PHARMACEUTICAL SCIENCE

Innovations in Precision Oncology: The Technical Contributions of Aaron M. Mohs, PhD to Bioimaging and Nanomedicine

Published: November 12, 2025 | Index ID: #611

The landscape of modern oncology is undergoing a radical transformation, shifting from generalized therapeutic interventions toward highly localized, precision-based surgical and pharmacological strategies. At the forefront of this evolution is the integration of **nanotechnology** with **biomedical imaging**. One of the primary figures contributing to this interdisciplinary field is **Dr. Aaron M. Mohs**, an Associate Professor and Associate Dean for Research and Graduate Studies at the **University of Nebraska Medical Center (UNMC)**. Dr. Mohs' work focuses on the development of novel imaging contrast agents and optical instrumentation designed specifically for the **image-guided surgical removal of tumors**. This technical analysis explores the foundational chemistry, the engineering of fluorescent conjugates, and the clinical implications of the research conducted within the Mohs Lab.

The Academic and Professional Foundation of Dr. Aaron M. Mohs

To understand the technical complexity of Dr. Mohs' current research, it is essential to examine the academic trajectory that informed his expertise in **pharmaceutical chemistry** and **biomedical engineering**. Dr. Mohs earned his Bachelor of Arts in Chemistry from St. John's University/College of St. Benedict in 2002. His formative doctoral training was completed at the University of Utah under the mentorship of Dr. Zheng-Rong Lu, where he focused on the development of **biodegradable gadolinium (III)-based blood-pool contrast agents**for Magnetic Resonance Imaging (MRI).

Following his Ph.D., Dr. Mohs pursued a postdoctoral fellowship at the joint **Emory University–Georgia Institute of Technology** Department of Biomedical Engineering. Working under Dr. Shuming Nie, a pioneer in the application of nanotechnology to bioimaging, Mohs specialized in the development of **near-infrared (NIR) fluorescent nanoparticles**. This period was critical in bridging the gap between polymer chemistry and real-time intraoperative imaging, setting the stage for his current roles at the UNMC College of Pharmacy and the **Fred and Pamela Buffett Cancer Center**.

Theoretical Framework: Near-Infrared (NIR) Fluorescence in Oncology

The primary challenge in surgical oncology is the clear differentiation between malignant tissue and healthy surrounding parenchyma. Standard white-light surgery relies on the surgeon's visual and tactile perception, which often fails to detect **micro-metastases** or deep-seated tumor margins. Dr. Mohs' research addresses this via **Near-Infrared (NIR) Fluorescence**.

Physics of the NIR Window

The biological "optical window" exists in the NIR spectrum, typically between **700 nm and 900 nm**. In this range, the absorption and scattering of light by water, hemoglobin, and lipids are at their lowest. This allows for:

- Increased Tissue Penetration: NIR light can penetrate several centimeters into tissue, compared to only millimeters for visible light.
- Reduced Autofluorescence: Biological tissues naturally fluoresce under UV or visible light, creating

background noise. NIR light minimizes this interference, resulting in a significantly higher Signal-to-Background Ratio (SBR).

The Concept of Signal-to-Background Ratio (SBR)

The efficacy of an imaging agent is mathematically defined by the SBR formula:

SBR = (I_tumor - I_background) / <5öæö—6P

Where *I_tumor* is the intensity of the signal from the cancerous site, *I_background* is the signal from the surrounding healthy tissue, and <*5öæö~~+~~ep*6P represents the standard deviation of the background signal. Dr. Mohs' research into **hyaluronic acid conjugates** is specifically designed to maximize *I_tumor* while minimizing *I_background* through selective molecular targeting.

Technical Synthesis: Hyaluronic Acid (HA) Nanoparticles

A core pillar of the Mohs Lab's research is the development of **Hyaluronic Acid (HA) conjugates**. Hyaluronic acid is a naturally occurring glycosaminoglycan with a high affinity for the **CD44 receptor**, which is frequently overexpressed on the surface of various cancer cells, including those found in breast, lung, and head and neck cancers.

Chemical Engineering of HA-Dye Conjugates

The synthesis of these agents involves the covalent attachment of a NIR fluorophore (such as Indocyanine Green derivatives or cyanine dyes) to the HA polymer backbone. This process requires precise control over the **Degree of Substitution (DS)**. If the DS is too low, the signal is insufficient for detection. If it is too high, **fluorescence quenching**(the Forster Resonance Energy Transfer or FRET between adjacent fluorophores) occurs, rendering the agent invisible.

The "tuned" nature of these conjugates refers to the optimization of the polymer molecular weight and the linker chemistry to ensure that the nanoparticle remains stable in the bloodstream but becomes highly fluorescent upon reaching the tumor microenvironment or being internalized by the cell.

Pharmacokinetics and Biodistribution

The behavior of HA-based nanoparticles in a biological system is governed by several factors:

1. Enhanced Permeability and Retention (EPR) Effect: Small nanoparticles (typically 20-200 nm) can leak through the disorganized vasculature of tumors but are too large to escape healthy blood vessels.
2. Active Targeting: The specific binding of HA to CD44 receptors facilitates receptor-mediated endocytosis, concentrating the imaging agent within the tumor cell.
3. Renal vs. Hepatic Clearance: The molecular weight of the HA carrier determines whether the agent is cleared through the kidneys (low MW) or processed by the liver (high MW).

Comparison of Bioimaging Modalities in Surgical Settings

To contextualize the importance of Dr. Mohs' work, it is necessary to compare Optical Imaging (the focus of his lab) with other established modalities used in oncology.

Feature	Magnetic Resonance Imaging (MRI)	Positron Emission Tomography (PET)	NIR Optical Imaging (Mohs Research)
Resolution	High (Sub-millimeter)	Low (4-10 mm)	High (Micrometer scale)
Real-time Utility	Limited (requires shielding)	None (static scans)	Excellent (Intraoperative)
Sensitivity	Low (Molar range)	High (Picomolar range)	High (Nanomolar range)
Ionizing Radiation	No	Yes	No
Primary Application	Pre-operative Planning	Staging/Metastasis detection	Tumor Margin Resection

Image-Guided Surgery (IGS) Workflow

The practical application of Dr. Mohs' research manifests in the **Image-Guided Surgery (IGS)**workflow. This procedural execution is designed to assist surgeons in identifying "the edge" of a tumor in real-time. The workflow generally follows these steps:

1. Pre-operative Contrast Administration

The patient is injected with the HA-NIR conjugate. The timing of this injection is critical; it must allow for sufficient accumulation in the tumor via the EPR effect and active targeting, while allowing enough time for the "washout" of the agent from the vascular system to reduce background noise.

2. Intraoperative Visualization

During the surgical procedure, the surgical field is illuminated with a specific laser or LED light source tuned to the excitation wavelength of the fluorophore. A specialized NIR-sensitive camera captures the emitted light, which is then processed and overlaid onto a standard white-light video feed.

3. Precision Resection

The surgeon uses the real-time fluorescence map to guide the scalpel. Areas that exhibit high fluorescence intensity indicate the presence of tumor cells. This allows for the removal of **positive margins**that would otherwise be invisible to the naked eye. Conversely, it helps preserve vital healthy structures (nerves, blood vessels) that do not show fluorescence.

4. Ex Vivo Verification

Once the tumor is removed, the specimen can be scanned again to ensure the margins are "clean." If fluorescence is detected at the edge of the removed tissue, it suggests that cancerous cells may still remain in the patient, prompting further exploration.

Technical Challenges and Engineering Solutions

Despite the promise of NIR-guided surgery, several technical hurdles exist that the Mohs Lab and the wider research community are actively addressing.

Quenching and Aggregation

Fluorescent dyes often aggregate when conjugated to polymers, leading to a loss of signal. This is known as

aggregation-caused quenching (ACQ). Dr. Mohs' work involves the use of **Aggregation-Induced Emission (AIE)** luminogens or the implementation of specific chemical spacers that maintain distance between dye molecules on the HA backbone, ensuring high quantum yields.

Instrumentation Sensitivity

Optical imaging requires highly sensitive detectors. The **Complementary Metal-Oxide-Semiconductor (CMOS)** sensors or **Charge-Coupled Device (CCD)**cameras used in the operating room must be capable of filtering out ambient room light while capturing low-intensity NIR photons. The Mohs group collaborates on the development of optical instrumentation that can handle these dynamic ranges.

Regulatory and Toxicological Barriers

Moving a new nanoparticle from the bench to the bedside requires rigorous **toxicological profiling**. Because HA is endogenous, it is generally considered safe. However, the synthetic linkers and the fluorophores must be evaluated for long-term toxicity, clearance rates, and potential immunogenicity. Dr. Mohs' background in pharmaceutics is vital here for navigating the FDA's **Investigational New Drug (IND)** application process.

The Role of Gadolinium-Based Blood-Pool Agents

While much of the recent focus is on fluorescence, Dr. Mohs' earlier work with **Gadolinium (III)** remains foundational to the field of **multimodal imaging**. Blood-pool contrast agents differ from standard extracellular fluid (ECF) agents because they remain in the vasculature for an extended period. This is particularly useful for:

- Angiography: Visualizing tumor vascularization in high detail.
- Permeability Mapping: Quantifying the leakiness of tumor vessels to predict how well chemotherapy might penetrate a specific lesion.
- Hybrid Imaging: Developing agents that are both paramagnetic (for MRI) and fluorescent (for surgery), allowing for the same molecule to be used from diagnosis through resection.

Research Environment: The Fred and Pamela Buffett Cancer Center

The efficacy of Dr. Mohs' research is amplified by his position within the **Fred and Pamela Buffett Cancer Center** and **UNMC**. This environment allows for a bench-to-bedside approach. As the Associate Dean for Research, Dr. Mohs oversees the integration of basic pharmaceutical science with clinical oncology. This collaborative ecosystem is essential for conducting **translational research**, where findings in a lab environment are tested in animal models (such as transgenic mouse models of cancer) and eventually moved into human clinical trials.

Interdisciplinary Collaboration

The Mohs Lab members often come from diverse backgrounds, including:

- Medicinal Chemists: Who focus on the synthesis of new fluorophores and ligand-attachment strategies.
- Biomedical Engineers: Who design the imaging systems and data processing algorithms.
- Cancer Biologists: Who study the CD44 expression patterns and the molecular mechanisms of nanoparticle uptake.
- Clinicians: Who provide feedback on the surgical utility and ergonomic requirements of the imaging systems.

Practical Implementation: A Field Guide for Researchers

For researchers looking to implement similar nanoparticle-based imaging strategies, the following technical checklist is derived from the methodologies practiced by leaders in the field like Dr. Mohs:

1. Ligand Selection: Identify a receptor (e.g., CD44, EGFR, HER2) that is uniquely overexpressed in the target tissue.
2. Carrier Optimization: Choose a biocompatible polymer (e.g., Hyaluronic acid, PEG, Chitosan). Consider the molecular weight's impact on half-life.
3. Fluorophore Integration: Select a dye with an excitation/emission profile in the NIR-I (700-900nm) or NIR-II (1000-1700nm) window.
4. Characterization: Use Dynamic Light Scattering (DLS) to measure hydrodynamic diameter and Zeta Potential to assess surface charge.
5. In Vitro Validation: Perform cell uptake studies using flow cytometry and confocal microscopy to confirm receptor-mediated entry.
6. In Vivo Modeling: Utilize orthotopic tumor models to simulate the actual anatomical location of the cancer, as this affects the optical depth and background interference.

Troubleshooting Failure Modes in Optical Imaging

In the development of imaging agents, several operational challenges frequently arise. Below are common failure modes and their technical solutions.

Problem: High Background Signal in the Liver

Cause: Nanoparticles are too hydrophobic or too large, leading to sequestration by the **Reticuloendothelial System (RES)**.

Solution: Increase the **PEGylation** density to provide a "stealth" effect, or reduce the molecular weight of the HA carrier to shift clearance toward the renal pathway.

Problem: Rapid Photobleaching

Cause: The fluorophore degrades under the intense excitation light of the surgical laser.

Solution: Utilize more photostable dyes like **phthalocyanines** or encapsulate the dye within a protective silica or lipid shell.

Problem: False Positives in Inflammation

Cause: The EPR effect is not specific to cancer; inflamed tissues also have leaky vasculature.

Solution: Enhance the **Active Targeting** component. Instead of relying on passive accumulation, ensure the agent requires a specific enzymatic cleavage (e.g., by matrix metalloproteinases) before it becomes fluorescent.

Synthesizing the Future of Bioimaging

The work of Dr. Aaron M. Mohs represents a critical bridge between the theoretical potential of nanotechnology and the practical needs of the surgical suite. By leveraging the biological properties of hyaluronic acid and the physics of the near-infrared spectrum, his research is paving the way for a future where surgeons no longer have to "fly blind." The development of tuned, targeted, and highly sensitive contrast agents ensures that tumor margins are identified with unprecedented precision, ultimately leading to lower recurrence rates and improved patient outcomes.

As the pharmaceutical sciences continue to evolve, the integration of **artificial intelligence (AI)** with intraoperative imaging—to automatically highlight suspicious tissues—and the development of **theranostics** (agents that both image and treat) will likely be the next frontiers. With leaders like Dr. Mohs guiding both the research and the academic development of the next generation of scientists at UNMC, the transition toward truly personalized

surgical oncology is well within reach. The ongoing commitment to technical rigor, interdisciplinary collaboration, and clinical relevance remains the hallmark of this significant body of work.

Baca Juga (Artikel Terkait)

- **The Comprehensive Guide to Biosimilars and Interchangeable Biologics: Strategic and Tactical Frameworks for Modern Healthcare**
  URL: http://alghafgolden.com/biosimilars-and-interchangeable-biologics-strategic-tactical-guide.pdf
- **The Comprehensive Technical Guide to Pharmaceutical Pharmacology and Medication Management**
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