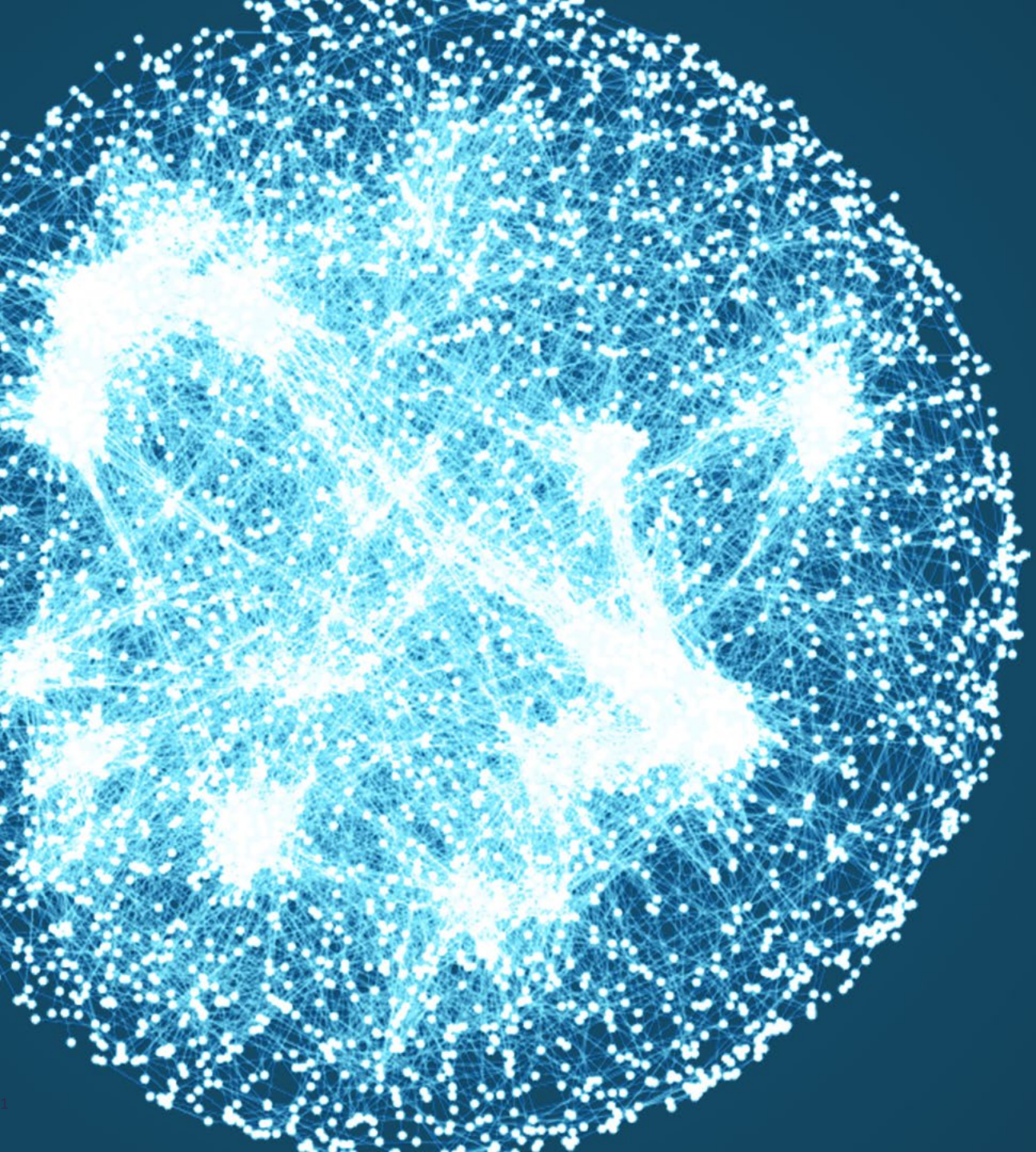


IDEAYA Investor R&D Day
December 12, 2022
NASDAQ: **IDYA**

IDEAYA Biosciences

Improving Lives Through Transformative Precision Medicine

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, 2021, 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.

IDEAYA Investor R&D Day

Welcome and Introduction

Yujiro S. Hata
IDEAYA Biosciences
President and Chief Executive Officer

IDEAYA Investor R&D Day

Welcome to our Participants and Guest Speakers

Frank McCormick, Ph.D., FRS, D.Sc (Hon)

University of California San Francisco (UCSF)

Carol Shields, M.D.

Thomas Jefferson University

Karlene Cimprich, Ph.D.

Stanford University

Mathew Garnett, Ph.D.

Wellcome Sanger Institute

Timothy Yap, M.D.

M.D. Anderson Cancer Center

Ben Schwartz, Ph.D.

GSK

IDEAYA Investor R&D Day

Agenda Topics

The Synthetic Lethality Paradigm

- Overview of Synthetic Lethality Therapy Opportunity in Oncology
- IDEAYA Vision, Strategy and Pipeline

Darovasertib Clinical Evaluation in Neoadjuvant Uveal Melanoma

- Clinical Development Plan and Potential Patient Impact

Mechanistic Advances Support Combination Approaches to Treat MTAP Deleted Tumors

- Dual Synthetic Lethal Strategy for MAT2A Clinical Combination Therapies

Selective Essentiality in DNA Damage Repair

- Introduction – IDEAYA's DDR Synthetic Lethality Pipeline
- Targeting Replication Stress is an Emerging Synthetic Lethality Paradigm
- Novel Approach to HRD: IDE161 PARG inhibitor Preclinical Activity and Clinical Development Plan
- Werner Helicase is a Cornerstone Synthetic Lethality Target for MSI-High Cancers
- Targeting Pol Theta to Enhance and Maintain Control of HRD Tumors

Closing Remarks and Analyst Q&A

The Synthetic Lethal Paradigm

Overview of Synthetic Lethality Therapy Opportunity in Oncology

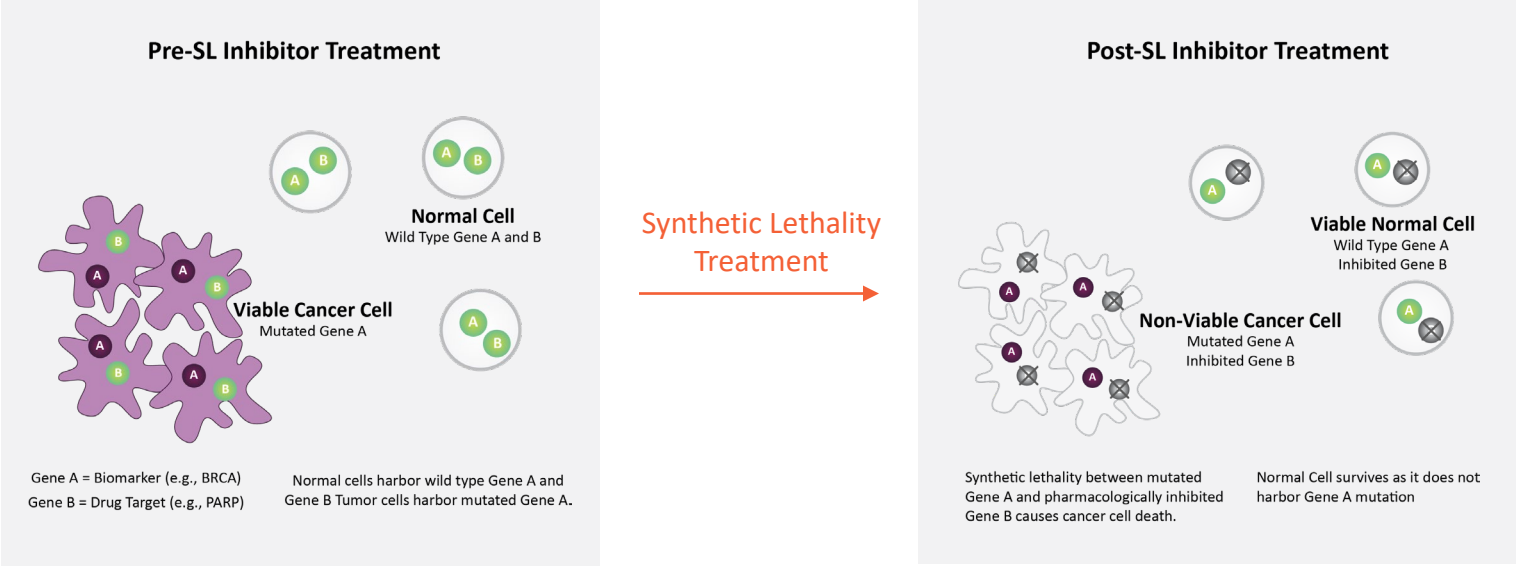
Frank McCormick, Ph.D., FRS, D.Sc (Hon)
University of California San Francisco (UCSF)
Professor, Helen Diller Family Comprehensive Cancer Center and Department of Cellular and Molecular Pharmacology
Chair, David A. Wood Distinguished Professorship of Tumor Biology and Cancer Research

The Power of Synthetic Lethality in Cancer Drug Development

Synthetic Lethal Targets in Oncology create Opportunities for New Therapies

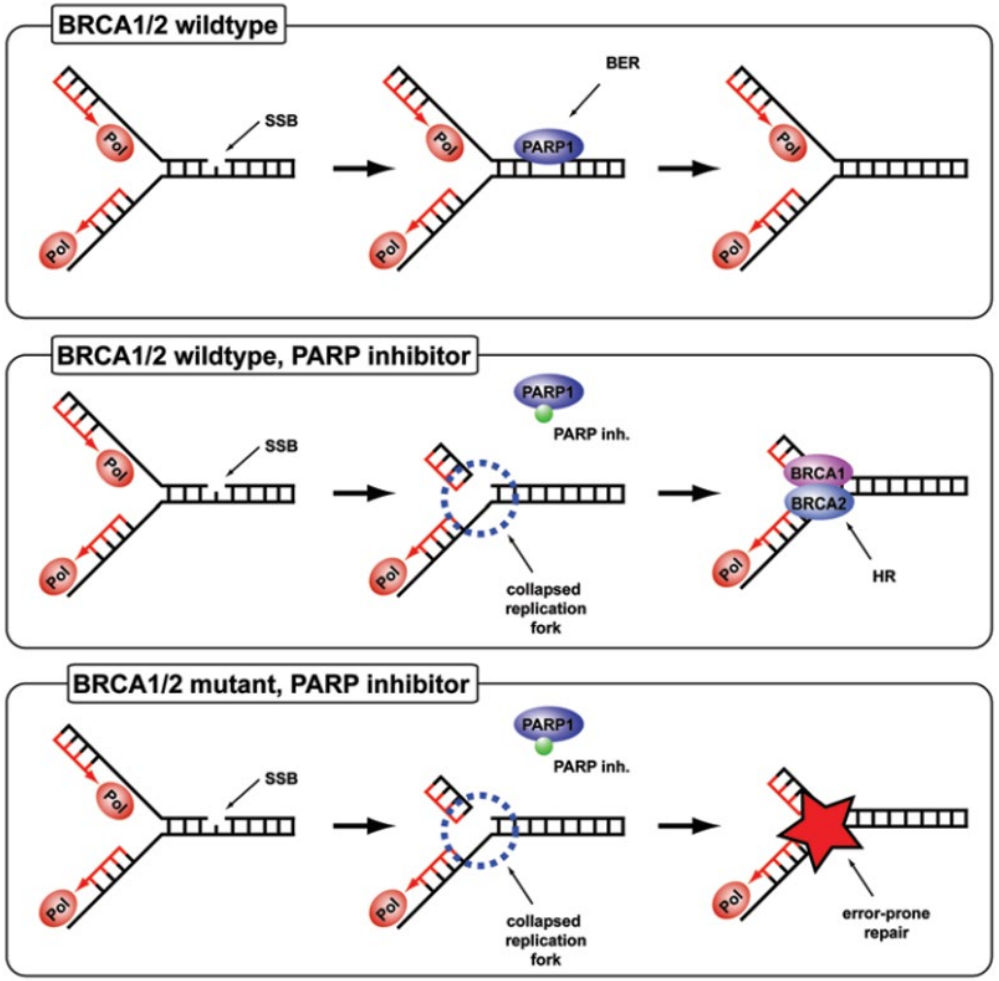
Synthetic lethality occurs in genetics when the simultaneous perturbation of two genes results in cellular or organismal death

In cancer, a synthetic lethal target is a protein that is dispensable in normal cells but becomes essential in cells expressing on oncogene or losing a tumor suppressor. This protein is an ideal cancer target.



The Power of Synthetic Lethality in Cancer Drug Development

Example One – PARP Inhibition in Tumors Having BRCA1/2 Mutations



Normal Cells: Single-strand breaks (SSBs) are repaired by PARP

Normal Cells: Inhibiting PARP → BRCA1/2 proteins take over

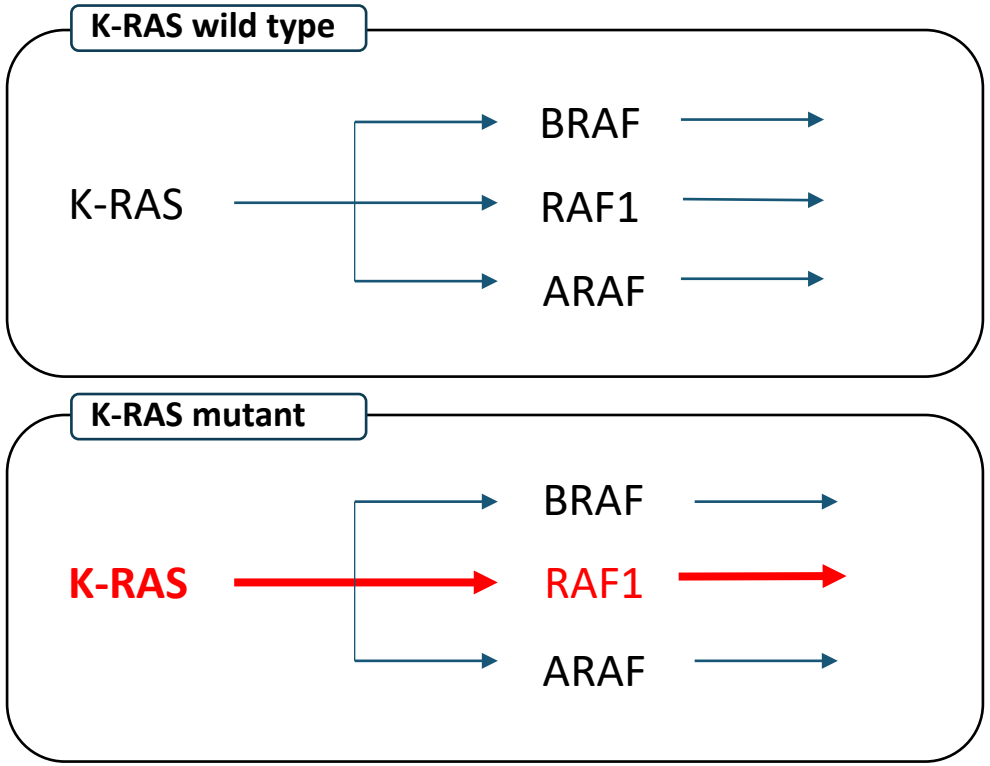
BRCA-deficient Cancer Cells: Inhibiting PARP → cells die

Exploiting synthetic lethal interactions for targeted cancer therapy. H. Christian Reinhardt, Hai Jiang, Michael T. Hemann & Michael B. Yaffe

IDEAYA BIOSCIENCES

The Power of Synthetic Lethality in Cancer Drug Development

Example Two – RAF1 Inhibition in Tumors having KRAS Mutations

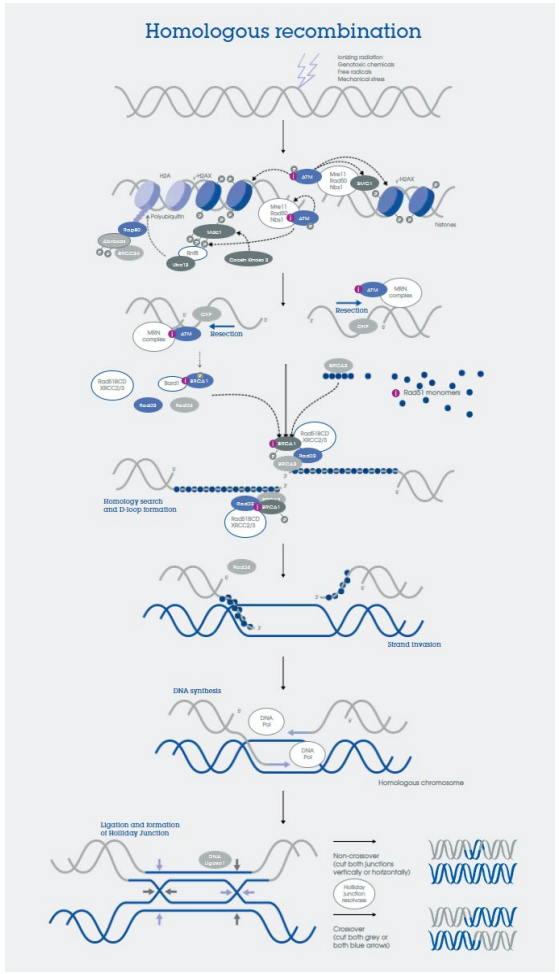


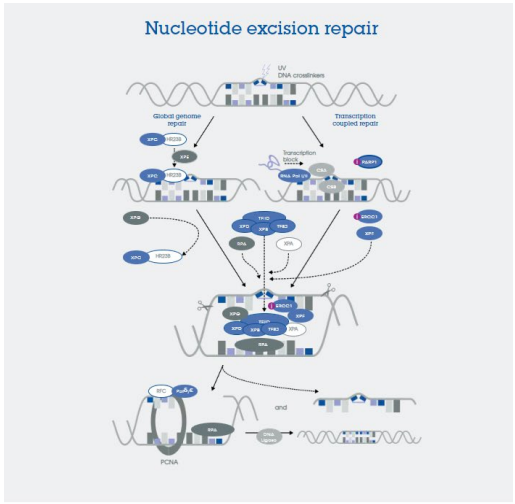
Normal Cells: K-RAS activates 3 RAF isoforms; ablation of any RAF isoform has no effect

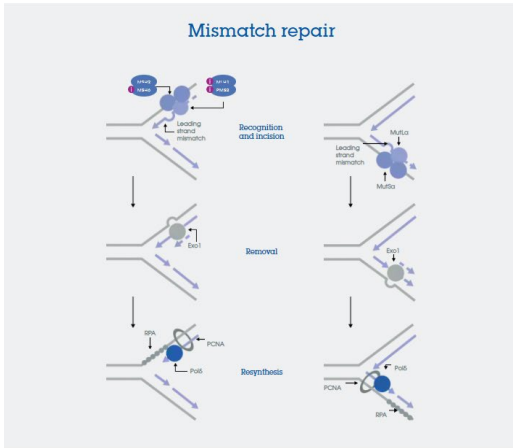
K-RAS-mutant Cancer Cells: Ablation of RAF1, but not ARAF or BRAF, causes tumor regression

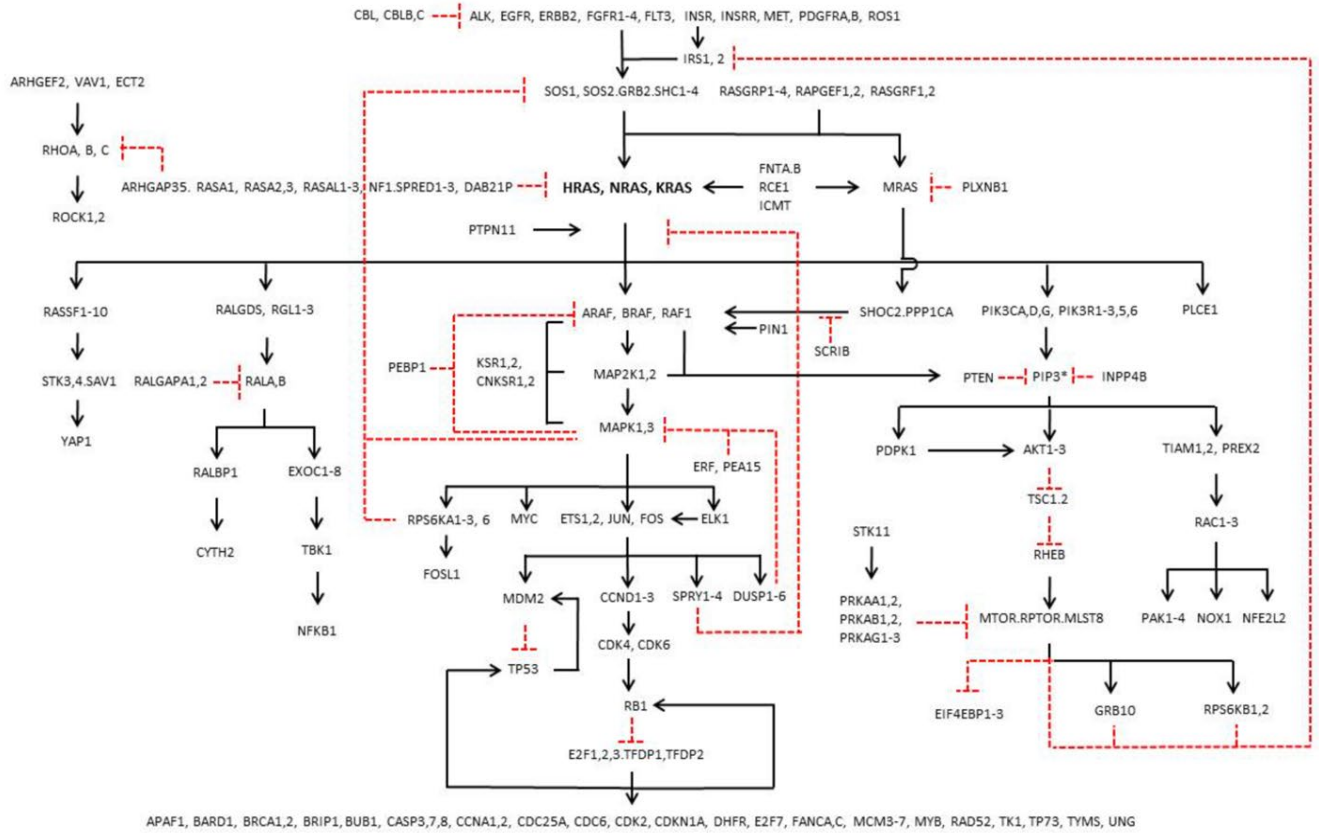
The Power of Synthetic Lethality in Cancer Drug Development

SL Targets emerge from a Deep Understanding of Specific Signaling Networks









The Power of Synthetic Lethality in Cancer Drug Development

IDEAYA Synthetic Lethality Platform

IDEAYA is drawing on its expertise in cancer networks and using proprietary platforms to identify novel SL relationships

Novel Synthetic Lethality Platform and Data Integration

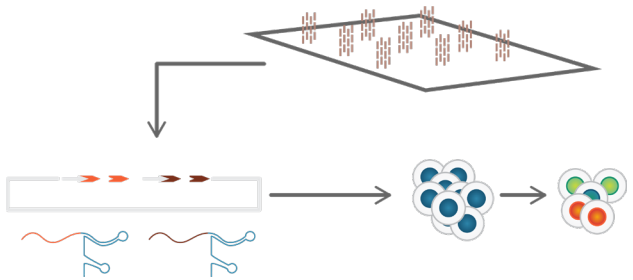
IDEAYA SL Platform integrates extensive proprietary and public data sets with orthogonal and complementary content

Bioinformatic analysis enables identification and validation of synthetic lethal target / biomarker interactions across vast datasets

Robust SL interactions validated genetically (Dual CRISPR, paralogues, isogenic pairs, CRISPR/siRNA), pharmacologically and *in vivo*

DECIPHER™

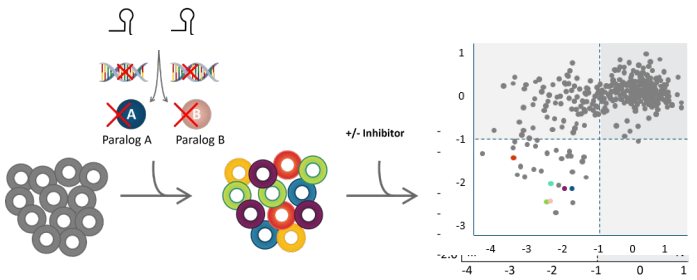
Dual CRISPR SL Library in DNA Damage Repair [2]



Evaluation of DNA Damage Targets synthetic lethal with tumor suppressor or oncogenes

PAGEO™

Paralogous Gene Evaluation in Ovarian Cancer [1]



Evaluation of SL targets in context of functionally redundant paralogous genes in ovarian cancer

Partnership Datasets

Cancer Dependency Map – Broad Institute

Foundation Insights™ – Foundation Medicine

depmap portal | FOUNDATIONINSIGHTS™

Public Databases

IDEAYA data mining and analysis across data sets

PROJECTGENIE | TCGA | MSK-IMPACT™ | Project Achilles | BioPortal | CCLE

[1, 2] IDEAYA Proprietary Libraries and Datasets – Strategic Collaborations with Broad Institute[1] and UC San Diego[2]

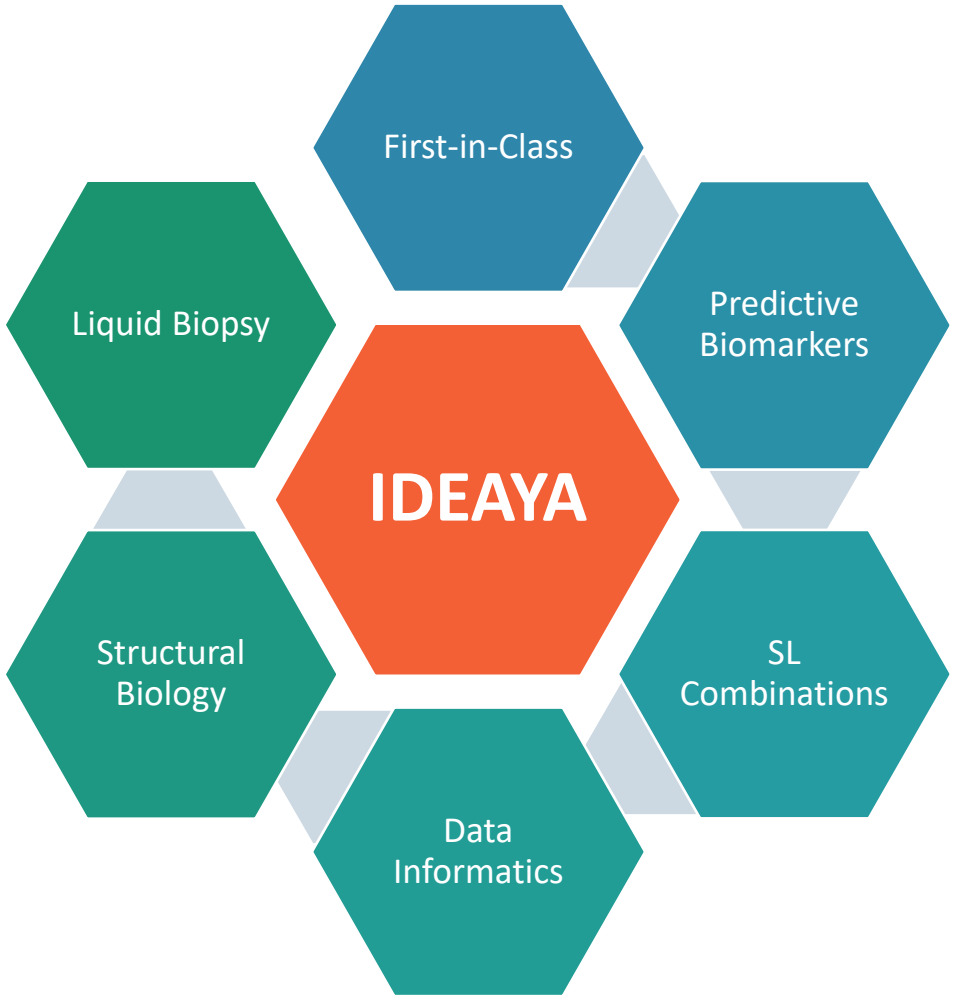
The Synthetic Lethality Paradigm

IDEAYA Vision, Strategy and Pipeline

Yujiro S. Hata
IDEAYA Biosciences
President and Chief Executive Officer

IDEAYA Vision & Strategy

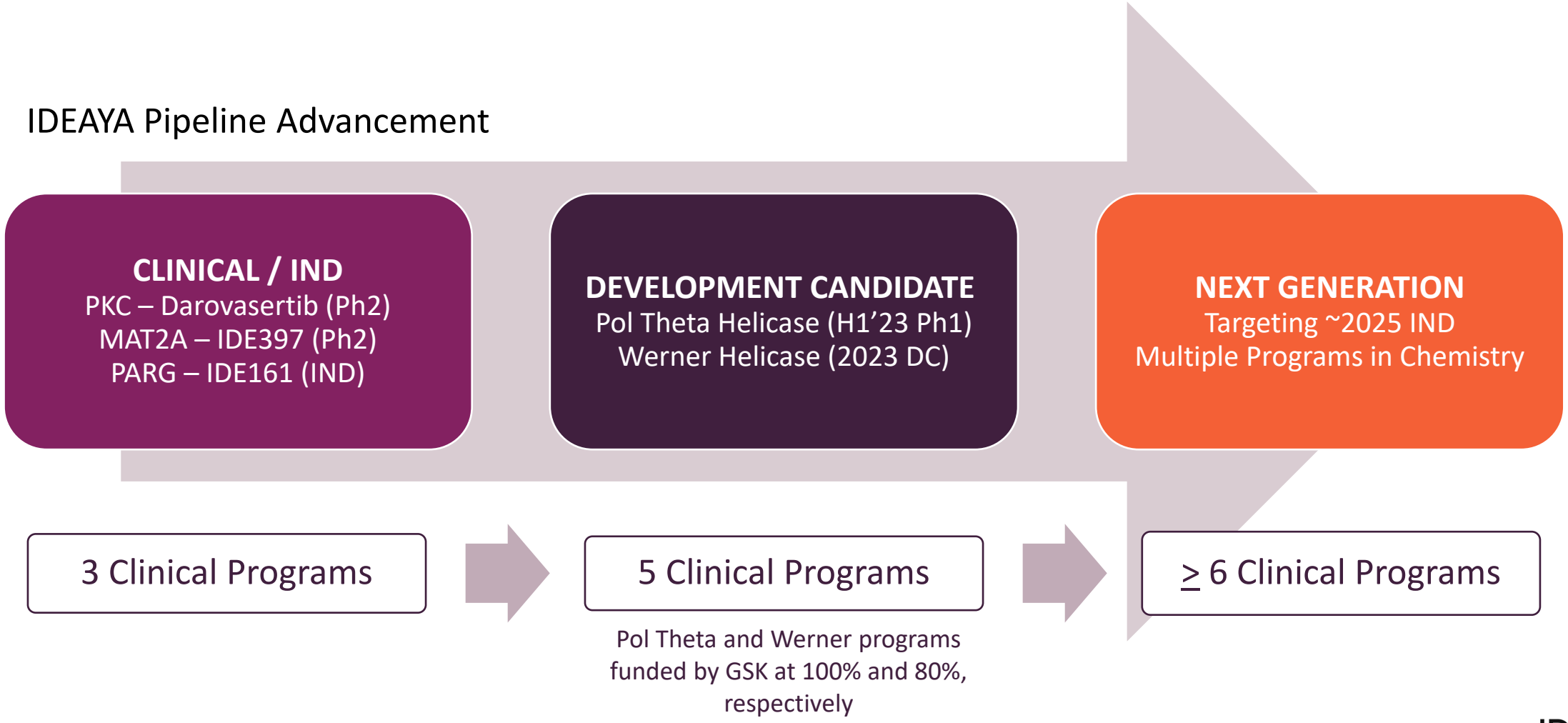
Improving Lives through Transformative Precision Medicines



Building the leading Synthetic Lethality Precision Medicine Oncology Company

IDEAYA Synthetic Lethality Pipeline

Targeting ≥6 First-in-Class Clinical Programs under our 2026 Cash Runway



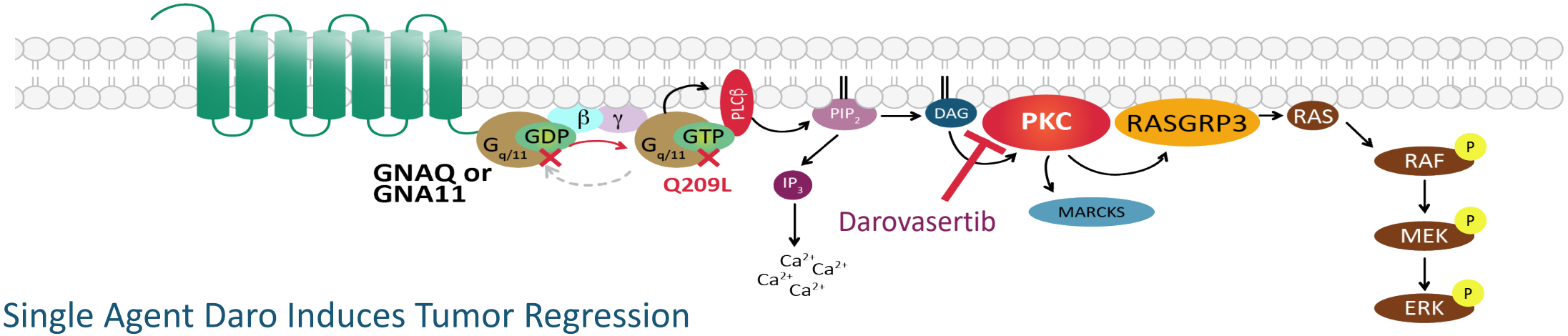
Darovasertib Clinical Evaluation in Neoadjuvant Uveal Melanoma

Clinical Development Plan and Potential Patient Impact

Carol Shields, M.D.
Thomas Jefferson University
Chief, Ocular Oncology Service at Wills Eye Hospital
Professor of Ophthalmology

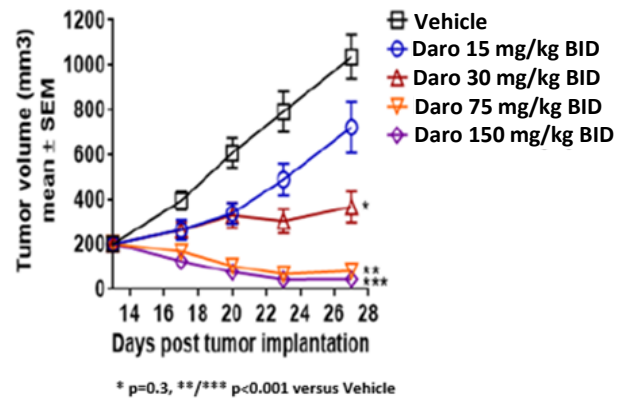
Darovasertib in Neoadjuvant Primary Uveal Melanoma

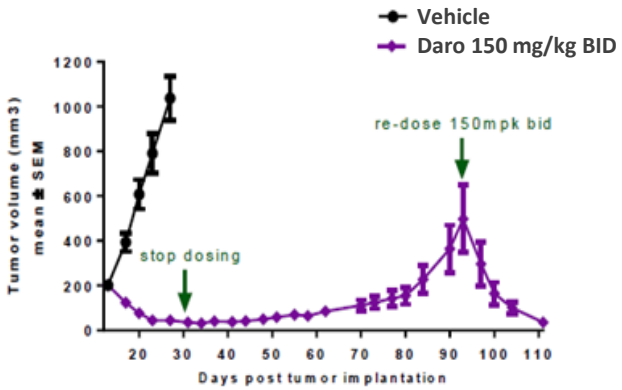
Mutations in GNAQ / GNA11 activate PKC Signaling, a genetic driver of Uveal Melanoma



Single Agent Daro Induces Tumor Regression

92.1 mutant GNAQ xenograft (uveal melanoma cell line)





Darovasertib is an investigational potent and selective PKC inhibitor, orally administered

GNAQ or GNA11 mutations activating PKC signaling occur in >~90% of UM patients

UM is currently treated with enucleation and/or radiation as primary therapy

No approved systemic therapies for (Neo)Adjuvant UM

Van Raamsdonk, CD, et. al, Nature 2009; Van Raamsdonk CD, et. al, NEJM 2010; Piperno-Neumann S, et. al, J Clin Oncol 2014

Darovasertib in Neoadjuvant Primary Uveal Melanoma

High Unmet Need with Opportunity to Improve Patient Outcomes

Current Treatment Approach following diagnosis of UM depends on tumor size and location within the eye:

- Enucleation in Large Tumors
- Radiation Therapy in Small and Medium Tumors

Poor Vision (≤20/200) occurs in about 70%-80% of patients with UM (including enucleation)

Metastasis occurs in up to ~50% of patients with UM

Neoadjuvant or Adjuvant Systemic Therapy might:

Reduce or Prevent Micrometastases and Save Lives

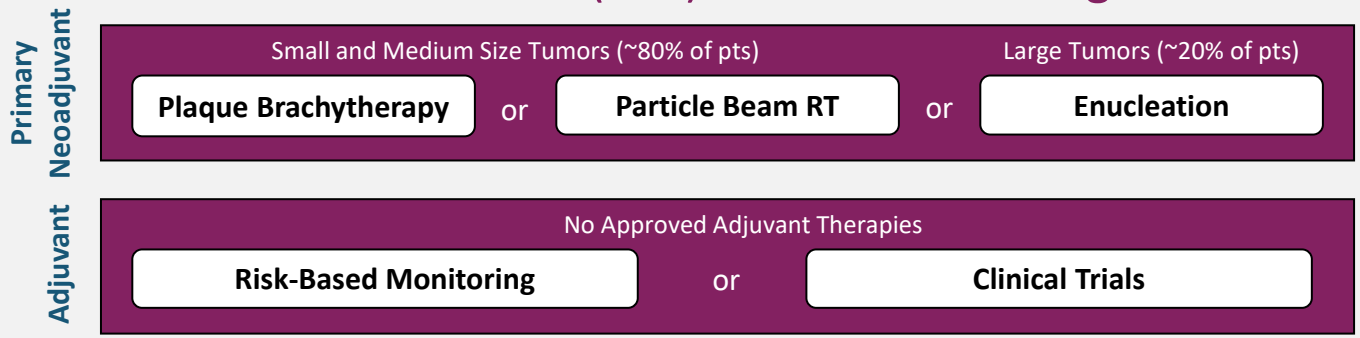
- Save the Eye by avoiding enucleation, and allow consolidation with Plaque Radiotherapy
- Reduce the Tumor Thickness in the Eye enabling treatment with less radiation and improved vision

Paradigm Shifting Opportunity: We have never had a therapy that could potentially:

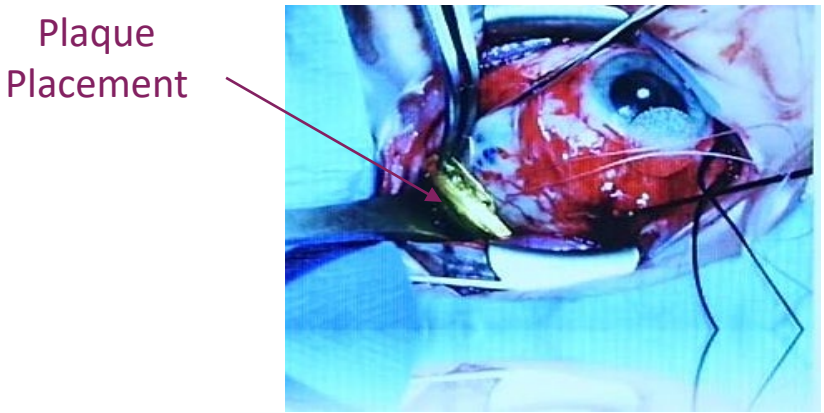
- Preserve the Eye
- Protect Vision
- Save Lives

Potential to Broadly Impact UM, a disease with annual incidence of ~8,000 – 9,000 patients in US and Europe

Uveal Melanoma (UM) Treatment Paradigm



Plaque Brachytherapy Treatment



Iodine-125 Plaque Surgery, UCLA

Preliminary Clinical Proof-of-Concept for Darovasertib in (Neo)Adjuvant UM

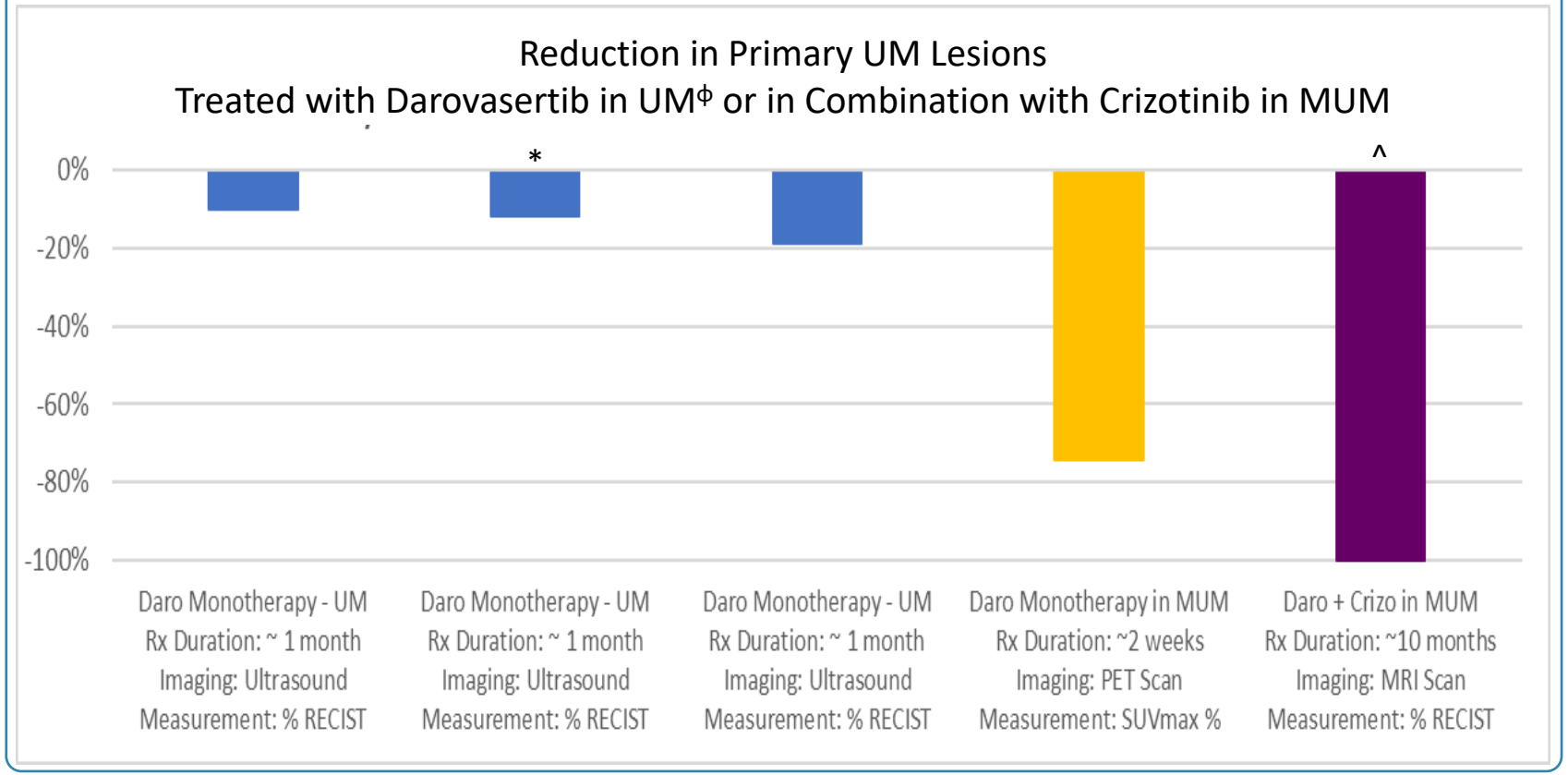
Observed 100% Tumor Reduction by RECIST in Primary Eye Lesion ^

Each Reported Case of Primary Eye Lesion has shown Reduction in Lesion Size with Darovasertib Treatment

Darovasertib (Neo)adjuvant UM

- All primary ocular tumor lesions have responded to darovasertib
- Consistent and clear evidence of response with 1 month of darovasertib monotherapy in NADOM IST per protocol design
  - Provides rationale to treat to maximal response for clinically meaningful improvement in primary therapies
- Well tolerated oral treatment

Reduction in Primary UM Lesions with Monotherapy & Combination Therapy



Φ Data from NADOM IST courtesy of Professor Anthony Joshua, MBBS, PhD, FRACP, St. Vincent's Hospital
* Patient showed ~42% SUVmax reduction by PET scan after 1 month
^ Patient's non-target ocular lesion scored by investigator as "Absent" by MRI RECIST, with an observed ~81% reduction of apical tumor height by ultrasound relative to baseline intact primary lesion with 10 months of treatment

Preliminary Clinical Proof-of-Concept for Darovasertib in (Neo)Adjuvant UM

Observed 100% Tumor Reduction by RECIST in Primary Eye Lesion

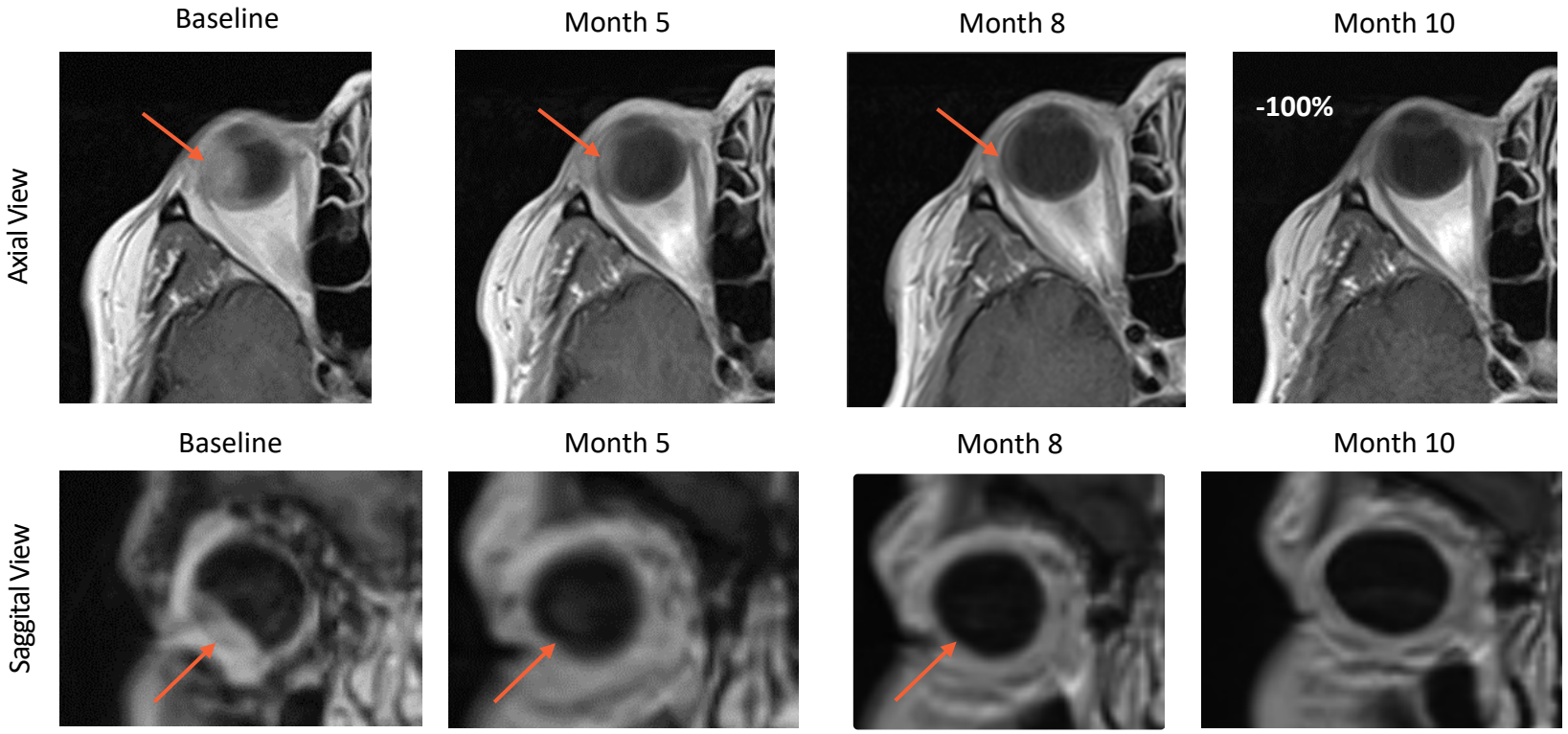
Case Study of MUM Patient Treated with Daro + Crizo

- 50+ year old pt
- First-Line MUM
- Intact 1^{o} lesion
- Daro + Crizo
- 100% tumor reduction in ocular lesion by MRI; RECIST, v1.1
- Visual symptoms resolved
- Confirmed PR

Patient Remains on Treatment at ~ 11 mo

Daro + Crizo Combination Therapy in MUM Patient With Intact Primary

Observed 100% Tumor Reduction in Uvea Lesion^



Images (MRI) courtesy of Marcus Butler, MD

^ Patient's non-target ocular lesion scored by investigator as "Absent" by MRI RECIST, with an observed ~81% reduction of apical tumor height by ultrasound relative to baseline intact primary lesion with 10 months of treatment

IDEAYA Data ; confirmed PR by RECIST 1.1,

Darovasertib in Primary (Neo)Adjuvant Uveal Melanoma

IDEAYA Phase 2 Study of Neoadjuvant / Adjuvant Monotherapy Treatment

Phase 2 Study for (Neo)Adujvant UM [1]

Primary Uveal Melanoma Patients

Cohort 1: Tumors require Enucleation

Cohort 2: Tumors require Plaque Brachytherapy

Neoadjuvant Therapy

Treat Until Maximum Benefit

Definitive Primary Therapy

Clinical Objective to Evaluate
Vision / Organ Preservation

Adjuvant Therapy

Clinical Objective to Evaluate
Relapse Free Survival and Useful Vision

[1] Preliminary Phase 2 study plan, pending investigator and regulatory guidance

Primary Endpoints for Neoadjuvant Therapy

- Both Cohorts: Safety / Tolerability
- Cohort 1: Eye Preservation (e.g., ↓ in % of Patients undergoing Enucleation as Primary Treatment)
- Cohort 2: Preserve / Protect Vision (e.g., ↓ in radiation dose during Brachytherapy as Primary Treatment)

→ Efficient Proof-of-Concept Study: Neoadjuvant Endpoints anticipated to be proximal in time to definitive Primary Therapy

Secondary Endpoints for Follow-Up Adjuvant Therapy

- Relapse Free Survival
- Useful Vision

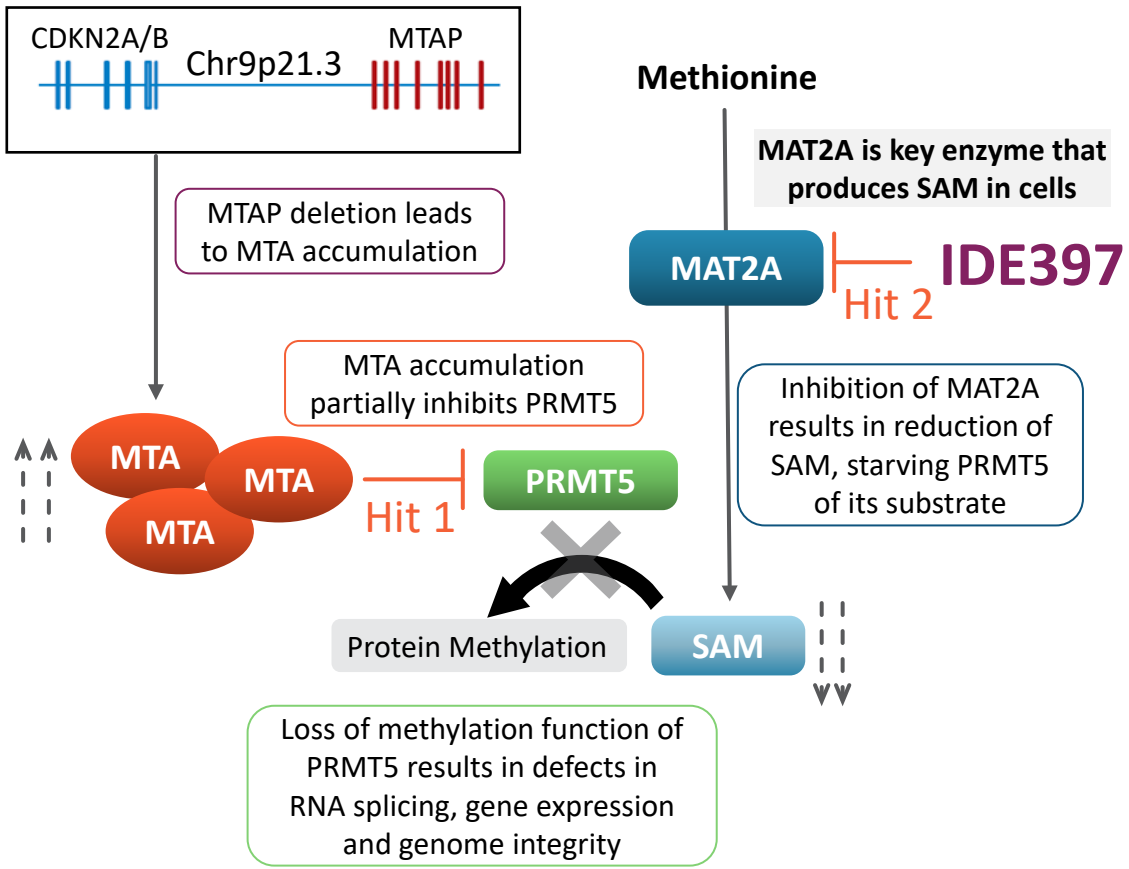
Mechanistic Advances Support Combination Approaches to Treat MTAP Deleted Tumors

Dual Synthetic Lethal Strategy for MAT2A Clinical Combination Therapies

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

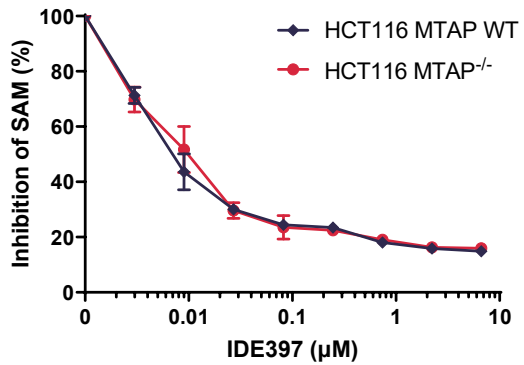
MAT2A inhibition is Synthetic Lethal with MTAP Deletion

MTAP is co-deleted with CDKN2A/B in 15% of Solid Tumors

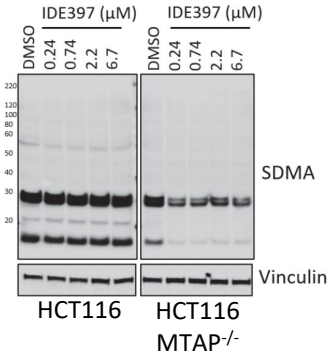


IDE397 is a potent and selective MAT2A Inhibitor

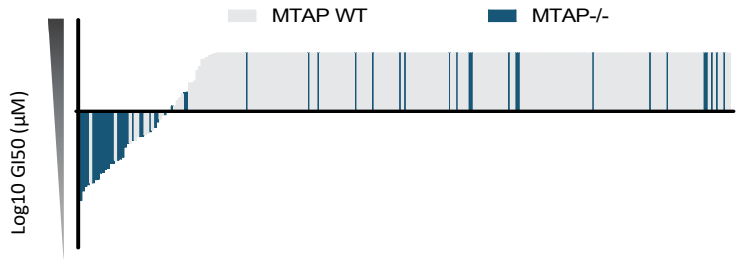
IDE397 inhibits cellular SAM synthesis



IDE397 selectively impairs protein methylation in MTAP$^{-/-}$ cells



IDE397 selectively kills MTAP-null Cancer Cells



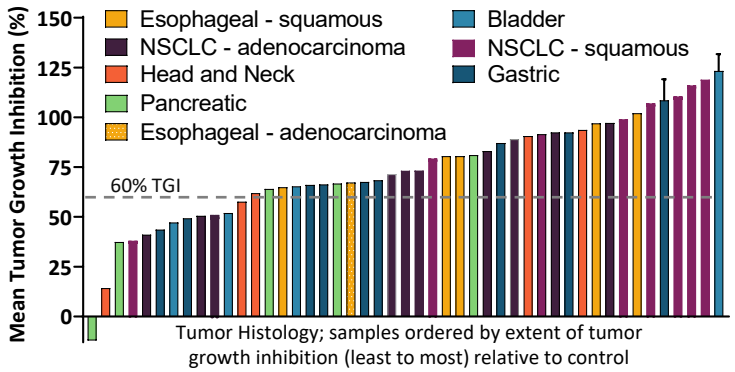
Addressable Patient Population of ~75,000 estimated in US, EU5 and JP across six indications, including NSCLC, head and neck, bladder, gastric, pancreatic and esophageal cancers

IDE397 demonstrates Broad Efficacy across MTAP-deficient PDX Models

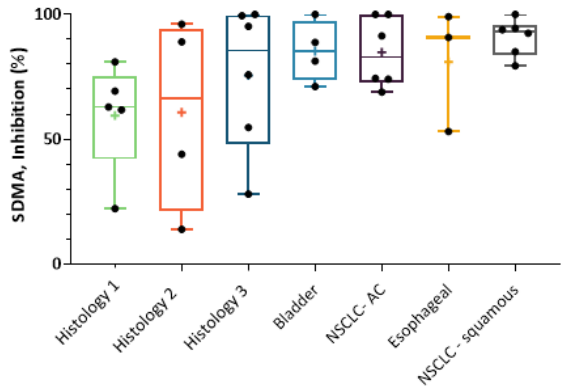
Deep regressions are enriched in NSCLC-squamous (LUSC) with Maximal Pathway Suppression

IDE397 Efficacy: 47 MTAP$^{-/-}$ PDX Models

TGI with IDE397 (30mpk) in MTAP-/- PDX Panel

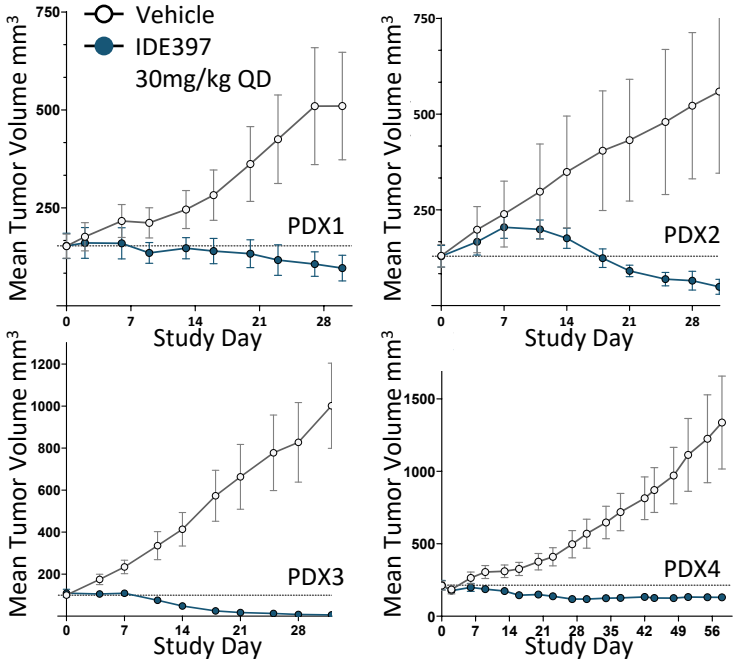


SDMA Suppression in Residual Tumors* at End of Study

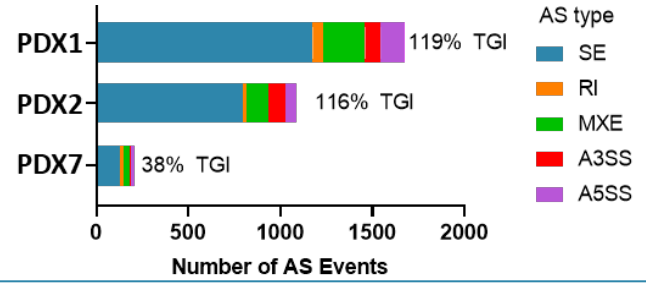


*2 of 8 LUSC unevaluable due to insufficient residual tumor burden

50% LUSC respond with Regressions



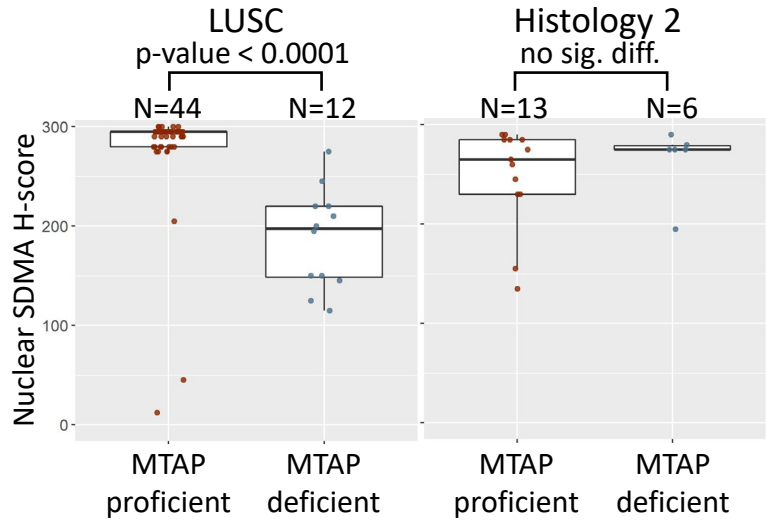
IDE397 strongly perturbs mRNA splicing *in vivo*

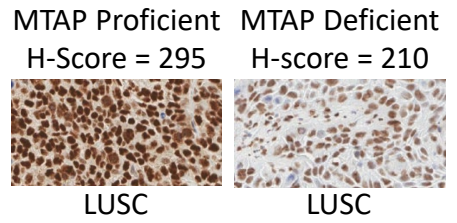


Endogenous Suppression in MTAP$^{-/-}$ LUSC

Robust association of MTAP$^{-/-}$ with partial methylation pathway suppression in LUSC

PDX Tissue Microarray*





*MTAP status confirmed by both NGS and CAP/CLIA IHC

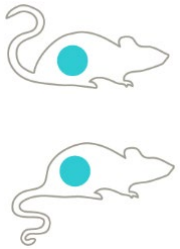
IDE397 is a Potential Backbone for SL Combination Therapy in MTAP$^{-/-}$ Tumors

MAT2Ai induces Biological Responses in MTAP$^{-/-}$ Tumors that are Synthetic Lethal with select Chemotherapies and Targeted Therapies in Multiple Disease Indications with High Unmet Clinical Need

Strategy for Identification of Synergistic IDE397 Combination Opportunities

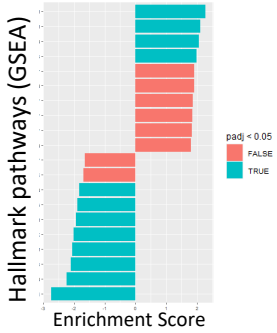
1 Molecular profiling of drug effect on MTAP$^{-/-}$ tumors *in vivo*

Multi-lineage PDX RNAseq



IDE397 treated
vs
Vehicle treated

Consensus IDE397 GE response

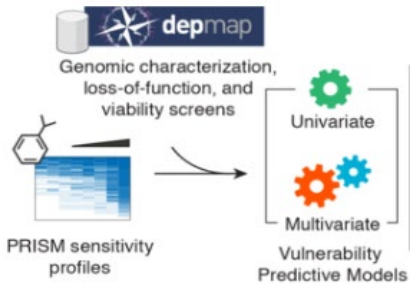


IDE397 perturbs biological processes supporting:

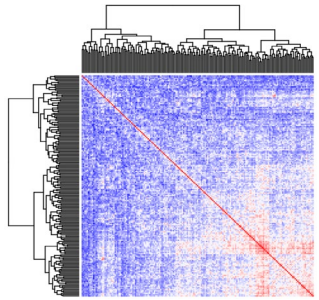
- pre-mRNA splicing
- genome integrity
- mitotic spindle assembly

2 Chemogenomic evaluation of selective drug sensitivities in MTAP$^{-/-}$ across the CCLE

184 drug sensitivity profiles across ~1000 cancer cell lines



IDE397 correlation consensus cluster

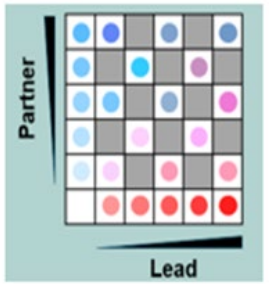


Compounds enriched in *MTAP*$^{-/-}$ cell lines perturb same biological processes as IDE397:

- pre-mRNA splicing
- genome stability
- microtubule stability

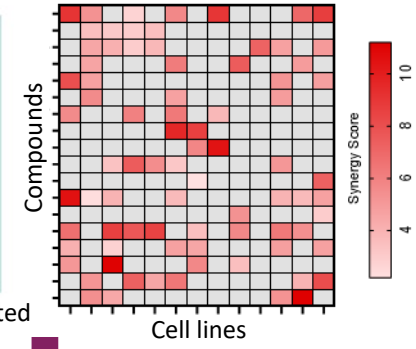
3 High throughput in vitro drug combination screens

Dose matrix for synergy detection



>400 compounds evaluated

Hits with IDE397 synergy



IDE397 synergy observed with taxanes, platins, targeted DDR, splicing inhibitors, anti-folates

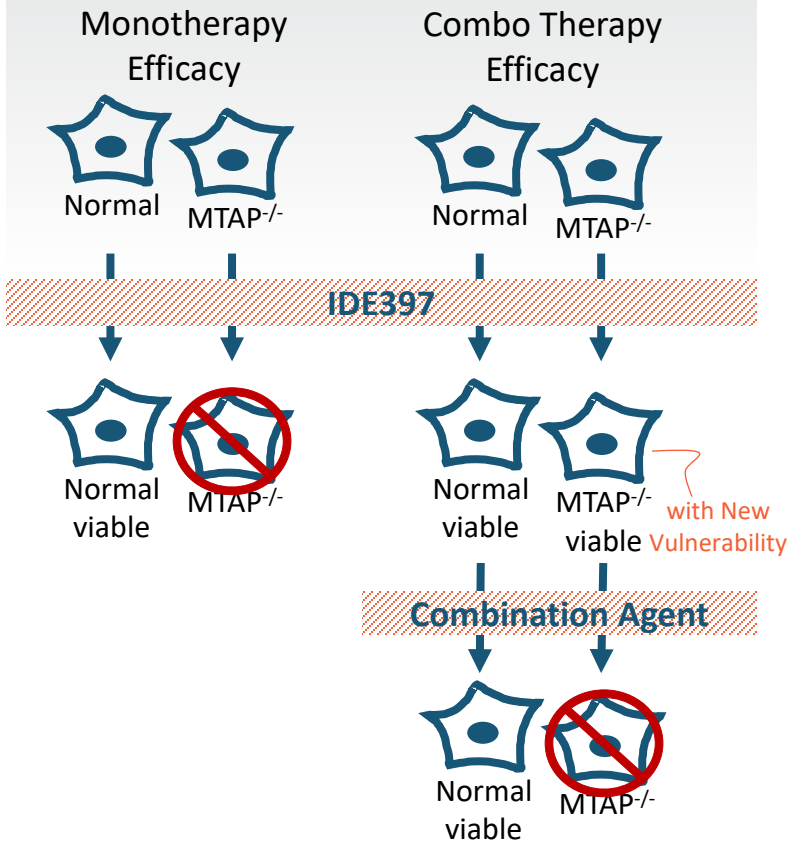
- synergy is on-mechanism
- presents strategy for synthetic lethal combinations

Precision Medicine Strategy: Synthetic Lethal Combination Therapies

IDE397 Combination Opportunities with Pemetrexed and PRMT5i ^{MTA}

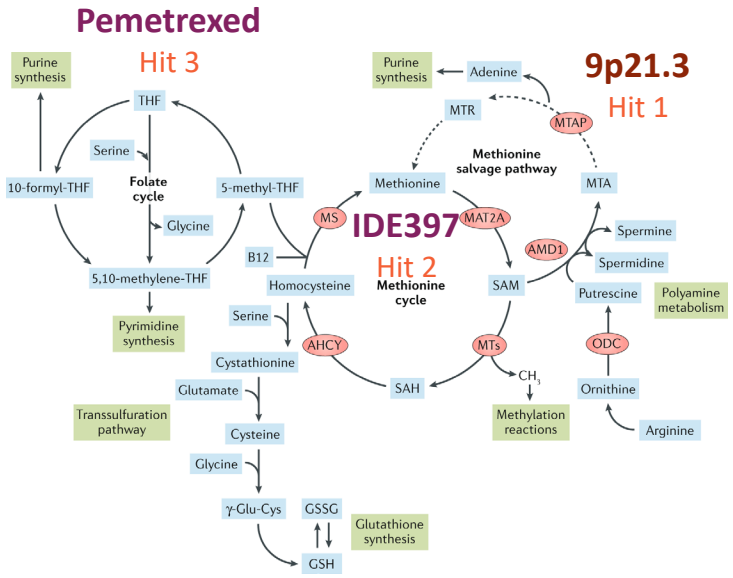
Potential to Broaden Indication-Agnostic Therapeutic response to IDE397

Chemically Conferred MTAP-/- SL



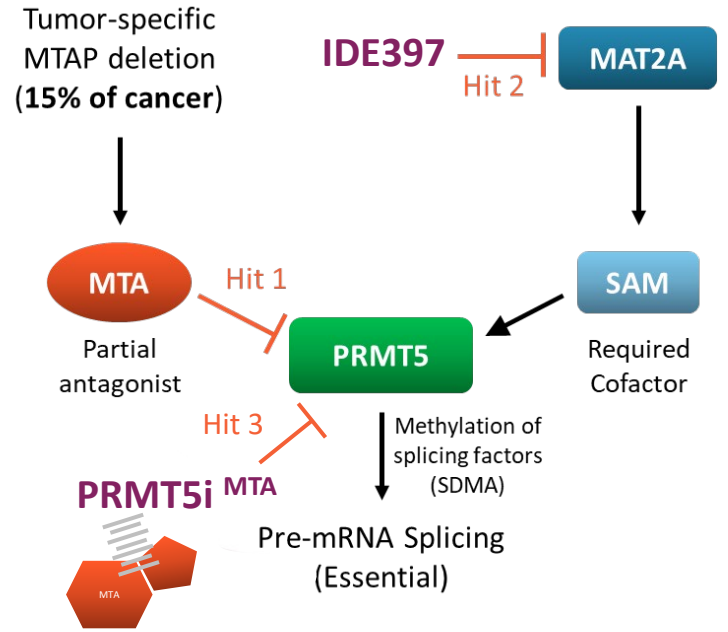
IDE397 + Pemetrexed

Intersecting Biology with Pemetrexed



IDE397 + PRMT5i ^{MTA}

Maximal pathway inhibition with PRMT5i^{MTA}



Sanderson et al. 2019 Nature Reviews Cancer

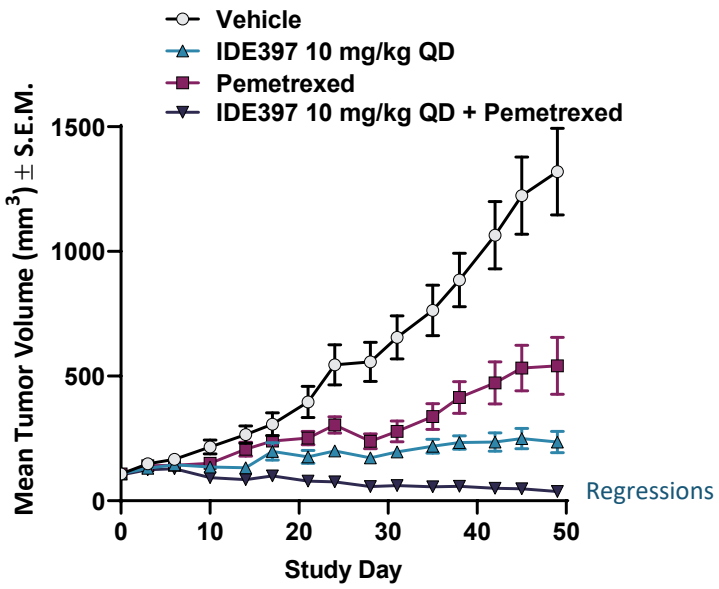
PRMT5i ^{MTA} = MTA-cooperative PRMT5 inhibitor

Robust Efficacy in key MTAP$^{-/-}$ Indications

Combinations show Regression and Complete Responses at Doses well below typical Monotherapy Dose

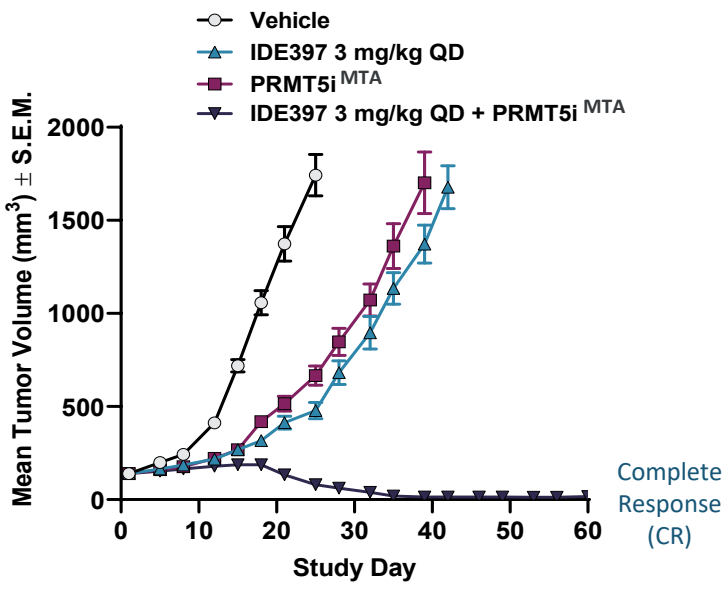
IDE397 + Pemetrexed in LUAD

LXFA737 NSCLC MTAP$^{-/-}$ PDX Model



IDE397 + PRMT5i ^{MTA} in LUAD

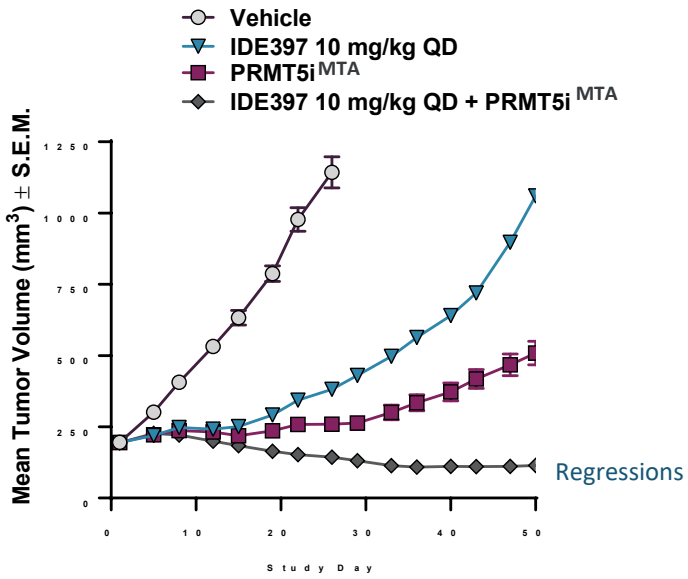
H838 NSCLC MTAP$^{-/-}$ CDX Model



PRMT5i ^{MTA} = representative MTA-cooperative inhibitor of PRMT5

IDE397 + PRMT5i ^{MTA} in Pancreatic

BXPC3 Pancreatic MTAP$^{-/-}$ CDX Model



PRMT5i ^{MTA} = representative MTA-cooperative inhibitor of PRMT5

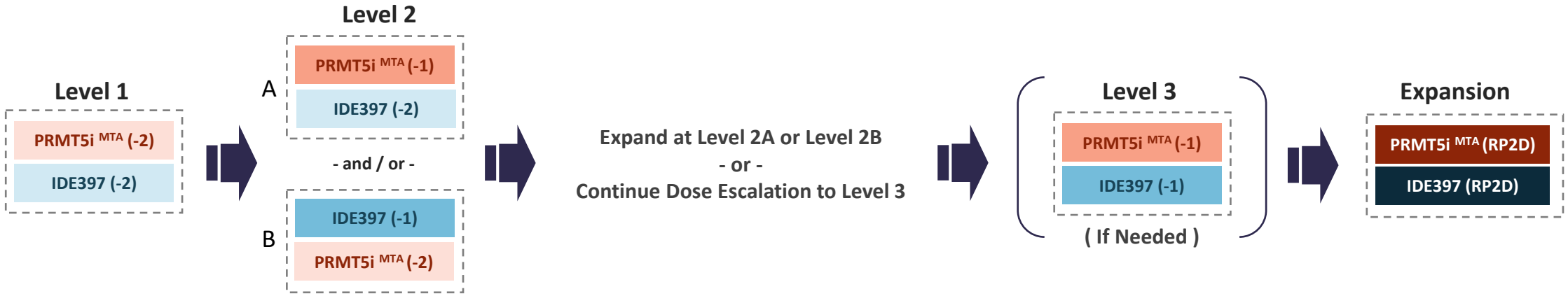
- IDE397 dosed at 10 or 3 mg/kg QD = 1/3 or 1/10th typical maximally efficacious preclinical dose of 30 mg/kg QD
- IDE397+PRMT5i ^{MTA} combinations well tolerated
- Body weight loss noted in pemetrexed combination primarily driven by poor tolerability of pemetrexed in mice

IDE397 + PRMT5i ^{MTA} Dual Synthetic Lethality Combination

Conceptual Approach for Dose Escalation and Optimization *

Combination Dose Escalation Enables Dose Optimization and Potential to Evaluate Clinical POC

Goal to determine doses for Maximal Patient Benefit (Efficacy : Tolerability)



Clinical Evaluation of IDE397 + PRMT5i ^{MTA} Combination *

- Indication-Focused Dose Escalation
- Combination Activity anticipated at doses lower than monotherapy RPD2 doses for each of IDE397 and PRMT5i ^{MTA}, based on Preclinical Studies with representative MTA-cooperative PRMT5 Inhibitor

* Preliminary approach, based on KOL feedback and preclinical data for IDE397 combination with representative MTA-cooperative PRMT5 inhibitor

Selective Essentiality in DNA Damage Repair

Introduction – IDEAYA's DDR Synthetic Lethality Pipeline

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

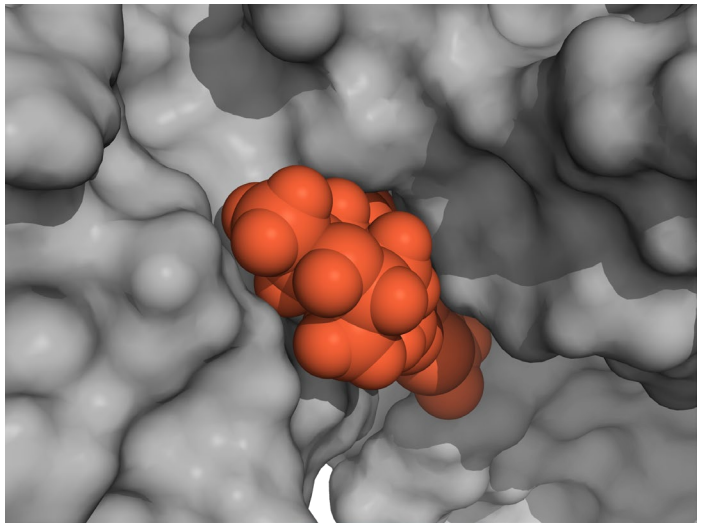
IDEAYA's Potential First-in-Class Synthetic Lethality DDR Pipeline

Synthetic Lethality with Tumor-Promoting defects in DNA Repair Mechanisms

IDE161

PARG Inhibitor

Development Candidate



IND submitted Q4 2022

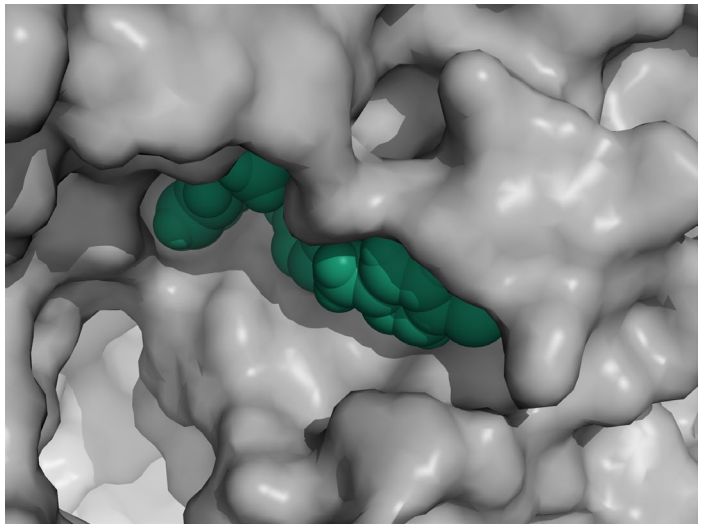
Phase 1 focus on HRD Monotherapy

Potential to develop beyond HRD

Polθ ϕ

Helicase Inhibitor

Development Candidate

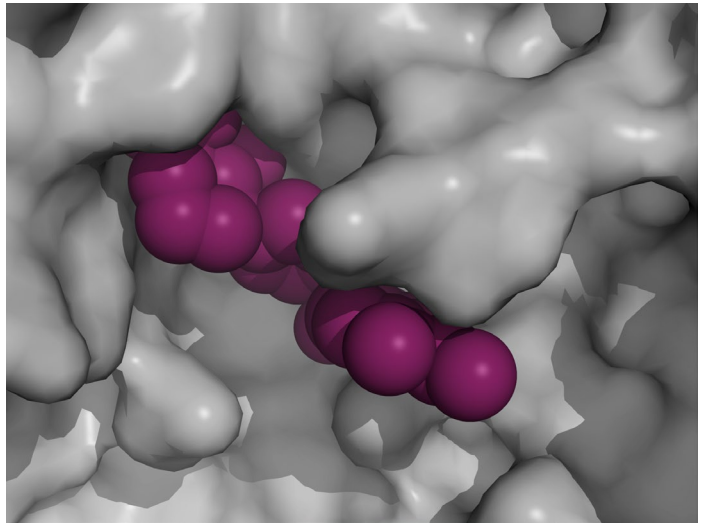


Targeting First-in-Human H1 2023

Niraparib combination in HRD

Werner ϕ

Helicase Inhibitor



Targeting Development Candidate in 2023

MSI-high tumor agnostic

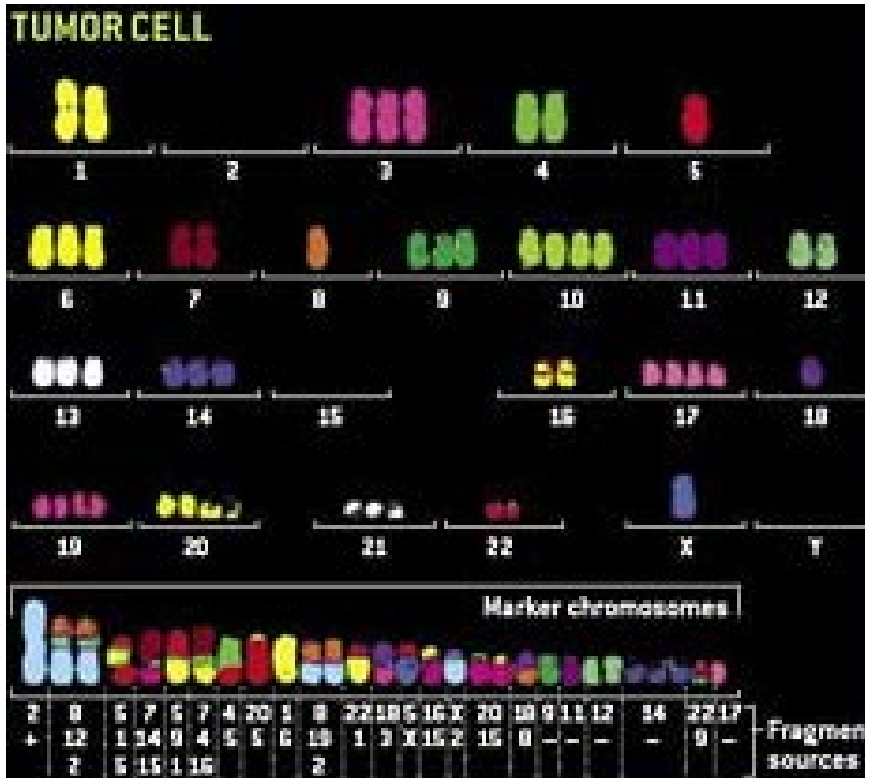
ϕ Pursuant to GSK Collaboration, Option and License Agreement

Selective Essentiality in DNA Damage Repair

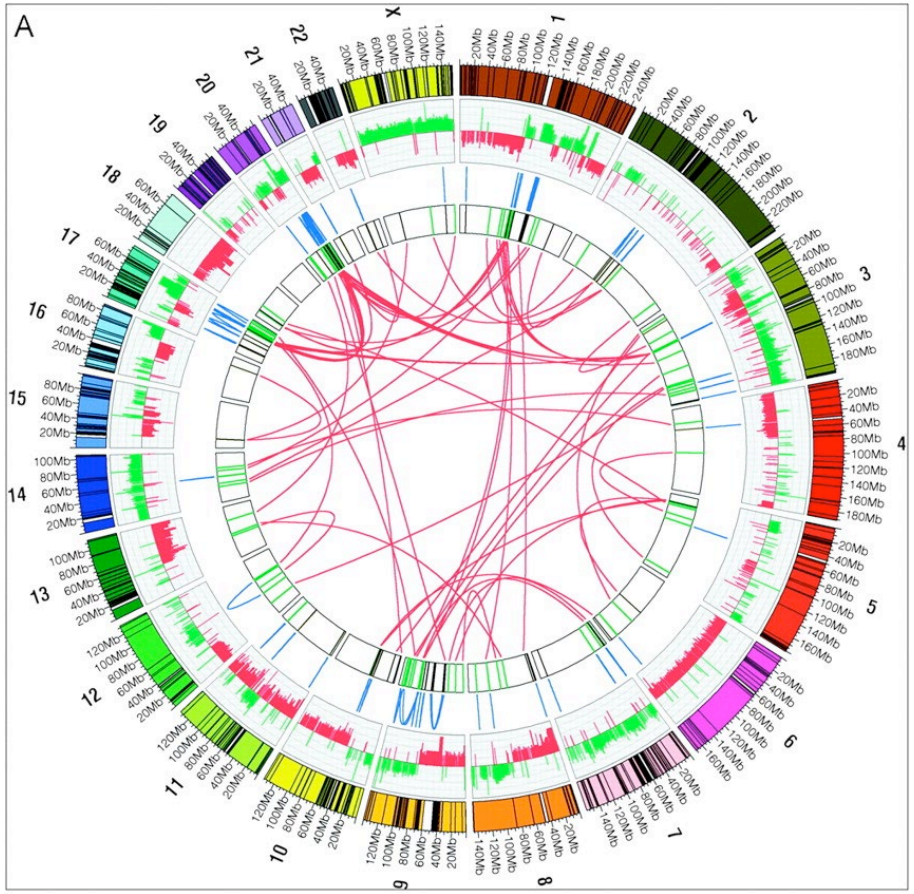
Targeting Replication Stress as an Emerging Synthetic Lethality Paradigm

Karlene Cimprich, Ph.D.
Stanford University
Professor, Chemical and Systems Biology and (by courtesy) Biochemistry
Member, Stanford Cancer Institute

Genome Instability in Cancer Cells



Scientific American, 2007



Hampton et al, Genome Research, 2009

Breast Cancer Cell Genome (MCF7)

Genome Instability is a Hallmark of Cancer

Genome Instability

Proliferative signaling
Loss of growth suppression
Invasion and metastasis
Resistance to cell death
Angiogenesis
Replicative immortality
Deregulated energetics
Genome instability
Inflammation
Avoiding immune destruction

Figure modified from Negrini, Nature Reviews, 2010

Replication Stress is a Hallmark of Cancer

Oncogene-Activated
Growth Signaling

DNA Damage and
DNA Replication Stress

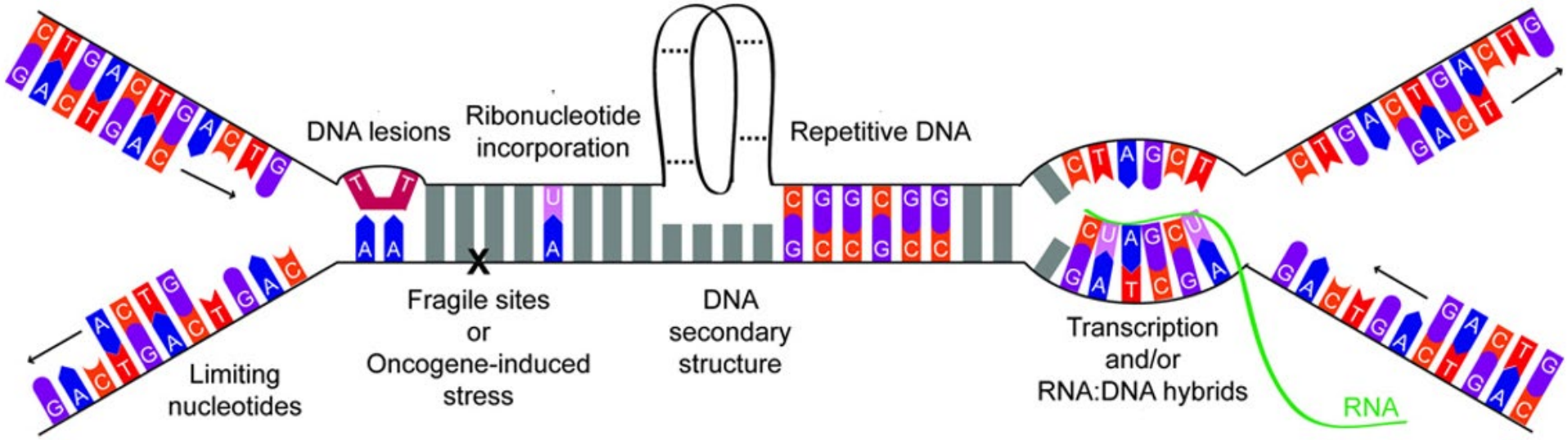
Genome Instability

Replication Stress can be induced by oncogenes, tumor suppressors, hormones, DNA damage and DNA repair defects

Figure modified from Negrini, *Nature Reviews*, 2010

IDEAYA BIOSCIENCES

Replication Stress as a Source of Genome Instability



Stalled replication forks are ….

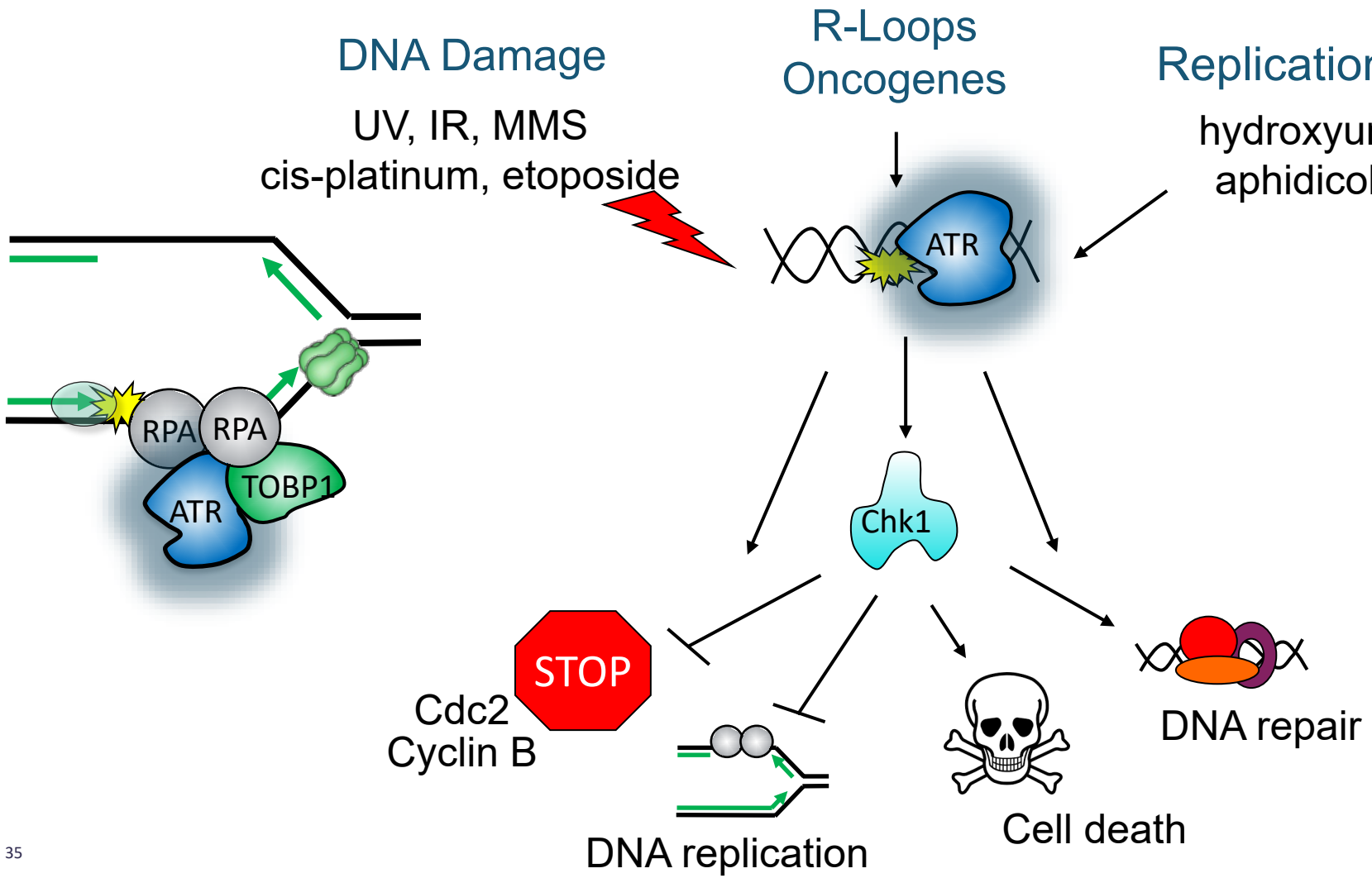
…. difficult to repair

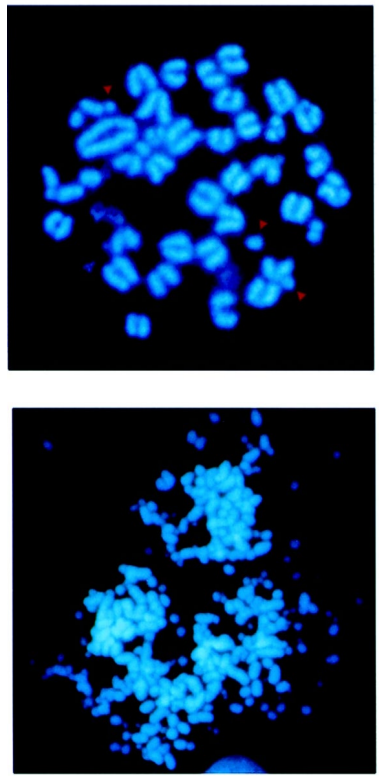
…. prone to breakage and rearrangement

Figure adapted from Zeman and Cimprich, Nature Cell Biology 2014

Elucidation of Replication Stress Response

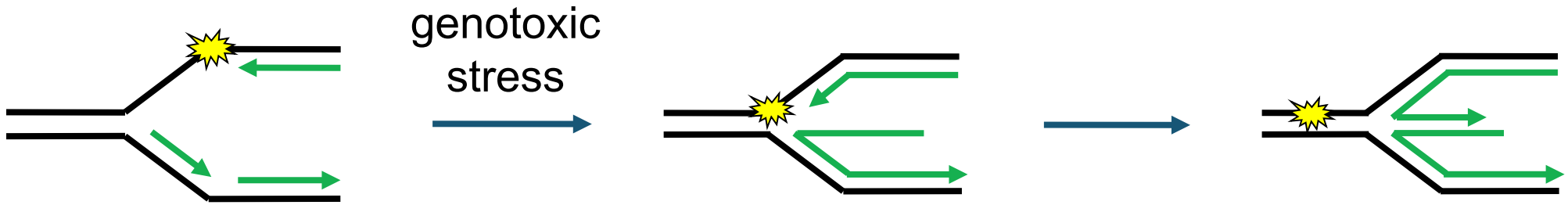
Many aspects of Replication Stress Response Coordinated through ATR Kinase

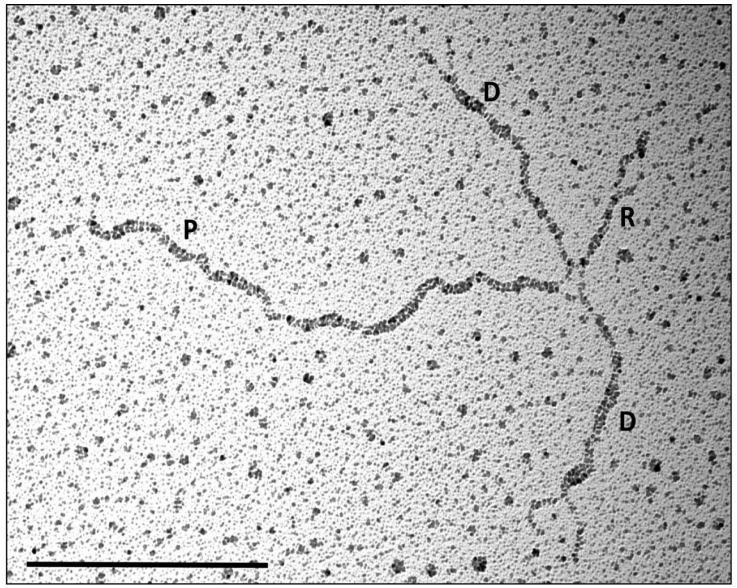




Brown & Baltimore Genes Dev. 2000

Replication Forks Reverse as a Stress Response

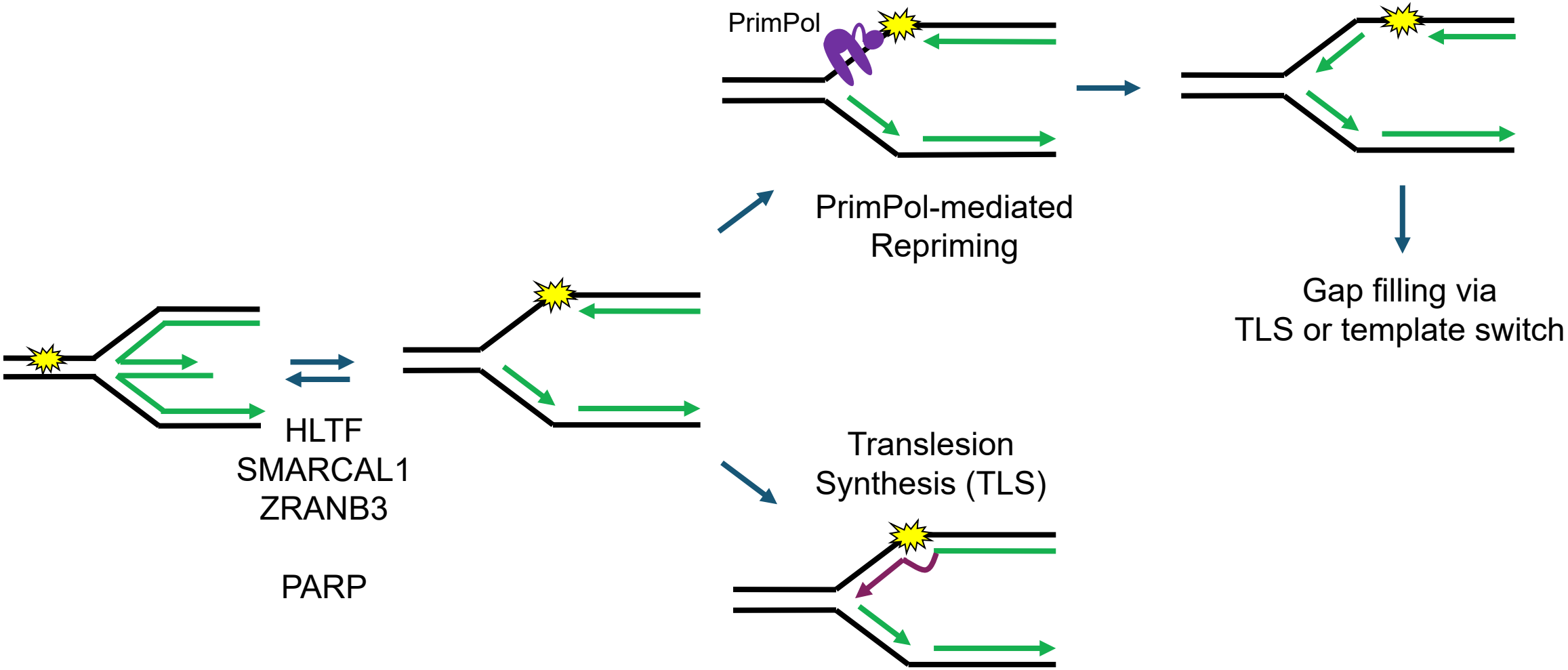




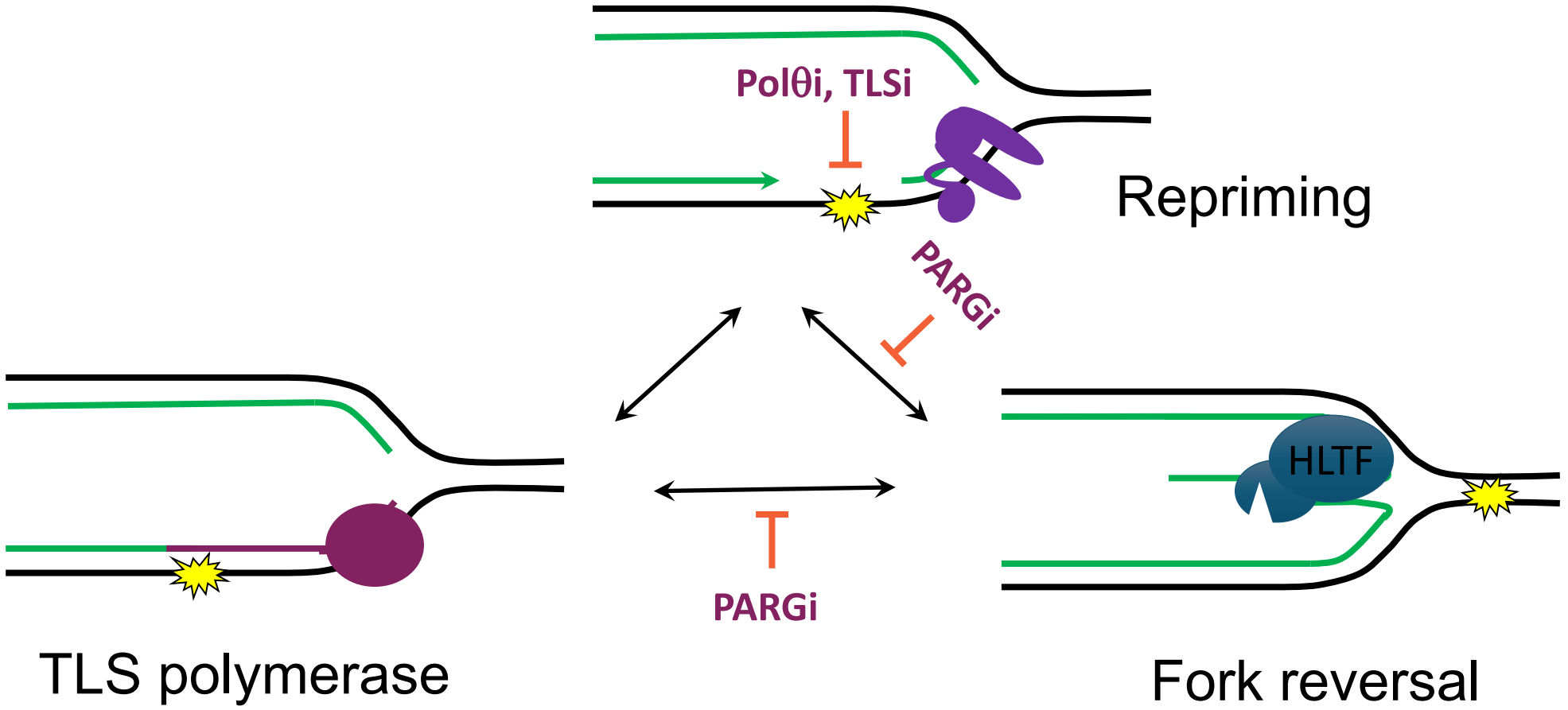
- Slows fork progression
- Induced by various DNA damaging agents at ~25% of forks

Zellweger et al., *J Cell Bio* (2015)

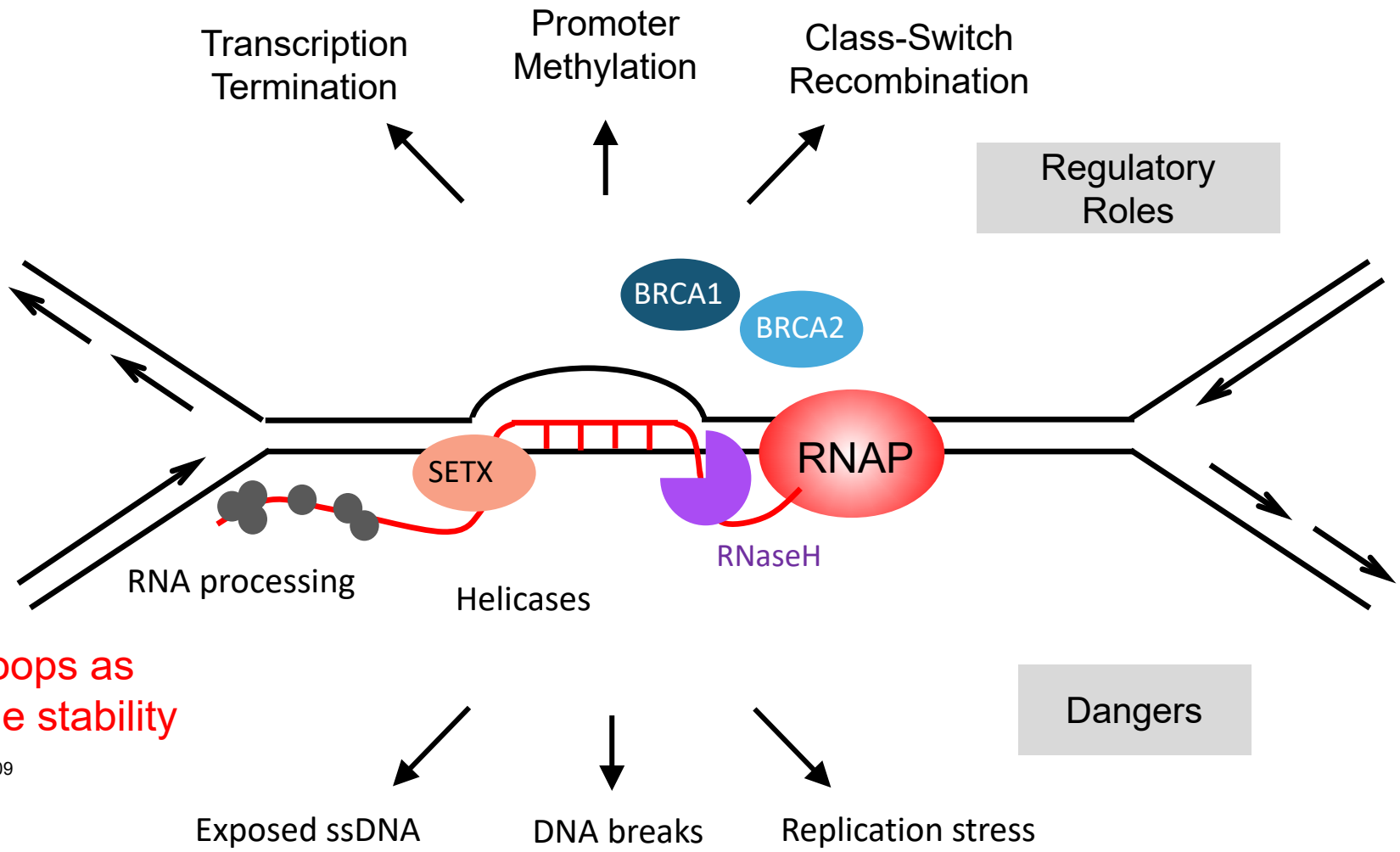
Replication Fork Plasticity and Adaptability Promotes Tolerance to Replication Stress



Repriming and Translesion Synthesis (TLS) as Mechanisms for Stress Resistance and Therapeutic Vulnerabilities



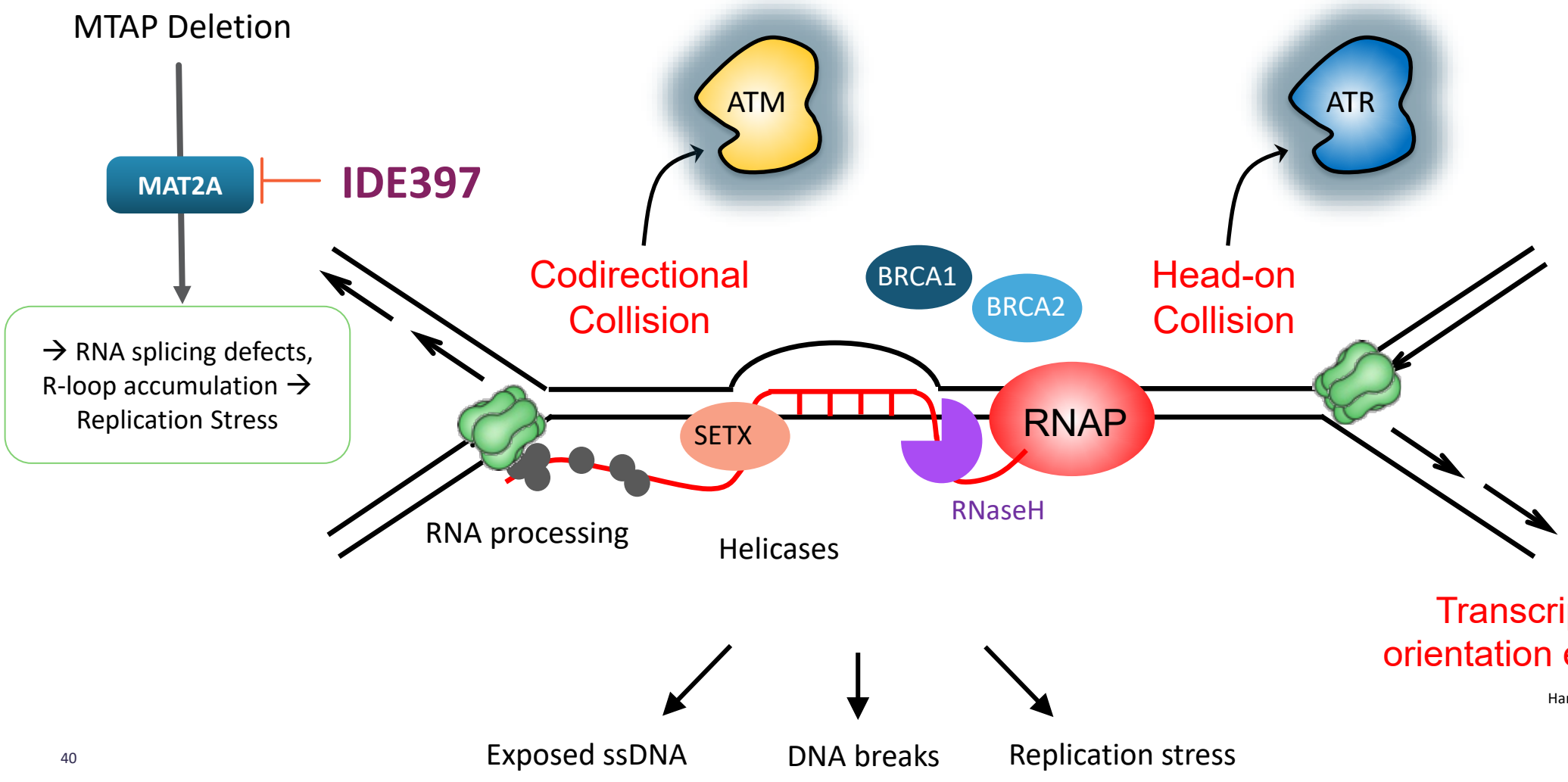
R-loops: A Double-Edged Sword



Identifying R-loops as threats to genome stability

Paulsen et al., Mol Cell, 2009

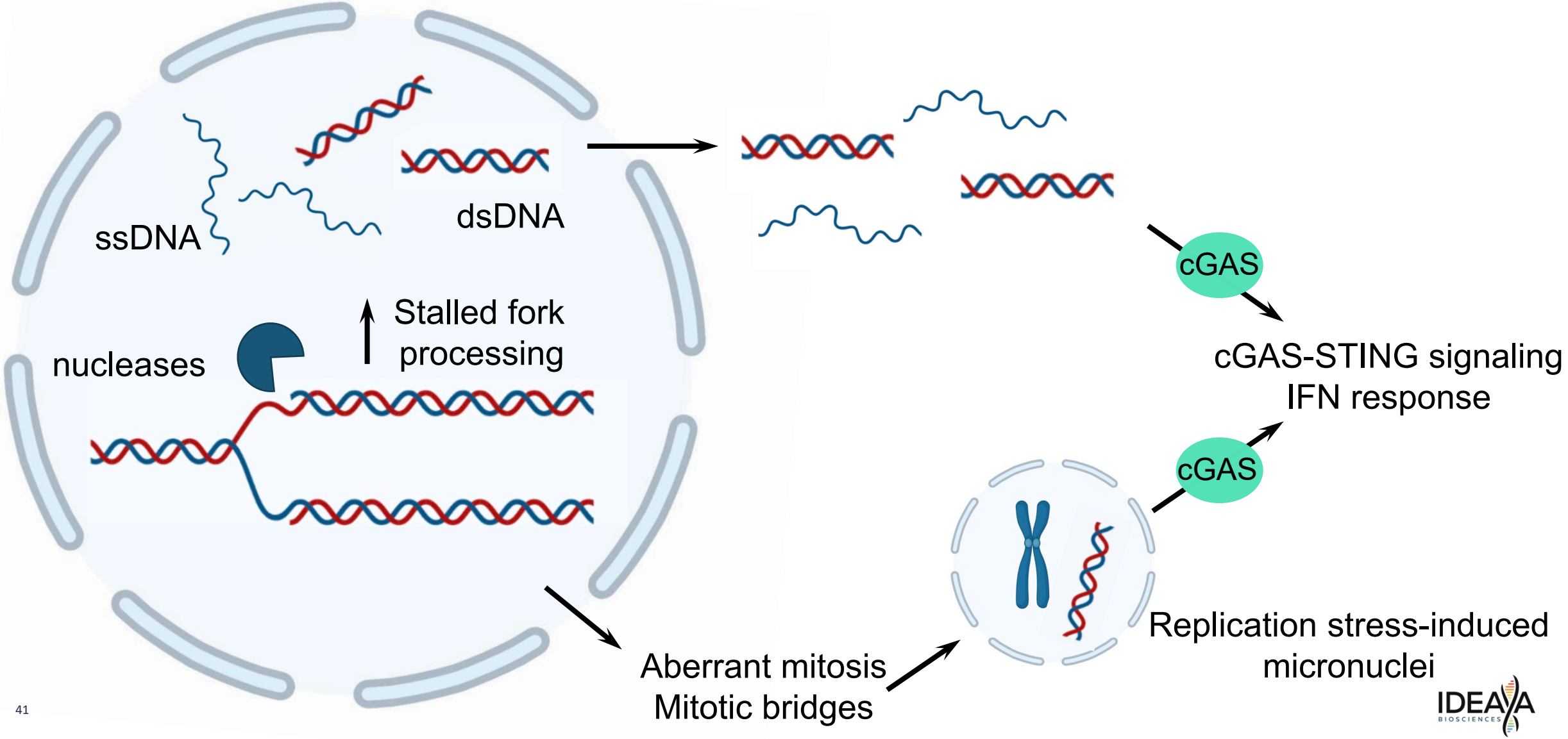
Fork Collisions with R-loops are a Source of DNA Replication Stress



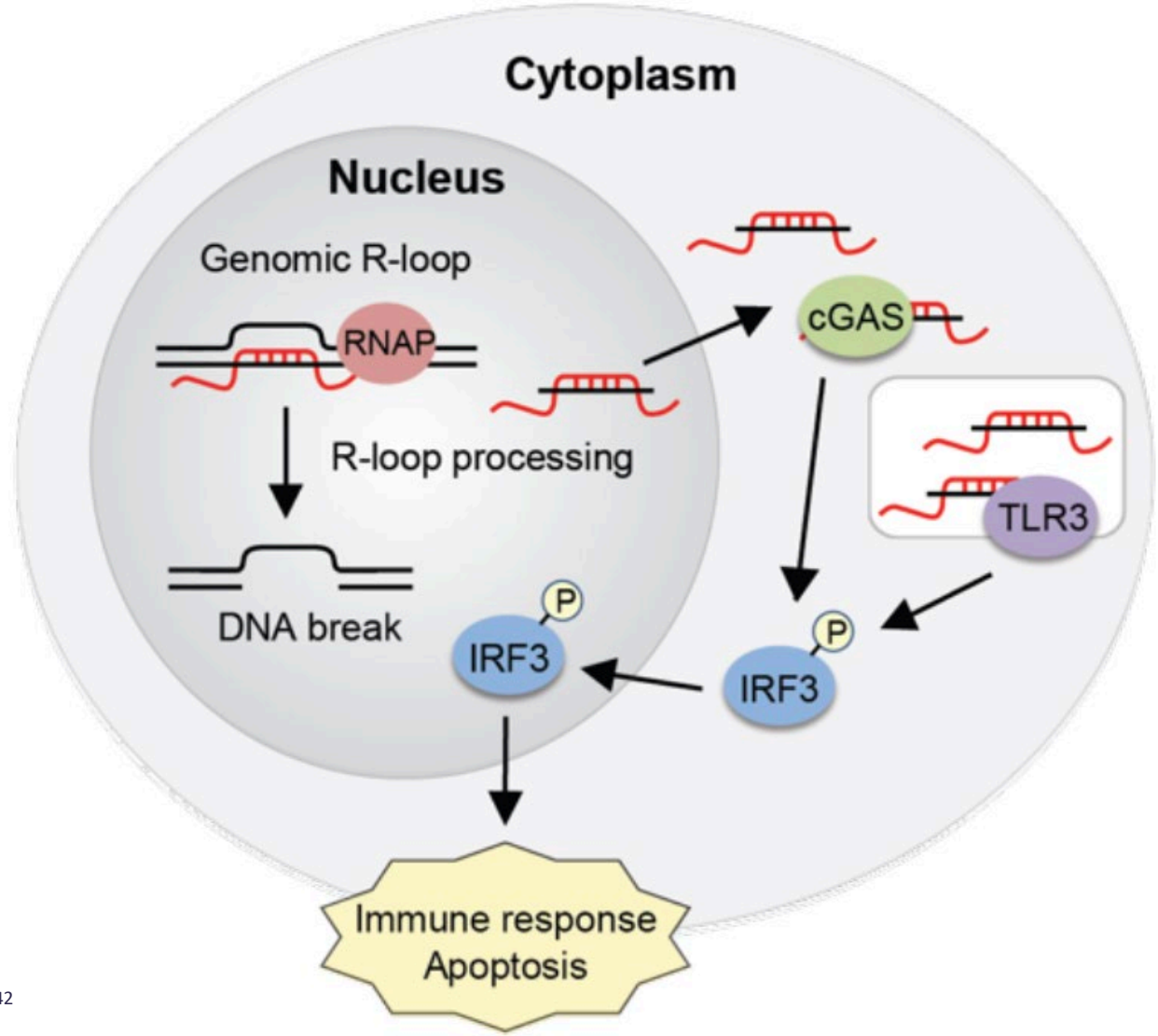
Transcription-replication orientation effects and R-loops

Hamperl et al, Cell (2017)

Interplay Between Replication Stress and the Immune Response



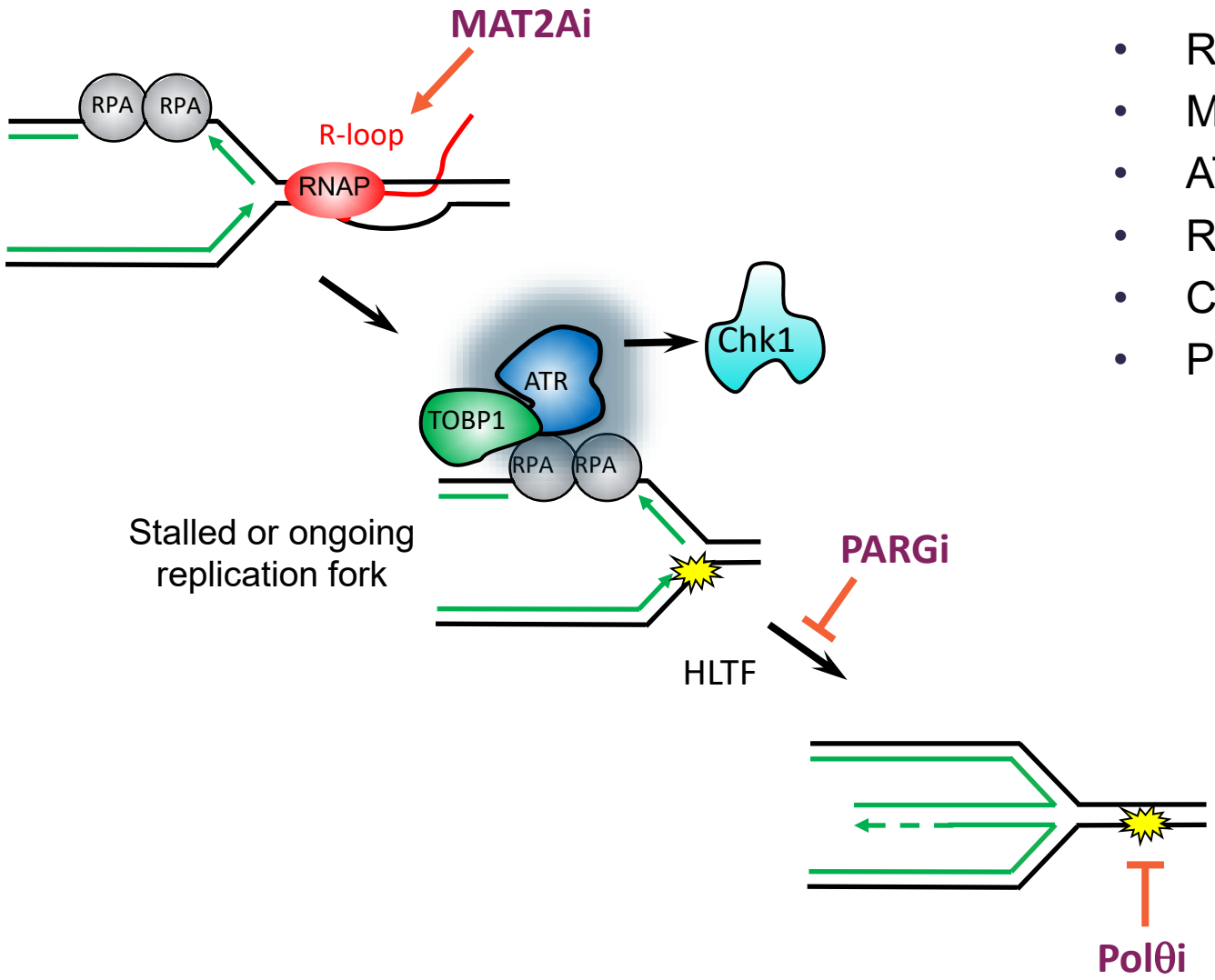
Nuclear-derived Cytoplasmic RNA-DNA Hybrids Activate Innate Immune Response



- R-loop perturbation induces XPG-dependent accumulation of cytoplasmic RNA-DNA hybrids
- Cytoplasmic hybrids are derived from a subset of nuclear R-loops with distinct properties
- Cytoplasmic hybrids activate an innate immune response, leading to IRF3 signaling and apoptosis

Crossley, Song...Cimprich et al, Nature in press

Exploiting Replication Stress in Cancer Treatment



- Replication stress → cancer hallmark
- Many causes of stress including R-loops
- ATR mediates replication stress response
- Replication stress response → survival
- Cancer cells tolerate replication stress
- Potential Therapeutic Targets:
  - Replication stress response (ATR, Chk1)
  - Damage tolerance pathways
  - R-loop processing pathways (IDE397)
  - Inhibition of replication fork restart (IDE161)
  - Inhibition of translesion synthesis (Polθ: emerging evidence in the setting of BRCA/RAD51)
  - Immunotherapy combinations

Selective Essentiality in DNA Damage Repair

Novel Approach to HRD: IDE161 PARG inhibitor Preclinical Activity and Clinical Development Plan

Timothy Yap, M.D.

M.D. Anderson Cancer Center

Associate Professor, Department for Investigational Cancer Therapeutics and Department of Thoracic/Head and Neck Medical Oncology

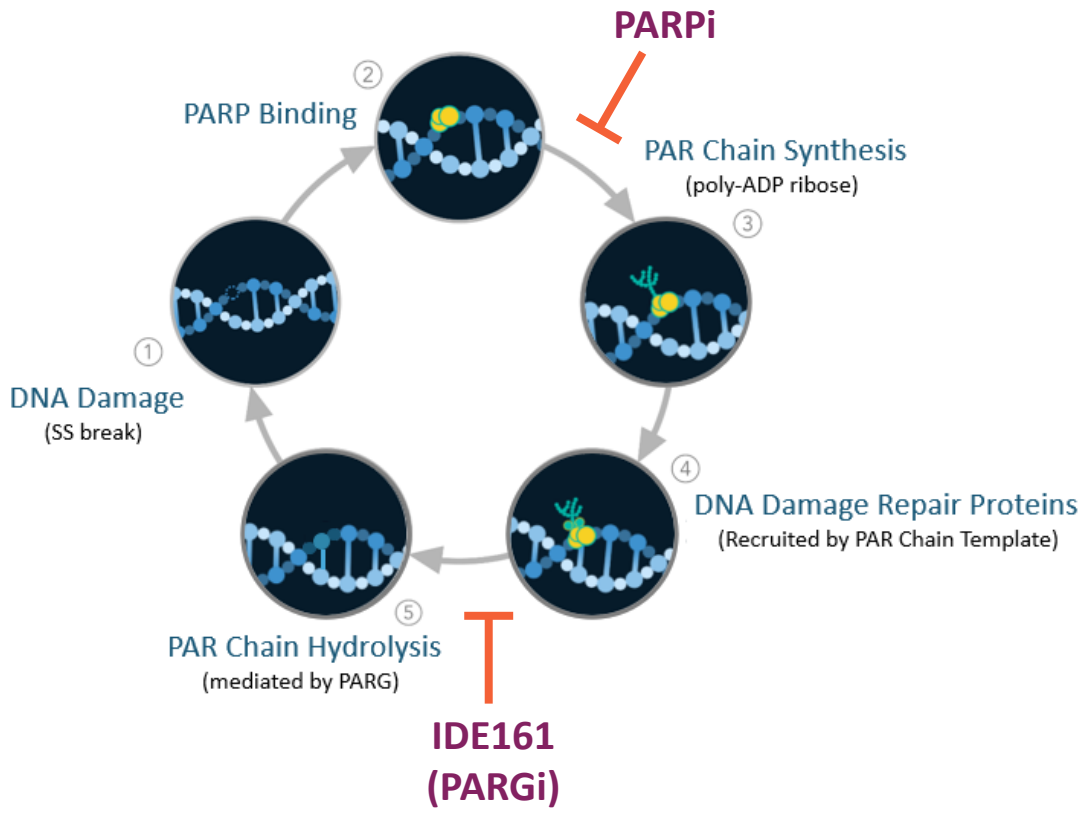
Medical Director, Institute for Applied Cancer Science

Associate Director of Translational Research, Institute for Personalized Cancer Therapy

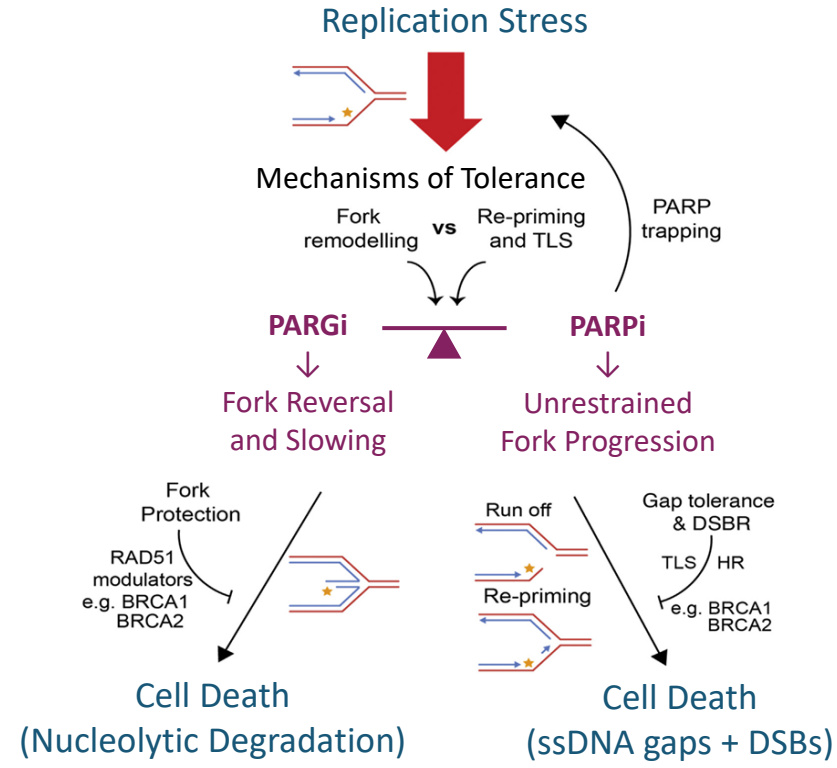
Poly(ADP-ribose) glycohydrolase (PARG)

PARG is a Novel, Mechanistically-Differentiated Target in a Clinically Validated Pathway

PARG Activity is required to resolve DNA Repair



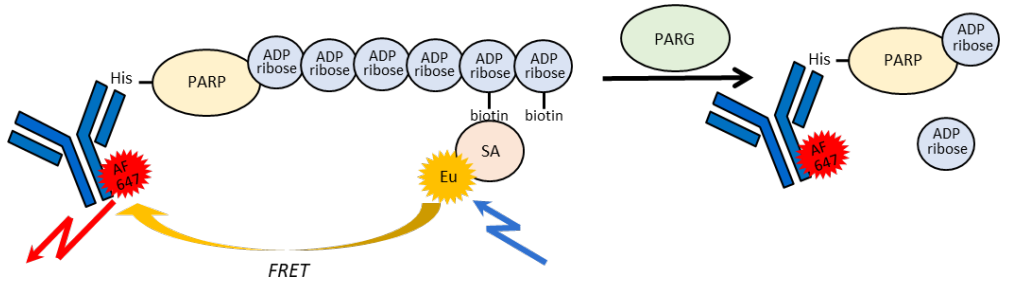
PARG and PARP Inhibition have Distinct Consequences

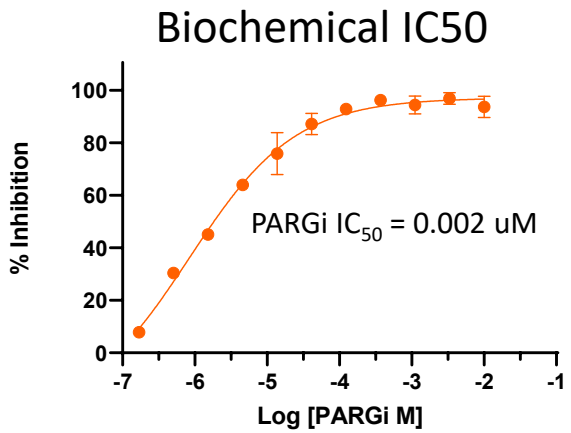


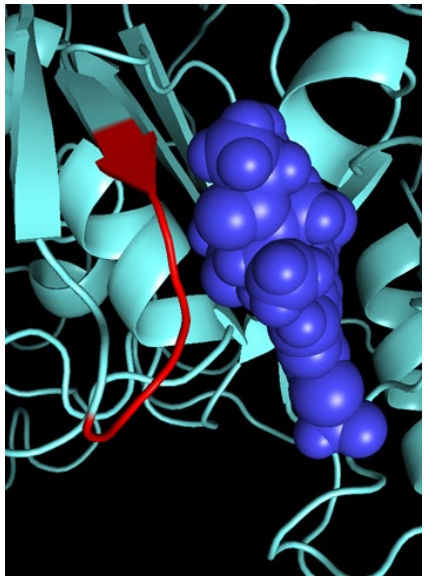
Pillay et al., *Progress in Biophysics and Molecular Biology* 2021
McDermott et al., *Cancer Cell* 2019
Zeman and Cimprich, *Nature Cell Biology* 2014

IDE161 is a Potent Biochemical and Cellular PARG Inhibitor

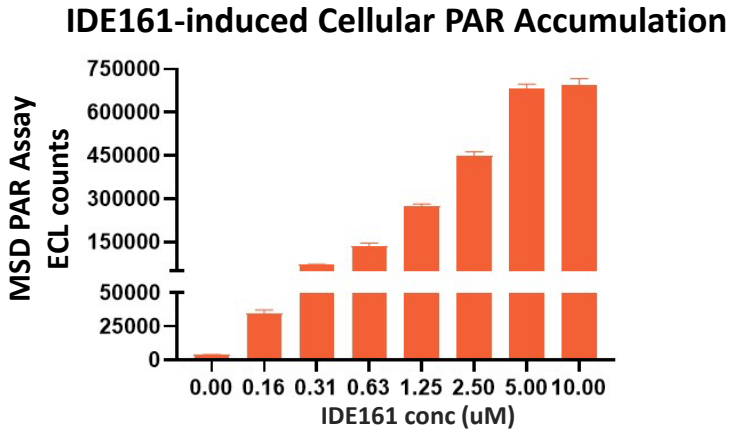
Structure-Enabled Discovery strategy Delivered Lead Series

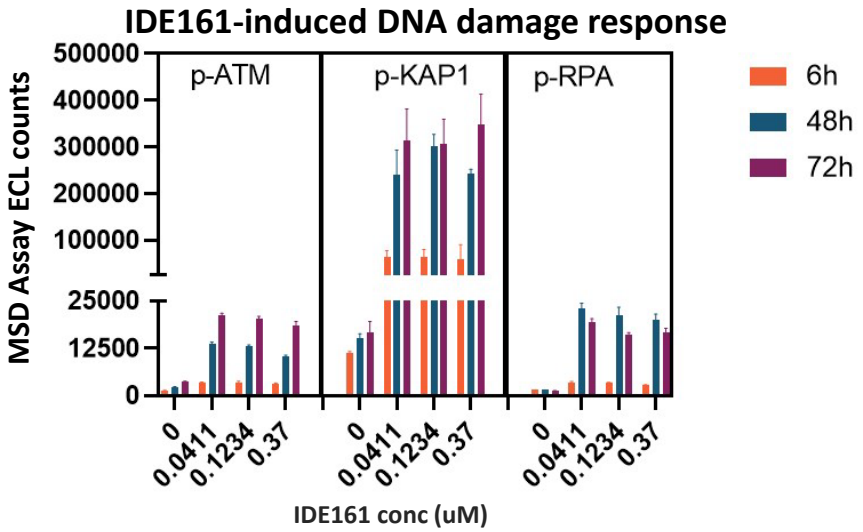






IDE161 induces PAR Accumulation and Selective DDR



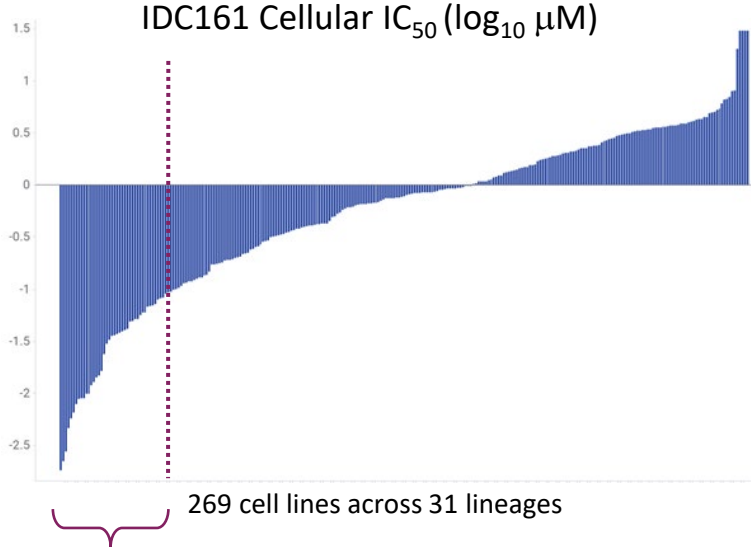


PARG Inhibition is Synthetic Lethal with HRD and Differentiates from PARPi

IDE161 Sensitivity Profile in Cell Panel

Cellular response profiles reveal mechanistic associations with PARGi sensitivity

IDC161 Cellular IC_{50} (log_{10} µM)



Top predictive response biomarkers* include HRD, replication stress, nucleotide excision repair and parylation cycle

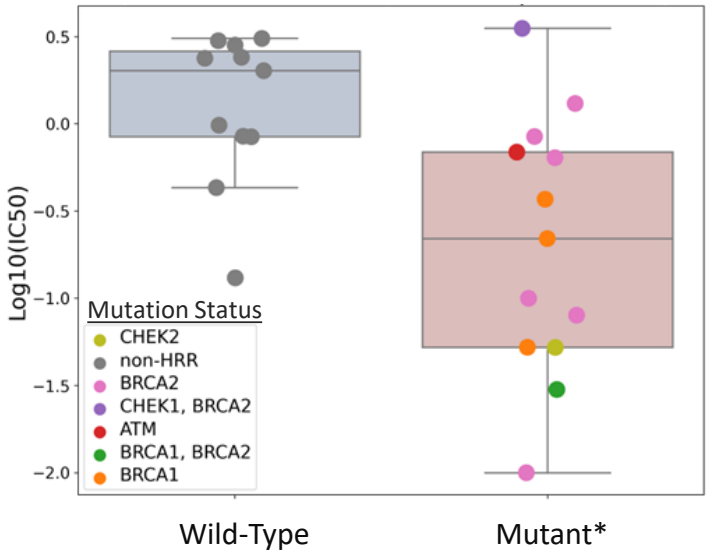
* Based on univariate and multivariate pan-cancer and lineage-specific molecular feature analysis

IDE161 Sensitivity in HRD Breast Cancer

Response to IDE161 is strongly associated with HRD status in Breast Cancer Cell Lines

Cellular antiproliferative response to IDE161 stratified by HRR status

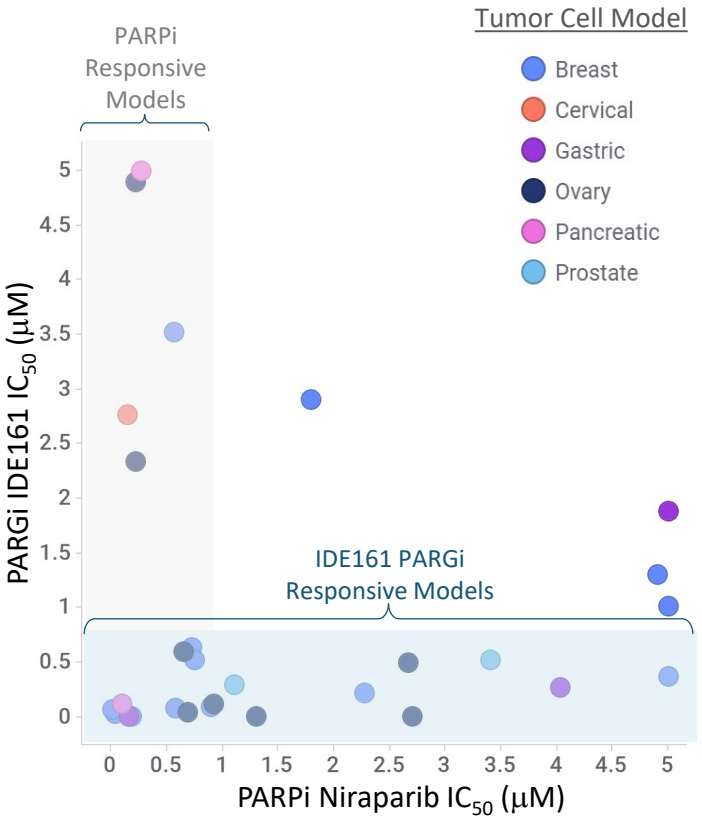
(Breast Cancer: n=24, Wilcoxon pval=0.008)



*HRR mutation status assigned according Foundation Medicine HRR gene panel: ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L

IDE161 Selective Sensitivity vs PARPi

HRD cell lines are selectively sensitive to IDE161 versus PARPi

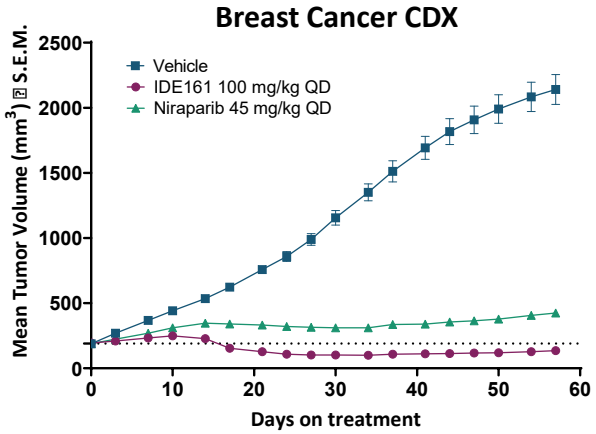


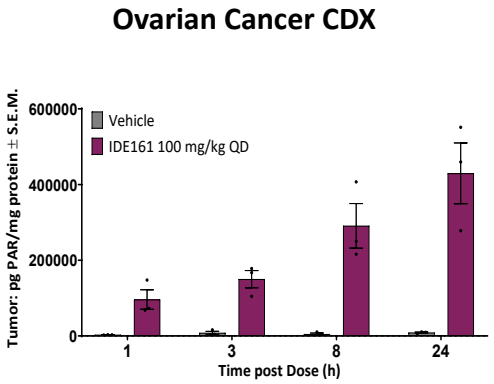
IDE161 is Active and Well-Tolerated in HRD Tumor Models

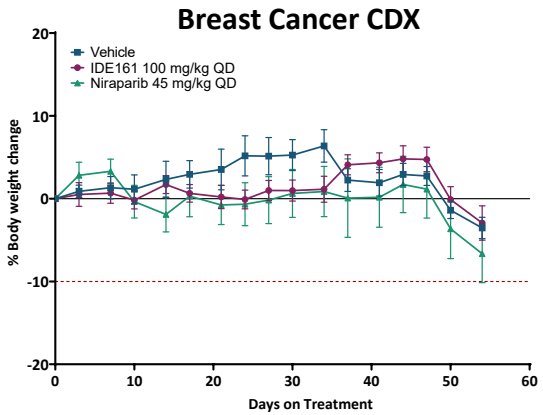
Observed PARG inhibitor Activity is Distinct from PARP Inhibition

Durable Disease Control with IDE161 in BRCA-altered CDX

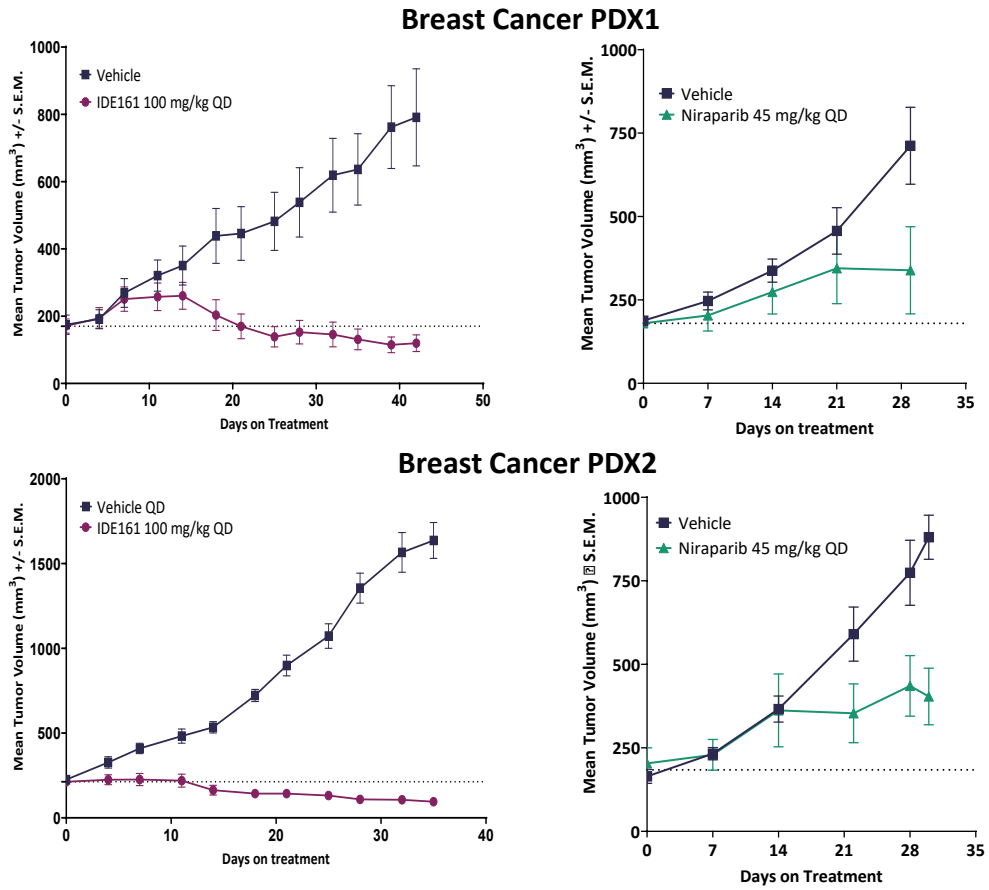
- Durable regressions (vs stasis with niraparib)
- Robust dose- and time-dependent PAR accumulation
- Well tolerated; no body weight loss >10%







Regression in BRCA altered BC PDX with IDE161 vs. PARPi



IDE161 Demonstrates Favorable Safety Profile in Preclinical Studies

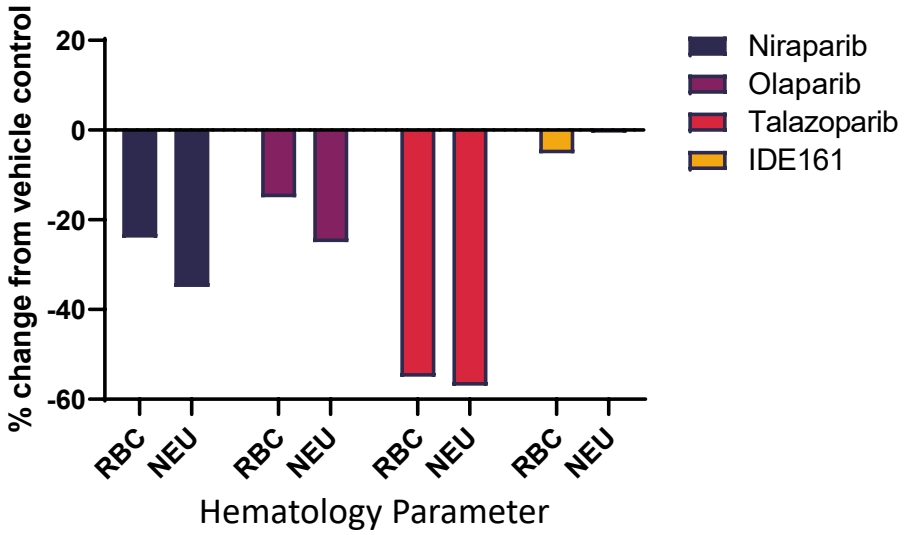
Non-Clinical Pharmacology and Toxicology Studies Support Clinical Evaluation

IDE161 Differentiates versus PARPi in Nonclinical Safety Studies

PARP inhibition causes myelosuppression in rat and dog at clinically relevant systemic exposures

In contrast, IDE161 does not alter hematology parameters in rodents at relevant exposures associated with the estimated therapeutic dose

IDE161 versus PARPi in Rat Studies *



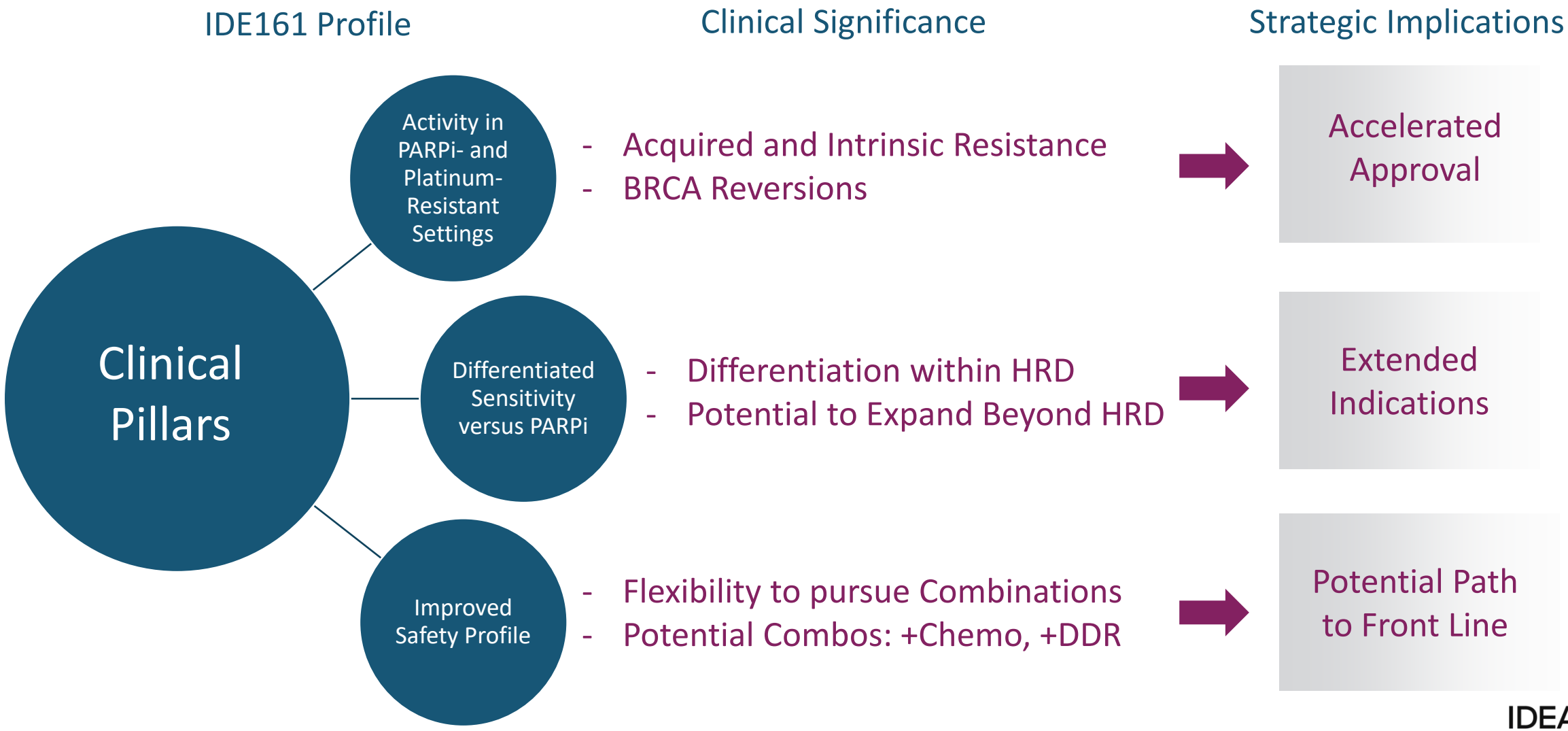
IDE161 Drug Product

* PARPi data extracted from repeat dose toxicology data presented in NDA reviews (Drugs@FDA.gov) and prescribing labels. Species chosen for data illustration (rat) was based on availability of data at a dose level that most closely approximated systemic exposure (AUC) associated with the clinically recommended dose.

- IDE161 well tolerated preclinically with tumor regressions observed at doses below mouse MTD
- Human efficacious dose projection based on maximum efficacious dose in mouse (100 mg/kg/day) which covers cellular IC_{90} for ≥ 22 hours
- Data from GLP toxicology studies support a proposed safe starting dose of 0.5X the estimated therapeutic dose
- IDE161 API synthetic process and drug product tablet formulation developed

IDE161 Clinical Development Opportunities

Clinical Pillars Support Evaluation in Multiple Clinical Settings



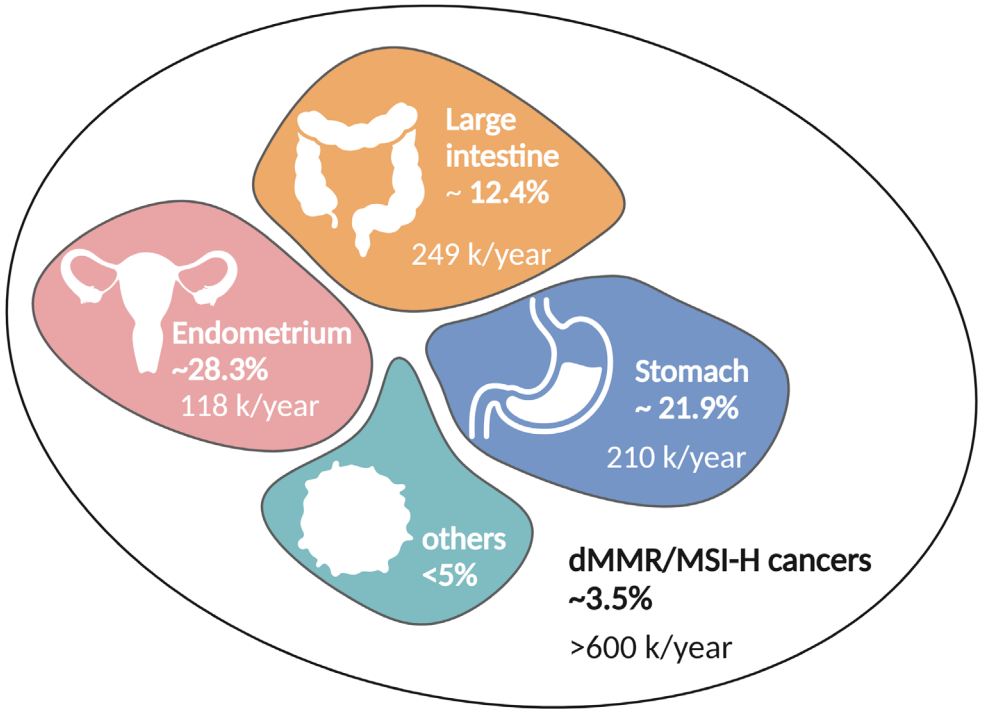
Selective Essentiality in DNA Damage Repair

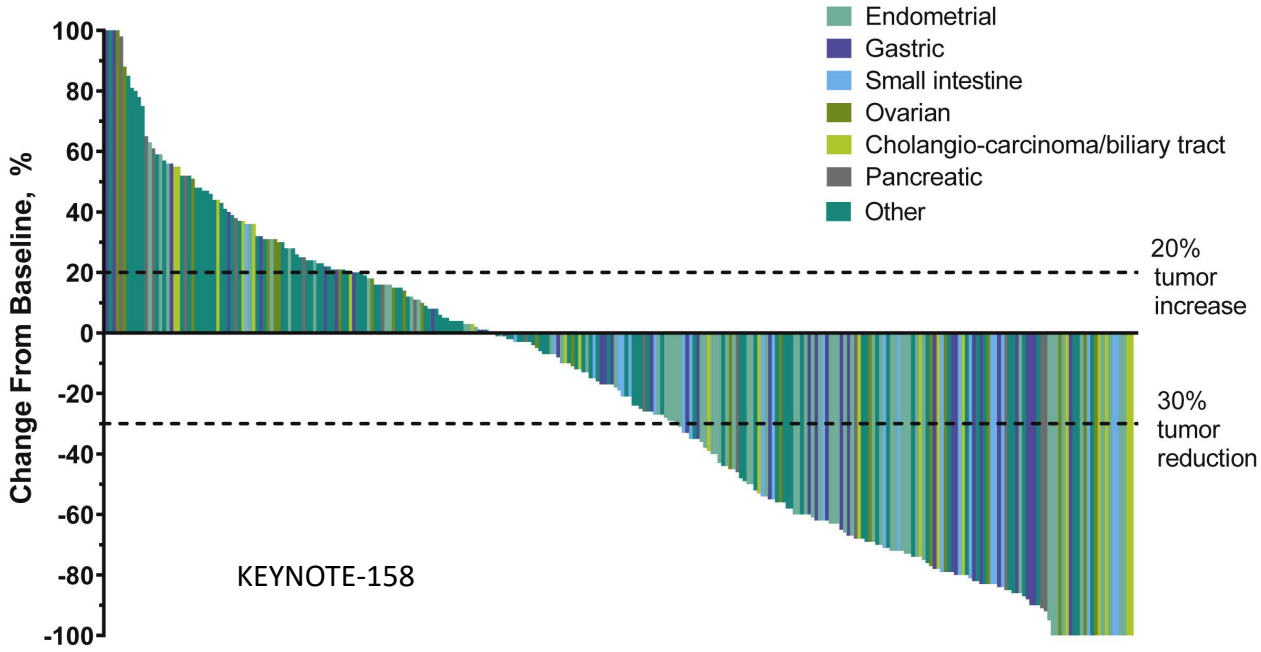
Werner Helicase is a Cornerstone Synthetic Lethality Target for MSI-High Cancers

Mathew Garnett, Ph.D.
Wellcome Sanger Institute
Leader, Translational Cancer Genomics

Werner Helicase Synthetic Lethality Program

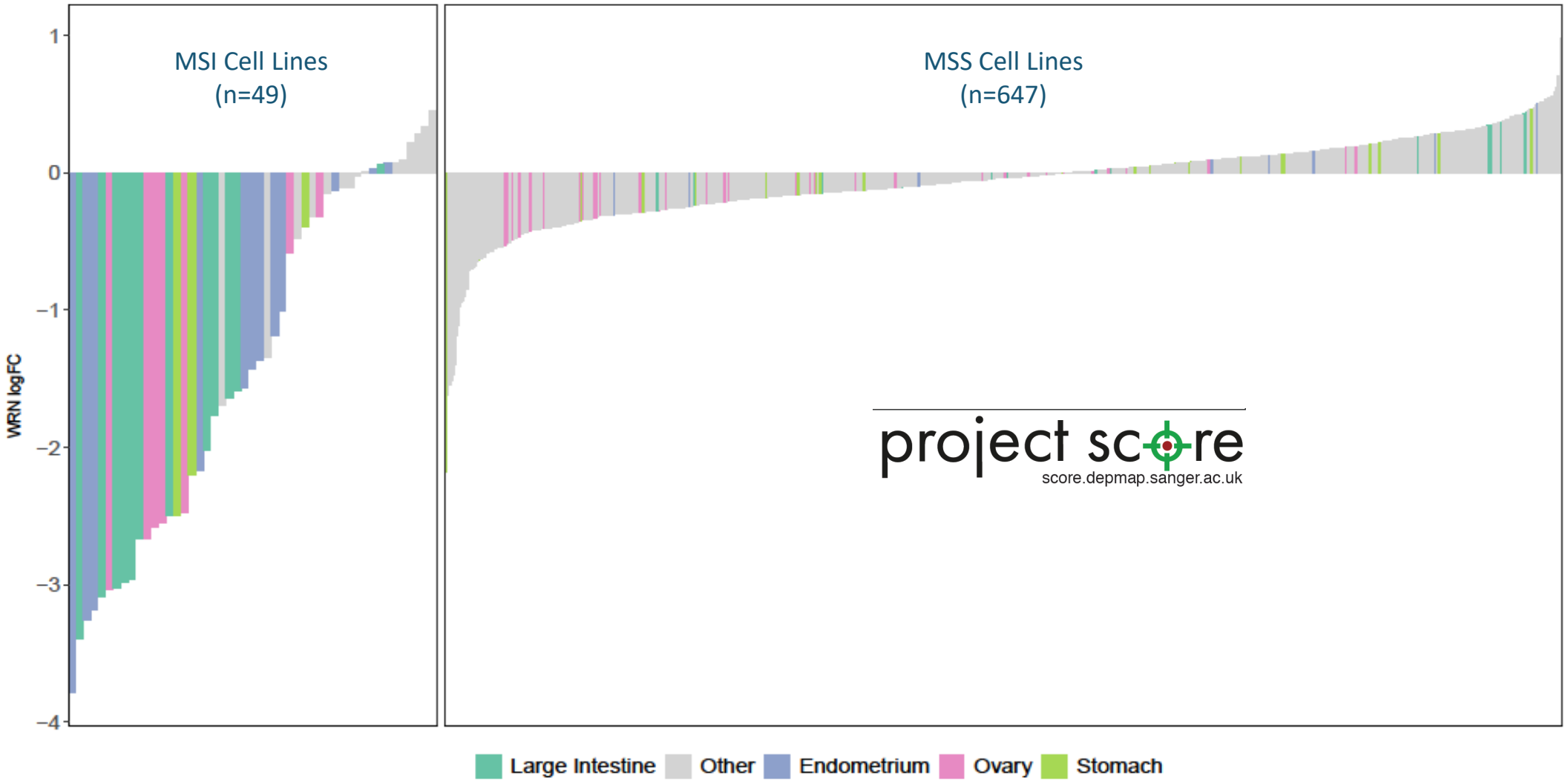
MSI Cancers: Prevalence and Potential Therapeutic Strategies





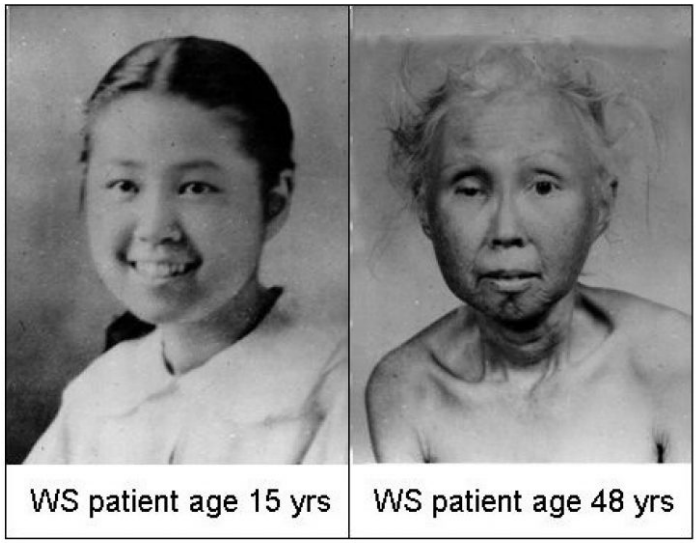
Cortes-Ciriano et al., Nature Comm. 2017
World Cancer Research Fund International (2020)
Maio et al., Ann. Oncol. 2022

Werner Helicase – Dependence in Cancer Cell Models

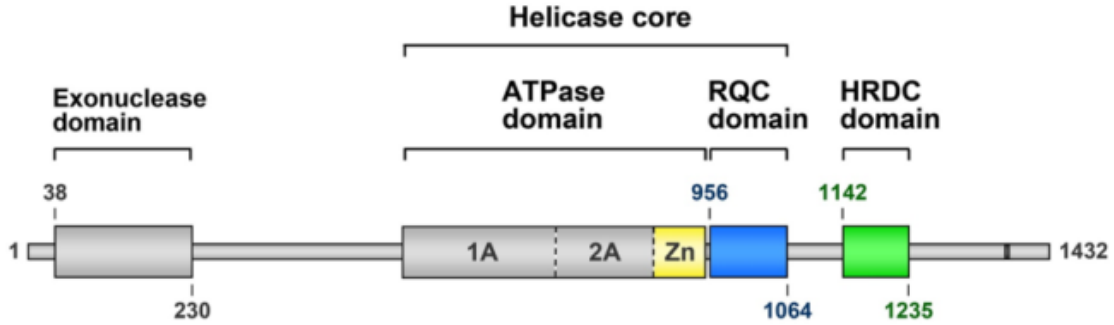


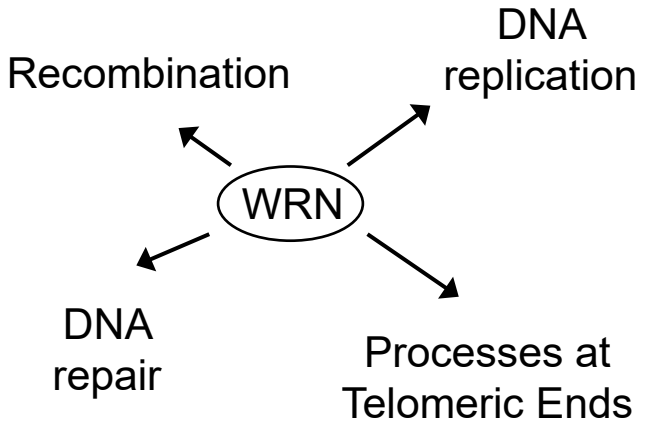
Behan et al. Nature 2019
Pacini et al, Nat Com. 2021

Werner Syndrome RecQ Helicase

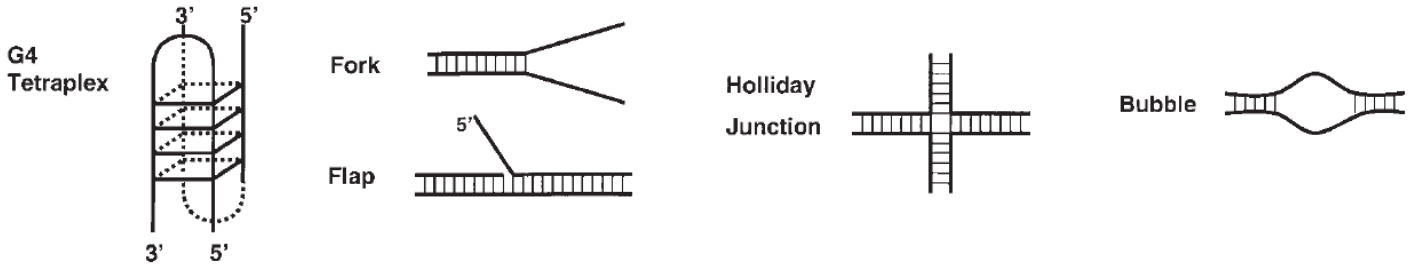


WRN Helicase Protein



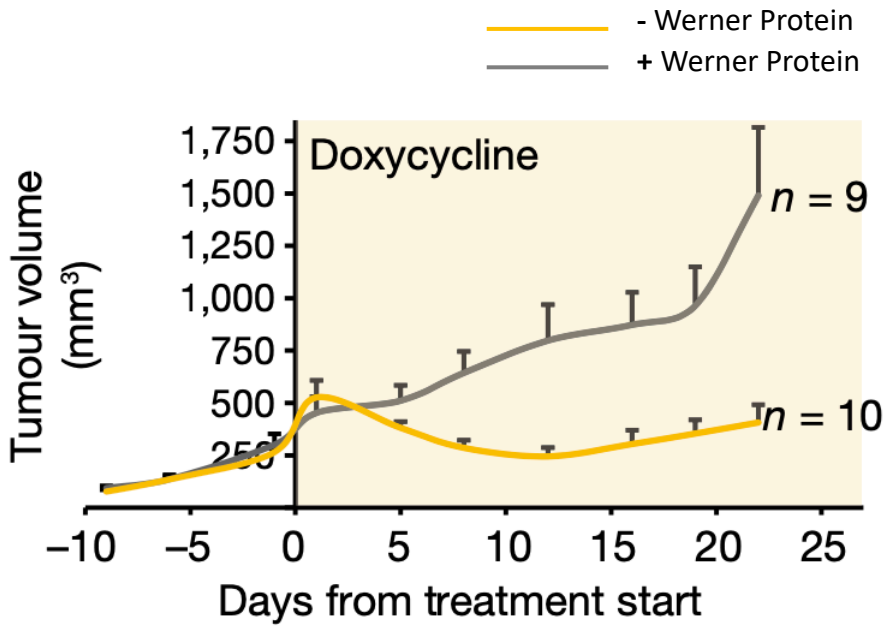


WRN Helicase Substrates

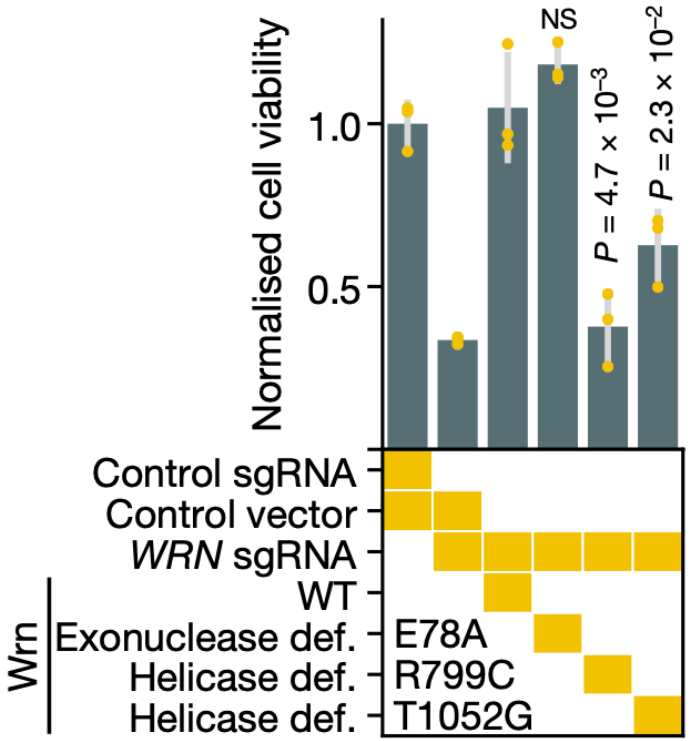


Werner Helicase is a Target in Cancers with High MSI

WRN is necessary for *in vivo* growth of CRC MSI-H Cells



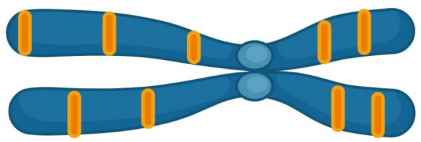
Helicase Activity Essential for MSI-H SL Relationship



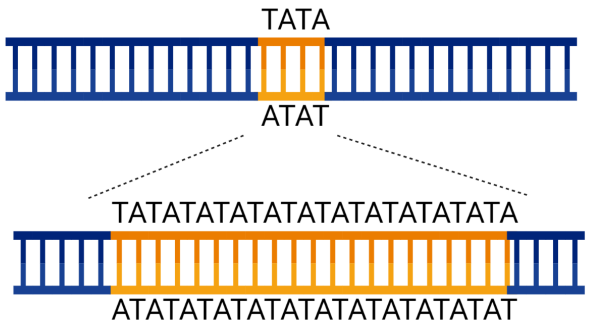
Behan et al. Nature 2019

MSI = Microsattelite Instability; MSI-H = MSI High

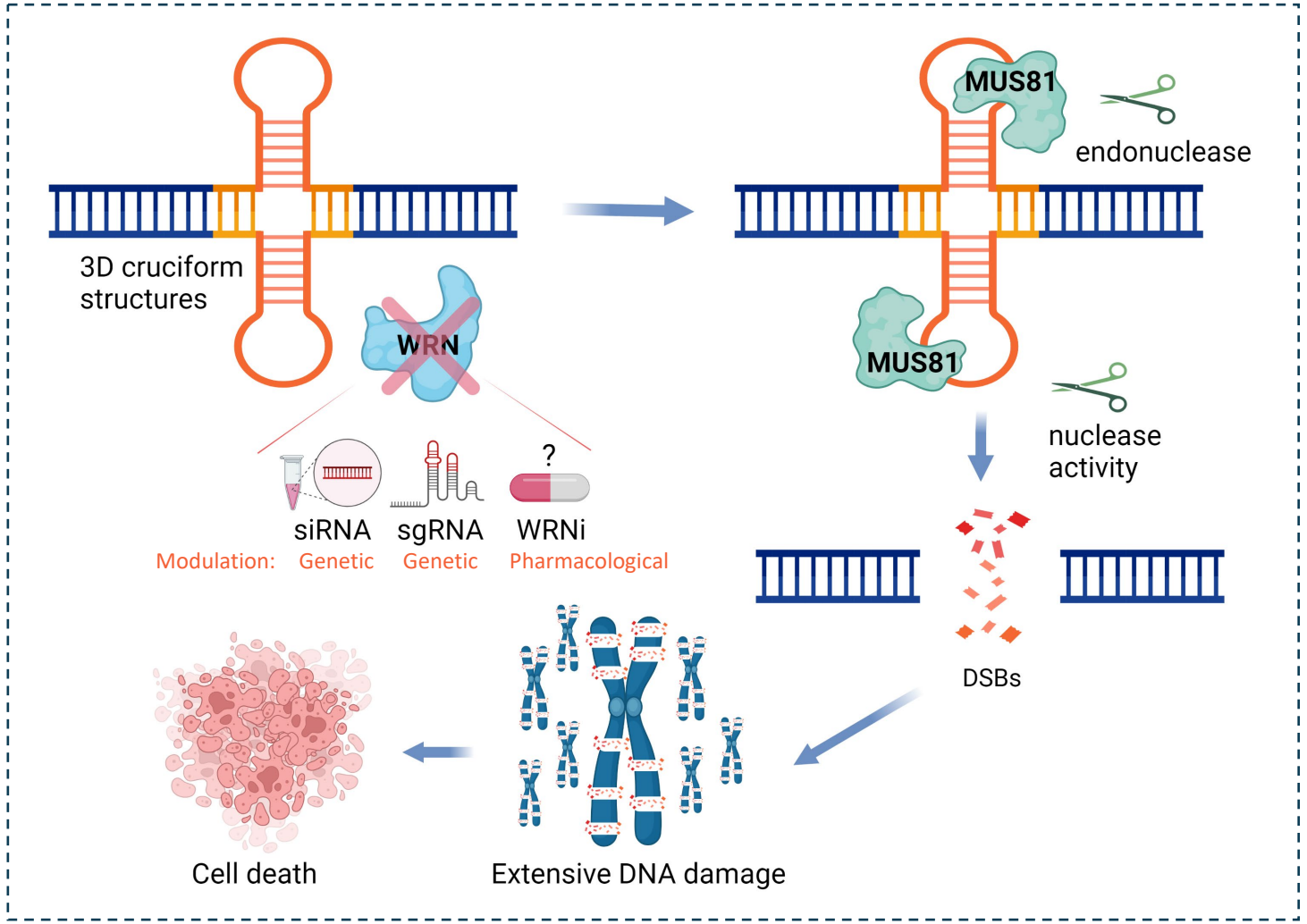
Werner Helicase Synthetic Lethality in MSI-High Cancer Cells



$(TA)_n$ repeats regions



$(TA)_n$ repeat expansions - MSI



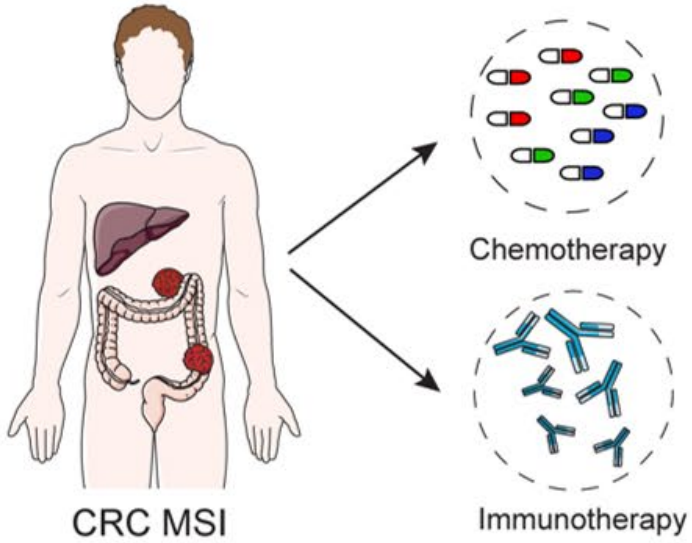
Wietmarschen et al., Nature 2020

Werner Dependency in Models of Therapy Resistance

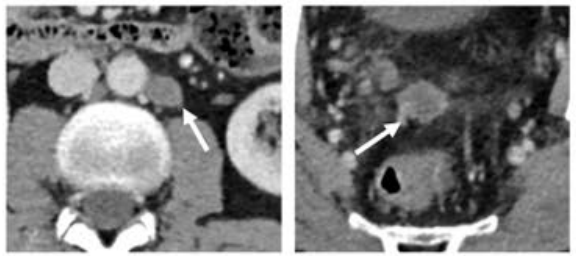

RESEARCH BRIEF

Werner Helicase Is a Synthetic-Lethal Vulnerability in Mismatch Repair–Deficient Colorectal Cancer Refractory to Targeted Therapies, Chemotherapy, and Immunotherapy

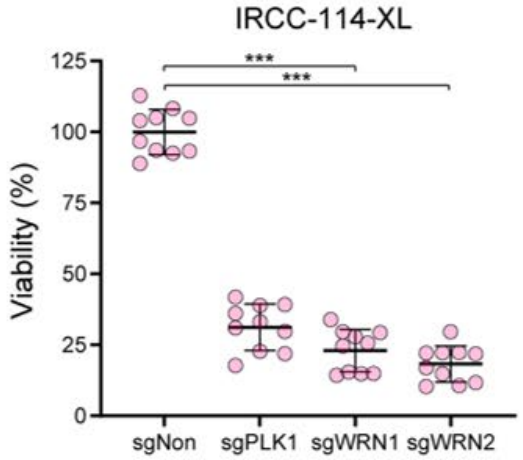
Gabriele Picco[1], Chiara M. Cattaneo[2,3], Esmée J. van Vliet[1], Giovanni Crisafulli[4,5], Giuseppe Rospo[4,5], Sarah Consonni[1], Sara F. Vieira[1], Iñigo Sánchez Rodríguez[2,3], Carlotta Cancelliere[4], Ruby Banerjee[1], Luuk J. Schipper[2,3], Daniele Oddo[4,5], Krijn K. Dijkstra[2,3], Jindrich Cinatl[6], Martin Michaelis[7], Fengtang Yang[1], Cell Model Network UK Group[1], Federica Di Nicolantonio[4,5], Andrea Sartore-Bianchi[8,9], Salvatore Siena[8,9], Sabrina Arena[4,5], Emile E. Voest[2,3], Alberto Bardelli[4,5], and Mathew J. Garnett[1]



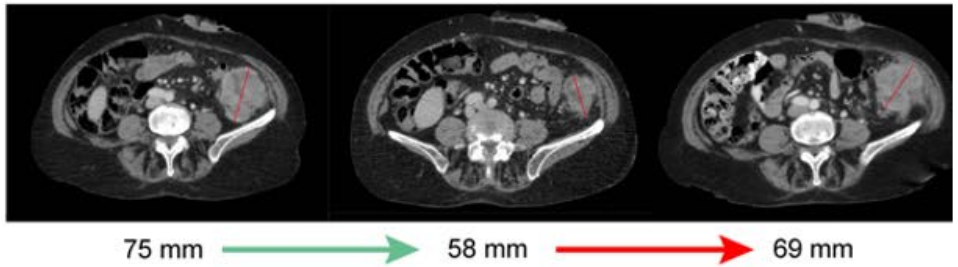
Resistance to Chemotherapy (mFOLFOX)

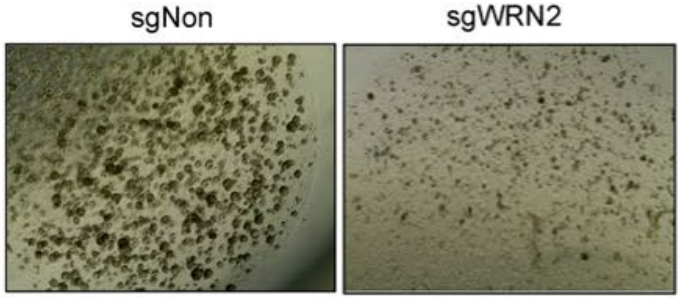


Progressive disease



Resistance to Immunotherapy (nivolumab)

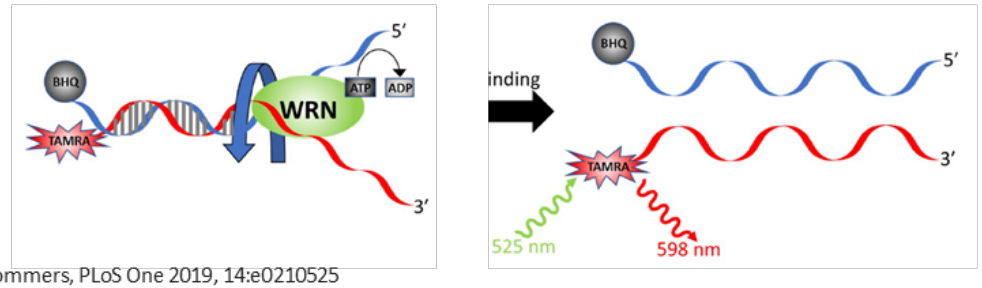




Picco et al., Cancer Discovery 2021

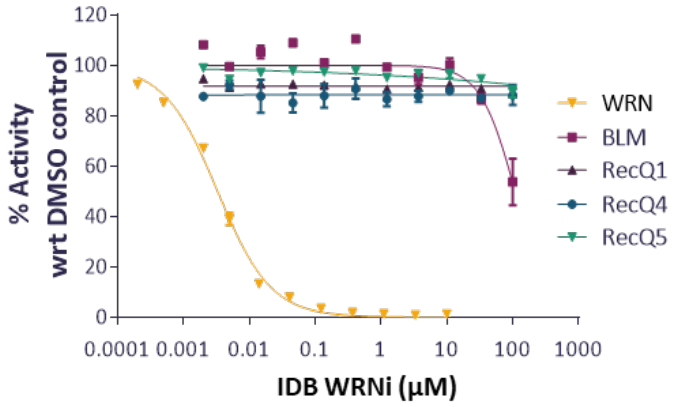
IDEAYA Discovery of Selective Werner Inhibitor

WRN Inhibitor selectively inhibits DNA Unwinding

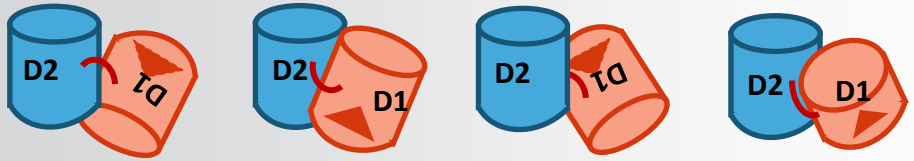


[2] Sommers, PLoS One 2019, 14:e0210525

WRNi selective for WRN over other RecQ helicase family members



Co-crystal Structures drive Affinity Improvements

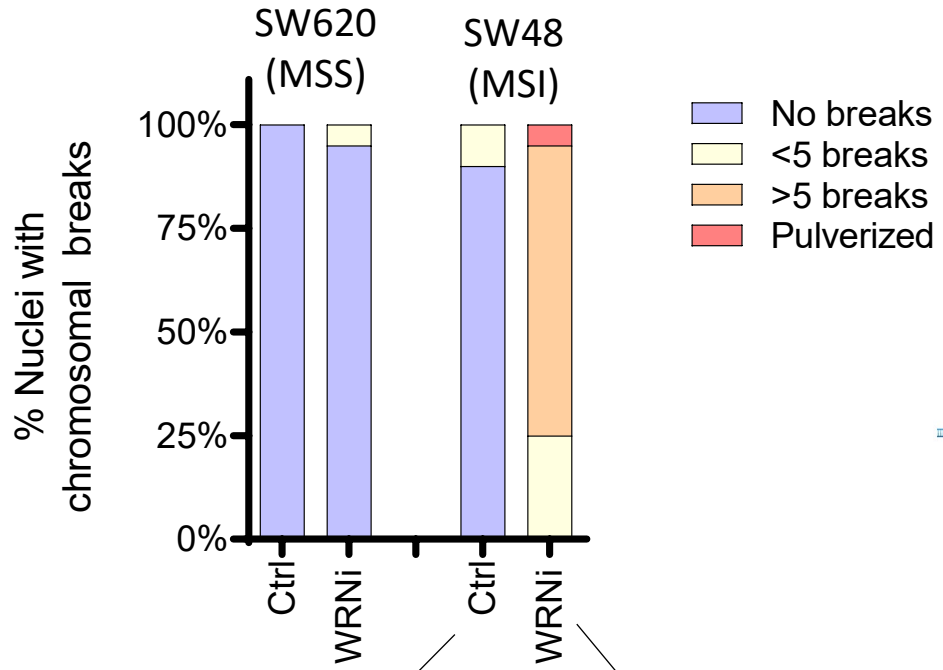


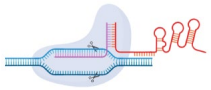
Solved > 85 X-ray co-crystal structures with multiple conformations of the helicase D1 and D2 domains

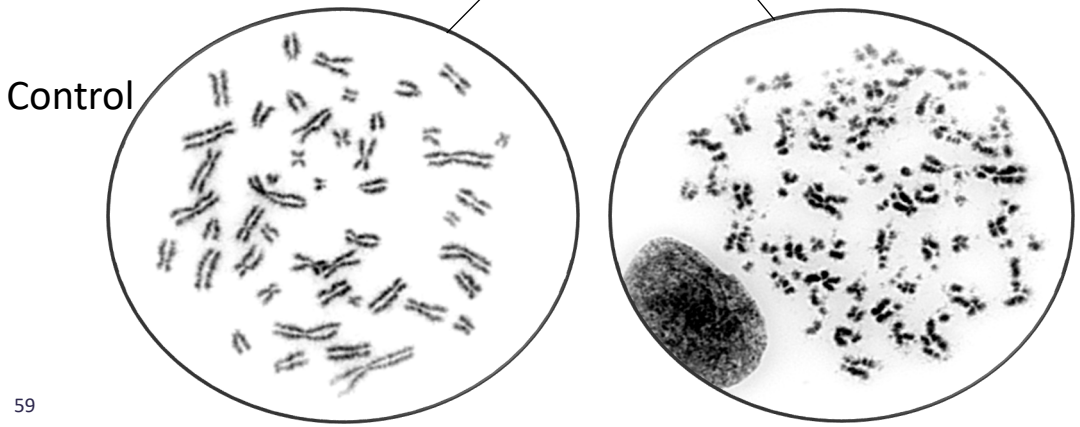
Initial Hits
Low Affinity
Poor Druglike Properties

Improved Inhibitors
High Affinity
Good Druglike Properties

Werner Inhibitors induce DSB and inhibit MSI Cell Growth



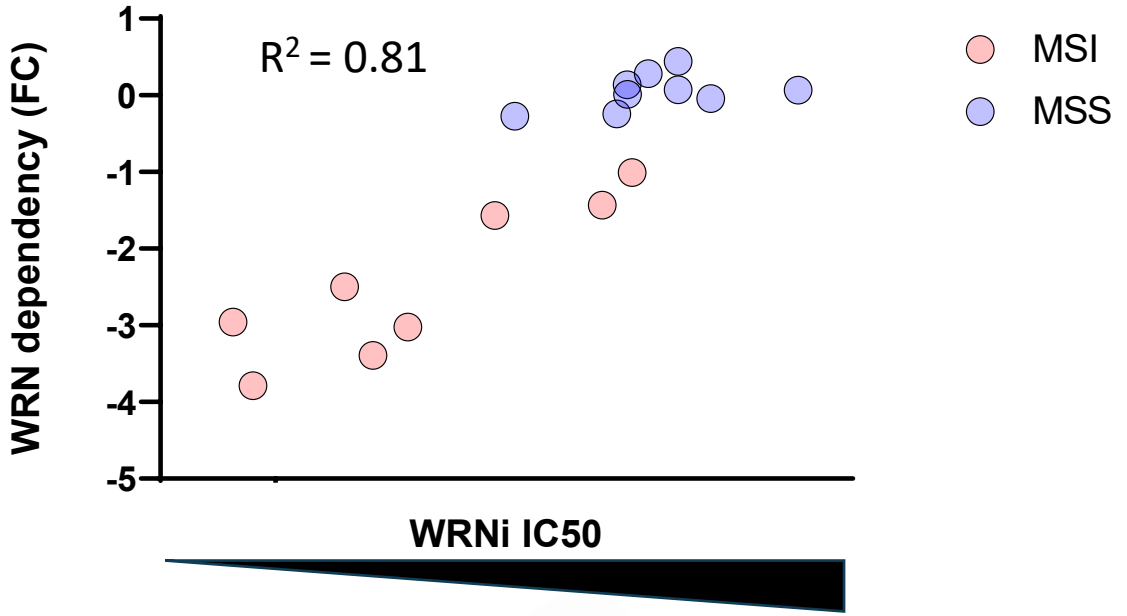




WRNi

Pharmacological

Endometrium and Large Intestine Cell Lines

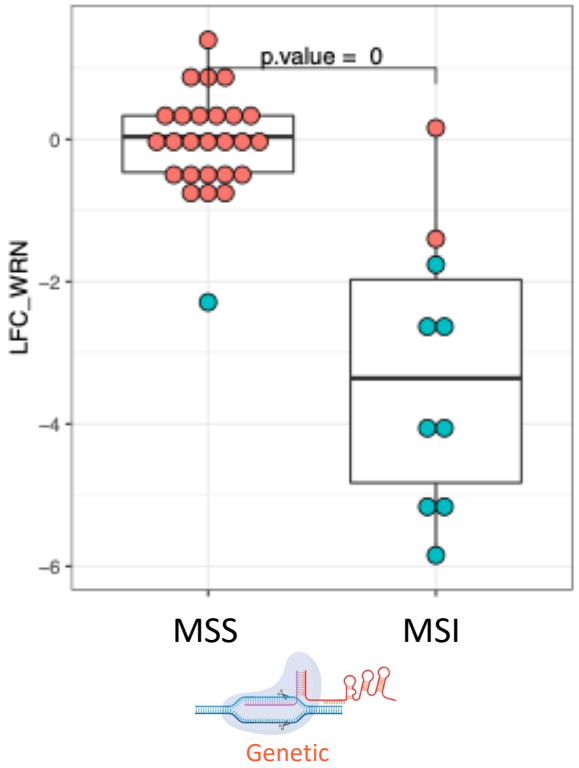


Pharmacological

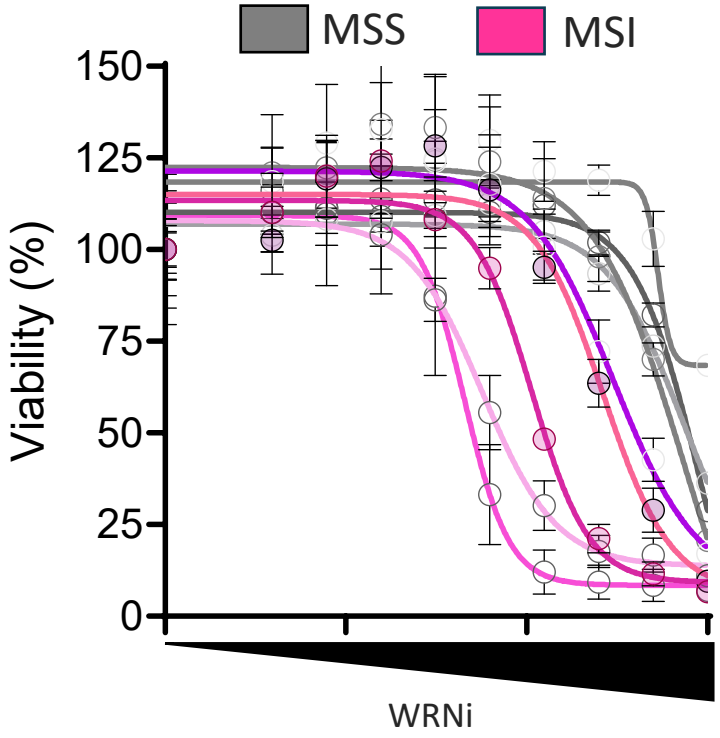
Pacini et al, Nat Com. 2021

Werner Dependency in Patient-Derived MSI CRC Organoids

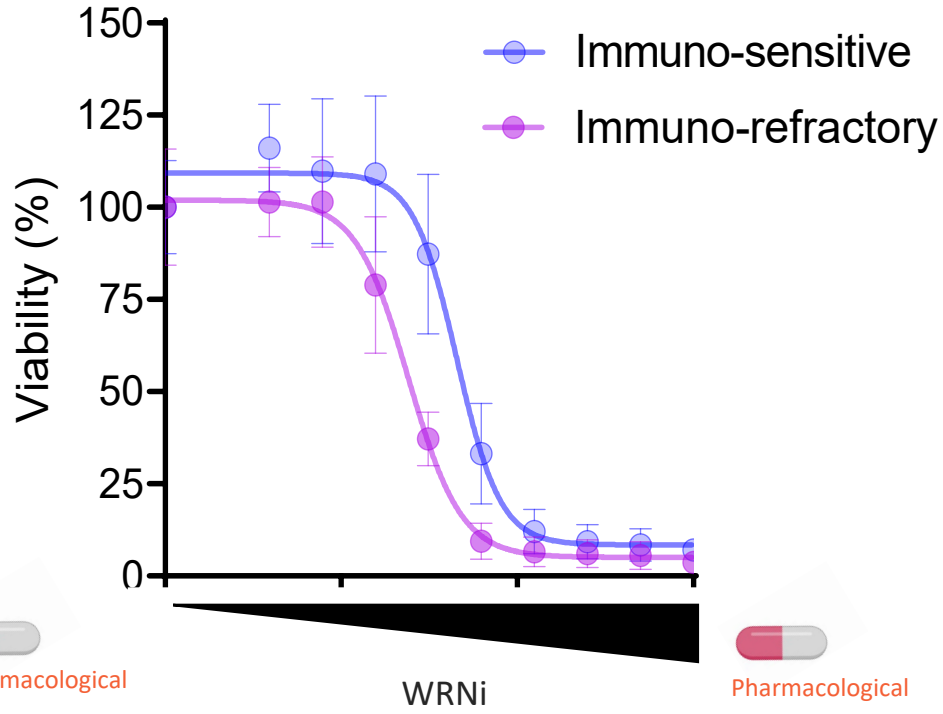
Genetic Dependency in MSI / MSS Organoids



Pharmacologic Sensitivity in MSI / MSS Organoids

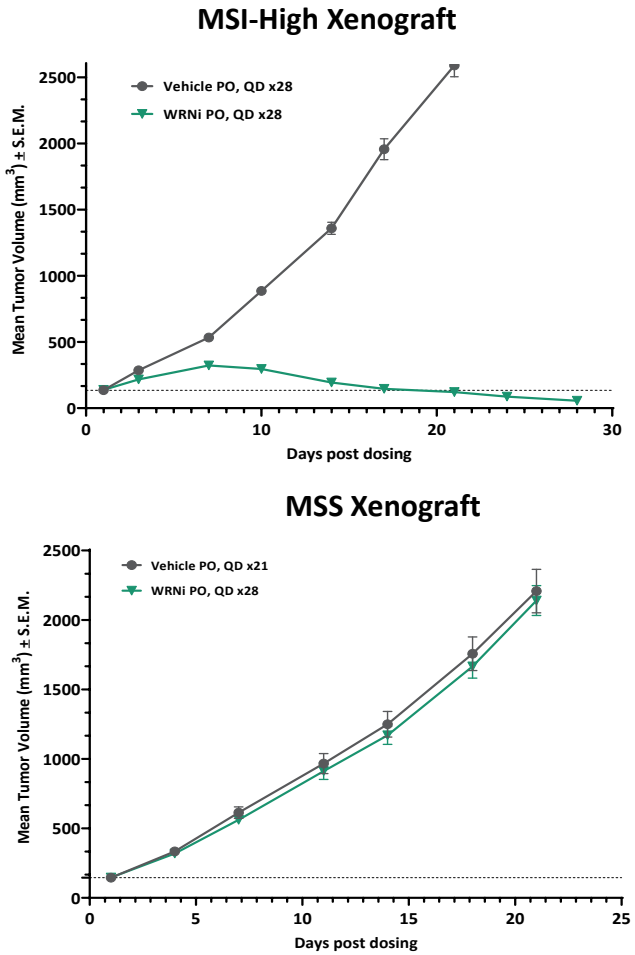


Pharmacological Sensitivity in Immunotherapy-Refractory MSI Organoids



Werner Inhibitors Selectively Induce Tumor Regressions *In Vivo*

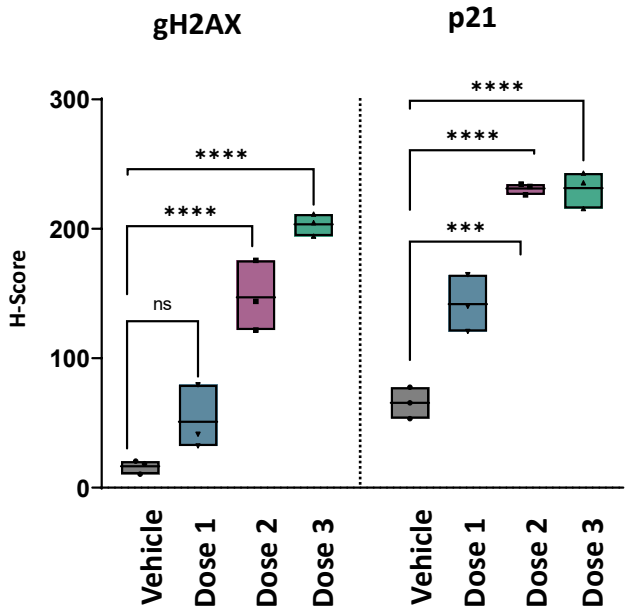
MSI-high Selective Tumor Reduction



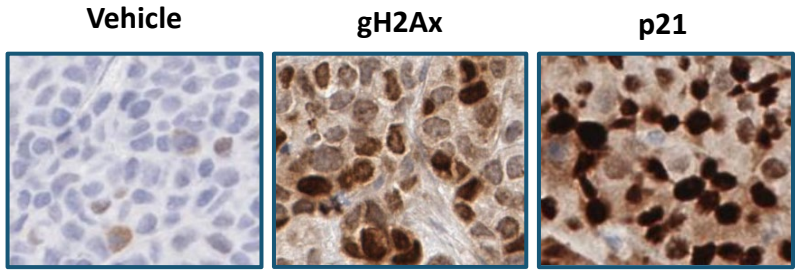
Pharmacological

Dose-dependent Tumor PD Marker Movement

MSI-High Tumor PD
Day 3 (3h after Tx)



Histology Stains
(Dose 2)



Pharmacological

Selective Essentiality in DNA Damage Repair

Targeting PolQ to Enhance and Maintain Control of HRD Tumors

Ben Schwartz, Ph.D.
GSK
Vice President, Head of the Oncology Synthetic Lethality Research Unit

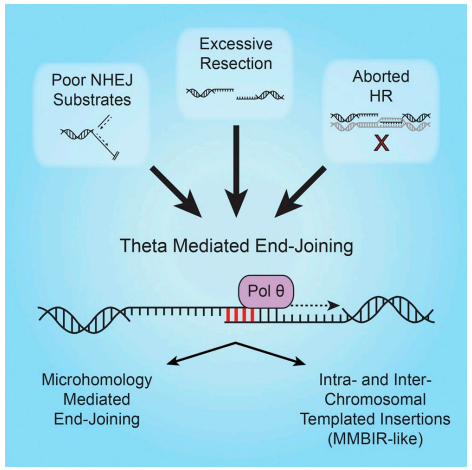
Polymerase Theta (Polθ) Synthetic Lethality Program

FIC Helicase Inhibitor is Synthetic Lethal to HR and NHEJ Perturbation

Role of Polθ in Tumor Biology

Polθ is an error-prone helicase/polymerase

Polθ DNA break end-joining is critical when canonical repair pathways fail



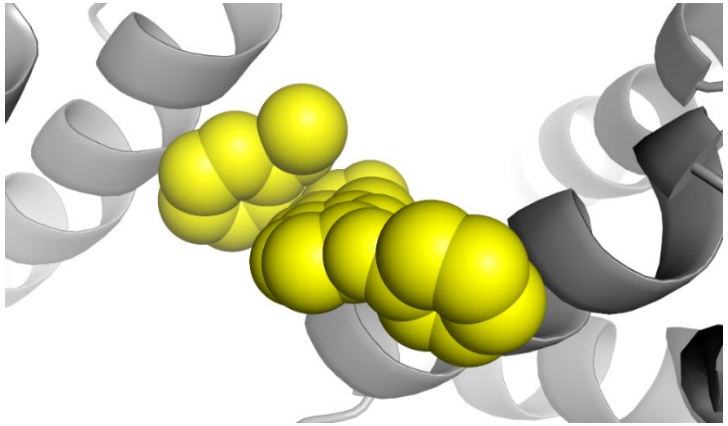
D. Wyatt et al. *Mol Cell* (2016)

Polθ Inhibitor Drug Discovery

Discovered Polθ inhibitors with IC_{50} <10 nM in biochemical assays against Polθ

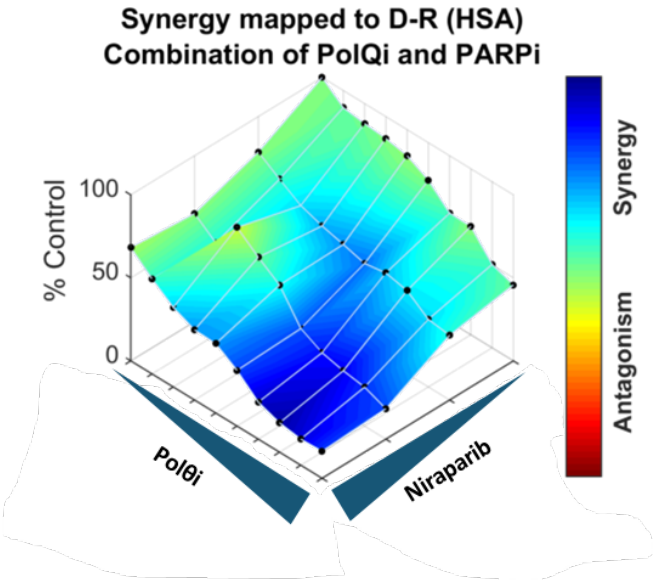
Drug-like properties of Polθ inhibitors support oral dosing in humans

Development candidate nominated in 2022



Polθi Impact on HRD Cells

Polθ inhibition is synthetic lethal with PARP inhibition in HR-deficient cancer cells

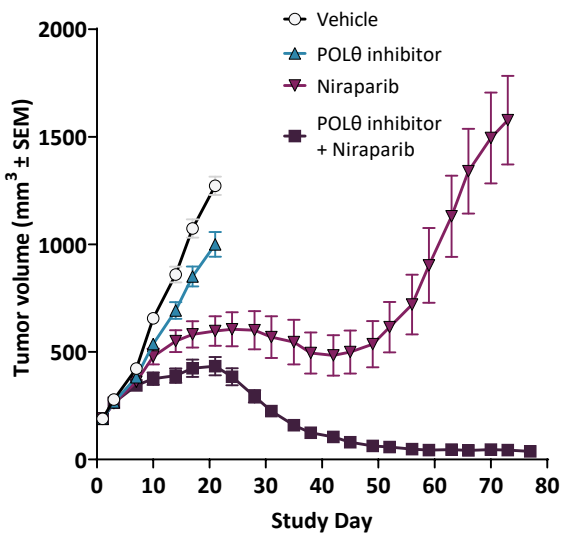


Polymerase Theta (Polθ) Synthetic Lethality Program

Preclinical Proof-of-Concept for Deep and Durable Synthetic Lethality with PARPi

Polθ Helicase Inhibitor *in vivo* Activity

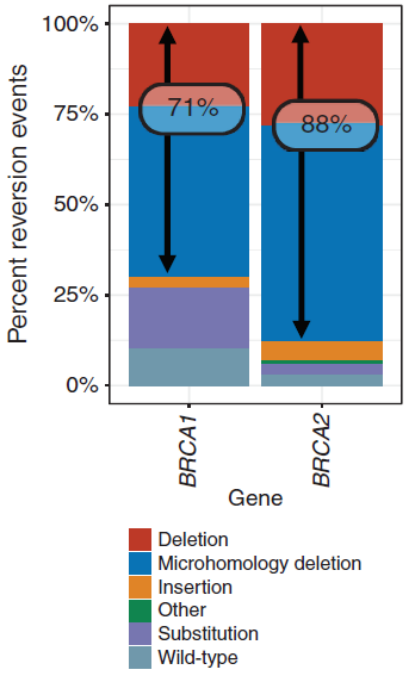
Polθ Helicase Inhibitor + PARP Inhibitor



Observed Deep and Durable Responses in Multiple Xenograft Models

BRCA 1/2 Clinical Reversions

BRCA Reversions mediated by MMEJ



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

Clinical Development Strategy

Pol Theta Helicase Inhibitor + PARP Inhibitor

Pol Theta Helicase Inhibitors Disrupt MMEJ Alternative DNA Damage Repair:

- Inhibit DSB Repair by MMEJ
- Dysregulate Replication Fork Stabilization

Potentiate PARPi Efficacy	Overcome PARPi Resistance	Prevent PARPi Resistance

Potential Clinical Opportunities

IDEAYA Investor R&D Day

Closing Remarks

Yujiro S. Hata
IDEAYA Biosciences
President and Chief Executive Officer

IDEAYA Investor R&D Day

Closing Remarks

Industry Leading Potential First-in-Class Clinical Stage Synthetic Lethality Pipeline

- 3 First-in-Class Clinical- or IND- Stage Programs
  - Darovasertib (PKC, Ph2), IDE397 (MAT2A, Ph2), and IDE161 (PARG, IND Filed)
- 2 Development Candidate- or Preclinical- Stage Programs
  - Pol-Theta Helicase (Targeting Ph1 FPI, H1 2023); Werner Helicase (Targeting DC, 2023)
- Next Generation Synthetic Lethality Programs
  - Targeting IND(s) in ~2025

Investment Priorities to Enhance SL Pipeline and Platform Capabilities

- Data Informatics
  - Become leader in SL Bioinformatics / Machine Learning / Target and Biomarker Discovery
- Structurally-Enabled Drug Discovery
  - Enhance SL Drug Discovery Platform to advance First-in-Class SL Targets and Product Profiles
- Liquid Biopsy
  - Enable non-invasive Patient Selection and PD Response Evaluation Clinically
- Synthetic Lethal Combinations
  - Enable First-in-Class SL Combos: PKC-cMET, MAT2A-PRMT5, PARP-Pol Theta, Werner-PD1

IDEAYA Investor R&D Day

Analyst Q&A

Yujiro S. Hata
IDEAYA Biosciences
President and Chief Executive Officer