'Unassuming' enzyme opens way for new medical treatments

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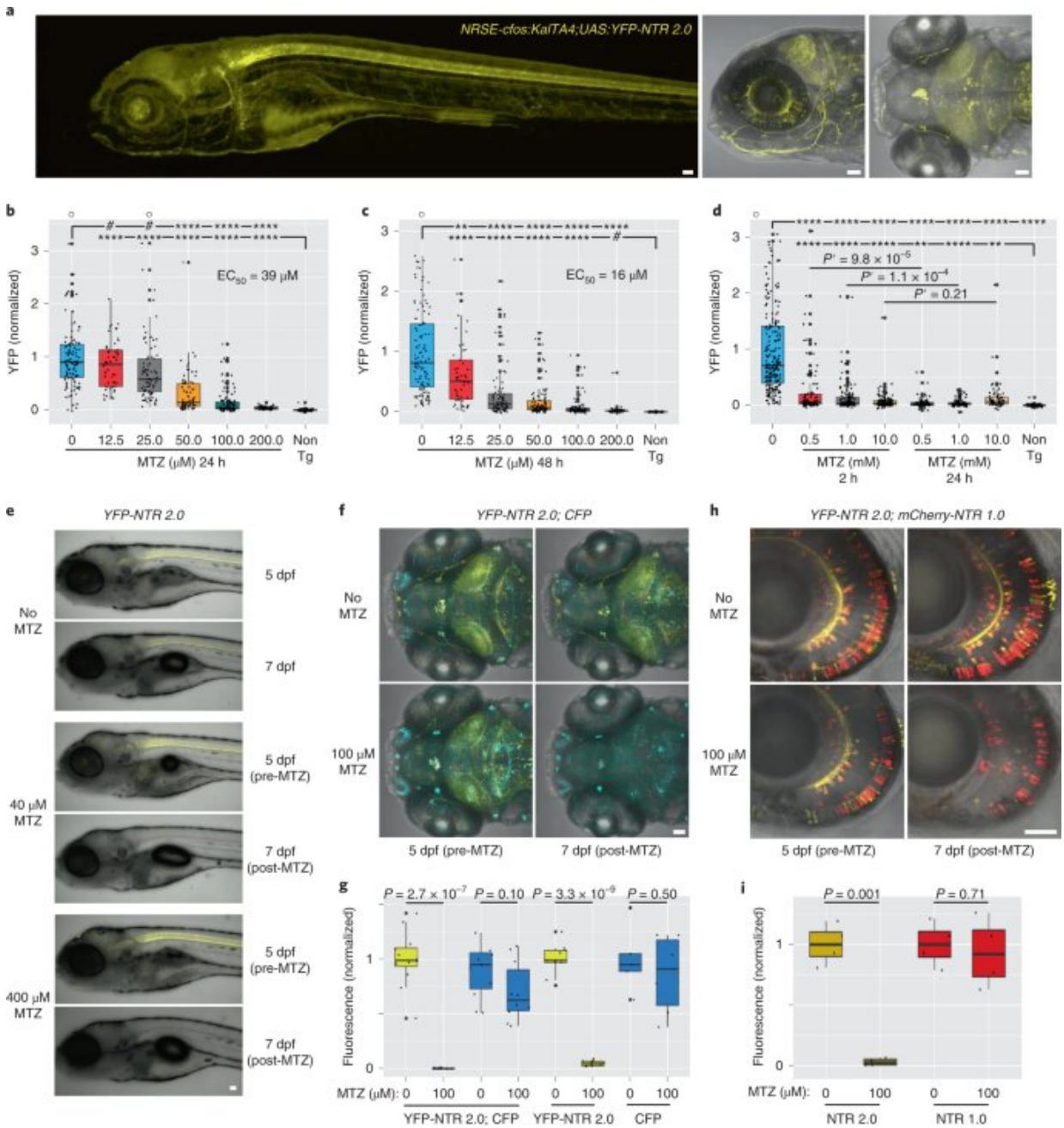

NTR 2.0 enhances cell ablation efficacy in zebrafish. Credit: DOI: 10.1038/s41592-021-01364-4

It sounds like a plot for a Cold War thriller—training a gene to infiltrate a cell and reside there, unnoticed, until an external self-destruct signal induces it to destroy its new home.

However, this is not a Le Carré spy novel, but a piece of cutting-edge biomedical science undertaken by researchers from Te Herenga Waka—Victoria University of Wellington, and their Johns Hopkins University collaborators in the United States, that could have important applications in the treatment of cancer and other conditions.

Their paper has just been published in the journal *Nature Methods*.

David Ackerley, professor of biotechnology in the University's Te Kura Mātauranga Koiora—School of Biological Sciences and leader of the New Zealand part of the study, says the agent in question is an "unassuming" bacterial enzyme called nitroreductase.

"While medical researchers usually want to focus more on ways to keep our cells alive, rather than killing them, being able to activate a genetic 'kill switch' that will target a precisely-defined set of cells actually has a wide range of uses.

"It can allow researchers to understand how certain cells function, by observing the effect of removing them from a model system, or screening for drugs that favor the regeneration and regrowth of those cells.

"A reliable 'kill switch' also enables doctors to trial otherwise risky new therapies, like engineering bone marrow or blood cells to protect vulnerable patients against a wide range of diseases."

The need for this was illustrated by a gene therapy-trial in the early 2000s, which showed much promise for curing "bubble-baby disease," where babies with immunodeficiency disorders must otherwise be raised in entirely sterile conditions, Professor Ackerley says.

"While some patients were completely cured by the gene therapy, unfortunately it caused leukemia in others.

"Had the delivered genes included a safe and reliable 'kill switch," doctors would have been able to immediately eliminate any cancerous cells that had arisen. However, ensuring both safety and reliability is a scientific challenge."

Co-leader of the study Professor Jeff Mumm, from the Wilmer Eye Institute at Johns Hopkins University, envisaged an elegant solution—a gene that encodes an enzyme able to activate an artificial drug from a non-toxic to a toxic form.

"That way, the gene would be completely inert in any natural context, and a scientist or doctor could have total control over silencing cells containing that gene, by choosing when to administer the drug."

Professor Mumm's preferred drug was metronidazole—a common antibiotic known to be safe in patients, but able to be converted by certain enzymes to a toxic form that is 100 percent-contained by the activating cell, Professor Ackerley says.

"That property enables very clean elimination of target cells, without harm to neighboring non-target cells. But Jeff's problem was that

because metronidazole is a very artificial drug, nature has never evolved specific enzymes to be good at activating it.

"Our microbial biotechnology team has a lot of experience engineering enzymes to activate drugs like metronidazole and so we stepped in to help."

Lead researcher and Te Herenga Waka postdoctoral fellow Dr. Abby Sharrock, and key team member and University research fellow Dr. Elsie Williams studied a family of related enzymes that were promising but inefficient with metronidazole, and proposed two changes they might be able to make to substantially boost this activity.

Professor Ackerley says the result is an enzyme able to kill cells at 100-fold lower doses of metronidazole, "opening the way to many different research and medical applications not previously possible."

"Although our paper has only just been published, dozens of research teams from around the world have already requested the gene encoding the team's engineered enzyme.

"We are optimistic that our enhanced enzyme will spur breakthroughs in treatment of a wide-range of disorders, including various cancers and degenerative conditions."

More information: Abigail V. Sharrock et al, NTR 2.0: a rationally engineered prodrug-converting enzyme with substantially enhanced efficacy for targeted cell ablation, *Nature Methods* (2022). DOI: 10.1038/s41592-021-01364-4

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