REPORT update* 2016

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PREFACE

The general objective of the **Louvain Drug Research Institute (LDRI)** is to develop fundamental and/or applied cutting-edge research, in the field of drugs. Overall research activities are developed from target identification & validation to clinical practice through hit identification/hit to lead, preclinical evaluation, pharmaceutics, clinical assays and optimization of clinical practice.

The LDRI is located on the Health Sciences Campus of the **Université catholique de Louvain** (UCLouvain) in Brussels. One related University Hospital (**Cliniques Universitaires St Luc**) is located within walking distance of the Institute. Around 140 persons are currently working in the Institute.

Since its creation 6 years ago, the LDRI increased the external visibility of its research activities, and increased its autonomy to adapt its resources to research priorities and needs. Research excellence conducted at the LDRI has led to a constant increase both in the number and in the quality of the publications in well recognized international journals. According to the prestigious QS World University Ranking 2016, our research activities in Pharmacy and Pharmacology are recognized in the Top 51-100 Universities over the world, UCLouvain being ranked as the first French-speaking University in Belgium, and the second at the national level after the KULeuven. In 2016, 4 principal investigators of LDRI were among the highly cited researchers worldwide (Thompson-Reuters).

"**Bridging sciences for better health**" is the LDRI’s motto. The LDRI is proud of the diversity and wealth of its research despite its relatively small size, and the limited number of senior researchers who are also involved in teaching and institutional activities. The members of the LDRI join their forces to form a multidisciplinary Institute where all major aspects of the drug are covered. The research activities range from the design or identification of a new drug (and the discovery of new targets) to its optimal use through up-to-date methodology of evaluation. The approaches use in vitro (membranes and cells) and in vivo pre-clinical models (small animals). Patients-oriented research is focused on the pharmacokinetics / pharmacogenomics and clinical pharmacy.

The LDRI is organized in seven functional research groups led by highly motivated academics. The research groups are closely linked by a series of common research projects, and they share modern scientific equipments. The Institute is also supported by two technology platforms that gather experts and outstanding equipments in innovative technologies (Mass Spectrometry and Magnetic Resonance). Most groups in LDRI are participating in interdisciplinary research projects with other UCLouvain Institutes (within the Health Sector, with the Science and Technology Sector such as Institute of Life Science, and Institute of...
Condensed Matter and Nanosciences, as well as with the Human Sciences Sector), or with Universities and industries located in Belgium or abroad.

The LDRI is also a wealthy niche for the education of young researchers. To stimulate continuously the interdisciplinary approach, research seminars are organized weekly and alternate presentations by senior researchers, generally coming from other institutions, and data-club presented by young researchers enrolled in the Doctoral School in Biomedical and Pharmaceutical Sciences. We are also happy to have a continuous influx of doctoral students and post-docs with a large proportion of international scientists.

In addition to training young researchers, the LDRI ensures the continuous dissemination of knowledge to the scientific community, and offers expertise for the authorities of public health and/or pharmaceutical, chemical and biotechnologies industries.

Thanks to our internationally competitive research, our involvement in creating and fostering new knowledge with a direct impact in healthcare, and our ambition to develop efficient partnerships with industry and society, the LDRI activities closely meet the ambition of the League of European Research Universities.

In this report update, a brief overview is presented concerning our objectives and mission statements, research groups, decisions making and management, human resources, funding, and scientific output of the LDRI as a whole.

We hope that this report will enrich the visibility of the Louvain Drug Research Institute. Enjoy the reading!

Nathalie Delzenne,
President of the LDRI

Raphaël Frédérick, Giulio Muccioli and Françoise Van Bambeke,
Vice-Presidents of the LDRI
SECTION I - LDRI GENERAL PRESENTATION

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I. Objectives and mission statements

The general objective of the Louvain Drug Research Institute (LDRI) is to develop and maintain fundamental and/or applied research projects in the field of drugs within the Health Sciences Sector of the Université catholique de Louvain.

The research axes encompass the discovery and the conception of new active molecules, the study of their pharmacological profile, their metabolism and toxicity, their formulation, and the optimization of their use. These research projects are supported by two technological platforms: mass spectrometry analyses and pre-clinical magnetic resonance.

Research Excellence conducted at the Louvain Drug Research Institute must ensure the following:

- Publications in well recognized international journals and/or patents,
- Training of young researchers,
- Dissemination of knowledge to the scientific community,
- Expertise for public authorities health and/or pharmaceutical, chemical and biotechnological industries.

II. Research fields and groups

Overall, research activities are developed around three poles that range from the design of drugs (and the discovery of new targets) to their optimal use through all modern means of evaluation.

- **Design and research of new active molecules pole** includes 2 research groups: Medicinal Chemistry (CMFA; rational based-synthesis of new compounds) and Pharmacognosy (GNOS; extraction and identification of new active principles from plants). These groups work in close collaboration with the research group focused on Bioanalysis and Pharmacology of Bioactive Lipids (BPBL), mainly for optimization of analytical procedures.

- Research focused on **evaluation and characterisation of new targets** are performed by two research groups: (i) TFAR (Translational Research from Experimental and Clinical Pharmacology to Treatment Optimization) that includes FACM, CLIP and PMGK groups. (ii) MNUT (Metabolism and Nutrition; metabolomics and integrative physiology, innovative, therapeutic and nutritional approaches).

- Finally, implementation and clinical evaluation research are covered by work performed by (i) Population Pharmacokinetics and Pharmacometrics (TFAR/PMGK), (ii) Advanced Drug Delivery and Biomaterials (ADDB; use of drug delivery systems and biomaterials as a means to improve therapeutic outcomes of drugs), (iii) Biomedical Magnetic Resonance (REMA; development of innovative tools using magnetic resonance with applications mainly in oncology) and (iv) Clinical Pharmacy (TFAR/CLIP; evaluation of the quality of use in medicine and clinical practice) research groups.
All major aspects of the drug are covered from its design to its use. The approaches use *in vitro* (membranes and cells) and *in vivo* models (small animals). Patient-oriented research is focused on pharmacokinetics and clinical pharmacy.

**III. Decision-making and management**

The LDRI Management Committee is currently composed of a President (Nathalie Delzenne) and three Vice-Presidents (Raphaël Frédérick, Giulio Muccioli and Françoise Van Bambeke) elected by the LDRI Council.

The Board and the Council ensure the proper functioning of the Institute and are responsible for all major decisions concerning the LDRI.

The Board is composed of the President and Vice-Presidents of the Institute and representatives of the temporary scientific (2), administrative and technical staff (2) and academic (2) elected by their peers.

The Council is composed of the permanent scientific and academic LDRI members and representatives of the scientific (3), administrative and technical staff (2). It elects the President and three Vice-Presidents.

An International Scientific Council which has been enlarged to five members provides advices on the research and recruitment strategy. Members until 2016 are C. Hughes (Queen’s University, Belfast), D. Crommelin (Dutch Top Institute Pharma, Leiden; University of Utrecht), J.L. Veuthey (Université de Genève), E. De Clercq (REGA Institute, KUL Leuven) and B. Staels (Université de Lille / Institut Pasteur Lille).
IV. Human Resources

**Total staff** of the LDRI in 2016: 143 persons (109 FTE).

**Academic staff:**
Due mainly to part-time contracts, the 20 Principal Investigators stand for 19.2 FTE. 5 FTE senior researchers are paid by FNRS and are included in the academic staff.

**Scientific staff:**
27 post-doctoral fellows and 79 PhD students, including 23 teaching assistants, are working in LDRI. Part of the other PhD students are cosupervised and some are also affiliated to other institutes or universities.

The technical and administrative staff represents 32 people corresponding to around 20 FTE.

**Staff of the LDRI in 2016**

The LDRI staff creates an international environment: 50% of the PhD students and 63% of the post-doctoral fellows are coming from abroad.

The main sources of staff funding are UCL (37%), FNRS (32%), the Belgian regions (16%) and the European Union (9%). The FNRS pays the salary of 5 permanent principal investigators, 11 postdoctoral researchers, and 25 PhD students (including FRIA - Fund for Research Training in Industry and Agriculture - and Televie doctoral grants). 23 teaching assistants are funded by UCL. They spend 50% of their time for research.

Sources of funding of LDRI staff in 2016

*Competitive grants from UCL,
FSR : « Fonds Spéciaux de recherche »
ARC : Actions de Recherche Concertées
Coop : Cooperation
FNRS: National Fund for scientific Research

The background of the scientists is also diversified reflecting the multidisciplinary research. Among the PhD students, pharmacists, bioengineers, engineers, chemists, biologists, physicists, MD or masters in biomedical sciences, are affiliated in the LDRI for their PhD theses.
V. Fundings

The annual turnover of the LDRI is around 9.62 millions € (8.15 M€ in 2015). (To be noted: the annual turnover includes equipment; NMR was attributed to the NEST platform)

The members of LDRI are very active in obtaining financial incomes from third parties. The external resources increased progressively from 2.49M€ in 2006 to 7.4M€ in 2016. The percentage of the total budget from third parties represents 77% of the total budget.


The funding of LDRI, provided by the regular budget of UCL, mainly covers the salaries: 2.3M€ for the FTE affiliated to LDRI (37% of the staff budget).
VI. Scientific Output

The scientific output of LDRI is mainly estimated from publications in well recognised international journals and by the training of young researchers. Dissemination of knowledge to the scientific community as well as expertise for Public Health Authorities and/or pharmaceutical, chemical, and biotechnological companies and/or research agencies are not illustrated in an exhaustive way in the present report, even though most of the academics are active in these domains.

Publications

Altogether, all the research groups of the LDRI published 552 scientific articles in international journals or book chapters during the last four years (2012-2016). 8% of these publications (n=35) associated at least two groups belonging to the LDRI.

The mean Impact Factor (IF) of the publications during the period 2009-2016 is 4.4 (including review papers and educational papers). The mean IF for original papers is 4.9. 82% of the publications of the LDRI were published in journals with an IF ≥ 2 and 44% in journals with an IF ≥ 4 (between 2009 and 2016). The distribution of publications per impact factor is shown hereafter.

Over the last 15 years, there was an increase in the number of publications as well as in the quality of these papers, as demonstrated by the global increase in the impact factor of the journals where we publish.
Training in research

79 PhD students are presently (January 2017) supervised by the PI of the LDRI. All of them are enrolled in the doctoral school of biomedical and pharmaceutical sciences (orientation: Pharmaceutical Sciences), and 7 PhD theses are in progress under our supervision in other fields (chemistry, engineering, or co-tutorship with foreign universities). 55 PhD theses supervised by the LDRI Research Groups were defended during the period 2012-2016.

In addition to doctoral formation, all principal investigators of research groups are promoters of Master Degree theses in Biomedical Sciences, Pharmacy, Biology… and of Bachelor’s degree dissertations (technicians…).

Seminars-Symposia

The LDRI seminars are attended by researchers or other professionals having an interest for scientific areas related to drugs in a broad context (from basic sciences to clinical applications). They alternate presentations by junior scientists from the Institute and by senior scientists (from the Institute, from other Institutes within the University, from other Universities in Belgium or abroad, from the Industry).

Expertise

All principal investigators of research groups are recognised for their expertises by the Authorities of Public Health and/or pharmaceutical, chemical and biotechnological industries, and/or research agencies. They participate as (co) leaders or members of:
- Superior Health Council (Belgium), Belgium Nutrition Society (Belgium)
- Royal Academy of Medicine (3 members)
- European Medecine Agency (EMA)
- Public Health Institute
- Federal Agency for Medecine and Health products
- Federal Agency for Nuclear Control
- Advisory Board related to preclinical or clinical development of new antibiotics
- French National Research Agencies (ANR and HCERES)
- Fonds Wetenschappelijk Onderzoek (FWO) (The list is illustrative rather than exhaustive).

Collaborative projects with industries

Many collaborative projects are ongoing both with industries (GlaxoSmithkline Biologicals, Astra Zeneca, Danone, Cargill) and SME (Melinta Therapeutics, Debiopharm, Thrombogenics, Voco gmbh, Saremco, Heraeus-Kulzer, Coltene, Septodont, Kuraray, Biocodex, Pileje, Normoxys…).

Key Awards 2016

Laure Bindels: Prix Maurice Godin-Maria Savelkoul (Académie Royale de Médecine de Belgique). Amount: 3 000€

Nathalie Delzenne and Patrice Cani: International Prize « Fondation de Physiopathologie Pr. Lucien Dautrebande ». Amount: 50 000€

Bénédicte Jordan: Prix Maes (Health Sciences Sector / UCL). Amount: 10 000€

Raphaël Frédérick: Fond Maisin 2016. Amount: 20 000€

Highly cited researcher 2016: Patrice Cani, Fabienne Danhier, Nathalie Delzenne and Véronique Préat.
PLENARY LECTURES by EXTERNAL SPEAKERS 2016

Prof. Mireille DEMOULIN  
Centre for Protein Engineering, Ulg  
Mechanism of aggregation of polyglutamine proteins that are associated with neurodegenerative amyloidoses

Prof. William COUET  
Inserm U-1070 Pharmacologie des Anti-Infectieux, Université de Poitiers, France  
Biopharmaceutical classification of anti-microbial agents

Prof. Christian GISKE  
Karolinska Institutet, Infectious Diseases Unit, Stockholm, Sweden  
Next-generation sequencing for tracking of epidemic clones of extensively drug-resistant Escherichia coli and Klebsiella pneumonias

Prof. Koen AUGUSTYNS  
Antwerpen University  
Activity-based probes to image proteolytic activity in oncology

Prof. Paul MICHELS  
Centre for Immunity, Infection and Evolution (CIEE) and Centre for Translational and Chemical Biology (CTCB), School of Biological Sciences, University of Edinburgh, Scotland  
Drug discovery for neglected tropical diseases caused by trypanosomatids; development of selective phosphofructokinase inhibitors with anti-parasite activity

Prof. Kristin VERBEKE  
Translational Research in GastroIntestinal Disorders, KULeuven  
Short Chain Fatty Acids as mediators between the diet, the microbiota and the host

Dr Pascal GERVOIS  
Biomedical Research Institute, Hasselt University  
Neuroregeneration with human dental stem cells

Prof. Bruno FLAMION  
University of Namur  
Medicine Adaptive Pathways to Patients (MAPPs): a European innovative approach to bring new drugs to patients

Prof. Barbara CLAUS  
Pharmacy Department, UZGent  
Clinical and economic value of in-hospital clinical pharmacy activities: where are we, anno 2016, in Belgium?
TECHNOLOGY PLATFORMS

I) MASSMET PLATFORM

The MASSMET platform is an analytical platform applying mass spectrometry analysis to small metabolites and to compounds of biological or pharmaceutical interest. It provides a support in analytical chemistry mainly through the development of chromatographic methods coupled to mass spectrometry detection, with a particular focus on the detection, identification and quantification of “small molecules” in complex matrices. As such, the expertise provided by the platform is important for numerous labs within the LDRI and the “Health Sector”, as well as for labs of the “Sciences and Technology Sector”.

To this aim, we share the use of several analytical equipments located both in Brussels (mainly at the LDRI) and at Louvain-la-Neuve (mainly at the ISV). These equipments include (but are not limited to):

- ThermoScientific LTQ – ORBITRAP –XL high resolution mass spectrometer (shown on the right)
- ThermoScientific Trace GC-MS
- Thermoscientific LCQ Advantage mass spectrometer
- ThermoScientific DSQ GC mass spectrometer
- Several chromatographic systems (HPLC, UPLC, GC) using UV, DAD, or FID detectors are also available.

The interest and importance of the expertise of the MASSMET platform is shown by the numerous publications that benefited from the data obtained using the equipment and/or expertise of the platform. Examples of such studies involving LDRI research groups include the quantification of antibiotics from cell cultures (T FAR-FACM), the quantification of transcellular transport (ADDB), the quantification of endogenous metabolites from microorganisms, cells, tissues (BPBL – MNUT – TFAR-FACM), the identification of metabolites from plants (GNOS), the quantification of endogenous and exogenous metabolites in plasma (BPBL – ADDB – GNOS) and the determination of the nature and purity of compounds of synthetic origin (CMFA). An exhaustive list of collaborations (within and outside the LDRI) and publications is available on the platform website (https://uclouvain.be/en/research-institutes/ldri/massmet.html).
II) NUCLEAR & ELECTRONIC SPIN TECHNOLOGIES (NEST) PLATFORM

The NEST platform accommodates cutting-edge MR technologies (Magnetic Resonance Imaging or MRI, High resolution NMR spectroscopy, Electron Paramagnetic Resonance or EPR, and Dynamic Nuclear Polarization or DNP) dedicated to studies on biological samples and on small animals. These technologies provide convenient biomarkers for monitoring (patho) physiological parameters and the response to pharmacological treatments. The platform provides a support and expertise in the application of magnetic resonance (MRI, MRS, EPR) in pharmaceutical and biomedical sciences.

Equipments

**Magnetic Resonance Imaging**

Horizontal High-Field NMR System (Bruker Biospec 11.7/16) operating at 11.7 Tesla for MRI and MRS on small animals (bore diameter of 16 cm).

This system is equipped with:
- $^1$H-NMR:
  - cryoprobe
  - whole body coil (mouse, rat)
  - phase-array coil (4 channels, heart studies)
  - $^1$H-$^{13}$C surface coil
- $^1$H-$^3$P surface coil
- $^1$H-$^{17}$O surface coil
- $^1$H-$^{19}$F surface coil

**High Resolution NMR Spectroscopy**

- 600 MHz NMR spectrometer (Bruker Avance III HD 600)
- Broadband BBO cryoprobe head (multi nuclei)
- Automated sample changer (24 samples, storage at 4 to 40°C)
- 4 mm HRMAS dual inverse probe 1H/13C
- TopSpin for 1D/2D/3D data processing
- AMIX license for exploration of NMR data
- Metabolite database BBIOREFCODE (pH 3-8) for metabolites in body fluids
**Dynamic Nuclear Polarization**

- Hypersense system able to hyperpolarize $^{13}$C-enriched substrates for in vivo monitoring of metabolic fluxes:
  - fumarate/malate
  - pyruvate/lactate

This system is used in combination with the MRI system for detections of the metabolites using $^{13}$C-MRS coils.

**Electron Paramagnetic Resonance**

- *Preclinical EPR*:
  - EPR Spectrometer 9 GHz (Bruker EMX) for in vitro studies
  - EPR Spectrometer 9 GHz (Magnetech Miniscope MS200) for in vitro studies
  - EPR Spectrometer 1 GHz for in vivo studies Magnetech
  - EPR imaging and spectroscopy 1 GHz / 9 GHz (Bruker Elekysys) for in vitro and in vivo studies

- *Clinical EPR*:
  - Clin-FPR Spectrometer 1 GHz
  - 2nd system worldwide
  - Human superficial tissue oxygenation measurements (diabetic foot, head & neck tumors, )
Support to research activities

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<tr>
<th>NMR and MRI</th>
<th>EPR spectroscopy and imaging</th>
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<tr>
<td>• Metabolism (NMR spectroscopy)</td>
<td>• Free radicals measurements</td>
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<td>• Metabolomics</td>
<td>• Free radicals characterization by spin trapping</td>
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<td>• In vivo anatomical structures</td>
<td>• Quantification of melanin / melanoma cells in tissues</td>
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<td>• Vessels architecture (micro-angiography)</td>
<td>• Molecular dynamics, microviscosity, micropolarity in tissues</td>
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<td>• Tissue perfusion (by Dynamic Contrast Enhanced MRI, DCE-MRI)</td>
<td>• Dosimetry (retrospective dosimetry in bones and teeth, dosimetry in phantoms)</td>
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<td>• Oxygen and pH measurements</td>
<td>• Tissue oxygenation and Oxygen consumption</td>
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<td>• Oxygen consumption</td>
<td>• Redox status, pH</td>
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<td>• Heart physiology (ventricle function)</td>
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<td>• Cell death (Microscopic water diffusion)</td>
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<td>• MRI-based cell tracking</td>
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<td>• Assessment of drug delivery</td>
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The utility and importance of the expertise of the Pre-clinical MR platform is testified by the numerous publications that benefited from the data obtained using the equipment and expertise of the platform. Illustrative examples involving LDRI or Health Sector research groups include the characterization of new drug delivery systems (ADDB/LDRI), characterization of spinal cord regeneration (ADDB/LDRI), identification of free radicals involved in toxicological processes (MNUT, LDRI/MORF,IREC), characterization of the tumor microenvironment (REMA/LDRI), characterization of dental resins (ADDB/LDRI), characterization of angiogenic process and tumor metabolism (FATH/IREC), identification of early markers of response to targeted therapies (MIRO/IREC), oxygenation of pancreas islets grafts (CHEX/IREC), ovarian grafts (GYNE/IREC), endometrium grafts (CELL/DDUV), cardiac function (FATH, CARD/IREC), validation of PET tracers (MIRO/IREC).


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