Institution: Queen's University Belfast		
Unit of Assessment: 8		
Title of case study: Synthesis of a new class of chemical compounds leads to discovery of Ridinilazole: a major new antibiotic to treat *Clostridium difficile*.		
Period when the underpinning research was undertaken: 2000-2008		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s): **John Mann**	**Role(s) (e.g. job title):** **Professor**	**Period(s) employed by submitting HEI:** **1999 - 2008**
Period when the claimed impact occurred: 2014-2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Clostridium difficile (*C. diff.*) infection is a serious hospital-associated bacterial disease caused by an extremely challenging pathogen. It is estimated to cause over 30,000 deaths annually in the USA with associated annual acute care costs at USD4,800,000,000.
A series of bis-benzimidazole (BBZ) compounds synthesised by the Mann group in QUB and collaborators led to the discovery of Ridinilazole, which is closely related to the original BBZ compounds. Ridinilazole, which has shown considerable promise as a new antibiotic specifically targeting *C.diff.* is being brought to market by Summit Therapeutics.
In Phase 2 clinical trials (2014 – 2016), Ridinilazole demonstrated statistical superiority over the current standard-of-care drug vancomycin. The results were so strong that the US Food and Drug Administration has accorded the drug 'Fast Track (development)' status and 'Qualified Infectious Disease Product' status. In 2017, the US government's Biomedical Advanced Research and Development Authority awarded Summit Therapeutics a contract worth USD62,000,000 to support the clinical and regulatory development of Ridinilazole. Phase 3 clinical trials are now in progress.

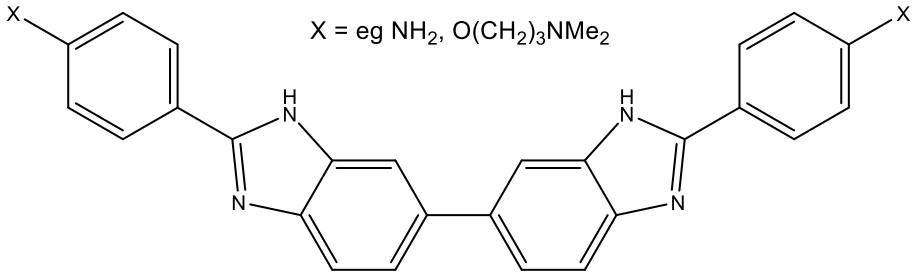
2. Underpinning research

John Mann and his research group were active in QUB from 1999 to 2008. He had collaborated with a group led by Stephen Neidle (University of Reading and Institute of Cancer Research) on a number of occasions, primarily in their work directed towards new anticancer agents. Mann and Neidle filed a US patent application describing the synthesis and potential anti-cancer activity of a new class of chemical compounds designed to interact with DNA (bis-benzimidazoles, BBZs) in 2000 **[R1].** Although one of the resultant derivatives showed some modest anti-tumour activity in human cancer xenograft models, this was insufficient to convince external funders. Mann continued to work on BBZ compounds, in particular publishing an improved synthetic method in 2006. **[R2]**

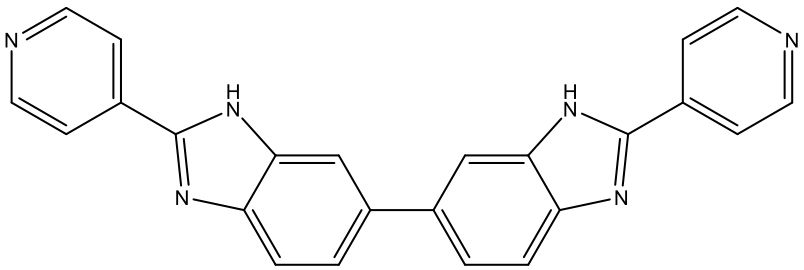
A paper describing the development of this underpinning research and how it led up to the discovery of Ridinilazole was retrospectively published in 2015 by Mann *et al.* (*J. Mann, P.W. Taylor, S. Neidle, et al., The discovery of a novel antibiotic for the treatment of Clostridium difficile infections: a story of an effective academic–industrial partnership, Med. Chem. Comm., 2015, **6**, 1420-26. (DOI: 10.1039/C5MD00238A)*). This paper includes a description of how in 2007 a collaboration between microbiologist Professor Taylor (UCL), Neidle (then UCL) and Mann (QUB), screened a number of the BBZ compounds, including ten from the original series synthesised by Mann and co-workers, which found that some were potent inhibitors of a panel of clinically-derived MRSA *Staphylococcus aureus* pathogens. This work was ultimately published in 2013 (*J. B. Moreira, J. Mann, S. Neidle, T. D. McHugh and P. W.*

Taylor, Antibacterial activity of head-to-head bis- benzimidazoles, Int. J. Antimicrob. Agents, 2013, 42, 361-366. (DOI: 10.1016/j.ijantimicag.2013.04.033).

Mann's interactions with Summit Therapeutics (www.summitplc.com) began in 2007 with a project in which they agreed to evaluate the anti-MRSA activity of a set of BBZ compounds. Subsequently, the Neidle and Mann groups then joined together with Summit Therapeutics, who commissioned *C. diff* compound evaluation, and potent activity was observed in several of the uncharged BBZ compounds synthesised by the Mann group. A comprehensive medicinal chemistry programme to optimise activity with appropriate physicochemical properties was then carried out. This medicinal chemistry effort found that the structure–activity requirements were exceptionally narrow and that significant deviations from the original BBZ structures (developed at QUB) were not tolerated and that the overall curvature and shape of the BBZ scaffold are absolute requirements for retention of activity.
Further development of the series of compounds by Summit Theraputics led to the novel antibiotic SMT19969 (Ridinilazole), which is closely based on the original BBZ compounds invented by Mann and Neidle and synthesised in the underpinning research carried out at QUB, as can be seen in the following scheme.



Range of symmetrical BBZs first synthesised by Mann *et al.*



SMT19969 Ridinilazole

The 2015 *Med. Chem. Comm* paper referred to above contains a detailed historical acount of the entire process and Mann's contribution to the development of the drug is also described in a detailed testimonial by the Director of Chemistry at Summit Therapeutics **[E1],** who characterises the development as a successful collaboration between industry and academia.

3. References to the research

[R1] *Bis-benzazoles and their use as antineoplastic agents***,** Patents jointly registered by Queen's University Belfast, The University of Reading, Institute of Cancer Research.
US patent:
https://patentimages.storage.googleapis.com/1a/29/1b/8672874c625b91/US6589971.pdf

[R2] C. Le Sann, A. Baron, J, Mann *et al*. New mustard-linked 2-aryl-bis-benzimidazoles with anti-proliferative activity. *Organic & Biomolecular Chemistry*, 2006, **4**, 1305–1312. (DOI: 10.1039/b600567e).

4. Details of the impact

C. difficile (C. diff) infections are a major problem; in 2015-16 in the UK alone, there were 5,200 cases in hospitals and more than 14,000 in primary care institutions. It is estimated that there are more than 1,000,000 cases in the US and Europe each year. This anaerobic bacterium usually affects patients with pneumonia or cancer who have been treated with broad spectrum antibiotics (especially cephalosporins) which have destroyed their natural gut flora. Although there are two drugs (metronidazole and vancomycin) that are currently partially effective, *C. diff* infections still cause >30,000 deaths annually in the USA and >10,000 in Western Europe each year. The economic cost of *C. diff* infection is significant, with one study estimating annual acute care costs at USD4,800,000,000 in the USA. New therapies are thus desperately needed.
The new antibiotic Ridinilazole, which has grown directly from the invention of the BBZ series of compounds by Mann and Neidle, is such a drug. Ridinilazole is structurally very closely related to the original BBZ compounds invented by Stephen Neidle and John Mann (see structures above), and represents a fundamental repositioning of particular BBZ compounds from generalised cell proliferation inhibitors to targeted anti-infective agents. The impact which has grown from Mann's original synthetic work and subsequent collaboration with Summit Therapeutics is that a major new drug has been developed and within the current REF period has been advanced through Phase 2 clinical trials, attracted significant support and recognition from the US Food and Drug Administration and Department of Health and Human Services and is now well through Phase 3 clinical trials.

Development of Ridinilazole is a major programme for Summit Therapeutics **[E1, E2]**. Phase I clinical evaluation was highly successful. Owing to its highly targeted spectrum of activity and ability to spare the normal gut microbiota, Ridinilazole was found to provide significant advantages over metronidazole and vancomycin, the mainstay antibiotics for *C. diff* infections (CDI). In addition, oral ridinilazole is well tolerated and exhibits a prolonged post-antibiotic effect **[E3].**

Phase 2 (2014 – 2016) clinical evaluation at hospitals in the USA and Canada was completed with a strong demonstration of clinical efficacy. Participants with signs and symptoms of CDI and a positive diagnostic test result were recruited from 33 centres in the USA and Canada and randomly assigned to receive oral Ridinilazole (200 mg every 12 h) or oral vancomycin (125 mg every 6 h) for 10 days. Participants receiving Ridinilazole were cured of the infection and remained disease-free for at least 30 days. In particular**, Ridinilazole, gave a 50% increase in sustained clinical response compared to vancomycin, which is the current drug of choice for serious cases of *C. difficile* infection.** Indeed, this meant that Ridinilazole demonstrated statistical superiority over standard-of-care vancomycin, which is a rare feat in antimicrobial trials. This demonstrates that the new insights into approaches for treating *C. diff* infections made possible by the underpinning work on BBZ compounds can lead to real clinical improvements **[E4].**

The success of the Phase 2 trial had a significant impact on the care of the patient group who received the drug and showed clinical benefit but moving forward this drug has the potential to dramatically improve the care of many thousands of patients annually.

The **FDA has accorded the drug Fast Track (development) status and Qualified Infectious Disease Product status**, which affords a number of advantages including an extension of marketing exclusivity for the drug **[E5].**

Phase 3 clinical trials, which began in Jan 2019, signal a major development in the treatment of an infection for which current therapies are ineffective and which causes tens of thousands of fatalities every year **[E6], [E7].** It therefore has global reach and significance, as reflected in the level of investment for the Phase 3 clinical trial. Notably **BARDA (Biomedical Advanced Research and Development Authority), an agency of the US government's Department of Health and Human Services, has awarded Summit a contract worth up**

to USD62,000,000 to support the clinical and regulatory development of Ridinilazole [E8].

In Nov 2020, Summit announced the successful conclusion of a further USD50,000,000 investment round which will support commercial development of Ridinilazole **[E9].**

5. Sources to corroborate the impact

[E1] Link from research to industry – testimonial from the Director of Chemistry at Summit Therapeutics.

[E2] Overview of Summit Therapeutics' effort against *C. diff*:
https://www.summitplc.com/our-programmes/c-difficile-infection/

[E3] Summary of Phase 1 trial results:
Ridinilazole: a novel therapy for Clostridium difficile infection Richard J Vickers et al Int J Antimicrob Agents 2016 Aug;48(2):137-43. doi: 10.1016/j.ijantimicag.2016.04.026

[E4] Report on results of Phase 2 clinical trail
Vickers RJ, Tillotson GS, Nathan R, et al. Efficacy and safety of ridinilazole compared with vancomycin for the treatment of Clostridium difficile infection: a phase 2, randomised, double-blind, active-controlled, non-inferiority study [published online April 28, 2017. Lancet Infect Dis. doi:10.1016/S1473-3099(17)30235-9.

[E5] Press release around FDA granting QIDP designation
https://www.summittxinc.com/app/uploads/2018/06/2014_RNS_27-QIDP-Status-for-SMT19969-FINAL.pdf

[E6] Summit Press release on Phase 3 Trials and talks with EMA and FDA
https://globenewswire.com/news-release/2017/02/01/912833/0/en/Summit-Outline-Phase-3-Programme-for-Novel-CDI-Antibiotic-Ridinilazole.html

[E7] Link to information on Phase 3 clinical trials:
https://www.ricodify.com/ Further details on each of the two trials are available at:
https://clinicaltrials.gov/ct2/show/NCT03595553
https://clinicaltrials.gov/ct2/show/NCT03595566

[E8] Press release - Summit Awarded BARDA Contract Worth Up to USD62,000,000 to Support the Development of Ridinilazole for the Treatment of C. difficile Infection
https://web.archive.org/web/20190621110126/http://www.globenewswire.com/news-release/2017/09/11/1117377/0/en/Summit-Awarded-BARDA-Contract-Worth-Up-to-62-Million-to-Support-the-Development-of-Ridinilazole-for-the-Treatment-of-C-difficile-Infection.html

[E9] Press release describing further USD50,000,000 finance for Summit Therapeutics:
https://www.summittxinc.com/app/uploads/2020/11/2020_PR_22_Financing-closed.pdf