DISCOVERY AND CHARACTERIZATION OF A SELECTIVE, ORALLY BIOAVAILABLE PAD4 INHIBITOR TO TARGET NETS DRIVEN AUTOIMMUNE AND INFLAMMATORY DISEASES

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ABSTRACT

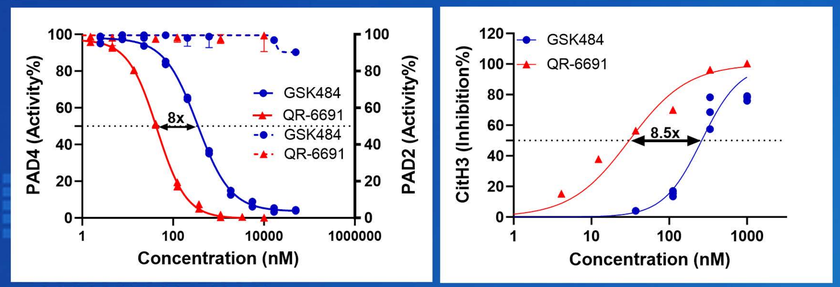
Protein arginine deiminases (PAD) 4 is an enzyme that catalyzes the conversion of protein-embedded arginine to citrulline. It is essential for neutrophil extracellular traps (NETs) formation which is implicated in multiple immune-mediated pathological conditions. However, the development of a drug-like PAD4 inhibitor has been challenging. Here, we report the discovery and characterization of a potent, selective and orally bioavailable small molecule PAD4 inhibitor.

POTENTIAL INDICATIONS

AUTOIMMUNE DISEASES	• Rheumatoid Arthritis • Systemic Lupus Erythematosus • Inflammatory Bowel Disease
ONCOLOGY	• Cancer Metastasis
OTHER INDICATIONS	• Cystic Fibrosis • Sepsis • COVID-19

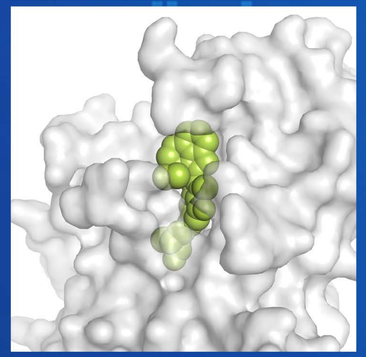
RESULTS

Fig 1: Biochemical and Cellular activity of QR-6691



QR-6691: IC_{50} = 46 nM (ammonia release assay)
QR-6691: IC_{50} = 22 nM (dHL-60, A23187, Cit H3 ELISA)

Fig 2: Co-crystal of QR-6691 and PAD4



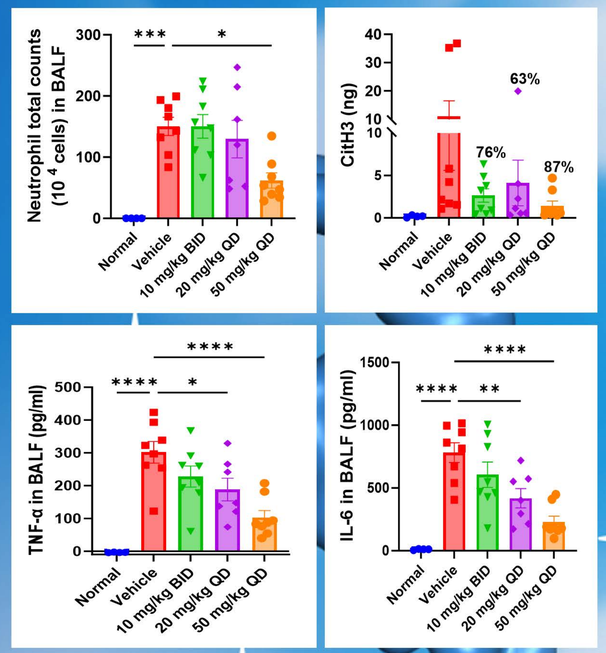
Resolution of this complex structure is 2.8 Å

Table: ADME and safety properties of QR-6691

in vitro ADME	$f_{b,p}$ (%)	Mouse/Rat/Dog/Human	< 95%
	Liver microsomes (Cl_{int}, μL/min/mg)	Rat/Dog/Human	< 30
	Hepatocytes (Cl_{int}, μL/min/million cells)	Rat/Dog/Human	< 12
Early Safety	CYP inhibition (IC_{50}, μM)	HLM	> 10
	hERG Inhibition (IC_{50}, μM)	Whole Cell Patch	> 10
In vivo PK	Rat	Bioavailability (F%), po	> 40
	Dog	Bioavailability (F%), po	> 90

Favorable oral PK properties in preclinical species

Fig 3: QR-6691 demonstrated potent efficacy in animal study



Mouse model: Intranasally administrated LPS to induce lung inflammation
QR-6691 suppressed the NETs formation and cytokine production in a dose-dependent manner.

CONCLUSIONS

1. QR-6691 is a potent, selective and orally bioavailable PAD4 inhibitor
2. QR-6691 dose-dependently suppressed NETs formation *in vivo*
3. QR-6691 is at preclinical development

SCAN ME

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