



## **Top Institute Pharma**

### **International Scientific Review Committee**

Report on the second meeting, October 19 and 20, 2006 in Leiden, the Netherlands

First version November 7, 2006

Second version November 20, 2006 – approved by all ISRC members

## **Report of the second meeting of the International Scientific Review Committee (ISRC) on October 19 and 20, 2006, in Leiden**

### **Summary**

The ISRC, in her meeting of October 19 and 20, 2006, concludes that TI Pharma will be running a high quality, coherent and balanced Strategic Research Program based on the accepted projects after the first and second call. The objectives set in the Priority Medicines report are adequately addressed, especially when taking into account the ongoing work on shaping projects in Theme 4, Infectious Diseases.

The Committee is impressed by the progress made since her meeting in April, especially with regards to reaching an agreement on ground rules for intellectual property rights. In this second report the committee formulates recommendations for TI Pharma to help in shaping a strong Institute.

## **Introduction**

On Thursday October 19 and Friday October 20 the ISRC convened for the second time with the TI Pharma Management Team.

Members of the ISRC are:

- Prof. dr. E.J. Ruitenbergh (chair, Professor of International Public Health, Free University Amsterdam, ex RIVM and Sanquin)
- Prof. dr. A.T. Florence (former Dean of the London School of Pharmacy, unable to attend the second meeting)
- Prof. dr. P. Krosgard Larsen (President of the Carlsberg Foundation and professor at the Danish University of Pharmaceutical Sciences)
- Dr. R. Laing (WHO Geneva, author of the Priority Medicines report)
- Prof. dr. L. Lesko (Food and Drug Administration, USA, unable to attend the second meeting for private reasons)
- Prof. dr. R. Metternich (ex Head of Research, Schering AG, Berlin)
- Prof. dr. T.M. Jones, CBE (ex Wellcome Foundation, ex ABPI)

The committee met with the TI Pharma staff and discussed the challenges and the approach to startup TI Pharma. Two main questions were addressed with respect to Strategic Research Program, based on the result of the first and second call:

- 1) Does the program fit with the mission and objectives?
- 2) Does the program adequately address the objectives set in the Priority Medicines report?

This report summarizes the findings and recommendations of the second meeting. First, the observations and suggestions with respect to the operational start are reported, mainly based on a meeting with TI Pharma staff. Secondly, comments on the strategic research program are discussed. The report ends with recommendations of the ISRC to the Executive Board and Management Team of TI Pharma.

## **Agenda & Methodology**

The committee convened for an afternoon session and a full day to discuss the current status of TI Pharma and her Strategic Research Program. The Thursday afternoon was devoted to discussion with the office staff to discuss the operational start. An informal dinner with staff, Management Team and Executive Board was held on Thursday evening. On the Friday morning the strategic research program was presented and discussed. On Friday afternoon 3 Principal Investigators presented their projects, both from a content as well as from an organizational point of view. General remarks with respect to these projects, based on discussion with the PI's, are included in this report.

To prepare for the meeting the members of the ISRC were provided with the following information:

- The full project proposals of all projects accepted in the first and second call
- The full project proposals of projects still under discussion in the second call
- The TI Pharma preliminary strategic research program

## **Operational start**

Different aspects of the operational start were discussed. Comments made per subject are discussed below.

### **Intellectual Property**

The IP ground rules established is a defensible compromise for an issue which has no easy answers. It is signed by the Minister. The committee congratulated TI Pharma for achieving this. The purpose of TI Pharma is not to establish a revolving fund by IP protection but to build highly educated research capacity and a high quality research infrastructure for pharmaceutical research in the Netherlands. The 10% ownership is the 'oil in the machine'. The committee advises TI Pharma to prepare IP related Questions & Answers to have the answers ready when questions arise, from whatever direction.

### **Program Management**

The ideas of the program managers with respect to monitoring of the program and creating synergy were discussed. Good progress has been made with starting up the different projects. A status update is included as an appendix to this report. Defining milestones is important and possible for the first two years but will become a challenge for the longer term.

To create synergy, top down meetings, organized by TI Pharma for all researchers within a Theme or Discipline are a good idea.

The bottom up meetings of peer groups without interference from senior researchers need to be catalyzed by TI Pharma program management. Clear objectives should be defined for these meetings. Take notice that PhD students and post-docs have different priorities. The bottom up meetings certainly help in strengthening translational aspects. There is a clear link here with education and training and it will be an initiative that will pay off in the long run: creating networks which last 10 to 20 years.

The ISRC would like to advise to hire one or two additional program managers. They can be very valuable for the total program. For the big projects dedicated project leaders should be recruited within the project budget to help the PI in running the project, also from a content perspective (which is explicitly not the task of TI Pharma program management). It will also help to create absorption capacity for the numerous PhD and post-doc positions.

Monitoring of the quality and progress of the total program will be discussed in the next ISRC meeting. Review of the program via presentations of Principal Investigators to the ISRC should be more than sufficient. TI Pharma is not only about obtaining scientific results, it is also about educating a workforce of more than 300 high quality researchers.

### **Communication**

The ideas presented on different lines of communication to different stakeholder groups and means to be used for it sound very good. In its communications strategy TI Pharma should make sure to devote sufficient attention to the international aspects, especially the European Union. With respect to the different stakeholder groups, make sure to involve patient groups at the right moment. TI Pharma research output will not provide short term solutions. It is a good idea that the umbrella patient groups organization is represented in the Board of Trustees.

## **Human Resources**

Recruiting top quality researchers to execute the strategic research program is a big challenge. The setup of employment at the different partners paid by TI Pharma budget is a good idea. A good term should be found for PhDs and post-docs paid through TI Pharma, be it fellows, scholars, or something else. These are not TI Pharma employees!

Co-branding in advertisements should be used to make sure TI Pharma is marketed. A lot of value can be added when the facilitating role is executed professionally. A SWOT analysis should be made to identify the areas where TI Pharma can add value in recruitment for her academic and industrial partners. This SWOT analysis will also be very useful for other initiatives. Experiences at different other initiatives which recruit internationally may be build upon (Tropical Institute, Commonwealth fellowships, ...).

Make sure TI Pharma funded researchers will feel a TI Pharma identity. The suggested awards for research related results certainly help, as long as it is an award and not a standard that you'll get it. Rewards can be token awards or materialized, for example scarves, ties, etc.

Building the research capacity is one thing, for a later moment working out a strategy to keep the capacity in the Netherlands, or Europe, is a next thing.

## **Education and training**

TI Pharma Education and Training builds upon the range of existing courses. The idea of the Education and Training working group to start developing new courses in two areas with a specific need is very good. Next to the business skills area, especially the course to provide an overview of the entire drug design and development process is highly relevant. It is good that the regulator is on board, which is crucial to make this course a success. Although the ISRC is aware of the fact that efforts should be focused now, it may be a good idea to develop a course with the regulatory process as the core as well. There is too much lack of understanding of for example GMP and GLP. Also, a new world is developing with the possible introduction of conditional approval. A Master class, instead of a course, may be another way to address this topic.

Master classes are an excellent idea. The Pharmaceutical Sciences World Congress in April provides an excellent starting point for a first (set of) Master class(es). The ISRC will support TI Pharma in getting top people, including R&D directors, to teach in these Master classes. Master classes also contribute to the international positioning of TI Pharma. A master class should typically host a maximum of 30 researchers and have a strong interactive character.

## **International positioning**

TI Pharma is an excellent, best in class example for the current Innovative Medicines Initiative within the EU 7<sup>th</sup> framework program. Experiences from TI Pharma, in building and managing the consortium, setting up IP, etc. should be shared with and communicated to Brussels. There is clearly work to be done on the marketing side. ISRC members will help in approaching the different bodies, like EFPIA.

For future positioning TI Pharma has to build upon her key asset: the consortia formed by large and small industry and academia.

Overall the committee is impressed by the progress TI Pharma has made in starting up its activities since the meeting in April.

## **Research program and Priority Medicines**

TI Pharma has a strong Strategic Research Program, which closely links to the framework anticipated by the European Union Innovative Medicines Initiative. Within the different Disciplines, Lead optimization can be found implicit in Discipline 2 and 3.

Before judging individual proposals the quality of the TI Pharma research program is reflected in the fact that only one third of the submitted projects proposals is accepted. This ensured that a rigorous selection on quality was possible.

### **Theme 1 – (Auto-)Immune diseases**

This Theme contained the large and strong COPD consortium in which three Dutch centers of excellence are linked. It is good that the scope within this Theme is extended to osteoarthritis and specific novel treatments.

### **Theme 2 – Cardiovascular diseases**

This Theme focuses on novel treatments on the one hand, and some side effects on the other. No new quality proposals on stroke were received in the second call, but overall the portfolio shows a healthy mix of projects covering a.o. both wet and dry stroke. Fixed Dose Combinations are dealt with both in Discipline 6 as well as in Discipline 2, PK/PD modeling. Especially the regulatory approval philosophy will need attention. Johnson & Johnson is pulling out in one project on CV side effects, the responsible PI, with help of the Management Team, is seeking new partners.

### **Theme 3 – Neoplastic diseases**

The ISRC is really satisfied with the scope of the consortia within this Theme, especially taking into account the work to be performed within the Center for Translational Molecular Medicine. In the next ISRC meeting a PI of a project within this Theme will be invited to the meeting.

### **Theme 4 – Infectious diseases**

The MRSA project (which is still under discussion) is high risk but very suitable to be included in the TI Pharma strategic research program. The final proposal will be sent to the ISRC as soon as it is received by TI Pharma. The project to develop sensitizers to current antibiotics for antibiotic-resistant bacteria looks very interesting. The committee appreciates the dedicated efforts TI Pharma senior staff have made to strengthen this Theme and address Priority Medicines objectives. Overall this Theme is now well balanced.

### **Theme 5 – CNS diseases**

Brain diseases are now properly addressed. The RNA interference technology is interesting. Delivery and design may form an issue here. Especially the delivery issue could be a topic for a third call, once relevant.

### **Theme 6 – Efficiency analysis**

With two strong projects and sufficient budget allocated to them, Theme 6 is well equipped to contribute to the mission of TI Pharma. A dedicated project manager for the Mondriaan project may prove to be very valuable (such a position would be a useful instrument for other large projects as well, as discussed above). In Australia an example of how the regulator can be involved is present; contacts will be provided. The Mondriaan project was discussed extensively in the Friday afternoon session.

### **Discipline 1 - Therapeutic Target Finding, Validation and Animal Models**

The Toll Like Receptor project is a promising project dealing with a rather new receptor family. The Discipline was not enlarged in the second call. The TLR project was discussed extensively in the Friday afternoon session.

### **Discipline 2 - Lead Selection, In-Silico and PK/PD Modeling**

The PK/PD modeling project is world class and at the forefront in this field. It is good to see that this project is extended. The PK/PD project was discussed extensively in the Friday afternoon session, especially the project organization was praised.

### **Discipline 3 - Predictive Drug Disposition and Toxicology**

This Discipline is now properly addressed with a strong translational project which also has a strong synergy with the epidemiological databases within Theme 6. The biomarker finding character of the project ensures a close link with Discipline 4.

### **Discipline 4 – Biomarkers and Bio-sensing**

Although this Discipline has only one project itself, biomarkers are an important topic which is addressed in different Theme projects. It may be wise to combine Discipline 3 and 4.

### **Discipline 5 - Drug Formulation, Delivery and Targeting**

The project on alternatives for conventional multiple-injection vaccines is relevant a.o. for Neoplastic and Infectious diseases.

### **Discipline 6 – Pharmaceutical Production Technologies**

It is good to see that this Discipline hosts two highly relevant projects. The thermal stability project should, in view of Priority Medicines, focus on two protein formulations: oxytocin and insulin. The project on generic fixed dose combinations should tie in closely with the workshop on neglected diseases.

### **General research program related comments**

The ISRC appreciates the fact that, for a number of projects, industrial partners dare to invest in high risk proposals. Furthermore, the TI Pharma approach to try to solve current problems while developing a large research work force is very good.

### **Workshop on Neglected Diseases**

The workshop on Neglected Diseases, discussed in the first ISRC meeting, is under way and will be held in January 2007. The DNDI (Drugs for Neglected Diseases Initiative) will contribute to this workshop as well as different product development organizations, including ones focused on diagnostics. The morning should be devoted to short talks to inform each other of capabilities and needs. In the afternoon different break-out groups can discuss possible matches between parties.

Organizations that should be involved are MMV (Medicines for Malaria Venture) and EMVI (European Malaria Vaccine Initiative), GATB (Global Alliance for Tuberculosis drug development), FIND (Foundation for Innovative New Diagnostics) and DNDI. Via the association for tropical medicine an overview can be obtained of activities in the Netherlands in this area. The workshop should not only focus on treatment strategies for tropical diseases per se but also consider formulation issues, for example for pediatric and the elderly.

## Recommendations

The ISRC is impressed by the breadth and quality of the response in both the first and second call in each of the different Therapeutic Areas. This has enabled TI Pharma to establish a high quality Strategic Research Program. The balance in subjects as well as in budget terms reflects an adequate balance in view of the needs. The overall program is well designed. Some projects are in really difficult areas and it is good to see that industrial partners are willing to invest in these areas. The committee concludes that the Strategic Research Program fits with the mission, and adequately addresses the objectives of Priority Medicines.

The committee has been informed on the collaboration and synergies with the two other large initiatives: the recently established Center for Translational Molecular Medicine and the detailed plans to start a program on BioMedical Materials. The committee is highly excited about the opportunities for the Netherlands to really make a difference in healthcare innovations. Further discussions between the three institutes, especially on Theme 2, Cardiovascular disease and Theme 3, Neoplastic disease, are encouraged.

The committee sees building the human resource force as a main challenge. An analysis should be made to identify the expertise needed to facilitate dedicated recruiting. Once recruited, education and training is a clear task for TI Pharma, not only via courses and master classes but moreover 'at the bench' itself. Creating links between scientists and clinicians is part of this. As discussed in the education and training paragraph, post-docs and PhD students should be involved in the discussions on the education and training programs to be set up.

The committee is pleased to see that the regulatory agency is on board in the education and training program as well as a participant in some projects. Illustrative of their involvement is the fact that TI Pharma is asked to give presentations to them. With the Board of Trustees (BoT) meeting underway, the ISRC recommends that this board gives its view on how the regulatory agency should be involved. Patient groups should be involved at the highest level (umbrella organization). Disease specific patient groups could advise on the program in general terms, relevant remarks are welcome, but are of a purely advisory nature.

The committee is pleased with the performance of the staff recruited for the TI Pharma office so far and impressed by the progress made during the last half year. The agreement reached on IP rights is a good job being the result of substantial efforts in a complex arena to get a general agreement which is acceptable by all parties. The 10% ownership is not meant to make TI Pharma a self-sustaining organization, but reflects the wish of TI Pharma to be a stakeholder. The agreement reached should be used in other public private partnerships as well as in European initiatives.

Overall, the committee is of the opinion that TI Pharma has made excellent progress in her startup phase. Dozens of new ideas emerged during the meeting, but first TI Pharma will have to show that it is able to deliver before imposing TI Pharma with new tasks and objectives. The committee is confident that TI Pharma will be a success. In April 2007 the ISRC will meet again to discuss, amongst others, monitoring the output of the total program.

## Appendix

### Progress in starting up the TI Pharma project portfolio (status October 20, 2006)

| Nr                  | Title  | Status   | First meeting | Detailed budget and project plan received | Second meeting to discuss budget and plan | Budget and plan reviewed and approved |
|---------------------|--|----------|---------------|---|---|---------------------------------------|
| <b>First call:</b>  |  |          |               |   |   |                                       |
| D1-101              | Exploitation of Toll-like receptors in Drug Discovery                            | Accepted |               |   |   |                                       |
| D1-105              | The GPCR Forum. Novel concepts and tools for established target                  | Accepted |               |   |   |                                       |
| D2-101              | An integrated strategy for in silico prediction and clinical evaluation          | Accepted |               |   |   |                                       |
| D2-102              | Metabolic stability assessment as new tool in the Hit-to-Lead selection          | Accepted |               |   |   |                                       |
| D2-103              | New approaches for Ligand-Gated Ion Channel (LGIC) drug discovery                | Accepted |               |   |   |                                       |
| D2-104              | Mechanism-based PK/PD modeling platform  | Accepted |               |   |   |                                       |
| D4-102              | The CSF proteome / metabolome as primary biomarker compartment                   | Accepted |               |   |   |                                       |
| D5-106              | VACCINE DELIVERY: ALTERNATIVES FOR CONVENTIONAL METHODS                          | Accepted |               |   |   |                                       |
| T1-103              | CXC chemokine receptors: potential targets for chronic inflammation              | Accepted |               |   |   |                                       |
| T1-106              | Glucocorticoid-induced insulin-resistance  | Accepted |               |   |   |                                       |
| T1-108              | Acute and chronic inflammatory responses   | Accepted |               |   |   |                                       |
| T2-110              | Nuclear receptors as targets for anti-atherosclerotic therapies                  | Accepted |               |   |   |                                       |
| T2-111              | Recombinant factor XI and IX variants as the basis for the development           | Accepted |               |   |   |                                       |
| T2-105              | Investigation of drug induced weight alterations to identify novel targets       | Accepted |               |   |   |                                       |
| T2-108              | Metalloproteases and Novel Targets in Endothelial Dysfunction                    | Accepted |               |   |   |                                       |
| T3-112              | TNF ligands in cancer  | Accepted |               |   |   |                                       |
| T3-103              | Identification of novel kinases involved in cancer-relevant processes            | Accepted |               |   |   |                                       |
| T3-105              | Kinases in cancer  | Accepted |               |   |   |                                       |
| T3-106              | Novel cancer drugs based on signal transduction pathways                         | Accepted |               |   |   |                                       |
| T3-107              | Nuclear receptors in targeted cancer therapy: improved methods and               | Accepted |               |   |   |                                       |
| T3-108              | Predicting drug responses in breast cancer                                       | Accepted |               |   |   |                                       |
| T4-101              | Antibodies against Klebsiella pneumoniae as an alternative                       | Accepted |               |   |   |                                       |
| T4-102              | Design of Predictive Models, Drug Delivery, and Live-virus Malaria               | Accepted |               |   |   |                                       |
| T4-103              | Establishment of validated animal models for human influenza and                 | Discuss  |               |   |   |                                       |
| T5-105              | Nanoscience as a tool for improving bioavailability and Blood Brain              | Accepted |               |   |   |                                       |
| T5-107              | The neurophysiological role of the endocannabinoid system in sleep               | Accepted |               |   |   |                                       |
| T5-108              | Validation of the use of fMRI as an objective measure in clinical practice       | Accepted |               |   |   |                                       |
| T6-101              | The Mondriaan Project : The Dutch health care landscape as a project             | Accepted |               |   |   |                                       |
| <b>Second call:</b> |  |          |               |   |   |                                       |
| D3-201              | Towards novel translational safety biomarkers for adverse drug reactions         | Accepted |               |   |   |                                       |
| D6-202              | Hot medicines <sup>®</sup> : breaking the cold chain requirement for polypeptide | Accepted |               |   |   |                                       |
| D6-203              | DESIGN QUALITY INTO PRODUCTS   | Accepted |               |   |   |                                       |
| T1-201              | Transition of systemic inflammation into multiorgan pathology                    | Accepted |               |   |   |                                       |
| T1-213              | Osteo-arthritis: models, mechanisms and markers for patient stratification       | Accepted |               |   |   |                                       |
| T1-214              | Immune modulation and tolerance induction, prevention and inhibition             | Accepted |               |   |   |                                       |
| T1-215              | Neuromodulation of innate immune responses                                       | Accepted |               |   |   |                                       |
| T4-209              | New antibiotics to fight antimicrobial resistance                                | Accepted |               |   |   |                                       |
| T5-203              | A translational pharmacogenomics approach to improve drug development            | Accepted |               |   |   |                                       |
| T5-207              | Parkinson and Alzheimer disease: from dysregulated human brain                   | Accepted |               |   |   |                                       |
| T5-209              | Novel susceptibility pathways and drug targets for psychosis                     | Accepted |               |   |   |                                       |
| T5-210              | Rapid in vivo CNS drug target validation and therapeutic potential               | Accepted |               |   |   |                                       |
| T6-202              | The Escher Project: Science driven drug regulation and innovative                | Accepted |               |   |   |                                       |
| D2-201              | Mechanism-based PK/PD modeling platform  | Discuss  |               | extension on D2-104                       |   |                                       |
| D5-203              | New nano-sized formulation technology for hydrophobic drugs                      | Discuss  |               |   |   |                                       |
| T4-211              | Efficient Eradication of (Multidrug)Resistant Bacteria                           | Discuss  |               |   |   |                                       |
| T4-212              | A multidisciplinary approach to monitor and select effective therapies           | Discuss  |               |   |   |                                       |
| T4-213              | Protective human antibodies against multi-drug resistant Staphylococcus          | Discuss  |               |   |   |                                       |
| T5-211              | Novel inroads towards biomarkers and therapies for neurodegeneration             | Discuss  |               | integrated with T5-207                    |   |                                       |