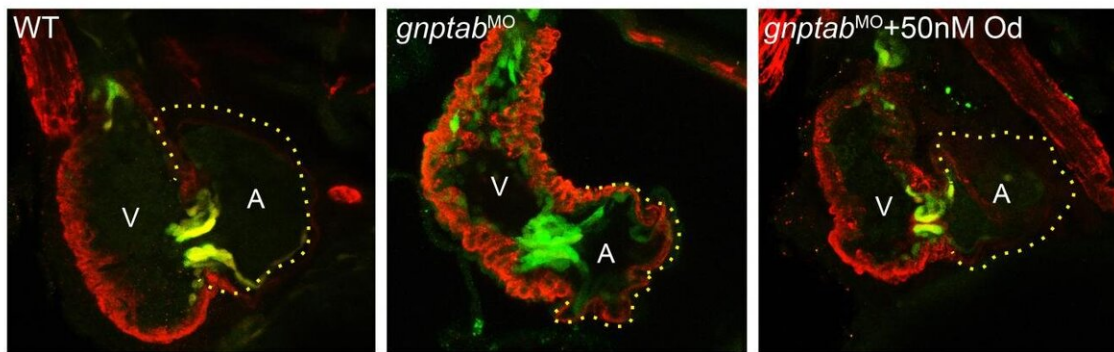


Rare congenital heart defect rescued by protease inhibition

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Confocal analyses show that treatment with 50 nM of odanacatib restores normal morphology to MLII zebrafish hearts and valves. Credit: Greenwood Genetic Center

A research team at the Greenwood Genetic Center (GGC) has successfully used small molecules to restore normal heart and valve development in an animal model for Mucopolysaccharidosis II (ML II), a rare genetic disorder. Progressive heart disease is commonly associated with ML II. The study is reported in this month's *JCI Insight*.

The small molecules included the cathepsin protease K inhibitor, odanacatib, and an inhibitor of TGF β growth factor signaling. Cathepsin proteases have been associated with later-onset heart disease including atherosclerosis, [cardiac hypertrophy](#), and valvular stenosis, but their role

in congenital heart defects has been unclear. The current study offers new insight into how mislocalizing proteases like cathepsin K alter embryonic heart development in a zebrafish model of ML II.

"Mutations in GNPTAB, the gene responsible for ML II, alter the localization and increase the activity of cathepsin proteases. This disturbs growth factor signaling and disrupts heart and valve development in our GNPTAB deficient zebrafish embryos," said Heather Flanagan-Steet, Ph.D., Director of the Hazel and Bill Allin Aquaculture Facility and Director of Functional Studies at GGC. "By inhibiting this process, normal cardiac development was restored. This finding highlights the potential of [small molecules](#) and validates the need for further studies into their efficacy."

Flanagan-Steet noted that she hopes the current work with ML II zebrafish will provide the basis to move one step closer to a treatment.

More information: Po-Nien Lu et al, Inappropriate cathepsin K secretion promotes its enzymatic activation driving heart and valve malformation, *JCI Insight* (2020). [DOI: 10.1172/jci.insight.133019](https://doi.org/10.1172/jci.insight.133019)

Provided by Greenwood Genetic Center

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