Repurposing Drugs that were not successful in their first indication

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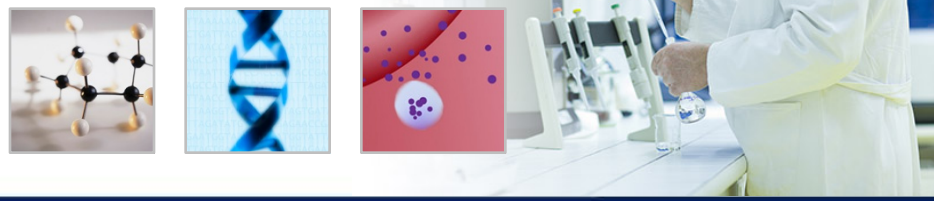
Historical Perspective: Thalidomide as the Anchor to a Multidrug Franchise

Outline

- Opportunism & Value Creation : Thalidomide Story
- Integrating Science to Reframe the Value Proposition
- Lessons Learned



Thalidomide History

- Grünenthal: October 1, 1957 OTC sedative, addressed symptoms morning sickness of pregnant women

- December 25, 1956 : first phocomelia victim

- December 1961 McBride sends letter to Lancet
- Nov 1961 Lenz informs Grunenthal

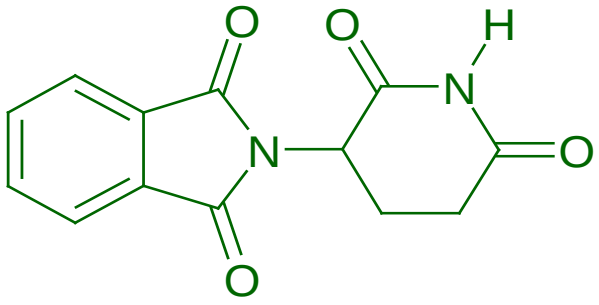
- Frances Oldham Kelsey

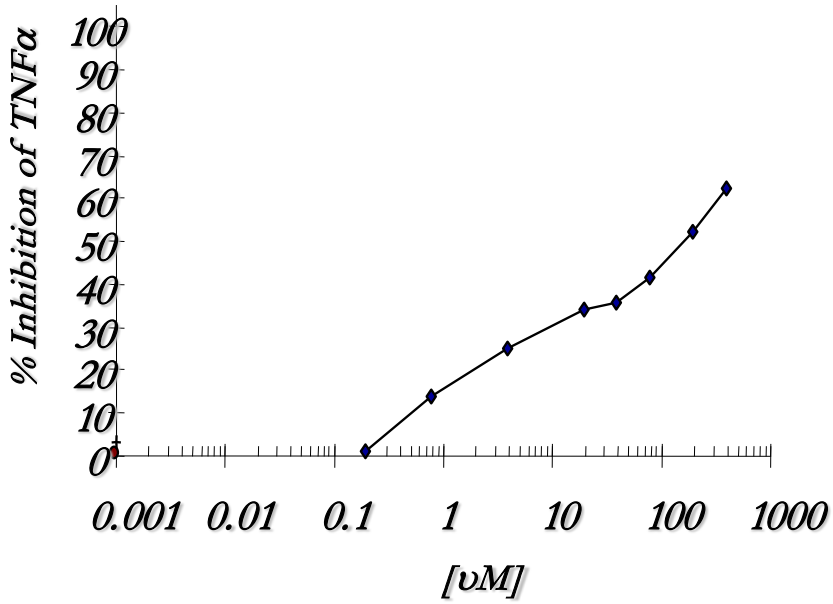
Convergent Events in Repurposing Thalidomide

- Thalidomide anti-inflammatory activity in leprosy
- Gilla Kaplan (Rockefeller) defines Thal activity to reduce TNFα responses in monocytes/macrophages
- AIDS community bringing Thalidomide back to US to treat cachexia + promising HIV data, 1990's
- FDA concerned about "grey/black" market Thalidomide access
- David Stirling (Celgene) and Gilla Kaplan collaborate
- 1998 FDA approval of THALOMID for Erythema nodosum leprosum (ENL) with STEPS (REMS) program
- Aggressive program to identify
  - Alternative drugs with reduced safety liabilities
  - Additional therapeutic applications
  - Mechanism: Cellular and Molecular

Thalidomide

- TNF IC_{50} = 194 μM
- Hydrolyzes to inactive substances with a $T_{1/2}$ of 15 minutes at pH 7.4
- *Human Teratogen*
- *No acute toxicity in animals and humans*

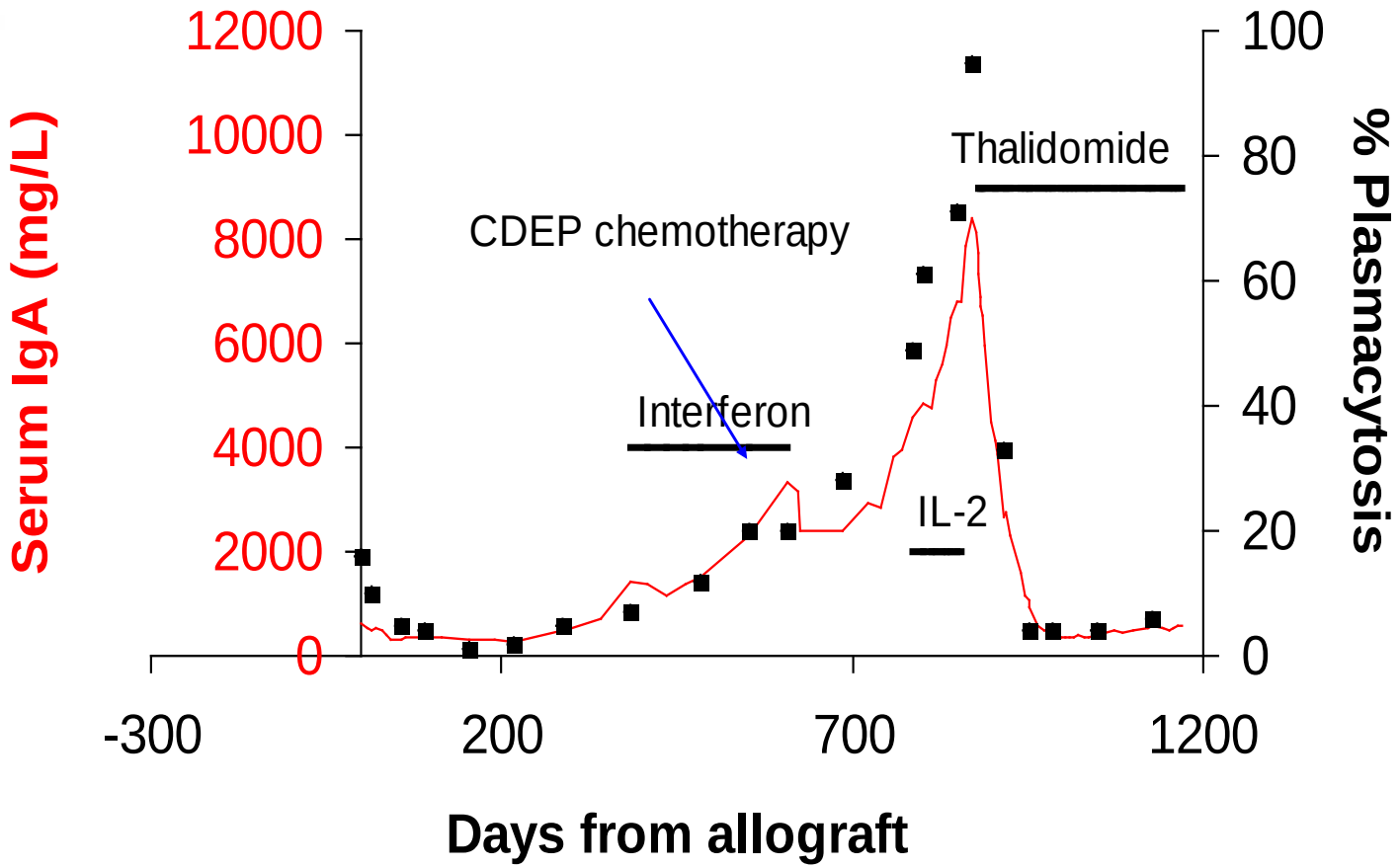




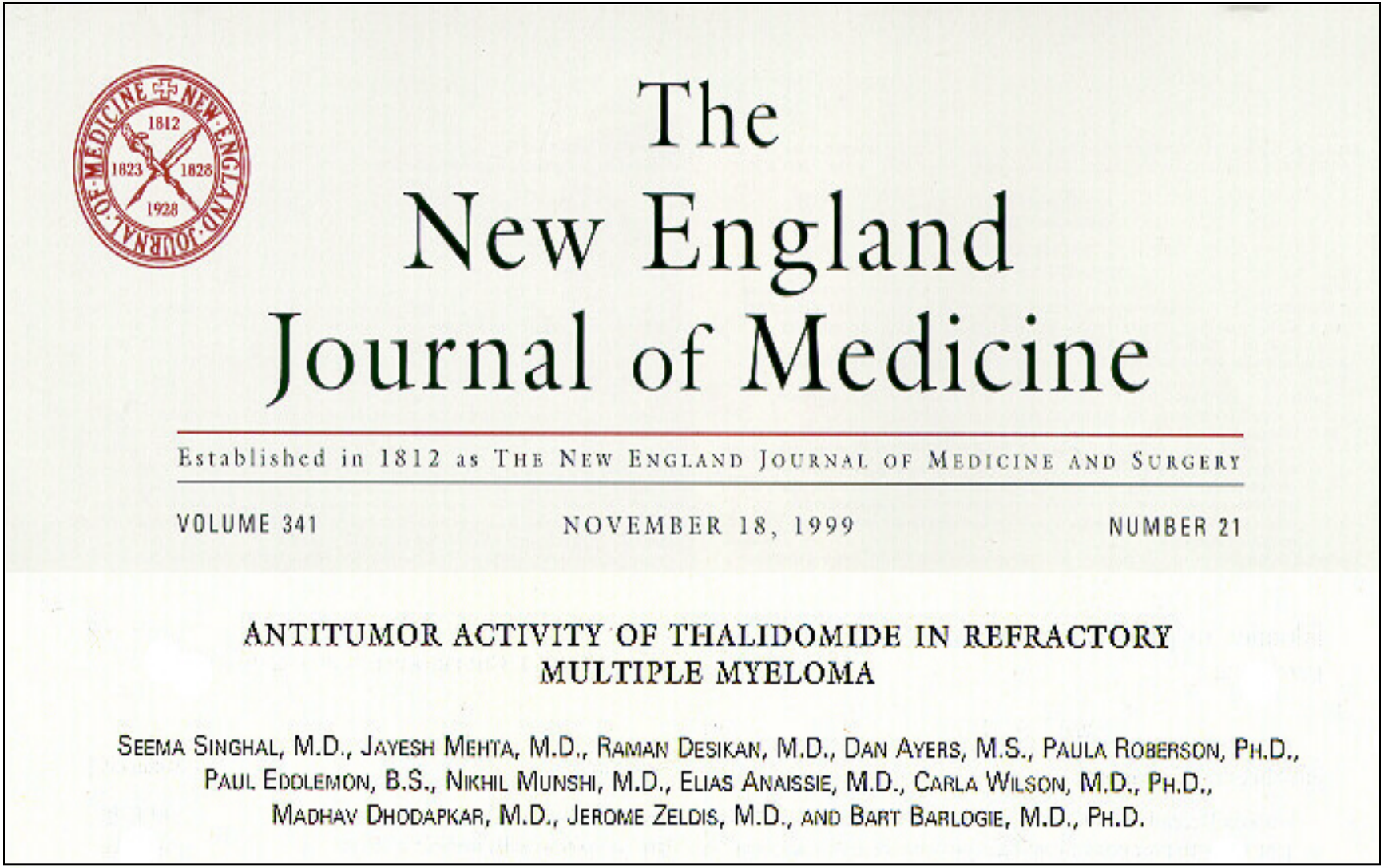
Thalidomide: "Perfect Storm" for Repurposing Campaign

- Teratogenicity, neuritis & other side effects drove the aggressive chemical "morphing" program
- Rodent model systems poorly responsive: Emphasis on human tissue assays, models, primate toxicology
- Academic insights directed focus on first 2 "new" hematology indications
  - Revlimid Transfusion dependent low risk or Int-1 del5q MDS (12/05)
  - Thalidomide + dex NDMM (5/06)
  - Revlimid + dex in MM with 1 prior therapy (6/07)
- Differential activities of Drug Candidates drove
  - New drug discovery programs
  - Search for Mechanism(s) of action
  - Search for new indications

Initial Observation in MM….



Led to Larger Experience…



The New England Journal of Medicine

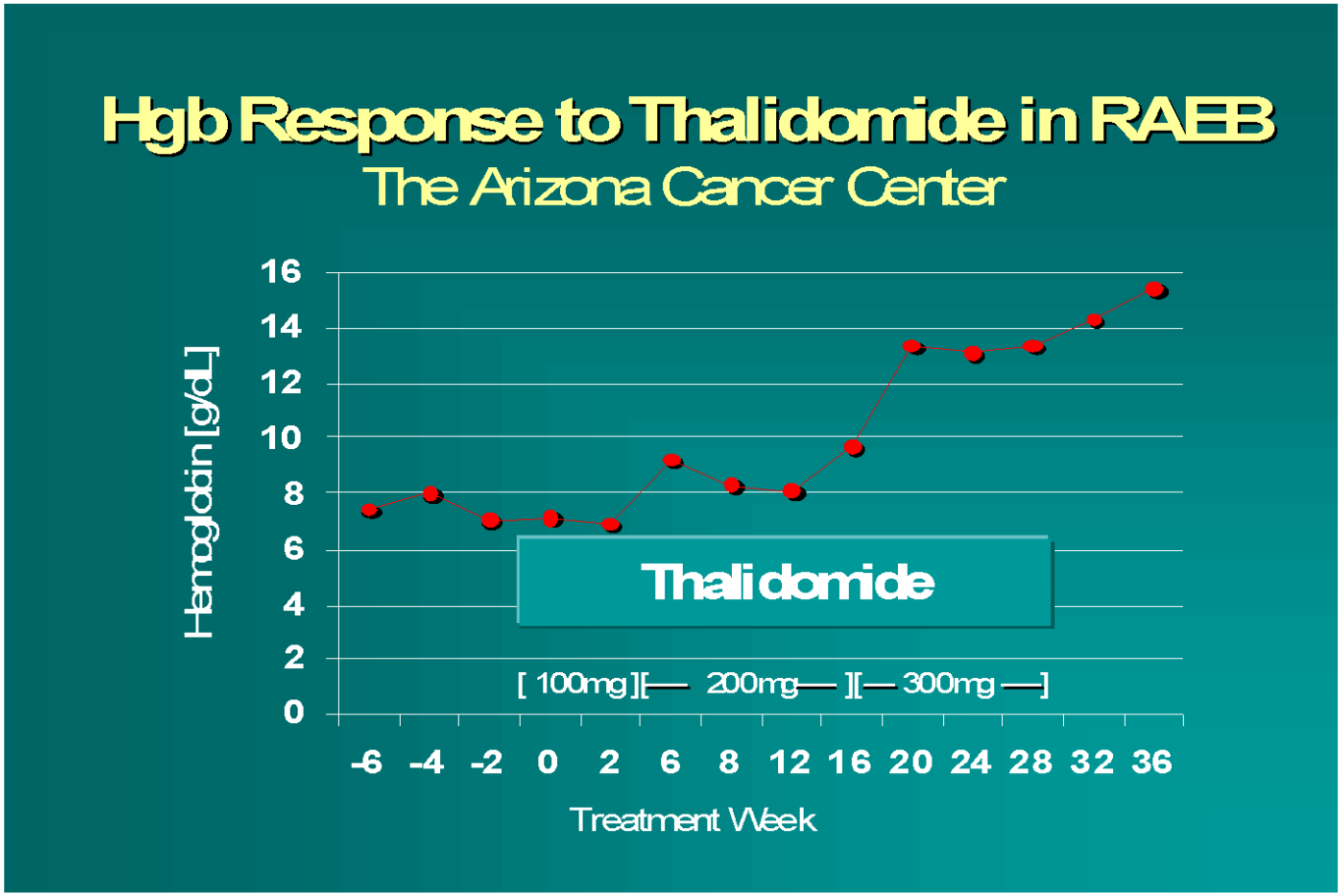
Established in 1812 as The New England Journal of Medicine and Surgery

VOLUME 341 NOVEMBER 18, 1999 NUMBER 21

ANTITUMOR ACTIVITY OF THALIDOMIDE IN REFRACTORY MULTIPLE MYELOMA

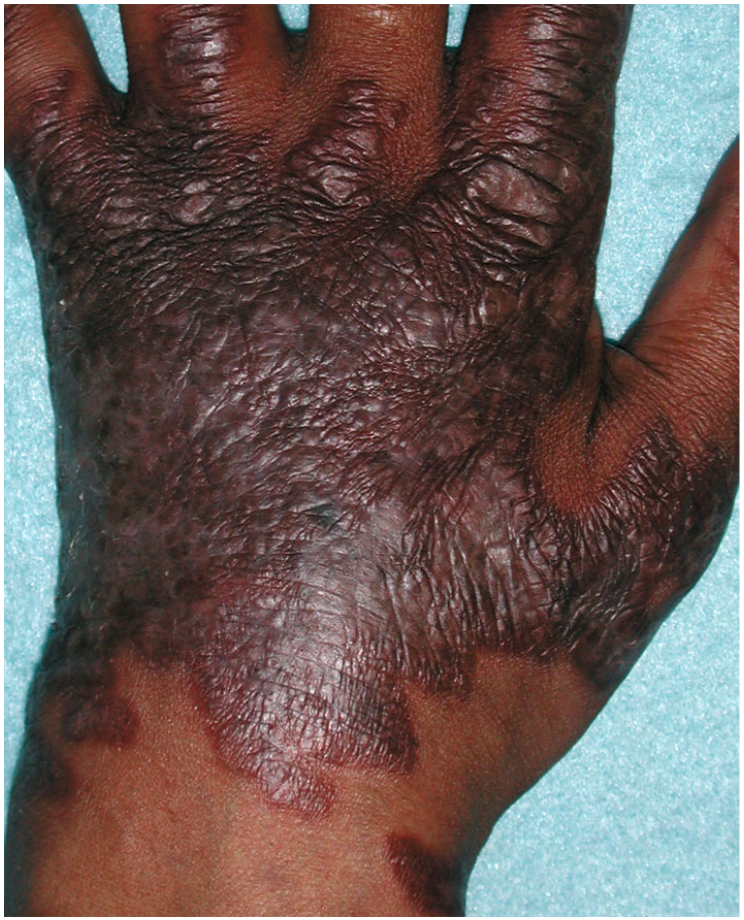
Seema Singhal, M.D., Jayesh Mehta, M.D., Raman Desikan, M.D., Dan Ayers, M.S., Paula Roberson, Ph.D., Paul Eddlemon, B.S., Nikhil Munshi, M.D., Elias Anaissie, M.D., Carla Wilson, M.D., Ph.D., Madhav Dhodapkar, M.D., Jerome Zeldis, M.D., and Bart Barlogie, M.D., Ph.D.

Refractory Anemia with Excessive Blasts=MDS

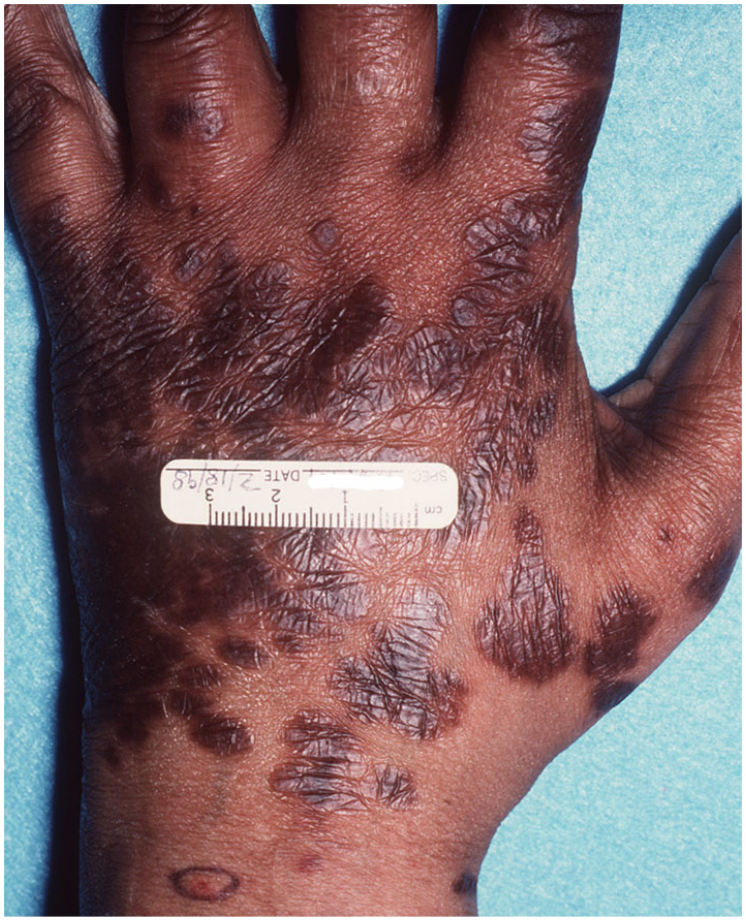


A. List, University of Arizona, unpublished

Observations Validated in Cutaneous Sarcoidosis



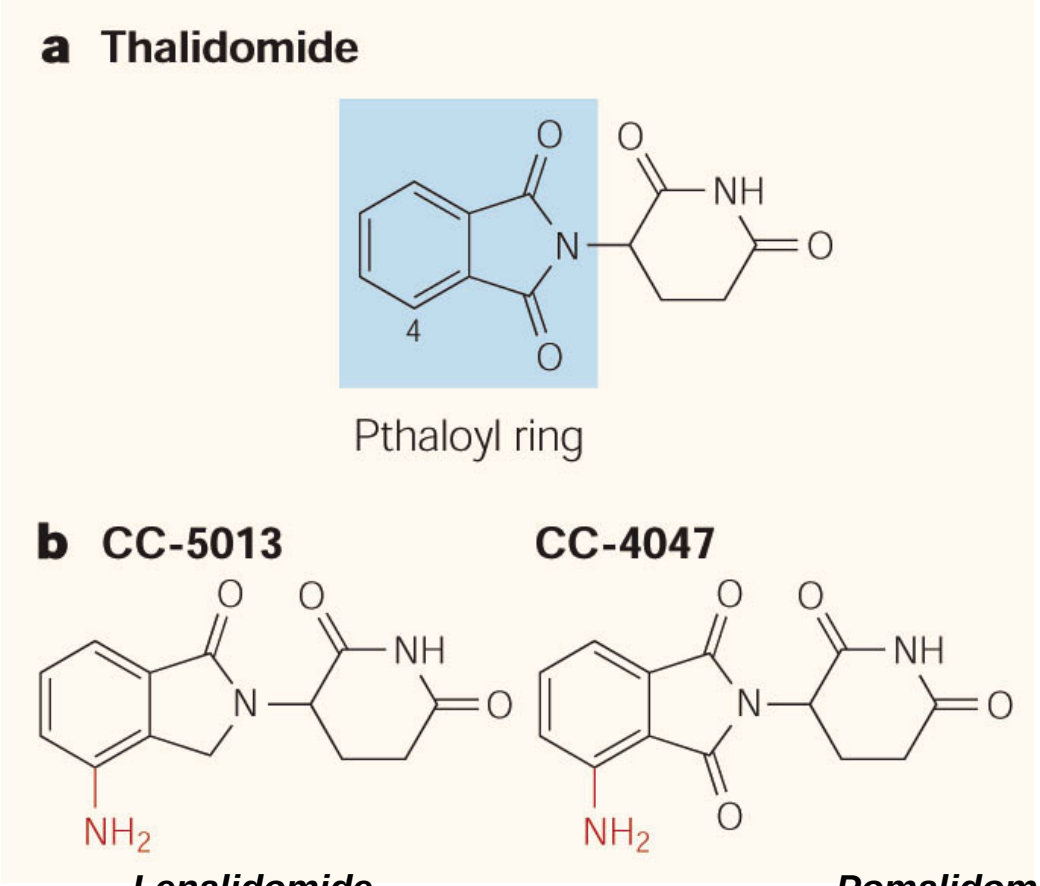
Week 0



Week 16

Oliver SJ, et al. Clin Immunol 2002

Transitioning Thalidomide to 2nd Generation IMiDs ®

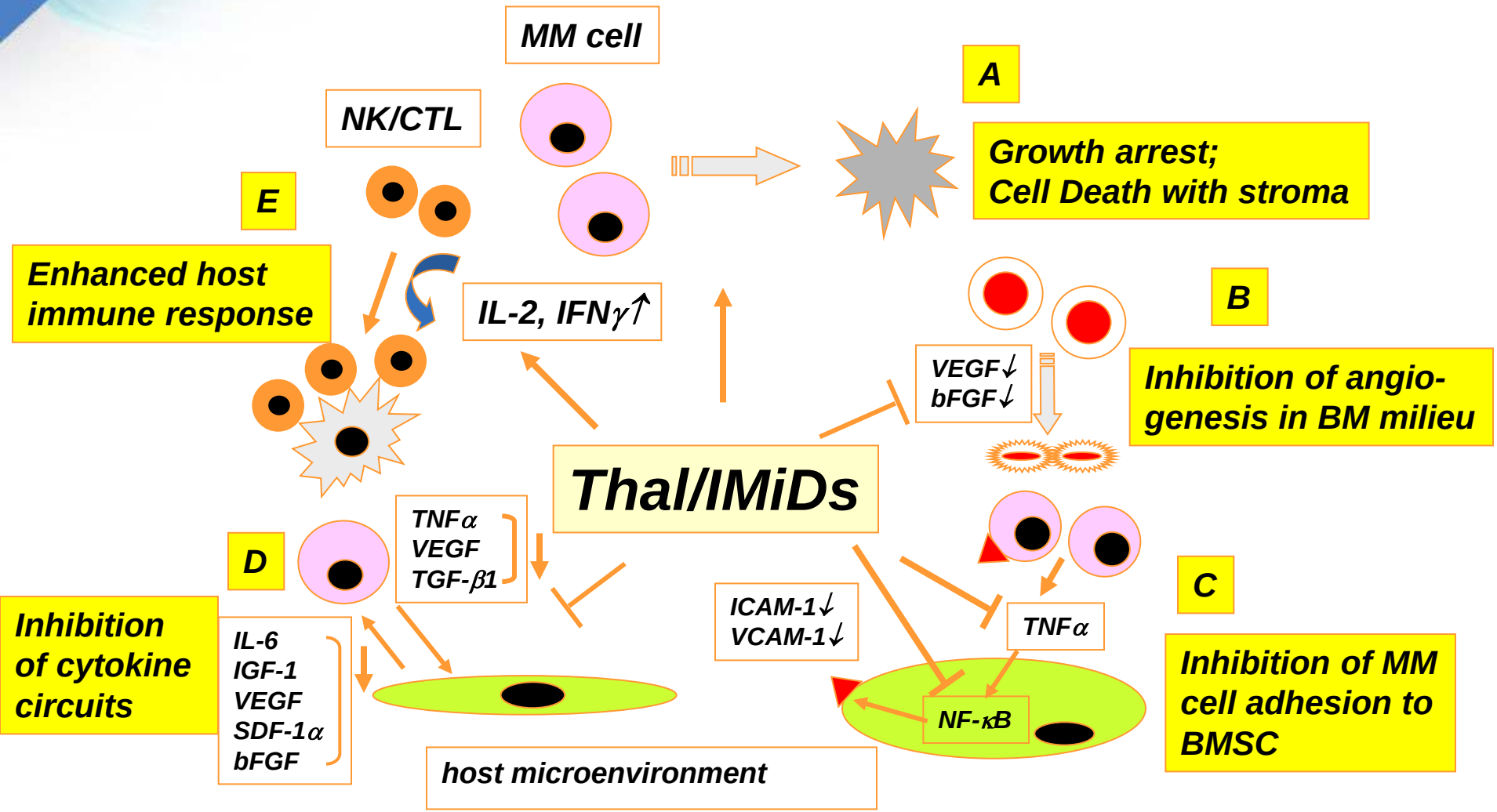


Lenalidomide ***Pomalidomide***

Lenalidomide vs Thalidomide

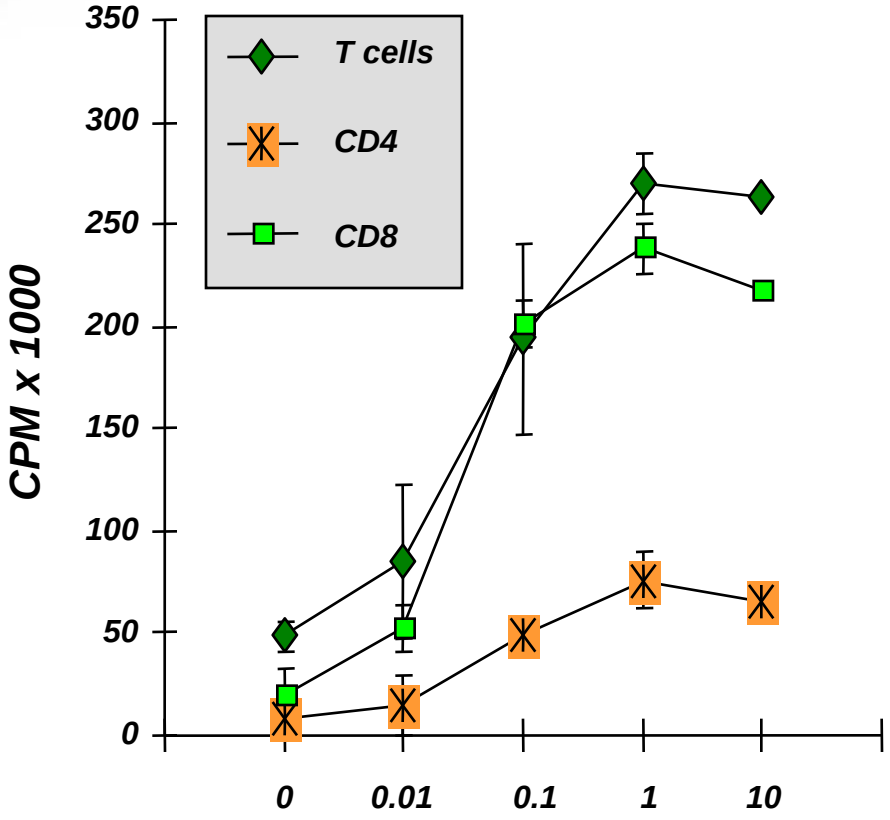
↑ Inhibition of TNFα	= Teratogenicity
– IL-10 stimulation	↓ Sedation
↓ Inhibition of angiogenesis	↓ Constipation
↑ Stimulate T-cell function	↓ Peripheral neuropathy

Pleiotropic Activities Demonstrated

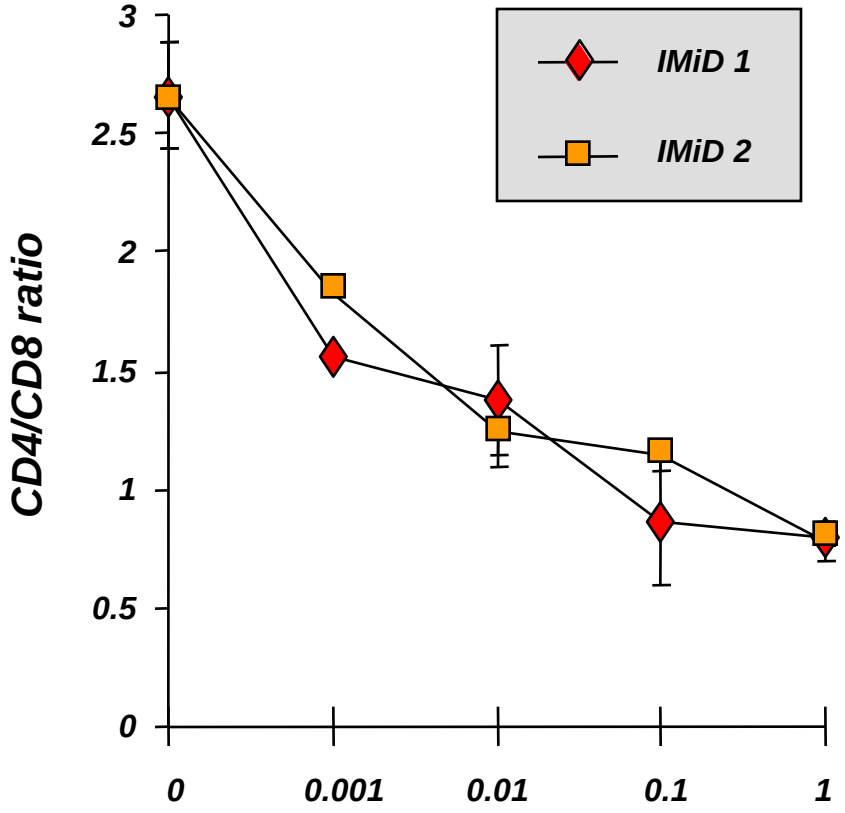


Differential Co-stimulation of T cells by IMiDs ®

Proliferation of T cell subsets

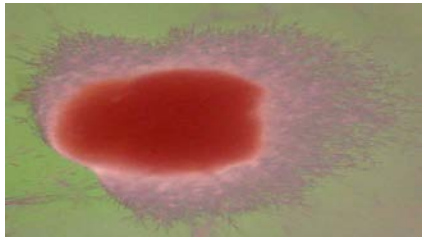


CD4/CD8 ratios in unsorted T cells

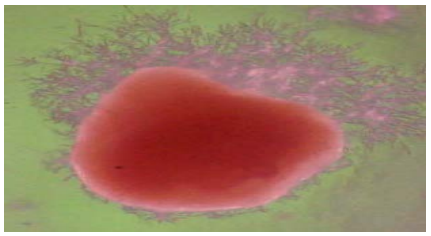


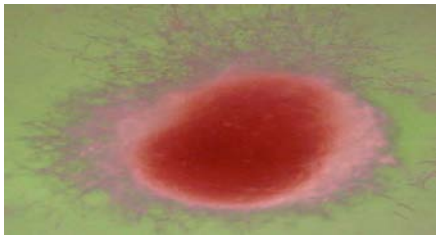
Anti-Angiogenic Activity in Human Umbilical Artery Explants

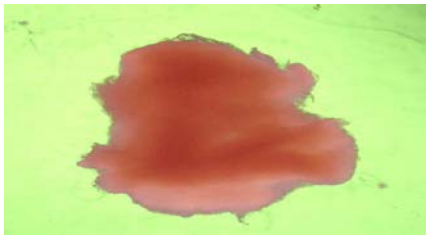
No treatment



Thalidomide







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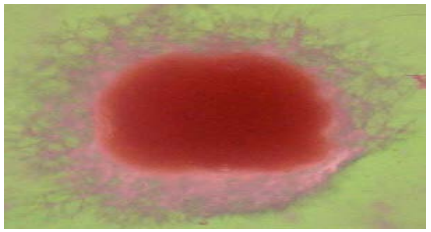
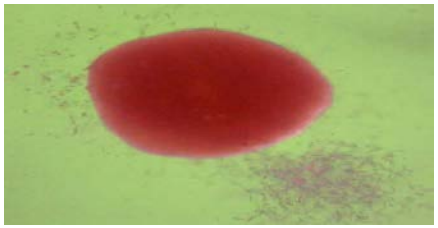
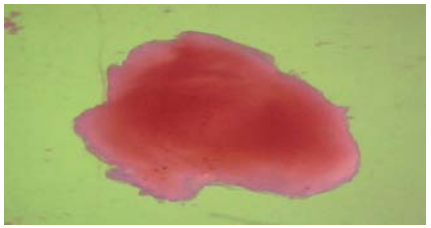






0.1 μM ***1 μM*** ***100 μM***

Identification of the Primary Target of Thalidomide Teratogenicity (Ito et al. Science 327,1345-50, March 12, 2010)

RESEARCH ARTICLE

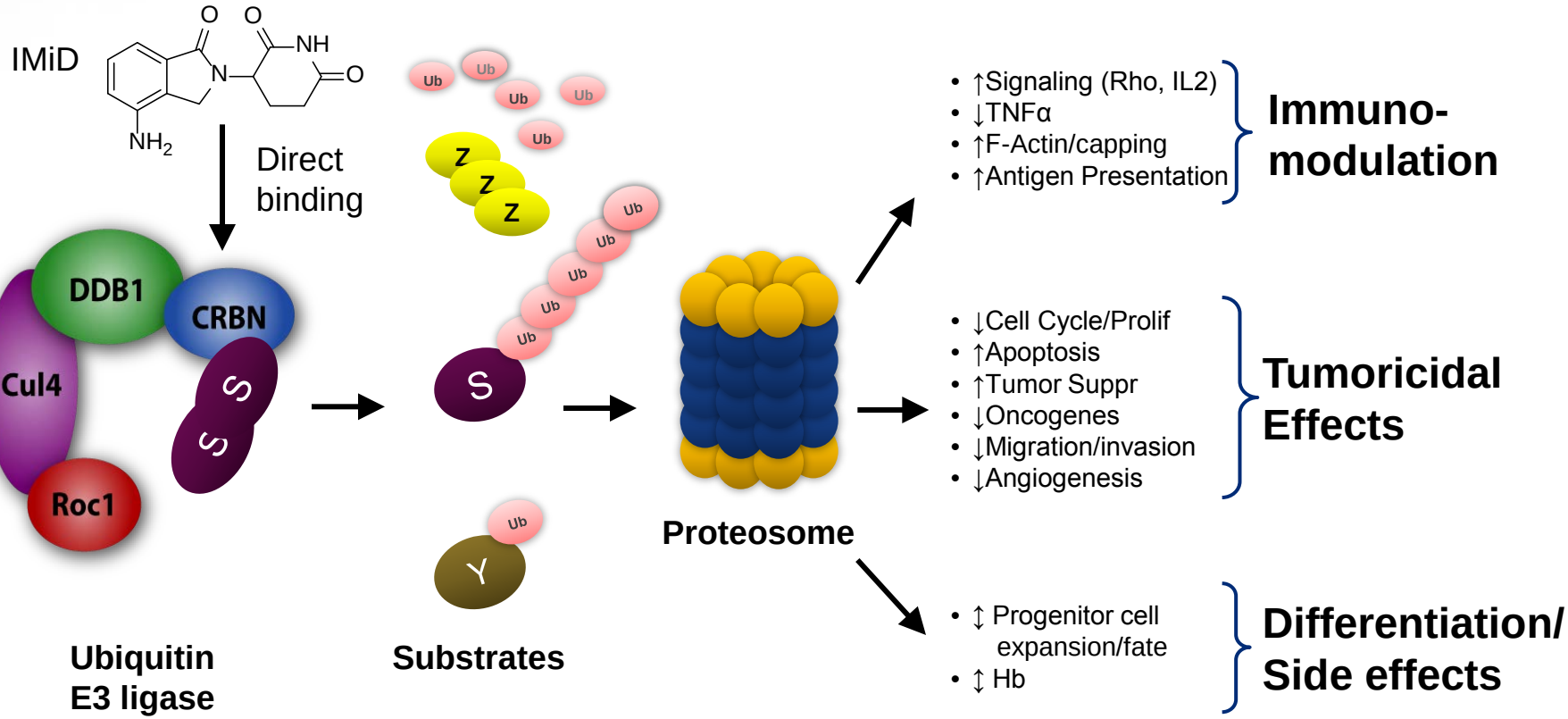
Identification of a Primary Target of Thalidomide Teratogenicity

Takumi Ito,[1]* Hideki Ando,[2]* Takayuki Suzuki,[3,4] Toshihiko Ogura,[3] Kentaro Hotta,[2] Yoshimasa Imamura,[5] Yuki Yamaguchi,[2] Hiroshi Handa[1,2]†

Half a century ago, thalidomide was widely prescribed to pregnant women as a sedative but was found to be teratogenic, causing multiple birth defects. Today, thalidomide is still used in the treatment of leprosy and multiple myeloma, although how it causes limb malformation and other developmental defects is unknown. Here, we identified cereblon (CRBN) as a thalidomide-binding protein. CRBN forms an E3 ubiquitin ligase complex with damaged DNA binding protein 1 (DDB1) and Cul4A that is important for limb outgrowth and expression of the fibroblast growth factor Fgf8 in zebrafish and chicks. Thalidomide initiates its teratogenic effects by binding to CRBN and inhibiting the associated ubiquitin ligase activity. This study reveals a basis for thalidomide teratogenicity and may contribute to the development of new thalidomide derivatives without teratogenic activity.

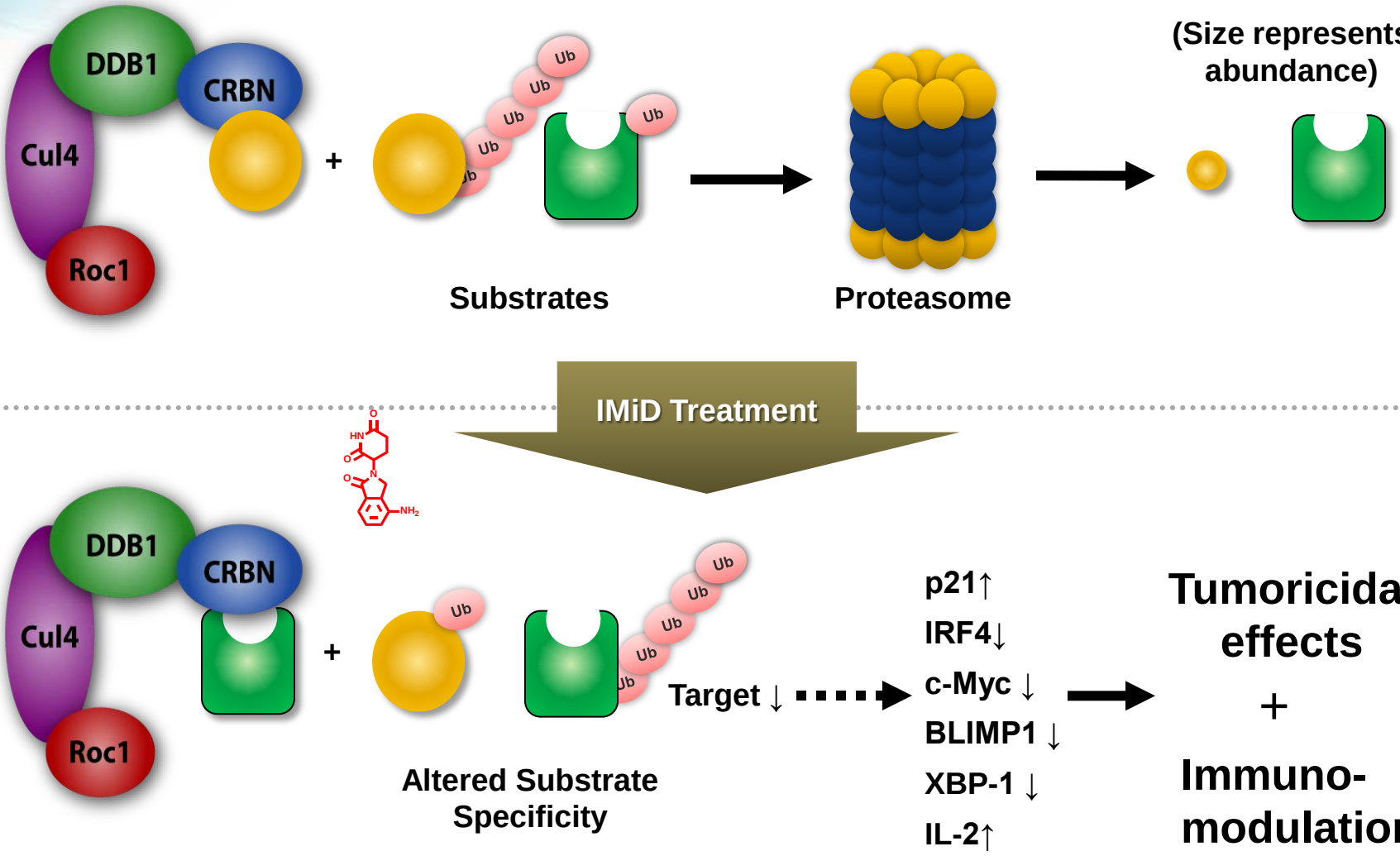
Binding of thalidomide to CRBN and DDB1. To purify thalidomide-binding proteins, we performed affinity purification using ferrite-glycidyl methacrylate (FG) beads (*9*). The carboxylic thalidomide derivative FR259625 was covalently conjugated to the beads (fig. S1) and incubated with human HeLa cell extracts (*10*). After extensive washing, bound proteins were eluted with free thalidomide, and the eluate fractions were subjected to SDS gel electrophoresis and silver staining. Two polypeptides were specifically eluted (Fig. 1A, lane 3). When free thalidomide was added to extracts before incubation with the beads, the yields of these proteins were reduced (Fig. 1A, lane 4), which suggested that these proteins specifically interact with thalidomide. The 127- and 55-kD proteins were therefore subjected to proteolytic digestion and tandem mass spectrometry and were identified as CRBN and damaged DNA

IMiDs®: CRBN / E3 ligase Engagement Modulates Protein Homeostasis



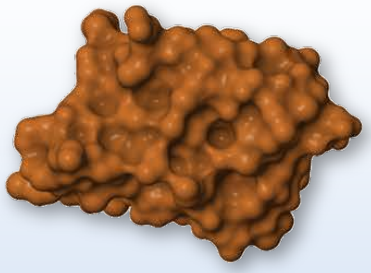
Protein Homeostasis

IMiDs alter the balance of protein ubiquitination and degradation



CRBN Crystal Structures

Enable new IP / structure-activity relationships



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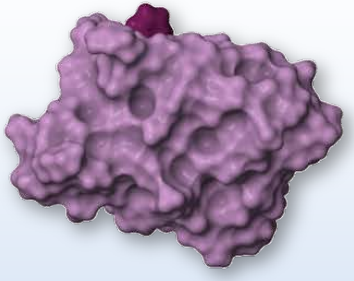

Thalidomide
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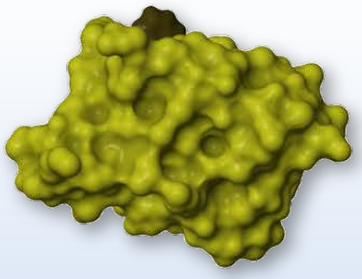

Pomalidomide
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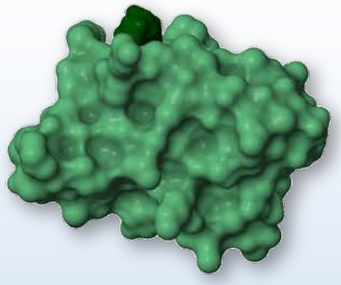

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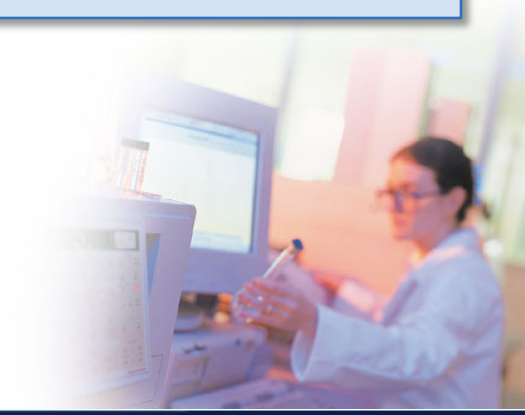
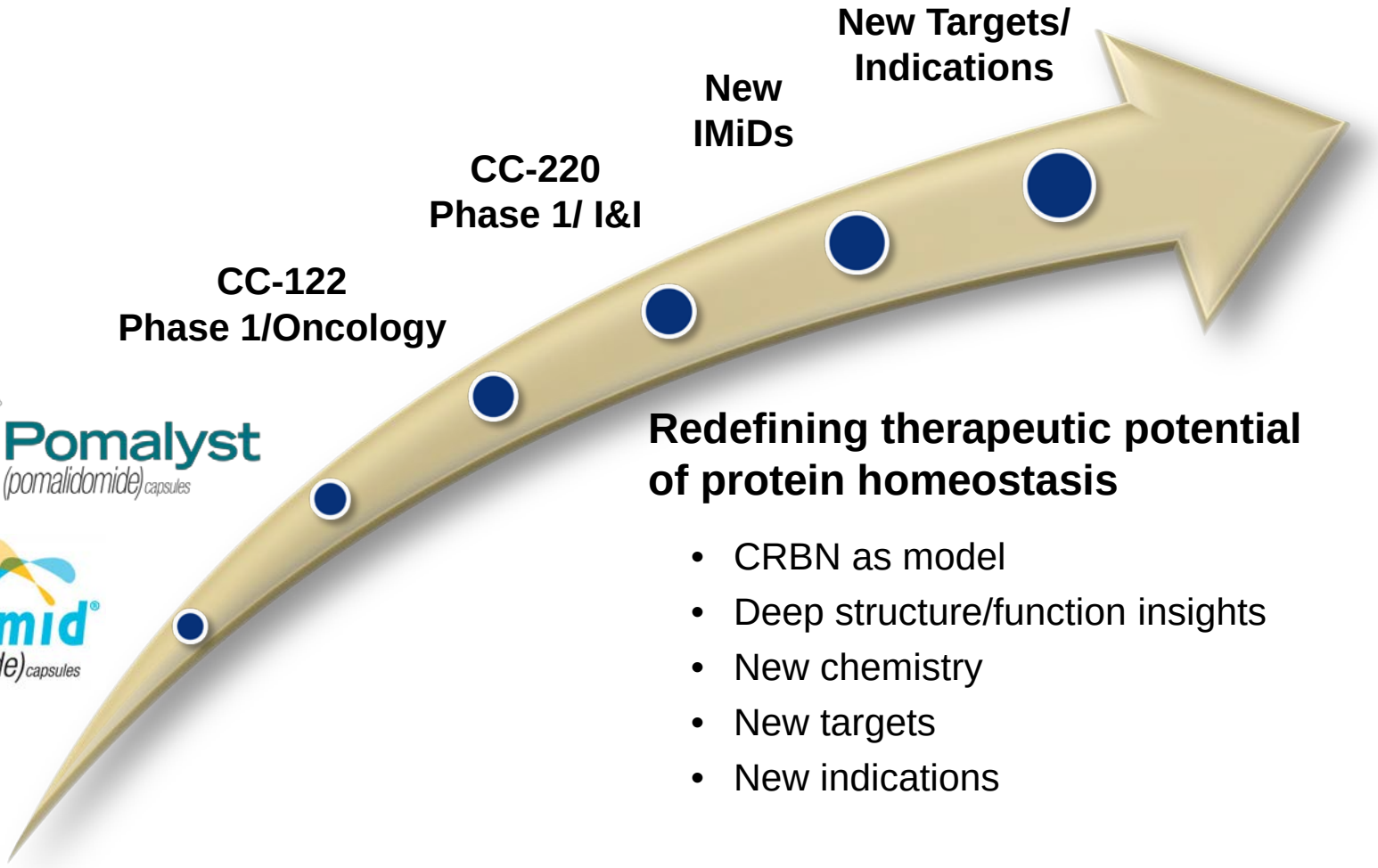


Next Generation IMiDs® / Targeting Protein Homeostasis



Redefining therapeutic potential of protein homeostasis

- CRBN as model
- Deep structure/function insights
- New chemistry
- New targets
- New indications

Lessons Learned