

Fluorescent Peptides Help Nerves Glow in Surgery

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Accidental damage to thin or buried nerves during surgery can have severe consequences, from chronic pain to permanent paralysis. Scientists at the University of California, San Diego School of Medicine may have found a remedy: injectable fluorescent peptides that cause hard-to-see peripheral nerves to glow, alerting surgeons to their location even before the nerves are encountered.

The findings are published in the Feb. 6 advance online edition of the journal *Nature Biotechnology*.

Nerve preservation is important in almost every kind of surgery, but it can be challenging, said Quyen T. Nguyen, MD, PhD, assistant professor of Head and Neck Surgery and the study's corresponding author. "For example, if the nerves are invaded by a tumor. Or, if surgery is required in the setting of trauma or infection, the affected nerves might not look as they normally would, or their location may be distorted."

Nguyen and colleagues at the Moores Cancer Center developed and injected a systemic, fluorescently labeled peptide (a protein fragment consisting of amino acids) into mice. The peptide preferentially binds to peripheral nerve tissue, creating a distinct contrast (up to tenfold) from adjacent non-nerve tissues. The effect occurs within two hours and lasts for six to eight hours, with no observable effect upon the activity of the fluorescent nerves or behavior of the animals.

"Of course, we have yet to test the peptide in patients, but we have shown that the fluorescent probe also labels nerves in human tissue samples," Nguyen said. Interestingly, fluorescence labeling occurs even in nerves that have been damaged or severed, provided they retain a blood supply. The discovery suggests fluorescence labeling might be a useful tool in future surgeries to repair injured nerves.

Currently, the ability to avoid accidental damage to nerves during surgery depends primarily upon the skill of the surgeon, and electromyographic monitoring. This technique employs stimulating electrodes to identify motor nerves, but not sensory nerves such as the neurovascular bundle around the prostate gland, damage of which can lead to urinary incontinence and erectile dysfunction following prostate surgery.

The new study complements earlier work in surgical molecular navigation by Nguyen and Roger Tsien, PhD, Howard Hughes Medical Institute investigator, UCSD professor of pharmacology, chemistry and biochemistry, a co-author of the paper and co-winner of the 2008 Nobel Prize in chemistry for his work on green fluorescent protein. In 2010, for example, the scientists and colleagues published papers describing the use of activated, fluorescent probes to tag cancer cells in mice. The ultimate goal of their work is to help surgeons identify and remove all malignant tissues by lighting up cancer cells, thus reducing the chance of recurrence and improving patient survival rates.

"The analogy I use is that when construction workers are excavating, they need a map showing where the existing underground electrical cables are actually buried, not just old plans of questionable accuracy," said Tsien. "Likewise when surgeons are taking out tumors, they need a live map showing where the nerves are actually located, not just a static diagram of where they usually lie in the average patient."

The researchers continue to refine their probes in animal models and prepare for eventual human clinical trials.

Co-authors of the paper include Michael A. Whitney and Beth Friedman, Department of Pharmacology, UCSD; Jessica L. Crisp, Department of Chemistry and Biochemistry, UCSD; Linda T. Nguyen, Division of Otolaryngology-Head and Neck Surgery, UCSD; Larry A. Gross and Paul Steinbach, Howard Hughes Medical Institute, UCSD. These studies were supported by funding from the Howard Hughes Medical Institute, the Burrough-Wellcome Fund and grants from the National Institutes of Health (Awards #5K08EB008122 and #NS27177). Quyen Nguyen, Michael Whitney and Roger Tsien are inventors of a technology that has been licensed by the University to Avelas Biosciences and has an equity interest in the company. The terms of this arrangement have been reviewed and approved by the University of California, San Diego in accordance with its conflict of interest policies.

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