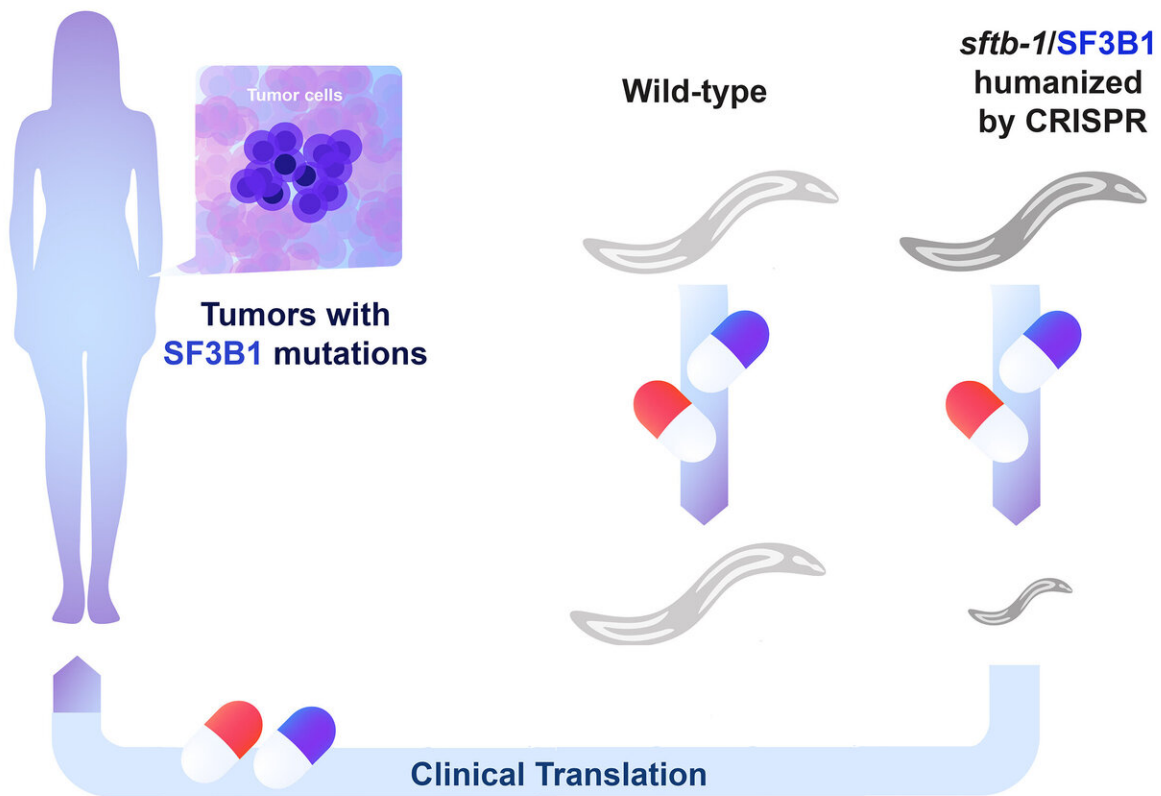


CRISPR-edited *C. elegans* identifies vulnerabilities in cancer

October 24 2019



Humanizing worms makes them sensitive to a cancer drug and identifies weak points of tumor cells. Credit: IDIBELL

A one-millimeter worm, the nematode *Caenorhabditis elegans*, is an animal model widely used in biomedical research by hundreds of

laboratories around the world. Surprisingly, it has approximately the same number of genes that humans have, about 20,000. In addition, most human disease-causing genes have their counterparts, or orthologs, in *C. elegans* worms.

Thus, for example, the human SF3B1 gene, which is mutated in different types of cancers, mainly in leukemia but also in some breast or prostate tumors, is very similar to the sftb-1 gene of *C. elegans* [worms](#). In fact, 89 percent of the amino acid sequence of the human SF3B1 protein in its most cancer-affected region are identical. Some of these [amino acids](#) are conserved from worms to humans, including those that are mutated in some tumors.

A group of researchers led by Dr. Julián Cerón of the Bellvitge Biomedical Research Institute (IDIBELL), has taken advantage of the similarity between these amino acids and their experience in CRISPR gene editing to mimic in *C. elegans*, the SF3B1 mutations found in tumors.

These investigations have allowed the use of worms to identify possible weaknesses or vulnerabilities of cancer cells carrying mutations in SF3B1. Thus, the researchers point to three other splicing factors, which work together with SF3B1 in the processing of messenger RNA, as targets for therapeutic molecules that kill cancer cells harboring mutations in SF3B1, but not normal cells. This research, which is part of the doctoral thesis of Xènia Serrat, and in collaboration with researchers from the Pasteur Institute in Paris, has just been published in the journal *PLoS Genetics*.

IDIBELL researchers have not only reproduced the mutations of cancer patients in worms, but have also humanized the region of the SF3B1 protein that binds to Pladienolide B, a molecule from which drugs that are in clinical trials for the treatment of cancer have been derived. This

advance will allow the testing of more molecules derived from Pladienolide B, with the goal of selecting the most efficient as an anti-tumor agent.

Thanks to CRISPR technology, in which Dr. Cerón's group is a specialist, the functional replacement of *C. elegans* proteins with their human counterparts will allow these humanized worms to be used as models for investigating the mechanisms of different diseases and use them as tools of prognosis, and as a platform for seeking new drugs in a fast, efficient, and ethically responsible manner.

More information: Xènia Serrat et al. CRISPR editing of *sftb-1/SF3B1* in *Caenorhabditis elegans* allows the identification of synthetic interactions with cancer-related mutations and the chemical inhibition of splicing, *PLOS Genetics* (2019). [DOI: 10.1371/journal.pgen.1008464](https://doi.org/10.1371/journal.pgen.1008464)

Provided by IDIBELL-Bellvitge Biomedical Research Institute

Citation: CRISPR-edited *C. elegans* identifies vulnerabilities in cancer (2019, October 24) retrieved 19 April 2024 from <https://medicalxpress.com/news/2019-10-crispr-edited-elegans-vulnerabilities-cancer.html>

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