



SELECTED OPPORTUNITIES IN RESPIRATORY DISEASES

New antisense oligonucleotide targeting all cystic fibrosis patients (BIO15170, 17486 & 19424)

NEW ANTISENSE OLIGONUCLEOTIDE TARGETING ALL CYSTIC FIBROSIS PATIENTS (BIO15170, 17486 & 19424)

Product factsheet

In vitro POC
Human data
In vivo POC

▶ Target:

- ◆ ANO1 mRNA.
 - ◆ ANO1 (Anoctamin 1; TMEM16A), is a Ca²⁺-activated Cl⁻ channel.
 - ◆ ANO1 is an alternative chloride channel able to compensate for CFTR function impairment in Cystic Fibrosis (CF) patients.

▶ **Product:** Antisense Oligonucleotide Target Site Blocker (TSB) that binds to a specific microRNA recognition site of ANO1 mRNA.

▶ **Application:** All cystic fibrosis patients: no genotype dependency.

▶ POC:

- ◆ ANO1 chloride channel activity is decreased in CF bronchial epithelial cells due to a decrease in ANO1 protein expression.
- ◆ Use of specific TSB oligonucleotides allows to increase ANO1 expression, chloride activity and mucus dynamics in primary CF cells isolated from bronchial biopsies from CF patients (F508del/F508del; F508Del + 1717-1G>A; 2184ΔA + W1282X).
- ◆ Additive effect of the TSB on the mucus dynamics in Orkambi treated primary human bronchial epithelial and fully differentiated cells isolated from bronchial biopsies from CF patients (2184ΔA + W1282X; F508Del + 1717-1G>A).
- ◆ Specific TSB increases ANO1 chloride activity and mucus dynamics in trachea of CF mice.
- ◆ TSB significantly improves survival in a mice model of CF.
- ◆ Fluorescent TSB is detectable until 30 days after Sub-cutaneous injection or intra-nasal instillation.
- ◆ A histopathological NOEL (No Observed Effect Level) could be established at the applied dose of 500mg/kg for the TSB.

▶ Publications:

- ◆ Sonnevile F et al. Nat. Comm, 2017; Sept 27; 8(1):710
- ◆ Ruffin M et al. Biochim. Biophys. Acta. 2013 Dec;1832(12):2340-51

▶ **Patent Applications:** PCT/EP2016/065565, PCT/EP2018/078283, PCT/FR2019/052466

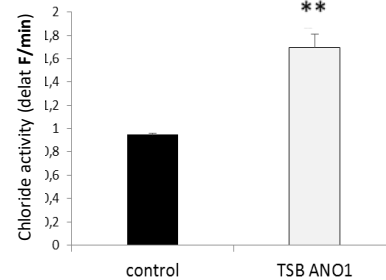
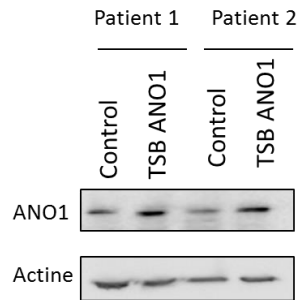
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Proof of concept

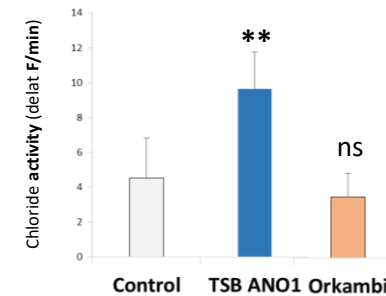
Primary cells of CF patients

Use of a specific TSB allows to increase ANO1 expression, chloride activity and mucus dynamics in primary CF cells isolated from bronchial biopsies from CF patients

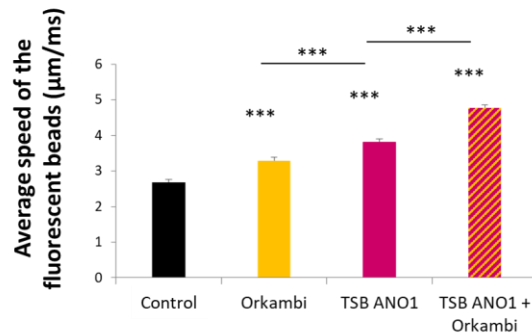
F508Del / F508Del patients



F508Del + 1717-1G>A patients

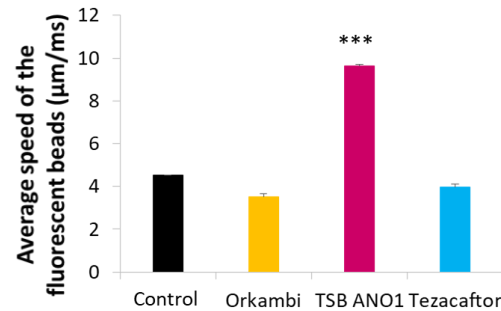


F508Del / F508Del patients

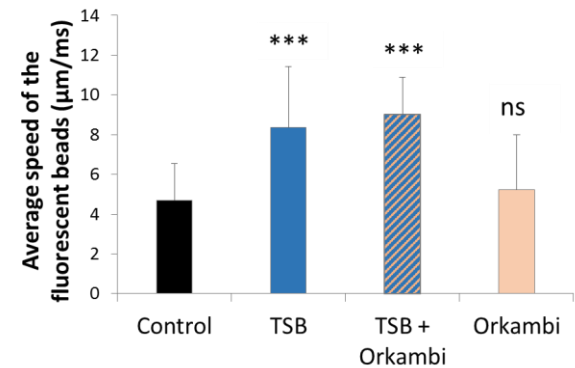


TSB was tested at 50nM

F508Del + 1717-1G>A patients



2184ΔA + W1282X patients

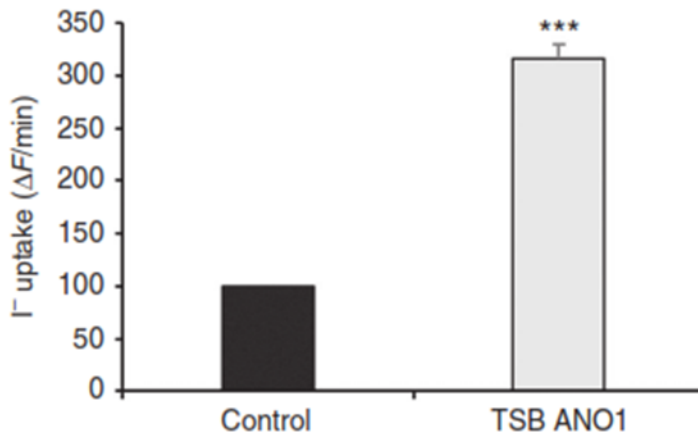


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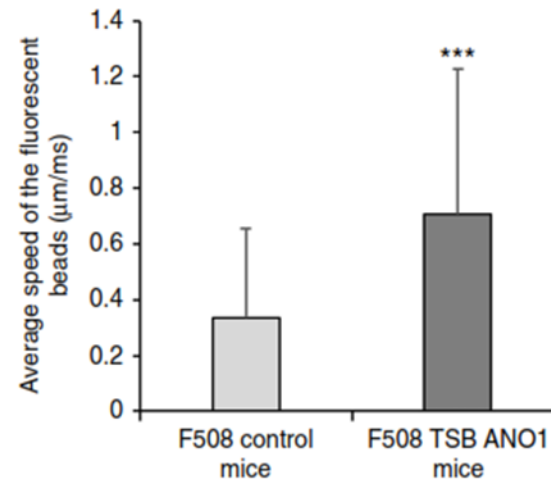
Proof of concept

In vivo POC

TSB restores ANO1 chloride efflux and increases mucociliary clearance in the trachea of CF mice



Effect of ASO on chloride efflux on tracheal epithelial cells from CF airway mice



Effect of ASO on mucociliary clearance of CF mice

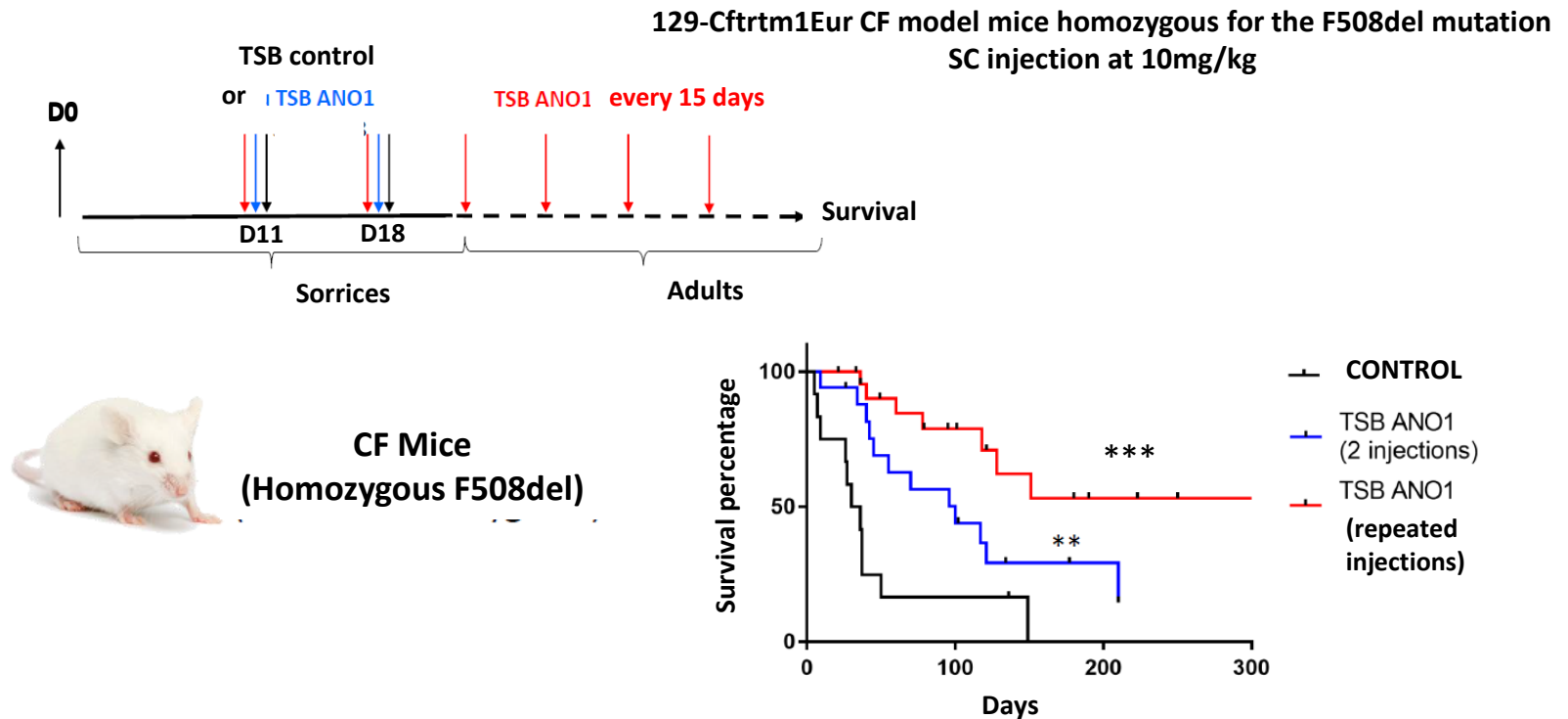
F508del CF Mice were treated with two nasal administration at day 7 and 11 of TSB at the concentration of 10 mg/kg. Mice were sacrificed at day 18.

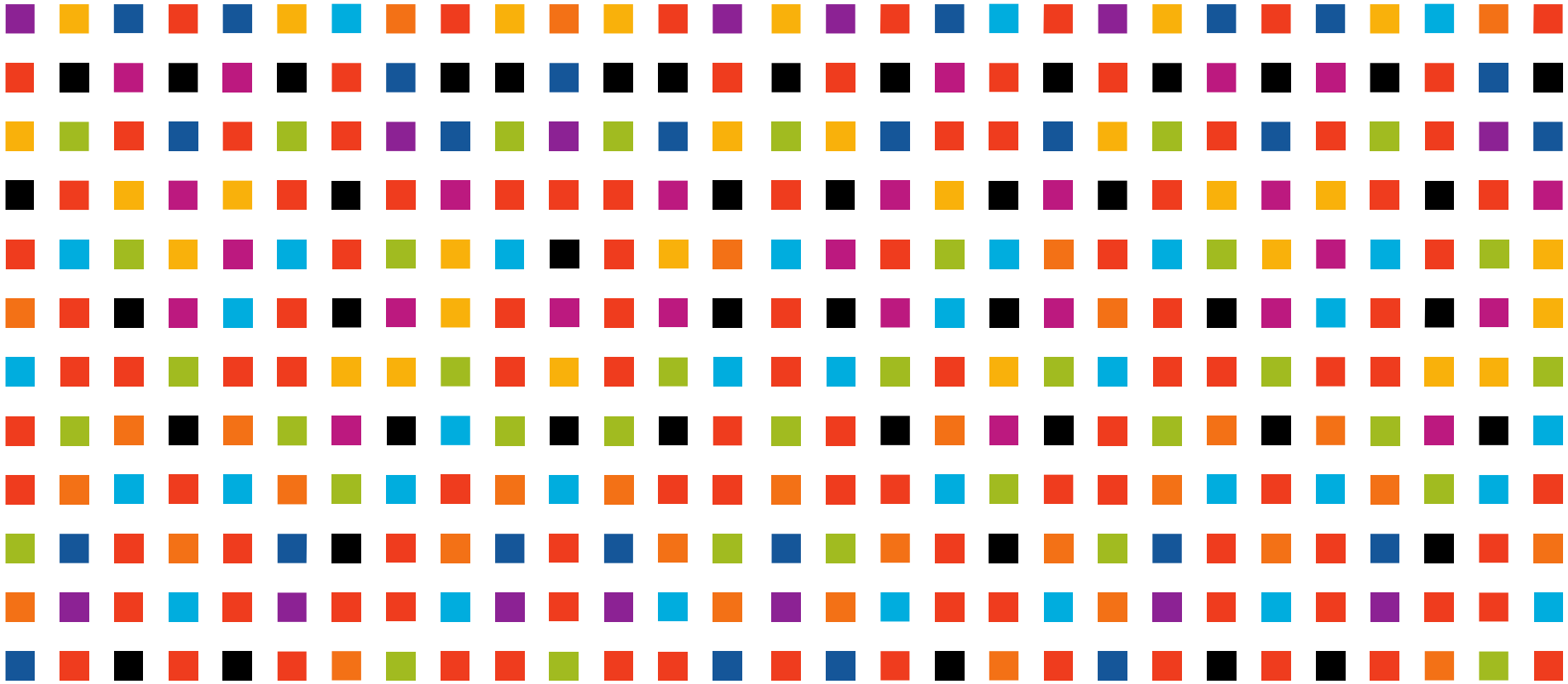
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Proof of concept

In vivo POC

Administration of the TSB improves survival in a mice model of Cystic Fibrosis





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