How do we define a (clinically-relevant) inhibitor?

Carol K. Kasper
Is an inhibitor clinically relevant if:

1. Concentrate, in usual doses, does not control bleeding?

2. In-vivo recovery measurement is clearly abnormal? (60% or less?) or

3. Half-life is clearly abnormal? (we established our own norms, see next slide, for early-phase half-life, suitable for a clinic day)
95 patients, severe hemophilia A, no known inhibitor, pre-op half-life studies in our HTC

<table>
<thead>
<tr>
<th>Time post-infusion</th>
<th>Mean FVIII as % of 10-minute level</th>
<th>Mean minus 2 SD</th>
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</thead>
<tbody>
<tr>
<td>10 minutes</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>60 minutes</td>
<td>75</td>
<td>57.4</td>
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<tr>
<td>90 minutes</td>
<td>63</td>
<td>47.0</td>
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<tr>
<td>3 hours</td>
<td>52</td>
<td>32.4</td>
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<tr>
<td>6 hours</td>
<td>41</td>
<td>23.0</td>
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*In vivo* tests are more sensitive than the Bethesda test. One can have a normal *in vitro* result but modestly abnormal *in vivo* results, modestly? clinically significant.

A memorable patient, Mr. X., age 45, severe hemophilia A, very heavily treated. Bethesda tests always negative including three days before surgery. *In vivo* recovery of pre-op concentrate normal (FVIII assayed pre-op). Two hours into surgery, bleeding heavily, FVIII < 1%. His low-level inhibitor lasted a few days and never recurred.
Can an in vitro test pick up a low-level inhibitor?

The Bethesda test was not designed to be sensitive. It was designed to be acceptable to a committee. The NIH said it wouldn’t fund any inhibitor studies unless a common test was designed and used.

Dr. Judith Pool and I published a letter-to-the-editor, together with the description of the Bethesda test, suggesting possible modifications to make it more sensitive when a low-level inhibitor is suspected.
The **cut-off point** in the Bethesda test is **ARBITRARY**.

A high cut-off point reduces false positives. A low cut-off point reduces false-negatives.

It’s helpful for a lab to gain experience with definite but low-level inhibitors, e.g., from a patient whose inhibitor is declining with immune tolerance therapy.

That may help the lab choose the cut-off point that makes the most sense for that lab.
My lab, in a clinical center, a hospital with a lot of surgery, was concerned with not missing a low-level inhibitor if possible. We chose a low cut-off point and got some possible false-positives but we could re-test and otherwise follow these patients to see if they really had inhibitors.
When we need a yes/no answer, let’s make a decision for that particular study, without demanding world-wide uniformity.

We may be stuck with local criteria for the presence or absence of an inhibitor.

We may be stuck with general ranges – more than 5 BU? 1-5 BU? Less than one BU but we think a low-level inhibitor is present?.

Thank you!