A multicentre comparison of platelet aggregation agonists including comparator materials

PLATELET AGGREGATION PROJECT STANDARDIZATION – PAPS Study

SSC Platelet Physiology

- **Person responsible**: Chair: Marie Lordkipanidze PI : Marie-Christine Alessi
  - In collaboration with: The National Institute for Biological Standardisation and Control (NIBSC) and Stago Diagnostica.

- **Design**: Multicentre study

- **Aim/Objective/Rationale**:

  Light transmission aggregometry (LTA) is the 'gold standard' for platelet function analysis, but standardisation in clinical practice is inadequate (1,2). A recent study carried out in Germany and Austria highlighted that a major source of inter-laboratory variation is the in-house reagents used by the laboratories, rather than the LTA method itself (3). As part of the Platelet Physiology subcommittee of the International Society for Thrombosis and Haemostasis (ISTH), we have initiated an international, multi-centre study to evaluate the extent of variability amongst commercial and in-house agonists. Our study also includes reference materials from the National Institute for Biological Standardisation and Control (NIBSC) and commercial agonists from Stago. These reference materials will permit quantification of variation between platelet agonists as well as provide evidence to support the establishment of reference materials to standardise platelet aggregation.

- **Methodology**:

  Before starting this project we conducted a feasibility study to identify study participants, determine the reagents and equipment they use, and find a suitable start date. Amongst the 28 responses we received, there was considerable variation with regards to agonist supplier (cf table indicating the number of different commercially available agonists used by study respondents).

<table>
<thead>
<tr>
<th>Collagen</th>
<th>PAR-4AP</th>
<th>TRAP-6</th>
<th>CRP-XL</th>
<th>ADP</th>
<th>Epinephrine</th>
<th>Arachidonic Acid</th>
<th>U46619</th>
<th>Ristocetin</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>3</td>
<td>7</td>
<td>2</td>
<td>7</td>
<td>8</td>
<td>7</td>
<td>9</td>
<td>8</td>
</tr>
</tbody>
</table>

To proceed, comparator agonists must be shipped to study participants. The NIBSC has already prepared the comparator material for the biological agonists: collagen, TRAP6, CRP-XL and PAR4-AP and determined their EC$_{50}$ values (200 vials of each agonist). Stago Diagnostica will provide the non-biological agonists (arachidonic acid, ADP, Ristocetin, Epinephrine, U46619).

Five concentrations of the in-house agonists and the comparators will be tested in parallel in different PRP samples from healthy volunteers according to a standard operating procedure. The EC$_{50}$ of each reagent will be determined and by comparing these data to the comparator (NIBSC/Stago) reagents,
the degree of variability between in-house agonists and laboratory procedures can be determined. Participating laboratories will use freshly isolated platelet-rich plasma (PRP) from healthy volunteers (donor from the general population without acute or chronic disease not receiving any medication for at least 10 days). PRP samples will be prepared according to ISTH recommendations (4,5) and the number of donors defined by power calculations to ensure statistical power. Results will be sent electronically to the responsible person(s) defined above.

- **Expected timeline:**
  - Project stage/set up: 2018
  - Launch: end of 2019
  - Duration: 1 to 2 years
  - Finalization/analysis: end of 2020 or 2021
  - Reporting: ISTH congress 2021 or 2022

- **Expected outcomes** (ie. publications):
  - Design presentation and feedback from community at ISTH 2019 in Melbourne
  - Progress presentation at ISTH 2020 in Milan with feedback from community
  - Final presentation at ISTH 2021 or 2022
  - Publication as SSC Official Communication in JTH

- **Summary of project set/up and management, required infrastructure and resources**

  The project will be chaired by Pr MC Alessi with additional input and guidance from the co-chairs of the Platelet Physiology SSC and the NIBSC. We estimate we will require active participations from 30 international sites to meet the study sample size. We will request access to RedCap for sites to securely communicate their results, and for safe archiving of data. Statistical analysis will be performed by a statistician and will benefit the help of the NIBSC.

- **References:**
  1. Lordkipanidzé M. Platelet function tests. *Semin Thromb Hemost* 2016; 42; 258–267