Institution: University of Southampton		
Unit of Assessment: 01 Clinical Medicine		
Title of case study: 01-05 Agile drug development and point of care testing for diagnosis and treatment of asthma, COPD and COVID-19		
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:**
Tristan Clark	Associate Professor and Honorary Consultant in Infectious Diseases	October 2013 – present
Donna Davies	Professor of Respiratory Cell and Molecular Biology	May 1985 – present
Ratko Djukanovic	Professor of Medicine	March 1988 – present
Nick Francis	Professor of Primary Care Research	September 2019 – present
Stephen Holgate	Medical Research Council Clinical Professor of Immunopharmacology and	November 1975 – present
Tom Wilkinson	Honorary Consultant Physician Professor of Respiratory Medicine and Honorary NHS Consultant Physician	August 2007 - present
Period when the claimed impact occurred: August 2013 – December 2020		
Is this case study continued from a case study submitted in 2014? Y		

1. Summary of the impact

The University of Southampton (UoS) has developed a successful therapy for virus-induced inflammatory lung conditions including asthma, chronic obstructive pulmonary disease (COPD) and COVID-19. UoS's pioneering use of inhaled interferon beta (INF-β) in the early 2000s led to the spin-out of **Synairgen**, which since August 2013 has raised more than GBP129m to fund clinical trials, has grown its market capitalisation tenfold to GBP300m and has received GBP10m through licensing. It has improved patient outcomes, clinical practice and wealth creation:

- A successful phase II trial of INF-β in **asthma** led to a 2014 licence deal with Astrazeneca with milestones worth up to USD225m.
- GBP4m was raised for a 2018 phase II clinical trial in **COPD**, boosting patients' antiviral lung defence and leading to a further GBP2.9m investment.
- In a 2020 phase II clinical trial in patients with **COVID-19**, IFN-β treatment lowered patients' risk of developing severe disease by 72% and doubled the likelihood of recovery. The led to a global GBP30m phase III trial, international media attention and an immediate fivefold growth in Synairgen's share price.
- Effective recruitment for the trials was enabled using a rapid point of care (**POC**) test for viral infection developed by UoS, which reduced COVID diagnosis time from 21.3 hours to 1.7 hours. The POC testing model has contributed to Public Health England guidance and is in the process of being rolled out to all acute trusts across the country.

2. Underpinning research

The University of Southampton has been at the forefront of respiratory disease research for the past 30 years, discovering many of the key mechanisms using *in vivo* studies and *ex vivo* lung tissue, and pioneering stratification methods to provide a better understanding of diseases, such as asthma and COPD. This long-standing respiratory disease expertise enabled Southampton's scientific community rapidly to respond to the COVID-19 pandemic with positive results for patients and industry.

Through controlled infection of human volunteers, research led by Professor Stephen Holgate published in 2000 [**3.1**] found the airway epithelium plays a pivotal role in acting as a "host" for common cold viruses, and that rhinovirus infections of the lower respiratory tract are directly linked with asthma exacerbations. This stimulated the discovery by Professor Donna Davies and

her team of a deficiency in the production of anti-viral interferons by bronchial epithelial cells grown from asthmatic donors [**3.2**]. Crucially, the cells could be protected against virus infection by adding exogenous interferon beta (IFN-β), a breakthrough in the search for therapy. This led to the formation of the spin-out company, Synairgen in 2003.

In 2010-2012 a phase II trial led by Professor Ratko Djukanovic studied the effect of nebulised IFN-β on worsening of asthma symptoms caused by viral infections. Asthmatics treated with IFN-β within 24 hours of developing symptoms of upper respiratory viral infection exhibited recovery of lung function decline induced by the infection/exacerbation, resulting in reduced need for additional treatment when compared to placebo. This demonstrated that asthmatics with severe asthma benefited most in terms of preventing symptom deterioration. Furthermore, the study provided vital evidence for the mechanisms of action based on biomarkers quantified in blood and induced sputum [**3.3**].

This led to a larger phase II trial (INEXAS) in 2015-2016, led by AstraZeneca, which was halted "because of difficulty in determining primary endpoint as there were very low numbers of severe exacerbations overall". Nonetheless, subsequent analysis of the INEXAS trial data showed a significant benefit from IFN-β in those difficult-to-treat patients who were virus-positive. After careful reflection and further negotiations, AstraZeneca returned the programme to Synairgen to develop further.

The effectiveness of IFN-β as a therapeutic for **COPD** was investigated in 2017 by Professor Tom Wilkinson, who showed that epithelial senescence prevented apoptosis of virally infected cells and that IFN-β was protective against infection [**3.4**]. He also showed that corticosteroids given to COPD patients both daily and (at high systemic doses) during infectious exacerbations impair IFN-β mediated anti-viral immunity. The asthma trials and this additional research led to Synairgen assessing IFN-β as a potential therapeutic for COPD.

To facilitate the subsequent phase II clinical trial of IFN-β in patients with COPD, patients were recruited using a rapid point of care (**POC**) test for viral infection pioneered by Dr Tristan Clark, significantly reducing the number of subjects required for the trial. The POC test is a syndromic test carried out in a sample-to-answer platform where a swab taken from a patient's nose is analysed and results given in 1.7 hours. A randomised control trial (ResPOC, 2015-2016), which involved more than 700 patients with acute respiratory illness, including pneumonia and exacerbations of asthma and COPD, demonstrated that the POC test resulted in shorter courses of antibiotics and hospital stays [**3.5**].

At the very early stages of the **COVID-19** pandemic in January 2020, the Southampton team's research efforts turned to the SARS-CoV-2 virus, which had evolved mechanisms to suppress IFN-β production, allowing it to evade the innate immune system. Synairgen pivoted from the COPD trial to test the hypothesis that IFN-β may reduce the morbidity associated with inflammation resulting from SARS-CoV-2 infection. In February 2020, Wilkinson rapidly set up a phase II clinical trial to test IFN-β on patients with COVID-19. The team received key support from the Urgent Public Health (UPH) panel as a priority trial for Clinical Research Network sites to support. The trial completed in May and showed that IFN-β treatment resulted in a 72% lower risk of developing severe disease compared to placebo and that patients were more than twice as likely to recover from COVID-19 as those on placebo during treatment [**3.6**].

Led by Professor Nick Francis, the trial was expanded in May to include 120 patients based in a community setting. Discussions began in autumn 2020 with Operation Warp Speed (OWS), a public–private partnership initiated by the U.S. government to facilitate and accelerate the development, manufacturing, and distribution of COVID-19 vaccines; IFN-β was selected as one of the arms in the ACTIV-2 trial and first patients were enrolled in January 2021.

3. References to the research

3.1 Papadopoulos NG, Bates PJ, Bardin PG, Papi A, Leir SH, Fraenkel DJ, Meyer J, Lackie PM, Sanderson G, Holgate ST and Johnston SL. Rhinoviruses infect the lower airways. J Infect Dis. 2000;181:1875-1884. https://doi.org/10.1086/315513

3.2 Wark PA, Johnston SL, Bucchieri F, Powell R, Puddicombe S, Laza-Stanca V, Holgate ST and Davies DE. Asthmatic bronchial epithelial cells have a deficient innate immune response to infection with rhinovirus. J Exp Med. 2005;201(6):937-947. https://doi.org/10.1084/jem.20041901

3.3 Djukanovic R, Harrison T, Johnston SL, et al. The effect of inhaled IFN-beta on worsening of asthma symptoms caused by viral infections. A randomized trial. Am J Respir Crit Care Med. 2014;190(2):145-154. https://doi.org/10.1164/rccm.201312-2235oc

3.4 Watson A, Spalluto CM, McCrae C, Cellura D, Burke H, Cunoosamy D, Freeman, Hicks A, Hühn M, Ostridge K, Staples KJ, Vaarala O and Wilkinson T. Dynamics of IFN-β Responses during Respiratory Viral Infection. Insights for Therapeutic Strategies. Am J Respir Crit Care Med. 2019; 201(1):83-94. https://doi.org/10.1164/rccm.201901-0214oc

3.5 Brendish N, Malachira A, Armstrong L, Houghton R, Aitken S, Nyimbili E, Ewings S, Lillie PJ, Clark TW. Routine molecular point-of-care testing for respiratory viruses in adults presenting to hospital with acute respiratory illness (ResPOC): a pragmatic, open-label, randomised controlled trial. Lancet Respir Med 2017; 5: 401–411. https://doi.org/10.1016/S2213-2600(17)30120-0

3.6 Monk PD, Marsden RJ, Tear VJ, Brookes J, Batten TN, Mankowski M, Gabbay FJ, Davies DE, Holgate ST, Ho LP, Clark T, Djukanovic R, Wilkinson TMA. Safety and efficacy of inhaled nebulised interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Respir Med 2020. https://doi.org/10.1016/S2213-2600(20)30511-7

Funding

- 2003-2005: Davies DE, Holgate ST; Asthma UK. Rhinovirus infection and activation of the epithelial-mesenchymal trophic unit in asthma. GBP122,694
- 2010-2012: Djukanovic R Phase II asthma trial GBP6m funded by Synairgen
- 2014-2015: Clark T et al. ResPOC funded by University Hospital Southampton
- 2016-2020: Clark T: Evaluating the impact of a molecular point-of-care test and treat strategy for influenza in hospitalised adults. NIHR Post Doctoral Fellowship £552,000
- 2017 Wilkinson initial COPD work. GBP2m EU grant from AstraZeneca
- 2020 phase II COVID-19 trial GBP5m raised by Synairgen

4. Details of the impact

Research at the University of Southampton (UoS) over the past 30 years has led directly to the development of nebulised IFN-β as a new, successful therapy for inflammatory lung conditions such as asthma and COPD. This therapy has had tangible impacts on patient health and wealth creation, culminating in a successful clinical trial during the COVID-19 pandemic.

Formation of Synairgen (covered in REF 2014)

Synairgen was founded in June 2003 by Holgate, Davies and Djukanovic, with investment from IP2IPO Group plc (now IP Group). It was floated on the Alternative Investment Market (AIM) in October 2004, raising GBP10,500,000. [**5.1**]

In March 2004, UoS filed a patent for the use of inhaled IFN-β for treatment of virus-induced exacerbations of asthma and COPD. This allowed the pioneering research to continue through clinical trials testing IFN-β for asthma and COPD. [**5.1**]

From 2008 Synairgen concentrated its effort on the clinical development of inhaled IFN-β for the treatment of exacerbations of asthma and COPD caused by respiratory viruses. In 2009 Synairgen completed Phase I trials in moderately asthmatic subjects and progressed to Phase II proof of concept studies. Underlining significant investor confidence, the company raised GBP6,000,000 in 2009 to fund phase II clinical trials in asthma and GBP2,500,000 in 2011 to accelerate completion of asthma phase II, conduct various in vitro experiments and fund avian flu research. [**5.1**]

Synairgen's market capitalisation was GBP26,307,751 at the end of 31 July 2013. [**5.1**]

Continued success of Synairgen and nebulised IFN-β for treatment of asthma

Since August 2013, Synairgen has increased the number of staff employed on its drug development from 15 to 19 and aided the career of staff including 9 scientists, 3 nurses and 7 trial managers, either employed directly or indirectly by the company. Its market capitalisation was GBP305,869,035 at when markets closed on 31 December 2020. [**5.1**]

Southampton's phase II trial of nebulised IFN-β in asthma led to a global license deal between Synairgen and AstraZeneca in 2014, with an upfront payment of USD7,250,000 (06-2014) and

potential development, regulatory and commercial milestones of up to USD225,000,000 as well as tiered royalties, a proportion of which goes to the University. [**5.2**]

Nebulised IFN-β for the treatment of chronic obstructive pulmonary disease (COPD)

In December 2017, Synairgen changed its strategic direction to assess IFN-β as a potential therapy for COPD. A phase II Clinical Trial of IFN-β in patients with COPD was launched in February 2018 by Wilkinson and raised GBP4,000,000. The first part of the trial was successful, showing that IFN-β boosts antiviral lung defense mechanisms in the absence of a respiratory virus. This led Synairgen to raise GBP2,900,000 in September 2018 to expand the trial from 80 to 120 patients with a confirmed respiratory viral infection. By February 2020 recruitment was almost completed when the COVID-19 outbreak started to gain momentum in the UK. [**5.1**]

Nebulised IFN-β for the treatment of COVID-19

Synairgen raised GBP5,000,000 for the University's phase II clinical trial to test IFN-β on patients with COVID-19, which got Medicines and Healthcare products Regulatory Agency (MHRA) and ethics approval within days and was established within four weeks, an unprecedented timeframe for a trial. It involved nine other hospital sites within the UK, recruiting 101 patients, and the first part of the trial was completed within seven weeks. Following the success of the first stage, £3m was raised to expand the trial in May 2020 to include an additional 120 patients in the community setting. [**5.1**]

Results released in July 2020, showed that patients who received IFN-β had a 72% lower risk of developing severe COVID-19 compared to placebo and were more than twice as likely to recover from the disease as those on placebo. It also showed breathlessness was markedly reduced. There were no deaths among the patients who received IFN-β, demonstrating its huge "*potential as an inhaled drug to be able to restore the lung's immune response, enhancing protection, accelerating recovery and countering the impact of SARS-CoV-2 virus."* [**5.3**]

The phase II trial and subsequent results had a substantial impact on Synairgen's share price. Within the first 48 hours of the trial launching on 18 March 2020, Synairgen's share price doubled from GBP0.24 to GBP0.49. Upon release of the positive results in July, the share price soared as much as 552%, taking its year-to-date gain to about 3,194%. [**5.4**].

The launch of each stage of the trial, as well as the announcement of the results, attracted worldwide media attention. Coverage in July 2020 of the first results was across broadcast, radio, print and online platforms including outlets such as The Guardian, New York Times, The Brussels Times, CNN, BBC Radio 4 and Bloomberg [**5.5**].

These positive results led to Synairgen's inhaled IFN-β being selected for the US Government funded ACTIV-2 trial (estimated value GBP100m) [**5.6**] which evaluates treating patients with mild to moderate COVID-19 symptoms not yet requiring hospitalisation. Additionally, Synairgen has commenced an in-patient global Phase III trial launched in December 2020 [**5.7**], funded through a GBP87,000,000 placement on the London Stock Exchange and led by Wilkinson. This international trial will recruit up to 610 patients and continue to evaluate IFN-β as a treatment of hospitalised COVID-19 patients, aimed at preventing the need for ventilation, and accelerating recovery.

Synairgen's Investigational New Drug application to the US Food and Drug Administration (FDA) to evaluate IFN-β as a treatment for patients with COVID-19 was approved in December 2020, enabling Synairgen to initiate the Phase III trial in the US [**5.7**]. The FDA awarded it Fast Track status, enhancing the ability of Synairgen to interact with the FDA and shortening review timelines [**5.8**].

Rapid point of care (POC) test for viral infection

The development of the POC test for respiratory infections underpinned the success of the trials for both COPD and COVID-19 by providing quicker patient diagnosis, leading to more effective recruitment. Patients who received a positive POC test for COVID-19 were recruited into the trial two days earlier than patients who were tested by the lab. This successful POC testing strategy has led to further trials, which have had an impact in the clinical setting.

The ResPOC study led to an NIHR post-doctoral fellowship for Clark in 2016 to carry out a randomised control trial to assess the POC test for patients with influenza symptoms. Patients

who received the POC test were given antiviral treatment on average 28 hours more quickly than those who did not have the test. Patients who had influenza diagnosed by the POC test were also isolated more appropriately and rapidly [**5.9**].

Southampton's POC test research underpinned and was cited in Public Health England guidance, published in November 2018 and updated in October 2019, describing the benefits of implementing POC testing in hospital settings. Southampton was described as an Early Adopter (EA) site where "successful outcomes reported by EA groups include improved patient triage, better cohorting and use of isolation rooms during periods of winter pressure." [**5.10**]

During Synairgen's COVID-19 trial, the POC test had positive impacts on waiting times for COVID-19 results and patient flow through Southampton General Hospital. A clinical impact assessment trial of POC testing during the first wave of the pandemic showed that instead of taking a day to receive results, clinical staff received results in just 1.7 hours on average. Patients who received the test were transferred to the appropriate ward within eight hours, compared to 28 hours for those who did not. Additionally, patients in the emergency department who received the POC test were not transferred to an assessment area unnecessarily. This resulted in fewer bed moves, reducing the need for deep cleaning and staff exposure to COVID-19 in contaminated areas. [**5.11**]

Due to Southampton's ground-breaking work with the POC test, Clark was asked to contribute to the Academy of Medical Sciences' *Preparing for Winter* report, which gave a 'reasonable worst case scenario' of between 24,500 and 251,000 virus related deaths in hospital, peaking in January and February 2021. This report and the successful results of the POC test in Southampton led to Clark being seconded to the Department of Health & Social Care to assist in the national roll out of POC tests to all acute trusts. [**5.12**]

5. Sources to corroborate the impact

5.1 Letter from CEO, Synairgen plc.

5.2 AstraZeneca Press release 12 June 2014 https://www.astrazeneca.com/media-centre/press-releases/2014/astrazeneca-synairgen-sng001-novel-immuno-modulatory-therapy-asthma-12062014.html (PDF supplied)

5.3 Synairgen press release announcing results from Phase II clinical trial of IFN-β in COVID-19 patients https://www.synairgen.com/umbraco/Surface/Download/GetFile?cid=1130026e-0983-4338-b648-4ac7928b9a37 (PDF supplied)

5.4 https://www.bloomberg.com/news/articles/2020-07-20/tiny-u-k-company-s-stock-soars-373-as-drug-cuts-covid-19-risk (PDF supplied)

5.5 Synairgen media monitoring report.

5.6 ACTIV-2 trial: https://www.clinicaltrials.gov/ct2/show/NCT04518410

5.7 Phase III global trial, 18 December 2020: https://www.synairgen.com/umbraco/Surface/Download/GetFile?cid=4a03ee82-735c-4a1c-8372-e6b5a75b243b (PDF supplied)

5.8 https://www.sharesmagazine.co.uk/news/shares/synairgen-surges-on-fda-fast-track-status-for-covid-19 (PDF supplied)

5.9 Tristan W Clark et al. Clinical impact of a routine, molecular, point-of-care, test-and-treat strategy for influenza in adults admitted to hospital (FluPOC): a multicentre, open-label, randomised controlled trial. Lancet Respiratory Medicine. 2020 https://doi.org/10.1016/S2213-2600(20)30469-0

5.10 Public Health England report: *Point of care tests for influenza and other respiratory viruses* https://www.gov.uk/government/publications/point-of-care-tests-for-influenza-and-other-respiratory-viruses (PDF supplied)

5.11 Tristan W Clark et al. Clinical impact of molecular point-of-care testing for suspected COVID-19 in hospital (COV-19POC): a prospective, interventional, non-randomised, controlled study. Lancet Respiratory Medicine. 2020 https://doi.org/10.1016/S2213-2600(20)30454-9. Also reported on BBC news, 9 October 2020 - https://www.bbc.co.uk/news/health-54468993

5.12 Details of secondment, Department of Health & Social Care.