HCV

Drug

Resistance

Advisory

Group

HCV DRAG: Today's Agenda

HCV DRAG/HCNG Group	Jean-Michel Pawlotsky
Sequence Analysis Working Group	Ann Kwong
Phenotype Working Group	Neil Parkin
Clinical Working Group	Chip Schooley
Moving forward/Next steps	Group

HCV DRAG: RDWG

- Resistance database working group (RDWG)
  - **Volunteers**
  - Connect with all three existing databases
    - Meet in Paris, Feb
    - Input re Stanford HIV database
    - Visible genetics?
  - Issues:
    - Which database?
    - QC issues
    - Submission of pre-therapy sequences (informed consent)
      - Information on regional distribution
    - Submission of post-therepy sequences

HCV DRAG: Data sharing and bases- can we do something now?

- Issues
  - Patient consent might not explicitly cover downloading their info into a public data base
  - The information is very valuable- for commercial assay design (primer info)
  - Sequence data can be very “messy”, don’t want messed up data bases>> delay availability
- Confidence building first step- deposit polymorphism information
  - Prefer individual patient data,
  - But if consent is still a legal problem, 10% of Y patients with geno X from Spain have a polymorphism Z at amino acid position A is doable and valuable

HCV DRAG: VIP WG

- Validation & Implementation of Procedures Working Group (VIP WG)
  - Detailed recommendations on:
    - Validation of sequencing and phenotypic assays
    - Procedures to implement appropriate quality controlled and assured protocols and processes
- **Volunteers?**

HCV DRAG: Nomenclature

- Drug class names:
  - (HCV) PIs
  - (HCV) NIs
  - (HCV) NNIs
- NNI binding site names:
  - Palm/thumb vs NNI sites 1-4?
- Sequences
  - Long version: HCV1a_NS3_R155K
  - Short version (in context): R155K

HCV DRAG: Sequencing following drug failures

- If mechanism of action/resistance for investigational compound is established in preclinical studies (big picture defined):
  - Sequence gene(s) of interest
  - Not necessary to look for IFN/RBV resistance
- If mechanism not defined in preclinical studies
  - More aggressive sequencing required
  - Whole genome sequencing last resort?

HCV DRAG: Potency vs effectiveness

- Revise document to distinguish potency vs effectiveness
  - Potency: related to concentration?
  - Effectiveness: related to viral load/resistance emergence?

HCV DRAG: Validation of different assays

- Groups should be encouraged to provide comparative information between non-replicon assays and a widely available replicon assay for obvious, well-defined mutants

HCV DRAG: Replication capacity

- Effect of backbone on RC can be very large
  - Compatibility issues restrict value of RC on pt isolates
- May be useful in well-defined systems

HCV DRAG: Clinical study considerations

- Should the HCV DRAG be giving specific recommendations on early clinical trial design to maximize the potential for viral kinetic and resistance information?

HCV DRAG: Sequencing after breakthrough

- Distinguish between on-therapy and off-therapy phases
- Recommend longitudinal sample collection
- Recommendations for monitoring for reversion following end of treatment, including (and maybe especially) in early monotherapy studies
- Best place for discussion of this issue: Sequencing or clinical section?
  - Recommendations for protocol design

HCV DRAG: POC studies

- How many days of dosing is needed to establish doses?
- What is the effect of perturbing the quasispecies by short-term monotherapy?
- Document should spend time on design of studies to assess persistence
- Important to understand clearance of wt virus and how that affects rebound

HCV DRAG: Monotherapy studies

- Optimal duration
  - 7 days?
  - 1st phase vs 2nd phase
  - Input from viral kinetic models?

HCV DRAG: Special populations

- Transplant pts
- Multiple genotype pts

HCV DRAG: Combo studies

- Combination small-molecule studies
  - Most appropriate context?
    - Alone (2 drugs)?
    - Combo with PEG or RBV?
    - Combo with PEG/RBV?
- Regulatory
  - FDA may consider small exploratory dual therapy studies

HCV DRAG: Materials Repository

- Consider combined repository for US and EU
  - Paperwork considerations
- What would be deposited?
  - Standard strains
  - Clinical specimens
    - Require explicit informed consent
    - Account for regional differences

HCV DRAG: The Future?

- Should the OC pursue avenues to fund this group with the Forum for 2008?
  - Two meetings
  - Teleconferences