

Scientists identify propranolol's target in treating rare condition and hemangiomas

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The discovery of a new target for the blood-pressure medication propranolol may lead to the development of new and safer therapies for vascular diseases, according to new findings published in *eLife*.

The study also helps explain how propranolol is able to shrink benign tumours in infants called hemangiomas and relieve symptoms in some individuals born with a rare condition called hypotrichosis-lymphedema-telangiectasia and renal syndrome (HLTRS), which causes an overgrowth of blood vessels.

Propranolol's ability to block adrenaline receptors has made it a mainstay of treatment for hypertension and other heart-related conditions for decades. More recently, the drug has been repurposed to treat hemangiomas, although it was not clear how it is able to shrink the tumours. But then an adolescent patient with unusually mild symptoms of HLTRS, which is caused by mutations in a gene called SOX18, was found. The patient had been taking high doses of propranolol since a young age to control [high blood pressure](#).

"The milder symptoms seen in this HLTRS patient taking propranolol raised the possibility that the drug has a SOX18-dependent molecular mode of action in addition to its beta-blocking activity," says co-lead author Jeroen Overman, a Ph.D. student at the Institute for Molecular Bioscience, The University of Queensland, Australia.

When a 17-month-old patient in Dubai with HLTRS and a mutation in

SOX18 developed [heart problems](#), his physicians and parents chose to try propranolol. This treatment rapidly resolved the child's heart problem, further bolstering the idea that the drug targeted SOX18.

The team conducted experiments in cells grown in the laboratory, and confirmed that propranolol directly interferes with SOX18 activity by preventing it from binding with other SOX18 proteins. Later studies in mice, whereby the researchers treated eight-day-old mice that had SOX18 mutations with propranolol, revealed that the drug eliminated the HLTRS-like overgrowth of blood vessels in the cornea usually seen in mice with these mutations.

Finally, a collaborative team at Boston Children's Hospital, led by co-senior author Joyce Bischoff, treated hemangioma cells collected from patients and grown in the laboratory with propranolol. They found that the drug's SOX18-blocking action stopped the differentiation of the tumour cells. Specifically, they showed that one component of propranolol, called the R(+) enantiomer, is responsible for the SOX18-blocking effect, while its mirror image, S(-) enantiomer, had only a weak effect.

"This discovery suggests that it might be possible to treat hemangiomas or HLTRS using only the R(+) enantiomer of propranolol," says co-senior author Mathias Francois, Ph.D., Associate Professor at the Institute for Molecular Bioscience at The University of Queensland. "This would allow for lower doses of the medication or a shorter duration of therapy, and sparing patients from potential side effects related to beta-blockers."

In addition to opening the door for improved treatment for hemangioma or HLTRS, the discovery may lead to the development of new therapies for other conditions that involve excessive growth of blood-vessel cells. "Our work may enable the repurposing of the R(+) enantiomer of

[propranolol](#) as a treatment for a broad range of conditions which include vascular disorders," concludes Joyce Bischoff, Ph.D., Principal Investigator in the Vascular Biology Program and Professor in the Department of Surgery at Boston Children's Hospital and Harvard Medical School, Boston, US.

More information: Jeroen Overman et al, R-propranolol is a small molecule inhibitor of the SOX18 transcription factor in a rare vascular syndrome and hemangioma, *eLife* (2019). [DOI: 10.7554/eLife.43026](https://doi.org/10.7554/eLife.43026)

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