Super fruit fly may lead to healthier humans

June 8 2007

In a triumph for pests, scientists have figured out how to make the fruit fly live longer. But humans still may get something out of the deal. As reported online in *Nature Chemical Biology*, the discovery that a single protein can inhibit aging holds implications for human longevity and for treatment of some of the world's most feared diseases.

"This work is important for two reasons," said study author Richard Roberts, associate professor of chemistry, chemical engineering and biology at the University of Southern California.

"First, it demonstrates that a single inhibitor can dramatically alter lifespan, a very complex trait. It is remarkable that you can alter it with a single genetic change.

"We don't really need to make fruit flies live longer, but if we understand how to do this, our approach may have direct application to higher organisms, such as ourselves."

Secondly, Roberts said, the method used by his research group to make the inhibiting proteins "opens the possibility of developing a lot of new therapeutics."

The study describes a new method for blocking receptors involved in aging and disease across many species, including humans.

Receptors are proteins that transmit signals across a cell membrane. In the fruit fly, Roberts and his team manufactured short proteins that

blocked a receptor involved in fruit fly aging, as previously demonstrated by co-author Seymour Benzer of Caltech.

Flies with a blocked receptor saw their lives extended by a third, with no apparent side effects.

The same blocking strategy should work in all such receptors, known as class B GPCRs (for G protein-coupled receptors). Many GPCRs figure prominently in disease as well as in normal development, Roberts said.

“It is the most targeted family of receptors” by drug manufacturers, Roberts said, estimating that a quarter of all pharmaceuticals focus on GPCRs.

“This approach should be generally applicable.”

And generally powerful, given that GPCRs are notoriously unstable and difficult to work with. The Roberts group went around the problem by cutting off the unstable part of the receptor and running experiments only on the part of the receptor that sticks out of the cell.

Though there were no guarantees that inhibiting one part of the receptor would incapacitate the whole, the strategy succeeded.

Roberts’ method builds on his co-discovery, in 1997, of a simple method for building libraries of trillions of short proteins, or peptides.

Unlike DNA, which can be copied and multiplied millions of times with polymerase chain reaction (PCR), proteins cannot be copied directly.

But Roberts and Jack Szostak of Massachusetts General Hospital thought of fusing peptides to the bits of messenger RNA that contained their sequence.

“Essentially, we developed a way to do PCR on proteins,” Roberts said.

The use of RNA-peptide fusions allowed the easy creation and multiplication of randomly generated peptides. Roberts termed this approach “Irrational Design.”

In the new study, Roberts and his group literally threw trillions of peptides at the receptor and saved the ones that stuck.

“We let the molecules themselves decide if they bind, rather than trying to design them rationally,” he said.

After multiple cycles, the researchers had a group of peptides that stuck to the receptor and not to any other protein.

Fruit flies genetically altered to produce such peptides lived longer, suggesting that the peptides were interfering with the receptor’s normal function.

Why these particular peptides work, and why the receptor they target plays such an important role in fruit fly aging, remain the bigger and as yet unanswered questions.

Print publication of the *Nature Chemical Biology* study is expected later this summer.

Source: University of Southern California