STRATEGIC RESEARCH PROGRAM
AUG 09, 2006

Introduction
The Strategic Research Program of the Top Institute Pharma (TI Pharma) is based upon a matrix of Therapeutic Areas and Enabling Technologies (see fig. 1).
The Therapeutic Areas are directly related to Priority Medicines (see “Priority Medicines for Europe and the World”, a report of the World Health Organization), the Enabling Technologies are relevant to research across the various Therapeutic Areas.

The official TI Pharma foundation was established just recently, on July 11, 2006. Before that, in the startup phase of the Institute, two calls for proposals were issued to create a Strategic Research Program of top quality projects within the framework of Priority Medicines.

In this document the matrix of Therapeutic Areas (Themes) and Enabling Technologies (Disciplines) is briefly introduced as well as the selected projects as they fit into this matrix. Furthermore, some special focal areas mentioned in the Priority Medicines report are discussed. Finally, the place of innovations in the strategic research program is presented.

The preliminary Strategic Research Program was discussed extensively with TI Pharma's International Scientific Review Committee (ISRC). The ISRC report (doc 05 in the Subsidy Request Dossier) concludes that *'TI Pharma will have a high quality and well-balanced project portfolio, which adequately addresses most aspects of the Priority Medicines report*'.

Once all projects selected are under way, the final version of the Strategic Research Program of TI Pharma will be prepared. This final version will be included in the first TI Pharma annual report, due early 2007.

Framework
The Strategic Research Program builds upon a matrix (see below) of Therapeutic Indications (Themes) and Enabling Technologies (Disciplines).

Therapeutic indications / Enabling technologies	T1: (Auto-)Immune Diseases	T2: Cardio-vascular Diseases	T3: Neoplastic Diseases	T4: Infectious Diseases	T5: CNS Diseases
D1: Therapeutic Target Finding, Validation & Animal Models					
D2: Lead Selection and In-Silico Modeling					
D3: Predictive Drug Disposition and Toxicology					
D4: Biomarkers and Bio-sensoring					
D5: Drug Formulation, Delivery and Targeting					
D6: Pharmaceutical Prod. Technologies					

T6: Special overall Research Platform:

Efficiency Analysis of the Process of Drugs Discovery, Development and Utilization

This special platform will cover (amongst others):
- efficiency improvement of drug development
- societal acceptance of drug development

Figure 1: Research matrix of Therapeutic Indications (Themes) and Enabling Technologies (Disciplines)

Content of the Program

The following gives an overview of the projects selected by TI Pharma and the position they have in the Strategic Research Program of the Institute (for full titles of project codes, see the list on pages 9 and 10.

Theme 1, (Auto) Immune Diseases

In Theme 1, projects concentrate either on specific areas like Chronic Obstructive Pulmonary Disease (COPD) and Osteoarthritis, or deal with novel ways to modulate the immune system. In COPD a strong platform has been established (projects T1-108, consisting of former T1-8 and T1-9, and T1-201). In the projects involved the relation between a.o. smoking and the development of COPD is studied, involving pheno- and genotyping of subjects, finding new biomarkers and novel treatment options. The osteoarthritis project (T1-201) addresses the development of biomarkers and personalized treatment strategies.
The projects dealing more generally with the immune system and its therapeutic aspects involve new drug targets (T1-103, T1-214, T1-215) and novel ways to make existing treatments more effective by eliminating limiting serious chronic side-effects (T1-106). The project on Toll-like Receptors (D1-101) is potentially of relevance for all immunological indications, but specifically so for COPD.

Theme 2, Cardiovascular Diseases

The projects in Theme 2 concern two major areas: novel treatments for cardiovascular (CV) diseases and cardiovascular side-effects of non-CV drugs. To the first category belong two projects directed at new drug targets in atherosclerosis (T2-108, T2-110), one project specifically aimed at balanced treatment of “wet” and “dry” strokes (T2-111) with a potential spin-off towards post-partum haemorrhage. Related to the latter indication is also project D6-202, dealing with a.o. developing heat-stable formulations of peptide/protein containing drugs, including oxytocin. Another project in the “novel treatment” category (D6-203) concentrates on new pharmaceutical technologies to enable rational development of Fixed-Dose-Combinations for a.o. cardiovascular disease.
In the second area (CV side-effects) one project studies detrimental metabolic adverse effects of psychotropic drugs (obesity, diabetes, CV disorders), in order to eliminate such side-effects and detect new targets for treatment of metabolic conditions. Another (D2-101) regards the cardio-toxicity of drugs and aims at novel ways to eliminate potentially cardio-toxic drugs early in the drug development process by applying translational methods.

Theme 3, Neoplastic Diseases (oncology)

Three projects in Theme 3 concentrate on various types of kinases (T3-103, T3-105, T3-106), enzymes, playing an important role in the genesis of tumours, which are receiving much attention as targets for novel anti-tumour treatments. Two other projects target hormone-sensitive tumours (breast, prostate), one identifying novel nuclear receptors (T3-107) as targets for potential new treatments, the other aiming at identifying biomarkers and genetic patient profiles that will predict treatment outcome (personalized medicine!). One final project concerns potential novel anti-cancer drugs related to Tumour Necrosis Factor.
From a different treatment angle, the project on Toll-like Receptors (D1-101) could generate anti-cancer vaccines.

Theme 4, Infectious diseases
Most projects in the Infectious Diseases area are directed towards drug-resistant micro-organisms. Two projects (T4-101, T4-213) deal with antibodies and/or vaccines against "problem bacteria"; *Klebsiella pneumoniae, Staphylococcus Aureus*), one (T4-102) is on a vaccine for (chemotherapy resistant) malaria whereas two other projects deal with novel antibiotics (T4-209) or sensitizers to existent antibiotics (T4-211) for the treatment of antibiotic-resistant bacteria.

Two other projects have a different character, they concentrate on improvement of models, development processes and efficacy assessments for influenza vaccines (T4-103) and HIV treatment (T4-212).
Important for this therapeutic area are also projects on Toll-like receptors (D1-101), on potential Fixed Dose Combinations for the treatment of HIV (D6-203), on novel ways of vaccine delivery, to eliminate multiple injections (D5-106) and on eliminating cold-chain requirements for protein containing drugs, like vaccines (D6-202).

On special request of TI Pharma a special working group is currently formulating proposals for a generalistic approach towards viral vaccines.

Theme 5, Central Nervous System (CNS) disorders
In the CNS area three projects deal with new approaches for the treatment of degenerative brain diseases (like Alzheimer, Parkinson, schizophrenia), T5-207, T5-209 and T5-211 (the latter will probably be combined with T5-209, in view of the apparent synergies). A new treatment modality specific for Alzheimer is being developed in project D2-103, which may also have a spin-off in the direction of smoking cessation (COPD!). Another project of relevance to this area is T5-107, concerning the endo-cannabinoid system in the brain which is involved in nicotine dependence, eating disorders, cognition and pain perception. Treatment of pain is considered a CNS indication, but it is of utmost relevance for e.g. cancer and arthritis. Project T5-108 is concentrating on translational research into biomarkers for main and side-effects of analgesics, which will enable more efficient development of more efficacious and safer pain killers.

For general application in the field of development of drugs for brain disorders three projects are important: one (T5-105) which develops new technologies to get drugs specifically past the blood-brain barrier into the brain, one to validate animal models for CNS diseases more rapidly (T5-210), making the development process for such drugs much more efficient, and one (T5-203) concentrating on a pharmaco-genomics approach to enable development of psychiatric drugs with a better chance of efficacy (personalized medicine!) and a shorter, more efficient development process.

In addition to this, project D4-102 deals with the cerebrospinal fluid compartment as a rich source for biomarkers to be used for all kinds of brain disorders, neurological as well as psychiatric. In order to achieve maximal synergy, results from the general CNS-applicability projects (T5-105, T5-203, T5-210, T5-203 and D4-102) will be shared regularly between all CNS projects.

Theme 6, Efficiency analysis of the process of Drugs discovery, Development and Utilization

Although not a Therapeutic Area, this Theme is an important one, with two main aspects. One is the use of epidemiological data bases (T6-101, T6-202) to enable naturalistic modelling of large-scale clinical trials with new drugs, making the drug development process quicker and more efficient and to keep closely track of emerging efficacy and safety profiles of drugs novel to the market.

The other aspect is to involve regulators in evolving new ways of drug discovery and drug development at the earliest possible stage. No specific projects have been drawn up for this, but they apply to most of the projects as stated above.

Discipline 1, Therapeutic Target finding, validation and animal models.

Although target finding and validation is part of many of the projects in the various Therapeutic Areas, two projects specifically are listed under this Discipline because they are expected to generate results for most if not all of the Therapeutic Areas. One is D1-101, concentrating on Toll-like receptors, the sentinels of the innate immune system. The other one (D1-105) is concentrating on new ligands (especially lipids, peptides and proteins) for the well-known G-protein coupled receptor (GPCR) family. Although 40-50% of all existing drugs are acting via members of this receptor super-family, it is expected that many more novel drugs can be found by further unravelling the secrets of GPCRs.

Discipline 2, Lead selection & in silico modelling

Whereas Discipline 1 approaches drug discovery from the point of novel targets, Discipline 2 is mainly concerned with novel methods to be used in the drug discovery and development process that could lead to better prediction of side effects (D2-101), pharmaco-kinetics in relation to efficacy (D2-104), metabolic stability, with the potential to generate novel, metabolism-generated drug classes ((D2-102) and structure-based design of novel drugs acting via the nicotinic ACh–operated ion channel (D2-103). As indicated earlier, the latter project has close ties with Theme 1 (COPD) and Theme 5 (Alzheimer, Parkinson).

It is important to note that the mechanism-based PK/PD modelling platform (D2-104) will allow incorporation of paediatric and geriatric populations as well as women in their studies. This will result in the design of treatment protocols specific for these groups.

Discipline 3, Predictive drug disposition and toxicology

One project (D3-201) with a strong translational, biomarker finding character is present in this category. It aims to identify biomarkers for adverse drug reactions that are generally not picked up during regular drug development but emerge only after introduction in the market and broad exposure, often leading to drug withdrawals, not to mention unnecessary suffering. Strong synergy exists with Theme 6 projects T6-101 and T6-202 (epidemiological databases).

Discipline 4, Biomarkers and biosensoring

Many of the projects belonging to the various Therapeutic Areas work on identifying biomarkers that will be used for biosensoring within the framework of translational studies. One project, the CSF proteome/metabolome project (D4-102), is categorized in this area, but it is strongly linked to the CNS area, as already mentioned under Theme 5.

Discipline 5, Drug formulation, delivery and targeting
Two projects are listed under this heading. One is D5-106, aiming at developing alternatives for the conventional multiple-injection vaccines. Of course, this project has main importance for Theme 4, Infectious Diseases and, to a lesser extent, to Neoplastic Diseases (Theme 3). The other project, D5-102 relates to the immunogenicity of therapeutic proteins. This project is more general in character and is to a certain extent related to production technology.

Discipline 6, Pharmaceutical production technologies
Two projects, specifically invited by the TI Pharma Management Team, address production technologies, with a clear-cut Priority Medicines goal.

The first (D6-202) deals with improving the thermal stability of drug formulations containing peptides or proteins. It is important for the developing world that requirements for refrigeration etc. are eliminated. This applies to e.g. oxytocin (post-partum haemorrhage) and insulin (diabetics in developing countries, travelling diabetics). The second project (D6-203) studies new technologies to, amongst others, enable rational design of Fixed Dose Combinations, which can be used for HIV, cardiovascular disease, etc., ensuring better compliance and thereby better efficacy.

Relation of the program to Priority Medicines
The Strategic Research Program prominently addresses therapeutic indications mentioned in the Priority Medicines (PM) report. Figure 2 below shows the project numbers of projects which have a direct link (bold) or indirect link (normal) with PM under the various therapeutic indications.

Theme 1 (Auto-) Immune diseases	**Theme 2** Cardiovascular diseases	**Theme 3** Neoplastic diseases	**Theme 4** Infectious diseases	**Theme 5** CNS diseases
Osteoarthritis **D1-101**, **D1-105, T1-213** D5-106, T1-103, T1-106, T5-108 COPD **D1-101**, **D1-105**, **T1-103**, **D2-103** (nicotine) **T1-105**, **T1-108**, **T5-107** (via nicotine) **T1-201**, T1-214	Cardiovascular **D1-101**, **D1-105**, **T2-105**, **T2-108**, **T2-110** T1-103, T1-106 Acute Stroke **T2-110**, **T2-111** D1-101, T2-108,	Lung cancer **D1-101**, **D5-106**, **T3-103** D1-103, D1-105 Breast cancer **T3-105**, **T3-108** Intestinal cancer **T3-106**, **T3-107** Other **T3-112** T5-108	Bacterial resistance **T4-101, T4-209, T4-211** Influenza **D5-106**, **T4-103** Tuberculosis **D1-101**, **D5-106** HIV/Aids **D5-106**, **T4-212,** D1-101, D1-103 Malaria **D5-106**, **T4-102**, D1-101	Alzheimer **D2-103, T5-207, T5-211,** T5-107, T5-210 Depression – elderly **D1-105**, **D2-104**, **D4-102**, **T5-105** D2-103, T5-210

Figure 2: Link with Priority Medicines

Next to the links within the Therapeutic Areas, three other indications mentioned in the PM report are directly or indirectly linked to TI Pharma projects:

- Alcoholic diseases: D1-105, T5-107, and indirectly D2-103.
- Diabetes: T1-106, T2-105, and indirectly D1-103, T2-110 and T5-108.
- Postpartum hemorrhage: D6-202, and indirectly T2-111.

Relevance of the program for novel drug discovery and development
The world needs novel drugs for any of the three following reasons:

1. There is currently no treatment available.
2. Current drugs have insufficient efficacy.
3. Current drugs suffer from insufficient safety.

The projects in the TI Pharma Strategic Research Program fit into either of the three categories as follows:

Area 1) Currently no treatment available
Projects focus, amongst others, on finding novel drug targets for specific therapeutic indications like osteoarthritis, COPD, Alzheimer, Influenza and, more indirectly, Alcoholic and Nicotine-related diseases. Specific projects are D1-101, D2-103, D4-102, T1-108, T4-103, T5-107, T1-201, T1-213, T1-214, T1-215, T5-207 and more indirectly, D1-105.

Area 2) Insufficient efficacy
In some cases projects focus on disease modification rather than symptomatic relief, by looking for new drug targets: D1-101, D4-102, T2-110, T3-103, T3-105, T3-106, T4-102, T5-203 and T5-209 or new drug classes (D1-105, D2-102 and T3-107). Other projects have existing drugs as a basis and are aimed at optimization of formulation, route of administration, treatment protocol, etc. in order to e.g. enhance exposure and/or compliance and, thereby, improve efficacy.

Such projects are:
- Elderly / paediatric: D2-104, D5-106 and T5-105.
- Prediction of long term outcome: D2-104, T1-108, T3-108 and T3-112.
- Cold chain requirement: D6-202.
- Fixed Dose Combination Design: D6-203.

Finally, a couple of projects deal with evading or breaking the resistance of micro-organisms towards existing chemotherapy: T4-102 (malaria), T4-209, T4-211 and T4-212.

Area 3) Insufficient safety
Projects focusing on side effects of various therapies:
- Corticosteroids, psychiatric drugs, of therapeutic proteins: D2-101, D2-104 and T2-105.
- Novel drug classes: safety prediction, early biomarkers: D1-105, D2-102, T1-106, T2-111 and indirectly T5-108.
- Biomarkers for adverse drug reactions: D3-201.

Innovation aspects of the program

The Strategic Research Program focuses on innovations in six different areas important for drug development in which the various projects fit as follows:

Topic	Projects	Focus
New targets	T1-103, D1-105 T3-103,105,106 T2-110 T2-110 T3-112 T5-107, T5-209 D2-103	u (Toll like) receptors, nuclear receptors, GPCR, CXCR u Intracellular proteins: kinases, kinome identification u Extracellular proteins: metalloproteases u TRAIL u Encannabinoids u Ligand-gated ion channels
New biomarkers	T1-106, T3-103,106, D4-102, D3-201 T1-201, 213, 214, 215	u CSF metabolome u Proteome (validation) u Several others
New methods / more efficient R&D	Several, including T1-106, D4-102, T4-212, T5-203, T5-211, T1-213, T5-210, T6-202, D2-201	u Functional tests u Diagnostics tests to improve therapeutic impact u PK/PD modelling
Safety / new safe medicines	D2-101 T2-105, D4-102 T1-106 T2-111 D3-201	u QT prolongation u Drug induced weight gain / metabolic syndrome u Corticosteroid-induced insulin resistance u Thrombosis u Biomarkers for adverse drug reactions
New drug classes	D2-102 T4-101, 102, (103), D1-101, D5-106 T4-209, 211	u Metabolic stability u Compound (group) oriented u Anti-infectives u Vaccines
Improving existing drugs	D6-202, 203 D5-203	u Reduce cold chain requirement u Parametric design Fixed Dose Combinations u Existing drugs: improved efficacy and affordability

Figure 3: Focus within each of the six innovation areas

Distribution of funds over therapeutic areas and enabling technologies

The distribution of funds over the various Therapeutic Areas (Themes) and Enabling Technologies (Disciplines) is shown in figure 4.

It is clear that the Therapeutic Areas consume, as expected, approx. 75% of all funds, whereas the enabling technologies requires approx. 25%. This illustrates that the Strategic Research Program of TI Pharma is strongly disease-focused, not purely technology driven. Taking contributions from projects listed under enabling technologies to therapeutic areas into account, the distribution of funds over the 5 broad indications is more or less even. Not only in terms of content (see previous pages) but also in terms of resource allocation, the strategic research program is rather well-balanced.

It should be noted that the numbers shown are for a large part “requested” funds, final numbers may be slightly lower after project negotiations have been completed.

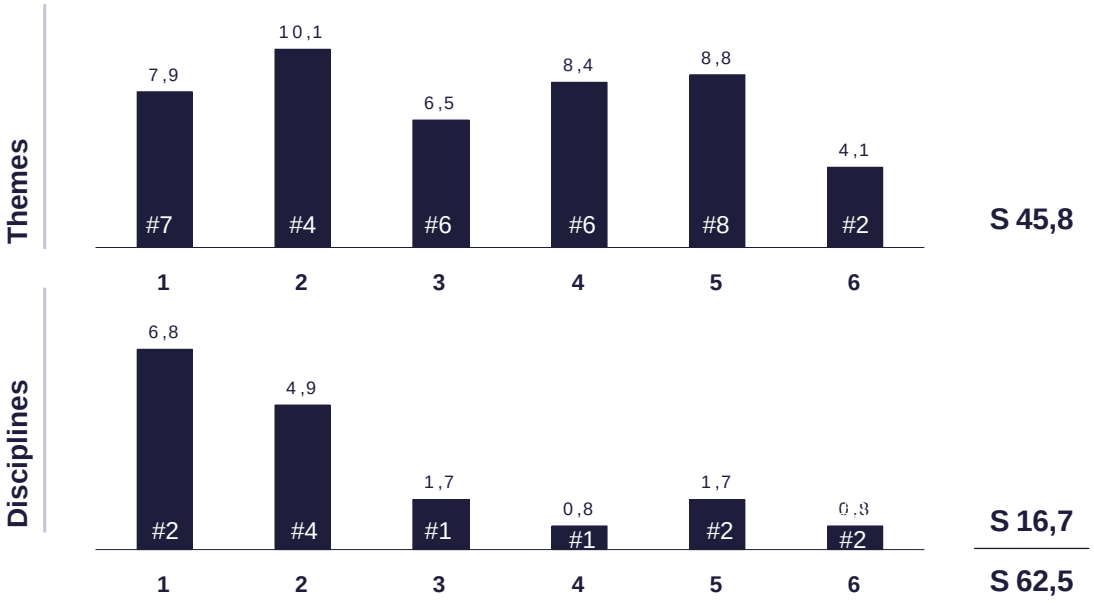

Figure 4: Size (in EUR m) and number of projects (1st and 2nd call) per Theme and Discipline

Participants in the TI Pharma Strategic Research Program

The Dutch Universities (including the UMCs) are involved in almost all Therapeutic Areas (see next page). The industrial partners (> 30!) are more spread over the various Therapeutic Areas. This is understandable, since many (especially the SMEs) are specializing in certain indications or technologies. Only the medium-sized pharmaceutical partners are broadly involved in Therapeutic Areas and Enabling Technologies. It is clear that “Big Pharma” is under-represented, due tot the fact that they have no direct R&D presence in the Netherlands. In order to fulfill TI Pharma’s mission to make the Netherlands a place Big Pharma cannot circumvent in the future to perform, or have performed, pharmaceutical R&D, the larger foreign pharmaceutical companies will have to become involved in TI Pharma’s research program. The TI Pharma Management Team is currently working on this.

Partners & Participants	Themes						Disciplines					
Academic:	1	2	3	4	5	6	1	2	3	4	5	6
CHDR	■											
Erasmus Universiteit Rotterdam	■		■	■	■	■		■		■		
Hubrecht Laboratory			■									
NIN					■							
NKI			■					■				
Rijks Universiteit Groningen	■	■	■		■	■	■	■	■	■	■	■
RU Nijmegen		■		■	■		■	■	■	■		
TNO	■	■		■			■			■		■
Universiteit Leiden	■	■	■	■	■		■	■	■	■	■	■
Universiteit Utrecht	■	■	■	■	■	■	■	■	■		■	
Universiteit van Amsterdam	■	■	■		■							
Universiteit van Maastricht	■	■					■					
Vrije Universiteit Amsterdam	■	■	■	■	■		■	■	■		■	
Industrial:	1	2	3	4	5	6	1	2	3	4	5	6
Agendia			■									
Altana	■							■				
AM Pharma				■								
Astra-Zeneca	■											
Bio-Detection Systems									■			
Centocor / J&J	■				■			■				
Crucell		■		■								
DNAge					■							
Eli Lilly								■	■			
Fuiji											■	
GSK	■			■		■		■				
HAL Allergy	■											
IQ Corporation	■			■								
ISA							■					
Kiadis			■									
Lundbeck					■							
Merck						■						
NOTOX									■			
Novartis									■			
Numico Research	■	■					■					
NVI											■	
Octoplus				■							■	■
Organon	■	■	■		■	■	■	■	■	■		■
Pamgene									■			
Pepscan Systems	■		■	■					■			
Pfizer, UK								■				
Pharma-Bio Research		■			■			■				
Prosensa				■	■							
PROXY Laboratories				■								
Pyxis Discovery					■							
Solvay Pharmaceuticals		■			■		■	■	■	■		■
WINAp						■						

List of Projects

First call:

NUMBER:	TITLE:	
D1-101	Exploitation of Toll-like receptors in Drug Discovery	
D1-105	The GPCR Forum: Novel concepts and tools for established targets.	
D2-101	An integrated strategy for in silico prediction and clinical evaluation of the cardiotoxicity of drug candidates	
D2-102	Metabolic stability assessment as new tool in the Hit-to-Lead selection process and the generation of new lead compound libraries.	
D2-103	New approaches for Ligand-Gated Ion Channel (LGIC) drug discovery	
D2-104	Mechanism-based PK/PD modelling platform	
D4-102	The CSF proteome / metabolome as primary biomarker compartment for CNS disorders	
D5-106	Vaccine Delivery: alternatives for conventional multiple injection vaccines	
T1-103	CXC chemokine receptors: potential targets for chronic inflammatory diseases	
T1-106	Glucocorticoid-induced insulin-resistance	
T1-108	Acute and chronic inflammatory responses induced by smoking in individuals being susceptible and non-susceptible for development of COPD: From specific disease phenotyping towards novel tailor-made therapy	
T2-105	Investigation of drug induced weight alterations to identify novel therapeutic strategies for the treatment of obesity, dyslipidemia and diabetes	
T2-108	Metalloproteases and Novel Targets in Endothelial Dysfunction	
T2-110	Nuclear receptors as targets for anti-atherosclerotic therapies	
T2-111	Recombinant factor XI and IX variants as the basis for the development of novel pro- and anticoagulant drugs	
T3-103	Identification of novel kinases involved in cancer-relevant processes	
T3-105	Kinases in cancer	
T3-106	Novel cancer drugs based on signal transduction pathways	
T3-107	Nuclear receptors in targeted cancer therapy: improved methods for candidate selection.	
T3-108	Predicting drug responses in breast cancer	
T3-112	TNF ligands in cancer	
T4-101	Antibodies against Klebsiella pneumoniae as an alternative	
T4-102	Design of Predictive Models, Drug Delivery, and Live-virus Malaria Vaccines for the Developing World	
T4-103	Establishment of validated animal models for human influenza and RSV	*Further discussion*
T5-105	Nanoscience as a tool for improving bioavailability and Blood Brain Barrier penetration of CNS drugs	
T5-107	The neurophysiological role of the endocannabinoid system in support of smoking cessation, fighting addiction and treating cognitive decline	
T5-108	Validation of the use of fMRI as an objective measure in clinical pain models	
T6-101	The Mondriaan Project : The Dutch health care landscape as a ‘population laboratory’	

Second call:

NUMBER:	TITLE:	STATUS:
D3-201	Towards novel translational safety biomarkers for adverse drug toxicity	Accepted
D6-202	Hot medicines: breaking the cold chain requirement for polypeptide-based priority medicines.	Accepted
D6-203	Design quality into products	Accepted
T1-201	Transition of systemic inflammation into multiorgan pathology	Accepted
T1-213	Osteoarthritis: models, mechanisms and markers for patient stratification	Accepted
T1-214	Immune modulation and tolerance induction, prevention and inhibition of inflammatory diseases	Accepted
T1-215	Neuromodulation of innate immune responses	Accepted
T4-209	New antibiotics to fight antimicrobial resistance	Accepted
T5-203	A translational pharmacogenomics approach to improve drug development strategies for psychiatric disorders	Accepted
T5-207	Parkinson and Alzheimer disease: from dysregulated human brain targets towards novel therapeutics	Accepted
T5-209	Novel susceptibility pathways and drug targets for psychosis	Accepted
T5-210	Rapid in vivo CNS drug target validation and therapeutic potential by RNA-interference'	Accepted
T6-202	The Escher Project: Science driven drug regulation and innovative research throughout phased drug development	Accepted
D2-201	Mechanism-based PK/PD modelling platform - extension	Discuss
D5-203	New nano-sized formulation technology for hydrophobic drugs	Discuss
T4-211	Efficient Eradication of (Multidrug) Resistant Bacteria	Discuss
T4-212	A multidisciplinary approach to monitor and select effective therapy in HIV infection	Discuss
T5-211	Novel inroads towards biomarkers and therapies for neurodegenerative diseases	Discuss
T4-213	Protective human antibodies against multi-drug resistant *Staphylococcus aureus* (AntiStaph)	Discuss

The last six projects will be added to the Accepted list after further discussion.

NB: Detailed project proposals are available on request at the TI Pharma office in Leiden. Once project contracts have been finalized short project summaries will be published on the TI Pharma website.