

Future Collaborations: Synopsis of Small Group Breakout Sessions

Group A: Diagnostic and Drug Susceptibility Testing

Facilitator: Mary Ann De Groot, Colorado State University

COLLABORATIVE PROJECTS

- 1) Microphage: Partner to be identified. Goal is to propel the use of phage for diagnostics for TB
Advantages: cheap, rapid and direct using an easy to read device
Jack and Scott will meet with Academic people at CSU, NJC and UCDHSC to identify a PI for an R21 grant.
During discussions with the academic labs, the company will seek collaborations and also learn how to apply for funding.
- 2) Molecular Probes. Identify who is interested (potentially M. De Groot in close working relations with Norm Pace and Dan Frank at looking at probes hybridized after a period of incubation with drug or no drug to determinant if probes can be used for drug susceptibility testing). Mary Ann will discuss further with Norm Pace. Probes are attractive as the LED microscopes are becoming cheaper and this may work in developing world.
- 3) Dean Crick and M. De Groot will ask around if there are any vet students interested in using animals for detecting TB infected patients in a crowded waiting room similar to what dogs do with epilepsy patients to predict and warn in the event of a seizure coming on.
- 4) NIH has an emphasis on children being included in diagnostics so Carlos will be collecting samples with the string test and his induced sputum tests. Samples will be saved and shared.
- 5) Tom Campbell and other members of ACTG will have field places to test any tests that may come out of this effort (Tom's involvement in Zimbabwe and Carlos in Columbia).

PRESENTATION/DISCUSSION POINTS

- Ian said don't do R21, go the STTRs or SBIR. Christine Sizemore said that maybe now the R-series of grants may be better as the NIH is now emphasizing diagnostics more than it did in the past. Good news hopefully for diagnostics.
- Scott said he doesn't have the expertise but Microphage and does not have BSL-3 lab so point number 1 above is key
- Request SBIR since it is a product and it goes through SBIR study section.
- Christine: NIH needs to address how they can do diagnostics better to make it more successful. They are trying to figure out how to fix it.
- Pat Brennan: Looking for LAM (was at FIND in Geneva last week). His group has the tools, molecular tests, antibodies and knowledge that could enter into collaborations.
- LAM serum was forming complexes so they moved to urinary tests. Will include Dr. Brennan on this to see if specific projects can emerge.

Group B: Pharmacokinetics

Facilitator: Peter Anderson, UCDHSC

COLLABORATIVE PROJECT:

1) New RFA for R01/NIH: PK in Peds and this fits well as a grant opportunity with other focus groups.

PRESENTATION/DISCUSSION POINTS

- Limited Sampling: patients with most variable PK (infants, elderly, very sick) are the most difficult to get the samples on. Traditionally, in order to best create a PK picture, is to get multiple samples. Novel ideas: Develop a non-invasive, field-ready method for quantifying PK in difficult to sample patients. For example, saliva, urine, but most promising is dried blood spots on paper which could then be reconstituted for drug concentrations. Start with a study to validate the idea (developing the lab technique and performing a proof-of-concept evaluation).
- Some of the most promising TB agents in development are highly lipophilic. A serious PK problem with such agents is bioavailability and formulations and some highly active drugs are killed because of these problems. Some of the lessons we have learned in the HIV field with highly lipophilic protease inhibitors may be relevant for TB drugs (e.g. wax matrices for tablets, etc). Other ideas that were discussed include nanotechnology-delivery. These ideas could be tested in animals using PK.
- Novel Delivery Mechanisms: Inhaled drugs: can we make inhaled formulations of aminoglycosides (for example) for tissue-targeted delivery. Problems: not every TB patient is infected in the lungs only.

Group C: Vaccines

Facilitator: Edward Janoff, UCDHSC

Rapporteur: Ed Chan, NJ, VA

PRESENTATION/DISCUSSION POINTS

Several potential vaccine projects were discussed:

1) Strain-specific virulence. The question is whether both common laboratory strains (e.g., RV) and virulent clinical strains elicit the same quality and magnitude of pathology in animal models (mouse vs. guinea pig).

2) Strain-specific protection: The question was whether vaccine (BCG and newer candidates) protects equally well against common lab strains (e.g. RV) compared with virulent clinical strains. These tests can be done in the animal model, either mouse or guinea pig,.

Each of the above studies could be addressed in a

3) Therapeutic vaccine. The question is whether i) vaccine enhances outcome of therapy with antimicrobials and/or ii) whether vaccine would delay disease progression in cases

of MDR so disease would progress less quickly if initial drug regimen proved ineffective while sensitivities were pending. Many deaths from MDR occur quickly, particularly among patients with HIV coinfection. Using strains selected above, would a) infect with either MDR, virulent or lab strains, b) give vaccine or placebo, c) give antimicrobial treatment or not, and d) follow outcome and pathology in the 6 groups.

4) CD4-dependence of TB Vaccines. CD8-mediated protection, whether from CTL or other functions, may occur independently of CD4 direction. In the context of HIV or in considering HIV, animals could be a) CD4 depleted or replete, b) immunized with e.g. SecA2 vaccine, c) monitor CD8 responses. Future animal studies could involve challenge of the CD4-replete or depleted animals with live TB and follow clinical and microbiologic outcomes. The limitation for any testing in HIV-infected patients is the early stage of development of the vaccine and that the vaccine is live.

COLLABORATIVE PROJECT:

AERAS, CSU Mycos:

- Source of clinical isolates and source of vaccines will come from AERAS foundations.
- AERAS can test the vaccine
- Design rational animal model testing (clinically relevant)

Biologic questions included discussion of when you catch TB, you don't instantly generate immunity, responses which may require 90 days in a mouse. If you design a therapeutic vaccine, given after infection is diagnosed, could accelerated the host response to the hosts benefit or detriment. If infection-related responses are already present at diagnosis, would the vaccine have an effect. May be useful if TB-exposed but not infected subjects. Limitations of the discussions were also how to make these projects collaborative and to extend testing to humans.

Group D: Pre-Clinical Drug Development

Facilitator: Richard Slayden, Colorado State University

GOALS

- 1) To arrive at consensus about a strategy of drug development and slot people from this conference into this strategy
- 2) Discuss appropriate strategies for target discovery and development
- 3) Identification of drug classes: rational drug discovery or optimization of existing lead candidates
- 4) Identify access to molecular libraries and medicinal chemistry
- 5) Identify expertise in promoting lead drug candidates beyond preclinical stages of development
- 6) Identify potential funding strategies to support such a large drug discovery effort.

COLLABORATIVE PROJECT AND TASKS

- 1) To identify suitable libraries for the effort we are about to undertake. Sources outside or lead compounds within that group
- 2) How support library with medicinal chemistry? Need to get medicinal chem. People involved

- 3) Strategies and approaches to improve on PK/PD, bio availability and deliverability
- 4) Strategy regarding the transition between identification and development of preclinical leads
- 5) Optimizing use of existing drugs (lead optimization vs. optimizing old)

ACCOMPLISHMENTS

- 1) Established the Colorado Pre Clinical Drug Development Consortium (CPCDDC)

OTHER DISCUSSION/IDEAS

Potential International Sites

- CFAR: have Zimbabwe site and Uganda site
- TBTC: high enrollment sites as well (Brazil, Spain and S. Africa)

Group E: BIOMARKERS

Facilitator: Bob Horsburgh, Boston University School of Public Health and CFAR Visiting Scholar

COLLABORATIVE PROJECTS:

Project #1: Evaluation of animal model data.

- Need to look at existing patterns of soluble immunologic markers in serum in animals being treated for TB
- Small grant could support analysis
- Research Question: what patterns of IL-10, TGF-beta, sCD14, others are optimally predictive of responses to therapy in animal models?

Project #2: Microbiologic markers

- In humans, Ag85 and LAM are both detectable in serum and perhaps in urine
- These are being evaluated for diagnosis but not for prognosis
- Prospective evaluation of these in a clinical trial is a logical step. First we need some data from patients on treatment to determine that these are feasible

Other Ideas

- IGRA tests – not practical for clinical trial because need PBMC
- Bacterial gene products - need to better characterize
- Detection by microarrays – need animal model data. There is a group working on this, funded by the Global Alliance