Speaker Disclosures

Patrick Flume, MD

Grants and/or Consulting
Bayer, Corbus, Cystic Fibrosis Foundation Therapeutics, Gilead, Hill-Rom Services, Insmed, Nivalis, National Institutes of Health, Novartis, Pharmaxis, Pro-QR, Proteostasis, Raptor, Savara, Vertex

Kris De Boeck, MD, PhD

Grants and/or Consulting
Ablynx, Aptalis, Bayer, Boehringer, Chiesi, Galapagos/Abbvie, Gilead, Pharmaxis, PTC, ProQr, Protalix, Raptor, Vertex
Welcome to Plenary 2
Clinical Research: A Worldwide CF Community Effort
Michael P. Boyle, M.D.
Senior Vice President of Therapeutics Development
Preston W. Campbell, III, M.D.
President and Chief Executive Officer
The Carolyn and C. Richard Mattingly Leadership in Mental Health Care Award

In recognition of leadership and a commitment to the mental health and well-being of individuals with cystic fibrosis.
The Carolyn and C. Richard Mattingly Leadership in Mental Health Care Award

Alexandra L. Quittner, Ph.D.
University of Miami
Michael P. Boyle, M.D.
Senior Vice President of Therapeutics Development
Clinical Research: A Worldwide CF Community Effort

Patrick Flume, M.D.
Medical University of South Carolina

Kris De Boeck, M.D., Ph.D.
University of Leuven, Belgium

#NACFC
Clinical Research: A Worldwide CF Community Effort
A brief historical perspective

• 1989: CF gene is discovered
• 1990: I start my pulmonary/critical care fellowship at UNC
• 1993: Ron Crystal gave plenary on future of gene therapy
The moon may still seem far away
but we have never been so close
Cystic Fibrosis lung disease – pathogenesis and targets for therapy

Gene mutations

↓ CFTR quantity

↓ CFTR function

Abnormal ASL

Impaired MCC

Obstruction

Infection

Inflammation

Progressive, irreversible lung damage

Respiratory failure

New treatments address underlying CF defect
More specific, targeted

Current treatments address downstream complications of CF defect

Gene mutations

↓ CFTR quantity

↓ CFTR function

Abnormal ASL

Impaired MCC

Obstruction

Infection

Inflammation

Progressive, irreversible lung damage

Respiratory failure
Cystic Fibrosis lung disease - pathogenesis and targets for therapy -

New treatments address underlying CF defect
More specific, targeted

Gene mutations

↓ CFTR quantity

↓ CFTR function

↓ CFTR activity
Sweat chloride and clinical presentation

![Graph showing Sweat Chloride Concentration (mM) with not CF and CF indicated]

- Sweat chloride concentration is measured in millimoles per liter (mM).
- Values below 60 mM are considered not CF, while values above 60 mM are considered CF.

Sweat chloride concentration helps in diagnosing cystic fibrosis (CF).
Sweat chloride and CFTR activity

Relative CFTR Activity (% of wild type)

Sweat Chloride Concentration (mM)

not CF

CF
CFTR activity and CFTR mutation

Relative CFTR Activity (% of wild type)

not CF

CF

F508del/F508del  gating nonsense  other  1 or 2 mild mutations
Approaches to increasing CFTR activity

- **Increase the opening time of CFTR protein resulting in greater ion flow**
  - Potentiators

- **Prolong presence of CFTR protein**
  - GSNOR inhibitors

- **Facilitate processing and trafficking of CFTR protein**
  - Correctors
  - Next-generation correctors

- **Increase the amount of immature CFTR protein**
  - Gene therapy
  - DNA editing
  - mRNA editing
  - Read-through premature stop codons
  - Amplifiers (increased translation)

*Figure adapted from Po-Shun Lee (Proteostasis)*
Why should we feel we are any closer?

The success of ivacaftor in G551D patients

Ramsey et al., NEJM 2011; 365: 1663-1672
The success of ivacaftor in G551D patients

Ramsey et al., NEJM 2011; 365: 1663-1672
Targeting CFTR gating mutations

ivacaftor

Relative CFTR Activity (% of wild type)

not CF

CF

F508del/F508del

gating nonsense

other

1 or 2 mild mutations
Prolonged benefit of ivacaftor

Sawicki et al., Am J Respir Crit Care Med 2015; 192: 836-842
Targeting F508del/F508del

- ivacaftor
- G551D
- Lumacaftor/ivacaftor

Interim PROSPECT study data
F508del/F508del

Sweat Chloride Concentration (mM)

Time (Weeks)

not CF

CF

Steve Rowe
Workshop 18
Friday 3:20 PM
Targeting F508del/F508del

lumacaftor/ivacaftor

Relative CFTR Activity (% of wild type)

not CF

CF

F508del/F508del

gating

nonsense

other

1 or 2 mild mutations
Long-term lumacaftor/ivacaftor benefit in F508del homozygotes

Presented by Mike Konstan at Workshop 07 and Poster #180
Long-term lumacaftor/ivacaftor benefit in F508del homozygotes

Presented by Mike Konstan at Workshop 07 and Poster #180
Emerging (next-generation) F508del corrector molecules

Relative CFTR Restoration

- G551D ivacaftor
- F508del/F508del
- F508del/other
- F508del/F508del
- F508del/other

Presented by Eric Sorscher, Plenary 1
Success with F508del heterozygotes will have broad effect

~80% are F508del heterozygotes
Opportunities for improvement in targeted therapy

- We want drugs with greater benefits
  - Even greater impact on CFTR activity
  - Greater effect on other organs (e.g. sinuses)

- We want to treat all patients
  - Need to address other mutations

- We want to treat patients earlier in stage of disease
  - Younger patients
  - Milder lung disease (perhaps even apparently normal)
Expanding access to younger patients
Expanding access to younger patients
Expanding access to all
The moon shot
Modulator pipeline is diversified and very robust

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<th>Phase 3</th>
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Don’t forget the downstream improvements as well

mutant CFTR

abnormal secretion

defective mucociliary clearance

infection

inflammation

altered inflammatory response

NVP-QBE170

VX-371

oligoG

SPX-101

PRX-110

NVP-QBE170

fosfomycin/tobramycin

dry powder vancomycin

inhaled NO

gallium

JBT-101

CTX-4420

GS-5745

LAU-7B

STOP
WOW
Time for a reality check

- We have a lot of studies ongoing and about to start
- This will require recruitment of a large number of subjects
A little more perspective

Historical participation from TDN sites will not predict sufficient enrollment in upcoming trials

Spinal Tap
Seems to be an enormous hurdle

How do we get this done?
Teamwork
Basic scientists

– They made the discovery of the pathways and the potential drugs
– They have done the preliminary work to support human trials
Clinical research teams

– Clinical investigators and research coordinators/staff
  • Help with study design and feasibility
  • Recruitment and implementation of the trials

– Includes regulatory staff
  • IRBs
  • Grants and contracts
Clinical care teams

– Consists of local teams (those at same sites as research teams)
  • Participate in recruitment of subjects
  • Interact with the research teams to optimize clinical care
– Consists of other teams not participating in those trials
  • Referring eligible patients for participation
Patients and Families

– Remember: no subjects, no data, no answer
– We owe tremendous gratitude to all persons who have ever participated in a clinical trial

But wait: could there be a benefit of participating in clinical trials?
Participation in a Clinical Trial Enhances Adherence

• Reported adherence in CF trials
  – Tobramycin inhalation solution (88-93%)\(^1\)
    • Used at least 75% of ampules
  – Ivacaftor (89-91%)\(^2\)
    • Total dose counted

• Adherence to non-trial-related treatments also tend to increase\(^3\)
  – Medication refills increased during trial but then decreased back to baseline afterwards

• Idea for QI project to improve adherence: enroll in trials?

Therapeutic Development Network

– Coordinating center
  • Help with study design and feasibility
  • Manage trials

– Work of TDN committees:
  • Prioritization of trials (PRC)
  • Dissemination of results
    (publication committee)
Cystic Fibrosis Foundation

- Support of the TDN
- ARC awards
- Website

![Clinical Trial Finder](image-url)
Regulatory Agencies

– perform final review and determination of whether to approve
– establish guidance on requirements of studies
– contribute to key study design questions
Industry

– Access to massive resources
  • Capital
  • Technical Expertise
    – Discovery
    – Manufacturing
    – Preclinical and clinical development

– Requirements for regulatory approval bring rigor to commercial clinical trials
There will be some stumbles

- Not all of these compounds will make it to market
  - Lack of efficacy
  - Adverse events
- Only failure is incomplete enrollment
  - Then we do not answer the question
Our goal is not to get one person on the moon…

Our goal is to get EVERYONE on the moon… for the rest of their lives!
Our goal is not to get one person on the moon...

Our goal is to get EVERYONE on the moon...

for the rest of their lives!
And what about CF research in Europe and Oceania?
Cystic fibrosis registries: Australia and New Zealand

<table>
<thead>
<tr>
<th></th>
<th>Australia</th>
<th>New Zealand</th>
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<tbody>
<tr>
<td>Patients</td>
<td>3294</td>
<td>423</td>
</tr>
<tr>
<td>Care Centres</td>
<td>23</td>
<td>12</td>
</tr>
<tr>
<td>Adult Patients</td>
<td>51,1% (&gt;18 yrs)</td>
<td>50,6% (&gt;16 yrs)</td>
</tr>
<tr>
<td>Different CFTR mutations</td>
<td>337</td>
<td>100</td>
</tr>
</tbody>
</table>
Cystic Fibrosis Australia wants to boost clinical trials

Information, access, building capacity

- Website CF LIVES MATTERS clinical trial info and education
- Social media platforms – Newsletters, research road shows, community consultation – CF CAN, CFA’s new advocacy network – Collaboration with other non-profits (mental health, diabetes, ..)
- Discuss via ‘Consumer connect’ – Digital meeting place to support trial education and information
- Clinician’s forum – Meet and increase number of clinical trial facilities

In close collaboration and with support from CFF

Courtesy Nettie Burke, CEO of CFA
Research focus: The young child with CF
Talamo award winners

**COMBAT CF:**
Can azithromycin started from infancy prevent bronchiectasis?
– 128/130 infants recruited
– Results expected 2020

**CF IDEA**
Can insulin started in ‘prediabetic’ stage improve weight and lung function?
– Open label insulin detemir QD 12 months
– 73/100 patients recruited
– Results ≥2017
The European Cystic Fibrosis Society Patient Registry
The European Cystic Fibrosis Society Patient Registry

30 countries
38,985 patients
1,300 different CFTR mutations

ECFSPR Annual Report 2013
European CF Society-Clinical Trials Network (CTN)

- 15 countries
- 43 sites
- 17,500 patients
How did ECFS-CTN become successful so quickly?

• ‘Copying’ the TDN model
• Working together and sharing responsibilities
• A superb administrative core team
• Staying in close collaboration with CFF-TDN
  – Thank you BB, PC, MB, GRB, BR, ...
  ... and the ENTIRE TDN team
• Support from CF Europe
What is success in the CTN?

- Producing high-quality data via
  - training
  - standardization
- Finishing trials on target
  - working hard in 38 studies
- Inclusion of 499 children and 958 adults
  - 1457 total subjects
- Empowering patients and parents
  - clinical trial review
  - young patient groups
  - room for PI-initiated trials

We have worked with 30 different commercial and 4 different academic sponsors

Abbott, Abbvie, Algipharma, Anthera, Aptalis, Bayer, Boehringer Ingelheim, Cellectasys, Chiesi, Concert, Corbus, CSL Behring, Eurand/CROM, Flatley, Forest, Galapagos, Gilead, Grifols, GSK, Insmed/Transave, Inspire, MPEX, Novartis, Pharmaxis, Polyphor, ProQR Therapeutics, Proteostasis, PTC, Savara, Vertex, CHU Brest, German MI, University Hospitals Bristol, University Hospital Wurzburg
Trials with selected EU sponsors

**Algipharma:**
- Can inhaled Oligo G (TID 28d) improve lung function in adults with chronic *Pa* infection?
  - 56 patients completed the trial

**Galapagos: CFTR potentiator GLPG 1835**
- 4wk open-label increasing doses to assess safety and effect on sweat chloride
  - In class III mutation S1251N (Poster 253) PI K De Boeck
  - In class III mutation G551D PI J Davies
What is the further ambition of ECFS-CTN?

• Build capacity
  – With help of PI’s and patients...
  – New recruitments of research coordinators via major financial support from CFF

• Partner with CF Europe towards a common research agenda
  – Start EU-wide Investigator-Initiated clinical trials

• Hear the patients’ voices: it is their future
Our dream is to help every single person with CF

• 1300 different *CFTR* mutations are in the ECFSPR

• A growing pipeline of compounds attacking the basic defect:
  – correctors, potentiators, stop codon read-through, CFTR stabilizers, CFTR amplifier, mRNA correction, gene therapy, gene editing...

• Precision medicine: which treatment can help me with my ‘rare genotype’?
  – And later?? ... which is best for my F508del/F508del?

• Organoids: a biomarker that can predict treatment response
  – Dekkers 2016 Sci Transl Med
KDB4 will ask one of my team to send short video clip
Kris De Boeck, 10/7/2016
Organoids grown from rectum suction biopsies

Non-CF | F508del/S1251N | F508del/S1251N + ivacaftor

Anabela Ramalho, CF reference Centre, KU Leuven, SCIL Lab Belgium
Treating patients with rare mutations

- **Standardize organoid technology**
  - Start small and roll out over EU and beyond

- **Involve**
  - Patients and patient organisations
    - Do you know your mutations?
    - Which treatment improves CFTR function in your organoids?
  - Regulators
    - Find the path to drug licensing
    - Standardized clinical trials in patients responsive in organoids
    - Build further on *ex vivo-* *in vivo* correlations
      - Dekkers 2016 Sci Transl Med
  - Pharma companies
    - Find the best treatment combination for every patient
Other important trials

CFMATTERS
– Does lung function recover better after microbiome-determined antibiotic therapy than after standard empiric antibiotic *Pa* therapy?
  • 166/252 pts recruited

ACTIVATE CF
– Does 3h of intense exercise/wk during 1 year improve FEV₁?
  • 116/292 pts recruited
A sample from the research agenda in UK

TORPEDO
– Is IV therapy for *Pa* eradication superior to oral plus inhaled?
  • 274/285 patients recruited

CF START
– Does oral anti-*S aureus* prophylaxis from infancy speed up *Pa* acquisition?
  • UK Registry study, start Aug 2016, end 2026

UK GENE THERAPY CONSORTIUM
– ‘Wave 2’ vector F/HN-pseudotyped lentivirus
The UK CF TRUST clinical trial accelerator program

• Increase capacity for clinical trials
• Bring equity of access to clinical trials
• A UK network of clinical trial coordinators
• Better use of the CF registry
• Information and involvement of people with CF

‘When Formula 1 teams like McLaren or Ferrari design and test a new car, they need lots of input from their drivers. When it comes to designing and testing new CF treatments, we are the drivers and we need to speak up.’

-Oli Rayner
America, Australia, Europe and beyond

- We need all parties on board
  - Patients who embrace research as their ticket to the future
  - Patients who voice their priorities for research

- Growing research networks
America, Oceania, Europe and beyond

- Global participation to advance as fast as possible
maybe on this slide patient pictures can fly in ... as stars left and then right..

since they are the 'stars' in this entire endeavour..

or is this too melodramatic
America, Oceania, Europe and beyond

- Global participation to advance as fast as possible
Acknowledgements

- ECFS-CTN and ECFSPR
- CF Europe, UK CF TRUST, CF AUSTRALIA
- CFF and CFF-TDN
- PI’s who shared information on their trial/program
- Patients who so enthusiastically sent pictures
- Anabela Ramalho, Leuven SCIL
- Dutch VanDevanter

- SORRY if your study or picture was not selected in this presentation...
FOR PLACEMENT ONLY
Go to the live video of the three remote participants

#NACFC