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CONICYT
FONDAP - FONDECYT

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SCIENCE AND TECHNOLOGY
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DATE

NATIONAL PROGRAM FOR ADVANCE RESEARCH CENTERS (FONDAP)

CONTINUITY PLAN EVALUATION REPORT

This form is intended to facilitate your work as a referee and standardize the evaluation reports. Each topic is expected to be evaluated with concepts ranging from outstanding to poor and detailed technical comments supporting your views on the proposal and the site visit. If the proposal or the site visit do not contain information on the given topic, please indicate so in your evaluation.
Your final overall comments and recommendations are an important part of the review process.

I. PROJECT INFORMATION
CENTER'S NAME: Center for Molecular Studies of the Cell (CEMC)
DIRECTOR: Dr Cecilia Hidalgo

II. EVALUATION PANEL			
REFEREE NAME	ORGANIZATION/ INSTITUTION	E - MAIL	SIGNATURE
Prof Peter McNaughton	University of Cambridge, UK	pam42@cam.ac.uk	
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III. PROPOSAL EVALUATION

1.- Goals and objectives for the next five-year period

i.- Comments

Introduction: the first five years

The FONDAP Center for Molecular Studies of the Cell (CEMC) brings together a group of six established investigators with cognate interests in cell signaling. In operation since 2002, the center comprises group leaders with interests in calcium release in skeletal muscle and neurons (Cecilia Hidalgo, Director), the role of caveolin in colon carcinoma tumorigenesis (Andrew Quest, Deputy Director), role of StAR in steroidogenesis in human corpus luteum (Luigi Devoto), slow Ca signals and regulation of gene expression in skeletal muscle (Enrique Jaimovich), cation channels involved in apoptosis (Stutzin) and cell death signaling in cardiomyocytes (Sergio Lavandero). All Center participants are substantial scientists with international reputations, publishing in the main in internationally recognized journals. Few of the Center participants had worked together before, apart from an already established collaboration between Hidalgo and Jaimovich, so the aim of increasing collaborative research through the formation of the Center was a laudable and realizable one.

One of the main aims of the Center was to foster research links between groups, both by the formation of joint research projects and by sharing equipment. Achievement of this aim has been highly successful. Collaboration was fostered initially by co-direction of PhD theses. This has led to several co-authored manuscripts, with others in the pipeline. To date 59 thesis projects have been initiated, with 11 being joint, and 25 have been completed. It was noticeable to us that in a substantial number of cases these publications had as their first authors PhD students in a Center lab, a valuable addition to the CV of a young investigator. At a later stage 16 postdocs were appointed, but it is too early for a significant number of joint publications to have fed through from these appointments.

A second major aim was to improve training of young investigators. Five young “associate investigators” were appointed, of whom three remain at the start of the second five-year period (Hetz, Mears and Michea). These associates do not receive direct funding from the Center, apart from a salary supplement, but they have access to Center facilities and have a number of joint projects with Center Principal Investigators (PIs). The Center contains a large number of doctoral and postdoctoral workers, with approximately one third being funded through the FONDAP Center, one third through CONICYT bursaries or FONDECYT grants, and one third though other means. A number of advanced training courses were organized, with at least one major conference featuring overseas speakers being organized per year. In our interviews with student and postgraduate audiences all were emphatic in their appreciation of these courses, and of the opportunity they offered for them to interact with leading scientists from overseas.

A final principal aim of the Center was to promote outreach activities to specialized and to non-specialized audiences. The former aim is met through provision of the advanced training courses noted

above. Center scientific activities are also publicized to non-specialized audiences through participation in the EXPLORA program of CONICYT, and via the website, newspaper articles and by other means.

Goals and objectives for the next five year period

The principal over-arching research objective for the next five-year period is to focus collaborative efforts in three interrelated cell-signaling areas where there is existing overlap between the current individual research projects of two or more team members, namely: Redox signaling, Calcium signaling, and Cell death. The focus will be mainly on cell types already being studied in the Center, namely excitable cells (muscle and neurons), hormone-secreting cells (pancreatic β cells and progesterone-secreting human ovarian cells) and normal and cancerous epithelial cells. This new strategy of focused collaborative projects represents a further step in bringing the research areas of Center members into focus on a small group of related problems. By pooling efforts in this way the Center aims to generate publications in higher-impact journals.

A second major aim will be to enhance the technical capabilities of the group by acquiring the following: space in an existing barrier animal facility suitable for work with genetically modified animals; facilities for adenovirus and lentivirus construction, and appropriate animal facilities to allow injection of these constructs into rodent models; enhancement of existing calcium imaging facilities; and access to proteomics and transcriptomics facilities.

A third major aim will be to enhance the physical environment by refurbishing a derelict building adjacent to the Facultad de Medicina, to which the four Center members currently located there (Hidalgo, Jaimovich, Stutzin and Quest) will move. Devoto and Lavandero are located further away and will not join other staff in the new building. This move will improve lab facilities, which are currently cramped and substandard, for the four members who will move, and will improve the possibilities for close collaboration between them. Refurbishment of the building will be financed by the Universidad de Chile.

A fourth aim is, through focused basic research, to address problems in human health relevant to the country. With this aim in mind a number of collaborative projects will be initiated with clinical researchers, particularly in the areas of cancer and age-related pathologies, funded by small seed grants from the Center. In addition, CEMC PIs have the expertise to propose and participate in Phase I or II clinical trials. They will establish alliances with groups of accredited physicians that hold standards of Good Clinical Practice (GCP) in order to conduct phase III trials.

In terms of postgraduate research training, further efforts will be made to send CEMC students to foreign laboratories in exchange programs. Up to twelve students will be trained in such exchanges. No other major changes are planned in the training and outreach programs of the Center, which will continue in the form noted above. The training programs for advanced students and postdoctoral workers are, as noted above, already well established and successful.

ii.- Evaluation

X			

Outstanding Very Good Good Poor

2.- Expected educational impact of the center in the short and long term. Please analyze the Center strategy to influence human resource formation (PhD students and postdoctoral fellows).

i.- Comments

An extensive training program has been set-up within the Center of Excellence that currently includes 49 PhD students and 18 postdoctoral fellows. This represents a considerable effort in term of training of students at a level that should allow their forthcoming insertion in academic or industrial activities. It should be noted that the scientific training of the PhD students in the laboratories and more generally within the network is achieved in a satisfactory way by qualified researchers, including postdoctoral fellows, since a substantial proportion of them have two supervisors from different teams. This is illustrated by the involvement of most of the students in at least one publication, which often appears in periodicals with a good impact factor. It should be added that the training of students in several techniques of molecular biology, together with other tools such as the use of transgenic animals and confocal microscopy, should be enhanced within a few months by the implementation of high performance liquid chromatography associated with tandem mass spectrometry for proteomics, and lentiviral vector technology for the production of gene specific interfering RNAs for the inactivation of gene of interest in animals. It is clear that the introduction of the latter techniques should provide further high-level training for many of the Center PhD students and postdoctoral fellows. Another positive aspect that should be taken into consideration is the possibility for most of the postdoctoral fellows to be involved in the training of PhD and undergraduate students. It may also be stressed that the clinical environment and the development of translational studies with biomedical aims within the Center should be highly beneficial for students searching for positions in more applied research fields.

The training of the students and postdoctoral fellows is also efficiently completed by the excellent scientific environment provided by CEMC, with the organization of weekly seminars that allow dissemination and discussions of the results of ongoing investigations. This is further strengthened by the existence of three interfaculty post-graduate courses of the Universidad de Chile devoted to cell signaling and molecular biology. The organization of one international conference annually by the network should favor discussions and contact with outstanding participants from abroad. Therefore the training provided to the students and postdoctoral is overall is of great value both from a practical point of view (we note the course aimed at training students for reading and writing papers in English) and from basic points of view. This training should contribute to the formation of scientists who are essential for the development of the country (University, industry ...).

ii.- Evaluation

Outstanding	Very Good	Good	Poor
X			

3.- Initiatives proposed to be undertaken by the Center related to scientific and technological innovation and its applications to the development of the country. Please analyze the Center strategy to get involved with problems concerned with the development of the country.

i.- Comments

The center has provided research of excellence individually and in collaboration in the general area of signal transduction in normal and aberrant cells during the five year period, as summarized in section 1. The areas of research were related to calcium signaling, cancer, cardiac cell death, ovarian steroidogenesis, ion channel mediated cell death. These areas of research used approaches by classical techniques including molecular biology, cell biology, cell culture, electrophysiology, and calcium imaging. Each team has specific skills in one approach, which has promoted collaborations between PIs as attested by copublications and cross-training of students to allow them to use all the techniques available. The proposal for the next five years is also based on the study of signal transduction mechanisms in mammalian cells but is more focused on three interrelated cell signalling areas (redox signalling, calcium signalling and cell death) in which the PIs have established high international reputations through high-impact publications in the past five year period.

The new research proposal is associated with the development of new strategies involving scientific and technological innovations in several ways that will be of major interest for the country. The recruitment of three new associates (Hetz, Mears and Michea) as fully independent investigators will favor the development of key technical platforms to be used by the center, and will also be advantageous to other researchers of the same campus and elsewhere. These include animal facilities to generate and breed genetically modified mouse models, adenovirus and lentiviruses technologies to transfer constructs into cells and intact animals in order to inactivate specific genes, calcium imaging including access to confocal and (in the future) two-photon microscopy, transcriptomics to assess gene repertoire expression level, and finally proteomics. This last technique is a good example of a new technical innovation in the biomedical area which allows protein complexes important in transduction mechanisms to be identified, but it is based on very expensive equipment requiring coordination of several centers or laboratories, on several sources of funding, on a specific organisation and on specific dedicated personnel. Currently the use of this technology is not available in Chile and can only be achieved through collaboration with foreign labs, an approach which has many limitations. Setting up this new technology as a coordinated process within the university is an important issue for the Chilean scientific community and can generate applications in other fields of research including clinical research.

Cell signaling mechanisms are proposed to be investigated in different cell types (cardiac and skeletal myocytes, neurons, pancreatic β-cells, ovarian cells, and normal and cancerous epithelial cells) relevant to common pathologies. The center plans to promote research addressing human health problems of relevance to the country. The center also proposes to expand interactions with clinical and other researchers in health related areas. Their research on targets relevant to various diseases (cancer, cardiovascular, myopathies, memory..) is expected to interest pharmaceutical companies within or outside the country. In addition, the basic/clinical interaction which is a feature of the continuity plan can lead to new therapies. Insights gained on ovarian cell function, in particular, can lead to applications in terms of contraception or fertility. All these aspects should be considered in evaluating the potential components of Center research activities that can generate patenting or financial support from industry. This seems quite consistent with the recent establishment of a special licensing and patenting unit within

the University of Chile, mentioned to us by the University authorities, which will aim to promote such developments.

ii.- Evaluation

☐	☒	☐	☐
Outstanding	Very Good	Good	Poor

4.- Main goal changes since the first proposal of the Center and their effects in the plan for the following period.

i.- Comments

There have been no major goal changes proposed for the second five-year period from those present at the start of the first five-year period, but there have been a number of elaborations and extensions of pre-existing goals. The evaluation panel was impressed with the way in which goals outlined in the initial proposal have been achieved, and we support the reformulation of goals proposed for the second period. The main elaborations of the initial goals were summarized in Section 1, and are briefly reviewed here with further comments.

1. *Focus of collaborative effort around three main areas of research complementarity, namely Redox signaling, Calcium signaling, and Cell death.* The panel was impressed by the way in which team members had forged collaborations in complementary areas in the first five year period of the Center. Positive outcomes of collaboration include a higher publication rate and a higher rate of citation of Center publications than prior to formation of the Center. The opportunity for graduate and postdoctoral workers to access equipment from several Center groups, and thereby to gain experience in an extended range of modern research methods, has also been a highly positive development. The further focusing of research aims round a small group of complementary themes in the second five-year period of the Center represents a logical and desirable forward move which will enhance all of the above positive outcomes.
2. *Enhancement of the technical capabilities of the Center.* Purchases of equipment using funds from the FONDAP grant and from other sources have significantly enhanced Center technical capabilities during the first five-year period, but it remains an inescapable fact that the level of technical equipment is still well behind that of leading labs in Europe and the USA. Access to barrier animal facilities suitable for creating and breeding transgenic or immune-compromised mice (such as the nude mice important for the program of Quest); facilities for creating viral constructs and for using them to manipulate gene expression in intact animals; confocal and two-photon microscopy; and facilities for proteomics and transcriptomics are considered normal in leading laboratories, and to publish in front-rank journals the use of a combination of such techniques is usually required. In this context, therefore, the proposal to acquire some of these facilities during the second five-year term of the Center must be regarded as an essential progression. We note that the availability of such facilities will also be highly beneficial to other workers in Chile, where some of the above-mentioned facilities are currently not available in any location.
3. *Improvement of the physical environment, mainly through refurbishment of an existing derelict building.* The existing facilities for some of the groups (principally the groups of Hidalgo and Jaimovich) are cramped and substandard. The refurbishment of an adjacent derelict building, and the move there of the four groups currently housed in the Facultad de Medicina to modern research facilities in this new building, which has been agreed and will be financed by the University authorities, must therefore be regarded as a highly desirable outcome. The evaluation panel strongly supports this development and urges the University authorities to implement the planned refurbishment without delay and to a high standard.
4. *Development of themes in translational research relevant to human health.* The main focus of the majority of Center members (with the exception of Devoto) has in the past been on fundamental research, and from its inception one aim of the Center has been (partly through the inclusion of Devoto amongst founder members of the Center) to promote research with applicability to clinical

medicine. The Advisory Panel in its report at the two-year mark had also urged the Center to devote a part of its efforts to translational research. Several research lines proposed in the plan for the next five years of the Center contain a translational element (see section 5. below). A second proposal is to develop clinically oriented projects through the provision of small seed funds to clinical colleagues, with the aim of carrying out preliminary experiments which could later form the basis of full applications to (for example) FONDECYT. The evaluation panel could see several areas of current Center research with possible clinical outcomes, and we strongly support this positive development.

5. *Training of students and postdoctoral workers.* The existing program has been successful in allowing students and postdocs to have access to a wider range of ideas and techniques through collaborations and joint supervision of projects and through access to advanced taught courses, workshops,and conferences, as was confirmed to the evaluation panel in our private meetings with PhD students and postdocs. The proposal for the next five years is to continue with the existing program, with the main extension being that further efforts will be made to send successful postdocs to collaborator labs overseas. Outreach activities to non-specialist audiences will continue as outlined in the proposal for the first five years.

ii.- Evaluation

[X]	[ ]	[ ]	[ ]
Outstanding	Very Good	Good	Poor

5.- Research lines of the Center, including their feasibility and validity.

i.- Comments

- The CEMC research center focuses on the study of the signal transduction mechanisms in cells from different tissues in normal and pathological situations.
- The general aim is to understand the role of signaling molecules in a variety of cell functions. The research areas addressed include calcium signaling in muscle and neurons, hormone production and regulation (steroidogenesis), and cell death and the dysfunction of these transduction pathways in related pathologies
- The center activities have been based on the work of six interacting groups conducting specific research programs and using complementary approaches. Three new investigators were added in the continuity plan (see next section)
- Pathophysiological aspects initiate translational studies and establish links between fundamental and clinical research which will be expanded in the next five years.

Six individual research lines are to be continued and follow on from those proposed at the original creation of the CEMC FONDAP Center:

- The first research line is led by Dr. Cecilia Hidalgo, who proposed a program focused on RYR receptors, a field in which she has an international reputation. These RYR receptors, which release intracellular calcium, are known to mediate contractile activity in muscle cells, but their role in neurons is much less clear and likely involves many cellular functions, proliferation/differentiation processes and gene transcription, all of which are affected in pathological states. The group is focusing on the redox regulation of RYR activity. Calcium signals vary in amplitude and in their temporal properties in order to trigger different cellular functions. The redox state in the cytoplasm of a cell is very important in terms of physiology and is a major player in aging and various pathologies in muscle, cardiac or neuronal tissues (ischemia/reperfusion, pain, cancer, …) in which Reactive Oxygen Species (ROS) are produced. The group proposes to study the participation of redox-stimulated calcium-induced calcium release (CICR) in skeletal and cardiac muscle, and in pancreatic, ovarian and neuronal cells.
- The second research line is conducted by Dr. Andrew Quest and is focused on cellular mechanisms of cell proliferation and cancer. The main interest of the group is in caveolin –1, whose expression is downregulated in transformed cell lines, while its re-expression in later stages of tumorigenesis is associated with a tumor promoting ability. They demonstrated that calveolin-1 functions as a tumor suppressor through E-cadherin dependent inhibition of target genes, including the tumor promoters survivin and COX2. The main goals are: to investigate the underlying mechanisms by which caveolin-1 regulates the expression of survivin and COX2, in relation to its tumor-suppressing activity; to study the role of the presence of E-cadherin in this process; to investigate the mechanisms of re-expression of caveolin 1 in tumor cells; and in addition to investigate why its re-expression in the absence of E-cadherin is associated with a metastatic potential.
- The third line of research is headed by Dr. Enrique Jaimovich and concerns studies relating to calcium signaling in skeletal muscle. The calcium transients following depolarization can be modeled by two spatially and kinetically different components. A fast and a slow calcium release have been identified by this group, the fast being related to excitation-contraction coupling, but of the second

phase much less known in terms of function. The new project is focused on excitation-transcription coupling studies and in particular the role of the voltage-dependent calcium channel (DHPR), hormone receptors and intracellular calcium releasing stores whose calcium release function is mediated by the IP_3 receptor. The aims of the project will be to investigate in both skeletal and cardiac muscle the metabotropic role of the DHPR and the molecular determinants of its modulation by G proteins; the role of nuclear calcium in gene transcription; the molecular links between plasma membrane and nucleus which govern transcription; and finally the alterations of these processes in muscular pathologies, including muscular dystrophies, aging-related muscle wasting and heart failure. The relationships between hormone receptors and these pathways will be investigated in other pathologies including diabetes.

- The fourth research line is headed by Dr. Luigi Devoto who, in the five past years, has worked on endocrine regulation of the human Corpus Luteum (hCL) and has focused on a regulatory protein involved in the steroidogenic machinery named StAR (steroidogenic acute regulatory protein). They have elucidated reduced expression in hCL at the end of the luteal phase, localisation of StAR in cells of the hCL, effect of hCG administration in women, induction of the types of cell death in luteal cells and role of GnRH antagonists in these processes *in vivo* in women. The new project to be developed in the next five years concerns the mechanisms that control hCL functional regression. In particular, these studies include cell death mechanisms in luteal cells and effects of redox mechanisms on this process. This clinical group uses human clinical and surgical samples and the new program expands their collaborations with other groups of CEMC. The continuity plan will clearly stimulate the transfer of fundamental research concepts to clinical relevant perspectives in this field of endocrinology.
- The fifth line of research is based on electrophysiological approaches associated with structure /function studies and protein-protein interactions. The group, led by Dr. Andres Stutzin, has been focusing in recent years on the role of the Non-Selective Cation Channel (NSCC) in necrotic cell death associated with a gain of Na^+ and cell swelling. They now focus on the study of a family of channels (TRP) and have identified one member, TRPM4b, which is modulated by oxidative stress and is probably involved in necrotic cell death and cell cycle control. Their studies involve recombinant channel manipulations, identification of the molecular determinants of their regulation and identification by a proteomic approach of interacting proteins which may modulate their activity. The mechanisms linking the channel to the cell cycle or to cell death via redox-sensitive pathways will be investigated.
- The sixth research line in the initial proposal involved Dr. Felipe Sierra. His project was focused on defects in transduction pathways during aging which might lead to lower capacity of adaptation to environmental changes or stress. His work on aged animals showed reduced responsiveness to LPS treatment and modifications of the ERK pathways. Dr. Sierra left CECM during the first year to become a full Professor in another university and this line of research was stopped. He was the replaced by another PI: Dr. Sergio Lavandero. This main change from the initial proposal is described in the next section.

ii.- Evaluation

Outstanding	Very Good	Good	Poor
☐	☒	☐	☐

6.- When applicable, new lines of research that arose during this period and how they were considered in the present proposal.

i.- Comments

A major change that occurred early within CEMC was the departure of Dr. Felipe Sierra, one of the 6 initially proposed PIs. This had as an immediate consequence the loss of the topic devoted to signal transduction in aging processes, which obviously is a relevant one for neurodegenerative diseases in particular. However, the choice of Dr. Sergio Lavandero from the Faculty of Chemical and Pharmaceutical Sciences at the North Campus of Universidad de Chile as a substitute has been judicious and beneficial for the network. The theme addressed by Dr. Lavandero's team, cell death and survival in cardiac myocytes, fits well within the main objectives of the Center and has already stimulated fruitful cooperative studies with other research teams of CEMC. This research direction also strengthens scientific activities around cardiovascular diseases, in which Dr. Luis Michea, a newly recruited young investigator, is involved. As an additional positive consequence this research area has already led to the development of cooperative projects with more clinically orientated scientists at University de Chile and elsewhere. In addition, Dr. Lavandero's contribution has benefited the Center in the enlargement of the recruitment of doctoral students from PhD programmes other than that dependent on Biomedical Sciences. This has been assisted by the strong involvement of the PIs in the coordination and teaching activities in four cross-faculty postgraduate courses that are available for PhD students at Universidad de Chile.

The recent arrival of three talented young researchers who have joined CEMC as independent associates with their own funding resources is also an event of major importance. These associates are likely to simulate research activities in most of the domains addressed in the network. Emphasis is placed by Dr. Claudio Hetz on studies aimed at better understanding the processes involved in the regulation of the unfolded protein response, and at assessing its role in neurodegenerative diseases. David Mears' program focuses also on research aspects that may have clinical endpoints by studying pancreatic β cell function in normal and pathological cells. This also applies to Dr. Luis Michea's project that is related to the determination of transduction mechanism of mineralocorticoid dependent cardiovascular damage, with emphasis on the role of hypertension and vascular calcification. These activities have been well and rapidly integrated in the overall research network. This is likely to be explained by the high scientific and human capabilities of the three young investigators who all show an impressive researcher profile together with a high-level training experience in cutting-edge molecular biological techniques.

The insertion of Dr. Lavandero and of the three young investigators in CEMC has also had other beneficial consequences for the development and reinforcement of the technical platform, with the implementation of new tools that are accessible to the members of the Center and probably also to scientists from other research laboratories. This concerns in particular the introduction of the adenovirus and lentivirus approaches by Drs. Lavandero and Hetz respectively that should open new relevant research possibilities. It may be added that the expected purchase of a high performance liquid chromatography-tandem mass spectrometer apparatus, a technique for which access is currently only possible through cooperation with overseas laboratories, should also stimulate research activities in the proteomic field.

A final remark deals with the implementation of two competitive starting grants that have involved clinically orientated researchers with scientists from CEMC. This initiative should favor the emergence of joint clinical-basic science projects and should be further developed.

ii.- Evaluation

☐	☒	☐	☐
Outstanding	Very Good	Good	Poor

7.- Synergies and interactions between the members of the Center and their purpose in the Continuity Plan (not only based on publications or theses, but also, for example, on emerging new research lines in the near future). Remember that the whole should be greater than the sum of work of individual researchers.

i.- Comments

The number of publications, their level in terms of the impact factors of the journals in which they are published, and the frequency with which they are cited by other workers have all increased during the first five-year period of the Center. The collaboration between PIs is probably a main factor in the progression in the number and quality of publications. The groups have clearly built a framework for interactions that supersede traditional relationships and bring added value both at the technical and intellectual levels. The important technological transfer between groups (electrophysiology, imaging, proteomics, viral and cell cultures…) during the five past years has fostered the emergence of new and original research areas in each group. The continuity plan focuses on common research lines in which the center has international visibility (cell death, calcium signaling, redox mechanism). Each group uses similar strategies and technologies to investigate these common signaling pathways in different cell types (skeletal, cardiac, endocrine, neuronal), cell function and in pathologies (cardiovascular, cancer, diabetes, Parkinson, Alzheimer…). We also note that the strong development of studies on animal models, recommended during the last visit, which has established a link between *in vitro* studies, animal models of pathologies and clinical research. The location of four of the groups in the same refurbished building will be important in promoting the research activities of the center by bringing together key technical platforms needed for completion of the program.

The Center has stimulated the collaborations between the PIs' groups, but also one can note the active participation of the co-investigators. New complementary research areas and new technologies are coming from the recruitment of 3 talented new associate researchers (further developed in the next section) who have joined the center, and from the international collaborations network (giving access to some approaches which are missing at the moment in the center but will be also developed during the next five years in the new building). Altogether these conditions provide a high feasibility to the new research program proposed. The increasing contacts with several countries also provide appropriate and complementary skills including training of students with new technologies.

ii.- Evaluation

X			
Outstanding	Very Good	Good	Poor

8.- Center organization net including its nearest links (companies, associated institution, other units within the same institution, etc), and international and national collaboration.

i.- Comments

The director of the CEMC runs the center in a democratic, way taking all decisions collectively with the deputy director and the other PIs. All the PIs meet with the director weekly and a good example of this positive and fruitful interaction is the equal way in which the budget remaining after common facilities costs have been paid is shared between each PI, independently of the number or researchers/students in the group. There is a flexible coordination in the management of the budget according to need. Another example of the collective behavior and solidarity between PIs was the joint effort made to allow the completion of the PhD theses of all the former students of P Sierra group (who left the center in the first year).

In basic and clinical research a large network of collaborations appears between different research and clinical units within the University of Chile and other institutions including Hospital Clinico U. de Chile, IBCM, IDIMI, Hospital San Borja Arraran and the Universidad Catolica. This network of collaboration will be extended by the association with the center of three talented young researchers who will further promote the development of biomedical research.

We noted the emergence of a new line of research within the center dedicated to neurological endpoints which will open new clinical collaborations in the field of neurodegenerative diseases and aging. Translational activities on potential drug targets (such as RYR receptors, caveolin 1, cardioprotection, contraception, fertility……..) should allow the center to set up collaborations with pharmaceutical industries both outside and inside the country. Such funding for clinical research has already been achieved by the group of L. Devoto.

ii.- Evaluation

	X		
Outstanding	Very Good	Good	Poor

9.- Outreach strategy.

i.- Comments

As outlined in section 1 and 2, the outreach program that was set up is of high quality, particularly in its provision of advanced training courses and international conferences, and we believe that it reaches most of its expected objectives.

ii.- Evaluation

X			
Outstanding	Very Good	Good	Poor

10.- Economic feasibility: coherence between needs, operational costs, new positions, major equipment, traveling and per diem, among others, and proposed activities (1US$ ≈ 550 Chilean pesos).

i.- Comments

The comments in this section apply to the budget requested from FONDAP, and in the following section to the Institutional commitment.

The overall budget requested is $600m Chilean pesos pa. Approximately 60% of the budget is for salaries, of which about half is for salary supplements for PIs and associate investigators. The need for salary supplements is unfamiliar to the evaluation panel, all of whom work in European institutions, but we understand that it is well accepted in the Chilean context. The bulk of the remainder is for technicians, many of whom are students on short-term contracts, with further small amounts for administrative personnel, graduate students and postdoctoral fellows.

Travel expenses account for only 3% of the budget, and are clearly important in terms of enabling PIs and others to travel both within Chile and to overseas destinations. Our view is that a spending a larger proportion of the overall budget on travel would be justified, unless there are other sources for funding travel which have not been identified to us (NB we note in addition a small institutional commitment to funding travel – see below). Arranging for students and postdocs to make visits to overseas labs to learn and implement new techniques and to extend their range of academic contacts at a critical stage of their careers is a particularly valuable use of travel funds.

Operational expenses (consumables items to be used in experiments) are another large commitment, approximately 25% of the overall budget. However, at approximately $25m (Chilean pesos) per PI per year these expenses are modest by European standards, particularly when considering the technical sophistication of many of the experiments proposed, the numbers of investigators to be supported in each group and the high relative cost of most consumables in Chile. Some of the techniques proposed, especially HPLC-MS/MS, other proteomic technologies, molecular biology, and the generation and maintenance of transgenic mouse colonies, are extremely expensive and the proposed consumables budget would appear inadequate to support such technologies within the envelope of FONDAP funding.

Finally, equipment accounts for only around 10% of the budget in early years, falling to zero in later years. We are unclear where the funding will come from for the large number of expensive technologies mentioned in previous sections, particularly as the Institutional commitment for equipment is zero (see below).

While we have not identified funding adequate to support the proposed experiments in the budgets supplied to us, and in particular for the provision of large items of equipment, we nonetheless note that such items are very important for the proposed experiments and we are clear that the ambitious research program proposed will not be fully realizable without them. We wish the CEMC investigators every success in raising the funding for these items from other sources.

ii.- Evaluation ***Not applicable owing to lack of information***

11.- Economic feasibility for Institutional commitment: coherence between needs, operational costs, new positions, major equipment, traveling and per diem, infrastructure, among others, and proposed activities (1US$ ≈ 550 Chilean pesos). Resources coming from other sources considering that other funds make the Center activities more consistent.

i.- Comments

The overall institutional commitment is c. $600m in the first year, decreasing to c. $200m pa in later years. The heavy weighting of the budget in early years arises from the capital sum required to refurbish the new building for 4 of the CEMC PIs. We strongly support the spending of this sum of money to provide an adequate infrastructure for the CEMC, and we are surprised at the relatively modest cost (in European terms) for refurbishing a large and derelict building to modern research standards.

In addition the institutional commitment comprises substantial amounts for base salaries for staff (scientific, technical and administrative), a modest amount for travel, and a small contribution ($10m pa, or $1.5m pa per PI) for consumables and other operational expenses.

ii.- Evaluation ***Not applicable owing to lack of information***

12.- Final overall comments and recommendations.

i.- Comments

Overview

1. The evaluation panel had a very positive impression overall of the Center for Molecular Studies of the Cell, both in terms of past achievements and when considering the Continuity Plan proposals for the next five-year period.
2. We note a significant increase in the number, impact and citation rate of Center publications during the first five-year period. Collaboration between CEMC labs has been a major factor in this increase in publication impact.
3. A number of excellent training programs have been introduced, to the benefit particularly of younger workers associated with the Center. The EXPLORA program has provided outreach to a younger audience.
4. The evaluation panel was impressed by the positive attitude and high level of motivation of younger members of the Center.
5. The Continuity Plan proposes a more focused research approach which will promote collaboration between Center labs.
6. A building will be refurbished for four of the Center members, and will provide a vital improvement in the research infrastructure.
7. A number of modern research technologies are currently being or will soon be introduced, to the benefit of all participant labs.
8. Recruitment of three highly talented younger associate researchers trained in overseas labs will further promote biomedical research in the Center and will lead to the setup of new technical facilities required by the program.
9. Technical capabilities will be enhanced by the implementation of facilities for transgenic animals, virus transfection methods, and proteomics. Animal models should form a vital component of future studies in the Center as they provide an essential link between cellular and clinical studies.
10. Translational research activities will be fostered through a new program of start-up grants in collaboration with clinical colleagues, including in the new field of neurodegeneration.

Recommendations

1. The publication record of Center members is in general very good, with a steady production of papers in leading international journals. However, with the exception of one paper from Quest this year in PNAS, there are no papers in "top-echelon" journals such as Nature, Science, Cell, Neuron, EMBO J, and PNAS. A major ideal aim of future years should be to attempt to secure at least a few publications in these premier league journals.
2. Several new technologies are essential for the feasibility of the proposed research program. Identification of funding sources for these technologies must be a major priority for the Center.
3. The web site needs to be updated and expanded as an interface with external collaborators and as a tool to improve internal communication between Center members.
4. Continuity beyond the next five-year period of FONDAP support needs to be ensured.