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TRANSLATION IN BRIEF

THREE TIMES A CHARM

With this month's deal between [Momenta Pharmaceuticals Inc.](#) (NASDAQ:MNTA) and [CSL Ltd.](#) (ASX:CSL), the partners are hoping to take IVIG therapy for autoimmune diseases to the next level by homing in on the cornerstone of how the therapy works — [Fcγ receptor](#) (FCGR) inhibition. The goal is to define the optimal number and composition of Fc domains required to recapitulate the breadth of IVIG activity, but produce greater potency.

The deal includes Momenta's lead candidate [M230](#), a trimer of Fc proteins that sequesters all members of the FCGR family and prevents their activation by self-injurious autoantibodies. CSL gets worldwide rights to M230 and follow-on compounds, and Momenta gets \$50 million upfront with milestones of up to \$550 million. Momenta is also eligible for mid-single to low-double digit royalties on M230; milestones and royalties for other candidates will be negotiated later.

Momenta SVP of Research Anthony Manning told BioCentury that M230 represents a significant advance on intravenous immunoglobulin (IVIG), which is made by isolating antibodies from the blood of healthy volunteers, but has poorly defined compositions and complex effects in patients.

"I think many of the analysts thought 'oh you're just going to replace IVIG with a recombinant product.' But, we're going to take one of the mechanisms of action of IVIG and make a much more potent and effective molecule," said Manning. He added that the companies plan to test the compound in patients who don't respond to IVIG.

At least five companies market IVIG products, including CSL which has [Privigen](#), and [Johnson & Johnson](#) (NYSE:JNJ), which has [IVIG](#). At least four companies are developing more potent IVIGs, including Momenta's sialylated immunoglobulin (see "[Invigorating IVIG](#)," *BioCentury Innovations* (Oct. 9, 2014)).

Manning said previous attempts to replicate the anti-inflammatory effects of IVIG therapies with Fc proteins gave inconsistent results, as the structural composition of the preparations contained variable numbers of monomers and multimers of different orders.

Momenta has been taking a more systematic approach, he said.

In a paper published in *Science Translational Medicine* in November 2016, Momenta scientists made multimers of defined

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Anthony Manning, Momenta

numbers of Fc proteins and tested them in human immune cell assays to measure inflammatory responses. They found that trimers were more potent than monomers, whereas multimers containing five or more Fc proteins exacerbated symptoms because they activated, rather than inhibited FCGRs.

"Our work suggests you need to cluster at least five receptors before they will create a competent signaling complex," said Manning. "So what the tri mode does is it binds and sequesters groups of three receptors and doesn't allow them to get activated."

The trimers were also easy to assemble from three separate Fc proteins, with two of the proteins containing complimentary "knob and hole" mutations in their CH3 domains that led to efficient dimerization and the third containing electrostatic mutations in the CH3 domain that helped it integrate and make the third arm of a Y-shaped trimer.

In mouse models of rheumatoid arthritis, immune thrombocytopenic purpura (ITP) and the skin blistering disease epidermolysis bullosa acquisita, the team showed the Fc trimer provided significant therapeutic benefit compared with vehicle and was 10- to 40-fold more potent than an IVIG therapy (see *Distillery, Autoimmune Disease*).

Because other immunosuppressive therapies for autoimmunity increase risk of infection, the Momenta team administered the trimer to rodents and monkeys housed under non-sterile conditions. After three months of dosing, the company found no infections in any of the animals, similar to vehicle-treated animals. "We have gone to the maximum feasible dose possible," said Manning. "We were up in the hundreds of milligrams per kilo. I can tell you over the three months we had completely

saturated every Fcγ receptor for twenty four hours every day and to date, the toxicology profile is very, very benign.”

CSL and Momenta plan to initiate a clinical trial for M230 this year.

Several other compounds in development are targeting the Fc fragment of IgG receptor transporter α (FCRN; FCGRT), including Momenta’s anti-FCRN antibody, M281, which is in Phase I for unspecified autoimmune diseases (see “Gobbling Globulins.” *BioCentury*, Jan. 9, 2017). Amgen Inc.

(NASDAQ:AMGN) and Xencor Inc. (NASDAQ:XNCR) have bispecific antibodies, AMG 729 and XmAb5871 respectively, that bind CD19 and Fcγ receptor IIb (FCGR2B; CD32B), in the clinic for rheumatoid arthritis and lupus, and Shire plc (LSE:SHP; NASDAQ:SHPG) has the soluble FcR, SM101, in Phase II testing for lupus. Ortiz, D., et al. “Elucidating the interplay between IgG-Fc valency and FcγR activation for the design of immune complex inhibitors.” *Science Translational Medicine* (2016). ■

— Michael Leviten

BIOCENTURY INC.

NEWSROOM

pressreleases@biocentury.com

SAN CARLOS, CA

+1 650-595-5333; Fax: +1 650-595-5589

CHICAGO

+1 312-755-0798; Fax: +1 650-595-5589

WASHINGTON, DC

+1 202-462-9582; Fax: +1 202-667-2922

UNITED KINGDOM

+44 (0)1865-512184; Fax: +1 650-595-5589

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