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Presentation Title: Toward a gene therapy for Glut1 Deficiency Syndrome.

Synopsis of Presentation

The ketogenic diet is the mainstay for patients with Glut1DS. While the diet mitigates Glut1DS symptoms in many instances, it does not address the entirety of the disease burden experienced by patients. Moreover, it fails to address the *root cause* of Glut1DS – low brain Glut1 protein and, consequently, low brain glucose; glucose is the preferred source of energy for the organ. The Monani lab wishes to address this caveat. To do so, we are attempting to develop a gene therapy for Glut1DS. In previous work, we showed that delivering a normal copy of the Glut1 gene in a therapeutic AAV viral vector successfully arrested, indeed reversed, Glut1DS in a mouse model of the disease. This raises optimism that the same approach can be used in the clinic to improve upon and effectively treat Glut1DS. Yet, there are caveats associated with the strategy such as the potential for raising Glut1 levels beyond what is required for normal brain function. To address this possibility, the Monani lab is also developing an alternate gene therapy approach. In this second approach, we swap the Glut1 gene in the therapeutic vector with a regulatory molecule that operates by inducing the *normal* Glut1 copy, which is present in most patients to produce an incremental increase in Glut1 to compensate for the absence of functional protein from the "diseased" gene copy. We have tested this approach in mouse models and shown that it too effectively ameliorates Glut1DS.

Our next step is to translate the two approaches described above into a clinical treatment. To do so requires us to identify a therapeutic viral vector that delivers our biomolecules of interest (Glut1 or the regulatory molecule) to the *brain endothelial* cells in the human patient; the vector we used for our mouse experiments does not work very well to deliver therapeutic genes to these cells in primate models and is therefore unlikely to function effectively in human patients. Accordingly, we tested a half dozen or so new therapeutic vectors and have identified two promising candidates for use in the clinic. We are now in the process of testing these in a non-human primate model. Successful transfer of genes using these vectors to the non-human primate cells of interest will raise optimism that one or both could be used in the clinic. In parallel studies, we have identified a "control element" from the human Glut1 gene that ensures that our biomolecules will be expressed at the correct levels and in the right cells for the treatment of human Glut1 deficiency. Future work will test the safety of our therapeutic vectors and therapeutic molecules in model organisms. A successful outcome will set the stage for conversations with the FDA to initiate Phase 1 clinical trials. Considering our success in developing gene therapy for another rare disease, spinal muscular atrophy, which we have spent many years studying, we are optimistic that effective gene therapy for Glut1DS will become available to patients in the near future.