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: 275594
Committee Code/Code du comité: GMX

Applicants/Candidats: Dr. Anne-Claude GINGRAS

With/Avec: Dr. P. FILIPPAKOPOULOS Dr. A. PAWSON

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

Title/Titre: A systems approach towards the therapeutic modulation of the acetylome

Primary Inst./Inst. principal: Cancer Research
Other Related Inst./ Autres inst. connexes: Genetics

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:	Genomics
Number reviewed/ Demandes examinées:	34
Application rank within the committee/ Rang de la demande dans le comité:	6
Percent Rank within the committee / Rang en pourcentage au sein du comité:	17.65%
Rated / Cote:	4.43
Recommended Term/ Durée recommandée:	4 years/ans 0 months/mois
Recommended average annual operating amount/ Montant annuel moyen recommandé pour le fonctionnement:	$260,794
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: 275594

Committee Code/Code du comité: GMX

Applicants/Candidats: Dr. Anne-Claude GINGRAS

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Title/Titre: A systems approach towards the therapeutic modulation of the acetylome

Primary Inst./ Inst. principal: Cancer Research

Other Related Inst./ Autres inst. connexes: Genetics

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: $202,115

Equipment amount/ Montant pour les appareils: $0

Term/Durée: **4** **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: Genomics

Number reviewed/ Nbre de demandes examinées: 34

Number approved in that committee/ Nbre de demandes approuvées dans ce comité: 7

Application rank within the committee/ Rang de la demande dans ce comité: 6

Percent Rank Within the Committee/ Rang en pourcentage au sein du comité: 17.65%

Rating/ Cote: 4.43

Recommended average annual amount/ Montant annuel moyen recommandé: $260,794

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: Cancer Research (bridge funding)	Not Approved	201203IC1	281190
Operating Grant - PA: Institute of Genetics Bridge Funding	Not Approved	201203IG1	281528

*** 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

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Institute of Infection and Immunity

Institute of Musculoskeletal Health and Arthritis

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Institute of Nutrition, Metabolism and Diabetes

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Institut de la santé des Autochtones

Institut du vieillissement

Institut du cancer

Institut de la santé circulatoire et respiratoire

Institut de la santé des femmes et des hommes

Institut de génétique

Institut des services et des politiques de la santé

Institut du développement et de la santé des enfants et des adolescents

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 "A systems approach towards the therapeutic modulation of the acetylome". 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-GMX-275594-145818-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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Samuel Lunenfeld Research Institute
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Samuel Lunenfeld Research Institute
600 University Avenue, Room 992A
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

Canadian Institutes of Health Research
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Président

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303012-201203MOP-GMX-275594-145818-CONGR

Canada

Review Type/Type dévaluation:	External Referee A/Examinateur externe A
Name of Applicant/Nom du chercheur:	GINGRAS, Anne-Claude
Application No./Numéro de demande:	275594
Agency/Agence:	CIHR/IRSC
Competition/Concours:	2012-03-01 Operating Grant/Subvention de fonctionnement
Committee/Comité:	Genomics/Génomique
Title/Titre:	A systems approach towards the therapeutic modulation of the acetylome

Assessment/Évaluation:

This proposal from Drs. Gingras, Pawson (Toronto) and Filippakopoulos (Oxford, UK) aims to analyze the interactome of the human acetylation machinery and define the binding specificity of the bromodomains (that binds to acetylated peptides) and the specificity of related inhibitors. Overall, this is an ambitious and original proposal from highly productive PIs. It is becoming apparent that acetylation is a major post-translation modification that is not just restricted to histone proteins, and that it affects an important portion of the proteome. Misregulation/mutations of proteins implicated in acetylation have also been associated with many diseases most notably cancers. This timely proposal will focus and prioritize genes implicated in cancer progression; e.g., products of chromosomal translocated with BRD3,4 and NUT that are implicated in NUT midline carcinoma (NMC), a rare but aggressive squamous carcinoma. Potentially, it will provide pertinent information to better understand the progression of these diseases. In addition, the PIs will also investigate the specificity of new inhibitors (small chemicals; Fabs) of bromodomains that bind to acetylated proteins.

Aim1
The PIs will expend their mass spectrometry (MS) analysis to ~80 human proteins implicated in acetylation (Aim1.1): including all acetylases – KAT; deacetylases – KDAC; and binders or readers with bromodomains. In addition, several hits (up to 50) will be used for "reverse" IP-MS experiments (Aim1.2). Detailed validations and biological relevance analysis will also be performed (1.2). By nature, it is difficult to predict what will be the emphasis of these follow up studies, but the PIs have an outstanding track record in this area. The techniques for these two subaims are well established in the laboratories of Gingras and colleagues, and the number of proteins to assess is within the scope of previous studies. As a matter of fact, a large portion of this analysis was already performed and was included in preliminary data. While the proposed methods are not totally novel, this is a solid aim, in line with what is done in the best proteomic labs. Importantly, the PIs will use the very effective SAINT approach to identify common contaminants. Also, Gingras and colleagues will specifically adapt the IP conditions to accommodate chromatin-associated proteins that are typically poorly soluble. *Less clear is what will be the main focus/outcome of the proposed functional enrichment analysis (e.g., how to distinguish substrates to co-factors; having said that, complementary analyses in Aim2-3 will provide additional information).* The clustering shown in Fig10 is interesting; several HDACs are closely associated – could that argue that several of these pathways are redundant?
Aberrant translocation fusion products implicated in cancer will be further assessed using the new SWATH quantitative methods established by one of the PI (Aim1.3). The aim here is to identify which proteins are specifically interacting (or not) with the fusion proteins compared to the non-truncated proteins. *Less clear is whether the severe phenotypes in NMC are really related to acetylation (i.e, requiring the functional bromodomains), as opposed to upregulating expression of the other fragment of the fusion protein.* Finally, using Fabs generated by phage display (Aim 1.4), Gringras and colleagues will pull-down endogenous

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Agency/Agence:	CIHR/IRSC
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Assessment/Évaluation:

proteins containing bromodomains. A major advantage of this approach is that different cell lines or tissues could be assessed. The PIs and their collaborator, Dr. Sidhu (Toronto), have already generated reagents. *Preliminary data showing the specificity of these reagents would have been appreciated. The scope of this subaim is less defined and a bit broad.*

Aim2

In this highly innovative aim, Gingras and colleagues will use a combination of approaches to identify specific acetylated proteins/peptides binding to different bromodomains. In Aim 2.1, they will compare using quantitative MS pull downs of wild-type bromodomains with their counter part containing point-mutations (that should prevent binding to acetylated proteins). This sub-aim is very complementary to Aim1 and should not be problematic. *The experimental design for Aim 2.2 is not clear.* The PIs probably refer to the approach described in Figure 14. If so they will use a combinatory approach (to expand on Aim 2.1) by adding a second step to specifically enrich for acetylated peptides using an antibody against acetylated peptides. Gingras and colleagues have already generated preliminary data to show feasibility. *It is not clear whether recombinant domain or immune-tagged proteins will be used in this approach. One possible pitfall is that the anti-acetylated antibody may introduce a bias for certain sites.* Aim2.3 is high-risk but very innovative. Gingras and colleagues will attempt to identify acetylated peptides using recombinant bromodomains from a peptide mixture (after a proteolytic digest of a whole protein mixture). One advantage is that various cell-line/tissues can be analyzed and binding specificity for a given domain will be analyzed in an unbiased manner. To increase sensitivity/yield, the PIs have already generated an antibody to potentially pre-enrich acetylated peptides (see also Aim 2.2). Gingras and colleagues have already generated several reagents for this sub-aim and have a solid track record for using innovative methods. Thus, they have a good chance to be successful. Altogether this aim will potentially bring the PIs to the forefront of acetylome analysis.

Aim3

In this aim the PIs will adapt a published method to specifically identify substrates of acetylase and deacetylase. This is an ambitious aim that would nicely complement the work in Aims 1 and 2. *However, no preliminary data was really presented. While I have no doubt that Gingras and colleagues have the ability to tackle this problem, this aim may be over-reaching within the proposed time frame (4 years). No dedicated personal for this aim was also indicated in budget (unless I missed it)*.

Aim4

This aim is highly complementary to Aim 2 and aims at characterizing inhibitors of bromodomains. The PIs will first focus on a first set of inhibitors but more reagents from their collaborators (Knapp and Sidhu) are expected in the next coming years. In aim 4.1 and 4.2, Gingras and colleagues will characterize small

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Agency/Agence:	CIHR/IRSC
Competition/Concours:	2012-03-01 Operating Grant/Subvention de fonctionnement
Committee/Comité:	Genomics/Génomique
Title/Titre:	A systems approach towards the therapeutic modulation of the acetylome

Assessment/Évaluation:

chemicals to determine whether they efficiently inhibit the binding to acetylated peptides/proteins. These two sub-aims are feasible and within the scope of the study. *Less clear is how the PIs will further expand these analyses to demonstrate specificity of these reagents for a given bromodomain.* In Aim4.3, Gingras and colleagues will test whether Fabs (see also Aim1.4) ectopically expressed in the cell can also disrupt the interactome of a specific target. *Again specificity of the reagents should be addressed.*

Overall this is a very strong and ambitious proposal highly relevant to human health and disease. The multiple approaches to analyze the acetylome and related proteins is highly innovative. Gingras and colleagues have a solid track-record and already have generated preliminary data for this study; thus they will likely complete a large portion of this proposal. The budget is adequate, although given the scope of the proposal, five years would be a more realistic timeline (a figure summarizing the timeline for each aim would have been useful).

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:	275594
Agency/Agence:	CIHR/IRSC
Competition/Concours:	2012-03-01 Operating Grant/Subvention de fonctionnement
Committee/Comité:	Genomics/Génomique
Title/Titre:	A systems approach towards the therapeutic modulation of the acetylome

Assessment/Évaluation:

Dr. Gingras is among our most if not the most talented young protein chemists in Canada and the world. She has made numerous landmark contributions, both technical and conceptual, to the analysis of protein complexes, on a large scale. These include particularly challenging problems such as isolating chromatin-associated protein complexes described here. Among her numerous contributions, Dr. Gingras recently published an article in which she describes results that suggests the highly integrated nature of kinase networks; a result that challenges existing notions of signaling network wiring. Technical advances in that paper are directly relevant to success of the proposed project. Dr. Filippakopoulos is a new investigator at Oxford, expert in large-scale analysis of protein structure by X-ray crystallography, having worked with the Structural Genomics Consortion. He is the first author and the attached manuscript describing a detailed analysis of the structures and binding properties of 23 bromo domains and complexes with a drug. Dr. Pawson is Dr. Pawson.

The applicants present an exhaustive and detailed account of how they are going to map out the human interactome of N-acetylated lysine peptide binding domains called “Bromos”. As the applicants relate, proteins containing these domains are the “readers” of protein acetylation, a key regulatory post-translational modification (PTM) implicated in, among other processes, chromatin remodeling underlying the regulation of gene transcription and replication. Lysine acetylation has been implicated in the pathogenesis of cancers and several drug candidates targeting bromo domains and acetylation and deacetylation enzymes have been developed. There are only 75 human bromo domain-containing proteins, but very little is known about what proteins these bind to and therefore the specificities and potential functions of the interactions. Thus, the primary motivation of this study is to perform a massive analysis of interactions for a majority (57) of the bromo domain containing proteins, interactions under different conditions (e.g. cell cycle arrested and in the presence of a bromo domain binding site blocker. At the same time, ongoing efforts to determine structures (of which they have already determined 23) of bromo domains will be carried out at peptide mapping studies performed to determine optimal binding sequences.

There are multiple levels to which this problem is going to be attacked, but essentially this is an analytical protein-structural study at large scale. Central to all of the aims are mass spectroscopic and auxiliary protein preparation procedures aimed at both achieving maximal coverage of potential interactions of bromo-domain containing proteins and bromo domains individually. A substantial amount of published and preliminary data are provided, both on the techniques that the applicants will employ and the methods of data analysis that will be utilized. Interactomics is a difficult business, because while it can be relatively easy to put proteins out of a lysate and analysis them, it is much another thing to prove that they have any biological meaning at all. In this respect the applicants clearly understand every potential pitfall and have included all possible controls (as

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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:

near as I can figure) to assure that interactions observed hold some meaning. Just as one example they propose exhaustive, redundant experiments, testing full-length protein and individual bromo domains themselves for identified targets. On the other side they are careful to confirm the target proteins they identify are in fact acetylated. Retesting of point-mutated bromo-domains, purification of antigenic peptide-tagged versus antibody purification experiments are proposed adding to the list of careful controls proposed. Further, testing of inhibitors at different stages of the cell cycle may enrich for individual interactions as well as going some distance to establishing biological relevance of individual interactions as on or off under different conditions. They also propose peptide SPOT arrays to fully test for optimal sequences and I presume, will compare results of these experiments to sequences of proteins identified as prey. If not, this would be a good strategy. Unless I missed something, I don't think they proposed this but they are collaborating with Dev Sidhu who has successfully applied this strategy to identifying distributions of sequences that bind to SH3 and PDZ domains. I do understand, and the applicants do point out that binding may be modulated by other PTMs nearby as they are in histones, but perhaps this is not generally the case and at any rate would be worth investigating.

At the end of the day, results of the efforts described in this proposal will be an interactome data set of great scope and validation within a network of protein involved, at least, in chromatin remodeling. It will thus be grist for the mill of countless research efforts around the world. This application should be funded at high priority.

No Budget issues. Dr. Filippakopoulos, though a co-applicant, would not receive funds for this 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:	275594
Agency/Agence:	CIHR/IRSC
Competition/Concours:	2012-03-01 Operating Grant/Subvention de fonctionnement
Committee/Comité:	Genomics/Génomique
Title/Titre:	A systems approach towards the therapeutic modulation of the acetylome

Assessment/Évaluation:

This project aims to examine lysine acetylation (acetlytransferases and deactylases) processes which is recognized as a more global process not restricted to histones but rather thousands of proteins.
Work already done has resulted in cloning two thirds of the known genes in acetyl-lysine signaling and their expression in mammalian cell lines. This work is in collaboration with the Oxford SGC group (P.F.). This work has also identified compounds that will disrupt interactions of bromodomains (BD) and acetylated peptides. These reagents set the basis for the proposed studies to identify the interactome of the human acetylation components; define the specificity for each protein with BD for acetylated lysine; define the acetylome specificity map; and test new BD inhibitors.
The methods to be used (AP-MS and mChIP followed by relatively standard analyses) are well in hand and in use within the project labs. The experience of the group and the familiarity of the methods give a high likelihood for success. Biological replicates are planned for reduction of background along with a strict SAINT cutoff metric. The resulting acetylome network map will be a valuable resource.
Once the network is identified, a larger question is how the specificity of lysine acetylation recognition is mediated. An additional purification of acetylated peptides (anti-KAc Ab) will enable a higher resolution of the potential interactions. As well, w.t and mutant defective BD will be used to quantify interactors in AP-MS.
Aim 3 will attempt to identify targets of known KDAC using a published method to cap exposed lysines in cell extract followed by incubation with the recombinant KDAC. Newly exposed lysines are captured and identified with MS. The method for KAT target identification is less well defined and largely relies on a set of putative substrates.
The methods developed provide a means for testing small molecule BD inhibitors and Fabs. This will not be a high-throughput screen but rather a means for testing molecules designed from crystal structures.
Aims and methods are complementary throughout. In some areas experimental detail could have been enriched but supporting documentation supported most points. Overall the application is perhaps too ambitious but the productivity of these groups is high.
A welcome addition to the proposal is an attempt to quantify interactions in mutated proteins (BRD4-NUT fusion) in a cancer. The associated NMC cancer is rare but it is a good target for BD inhibitor therapeutics due to its seemingly simple driving mechanism.
The acetylome players are often mutated in cancer genomes. This research may shed light on new potential therapeutic approaches exploiting this process as has already been demonstrated (P.F.)
This is a very strong research team who have been highly productive and are leaders in their field. This project is well within their expertise. Collaborations have been longstanding.
Budget is well-justified.

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:	275594
Agency/Agence:	CIHR/IRSC
Competition/Concours:	2012-03-01 Operating Grant/Subvention de fonctionnement
Committee/Comité:	Genomics/Génomique
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Assessment/Évaluation:

Dr. Gingras is an expert on protein MS and had made numerous contributions to unravelling PPI networks. Dr. Filippakopoulos is a new investigator and expert in large-scale analysis of protein structure by X-ray crystallography. The committee felt this was a strong proposal, authored by a strong team that has been very productive. The panel discussed the feasibility of the project as it appeared somewhat overambitious. The proposal also lacked experimental details in some of the aims, in particular regarding the biological follow-up. Preliminary data for aim 3 would have strengthened this section.