Institution: Queen's University Belfast

Unit of Assessment: UoA 3

Title of case study:

Transforming the lives of people with Cystic Fibrosis through novel therapies

Period when the underpinning research was undertaken: 2011-2020

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:**
Prof Stuart Elborn	Faculty Pro Vice Chancellor	2002-2014, 2016-2020
Dr Damian Downey	Clinical Senior Lecturer	2017-2020
Prof Judy Bradley	Director of Clinical Research Facility	2015-2020

Period when the claimed impact occurred: 2013-2020

Is this case study continued from a case study submitted in 2014? N

Summary of the impact

There are over 10,500 people with Cystic Fibrosis (pwCF) in the UK, accounting for 9,500 hospital admissions and over 100,000 bed days a year. A Queen's University Belfast (QUB) research team has transformed the lives of thousands of pwCF by leading on the clinical development of treatments that address the underlying genetic deficit. These transformative therapies improve lung health and have **underpinned the regulatory approval and marketing of 4 breakthrough CF therapies**. The most recent, **Trikafta/Kaftrio**, targets mutations present in 90% of pwCF, hailed by the FDA as a **"landmark approval"**. **It generated approx. USD4,000,000,000 in sales revenue in 2020**.

2. Underpinning research

There are over 80,000 people living with CF globally, including 10,500 in the UK. The condition is caused by a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene which is responsible for the regulation of salt and water levels in the body. It affects many organs in the body, particularly the lungs and gut, with mutations leading to the build-up of thick mucus. In the airways, this can result in multiple chest infections, resulting in lung damage and an early death.

The QUB CF Research Team led by Elborn and Downey are recognised as world leaders in CF research. Elborn was the founder of the European Cystic Fibrosis Society - Clinical Trials Network (ECFS-CTN) in 2008 with Downey now serving as the Director.

Elborn and Downey have worked for over 12 years supporting the development of drugs that improve the function of CTFR. This work included the development of clinical trial protocols, and inclusion of key outcome measures such as; lung function (FEV_1), pulmonary exacerbation rate, and Quality of Life (QoL) tools for use in clinical trials of new therapeutics. Working with industry, clinical trial networks and contract research organisations and colleagues at other HEIs, such as Imperial College, they have developed expertise in the delivery of clinical trials of single and multiple combination therapies.

CFTR Single Therapy

The work of Elborn and colleagues was pivotal in the delivery of phase 2 and 3 clinical trials of Ivacaftor (trade name **Kalydeco**), the first CFTR modulator therapy for people with the G551D gene mutation (4-5% of CF population) **[R1]**.

CFTR Dual Therapy

Following the success of these single therapy trials, the CF group **co-led the phase 3** trials of 2 dual CFTR modulator therapies, Lumacaftor-Ivacaftor (**Orkambi**) **[R2]** and Tezacacftor-Ivacaftor, (**Symdeko [US]/Symkevi [EU]**) **[R3]** for pwCF with two copies of F508del mutation (almost 50% of pwCF) between 2015 and 2017.

The effect of **Orkambi** was investigated in the TRAFFIC (NCT01807923) and TRANSPORT (NCT01807949) trials in 2014 with Elborn as **Co-Chief Investigator [R2]**. Over 1100 pwCF were included in these studies, which demonstrated improvements in lung function and body mass index. Decreases in the rate of pulmonary exacerbations were also observed.

Elborn was also **Co-Chief Investigator** in the EVOLVE trial (NCT02347657) which studied the effects of **Symdeko/Symkevi** in pwCF over 24 weeks compared to placebo **[R3].** The group who received the **Symdeko/Symkevi** combination showed an improvement in lung function compared to placebo. The treated group also showed a **35% reduction** in the annualized rate of pulmonary exacerbations relative to the placebo group.

CFTR Triple Therapy

The culmination of years of drug development resulted in the world's first trials of "triple therapy" for CF. **Downey** was the **UK lead for the phase 3 clinical trials** of Elexacaftor-Tezacaftor-Ivacaftor (**Trikafta [US]/Kaftrio [EU]**) in 2018. A study in pwCF with two copies of the F508del mutation reported a significant increase in lung function ($ppFEV_1$ of 10%) between pwCF receiving **Trikafta/Kaftrio** in comparison to those receiving **Symdeko [R4]**.

3. References to the research

R1) Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Drevinek P, Griese M, McKoneEF, Wainwright CE, Konstan MW, Moss R, Ratjen F, Sermet-Gaudelus I, Rowe SM, Don QM, Rodriguez S, Yen K, Ordonez C, **Elborn JS**, and VX08-770-102 Study Group (2011) A CFTR Potentiator in Patients with Cystic Fibrosis and the G551D Mutation, *New England Journal of Medicine 365*, 1663-1672. DOI: 10.1056/NEJMoa1105185

R2) Wainwright CE, **Elborn JS**, Ramsey BW, Marigowda G, Huang X, Cipolli M, Colombo C, Davies, JC, De Boeck K, Flume PA, Konstan MW, McColley SA, McCoy K, McKone EF, Munck A, Ratjen F, Rowe SM, Waltz D, Boyle MP., TRAFFIC Study Group; TRANSPORT Study Group (2015) Lumacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR. *New England Journal of Medicine 373*, 220-231. DOI: 10.1056/NEJMoa1409547

R3) Taylor-Cousar JL, Munck A, McKone EF, van der Ent CK, Moeller A, Simard C, Wang LT, Ingenito EP, McKee C, Lu YM, Lekstrom-Himes J, and **Elborn, J. S**. (2017) Tezacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del, *New England Journal of Medicine 377*, 2013-2023. DOI: 10.1056/NEJMoa1709846

R4) Heijerman HGM, McKone EF, **Downey DG**, Van Braeckel E, Rowe SM, Tullis E, Mall MA, Welter JJ, Ramsey BW, McKee CM, Marigowda G, Moskowitz SM, Waltz D, Sosnay PR, Simard C, Ahluwalia N, Xuan FJ, Zhang YH, Taylor-Cousar JL, McCoy KS, and VX17-445-108 Trial Group (2019) Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial, *Lancet 394*, 1940-1948. doi: 10.1016/S0140-6736(19)32597-8

4. Details of the impact

CF is a life-limiting genetic disease that affects many organs in the body, particularly the lungs. People with CF (pwCF) have a range of symptoms including, breathlessness, sputum production and the inability to effectively digest food. Additional complications include liver failure, diabetes, bone disease and infertility. Until recently, treatments have been focused on symptom control. However, **during the last decade, the work of the Queen's University Belfast CF Research Team has been at the forefront of major advancements in drugs targeting the underlying genetic deficit.** A number of key impacts have emerged from this approach:

Impact on drug development pipeline

Extensive clinical trial experience coupled with the Clinical Trial Network infrastructure (established by Queen's and the Belfast Health and Social Care Trust) resulted in Elborn and Downey playing a pivotal role in a drug development programme working alongside Vertex Pharmaceuticals to deliver trials for **single, double and triple therapies** in CF.

The Vice-President Medical Affairs and the Clinical Development Senior Medical Director of Vertex commented on working with Professor Elborn, Dr Downey and their team:

*"Their expertise in Cystic Fibrosis, and with respect to clinical trials has hugely contributed to the outstanding progress in treating this severe, life shortening disease across more than a decade of dedicated help and knowledge".***[S1]**

The most recent trials successfully demonstrated that a combination of drugs can treat up to 90% of pwCF by addressing the underlying cause of their disease. This new "triple therapy" results in a significant improvement in lung function and quality of life and also reduces the frequency of chest infections **[R4].** Both the Food and Drug Administration and the European Medicines Agency approved Trikafta/Kaftrio for use in 2020 **[S2].**

The table below shows the percentage of the CF population who can potentially benefit from the therapies developed in each successive trial and the sales revenue generated in 2020 **[S3]**. Development of CFTR modulator drugs has also resulted in considerable economic benefits for Vertex Pharmaceuticals, for example **Trikafta/Kaftrio generated approximately USD4,000,000,000 in sales revenue for the 12 months ending December 31st 2020 [S3].**

Table 1: Summary of percentage of pwCF benefiting from new therapies and sales generated

Name of Drug	Year of license	% CF population globally	Sales revenue 2020
Kalydeco	FDA 2012 EMA 2012	5% (10% Ireland)	USD803,000,000
Orkambi	FDA 2015 EMA 2015	50%	USD908,000,000
Symdeko [US]/Symkevi [EU]	FDA 2018 EMA 2018	50%	USD629,000,000
Trikafta [US] /Kaftrio [EU]	FDA 2019 EMA 2020	90%	USD3,864,000,000

Trikafta/Kaftrio was hailed as a "**landmark approval"** by the FDA having an expedited approval process including Priority Review, Fast Track, Breakthrough Therapy, and orphan drug designation.

Commenting on Trikafta/Kaftrio Acting FDA Commissioner Ned Sharpless, M.D. stated:

"*In the past few years, we have seen remarkable breakthroughs in therapies to treat cystic fibrosis and improve patients' quality of life, yet many subgroups of cystic fibrosis patients did not have approved treatment options. That's why we used all available programs… to help advance today's approval in the most efficient manner possible, while also adhering to our high standards.*

Because of Trikafta's benefit to the cystic fibrosis community, the FDA reviewed and approved Trikafta in approximately three months, ahead of the March 19, 2020 review goal date" **[S4].**

Impact on patients

The most important impact of the QUB research is the benefit to pwCF treated with the therapies described above. Evidence from the phase 2 and phase 3 trials in which Elborn and Downey acted as Chief Investigator or Co-Chief Investigators clearly demonstrates the transformative effect of these breakthrough therapies. Downey's joint role within Queen's and the NHS has allowed him to lead the introduction of Kaftrio in Northern Ireland ensuring that over 90% of the CF population have access to this CFTR modulator therapy.

Delivery of the trials in Belfast, has brought huge benefits to the local population of pwCF and provided early access to treatments not yet available as part of standard care. Trial results showed improvements in key outcomes, for example, lung function, sweat chloride (an *in-vivo* marker of CFTR function), quality of life and bodyweight. Results from a Trikafta/Kaftrio trial also showed a **reduction in pulmonary exacerbations of 63%[R4].**

These improvements in clinical outcomes have huge personal significance to pwCF as it allows them to regain some aspects of normal life without weeks spent in hospital and allowing them to spend time with their families.

Speaking about the beneficial effect of Trikafta/Kaftrio, a CF patient commented:

"*This drug has given me a holiday from my CF- the amount of work I had to do every day, now I only need to do 15 mins of physio in the morning as opposed to a number of times throughout the day…felt a difference within a day and can't believe the energy I have, feel like I can plan things and be able to do them*"**[S5].**

Another CF patient said:
"*It's like a miracle, change is unbelievable…full of life and energy. No cough, weight on. Mentally so good and motivated to start up a wee business*" **[S5].**

The importance of the CFTR modulators has also been recognised by experts in the international CF community. National Institutes of Health Director, Francis Collins, who with colleagues discovered the CFTR mutation in 1989 spoke about the importance of the Trikafta phase 3 trial results (in which **Downey** was an author) during an interview in November 2019.

He stated

"…it has been 30 years that we've been hoping and dreaming for a day like this, where you could look at data and just absolutely - your jaw drops because it is so impressive and so good. Now we are at the point with this triple therapy where 90% of people with cystic fibrosis are going to have substantial and amazing benefit from the drug therapy that looks as if it will convert what has been otherwise a very threatening and potentially fatal disease into a chronic illness that's going to require treatment but which should allow people to live much more normal lives…." **[S6].**

Impact on Patient and Public Involvement

Elborn was instrumental in the establishment of the ECFS-CTN while President of the European CF Society. Downey is now Director of the ECFS-CTN and it has grown to encompass 58 CF research centres (including QUB) in 17 different countries across Europe, caring for 21,500 adult and paediatric pwCF which is over 20% of the world population of pwCF. As a result, pwCF or parents of children with CF are part of the clinical trial review process to ensure that the study design is agreeable to patients. ECFS-CTN sites prioritise trials for which the protocol has been reviewed and approved by teams that include, CF patient/parents, doctors, research coordinators, and statisticians. This improves trial design, ensures an acceptable burden of participation and prioritises impactful trials (to best use the limited patient population). To date, over 140 protocols have been reviewed. The current President of the European Cystic Fibrosis Society has highlighted the key role played by Professor Elborn and Dr Downey in the establishment, development and leadership of the ECFS-CTN:

"Under Prof Stuart Elborn's Presidency of the Society, the ECFS formed the clinical trials network (CTN) 10 years ago to optimise the delivery of clinical trials of candidate drugs through collaborative work of large and experienced CF centres. Prof Elborn was instrumental in inception, design, and execution of the CTN. This has been supported and driven by Dr Downey in more recent years, as Co-Director and now… Prof Elborn and Dr Downey have also led these pivotal CFTR modulator clinical trials in the UK and beyond, demonstrating their dedication to improving the lives of people with CF." **[S7]**

5. Sources to corroborate the impact

S1) Testimonial from Vertex Pharmaceuticals

S2) Cystic Fibrosis Trust article on Trikafta/Kaftrio Triple combination therapy Kaftrio (Trikafta in the US) (cysticfibrosis.org.uk)

S3) Vertex Full-Year and Fourth-Quarter 2020 Financial Results, see page 2 of pdf

S4) FDA News Release on Trikafta/Kaftrio approval FDA approves new breakthrough therapy for cystic fibrosis | FDA

S5) CF patient testimonials provided by Belfast Health and Social Care Trust

S6) Transcript of interview with Francis Collins on triple therapy New Hope For Patients Living With Cystic Fibrosis After Scientists Unveil Therapy : NPR

S7) Testimonial from President of the European Cystic Fibrosis Society