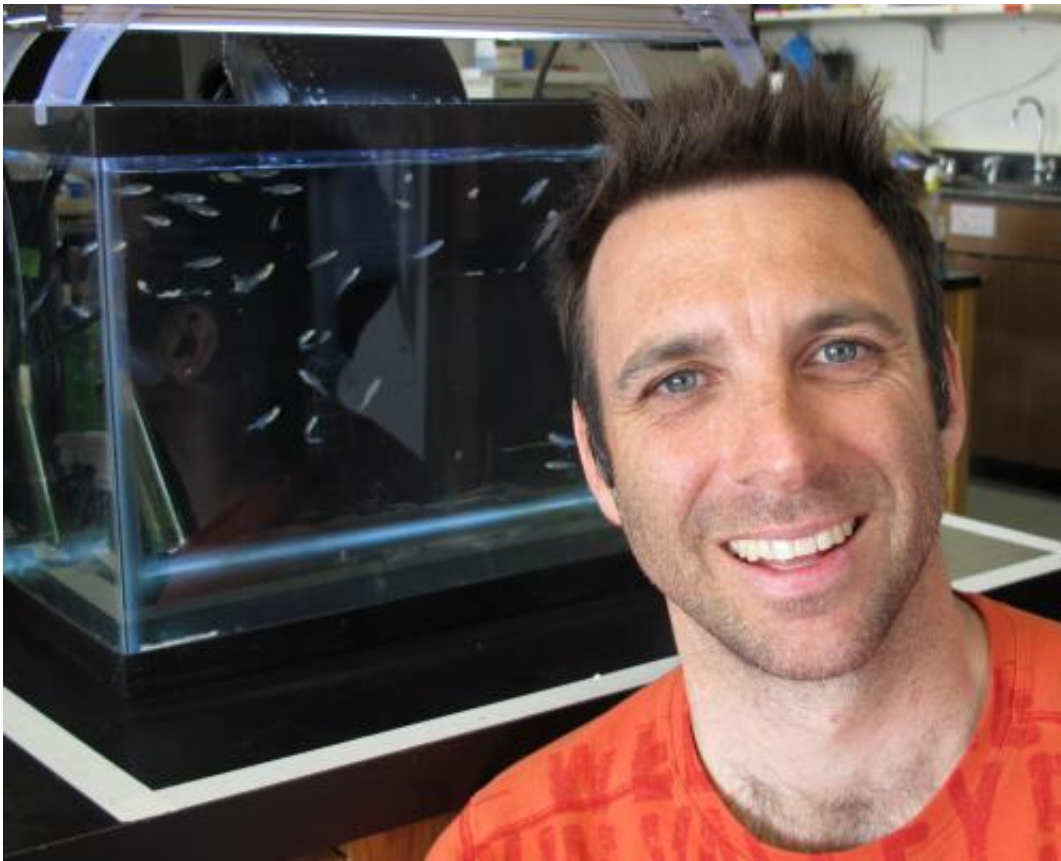


First steps of synapse building is captured in live zebra fish embryos

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Philip Washbourne of the University of Oregon Institute of Neuroscience has provided perhaps the first look of early synapse construction in a live vertebrate. He captured the orderly movement of proteins along axons in zebra fish embryos. Credit: University of Oregon

Using spinning disk microscopy on barely day-old zebra fish embryos,

University of Oregon scientists have gained a new window on how synapse-building components move to worksites in the central nervous system.

What researchers captured in these see-through embryos—in what may be one of the first views of early glutamate-driven synapse formation in a living vertebrate—were orderly movements of protein-carrying packets along axons to a specific site where a synapse would be formed.

The discovery, in research funded by the National Institutes of Health, is described in a paper placed online ahead of publication in the April 25 issue of the open-access journal *Cell Reports*. It is noteworthy because most synapses formed in [vertebrates](#) use [glutamate](#) as a [neurotransmitter](#), and breakdowns in the process have been tied to conditions such as autism, schizophrenia and [mental retardation](#).

The [zebra fish](#) has become one of the leading research models for studying early development, in general, and human-disease states. In this case, researchers used immunofluorescence labeling to highlight the area they put under the [microscopes](#). The embryos they studied were barely 24-hours old and a millimeter in length, but neurons in their spinal cord were already forming connections called [synapses](#). Images were taken every 30 seconds over two hours.

"If we zoom out a bit and look at development in the human, the majority of synapse formation occurs in the cortex after birth and continues for the first two years in a baby's life," said Philip Washbourne, a professor of biology and member of the UO's Institute of Neuroscience.

Previous studies, done in vitro, contradicted each other, with one, in 2000, identifying a single packet of building blocks arriving at a pre-synaptic terminal. The other, in 2004, identified two protein packets.

After watching the process unfold live, with imaging over long time spans, Washbourne said: "We now see at least three, and maybe more, such deliveries."

"[Axons](#) are long processes—think of them as highways—of neurons. In humans, these can be a meter long, from spinal cord to your big toe," he said. It's in the cell body where all the proteins are made, and they have to be transported out. Is it done by a single bus or by several cars? These results point to additional layers of complexity in the established mechanisms of synaptogenesis."

The new research also showed that sequence also is crucial. Two different pre-synaptic packages of molecules repeatedly arrived in the same order. A key building block—the protein synapsin—always arrived third. As these delivery vehicles traveled the axonal highway, another protein, a cyclin-dependent kinase known as Cdk5, acts as a stoplight at the synapse-construction site, where phosphorylation occurs. More research is needed on Cdk5, Washbourne said.

"Understanding how all this happens will inform us to what's going wrong in neurodevelopment that leads to diseases," Washbourne said.

"We have indications that the glue that gets all this going includes a gene that has been linked to autism, so knowing how these molecules start the process of synapse formation—and what goes wrong in people with mutations in these genes—might allow for a therapeutic targeting to correct the mutations and manipulate the stop signs."

Provided by University of Oregon

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