

# Assessment of Research Quality

**Leiden Academic Centre for Drug Research (LACDR)**

**2009-2015**

**Final report – January 2017**

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## 1. Introduction

### 1.1 Background

This report describes the assessment of the quality and relevance of research conducted at the Leiden Academic Centre for Drug Research (LACDR) in the period 2009-2015 and suggests improvements to these where necessary. LACDR is one of the eight research institutes of the Faculty of Science at Leiden University, the Netherlands. The assessment was performed by an external assessment committee using the Standard Evaluation Protocol (SEP) 2015-2021.<sup>1</sup> SEP assessments focus on the strategic choices and future prospects of research groups.

Target groups that are served by this assessment include:

- **LACDR's researchers and group leaders** need to know how the quality of LACDR research, its societal relevance, and its strategy are perceived by independent experts and how these elements can be improved.
- **The Board of the University of Leiden** wishes to track the impact of its research policy.
- **The Dutch government** wants to know the outcomes of assessments in connection with the institution's accountability for expenditure and its own efforts to support an outstanding research system.
- **Society and the private sector** seek to solve a variety of problems using the knowledge that LACDR research delivers.

### 1.2 Members of the assessment committee

The board of Leiden University has appointed as members of the assessment committee

- Professor H.A.J. Struijker-Boudier, *chair* (Maastricht University, the Netherlands),
- Professor A.R. Boobis (Imperial College London, UK),
- Professor S. Frøkjær (University of Copenhagen, Denmark),
- Professor D. Kell (University of Manchester, UK),
- Dr C. Perros-Huguet (Alexion Pharmaceuticals, USA).

Dr Linda van den Berg (Washoe Life Science Communications) served as the secretary to the assessment committee. Short CVs of the committee members are provided in Appendix 1. This report represents the consensus view of the committee.

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<sup>1</sup> The SEP was drawn up and adopted by the Association of Universities in the Netherlands (VSNU), the Netherlands Organisation for Scientific Research (NWO), and the Royal Netherlands Academy of Arts and Sciences (KNAW). All research conducted at Dutch universities, university medical centres, and NWO or KNAW institutes is assessed once every six years in accordance with the SEP.

### 1.3 Procedures followed

The assessment committee evaluated LACDR research based on LACDR's self-assessment and interviews with LACDR representatives during a site visit in November 2016. The previous LACDR assessment report (2002-2008) was also provided as reference material. The site visit programme is listed in Appendix 2. The committee took into account international trends and developments in science and society as it formed its judgement. In addition, the committee bore in mind LACDR's strategy in formulating its recommendations.

#### *Qualitative and quantitative assessment of LACDR research*

The assessment committee made a qualitative judgement of LACDR and its three research clusters based on three assessment criteria:

1. *research quality*, i.e., contribution to scientific knowledge, scale of research results (scientific publications, instruments, and infrastructure produced and other contributions to science);
2. *relevance to society*, i.e., quality, scale, and relevance of contributions (advisory reports for policy, contributions to public debates, etc.) targeting groups that LACDR has itself designated as target groups (patients, the general public, students, and industry);
3. *viability*, i.e., the strategy that LACDR intends to pursue in the future and the extent to which it can meet its targets in research and society during this period, the governance and leadership skills of LACDR's management.

For LACDR as a whole, the qualitative assessments were supplemented by numerical scores (1–4) for each of the three criteria.

#### *Assessment of LACDR's PhD programme*

The assessment committee also considered the supervision and instruction of PhD candidates at LACDR. During the site visit, the committee interviewed six PhD students, who were in varying stages of the PhD track. The committee assumed that these individuals provided opinions that are representative of the group at large. The following topics were considered:

- institutional context of the PhD programme,
- programme content and structure,
- supervision and the effectiveness of programme plans and supervision plans,
- quality assurance,
- guidance of PhD candidates to the job market,
- duration, success rate, and exit numbers, and career prospects.

#### *Assessment of the LACDR research integrity policy*

The committee also considered LACDR's policy on research integrity and the way in which violations of such integrity are prevented. This was discussed during the site visit. The committee was interested in how LACDR deals with research data, data management and integrity, and the extent to which a critical pursuit of science occurs at LACDR.

#### **1.4 Research unit under assessment: Leiden Academic Centre for Drug Research**

The Leiden Academic Centre for Drug Research (LACDR) is a centre of excellence for multidisciplinary drug research. LACDR's mission is to be at the frontline of the development of novel concepts and approaches in research for the discovery and optimisation of drugs and personalised medicines. This should lead to safe and effective pharmaceutical treatments. In addition, the centre trains and educates scientists who can further this aim. In 2016, LACDR moved into a new, state-of-the-art research building, which was designed to stimulate interaction between scientists and sharing of facilities and infrastructure.

In 2015, LACDR employed 122 researchers (69 PhD students, 31 post-docs, and 22 senior staff members) and 48 support staff members (see Table 1 in Appendix 3 for further details). Professor Hubertus Irth was appointed as the Scientific Director of LACDR from September 2016; his predecessors are Professor Piet Hein van der Graaf (2013-2016) and Professor Meindert Danhof (2009-2012). Direct funding (46%) and external funding (54%) are balanced at LACDR and the centre has been very successful in obtaining European funding (FP7/H2020 and IMI). The current ratio in research and education income is almost 50:50. However, the proportion of education income is increasing because of the increase in student enrolment since 2012. (LACDR is responsible for the Biopharmaceutical Sciences Bachelor and Master programmes at Leiden University.) Further details about LACDR's financing are provided in Table 2 of Appendix 3.

LACDR is one of the eight research institutes of the Faculty of Science at Leiden University and LACDR researchers collaborate with the other institutes (e.g., in the fields of chemistry, biology, informatics, and mathematics). In addition, LACDR is located at Leiden Bioscience Park, with Leiden University Medical Centre and the Centre for Human Drug Research, both strong partners for translational drug research, in close proximity. LACDR is active in a large national and international network of academic institutes, biotech and pharma companies.

## 2. Assessment of LACDR research

### 2.1 LACDR's strategy and targets

LACDR's mission is to develop innovative concepts in drug research that facilitate the development of safe and effective pharmaceutical treatments. It was the initial impression of the review committee that LACDR wants to position itself as an institute that covers the process of both drug discovery and clinical development. This would be a strategy similar to that of pharmaceutical companies.

However, during the site visit it became clear that the primary strategic goal of LACDR is the development of **novel concepts and technologies underlying and enabling drug discovery and development**. In addition, the centre trains and educates scientists who can further this aim. LACDR has so far focused on specific disease areas (mainly cardiovascular diseases, central nervous system disorders, and cancer), but the concepts can be applied more widely.

LACDR ended its collaboration with VU University Amsterdam in 2011, shifting to collaboration with local medical centres. To bring more focus to its research and to deal with a reduction in direct funding, LACDR reorganised its research, resulting in the formation of three clusters in 2012:

1. Systems Pharmacology (former divisions Pharmacology and Analytical Biosciences)
2. Bio-therapeutics (former divisions Biopharmaceutics and Drug Delivery technology)
3. Drug & Target Discovery (former divisions Toxicology and Medicinal Chemistry)

These clusters were formed based on scientific excellence and long-term critical mass. Important characteristics of LACDR research are the focus on personalised medicine, the translational nature of the research, and the use of state-of-the-art technology and computational approaches. LACDR has invested in high-end research infrastructure such as the BioMedical Metabolomics Facility Leiden and the Cell Observatory High Throughput Microscopy Screening Facility to ensure its strategic position in national and international collaborations.

LACDR has forged many strategic partnerships to fulfil its mission and to strengthen the translational nature of its research. Within the Faculty of Science of Leiden University, LACDR scientists collaborate with the Leiden Institute of Chemistry, Leiden Institute of Physics, Institute of Biology, Leiden Institute of Advanced Computer Science, and Mathematics Institute. LACDR also collaborates intensively with Leiden University Medical Centre (LUMC) and the Centre for Human Drug Research (CHDR, Leiden). Examples of national collaborations are projects with the Medical Delta partners, the Netherlands Cancer Institute, Intravacc, and the Dutch Medicines Evaluation Board. International partners include LERU, ULLA, Duke Medical Centre, the Mayo Clinic, the NIH pharmacometabolomics network, and the Sino-Dutch Centre for Personalised and Preventive Medicine.

## 2.2 Assessment Leiden Academic Centre for Drug Research as a whole

### *Research quality*

The committee rates LACDR's overall research quality as **excellent**. LACDR ranks among the best academic pharmaceutical science groups in the world and is highly respected in the field. The centre has published many high-impact papers over the last six years. LACDR is true to its mission to perform research to facilitate pharmaceutical drug development, which is illustrated by the large number of translatable results that LACDR has made available for other parties to be taken further (e.g., novel drug targets for metastatic triple negative breast cancer, the structure of an adenosine receptor that plays a critical role in important physiological processes, a PK model of paracetamol in zebrafish which demonstrates the potential of zebrafish larvae for translational drug screening, the role of the lipid transporter SR-B1 in cholesterol and hormone metabolism, the preclinical development of a universal influenza vaccine, and metabolic biomarkers for the onset of Alzheimer's disease).

In addition, LACDR has developed several advanced technological facilities, most notably the BioMedical Metabolomics Facility Leiden and High Throughput Microscopy Screening Facility. These facilities support LACDR's own outstanding research, but they are also available for academic and industrial collaborators, thus further contributing to the advancement of science within and beyond its own walls. The facilities are embedded in national and European infrastructure organisations such as the Dutch Techcentre for Life Sciences (DTL) and EuroBioimaging. LACDR also invests in making software tools, computational models, and data sets available to peers.

The committee recognises that LACDR has gone through a major transition (i.e., the reorganisation in 2011, followed by the formation of three novel clusters in 2012). However, a phoenix seems to have emerged from the ashes of this reorganisation: LACDR has managed to adapt to recent developments in biomedical and pharmaceutical science. LACDR currently is a very modern institute that uses advanced technologies and computational approaches that lie at the basis of drug discovery and development.

### *Relevance to society*

LACDR's research is **highly relevant** to society. The research aims to find ways to treat or cure people whose lives are impacted by health problems. LACDR collaborates closely with pharmaceutical companies, biotechnology companies, and clinics to ensure that its results have the greatest opportunity of being translated into novel treatments. LURIS (the joint knowledge exchange office of Leiden University and LUMC) assists researchers in bringing their discoveries to the market. The committee did notice that, although LACDR has made substantial progress in translational medicine, it seems to have a rather reactive role in collaborations with medical research groups. We will provide recommendations on how this issue might be addressed in Chapter 4.

In the context of relevance to society, it is appropriate to mention here that 'personalised medicine' has been selected as an important research theme by the general Dutch public in the 'Dutch National

Research Agenda' project<sup>2</sup>. Personalised medicine is a major focus of LACDR and it is the committee's impression that LACDR is well-positioned to play a leading role in the Personalised Medicine Exemplary Route of the Dutch National Research Agenda. Examples of this would be the application of platform technologies to identify biomarkers and the pharmacokinetic and pharmacodynamic modelling of existing medicines (e.g., paracetamol or morphine) to recommend more adequate dosage for young infants and obese patients. In addition, LACDR may contribute to the routes 'regenerative medicine', 'prevention', and 'analysis' (i.e., analytic chemistry).

### *Viability*

Overall, LACDR has many assets and the committee therefore rates its viability as **very good**. The centre has been highly successful in obtaining funding from organisations such as TI Pharma, the EU, NWO, the Dutch Heart Foundation, and the Dutch Cancer Society. The committee praises the strong leadership of LACDR's cluster heads. In addition, the committee would like to give credit to the Scientific Director Hubertus Irth, who has managed to make substantial progress in a short period of time. (He was appointed as the Scientific Director of LACDR on 1 September 2016.)

The committee was impressed by the high productivity of LACDR, i.e., amount of high-quality work it has performed with a small number of staff members. At the same time, this situation gives rise to concerns, as will be outlined below. LACDR's Bachelor's programme in biopharmaceutical sciences has been extremely popular in the last few years, with currently about 300 new students enrolling per year. Although this gives rise to practical problems (i.e., a high teaching load, see below), the students are a great asset to the centre, both as a source of talented young professionals and as a source of financial revenue. LACDR's high-end technological equipment and the associated expertise are a very strong feature, which can attract top scientists.

However, the committee has also identified potential threats to the long-term sustainability of LACDR. Several of these relate to personnel planning:

- The immense workload of LACDR researchers creates an unsustainable situation. This applies to principal investigators as well as postdocs and PhD students and is largely the result of the extremely high teaching load.
- The clusters are vulnerable because they are led by a small number of senior researchers, some of whom are approaching retirement. In addition, there does not seem to be a clear succession plan in place for senior scientists, painfully illustrated by two critical open positions in the cluster Systems Pharmacology at the time of the site visit.

The committee also has concerns about the centre's technological infrastructure. As mentioned above, LACDR's equipment and the associated expertise are a great asset. However,

- the maintenance of this equipment and keeping it up to date is very expensive;

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<sup>2</sup> In 2015, all Dutch citizens could submit their questions to science on the website 'wetenschapsagenda.nl'. These questions have been clustered in themes. The resulting agenda was launched in November 2015. In the short and medium term, the Dutch National Research Agenda will be translated into the profiles of universities and universities of applied sciences, the programming of the knowledge coalition's partners, the direction in which the national research institutes develop, and into investments in large-scale research facilities.

- LACDR seems to lack a proper IT infrastructure and support staff to facilitate the data-intensive research associated with these technologies.

The committee will provide recommendations on how to deal with these concerns in Chapter 4.

#### *Summary in numerical scores*

In line with the qualitative judgements of LACDR research described above, the committee has assigned LACDR to a discrete category for each of the assessment criteria. The four possible categories are excellent (=1), very good (=2), good (=3), and unsatisfactory (=4); the scores are explained in more detail in Appendix 4.

	<b>Research quality</b>	<b>Relevance to society</b>	<b>Viability</b>
<b>LACDR as a whole</b>	1	1	2

### **2.3 Assessment Systems Pharmacology cluster**

The cluster Systems Pharmacology combines the former divisions of Pharmacology (Professor van der Graaf and Professor Knibbe (both extraordinary) and Professor Danhof) and Analytical Biosciences (Professor Hankemeier and Professor van der Greef). The cluster's focus is on personalised medicine and translational systems pharmacology. They aim to obtain a systems-level understanding of disease progression and drug response, which may be used to develop personalised treatments. To this end, the group collects data (especially metabolomics data) from patients, patient-derived *in vitro* models, and *in vivo* murine models, and uses these data for systems pharmacology modelling, mainly under the physiologically based pharmacokinetic (PBPK) formalism. For instance, they have used metabolomics to discover biomarkers that can predict a patient's response to aspirin as an antiplatelet therapy.

#### *Research quality and relevance to society*

The committee is impressed by the research quality of the Systems Pharmacology cluster. The group nicely integrates novel bioanalytical and computational approaches, has published many biomarker papers, understands the statistical issues that bedevil the field, and is among a small group of world-leading laboratories in the field of metabolomics. The BioMedical Metabolomics Facility Leiden is of high value and the committee applauds the plans for collaboration within the Dutch X-omics consortium. Another asset of this cluster (and here it is unique in the group of top metabolomics centres) is the organ-on-a-chip system that was designed by LACDR researchers and is now further developed in a spin-off company. Although similar systems have been developed by other research groups in the world, the LACDR system is unique in that it is high-throughput and thus more amenable to support drug discovery. The committee recognises that the system could be pushed forward by extending to other organs. For example, building on LACDR's expertise in central nervous system, a blood brain barrier system could be of value in both drug discovery and toxicology assessment.

Given its focus on personalised and translational pharmacology, this cluster's research is highly relevant to society. For instance, they developed a new model-derived dosing regimen for morphine in neonates, which has resulted in significantly lower doses administered in the clinic. In addition, the group has organised workshops for clinical pharmacologists on an improved dosing regimen in extreme populations such as neonates and morbidly obese patients. The close involvement of clinicians was instrumental here, and can usefully be expanded.

### *Viability*

In spite of the very positive impression, the committee also identified potential threats to the long-term sustainability of this cluster. Many of these were already discussed in the context of LACDR as a whole in paragraph 2.2 of this report, but we will briefly summarize them here:

- A major concern is the fact that there were two critical vacancies for senior staff members in this cluster at the time of the site visit. This issue should be resolved a.s.a.p.
- The cluster is strongly technology-driven at the moment. A more problem-driven approach may be necessary in the future (i.e., which kinds of diseases one would focus on as exemplars of the power of the technology). In addition, more focus on valorisation may be warranted.
- The excellent research of this cluster strongly relies on the high-end equipment that is present at LACDR. It is recognised as a challenge to keep such expensive equipment up-to-date, but it is also recognised that the group has excellent relationships with all the major manufacturers, which can help considerably in terms of good deals, etc.
- IT facilities and staff to support the cluster's data-intensive research seem to be the Achilles' heel and it is only going to get much worse. The latest SWATH proteomics technologies produce data files of 75Gbytes when translated to mzXML, and dealing with these requires plenty of specialist infrastructure and specialist expertise. The committee advises LACDR as a whole to find a solution for this problem.
- Although the cluster has multiple collaborations with clinical research groups, the cluster seems to have a rather reactive role in a number of these projects.

The committee will provide recommendations on how to deal with these concerns in Chapter 4.

## **2.4 Assessment Bio-therapeutics cluster**

The cluster Bio-therapeutics consists of the former divisions Biopharmaceutics (Professor Kuiper and Professor van Eck) and Drug Delivery Technology (Professor Bouwstra and Professor Jiskoot). The merge of the two divisions seems to be a success. The cluster develops innovative biopharmaceutical concepts to intervene in immune-based disorders. They aim to identify druggable targets in immune-driven diseases such as atherosclerosis, which may be selectively manipulated with biologics such as vaccines and therapeutic proteins (monoclonal antibodies). To identify new targets, they apply systems immunology and immune-metabolic methods. In addition, they design novel techniques and routes to deliver drugs, and aim to specifically target the disease site in order to maximise the therapeutic effect while minimising undesired side-effects.

### *Research quality and relevance to society*

The committee considers this cluster's research as state-of-the-art. For instance, the work on vaccination through transdermal drug delivery (i.e., microneedles) and the work on vaccines to treat

atherosclerosis are very impressive. The research is highly relevant to society as the group has developed several promising concepts to intervene in immune-based diseases, as well as innovative drug delivery methods. For instance, the group has designed novel formulations to treat patients with inflammatory skin disease, which are currently being tested in clinical studies in collaboration with LUMC. The activities related to protein stability and immunogenicity are another example of research which is highly recognised internationally.

#### *Viability*

The committee was positively surprised to see how well the merger of the two divisions has progressed. There is substantial complementarity within the two legacy groups, thus the world-class work on drug delivery has been further secured in the newly established cluster supported by the shift to vaccination. The focus on vaccination is an appropriate change of direction in face of the developments in the field. LACDR's new animal research facility, which is coordinated by the cluster BioTherapeutics, features up-to-date surgery facilities and non-invasive whole animal bioluminescence imaging equipment, supporting the centre's animal studies. However, the concerns that were expressed in paragraph 2.2 with respect to LACDR as a whole also apply to this cluster, in particular the small number of principal investigators leading the cluster and the critical dependence on Professor Bouwstra for expertise in transdermal delivery.

### **2.5 Assessment Drug & Target discovery cluster**

The cluster Drug & Target Discovery combines the former divisions of Toxicology (Professor van de Water) and Medicinal Chemistry (Professor IJzerman). The cluster's focus is on imaging-based phenotypic screening to identify drug targets and lead compounds. The group uses quantitative systems biology modelling and mechanistic toxicology-based quantitative imaging to predict the efficacy and safety of drugs, the focus on efficacy being on cancer metastasis and therapy resistance. They complement this work with pharmacology studies of drug-target interaction (target affinity, target specificity, residence time, and kinetics of the interaction), for instance using cheminformatics approaches and structural biology. Bioinformatics approaches to novel drug targets are leveraged to account for population variation at the protein level.

#### *Research quality and relevance to society*

The committee regards this cluster as a very strong group, with scientifically active principal investigators that are all world leaders. The group's cell observatory work on liver is particularly outstanding and it could easily be extended to other organs such as the kidney, neuronal and cardiovascular systems. The High Throughput Microscopy Screening Facility is a valuable research infrastructure that is also offered to researchers outside LACDR. The translational impact of the work is large. Examples of highlights are the identification of novel drug targets for metastatic triple negative breast cancer, determination of how certain G-protein coupled receptors function, development of novel models to study liver injury, and the identification of a novel kinase (SYK) as a potential drug target in some forms of metastatic cancer such as prostate.

#### *Viability*

Again, the committee has some concerns, most of which were already discussed in paragraph 2.2:

- The committee felt slightly confused by the cluster's name, which might give the impression that the group functions as a drug discovery unit. The name does not honour the group's excellent work. The committee would suggest a name change, for instance into 'Combinatorial and phenotypic pharmacology'.
- The group is very strong in each of the six components (cancer drug target discovery, computational & chemical biology, GPCR ligands, novel receptor concepts, drug safety, and computational biology) but the components seem a series of interlocking projects rather than a truly integrated pipeline. Further integration of the projects will improve the research quality. In addition, the committee thinks the cluster would benefit from more focus.
- The cluster has been particularly successful in grant applications recently. Without additional staff, the number of new projects, together with the high number of students, could well lead to the group leaders becoming over-stretched. This needs to be considered in forward planning by the cluster.
- As with the Systems Pharmacology cluster, this group would benefit from more IT support, for instance a scientific programmer.

### 3. Assessment of PhD programme and research integrity policy

#### 3.1 Quality and organisation of LACDR's PhD programme

Training the next generation of pharmaceutical scientists clearly is an important component of LACDR's mission. Overall, the committee is impressed by the **high quality** of LACDR's PhD programme. The six PhD students that were interviewed during the site visit were extremely positive about the PhD programme. They mentioned the good atmosphere at LACDR, with people collaborating rather than competing with each other and being open to criticism. In addition, access to scientific papers, high-end equipment and expertise does not seem to be a limitation. The committee also values the close ties with the education activities of the European University Consortium for Pharmaceutical Sciences (ULLA).

The committee has one major concern: the immense teaching load. The PhD candidates expressed this problem in a survey conducted by LACDR and during the site visit. LACDR's PhD candidates are intensively involved in teaching and supervising students of the biopharmaceutical sciences Bachelor and Master programmes. This requires an average contribution of 8 weeks per academic year, in some cases extending to 12 weeks. The committee is concerned that this may decrease the PhD candidates' competitiveness with peers at other institutes that do not have such heavy teaching responsibilities. We will elaborate on how to deal with this issue in Chapter 4.

##### *Institutional context of the PhD programme*

The committee learned that in 2015, LACDR hosted 69 PhD candidates, who were formally embedded in the graduate school of the Faculty of Science of Leiden University. The graduate school handles the registration of all PhD students, as well as the administrative procedures preceding the approval of the manuscript and the public defence of the thesis.

##### *Quality assurance and supervision*

The committee felt that the supervision of PhD students at LACDR is well-structured. LACDR has established a PhD Education & Supervision Programme in addition to the graduate school of the Faculty of Science. Starting with the cohort of 2013, all PhD students are officially enrolled in this programme. As part of the programme, individual guidance is offered by a PhD Advisory Committee, which typically consists of the Scientific Director of LACDR, the promotor(s), co-promotor(s), and an external advisor. The PhD candidate meets with this committee on at least four occasions during the four-year PhD track (at 2 months, 9 months, 2 years, and 3 years into the programme).

The plans for education and training of each PhD student are summarised in an individual Education and Supervision Plan, which is devised by the PhD student in close collaboration with the supervisor. The plan is used to monitor the student's progress in research (progress, presentations, publications), education (mandatory courses of the graduate school and the LACDR Education & Supervision Programme, elective courses), and teaching (classroom teaching, lab courses in the BSc and MSc programme Biopharmaceutical Sciences).

The interviewed students indicated that they met with their supervisors weekly or biweekly. In case of problems or conflicts, PhD students can turn to their designated mentor, who is from another division or a university confident. There is also a course 'How to manage your professor'. Rules for authorship are usually discussed at the start of a research project.

#### *Programme content and structure*

LACDR has a 10 ECTS points training plan, which consists of a LACDR introductory course, several mandatory courses in personal skills, and optional courses dedicated to specific professional skills. The mandatory courses are organised by the graduate school of the Faculty of Science and focus on personal and professional skills such as presentation skills, time management, data management, teaching & supervision, and writing science press releases. The optional courses are organised by LACDR or other institutes, for instance a CSC introduction programme, an Advanced Drug Delivery & Drug Targeting course, the ULLA summer school, the ULLA workshop, and computational courses such as the basics of programming in R.

LACDR also strongly supports and facilitates temporary placement of its PhD student in international academic labs during their training, for example six months' secondment in UK or US university labs were highlighted by the students.

The interviewed students also indicated that many students actually follow additional courses on top of the 10 ECTS requirement. In addition to the courses, there are biyearly LACDR symposiums and monthly cluster meetings. Some of the divisions have journal clubs. The students are also encouraged to present their work at international conferences.

#### *Success rate, duration, and exit numbers*

The Faculty of Science strives for a successful PhD thesis defence within six years. In the past years, the percentage of successful defences within six years has increased from 50% (for students that enrolled in 2006) to 77% (for those that enrolled in 2009). LACDR aims to bring this up to 80%.

#### *Guidance of PhD candidates to the job market and career prospects*

Most LACDR PhD candidates are successful in finding a job soon after completing their PhD. The majority continue their career by entering the pharmaceutical industry and some continue as a researcher in an academic setting.

### **3.2 Research integrity policy**

The assessment committee considered LACDR's research integrity policy and the way in which violations of such integrity are prevented. All of the committee's questions on this subject were adequately addressed by LACDR's staff. Appropriate measures to ensure research integrity are in place at LACDR, including:

- LACDR follows Leiden University's formal guidelines on research integrity.
- Each scientist at LACDR signs the code of conduct on scientific integrity as issued by VSNU (Association of Dutch Universities), which includes topics such as honesty and scrupulousness, reliability, verifiability, impartiality, independence, and responsibility.

- The Leiden University Executive Board has set criteria for data management that Leiden researchers are required to meet, including access to raw data in a structured, transparent, and understandable manner. The new regulations will be adhered to by all Leiden Institutes in 2018 at the latest. LACDR had already installed its own data management strategy before the university issued these new guidelines, including a Good Academic Research Practice structure.
- PhD students follow mandatory courses about research integrity and data management. In addition, data management plans are used in the PhD programme and these are updated regularly. Supervisors regularly draw attention to researchers' obligations to science and society. All PhD theses are checked for plagiarism before submission to the doctorate committee.
- The BioMedical Metabolomics Facility Leiden operates under ISO17025 guidelines. These include the use of validated platforms and a well-documented quality control data pipeline.
- In 2017, all LACDR researchers will start using electronic lab books. These will be regularly checked for accuracy, completeness, and the traceability of data. They will be approved and countersigned by an independent yet knowledgeable observer. The committee recommends putting in place a proper system for countersigning as well as adequate IT support infrastructure.
- LACDR is aware of the risk for conflicts of interest. Therefore, all professional activities by members of the scientific staff are made public, and all data generated by PhD students, post-docs and technicians are stored. LURIS (the joint knowledge exchange office of Leiden University and LUMC) assists LACDR in ensuring research integrity.
- To protect the privacy of patients that participate in studies, LACDR follows the guidelines of the ethical commission associated with each project, anonymises patient data correctly, and stores data on secure servers, carefully controlling who has access.
- Animal experiments are only started when approved by the national regulatory authorities, and when fully compliant with the Dutch governmental guidelines, which in turn are compliant with the guidelines from Directive 2010/63/EU of the European Parliament. LACDR ascribes to the principle of the 3Rs (replacing, reducing, and refining the use of animals) and has made important contributions to this. LACDR has developed *in vitro* systems to replace and reduce the number of animals used. Refinement is realised through a systems approach, extracting a maximal amount of data per animal.

## 4. Recommendations

### 4.1 Quality of the research unit

#### 1) *Strategy in general*

Following the reorganisation in 2011, LACDR has transformed the nature of its studies from classical pharmaceutical research into a modern and innovative approach to pharmaceutical sciences, supported by technological platforms such as the cell observatory, metabolomics platform, and organ-on-a-chip technology. This has allowed LACDR to create a world-class innovative science-driven drug research programme. This profile was not immediately evident from externally-facing information; it was the initial impression of the review committee that LACDR wants to position itself as an institute with an almost industrial drug discovery-drug development programme. The committee therefore recommends that LACDR works on a clearer articulation of its profile and objective function.

The reorganisation from seven divisions to three clusters is on its way to becoming a successful operation. The committee has heard several examples of fruitful collaborations within and between clusters and wishes to commend the Centre on the progress made in truly integrating the divisions. However, more work needs to be done and it would be good to define a mission and vision for the three individual clusters to clarify their strategies.

#### 2) *Focus on translational research*

Although LACDR collaborates intensively with industrial and clinical partners to strengthen the translational nature of its research, it seems to have a rather reactive role in many such collaborations. The committee encourages LACDR to take a more proactive role in alliances with the medical world, for instance through more joint appointments of principal investigators. Such joint appointments should be part of a larger personnel plan (see recommendation 4 about personnel planning). This will close the loop of LACDR's translational research.

#### 3) *Challenges of technology-driven, data-intensive research*

LACDR's technical equipment is one of its great assets. However, to remain at the cutting edge of international research, it is necessary to properly maintain these instruments and to keep them up to date, which is very expensive. LACDR has been doing very well in obtaining grants in the last six years, but the committee expects more sober times ahead (for science in general) and encourages creative approaches to addressing this challenge.

In addition, LACDR appears to lack a proper IT infrastructure and support staff to facilitate the data-intensive research that comes with the high-end technologies. Investing in such resources will increase the productivity of the centre, especially given the excellent new appointments in cheminformatics. The committee thinks it is wise to invest in this, probably at the level of the Faculty of Science or even at the level of Leiden University.

LACDR is increasingly focusing on computational aspects of drug research. The combination of computational work with experimental (i.e., laboratory) work is a major strength of LACDR. In an era where the important role of 'artificial intelligence' in science is increasingly recognised, the committee thinks LACDR should continue to invest in computational approaches. In fact, LACDR should probably incorporate even more computational studies in their work and combine these with the cell observatory system and organ-on-a-chip as well.

#### *4) Personnel planning*

The high workload of LACDR researchers creates an unsustainable situation. This applies to principal investigators as well as postdocs and PhD students, and is the result of both the extremely high teaching load and the small number of principal investigators. In addition, the small number of researchers at the top makes the clusters vulnerable to expected and unexpected departures of key researchers, especially since some of the senior researchers are approaching retirement. This is painfully illustrated by two critical open positions in the cluster Systems Pharmacology at the time of the site visit.

We encourage LACDR to appoint a 'search committee' that will consult LACDR members on which top researchers should be recruited to increase the critical mass of the clusters in which specific areas and to compensate for the expected departure of senior staff members well in advance. In general, LACDR should work on a clear strategy to recruit and retain top scientists, and to ensure the gender balance of its staff. As mentioned above in recommendation 2, joint appointments (i.e., partly LACDR, partly clinical) should be part of the strategy. To lessen the burden of teaching on LACDR's scientists (in particular the PhD students), the committee recommends hiring dedicated teaching staff and using innovative teaching methods to increase the efficiency of the education.

## **4.2 PhD programme**

### *1) Teaching load*

As was already discussed in Paragraph 4.1, the teaching load of LACDR researchers is extremely high due to the rapid increase in student enrolment since 2012. A large part of this teaching load is carried by the PhD students. Although teaching is a valuable experience for PhD students, the time spent on teaching is too high. The committee is concerned that this may have a negative impact on the competitiveness of these young professionals in the international field, for example by lengthening the time to completion. The committee recommends hiring dedicated teaching staff to partially relieve the PhD students from their teaching load. In addition, innovative teaching methods may be used to increase the efficiency of the education.

### *2) Marie Curie and international students*

With approximately 50% of the PhD students having a Dutch nationality, the proportion of international students in LACDR's PhD programme is satisfactory. However, the committee did note a

relative lack of Marie Curie fellows at LACDR. We encourage LACDR to pursue these valuable fellowships.

### *3) Duration of the PhD tracks*

The committee learned that the Faculty of Science of Leiden University strives for a successful PhD thesis defence within six years. LACDR aims to bring the percentage of successful defences within six years up to 80%. The committee encourages LACDR to aim for an average duration of five years, because it is important for young professionals to take the next step in their careers within an acceptable period of time. This would be assisted by a lowered teaching load. In addition, unnecessary delays between manuscript submission and defence should be avoided.

### **4.3 Research integrity**

Recommendations beyond existing practice are not deemed necessary.

## **Appendix 1.** Short CVs of the members of the assessment committee

### **Professor H.A.J. Struijker-Boudier** (chairman)

Harry Struijker-Boudier is Professor *emeritus* of Pharmacology at Maastricht University (the Netherlands). His primary interests are pharmacology education and cardiovascular pharmacology research. Struijker-Boudier received his MSc (pharmacochemistry and biochemistry) in 1973 and his PhD in pharmacology (*cum laude*) in 1975 from Radboud University Nijmegen (the Netherlands). In the period 1976-1977, he performed a postdoctoral fellowship at the Department of Physiology and Biophysics of the University of Mississippi Medical School (Jackson, USA). In 1977, Struijker-Boudier was appointed to the University of Maastricht, from 1980 as a Professor of Pharmacology. He was the head of the Department of Pharmacology and Toxicology in the period 1983-1999. In 1991, he spent a sabbatical year as a Visiting Professor at the Cardiovascular Institute of INSERM in the Hôpital Lariboisière in Paris (France). From 1999-2006, he was the scientific director of the Cardiovascular Research Institute Maastricht (CARIM). Struijker-Boudier has served as a board member for numerous international organisations. For instance, he was Vice President of the European Society of Hypertension until 2011 and he was a member of the Health Council of the Netherlands in the period 1992-2006. He is *doctor honoris causa* of the Université de Liège (Belgium), recipient of the Descartes-Huygens prize of the French Government, and Officer of the Order of Oranje-Nassau of the Dutch Royal House.

### **Professor A.R. Boobis**

Alan Boobis is Professor of Biochemical Pharmacology at Imperial College London (UK). His research interests include mechanistic toxicology, drug metabolism, biomarker discovery in toxicology, using protein-based approaches and the application of this knowledge in risk assessment. Boobis received his BSc (pharmacology) in 1971 and his PhD in pharmacology in 1974 from the University of Glasgow (UK). Boobis then worked as a Fogarty Visiting Fellow for two years at the National Institutes of Health (Bethesda, MD, USA). In 1976, he joined the Department of Clinical Pharmacology at the Royal Postgraduate Medical School (now Imperial College London), as an MRC research training fellow. He was promoted to Professor of Biochemical Pharmacology in 1996. He currently also is director of the Toxicology Unit (supported by Public Health England and the Department of Health), based in Imperial College London. Boobis has served as a board member for numerous grant review and advisory committees. For instance, he was deputy chair of the U.K. Advisory Committee on Pesticides (1999-2002) and is currently chair of the Committee on Toxicity (from 2015); he has served as president of Eurotox; and he is a past chair of the British Toxicology Society. He is currently a member of several IPCS working groups, JECFA (member/chair), JMPR (member/chair), and the Committee on the Medical Effects of Air Pollutants. In 2003, Boobis was made an Officer of the Order of the British Empire (OBE) for his work on risk assessment of pesticides. He is an Honorary Member of EUROTOX, recipient of the EUROTOX Merit Award, The British Toxicology Society John Barnes Prize Lecture, the Royal Society of Chemistry Toxicology Award and the US Society of Toxicology Arnold J. Lehman Award. He has been elected Fellow of the British Toxicology Society, the Royal Society of Biology and the British Pharmacology Society.

### **Professor S. Frøkjær**

Sven Frøkjær is Professor of Pharmaceutical Sciences at the University of Copenhagen (Denmark). His main research interest is peptide and protein formulation, with a special emphasis on particulate drug delivery systems and peptide transport across biological membranes. Frøkjær received his MSc

(pharmaceutical sciences) in 1970 and his PhD in physical chemistry in 1973 from the Danish University of Pharmaceutical Sciences. Frøkjær spent nearly 20 years at Novo Nordisk A/S, where he was involved in research on drug delivery systems and various aspects of peptide and protein formulation. In 1993, he was appointed a Professor of Pharmaceutics at the Department of Pharmaceutics. He was Rector at the Danish University of Pharmaceutical Sciences from 2003 to 2007. After the merge with the University of Copenhagen, Frøkjær became Dean at the Faculty of Pharmaceutical Sciences. Since 2012 and until 2016, he has been Vice-Dean at the Faculty of Health and Medical Sciences of the University of Copenhagen. From 2002 to 2005, he was the director of the industrial-oriented graduate research school Drug Research Academy where he is now chairman of the board. Frøkjær is a member of several boards and committees including The Danish Pharmacopeia Commission and the Medicinal Products Committee under the Danish Medicines Agency. He serves as member of editorial boards on several pharmaceutical journals. He has also served as member at the Danish Medical Research Council for a period of five years. Frøkjær is the co-founder of two biotech companies, Lica Pharmaceuticals A/S and LiPlasome Pharma A/S.

#### **Professor D. Kell**

Douglas Kell is Professor of Bioanalytical Science at the University of Manchester (UK). He is interested in the development and application of novel analytical methods to the solution of complex biological problems (especially including Systems Biology). Kell received his BSc (Biochemistry) in 1975, with a Distinction in Chemical Pharmacology, and his PhD in Bioenergetics in 1978 from the University of Oxford. He worked at University College of Wales in Aberystwyth from 1978 to 2002, where he was Director of Research at the Institute of Biological Sciences, from 1997 to 2002. In 2002, Kell moved to the University of Manchester as EPSRC/Royal Society of Chemistry Research Chair in Bioanalytical Sciences. He was the Director of the BBSRC/EPSRC funded Manchester Centre for Integrative Systems Biology in the period 2005-2008. From 2008 to 2013, he was Chief Executive of the Biotechnology and Biological Sciences Research Council (0.8 FTE). Kell was appointed Commander of the Order of the British Empire in the 2014 New Year Honours 'for services to science and research'. He is also a Fellow of the Learned Society of Wales (LSW), the Royal Society of Biology (RSB) and the American Association for the Advancement of Science (AAAS).

#### **Dr C. Perros-Huguet**

Christelle Perros-Huguet is Head Internal Research at Alexion Pharmaceuticals, focusing on developing novel transformative therapies for the treatment of rare and devastating diseases. She studied in France, Germany and Switzerland, receiving a French University Diploma in Technology (DUT) in applied biology and biochemistry in 1989 and a European Engineering degree in biotechnology sciences in 1992. She obtained a PhD in molecular and cellular biology from the Institute Pasteur in France in 1997. Prior to her current role, Perros-Huguet held several leadership positions at Pfizer, including Global Head of Pharmacokinetic, Dynamic and Metabolism NCE (1997-2011) and Chief Scientific Officer of Pfizer's Inflammation and Remodeling Research Unit (2011-2015).

#### **Dr Linda van den Berg**

Linda van den Berg assisted the committee as an external independent secretary. She is a self-employed science writer and communications consultant with a background in biomedical sciences. Her company *Washoe Life Science Communications* offers a variety of communication services to academic institutes and companies.

## Appendix 2. LACDR site visit programme

*Tuesday 29 November 2016*

Time	
13.00 - 14.00	Arrival at Leiden University and lunch
14.00 - 15.00	Preparatory meeting
15.00 - 16.30	Management meeting including presentation by scientific director
16.30 - 17.30	Lab tour
17.30 - 18.30	Committee meeting
18.30	Dinner

*Wednesday 30 November 2016*

Time	
8.45 - 9.00	Arrival committee at Leiden University
9.00 - 10.00	Cluster Systems Pharmacology
10.00 - 11.00	Cluster BioTherapeutics
11.00 - 11.15	break
11.15 - 12.15	Cluster Drug & Target Discovery
12.15 - 13.15	lunch
13.15 - 14.00	PhD students
14.00 - 14.30	Management (optional, final questions)
14.30 - 16.00	Committee meeting
16.00 -	Oral presentation chairman and drinks

### Appendix 3. Quantitative data on LACDR's composition and financing

**Table 1: LACDR research staff**

	2009		2010		2011		2012		2013		2014		2015	
	#	FTE	#	FTE	#	FTE	#	FTE	#	FTE	#	FTE	#	FTE
Scientific staff	27	10.7	24	9.4	21	8.3	21	6.5	17	5.4	21	7.0	22	8.1
Post-docs	50	41.6	52	45	40	42.2	43	24.1	38	22.2	32	18.8	31	18.6
PhD students	65	47.5	64	48.9	65	45.9	59	43.5	78	43.5	67	43.5	69	51.8
<b>Total Research staff</b>	<b>142</b>	<b>99.9</b>	<b>140</b>	<b>103.3</b>	<b>126</b>	<b>96.5</b>	<b>123</b>	<b>74.2</b>	<b>133</b>	<b>71.19</b>	<b>120</b>	<b>69.3</b>	<b>122</b>	<b>78.5</b>
Total support staff	62	62.6	53	44.3	44	39.1	38	33.5	37	31.5	42	35.8	48	41.9
Visiting scientists	1	1	2	1.3	3	2.5	3	1.7	4	3.0	5	3.2	4	2.4
<b>Total staff</b>	<b>205</b>	<b>163.6</b>	<b>195</b>	<b>149.0</b>	<b>170</b>	<b>138.1</b>	<b>164</b>	<b>75.8</b>	<b>174</b>	<b>74.3</b>	<b>167</b>	<b>108.4</b>	<b>174</b>	<b>80.9</b>

Scientific staff: fte is based on 40% research time

Post-docs: fte is based on 90% research time

PhD candidates: fte is based on 75% research time

Support staff: fte is based on 100% research time

**Table 2: LACDR funding in M€ (%)**

	2009		2010		2011		2012		2013		2014		2015	
	M€	%	M€	%	M€	%	M€	%	M€	%	M€	%	M€	%
<b>Funding</b>														
Direct funding (1)	5.7	35	4.7	28	5.1	35	4.7	34	5.3	37	5.7	45	6.3	46
Research (1.1)	2.2	13	2.2	13	2.6	18	2.7	20	3.0	21	3.0	24	2.7	24
Other (1.2)	3.5	22	2.5	15	2.6	17	2.0	14	2.3	16	2.7	21	3.0	22
Research grants (2)	5.2	32	5.7	36	5.7	39	5.8	43	5.6	46	3.9	30	4.7	34
Contract research (3)	5.3	33	5.3	34	3.8	26	3.2	23	2.4	17	3.1	25	2.6	20
Other (4)	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0
<b>Total funding</b>	<b>16.2</b>	<b>100</b>	<b>15.6</b>	<b>100</b>	<b>14.7</b>	<b>100</b>	<b>13.8</b>	<b>100</b>	<b>14.5</b>	<b>100</b>	<b>12.7</b>	<b>100</b>	<b>13.6</b>	<b>100</b>
<b>Expenditure</b>														
Personnel costs	11.2	66	11.8	71	11.2	72	8.1	62	9.7	67	8.7	69	8.9	66
Other costs	5.8	34	4.9	29	4.4	28	5.0	38	4.7	33	3.9	31	4.6	34
<b>Total expenditure</b>	<b>17</b>	<b>100</b>	<b>16.7</b>	<b>100</b>	<b>15.6</b>	<b>100</b>	<b>13.1</b>	<b>100</b>	<b>14.4</b>	<b>100</b>	<b>12.6</b>	<b>100</b>	<b>13.5</b>	<b>100</b>

Note 1: Direct funding by the University

Note 1.1: Direct funding research obtained by scientific staff on national scientific grants and delivered PhD theses.

Note 1.2: Direct funding other contains income obtained through education and temporary funding (such as increase in salaries through CAO changes, investments etc.)

Note 2: Research grants obtained in national and international scientific competition (e.g. grants from NWO, Royal academy, Horizon2020, FP7, STW)

Note 3: Research contracts for specific research projects obtained from external organisations, such as industry, governmental ministries, European organisations, charitable organisations

Note 4: Funds that do not fit into any of the other categories

#### Appendix 4. Explanation of the categories utilised

Category	Meaning	Research quality	Relevance to society	Viability
1	World leading/ excellent	The research unit has been shown to be one of the few most influential research groups in the world in its particular field.	The research unit makes an outstanding contribution to society.	The research unit is excellently equipped for the future.
2	Very good	The research unit conducts very good, internationally recognised research.	The research unit makes a very good contribution to society.	The research unit is very well equipped for the future.
3	Good	The research unit conducts good research.	The research unit makes a good contribution to society.	The research unit makes responsible strategic decisions and is therefore well equipped for the future.
4	Unsatisfactory	The research unit does not achieve satisfactory results in its field.	The research unit does not make a satisfactory contribution to society.	The research unit is not adequately equipped for the future.

Source: Standard Evaluation Protocol 2015 - 2021