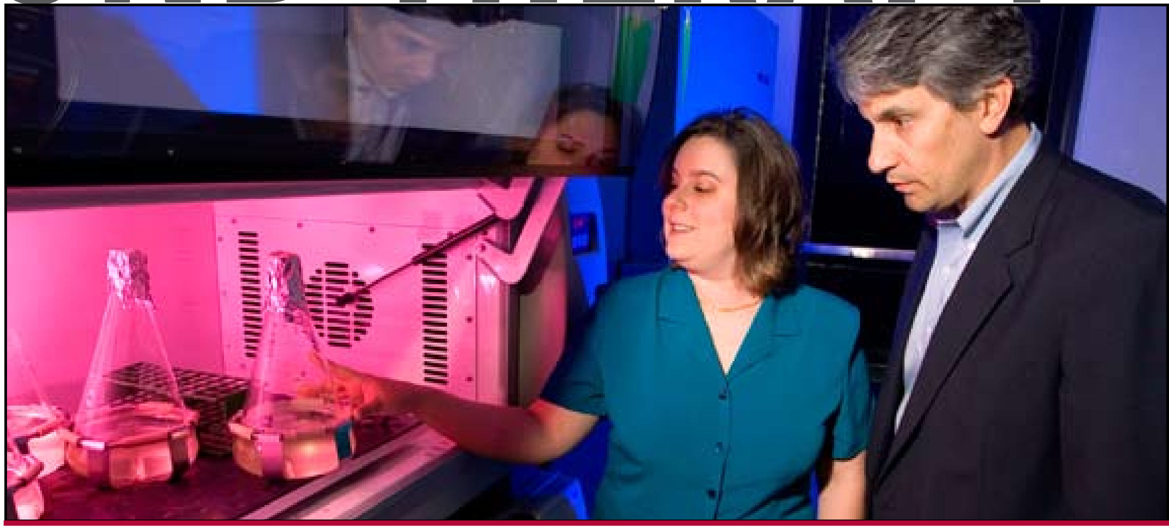
Research collaboration 'translates' into potential

WOUND THERAPY



Bioengineering Assistant Professor Jennifer Cochran shows surgery Professor Michael Longaker a beaker in which yeast is making an enhanced version of a protein instrumental in healing skin wounds.

BY DAVID ORENSTEIN

For a cut in the skin to begin healing healthy skin cells must gather in the affected area and then multiply. When Jennifer Cochran joined the Stanford Bioengineering faculty as an assistant professor in 2005, she had engineered proteins to greatly enhance the wound-healing process. Coming to Stanford gave her the opportunity to team up with doctors at the medical center. Now they are working together to turn her engineered proteins into therapies for patients, such as diabetics, who suffer from chronic skin lesions.

"The clinical collaboration here with Drs. Mike Longaker and George Yang in the Department of Surgery has now allowed us to take this project to the next level," Cochran says. "We can start looking at the therapeutic efficacy of these proteins."

This promising effort to turn an innovation from a bioengineer's lab benchtop into a treatment for patients is called "translational research." It is a movement meant to bridge the gap between basic research and medical practice. Traditionally a researcher like Cochran wouldn't connect with physicians such as Longaker and Yang. But as a joint department of the schools of medicine and engineering, Stanford's Department of Bioengineering is tailor-made to ensure those collaborations. Sure enough, in November 2005 the department was one of only nine around the country to win a Translational Research Partnership Award from the Wallace H. Coulter Foundation. The award gives the department $580,000 in each of the next five years to fund projects in which professors collaborate with clinicians on translational research.

LICKING THE TOUGH WOUNDS

In April 2006, the department granted $100,000 from the award to fund the effort by Cochran, Longaker, Yang, and Surgery Research Fellow Dr. Daphne Ly to develop a therapeutic application based upon Cochran's initial protein engineering work. The goal is a treatment for chronic wounds that are too persistent for the body to heal naturally. Currently only a couple of treatments are available and they are expensive, onerous to use, and offer only small benefits. By contrast, the team thinks its approach may be cheaper, easier to use and more effective.

Their approach is to accelerate a process the body already uses to heal skin wounds by delivering an enhanced version of a naturally occurring protein that plays a key role in the process. The protein is called epidermal growth factor (EGF). In fact, Longaker says, animals lick their wounds because their saliva includes a high concentration of EGF.

The translational aspects of Stanford make this a great place to do research.

Wound healing is a complicated series of biochemical interactions among many different cells and proteins, but it is clear that EGF is a major player in that sequence. When skin is damaged, the body releases EGF into the area. The presence of EGF attracts nearby connective tissue cells called fibroblasts. The EGF then signals the fibroblasts to begin producing collagen in the area of the wound, to build the foundation of new skin tissue. The fibroblasts then produce their own EGF, which entices cells that make up the outer layer of skin, called keratinocytes, to gather and multiply, essentially paving over the collagen and closing the wound.

Under normal circumstances, the body can use this process to heal a wound. But in diabetics, cells called neutrophils that are responsible for helping clean the wound site, stick around too long and actually undermine healing. They clear out new tissue instead of just damaged tissue. As a result the lesions remain open. In the past, researchers have strived to overcome this by applying EGF, but the approach hasn't worked because EGF only remains in the wound site for about seven minutes before it disperses. This is not enough time to rebuild tissue to outpace the neutrophils.

"Our therapeutic rationale is that if we made EGF that was more persistent so that it was present on the receptors of the cells for longer periods of time, then it could have an enhanced biological effect," Cochran says.

And so while she was a postdoctoral fellow at the Massachusetts Institute of Technology, Cochran and colleagues there made such EGF proteins. To do so, she used a technique called "directed evolution." Essentially she took the DNA that cells naturally use to make EGF in the body and put it through an intentionally error-prone process that causes the DNA to replicate tens of millions of times with all kinds of mutations resulting from the errors. She then devised a test that sorted through all the EGF proteins these mutant DNA produced in yeast to select modified EGF that associated more strongly with EGF receptors.

Through this process, Cochran has found a dozen mutants with about 30 times more receptor-binding affinity than natural EGF. Since coming to Stanford, Cochran has been producing batches of these more promising EGF mutants for the regimen of testing required to devise a working therapy. In preliminary experiments on the EGF mutants at Stanford, the increased binding strength appeared to result in engineered EGF having longer lasting biological effects.

DEVELOPING A THERAPY

To minimize animal testing, the group has been doing its initial clinical testing with cell-based "scratch assays." In these experiments Ly scratches a 2 millimeter line through a thin layer of skin tissue in a Petri dish, creating a gap in the tissue. Ly then adds Cochran's engineered EGF proteins in a saline solution and tracks what happens. In these preliminary experiments, the tissue has been able to close the gaps within 48 hours, a whole day faster than with natural EGF. This result suggests that the enhanced EGF promotes healing.

Once the scratch assays have told the team which EGF mutant is the most promising, Longaker and Yang's groups will begin testing topical formulations, such as gels, with the enhanced EGF on diabetic mice. Ultimately, over a period of perhaps several years, the group hopes to put the treatment they develop through the clinical trials the Food and Drug Administration requires of treatments before they can be deemed safe and effective for patients.

The engineered EGF is just the first of many research results that Cochran hopes she'll be able to turn into treatments for patients, now that she's on the Farm. Protein research in her group is also directed toward potential applications in neural cell regeneration, vascular tissue engineering, and cancer therapy. "The translational aspects of Stanford make this a great place to do research," she says.