

Cancer: Can CRISPR Become a Game Changer?

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ABSTRACT

Recent development in CRISPR technologies has emerged as a powerful tool for genome editing, which can become a powerful diagnostic and therapeutic option for cancer patients. While literature search demonstrates some successes in this dimension in animal models and phase-I human trials, still the promised panacea has shortcomings in terms of off-target mutations (OTMs), minimal efficiency, and tailoring individualised interventions. While there is a promise for the future, although the CRISPR technology still has to climb up the ladder in terms of improvements with more enhanced efficiency tools for delivering the payload into cell and reducing the off-target mutations.

Key Words: CRISPR, Oncology, Off-target mutations (OTMs), Genome editing, 3-D cell cultures.

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The pathology, cancer, dates to the times of the Egyptian empires where the Edwin Smith Papyrus from 2000 BC, mentioned a disease in breast needing removal.¹ Over times, cancer incidence steadily increased with clear mentions from historical data coming from the 16th century.² Current biostatistics indicated a clear trend in cancer surge with GLOBOCAN 2018 depicting an 18.1 million cancer diagnoses with almost 9.1 million deaths attributed to this disease.³ Alarming, rather horrifying remains the future statistical projections for developing countries to have an increase in cancer incidence by 80% to 100% by the year 2030.⁴ Prasad *et al.* have estimated total spending of up to 100 billion USD on anti-cancer therapeutics to 150 billion by 2020, which will not be manageable by developing and under-developed countries.⁵ These mounting costs will not only trouble the rich nations but the major issues will be faced by the developing and evolving economies where both direct and indirect mortality will consume a major chunk of healthcare budgetary allocations and loss of human resource productivity.

Despite the rapid and ominousness showcasing of cancer threat, customary therapeutic options for this menace shuffle between surgery, chemotherapy, and radiation. Notwithstanding the successes of these improved and targeted modalities of cancer therapies, real-time curative treatments rooting out disease still remain far from optimum with many patients finally succumbing to primary pathology or the side effects associated with therapy.

Oncological sciences on one side face limitations in terms of precision medicine but also remain insufficient in terms of adding quality to remaining life years.⁶ The pharmaceutical industry keeps on introducing better and improvised versions with several newer therapeutic targets with immune boosters to counter the cancer challenge, still the author believes that paradigm shifts in treatment approaches are needed. The science of pathology has to get deeper not only to explore genetic causation but also to find efficacious and micro precise novel therapeutic targets for this evolving pandemic of coming times. This realisation of the wholesome diagnostic evaluation of cancer histopathology, tumour microenvironment, genetic roots, possible *in vitro* assessment of therapy efficacy, and prognostic evaluation have been foreseen with the need for machine-based algorithmic deep learning that is superseding the conventional approaches.⁷

One emerging but slightly differential concept is gene therapy for cancer which has the potential to be curative with possibly less side effects and the capability to improve the quality in patients' life. In this regard, CRISPR/Cas technology amidst other gene therapy modalities like RNA interference, zinc finger nucleases (ZFN), and transcription activator-like effector nucleases (TALEN) have emerged as a conspicuously effective genome editing modality with minimal off-target-mutations (OTMs).⁸ So, what promise CRISPR technologies carry which may supersede traditional therapeutics? With the advent of micro precise gene editing tools in terms of target code recognition, scissoring by using specified nucleases (Cas proteins), and fixing the genetic mutation by inserting or deleting the codon sequences CRISPR/Cas technologies are fast emerging as a medic's tool for accurate diagnostics and curative cancer therapies.⁹ Though conceptually appealing, still most of the data has yet to climb the translational ladder before being accredited for lab and clinical work up. Prelimi-

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nary research data on progresses made by incorporating CRISPR/Cas technologies in the field of oncological diagnosis, genetic disease identification, drug resistance studies, and therapeutic utility along with challenges and possible bench to bedside translation requirements remains ongoing.¹⁰ Sabit *et al.* have evaluated the use of CRISPR/Cas9 in animal data for breast cancer to learn the possible translation of this genetic technique both as a diagnostic and therapeutic tool in humans with variable success rates.¹¹ Recently reported first human phase-I trial in patients with advanced staged non small cell lung cancer incorporated CRISPR/Cas9 edited T-cells indicated median overall survival and progression-free survival to be approximated to 42.6 and 7.7 weeks with low OTMs, thus allowing a small leap forward towards desirable endpoints and therapy safety.¹² These selected referenced examples identify a dimension towards the futuristic path for CRISPR/Cas gene therapy to evolve as a diagnostic and therapeutic option. In vitro data for various CRISPR screens in 3-D cell culture models can predict therapy response, but CRISPR/Cas tailoring for a specified tumour and exact delivery remains challenging. CRISPR/Cas technologies are expanding and improving as genome editing tool with newer innovations entering the research and clinical arena regularly for its dual diagnostic and possible therapeutic roles.

While the cancer threat stays as one of the challenging possible pandemics of coming times, hope is on the horizon in the shape of various newer, innovative, and novel biotechnological methods for both diagnostic help and therapeutic intervention. The word 'change' is entering the clinical markets with a speed never seen ever before making some previously in vogue diagnostic and therapeutic strategies redundant and requiring replacement. New entrants like gene therapy will appear as a tangible and possibly realistic option in the near future. Overtime CRISPR with Cas nucleases is being improvised further to suit specified patient requirements in specific tumours, with specific patient needs and promising in terms of limited side effects. These technologies, without an element of doubt are appealing to help provided diagnosticians and physicians with nano precise and accurate tools to define cancer genetics within the surrounding microenvironment for rooting out the ill-functional genes. The author hopes that this treatment will probably emerge as a step forward toward cancer curative strategy. CRISPR/Cas technologies are most likely to emerge as a game-changer in the current fight against oncological pathologies.

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