EUROpean consortium for antiCALINs as next generation high-affinity protein therapeutics (EUROCALIN)

Summary

The EUROCALIN consortium aims to develop and produce an Anticalin, a member of a novel high-affinity scaffold derived from the lipocalin protein family. The Anticalin is specific for hepcidin which is a central regulator of iron homeostasis, and will be used to antagonize hepcidin for the treatment of “anemia of chronic disease” (ACD).

The consortium has already generated proof-of-concept data in an animal model with early candidates.

The project aims at identifying, validating, and developing a specific, high affinity drug candidate based on the lipocalin scaffold as promising alternatives to immunoglobulins and a therapeutic approach based on the neutralization of hepcidin.

Animal models will be developed and utilized to characterize pharmacokinetic and pharmacodynamic relationships, to optimize dosing, to determine safety, and potential synergy with ESA’s. Furthermore, production processes will be optimized leading to a scalable GMP process which provides material for preclinical and clinical studies to establish the safety, tolerability, and PK/PD of an Anticalin hepcidin blocker (Phase I/II).

eurocalin-fp7.eu

Anticalins® are novel, next generation therapeutic proteins designed to bind and antagonize a wide spectrum of ligands.

The EUROCALIN project focuses on an Anticalin specific for hepcidin, called PRS-080. This Anticalin is the proprietary discovery of Pieris AG, an independent biotechnology company. Pieris has developed the PRS-080 molecule to the proof-of-concept stage and will oversee the consortium’s progress as project coordinator.

Anticalins® (red) are genetically modified lipocalins that can target almost any desired molecule (blue).

Anticalin bound to the peptide hepcidin

Unlike immunoglobulins, they can be produced at low cost in microbial expression systems, are expected to be non-immunogenic and offer therapeutic advantages where antibody effector functions are not desired.

Crystal structure of Anticalin (PRS-080) in complex with human hepcidin

Co-crystal structure, top view

Co-crystal structure, side view

PRS-080
Hepcidin
PRS-080 randomized positions

Rationale engineering at the natural binding pocket generated a hepcidin-specific binding surface

Hepcidin is buried in the pocket consistent with the observed pharmacological properties

Curtesy of Prof. Arne Skerra, Technical University Munich

Anemia of chronic disease

Anemia of chronic disease (ACD), the most frequent anemia in hospitalized patients, develops in subjects suffering from infections, inflammatory and autoimmune disease, cancer and chronic kidney disease. ACD is a condition marked by a deficiency of red blood cells or of hemoglobin in the blood, resulting in pallor and weariness. The major pathophysiological factor in ACD is retention of iron, rendering the metal ion unavailable for generation of red blood cells (erythropoiesis). The Consortium’s goal is to release available iron from tissue stores through preserving the function of ferroportin, the only cellular iron exporter of the body. The Anticalin does this by blocking the interaction of hepcidin with ferroportin which prevents hepcidin-induced degradation of the receptor in e.g. liver and spleen. ACD is often successfully treated by Erythropoiesis-Stimulating Agents (ESA). However, a significant number of patients are hypo- or non-responsive to ESA. Anti-hepcidin therapies, alone or together with ESAs, may improve anemia and the patients’ erythropoietic response and enable the use of no or even much lower ESA doses, avoiding the potential detrimental effects of high doses of ESA.

EUROCALIN project overview

Prefectiional research Clinical trial

Back-up candidates

Formulation

Dissemination

Translation

Preclinical research Production/formulation Clinical trial

The EUROCALIN consortium will develop, manufacture and clinically test an Anticalin specific for hepcidin, a small peptide circulating in human blood that is considered to be a key regulator of iron homeostasis and, therefore, an important target for the treatment of multiple types of anemia.