evotec

#RESEARCHNEVERSTOPS

Evotec's drug discovery capabilities in: The DNA Damage Response (DDR)

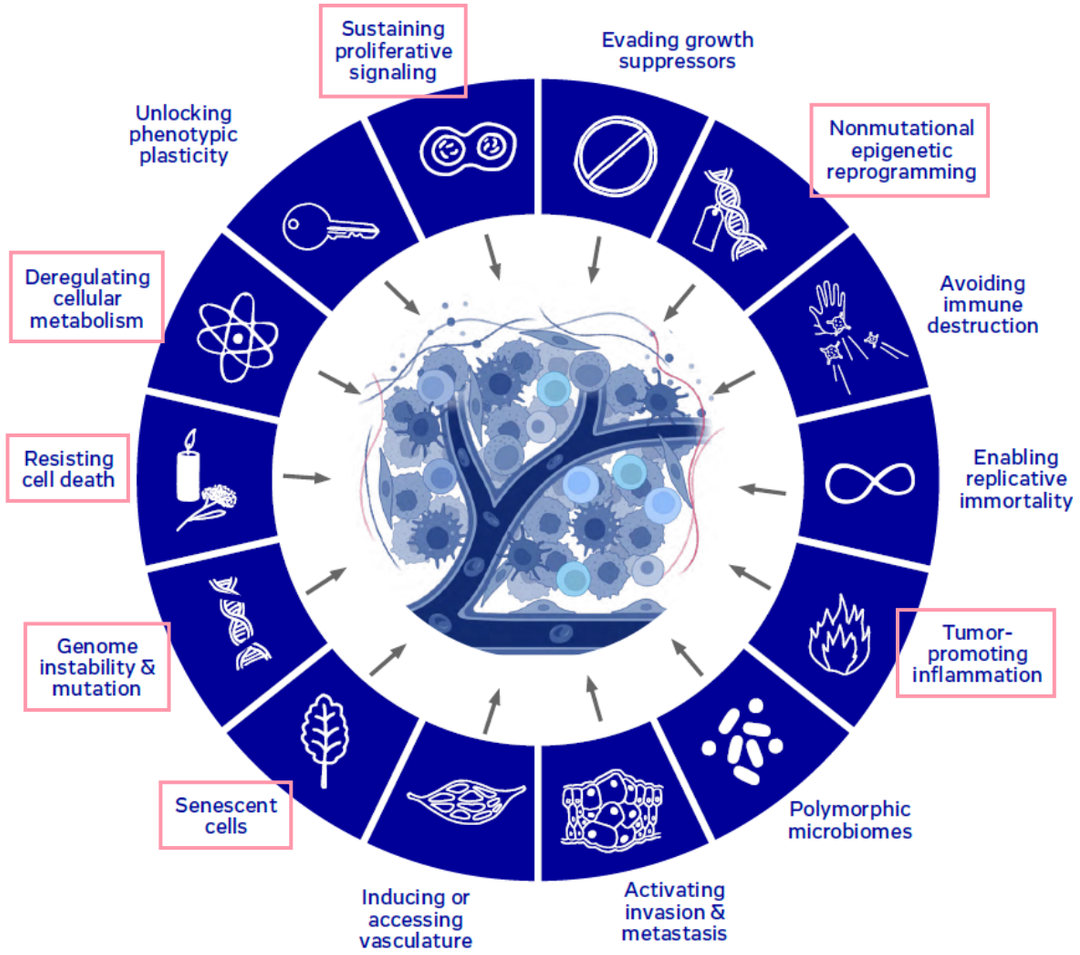
World-class DDR mechanistic target validation, models and screens

Contents

Contents

Focusing on innovative targets with first-in-class potential

Evotec oncology themes to support integrated drug discovery from concept to clinic



DDR encompasses several Hallmarks of Cancer

- DNA damage occurs constantly in cells by exogenous and endogenous stressors
- Cells have evolved a complex, coordinated DNA damage response (DDR) comprising numerous signalling pathways and machineries
- The DDR therefore impacts damage-induced genome stability, the cell cycle, chromatin remodelling, metabolism, immunogenicity, telomere maintenance, senescence and apoptosis

Adapted from: Hanahan D. Hallmarks of cancer: New Dimensions. Cancer Discovery (2022)

Drugging the DNA damage response (DDR)

Synthetic Lethal vulnerabilities defining patient populations (clinical Line of Sight, LoS)

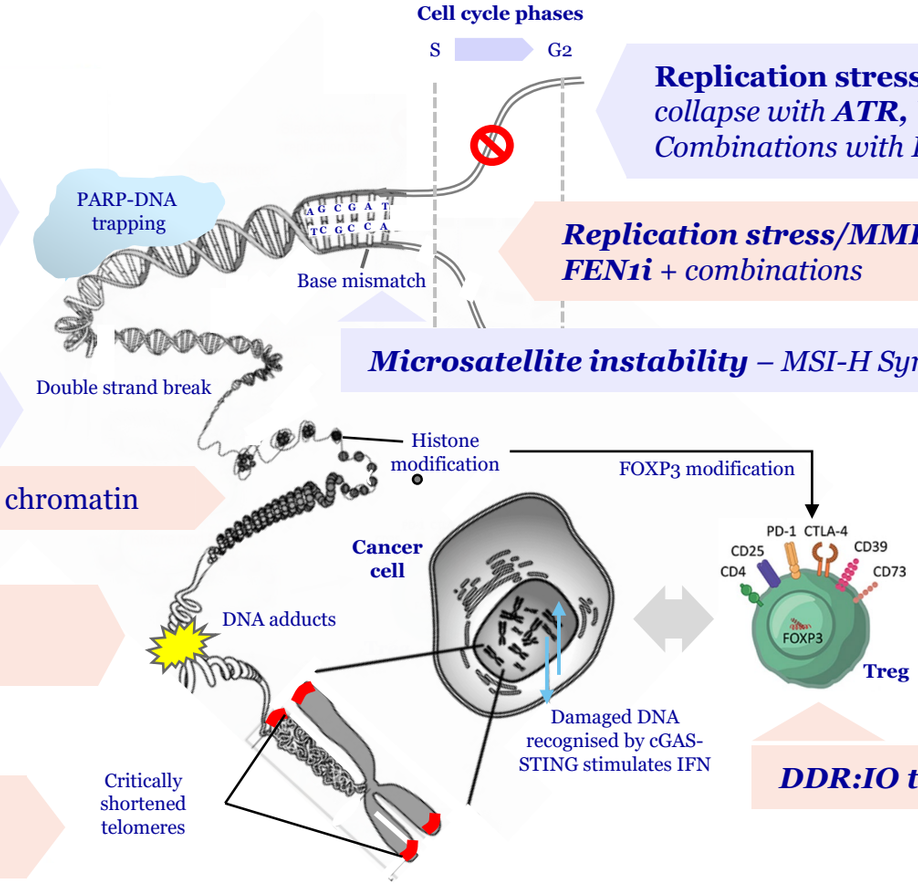
Trapping PARP1 on DNA *– next gen PARP1-selective trapping. Synthetic Lethal with BRCAm/HRD*

DSB repair – Targeting *NHEJ, HR & MMEJ with **ATM, DNA-PK & Pol theta** inhibitors. Combinations with radiation/PARPi*

Histone readers/writers - Signal damaged chromatin

Nucleotide excision repair and Topoisomerase trapping
Repairs bulky lesions; inhibitors would sensitise to chemos

Alternative Lengthening of Telomeres



Replication stress – *Exacerbating replication fork stalling/ collapse with **ATR, Wee1, Chk1, PKMYT1** inhibitors. Combinations with PARPi.*

Replication stress/MMEJ-dependency *– Synthetic lethal with **FEN1i** + combinations*

Microsatellite instability *– MSI-H Synthetic lethal with **WRNi***

DDR:IO targets

Adapted from: REVIEW article Front. Immunol., 03 December 2019 Sec. T Cell Biology Volume 10 - 2019 | and from https://www.physio-pedia.com/Genetic_Conditions_and_Inheritance

Summary of our DDR platforms

Screening single-agent and combination activity in early drug discovery

Biochemical assays for targets of the DDR pathways

- Parylation, kinases & ATPases (ATPase Glo), Polymerase (primer extension), Helicase (strand displacement) & Nuclease (DNA fluorescent polarisation)

Cellular assays for DDR targets and cell cycle checkpoints

- High content analysis for RAD51 and γH2AX foci, pCHK1, pATM, pRAD50, Cell cycle, parylation (*in vivo* PD biomarkers)
- Phenotypic assays – viability, proliferation (incucyte, CTG, CFA), apoptosis in synthetic lethal isogenic and resistance models:
  - HR-deficient ($BRCA2^{-/-}$) vs wt (DLD1 matched pair) (grow *in vivo*)
  - Generating acquired PARPi- and radiation-resistant clones
- NHEJ, MMEJ, HR repair reporter assays
- PARP-trapping assay
- Replication Stress assessment using Genomic Vision (combing, fork speed etc.)
- HiBit-based proteomic degradation platform (volcano plotting the expression of the proteome) – suitable for smRNAi platforms EVT offer

Combinations with established DDR agents to tackle resistance

- Radiation (x-ray), radiomimetics e.g. neocarzinostatin), DDRi: PARPi, ATRi, Wee1i, ATMi, topoisomerase inhibitors & ADCs (e.g. Enhertu), carboplatin

CRISPR (whole-genome or focussed library) drop out screens

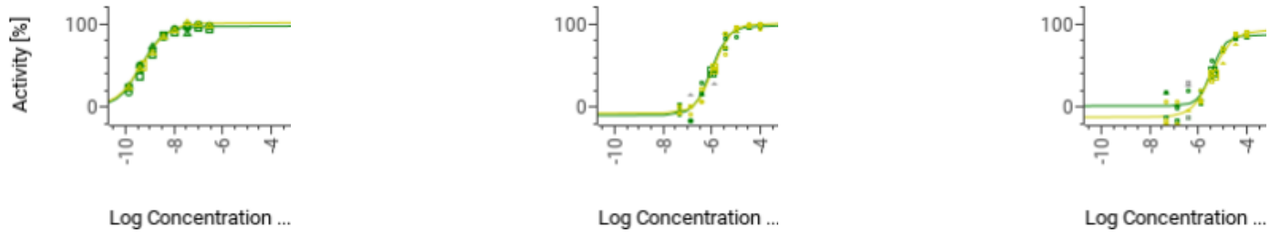
- for synthetic lethal identification, bioinformatic support and building machine-learning/AI

Contents

Biochemical assays: *Kinase and ATPase activity*

ADP-Glo™ Kinase Assay from Promega

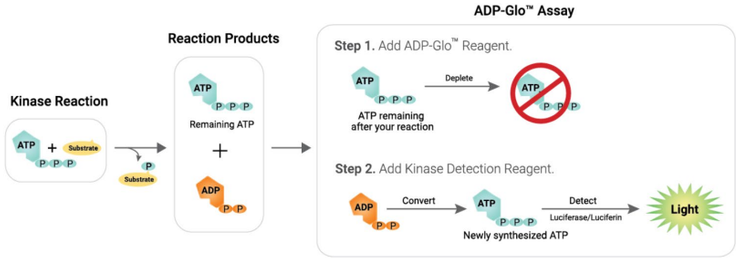
- **Aim**
  - Evaluate compounds potency *in vitro* for both helicases and kinases
- **Assay type**
  - Enzymatic reaction using either truncated (kinase/ATPase domain) or full-length protein
- **Throughput**
  - 31 compounds in dose-response – SAR driver
  - QC monitoring through assay performance (Z' and S/B) and pharmacological inhibition (reference compound IC_{50} values reproducibility)
- Assay can be developed for any polymerase



	Compound X	Compound Y	Compound Z
pIC_{50}	9.3	5.9	5.4

Assay principle

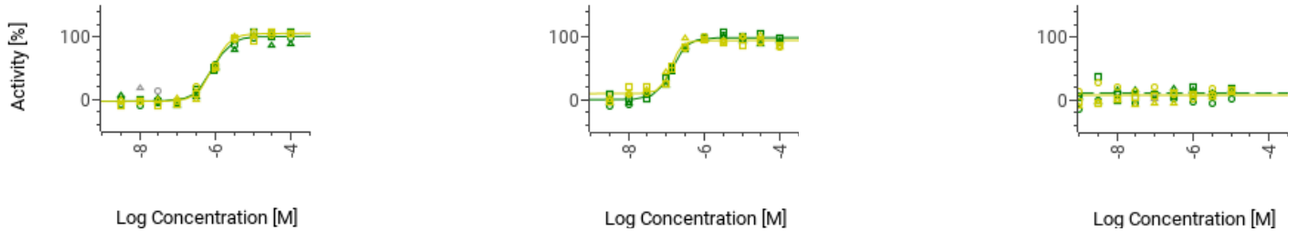
Measurement of ATP conversion using the Promega ADP-Glo™ Kinase assay. Upon ATPase/kinase activity, robust and stable luminescent signal is generated.



Biochemical assays: *Polymerase activity*

Strand-displacement assay

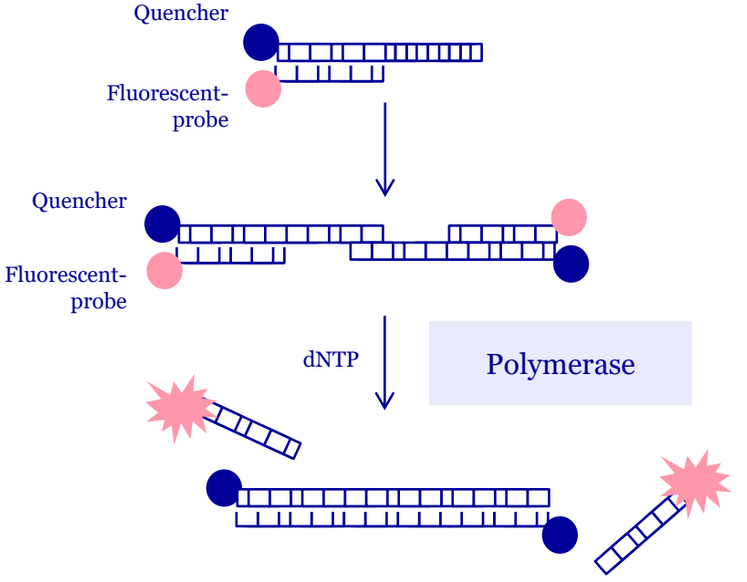
- **Aim**
  - Evaluate compounds potency *in vitro* for polymerases
- **Assay type**
  - Enzymatic reaction using either truncated (polymerase domain) or full-length protein
- **Throughput**
  - 31 compounds in dose-response – SAR driver
  - QC monitoring through assay performance (Z' and S/B) and pharmacological inhibition (reference compound IC_{50} values reproducibility)
- Assay can be developed for any polymerase and can be considered as orthogonal validation method



	Compound X	Compound Y	Compound Z
pIC_{50}	6.0	6.8	>4

Assay principle

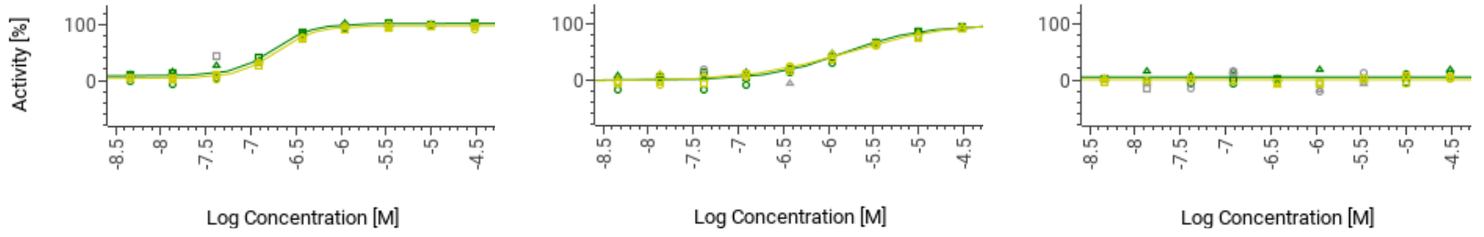
Quantification of polymerase activity relying on the ability of the polymerase to displace downstream DNA encountered during synthesis. This displacement prevents the quenching of the fluorescent probe.



Biochemical assays: *Helicase activity*

Strand-displacement assay

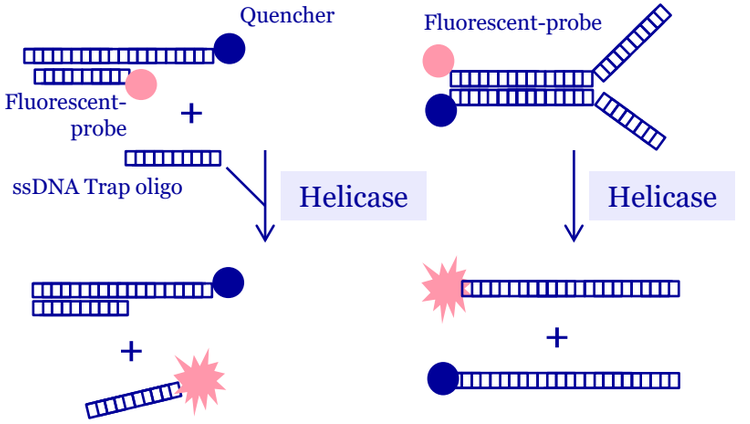
- **Aim**
  - Evaluate compounds potency *in vitro* for helicases
- **Assay type**
  - Enzymatic reaction using truncated protein (helicase domain)
- **Throughput**
  - 31 compounds in dose-response – SAR driver
  - QC monitoring through assay performance (Z' and S/B) and pharmacological inhibition (reference compound IC_{50} values reproducibility)
- Assay can be developed for any helicase displaying DNA-unwinding activity



	Compound X	Compound Y	Compound Z
pIC_{50}	6.7	5.8	>4.5

Assay principle

- Fluorometric measurement of ssDNA substrate arising from unwinding activity of the helicase. The DNA displacement prevents the quenching of the fluorescent probe



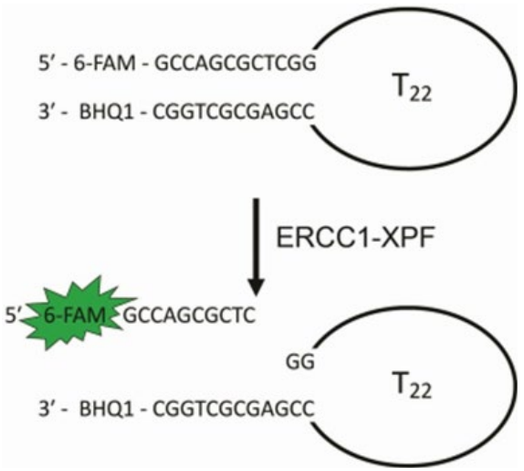
- Assay can be developed either with or without ssDNA trap to stabilise the fluorescent signal

Biochemical assays: *Nuclease activity*

Choice of DNA quenching or protein-protein interaction determination if in an active complex

Enzymatic assay (fluorescent DNA substrate)

- E.g. for endonuclease activity
- Synthesis of Molecular beacon probes
  - Reflexion on another fluorochrome to avoid compounds autofluorescencing

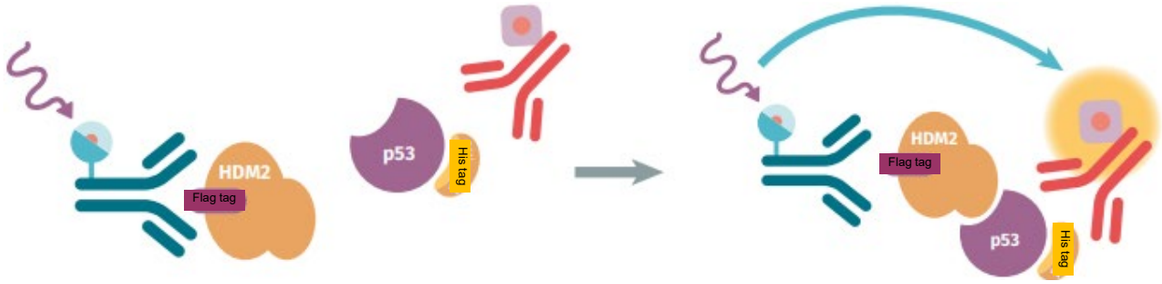


Bowles M. et al., Nucleic Acids Research, 2012, Vol. 40, No. 13

Dye	Quencher
6-FAM	BHQ1
HEX	Lowa Black FQ
TET	Lowa Black FQ
TYE 563 / TYE 665	Lowa Black RQ

PPI assay (HTRF assay)

- Working on 2 independent proteins
- (HTRF technology
  - MAB Anti 6His / Mab Anti Flag
  - Choice of acceptor and donor on each MAB (d2, Eu-cryptate, Tb cryptate, XL665). E.g. as for p53-MDM2



  - A counter-assay based on a doubled-tagged peptide to filter out positive compounds interfering with the readout (Kit interference available)

Contents

Assaying DNA double strand break repair

Measuring the sub-pathways of DSBR

The four major pathways to repair DNA Double-Strand Breaks (DSBs)

a) Unprocessed DSBs can be repaired through classic **non-homologous end joining (cNHEJ)** allowing the two ends of the DSB to be re-ligated

b) DSB ends can also be processed by the MRN complex and its interacting factors to yield short 3' ssDNA overhangs

c) The short 3' ssDNA overhangs can then be channeled into the **microhomology-mediated end joining (MMEJ)** pathway

d) Alternatively, the DSB ends can undergo further long-range resection by either EXO1 or BLM/DNA2.
These longer ssDNA overhangs are first bound by RPA and can then be channeled into the.

e) **Single Strand Annealing (SSA)** pathway, which is mediated by the protein RAD52

f) Alternatively, the RPA-ssDNA can serve as a substrate for the RAD51 filament assembly, allowing the resulting DNA intermediates to be directed towards repair by

g) **Homologous Recombination (HR).**
For HR, both ssDNA & dsDNA templated homology repair (HDR) pathways are used.

https://pubmed.ncbi.nlm.nih.gov/33896583/

Traffic Light reporter assays for HR, NHEJ and MMEJ pathways

Workflow for compound screening

Cell seeding

Cells

1) GFP report cassette
2) GFP report cassette

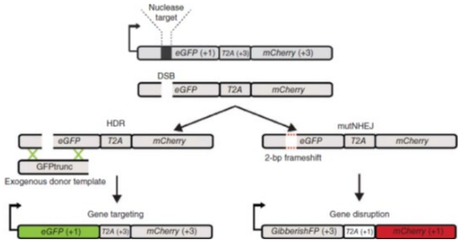
+ Cas9/sgRNA (Cre/lox)

Lentiviral particles

- Cells 1 > Cas9/sgRNA
- Cells 2 > Cre recombinase

Induction of DSBs and compound treatment

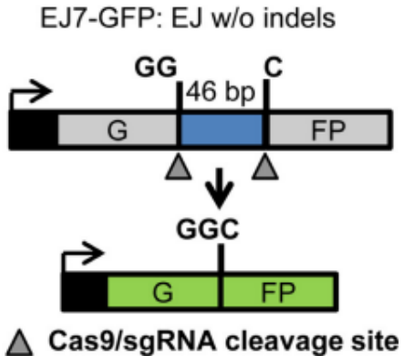
Homologous Recombination **(HR)**



A) Positive control inhibition

- ATMi (AZD1390)
- ATM-siRNA

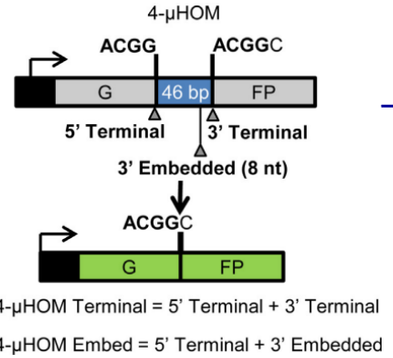
Non-homologous end joining **(NHEJ)**



B) Positive control inhibition

- DNAPKi (AZD7648)
- Ku70/80 siRNA

Micro-mediated end joining **(MMEJ)**



C) Positive control inhibition

- PolQi (ART812)
- FEN1 (published compounds/siRNA)

Quantification of GFP+ cells

Micro-mediated end joining **(MMEJ)**

Cytation
(Adherent cells)

Flow cytometry
(Suspension cells)

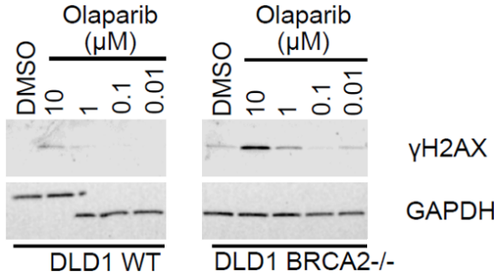
For the HR vector: HR, the full *eGFP* sequence will be reconstituted and cells will fluoresce green

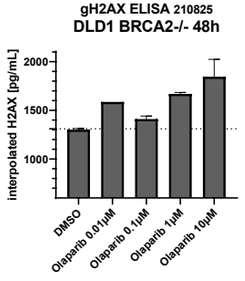
Reference: Bhargava et al., 2018. C-NHEJ without indels is robust and requires synergistic function of distinct XLF domains. Nature Communications. DOI: 10.1038/s41467-018-04867-5

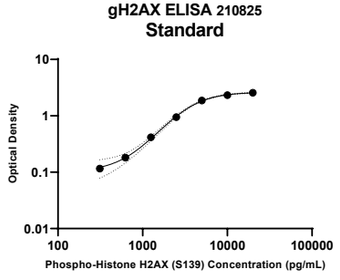
Cellular biomarkers of DNA Double Strand Break detection

Quantify γH2AX foci and Rad51 as a proxy for DSB induction using high-content imaging

- **Rationale**
  - Double-Strand breaks induce γH2AX foci formation
  - Phosphorylation on Serine 139 is mediated by the kinases ATM, ATR and DNA-PK and is an early cellular response to DSBs
- **Throughput**
  - 27 compounds in dose-response
  - Suitable for Tier1 assay
- **Possibility of multiplexing** (Up to 4 colours): with other biomarkers (ex Rad51 for HR) or with cell cycle marker (ex EdU, H3S10-P)
- Alternative technologies to be considered for *in vivo* studies:
  - Detection of γH2AX by Western Blot and ELISA

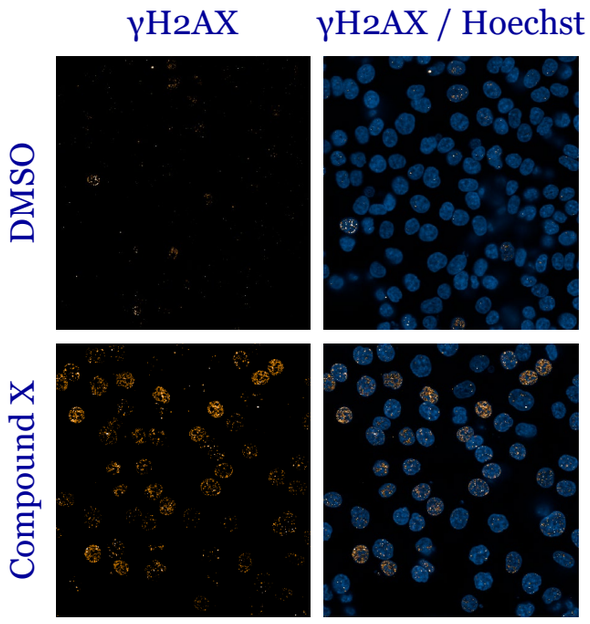


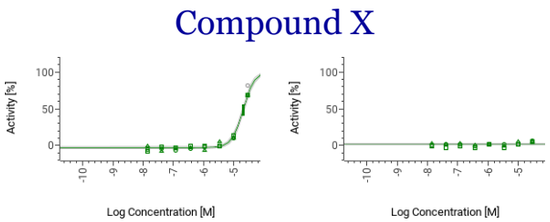




Case study:

screening in HCT116 using Operetta® technology





Activity expressed as % of γH2AX-positive cells – Etoposide used as 100% activity

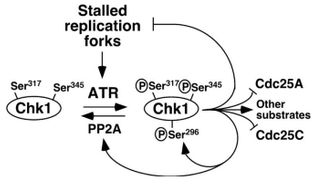
Readout	Cell line	pIC_{50}
% γH2Ax positive cells	HCT116	4.67
% γH2Ax positive cells	SW620	inactive

γH2AX detection also developed in SW480, RKO, DLD1, Kuramochi, U2OS and HT1299 cell lines

Cellular assays: *Phosphorylation events during DDR signaling*

Phosphorylation of Chk1 – AlphaLISA® SureFire® Ultra™ p-CHK1 (Ser345)

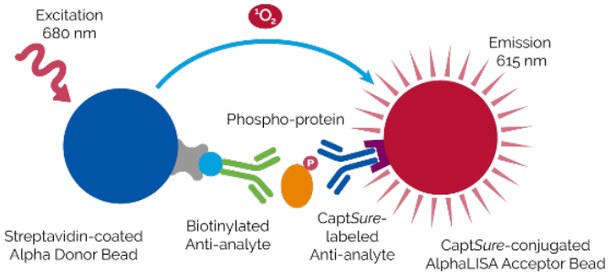
- **Rationale**
  - Direct monitoring of Chk1 phosphorylation
  - Indirect monitoring of Replication stress: Replication stress induces phosphorylation of checkpoint kinases Chk1 through ATR activation



- **Throughput**
  - 27 compounds in dose-response
  - Suitable for Tier1 assay
- **Additional targets for potential assay development using AlphaLISA**
  - p-ATM (S1981) for DSB signalling as alternative to γH2AX
  - p-Chk2
  - p-RAD50
  - p-KAP1

Assay principle

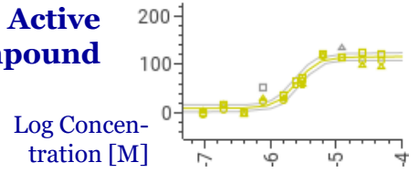
The AlphaLISA® SureFire® Ultra™ p-Chk1 (Ser345) assay is a sandwich immunoassay for quantitative detection of phospho-Chk1 (Ser345) in cellular lysates using Alpha Technology



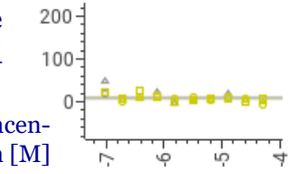
Case Study: Phosphorylation of Chk1after treatment (21h) in dose-response of inhibitor in Colo-320DM cells

% of activity compare to reference compound

Active Compound



Inactive Compound



Inhibition of protein X induces replication stress and subsequent phosphorylation of Chk1

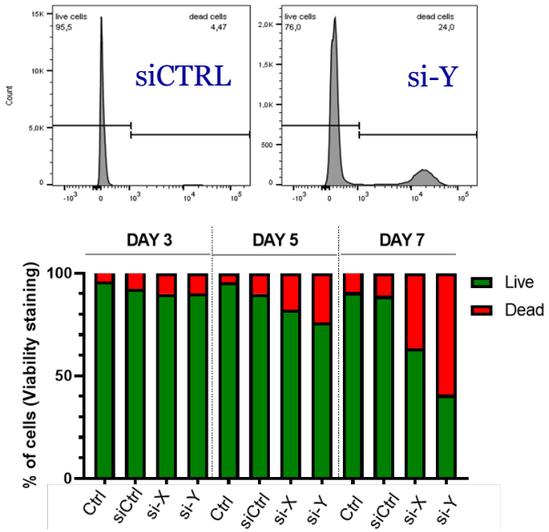
Cellular assays: *Flow cytometry*

Phosphorylation of Chk1 – AlphaLISA® SureFire® Ultra™ p-CHK1 (Ser345)

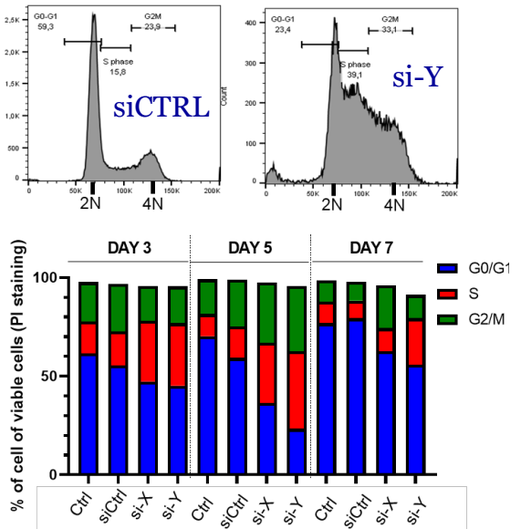
- **Rationale:** DNA damage induces cell cycle arrest and/or cell death
- **Assay principle:** Analysis of cell viability (Via far Red Fluorescent dye) and cell cycle (Propidium iodide)
- **FACS park**
  - BD FACS Canto II
  - BD Fortessa X20
  - Biorad ZE5
- **Throughput**
  - Not suitable for Tier1
  - More suitable for target validation or Tier2 or Tier3 assays
- Possibility of co-staining with cell cycle marker (ex. Edu, H3S10-P) and/or with DNA damage marker (ex. γH2AX, pKAP1[1])

Case study: Target validation FACS analysis of BT20 cells transfected with siRNA

Viability Analysis



Cell cycle Analysis



Depletion of the target induces cell death and accumulation in S phase

1 not yet developed

Cellular assays: *Replication stress markers*

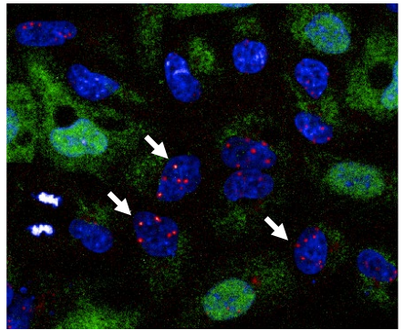
High content microscopy to count 53BP1 bodies and micronuclei

- **Rationale:** Replication stress increases chromosomal lesion transmitted to daughter cells, characterised by cells in G1 with 53BP1 bodies and micronuclei
- **Assay principle:** Quantification of 53BP1 bodies and micronuclei in G1-cells using high-content imaging
- **Throughput:** up to 27 compounds in dose-response
- **Assay to be adapted for the cell line of interest for optimal condition:**
  - Cell density
  - Kinetic of inhibitor exposure
  - DMSO tolerance
  - 96/384 well plate format
- **Multiplexing with Rad51 foci**
- **Nanopore to measure fork stalling in development**

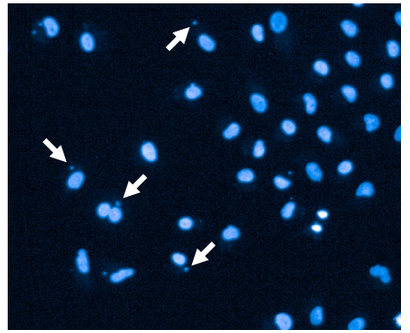
Operetta® technology

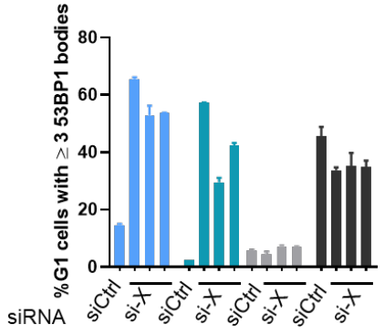
Case study: Target validation FACS analysis of BT20 cells transfected with siRNA

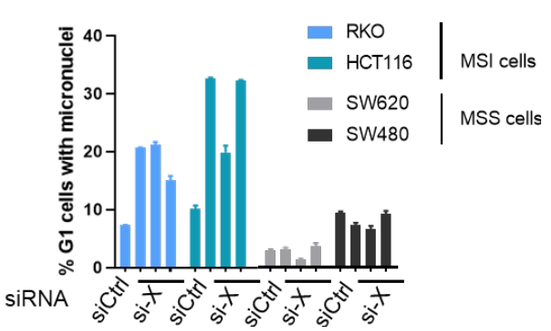
53BP1 bodies



Micro-nulei





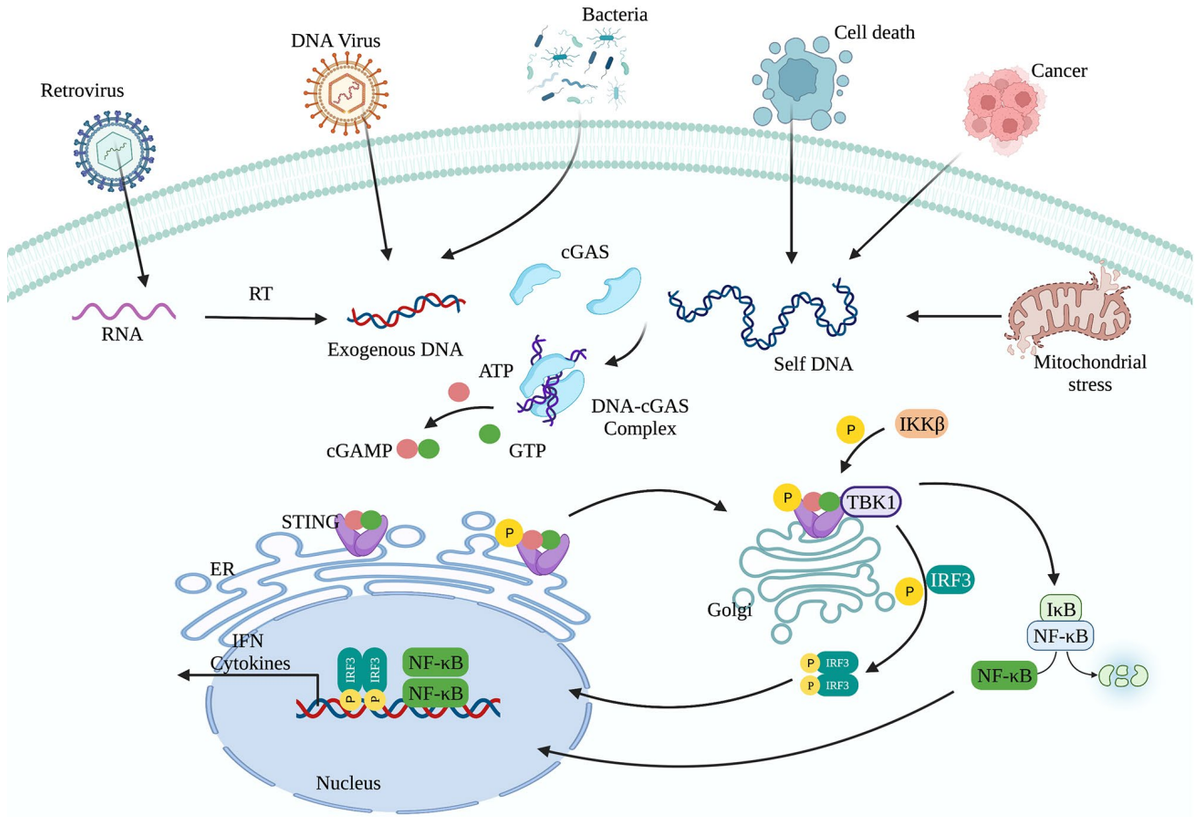


Down-regulation of X by siRNA increases 53BP1 bodies & micronuclei specifically in MSI cells

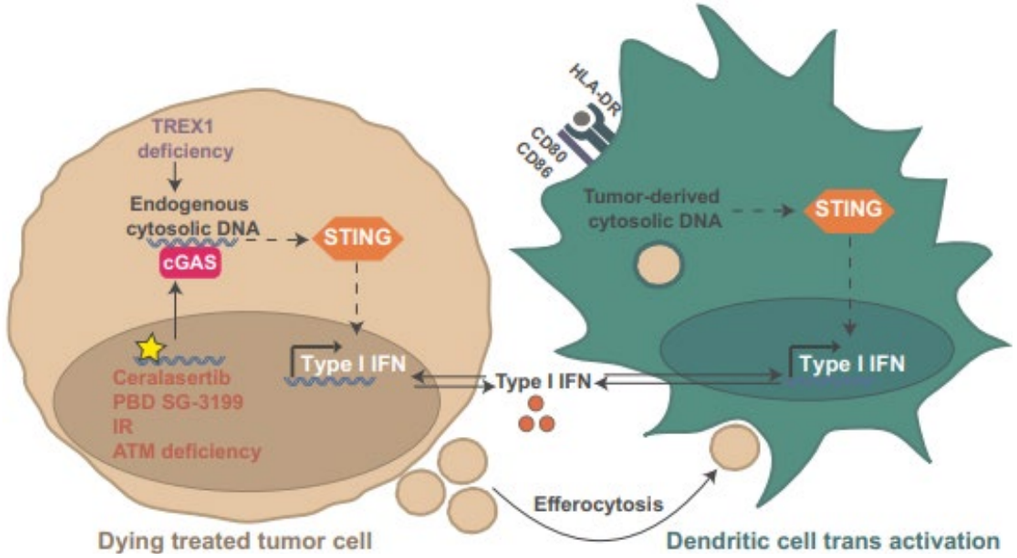
Contents

The cGAS / STING signals DNA damage to the IFN system

Micronuclei and PD biomarkers alerting the interferon system to DNA damage



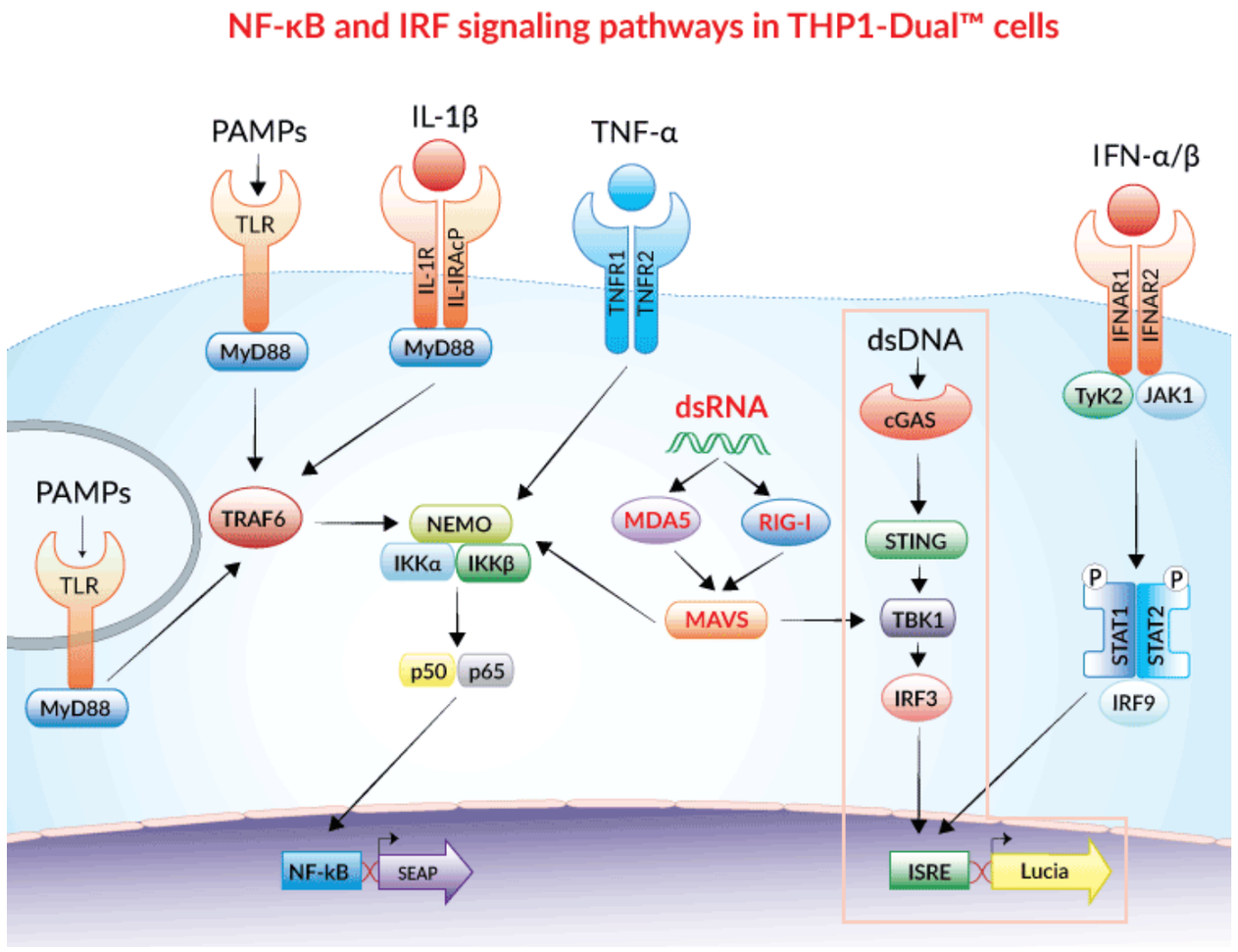
- Activation of the cGAS/STING pathway by viral or un-repaired damaged DNA exported from the nucleus initiates the expression of interferon stimulated genes (ISGs)
- Targeting the cGAS-STING signaling pathway is a strategy to boost IFN responses and pathway activation acts a PD biomarker to support IO:DDRi combination therapies



Wang et al., Frontiers in Immunology, 2022
Lopez-Pelaez et al Oncoimmunology 2022

Assays developed with THP1 dual™ cells (from Invivogen)

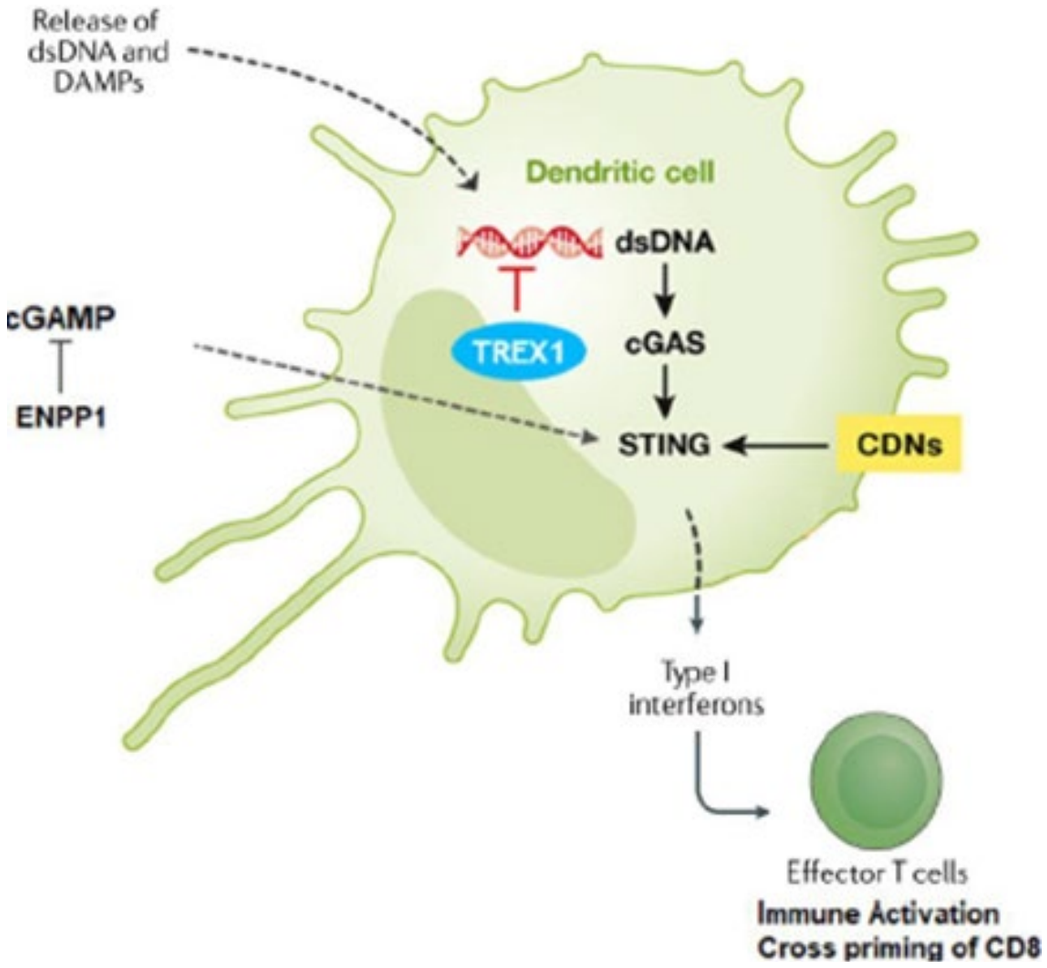
NF-κB-SEAP and IRF-Lucia luciferase Reporter Monocyte



- Cells:
  - **THP1-Dual™ cells:** Lucia luciferase reporter gene under the control of a interferon-stimulated gene minimal promoter
  - **THP1-Dual™ cells KO** for different molecules of the cGAS/STING pathway available: i.e. cGAS KO, TREX1 KO, STING KO, IRF3 KO, TBK1 KO
- 2 assays developed at Evotec:
  - Stimulation of the IFN pathway by transfection using VACV70, a viral oligonucleotide (48h)
  - Stimulation of the IFN pathway by cGAMP, a STING agonist, in presence of lyovec (24h)
- Read out:
  - Luminescence detection with QuantiLUC reagent (Luciferase substrate) – Pherastar
  - CellTiterFluor or for viability assay

cGAS / STING pathway activity

Assay on primary cells under development

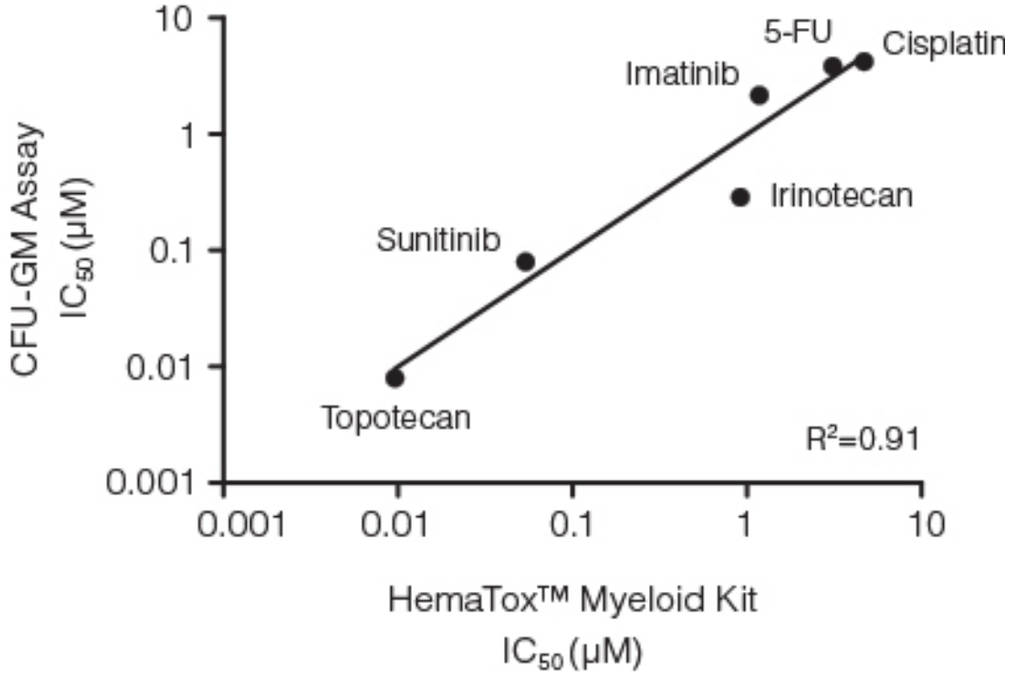


- **Background:** Stimulation of the the cGAS/STING IFN pathway by transfection using dsDNA, at a sub-optimal dose to evaluate compounds able to increase this response
- **Experimental settings:**
  - Primary cells: PBMC, macrophages or monocytes
  - Identify drug efficacy to activate immune myeloid cells
- **Outcome:** dose-dependent IFN response of primary immune cells
- **Read out under evaluation:**
  - Cytokines production: IFN-β, CXCL10, IFN-α, IL12, TNF-α, IL6, IL1β, IL18, IFN
  - mRNA analysis: ISG genes
  - Protein phosphorylation
    - cGAS / STING pathway: pSTING, pIRF3
    - IFN signaling: pSTAT1

Contents

HemaTox Assay

Description



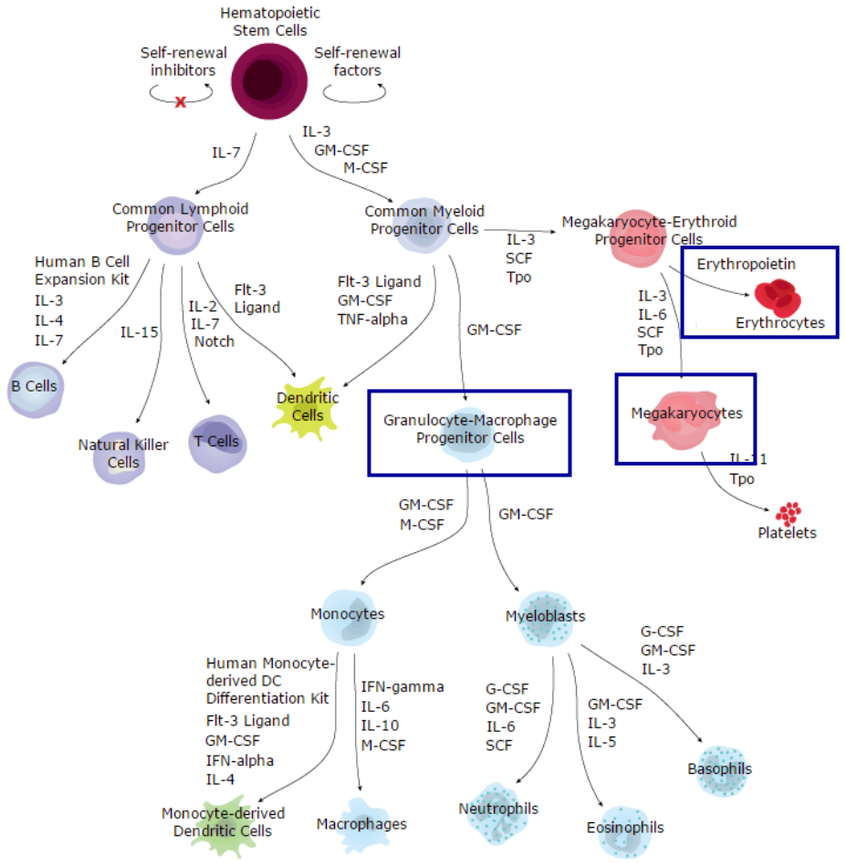
Correlation Between IC_{50} Values for Six Drugs Measured Using the CFU-GM Assay and the 96-Well Plate Liquid Culture-Based HemaTox™ Myeloid Kit (Stemcell Thechnologies)

- HemaTox™ kits have been developed for testing the effects of drugs on the growth and lineage-specific differentiation of human hematopoietic stem and progenitor cells (HSPCs). Each kit tests for the effect of drugs on the outgrowth of specific progenitor cell lineages, from $CD34^+$ cells isolated from cord blood (CB) or bone marrow (BM). The HemaTox™ Erythroid Kit, HemaTox™ Myeloid Kit and HemaTox™ Megakaryocyte Kit are designed to test erythroid, myeloid and megakaryocyte-specific toxicity, respectively.
- https://www.stemcell.com/products/brands/hematox-in-vitro-hematotoxicity-testing.html
- HemTox is implemented at Evotec in a 384-Well plate format

HemaTox Assay

Description

Hematopoietic Stem Cell Differentiation Pathways & Lineage-specific Markers



- Differentiation of different HSC progenitors
  - Erythroid kit (7 days)
    - CD71
    - GlyA
  - Megakaryocyte kit (10 days)
    - CD41
    - CD45
  - Myeloid kit (7 days)
    - CD15
    - CD13
- Quantify the proliferation and differentiation of human hematopoietic stem cells
- Quantification of absolute cell numbers by flow cytometry
- High throughput capacity (384-well format)
- Including the senescence marker p21

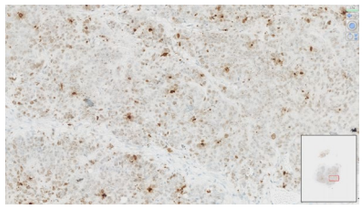
Contents

Subcutaneous BRCA2 deficient/proficient DLD1 xenograft model

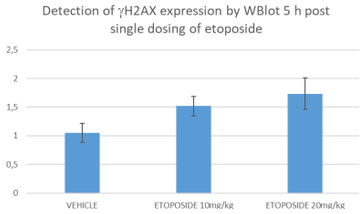
PK/PD studies of inhibitor as single agent

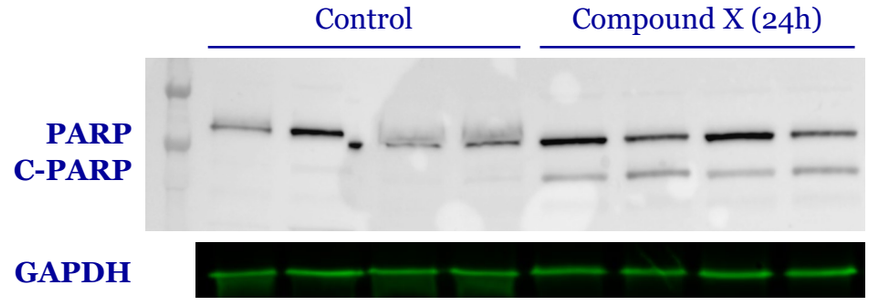
- **Objective:**
  - Assess the concentration of inhibitor after a single oral administration in blood, tumour and a surrogate tissue (e.g. Spleen)
  - Assess PD markers modulation in tumors
- **Study design:** Female Nude mice s.c. injected with DLD1 BRCA2 deficient or proficient cells

s.c. injection of DLD1-BRCA2$^{-/-}$ or$^{+/+}$ cells



γH2AX foci in DLD1 BRCA2$^{-/-}$ tumor





→ Sample collection → Sample collection

End point

- Blood collection
  - Compound concentration (Bioanalysis)
- Tumour sampling
  - Compound concentration (Bioanalysis)
- Spleen
  - Compound concentration (Bioanalysis)

PD markers

- γH2AX expression by ELISA or WBlot and IHC
- C-PARP by WBlot
- C-Casp3 by Wblot
- Potential for pRAD50, pKAP1, pRPA

1 Sampling times will be confirmed after PK study in mice

In vivo evaluation for DDR drug discovery

Mechanism of action, PK/PD relationship, tolerability and efficacy in tumour models

Compounds with **suitable *in vivo* PK properties** and bespoke formulation dosed (oral gavage/I.V)

- PK/PD assessment in e.g. BRCA2$^{-/-\text{ or }+/+}$ DLDL1 xenograft model
- DDR agent administered as single agent

- Evaluate **tolerability** after repeated dosing in non-tumour bearing mice to select tolerated dose and schedules
  - Sample organs and blood

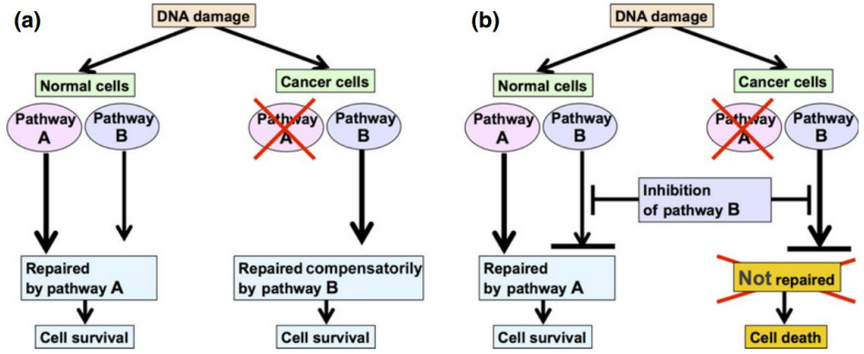
- Assess **antitumor efficacy and therapeutic window of selected cpds** in tumor-bearing mice
  - Sample tumors and blood at end of study to measure PD markers, blood cell count and compound concentration
  - mouse models:
    - Xenograft DLD1
    - Syngeneic B16 (melanoma) and MCA205 (fibrosarcoma)
  - Inhibitors as singe agent in DLD1 model and in combination with ICT in B16 model

Contents

Synthetic lethal CRISPR screening and analysis

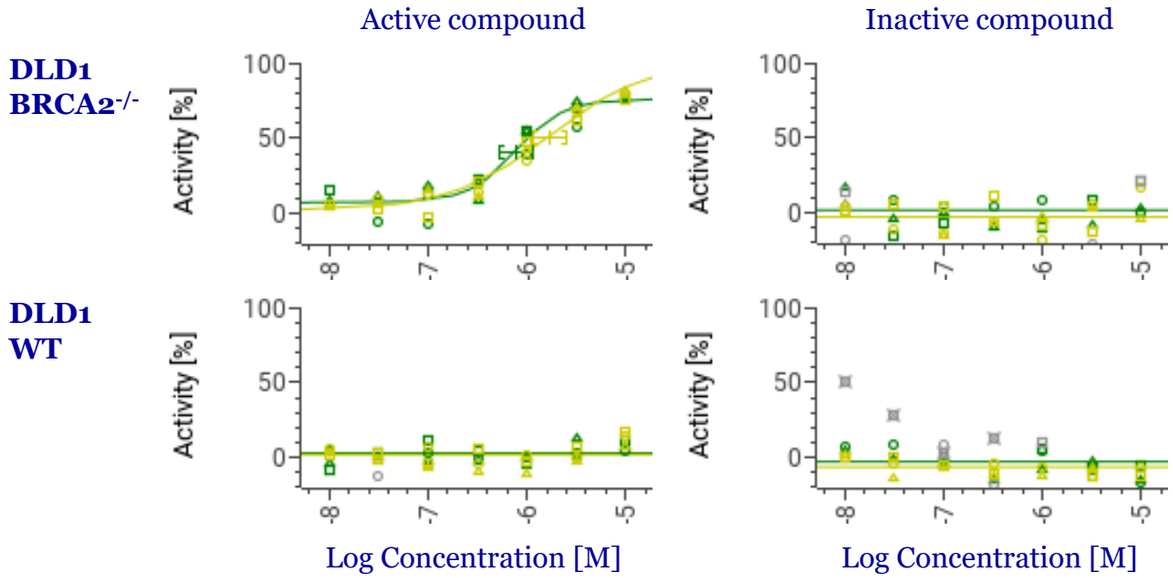
Targeting DNA repair pathway in DNA repair deficient background

- **Rationale:** DNA damage are detected and repaired by different specific and redundant pathways. (a) Inactivation of one pathway (pathway A) will be compensated by a second pathway B. (b) Targeting DNA repair in cancer cells with mutation in DNA repair pathway to induce synthetic lethality.



- **Assay principle:** Quantify of cell survival in different cellular background (ex. homologous recombination inactive (Brca2$^{-/-}$), NHEJ inactive (XRCC4$^{-/-}$))
- **Read out of viability:** Cell titre Glo® or Incucyte®
- **Throughput**
  - 27 compounds in dose response
  - Suitable for Tier1 assay

Case study: Monitoring synthetic lethality of HR deficient cell line (pathway A) with compound targeting pathway B. Measurement of cell viability by CTG after 6-days of exposure to compound, % of activity normalized to staurosporine induced cell death.



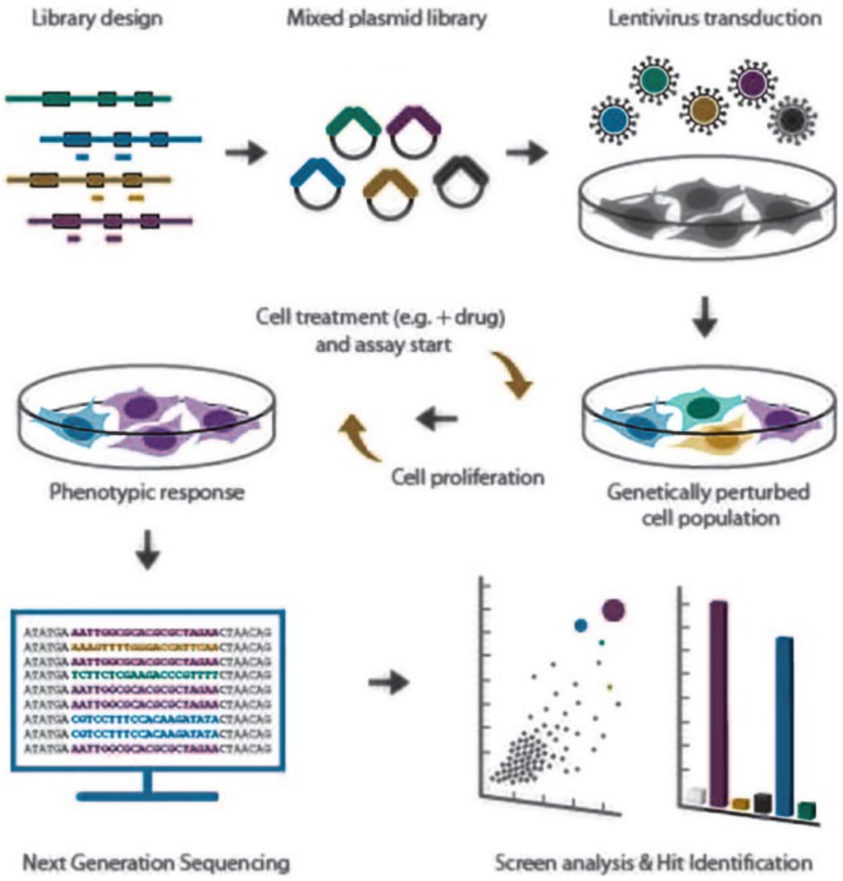
Active compound induces cell death in a dose response manner in HR deficient cell line (DLD1 BRCA2$^{-/-}$) but not in isogenic HR proficient cell line (DLD1 wt)

Hosoya and Miyagawa Cancer Science 2014

Pooled CRISPR screening @ Evotec

A versatile tool to support Target ID, Target deconvolution, Target deep scanning and else

Overview on pooled screening workflow



Pooled Screening enabled at Evotec:

- Experienced genetic screening team to run pooled screens in different biological settings and contexts
  - Expert project oversight
  - Lentivirus infection and cell pool handling
    - In-house lentivirus generation currently being established
  - Phenotypic screening
    - Positive and negative selection
    - FACS sorting (sorter in-house)
    - Cell line engineering team to construct reporter lines
- Bioinformatics team to support library design and screen analysis
- Molecular biology platform:
  - Plasmid library cloning
  - NGS library generation
  - NGS platform for in-house rapid data generation (NovaSeq6000)

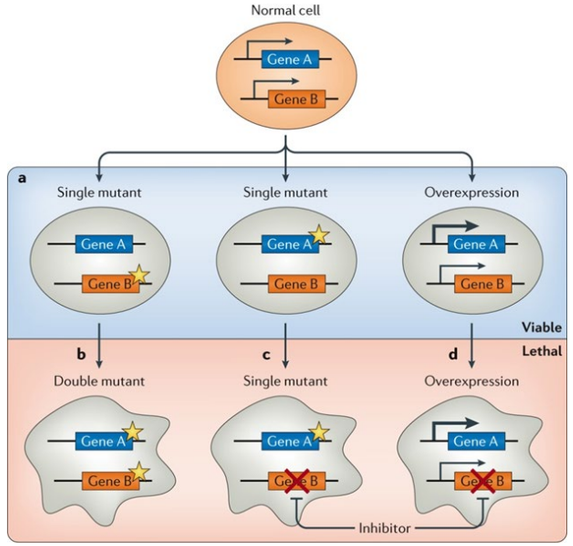
Adapted from CRISPR: A Screener's Guide; le Sage et al. SLAS Discovery 2019

Whole genome wide pooled CRISPR screening for novel target ID

Case Study: Identification of novel synthetic lethality interactions

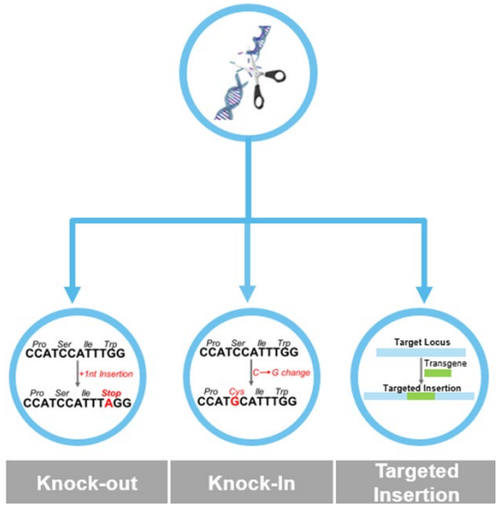
Synthetic lethality for novel cancer target discovery

- Exploiting synthetic lethality to target non-druggable mutations and events in cancer
- Increasing the target space for cancer drug discovery



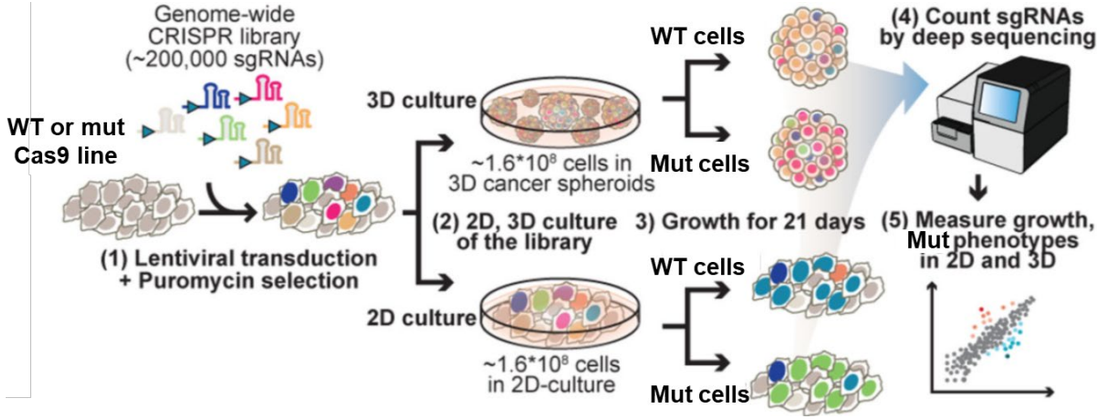
Engineering of relevant cell models for target discovery

- Engineer disease relevant mutants in the same cell background
- Usage of isogenic pairs for screening control to screen across cell lines



Whole genome screening: Combined 2D and 3D efforts

- Pooled whole genome CRISPR drop out screening as established high throughput screening approach for synthetic lethality
- Option to screen in 3D and combine 2D and 3D assessment to maximize value for target identification

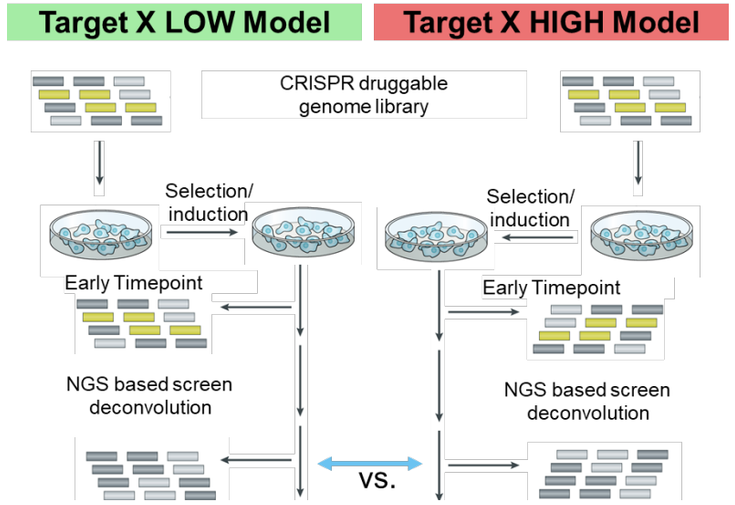


Adapted from O`Neil et al., Nature Genetics, June 2017
Adapted from Han et al. Nature April 2020

Newly identified targets validated across *in vitro* models

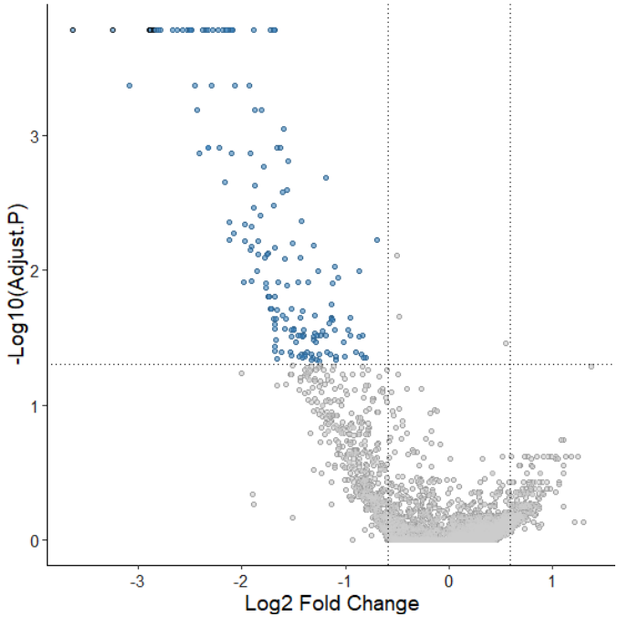
Case Study: Identification of novel synthetic lethality interactions

Synthetic lethality screening



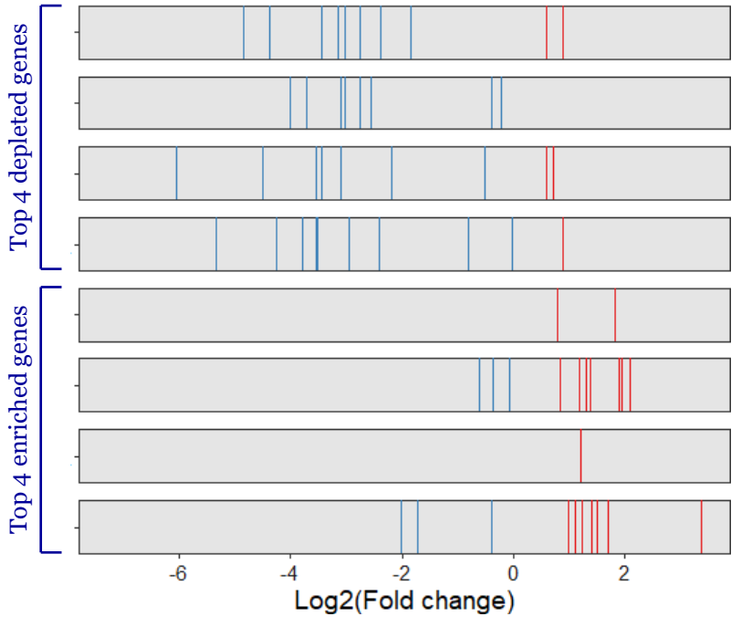
- Bioinformatic mapping of NGS reads and data analysis
- Comparison of genes dropping out between HIGH and LOW models
- Hit identification with high statistical power

Hits from the primary screen



- Volcano plot displaying the $\log_2$ Fold Change and adj. *P* value for all genes identified in the screen

sgRNA performance analysis



- Bioinformatic analysis of the top targets
- Visualization of the rank of sgRNAs targeting top selected genes

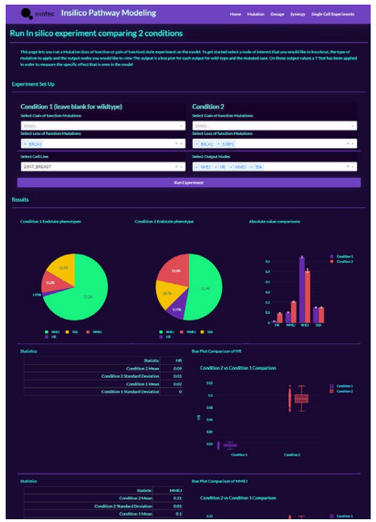
Adapted from O`Neil et al., Nature Genetics, June 2017
Adapted from Han et al. Nature April 2020

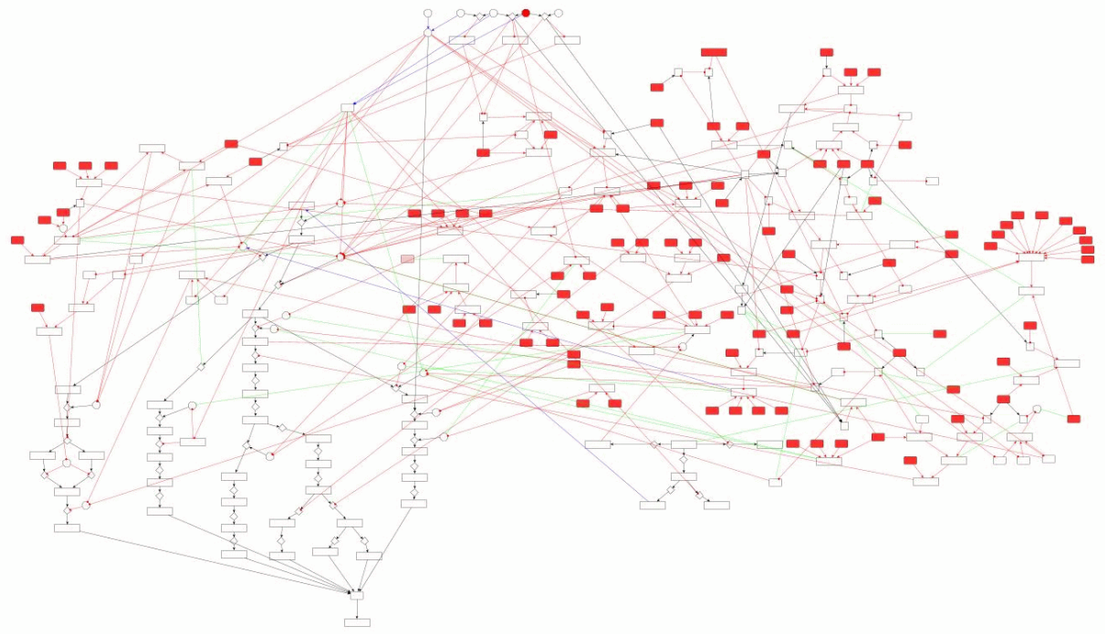
Causal AI for unraveling the complexity of DDR regulation

- **AI / ML in modeling of DDR regulation mechanisms**
  - *Causal AI* (automated reasoning, explainability, using existing knowledge, concepts, distilling causations from correlations)
- **Methodology of accelerated semi-automated causal model building**
  - based on BioFuzzNet open-source algorithm from IBM Research
  - model trained on facts (causal statements, “A causes B”) and data (e.g. DDRcs CRISPR data portal)
  - validated on preexisting open-source models
  - use of the Evotec internal knowledge base, Large Language Models for accelerating biocurator work

In silico DDR pathway model simulation app

- designed to be used by non-experts as a simple web app
- Relevant for a large family of DDR-related drugs
- Done in close collaboration with Evotec IVB DDR experts

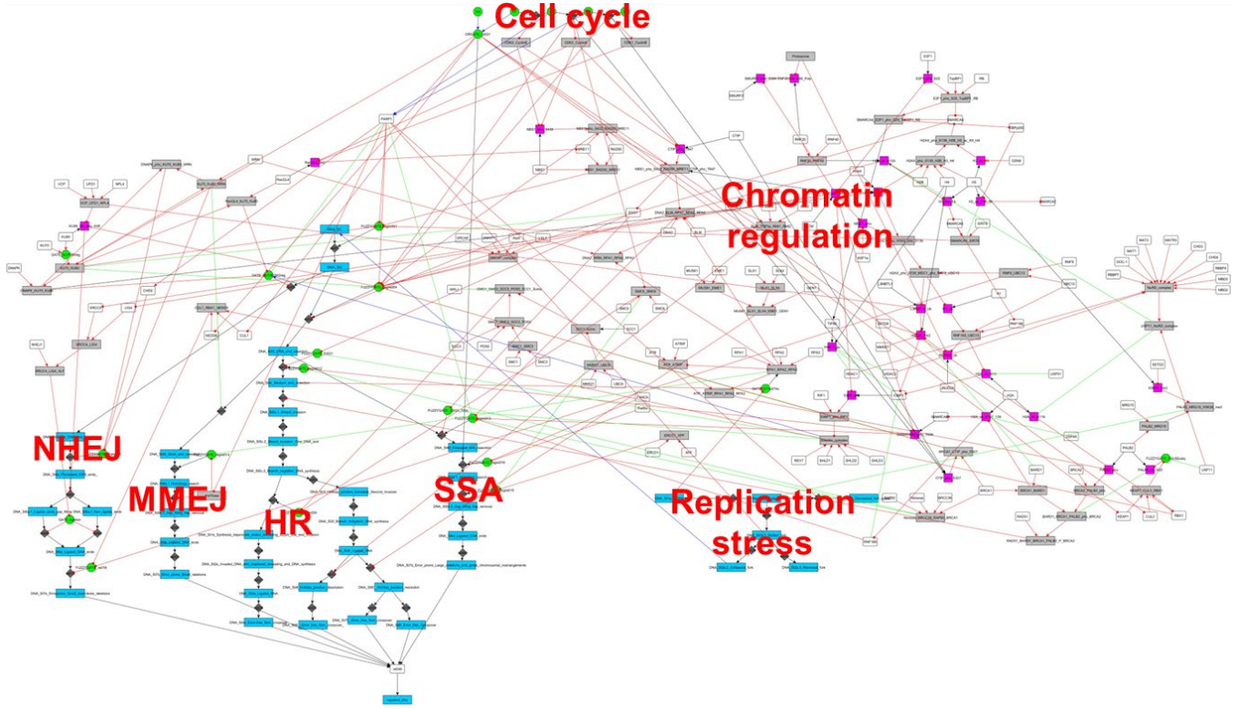




In silico mechanistic & executable models of DDR regulation

Our DDR model represents the mechanism of activating DSB-repair/response pathways (NHEJ, MMEJ, HR, SSA) following the induction of DSBs

Learning from the role of PARP1 trapping on DNA, with its implication in replication stress and single-stranded break repair



Powering drug discovery

By aggregating available knowledge and small/large-scale, public/internal datasets in a predictive model, our Model

- Rationalizes experimental design, suggesting perturbations, biomarkers and readouts
- Supports target selection and triaging
- Suggests selecting combination of targets (synthetic lethality)
- Takes into account off-target effects
- Evaluates hypotheses of target MoA

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