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Novel inhibitor of DNA ligase IV with a promising cancer therapeutic potential

Cancer is a dreaded disease where effective and cheap drugs are wanting. A large body of research is trying to identify anti-cancer molecules from nature, including plants, marine organisms, microorganisms, etc., and to ultimately synthesize promising molecules in the laboratory. Antibodies to tumour antigens/receptors, microtubule inhibitors and DNA linking agents have been developed and used as drugs. Today the thrust is on identifying druggable molecules within the tumour cell. Small molecule inhibitors, targeted against crucial enzymes such as kinases, has led to the discovery of important anti-cancer drugs such as Glivec and Gefitinib. There is a great deal of interest in the development and use of therapeutics that target DNA repair pathways. Raghavan and his group chose Ligase IV as their target in the DNA repair pathway (Srivastava *et al.* 2012)

Maintenance of genomic integrity is essential for cell homeostasis. Efficient repair of DNA damage ensures genomic stability. However, cancer therapies such as radiation and chemotherapy function by damaging genomic DNA, by specifically targeting rapidly dividing cancer cells, ultimately leading to cell death. Most of the cancer cells are repair-deficient, thereby providing a therapeutic opportunity to target DNA repair machinery. Although radiation and genotoxic drugs are initially effective in arresting tumour growth and reducing tumour burden, resistance and disease progression eventually occur. The resistance is acquired due to constant selection pressure by the therapeutics.

Genetic mutations in the DNA repair genes are not only the initiating event in a cancer cell but also its limitation because the mutated gene function is often required by the cancer cell to maintain its own survival. This limitation has been exploited to specifically kill the tumour cells by targeting the mutated DNA repair gene while sparing the normal ones, a concept known as 'synthetic lethality' (Kaelin 2005). One of the main DNA damage repair pathways is double strand break (DSB) repair, which includes non-homologous end joining (NHEJ) and homologous recombination (HR). It is plausible that targeting the molecular machinery driving the DNA damage repair (DDR), particularly NHEJ with small molecule inhibitors, will effectively enhance the efficacy of current cancer treatments that generate DNA damage and exploit synthetic lethal interactions.

Radiation therapy and chemotherapy leads to DSB where NHEJ plays a major role in providing resistance to these agents in a cancer cell. The initial inhibitor L189 against Ligase I, III and IV reported in literature was non-specific (Chen *et al*. 2008). Raghavan and his group overcame this limitation by targeted design using specific docking of Ligase IV and comparing with L189 (Srivastava *et al*. 2012). The clever strategy led to the discovery of a novel specific inhibitor SCR7 for Ligase IV. Using elegant experiments on cell lines and mouse model the authors convincingly demonstrated that SCR7 was a specific Ligase IV inhibitor. SCR7 inhibits end joining of double strand breaks in diverse cell types resulting in tumour regression by activation of p53 mediated apoptosis (figure 1). Notably SCR7 treatment did not result in any adverse effects in mice and did not inhibit Ligase III.

The authors have envisaged and addressed the likely limitations of SCR7 as a potential anti-cancer drug in humans and have proposed that cancer cells, due to their higher replication, high DNA damage rate and defective cell-cycle checkpoints, will be more sensitive to SCR7 compared to surrounding normal tissues (Srivastava *et al.* 2012). This may also reduce the possibility of resistance to SCR7. The therapeutic efficacy of SCR7 could be enhanced by specific delivery of SCR7 to the tumour tissue and as adjuvant cancer therapy.

Keywords. Anti-cancer drug; DNA repair; ligase IV; non-homologous end-joining

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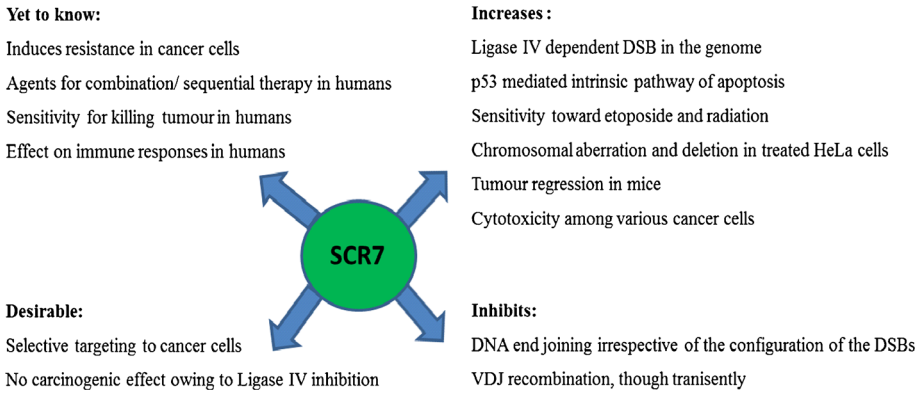

Figure 1. SCR7 its biological effects in increasing and inhibiting cellular processes and aspects that are yet unknown and are desirable to be known for an effective therapeutic.

Although SCR7 is a promising anti-cancer drug, it is likely that it may not be effective in tumours with Ligase IV mutations, or inactive p53, or mutated ATM. It may be necessary to study the mutation profile of Ligase IV in diverse cancers to foresee the application of SCR7 as a therapeutic agent. Given the observation that SCR7-treated mice showed transitory reduction in B and T cell population, the long-term effect of SCR7 on immune response needs to be established. It is known that alternative NHEJ compensates for defective NHEJ by repairing the DSB. The current study demonstrates that SCR7 did not affect Ligase III, an important component of NHEJ, and there was increased DSB. However, studies on long-term and dose-dependent effect of SCR7 treatment on alt-NHEJ are warranted, as they may result in acquired resistance. It would be interesting to pursue why K562 cells did not undergo apoptosis upon SCR7 treatment as reported by Raghavan's group.

SCR7 appears to be a potential cytotoxic anti-cancer drug candidate that can be used either alone or in combination with conventional DNA damaging drugs, owing to its specificity and absence of adverse effects in mice model. However, the effect of SCR7 in base excision repair needs to be studied. It will also be a useful tool to study NHEJ, alt-NHEJ and micro-homology mediated end joining in more details. Most of the NHEJ inhibitors have limitations such as lack of specificity, poor solubility in aqueous solution, and *in vivo* toxicity. We hope that SCR7 will overcome these limitations and be a promising new drug against cancers.

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