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Editorial

Bench to clinic - Molecular oncology fast tracking cures

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BASE EDITING IN CLINICAL ONCOLOGY – FROM BENCH TO CURE

On December 13, 2022, the news was out. Base editing had delivered on its' promise of being a cure for incurable cancers. A 13-year-old girl with T cell acute lymphoblastic leukemia, a rare type of leukemia, was the first one to be treated using base edited T cells in May 2022.[1] Patients entering the clinical trial are those for whom all other options of treatment have been exhausted.

Treatment of T-cell leukemias has been challenging with traditional Chimeric Antigen Receptor (CAR) T-Cell Therapy since engineering T cells to destroy the cancerous T cells often ends up with the T cells attacking each other even before the treatment can begin. In the current clinical trial that is being conducted at Great Ormond Street Hospital for Children and UCL Institute of Child Health, the T cells undergo additional processing to remove "flags" to help them become "invisible" to each other and to other cancer treatments.[2] Then they are modified in a way that they can target and attack cancerous T cells.

Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-CRISPR associated system (Cas)-9/base editing technology has moved rapidly from the bench to the clinic. In 1987, Japanese researchers studying *Escherichia coli* genes noted a set of 29-nucleotide repeats, separated by unrelated, and nonrepetitive short sequences (spacers).[3] Many more reports followed in bacteria concerning the CRISPR associated system (Cas) in their immunity against viruses. Many years later, scientists saw its' utility in the editing of human DNA and it moved quickly from a serendipitous observation[4] to the Nobel prize in 2020, to curing "untreatable diseases." Clearly, it was only a matter of time before cancers, especially leukemias, would see this rapidly developing treatment enter clinical trials.

Among the multiple applications of CRISPR in oncology,[5] including novel therapeutic target discovery, gene knockout, or enhancement (*in vitro*/*in vivo*) in a laboratory setting or clinic. Of course, the complete cure and reversal of a treatment-resistant cancer are definitely a favorite outcome and one worth celebrating.

CAPS SCREENING IMPROVES PANCREATIC CANCER SURVIVAL RATES

In a multicenter prospective cohort study of pancreatic cancers (CAPS screening) that opened enrollment in 2014 and closed in June 2021, 1461 patients were enrolled.[6] Of the patients enrolled, 48.5% carried a pathogenic germline variant, of which a larger proportion (18.4%) were BRCA2. A total of nine patients were diagnosed with pancreatic cancer of which 7 were Stage I. The 5-year overall survival rate among those found with pancreatic cancer through this screening was 73.3%.

PATHOGENIC VARIANTS IN THE SUCCINATE DEHYDROGENASE COMPLEX D (SDHD) GENE IN PARAGANGLIOMAS

To understand potential genotype-phenotype factors for people with pathogenic mutations in the SDHD gene (encoding SDHD), a multigenerational family was studied.[7] Genetic, medical, and family histories were gathered on people who had been found in a kindred with the paternally inherited SDHD p.Trp43* mutation. This information included clinical traits, tumor testing if it had been done, and therapy. 41 SDHx-related cancers in 11 individuals with the SDHD pathogenic mutation were diagnosed in the entire family. Seven patients acquired tumors beyond the head and neck region, whereas eight patients developed 27 head and neck paragangliomas of various causes. The average age of the initial tumor diagnosis ranged from 10 to 45 years old, and many people had numerous tumors. This suggests that individuals with the SDHD p.Trp43* variation may be at increased risk for malignancies connected to SDHx.

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