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 CENTER FOR MOLECULAR STUDIES OF THE CELL
DIRECTOR: ANDRÉS STUTZIN, DEPUTY DIRECTOR : ANDREW FG QUEST

II. EVALUATION PANEL

NAME	ORGANIZATION/ INSTITUTION	E-MAIL	SIGNATURE
Evaluador 1			

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

PROGRAM'S NAME Oxidative Stimulation of Calcium Release from Intracellular Stores: Possible Role in Excitable and Endocrine Cell Function

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 The cellular machinery for calcium-dependent regulation of gene expression in muscle cells

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 reached outcomes related to proposal 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		

If there had been none, please disregard this question

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PROGRAM'S NAME Caveolin-1 as a conditional tumor suppressor in cancer: identification of the mechanisms that control caveolin-1 expression and cellular parameters that define caveolin-1 function as a tumor suppressor.
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 Sergio Lavandero
PRINCIPAL INVESTIGATOR: Cell death & survival signaling in cardiac myocytes

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 cross talk between the human corpus luteum and endometrium. Significance for infertility treatment and fertility regulation.
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: Regulation of the unfolded protein response and its role in neurological conditions.
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 and transduction mechanisms of mineralocorticoid dependent cardiovascular damage: focus in hypertension and vascular calcification.
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		

PROGRAM'S NAME: The role of TRPM4 channels in cell cycle and non-apoptotic cell death.
PRINCIPAL INVESTIGATOR: Andrès Stuzin

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

Signature reviewer

Evaluation Date: November 18th,2011

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 report presented is an updating of the one submitted less than one year ago. The objectives are pertinent and fully relevant, both regarding the present state of the art in the tackled fields with regards to the gathered competences and equipment. For each of the programs significant progresses have been done in line with the fixed objectives.

On the whole, it shows that the groups are solidly established, technically highly competent and connected with each others, with most of them now engaged into active collaboration projects. In support, joint projects with the participation of 2 or more PI have produced several (8) very good publications. This reviewer feels that cross dissemination of knowledge and expertise between the groups is clearly boosting quality and originality.

The quantity of the research executed at CEMC evaluated on the number of publications is very satisfactory. This reviewer noticed a remarkable net increase in productivity since the number of publications raised from 27 (previous report) to 63 with some expected heterogeneity as completion of a publication usually takes more than a year.

The quality is overall very good with an average impact factor of 5.497 which remains rather constant since the last report. Importantly, an increasing number of publications has been co-signed by post docs.

The most impressive performance of the center is the dedicated involvement of its members in training activities. The PIs and co-investigators developed or contributed to several educational programs. As a concrete output of this effort is for example the ongoing tutoring of 46 PhD theses . Since several post docs have now left the CEMC it would be interesting to get a survey about their professional insertion.

Favoring special formation in oral communication skills in scientific English is an initiative that should be pursued and encouraged.

All the teams have established collaborations locally with well-known FONDAP centers, and internationally. A PI has made a short sabbatical in Australia. Contacts are established with international leaders (i.e. Guido Kroemer for cell death). Moreover, the joint organization with the International Cell Death Society, of the ICDS 2011 Meeting "Signaling in cell death survival, proliferation and degeneration" in Brazil is an excellent initiative that promoted CECM international visibility.

CECM is actively involved in the diffusion of science. Efforts are made to make the general public understand the latest advances in research.

In conclusion, this report shows the excellent collaborative spirit and motivation of all group members. The CEMC appears to have gained a steady state and international recognition. The reviewer encourages the director and the PIs to maintain its spirit and to aim maintaining competitive high quality publications.

RECOMMENDATIONS TO THE CENTER DIRECTOR:
(only if report is approved)

(a) There appears to be a good allocation of the resources. As already pointed last year, **core facilities** are of crucial importance for maintaining competitive research and to enable synergies of know-how between the groups. Therefore, I strongly recommend that hiring competent personnel to run them, and buying state of the art equipment remains a priority. The Center should also be helped by agencies to improve the animal facilities.

(b) Some teams are young (CHe, and the associate LM) and therefore smaller with so far no co-investigators. While Che appears to be doing very well LM whose relevance of the project is indubitable, presents a very challenging program for a small group in a very competitive field. Put some attention to the fact that he succeeds reaching the critical manpower required for securing the project and/ or focusses on the more promissing axes.

Comisión Nacional de Investigación Científica y Tecnológica – CONICYT

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 Andres Stutzin

II. EVALUATION PANEL

NAME	ORGANIZATION/ INSTITUTION	E-MAIL	SIGNATURE
Evaluador 2			

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

PROGRAM'S NAME
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
PRINCIPAL INVESTIGATOR: Andres 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				
PRINCIPAL INVESTIGATOR : ENRIQUE JAIMOVITCH				
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 reached outcomes related to proposal 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			

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

PROGRAM'S NAME				
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 reached outcomes related to proposal 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			

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

PROGRAM'S NAME				
PRINCIPAL INVESTIGATOR : CLAUDIO HETZ				
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	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 with other ongoing programs of the Center	x			
Diffusion of the results	x			

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

PROGRAM'S NAME				
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 reached outcomes related to proposal 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			

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

PROGRAM'S NAME				
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 reached outcomes related to proposal 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			

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

PROGRAM'S NAME				
PRINCIPAL INVESTIGATOR : LUIS MICHEA				
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	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 with other ongoing programs of the Center	x			
Diffusion of the results	x			

***** 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				

RECOMMENDATIONS **(see following concepts)**

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

Evaluation Date _____ Signature reviewer

EVALUATION CONCEPTS
ANNUAL REPORT

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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 CEMC center for 2010-2011 (year 9) is still composed of 8 research groups and led by 7 PIs and 1 co-PI, most of them located on the north campus. The co-PI is expected to be promoted PI during year 10. They are assisted by around 25 associate researchers, PhD students (55 from different PhD programs), postdoc (16), undergraduates and about 30 technicians. CEMC activities include research and training programs and also aims to promote the diffusion of science in Chile at other universities and for a large public through the organisation of scientific meetings. The CEMC center was approved for a further five years of funding in 2007. The research activities of the center still remain focused on signal transduction mechanisms operating in normal and pathological situations in various tissues, underlying neuronal plasticity and neurodegenerative diseases, proliferation, apoptosis and cancer, hormone generation and effects, muscle and cardiac physiology including cardiovascular diseases.
The major research activities of the PIs include studies on calcium signalling, redox-related processes, proliferation and cell death mechanisms, ion channels and the relations between proteins misfolding and diseases. These topics and approaches generate collaborations between the PIs and their collaborators including several transversal studies with clinicians.

Research activities

Andres Stutzin has replaced recently Cecilia Hidalgo as center director in March 2010 and has been successful in promoting the quality and quantity of research executed at the CEMC. It is remarkable that all the PIs including those recently recruited, have increased their output and productivity each year bringing the average impact factor for publications during this period to 5.5. The number of ISI publications compared to the previous period increased from 27 to 63 and about one third of them are published in journals ranked within the top 10% of their field. The number of joint publications in CEMC is still progressing (from 4 to 8) and in particular the increase in collaborative publications with national or international research institutions is spectacular (8 to 44). This is attested to by the increased visibility and communication of the center that has been developed. The present and previous directors have stimulated the collaboration between groups and the strategy developed for Ph. D. (co-tutoring) and post doctoral (projects shared between two groups) has probably stimulated the process. It is also impressive to note that 46 theses have been undertaken during this time period, 9 of which were completed (including 3 co-tutored). It is also important to note the large increase in publications implicating postdoctoral fellows during this period in full agreement with the recommendations in previous reports. The increased impact of the publications, the quality of student training and the various outreach activities and

strategies developed for promoting the research activities of the center (including international courses, student exchange programs, workshops, external communications and several different types of meetings) has largely increased the visibility of the center as borne out by the impressive number of international collaborations with prestigious laboratories. Furthermore, the center actively participated in the ICDS meeting 2011 in Brasil that provided a further opportunity for students to make contact with international scientists.
One also can congratulate the choice by the initial CEMC PIs of the two new associate researchers. Claudio Hetz is now a full PI and Luis Michea is previewed to become a PI next year. They both have been very productive and are well integrated in the center and developing joint research projects with other senior PIs. This also highlights the quality of the relationships amongst PIs, which underlies both the successful research activities and effective student training. Weekly or biweekly meetings and the CEMC institutional retreat organized in 2011 facilitate the communication between PIs and students. Courses devoted to written and oral communications, reading and discussing papers, improving knowledge of English are considered as important issues as publishing papers in high ranked journals or presenting results at international meetings. It is clear that the PIs by their participation in various Ph. D. programs in different faculties of the Universitad de Chile contribute largely to the preparation of a new generation of basic and clinical researchers. It is noteworthy that training concerns not only Ph. D. students but also undergraduate students and medical students to help them to run independent projects. Collaborative projects associating basic and clinical data has lead to both international funding and publications.
It is important to note that the CEMC has developed a number of core facilities to provide researchers (both CEMC and from other Chilean universities) technologies needed for competitive research programs. All PIs are involved in the development and maintenance of these core facilities such as adenovirus construct production (and recently lentivirus), confocal microscopy and flow cytometry. The confocal microscope and the spinning disk confocal microcope are overused and priory should probably be given to further equipping these core facilities and including animal facilities as the need of in vivo experiments grows. But the reviewer is aware of the associated costs and it will be necessary to set up a committee for the selection of the most relevant projects. The CEMC direction is managing the relocation of CEMC groups following the earthquake into a new space available at the medical school. This will accommodate 5 of the 8 PIs and core facilities in this area. This is quite important to stimulate interactions.

The individual projects concern various organs and tissues and various approaches. In particular, studies on calcium and redox signalling pathways, intracellular calcium releasing proteins such are RYR and IP3 receptors initiated several years ago by the senior PIs and can be considered as a signature of the center. These studies on skeletal muscle have been transposed to others organs inducing collaborations between various PIs in neuronal, endocrine, ovarian, cardiovascular cells.
The group of C Hidalgo focuses on the key role of RYR as cellular redox sensors to

modulate the Calcium-Induced Calcium -Release in cells. They have shown that ROS stimulates RYR-mediated calcium release in neuronal and pancreatic cells leading to two papers in in Antiox. Redox. Signal. (IF>8) and another in J. Biol. chem in 2011. Data on ROS-induced RyR mediated signals were also obtained in pancreatic islets and human granulosa ovarian cells through collaborations with other PIs (Two papers in revision). Interestingly, these studies concern neuronal process such as spine formation but also integrate functions such are special to memory. An article in the prestigious journal PNAS in 2011 demonstrates the role of RyR isoforms (2 and 3) in BDNF action. Amyloid Beta peptide oligomers are also able to inhibit this process as described in two other papers. A collaboration with almost all PIs is going on as well as several with international groups in Brasil, USA and France.

The work of the group of E Jaimovich on calcium signalling in skeletal muscle and neurons is innovative, focused on excitation-transcription coupling. Several proteins involved in the E-T coupling have been identified in addition to Cav1.1 such as pannexin1, a channel that allows exit of ATP upon electrical stimulation and P2Y2. The role of dystrophin in E-T coupling was also investigated in the mdx mouse. Studies of the relationships between electrical stimulation, ATP release, insulin levels, glucose uptake, Akt phosphorylation led to interesting results and a Ph.D. thesis before being published. He is an expert in calcium imaging initially in skeletal muscle cells, collaborations are also carried out in other cell types with several PIs. These include studies on the role of RYR isoforms in hipocampal spine formation under the action of BDNF and in memory processes. International collaborations are still focused on the redox regulation of RYR receptors in skeletal muscle and heart (and involve groups from France, USA and recently Belgium).

The group of A Quest aim to identify the mechanisms involved in caveolin-1 function as a tumor repressor and regulate target genes such as survivin and COX2.In addition they investigate how E-cadherin is involved in this action. They also try to evaluate if the re-expression of cavelolin 1 in the absence of E-cadherin is associated to a metastatic phenotype and/or multidrug resistance on cancer cells. They have demonstrated that survivin promotes angiogenesis in vivo, an effect dependent on VEGF. Both Caveolin-1 and E-Cadherin were expressed in B16F10 melanomas and the presence of E-Cadherin enhanced tumor suppression by Caveolin-1 while inhibiting the ability of caveolin -1 to promote metastasis. Collaboration with another PI (C. Hetz) demonstrated the role of caveolin-1 in the UPR (Unfolded Protein Response). Other studies of the effects of caveolin-1 in the absence of E-cadherin were conducted on colon cancer and one can consider that this group also addressed successfully their objectives during this period. These studies produced 12 papers in high ranked journals with 6 among them involving national or international collaborations. Many students have been trained by the group which is highly implicated in post-graduate courses and training of students.

The group of Sergio Lavandero is focused on cardiac cells and in particular mechanisms of cells death following ischemia/reperfusion and hyper or hypo-osmotic stress. Osmotic stress and ischemia/reperfusion-induced cell death involves various

signalling pathways to produce necrosis, apoptosis, and autophagy and by acting through mitochondria signalling pathways modulated by IGF-1 . They demonstrate the participation of Bcl2 family protein and IP3 R in apoptosis and autophagy and the role of the Bag3-Bcl2 complex. Several Ph. D. thesis have been devoted to this topic including a study showing the down regulation of the RyR2 receptor in I/R via the proteasome. Another aim has focused on mitochondrial dynamics in the regulation of cell death and showed that prevention of fission reduced infarct area in I/R and prevented NE dependent hypertrophy. Finally this group explored the Calcium signalling pathways triggered by IGF-1 and other related tyrosine kinase receptors such as insulin in several conditions including hypertrophy. Collaborations are active with all the PIs of the center, and a large number of national and international collaborations are reported (USA, Canada, Spain , France, Germany). In addition 16 ISI papers were published during this short period mostly in excellent journals and 8 clinical papers. Also an excellent participation to the formation of students can be noted.

As already mentioned previously, the group of Luigi Devoto is particularly associated to clinical practice and clinical research. This group still works on the molecular mechanisms that control human corpus luteum demise. Working on steroidogenic cells they demonstrated metabolites of estrogens having proliferative, anti-angiogenic and proapoptotic effects. They also identified the progesterone receptor isoform and its role in pre-ovulatory granulosa cells. They continued to explore the Human chorionic gonadotropin hCG signaling in endometrial stromal cells to conclude that the cascade involves Erk and Akt activation during the window of implantation. They still study Polycystic Ovary Syndrome (PCOS) in women and identified this year a down-regulation of glucose-transporters in PCOS mural granulosa cells and an interesting effect of PPARγ agonists that stimulate glucose uptake through GLUT4 elevation. A participation of NK-kB was also demonstrated in endometriosis pathophysiology. Their studies are to be published in the journal Fertility and Sterility (IF 3.5). The research topics of this group are highly related to clinical and pathological situations and to human heath applications. I still believe that the interaction between clinicians and basic researchers is an important issue for CEMC and can stimulate transversal studies. It seems to me that the CEMC center has developed these interactions between fundamental and clinical research that will be beneficial for the future careers to both basic and clinical researchers including students. Consistent with this idea, this group has established collaborations with the other PIs and contributes to the training of Ph.D. and postdoctoral students. It is also important for medical students to interact with basic research groups. The group publishes regularly but mainly journals dedicated to this field such as Fertil Steril.

Claudio Hetz is a young PI at the center. His work concerns protein misfolding occurring during stress injuries. ER (Endoplasmic reticulum)-stress triggers a complex adaptive response named UPR (Unfolded Protein Response) that aims to restore homeostasis in the organelle. The mechanisms of neuronal loss in neurodegenerative pathologies such as Parkinson, Alzheimer, and ALS remains unknown and inclusions containing disease-specific misfolded proteins are a feature of these pathologies. His

project aims to demonstrate the role of ER stress in the elimination of these misfolded mutant proteins. His strategy is to manipulate ER stress levels using cellular and animal models of neurodegenerative disease in particular of Huntington Disease. In addition he has authored remarkable papers in PNAS (2008), Mol Cell and Genes & Development (2009) with editorial comments, 19 papers have been published between 2010 and 2011 including very high ranked journals (Embo J, J Neurosci…) and invited reviews in prestigious journals such as "Current Opinion in Cell Biol" and in particular "Physiological Reviews" which just appeared in November 2011. C Hetz is well integrated in the center and collaborates with other PIs working on prion (AS) with an article in PlosOne (2010) and Alzheimer (CH). These studies should help to identify new therapeutic drug strategies in neurodegenerative disorders, which is a major issue. His group appears highly competitive in this field.

Andreas Stutzin is now the new director of CEMC and a specialist of ion channels. He is working on TRPM4 channels expressed in epithelium cell lines and primary cultures to exploring their function in cell death, proliferation and migration. They developed a transgenic mouse based on a dominant negative TRPM4 construct (under the control of specific promoters of the prostate and CNS). Preliminary data on anatomopathologia of the prostates performed this year indicate a hyperplasia when compared to wt animals. This line has been mated to TRAMP mice to study a possible interaction with the development of spontaneous prostate cancer. They showed also the H2O2-induced TRPM4 activation is related the redox modification of Cys 1093, a work published in J Biol Chem (2010). The mechanism is addressed in more details by using TRPM4 mutants without channel activity to separate TRPM4 functions. Another collaborative project concerns glutamatergic neurons and redox state (published in BBRC this year). Andreas Stutzin continues his collaboration with Diego Varela (Varela et al 2010, J Biol Chem) on a new topic concerning the effect of AngII on L-type calcium channels (Channels, 2011). In addition to his new function of director, his group has provided a very good record of international publications.

Luis Michea is an associate PI focused on cardiovascular damage induced by mineralocorticoids in the cardiovascular system. The aims are to understand the deleterious effects of aldosterone in the cardiovascular system with the objectives of developing MR antagonists to prevent cardiovascular damage and chronic renal failure. Considering the cardiovascular damage induced by Chronic Renal Failure (CRF) in patients, therapeutic interest in MR antagonists is explored in relevant animal models of CRF. These studies aim to have clinical implications for patients with end stage renal disease. Luis Michea demonstrated the beneficial role of spironolactone in a previous paper (Hypertension 2009) a paper highlighted by an editorial comment. He has studied the production of spironolactone and in a rat model (Doca+salt uninephrectomized) shown the activation of the Th17 pathway in the heart and kidney of these animals, an effect prevented by spironolactone. They also showed that specific anti-IL17 antibodies could prevent hypertension. The role of MR-activation on osteoblastic differentiation of smooth muscle cells was studies as well as the effect of

stanniocalcin-1 (a candidate paracrine factor identified in fish). Preliminary data fit with this hypothesis and STC1 expression favors vascular calcification in CRF. The levels of STC1 are in parallel measured in hemodialisis patient. The use of siRNA to inactivate STC1 and of a KO mouse are planned Another project is focused on FGF23, a protein which increases phosphate excretion and reduces mineralization of osteoblastic cells in vitro. Glucocorticoids (GC) are used in immunosuppressant therapy in pediatric patients and they are known to reduce bone mineralization and increases fracture risk. The levels of this protein are measured in a cohort of pediatric patients and bone explants are used to explore the effects of GC antagonists in relation with the level of FGF23. Papers published in "Hypertension" in 2009 and in J. Immunol (2010) attest for the quality of the studies of Luis Michea as well as excellent international collaborations with world specialists of the field (F Jaisser in Paris). In addition two papers have been published in 2010 and two in 2011 (J Hypertension and J Neurochem). The transversal studies in patients with clinicians from other Chilean universities are also noteworthy, these studies having direct interest for clinical applications. He also collaborates within the center with other PIs which is promising for the future. His promotion as a PI appears quite justified.

Training Activities and Networking

Training of students and young researchers continues to be excellent. The PIs of CEMC are involved in 9 Ph.D. programs and in two post-doctoral courses based on the main research skills of the center such as in cell signaling, calcium signaling, cell death with a real will to develop translational research. Some courses are common to Ph.D. student programs and may be inter-faculty. All the PIs are involved in these training courses at various degrees.
As suggested in the past years, students are trained in the practice of English which is essential for many reasons including writing papers or participation to international meetings. A good example in 2011 is the international meeting on cell death organized in Brasil in which 4 PIs in addition of Sergio Lavandero (co-organizer) participated as invited speakers. They all will participate in a special edition of Current Molecular Medecine. Interestingly, the PIs are also involved in the undergraduate training programs probably enhancing the recruitment the best potential Ph.D. Students from different universities. The PIs have participated to important international meetings (Brasil, Spain, Italy (IBRO), USA (Neurosciences San Diego, Canada (FASEB), Mexico, Argentina, and many in Chile (total over 150).
An impressive number of national and international collaborations is listed in the document supported by collaborative publications in high ranked journals. In addition to the participation of PIs to scientific meetings through invited lectures they also contributed to the organization of scientific sessions. The contacts with researchers from other countries favors the exchanges between institutions (sabattical periods for seniors and postdoctoral periods for students). Alltogether this networking clearly increases the international visibility of the center .
General comments

To my opinion, the PIs have achieved most of the scientific goals stipulated in the last annual report. The publication record includes very good and also excellent papers, some being the result of international collaborations. The average publication level of the center has significantly increased the two past years and one can congratulate the PIs and encourage them to maintain this level and progress. The strategy to integrate two co-PIs as full PIs looks to me very positive and promising for the center in the future. The new director, Andreas Stutzin, has been successful in managing the center and promoting CEMC activities and the development of core facilities.
This excellent scientific activity has been accomplished in spite of adverse conditions induced by the strong earthquake of magnitude 8,8 which stopped the project of a new building to hold all the PIs and core facilities. A solution has rapidly emerged based on the renovation of the building B wing of the faculty that will soon provide a space (2500m2) for the majority of PIs (5) around common facilities in the basement. This is an important issue to promote exchanges and initiate collaborations between PIs and also between students.

Highlight of several strong points:

Various indicators highlight the quality of research at CEMC

-The increase in the number and more importantly in the impact of international publications, which demonstrates the quality of the science and both the visibility of the PIs and of the center. 63 ISI publications were produced in this short period with an average IF of 5.5. They include articles or reviews published in prestigious journals (PNAS, Science (perspective article), EMBO J, FASEB J, J Neurosci, Hypertension, Antiox.Redox.Signal. Physiol Rev…..)

-The close collaborations established between PIs and the strategy of co-tutoring of Ph.D. students by two PIs and also the implication of postdoctoral fellows in projects shared by two PIs.

-The identification by CEMC PIs of new concepts in cell death/survival and calcium signaling: Role of RYR and IP3 receptors, Caveolin-1, TRPM4, GLUT 4, the importance of misfolded proteins in neurodegenerative diseases or new targets in cardiovascular pathologies. The new targets and mechanisms identified by senior PIs of CEMC in Ca signaling have been transposed to different physiological functions in different organs.

-The excellent quality of training of students (around 80 ongoing Ph.D. theses during the period 2010/2011). Including co-tutoring and joint projects for post-doc between two PIs. Many efforts have been produced to improve the formation of young researchers (courses, seminars, lab meetings and retreats). All PIs are involved in several Ph.D. programs and in the organization of post-graduate courses or symposia in the different universities of Chile. The CEMC has become a reference in the training

of scientific and medical research in Chile.

-An impressive level of research networking: Each PI has established collaborations with other Chilean institutions and universities. The collaborations developed by CEMC for research activities include clinical research through exchanges between the medical school and ICBM and include a significant number of joint programs with other Chilean institutions. It is clear that the collaborations at the international level with institutions in USA, South America and Europe also contributed to increased level and number of publications. Also the participations to the main international meetings with oral presentations.

-Improvement of the core facilities: Core facilities are needed for competitive research and represent a major source of expenses. These core facilities concern more than 200 persons and in particular confocal microscopy is required for most PIs projects. It is not surprising that confocal facility is heavily used and one can only approve the acquisition of a spinning disk microscope.
It is considered that these excellent research activities of CEMC are managed with a moderate budget for core facilities in comparison to equivalent centers in other countries. It appears that PIs are more and more successful in obtaining grants (2010-2011) from conicyt/Fondecyt.

- Noteworthy, the website has been improved and a communication company hired to improve outreach to the general public. This may help to get funds from new public or private organizations in particular for large equipment to develop the core facilities.

Weaknesses?

The reviewer did not identify any major weaknesses in the research activities or in the research strategies of the center during this period. It seems to me that all PIs have been successful. Their close collaboration gives a lot of consistency to the project and encourages teamwork while increasing the quality of research and level of publications. It also promotes the training of students and it should be noted the strong involvement of all PIs in various courses related to the main topics of the center.
Possibility of patenting may be considered since some PIs develop transerval research in fields of high medical relevance

RECOMMENDATIONS TO THE CENTER DIRECTOR:
(only if report is approved))
I think most objective were achieved during the period. The center's activities have continued to progress with an increase in the number but also in the impact of international publications. As a result, the center has increased its visibility and has developed an impressive international network of collaborations. There is a very good complementarity between the senior and junior PIs with close interactions. It will be necessary ensure the development of common platforms which are a key for a competitive research. Patenting some results of translational research may be considered if medical applications are expected.