OPINION

Personalizing medicine

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Alysson Muotri, assistant professor of pediatrics at the University of California, San Diego, has given a whole new meaning to the tradition of the tooth fairy.

A couple of years ago, Muotri and his collaborators developed a way to **use stem cells from dental pulp**, collected from the innards of lost teeth, to create induced pluripotent stem (iPS) cells — adult cells that have been reprogrammed to a more flexible state.

Muotri is planning to build a bank of such cells from children with autism. By differentiating the stem cells into neurons, he says he hopes to understand the molecular and cellular changes that underlie the disorder, particularly for so-called idiopathic autism — with no known cause — which makes up the bulk of cases.

The tooth fairy approach avoids a trip to the doctor and a skin biopsy, both of which can be especially distressing for children with autism. (iPS cells are typically derived from skin samples.) And teeth can be sent from anywhere in the world.

Ultimately, neurons derived from an individual with autism could be used to select the best therapy for that person. Muotri is already trying a simplified version of this approach, which he presented last month at the **Translational Neuroscience Symposium** in Switzerland.

Starting with samples from a child in Brazil, researchers discovered the child has a translocation, or

DNA swap, affecting two genes: VPRVP, which is involved in the cell cycle but not expressed in the nervous system, and TRPC6, a calcium channel expressed in parts of **synapses**, the connections between neurons, throughout development.

Gene expression studies revealed that iPS cells derived from the child produce only half the normal amount of TRPC6 protein. After differentiating iPS cells in a dish into cortical neurons, researchers found his cells have fewer **dendritic spines** — small bumps on neurons that receive inputs from other cells — than those derived from controls.

Analyzing a second child who has similar outward symptoms to the child with the translocation, researchers found some molecular similarities. Although this child does not have a deletion or translocation of TRPC6, he also has fewer spines on iPS cell-derived neurons.

What's more, both have fewer glutamate synapses, neuronal connections that mediate excitatory signals. Muotri says that is similar to neurons from people with Rett syndrome, a rare inherited disorder that shares some symptoms of autism.

He speculates that **MeCP2**, the gene that is disrupted in Rett syndrome, regulates TRPC6. When they examined iPS cell-derived neurons from someone with Rett, they found low expression of the TRPC6 gene, he says. These results have not yet been published.

How significant these differences are is a matter of some debate. Some scientists argue that the **variability inherent in making iPS cells** makes it difficult to determine whether the disparities can be attributed to the disorder itself or merely to small differences in the cells' origins.

Muotri says he hopes that the National Institutes of Health or other organizations will spearhead an iPS cell consortium to try to answer some of these questions. Academic labs such as his own don't have the resources to create and bank large numbers of cell lines, he says. In fact, the tooth fairy project is on hold, because the lab doesn't have enough people to process the cells.

A strain of **mice lacking the TRPC6 gene** is available but has been little studied. Neurons from adult mice, however, have fewer glutamate synapses, similar to those seen in human TRPC6-deficient cells made from the boys with autism, says Muotri.

Muotri and his collaborators are trying to figure out whether these findings can be used for personalized therapy. Hyperforin, a component of the herbal remedy St. John's wort, has been shown to activate TRPC6 channels. In neurons, hyperforin increases activation of TRPC6, says Muotri.

The outcome of the story is somewhat muddy, as expected in a trial of one. One of the children was given St. John's wort, which is available over the counter, by his parents. After several months of treatment, the father and therapists reported a behavioral change, and the school

reported improved attention, but the mother says she did not see any changes.

If there is behavioral change, “We don’t know if it’s due to the drug or not,” says Muotri. “But it’s very exciting that we found a kid with a similar phenotype to the child with the translocation and saw similar molecular defects in iPS cell-derived neurons.”