IDEAYA Synthetic Lethality Investor Day
April 20, 2021
NASDAQ: **IDYA**

IDEAYA Biosciences

Improving Lives Through Transformative Precision Medicines

Safe Harbor Statement

Certain statements in this presentation and the accompanying oral commentary are forward-looking statements. These statements relate to future events or the future financial performance of IDEAYA Biosciences, Inc. (the “Company”) and involve known and unknown risks, uncertainties and other factors that may cause the actual results, levels of activity, performance or achievements of the Company or its industry to be materially different from those expressed or implied by any forward-looking statements. In some cases, forward-looking statements can be identified by terminology such as “may,” “will,” “could,” “would,” “should,” “expect,” “plan,” “anticipate,” “intend,” “believe,” “estimate,” “predict,” “potential” or other comparable terminology. All statements other than statements of historical fact could be deemed forward-looking, including any expectations regarding the Company’s target discovery platform or new target validation efforts as creating opportunities for research and development initiatives; any projections of financial information, market opportunities, cash runway or profitability; any statements about historical results that may suggest trends for the Company's business; any statements of the plans, strategies, and objectives of management for development programs or future operations; any statements about the timing of preclinical research, clinical development, regulatory filings, manufacturing or release of data; any statements of expectation or belief regarding future events, potential markets or market size, technology developments, or receipt of cash milestones, option exercise fees or royalties; and any statements of assumptions underlying any of the items mentioned. The Company has based these forward-looking statements on its current expectations, assumptions, estimates and projections. While the Company believes these expectations, assumptions, estimates and projections are reasonable, such forward-looking statements are only predictions and involve known and unknown risks and uncertainties, many of which are beyond the Company's control. These and other important factors may cause actual results, performance or achievements to differ materially from those expressed or implied by these forward-looking statements. The forward-looking statements in this presentation are made only as of the date hereof. For a further description of the risks and uncertainties that could cause actual results to differ from those expressed in these forward-looking statements, as well as risks relating to the business of the Company in general, see the Company's periodic filings with the Securities and Exchange Commission (the "SEC"), including its Annual Report on Form 10-K for the year ended December 31, 2020 and any current and periodic reports filed thereafter. Except as required by law, the Company assumes no obligation and does not intend to update these forward-looking statements or to conform these statements to actual results or to changes in the Company's expectations.

This presentation concerns anticipated products that are under clinical investigation and which have not yet been approved for marketing by the U.S. Food and Drug Administration (FDA). It is currently limited by Federal law to investigational use, and no representation is made as to its safety or effectiveness for the purposes for which it is being investigated.

Welcome and Introduction

Yujiro Hata – President and Chief Executive Officer
IDEAYA Biosciences

Welcome to our >100 Registered Participants and Guest Speakers!

IDEAYA's Inaugural Synthetic Lethality Investor Day

Benjamin Schwartz, Ph.D.
GSK, Vice President, Head of Synthetic Lethality Research Unit

William Sellers, M.D.
Broad Institute, Core Institute Member, Director of the Cancer Program

Alan D'Andrea, M.D.
Harvard Dana Farber, Director of Center of DNA Damage and Repair

Agenda

Welcome and Introduction

Yujiro Hata

Synthetic Lethality: Emerging Area within Precision Medicine and GSK-IDEAYA Partnership

Ben Schwartz (GSK)

IDE397: Targeting MAT2A in MTAP-Deletion Tumors

Bill Sellers (Broad), Mark Lackner, Matt Maurer

Werner Helicase: Compelling Synthetic Lethality Target (Roundtable)

Introduction: Ben Schwartz (GSK)
Panelists: Bill Sellers (Broad), Ben Schwartz (GSK), Mike Dillon
Moderator: Yujiro Hata

Pol-Theta: Key Target in MMEJ DNA Damage Repair Pathway

Alan D'Andrea (Harvard), Mike Dillon, Ben Schwartz (GSK)

PARG: Novel Target in Clinically-Validated Pathway

Mike Dillon, Mark Lackner

Analyst Q&A and Closing

Yujiro Hata

IDEAYA's Precision Medicine Oncology Pipeline

Building the Industry Leading Synthetic Lethality Focused Biotechnology Company

Precision Medicine Pipeline

		Modality/Indication	Biomarker	Preclinical	IND Enabling	Phase 1	Phase 2	2021 Goals	Collaborations	Commercial (IDEAYA)
Synthetic Lethality	**IDE397** *MAT2A*	Solid Tumors Monotherapy	MTAP					Clinical Pharmacodynamic Data	gsk (1)	US 50/50 Profit Share Ex-US Royalties
		Solid Tumors Combinations	MTAP					Preclinical Data to enable Combos (PRMTi, Taxanes, Others)		
	PARG	Ovarian, Gastric, Breast Cancers	Defined Biomarker					Select Development Candidate	CANCER RESEARCH UK (2)	WW Commercial Rights
	Pol Theta	Small Molecule Protein Degraders	HRD					Select Development Candidate	gsk (1)	Global Royalties
	WRN	GI Cancers	High-MSI					Chemistry Lead Optimization	gsk (1)	US 50/50 Profit Share Ex-US Royalties
	Platform	Solid Tumors	Defined Biomarker					Lead Series (DNA Damage Targets, MTAP-SL) New Target / Biomarker Validation		WW Commercial Rights
Kinase	**IDE196** *PKC*	MUM MEK Combo GNAQ/11 Mono	GNAQ/11					FDA Guidance H2 2021 on Potential Registrational Study in MUM based on Monotherapy OS and/or Darovasertib (IDE196) + Binimetinib Combination Data	Pfizer (3)	WW Commercial Rights
		MUM cMET Combo	GNAQ/11							

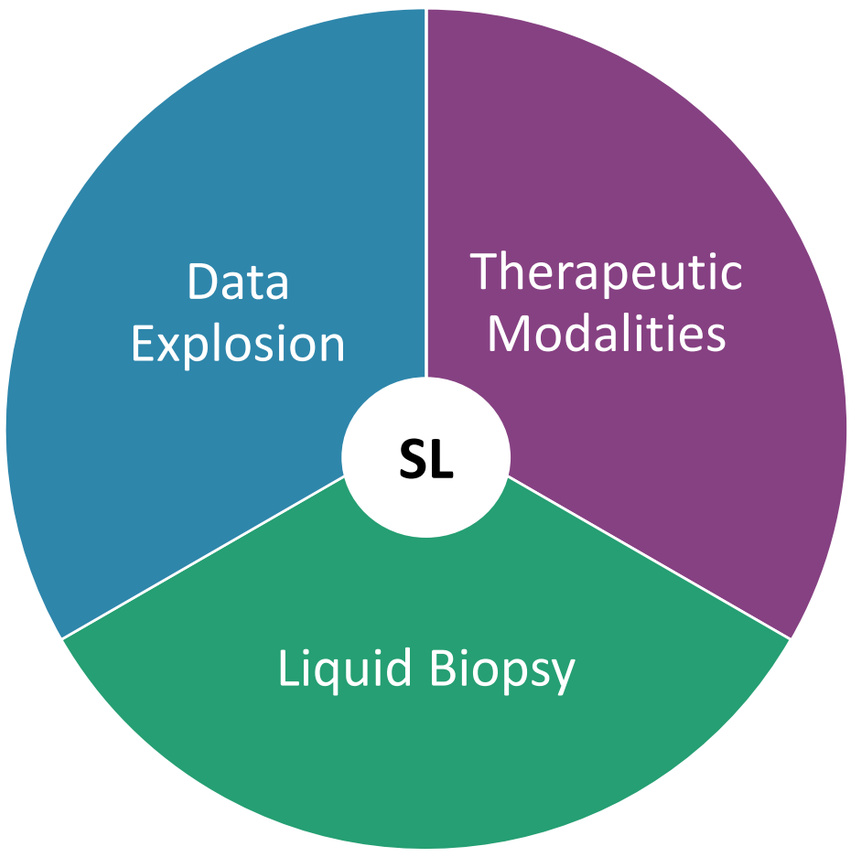
(1) Pursuant to GSK Collaboration, Option and License Agreement: MAT2A and WRN: 50/50 US Profits + ex-US Royalties; Polθ: Global Royalties
(2) Pursuant to CRUK Evaluation, Option and License Agreement, with ongoing Collaborative Research; IDEAYA controls all Commercial Rights
(3) Pursuant to Pfizer Clinical Trial Collaboration and Supply Agreement for MEK and cMET Combinations; IDEAYA retains all IDE196 Commercial Rights

DDT = DNA Damage Target, WRN = Werner Helicase, Polθ = DNA Polymerase Theta, HRD = homologous recombination deficiency, MSI = microsatellite instability
PKC = protein kinase C, MUM = metastatic uveal melanoma, SWS = Sturge-Weber Syndrome

= Target Program Milestone through 2021

Three Revolutions Intersecting with Synthetic Lethality

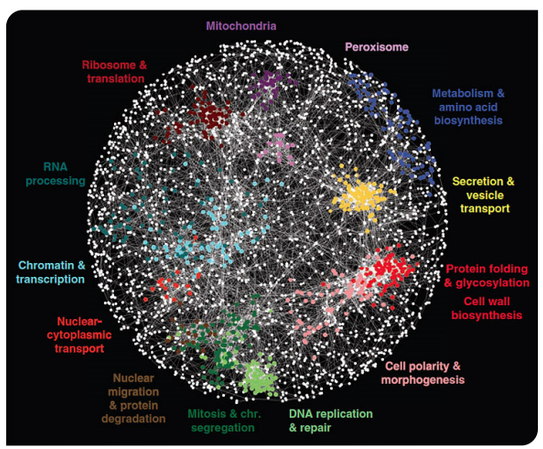
Convergence of Advances in Informatics, Drug Discovery and Translational Biology



Cancer's High Mutation Frequency Creates Enormous Opportunity for SL Therapies

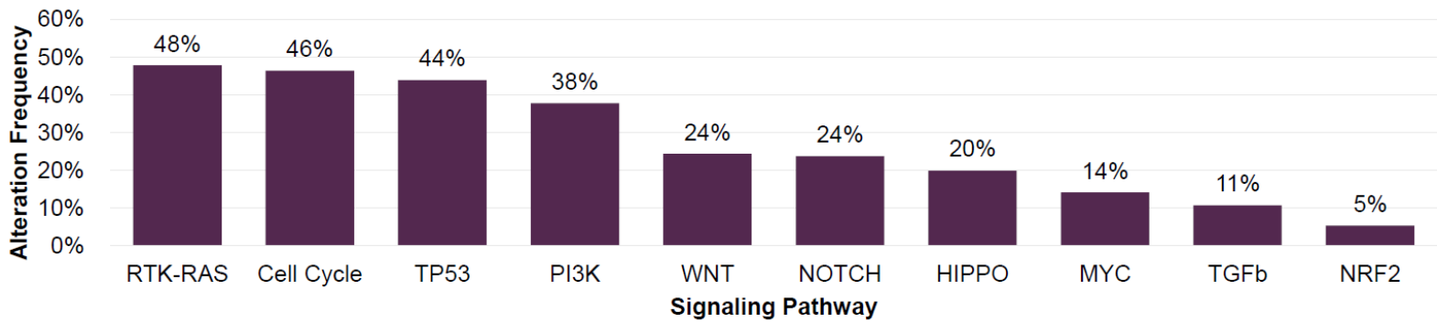
~30k Gene Mutations and Opportunity to Drug "Loss of Function" Mutations

Hundreds of Millions of SL Interaction Data Points Have Been Generated and Growing Rapidly



Reference: Charles Boone

Oncogenic Pathway Mutation Frequency
(N=9,125 Tumor Samples Across 33 Cancer Types)



Select Targets (% frequency)	RTK-RAS	Cell Cycle	TP53	PI3K	Wnt	NOTCH	HIPPO	MYC	TGF-b	NRF2
	RAS (13%)	CCND1-3 (10%)	MDM2 (3%)	RICTOR (3%)	CTNNB1 (3%)	KDM5A (2%)	YAP1 (2%)	MYC (8%)	TGFBR1 (1%)	NFE2L2 (3%)
	RAC1 (2%)	E2F1 (2%)	MDM4 (3%)	RPTOR (2%)	TCF7 (7%)	ARRDC1 (1%)	TEAD2 (<1%)	MYCN (1%)	TGFBR2 (3%)	KEAP1 (1%)
	IGF1R (2%)	E2F3 (2%)	TP53 (38%)	AKT1 (2%)	APC (6%)	NOTCH1-4	FAT1-4 (8%)	MGA (6%)	SMAD2 (1%)	CUL3 (1%)
	RAF1 (1%)	CDKN2A (29%)	CDKN2A (29%)	AKT2 (2%)	RNF43 (2%)	NOV (3%)	LATS1/2 (7%)	MAX (<1%)	SMAD3 (1%)	
	MAPK1 (1%)	CDKN2B (11%)	ATM (3%)	PTEN (12%)	ZNRF3 (1%)	CNTN6 (2%)	DCHS1/2 (2%)	MXI1 (<1%)	SMAD4 (4%)	
	PTPN11 (<1%)	CDKN2C (<1%)	CHEK2 (<1%)	PIK3R1 (4%)	DKK1-4 (1%)	FBXW7 (4%)	NF2 (1%)	MNT (<1%)	ACVR2A (2%)	
	SOS1 (<1%)	RB1 (6%)	RPS6KA (<1%)	PIK3R3 (<1%)	AXIN1 (1%)	CREBBP (2%)	TAOK1-3 (1%)	MLX (<1%)	ACVR1B (<1%)	
	RIT1 (<1%)	CCNE1 (3%)		STK11 (2%)	AXIN2 (<1%)	EP300 (2%)	SAV1 (<1%)			
	NF1 (5%)	CDKN1A (1%)		TSC1 (1%)	AMER1 (1%)	HES-X (1%)	STK3/4 (<1%)			
	RASA1 (2%)	CDKN1B (1%)		TSC2 (1%)	TLE3 (1%)	NCOR1 (2%)	MOB1 (<1%)			
	CBL (1%)			PPP2R1A (1%)	TLE4 (1%)	NCOR2 (1%)	CRB1/2 (<1%)			
	ERRFI1 (1%)			INPP4B (1%)		SPEN (1%)				

MAPK & cell cycle drug development potentially facilitated by prevalence of gain-of-function mutations

SL potentially more attractive for loss-of-function mutations, which may be harder to directly drug (vs gain-of-function)

Source: Guggenheim Securities, LLC Report: Synthetic Lethality Primer (March 2021)

Red text denotes activating oncogene; Blue text denotes loss-of-function mutation, potentially on a tumor suppressor

IDEAYA BIOSCIENCES

IDEAYA Vision / Response: Technology Investment Priorities

Enhance IDEAYA's Platform and Leadership in Synthetic Lethality

Data Explosion

Become industry leader in SL Bioinformatics / Machine Learning Target and Biomarker Discovery

- IDEAYA Bioinformatics / Machine Learning capabilities built to mine vast SL public and private data sets
- Iterative process between IDEAYA bioinformatics and SL biologists to develop most predictive and powerful algorithms developed specifically for SL target and biomarker discovery

Therapeutic Modalities

Enhance Pre-Eminent SL Drug Discovery Platform to Pursue Additional Potential First-in-Class SL Targets

- Expand and capitalize on new modalities in drug discovery, including protein degrader platform
- Leverage technology advances (e.g., Cryo-EM, 2017 Nobel Prize) to enhance Structure-Based Drug Design platform

Liquid Biopsy

Apply Next Generation Diagnostic Platforms to Enhance Clinical Population and PD Markers

- Utilize recent advances in ctDNA to patient select for "loss of function" SL mutations / biomarkers
- Non-invasive ctDNA PD markers provide powerful platform across IDEAYA's First-in-Class SL programs

IDEAYA BIOSCIENCES

IDEAYA Bioinformatics Platform

Vast Public and Proprietary Data Sets Being Analyzed to Prioritize Novel SL Targets

Synthetic Lethality Target Identification

- Computational effort to mine relevant public data for SL pairs
- IDEAYA algorithms developed for SL target and biomarker discovery and patient stratification

CCLE Cancer Cell Line Encyclopedia
cBioPortal FOR CANCER GENOMICS
TCGA

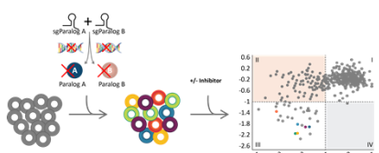
DepMap Consortium

- DepMap consortium membership deepens access to genome-wide CRISPR SL screen data to inform IDEAYA programs

depmap | Cancer Dependency Map

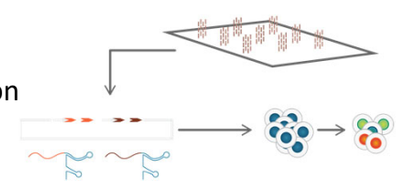
PAGEO™ Paralog Screens

- Ovarian Dual gRNA CRISPR paralog screens with functional redundancy that are hidden in single gRNA CRISPR screens
- Comprehensive set of paralog gene pairs involved in DDR



DECIPHER™ Dual CRISPR Screens

- Dual CRISPR DDR Library data analysis and hit prioritization
- Results demonstrate encouraging pairwise interaction effects and target validation ongoing



Big Data

IDEAYA Integrates Proprietary, Partner and Public Synthetic Lethality Data Sets

Hundred of Millions of Synthetic Lethality Data Points being analyzed

Data sets are growing rapidly with SL data points anticipated to reach billions

IDEAYA Bioinformatics

Machine Learning / AI

Data integration and unsupervised machine learning

Iterative process with SL Biologists to develop most powerful algorithms for SL target & biomarker discovery

Determine SL pairs with the strongest signal to noise ratio

Enables SL Target and Biomarker Discovery and Prioritization

IDEAYA BIOSCIENCES

IDEAYA Pipeline Development to Drive Long-Term Growth

Establish IDEAYA as the industry leader in MTAP-deletion (~15% of solid tumors)

- IDE397 in Phase 1
- Advancing 2nd MTAP-SL program (target not disclosed), with potential to be combinable with IDE397

Advance SL pipeline, including new modalities targeting large solid tumor populations

- Pol Theta degrader with GSK
- Advance next generation of potential first-in-class SL programs guided by target biology

Grow potential First-in-Class SL / DDT pipeline, including beyond HRD population

- Werner Helicase with GSK (High-MSI biomarker)
- PARG, wholly-owned (novel HRD biomarker)
- High value targets from IDEAYA platform undergoing validation beyond HRD biomarker population

Synthetic Lethality: Emerging Area within Precision Medicine and GSK-IDEAYA Partnership

Benjamin Schwartz, Ph.D. – Vice President, Head of Oncology Synthetic Lethality Research Unit
GlaxoSmithKline

GSK Oncology R&D Strategy

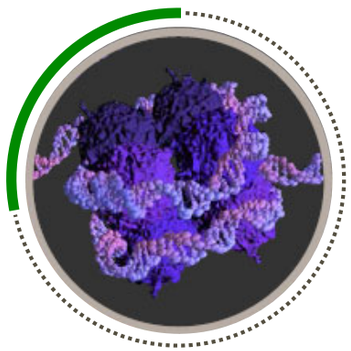
Aiming to maximize survival through transformational medicines and combinations

First-in-class medicines

Combination therapy

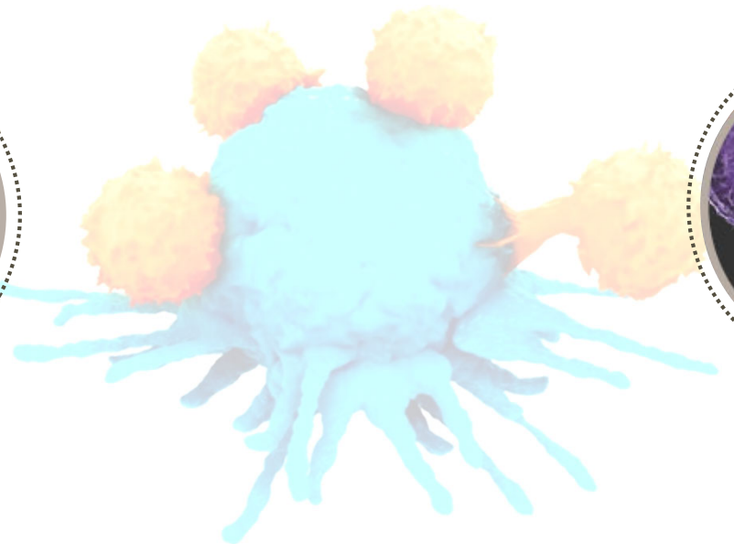
- Reprogram cancer cells
- Stimulate anti-tumor immunity
- Cells as medicines

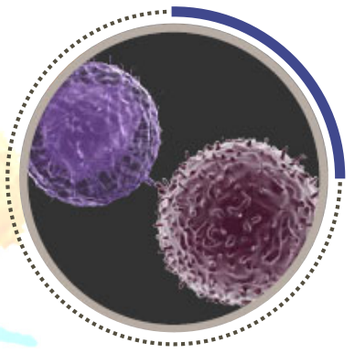
GSK Pipeline



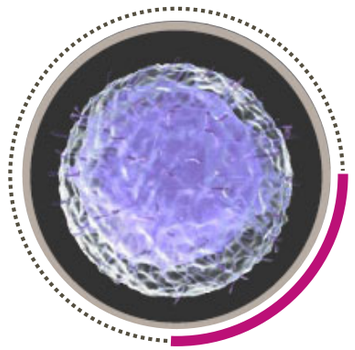
Cancer epigenetics

Synthetic lethality





Immuno-oncology



Oncology cell therapy

Oncology Synthetic Lethality

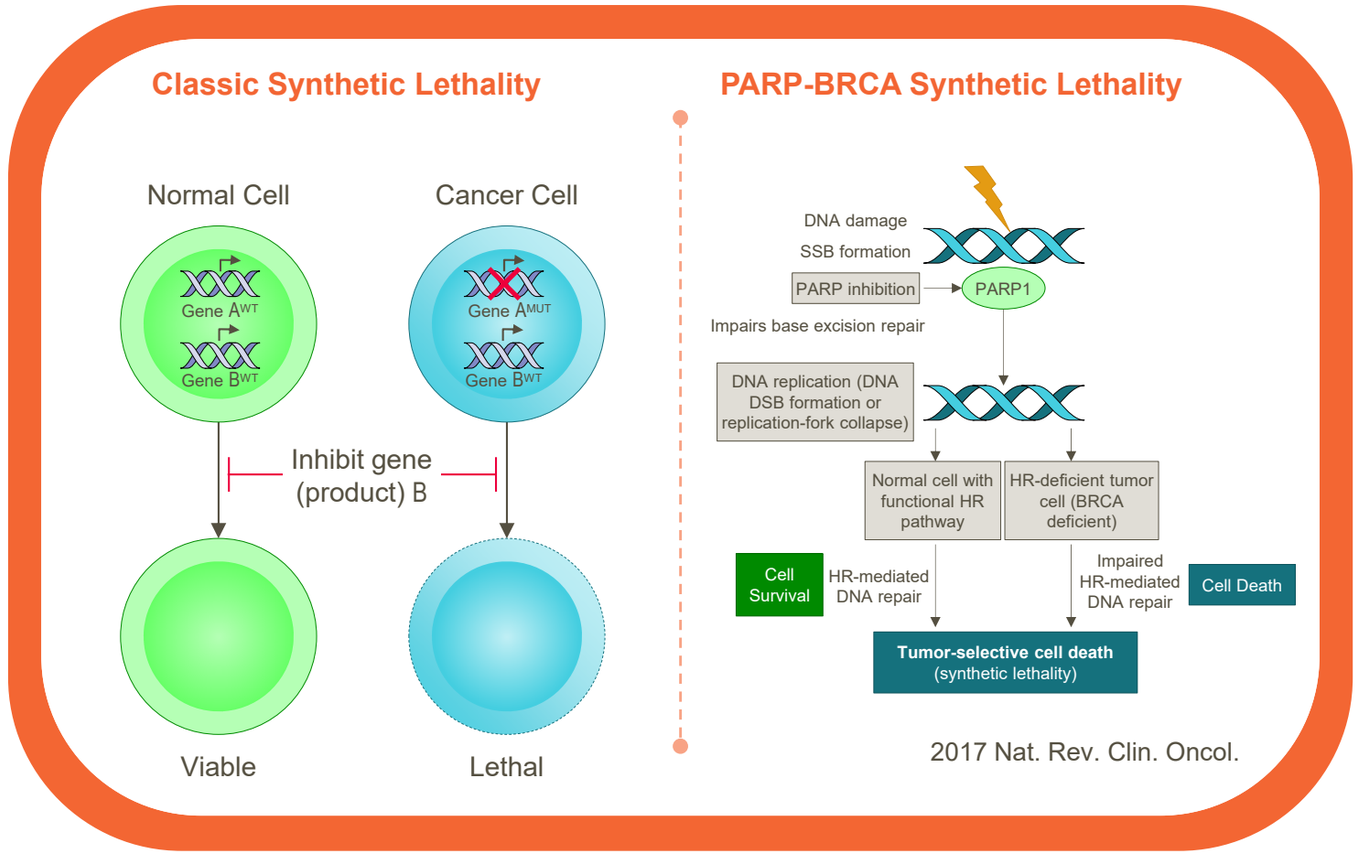
Discovery of novel oncology targets

What is synthetic lethality?

- The loss of gene A or gene B in isolation is tolerated but their combined loss is lethal
- Genes A and B may play functionally redundant roles in the cell as means of buffering

How does this apply to oncology?

- In cancer mutational loss of a tumor suppressor is difficult to target directly, but these cells may be susceptible to inhibition of more tractable targets due to their synthetic lethal relationship
- A clinically validated example is the use of PARP inhibitors for ovarian cancers with BRCA mutations (Olaparib, Rucaparib, Niraparib)

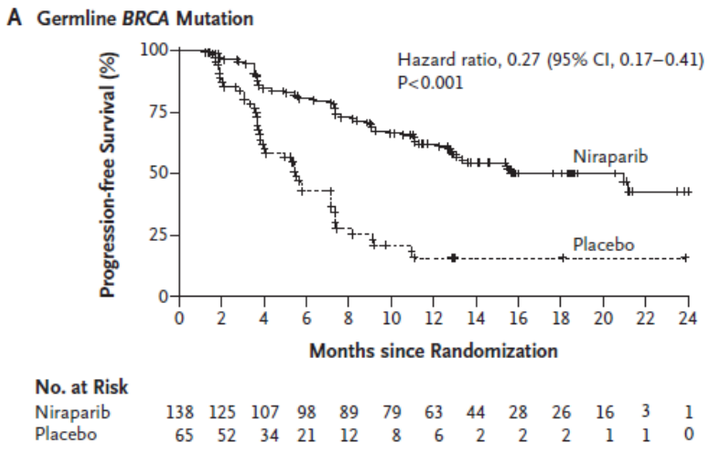


Oncology Synthetic Lethality

Why GSK & Other Companies are Investing Now

Clinical Validation (PARP Inhibitors)

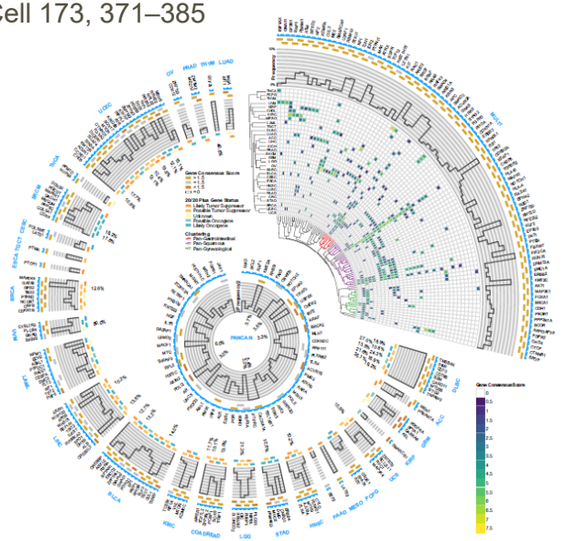
NOVA Clinical Trial



Profound clinical benefit from a genomics-driven approach to patient stratification & care

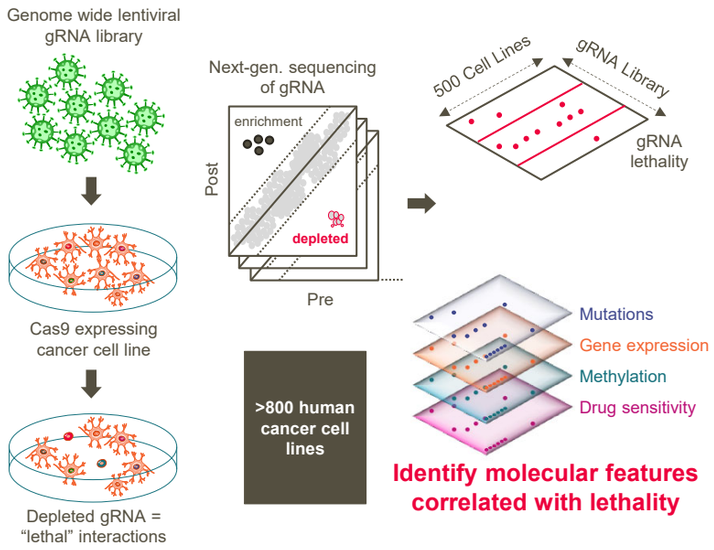
Maturation of Tumor Clinicogenomics

2018, Cell 173, 371–385



Molecular characterization of tens of thousands of cancer genomes across >30 tumor types are now available

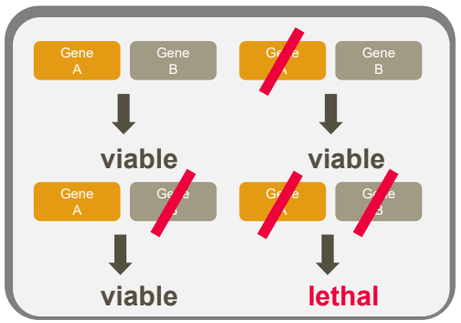
Genome Wide Cancer Lethality Screens



The dependencies of cancer genomes are only now being unlocked at scale by CRISPR functional genomic screens

GSK Synthetic Lethality Strategy is Guided by Two Areas of Focus

Utilizing internal & external resources to achieve our goals



Build Industry Leading Synthetic Lethality Portfolio

Expand Patient Population Benefitting from Zejula

Zejula® niraparib

External Opportunities

Internal RU Science

Functional Genomics

Business Development Landscape

Alignment with GSK Strategy

What we are Looking For

Program Criteria

- Single agent activity
- Clear response biomarker
- Transformative for patients
- Synergy with GSK clinical portfolio
- Low toxicity
- First/best in class

Who we are Looking For

Partner Criteria

- Asset focused
- Multiple programs for pipeline build
- Shared focus & values
- Strong leadership & experience

External Opportunities

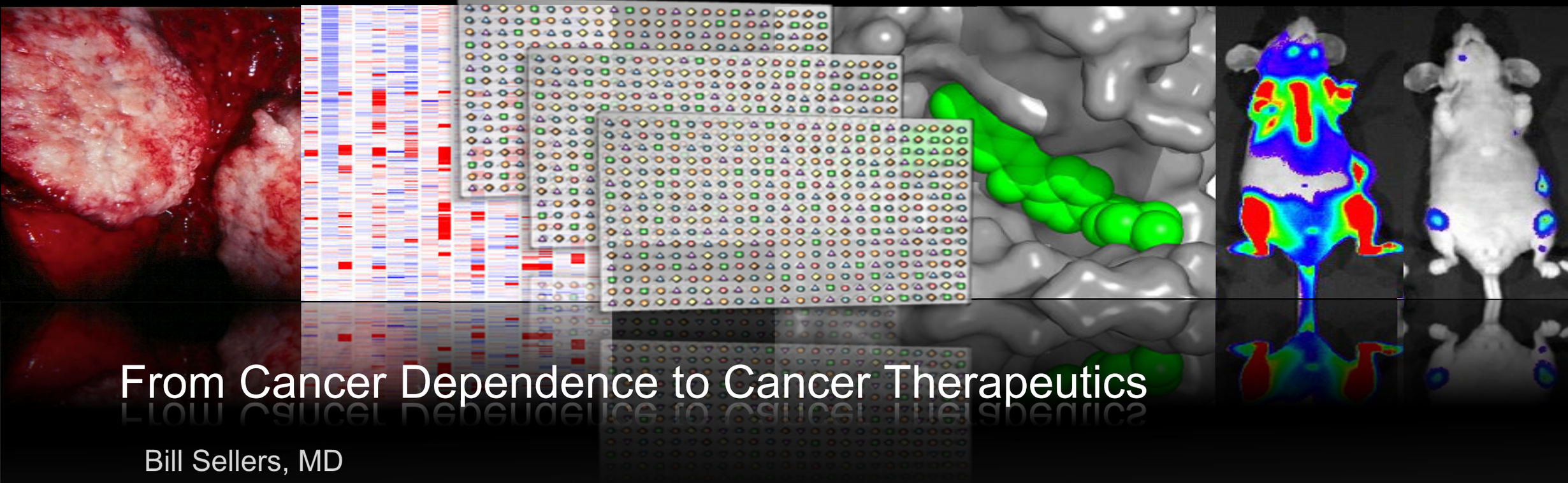
IDEAYA BIOSCIENCES

- Close collaboration on all assets
- Integrated discovery teams for WRN & POLQ
- Synergy seeking with GSK targeted and IO clinical assets

IDE397: Targeting MAT2A in MTAP-Deleted Tumors

MAT2A Biology

William Sellers, M.D. – Core Institute Member and Director of the Cancer Program
Broad Institute of MIT and Harvard



From Cancer Dependence to Cancer Therapeutics

Bill Sellers, MD
Core Institute Member, Cancer Program Director
Broad Institute
Professor of Medicine
Dana-Farber Cancer Institute
Harvard Medical School

BROAD INSTITUTE

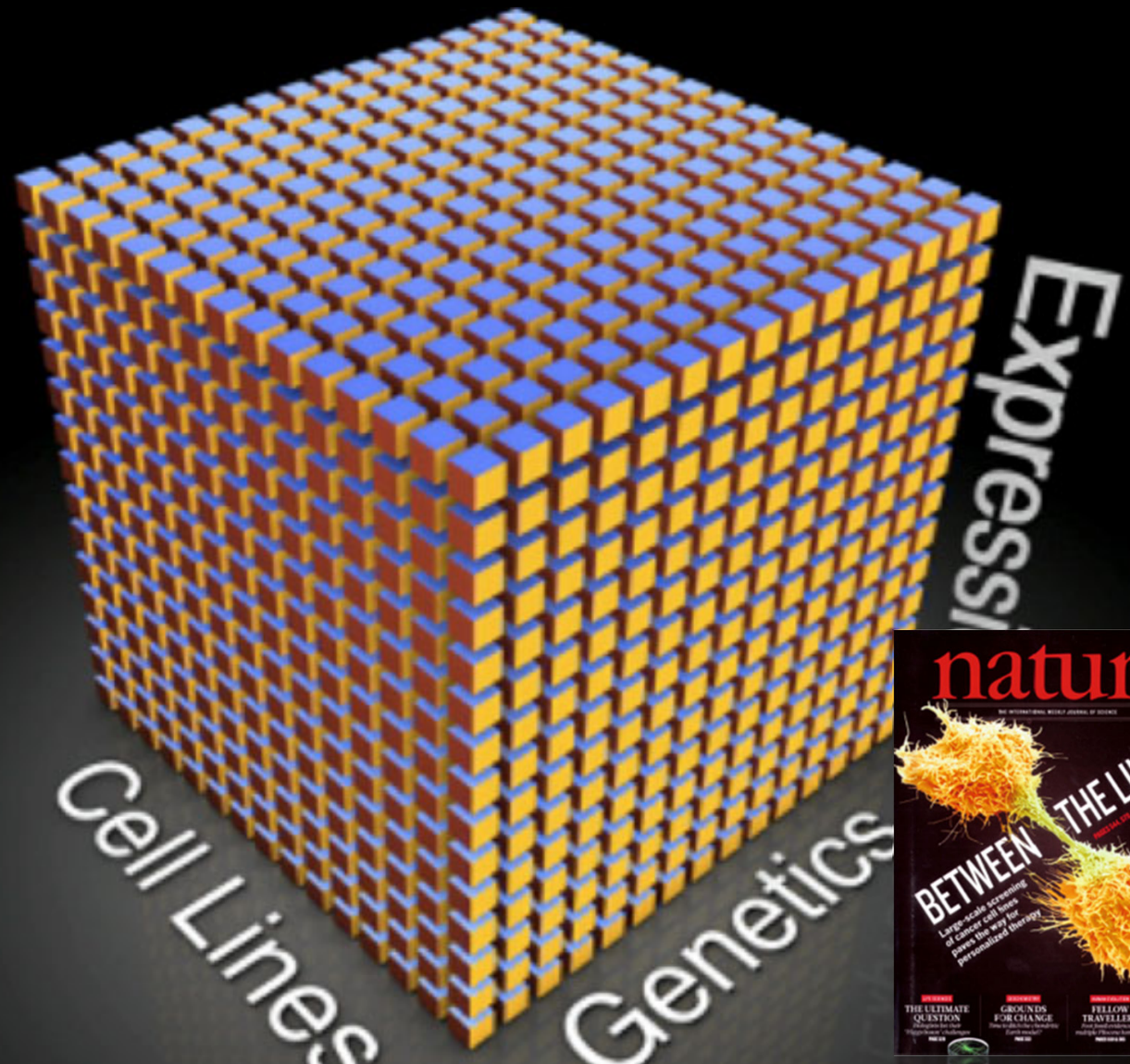
The Cell Line Encyclopedia

Our Questions:

What genes/proteins are required for maintenance of the cancer phenotype?

What is the contextual basis for such dependencies?

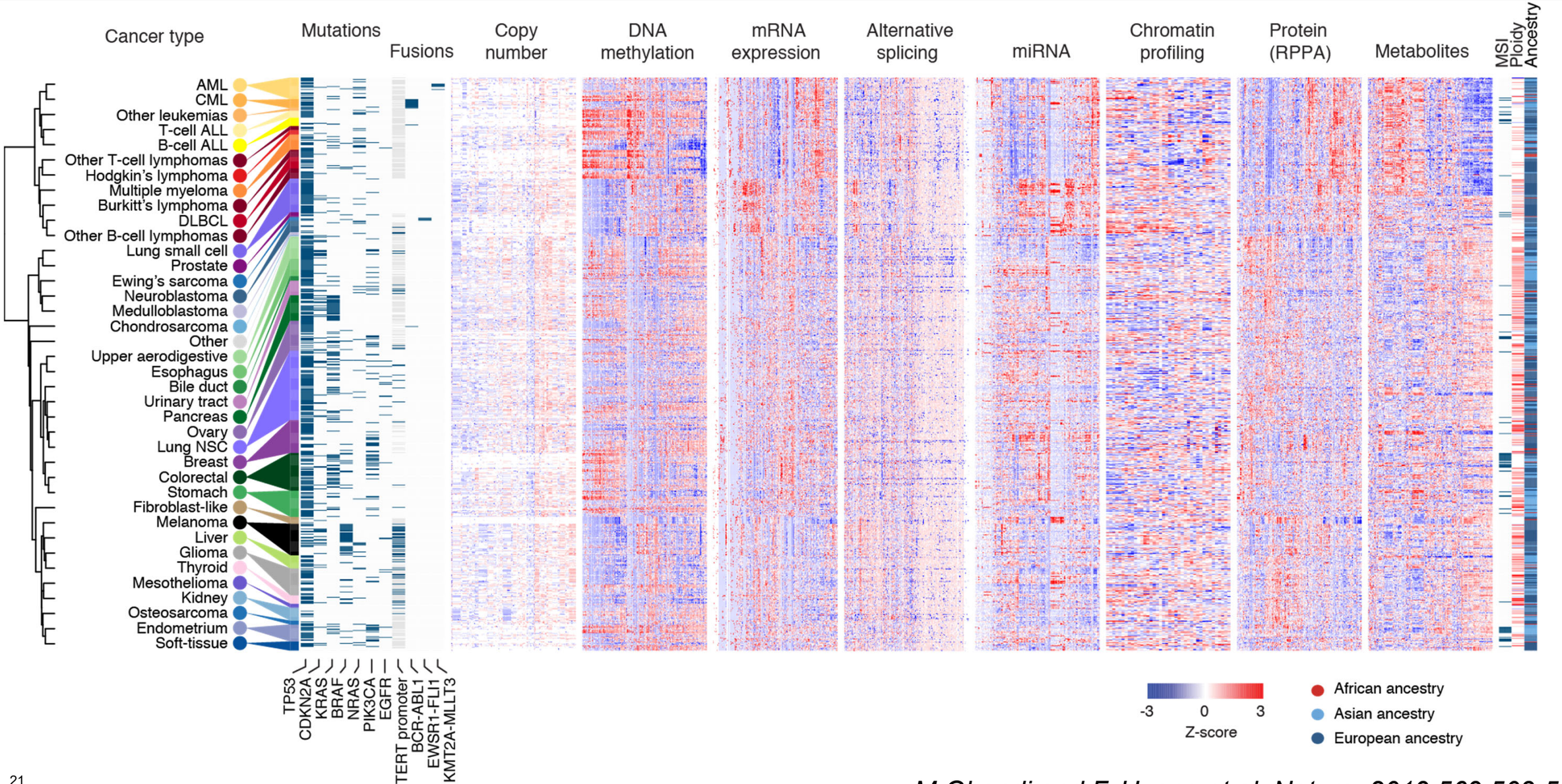
How do we drug such dependencies?



Broad-Novartis Collaboration

Barretina, Caponigro et al. 2012 Nature

Phase II: Advancing the molecular annotations of the CCLE



M Ghandi and F. Huang et al. Nature. 2019;569:503-508

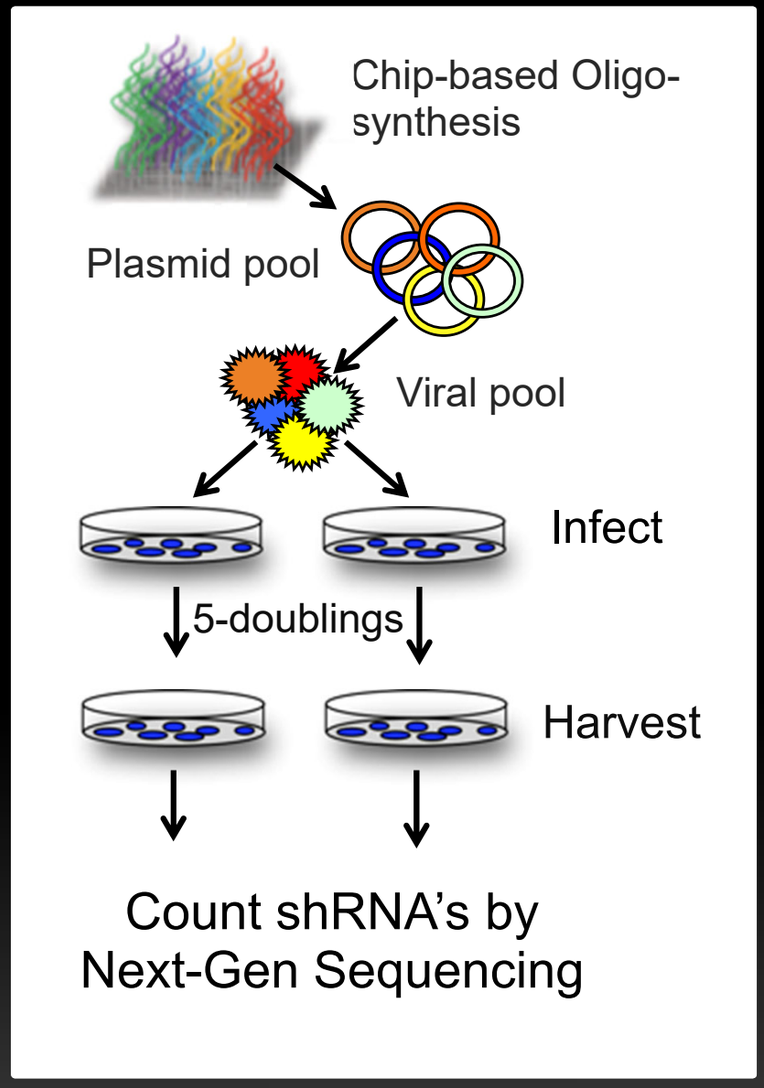
DRIVE: Deep RNAi Interrogation of Viability Effects

What genes/proteins are required for maintenance of the cancer phenotype?

What is the contextual basis for such dependencies?

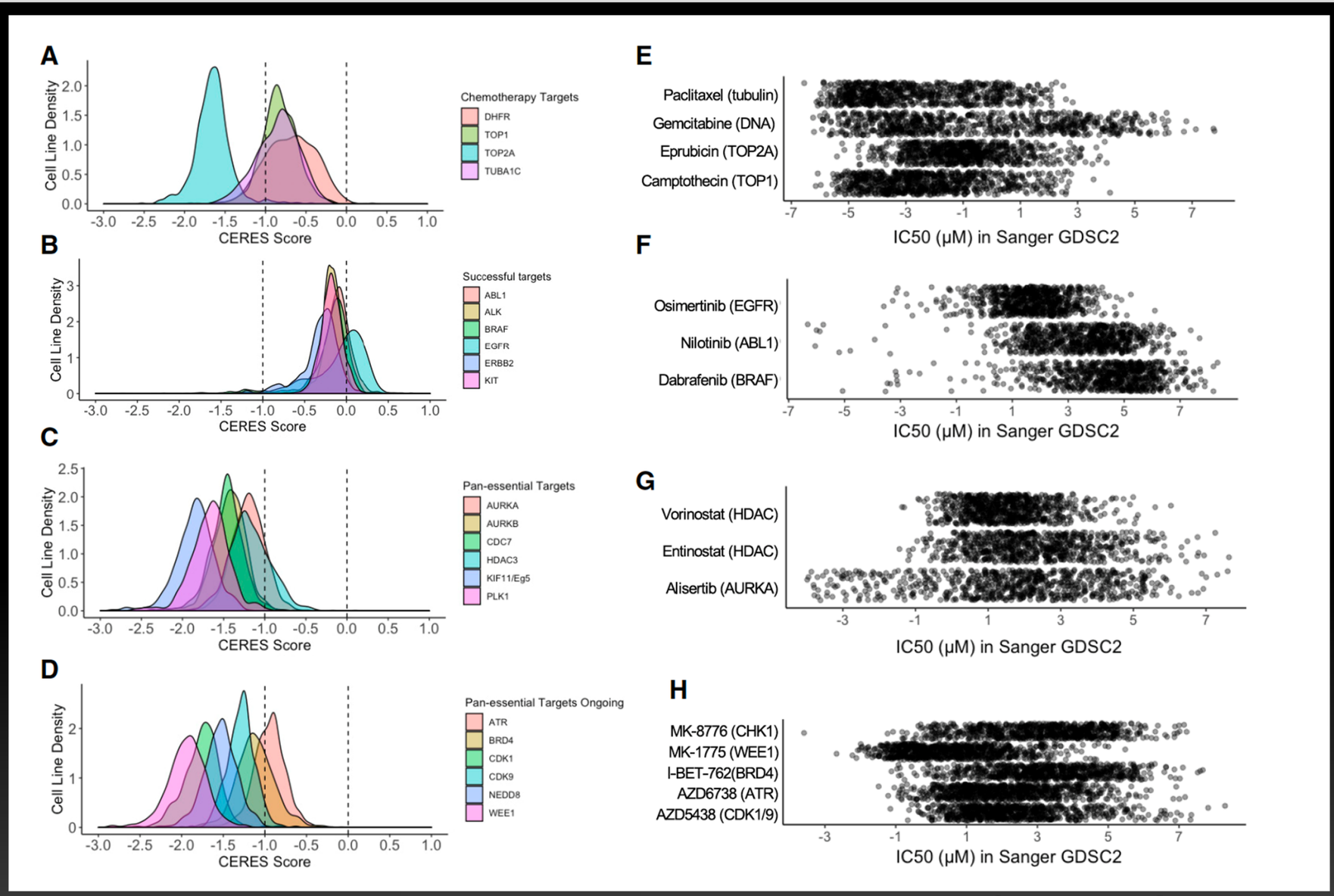
Functional Genomic Approaches:
Project DRIVE: 7,800 genes, 20 shRNAs per gene

DepMap: Whole Genome, 4 sgRNAs per gene

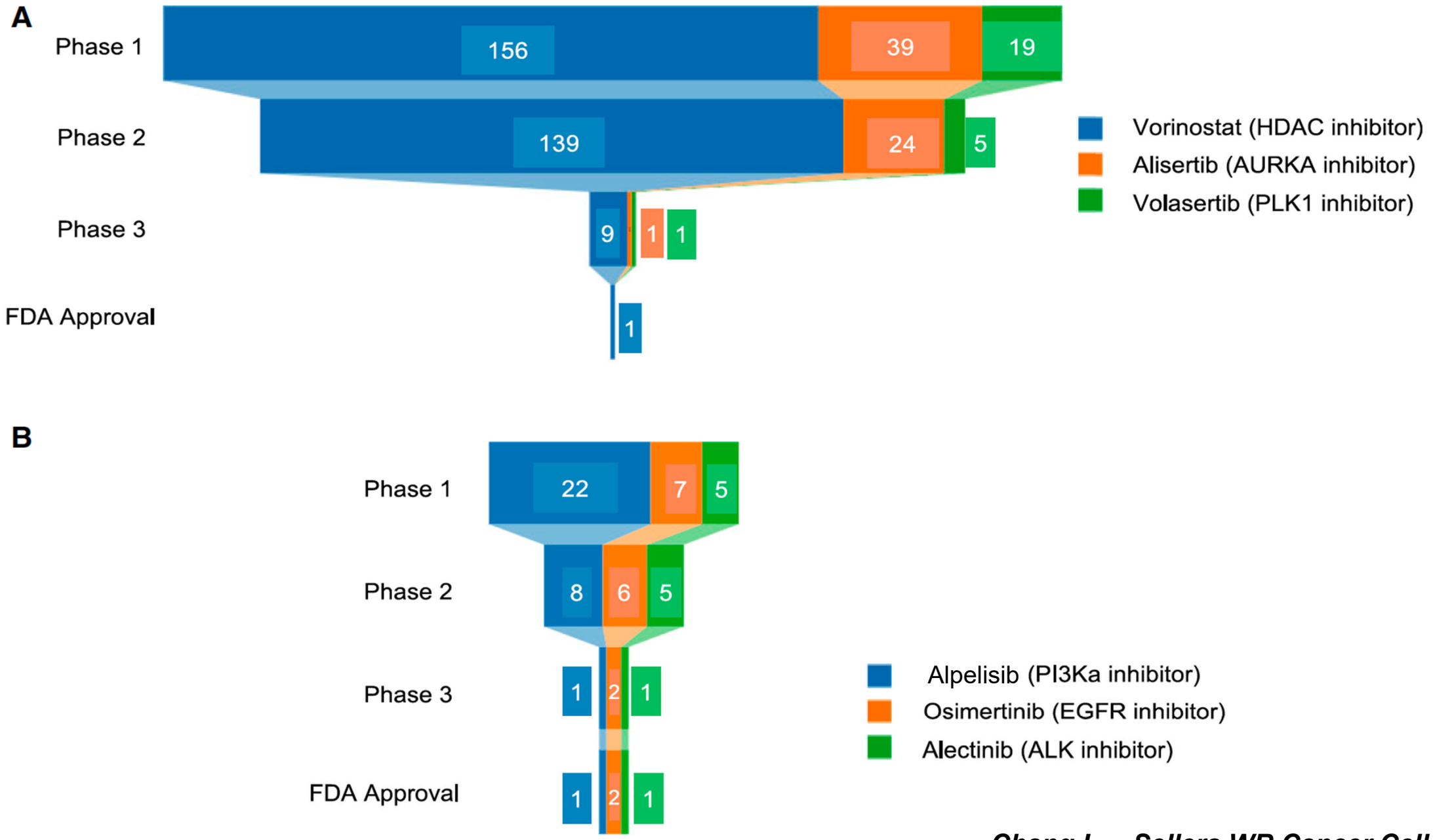


McDonald et al. Cell. 2017 170:577-592

Two general classes of targets – pan-essentials and selective essentials

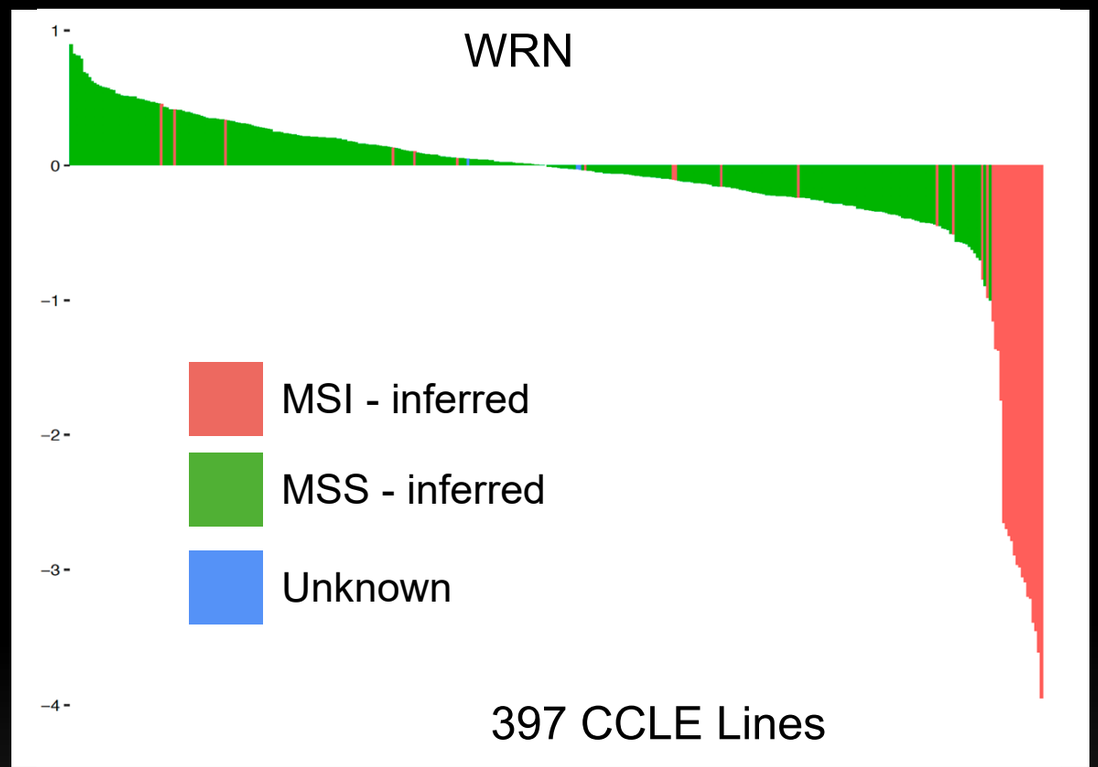


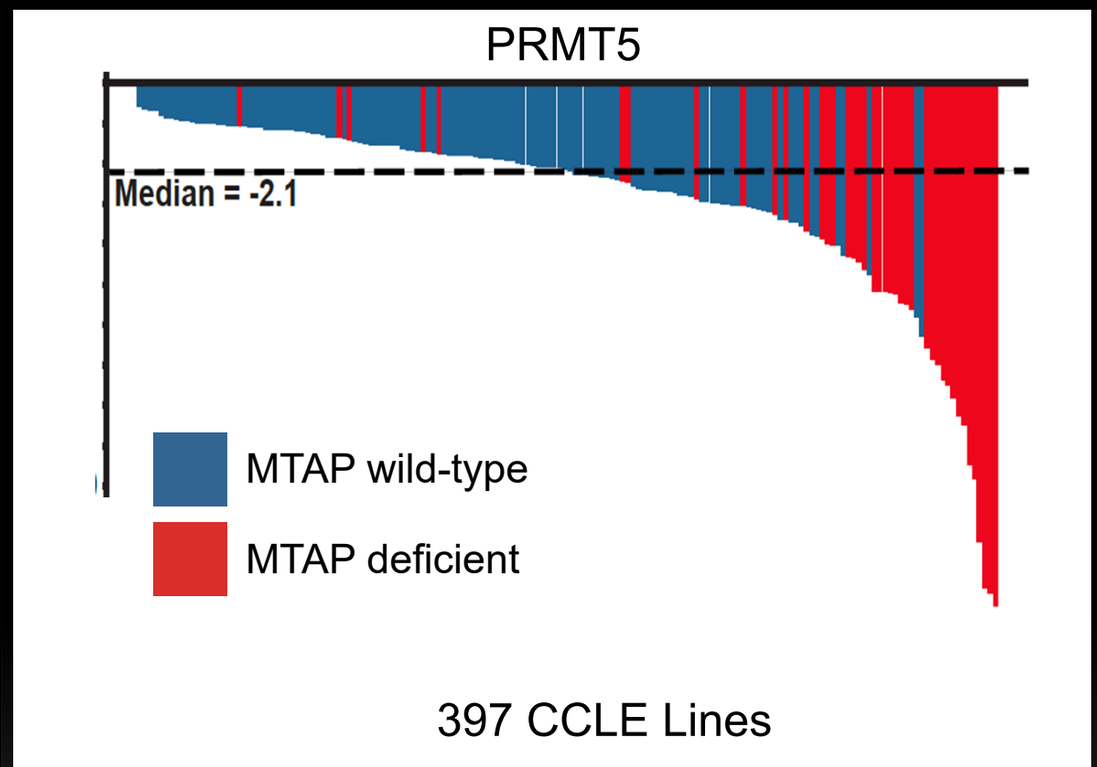
Chang L….Sellers WR *Cancer Cell 2021*



Chang L….Sellers WR Cancer Cell 2021

New cancer dependencies from single-gene perturbations

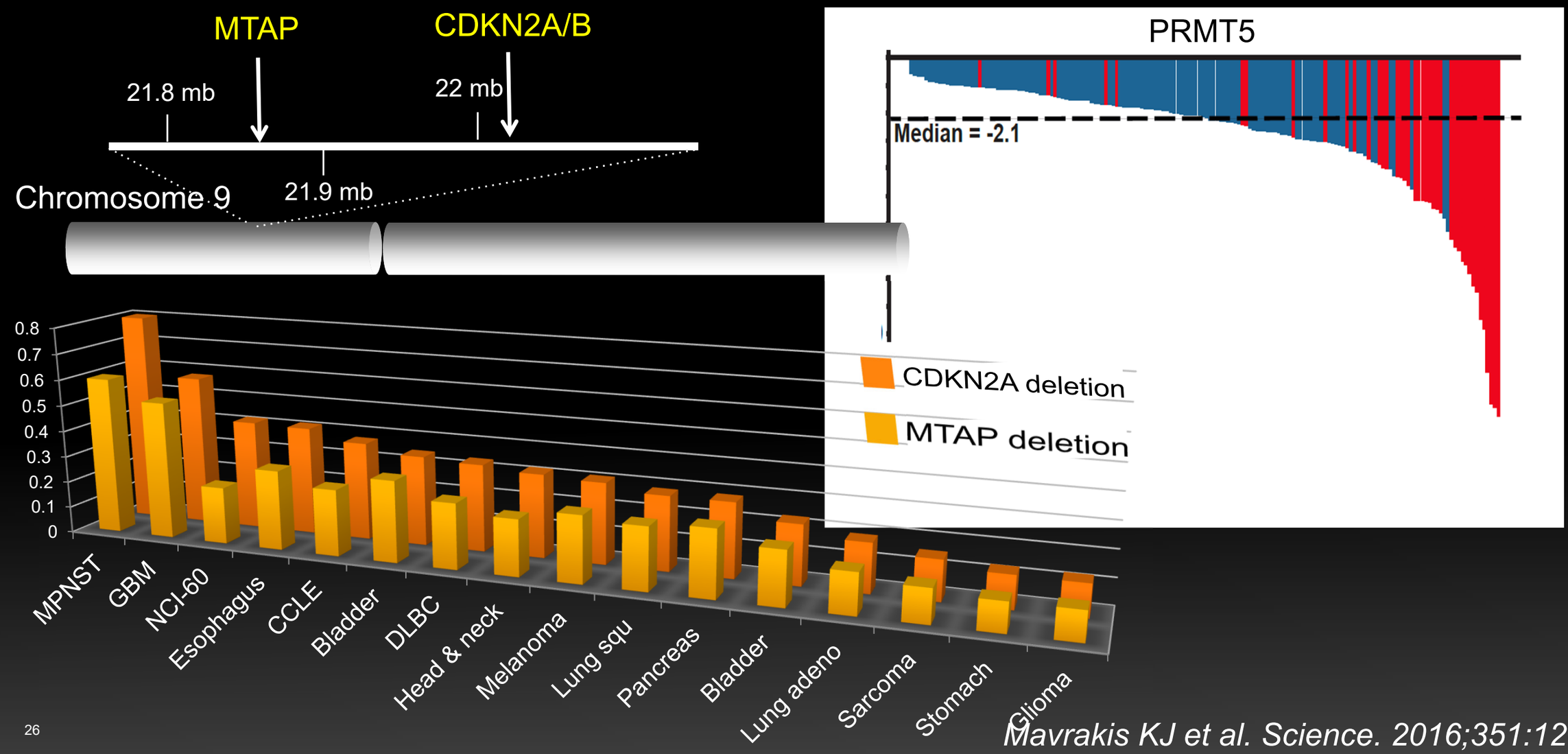




Chan EM, et al. Nature. 2019;568:551-6

Mavrakis KJ et al. Science. 2016;351:1208-13

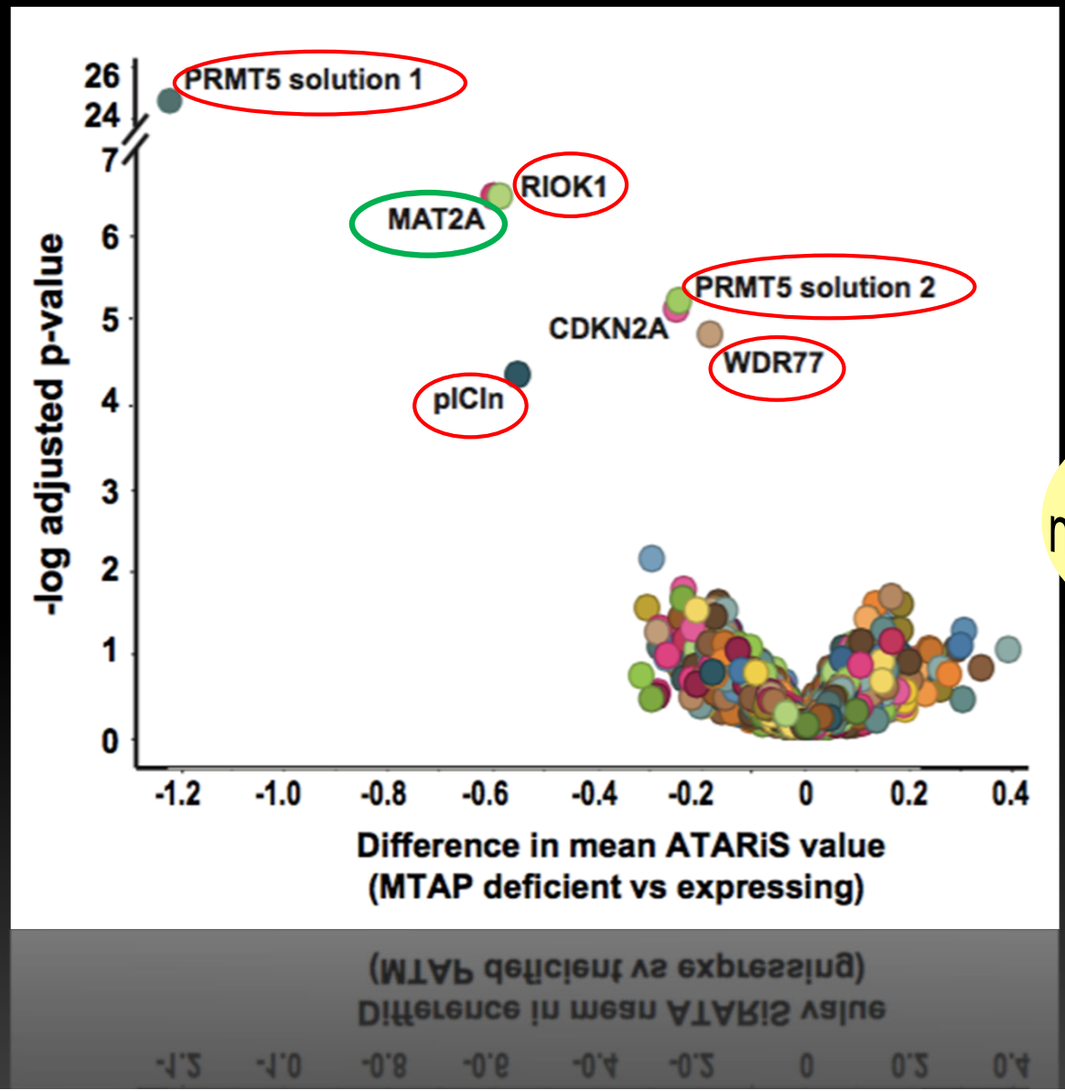
MTAP and CDKN2A are frequently co-deleted

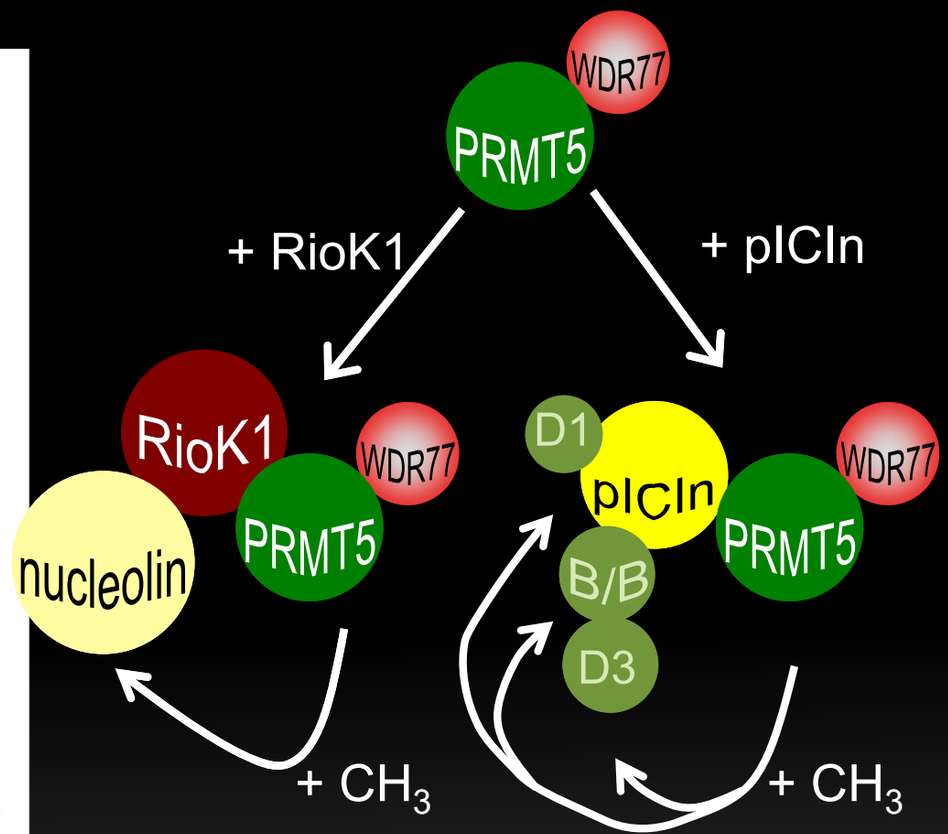


Mavrakis KJ et al. Science. 2016;351:1208-13

MAT2A and PRMT5 methylosome are synthetic lethal with MTAP deletion

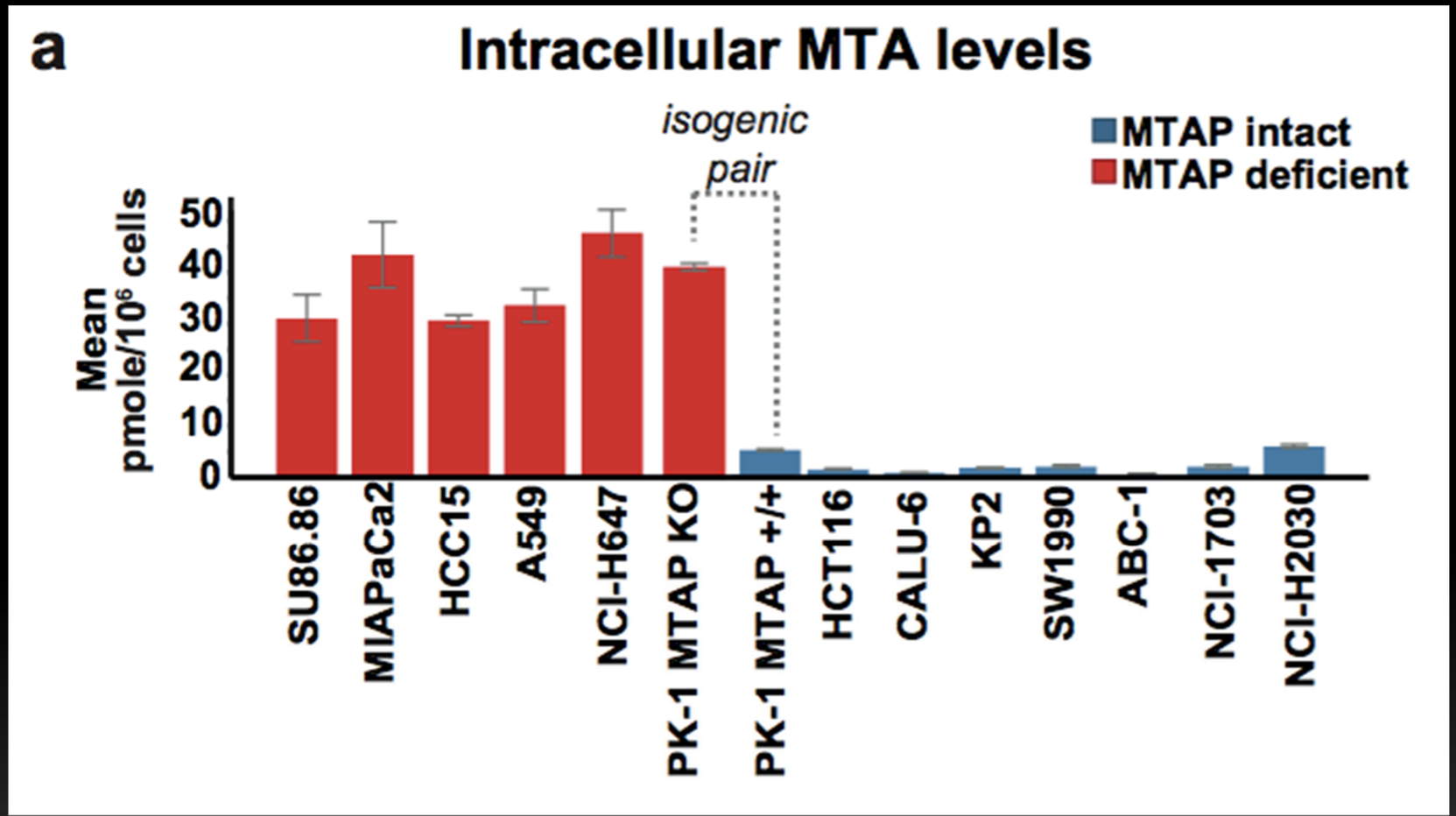
Directly compare MTAP^{del} vs MTAP^{wt} cells for shRNA sensitivity





Mavrakis KJ et al. Science. 2016;351:1208-13

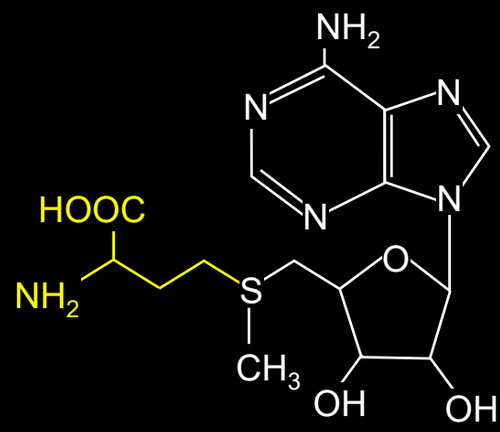
MTAP loss leads to substantial increases in MTA



Mavrakis KJ et al. Science. 2016;351:1208-13

Is MTA a competitive inhibitor of HMTs?

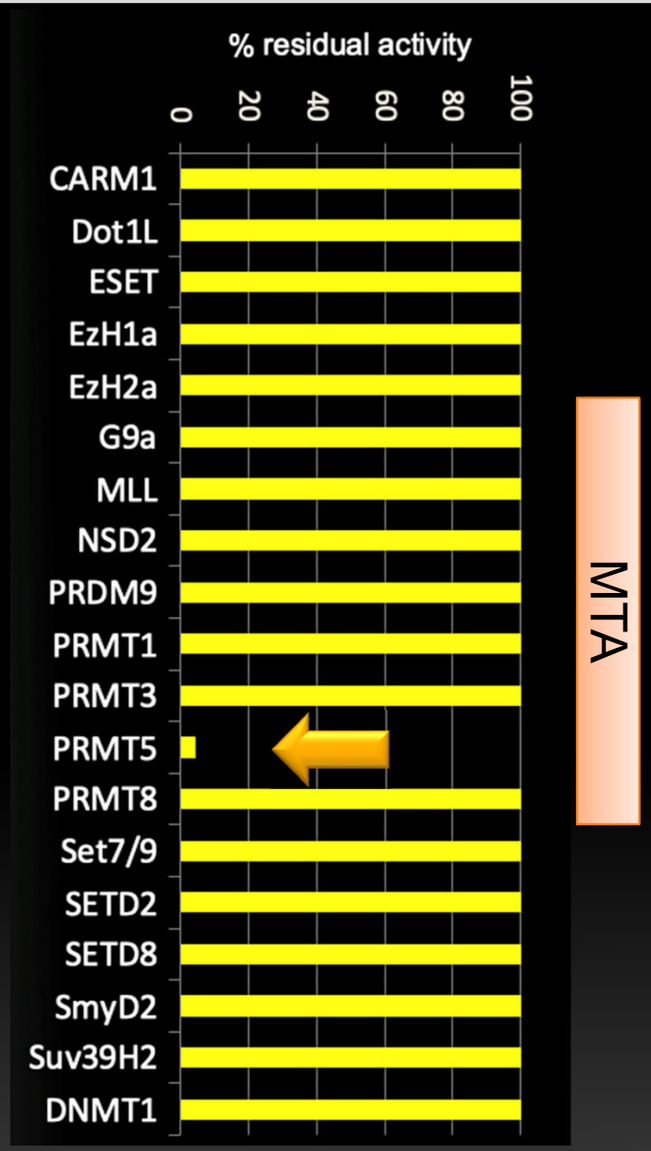
Methylthioadenosine
(MTA)

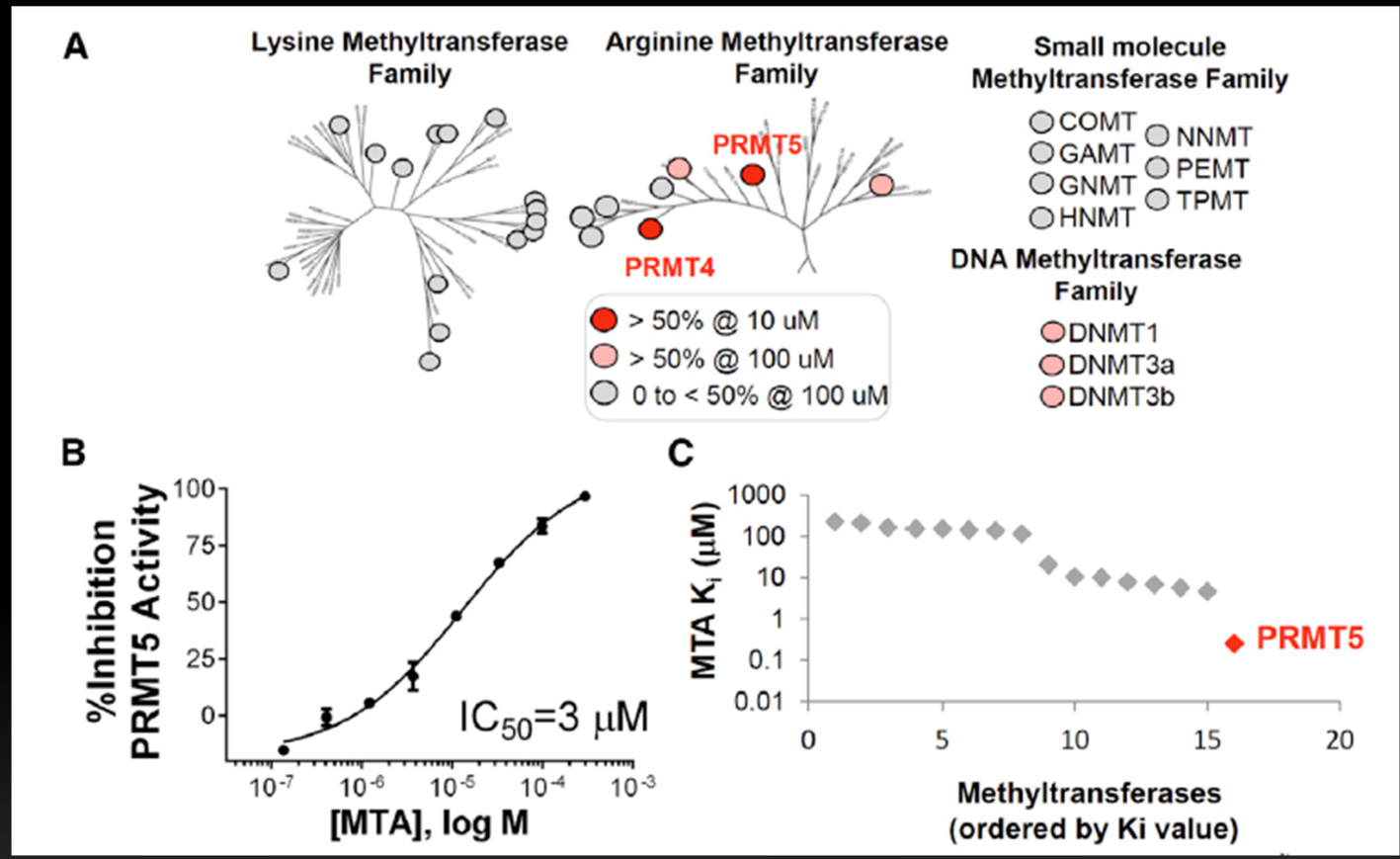


S-adenosylmethionine
(SAM)

Loss of MTAP results in accumulation of MTA that decreases symmetric and asymmetric protein methylation by inhibition of PRMT family. (*Williams-Ashman HG*, *Biochem Pharmacol 31:277–288. 1982*; *Limm K. et al., Eur J Cancer 49 2013)*

MTA is a selective inhibitor of PRMT5

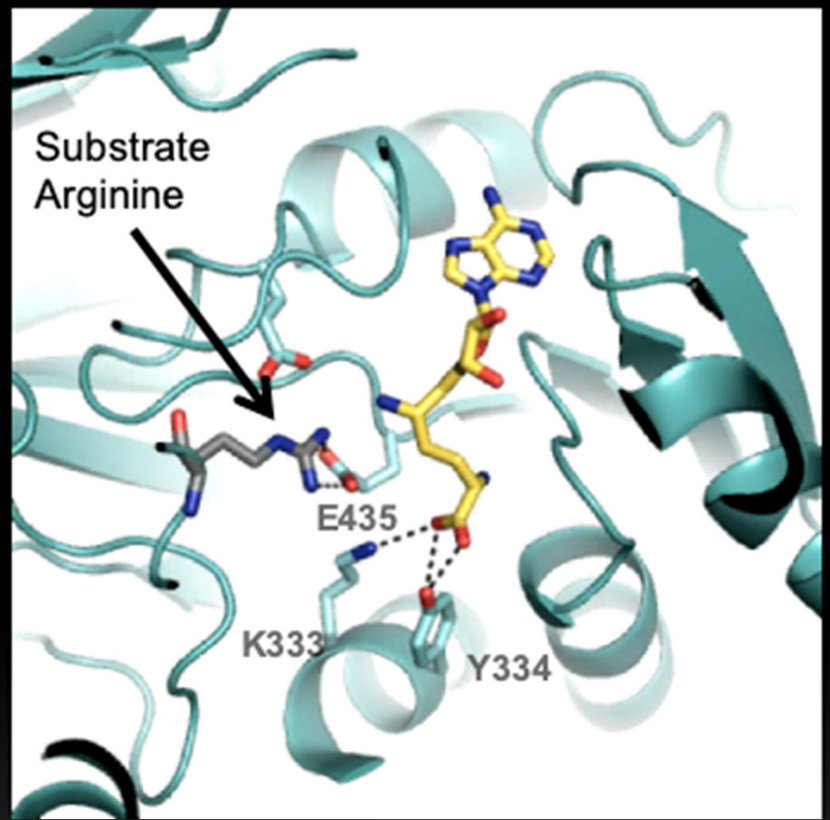




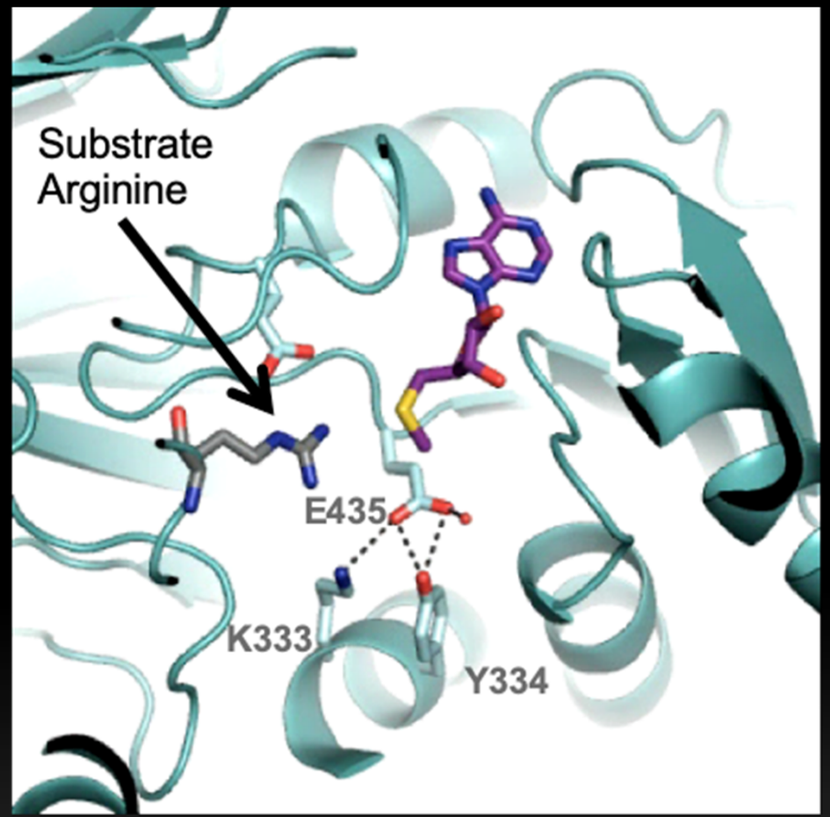
Mavrakis KJ et al. Science. 2016;351:1208-13

Marjon et al Cancer Cell 2016

The Structural basis for MTA inhibition of PRMT5



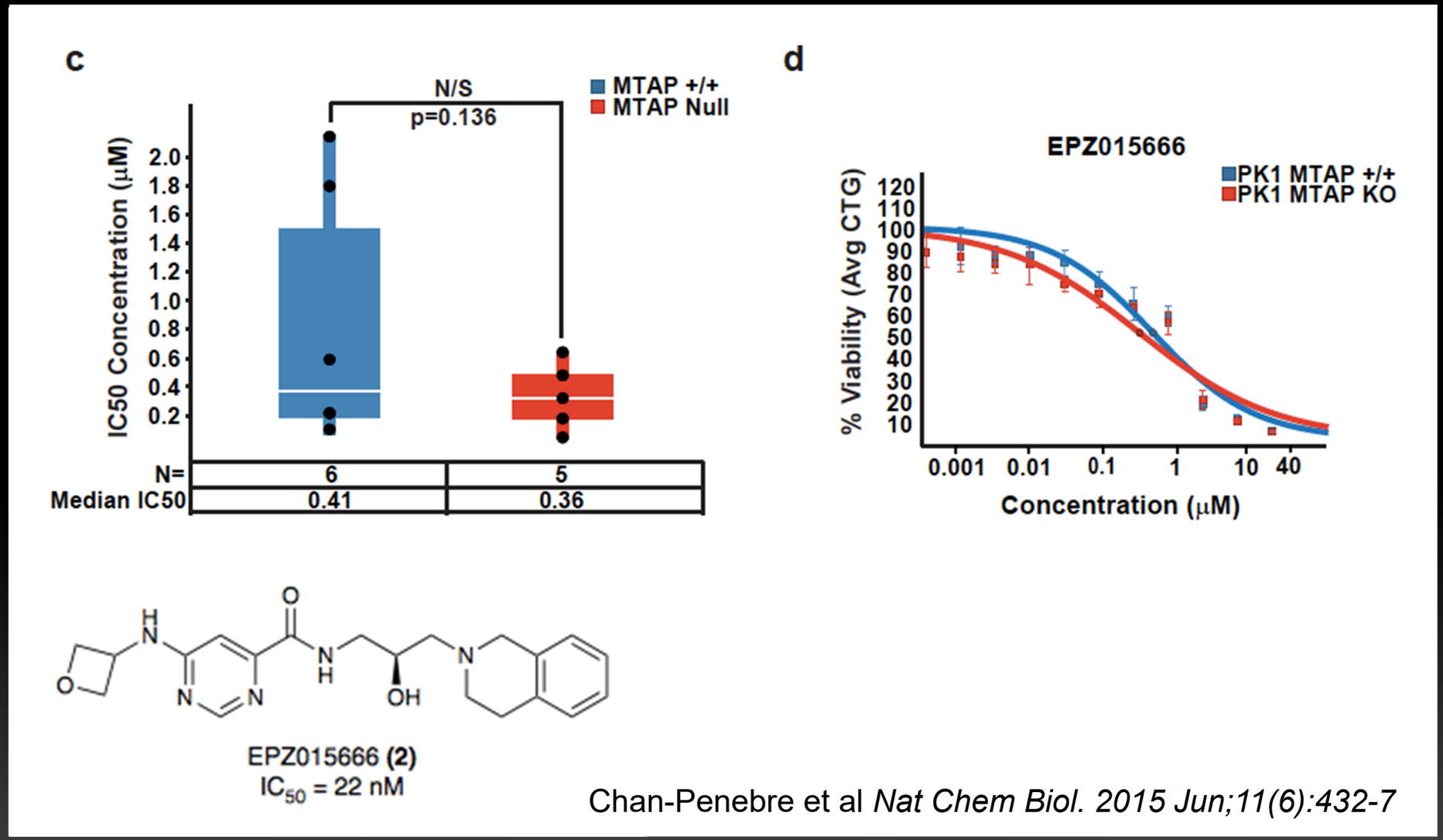
Sinefungin (SAM analogue)



Methylthioadenosine (MTA)

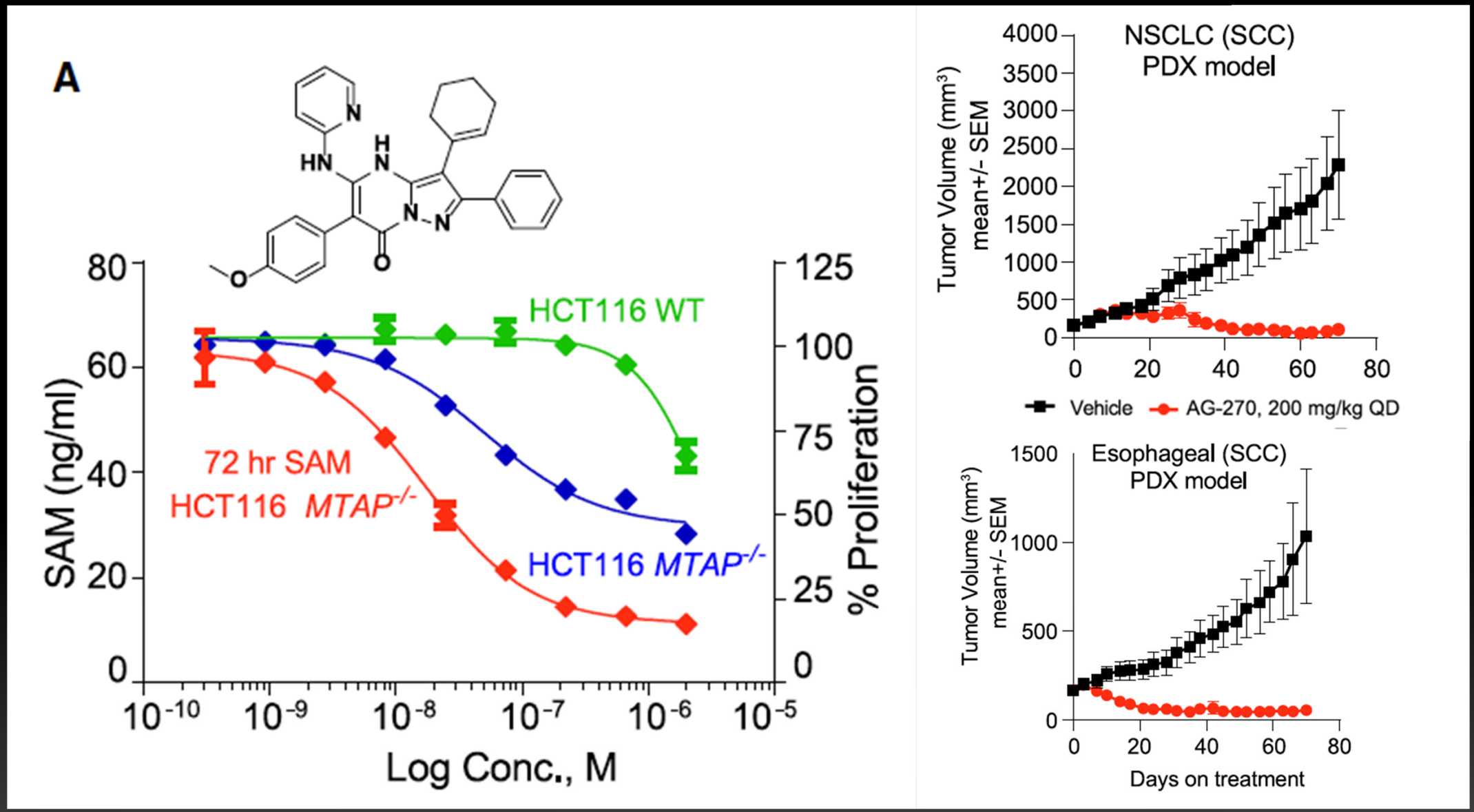
Mavrakis KJ et al. Science. 2016;351:1208-13

SAM cooperative PRMT5 inhibitors do not exploit the MTA:SAM differences



Chan-Penebre et al *Nat Chem Biol. 2015 Jun;11(6):432-7*

MAT2A inhibitors impair the viability of MTAP null cancers



Kalev et al Cancer Cell 39, 209–224,

Summary

- MAT2A and PRMT5 are synthetic lethal in the context of MTAP deficient tumors
- MTAP is frequently co-deleted with CDKN2A (P16) the most commonly deleted tumor suppressor gene
- MAT2A inhibitors have demonstrated in vivo activity in preclinical models.

IDE397: Targeting MAT2A in MTAP-Deleted Tumors

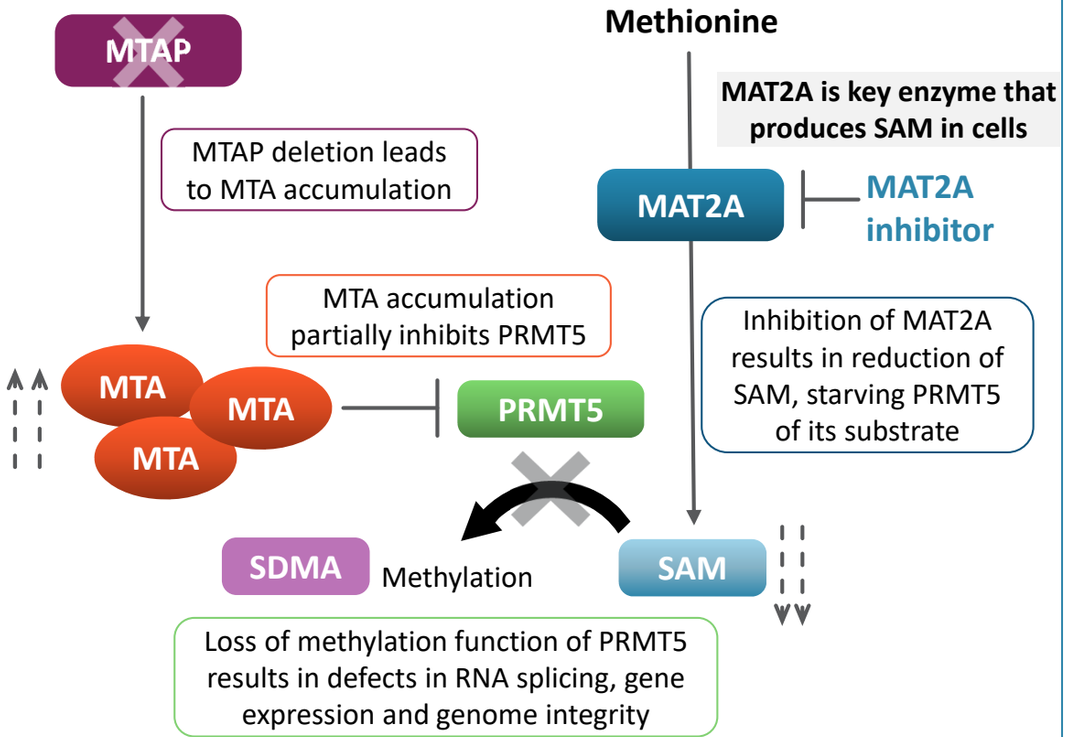
IDE397 Clinical Candidate

Mark Lackner, Ph.D. – Senior Vice President, Head of Biology and Translational Sciences
IDEAYA Biosciences

MAT2A Inhibition is Synthetic Lethal with MTAP Deletion

MTAP Deletion Prevalence ~15% of all Solid Tumors

MTAP-MAT2A Synthetic Lethality Biology



MTAP Deletion Prevalence

Cancer Type	N	MTAP Deletions (%)
Glioblastoma	592	41
Mesothelioma	87	32
Esophageal	95	28
Bladder	411	26
Pancreatic	184	22
Melanoma	448	16
Lung Cancer (NSCLC)	1053	15
Head and Neck	523	14
Sarcoma	255	10
Esophagogastric	514	10
Diffuse Glioma	513	9
Breast	1084	3
Ovarian	585	3
Adrenocortical	92	3
Thymic	123	3
Hepatocellular	369	3
Renal non-clear cell	348	2

Data from The Cancer Genome Atlas in cBioPortal

Clear predictive and pharmacodynamic biomarkers provide roadmap for clinical patient selection and translational studies

IDEAYA BIOSCIENCES

IDE397: MAT2A Inhibitor

Preclinical Evaluation of IDE397 – Differentiated Profile and Selective for MTAP-/- Cell Lines

IDE397 Target Product Profile

IDE397 demonstrates superior cellular potency and selectivity compared to AG-270

IDE397 has not caused preclinical liver injury or increased bilirubin

- Not an inhibitor of UGT1A1 (AG270 noted to inhibit UGT1A1) [1] or BSEP transporters at relevant concentrations
- Liver injury not observed in tox studies

IDE397 has favorable physical properties, including solubility

- AG-270 observed non-linear exposure >200mg QD (GI absorption)

IDE397 demonstrates *in vivo* efficacy and PD modulation at 5 to 30mg/kg

- AG270 published preclinical dose typically 200mg/kg [1]

Biochemical and *in vitro* Potency

	IDE397	AG270
MAT2A biochemical IC_{50} (nM)	7	14
KP4 EC_{50} cellular (nM) MAT2A dependent	14	731
BXPC3 cellular EC_{50} (nM) MAT2A independent	13200	1630
HuCCT1 cellular EC_{50} (nM) MAT2A independent	>20000	**1400**

Differentiating ADME/Physicochemical Properties

	IDE397	AG270
BSEP inhibition @10μM (%)	1	**25.2**
UGT1A1 inhibition (%)	34	83
PXR Emax @30 μM (%)	9	**35**
Solubility @pH 7.4 (μM)	>100μM	**BLOQ***

IDEAYA Data

*BLOQ = below limit of quantitation

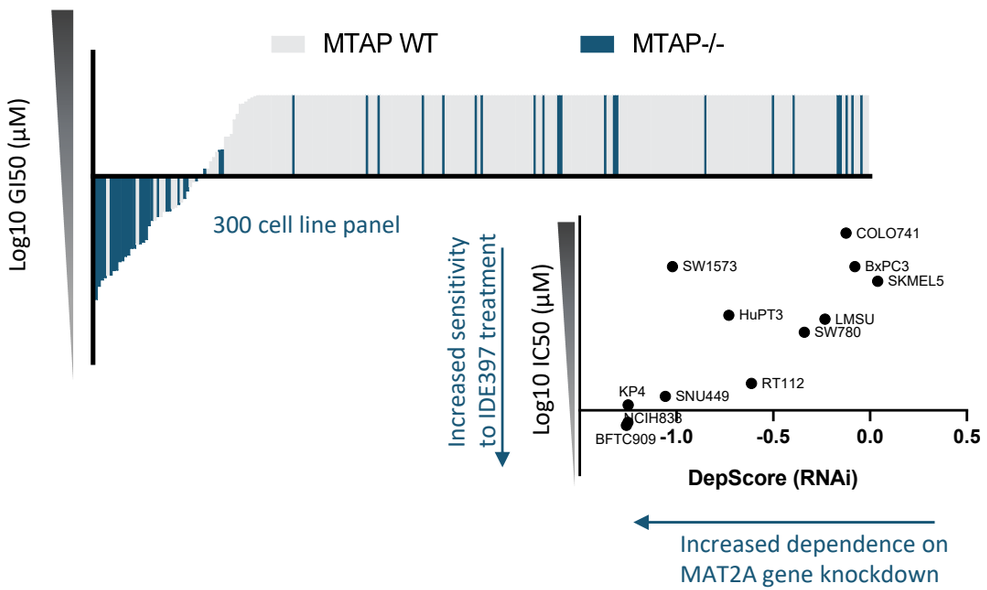
(1) Agios, AACR 2019, Keystone 2019, Triple Meeting 2019 (Webcast Call Q&A), J Med Chem 2021

IDEAYA BIOSCIENCES

IDE397: MAT2A Development Candidate *in vitro* Profile

IDE397 is selective for MTAP-/- Cell Lines

IDE397 is Selective for MTAP-/- Cell Lines

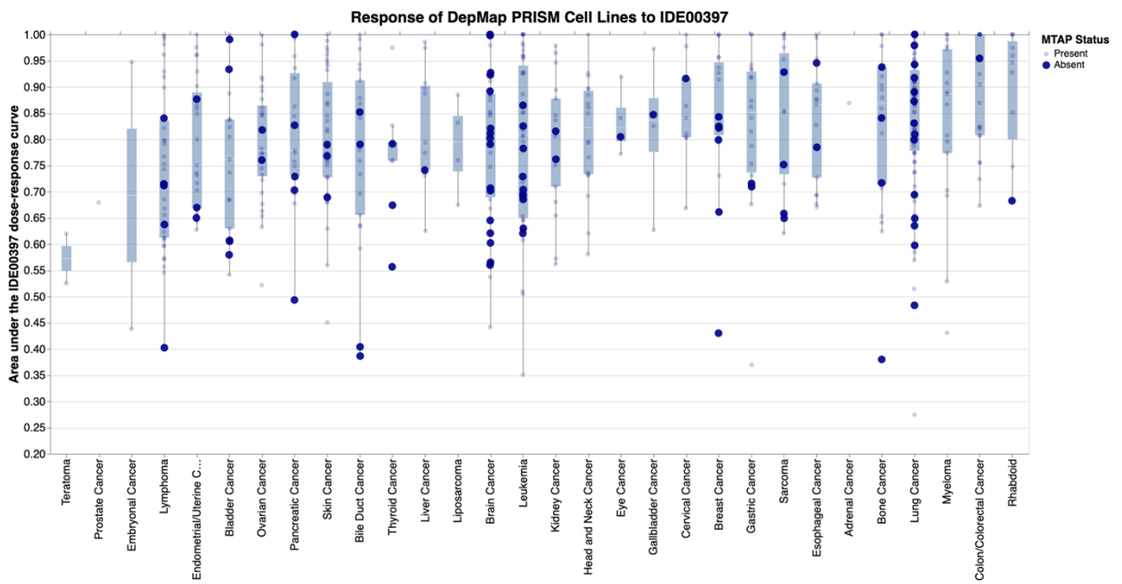


MTAP-/- cell lines are sensitive to IDE397

MTAP WT cell lines are generally insensitive

Pharmacological inhibition correlates with MAT2A genetic knockdown

IDE397 has Broad Activity across Tumor Types



~800 cell line panel

Differential sensitivity across tumor types; potential for discovery of additional predictive biomarkers

MTAP gene expression and copy number loss emerge as top predictors of sensitivity across cell lines

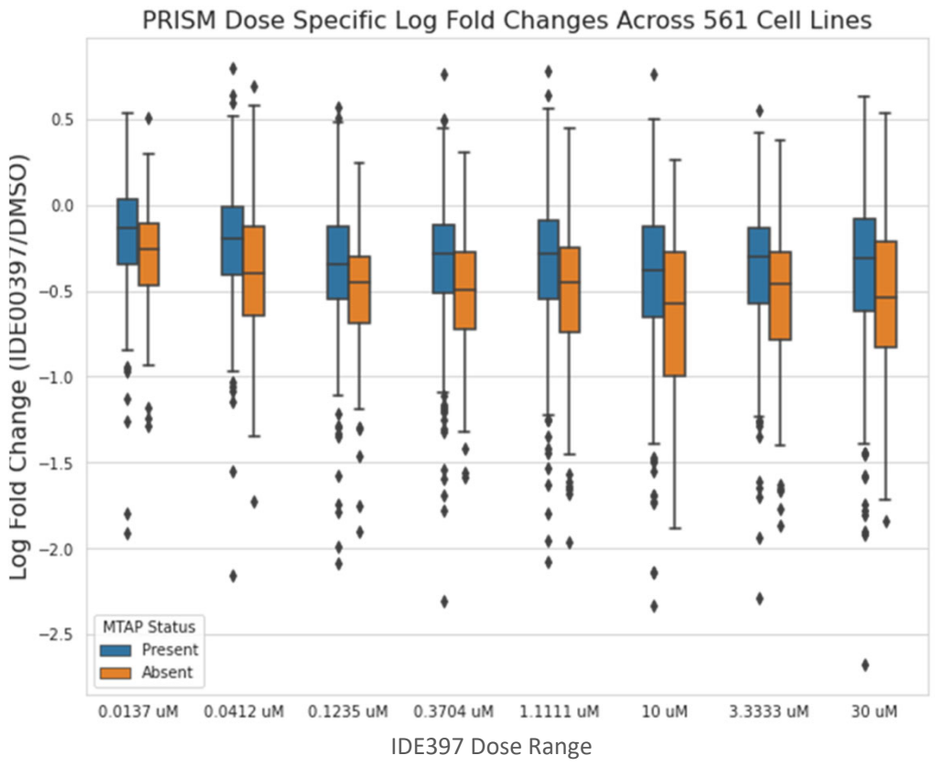
IDEAYA Data

IDEAYA Analysis / PRISM Screen - Broad DepMAP Consortium

Response to IDE397 stratified by MTAP Status in Broad PRISM Panel

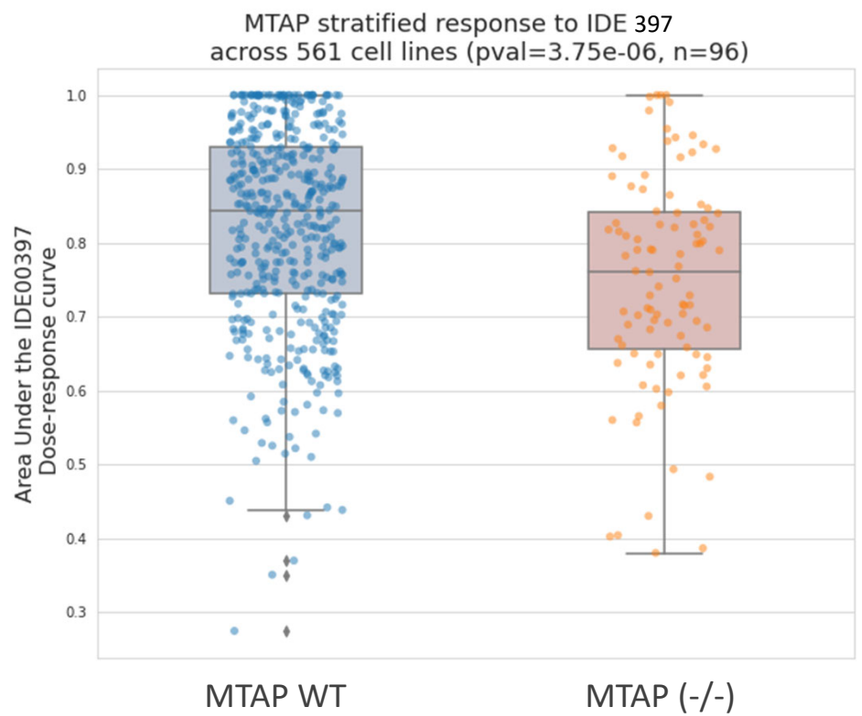
IDE397 has broad activity across tumor types with clear MTAP dependence

IDE397 sensitivity shows a clear dependence on MTAP status



IDEAYA Analysis / PRISM Screen - Broad DepMAP Consortium

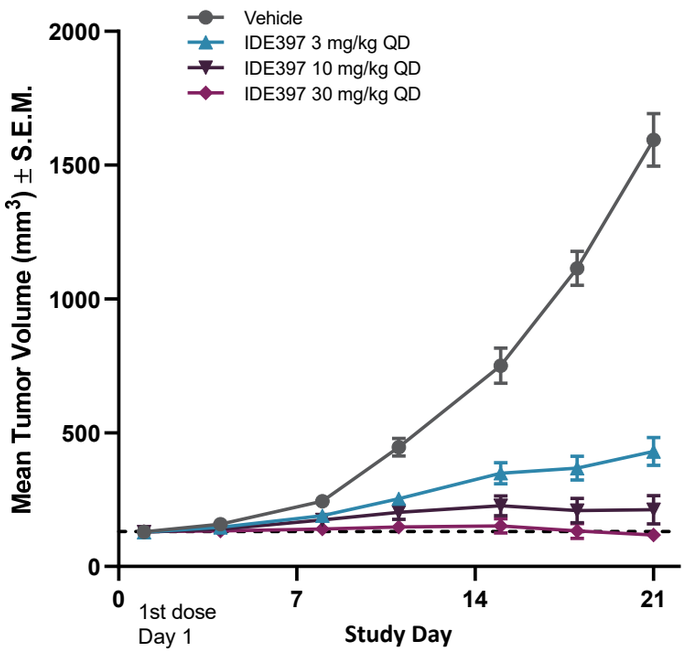
MTAP status significantly correlated with sensitivity



IDEAYA Analysis / PRISM Screen - Broad DepMAP Consortium

IDE397 Monotherapy Demonstrates Tumor Regressions and Robust PD Modulation in CDX Xenograft models

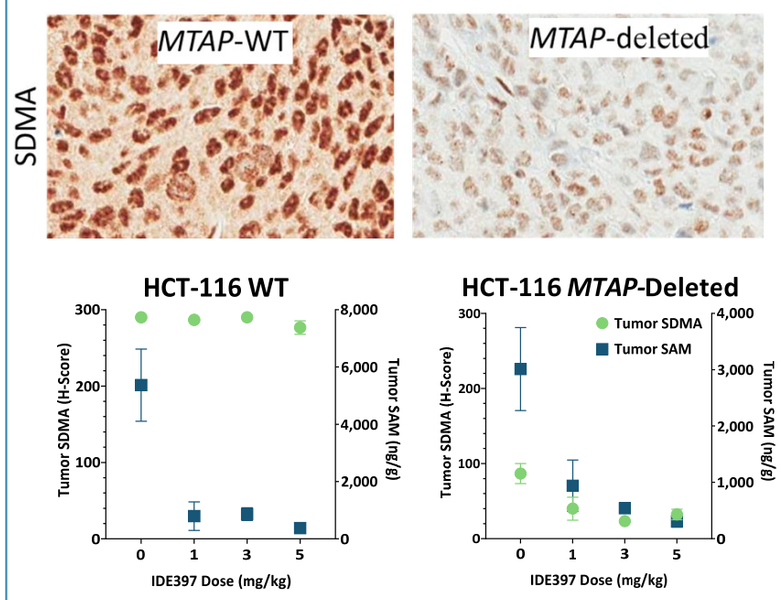
NSCLC Endogenous MTAP-/- CDX Model

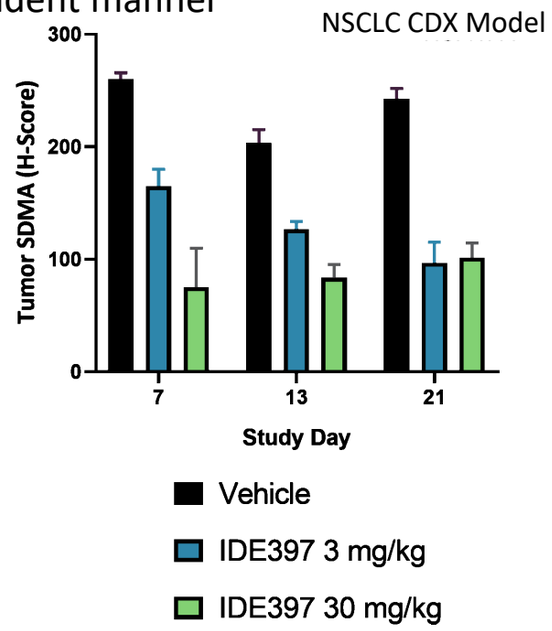


IDEAYA Data

SDMA and SAM are Proximal PD Biomarkers of MAT2A inhibition

SDMA and SAM are modulated in a dose dependent manner





IDE397 also results in dose dependent increases in MTA levels and a variety of downstream metabolic and gene expression changes

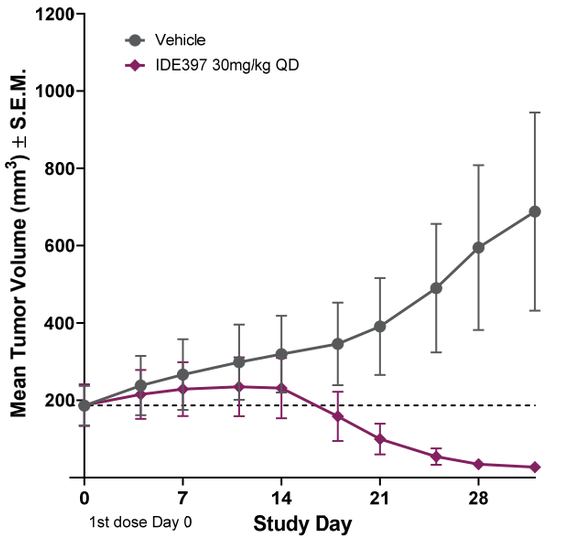
IDEAYA Data: Fischer et. al., AACR 2021

Robust dose dependent efficacy and PD modulation observed in NSCLC CDX Model

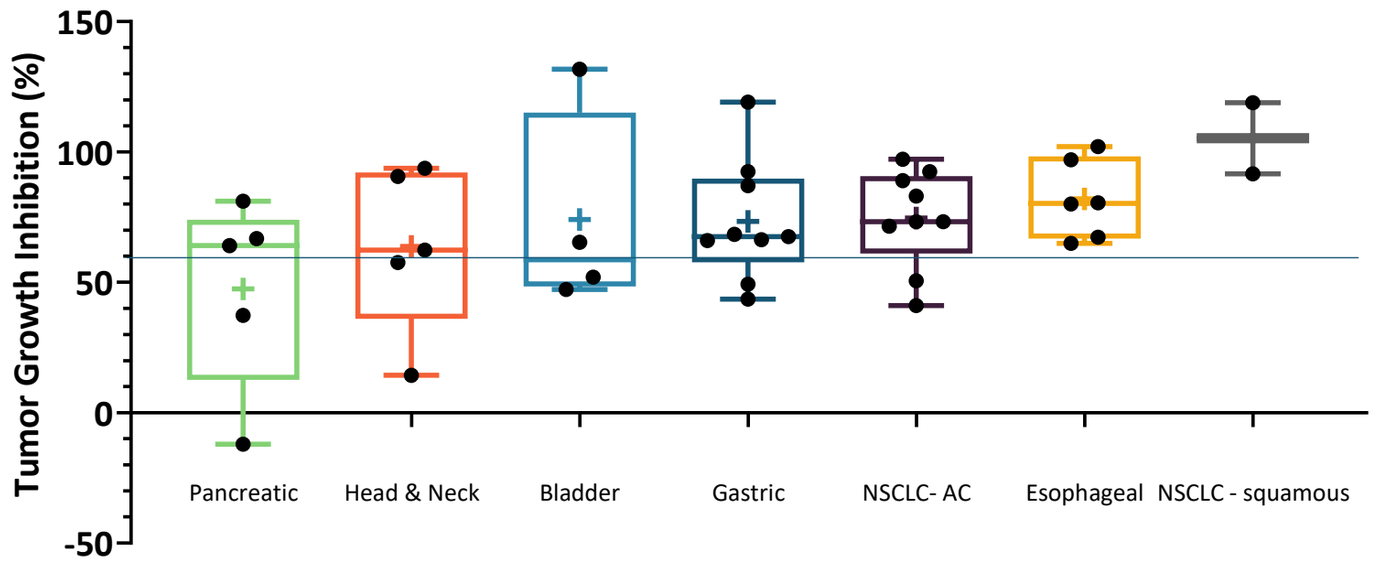
IDE397: PDX Study of >40 MTAP-/- Models in Multiple Indications

Monotherapy Tumor Regressions & Significant TGI Across Multiple Solid Tumor Types [1]

Bladder PDX Model



IDEAYA Data



(1) IDEAYA Data: Fischer et. al., AACR 2021

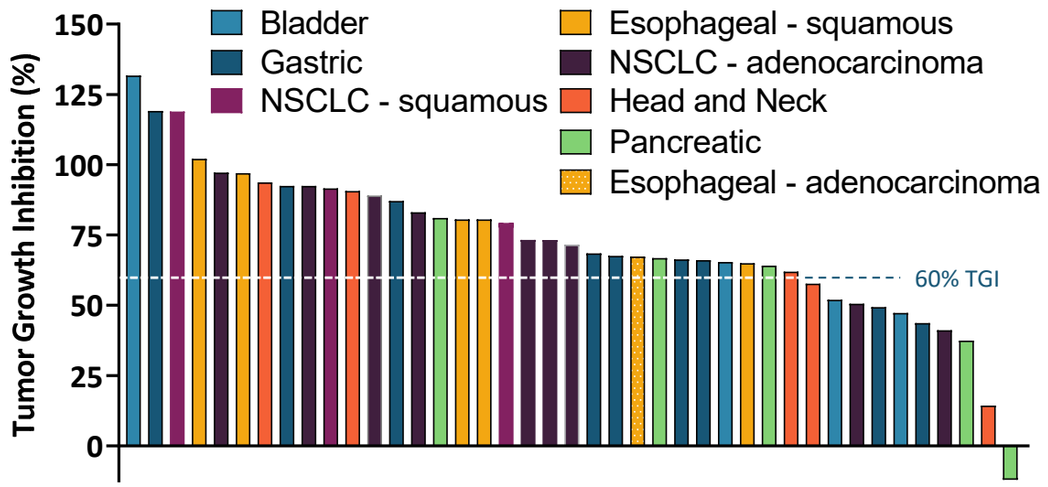
IDE397 evaluation in Patient Derived Xenograft (PDX) models with homozygous MTAP deletions in Solid Tumors

- Tumor Regressions (≥ 100% TGI) observed in multiple PDX models and across multiple indications
- Sensitive models in all indications but average sensitivity varies across indications

IDE397: Preclinical Study in *MTAP-/-* Patient-derived Xenograft Models

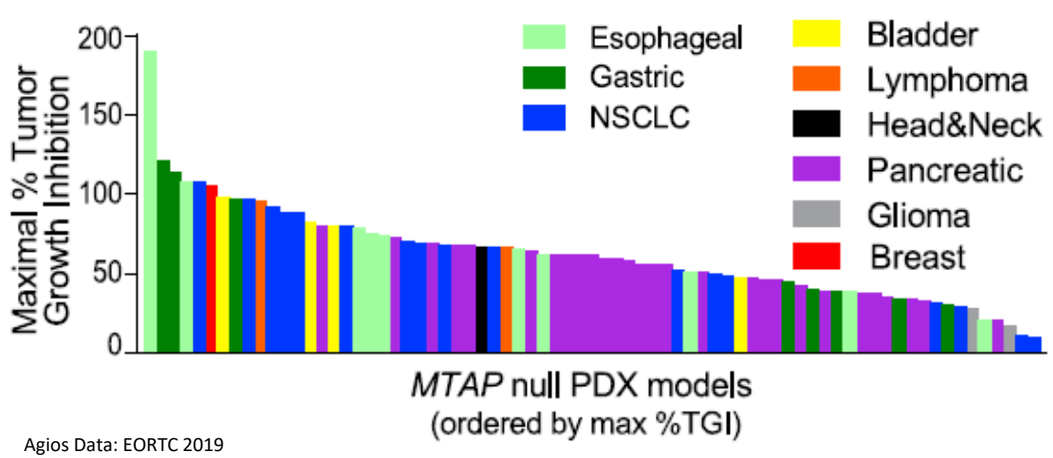
IDE397 demonstrates favorable Efficacy relative to reported AG-270 PDX Data

IDE397 30mg/kg dose



IDEAYA Data

AG-270 200 mg/kg dose



Agios Data: EORTC 2019

	IDE397 (30mg/kg)	AG-270 (200mg/kg)
Models with >60% TGI[1]	76%	49%

"Agents that led to greater than 60% TGI in preclinical models, at clinically relevant exposures, are more likely to lead to responses in the clinic" [1]

(1) Wong et al., Clin Cancer Res 2012

IDE397 Combination Strategy

Multiple approaches initiated to identify Novel Combination Partners

Multiple Combination Approaches

Large scale drug combination screen

- 14 MTAP-deleted cell lines representing multiple indications screened with over 100 compounds representing broad range of oncology pathways

Ex vivo Approaches

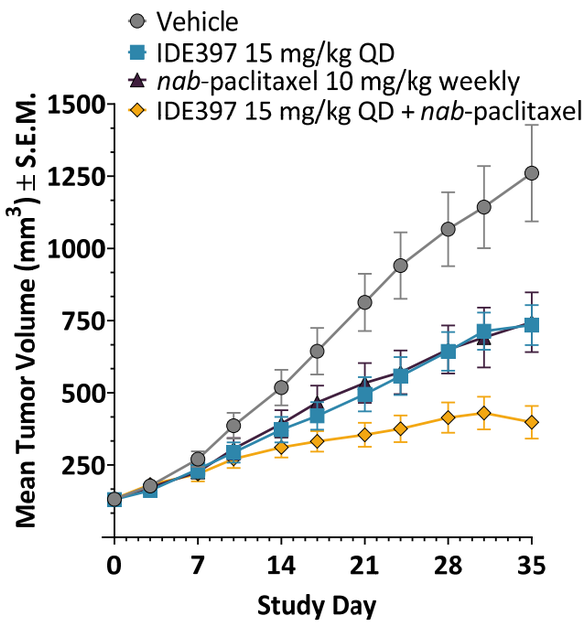
- CDX-derived spheroids and PDX-derived organoids to recapitulate *in vivo* conditions of tumor growth and immune interactions

In vivo Approaches

- CDX and PDX models are being tested with standard of care and rational combinations based on co-occurring mutations

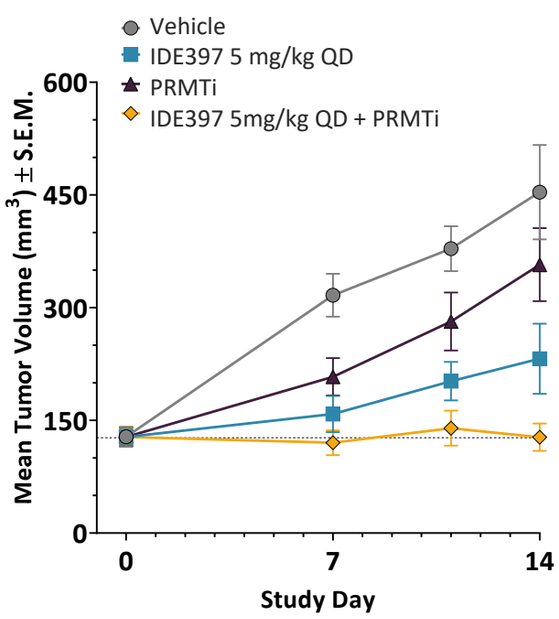
Strong *in vivo* Combination Effects with Taxanes and PRMTi

IDE397 + nab-Paclitaxel
Pancreatic PDX Model



p= 0.0019: IDE397 + nab-paclitaxel
vs nab-Paclitaxel monotherapy

IDE397 + PRMT Inhibitor
HCT-116 MTAP(-/-) Model



P<0.001: IDE397 + PRMTi
vs PRMTi monotherapy

IDEAYA / GSK Data

IDE397 Translational Strategy

Robust assays to inform Clinical Development

IDE397 Translational Plans

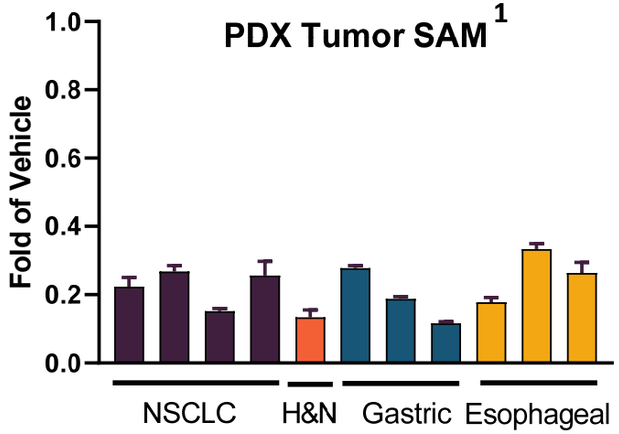
Assays in place for plasma SAM, tumor SAM and tumor SDMA

IDE397 causes robust tumor PD response in PDX models

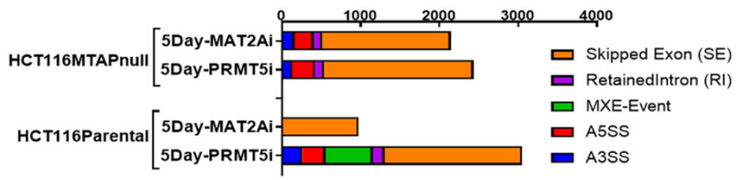
- 80-90% tumor SAM reduction in PDx models
- AG-270 showed variable and inconsistent PD modulation in Phase I paired biopsies

Multiple assays evaluating splicing, gene expression and metabolomics

PDX Tumor SAM [1]

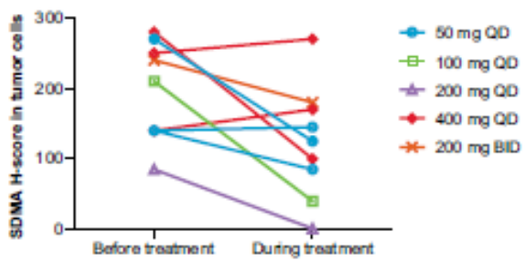


RNAseq analysis of treated cells[2]



1 IDEAYA Data Fischer et al AACR 2021
2 IDEAYA Data Bhola et al AACR 2021

Agios Phase I Tumor SDMA Data[3]



SEM = standard error of the mean

Cohort	SDMA relative % change (H-score) Mean ± SEM
50 mg QD (n=3)	–29.8 ± 17.2
100 mg QD (n=1)	–80.9
200 mg QD (n=1)	–98.8
400 mg QD (n=3)	–11.6 ± 26.6
200 mg BID (n=1)	–25
Total (n=9)	**–36.5 ± 14.0**

3 Agios Data: EORTC 2019

IDE397: Targeting MAT2A in MTAP-Deleted Tumors

IDE397 Clinical Development Plan

Matthew Maurer, M.D. – Vice President, Head of Clinical Oncology and Medical Affairs
IDEAYA Biosciences

IDE397: Targeting MAT2A in MTAP Deletion Tumors

Clinical Development Approach

IDE397 Clinical Development in Solid Tumors

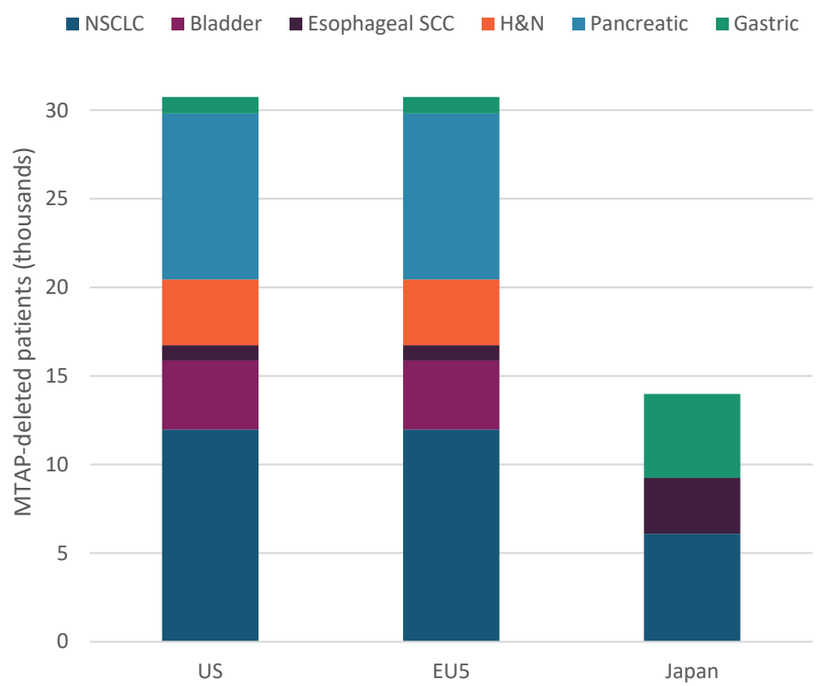
- IDE397 is a potential first in class/best in class MAT2A inhibitor
- Patient selection based on defined genetic biomarker defined (MTAP deletion)
- Potency permissive of potential single agent activity
- Tolerability permissive of broad combination potential

Summary of Addressable MTAP-Deletion Patient Populations

MTAP-Deletion observed in ~15% of Solid Tumors

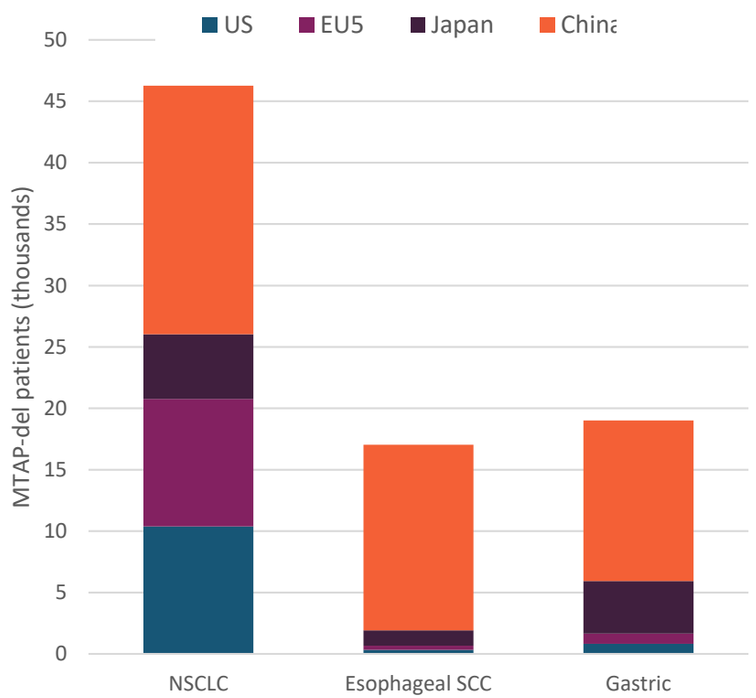
Addressable MTAP-Deletion Patient Populations

~75,000 pts per year in US, EU5 and JP (6 tumor types)



Solid Tumor Indications of Clinical Relevance

NSCLC, Esophageal and Gastric Cancers



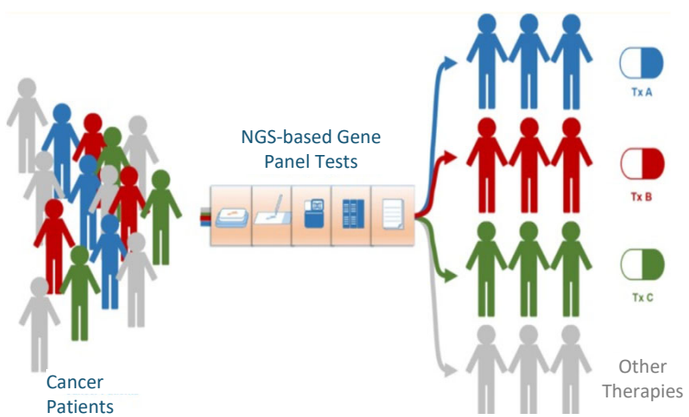
MTAP-Deletion Patient Selection

NGS, IHC, and ctDNA Assays to Identify Patients with MTAP Deletion

Next Generation Sequencing (NGS)

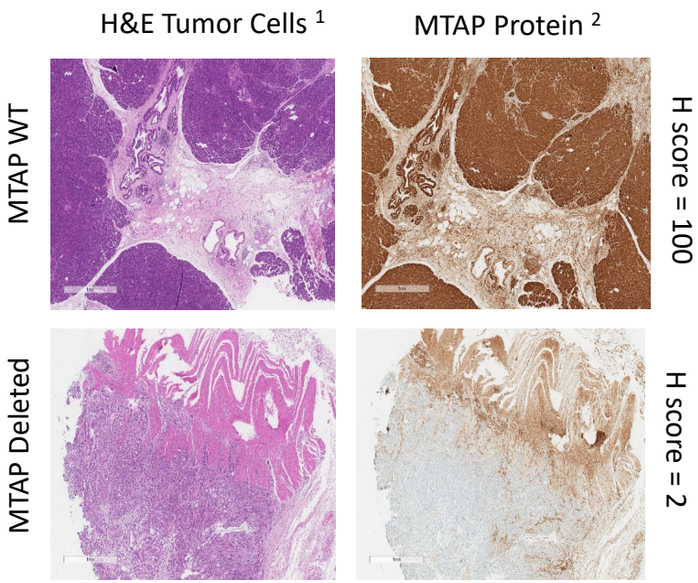
NGS-based gene panel tests identify MTAP deletion and enable patient selection for treatment with IDE397

Commercially available tissue based NGS gene panel tests include FoundationOne CDx, Tempus xT, others



Cancer Sci. 110(1): 6–15, Nagahashi et al. (Jan 2019)

IHC Assay Developed with Ventana



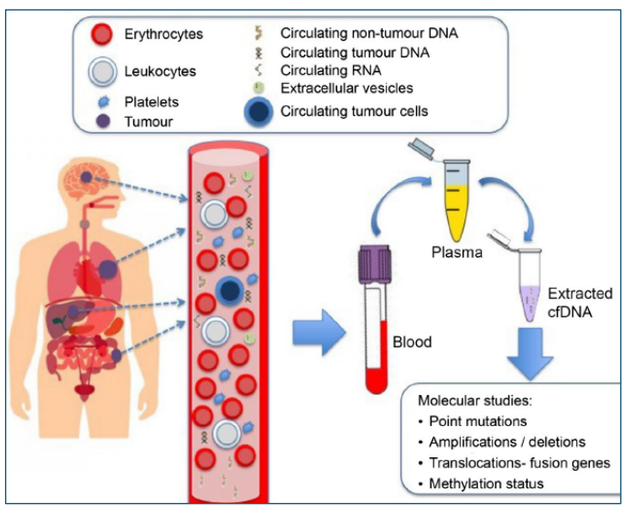
(1) H&E stain identifies cell types by deep purple color in tumor biopsies
(2) MTAP stain identifies MTAP protein levels with semi-quantitative scoring (e.g., 100 = high, 1 = low)

IDEAYA / Ventana Data

MTAP Liquid Biopsy Assay

Leverage non-invasive liquid biopsy tests as method for detecting gene deletions from ctDNA

Discussions ongoing with anticipated commercial availability by 2022

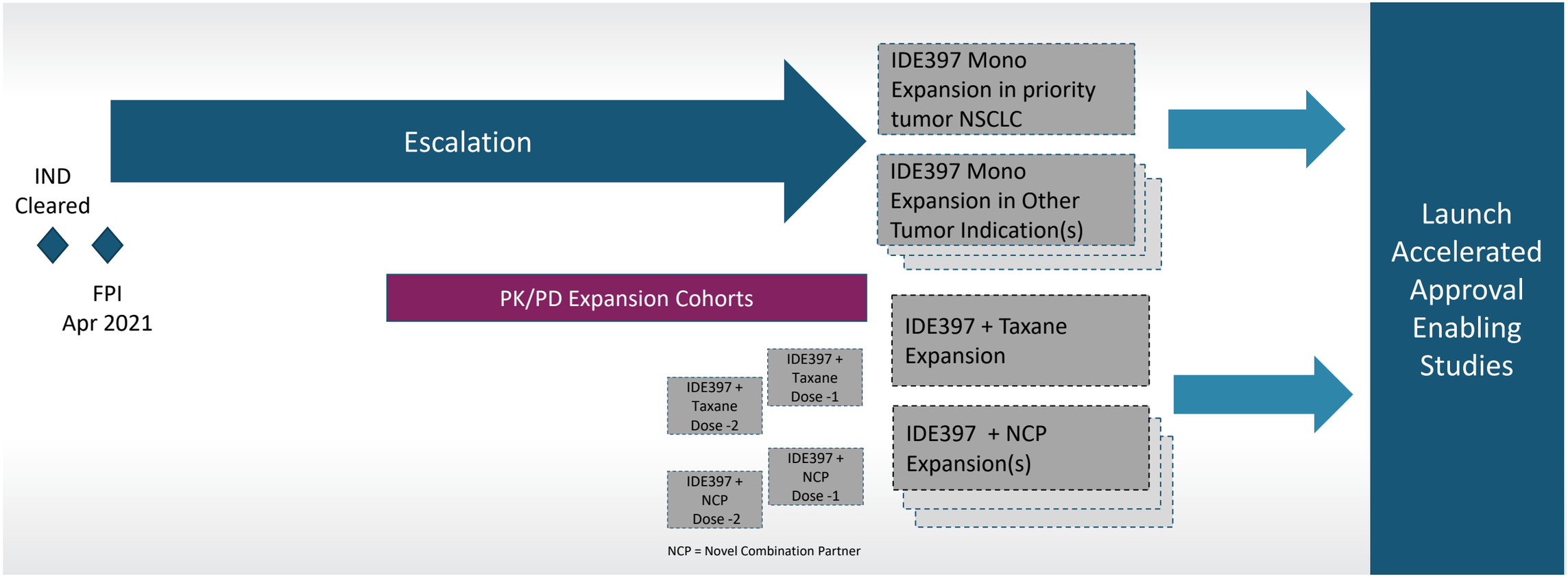


Clinical and Translational Oncology (2020) 22:823–834)

IDE397 Phase 1 Clinical Trial

Comprehensive Approach for Concurrent Evaluation of Monotherapy and Combinations

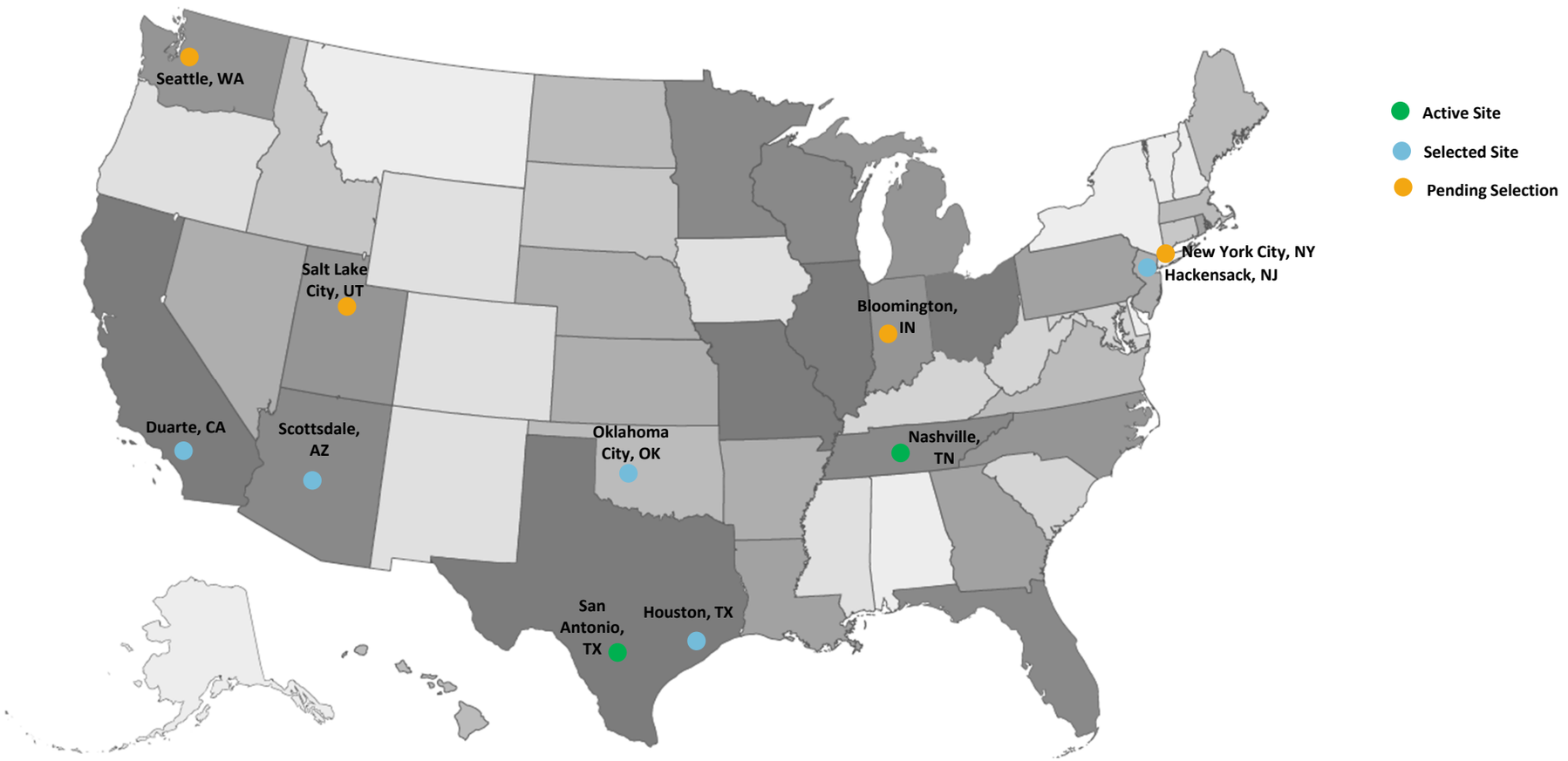
Phase 1 Dose Escalation and Expansion



NCP = Novel Combination Partner

Next Generation Sequencing + IDE397 Phase 1 Study Centers

Geographic Diversity for Enrollment



NSCLC Analysis – Opportunities Across Treatment Lines and Combinations

Leverages Preclinical Data and Sensitivity across Adeno and Squamous Histologies

Broad Opportunities in NSCLC

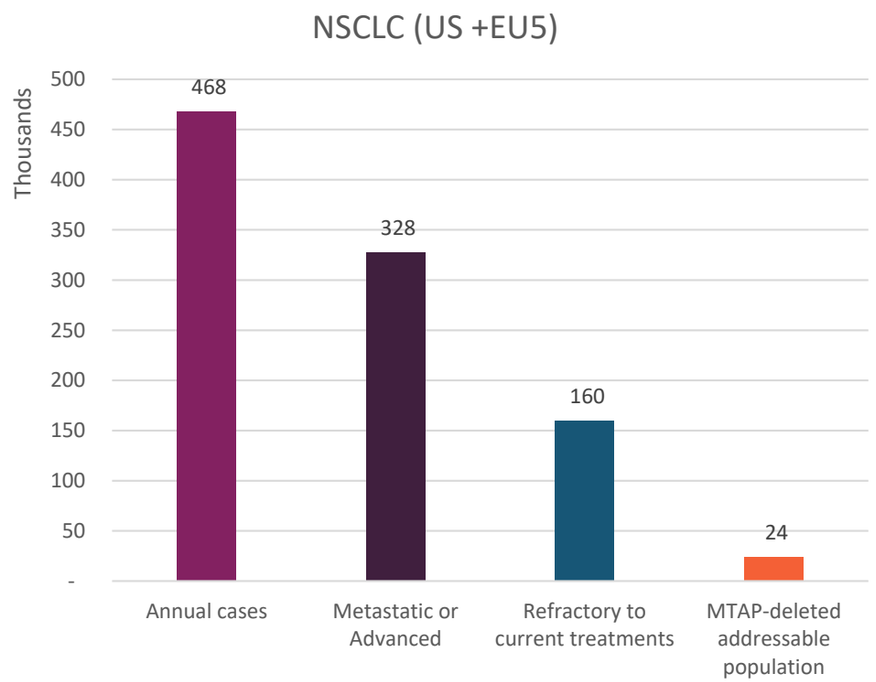
Possible Single Agent and Combination Strategies

- 2-3L+: IDE397 monotherapy single arm rapid assessment
- 2-3L: IDE397 + novel combination partner (NCP)
- 2L: IDE397 + taxane or gemcitabine
- 1L: IDE397 + IO/chemo

Increased opportunity in 2L+ given IO has moved into 1L

Aggregate targetable mutations remain minority of the population

Addressable Population (15% MTAP loss)



Additional Priority Tumor Types Driven by Preclinical Data

Broad Clinical Development Opportunities across Multiple Major Tumor Types

Gastroesophageal and Head & Neck Cancers Each Indication is ~14% MTAP Loss

Possible Single Agent and Combination Strategies

- 2-3L+: IDE397 monotherapy single arm rapid assessment
- 2-3L: IDE397 + novel combination partner (NCP)
- 2L: IDE397 + taxane
- 1L: IDE397 + IO/chemo

Large potential opportunity in Asia

Possible enrichment in HPV negative population

Additional Potential Tumor Types Possible Single Agent / Combinations

Other Potential MTAP-deletion Indications

- Bladder
- Pancreatic
- Mesothelioma
- Melanoma
- RCC
- Breast
- HCC

GBM not in scope (engineered lack of significant CNS penetration)

Opportunities for Combination Synergy across Diverse MOAs

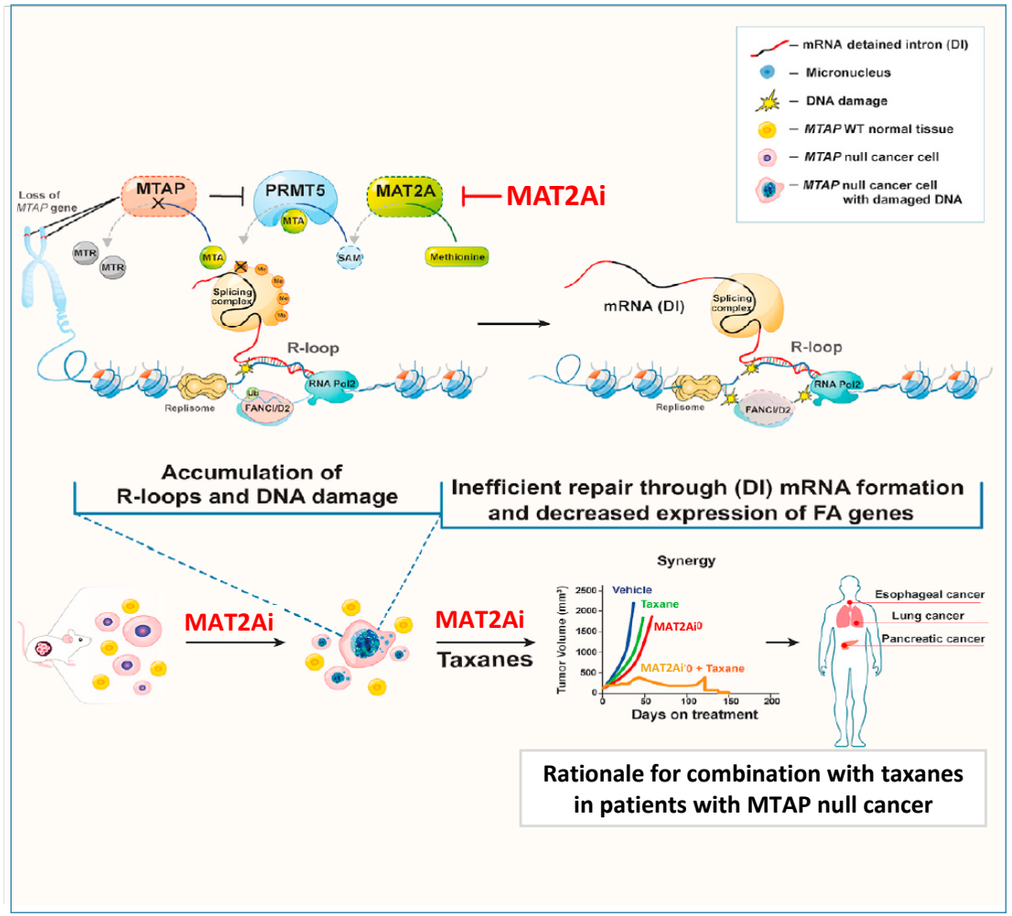
Ongoing Preclinical Effort to identify Optimal Synergistic Combination Partners

Combination Partners

Preclinical evidence of synergy with anti-mitotics (taxanes)

Multiple additional opportunities being evaluated

- DNA Damage Agents
- Anti-metabolites
- Immunotherapy
- Novel Combination Partners
  - PRMT inhibitors
  - KRAS inhibitors (28% [3.9% G12C] of MTAP deleted tumors)*
  - Overlap with other targetable mutations could inform future combinations



* Annals of Oncology, Volume 31, Issue S4, Poster 134P (Sokol et al., 2020)

Adapted from Cancer Cell 2021 Feb 8;39(2):209-224.e11

Leveraging GSK Collaboration

Collaboration Goal to Accelerate and Optimize SL Drug Development and Increase POS

Collaboration Synergies and Benefits

GSK is a large pharma leader in synthetic lethality

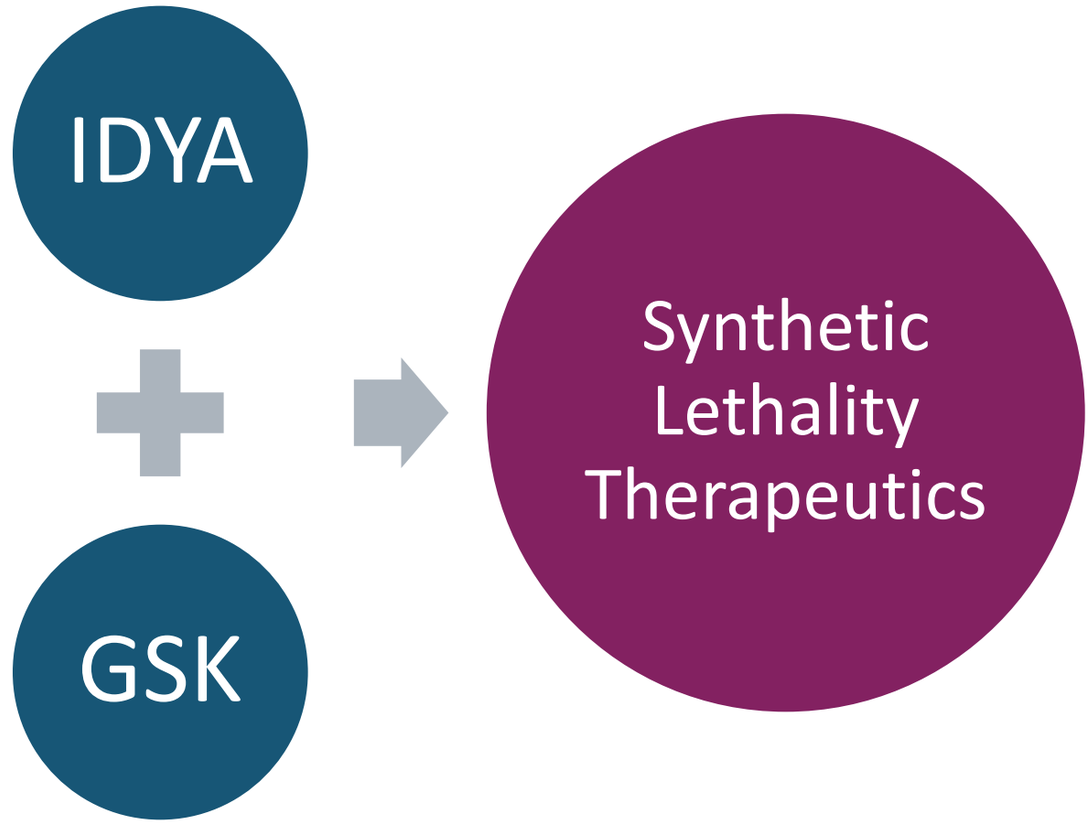
Depth and breadth of resources and clinical development knowledge and capabilities

- Clinical development strategy and execution
- IHC diagnostic development

Preclinical and clinical testing in the relevant therapeutic pathways

- Collaboration in preclinical combination studies
- Assets in development with combination potential

Global footprint



Differentiated to be Best-in-Class and Potential to be First-in-Class

Broad Opportunities and Options for Clinical Development

Target Product Profiles – IDE397 versus AG270

Attribute	IDE397	AG-270
Potential for Single Agent Activity	Yes	Not being pursued
Safety Profile	No anticipated liver toxicity	Liver toxicity
Patient Selection	MTAP loss	MTAP or CDKN2A loss
Combination Opportunities	Diverse – Multiple Combo Partners	Focus on chemotherapy
Tumor Histologies	Broad opportunities remain	Focus on NSCLC and Pancreatic

Werner Helicase: Compelling Synthetic Lethality Target

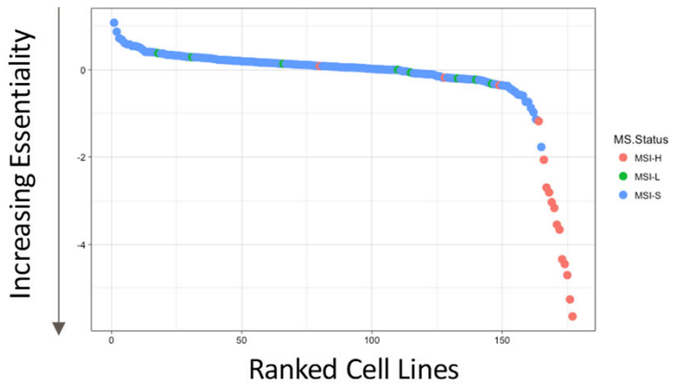
Introduction

Benjamin Schwartz, Ph.D. – Vice President, Head of Oncology Synthetic Lethality Research Unit GlaxoSmithKline

WRN Helicase: Synthetic Lethality in MSI Tumors

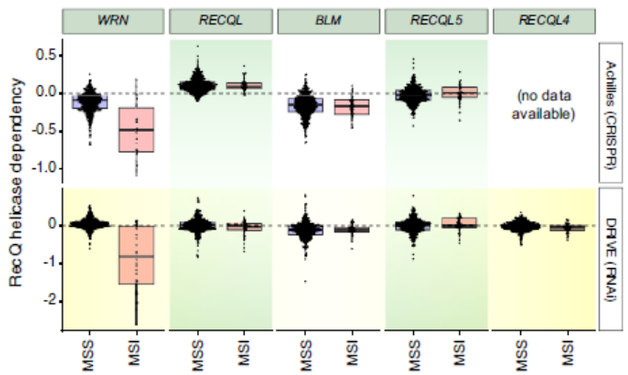
Using Genome-Wide Approaches to Find the Next PARP-like Opportunity

Project SCORE



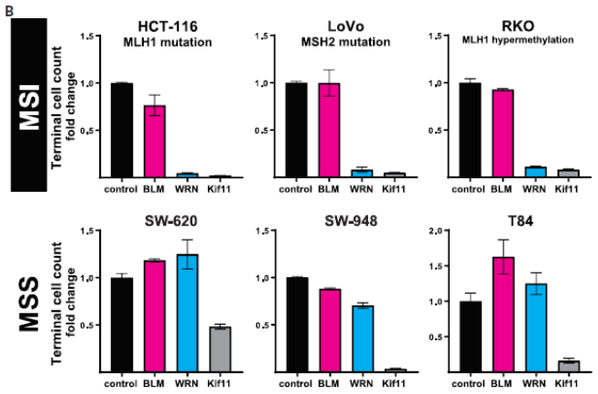
2019 Nature, 568, 511

Project Achilles



2019 Nature, 568, 551

IDEAYA



2019 iScience, 13, 488

- High correlation between WRN sensitivity and MSI status
- Rescue experiments consistently identify helicase domain as relevant for SL
- Genetic validation of SL in pre-clinical in vivo systems

Werner Helicase: Compelling Synthetic Lethality Target

Panel Discussion

William Sellers, M.D. – Core Institute Member and Director of the Cancer Program
Broad Institute of MIT and Harvard

Benjamin Schwartz, Ph.D. – Vice President, Head of Oncology Synthetic Lethality Research Unit GlaxoSmithKline

Michael Dillon, Ph.D. – Senior Vice President, Chief Scientific Officer
IDEAYA Biosciences

Pol Theta: Key Target in MMEJ DNA Damage Repair Pathway

Pol Theta Biology

Alan D'Andrea, M.D. – Director, Center of DNA Damage and Repair
Dana Farber Cancer Institute of Harvard Medical School

Polymerase Theta Inhibition Kills Homologous Recombination-Deficient Tumors

Alan D'Andrea

Fuller-American Cancer Society Professor
Dana-Farber Cancer Institute
Harvard Medical School

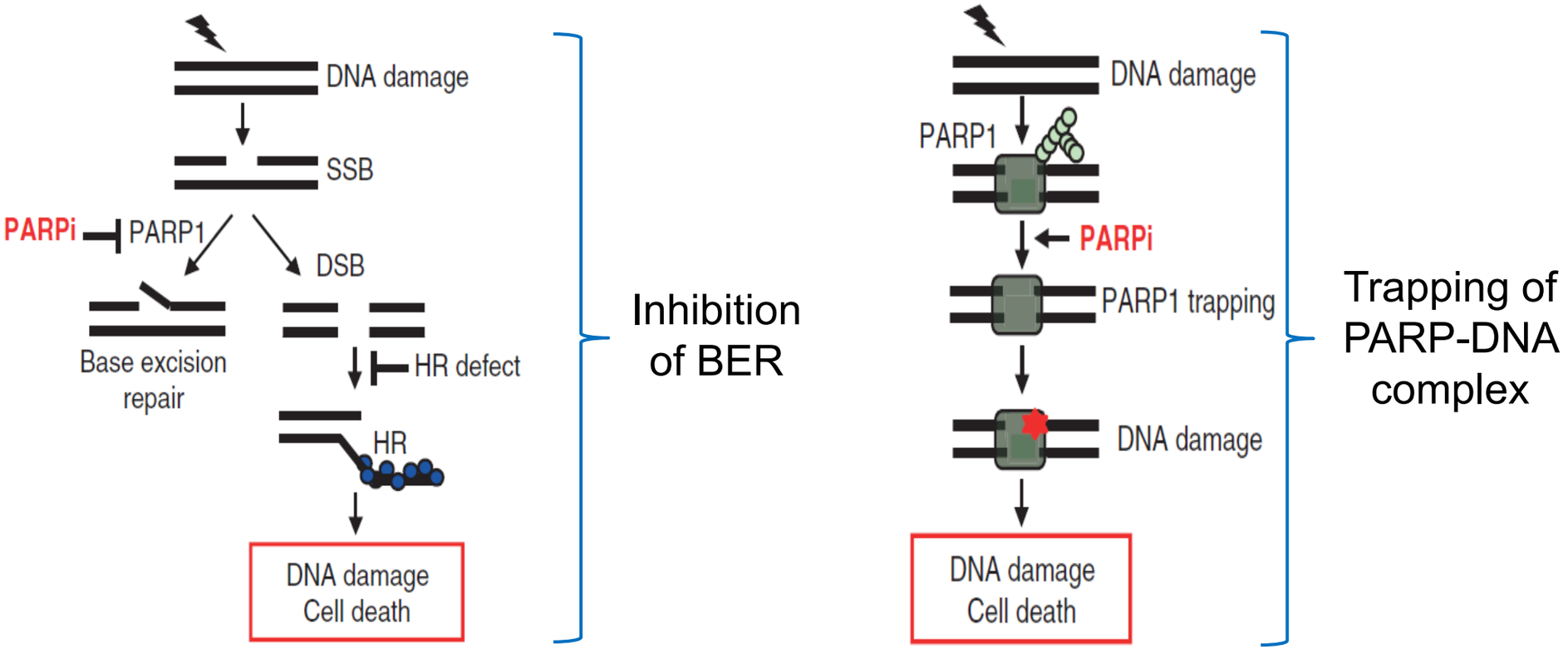
DANA-FARBER CANCER INSTITUTE

SUSAN F. SMITH CENTER FOR WOMEN'S CANCERS

INTRODUCTION

- Many Solid Tumors are Homologous Recombination (HR)-deficient
- PARP inhibitors (PARPi) kill HR deficient tumors
- HR-Deficient tumor cells become resistant to PARPi, often by restoring HR
- PARPi resistance is a major problem in the clinic
- There is a major need for a drug which can overcome PARPi resistance

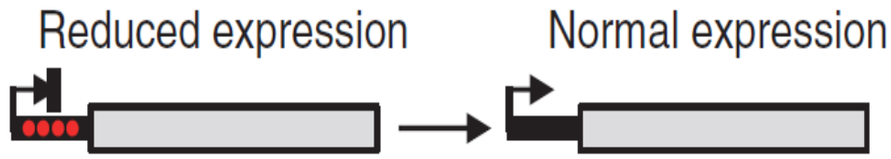
How do PARP inhibitors kill HR deficient tumor cells?



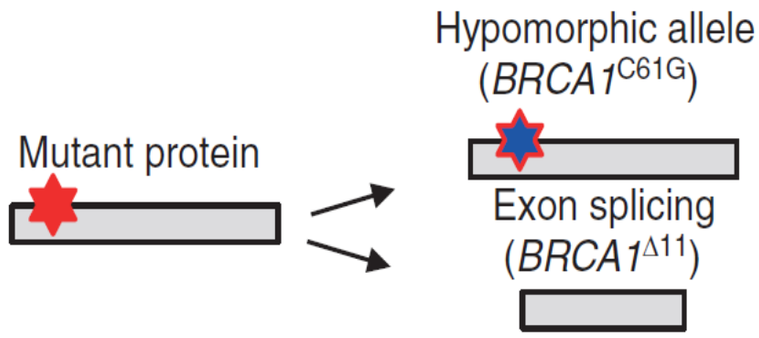
What are the mechanisms of PARPi Resistance? Restoration of HR proficiency

1. Somatic reversion or restoration of ORF

2. Epigenetic reversion of *BRCA1* promoter hypermethylation

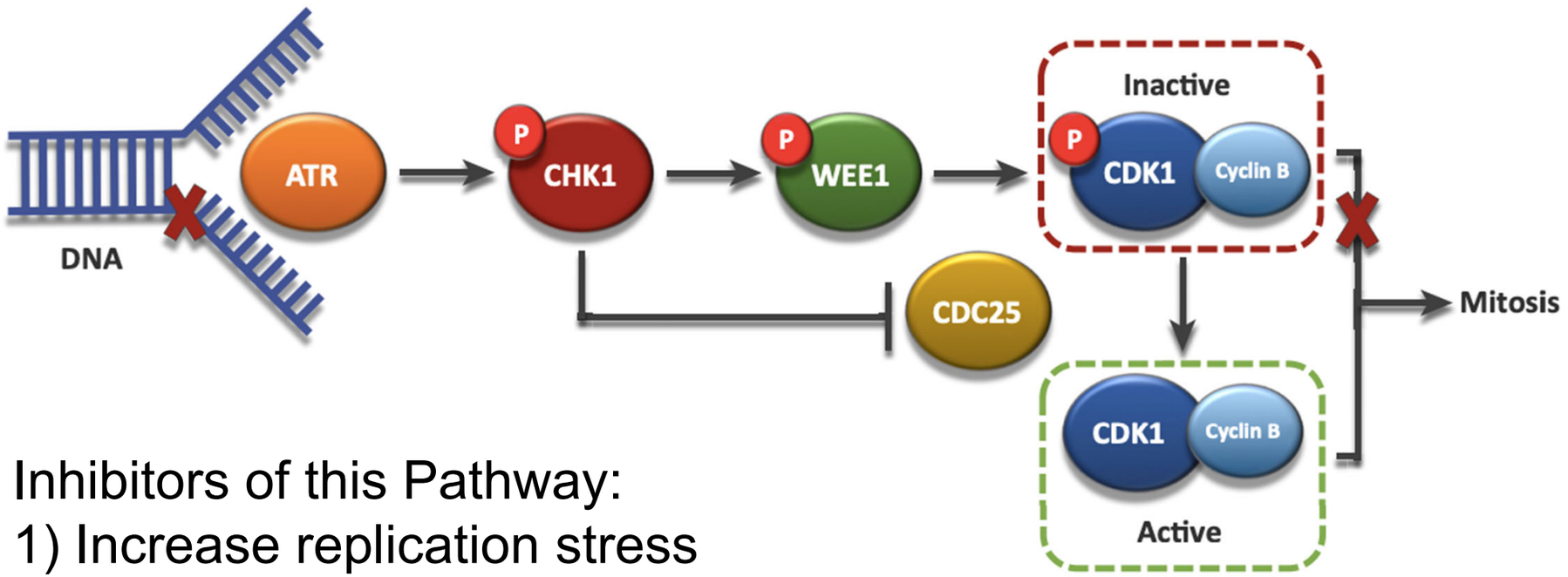


3. Hypomorphic *BRCA1* or *BRCA2* allele



Sakai et al. Nature 2008, Edwards et al. Nature 2008, Norquist et al. JCO 2011, Patch et al. Nature 20015, Bouwman et al. Clin Can Res 2014

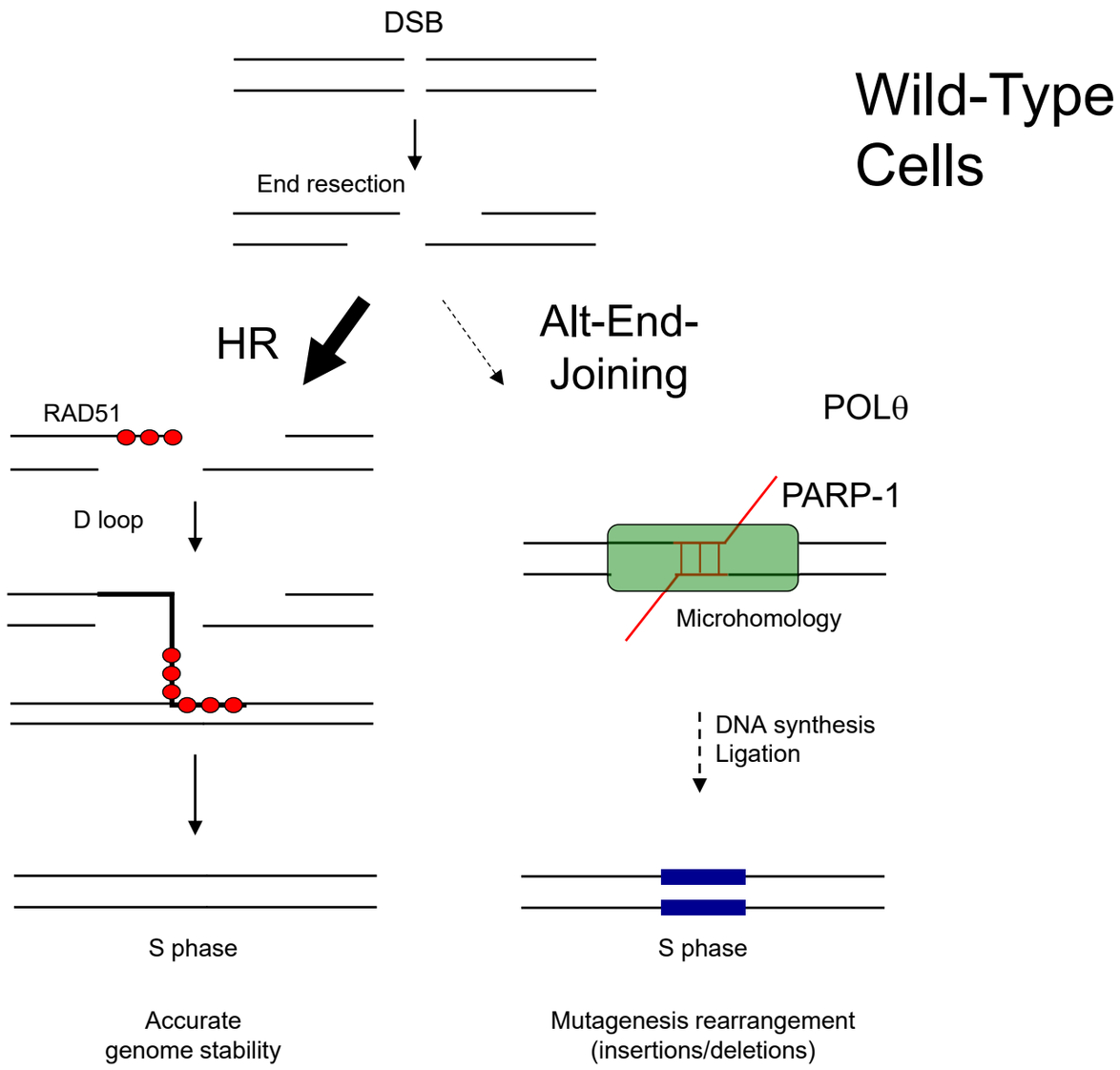
Upregulation of the ATR/CHK1/WEE1 pathway can also cause PARPi Resistance



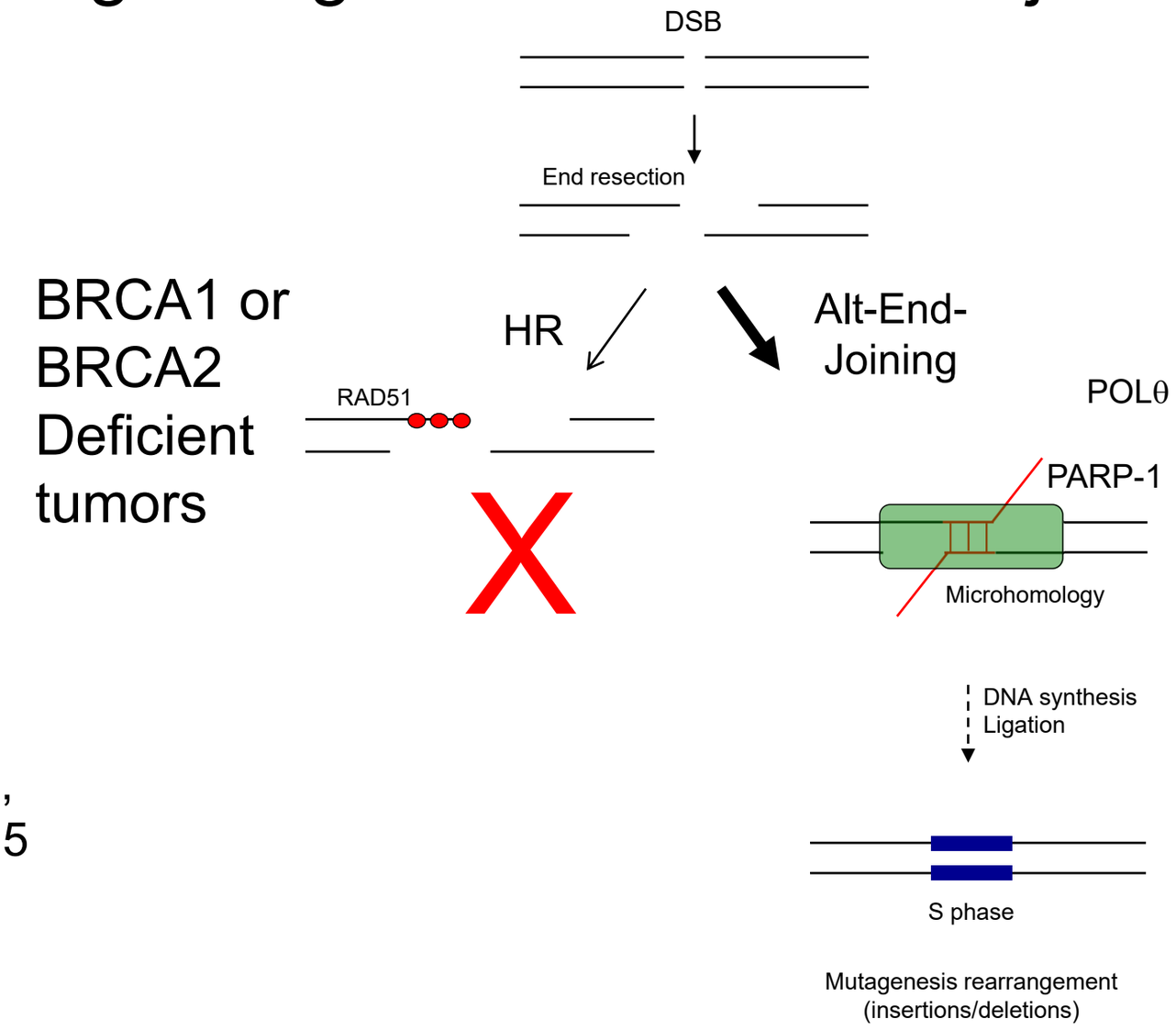
Inhibitors of this Pathway:

1) Increase replication stress
2) Inactivate the G2/M checkpoint
3) Overcome PARPi Resistance

Two Pathways Repair Double Strand Breaks during S phase



HR-Deficient Tumors can acquire PARP inhibitor resistance by upregulating the Alternative End-joining Pathway



Ceccaldi et al,
Nature, 2015

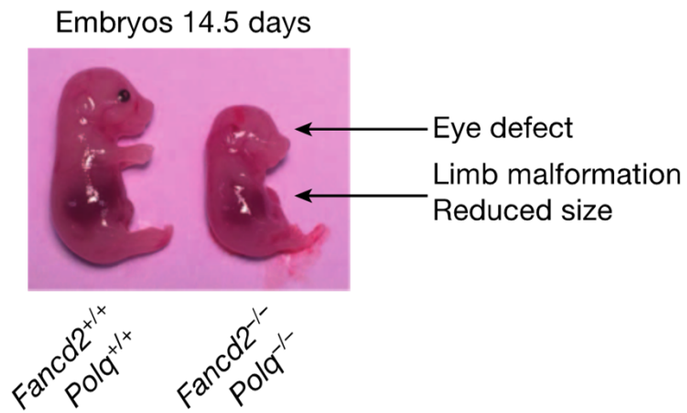
Cosmic
Signature 3

Synthetic Lethality between HR and Polθ-mediated alt-EJ

Fancd2$^{-/-}$
HR deficiency
Mild phenotype

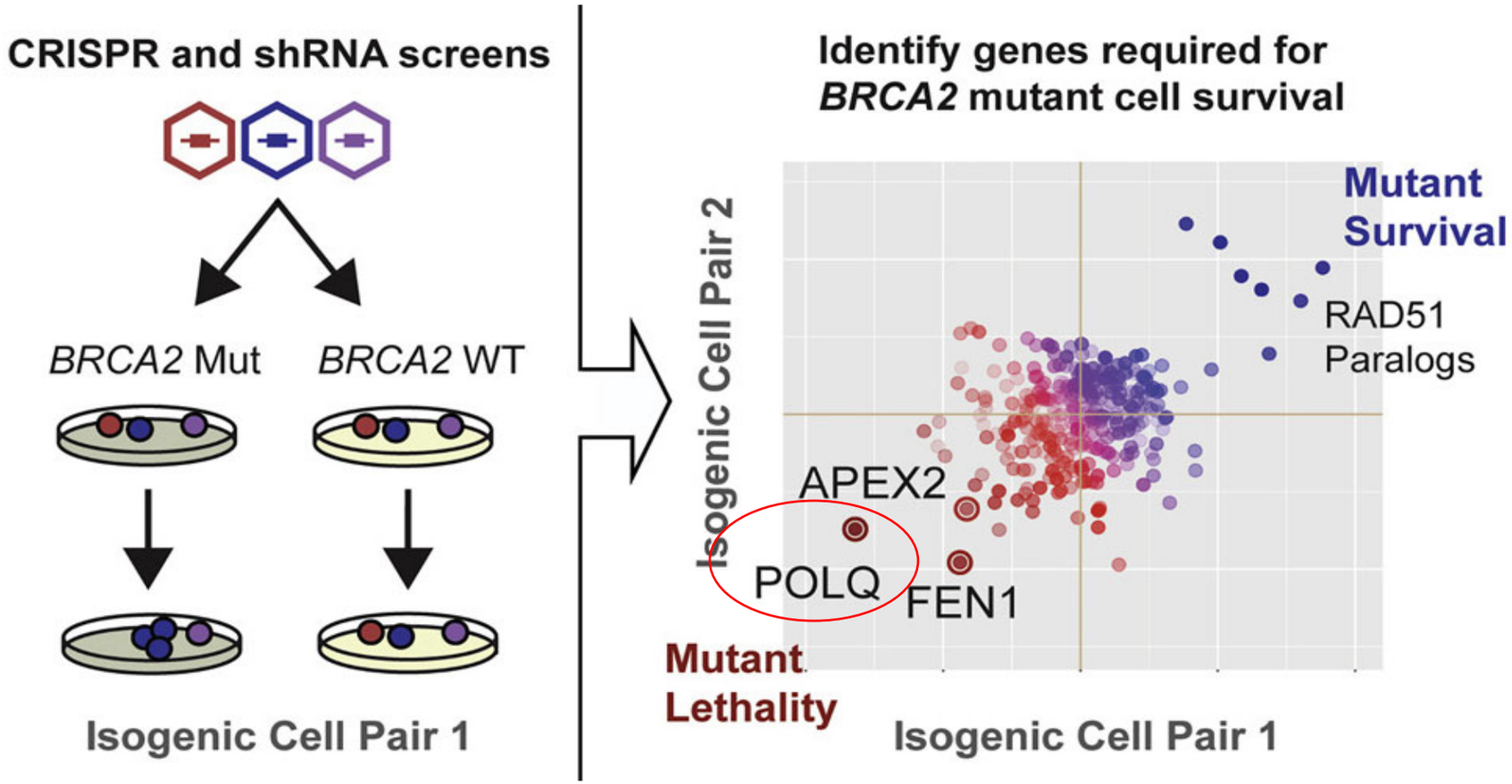
Polq$^{-/-}$
Alt-EJ deficiency
Mild phenotype

Double Knockout
Embryonic lethal



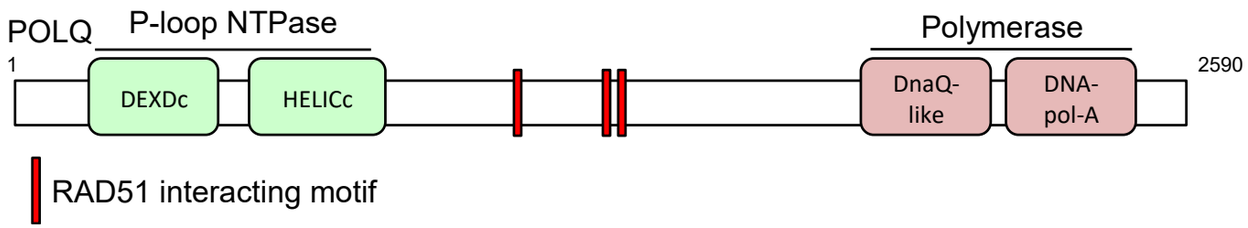
Ceccaldi et al,
Nature, 2015

POLQ is also synthetic lethal with BRCA2



Mengwasser, K. E., R. O. Adeyemi, Y. Leng, M. Y. Choi, C. Clairmont, A. D. D'Andrea and S. J. Elledge. Mol Cell 2019

POLQ has two enzymatic domains
Which should be targeted in cancers?



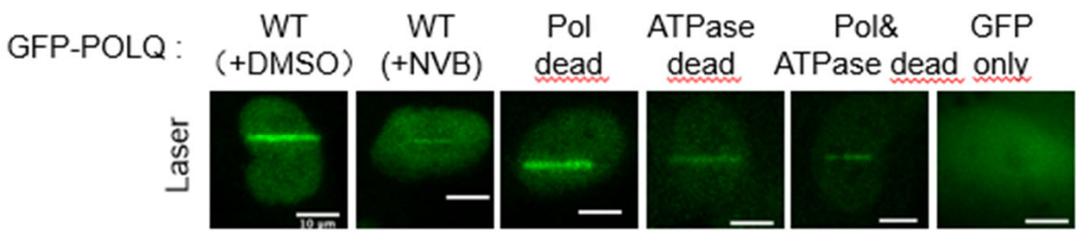
ATPase domain

-strips RAD51 and pRPA from sites of abortive HR repair

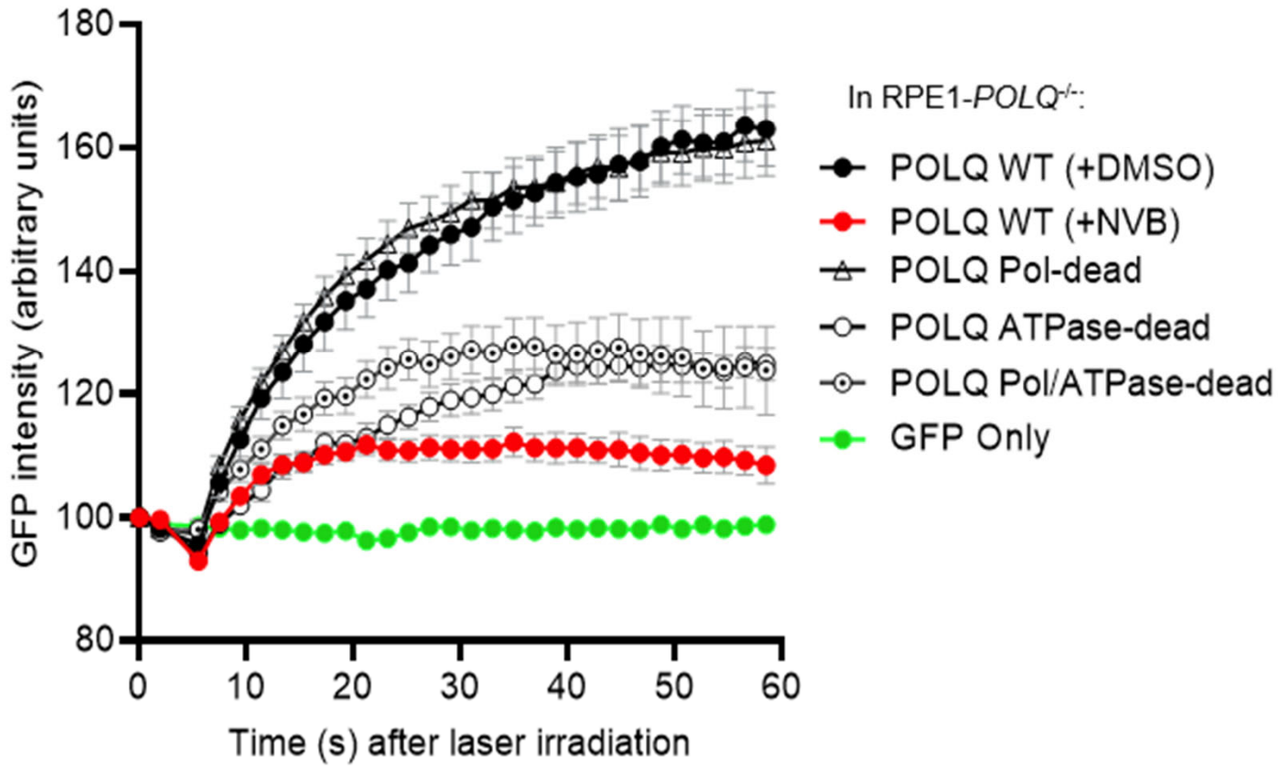
Polymerase Domain

-performs MMEJ Repair

The ATPase domain of POLQ is required for recruitment to DNA damage sites



ATPase Activity is Required for POLQ Recruitment



Summary: POLTheta Inhibitors Kill HR Deficient Tumors

- HR-Deficient Tumors are PARPi Sensitive but acquire PARPi resistance by multiple mechanisms, often from restoring HR repair
- HR-Deficient Tumors are sensitive to either PARPi or POLq knockdown
- Targeting either the ATPase domain or the Polymerase Domain is a suitable strategy for the development of POLq inhibitors
- Tumors with Acquired PARPi Resistance resulting from multiple mechanisms appear to remain sensitive to POLq knockdown

Acknowledgments

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Connor Dunn
Lucas Galli
Carter
Feng Li
Hanrong Feng
Tin Phan
Kelsey McQueen
Jeffrey Patterson-Fortin

Former Lab Members
Raphael Ceccaldi
Sarah Hill
Anniina Farkkila

CDDR Collaborators
Geoffrey Shapiro
Kalindi Parmar
JB Lazaro
Bose Kochupurakkal
Arindam Bose
Sharmistha Pal
Hunter Reavis
Larissa Sambel
Elizaveta Reznichenko
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Dipanjan Chowdhury

Ceccaldi Laboratory
Raphael Ceccaldi
Camille Gelot
Hatice Yucel

Tainer Laboratory
John Tainer
Aleem Syed

Blagg Laboratory
Brian Blagg
Rachel Davis

Shapiro Laboratory
Geoffrey Shapiro
Constantia Pantelidou

SUSAN F. SMITH
CENTER FOR
WOMEN'S CANCERS

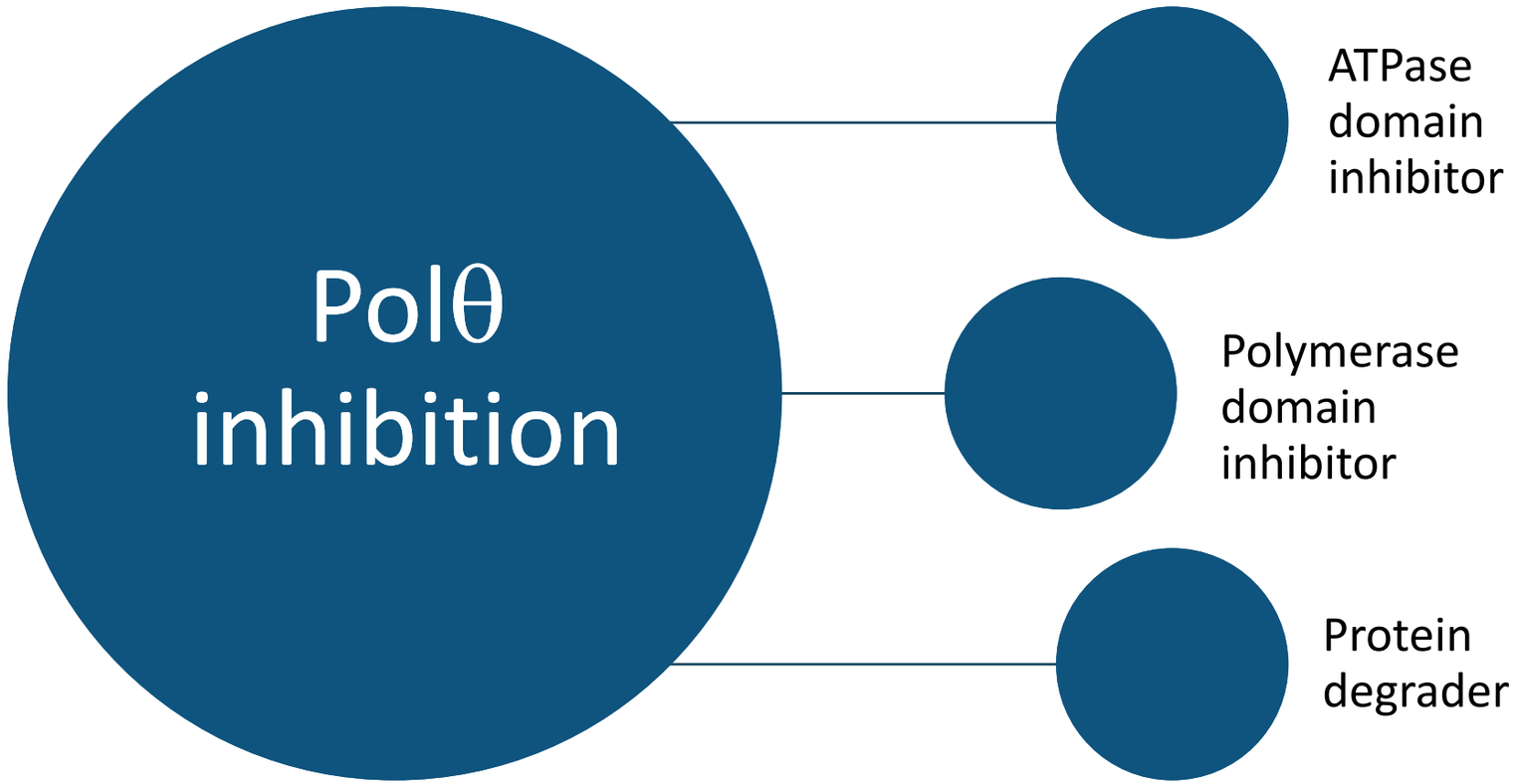
Pol Theta: Key Target in MMEJ DNA Damage Repair Pathway

IDEAYA Pol Theta ATPase Inhibitor Preclinical Program

Michael Dillon, Ph.D. – Senior Vice President, Chief Scientific Officer
IDEAYA Biosciences

Multiple Strategies Ongoing to Drug Pol Theta

Ideaya / GSK Joint Collaboration Teams



Targeting ATPase domain Development Compound Nomination in 2021

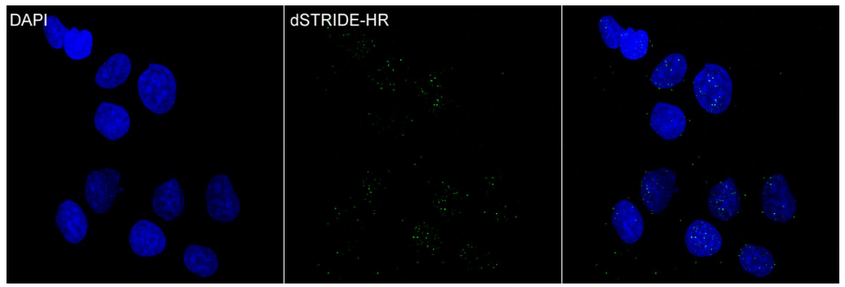
Polθ ATPase Activity is needed for DNA Repair

IDEAYA's Lead Pol Theta program directed to an ATPase inhibitor

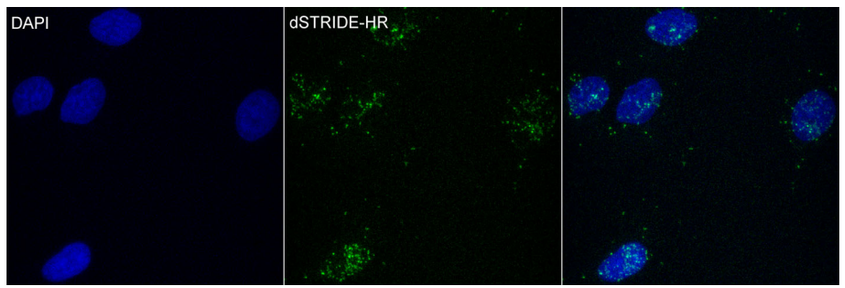
dSTRIDE-HR Assay

U2OS Polθ WT and U2OS Polθ K121A (ATPase mutant) cells used in dSTRIDE-HR assay

U2OS WT
No treatment

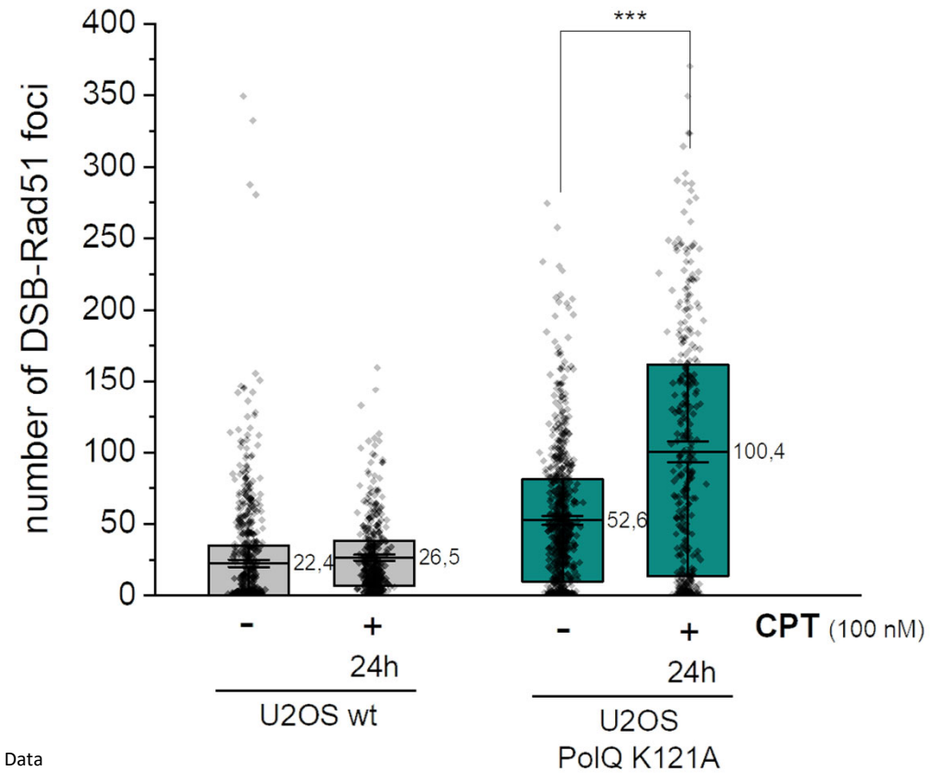


U2OS K121A
No treatment



IDEAYA Data

Polθ ATPase mutant shows increased DSB-Rad51 Foci

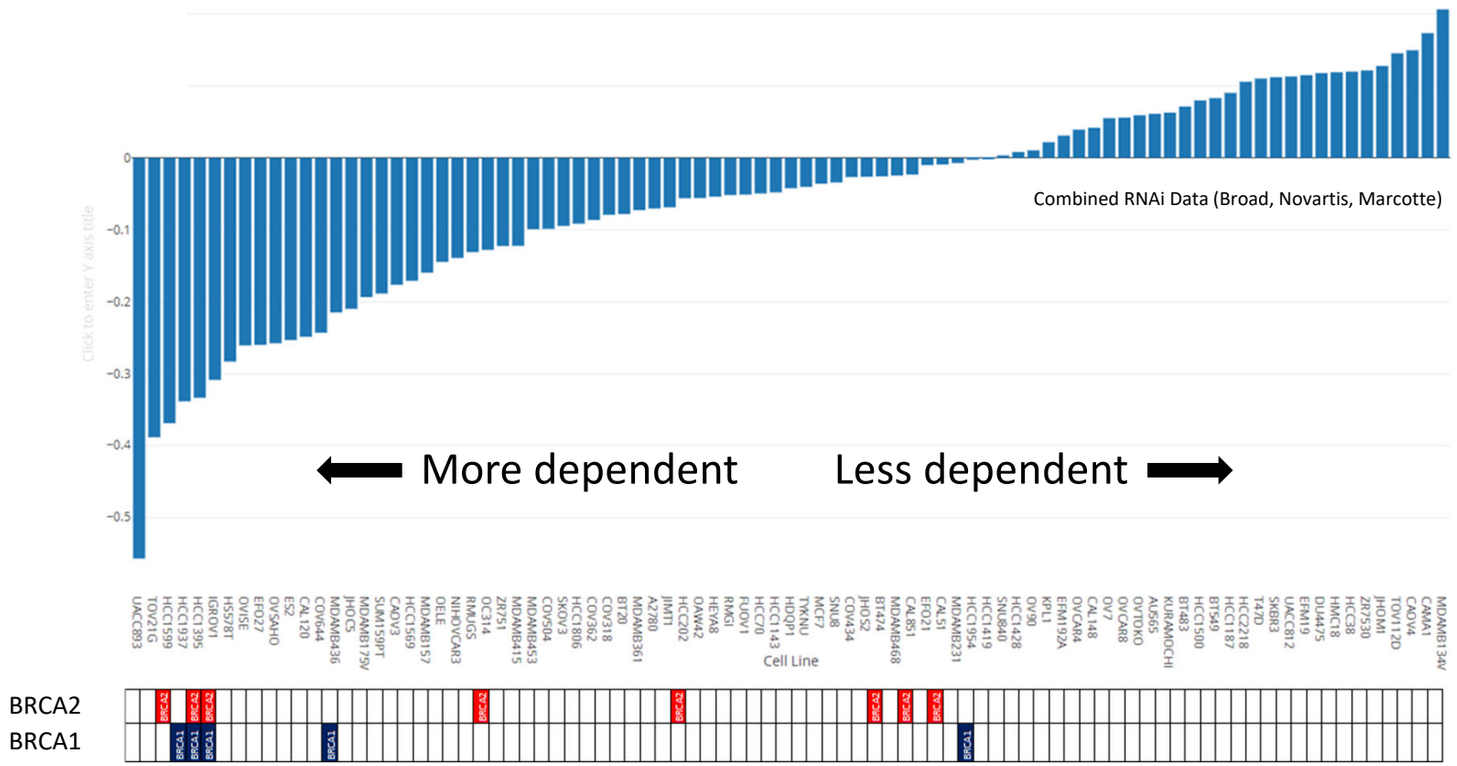


IDEAYA Data

Cancer Dependency Map Analysis

Breast and Ovarian Cell Lines have Strong Dependence on Polθ

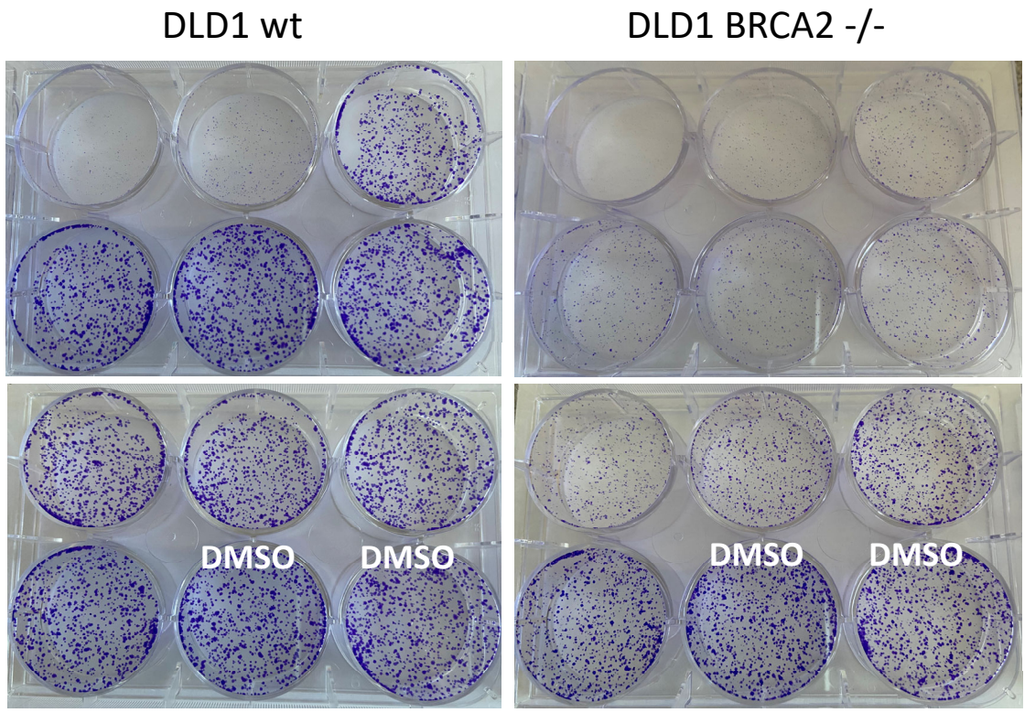
Genetic Knockdown Data



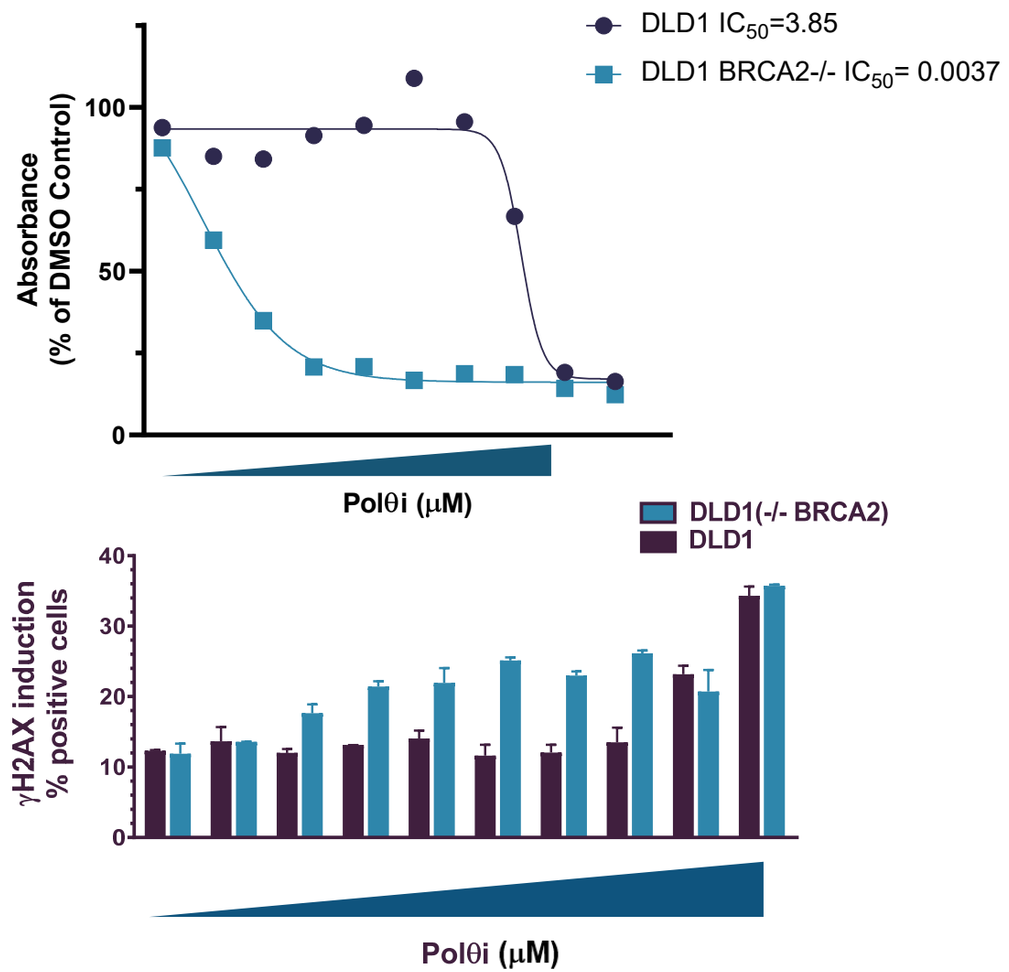
Several BRCA1 and BRCA2 mutant lines show strong Polθ dependence

IDEAYA Polθ ATPase Inhibitors Increase DNA Damage and Decrease Viability in DLD1 Cells in a BRCA2 Dependent Manner

DLD1 isogenic cell line Clonogenic Assay



γH2AX induction at significantly lower concentration in DLD1 BRCA2-/- cells when compared to DLD1 wt

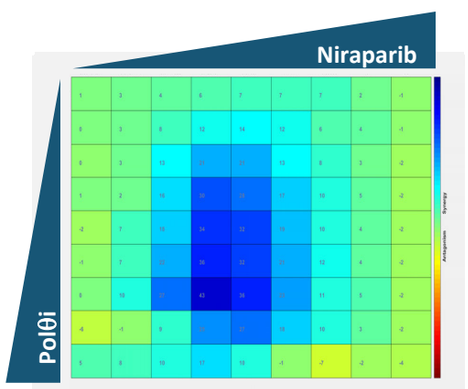


IDEAYA Polθ ATPase Inhibitors are Synergistic with niraparib in DLD1 BRCA2-/- Cells but not in Parental DLD1wt Cells

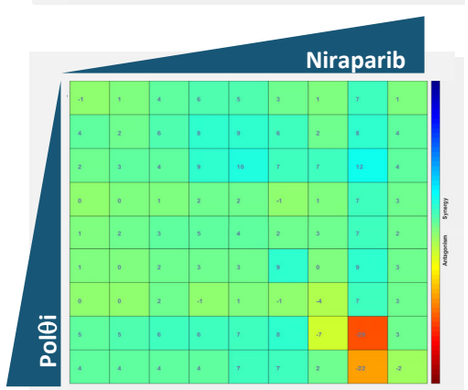
DLD1 isogenic cell line γH2AX Assay

HSA Model

DLD1 BRCA2-/-

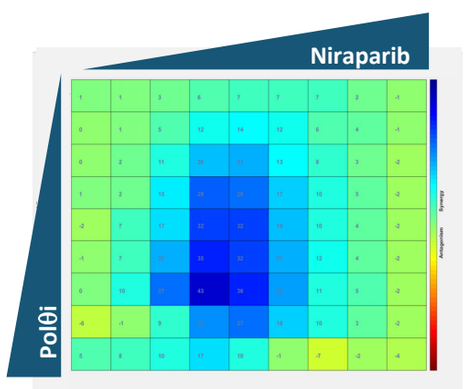


DLD1 WT

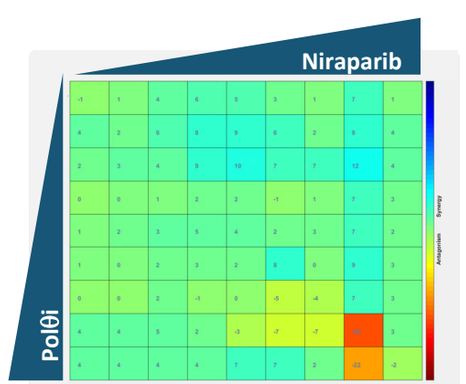


Loewe Model

DLD1 BRCA2-/-

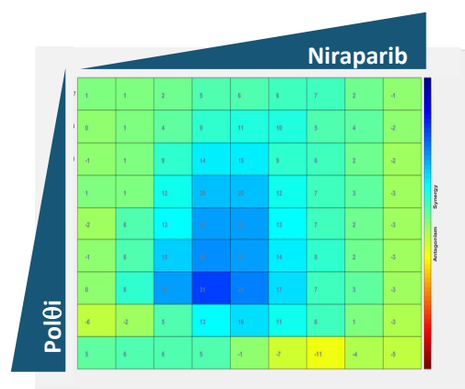


DLD1 WT

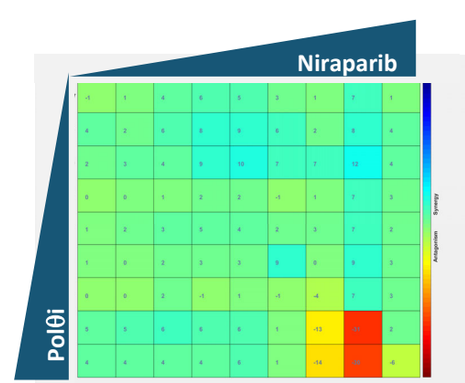


Bliss Model

DLD1 BRCA2-/-

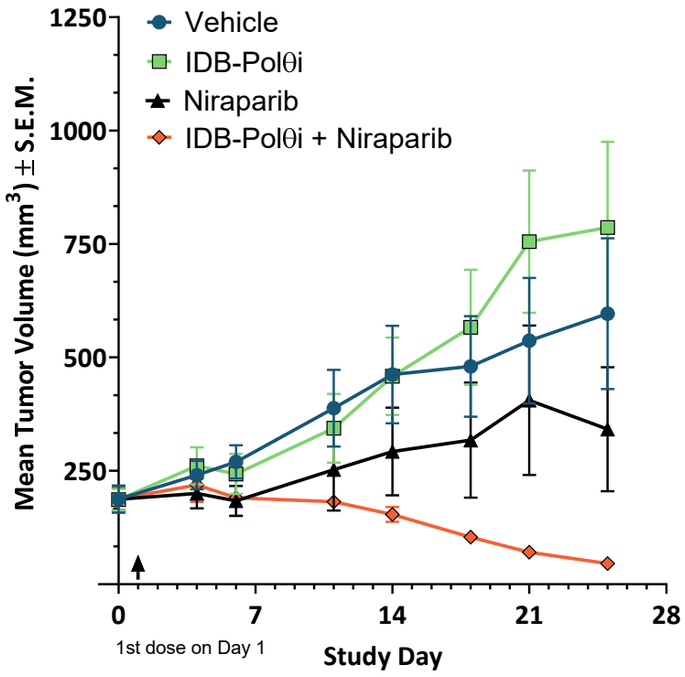


DLD1 WT

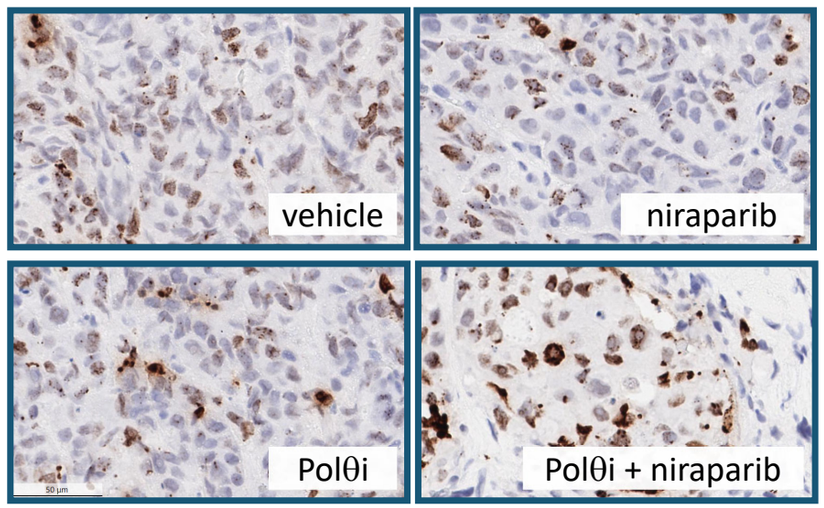


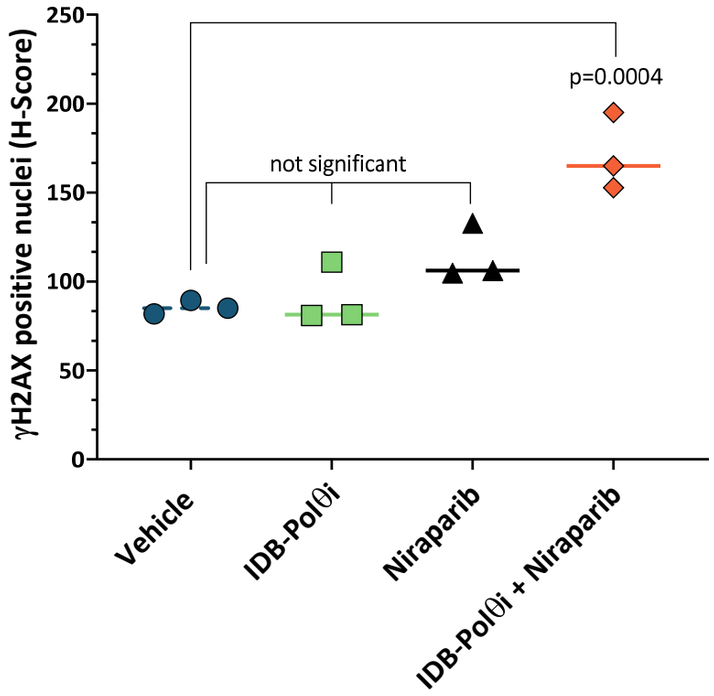
IDEAYA Polθ ATPase Inhibitors in Combination with niraparib induce DNA Damage resulting in Tumor Regression

DLD1 BRCA2-/- *in vivo* xenograft Study



IHC for γH2AX





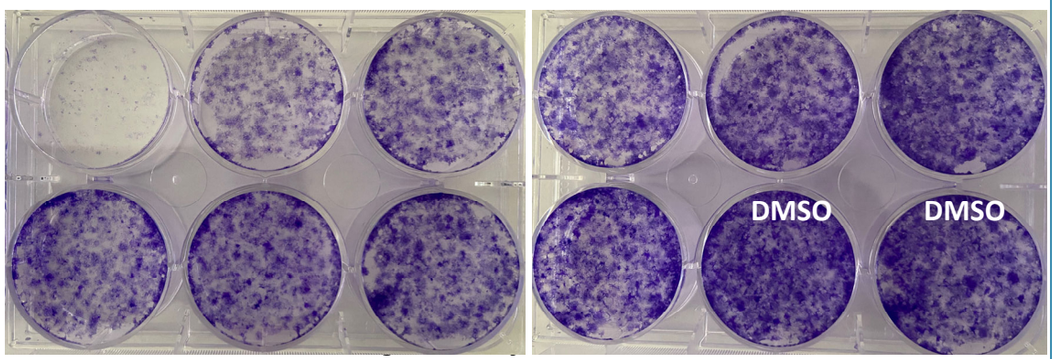
Regressions observed for all animals dosed with combination

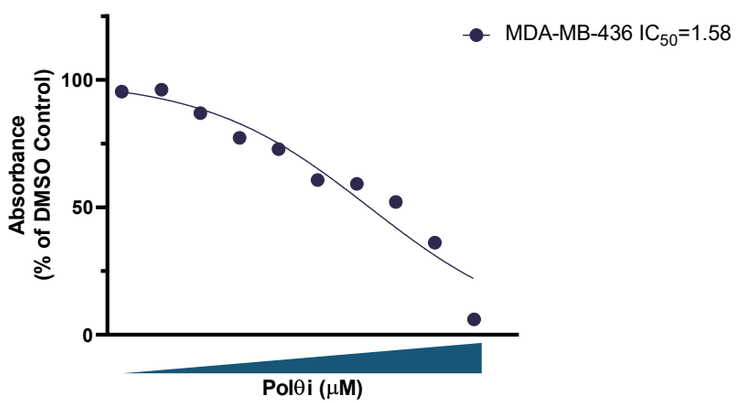
Polθi in combination with niraparib demonstrates significant enhancement of DNA Damage

Monotherapy and Combination TGI observed with IDEAYA Polθ ATPase Inhibitor and niraparib in MDA-MB-436 CDX Model

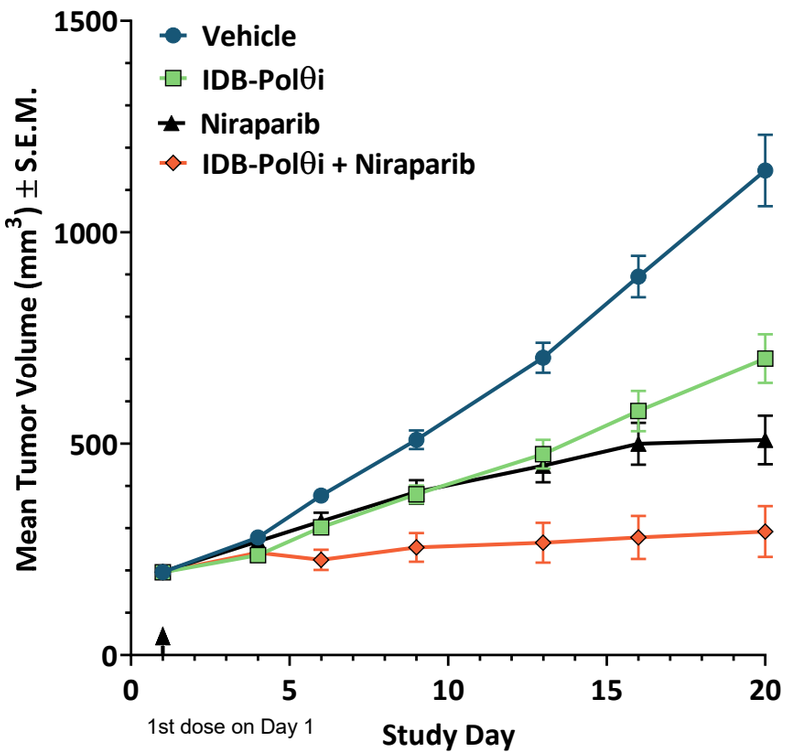
MDA-MB-436: endogenous BRCA1 mutated TNBC cell line

MDA-MB-436 identified as sensitive *in vitro*



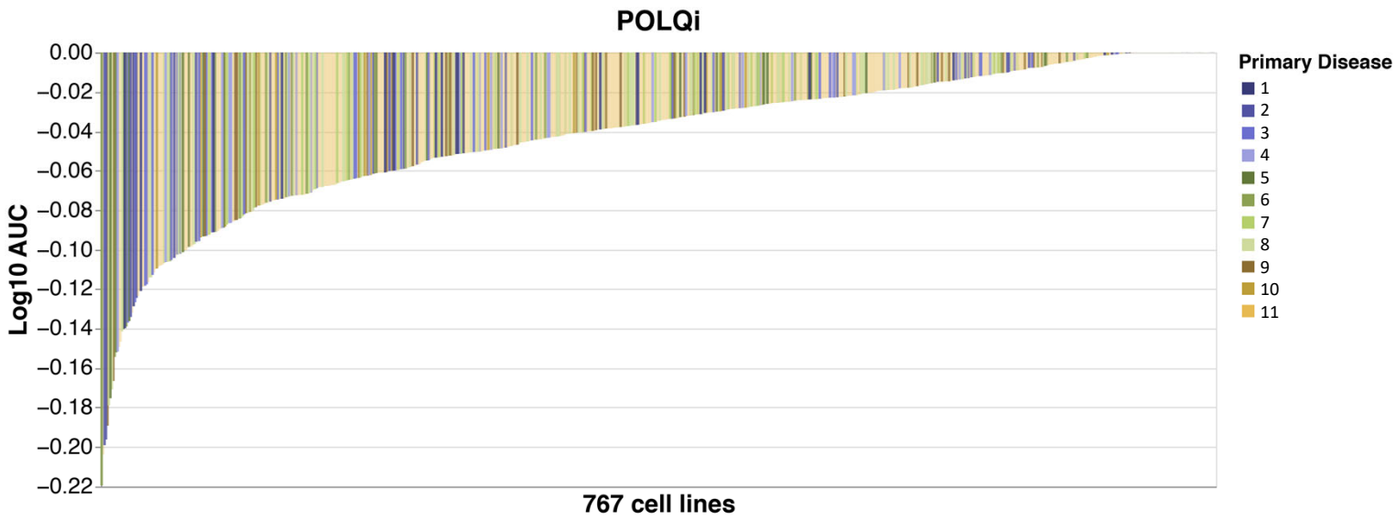


Monotherapy and Combination TGI with niraparib *in vivo*

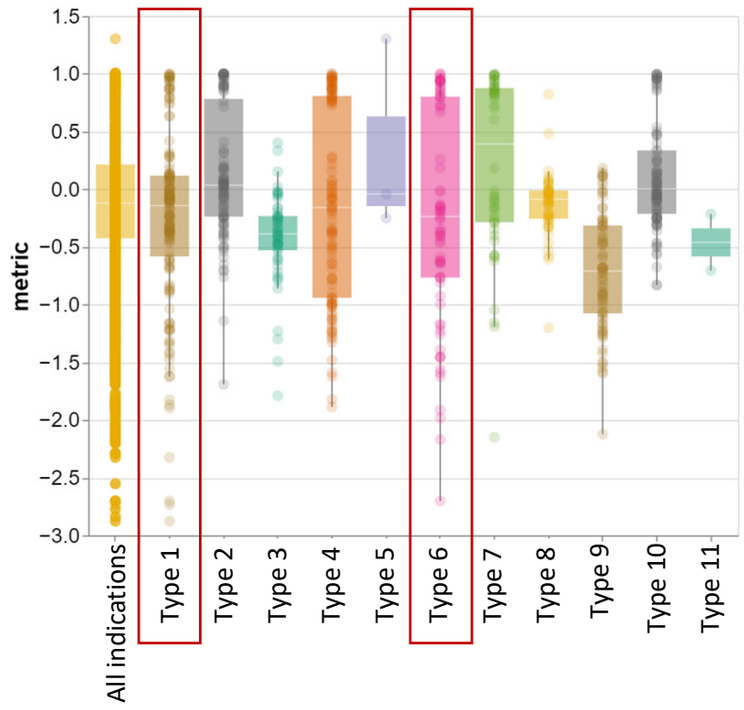


PRISM Screen Identifies Additional Cell Lines Sensitive to Single Agent IDEAYA Polθ ATPase Inhibitor

Sensitivity observed in a large set of *in vitro* Cell Models



Tumor Types 1 and 6 show Increased Sensitivity



Potential for Opportunity Expansion: Genomic and Proteomic analysis of Polθi-sensitive lines informs understanding of biomarker landscape with potential to expand target patient population

Pol Theta: Key Target in MMEJ DNA Damage Repair Pathway

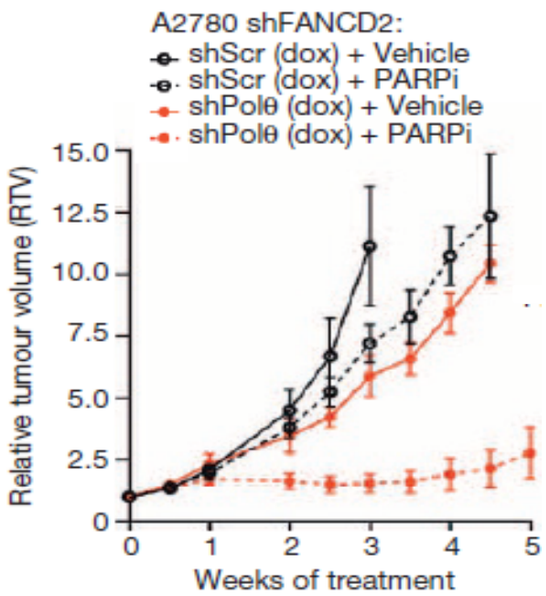
Pol Theta Clinical Considerations

Benjamin Schwartz, Ph.D. – Vice President, Head of Oncology Synthetic Lethality Research Unit
GlaxoSmithKline

Combination of PARPi and PolQi

Multiple mechanisms for efficacy

PARP and POLQ Synergy



Nature 2015, DOI: 10.1038/nature14184

Potentiate PARPi efficacy

- Inhibit DSB repair by MMEJ
- Dysregulate replication fork stabilization

PARPi + **PolQi**

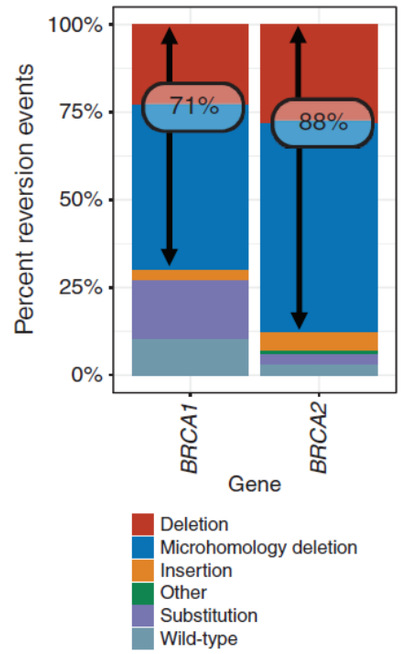
Overcome PARPi resistance

- Dysregulate replication fork stabilization

Prevent PARPi resistance

- Inhibit BRCA reversion mutation through MMEJ

BRCA Clinical Reversion Mechanisms



Cancer Res. 2020, DOI: 10.1158/2159-8290

PARG: Novel Target in Clinically Validated Pathway

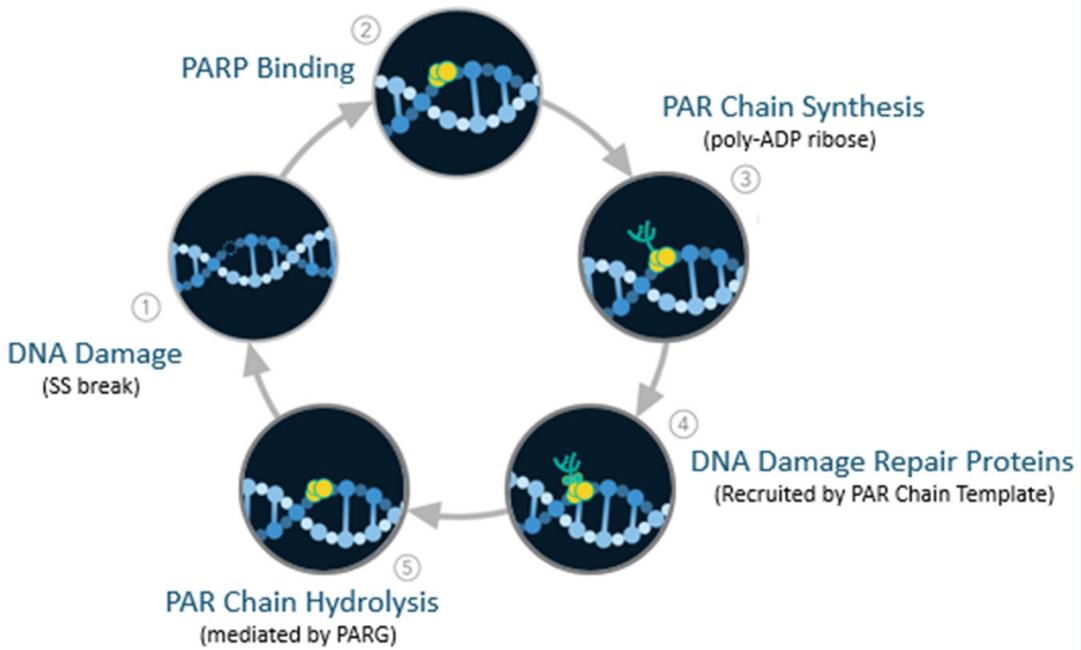
IDEAYA PARG Inhibitor Preclinical Program

Michael Dillon, Ph.D. – Senior Vice President, Chief Scientific Officer
IDEAYA Biosciences

PARG Synthetic Lethality Program

Novel Target in Clinically Validated Pathway

PARG Biology



PARG Function is Essential to DNA Repair

Poly(ADP-ribose) glycohydrolase (PARG) plays a pivotal role in the regulation of DNA repair mechanisms; acts in same pathway as PARP

In response to DNA damage, PARP uses NAD+ to make Poly(ADP-ribose) (PAR) at sites of damage. PARG is the primary hydrolase in PAR degradation completing the repair cycle

PAR is a post-translational modification that recruits DNA damage repair enzymes

Inhibition of PARG leads to a decrease in cellular NAD+ levels, decrease in active PARP recycling, and incomplete DNA SSB repair

PARPi and PARGi induce replication stress in different settings leading to apoptosis through different mechanisms

IDEAYA BIOSCIENCES

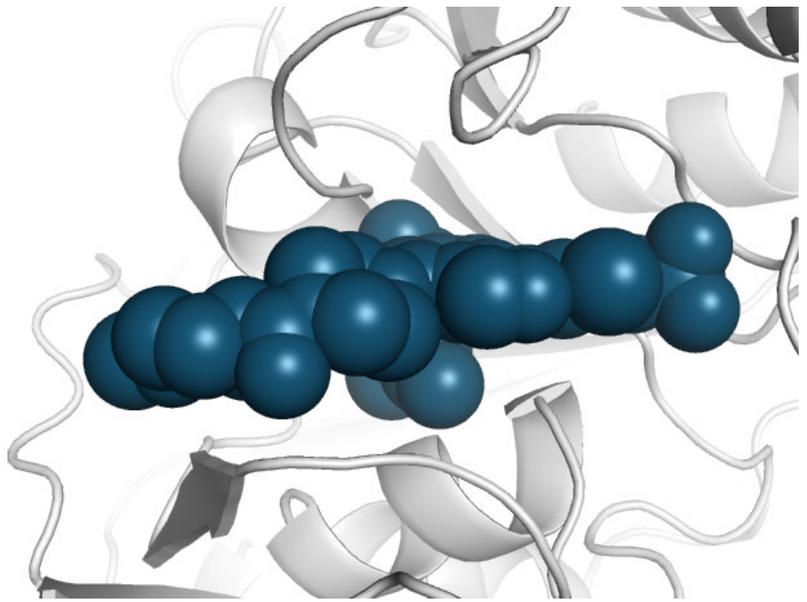
PARG Synthetic Lethality Program

Novel Target in Clinically Validated Pathway

PARG Program – Highlights

- Multiple potent cellularly active compounds demonstrate PD response – *in vitro* and *in vivo* PAR accumulation (PD)
- Multiple compounds demonstrate *in vivo* efficacy in defined biomarker-selected cell-lines derived xenograft (CDX) models
- Broad cell line screen identifies potential for opportunity expansion
- Targeting Development Compound Nomination in 2021

PARG Drug Discovery Program



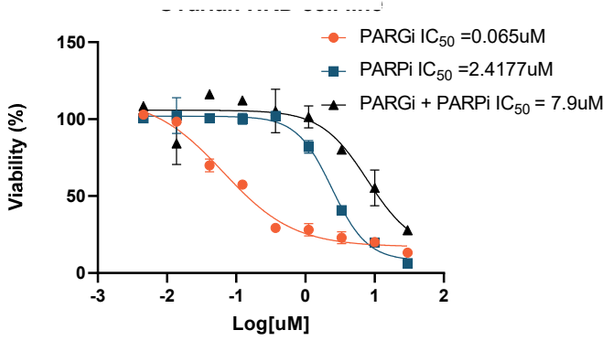
First in class lead optimization program guided by structure-based drug design

IDEAYA Data

Biomarker Selected *in vitro* and *in vivo* Models are Sensitive to IDB-PARGi

Differentiated activity to PARP inhibition in Ovarian Cancer Model

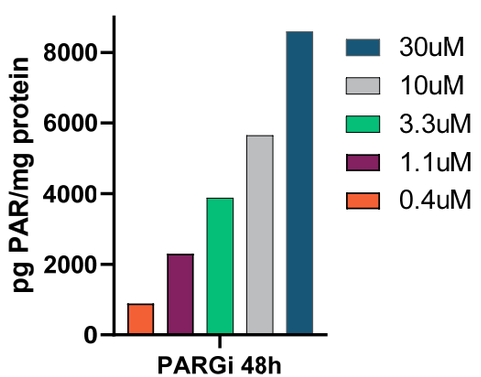
Ovarian Cancer HRD cell line *in vitro* Profile



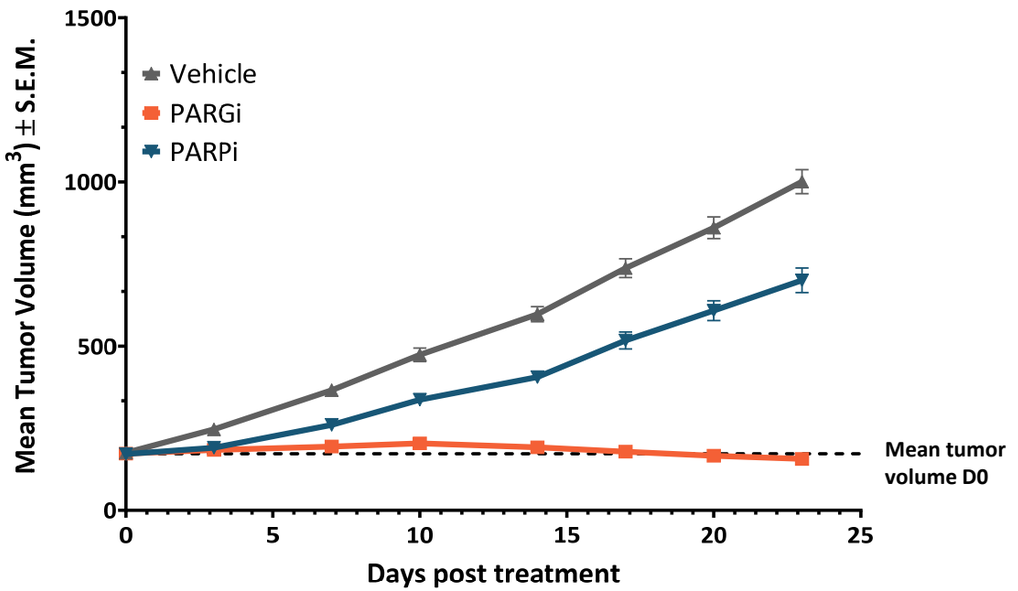
Consistent with an on target cellular mechanism of action, PARP1 inhibition (dosed at IC_{10}) antagonizes PARG inhibition

Dose-dependent poly-PAR accumulation with increasing exposure to IDB-PARGi in PARGi-sensitive HRD cell lines

Data further confirms an on-target cellular MOA of PARGi



Ovarian Cancer HRD cell line *in vivo* CDX Model

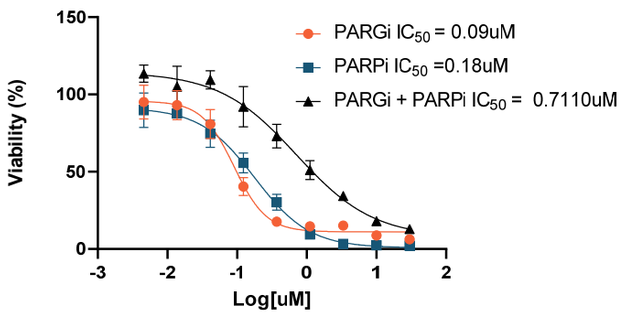


IDB-PARGi demonstrates enhanced tumor growth inhibition (TGI) relative to a PARP inhibitor, and tumor regression

Biomarker Selected *in vitro* and *in vivo* Models are Sensitive to IDB-PARGi

Differentiated activity to PARP inhibition in Gastric Cancer Model

Gastric Cancer HRD cell line *in vitro* Cell Profile



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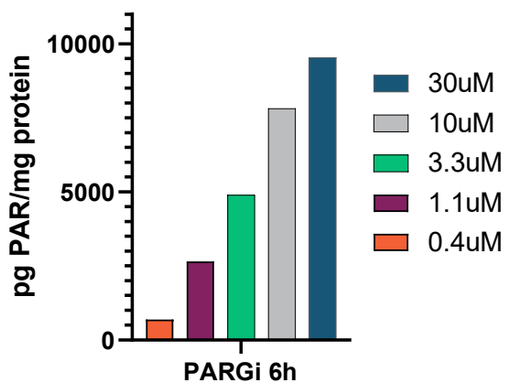
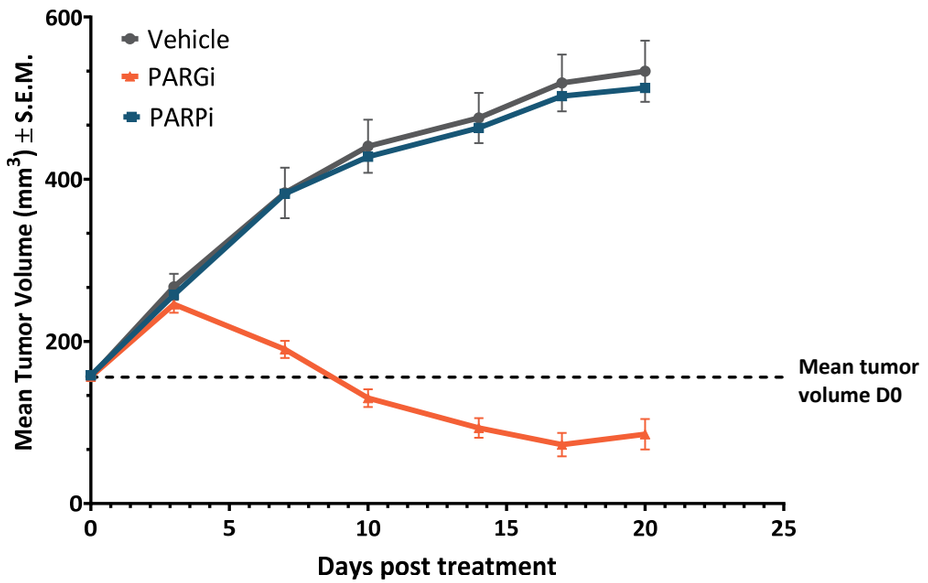


Gastric Cancer HRD cell line *in vivo* CDX Model

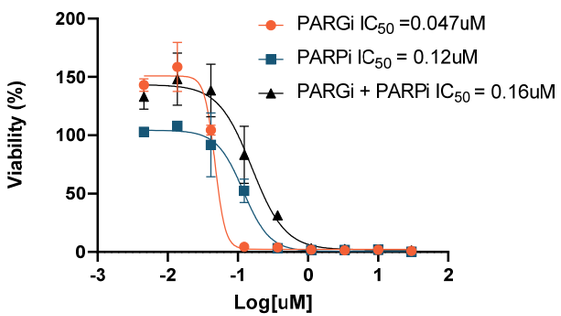


IDB-PARGi demonstrates enhanced tumor growth inhibition (TGI) and tumor regression in PARPi refractory setting

Biomarker Selected *in vitro* and *in vivo* Models are Sensitive to IDB-PARGi

Differentiated activity to PARP inhibition in Breast Cancer Model

Breast Cancer HRD cell line *in vitro* cell Profile



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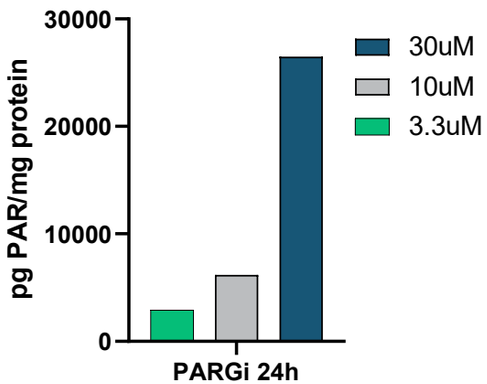
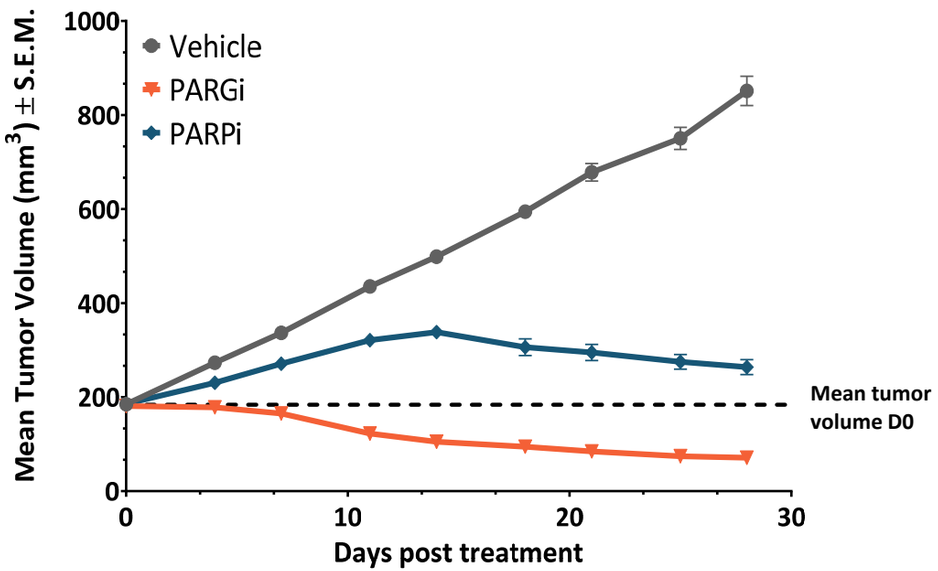


Breast Cancer HRD cell line *in vivo* CDX Model

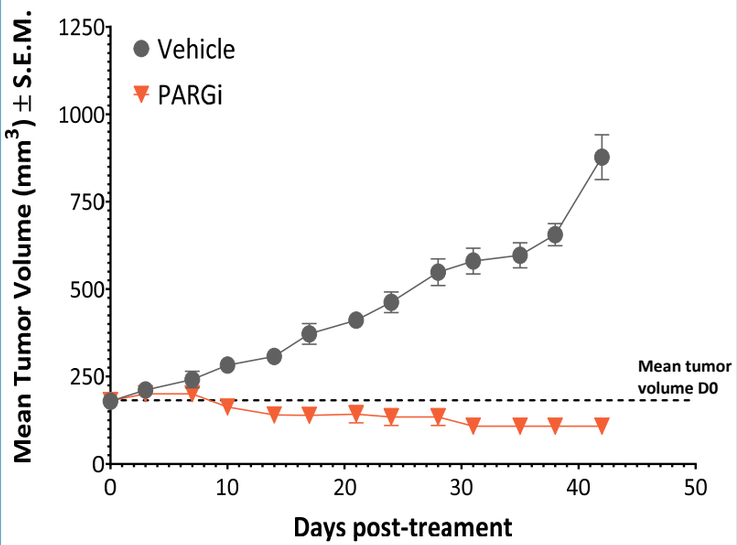


IDB-PARGi demonstrates enhanced tumor growth inhibition (TGI) relative to a PARP inhibitor, and tumor regression

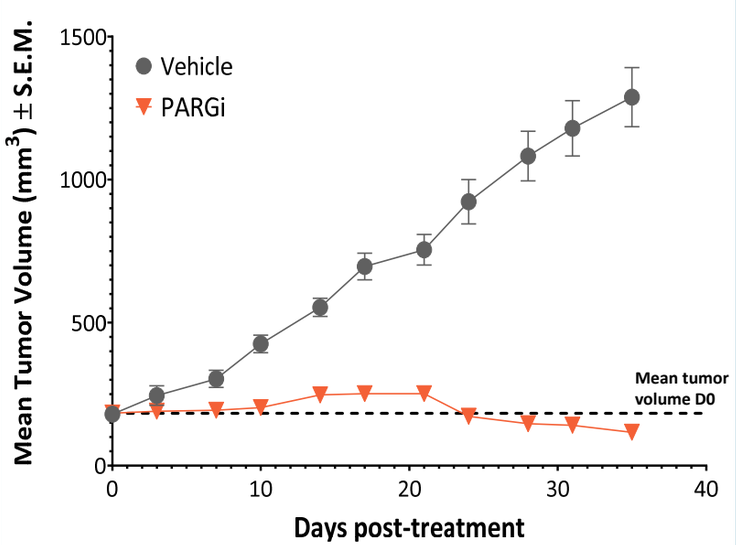
IDEAYA PARGi shows Robust TGI in Breast PDX Models

Monotherapy Tumor Regressions observed across Multiple Breast PDX Models

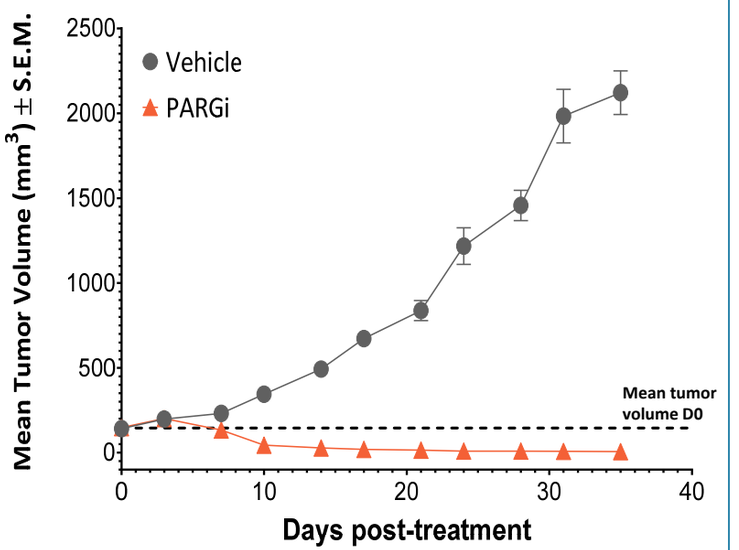
Breast Cancer PDX Model 1



Breast Cancer PDX Model 2



Breast Cancer PDX Model 3



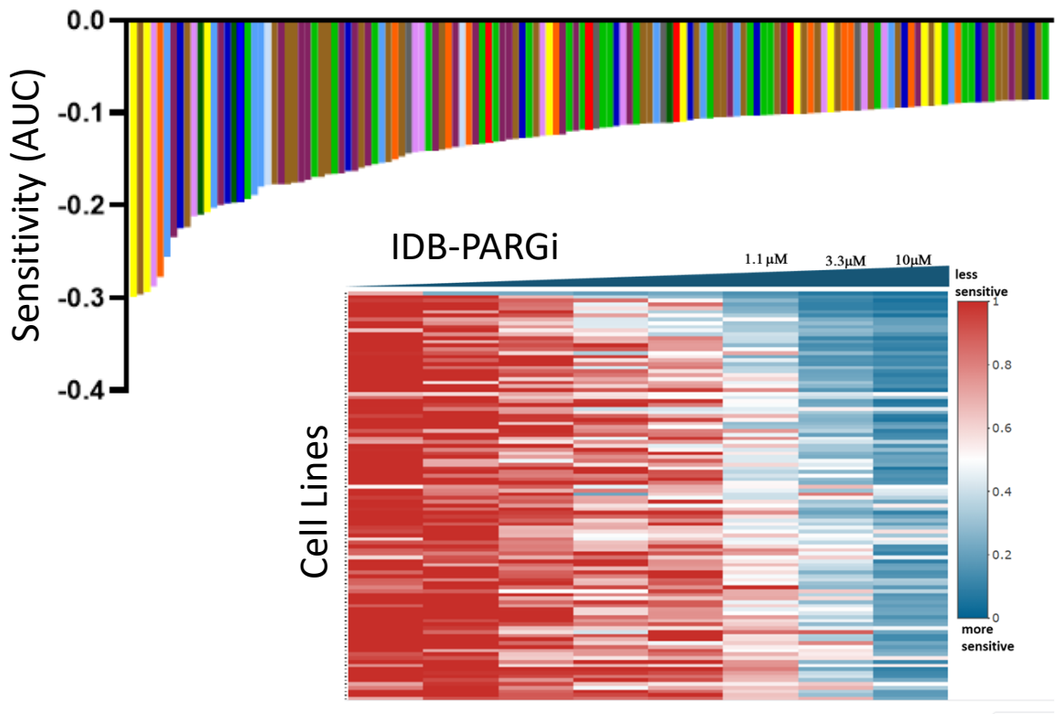
Evaluation of IDB-PARG in Patient Derived Xenograft (PDX) models in Breast Cancer

- Tumor Regressions (≥ 100% TGI) observed in multiple PDX models with defined genetic and subtyping profiles
- Enhanced Tumor Growth Inhibition (TGI) relative to Niraparib (PARPi) observed in some models

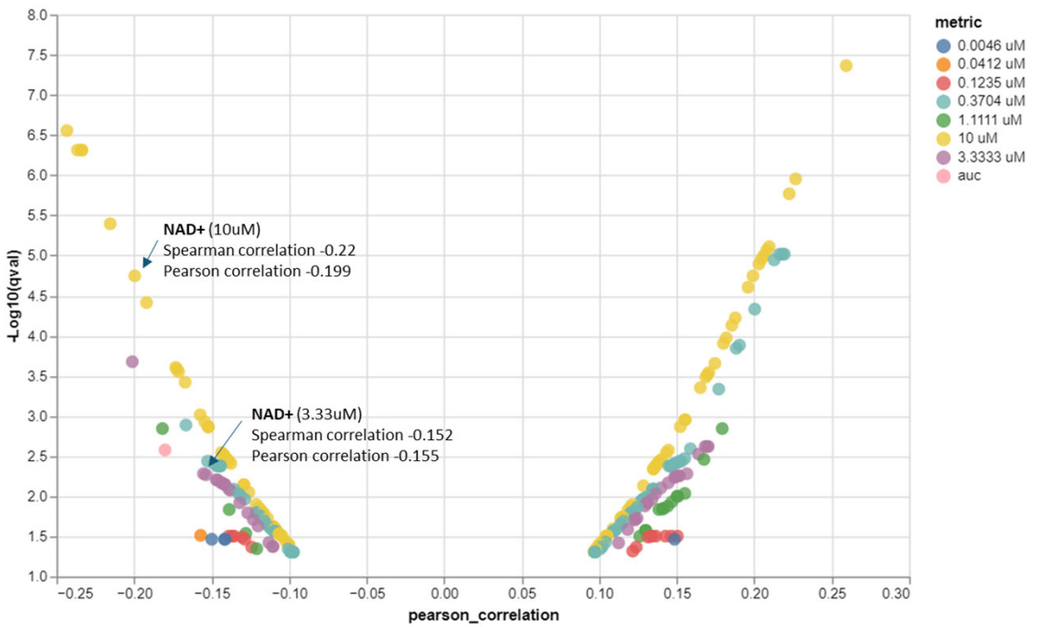
PRISM Screen Identifies Additional Tumor Lineages and Indications Sensitive to Single Agent IDEAYA PARG Inhibitor

Various models demonstrate sensitivity to IDEAYA PARGi

Cell Lines (n=~800)



Low NAD levels associated with PARGi Sensitivity



- NAD levels inversely correlate with IDB-PARGi sensitivity consistent with PARG MOA and suggesting important contributions of metabolic pathways
- Additional biomarker discovery ongoing with potential for opportunity expansion

IDEAYA Analysis / PRISM Screen - Broad DepMAP Consortium

PARG: Novel Target in Clinically Validated Pathway

IDEAYA PARG Translational Biology

Mark Lackner, Ph.D. – Senior Vice President, Head of Biology and Translational Sciences
IDEAYA Biosciences

PARG Patient Selection Biomarkers

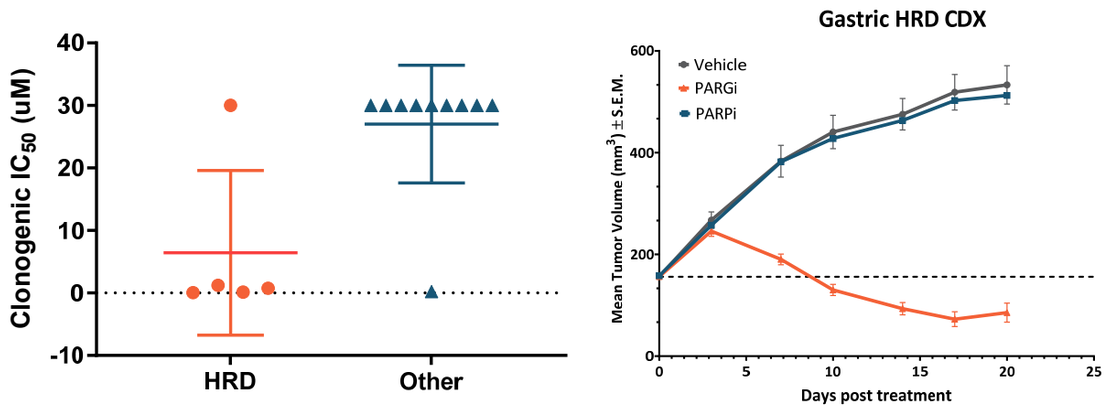
Multiple Possibilities for Clinical Stratification

Homologous Recombination Deficiency (HRD)

Cell lines with HRD phenotype are sensitive to PARG inhibition in clonogenic assays [1]

PARGi has activity in PARPi resistant xenografts and PDx models, suggesting path to enrolling PARP refractory patients

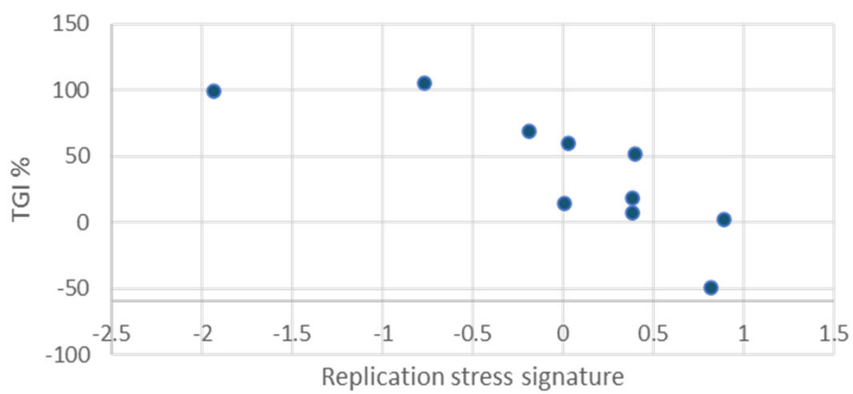
[1] Abed et al IDEAYA AACR Poster 2021



Replication Stress Signature

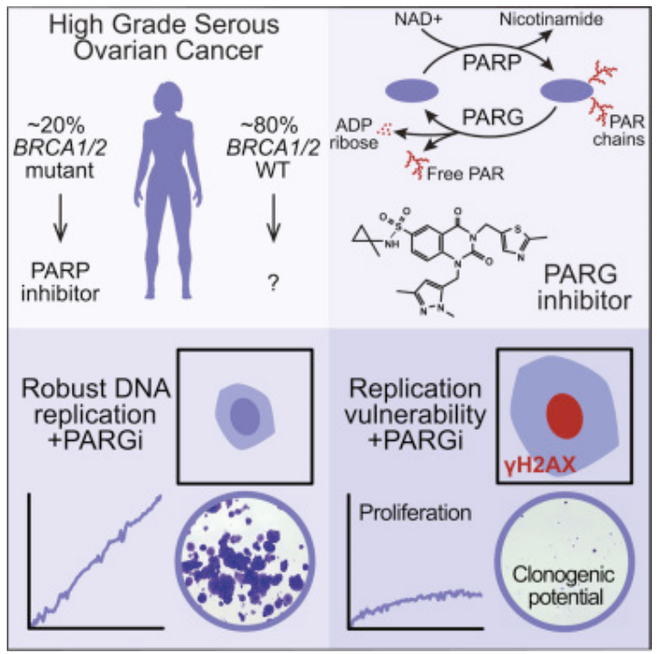
PARGi response in PDx models can be predicted using a pre-defined replication stress signature that has been previously described [2]

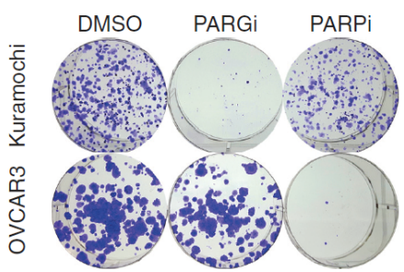
[2] Cancer Cell Vol 35 (2019): 519-533.



Clinical opportunity in PARP inhibitor Refractory and Resistant Cancer

Unmet need remains in large proportion of patients with HRD malignancies





PARPi and PARGi often show mutually exclusive activity

Provides rationale for PARGi in PARP resistant population

PARP Inhibitor	Ovarian	Pancreas	Breast	Prostate
Olaparib	Maintenance after response to platinum* or mBRCA with 3+ prior lines (ORR 34%)	Maintenance after benefit to platinum (ORR 23%)	mBRCA HER2 neg. pretreated (ORR 52%)	HRD pretreated mCRPC (ORR 33%)
Rucaparib	Maintenance after response to platinum* or mBRCA with 2 prior lines (ORR 54%)			mBRCA pretreated mCRPC (ORR 44%)
Niraparib	Maintenance after response to platinum* or HRD with 3+ prior lines (ORR 24%)			
Talazoparib			mBRCA HER2 neg. largely 1+ prior line (ORR 50%)	

*12m PFS rates in range of approximately 50-70%

Pillay et al Cancer Cell 2019

Closing Remarks and Analyst Q&A

Yujiro Hata – President and Chief Executive Officer
IDEAYA Biosciences

Closing Remarks - Inaugural IDEAYA SL Investor Day

Industry Leading Potential 1st-in-Class Clinical Stage SL Pipeline

- **Establish IDEAYA as the industry leader in MTAP-deletion (~15% of solid tumors)**
  - IDE397 in Phase 1, potential First-in-Class monotherapy / Best-in-Class MAT2A inhibitor
  - Advancing 2nd MTAP-SL program (target not disclosed), with potential to be combinable with IDE397
- **2 Development Candidates targeted in 2021**
  - PARG, wholly-owned (novel HRD biomarker); Pol-Theta, GSK partnership (HRD & PARP combo)
- **Advance next generation of potential 1st-in-class SL programs**
  - Significant progress toward potential First-in-Class WRN helicase inhibitor (hMSI)
  - Early portfolio of SL targets beyond HRD population undergoing validation

Technological Investment Priorities to Enhance SL Platform Capabilities

- **Data Explosion**
  - Become industry leader in SL bioinformatics / machine learning target and biomarker discovery
- **Therapeutic Modalities**
  - Enhance SL drug discovery platform, including protein degraders, to pursue additional potential First-in-Class SL targets
- **Liquid Biopsy**
  - Apply non-invasive patient selection for “loss-of-function” mutations, and novel PD markers

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