NANOBODIES TO POTENTIATE CYSTIC FIBROSIS TREATMENTS

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- Protein stability
- Nanobodies

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THE TECHNOLOGY IN A NUTSHELL

This technology aims to potentiate approved treatment for cystic fibrosis by enhancing the thermal stability of the faulty cystic fibrosis transmembrane conductance regulator (CFTR) protein. In vitro, these patented nanobodies improved the efficacy of the currently approved gold standard treatment (combination of Elexacaftor, Tezacaftor and Ivacaftor) on chloride ion transport.

STATE OF THE ART

Cystic fibrosis is caused by CFTR gene mutations, with F508del being the most common (prevalence of approximately 70%-80% of patients). The F508del mutation destabilizes the CFTR protein, causing misfolding and reduced thermostability, which disrupts ion transport, leading to accumulation of thick mucus and chronic infections. Recent cryo-EM studies have detailed CFTR's structure, highlighting the instability of its nucleotide-binding domains (NBDs) as a key factor in CF pathology (Zhou et al., 2020, Nature; Liu et al., 2017, Science; Sohma et al., 2020, Nature Communications). The FDA-approved treatment developed by Vertex Pharmaceuticals has shown excellent results in most of patients with the F508del mutation leading to increased life expectancy. However, for some patients with the same mutation, this therapy is either less effective or doesn't work, and it has little to no impact on patient with other CFTR protein mutations.

THE INVENTION

Our patented nanobodies bind to the nucleotide-binding domain 1 (NBD1) and thermally stabilize the F508del mutant CFTR by increasing its melting temperature. This invention aims at enhancing the efficacy of existing cystic fibrosis therapies, specifically the currently approved gold standard treatment, which consists of the combination of Elexacaftor, Tezacaftor, and Ivacaftor.

KEY ADVANTAGES OF THE TECHNOLOGY

- **Targeted** F508del mutant **CFTR Stabilization**: restores the thermodynamic stability of the F508del mutant CFTR.
- **Optimized** F508del mutant **CFTR Functionality**: enhances the chloride ion transport in vitro.
- **Potential to enhance the response to existing therapies**: potential to enhance the response of patients with the F508del mutation who currently show limited or no response to available treatments.

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TECHNOLOGY READINESS LEVEL

1 2 **3** 4 5 6 7 8 9

TRL-3 Proof of concept of the technology on a preclinical model.

POTENTIAL APPLICATIONS in CFTR Treatment

- **Enhancing CFTR Stability in patients displaying the F508del mutation**: as it was shown in vitro, the binding agent may act as a potentiator of the existing treatment that stabilizes the CFTR in patients. By stabilizing CFTR, our agent supports the recovery of its activity, improving chloride ion transport. This, in turn, may enhance mucus hydration and lung functionality.

- **Enhancing CFTR Stability for other mutations**: our agent might be useful for other mutations affecting the CFTR which are not targeted by existing therapies. This remains to be investigated.

PRINCIPAL INVESTIGATOR

Cédric Govaerts is a renowned senior researcher at FNRS and ULB, as well as an affiliated researcher at WEL Research Institute in the field of biological sciences, specializing in the study of membrane transporters. He holds a PhD in Sciences from ULB (2001). After completing his doctorate at the Institute for Interdisciplinary Research in Human and Nuclear Biology at ULB, he pursued a postdoctoral fellowship at the University of California, where he collaborated closely with Nobel laureate Stanley B. Prusiner. Currently a Senior Researcher at FNRS in the "Structure and Function of Biological Membranes" laboratory at ULB, he is known for his interdisciplinary approach and his ability to establish successful international collaborations. In recent years, he has received prestigious funding and mandates from various institutions, including WELBIO, the Belgian American Education Foundation, and the Forton Fund.

RELEVANT PUBLICATIONS

> Domain-interface dynamics of CFTR revealed by stabilizing nanobodies. Sigoillot, M., Overtus, M., Grodecka, M., Scholl, D., Garcia-Pino, A., Laeremans, T., He, L., Pardon, E., Hildebrandt, E., Urbatsch, I., Steyaert, J., Riordan, J. R., & Govaerts, C. (2019). *Nature Communications, 10* (1), 2636.

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