Evaluation Panel: HEALTH SCIENCES - Clinical and Translational Research

Panel Members

Ulrik Ringborg (Chair)	Karolinska University Hospital Solna, Sweden
Alex Markham	MRC Medical Bioinformatics Centre in Leeds, United Kingdom
Günther Deuschl	University of Kiel, Germany
Heinz-Peter Schlemmer	German Cancer Research Centre (DKFZ), Germany
Karin Sipido	University of Leuven, The Netherlands
Kirsi Vähäkangas	Eastern University of Finland, Finland
Marco Pierotti	Campus IFOM-IEO – Milan, Italy
Maria Grazia Daidone	Instituto Nazionale dei Tumori, Italy
Ulf Smith	University of Gothenburg, Sweden

R&D Units

Centro Cardiovascular da Universidade de Lisboa (CCUL)	Associação para a Investigação e Desenvolvimento da Faculdade de Medicina (AIDFM/FM/ULisboa)
Centro de Imagem Biomédica e Investigação Translacional (CIBIT)	Universidade de Coimbra (UC)
Centro de Investigação do Instituto Português de Oncologia do Porto (CI-IPOP)	Instituto Português de Oncologia do Porto Francisco Gentil, EPE (IPO Porto)
Centro de Investigação Farmacológica e Inovação Medicamentosa (MedInUP)	Instituto de Ciências Biomédicas Abel Salazar (ICBAS/UP)
Centro de Investigação Interdisciplinar Egas Moniz (CiiEM)	Egas Moniz - Cooperativa de Ensino Superior, CRL (CESEM)
Centro de Investigação Interdisciplinar em Saúde (CIIS)	Universidade Católica Portuguesa (UCP)
Centro de Toxicogenómica e Saúde Humana (ToxOmics)	Faculdade de Ciências Médicas (FCM/UNL)
iNOVA4Health - Programa de Medicina Translacional (iBET, CEDOC/FCM, IPOLFG e ITQB) (iNOVA4Health)	Instituto de Biologia Experimental e Tecnológica (IBET)
Unidade de Investigação e Desenvolvimento Cardiovascular (UnIC)	Faculdade de Medicina da Universidade do Porto (FM/UP)
Unidade Multidisciplinar de Investigação Biomédica - UMIB (UMIB)	Instituto de Ciências Biomédicas Abel Salazar (ICBAS/UP)

Evaluation Panel: HEALTH SCIENCES - Clinical and Translational Research

R&D Unit: Centro Cardiovascular da Universidade de Lisboa (CCUL)
Coordinator: Fausto José da Conceição Alexandre Pinto
Integrated PhD Researchers: 32

Overall Quality Grade: VERY GOOD
Evaluation Criteria Ratings
(A) Quality, merit, relevance and internationalization of the R&D activities of the Integrated Researchers in the R&D Unit Application: 4
(B) Merit of the team of Integrated Researchers: 4
(C) Appropriateness of objectives, strategy, plan of activities and organization: 4

Base Funding for (2020-2023): 279 K€
Recommended Programmatic Support
Programmatic Funding: 418 K€, including for 1 (Junior) New PhD Researcher Contract.

Justification, Comments and Recommendations
The Cardiovascular Center at the University of Lisbon (CCUL) is a biomedical research institute of the School of Medicine of the Universidade de Lisboa. It is part of the Academic Medical Centre that includes the Santa Maria University Hospital and the Instituto de Medicina Molecular João Lobo Antunes. CCUL is a cardiovascular R&D Unit with long-standing clinical research activities, training and education in medicine. It includes 62 Integrated Researchers, 32 with PhD degrees. The Unit has apparently undergone major restructuring under the previous period where translational studies were emphasized and which should focus more on mechanisms rather than merely associations. The Unit has also initiated more basic science and translational research and recruited expertise in angiogenesis, animal studies and genetics/epigenetics. CCUL has markedly increased the international collaborations and clinical trial activities. No doubt that the current Director has been instrumental for this with his international contacts as a former president of ESC. The Unit is a prominent Center for clinical cardiovascular disease and has made contributions in several topics of important medical concerns in cardiovascular medicine, i.e. atrial fibrillation, heart failure, ischemic disease and valve disease. A specific topic is the rare disease FAP where cardiovascular abnormalities may be an early sign. Transversal themes are early risk detection and (imaging) biomarkers.

The selected publication output is increasing annually and contains contributions in good to very good international journals. Two publications are meta-analyses. CCUL has an extensive international network and Prof. Pinto's role in the European Society of Cardiology and other international societies in the field has had important impact for the Unit.

CCUL is clearly engaged in clinical studies with industry partners and also in three EU projects that provide a growing stream of funding in the last years. Overall, international funding is larger than national funding, which attests to a strong international activity. The total budget has not been so large to cover the research ambitions spanning from basic to clinical research.

In relation to the size of the team and the funding, the Unit has been quite successful in its research achievements and, overall, the international productivity is quite good. Current clinical trials are mainly phase 3-4 but plans are under way to also have a structure for phase I-II studies. It is quite clear the leadership is very dynamic and that the Center is showing annual expansion in activities and outreach. Postdocs and PhD students are encouraged to participate in international meetings and some funding is also made available. Between 2013 and 2017, there were a total of 177 indexed publications, of which around 60% were joint publications with authors from more than 20 different countries.

Future plans are to continue the clinical research activities and international collaborations and to become broader with more translational expertise. Specifically, there are plans to expand methodological expertise in epi/genetics, animal studies and also clinical translational studies for instance in diabetic cardiovascular complications and cardiotoxicity following oncological therapy. Portugal has a high prevalence of diabetes and CVD and is in need of preventive actions. The Unit is particularly well suited for this considering its high clinical standards, interactions with other specialties and investigative resources. Initial activities informing young individuals of healthy living is also one step in this area. The preclinical data over the positive effects of low dose radiation on angiogenesis is quite interesting and a pilot clinical trial may identify new avenues to treat patients with peripheral ischemic disease resistant to current therapies.

It is now important for the Unit to make clear and distinct plans for future translational research activities. This is also identified as a major priority in the Unit application but the exact areas and plans are less clear. New groups have been incorporated and more focus to optimize resources could be considered.

In summary, this is a growing Unit with annual increase in funding, clinical trials and other research activities. It is likely that this will continue over the next funding period. A more detailed strategic planning of research organization and activities is recommended.

The Unit is quite productive with many publications including international collaborations. The translational research approach has been further improved and expertise in basic science has been recruited. The clinical studies with required imaging and other technologies are quite impressive and it is clear that the Unit is an attractive international research partner. Integration of basic and medical researchers has been clearly documented, also in several publications. In summary, this is a well integrated Unit with very high clinical expertise and with increasing translational medicine approach. Continuation along these paths is identified in the Unit application and should lead to further strengthening its international reputation.

The plan to further integrate the Unit translational research approach and recruit needed expertise is important for enhancing its international competitiveness. The clinical standards are high and incorporate extensive technical expertise. Identification of the potential effect of low dose radiation on angiogenesis is clearly interesting and this may evolve into future therapy of compromised patients. A further focus on large patient groups with high risk of cardiovascular disease such as diabetes would be important for Portugal considering its high prevalence of both these costly conditions. In summary, the plans are well founded and should be implemented.

Type of new researcher:
The support for hiring a new PhD Researchers should be used to strengthern translational expertise in order to accomplish the UNit plans to expand this type of research and to allow new insight into disease mechnisms in clinical cardiology.

Evaluation Panel: HEALTH SCIENCES - Clinical and Translational Research

R&D Unit: Centro de Imagem Biomédica e Investigação Translacional (CIBIT)
Coordinator: Miguel de Sá e Sousa de Castelo-Branco
Integrated PhD Researchers: 44

Overall Quality Grade: EXCELLENT
Evaluation Criteria Ratings
(A) Quality, merit, relevance and internationalization of the R&D activities of the Integrated Researchers in the R&D Unit Application: 5
(B) Merit of the team of Integrated Researchers: 5
(C) Appropriateness of objectives, strategy, plan of activities and organization: 4

Base Funding for (2020-2023): 655 K€
Recommended Programmatic Support
PhD Fellowships: 10
Programmatic Funding: 696 K€, including for 2 (Junior) New PhD Researchers Contracts.

Justification, Comments and Recommendations
The Coimbra Institute for Biomedical Imaging and Translational Research (CIBIT) is the largest imaging facility in Portugal which is newly structured out of a number of previously existing research groups which already had a longstanding collaboration. The thematic lines deal with important challenges for society: (1) normal aging; (2) Neurodegenerative disorders; (3) Neurodevelopmental disorders; (4) Cortical plasticity in the maturing and adult brain; (5) Neuropsychiatric disorders with focus on decision making and cognitive control. CIBIT conducts internationally competitive research on neuroscience with focus on bridging the translational gap between basic, preclinical and clinical research.

The presented research covers important papers in high-ranking journals related to the Redgrave model of the basal ganglia on habitual versus goal-directed learning, specific loop abnormalities in neurofibromatosis and spinocerebellar ataxia and important work on the neurovascular coupling with multifocal intraocular lenses and their adaptive changes of the visual cortical processing. Autism-spectrum disorders are an important part of the current and future activities. An important strength of the group is the combination of the different imaging modalities from MRI, PET to EEG and fNIR. A particular merit is the development of new molecules/radiopharmaceuticals.

CIBIT is involved in 3 European H2020 projects (RADICAL, BRAINTRAIN and STIPED). Also they participated in a European Consortium, EU-AIMS, which was just awarded a European IMI-2 grant. They are also participating in a SME instrument H2020 clinical trial to validate a new imaging marker for liver inflammation.

They hold several Research contracts and agreements with industry both in R&D (IBA, Siemens, Icnas-Produção) and Clinical trials (Biogen, Roche, Merck, PPDA, and others). They have several investigator driven trials approved in the fields of Medical Devices (EU projects STIPED and BRAINTRAIN) and Radiopharmaceuticals. They recently installed an MR (9.4 Tesla) and PET animal facility for full implementation of translational research using similar methods in animals and humans. They received substantial EU-funding. External awards essentially doubled their funding income. Translation research is conducted by clinical trials and investigator own trials.

CIBIT has international standing with Profs. Sousa de Castelo-Branco and Abrunhosa as the internationally known leaders. The group comprises a total of 44 PIs who have many international connections, with some having a high profile in the international community. The combination of all subspecialities relevant for the research questions (neurologists, radiologists, psychiatrists, psychologists, radiochemists and many others provides the basis for integrated research. The international connections of the group are multifold (medical branch of the EuroBioimaging Network, BrainImaging network BIN).

The plan for future activities provides 3 scientific work packages concentrating on preclinical research, molecular imaging (WP 1); neuroimaging and clinical neuroimaging covering neurodevelopmental disorders and aging and neuroengineering and device development (WP 2); development of imaging biomarkers and neurophysiological approaches to the function of relevant network properties of the brain (WP 3). This is complemented by two work packages related to technology development and transfer (WP 4) and training of PhD's and reserachers (WP 5).

The Unit has a very good, focused and balanced strategy for the future with regard to basic and translational science, technology transfer and training. Some recommendations are addressing possible structural improvements. Concerning translational research, a unit is needed that transparently deals with regulatory, governmental and legal issues. This should be established. Multidisciplinary research should be supported by improved communication strategies between different research groups.

The organization structure is not yet mature and can be improved. Instead of only one coordinator, a coordinating group, a steering committee and an advisory board should be established.

During the visit the Evaluation Panel found the PhD students and the PIs highly motivated and in good standing. As for all R&D Units, lack of protected time for researchers with clinical duties is a problem to be centrally solved by the Ministry. A program for sustainable recruitment of young talents as well as for career development should be established. Recruiting multidisciplinary profiles will support more active imaging protocol and technology development.

It is special to this Unit that they were able to develop a business branch together with the university clinic to produce compounds for marketing within Portugal. This activity was specially achnowledged by the Evaluation Panel and is considered a role model. This activity should be further strengthened. In case of the research, development and production of biomarkers/radiotracers also for cardiovascular and oncologic imaging, connections to UnIC, CCUL and CI-IPOP should be envisaged.

The request is for a total of 27 PhD students. The Centre will develop a specific PhD program dedicated to functional imaging, but currently PhD students are involved in several existing doctoral programs. The Evaluation Panel supports the development of their own school but recommends ongoing close relation to the existing schools. The number of PhD positions should be 10. Further PhD positions should come from other sources.

In its application the Unit requests support for 4 new researchers: 1 for MR- and PET-physics; 1 for mathematical approaches to imaging data; 1 for clinical trials; 1 unspecified. The Evaluation Panel finds that the physics PhD and the big data analyst are the most needed requests but leaves CIBIT freedom to decide on the best use of these positions to achieve its goals.

The Programmatic Funding should cover costs for researchers, infrastructure, participation in international activities and other support.

Evaluation Panel: HEALTH SCIENCES - Clinical and Translational Research

R&D Unit: Centro de Investigação do Instituto Português de Oncologia do Porto (CI-IPOP)
Coordinator: Manuel António Rodrigues Teixeira
Integrated PhD Researchers: 45

Overall Quality Grade: EXCELLENT
Evaluation Criteria Ratings
(A) Quality, merit, relevance and internationalization of the R&D activities of the Integrated Researchers in the R&D Unit Application: 5
(B) Merit of the team of Integrated Researchers: 4
(C) Appropriateness of objectives, strategy, plan of activities and organization: 5

Base Funding for (2020-2023): 546 K€
Recommended Programmatic Support
PhD Fellowships: 8
Programmatic Funding: 696 K€, including for 2 (Junior) New PhD Researchers Contracts.

Justification, Comments and Recommendations
The IPO Porto Research Center (CI-IPOP) is entirely embedded in the Instituto Português de Oncologia do Porto Francisco Gentil (IPO-Porto), which together with the IPO Coimbra and the IPO Lisboa are the leading Cancer Centers of the country. Its outstanding role in many different cancer related fields, such as patient care, teaching and research, has been recognized by the Organization of the European Cancer Institutes (OECI) which has designated IPO Porto as a Comprehensive Cancer Center.

The FCT has recognized this R&D Unit since 2004. Its general objective is the understanding of the pathobiological mechanisms of carcinogenesis. This evaluation has regarded the activities carried on by 5 research groups working during the considered period, on translational cancer research, namely: Cancer Genetics Group; Cancer Biology and Epidemiology Group; Molecular Oncology and Viral Pathology Group; Experimental Pathology and Therapeutics Group; and Medical Physics, Radiobiology and Radiation Protection group. In 2018, two new Groups have been created: the Cancer Epidemiology Group and the Management Outcomes Research and Economics in Healthcare Group. The addition of these two new groups received very positive comments from the Review Group, especially at the light of the explanation by the Director of the Unit that a process of integration of the three existing Cancer Registries in Portugal is going on. At the end, integrated National Cancer Registries will allow full activity of the new Research Groups. Their research products will be a major driving force for innovation both for research programs and management of cancer in the country. Looking at the previously obtained results, as an overall conclusion the Unit has demonstrated a clear capacity to combine basic research with the ability to translate the innovative discoveries. They conduct mono- and multicenter clinical trials to introduce new diagnostic tools and innovative therapeutic approaches to cancer.

In this context, several accomplishments in the field of urological cancer research (prostate, bladder and kidney) have been recognized as significant internationally leading contributions for the advancement of the respective fields and together with other relevant results obtained in studies on mechanisms of carcinogenesis in both inherited and sporadic cancers, it is rated as an excellent Centre.

The number of integrated researchers has fluctuated a little bit in the years considered (between 116 and 194 overall and 130 in 2017). The Director Manuel Teixeira is a MD/PhD with a strong record in molecular genetics of cancer. The majority of the Integrated Researchers support the translation mission of the Unit. The research governance of the Unit is supported by a Coordinating Scientific Council, which includes, among others, Postdoc and PhD student elected representatives. As mentioned before, with the addition of the two new groups, Epidemiology and Outcomes Research Groups, the Unit now has seven research groups plus the Clinical Research Unit which is fully integrated with the rest of the team.

The analysis of the combined scientific (including publication records which report papers in relevant top journals mainly thanks to participation to international Consortia), teaching and clinical activities of the Unit, led to rate the Unit for criterium B with 4. Considering also the collaboration with national and international groups and the participation, mainly in the field of the assessment of cancer genetic risk, to international Consortia (CIMBA, IMPACT and BCAC among

others), led to the rating 4, although there are inevitably differences among the participating Research Groups with, for example, the Cancer Genetics group standing out as the most prominent in terms of novel and relevant contributions. Certainly, the quality of the team could improve further towards excellence.

The Objectives and the strategy of this R&D Unit for the next five years, while confirming the general long term overarching objective to improve the understanding of the patho-biological mechanisms of cancer, have been clearly and comprehensively broken down into more specific aims for each of the research groups:

- Cancer Genetics Group – The main research theme will be on prostate to find the missing heritability by combining exome sequencing and haplotype analysis in a population with strong founder effects. Positive results in this setting will significantly increase our capacity to manage this very relevant oncological problem.
- Cancer Biology and Epigenetics Group – The contribution of epigenetics will be addressed in tumors of the urogenital tract, with the aim to develop biomarkers for an early detection of cancer and new therapeutic avenues.
- Molecular Oncology and Viral Pathology Group – Pharmacogenomics and molecular epidemiology will be the major research themes together with further studies on the role of tumor viruses such as HPV.
- Experimental Pathology and Therapeutics Group – They are particularly focused on an interesting area of cancer-specific glyoconjugates in precision medicine and in this context, the possible therapeutic efficacy of the new field of CAR-T therapy.
- Medical Physics and Radiation Protection Group – A new software package will be tested further thanks also to their recent joining to the European Radiation Dosimetry Group (EURADOS).
- Cancer Epidemiology Group – It is one of the two new Units. Their activity has involved two aspects, a population one (Northern Region of Portugal) and hospital level studies (IPO Porto). It has been recommended by the Evaluation Panel, if possible, to extend their collaboration with the other two cancer registries to improve their analysis capacity, since the patients referred to IPO Porto come from all the regions of the country.
- Management, Outcome Research, etc. This is the second new group. It intends to create innovative approaches to this important developing field by taking a multidisciplinary perspective and seeking national and international collaborations.

The Clinical Research Unit will continue to support the participation of IPO mainly in international clinical trials (e.g. with EORTC) intensifying its collaborations with the Pharma industry. In this context it is relevant to note that the Unit is economically self-sustainable and contributes with funding to the other translational research carried on in IPO.

In addition, the Centre will continue to contribute significantly to the advancement and disemination of knowledge related to cancer research, care and cure, in the society at several levels.

The structure hosting the Research Groups (which are all an integral part of it) has been internationally recognized as a Comprehensive Cancer Center by a leading European Cancer Organization, OECI. The top accomplishments of the Unit are illustrated by their scientific productivity, in particular with original significant contributions in the field of urological tumors, participation to multi-centre clinical trials (including some of phase I and II), participation in many international Consortia for inherited or rare forms of cancer, strong governance and a convincing future development plan.

Srong points: Cancer Genetics and Experimental Pathology and Therapeutics. In perspective, outstanding accomplishments are expected from the two new RGs, Epidemiology and Outcomes Research. The Clinical Research Unit has a strong reckord with phase I/II clinical trials and has achieved economic sustainability,

Recommendations:
A) Improve the leading role of the Centre in Cancer Epidemiology by interacting with the two other regional Portuguese cancer registries.
B) Improve the role in the international setting of inherited forms of cancer by networking with the other Centers which are dealing with this problem in the country (e.g. the other two IPOs).
C) Try to improve the quality of clinical trials by increasing the number of the early trials (phase I and II) and of those being investigators driven.
D) Develop a clear and sustainable plan for the local OMICs support for precision medicine in cancer and for the needed bioinformatics aspects.

They have requested for the period 2019-2022 a total of 8 fellowships for PhD students in the following areas: (1) research program associated with early phase clinical trials, (2) translational research program to improve cancer screening/early detection and diagnosis, (3) translational research using liquid biopsies for disease stratification and monitoring, (4) bioinformatics, bio-imaging, big data and outcome research. This request and the relative stratification of these research human resources is fully supported by the Evaluation Panel.

Evaluation Panel: HEALTH SCIENCES - Clinical and Translational Research

R&D Unit: Centro de Investigação Farmacológica e Inovação Medicamentosa (MedInUP)
Coordinator: Patrício Manuel Vieira Araújo Soares da Silva
Integrated PhD Researchers: 20

Overall Quality Grade: GOOD
Evaluation Criteria Ratings
(A) Quality, merit, relevance and internationalization of the R&D activities of the Integrated Researchers in the R&D Unit Application: 3
(B) Merit of the team of Integrated Researchers: 3
(C) Appropriateness of objectives, strategy, plan of activities and organization: 3

Base Funding for (2020-2023): 157 K€
Recommended Programmatic Support
PhD Fellowships: 4
Programmatic Funding: 276 K€, including for 1 (Junior) New PhD Researcher Contract.

Justification, Comments and Recommendations
This Unit has 20 integrated PhD Researchers. They have affiliations across Faculties in the University of Porto. The Site Visit proved to be particularly useful in terms of addressing a number of issues, which had been difficult to fully understand and analyse from the Unit application documents.

The impression that the Director (Prof. Soares da Silva) is a well-respected pharmacologist was confirmed on the visit. Although there are also some investigators in the Unit who publish at "national leadership level" or approaching it, the final impression was that a significant number of the Integrated Researchers were still struggling to deliver consistently at that level.

They have been through a difficult period of restructuring, with withdrawal of FCT funding from 2013-16. They now see themselves as being in a recovery phase. This has yet to be fully reflected in a significant quantum change in their combined published (and other) outputs. However, there was support for the Director to continue with the process of rebuilding and re-focusing the efforts of the Unit in the coming period.

Since the submission of their application there has been a modest pickup in external project funding, although, as yet, they are not achieving consistent success in the major European funding competitions. Their income from Pharma sources remains less than might be expected for a focused Drug Discovery and Innovative Medicines team. They plan to continue their efforts to improve performance in these critical areas. That said, they do have an international presence and interact to a fair level in European scientific affairs in their field, primarily as a result of their Director reputation.

Their Governance appears satisfactory with local, national and international involvement, the latter through an adequate International Scientific Advisory Board.

Their split site working, although unavoidable it seems, is obviously not ideal. It will inevitably have an effect on the development of scientific synergies. There was no short term plan to change these working arrangements.

The impression obtained from the application is that although they had obvious strengths and areas of expertise, they lacked focus. They were working in almost every disease area and on a massive range of diverse therapeutic targets. This was particularly difficult to understand when their research income remains relatively low.

They have had significant successes: in Parkinson's disease; in epilepsy research; in purinergic pharmacology (with a focus on bladder function); and in cardiology (heart failure and pre-clinical hypertension research). However, this seemed diluted by lots of less competitive activity in too many other disease areas.

It was not clear what level of research competitiveness was required before new investigators were allowed to join the Unit. This may explain why the range of activities described was so broad. This breadth of activity, almost for the sake of working in all areas, was not persuasive to the Evaluation Panel.

There were elements missing from the Unit that surprised the Evaluation Panel by their absence. There was no clear route through to Phase 1 clinical evaluation in man, which meant that real "translational medicine" was not easily going to be possible, at least in the short and medium terms. This ought to be a high priority to be addressed in the coming quinquennium. The sensible way to achieve this might be to work with others in Porto (the cardiologists, the oncologists, others?) who are more advanced in these areas, rather than trying to re-invent this very expensive wheel themselves.

Similarly, there was no high-quality structural biology or medicinal chemistry included in the application. No clear strategy emerged at the Site Visit about how they might access these technologies through collaboration.

Their requests for a very wide range of new equipment (genomics, proteomics, metabolomics and bio-imaging in particular) are difficult to support. There was no clear connection between their actual research activities and these well-established technologies. They do not have a strong track record in the sorts of "biomarker" research that require access to this equipment base. We were also unimpressed by their statements that this would allow them to offer these technologies as a service to others.

These "OMICS" technologies are extremely expensive to provide. We suggest that the FCT ought to look carefully at exactly what is currently available across the research community in Porto. A regional strategy should be developed to provide shared "OMICS" facilities, accessible to all under agreed criteria of research quality and justification, and charged for on a service basis. This would allow core staff to be provided to run the infrastructure on a professional basis. The Porto Universities might be expected to contribute to such a centralised, shared facility? This is discussed further below. Doubtless, this will be politically challenging, but it is probably essential.

In summary, the Evaluation Panel felt that the Center for Drug Discovery and Innovative Medicines had made sufficient progress, on a difficult journey of re-configuration, to merit some support in the coming funding period. Our score of 3 reflects our support, but also some reservations and our recommendations as to where their future efforts should be focused.

The Unit Reasearchers provide a PhD Programme in Experimental and Clinical Pharmacology and Toxicology. We met with the current cohort of 24 PhD students in the Unit, in private session. Compared with the PhD students we saw in other Centers, we were less impressed with the cohort in this Unit. There was a sense of some isolation in individual research groups. Their interactions amongst themselves were less prominent than in some other Centers.

There were only a couple of MD/PhDs involved. This was particularly unhelpful as building closer links with the clinic for eventual Phase 1 activity is so important.

Essentially all the students on the PhD Programme were local graduates from Porto. We felt that the ability to attract PhD students from other places was a useful litmus test of the attractiveness of the Center to young scientists at the beginnings of their careers. This Center was amongst the weakest from that perspective.

There was a sense that the individual Investigators and their Research Groups in the Center rather kept themselves to themselves scientifically. We were comfortable that formal supervision arrangements and dual supervision were usually the norm. However, some students still had single PhD supervisors.

One striking element was the session we had with the Postdoctoral Fellows in the Unit. There were only two of these key individuals available. This suggested that many groups consist entirely of a PI plus graduate students. This is not ideal. We were also therefore unable to draw specific conclusions about the opportunities for young investigators to make the transition from Postdoc to a “Tenure Track” position.

Scrutiny of their ORCID submissions confirmed the impression that the majority of them publish in specialised journals in their fields, at best. There were a few higher impact contributions but these were primarily from a small subset of their team members.

It was hard to be convinced that there was a universal appreciation and acceptance across the whole Unit of the need to drive up the quality of their published outputs (as evidenced by impact factors of their publications). This will be a challenge for the Director in the coming period.

We were concerned that there should be focus on a narrower range of disease areas, methodological approaches and potential molecular targets, in the coming period. There was a lack of clarity as to where groups of investigators came together effectively to share communal equipment platforms.

Their application requested a significant amount of funding for equipment. This was not particularly well justified. We did not see a strong case to provide a Micro CT capability. This reflects the fact that they are some way away from regular “First in Man” evaluations. Their case for Micro CT animal capability is therefore hard to justify at this stage. Similarly, they have aspirations to get into Genomics, Proteomics and Metabolomics at this point and request equipment to achieve this. Again, the absolute justification for any of this is not strong enough. They do not have track records in any of these areas and they therefore lack experienced core staff to run what is sophisticated kit.

Some of their requests are for more routine equipment: new cell culture hoods; etc. Perhaps they can decide how to do this from the core funding awarded? We think the case for the quantitative RT-PCR machine is strong as it would service numerous groups.

An example of their thought processes and the challenges that might emerge could be their developing interest in “Inflammation”. Whilst this is important, there must be concerns about how the Unit can become internationally competitive in a field where other jurisdictions have such strengths. Can they build the levels and depth of expertise in the many branches of immunology that this might require? How does this evolve from their current activities? What strengths do they currently expand from?

The example of asking to make an appointment of a new PI to work in the area of heart failure illustrates our concerns. How can a single new investigator become internationally competitive in such a crowded field? Why not do this in collaboration with excellent cardiology researchers in the same building?

We asked the Unit about succession planning, given their levels of dependence on the current Director. They appreciate that this is an issue and have agreed that it should remain high on their agenda over the next funding period.

In summary, we felt that their performance merited a score of 3.

The Programmatic Funding awarded should be used to hire one young "Tenure Track" investigator, as opposed to the more senior investigator described in the application.

Besides the core funding awarded to this Unit, the Evaluation Panel recommends support for 4 PhD studentships and a single "Tenure Track" PI appointment. The latter ought to be an appointment for the duration of this funding period, with the expectation that the host Institution will take on the salary on a permanent basis subject to satisfactory progress through this probationary period.

There is an expectation that the Center would use its core award for the replacement of core equipment that is clearly necessary. We were not supportive of going into mainstream "OMICS" research through equipment purchase at this stage. They should do this collaboratively where necessary.

Evaluation Panel: HEALTH SCIENCES - Clinical and Translational Research

R&D Unit: Centro de Investigação Interdisciplinar Egas Moniz (CiiEM)
Coordinator: José João Baltazar Mendes
Integrated PhD Researchers: 43

Overall Quality Grade: GOOD
Evaluation Criteria Ratings
(A) Quality, merit, relevance and internationalization of the R&D activities of the Integrated Researchers in the R&D Unit Application: 3
(B) Merit of the team of Integrated Researchers: 3
(C) Appropriateness of objectives, strategy, plan of activities and organization: 3

Base Funding for (2020-2023): 470 K€
Recommended Programmatic Support
PhD Fellowships: 3
Programmatic Funding: 276 K€, including for 1 (Junior) New PhD Researcher Contract.

Justification, Comments and Recommendations
CiiEM, recently implemented, is composed of 18 laboratories forming the Egas Moniz Interdisciplinar Research Centre – Cooperativa de Ensino Superior, CRL. It aims at activating programmes of translational research and training/education in collaboration with other functional structures of the CiiEM and in association with the scientific community to promote interactions in different contexts, including health, health-related sciences and social services. After the 2013 evaluation and with the support of a Scientific Advisory Board (SAB) which included staff members of the European Commission, the CiiEM underwent a restructuring under a new Board of Directors, which included the implementation of: a) governance structures, to foster a qualitative improvement and the adaptation to the growing demands of its environment, b) strategic plan, organisation to define the guidelines for CiiEM activity for the successive years, c) annual monitoring plan of the performances of the Center and of its staff. Currently, the scientific activities are organised in a broad spectrum of thematic areas: environmental health, clinical research, public health microbiology, forensic science and psychology but, notwithstanding some progress made in the last 5 years, much effort still should be done for achieving scientific excellence. CiiEM has eventually grown substantially in size (the number of Integrated Researchers – all with PhD - increased from 29 to 43 in the time interval 2013-2017), without a similar improved quality of its research activities. The total funding was mainly (83%) from FCT, while international competitive funding (from European Commission, companies and industries) represented only 14% of the total and decreased in the last 3 years. The publication output seems to have increased since 2017, but in general in journals with a median-low impact factor (PLoS One, Biomaterials, Brain, Acta Biomaterialia, etc.), with just one publication in Lancet on Healthcare Access and Quality Index, as co-authors among the GBD 2015 Healthcare Access and Quality Collaborators, 2017, not included among the 10 papers mentioned in the application.

In terms of quality, merit, relevance and achievements of the R&D activity in the years 2013-2017, CiiEM's strengths include:

- A. The development of new systems for the treatment/prophylaxis of ocular diseases, based on contact and intraocular lenses aimed to achieve controlled drug release, of particular interest to industries and with an international perspective. In fact, CiiEM coordinated the European Research Project SurfLenses (M-ERANET), a multidisciplinary project involving researchers, clinicians and industry for treatment and prophylaxis of ocular diseases (17 publications, 10 invited lectures and a remarkable training of human resources: 6 PhD students and 14 MSc students). Devices developed within this project are considered as a major clinical advance, since they improve quality of life in the long term, and the project was classified a "success story" of the M-ERANET program.
- B. An Electron Microscopy laboratory created in 2014 in partnership with Duke University (US) and in collaboration with other Portuguese Institutions. It is an ultrastructural diagnosis reference unit with protocols shared with industries and hospitals to perform ultrastructural diagnosis in bioptical samples with national (other Egas Moniz labs, external institutions) and international (the Children's Hospital Colorado, USA, and Sheffield Hospital, UK) collaborations. This unit published 40 reports and organized 7 seminars and courses.
- C. Potentially clinically relevant findings demonstrating a role of lead in bone formation and resorption and consequent energy metabolism, and resulting in the need for re-evaluation of the existing physiologically based kinetic models for lead.

At present, CiiEM is involved in international projects and collaborates with foreign universities. It is desirable that it improves its visibility in the next years, not as few individual groups but as a pool of valuable scientific units. It could take advantage from its visionary policy of advanced training in the research environment, thus ideally setting the future position of CiiEM at the crossroad between academic education, industry and clinical practice.

However, in addition to the points of strength, CiiEM presents weaknesses that coud be overcome by a clearer focus of the research, a better integration among the different disciplines, and the presence of a supportive organization that could foster an increased internationalization. In particular, points of weakness are mainly due to:

- A. Fragmentation and relative dishomogeneity of the thematic areas, with difficult/minimal overlapping.
- B. Despite of the extensive and well-organized management structure there is a lack of a support organization for grant applications, administrative reporting and other tasks, technical transfer, and patenting and IP issues; it is questionable whether one fellow in science and technology, as such a recommendable idea, could fill this gap.
- C. Not sufficiently stringent criteria to define the quality of Integrated Researchers, since the minimun criterion to be a CiiEM Integrated Researcher in the application (3 scientific production indicators over the last 3 years) appears largely inadequate in terms of scientific excellence.
- D. Lack of ongoing collaborations with R&D Units endowing complementary expertise (i.e., the Clinical Dental Research Unit, with 60,000 consultations per year potentially provides an extensive source of dental data for research and would benefit from regional collaborations with experts in preventing and monitoring dental diseases from other R&D Institutes). Such integrative studies, addressed to respond to clear and focused questions, could be clinically and socially relevant in consideration of the prevalence of dental diseases in Portugal, which appears a public health concern.

In addition, although the component of public service complements and enhances the overall performance of the Forensic Science Unit, there are unresolved connections between research activity and public service. Furthermore, the high teaching load probably also impacts on research time.

In summary, according to the Evaluation Panel opinion, CiiEM with its team of Integrated PhD Researchers performed innovation and recognized quality and merit only in some of the thematic areas, contributing for some advancement of knowledge and/or its application in a national perspective, but with limited internationalization in consideration of its valuable size. Significant efforts and progress in restructuring made in the last years deserve some support for the next funding period.

The support of an External Advisory Board with a higher number of international members actively involved in research and with representatives from industry would contribute in reshaping the Center towards a more focused and integrated activity and development of an effective translational research.

Overall, in terms of merit of the team of Integrated Researchers, CiiEM staff includes a group of investigators with a valuable publication track and – for some of them – international visibility. Indeed, efforts have been set in place by CiiEM people to follow the comments of the External Advisory Board to implement the translational profile, extend the participation in European networks and projects, and to organize meetings.

Dr. José João Mendes is the Director of the Center since 2017, involved in the Clinical Dental Research Unit, with an intense teaching activity. He is Section Editor of the European Journal of Dentistry and of RevSALUS - Dentistry Section.

Prof. António Pedro Alves Matos is the Executive Director. He receives international recognition for his work on microscopy and ultrastructure applied to virology and pathology for diagnosis and research, and was elected as president of the International Society for Ultrastructural Pathology. His Electron Microscopy Laboratory is among the most productive of CiiEM, with national and international collaborations.

Dr. Ana Paula Serro has developed new lines of research in the area of biomaterials applied to human health, has several collaborations and publications (67) in specialist journals and coordinated the European project SurfLenses, that has been defined as a “success story” of the M-ERANET program.

In the toxicology area, Dr. Josè A.A. Brito and his group have shed new light on the effect of heavy metals on bone metabolism, with possible implications for metabolic diseases, such as diabetes.

There is a Doctoral Program in Biomedical Sciences within the Egas Moniz University, and the teaching staff – and most of the theses supervisors – consists almost entirely of integrated CiiEM scientists. Collaboration with national and

international scientists and student exchange is mentioned and confirmed by PhD students. At least 3 completed PhD projects during 2013-2017 are mentioned as well as 17 being currently under supervision.

Overall, the profile and standing of the researchers is very heterogeneous and probably related to different tasks and commitments. However, if only research is considered, further efforts are needed to improve the dissemination of results in international journals and to increase the scientific impact. The research carried out at CiiEM is of interest for the patients and its research outcomes should be disseminated among them to increase their understanding of the research structure, and to demonstrate the high qualitative and quantitative levels of e.g. the dental clinic. Moreover, the intra-center communication could be improved. In particular, the PhD students appeared less involved in the organisation of CiiEM compared to PhD students in some other Centers.

Based on these observations, the Evaluation Panel members believe that merit and activity of the CiiEM team of Integrated Researchers could be improved to reduce heterogeneity in performance.

The strategic plan has been neither fully explained in the application nor clearly understood during the interviews. The research activities are wide and a common denominator does not seem to be present. Dental research is considered to have special potential, although niches of quality and innovation are also present in other areas. Efforts should be made to develop a communication strategy to improve the visibility of CiiEM and the access of external organisations and of the general population to information on the Centre activities. It would also be good to implement a regular program of scientific meetings of excellent quality of specific thematic areas, guaranteed by peer review practices for acceptance with publication of communications. In this context, the implementation of an independent evaluation process of the researchers (also in terms of stringent criteria for the selection) and the performance of research groups would support the strategic plan and improve quality and efficiency. At the same time, internationalisation, with particular relevance to participation in EU Programmes that support research and innovation, is a clear and urgent need. So would be the implementation of a supportive legal data and project management infrastructure, including developing a portfolio of intellectual property attractive to the biomedical industry, aiming at gathering budget support to research and make it self-sustaining in the long term.

Funding from FCT is requested to grant 8 new students during 2019-2022 to enable continuity. However, according to the application only a few PhD students completed their PhD during 2013-2017 supervised by CiiEM scientists, and at least 17 students were under supervision in 2017. Some of these students belong to PhD Programs about to terminate in a few years. It is advisable to limit the number of new PhD students to allow a correct conclusion of the course of PhD studies among the remaining 17 students.

The new researcher tobe hired with support of the awarded Programmatic Funding should be a young "Tenure Track" investigator, as opposed to the 3 investigators described in the application, required to identify new research areas. Focus rather than new reasearch areas would be important. For this, it would be mandatory to identify and describe the needed scientific skills of the new recruit.

In particular, there is a plan to hire, in addition to a new PI and an auxiliary researcher, a fellow in science and technology to probe for funding opportunities, to provide administrative support, to collect activity data, to maintain CiiEM website and to promote dissemination. This could be a good idea, although if he/she is the only one carrying out these tasks in a Center of about 60 researches: it is a very tough task!

The request of 10 kEUR/year to support the cost of publication of the book of abstracts of the annual CiiEM Congress on Annals of Medicine does not appear to be a priority.

The application to FCT for additional 2 years funding for the Recovery Program is still undecided but of importance for plans.

Besides the core funding awarded to this Unit, the Evaluation Panel recommends support for 3 PhD fellowships and a single "Tenure Track" PI appointment. The latter ought to be an appointment for the duration of this funding period, with the expectation that the host Institution will take on the salary on a permanent basis subject to satisfactory progress through this probationary period.

Evaluation Panel: HEALTH SCIENCES - Clinical and Translational Research

R&D Unit: Centro de Investigação Interdisciplinar em Saúde (CIIS)
Coordinator: Marlene Maria Tourais Barros
Integrated PhD Researchers: 40

Overall Quality Grade: VERY GOOD
Evaluation Criteria Ratings
(A) Quality, merit, relevance and internationalization of the R&D activities of the Integrated Researchers in the R&D Unit Application: 4
(B) Merit of the team of Integrated Researchers: 3
(C) Appropriateness of objectives, strategy, plan of activities and organization: 4

Base Funding for (2020-2023): 585 K€
Recommended Programmatic Support
PhD Fellowships: 4
Programmatic Funding: 420 K€, including for 1 (Junior) New PhD Researcher Contract.

Justification, Comments and Recommendations
The Center of interdisciplinary health (CIIS) is a virtual research center based in three different locations in Viseu, Porto and Lisboa, all belonging to the Universidade Católica Portuguesa. It covers four research groups: (1) The precision dental health platform, (2) The salivaryTec platform, (3) The nursing research platform, (4) The translational neuroscience platform. The number of Integrated PhD Researchers is 40.

To this R&D Unit application is special that the researchers are belonging to the overall strategic plan of the Catholic University and feel committed to build a 'bridge from Research into the Society'. Much emphasis is put into the ethical and societal impact of their research, which was particularly recognized by this Evaluation Panel.

Overall the productivity of the past funding period has been good. The 10 submitted publications were all published in good, and some in very good journals. They have mostly contributed substantially to the field. In all four fields the R&D performed plays a national role. Particularly the platforms 1, 2 and 4 have many international relations, platform 3 has a national standing. Leadership is limited to Portugal for all platforms, but 1 and 2 may develop international standing in the near future. They are involved in several international projects.

The overall strategic plan is commendable. There is focusing of the activities in the dental research and salivary research platform. The use of salivary for diagnostic and monitoring purposes is not new, but in combination with the community health projects this may be a research area with much promise. The community approach was specifically appreciated by the board. The nursing platform has interesting research projects, including the work on silk-based materials already with a patent, which seem to be well-conducted, and the connection with the platforms 1 and 2 is worth mentioning as positive. For the neurophysiology lab, there is diversity of topics and some of the projects seem to be promising. The goal of developing a brain-computer-interface for controlling an exoskeleton is probably too ambitious and adapting goals to realistic aims is recommended. For all the platforms reconsideration of the strategic aims and particularly focusing the activities further is recommended.

During the site visit the Panel found the PhD students and the PIs highly motivated and in a good standing. As for all R&D Units the lack of protected time for researchers with a high clinical and teaching load is a problem that needs to be addressed at high level within the Ministry.

The speech and language laboratory is requesting two fellowships. Their projects need to be precisely defined, but given the specific orientation towards better communication for deaf people, the application can be accepted. Two further fellowships are asked for by the nursing platform, without specification of a project; they can be accepted as well.

Fundin for four new researchers is requested. One for big data analyses, which is reasonable given their many and increasing databases. This research may definitely increase and strengthen the available strategic line.The Evaluation Panel agreed with this position. The system biologist is wanted for the SalivaTec platform; despite the overarching plan, the need for this was not clear enough and resources are limited.

The two researchers requested in the application on epigenetic regulation and chronic myeloid neoplasms are not sufficiently motivated. The Evaluation Panel sees no need to open a new research field without sufficient manpower and equipment and recommends the group should concentrate on their existing main fields. Adding further subspecialities without clear need will not improve research performance.

Evaluation Panel: HEALTH SCIENCES - Clinical and Translational Research

R&D Unit: Centro de Toxicogenómica e Saúde Humana (ToxOmics)
Coordinator: José Alexandre Gusmão Rueff Tavares
Integrated PhD Researchers: 17

Overall Quality Grade: GOOD
Evaluation Criteria Ratings
(A) Quality, merit, relevance and internationalization of the R&D activities of the Integrated Researchers in the R&D Unit Application: 3
(B) Merit of the team of Integrated Researchers: 4
(C) Appropriateness of objectives, strategy, plan of activities and organization: 3

Base Funding for (2020-2023): 170 K€
Recommended Programmatic Support
Programmatic Funding: 278 K€, including for 1 (Junior) New PhD Researcher Contract.

Justification, Comments and Recommendations
ToxOmics (17 Integrated researchers with PhDs and 9 other researches, of which 4 are PhD students) is the only one among the Centers in this evaluation on translational research with a major emphasis in toxicology, and thus likely to be of national importance. The aims are 1) to identify toxic stressors (including toxicity of drugs), 2) especially in relation to cancer, to evaluate cellular events after exposure including repair responses, as well as to identify genetic variation in these events, 3) to identify aberrations in hallmark genes and their expression as susceptibility factors, and 4) based on all the previous to develop omics-based biomarkers. Responses at cellular level of drugs and other xenobiotics are mechanistically inseparable, and thus drug responses and resistance are not too far from the other, more toxicologically oriented aims.

Among the most challenging environmental/occupational exposures are the nanomaterials, and so far the problem of toxicity testing of nanomaterials has not been solved. In this area the group has established international collaborations, including EU-projects. In general, the expertise of the group is well placed to pursue the set aims. In this area the group has participated two EU projects (NANOGENOTOX, NANoREG (most involved scientist from the Center has been MJ Silva).

The approaches range from exposure and biotransformation (xenobiotic metabolism) to responses, genetic variability in these, and development of 1) genetically engineered system to evaluate metabolism of DNA-damaging agents and 2) omics-based biomarkers of disease. The specific topics are thus diverse under this umbrella and reflect activities of the 3 nuclear researchers. The narrative is quite convincing of a productive Unit. The team is well tuned into important questions for healthy living, i.e. the impact of potential toxic products, and the underlying mechanisms, as well as related mechanistic aspects of responses to xenobiotics, as well as in the development of toxicity test systems for risk assessment.

Strong aspects are the participation in EU projects (though apparently with modest funding) and other collaborations. ToxOmics scientists have collaborators abroad in several countries (USA, France, Germany, The Netherlands, Switzerland). All-in all, ToxOmics is a good team that could still improve its standing internationally through intensified collaborations and international contacts, especially within toxicology.

Overall, the leading team is good. Though there is evidence of international networking, the evidence for international standing such as editorial tasks or memberships in international committees is limited. In the website of ToxOmics about 90 publications are listed 2013-2017. While the related papers are not of particularly high impact in terms of journals, it should be taken into account that in toxicology, as it is a relatively small research area, journal impact over 3 is considered very respectable (e.g. Chem Res Toxicol with Impact Factor 3.4 where the prototype of human CYP competent high throughput method with M. Kranendonk as the senior author was published). The review ‘Cancer Drug Resistance: Overviews and Methods’ by José Rueff and António Sebastião Rodrigues has already received 20 citations by now.

Considering the size of the Center, senior scientists of ToxOmics have been very active in scientific training during the past period (2013-2017) producing 15 completed PhD and 24 MSc thesis. Members of ToxOmics also collaborate with 2 MSc and 2 PhD programs, lecturing and being responsible for some "curricular units" especially in genetics and genetic toxicology. Scientific committees include 2 ToxOmics scientists. Worth mentioning are international collaboration in PhD training with Portuguese speaking countries (e.g. Brazil), and the involvement in training activities for health professionals of the National Institute of Public Health in Angola.

Collaboration and knowledge transfer with SAPEC AGRO include an advanced course "Mutagenicity Tests-Ames Test" and supervision of the construction of cytogenetics and genetic toxicology laboratories. Collaboration in Horizon2020 projects with this company has been established. In addition, a workshop was organized 2016 in Lisbon by H Louro & MJ Silva in cooperation with Paralab: Trends in Nanobioparticles Characterization.

Recommendations:
The Center covers too many areas for a small center. It would be better to concentrate efforts in areas where the Center is the strongest. In translational toxicology the Center is probably the leader (or one of the leaders) in Portugal. Actually, in this area the Center could utilize all of its strenghts: creating innovations based on basic findings of their own and those from the literature in the field of exposure assessment and early disease (omics biomarkers), toxicity testing for chemical risk assessment of new emerging chemicals (futher development of the already existing testing system for potential genotoxic carcinogens, and creating new innovations), creating e.g. basic research and testing innovations in the difficult field of nanotoxicology (already achievements and international contacts), and genetic determinants of susceptibility to toxicity of chemicals (already achievements in the following related topics: polymorphisms within genes related to xenobiotic metabolism, important for detoxication and carcinogen activation; DNA-repair enzymes important in protection from genotoxic carcinogens).

However, basic molecular carcinogenesis is a highly competitive field, and it is represented by several other Centers operating in Portugal in translational cancer research. Also, sleep disorders are studied by several other Portuguese Centers, and this field also dilutes out the possibilities and concentration on their strenghts.

In the application, a new group is proposed on "Genes and ethics", with Helena Borba (PhD in molecular genetics; post-graduation in bioethics) as the head. Among the applications this is the only one proposing such an initiative in research ethics. This sounds very good, considering the known ethical implications of any genetic/genomic research, and shows the sensitivity of researchers to problems generated by genetic/genomic research and their compliance with ELSI issues. The "Genes and ethics" group is presented as a focus group consisting of persons with knowledge and experience in ethics coming from biomedical research, clinical genetics, philosophy and law as well as experts in science communication on genetics and ethics. The aim is transdisciplinary discussions about ethics and critical analysis of the research and processes. In addition, such a group could also lead a concerted effort to do research on status and development of research ethics in genetics in Portugal. Although many opinions and review articles exist in research ethics in genetics, very little empirical research has been published. In discussion it was clarified that such initiatives are already being planned.

The Unit engagement with industry partners is limited and overall budget is predominantly from FCT. There was a substantial reduction in funding for 2015-2016 and consequent reduction in the size of the Unit. This is likely to have impacted output. Funding in 2017 increased again. The requested budget is not sufficient for the ambitious plans. More investment in young researchers is warranted as well as a plan for future leadership.

The management Committee includes three Integrated Researchers of the Center, and deals with scientific/ technological, teaching, out-reach as well as administrative matters. Involvement of all the PIs in decisions about scientific matters and younger scientists in the management would be recommendable.

The External Advisory Board (former and proposed) includes three Portuguese members. Additional international members would definitely help in international contacts, tuning the activities in translational toxicology, and further development of the Center.

The Center requests funds for hiring new PhD holders, and the Panel recommends one in the area of their most need, for conducting R&D activities with a considerable degree of autonomy and able to guide and supervise younger researchers. This definition of the requirements means that the requested person could not be fresh from a doctoral school, but would need some years of postdoctoral training.

Toxomics supports its researchers to participate in a national research network with the aim to join the ESRFI (European Strategy Forum on Research Infrastructures) EU-Openscreen in high throughput and high content screening. Infrastructure, assays and a national compound library are planned to be provided. Currently 17 Portuguese institutions aim to participate and at least 12 are expected to actually join. The annual fee would be 5000 € per institute, and the total for 2019-2022 would be 4x5000 =20 000 EUR. This request is supported by the Evaluation Panel.

The rest of the requested funding supported by the Panel is to be used for advanced human resources and laboratory consumables essential for everyday functions.

Evaluation Panel: HEALTH SCIENCES - Clinical and Translational Research

R&D Unit: iNOVA4Health - Programa de Medicina Translacional
(iBET, CEDOC/FCM, IPOLFG e ITQB) (iNOVA4Health)
Coordinator: Manuel José Teixeira Carrondo
Integrated PhD Researchers: 162

Overall Quality Grade: EXCELLENT
Evaluation Criteria Ratings
(A) Quality, merit, relevance and internationalization of the R&D activities of the Integrated Researchers in the R&D Unit Application: 5
(B) Merit of the team of Integrated Researchers: 5
(C) Appropriateness of objectives, strategy, plan of activities and organization: 4

Base Funding for (2020-2023): 2579 K€
Recommended Programmatic Support
PhD Fellowships: 18
Programmatic Funding: 831 K€, including for 3 (Principal) New PhD Researchers Contracts.

Justification, Comments and Recommendations
The Unit iNOVA4Health (iN4H) is a large consortium gathered around the common goal to perform translational research, moving basic discovery research to innovation and clinical testing. iN4H brings together transdisciplinary and translational activities across four Centers. The coordination is at iBET, Instituto de Biologia Experimental e Tecnológica, in Oeirias, with the second Center, ITQB-NOVA, Instituto de Tecnologia Química e Biológica, at the same location, a third Center CEDOC/NMS, Centro de Estudos de Doenças Crónicas, located at ITQB-NOVA, and the fourth Center IPOLFG, Instituto Português de Oncologia de Lisboa Francisco Gentil. Furthermore, the Unit has partnership agreements with 13 other institutions, including research institutes, as well as hospitals, Bayer Pharma Company and a non-profit organization in support of diabetes patients (APDP). This alliance is well placed to fulfill the overarching mission of iN4H, namely to promote excellence in translational research that will emerge in precision medicine. iN4H can support its research activities by attracting external funding and by forming partnerships, including with industry. Major funding came through these international (competitive) granting, and public-private partnerships (PPP).

In the last FCT funding period iN4H has grown its publication output substantially. Attracting external funding, forging strategic collaborations and stimulating translational research led to high quality achievements in different areas. The application lists several high profile papers that were produced by the group as leaders, alone or in collaboration, and highlights major achievements. These link to different fields of discoveries and translation. Many years of preclinical research for gene therapy led by Dr. Seabra, currently group leader at iN4H, have resulted in a phase1/2 clinical trial of gene therapy to treat choroideremia. Within iN4H the group of Paula Alves has set up a high quality system to grow human stem cells, with a quality grade to support eventual clinical use, as well as diagnostic and discovery research. Another area highlighted is the discovery of a novel pathway to modulate insulin signaling that could hold promise for diabetes. This work in rodent models has attracted attention for further study in collaboration with industry. Work on neural development and control of neural stem cell fate, has resulted in an ERC starting grant and the recruitment of a junior scientist to iN4H to continue this work in iN4H. In the cancer field, novel ex vivo models based on patient tissues were successfully developed and can be used for future studies of mechanisms and diagnosis to guide therapy. The publications further include reports on work in pharmacology, infectious disease and development. Most of the work was performed in iN4H, in others iN4H was partners and all was published in high profile journals.

In the period 2013-2017, iN4H operated as a consortium of 17 research groups. Each group has meritorious output in this period. The research has in addition two overarching themes: CeaseAge, Chronic Diseases and Healthy Ageing and TReAT, Translating Research to Advanced Therapies. Regular meetings and central infrastructure support internal collaboration, and the training of PhD student ant younger researchers.

A major achievement has been the promotion of excellence and tackling of the most relevant research questions through quality control and prioritization of research projects across the themes. An External Advisory Board has helped in selection and awarding of internal grants that stimulated collaboration between research groups and cross-disciplinary research. This exercise created more cohesion in the group and led to a new structure for the future. The

External Advisory Board is comprised of world-class scientists, including industry experts, and is a major asset to the Unit.

The Evaluation Panel recognized the major achievements of iN4H but also found that the program could have been more performant towards clinical translation, as expected for the call. Although the questions are driven by medical needs, they remain mostly in the mechanistic preclinical discovery phase. The research has potential for translation but the implementation is lacking. There is little input from clinical partners visible in the output at this time. There is no participation in clinical research from iN4H in Portugal. Use of human tissues for stem cells and ex vivo studies is still limited. The activities towards health care and society are equally limited.

The attention for innovation and development of products for testing, (pre)treatment with companies has a long-term perspective towards health and therefore appreciated, but cannot replace more patient-oriented activities.

In summary, the outputs of the Unit underscore the translational and preclinical research activities of the Unit and their engagement in innovation for health in major disease areas, such as neurologic disease and cancer. The activities received international recognition but iN4H still needs to consolidate independent leadership status as international reference from Portugal. The translation toward clinical implementation, patient interaction and health promotion should be improved.

iN4H is a very large consortium with 162 integrated PhD researchers across the 18 research groups in 2018, compared to 127 in 2014. There was a fast growth after 2014, but this has stabilized and in 2017, the Comprehensive Health Research Center left iN4H. Presently, about half of the Integrated Researchers hold a MD degree.

The Coordinator, Prof. Carrondo, has an outstanding scientific record in the areas of cell biology and technology, engineering in virology and vaccine development and more recently stem cell biology. He has expertise in translation of findings into innovative products, developing pilot production and working with industry. He founded GenIBET Biopharmaceuticals and currently holds several positions in advisory boards. He has been a dynamic leader taking the group forward and stimulating collaborative work through different funding schemes. The management of the Unit is very well structured through a board with high-level representation from all participating institutes and discussing twice a year about management, budget and scientific reports.

The faculty consists of a good mixture of established senior investigators and a large cadre of younger investigators of high promise. Each of the 18 research groups has leaders with a very good to excellent record of accomplishment. It is notable and much appreciated that iN4H has attracted researchers who have had outstanding achievements in international positions and who now bring their experience and international networks to the Unit.

Each year, on average, 22 PhD students have graduated.

The quality of the team is recognized and the current strategy for recruitment is excellent.

In 2018, iN4H started a restructuring from projects to programmes, and establishing three novel thematic lines: Neuro-vision disorders, Cardiometabolic disorders and Cancer. These bring the different research groups together in an admirable way; through the ‘Lighthouse’ programmes, the Center stimulates collaborative activities.

The future plans retain a clear future perspective to preclinical research guided by medical needs, and pathways to innovation. However, the Evaluation Panel has some concerns that the future plans do not sufficiently address clinical needs. For better clinical translation, the iN4H will need effective collaborations with clinicians. The Unit has initiated such collaborations on a more personal basis, building a relationship of trust, e.g. in the field of ophthalmology, or studies in nutrition. More formal integration and associations within Portugal are possible and need further attention. A development plan for future leadership is needed.

The Unit has a very good training record and additional investment is to be supported. Yet, the number of PhD students fellowships requested was found excessive and the dispersion across different doctoral programs not very efficient. The Evaluation Panel recommends awarding 18 fellowships.

The request for funding to hire new PhD researchers presents a broad distribution of all research lines. It does not align with the recommendation for focus from the Panel. The Evaluation Panel recommends to award 3 researcher positions to strengthen translational and clinical research.

iN4H is a strong and dynamic Center. The Evaluation Panel recommends additional funding to be invested in strengthening translation towards clinical application and clinical research.

Evaluation Panel: HEALTH SCIENCES - Clinical and Translational Research

R&D Unit: Unidade de Investigação e Desenvolvimento Cardiovascular (UnIC)
Coordinator: Joaquim Adelino Correia Ferreira Leite Moreira
Integrated PhD Researchers: 49

Overall Quality Grade: EXCELLENT
Evaluation Criteria Ratings
(A) Quality, merit, relevance and internationalization of the R&D activities of the Integrated Researchers in the R&D Unit Application: 5
(B) Merit of the team of Integrated Researchers: 4
(C) Appropriateness of objectives, strategy, plan of activities and organization: 4

Base Funding for (2020-2023): 637 K€
Recommended Programmatic Support
PhD Fellowships: 9
Programmatic Funding: 696 K€, including for 2 (Auxiliar) New PhD Researchers Contracts.

Justification, Comments and Recommendations
The Cardiovascular Research and Development Center UniC, at the University of Porto and in partnership with the Centro Hospitalar de São João, was founded in 1994. It is fully dedicated to cardiovascular research, and thereby one of only two such R&D Units in Portugal. Its R&D spans from basic experimental to clinical research and outcome population studies in cardiovascular diseases, more specifically heart failure. UniC has grown substantially in size and quality of its research activities. In particular, since 2013 the number of researchers has grown by 40%, both in PhD and non-PhD researchers. Competitive funding has doubled, including funding from the EU in COST action and H2020 collaborative projects. The publication output has also grown by 40% with inreasing visibility and international profile. The publications that the Unit has presented as their major achievements are interventional and experimental studies that were led by UniC: two monocentric clinical studies in heart failure, a large multicenter clinical study on imaging in heart failure, and four experimental studies in a rat model of pulmonary hypertension and right heart failure, with international participation. These studies were all published in leading journals in the cardiovascular field. The UniC also led the two international consensus statements from the European Society of Cardiology working group on Myocardial Function on how to study heart failure with preserved ejection fraction (HFpEF) and how to study right ventricular function.

The Unit has developed a highly valuable biobank of myocardial tissues specimens through the engagement of the cardiosurgical team and the researchers at UniC. Within the world, such collections are rare, and the further planned development is a major asset of the Unit. It can support validation of translational research, exploration of molecular patterns and mechanistic research. The work links to the clinical data collection and data mining.

Another strength of the Unit is their competence and expertise in ventricular function supported by infrastructure for functional studies from single heart cells to in vivo heart function.

To develop translation of knowledge into clinical benefit, the Unit has studied the value of biomarkers in outcome prediction in heart failure and set up registries for further studies. Novel algorithms based on natural language processing of the electronic health records (patent submitted) could unlock valuable information.

The UniC reaches out to society through educational programs of health literacy and the importance of a healthy lifestyle for prevention.

In addition to these strengths, the Unit also has some weaknesses that need to be addressed. The clinical research activity should be strengthened. The data mining project will require focus and defining specific relevant questions. This work would benefit from international collaboration, and should include working with experts in the field of big data handling and in epidemiology. The UniC has acquired a strong position within Europe and should now reach out beyond and intensify collaboration with other leading groups in the world. They should aspire to publish their research in the top journals. Extending the Advisory Board with international members that are not collaborators and with representatives from industry will benefit the development of the translational research activities.

In summary, the outputs of the UniC underscore the translational and clinical research activities of the Unit and the internationally leading position in Europe for the study of HFpEF and right ventricular function. The further development of the human biobank, of outcome studies and data mining using HER, supported through international collaborations, will strengthen the clinical translation in these major challenges for cardiovascular medicine. Prevention and health promotion are important to complement this work.

The UniC team of Integrated Researchers with a PhD has grown steadily from 29 to >50 between 2013 and 2018. The majority of the researchers hold a MD/PhD degree, in support of the translational mission of the Unit and they participate in research at international level. There is a good gender balance in the team, including in the leadership.

The elected Coordinator, Prof. Adelino Leite-Moreira is a cardiovascular surgeon who has an excellent record of accomplishment of publications and has a high visibility and standing in the international community of heart failure. He is a driving force in the functional hemodynamic studies of heart failure and the main facilitator for the unique heart tissue biobank collection. He has participated in large international consortia and the writing of consensus documents. The research activities of UniC are led by five research topic coordinators; all of them have a very good record of accomplishments; e.g., Dr. Bettencourt leads the heart failure program and clinical studies on the value of biomarkers in predicting outcome and prognosis. On this topic, he has published well-cited papers as lead author, included in top journals of the cardiovascular field. Dr. Brás Silva leads the program on pulmonary hypertension. As an Assistant Professor since 2017, she is an early career scientist and has a very good record in experimental studies. Expert and technical support is provided through four Units. Dr. António Barros leads the data science unit. He is a bioinformatician with extensive international training and strong publication record. Dr. Tavares is in charge of the educational program, which includes the societal reach-out. She has published several papers on educational sciences.

Of note, the majority of the Integrated Researchers have an MD degree, supporting the translational mission of the UniC. This is also true for the PhD students, who form an enthusiastic and close-knit community, dedicated to improve cardiovascular medicine.

The quality of the team is recognized and could improve further. The Panel advises to place more focus on publishing in top journals with high competition and thereby further enhance impact of the work and give more visibility.

The UniC will continue its research in heart failure and HFpEF, which is a disease with increasing prevalence, linked to comorbidities such as diabetes and kidney disease. They wish to lead the research in this field and improve their international position. Pulmonary hypertension and right heart failure remain as topics with a strong experimental-translational component.

For the experimental translational work, the UniC wishes to consolidate its large animal research facility and expertise, which could also be used for surgical training.

The UniC plans to strengthen the clinical research and expand the patient cohort and data collection from clinical health records. They will improve the bioinformatics approach to gain insights in the value of different biomarkers and discover new parameters through data mining and machine learning algorithms. To this effect, they have recruited biostatisticians and experts in data mining, a field where they also plan for further investment. The biobank is highly valuable asset that requires continued investment and needs to be opened for collaboration.

These plans for future activities are addressing important medical needs in cardiovascular disease. It is important for UniC to maintain focus and consider further concentration on fewer topics, rather than add new topics, with the ambition to have more impact and leadership in the field.

The UniC has secured good funding for translational research but could possibly increase its public-private collaborations with industry and increase its clinical trial activity. Outcome and effectiveness studies are part of UniC's program that could further expand.

Prevention is an important pillar in fighting cardiovascular disease. Health promotion and studies in prevention could be strengthened.

The UniC has requested 16 PhD fellowships for the next funding period. This would double the number of fellowships already secured. UniC has an excellent training record in particular for MD/PhDs and additional investment is to be

supported. Yet, the number requested seems excessive and the Evaluation Panel advises to award 9 fellowships in the program Doctoral Programme in Cardiovascular Sciences.

UniC requests support for 9 additional PhD researchers. The motivation for these researchers stems from the areas they want to develop. The Panel finds support for additional researchers justified. Strengthening the team of the data sciences will support two important research lines: the use of EHR and the data registries, and the translational biomarker studies. Researchers with a medical training to engage in the clinical research will support the Panel recommendation to develop the clinical research. The request for additional 6 Assistant Researchers presents a broad distribution of all research lines. It does not align with the recommendation for focus from the Panel.

The UniC has a very dynamic group of young researchers, mostly with MD degree, who testified on the quality of training for translational and clinical medicine. Providing more positions will support the translational qualification in cardiovascular research and the needed expansion of clinical research and use of clinical data. The UniC requested startup funds for the newly hired researchers. The Evaluation Panel considers that the Unit deserves additional support and hence proposes additional funds for that and for enhancing international networking. Using this support to participate in ESFRI programs is strongly recommended: accreditation of the biobank and integration in BBMRI; participation in ECRIN and ELIXIR.

Evaluation Panel: HEALTH SCIENCES - Clinical and Translational Research

R&D Unit: Unidade Multidisciplinar de Investigação Biomédica (UMIB)
Coordinator: Lídia Mariana Rodrigues Pereira Monteiro
Integrated PhD Researchers: 55

Overall Quality Grade: VERY GOOD
Evaluation Criteria Ratings
(A) Quality, merit, relevance and internationalization of the R&D activities of the Integrated Researchers in the R&D Unit Application: 4
(B) Merit of the team of Integrated Researchers: 3
(C) Appropriateness of objectives, strategy, plan of activities and organization: 3

Base Funding for (2020-2023): 533 K€
Recommended Programmatic Support
PhD Fellowships: 5
Programmatic Funding: 413 K€, including for 1 (Junior) New PhD Researcher Contract.

Justification, Comments and Recommendations
This Unit is a multidisciplinary research Institute based in the Institute of Biomedical Sciences Abel Salazar and in close proximity of the Centro Hospitalar do Porto (CHP). Thus, it has the advantage of being close to the hospital which is important for recruitment of clinical cohorts and samples and to have the research laboratories nearby. The Unit changed leadership during the previous funding period and has initiated a number of changes which are still in progress. The present leadership is organized such that the Executive Board consists of the Unit Coordinator together with the Director of the Dept. of Education, Training and Research. The major scientific priorities are decided by the Executive Board together with the Scientific Committee representing all major team Senior Principal research leaders. This allows for a good integration of responsibilities and should ensure good implementation of decisions.
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The Center is mainly focused on four research pillars: Hereditary & Genetic diseases; Metabolic, Cardiovascular & Endocrine disorders; Immunity, Infection & Inflammation and Oncology & Oncobiology. The Unit has been quite productive and published 148 scientific articles by 2017. Although many are in low to medium impact international journals and national journals, there are also publications in international high impact journals including Blood, Nat Communications, Gastroenterology and Brain. Interestingly, they have identified several novel rare disorders, which is an important area of research and where they also are a national diagnostic center, involving both hematological, auto-immune disorders and also novel genetic and other markers for epilepsy and lung cancer. Additional translational research is documented by interesting clinical follow-up data on diabetes remission after bariatric surgery.

Taken together, the Unit has been quite productive during the previous funding period with efficient leadership and integration. There are several international collaborations and participations in European Networks. However, international funding, including from EU, is quite small and they should be more involved in international research applications. The closeness of research facilities and the hospital promotes the involvement of medical doctors in the translational research.

The Unit is a national referral center for rare disorders but mainly for diagnostic purposes since they do not have specific clinical expertise or resources for treating these patients, what may require extensive resources.

The requests prioritize recruitment of 5 new researchers to “re-vitalize” the research team, probably meaning new technical expertise. They will both participate in the ongoing research but also further expand on existing omics technologies and bioinformatics. It is also planned to allow better access to large clinical databases for epidemiology and quality of clinical care. They also plan to further foster international collaborations and to participate in European Networks (10 kEUR requested). A major plan is to expand on existing omics technologies with both equipment and support. This is both for own research purposes as well as for the national diagnostic procedures on rare disorders (600 kEUR requested). In addition, it is planned that the Unit could become a national omics center which could be used by others on a fee for service basis. It is not clear that such a national omics center is needed since many of our visited Units reported on own facilities. Furthermore, such plans need to be agreed upon by the national users including specific resources needed, but no such plans or agreements by others were reported on.

UMIB has undergone positive changes under the new leadership and has been quite productive scientifically. It is a national reference center and has clear international interactions. However, the plans for investing into a national omics center are too premature and not convincingly demonstrated as a need and agreed on by potential users.

The translational approach and scientific expertise of Principal Investigators in the different areas is documented by the publications where several are in major international journals. The Unit has organized a PhD course in "Clinical Endocrinology and Metabolism", which transverses several of their research areas and seems to be well planned. Discussions with PhD students and Postdocs also gave the impression of positive involvement, and most participants were MDs, which is a clear merit from an international perspective where this is less frequent. It was also positive to hear that PhD students were involved in the Media Board and thus the responsibility of informing the public about ongoing research.

Taken together, the Unit has good expertise in their research areas, but should further enhance its international collaborations both in terms of own involvement but also to acquire additional funding. It is surprisingly small, if any, the expected international and EU funding by the Unit. Further promoting international collaborations should be a high priority and make the Unit more competitive from an international perspective. From a national perspective the Unit is quite successful.

The objective to "re-vitalize" research is commendable and should be promoted. The request of funds for participation in EU networks and is part of the desirable improved internationalization. PhD student grants should also be allowed according to their merit. It is also a good plan to use funding for better infrastructure, including also better administrative support for writing large grant proposals. However, the request for a national omics center is not reasonable at present; considerably better planning is required.

The funding recommend is for priorities in participation in the European network ECRIM and an eligible request, and for administrative research support, upgrading of omics equipment, and ongoing research activities. The Evaluation Panel also recommeds funding for hiring a new researcher for ongoing activities, but the area is not defined by the Panel and is to be decided by the Executive Board. Besides, the Panel recommends awarding 8 PhD students fellowships.