

Science News

from research organizations

'Frameshifting' therapy for mast cell cancers reduces size, spread

Date: August 10, 2021

Source: North Carolina State University

Summary: A potential new treatment for mast cell cancers reduces the number of mast cells by 'mutating' the messenger RNA (mRNA) before it can deliver instructions for manufacturing the gene responsible for cell proliferation. The method, known as frameshifting, changes the pre-mRNA so that the mature mRNA is degraded and any protein produced from its instructions is altered and inert. In a mouse model, frameshifting directed at the c-KIT gene reduced mast cell tumor size and prevented infiltration into other organs.

Share: [!\[\]\(17413706fd4997a1a4bdf85c6864eee1_img.jpg\)](#) [!\[\]\(f419710cbe076aa30a9c6c031b5cbe84_img.jpg\)](#) [!\[\]\(2726020a4107bdc9042b257034f90eb3_img.jpg\)](#) [!\[\]\(9459655bf14a84f4d775e8d814cca8c9_img.jpg\)](#) [!\[\]\(de47dbdca34225b222a4a87ac0e499b3_img.jpg\)](#)

FULL STORY

A potential new treatment for mast cell cancers reduces the number of mast cells by "mutating" the messenger RNA (mRNA) before it can deliver instructions for manufacturing the gene responsible for cell proliferation. The method, known as frameshifting, changes the pre-mRNA so that the mature mRNA is degraded and any protein produced from its instructions is altered and inert. In a mouse model, frameshifting directed at the c-KIT gene reduced mast cell tumor size and prevented infiltration into other organs.

Mast cells regulate immune responses. But too many mast cells can result in a number of diseases, the most serious of which are mast cell leukemia and mast cell sarcoma. A gene known as c-KIT produces a protein, KIT, which is associated with mast cell survival and proliferation. C-KIT mutations can increase proliferation of mast cells in multiple organs, leading to mast cell cancers.

"Current treatments for mast cell cancers target signaling from the receptor encoded by the c-KIT gene, and the efficacy of current therapies can be negatively affected by c-KIT mutations associated with disease development," says Glenn Cruse, assistant professor of immunology at North Carolina State University and corresponding author of the research. "We are targeting the gene itself, regardless of mutation. If we target the gene that drives progression, then we can target the disease."

Cruse and a team of researchers from NC State and the National Institutes of Health (NIH) used a technique known as exon skipping to produce the frameshift mutation.

Before a gene or protein is produced, the pre-mRNA, which is composed of both coding and non-coding regions called exons and introns, is spliced so that introns are removed and only the exons -- a gene's "production instructions" -- remain. The resulting mature mRNA then delivers its instructions and the gene or protein is produced. If something goes wrong or a mutation occurs, a stop codon -- a short sequence in the mRNA -- stops production of the faulty protein by causing that strand of the mRNA to be degraded or destroyed.

The researchers used this mechanism to their advantage by binding a short RNA molecule called an oligonucleotide to exon 4 within the c-KIT pre-mRNA, effectively fooling the splicing proteins into thinking the exon was an intron, and removing it. The missing, or skipped, exon creates a frameshift in the reading frame of the mRNA, causing it to be recognized as a mutant and degraded.

"We are altering the message that makes the protein -- flipping an 'on' switch to 'off,'" Cruse says. "If you get mRNA to produce a protein that is mutated and severely truncated, your cell will recognize that and degrade the message so that the protein isn't produced."

The researchers used their frameshifted c-KIT mRNA approach on mast cell leukemia cells in vitro and found that KIT protein expression, signaling and function were reduced. The cancer cells stopped proliferating and began dying within hours. In a mouse model, tumor growth and infiltration of other organs were reduced and tumor cell death increased when the frameshifted c-KIT mRNA was induced.

"The other advantage to our technique is that it solves the problem of degradation evasion," Cruse says. "Occasionally faulty messages will evade degradation and their mutated proteins get produced anyway. But proteins produced by the frameshifted c-KIT mRNA are inert, or non-functional. So even if they get produced, they cannot cause more harm."

The research appears in *Molecular Therapy* and is supported by the National Institutes of Health. NC State postdoctoral researcher Douglas Snider is first author. The technology described in the paper has been licensed by Hoth Therapeutics.

Story Source:

Materials provided by **North Carolina State University**. Original written by Tracey Peake. *Note: Content may be edited for style and length.*

Journal Reference:

1. Douglas B. Snider, Greer K. Arthur, Guido H. Falduto, Ana Olivera, Lauren C. Ehrhardt-Humbert, Emmaline Smith, Cierra Smith, Dean D. Metcalfe, Glenn Cruse. **Targeting KIT by frameshifting mRNA transcripts as a therapeutic strategy for aggressive mast cell neoplasms.** *Molecular Therapy*, 2021; DOI: 10.1016/j.ymthe.2021.08.009

Cite This Page:

MLA	APA	Chicago
-----	-----	---------

North Carolina State University. "'Frameshifting' therapy for mast cell cancers reduces size, spread." ScienceDaily. ScienceDaily, 10 August 2021. <www.sciencedaily.com/releases/2021/08/210810161349.htm>.

RELATED STORIES

Protein-Gene Interactions Involved in Alzheimer's Disease

July 23, 2019 — UC San Diego researchers have used the transcriptome -- the sum of all messenger RNA (mRNA) molecules expressed from genes -- to map protein-gene interactions involved in Alzheimer's ...

It's All in the Code: Protein Production Efficiency Can Be Predicted by Gene Sequence

Feb. 4, 2019 — Scientists explored mRNA and protein public databases to unravel hidden meanings of the genetic code. Using a metric derived from mRNA codon composition, they found out how gene sequence choice can ...

The Search for the Origin of Mast Cells

June 4, 2018 — A team of researchers has proven that not all of the immune system's important mast cells are produced in bone marrow, as was previously thought. Scientists found embryonic mast cells in mice with ...

Proof-of Principle Study Finds Imatinib Improves Symptoms for Patients With Severe Asthma

May 17, 2017 — In a new, proof-of-principle study researchers have found that targeting the mast cells with imatinib, a drug used to effectively treat certain forms of cancer, improved airway hyperresponsiveness, a ...

FROM AROUND THE WEB

ScienceDaily shares links with sites in the TrendMD network and earns revenue from third-party advertisers, where indicated.

Identification of novel mutations of SLC4A11 gene in patients with congenital hereditary endothelial dystrophy

Li Yue et al., Chinese Medical Journals Publishing House Co., Ltd., 2021

MET Exon 14 Skipping Mutations in Non-Small-Cell Lung Cancer: An Overview of Biology, Clinical Outcomes, and Testing Considerations

Mark A. Socinski et al., JCO PO, 2021

Disruption of splicing-regulatory elements using CRISPR/Cas9 to rescue spinal muscular atrophy in human iPSCs and mice

Jin-Jing Li et al., National Science Review, 2019

Functional RNA Studies Are a Useful Tool in Variant Classification but Must Be Used With Caution: A Case Study of One BRCA2 Variant

Paola Nix et al., JCO PO, 2020

Tumor Suppressor Tolerance: Reversion Mutations in BRCA1 and BRCA2 and Resistance to PARP Inhibitors and Platinum

Shridar Ganesan et al., JCO PO, 2018

Veracyte Q3 Revenues Decline 6 Percent

GenomeWeb, 2017

A CRISPR Approach For a Common Inherited Disease

Author: Leslie Mertz, IEEE PULSE, 2018

People in the News: Heikki Lanckriet, Pilar de la Huerta, Peter Llewellyn-Davis, and Joris Veltman

GenomeWeb, 2017

Free Subscriptions

Get the latest science news with ScienceDaily's free email newsletters, updated daily and weekly. Or view hourly updated newsfeeds in your RSS reader:

 [Email Newsletters](#)

 [RSS Feeds](#)

Follow Us

Keep up to date with the latest news from ScienceDaily via social networks:

 [Facebook](#)

 [Twitter](#)

 [LinkedIn](#)

Have Feedback?

Tell us what you think of ScienceDaily -- we welcome both positive and negative comments. Have any problems using the site? Questions?

 [Leave Feedback](#)

 [Contact Us](#)

[About This Site](#) | [Staff](#) | [Reviews](#) | [Contribute](#) | [Advertise](#) | [Privacy Policy](#) | [Editorial Policy](#) | [Terms of Use](#)

Copyright 2021 ScienceDaily or by other parties, where indicated. All rights controlled by their respective owners. Content on this website is for information only. It is not intended to provide medical or other professional advice. Views expressed here do not necessarily reflect those of ScienceDaily, its staff, its contributors, or its partners.

Financial support for ScienceDaily comes from advertisements and referral programs, where indicated.

— [CCPA: Do Not Sell My Information](#) — — [GDPR: Privacy Settings](#) —