BREAKSIGHT, INC. — MONTHLY GENOME INTEGRITY BRIEF

THE BREAK REPORT

SEPTEMBER 2026
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LEAD — SYNTHETIC LETHALITY

Replication stress-paired mechanisms reach the clinic

The Phase I MYTHIC study has read out a second, chemotherapy-free pairing: PKMYT1 inhibitor lunresertib with WEE1 inhibitor zedoresertib, in tumors selected for *CCNE1* amplification or *FBXW7* and *PPP2R1A* alterations. Response rates reached 50% in platinum-resistant ovarian cancer at the initial recommended phase 2 dose, and the pairing garnered FDA fast track status in that setting days later.[1] Two checkpoint kinases in the absence of a cytotoxic backbone exemplifies synthetic lethality built on replication stress rather than a repair defect. The mechanism follows a sequence of well-defined events: replication forks stall, repair is triggered, forks that cannot recover collapse into breaks, and accumulating breaks lead to cell death.[2]

THE SELECTION PROBLEM

These regimens act on **where and how much the genome breaks** — yet selection still leans on mutation panels drawn from the ~1.5% of the genome that codes for protein.[3]

IN BRIEF

Fragmentomics closes the MRD gap

Fragment length profiles of cfDNA separated into ~10 bp periodic components distinguished tumor-associated shifts from nucleosomal origin.[4] On tumor-informed panels, fragment features enhanced early detection in combination with clinical risk factors.

Repeats in disease

Over 60 disorders are tied to repeat-tract length, with dispersion across both non-coding and coding regions, and nearly all invisible to short-read panels.[5] Long-read runs return length, interruptions and methylation together — confirmatory work turning into discovery.

AI meets the resolution limit

A 1 Mb-context model predicts functional tracks at base resolution, matching or beating prior models in 25 of 26 variant-effect tests.[6] The limit for DNA damage predicted outcomes now is not the model but the break data available to train it.

THE LANDSCAPE

Replication-stress and repair targets in clinical development — one representative agent per category. Selection biomarkers remain genotype-based, drawn from protein-coding sequence.

TARGET	REPRESENTATIVE AGENT	SELECTION BIOMARKER IN TRIALS	STAGE
PARP1/2	Olaparib	*BRCA1/2*, HRD score	Approved
ATR	Camonsertib	*ATM*, *SETD2* and other DDR loss	Phase I/II
PARP1-selective	Saruparib	*BRCA1/2*, *PALB2*, *RAD51C/D*	Phase III
WEE1	Zedoresertib	*CCNE1* amp, *FBXW7*/ *PPP2R1A* loss	Phase I
PKMYT1	Lunresertib	*CCNE1* amplification, *FBXW7* loss	Phase I/II
Polθ	ART4215	HR deficiency	Phase I
USP1	KSQ-4279	*BRCA*-mutant, PARP-resistant	Phase I

DAMAGE & AGING

Fault lines of an aging genome

Unrepaired damage is now argued to sit at the centre of aging.[7] Mutation signatures record repair long past; active DNA break distributions in young versus aged tissue can localize where vulnerabilities accrue.

98% of the genome lies outside the coding exons where nearly every current DNA biomarker sits.[3]

WHAT WE'RE READING

Three papers we hand to anyone new to break mapping — none recent, but lays the ground-work for the themes we explore here

METHOD

BrITL-Seq

Selective capture and genome-wide mapping of DNA double-strand breaks — pinpoints *where* a genome breaks, not just *how much*.

Shastri et al., *Mol Cell* 2018;72:222–238

BIOMARKER ORIGINS

cfDNA nucleosome footprints

Where analysis of fragmentation patterns begins: cfDNA in the plasma recapitulates nucleosome positions, allowing fragment mapping and profiling to carry data on the tissue of origin.

Snyder et al., *Cell* 2016;164:57–68

NON-CODING STRUCTURE

G-quadruplexes in chromatin

G4 structures map to regulatory, nucleosome-depleted chromatin — structurally distinct, associated with highly transcribed genes, and prone to breakage under replication stress.

Hänsel-Hertsch et al., *Nat Genet* 2016;48:1267–1272

FROM BREAKSIGHT

Mapping where the genome breaks

BreakSight's mission is to enable discovery of novel DNA biomarkers of therapeutic response by tagging and localizing double-strand breaks from drug treatment across coding and non-coding sequence alike.

DDSITE

Capture and sequencing of break sites genome-wide, post-treatment or in a repair-deficient model.

DDINSIGHT

Reproducible break-site calling, treatment comparison, motif analysis and repeat enrichment at called sites.

WHERE THIS POINTS

Paired DDR inhibitors, fragmentomic MRD and repeat-resolved diagnostics all read the genome indirectly. Treatment-specific break landscapes add resolved data on acute genome-wide dynamics.

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TERMS USED IN THIS ISSUE

SYNTHETIC LETHALITY

Two defects each survivable alone, but together, are lethal — the basis of PARP inhibition in *BRCA* tumors.

REPLICATION STRESS

Replication forks that slow or stall during S-phase of the cell cycle; if left unresolved, they collapse into breaks.[2]

FRAGMENTOMICS

Reading cell-free DNA by fragment length and nucleosome footprint, not by sequence variants.[9]

MRD

Minimal residual disease — the presence of tumor cells below imaging detection, often tracked in plasma.

NEXT ISSUE · OCTOBER 2026 — Polθ and USP1: the next synthetic-lethal wave, and where resistance sits outside the exome.

SOURCES

1. Yap et al., MYTHIC Phase I, lunresertib + zedoresertib, AACR 2026, abstract CT022; Debiopharm fast-track announcement, 20 Apr 2026. **2.** Zeman & Cimprich, *Nat Cell Biol* 2014;16:2–9. **3.** Int. Human Genome Sequencing Consortium, *Nature* 2001;409:860–921; ENCODE Project Consortium, *Nature* 2012;489:57–74. **4.** Zhou et al., *Nat Commun* 2026;17:6226; Mathios et al., *Nat Commun* 2021;12:5060. **5.** Liu & Li, *Brief Bioinform* 2026;27:bbag031; Depienne & Mandel, *Am J Hum Genet* 2021;108:764–785. **6.** Avsec et al., *Nature* 2026;649(8099):1206–1218. **7.** Schumacher et al., *Nature* 2021;592:695–703. **8.** Shastri et al., *Mol Cell* 2018;72:222–238. **9.** Snyder et al., *Cell* 2016;164:57–68. **10.** Hänsel-Hertsch et al., *Nat Genet* 2016;48:1267–1272.