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# A novel approach for acute leukocyte mobilization from the bone marrow

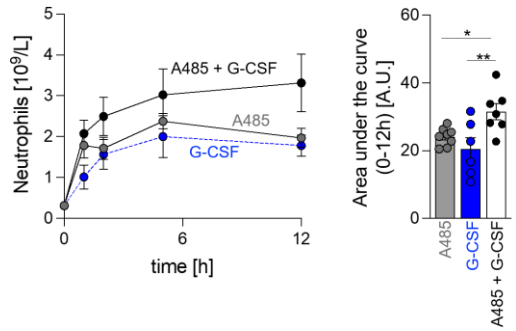
Keywords: Neutropenia, cytopenia, adjuvant cancer care, small molecule, bone marrow mobilization, neutropenic fever

## INVENTION NOVELTY

Addressing the previously unnoticed target CBP/p300 by a small molecule inhibitor, the technology provides an alternative and improved option for the treatment of cytopenias. Neutropenia refers to the decrease in a particular subset of white blood cells, namely neutrophil granulocytes, and can arise from a variety of underlying factors, such as genetic disorders, autoimmune diseases, or toxic insults, including chemotherapy. Patients undergoing chemotherapy frequently develop neutropenia, a condition that is associated with an increased risk of contracting serious infections and a high mortality rate. Besides supportive care, no treatment options for such an acute neutropenic fever exist, making the development of therapeutic strategies crucial.

## VALUE PROPOSITION

G-CSF and its derivatives can be used prophylactically together with or after chemotherapy administration to mitigate the frequency and severity of neutropenia, thereby antagonizing infectious complications. However, infections still occur (referred to as “neutropenic fever”) and supplementation of G-CSF does not confer clear clinical benefits in such individuals. This may, in part, be explained by a prolonged effect of G-CSF on the bone marrow with resultant neutrophilia culminating in immunopathology. The identified drug A485 rapidly expands the blood neutrophil compartment by mobilizing neutrophils from the bone marrow. A485 is as effective as G-CSF and elicits additive effects when combined with G-CSF, but acts significantly shorter. In a model of bone marrow injury and bacterial sepsis it augments host defenses, leading to improved pathogen clearance and survival. It may thus prove valuable as a complementary therapeutic strategy to G-CSF in the clinics, particularly in the setting of neutropenic fever, where G-CSF is ineffective. A485 is orally available, showed no toxic or pro-inflammatory effects in healthy rodents, and also has anti-tumor effects *in vitro* and *in vivo*, further suggesting potential in the setting of adjuvant cancer care.




*Blood neutrophil kinetics in response to different treatments. (source: Jaschke et al., Immunity 2024)*

## TECHNOLOGY DESCRIPTION

The injection of A485 caused rapid and transient bone marrow mobilization of leukocytes, as confirmed by a cell tracking approach. These effects were sustained in two models of leukopenia. Additional experiments demonstrated that the compound acts mechanistically distinct from G-CSF through a neuroendocrine effector cascade. Moreover, data from a cohort of patients with a rare developmental disorder caused by mutations in A485’s cellular target suggest that the respective domain plays a role in controlling human leukocyte compartment sizes. These findings support the relevance and therapeutic potential of this approach in a human setting.

## COMMERCIAL OPPORTUNITY

The technology is available for licensing and/or further co-development.

## DEVELOPMENT STATUS

Proof of concept established in three mouse models of disease. First experiments on pharmacokinetics and toxicity performed.

## PATENT SITUATION

Priority establishing European patent application was filed (priority date August 15th, 2023).

## FURTHER READING

Jaschke et al., Immunity 2024, DOI: 10.1016/j.immuni.2024.01.005

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