

**DEPARTMENT OF COMMUNITY AND PREVENTIVE MEDICINE
RESEARCH PROPOSAL**

**The Effects of Potent Inflammation Resolving Lipid Mediators on Platelet
Function in *ex-vivo* Diabetic Blood
Pedro M. Calderón Artero**

BACKGROUND: Heart disease, stroke and other cerebrovascular diseases are the cause of 4.8 million deaths each year in middle to high income countries. Cardiovascular disease alone accounts for more than 900,000 deaths per year in the United States, with the majority of these deaths attributed to heart attacks. The underlying mechanism, atherosclerotic plaque disruption, leads to platelet activation, ultimately resulting in fibrin-rich thrombus formation with eventual compromise of the vascular supply. Despite clear documented benefits in reducing cardiovascular disease found in landmark studies, some researchers have recently argued that the anti-platelet effects of aspirin are limited in some populations. In particular, aspirin therapy in diabetic subjects may not be as effective as in healthy individuals. In this study, the potential for potent lipid mediators, that are generated from omega-3 fatty acids, to attenuate platelet hyperactivity is investigated.

OBJECTIVE: To investigate the *ex-vivo* effects of the potent lipid mediators resolvin D1 (RvD1) and 17(R)-resolvin (17(R)RvD1) on measures of platelet activation via PAC-1, P-selectin and CD40 Ligand platelet surface marker expression in diabetics and healthy adults. In addition, my objective is also to evaluate the effects of these resolvin molecules on the formation of platelet-leukocyte aggregates (PLA) *ex-vivo* after exogenous platelet activation in the same diabetic and healthy adults by measures of double positivity of platelet specific and leukocyte specific markers.

METHODOLOGY: The University of Rochester General Clinical Research Center will be used for screening and blood sample collection. Blood for flow cytometry analysis will be collected in sodium citrate tubes. Diluted blood will be incubated with RvD1 10-100 μ M, 17(R)RvD1 10-100 μ M (Cayman Chemical, Ann Arbor, MI) or vehicle. Control, adenosine diphosphate or arachidonic acid activated samples will then be incubated with saturating concentrations of anti-CD42a-PE and anti-CD62-FITC or with anti CD154-APC, anti-CD45-Pe-Cy5, anti-PAC1-FITC and anti-CD42a-PE. Platelet leukocyte aggregates will be evaluated by double CD45 (leukocyte specific) and CD42a (platelet specific) fluorescence. All samples will be analyzed at the University of Rochester Cardiovascular Research Institute. Data will be analyzed using Flow Jo® software. PLA will be reported as percent of the total leukocyte population. ANOVA and two-sided student t-tests will be used to evaluate differences across different drug concentrations. P-values less than 0.05 will be considered statistically significant.

TRANSLATIONAL APPLICATION: This project should elucidate if these novel resolvin molecules hold some promise as therapeutic agents in the prevention of cardiovascular diseases by inhibiting platelet function.

**Committee Chair:
Robert Block, MD, MPH, FACP**

**Committee Members:
Steve Georas, MD
Craig Morrell, DvM, PhD
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**Monday, April 12, 2010
12:00PM – 12:30PM
Helen Wood Hall, Room 1W501**

EVERYONE IS WELCOME