Complementing cancer

By Brian Moy, Staff Writer

There are at least 10 compounds targeting different elements of the complement cascade in the biopharma pipeline, ranging from preclinical candidates to marketed drugs for a plethora of diseases, including ophthalmic, cardiovascular, inflammatory and autoimmune indications (see Table 1, “Targeting the complement cascade”). Now, research from a group at the **University of Pennsylvania** suggests that inhibiting the complement component 5a receptor 1 could be useful for treating tumors.¹

Although the finding opens up new therapeutic real estate for complement inhibitors, additional research needs to determine

which types of cancer would benefit from complement component 5a receptor 1 (C5AR1; C5A) inhibition before clinical application of complement-directed cancer therapies can take shape.

In a paper in *Nature Immunology*, the UPenn researchers show that activation of the complement system in a mouse TC-1 tumor model of cervical cancer led to the generation of complement component 5. That, in turn, increased tumor growth by recruiting myeloid-derived suppressor cells (MDSCs).

MDSCs produce large quantities of reactive oxygen species (ROS) and reactive nitrogen species (RNS) that are thought to directly inhibit the antitumor CD8⁺ T cell-dependent immune response.²

In mice with tumor cells, a C5AR1 antagonist slowed tumor growth and increased the CD8⁺ T cell antitumor response compared with what was seen in control mice. The enhanced immune response also was associated with inhibited recruitment of MDSCs and less production of ROS and RNS.

John Lambris, the principal investigator on the study and the Dr. Ralph and Sallie Weaver Professor of Research Medicine at UPenn, told *SciBX* that “the crucial question is why in some tumors does inhibiting inflammation prevent tumor growth, whereas in others it promotes growth? Our findings show that complement,

Table 1. Targeting the complement cascade. At least 10 compounds targeting elements in the complement cascade are in development for a variety of indications.

Company	Product	Description	Indication	Status
Alexion Pharmaceuticals Inc. (NASDAQ:ALXN)	Soliris eculizumab	Humanized mAb against complement component 5 (C5)	Paroxysmal nocturnal hemoglobinuria (PNH)	Marketed in U.S. and Europe
CSL Ltd. (ASX:CSL)	Beriner P C1-INH concentrate	Plasma-derived human complement component 1 esterase (C1 esterase) inhibitor	Hereditary angioedema (HAE)	Marketed in Germany, Austria, Switzerland, Japan and other countries; under review in U.S.
Lev Pharmaceuticals Inc. (OTCBB:LEVP)	Cinryze C1-INH	C1 esterase inhibitor	HAE	FDA approved
Pharming Group N.V. (Euronext:PHARM)	Rhucin C1 inhibitor	Recombinant human C1 esterase inhibitor	HAE	Phase III
Biothera	Imprime PGG	Soluble β-glucan derived from the cell walls of <i>Saccharomyces cerevisiae</i> that targets complement receptor 3 (CR3; CD11b)	Colorectal cancer	Phase I/II
Ophthotech Corp./Archemix Corp.	ARC1905	Aptamer against C5	Age-related macular degeneration (AMD)	Phase I
Potentia Pharmaceuticals Inc.	Compstatin (POT-4)	Synthetic peptide that inhibits complement component 3	AMD	Phase I
Arana Therapeutics Ltd. (ASX:AAH)	PMX53	Oral inhibitor of complement component 5a receptor 1 (CD88)	AMD	Preclinical
Optherion Inc.	Recombinant complement factor H (rhCFH)	Recombinant form of the protective variant of complement factor H (CFH)	AMD	Preclinical
Taligen Therapeutics Inc.	TT30	Fusion protein consisting of a complement receptor 2 fragment linked to a CFH inhibitor	AMD, lupus, rheumatoid arthritis and prevention of graft rejection	Preclinical

one of the key components of inflammation, can promote growth of a specific tumor in a specific environment.”

The university researchers also showed that blocking C5AR1 signaling decreased tumor growth rates with similar efficacy to that of Taxol paclitaxel, which is marketed by **Bristol-Myers Squibb Co.**

“Our findings show that complement, one of the key components of inflammation, can promote growth of a specific tumor in a specific environment.”

—John Lambris,
University of Pennsylvania

Typing class

The authors of the *Nature Immunology* paper wrote that, given the enormous diversity of neoplastic diseases, further studies will be needed to extend the findings to other types of cancer. Lambris and colleagues are tackling that question and are also further dissecting the mechanisms by which inflammation is involved in either inhibiting or promoting tumor cell growth.

Michael Holers, CSO at **Taligen Therapeutics Inc.**, said the major question is how relevant inhibiting complement is to a wide array of tumors. “While the strategy is indeed promising, there needs to be a lot more work to investigate if C5A inhibition is useful for treating other types of cancer. The *Nature Immunology* study only used a single tumor in a single model,” he said.

Taligen is developing TT30, a fusion protein consisting of a complement receptor 2 (CR2) fragment linked to a complement factor H (CFH) inhibitor that blocks the alternative complement pathway. The compound is in preclinical testing to treat age-related macular degeneration (AMD), lupus and rheumatoid arthritis (RA), and to prevent graft rejection.

Paul Olson, CSO at **Potentia Pharmaceuticals Inc.**, noted that “because C5A can recruit myeloid-derived suppressive cells, it is possible that patients with a high density of immunosuppressive cells in their tumors could benefit from treatment with a C5A inhibitor.”

Potentia’s Compstatin (POT-4), a synthetic peptide that inhibits complement component 3, is in Phase I testing to treat AMD.

According to Lambris, human MDSCs have been found in patients with head and neck, non-small cell lung, breast and renal cancer.

Safety first

If the UPenn findings extend to multiple tumor types, the researchers think complement inhibition could provide a less toxic alternative

to chemotherapeutics, as relatively few side effects have been reported with complement-directed therapies.³

The one marketed C5 inhibitor is Soliris eculizumab, an antibody from **Alexion Pharmaceuticals Inc.** that is approved to treat paroxysmal nocturnal hemoglobinuria (PNH), a debilitating genetic disorder characterized by hemolysis, or the chronic destruction of red blood cells. Side effects on the drug’s label include headache, nasopharyngitis and an increased risk of meningococcal infections.

However, Taligen’s Holers noted that “as complement inhibition extends to diseases beyond PNH, it is unclear how the safety profile of such therapeutics that require systemic inhibition for efficacy will play out.”

Steven Karel, COO at **Biothera**, voiced a specific concern with complement inhibition: “Although blocking C5A had a positive anti-tumor effect, it could also block the body’s response to naturally fight off infections,” a process for which C5A is critical.

Biothera’s Imprime PGG, a soluble β -glucan derived from the cell walls of *Saccharomyces cerevisiae*, is in Phase II testing to treat colorectal cancer.

A provisional patent application has been filed by the UPenn researchers for the use of complement inhibitors to treat cancer and the IP is available for licensing.

REFERENCES

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COMPANIES AND INSTITUTIONS MENTIONED

Alexion Pharmaceuticals Inc. (NASDAQ:ALXN), Cheshire, Conn.
Biothera, Eagan, Minn.
Bristol-Myers Squibb Co. (NYSE:BMJ), New York, N.Y.
Potentia Pharmaceuticals Inc., Louisville, Ky.
Taligen Therapeutics Inc., Aurora, Colo.
University of Pennsylvania, Philadelphia, Pa.