ESTADO FINAL RESOLUCION DEL CONSEJO	FECHA	
Observaciones: _____		**1. APROBADO** **2. PENDIENTE** **3. RECHAZADO** **4. A FISCALIA**
_____		

This is only for internal use of FONDAP

EVALUATION REPORT
CENTERS FOR ADVANCED RESEARCH

I. PROJECT INFORMATION

CENTER'S NAME	Centro de Estudios Moleculares de la Célula
DIRECTOR	Cecilia Hidalgo T.

II. EVALUATION PANEL

NAME	ORGANIZATION/ INSTITUTION	E-MAIL	SIGNATURE
Prof Peter A. McNaughton	Dept of Pharmacology University of Cambridge	pam42@cam.ac.uk	

III. PROGRAMS EVALUATION (please fill up as many forms as programs exist within the Center)

PROGRAM'S NAME Oxidative stimulation…

PRINCIPAL INVESTIGATOR Cecilia Hidalgo

ITEM	Total/ Good	Partial/ Regular	Insufficient/ Deficient	Internal use
Degree of adoption of suggestions from the last report *	X			
Accomplishment of objectives and goals of the reported program	X			
Quantity of the results reached regarding the objectives and goals	X			
Quality of reached outcomes related to proposal objectives and goals	X			
Degree of integration with other ongoing programs of the Center	X			
Diffusion of the results	X			

PROGRAM'S NAME Caveolin-1……

PRINCIPAL INVESTIGATOR Andrew Quest

ITEM	Total/ Good	Partial/ Regular	Insufficient/ Deficient	Internal use
Degree of adoption of suggestions from the last report *	X			
Accomplishment of objectives and goals of the reported program	X			
Quantity of the results reached regarding the objectives and goals	X			
Quality of reached outcomes related to proposal objectives and goals	X			
Degree of integration with other ongoing programs of the Center	X			
Diffusion of the results	X			

PROGRAM'S NAME Endocrine and molecular…
PRINCIPAL INVESTIGATOR Luigi Devoto

ITEM	Total/ Good	Partial/ Regular	Insufficient/ Deficient	Internal use
Degree of adoption of suggestions from the last report *	X			
Accomplishment of objectives and goals of the reported program	X			
Quantity of the results reached regarding the objectives and goals	X			
Quality of reached outcomes related to proposal objectives and goals	X			
Degree of integration with other ongoing programs of the Center	X			
Diffusion of the results	X			

PROGRAM'S NAME The cellular machinery..…
PRINCIPAL INVESTIGATOR Enrique Jaimovich

ITEM	Total/ Good	Partial/ Regular	Insufficient/ Deficient	Internal use
Degree of adoption of suggestions from the last report *	X			
Accomplishment of objectives and goals of the reported program	X			
Quantity of the results reached regarding the objectives and goals	X			
Quality of reached outcomes related to proposal objectives and goals	X			
Degree of integration with other ongoing programs of the Center	X			
Diffusion of the results	X			

PROGRAM'S NAME Cell death…
PRINCIPAL INVESTIGATOR Sergio Lavandero

ITEM	Total/ Good	Partial/ Regular	Insufficient/ Deficient	Internal use
Degree of adoption of suggestions from the last report *	X			
Accomplishment of objectives and goals of the reported program	X			
Quantity of the results reached regarding the objectives and goals	X			
Quality of reached outcomes related to proposal objectives and goals	X			
Degree of integration with other ongoing programs of the Center	X			
Diffusion of the results	X			

PROGRAM'S NAME Role of TRPM4……
PRINCIPAL INVESTIGATOR Andrés Stutzin

ITEM	Total/ Good	Partial/ Regular	Insufficient/ Deficient	Internal use
Degree of adoption of suggestions from the last report *	X			
Accomplishment of objectives and goals of the reported program	X			
Quantity of the results reached regarding the objectives and goals	X			
Quality of reached outcomes related to proposal objectives and goals	X			
Degree of integration with other ongoing programs of the Center	X			
Diffusion of the results	X			

PROGRAM'S NAME Stress signals…
PRINCIPAL INVESTIGATOR Claudio Hetz

ITEM	Total/ Good	Partial/ Regular	Insufficient/ Deficient	Internal use
Degree of adoption of suggestions from the last report *	X			
Accomplishment of objectives and goals of the reported program	X			
Quantity of the results reached regarding the objectives and goals	X			
Quality of reached outcomes related to proposal objectives and goals	X			
Degree of integration with other ongoing programs of the Center	X			
Diffusion of the results	X			

PROGRAM'S NAME New cell targets…
PRINCIPAL INVESTIGATOR Luis Michea

ITEM	Total/ Good	Partial/ Regular	Insufficient/ Deficient	Internal use
Degree of adoption of suggestions from the last report *	X			
Accomplishment of objectives and goals of the reported program	X			
Quantity of the results reached regarding the objectives and goals	X			
Quality of reached outcomes related to proposal objectives and goals	X			
Degree of integration with other ongoing programs of the Center	X			
Diffusion of the results	X			

IV. CENTER EVALUATION

ITEM	Total/ Good	Partial/ Regular	Insufficient/ Deficient	Uso Interno
Degree of adoption of suggestions from the last report *	X			
Accomplishment of objectives and goals of the Center	X			
Quantity of reached outcomes related to proposal objectives and goals	X			
Quality of reached outcomes related to proposal objectives and goals	X			
Degree of integration between the programs of the Center	X			
Creation and reinforcement of international networks	X			
Outreach	X			
Diffusion of results	X			
Establishment and tasks of the Advisory Committee	X			

RECOMMENDATIONS **(see following concepts)**

X					
APPROVE	APPROVAL WITH SUGGESTIONS	ADDITIONAL INFO.	PENDING	REJECT	FONDECYT USE

26 November 2008 Signature reviewer

EVALUATION CONCEPTS
ANNUAL REPORT

1. **Approve:** The reviewer recommends to accept the report in its present form since he/she considers objectives and goals fully accomplished and all relevant issues covered by the report.

2. **Approval with suggestions or minor observations**

2.1 ***Minor observations*:** The reviewer recommends the approval of the report despite the justified incompleteness of some aspects that does not constitute an obstacle for the continuity of the Center activities.

2.2 ***Suggestions***: The reviewer recommends minor changes in order to improve the future performance of the Center.

3. A**dditional information:** The reviewer requires additional documentation or specific explanations to fully evaluate the report.

4. **Pending:** The reviewer makes significant observations to the report and conditions its approval to the accomplishment of specific demands.

5. **Reject:** The reviewer has strong objections to the contents of the report.

EVALUATION COMMENTS:

The previous 5-year report team (of which I was a member) had noted the following recommendations for the renewal of the Centre:

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.

The report outlines the response to these recommendations. In brief, these are:

1. There is a continued steady increase in both the number and the impact factor of publications from the centre. The average impact factor of journals is now above 4.5, while the average from 2002-7 was 3.8. The number of publications has also increased. A significant number of publications (10%) are collaborative efforts between Centre members. This is a very creditable achievement.
2. A number of major technologies had been proposed for the second 5-year period and it was unclear how these would be funded. While the report is unable to give a complete reply on this issue, it is clear that substantial efforts are being made, with some degree of success, towards either acquiring funds to purchase new technologies (e.g. in vivo and confocal imaging systems, flow cytometer) or to accessing facilities available elsewhere (proteomics, crystallography).
3. The web asite has been substantially improved and now offers a clear view of Centre activities and participants. There are plans to further upgrade the site. The employment of a journalist has raised the profile of the Centre in the local press.
4. The continuity issue, partly relating to the retirement of the current Director in the next few years, is being addressed but has not yet been resolved. Regarding longer-term funding, a strategic plan is in preparation.

In addition, the previous report had raised in a confidential section some other matters, some of which are addressed by the remarks above, and some of which were relevant only to the organization of the visit. The main aspects on which I would have appreciated explicit comment are:

"We felt some concern at the large number of PhD students in proportion to the relatively small number of postdocs in one group. The large number of PhDs raises the possibility of several problems, including inadequate supervision and a reduced likelihood that PhDs would be able to secure first-author publications in high-quality journals."

The group concerned still seems very large (33 members in the website photo). This is not

necessarily a bad thing provided younger members are receiving adequate supervision from more senior postdocs in the group, but I mention it again as a possible area for concern.

“The small sums allocated to travel are also a matter for concern.”

This is not explicitly address in the present report. I would emphasise again that the ability to travel from a relatively isolated country such as Chile to other major scientific centres is a vital component of scientific success, most particularly for younger scientists, and one that it is worth sacrificing funding in other areas in order to achieve.

ESTADO FINAL RESOLUCION DEL CONSEJO	FECHA	
Observaciones: _____		**1. APROBADO** **2. PENDIENTE** **3. RECHAZADO** **4. A FISCALIA**
_____		

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EVALUATION REPORT
CENTERS FOR ADVANCED RESEARCH

I. PROJECT INFORMATION

CENTER'S NAME **CEMC**
DIRECTOR Cecilia HIDALGO

II. EVALUATION PANEL

NAME	ORGANIZATION/ INSTITUTION	E-MAIL	SIGNATURE
NARGEOT Joel	CNRS	Joel.nargeot@igf.cnrs.fr	

III. PROGRAMS EVALUATION (please fill up as many forms as programs exist within the Center)

PROGRAM'S NAME
PRINCIPAL INVESTIGATOR

ITEM	Total/ Good	Partial/ Regular	Insufficient/ Deficient	Internal use
Degree of adoption of suggestions from the last report *				
Accomplishment of objectives and goals of the reported program				
Quantity of the results reached regarding the objectives and goals				
Quality of reached outcomes related to proposal objectives and goals				
Degree of integration with other ongoing programs of the Center				
Diffusion of the results				

PROGRAM'S NAME
PRINCIPAL INVESTIGATOR

ITEM	Total/ Good	Partial/ Regular	Insufficient/ Deficient	Internal use
Degree of adoption of suggestions from the last report *				
Accomplishment of objectives and goals of the reported program				
Quantity of reached outcomes related to proposal objectives and goals				
Quality of reached outcomes related to proposal objectives and goals				
Degree of integration with other ongoing programs of the Center				
Diffusion of the results				

***** If there had been none, please disregard this question

IV. CENTER EVALUATION

ITEM	Total/ Good	Partial/ Regular	Insufficient/ Deficient	Uso Interno
Degree of adoption of suggestions from the last report *	x			
Accomplishment of objectives and goals of the Center	x			
Quantity of reached outcomes related to proposal objectives and goals	x			
Quality of reached outcomes related to proposal objectives and goals	x			
Degree of integration between the programs of the Center	x			
Creation and reinforcement of international networks	x			
Outreach	x			
Diffusion of results	x			
Establishment and tasks of the Advisory Committee	x			

RECOMMENDATIONS **(see following concepts)**

X ☐ ☐ ☐ ☐ ☐ ☐

APPROVE

☐☐☐

11 24 2008

Evaluation Date Signature reviewer

EVALUATION CONCEPTS
ANNUAL REPORT

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5. **Reject:** The reviewer has strong objections to the contents of the report.

EVALUATION COMMENTS:

The CEMC research center is focused on the study of the signal transduction mechanisms in cells from different tissues in normal and pathological situations.
The project aim to understand the basic mechanisms underlying neuronal plasticity and degeneration, cancer , hormone metabolism during steroidogenesis, muscle physiology related to calcium signaling and cell death. They also proposed to investigate situations such as aging and pathophysiology related to dysfunctions of these transduction pathways in cancer, cardiovascular and endocrine cells disorders. The study of calcium signaling occurring both in the cytoplasm and in the nucleus and cell death are a major issue of the studies of most groups leading to important collaborative work.
The center activity is based on the activity of six PI groups, interacting in many ways. They have specific research areas in different tissues but they share complementary approaches and concepts in signal transduction, for instance the implication of redox-regulation in the development of various diseases. It is postulated that many cell functions in different tissues are mediated through similar second messengers cascades. The interaction between the different groups allows both studies of the molecular mechanisms leading to pathologies and also to dissect from pathologies the related dysfunction in signaling molecules. This is attested by transversal studies and the existence of strong and increasing links between fundamental and clinical researches in the new project. In addition to the 6 PI groups , three young and bright associate scientists have been incorporated since about one year and half. Their topics are well integrated in the field of the CEMC program: Their contribution is evidenced by the collaborative work established with some PIs. One of these PIs associate investigator, Dr David Mears, has however left the center to take a position in USA but collaborations will been maintained with several PIs.

Eight groups (6 PIs and 2 associates) are presently involved in the FONDAP program. However, it can also be noticed that a previous postdoctoral fellow has become a co-investigator in the group of Andrew Quest and a young MD has returned from a post doctoral training in North Carolina to take a position of assistant professor in the department of obstetrics and genecology which let expect that new talented young scientist will join the FONDAP program in the coming years.

The group leaded by Cecilia Hidalgo proposed to further explore the redox regulation of the Ryanodine (RYRs) receptors, a field in which the group has international reputation. These RYRs mediate contractile activity in skeletal muscle and heart but their role in neurons has been less investigated and they are expected to be involved in many calcium –dependent cellular functions . The studies not only consider the elevation of intracellular calcium but also the spatial and temporal properties of the intracellular calcium transients. RYR receptors are linked to other proteins to regulate calcium homeostasis such as voltage dependent calcium channels, Na/Ca exchangers and calcium pumps. Redox state in a cell is very relevant in terms of pathophysiology and seems a major player in various situations such as aging or pathologies affecting muscular, cardiac or neuronal tissues (ischemia/reperfusion, pain, cancer ,…) in which ROS are produced. They have explored ischemic rat brain and shown that ischemia increases RYR2 S-nitrosylation and S-glutathionylation which contributes to enhance calcium signals and cell death. These important data have been published in “The journal of Neurosience”, an international reference in this domain. In addition, other studies in collaboration with a co-investigator of CEMC showed that iron promotes ROS generation and enhances RYR-mediated Ca release and activates the ERK1/2 cascade, these pathways being involved in sustained LTP. Transversal collaborations were established with the other PIs, Luigi Devoto and Enrique Jaimovich on RYR-mediated calcium release and progesterone secretion and also on insulin secretion with David Mears. In addition, novel data indicate the regulation of the expression of RYR2 and RYR3 and of a iron transporter after a special memory task. All these data should be published in the coming

year. Another important result concerns the participation of RYR –mediated nuclear calcium signals in gene transcription controlling morphological changes occurring during synaptic plasticity. They also suggest that amyloid beta peptides involved in neurogenerative diseases can down-regulate RYR2 and RYR3 mRNA levels although this is not quite consistent with an expected calcium-dependent toxicity. Anyway, the group had regularly published high level papers in the past years and continues to provide innovative hypothesis in the field of RYR receptors and their role in various tissues functions.
The group of A Quest focused on cancer identified the anti-apoptotic protein surviving as a target gene that is suppressed by caveolin -1 presence via a mechanism involving the β-catenin/Tcf-lef pathway. Caveolin –1 expression is down-regulated in transformed cell lines. They evidenced previously that calveolin-1 functions as a tumor suppressor in colon cancer cells and postulate that this property involves inhibition of target genes including surviving and COX2 via E-cadherin-dependent mechanisms. Their studies indicate that Caveolin-1 suppresses Survivin expression by reducing β-catenin/TCf/LEf pathways transcription by a direct sequestration of β-catenin to the membrane but also indirectly by restraining the COX2-PGE2 amplification loop. These data are under publication. Other important issues are that E-cadherin is required for caveolin-1 to suppress COX2 expression via the same pathway, and the role of PGE2. E-cadherin is a surface protein frequently lost during metastasis and recent data aimed to demonstrate *in vivo* on mouse models that E-cadherin modulates the ability of caveolin-1 to act as a tumor suppressor. In a recent study, intriguing data were obtained *in vitro* and *in vivo* on the role of caveolin-1 during metastasis and tumor formation which means that the mechanisms that might explain a tumor suppressing activity of caveolin-1 are still unclear. Note that these pathways involving caveolin1, COX2, β-catenin are very relevant to the pathology and intensive research is conducted in this domain at the international level. The group of A Quest, considering the project, hypothesis and publications is well positioned on the international scene. Also, collaborations with other PIs or FONDAP co-investigators involving PKCα, surviving or caveolin-1 have also led to collaborative publications in press.

The research project is leaded by Luigi Devoto provided studied of a regulatory protein StAR invoved in the steroidogenic machinery: The background of the group is more clinical which allows interesting transversal and collaborative studies in association with other PIs. The object was to elucidate the regulation of StAR expression in relation with progesterone secretion by the human corpus luteum, to study its phosphorylation in different situations within the cycle and the effects of antagonist of hormones involved in the ovarian cycle in particular hcG or GnRH antagonists. The regulation of StAR by PKC and NO have been investigated in human luteal cultures of different ages . They combine ultrastructural studies, apoptotic markers ton study the steroidogenic response in the regressing CL induced by a GnRH which led to a major publication in 2007 . This study suggests multiple patways invoved in the death on LC including apoptotic and non apoptotic cell death. Interestingly, hCG administration to women in the mid-luteal phase restores steroidogenesis function , decreases the apoptotic process and restores PKA and IP3 signaling. Among the signaling pathways involved in by hCG action, a collaborative study with another PI (A Stutzin) evidences a chloride channel as a main actor in the cascade, a work published in the excellent journal “endocrinology”. As mentioned, this group is oriented towards human pathology and connected to many clinical programs . One is the uptake of glucose in human granulosa cells with focus on the PCOS disease in women which shows a reduction in GLUT1 and GLUT4 transporters. One can also underline the publication of several book chapters or reviews attesting that the group has international expertise in this field.

The group Enrique Jaimovich is also well known for studies related to calcium signaling in skeletal muscle. The calcium transients following depolarization can be modeled into two components spatially and kinetically different. A fast and a slow calcium release have been identified by this group, the fast one related to excitation-contraction coupling, the second much less known in terms of function. A rather recent concept concerns the excitation-transcription coupling via calcium signaling in nucleus in which DHPR, hormone receptors, intracellular calcium releasing stores such as IP3R have been postulated to be involved. This group has focused for instance on nuclear membrane and their work

using a toxin strongly suggests that tetanus is the physiological stimulus for the IP3-dependent calcium signal involved in the regulation of gene expression. Tetanic stimuli would also affect extracellular nucleotides concentration to promote calcium transients for instance via purinergic receptors. Electrical stimulation also generates NFAT-transcription and translocation and the feature of their studiy is that its provide experimental evidence for two independent pathways of calcium-release dependent excitation-transcription coupling in skeletal muscle both triggered by the same voltage sensor but activating two different intracellular release channels. This group also investigate muscular pathologies using dystrophic cells from animal models or human. They first evidence that IP3R are located in both cytoplasm and nucleus, then that dystrophic cells in a pathology such as RCDMD over-express type 2-IP3R in nucleus, and that IP3R-mediated signals induce phosphorylation of ERK1/2 in normal but not in dystrophic cells. They also provide a study of gene profiling in RCMH and RCDMD versus control myotubes and found 44 common genes differently expressed in both cell lines upon electrical stimulation. Calcium signals are also studied in the mitochondria following electrical stimulation. In addition, the hypothesis of ROS generation by insulin was suggested and evidenced and was demonstrated to occur through NADPH activation. The ROS increase would be required for the IP3-mediated calcium rise. The work of this group can also be considered as very competitive at the international level and this is attested by regular publications in high impact journals and by frequent communications in international meetings. E Jaimovitch's group interacts also actively with other PIs and international groups in France or USA.

The electrophysiological group of Dr. Stutzin has been focused in the past on Necrotic Cell death associated to a gain of Na+ and cell swelling. Following the cloning of the TRPM4b channel, these studies have taken on a new dimension with the hypothesis of this channel as the most likely candidate for the so-called NSCC current that contributes to swelling and necrosis. TRPM4b channel is ROS, Ca^{2+}- and pH-dependent. The project has taken a new direction and is focused on the modulation of TRPM4 by oxidative stress. The gropus is now investigating the H2O2 –induced TRPM4 activation and its correlation with cell death using an original and modern approach (shRNA) and this work is mentioned to be be published soon . This work finds extension in neuronal physiology since they suggest that in reperfusion after injury a similar current related to TRPM4 might be responsible for injury. Structure-function studies are conducted to understand the mechanisms involved in the loss of desensitization and the tyrosine and serine phosphorylation of the channel. A manuscript should also appear in the following months. Finaly this group is also collaborating with other PIs. In particular a study of proliferation in cancer associates downregulation of b-catenin by TRPM4. It has to be noted that previous studies on the VSOR Cl- channels have been recently published in high impact journals (Cell Physiol and Biochem and in endocrinology in collaboration with the group of L Devoto.). The new direction of Dr Stutzin who has a high expertise in electrophysiological techniques appears quite justified and has already been quite productive

The group of S Lavendero is focused on cardiovascular diseases and in particular on the relation between ischemia, apoptosis and calcium signaling. These studies share common hypothesis with other groups such as the role of nuclear calcium transients , ischemia-reperfusion injury associated to mitchondria alteration, apoptosis and cell death. They demonstrated new IGF-1 transduction pathway linked to nuclear calcium signaling, dissected the hyper-osmotic stress (occurring during ischemia) transduction pathways leading to calcium overload involving IP3 Receptor, mitochondria and a caspase-independent mechanism. These studies have been submitted for publication. Further investigation of the cascades involved in the IGF-1 effects is proposed. The hypothesis of a physical interaction between plasma and nuclear membrane is attractive, and confocal microscopy experiments will be used to explore this hypothesis. They also associate *in vitro* and *in vivo* models to study ischemia-reperfusion and use the high-technology of viral constructions as an approach for gene inactivation or overexpression in cardiomyocytes. This group is very active also in the development of collaboration both with other PIs and co-investigators and also abroad in Chile or France. This excellent activity is attested by the large number of publications published recently (19 ISI papers)

In addition to the 6 PIs, three associate young investigators have been added about two years ago into the project but only two remain now in the center.
Claudio Hetz is developing a new innovative area of research which seems very important for understanding and for potential therapeutics applications in neurodegenerative disorders. This project concerns the folding of proteins involved in the secretory pathway and occurring in the ER. The adaptive response to ER stress is UPR although XBP-1 KO mice did not affect severity of Prion disease. This work was published in the top journal PNAS in 2008 . He will now analyse the mechanisms involved in the regulation of UPR and "UPRosome" to design new therapeutic strategies in neurological disorders. One can note that his group published 11 articles in 2007-2008, obtained 4 international grants, developed collaborations with other PIs (Quest, Lavendero) and with several international laboratories.

Luis Michea is another associate investigator focalized on cardiovascular damage induced by mineralocorticoides (MR) such as hypertension and calcification. His studies are devoted to mechanisms involved in the rennin-angiotensin system which is overactivated in cardiac pathologies including hypertrophy and heart failure and renal injury to develop pharmacological strategies (MR antagonists) to prevent in particular chronic renal failure. His studies are well integrated in the CEMC program because oriented in the analysis of the oxidative stress and related to calcium overload and inflammation. These studies have also clinical implications and concern patients with end stage renal disease (ESRD). Using human tissue samples and animal models, they have been able to publish a very interesting paper showing the beneficial role of spironolactone in the journal "hypertension" associated with an editorial comment attesting the novelty of the research. These studies in cardiac tissue but also in associated myopathies generate collaborations with Lavendero and jaimovich but also with Stutzin in human mesothelial cells.

Finaly, David Mears was a bright associate investigator joining CEMC at the previous evaluation. He provided interesting studies in pancreatic β-cell physiology but he has now left for a US laboratory. It is expected to keep collaborations with the CEMC PIs in the future which will be a good transition. As we will discussed later it might be important to replace this group in a near future. The addition of new young talented investigators with high international links appears important for the future of the CMEC.
It comes out from the detailed analysis of the activities of each PI's group including young associate investigators that they have innovative and coherent research programs and have achieved most of the goals stipulated upon CEMC renewal.

Visibility of the center

-In terms of publications the number of ISI publications (39 between 2007-2008) has increased and the average by PI and by year is probably similar and sometimes over international standarts in European or North American laboratories. Interestingly, as recommended by the evaluation committee, the average impact factor has significantly increased and 25% of the publications are in the top 10% in their respective field. Among the publications and considering the CEMC in the 2002 period where papers in generalist reviews such as J Biol Chem emerged, one can now find articles in the journal of Neurosciences or PNAS attesting the increasing visibility of the research in the CEMC center and the presence of young investigators with high international networks should accelerate the process.

-The second strong aspect in the CEMC center is the quantity and quality of training programs for either graduate or postgraduate students. The participation of the center in the formation of undergraduates, graduate or postdoctoral student is remarkable. Fondap PIs and collaborators are deeply involved in post-graduate activities. International course symposium has been organized in endocrinology and CEMC members are involved in many PhD programs (biomedical, biochemistry, pharmacology, pharmaceutical sciences, dental and medical sciences) in the University of Chile. Two advanced post-graduate courses have also been organized in 2008 by PIs concerning different PhD programs. One can underline the strategy of co-tutoring student projects by two PIs. Among 60 PhD projects, 14 are co-

tutored by two PIs which probably help to produce the large number of collaborative articles in high impact factor journals by transferring new concepts or technological innovations from one group to another in rather different research areas. As recommended during the evaluation, the center has introduced new courses to improve reading and writing in English and to improve oral skills. Brief meetings between PIs and co-PIs and for FONDAP members as well as a 2 days annual retreat are also organized.

-One can also notice the development the development of translational research and new clinical projects in particular with the medical school.

-A web site has been developed as suggested and this is a factor to increase the visibility of the center.

-Productive and innovative collaborative projects will soon be favored by the construction of a new building in which at least 4 PIs will be located. This was a strong recommendation of the last evaluation committee to the institution and represent a major issue

-independent granting and external collaborations seem to increase, other important issues for the evolution and visibility of the center . I am confident in the potential of the PIs to promote their research in international networks. This led to some modifications in the utilization of the funds that seem justified.

In conclusion, considering all the indications contained in the document, it is clear that the CEMC center pursues a research of high quality and that evolution of the research in terms of publications, impact factor, international visibility and collaborative programs is positive. In addition, the reviewer is impressed by the number and quality of student training at different levels and by the collaborative activity between groups that may be related to the exchange of students between labs and co-tutoring. This situation will be even improved by the opening of a new building, an important step to further promote the development of the center.

As a recommendation from the reviewers during the last visit, it is encouraged to develop technical key platforms which we know already to exist on the site but are poorly described in the present document.
Because the director and some PIs may leave the center for retirement in a relative short future, it might be important to recruit some new PIs or to promote co-investigators to assure the follow up of the research axis developed in their respective groups in which several concepts, for instance on redox-regulation or in calcium signaling have emerged and lead to major transversal programs, in order to maintain and promote high expertise in this field.

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