TARGETING VAV1 IN AUTOIMMUNE/INFLAMMATORY DISEASES: EXPLORING THE POTENTIAL OF MGD-BASED INTERVENTIONS

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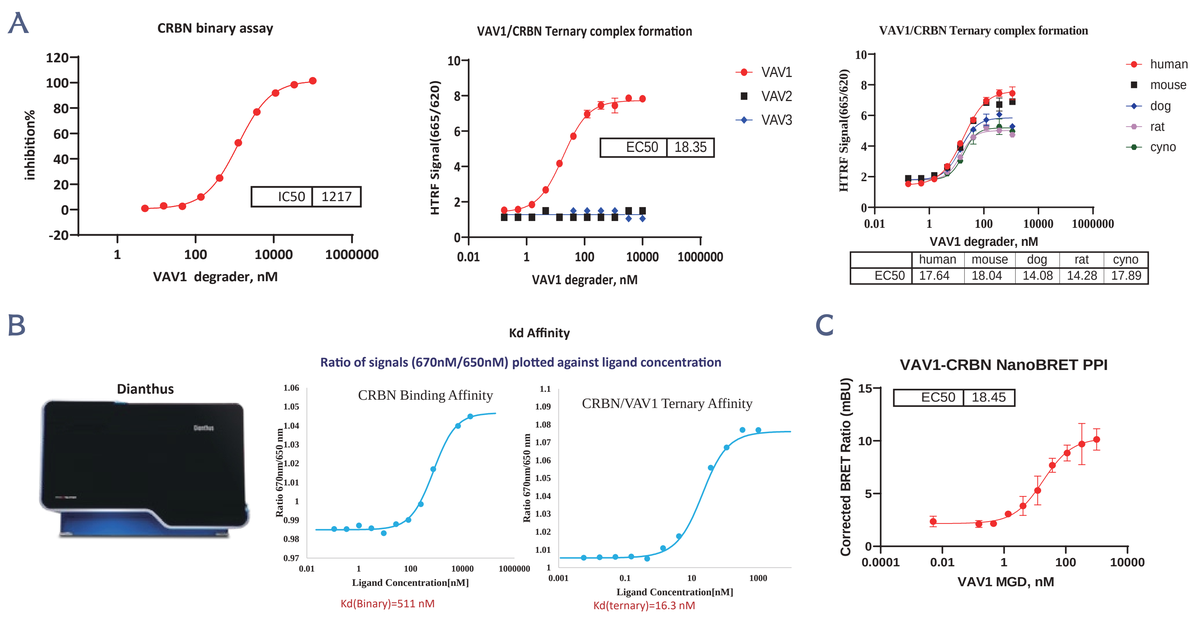
Abstract

The development of targeted therapies was a major milestone in improving treatment for certain autoimmune and inflammatory diseases. Recently, VAV1 has emerged as a promising therapeutic target in conditions such as rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, and psoriasis. As a dual-function GEF with both catalytic and scaffolding properties, VAV1 plays a key role in T/B cell activation, differentiation and cytokine production. Based on this, the use of molecular glue degraders (MGDs), such as first in class VAV1 MGD-MRT6160 (clinical Phase I), has shown remarkable potential in treating immunology and inflammatory diseases by inducing target protein degradation.

Our platform, integrating with a suite of state-of-the-art in vitro assays and in vivo studies, facilitates the investigation and screening for novel therapeutic agents from early discovery to preclinical readiness.

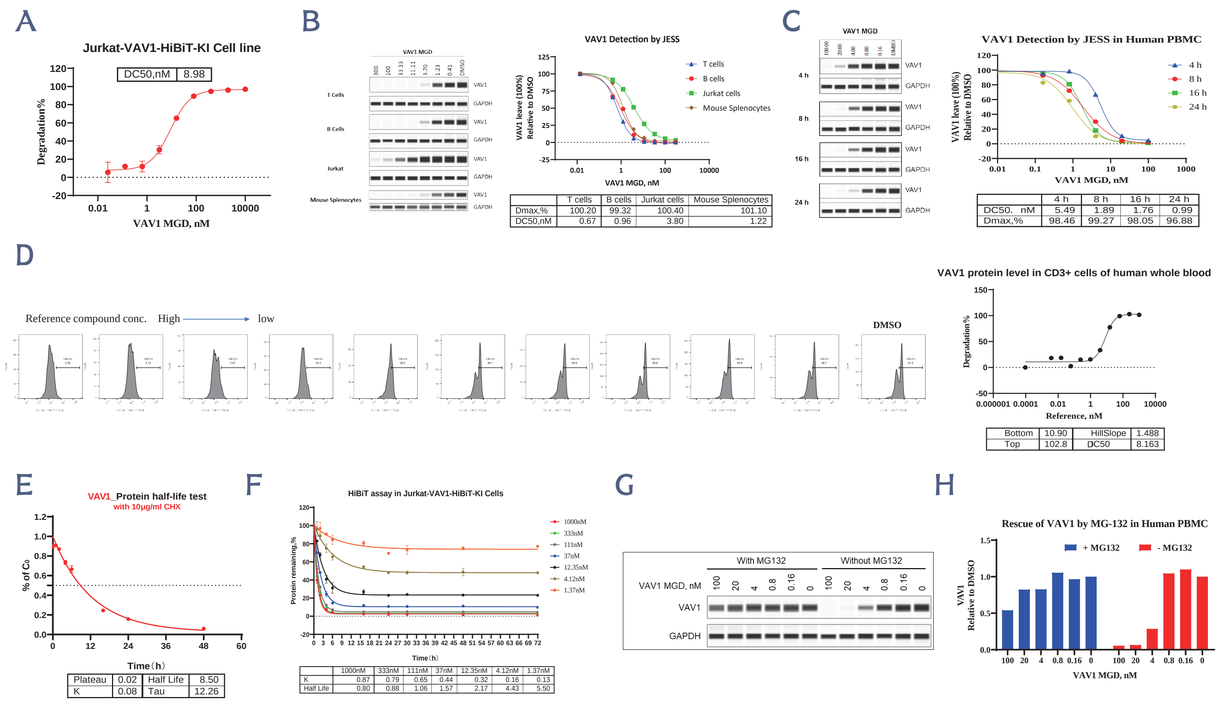
Binding



	human	mouse	dog	rat	cyno
EC50	17.64	18.04	14.08	14.28	17.89

Figure 1: CRBN Binary/Ternary Formation Analysis Using Biochemical, Biophysical and Cellular based assay.
CRBN&MGD binary binding and CRBN/VAV1 ternary complex formation using TR-FRET A) ,Dianthus spectral shift assay B) and cellular NanoBRET assay C).

Degradation MOA



	T cells	B cells	Jurkat cells	Mouse Splenocytes
Dmax,%	100.20	99.32	100.40	101.10
DC50,nM	0.67	0.96	3.80	1.22

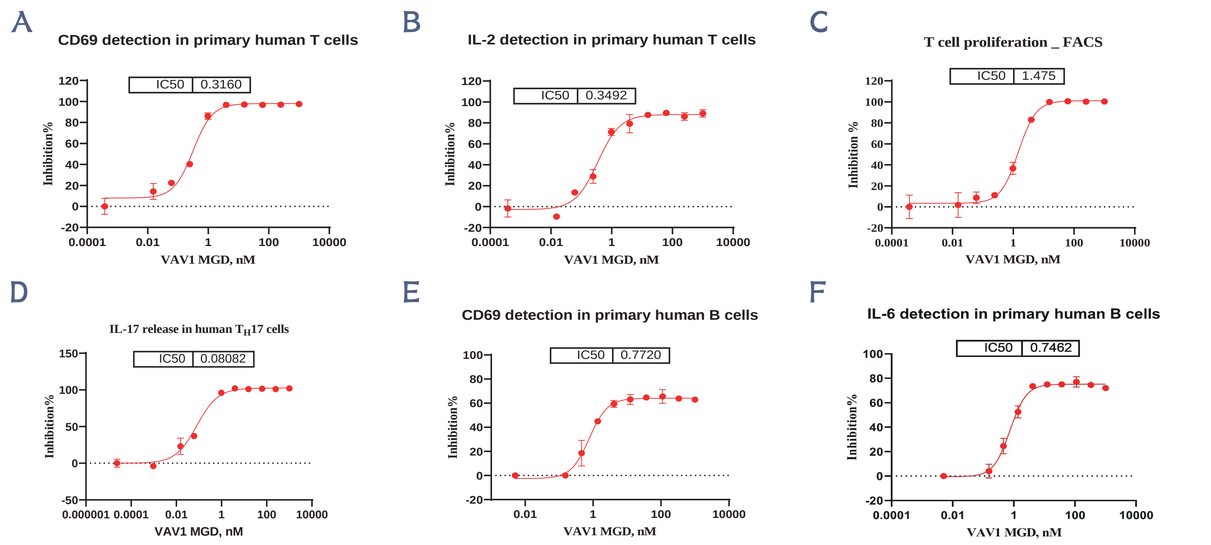
	4 h	8 h	16 h	24 h
DC50, nM	5.49	1.89	1.76	0.99
Dmax,%	98.46	99.27	98.05	96.88

	1000nM	333nM	111nM	37nM	12.35nM	4.12nM	1.37nM
K	0.87	0.79	0.65	0.44	0.32	0.16	0.13
Half Life	0.80	0.88	1.06	1.57	2.17	4.43	5.50

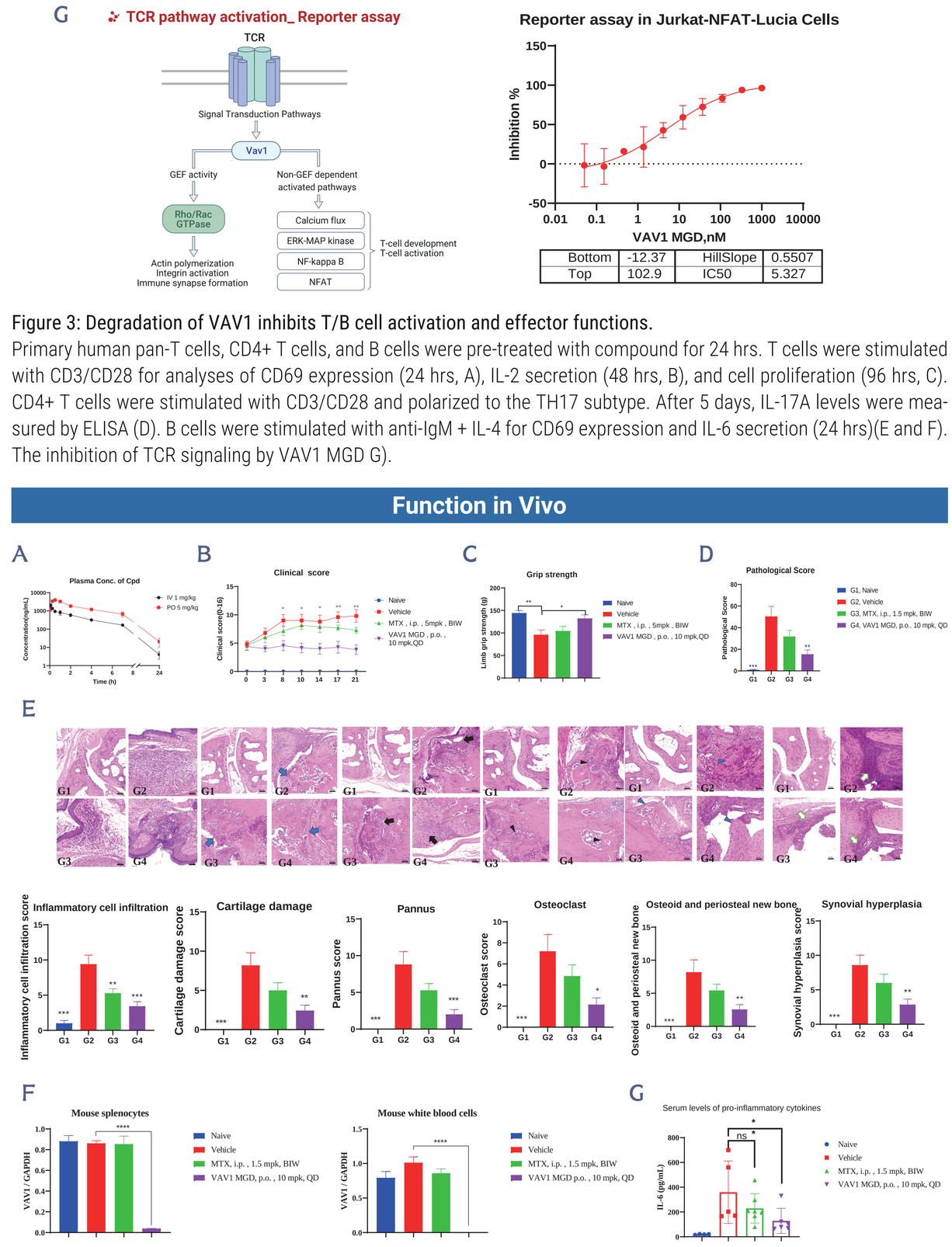
Plateau	0.02	Half Life	8.50
K	0.08	Tau	12.26

Figure 2: VAV1 Degradation Analysis by HiBiT assay, Jess, FACS system and MOA studies.
VAV1 degradation data in Jurkat-VAV1-HiBiT-KI cells A),in Jurkat, T,B and mouse splenocytes B), Time-dependent VAV1 degradation in PBMC cells C) and in human whole blood D), VAV1 half-life E), degradation kinetics F) and degradation pathway G).

Function in Vitro



Function in Vivo



Bottom	-12.37	HillSlope	0.5507
Top	102.9	IC50	5.327

Figure 3: Degradation of VAV1 inhibits T/B cell activation and effector functions.
Primary human pan-T cells, CD4+ T cells, and B cells were pre-treated with compound for 24 hrs. T cells were stimulated with CD3/CD28 for analyses of CD69 expression (24 hrs, A), IL-2 secretion (48 hrs, B), and cell proliferation (96 hrs, C). CD4+ T cells were stimulated with CD3/CD28 and polarized to the TH17 subtype. After 5 days, IL-17A levels were measured by ELISA (D). B cells were stimulated with anti-IgM + IL-4 for CD69 expression and IL-6 secretion (24 hrs)(E and F). The inhibition of TCR signaling by VAV1 MGD G).

Figure 4: VAV1 MGD In vivo Efficacy test and PD marker detection on CIA mouse.
VAV1 MGD PK data A); After group administration to the endpoint(Day21), the joint clinical score of the mouse B), Mouse grip test 20 days after dosing C), Pathological score of the paws D). Each group compared with Vehicle group,*p＜0.05,**p＜0.01,***p＜0.001.
Typical pathological changes in the PAWS of CIA mouse E).
Oral dosing of VAV1 MGD in CIA mouse for 21 days lead to nearly completely degradation of VAV1 F) ;
The level of pro-inflammatory IL-6 in serum samples was significantly reduced in VAV1 MGD treated group. **P＜0.01. G).

Selectivity & Safety

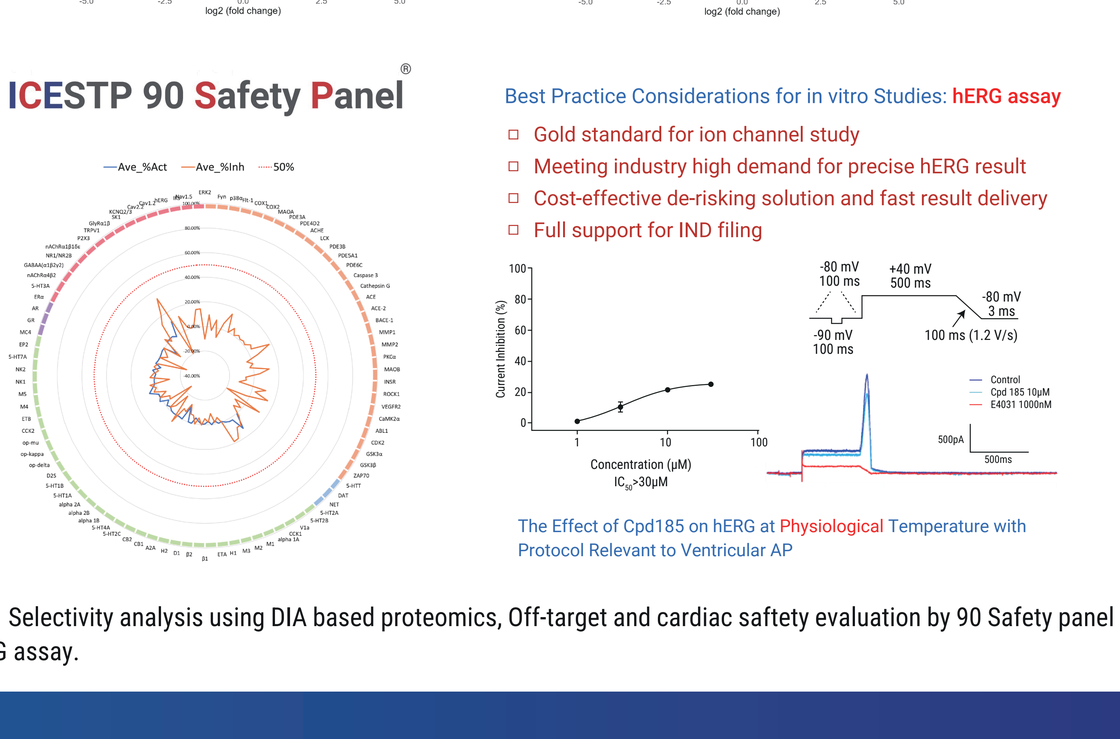


Figure 5: Selectivity analysis using DIA based proteomics, Off-target and cardiac saftety evaluation by 90 Safety panel and hERG assay.