

# Molecular Framework Proves a Fertile Find

*Insights from a newly solved structure could lead to improved fertility drugs, or to contraceptives for both men and women.*

**WHY DO RESEARCHERS WORK SO HARD TO** make three-dimensional crystal structures of molecules and their minuscule kin? “Most of these structures end up being a wellspring of ideas,” says HHMI investigator Wayne A. Hendrickson. “They are often filled with unexpected things.”

So it was with Hendrickson’s recent work to solve the crystal structure of a particular complex—follicle-stimulating hormone (FSH) binding to its receptor. The structure not only yielded clues about how the interaction works, but opened new research avenues for fertility treatments as well as contraception. Medical practitioners already use FSH injections for treating infertility, but researchers think that if they learn how FSH binds to its receptor on the surface of cells, they may be able to improve such therapies.

One of a family of signaling molecules—including luteinizing hormone, chorionic gonadotropin, and thyroid-stimulating hormone—FSH is a key regulator in human reproduction, controlling egg development in women and sperm production in men. Each of these hormones is composed of an  $\alpha$  and a  $\beta$  subunit. Because they all use the same  $\alpha$  subunit, researchers thought the specificity they have for their own receptors had to come from the  $\beta$  subunit.

Hints that this might not be strictly true had already come from the x-ray crystal structure of FSH alone, which James Dias and colleagues at the Wadsworth Center in the New York State Department of Health solved in 2001. But knowledge of that structure left open some big mysteries, including how an apparently disordered (flexible) C-terminal tail in the  $\alpha$  subunit fit into the complex.

Now that Hendrickson, a professor of biochemistry and molecular biophysics at Columbia University College of Physicians and Surgeons, and Qing Fan, a postdoctoral fellow in his laboratory, have solved the structure of the hormone bound to the extracellular domain of

the receptor, it’s clear why the  $\alpha$ -subunit tail is so important. If it is mutated or deleted, the hormone can’t bind to the receptor. The researchers reported their results in the January 20, 2005, issue of *Nature*.

For Hendrickson, though, the excitement of the work comes not just from the answers it provides but from the new ideas it generates. For example, in many protein-protein interactions, the interface between the molecules tends to be “greasy” and excludes water, but

and we couldn’t have gotten that information without the structure.”

The new structure provided by Hendrickson and Fan gives a picture of how the hormone interacts with part of the receptor protein, but it doesn’t show how the receptor becomes activated in response to hormone binding. To observe that phenomenon, the researchers think they need to see the hormone binding to the whole receptor protein, including the membrane-spanning region. This presents a



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in this case the contact area between the receptor and the hormone was highly charged, full of negative and positive charges attracting each other.

“We knew that charge was important in the binding,” says Dias, “but the new structure showed us that stereochemistry [the spatial arrangement or organization of the molecules] was also important

formidable challenge because proteins that are designed to reside in membranes are difficult to purify and crystallize.

Meanwhile, the team is starting to think about how the current structure might be used in medical practice. “Protein-protein interfaces are notoriously difficult to disrupt with small-molecule drugs,” says Hendrickson. “But if we could disrupt the hormone-receptor interaction, we’d instantly have a contraception approach that works for both men and women.” Conversely, better knowledge of how FSH interacts with its receptor might also help researchers develop a new, orally available mimic that could be used to treat infertility by stimulating egg or sperm production. ■

- Rabiya S. Tuma -