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Undergraduate

Rare Earth Nanoprobes in Revolutionizing Breast Cancer Surgery

BY: SANIA MOGHE

Breast cancer is the world's most common cancer, with over 300,000 new cases diagnosed yearly in the United States alone. For localized, or non-metastasized, cancer, tumor removal surgery is the most widespread treatment method for breast cancer. However, due to non-optimal cancer visualization techniques during surgery, the re-excision rates for breast cancer (the need for a second surgery) are around 20-30%.¹ Re-excision is not only invasive and costly, but increases patient anxiety, affects cosmetic results, and opens doors for wound infection.² That being said, it is imperative for the healthcare industry to make strides in reducing these overall re-excision rates. This goal is materializing through the use of near infrared technology, which allows for more concrete cancer visualization.

THE UNMET NEED

During the early stages of breast cancer, cancerous cells conglomerate into a tumor within breast tissues. While performing breast cancer surgery, surgeons map out a resection margin that demarcates the tumor from healthy tissue.³ Surgeons then cut the tumor out using the resection margin as a guide. In order to create the most accurate resection margin, surgeons adhere to minute visual cues to identify differences between cancerous and healthy regions. These differences could be chemical or physiological and include variations in color, bleeding patterns, cell

density, and calcium deposition.²

A major problem, however, is that surgeons are often left to their professional judgment and the naked eye to find the tumor's edges. If the tumor margin is especially ambiguous, then surgeons may accidentally leave cancerous cells and cell conglomerates behind. As Dr. Daniel Orringer, a surgeon at the University of Michigan, claims, "in a lot of cases, we leave tumors behind that could be safely removed if only we were able to better visualize it."⁴ Lingering cancer cells can continue to divide and risk the formation of new tumors post-operation, contributing to high re-excision rates.

New and effective ways of visualizing cancerous cells during surgery can prevent cancerous cells from lingering post-op and decrease re-excision rates. Through the use of near infrared (NIR) light beams, surgeons have the ability to view cancerous cells in real-time during operation and remove them accordingly, thus eliminating the need for external pathology reviews or underestimating resection margins. One of these specific NIR visualization tools involves the creation of lab-made crystalline molecules known as rare-earth nanoprobes.

HOW THE PROBES EMIT LIGHT

Rare-earth nanoprobes are tiny, lab-made vessels composed primarily of rare earth elements, such as ytterbium, erbium, holmium, thulium, and praseodymium. These

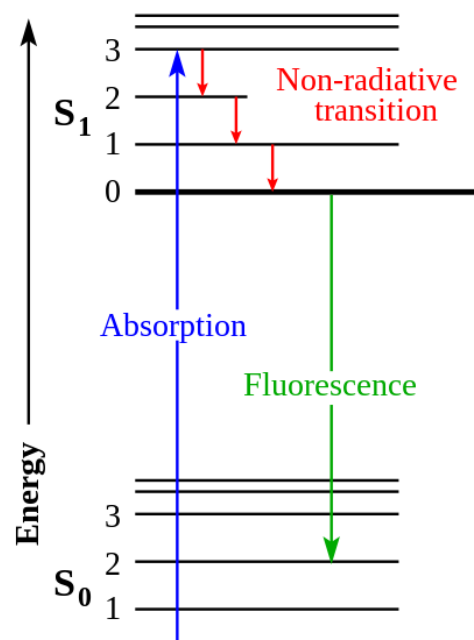


Figure #1: This image represents how electrons jump and fall from different energy sublevels (represented by the bars) during excitation and relaxation. At first, when the electrons are bombarded with energy, they jump up to higher energy sublevels (blue). Almost instantaneously, these electrons fall back down to a lower orbital sublevel to achieve stability. When the electrons fall down to specific orbital levels, they release energy in the form of short wave infrared fluorescence (green).

atoms are collectively known as lanthanides, and possess important visual properties.⁵ When exposed to a specific form of near-

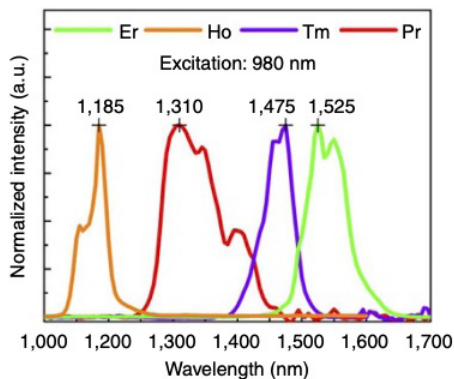


Figure #2: This graph shows the specific emission wavelengths of the different rare earth elements after being excited by near infrared light. When electrons fall to a lower orbital level, they will emit the above wavelengths. The variations in wavelength of emitted light correspond to variations in fluorescence color.

infrared light (NIR), with a wavelength of 980 nm, rare earth elements fluoresce bright colors. How does this fluorescence work? In the atomic model, negatively charged electrons are constantly moving around the atom's positively charged nucleus in orbitals of varying densities and locations. When exposed to an energy source like NIR light, the electrons of rare earth elements gain energy and jump to a higher energy orbital, thus overcoming nuclear attractive forces. The process of energy absorption is known as electron excitation. However, given that lower energy states are more thermodynamically stable, electrons eventually fall back to a lower energy sublevel, releasing energy as they return to their original state.⁶ While some of this emitted energy is dissipated within the environment, the rest of it is released in the form of short-wave infrared light waves (SWIR). Due to SWIR's high reflectivity and penetrability, humans can easily perceive SWIR emanating from the probes in the form of brightly colored fluorescence while wearing infrared goggles.

BIOCOMPATIBILITY AND CANCER DETECTION

Typically, rare earth nanoparticles are rejected by the human body because they cannot be naturally metabolized. However, albumin, a liver protein that assists in moving small molecules through blood, has the ability to make these nanocrystals biocompatible. Once encompassed within an albumin membrane, the human body can easily intake and transport these probes without flagging

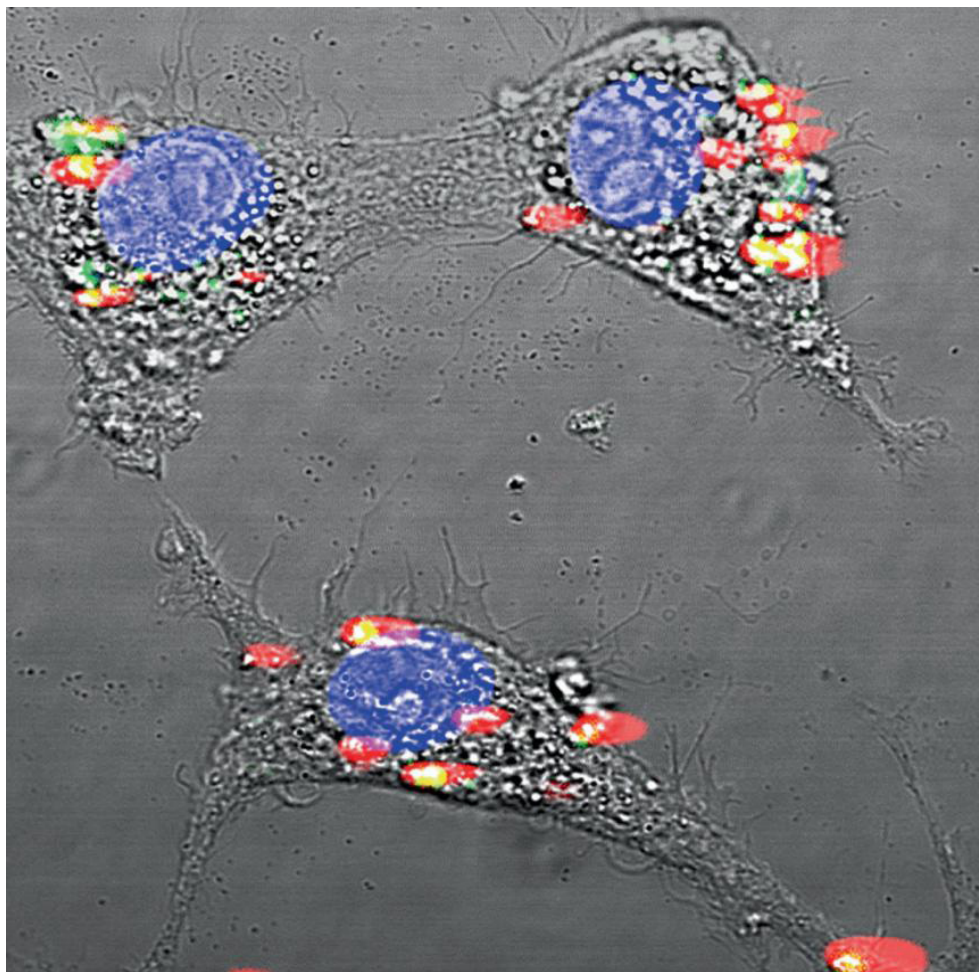


Figure #3: These are photos of the albumin-engulfed nanoprobe under the presence of near infrared light. The different color fluorescence represents the different rare earth elements within the probe emitting different wavelengths of short wave infrared light.

them as foreign molecules.

Proteins like albumin are composed of amino acids which possess specific chemical groups, called functional groups. The functional groups are composed of different atoms and charges and have the ability to bind to other molecules, such as a cancer antibody. Antibodies are small proteins that attach to receptors on threat-posing substances—in this case, harmful cancer cells. Many cancer antibodies are known by scientists and can be commercially purchased or produced in a lab. Through capitalizing on the bonding affinity between functional groups, the albumin-bound rare earth nanoparticles can be bonded to these antibodies before injection into the body. These nanoprobe-antibody conjugates will then be transported throughout the human body and bond to only cancerous cells where they can fluoresce under NIR exposure.

POTENTIAL IMPLICATIONS

Once an incision is made in the breast

during breast cancer surgery, surgeons can inject nanoparticles directly into the tumor so that they can bond to cancer cells and pre-metastatic lesions along the resection margin within a few minutes. After shining a NIR beam over the surgical site, surgeons will be able to identify all of the fluorescing cancer cells under a screening device and easily remove them, thus greatly reducing the need for re-excision. Following surgery, nanoparticles will leave the body naturally within two days in the form of excretion.

FUTURE USES

Within smaller mammals, such as mice, rare-earth nanoparticles can also be used as a general pre-emptive cancer detection device. Rather than resorting to invasive biopsies or expensive MRI scans, the nanoparticles can be injected intravenously into the mouse and travel around the body while attaching to undetected cancer cells. Given that each rare earth element emits a different wavelength

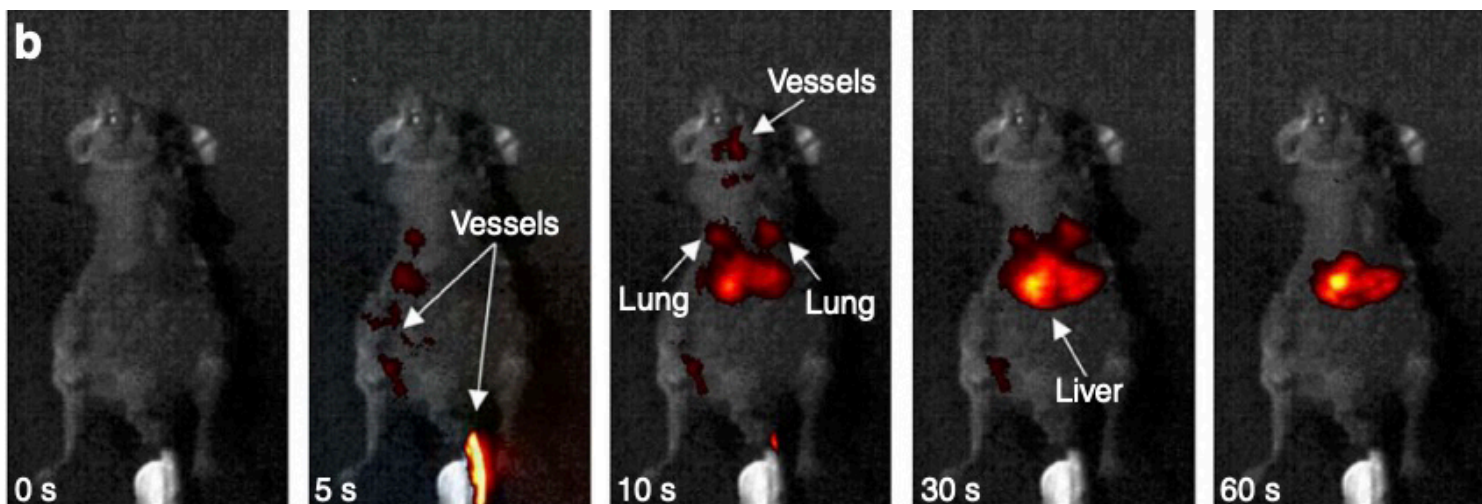


Figure #4: The lab photos above were taken under exposure to near infrared light and reveal the nanoprobes fluorescing various cancer tissues in the liver, lungs, and blood vessels of a mouse specimen. Thus, the rare earth nanoprobes enhance visualization of cancerous regions by emitting easily perceptible short wave infrared light.

of SWIR, and thus a slightly different color after exposure to NIR, these nanoprobes can be “programmed” to glow a distinct color when attached to a specific cancer, whether breast cancer, melanoma, or leukemia. This means that preemptive cancer detection could potentially happen in one sweep. However, since humans are much larger in size and more anatomically complex than mice, further research is needed to see if rare earth nanoprobes could provide efficient and accurate means of multi-faceted cancer detection in humans.

CONCLUSION

It is widely known that the most proactive way to treat cancer is to detect it early. In terms of breast cancer, the five year-relative survival rate for Stages 0-1 is almost 100%, whereas the survival rate for Stage 4 is less than 28%.⁷ To prevent late-stage progression, it is imperative that cancer cells are thoroughly removed during the first surgery and are not left to linger and divide further. Through the use of near infrared technology, visualization devices like rare earth nanoprobes have the ability to assist in the complete removal of cancer cells, thus increasing relative survival rates and revolutionizing the field of cancer altogether.

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