

## On the article “*Drugs targeting protease-activated receptor-4 improve the anti-thrombotic therapeutic window*”

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French and Hamilton reviewed our publication entitled “*Blockade of protease-activated receptor-4 provides robust antithrombotic activity with low bleeding*” (1) positively and provided ideas and insights for future research on the drug target protease-activated receptor-4 (PAR4) (2). We have a few remarks addressing the concerns raised by French and Hamilton.

- (I) The editorial suggests that the genetic variant of PAR4 may alter receptor pharmacology. We have addressed this issue via mutagenesis study and *ex vivo* platelet aggregation study in a phase I study of a PAR4 antagonist BMS-986120 (3). Based on site directed mutagenesis studies we showed that the A120T variant of PAR4 has no apparent impact on calcium signaling in response to PAR4 activating peptide or platelet response to a PAR4 antagonist. Thus, in healthy human subjects, the pharmacodynamic effect of BMS-986120 does not apparently differ in subjects carrying alanine (AA) or threonine (TT) variants of PAR4 (3);
- (II) The editorial also raised a question on the benefits and risk of PAR4 antagonism combining with current standard of care. We’ll report a study addressing this issue at the American Heart Association meeting in Anaheim, California on November 13, 2017. Our study showed that BMS-986141, a PAR4 antagonist, alone or combined with aspirin prevents occlusive arterial thrombosis with low bleeding time increases in monkey models of arterial thrombosis and bleeding time.

We cannot disclose the data in detail now because of the embargo policies of the American Heart Association;

- (III) The statement on the BMS-986120 effect on alpha-thrombin inhibition is incorrect. We have shown effective inhibition of alpha-thrombin (2.5 nM) response in our paper (1). Combination of PAR1 and PAR4 inhibition was more effective at inhibiting the effect of higher concentration of thrombin (5 nM);
- (IV) Further evidence to support the reversibility of PAR4 antagonists was provided by the human phase I study, which demonstrated that the PAR4 antagonist BMS-986120 is a reversible antiplatelet agent (4);
- (V) Further evidence to support the proof of concept of the drug target PAR4 was provided by the phase I *ex vivo* human proof of concept study showing that the PAR4 antagonist BMS-986120 inhibited thrombus formation *ex vivo* in a human chamber of thrombosis (5).

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### Footnote

*Conflicts of Interest:* PC Wong and J Yang are employees of Bristol-Myers Squibb.

## References

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