Identification of GSK3 as a primary target of IMiDs and biomarker of clinical response using Drosophila

Suzanne Trudel, Sam E. Scanga, , Fabrizio G. Mastronardi, Ellen N. Wei, Frank Mercurio, Antonia Lopez-Girona, Svetlana Gaidarova, David Webb, Christine Chen, A. Keith Stewart and Armen S. Manoukian

Nie można obecnie wyświetlić tego obrazu.

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Disclosures

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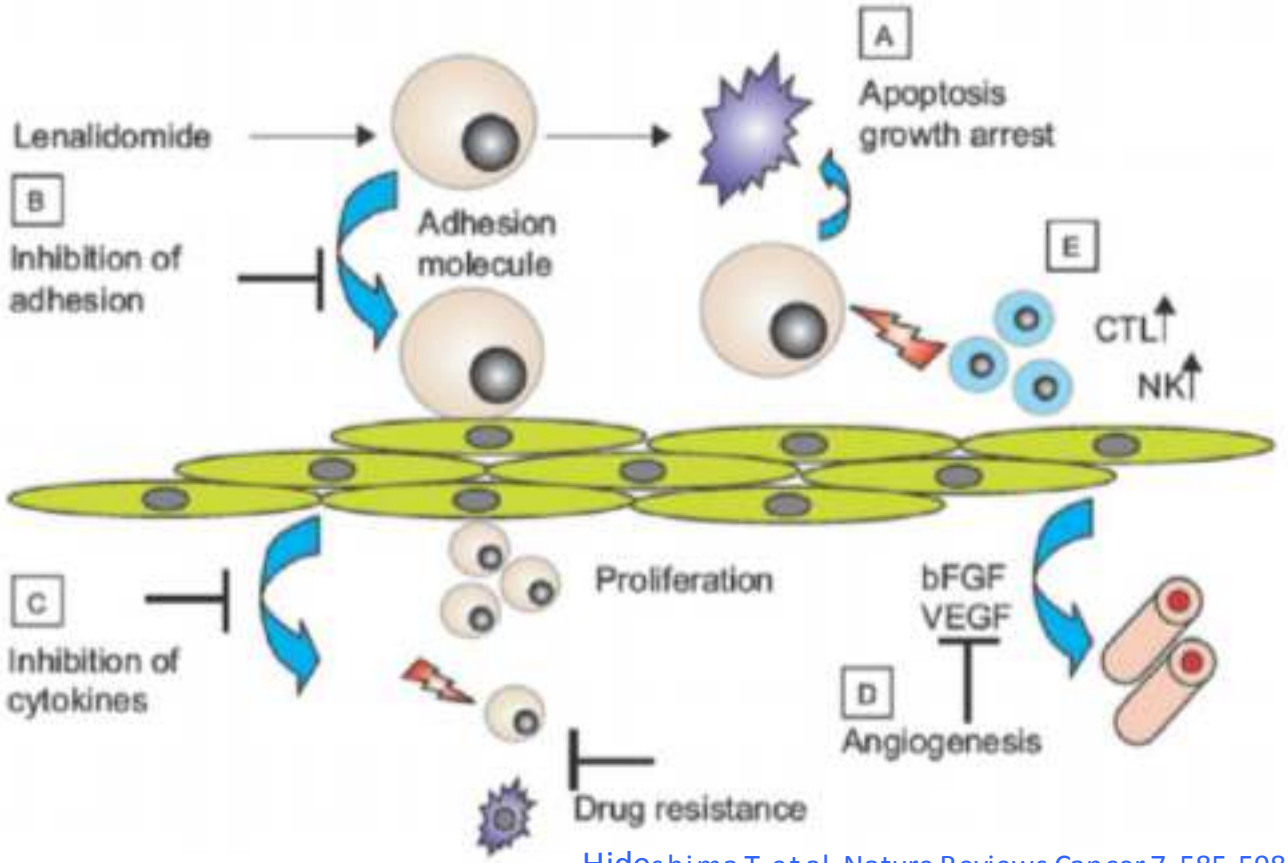
Thalidomide and IMiDs: Mechanisms of Action (MOA)

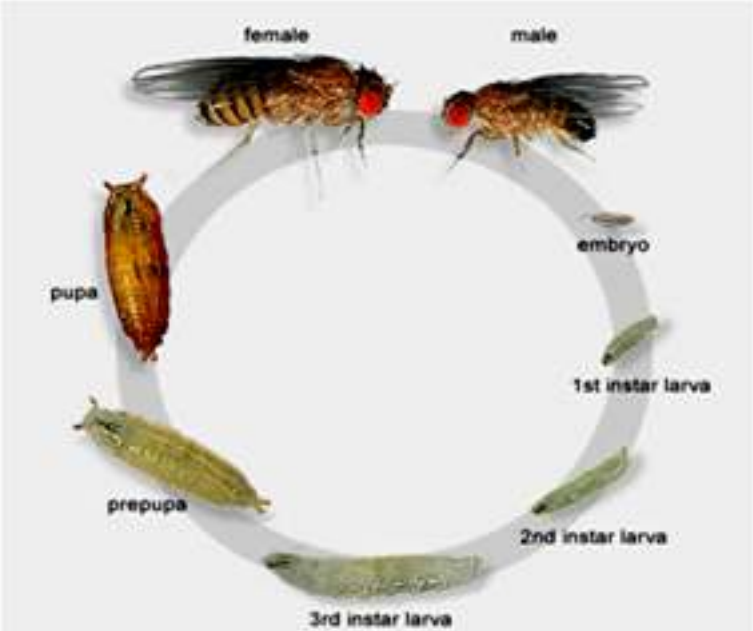
- Pre-clinical studies have revealed multiple direct and indirect antitumor activities



Hideshima T, et al. Nature Reviews Cancer 7, 585-598 (August 2007)

- Recent studies have identified cerebron (CRBN) as a putative target of thalidomide induced teratogenicity
- A unifying molecular MOA to explain the pleiotropic antitumor activity has not yet been clearly defined

Drug Discovery Platform in *Drosophila*



Drosophila life cycle

Larval Imaginal Discs

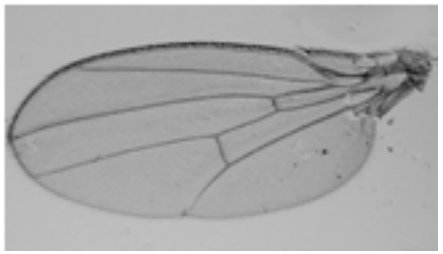
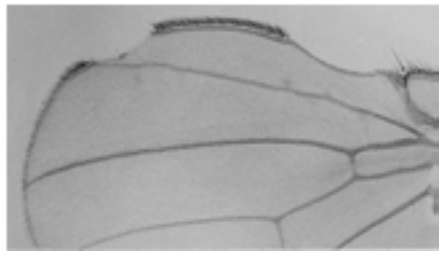

***wingless* protein**

signal


***Distalless* protein**

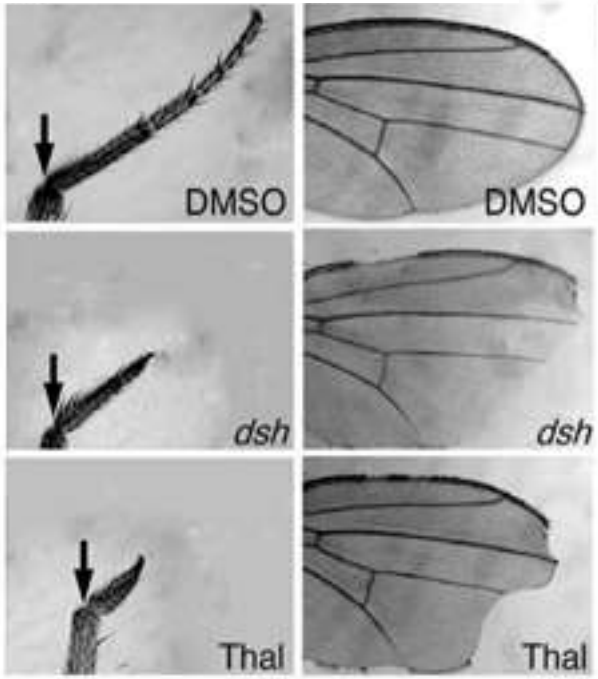
effector

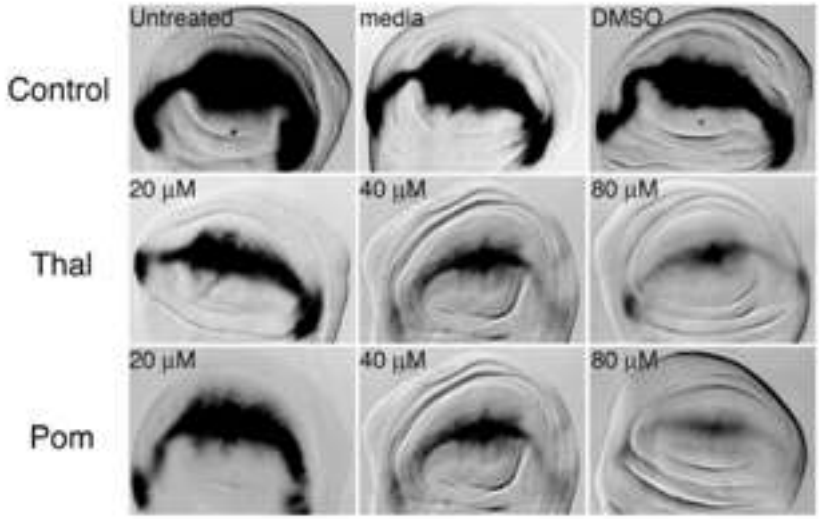
Adult fly wing



Final structure

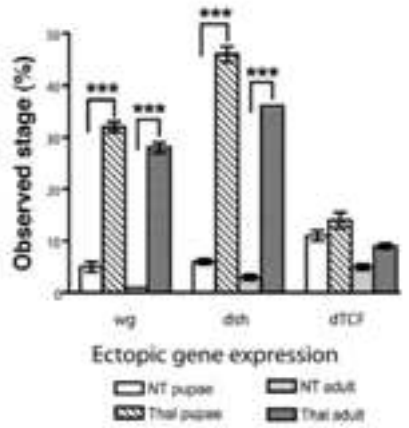
- Mechanism of Action elucidation
- Library screening for new compound identification

Thalidomide Feeding Phenocopies Wg Pathway Mutant Phenotype





DMSO Thal



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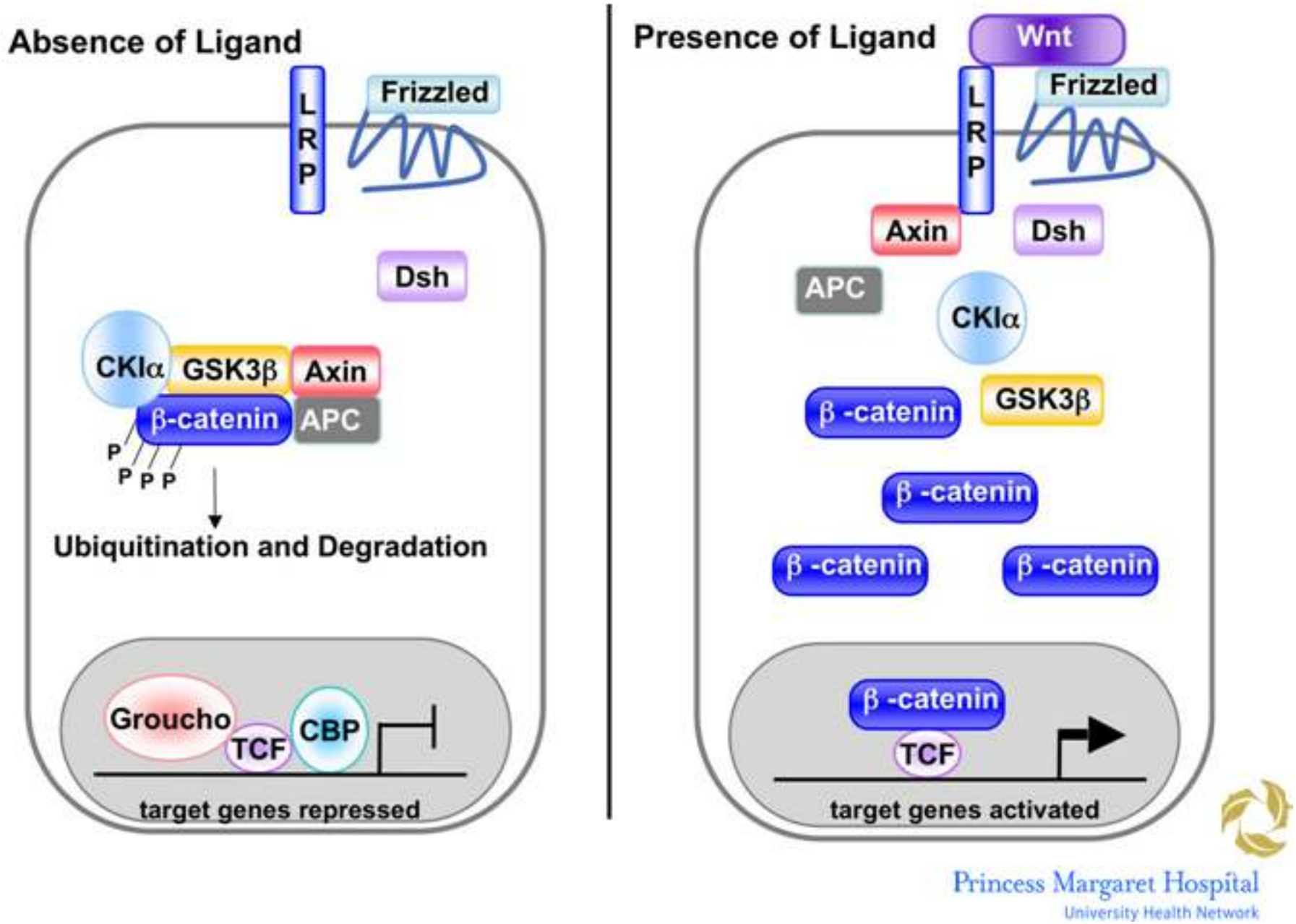
Wnt/Wg Signaling Pathway



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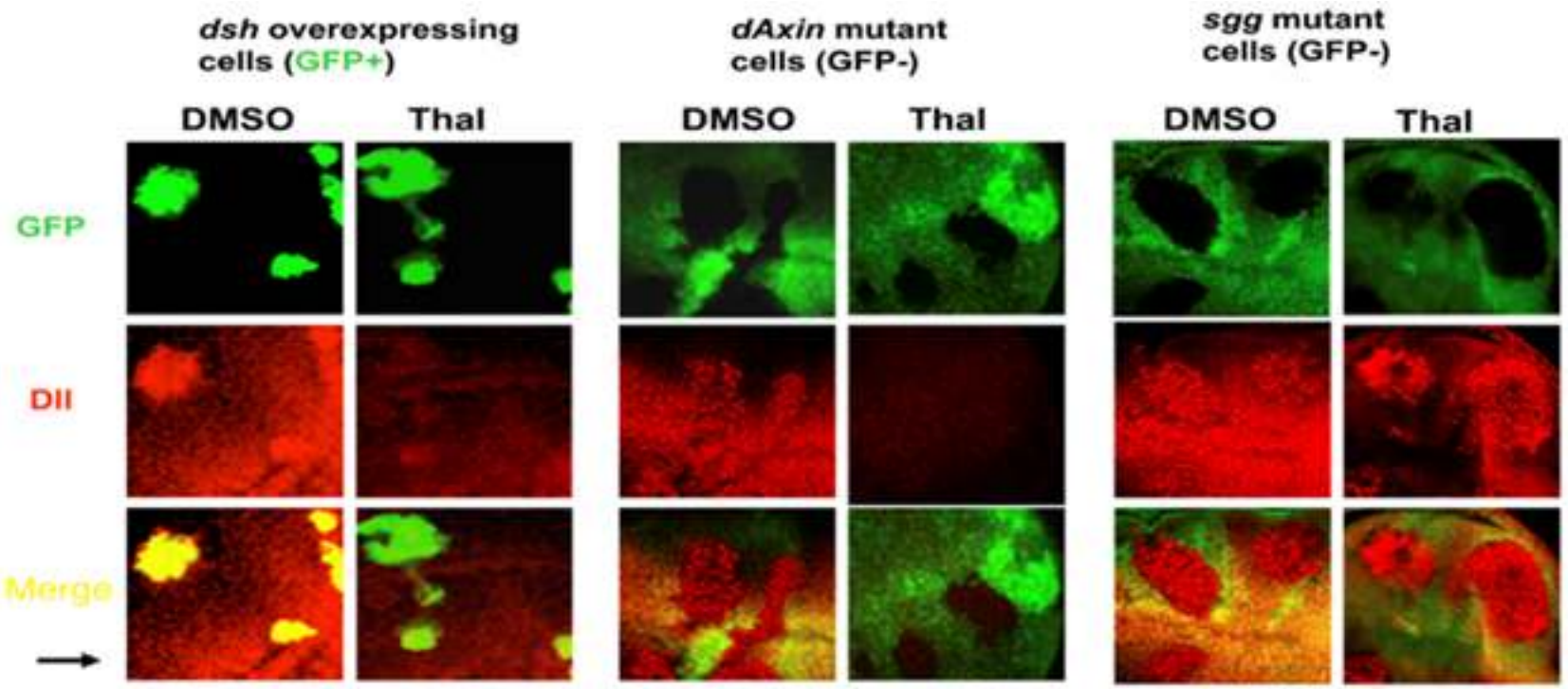
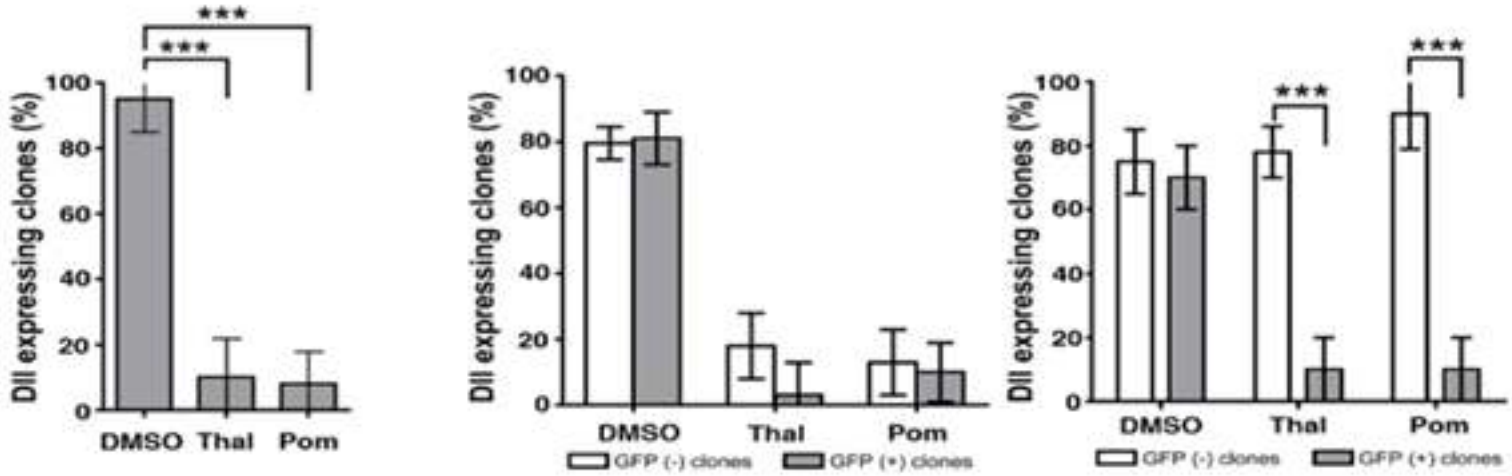
IMiD Effects are Downstream of dAxin and Sgg/GSK3





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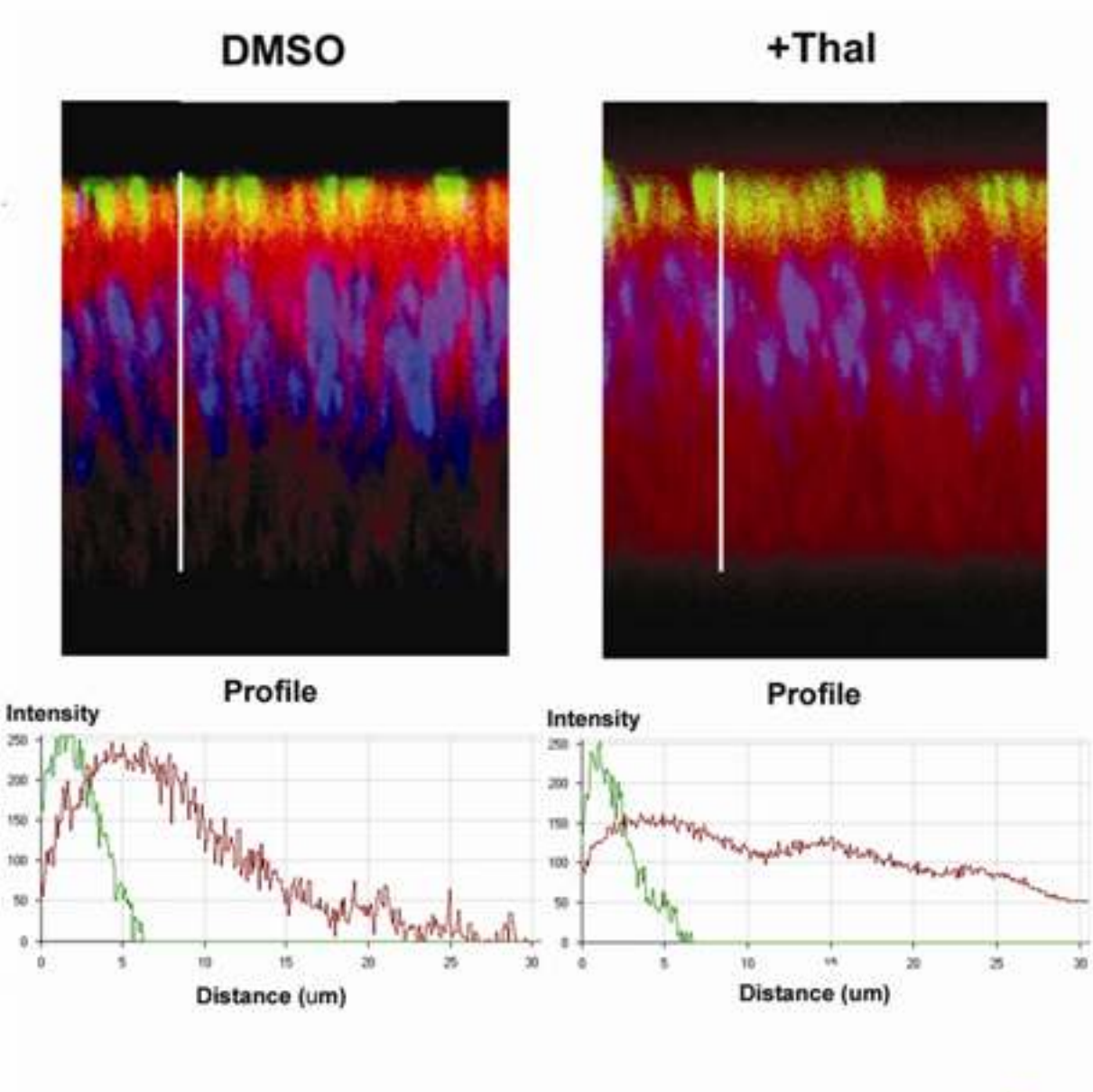
IMiDs Disrupt Apical Localization of Sgg/GSK3

Sgg

Tubulin

DAPI



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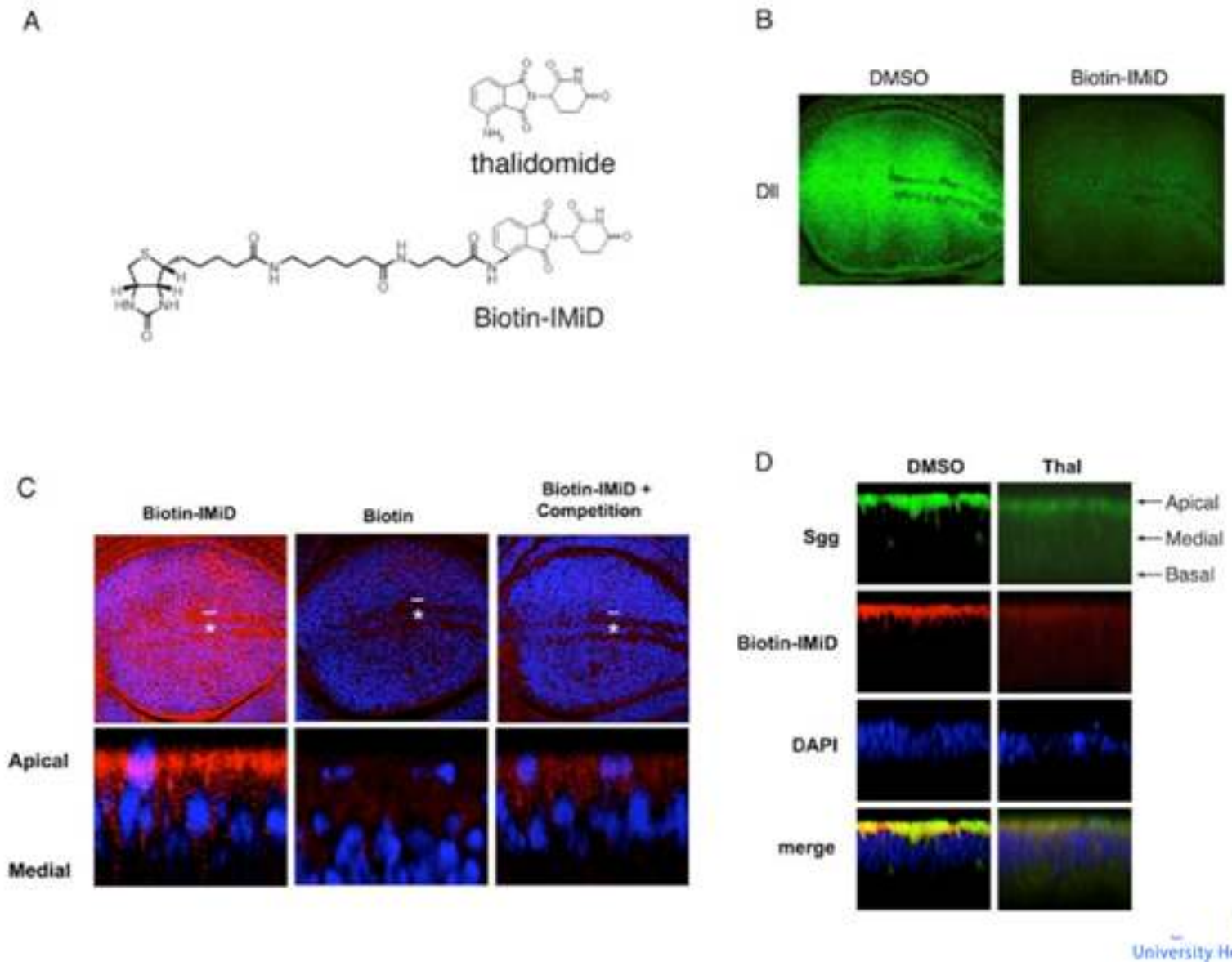
Sgg/GSK3 is a Component of the Biotin-IMiD Binding Complex In Vivo



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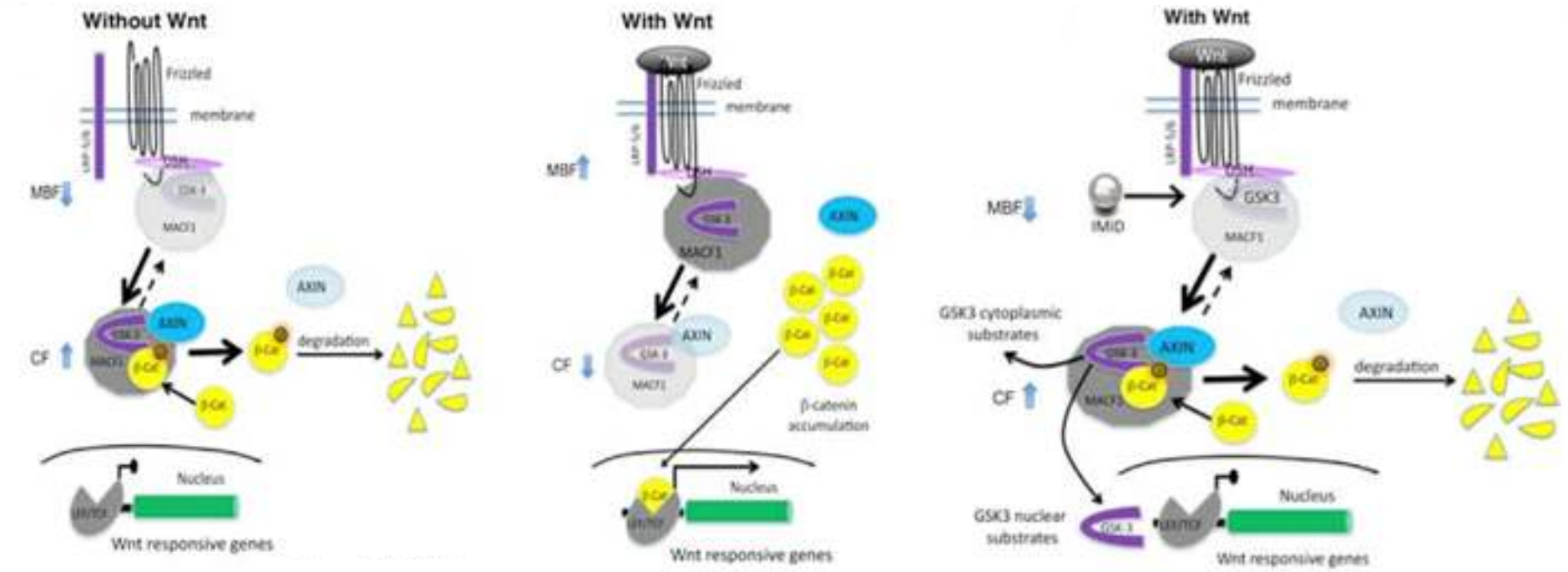
Proposed Model of Thalidomide and IMiD Targeting In *Drosophila*



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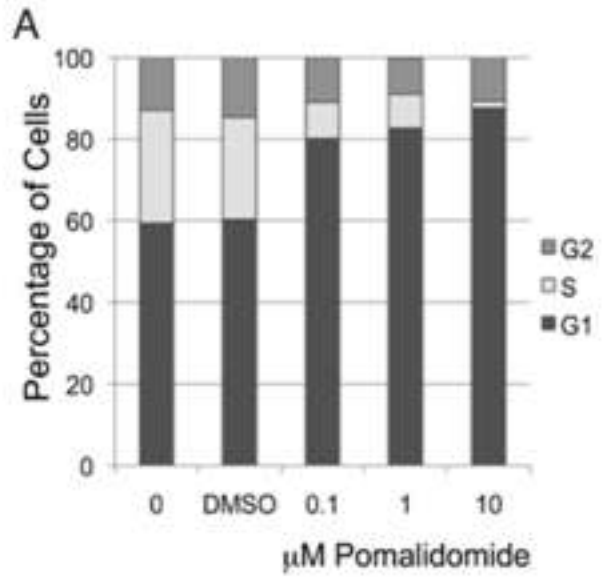
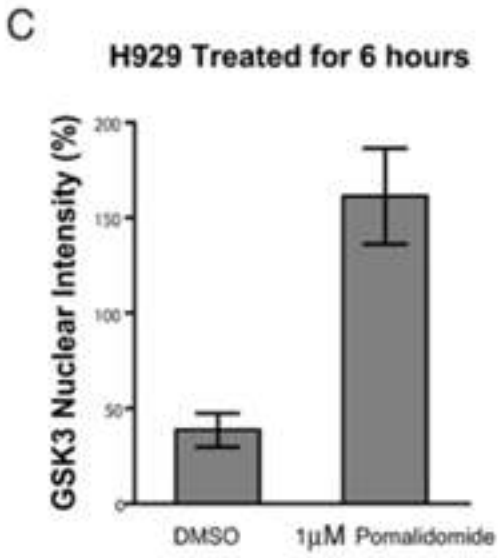
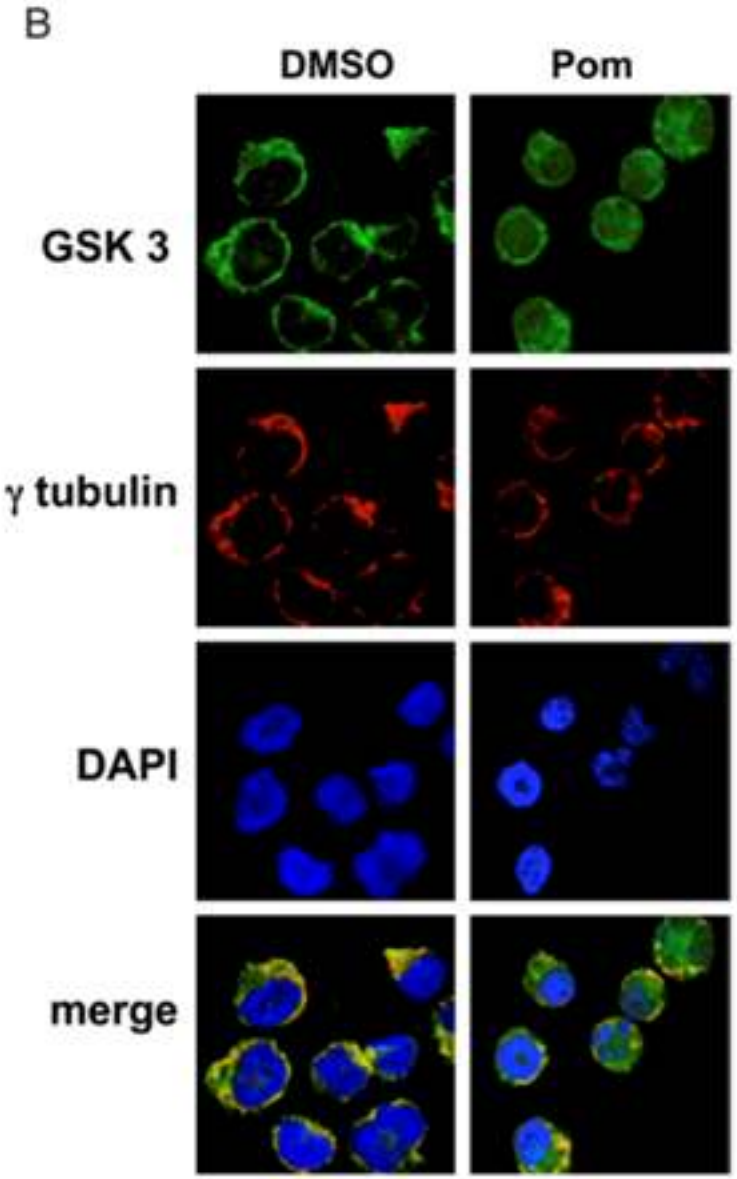
IMiDs Disrupt GSK3 Localization in Myeloma Cells







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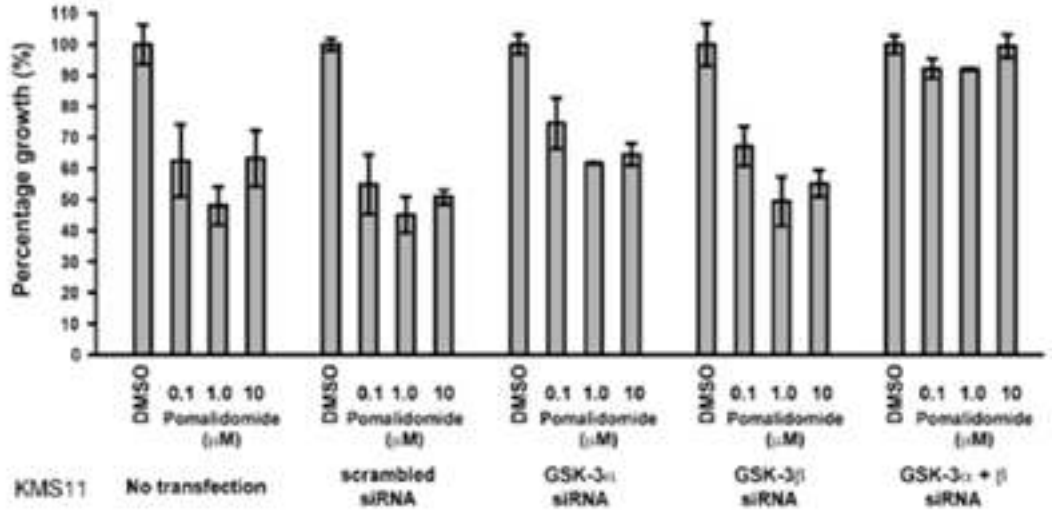
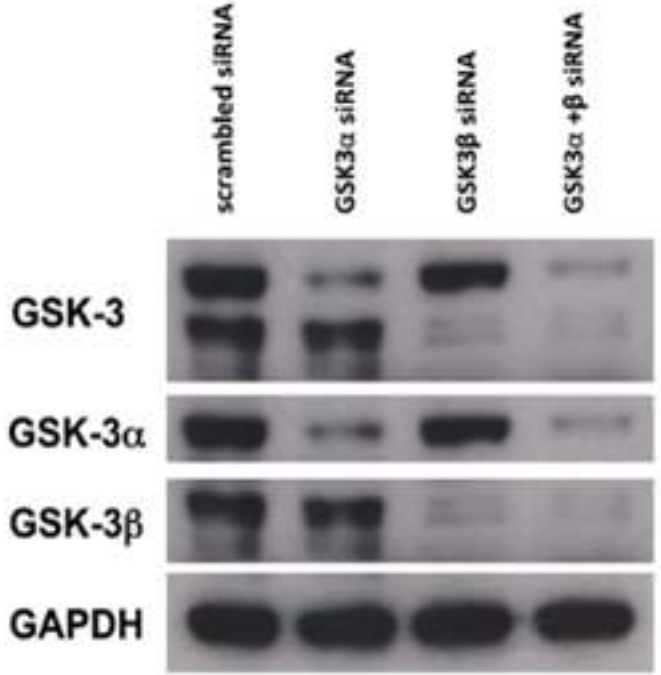
GSK3 is Required for IMiD Activity in Myeloma Cells





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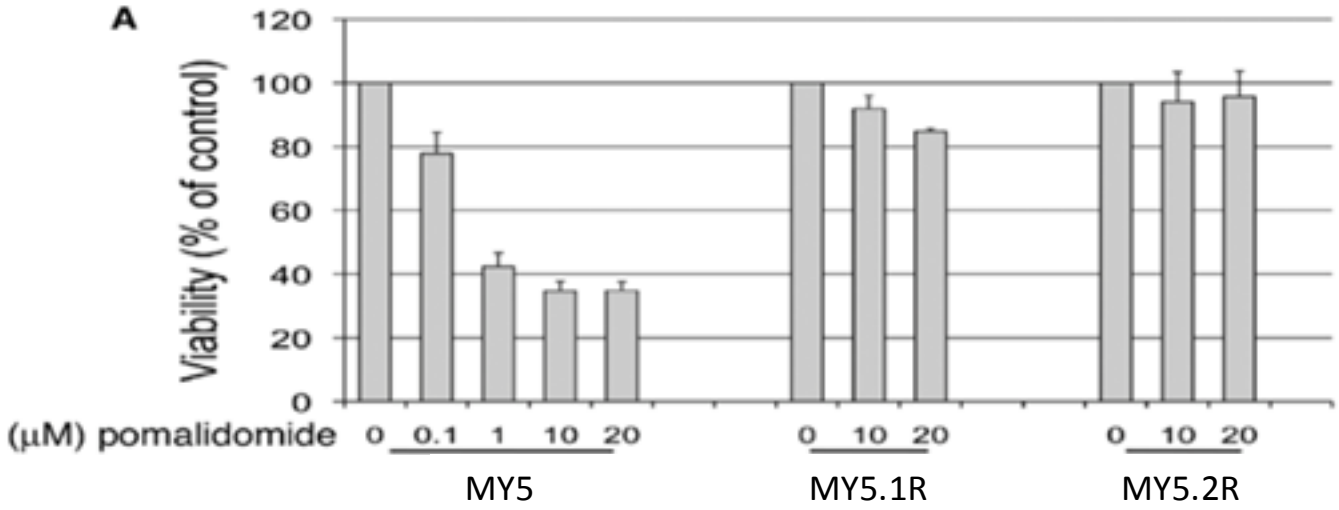
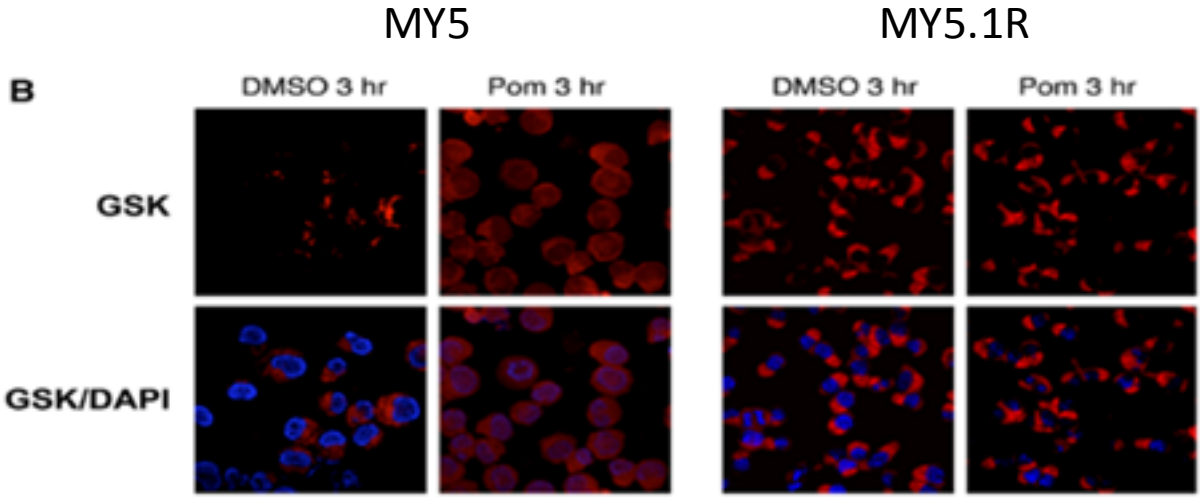
IMiDs Fail to Induce GSK3 Nuclear Localization in IMiD Resistant Cells





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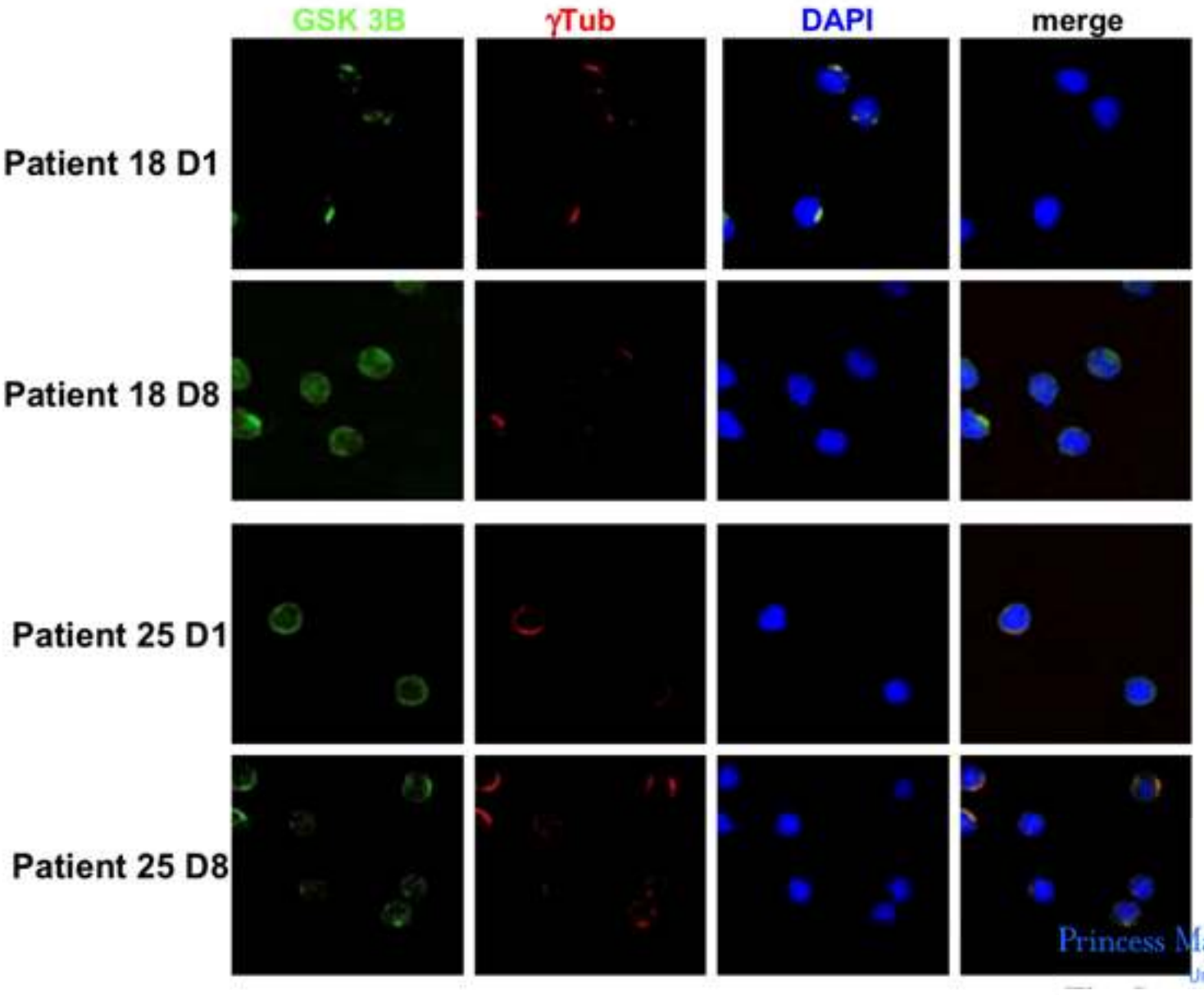
GSK3 Localization Predicts for Lenalidomide Response in CLL



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Conclusions:

- GSK3 is required for thalidomide and IMiD activity

- modulation of GSK3 activity by subcellular relocalization may account for the pleiotropic anti-cancer and teratogenic activity of IMiDs

- GSK3 localization is potential biomarker for IMiD resistance

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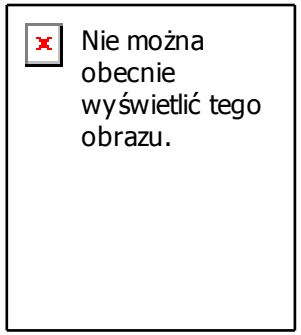
Acknowledgements



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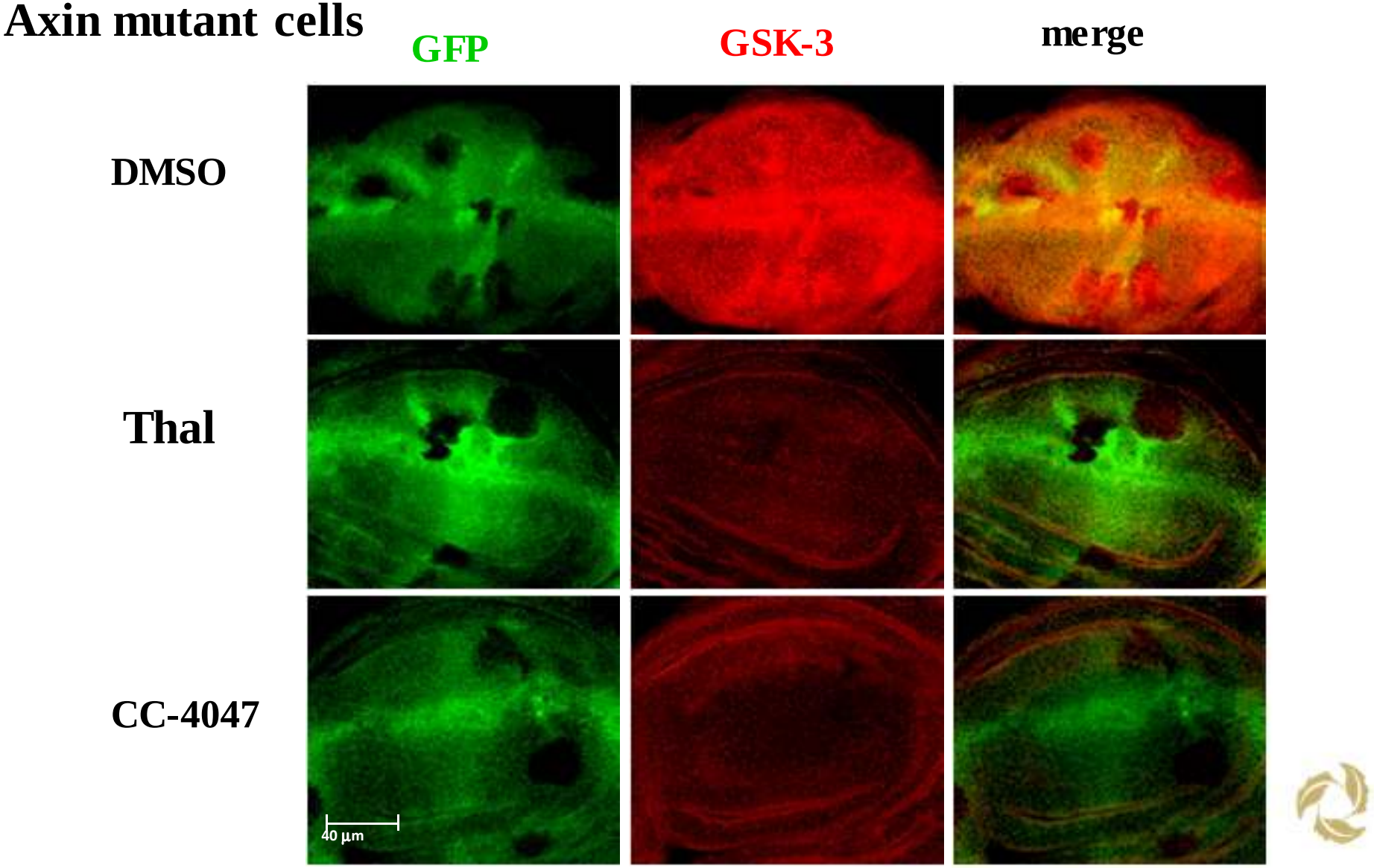
IMiDS Reverse the Ectopic/Apical Localization of Sgg/GSK3 in dAxin Mutant cells



IMiD Treatment Upregulates the GSK3 Substrate, p27