Novel, Highly Potent NBD1 Stabilizing Development Candidates Enable Full ΔF508-CFTR Correction and a Path to Wild-type Function

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Abstract

Background: ΔF508-CFTR is the most prevalent CFTR mutation in cystic fibrosis. ΔF508-CFTR results in the loss of phenylalanine 508 (F508) within CFTR’s first nucleotide binding domain (NBD1). This results in NBD1 destabilization, which contributes centrally to defective ΔF508-CFTR folding, trafficking, and function [1]. As F508 also participates in the interface of NBD1 with CFTR intracellular loop 4 (ICL4) and transmembrane domain 1 (TM1), ΔF508 further weakens CFTR domain assembly, adding to its dysfunction [2]. Complete pharmacological correction of ΔF508-CFTR will likely require drugs that both fully stabilize NBD1 and restore normal CFTR domain interactions [2]. Approved CFTR modulators provide clinical benefits to eligible patients through an impact on ΔF508-CFTR. However, approved modulators have no direct impact on NBD1 and do not fully correct CFTR function in most people with CF [3]. After over a decade of research, our science team discovered SION-638 as a first-in-class modulator that directly stabilizes NBD1 in a naïve conformation. Here we describe previously undisclosed development candidates from a second series of NBD1 stabilizers with significantly improved activity and potency compared to SION-638. By developing complementary ICL4- and TM1-directed modulators to use in combination with NBD1 stabilizers.

Methods: In rigorously validated functional and biochemical assays, we demonstrated the activity of a new series of Sionna NBD1 stabilizers alone and in combination with Sionna ICL4 and TM1-directed correctors, and with approved CFTR modulators.

Results: In the clinically predictive CFHBE model and other preclinical systems, we demonstrate that highly potent Sionna Series 2 NBD1 stabilizers can fully restore ΔF508-CFTR maturation, trafficking, and function to wild-type levels in double combinations with mechanistically complementary modulators, including Sionna ICL4 or TM1-directed development candidates, or when added to current standard-of-care modulators.

Introduction

ΔF508-CFTR leads to NBD1 instability and defective CFTR domain assembly

Suppressor mutations that stabilize NBD1 and the NBD1-ICL4 interface restore ΔF508-CFTR maturation to wild-type (WT) levels: a roadmap to more effective therapies.

ΔNBD1 was considered undruggable.

To address the key drivers of ΔF508-CFTR dysfunction, Sionna is developing first-in-class NBD1 stabilizers plus novel modulators that correct CFTR assembly. We leverage 14 years of effort and investment by Genczyme, Sanofi, and CFF, and Sionna.

We show that NBD1 stabilizers synergize with ICL4 and TM1 correctors enabling full correction.

First-in-class NBD1 stabilizer SION-638 is now in Phase 1.

We are advancing additional NBD1 and other modulators to enable full ΔF508-CFTR correction.

ICL4-directed corrector SION-109 is progressing to Phase 1 studies.

NBD1 Stabilizer SION-638 Increases ΔF508-CFTR Function

SION-638 increases ΔF508-NBD1 stability above WT-NBD1 levels and ΔF508-CFTR channel activity to WT levels if combined with complementary modulators.

SION-638 increases FSK+DMSO relative peak fluorescence above WT-NBD1 and WT-CFTR.

SION-638-treated ΔF508-NBD1 has a greater stability than that of untreated WT-NBD1.

SION-638 Stabilizes the NBD1 Domain of CFTR

Differential static light scattering was used to assess the ability of Development Candidate SION-719 to stabilize NBD1.

SION-719 increases ΔF508-NBD1 stability by more than 16°C, and ΔION-638 increases ΔF508-NBD1 stability by 10.4°C. Approved modulator alfaxacar (ELX), ivacaftor (IVA), and tezaacar (TEZ) have no direct impact on NBD1 stability.

SION-719 Improves ΔF508 Maturation and Function

NBD1 stabilizer SION-719 corrects ΔF508-CFTR maturation and channel function to fully WT levels when combined with complementary CFTR modulators.

SION-451 Improves ΔF508 Maturation and Function

NBD1 stabilizer SION-451 corrects ΔF508-CFTR maturation and function channel to fully WT levels when combined with complementary CFTR modulators.

Conclusions

Sionna is advancing small molecule stabilizers of CFTR NBD1, a novel therapeutic class with the potential to fully correct ΔF508 CFTR. These include the highly potent development candidates SION-638 and SION-109, and clinical-stage SION-109 and ICL4 and TM1 modulators, which include clinical candidates SION-676 and SION-109, which synergize with NBD1 stabilizers, enabling Sionna combinations with the potential to normalize ΔF508-CFTR function.

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References