Scientists map molecular interactions at point of conception

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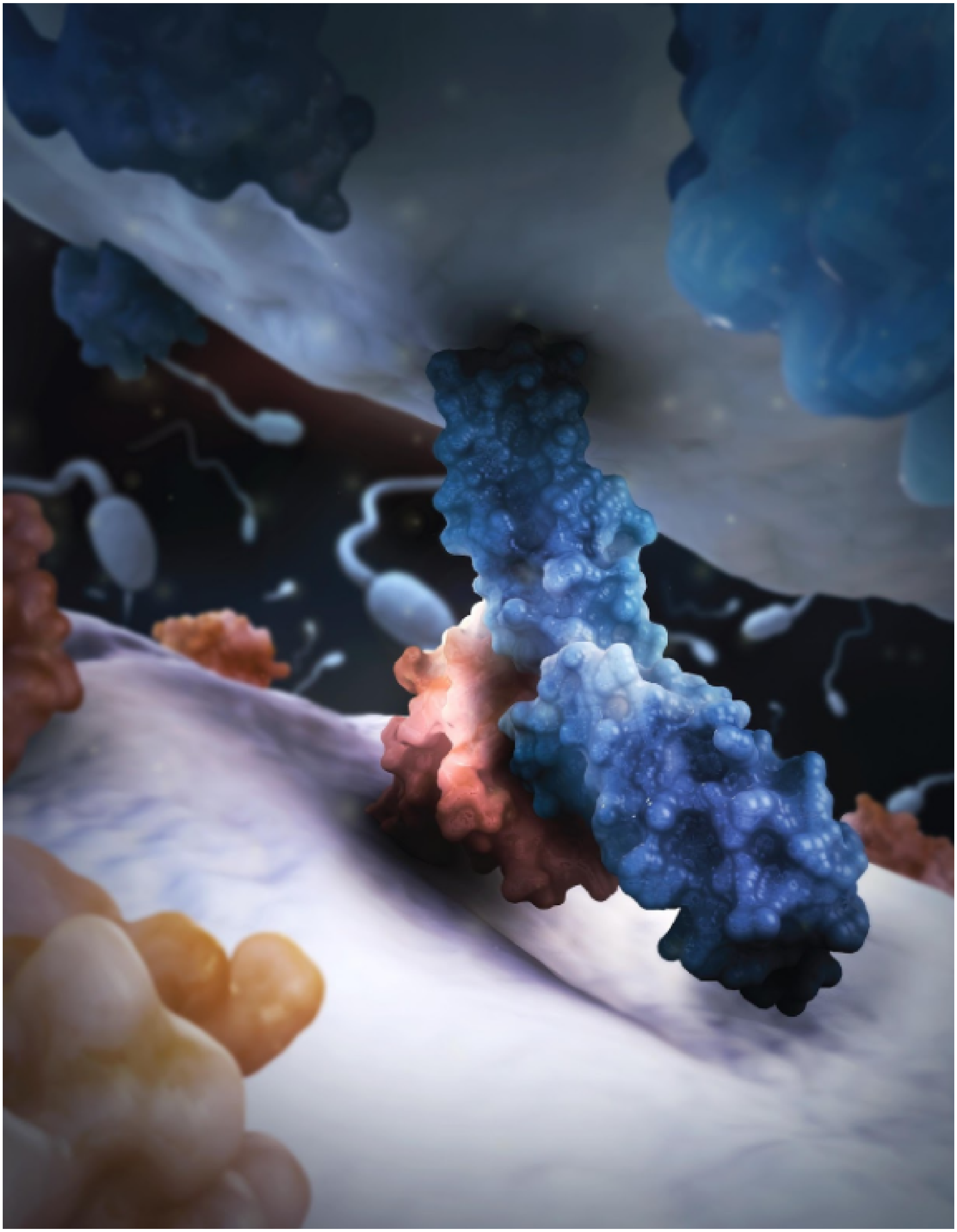

Credit: University of Toronto

Researchers at the University of Toronto have uncovered the first interactions between the human sperm and egg—the initial steps in the creation of human life. The discovery lays a foundation to better understand fertilization and could lead to the development of non-hormonal contraceptives.

"We've provided the first atomic-level, 3D images of the molecular interplay between egg and sperm at the point of conception," says Jeffrey Lee, a professor in the Department of Laboratory Medicine and Pathobiology at U of T who holds the Canada Research Chair in Structural Virology. "Our models describe how the Izumo1 sperm and Juno egg proteins interact at the site of fusion. This provides a blueprint for the development of non-hormonal contraceptives."

The journal *Nature* published the findings online June 15, 2016.

Izumo1, named after a Japanese shrine dedicated to marriage, and Juno, named for the Roman goddess of marriage and conception, play key roles in fertility. However, scientists have known very little about the exact way sperm fuses to an egg—despite its central importance for reproductive medicine.

Studies of how these two proteins bind had been hindered by difficulties in producing stable proteins in the laboratory. Lee and his lab solved this problem by using insect cells to make the proteins. Then, they used X-ray crystallography to recreate the structure of the proteins in 3D.

The researchers used powerful, focused X-rays from the Canadian Light Source synchrotron in Saskatoon to diffract their human Izumo1-Juno protein crystals. Using advanced computational algorithms, they determined the precise 3D coordinates of every atom in the protein structures to provide an architectural blueprint — allowing them to see how the proteins interact.

The group found that Izumo1 consists of two domains attached by a hinge-like structure and that it adopts a boomerang shape on the sperm surface. "Probably the biggest surprise was that Izumo1 has an architecture that is completely different from other viral and cellular fusion proteins," says Halil Aydin, first author on the study and a doctoral student in Lee's lab.

The team showed that Izumo1 undergoes a conformational change and abandons its boomerang shape upon binding with Juno. Working with researchers at the University of California, San Diego, they also found that the bound Izumo1 is stabilized in a locked, upright position.

The interaction between Izumo1 and Juno, it turns out, is conserved in humans and primates but varies across mammalian species. "The specific human Izumo1 and Juno interaction may provide an additional barrier to cross-species fertilization," says Aydin.

The researchers also discovered the human Izumo1 and Juno bind together very tightly, contrary to what many researchers believed. After fertilization, the egg sheds Juno molecules from its surface. The tight binding of shed Juno may block or neutralize incoming sperm to prevent more than one sperm from fertilizing the egg.

More questions need answering about how the sperm and egg fuse, says Lee. In particular, what other proteins may be critical for the process. So far, an understanding of many cell fusion mechanisms have been based on how viruses fuse with cells.

"It will definitely be exciting work for us to elucidate the precise mechanism of sperm-egg fusion and to understand how various fusion processes in biology are similar or different," says Lee. "We've laid a strong foundation that we and others can build on. This is a pure basic science study that now provides guidance for other biologists and clinical investigators to open up new lines of inquiry."

More information: Halil Aydin et al. Molecular architecture of the human sperm IZUMO1 and egg JUNO fertilization complex, *Nature* (2016). DOI: 10.1038/nature18595

Provided by University of Toronto