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JULY 11, 2019

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"BRIDGING THE UNDERSTANDING OF FIBROSIS AND ONCOLOGY, AND HOW THAT MOLDS THE TUMOR MICROENVIRONMENT, IS A MAJOR FOCUS."

JOANNE HULME, NORTHERN BIOLOGICS

TARGETS & MECHANISMS

The tumor stroma rises as the newest source of immuno-oncology targets

BY LAUREN MARTZ, ASSOCIATE EDITOR

With a spate of therapies entering the clinic, the next frontier in the fight against resistance to checkpoint inhibitors will be the stroma. The lead target marks a resurgence of interest in TGFβ, and behind it companies are interrogating a series of other mechanisms to uncover how stroma locks immune cells out of tumors.

At least seven therapeutic agents inhibiting TGFβ have started early stage combination trials with checkpoint inhibitors, and an eighth is slated to enter the clinic next year (see Table: "TGFβ Checkpoint Combination Trials").

In addition, at least two companies gearing up for the clinic this year are targeting other stromal proteins, and a third plans to disclose a first-in-class stromal target in early fall. Wnt pathway modulators in checkpoint combo trials may also affect the tissue compartment.

The stroma is a collagen- and elastin-rich matrix of connective tissue surrounding tumors. As an anatomical structure, the tumor stroma has been recognized for more than 60 years, but investigators are only now beginning to understand its function in cancer immunity.

The field's focus has largely been on cancer cells and immune cells, and the first priority for building on the success of PD-1 and PD-L1 therapies has been to test them in combination with other agents that target immune cells, or with approved chemotherapies. But disappointing readouts from several early checkpoint combination trials has turned the

spotlight to resistance mechanisms, which investigators hope will yield better targets.

With increasing attention on the immunosuppressive tumor microenvironment as a major driver of resistance, and characterizations of "hot" and "cold" tumors depending on the level of immune cell infiltration, researchers have found a midway point in a stroma-driven resistance phenotype — dubbed immune exclusion — in which immune effector cells surround the tumor but are unable to enter it.

The phenotype has benefits over fully cold tumors which lack no immune cells in or around them. In cases of immune exclusion, there are inroads for therapeutic intervention; the challenge is breaking down the barriers that keep the immune cells out.

The growing focus on the stroma has ignited a wave of interest in TGFβ, an old target now assigned a new role in immunosuppression. TGFβ is associated with immune excluded phenotypes and is secreted by cancer-associated fibroblasts — key components of the tumor stroma.

"In human cancers showing the immune exclusion phenotype, TGFβ1 is driving that immune exclusion. It's pretty clear this is the driving molecule," said Alan Buckler, CSO of Scholar Rock Holding Corp., which has a preclinical program targeting the TGFβ1 precursor.

While the target has not historically yielded much success, companies with TGFβ inhibitors are confident they have found ways around the

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toxicity issues of past programs, and they aren't worried that some TGFβ inhibitors haven't shown single-agent activity in preclinical models.

"The absence of single-agent activity is neither a surprise nor a requirement, and we feel many combinations tried in recent months or years didn't have the same depth of scientific rationale. It was a bit more throwing spaghetti against the wall," Nagesh Mahanthappa, CEO and president of Scholar Rock, told BioCentury.

As these clinical trials ramp up, investigators continue to unravel the mechanisms by which the stromal compartment excludes T cells from tumors. Doing so could lead to new and better therapeutic targets, though translating them will require overcoming the poorly representative preclinical models.

Another look at TGFβ

The concept of targeting immune exclusion gained steam last February when a pair of studies pinned down TGFβ as a key driver of the mechanism.

Companies have been trying to tease out the complicated roles of TGFβ in cancer for many years, but the growth factor's wide-reaching physiological functions and toxicity have been fundamental challenges. The two *Nature* papers, combined with new ways of drugging the protein, are creating a path forward.

"We believe there is also a role for activated stroma and related cell types, and are actively studying both the immune and stromal cellular players in this space," she said.

A separate team from the Institute for Research in Biomedicine found similar results in mouse models of colorectal cancer in the second *Nature* study. Mice with immune excluded colorectal cancers were resistant to PD-1 and PD-L1 inhibition, and the TGFβ inhibitor galunisertib (LY2157299) from Eli Lilly and Co. increased sensitivity to checkpoint blockade (see "TGFB Inhibition Could Treat Checkpoint Inhibitor-Resistant Cancer").

"These publications in the TGFβ space have increased interest in mechanisms of fibrosis for immuno-oncology, and how the stromal microenvironment is playing a critical role in influencing the ability of certain cancers to respond to checkpoints," said Joanne Hulme, VP and head of research at cancer company Northern Biologics Inc.

TGFβ deal flow

A pair of deals this year threw additional weight behind the mechanism of TGFβ in checkpoint blockade resistance.

Merck & Co. Inc.'s takeout of Tilos Therapeutics Inc. for up to $773 million, announced in June, is sign of renewed interest in TGFβ, said Hulme (see "Tilos Takeout Sees Merck Tapping TGFβ").

"WE THINK IT'S IMPORTANT TO TURN THEM ALL OFF, NOT JUST TGFB."

JOHN BEADLE, PSIOXUS

One of the studies, from Roche's Genentech Inc., unit linked a lack of clinical response to PD-L1 blockade to high levels of TGFβ signaling in tumor fibroblasts. The researchers employed genetic sequencing of biopsies from urothelial cancer patients after treatment with the anti-PD-L1 mAb Tarcentriq atezolizumab, and demonstrated high TGFβ signaling occurred in immune-excluded tumors.

Mice treated with a combination of antibodies blocking TGFβ and PD-L1 had more T cell penetration and tumor regression than mice treated with either agent alone.

Genentech hasn't disclosed a clinical trial combining TGFβ and checkpoint inhibition, but Shannon Turley, staff scientist in cancer immunology, told BioCentury the company is "focused on better understanding the biology of TGFβ signaling as it relates to the immune-excluded tumor phenotype."

The acquisition followed a February deal in which GlaxoSmithKline plc paid Merck KGaA €300 million ($336.93 million) to license M7824, a first-in-class bispecific fusion protein against PD-L1 and TGFβ that is in several Phase I and II cancer trials (see "Merck KGaA's Large-Scale Partnering").

Tilos is developing inhibitors of TGFβ LAP, a precursor to TGFβ. The LAP peptide is cleaved from TGFβ to activate the protein. The idea is that targeting the precursor will avoid the safety and selectivity problems that have dogged inhibitors of the active protein.

According to Scholar Rock's Mahanthappa, the biggest challenge in targeting TGFβ has been isoform selectivity. While selective blockade of TGFβ1 stimulates anti-tumor immunity, cross-reactivity with the other isoforms can cause severe cardiovascular toxicity, a problem that has killed programs in the past.

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Antibodies don't distinguish well between mature TGFβ isoforms, but the precursor forms of the proteins are sufficiently different.

The other benefit of going after the proprotein, said Mahanthappa, is that the active protein is short-lived. "Instead of chasing after a ghost with a half-life of two minutes, we can make antibodies to the precursor that jam the lock and prevent activation in the first place."

Still, Mahanthappa said he's not worried about the fact that some TGFβ inhibitors may lack single-agent activity. Last year's meltdown of a PD-1/IDO combination, after IDO failed to show single-agent activity, called into question the idea of paring PD-1 therapy with any compound that isn't effective on its own (see "Lessons from the ECHO Chamber").

TGFβ-checkpoint combination trials

Since a pair of studies, published just over a year ago, linked transforming growth factor β (TGFβ) to checkpoint inhibitor resistance due to a failure of immune cells to penetrate tumors, immuno-oncology companies have jumped at the chance to target the heavily-researched fibrotic protein in checkpoint combination trials. At least seven therapies targeting TGFβ signaling are in combination studies with checkpoint inhibitors for cancer, and at least two other companies with preclinical therapies are planning combination studies. Three of those agents — ABBV-151 from **AbbVie Inc.** (NYSE:ABBV), SRK-181 from **Scholar Rock Holding Corp.** (NASDAQ:SRRK) and **Tilos Therapeutics Inc.'s** Anti-LAP antibody — work by targeting TGFβ's latent complex, which may afford greater selectivity and fewer toxicities than mAbs against active TGFβ. While M7824, which was recently licensed to **GlaxoSmithKline plc** (LSE:GSK; NYSE:GSK) from **Merck KGaA** (Xetra:MRK), is not being evaluated with a checkpoint inhibitor, the fuson protein itself combines a checkpoint inhibitor with a TGFβ inhibitor. Scholar Rock Holding Corp. and Tilos Therapeutics have not initiated clinical trials, but each told BioCentury they plan to evaluate the antibodies in combination with checkpoint inhibitors. *Source: Company websites, ClinicalTrials.gov, BCIQ: BioCentury Online Intelligence*

Company	Product	Description	Checkpoint inhibitor (Target; company)	Indication	Phase
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK); **Merck KGaA** (Xetra:MRK)	M7824 (bintrafusp alfa)	Anti-PD-L1/TGFβ fusion protein	None	Non-small cell lung cancer (NSCLC)	Phase II
				HPV-associated cancers	
				Biliary tract cancer	
				Prostate cancer	
Gradalis Inc.	Vigil vaccine (fang vaccine)	Autologous tumor-based vaccine that delivers a gene encoding shRNA against furin paired basic amino acid cleaving enzyme (FURIN) to prevent TGFβ1 and TGFβ2 activation and a gene encoding granulocyte macrophage colony-stimulating factor (GM-CSF; CSF2)	Imfinzi durvalumab (PD-L1; **AstraZeneca plc** (LSE:AZN; NYSE:AZN))	Breast cancer; other solid tumors	Phase II
			Targentriq atezolizumab (PD-L1; **Roche** (SIX:ROG; OTCQX:RHHBY))	Gynecological cancers	Phase II
			Keytruda pembrolizumab (PD-1; **Merck & Co. Inc.** (NYSE:MRK))	Melanoma	Phase I
MedPacto Inc.	Vactosertib (TEW-7197)	Transforming growth factor β receptor 1 (TGFBR1; ALK5) inhibitor	Keytruda	Colorectal cancer; gastric cancer	Phase Ib/IIa
			Imfinzi	NSCLC	Phase Ib/IIa
AbbVie Inc. (NYSE:ABBV); **argenx S.E.** (Euronext:AGNX; NASDAQ:AGNX)	ABBV-151 (ARGX-115)	Leucine-rich repeat containing 32 (LRRC32; GARP)-TGFβ1 antibody	ABBV-181 (PD-1; **AbbVie**)	Solid tumors	Phase I
Eli Lilly & Co. (NYSE:LLY)	LY3200882	TGFβR1 inhibitor	LY3300054 (PD-L1; **Eli Lilly**)	Solid tumors	Phase I
Novartis AG (NYSE:NVS; SWX:NOVN)	NIS793	Anti-TGFβ1 mAb	spartalizumab (PDR001) (PD-1; **Novartis**)	Solid tumors	Phase I
Sanofi (Euronext:SAN; NASDAQ:SNY)	SAR439459	Anti-TGFβ mAb	Libtayo cemiplimab-rwlc (PD-1; **Regeneron Pharmaceuticals Inc.** (NASDAQ:RGEN))	Solid tumors	Phase I
Scholar Rock Holding Corp. (NASDAQ:SRRK)	SRK-181	TGFβ1 antibody	N/A	Solid tumors	Preclinical
Tilos Therapeutics Inc.; Merck & Co. Inc. (NYSE:MRK)	Anti-LAP antibody	Anti-Transforming growth factor β latency-associated peptide (TGFβ LAP) antibody	N/A	Undisclosed	Preclinical

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He said the science behind the synergistic effects of TGFβ and checkpoint inhibitors gives these programs a better shot, even without single-agent activity. "We think the underlying science is so compelling and is rooted in actual clinical insights, and that gives us confidence," he said.

Scholar Rock's trial of SRK-181 is scheduled to begin Phase I testing next year. Tilos hasn't set a clinical start date, but CSO Jessie English told BioCentury combination studies with Merck's PD-1 inhibitor Keytruda pembrolizumab are an obvious path forward.

Two of the seven TGFβ programs in the clinic are in Phase II efficacy studies; neither is a traditional mAb or small molecule. The first readout could come as soon as next year.

Stroma targeting in immuno-oncology

While English and Mahanthappa are confident that TGFβ is a dominant signaling pathway in immune exclusion, three other biotech execs interviewed by BioCentury think hitting that target will only address part of the problem.

PsiOxus Therapeutics Ltd. CEO John Beadle agreed that TGFβ is a key component but noted that cancer-associated fibroblasts use multiple mechanisms to suppress the immune system. "We think it's important to turn them all off, not just TGFβ," he said.

"I think the belief that TGFβ will solve the issue will turn out to be incorrect," he added. "It may be very important, but not be the only mechanism, in the same way PD-1 has proven to be exceptionally interesting and exciting but hasn't solved the problem in the majority of patients."

PsiOxus is taking a multi-pronged gene therapy approach to deplete tumor fibroblasts while triggering T cell activity. The company's adenoviral vector NG-641 carries four genes: an anti-FAP-CD3 bispecific that directs T cells to kill tumor fibroblasts expressing the cell surface glycoprotein FAP; two chemokines — CXCL9 and CXCL10 — that bring T cells into the tumor; and IFNα, the end-product of the STING pathway that activates antigen presenting cells.

PsiOxus plans to begin clinical testing of the gene therapy later this year as a single-agent in a tumor agnostic trial.

Another alternative to TGFβ is the Wnt pathway, which has also been linked to immune exclusion in genetic studies.

The Wnt pathway has also long been linked to cancer but is challenging to target because of its complexity and large number of receptors, said Hulme. Potential therapeutic targets in the Wnt pathway include DKK1, a pathway antagonist, and PORCN, an enzyme that processes Wnt proteins.

Leap Therapeutics Inc. has the DKK1 inhibitor DKN-01 in Phase I/II testing with Keytruda for gastroesophageal cancer. The company is also planning a Phase II trial in combination with Tecentriq for the same indication.

Redx Pharma plc's PORCN inhibitor RXC004 is in Phase I testing with PD-1/PD-L1 inhibitors in colorectal cancer after its Phase I/IIa trial was suspended last year for safety concerns.

"Epithelial-mesenchymal transition can be driven by both Wnt and TGFβ pathways, and the contribution of each pathway may vary across different tumor types," said English.

Northern Biologics is stepping into the immune exclusion arena with a preclinical program against a novel, undisclosed target.

"Bridging the understanding of fibrosis and oncology, and how that shapes the tumor microenvironment, is a key focus of the company going forward," said Hulme.

"We think immune exclusion is an exciting and untapped area in the crowded space of improving responsiveness to checkpoint inhibitors," said Hulme, adding that the company's molecule modulates both T cell exclusion and myeloid suppressive mechanisms.

She said the company expects to disclose its target and additional details of the program by early this fall.

Rather than targeting the stroma directly, Molecular Partners Inc. is hijacking stromal cells to gain access and proximity to the tumor.

"WE BELIEVE THERE IS ALSO A ROLE FOR ACTIVATED STROMA AND RELATED CELL TYPES."

SHANNON TURLEY, GENENTECH

The biotech's MP0310 uses its DARPin technology to combine a localizer that targets FAP on tumor fibroblasts with a 4-1BB T cell stimulator. The company plans to begin clinical testing this year.

Unraveling immune exclusion

All five biotech and pharma representatives agreed that the immuno-oncology field is just beginning to unravel the mechanisms underlying the immune-exclusion phenotype.

The wealth of patient data from the first wave of checkpoint combination studies will undoubtedly help tease out these mechanisms.

"We've seen this enormous global experiment looking at checkpoint inhibitors and combination therapies, and while we haven't seen too many successes, the trials have generated a vast amount of translational data where pre- and post-treatment biopsies show which tumors are and are not responding. I think this will lead to more understanding of what drives resistance, and more success in the next generation," said Beadle.

Molecular Partners COO Michael Stumpp added that greater access to data will trigger progress. "We need to use computer-based data analysis to share and analyze the data across clinical studies. I think we'll be seeing breakthroughs in the next 2-5 years," he told BioCentury.

Sanofi has been using patient biopsy samples from before, during and after treatment with checkpoint inhibitors to develop new therapies targeting resistance mechanisms. The pharma has a TGFβ inhibitor,

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SAR439459, in Phase I testing with Libtayo cemiplimab-rwlc in solid tumors.

"In terms of immune exclusion, there's so much emerging science and we certainly have early programs we're not quite ready to discuss that are focused at other immunosuppressive mechanisms, including immune exclusion," said Dmitri Wiederschain, head of immuno-oncology research at Sanofi.

The pharma expects to report preliminary data from the Phase I combo study in the coming months. It is developing Libtayo with Regeneron Pharmaceuticals Inc.

Increased use of human biopsy samples could help overcome the poorly predictive preclinical models that represent one of the biggest hurdles in immune exclusion.

"IN HUMAN CANCERS SHOWING THE IMMUNE EXCLUSION PHENOTYPE, TGFB1 IS DRIVING THAT IMMUNE EXCLUSION."

ALAN BUCKLER, SCHOLAR ROCK

"Preclinical models are pretty sensitive to checkpoint blockade therapies, but many human patients are not. We've spent time trying to identify preclinical models that better reflect primary resistance," said Buckler.

Immune exclusion mechanisms vary across tumors, with different pathways likely at play in different people's cancers.

Beadle said that the immune exclusion pathways are likely much more complicated than we now appreciate. "I think there is a large number of potential targets. I think the STING pathway may play a role, and the whole arena of macrophage switching is important. I'm not yet convinced there's a standout pathway to address."

Moving beyond checkpoints

English told BioCentury the principal focus will likely remain on immune exclusion in tumors where a large percentage of patients have the phenotype, such as head and neck, microsatellite-stable colon, bladder, non-small cell lung cancer (NSCLC), renal cell carcinoma, triple-negative breast, pancreatic and prostate cancers.

But as the field advances, stroma-targeted therapies may find uses in tumors with dense fibrotic tissue, beyond immuno-oncology applications.

The stroma creates two levels of resistance: a physical barrier and immunosuppressive chemical milieu. Buckler thinks disrupting the former could help get a variety of therapies into tumors.

"The physical barrier is more for large molecules than immune cells. The emerging hypothesis is that immune cells get into the tumor through the vasculature, so there needs to be some form of exclusion that isn't just the physical barrier," said Buckler.

Beadle agreed. "If you can change the architecture of a stromally dense, plastic-type tumor like pancreatic or prostate cancer, you can make it more accessible to other agents like chemotherapies, which could create a response to standard of care."

Hulme added ovarian and breast cancer to the list of tumors "where stroma interplay is known to impact resistance to standard of care therapies."

According to English, TGFβ-blocking therapies may also be useful for enhancing the efficacy of radiation. TGFβ is upregulated during radiation, and is a known resistance mechanism in that context, she said. ◼

COMPANIES AND INSTITUTIONS MENTIONED

Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.

Genentech Inc., South San Francisco, Calif.

GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.

Institute for Research in Biomedicine, Barcelona, Spain

Leap Therapeutics Inc., Cambridge, Mass.

Merck & Co. Inc. (NYSE:MRK), Kenilworth, N.J.

Merck KGaA (Xetra:MRK), Darmstadt, Germany

Molecular Partners AG (SIX:MOLN), Schlieren, Switzerland

Northern Biologics Inc., Toronto, Canada

PsiOxus Therapeutics Ltd., Abingdon, U.K.

Redx Pharma plc (LSE:REDX), Liverpool, U.K.

Regeneron Pharmaceuticals Inc. (NASDAQ:RGEN), Tarrytown, N.Y.

Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland

Scholar Rock Holding Corp. (NASDAQ:SRRK), Cambridge, Mass.

Tilos Therapeutics Inc., Cambridge, Mass.

TARGETS

4-1BB (TNFRSF9; CD137) - Tumor necrosis factor receptor superfamily member 9

CXCL9 (MIG) - Chemokine CXC motif ligand 9

CXCL10 (IP-10) - Chemokine CXC motif ligand 10

DKK1 - Dickkopf homolog 1

FAP - Fibroblast activation protein

IDO (INDO) - Indoleamide 2,3-dioxygenase

IFNα - Interferon α

PD-1 (PDCD1; CD279) - Programmed cell death 1

PD-L1 (B7-H1; CD274) - Programmed cell death 1 ligand 1

PORCN - Porcupine homolog

STING (TMEM173) - Transmembrane protein 173

TGFβ1 - Transforming growth factor β1

TGFβ2 - Transforming growth factor β2

TGFβ LAP - Transforming growth factor latency-associated peptide