COMMUNITY AND STAKEHOLDER ENGAGEMENT:
BACK TO BASICS SCIENCE

CFAR WORKSHOP - UCSF Mission Bay
This workshop takes place on traditional homeland of the Ohlone people. It has significance for a wide range of connected yet distinct Indigenous Peoples to whom we give thanks for this opportunity to discuss and learn together.

MAY 17, 2019
ROBERT REINHARD, M.A.
Public/Global Health Consultant
DISCLOSURES

- No Financial Disclosures
- I’m Impatient

I'm selfish, impatient and a little insecure. I make mistakes, I am out of control and at times hard to handle. But if you can't handle me at my worst, then you sure as hell don't deserve me at my best.

MARILYN MONROE
WORDPORN.COM
• Instill confidence in a robust community engagement practice within early stage basic science research

• Provide suggestions how to carry that out
Overview
Clinical and translational research is characterized by a spectrum of activities where critical insights are passed between research modalities so that biomedical discoveries can lead to tangible improvements in human health. Explore the videos and interactive diagram to learn more.

Clinical and Translational Research Spectrum

Examples include:
- Human Physiology
- First in Humans (FiH)
- Healthy Volunteers
- Proof of Concept (POC)
- Phase 1 Clinical Trials

Examples include:
- Phase 2 Clinical Trials
- Phase 3 Clinical Trials

Examples include:
- Phase 4 Clinical Trials
- Health Services Research
- Dissemination
- Communication
- Implementation
- Clinical Outcomes Research

Examples include:
- Community-Based Participatory Research (CBPR)
- Cost-Effectiveness/Comparative Effectiveness
- Health Disparities
- Public Policy

Control of Experimental Conditions

Translational Activity

References:
Pathfinder is based on material contained in the following three journal references.


https://catalyst.harvard.edu/pathfinder/t1detail.html
HIV CURE AND VACCINE TO RESEARCH CONTEXT

- Exploratory HIV cure and vaccine research
- Missing correlates, markers, targets
- Cure definition subject to wide debate
- People are not Jurkat cells, mice, rabbits, cows or NHP

People supply samples:
primary cells, CSF, tissue in biopsy/autopsy
<table>
<thead>
<tr>
<th>EXPERIMENTAL MEDICINE</th>
<th>CLINICAL TRIAL/marketing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulate hypothesis, not product focused</td>
<td>Product development: phase 1-4</td>
</tr>
<tr>
<td>Data for a concept/safety</td>
<td>Safety/efficacy end goal</td>
</tr>
<tr>
<td>Humans are best preclinical animal</td>
<td>Humans are object of therapy</td>
</tr>
<tr>
<td>Exploring basic immunology/virology</td>
<td>Reducing/eliminating/preventing disease</td>
</tr>
<tr>
<td>Not GMP oriented</td>
<td>GMP included</td>
</tr>
</tbody>
</table>
HIV CURE RESEARCH ORIGINS

Martin Delaney attends CROI XV, finds Berlin patient poster
Preceded by years of advocates’ call for HIV immunotherapy research
Delaney Interview: http://www.thebody.com/content/art53674.html
Engagement ≠ Unilateral top/down education; study recruitment; consent; one off consultation

Citizen engagement

Citizens are "engaged" when they play an active role in defining issues, considering solutions, and identifying resources or priorities for action. This "meaningful involvement" can take place at a variety of stages in the research, planning, or implementation phases of a project.

Engagement = Mutual knowledge, translation and exchange (KTE); Involvement in purpose, design, execution, results dissemination throughout the course of study; professional collaboration
Stakeholder Engagement in HIV Cure Research: Lessons Learned from Other HIV Interventions and the Way Forward

Ying-Ru Lo, MD, Carissa Chu, BS, Jintanat Ananworanich, MD, PhD, Jean-Louis Exler, MD, and Joseph D. Tucker, MD, PhD, MA
Difficulties of Community Advisory Board only:

- Meaningful representation
- Soft and hard science
- Think globally act globally
- Covering all research steps and milestones
- Engaging the understudied* – [transgender people, coinfection, hemophiliacs, marginalized groups, youth]
- Language and mutual literacy

* The biological and social imperative
SUGGESTED PRACTICES - I

- Start to finish involvement
  - Grant application, study and protocol design drafting
  - ICF drafting and public facing materials
  - Encourage community members to obtain GCP certifications
  - Community budget in early stage
- Credit as a success marker: ICMJE criteria for authorship or contribution acknowledgement. Defining the Role of Authors and Contributors in publications
  

---

DON'T DO THIS! Or as in prior APCS slide
Structures and outreach – Remember what Warner Greene said

- CAB
- Baraza*
- The Buddy System - Science and community buddies at conferences, meetings, seminars
- Don’t confuse structure with outcome

*See Resource slide cite #5
Science Communication – Remember what Warner Greene said

• SOP for participant results dissemination in samples only or experimental medicine – the role of the lay draftsperson
• Get out of your lab or conference – be as cool 😎 as you think you are
• Get help from your buddy
• Community visit to lab and journal club
• Ask your buddy to present a journal article
Gene Therapy Researchers’ Assessments Of Risks And Perceptions Of Risk Acceptability In Clinical Trials

Claire T. Deakin¹,², Ian E. Alexander¹,³, Cliff A. Hooker⁴,⁵ and Ian H. Kerridge⁴,⁵

Molecular Therapy (2013) 21 806-815
<table>
<thead>
<tr>
<th>Scenario</th>
<th>No available treatment, death in infancy</th>
<th>No available treatment, death in early adulthood</th>
<th>No available treatment, death in childhood/adolescence</th>
<th>No available treatment, life expectancy reduced by 20 years</th>
<th>Disease curable by bone marrow transplant, with risks and side-effects</th>
<th>Disease controlled by blood transfusions</th>
<th>Disease controlled by diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell culture only, knock-out mouse available in 2 years</td>
<td>56.4%</td>
<td>53.2%</td>
<td>42.9%</td>
<td>26.8%</td>
<td>19.9%</td>
<td>16.0%</td>
<td>9.0%</td>
</tr>
<tr>
<td>Cell culture only</td>
<td>61.5%</td>
<td>57.1%</td>
<td>46.2%</td>
<td>33.3%</td>
<td>26.8%</td>
<td>19.9%</td>
<td>10.9%</td>
</tr>
<tr>
<td>Poor mouse model</td>
<td>81.4%</td>
<td>81.4%</td>
<td>71.2%</td>
<td>56.4%</td>
<td>44.2%</td>
<td>33.3%</td>
<td>23.7%</td>
</tr>
<tr>
<td>Good mouse model, large animal study would delay trial by 3 years</td>
<td>86.5%</td>
<td>87.2%</td>
<td>76.9%</td>
<td>59.8%</td>
<td>50.0%</td>
<td>37.8%</td>
<td>30.3%</td>
</tr>
<tr>
<td>Good mouse model and data from related phase I trial with low frequency AEs</td>
<td>91.0%</td>
<td>91.0%</td>
<td>86.5%</td>
<td>71.8%</td>
<td>61.5%</td>
<td>41.0%</td>
<td>30.3%</td>
</tr>
<tr>
<td>Good mouse model</td>
<td>90.4%</td>
<td>90.4%</td>
<td>88.5%</td>
<td>73.7%</td>
<td>64.7%</td>
<td>54.5%</td>
<td>39.1%</td>
</tr>
<tr>
<td>Good mouse model and data from related phase I trial with no AEs</td>
<td>96.2%</td>
<td>96.8%</td>
<td>93.6%</td>
<td>82.1%</td>
<td>76.0%</td>
<td>64.7%</td>
<td>64.7%</td>
</tr>
<tr>
<td>Large animal model</td>
<td>97.4%</td>
<td>99.4%</td>
<td>98.7%</td>
<td>93.6%</td>
<td>90.4%</td>
<td>83.3%</td>
<td>72.4%</td>
</tr>
</tbody>
</table>

Figure 1: Percentage of respondents who agreed it would be appropriate to recruit subjects to a phase I clinical trial for each of the hypothetical clinical scenarios based on data generated in each of the preclinical models. The radii of the circle behind each of the percentage values represents the relative proportions of respondents who agreed it would be appropriate to recruit subjects to a phase I trial. AEs, adverse events.
Thematic analysis indicated participants expressed initial fear about cell and gene therapy research. They articulated specific concerns about risks, including analytical treatment interruptions, and thought only a person in desperate straits would participate. They were satisfied with their health and quality of life on antiretroviral therapy.

Respondents’ willingness to risk death for a cure varied widely (median 10%, 75th percentile 50%). In multivariate analyses, willingness to risk death was associated with expected long-term side effects of ART, greater financial resources and being employed (all P < 0.05) but was not associated with perceptions of how their health would improve if cured.
A cure research proposal: HIV Cure in the setting of HIV/TB coinfection

https://www.dropbox.com/s/agxbeo4e3woz51i/affect%20of%20TB%20on%20HIV%20cure%20research%20journal%20club%20paper.pptx?dl=0

Immune system background:

• HIV-1 infects alveolar macrophages (AM), a reservoir and site of persistence
• Mtb and HIV-1 can co-locate in a single AM – pathways and signals and expression
• Coinfection contributes to increased immune activation persisting beyond TB clinical cure, higher surface markers (e.g. CD38) compared to monoinfection.
• Latent TB also increased levels of Tcell activation, cells are HIV(and reservoir) target
• HIV-1 viral heterogeneity in Mtb infected lung ↑ than in Mtb uninfected
• Pulmonary TB in HIV-1 + participants gives rise to 2-3 X greater HIV mutation frequency compared to HIV-1 monoinfected
• Spinal HIV-1 evolution may be specific with TB coinfection
• CD8 T cells show increased impairment compared to monoinfection

Elucidate repercussions of increased HIV-1 heterogeneity at the site of Mtb infection

Does it persist after antituberculosis treatment (ATT)

Are disease sites adequately penetrated by ART as prelude to immunotherapy

Do divergent HIV-1 quasispecies contribute to increased systemic HIV-1 viral fitness and accelerated progression to AIDS

Reservoir size, dissemination, cell type in coinfection

HIV persistence under various ART or ATT scenarios, latent infection, TB activation

TB Extra-pulmonary site susceptibility to HIV cure intervention

Suitability of strategies (e.g. TxVx vs cell/gene therapy to coinfected populations)
April 7, 2017

**NIH Funding Opportunity Title RFA - Dysregulation of Immune Cell Regulatory Pathways by Mtb in the Context of HIV Infection (R61/R33)**


---

May 13, 2019:

**NIAID Welcomes Opportunity to Broaden HIV-Related Basic Biomedical Research Portfolio**

Despite significant scientific advances, many important questions about HIV remain unanswered. These outstanding questions are particularly critical to the pursuit of a safe and highly effective HIV vaccine and a cure. Additionally, the basic biology of many critical co-infections, including tuberculosis and hepatitis B and C, remain essential research avenues that must be explored and addressed to improve the health of people with HIV.

TAKE AWAY

TO SCIENTIFIC INVESTIGATORS:
Community engagement is as complex as latency and persistence

TO NON-SCIENTISTS:
Cure advocacy asks as much study as Harrington, Snow and Delaney supplied to NIH in the 1980’s and 90’s

Mark Harrington: “affected communities should have input about the research agenda itself”
SELECTED RESOURCES


6. AVAC. CUREiculum Stakeholder Engagement in Cure Research https://www.avac.org/cure-curriculum/module2

ACKNOWLEDGEMENTS

San Francisco/Bay Area
Jonathan Fuchs, Monica Gandhi, Susan Buchbinder, Bill Snow, Matt Sharp

USA
Scott Hammer, Mark Harrington, Joseph Tucker, James Lavery, HVTN, AVAC

Canada
Darien Taylor, Craig McClure, Renée Masching, Wangari Tharao, Ron Rosenes, Trevor Stratton, Ken Monteith, Charlotte Guerlotté, José Sousa, Shari Margolese, Mario Ostrowski, Shariq Mujib, Rupert Kaul, Soo Chan Carusone, Sharmistha Mishra, Ann Burchell, Eric Arts, Keith Fowke, Petronela Ancuta, Nicolas Chomont, Jason Brophy, Fatima Kakkar, Canadian HIV Trials Network (CTN), Jennifer Gunning Int’l

Andy Lambert, Damian Kelly (Patient Advocacy Alliance), Sharon Lewin, IAS Towards an HIV Cure