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EMERGING COMPANY PROFILE | REPRINT FROM JUL. 10, 2024

Mestag: Attacking tumors from within

BY RICHARD GUY, BIOPHARMA ANALYST

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Immunology company Mestag believes that fibroblasts have been long overlooked as therapeutic targets and can be leveraged to treat cancer and inflammatory diseases. The company has raised $45 million and presented data for its lead program to treat solid tumors at AACR.

CEO Susan Hill told BioCentury that Cambridge, U.K.-basaed Mestag Therapeutics Ltd. was founded by a group of five scientists who had identified a distinct subpopulation of fibroblasts capable of inducing the formation of tertiary lymphoid structures (TLSs) — vascularized hubs of lymphocyte interaction and activation that arise from interactions between activated T and B cells and cytokines CCL19, CCL21 and CXCL13.

"They're like a SWAT team of the immune system," she said. "These structures form in a site of infection, they fight the infection, and then they disappear again when their job is done. That biology is quite well characterized. You also see it sometimes in inflammatory disease as well."

Hill said Mestag sees a role for TLSs in cancer based in part on their association with improved patient outcomes and response to checkpoint inhibitors — results that have since been reproduced across 9,000 patients with at least 12 different solid tumor types.

"TLSs are aggregates of immune cells that function like a germinal center in a lymph node," she said. "They're really important for educating immune effector cells to see tumor antigens."

Mestag's lead program is M300, a first-in-class bispecific that conditionally agonizes LTBR on fibroblast reticular cells. It's a pathway that Hill said is associated with formation of TLSs outside of tumors and in the lymph nodes.

"We know that TLSs rely on this pathway for their formation," she added. "Animals lacking lymphotoxin beta don't form lymph nodes or TLSs."

To ensure that the TLSs are induced in tumors, Mestag engineered M300 to agonize LTBR only upon co-engagement with FAP, a tumor microenvironment-specific marker expressed by cancer associated fibroblasts.

"We use FAP as a means of ensuring that it's conditionally active in the tumor. The FAP targets the bispecific into the tumor microenvironment, and it also helps to activate the LTBR pathway," she said.

She continued that a benefit of this approach is that it places antitumor B and T cells within the tumor.

"You're educating the immune system to see the tumor in the tumor," she said, continuing that a major drawback of other

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immunotherapeutic approaches is that the B and T cells are educated in lymph nodes located outside the tumor, to which they have to return to have an antitumor effect.

"Normally, when immune cells are educated to see tumor antigens, they have to exit the tumor to the draining lymph nodes. They get educated in the lymph node tissue, then lymphocytes that can see the tumor have to find their way back into the tumor. That's why there is an access problem, in part because they have to exit the tumor and then find their way back into the tumor to have an antitumor effect."

She added: "This is an entirely new mechanism in the treatment of solid tumors."

The company presented preclinical data for M300 at this year's American Association for Cancer Research (AACR) meeting that demonstrated the bispecific's efficacy as a monotherapy and in combination with a checkpoint inhibitor or tumor peptide antigen.

The company hopes to be in the clinic with M300 by early 2026 to treat solid tumors including Ras-positive lung cancer.

"The tumor types that we're thinking about going into are tumor types where we can take biopsy tissues before and after treatment," she said. "We want to look at TLS induction in the tumor."

The company is also considering advancing M300 as part of a combination with a radiotherapy, immunogenic chemotherapy, cancer vaccine or antibody-drug conjugate (ADC), all of which, Hill said, could improve the bispecific's efficacy by releasing antigens in the tumor microenvironment.

Mestag's second program is M402, a mAb to treat inflammatory diseases by dampening macrophage activation mediated by the immune complexes that form when auto-antibodies bind auto-antigens.

"We're focusing in on immune cell subsets that are not addressable with the current clinical programs," she said. "The targets that we're working on are modulated by fibroblast biology. They're influenced by the local fibroblasts in the disease environment and enable us to target these different immune cell subsets that the PD-1 agonists and the BTLA agonists can't reach."

Mestag has not disclosed M402's target, a stromal checkpoint, although Hill did say it is expressed on monocytes and dendritic cells and not on populations of B or T cells pursued by modalities targeting PD-1 or CTLA.

"We're looking at agonizing inhibitory receptors that will then dampen down immune cell subsets," said Hill, comparing the program to M300. "Here we're looking at how fibroblasts are influencing immune effector cells, but this time, rather than promoting activation of immune cells, we're dampening down the activation of immune cells and inflammatory disease."

> **"YOU'RE EDUCATING THE IMMUNE SYSTEM TO SEE THE TUMOR IN THE TUMOR."**
>
> **SUSAN HILL, MESTAG**

She continued, "We know that many of the substrates that fibroblasts produce influence some of these receptors. None of the existing approaches in these sorts of indications are really aimed at that biology and in many of the autoimmune inflammatory disease spaces there are upper thresholds of response."

One such disease is rheumatoid arthritis. "It's tempting to believe that there are mechanisms in the disease environment that are fibroblast-driven and putting an upper limit on some of these response rates. If we can figure that out, we might be able to enable a much broader proportion of patients to respond to some of the existing therapies and also develop new ones which are much more effective."

Mestag, which hopes to take M402 into the clinic shortly after M300, also has a platform that combines activated fibroblasts, human disease tissue and immune cells to discover therapeutic targets in fibroblasts using genetic knockouts. The platform, which is partnered with Johnson & Johnson (NYSE:JNJ) under a 2021 deal, is based on work by the company's academic founders — Brigham and Women's Hospital's Michael Brenner, the University of Oxford's Chris Buckley and Mark Coles, Harvard Medical School's Soumya Raychaudhuri, and Cold Spring Harbor Laboratory's David Tuveson — who developed methods to stably maintain the phenotype of activated fibroblast populations.

"Using the CRISPR based knockout screening, we're able to identify the targets that have a relevant impact in our disease model," Robert de Jonge, SVP, head of corporate development, told BioCentury. "We also spend a lot of time making sure that we're looking at the right endpoints by doing, for example, single-cell RNA sequencing with also proteomics in the assays and making sure that we overlay that with patient relevant datasets."

Inflammatory diseases of interest to Mestag in the context of its platform include inflammatory bowel disease and rhemuatoid arthritis — the company is studying the impact of fibroblasts on barrier integrity in both.

Other companies working with fibroblasts include FibroBiologics Inc. (NASDAQ:FBLG), which is developing

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them to treat degenerative disc disease and multiple sclerosis, and for diabetic wound care. However, in contrast to Mestag, FibroBiologics is using fibroblasts to create cell-based therapies that can be administered topically or by injection, and not to manipulate the immune system.

Mestag launched in April 2021 with $11 million in seed funding from founding investors SV Health Investors and Johnson & Johnson Innovation – JJDC. This seed round was extended to $45 million the following August. Forbion led the extension, with participation from GV and Northpond Ventures, and both founding investors.

COMPANY PROFILE

Mestag Therapeutics Ltd.

Cambridge, U.K.

Technology: Targeting fibroblasts to treat diseases of the immune system and cancer

Origin of technology: Brigham and Women's Hospital, Cold Spring Harbor Laboratory, Harvard Medical School, University of Oxford

Disease focus: Cancer, autoimmune, inflammation

Clinical status: Preclinical

Founded: 2020 by Michael Brenner, Chris Buckley, Mark Coles, Soumya Raychaudhuri and David Tuveson

Academic collaborators: Cold Spring Harbor Laboratory, Harvard Medical School, University of Oxford

Corporate partners: Johnson & Johnson

Number of employees: 35

Funds raised: $45 million

Investors: Forbion, GV, Johnson & Johnson Innovation – JJDC Inc., Northpond Ventures and SV Health Investors

CEO: Susan Hill

Issued Patents: None issued

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