Lenalidomide – meccanismo d'azione: è tutto chiaro?

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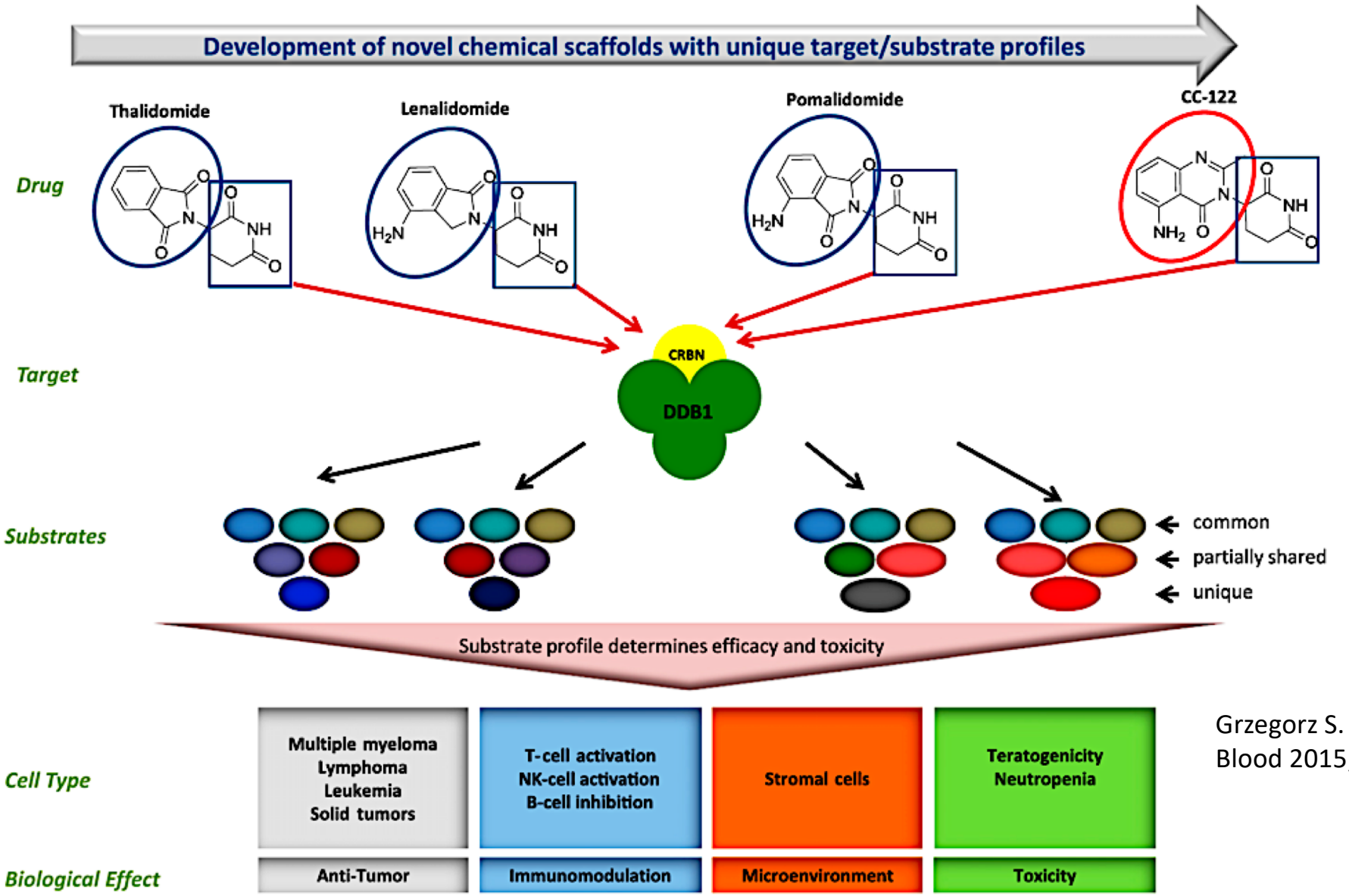
NUOVI ORIZZONTI TERAPEUTICI nel MONDO dei "LINFOMI"

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



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

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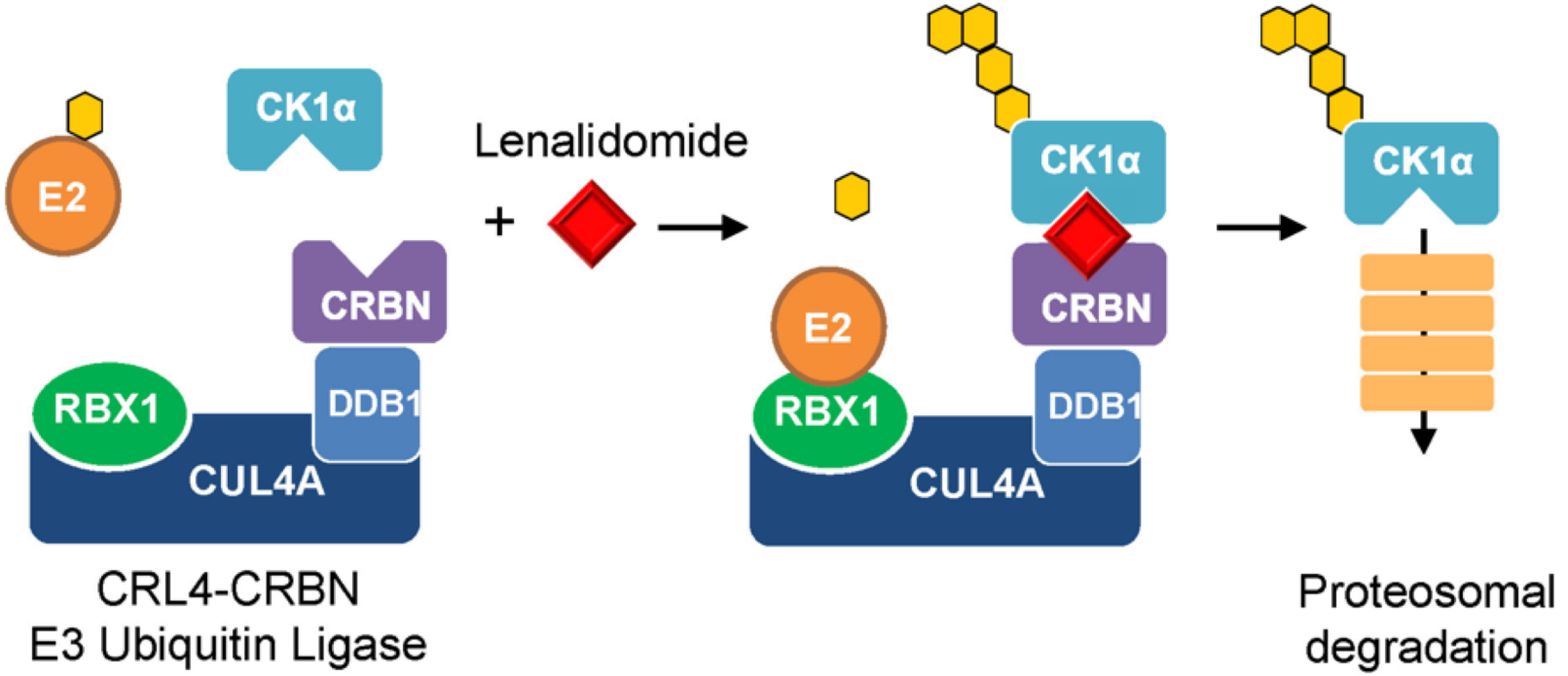
Lenalidomide-induced degradation of casein kinase 1α (CK1α)



CRL4: cereblon (CRBN) ubiquitin ligase
Cullin 4A: CUL4A

List A et al. 2015

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Differences between thalidomide, lenalidomide and pomalidomide

Name	Thalidomide	Lenalidomide	Pomalidomide
Empirical Formula	$C_{13}H_{10}N_2O_4$	$C_{13}H_{13}N_3O_3$	$C_{13}H_{11}N_3O_4$
Molecular weight	258.2	259.3	273.2
Chemical Structural	Thalidomide has two oxo groups in Phthaloyl ring	Lenalidomide has amino group at 4th position and single oxo group in Phthaloyl ring	Pomalidomide has amino group at 4th position and two oxo groups in Phthaloyl ring
Effects on T-cell proliferation	Thalidomide stimulates T cell proliferation and increases IFN-γ and IL-2 production	Lenalidomide is 100–1000 times more potent in stimulating T cell proliferation and IFN-γ and IL-2 production than thalidomide	Pomalidomide is similar to lenalidomide, in addition, it also enhances transcription factor T-bet, which reverts Th2 cells into Th1 like effector cells in vitro
Adverse Effects	Thalidomide has higher incidence of side effects like sedation, neuropathy and constipation.	Lenalidomide has lower incidence of adverse effects namely sedation, constipation and neuropathy than thalidomide.	Pomalidomide has lower incidence of adverse effects like sedation, constipation and neuropathy than thalidomide.
Teratogenecity	Thalidomide is a known teratogen.	Lenalidomide is not teratogenic in rabbit models	Pomalidomide is a known teratogen.

Kotla V et al. Journal of Hematology & Oncology 2009, 2:36

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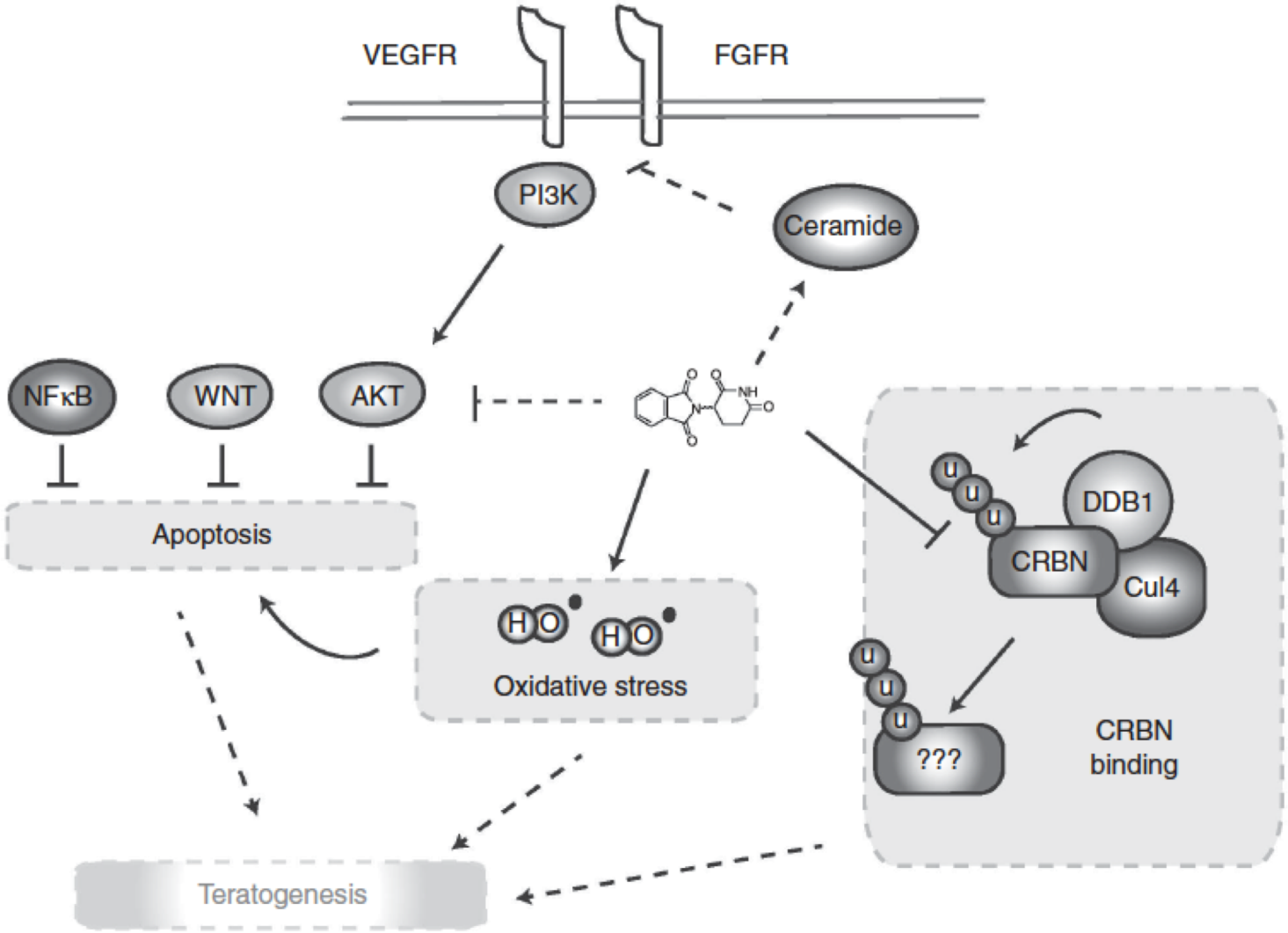
Pro-apoptotic, anti-angiogenic, oxidative and CRBN-mediated effects of thalidomide combine to induce teratogenicity



Shortt J et al. Oncogene (2013) 32, 4191–4202

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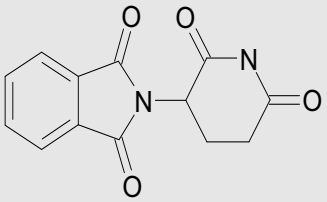
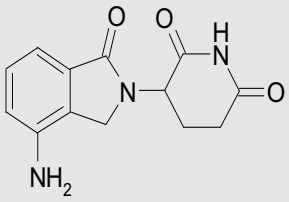
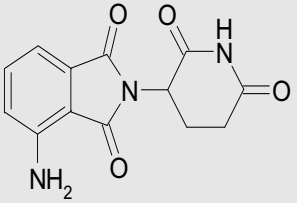
Characteristics of thalidomide and the IMDs lenalidomide and pomalidomide

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 24 Suppl. 1 (2010) S13–S19

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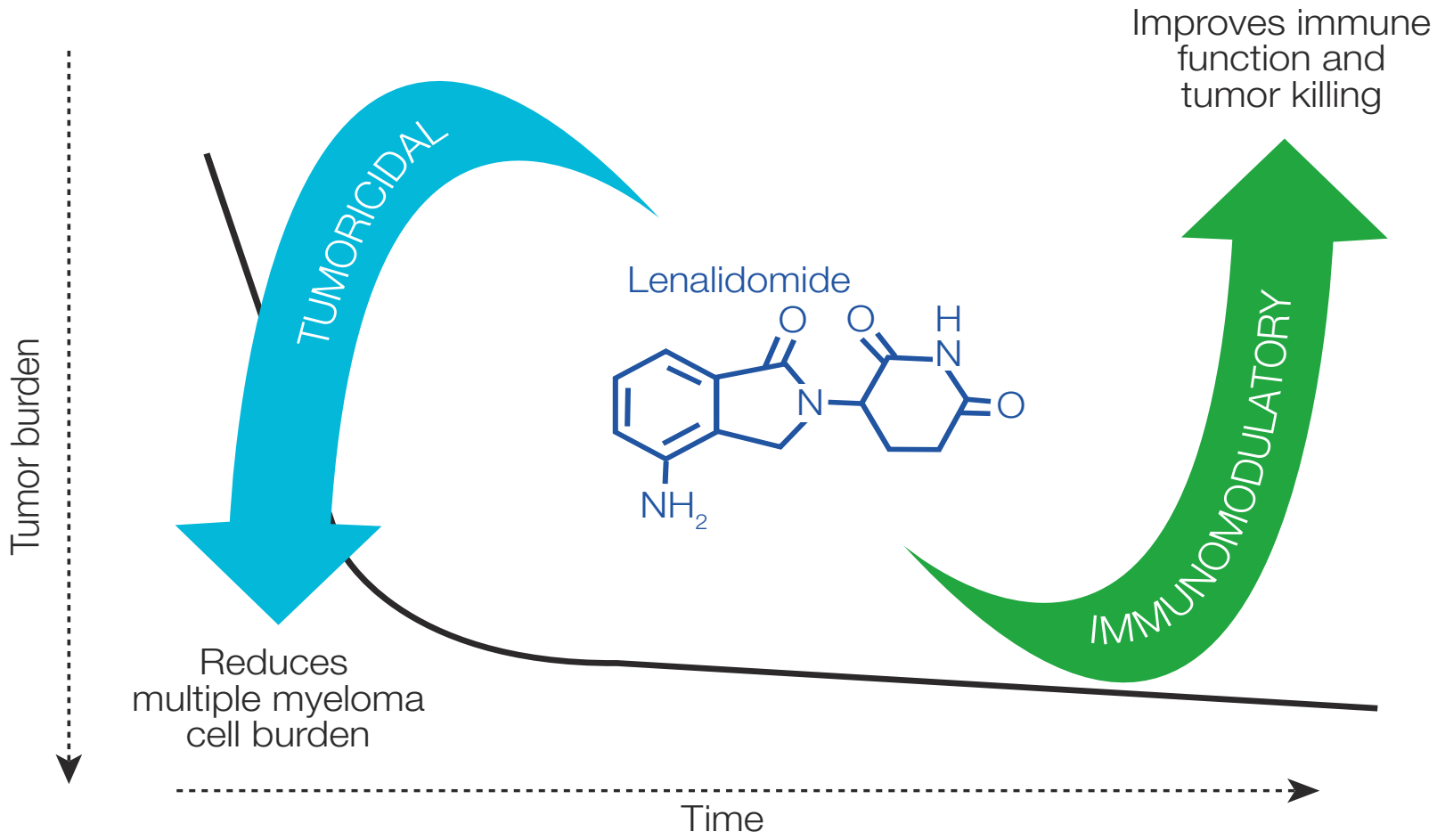
Lenalidomide has tumoricidal activity and immunomodulatory effect



Davies F, Baz R. Blood Reviews 24 Suppl. 1 (2010) S13–S19

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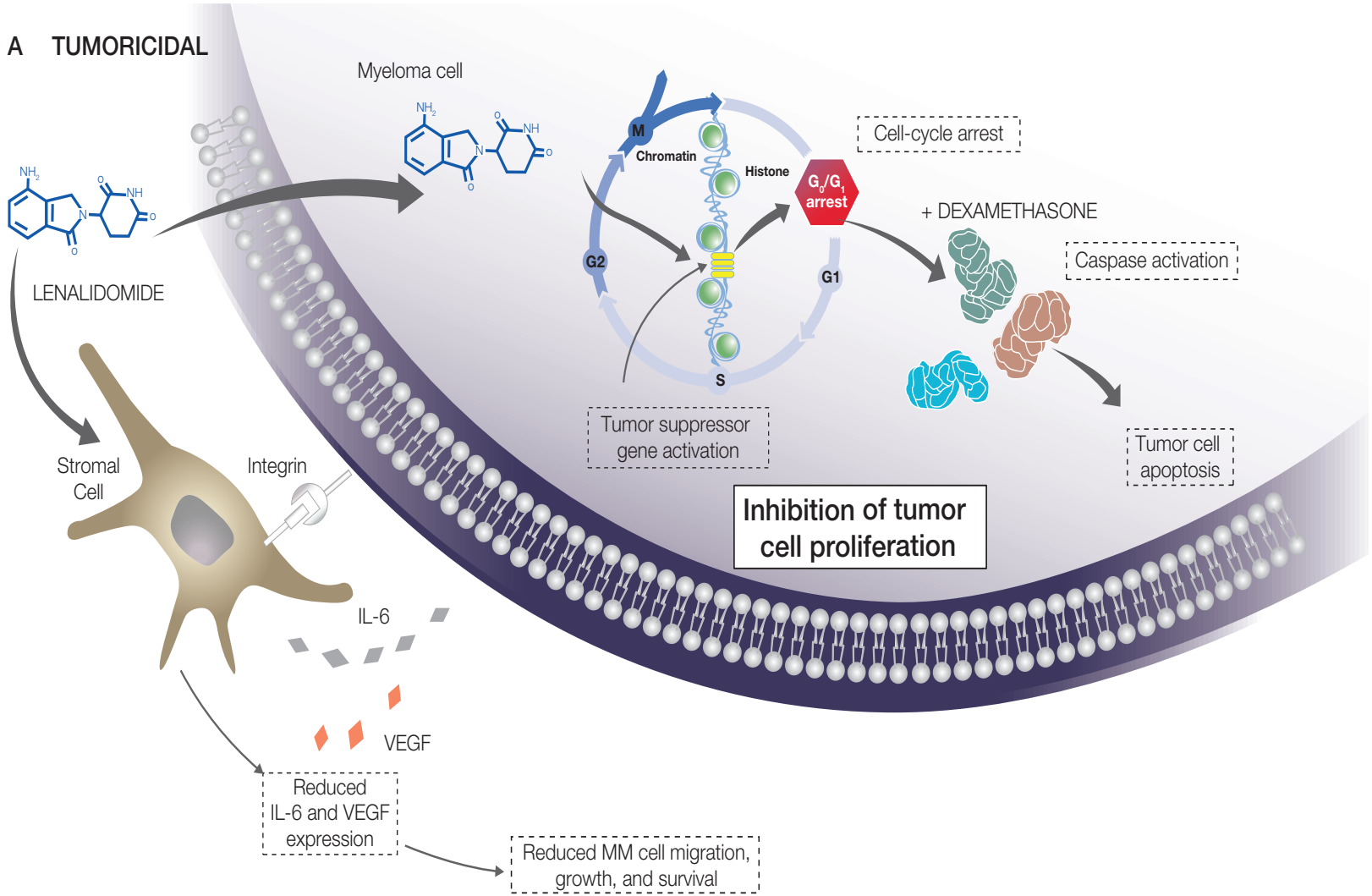
Mechanism of action of lenalidomide: **tumor cell death**



Davies F, Baz R. Blood Reviews 24 Suppl. 1 (2010) S13–S19

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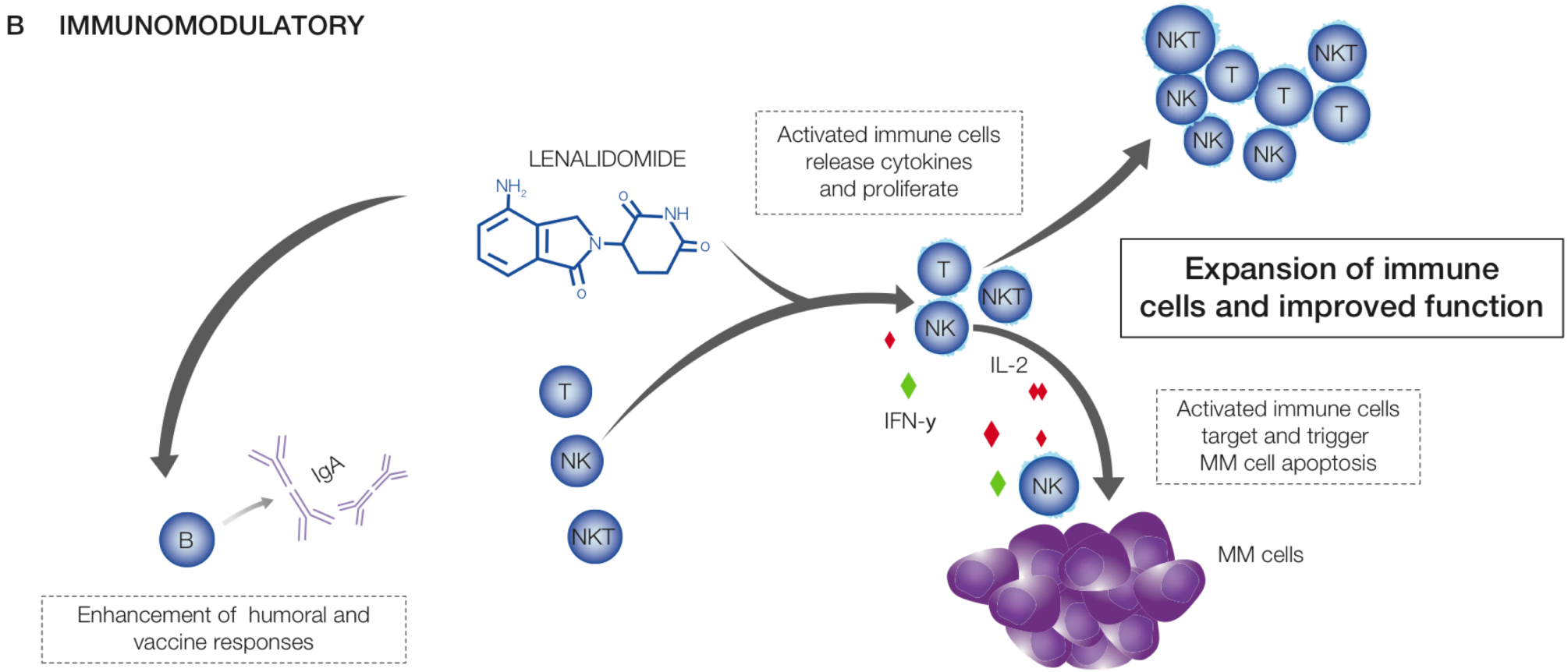
Mechanism of action of lenalidomide: **increased immune response**



Davies F, Baz R. Blood Reviews 24 Suppl. 1 (2010) S13–S19

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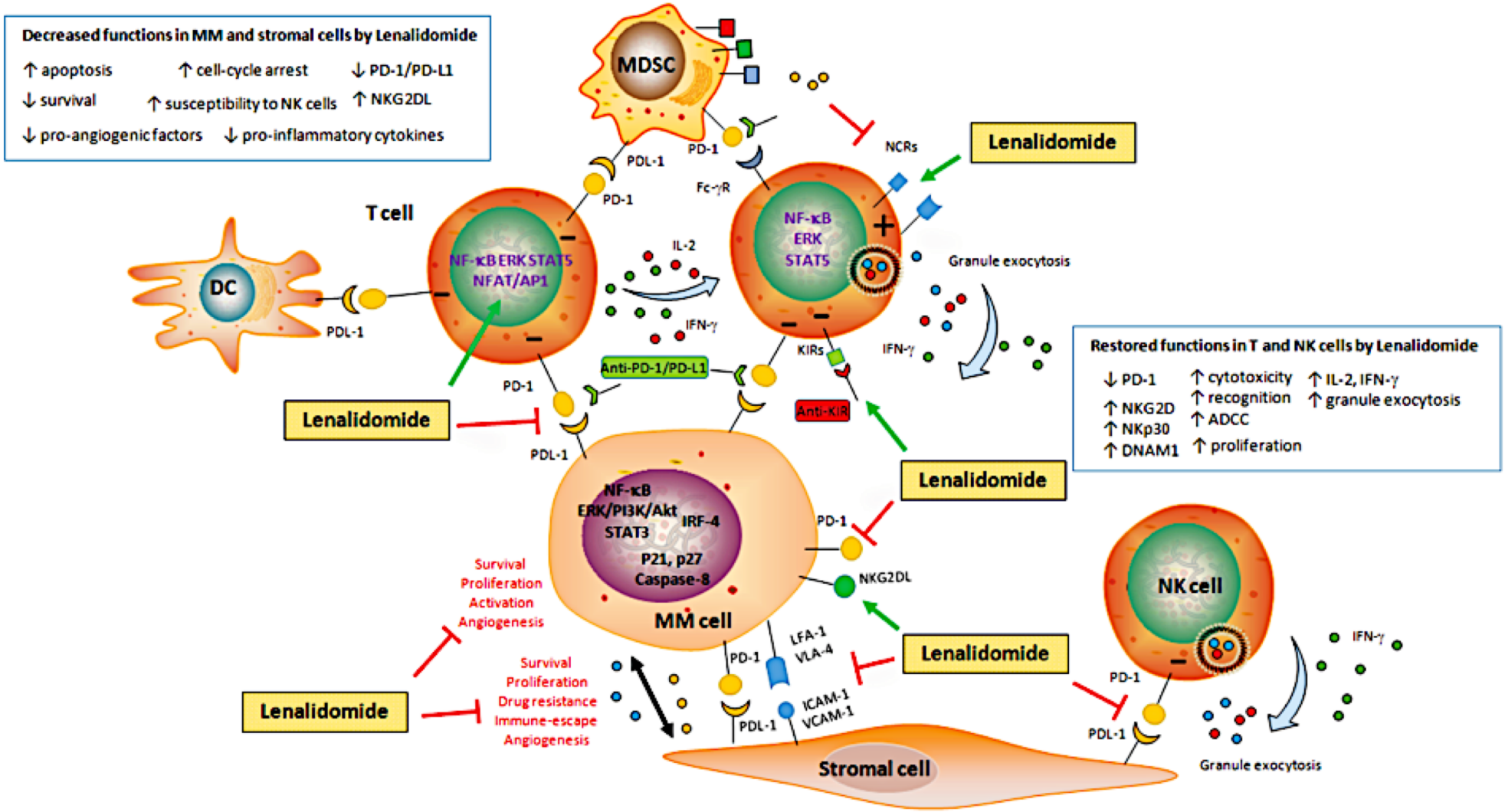
Lenalidomide down-regulates PD-1 on tumor cells and PD-L1 on both stromal and tumor cells, thus restoring **immune response**



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

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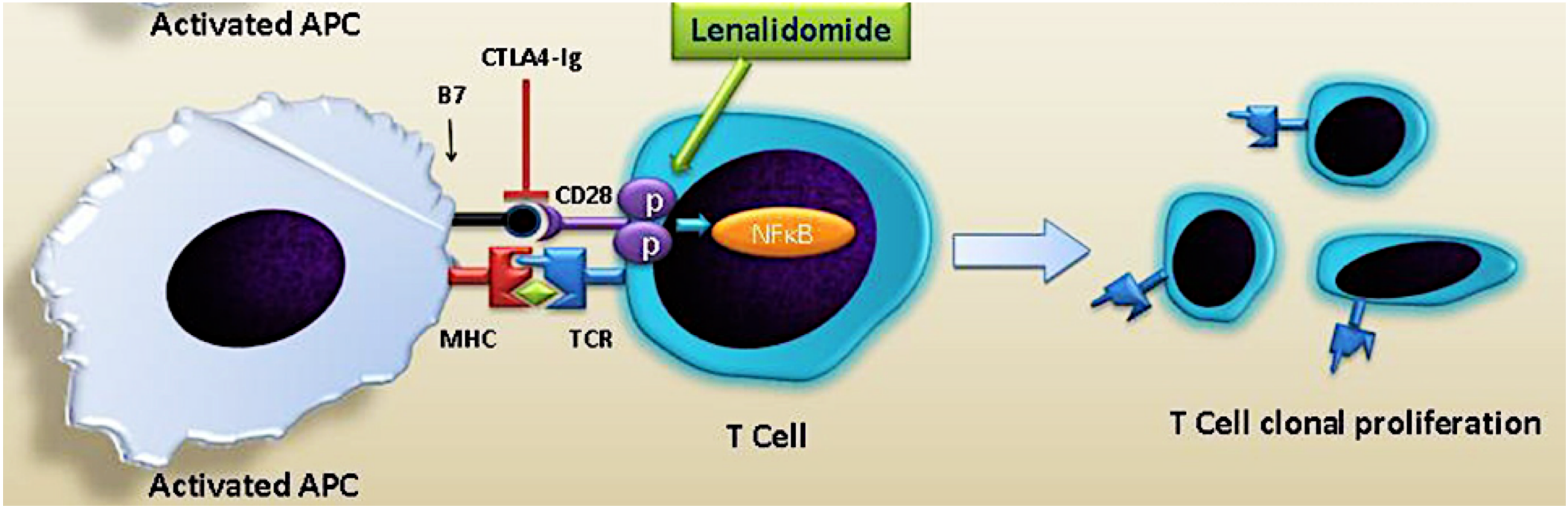
Lenalidomide induces tyrosine phosphorylation of CD28 on T cells leading to activation of downstream targets such as PI3K, GRB-2-OS, and NF-κb, thus leading to T cell clonal proliferation



Kotla V et al. Journal of Hematology & Oncology 2009, 2:36

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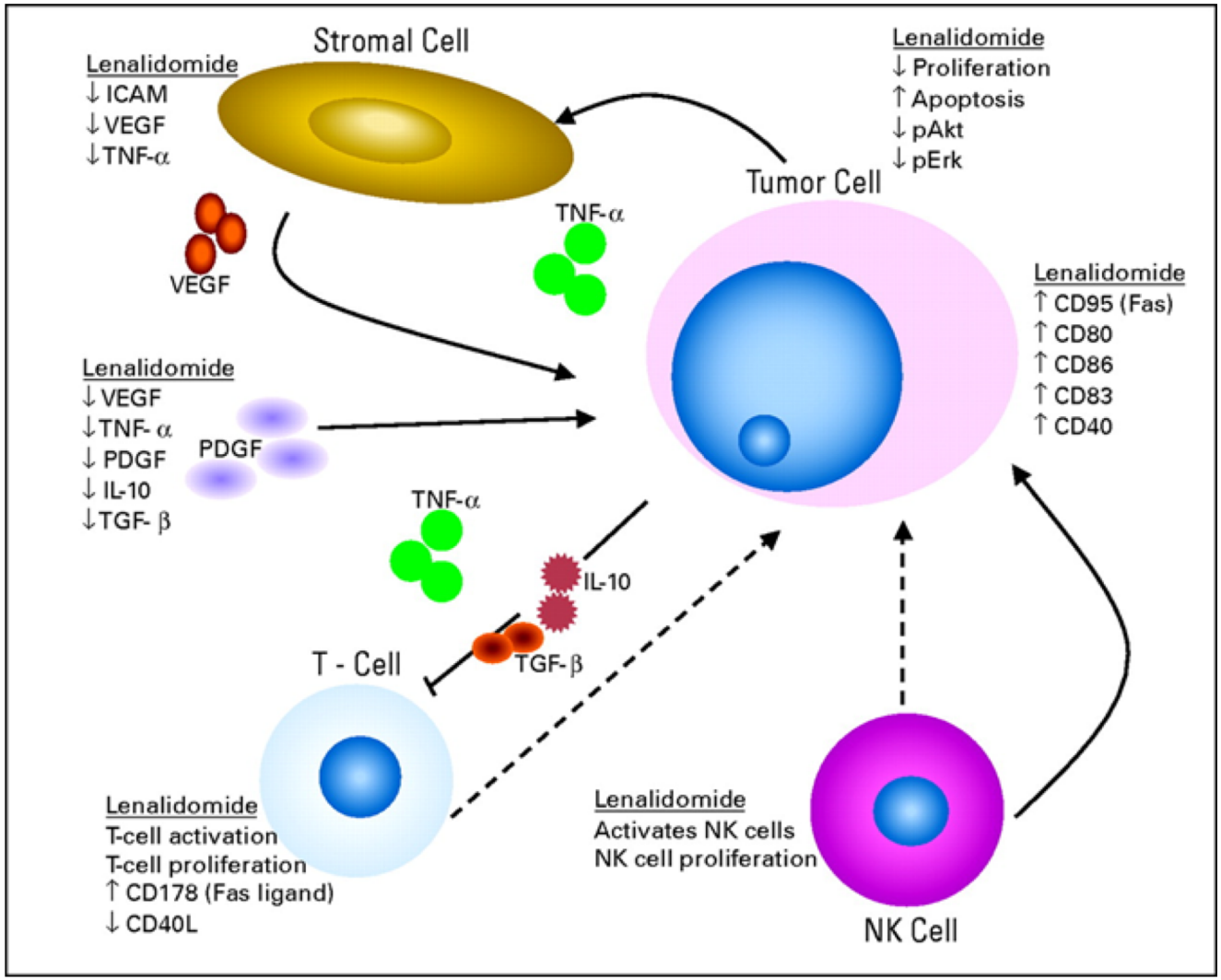
Mechanism of action of lenalidomide: **modulation of tumor microenvironment**



Chanan-Khan AA, et al. *J Clin Oncol.* 2008;26(9):1544-1552.

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Conclusions

- IMDs have a complex mechanism of action and a pharmacologic modelling is far from being defined
- Preclinical and clinical studies put forward a dual mechanism of action for lenalidomide, involving both a direct tumoricidal activity and immunomodulation.
- However, it is presently unclear which mechanism(s) are responsible for clinical activity in patients responding to therapy; mechanisms themselves may also differ depending on the underlying malignancies and their tumor micro-environment.