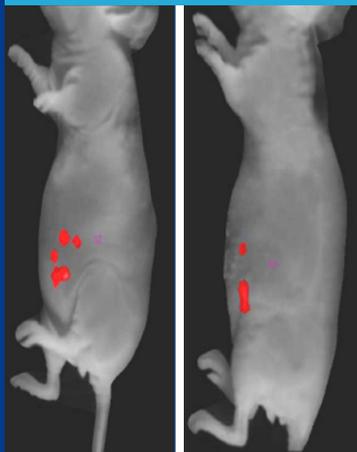


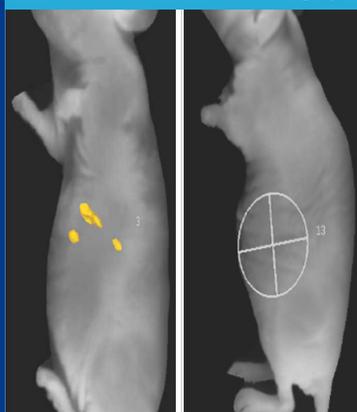
Monoacylated TLR2 Ligand Fluorescent Probe for Detection and Tumor Removal in Pancreatic Cancer Patients

Pre-surgery: 24 h Post-surgery 48 h

Standard Surgery



Fluorescent TRL2L-Guided Surgery



A monoacylated Toll-like Receptor (TLR2) ligand demonstrated significantly improved binding affinity and decreased agonistic activity in cancer cells over its diacylated predecessor. The diacylated TLR2 ligand had been previously shown to selectively target cancerous pancreatic tissue through binding with nanomolar affinity to TLR2, which is overexpressed in 70% of tumors, but minimally expressed in normal pancreas. The diacylated compound was conjugated to a near infrared fluorescent dye that could be used for more effective detection and tumor removal in pancreatic cancer patients. Preclinical murine studies with this diacylated fluorescent probe had been previously shown to significantly improve the removal of cancer cells from the pancreas.

COMMERCIAL OPPORTUNITY

- In 2015, an estimated 48,000 US cases of pancreatic cancer will be diagnosed and the current 5-year survival is less than 6%. Currently, only early treatment with complete surgical removal of the tumor (resection) is considered potentially curative by NCCN Guidelines, which is available to about 9,000 patients per year.
- An estimated 6,000 pancreatic cancer cases per year have high expression of TLR2. A fluorescent dye-conjugated TLR2 probe can be used to guide surgeons to simultaneously resect the tumor and find small local or regional nodal metastases missed by a CT scan, reducing the need for and costs of more complex and follow-up surgeries. This may help offset the high costs (\$32,000-\$94,000) associated with complex procedures, such as the Whipple procedure.
- The improved monoacylated TLR2 ligand has a more than four fold greater binding affinity for the receptor and is half as potent in activating downstream signaling from TLR than its diacylated predecessor.
- This probe could also be used as a diagnostic by conjugation with radiolabels for non-invasive PET detection and mapping of lymph node metastases to diagnose and stage patients with TLR2-positive pancreatic cancer.

TECHNOLOGY

A monoacylated Toll-like receptor 2 (TLR2) ligand, Compound 14, was synthesized based on a previously published diacylated TLR2 ligand. This monoacylated TLR2 ligand binds TLR2 with higher affinity ($K_i = 22\text{nM}$) when compared to its diacylated predecessor ($K_i = 91\text{ nM}$), as determined by a fluorescence competition binding assay in the pancreatic cancer cell line SU.86.86. The bioactivity of the monoacylated compound ($EC_{50} = 674\text{ nM}$) was determined to have significantly reduced agonistic activity ($p < 0.0001$) in an NF- κ B induction assay as compared to the diacylated counterpart ($EC_{50} = 20\text{ nM}$). An additional monoacylated compound conjugated at the N-terminus to the infrared dye 780 (IRDye780) was synthesized through Suzuki coupling. A pre-clinical efficacy study showed that all the mice whose tumors were removed using diacylated TLR2L-800 fluorescence-guidance ($n=5$) had no remaining cancer cells in the pancreas when compared to a control group of mice whose tumors were removed using standard non-guided surgeries ($n=3$) where all of the mice had remaining cancer cells in the pancreas ($p=0.018$) (see Figure above).

PUBLICATION/PATENT

- A. Huynh et al. (2012) *J. Med Chem.* (under review)
- Provisional patent application was filed on 3/26/15 for Dr. David Morse.

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LICENSING OPPORTUNITY

