

New model taps tiny, common tropical fish for large-scale drug screening to combat Cushing disease

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A common, tiny tropical fish plays a key role in a new model for Cushing disease, giving researchers a powerful tool to conduct extensive searches for effective treatments for this serious hormonal disorder, testing up to 300 drugs weekly.

The model - published online on May 2 by the *Proceedings of the National Academy of Sciences* -- was created in the laboratory of Shlomo Melmed, MD, dean of the medical faculty at Cedars-Sinai Medical Center, by his research team led by Ning-Ai Liu, MD, PhD.

They introduced into striped zebrafish - the freshwater translucent tropical *Danio rerio* -- the "pituitary tumor transforming gene" discovered in Melmed's lab in 1997. This caused the zebrafish to develop features of Cushing disease including: high levels of the stress-related hormone cortisol; diabetes; and heart disease. These zebrafish then were bred with fish that bear green fluorescent markers, allowing researchers to visualize in the resulting hybrids how drugs interact with the Cushing's disease pituitary tumors.

"This new model for Cushing disease means that we can more rapidly and effectively identify drugs that could be successful in fighting these tumors," Melmed said. "With no current [drug](#) therapies and limited options available to Cushing patients, it is our hope that our research will enable medical advances that will revolutionize how this disease is treated."

Cushing Disease often is caused by a pituitary tumor that triggers overproduction of a hormone, which, in turn, stimulates the adrenal gland to overproduce cortisol, affecting nearly every area of the body including the regulation of blood pressure and metabolism. This leads to serious health problems, including diabetes, hypertension,

osteoporosis, obesity (especially with a distinctive moon face and fatty tissue deposits in the midsection, upper back and between the shoulders) and cardiovascular disease.

There are no approved drugs that effectively target the pituitary tumors that frequently cause the disease. "Because the tumors can be too small to be detected by MRI and a complete tumor resection by surgery can be difficult in some cases, this leaves few treatment options for many with the disease," said Dr. Liu, an endocrinologist at Cedars Sinai.

In the initial test of the zebrafish model, researchers studied five drugs, including R-roscovitine, a drug in phase two trials to treat esophageal and non-small cell lung cancer. This drug was found to effectively suppress levels of hormone secreted by the pituitary tumor, as well as the level of cortisol and could be a potential treatment for fighting tumor growth.

Provided by Cedars-Sinai Medical Center

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