HCV

***D*rug**

***R*esistance**

***A*dvisory**

***G*roup**

Origin and Purpose

Initial Idea

QuickTime™ and a decompressor are needed to see this picture.

- Outgrowth of proposal at the 1st International Workshop on Hepatitis C: Resistance and New Compounds (2006)
- *Ad hoc* group approached the Forum for Collaborative HIV Research (FCHR) for organizational support

Purpose

- Bring together parties interested in and working in HCV drug resistance to discuss issues pertinent to HCV drug development and resistance testing
- Composition: representatives from industry, academics and regulatory agencies

Goals

- Produce consensus recommendations of appropriate methodology for HCV resistance testing
  - For drug development
  - For clinical practice
- Provide scientific guidance to facilitate discussion between industry, regulatory agencies, and other parties integral to HCV drug development and resistance

Working Groups

- Sequence Analysis Working Group (SAWG)
  - Ann Kwong, head
- Phenotype Working Group (PWG)
  - Isabel Najera, head
- Clinical Working Group (CWG)
  - Ira Jacobson, head
- Database Working Group (DWG)
  - Jean-Michel Pawlotsky, head

How the SAWG worked together

- Defined Major Issues in broad strokes
- Teleconference calls to discuss sub issues (questions) for each issue
- Draft Recommendation Team volunteered for each issue
- Recommendations compiled and edited by the entire team

HCV DRAG Steps in the creation of SAWG document

1. Bucket Issues into "Dale's Bins"

- Issues where a recommendation can be made after discussion within the working group
  - What region to sequence
  - Viral load requirements
  - Reference sequence
  - Nomenclature
  - Clonal vs population sequencing
- Issues where there are multiple solutions
  - Nomenclature
  - Clonal vs population sequencing
- Issues where not enough information is known to make a recommendation
  - New technologies

HCV DRAG Steps in the creation of SAWG document

2. Form SAWG/PAWG subteam to work on different questions

Issue #5 **Clonal vs population sequencing**

Team: Jean-Michel Pawlotsky, Rob Ralston, Joe Fitzgibbon, Anita Howe, Tara Kieffer, Isabel Najera (leader)

Questions

- Are they in competition or complementary?
- When best used? (POC studies, not phase III)
- Sampling frequency: rebound, retreatment, after dosing,
- Clonal analysis: How many clones should be sequenced?
- Effect of viral load on sampling/ amplification and representation
- Determination of mutation linkage
- Determination of in vivo replicative fitness Sequence analysis: calling mixtures in population sequencing

3. SAWG teleconference and full HCV DRAG discussion

Population vs clonal sequencing

- The use of clonal and population sequencing methods are complementary and can answer different questions.
- To assess the development of selection of resistance upon treatment (in any phase of clinical studies), it is recommended that the initial genetic characterization be performed using population sequencing.
- If population sequencing provides clear data that can explain the "observed" rebound (or if the observed rebound can be explained by other reasons, i.e poor PK), no clonal analysis would be required.

HCV DRAG Steps in the creation of SAWG document

4. Reduction of recommendations to writing

- 2007
  - Subteams wrote recommendations for draft manuscript
  - Sections edited by the entire team
- 2009
  - SAWG and PAWG manuscripts sent to Gastro
  - Editors asked that SAWG and PAWG manuscripts be combined
- 2010
  - Sequence and phenotypic analysis for resistance monitoring in hepatitis C virus drug development: Recommendations from the HCV DRAG, Gastro, in press

HCV DRAG Authorship reflects cross company, regulatory, and academic collaboration

AUTHORS NAMES AND AFFILIATIONS:

Sequence Analysis Working Group (SAWG) and Phenotype Analysis Working Group (PAWG). Ann D. Kwong (Chair, SAWG)[1*], Isabel Najera[2] (Chair, PAWG)[2*], Jill Bechtel[3], Scott Bowden[4], Joseph Fitzgibbon[5], Patrick Harrington[6†], Dale Kempf[7], Tara L. Kieffer[1], Diana Koletzki[8], George Kukolj[9], Sharlene Lim[10], Tami Pilot-Matias[7], Kai Lin[11], Nina Mani[12], Hongmei Mo[13], Jules O'Rear[6†], Michael Otto[14], Neil Parkin[15], Jean-Michel Pawlotsky[16], Chris Petropoulos[17], Gaston Picchio[18], Robert Ralston[19], Jacqueline D. Reeves[17], Robert T. Schooley[20], Scott Seiwert[10], David Standring[21], Lieven Stuyver[8], James Sullivan[1], Veronica Miller [12,], under the auspices of the Forum for Collaborative HIV Research and on behalf of the HCV Drug Development Advisory Group (HCV DRAG).

[1]Vertex Pharmaceuticals, Inc., Cambridge, MA USA
[2]Roche Palo Alto, LLC, Palo Alto, CA USA
[3]Glaxo Smith Kline, Research Triangle Park, NC USA
[4]Victorian Infectious Diseases Reference Laboratory, North Melbourne, Victoria Australia
[5]NIH / NIAID / DAIDS, Bethesda, MD USA
[6]FDA / CDER / OND / OAP/ Division of Antiviral Products, Silver Spring, MD USA
[7]Abbott Laboratories, Abbott Park, IL USA
[8]Virco BVBA, Beerse, Belgium