Next Generation Precision Cytotoxic Therapy

Molecular Precision × **M**echanistic Insight

Building on the momentum of Modifi Bio's success

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KL-50

- CNS penetrant
- Orally-bioavailable
- O^6-methylguanine DNA methyl transferase (MGMT) repair pathway selective DNA damaging agent

Reuters

World Business Markets Sustainability Legal Commentary Technology

Merck buys cancer therapy developer Modifi Biosciences for up to $1.3 bln

By Reuters

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BIOTECH

Merck sets sights on brain cancer with $30M Modifi acquisition

By Darren Incorvaia · Oct 23, 2024 7:05am

Engineer precision DNA lesions in DNA damage response deficient cancer
Circumvent Inhibition of Repair Proteins and Undruggable Oncogenes

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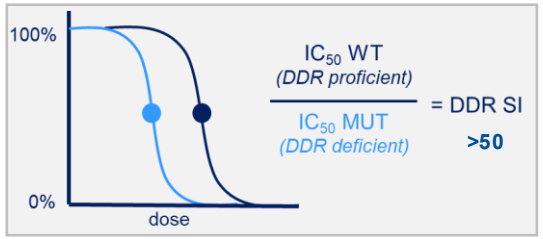
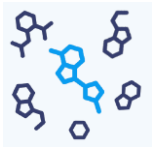
1° and 2° screens **Hit-to-lead** **Lead opt.**



Med. Chem Optimization
Oral bioavailability
CNS-penetration

DC

Efficacy
Safety
CDX PDX

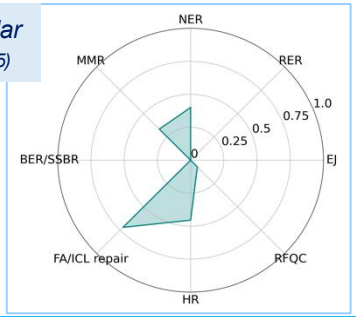


DNA lesion-inducing agent *library*

CRISPR-DDR MOA screen #

- Targeting key nodes within selected DNA repair pathways to establish a screening **platform** for pathway dependency
- Pulsing with **DNA lesion-inducing agents**
- Identifying precise DNA repair pathway dependency of individual lesion-inducing agent

Pathway Hit Proportion radar
0.5 µM Cisplatin (FDR < 0.05)



Identify precise DNA lesions to exploit DNA repair pathway dependencies in cancer

DDR: DNA damage response; TI: Therapeutics index; SI: Selectivity index; *# NAR Cancer 2026, 8, zcaf052*

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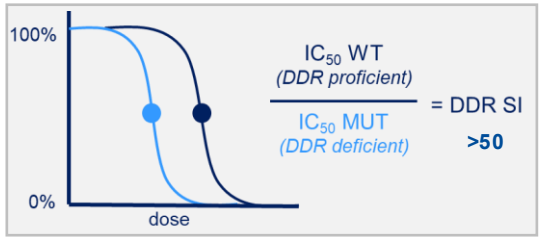

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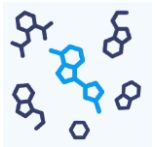

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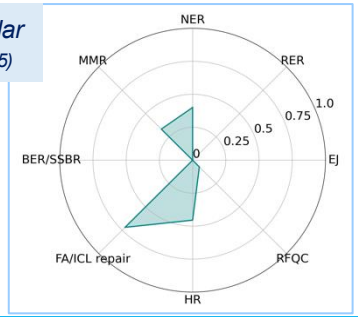
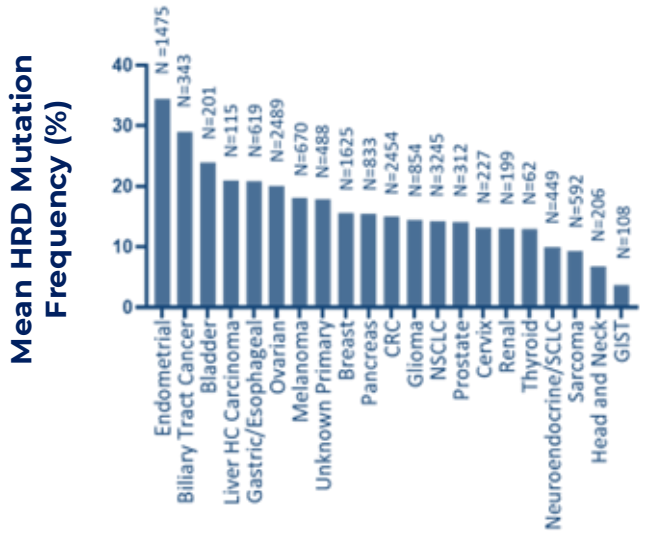


Identify precise DNA lesions to exploit DNA repair pathway dependencies in cancer

Pathway-specific program	Development Stage
Homologous recombination (HR)	Lead identified
Nucleotide excision repair (NER)	Hit identified
Mismatch repair (MMR)	Library under development



Data from Heeke et al, JCO Precision Oncology, Sep 2018

DDR: DNA damage response; TI: Therapeutics index; SI: Selectivity index; *# NAR Cancer 2026, 8, zcaf052*

* reference: Nat. Commun, 2017, 857

Developing precision DNA damaging agents for HRD cancers
Integrate two clinically-validated mechanisms

PARPis provide clinical POC

- Poly(ADP)-ribose polymerase (PARP) trapping validates therapeutic strategy
- Clinical biomarkers for HRD patient stratification well-developed
- *Limited efficacy - **50% of patients do not respond***
- ***~70% of patients** will develop PARPi resistance while retaining HRD status*
- *HRD market very large (PARPi market projected to reach >13B/y by 2031)*

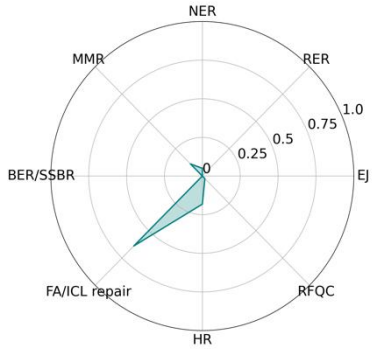
M2 lead asset: JH-708
Efficacious & Selective

Strict reliance on the HR – Fanconi Anemia repair pathway

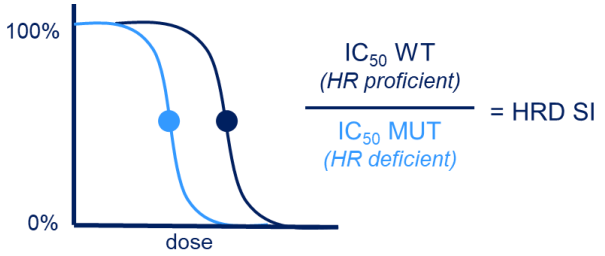
Enhanced Selectivity Index (SI)

- Forms DNA interstrand crosslinks *in cellulo*
- Enhanced Therapeutic Index (TI) and Selectivity Index (SI)
- Improved efficacy, duration, and tolerability
- High CNS penetration

0.5 µM JH-708



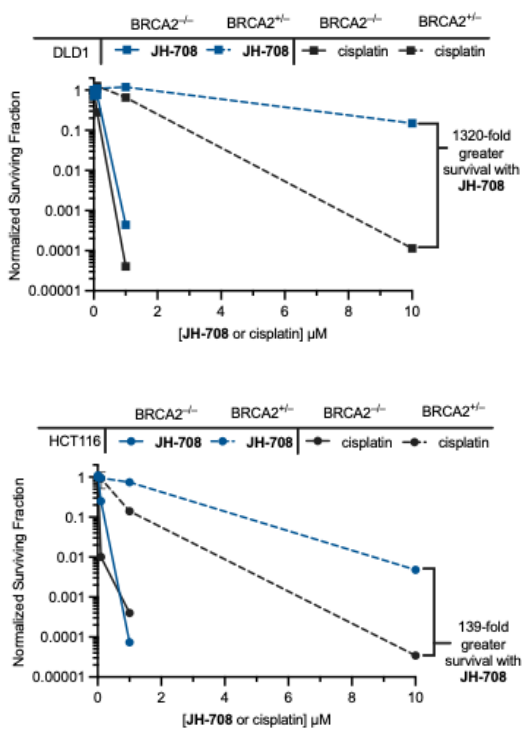
	olaparib	JH-708
HRD SI *	42	71

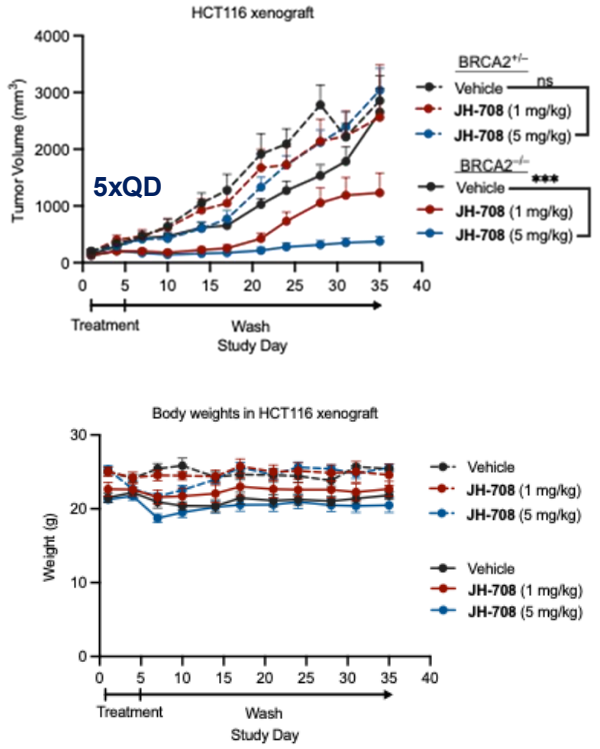


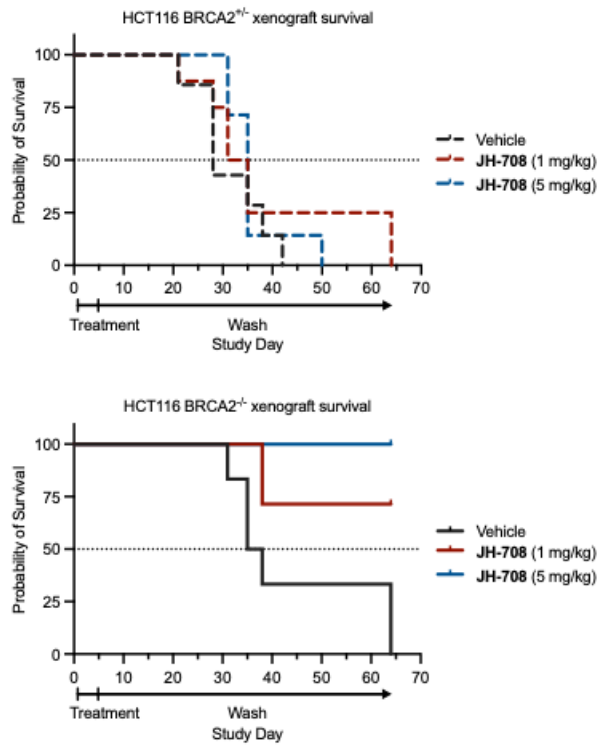
Tested in *:DLD1 cell line

JH-708: Potential best-in-class HRD-selective DNA damaging agent

*Selectively eradicates BRCA2-deficient cancer cells **in vitro***	*Selectively eradicates BRCA2-deficient tumors **in vivo***	*Extends survival in BRCA2-deficient tumor-bearing mice*







*Upcoming **in vivo** efficacy readouts :*	Establish chronic max. tolerated dose; Optimal dosing schedule (Oral/IP); Intracranial CDX study.

Full datasets available upon request

Data presented as mean ± SEM.

Clinical trial design

Tumor genotype (BRCA1/2, ATM, PALB2, RAD51C/D) readily-determined by NGS

Program A:

CNS tumors

Early line TNBC and Hormone Receptor (HR)+ breast cancer with brain metastases

Homologous recombination deficiency-like glioblastoma (GBM)

- 45% of patients with HRD TBNC will develop brain mets
- 10% of patients with HR+/HER2- will develop brain mets, 70% of breast cancer are HR+/HER2-
- HRD-like GBM – identified by Isocitrate Dehydrogenase (IDH) mutations; 5-10% of GBM

Program B:

Non-CNS tumors
- Platinum-resistant ovarian and PDAC

Phase IA, dose escalation

- Basket trial, advanced ovarian cancer and PDAC molecularly enriched for HRD (BRCA1/2, ATM, PALB2, RAD51C/D).

Phase IB, expansion

- High grade serous HRD OC stratified by PARPi exposure (naïve and treated)
- PDAC

  *44% of PDAC has HRD mutations**

reference: # NPJ Breast Cancer 2022, 46; * J. Clin. Oncol., 2021 2617

Superior HRD selectivity over competitors under clinical development

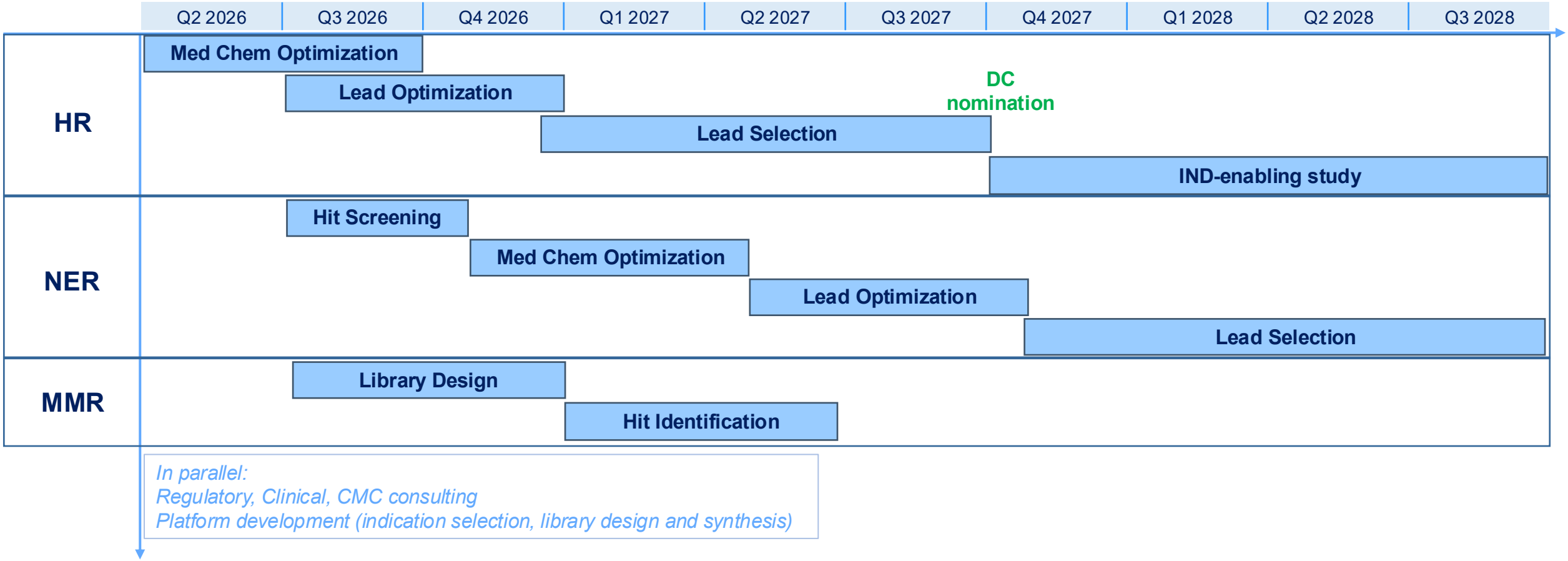
Compound	Company / status	Indication	HRD (BRCA2) selectivity	brain-to-plasma ratio (K_p)	MOA
LP-184 *	Lantern Pharma Phase 1a enrollment completed 3 FDA Fast Tract Designation	Refractory and relapsed solid tumors, last line, DDR status determined after enrollment	2	0.11	DNA mono-alkylating agent
CX-5461 #	Senhwa Biosciences Phase 1b expansion 3 FDA Fast Tract Designation	HRD pancreatic, prostate, breast, or ovarian cancer	9	0.10	DNA G-quadruplex stabilizer
JH-708 *	**Preclinical**	**HRD TNBC brain mets, ovarian, and pancreatic cancer**	**71**	**0.46**	**Interstrand crosslink**

JH-708 IP position: Provisional applications were filed by Yale University in November 2025

References: Kulkarni et al. *Cancer Res. Commun.* **2024**, 1199; Lal et al. *Clin. Cancer Res.* **2023**, 4209. *Nat. Commun.* **2022**, 3607

Tested in *:DLD1 cell line; # HCT116 cell line

M2 roadmap



Applying for SBIR

Raise seed round

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