FIRST RESULTS OF THE HIT-CF ORGANOID STUDY:

INTESTINAL ORGANOIDS DERIVED FROM CF PATIENTS WITH ULTRA-RARE MUTATIONS RESPOND TO THE COMBINATION OF DIROCAFTOR AND POSENACAFTOR

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Poster #374

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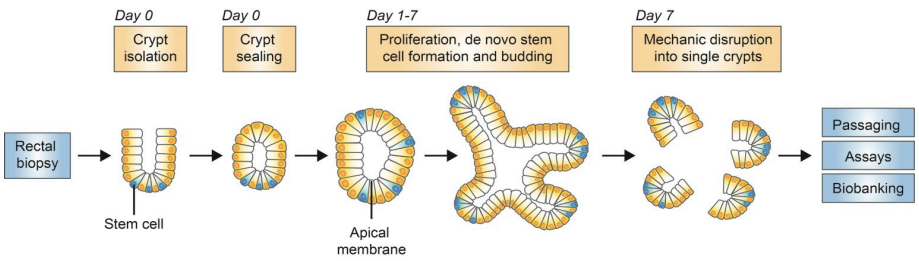
Introduction

Approved CFTR modulators were developed with product labels restricted to specific CF genotypes. This approach does not account for response heterogeneity among patients with the same genotype and prevents prediction of potential benefit for patients with other, more rare genotypes. Patient-derived cells such as rectal organoids have been demonstrated to accurately predict a donor's clinical benefit from approved CFTR modulators*. This encourages the pursuit of personalized therapies that are based on an individual's response as opposed to those based solely on their genotype. This strategy is being pioneered by HIT-CF (www.hitcf.org), a collaborative consortium created to realize personalized medicine for the treatment of CF.

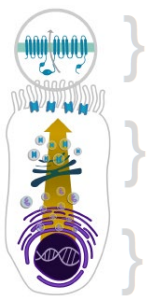
HIT-CF approach

- 502 rectal biopsies were collected from European and Israeli patients with CF bearing ultra-rare mutations:
- From biopsies intestinal organoids are cultured:



- Forskolin-induced swelling (FIS) assays are performed to detect organoid response to phase I/II drugs from Proteostasis Therapeutics and Eloxx Pharmaceuticals
- Patients for n-of-1 clinical trials will be selected based on organoid response

Investigated medicinal product



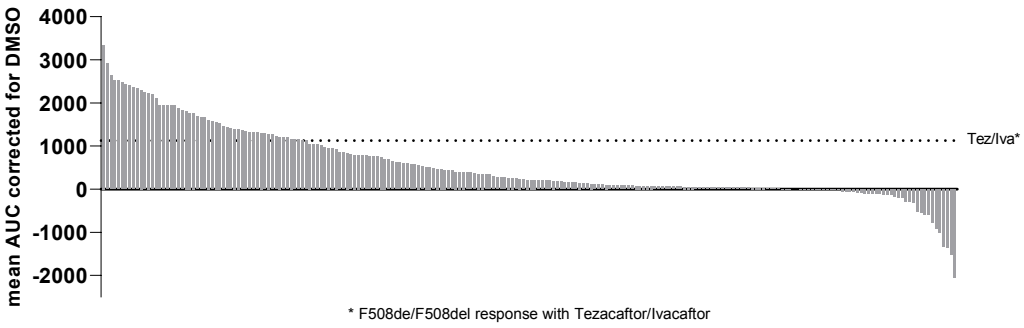
Dirocaftor (DIR) is a potentiator. It enhances the ion transport activity of the CFTR protein

Posenacaftor (POS) is a corrector which promotes the maturation of CFTR protein to the cell surface

Nesolicaftor (NES) is an amplifier which co-translationally increases the amount of CFTR protein

Results

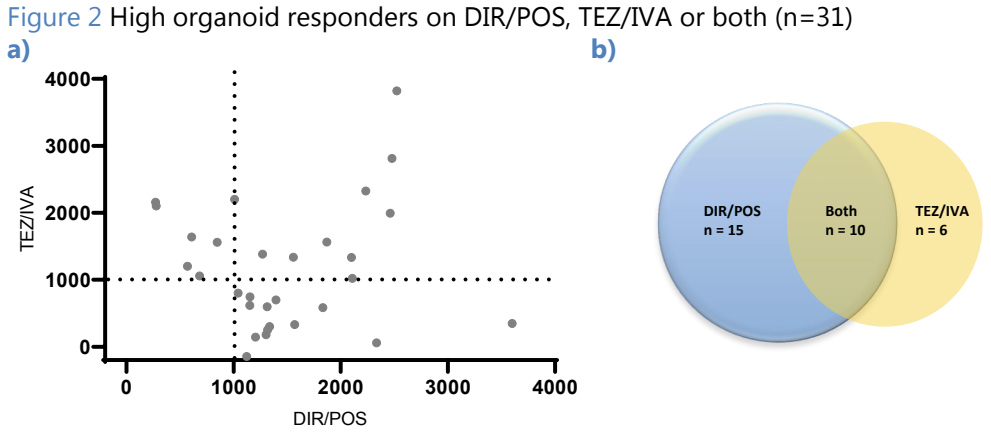
Figure 1 Organoid response from patients with ultra-rare CFTR mutations to DIR/POS (n=228)



Waterfall plot of FIS responses (0,32µM forskolin) upon 24h treatment with dirocaftor and posenacaftor. All AUC values are corrected for response on DMSO.

- >50% shows **a response to the combination of dirocaftor and posenacaftor** (Figure 1)
- 53 out of 228 (23%) organoids show **a higher response to dirocaftor/posenacaftor** than the reference Tezacaftor/Ivacaftor on F508del/F508del
- There is a **heterogeneity in response** to different modulators (Figure 2)
- More organonoids show solely a high organoid response to **the combination of dirocaftor and posenacaftor** than to the combination of tezacaftor and ivacaftor

Figure 2 High organoid responders on DIR/POS, TEZ/IVA or both (n=31)



a) Scatter plot of FIS responses (0,32µM forskolin) upon 24h treatment with dirocaftor and posenacaftor compared to 24h treatment with tezacaftor and ivacaftor. All samples showed have at least an AUC >1000 to DIR/POS or TEZ/IVA and have no pre-swelling. All AUC values are corrected for response on DMSO. b) Venn diagram with response to DIR/POS, TEZ/IVA or both (same data as scatter plot).

Conclusion

- A substantial proportion of patients with ultra-rare CFTR mutations show in vitro response to the combination of **dirocaftor and posenacaftor**
- There is a **heterogeneity in response** to different modulators favoring a personalized medicine approach

Future plans

- Highest responders will be selected for clinical trial (CHOICES) Q4 2020 with DIR/POS/NES. This will be a double-blind, placebo-controlled, crossover study, which will run in the ECFS-Clinical Trial Network (Figure 3).
- Same strategy will be applied for ELX-02 compound, screen expected Q4 2020.
- Biobank storage of all cultured organoids.

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*Dekkers *et al.*,2013

Figure 3 Potential sites CHOICES study

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