Near-Infrared Contrast Agents for Image-Guided Surgery

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Surgery is one of the main treatments for primary tumors and operations for limb amputation or limb sparing surgery aiming to remove the tumor completely. Presently, however, there isn't a single optical contrast agent that binds to tumors or specific tissues after intravenous injection and highlights its location and quantity. The technique of near-infrared (NIR) fluorescence imaging provides extremely low background since living tissue has minimal absorption and autofluorescence in the NIR range of 700-900 nm. Introducing an exogenous NIR fluorophore can produce a signal adequate for imaging.

NIR fluorescence has the potential to revolutionize image-guided surgery. Especially, the Frangioni's laboratory (BIDMC, Boston, MA) has already developed a surgical imaging system that simultaneously, and in real-time, acquires two independent wavelengths of NIR fluorescence emission images along with color video images. The imaging system has already been translated to the clinic, and is being formally evaluated in clinical trials. Nevertheless, the fundamental limitation to the future success of this technology is the development of NIR fluorophores that perform optimally in the body, and which can be made widely available to other academic researchers.

To be clinically viable, the ideal NIR fluorophore requires certain optical properties, including excitation and emission ≈800 nm, and a high extinction coefficient and quantum yield in serum. However, the reason why existing NIR fluorophores perform so poorly *in vivo* has to do with biodistribution and clearance. After intravenous injection, the ideal NIR fluorophore would rapidly equilibrate between the intravascular and extravascular spaces and would be cleared efficiently via renal filtration. To date, every NIR fluorophore described in the literature suffers from two fundamental flaws: 1) hepatic clearance, which results in NIR fluorescence signal throughout the GI tract that persists for hours, and/or 2) non-specific background uptake in normal tissues, which typically persists for hours and results in a low signal-to-background ratio (SBR).

The goal of this work is to develop a new class of ideal NIR fluorophores that can be injected into the bloodstream. These fluorophores would "stick" to tumors and other diseased tissue, but not to normal tissue. Currently, we are developing on the synthesis of optimized NIR fluorophores for *in vivo* and surgical imaging, on validating their use as targeted diagnostic agents for various diseases including cancer. Completion of these aims will lay the foundation for future clinical testing during image-guided surgery.

CURRICULUM VITAE

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Education

2008-2011	**Ph.D.** in Supramolecular Chemistry Japan Advanced Institute of Science and Technology, Nomi, Japan
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Careers

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2011-2014	**Post-Doctoral Fellow** Department of Medicine, Beth Israel Deaconess Medical Center of Harvard Medical School, Boston, MA, USA
2004-2007	**Research Assistant** Biomaterials & Tissue Engineering Lab, Korea Research Institute of Chemical Technology, Daejeon, Korea

Representative Publications

1. **Hyun H**, Owens EA, Park MH, Wada H, Frangioni JV, Henary M, Choi HS. Cartilage-specific near-infrared fluorophores for biomedical imaging. *Angew Chem Int Ed.* **2015**; in press.
2. **Hyun H (co-1st)**, Park MH, Owens EA, Wada H, Henary M, Handgraaf HJM, Vahrmeijer AL, Frangioni JV, Choi HS. Structure-inherent targeting of near-infrared fluorophores for parathyroid and thyroid gland imaging. *Nat Med.* **2015**; 21, 192-197.
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7. **Hyun H (co-1st)**, Ashitate Y, Kim SH, Lee JH, Henary M, Frangioni JV, Choi HS. Simultaneous mapping of pan and sentinel lymph nodes for real-time image-guided surgery. *Theranostics* **2014**; 4(7):693-700.
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