122 NET Formation Inhibitors

Asset Overview

Product Type	Small Molecule
Indication	Inflammatory diseases
Current Stage	Hit
Target(MoA)	NETs / NETosis
Brief Description	• Neutrophils respond to infections and release extracellular traps (NETs), which are antimicrobial and are made of DNA, histones, and neutrophil proteins. The timely removal of NETs may be crucial for tissue homeostasis to avoid presentation of self-antigens • Excessive NET formation is linked to several diseases • Imaging based phenotypic HTS of human primary neutrophils (190k compound library) identified multiple sub µM hits series for different phenotypes • Validation of hit compounds through assay cascade and additional functional PBMC assays
Organization	Lead Discovery Center

Differentiation

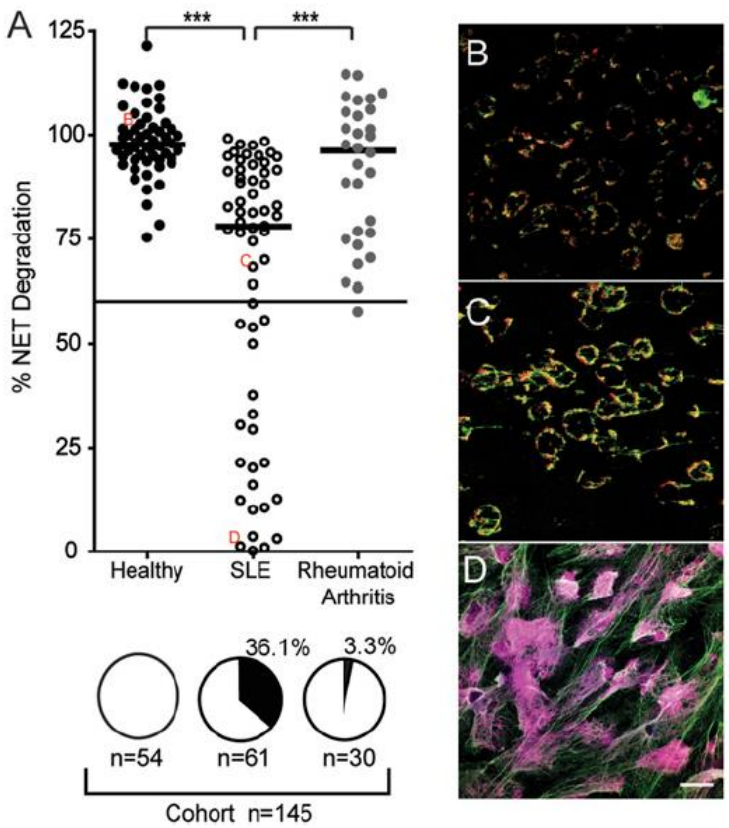
□ **Novel target with potentially various indications**

- Addressing a completely novel therapeutic principle with first in class potential
- Excessive NET formation is a pathogenic principle associated with many inflammatory pathologies incl. SLE, RA, atherosclerosis, thrombosis, sepsis, COPD, etc.

122 NET Formation Inhibitors

Key Data

NET degradation is impaired in a subset of SLE patients



(A) We activated neutrophils isolated from healthy donors to make NETs, incubated them with 10% sera from our cohort for 6 h, and quantified NET degradation. Each circle corresponds to one individual donor. The samples are grouped into healthy donors, SLE patients, and RA patients as indicated. One hundred percent NET degradation was determined using the serum from the healthy donor of the neutrophils. We arbitrarily considered sera that degrade at least 60% of the NETs within 6 h as normal (horizontal line). Sera from all healthy donors (n = 54, black circles) degraded NETs normally; 36.1% of SLE patient sera (n = 61, open circles) and 3.3% of the RA sera (n = 30, gray circles) degraded NETs poorly. ***P < 0.001; Kruskal-Wallis test with Dunn's post hoc comparisons. (B–D) NETs were exposed to representative sera (labeled B, C, or D in A), fixed and immunostained for myeloperoxidase (green) and histones (red). DNA (blue) was stained with Draq5. Representative micrographs show efficiency of NET degradation, with serum from a healthy donor (B), from an SLE patient who degraded NETs (C), and from an SLE patient who did not disassemble NETs (D). (Scale bar in D, 25 μm for B–D.)

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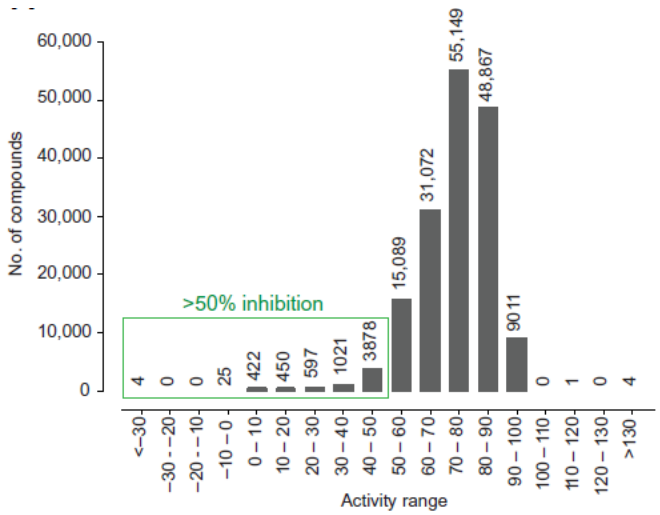
Key Data

Activity measured in % NET formation



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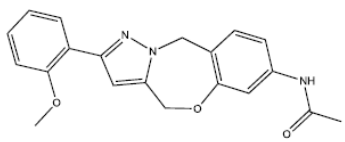

	NET formation	
	PMA	Cholest.
IC_{50} (μM)	5.61	0.304

Screening results. NETs were quantified by image acquisition.
A total of 6397 compounds reduced NET incidence to less than 50%, resulting in ≈3.4% hit rate.

Frontrunner Profile

Class II		
Activity		Best compounds: <10nM
hPBMC toxicity		no
SAR		clear, broad, activity improved
in vitro SPR	Solubility	low
	Permeability	medium
	MLM stability	good
	MLM Phase 2	compound-dependent
	Plasma stability (mouse)	compound-dependent
Metabolites analysis		*preliminary:* soft are addressable
Tool compound for target fishing		available
in vivo PK	$t_{1/2}$	medium
	V_d	low (except for LDC 202565)
	CL	low
	F%	good
	↑$AUC_{0\text{-}inf}$	linear
IP position		requires clear definition of scope

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Intellectual Property

Patent No.	
Application Date	
Status	
Country	

Contact Information

Contact Person	Sven Zimmer
Email	zimmer@lead-discovery.de
URL	https://www.lead-discovery.de/en/strategy/