Forum for Collaborative HIV Research

Working Group#1: Trial Endpoints, Biomarkers & Definitions

Forum HIV Cure Project: Focus on The Regulatory Pathway
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Comments from co-chairs

John Mellors and Mike Miller

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Subgroups

- Preclinical Testing & Trial Design Issues
- Biomarkers, Endpoints, Assays
- Definitions of Cure

Thanks To Working Group Members

Preclinical Testing & Trial Design Issues

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Biomarkers, Endpoints, Assays

Nicolas Chomont*, Tri Do, Susan Fiscus*, David Margolis, John Mellors, Chris Petropoulos, Una O'Doherty, Carol Weiss, Javier Martinez-Picado, Paul Sato, Tim Schacker, Janet Siliciano

Definitions of Cure

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Preclinical Testing & Trial Design Issues

Co-leads: rowena johnston* and mike miller

Building Preclinical Evidence To Support Clinical Testing: In Vitro/Ex Vivo

- Cell-based models can generate supportive evidence

For example:

- Assays to test effectiveness of inducers – measure cellular HIV RNA, protein expression, virus production, or infectious virus production:
  - Transformed cell lines
  - Ex vivo primary cell infection models
  - Authentic latently-infected cells from suppressed HIV-infected patients
- Assays to measure cell killing
  - e.g. CTL, antibodies

Building Preclinical Evidence To Support Clinical Testing: Animal Models

- Efficacy in animal models not generally required before proceeding to clinical studies in humans but can be supportive
- Relevance of the animal model will depend on the mechanism of the agent and biological question one is trying to answer
  - Plan to write position paper on current knowledge, gaps in research and the challenges on the road towards making recommendations for the use of animal models in cure research

Does a Predictor of Outcome in an Animal Model Need to be Validated as a Predictor of Outcome in Humans?

- A biomarker shown to be predictive in animals would initially be considered an exploratory biomarker
- All candidate biomarkers would require demonstration of clinical predictive value to be used for licensure

How Are Contributions of Individual Components of Combination Therapies Assessed?

- Multiple endpoints/biomarkers are likely to be required
  - definition of success is likely to differ depending on the curative intervention
- Evidence demonstrating the contributions of individuals agents within a combination would be needed
  - multiple ways to fulfill these requirements
    - biomarkers, factorial design, etc
  - will also depend on phase of testing

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Biomarkers, Endpoints & Assays

co-leads: susan fiscus* and nicolas chomont

What Biomarkers Should be Analyzed to Determine if a Therapeutic Effect of a Curative Intervention Has Been Achieved?

- Probably dependent on curative strategy
- To date, there are no validated biomarkers that predict the therapeutic effect of an intervention
  - Existing assays have not been standardized or validated, and have been assessed on relatively few subjects with highly variable results
- Both virologic and immunologic markers likely to be needed

Markers to Consider-Virologic

- Total and integrated HIV DNA
  - including total DNA in gut-associated lymphoid tissue (GALT) and rectal HIV RNA/DNA ratio
- Cell-associated HIV RNA
  - need more clarity on which species of RNA to measure
- Plasma HIV RNA
- Inducible cell-associated RNA or virus production from resting and total CD4+T cells
- Infectious virus recovery from resting CD4+T cells

Markers to Consider-Immunologic

- Cytokine production
- HIV specific T cells (tetramers) and PD-1
- HIV Abs
  - WB as screen, then Luciferase Immunoprecipitation Systems (LIPS)
- Activation markers
  - CD38/HLA DR

What Criteria Warrant An Analytical Treatment (ATI) Interruption?

- Which patients?
  - Uncertain, but emphasis on reducing risk
- How to perform?
  - Dependent on intervention and probability of rebound but monitor plasma HIV RNA 1-3x/week for 3-4 weeks, then less frequently
- Criteria to define therapeutic success after ATI?
  - Plasma HIV RNA < 200 c/ml
    - Clinical significance of <200 c/ml while off ART is unknown
    - Disease progression may still be possible.
  - No more than 25% decline in CD4+ T cells or a drop to <350 cells/mm^3

What Biomarkers Should be Analyzed as Predictors of Analytical Treatment Interruption Outcomes?

- To date, no validated biomarkers that predict viral rebound after ATI
- Validity of the marker may depend on the specific therapeutic strategy
  - Both virologic and immunologic markers will probably be needed
- Need more data
  - Select a few assays, standardize procedures, validate the assay, test in a number subjects (how many?)

Definitions of Cure

Co-leads: joe fitzgibbon* and mike lederman

Definition of "Cure"

- Data-driven term as a potential virologic endpoint for phase I/II clinical trials
  - $VSOT_{weeks}$: "Virologic Suppression Off Therapy" followed by a number that indicates the duration in weeks
  - Permutations of VSOT:
    - $VS_{LLD}OT_{weeks}$ to include the method (limit of detection of assay) used to define virologic suppression
    - Partial VSOT (pVSOT) to indicate suppression with VL<200 c/ml
    - Complete VSOT (cVSOT) to indicate undetectable plasma viral RNA by most sensitive assays

Definition of "Cure"-cont'd

- Is VSOT sufficient? How to include CD4+ decrease and immune activation/inflammation?
  - Preservation of CD4+ count
    - Uncertain; potential criteria: No more than 25% decline in CD4+ T cells or a drop to <350 cells/mm^3
  - Unclear whether viral eradication will lead to full immune restoration and normalization of activation and inflammation indices
    - Different eradication strategies may differentially affect immune restoration and activation
    - Need to be aware of potential trade offs between VSOT and persistent or increased immune activation/inflammation
  - Non-virologic endpoint criteria may need to be adjusted for infants and young children

HOW LOW SHOULD PLASMA HIV RNA BE?

- Stepwise approach in phase I/II studies; the sequence may differ depending on curative strategy
  1. <200 c/ml using standard clinical assays but detected on occasion using single copy assay (SCA)
     - Clinical significance of <200 c/ml while off ART is unknown
     - Disease progression may still be possible
  2. Consistently not detected using SCA and repeated measures to look for infectious virus in cells using best available assays
  3. When best available assays fail to show evidence for viral persistence, consider additional invasive studies to search for HIV in other reservoirs such as gut, lymph nodes, CNS
- Data will inform design of phase IIb/III clinical studies

HOW LONG SHOULD REMISSION BE?

- Ideally $VSOT_{\infty}$ (i.e. life-long)
  - not a practical endpoint for clinical trials
- $VSOT_{52}$ (i.e. one year) may be a good starting point, especially from the perspective of virologic control
  - Elite controllers with consecutive HIV RNA measurements <50-75 c/ml and at least 1 year follow-up had similar clinical outcomes as those followed longer[1]
  - One of the "Boston patients" maintained virologic suppression for 32 weeks post treatment interruption[2]
  - Uncertainty surrounding the importance of shorter intervals (e.g. six months)

[1] Olson et al. PLoS ONE 2014; 9(1): e86719 [2] Henrich et al. CROI 2014. Abstract 144LB

Definition of Cure & Mechanism of Remission

- Different definitions of cure are not needed for different populations (acute, chronic, neonate)
  - CD4+ and biomarker endpoints for infants and young children may be different from adults
- An identified mechanism of remission for a particular curative intervention would be desirable but not required as long as the intervention is shown to be safe and effective
- Regardless of mechanism, long-term follow-up patient registries is strongly recommended

WG Recommendations

- Position paper highlighting current knowledge and gaps in research on using preclinical animal models in HIV cure research.
- Biomarkers predictive of "cure"—need more data/studies
  - Select a few assays, standardize procedures, validate assays, test in subjects
- $VSOT_{weeks}$ as a virologic endpoint to be considered in clinical trials

Panel Discussion

- Damon Deming (CDER, FDA)
- Susan Fiscus (UNC)
- Joe Fitzgibbon (DAIDS, NIH)
- Richard Jefferys (TAG)
- Rowena Johnston (amfAR)
- John Mellors (UPitt), moderator
- Mike Miller (Merck), moderator

Discussion Questions

- What are potential limitations to the implementation of the VSOT terminology?
- What studies and additional collaborations are needed to accelerate the development of biomarkers that are predictive of VSOT?