

Berkeley



**FORUM**  
for Collaborative  
**RESEARCH**

# Session V: The CMV Refractory and Resistant Disease Definition Working Group

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# Definition of Drug Resistance

- A viral genetic alteration that decreases susceptibility to one or more antiviral drugs
- Question for discussion
  - As worded, this is a purely virologic definition, is not dependent on clinical criteria (treatment outcomes, etc)
  - Is this agreeable ?
  - If so, define the phenotypic criteria for resistance, the associated genetic changes, and how to detect and correlate them in diagnostic lab practice

# Drug Resistant Phenotype

- Detected as increased drug concentration required to reduce viral growth 50% (EC50)
- Questions of standardization
  - How much of an increase in EC50 defines resistance (statistically significant rise, 2x, 5x ?)
  - Assay standardization and controls (operator, inoculum and cell culture dependence of data) (readout of viral growth – plaque, DNA, reporter gene, etc) (controls, replicates, and technical standards ?) (no standardized proficiency testing system exists)

# Drug Resistant Genotype Definition

- Canonical mutations
  - The most common ones found in clinical specimens in association with a drug-resistant phenotype
  - Role in drug resistance confirmed by marker transfer to baseline laboratory strain (recombinant phenotyping)
  - Degree of resistance and cross-resistance established preferably after multiple independent studies
- Additional or accessory resistance mutations
  - Observed in vivo or in vitro and shown to confer specific levels of resistance by recombinant phenotyping
  - May add to other mutations to increase level of resistance

# Uncharacterized Mutations

- Other amino acid substitutions in genes implicated in drug resistance, with unknown phenotypic effects on drug resistance
  - Baseline sequence variants, previously known or unknown (if no prior drug exposure, often disregarded)
  - Changes from a baseline sequence after drug exposure (usually taken more seriously, but may just be infection by a different viral strain)
  - What to do with these findings in diagnostic practice and in clinical trials ?  
(how to determine if “resistance associated”)  
(criteria for selection for recombinant phenotyping)

# Best Practices for Resistance Monitoring

- Not issues of **definition**; should they be addressed in this document:
  - Indications for genotypic testing for resistance, in clinical practice and during clinical trials
  - Intervals and criteria for resistance testing in clinical trials
  - Quality control of genotypic testing – very important (specimen selection, handling, preparation, sequencing technology, authentication of sequence findings)
  - How to select unrecognized mutations for phenotyping
  - Interpretation of (levels of) phenotypic resistance with respect to need for/selection of alternative therapy