I nuovi immunomodulanti (CC-122)

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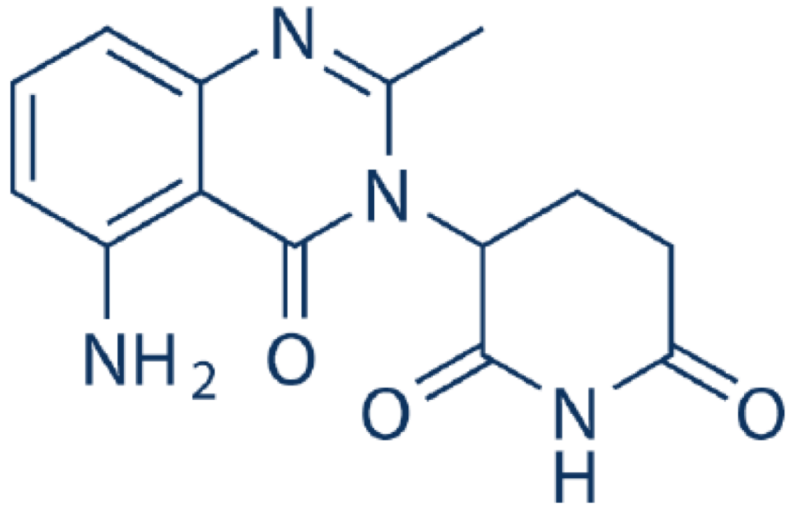
Chemical structure of avadomide (CC-122)



Avadomide (CC-122), a first-in-class drug termed pleiotropic pathway modifier (PPM), is a novel agent with antitumor and immunomodulatory activity. Its molecular target is the protein cereblon (CRBN), a substrate receptor of the cullin ring E3 ubiquitin ligase complex $CRL4^{CRBN}$

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Mechanism of action of avadomide

- CC122 is a novel agent with antitumor and immunomodulatory activity. It binds CRBN and induces degradation or short hairpin RNA-mediated knockdown of Aiolos and Ikaros (hematopoietic zinc-finger transcription factors) which correlates with increased transcription of IFN-stimulated genes independent of IFNα, β, and γ production and/or secretion and results in apoptosis in DLBCL cell lines.
- CC122 binding to CRBN recruits Aiolos and Ikaros; E3 ligase enzymatic activity is necessary for ubiquitination of Aiolos and Ikaros and thus for their proteasomal degradation.
- In patients, exposure to CC122 reduced expression levels of Aiolos and Ikaros in each patient by 25% to 50% demonstrating the utility of these 2 proteins as pharmacodynamic markers of CC122.

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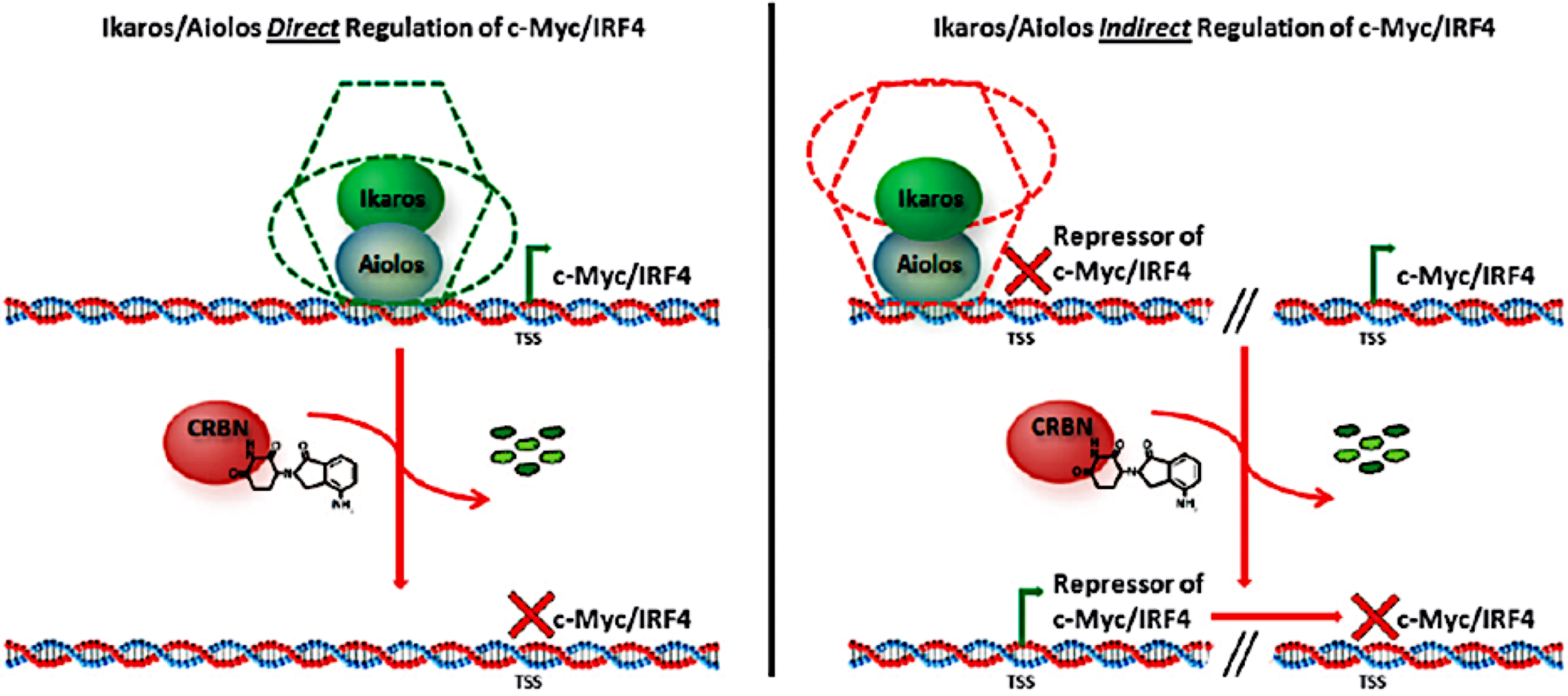
Graphical model explaining the potential mechanism of negative regulation of the c-Myc/IRF4 axis by PPMs



Bjorklund CC et al. Blood Cancer Journal (2015) 5, e354; doi:10.1038/bcj.2015.66

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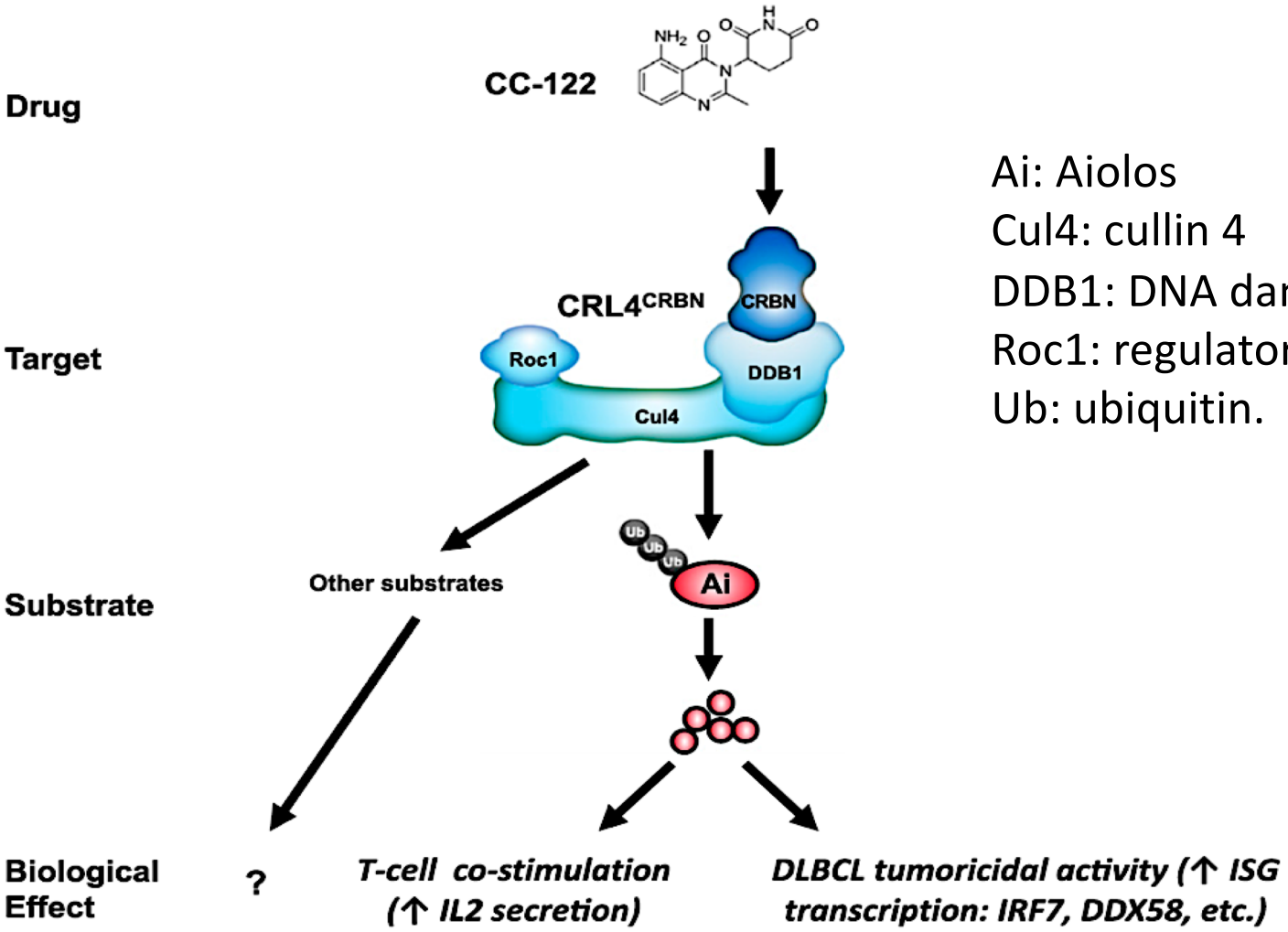
Model of CC-122 costimulation of T cells and tumoricidal activity through degradation of Aiolos and Ikaros



Ai: Aiolos
Cul4: cullin 4
DDB1: DNA damage binding protein-1
Roc1: regulator of cullins 1
Ub: ubiquitin.

Hagner P et al. Blood. 2015;126(6):779-789

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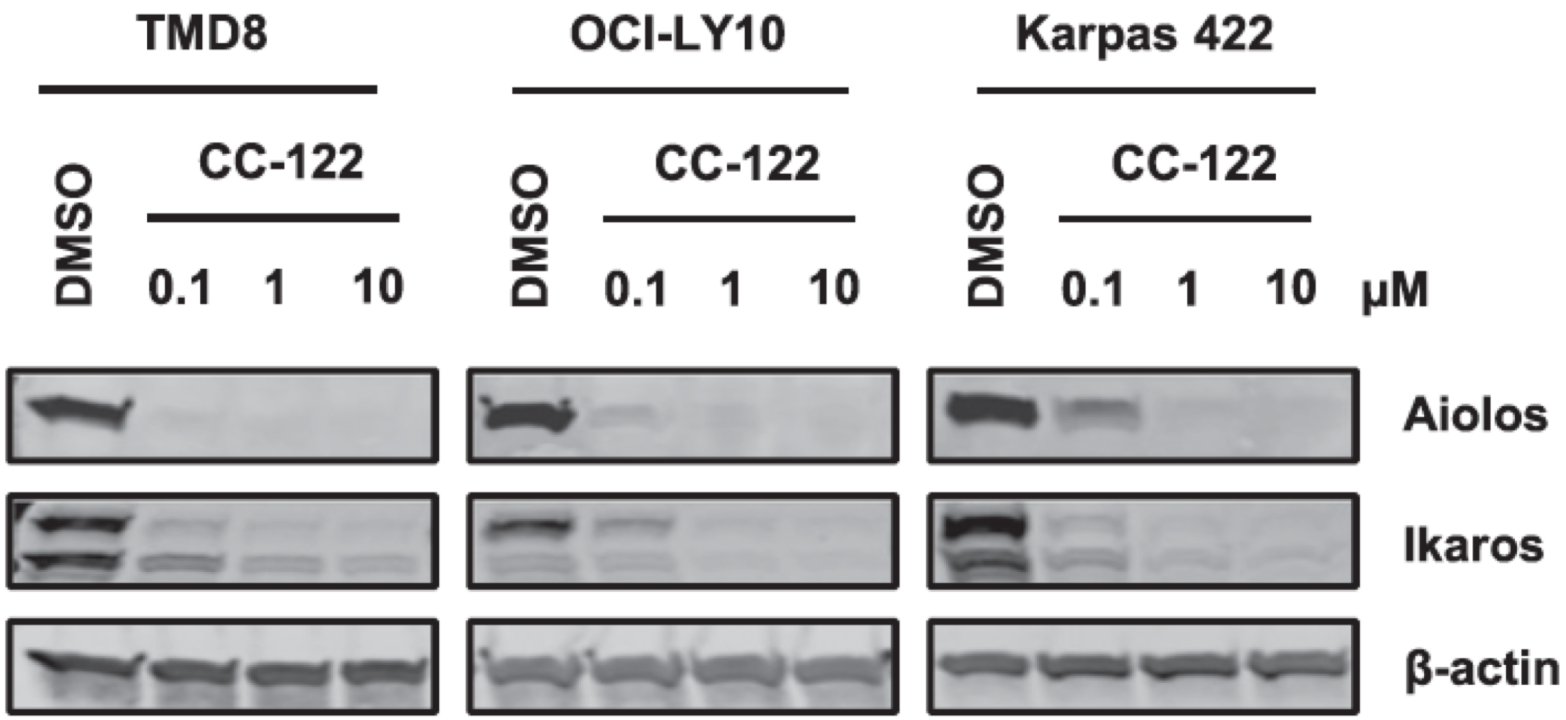
Aiolos and Ikaros are CRL4^{CRBN}-dependent substrates of CC-122



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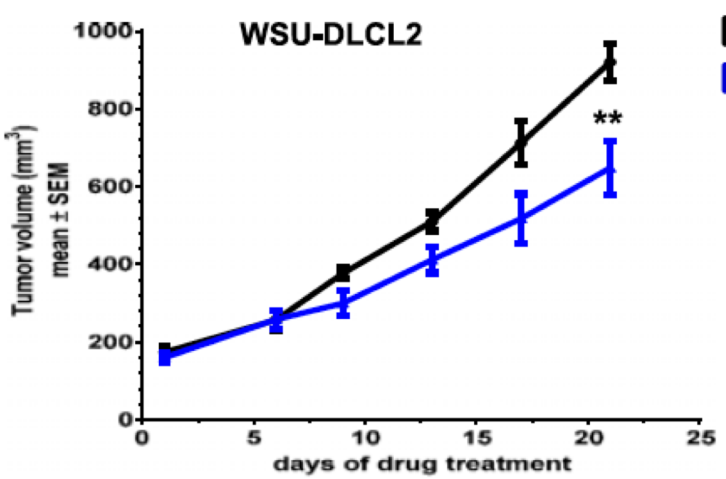
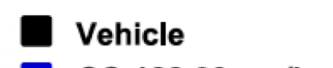
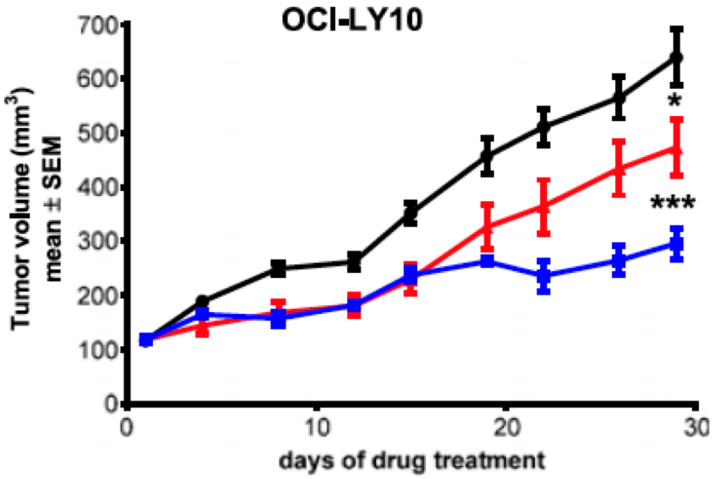
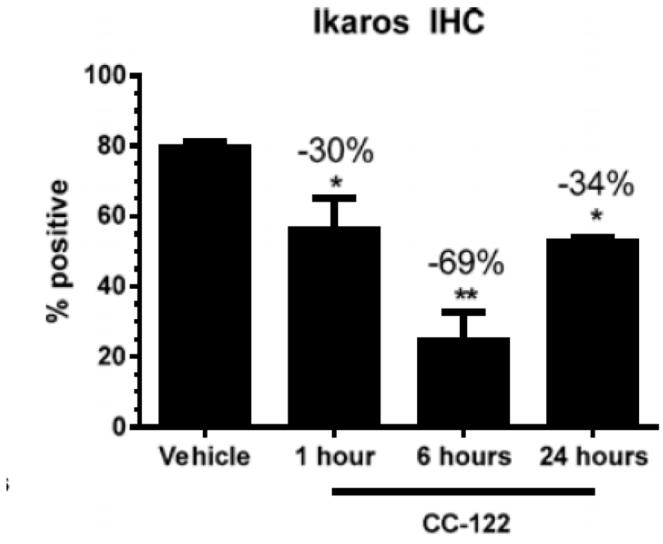
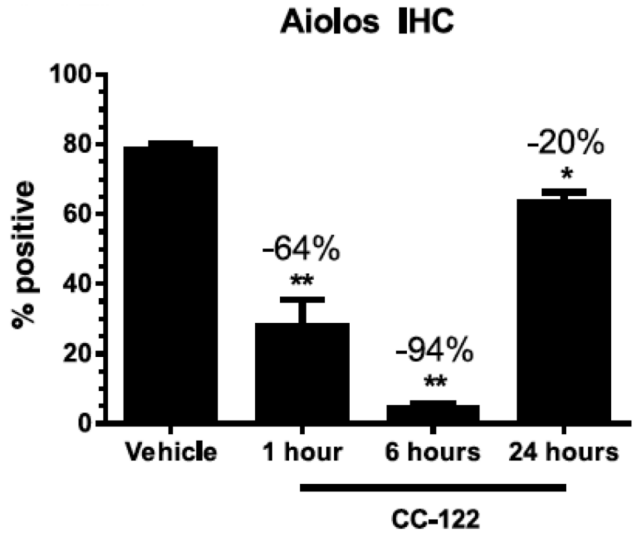
CC-122 reduces tumor growth and promotes degradation of Aiolos and Ikaros











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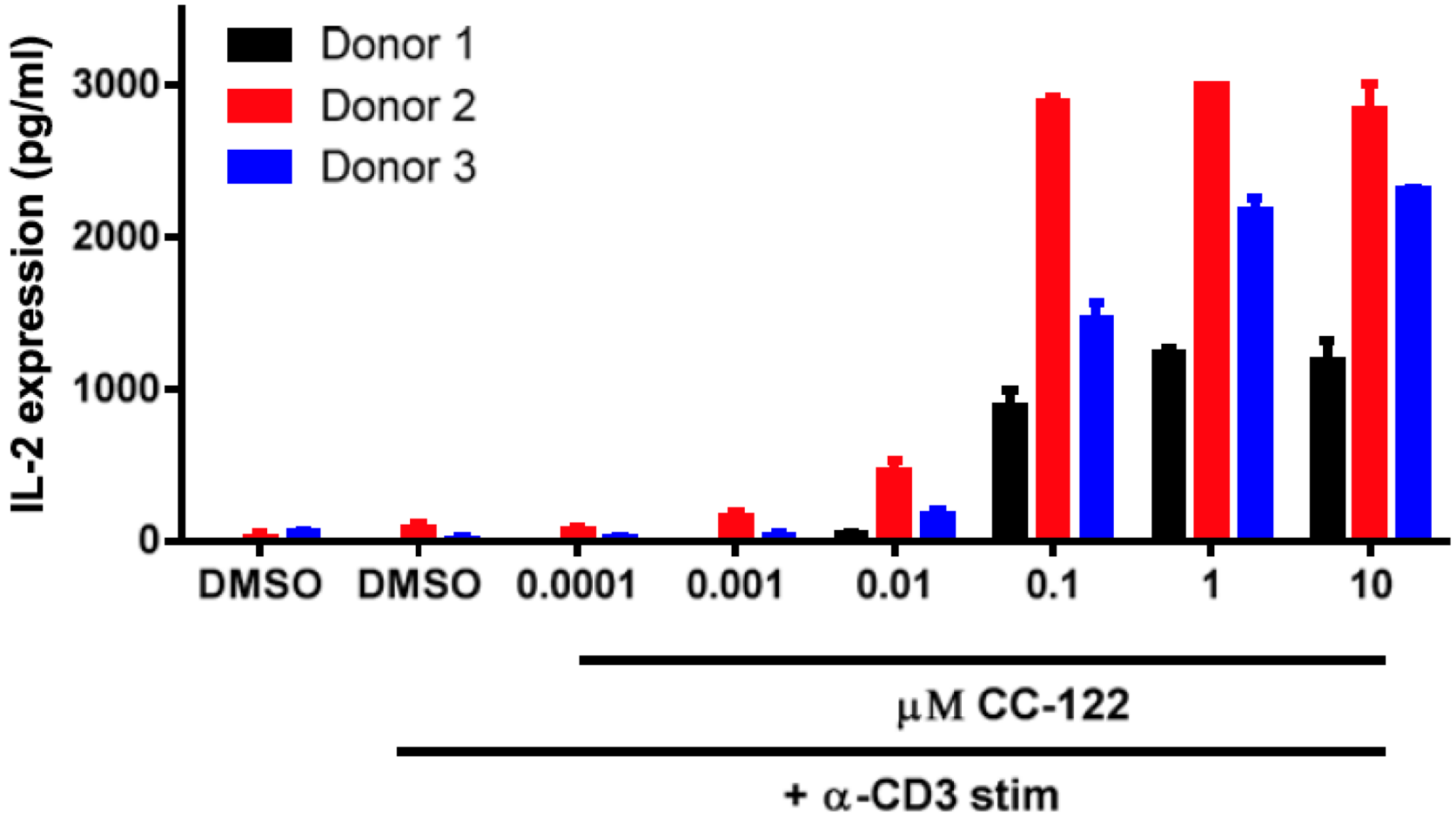
CC-122 increases IL-2 secretion



Hagner P et al. Blood. 2015;126(6):779-789

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Comparative efficacy of lenalidomide, pomalidomide and avadomide in vitro

Activity	Assay/Cell Line	LEN (μM)	POM (μM)	CC-122 (μM)
Immune modulation (EC_{50})	Whole blood TNF-α	>10	0.15	0.14
	T-cell IL-2	0.17	0.010	0.012
	NK-cell IFN-γ	0.052	0.0011	0.0015
Anti-proliferative (IC_{50})	H929 (MM)	1	0.09	0.09
	LEN-Resistant H929 (MM)	>30	6.0 to >30	0.8 to 2
	WSU-DLCL2 (GCB-DLBCL)	>100	NA	2.1
	SUDHL4 (GCB-DLBCL)	>100	NA	>10
	OCI-Ly19 (GCB DLBCL)	>100	NA	>10
	OCI-Ly10 (ABC-DLBCL)	0.15	NA	0.0085
	U2932 (ABC-DLBCL)	2.6	NA	0.12
	TMD8 (ABC-DLBCL)	75	NA	0.44
	RIVA (ABC-DLBCL)	>100	NA	4.3
	Karpas-1106P (PMBL-DLBCL)	>100	NA	0.71
Anti-angiogenesis (IC_{50})	Human Umbilical Artery	1.7	0.33	0.0094
Anti-platelet (IC_{50})	Immature MK colonies	0.41 to 1.3	0.35 to >10	>10
	Intermediate MK colonies	1.3 to >10	1.4 to >10	>10
CRBN binding (IC_{50})	CRBN competition binding to THAL-beads	2	2	20

Anita K Gandhi et al.
Blood 2012 120:2963

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Conclusions

- CC-122 is a novel non-phthalimide analog of the IMiDs immunomodulatory drugs (lenalidomide and pomalidomide) and a first in class PPM (Pleiotropic Pathway Modifier) compound with multiple biological activities including potent anti-proliferative activity against B-lineage cells (10-fold greater than lenalidomide), anti-angiogenic activity (100-fold greater than lenalidomide) and immunomodulatory effects (10-fold greater than lenalidomide).
- The molecular target of CC-122 is cereblon (CRBN), a substrate receptor of the Cullin ring E3 ubiquitin ligase complex (CRL4).
- CC-122 promotes ubiquitination of lymphoid transcription factors Ikaros (IKZF1) and Aiolos (IKZF3) in a CRBN-dependent manner, leading to their subsequent degradation.