Professor David Sheppard
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Professor of Physiology

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Summary

The cystic fibrosis transmembrane conductance regulator (CFTR) is a novel member of the ATP-binding cassette (ABC) transporter superfamily that forms an anion channel with complex regulation. CFTR is predominantly located in epithelia lining ducts and tubes throughout the body, although it is also expressed in some non-epithelial tissues, most notably cardiac myocytes. In epithelia, CFTR provides a pathway for the movement of chloride (Cl-) and bicarbonate anions across the apical (lumen-facing) membrane and a key point at which to regulate the rate of transepithelial salt and water transport.

Dysfunction of the CFTR Cl- channel is associated with a wide spectrum of disease. Mutations that, in general, abolish the function of CFTR cause the genetic disease cystic fibrosis (CF), which affects multiple organ systems in the body. By contrast, some forms of male infertility, chronic pancreatitis and bronchiectasis are caused by mutations that probably preserve partial CFTR function. These conditions, termed CFTR-related diseases, affect a single organ system in the body. Increased or inappropriate activity of the CFTR Cl- channel is associated with other diseases, such as secretory diarrhoea and autosomal dominant polycystic kidney disease.

In our studies of the CFTR, we have three specific research goals:

To understand the relationship between the structure and function of the CFTR Cl- channel

To learn how CF-associated mutations cause a loss of CFTR function

To identify new modulators of CFTR that might prove to be of value in the treatment of disease and elucidate their mechanism of action.

Biography

David N. Sheppard is a Reader in Physiology. He investigates the function of CFTR, the protein product of the gene defective in cystic fibrosis (CF). The goal of his research is to develop new drug therapies for CF patients that target the root cause of the disease.

After obtaining a PhD in Cell Physiology from the University of Cambridge with Dr. Francisco V. Sepúlveda, David worked with Prof. Michael J. Welsh at the University of Iowa in the period immediately following the demonstration that CFTR forms an epithelial chloride channel. Returning to the UK, he was a BBSRC Advanced Research Fellow at the University of Edinburgh before becoming a Lecturer at the University of Bristol.

David's work with Michael Welsh explain why some inherited defects in the CFTR gene are linked to a milder form of CF. Unlike other inherited defects in the CFTR gene, these defects form chloride channels that retain some activity. Work by David's own group in Bristol explain how some experimental treatments for CF restore activity to defective chloride channels.

David shared the 2010 ECFS Award for his leadership of the EuroCareCF project. Working with the European CF Society, EuroCareCF developed a European CF Patient Registry, helped establish a European Clinical Trials Network, trained clinicians, healthcare professionals and scientists, distributed resources and developed consensus guidelines for CF research and patient care.

Activities / Findings

- Mechanism of action of CFTR potentiators

- Revertant mutations correct CFTR gating defects
- Intracellular pH regulates directly the CFTR chloride channel

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Teaching

Undergraduate lectures on (i) muscle, (ii) the gastrointestinal tract, (iii) fetal physiology, (iv) cystic fibrosis and CFTR. Postgraduate supervision of PhD students.

Keywords

- CFTR
- chloride ion channel
- ABC transporters
- cystic fibrosis
- epithelia
- channel gating
- channel block
- CFTR potentiators

Skills

- Cystic fibrosis
- CFTR-related diseases
- secretory diarrhoea
- autosomal dominant polycystic kidney disease

Processes and functions

- Ion channel gating and permeation
- epithelial ion transport

Methodologies

- High-resolution single-channel recording
- kinetic analyses of channel gating
- Ussing chamber technique
- iodide efflux technique

Memberships

Organisations

School of Physiology, Pharmacology & Neuroscience

Research Areas

- CFTR modulation in health and disease

Selected publications

- Scott-Ward, TS, Cai, Z, Dawson, ES, Doherty, A, Da Paula, AC, Davidson, H, Porteous, DJ, Wainwright, BJ, Amaral, MD, Sheppard, DN & Boyd, AC, 2007, 'Chimeric constructs endow the human CFTR Cl(-)channel with the gating behavior of murine CFTR'. *Proceedings of the National Academy of Sciences of the United States of America*, vol 104., pp. 16365-16370

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Recent publications

- Liu, T, Bihler, H, Farinha, CM, Awatade, NT, Romão, AM, Mercadante, D, Cheng, Y, Musisi, I, Jantarajit, W, Wang, C, Cai, Z, Amaral, MD, Mense, M & Sheppard, DN, 2018, 'Partial rescue of F508del-cystic fibrosis transmembrane conductance regulator channel gating with modest improvement of protein processing, but not stability, by a dual-acting small molecule'. *British Journal of Pharmacology*, vol 175., pp. 1017-1038
- Wang, C, Cai, Z, Gosling, M & Sheppard, D, 2018, 'Potentiation of the cystic fibrosis transmembrane conductance regulator Cl- channel by ivacaftor is temperature-independent'. *AJP - Lung Cellular and Molecular Physiology*, vol 315., pp. 846-857

- Dias, CM, Li, H, Valkenier, H, Karagiannidis, LE, Gale, PA, Sheppard, DN & Davis, AP, 2018, 'Anion transport by *ortho*-phenylene bis-ureas across cell and vesicle membranes'. *Organic and Biomolecular Chemistry*, vol 16., pp. 1083-1087
- Spooner, M, Li, H, Marques, I, Costa, P, Wu, X, Howe, E, Busschaert, N, Moore, S, Light, ME, Sheppard, D, Félix, V & Gale, PA, 2018, 'Fluorinated synthetic anion carriers: experimental and computational insights into transmembrane chloride transport'. *Chemical Science*.
- Han, ST, Rab, A, Pellicore, MJ, Davis, EF, McCague, AF, Evans, TA, Joynt, AT, Lu, Z, Cai, Z, Raraigh, KS, Hong, JS, Sheppard, DN, Sorscher, EJ & Cutting, GR, 2018, 'Residual function of cystic fibrosis mutants predicts response to small molecule CFTR modulators'. *JCI Insight*, vol 3.
- Li, H, Pesce, E, Sheppard, DN, Singh, AK & Pedemonte, N, 2018, 'Therapeutic approaches to CFTR dysfunction: from discovery to drug development'. *Journal of Cystic Fibrosis*, vol 17., pp. S14-S21
- Noel, S, Sermet-Gaudelus, I & Sheppard, DN, 2018, 'N1303K: Leaving no stone unturned in the search for transformational therapeutics'. *Journal of Cystic Fibrosis*, vol 17., pp. 555-557
- Chen, J-H, Xu, W & Sheppard, D, 2017, 'Altering intracellular pH reveals the kinetic basis of intraburst gating in the CFTR Cl– channel'. *Journal of Physiology*, vol 595., pp. 1059?1076
- Kirchner, S, Cai, Z, Rauscher, R, Kastelic, N, Anding, M, Czech, A, Kleizen, B, Ostegaard, L, Braakman, I, Sheppard, D & Ignatova, Z, 2017, 'Alteration of protein function by a silent polymorphism linked to tRNA abundance'. *PLoS Biology*, vol 15.

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Networks & contacts

- Dr Christopher Boyd - University of Edinburgh
- Dr Stephen Husbands - University of Bath
- Prof Anthony Davies - School of Chemistry (Bristol)
- Dr Terry McMaster - School of Physics (Bristol)
- Prof Margarida Amaral - University of Lisboa - Portugal
- Dr Oscar Moran - Istituto di Biofisica - Genova - Italy