

# Antibody targeting of phosphatidylserine for detection and immunotherapy of cancer

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## Dear editor

Belzile et al introduce a novel therapeutic approach for cancer by antibody targeting of phosphatidylserine (PS).<sup>1</sup>

As is well known, antiphospholipid autoantibodies are associated with hypercoagulability disorders, particularly antiphospholipid syndrome (APS).<sup>2</sup>

While the hallmark autoantibodies of APS are anti-beta2 glycoprotein and anti-cardiolipin, over 30 other non-classic autoantibodies were reported in correlation with APS. Particular attention was dedicated to antiphosphatidylserine (aPS) – a remarkable autoantibody that was detected in 68–86% of APS patients.<sup>2</sup> aPS is associated with thrombosis, thrombocytopenia and hemolytic anemia.<sup>2</sup> Previously, we have described the pathogenicity of aPS on experimental mice models by induction of APS, both through passive transfer of purified human IgG aPS antibodies<sup>3</sup> and active immunization, whereas immunized mice with IgG aPS produced high titers of mouse aPS. The results demonstrated a clinical picture of APS by prolonged activated partial thromboplastin time, thrombocytopenia and increased rates of fetal resorptions.<sup>4</sup>

In another study that deals with the mechanism for fetal loss in APS, exposure of rat embryos and their yolk sacs to aPS led to an inhibition of the yolk sac growth and a higher apoptosis rate compared with the control group.<sup>5</sup> With this knowledge, cancer immunotherapy by antibody targeting the PS<sup>1</sup> raises questions regarding the development of thromboembolic events in patients who accept this therapy.

In general, antibody targeting of PS increases the risk of developing thromboembolic events as some individuals may have occult genetic predisposition which is unknown to the clinician when prescribing the medication. This risk is doubled in the target population for this therapy, as oncological patients have a higher tendency to develop hypercoagulability states, compared to healthy population.<sup>6</sup>

Thus, perhaps a specific follow-up is required for patients with a high risk for development of thromboembolic events in order to detect and treat these side effects in time. In addition, a prophylactic therapy with low-molecular-weight heparin or oral anticoagulants should be considered upon initiation of therapy with antibody targeting of PS.<sup>6</sup>

## Disclosure

The authors report no conflicts of interest in this communication.

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## Author's reply

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## Dear editor

We appreciate the comments from Zohar and Shoenfeld and agree that antibody targeting of phosphatidylserine (PS) for cancer therapy should be evaluated carefully. Bavituximab, a chimeric antibody targeting PS via the bridging protein  $\beta$ 2 glycoprotein 1 ( $\beta$ 2GP1),<sup>1</sup> has been in clinical testing since the mid-2000s. Phase I safety testing was reported by Gerber et al,<sup>2</sup> and additional clinical studies testing bavituximab have also been reported.<sup>3–6</sup> The general conclusion from the clinical studies to date is that bavituximab is well tolerated at doses up to 3 mg/kg weekly. A study worth considering in the context of antiphospholipid syndrome (APS) is that of Mineo et al,<sup>7</sup> which demonstrated that the antibody 1N11 attenuates APS-related thrombosis. 1N11 is a fully human antibody that targets PS via B2GP1 and phenocopies the anti-cancer activity of bavituximab in preclinical models.<sup>8</sup> Overall, the preclinical and clinical data generated thus far demonstrate that bavituximab is safe and does not promote hypercoagulability. The mechanism of action of bavituximab and 1N11 has not been elucidated completely but is an area of active research that will hopefully provide insight as to

how targeting PS with these antibodies can stimulate immune activation without inducing hypercoagulability.

## Disclosure

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