Workshop 15

*Detective Workshop: How to Solve the Mystery of Challenging Receptor Occupancy Assays*

Organizers/Facilitators:

Virginia Litwin, Covance Inc., USA
Cherie Green, Genentech, Inc., USA
Jennifer Stewart, Flow Contract Site Laboratory, USA
Receptor occupancy (RO) assays for biologics targeting cellular antigens are critical in the drug development process. This workshop will be an in depth discussion of the most challenging aspects of RO method development, validation, and implementation. The workshop is intended to find concrete solutions to specific challenges with a final outcome of a detailed white paper.

Five topics will be discussed during the Workshop. A brief presentation for each topic will be followed with open discussion.

1. Receptor (drug target expression)
   * Dim receptor (drug target) expression
   * Rare/infrequent target cell populations
   * Non-circulating/surrogate targets

2. Receptor (drug target) internalization and/or shedding with or without drug binding
   * How to assess and control receptor internalization and shedding especially with activation antigen?

3. Lack of Critical Reagents
   * Strategy for the situation where suitable competing and non-competing reagents are not available.

4. Variability
   * Day to day variability
   * Inter- and Intra-subject variability
   * Receptor (drug target) stability during sample collection, processing, and shipping

5. Reagents
   * Requirements for qualification, monitoring practices, and documentation of critical reagents such as non-commercial (in-house, home brew) reagents (antibodies, cellular controls).
Workshop 15--Summary

CYTO 2016 Meeting
Workshop Summary - “Detective Workshop: How to Solve the Mystery of Challenging Receptor Occupancy Assays”
June 13, 2016 at 16:45 - 18:00D

Facilitators:
Virginia Litwin, Hematology/Flow Cytometry, Covance Inc., virginia.litwin@covance.com
Cherie Green, Flow Cytometry Biomarker Development Sciences, Genentech, Inc., a Member of the Roche Group, green.cherie@gene.com
Jennifer Stewart, Flow Contract Site Laboratory, jennifer.stewart@fcslaboratory.com

Problem/Hypothesis
Receptor Occupancy (RO) assays for biologics targeting cellular antigens are critical in the drug development process. However, RO assays are among the most challenging flow cytometric methods to develop, validate, and implement.

Current State of Receptor Occupancy (RO) assays
The emerging importance of RO was highlighted by the March 2016 Special Issue of Cytometry Part B: Clinical Cytometry, dedicated to RO assays. In this issue, the importance of data generated from this assay format to confirm physical target coverage and support dose selection when combined with PK/PD modeling was emphasized as well as the potential pitfalls of the technology.
Desired State of RO Assays
This workshop was intended to be a follow up to the Special Issue where some of the more challenging aspects of RO assay design and implementation were discussed in detail. The desired state would be for experts to form and present a consensus on how to solve critical challenges of RO assay design and implementation.

Workshop Proposed Solutions
Topics discussed included, but were not limited to:

• Receptor (drug target expression): Dim receptor (drug target) expression; Rare/infrequent target cell populations; Non-circulating/surrogate targets.

• Receptor (drug target) internalization and/or shedding with or without drug binding: How to assess and control receptor internalization and shedding especially with activation antigen.

• Lack of Critical Reagents: Strategy for the situation where suitable competing and non-competing reagents are not available.

• Variability: Day to day variability; Inter- and Intra-subject variability; Receptor (drug target) stability during sample collection, processing, and shipping.

• Reagents: Requirements for qualification, monitoring practices, and documentation of critical reagents such as non-commercial (in-house, home brew) reagents (antibodies, cellular controls).

Next Steps
A sub-committee will be formed to present a consensus in the field for addressing the issues discussed during the Workshop. Potential team members/authors will be chosen from Workshop participants and other experts in the field, with the desired outcome being a white paper publication.