Editorial

Applications of fluorescent technology in neurosurgery

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Butte and colleagues report their work developing a sensitive camera system for detection of near-infrared (NIR) dyes and successfully demonstrate the ability to use a targeted NIR agent (a tumor-binding peptide, chlorotoxin, conjugated to the NIR contrast agent indocyanine green [ICG]).¹ Their paper presents a newer direction in which fluorescence-guided surgery may well be headed.

Near-infrared technologies have a number of potential strengths that make investigation of their possible clinical utility warranted.⁶ Neurosurgery is not naive to these, with neurosurgeons having already acquired experience with ICG in cerebrovascular applications; even protoporphyrin IX, the fluorophore of interest in 5-aminolevulinic acid (5-ALA) applications, emits a good portion of its fluorescence in the NIR range (although that portion of the spectrum has not been widely used). A third clinically used agent, methylene blue, in addition to its deep blue color, has an NIR emission that has been clinically explored.⁸

The better tissue penetration of the NIR portion compared with that of the visible portion of the spectrum generally utilized in 5-ALA applications renders possible subsurface (perhaps to a number of millimeters) tumor detection. With NIR dye there is also little autofluorescence from nontumor tissue to confound detection. There have been a handful of reports describing the use of ICG in neurosurgical tumor surgery.^{2–4} Our surgical colleagues outside of neurosurgery have a larger experience with using ICG for tumor detection (as well as NIR technology in tumor surgery in general). Clinical trials using ICG in detection of sentinel lymph nodes in surgery of breast, melanoma, head and neck, lung, esophageal, gastric, colorectal, cervical, vulvar, endometrial, and prostate malignancies have all been reported.⁸

Tremendous excitement has developed, however, regarding the use of targeted fluorescent agents—agents that by virtue of binding of a fluorophore to an antibody, peptide, or nanobody can selectively enable detection of specific tissues to a degree nonspecific agents generally do not. The contrast agent used by Butte and col-

leagues—a chlorotoxin-Cy5.5 conjugate—is such a targeted agent. There are many others, several of which are working their way toward clinical use. Conjugated to already available targeted antibodies, these new agents are generating similar excitement. A clinical trial using bevacizumab (targeting vascular endothelial growth factor [VEGF]) conjugated to IRDye 800CW for intraoperative guidance in breast cancer surgery is open and accruing patients (clinical trial no. NCT01508572 [ClinicalTrials.gov]).⁸ Similar targeting of epidermal growth factor receptor (EGFR) is under development. That such targeting could also be used to intraoperatively identify structures or tissue to be preserved has also been appreciated. Clinical use for targeting the ureter, bile duct, and possibly nerve has been envisioned.⁸ Yet another development in NIR contrast technology is that of “activatable” agents—agents that do not fluoresce until they have become activated by a specific molecular target.^{5,8} These agents are currently in preclinical stages of development.

For all its assets, NIR technology also has its limitations, perhaps the largest of which is its operating outside the visible portion of the spectrum. Unlike protoporphyrin IX or fluorescein whose appeal is the easy and intuitive integration into the workflow of the operating room, NIR agents require a technology to detect and display their presence in the surgical field. Indocyanine green-adapted microscopes for cerebrovascular applications require an interface with which neurosurgeons are already familiar. In this regard, Butte and colleagues have contributed to the field with their implementation of an optical system that is sensitive and efficient. They have characterized well its performance in phantom and animal models, demonstrating proof-of-concept and feasibility.¹

Just as with the development of NIR contrast agents, there is also much work in progress in NIR imaging systems. Of course, the NIR portion of the spectrum is subject to the same absorption and scattering phenomena as light in the visible wavelength is, and this can confound signal interpretation. These phenomena hinder quantitative measurements, but the methodologies to enable glean additional information from the fluorophore's presence in the surgical field are similarly under development. Spectrally resolving imaging technologies even enable detection and measurement of multiple fluorophores in the same field.⁹ In such a manner, quantitative assays of a given tissue's features, such as specific receptors, can become a reality.⁷

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