Technology offer IP-043

PAD4 Inhibition for NETosis-Related Diseases by Drug Repurposing

Gilteritinib, a drug approved by the FDA and EMA, has been identified by researchers from IMIB as a potent inhibitor of PAD4, a key enzyme in the formation of neutrophil extracellular traps (NETs), blocking NETosis at its origin, unlike therapies that degrade already formed NETs. This approach offers a novel therapeutic strategy to prevent and treat thrombotic, inflammatory, and autoimmune diseases associated with excessive NET formation.

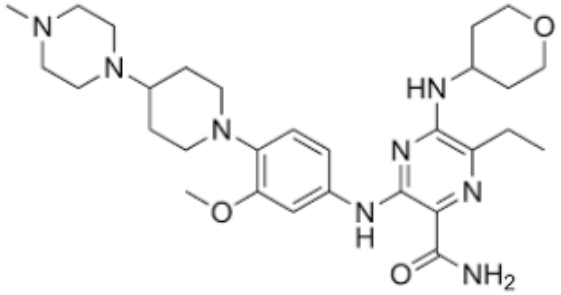

Figure. Structural formula

State of development

TRL-4 Laboratory validation

Objective of the collaboration

License and/or co-development

Industrial Property

Spanish patent application

Priority date: 24/10/2024

Contact

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Market needs

The dysregulated formation of neutrophil extracellular traps (NETs) contributes to the development of inflammatory, thrombotic, autoimmune diseases, and certain types of cancer. Neutrophils play a key role by releasing NETs as a defense mechanism, but their excessive presence promotes coagulation and inflammation. This dysregulation worsens pathologies by activating clotting factors and inhibiting natural anticoagulants. Current options, such as DNase I, have limitations including off-target effects and incomplete NET clearance. Therefore, there is an urgent need for therapies that effectively prevent or treat NETosis-associated diseases.

Technical solution from IMIB

This technology is based on the inhibition of NETosis through the therapeutic target Peptidylarginine Deiminase 4 (PAD4), a key enzyme involved in chromatin decondensation and NET formation. Using a structure-based virtual screening drug repurposing strategy, Gilteritinib — a drug approved by both the FDA and EMA — was identified as a potent PAD4 inhibitor. *In vitro* studies showed that Gilteritinib effectively reduces NET formation in human and murine neutrophils, thereby limiting thromboinflammation. *In vivo* models also demonstrated partial inhibition of reactive oxygen species and other related processes, positioning this approach as an alternative to DNase-based therapies.

Benefits

- Targeted inhibition of PAD4, the primary cause of NETosis, enhancing therapeutic efficacy.
- Gilteritinib is an FDA- and EMA-approved drug, facilitating repurposing and accelerating clinical translation.
- High specificity for PAD4, reducing interactions with off-target molecules.
- Lower risk of side effects by preserving essential immune functions such as phagocytosis.
- Potential short-term administration, minimizing the drug's cumulative toxicity.