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THINKSTOCK

STRATEGY

THE FLIP-SIDE OF IMMUNOTHERAPY

By Lauren Martz, Senior Writer

In the smaller print of last week's deal between [IFM Therapeutics Inc.](#) and [Bristol-Myers Squibb Co.](#) was the latest example of a growing trend of companies aiming to draw extra value out of a cancer target by using its opposite activity to treat autoimmunity.

The deal was noted mostly for its dollar value; BMS acquired two preclinical programs from IFM that stimulate the innate immune system targets [NLRP3](#) and [STING](#) for cancer, for an upfront payment of \$300 million and up to \$1 billion in milestones per program.

But the biotech also spun out IFM Therapeutics LLC to develop the remaining assets, which include a preclinical antagonist of [NLRP3](#) for inflammatory disease and fibrosis. That could lead the company not only into autoimmunity, but to non-alcoholic steatohepatitis (NASH) as well.

NLR proteins detect cellular threats by recognizing pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), and can then change shape to form an inflammasome and trigger inflammatory processes. Other members of the family pursued by IFM include [NLRP1](#), [NLRP3](#), [NLRP6](#), [NLRP10](#) and [NLRC4](#).

According to IFM CEO Gary Glick, the advantage of this target is that it has been researched for both diseases. "What's great about [NLRP3](#) in particular is that the biology of [IL-1](#) and [IL-18](#) produced as a result of activating the inflammasome, in terms of cancer and inflammation, is well known," he said.

[NLRP3](#) is expressed primarily in macrophages, dendritic cells and other immune cells. Agonizing the target activates the inflammasome, triggering T cells to secrete cytokines and ramping up the immune response to kill tumors.

However, in autoimmune diseases where the goal is to dampen excess activity of immune cells, antagonizing [NLRP3](#) prevents T cell activation and inflammation.

"Activating the innate immune system produces the first inflammatory spark that makes the whole system hot. By blocking [NLRP3](#), we're preventing the spark rather than putting out the fire," said Glick.

Such duality is found among scores of proteins, and positions the autoimmune field to benefit from the explosion of interest in immuno-oncology, which has been busy uncovering new targets and validating them as immune mediators. Because the cancer programs can establish target engagement and mechanism, they provide a solid foothold for pursuing the same proteins, with the opposite activity, in autoimmunity.

CHECKING IT TWICE

For checkpoint proteins, which are the most thoroughly interrogated immune targets in oncology, the reverse relationship exists to [NLRP3](#). With checkpoints, the goal in cancer is to develop inhibitors that remove the brakes on anti-tumor immunity, whereas for immune diseases the aim is to activate the proteins and clamp down on overactive immune pathways.

Still, companies using this strategy will have to answer the fundamental question: if blocking checkpoints can treat cancer, does agonizing them increase cancer risk?

While autoimmunity and inflammation are well-characterized liabilities of checkpoint blockers for cancer, it is not yet clear if the reverse is true, nor if it is, how extensive the risks might be.

Preclinical studies have shown links between suppression of T cell immunity and incidence of both cancer and infections. However, RA patients treated with CTLA-4 fusion protein Orenzia have not shown elevated cancer risk compared to the general patient population

At least six checkpoint targets are being investigated for autoimmunity, using a range of antibody and biologic approaches (see “Autoimmune Programs With Checkpoint Targets”).

Through its deal with IFM, BMS gained rights to the two immunology targets for cancer. However, BMS Head of Discovery Carl Decicco told BioCentury the company is also keeping a close eye on IFM’s autoimmune and inflammation programs, to which it has the right of first refusal.

“I’m hoping we will be able to bring those in house to help other parts of our portfolio like fibrosis and immunology,” he said.

BMS is one of at least five pharma that have shown interest in boosting the activity of checkpoint proteins to treat autoimmune diseases. The company already markets one such drug, Orenzia abatacept, to treat rheumatoid arthritis and other inflammatory conditions. Orenzia is a fusion protein consisting of the checkpoint protein CTLA-4 joined to the Fc domain of IgG1 to prolong circulation time.

AUTOIMMUNE PROGRAMS WITH CHECKPOINT TARGETS

While several marketed products inhibit immune checkpoints to treat cancer, biopharmas are developing at least nine programs to agonize or modulate checkpoints to treat autoimmune and inflammatory diseases. (A) Pfizer has an option from the BioRap Technologies Ltd. tech transfer arm of the Rappaport Family Institute for Research in the Biomedical Sciences at the **Technion - Israel Institute of Technology**. Source: BCIQ; Online Intelligence

COMPANY	PRODUCT	INDICATION	CHECKPOINT TARGET	DESCRIPTION	STATUS
AnaptysBio Inc. (NASDAQ:ANAB) / Celgene Corp. (NASDAQ:CELG)	CC-90006	Autoimmune disease	PD-1	PD-1 agonist antibody	Phase I
AstraZeneca plc (LSE:AZN; NYSE:AZN)	MEDI0700	Lupus	ICOSLG (B7-H2; B7RP1) - Inducible T cell co-stimulator ligand	Bispecific mAb targeting BLYS (BAFF) and ICOSLG	Phase I
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK) / Prima BioMed Ltd. (ASX:PRR; NASDAQ:PBMD)	GSK2831781	Psoriasis	LAG3 (CD223) - Lymphocyte-activation gene 3	Humanized antibody-dependent cell-mediated cytotoxicity (ADCC) enhanced mAb targeting LAG3	Phase I
Kymab Group Ltd.	KY1005	Psoriasis	OX40L (CD134L) - OX40 ligand	Anti-OX40 ligand mAb	Phase I
Genexine Inc. (KOSDAQ:095700) / Tasly Pharmaceutical Co. Ltd. (Shanghai:600535)	GX-P2	Psoriasis, inflammatory bowel disease (IBD)	PD-L1	PD-L1 fusion protein	Preclinical
Regen BioPharma Inc. (OTCQB:RGBP)	NR2F6 activator	Rheumatoid arthritis, psoriasis, IBD	NR2F6 (COUP-TFIII) - Nuclear receptor subfamily 2 group F member 6	NR2F6 activator	Preclinical
AnaptysBio Inc. (NASDAQ:ANAB)	Checkpoint agonists	Inflammatory disease	Undisclosed	Undisclosed checkpoint agonists	Preclinical
Eli Lilly & Co. Inc. (NYSE:LLY)	Checkpoint modulators	Lupus, Sjögren's Syndrome, IBD	Undisclosed	Undisclosed checkpoint modulators	Preclinical
Pfizer Inc. (NYSE:PFE) (A)	mAb immunomodulator	IBD, multiple sclerosis	Undisclosed	mAb binding to undisclosed checkpoint molecule	Preclinical

GlaxoSmithKline plc was among the first to disclose interest in checkpoint proteins for autoimmune diseases. In 2010, it licensed the anti-LAG3 mAb IMP731 from cancer play Immutep S.A. Immutep was acquired by Prima Biomed Ltd. in 2014, and the company is pursuing the target for both cancer and autoimmunity, with both blocking and agonistic antibodies.

At least twelve other companies are chasing LAG3 for cancer.

LAG3 has a complex profile. As a checkpoint protein it suppresses cytotoxic T cells. But it has a separate immunostimulatory effect in which it dampens Tregs. The protein is highly expressed on activated memory T cells that contribute to autoimmunity and inflammation.

IMP731 depletes LAG3-positive cells, which can relieve inflammation in pathologic autoimmune conditions. The compound is now in Phase I for psoriasis.

Eli Lilly and Co. has also shown signs of interest in checkpoints for both autoimmunity and cancer.

Last year, it formed a research collaboration with Regen around NRF26. Lilly supplied Regen with 21,000 compounds to screen for agonist and antagonist activity against NR2F6. Deal terms were not disclosed and the companies did not respond in time for publication to inquiries about the status of the partnership.

The pharma also formed a collaboration with Sanford-Burnham Medical Research Institute in 2015 to develop undisclosed checkpoint modulators for immunological and autoimmune disorders.

The poster child of checkpoint targets, PD-1/PD-L1, is also being pursued for autoimmunity. While more than three dozen companies have anti-PD-1 or PD-L1 products for cancer, two programs aim to increase its activity for immune disorders.

Because the cancer programs can establish target engagement and mechanism, they provide a solid foothold for pursuing the same proteins, with the opposite activity, in autoimmunity.

Regen BioPharma Inc. is likewise exploiting both sides of a checkpoint target, using its CheckPoint Immunology Inc. subsidiary formed earlier this year to develop treatments for cancer and autoimmune diseases by targeting NR2F6.

NR2F6 is a transcription factor that acts by transcriptionally repressing IL-17 expression in T cells involved in immune tolerance and autoimmunity. In 2015, researchers at the Medical University of Innsbruck demonstrated that inhibiting NR2F6 could increase tumor infiltration by IL-2- or IFN γ -expressing CD4⁺ or CD8⁺ T cells and decrease tumor growth in mice (see Distillery, Oct. 29, 2015)

Regen developed a high throughput screening program to find activators and inhibitors of NR2F6, and has disclosed three compounds, RG-NA01, RG-NI01 and RG-NI02, for autoimmunity. Through the subsidiary, the company is pursuing rheumatoid arthritis, inflammatory bowel disease and psoriasis with the activators, and bladder cancer, myelodysplastic syndrome and lung cancer with the inhibitors.

AnaptysBio Inc. has a PD-1 agonist antibody in Phase I testing for psoriasis. The compound is part of a larger program to exploit checkpoint targets for autoimmunity, and is partnered with Celgene Corp. who has worldwide commercial rights and is advancing the molecule in the clinic.

Genexine Inc. is also exploiting PD-1 signaling for immune disorders. The company's GX-P2 is a PD-L1 fusion protein that agonizes the PD-1 receptor, in preclinical development for psoriasis and inflammatory bowel disease (IBD).

CELLULAR DOUBLE-DIP

While these programs aim to harness cytotoxic T cells, others are pursuing different immune cell types that can be targeted for autoimmunity as well as cancer.

In 2015, ImCheck Therapeutics S.A.S. was launched to develop therapeutics targeting checkpoint receptors expressed on $\gamma\delta$ T cells, a less common T cell subset that can better penetrate solid tumors than the $\alpha\beta$ T cells targeted by most cancer immunotherapies. The company hasn't disclosed any specific

targets yet, but is pursuing targets on the $\gamma\delta$ T cells for both cancer and other immune-related diseases.

Tizona Therapeutics Inc. is focused on immunosuppressive Treg cells — a cell type involved in maintaining self-tolerance and preventing autoimmunity. With backing from Abingworth, **MPM Capital Inc.**, InterWest and a pair of corporate VCs, Tizona is inhibiting Treg targets including **CCR4** and **IL-35** to relieve immune suppression for cancer, while working on the same targets for autoimmunity.

And as immuno-oncology broadens its repertoire to encompass the innate immune system, autoimmunity stands to benefit from this too.

IFM's NLRP3 is one of at least two innate immune targets being exploited for autoimmunity in addition to cancer.

Last year, **Denceptor Therapeutics Ltd.** was launched to develop innate immune system modulators targeting dendritic cells for both types of diseases. For cancer, the company has agonistic mAbs targeting the **CD40** dendritic cell receptor fused to different cancer antigens to activate cytotoxic T cells. For autoimmune diseases, it is fusing mAbs targeting the **ASGPR** dendritic cell receptor to autoimmune targets to active immunosuppressive T cells.

Glick told BioCentury IFM will continue to work both sides of the line; while it will focus on inflammation and autoimmunity in “the short- and mid-term,” it is also working on oncology applications for targets other than NLRP3. The company expects to move into the clinic with its NLRP3 inhibitor for inflammation and/or immunity in the next 12-18 months.

The newco has no equity financing, and will operate from an option payment from BMS at least at the start, said Glick.

With its acquisition, BMS boosts its already robust immuno-oncology pipeline, adding more innate immunity targets to the predominantly adaptive immune targets it already contains. In addition to NK cell modulators licensed from **Innate Pharma S.A.**, Decicco said BMS is working on toll-like receptor (TLR) targets, although it hasn't disclosed any information on those programs.

The pharma anticipates bringing the acquired STING agonist into the clinic next year, and plans to test the STING and NLRP3 programs in combination with checkpoint inhibitors in the clinic. ■

COMPANIES AND INSTITUTIONS MENTIONED

AnaptysBio Inc. (NASDAQ:ANAB), San Diego, Calif.
Bristol-Myers Squibb Co. (NYSE:BMJ), New York, N.Y.
Celgene Corp. (NASDAQ:CELG), Summit, N.J.
Denceptor Therapeutics Ltd., Cambridge, U.K.
Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
Genexine Inc. (KOSDAQ:095700), Seoul, South Korea
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
IFM Therapeutics Inc., Boston, Mass.
ImCheck Therapeutics S.A.S., Marseille, France
Innate Pharma S.A.(Euronext:IPH), Marseille, France
Prima BioMed Ltd. (ASX:PRR; NASDAQ:PBMD), Sydney, Australia
Regen BioPharma Inc. (OTCQB:RGBP), La Mesa, Calif.
Sanford Burnham Prebys Medical Discovery Institute, La Jolla, Calif.
Tizona Therapeutics Inc., South San Francisco, Calif.

TARGETS

ASGR1 (ASGPR; CLEC4H1) - Asialoglycoprotein receptor 1
CCR4 (CD194) - CC chemokine receptor 4
CTLA-4 (CTLA4; CD152) - cytotoxic T-lymphocyte associated protein 4
IFN γ - Interferon γ
IL-1 - Interleukin-1
IL-2 - Interleukin-2
IL-17 - Interleukin-17
IL-18 - Interleukin-18
IL-35 - Interleukin-35
LAG3 (CD223) - Lymphocyte-activation gene 3
NLR4 - NLR family CARD domain containing 4
NLRP1 (NALP1) - NLR family pyrin domain containing 1
NLRP3 (NALP3; CIAS1) - NLR family pyrin domain containing 3
NLRP6 (NALP6) - NLR family pyrin domain containing 6
NLRP10 (NALP10) - NLR family pyrin domain containing 10
NR2F6 (COUP-TFIII) - Nuclear receptor subfamily 2 group F member 6
PD-1 (PDCD1; CD279) - Programmed cell death 1
PD-L1 (B7-H1; CD274) - Programmed cell death 1 ligand 1
STING (TMEM173) - Transmembrane protein 173

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