Personalized medicine for cystic fibrosis

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Disclosures

• Investigator in clinical trials (Vertex, PTC Therapeutics, Galapagos, PRO-QR)
• Unrestricted speakers fee and Advisory board from Vertex
• Travel grants and sponsoring for medical congresses from Bayer, Mylan, Abbott
Personalized medicine for cystic fibrosis

• CF: disease and genetics

• Trials of ‘mutation specific’ treatments for CF

• Future pathways to personalized medicine for CF
Cystic fibrosis is a rare disease
Cystic fibrosis is a recessive monogenic disease

- **CFTR** gene coding for a chloride channel: the Cystic Fibrosis Transmembrane Conductance Regulator
- Chromosome 7q31
- 2000 mutations reported
- F508del is very frequent, a few are rare, most are very rare
CFTR is a chloride channel
Cystic Fibrosis is a multisystem disease

- Progressive lung disease
  - Respiratory insufficiency
- Pancreatic insufficiency
  - Fat malabsorption
  - Wasting
- High sweat chloride
  - Diagnostic test
- Intestinal obstruction
- Diabetes
- Liver disease
Pathophysiology of lung disease in CF

1. **CFTR mutation**
2. **Abnormal CFTR protein**
3. **Abnormal salt and water transport**
4. **Altered dehydrated mucus**
5. **Airway obstruction**
6. **Infection**
7. **Inflammation and lung damage**
8. **Respiratory insufficiency**
9. **Thick secretions**
10. **Enzymes DNA**
Evolution vary between patients
Treatment for cystic fibrosis is (was) mainly symptom directed

- **CFTR mutation**
  - Abnormal CFTR protein
  - Abnormal salt and water transport
    - Thick secretions
      - Enzymes
        - DNA
          - Hypertonic saline
      - Salt transport modulators
    - Altered dehydrated mucus
      - Airway obstruction
        - Infection
          - Inflammation
            - Respiratory insufficiency
              - Lung transplantation
              - Hypertonic saline
              - Recombinant human DNAse
              - Chest physio
              - Bronchodil
              - Anti-inflammatory
              - Antibiotics
            - Inflammation and lung damage
              - Altered dehydrated mucus
              - Airway obstruction
              - Infection
            - Thick secretions
              - Enzymes
                - DNA
    - Hypertonic saline, mannitol
    - CFTR modulators
    - Gene therapy
    - mRNA therapy

Treatment for cystic fibrosis is (was) mainly symptom directed.
Cystic fibrosis is not exclusively a pediatric disease

ECFS patient registry 2014
Cystic Fibrosis is complex

The cure is complex

Someone I love is complex
CFTR mutations have different effects on CFTR production, processing and function

<table>
<thead>
<tr>
<th>Defect types</th>
<th>No protein</th>
<th>No traffic</th>
<th>No function</th>
<th>Less function</th>
<th>Less protein</th>
<th>Less stable</th>
</tr>
</thead>
</table>

Chloride transport through CFTR

CFTR channel function = \[ \text{NUMBERS} \times \text{EFFICIENCY} \]

NUMBERS

- \( N \) CFTR channels

EFFICIENCY

- \( P_o \) open probability
- Conductance

Classes:

- Class I, II, V, VI
- Class III
- Class IV

Bell (2015) Pharmacology & Therapeutics
Most mutations have complex effects
Potentiators activate CFTR channels with class III mutations

Allow opening of CFTR ion channels present at the cell surface
Ivacaftor (VX770) – Drug discovery

Ivacaftor increases the open probability of defective G551D channels

Van Goor F PNAS 2009
Ivacaftor phase II trial

Improvement in sweat chloride (biomarker) (Improvement in FEV$_1$ = surrogate endpoint)

Accurso NEJM 2010
Ivacaftor phase III trial

FEV$_1$ improved (surrogate endpoint)

CFQ-R improved (PRO)

Less Pulmonary Exacerbations (clinical endpoint)

Weight Improved (Biomarker)

Ramsey NEJM 2011
Ivacaftor in other gating mutations

Ivacaftor improves FEV$_1$ in patients with non G551D gating mutations

- 38 patients with one of 9 different ‘gating’ mutations
- Cross-over design

De Boeck JCF 2014
Responses may vary between the mutations tested

<table>
<thead>
<tr>
<th>Mutation, n</th>
<th>Absolute change from baseline in % predicted FEV$_1$, % points, mean (min, max)</th>
<th>Absolute change from baseline in sweat chloride at week 8, mmol/L, mean (min, max)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At week 2</td>
<td>At week 4</td>
</tr>
<tr>
<td>$G1244E$ (5)</td>
<td>11.08 (−5.20, 25.41)</td>
<td>5.54 (−4.63, 12.95)</td>
</tr>
<tr>
<td>$G1349D$ (2)</td>
<td>19.42 (5.49, 33.36)</td>
<td>18.48 (1.60, 35.37)</td>
</tr>
<tr>
<td>$G178R$ (5)</td>
<td>7.46 (1.42, 16.99)</td>
<td>10.23 (−2.31, 20.53)</td>
</tr>
<tr>
<td>$G551S$ (2)</td>
<td>−0.09 (−4.69, 4.51)</td>
<td>0.29 (−5.32, 5.89)</td>
</tr>
<tr>
<td>$G970R$ (4)</td>
<td>6.72 (0.52, 12.61)</td>
<td>6.76 (1.21, 14.23)</td>
</tr>
<tr>
<td>$S1251N$ (8)</td>
<td>2.14 (−23.28, 19.95)</td>
<td>7.66 (−13.20, 26.03)</td>
</tr>
<tr>
<td>$S1255P$ (2)</td>
<td>11.10 (8.25, 13.94)</td>
<td>8.73 (4.74, 12.73)</td>
</tr>
<tr>
<td>$S549N$ (6)</td>
<td>10.55 (5.11, 15.93)</td>
<td>8.06 (−9.29, 19.30)</td>
</tr>
<tr>
<td>$S549R$ (4)</td>
<td>3.47 (−3.55, 7.59)</td>
<td>4.11 (−3.78, 10.00)</td>
</tr>
<tr>
<td>Overall</td>
<td>7.23 (−23.28, 33.36)</td>
<td>7.55 (−13.20, 35.37)</td>
</tr>
</tbody>
</table>

(n = 38) (n = 38) (n = 37) (n = 36)

$^a$ Only one patient with the $G551S$ mutation completed 8 weeks of ivacaftor treatment.

De Boeck JCF 2014
Kalydeco® (Ivacaftor)

- FDA and EMA approved
  - Patients with CF
  - 2 years and older
  - With at least one of 9 listed gating mutations

- 0-14% of the patients have a G551D mutation

- Reimbursement in many countries at an incredible cost (250K euro/patient/year?)
Correctors improve trafficking of class II mutations
Ivacaftor+lumacaftor

• Trials in adults and also in children 5+ years
• Modest $FEV_1$ improvement 2.8–3.3%
• Less pulmonary exacerbations
• Change in sweat chloride around 10 mEq/L
Orkambi® (Lumacaftor+Ivacaftor)

• FDA and EMA approved
  – Patients 6+ with CF homozygote for F508del mutation
• Large proportion of the patients in most countries
• Reimbursement procedures ongoing in many countries
• Issues with
  – Moderate efficacy vs high cost (170K eutro/pat/year)
  – Safety issue, especially in patients with lowest FEV₁
`‘Read-through agents’ - Ataluren`

- Primary efficacy endpoint (improvement in FEV$_1$) not reached
- Post-hoc analysis showed a significant effect in patients not treated with aminoglycosides

**Graphs:**

**No Inhaled Aminoglycosides**
- Week 48 $\Delta = 5.7\%$
- $p = 0.008^*$
- Ataluren (N=72)
- Placebo (N=74)

**Any Inhaled Aminoglycosides**
- Week 48 $\Delta = -1.4\%$
- $p = 0.43^*$
- Ataluren (N=44)
- Placebo (N=42)

*Kerem 2014, Lancet Respir Med*
Ataluren – ‘Confirmatory trial’

- 279 patients with class I mutations (‘nonsense’)
- 48 weeks parallel placebo controlled Ataluren vs placebo in patients NOT using inhaled aminoglycosides
- No change in FEV$_1$
- No change in Pulmonary Exacerbations
- Development program for CF was stopped
What do we have now?

• One expensive and highly efficient drug for 10 gating mutations
• Expensive and moderately efficient drug for the most frequent mutation if homozygote
• No drug for nonsense mutations
• Many patients with rare mutations not tested for their response to ivacaftor and lumacaftor
Huge pipeline
What next?

• Advance the pipeline
• Make licensed drugs with clinically significant effect available to more eligible patients
• Expand the number of eligible patients
• Compare the efficacity of treatments and combinations
• Personalize treatments for each patient
Rare mutations

- CFTR2
  - Based on (expanding) international registry data (88,000 patients)
  - Analysis of 322 mutations, still expanding
  - 179 mutations* in less than 25 alleles, 97 in less than 10 alleles

- Most not functionally tested, no information about responsiveness to modulators

- Issues for trials with rare mutations patients
  - Low prevalence precludes large scale trials mutations
  - Suboptimal selection of candidates for a trial decreases the power of

*disease causing, unknown or varying clinical consequence)
Where do patients with rare mutations live?

No F508del and >= 1 missense not resp to Iva

n of patients without F508del and at least one missense mutation not responsive to Kalydeco

ECFPR 2014
Organoid culture from rectal biopsy

1. Rectal biopsy
2. Ex vivo intestinal current measurements
3. Crypt isolation
4. In vitro expansion
5. Passaging
6. CFTR function measurements
7. Biobanking

- Isolated crypt
- Crypt sealing
- Proliferation, de novo stem cell and bud formation
- Budding organoid
- Mechanic disruption into single crypts

Stem cell

d1  d3  d4  d7

Dekkers et al Rare Diseases 2013
Organoids as ex vivo CFTR biomarkers

Non-CF

CF - F508del/F508del

CF - F508del/F508del Ivacaftor+Lumacaftor
Forskolin induced swelling (FIS assay)

Non-CF
Forskolin induced swelling (FIS assay)
The ‘FIS assay’ measures the effect of modulators in organoids.
Ivacaftor, lumacaftor + combination in tested mutations

Clinical assessment of genotypes

Organoid swelling (0.128 μM fsk)

Clinical potential:
- High
- Medium
- Low

VX-809
VX-770
VX-809 + VX-770

FEV1 increase (%)

R = 0.8673
p = 0.0252

Dekkers J Sci Transl Med 2016
Dutch ‘Success story’ (n=2)

- Organoids of 2 patients with a G1249R mutation ('unclassified') responded to ivacaftor
Clinical improvement followed treatment with ivacaftor

Dekkers J Sci Transl Med 2016
Response to drugs vary within genotypes

Dekkers J Sci Transl Med 2016
Clinical responses are also variable

Boyle Lancet Resp Med 2014
Plan forward: personalized medicine for rare CFTR mutations

- Identify ‘responders’ with an in vitro assay such as organoids (patient derived>construct)

- Set up n-of-1 trials to assess clinical response in the ‘responding’ patients

- Treat patients showing a clinical response
Validation of the organoid assay

• Establish a well standardized, repeatable and portable in vitro assay

• Use clinical trial and follow-up data to establish the predictive value of the in vitro model

• Design optimized and standardized n-of-1 trials using correct endpoints
Practical implementation steps

- Collaborations between labs for optimization and standardization of the organoid technique
- Collect a large biobank of organoids from patients (with rare mutations or more common mutations)
- Give eligible patients access to the clinical trials
- Obtain funding and recruit expert centres for the clinical trials (CTN?)
- Discuss and implement innovative, adapted access programs to the drugs
The goal is...

• An efficient treatment for all patients, including patients with rare mutations

• The most efficient treatment for each patient

• At a reasonable cost
Take home

• Modulators are a revolution in the treatment of cystic fibrosis

• CFTR modulators are a good example of personalized medicine as they are mutation specific

• Validation of an in vitro predictive model would even allow to advance beyond ‘mutation-specific’ to ‘patient-tailored’ treatments

• This requires adaptations in the drug approval process and reimbursement policies that could benefit other diseases
HIT-CF project

Fig 1.1: Overall Approach (This figure will be explained in the Introduction section, page 6)