Institution: Imperial College London

Unit of Assessment: 01 Clinical Medicine

Title of case study: Leading a transformational change in treating cystic fibrosis.

Period when the underpinning research was undertaken: 2009-present

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:
Jane Davies	Professor of Paediatric Respirology & Experimental Medicine	1999 - present
Stuart Elborn	Clinical Chair in Respiratory Medicine	2016 - 2019
Rebecca Dobra	Clinical Research Fellow	2017 - present
Sandra Scott	Senior Research Nurse	1992 - present
Clare Saunders	Respiratory Research Physiologist	2006 - present

Period when the claimed impact occurred: 2014 - current

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

1. Summary of the impact (indicative maximum 100 words)

Small molecule, mutation-specific drugs that are transformative for people with cystic fibrosis (CF). These drugs target the underlying cause of disease, substantially improve lung function, reducing hospitalisation to treat pulmonary exacerbations. Their systemic administration also yields extra-pulmonary effects including digestive, nutritional and metabolic benefits. The first, ivacaftor, demonstrates improved survival and reduced need for lung transplantation. With rapid progression into younger age groups and the development, licensing and commissioning of multi-molecule combinations, these drugs improve the health and well-being of the majority (approximately 85%) of people with CF.

2. Underpinning research (indicative maximum 500 words)

The cause of CF remained elusive until discovery of the transmembrane conductance regulator (*CFTR*) gene in 1989. The resultant understanding of pathophysiological mechanisms in the airways, digestive and reproductive tracts of people with CF (pwCF) led to earlier diagnosis and the search for improved treatments, designed to correct the cellular defect at a genetic or protein level.

CFTR gene mutations impair either the amount of protein produced/reaching the cell surface or CFTR protein function. Most pwCF fall into the first category, possessing either one (~40-50%) or two (~40%) F508del mutations, resulting in protein misfolding and degradation before reaching the cell surface. 'Gating' mutations (~5% overall) produce CFTR that reaches the cell surface but fails to open ('gate').

CFTR modulator drugs, acting in a mutation-specific fashion have progressed from in vitro studies through to clinical availability: potentiators increase the function of correctly localised protein whereas correctors move misfolded protein up to the cell surface. Professor Jane Davies worked with Vertex Pharmaceuticals, driving a significant clinical trial programme evaluating pipeline drugs: ivacaftor, the first potentiator drug, is highly effective but only suitable for a small proportion of pwCF (5-7%, most having gating mutations); dual combinations tackling F508del with a misfolding corrector and potentiator (suitable for ~45%

pwCF); triple combinations directed at F508del and containing two misfolding correctors and a potentiator (suitable for ~85% pwCF).

In 2009 Davies led the UK arm of the pivotal phase 3 trial of ivacaftor in CF patients (≥12 years) with a gating mutation. This demonstrated very large improvements in lung function, nutrition and quality of life scores as well as reduced exacerbation frequency (1). A subsequent phase 3 trial in 2011, in younger (6-11 years) patients was designed and co-led globally by Davies and Felix Ratjen, Toronto. It demonstrated that ivacaftor significantly improved pulmonary function, body weight, and CFTR activity compared with placebo, thereby paving the way for early intervention. Since then, Davies has been global co-lead of all ivacaftor trials in preschool children and infants. For these age groups, conventional assessment of lung function (measured by spirometry) was not employed as it lacks sensitivity to early disease and is effort-dependent making it difficult for children. However, these trials were the first to show nutritional impact, illustrated by the recovery of exocrine paracrine function (2). The ivacaftor programme has supported European license extensions (marketed as Kalydeco) currently down to 4 months.

Efficacy of ivacaftor provided the foundation for multi-molecule combinations suitable for a much larger proportion of pwCF. The Imperial team trialled dual combinations of lumacaftor or tezacaftor combined with ivacaftor (3,4; combinations marketed as Orkambi and Symkevi respectively). Davies was global co-lead of adult (4) and pivotal, phase 3 paediatric ('EXPAND') trials of tezacaftor/ivacaftor (5). Davies was global co-lead for a phase 2 triple combination study for compound selection (6) and conducted phase 3 trials of the selected compound (elexacaftor/tezacaftor/ivacaftor; ETI; marketed as Kaftrio) at Royal Brompton Hospital. Davies is global lead for current trials of ETI in 6-11 year old children, and is leading an international trial in the youngest age group to date (2-5 year olds). Many of the paediatric trials have depended on a more sensitive lung function measure than FEV_1, Lung Clearance Index (LCI); she established and leads the European Core Facility standardising this procedure.

3. References to the research (indicative maximum of six references)

(1) Ramsey, B.W., Davies, J., McElvaney, N.G., Tullis, E., Bell, S.C., Dřevínek, P., Griese, M., McKone, E.F., Wainwright, C.E., Konstan, M.W., Moss, R., Ratjen, F., Sermet-Gaudelus, I., Rowe, S.M., Dong, Q., Rodriguez, S., Yen, K., Ordoñez, C., Elborn, J.S.; VX08-770-102 Study Group (2011). A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *N Engl J Med*; 365(18): 1663-72. DOI.

(2) Rosenfeld, M., Wainwright, C.E., Higgins, M., Wang, L.T., McKee, C., Campbell, D., Tian, S., Schneider, J., Cunningham, S., Davies, J.C.; ARRIVAL study group. (2018). Ivacaftor treatment of cystic fibrosis in children aged 12 to <24 months and with a CFTR gating mutation (ARRIVAL): a phase 3 single-arm study. *Lancet Respir Med*; 6(7): 545-553. DOI.

(3) Wainwright, C.E., Elborn, J.S., Ramsey, B.W., Marigowda, G., Huang, X., Cipolli, M., Colombo, C., Davies, J.C., De Boeck, K., Flume, P.A., Konstan, M.W., McColley, S.A., McCoy, K., McKone, E.F., Munck, A., Ratjen, F., Rowe, S.M., Waltz, D., Boyle, M.P.; TRAFFIC Study Group; TRANSPORT Study Group. (2015). Lumacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR. *N Engl J Med*; 6;373(3): 220-31. DOI.

(4) Rowe, S.M., Daines, C., Ringshausen, F.C., Kerem, E., Wilson, J., Tullis, E., Nair, N., Simard, C., Han, L., Ingenito, E.P., McKee, C., Lekstrom-Himes, J., Davies, J.C. (2017). Tezacaftor-Ivacaftor in Residual-Function Heterozygotes with Cystic Fibrosis. *N Engl J Med*; 377(21): 2024-2035. DOI.

(5) Davies, J.C., Sermet-Gaudelus, I., Naehrlich, L., Harris, R.S., Campbell, D., Ahluwalia, N., Short, C., Haseltine, E., Panorchan, P., Saunders, C., Owen, C.A., Wainwright, C.E.; VX16-661-115 Investigator Group. (2020). A phase 3, double-blind, parallel-group study to

evaluate the efficacy and safety of tezacaftor in combination with ivacaftor in participants 6 through 11 years of age with cystic fibrosis homozygous for F508del or heterozygous for the F508del-CFTR mutation and a residual function mutation. *J Cyst Fibros*; S1569-1993(20)30811-0. Epub 21 Sept 2020. DOI.

(6) Davies, J.C., Moskowitz, S.M., Brown, C., Horsley, A., Mall, M.A., McKone, E.F., Plant, B.J., Prais, D., Ramsey, B.W., Taylor-Cousar, J.L., Tullis, E., Uluer, A., McKee, C.M., Robertson, S., Shilling, R.A., Simard, C., Van Goor, F., Waltz, D., Xuan, F., Young, T., Rowe, S.M.; VX16-659-101 Study Group. (2018). VX-659-Tezacaftor-Ivacaftor in Patients with Cystic Fibrosis and One or Two Phe508del Alleles. *N Engl J Med*; 379(17): 1599-1611. DOI.

4. Details of the impact (indicative maximum 750 words)

Cystic fibrosis affects almost 11,000 people in the UK and an estimated 100,000 worldwide, and causes excessive airway mucus secretion, early and recurrent bacterial infection and inflammation leading to irreversible lung damage. Furthermore, the majority (>85%) of people experience digestive malfunction leading to poor weight gain and require digestive enzymes to be taken with all food and drink.

Until recently, all treatments for CF were directed at disease symptoms such as airway clearance (physiotherapy and muco-active inhaled drugs), antibiotics, nutritional supplements and treatments for complications such as diabetes and liver disease. During periods of stability, pwCF spend 1-2 hours daily on their treatments. Periods of ill-health frequently necessitate hospital admission (average 14 days) for intravenous antibiotics. Patients also experience acute loss of lung function, painful procedures (e.g. repeated venous access) and consequences of high dose antibiotics (allergies, gastrointestinal disturbance, development of antimicrobial resistance and drug toxicity including kidney damage and deafness). Despite this huge burden of treatment and healthcare costs, CF is progressive and relentless. Lung health is lost progressively and life expectancy severely reduced; even with advances in diagnosis and therapy over the last decades, median age of death in the UK is approximately 30 years. The only option for end-stage lung disease is transplantation, if available, but this is not curative and only has a 50% 5-yr survival.

CFTR modulators restore the defective cellular processes underlying key symptoms, significantly changing the approach to CF management and thus have been genuinely transformative.

Professor Davies' programme provided the critical clinical evidence for licensing the first of these drugs, ivacaftor (Kalydeco), by the European Medicines Agency (EMA) for ≥12 year olds in 2012, and younger children in 2015 [**A**]. Although only suitable for a minority (5-8%) of patients, its impacts have a far wider reach, as they provide evidence of the long-term benefits of CFTR functional restoration. Indeed, 4-5 year observational data collected through national (US and UK) patient registries confirm the acute improvements in lung function [**B**], but also describe slowing the rate of lung function loss; reduction in lung infection; hospitalisation and treatment for exacerbations; optimisation in nutritional health and quality of life scores with reduced frequency of diabetes. These benefits translated into prolonged survival and a reduced need for lung transplantation.

The dual combination Orkambi (lumacaftor/ivacaftor) was approved by the EMA in 2015 (≥12 years old) and in 2017, for patients ≥ 6 years old [**C**]. Findings from the EXPAND trial provided pivotal efficacy evidence that contributed to the approval of Symkevi (tezacaftor/ivacaftor) for 12 year olds in 2018 [**D**]. These dual combinations demonstrate a significant reduction in pulmonary exacerbation and improvements in LCI. Orkambi, Symkevi and Kalydeco were commissioned in England and Northern Ireland (October 2019); Orkambi and Symkevi were made available in Scotland (September 2019) and Wales (November 2019) [**E**].

The triple combination Trikafta/Kaftrio (elexacaftor/tezacaftor/ivacaftor) was approved for pwCF ≥12 years old by the FDA in 2019 and EMA in 2020 [**F**]. NHS England immediately announced availability of the drug to all eligible patients, giving >7,000 patients access to a CFTR modulator, subsequently followed by Wales, Northern Ireland and Scotland [**G**]. Data from the phase 3 trial in 6-11 year olds has been announced, with regulatory approval expected in Q4 2021 [**H**]. Trikafta/Kaftrio leads to greater restoration of CFTR function than ivacaftor in both laboratory and clinical assessments. Trials also demonstrated even greater acute benefits (lung function- FEV_1 increasing by 14%-, admissions to hospital, weight gain). The fact that this combination is suitable for approximately 80-85% of pwCF worldwide who possess 1 or 2 F508del mutations amplifies these impacts substantially.

The major impacts described thus far accrue in patients commencing these drugs as adolescents or adults. There is accumulating evidence that restoring CFTR function in early life, before end-organ damage is irreversible, could be even more impactful. The design of paediatric modulator trials, led globally by Davies, allowed rapid translation of early data from older cohorts in to younger/healthier children. The EMA has recently approved ivacaftor to treat babies as young as 4 months of age, shortly after their diagnosis [**I**].

Furthermore, for the first time, the field of treating CF has witnessed a substantial proportion of children demonstrating restored function of the pancreas, an organ hitherto considered irreversibly destroyed antenatally. For some children, early access to highly effective modulators, may lead to a complete change in the way CF manifests as a disease, with the possibility that life span could approach that of healthy people.

In the UK Kalydeco is available to infants ≥4 months with gating/ residual function mutations (~7-8%), Orkambi to children aged ≥ 2yrs with 2 copies of F508del (~45%), Symkevi to people aged ≥ 6 with 2 copies of F508del (~45%) or residual function mutations (~10%) and Kaftrio to individuals aged ≥ 12 years old with 1 or 2 copies of F508del (80-85%).

5. Sources to corroborate the impact (indicative maximum of 10 references)

[**A**] EMA approval document for Ivacaftor, 2015. https://www.ema.europa.eu/en/documents/variation-report/kalydeco-h-c-2494-x-0034-g-epar-assessment-report-extension_en.pdf (approval on page 60, study numbers VX08-770-102 and VX08-770-103 can be seen on page 13). Archived here.

[**B**] Volkova N, Moy K, Evans J, Campbell D, Tian S, Simard C, Higgins M, Konstan MW, Sawicki GS, Elbert A, Charman SC, Marshall BC, Bilton D. Disease progression in patients with cystic fibrosis treated with ivacaftor: Data from national US and UK registries. J Cyst Fibros. 2020 Jan;19(1):68-79. DOI.

[**C**] EMA Orkambi approval documents:
- Approval for use in patients 12 years and older:
https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-orkambi_en.pdf (approval) Archived here
https://www.ema.europa.eu/en/documents/assessment-report/orkambi-epar-public-assessment-report_en.pdf (evidence pack, see page 36, studies VX12-809-103 and VX12-809-104)
- Approval for use in patients 6 years and older:
https://www.ema.europa.eu/en/documents/smop/chmp-post-authorisation-summary-positive-opinion-orkambi-x-20_en.pdf (approval confirmation) Archived here
https://www.ema.europa.eu/en/documents/variation-report/orkambi-h-c-3954-p46-0091-epar-assessment-report_en.pdf (evidence, studies VX14-809-109 led by Prof Davies)

[**D**] https://www.ema.europa.eu/en/documents/assessment-report/symkevi-epar-public-assessment-report_en.pdf (see page 54 for study VX14-661-108 – included as a pivotal efficacy study). Archived here.

[**E**] UK Health Service Commissioning (Orkambi, Symkevi and Kalydeco):
- NHS England, 24 October 2019 (Archived here)
- Northern Ireland, Department of Health, 29 October 2019 (Archived here)
- Scottish Health Secretary, 12 September 2019 (Archived here)
- NHS Wales, 29 November 2019 (Archived here)

[**F**] https://www.ema.europa.eu/en/medicines/human/EPAR/kaftrio#authorisation-details-section (approval confirmation). Archived here.

[**G**] Health Service Commissioning of Trikafta/Kaftrio:
- NHS England (Archived here)
- NHS Wales (Archived here)
- Northern Ireland (Archived here)
- NHS Scotland (Archived here)

[**H**] https://investors.vrtx.com/news-releases/news-release-details/vertex-announces-positive-phase-3-study-trikaftar (Archived here)

[**I**] https://www.ema.europa.eu/en/documents/smop/chmp-post-authorisation-summary-positive-opinion-kalydeco-ii-86_en.pdf (Archived here)