A World Patent [**R2**]) and cognate patents were filed and awarded.

Iterative development of new compounds in the S-MGB library came through providing biological data to the chemists, who then varied the S-MGB template to make subsequent molecules with improved physicochemical properties desirable in a medicine: potency with respect to the infectious organism, and selectivity with respect to the animal or human host. The biology has shown that specific S-MGB members have high and selective activity against specific disease targets, including (separately) bacteria *Staphylococcus aureus* & *Clostridioides difficile*; animal parasite *Trypanosoma brucei brucei*; fungal pathogen *Cryptococcus neoformans*; and bacterial pathogen *Mycobacterium tuberculosis* [**R3**, **R4**].

Selection/evaluation of MGB-BP-3

The biologists within the team played a key role in the *in vitro* evaluation of the S-MGB library (2005-2013) that led to identification of MGB-BP-3 as lead compound for development. All members (~200) of the S-MGB family at that time (in 2013) were evaluated *in vitro* against a panel (>200) of pathogenic bacteria and fungi, including those isolated recently from the clinic as being resistant to multiple antibiotics. S-MGBs were also tested *in vitro* with human cell lines to establish the potential toxicity of each MGB in human therapy. From these collective data, a priority list emerged: compounds that killed bacteria (at around 0.2 μg/mL) but were not highly toxic (the so-called 'therapeutic window'). It transpired that the best anti-bacterial candidates were active against Gram-positive bacteria, which resulted in prioritisation of disease state *Clostridioides difficile,* which is the most prevalent causative pathogen of healthcare-associated diarrhoea world-wide, responsible for high levels of hospitalisation and morbidity.

Proof of concept in animal models was an important gateway for approval by the Medicines and Healthcare products Regulatory Agency (MHRA) of the Phase-I clinical trial of MGB-BP-3 in 2015. Strathclyde staff validated MGB-BP-3 using a murine thigh infection model, with *S. aureus* as the infective agent.

Approval by MHRA for the Phase-I trial also required determination of the frequency of mutation that could lead to resistance to MGB-BP-3. Further exhaustive tests, beyond the MHRA requirements, observed no mutation to resistance [**R5**]. This is an extremely important result in the context of MGB-BP-3's longevity as a clinical antibiotic and antibiotic use in general.

To support applications for final clinical approval, we undertook an extensive study of the mode of action of MGB-BP-3, using advanced molecular biological techniques such as RNA-Seq and DNase protection of target sequences when MGB-BP-3 is bound [**R5**]. The results are entirely consistent with multiple loci of action by MGB-BP-3 on the bacterial chromosome. This explains why no resistance is observed, as multiple mutations will not occur simultaneously. The identities of these loci are also consistent with the metabolic debilitation that results from action by MGB-BP-3 and kills the bacteria.

3. References to the research (Strathclyde-affiliated authors in **bold**; FWCI at 02/02/2021)

R1 **Anthony N.**, **Breen D.**, Clarke J., **Donoghue G.**, **Drummond A.**, **Ellis E.**, Gemmell C., **Helesbeux, J-J.**, **Hunter I**., **Khalaf A.**, **Mackay S.**, **Parkinson J.**, **Suckling C.** and **Waigh R.** (2007). Antimicrobial lexitropsins containing amide, amidine, and alkene linking groups. *Journal of Medicinal Chemistry,* 50: 6116-6125 https://doi.org/10.1021/jm070831g [FWCI:1.59]

R2 **Suckling** et al. (2008). Novel Minor Groove Binders. *World Patent* WO/2008/003698. Published 23.04.2008; US 8,012,967. https://bit.ly/3siALei

R3 Hlaka L., Rosslee M., Ozturk M., Kumar S., Parihar S., Brombacher F., **Khalaf A.**, **Carter K.,** Scott F., **Suckling C.** and Guler R. (2017). Evaluation of Minor Groove Binders (MGBs) as novel anti-mycobacterial agents, and the effect of using non-ionic surfactant vesicles as a delivery system to improve their efficacy. *Journal of Antimicrobial Chemotherapy*, 72: 3334-3341 https://doi.org/10.1093/jac/dkx326

R4 **Suckling, C.**, **Khalaf, A.**, Scott, F., **Tucker, N., Niemenen, L.**, **Lemonidis, K.**, **Hunter I**. (2017). Why antibacterial minor groove binders are a good thing. In *3rd International Electronic Conference on Medicinal Chemistry*. https://doi.org/10.3390/ecmc-3-04651

R5 **Kerr, L.**, Browning, D., Lemonidis, K., **Salih, T.**, **Hunter. I.**, **Suckling, C.**, **Tucker, N** (2020). Novel antibiotic mode of action by repression of promoter isomerisation. *bioRxiv*. https://doi.org/10.1101/2020.12.31.424950 [Uploaded to online repository 31/12/2020, evidence available from HEI on request]

Notes on the quality of research:

R1-**R4** were peer-reviewed ahead of publication. The body of underpinning research has been supported by over GBP945,000 of peer-reviewed funding, including:

- **Tucker, N.**, **Hunter I.**, **Suckling C**. Systematic Investigation of the extent and mechanisms of Minor Groove Binders in antibacterial and anticancer activity. Scottish Universities Life Sciences Alliance, 01/08/2013-31/07/2014, GBP49,073.
- **Hunter I.**, **Suckling C.**, **Tucker N.** The differing biological fates of DNA minor groove-binding (MGB) antibiotics in Gram-negative and Gram-Positive bacteria. BBSRC, 17/02/2014/16/02/2018, GBP369,782.
- **Hunter I.**, **Suckling C.**, **Tucker N.** The differing biological fates of DNA binding MGBs. MRC Confidence in Concept, 2013-2014, GBP112,902.
- **Scott, F.**, **Tucker N.**, **Hunter I.**, Dancer S., **Suckling C.** Accelerating clinical introduction of novel antibacterial drugs. Chief Scientist Office (Scotland), 01/11/2016-31/10/2017, GBP116,784.
- **Tucker N.**, **Hunter I.**, Dancer S., **Suckling C.** Investigating a novel class of gram-negative active antibiotics suitable for clinical use. Chief Scientist Office (Scotland), 01/11/2020-31/10/2022, GBP296,999.

4. Details of the impact

The discovery and development of S-MGB anti-infective compounds by the Strathclyde researchers has led to:

- An effective new drug with novel mode of action for the treatment of serious *C. difficile* infections, to combat hospitalisations and mortality;
- Formation of a new biotechnology company;
- Progress to successful international clinical trial programmes;
- A new class of antibiotic.

Economic Impact

Formation of MGB Biopharma, a new biotechnology company

Following the discovery of several highly active anti-bacterial compounds [**R1**] and the submission of patent applications with broad coverage of active compounds (US 8,012,967 [**R2**] and cognate patents), the University of Strathclyde sought a commercial partner to discover and develop new anti-infective drugs, particularly antibacterial drugs, based on Strathclyde's intellectual property of S-MGBs. A license was granted to Pharma Integra, a privately-owned drug development company, which was able to raise funds to establish a new, Scottish-based company, MGB Biopharma, for this purpose. MGB Biopharma began operations in 2009.

Economic Performance

MGB Biopharma has established itself as a commercially successful company. Since its formation, the company's researchers have worked closely with Strathclyde, undertaking the development of clinical candidate molecules selected from the range of compounds created at the University [**S1**]. MGB Biopharma is the sole licensee of the patented S-MGBs for anti-infective applications world-wide.

Since August 2013 the company has raised GBP5,980,000 in equity funding from investment syndicates and over GBP4,100,000 from public funds [**S1**], including a highly competitive GBP2,780,000 grant from Innovate UK in 2018 [**S2**]. In 2019, funding to complete MGB-BP-3's Phase-II trials was oversubscribed [**S1**]. Companies House lists 110 shareholders, the majority having taken equity as a result of this crowdfunding initiative [**S3**]. This demonstrates how MGB-BP-3, as a pre-clinical drug candidate, has caught the imagination of a broad range of investors – in a business area (often called the 'Valley of Death' for projects) that has been historically difficult to fund at this stage of development.

MGB Biopharma has also benefited from the **G**enerating **A**nti**b**iotics **I**ncentives **N**ow (GAIN) initiative in the USA [**S4**], which extends commercial exclusivity of MGB-BP-3 by five years (to 2032), making it a much more attractive commercial investment. GAIN is applicable to a limited

number of target pathogens including *C. difficile*, so treatment with MGB-BP-3 falls directly within the programme. As part of the GAIN initiative, MGB-BP-3 was granted Qualified Infectious Disease Product (QIDP) status by the US Food and Drug Administration in 2019, which accelerates its progress through subsequent clinical trials and simplifies its route to market [**S1**, **S4**].

In 2020, the US Senate approved the '**P**ioneering **A**ntimicrobial **S**ubscriptions **T**o **E**nd **U**p-surging **R**esistance' (PASTEUR) Act, which is an innovative financial model for development of antibiotics serving critical needs. It provides between USD750,000 and USD3,000,000,000 for each drug. MGB-BP-3 is eligible for development via PASTEUR [**S1**] on commencement of a Phase-III trial. In the pipeline of US legislature, the '**D**eveloping an **I**nnovative **S**trategy for **A**ntimicrobial **R**esistant **M**icro-organisms' (DISARM) Act will improve critical Medicare reimbursement of new infection-fighting drugs. The CEO of MGB Biopharma has indicated the applicability of MGB-BP-3 to this initiative [**S1**]. Taken together, it is clear that MGB-BP-3 addresses a critical market need for rapid development of a novel antibiotic that addresses antimicrobial resistance.

Health-care Impact

Progression of candidate molecule, MGB-BP-3, through clinical trials

In 2019, the US Centre for Disease Control (CDC) cited *Clostridioides (Clostridium) difficile* (C.Diff) as the second biggest issue in antimicrobial resistance in the USA, with 223,900 people requiring hospital care and linked mortality of 12,800 per annum [**S5**].

In clinical trial, MGB-BP-3 has shown outstanding activity against infections caused by C.Diff, which is the most prevalent causative pathogen of healthcare-associated diarrhoea worldwide. To date, an oral formulation of MGB-BP-3 has successfully completed an integrated Single Ascending Dose and Multiple Ascending Dose Phase-I clinical trial [**S6**] and Phase-II clinical trials [**S7**]. In the Phase-1 trial (2015 – 2016) carried out at Hammersmith Hospital, London, MGB-BP-3 caused no serious adverse effects and decreased/limited the proportion of Firmicutes (of which *C. difficile* is a member) in the gut microbiota, completely consistent with expectations from Strathclyde's laboratory research. In the Phase-IIa trial (2019/2020), carried out at several locations in the USA and Canada where there are stable populations of *C. difficile* patients, MGB-BP-3 fully met the requirements for safety, efficacy, and dose selection, demonstrating better-than-expected efficacy at its lowest dosage level, with no serious adverse effects [**S7a**].

The most significant benefit shown by MGB-BP-3 in the Phase-IIa trial was a complete absence of disease recurrence at the optimum dose, a unique advantage. In terms of its rapid and sustained action against C.Diff and its resilience to the generation of resistance, these trials have shown MGB-BP-3 to be superior to the current principal treatment for *C. difficile*, vancomycin. As reported by the CEO of MGB Biopharma:

> *'In 2020 MGB-BP-3 completed its Phase IIa clinical study in which it showed efficacy of 91% - 100% in both initial and sustained cure. These results compare favourably with vancomycin, the current standard of care, which has published data showing sustained cure of between 42% - 75% across several studies. This efficacy, together with its novel mechanism of action, excellent safety profile and lack of observed resistance make MGB-BP-3 a distinctive and commercially attractive drug.'* [**S1**]

The Clinical Lead and Principal Investigator of the Phase-II trial commented, '*I am most pleased to have contributed to the success of the Phase 2 clinical study of MGB-BP-3. There is a real need for new agents to address CDI and it is gratifying to see this agent progressing onto its next phase of study*'. [**S7b**] With a plan for a Phase-III clinical trial approved by the United States FDA (January 2021) [**S7b**], MGB Biopharma expects the drug to be fully licensed and commercialised in 2024/5 [**S1**].

MGB Biopharma also reports that it is developing an intravenous formulation of MGB-BP-3 for the treatment of systemic Gram-positive infections such as MRSA, which is currently at the late pre-

clinical stage. The Company is also conducting feasibility studies of topical applications of MGB-BP-3 for the treatment of serious Gram-positive skin infections [**S8a, b**].

A new class of antibiotic

The combined work of the University of Strathclyde and MGB Biopharma has been acknowledged in the TV (2015) and print (2018) media as a significant step in the global fight against anti-microbial resistance [**S9a, b**]. The ongoing success and importance of the MGB-BP-3 clinical trials have been stressed by the Clinical Lead and Principal Investigator of the Phase-II trial: '*C. difficile infection represents a major burden to the Canadian and US healthcare systems. A novel antibiotic that is able to kill this deadly pathogen before it is able to sporulate offers hope to patients and their families who suffer the pain and misery caused by this disease*' [**S7a**].

The World Health Organization (WHO) has defined criteria [**S10**] to classify a novel antibiotic:

1) represents a new chemical class;
2) aims at a new target;
3) has a new mode of action; and
4) has an absence of cross-resistance to existing anti-microbials.

WHO cites only four compounds that satisfy their criteria; **MGB-BP-3, delivered through the S-MGB project, is the fifth compound publicly recognised as entirely novel** [**S10**, p.47-48].

Antibiotic discovery and translation to the clinic has been the realm of 'big pharma'. It is remarkable that this multi-disciplinary Strathclyde team has, in partnership with SME MGB Biopharma, taken its lead compound to the final phase of clinical trials during the assessment period.

5. Sources to corroborate the impact

S1 Corroborating statement from CEO of MGB Biopharma, dated December 2020.

S2 MGB Biopharma. *Scottish Biopharmaceutical Company MGB Biopharma Receives £2.78m Grant Award For Phase IIa Clinical Trial*. 14th March 2019. https://bit.ly/2XU3tEL

S3 Companies House. Confirmation Statement for MGB Biopharma Ltd. Filed 07/07/2020. https://bit.ly/3r9xXQd

S4 MGB Biopharma. *MGB Biopharma Granted Qualified Infectious Disease Product (QIPD) and Fast Track Designation by U.S. FDA for the Treatment of Clostridium difficile-associated Diarrhoea (CDAD) for Tablet Presentation of MGB-BP-3*. 28th January 2019. https://bit.ly/3ioRVCU

S5 US Centre for Disease Control. Antibiotic Resistance Threats in the United States. https://bit.ly/3055kHT

S6 Drug Development & Delivery. *MGB Biopharma Successfully Completes Phase I Clinical Trial*. https://bit.ly/3nShwFq

S7 (a) MGB Biopharma. *MGB Biopharma Announces Successful Outcome from Phase II Clinical Study with MGB-BP-3*. 19th May 2020. https://bit.ly/35U0eS9
(b) MGB Biopharma. *MGB Biopharma Announces Successful End-of- Phase II meeting with FDA for MGB-BP-3.* 27th January 2021. https://bit.ly/3b6JdHe

S8 (a) MGB Biopharma. *Our Intravenous Programme*. https://bit.ly/2KzIDri
(b) MGB Biopharma. *Topical Programme*. https://bit.ly/3qCcIWC

S9 (a) BBC News. *New Antibiotic Could Transform C. Diff Treatment*. 31st August 2015. https://bbc.in/2Y7ILl3
(b) The Scotsman. *MGB Biopharma drug secures £4m funding*. 14th September 2018. https://bit.ly/2Nj9LMa

S10 Access to Medicine Foundation. Antimicrobial Resistance Benchmark 2018 (p. 47-48). https://bit.ly/3q986GO