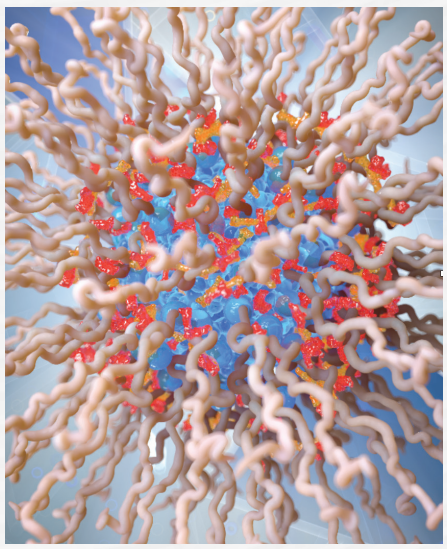
Fresh Faces Blazing a New Trail in Oncology with Intriguing Soft Tissue Sarcoma Clinical Data

A new kid on the block flips the script using a systems biology-inspired tissue-specific approach against metastatic cancer that normalizes the tumor microenvironment.

CANCER IS A SYSTEMIC DISEASE. Tumors take advantage of evolutionarily conserved biological processes to sustain their growth. Low oxygen and high acidity in tumor microenvironments activate a multitude of kinases, leading to the induction of key transcriptional regulators NF-kB, STAT3, and others. These transcriptional regulators, in turn, activate the production of thousands of inflammatory cytokines that propagate throughout the tumor microenvironment, sending inflammatory signals even to distantly located cells in the bone marrow.

"A single transcriptional factor expressed in tumors such as NF-kB or STAT3 activates thousands of genes which promote cancer survival and treatment resistance," said Ilya Rachman, co-founder and CEO of IMMiX Biopharma. "How can we arm ourselves with an equally dynamic toolkit to combat such a system?"



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ImmixBio's multi-action IMX-110 is comprised of a poly-kinase inhibitor complex and apoptosis inducer coupled with a negatively charged lipid.

Building on Nobel Prize winner David Baltimore's discoveries on the importance of activated NF-kB causing inflammation in cancer and promoting tumor survival, Rachman zeroed in on this link between oncology and inflammation. Cancer by definition frequently grows, outpacing its blood supply. The lack of oxygen-carrying blood (causing hypoxia) and the resultant acidic environment (acidosis) promotes inflammation. This inflammation, in turn, drives cancer survival and treatment resistance.

Rachman formed a team and founded Immix Biopharma, Inc. (ImmixBio), which engineered a tissue-specific approach to treat cancer by targeting this vicious inflammatory cycle driving cancer. They called their technology tumor microenvironment (TME) normalization because it normalized the hyper-inflammatory state of the tumor microenvironment.

Disrupting the system

Three broad cell types comprise the tumor microenvironment: fibroblasts, which provide structural and metabolic support, immune cells such as macrophages, and malignant cells. Each cell type detects and responds to changes in oxygen and acidity within the tumor microenvironment. Often, scientists only target one of these cell types to destroy cancer.

In contrast, ImmixBio's TME normalization technology targets all three cell types simultaneously. By using a broad-acting poly-kinase inhibitor, ImmixBio's therapies stop the cells from detecting changes in oxygen and acidity in the tumor microenvironment.

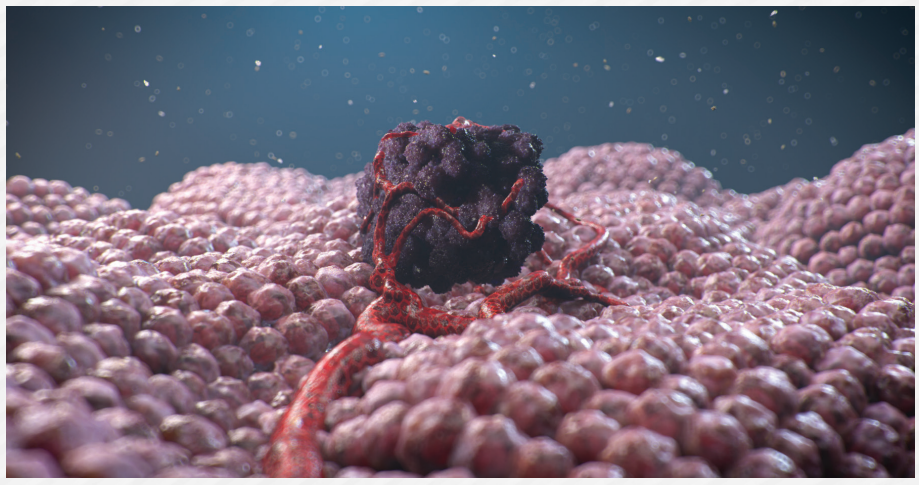
Isolating the tumor microenvironment and stopping the spread of inflammation is not enough to stop cancer. This required Rachman to pair his therapeutic with an apoptosis inducer that selectively targets and kills cancer cells.

"Therapies that we use today — any cytotoxic therapy — while killing cancer cell clones also induces defense mechanisms in surviving clones. That underlies the emergence of resistance or relapses, which we typically observe months after the initial therapy, especially in advanced forms of metastatic solid tumors," said Rachman.

Rachman's combination of a poly-kinase inhibitor and an apoptosis inducer guards against the emergence of resistance by ensuring that changes in the microenvironment caused by cell death and treatment are not recognized by other cells. If other cells cannot recognize these signals, then they cannot activate cascades of cytokine-induced defense mechanisms such as inflammation. "It's a one-two punch, but before we punch, we disable or weaken our opponent," said Rachman.

He combined both the poly-kinase inhibitor complex and apoptosis inducer with a negatively charged lipid. Once inside the body, the negatively charged lipid is drawn toward the positively charged tumor microenvironment, where it fuses with cell membranes and releases both the poly-kinase inhibitor and apoptosis inducer.

"The biggest challenge was to demonstrate with irrefutable initial proof of concept, that this idea, this approach, has a viable path forward. It has a basis for further investigation," said Rachman.



IMX-110 simultaneously prevents the spread of inflammation signals in the tumor microenvironment and targets cancer cells for destruction in a systems level approach to cancer death.

A measurable difference

"It sounds simple enough, but to accomplish anything of significance, it takes a team, a strategy. I knew I needed the best team on the planet to convert this vision into an executable reality," said Rachman.

With his co-founder Vladimir Torchilin, a professor at Northeastern University, former head of Chemistry at Massachusetts General Hospital/Harvard Medical School, Rachman recruited leading researchers across pharmacology, oncology, systems biology, drug discovery, financing, and business.

"After I saw what was behind the curtain, I absolutely decided that I must join," said Gabriel Morris, the chief financial officer of ImmixBio and a former executive at Goldman Sachs with a history of balancing financial risks to achieve clinical goals. "I could see how the technology could address the Achilles heel of resistance to current therapies in oncology and other areas."

Together Rachman, Torchilin, Morris, and their team of experts explored the utility of their TME technology as a treatment for soft tissue sarcoma (STS). Treating STS is particularly difficult, largely because STS cancers present as a diverse group of tumors.

"As we were working towards understanding the safety profile, possible adverse events, as well as the appropriate dose that will be taken to phase two, we had to start with patients who already had very few options available to them and had failed the approved standards of care," said Rachman.

The ImmixBio team tailored their multi-action therapeutic to include a form of doxorubicin, an apoptosis inducer commonly used as a first line of treatment for STS. They called their therapy IMX-110.

In STS, IMX-110 produced median progression-free survival of 4 months, a striking improvement from the 2.6 months or 1.7 months seen with other drugs presently on the market. Approximately 50% of patients achieved 6-month radiological progression-free survival with zero interruptions in therapy due to toxicity or severe adverse events. The therapy even shrunk the tumor of one STS patient for whom 13 different treatments had previously failed.

"As the clinical results have unfolded, seeing people's eyes light up and get super excited about what the potential is here, has been just an incredible, phenomenal journey to be on," said Morris. Now, Rachman and Morris have plans to also test IMX-110 as a first line therapy for STS.

The success of ImmixBio's multi-action therapeutic and TME normalization technology is not limited to STS. The system is modular. Researchers can use different apoptosis inducers that are effective for other cancer types.

TME normalization also allows scientists to target diseases caused by overactive immune cells. In these cases, they remove the apoptosis inducer and pair the poly-kinase complex with a disease-targeting antibody. Using this approach, Rachman and his team developed two new treatments for colorectal cancer and ulcerative colitis/severe Crohn's disease that are on track to receive clinical trial approval.

"The entire journey of seeing your thought experiment play out in reality, and being able to benefit a single human being is an incredible opportunity for which I'm immensely thankful," said Rachman. "The vast amount of scientific literature, our own amassed data with respect to safety, efficacy, and clinical benefit, is making me cautiously optimistic that incredible progress is just around the corner."

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