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Targeting platelets in RA

By Lauren Martz, Staff Writer

Harvard Medical School researchers have shown that platelets can contribute to inflammatory arthritis and have identified a collagen receptor on these cells that could be a target for treating RA.[1] But inhibiting the collagen receptor glycoprotein VI platelet (GPVI; GP6) may have to be tailored for joint-specific effects, as systemically blocking platelets could have antithrombotic effects that might pose a bleeding risk.

Over the years, a variety of other cell types such as lymphocytes, neutrophils, mast cells and synovial tissue cells have been implicated in inflammation related to RA. Eric Boilard and colleagues at Harvard hypothesized that platelets also might be involved. Boilard, a research fellow in the Division of Rheumatology, Immunology and Allergy at the medical school, based this hypothesis on reports that platelets release inflammatory mediators into the blood in atherosclerosis, another inflammatory condition.[2]

> **"As soon as you target this receptor you are interfering with blood clotting."**
> *—Neelima Joshi, Glenmark Pharmaceuticals Ltd.*

Using the platelet-specific marker integrin α_{2b} (GPIIb; CD41), Boilard's team detected the presence of platelet microparticles in synovial fluid from patients with RA, suggesting that platelets from the blood had infiltrated the inflamed joints. Microparticles are small vesicles produced by platelets upon activation, and their role in a range of diseases is under scrutiny.

The group also detected microparticles in samples from patients with other forms of inflammatory arthritis. There were no signs of microparticles in samples from patients with noninflammatory osteoarthritis, suggesting that platelet activation and microparticle formation are involved specifically in inflammatory arthritis.

The next steps were to show whether decreasing the levels of activated platelets would alter the course of disease and to determine how platelets are activated in arthritis.

In a mouse model of inflammatory arthritis, an anti–glycoprotein Ib platelet α-polypeptide (GP1BA; CD42b) antibody caused a >97.5% reduction in platelet counts for up to 6 days and resulted in reduced arthritis severity compared with no treatment.

In normal mice, the team tested genetic knockout and pharmacological inhibition of the multiple pathways by which platelets can become activated. Those studies pointed to the collagen receptor GPVI as a key player in inflammatory arthritis progression.

Knockout of GPVI reduced inflammatory arthritis scores compared with those for wild-type animals, thus confirming that collagen-triggered platelet activation plays a role in the disease.

Better RA models

The model used in the *Science* paper involved autoantibody-mediated induction of joint inflammation. Because this is a relatively specific model, other researchers wanted to see whether blocking GPVI is effective in models in which arthritis is induced by different means.

"There have to be more studies in different species and different models of RA to confirm that blocking the collagen receptor on platelets has a therapeutic effect," said Bernhard Nieswandt, chair of experimental biomedicine at the University Clinic and Rudolf Virchow Center at the **University of Wurzburg**.

Simon Pitchford, a Sackler research fellow at the Sackler Institute of Pulmonary Pharmacology at **King's College London**, also wanted to see the Harvard team's findings replicated in other models of RA.

Pitchford is particularly interested in the safety profile of GPVI antagonists, a point echoed by Neelima Joshi, SVP of biological research at **Glenmark Pharmaceuticals Ltd.**

"Anti-GPVI molecules interfere with thrombosis and hemostasis. It is a target on platelets that is very important for thrombus formation. As soon as you target this receptor you are interfering with blood clotting," Joshi said.

Glenmark's GRC 4039, a phosphodiesterase-4 (PDE-4) inhibitor, is in Phase I testing for RA.

"In healthy patients, the inhibitors probably wouldn't have too much of a negative effect," Nieswandt noted. "But in sick patients with widespread inflammation, the increased bleeding risk could be very dangerous. It has been relatively well recognized that patients with autoimmune inflammation are more susceptible to bleeding events on antithrombotic therapies."

He added: "The question is, do you want this bleeding risk in a patient suffering from widespread autoimmune disease? This effect could make the strategy a risk that not many companies would be willing to take. I would be very reluctant to use a systemic treatment in patients."

Because of the risks, Josefin-Beate Holz, CMO at **Ablynx N.V.**, told *SciBX* that it will be important to see how GPVI inhibitors measure up against other disease-modifying agents for RA. In particular, she said it will be important to assess their effects on inflammatory markers and disease scores.

Abylnx and **Pfizer Inc.** have an injectable nanobody targeting tumor necrosis factor-α (TNF-α) in Phase II testing to treat RA.

One potential way to improve the safety profile of GPVI antagonists would be to make them joint specific and not systemically available.

"Targeting GPVI may be risky as there may be a risk of incomplete platelet aggregation and hemorrhage," said Pitchford. "For this reason, a joint-targeted approach may well be worthwhile."

But Pitchford cautioned that such an approach may sacrifice some efficacy. "There may well be systemically activated platelets in RA,

and this would require further research in terms of specific pathway inhibition," he said.

Nevertheless, the strategy is worth pursuing, Pitchford told *SciBX*, because "targeting platelets in inflammation could bring forward a new class of drugs. The role of platelets being integral to the inflammatory response is only now being recognized."

The authors of the *Science* paper declined requests for an interview.

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