Development of Drug Treatments for Arteriovenous Malformations (AVMs)

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Arteriovenous malformation (AVM) is a congenital vascular anomaly. Lesions may affect the brain (intracranial) and any other area of the body (extracranial). Arteries are abnormally connected to veins through irregular blood vessels, instead of a normal capillary network (**Fig. 1**). They enlarge over time and cause disfigurement, ulceration, pain, bleeding, infection, heart failure, and death (**Fig. 2**). Unlike almost all other diseases, including cancer, *drugs for AVM do not exist*. Instead, management consists of surgical resection, radiation, or embolization. Unfortunately, AVM has a high recurrence rate after treatment and lesions are rarely cured. Dr. Arin Greene's team at Boston Children's Hospital found that the endothelial cells (ECs) lining the inside of blood vessels in extracranial AVMs have mutations in the *MAP2K1* gene. Interestingly, the same *MAP2K1* mutations are also found in multiple types of cancer. We do not understand how the MAP2K1 mutation causes AVMs and makes them enlarge. *Our ability to understand the mechanisms for AVM formation and develop drugs against AVM is hampered by the absence of an AVM animal model.* The goal of Dr. Greene's team is to create an animal model of AVM by introducing the most common AVM causing mutation (*MAP2K1*) into the genome of the endothelial cells of a mouse, thereby creating mice that will develop AVMs. Dr. Greene's group then will investigate whether treating AVMs in mice with FDA-approved drugs can prevent AVM formation, AVM growth, and/or shrink AVM size. The establishment of drugs for AVM for the first time would profoundly impact patients' lives. We will begin by developing oral drugs and then proceed to making drugs that could either be injected directly into AVMs or topical creams that could be applied to the skin involved with the AVM. Once we show that drugs work well in our animal model we would then begin studies testing the drugs in humans with AVMs.

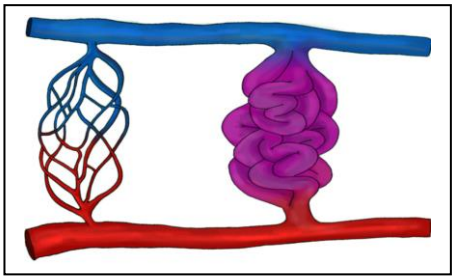

Fig. 1. (*Left*) Normally arteries (red) are connected to veins (blue) through capillaries where oxygen is delivered to tissues. (*Right*) AVMs have abnormal connections between arteries and veins through either a nidus or fistula.

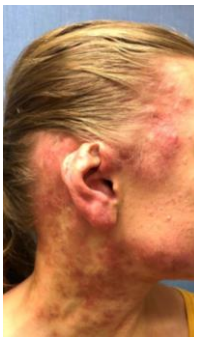

Fig. 2. Adult with an extracranial AVM and improved symptoms after experimental treatment with a *MAP2K1* inhibitor.

We will use CRISPR/Cas9 gene editing to create a mouse model of AVM (**Fig. 3**). We will replace the wild-type exon 2 of one *MAP2K1* allele with a mutant exon 2. To prevent expression of the mutant allele in all cells we introduce a LoxP flanked gene trap into intron 1. The gene trap halts RNA transcription before exon 2, rendering the mutant allele inactive. In the presence of Cre recombinase, the flanking LoxP sites will recombine, removing the gene trap and allowing expression of the mutant *MAP2K1* allele. By using a tamoxifen inducible version of the Cre recombinase protein (CreERT2) that is specifically expressed in endothelial cells (Cdh5-CreERT2), we can: (1) activate the mutant *MAP2K1* allele specifically in ECs and (2) expose the mice to low concentrations of tamoxifen to activate the mutant allele in only a limited number of ECs. *Once we have generated mammals containing AVMs we will then test FDA approved MAP2K1 inhibitors (Trametinib and Cobimetinib), as well as novel drugs, to determine if they are able to regress or prevent the progression of AVMs. We will test drugs topically, by injection, as well as systemically for their effects on AVMs. Results from these studies will be translated to clinical trials in humans (**Fig. 4**).*

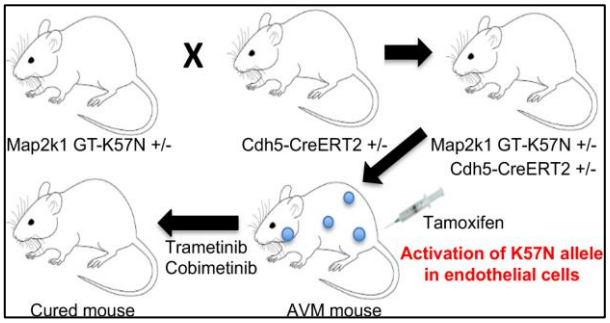

Fig. 3: Strategy for generating mice with AVMs and treating them with drugs.

Fig. 4. Our goal is to create drugs for the first time to prevent the progression of AVMs as well as to make them smaller.