# TI Pharma

## New tracks to medicines

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Public-private partnerships within pharmaceutical research are now so successful that it is easy to forget how unlikely they once seemed. Less than a decade ago, partnership between academic organisations, major industry players and SMEs was rare, and when they did occur, they were usually within isolated silos of activity.

The FES-funded (Dutch natural gas reserve fund) research portfolio triggered the creation of the Top Institute Pharma (TI Pharma). Following an invitation from large and small industry players and leading academic organisations, the Dutch government stepped in to encourage partnerships that could improve pharmaceutical research. This followed up on a report on priority medicines, commissioned by the government of the Netherlands during its EU presidency in 2004 and written by the WHO. No effective structure had previously existed to bring public and private organisations together, and the WHO report gave a clear strategic definition of public health priorities for medicine research – in particular for some high-impact topics that were not being addressed.

Since the first FES project started in 2007, scientific, financial and educational outcomes have exceeded all expectations. They include direct impacts on patient health and on the economy.

There have been notable scientific and even clinical successes. Positive results have emerged for many topics defined in the seminal 2004 WHO report ‘Priority Medicines for Europe and the World’, and awareness of those topics has grown dramatically. A highly skilled research cohort has been nurtured and given new, broader skills, and there is a strong and unprecedented atmosphere of collaboration.

This report looks at value generated both directly and indirectly by TI Pharma and the FES-funded research portfolio. In particular, it considers the programme’s impact on scientific know-how; on progress with priority medicines; on human capital development; and on the growth of collaboration within new networks. It also looks at what the future holds for collaborative research.

Know-how

Improved health and wealth, rooted in scientific excellence, were central FES portfolio objectives.

Direct patient benefits have already resulted, including a safe morphine regimen for newborns; new clinical protocols for COPD; a vaccine candidate against acute myeloid leukaemia; a disease registry for rare metabolic diseases (which will facilitate development for these so-called orphan diseases); and numerous other examples.

New test methods have been developed, and highly promising molecules and compound libraries have been identified. With a typical innovation ‘heartbeat’ in the life sciences sector of 10 to 15 years, there is a very good chance of new treatments still to come over the next few years, given the limited time that has elapsed so far. In addition, initiatives such as the Mondriaan patient data sharing project are set to yield important new insights into the use and effects of drugs in daily practice. This will lead to improvements to research into new treatments and to public health.

Economic performance has been equally strong. The Dutch government set TI Pharma a demanding financial goal: to double EUR 137 million of government funding, with half of the matched funds coming from academia and half from private sources. In fact, by conservative direct-impact measurements, government funding was more than tripled, and EUR 152 million came from private sources for collaborative projects with shared costs and benefits. A more realistic assessment taking indirect impacts into account, such as companies that have been able to grow thanks to the results of TI Pharma projects, suggests an even higher multiplier in excess of 6 (including EUR 353 million from private sources).

Health and wealth performance was based on excellence in science. Across almost 750 published results, scientific impact was independently assessed by CWTS (Centre for Science and Technology Studies) Leiden at a mean normalized citation score (MNCS) of 1.80, placing TI Pharma among institutions that distribute funding to fundamental research, and close to international leaders such as the Wellcome Trust.
Priority medicines

At the outset of the FES project, around 33% of priority medicine-focused research was expected to be successful. In the event, 39 out of 56 priority medicine projects resulted in a high impact – or 70%. The FES Review Committee’s judgement in November 2013 (see Appendix A) was unequivocal:

“The Committee is very pleased with the results of the TI Pharma FES programme in relation to WHO’s Priority Medicines initiative. The delivery exceeds the expectations of the Review Committee.”

In addition, TI Pharma was tasked with creating wider awareness of priority medicines. It did so in many ways, above all by engaging with stakeholders within the research programme that was developed in response to the WHO priority medicines report. The European Commission’s continued focus on the priority medicines agenda was shown by its request for a progress update, presented in July 2013, to be used as a resource when planning the European Union’s Horizon 2020 combined research programme. This update, like some previous reports (including, for example, a report from the OECD), cited TI Pharma as a case study. The FES Review Committee stated:

“It is clear that PPPs such as TI Pharma can be critical in achieving Priority Medicines objectives.”

Human capital

After six years, a whole new generation of scientists able to work in a multidisciplinary public-private setting has been nurtured. A cohort of 470 researchers has emerged with direct experience of working extensively in collaborative projects. This cohort has also participated in targeted courses designed to give an overview of the wider (pharmaceutical) environment, complementing their scientific education with an awareness of industry practices. Seven different education courses and an industry career day were run 39 times in total. Around 20% of attendees were from outside of the FES programme, showing the quality and external appeal of the courses.

One very notable impact from the programme was on employability: 98% of former TI Pharma PhD students and post-docs found a job on leaving the programme. 30% of these jobs were in industry and 32% were roles as senior researchers within knowledge institutes.

Networks

Open innovation rests on the quality and reach of networks and trust built within these networks. There is a widespread consensus that TI Pharma has made a substantial contribution. The FES Review Committee was clear in its assessment:

“The interactions between academia and industry changed from being somewhat distant, to a highly productive atmosphere of collaboration. TI Pharma played a significant role in managing and adapting to this transition in the Netherlands. As such, it is positioned to help the Netherlands gain the maximum benefit from the new environment.”

The arms’ length environment created by TI Pharma allowed various parties, who would otherwise find collaboration difficult, to work together in joint projects very successfully. A safe and trusted environment for discussion was thereby created, in which highly sensitive topics could be addressed. For example, the Escher project has addressed regulatory aspects of medicine development, and has developed the regulatory sciences field. Other projects examined the value of research with hindsight— including provision of evidence that studies with nonhuman primates are rarely predictive for the human situation.

Legacy

The achievements and anticipated successes still to come from the FES projects have left no doubt that this research model should be pursued in the future. New projects are already being developed and going live, funded from a variety of sources. These projects continue to contribute to know-how, priority medicines, network creation and the development of a more broadly educated research cohort.
The EU Lead Factory, launched in February 2013 as part of the Innovative Medicines Initiative (IMI), is an important example of how new collaborative networks can develop scientific results that would be unachievable by isolated organisations. This is a flagship open innovation resource for European academics, public bodies and SMEs, described by Nature in December 2013 as a “formidable factory”. 32 international partners are now working on the discovery of new drug lead molecules, with an essential role for TI Pharma as scientific programme office for the consortium.

The creation of future cohorts of industry-aware and collaboration-ready scientists remains a major priority. TI Pharma will be doing everything possible to secure the funding needed to ensure this.

In connection with this, work is ongoing to launch ‘Leiden Futurelab’ in 2014, building on the success of the FES education programme by offering a post-graduate and interactive learning environment for life science professionals.

Neglected diseases are still a core focus, and progress on treating diseases such as schistosomiasis and leishmaniasis will be possible only through the shared risks and shared resources that come with extensive cross-sector collaboration. FES projects have shown that shortcomings in the market can be addressed successfully in this way. Currently, for example, the Bill & Melinda Gates Foundation and the Japanese Global Health Innovative Technology (GHIT) fund are funding a partnership coordinated by TI Pharma to bring a paediatric product for schistosomiasis through the first clinical stage. Another example is the phosphodiesterase inhibitor project, which was started within the FES funded portfolio and is now continuing with EU funding, under TI Pharma programme management.

Regulatory issues involve sensitive discussions, as regulatory agencies need to guard their independent position in the interest of patients. Interactions with industry, government and others are also essential to improve access to safe and effective drugs. A sound scientific basis is instrumental when facilitating discussions between these stakeholders, and to progress the regulatory field. A specific example is the Non Biological Complex Drugs (NBCD) Working Group, hosted at TI Pharma. NBCDs are a special class of drugs, and the Working Group’s mission is to ensure that appropriate and harmonized science-based approval and post-approval standards are introduced globally for NBCDs and their follow-on versions, to ensure patient safety and benefit.

This report summarizes the results of a unique collaboration of 96 partners, including 26 knowledge institutes, 21 large and 43 smaller industrial players, as well as organizations such as the Dutch Medicines Evaluation Board and patient organizations. With generous co-funding from the Dutch government, we have built connections between these parties, so they have been able to work together on a very productive joint research agenda. Almost 2,000 people contributed to the programme over the last six years, of which 470 were newly educated researchers. We would like to thank the Dutch government, our partners and all those involved for making this endeavour a success so far, and we are looking forward to continuing our joint efforts to advance medicines research in the future.

Jorg Janssen
Managing Director

Ton Rijnders
Scientific Director
Origins: A major partnership in drug discovery & development

At the time of the 2004 Dutch presidency of the European Union, serious and widely acknowledged pharmaceutical sector challenges existed. Productivity had declined and is still declining within drug research and development, and many public health issues were too large for any one organisation to address.

In November 2004, a pivotal study was commissioned by the Dutch government during its 2004 European Union presidency. The result was publication of the WHO report ‘Priority Medicines for Europe and the World’. While presenting it, the Minister of Health made a commitment to address the priority medicines agenda and this triggered the establishment of the Top Institute Pharma (TI Pharma), to deliver on the report’s priorities.

Work on establishing TI Pharma began in Spring 2005, spearheaded by a working group of the Netherlands Federation for Innovative Drug Research (FIGON). In September 2005, the Dutch government decided to double the proposed investment by industrial and academic partners with an initial grant from the ‘FES fund’ of EUR 130 million. After procedures within parliament were complete, the TI Pharma foundation was established on July 11, 2006, as a public-private partnership of, at that time, almost 50 partners and participants from academia and industry. Half of the funding came from the Dutch Government, with 25% from the pharmaceutical industry and 25% from academia. All parties committed to continued funding for an initial period of four years.

The newly established organisation was tasked with building a far-reaching research portfolio, including call management, establishing contracts and engaging partners. Its role was to manage the portfolio over time, encouraging cross-fertilization between projects, and to coordinate all outputs including dissemination of results and stimulation of follow-up activities.

Training a new generation of scientists working across many disciplines within drug discovery and development was also a core priority.

The stated TI Pharma mission is “to establish, support and manage public-private collaborations between academia and the (inter-) national pharmaceutical industry in order to create ‘health & wealth’.”

In line with this mission, the following objectives were set:

Create, through synergy, excellence in ground-breaking, cross-disciplinary research, within the framework of Priority Medicines

Improve the efficiency of the entire drug development process, in direct contact with and with input from the regulator

Educate and train future generations of biomedical scientists

Expand into Europe, in terms of industrial and academic partners and in education & training

Projects began in 2007 and TI Pharma emerged as a forerunner in the creation of new and productive public-private cooperation. New partnerships were established on an unprecedented scale, not only by the standards of the Netherlands but by global standards.

A larger initiative, the Innovative Medicines Initiative (IMI), was launched subsequently in 2007/08. Experiences shared by TI Pharma teams helped to make an important contribution to this European initiative.
“It was both challenging and rewarding to help construct a collaborative platform, unifying vastly different partners. TI Pharma turns out to be a virtual institute with very tangible results, worth ‘to be continued’.”

Victor Nickolson
Managing Director TI Pharma, 2006-2008

“Scientists and entrepreneurs joining forces for the benefit of patients and the economy, it was a great pleasure to contribute in the startup of this institute.”

Hans van den Berg
Chair FIGON working group for the TI Pharma startup

“TI Pharma has proved to be extremely facilitating in boosting research in drug discovery and development in The Netherlands in recent years; it is very important that this accelerator function will remain very active for the advancement of the pharmaceutical sciences.”

Douwe Breimer
Professor of Pharmacology and past Rector Magnificus Leiden University
Ambitious and detailed ‘indicators for success’ were defined in 2006 and sent to the Tweede Kamer (House of Parliament). These indicators stated that TI Pharma would be ‘considered a success’ when the eleven targets listed below had been met.

The final FES Review Committee report makes it clear (Appendix A, Annex 3) that by 2013 the project was indeed a success: all targets were rated as ‘achieved’, except for target 9 and 10 with their eight-year timeframe, and this was rated as having made ‘very good progress’.

1. In two years, the first publications and patent applications originating from TI Pharma projects see daylight

2. In two years, the Priority Medicines agenda has been brought out into the open by TI Pharma and has received serious attention from the pharmaceutical industry

3. The majority of current TI Pharma consortia of industry, start-ups and academia are still working together in 3-4 years, and plan to continue this cooperation after their projects end, which proves that sustainable, multilateral cooperation has arisen

4. In 2-3 years TI Pharma has achieved European stature, resulting in international cooperation in the 7th framework programme

5. In 3-4 years it is clear that TI Pharma researchers are recruited by industry, knowledge institutes and regulatory agencies as a result of their clear vision of and broad experience in innovative and efficient, modern pharmaceutical research

6. In four years, more than a third of projects have met their expectations as described in the original project plans (the success rate of R&D projects in the pharmaceutical sector is notably lower)

7. Within four years, several spin-outs have formed as a result of TI Pharma projects

8. In four years, at least one new mechanism has been discovered that will lead to treatment for certain diseases

9. In 4-8 years based on TI Pharma projects, at least one symptomatic treatment of a disease is replaced with a treatment that tackles the root of the problem

10. In 4-8 years, a number of new biomarkers have been identified and validated, leading to:
   a. improvement in the design, development and evaluation of new drugs and
   b. more effective measurement of therapeutic effects and/or side effects of drugs

11. In 3-10 years it is obvious that the unique drug research infrastructure, built by TI Pharma, attracts significantly more R&D work from foreign pharmaceutical companies.

The quality of TI Pharma’s commitment and programme management is demonstrated by a very significant achievement: all eleven of the originally defined ‘indicators for success’ were either achieved on schedule or are on track to be achieved on schedule
Governance of TI Pharma was via a management team and two Boards. The overarching governing body was the Supervisory Board, which consisted of all partners active in the TI Pharma FES portfolio. From its midst, an Executive Board was appointed consisting of seven members, including academic leaders as well as large and small industry executives. Oversight by and advice from the International Scientific Review Committee ensured scientific quality within the portfolio, and this committee was involved in the review of the scientific quality of projects.

In addition, a Mid-Term Review was organized in late 2009 to assess the progress made and to make recommendations for the future. The full FES-funded portfolio was reviewed at the end of 2013. These independent assessments by internationally renowned experts ensured external validation of all activities, and provided further guidance for TI Pharma as an organisation.
Building upon the priority medicines agenda set by the 2004 WHO report, five disease areas formed the basis of the TI Pharma research agenda: (auto-)immune, cardio-vascular, cancer, infectious diseases and brain diseases.

Alongside these therapeutic areas, six enabling technologies were defined, spanning the entire drug discovery and development process, from target finding through to pharmaceutical production technologies.

In addition, a special research platform was established to work on the drug discovery and development process itself, and on the regulatory environment. Topics included regulatory sciences, efficiency improvements, access to patient data and public health.

FES-funded research projects were designed to deliver tangible results based on high quality science. Research was translational, with projects that progressed along the pharmaceutical R&D pipeline, all the way from early discovery towards preclinical and clinical stages.
All five calls for proposals differed in character and focus. As the FES Review Committee stated, they were not ‘one offs’, but rather evolved logically to stimulate the entire portfolio, with call procedures and acceptance criteria adapted in response to experiences during previous projects.

Initial calls in 2006 and 2007 were broader, covering different areas of the priority medicines agenda, while later calls addressed potential synergies between drugs, devices and diagnostics (Joint call), opportunities to build on the success of initial projects (Value Creation call) and to create further opportunities for SME-driven partnerships.

### 2006
First call for proposals:
industry and academia initiative
‘Bottom up’ – TI Pharma defines 6 therapeutic areas and 6 enabling technologies. Submissions invited from everybody, including non-founders.

**Total call budget:**
EUR 160 million
25% private participation

### 2007
Second call for proposals:
balancing the portfolio
‘Top down’ – themes and disciplines re-evaluated. Gaps identified with a focus, among others, on infectious diseases.

**Total call budget:**
EUR 80 million
25% private participation

### 2009
Joint call for proposals
Partnering with CTMM and BMM

**Total call budget:**
EUR 28 million
25% private participation

### 2011
Value Creation call
Follow-up for successful projects

**Total call budget:**
> EUR 15 million
At least 40% private participation

### 2012
SME Partnership call
Focus on SME partnerships

**Total call budget:**
> EUR 7.5 million
At least 40% private participation

### COLLABORATION WITH CTMM AND BMM: A JOINT CALL
A joint call in 2009 between Ti Pharma, the Center for Translational Molecular Medicine (CTMM) and the BioMedical Materials (BMM) programme exploited the skills of all three institutes.

The call encompassed diagnosis (CTMM), new drugs (Ti Pharma) and new devices (BMM) to address imaging-guided and targeted drug delivery.

Eight new projects resulted, one of which is coordinated by Ti Pharma.
Progress towards stated goals was rapid. First research projects started in 2007 and by the end of the year, the full research programme was up and running. The 74th and final FES-funded project started on January 2nd, 2013.

Instead of a full second round of government funding, TI Pharma received a small bridging fund of EUR 6 million in 2010. This change prompted a broadening of scope for TI Pharma. It began to seek additional opportunities to use its expertise in supporting public-private partnerships, providing transformative input and backup to projects that had no or reduced governmental funding.
Timeline

2010
- Q1: ISRC
- Q2: SME PARTNERSHIP CALL
- Q3: FES REVIEW MEETING
- Q4: 60th PROJECT AGREEMENT SIGNED

2011
- Q1: VALUE CREATION CALL
- Q2: STRATEGIC ACTION PLAN DEVELOPED
- Q3: MID TERM REVIEW REPORT
- Q4: SB MEETING

2012
- Q1: START NBCD
- Q2: SB MEETING
- Q3: STRATEGIC ACTION PLAN DEVELOPED
- Q4: SB MEETING

2013
- Q1: START SCHISTOSOMIASIS CONSORTIUM
- Q2: START IMI EUROPEAN LEAD FACTORY
- Q3: START IMI KIDD
- Q4: 74th PROJECT AGREEMENT SIGNED

2014
- Q1: START EU POEINPD PROJECT
- Q2: START ESCHER PROJECT WITH EFPIA
- Q3: FINAL SB MEETING
- Q4: FES REVIEW MEETING

13. TI PHARMA, NEW TRACKS TO MEDICINES
Chapter 3. Know-How

“...a programme of excellence like the one with impressive progress at TI Pharma is very well suited to develop the unique skills of the next generation of translational pharmaceutical and medical researchers.”

Povl Krogsgaard-Larsen
Past member of the ISRC and FES Review Committee; past President of the Carlsberg Foundation; professor at the University of Copenhagen

“It was good to see that industry executives, academic leaders, and biotech entrepreneurs joined forces to generate clout together and create an exciting, dynamic public-private research environment.”

Sijbalt Noorda
Former President of the Dutch Association of Universities (VSNU) and past Chair of the TI Pharma Supervisory Board
“TI Pharma offers a unique opportunity to integrate fundamental and applied research. Although differences between partners will always exist, in hindsight we are very proud of all connections that have been made between science, chemistry and people in our project!”

Anja Garritsen
PI Toll like receptor project and CEO InnatOss
The know-how generated by the FES-funded portfolio ranges from early discoveries to direct patient benefits, with significant progress seen in both. In several therapeutic areas, direct patient benefit has been delivered, as demonstrated below and by showcases elsewhere in this report. Both immediate and long term impacts have been produced by the enabling technologies projects. This chapter will look at the progress made to increase health and wealth, and at its basis within excellence in science.

**Health**

Direct patient benefits that have already resulted include a safe morphine dosage regimen for newborns; new clinical protocols for COPD; a vaccine candidate against acute myeloid leukaemia; a disease registry for rare metabolic diseases (which will facilitate development of diagnosis and treatment for this so-called orphan diseases); and numerous other examples. See the many showcases and case studies in this report for more.

Within the overall portfolio there is a variation in output across different therapeutic areas and enabling technologies, reflecting the challenges of each individual research field. Research projects that do not reach their originally anticipated goals can often, through serendipity, add as much knowledge to biopharmaceutical research as ‘successes’ would have done. Given the variability in outputs, it is therefore also valuable to form a high-level overview of the results and challenges by therapeutic area and technology cluster.

Results within auto-immune diseases include new biomarkers for multiple sclerosis, (pre-)clinical models and research tools for psoriasis. One specific area included studies on the effect of nutrition on the immune system, thereby connecting with food sciences. Projects with a clinical study encountered challenges such as difficulties in patient recruitment, and in one case the hypothesis on which the project was initially based turned out to be incorrect.

For cardiovascular diseases, general progress within drug research and development has been very
DIRECT PROJECT OUTPUT HAS BEEN CATEGORIZED IN SEVEN CATEGORIES

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TOTAL: 229
challenging during the period of TI Pharma activities. Results from the FES-funded portfolio are therefore in line with the limited success in the overall field. Another reason for disappointing output may be that, in hindsight, research plans were often found to be too ambitious.

Projects in cancer research were outperformers. Numerous research tools have been developed, and the output in terms of compounds and biomarkers is impressive. In addition, numerous (pre-)clinical models were delivered, adding to the translational output in this cluster of projects.

Infectious diseases also yielded many research successes. These included antibodies against bacteria such as MRSA; vaccine candidates for Chikungunya and Malaria; and optimized lead series for certain neglected tropical diseases. Almost all projects in this area showed a high impact on the priority medicines agenda, and some of the work is continuing as part of TI Pharma’s future research into neglected diseases.

In brain diseases (central nervous system) two projects outperformed, including the delivery of a new standard for pain measurement. Challenges encountered in this field included difficulties in translating animal model results to humans, as well as setbacks due to industry withdrawals from this field.

The special research platform dedicated to improving drug discovery, development and utilization (‘Theme 6’) was an outstanding success. Results from the Escher and Mondriaan projects can be seen in case studies in this report. In addition, three projects in the orphan disease area delivered tangible results, including the database already mentioned in the introduction. TI Pharma is continuing this special research platform, including the Escher Think Tank, in its future ‘multistakeholder interactions’ research line.

In technology projects, productivity was generally high. For example, a large number of compounds and libraries have been found. Both immediate and long term impacts have been produced by these

**Financial Goal: Multiplier of 2**

**Directly Attributable Multiplier**

Achieved: 3.1

**Broader ‘Clout’ Multiplier**

Achieved: At least 6

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**€ M**

**Total Multiplier**

X 3.1

X 6.3

**Builds, among others, on 36 patents**

**Government**

**Direct**

**Clout**

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**EU Funding**

**Academic**

**Industrial**
technology projects. Valuable tools that can help produce, predict and analyse important research outcomes have been developed. The impact of these newly developed research tools is not limited to the FES-funded programme, and the tools are currently used as standards that add value to future projects. Modelling projects, including the showcased PK/PD platform, have resulted in numerous clinical models. Finally, drug delivery and pharmaceutical technology projects have delivered many new (potential) formulations as well as new research tools.

In conclusion, the portfolio delivered many tangible results across many different categories. An analysis made towards the end of 2013, in preparation for the review committee visit, is summarized in the table on page 17. Of course equating numbers in various different categories is like comparing apples, pears and grapes. Nonetheless, the comparison shows the extensive impact made by the TI Pharma FES-funded portfolio on the (Dutch) research landscape. With a typical innovation ‘heartbeat’ in the life sciences sector of 10 to 15 years, there is a very good chance of new treatments still to come over the next few years, given the limited time that has elapsed so far. In addition, initiatives such as the Mondriaan patient data sharing project are set to yield important new insights into the use and effects of drugs in daily practice. This will lead to improvements both to research into new treatments and to public health.

**Wealth**

Economic performance has been equally strong. The Dutch government set TI Pharma a demanding financial goal: to double EUR 137 million of government funding, with half of the matched funds coming from academia and half from private sources. This split was achieved when the portfolio started, but subsequently improved further: in the last two calls (VCC and SPC), TI Pharma has been able to move towards a 1-to-1 private matching with respect to the subsidy, and 0.5 academic matching. Even before follow-up projects are taken into account, this result yields a multiplier of 2.5 within later projects.

Ultimately, by conservative direct-impact measurements, government funding was more than tripled during the FES-funded research. EUR 152 million came from private sources for collaborative projects with shared costs and benefits.

**RESULTS WERE PUBLISHED IN MORE THAN 750 PUBLICATIONS, WITH EXCELLENT SCIENTIFIC IMPACT**

Source: CWTS Leiden University
A more realistic assessment takes indirect impacts into account, such as companies that have been able to grow thanks to the results of TI Pharma projects. Such an assessment suggests an even higher multiplier in excess of 6, including EUR 353 million from private sources. The formation and extension of new partnerships has been an important contributor to this figure. Many new connections formed as a direct result of TI Pharma projects: 42 running projects have resulted in 74 additional new projects and/or partnerships. Among other outcomes, these are building upon 36 patents (and counting) generated in the FES-funded portfolio.

Science
The strong performance seen in building better health and wealth had its roots in excellent science. Across almost 750 published results, scientific impact was independently assessed by CWTS (Centre for Science and Technology Studies) Leiden at a mean normalized citation score (MNCS) of 1.80. This places TI Pharma among institutions that distribute funding to fundamental research, and close to international leaders such as the Wellcome Trust. Complex partnerships, especially those involved in drug research and development, need time to become established and to begin performing at full strength. When TI Pharma began the FES-funded research, a second round of financing was envisioned that would bring the first projects to maturity and deliver real world applications. The largest impact on health, wealth and science would thereby be secured.

The finalized FES portfolio has already resulted in clear benefit for patients, and a number of follow up projects have been started. In addition, the project portfolio has resulted in many opportunities to further develop the seeds already sown.

One very clear conclusion emerges: the partnership case counts.
AN EXPERIMENT WITH OUR PARTNERS, LEADING TO A PRODUCTIVE ATMOSPHERE OF COLLABORATION

PUBLIC PARTNERS

Academic
Centre for Human Drug Research (CHDR)
Drugs for Neglected Diseases initiative (DNDi)
Hubrecht Institute
Jan van Es Instituut
Netherlands Cancer Institute (NKI)
Netherlands Institute for Neuroscience (NIN)
Netherlands Vaccine Institute (NVI)
Royal Tropical Institute (KIT)
TNO Quality of Life
Academic Medical Center (AMC) Amsterdam
Erasmus MC (University Medical Center Rotterdam)
Leiden University Medical Center (LUMC)
Maastricht University Medical Center (MUMC)
Radboud University Nijmegen Medical Centre (RUNMC)
University Medical Center Groningen (UMCG)
University Medical Center Utrecht (UMCU)
VU University Medical Center (VUMC)
Leiden University
Maastricht University
Radboud University Nijmegen
University of Amsterdam (UvA)
University of Bern
University of Groningen (RUG)
University of Utrecht
VU University Amsterdam
Wageningen University and Research Center

Public Other
Dutch Health Care Insurance Board (CVZ)
Dutch Medicines Evaluation Board (CBG-MEB)
Life Sciences & Health (LSH)
ZonMw / Dutch Steering Committee Orphan Drugs

PRIVATE PARTNERS

SME
3D-PharmXchange BV
Aeon Astron Europe BV
Agamyxis
Agendia
Batavia Bioservices BV
Bio Detection Systems B.V.
BioMarin Europe Limited
BioNovion BV
Galapagos
BioNovion BV
DC Prime BV
Feycon Development & Implementation BV
Glycostem Therapeutics
HQ Medical BV
InTeRNA Technologies
IDTA Pharmaceuticals
IQ Corporation/IQ Therapeutics
ISA Pharmaceuticals B.V.
Lead Pharma Holding BV
Madam Therapeutics BV
Magistro
Mercachem B.V.
Mymetics B.V.
Netherlands Translational Research Center
Nivel
Novavax
OctoPlus
PamGene
Pepscan Presto
Percuros BV
Pivot Park Screening Centre BV
PRA International
Prosensa Therapeutics
PROXY Laboratories
QPS
Syncom
Synvolux Therapeutics
UbiQ Bio BV
Vaxinotics
ViroClinics Biosciences B.V.

Non-SME
AbbVie
Actelion Pharmaceuticals Nederland BV
Amgen B.V.
Astellas
AstraZeneca
Centocor
Danone Research
Eli Lilly
GE Healthcare
Genzyme
GlaxoSmithKline
Johnson & Johnson
LifeAssay Diagnostics (Pty) Ltd
Lundbeck A/S
MSD / Merck & Co.
Pfizer
Sanaria Inc.
Sanofi Aventis
Shire
Takeda
Vertex Pharmaceuticals Incorporated

Private Other
Foundation for Innovative New Diagnostics (FIND)
Nefarma

Wii Research Europe BV (legacy Notox BV)
WINap
Xpand Biotechnology BV

21. TI PHARMA. NEW TRACKS TO MEDICINES
Valorizing clinical and laboratory tools for improved diagnosis and subsequent treatment of Fabry disease

Fabry disease, one of the “Orphan diseases”, is an X-chromosomal-linked inherited multisystem disorder that belongs to the group of lysosomal storage disorders. The disease is caused by deficient activity of the lysosomal enzyme alpha Galactosidase A (AGAL), resulting in storage of glycolipids in vascular cells and several organs. Classical symptoms are angiokeratoma, neuropathic pain and cornea verticillata, but often patients present aspecific kidney, heart and brain involvement. Due to its rarity and aspecific symptoms, identification of true Fabry disease patients can be delayed. Increased awareness of Fabry disease and screening in risk groups have led to identification of alpha Galactosidase A mutations of unknown clinical significance. This can result in erroneously diagnosing patients who do not have Fabry disease.

The aim of this project is to establish an improved way of diagnosing, counselling and appropriately initiating treatment in Fabry patients with very expensive enzyme replacement therapy (costs around EUR 200k per patient per year).

Improved diagnosing of Fabry disease can lead to important benefits:

For patients: early diagnosis probably leads to better treatment outcomes. Currently, Fabry is sometimes diagnosed after the disease’s debilitating effects have had enormous impact on the patient. In addition, individuals who do not have Fabry disease will not suffer unnecessarily from misdiagnosis.

For health care costs: a general public health goal will be served by avoiding unnecessary, expensive treatment and interventions, as well as promoting more timely initiation of therapy.

The latter case (expensive treatment) has recently led to a national debate about costs for treatment of Fabry and other Orphan diseases: proper diagnosis is therefore more urgent than ever.

During the project, diagnostic algorithms are built and linked to standard biochemical and genetic tests, for each of the organ systems that can be affected by Fabry disease. This should lead to diagnosis “on the fly” with no extra burden for the adults and children being tested. Currently, diagnostic algorithms for patients with left ventricular hypertrophy or kidney disease have been created, and work is being performed to develop algorithms for other organs.

Partners:
Genzyme
Academic Medical Center Amsterdam
TI Pharma

Subsidizing partner:
Shire
A new approach to fighting cancer

One of the fastest moving fields in today’s biomedical research concerns small non-coding RNAs, both in general and within microRNA (miRNA) in particular. miRNAs provide a natural form of transcriptional interference, repressing protein function. In contrast to small molecules and biologics (like antibodies and siRNA), that hit just one single target, miRNAs can exert a “pleiotropic effect”, because one miRNA regulates many targets in a network/pathway. As such, miRNAs represent a new class of drugs with a new mode of action.

In this TI Pharma consortium, InteRNA, a small company and two academic groups joined forces and identified five promising miRNA candidates via a proliferation functional screen. Two of these candidates showed anti-tumour activity in vivo, when delivered systemically using an integrin-targeted systemic delivery vehicle.

Tumour growth inhibition was due to inhibition of micro-vasculature endothelial cell proliferation, and inhibition of tumour cell proliferation – and the best candidate is now being investigated for tumour growth inhibition efficacy in a dose response experiment.

Partners:
InteRNA technologies
VU University Medical Center
University of Utrecht
TI Pharma
Cancer is still one of the leading causes of death. The high incidence of cancer, the resistance of many cancer types to current treatments, combined with the struggle to find effective new medicines by the pharmaceutical industry demands innovative research efforts that can deliver novel therapies.

The FES-funded ‘Antibodies for Cancer’ project evaluated a set of monoclonal antibodies and assessed their potential as novel therapeutic agents. Previously, these antibodies were identified in a FES co-funded project, which resulted in a patent position – the basis upon which BioNovion was founded.

The identified antibodies target TNF (tumour necrosis factor) family members, which are key modulators of cell survival and cell death, mostly expressed by cells of the immune system. Cancer cells abuse these TNF family members to drive their own survival and proliferation. Activation of TNF receptors, or blockade of TNF ligands using monoclonal antibodies, is used either to simulate cancer immunity or to block cancer cell survival.

With the support of the ‘Antibodies for Cancer’ project, BioNovion, in intense collaboration with three excellent academic groups, developed the previously identified antibodies into clinical candidate antibodies, ready to initiate pre-clinical development and to study clinical efficacy in cancer patients. Although the FES co-funded project has ended, ongoing research collaboration between the partners continues to advance the antibodies to the clinic.

**Partners:**
BioNovion B.V.
Academic Medical Center Amsterdam
Netherlands Cancer Institute (NKI)
University Medical Center Groningen
TI Pharma
“TI Pharma brought drug development expertise and excellent scientific research together, which delivered three novel potential cancer therapeutic agents.”

Hans van Eenennaam
Chief Operational Officer, BioNovion B.V.
Chapter 4. Priority Medicines

“Building on the work done by TI Pharma to implement the recommendations of the 2004 Priority Medicines report has meant that the experiences gained have been translated into practical recommendations for the Horizon 2020 and IMI2 programmes. The government of the Netherlands deserves credit for supporting TI Pharma and the 2013 priority medicines update.”

Richard Laing
Past Medical Officer at the WHO and co-author of the Priority Medicines Report 2004 (and 2013 update); professor at Boston University

“Overall, although large and intermediate sized companies still represent the main engine for commercializing new medicines, SMEs, academic institutions, public bodies and PPPs represent an important source of innovation and enrich the product pipelines of larger companies.”

Helene Lincker
Writing in Nature, February 2014
The 2004 WHO ‘Priority Medicines for Europe and the World’ report was written against a background of concerns that incentives for biomedical innovation needed to be aligned better, in order to spur the development of new medicines for high-burden diseases and for conditions where there were unmet therapeutic needs. The report aimed, “…to establish a public-health-based medicines research and development (R&D) agenda and, where necessary, to help bridge the gap between public health needs and the development priorities of the pharmaceutical industry”. This 2004 report was a major driving force behind choices of TI Pharma’s FES-funded research topics.

21 priority medicine research topics were listed in the 2004 WHO report, and TI Pharma developed a detailed programme designed to focus on 15 of these. A research matrix was designed to address key ‘pharmacotherapeutic gaps’, and in particular those specified by the report within ‘Therapeutic Areas’ – where a special emphasis was placed by TI Pharma on neglected tropical diseases. The FES-funded programme was also active in so-called ‘cross-cutting themes’.

A majority of FES portfolio projects addressed priority medicines – 56 out of 74. Of those 56 projects focusing on priority medicines, 39 (70%) were assessed as having a high scientific impact.

TI Pharma was also cited as an important case study in the 2013 update published by WHO, ‘Priority Medicines for Europe and the World 2013 Update’. The update highlights the importance of areas in which TI Pharma has worked and is still working, such as integration of real-life data and a dialogue approach to regulatory questions. In addition, it underpins the value of the public-private collaborations as pioneered by TI Pharma.
“The Committee is very pleased with the results of the TI Pharma FES programme in relation to WHO’s Priority Medicines initiative. The delivery exceeds the expectations of the Review Committee.”

“It is clear that PPPs such as TI Pharma can be critical in achieving Priority Medicines objectives.”

FES Review Committee

THE FIFTEEN PRIORITY MEDICINES TOPICS ADDRESSED BY THE FES PORTFOLIO
- Infections due to antibacterial resistance
- Cardiovascular disease
- Diabetes
- Cancer
- HIV and AIDS
- Tuberculosis
- Neglected diseases
- Malaria
- Alzheimer disease
- Osteoarthritis
- Chronic obstructive pulmonary disease
- Postpartum haemorrhage

FES PORTFOLIO SPENDING BY THERAPEUTIC AREA AND ENABLING TECHNOLOGY

T1: (AUTO) IMMUNE DISEASES
T2: CARDIOVASCULAR DISEASES
T3: CANCER
T4: INFECTIOUS DISEASES
T5: BRAIN DISEASES
T6: MULTISTAKEHOLDER RESEARCH PLATFORM
D1: THERAPEUTIC TARGET FINDING, VALIDATION & ANIMAL MODELS
D2: LEAD SELECTION & IN-SILICO MODELLING
D3: PREDICTIVE DRUG DISPOSITION & TOXICOLOGY
D4: BIOMARKERS & BIO SENSORING
D5: DRUG FORMULATION, DELIVERY & TARGETING
D6: PHARMACEUTICAL PRODUCTION TECHNOLOGIES
Two TI Pharma projects were set up to address one of the most urgent challenges in breast cancer research – the selection of the right therapy for individual patients. Traditional endocrine therapy (one of the earliest and most effective therapies) has always been less effective by the fact that only around 50-60% of patients respond.

Collaborative FES-funded efforts involving NKI, EMC, Agendia and TI Pharma have improved two existing types of diagnostic tests, and yielded two new ones. All four tests are now on the market. These tests offer two highly significant clinical benefits.

First, the tests not only predict whether or not a therapy will be useful for a particular patient, but also give an indication of which therapy will have the highest chance of success. This can both improve quality of life (only effective therapies will be started) and reduce healthcare costs (fewer unnecessary treatments will be initiated).

Second, the tests have been developed to work with paraffin-embedded and preserved tissue (not frozen). This allows retro-analysis (eg for patients diagnosed with breast cancer in the past) and gives access to large sample cohorts for further research.

The four tests now in use:

**MammaPrint:**
Breast tumour typing with a prediction for remission (metastasizing) in the first five years after treatment, giving a definitive yes/no answer to chemotherapy decisions.

**TargetPrint:**
Breast tumour mRNA typing that assists in selection of hormonal therapy.

**BluePrint:**
Extensive breast tumour typing (molecular subtypes) that further assists in selection of the treatment with the best clinical outcome.

**TheraPrint:**
Genomic tumour fingerprinting that predicts the chance of the likely response or resistance to a variety of hormonal, chemical and biological therapies.

In 2013 alone, thousands of women worldwide have already been helped via diagnosis of their tumour using these tests – with sound advice on optimal type of treatment and a well-documented increase in life expectancy.

**Partners:**
Agendia
Netherlands Cancer Institute (NKI)
Erasmus Medical Center
TI Pharma
“To stop the spiraling cost of cancer treatment, a concerted effort is urgently needed to develop molecular diagnostics to better identify the patients that respond to expensive targeted therapies: It’s Diagnostics, Stupid.”

René Bernards in Cell (2010)
Professor at NKI, founder and CSO Agendia
A wealth of healthcare data is potentially available from doctors, pharmacies, hospitals and health insurance companies, but such data needs to be managed properly, whereby privacy is especially important. Governance from TI Pharma has helped multiple partners in the Mondriaan project to collaborate successfully over a period of six years. The result is a data extraction and data linkage infrastructure (a ‘patient catalogue’) that anonymises patient data to guarantee confidentiality.

The data are now ready to be used by academic and industrial researchers to improve healthcare, lower the price of medicines and make medicines reach patients faster. As well as being maintained by a central organisation, the system is also currently being rolled out to local hubs (eg Utrecht, Amsterdam, Groningen) and is further enriched on an ongoing basis with large Dutch healthcare databases. In addition, the project has provided an important template for a similar European database system of patient data. TI Pharma is continuing to provide governance for the Mondriaan Foundation, allowing long term continuation and impact on both national and international level.

**Partners:**
- GlaxoSmithKline
- University Medical Center Groningen
- Sanofi
- University of Utrecht
- University Medical Center Utrecht
- University of Groningen
- TI Pharma
“The Mondriaan consortium would like to thank TI Pharma for the excellent and flexible support offered in the past years. TI Pharma has proven itself to be a true partner for innovative organisations. We hope to cooperate with you in the years to come.”

Rick Grobbee
PI Mondriaan project, Professor of Clinical Epidemiology, University Medical Center Utrecht
Advanced diagnostics for neglected diseases

The neglected disease therapeutic monitoring project focused on three different diseases: Leishmaniasis, Tuberculosis and Trachoma

**Leishmaniasis**
A diagnostic assay was developed using LAMP technology. This technology allows DNA amplification to be performed at normal temperatures. Tests targeting both the cutaneous as well as the visceral clinical manifestation of leishmaniasis have been developed. The LAMP assay has a superior sensitivity and specificity above classical diagnostic methodologies like microscopy and culture. It is currently being tested for use in the field. A second (antigen ELISA) test-for-cure was successfully developed, and has now been included as a pharmaco-dynamic tool in a Drugs for Neglected Diseases initiative (DNDi) phase II drug study. It will be further developed using urine samples from Sudanese visceral leishmaniasis patients.

**Tuberculosis Treat to Test**
In view of the intrinsic difficulties of TB detection and the lack of progress towards a true simple near patient diagnostic, it was proposed to use immunological assays to explore the feasibility of a Monitoring Ongoing Treatment Effect in Tuberculosis strategy. Based on this concept, it was shown that within one week of treatment (among TB infected mice compared to placebo, but not in uninfected -and treated- mice) the systemic levels of four cytokines decreased within a concentration range measurable by ELISA. In TB patients on treatment it was confirmed that elevated serum levels of those cytokines in TB patients rapidly decrease towards baseline, reaching a significant difference within a few days after start of therapy. This occurred both in smear microscopy positive and negative patients. The result is an important new monitoring tool for optimizing the treatment of TB patients.

**Trachoma**
To detect and confirm remaining foci of *Chlamydia trachomatis* infection of eyes a simple and sensitive diagnostic test is still urgently needed. Current molecular assays depend on a laboratory for extraction and amplification of the nucleic acid target from eyelid fluid or scrapes. Isothermal recombinase polymerase amplification (RPA) for the detection of pathogens may be performed in a portable device and may require a relatively simple sample preparation compatible with the requirements of a field test.

A working assay for the detection of *Chlamydia trachomatis* bacteria has been developed, and is now being optimized in order to allow work with unpurified DNA.

**Partners:**
- Dutch Royal Tropical Institute (KIT)
- Foundation for Innovative New Diagnostics (FIND)
- Life Assay Diagnostics
- Leiden University Medical Center
- TI Pharma
An important outcome from the FES-funded portfolio is a new dosage regimen for morphine in newborns – and that regimen is now in clinical use. This result was achieved by bringing together clinical data from the project partners, allowing the characterization of developmental changes in pharmacokinetics where data are scarce, including the elderly and young children.

Information stored in public and private databases is used to create models to predict both what the human body does with the medicine (‘PK’) and what a medicine does with the human body (‘PD’). The FES-funded PK-PD research project created mechanism-based ‘pharmacokinetic’ and ‘pharmacodynamic’ models. These can be used when designing optimal clinical studies in drug development and for individualization of doses in clinical practice. The developed PK-PD model library and knowledge-based management system are used in PKPD platform 2.0.

**Partners:**
AstraZeneca
Erasmus Medical Center
GlaxoSmithKline
Johnson & Johnson
Eli Lilly
Leiden University
University of Utrecht
MSD
Pfizer
University of Groningen
Astellas
Takeda
TI Pharma
Chapter 5. Human Capital

“My PhD project was part of a large TI Pharma consortium. Thank you to all project members! I learned a lot from collaboration with scientists from other areas, outside my initial expertise.”

Linda Switzar
Was PhD student on the TI Pharma project 'Towards novel translational safety biomarkers for adverse drug toxicity'
Current job: Post-doctoral researcher at Leiden University Medical Centre (NL)

“One of the benefits is that participants are being challenged by their peers, which is good for their scientific and self development.”

Paul de Koning
VP, Head Global Clinical Pharmacology & Exploratory Development, Astellas Pharma

“The FES funded programme has educated a new generation of biomedical researchers who know how to work in a multidisciplinary setting.”

Daan Crommelin
Scientific Director TI Pharma, 2006-2011; professor at Utrecht University
It was explicit from the outset of the FES-funded research portfolio that sustained improvements to pharmaceuticals innovation would depend on educating a new generation of biomedical scientists, with individuals experienced in cross-sector collaboration.

In addition to providing on the job training within a multidisciplinary environment, the aim was to provide a bird’s-eye view of the multiple disciplines involved in biopharmaceutical research, via a curriculum that was customized for public-private partnership needs. Researchers emerging from the programme would be well placed to facilitate the kind of new industrial and academic partnerships needed to promote cooperation across Europe.

All of this meant creating an internationally recognized training network, and TI Pharma launched a series of specific ‘On Top’ courses for PhD students and post-doctoral researchers that were in addition to the existing education programme in Dutch universities. These courses were designed to develop both scientific and business skills. Eight different courses were run a total of 39 times, with a total 729 participants, of which 20% were guests (rather than TI Pharma researchers), proving the quality and external appeal of the courses.

**A BROADER PERSPECTIVE**

Thanks to FES-funded education initiatives managed by TI Pharma, 223 PhD students and 247 post-docs have gained detailed insights into drug development within a public-private setting.

Researchers were able to work closely with each other, sometimes at each other’s facilities, and the education and training programme provided a broader perspective than they would have enjoyed with a conventional programme.

The overall approach was highly interactive. It included sessions on business skills and provided unique networking opportunities.

The calibre of programme participants and their contributions to academia and industry are reflected by a number of grants and awards, including 9 Venis, 5 Vidis and 2 Vicis [all individual grants from the Dutch National Science Foundation]; 4 European Research Council (ERC) grants; 2 Koningin Wilhelmina research prizes; and a Spinoza award.

### A BROADER PERSPECTIVE

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Beyond education

TI Pharma PhD students and post-docs (‘fellows’) benefited from far more than formal education and training courses alone. As outlined above, the public-private setting in its own right provided a valuable multidisciplinary working environment for individuals who were developing their professional skills.

Fellows became part of a team following a directed research programme, with common goals. They were made aware of the value of their work to both academia and industry, and were regularly exposed to cross-disciplinary inputs. Work was often translational, yielding actual products or services.

By learning from partners and performing work across multiple partner locations, individuals enjoyed better networking and career prospects than an exclusively academic or industrial experience could have achieved. These prospects were improved further by internships: people on university payrolls were able to arrange to work for a period with industrial partners.

Talent programme

Each year, TI Pharma selected two ‘fellow talents of the year’. Those individuals were given the opportunity to join a unique international translational course (see www.eurekainstitute.org). In this way, not only was excellence rewarded but outperformance within the TI Pharma programme was made more widely visible.

Nationalities

Although the majority of TI Pharma fellows (PhD students and post-docs) were Dutch, many other nationalities were present. The table on this page illustrates the spread.

Employment

According to the review committee, this first TI Pharma cohort is well equipped to provide future key-leaders across industry, knowledge institutes and regulators.

An analysis was conducted in autumn 2013 of the 470 PhD students and post-docs with experience of the programme. 213 of these were still in their current job, or finishing their thesis or project. Of the 257 who had left the programme, an impressive 98% had found new jobs.
The 8 ‘on top’ courses

With durations ranging from 1-5 days, eight different courses were delivered to a total of 729 participants.

1. Drug Discovery & Development Cycle (including SafeSciMET)

A comprehensive introduction to the process that leads to a new medicine. Includes an overview of the steps in the process leading from drug discovery, via drug development, to drug marketing approval. A customized version was implemented in the SafeSciMET curriculum, as part of a European Masters degree for Advanced Safety Sciences (part of the European Innovative Medicines Initiative).

2. Business and Entrepreneurial Skills

A two-day course designed to create awareness of entrepreneurship. Included basic tools and concepts required to write business plans and investment proposals.

3. Drug Discovery Simulation

Simulation of the drug discovery process from target and lead discovery to optimization and preclinical safety tests. Interactive course, demonstrating required skills of various players in the drug discovery process.

4. Drug Development Simulation

Simulation of the drug development process from lead optimization to marketing strategies. Interactive course, demonstrating required skills of various players in the drug development process.

5. Biologicals Simulation

How to design and develop a pharmaceutical protein? The full development process of a biological, and of the role of different subsections: candidate selection, safety and toxicology testing, formulation development, clinical trial design. Interactive course, demonstrating required skills of various players in the development process of a biological.

6. Intellectual Property

How to identify and manage new inventions in (translational) complex research environments, and how to search for relevant patent and prior art information. Included issues around balancing open publication of results with patenting.

7. Project Management

Participants were educated to understand the critical success factors in leading scientific projects in a public private setting. They were made aware of their personal leadership style, they learned about how to successfully stimulate team members.

8. Industry/career day

Tailored to provide an introduction to various possible career opportunities inside and outside the pharmaceutical industry. Focused on 'non-academic' job opportunities: 'everything you always wanted to know about your future'. Included site-visits, plenary sessions and discussions in small groups with invited experts from organisations such as venture capital, publishers, merchant banks, large Pharma, start-ups, regulators and government.
“Much gratitude is due to my colleagues of the TI Pharma D2-102 project. Being whole-heartedly welcomed into such an excellent interdisciplinary team was surely a key to the success of my PhD work. The intense, but open and friendly scientific discussions at our meetings were a constant source of inspiration and guidance for my work.”

David Falck
Was PhD student at TI Pharma project ‘Metabolic stability assessment as a new tool in the Hit-to-Lead selection process’
Current job: Post-doctoral researcher at Leiden University Medical Centre [NL]

“Thanks to all my colleagues of TI Pharma for their inspiring collaboration over the past years. It was such a close collaboration that sometimes it was difficult to discriminate between you and the colleagues within my group at university [thanks as well to TI Pharma].”

Eelke van der Horst
Was PhD student at the TI Pharma project ‘The GPCR Forum: novel concepts and tools for established targets’
Current job: Post-doctoral researcher / scientific programmer at Leiden University Medical Center [NL]

“I have been a privilege to work in a consortium with such a strong commitment to one goal. Thanks to TI Pharma for not only funding my research but also offering me useful courses to broaden my knowledge and to develop my career. The concept of Public Private Partnerships definitely works!”

Ivo Ploemen
Was PhD student at the University Medical Centre Nijmegen [NL] working at the TI Pharma project “Development of an attenuated parasite vaccine for malaria.”
Current job: projectleader at Intravacc, Bilthoven [NL]

“The workshop on networking was really an eye opener. Networking is much more than drinking a beer or connecting via LinkedIn. It is about pro-actively maintaining your network, about obtaining real information – via personal contact – and about getting to know people’s second lives, their passions.”

Prescilla Jeurink
Was post-doctoral researcher at the TI Pharma project on TLR ligands and oligosaccharides at Danone Research - Centre for Specialized Nutrition
Current job: Senior scientist immunology at Nutricia Research, Utrecht [NL]

The simulations have given me a unique opportunity to gain hands-on experience and have enhanced my understanding of the various roles in the drug development process.”

Kristina Orrling
Was post-doctoral researcher at VU University Amsterdam during her work at the TI Pharma Phosphodieseterase inhibitors project. Before that she was senior scientist at Mercachem. Currently she is programme manager at TI Pharma [NL]
Interview: Hans de Waard

Hans de Waard has been employed by Novartis as a process engineer since May 1, 2012. Before that he was a PhD student at the University of Groningen, working on a TI Pharma project: Nanoscience as a Tool for Improving bioavailability and Blood Brain Barrier penetration of CNS drugs. The project completed at the end of 2011.

“The biggest prize for completing my PhD with TI Pharma was a huge and valuable network.”
When originally asked by his supervisor to do a PhD, Hans was not looking for a public-private setting, but he says there are big benefits in retrospect: "I have been given glimpses inside the workings of other universities and companies – the courses were also interesting and I was able to build a large network." He sees the latter as a very important reward: "The network I was able to build during my PhD period took my research a step further. I collaborated with multiple groups, and in our case the industrial partner was most visible. I got to know other people and see other ways of thinking – with social benefits too. It was good to see how others are doing research: their differences in vision, content and approach.

"Of course there are many similarities between conventional PhD work and that in a PPP setting, but the network is bigger with TI Pharma, including researchers doing other scientific work but who are in the same phase of their career. I collaborated with others, rather than experiencing the often relatively isolated conventional PhD model. Yearly Spring Meetings gave a further, safe environment for meeting people and hearing talks. I remember a member of the WHO in particular, who revealed a very interesting perspective, and we were able to talk to the speakers directly."

Hans says that partners within his project had very diverse interests: "One consortium group was working on chemistry, putting together different chemical building blocks. Another explored a drug given to rats with a sensor in their brains, to confirm drug delivery. Very different! Working with so many researchers meant I could easily discuss wider issues like your duty to publish, whether content is sufficient and how to handle reviewers’ comments."

Hans completed the Business & Entrepreneurial Skills (BES) course and the Drug Development Cycle (DDC) course, and particularly liked the BES course as something outside usual training. He says that the PPP environment was also helpful in providing milestones and a structure: “At the start of a PhD, seeing the whole project is difficult – you are very busy with your own business, and everything you do is fairly new. The design of the TI Pharma project opened my eyes during the four years, showing me more and more what others were doing, and the impact of your work on others. While employed at the university I had close contacts with our private partner, Solvay, working for example with them on measurements. Of course there are some consequences here too – you are occasionally driven in a different research direction to the one you might choose yourself."

In May 2012 Hans joined Novartis Pharma AG, and he says that he is convinced that his selection was helped by his demonstrable experience in working in a PPP setting, and by his insights into how research can be applied by others and for other purposes: “I’m in a team that develops new technologies, and my work is strongly science driven. It’s totally different to a university, where you tend to look at fundamental questions. Here the investment risks and potential drive us to implement as soon as possible. Although I would sometimes like to do further research, I like the pace and dynamics of industry. My public-private experience has helped me to balance different interests, and to look critically at my own work. What you develop is important, but so is creating support among stakeholders. In my case, there are still different departments with different interests within Novartis and research is always most valuable when you get buy-in. My experience with TI Pharma helped me get a job, and it is now helping me to navigate complex relationships and partnerships.”
“Looking back, I’m a strong supporter of a broad scientific life sciences institute that can bridge the worlds of pharmaceutical companies, academic scientists and government. Our Top Institute Pharma is a most ideal platform for it.”

Willem de Laat
Managing Director TI Pharma, 2008-2013; entrepreneur

“TI Pharma has been a visionary institute, creating value through the formation of a dedicated network, well ahead of its time when it was created in 2006. It’s now taking public-private partnerships to the next level, building further on their experience, network and expertise.”

Michel Dutrée
Director, Nefarma, industry association for the Dutch branches of innovative pharmaceutical companies
There were important industry-wide changes throughout the duration of the FES-funded research programme. Major pharmaceutical companies moved into open innovation and restructuring of their R&D sites; SMEs increasingly partnered with other organisations in order to climb the value chain; academia faced growing pressure to demonstrate added value for society; and governments saw a changing political and economic landscape, especially following the financial downturn starting in 2008.

TI Pharma was ideally placed to respond to these profound changes, by driving innovation and new partnership arrangements very actively. It has become, and remains, a widely acknowledged player in establishing effective strategies to cope with and promote evolving research needs. Ongoing contributions have helped to bring about more fruitful cross-sector collaborations and a general increase in confidence that new types of partnership can result in winning research outcomes.

The benefits of such partnerships have been numerous throughout the entire drug discovery, development and launch process, with sharing of data, compounds, technologies and development risks and costs. Sharing resources allows access to a much wider range of proprietary compounds, data and expertise, and TI Pharma has acted in a critically important ‘honest broker’ role, allowing participation from many types of organisation without jeopardising competitive positions.

For neglected diseases, shortcomings in the market can be addressed by sharing risks and TI Pharma has helped by supporting participants in finding partners and acquiring funding. Important contributions have also been made during multi-stakeholder discussions involving academia, industry and the regulator. More engaged stakeholders ensure a smoother discovery and development process, and TI Pharma facilitates ‘arm’s length’ discussions between partners who can have conflicting interests.

Above all, TI Pharma has been able to encourage, facilitate, support and manage a complex web of partnerships between all kinds of individuals and organisations. The network it has established has delivered not only proven and developing scientific results, but a cultural shift that continues to yield results.
**Spring Meetings**

Started in 2008, the annual Spring Meeting has been a prime showcase for the tangible benefits of pharmacotherapeutic research via open innovation. It has brought together all TI Pharma researchers and partners, and has become a major event — for example, the 2012 Spring Meeting gathered over 300 industrial researchers, academic scientists, regulatory experts and policymakers, with 100 research posters, workshops, 25 parallel sessions and plenary lectures by Chas Bountra (Structural Genomics Consortium) and Robert Williams (Cancer Research UK).

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**Spring Meeting 2014: New tracks to medicines**

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**SPRING MEETING**

2008: Spring Meeting: Kick-off
2009: Spring Meeting
2010: Spring Meeting
2011: Bee your Career
2012: Public-Private: Perfect!
2013: Inspiring Healthy Partnerships

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**PLENARY “TI PHARMA LECTURE”**

**SPEAKERS FIGON DMD:**

2007: Douwe Breimer (Uni Leiden)
The way forward
2008: Klaus Muller (Roche)
Continuous (r)evolution of concepts and technologies in drug discovery
2009: Chris Lipinski (Pfizer)
The good, the bad and the unknown in drug discovery: a very opinionated discussion
2010: Hans-Georg Eichler (EMA)
Successes and challenges in drug development, a regulatory perspective
2011: Tim Wells (MMV)
Public-Private-Development Organizations: the remedy for neglected diseases? How we can work together against a common enemy
2012: Onno van de Stolpe (Galapagos)
From drug target to billion dollar deal, how to build a biotech
2013: Gerry Davies (Uni Liverpool, IMI PreDICT-TB consortium)
Model-based preclinical development of antituberculosis drug combinations

---

**FIGON Dutch Medicine Days**

Complementing the Spring Meetings, the annual Dutch Medicine Days hosted by FIGON (Netherlands Federation for Innovative Drug Research) each autumn have allowed additional research exposure and interaction between researchers. Many researchers in the scientific programme have taken part, and seized opportunities to connect with stakeholders outside of the programme.
### Workshops on specific topics

<table>
<thead>
<tr>
<th>Workshop</th>
<th>Date</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>1] TI Pharma workshop: The new landscape of neglected disease drug</td>
<td>January 17, 2007</td>
<td>Bringing together Product Development Partnerships (PDPs), industry</td>
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<tr>
<td>development – January 17, 2007</td>
<td></td>
<td>and academia to meet and discuss different options for partnering</td>
</tr>
<tr>
<td>2] TI Pharma workshop: A systems view on the future of medicine:</td>
<td>June 23, 2008</td>
<td>Reflections on the anticipated explosion of research towards Chinese</td>
</tr>
<tr>
<td>inspiration from Chinese Medicine? – June 23, 2008</td>
<td></td>
<td>Medicine</td>
</tr>
<tr>
<td>3] TI Pharma workshop: Bioequivalence of complex drugs</td>
<td>October 8, 2009</td>
<td>International discussion on scientific and regulatory issues of complex</td>
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<td>drugs – October 8, 2009</td>
<td></td>
<td>drugs</td>
</tr>
<tr>
<td>4] TI Pharma and EUFEPS workshop: Bottlenecks identification in drug</td>
<td>January 22, 2009</td>
<td>Discussions between academia and industry about technical solutions</td>
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<tr>
<td>discovery... And solutions please! – January 22, 2009</td>
<td></td>
<td>to improve drug efficacy and safety</td>
</tr>
<tr>
<td>No.</td>
<td>Event Description</td>
<td></td>
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<tr>
<td>6)</td>
<td>CTMM, TI Pharma and BMM workshop: Imaging guided and targeted drug delivery - June 25, 2009. Setting the scene for a joint call by CTMM, TI Pharma and BMM in this emerging area of medical research.</td>
<td></td>
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<tr>
<td>9)</td>
<td>TI Pharma, CBG-MEB and University of Utrecht workshop: Animal free safety testing of new medicines – May 23, 2013. Discussing safe medicine development with minimization of animal testing.</td>
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</table>
Addressing the issue of animal testing is one of the areas where collaboration across all organisations involved – both public and private – is essential. This is an emotive and highly sensitive topic. More than 5,000 macaques and 68 chimpanzees have been used in more than 260 experiments since 1988, while evaluating the safety of biotechnological medicines.

Such testing may not yield very useful results, because new treatments can be highly specific – for example, where monoclonal antibodies are designed to bind to a specific human protein, which animals often lack entirely. Even if an animal does carry the same protein, other metabolic differences can be so big that results are questionable. However, any change to animal testing procedures must depend on firm scientific evidence, and on consensus among many different parties on how to implement these changes.

Started in February 2009, the TI Pharma project Predictive value of animal testing set about establishing a scientific basis for the use of animal testing in pharmaceutical research. It reviewed a whole range of drugs that had caused problems during the last fifteen years, and considered whether or not those problems had been revealed by the original animal testing.

The project ended in December 2013, and confirmed that in many (but not all) cases, animal testing could indeed largely be avoided. One of the project outputs was a PhD thesis from Peter van Meer, which concluded: “Our analysis suggests that the role of Non Human Primates should be limited in future therapeutic antibody development: The effects that are observed are either related to the pharmacology of the therapeutic antibody used or an immune response until immunogenicity interferes with the interpretation of study results. Therefore, extensive animal studies as they are done now are not recommended for antibodies.

Because the Dutch regulator was a partner in the project, the results are now also being discussed with national and European regulatory agencies. These discussions may lead to improved guidelines for some types of animal testing.

**Partners:**
Nefarma
Life Sciences Health
University of Utrecht
CBG MEB
TI Pharma
55. TI PHARMA. NEW TRACKS TO MEDICINES
Advancing the development and regulation of medicines: The Escher project

Scientific evidence and dialogue for the development and regulation of medicines

At the start of the Escher project in 2007, it was widely recognised that there were important challenges for pharmaceutical innovation – in terms of economics, addressing unmet medical needs and access to medicines. Regulation is an important factor: regulatory “checks and balances” are needed to ensure the quality, safety and effectiveness of medicines, but over-regulation can pose a threat to drug innovation by creating unnecessary barriers and increasing the cost and duration of development.

Key objectives for the Escher Project were to identify, evaluate and remove regulatory bottlenecks hampering the efficiency of pharmaceutical innovation; and to stimulate factors helping the improvement of the regulatory system. The project included four synergistic areas of research:

- Evidence generation methods and evidence requirements
- Scientific dialogue and stakeholder interaction
- The decision-making process and benefit-risk assessment
- Health technology assessment and evaluating societal impact

The project has been truly agenda-setting, engaging extensively with regulators, policy makers, companies, HTA agencies and patient organizations. Participation within international policy platforms continues – for example a new project started in 2013 in partnership with EFPIA & AESGP, facilitated by TI Pharma. Other projects are planned, and a valuable network of researchers, regulators and policy makers is now firmly established.

Although a Dutch initiative, the project used knowledge and expertise from many disciplines and institutions across the globe. The Escher project resulted in more than 80 publications, 16 PhD-projects (12 now finished) and 11 commissioned projects that delivered high-level think-tank papers. Additional outcomes include ADDIS (www.drugis.org), which supports the assessment of clinical trial data and structured decision-making, and PREscore, a tool for predicting efficacy and safety of medicines based on biomarkers.

www.escher-project.org

Partners:
Amgen
Erasmus University Rotterdam
GlaxoSmithKline
MSD
University Medical Center Groningen
University Medical Center Utrecht
University of Utrecht
WINap
TI Pharma
“The TI Pharma Escher project has allowed us to give a boost to regulatory science and will continue fuelling Dutch leadership in this field.”

Bert Leufkens
PI Escher project, chair of the Dutch Medicines Evaluation Board and professor at University of Utrecht
“TI Pharma’s SME Partnership Call has created important new opportunities for SMEs. For DCPrime this means that we can work together with experts of various disciplines and jointly develop a number of tools required for the further development of our vaccines. We expect that these vaccines will benefit large numbers of patients.”

Ada Kruisbeek
Founder and CSO DC Prime BV

“One of TI Pharma’s big strengths is that it knows how to manage money. That’s a skill that should be more widespread.”

Tim Wells
CSO Medicines for Malaria Venture
The stated goal of TI Pharma in 2006 was “Jointly shaping the future of medicine”, and the perceptions of many different participants in 2014 leave little doubt that this goal has been met in full. TI Pharma has been a highly successful player, first in the Netherlands, and in subsequent years also on the European stage and beyond, with headline achievements that are very significant. For example:

- 223 PhD students
- 247 post-docs
- 165 theses completed and defended by Feb 2014
- 6 years of programme management
- 11 running projects in the FES portfolio
- 63 projects closed by February 2014

At the outset, the TI Pharma FES portfolio had 25% private and 25% academic investment. This funded a programme within the framework of the ‘Priority Medicines for EU and the World’ agenda. All projects involved multilateral partnerships with shared costs, risks and benefits between the participating partners.

TI Pharma was able to gradually improve the funding split, and achieved 40% private plus 20% academic investment for follow up projects, with 40% subsidy. This demonstrates the willingness and interest of private partners to engage in the development of socially valuable medicines.

TI Pharma has managed 74 multilateral PPP projects within the FES portfolio. In all of these, multiple academic and industrial partners collaborated.

The initial 2005 TI Pharma business plan was driven by eight industrial partners (of which four were SMEs) and eight academic partners. The first TI Pharma projects started in 2007. By the end of the FES-funded work, the portfolio had connected 64 industrial partners (including 43 SMEs) and 26 academic partners, as well as six other stakeholders including Dutch regulator CBG (Medicines Evaluation Board) and the industry association for Dutch branches of innovative pharmaceutical companies (Nefarma).

Widely acknowledged expertise in call management has played a key role in TI Pharma’s many successes. The 2012 SME Partnership Call is a prime example. It matched seventeen industrial partners with academic research groups in eleven new projects for joint drug development. 40% of the budget came from private matching, and this call showed that SMEs want to form smaller consortia managed by TI Pharma. It also showed what can be achieved in smaller calls, with modest financial support from the government and increased industrial support.
By 2011, funding was split 40:20:40 (industry: academia: government).

**Example Timeline: SME Partnership Call in 2012, with maximum time for applicants**

### 2006
- **April 12**: Expression of interest deadline
- **April 28**: Full proposal deadline
- **May 15**: Info session
- **May 17**: Feedback on expression of interest

### 2011
- **June 14**: Call open
- **September 17**: Presentation to committee
- **September 28**: Comments reviewers to applicants
- **December 21**: Deadline for signing contract

#### Number of Weeks
- **2006**: 9 weeks
- **2011**: 10 weeks

---

**Number of weeks**: 9

**Number of weeks**: 10

**Number of weeks**: 2

**Number of weeks**: 1

**Number of weeks**: 7

**Number of weeks**: 5

---

61. Ti Pharma: New Tracks to Medicines
Overall, the total budget within the FES portfolio was EUR 274 million. TI Pharma’s turnover exceeded EUR 60 million in 2010, when the programme was at peak activity levels. Thanks to the SME Partnership Call, which used the remainder of the subsidy, turnover in 2012 and 2013 was still high, at just under EUR 30 million annually.

The figure shows turnover per year as of 2007, and the table shows funding from industry, academia and knowledge institutes as well as the government, over the entire programme.

Overall, including startup costs in 2005 and 2006, overhead costs were kept at 4.4%.

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**FES FUNDED PROJECT PORTFOLIO**

**2006–2013 (EUR MILLION)**

<table>
<thead>
<tr>
<th>FUNDING</th>
<th>%</th>
<th>COSTS</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>INDUSTRY</td>
<td>71.5</td>
<td>DIRECT PROJECT COSTS</td>
<td>254.1</td>
</tr>
<tr>
<td>ACADEMIA</td>
<td>65.5</td>
<td>EDUCATION &amp; TRAINING</td>
<td>1.8</td>
</tr>
<tr>
<td>SUBSIDY</td>
<td>137.0</td>
<td>INDIRECT PROJECT COSTS</td>
<td>6.1</td>
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<tr>
<td></td>
<td></td>
<td>HEAD OFFICE COSTS</td>
<td>12.0</td>
</tr>
<tr>
<td>TOTAL</td>
<td>274.0</td>
<td>TOTAL</td>
<td>274.0</td>
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</table>
Lessons learned

The breadth of projects undertaken and the number of partners involved allowed TI Pharma to develop a very detailed understanding of what criteria lead to successful outcomes or failures. In the case of the FES-funded portfolio, almost all projects were steered to a successful conclusion as defined by the people involved, with just two exceptions where projects were cut short after initial results were not promising.

The lessons learned spanned a whole range of issues: from Principal Investigator problems (not enough time, a new PI in a project, lack of commitment) through to project plans that were either too ambitious or not ambitious enough; and from patient recruitment issues in trials (too few subjects or too lengthy recruitment periods) through to industrial partners not delivering (loss of interest in the therapeutic area, or even bankruptcy).

One major lesson that was learned stood out: in any ‘problematic’ project, a ‘go/no go’ moment of decision should be available to the governing body.

---

FES PROGRAMME FUNDING 2007-2013

Turnover per year

EUR 1,000

FES PORTFOLIO: € 274M

2007 2008 2009 2010 2011 2012 2013

INDUSTRY

ACADEMIA

GOVERNMENT
“The impact of the FES funded portfolio on the Dutch knowledge infrastructure has been very strong, both in terms of health and wealth as well as scientifically. The Netherlands should be proud of the achievements and should continue this type of support.”

Joost Ruitenberg
Chair ISRC and FES Review Committee; professor of International Public Health, VU University Amsterdam

“TI Pharma’s partnerships result in a synergy that really drives the science further than the individual parties could achieve working alone.”

Jan Raaijmakers
Past VP External Scientific Collaborations GSK Europe, chair TI Pharma Board of Directors
“The PPP approach for research projects is very interesting for the Dutch Cancer Society (KWF). As a health foundation we are investigating our strategic role in these partnerships.”

Wia Timmerman
Project leader Translation at Dutch Cancer Society

“Running public-private partnerships is a profession by itself. TI Pharma is an excellent example of how you can do this in an effective way.”

Hugo Hurts
Director Pharmaceutical Affairs and Medical Technology, Dutch Ministry of Health, Welfare and Sport
Shaping the future of medicine

Outcomes from the FES-funded portfolio, managed by TI Pharma, leave little room for doubt: it is the partnership case that really counts.

The programme has demonstrated very actively the benefits of sharing data, compounds and technology during the discovery phase, and sharing risks and costs during the development phase. It has also shown how common interests and data sharing can be established during the launch phase. The fact is that when resources are shared, larger problems can be tackled at higher efficiencies, and with effective management of multi-stakeholder interactions and requirements.

In order to thrive, open innovation requires many initial and ongoing conditions, and trust is a pivotal element. As an arm’s-length and trusted custodian, TI Pharma is able to provide governance, scientific expertise and practical support for complex, pre-competitive projects involving public-private consortia. The core capabilities that TI Pharma has built up in programme management, knowledge sharing and partnering are rare – especially in the particular combination offered by TI Pharma.

All of this means that the work started in 2006 goes on. In 2011, TI Pharma presented a vision of its role as an independent research enabler. Based on its experience of managing 74 public-private partnerships with a combined budget of EUR 274 million, TI Pharma has reached out to offer its services to consortia outside its own FES funded portfolio.

As the FES-funded portfolio began to draw to a close, TI Pharma started to gain new assignments. Now, in 2014, and with the help of existing and developing partnerships, TI Pharma is focusing on three core areas. These are the areas where maximum value can be added thanks to TI Pharma’s particular areas of expertise: resource sharing, neglected diseases and multi-stakeholder interactions.

<table>
<thead>
<tr>
<th>PLATFORM</th>
<th>PARTNERSHIP CASE</th>
<th>TI PHARMA ADDED VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>RESOURCE SHARING</td>
<td>COMBINING PROPRIETARY RESOURCES (COMPOUNDS, DATA, KNOWLEDGE...)</td>
<td>HONEST BROKER</td>
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<td></td>
<td>SURPASSING WHAT ANY ONE PARTNER COULD ACHIEVE INDIVIDUALLY</td>
<td>INTERMEDIATE ROLE: FACILITATING THE SAFE SHARING OF COMPETITIVE INFORMATION</td>
</tr>
<tr>
<td>NEGLECTED DISEASES</td>
<td>OVERCOMING MARKET FAILURE BY SHARING RISKS AND COMBINING RESOURCES</td>
<td>FINDING PARTNERS, FUNDRAISING AND FACILITATING DEVELOPMENT PARTNERSHIPS</td>
</tr>
<tr>
<td>MULTI-STAKEHOLDER INTERACTIONS</td>
<td>ENGAGING STAKEHOLDERS AND IMPROVING ASPECTS OF THE DRUG DISCOVERY AND DEVELOPMENT PROCESS</td>
<td>ENABLING ARM’S LENGTH DISCUSSIONS BETWEEN PARTNERS WHO OFTEN HAVE CONFLICTING INTERESTS</td>
</tr>
</tbody>
</table>
### Turnover New Assignments
2011-2014

<table>
<thead>
<tr>
<th>Year</th>
<th>Estimate (EUR 1,000)</th>
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<tbody>
<tr>
<td>2011</td>
<td>0</td>
</tr>
<tr>
<td>2012</td>
<td>500</td>
</tr>
<tr>
<td>2013</td>
<td>1,000</td>
</tr>
<tr>
<td>2014</td>
<td>2,000</td>
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</tbody>
</table>

#### Diagram

**Contract Activities**

**IMI/EU Funded Projects**

*67. TI Pharma, New Tracks to Medicines*
Interview: Anke Müller-Fahrnow

Anke Müller-Fahrnow is vice president at Bayer HealthCare Pharmaceuticals in Berlin. She leads the IMI project ‘Kinetics for drug discovery (K4DD)’ for which TI Pharma currently performs programme management, and delivers communications and educational support.

“I think working together in a PPP will become more important not only to Bayer but also to other companies”
Anke is certain that good programme management creates substantial added value in research projects: “Different types of research questions need different types of programme or project management. In the very early phases of a drug discovery project teams typically consist of only a few people working together. At this stage, projects at Bayer are typically led by scientists who work together on a scientist-to-scientist basis.

When projects get bigger, we need a more professional approach to programme management—someone who can set up a project; efficiently present results and issues; set up a clear project plan with milestones and deliverables; drive decision making; and help partners to develop a way of collaborating.”

Anke says that the bigger a project, and the more diverse the backgrounds of different project partners, the more important such a role is: “The goal of the K4DD project is to improve our understanding of how potential drugs bind with their target, and to develop methods and tools that allow researchers to study drug-target interactions with greater ease. These tools would help researchers to determine whether a drug candidate is likely to be safe and effective much earlier in the drug development process. Ultimately, this would mean faster access for patients to new effective and safe drugs. Working in a PPP, with a project like K4DD, provides many opportunities but the challenge lies in creating a win-win situation for all partners. That’s where excellent programme management comes in.”

“We come from different professional and cultural backgrounds, with different ideas on deliverables and success factors. For us in the pharmaceutical industry, it’s crucial to identify new development candidates that finally make it as drugs that are beneficial to patients. That’s the driver for us. For many academic partners, high quality scientific research that can be published is the goal. The mutual area of overlap is where a PPP can be successful, and that requires a clear understanding of each other’s needs. We must identify differences, agree what can and cannot be shared, and establish what every partner contributes.”

The goal of a project is what Anke sees as determining whether or not a PPP-setting is suitable. “One important aspect for PPPs is the technology area and the work on research tools. If the goal is drug discovery, and bringing something to the market, it is important that our development compounds can be IP protected. This is typically not done in consortia with many different partners.

“Within K4DD, TI Pharma contributes experience, and clear ideas on what works or does not work in consortia. They understand interacting with partners, how to manage expectations, and more. Of course they also provide the necessary day-to-day infrastructure for managing a complex project. That includes setting up meetings; reporting to IMI; providing an overview of all milestones and deliverables; and providing an IT platform.

As far as the future is concerned, Anke thinks that PPPs will become ever-more important: “I think working together in a PPP will become more important not only to Bayer but also to other companies. TI Pharma knows everything about the “do’s and “don’t”s in such collaborations, and it’s great to have such an organization.

“It is excellent to have someone who already has the necessary infrastructure in place – someone who has a good overview of funding agencies, and who has already worked with relevant partners. TI Pharma has the previous experience, together the view of both academia and the pharma industry, that can make a real difference. They also help to make things sustainable – how do we go forward after a project? What will we do with the results, the database and training for our PhD students and Post-docs?

“TI Pharma’s programme managers have all completed a PhD in a relevant area. It helps tremendously when a programme manager understands the language of partners working together in a PPP. It means we can quickly determine what is important, what is not so important, and what options are open for negotiations in the team. Issues like these can make a fundamental difference to research and commercial outcomes.”
Launched at the beginning of 2013, the European Lead Factory is a pan-European drug discovery project, and a flagship open innovation resource for academia, public organisations, large pharma companies and SMEs. TI Pharma runs the programme office for an international consortium of 32 partners, with funding from IMI and in-kind contribution from various partners, offering facilities that are open to non-contractual partners. Academics and SMEs enjoy access to an ‘industry-like’ discovery platform – one that encourages active participation.

The European Lead Factory is currently actively seeking high quality biology targets. The goal is to provide target contributors with ultra-high throughput screening and a list of high quality hit compounds, and opportunities for collaboration. It means substantial cost savings and a very productive exchange of ideas.

New chemistry scaffolds are also being sought. A 300,000-strong compound collection has already been contributed by EFPIA consortium members, and a key project goal is to add a further 200,000 innovative compounds, carefully selected from academia and SMEs for novelty, drug-like properties, diversity and synthetic tractability. This will result in a Joint European Compound Collection, that will be used to screen against biology targets.

Partners:
- AstraZeneca
- Bayer
- BioAscent
- ChemAxon
- Edelsis
- GABO-mi
- Janssen
- Lead Discovery Center
- Leiden University
- Lundbeck
- Max Planck Institute of Molecular Physiology
- Mercachem
- Pivot Park Screening Centre
- Merck
- Netherlands Cancer Institute (NKI)
- Radboud University Nijmegen
- Rijksuniversiteit Groningen
- Sanofi
- Sygnature Discovery
- Syncom
- Taros Chemicals
- Technical University of Denmark
- UCB Pharma
- University of Dundee
- University of Duisburg-Essen
- University of Leeds
- University of Nottingham
- VU University Amsterdam
- TI Pharma

A “formidable factory”
Nature, December 2013
STATE-OF-THE-ART ULTRA-HIGH THROUGHPUT SCREENING SYSTEM AT PIVOT PARK SCREENING CENTRE
Developing a new paediatric formulation to combat schistosomiasis

A drug to treat schistosomiasis in very young children

An international nonprofit consortium on schistosomiasis was launched in 2012 as a public-private partnership, and it is developing a paediatric version of praziquantel, a drug used to treat schistosomiasis (also called Bilharzia or Snail fever). This severe and chronic inflammatory disease, caused by parasitic worms, affects an estimated 243 million people, including around 10-20 million preschool-age children. At its worst, it can kill, and it leaves many children with anaemia, reduced growth or reduced learning ability.

With coordination by TI Pharma, the consortium has brought together the expertise of Astellas, Merck Serono and Swiss TPH in creating a new formulation for very young children, performing a pre-clinical development programme, and attracting funding from the Bill and Melinda Gates Foundation. Progress has been very rapid: several promising paediatric candidates had been developed by the end of 2013. New partners are joining and new funding from the Japanese GHIT Fund has recently been announced that will help to take these candidates into the clinical testing stage.

Partners:
Merck Serono
Astellas Pharma
Swiss TPH
Farmanguinhos
Simcyp
TI Pharma

Funders:
Bill & Melinda Gates Foundation
Global Health Innovative Technology Fund
Appendix
Review of the TI Pharma FES Programme 2006 - 2013

Final Report
28 January 2014

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<th>Description</th>
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<tr>
<td>ABPI</td>
<td>Association of the British Pharmaceutical Industry</td>
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<td>BMM</td>
<td>BioMedical Materials programme</td>
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<td>CNS</td>
<td>Central nervous system</td>
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<tr>
<td>CTMM</td>
<td>Center for Translational Molecular Medicine</td>
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<tr>
<td>CWTS</td>
<td>Centre for Science and Technology Studies, Leiden University</td>
</tr>
<tr>
<td>ETHZ</td>
<td>Eidgenössische Technische Hochschule Zürich</td>
</tr>
<tr>
<td>FES</td>
<td>Economic Structure Enhancement Fund (Fonds Economische Structuurversterking)</td>
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<td>ISRC</td>
<td>International Scientific Review Committee</td>
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<tr>
<td>IMI</td>
<td>Innovative Medicines Initiative</td>
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<tr>
<td>IP</td>
<td>Intellectual Property</td>
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<tr>
<td>K4DD</td>
<td>Kinetics for Drug Discovery</td>
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<tr>
<td>MNCS</td>
<td>Mean Normalised Citation Score</td>
</tr>
<tr>
<td>MTRC</td>
<td>Mid-Term Review Committee</td>
</tr>
<tr>
<td>OECD</td>
<td>Organisation for Economic Co-operation and Development</td>
</tr>
<tr>
<td>PI</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>PPP</td>
<td>Public-Private Partnership</td>
</tr>
<tr>
<td>TI Pharma</td>
<td>Top Institute Pharma</td>
</tr>
<tr>
<td>RIVM</td>
<td>National Institute for Public Health and the Environment (Rijksinstituut voor Volksgezondheid en Milieu)</td>
</tr>
<tr>
<td>SMEs</td>
<td>Small and medium enterprises</td>
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<td>SPC</td>
<td>SME Partnership Call</td>
</tr>
<tr>
<td>VCC</td>
<td>Value Creation Call</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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1. Composition of the Review Committee

The Members and the Chair of the FES Review Committee are appointed by the Executive Board of Top Institute Pharma (TI Pharma) for the period of the FES Review, held during winter 2013-2014. The FES Review Committee consists of eight Members. These Members reflect a representation of expertise from academia, industry and public health organizations. The FES Review Committee is composed of a selection of (former) Members of TI Pharma’s International Scientific Review Committee (ISRC) and the Mid Term Review Committee (MTRC). Members participate in the FES Review Committee in their individual capacity.

Members of the Review Committee:

Prof. dr. E.J. (Joost) Ruitenberg
ISRC chair, Professor of International Public Health, VU University Amsterdam; previously (a.o.): RIVM and Sanquin

Dr. T. (Tim) Wells
ISRC member; Chief Scientific Officer, Medicines for Malaria Venture

Prof. dr. T.M. (Trevor) Jones,
CBE ISRC member; previously (a.o.): Wellcome Foundation, ABPI

Dr. R. (Richard) Laing
ISRC member; World Health Organization (WHO) author of the Priority Medicines Report

Prof. dr. G. (Gerd) Folkers
ISRC member; Director Collegium Helvetica, Swiss Federal Institute of Technology in Zurich (ETHZ) and member of the Swiss National Research Council

Prof. dr. P. (Povl) Krogsgaard-Larsen
Past member of the ISRC, professor at the University of Copenhagen; previously (a.o.): President of the Carlsberg Foundation

Dr. L.H.T. (Lex) van der Ploeg
Past member of the MTRC; Managing Director VDP LLC; previously (a.o.): Abraxis/Celgene, Merck, Columbia University

Prof. Dr. H.A. (Harry) Struijker Boudier
Past member of the MTRC; Professor at Maastricht University

Secretariat:
Two Secretaries supported the Committee:

Dr. J.S.B. (Jon) de Vlieger [TI Pharma, preparation of information for the Committee and coordination of the meeting] and Dr. P. (Pieter) Stolk [Exon Consultancy, facilitation of discussions and drafting report of the Committee].
This report represents the results of the independent review of the FES (Fonds Economische Structuurversterking) subsidized Portfolio, as run by TI Pharma. The review was conducted by the TI Pharma FES Review Committee.

The first project in the TI Pharma FES Portfolio was launched in 2007 and in the six years that have passed since then, 74 public-private consortia have been set up using the FES funding. The TI Pharma FES programme ran during a period of profound change in the Dutch and European pharmaceutical landscape. This included extensive downsizing and restructuring of research in large pharmaceutical companies, including closure of research sites and also significant pressure on health care budgets. Over this period, the interactions between academia and industry changed from being somewhat distant to a productive atmosphere of collaboration.

In November 2013, the Executive Board of TI Pharma appointed an independent Review Committee to make an assessment of the TI Pharma FES portfolio. The objective of this 2013 FES Review was to identify the extent to which TI Pharma is achieving its mission, as set out for the FES funded programme (Annex 1). The 2013 Review is a follow-up to the TI Pharma Mid-Term Review, held in November 2009, and is meant as a final review of the FES funded portfolio.

In particular, the three main questions addressed by the Committee include:

Question 1: What is the societal, economical and scientific value of the direct and indirect output generated with the FES funded portfolio?

Question 2: What has been the impact of the FES funded portfolio on:
   a. The (Dutch) knowledge infrastructure;
   b. Human capital;
   c. Priority Medicines;
   d. Positioning of public-private partnerships and their added value in the area of pharmaceutical research and development? In short, the added value of the TI Pharma organization itself.

Question 3: What are the lessons learned from running such a large-scale public-private research portfolio?

The Committee evaluated these questions against the background of the defined ‘indicators for success’ and the objectives of TI Pharma as set out at the creation of TI Pharma.

To facilitate its review, the Committee received detailed documentation about the TI Pharma FES programme, and its outcomes for each project and for every strategic theme, such as human capital. In addition, the Committee received an independent assessment of the scientific impact of the TI Pharma FES Programme, based on citation scores from the Centre for Science and Technology Studies (CWTS) of Leiden University.

On November 27 and 28, the FES Review Committee visited the TI Pharma office for discussions and meetings with TI Pharma staff, project researchers and stakeholders. These included SMEs (Small and Medium Enterprises); academics, including PhD students and post-docs; and academic technology transfer officers. The programme for this site visit is included as Annex 2.

The main body of the report starts with a summary of key conclusions of the Committee (Section 3). Section 4 reviews the activities of the TI Pharma organization when it comes to building and managing the FES portfolio. Sections 5 and 6 take a deeper look at the impact of the FES programme on the Dutch knowledge landscape; human capital; the Priority Medicines agenda; and what value has been generated in the TI Pharma organization itself through the FES funded portfolio (addressing questions 1, 2 and 3 above). A section with key recommendations for a future programme concludes the report.

Note that the report reflects the consensus opinion of the TI Pharma FES Review Committee, and is supported by all Committee members.
3. Key conclusions of the FES Review

Based on its assessment, the Committee highlights four main conclusions:

The TI Pharma FES programme gained core expertise and as a result significantly enhanced collaborative interactions between academia, large companies and SMEs.

The TI Pharma FES programme ran during a period of profound change in the Dutch and European pharmaceutical landscape. This included extensive downsizing and restructuring of research in large pharmaceutical companies, including closure of research sites, and also significant pressure on health care budgets. The interactions between academia and industry changed from being somewhat distant to a productive atmosphere of collaboration. TI Pharma played a significant initial role in helping to manage and adapt to this transition in the Netherlands. As such, TI Pharma has learned from its early development stages and gained know-how that positions TI Pharma to help the Netherlands gain the maximum benefit from a new and evolving pharmaceutical and biotechnology business environment.

TI Pharma has demonstrated professional programme management of the FES funding.

The TI Pharma experience continues to be a role model outside of the Netherlands in encouraging new models of pharmaceutical innovation through Public Private Partnerships (e.g. the discussion of TI Pharma in publications of the WHO and the OECD). As such, the TI Pharma organization and the infrastructure put in place represent a critical starting point through which future PPP projects in and outside the Netherlands can be enabled.

The programme has shown the flexibility to cope with challenges, despite its relatively short timeline and the fact that funding was to be allocated based on a broad mandate covering an ambitious research agenda.

In the light of this flexibility, the Committee underlines that in the future, a public-private partnership built along similar lines to TI Pharma, should have an increased focus on SMEs (as was achieved in the TI Pharma SME Partnership Call), alongside alternative academic structures with the flexibility to define its therapeutic and technology focus. Defining the funding mandate more carefully will play a pivotal role in building a strong health and information based technology and investment structure for the Dutch life sciences and health sector.

The continued success of some of the projects initiated six years ago outlines that the value of the results, both in terms of human capital and tangible assets (inventions, compounds, tools etc.) will continue to rise.

It should be kept in mind that given the relatively recent start of the initiative, it is too early to perform a final evaluation of the outcomes and full public health impact of the TI Pharma FES programme.

When the TI Pharma FES programme was launched, 11 ‘indicators for success’ were identified and sent to the Dutch parliament. The Committee included these indicators for success in its evaluation. In Annex 3, the conclusions from the Report are discussed for each of the indicators.

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1 Dutch House of Representatives. File number 30502, nr. 5 (appendix); Kamerstukken II 2005/06, 30502, nr. 5, bijlage.
4. Activities of TI Pharma for the FES funded programme and outputs

The first projects in the TI Pharma FES portfolio were launched in 2007, and the last projects were granted FES funding in 2012. Over this six-year period, the structure of the Dutch (and international) pharmaceutical sector changed dramatically. In addition, this period was marked by policy changes in the financing of research in many countries, sometimes driven by the post-2008 economic downturn. This period also saw the launch of a number of new European programmes in the field of pharmaceuticals, such as the Innovative Medicines Initiative. TI Pharma was one of the earlier initiatives in Europe and, as such, a forerunner.

This section looks at three different topics: building the portfolio; managing the portfolio; and coordinating outputs from projects.

4.1 Building the portfolio

Over the period 2007–2013, TI Pharma allocated €137 million in FES funding, resulting in a total research budget of €274 million. According to the Committee, TI Pharma nurtured and built this portfolio, and methods to guide and maintain it, in an effective, professional and responsible way.

TI Pharma has issued five different calls for proposals, each of them differing in character and focus. For example, while initial calls (2006, 2007) were broader, to cover different areas of the Priority Medicines agenda, later calls were targeted at creating synergies between drugs, devices and diagnostics (‘Joint Call’, 2009), building on the success of the initial projects (‘Value Creation Call’, 2011), or creating new partnerships with SMEs (‘SME Partnership Call’, 2012). The Committee is of the opinion that all TI Pharma calls were overall well-balanced, with good processes and timelines. Calls were not ‘one offs’ but evolved in a logical way to stimulate the entire portfolio. The organization has shown that it has learned to adapt the ‘call procedure’ and the acceptance criteria to the needs of the changing environment. The SME Partnership Call (SPC) is a clear example of this ‘learning and development’ process and could be a model for the future. The experience developed at TI Pharma represents one of its assets.

The selection of the projects was transparent, and based on fulfilling the objectives of the overall FES programme. With hindsight, TI Pharma now recognises that it was hampered by the considerations of the original mandate, such as the need to deploy the budget rapidly and the request to cover a broad spectrum of therapeutic areas and technologies identified in the Priority Medicines for Europe and the World Report 2004.

The initial Intellectual Property (IP) model for FES-funded TI Pharma projects was based on ‘joint ownership’, with 10% of the IP generated being owned by the TI Pharma Foundation, and 90% being distributed pro rata among the consortium, based on aggregate contributions. Since then, the view on how best to deal with IP distribution amongst the partners has evolved. While the default setting has always been 10% ownership for the foundation, in later calls TI Pharma has been more flexible in negotiating other distributions. For example, in the SME partnership call, TI Pharma waived its 10% ownership rights at the start of some of the projects. This was in line with recent national developments where the model for new calls follows the inventor ownership rules. The Committee strongly supports this movement and believes that the new IP model more closely reflects the needs of consortia in this sector.

4.2 Managing the portfolio

TI Pharma has demonstrated professional programme management of the FES programme. Clear reporting and monitoring procedures have been put in place by TI Pharma as the programme matured. TI Pharma Programme Management has brought expertise concerning both content and processes to the projects, and has added significant value in this way. Project management systems established by TI Pharma (such as the IT infrastructure) have responded well to the new demands of public-private partnerships. This is also shown by the fact that the IT infrastructure, such as TI Plaza, is being used by other projects outside of the TI Pharma FES portfolio (e.g. within several IMI projects).
One of the key lessons learned from the portfolio management activities was that future programmes should have enough flexibility to change course or alter project size. For example, some successful projects may need to be expanded, while less successful projects may need to be discontinued. The educational/PhD mandate of the FES programme only allowed for very limited flexibility. In future programmes, the governance model of the partnership should enable the Principal Investigator and the governance body/central entity to make more productive portfolio management decisions, taking into consideration how a balance can best be found between value creation and education & training. It is likely that educational and graduate training objectives cannot fit in a funding mandate that also includes fast and flexible innovation-driven programme maturation, moving towards competitive stages.

4.3 Coordinating the output

The TI Pharma office has played an active role in monitoring the progress and output of the individual projects. The organization has set up a strong reporting and assessment process. The TI Pharma programme management team is well informed about what is occurring in individual projects and what is needed to address problems, or how projects can be progressed towards real-world application.

The Committee was provided with an in-depth analysis of the portfolio and its achievements. This analysis did cover leads for new medicines, and also highlighted the value of new tools and methods that can aid pharmaceutical research and development in the future. The different levels of success in different therapeutic areas accurately represent the relative difficulties. For example, metrics for discovery success vary when compared between CNS and infectious disease research and development. It is also important to note that, as with many (industrial) R&D projects and despite good scientific effort, the results of individual projects do not always show adequate potential to warrant continued investment.

Several projects have progressed significantly (including the identification of some new chemical entities and biomarkers), moving towards clinical evaluation or commercialization. Indeed, some projects have already resulted in changes in day-to-day clinical practice (for example, morphine dosage for newborns and a COPD treatment protocol). In addition, projects in areas of market failure, and involving high medical need in low- and middle-income countries, have made good technical progress (for example, the heat stable oxytocin project). However, commercial realities mean that these advances will need additional financial and management attention to assess their full potential and possibly progress them to commercial products, thereby addressing a Priority Medicines pharmacotherapeutic gap.
5. Impact of the FES funded programme

The Committee evaluated the impact of the FES funded programme on four different areas: the Dutch knowledge infrastructure; human capital; the impact on furthering the Priority Medicines agenda; and, finally, the Committee assessed the value that lies within the TI Pharma organization.

5.1 Dutch knowledge infrastructure

TI Pharma has contributed to the Dutch knowledge infrastructure in two main ways: by generating new scientific knowledge and by building infrastructure and research platforms that are of value for future applications.

Scientific knowledge generated

It is the view of the Committee, that the quality of the scientific work within the TI Pharma portfolio is overall good, competitive with other funding mechanisms such as ‘pure’ funding bodies (national science foundations, health funds etc.) and includes high-impact and highly relevant publications. Output and impact varied between projects, but this is to be expected in such a broad portfolio of research projects. The International Scientific Review Committee played an important role by providing intermediate assessment and guidance.

As far as the impact of the scientific output is concerned: the Committee took into consideration the independent analysis provided by the Centre for Science and Technology Studies (CWTS) of Leiden University. CWTS conducted an assessment of the citation scores of publications from the FES programme using a bibliometric measure that is often used for this purpose: the Mean Normalized Citation Score, where a higher score signifies increased impact. For the TI Pharma FES portfolio, the MNCS of 1.8 was comparable to Dutch ‘pure’ funding bodies in the medical and life sciences field. Funding bodies used for this comparison were Technology Foundation STW (MNCS = 1.35); The Netherlands Organisation for Health Research and Development ZonMw (MNCS = 1.57); and The Netherlands Organisation for Scientific Research NWO (MNCS = 1.83). Publications of the TI Pharma FES portfolio are at a similar or at a higher level of scientific impact as these other organizations. A comparison of citation scores in an international context with the Wellcome Trust (MNCS = 1.91) showed that the TI Pharma FES portfolio is within the same range for scientific impact, but at a somewhat lower level.

Building infrastructures and research platforms

Valuable platforms have been built. For example, the Mondriaan programme capitalizes on unique Dutch health care infrastructure to enable (pharmaco-)epidemiological studies. The Escher programme has set up an international platform for facilitating innovation by addressing regulatory barriers. In addition, several TI Pharma projects and collaborations have formed the nucleus of IMI projects or independent research collaborations. Now that these platforms have been set up, future activities can put additional emphasis on translating results to clinical practice. The Committee believes that continuity of these platforms is important in order to capture their value for public health.

Another way in which the relevance of output can be measured, is through a so-called ‘multiplier’ on the initial investment. At the request of the Committee, TI Pharma staff provided additional information about the ‘multiplier’ for each euro of funding in the FES portfolio. The direct multiplier takes into account all TI Pharma projects and their direct follow-up projects. The analysis of the FES portfolio showed a direct multiplier of 3.1. The total multiplier (which includes direct as well as indirect and associated follow-up activities) was at least 6.0. This analysis was conducted with conservative estimates; for example, the MNCS reflects the average number of citations of the publications of an organization, normalized for field differences and publication year. An MNCS value of two, for instance, means that the publications of an organization have been cited twice above world average. For a more detailed explanation of this indicator, see http://www.leidenranking.com/methodology/indicators.
additional Dutch government subsidies were not included in the multiplier calculations. Although such analyses need to be interpreted with some restraint, since there can be uncertainty as to which additional investments can directly be attributed to the FES funded initiatives, the Committee believes that this analysis supports the conclusion that the FES funding has been invested responsibly and has resulted in a positive return for the Dutch knowledge economy, based on the conservative estimates.

The Committee recommends that stakeholders should support further investments in detailed analyses of the (long-term) impact of such investments.

5.2 Human capital

One of the objectives of the TI Pharma programme was to ‘Educate and train future generations of biomedical scientists’. This was translated into a strong focus on PhDs and post-doctoral fellows. TI Pharma has trained a first group of current and future academic, regulatory and industrial leaders (including 470 PhD and post-doctoral fellows) who have experience in establishing and collaborating within academic–industrial partnerships. The educational programme, workshops and annual meetings have created an environment that changes the way faculty and students think about pharmaceutical innovation in the Netherlands, and has helped to educate faculty members, graduate students and post-doctoral fellows alike. Based on the interviews that Committee members conducted with (former) TI Pharma fellows and faculty members, the Committee noted the added value that working in a public-private partnership can have for the professional development of young researchers.

These educational activities were effectively incorporated in the FES research programme. The education and training programme addressed gaps in existing university and company curricula or training activities. The Committee appreciated the quality of the education & training activities and the positive feedback from participants. The Committee was pleased to note that 98% of TI Pharma fellows are employed at other organizations after leaving TI Pharma projects, and that there was a good mix of fellows moving into research positions in research organizations (50%) or positions in industry (30%). The Committee recommends that the network of TI Pharma fellows is maintained and tracked in order to follow this first cohort.

5.3 Priority Medicines

The 2004 WHO ‘Priority Medicines for Europe and the World’ report set out an important guiding principle for the TI Pharma FES portfolio. The TI Pharma research matrix was designed with the key ‘pharmacotherapeutic gaps’ identified in the Priority Medicines report in mind (in particular the ‘Therapeutic Areas’). In addition to the therapeutic areas as defined in Chapter 6 of the Priority Medicines 2004 report, the programme has also been active in so-called ‘cross-cutting themes’, especially orphan diseases.

The Committee is very pleased with the results of the TI Pharma FES programme in relation to WHO’s Priority Medicines initiative. The delivery exceeds the expectations of the Review Committee. It is clear that PPPs such as TI Pharma can be critical in achieving Priority Medicines objectives. Some of the projects (such as the ‘Hot Medicines’ project which aimed to create a heat stable version of oxytocin) would not have been started without TI Pharma.

In the WHO report ‘Priority Medicines for Europe and the World 2013 Update’, TI Pharma is highlighted as a case study, together with a number of other PPPs. The report discusses the main challenges for PPPs and how these can be addressed. In addition, many of the areas in Chapter 8 of the WHO 2013 Update have been addressed in the current program, for example the integration of real-life data and the dialogue approach to regulatory questions.

The mandate of TI Pharma was to cover Priority Medicines ‘in general’ and the Committee concluded that TI Pharma has done well given this broad mandate. It is suggested that funders may design future programmes with a more restricted mission in mind, focusing on strengths and areas where the highest value can be attained.

5.4 Value generated within the TI Pharma organization

In addition to the results of the projects, a further important aspect to consider is the value created within the TI Pharma organization itself. When the TI Pharma FES portfolio was launched, public-private partnerships in the pharmaceutical sector were a relatively new concept. This implied that the TI Pharma organization, to a large extent, ‘learned by doing’. As a result of this, capabilities and know-how were developed within the TI Pharma organization allowing the execution of PPPs for translational research in the pharmaceutical sector, with a focus on fulfilling the Priority Medicines recommendations. TI Pharma’s track record is evidence of its capability to coordinate and manage these complex projects and their stakeholders, both scientifically and financially. The Committee sees opportunities to closely align future TI Pharma work with synergistic initiatives, such as other PPP programmes. The Committee could envision a role for the Dutch government to back this strategy enabled by TI Pharma, as part of a new economic development
initiative where TI Pharma, together with other, highly successful and diverse initiatives in Europe, Japan, and Asia will benefit from each other’s experiences. It seems obvious that the visionary initiatives have helped build a strong R&D workforce, technology transfer capabilities and start-ups, thus enhancing economic value and wellbeing.

The know-how in the TI Pharma organization and the value of the infrastructure that has been put in place represent a critical starting point through which future PPP projects can be enabled. The Committee suggests that this could include future funding through the Dutch government and/or European initiatives. This is illustrated by many of the later projects that demonstrate a wider role for TI Pharma management expertise, and also by TI Pharma’s role within EU projects. It is the view of the Committee that there is an important role for organizations such as TI Pharma in areas such as resource sharing and multi-stakeholder interactions (academia, industry & regulators). IMI Projects such as the European Lead Factory, K4DD and other projects, such as the continuation of the Escher platform, are good examples of this new way of working in the pharmaceutical field and clearly demonstrate the role that TI Pharma is already playing in this arena. In addition, intermediary organizations such as TI Pharma will also play an important role in building and managing partnerships, for example those aimed at developing solutions for neglected tropical diseases.
6. Recommendations for future FES programmes

Based on its assessment of the TI Pharma FES portfolio, the Committee wishes to make a number of recommendations to decision-makers that can hopefully aid in designing future public-private programmes in the pharmaceuticals and broader life sciences sector.

Future programmes should allow a balanced approach to collaboration with both SMEs and larger pharmaceutical companies, especially in the areas of IP structure, funding requirements and agenda setting. The most recent TI Pharma calls, such as the SME partnership call, are good examples of how this can work in practice.

The focus of future programmes in this area should not (only) be limited to Dutch innovation, intellectual capital and expertise. Inventions and ideas need to be scouted internationally and brought to the Netherlands; in this way, contributions to the Dutch knowledge economy can be strongest. The Committee also suggests that a re-evaluation is conducted as to how the arguments for staying within the ‘pre-competitive’ sphere (e.g., for legal reasons) can be aligned with the need to allocate public funding in such a way that it is used in an optimal fashion for value creation and addressing public health needs. Next steps should optimally enable the Dutch life sciences and health sector, where numerous funding initiatives are feasible that can create economic wealth and address public health needs, without cannibalising existing Dutch basic research efforts.

The FES programme represented a mix of objectives with: i) a suitably aggressive emphasis on clinical and economical value creation; and ii) a focus on education & training, albeit all under a single funding mandate. These two objectives can sometimes be conflicting. Where possible, more emphasis should be given to projects that include post-doctoral researchers rather than PhD students, to allow for better programme flexibility and also to allow more active management of projects by TI Pharma staff while they are underway.

Within the TI Pharma FES programme, there was a strong pressure to ensure the spending of the full funding in a short period of time, in anticipation of a second funding round. This led to the deployment of the majority of the funding in less than two years. In hindsight, a longer time horizon, at least twice as long or supported with additional funding at the back end, would have allowed more optimal use of the funds, assuring support for the best projects and helping to mature these to real-world applications.

A future governance structure of public-private partnerships needs to allow organisations such as TI Pharma and its partners additional opportunities to monitor and control the development of projects, up to and including potential discontinuation of individual projects.
Annex 1: Terms of reference of the Committee

1. Objective of the FES Review 2013

The objective of the FES Review 2013 is to identify to what extent TI Pharma is achieving its mission as set out for the FES funded programme. More specifically, performance will be evaluated against the indicators for success and objectives of TI Pharma as defined at the start (Appendix I). The Review will assess how the TI Pharma organization has dealt with the recommendations from the Mid Term Review (MTR), and the changing environment for TI Pharma after the MTR. The Review aims to deliver an in depth evaluation of the direct and indirect output and the broader impact of the programme, based on a thorough portfolio analysis.

Questions to the Review Committee include:
- What is the societal, economical and scientific value of the direct and indirect output generated with the FES funded portfolio?
- What has been the impact of the FES funded portfolio on:
  - the (Dutch) knowledge infrastructure;
  - Human capital;
  - Priority Medicines;
  - Positioning of public-private partnerships and their added value in the area of pharmaceutical research and development?
- What are the lessons learned from running such a large-scale public-private research portfolio?

2. The FES Review Committee

The Executive Board has instituted the FES Review Committee as an advisory body. Taking the Mid Term Review Report (2009) as a starting point, the FES Review Committee will evaluate the performance and assess output of TI Pharma in relation to its objectives and indicators for success. The FES Review Committee will consider the different aspects (e.g., scientific output, human capital, impact on Priority Medicines) of TI Pharma in the context of the entire institute (a ‘holistic’ approach). The specific tasks of the Review Committee are outlined in this document.

3. Composition of the FES Review Committee

The FES Review Committee consists of eight Members. The Members reflect a balanced representation of expertise from academia, industry and public health organizations. Collectively, the FES Review Committee Members have the (scientific) competencies needed to assess TI Pharma’s FES funded programme. The FES Review Committee is composed of a selection of (former) Members of TI Pharma’s International Scientific Review Committee and the Mid Term Review Committee. Members participate in the FES Review Committee in their individual capacity. The Members and the Chair of the FES Review Committee are appointed by the Executive Board of TI Pharma for the period of the FES Review to be held in winter 2013-2014.

The composition of the FES Review Committee is as follows:
- **Prof. dr. E.J. Ruitenberg** (ISRC chair; Professor of International Public Health, VU University Amsterdam, ex RIVM and Sanquin)
- **Dr. T. Wells** (ISRC member; CSO, Medicines for Malaria Venture)
- **Prof. dr. T.M. Jones**, CBE (ISRC member; ex Wellcome Foundation, ex ABPI)
- **Prof. dr. R. Laing** (ISRC member; WHO, author of the Priority Medicines report)
- **Prof. dr. G. Folkers** (ISRC member; Director Collegium Helvetica, ETH Zurich and member of the Swiss National Research Council)
- **Prof. dr. P. Krogsgaard-Larsen** (past member of the ISRC; ex President of the Carlsberg Foundation and professor at the University of Copenhagen)
- **Dr. L.H.T. van der Ploeg** (past member of the MTRC; Managing Director VDP LLC, ex Abraaxis/Celgene, ex Merck Boston)
- **Prof. Dr. H.A. Struijker Boudier** (past member of the MTRC; Professor at Maastricht University)

The Committee is supported by **Dr. Jon de Vlieger** (Secretary, TI Pharma) and **Dr. Pieter Stolk** (External).
4. Tasks of the FES Review Committee

The Members of the FES Review Committee should assess the following aspects of the TI Pharma FES funded programme (see diagram above).

5. Meetings

The FES Review Committee will meet in person to discuss the questions asked to the committee. The meeting will be held in The Netherlands at TI Pharma on Thursday November 28th 2013. A provisional agenda shall be drawn up by the Chair of the Committee, together with the Secretary, Jon de Vlieger. The FES Review Committee may invite non–member experts to participate in its meetings for advice. In case Committee Members are not able to join the meeting in person, TI Pharma will secure their input by arranging a side meeting prior to November 28th.

6. Report

A meeting report will be written by the secretary and sent around for commenting and final approval to the Committee. The report will be presented to the Dutch Ministry of Health in early January 2014. In March and April 2014, TI Pharma will disseminate the results of the FES funded programme through its communication channels (e.g. by publication on the website), with the Spring Meeting on April 15, 2014 in Amersfoort as the main event.

7. Transparency of the Final Review process

TI Pharma will make public the names of the members of the FES Review Committee via the TI Pharma web site. The report of the FES Review Committee shall be published on the website of TI Pharma.

8. Information and facilities

The TI Pharma office shall provide the FES Review Committee with all needed and appropriate information and facilities to enable the Committee to carry out its work.

Documents provided to the Committee will include:
- Business plan (July 2005)
- ‘Indicatoren voor succes’ (July 2006)
- Mid Term Review report (January 2010)
- ISRC reports 2006 – 2013
- Annual reports 2006 – 2012
- TI Pharma strategy & action plan 2011-2014 (June 2011, confidential internal document)
- FES project portfolio analysis (October 2013, confidential internal document)
- Update on running business of TI Pharma: newly acquired projects, including the European Lead Factory (November 2013, confidential internal document)
In addition, if the Committee requires additional documents, they can request further information from the TI Pharma office through the Secretary of the Committee.

9. Confidentiality and conflict of interest

Members of the Review Committee are required to not divulge any information given to them in the context of the FES Review, unless it has been indicated by the Executive Board that the information is public. If not already having a permanent non-disclosure agreement with TI Pharma, Members of the FES Review Committee shall sign a non-disclosure agreement before receiving any information about TI Pharma projects and activities. Members of the Review Committee must not seek or act in any way to take undue advantage of, or exercise undue influence on TI Pharma or any of its partners. Members of the Review Committee must inform TI Pharma of all conflicts interests, which could be considered to affect their independence. When a member of the Review Committee is in breach of any of the requirements set out above, he/she will be considered as no longer being in a position to stay as a member of the Committee.

10. Reimbursement of costs

Travel costs, and subsistence expenses will be reimbursed. The honorarium is €1000,- per day; the workload is estimated to be 2 days. The TI Pharma office (Denis Groot) will handle all claims on behalf of TI Pharma.

11. Entry into force

This mandate will come into force upon the adoption by the Executive Board of TI Pharma.

Acknowledged by:

Signature
Name
Date
General outline of the day:

**9:00AM – 12:30AM**

**MISSION AND OBJECTIVES OF THE SUBSIDIZED PROGRAMME**

- **9:00AM - 12:30AM**
  - Building the Portfolio
  - Managing the Portfolio
  - Coordinating the Output

**9:00AM – 7:00PM**

**IMPACT**

- **9:00AM – 7:00PM**
  - [Dutch] Knowledge Infrastructure
  - Human Capital
  - Priority Medicines
  - Value TI Pharma Organization

**Proposed detailed agenda:**

**9:00** Welcome and introduction

**9:15** Scoping, practicalities for the day, internal arrangements

**9:30** Mission and objectives of the subsidized programme

**10:00** Discussion with management: Jorg Janssen and Ton Rijnders

**11:00** Building and managing the subsidized programme

**11:45 – 12:30** Lunch and consolidation of morning discussions

**12:30** Discussions with former managing director: Willem de Laat

**13:00** Group discussion with:
  - Former TI Pharma fellows: Kolkman, Heitman, Orrling
  - Senior team members in consortia: SMEs – Kruisbeek, Van Eenennaam, Academia - Sauerwein (research), IJzerman (research), MacDonald (technology transfer)

**14:50** Consolidation of interview round

**15:00** FES portfolio analysis discussion

**15:45 – 16:00** Break

**16:00** Human capital

**16:30** Impact on Priority Medicines

**17:00** Value of the TI Pharma organization

**17:30 – 18:30** Working Dinner – Further Discussions

**18:30** Concluding & reporting

**19:00** End of meeting
When the TI Pharma FES programme was launched, eleven ‘indicators for success’ were identified and sent to the Dutch parliament. The Committee evaluated the performance of TI Pharma against these indicators, and an assessment for each indicator (bold) is given below. We have clustered indicators 8–10, as these are best discussed in combination.

### 1. In two years, the first publications and patent applications originating from TI Pharma projects see daylight;
Achieved. The FES programme has resulted in 725 publications and 34 patent applications so far. The first patent application was submitted in 2008, and first publications appeared shortly after the start of the FES programme in 2007.

### 2. In two years, Priority Medicines has been brought to the public attention by TI Pharma and received serious attention from the pharmaceutical industry;
Achieved. The 2004 WHO report ‘Priority Medicines for Europe and the World’ set out an important guiding principle for the TI Pharma FES portfolio. The TI Pharma research matrix was designed with the key ‘pharmaco-therapeutic gaps’ identified in the Priority Medicines report in mind (in particular the ‘Therapeutic Areas’). In addition to the therapeutic areas as defined in Chapter 6 of the Priority Medicines 2004 report, the programme has also been active in so-called ‘cross-cutting themes’, especially orphan diseases. The report also featured prominently in TI Pharma communications.

In the 2013 WHO ‘Priority Medicines for Europe and the World 2013 Update’, TI Pharma is highlighted as a case study, together with a number of other PPPs. The report discusses the main challenges for PPPs and how these can be addressed.

The WHO 2013 Update provides an important input for the IMI 2 Strategic Research Agenda. Additionally, various pharmaceutical companies were involved in providing comments and feedback to the authors of the 2013 Update Report. This indicates the interest from pharmaceutical companies in Priority Medicines.

3. The majority of current TI Pharma consortia of industry, start-ups and academia are still working together in 3-4 years, and plan to continue this cooperation after their projects end, which proves that sustainable, multilateral cooperation has arisen;
Achieved. Almost all TI Pharma consortia collaborated for the full project period; two projects were discontinued earlier. Of the 58 projects that have run for three years or more at the moment of writing, 42 projects have resulted in some form of project continuation.

The sustainability of the collaboration after the end of a project can be quantified by looking at the multiplier for the initial investment. The direct multiplier takes into account all TI Pharma projects and their direct follow up projects. The analysis of the FES portfolio showed a direct multiplier for the initial investment of 3.1. The total multiplier (which includes direct as well as indirect and associated follow-up activities) was at least 4.3.

### 4. In 2-3 years TI Pharma has achieved European stature, resulting in international cooperation in the 7th Framework Programme;
Achieved. Several TI Pharma projects and collaborations have formed the nucleus of IMI projects or independent research collaborations. The know-how in the TI Pharma organization and the value of the infrastructure that has been put in place represent the critical starting point through which future PPP projects can be enabled. This is illustrated by the wider role for TI Pharma management
expertise demonstrated by later projects and also by EU projects. The role for organizations such as TI Pharma is important in areas such as resource sharing and multi-stakeholder interactions (academia, industry & regulators). IMI Projects such as the European Lead Factory and K4DD are a good example of this new way of working in pharma and the role that TI Pharma is already playing in this.

5. In 3-4 years it is clear that TI Pharma researchers are recruited by industry, knowledge institutes and regulatory agencies as a result of their clear vision of and broad experience in innovative and efficient, modern pharmaceutical research;

Achieved. 98% of TI Pharma fellows have been employed at other organizations after leaving TI Pharma, and there was a good mix of fellows moving into research positions in research organizations (50%) or positions in companies (30%). From the interviews that Committee members had with (former) TI Pharma fellows, the Committee noted the added value that working in a public-private partnership can have for the professional development of young researchers. The Committee recommends that the network of TI Pharma fellows is maintained and tracked in order to follow this first cohort.

6. In four years, more than a third of projects have met their expectations as described in the original project plans (the success rate of R&D projects in the pharmaceutical sector is notably lower);

Achieved. According to the ISRC, most projects have made good progress, and overall scientific quality is good. A self-assessment by TI Pharma staff rated 46 out of 74 projects as having a 'high' level of output. The Committee was provided with an in-depth analysis of the portfolio, and of what has been achieved, which supported this conclusion. This analysis covered leads for new medicines, and also highlighted the value of new tools and methods that can aid pharmaceutical research and development in the future. The different levels of success in different therapeutic areas accurately represent the relative difficulties. For example, standard metrics of discovery vary between CNS and infectious disease research and development. It is also important to note that as with many (industrial) R&D projects, despite good scientific effort, the results of individual projects do not always show adequate potential to warrant further investment.

7. Within four years, several spin-outs have formed as a result of TI Pharma projects;

Achieved. As a result of the FES portfolio, six spin-offs have been launched up to the date of this report.

8. In four years, at least 1 new mechanism has been discovered that will lead to treatment for certain diseases;

9. In 4-8 years based on TI Pharma projects, at least 1 symptomatic treatment of a disease is replaced with a treatment that tackles the root of the problem;

10. In 4-8 years, a number of new biomarkers have been identified and validated, leading to:
   a. Improvement in the design, development and evaluation of new drugs and
   b. More effective measurement of therapeutic effects and/or side effects of drugs

Very good progress. It should be noted that the eight-year timeframe has not yet been completed [indicator 9-10]). It is therefore too early to perform a final evaluation of the deliverables of TI Pharma and its projects.

Nevertheless, many projects have progressed significantly (including the discovery of some new chemical entities and biomarkers), moving towards clinical evaluation or commercialization. Furthermore, the results of some projects have already improved day-to-day clinical practice (for example, morphine dosage for newborns and a COPD treatment protocol). In addition, in areas of market failure and of high medical need for low- and middle-income countries, some projects have made good technical progress (for example, the heat stable oxytocin project). It is also noteworthy that valuable platforms have been built. For example, the Mondriaan programme capitalizes on Dutch health care infrastructure to enable (pharmaco-)epidemiological studies. The Escher programme has set up an international platform for facilitating innovation by addressing regulatory barriers (including, for example, work on biomarkers).

The TI Pharma FES programme represented a mix of objectives with: i) a suitably aggressive emphasis on clinical and economical value creation; and ii) a focus on education & training, albeit all under a single funding mandate. Additionally, the work in the FES programme needed to cover a broad area of the Priority Medicines Agenda and focus on pre-competitive research. Against this background, the Committee concludes that the TI Pharma FES portfolio performed well in light of the ambitions of indicators 8-10. It should be noted that the time from discovery to marketing an entirely new treatment for
a disease (as distinct from improving symptomatic treatment) is generally 10-13 years, i.e. the 4-8 years expectation after the start of the FES programme (indicator 9) now appears unrealistic.

The Committee is particularly pleased with the results of the TI Pharma FES programme in relation to WHO’s Priority Medicines initiative. Delivery exceeds the expectations of the Review Committee.

11. In 3-10 years it is obvious that the unique drug research infrastructure, built by TI Pharma, attracts significantly more R&D work from foreign pharmaceutical companies.

Achieved. The know-how in the TI Pharma organization and the value of the infrastructure that has been put in place represent the critical starting point through which future PPP projects can be enabled. This is illustrated by the wider role for TI Pharma management expertise demonstrated by later projects and also by EU projects. It is the view of the Committee that there is an important role for organizations such as TI Pharma in areas such as resource sharing and multi-stakeholder interactions (academia, industry & regulators). IMI Projects such as the European Lead Factory and K4DD are a good example of this new way of working in the pharmaceutical field and clearly demonstrate the role that TI Pharma is already playing in this arena. In addition, intermediary organizations such as TI Pharma will also play an important role in building and managing partnerships, for example those aimed at developing solutions for neglected tropical diseases.
The FES funded portfolio consists of 74 projects in total for which the short title and partners are listed below.

A description of each project can be found online at [www.tifharma.com/pharmaceutical-research-projects](http://www.tifharma.com/pharmaceutical-research-projects)

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<td>GPCR Forum</td>
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<td>Cardiotoxicity</td>
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<td>Metabolic stability</td>
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<td>D5-402</td>
<td>The ProGraft Study (joint call)</td>
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<td>Nasal RSV vaccine</td>
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APPENDIX B

96. TI PHARMA, NEW TRACKS TO MEDICINES
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INFORMATION

Visit:
TI Pharma
Galileiweg 8
2333 BD Leiden
The Netherlands

Contact:
PO Box 142
2300 AC Leiden
The Netherlands

Tel.  +31 071-332-2030
Fax:  +31 071-332-2031

Email: info@tipharma.com

www.tipharma.com

Written & edited by Paul Bancroft
Design & Art Direction: Zoo&Co.