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Exploring & neutralizing Human Glycoprotein VI-collagen interaction: Creation & characterization of synthetic peptides & humanized anti-thrombotic antibody fragments

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Abstract

Glycoprotein VI (GPVI), a key receptor for platelet activation by collagen, plays a critical role in haemostasis *in vivo*. The GPVI-collagen interaction has been clearly involved in the formation of thrombi on atherosclerotic lesion that are responsible for acute ischemic events. The neutralization of the collagen- GPVI interaction thus represents a promising strategy to develop novel antithrombotic agents. Two approaches were evaluated in this study: 1) Blocking GPVI with antibody fragments, and 2) Triggering a binding competition using a novel synthetic peptidomimetic.

1: Starting from a well-characterized hybridoma secreting an IgGk, a recombinant single chain antibody fragment (scFv) was designed and characterized. It retains the binding proprieties of the parental IgG (e.g. high affinity, neutralization of GPVI-collagen). The purified scFv inhibits the platelet aggregation induced by collagen in conditions which mimic the arterial flow. Humanized scFvs were finally obtained and can be use as building units to create larger antibody fragment with therapeutic potential. Furthermore, the strategy developed here is simple, efficient and straightforward and could also be used for humanizing other antibodies.

2: Using a molecular evolution procedure, a set of peptidomimetics of human GPVI were identified and synthetized. One of them binds to collagen with a nanomolar affinity *invitro* and competes with GPVI for binding to collagen. Collagen accumulation (fibrosis) was detected *in vivo* using a radiolabelled peptide and this capacity can be used to develop a non-invasive isotopic imagery method for the diagnostic and the evolution of fibrosis.

Biography

Julien Muzard, 33 years old, completes his PhD in Biotechnology (University Paris Diderot) in 2007 and spent the five years as postdoc. The first was at Paris-Tech, followed by positions at the Center for Molecular Innovation and Drug Discovery, University College Dublin. He is now a fellow in Computational Biology at CNAM University, Paris. His interests are mostly related to in silico, in vitro and in vivo aspects of binding recognition and the creation of molecular entities from scratch. Julien is coauthor on ~20 publications and main inventor on 5 patents granted in various disciplines (basic research, diagnostics and therapeutics).