Report on the Activities of the ECFS Cystic Fibrosis Molecular & Cell Biology and Physiology Basic Science Working Group (ECFS Basic Science WG)

Mo18 Report

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1. Goals

The ECFS Basic Science WG (BSWG) was created in October 2014 with the following goals:

1) Widening the number of European scientists doing fundamental research on those areas of CF as ECFS members, in particular to attract, train and maintain younger investigators in the CF field;
2) Disseminating recommendations for best reagents (e.g. cell lines, compounds, antibodies, etc) on ECFS website and promoting best practice procedures;
3) Developing a network (jointly with ECFS-CTN and Registry) for the creation of biobanks of CF patients' materials across Europe for the generation (e.g., primary cultures of epithelial cells, intestinal organoids, etc) and distribution of resources for CF research;
4) Producing consensus guidelines for standardization of research-derived laboratory techniques that can be applied to the clinic (e.g., novel biomarkers to be used in CF diagnosis or as "surrogate endpoints" for clinical trials, etc.)
5) Prioritizing topics related to emergent needs in the field so as to create "task forces" (e.g., on CFTR structure, animal models, high-throughput screens, etc.);
6) Promoting excellence in CF research by fostering European-scale research to avoid effort duplication at national level and fragmentation and to achieve competitiveness for EU consortia
7) Liaising with basic scientists in other societies and patients association to maximize and optimize efforts)

2. Activities

2.1. Second Meeting of the BSWG

The BSWG organized its 2nd meeting which took place on 30 March as a Satellite meeting before the Basic Science Conference in Pisa (Calambrone), Italy, 30 March – 3 April 2016. The purpose of this 2nd meeting was to discuss the contribution of the BSWG to the ECFS "*Task*

Force on Personalised Medicine for CF". The following topics were proposed to be discussed by the participants[1]:

How can Basic science help Personalised Medicine?

1. Validation/ optimization of novel biomarkers
2. Assays for improved endpoints to evaluate novel drugs: cilia beating, ASL height, patch-clamp for nasal cells
    a. Find the hub labs which can do this in different countries as a service
3. Drug discovery in academia: alternative channels

The 2nd meeting of the ECFS BSWG, counted with **35 participants** (see list in Annex 1). These split into 3 discussion subgroups (for topics 1-3) which nominated a 'rapporteur' per group, then discussed for 90 min and finally presented the conclusions (10 min each) focussed on each topic as follows.

1. **Validation and optimization of novel biomarkers Assays for improved endpoints for preclinical evaluation of novel drugs** (Rapporteur – Kris de Boeck)

The pipeline of CFTR modulators to improve CFTR function in patients with cystic fibrosis (CF) is growing. At present, more than 2000 different CFTR mutations have been reported in the CFTR gene. Both aspects underpin the need for novel biomarkers of CFTR function in patients with CF. To facilitate personalized medicine, especially in patients with rare CFTR mutations, these biomarkers must reliably quantify CFTR function and how this can be augmented by CFTR modulators. This subgroup considered that for personalized *ex vivo* drug testing intestinal organoids and nasal cells are most promising).

2. **Assays for improved endpoints for preclinical evaluation of novel drugs** (Rapporteur – Marcus Mall)

While high-throughput drug discovery approaches have led to the development of ivacaftor (VX-770) as the first clinical CFTR modulator with substantial clinical benefits in patients with G551D and some other CFTR gating mutations, they has also resulted in an apparent efficacy ceiling in the rescue of other CFTR mutations including the most common mutation F508del. Therefore, additional endpoints are required for preclinical evaluation that capture response to novel drugs beyond CFTR chloride (Cl^-) channel function. Thus, preclinical endpoints should include functional restoration of airway surface liquid (ASL) depth, mucus concentration (% solids or partial osmotic pressure), ciliary beat frequency (CBF) and mucociliary transport (MCT). The discussion of this subgroup also focussed on how to extend assays to other endpoints, like CFTR-mediated bicarbonate transport, as well to others so as to account for the roles played in CF pathogenesis by: submucosal glands, genetic and/or environmental modifiers, inflammatory response, bacterial infections, etc.

[1] The topic of Biobanks was discussed in a subsequent session organized by the National Patients Organizations, and thus it was not included in this meeting's discussions.

3. **Alternative channels and other complementary approaches to CFTR mutation-specific modulators** (Rapporteur – Jeff Beekman)

The efficacy of current CFTR modulators remains limited for the majority of patients with CF, indicating the need for mutation-independent therapeutic approaches to restore ion transport of CF epithelia. The discussion focused on other alternative channels that may bypass CFTR-dependent defects in Cl^- and bicarbonate secretion, and how we can move forward to further validate alternative channels as drug targets for CF. We further discussed potential therapeutic implications of CRISPR-Cas9 CFTR gene editing

The BSWG considers that this will be a useful contribution to keep the discussion going and kick-off for the ECFS task force on this important topic. Therefore, the full conclusions of these discussion groups are soon to be published as a meeting report in *Journal of Cystic Fibrosis*.

In addition, the working group will host a symposium on topics pertinent to Personalized Medicine for CF at next year's Basic Science Conference. This symposium will include basic and clinical scientists working on innovative research in the translational arena with the aim to foster the discussion on how findings from basic research can be translated more rapidly into effective targeted therapies for a larger proportion of patients with CF.

2.2. BSWG Workshop

The BSWG will organize a 'hands-on' Workshop on "*Epithelial Systems: Physiology and Pathophysiology*" which will take place at the Faculty of Sciences of the University of Lisboa (FCUL), Portugal, between 18 – 22 July 2016.

This workshop (open to 12 participants) aims to elucidate researchers from the CF community on the theoretical aspects of basic CF science, as well as provide practical training in the new techniques underlying current and novel biomarkers based on CFTR activity and other molecular and cell biology parameters.

The Workshop was already widely disseminated at the ECFS Basic Science Conference (posters and slides between sessions), by direct mailing to ECFS CTN centres and members of the Newborn Screen WG. It is also disseminated via the ECFS webpage[2].

It counts with the support of National Patients Organizations from Belgium, Germany, Italy and The Netherlands, in the form of travel grants for participants from the respective countries.

See poster and programme of the 2016 BSWG Workshop in Annex 2.

[2] https://www.ecfs.eu/sites/default/files/images/BSWG_0.pdf

Annex 1 – List of Participants at the 2nd BSWG meeting (30 March 2016)

The 2nd meeting of the ECFS BSWG, counted with **35 participants**, of which 21 are full BSWG members (ECFS/BSWG membership to be confirmed by email):

Name	Institution, City, Country
Group 1 – Biomaker Validation (8)	
Kris de Boeck	University Hospital Gasthuisberg Leuven, Belgium
Luigi Maiuri	European Institute for Research in Cystic Fibrosis, Milan, Italy
Vincent Gulmans	Dutch Cystic Fibrosis Foundation (NCFS), Baarn, Netherlands
Bill Skach	Cystic Fibrosis Foundation, Bethesda, MD, United States
Preston Campbell	US CF Foundation, Bethesda, MD, United States
Virginia de Rose	University of Torino, Orbassano, Torino, Italy
Paola Melotti	Azienda Ospedaliera Universitaria Integrata di Verona, Italy
Anna Baruzzi	University of Verona, Verona, Italy
Group 2 – Assays for improved endpoints (11)	
Marcus Mall	University Children's Hospital, Heidelberg, Germany
Sabrina Nöel	Université Catholique de Louvain, Brussels, Belgium
Kirsten Look	Nivalis Therapeutics, Boulder, United States
Paola Vergani	University College London, London, United Kingdom
David Sheppard*	University of Bristol, United Kingdom
Aurelié Crabbé	Ghent University, Ghent, Belgium
Lionel Froux*	University of Poitiers, France
Khadidja Sidelarbi*	University of Poitiers, France
Claudio Sorio	General Pathology Section, Verona, Italy
Carlos Farinha	Faculty of Sciences, University of Lisboa, Portugal
Hugo de Jonge	Erasmus University Medical Center, Rotterdam, Netherlands
Group 3 – Drug Discovery in Academia (16)	
Jeffrey Beekman	University Medical Center Utrecht, Utrecht, Netherlands
Margarida Amaral	Faculty of Sciences, University of Lisboa, Portugal
John Hanrahan	McGill University, Montreal, Canada
Frederic Becq*	University of Poitiers, France
Mike Gray	Newcastle University, Newcastle upon Tyne, UK
Clarisse Vandebrouck*	University of Poitiers, France
Caroline Norez*	University of Poitiers, France
Guy Moss*	University College London
Ines Pankonien*	Faculty of Sciences, University of Lisboa, Portugal
Janet Allen*	CF Trust, London, United Kingdom
Marija Zecevic*	Zebra Ventures
Alessandra Ghigo	University of Torino, Torino, Italy
Veronique Marguerite-Heissat	Vaincre La Mucoviscidose, Paris, France
Johanna Salomon	University of Heidelberg, Heidelberg, Germany
Stephen Hart	University College London, London, United Kingdom
Michele Samaja	University of Milan

*Participants who attended the meeting who did not pre-enrol

Pre-enrolled who did not participate (7)	
Name	**Institution, City, Country**
Bill Balch	The Scripps Research Institute, La Jolla, United States
Onofrio Laselva	University of Bari, Bari, Italy
Jacquelien, Noordhoek	NCFS, Baarn, Netherlands
Ruth Olmer	MHH, Hannover, Germany
Anna Semaniakou	Dalhousie University, Halifax, Canada
Rob Tarran	University of North Carolina, Chapel Hill, NC, United States
Jean Tyrrell	Royal College of Surgeons in Ireland, Dublin, Ireland

Annex 2 – Poster and Programme of the 2016 BSWG Workshop