Institution: University College London

Unit of Assessment: 3 Allied Health Professions, Dentistry, Nursing and Pharmacy

Title of case study: Clinical development of a novel first-in-class antibiotic for the treatment of *Clostridiodes difficile* infections

Period when the underpinning research was undertaken: 2002-2015

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:
Professor Stephen Neidle	(Currently Emeritus) Chair in Chemical Biology	2002 – 2016 (Emeritus 2016-present)
Professor Peter Taylor	Chair in Microbiology	1998 – present

Period when the claimed impact occurred: 2007-present

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact

Based on initial work by Neidle, Taylor and co-workers on bis-benzimidazoles as DNA ligands, Summit Therapeutics (UK) have developed ridinilazole, a novel precision antibiotic for the treatment of *Clostridiodes difficile* gut infections. Ridinilazole is currently in Phase 3 clinical trials and its development has attracted significant investment from external agencies, raising over USD150,000,000 from the Wellcome Trust, BADAR (USA) and the private investor Robert Duggan (now CEO), reporting improvement in patient outcomes in Phase 2 studies. Summit Therapeutics has gone from a small biotech company to a Nasdaq-listed international business. The development of this first-in-class antibiotic has considerable strategic significance to the sector and to the discovery of novel and selective antibiotics.

2. Research underpinning the impact

The collaboration that led to the original development of ridinilazole is based on a body of work by Neidle and John Mann (Queen's University Belfast) who discovered a novel class of DNA binding compounds based on bis-benzimidazole (BBZs) [**R1**]; a patent was granted in 2003 relating to the potential anticancer activity of BBZs [**R2**].

On moving to the UCL School of Pharmacy in 2002, Neidle collaborated with microbiologist Professor Peter Taylor to investigate BBZs as potential inhibitors of the bacterial DNA gyrase enzyme, in a deliberate repositioning strategy for the BBZs (subsequently published as **R3**, **R4**). Promising initial data led to two successful grant applications to the MRC and the Royal Pharmaceutical Society that allowed the assessment of the antibacterial potential of a wider collection of BBZs. A subsequent detailed investigation of the anti-*staphylococcal* mode of action using a microarray approach showed that BBZs have a complex, multifactorial antibacterial mechanism which includes the capacity to inhibit the binding of DNA gyrase to DNA and to promote the accumulation of single-stranded DNA breaks [**R3**, **R4**].

These studies marked the beginning of the collaboration with Summit Therapeutics, a pharmaceutical company based in Oxford, UK [**R5**]. In 2007, Summit and the School of Pharmacy developed a joint strategy for the future development of BBZs. Specifically, Summit suggested that the localization in the gut might make *Clostridium difficile* (now *Clostridiodes difficile)* gastrointestinal infections a suitable target. Summit commissioned *C. difficile* compound evaluation at several CROs. Potent activity was observed in several of the

uncharged initial BBZ compounds which, significantly, had previously been found at UCL to be non-cytotoxic and hence were more likely to be safe for humans.

Summit then embarked on a comprehensive medicinal chemistry programme to optimise activity against *C. difficile*. This work culminated in the discovery of the novel antibiotic SMT19969 (now called ridinilazole), which is very closely related to the original BBZ compounds synthesised by Neidle and Mann. A subsequent Wellcome Trust Seeding Drug Discovery funded project funded further development, together with extensive animal and pre-clinical toxicology work on the lead compound, with the Neidle laboratory working on mode-of-action studies.

The underpinning research and development of the collaboration has been published as a narrative in its own right [**R5**] as an example of a series of novel compounds being synthesised and evaluated in academia, their potential activities repurposed and refined and then lead compounds/clinical candidate developed in industry. Given its first-in-class and precision status, the molecule continues to be the subject of intense study. For example, recent work [**R6**] has indicated that ridinilazole protects the microbiome more effectively than vancomycin (the current standard of care for this disease) while also promoting the production of secondary bile acids which are associated with inhibition of vegetative growth of the bacteria. This is potentially highly significant, as dysbiosis of the gut microbiota due to antibiotic exposure is a major risk factor for the disease and is believed to contribute to re-infection.

3. References to the research

R1. Mann J, Baron A, Opoku-Boahen Y, Johansson E, Parkinson G, Kelland LR, Neidle S. A new class of symmetric bisbenzimidazole-based DNA minor groove-binding agents showing antitumor activity. J Med Chem. 2001 Jan 18;44(2):138-44. doi: 10.1021/jm000297b.

R2. J. Mann and S. Neidle, US Pat., No. US6589971B1, 2003.

R3. Dale AG, Hinds J, Mann J, Taylor PW, Neidle S. Symmetric bis-benzimidazoles are potent anti-staphylococcal agents with dual inhibitory mechanisms against DNA gyrase. Biochemistry. 2012 Jul;51(29):5860-5871. doi: 10.1021/bi300645n.

R4. Moreira JB, Mann J, Neidle S, McHugh TD, Taylor PW. Antibacterial activity of head-to-head bis-benzimidazoles. Int J Antimicrob Agents. 2013 Oct;42(4):361-6. doi: 10.1016/j.ijantimicag.2013.04.033.

R5. Mann, J; Taylor, PW; Dorgan, CR; Johnson, PD; Wilson, FX; Vickers, R; Dale, AG; (2015) The discovery of a novel antibiotic for the treatment of Clostridium difficile infections: a story of an effective academic-industrial partnership. MedChemComm, 6 (8) pp. 1420-1426. 10.1039/c5md00238a.

R6. Qian X, Yanagi K, Kane AV, Alden N, Lei M, Snydman DR, Vickers RJ, Lee K, Thorpe CM. Ridinilazole, a narrow spectrum antibiotic for treatment of *Clostridioides difficile* infection, enhances preservation of microbiota-dependent bile acids. Am J Physiol Gastrointest Liver Physiol. 2020 Aug 1;319(2):G227-G237. doi: 10.1152/ajpgi.00046.2020.

4. Details of the impact

Inward investment and the development of Summit Therapeutics

When Summit Therapeutics began work with the Neidle group in 2007, the company was a small biotech based in Oxford, UK. By December 2019, Summit raised over USD150,000,000, of investment, with the major shareholder being billionaire entrepreneur Robert Duggan. Duggan, who is now acting CEO, himself invested USD75,000,000 [**S1**] in order to support

the companies Phase 3 Clinical Trials of ridinilazole. Summit is now an international Nasdaq-listed public company with three further pipeline streams and a proprietary discovery platform (Discuva) [**S2**], all focused on the development of novel antibiotics based on the success of ridinilazole.

The inward investment that Summit has raised has allowed the company to grow in this way began with a Wellcome Trust Seeding Drug Discovery Grant (on which Neidle was a funded collaborator) to perform further chemistry, mode-of-action studies and pre-clinical work. The Wellcome Trust then supported Phase I studies (concluded 2012) followed by USD70,000,000 from BARDA (Biomedical Advanced Research and Development Authority) in the US to fund Phase 2 studies (completed in 2015). Robert Duggan invested USD25,000,000 in 2018 and USD50,000,000 in 2019; Phase 3 studies are currently underway and the results are expected to be available in 2021.

The success in securing investment and associated company growth is openly ascribed to the success of ridinilazole; The Chief Scientific Officer of Summit [**S3**] has stated: "*The collaboration between Summit and UCL to drive the preclinical program is an excellent example of the type of industry-academia drug discovery collaboration that is now quite common across both biotech and big pharma. Ridinilazole has advanced directly through this collaboration but also indirectly through the foundation work of Professor Neidle at UCL over the previous nearly 20 years*" and goes on to state that "*The origin of ridinilazole is indelibly linked with a research collaboration that started over a decade ago between Summit and the academic groups of Professors Stephen Neidle (UCL) and John Mann (University of Belfast).*" There is a royalty agreement in place between UCL and Summit Therapeutics, reflecting the contribution made by Neidle and Taylor to the development of ridinilazole.

Successful patient outcomes in the Phase 2 ridinilazole study

The Phase 2 study for ridinilazole (initiated 2014) involved 100 patients in the US and Canada, and was performed as a double-blind comparison to the current standard of care, vancomycin. The outcomes showed not just equivalence but significant improvements in patient outcomes. In addition, where reoccurrence is a major issue for *C. difficile* infection (CDI), Ridinilazole showed significant advantages in terms of clinical cure (77.8% for ridinilazole *vs.* 68.7% for vancomycin), sustained clinical response (66.7% for ridinilazole *vs.* 42.4% for vancomycin) and prevention of reoccurrence (14.3% for ridinilazole *vs.* 34.8% for vancomycin) [**S4**]. The trial also highlighted a sustained clinical response, indicating where patients were free from disease after ten days of treatment and remained free from disease for 30 days after treatment ended.

Phase 2 also reported alleviated symptoms related to quality of life index indicators such as mobility, self-care, pain/discomfort and mental health issues such as anxiety and depression [**S5**]. The Chief Communications Officer of Summit stated, '*As early as Day five, patients treated with ridinilazole reported significant improvements in index scores (p=0.008), a measure which combines scores from the five domains, and visual analogue scale (VAS) scores (p=0.01), which is a self-reported score of overall health. As an example, by Day 40 of the trial, patients treated with ridinilazole had improved significantly more than vancomycin in anxiety and depression*'. These results, along with the statistical superiority achieved in the primary clinical endpoint of sustained clinical response, supported the continued development of ridinilazole. As a consequence, the US FDA accorded the drug Fast Track Development and Qualified Infectious Disease Product status, which includes an extension of marketing exclusivity [**S5**].

C. difficile gastric infection is an extremely serious condition with over 1 million cases in the US and Europe per annum and circa 29,000 annual deaths in the US. While the number of patients that have benefited from the drug thus far is limited by the regulatory status, this nevertheless represents a significant alleviation of suffering and risk of mortality for those involved in the trials to date. The current Phase 3 studies involve 1360 patients (two global

studies of 680 patients) across North America, Australia, Asia, Europe and South America [**S6**].

The strategic importance of ridinilazole

Over and above the success story of a small UK biotech company managing to bring a drug to Phase 3 (without the company or drug being sold to a more established concern), the ridinilazole narrative has several aspects that distinguish it from other development journeys. In the first instance, the need for new and novel classes of antibiotics, and the associated difficulties with bringing such molecules to market, is well established [**S7**]. Furthermore, treatment of *C. difficile* is a major priority within this arena; the FDA has also designated *C. difficile* as one of three pathogens that pose an immediate public health threat requiring urgent action. Secondly, the drug is a first in class molecule. More specifically, the use of BBZ scaffolds as minor-groove binding compounds represents a new approach to treatment, opening possibilities not only of further analogues but also carrying implications for reduced resistance. Finally, the mechanism of action and the interaction with the gut microbiome are of themselves of great interest to the sector. The 'microbiome friendly' activity of ridinilazole in promoting the generation of secondary bile acids which in turn inhibit vegetative growth [**R6**] presents the possibility to the sector of designing mechanism-targeted drugs that manipulate microbiome composition and activity, to the benefit of the patient and the sector.

5. Sources to corroborate the impact

[S1] 'Summit Therapeutics appoints controlling shareholder biotech billionaire Bob Duggan as its executive chairman'. *Proactive Investors*, 26 February 2020. https://www.proactiveinvestors.co.uk/companies/news/913735/summit-therapeutics-appoints-controlling-shareholder-biotech-billionaire-bob-duggan-as-its-executive-chairman-913735.html

[S2] Company website https://www.summitplc.com/

[S3] Testimonial from CSO of Summit Pharmaceuticals

[S4] Vickers RJ, Tillotson GS, Nathan R, Hazan S, Pullman J, Lucasti C, Deck K, Yacyshyn B, Maliakkal B, Pesant Y, Tejura B, Roblin D, Gerding DN, Wilcox MH; CoDIFy study group. 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. Lancet Infect Dis. 2017 Jul;17(7):735-744. doi: 10.1016/S1473-3099(17)30235-9

[S5] Summit press release on Phase 2 outcomes: https://www.summittxinc.com/app/uploads/2019/10/2019_RNS_35-ID-Week-QoL-Data-FINAL.pdf

[S6] Phase 3 Clinical Trial and Map https://www.ricodify.com/

[S7] McKenna M. The antibiotic paradox: why companies can't afford to create life-saving drugs. Nature. 2020 Aug;584(7821):338-341.doi: 10.1038/d41586-020-02418-x