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

# IDEAYA Biosciences

## Improving Lives Through Transformative Precision Medicines

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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 | | | | | | | |

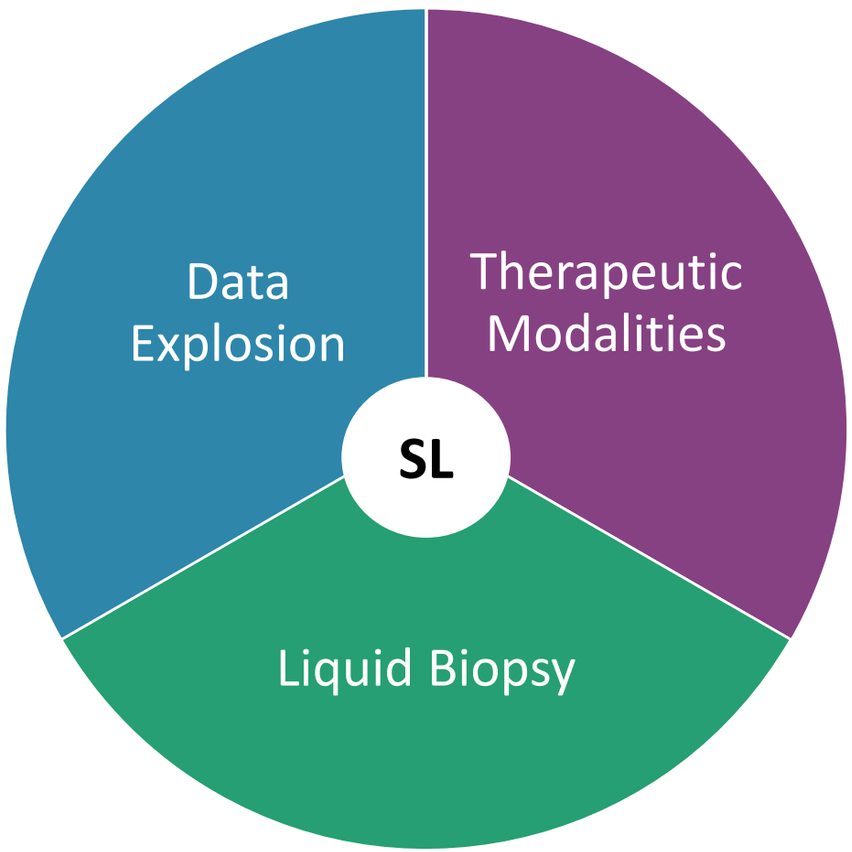
(1) Pursuant to GSK Collaboration, Option and License Agreement: MAT2A and WRN: 50/50 US Profits + ex-US Royalties; Polθ: Global Royalties
(2) Pursuant to CRUK Evaluation, Option and License Agreement, with ongoing Collaborative Research; IDEAYA controls all Commercial Rights
(3) Pursuant to Pfizer Clinical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

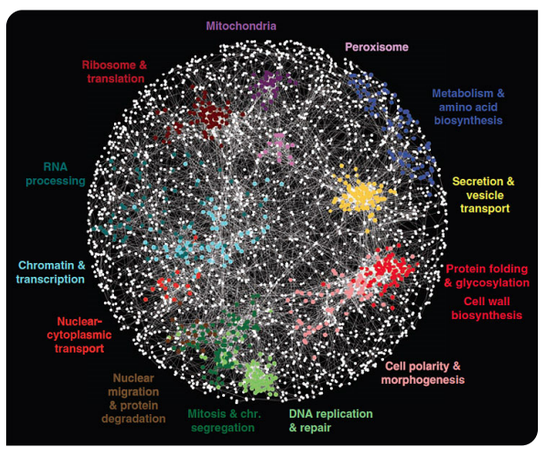
Convergence of Advances in Informatics, Drug Discovery and Translational Biology



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

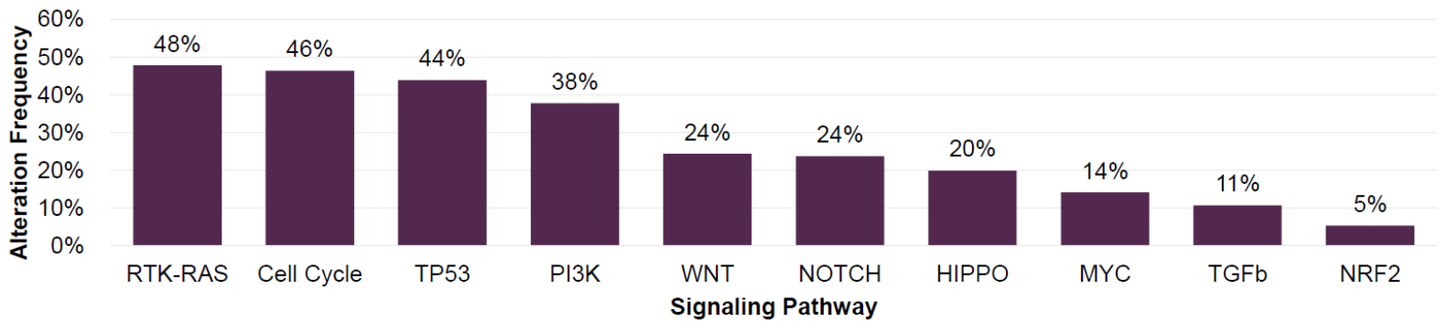
## ~30k Gene Mutations and Opportunity to Drug "Loss of Function" Mutations

***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***



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# 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

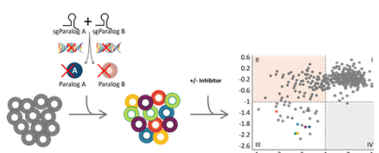
### DepMap Consortium

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

depmap | Cancer Dependency Map

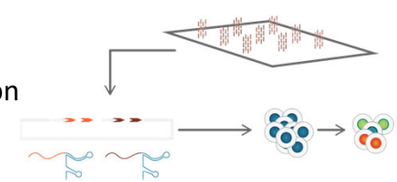
### PAGEO™ Paralog Screens

- 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



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# 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

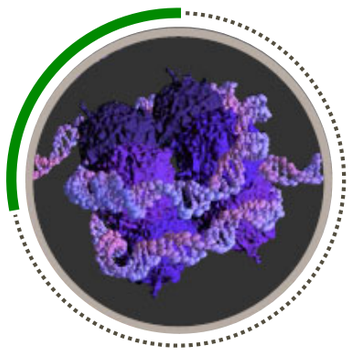
Aiming to maximize survival through transformational medicines and combinations

First-in-class medicines

Combination therapy

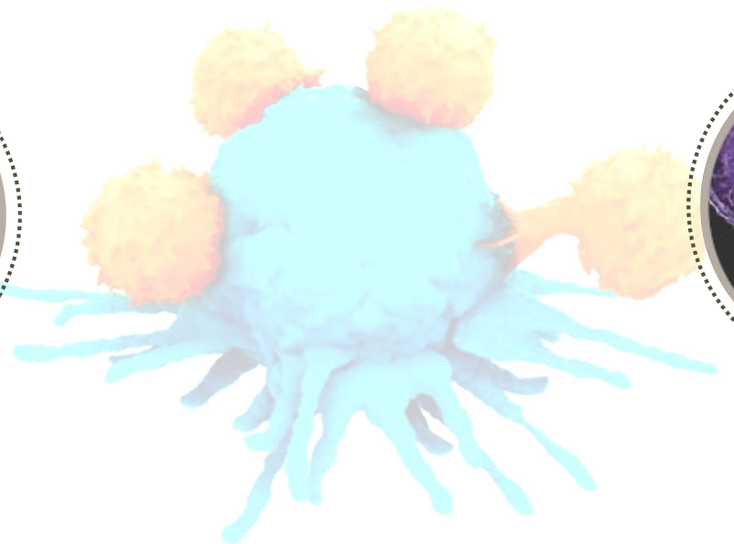
- Reprogram cancer cells
- Stimulate anti-tumor immunity
- Cells as medicines

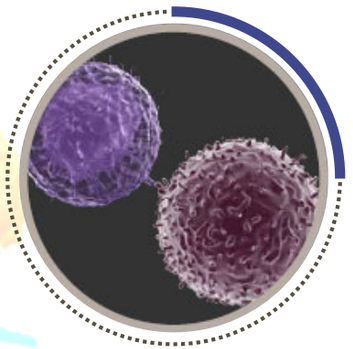
## GSK Pipeline



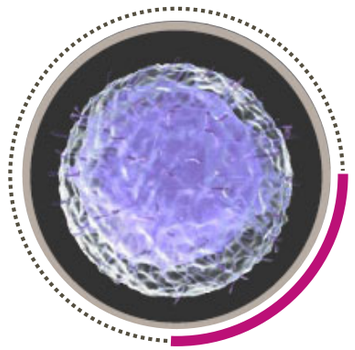
Cancer epigenetics

Synthetic lethality





Immuno-oncology



Oncology cell therapy

# Oncology Synthetic Lethality

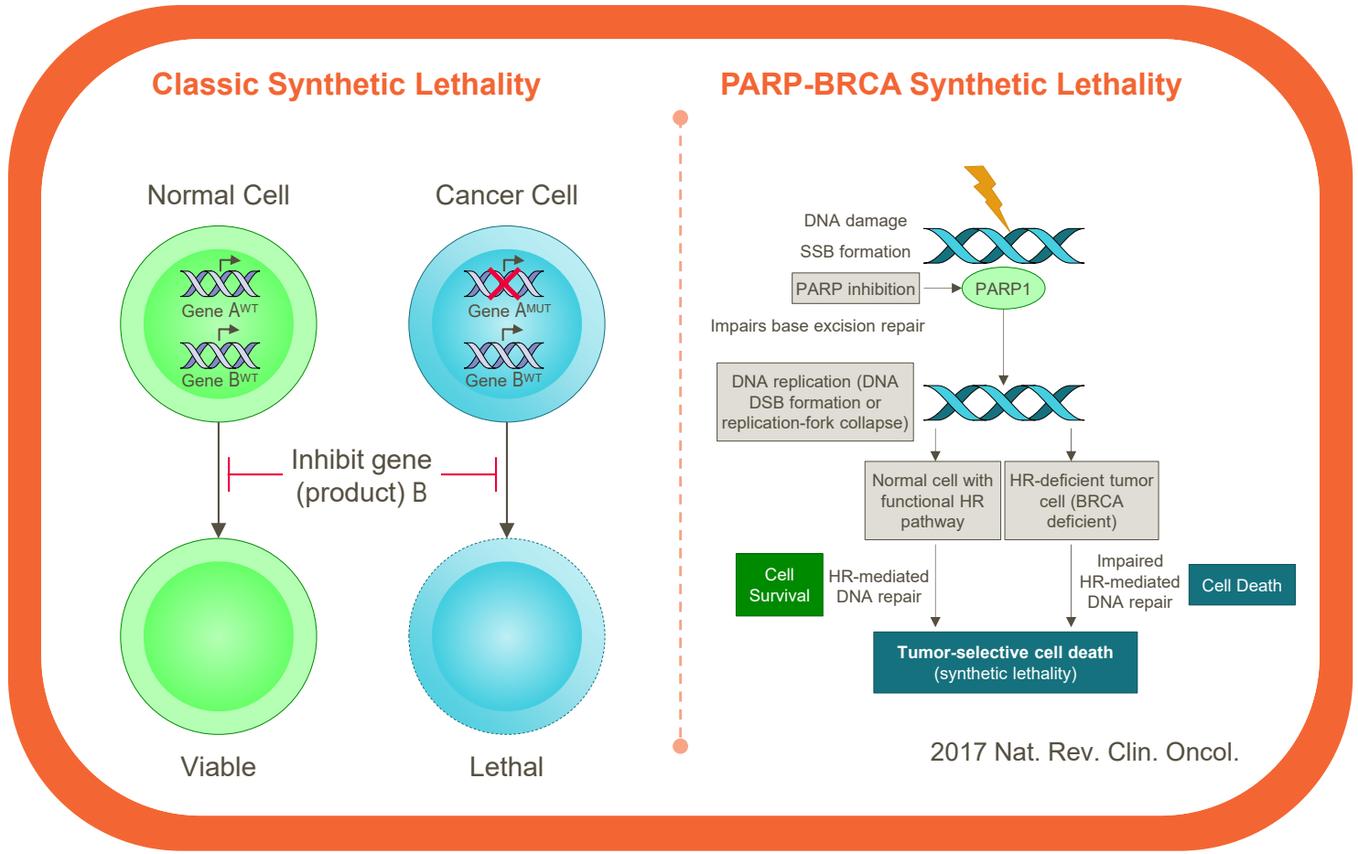
## Discovery of novel oncology targets

### 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)

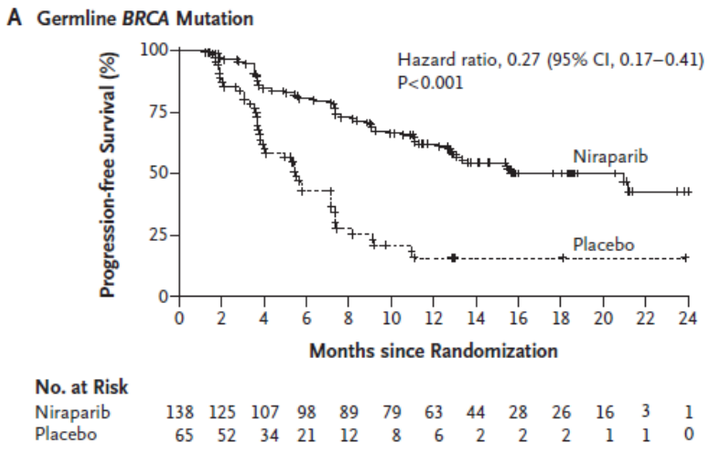


# Oncology Synthetic Lethality

## Why GSK & Other Companies are Investing Now

### Clinical Validation (PARP Inhibitors)

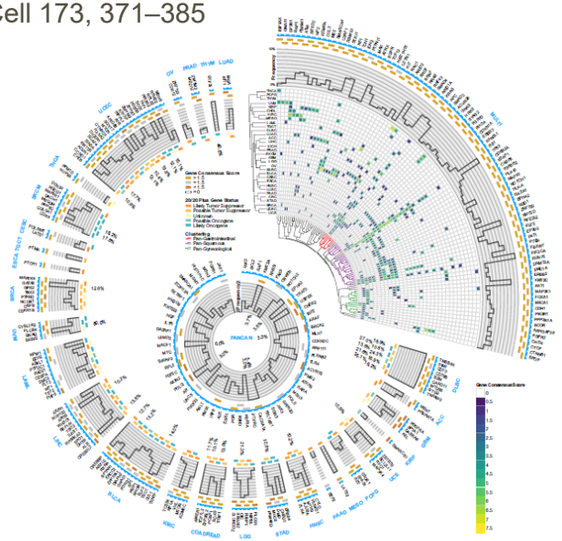
NOVA Clinical Trial




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

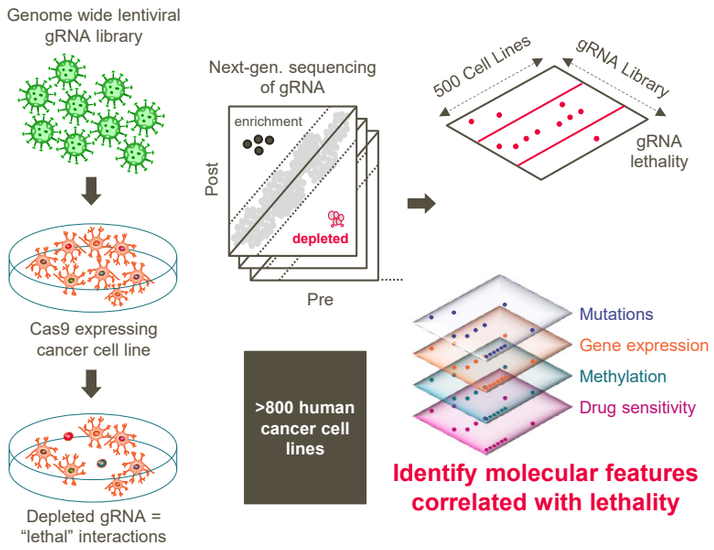
### Maturation of Tumor Clinicogenomics

2018, Cell 173, 371–385



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

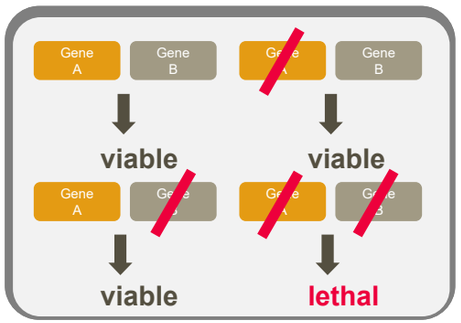
### Genome Wide Cancer Lethality Screens




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**

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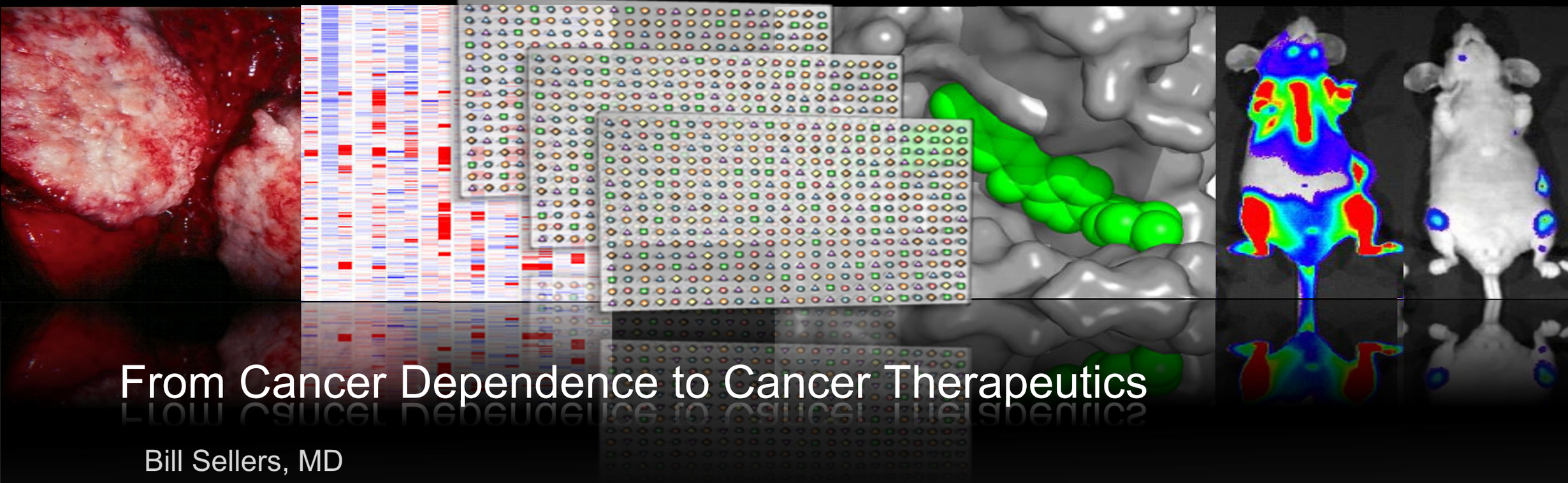
- Close collaboration on all assets
- Integrated discovery teams for WRN & POLQ
- Synergy seeking with GSK targeted and IO clinical assets

# 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

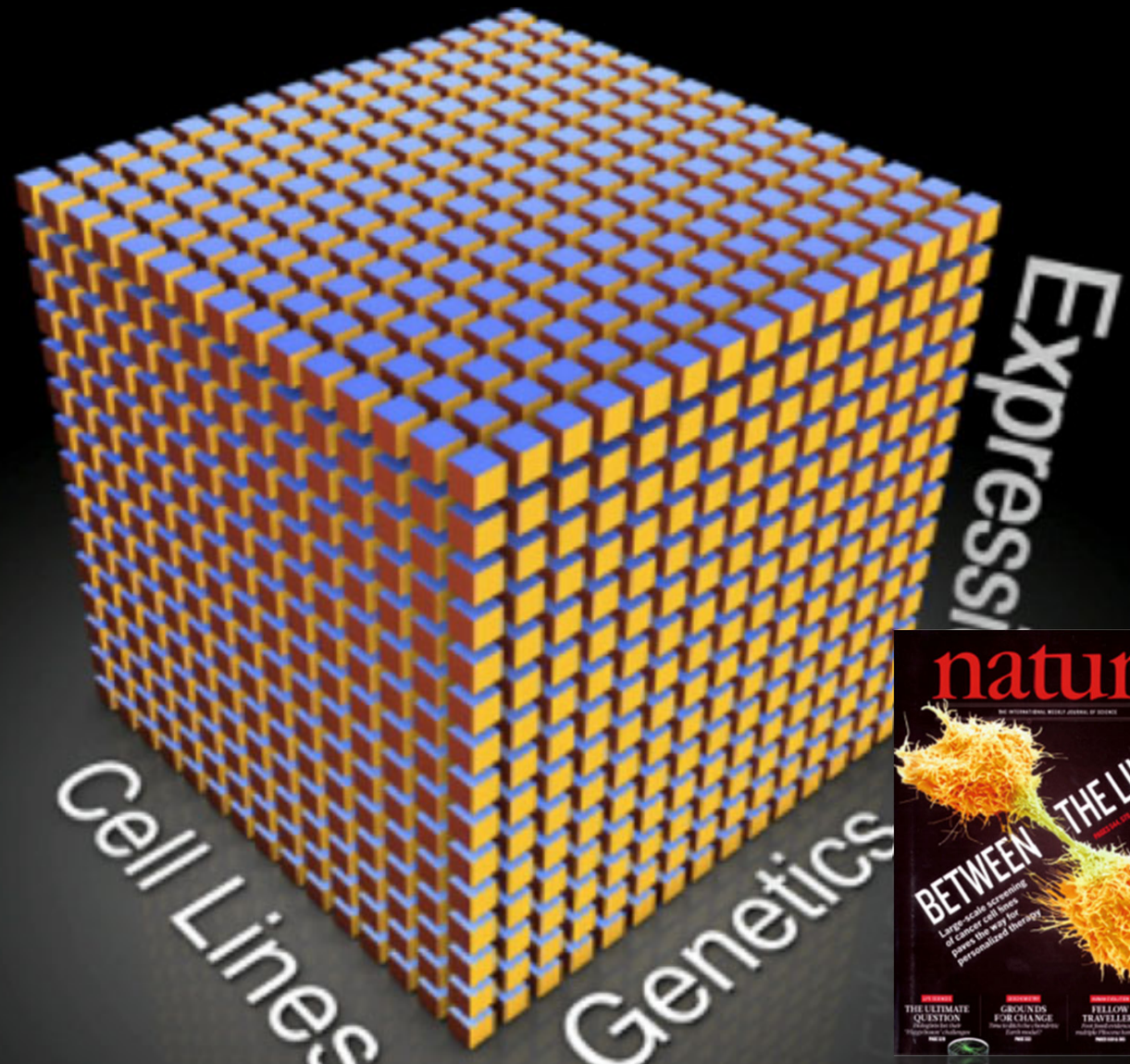
# The Cell Line Encyclopedia

## 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?



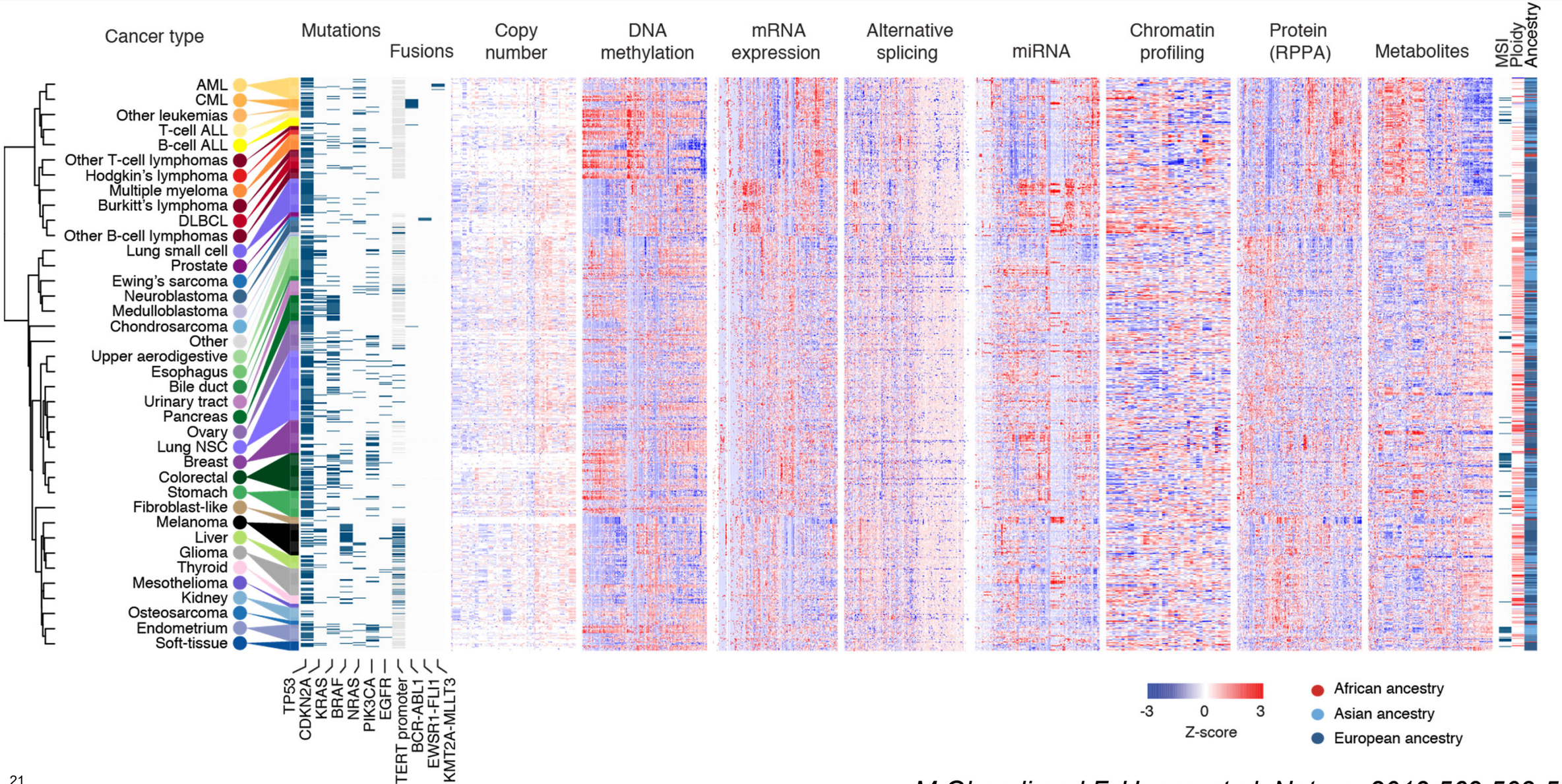




*Broad-Novartis Collaboration*

*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*

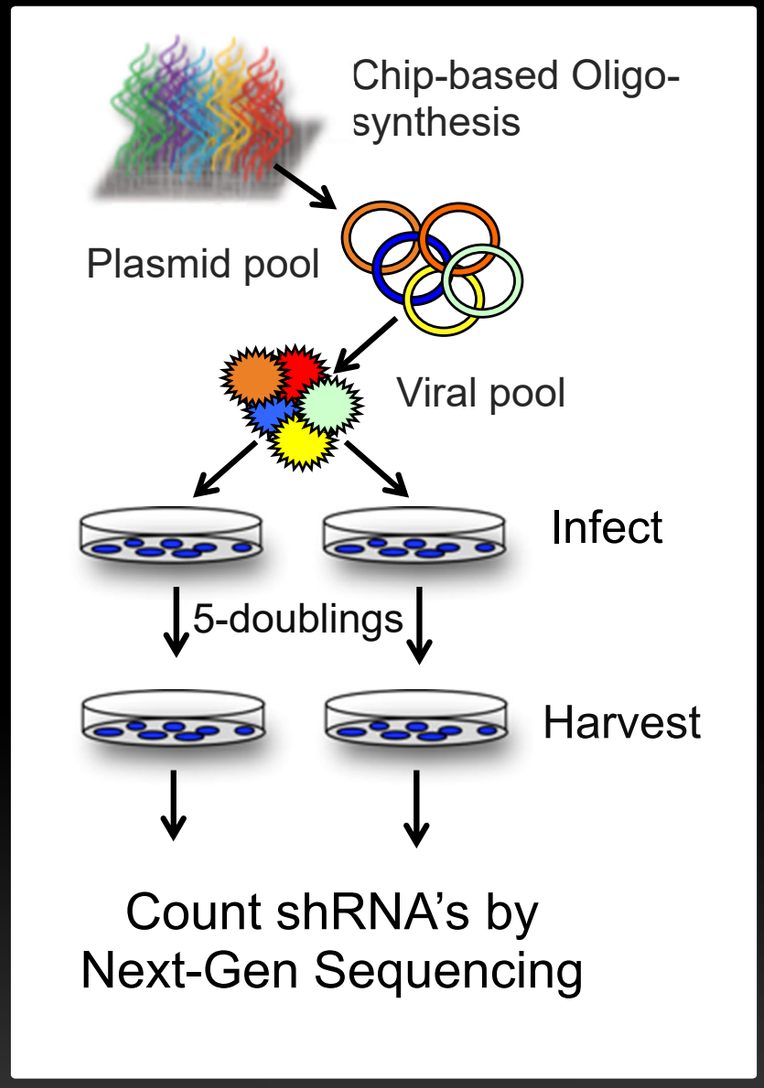
# DRIVE: Deep RNAi Interrogation of Viability Effects

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

What is the contextual basis for such dependencies?

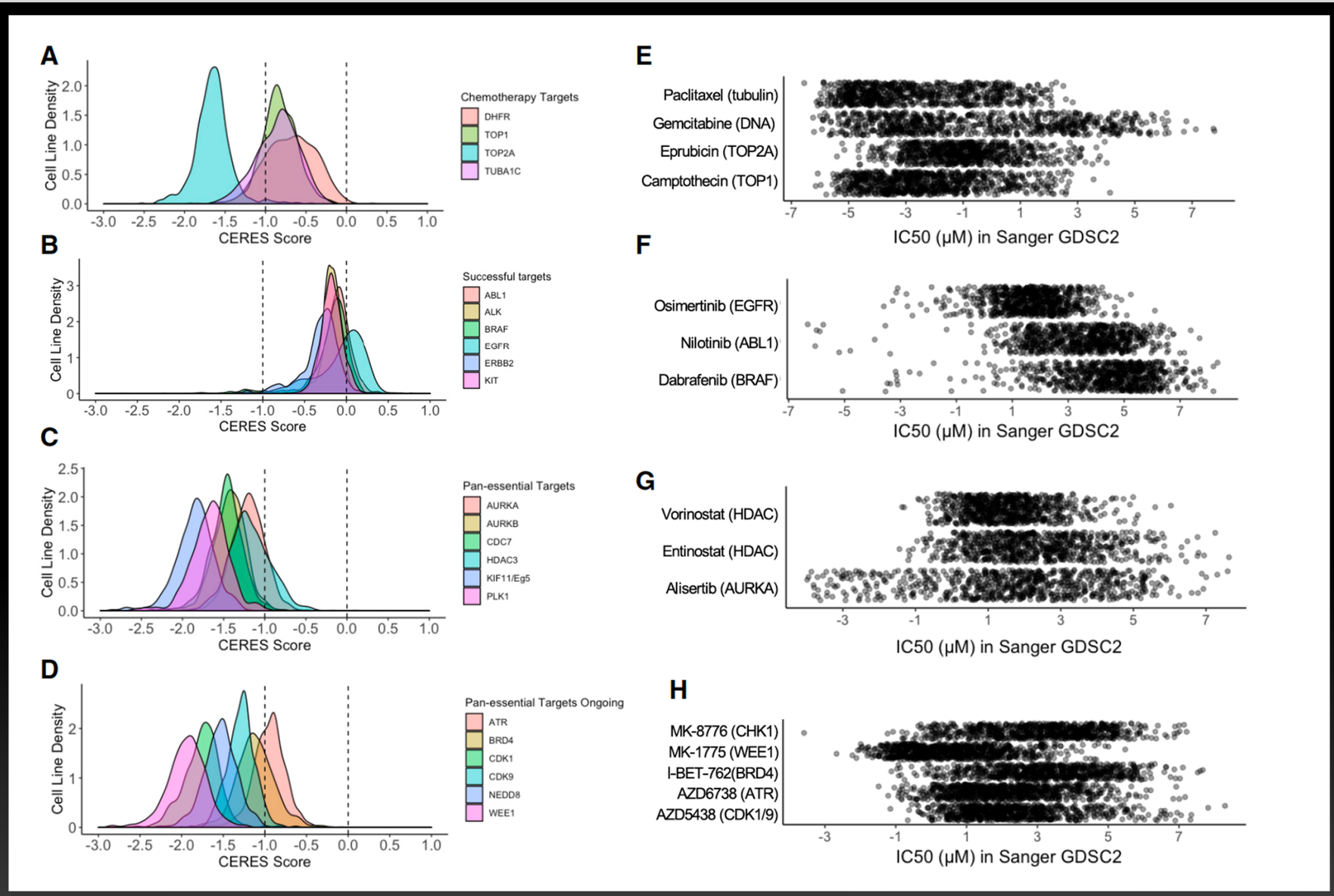
Functional Genomic Approaches:
Project DRIVE: 7,800 genes, 20 shRNAs per gene

DepMap: Whole Genome, 4 sgRNAs per gene



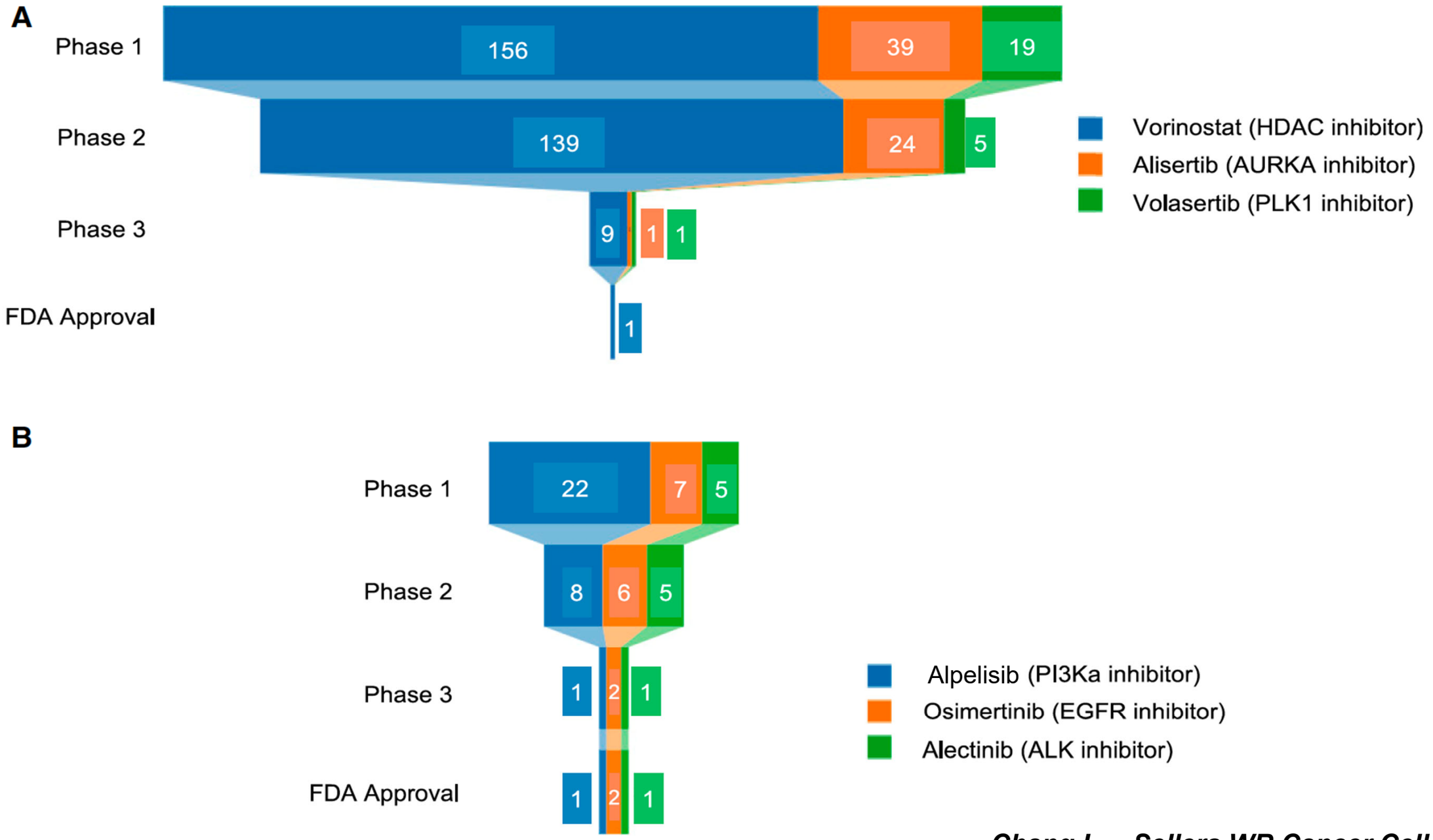

*McDonald et al. Cell. 2017 170:577-592*

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





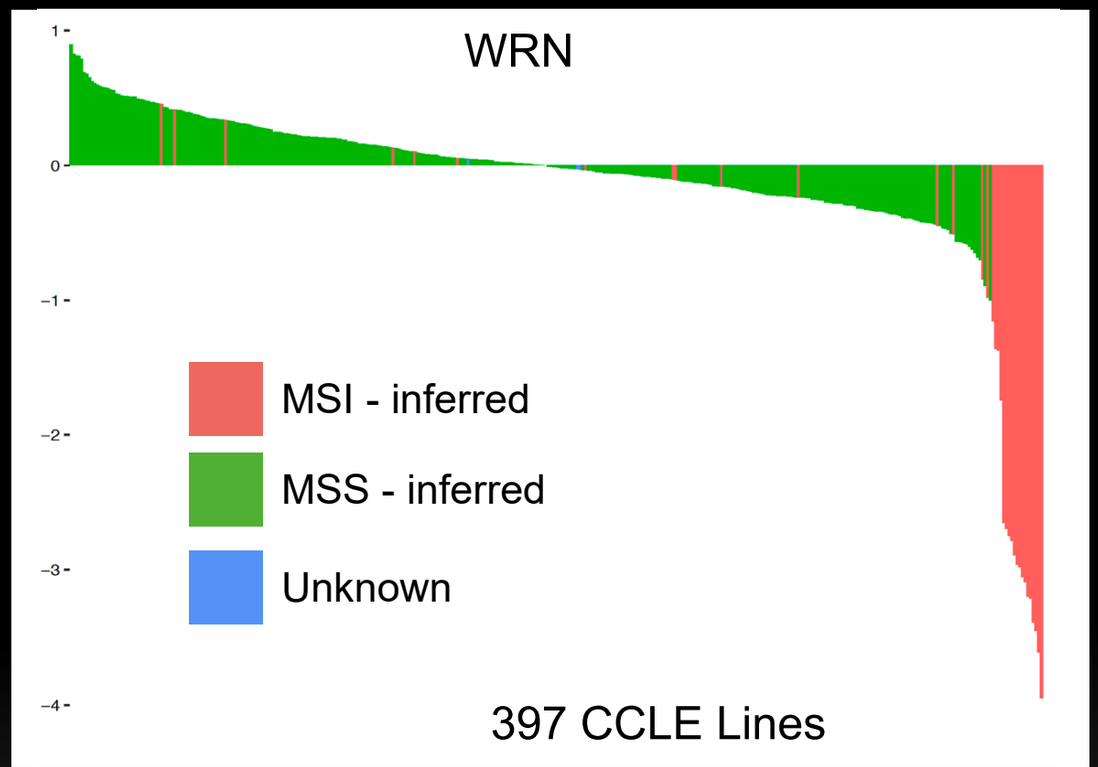

***Chang L….Sellers WR*** *Cancer Cell 2021*

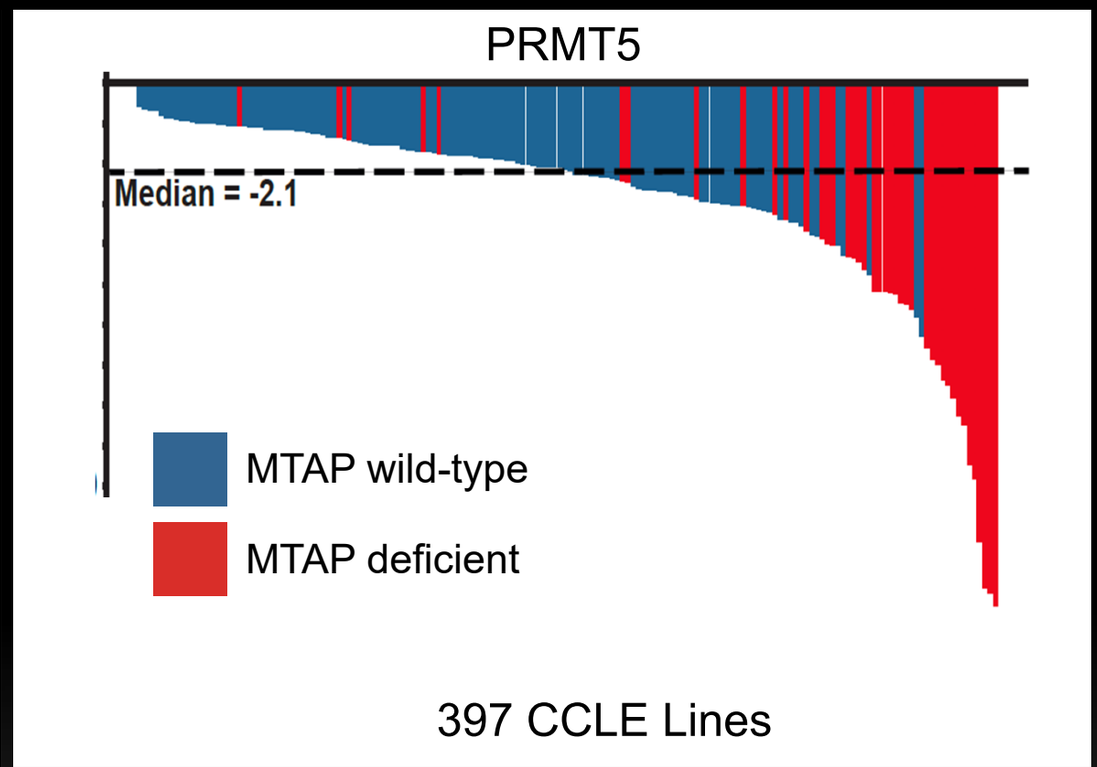





***Chang L….Sellers WR Cancer Cell 2021***

# New cancer dependencies from single-gene perturbations



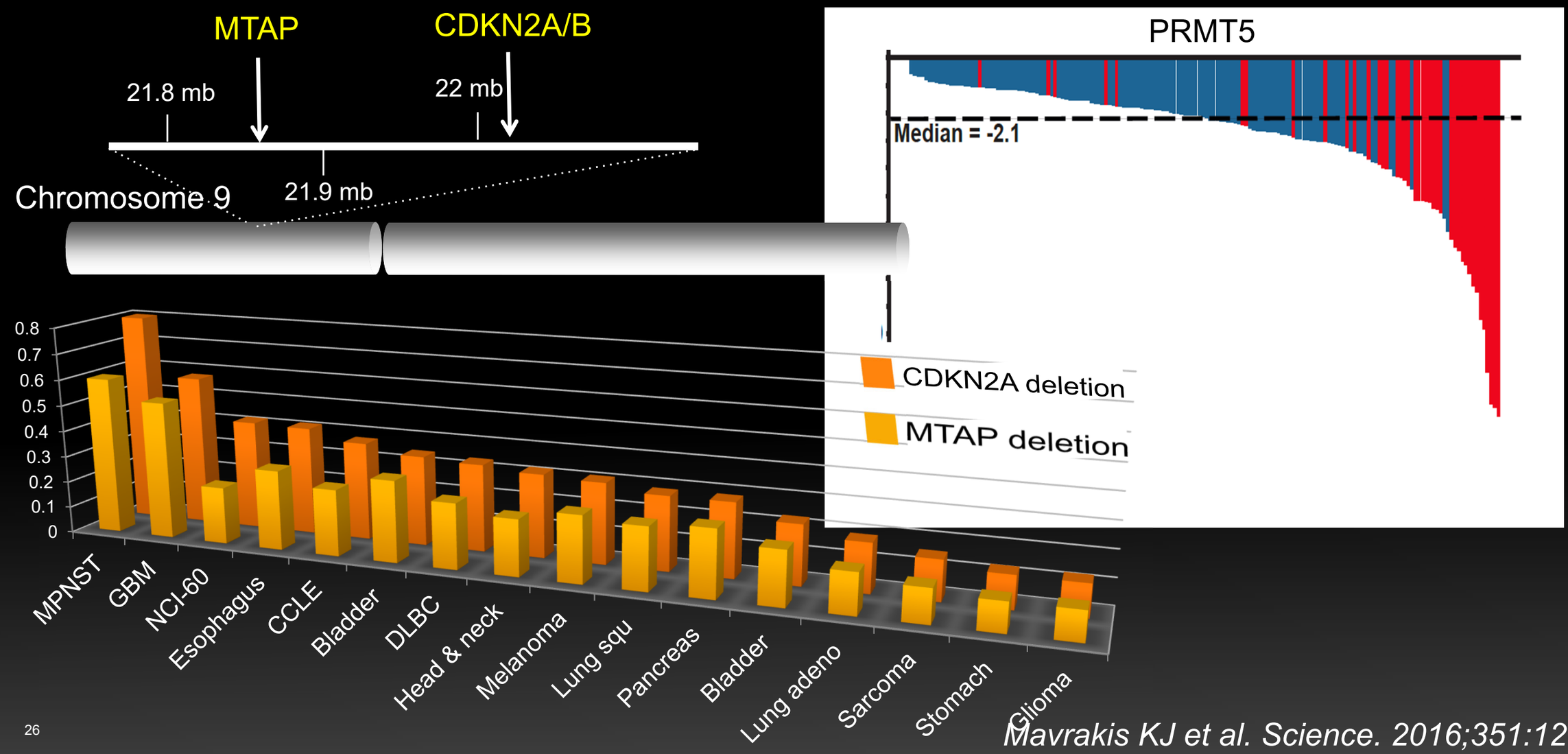






*Chan EM, et al. Nature. 2019;568:551-6*

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

# MTAP and CDKN2A are frequently co-deleted

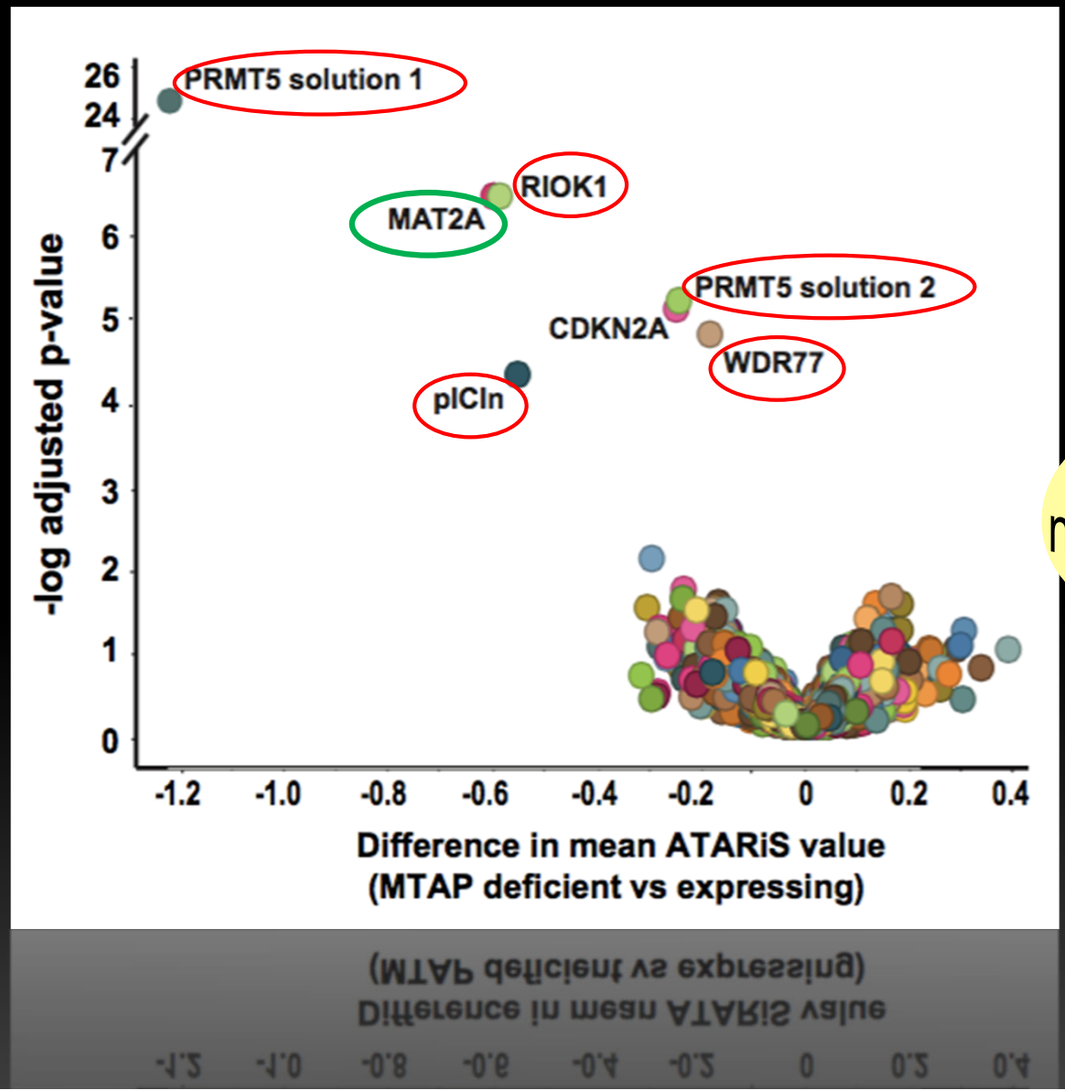


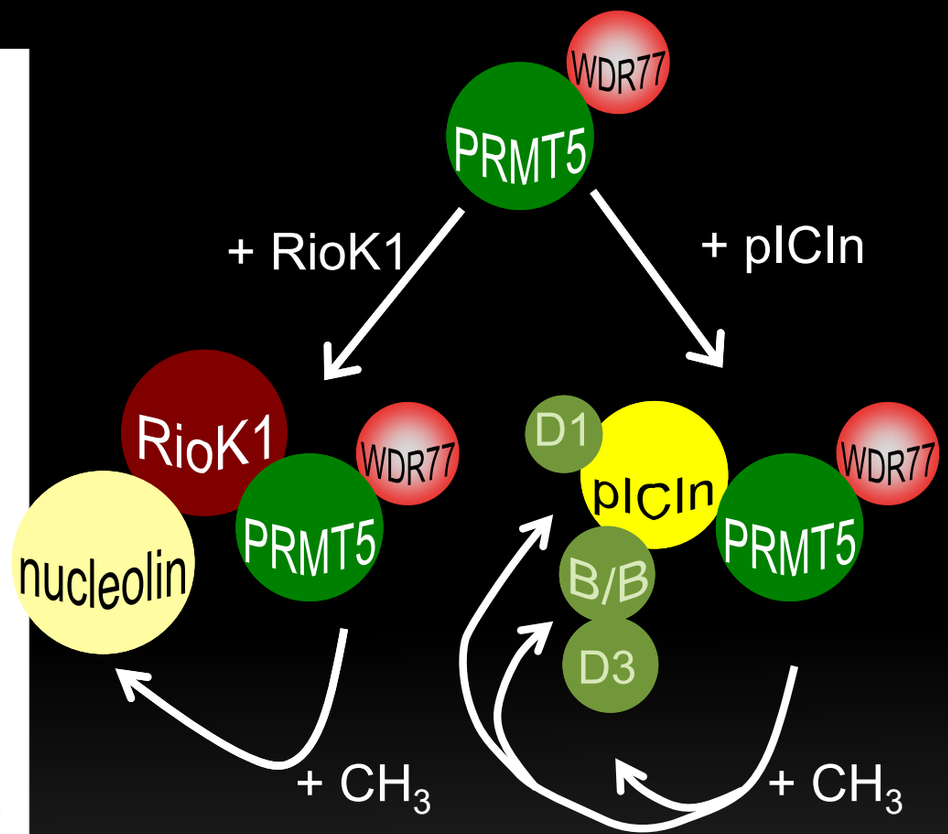



*Mavrakis KJ et al. Science. 2016;351:1208-13*

# MAT2A and PRMT5 methylosome are synthetic lethal with MTAP deletion

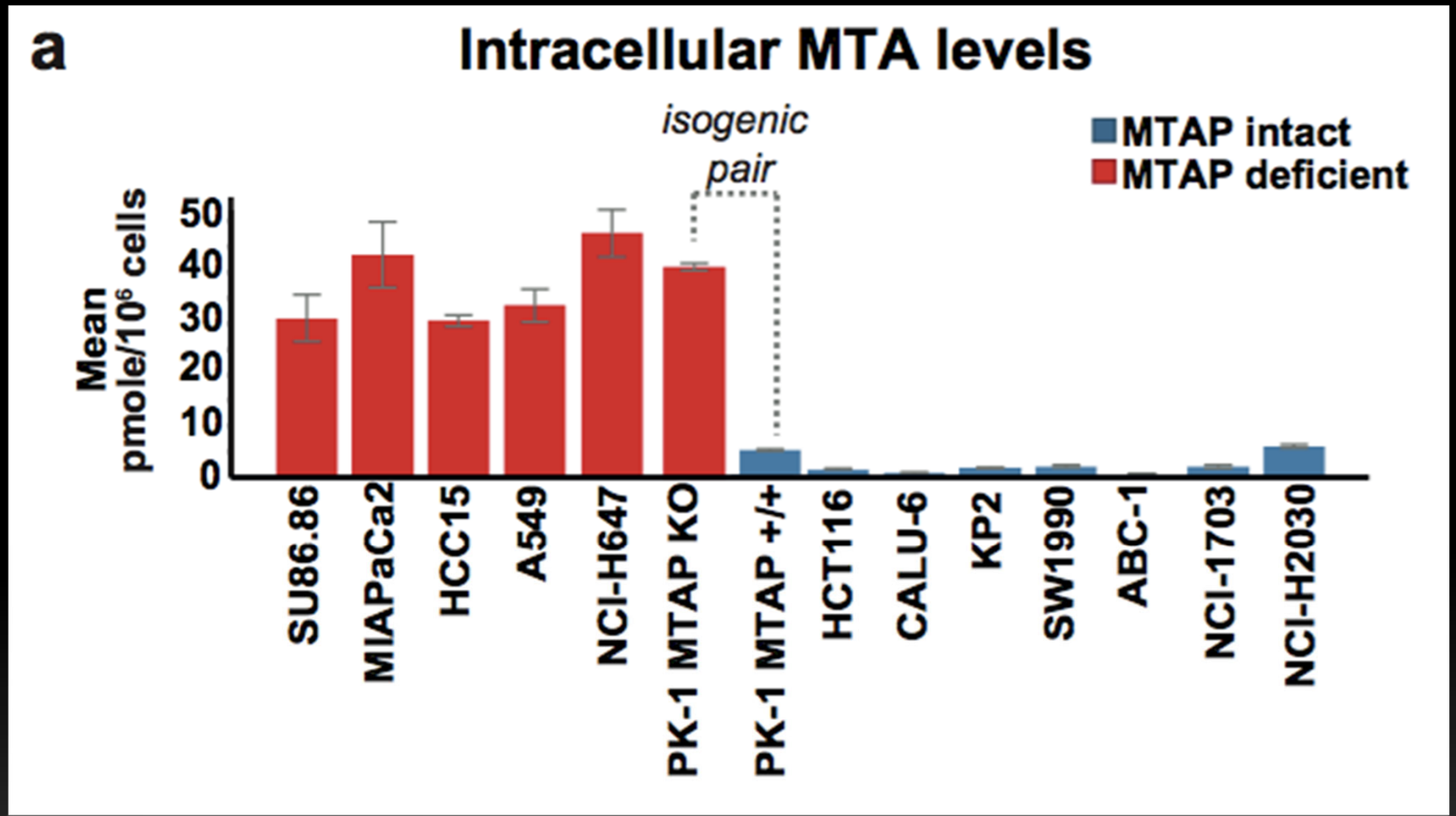
Directly compare MTAP$^{del}$ vs MTAP$^{wt}$ cells for shRNA sensitivity




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

# MTAP loss leads to substantial increases in MTA

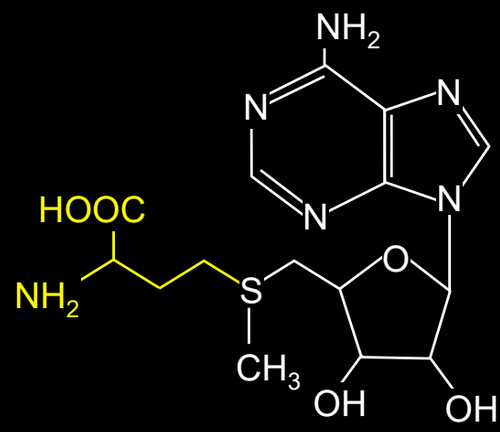





*Mavrakis KJ et al. Science. 2016;351:1208-13*

# Is MTA a competitive inhibitor of HMTs?

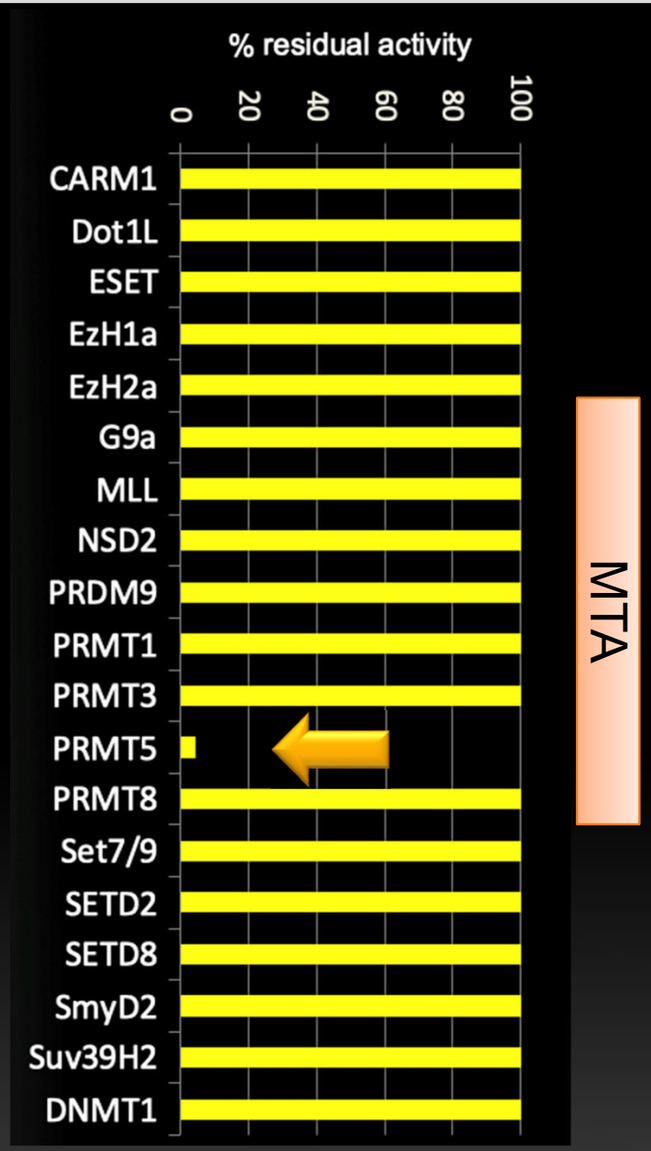

Methylthioadenosine
(MTA)

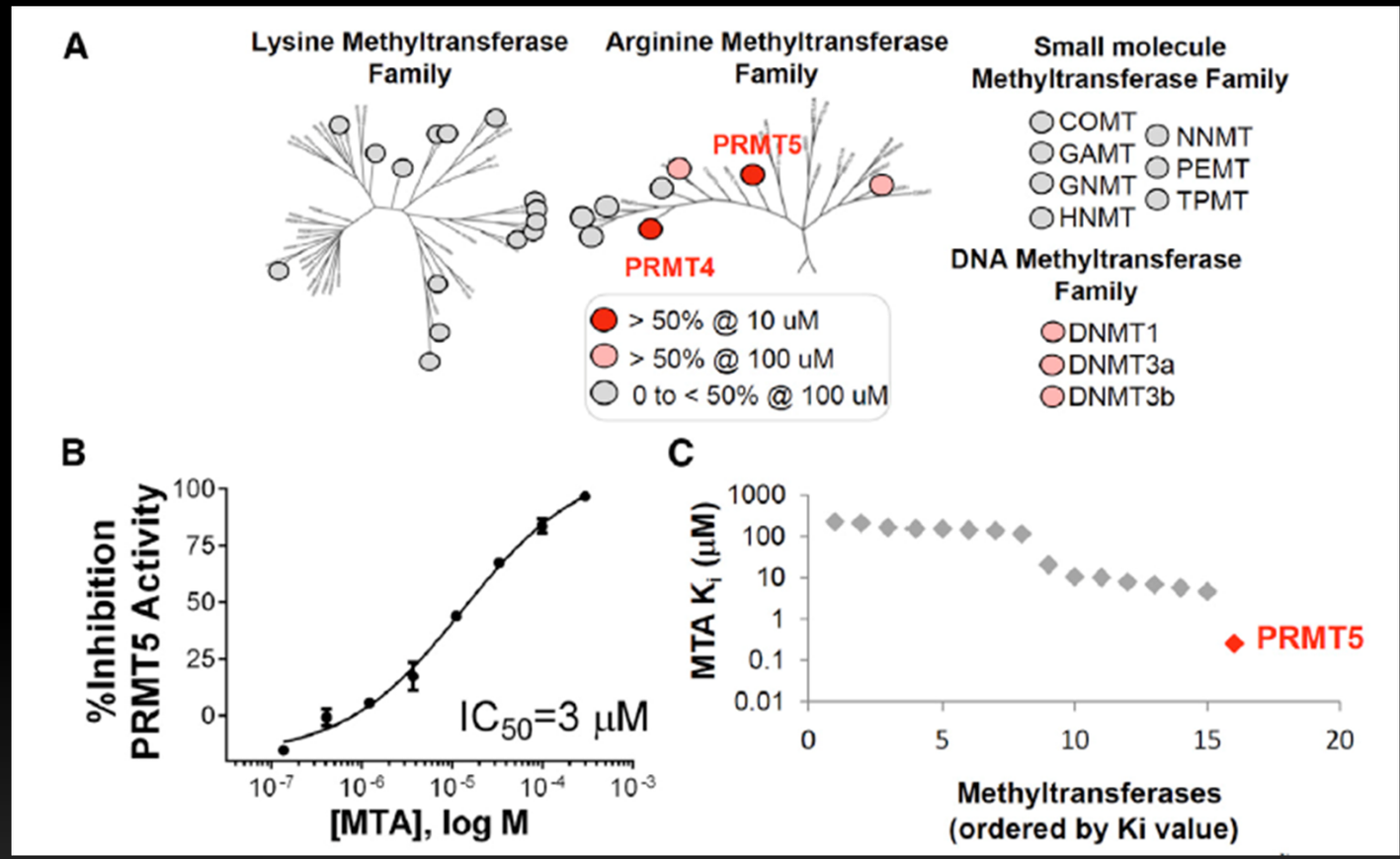



S-adenosylmethionine
(SAM)

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



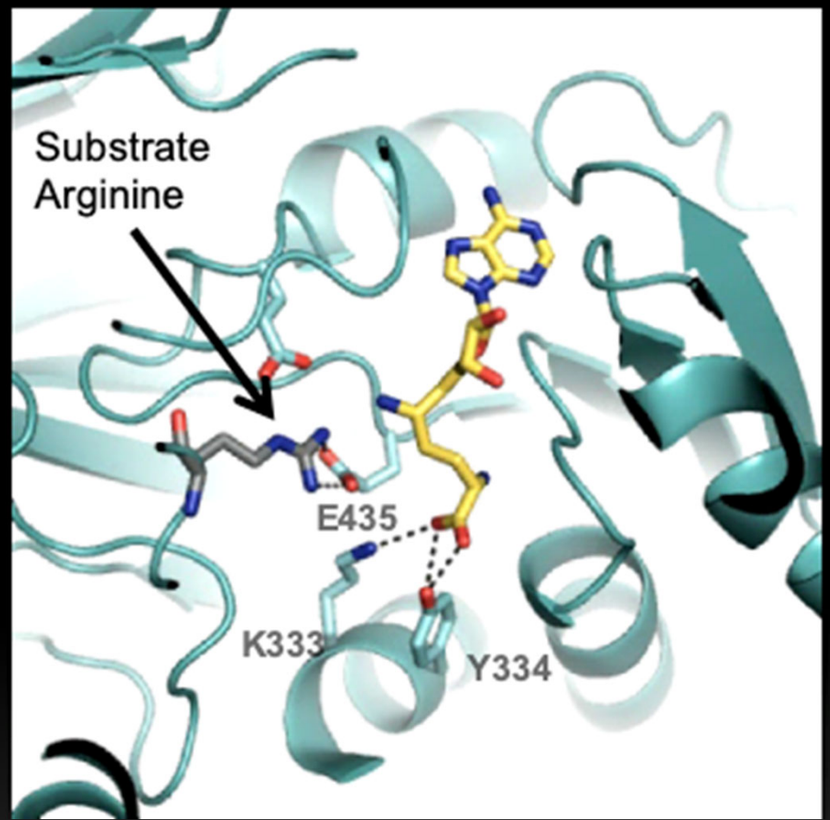





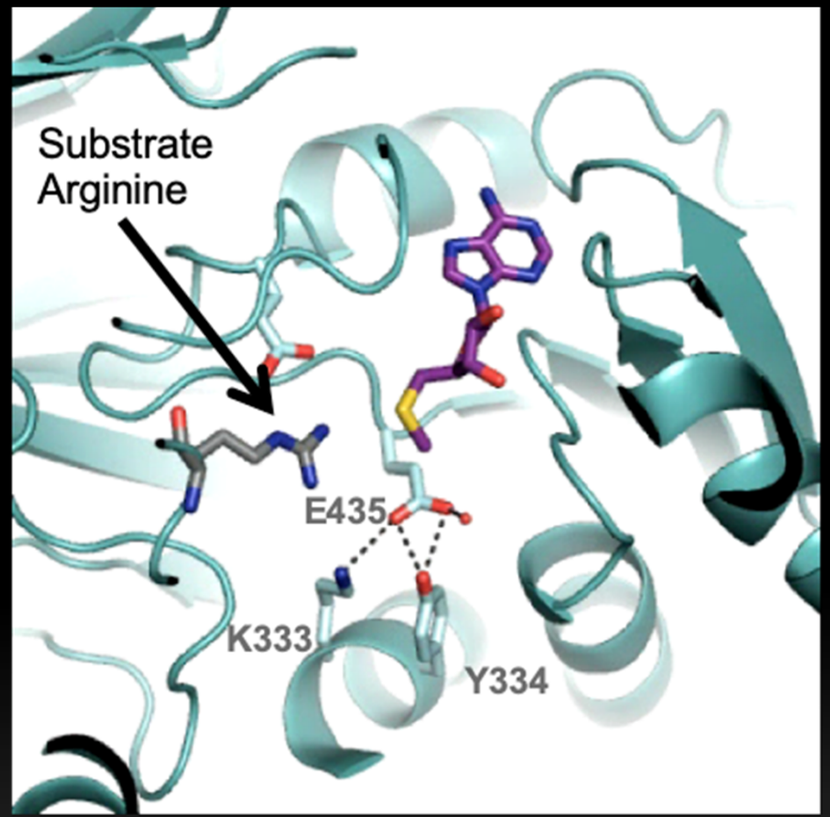

*Mavrakis KJ et al. Science. 2016;351:1208-13*

*Marjon et al Cancer Cell 2016*

# The Structural basis for MTA inhibition of PRMT5




Sinefungin (SAM analogue)

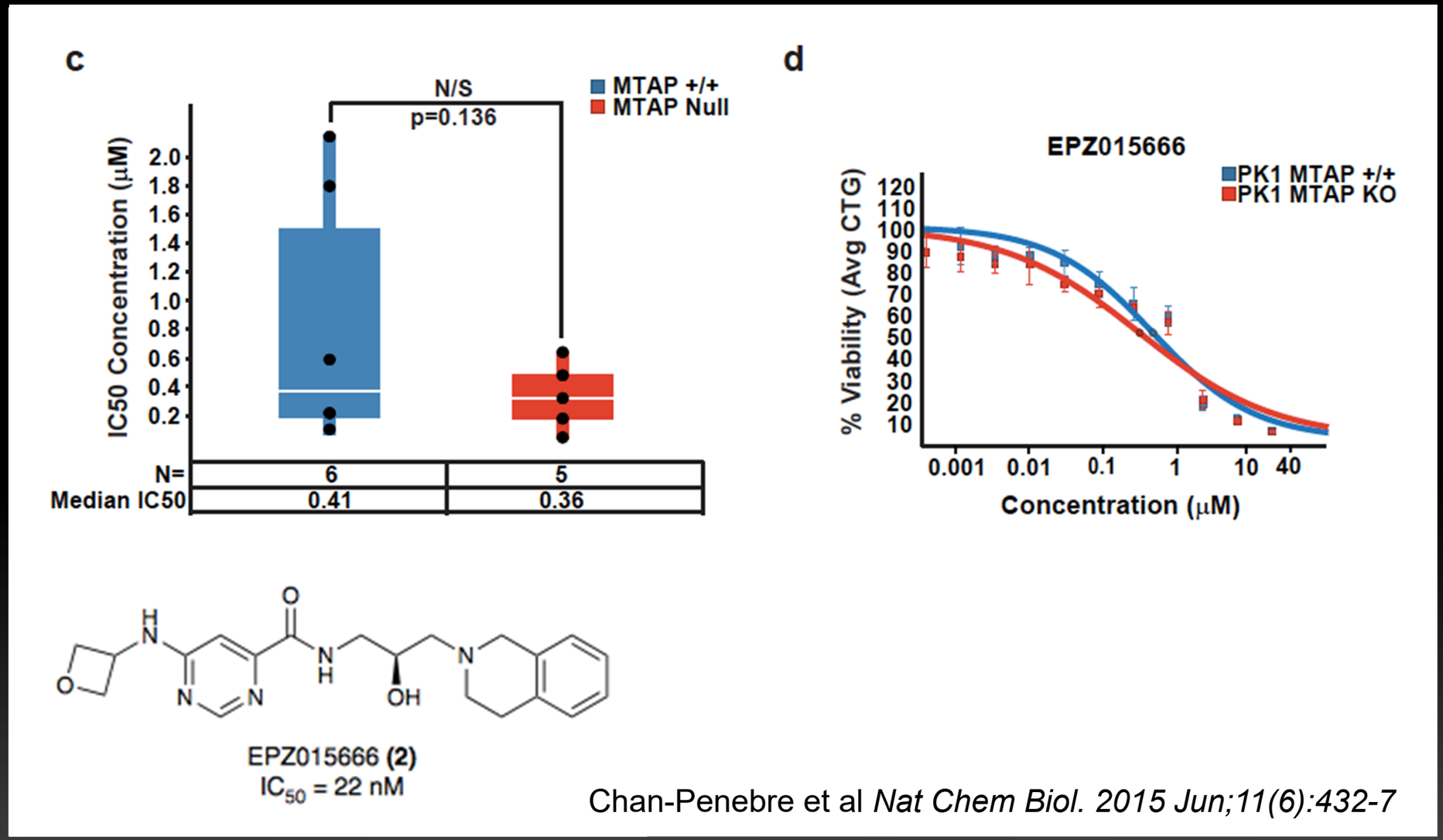



Methylthioadenosine (MTA)



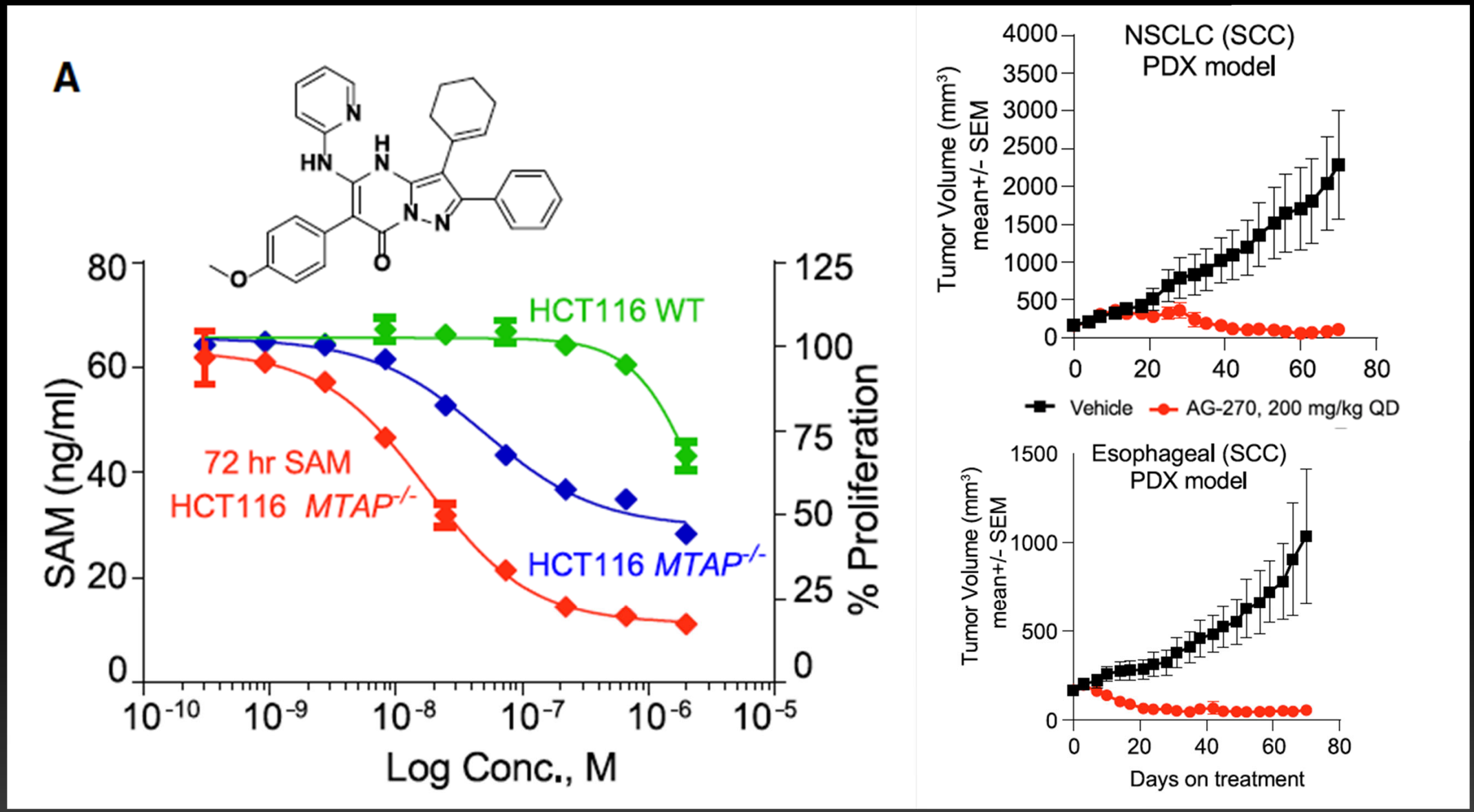
*Mavrakis KJ et al. Science. 2016;351:1208-13*

# 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

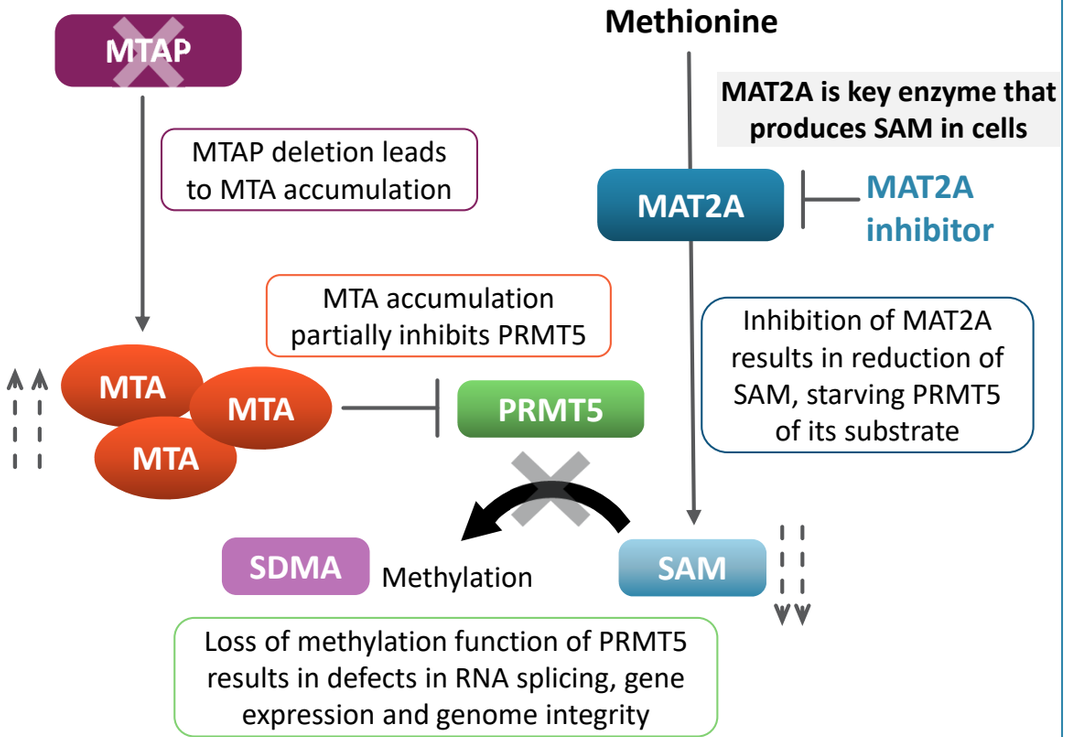
## IDE397 Clinical Candidate

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

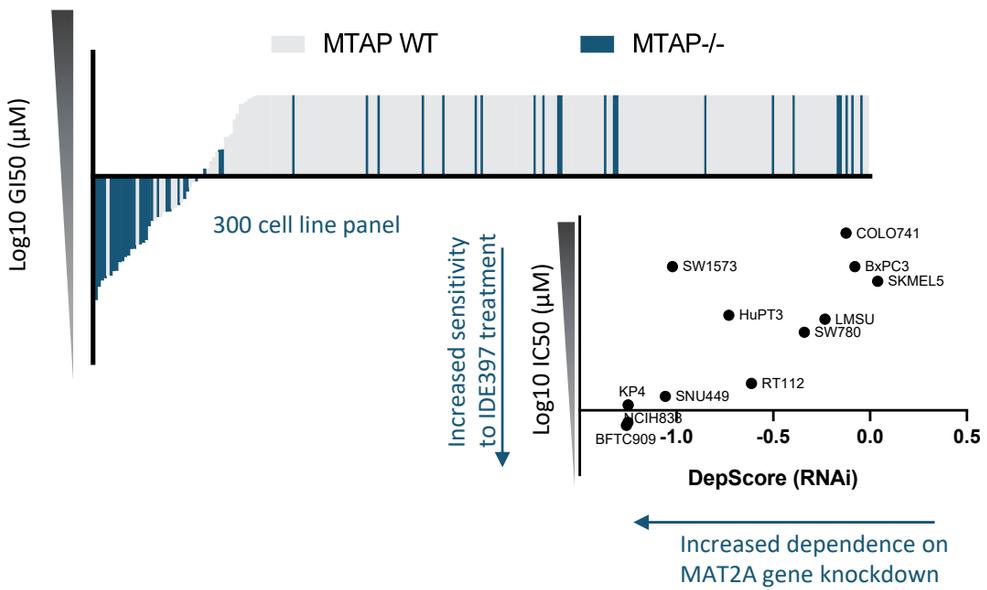


IDEAYA BIOSCIENCES

# IDE397: MAT2A Development Candidate *in vitro* Profile

## IDE397 is selective for MTAP-/- Cell Lines

### IDE397 is Selective for MTAP-/- Cell Lines

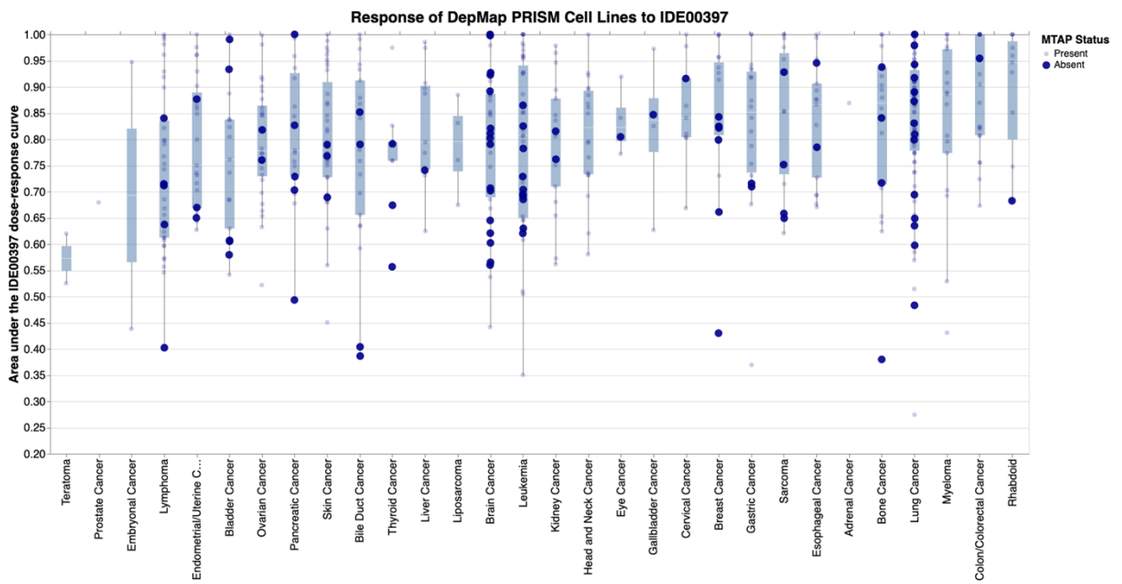



MTAP-/- cell lines are sensitive to IDE397

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

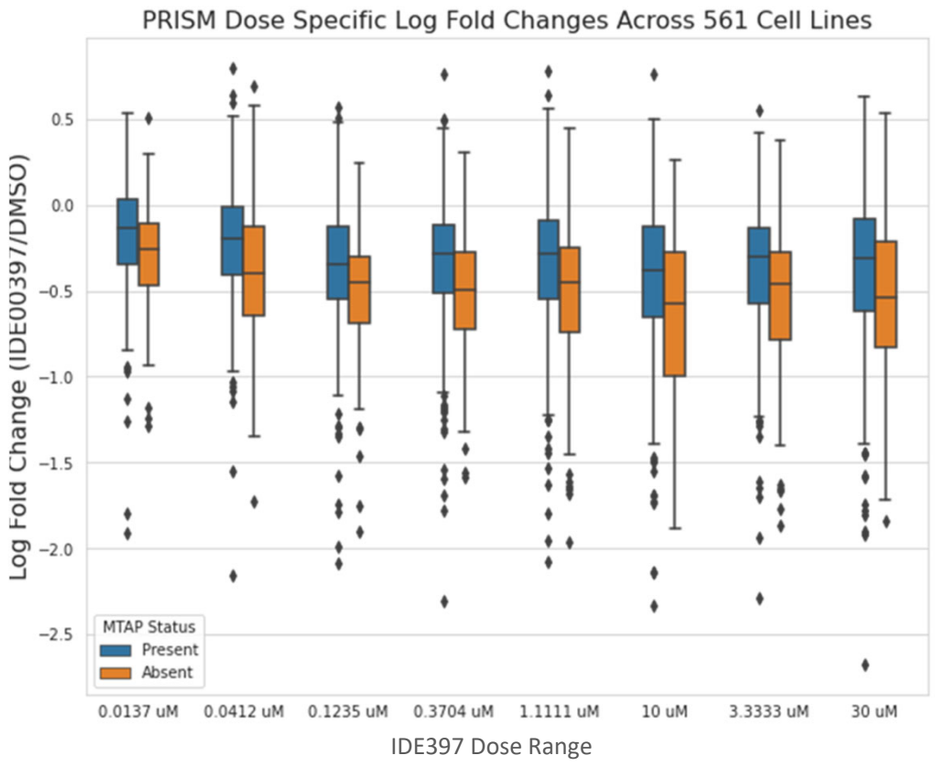
IDEAYA Data

IDEAYA Analysis / PRISM Screen - Broad DepMAP Consortium

# Response to IDE397 stratified by MTAP Status in Broad PRISM Panel

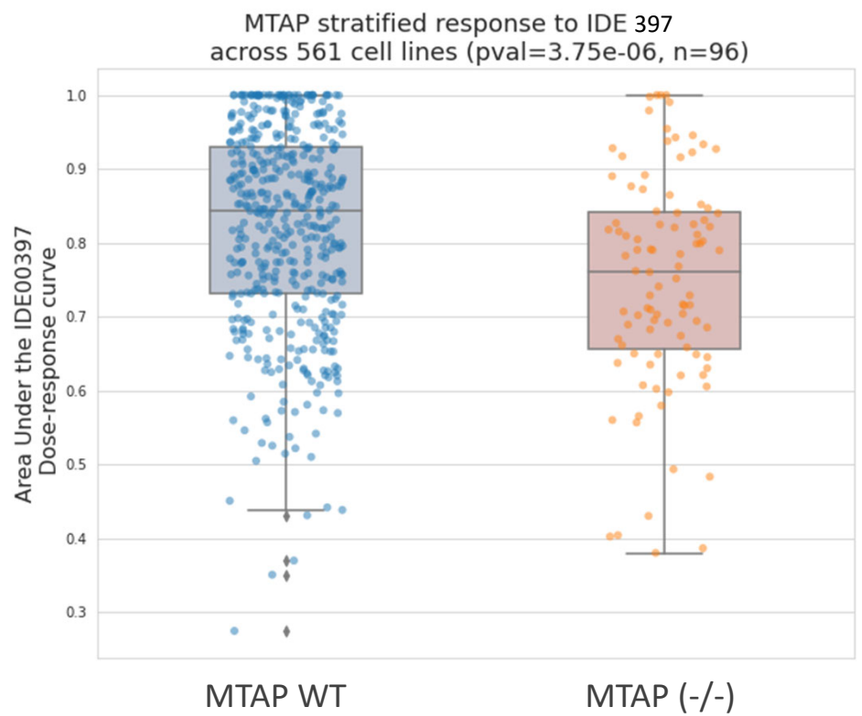
IDE397 has broad activity across tumor types with clear MTAP dependence

## IDE397 sensitivity shows a clear dependence on MTAP status




IDEAYA Analysis / PRISM Screen - Broad DepMAP Consortium

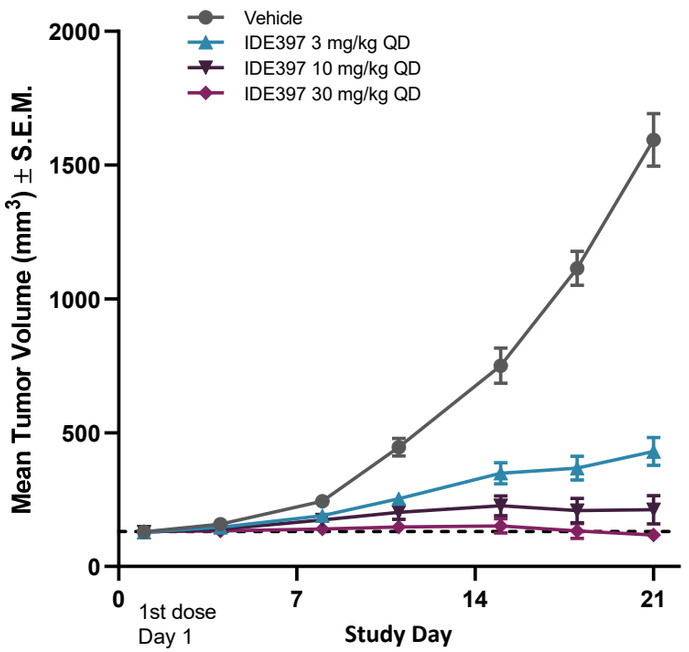
## MTAP status significantly correlated with sensitivity




IDEAYA Analysis / PRISM Screen - Broad DepMAP Consortium

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

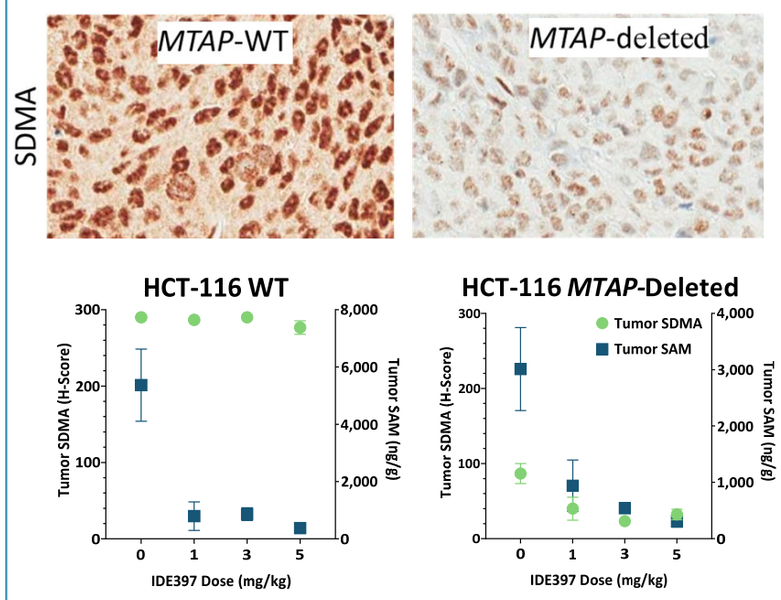
## NSCLC Endogenous MTAP-/- CDX Model

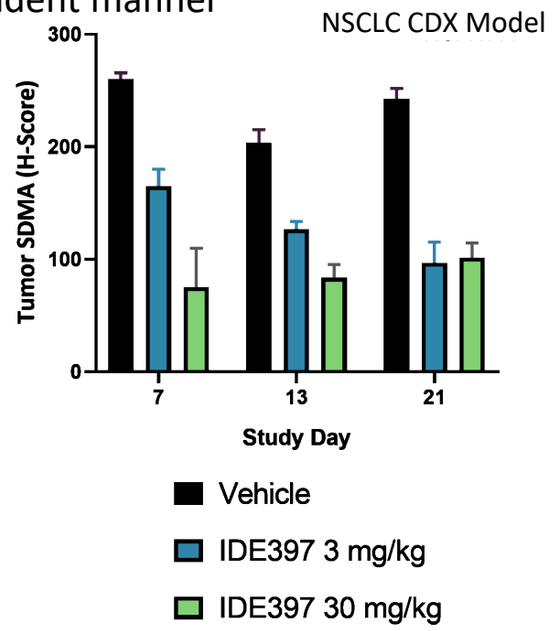



IDEAYA Data

## 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

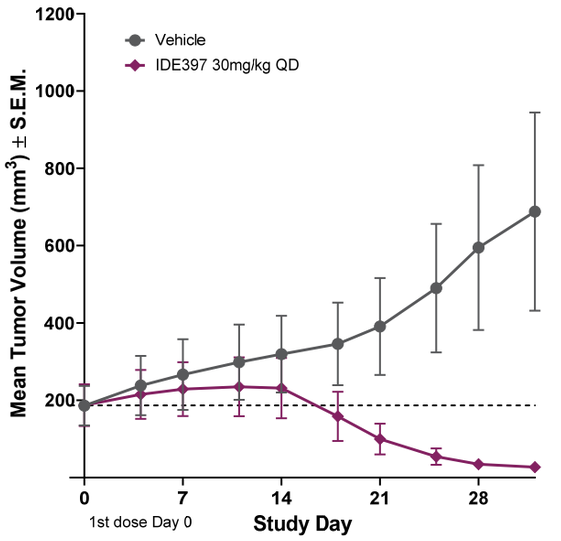
IDEAYA Data: Fischer et. al., AACR 2021

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

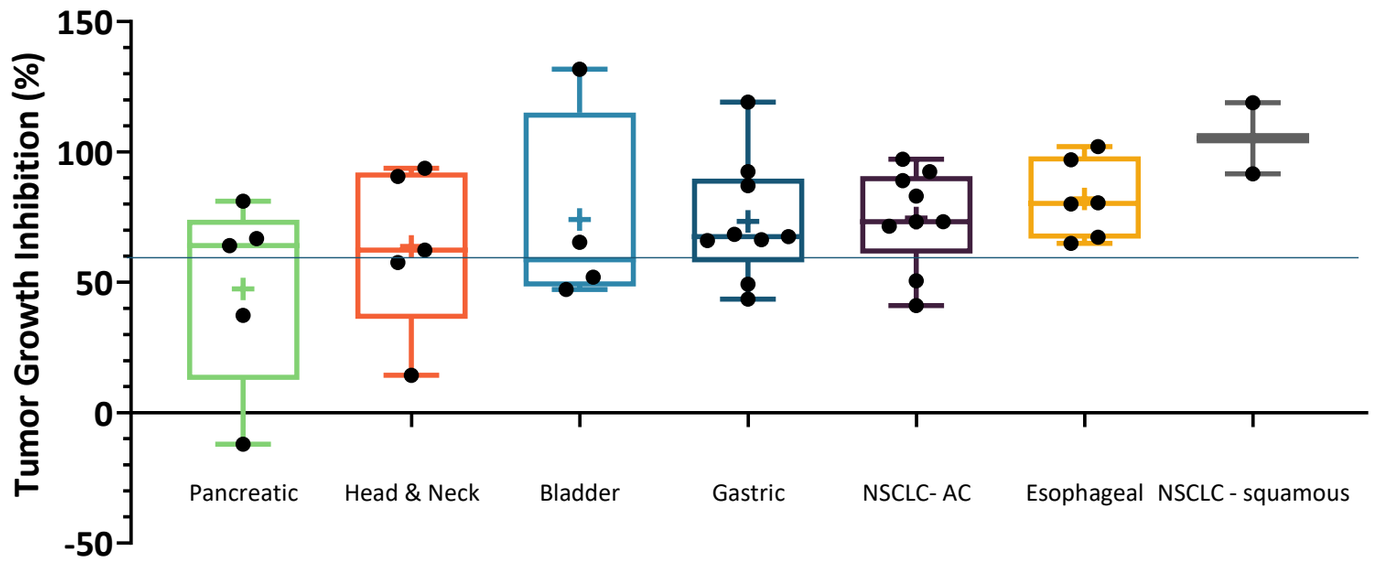
# IDE397: PDX Study of >40 MTAP-/- Models in Multiple Indications

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

### Bladder PDX Model




IDEAYA Data




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

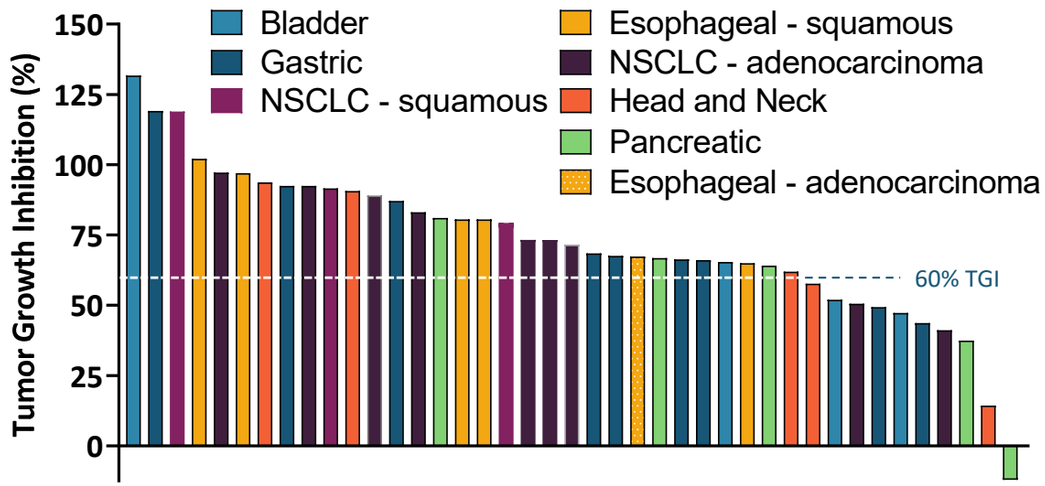
### IDE397 evaluation in Patient Derived Xenograft (PDX) models with homozygous MTAP deletions in Solid Tumors

- 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

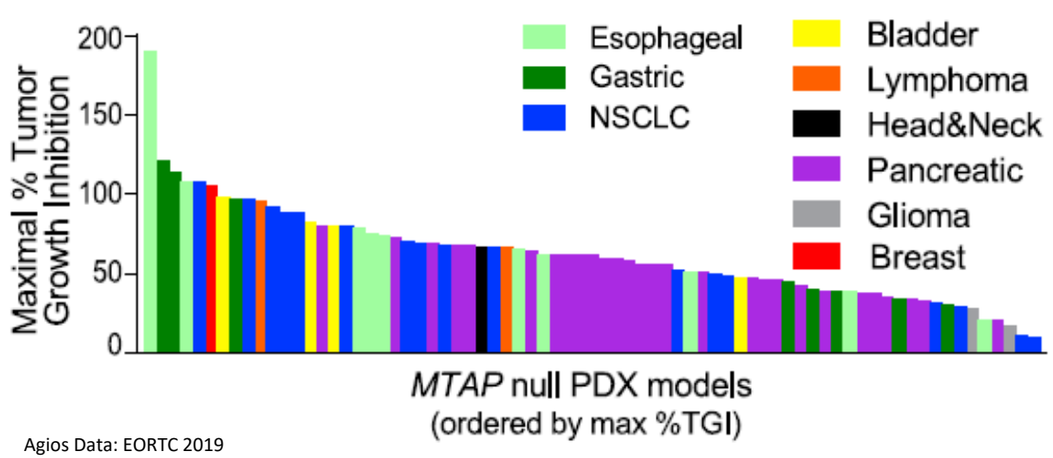
## IDE397 demonstrates favorable Efficacy relative to reported AG-270 PDX Data

**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

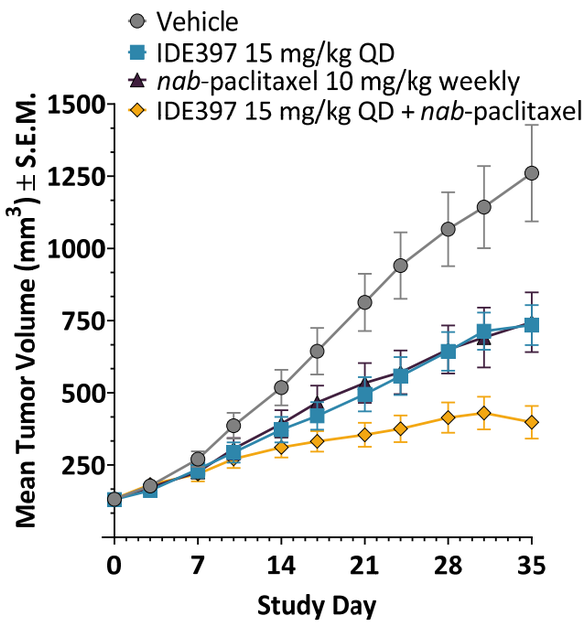
- CDX-derived spheroids and PDX-derived organoids to recapitulate *in vivo* conditions of tumor growth and immune interactions

*In vivo* Approaches

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

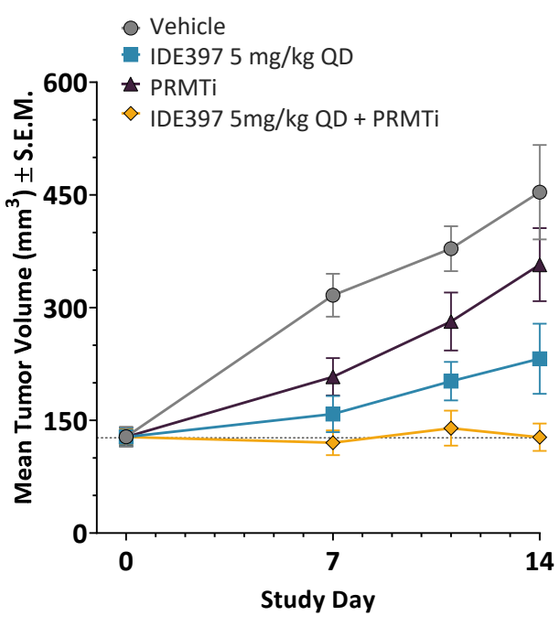
### Strong *in vivo* Combination Effects with Taxanes and PRMTi

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

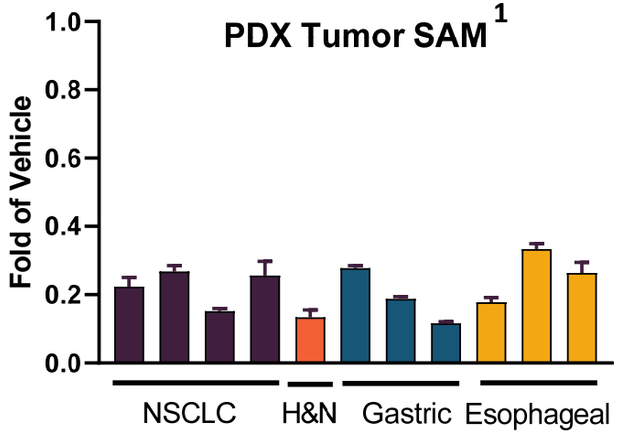
Assays in place for plasma SAM, tumor SAM and tumor SDMA

IDE397 causes robust tumor PD response in PDX models

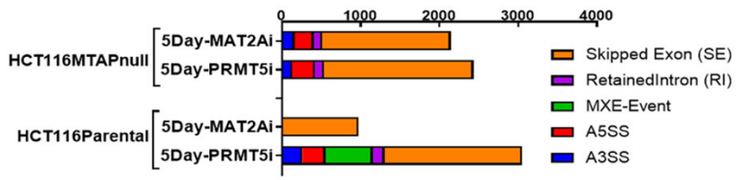
- 80-90% tumor SAM reduction in PDx models
- AG-270 showed variable and inconsistent PD modulation in Phase I paired biopsies

Multiple assays evaluating splicing, gene expression and metabolomics

**PDX Tumor SAM** [1]

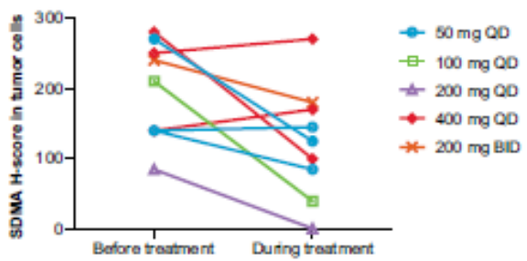



**RNAseq analysis of treated cells**[2]




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

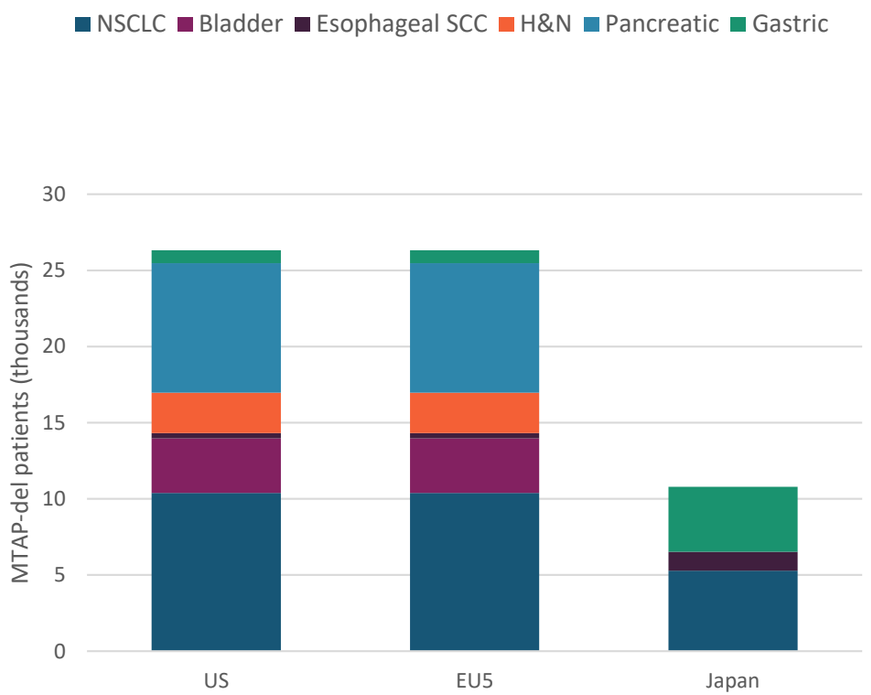
- IDE397 is a potential first in class/best in class MAT2A inhibitor
- Patient selection based on defined genetic biomarker defined (MTAP deletion)
- Potency permissive of potential single agent activity
- Tolerability permissive of broad combination potential

# Summary of Addressable MTAP-Deletion Patient Populations

## MTAP-Deletion observed in ~15% of Solid Tumors

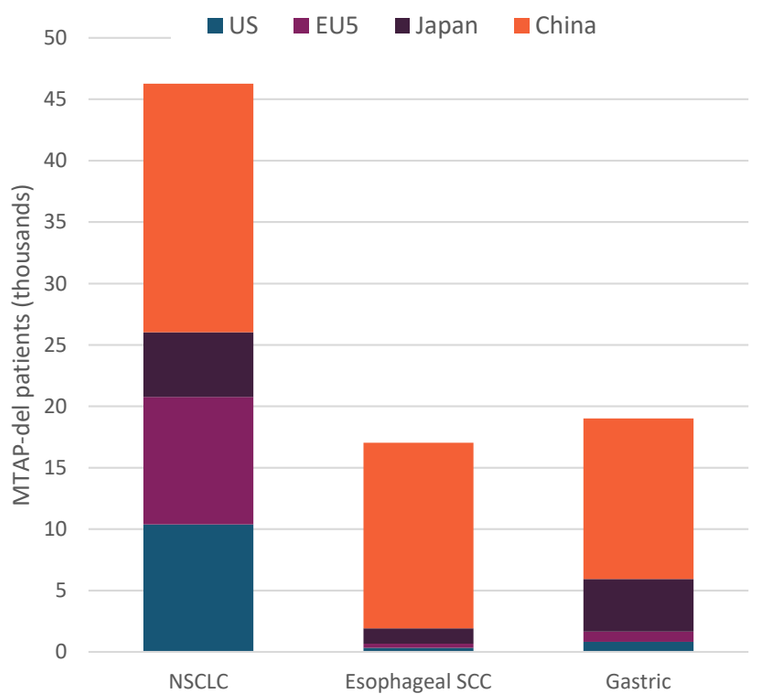
### Addressable MTAP-Deletion Patient Populations

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




### Solid Tumor Indications of Clinical Relevance

NSCLC, Esophageal and Gastric Cancers



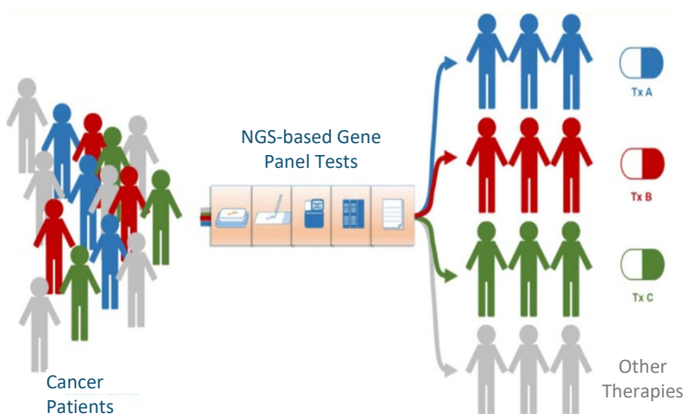
# MTAP-Deletion Patient Selection

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

### Next Generation Sequencing (NGS)

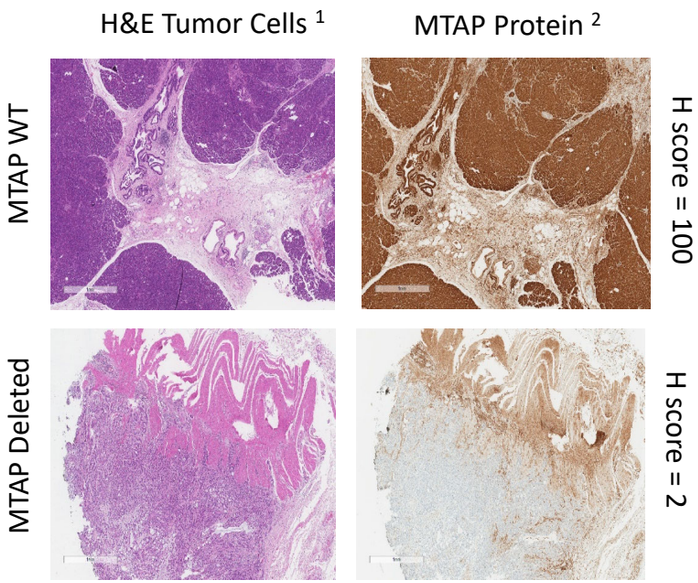
NGS-based gene panel tests identify MTAP deletion and enable patient selection for treatment with IDE397

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



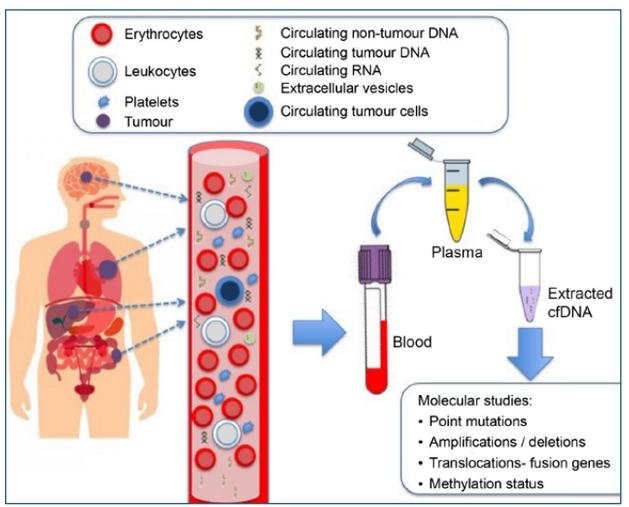

(1) H&E stain identifies cell types by deep purple color in tumor biopsies
(2) MTAP stain identifies MTAP protein levels with semi-quantitative scoring (e.g., 100 = high, 1 = low)

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

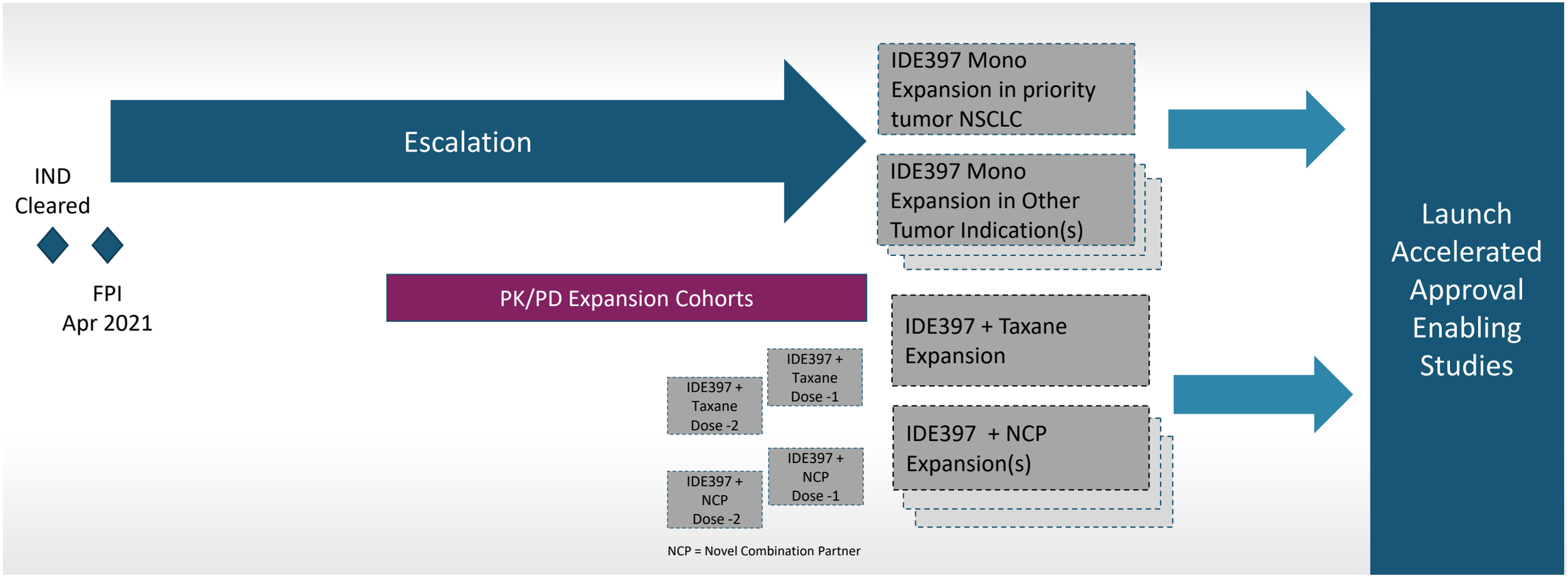



Clinical and Translational Oncology (2020) 22:823–834)

# IDE397 Phase 1 Clinical Trial

## Comprehensive Approach for Concurrent Evaluation of Monotherapy and Combinations

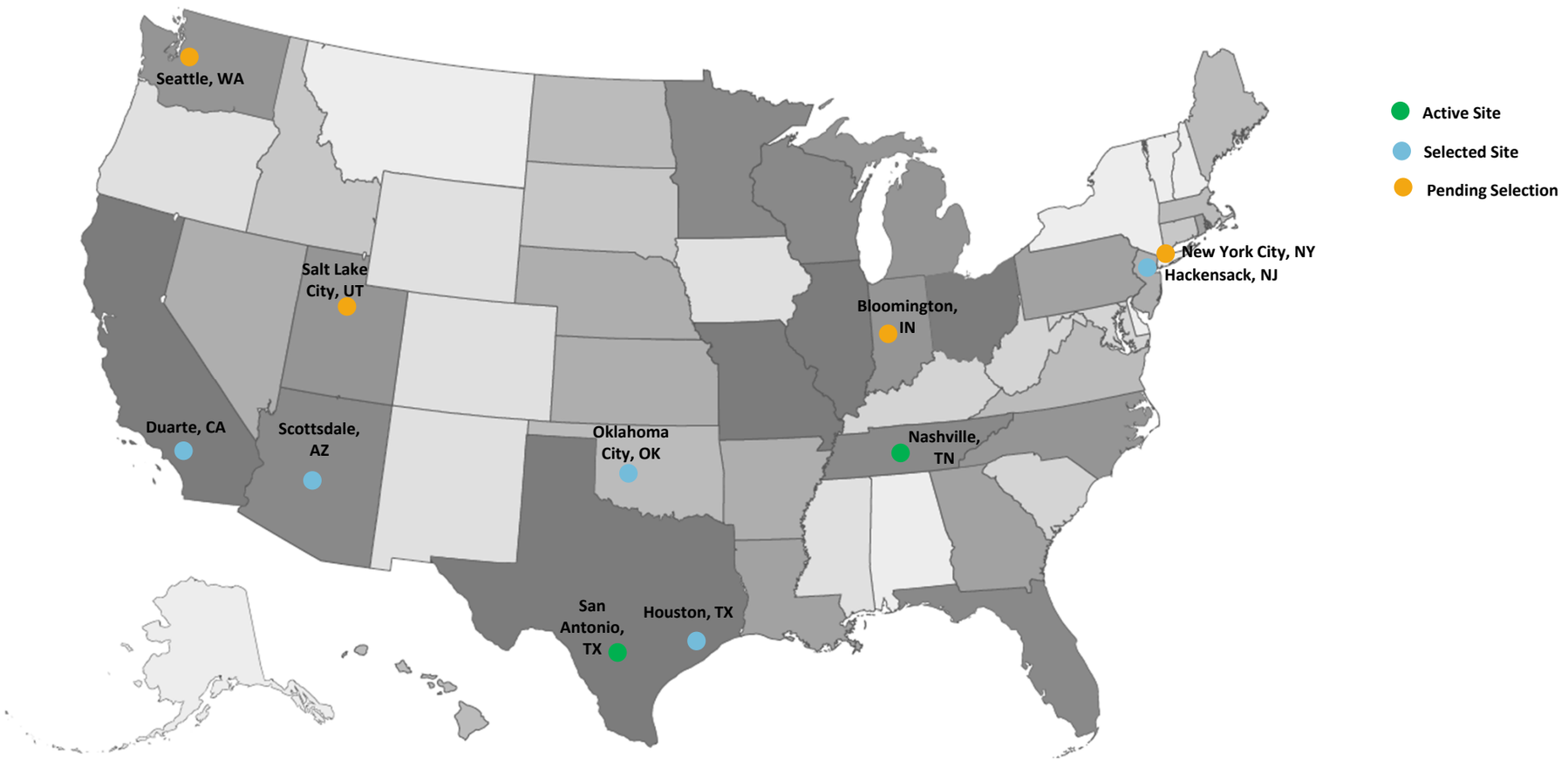
### Phase 1 Dose Escalation and Expansion




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

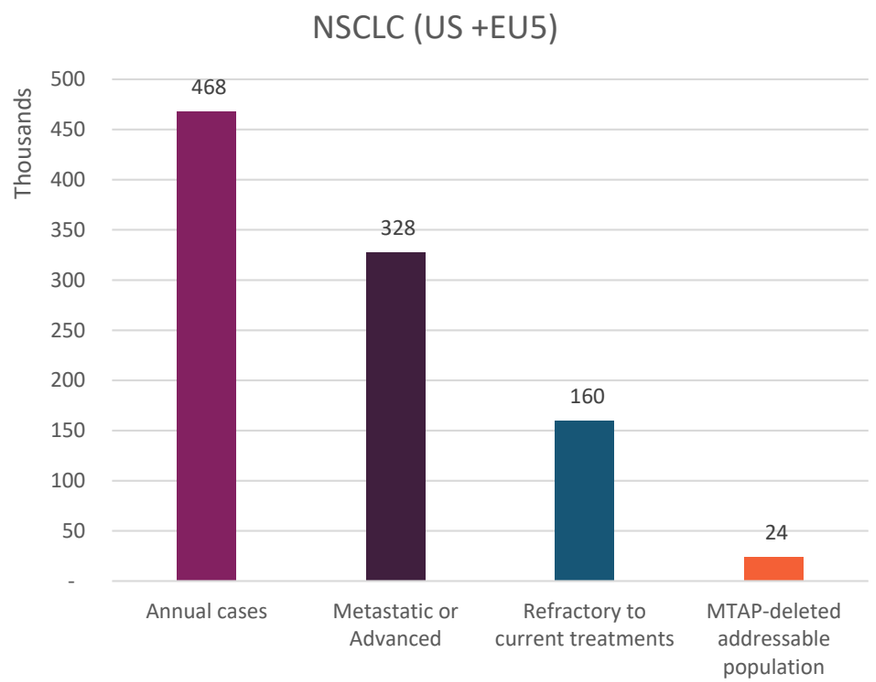
Possible Single Agent and Combination Strategies

- 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

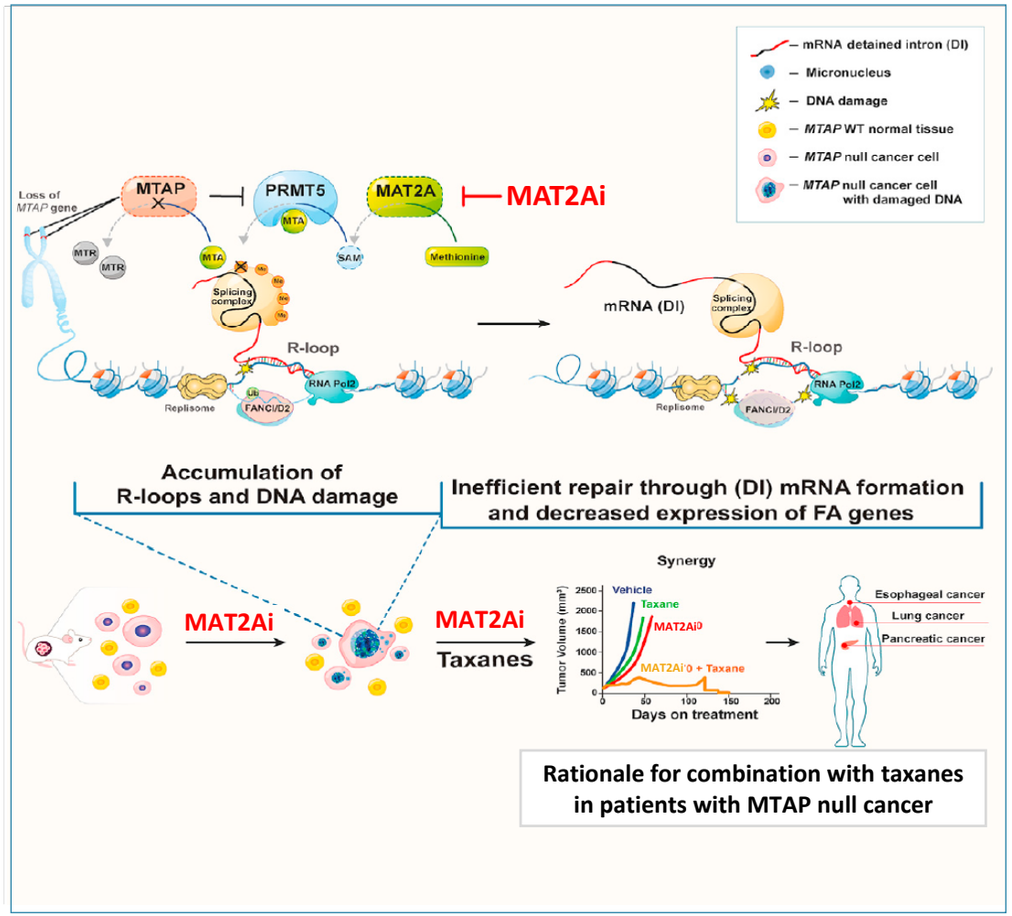
## Ongoing Preclinical Effort to identify Optimal Synergistic Combination Partners

### 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

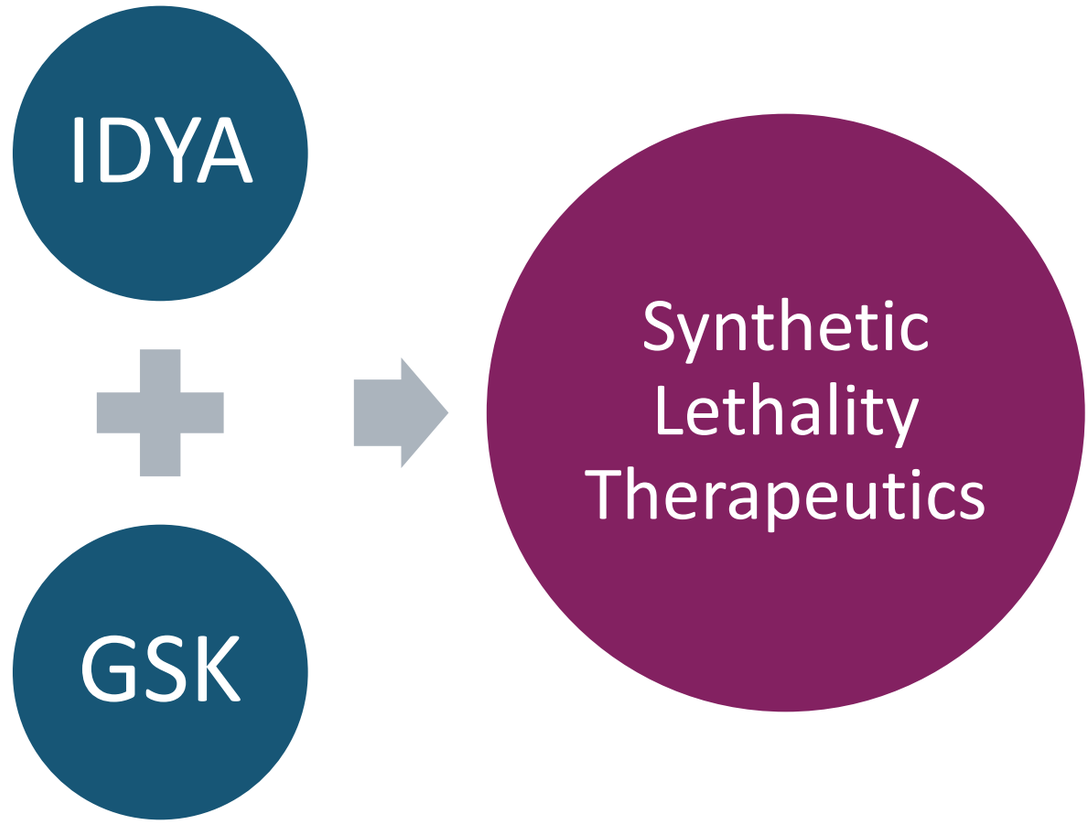
Depth and breadth of resources and clinical development knowledge and capabilities

- 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

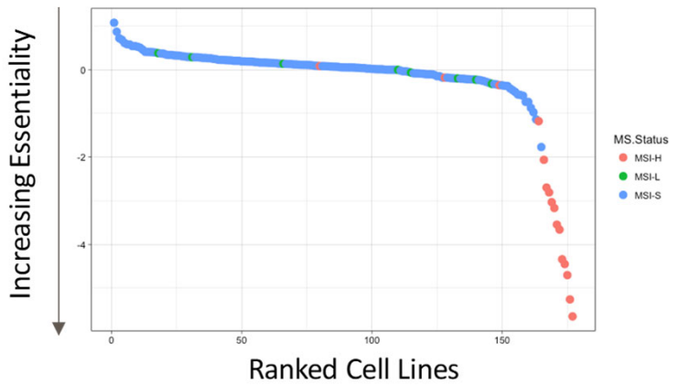
## Introduction

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

# WRN Helicase: Synthetic Lethality in MSI Tumors

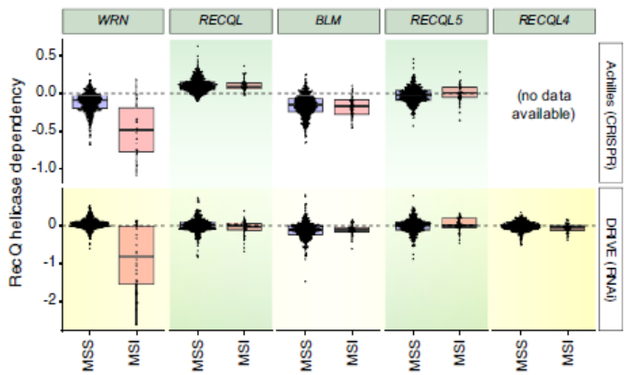
## Using Genome-Wide Approaches to Find the Next PARP-like Opportunity

### Project SCORE



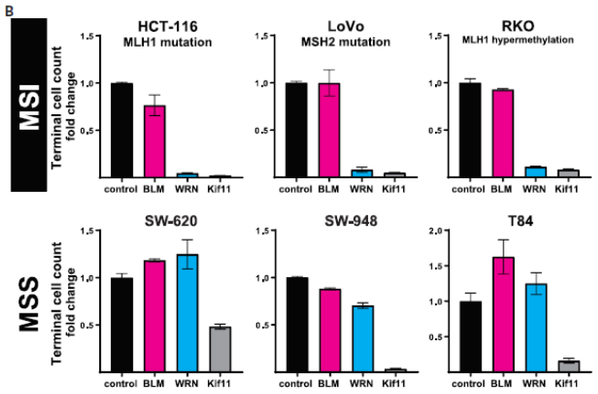

2019 Nature, 568, 511

### 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

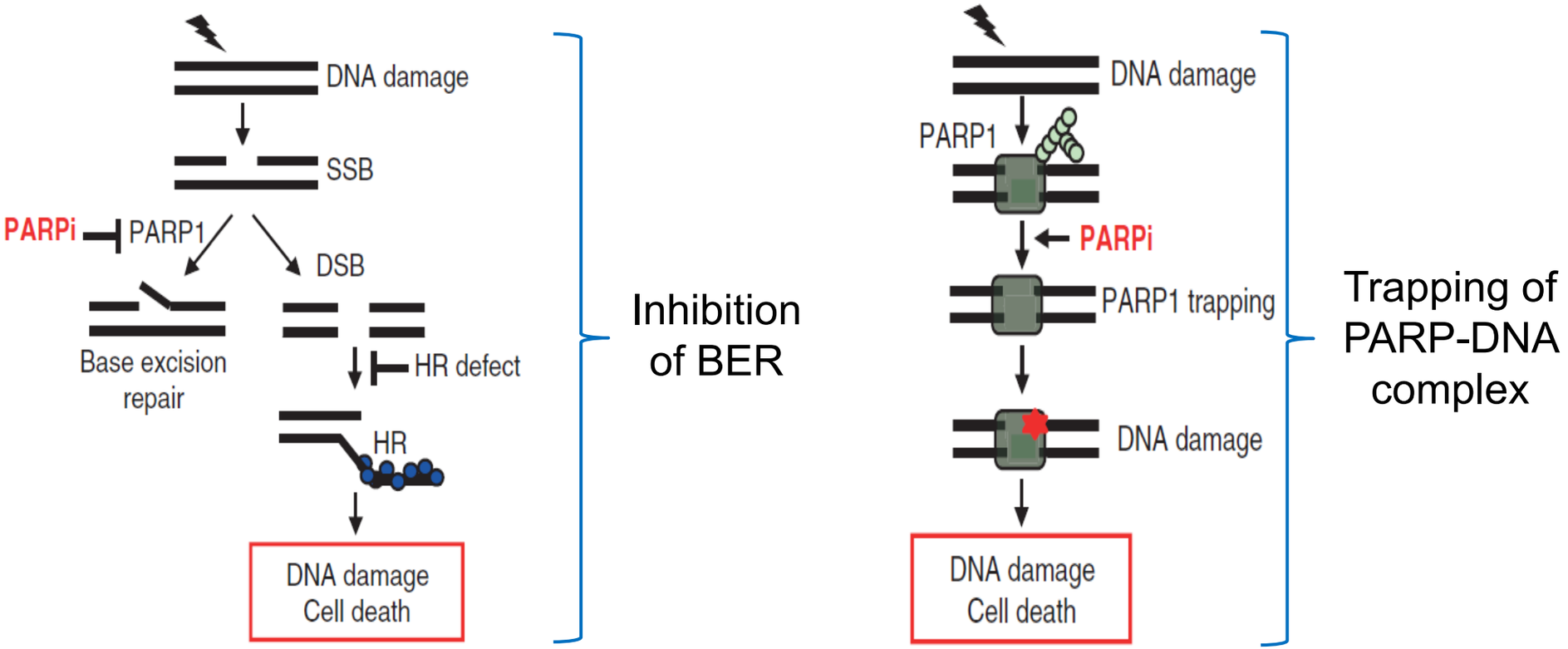
DANA-FARBER CANCER INSTITUTE

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

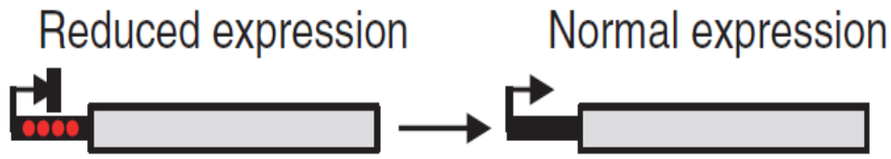
# How do PARP inhibitors kill HR deficient tumor cells?



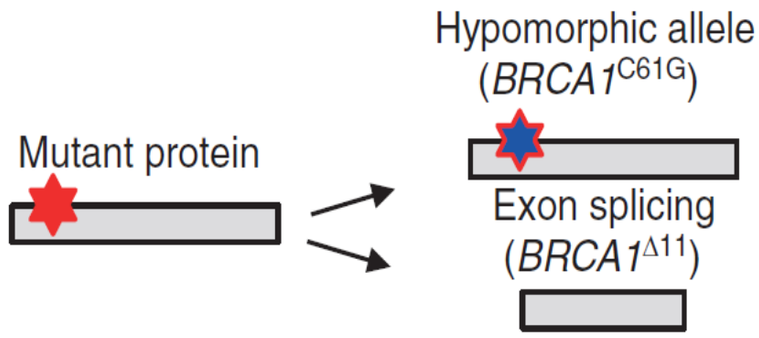
# What are the mechanisms of PARPi Resistance? Restoration of HR proficiency

1. Somatic reversion or restoration of ORF


2. Epigenetic reversion of *BRCA1* promoter hypermethylation

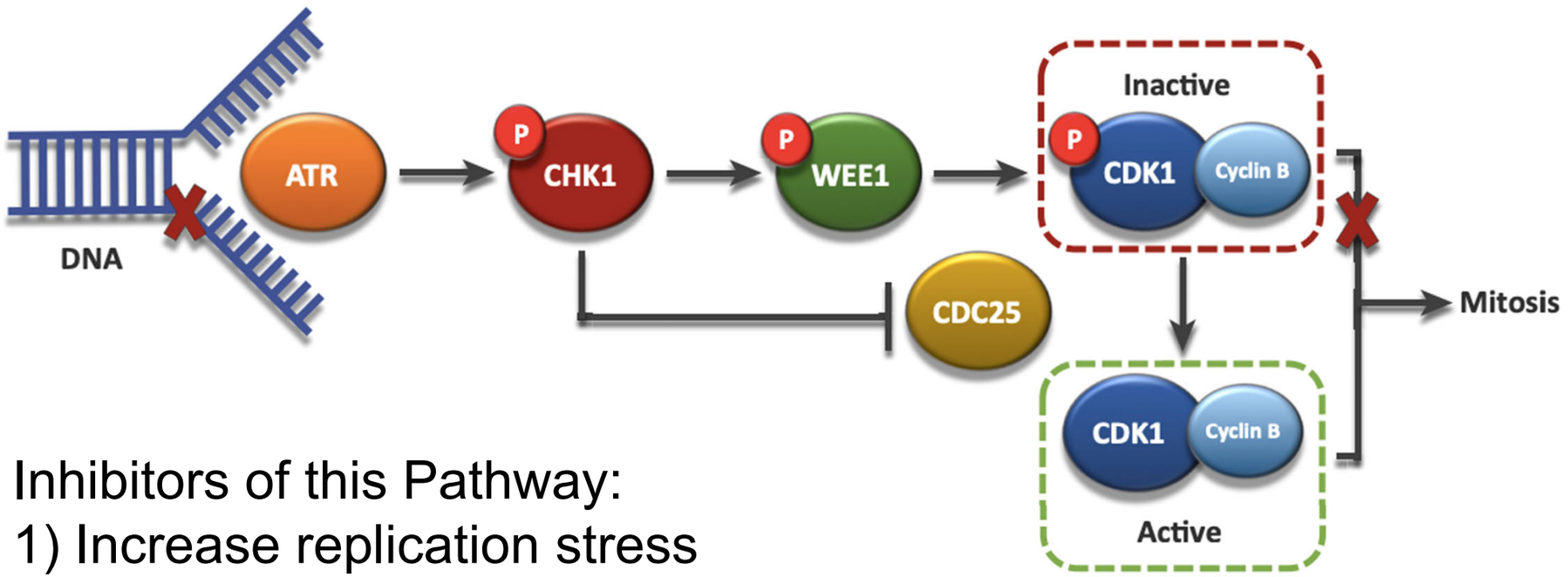



3. Hypomorphic *BRCA1* or *BRCA2* allele




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

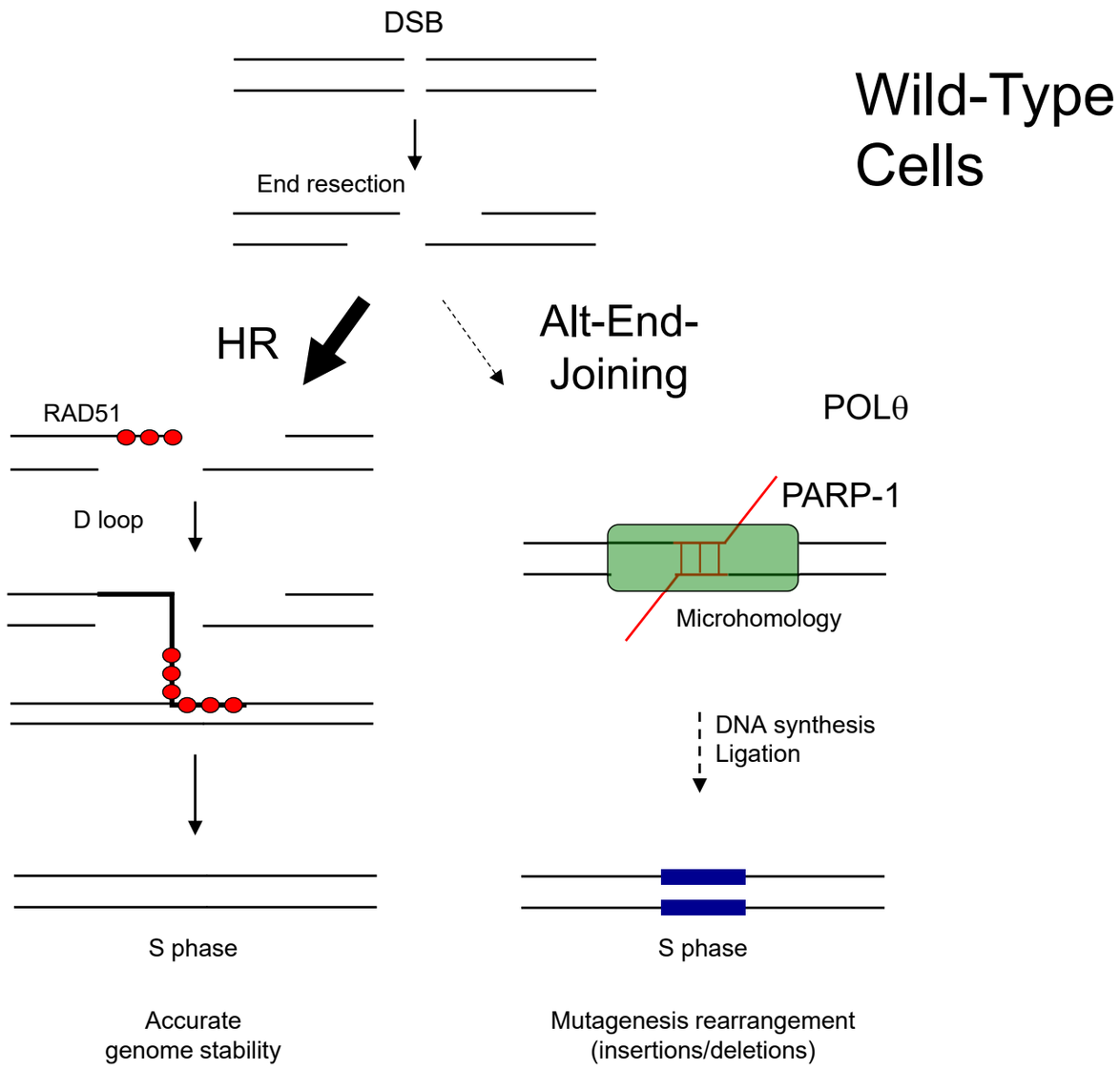
# Upregulation of the ATR/CHK1/WEE1 pathway can also cause PARPi Resistance



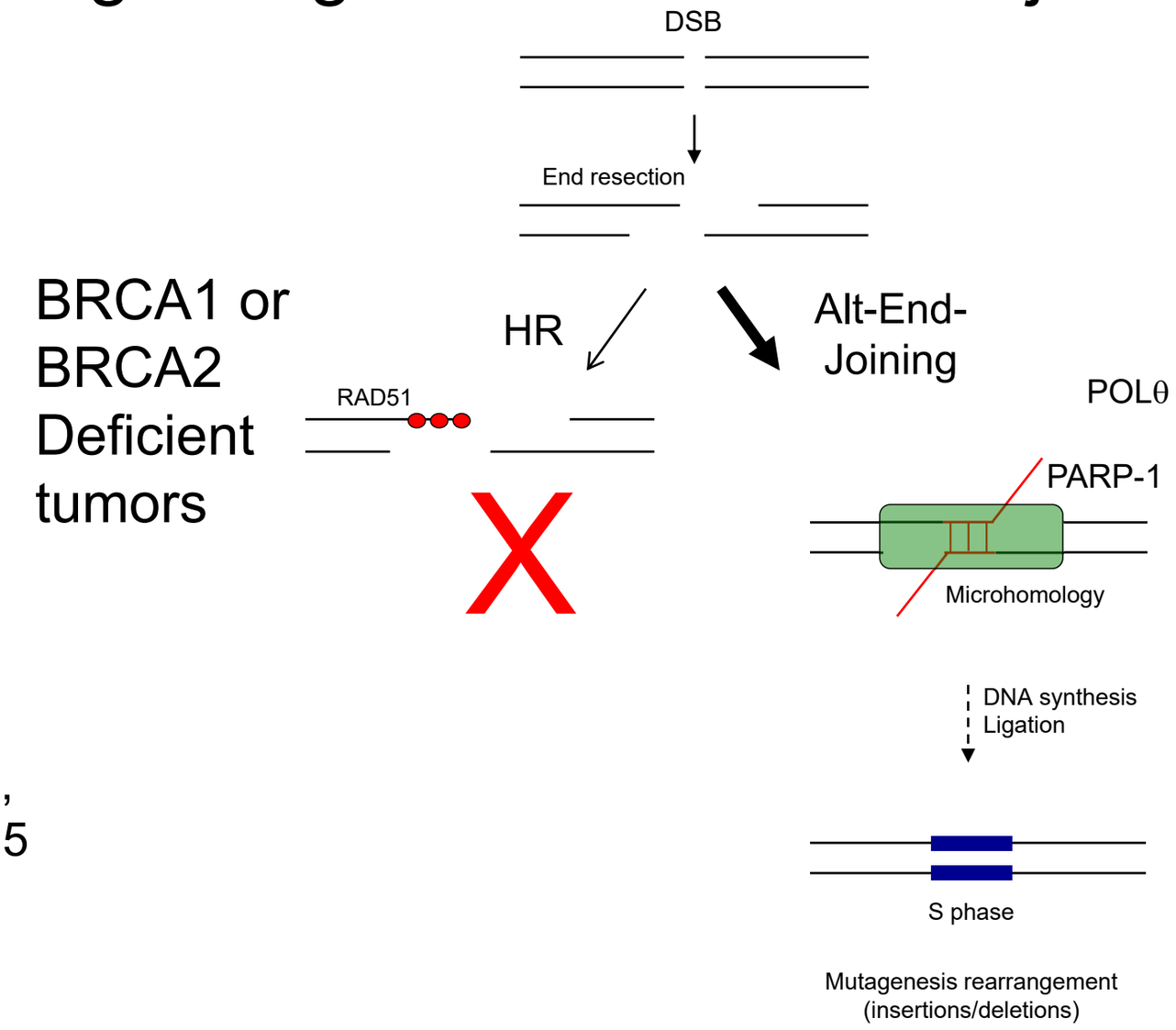

Inhibitors of this Pathway:

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

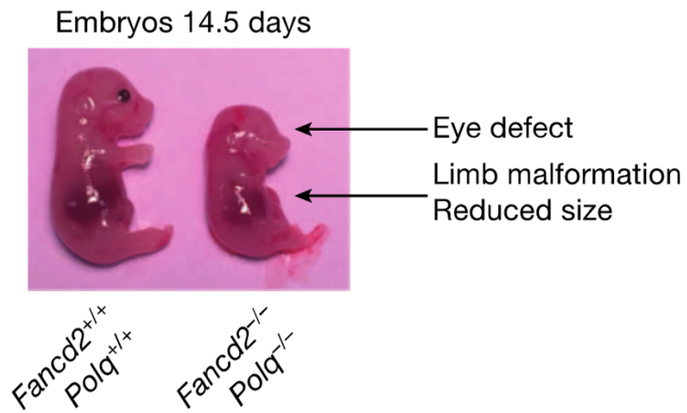
Cosmic
Signature 3

# Synthetic Lethality between HR and Polθ-mediated alt-EJ

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

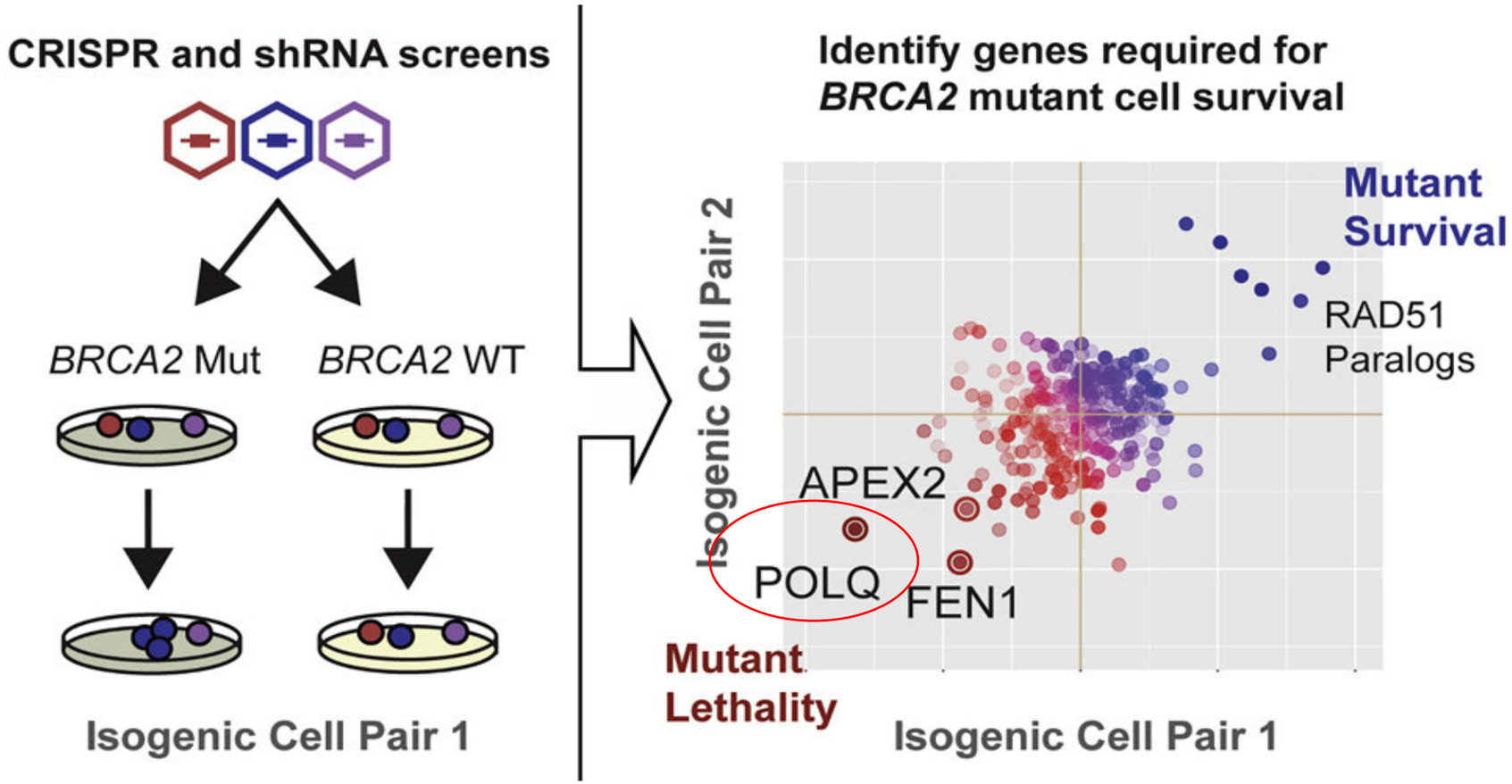
*Polq*$^{-/-}$
Alt-EJ deficiency
Mild phenotype

**Double Knockout**
**Embryonic lethal**



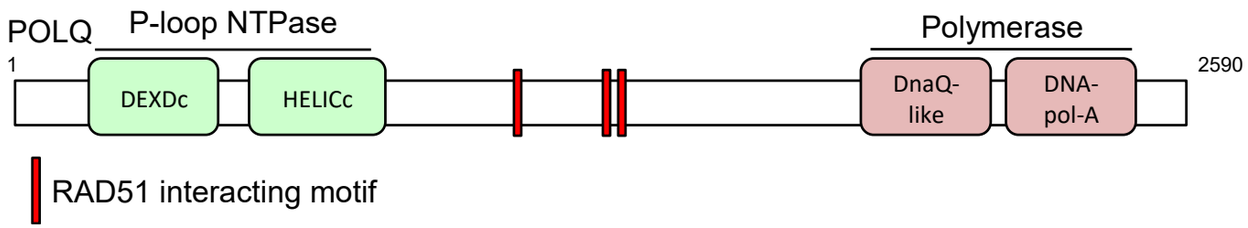

Ceccaldi et al,
*Nature*, 2015

# 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?



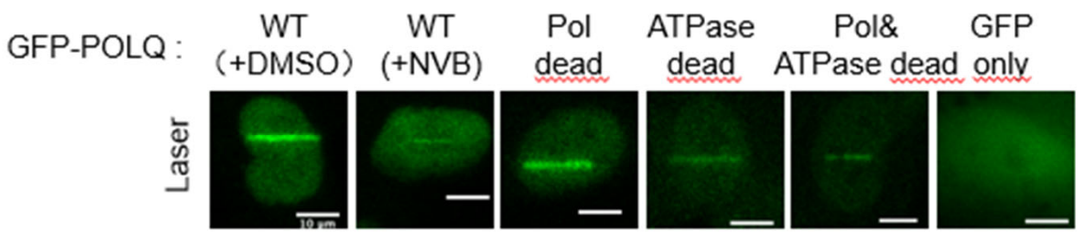

ATPase domain

-strips RAD51 and pRPA from sites of abortive HR repair

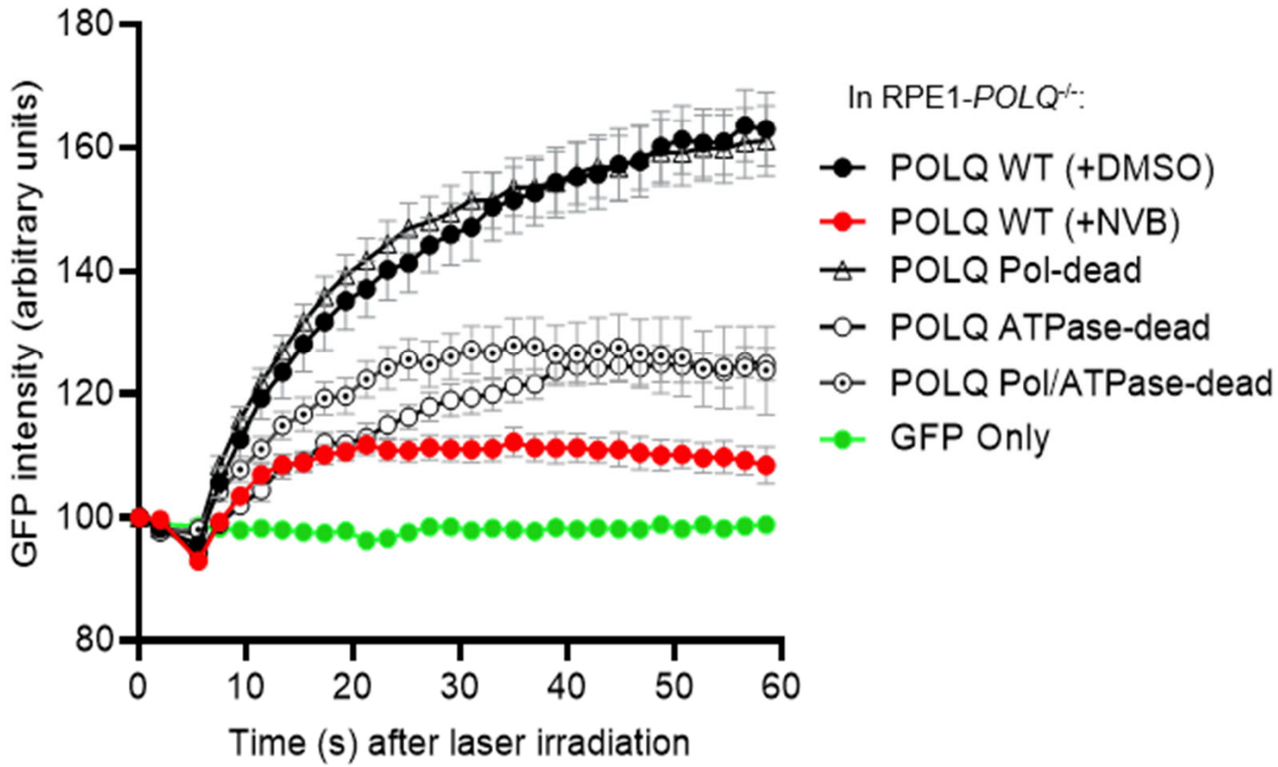
Polymerase Domain

-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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Aleem Syed

**Blagg Laboratory**
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Rachel Davis

**Shapiro Laboratory**
Geoffrey Shapiro
Constantia Pantelidou



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WOMEN'S CANCERS

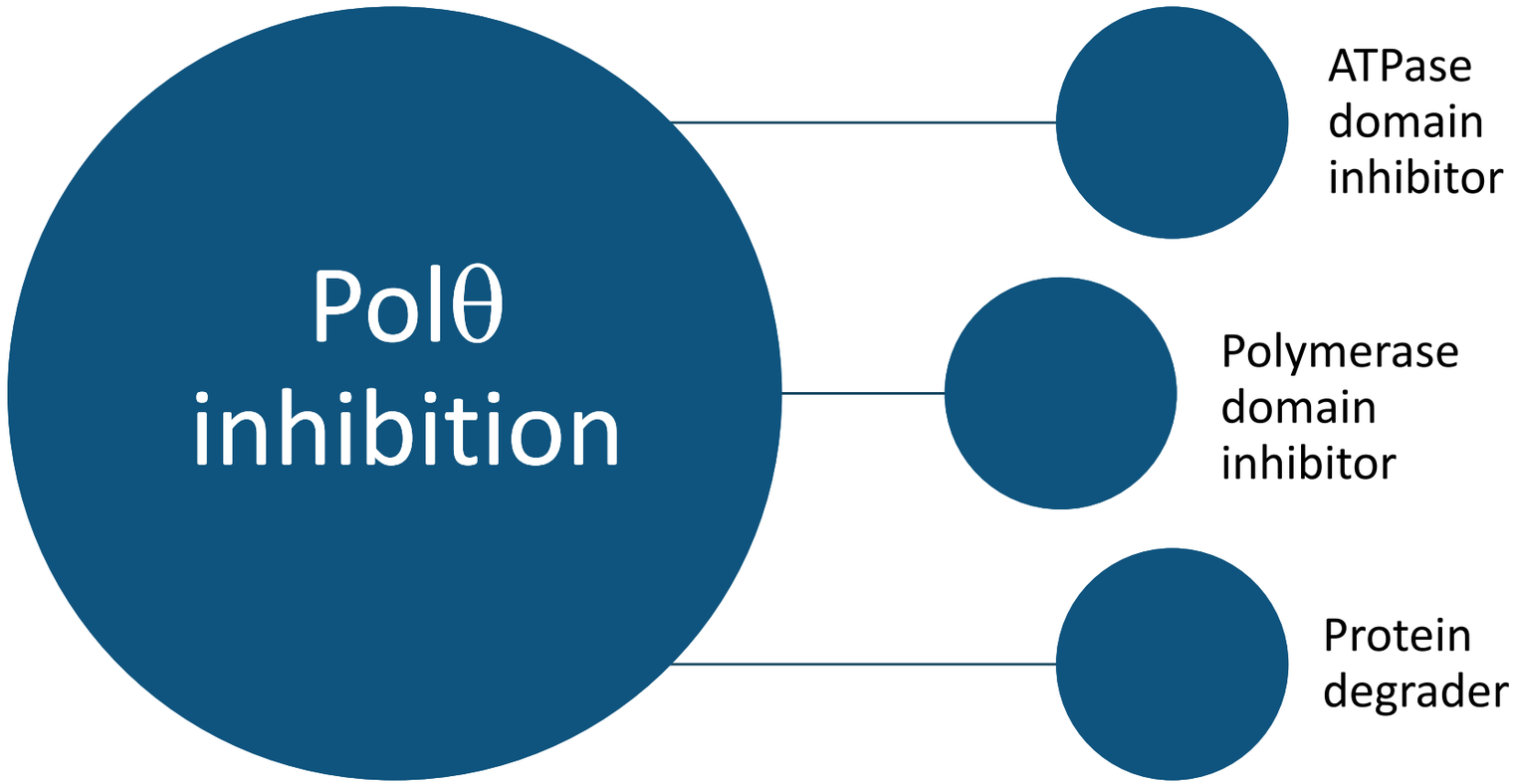

# Pol Theta: Key Target in MMEJ DNA Damage Repair Pathway

## 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

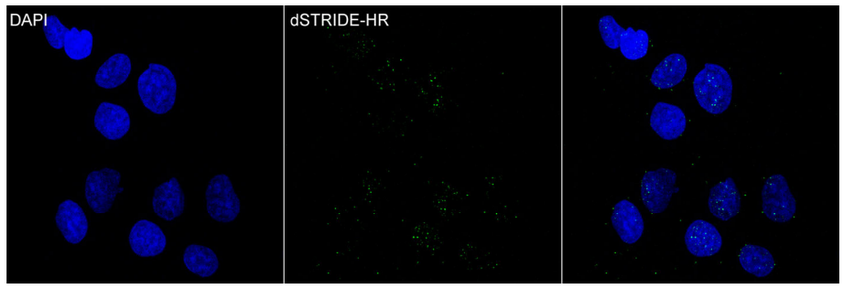
# Polθ ATPase Activity is needed for DNA Repair

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

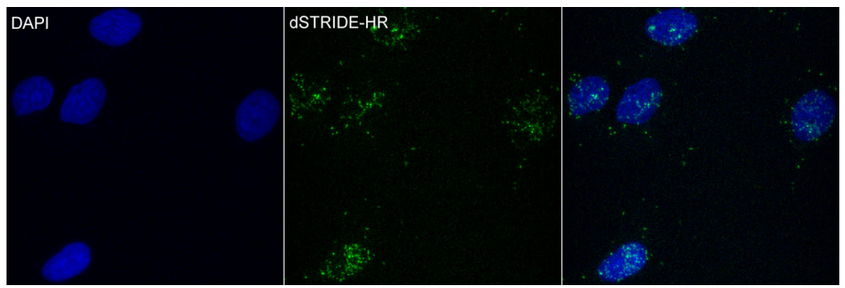
### dSTRIDE-HR Assay

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

U2OS WT
No treatment

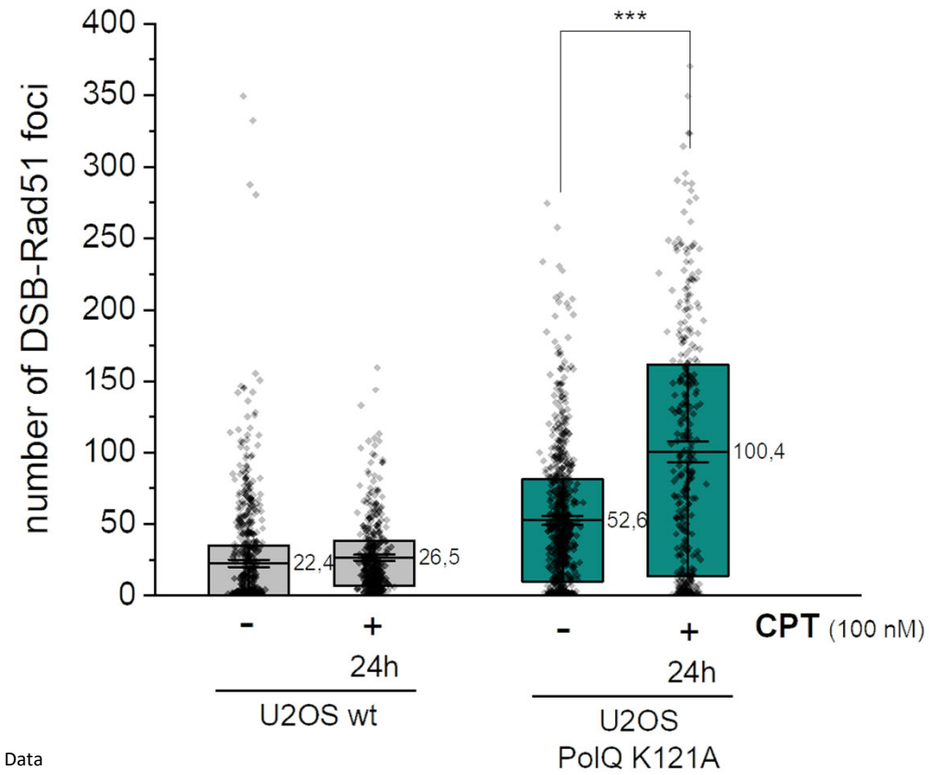



U2OS K121A
No treatment




IDEAYA Data

### Polθ ATPase mutant shows increased DSB-Rad51 Foci

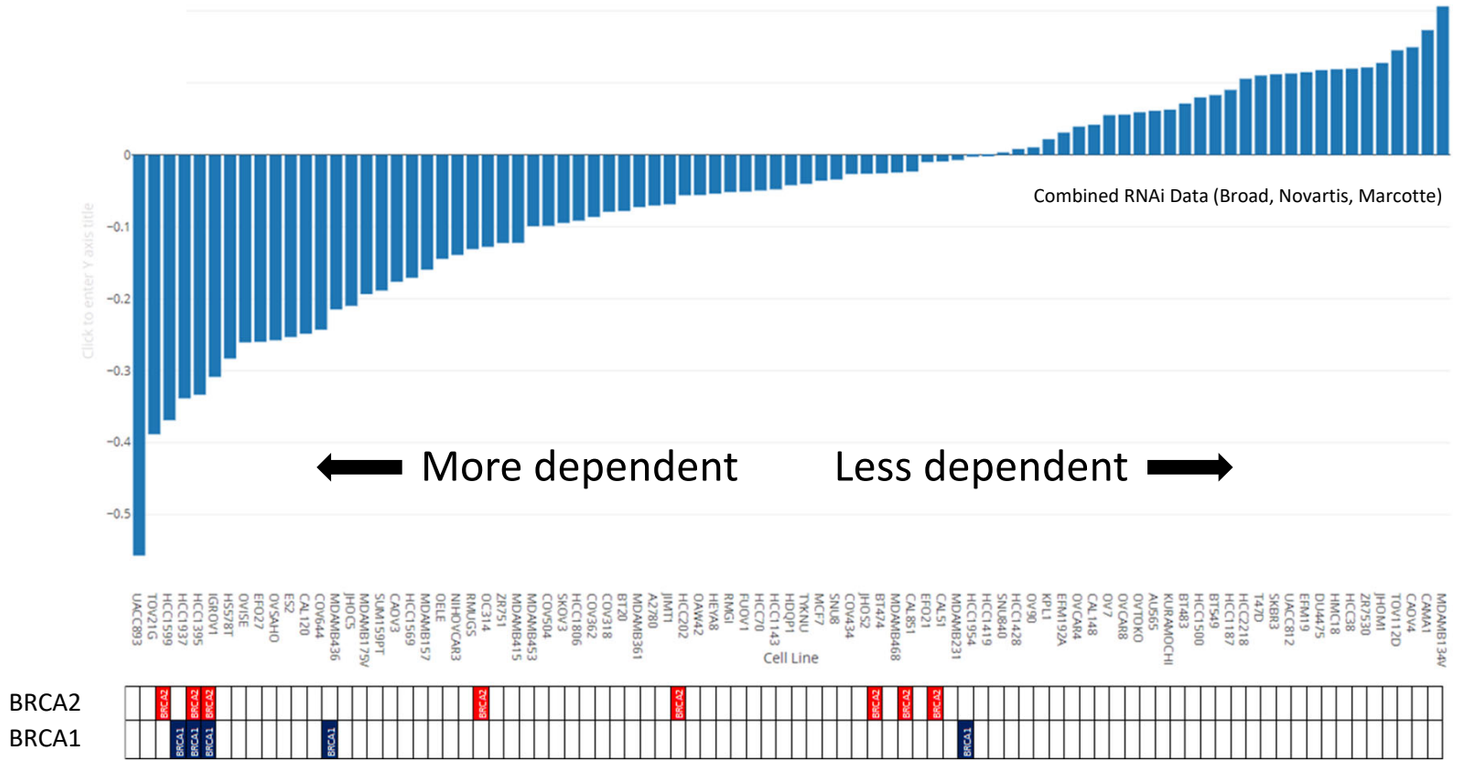



IDEAYA Data

# Cancer Dependency Map Analysis

## Breast and Ovarian Cell Lines have Strong Dependence on Polθ

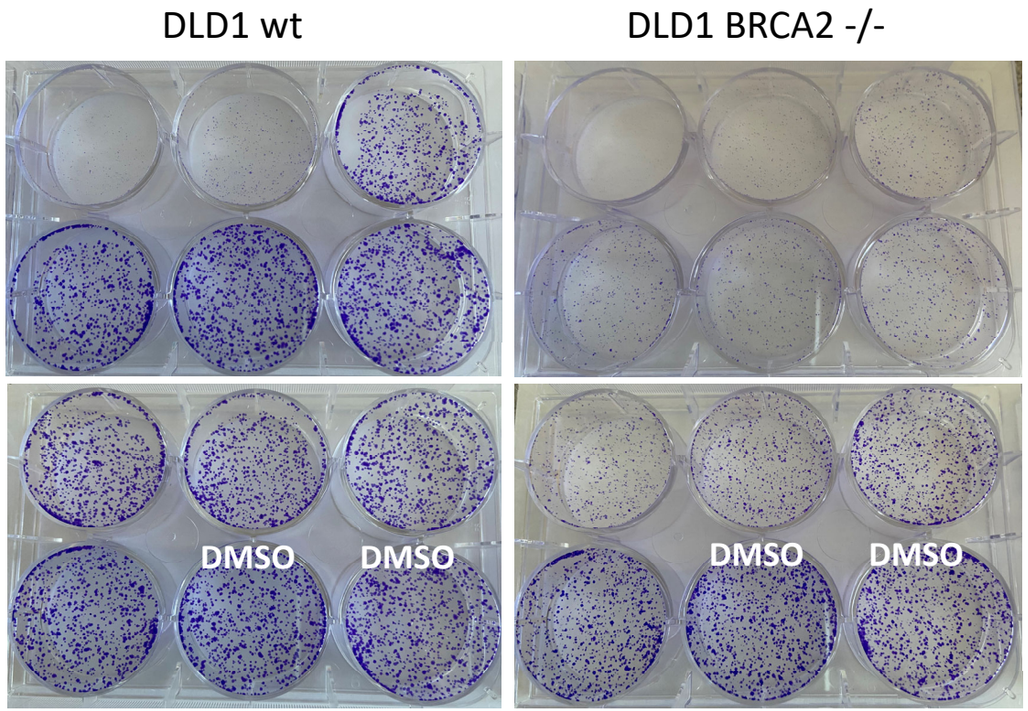
### Genetic Knockdown Data



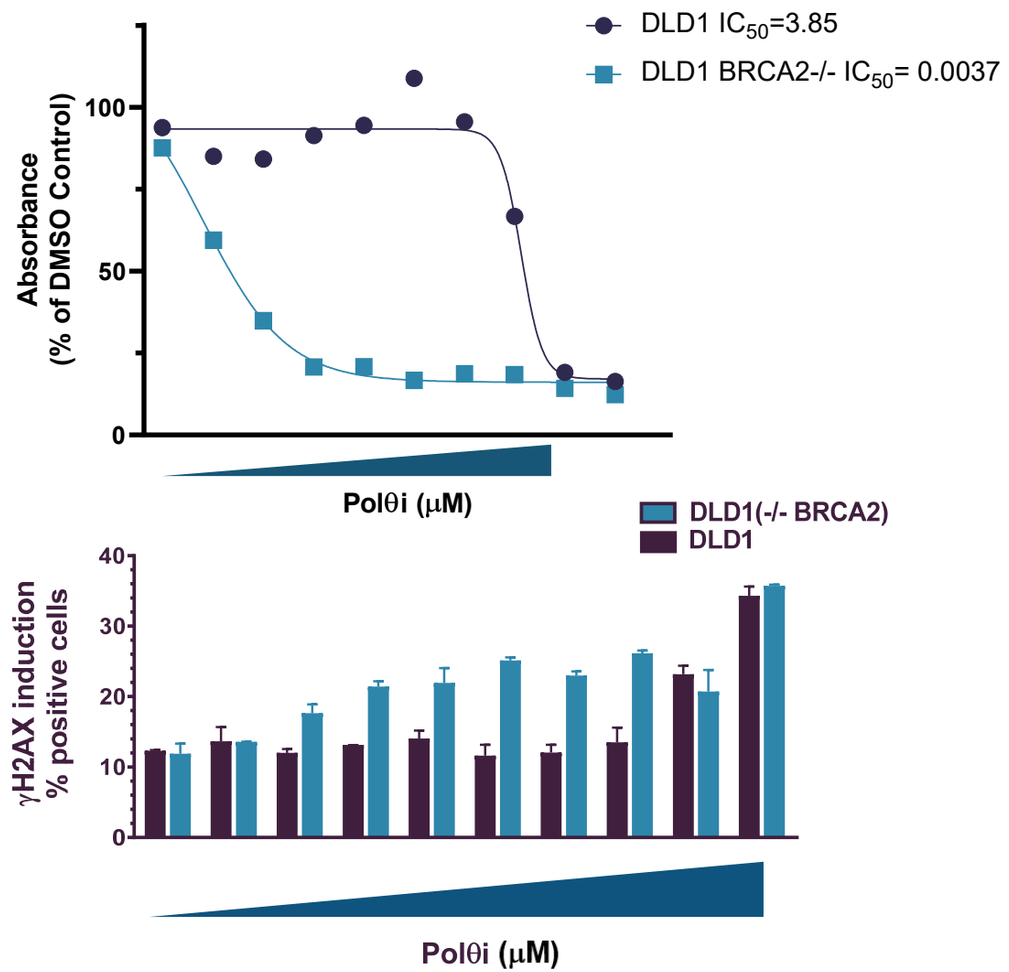

Several BRCA1 and BRCA2 mutant lines show strong Polθ dependence

# 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

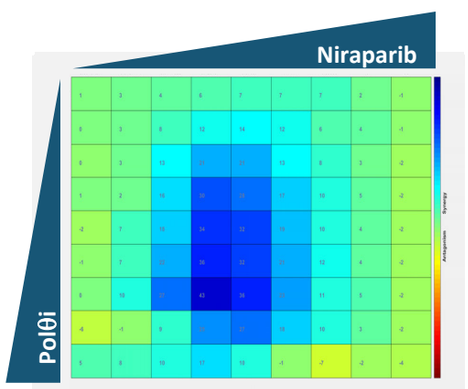


# IDEAYA Polθ ATPase Inhibitors are Synergistic with niraparib in DLD1 BRCA2-/- Cells but not in Parental DLD1wt Cells

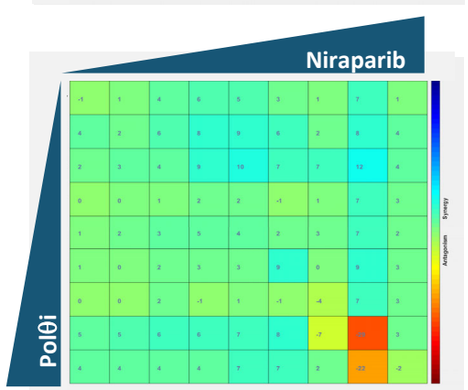
## DLD1 isogenic cell line γH2AX Assay

### HSA Model

DLD1 BRCA2-/-

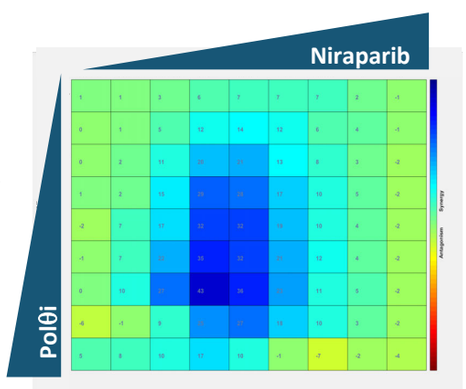



DLD1 WT

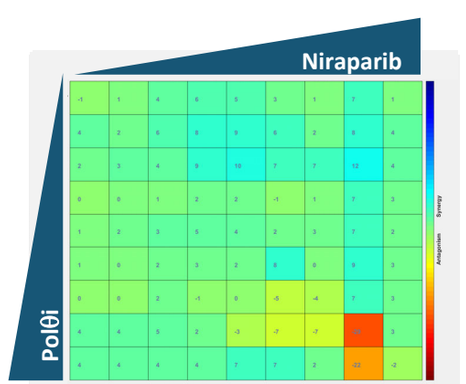



### Loewe Model

DLD1 BRCA2-/-

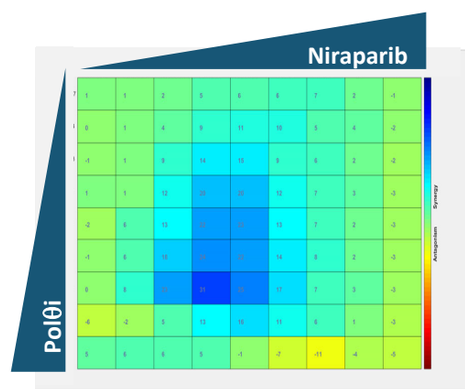



DLD1 WT

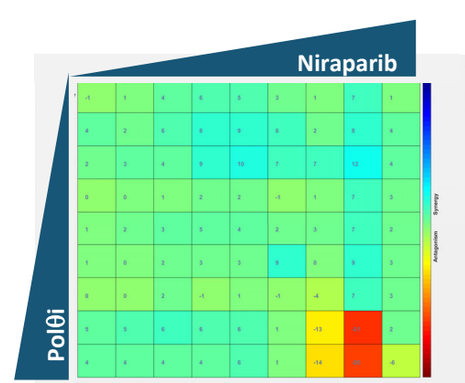



### Bliss Model

DLD1 BRCA2-/-

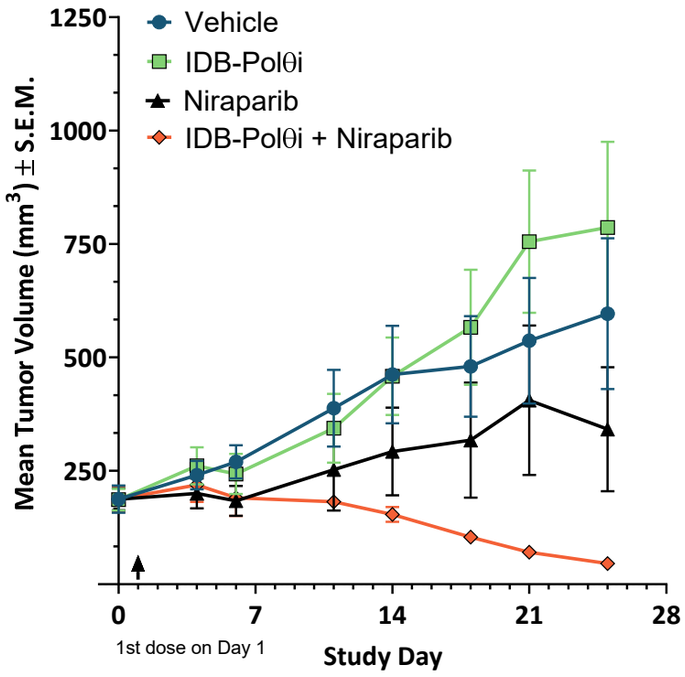



DLD1 WT

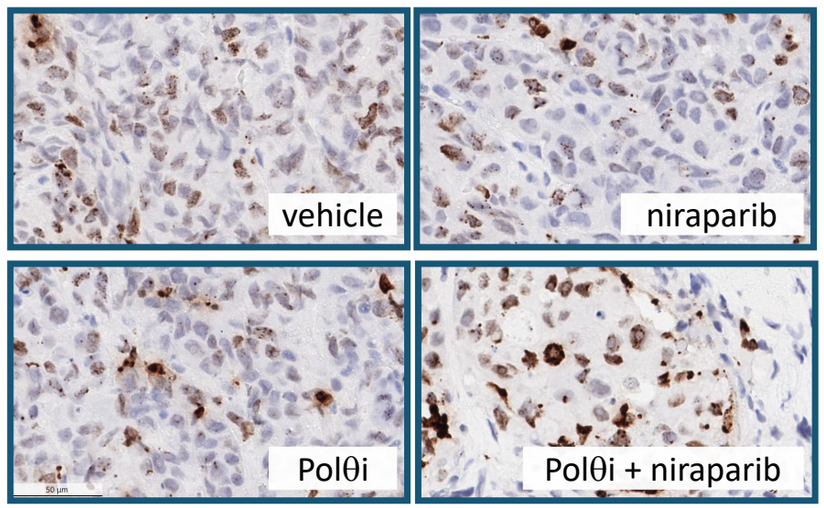


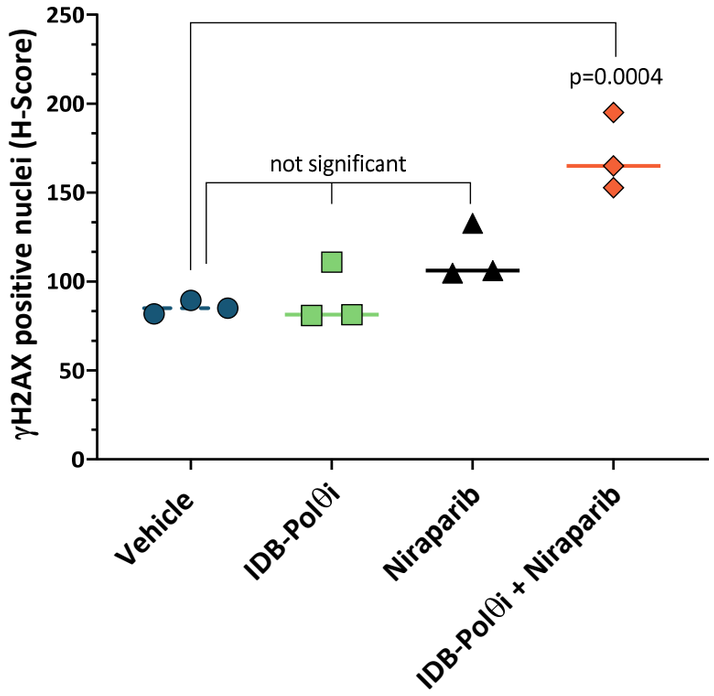
# IDEAYA Polθ ATPase Inhibitors in Combination with niraparib induce DNA Damage resulting in Tumor Regression

## DLD1 BRCA2-/- *in vivo* xenograft Study




IHC for γH2AX



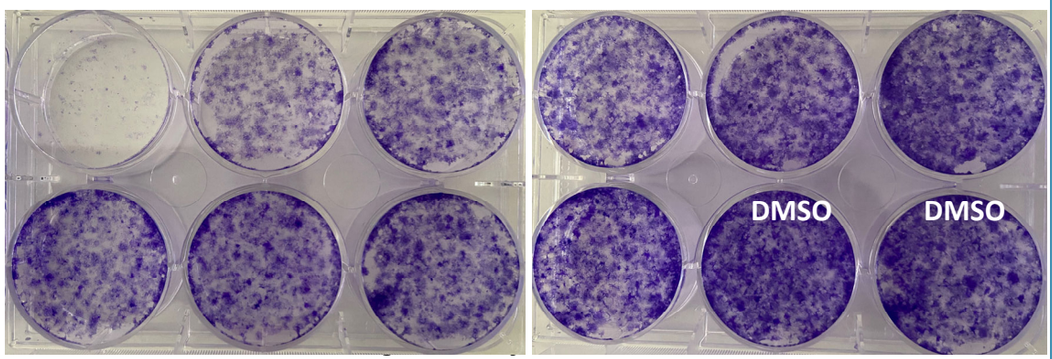

Regressions observed for all animals dosed with combination

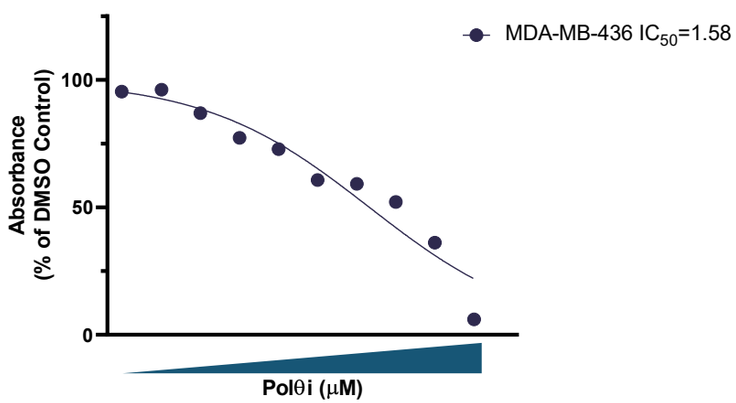
Polθi in combination with niraparib demonstrates significant enhancement of DNA Damage

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

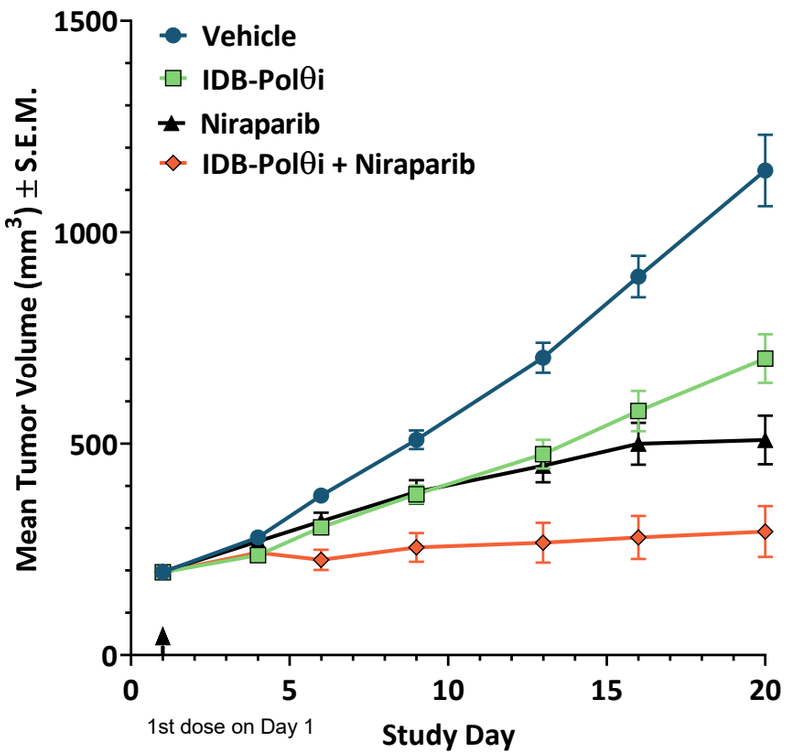
MDA-MB-436: endogenous BRCA1 mutated TNBC cell line

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



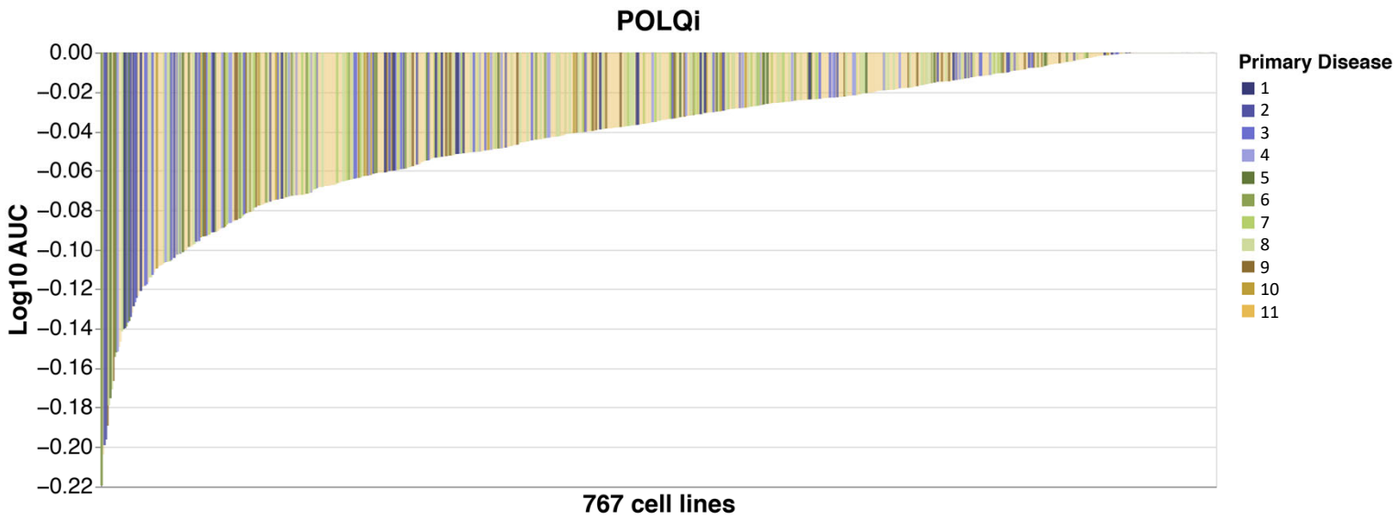




## Monotherapy and Combination TGI with niraparib *in vivo*

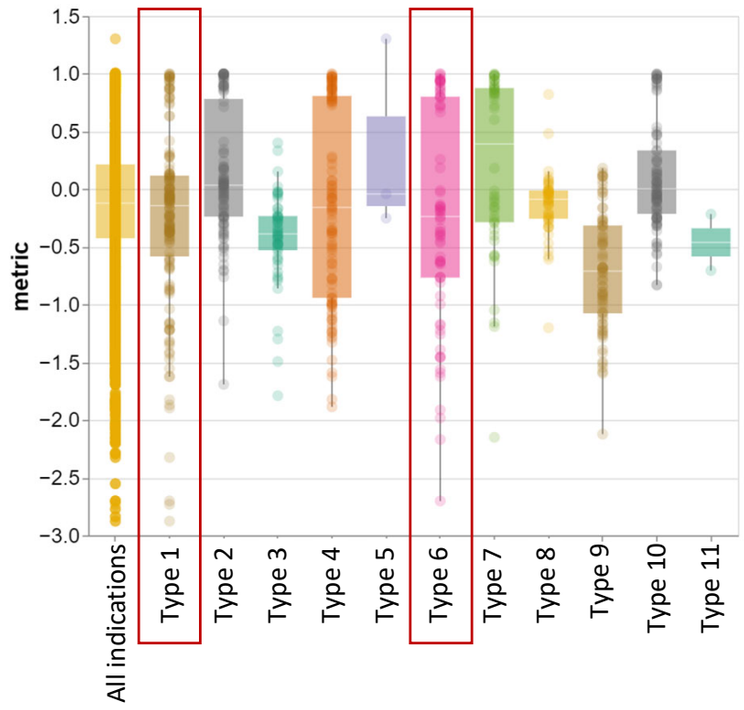


# PRISM Screen Identifies Additional Cell Lines Sensitive to Single Agent IDEAYA Polθ ATPase Inhibitor

## 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

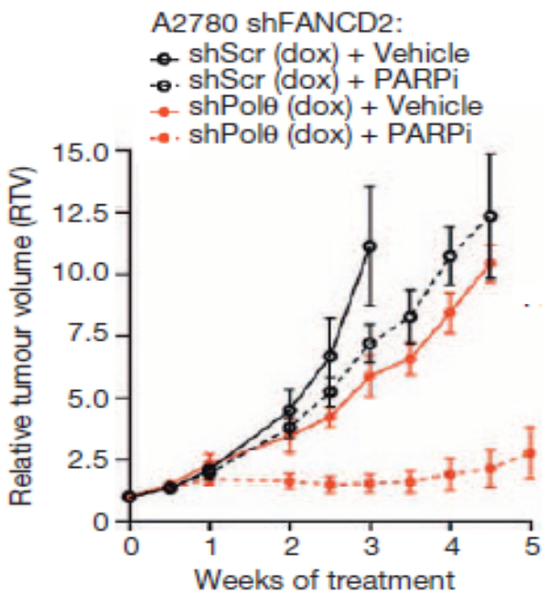
## Pol Theta Clinical Considerations

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**

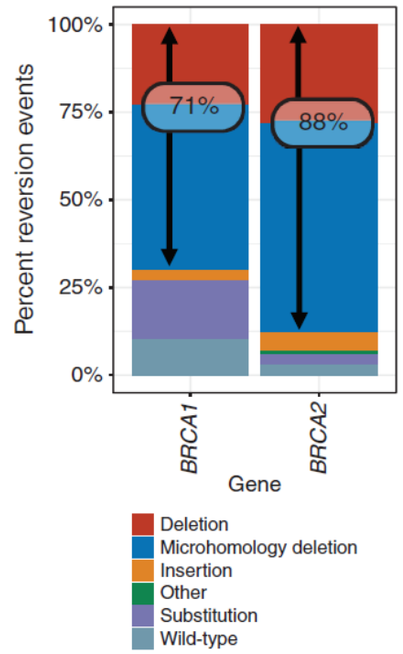
### Overcome PARPi resistance

- 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

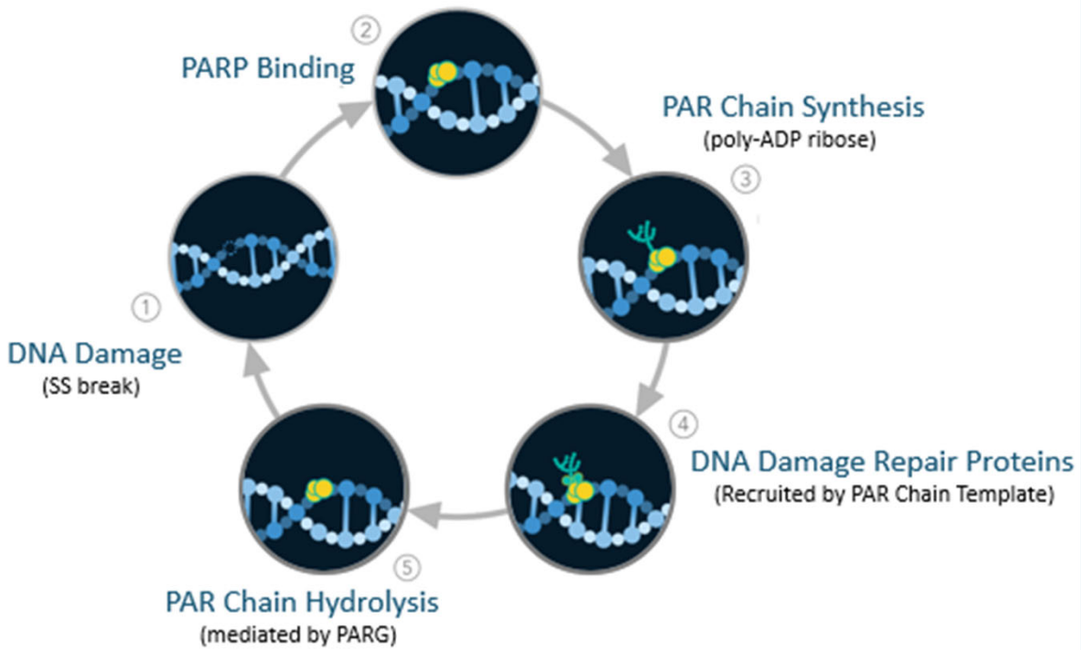
## IDEAYA PARG Inhibitor Preclinical Program

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

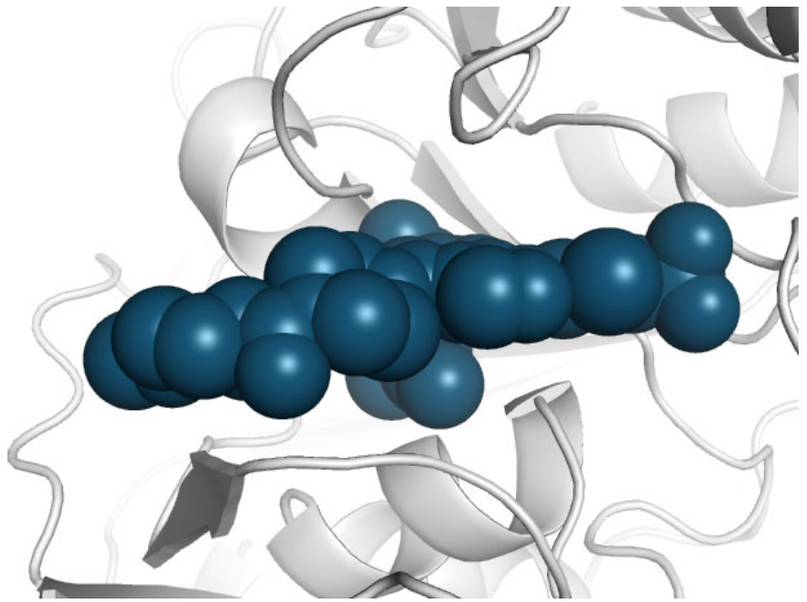
# PARG Synthetic Lethality Program

## 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**



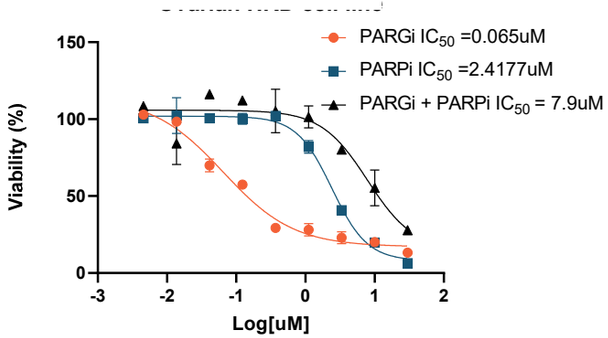
First in class lead optimization program guided by structure-based drug design

IDEAYA Data

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

## Differentiated activity to PARP inhibition in Ovarian Cancer Model

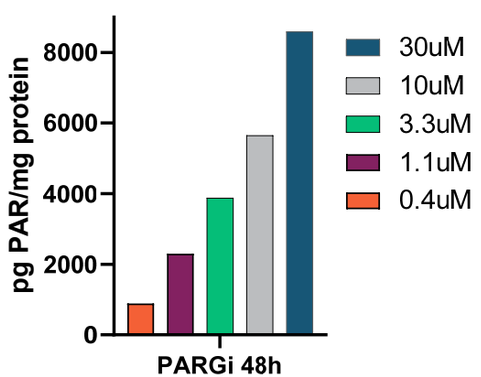
### Ovarian Cancer HRD cell line *in vitro* Profile



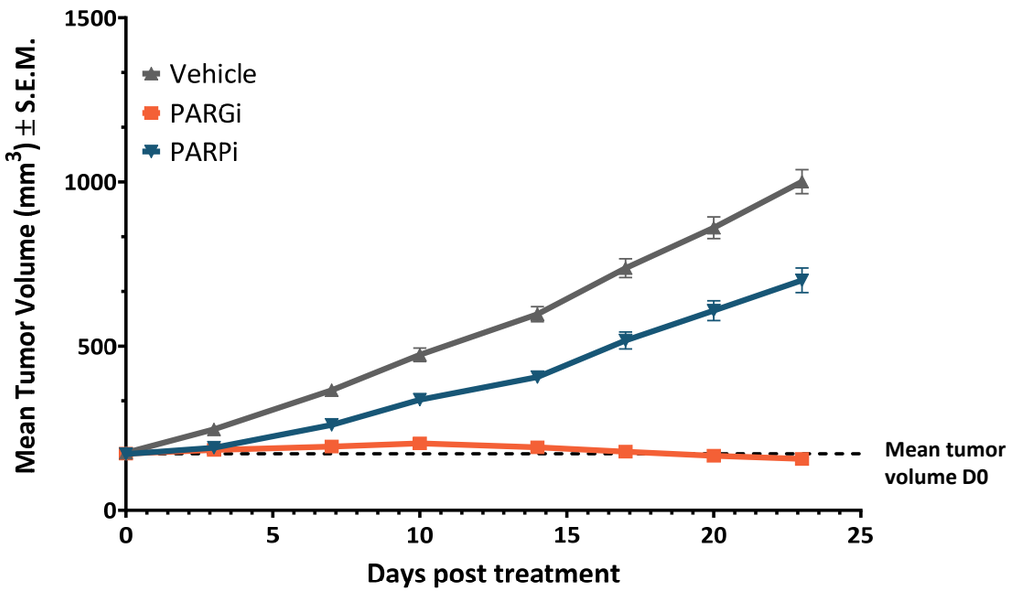

Consistent with an on target cellular mechanism of action, PARP1 inhibition (dosed at $IC_{10}$) antagonizes PARG inhibition

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

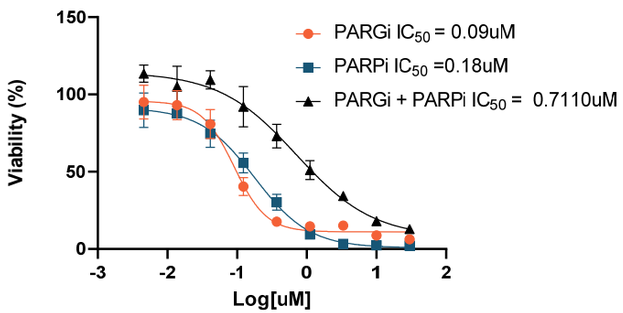



IDB-PARGi demonstrates enhanced tumor growth inhibition (TGI) relative to a PARP inhibitor, and tumor regression

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

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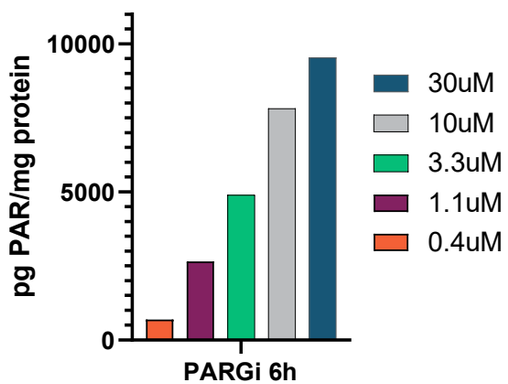
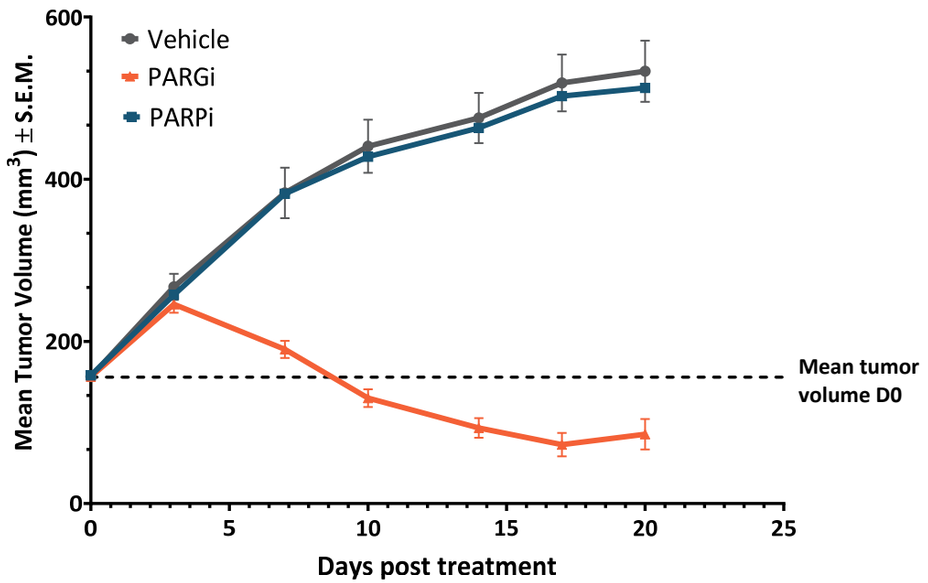



### Gastric Cancer HRD cell line *in vivo* CDX Model

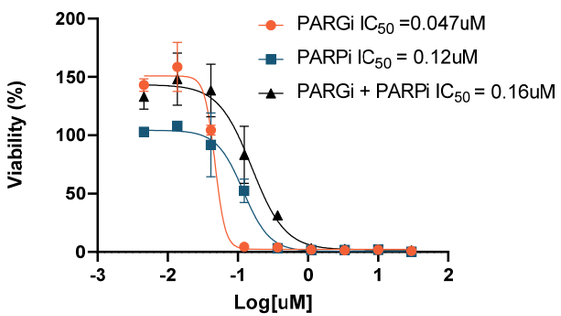



IDB-PARGi demonstrates enhanced tumor growth inhibition (TGI) and tumor regression in PARPi refractory setting

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

## Differentiated activity to PARP inhibition in Breast Cancer Model

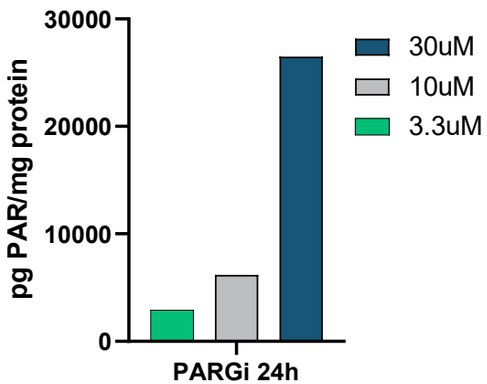
### Breast Cancer HRD cell line *in vitro* cell Profile



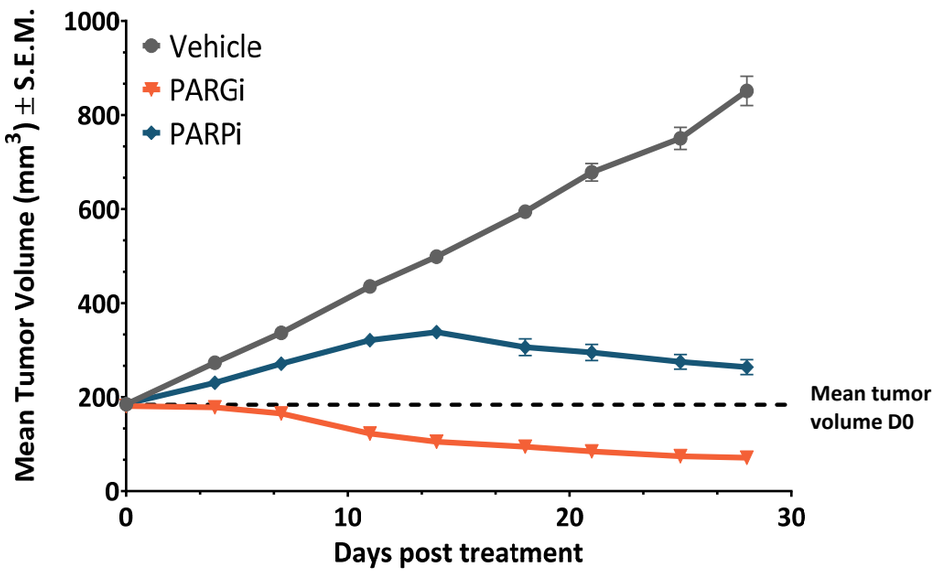

Consistent with an on target cellular mechanism of action, PARP1 inhibition (dosed at $IC_{10}$) antagonizes PARG inhibition

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

The data further confirms an on-target cellular MOA of the PARGi.




### Breast Cancer HRD cell line *in vivo* CDX Model

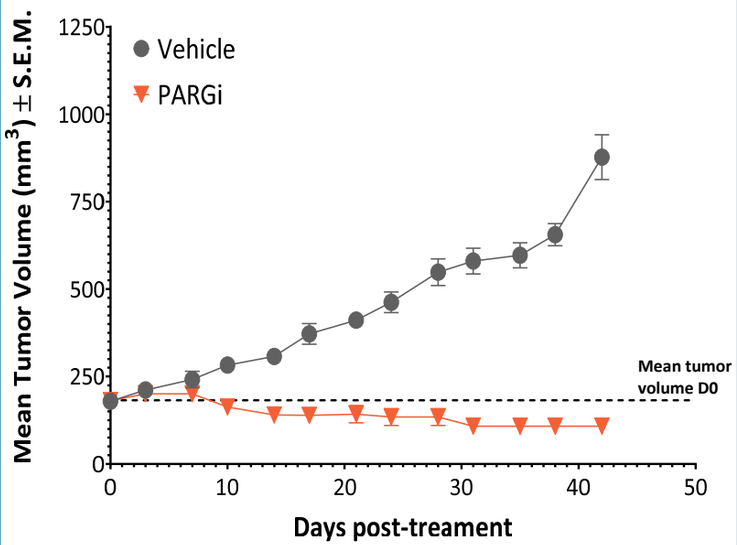



IDB-PARGi demonstrates enhanced tumor growth inhibition (TGI) relative to a PARP inhibitor, and tumor regression

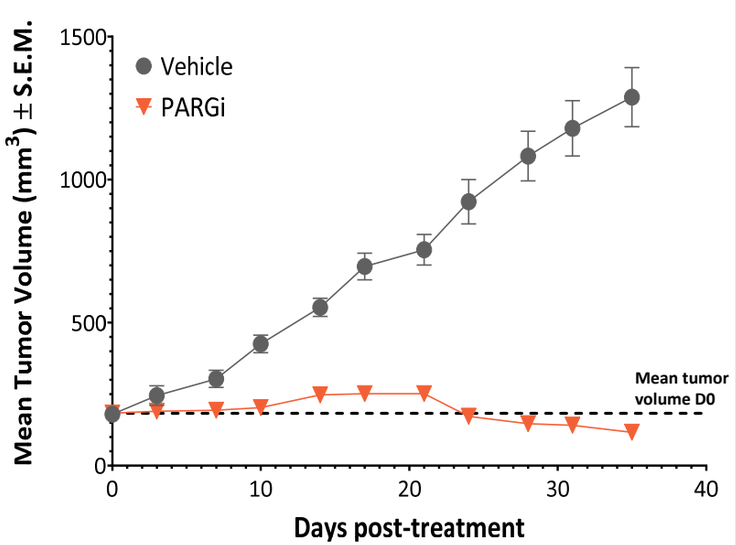
# IDEAYA PARGi shows Robust TGI in Breast PDX Models

## Monotherapy Tumor Regressions observed across Multiple Breast PDX Models

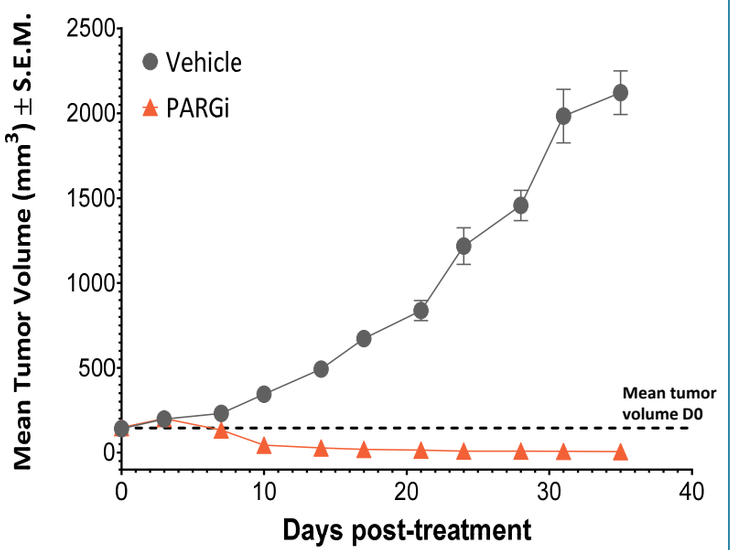
### Breast Cancer PDX Model 1




### Breast Cancer PDX Model 2




### Breast Cancer PDX Model 3



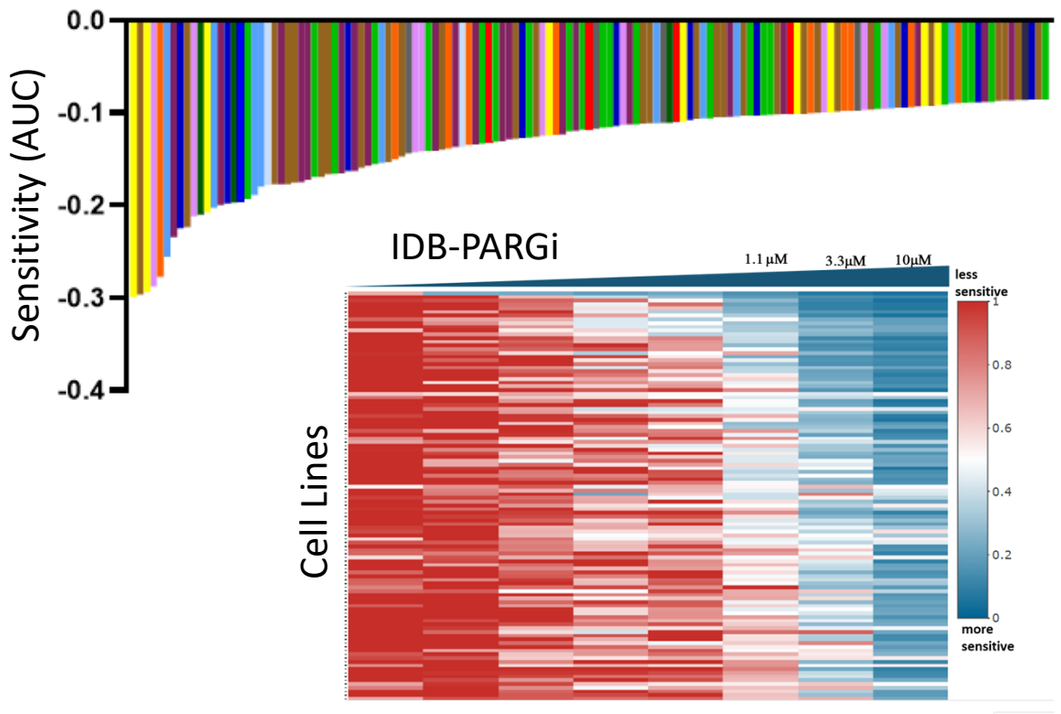

## Evaluation of IDB-PARG in Patient Derived Xenograft (PDX) models in Breast Cancer

- 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

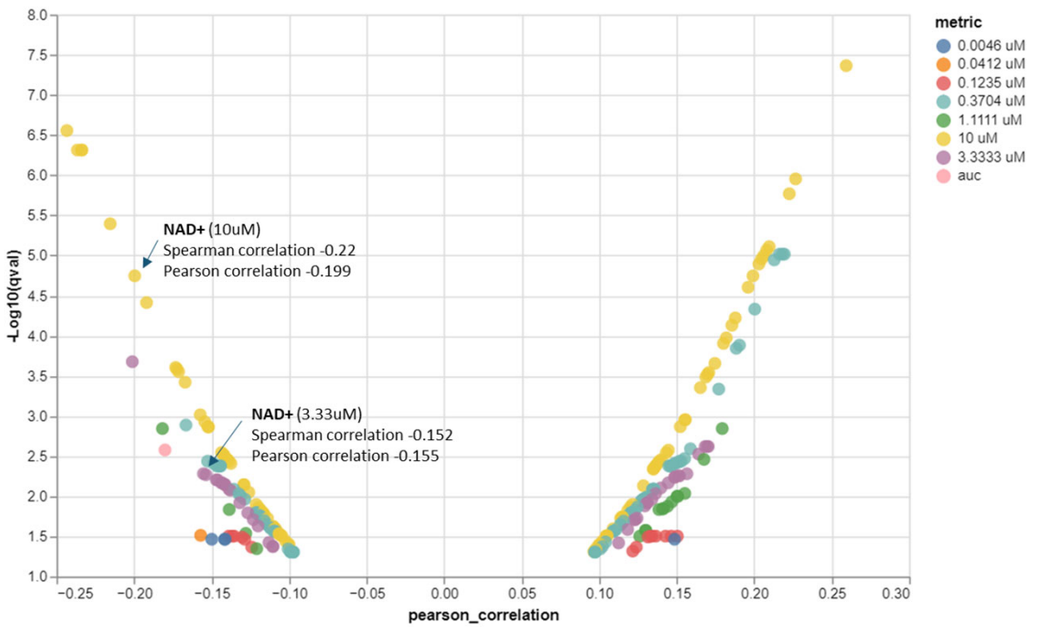
# PRISM Screen Identifies Additional Tumor Lineages and Indications Sensitive to Single Agent IDEAYA PARG Inhibitor

## 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

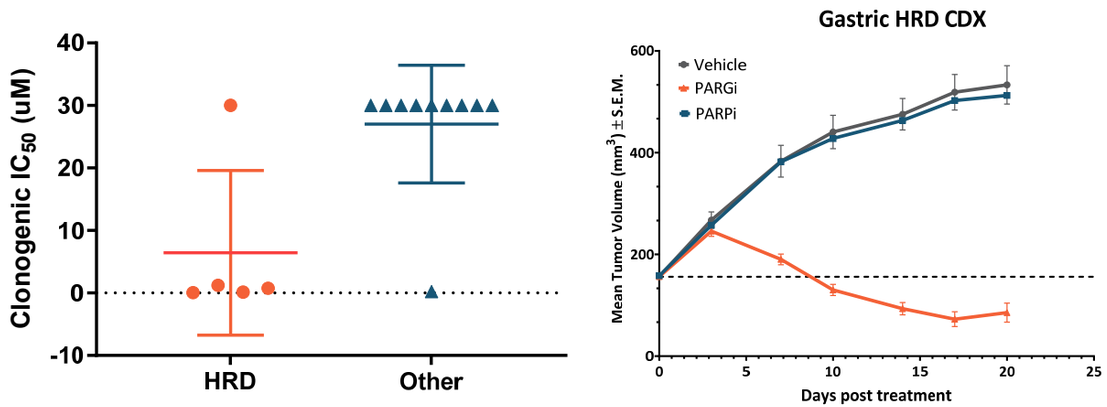
## Multiple Possibilities for Clinical Stratification

### 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

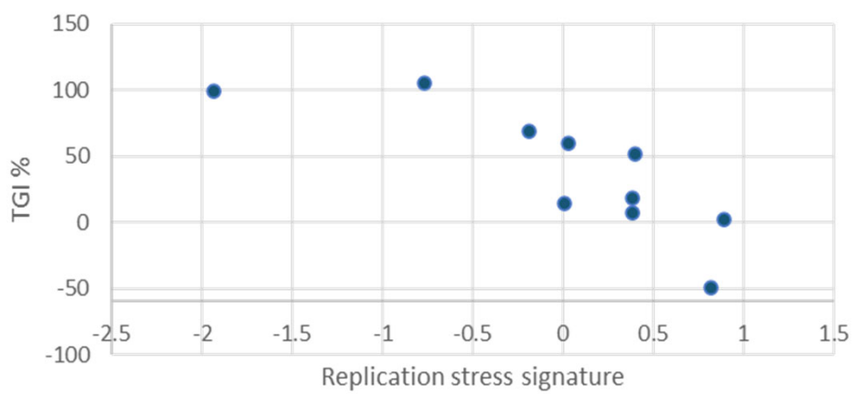
[1] Abed et al IDEAYA AACR Poster 2021




### Replication Stress Signature

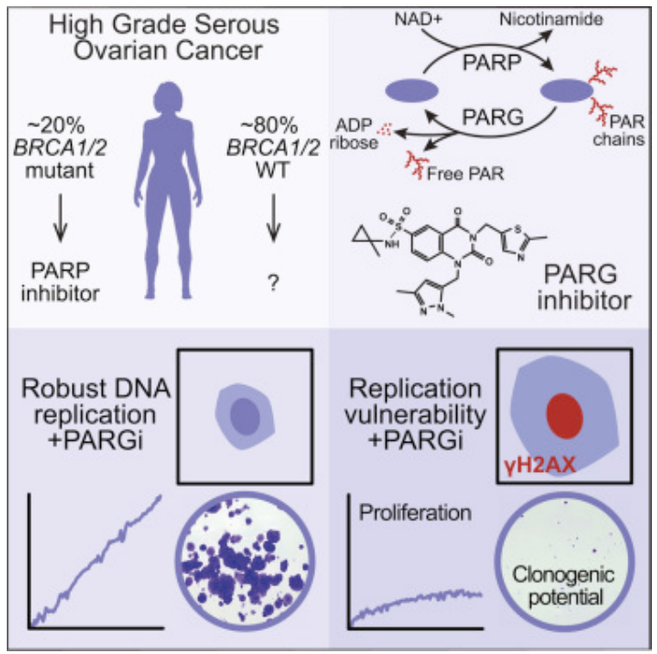
PARGi response in PDx models can be predicted using a pre-defined replication stress signature that has been previously described [2]

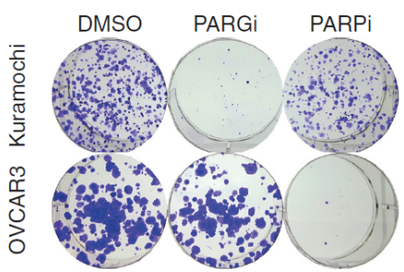
[2] Cancer Cell Vol 35 (2019): 519-533.



# 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



IDEAYA BIOSCIENCES