Antiplatelets In The Pipelines

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Stages of drug development

- Average time to develop new drug is 10 -12 years.
- On an average out of 10,000 – 30,000 potential substances only 1 could make it to the market.
- As per 2006 estimates, the cost of bringing a new drug could vary from 500 million to 2,000 million USD.
"Tell me... what IS in the pipeline?"
Stages of platelet activation

1- Adhesion
2- Shape change from discoid to amoeboid
3- Granule release and calcium mobilization
4- Aggregation

Stages of platelet adhesion, activation, and aggregation.

Kiefer and Becker, Circulation. 2009;120:2488-2495
Inhibitors of Platelet Adhesion and Aggregation

- Adhesion inhibitors
- Aggregation inhibitors
- Signal transduction inhibitors
- P-selectin Antagonists.
<table>
<thead>
<tr>
<th>Receptor/Target and Agent</th>
<th>Structure</th>
<th>Company</th>
<th>Status in Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>VWF</td>
<td>Murine monoclonal antibody</td>
<td>Ajinomoto</td>
<td>Preclinical</td>
</tr>
<tr>
<td>AU42523-28</td>
<td>Human monoclonal antibody</td>
<td>Ajinomoto</td>
<td>Preclinical</td>
</tr>
<tr>
<td>R6.3</td>
<td>Oligonucleotide aptamer</td>
<td>Academic</td>
<td>Preclinical</td>
</tr>
<tr>
<td>R6.14</td>
<td>Oligonucleotide aptamer</td>
<td>Academic</td>
<td>Preclinical</td>
</tr>
<tr>
<td>ARC1779</td>
<td>Oligonucleotide aptamer</td>
<td>Archmix</td>
<td>Phase II clinical trial</td>
</tr>
<tr>
<td>GP Ib/MIX</td>
<td>Inhibitory peptide</td>
<td>Academic</td>
<td>Preclinical</td>
</tr>
<tr>
<td>R9.557</td>
<td>Monoclonal antibody</td>
<td>K.U. Leuven Research and Development</td>
<td>Preclinical</td>
</tr>
<tr>
<td>SB-6</td>
<td>Monoclonal antibody</td>
<td>Academic</td>
<td>Preclinical</td>
</tr>
<tr>
<td>GP VI</td>
<td>Monoclonal antibody</td>
<td>Academic</td>
<td>Preclinical</td>
</tr>
<tr>
<td>JAQ1</td>
<td>Monoclonal antibody</td>
<td>Otsuka Pharmaceutical</td>
<td>Preclinical</td>
</tr>
<tr>
<td>OM2*</td>
<td>Monoclonal antibody</td>
<td>Otsuka Pharmaceutical</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Soluble GP VI Inhibitor</td>
<td>Small inhibitory antibody decay</td>
<td>Academic</td>
<td>Preclinical</td>
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<tr>
<td>EXP3179</td>
<td>Angiotensin II type 1 receptor metabolite</td>
<td>Merck</td>
<td>Preclinical</td>
</tr>
<tr>
<td>GP Ia/II</td>
<td>Recombinant protein inhibitor</td>
<td>Academic</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Small molecule inhibitors</td>
<td>Synthetic I domain atherosclerotic inhibitor</td>
<td>Academic</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Collagen</td>
<td>Recombinant protein inhibitor</td>
<td>Otsuka Pharmaceutical</td>
<td>Preclinical</td>
</tr>
<tr>
<td>AAPP*</td>
<td>Recombinant protein inhibitor</td>
<td>Otsuka Pharmaceutical</td>
<td>Preclinical</td>
</tr>
<tr>
<td>RSK</td>
<td>Isoform specific enzyme inhibitor</td>
<td>Academic</td>
<td>Preclinical</td>
</tr>
</tbody>
</table>

Kiefer and Becker, Circulation. 2009;120:2488-2495

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Product Development Portfolio
Last update: Oct. 17, 2013

**RG1512 Inclacumab**

**Description/Summary:**
Inclacumab is a fully human monoclonal Ab designed to neutralize P-selectin, a multifunctional molecule at the interface of inflammation and thrombosis. By inhibiting both inflammatory and thrombotic reactions, anti-P-selectin could be an effective therapy for cardiovascular diseases.

**Managed by:** Pharma Research and Early Development

**Partner:** Genmab

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**Comprehensive antithrombotic pipeline**

- **REG1:** pegnivacogin (IV bolus) + anivamersen (IV bolus)
  - ACS - PCI
  - Open Heart Surgery (incl. CABG)

- **REG2:** pegnivacogin (SC inj.) + anivamersen (IV bolus)
  - VTE Prophylaxis
  - REG2 is a twice/month subcutaneous injection with its matched active control agent

- **REG3:** RB571 (IV) + RB515 (IV)
  - REG3 is a GPVI inhibitor with its matched active control agent
  - Initial indication: Diabetic vasculopathy

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Regado's lead anti-platelet candidate, REG3, consists of a specific GPVI inhibitor and its active control agent (RB571 and RB515, respectively). GPVI, the platelet-specific major collagen receptor, has been implicated in a wide range of platelet-mediated diseases including ACS, rheumatoid arthritis and diabetic vasculopathy. **REG3 is planned to enter phase 1 human clinical testing in 2013.**
Prostanoids

- There are five physiologically important prostanoids, i.e., PGD₂, PGE₂, PGF₂α, PGI₂ and TXA₂.
- Prostanoids elicit their effect by direct modulation of respective prostanoid receptors. Eight of these have been cloned and characterized to be members of the G protein-coupled receptor (GPCR) rhodopsin-like family.

Singh and Kiselyov. THOMSON REUTERS – Drugs of the Future 2010, 35(1)

Four subtypes of bovine EP3 have been cloned (designated A, B, C and D). They have opposing effects on adenylate cyclase activity.

### Table 6. Comparison of selected EP3 receptor antagonists.

<table>
<thead>
<tr>
<th>Activities</th>
<th>Merck series (79-81)</th>
<th>CSK (82)</th>
<th>DC-041</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In vitro</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NEP2 EC50 (nM)</td>
<td>3</td>
<td>2.1</td>
<td>25</td>
</tr>
<tr>
<td>mEP2 IC50 (nM)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Plasma protein binding (fold shift)</td>
<td>NR</td>
<td>20x (+0.05% HSA)</td>
<td>NR</td>
</tr>
<tr>
<td>Platelet aggregation (using NEP2 in the presence of collagen as coaggregant) (S1)</td>
<td>NR</td>
<td>5.6 x 100%</td>
<td>NR</td>
</tr>
<tr>
<td>Pharmacokinetics (rat) = 1%, %F</td>
<td>NR</td>
<td>5.6 x 100%</td>
<td>NR</td>
</tr>
<tr>
<td>Indication</td>
<td>Not disclosed</td>
<td>Bladder function</td>
<td></td>
</tr>
<tr>
<td>Overall status</td>
<td>Lead</td>
<td>Lead</td>
<td>Lead</td>
</tr>
</tbody>
</table>

NR, not reported; HAS, human serum albumin; HS, human serum. *Data reported for rat EP3 receptor.

By deCODE genetics, Iceland
Thromboxane receptor inhibitors

- Pharmacological advantages over aspirin:
  - they also inhibit other thromboxane receptor ligands such as endoperoxidase, prostanoids and isoprostanes.
  - They antagonize the effects of TxA2 on thromboxane receptors present on other cells such as monocytes and vascular cells.
  - preserve the beneficial cyclooxygenase-1 (COX-1) endothelial production of prostacyclin, leading to inhibition of platelet aggregation and vasodilation.

- Numerous thromboxane receptor antagonists have been developed; however, only a few have progressed beyond phase II trials due to safety concerns.
Terutroban (formerly S18886)

- Is an oral reversible inhibitor of the thromboxane receptor.
- Phase III
- Its antiplatelet action is similar to that of aspirin, with an additional antithrombotic effect: a decreased fibrinogen deposition under shear conditions.
- Acts directly on the thromboxane receptor. Thus, it can inhibit not only TxA2 but also other eicosanoids not affected by aspirin, such as hydroxyeicosatetraenoic acids (HETEs) and isoprostanes.
- In a pharmacokinetic-pharmacodynamic study, the maximal inhibitory effect was achieved after 1 h in patients with peripheral artery disease.

Terutroban (formerly S18886) cont.

- In animal models, it has also shown to:
  - Reduce stent thrombosis as effectively as the combination of aspirin and clopidogrel, with a more favorable bleeding profile,
  - To prevent atherosclerosis and to induce plaque regression.
  - A single dose of 10 mg improved endothelial function (flow-mediated and acetylcholine-mediated vasodilatation) in 12 CAD patients.
Terutroban vs aspirin in patients with stroke/TIA: PERFORM trial

19,000 patients in 802 centers in 46 countries
Mean follow up 2.3 yrs

Primary endpoint: composite stroke, mi, vascular death

PERFORM Trial

- a randomised, double-blind, parallel-group trial.
- The trial did not meet the predefined criteria for non-inferiority, with similar rates of the primary endpoint with both terutroban and aspirin, without safety advantages for terutroban.
- In a worldwide perspective, aspirin remains the gold standard antiplatelet drug for secondary stroke prevention in view of its efficacy, tolerance, and cost.
**Nitric oxide-releasing aspirin: NCX-4016**

- In phase II
- A combination of antithrombotic, anti-atherogenic and vasodilatory effects, with a better gastroenteric safety profile
- NO has an additional inhibitory effects on platelet aggregation
- May prevent shear stress-induced platelet activation, as well as the formation of superoxide and reactive oxygen species in the vascular wall.
- In vitro antiplatelet effects of NCX-4016 are even stronger than those of aspirin

By Nicox

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**Nitric oxide-releasing aspirin: NCX-4016**

- Interestingly, NCX-4016 (800 mg thrice daily) but not aspirin improves effort-induced endothelial dysfunction in patients with intermittent claudication.
- In rat model of carotid balloon injury treatment, NCX-4016 resulted in increased availability of nitric oxide and lower rate of restenosis, when compared with that of aspirin. This effect was associated with diminished vascular smooth muscle cell proliferation. It might be a useful adjunct for preventing restenosis after PCI.
Thrombin Receptor Protease activable receptor-1 (PAR-1) Antagonists
Vorapaxar (SCH530348)

- It is highly selective for PAR-1 and does not affect other platelet activation pathways. It blocks thrombin-mediated platelet activation without interfering with thrombin-mediated cleavage of fibrinogen, the final step of coagulation.
- In phase III research
Vorapaxar (SCH530348) cont.

- However, in a phase III trial (TRA-CER), the addition of vorapaxar to standard antiplatelet therapy in patients with ACS, did not significantly reduce the primary composite end point but significantly increased the risk of major (moderate and severe) bleeding, including intracranial hemorrhage.

TRA 2°P-TIMI 50 Trial: Vorapaxar for Secondary Prevention after Myocardial Infarction

- Included pts with MI within the previous 2 weeks to 12 months.
- For patients with a history of MI, inhibition of PAR 1 with vorapaxar reduces the risk of cardiovascular death or ischaemic events when added to standard antiplatelet treatment, including aspirin, and increases the risk of moderate or severe bleeding.

Atopaxar (E5555)

- PAR 1 antagonist
- An extensive phase II program (LANCELOT-CAD trial, J-LANCELOT) has shown that:
  - its co-administration in patients with ACS or CAD on top of the current antiplatelet therapy was generally well tolerated with no statistically significant increase in major bleeding events according to CURE- and TIMI-criteria, but with a tended to have more minor and minimal bleeding complications.
  - Although not powered for primary efficacy end points, the data suggest that the additional administration of atopaxar to dual antiplatelet therapy might be beneficial in preventing recurrent ischaemic events.
Purinergic receptors (Purinoceptors)

- ADP Receptor antagonists
- ATP Receptor antagonists

activate platelets by inducing a very rapid influx of Ca\(^{2+}\) from the extracellular medium, which is associated with platelet shape change and rapidly reversible aggregation - slowly progressive and sustained platelet aggregation not preceded by shape change.
Cangrelor

- Cangrelor is an intravenous ADP receptor antagonist that is rapidly acting, potent, and reversible, with return of normal platelet function within an hour.
- Cangrelor was studied previously in two large Phase 3 PCI trials, CHAMPION PCI and CHAMPION PLATFORM. Neither study met its primary endpoint, but the secondary endpoint of stent thrombosis at 48 hours was significantly reduced in CHAMPION PLATFORM and in a prespecified pooled analysis of the two trials. There was no excess in severe bleeding.
- The potential efficacy signal prompted the investigators to launch the CHAMPION PHOENIX trial.

Harrington RA, et al. CHAMPION PCI. NEJM 2009
Bhatt DL, et al. CHAMPION PLATFORM. NEJM 2009
CHAMPION PHOENIX Study Design

CHAMPION PHOENIX
N = 10,942 MITT
SA/ NSTE-ACS/ STEMI
Patients requiring PCI
P2Y₁₂ inhibitor naïve
(last 7 days)

Randomization occurred once suitability for PCI was confirmed either by angiography or STEMI diagnosis. Double blind study medication was administered as soon as possible following randomization.

Study drug infusion (cangrelor or matching placebo) was continued for 2–4 hours at the discretion of the treating physician. At the end of the infusion patients received a loading dose of clopidogrel or matching placebo and were transitioned to maintenance clopidogrel therapy.

Clopidogrel loading dose (or matching placebo) was administered as directed by the investigator. At the time of patient randomization, a clopidogrel loading dose of 600 mg or 300 mg was specified by the investigator.

MITT=modified intent-to-treat; NSTE-ACS=non-ST-elevation acute coronary syndrome; PCI=percutaneous coronary intervention; SA=stable angina; STEMI=ST-elevation MI.

Death/ MI/ IDR/ Stent Thrombosis within 48 Hours

Number needed to treat= 84 (95% CI, 49 to 285)

Log Rank P Value = 0.006

Stent Thrombosis within 48 Hours

- Event Rate (%)
  - Cangrelor: 0.8%
  - Clopidogrel: 1.4%

Log Rank P Value = 0.01

Patient at Risk
- Cangrelor: 5472
- Clopidogrel: 5470

Hours from Randomization
- Cangrelor: 5426, 5421, 5419, 5419, 5418, 5417, 5416, 5414
- Clopidogrel: 5392, 5389, 5388, 5386, 5385, 5385, 5383, 5383

Efficacy Outcomes at 30 Days, MITT

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cangrelor (N=5472)</th>
<th>Clopidogrel (N=5470)</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death/MI/IDR/ST</td>
<td>326/5462 (6.0%)</td>
<td>380/5457 (7.0%)</td>
<td>0.85 (0.73, 0.99)</td>
<td>0.03</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>71/5462 (1.3%)</td>
<td>104/5457 (1.9%)</td>
<td>0.68 (0.50, 0.92)</td>
<td>0.01</td>
</tr>
<tr>
<td>MI</td>
<td>225/5462 (4.1%)</td>
<td>272/5457 (5.0%)</td>
<td>0.82 (0.68, 0.98)</td>
<td>0.03</td>
</tr>
<tr>
<td>Q-wave MI</td>
<td>14/5462 (0.3%)</td>
<td>22/5457 (0.4%)</td>
<td>0.63 (0.32, 1.24)</td>
<td>0.18</td>
</tr>
<tr>
<td>IDR</td>
<td>56/5462 (1.0%)</td>
<td>66/5457 (1.2%)</td>
<td>0.85 (0.59, 1.21)</td>
<td>0.36</td>
</tr>
<tr>
<td>Death</td>
<td>60/5462 (1.1%)</td>
<td>55/5457 (1.0%)</td>
<td>1.09 (0.76, 1.58)</td>
<td>0.64</td>
</tr>
<tr>
<td>CV Death</td>
<td>48/5462 (0.9%)</td>
<td>46/5457 (0.8%)</td>
<td>1.04 (0.69, 1.57)</td>
<td>0.84</td>
</tr>
</tbody>
</table>
## Non-CABG Bleeding at 48 Hours, Safety

<table>
<thead>
<tr>
<th>Bleeding Scale</th>
<th>Cangrelor (N=5529)</th>
<th>Clopidogrel (N=5527)</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GUSTO Severe</td>
<td>9 (0.16%)</td>
<td>6 (0.11%)</td>
<td>1.50 (0.53,4.22)</td>
<td>0.44</td>
</tr>
<tr>
<td>GUSTO Moderate</td>
<td>22 (0.4%)</td>
<td>13 (0.2%)</td>
<td>1.69 (0.85,3.37)</td>
<td>0.13</td>
</tr>
<tr>
<td>GUSTO Severe + Moderate</td>
<td>31 (0.6%)</td>
<td>19 (0.3%)</td>
<td>1.63 (0.92,2.90)</td>
<td>0.09</td>
</tr>
<tr>
<td>TIMI Major</td>
<td>5 (0.1%)</td>
<td>5 (0.1%)</td>
<td>1.00 (0.29,3.45)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>TIMI Minor</td>
<td>9 (0.2%)</td>
<td>3 (0.1%)</td>
<td>3.00 (0.81,11.10)</td>
<td>0.08</td>
</tr>
<tr>
<td>TIMI Major + Minor</td>
<td>14 (0.3%)</td>
<td>8 (0.1%)</td>
<td>1.75 (0.73,4.18)</td>
<td>0.2</td>
</tr>
<tr>
<td>Any Blood Transfusion</td>
<td>25 (0.5%)</td>
<td>16 (0.3%)</td>
<td>1.56 (0.83,2.93)</td>
<td>0.16</td>
</tr>
<tr>
<td>AUCITY Major</td>
<td>235 (4.3%)</td>
<td>139 (2.5%)</td>
<td>1.72 (1.39,2.13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AUCITY w/out hematoma</td>
<td>42 (0.8%)</td>
<td>26 (0.5%)</td>
<td>1.62 (0.99,2.64)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

**Linogrel (PRT060128; Novartis)**

- Elinogrel is an investigational, direct-acting, reversible P2Y12 antagonist with a novel structure.
- Elinogrel can be administered orally or intravenously.
- High platelet reactivity to ADP in patients on clopidogrel can be reversibly overcome by elinogrel.
- After successful phase 2 studies (e.g., INNOVATE-PCI, presented in abstract form at the European Society of Cardiology 2010 Congress), a phase 3 trial of elinogrel is currently in the planning stage.
They concluded that 5HT2A R antagonists do not inhibit platelet activation induced by physiologic agonists (collagen and thrombin) and, more importantly, pathophysiologic stimuli (atherosclerotic plaque) in humans. They therefore do not constitute a promising strategy for antiplatelet therapy.

Take home message

- There are plenty of antiplatelet agents currently in the pipelines in different phases in drug development.
- The process of platelet activation is a complex one with multiple interacting mechanisms.
- Current researches are targeting most of these mechanisms to inhibit platelet activity.
- Only few of them are expected to make their way to the market to be used in clinical practice.
Thank You