Report of the External Evaluation Panel to the Danish National Research Foundation [DNRF] Regarding the Research Center for Vitamins and Vaccines [CVIVA]

Panel Members: Professors Camille Locht, William Schaffner, & Geoffrey A.Weinberg

Research quality, relevance, originality, and focus

Progress to date

- Please comment on the development of the center's activities in relation to the aims specified in the original research plan and on any substantial changes according to this plan. Also comment/consider the choice of research questions, theories and methods.

  Generally speaking, the CVIVA project as a whole is well on track. Most of the proposed work in the original project has been done or is in progress, such as the observational studies (WP 5, 6), the randomized controlled trials (WP 1-3), and the development of statistical methods (WP 7). Immunological studies are also under way (WP8), but so far we have not seen any work done on infant blood. The proposed murine model work has changed. Originally it was proposed to use a murine ovalbumin model and pneumococcal sepsis model to look at the effect of DTP vaccines (WP 9). This was not done, but it has been replaced by very in-depth mechanistic work on the effect of BCG on the shaping of the innate immune responses, with the concept of "trained innate immunity". Original partners (Mahon and Ross) have been replaced by other partners (Netea, Kollmann) for reasons uncertain to the panel. However, the new work was a notable addition to the project. Concerning WP 4 (cost-effectiveness studies), no results were presented, but this may be due to the fact that these studies depend on the completion of WP 1-3.

  The research questions are of utmost importance and relevant to public health issues all over the world. If the hypotheses are proved to be true, they may have profound effects on global vaccination policies. The proposed new paradigms (9) emerge from the CVIVA group's observational studies. The group then tries to provide "proof" of the paradigms by more observational studies, some randomized controlled studies, and novel epidemiological approaches such as triangulation. Their initial observations were done in Guinea Bissau, but further observational studies have been completed in other sites, such as Denmark, taking advantage of its unique comprehensive population medical database.

  Concerning the methods used, the CVIVA research strategy appears to the Panel to most often consist of deriving a hypothesis from observational studies, and then do all possible to prove the hypothesis by replication, rather than to take a more neutral position, and perhaps take the opposite stand and try to disprove the hypothesis by experimental trials. This may sometimes lead to reanalyzing results with different parameters/criteria if the first results do not match the hypotheses (e.g. when the NSE effects of BCG vaccination were examined in Denmark, using hospitalization as an endpoint, the results did not confirm the original observations made in Guinea Bissau. Then the data were re-examined and a correlation was found with atopy). A more cautious attitude in the presentation of their conclusions would be advisable (e.g. possible negative nonspecific effects of DTP vaccine are often cited as proven, despite citing hazard ratios with confidence intervals crossing zero). Nevertheless, following observational studies with randomized controlled trials is being pursued by the group and is judged by the Panel as being an appropriate strategy. Perhaps the cleanest way to do this would be to introduce a new live vaccine (e.g. varicella vaccine) into a carefully monitored, prospective randomized controlled trial in Guinea Bissau to examine non-specific effects, without confounding by either national immunization campaigns or missing data from parental vaccine cards.

- Please comment on the highlights of the research findings and the extent to which they represent remarkable theoretical and conceptual developments.

  There is no doubt that the CVIVA group has made unique observations, which have drawn the attention of the world's vaccine community to examine unexpected effects of vaccines. It is now generally accepted that live attenuated vaccines have some degree of beneficial non-specific effects. The group's observational and randomized controlled studies are now being strengthened by mechanistic insights and the documentation of innate immune training. Their hypothesis on the negative effects of non-live vaccines still remains an open question in the Panel's view. For the moment there is no mechanistic hypothesis to support these proposed effects, and as noted above, some of the observed hazard ratios have wide confidence intervals which cross zero. The same is the case for observations on the role of previous maternal vaccination on the non-specific effects in children. If this latter concept were true, however, this would lead to a totally new paradigm in immunology. The first five years of the project have generated new proposed paradigm shifts.

- Has the center made a substantial contribution to breakthrough international research within the field? What is the international status of the group within its fields of research?

  The work of the CVIVA has clearly generated discussions in the vaccine community, including at the WHO, led to several SAGE meetings, position papers and spirited discussion. The group is very well known, as evidenced by the many invitations to talk in international meetings, by the participation of their members in international advisory groups. Papers are published in high-ranked international scientific and medical journals.

- Please comment on the level of ambition as well as the originality, novelty, quality, progress and relevance of the research carried out at the center from its initiation. Would you consider the center has been willing to take risks/chances in order to confront major new research challenges and to what extent has it led to truly novel and scientifically daring projects?

  The CVIVA is virtually "defined" by originality, novelty and risk taking. The proposal of new paradigms is inherently risky in the scientific community, and the group has proposed no fewer than 9 new paradigms. They are not afraid of contrasting their paradigm shifts with the main-stream thinking. Actually the evolution of the work has led to further new proposed paradigms. Although some of the paradigm shifts are now based on solid evidence, others are still awaiting for confirmation and mechanistic explanations. This constitutes the bulk of the research plans for the next five years.

- Please summarize by pointing to three weaknesses, that is, areas where the center can improve, and three strengths, that is, areas where the center is doing well.

  <u>Strengths:</u>
  (i) Very strong commitments in the project at all levels (PI, students, post-docs, apparently also the clinical research staff in Guinea Bissau).
  (ii) Very good and effective multidisciplinary approach to the project. Starting from a rather small group, complementary expertise was gradually called into the project--statisticians, clinical staff, basic immunologist--with special care to the casting of the best collaborators in the different fields.
  (iii) Communication through scientific publications and oral presentations is excellent.

Weaknesses:

(i) The center could improve by recognizing that they often give the impression that their subsequent data collection is geared solely toward supporting their pre-conceived conclusions. Presenting the interpretation of their results as supporting the hypothesis rather than as conclusive evidence of some of the paradigms may be advisable.

(ii) Although excellent collaborations have been initiated with experts in the field of trained innate immunity, the Panel believes that there is still no clear plan to investigate the mechanistic bases of some of the proposed paradigms. This may perhaps require further collaborations with other groups.

(iii) It would be beneficial for the center if they could stimulate other groups to replicate the observational and clinical trials data in different settings outside of Guinea Bissau, especially in other lesser developed countries, using common protocols. This could be done in collaboration or independently. Triangulation of data from other sites [eg, a multi-center approach] would be a stronger proof than triangulation of multiple studies from the same site and population, in which an undetected systematic bias may confound results even across time.

- Has the center been able to influence the line of thinking in research in neighboring fields or in areas not immediately related to the center's core research activities? Please specify.

  Yes, definitely. The field epidemiology studies have stimulated work in basic immunology. There has also been stimulation to develop or adapt statistical methodologies to observational field studies.

The research plan for another 4-year period

- Is the research plan for the next period realistic and original?

  There is no doubt that the research plan for the next period is highly original, integrating a truly multidisciplinary approach with carefully selected collaborations. The project is very ambitious. The research plan is based on generating data to support all 9 paradigm shifts described by the CVIVA group. The Panel expresses concern that the completion of all studies supporting all 9 paradigm shifts may not be realistic within the next 5 years. Whereas some of the paradigm shifts are well supported by the already generated scientific evidence (e.g. paradigm 1), some will still require extensive efforts on several lines of investigation to reach general acceptance (e.g. paradigms 5, 8, 9). This may be difficult to achieve within 5 years.

- Does the plan comprise new and ambitious activities and take up major new research challenges, or is it rather an extrapolation of the ongoing research?

  Obviously, this project is a continuation of the originally proposed project, but new research activities have been added, especially on the basic immunology aspect. Finding experimental models that will identify the underlying mechanisms of all 9 paradigm shifts may be very difficult and not feasible within the next 5 years. Therefore, care should be taken to explore the most appropriate models that are directly linked to the paradigm shifts. The Panel is not certain that some of the proposed animal models (e.g. the murine sepsis model) really fulfill this goal.

- Please indicate the scientifically daring and potentially groundbreaking projects in the research plan. Does the plan reflect an innovative environment?

  Challenging the current vaccination and vitamin A supplementation policies is by definition daring and potentially groundbreaking. The multidisciplinary nature of the project has led to an innovative environment. Innovation is evident in the different aspects of the proposal, e.g. innovative epidemiologic approaches (eg considering triangulation of studies) and basic immunological investigations.

- Please summarize by pointing to three weaknesses, that is, areas where the center can improve, and three strengths, that is, areas where the center in particular shows promise.

  Strengths:
  (i) The multi-disciplinary nature of the project has been enlarged over the past period of the project.
  (ii) The plan for the coming 5 years linearly builds on the main results of the first 5 years.
  (iii) The team is composed of very motivated, hard working members.

  Weaknesses:
  (i) The Panel fears that some of the objectives are over-ambitious. It may therefore be advisable to prioritize some of the tasks.
  (ii) There is an inherent disconnect between some of the paradigms, such as paradigms 4 and 8. If vaccines have long-term imprinting effects, as postulated by P8, why [and how, mechanistically speaking] would the most recent vaccination have the strongest impact on mortality, as suggested by P4?
  (iii) It is not clear how some of the proposed animals studies are directly connected to the most important epidemiologic observations made to sustain some of the paradigms, e.g. the murine sepsis model. It may be more useful to look into other models, such as an animal RSV model, as RSV infection is apparently the primary infection affected by NSEs according some of the group's published and unpublished data.

Organization and management of the center

- Please comment on the organization of the center in light of the research carried out and the aims of the center as a whole.

  The center is essentially staffed by few PIs with permanent positions and many post-docs and PhD students with non-permanent positions. Some of these non-permanent positions play key roles in the center. Therefore, the Panel had some concern about the sustainability of the Center. Is there a plan for the succession of Prof. P. Aaby in Guinea Bissau? Will non-permanent post-docs and PhDs continue to be able to mentor more junior members?

  The aims of the center are clear: looking at non-specific effects of vaccines and the effect of vitamin supplementation on vaccines. The expertise to tackle these questions is present in the group as it is for the moment.

- Has the center's chosen structure and management facilitated a coherent, dynamic and creative research environment?

  The center is very dynamic and composed of highly motivated members. Although all the post-doctoral fellows and PhD students have a high degree of independence, all appear to effectively adhere to the main project. Expertise of the different groups within the center is highly complementary. There is a lot of

interactions between the different members and many discussions at all levels, which has generated a very rich and creative environment.

- Is the center leader recognized as an outstanding researcher, a competent leader, an experienced coach and a qualified research supervisor? Please also assess the role and qualifications of the other senior researchers.

  The leader of the center as a whole is Prof. Christine Benn. She is very well recognized in her field at an international level. She has done outstanding work. She has been invited to many international scientific meetings and has been member of working groups at the NIH and WHO/SAGE. She has obtained several national awards and has been granted a European Research Council grant. She has published 189 research articles, some of which published in high-ranking journals (CID, BMJ). She has been or is currently the supervisor of 24 PhD students and more than 40 Master students.

  The other permanent senior research staff is composed of Prof. P. Aaby, very well known in the vaccine field, especially for having provided the first observations on NSE, and Ane Baerent Fisker, Associate Professor at the University of Southern Denmark and Senior Researcher at CVIVA. She has extensive experience in conducting clinical trials in Guinea Bissau, has supervised several PhD and Master students, published 53 articles (including a senior author article in CID). Other staff is non-permanent.

- Please consider the future aspects of the center. Is a gradual succession of staff ensured so that the environment remains vital and includes new generations of researchers? If relevant, address the question of a possible generational shift.

  Prof. Christine Benn has been appointed the director of CVIVA in 2012, which should secure the directorship position for the foreseeable future. Although not explicitly stated, it seems to the panel that Prof. A. Baerent-Fisker may be the successor of Prof. P. Aaby, which should ensure the continuation of the activities in Guinea Bissau. Most of the research staff is on a non-permanent basis, therefore likely to be renewed at a regular pace. This should ensure new blood coming in and the dynamics of the center.

- Please consider the issue of attracting excellent researchers from outside Denmark and comment on the number of Ph.D. students, post-docs, and senior researchers visiting the center, in particular stays for longer periods of time (more than 3 weeks at the center).

  The center has certainly attracted excellent researchers from outside Denmark into the project. An outstanding example is Prof. Mihai Netea from the Radboud University of Nijmegen. The center has attracted many very good PhD students and post-doctoral fellows, but they virtually all are from Denmark. Essentially after obtaining their PhD, their careers are pursued solely in Denmark. The Panel finds it surprising that, considering the importance of the research subject, the international visibility and high publication output, the Center has neither attracted more international PhD students and post-doctoral fellows, nor placed their graduates internationally. A table was provided concerning visiting scholars or students: 9 from 7 different countries, 4 from different African countries and one from Bangladesh.

- Is the center an attractive unit for recruiting and training younger researchers?

  Yes, the center is certainly attractive. Discussion with the students and post-doctoral fellows indicated that they were all very enthusiastic and committed. They seemed very bright and were apparently very satisfied with the research environment and the mentorship offered.

- Has the training of Ph.D. students been of a reasonable magnitude in relation to the center's overall aim and strategy? What is the standard of the Ph.D. training? What is a typical career path after the Ph.D. degree?

  The PhD students and post-docs are very productive in terms of publication output. Training seems to be satisfying and at the high standards for European Universities. The Panel felt that the career path of most of the PhD students is uncertain. Many them are MDs and will go to clinical practice, but the others expressed concerns about their academic and research future.

- How do you assess the center's resources and the impact of the center's activities on the environment within the host institution?

  The center's financial resources appear to be adequate for the current research, and the host institute SSI supplies roughly 15%. However, the Panel has some concerns about the cost of the many proposed future research projects to support all of the 9 paradigms. SSI does appear to support the center's activities, essentially by both housing the Center and by funding some permanent positions. This implies that the Center is beneficial for the host institution. The Panel did not meet with any of the host institution staff, however.

- Please summarize by pointing to three weaknesses, that is, areas where the center can improve, and three strengths, that is, areas where the center is doing well.

  <u>Strengths:</u>

  (i) Highly motivated and hard-working staff.

  (ii) Appropriate financial resources and space.

  (iii) Serene working atmosphere with a good balance between the African and Danish sites.

  <u>Weaknesses:</u>

  (i) Problem of career mentoring. Research career pathway of most PhD students and Post-docs is uncertain.

  (ii) Insufficient foreign PhD students and Post-docs, coming from countries other than Denmark and Guinea Bissau.

  (iii) Very little (if any) mobility of Danish PhD students and post-docs to other countries to pursue an academic career.

Outreach activities

- Indicate to what degree national and international collaboration has enhanced the center's work.

  The national and international collaboration is essential to pin down potential mechanisms of the observed NSEs. This has been successfully initiated and should be a major focus for the next 5 years.

- Please appraise the cooperation with universities and other research institutes as well as industry, where relevant.

  As stated above, the cooperation with other university and research institutes has been essential and will continue to be so in the future. No collaboration with industry was mentioned. In one way it is good for the Center, as it shows independence.

- Please comment on the standard of the publication list in terms of strategy and actual activity.

  Publication list is abundant. The papers often appear in peer-reviewed journals, which are highly regarded. Junior scientists are encouraged to sign papers as first authors and to take the initiative to produce a first paper outline or draft.

- Also comment on the dissemination and exploitation of the research results as well as any patent activities.

  Presentations at international meetings are given regularly. The Center reaches out to international organizations, such as WHO and participates in panels.

Concluding remarks

- Please point out the center's top three strengths and its three weakest points. Furthermore, add some concluding remarks on the center's overall standing in comparison to world-leading environments within the field.

  Strengths:
  (i) The Center deals with a very important and innovative topic that potentially has a high impact on global health and immunization policy, as well as a high potential for paradigm shifts in basic immunology.
  (ii) High quality of the staff and high motivation of everybody involved.
  (iii) Strong multidisciplinary approach to the scientific question.

  Weaknesses:
  (i) Perhaps the Center chases too many paradigm shifts at once.
  (ii) The mechanistic work needs to be amplified and focused on the most outstanding results coming out of the observational and clinical studies.
  (iii) The Panel suggests to further reach out to other countries in order to stimulate work that might replicate the initial findings in different settings, and to stimulate exchange of PhD students and post-docs for their own career developments.

- Give an overall grading of the quality of the center and the research carried out from a national and an international perspective, with emphasis on identifying strong research and successful constellations. Rate the quality of the research according to the following scale:

  Excellent – The center is excellent from an international perspective.

  Very good – The center's research is of a very high quality and attracts wide national and international attention.

  Good – The center attracts national attention and possesses international potential.

  Insufficient – The research is insufficient and research activities should be revised.

The Panel feels that overall rating of CVIVA should be excellent, that the scientific project goals continue to be risky, but have the potential for major paradigm change[s]. The organization is solid, and the training appears to be sound. If some of the above suggestions are taken into account, the Panel feels that the next five years should even be more successful.