

## Impact case study (REF3)

<b>Institution:</b> University of Strathclyde		
<b>Unit of Assessment:</b> B8 - Chemistry		
<b>Title of case study:</b> A new class of anti-infective drugs from DNA Minor Groove Binders		
<b>Period when the underpinning research was undertaken:</b> 2000 - 2020		
<b>Details of staff conducting the underpinning research from the submitting unit:</b>		
<b>Name(s):</b>	<b>Role(s) (e.g. job title):</b>	<b>Period(s) employed by submitting HEI:</b>
Prof Colin Suckling	Professor	01/09/1972 – 31/07/2014
Dr John Parkinson	Senior Research Fellow	01/12/2001 – present
Dr Abedawn Khalaf	Research Fellow	16/01/1989 – 17/11/2017
Dr Fraser Scott	Research Associate; Lecturer	27/10/2014-21/10/2016; 01/06/2019-present
<b>Period when the claimed impact occurred:</b> August 2013 – December 2020		
<b>Is this case study continued from a case study submitted in 2014?</b> No		
<b>1. Summary of the impact</b>		
<p>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 <i>Clostridioides difficile</i> 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 Scottish 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.</p>		
<b>2. Underpinning research</b>		
<b>Context</b>		
<p>The treatment of infectious diseases has become increasingly challenging because of the widespread emergence of resistance to existing drugs. This antimicrobial resistance (AMR) affects bacterial, fungal, and parasitic pathogens and many potentially lethal diseases world-wide. The COVID-19 epidemic, for which no effective treatments are yet established, emphasises the need for new anti-infective drugs. Since 2000, a multidisciplinary team of chemists and biologists at Strathclyde, led by Prof Colin Suckling, has been seeking new ways to tackle AMR. Collaborating with academics from Australia, Brazil, India, South Africa and Switzerland together with the Universities of Glasgow and Manchester, they have discovered pluripotent anti-infective compounds that are resilient to the development of resistance in a class of compounds known as minor groove binders (MGBs). Owing to their mode of action, binding to the minor groove of DNA, MGBs have the potential to treat many types of infection whilst remaining resilient to the development of resistance. The challenge in this work is to obtain both high activity against the infectious agent and avoid toxicity to the patient, whether human or animal.</p>		
<b>Key findings</b>		
<p>Strathclyde-MGBs (S-MGBs) are loosely based on the structure of the natural product, distamycin. The key initial discovery was of a novel MGB that had high antibacterial activity (MGB-BP-3) [R1]. To support its formulation and the discovery of further new active S-MGBs, the physicochemical properties of antibacterial S-MGBs were established at Strathclyde. Subsequent work, led by Suckling's group, has focussed on systematic and imaginative variation of the detailed structure of the S-MGB in order to identify components of the structure that contribute to an improved profile with respect to physicochemical properties, potency, and selectivity, all of which are important in an effective medicine.</p> <p>Suckling and colleagues introduced inventive modifications to the biomolecular structure that were substantially different from the prototype, distamycin. In this way it was possible to obtain compounds with high and selective activity against several disease targets. These targets, which</p>		

are difficult to combat, include the Gram-positive bacterium *Clostridioides (Clostridium) difficile*; *Trypanosoma brucei brucei*, a pathogen of African animal trypanosomiasis [R2]; the malaria-causing parasite *Plasmodium falciparum* [R3]; the fungal pathogen *Cryptococcus neoformans* [R4]; and the tuberculosis pathogen *Mycobacterium tuberculosis* [R5]. Following their synthesis, the S-MGBs made by the Strathclyde team were evaluated *in vitro* to provide a profile of biological activity from which selected compounds were tested in proof-of-concept *in vivo* experiments at several collaborating laboratories in the UK and abroad (Dundee, Glasgow, Manchester, Cape Town and Pune). Colleagues at the Strathclyde Institute for Pharmacy and Biomedical Sciences played a key role in the *in vitro* evaluation and in studies of the mechanism of action, which have strongly supported the original design concept, in particular the binding to specific promoter regions of DNA leading to the important resilience to the development of antimicrobial resistance [R6].

### 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. DOI: [10.1021/jm070831q](https://doi.org/10.1021/jm070831q) [FWCI:1.59]
- R2 Giordani F., Khalaf A., Gillingwater K., Munday J., de Koning H., Suckling C., Barrett M. and Scott F.** (2019) Novel Minor Groove Binders cure animal African trypanosomiasis in an *in vivo* mouse model. *Journal of Medicinal Chemistry* 62: 3021–3035. DOI: [10.1021/acs.jmedchem.8b01847](https://doi.org/10.1021/acs.jmedchem.8b01847) [REF2]
- R3 Scott F., Khalaf A., Duffy S., Avery V. and Suckling C.** (2016). Selective anti-malarial minor groove binders. *Bioorganic & Medicinal Chemistry Letters* 26: 3326-3329. DOI: [10.1016/j.bmcl.2016.05.039](https://doi.org/10.1016/j.bmcl.2016.05.039).
- R4 Scott F., Nichol R., Khalaf A., Giordani F., Gillingwater K., Ramu S., Elliott A., Zuegg J., Duffy P., Rosslee M-J., Hlaka L., Kumar S., Ozturk M., Brombacher F., Barrett M., Guler R. and Suckling C.** (2017). An evaluation of Minor Groove Binders as anti-fungal and anti-mycobacterial therapeutics. *European Journal of Medicinal Chemistry* 136: 561-572. DOI: [10.1016/j.ejmech.2017.05.039](https://doi.org/10.1016/j.ejmech.2017.05.039)
- R5 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. DOI: [10.1093/jac/dkx326](https://doi.org/10.1093/jac/dkx326)
- R6 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*. DOI: [10.1101/2020.12.31.424950](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-R5** were peer-reviewed ahead of publication. The body of underpinning research has been supported by GBP1,528,460 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.

- **Suckling C., Burley G.** A new drug discovery pipeline for animal African trypanosomiasis. BBSRC & Global Alliance for Livestock Veterinary Medicines, 01/04/2016-31/03/2020, GBP325,373.
- **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.
- **Hunter I., Scott F., Suckling C.** Accelerated introduction of a novel class of resistance-proof antiviral drugs: Strathclyde Minor Groove Binders. Chief Scientist Office (Scotland), 2020, GBP294,897.

#### 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 **Generating Antibiotics Incentives Now (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 'Pioneering Antimicrobial Subscriptions To End Up-surg-ing Resistance' (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 'Developing an Innovative Strategy for Antimicrobial Resistant Micro-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-I 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 antimicrobial 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*. 14<sup>th</sup> 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*. 28<sup>th</sup> 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*. 19<sup>th</sup> May 2020. <https://bit.ly/35U0eS9>

(b) MGB Biopharma. *MGB Biopharma Announces Successful End-of- Phase II meeting with FDA for MGB-BP-3*. 27<sup>th</sup> 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/3qCclWC>

**S9** (a) BBC News. *New Antibiotic Could Transform C. Diff Treatment*. 31<sup>st</sup> August 2015. <https://bbc.in/2Y7ILl3>

(b) The Scotsman. *MGB Biopharma drug secures £4m funding*. 14<sup>th</sup> September 2018. <https://bit.ly/2Nj9LMa>

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