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Invited Review

Cystic fibrosis research topics featured at the 14th ECFS Basic Science Conference: Chairman's summary

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Abstract

In recent years, tremendous progress has been made in the development of novel drugs targeting the basic defect in patients with cystic fibrosis (CF). This breakthrough is based on a solid foundation of knowledge on CFTR's function in health and how mutations in CFTR cause CF multi-organ disease. This knowledge has been collected and continuously expanded by an active and persistent CF research community and has paved the way for precision medicine for CF. Since 2004, the European Cystic Fibrosis Society (ECFS) has held an annual Basic Science Conference that has evolved as an international forum for interdisciplinary discussion of hot topics and unsolved questions related to CF research. This Special Issue reviews CF research topics featured at the 14th ECFS Basic Science Conference and provides an up-to-date overview of recent progress in our understanding of CFTR structure and function, disease mechanisms implicated in airway mucus plugging, inflammation and abnormal host-pathogen interactions, and advancements with enhanced cell and animal model systems and breakthrough therapies directed at mutant CFTR or alternative targets. In addition, this Special Issue also identifies a number of fundamental questions and hurdles that still have to be overcome to realize the full potential of precision medicine and develop transformative therapies for all patients with CF.

Keywords: Cystic fibrosis; CFTR; Basic research; Novel therapies; Precision medicine

1. Introduction

Over the past decade, tremendous progress has been made in the development of novel drugs targeting the basic defect in patients with cystic fibrosis (CF) [1–3]. In a subgroup of patients with specific mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, such as the *G551D* gating mutation, treatment with CFTR modulators has already been transformative providing an important proof-of-concept and, for the first time, raising realistic hope that effective targeted therapies may become available for most patients with CF in the foreseeable future [4,5]. The recent breakthrough in the development of therapeutic agents targeting mutant CFTR is based on a solid and still growing foundation of knowledge on CFTR's function in health and how mutations in CFTR cause chronic disease of the lungs and many other epithelial organs [6–8]. Indeed, CFTR probably belongs to the most broadly investigated proteins and this unique knowledge base has been created by a highly dedicated community of scientists from a wide range of disciplines including physiology, genetics, molecular biology, biochemistry, pharmacology, immunology, microbiology and beyond. This research community is dedicated to understand CF disease mechanisms from the molecular to the whole organ level working towards the development of effective therapies for all

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patients with CF. Regular exchange and discussion of emerging data and new ideas among scientists with expertise in these different areas is a key element driving progress towards this common goal.

2. The ECFS Basic Science Conference

Since 2004, the European Cystic Fibrosis Society (ECFS) has held an annual Basic Science Conference to provide a forum for interdisciplinary discussion to foster basic CF-related research in Europe and beyond. The conference program features single session symposia covering topics of 1) CFTR genetics, structure, folding, trafficking and function; 2) cell biology and ion transport physiology; 3) novel therapeutic approaches; 4) CF model systems; 5) mucins & mucus; 6) inflammation; 7) infection and host-pathogen interactions; and, more recently, 8) translational CF research. Each symposium is composed of invited presentations by renowned experts in the respective field, as well as oral presentations by young investigators selected by blinded peer review from abstracts submitted to the conference. This single session format, together with selected plenary lectures on hot topics, interactive poster sessions, special interest group discussions and pro-con debates regularly included in the program has stimulated discussion and led to new ideas and collaborations across the field of CF research. With a limit of ~200 attendants in a retreat-like environment, the ECFS Basic Science Conference has also fostered informal discussion between young scientists and senior investigators that plays a vital role in the establishment of new mentorships and training opportunities for the next generation of CF researchers.

The purpose of this Special Issue is to make the CF research discussed at the 14th ECFS Basic Science Conference, held in Albufeira, Portugal, 29 March to 1 April 2017, accessible to the broader CF community and beyond. Therefore, the speakers of each symposium were invited to jointly write a concise review article on the topic of their symposium with a focus on current developments of the field including the content of their presentations, open questions and future research directions. Together, the articles authored by renowned experts in the field collated in this Special Issue provide succinct summary on the core content of the conference and an up-to-date orientation on recent highlights and breakthroughs in basic and translational CF research.

3. CFTR structure and function

One of the major recent highlights in basic CF research was the solution of the 3D structure of full length CFTR by cryo-electron microscopy (cryo-EM) [9,10]. The article by Callebaut and colleagues reviews this breakthrough and provides a perspective on the importance of these data for our understanding of normal CFTR channel gating, the impact of specific mutations on CFTR structure and function, as well as potential opportunities for structure-based drug design and optimization [11]. Next, Farinha and colleagues summarize recent findings on interactions of CFTR with other proteins and lipids that are implicated in modulating the biogenesis, exit from the endoplasmic reticulum, trafficking, stability and anion channel activity of wild-type and mutant CFTR, and discuss how these interactions may be targeted to improve therapeutic rescue of CF-causing mutants [12].

4. Ion transport and novel therapies

The key topic of novel CFTR-directed therapies is further developed by Li and colleagues. Their article provides an up-to-date summary on triple combination therapies combining a CFTR potentiator with two CFTR correctors for simultaneous targeting of multiple defects in F508del-CFTR folding and assembly to break the efficacy ceiling that has been associated with combination therapies containing one CFTR corrector only [13–15]. Further, this article provides a perspective on how proteostasis modulators may be explored as therapeutic targets to enhance plasma membrane expression of F508del-CFTR [13], and how artificial anion transporters may be utilized to bypass CFTR dysfunction, especially in patients carrying *CFTR* genotypes that are not responsive to CFTR-directed approaches [13]. In addition to CFTR, the epithelial Na^+ channel (ENaC) and alternative Cl^- channels have long been implicated as alternative targets to compensate for CFTR dysfunction and improve surface hydration in the airways [5]. The article by Martin and colleagues reviews recent developments in this area with a focus on novel strategies that reduce ENaC activity with compounds that inhibit channel activation by proteolytic cleavage and/or by promoting retrieval from the plasma membrane [16]. Further, this article explores recent experimental data on the alternative Cl^- channels TMEM16A and SLC26A9, as well as the H^+/K^+-ATPase ATP12A as targets that may be incorporated in a multi-tracked strategy to improve hydration and pH regulation critical for efficient mucociliary transport and bacterial killing on airway surfaces independent of CFTR mutation [16,17].

5. Model systems

CF research has benefitted enormously from animal models and cell based model systems that have been instrumental for advances in our understanding of CF disease pathogenesis from the single cell to whole organism level [18–24]. Rosen and colleagues review the latest lessons learnt on CF-related multi-organ disease from animal models including recent data from the CF ferret providing novel insights into the pathogenesis of early pancreatic disease and CF-related diabetes mellitus (CFRD) [25]. In addition, this article presents recent advances in genome editing using the CRISPR/Cas9 and alternative systems for a broad spectrum of applications highly relevant for CF research [26]. These range from expression of CFTR in primary airway epithelial cell, intestinal organoids or induced pluripotent stem cell (iPS)-derived airway models for drug screening to genetic editing of somatic cells of patients with CF for cell or gene therapy approaches [25].

6. Mucins & mucus

Highly viscous mucus that plugs airways, causes airflow obstruction and forms a nidus for bacterial infection and inflammation is a hallmark of CF lung disease [27]. Yet, our understanding of the relative roles of factor that contribute to the formation of abnormal mucus in CF airways, including abnormal CFTR-dependent secretion of Cl^-, bicarbonate and fluid in submucosal glands and increased ENaC-mediated absorption of Na^+ and fluid from airway surfaces, remains limited [28–34]. Wine and colleagues summarize current progress in this challenging area with a focus on defects in submucosal glands and how these may affect the function of gland-derived mucus strands and their contribution to mucociliary clearance (MCC) on the airway surface [35]. In addition, this article introduces a modified high resolution optical coherence tomography (OCT) technique [36] that enables measurements of mucus transport in vivo and may thus be useful for preclinical to clinical development and evaluation of strategies designed to improve clearance of abnormal mucus in CF [35].

7. Inflammation, infection and host-pathogen interaction

Chronic non-resolving inflammation, abnormal host-pathogen interaction and chronic bacterial infection remain key issues for lung disease severity and progression in patients with CF [37–39]. In this arena, the article of Bragonzi and colleagues explores emerging data on novel aspects of dysregulation of innate host defenses that imply a role of bioactive lipids and the cysteine protease cathepsin S in the pathogenesis and as potential biomarkers of early inflammation in CF lung disease [40]. Further, this article introduces a novel approach utilizing collaborative cross (CC) mice that mimic the genetic diversity of the human population [41] to identify modifiers of host-pathogen interaction and susceptibility to chronic airway infection with *Pseudomonas aeruginosa* [40].

8. Translational research

With the tremendous progress made over the past decade, especially in the area of CFTR-directed therapeutics, translational research has emerged as an important discipline to forward basic research findings to the clinical arena. The article by Hagemeijer and colleagues presents several hot topics related to an overarching strategy for the development of efficient personalized therapies for all patients with CF (REF to be added when paper is online). Their article reviews the current state-of-the-art of using intestinal organoids for biomarker assays to determine individual responses to different CFTR modulators and modulator combinations, as well as recent insights into genetic modifiers of CFTR modulator efficacy [42,44]. In addition, novel CFTR mutation-specific approaches such as non-viral CRISPR/Cas9-mediated gene editing using nanoparticle delivery and the use of modified t-RNAs as a novel approach for nonsense mutations are discussed [44]. The CFTR biomarker assays in intestinal organoids can now be complemented by approaches using conditionally reprogrammed human nasal or bronchial airway epithelial cells [23,43]. As presented in the article by Cholon and Gentzsch, these conditionally reprogrammed airway cells can be easily obtained by nasal or bronchial brushings from patients with specific CFTR genotypes [45]. These cells retain most of the properties of primary airway cells and can be used for planar cultures as well as spheroids (naso- and bronchospheres) to measure fluid transport, viscoelastic properties of mucus and patient-specific drug responses in the context of the airway cell environment. These approaches outlined by Hagemeijer et al. and Cholon and Gentzsch [44,45] will likely be instrumental in realizing the potential of a new era of precision medicine for a growing number of patients with CF.

9. Conclusions

Collectively, the concise reviews of the topics of the symposia held at the 14th ECFS Basic Science Conference collated in this Special Issue provide an up-to-date overview of the most important recent advances in basic and translational CF research that have opened a bright perspective for precision medicine for CF. However, the articles also highlight a number of fundamental unanswered questions and significant hurdles that still have to be tackled by an active CF research community to translate the proof-of-concept data obtained over the past years to transformative therapies for all patients with CF.

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Conflict of interest

T.C. Hwang has a sponsored research and service agreement with AbbVie. The rest of the authors declare that they have no relevant conflicts of interest related to this work.

Author contributions

M.A.M drafted the manuscript. All authors revised the text critically for important intellectual content and approved the final version of the manuscript.

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