Enhanced Complement Factor I (CFI) properties of CB 4332 for replacement therapy in CFI deficiency

P 003

E. Gorina[1], J. McGuire[1], N. LeMoan[1], L. Holten-Andersen[1], K. Marchbank[2], JK. Jensen[3], T. Knudsen[1], G. Blouse[1]

[1]Catalyst Biosciences, South San Francisco, United States, [2]Institute of Cellular Medicine, Newcastle University, Newcastle England. [3]Aarhus University, Aarhus, Denmark

Background

+ CFI is a key complement regulator. CFI deficiency leads to complement dysfunction and has been described as disease-inducing (1). CFI deficiencies are predominantly an autosomal recessive genetic abnormality. The resulting decrease in CFI antigen levels or defective activity may lead to uncontrolled C3b and C4b activation and complement factor 3 (C3) convertase activity with a subsequent consumption of C3. The degree of CFI deficiency often determines the clinical phenotype: complete deficiency typically results in increased susceptibility to infections caused by encapsulated bacteria (2, 3) while partial deficiency generally result in an increased incidence of autoimmune and immune-complex diseases including glomerulonephritis and vasculitis (Figure 2).

Enhanced CFI; CB 4332

+ CFI is a key regulator of all three complement pathways at the pivotal C3 convertase step (Figure 1). CFI cleaves the activated complement components C3b and C4b into inactive fragments in the presence of specific cofactors, thus regulating downstream complement activity.
+ CB 4332 is an engineered CFI with an extended half-life that retains the biological activity of endogenous CFI and is intended for once-weekly subcutaneous (SQ) administration..

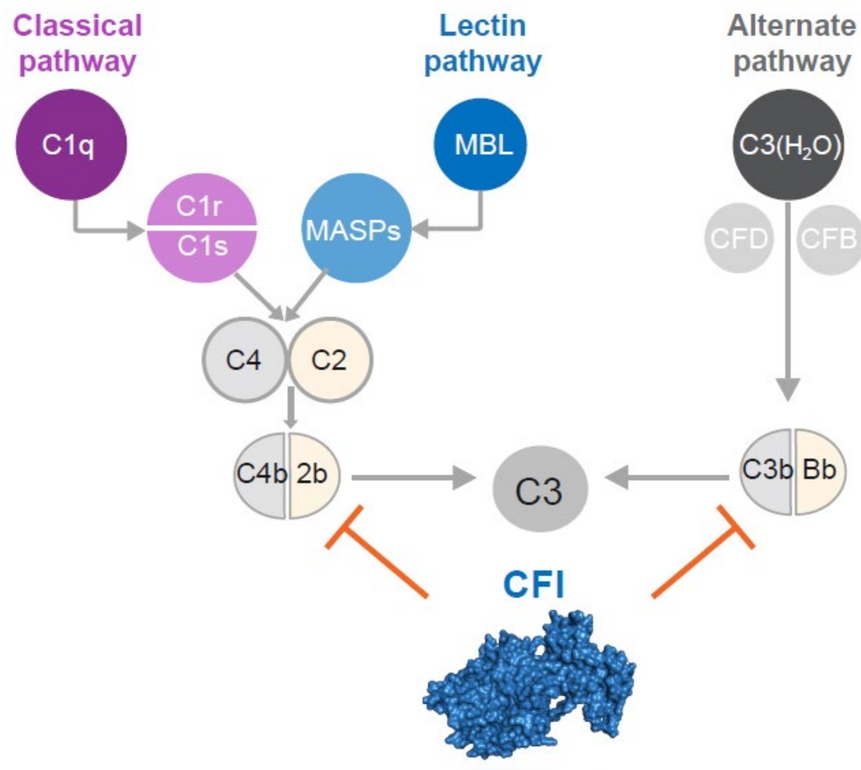
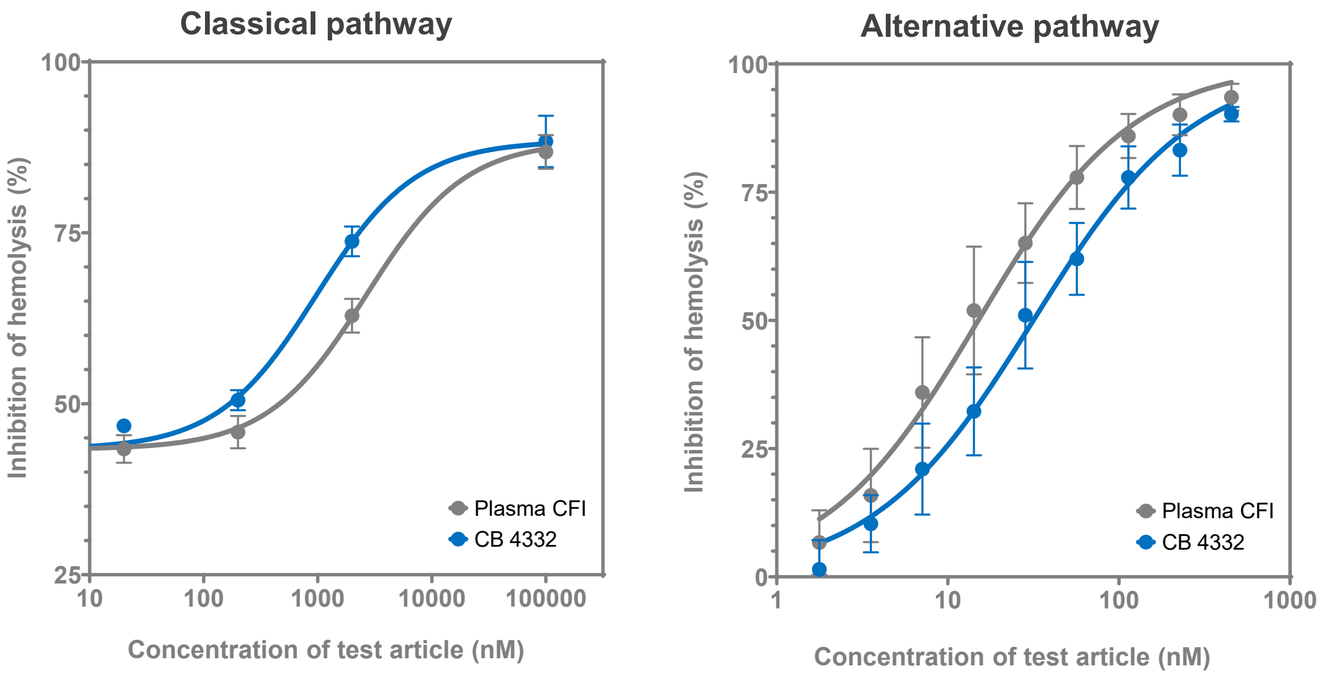


Figure 1. Schematic of CFI as down-regulator of all 3 complement pathways

Results

+ CB 4322 shows comparable function and potency to plasma-derived CFI using in vitro enzyme linked immunosorbent assay (ELISA) and ex vivo hemolytic assays, of the alternate and the classical pathways in terms of C3b and C4b cleavage, respectively



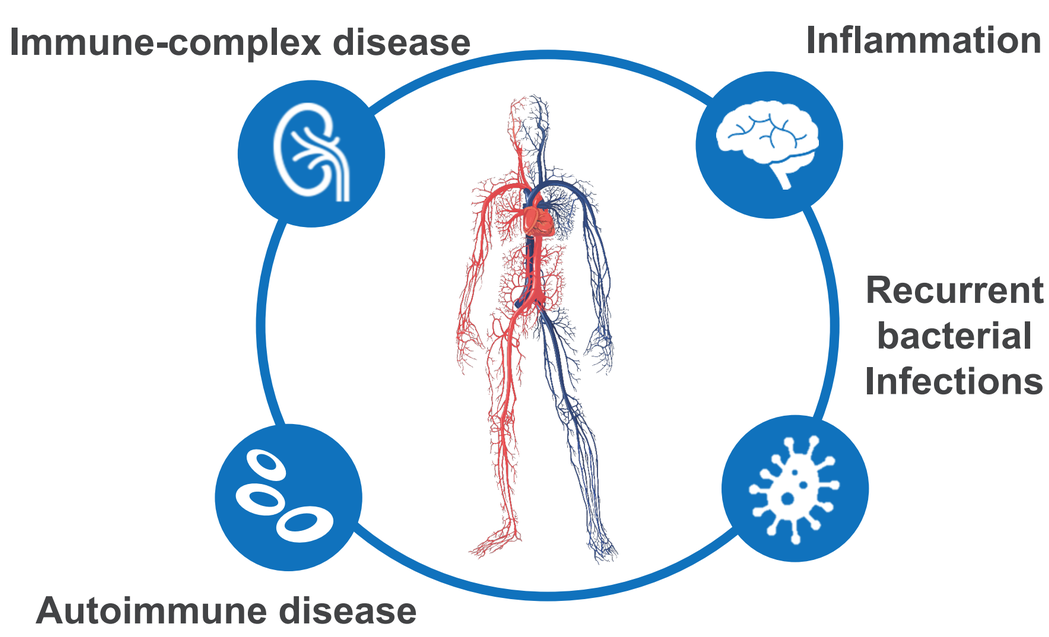
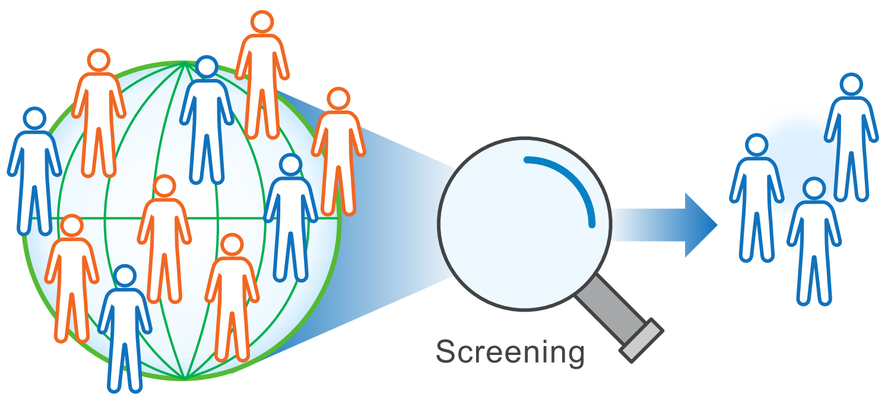


Figure 2. Potential uses of CFI replacement or supplemental therapy (1-4)

+ CB 4332 shows improved pharmacokinetic properties in non-human primates when compared to plasma-derived human CFI – data support a weekly SQ dosing if confirmed in humans. CB 4332 has the potential to become the first replacement therapy intended to address the heterogeneous clinical phenotypes of individuals with CFI deficiencies by supplying the missing CFI which is their common root cause. (e.g., repetitive bacterial infections like meningitis or pneumonias, auto-immune diseases like vasculitis or immune complex disease like glomerulonephritis.)
+ Catalyst has initiated global screening –**C**on**FI**rm- and natural history –**C**on**FI**dence- studies aimed at identifying people with CFI deficiencies and to further evaluate clinical outcomes, complement biomarkers, safety and effectiveness of their current treatments in preparation for the initiation of the clinical development program of CB 4332 in 2022. Raising awareness, early diagnosis and eventually treatment of CFI deficiency may prove very beneficial for the affected population (4).



→ Identifies target population / Feeds ConFIdence Study / Discovers undiagnosed disease

ConFIrm study

ConFIdence study

→ Prospective clinical outcomes & biomarkers assessment of CFI-deficiency disease

CB 4332 Phase 1/2 Trial

To our knowledge CB 4332 is the only Complement Factor I in development with the potential to be used as replacement therapy in patients with CFI-deficiencies, and possibly also in certain conditions resulting from complement dysfunctions in which additional upstream regulation may prove beneficial. CB 4332 will enter clinical trials in 2022.

Bibliography

+ 1. Alba-Domínguez et al. Complement factor I deficiency: a not so rare immune defect. Characterization of new mutations and the first large gene deletion. Orphanet Journal of Rare Diseases, 2012.
+ 2. Naesens L, et al. Plasma C3d levels as a diagnostic marker for complete complement factor I deficiency, Journal of Allergy and Clinical Immunology, 2020.
+ 3. Grumach, A. et al. Recurrent infections in partial complement factor I deficiency: evaluation of three generations of a Brazilian family. British Society for Immunology, Clinical and Experimental Immunology, 2005.
+ 4. Franco-Jarava C. et al. Early Versus Late Diagnosis of Complement Factor I Deficiency: Clinical Consequences Illustrated in Two Families with Novel Homozygous CFI Mutations. J Clin Immunol, 2017

International Conference on Complement Therapeutics ICCT, Ioannina, Greece. September 8-12