June/Juin 08, 2012
DCO150GP

Canadian Institutes of Health Research/Instituts de recherche en santé du Canada
Notice of Recommendation/Avis de recommandation

Application Number/Numéro de la demande: 273784
Committee Code/Code du comité: CP

Applicants/Candidats: Dr. Anne-Claude GINGRAS

With/Avec: Dr. B. DERRY

Institution paid/ Établissement payé: Mount Sinai Hospital (Toronto)

Title/Titre: Molecular mechanisms of cerebral cavernous malformations

Primary Inst./Inst. principal: Genetics
Other Related Inst./ Autres inst. connexes: Circulatory and Respiratory Health

Competition /Concours: Operating Grant
March/Mars 01, 2012

Number in competition/Nbre de demandes dans le concours: 2284

Peer Review Committee Recommendation, for your information and use/ Recommandation du comité d'examen par les pairs, pour fins d'information et d'utilisation:

Committee/Comité:	Cell Physiology
Number reviewed/ Demandes examinées:	53
Application rank within the committee/ Rang de la demande dans le comité:	1
Percent Rank within the committee / Rang en pourcentage au sein du comité:	1.89%
Rated / Cote:	4.67
Recommended Term/ Durée recommandée:	5 years/ans 0 months/mois
Recommended average annual operating amount/ Montant annuel moyen recommandé pour le fonctionnement:	$245,196
Recommended equipment amount/ Montant recommandé pour les appareils:	$0

This document is for information only.
An application rated below 3.50 is ineligible for CIHR funding. For applications rated 3.50 and above, please note that it is the application's rank within the peer review committee that determines whether it is funded, rather than its absolute rating. The final funding decision will be communicated in the Notice of Decision.

Document à titre d'information seulement.
Une demande cotée en dessous de 3,5 n'est pas admissible au financement des IRSC. En ce qui a trait aux demandes cotées 3,50 ou plus, veuillez noter que l'on détermine l'attribution des fonds en fonction du classement obtenu au sein du comité d'examen par les pairs plutôt qu'en fonction du classement absolu. La décision finale relative au financement sera communiquée dans l'Avis de décision.

June/Juin 21, 2012

DC0190GP

Canadian Institutes of Health Research / Instituts de recherche en santé du Canada

Notice of Decision / Avis de décision

Application Number/Numéro de la demande: 273784

Committee Code/Code du comité: CP

Applicants/Candidats: Dr. Anne-Claude GINGRAS

With/Avec: Dr. B. DERRY

Institution paid/ Établissement payé: Mount Sinai Hospital (Toronto)

Title/Titre: Molecular mechanisms of cerebral cavernous malformations

Primary Inst./ Inst. principal: Genetics

Other Related Inst./ Autres inst. connexes: Circulatory and Respiratory Health

Competition Outcome/Résultats du concours: Operating Grant
March/Mars 01, 2012

Number in competition/Nbre de demandes dans le concours: 2284

Number approved/Nbre de demandes approuvées: 400

Decision on your application/ Décision sur votre demande: Approved

Average annual amount/ Montant annuel moyen: $190,027

Equipment amount/ Montant pour les appareils: $0

Term/Durée: **5** **yrs/ans** **0** **months/mois**

Peer Review Committee Recommendation, for your information and use/ Recommandation du comité d'examen par les pairs, pour fins d'information et d'utilisation:

Committee/Comité: Cell Physiology

Number reviewed/ Nbre de demandes examinées: 53

Number approved in that committee/ Nbre de demandes approuvées dans ce comité: 9

Application rank within the committee/ Rang de la demande dans ce comité: 1

Percent Rank Within the Committee/ Rang en pourcentage au sein du comité: 1.89%

Rating/ Cote: 4.67

Recommended average annual amount/ Montant annuel moyen recommandé: $245,196

Recommended equipment amount/ Montant recommandé pour les appareils: $0

Additional Funding Opportunities/ Opportunités de financement additionnelles	Decision/ Décision	Competition Code/ Cote de concours	Application Number/ Numéro de la demande
Operating Grant - PA: Institute of Genetics Bridge Funding	Not Approved	201203IG1	282079

*** Applications receiving a score of less than 3.5 on any evaluation criteria will not be considered for Funding. / Les demandes qui ont reçu une note inférieure à 3.5 pour n'importe quel des critères d'évaluation ne sont pas admissibles.

CIHR IRSC

Institute of Aboriginal Peoples' Health
Institute of Aging
Institute of Cancer Research
Institute of Circulatory and Respiratory Health
Institute of Gender and Health
Institute of Genetics
Institute of Health Services and Policy Research
Institute of Human Development and Child and Youth Health
Institute of Infection and Immunity
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Institut du cancer
Institut de la santé circulatoire et respiratoire
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Institut des maladies infectieuses et immunitaires
Institut de l'appareil locomoteur et de l'arthrite
Institut des neurosciences, de la santé mentale et des toxicomanies
Institut de la nutrition, du métabolisme et du diabète
Institut de la santé publique et des populations

June 21, 2012

Dr. Anne-Claude GINGRAS
Samuel Lunenfeld Research Institute
Mt. Sinai Hospital
Joseph and Wolf Lebovic Health Complex
Samuel Lunenfeld Research Institute
600 University Avenue, Room 992A
Toronto, Ontario M5G 1X5

Dear Dr. GINGRAS:

We are pleased to inform you that the Canadian Institutes of Health Research (CIHR) has approved your recent application entitled "Molecular mechanisms of cerebral cavernous malformations". If you are receiving this letter through ResearchNet, your Authorization for Funding will follow in the mail otherwise it is enclosed in this package.

If you have not already received the review documents related to your proposal, please contact us. Should you have any questions about the review process, please address them directly to CIHR staff. Do not contact the officers or members of the peer review committee. As CIHR does not notify co-applicants of the decision, we ask that you inform those individuals involved, along with their research institutions (if different from your own), of the outcome of this application.

Congratulations on your success in this competition.

Dale Dempsey
Deputy Director, Program Delivery
Research and Knowledge Translation Portfolio

303001-201203MOP-CP-273784-145818-DLGAR

Canadian Institutes of Health Research
Room 97, 160 Elgin Steet, Address locator: 4809A
Ottawa, (Ontario) K1A 0W9 Tel.: (613) 941-2672
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Toronto, Ontario M5G 1X5

Dear Dr. GINGRAS:

Congratulations on your success in the recent Canadian Institutes of Health Research funding competition. You should take great pride in your success, particularly in light of the very competitive nature of CIHR peer review.

As you know, peer review is the cornerstone of our research funding system. This process rests on the kind voluntarism of your colleagues at other institutions who generously gave their time to review your application.

The Canadian Institutes of Health Research is committed to building an innovative national health research enterprise. To this end we have undertaken the development of a renewed strategic plan for CIHR, our Health Research Roadmap which has required support from researchers, policy makers, the voluntary sector and the Canadian public. To meet CIHR goals, we must share our knowledge. That is why we encourage you to work with your institution to communicate to Canadians about the work you are doing. To simplify this process, we have developed guidelines on public communication which you can find on our website at http://www.cihr-irsc.gc.ca/e/30789.html.

Once again, congratulations and I wish you success in your research.

Yours sincerely,

Alain Beaudet, MD, Ph.D.
President

President

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Président

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303012-201203MOP-CP-273784-145818-CONGR

Canada

Review Type/Type dévaluation:	Committee Member 1/Membre de comité 1
Name of Applicant/Nom du chercheur:	GINGRAS, Anne-Claude
Application No./Numéro de demande:	273784
Agency/Agence:	CIHR/IRSC
Competition/Concours:	2012-03-01 Operating Grant/Subvention de fonctionnement
Committee/Comité:	Cell Physiology/Physiologie cellulaire
Title/Titre:	Molecular mechanisms of cerebral cavernous malformations

Assessment/Évaluation:

Applicants:
This application has two applicants with complementary expertise. Dr. Anne-Claude Gingras is currently an Associate Professor in the Department of Molecular Genetics at the University of Toronto and Senior Investigator at the Samuel Lunenfeld Research Institute. Dr. Gingras also holds the Lea Reichmann Chair in Cancer Proteomics and a Canada Research Chair in Functional Proteomics. It is evident from her track record that Dr. Gingras has rapidly emerged as a dynamic and productive researcher. She is clearly on a trajectory to become an international leader in the field of proteomics. Her CV lists more than 70 career publications and about 20 book chapters – including nearly 30 publications (excluding book chapters) published since 2007. While a number of these papers represent collaborative work, a very respectable number of the papers arise from the Gingras laboratory. Moreover, the quality of the publications is outstanding – with a number of the papers appearing in Nature, Science and/or Cell family publications. The Gingras laboratory is currently supported by funds from a variety of sources including the NIH, CIHR, Ontario Research Fund and CCSRI. However, it would appear that Operating Grants are restricted to one grant from the CIHR and one from the CCSRI (as well as a one-year bridge grant from CIHR that is supporting the project described in this application). Overall, there is ample evidence that Dr. Gingras and her lab are ideally situated to perform the proteomics work that is part of this application.

Dr. Derry is a Senior Scientist in the Developmental and Stem Cell Biology Program at the Hospital for Sick Children and is also an Associate Professor in the Department of Molecular Genetics at the University of Toronto. He has long-standing expertise in the use of C. elegans as a model system and has been an active participant in the CCM (ie. cerebral cavernous malformations) field for the past few years. Dr. Derry's CV lists a total of 23 career publications including 8 papers published since 2007 that are universally published in respected and rigorous journals (JBC, Current Biology, Cell Death and Differentiation). The Derry lab is currently supported by 2 Operating Grants from the CIHR with additional funding from the SickKids Foundation and a CIHR/Terry Fox Foundation Training Grant (as well as a one year bridge grant from the CIHR for the current project). Overall, Dr. Derry's productivity is reasonable but not at same level as Dr. Gingras (but of course, there are few researchers currently matching Dr. Gingras' record). Importantly, Dr. Derry's record documents expertise that is directly relevant to the proposed studies as it would appear that his lab is ideally situated to perform the worm studies that are proposed in this application. Additionally, the publication records of both Drs. Derry and Gingras substantiates their capacity to work together productivity.

In addition to the two applicants, this application is accompanied by letters of support from a number of collaborators. Most notable of these letters is the documented collaborative interest of Dr. Awad (University of Chicago) and Dr. Gunel (Yale University) who are both neurologists with interests in the pathogenesis and treatment of CCMs. While beyond the scope of the current application, the documented interest of these

Review Type/Type dévaluation:	Committee Member 1/Membre de comité 1
Name of Applicant/Nom du chercheur:	GINGRAS, Anne-Claude
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Competition/Concours:	2012-03-01 Operating Grant/Subvention de fonctionnement
Committee/Comité:	Cell Physiology/Physiologie cellulaire
Title/Titre:	Molecular mechanisms of cerebral cavernous malformations

Assessment/Évaluation:

individuals provides assurances that these studies might ultimately have some direct implications for treatment.

Project Overview
This is an application that seeks to extend funding for a project that received 1 year of bridge funding arising from a score of 4.47 in the last Operating Grant competition. The overall objective of this project is to elucidate the underlying basis for Cerebral Cavernous Malformations (CCMs), a condition that afflicts up to 0.5% of the population (ie. presumably > 150,000 Canadians). It would appear that this project represents a natural convergence of research activities arising from proteomic studies performed in the Gingras laboratory using human cell line models and genetic studies in C. elegans performed in the Derry laboratory. Based on the identification of three genes (designated CCM1, CCM2, CCM3) in familial forms of CCMs and their functional conversation between species, Drs. Gingras and Derry have combined forces to elaborate both physical and genetic interactions of the CCM1, CCM2, CCM3 in human (or mammalian) cells and in worms. The underlying tenet supporting this work is that a thorough understanding of the networks involving CCM1, CCM2 and CCM3 will instruct an understanding of their role(s) in CCMs with the promise of ultimately guiding treatment. There are 3 broad aims outlined in the proposal. I) Establish physical interaction maps for CCM proteins in mammalian cells and in worms, II) Define the genetic interactions for CCM1 and CCM3, and III) Identify substrates for GCKIII kinases that have been shown to interact with CCM protein complexes (presumably through interactions with CCM3).

General Assessment
On the whole, this is a very clearly written proposal that is supported by an extensive amount of preliminary data and schematic illustrations of workflows for proteomic and genetic analyses. The only exceptions to the clarity of the presentation are the Response to Previous Reviews and the Summary of Progress that are slightly less polished than other components of the proposal. The proposed studies represent both a logical extension of previous work and a natural opportunity to capture synergy through the use of complementary experimental approaches and model systems. Preliminary data and the documented expertise of the applicants provides very strong assurances that a considerable amount of original data will emerge from this project. In my opinion, there are no major weaknesses – especially with the technical aspects of the proposal. At the same time, there are some issues for consideration as this project moves forward.

Specific issues for consideration include:
i) As noted above, the backgrounds and track records of Drs. Gingras and Derry provide high confidence

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Title/Titre:	Molecular mechanisms of cerebral cavernous malformations

Assessment/Évaluation:

that the proteomics and genetic studies will be productive. By comparison, while it is evident that comprehensive elaboration of physical and genetic interaction networks will be important to understanding the pathogenesis of CCMs, it remains to be seen how the diagnosis and treatment of CCMs will be impacted by theses studies. This comment is not intended as a criticism. Rather, it is encouragement to the applicants to ensure that Drs. Awad, Gunel and others stay engaged in this project.

ii) On the whole, the applicants have thoroughly described the methodogical approaches to be employed – and thoughtfully discussed expected outcomes. By necessity (as is the case when using discovery-based strategies), there is less precision in the description of next steps. For example, Aim 2 suggests that "each" of the interaction partners will be tested. Furthermore, the same paragraph suggests that "As new biological readouts become available, new assays will also be implemented". On the one hand, these statements illustrate that the applicants will restrict bias in their studies and will continually adapt their activities to capitalize on new advances. However, on the other hand, it becomes difficult to assess at what stage this work will lead to advances that will directly impact understanding of the pathogenesis of CCMs. Again, this comment is not raised as a criticism – but again raises the importance of maintaining the involvement of disease experts who can/will recognize advances with translational potential.

iii) From my perspective, the third aim is the one with perhaps the most promise – but also the most concerns. From the discussion of this aim, it is evident that the applicants possess a good understanding of the technical aspects of the work and the challenges that will be encountered. My concerns primarily arise from the ability of kinases to phosphorylate substrates in vitro that may not be physiological relevant. Consequently, while the use of FSBA to inactivate kinases before adding a kinase of interest is a technically clever strategy, this approach could yield the identification of many candidate substrates (especially the abundant proteins) that are not actual physiological substrates. The requirement to add exogenous kinase compounds this concern since there is no way to restrict the added kinase to it normal physiological localization and/or complexes. For the GCKIII kinases, how many in vitro substrates are likely to be actual physiological substrates? I don't lack confidence in the applicants but anticipate that this aspect of this work will require careful management.

Overall, this is an ambitious proposal with tremendous promise. However, as is the case with many proteomics/genetics studies, active project management is required to ensure that the project is productive.

Budget

The application requests support for activities in the laboratories of both applicants. For the Gingras lab, support is requested for a lab manager (50%), programmer (20%), and PDF (100%). For the Derry lab, support is requested for one graduate student (100%) and 1 PDF (100%). In addition to these individuals, one additional student (Michelle Kean who is supported by a CGS Scholarship) will work on this project. Overall,

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Competition/Concours:	2012-03-01 Operating Grant/Subvention de fonctionnement
Committee/Comité:	Cell Physiology/Physiologie cellulaire
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Assessment/Évaluation:

the request is well substantiated and carefully justified. Although higher than most budgets, the request is in line with the scope of the proposed studies and the needs of the project.

Review Type/Type dévaluation:	Committee Member 2/Membre de comité 2
Name of Applicant/Nom du chercheur:	GINGRAS, Anne-Claude
Application No./Numéro de demande:	273784
Agency/Agence:	CIHR/IRSC
Competition/Concours:	2012-03-01 Operating Grant/Subvention de fonctionnement
Committee/Comité:	Cell Physiology/Physiologie cellulaire
Title/Titre:	Molecular mechanisms of cerebral cavernous malformations

Assessment/Évaluation:

Applicant: Dr Gingras is an associate professor and senior investigator at the Samuel Lunenfeld RI in Toronto where she began her career as an independent researcher in 2005. She holds a tier II CRC and is supported by grants from CIHR (2010-15, 192k/yr) and CCSRI (2009-14, $138k/yr) as well as grants from NIH, ORF and CIHR as co-applicant. She has published 28 research papers in the last 5 years and is senior author on 4 (JBC, Mol Cell Proteomics, Proteomics) and co-senior author on 6 (EMBO R, Science, Nature Biotech, Nature Methods, Proteomics, JBC) of them. She also contributed an additional 9 review articles during this time.

Dr Brent Derry is a senior investigator at the Hospital for Sick Children where he began as an independent investigator in 2003. He is currently supported by grants from CIHR (2009-14, $118k/yr; 2010-15, $112k/yr) and is coPI on an additional CIHR grant. In the last 5 years Dr Derry has published 8 papers, 4 as senior author (CD&D x2, Curr Biol x 2) and 1 as first author (CD&D).

This is a re-submission of a new application seeking 5 years of support at $260796/Year. In the last competition it a score of 4.47, finished 8th (7 were funded) and received 100K in bridging funds for one year.

Project Description: Investigate the function of the three related proteins CCM1-3, connected to the formation of Cerebral Cavernous Malformations (CCMs). A powerful combination of proteomic and genetic approaches will be used to investigate the function of these proteins. A worm model has been developed for CCM function and can be used to test in vivo the candidate CCM interactors identified biochemically.

Aim1 Generate a CCM interaction map using a HEK293 over-expression system. This system has been engineered to allow the “Flping” in of a single copy of a gene of interest whose expression can be precisely controlled by a Tet inducible promoter. This will be/has been used to identify the interacting partners of CCM1-3 and will be used to build interaction maps of the CCM binding partners. The interaction data will also be confirmed in endothelial cells (the relevant cell-type affected in the disease). An attempt will be made to use GFP-tagged versions of CCM1&3 to identify the worm CCM interactome. Worms have CCM1 and 3 (but not 2).

In the longer term the regulation of the formation of CCM complexes will be assessed in cell culture following treatment with various agents thought to impact on CCM function. Finally the domains responsible for the various interactions will be mapped using deletion derivatives of the proteins of interest.

Aim2 Uses worm genetics to assess the role of CCM interactors in CCM function in vivo. In part A mutants of known CCM binding partners will be assessed for function in the worm “vasculature” model. In B, a

Review Type/Type dévaluation:	Committee Member 2/Membre de comité 2
Name of Applicant/Nom du chercheur:	GINGRAS, Anne-Claude
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Competition/Concours:	2012-03-01 Operating Grant/Subvention de fonctionnement
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Assessment/Évaluation:

CCM3 RNAi modifier screen will be used to identify new partners. Some bona fide hits already turned up in first round. In C, the expression patterns of novel CCM binders will be assessed using GFP-fusion and promoter truncation analysis. As described this seems overly ambitious for the 30-50 anticipated hits.

Aim3. Identify GCKIII substrates. GCKIII kinases are CCM3 binding partners. GCKIII substrates will be identified within the known CCM protein complexes using in vitro kinase assays for likely candidates. This will be expanded to an unbiased approach using an FSBA treated endothelial cell lysate as a substrate for identifying GCKII substrates on a global basis. Some problems are noted with this approach such as interference from pre-existing phosphorylation events. The suggestion to eliminate this by pre-treatment with phosphatases raises the question as to how the PPase will be removed before kinase treatment? In all cases candidate substrates will be tested directly in vivo using RNAi to test for the ability of the kinase to target the protein in cells as well as by using site-directed mutagenesis to mutate the putative target sites. Eventually phospho-specific antibodies will be attempted to be made.

Only minor criticisms overall. For example, Figure 6c is apparently mislabeled; there should not be any flag-ccm2 in the right hand lane of the anti-flag blot in the bottom right.

Parts of each aim might also be considered to overly ambitious, but criteria for assigning priority to “hits” are noted and the applicants seem well-placed to achieve the stated goals.

Budget: 1 research assistant (50%), 1 programmer (part salary), 2PDFs, 2 students.

Summary: Outstanding (if ambitious) grant supported a by a wealth of preliminary data from two excellent scientists.

Review Type/Type dévaluation:	SO Notes /Notes de l'agent scientifique
Name of Applicant/Nom du chercheur:	GINGRAS, Anne-Claude
Application No./Numéro de demande:	273784
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Competition/Concours:	2012-03-01 Operating Grant/Subvention de fonctionnement
Committee/Comité:	Cell Physiology/Physiologie cellulaire
Title/Titre:	Molecular mechanisms of cerebral cavernous malformations

Assessment/Évaluation:

The proposal is focused on the medical problem of cerebral cavernous malformation. Three genes, CCM1-3 are linked to genetic forms of the disease. The combination of proteomics and genetic studies in *c. elegans* provided by the co-applicants is ideal to study the role of these proteins in normal and disease states. The translation aspects of this grant are clear and the applicants are applauded for partnering with relevant MDs.

There was a great deal of enthusiasm for this grant. The scale of the work is enormous, yet feasible. The proposal was laid out clearly.