Animal Model Workshop

Choosing Kidney Cancer Targets and Models Wisely

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Dana-Farber Cancer Institute and Harvard Medical School
Investigator
Howard Hughes Medical Institute

September 11-13, 2025

Session 2: Challenges and Specifics of Creating Good Model

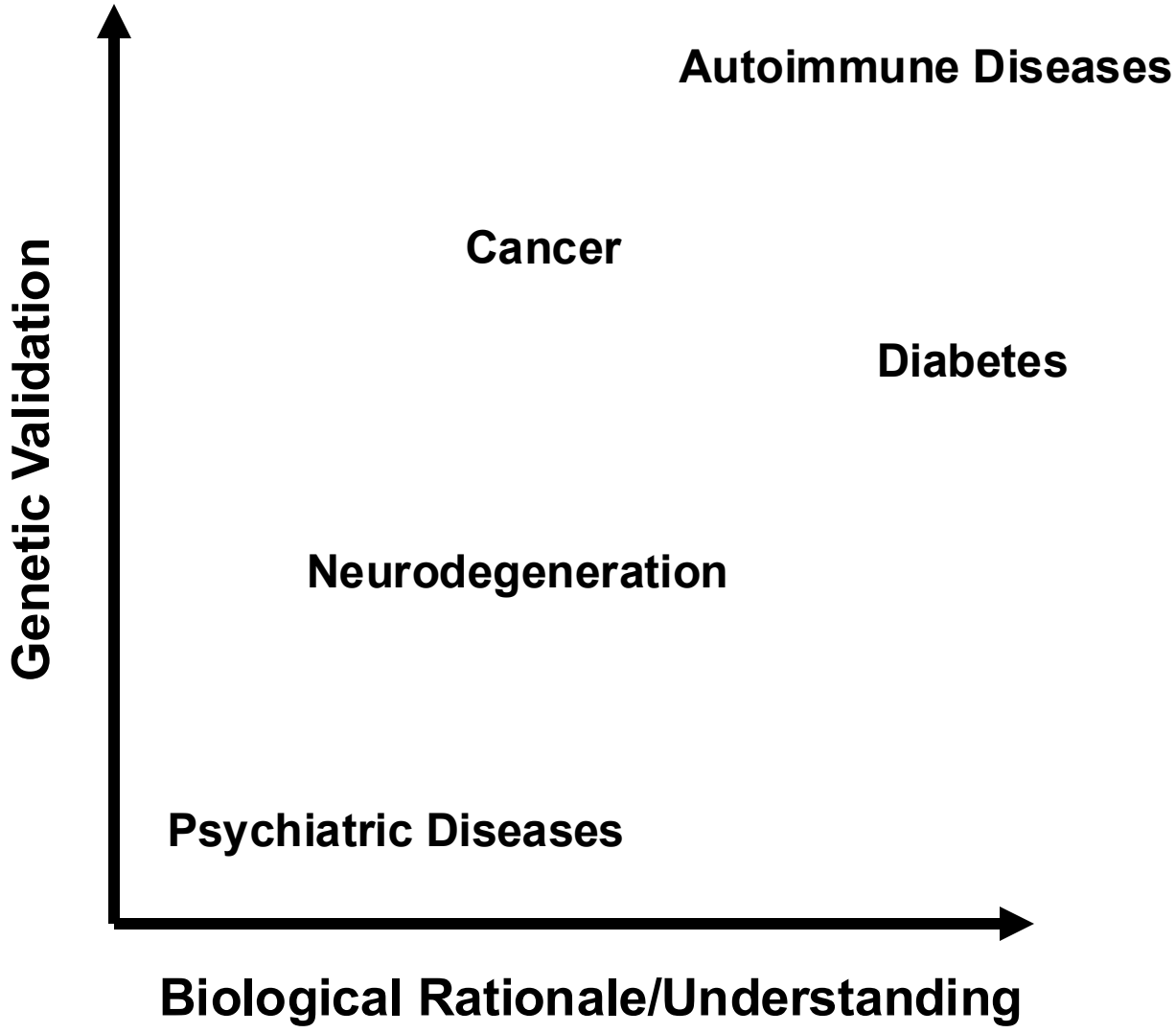
KidneyCancerAssociation® IN PARTNERSHIP WITH UTSouthwestern Medical Center Kidney Cancer Program

KidneyCancerAssociation® IN PARTNERSHIP WITH UTSouthwestern Medical Center Kidney Cancer Program

Disclosure

- I have a financial interest in Fibrogen, Inc., which is developing prolyl hydroxylase inhibitors for the treatment of anemia and ischemic diseases
- I am on Lilly Board of Directors
- I am a cofounder of Tango Therapeutics, Inc., which is developing cancer drugs based on synthetic lethality
- I have a financial interest in HIF2 inhibitor Belzutifan (being developed by Merck)
- I am on LifeMine Therapeutics Board of Directors
- I am on Circle Pharma Scientific Advisory Board
- I advise Nextech Invest and Casdin Capital

Drug Development Success Increases with High Quality Targets (Genetically Validated and Biology Understood)



nature genetics

The support of human genetic evidence for approved drug indications

Matthew R Nelson[1], Hannah Tipney[2], Jeffery L Painter[1], Judong Shen[1], Paola Nicoletti[3], Yufeng Shen[3,4], Aris Floratos[3,4], Pak Chung Sham[5,6], Mulin Jun Li[6,7], Junwen Wang[6,7], Lon R Cardon[8], John C Whittaker[2] & Philippe Sanseau[2]

PLOS GENETICS

RESEARCH ARTICLE

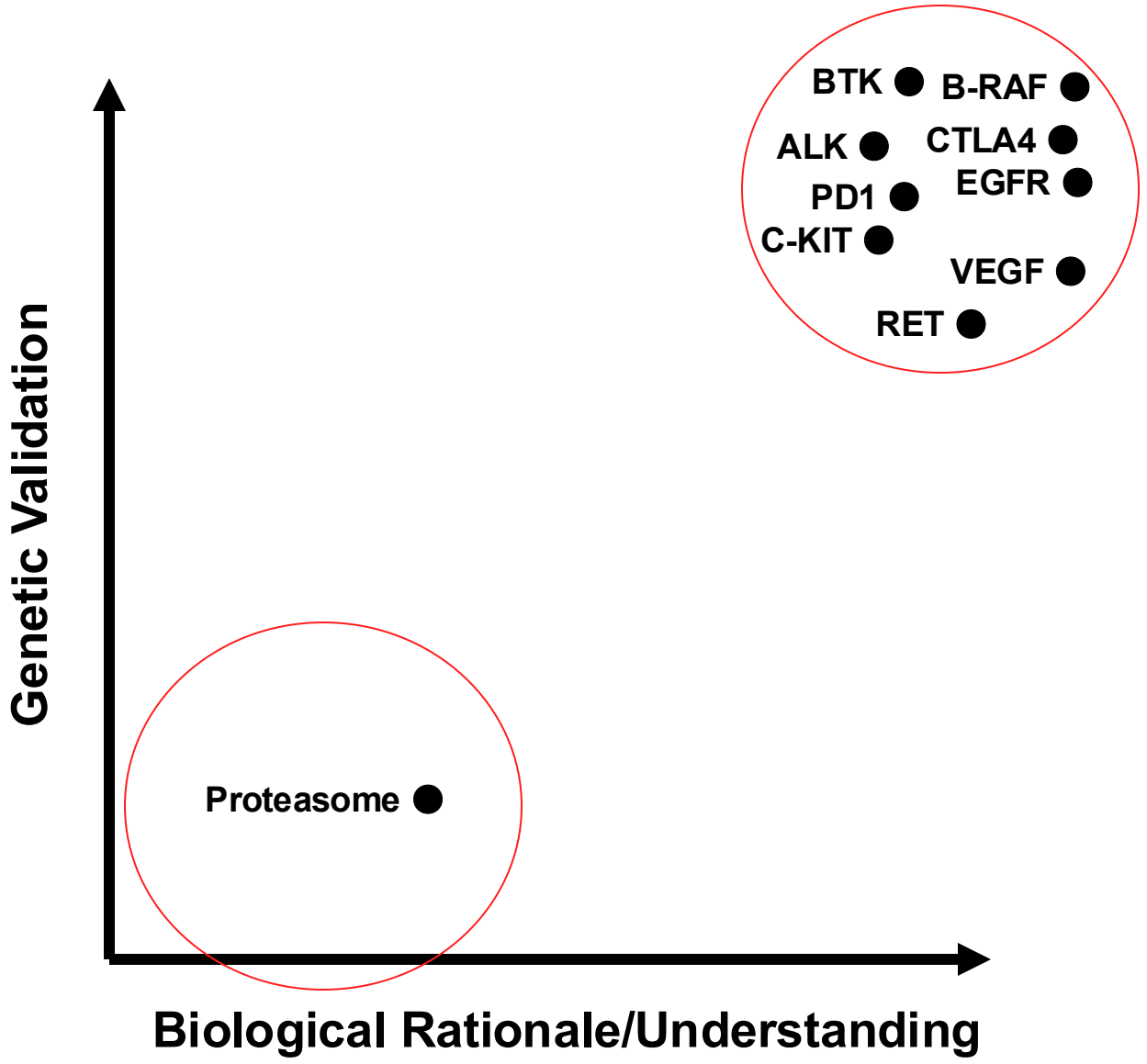
Are drug targets with genetic support twice as likely to be approved? Revised estimates of the impact of genetic support for drug mechanisms on the probability of drug approval

Emily A. King*, J. Wade Davis, Jacob F. Degner

Department of Computational Genomics, AbbVie, North Chicago, Illinois, United States of America

* emily.king@abbvie.com

Targets of Some Recent Cancer Approvals



Genetic Validation of CTLA-4

Immunity

Cell PRESS

Volume 3, Issue 5, November 1995, Pages 541-547

Article

Loss of CTLA-4 leads to massive lymphoproliferation and fatal multiorgan tissue destruction, revealing a critical negative regulatory role of CTLA-4

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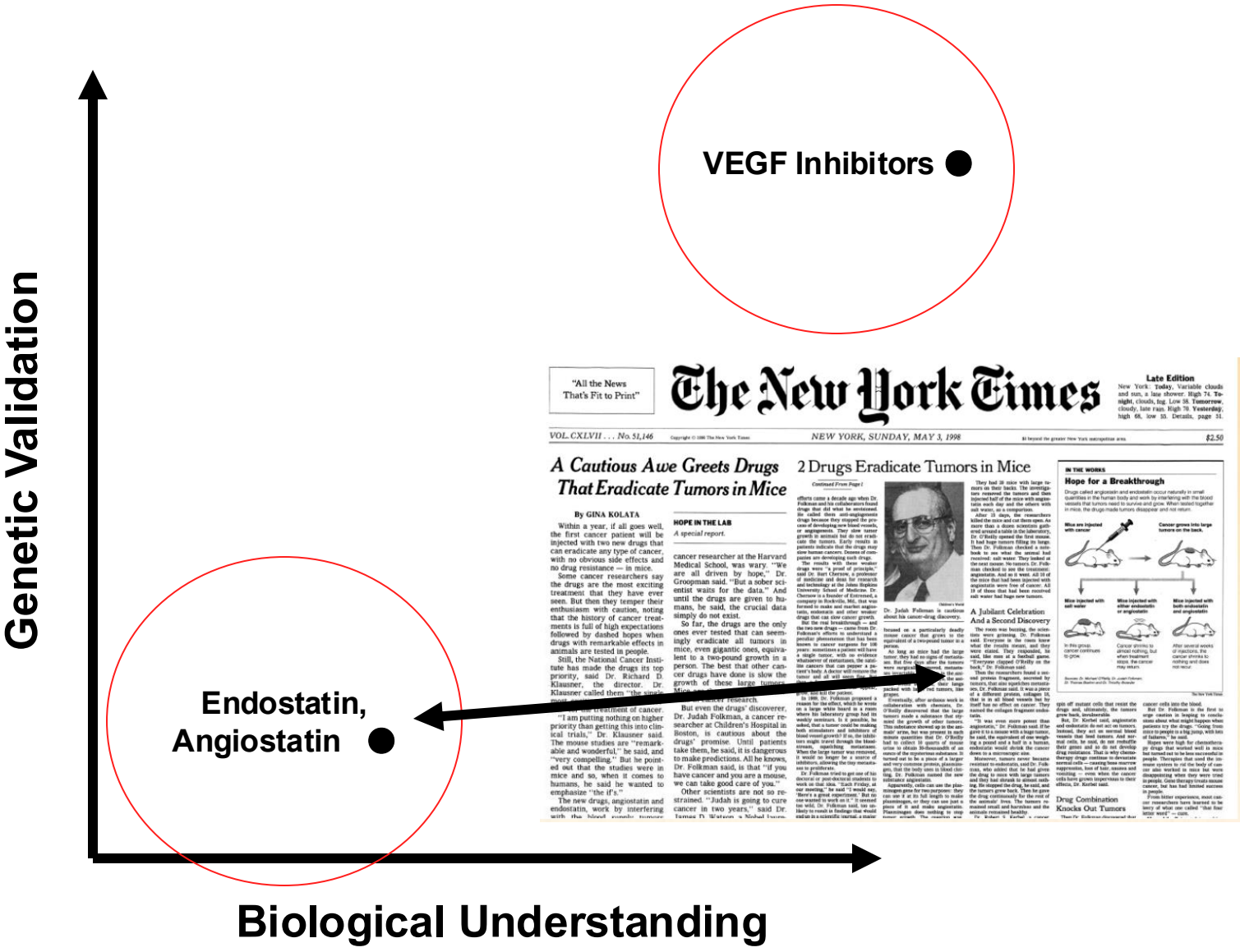
REPORTS

Lymphoproliferative Disorders with Early Lethality in Mice Deficient in *Ctla-4*

Paul Waterhouse, Josef M. Penninger, Emma Timms, Andrew Wakeham, Arda Shahinian, Kelvin P. Lee, Craig B. Thompson, Henrik Griesser, Tak W. Mak(1)

Science 10 Nov 1995:
Vol. 270, Issue 5238, pp. 985-988
DOI: 10.1126/science.270.5238.985

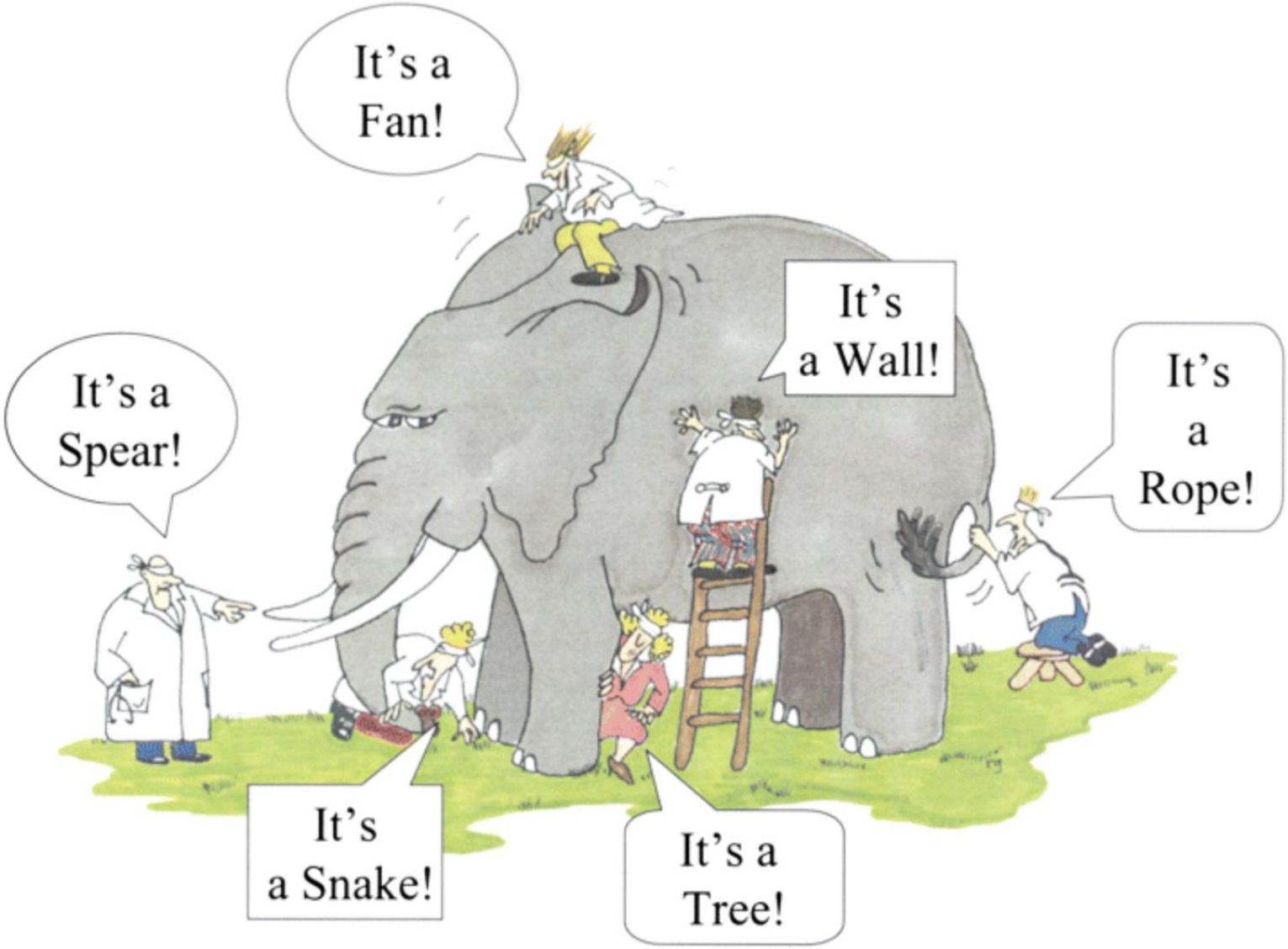
Angiogenesis Inhibitors



Genetics Establishes Causality

△Target Gene → △ Phenotype

Studying Cancer Without Genetics on Your Side



Genetic Validation Can Take Multiple Forms

- Germline Human Variants/Mutations
- Recurrent Somatic Mutations
- (Properly Controlled) Somatic Knockout/Knockdown Studies (e.g. with CRISPR/Cas9, RNA Interference)
- Mouse Knockout Studies

Drugging the "Undruggable"

- **Target Critical Downstream Effectors (Epistasis)**
- **Look for Allosteric Inhibitors**
- **Exploit Synthetic Lethal Interactions**
- **Search for Degraders**

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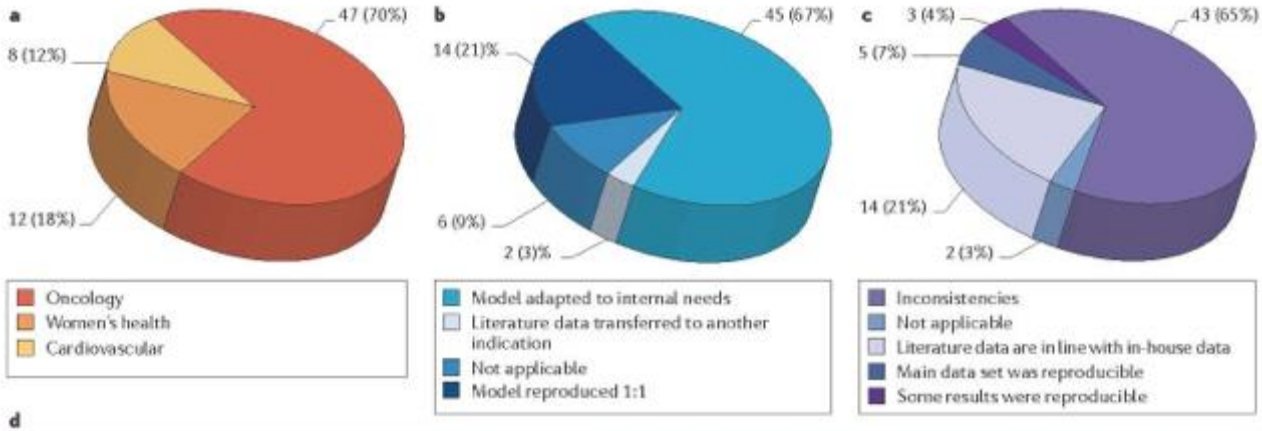
Believe it or not: how much can we rely on published data on potential drug targets?

Florian Prinz, Thomas Schlange and Khusru Asadullah

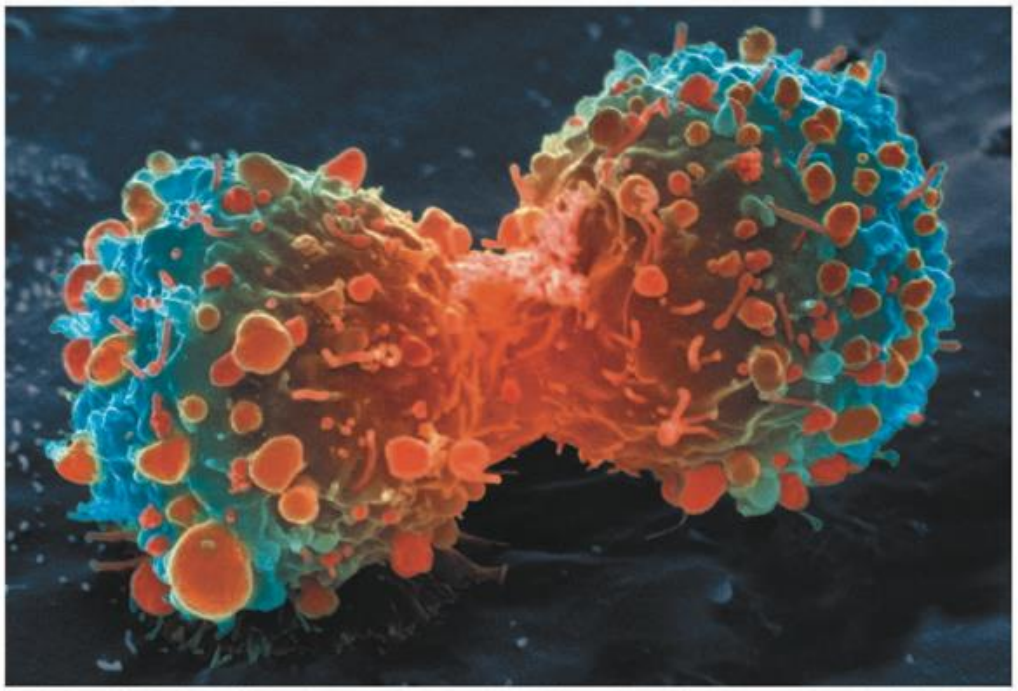


d

	Model reproduced 1:1	Model adapted to internal needs (cell line, assays)	Literature data transferred to another indication	Not applicable
In-house data in line with published results	1 (7%)	12 (86%)	0	1 (7%)
Inconsistencies that led to project termination	11 (26%)	26 (60%)	2 (5%)	4 (9%)

NATURE REVIEWS | DRUG DISCOVERY Vol. 10:712, 2011

COMMENT



S. GSCHMEISSNER/SPL

Many landmark findings in preclinical oncology research are not reproducible, in part because of inadequate cell lines and animal models.

Raise standards for preclinical cancer research

C. Glenn Begley and **Lee M. Ellis** propose how methods, publications and incentives must change if patients are to benefit.

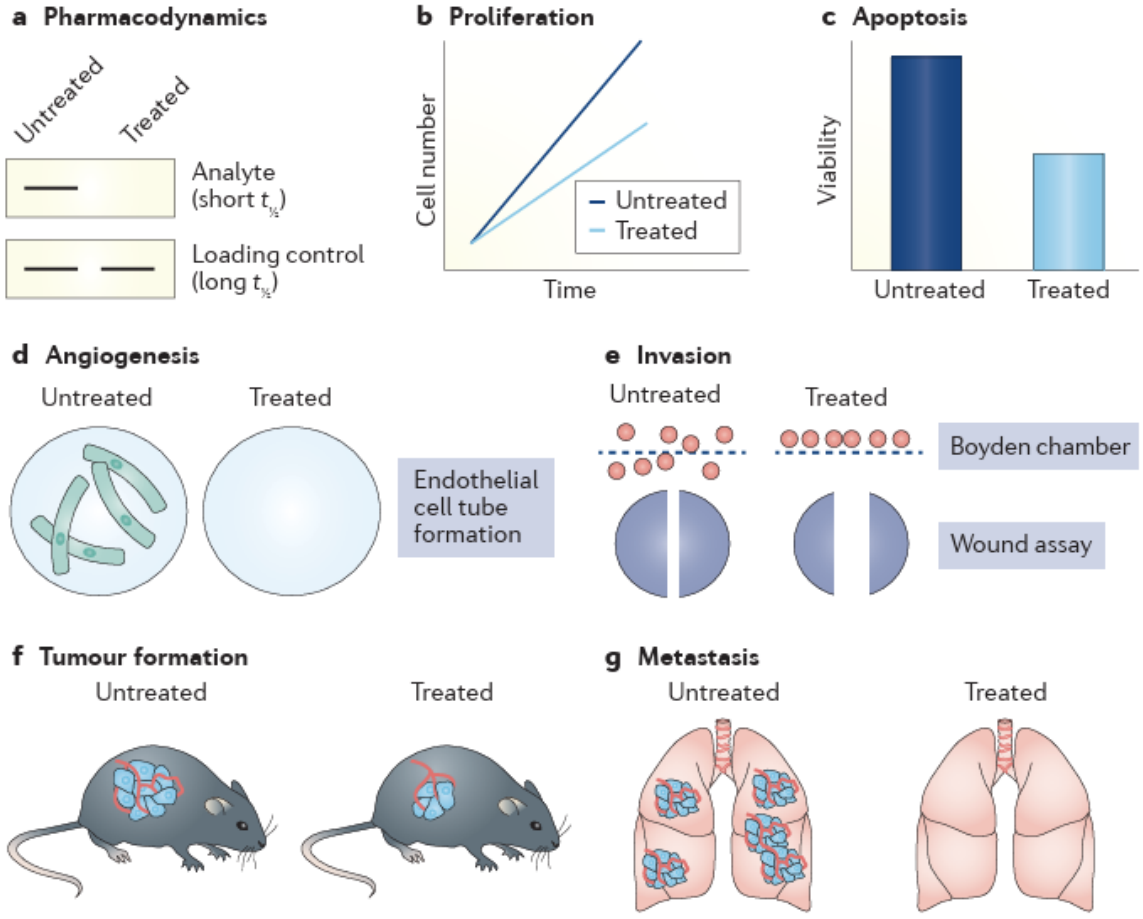
OPINION

Common pitfalls in preclinical cancer target validation

William G. Kaelin Jr

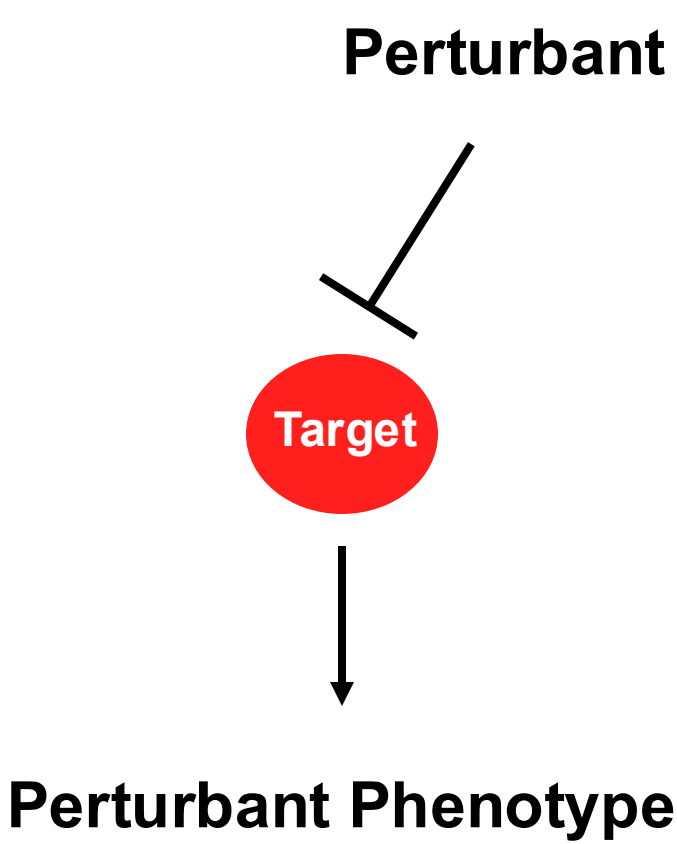
Nat Rev Cancer. 17:425-440, 2017

Common ”Down” Assays in Cancer Biology



Kaelin, Nature Reviews Cancer, 2017

The Off-Target Problem



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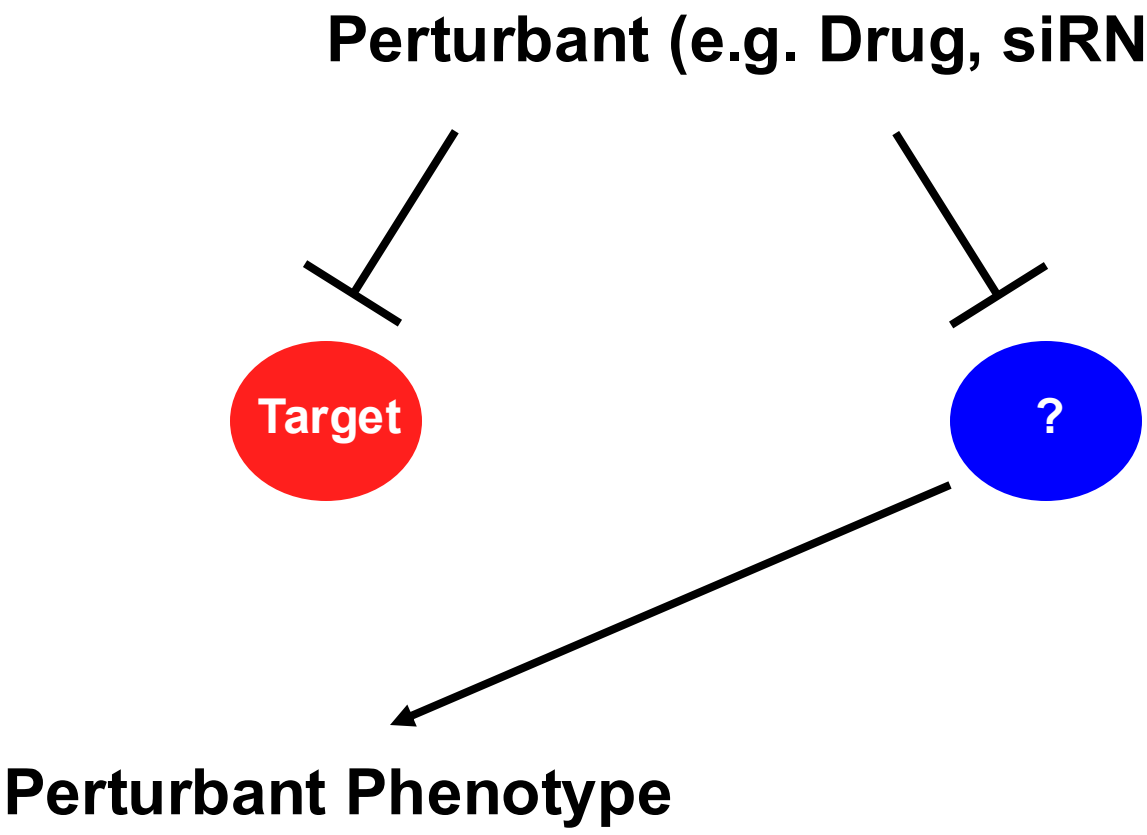
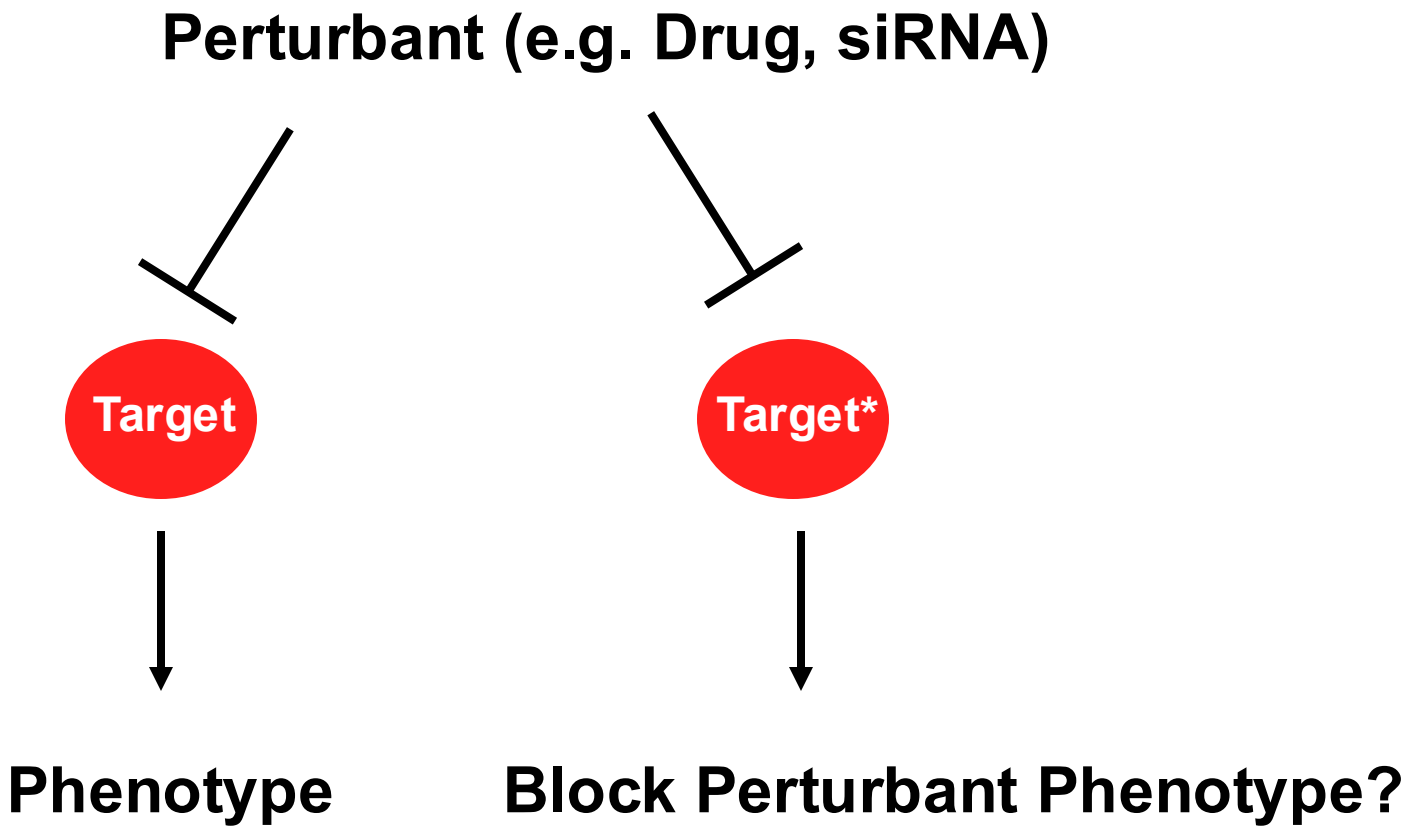


Rescue with Perturbant-Resistant Target



LETTER

doi:10.1038/nature19795

On-target efficacy of a HIF-2α antagonist in preclinical kidney cancer models

Hyejin Cho[1], Xinlin Du[2], James P. Rizzi[2], Ella Liberzon[1], Abhishek A. Chakraborty[1], Wenhua Gao[1], Ingrid Carvo[1,3], Sabina Signoretti[1,3], Richard K. Bruick[4], John A. Josey[2], Eli M. Wallace[2] & William G. Kaelin Jr[1,5]

LETTER

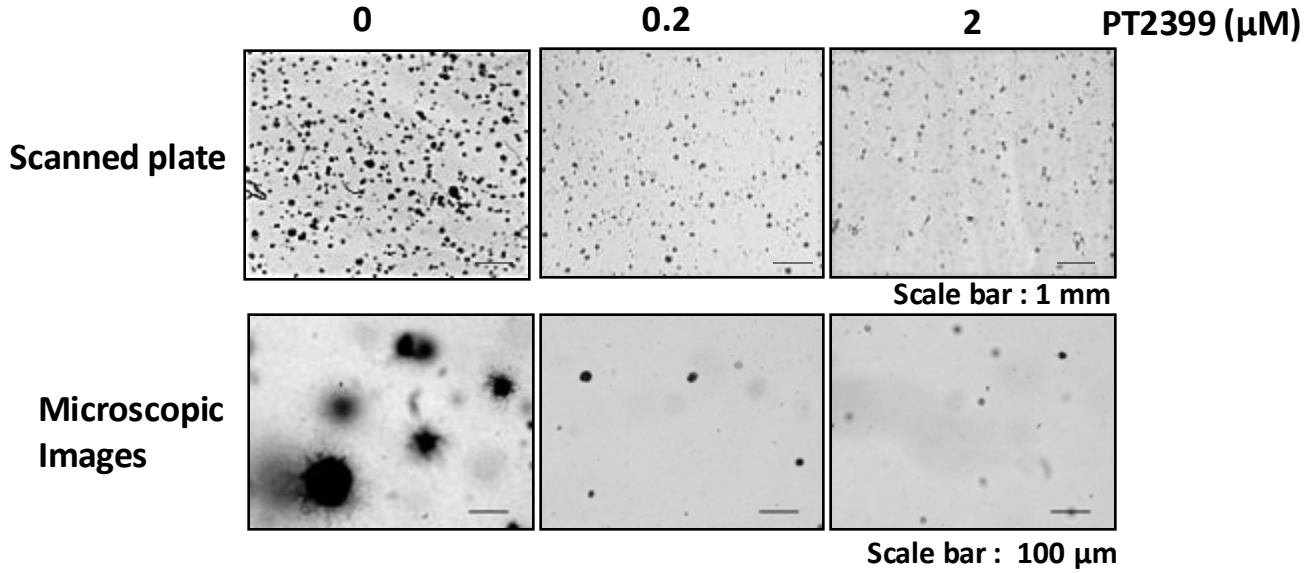
doi:10.1038/nature19796

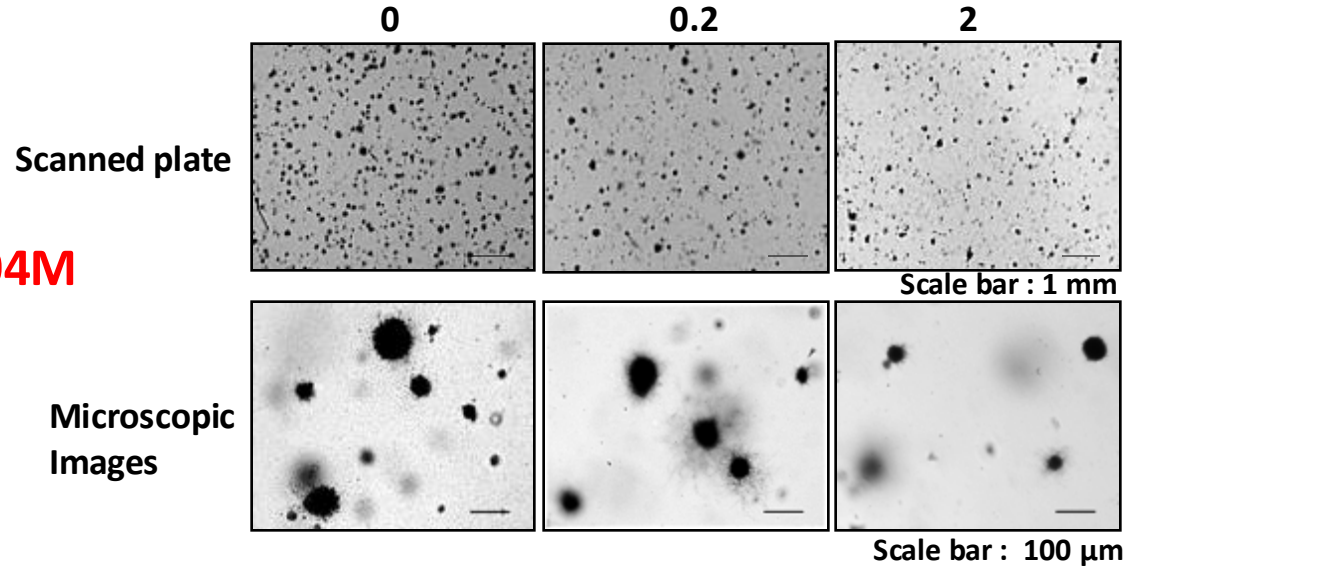
Targeting renal cell carcinoma with a HIF-2 antagonist

Wenfang Chen[1,2,3]*, Haley Hill[1,2]*, Alana Christie[1]*, Min Soo Kim[1,4]*, Eboni Holloman[1,2], Andrea Pavia-Jimenez[1,2], Farrah Homayoun[1,2], Yuanqing Ma[1,2], Nirav Patel[1,2], Paul Yell[5], Guiyang Hao[6], Qurratulain Yousuf[1,2], Allison Joyce[1,2], Ivan Pedrosa[1,6], Heather Geiger[7], He Zhang[1,4], Jenny Chang[1], Kevin H. Gardner[8,9,10], Richard K. Bruick[1,11], Catherine Reeves[7], Tae Hyun Hwang[1,4], Kevin Courtney[1,2], Eugene Frenkel[1,2], Xiankai Sun[1,6], Naseem Zojwalla[12], Tai Wong[12], James P. Rizzi[12], Eli M. Wallace[12], John A. Josey[12], Yang Xie[1,4], Xian-Jin Xie[1,4], Payal Kapur[1,13], Renée M. McKay[1,2] & James Brugarolas[1,2]

NATURE NOVEMBER 2016

Inhibition of VHL-Defective Renal Cell Carcinoma by PT2399: Soft Agar Assays





Kidney Cancer Models

- Cancer Cell Lines in 2D Cultures
- Cancer Cell Lines in Soft Agar
- Subcutaneous Cell Line Xenografts
- Orthotopic Cell Line Xenografts
- Patient-Derived Xenografts
- Genetically-Engineered Mouse Models

Choosing Models

- **The Suitability of a Model DEPENDS ON THE QUESTION(S) BEING ASKED**
- **Corroborating Lines of Evidence are a Scientist's Best Friend***

Genetic Validation of CTLA-4

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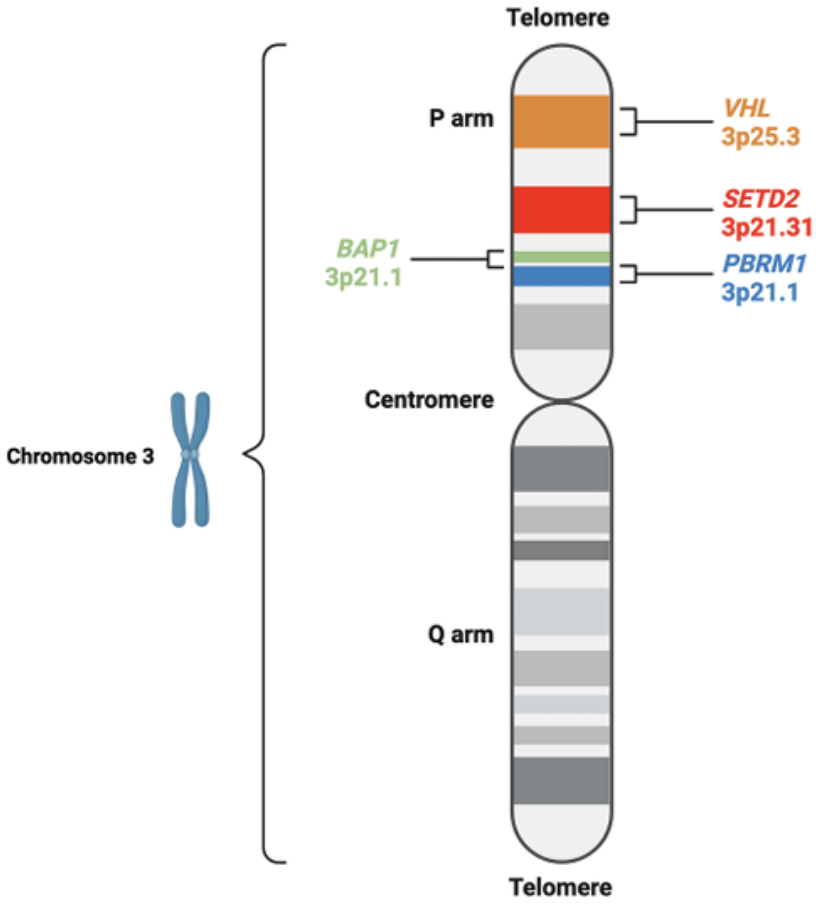
Challenges Making VHL-/- ccRCC GEMS

Germline Cancer Gene Mutations: Humans and Mice Might be "Wired" Differently with Respect to Tissue Tropism

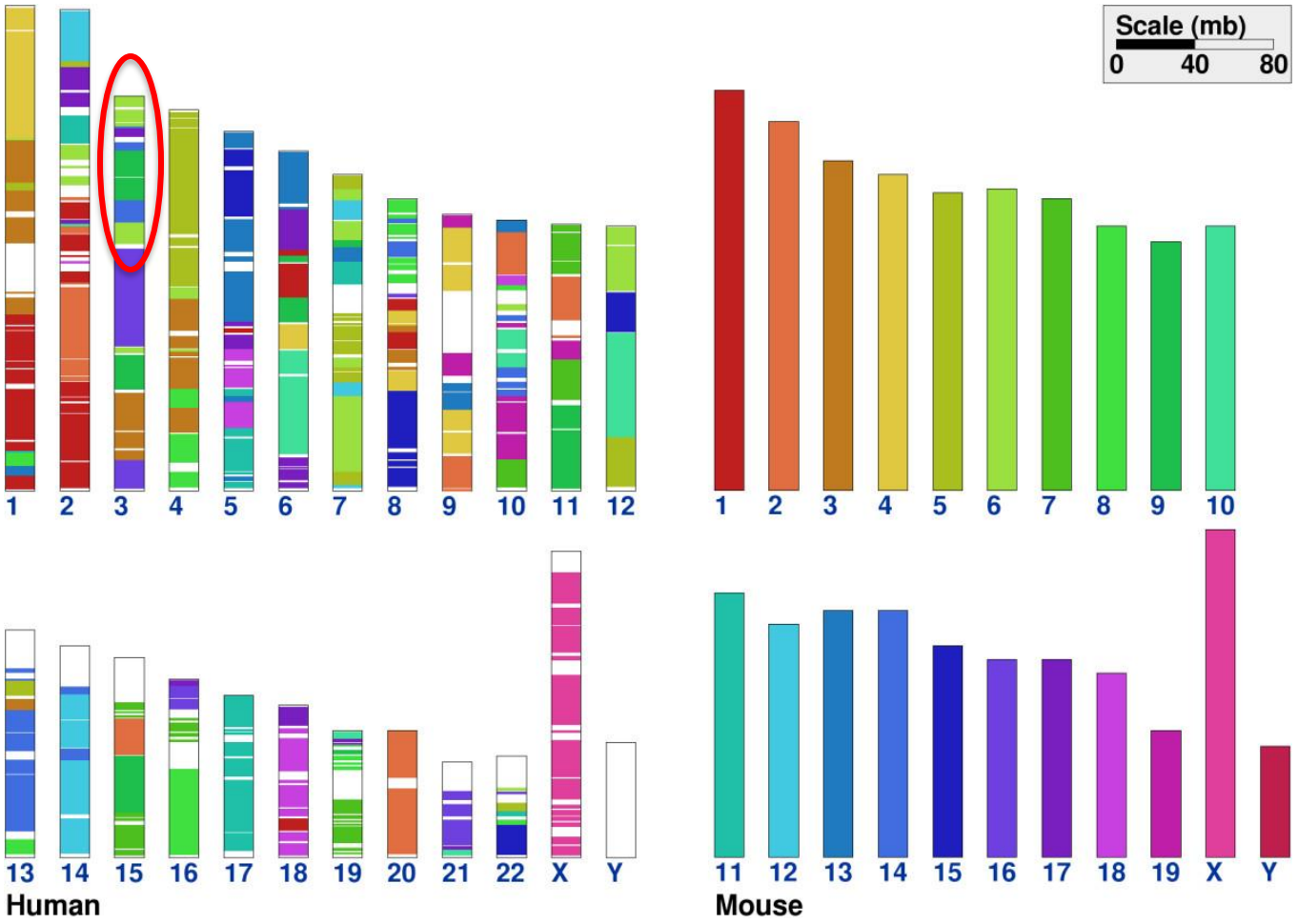
	Humans	Mice
RB1	Retinoblastoma, Sarcoma	Pituitary and Thyroid NE Tumors
TP53	Breast Ca, Sarcoma, etc.	Lymphoma
APC	Large Bowel Cancer	Small Bowel Cancer
BRCA1	Breast Ca, Ovarian Ca, etc.	None
VHL	Kidney Ca, etc.	None

Chromosome 3p Loss Affects Multiple Kidney Cancer Suppressors

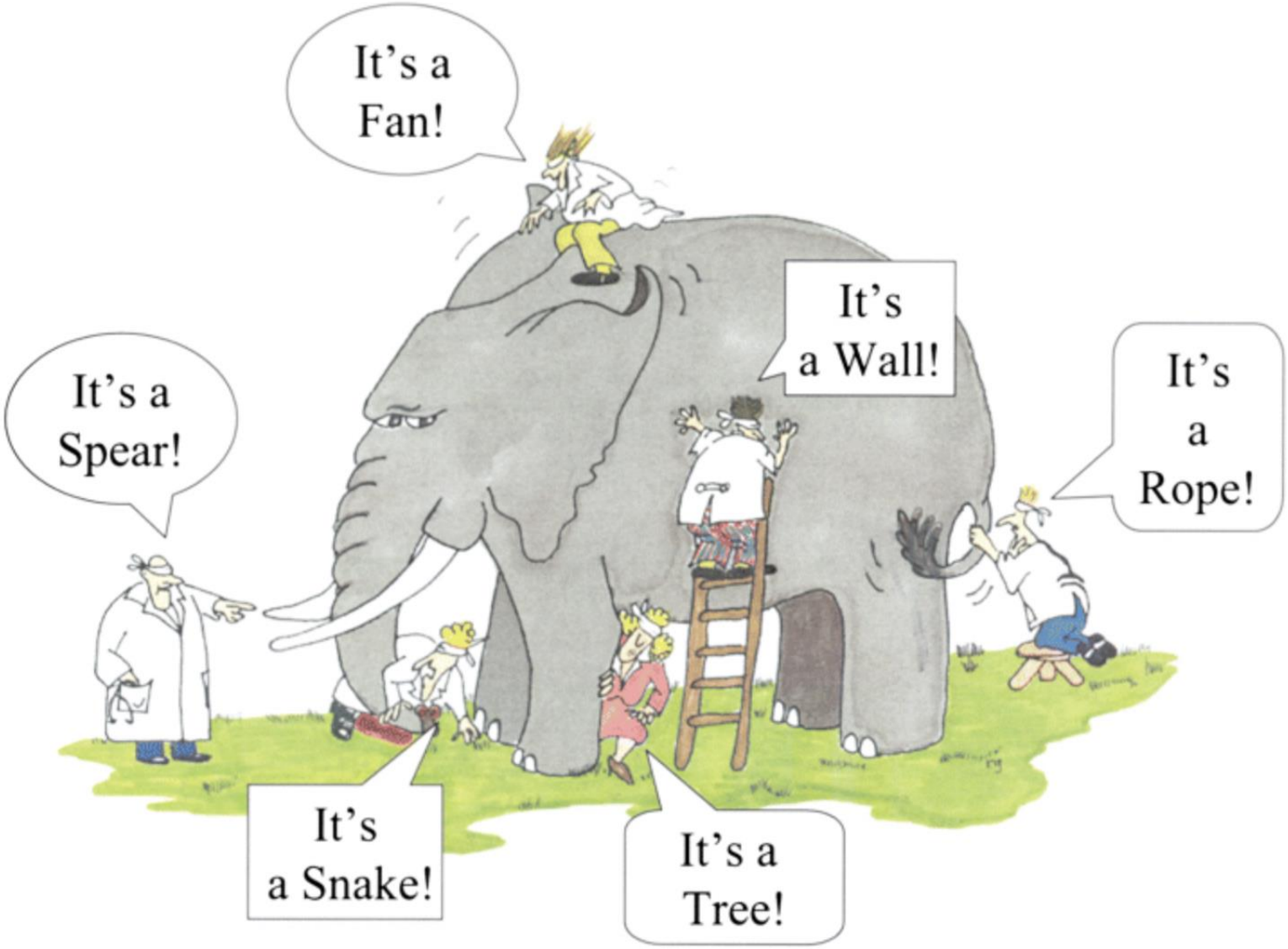


Pathology - Research and Practice 254 (2024) 155142

Lack of Synteny Between Humans and Mice

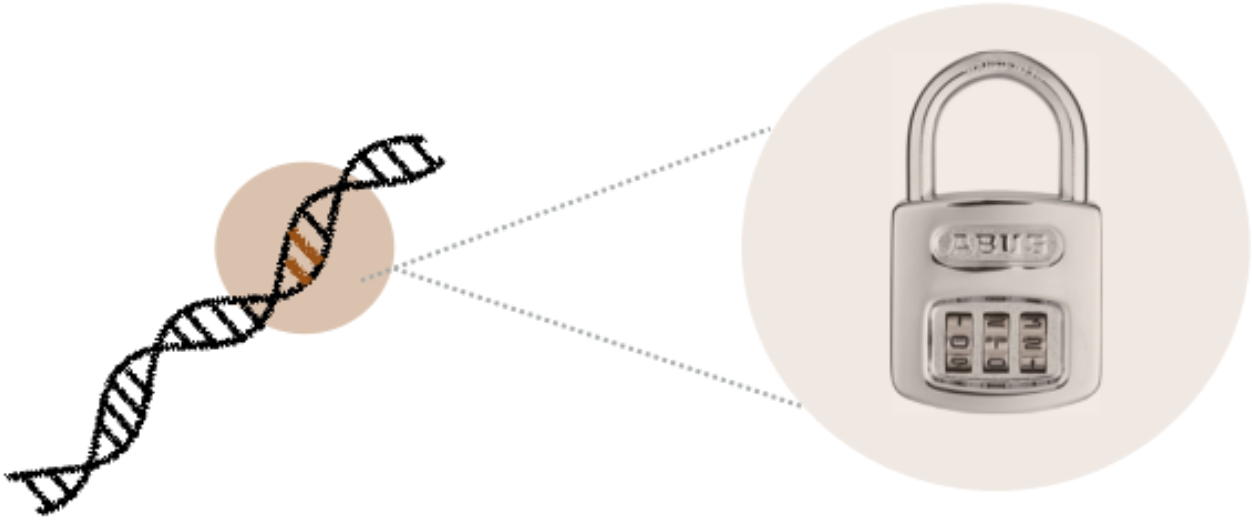


Studying Cancer Without Genetics on Your Side



The Multiple Mutation Problem

“Cancer Cells harbor too many mutations- we will never be able to fix them all” (countless naysayers)

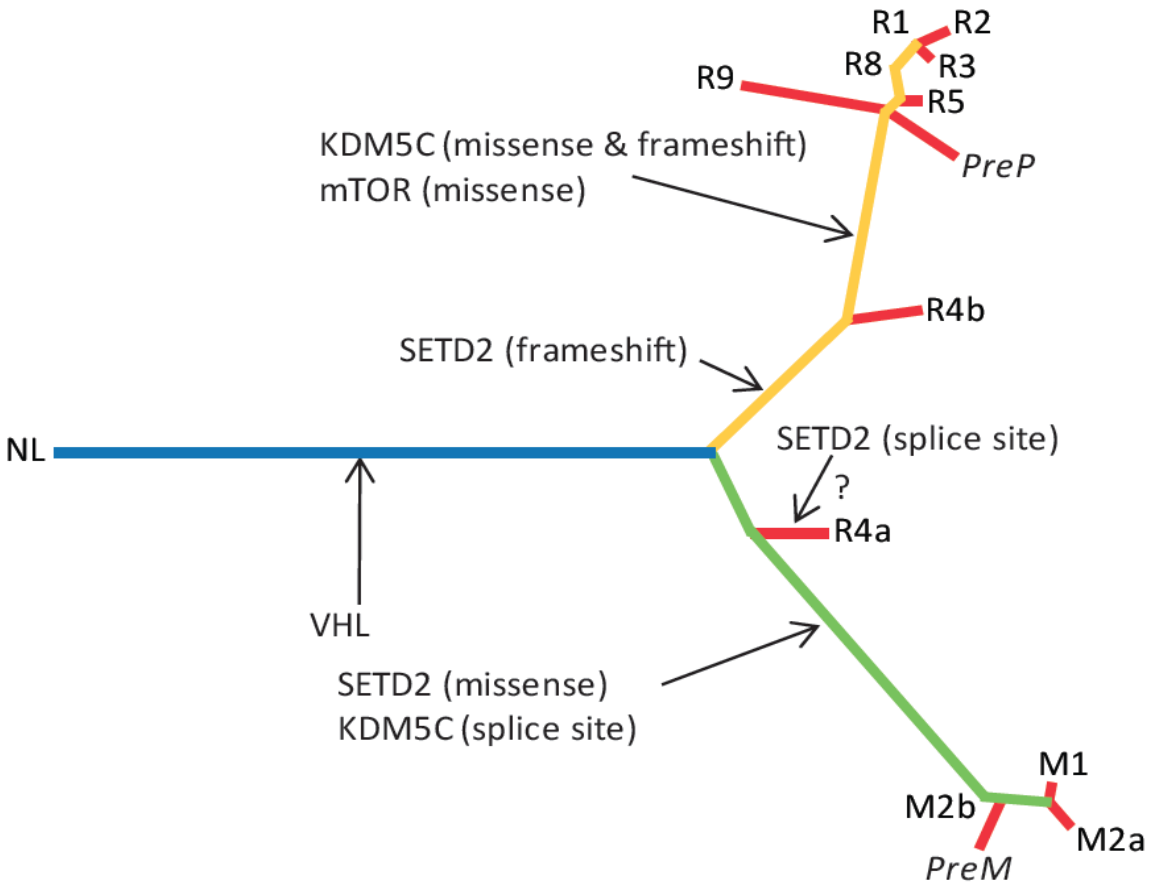


Genetic Interdependence

Hypothesis: Some Late Mutations (Driver or Passenger) in a Tumor are Only Tolerated Because of the Mutations that Preceded Them

If True, Correcting Early Mutations should Selectively Kill Tumor Cells

Truncal vs Branch Mutations During Tumor Evolution: One ccRCC Example

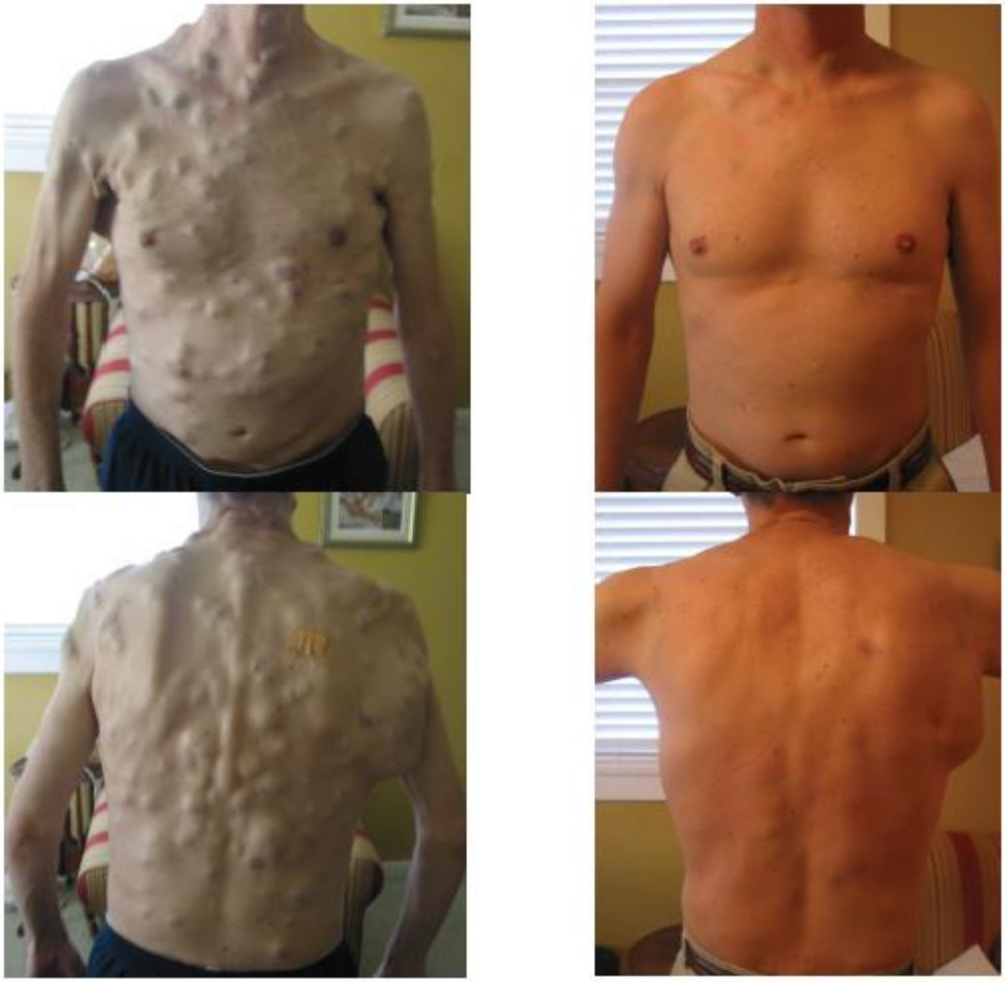


Gerlinger M et al. N Engl J Med 2012;366:883-892.

Successfully Targeting Early Mutations

- Her2/Neu –Breast Cancer
- EGFR – Lung Cancer
- c-KIT - GIST
- B-Raf - Melanoma
- ALK – Lung Cancer
- ROS- Lung Cancer
- Etc.

Clinical Response and Resistance to RAF Inhibition in Melanoma



October, 2009 January, 2010

Wagle et al JCO 2011

Solution 1: Combination Chemotherapy

1 cm^3 Tumor = 10^9 Cells

Tumor Burden in Most Cancer Patients = 10^{10}-10^{12} Cells

Assume 1/1,000,000 Cells Resistant to Any One Drug

Then:

Chance of Cure with Single Agent is Approximately ZERO

However:

Probability of Any One Cell Being Resistant to 3 Non-Cross Resistant Drugs is 10^{-6} x 10^{-6} x 10^{-6} = 10^{-18}

eLIFE elifesciences.org

RESEARCH ARTICLE

A curative combination cancer therapy achieves high fractional cell killing through low cross-resistance and drug additivity

Adam C Palmer[1†‡], Christopher Chidley[1†], Peter K Sorger[1,2*]

[1]Laboratory of Systems Pharmacology, Harvard Medical School, Boston, United States; [2]Department of Systems Biology, Harvard Medical School, Boston, United States

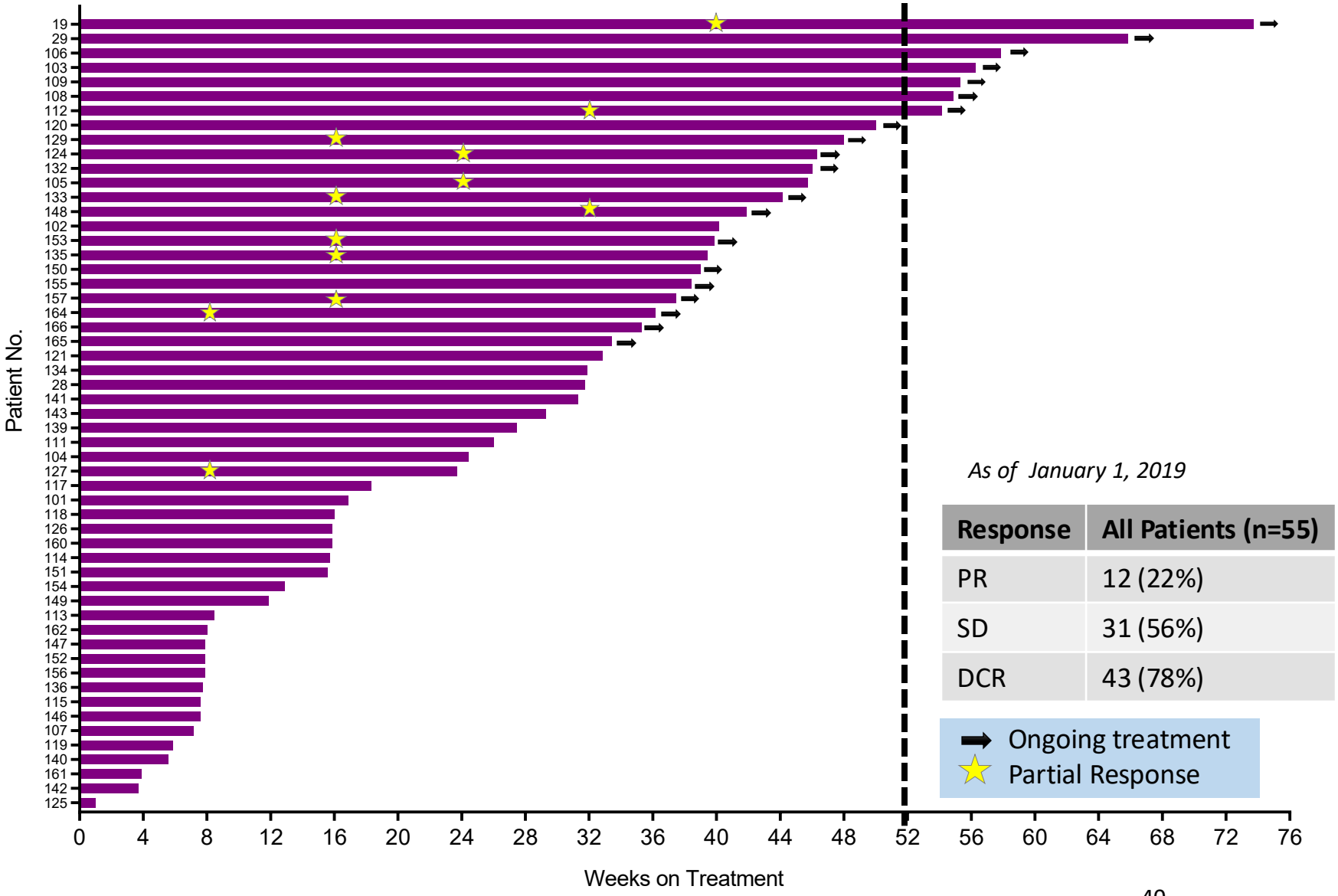
Palmer *et al*. eLife 2019;8:e50036. DOI: https://doi.org/10.7554/eLife.50036

Getting to Combinations

- **Potency and Specificity Will Matter (!)**
  - **The best drug for the eventual combination might not be the best drug as monotherapy**
- **Need to Get Out of Rotating Single Agent Mindset**
- **Beware of Using Drugs at Single Agent MTD**
- **Need to Think Creatively About Clinical Trial Designs**

Solution 2. Treat Earlier!

HIF2 Inhibitor Belzutifan in Patients with Advanced Kidney Cancer (Phase 1/2)

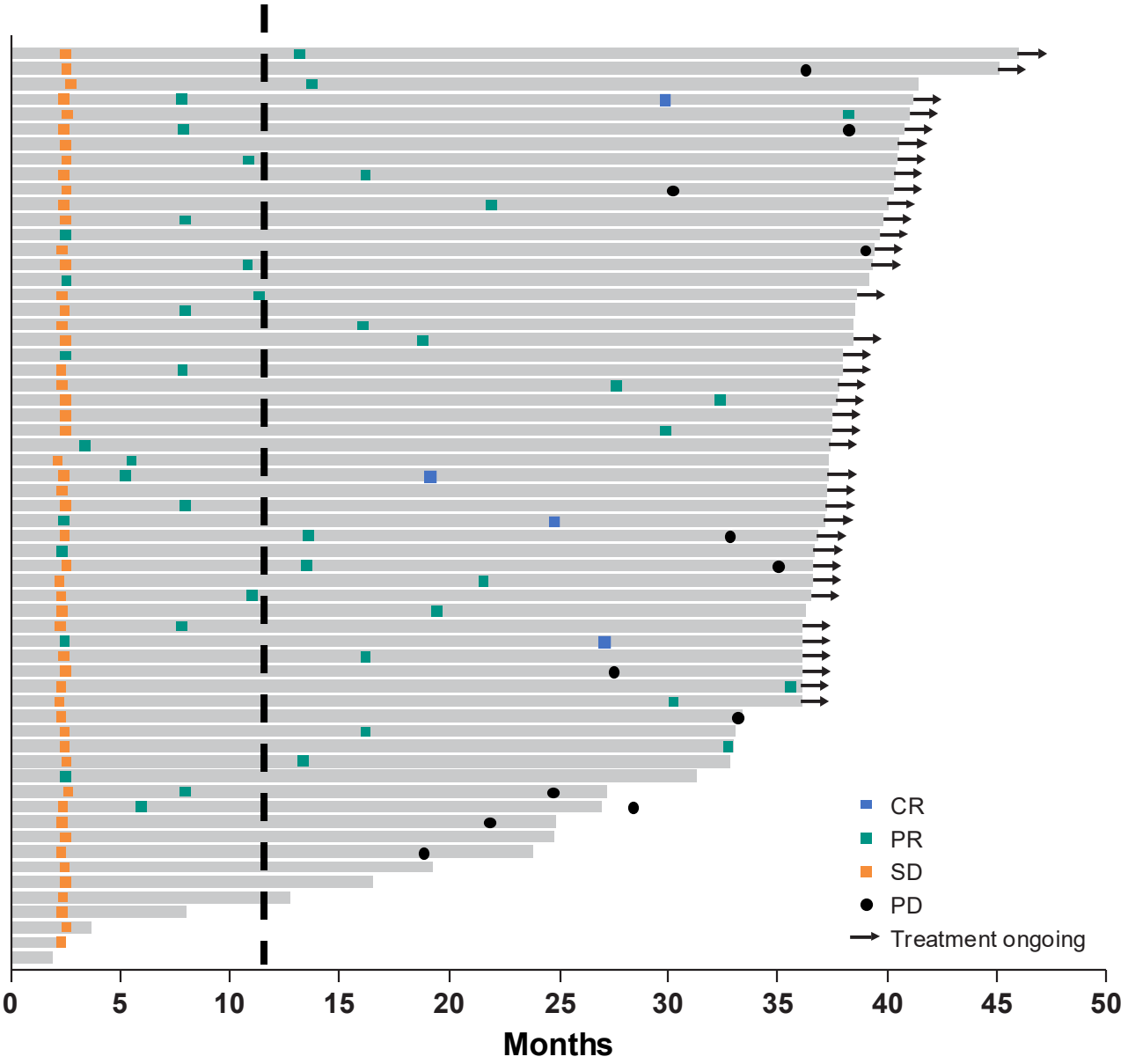


As of January 1, 2019

Response	All Patients (n=55)
PR	12 (22%)
SD	31 (56%)
DCR	43 (78%)

➡ Ongoing treatment
★ Partial Response

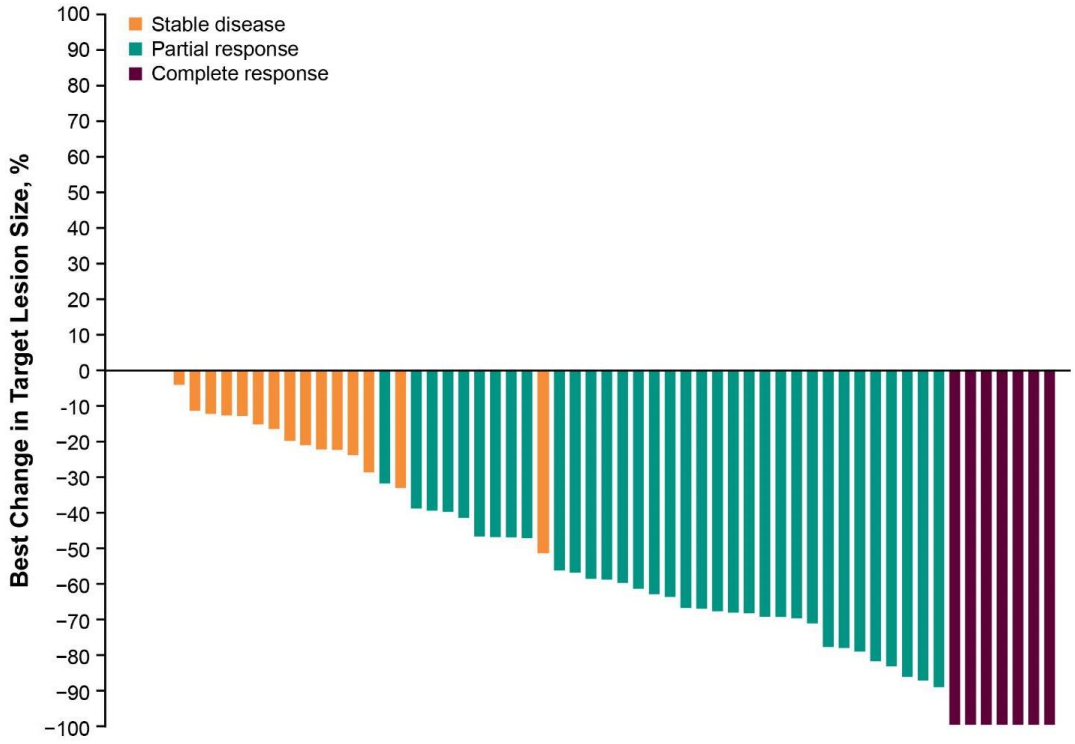
Treatment of VHL Disease Patients with Belzutifan



Srinivasan et al ESMO 2023

Treatment of VHL Disease–Associated RCC with Belzutifan

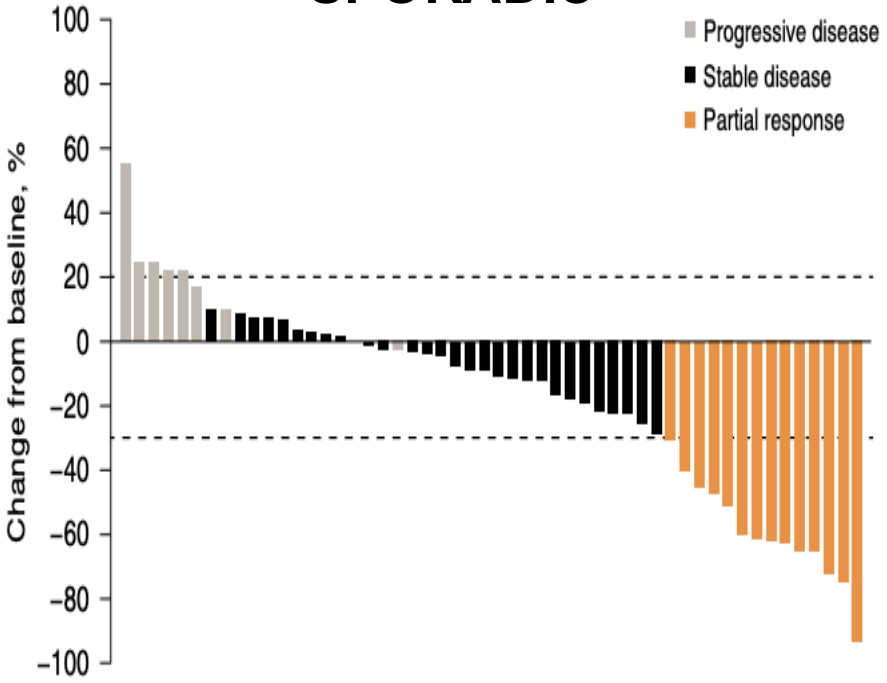
	RCC N = 61
ORR, % (95% CI)	**67 (54-79)**
Best response n (%)	
CR	7 (11)
PR	34 (56)
SD	19 (31)
PD	0
NE[a]	1 (2)



Srinivasan et al Lancet Oncology 2025

Treatment of ccRCC with Belzutifan

SPORADIC



Choueiri et al Nat Med 2021

VHL DISEASE

Srinivasan et al Lancet Oncology 2025

[a]1 patient discontinued the study before the first postbaseline tumor assessment. Data cutoff date: April 1, 2022.