Non-factor replacement strategies: Anti-coagulant inhibition and factor VIII mimetic
### DISCLOSURES FOR: GARY E. GILBERT

<table>
<thead>
<tr>
<th>Conflict</th>
<th>Disclosure - if conflict of interest exists</th>
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<tbody>
<tr>
<td>Research Support</td>
<td>Baxter, Veterans administration, B-BIC</td>
</tr>
<tr>
<td>Director, Officer, Employee</td>
<td>Little Sparrows Technologies, Inc</td>
</tr>
<tr>
<td>Shareholder</td>
<td>N/A</td>
</tr>
<tr>
<td>Honoraria</td>
<td>N/A</td>
</tr>
<tr>
<td>Advisory Committee</td>
<td>Bayer, Baxalta</td>
</tr>
<tr>
<td>Consultant</td>
<td>N/A</td>
</tr>
<tr>
<td>Intellectual Property</td>
<td>Methods and Assays for Factor VIII Activity U.S. Patent 61/904,948 -pending</td>
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Rationales For Non-factor Therapies

**HAEMOPHILIA**
People with haemophilia do not produce enough factor VIII or factor IX, proteins that play a crucial part in clotting.

**FACTOR REPLACEMENT TREATMENT**
To prevent and staunch bleeding, physicians typically give patients with haemophilia infusions of the factors they lack. Adding these extra factors restores the balance between bleeding and clotting.

**ANTICOAGULANT INHIBITION TREATMENT**
An approach under development restores balance instead by inhibiting the proteins that prevent clotting – natural anticoagulants such as tissue factor pathway inhibitor (TFPI) and antithrombin.
Localization & regulation of factor Xa production – how much does it matter?

PS-rich sites (fVIIIa, fXa, fX, fVIIa)

fVIIIa:
Binding sites on subset of platelets
Produces fXa burst, short duration
<table>
<thead>
<tr>
<th>Drug, Company</th>
<th>Target</th>
<th>Indication, Stage</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE 910, Genentech – Roche</td>
<td>Factor IXa</td>
<td>Hem A, prophylaxis, Phase I, II</td>
<td>fVIII mimetic, Bispecific Ab</td>
</tr>
<tr>
<td>ALN-AT3, Alnylam</td>
<td>Antithrombin III</td>
<td>Hem A &amp; B, Phase I</td>
<td>RNAi</td>
</tr>
<tr>
<td>BAX499, Baxalta</td>
<td>TFPI</td>
<td>Hem A &amp; B, Phase I (no longer under development)</td>
<td>RNA aptamer</td>
</tr>
<tr>
<td>Concizumab, Novo Nordisk</td>
<td>TFPI</td>
<td>Hem A &amp; B, Phase I</td>
<td>Monoclonal Ab for SC injection</td>
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</table>
ACE910 – a bispecific antibody

Affinity of factor VIII for fIXa >300 x for factor X >10x → different behavior

Sampei et al. 2013 pone-0057479-g001
Biochemistry of ACE910

Low affinity →
Activity ceiling
Activity plateau over 3x
Competes with fVIIIa

[fX] 8%

[Cofactor] (ACE910 or fVIIIa)

K_D
The potential of bispecific antibodies for treatment of hemophilia A

Shima M  (ISTH 7/2015)

Phase I study…64 Japanese and Caucasian healthy adults …
There was no safety issue… half-life … 30 days

(Phase II) …
18 Japanese patients with severe hemophilia A.. once-weekly SC ACE910 …
for 12 successive weeks with dose – ABR effect of:
  0.3 (C1) – 32.5 → 2
  1 (C2) – 18.3 → 1.2
  3 mg/ kg (C3) – 15.2 → 0

All adverse events were mild or moderate. No thromboembolic AEs
7 patients had FVIII inhibitors.
Antithrombin III (ATIII) inhibition with RNAi

Preclinical data for ALN-AT3 (antithrombin III RNAi)

Mouse survival and hemostasis

Primate ATIII levels and plasma thrombin generation

Sehgal A et al. 2015 Nat Med
Effect of Concizumab (anti-TFPI) on bleeding in rabbit hemophilia

Effect on cuticle bleeding

Effectiveness after bleeding started

Hilden I et al. 2012 Blood
## Predicted dosing and risks

<table>
<thead>
<tr>
<th>Drug, Company</th>
<th>Target</th>
<th>Administration/frequency</th>
<th>Risk</th>
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<tr>
<td>ACE 910, Genentech – Roche</td>
<td>Factor IXa</td>
<td>Subcutaneous, weekly (? Q 2-4 wk)</td>
<td>May prevent rescue with factor VIII</td>
</tr>
<tr>
<td>ALN-AT3, Alnylam</td>
<td>Antithrombin III</td>
<td>Subcutaneous, monthly</td>
<td>Thrombosis risk if rescue with factor VIII or IX</td>
</tr>
<tr>
<td>BAX499, Baxalta</td>
<td>TFPI</td>
<td></td>
<td>Excess bleeding Highlights complexity of TFPI inhibition</td>
</tr>
<tr>
<td>Concizumab, Novo Nordisk</td>
<td>TFPI</td>
<td>Subcutaneous, weekly?</td>
<td>Thrombosis risk if rescue with factor VIII or IX</td>
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</table>
Preclinical and early clinical data suggests:

Factor VIII mimetic and anti-inhibitors may not be as effective as fVIII or fIX but they are likely to be good enough for treatment of inhibitor patients and possibly for primary prophylaxis – with weekly to monthly subcutaneous dosing

Concerns:
1) Successful rescue of bleeding episodes with fVIII (ACE910)
2) Adequate prophylaxis – particularly long term (cumulative effect of minor bleeding episodes that may be qualitatively different)
3) Thrombotic risk – particularly during rescue with fVIII or fIX
THANK YOU