Report:
International Symposium on Natural Immunity to HIV
Consortium Building

Winnipeg, Manitoba

November 15 – 17, 2009

Prepared for

The International Symposium on Natural Immunity Scientific Steering Committee

Prepared by:

The International Centre for Infectious Diseases

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Table of Contents

Meeting Agenda

Sunday November 15

18:30 – 21:00	**Registration**
19:00 – 22:00	**Welcome Reception** • *Remarks and Introduction* ◦ *Heather Medwick, A/President and CEO, ICID* ◦ *Dr. Frank Plummer, Scientific General, National Microbiology Laboratory, PHAC* **Poster Viewing**

Monday November 16

8:30 – 9:00		**Welcome and Opening Remarks** • *Frank Plummer – Scientific General, National Microbiology Laboratory, PHAC* • *David Butler-Jones – Chief Public Health Officer, PHAC* • *Digvar Jayas, Vice-President (Research) University of Manitoba*
9:00 – 10:00		**Keynote Presentation** • Gene Shearer – Senior Investigator, NIH *Historical Perspective of Exposed Seronegatives (ESN) – Has nature done the experiment for us?*
SESSION: Correlates of Protection Against HIV infection • *Chair: Blake T. Ball, A/Chief, National Laboratory for HIV Immunology.*	10:00 – 10:30	**HIV and Host Genetics** • Amalio Telenti – Director, Institute of Microbiology, University of Lausanne *Integrating Large Scale Genomic Data*
	10:50 – 11:20	**Systems Biology** • Elias Haddad – Associate Scientist, Vaccine and Gene Therapy Institute. *The Study of Immunological Memory during HIV Infection.*
	11:20 – 11:50	**Mucosal Factors** • Kristina Broliden – Head, Infectious Disease Unit, Karolinska University Hospital *Mucosal Immune Responses in the Genital tract of HIV-Exposed Uninfected.*
	12:50 – 12:00	**Summary and Discussion**
	12:00 – 13:30	**Working Lunch – Panelist Discusson: Genetic Factors** • Blake T. Ball - A/Chief, National Laboratory for HIV Immunology. • Panelist: Mario Clerici, Paul McLaren, Elias Haddad
	13:30 – 14:00	**Innate Factors** • Galit Alter - Assistant Professor of Medicine, Ragon Institute. *Innate Immune Function in HIV Infection.*
	14:00 – 14:30	**Viral Factors** • Thomas J. Hope – Professor, Northwestern University *Interaction of HIV with Male and Female Genital Mucosal Barriers*
	14:30 – 15:00	**Animal Models** • Cristian Apetrei – Associate Professor, University of Pittsburgh *Natural Resistance to Lentiviral Infection: Lessons from Animal models.*
	15:00 – 15:10	**Discussion and Summary**
	15:30 – 16:00	**Vaccine** • Merlin Robb – Deputy Director (Clinical), U.S. Military HIV Reseach Program *RV144: the Thai Phase III Efficacy Study of ALVAC-HIV Prime and AIDSVAX Boost: Implications for Future Studies*
	16:00 – 16:30	**Protective Immunity** • Michael Lederman – Professor of Medicine, Case Western Reserve University *What we know, what we don't*
	16:30 – 17:00	**Lessons Learned** • Gianfranco Pancino – Director, Research Unit, Pasteur Institute. *Studies on HIV-exposed uninfected individuals in Asia and Africa.*
	17:00 – 17:10	**Summary and Discussion**
18:15 – 22:00		**Winnipeg Art Gallery Dinner Excursion and Keynote Presentation** • Bruce Walker – Director, Harvard University Center for AIDS Research *The International HIV Controllers Study: Lessons Learned.*

Tuesday November 17

8:15 – 8:30		**Introduction of consortium concept and discussion groups** • Blake T. Ball - A/Chief, National Laboratory for HIV Immunology. • Yegor Voronin – Science Officer, Global HIV Vaccine Enterprise
Session: Exposed, Uninfected Groups • *Chair: Keith Fowke - Professor, University of Manitoba*	8:30 – 9:00	**Commercial Sex Workers – Building Relationship** • Joshua Kimani – Clinical Director, University of Nairobi and University of Manitoba *Driving Kenyan HIV/AIDS research: The studies among female sex workers*
	9:00 – 9:30	**Commercial Sex Workers** • Keith Fowke – Professor, University of Manitoba *The Role of Immune Quiescence in Protecting against HIV Infection*
	9:30 – 10:00	**Discordant Couples** • Mario S. Clerici – Chair, Immunology, University of Milan *A Role for Innate Immunity in the Resistance to HIV Infection in Discordant Heterosexual Couples*
	10:30 – 11:00	**Intravenous Drug Users** • Nicole Bernard – Associate Professor, McGill University. *A role for Natural Killer (NK) cells in protection from HIV Infection: HLA/KIR genotype and NK functional potential*
	11:00 – 11:30	**Men who have Sex with Men** • Roger Detels – Professor, University of California *Studies on Resistance to HIV Infection in the MACS*
	11:30 – 12:00	**Breast Milk** • Grace Aldrovandi – Associate Professor, University of Southern California. *Exploring the Milky Way: What Breasts and Babies can teach us about Innate Immunity*
	12:00 – 12:30	**Summary and Discussion**
12:30 – 13:30		**Working Lunch – Panelist Discussion: Immune Correlates of Protection** • Keith Fowke – Professor, University of Manitoba • Panelist: Michael Lederman, Galit Alter, Kristina Broliden
13:30 – 15:00		**Breakout Sessions – Consortia Building** • Discordant Couples • Commercial Sex Workers / Men who have Sex with Men • Intravenous Drug Users / Mother to Child Transmission / Additional
15:15 – 17:30		**Summary of Breakout Sessions , Consortia Discussion**
17:30 – 18:00		**Final Comments, Closing Remarks, Announcement of 2010 Meeting**
18:00 – 19:00		**Casual Buffet Dinner**

Executive Summary

In partnership with the Public Health Agency of Canada (PHAC) and the University of Manitoba, the International Centre for Infectious Diseases hosted an international event to bring together top researchers from around the world to share research and form collaborations. The first goal of the program was to bring together 100 leaders in HIV/AIDS from around the world including researchers, key stakeholders and thought leaders in immunology, genetics and systems biology to share research findings. The second goal was to create a consortium that will develop a framework for assembling and correlating the existing data and drive and support new and expanded international research activities to build scientific knowledge that will inform the development of an HIV/AIDS vaccine.

HIV/AIDS research groups have repeatedly encountered individuals who appear to be immune to infection as judged from their seronegative status after repeated exposure to the virus. This natural resistance or immunity to infection offers a potential basis of an HIV/AIDS vaccine, but progress has been slowed by small sample sizes and a lack of a common research framework. This report presents the consortium discussions and conclusions of the participants of the symposium, including the necessity of a consortium to advance the research and the potential structure and objectives of such a consortium. This report will not discuss the research findings that were presented during the symposium.

During the program, group discussions were held to discuss the formation of a consortium. Each discussion group consisted of participants representing research on cohorts of specific types, including: (i) discordant couples, (ii) commercial sex workers or men who have sex with men, (iii) injection drug users, mother to child transmission and others. Each group was asked to discuss if a consortium should be founded and what the objectives of such a consortium should be. The body of this report details the results of these group sessions as well as the two working lunches and the final discussions as they relate to the consortium building proposal.

Overall, the participants were very supportive of the research consortium concept to help advance the research in the area of immunity or resistance to HIV. It was generally felt that the consortium would benefit the field by introducing standards and definitions, allowing for a more accurate comparison of data between different trials and cohorts, as currently there are significant differences in the measures of exposure, risk and methods for testing.

During the course of the discussions, a number of specific areas were defined as a priority for the consortium including:

- The development of a consensus for the unification of terminology and the preparation of definitions applicable to all cohorts. The use of Exposed, Seronegative (ESN), Exposed uninfected and HIV Resistant as well as some others were proposed, with some opposition to a definition with ‘seronegative’. It was determined that the chosen term and the definition should be published in an opinion or editorial article.
- The necessity for a series of integrated definitions of the risks and exposures in different cohorts to be identified. This could be done through the distribution of a series of questionnaires to cohorts (for example using a website) to ensure that similar criteria are used for determining risk of infection or exposure. This would also include the requirements for negative controls in various studies to ensure the identification of potential mechanisms of resistance. Common statistical analyses and cut-offs should be defined and used throughout the field to determine the confidence for the observed resistance phenotype.
- The sharing of current methods and protocols, particularly the use of older methods (immunohistochemistry) and the storage and sharing of materials.
- Protocols and methods, as well as the experience in developing them, should be sourced from other groups that have produced unified method sets (such as HIV Vaccine Trials Network (HVTN)) to improve

the process.

- The implementation of a general communication strategy was identified as a priority to allow the communication between groups as well as the identification of resources (sample materials, methods collections, etc.) that may be available but unknown.
- The inclusion of other specialities and disciplines was considered essential to encourage development of novel methods for research.
- Focus groups and sub-consortium collaborations were suggested to encourage improved consistency between cohorts. For example, focus groups enhancing communications between the discordant couple cohorts encouraging the use of similar methods to determine risk of infection and resistance.

There was an agreement with the proposed model of implementation of the consortium. Specifically, the group recommended a step wise increase in the role and responsibility of the consortium, building toward a fully active research consortium able to sponsor and run research programs. Specific recommendations were:

- Implement communications and information sharing strategies, such as a web site and other interactive (small group forums, online community) communication strategies.
- Initiate a resource centre providing research tools, such as questionnaires and definitions. Publish the availability of these resources in a variety of media sources, including opinion and editorial reports.
- Provide an avenue for research groups to share information regarding available resources including samples or materials, expertise, protocols and methods, and underutilized infrastructure. Such an avenue includes electronic communications as well as physical small group meetings.
- Expand the consortium over time to include full research programs and activities.
- The group responsible for the symposium should continue as the interim steering and management team until a more formal mechanism for the appointment of future members is devised.

Continued meetings are also encouraged, with a yearly general meeting, perhaps at a variety of international locations. The consortium should not be limited to the participants of the November meeting, but should be extended to recruit other groups who were not represented.

Meeting Report

Précis

The International Symposium on Natural Immunity to HIV was convened with two major goals; the first was to bring together a group of leading international researchers in the HIV/AIDS field to share research findings, particularly in the areas of immunology, genetics and systems biology. The second goal was to establish a consortium that will develop a framework for assembling and correlating the existing data, and drive and support new and expanded international research activities to build scientific knowledge that will inform the development of an HIV/AIDS vaccine.

The objective of this report is to detail the discussions relating to the second goal. Specifically, the participant discussions on the need, model and terms of reference for a consortium are included. These discussions were held during two working lunches and during a series of group discussions held during the second day of the symposium. This document includes a summary of each of the working lunches as well as summaries of the working group and the final symposium discussions regarding the formation of a consortium.

Presentation of the Natural Immunity Consortium Concept

Dr. Blake Ball presented two draft documents to the group for discussion: a Natural Immunity Consortium Model (NIC Model) and the NIC Scientific Steering Committee Terms of Reference. These two documents outlined a proposed structure, goals, operation and mechanism for implementing the consortium and are summarized here. The complete documents can be found in the appendix to this document.

The draft NIC research consortium model recommended an overall mandate of the consortium to include shared research projects, building site capacity, developing shared protocols and definitions as well as sharing both data and specimens to further research. Three building blocks are required to support this mandate: External funding (for example through NIH, CIHR, BMGF or others); a Scientific Steering Committee; and a Secretariat Management Platform. The foundation of the consortium would include 35 to 50 scientists representing their cohorts. The foundation group would determine the research priorities and actively participate in the consortium research projects, as well as electing the steering committee members. The Scientific Steering Committee would be composed of 8 to 10 members with ongoing representation from the National Microbiology Laboratory and the University of Manitoba and chaired by a committee elected member. Other representation on the committee would include best in class researchers in the fields of genetics, immunology, epidemiology, systems biology and virology. The committee would be responsible for the facilitation of the research priorities as determined by consortium members. The committee would likely be required to meet three to four times per year. The Secretariat would provide coordination and management activities through the International Centre for Infectious Diseases (ICID), including meeting coordination, supporting the development of research proposals, providing project coordination and managing the communications channels.

The terms of reference document provided to the symposium participants further defined the goals and a proposed mechanism for the implementation of the consortium. The overall mandate proposed was *to facilitate the discovery and validation of correlates of protection to HIV infection on subjects who are exposed to HIV, but yet remain uninfected in order to facilitate novel knowledge and approaches for HIV vaccines, microbicides and novel therapeutic development*. Six key requirements to support the mandate include the development of infrastructure to support knowledge, data and experience sharing; to develop and expand site capacity; to develop and share protocols and definitions; to encourage and facilitate collaboration; to encourage data, scientific approach and specimen sharing; and to develop shared funding proposals and studies. The consortium will also serve as a point of contact to strengthen collaboration and information sharing with scientists working in other areas of HIV research, including basic immunology, animal models and clinical research.

The consortium would be implemented in two phases: the first phase would be largely virtual and encourage

improved communications and knowledge sharing while the second phase would include the development of a formal research community including physical infrastructure and personnel. Phase I would utilize annual meetings, websites and shared databases to share best practices, approaches and research protocols to build intellectual, scientific and process capacity. The consortium would also encourage the virtual sharing of specimen inventories, encourage collaboration through study groups and support and assist in development of joint funding proposals, largely through the matching of like minded or complimentary researchers to facilitate grant submissions. Phase II would expand on the consortium through the building of capacity, allow the sharing of physical resources (specimens, reagents) and directly develop program grants involving multi-site groups.

Working Lunch: Panelist Discussion – Genetic Factors

Discussion during the first working lunch, chaired by Blake Ball, was related to the genetic factors of resistance to HIV infection even following high risk exposure to the virus. Panelists included K. Fowke, M. Lederman, G. Alter, K. Broliden. Particular questions requiring answers involve the nature of the cellular machinery that is required to allow viral replication and dissemination, and the importance of the cell status during exposure to the likelihood of infection. Multiple factors were identified as being important for the infection process:

- Cyclophilin
- PCK
- Elafin / Trippin-2
- Intron or promoter region of Rac2
- IFN-gamma stimulated gene sets

- It is unknown if multiple factors are utilized in a common mechanism or if combinations of factors are acting within a single individual.

Further discussion ensued with respect to the experimentation necessary to determine genetic factors involved in infection and resistance. Participants noted that in order to identify these factors and their relative importance, the use of Genome Wide Association Studies (GWAS) can be useful, although it does not rely on a specific hypothesis. GWAS is actually hypothesis-generating research, suggesting possible mechanisms and targets that can be further tested in hypothesis-driven research. Specific instrumentation can be designed to determine the impact of genetic factors on acquisition of infection or the viral load. Several requirements for the identification of factors were noted:

- There was a discussion regarding Stringency in that some argued that is essential to accurately identify the factors, while others suggest that stringency is actually not very essential in a hypothesis-generating research, as it is far more important not to miss a real signal than to exclude all the false signals. That is if one is looking for a clue, then a type I error is better than a type II error.
- Strong requirement to validate all studies.
- Recognition that the genes associated with disease progression may be different than those that are associated with acquisition and infection.
- The differences in the epidemiology of each cohort must be carefully examined, to determine the characteristics of exposure, the description of the risk, and include tools to accurately assess the risk and the likelihood of exposure. Included with this, there is the necessity to include controls that are well defined, as well as the description of a well defined phenotype of the exposed individuals.

Working Lunch: Panelist Discussion – Immune Correlates of Protection

The discussions in this working lunch, chaired by Keith Fowke, principally centred on aspects of testing for immune correlates of protection, particularly how a consortium may be able to assist in improving the current research programs or encourage future programs. Panelists included Blake Ball, Paul McLaren, Mario Clerici,

Elias Haddad. The discussion focussed on two main aspects: technical challenges that are currently being faced in laboratory to ensure adequate testing and material availability and the strategic advances that a consortium may be able to offer.

The technical challenges currently faced for the advancement of research into the resistance to HIV infection are primarily in the areas of testing and data collection. For example:

- Older testing methods, specifically immunohistochemistry, still have importance, particularly in testing various levels of mucosal samples (mucus layer, intraepithelial, submucosa, rectal washes and biopsies, or penile swabs).
- The material available from a biopsy sample is limited, thus the use of other techniques to preserve or extend the material should be considered, for example a microwell slide format allowing the measure of sixteen different cytokines from small samples.
    - This format will allow for testing of a wider range of parameters with limited materials, which will extend the understanding of the biology of the cell. These assays could be extended to allow for cell killing assays with various treatments.
- There is significant safety concern for the use of more invasive sampling techniques such as biopsy, particularly in groups at high risk for infection, which may lead to an increased chance of infection should healing following the biopsy be inadequate.
- There is a demand for the development of assays to determine why a cell is protected from infection, whereas current assays use high multiplicity of infection. Additionally, the utility of infectivity assays ex vivo on unstimulated cells were discussed during the meeting.
    - To achieve this, cells could be exposed to various cytokines and chemokines to induce replication. However, it will be important to differentiate between the differences in cellular micro-environment and virus exposure levels. To address this, it will be necessary to consider moderately invasive sampling methods to test the appropriate cells.
    - Other techniques, such as histoculture or other more subtle assays, could be used. However, to achieve this, collaborations with immunologists would be required.
- The source material must be considered for each assay. There are a number of assays that are best conducted on recently collected and unfrozen material, while other assays may utilize frozen material. The identification and differentiation of these assays and source materials is essential to preserve and make best use of the limited sample materials that are available.
    - Extending this, there are certain cell types that are more quickly lost, as they are more sensitive to manipulations and storage, or are more difficult to maintain. These cell types generally require immediate analysis, even with improved collection with methods such as leukophoresis.
- Any assay that is used must have a robust control data set established. The current control datasets are usually insufficient in size and may interfere with the ability of researchers to identify plausible mechanisms of, or factors important for, resistance.
- With immune assays, there is the need for technique development to allow for collection and testing in various locations and conditions to mitigate the loss of cell types during storage or shipping. Collection of a blood bag may be suitable until the problem with leukophoresis is solved; however, this still limits the available material. Chemical manipulation(s) of the samples may allow for longer preservation of the cells.
- Further, the assays should focus on tests specific for the HIV virus, rather than on other virus particles that may be present.

There were a number of strategic initiatives that the group suggested for the implementation of assays to test for immune correlates of protection:

- The criteria for the definition of "high risk" must be identified to allow for the collection of appropriate high risk materials and allow for the easier understanding of research in "high risk" groups.
- To ensure that proper controls are used and available, the consortium must define the characteristics of acceptable negative controls for the assays. Further, to assist research, a pool of controls could be established and distributed to the research members to ensure similarity between facilities for the development and validation of new assays.
- To ensure the most effective use of resources for the development of assays, a number of recommendations were made:
  - Establish centralized, regional laboratories to help alleviate issues of shipping sample material.
  - Identify the lessons learned from other consortia, including the HVTN and HPTN groups in the USA, as well as utilizing the protocols developed, where appropriate.
  - Further assay development should be encouraged from larger collaborative groups rather than individual groups.
- There is a consensus that everyone wishes to have fresh samples. However, this is difficult until a method for preserving various cell types can be developed. However, participants noted that there are more advantages to a consortium rather than just sharing of samples.
  - Although there is some good experience with rapid shipment of fresh whole blood, with appropriate shipping controls and planning and testing within 24 hours of collection, it is likely not suitable for large scale use as 80% of immune activation in cells is estimated to be is lost within 4 hours of collection in fresh samples.

Breakout Sessions – Consortia Building

Three separate working groups were convened to discuss the opportunities and challenges for the development of a consortium for researchers associated with a number of different cohort types. The three discussion groups were associated with cohorts of (i) *discordant couples*, (ii) *commercial sex workers and men who have sex with men,* and (iii) *intravenous drug users, mother to child transmission, and other*. The groups were asked to identify resources that could be shared that would advance the research in the specific area, as well as particular issues for collaborations which a consortium may assist in addressing. Following is the summary of the discussions and the summary presentations made by the chair of each working group.

Discordant couples (Chair: M. Clerici)

The members of this discussion group all agreed that a consortium would offer strong advantages for research. The discussion leader for this group reported that there was less difficulty for this group when talking about the cohorts than in the other discussion groups as most of the participants in the forum were following cohorts of discordant couples, however, there was some discussion on the type of couples that should be included (heterosexual or homosexual). It was noted that there are a number of different cohorts globally, with cohorts in Italy (100 couples), Columbia (800 couples) and Africa (Zambia, Rwanda, Nairobi, Kampala) with the larger cohorts located in Africa (1000 couples and greater).

A number of issues were identified in the study of discordant couples that a consortium may be able to help address:

- The definition of risk is highly variable. It was suggested that a questionnaire or set of common questions should be created and shared (perhaps using a website) among all those who are working on similar cohorts to more accurately determine the exposure in the cohort. This is necessary as each

cohort defines risk in different ways and this prevents the comparison of the cohorts or results in less stringent requirements for resistance within certain cohorts. For example, the UK and the Italian cohorts define the 'at risk' group as those who have between 25 and 40 non-protected sexual encounters per year, while in Columbia, this definition is two per week.

  - Main recommendations for a questionnaire: Definition of exposure is 25 to 40 exposures per year; Sexual activity outside partnerships; Anti-retroviral use; male circumcision (both inspection and self report); sperm on a vaginal swab.

- The definition of an Exposed, Seronegative (ESN) individual for these cohorts may be problematic as the risk factors and exposures are very different from those of sex trade workers.
- There are issues with the actual exposure within the different cohorts; to address this, the partner viral load must be assessed. Couples where the infected individual has very low viral load, such as those receiving aggressive antiviral treatment, may have to be discarded. However, the viral load requirements must be defined. There was some discussion in the group with a number of participants suggesting that all discordant couples should be retained, but it was noted this may mask the effects of different characteristics associated with resistance or immunity.
  - The cohorts must define the extreme phenotype of resistance to address this problem. This requires the establishment of standards to unambiguously define the actual exposure in the uninfected partners. The organizers of each cohort will likely know the couples to whom this applies.
  - To gain a better understanding of the risk of HIV infection, surrogate measures, such as HSV2 incidence, can be used.
  - The gender of the infected individual in the couple must be taken into account.

There were a number of other aspects that were discussed during the session. Regarding the semantics, this group suggested that the term that should be used was Exposed, Seronegative, but it was accepted that this would not work with babies who are seropositive. Also, the participants in this discussion session noted that there was a demand and requirement for the standardization of assays.

During the discussion, there were a number of concerns that were raised. There was some question regarding the reliability of patient reported exposures, particularly condom usage; as the high rate of pregnancies that are observed does not support the high rate of condom usage that is reported. The use of a sexual log or diary may be a way to improve the accuracy of reporting as recall bias is lessened. Further, the sampling of data should include both sexual partners.

It was noted that a strong benefit of a consortium would be the ability to share information, particularly questionnaires (used to identify risk taking behaviours and other exposure factors) and which definitions to apply (such as ESN). Such a consortium could also allow for the establishment of linkages and collaborations, to form focus groups to do qualitative research and understanding the questions that should be asked, and provide the potential for sharing of appropriate materials. This may lead to the collection of further discordant couple groups, facilitating a more rational vaccine development.

A recommendation was made that researchers should encourage the service sector to undertake testing of both members of a couple when testing either partner as a routine practice. This would ease the recruitment of discordant couples for research purposes as well as having a strong impact on other public health issues, such as decreasing the rate of unwanted pregnancies, STI, HIV transmission and even violence. Expanding on this, it should be encouraged that vaginal swabbing be undertaken to confirm unprotected sexual activity in discordant couples, as semen remains in the vaginal vault for a number of days. Finally, it was noted that while most discordant couples are generally practising safer sexual activities they may occasionally fail to take precautions; this leads to a question of the definition of high risk and whether time scales should be used to determine risk (for example, sexual activities in the past 3 months).

Commercial Sex Workers / Men who have Sex with Men (Chair: F. Plummer)
All the members of the discussion group agreed with the need to form a consortium, however, they proposed different focuses that would most benefit their particular groups. Generally, there were three different groups represented: those with access to the cohorts and sample material derived from the cohort but with insufficient resources to adequately research these samples; those with facilities to process and test samples but who lack access to sufficient materials; and those who are interested in improving assays and nomenclature.

Of particular interest to those in the room was the definition of resistance or ESN. The group noted that finding a consensus for the terminology should be one of the first activities undertaken by the consortium, as it is largely a communications exercise and does not require extensive commitment of resources, such as samples. In discussions regarding the definition of infection resistant individuals, a number of points were made:

- The term seronegative is likely to become redundant and does not really reflect an exposure to the virus.
- The term natural immunity is not likely accurate as individuals may remain uninfected while they are not actually immune.
- The term resistant was considered a good term, however, it was generally agreed that there would have to be modifiers included to indicate the level of exposure (such as single event, daily exposure, etc.).
- The participants suggested that two terms should be used when discussing the resistance, both the level of risk (such as the likelihood of an individual being infected) as well as the degree of resistance. There was some discussion as to whether the definition should include various levels of resistance, such as highly resistant, elite resistance, etc.
    - It was noted that using just the term resistance may be confusing for other areas of the field where it is used to refer to viral resistance to drug treatments; HIV resistant should be used instead.

Further discussion noted that resistance is a complex and wide ranging issue.

- The risk of infection is very dependent on a number of factors, which are often not fully considered. For example, a discordant couple may seem to be at high risk for infection, but if the infected partner is aggressively treated the viral load may be low which lowers the infection risk. Further, the uninfected partner is being exposed to the same viral strain and may develop resistance, but only to that one strain.

Following the discussion on the definition of terms, the group discussed types of studies as well as challenges and opportunities for being part of the consortium. While this had been discussed at the working lunch previously, this session further expanded the discussion.

- There is a general lack of understanding of mucosal immunology in general, and specifically, it may be necessary to have a better understanding of the environment of the cells to understand resistance. It is possible that there is not a single specific resistance factor.
    - There has been resistance to utilizing mucosal immunologists in HIV research and current understanding of the differences between mucosal sites (anal vs. vaginal or intestinal) is poor. The resistance may be related to the route of viral entry.

Following the group discussion, the chair presented a summary of the findings. He reported that the group had found complimentarity between many participants; some had samples, others technologies, and that this was a good indication that a successful consortium or collaboration could be set up. The biggest issue was that funding was limited. The group focused on how to go forward and made some recommendations:

- Proceed in a stepwise fashion, slowly expanding the scope of the consortium as more resources are available and trust of the research groups are gained.
- It was recommended that the steering committee for the ISNIH should constitute the interim consortium

steering committee with a search initiated for further resources.

- The initial steps of the consortium with respect to members should be in the area of communication, providing information to both participants of the meeting and those who could not attend. This could be provided through a secretariat, which would also be available to facilitate smaller scale collaborations while not taking part in the research.
    - However, as the role of the consortium is expanded, it can undertake project development.
- Finally, the chair noted that they had extensive discussion on the terms that should be used for resistance and noted that the group suggested that an opinion article or editorial would be an effective mechanism for the dissemination of the definitions and the new terms that are being considered.

Intravenous Drug Users / Mother to Child Transmission / Other (M. Lederman)

The chair of this group noted that the questions addressed during the group discussion were complicated by the presence of representatives from five distinct types of cohorts. These cohort types included babies, injection drug users, haemophiliacs, blood product recipients, and the Chinese village cohorts exposed as a group to contaminated blood. The participants in the group represented nine separate cohorts, and of that nine, 7.5 suggested that they are strongly supportive of the creation of the consortium. Five of the cohorts are currently mature and wide ranging, two are growing, and two are complete or gone, however, samples are still available and at least one may be able to be revived. A further youth cohort in Vancouver has just been started.

The discussion evolved around each of the specific groups:

- Babies and maternal to infant transmission primarily through breast milk.
    - There are many research strengths for this cohort particularly as risk could be quantified by maternal viral load measures, feeding practices and host issues such as mastitis. Further, the source of the virus can be easily identified allowing for a better understanding of viral sequence heterogeneity, host – recipient interactions and host titre.
        - The bimodal risk of infection (once when breast feeding, again at sexual activity later in life) for these individuals leads to possible research programs to identify further characteristics of the resistance, particularly when considering exposure to different viral strains at different times of life.
    - There are a number of issues with these cohorts. These children are often difficult to find and with the aggressive maternal treatment the risk of transmission may be lower. This use of antiviral treatment may mask innate immunity. Further, there are issues with continued access to the children, as they may be difficult to find both at birth and later in life.
    - To overcome some of the problems with the cohorts, careful selection of the mothers may help; by selecting mothers with very recent infections (just prior to birth) or mothers with high viral loads it may be possible to identify children with innate immunity. However, there is limited number of individuals who fit these categories.
- Injection drug users.
    - There is a high risk and prevalence of infection in this group; further, the source of infection and virus may be identified by testing the drug paraphernalia for virus load and strain. These cohorts are often local to major research centres and therefore are readily accessible.
    - The route of exposure of these individuals is different than sexual transmission. The virus is exposed to different tissues, but this may provide a better understanding of the differences when compared with mucosal exposures. There may be possible issues related to the ethnicity of the group.

- Some of the possible issues with the group include poor histories and multiple routes of infection with a variety of viral sources (for example, users sharing drug paraphernalia and trading sex for drugs). The cohort may be difficult to follow over the longer term and, in non-western countries, the cohort tends to be only men. Finally, the risk of infection may be lowered by the requirement to heat certain drugs prior to injection, leading to lower live virus exposure and an overestimate of resistance.
- To carry out research in this group, self reported drug use (frequency of injection, sharing of needles, testing of drug paraphernalia for viral evidence in needles) can be used to gain an understanding of the exposure to the virus as a relationship to the frequency of drug use.

- Haemophiliacs
  - There are a number of advantages to treating this group of individuals, including a quantifiable risk; good length of follow-up (as these individuals are still in care for haemophilia and the identification of the physicians is possible, although difficult). This group can also be used to support the genetics of resistance. There are also a number of members in the group who will likely have maintained higher risk or continued exposure through other routes and identification of resistance in these would provide additional insight.
    - Currently, there is a cohort of 600 to 1000 haemophiliacs being identified. There is currently an ongoing effort to organize the cohort to allow for in-depth research and the identification of factors associated with resistance.
  - There are a number of significant issues associated with this group. The last exposure was in 1985, although there is still some question about exposures after the cleanup of the patient blood supply. There are also no women represented in the cohort and there are significant issues with access to the cohort with the requirement for the reorganization of the group. Finally, the members of this group have had sustained and continuous exposures to alloantigens due to treatment of their disease.
- Using cohorts exposed to potentially contaminated blood and blood products is logistically very difficult. Although the group is interesting, this is too complicated for considering pursuit.
- Three Chinese community cohorts, in which communities were exposed to contaminated blood and blood products, are said to exist. During the discussion, a number of potential contacts for individuals that can identify these cohorts were collected and these individuals will be contacted to determine if a possibility for research with these cohorts exist.

The report back concluded with the discussion of a number of activities that should be completed. The group suggested that it was important to identify the site of first infection in people with parenteral exposure or through oral exposure to breast milk in children. To achieve this, studies in areas with high rates of HIV in neonates should be encouraged while primate studies could be used to identify if the spleen or other filtration sites may be the initial site of infection following parenteral exposure.

Final Comments and Closing Remarks

Blake Ball briefly summarized the results of the discussions during the course of the meeting. He expressed concern about the definition of high risk, noting that it does not have a strong comparator, and that this is a concern for all the groups. He noted that this is clearly study dependent for the appropriate controls and that there may not be a solid answer in this presentation. Moving forward, a working group is to be struck to make a determination of what a suitable control group would be for the various study types.

Further to this, the use of the terms HIV resistant and ESN would have to be determined. There was a strong objection to the use of seronegative. However, it was agreed that a common definition and language was required to raise the profile of this research in general and to facilitate discussions with the general scientific

community. It was noted that failure to lobby, both within the overall scientific community and outside the community, may have delayed the utility of studies of exposed, yet uninfected subjects towards the development of a vaccine for HIV and that this was, at least in part, caused by the failure of the group to use consistent language and maintain strong cohesion between group members.

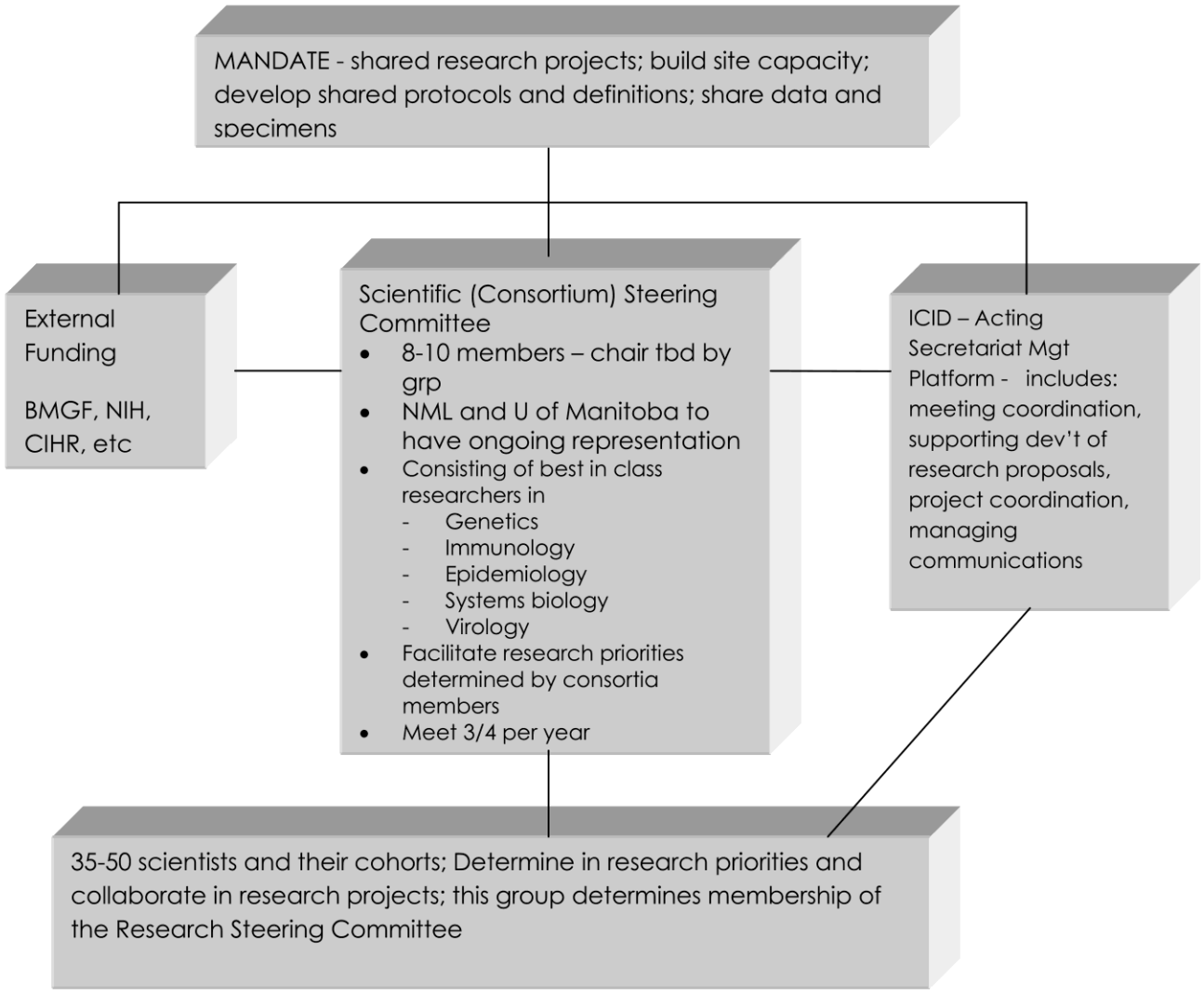
At the close of the session, it was agreed that another symposium on natural immunity should be held next year; there were various offers to hold the symposium at a number of locations. Blake Ball thanked the participants and the sponsors prior to closing the meeting.

Potential Partnerships resulting from ISNIH

An anticipated goal of this meeting was to bring researchers together to share information on EU studies. As a result, a number of potential collaborations have been formed. Approximately twenty new collaborative arrangements have been developed and data is still being gathered as to the extent of the collaboration.

Appendix

Draft NIC Research Consortium Model



Natural Immunity Consortia Scientific Steering Committee Draft Terms of Reference

Mandate of the Natural Immunity to HIV Consortium (NIHC or NIC)

The mandate of the Natural Immunity Consortium is to facilitate discovery and validation of correlates of protection to HIV infection on subjects who are exposed to HIV, but yet remain uninfected in order to facilitate novel knowledge and approaches for HIV vaccines, microbicides and novel therapeutic development by:

1. creating the supporting infrastructure to: share knowledge, data and experiences;
2. develop and expand site capacity;
3. develop shared protocols and definitions;
4. encourage and facilitate collaboration
5. encourage the sharing of data, scientific approaches and specimens
6. develop shared funding proposals and studies

Ideally, the mandate would be implemented using a phased-in approach with phase 1 being the establishment of a virtual consortia with modest infrastructure and support and phase 2 the establishment of a formal research community with direct research infrastructure, funding and support.

Phase 1: “Virtual” Consortia

- Share knowledge, information, definitions and data thru annual meetings ,online websites and shared databases
- Build intellectual, scientific, and process based capacity thru exchange of best practices, approaches and research protocols
- Facilitate and encourage collaboration by establishing virtual inventories of specimens, study groups and scientific approaches
- Help develop joint funding proposals by matching like minded researchers and facitilitating grant submissions

This would be supported by a modest infrastructure of administrative support, databases, scientific and legal expertise to facilitate these activities

Phase 2: Formal research community

- Build capacity with hiring of technical, personal, and physical infrastructure support
- Facilitate and encourage collaboration by establishment and implementation of shared protocols, common reagents, technical and scientific staff, and physical specimen and data repositories available to members
- Develop program grants, multi site studies and group wide funding proposals

This would be supported by physical research infrastructure (bricks, mortar, people) available to the consortia community as well as the intellectual and administrative support described above.