Lenalidomide – meccanismo d'azione: è tutto chiaro?

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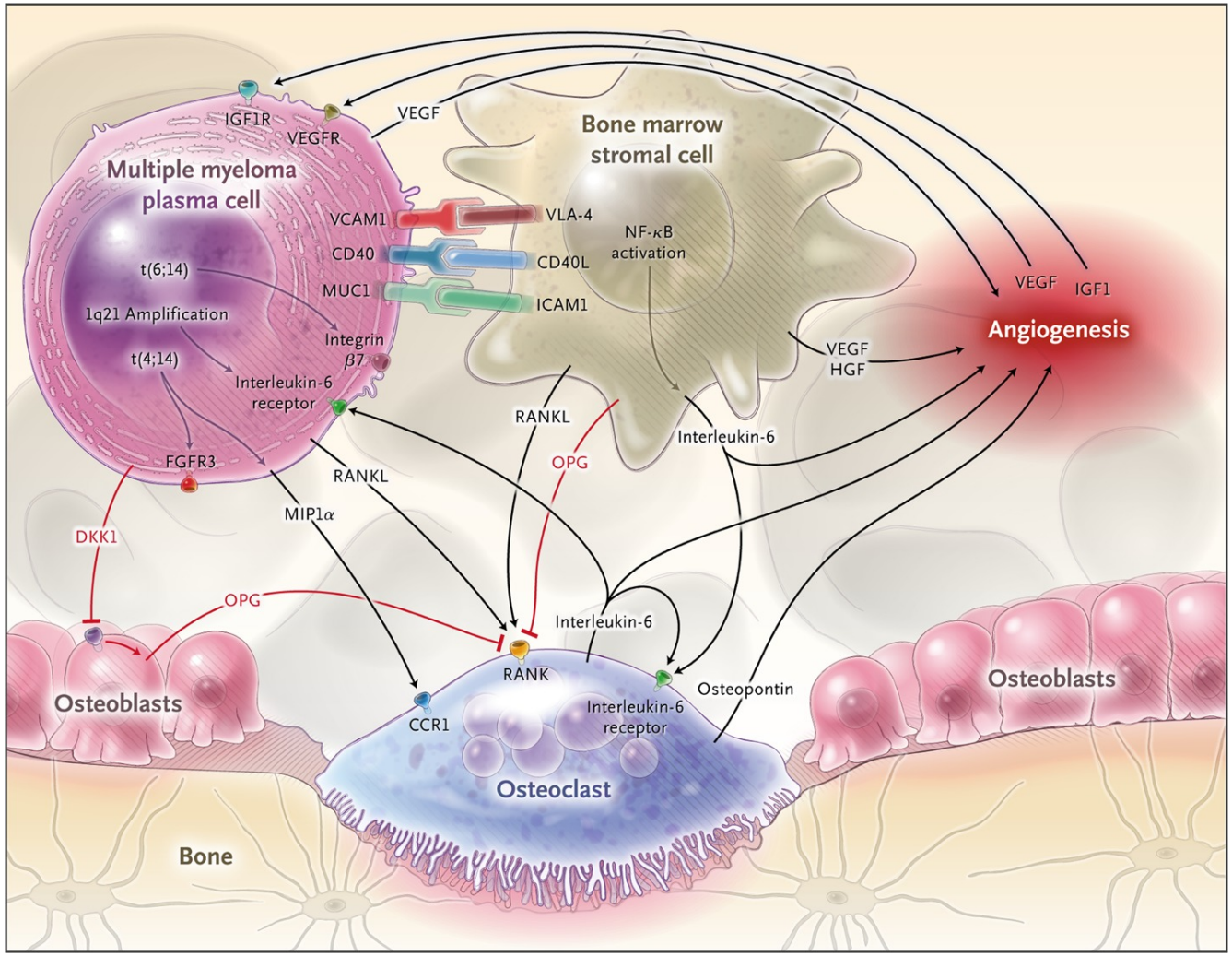
Disclosure

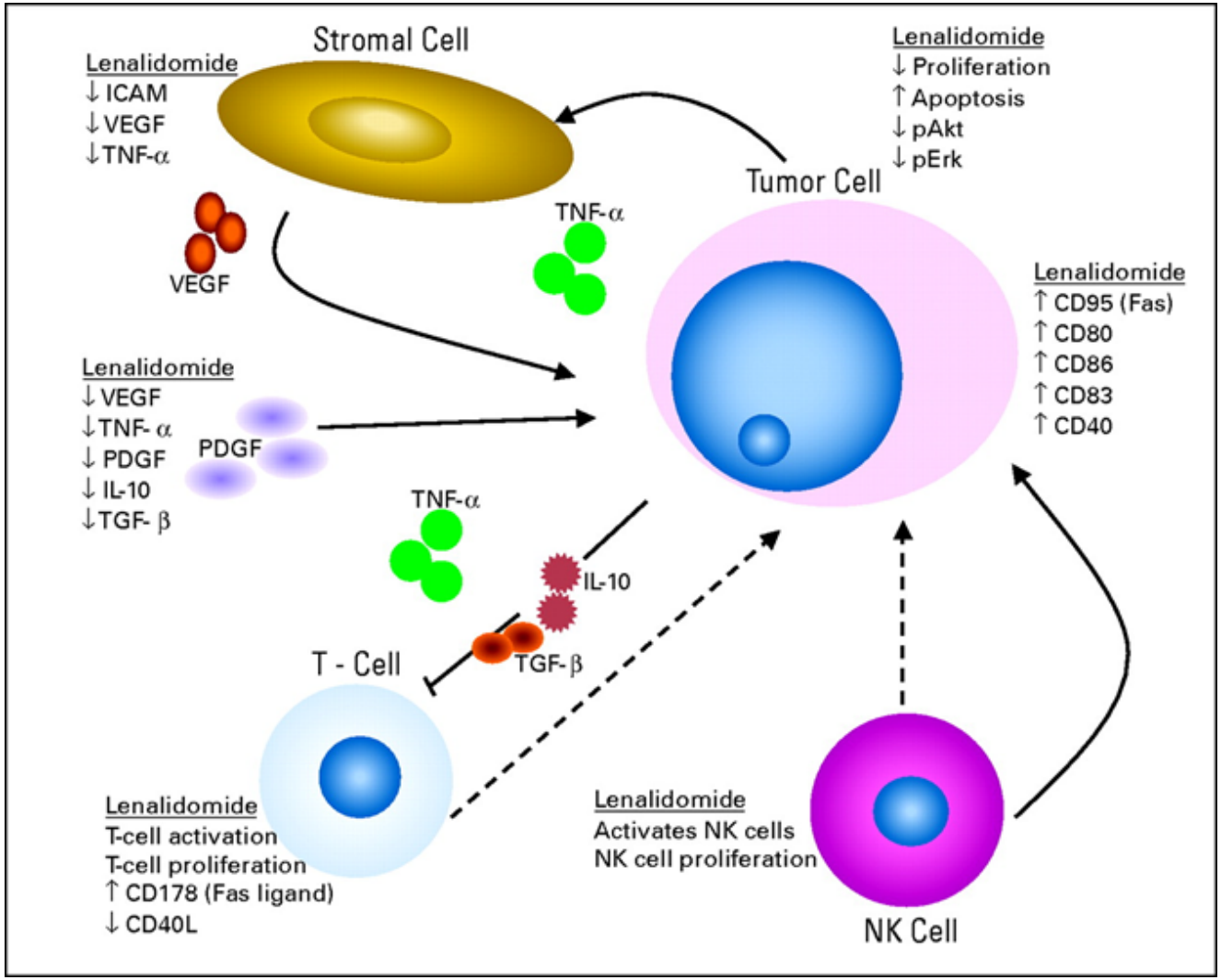
- Board member/Advisory panel
  - Teva, Pfizer
- Consultant
  - Gilead, Roche, Pfizer, Lilly

Molecular/cellular pathogenesis of multiple myeloma



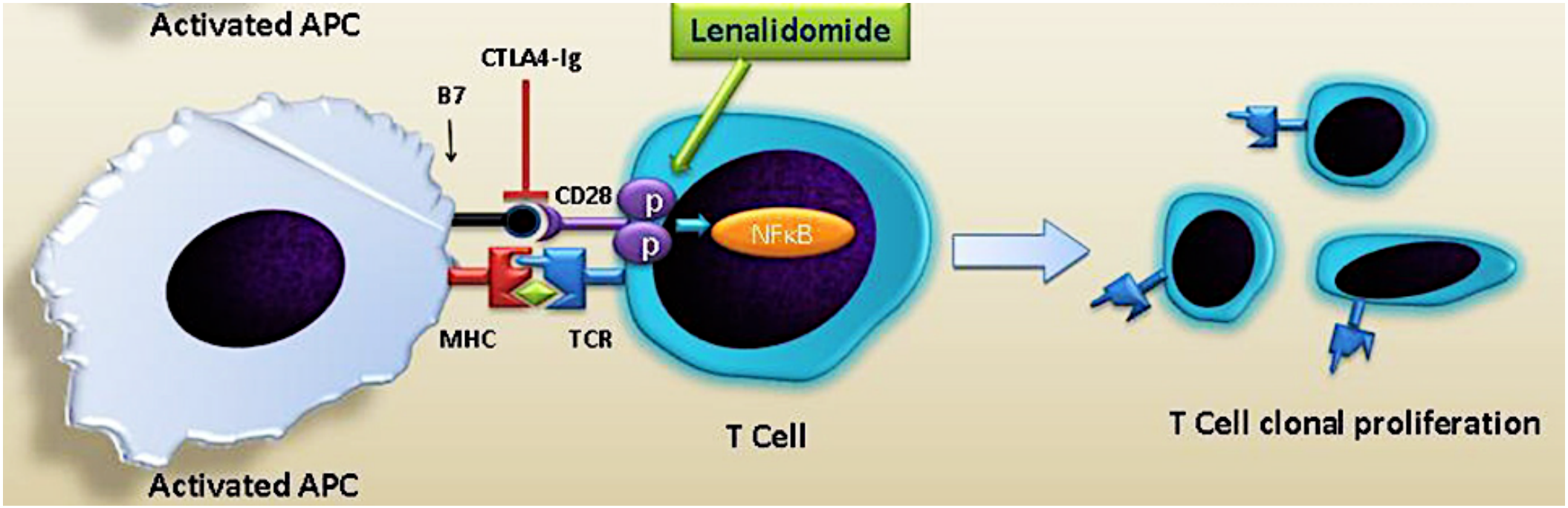
Palumbo and Anderson. NEJM 2011

What lenalidomide does



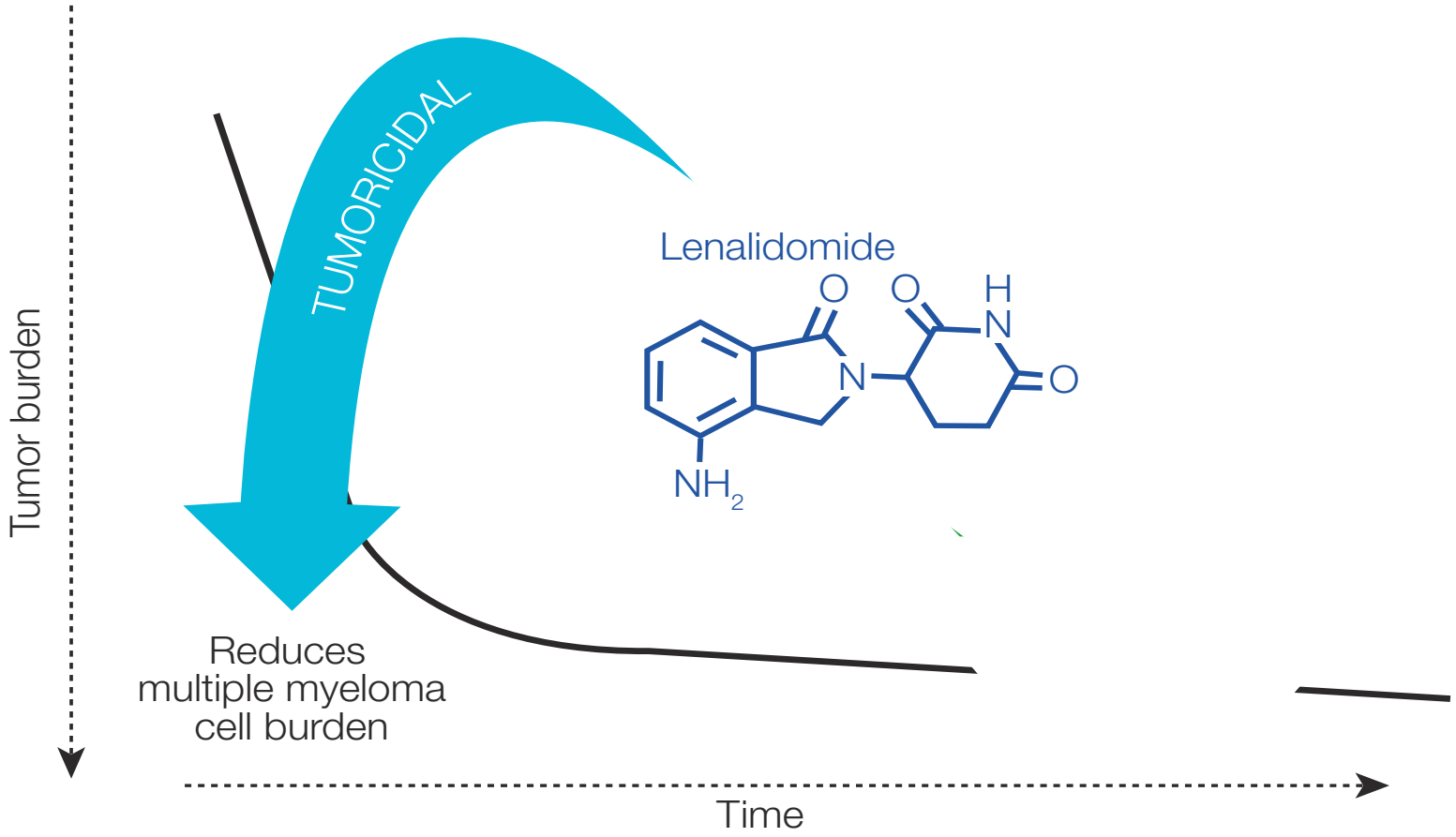
Chanan-Khan, et al. *J Clin Oncol.* 2008

Tyrosine phosphorylation of CD28 on T cells by lenalidomide activates downstream targets (eg, PI3K, GRB-2-OS, and NF-κb) leading to T cell clonal proliferation



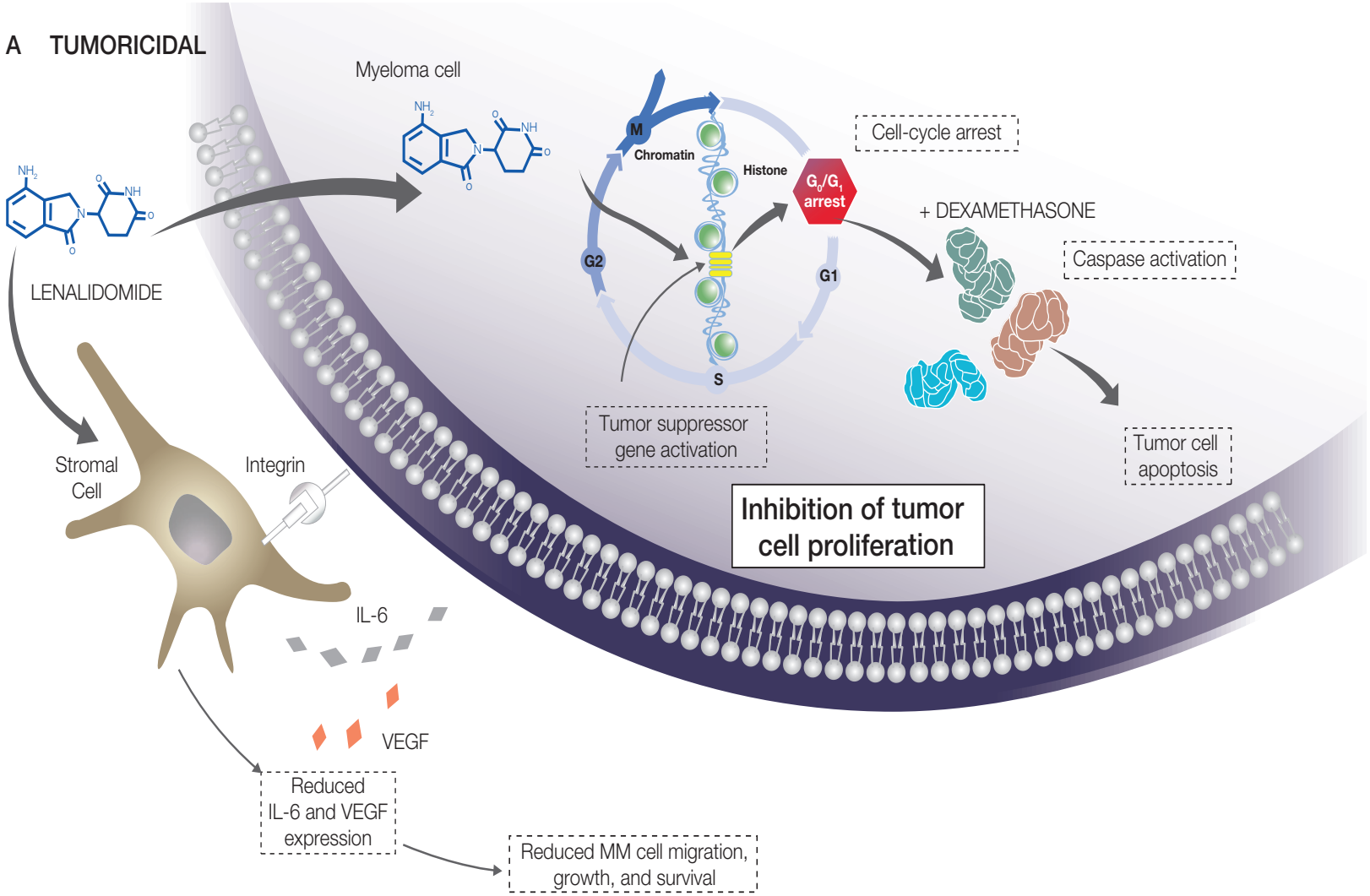
Kotla V et al. Journal of Hematology & Oncology 2009

Lenalidomide has tumoricidal activity



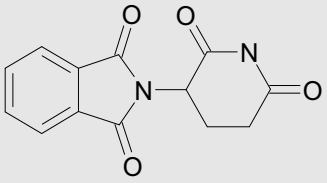
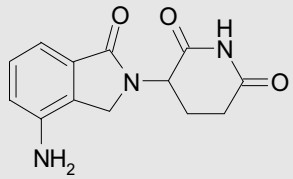
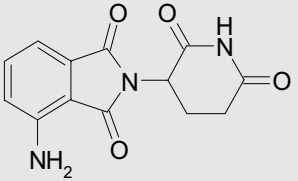
Davies F, Baz R. Blood Reviews 2010

Mechanism of tumor cell death and disruption of stromal support by lenalidomide



Davies F, Baz R. Blood Reviews 2010

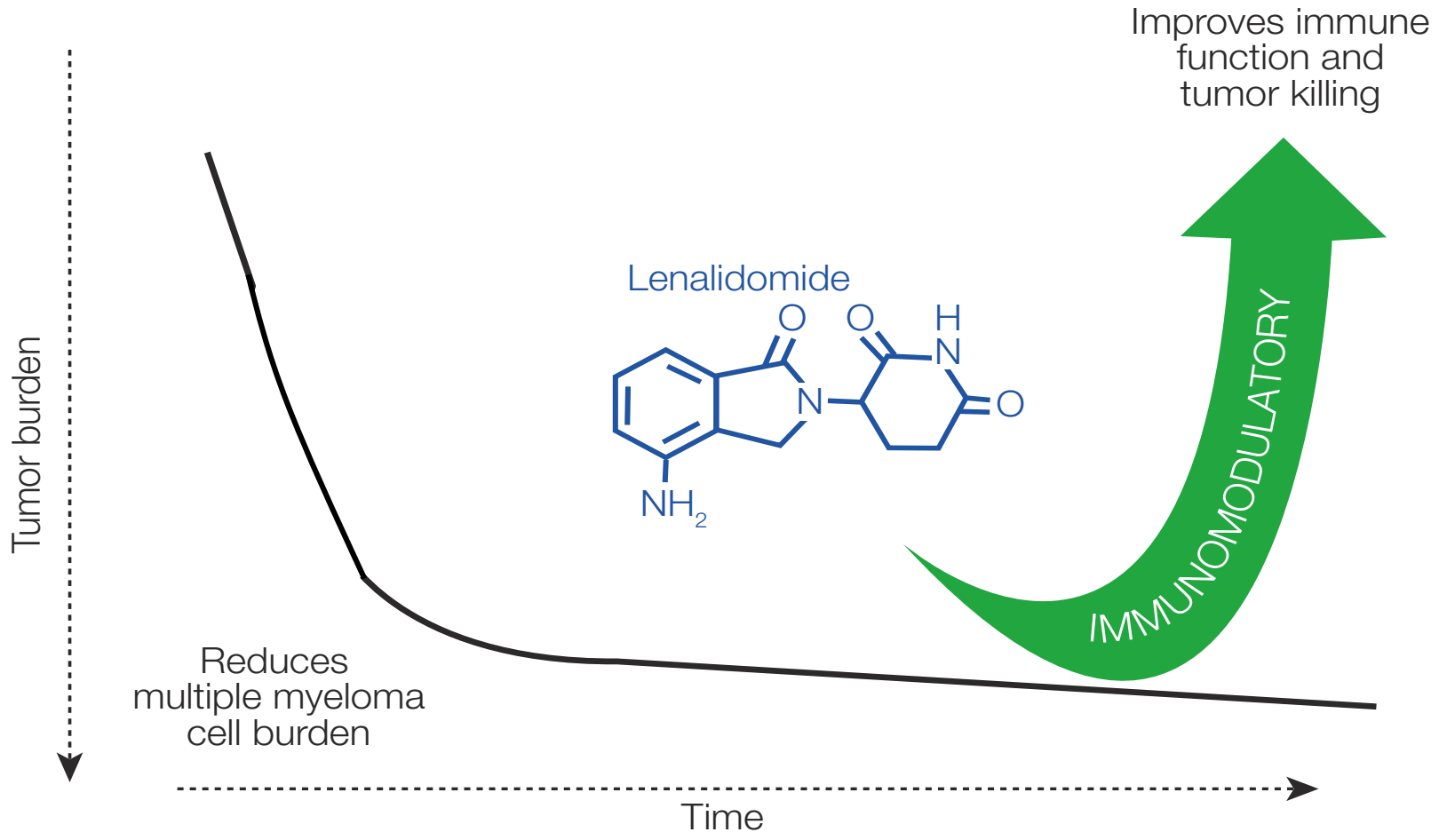
Characteristics of thalidomide and the IMiDs lenalidomide and pomalidomide

Characteristic	Thalidomide	Immunomodulatory compounds	
		Lenalidomide	Pomalidomide
Structure			
Plasma C_{max}, μM[7,8]	5.4	2.2 [a]	0.19
Tumoricidal properties Inhibition of DNA synthesis in MM.1S cell line, IC_{50}, μM[9]	>100	0.1–1	0.01–0.1
Immunomodulation Interleukin-2 enhancement, EC_{50}, μM[10]	>100	0.15	0.010
Antiangiogenesis Inhibition of sprout formation from human umbilical artery ring explants, IC_{50}, μM[11]	~0.1	~1.0	0.1–1.0

[a] C_{max} reported in ng/mL.

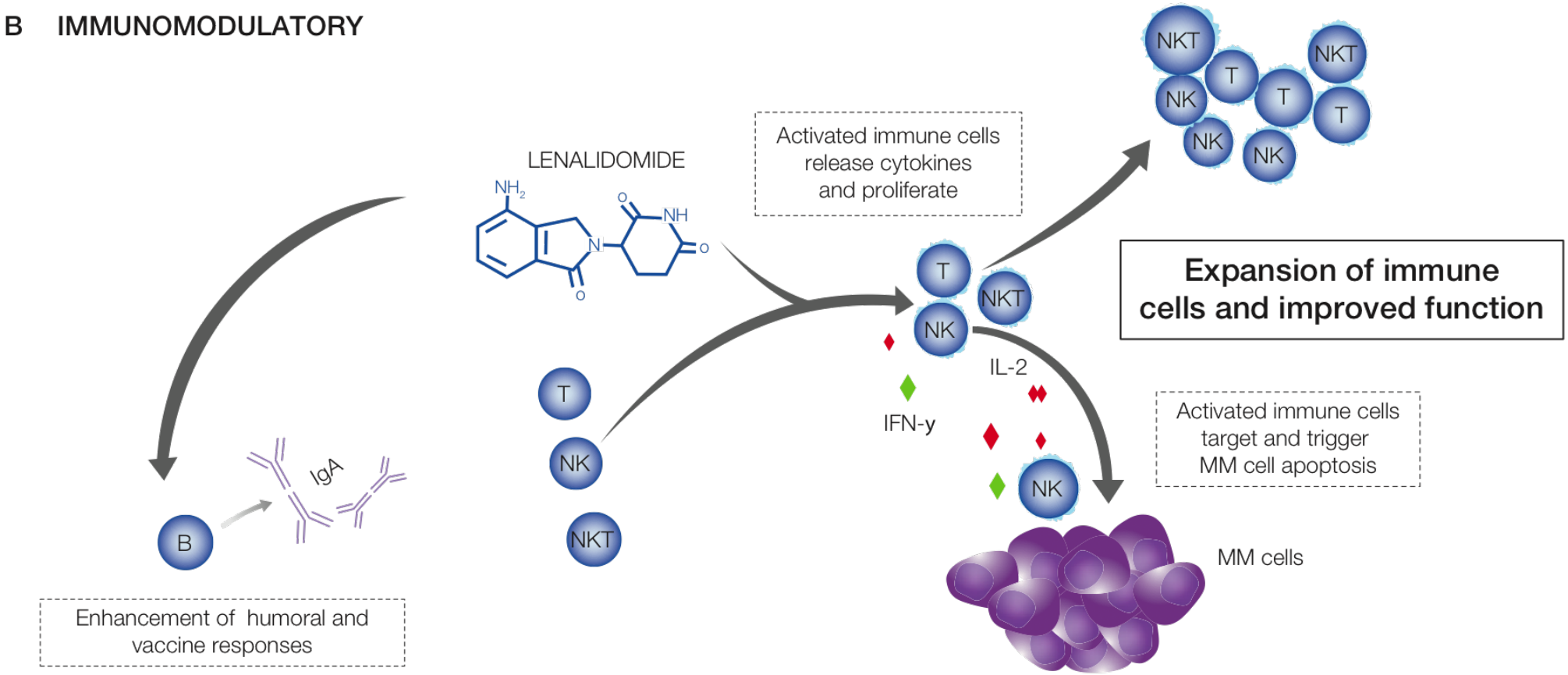
Davies F, Baz R. Blood Reviews 2010

Lenalidomide has immunomodulatory effect



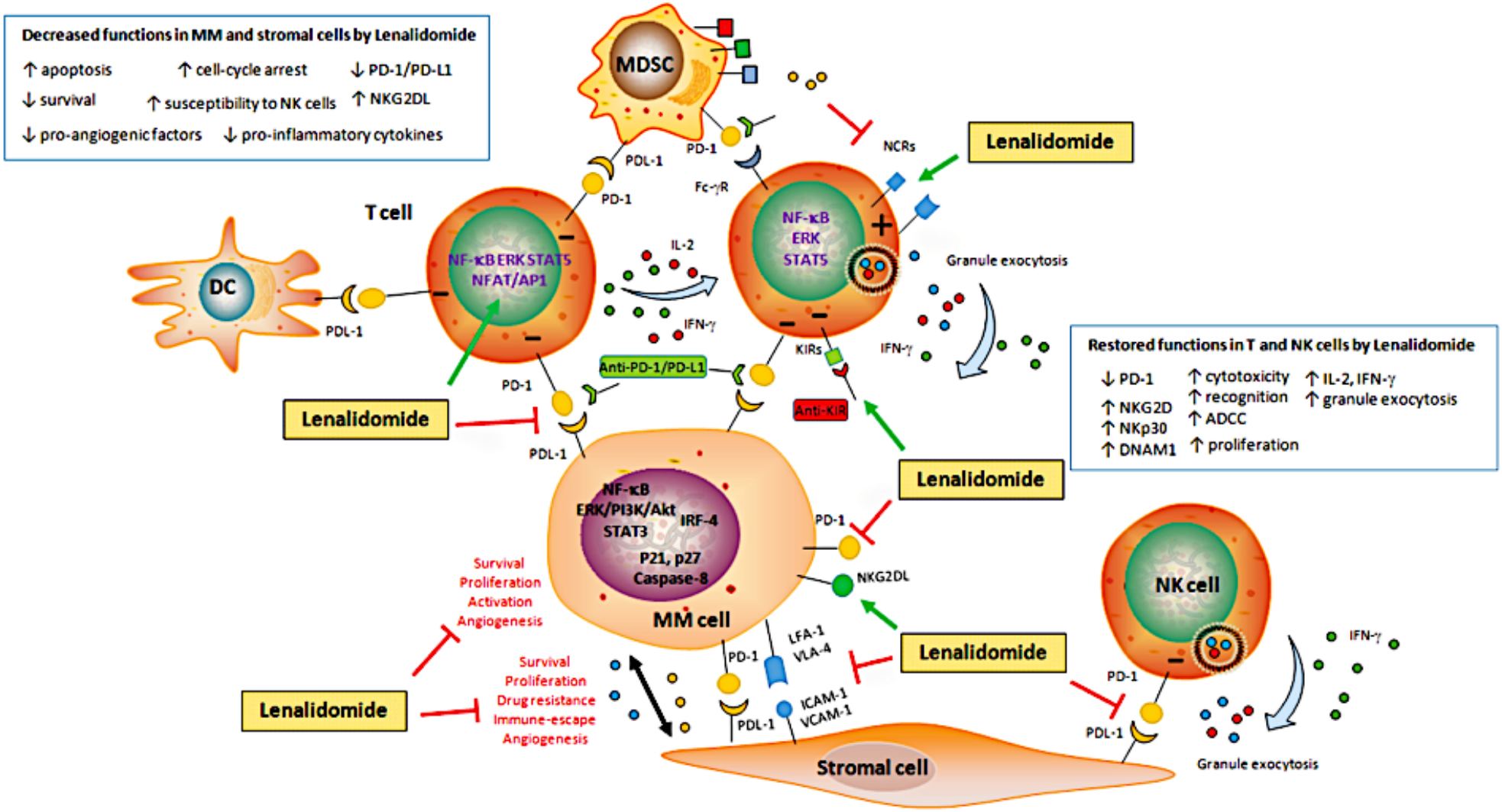
Davies F, Baz R. Blood Reviews 2010

Lenalidomide increases immune response



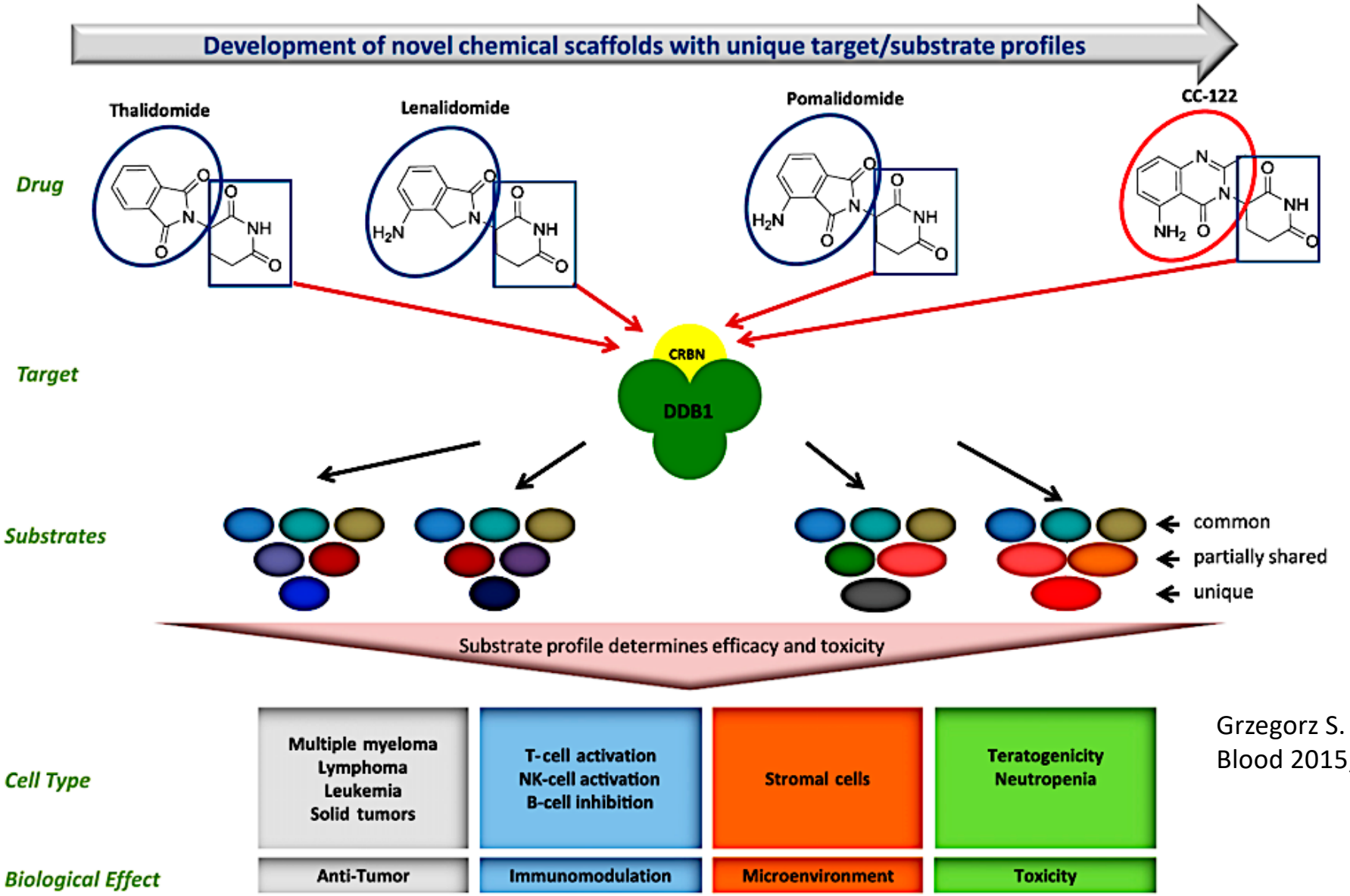
Davies F, Baz R. Blood Reviews 2010

Lenalidomide down-regulates PD-1 on tumor cells and PD-L1 on both stromal and tumor cells, thus restoring immune response



Giuliani M et al. Oncotarget 2017; 8(14):24031-24044

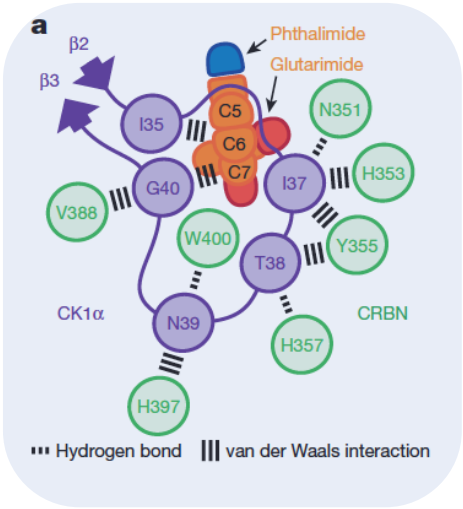
Schematic model of cereblon (CRBN) binding resulting in pleiotropic activity of novel drugs

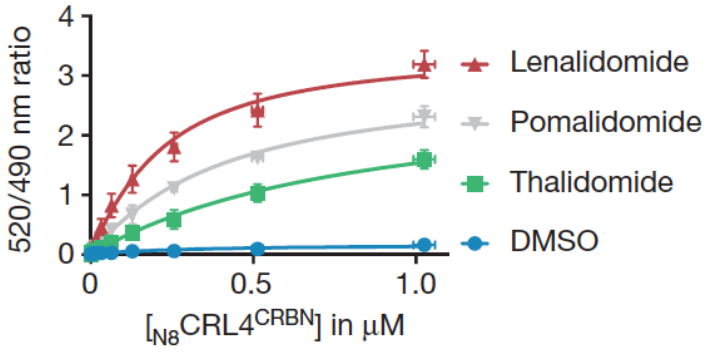


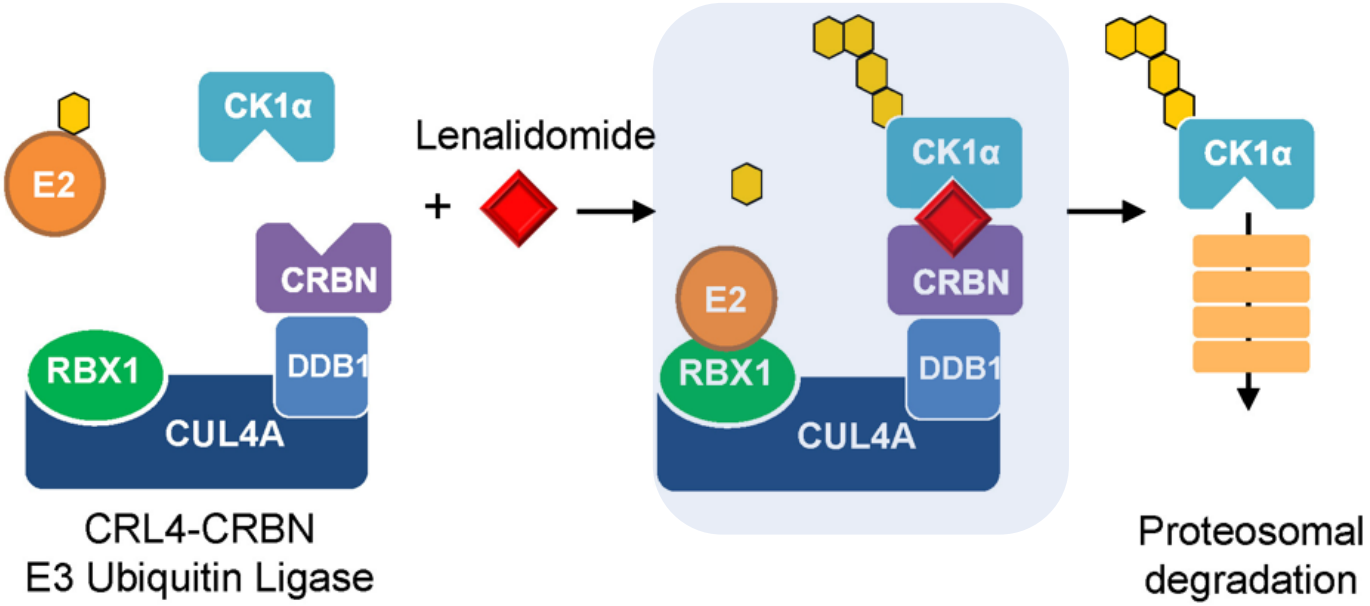
Grzegorz S. Nowakowski
Blood 2015;126(6):698

Lenalidomide-induced degradation of casein kinase 1α (CK1α)

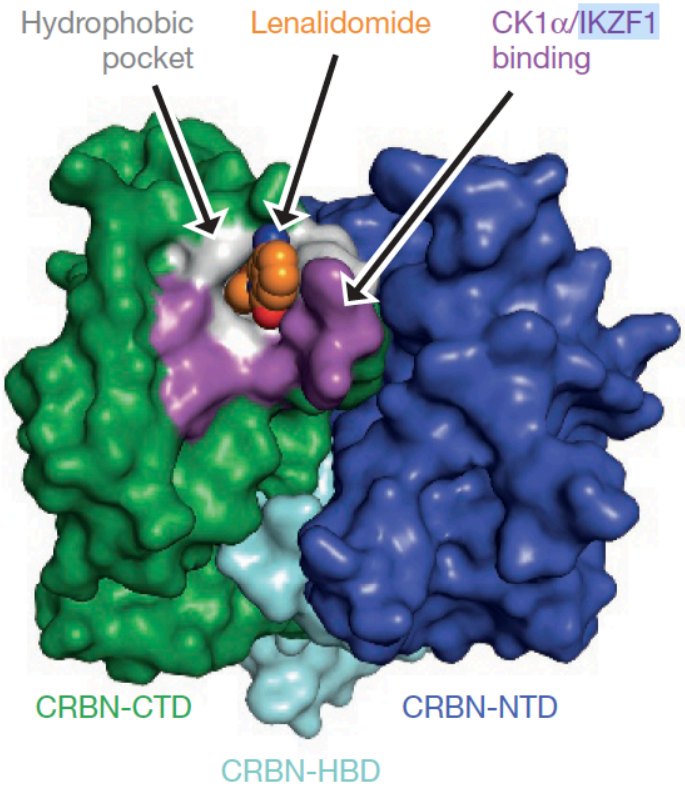
Petzold et al., Nature 2014
List et al. 2015







Degradation of Ikaros family trascription factors provides a mechanism for lenalidomide's effects in multiple myeloma



CK1α and IKZF1 share a common CRBN interface

IKZF1/3 are essential for B-cell differentiation and multiple myeloma cells survival

Interaction with IKZF1/3 may explain lenalidomide efficacy in mantle cell lymphoma and chronic lymphocytic leukemia

IKZF3 regulates expression of IRF4 (positive feedback loop with the oncogene MYC) and induces a transcriptional repression of the IL2 gene

Petzold et al., Nature 2014

Conclusions

- Lenalidomide has a complex mechanism of action
- Preclinical and clinical studies put forward a dual mechanism of action for lenalidomide: a direct tumoricidal activity and immunomodulation
- Interaction with CRBN and the consequent degradation of endogenous substrates (e.g., Ikaros family trascription factors) may partially account for the mechanism of lenalidomide action in MM