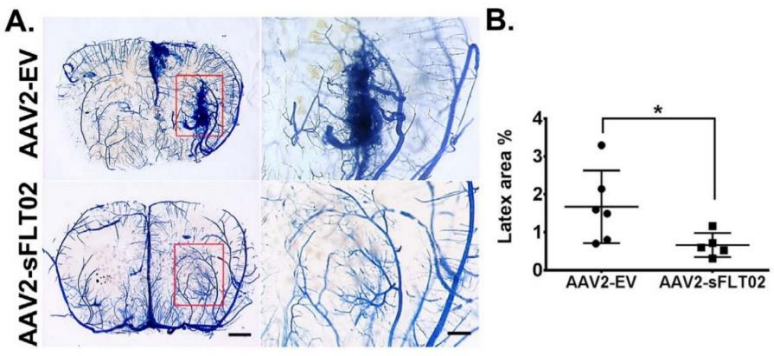
Using Gene Therapy to Reduce Severity of Brain Arteriovenous Malformations in HHT

Arteriovenous malformations (AVMs) that occur in the brain of HHT patients create a risk for rupture and bleeding inside the skull. If AVM rupture occurs, it can be life threatening and the treatment to stop bleeding can sometimes cause more problems. Therefore, the need to find and implement better and safer treatments is highly relevant. Dr. Wan Zhu from Dr. Hua Su's Lab at the University of California San Francisco is using gene therapy to minimize the severity and impact of brain AVMs.

When AVMs are present in the brain or other organs, a protein called vascular endothelial growth factor, or VEGF, is also present in higher than normal amounts. VEGF signals the body to stimulate blood vessel growth, and it is thought that increased VEGF plays a role in AVM formation. Blocking VEGF throughout the body in order to minimize AVMs can have negative consequences because the body needs VEGF for regular blood vessel formation. The researchers at UCSF used targeted gene therapy to block VEGF in the brains of mice and saw successful reduction in size and severity of their AVMs.

Endoglin, a gene that causes HHT, was knocked-out, or mutated, in mice, allowing the mice to have a malfunctioning endoglin protein like human HHT patients do. Endoglin is a protein involved in the formation of blood vessels, and these mice were able to develop brain AVMs that Dr. Su and her team could study. If the endoglin knock-out mice were injected with a protein that binds to VEGF (AAV2-sFLT02) at the same time their endoglin gene was disrupted, it prevented the mice from developing brain AVMs. These mice were compared to mice with the endoglin knockout who were injected with a control substance that would not stop the formation of AVMs (AAV2-EV).



In figure A, blood in the mouse brain was replaced with a colored latex that allowed researchers to see AVMs. Inside the red rectangle of the top photo, the control mouse's brain had a large AVM. However, the mouse brain treated with the VEGF inhibitor did not develop AVMs during the same timeframe. Figure B has circles and squares that represent individual mice from each of these groups. The figure is showing how much latex was in the brain of each mouse, with more latex representative of AVMs. The mice treated with the VEGF inhibitor showed significantly less latex compared to the control.

Once the researchers saw they could stop AVMs from forming, they wanted to see what the VEGF inhibitor would do to mice that already had brain AVMs. When mice were injected with the inhibitor, it greatly reduced the severity of their AVMs and that group's mice lived longer than the group that did not get the inhibitor. This important research paves the way for gene therapy in HHT patients as a way to reduce the severity of brain AVMs.