Targeting ZNF827
for synthetic lethality in cancer

CHILDREN'S MEDICAL RESEARCH INSTITUTE
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The Problem

Cancer remains a leading cause of mortality worldwide with 17 million new cases and 9.6 million deaths globally in 2018.

Genome instability is a hallmark of cancer cells and a mechanism of carcinogenesis. A major source of genome instability arises from defective DNA damage response (DDR) and DNA repair pathways. Mutations in these repair pathways limit DNA repair capacity and give rise to cancer predisposition. Inhibition of DDR and repair pathways can be further exploited by causing excessive genomic instability that is ultimately catastrophic to some cancer cells. For this reason, DNA repair pathways have attracted a lot of interest as targets for novel and specific cancer treatments, both independently and in the context of synthetic lethality, whereby simultaneous perturbations of two genes result in cell death.

The success of synthetic lethality-based anticancer therapeutics is highlighted by the recent registration of poly (ADP-ribose) polymerase (PARP) inhibitors to treat homologous recombination (HR) deficient breast and ovarian cancers with BRCA1/2 mutations.

DNA double strand breaks (DSBs) represent the most catastrophic form of DNA lesions. The two major mechanisms of DSB repair are HR and non-homologous end joining (NHEJ) **(Figure 1)**. HR is the most error-free and reliable repair pathway but relies on the generation of single-stranded DNA (ssDNA). ssDNA is unstable and prone to chemical and nucleolytic attack. Protection of ssDNA and its correct triage into the appropriate DNA repair pathway is important for the maintenance of genome stability.

The Solution

ZNF827 is a largely uncharacterised protein which has been implicated in DNA repair through its interaction with telomeres (caps on the ends of chromosomes). CMRI scientists have recently shown that ZNF827 plays an important role in the DNA damage response. It binds directly to ssDNA and interacts with two key molecules in DNA repair, replication protein A (RPA) and topoisomerase 2-binding protein 1 (TOPBP1).

CMRI data shows that ZNF827 depletion reduces cell proliferation and induces apoptosis (death) of cancer cells. Importantly, our data also indicates that ZNF827 depletion in conjunction with treatment with an anti-cancer DNA damage-inducing agent (topotecan) can produce a synergistic effect **(Figure 2)**.

In summary, CMRI has discovered: 1) a new target for inhibiting growth and viability of cancer cells and 2) a method of sensitizing cancer cells to therapy with anti-cancer agents – synthetic lethality.

We anticipate that ZNF827 inhibition will induce synthetic lethality with other DNA damage causing agents (e.g. topoisomerase or PARP inhibitors), especially when cancers engage the HR pathway of DNA damage repair.

Seeking an industry partner for sponsored R & D and/or licensing arrangements, for the commercialisation of a ZNF827-specific inhibitor.

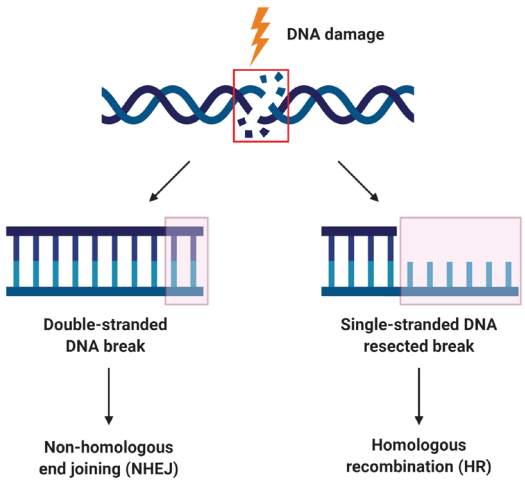

Figure 1: DNA damage repair pathways.

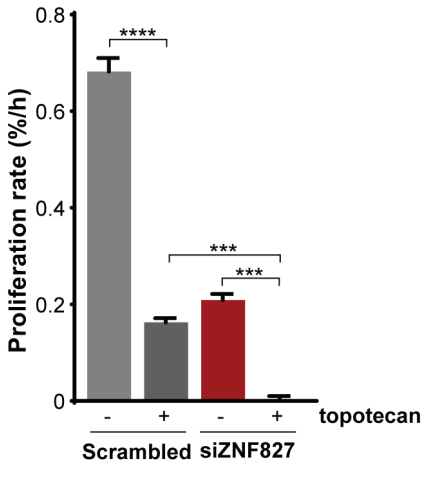

Figure 2: Live cell imaging experiment showing a marked reduction in cancer cell proliferation with ZNF827 depletion alone (single agent efficacy), as well as synthetic lethality with topotecan treatment (synergistic efficacy).

Our Strategy

Further biological characterisation of this novel zinc finger protein is currently underway. It is our intention to develop a small molecule that displays binding affinity and specificity towards ZNF827; to prevent its mechanism of action in facilitating cancer cell survival. We envisage that this small molecule will ultimately act as an adjuvant to existing or novel DNA damage agents (such as topotecan) to exacerbate DNA damage and induce cancer cell death **(Figure 3)**. As such, the proposed therapeutic avenue mimics the effects of PARP inhibitors in patients with BRCA1 mutations **(Figure 4)**.

While zinc finger proteins have long been identified as "undruggable" due to their lack of enzymatic activity, recent and dramatic advances in small molecule-mediated protein degradation means that this physiology is now capable of pharmacological targeting for therapeutic benefit. We are seeking a strategically aligned commercial partner with expertise in small-molecule-mediated proteasomal degradation, zinc finger targeting expertise and/or a strong interest in synthetic lethality for cancer who are willing to support the commercialisation of a ZNF827-based therapeutic.

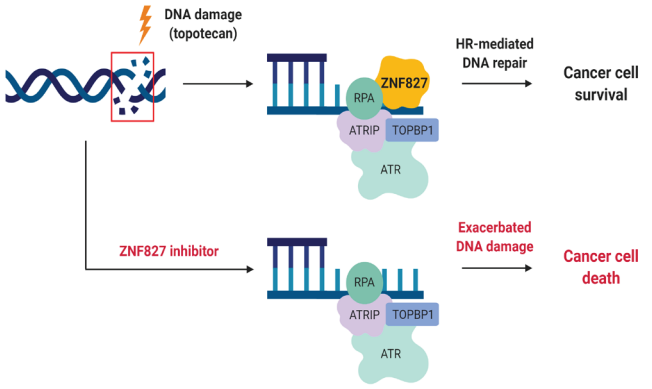

Figure 3: DNA damage response involving ZNF827 and how its inhibition results in cancer cell death.

Repair pathway target	DNA damage inducing agent
BRCA1 (pre-existing mutation)	PARP inhibition (olaparib)
ZNF827 (novel target for inhibition)	Topoisomerase inhibition (topotecan)

Figure 4: Summary of synthetic lethality approaches.

Our Competitive Advantages

- World-leading scientists in telomere biology and the DNA damage response.
- Identification of a novel synthetic lethal interaction partner, with a provisional patent covering this target filed.
- Multiple partnerships with DNA damage agent developers are anticipated.

The Market

- The worldwide cancer therapeutics market was $US166.5 billion in 2021.
- The global topoisomerase and PARP inhibitor market (for which ZNF827 co-therapy would increase efficacy) is expected to reach $US6.8 billion by 2024.
- In clinical use: 6 PARP and 13 topoisomerase inhibitors (marked for multiple indications).

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