Researcher shines light on the search for new drugs

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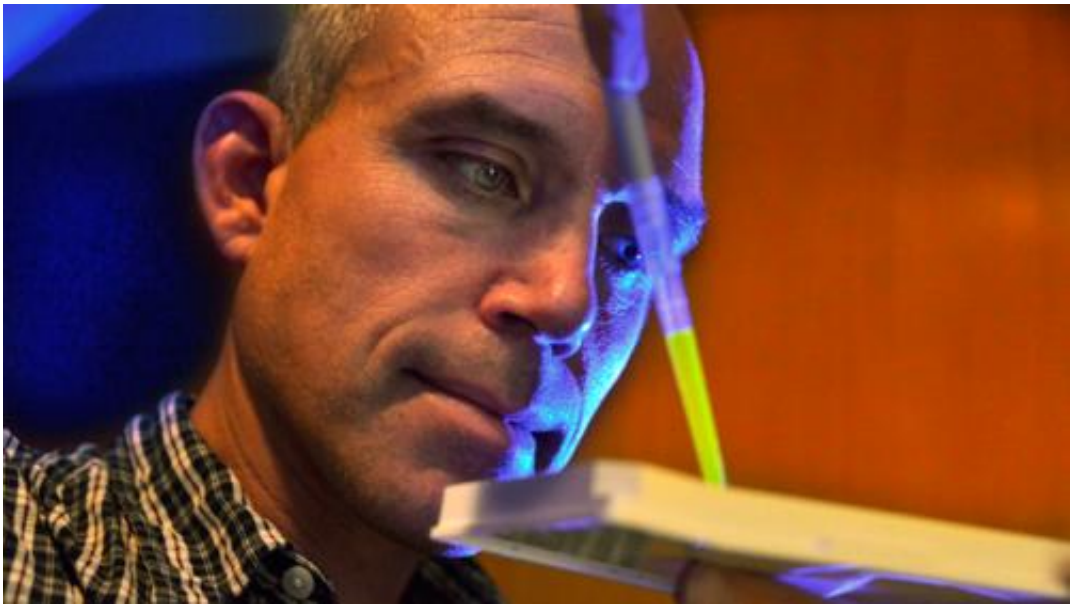

Dr. Nevin Lambert is a biophysicist at the MCG at Georgia Regents University. Credit: Phil Jones

They are the largest family of receptors on the surface of our cells, and they help us maintain basics like blood pressure and heart rate.

These important day jobs make G protein-coupled receptors natural targets for drugs that can lower blood pressure or dilate an airway, scientists say. In fact, of all the drugs out there, nearly half act by first sticking to a G protein-coupled receptor, said Dr. Nevin Lambert,

biophysicist at the Medical College of Georgia at Georgia Regents University.

However, just how many targets the receptors offer remains a much-debated issue.

"If you imagine opening a box and finding a whole bunch of new drug targets that nobody has found before, that would be cool, and you have lots more ways to change things," Lambert said.

If such a treasure trove sounds too good to be true, Lambert suspects it probably is. He just received a $900,000 grant from the National Institutes of Health's National Institute of General Medical Sciences that is enabling him to resolve the hotly debated issue in new drug development.

The math already looks good, with about 350 G protein-coupled receptors involved in a myriad of basic physiological functions that might need adjusting to improve health. In fact, a single receptor can be a target for multiple agents found in nature and drugstores. But, for nearly two decades, the potential has been even more enticing.

In addition to being a high-functioning single molecule, it's widely held that two G protein-coupled receptors regularly chemically bind, creating what's termed a dimer, which has a whole different function than the two individual receptors.

"If this is true, then the potential for future drug discovery would be immense," Lambert said.

Drug companies have an obvious interest in the possibilities, but the reality has not panned out.

"The real question is: How many drug targets are there? Are there a few hundred or thousands? We are testing that question, basically." Lambert suspects that surprisingly few drug targets have appeared because the receptors might not actually be dimers.

Receptors are constantly scurrying around the cell surface and wiggling like a Slinky toy. When scientists have looked at them, primarily with a technique called luminescence energy transfer, which uses the natural glow of a sea pansy protein to light up a receptor, the thinking has been that if another receptor is close enough to bask in its glow, the two have formed a dimer.

Lambert suspects that light transfer is really a matter of random proximity for a few fractions of a second by the constantly moving receptors. "It's in the light, but it can be by chance," he said.

To definitively answer whether these are real or accidental relationships, Lambert is adding a little more light. He is still using the sea pansy protein to give some receptors a blue glow; he's also fusing a yellow fluorescent jelly-fish protein to others. While he knows there will still be lots of energy transfer as the receptors scuttle about, Lambert is looking at the distance between yellow and blue receptors as the total number of receptors changes. If the blue and yellow receptors are not dimers, he expects the distance between them to shrink because there is simply less room. If actual dimers are forming, the minute distance between the receptors won't and really can't change as the crowd thickens. He's repeating this process in a lot of different cell types and tissues.

The issue of whether G protein-coupled receptors form dimers needs resolving, Lambert said, because, while he and others like the notion of thousands of additional treatment targets for a host of ailments, searches based on a false premise waste research resources.

Lambert also recently received a second NIGMS grant to better define these receptors' relationships with G proteins, from which they get their name and their ability to take action.

While it's interesting science, this question also gets back to the issue of maximizing drug development, Lambert said. Do receptors carry their own G protein around with them that they interact with when stimulated by a hormone or drug, or can they interact with a wide range of G proteins?

He'll be looking at some of the same receptors, but this time, in collaboration with researchers at Columbia University in New York, he'll look at individual receptors in real time to see whether, as they move around the cell surface, a protein is traveling with them just below the cell surface. Or, do these receptors travel independently and couple with a G protein floating inside the cell only when activated?

This time he suspects a one-on-one relationship. "The question is, does one receptor stick to one G protein for a really long period of time or do they just bounce off each other very quickly?" The ability to analyze one molecule at a time should yield the answer.

Lambert notes that humans have some 600 additional G protein-coupled receptors involved in the sense of smell; dogs have thousands. The number involved in other physiological functions reflects the body's complexity, with humans having about 350, and some plants having just one.

In addition to helping scientists see receptors, sea pansies, an animal related to sea jellies, create some of the sparkles and flashes visible in the ocean at night.