How Imaging Can Drive More *Effective Combination Immunotherapy* in Oncology

Immunotherapy has revolutionized cancer treatment.

It offers hope for patients with various malignancies. But the complexity of tumor microenvironments and the variability in patient responses necessitate more personalized approaches than what statistical analysis provides alone.

Imaging, particularly CD8 imaging, has emerged as a powerful tool that can help researchers and clinicians optimize dosage, improve sequencing and improve overall survival in oncology. This white paper explores how imaging can drive more effective combination immunotherapy in oncology.

The role of CD8 imaging in cancer therapy

To create truly personalized medicine in oncology, you need statistically proven tools that work on the individuals in question. Critical PET imaging such as CD8 can provide researchers with the insights needed to move from precision medicine to personalized medicine.

About CD8

CD8+ T Cells (CD8 for short) are called by some the "foot soldiers of the immune system." CD8 stands for cluster of differentiation 8 and is a membrane glycoprotein that serves crucial functions in immune response, notably in the body's natural immune response to cancer.

CD8 cells interact with both the T-cell receptor (TCR) and MHC class I proteins presented by antigen presenting cells (APCs) that can appear from viruses or tumors. This leads to the expansion and differentiation into cytotoxic effector cells that help clear the body of infection while aiming to minimize damage to other tissue.

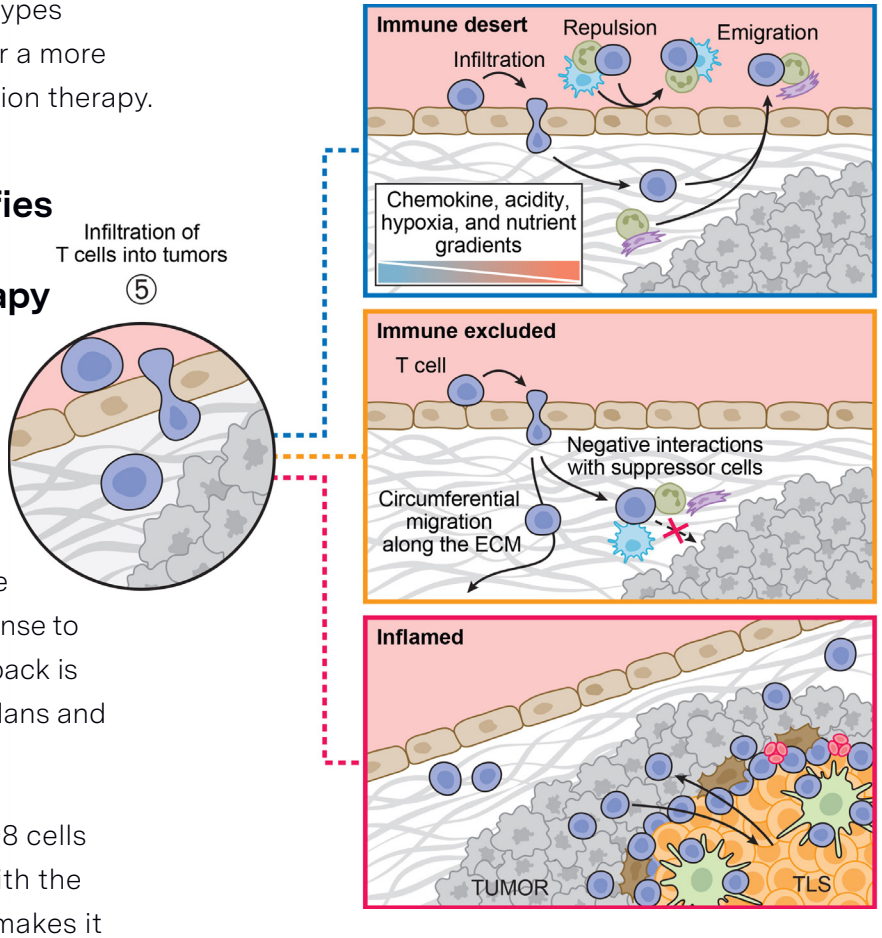
Because tumors exhibit significant heterogeneity, both within a single tumor and between different tumors, traditional biopsy methods provide limited information and often miss the broader context of the tumor microenvironment. CD8 imaging offers a comprehensive view, revealing the distribution and activity of cytotoxic T cells within tumors. And interrogating specific immunotypes identified by CD8 imaging allows for a more personalized approach to combination therapy.

How CD8 imaging identifies immunotype to inform combination immunotherapy

CD8 imaging serves as a pharmacodynamic readout, allowing clinicians to monitor the infiltration and activity of cytotoxic T cells (also known as a killer T cell, which are the cells actually doing the damage to a virus or tumor) in response to immunotherapy. This real-time feedback is invaluable for adjusting treatment plans and improving outcomes.

That's because the presence of CD8 cells coincides about 90% of the time with the presence of cytotoxic T cells. This makes it a nearly universal biomarker for efficacy in cancer treatment.

Thus, with CD8 PET whole-body imaging, researchers can identify intertumoral and intratumoral heterogeneity, develop combination cancer immunotherapies adapted to the tumor microenvironment and determine the immune response to checkpoint inhibitors.



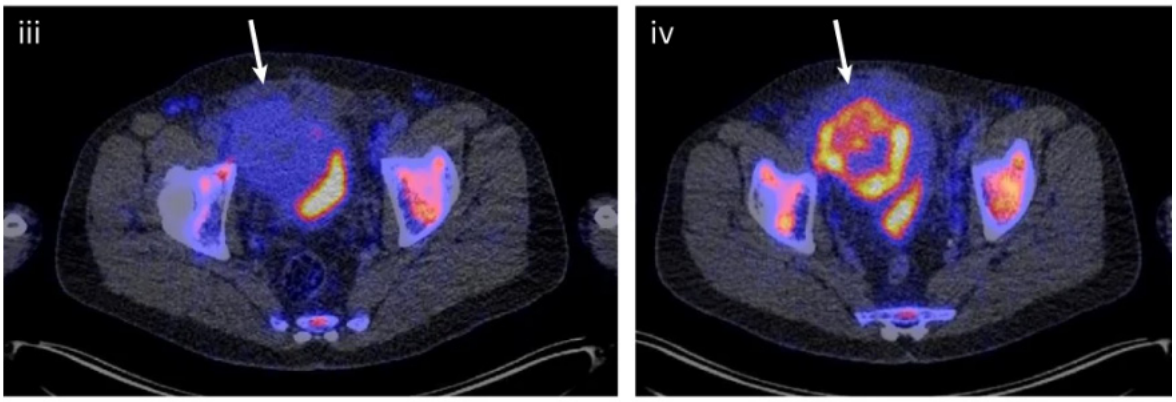
[Source: https://www.cell.com/immunity/fulltext/S1074-7613(23)00416-8]

Flywheel

Pervesical dMMR urothelial cell cancer lesion

Baseline, Pretreatment

On-treatment



Caption: In this image, the presence of CD8 cells in the thyroid can help researchers and clinicians optimize dosage, compare how different cohorts react to treatments, and prioritize tumor types, indications and immunotherapy combinations.

About Checkpoint Inhibitors

Checkpoint inhibitors are a type of immunotherapy that help the immune system fight cancer. Normally, immune checkpoints act as brakes, preventing T cells from becoming too aggressive and attacking healthy cells. Cancer cells can exploit this by producing proteins that engage with checkpoint proteins on T cells, sending an "off" signal that weakens the immune response. Checkpoint inhibitors block this interaction, allowing T cells to recognize and destroy cancer cells more effectively.

Several checkpoint inhibitors target specific proteins like CTLA-4, PD-1 or PD-L1. Tumors, such as those in lung, skin and kidney cancers, often produce excess PD-L1 to suppress T cells. By inhibiting these proteins, these drugs re-energize the immune system's ability to fight cancer, providing an effective treatment for many cancer types, including breast, bladder and colon cancers.

By visualizing CD8 cells, clinicians can tailor existing therapies such as chemotherapy, radiation therapy and checkpoint inhibitors. For instance, understanding the presence and activity of CD8 cells can help optimize the dosage of chemotherapy and radiation, minimizing toxicity while maximizing therapeutic benefits.

This kind of personalized cancer care assumes that combination therapy is essential to overcoming resistance to treatment and improving outcomes. Because tumors are adaptive and genetically unstable, they can easily evade many monotherapies, although there are some populations that will respond well to monotherapies.

The concept of personalized care also assumes currently available drugs can be optimized, including chemotherapy and radiotherapy. Chemotherapies are generally approved on maximum tolerated dose (MTD) based on dose-limiting toxicities (DLT), although the FDA has said it would begin requiring pharmaceutical companies to test different doses.

Similarly, in radiation therapy, ablating a tumor can actually kill CD8 cells along with the tumor, which is not ideal for maximizing immune response. Thus, personalized care using CD8 as the biomarker can help optimize chemotherapy and radiation therapy in order to maximize immunogenic cell death and improve outcomes while minimizing adverse side effects.

How using CD8 imaging as a biomarker for immune response works in practice

In practice, this workflow starts by capturing a baseline scan to see what the tumors in question look like and how much CD8 cells have infiltrated the body, based on the combination of therapies used. Within 30 days, you can take new scans and based on those findings, take chemotherapy and radiotherapy MTD and dial it back to a dosage that maintains CD8 infiltration and its associated level of immunogenic cell death while reducing the incidence of toxicity and adverse events.

Within six months, you compare new scans with reduced dosages to control groups with MTD to see how CD8 infiltration has changed, therefore determining if this reduced dosage is just as effective.

Based on these findings, combining various combinations of therapies and dosages amid new patient cohorts is key to finding the right balance of immunotherapy, chemotherapy and radiotherapy that maximizes patient outcomes for specific tumor types.

Challenges and opportunities

Despite this progress in combination therapy, challenges remain in maximizing efficiency, standardizing imaging criteria and integrating imaging data into clinical workflows. Currently, tinkering with therapies to find the most effective combinations involves many people doing many hours of work, impeding the time to market for new combination therapies.

Advances in imaging technologies and data analysis are crucial for overcoming these hurdles and fully realizing the potential of combination immunotherapy. An imaging data platform can help researchers find and manage separate patient cohorts within their data so they can develop adaptive clinical trials, testing novel immunotherapy combinations with decisions guided by CD8 imaging and diagnostic tools.

For example, researchers could find patients who have never had a checkpoint inhibitor and offer it to them, a strong motivation for enrollment. For patients that respond to the inhibitor alone, they can stay on it, while for the remaining patients (which would make up about 70% of enrollees), CD8 imaging can help inform tumor biopsies and testing various combinations of therapies.

Artificial intelligence (AI) has emerged as one way to advance this process more efficiently, complementing the important work done by researchers. This allows them to use algorithms to review more scans, more quickly, and gauge the effectiveness of various combination therapies than could be accomplished in the same time by researchers alone.

How Flywheel can help

Flywheel, a leading medical imaging data management platform, can play a pivotal role in advancing imaging-driven immunotherapy. By leveraging Flywheel's capabilities, researchers and clinicians can better grasp all of the imaging available to them and efficiently analyze it to design clinical trials, develop AI and accelerate innovation.

Streamline imaging data management

Flywheel's platform facilitates the organization, storage and sharing of imaging data, ensuring that critical information is readily accessible for analysis and decision-making. It allows for rapid data capture with connectors for PACS, RIS, raw data and file systems; offers support for various imaging modalities including CT, MRI, PET, X-ray, ultrasound and more; and the ability to pull in additional datasets with Flywheel Exchange.

Maintain compliance and security

Flywheel offers a validated version of its Core product to help organizations achieve 21 CFR Part 11 compliance for FDA submission. This

enables reproducibility of projects, including versions, inputs, status and outputs, and provides the audit trails, digital signatures and approval workflows needed to ensure tracking and authorization.

Integrate AI and machine learning

Flywheel's integration with AI and machine learning technologies can automate the interpretation of complex imaging data, reducing the burden on clinicians and improving the precision of treatment plans. Flywheel Gears offer data pre-processing workflows and AI-powered analytic pipelines to expand the bandwidth and capabilities of oncology researchers, with the ability to create custom Gears or utilize ready-to-use applications from the Flywheel Gear Exchange.

In addition, Flywheel offers:

- A robust, built-in radiology-grade viewer
- Streamlined annotation and tumor segmentation
- Blinded reader workflows and task management
- Customizable de-identification
- Support for multimodal data
- Extensible design, with open architecture for access by any platform

Getting started with Flywheel

Imaging data holds immense potential in driving the success of combination immunotherapy in oncology. By providing detailed insights into tumor microenvironments and treatment responses, imaging enables more personalized and effective cancer therapies. Platforms like Flywheel are instrumental in harnessing the power of imaging, facilitating data management, analysis and collaboration to drive development of the next lifesaving treatments in cancer care.

Read more about Flywheel's ***capabilities for oncology researchers****.*
Get in touch *to get started with Flywheel.*

Sources

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