

### Lenalidomide – meccanismo d'azione: è tutto chiaro?

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- Ipsen, Novartis, Pfizer, Sanofi Genzyme, AstraZeneca, Janssen, Gilead, EUSA Pharma, Roche, Lilly (scientific advisory board, consulting relationship)
- Ipsen, Sanofi Genzyme, Roche, Lilly (travel, accommodation, expenses)

## Characteristics of thalidomide and the IMiDs lenalidomide and pomalidomide



Characteristic	Thalidomide	Immunomodulatory compounds	
		Lenalidomide	Pomalidomide
Structure		$N \rightarrow N \rightarrow N$	$N \rightarrow N$
Plasma C <sub>max</sub> , μM <sup>7,8</sup>	5.4	2.2 <sup>a</sup>	0.19
Tumoricidal properties Inhibition of DNA synthesis in MM.1S cell line, IC $_{50}$ , $\mu M^9$	>100	0.1-1	0.01-0.1
Immunomodulation Interleukin-2 enhancement, EC <sub>50</sub> , μM <sup>10</sup>	>100	0.15	0.010
Antiangiogenesis Inhibition of sprout formation from human umbilical artery ring explants, $IC_{50},\mu M^{11}$	~0.1	~1.0	0.1–1.0
<sup>a</sup> C <sub>max</sub> reported in ng/mL.			

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

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



### **Cereblon: cellular functions**



- Cereblon on chromosome 3 was first described as associated with human cognitive functions (Cerebral protein with Lon protease)
- Functions in the brain as an ionic channel regulator
- Highly conserved from plants to humans, broadly expressed
- Regulates AMP kinase in insulin resistance, obesity
- Forms an E3 ubiquitin ligase complex with DDB1 (Damage Specific DNA Binding Protein 1), Cul4A (ubiquitin ligase component of a multimeric complex involved in the degradation of DNA damage-response proteins), Roc1 (regulator of cullins-1).

Lenalidomide induces degradation of IKAROS family zinc finger proteins (IKZF1/3) hematopoietic-specific transcription factors involved in the regulation of lymphocyte development



A. Keith Stewart: IMiDs: mechanism of action and future applications - Mayo Clinic

# Cereblon levels are highest in MM, leukemias, and neuroblastoma



CRBN - Entrez ID: 51185



## Lenalidomide-resistant multiple myeloma cells lack cereblon



## Lenalidomide has tumoricidal activity and immunomodulatory effect





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#### Mechanism of action of lenalidomide Tumor cell death





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#### Mechanism of action of lenalidomide Increased immune response





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#### Mechanism of action of lenalidomide Down-regulation of PD-1 and PD-L1 on tumor/T-cells



#### Mechanism of action of lenalidomide P-CD28 and PI3K, GRB-2-OS, and NF-кB activation



#### Mechanism of action of lenalidomide Modulation of tumor microenvironment





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



#### Lenalidomide

- Rapid absorption and good bioavailability
- no CYP metabolism, no dose adjustment on the basis of age, ethnicity, mild hepatic impairment, or drug–drug interactions.

#### Pomalidomide

https://www.drugbank.ca/

http://www.bccancer.bc.ca/

- Rapid absorption and good bioavailability
- Extensive hepatic metabolism by CYP1A2 and CYP3A4 (less than 2% is eliminated as parent compound). The metabolites are 26-fold less active than pomalidomide.
- Pomalidomide dose should be reduced by 50% if coadministered with strong CYP1A2 inhibitors (ciprofloxacin, fluvoxamine) and strong CYP3A/P-gp inhibitors.

### DDIs of lenalidomide and pomalidomide



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### Conclusions



- IMiDs 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.
- Lenalidomide is not metabolised to a significant extent and has favorable pharmacokinetics; drug-drug interactions are unlikely to occur.