Vaccine Research Center
National Institute of Allergy and Infectious Diseases
National Institutes of Health

Clinical Protocol Planning Meeting Minutes

June 21, 1999
Building 31, Room 7A-24
1:00 p.m.- 4:00 p.m.

VACCINE RESEARCH CENTER

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I. Scope of Clinical Protocols

Dr. Gary Nabel, Director, Vaccine Research Center (VRC), opened the meeting by thanking the participants for setting aside the time to attend and asking each person to introduce themselves. He added that he was gratified that the meeting brought together colleagues from the NIH, industry, academia, and the FDA.

The impetus for this meeting was the suggestion, at the most recent AIDS Vaccine Research Committee (AVRC) meeting, that some vaccine candidates be put forward for clinical studies. Modified vaccinia ankara (MVA) was noted as the most promising candidate, judging from animal studies; however, it was realized that there is currently little information available to predict what would be learned from the studies, how to determine if MVA was the preferred vector, or what would be the preferred inserts for beginning studies. Thus, in order to develop individual clinical candidates, there needs to be a more informative method whereby potential vectors and inserts can be identified.

The objective of this meeting, therefore, was to develop a comprehensive plan that could be implemented to compare identical DNA inserts inserted into different vaccine candidate vectors. These candidates would then be tested in "limited" Phase I studies, often involving less than 20 participants, more for informational purposes than classical Phase I trials that determine safety and advancement to Phase II trials. It would be expected that the majority of these limited Phase I candidates would not advance further. Discussion arose regarding what types of information would be sought, and Dr. Nabel indicated that those issues are some of the important items to be decided at this meeting; in particular, safety considerations, immunological parameters, and identification of the most informative assays.

Parallel Animal Studies

In addition to planning for these candidate vaccines, Dr. Malcolm Martin suggested that if these studies were to be done in humans, the same studies should also be done in non-human primates and rodents. In this way, one can begin to assemble a database to understand the predictive utility of rodent and primate models for human disease. There was some discussion on the issue of whether or not the primate studies would involve both challenge and immunogenicity studies. Dr. Nabel noted that unless there was reason to do otherwise, he would not want to wait for challenge study results from the animal experiments, but would rather safely fast-track the human studies. Dr. Karen Goldenthal (CBER, FDA) indicated that they have never required challenge studies prior to Phase I studies unless there was an extraordinarily high risk.

State of Current Research

Dr. Barney Graham presented information on the current state of clinical vaccine trials. In humans, there have been approximately 40 different vaccine strategies tested, if one

counts a new adjuvant as a new strategy. In reality, it is probably closer to 10 different strategies tested. Out of these, only four have moved forward in clinical studies. Out of the 40 immunogens, many, but not all, varieties of the subunit envelope, i.e., monomer, etc., have been tested. There have been 8-10 novel adjuvants included.

The vectors that were used include poxvirus vectors, vaccinia (Wyeth strain), canarypoxvirus, but not the vaccinia strain MVA. There has been one DNA trial and many peptide trials. . A number of approaches have been tested in each of these categories. One participant noted that, in general, the human studies are approximately one to three years behind the non-human studies.

Dr. Graham suggested that after immunogenicity and toxicity studies have been performed in rodents and non-human primates, it is appropriate to do more extensive human immunogenicity studies in the limited Phase I studies if challenge studies are done in parallel in rodent and non-human primates. He thinks the challenge studies are essential in order to determine which candidates are worth moving forward.

Dr. Nabel posed the question of what to do in the possible cases where immunogenicity may be different in the non-human primate and human, especially those cases where immunogenicity may not be detected in the primate model but is nonetheless present in the human. Dr. Graham noted that this is an area that needs great attention and that the intense investment of resources required for these studies and the lack of coordination of studies has contributed to the dearth of knowledge whereby one could know/predict such a thing. Dr. Graham observed that given the difficulty of taking a product from preclinical studies to clinical trial, most industry laboratories could only manage developing one concept at a time. [In this respect, it is important to add that only one academician (Dr. Bart Haynes) has been successful in taking a product from preclinical to clinical development.] Thus, there are a number of groups working on the same strategy, when a more productive use of time and resources would be a coordinated effort to look at perhaps similar vectors with different genes. Individual investigators are approaching this model, however, industry, at the level of manufacturing, still has obstacles to overcome, one of which is matching the particulars of gene and protein expression, etc. Dr. Nabel suggested that the VRC, and perhaps the NIH intramural and extramural communities, could help identify sources and resources to make candidate vaccines.

II. Identification of Relevant Existing Immunogens and Vectors

Dr. Nabel asked the participants to list the most viable vector candidates to move forward, and for which comparisons would be desirable. These are listed in the tables below.

Promising DNA/Viral Vectors

Poxviruses	DNA	Alphaviruses	Adenovirus
ALVAC™ MVA NYVAC Fowlpox	Currently in Phase I trials		

Promising Bacterial Vectors

Salmonella	Shigella	Bacille Calmette-Guerin (BCG)	Listeria
Currently in Phase I Trials.	In laboratory stage; one-two years from Phase I.	In preclinical stage	In laboratory stage; one-two years from Phase I.

Dr. Michel Klein observed that he does not believe a single vector will produce the necessary response and that the best protective response will require a combination of vectors. Others agreed with this observation and would like to see the vectors noted above tested alone and in combination.

Dr. Klein also suggested that vectors should be compared within families and with regard to such issues as: insertion, optimization variables, purification processes, commercial viability, and regulatory issues. Others cautioned others that decisions to exclude any vector should not be made in the preclinical models since it is important to see how vectors compare in human studies, as the vector-host interaction may affect immunogenicity.

Vector Comparisons

There was considerable discussion regarding how to compare vaccine candidates since an optimal insert in one vector may be a deleterious one in another. Issues discussed include using the same insert, using similar inserts and trying to obtain comparable levels of expression, or using the same epitope and the same targets [i.e., cytotoxic T lymphocyte (CTL) response or antibody production].

Vector comparisons are compounded with respect to industry since the issue of comparisons between candidates raises the question of whether each company should optimize their system and then try to compare it to others or whether one individual

should try to optimize each company's candidate and then pick the best ones. There was general agreement that one will need to use the same set of epitopes and use the same endpoints (assays), which also need to be optimized and standardized. What those epitopes and endpoints will be depend on the questions being asked. However, there needs to be some standardization so that researchers try to answer the same and/or similar questions with comparable measurements. Additionally, there is the need to improve existing immunological assays and develop new ones. Again, purification procedures should be included in the need for standardization and optimization. Lastly, keeping the inserts the same would allow some measure of potency.

Dr. Norman Letvin's group is beginning a study that will look at 89.6 *env* and *gag/ protease* inserts in three different vectors. The promoters are the same, but there are, by necessity, different insertion sites. There will be similar assays, and the epitopes are the same. This is a beginning study toward amassing a database.

It was suggested that there is also a need to standardize the primate challenge studies with respect to such issues as antigen, species of monkeys, and assay techniques. The comparative database being established on all fronts will be useful for judging new assays and developments. Again, it should be emphasized that as evaluation methods are developed, a parallel structure of non-human primate studies should also be kept, even if one is only able to perform half of the animal studies due to limited candidate vaccine material.

Clinical Trial Considerations (See also Section VIII)

With respect to the conduct of the clinical trial, questions about design and doses arose. Design issues to consider in the trials include the route of injection, the genetic background of the recipient, prime and boost regimens, and the possible addition of cytokines. It is also important to remember that often the trial will not be evaluating a single vector at a time, but looking at combinations given with different priming and boosting regimens. This complicates the design.

Regarding doses, two different approaches were suggested. First, from a practical and commercial standpoint, it was suggested that perhaps an optimal dose should not be given if it would be commercially impractical to produce due to the high doses required. Additionally, it was observed, comparing optimal doses may not be useful since if these are maximum responses, it may be difficult to differentiate responses. A second approach would be to administer a dose that seems reasonable and then observe the degree of protection. These are two very different approaches. Many participants thought they would not want to exclude a candidate or work with less than complete optimization based on production considerations even though this is a reality for a company. Acknowledgment was made, however, of the additional complexities that arise due to the need for more than one vector in the prime/boost regimens.

Dr. Nabel suggested that the VRC could probably serve both interests by conducting the limited Phase I trials with small lots of candidate vaccine material. It may be that the

development of the best candidates for some of these studies is not practical for a company to do given the costs and liability issues for a trial with 20 people. He mentioned that an alternative is that production of a company's promising candidate be contracted out to a third party. The VRC and NIH can assist by providing a program specialist to work with the company and contractor to provide quality assurance and control as well as consistency. The VRC could potentially do some production work if contractors cannot be identified. It may turn out that once the information is obtained from these experiments, the questions related to an optimal or reasonable dose may change.

III. Industrial/Academic/Government Roles

A. The AIDS Vaccine Evaluation Group (AVEG), which supports the study of HIV vaccine candidates in human trials, is an excellent resource due to their extensive experience and the number of trials they have accomplished. Other clinical research centers can also be employed.

B. The VRC will be available to help with some of the vector modification, standardization process, and clinical assay development. The VRC also can help coordinate activities for different quarters as well as interface with the FDA.

C. Biotechnology/pharmaceutical companies provide an extensive resource. However, there is an understanding that there is a limit to their resources. The other alternative is to contract out to a third party. If allocation is a problem, again, the VRC may make a candidate. Areas in which investigators and industry can optimize working relationships were discussed. One attendee has had the experience of trying to mount a similar set of experiments, i.e., to look at parallel constructs, but found the biggest problem was that industry was not committed to allocating the resources needed to produce these parallel constructs. Thus, the possibility of third-party production may have a substantial impact on that area. Industry representatives noted that often the problem is that researchers want to partner with them, but the ideas are not firm or have not been refined to serve both the researcher's and industry's interests. In addition, industry cannot commit and/or shift resources quickly. They must prioritize their resources and know experimental details in order to provide a justification for shifting to that area. Thus, the farther ahead the researcher can envision the project and set up talks with a company, the easier it will be to shift resources to such a project.

D. Academia will presumably be developing new technology and assay standardization. Also the NIH-supported clinical research centers will likely want to participate in the clinical trials.

Participants noted that a structure for communication is needed so that investigators in all arenas are informed. For example, industry representatives requested that investigators communicate results to a company regarding materials they have produced prior to public disclosure of that data. Dr. Nabel noted that the meeting minutes produced are the

beginning of such a process, and that the VRC would like to identify a person who is a clinical protocol/program development person to dedicate to this effort.

IV. Definition of cDNA Inserts for Gene-based Vectors and for Comparison Studies

Regarding inserts, the consensus of the participants was that most experts agree that there is not a strong reason to pick one insert over another. They also noted, however, that it would be important not to insert so many genes that expression is compromised. An important advance is that a CTL response to a particular epitope can now often be differentiated from the CTL response to another epitope. One participant was able to differentiate the CTL response to *env* alone, *env* plus *gag*, and *env* plus *gag* plus *protease*. However, addition of other epitopes makes it difficult to see the CTL response for each insert.

For comparison studies, it would be ideal to keep the inserts identical right now since previous studies have defied comparisons as they have often used different species, challenge studies, and study designs. Dr. Nabel agreed but also noted it would be worthwhile attempting to pick some immunogens with inherently different immunogenicity via how they induce. Thus, one may not be testing the efficiency of a specific insert, but one could test how well a vector induces a response, i.e., whether *nef* in DNA induces Th2, whereas in vaccinia it induces Th1 responses.

Regarding vectors, there appears to be some advantage to each vector. Vaccinia produces the best response in naïve patients; ALVAC™ [a genetically engineered HIV vaccine composed of a live, weakened canarypox virus] seems to produce a better CTL response than standard vaccinia; and pox vector generally provides an acceptable response.

Inserts to be considered

Env inserts to be considered, either alone or in combination:

- 89.6 is from a primary isolate and has mid-range neutralizing ability. It is being well-studied in primates. Dr. Nabel would not want to limit studies to just 89.6 since there could be an aspect of its action in primates that does not translate to humans.
- CCR5-tropic gp 160 is most relevant to the virus detected in primary infection.
- CXCR4-tropic gp160.

Other gene inserts to be considered:

- *gag*
- *nef*
- *gag-pol* may be a good prototype since it has particle formation abilities. It provides more than one antigen and should be able to produce a good CTL response. It was noted that *pol* would have to be modified for safety.
- *gag* plus *protease*

Final recommendations for cDNA inserts, alone or in combination (tentative):

- *gag-pol*
- codon-optimized 89.6 gp150
- codon-optimized R5 gp150 with a *nef* fusion to provide more immunogenicity.

It was also decided that *env* gp150 will be used since there are more epitopes exposed than gp120 but it is less toxic in pox virus than gp160.

Tat and *Rev* were also mentioned, but will not be considered at this time since their immunogenicity is not high and there are some potential problems with *Tat* being toxic to producer cells.

V. Discussion of Clinical Assays

A. Current Clinical Assays

Currently, quantitative antibody measurements are relatively easy. Neutralization studies should also be performed; however, it is not clear what they mean. This assay may benefit from further standardization and improvement. For helper T cell responses, interferon gamma is probably a better indicator than interleukin 4 or interleukin 10. Also, antibody responses would probably be easier to standardize than CTL. However, it is not clear how predictive these responses would be.

B. Desirable assays for comparative immune analyses

The tetramer, ELISpot, functional killing and intracellular cytokine assays would all be useful, but are at varying stages of development as discussed below.

There was a difference of opinion regarding the tetramer assay. Some participants thought it could not be used until the epitopes are identified, others thought the identification of the HLA type was enough. Concern was raised about using this assay before the epitopes are identified since AVEG is finding new epitopes arising that may complicate the tetramer binding. All participants agreed that this will be a good assay when the epitopes are available as it will be a fast assay.

Some participants also thought the tetramer assay was not as useful as intracellular cytokine staining and subsequent flow cytometry. This test would be more universal and not based on a well, as is the ELISpot, since all that is needed is antigen stimulation. It was agreed that the intracellular cytokine assay will be the gold standard once it is better developed. However, it currently has an unacceptable background level.

The ELISpot assay, with peptide or with antigen, is currently available. Some participants do not like the ELISpot assay because the size of the spots are different, and it is not clear that readers are blinded or reading them the same way. The consensus, however, was that the ELISpot assay is making progress. Functional killing assays are also currently available and useful.

Overall, concern was raised that the meaning of many of these assays is not clear. They should all be done for the sake of comparison, but work is needed to standardize the assays and procedures so that these comparisons will be informative. Dr. Nabel remarked that clinical assay development is a goal of the VRC, thus, the VRC will support this effort. Prior to finalization of the protocol, Dr. Nabel plans to convene additional planning meetings among the involved parties.

It is planned that this will be a VRC/AVEG trial.

VI. Identification of Production Sites

The potential for third-party production was reiterated as a useful method of production.

In addition, Dr. Peggy Johnston, NIAID, presented NIAID's current extramural efforts in production needs that would benefit the VRC. NIAID has put out a call for contracts that would develop pools of contractors with expertise in: 1) Good Manufacturing Practices (GMP); 2) preclinical Investigational New Drug (IND)-directed studies that need to be done to submit an IND; and 3) IND preparation. Products for GMP include peptides, subunit protein, DNA, vectors, particle design or whole killed and live attenuated viruses. NIAID obtained two categories of responses - half will produce whatever a client wants; half will participate in particular designs. Results of the bid will be known by end of the fiscal year. There will be room and space to accommodate intramural needs as the contract does allow for intramural laboratories to put money into the contract and then use it as it desires.

A third resource for these studies, in terms of information, may be The Vaccine Resources Development Group (VRDG) which is a new group that has set some priorities for their first round of production and studies. They will prepare a primary isolate of gp120 for clinical testing and conduct a prime/boost protocol. They also have high enthusiasm for MVA since it appears to have proven itself in the primate model. They recommended moving ahead quickly to get production issues resolved and expect that AVEG has the experience so that it can do some comparison studies along with the planned studies. This MVA study could complement and serve as a baseline for studies to come from the VRC. Additionally, the VRDG is considering using some particle designs, but not DNA at this time since these designs need further optimization.

For the VRC studies, the question was raised as to whether the capability exists for production of multiple vectors and multiple inserts with several pox vectors. Industry can make 10-12 production lots per year (GMP quality). The cost per lot varies from one-half million dollars to several million dollars. For the planned limited Phase I studies, GMP material may not be needed; however, it is difficult to obtain "earlier-release" material from companies because of their quality assurance departments. Additionally, the FDA would need to approve such production.

These production issues brought up several items that were addressed to the FDA participants. Dr. Nabel raised the concern of the current requirement of integration studies for DNA candidate AIDS vaccines. These studies appear to significantly delay Phase I studies by approximately 6 months and cost perhaps an extra $100,000. Dr. Nabel thought it was worth discussing since even though some positive integration results have been seen, he is not convinced that these are not false positives detected since the limits of detection are so low. Thus, it is difficult to know what these numbers mean. Additionally, other "products" are not held to the same standard, i.e., adenovirus. FDA representatives indicated that the best way to address these issues might be a workshop because a consensus was formed two years prior that these types of studies were reasonable. Some topics that could be covered in the integration workshop would be what risks are associated with viral integration, what levels are acceptable, and what are the comparisons (i.e., is the background rate of mutation the correct metric to compare with rates of integration). Dr. Nabel suggested that the integration issue could be provided to patients in the informed consent information, and he questions whether many other past vaccines have been evaluated for integration.

VII. Preclinical Trial Design (Rodent and Non-human Primate)

This discussion was tabled until a future meeting.

VIII. Clinical Trial Design

Once the candidate vaccines have been made, the clinical protocol will involve some combination of prime and boost treatment with homologous and probably with heterologous products. From a regulation standpoint, heterologous boosts are allowed if there is sufficient safety data (which would depend on the vector and the particular situation). For example, generally, if the prime component alone and potential boost component alone produced acceptable safety results, then the combination in a prime/boost protocol should not be a problem.

Intervals for prime/boost should be somewhere between one to twelve months; anything less than three months would really be considered a secondary priming. Some participants would suggest no less than six months to test a prime/boost regimen. Representatives from Therion noted they have tried an accelerated protocol by providing four doses of avipox in 28 days instead of six months. PMC representatives noted a trial where four doses of canarypox was administered over 28 days instead of six months (Belshe et al., *AIDS* 12:2407-2415, 1998). FDA representatives noted that this could be very advantageous for high risk groups who might become infected within a traditional six month period vaccination period.

Additional comments about trial design and doses are recorded under Section II.

In conclusion, Dr. Nabel noted that there were many six-month periods involved in the development and conduct of even a limited Phase I trial. This appears to translate into what is currently the case, that only one new product can be tested every two years.

Improved coordination, communication and production may be able to address these issues.

Recommendations:

1. Immunogenicity studies should be done in the limited Phase I studies with challenge studies done in parallel in rodents and non-human primates.

2. A coordinated effort is needed among investigators and companies in order to best use resources and time and to optimize the number of products tested. The VRC can help in this endeavor as it would like to identify a person who is a clinical protocol/program development person dedicated to the AIDS vaccine coordination effort.

3. In order to produce the best immunological protective response, more than one vector will be needed. Thus, vectors should be tested alone and in combination.

4. Decisions to exclude any vector should not be made in the preclinical models since it would be important to see how vectors compare in human studies, as the vector-host interaction may affect immunogenicity.

5. Vector comparisons should be made within families and with regard to such issues as: insertion, optimization variables, purification processes, commercial viability, and regulatory issues. The same set of epitopes and the same endpoints (assays) should be used for comparisons. The assays need to be optimized and standardized.

6. There is a need to improve existing immunological assays and develop new ones. The VRC will play a key role in this. Immunological assays, in general, need to be standardized.

7. Challenge studies need to be standardized with respect to antigen, species of monkeys, and assay techniques.

8. All human studies should also be done in parallel in rodents and non-human primates even if only some of the animal studies are possible due to limited candidate vaccine material.

9. Alternatives to industry production of small vaccine lots for the limited Phase I trials are 1) third-party contractors, potentially under the auspices of the VRC for quality assurance and coordination, 2) VRC production of some lots, and 3) use of NIAID's current extramural contract for producers.

10. A structure for communication among all those in the field is needed.

11. Tentative recommendations for inserts: *gag-pol*, a codon-optimized 89.6, and a codon-optimized CCR5 with a *nef* fusion to provide more immunogenicity. *Env*

gp150 will be used since there are more epitopes exposed. These inserts can be used alone or in combination in the trials.

12. All available assays should be conducted for comparisons, and standardization of immune assays is essential.

13. Further discussion of integration study issues should be sought with FDA. Integration study issues are specific to DNA-based immunogens.

14. We need to discuss the importance of discriminating between uninfected, vaccinated volunteers and infected individuals.

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Clinical Protocol Planning Meeting
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