

## Analysis and diagnostic role of platelet ADP receptor signalling

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Pharmacological platelet inhibitors are a corner stone of modern cardiovascular therapy and preventive medicine. However, there is a growing body of evidence that diminished therapeutic efficacy of anti-platelet medication is associated with increased risk of recurrent adverse cardiovascular events(1). Our laboratory previously identified the human platelet P2Y<sub>12</sub> ADP receptor as the thienopyridine target and developed a flow cytometric assay for the analysis of P2Y<sub>12</sub> receptor function, based on ADP-induced inhibition of prostaglandin (PGE<sub>1</sub>, PGI<sub>2</sub>)-stimulated, cAMP-mediated VASP-phosphorylation. The use of the VASP assay for calculation of a platelet reactivity index (PRI) is now “the gold standard” method for evaluating P2Y<sub>12</sub> receptor inhibition analysed *ex vivo*. A wide inter-individual variability in clopidogrel responsiveness was already observed in our earlier studies and later confirmed in many clinical studies. Clopidogrel is a thienopyridine with proven antithrombotic efficacy, but it has some important drawbacks (properties as a pro-drug that needs to be metabolized to its active metabolite; delayed onset and offset of action; high inter-individual variability in pharmacological response. Therefore, current studies focus on the mechanisms of ADP receptor signaling and on the development of a new generation of ADP receptor antagonists (prasugrel, cangrelor, ticagrelor and others). Our own studies, as part of a BMBF network project SARA (System biology of prostaglandin and ADP P2Y<sub>12</sub> receptor signaling pathways) currently address the molecular mechanisms and interaction of ADP and prostacyclin receptor signaling in human platelets using a phosphoproteomic approach (2). These approaches will be discussed.

1. Sweeny JM,, Gorog DA, Fuster V. *Antiplatelet drug 'resistance'. mechanisms and clinical measurements. Nat Rev Cardiol* 2009;6 : 273-282
2. Lewandrowski U et al (2009) *Platelet membrane proteomics: a novel repository for functional research. Blood* 114(1):e10-9.