FULL NAME: Michael T Hallett		
POSITION TITLE: Professor, Department of Biology, Centre for Structural and Functional Genomics		
INSTITUTION: Concordia University		
FULL ADDRESS: 7141 Rue Sherbrooke Ouest, Rm 120.07, Montreal, Quebec, Canada, H4B 1R6		
TELEPHONE: +1-514-848-2424 ex 2296	EMAIL: Michael.Hallett@concordia.ca	
WEB-ADDRESS: <u>http://www.bci.mcgill.ca</u>		

ACADEMIC BACKGROUND				
Degree Type	MM/YY	Discipline/Field/Specialty	Institution & Country	
Post-doctorate	07/00	Computational Biology	Swiss Federal Institute of Technology (ETH)	
Doctorate	06/96	Computer Science University of Victoria, Canada		
Bachelor's	06/92	Computer Science	Queen's University, Canada	

WORK EXPERIENCE			
Position, Organization	Department/Division	Start Date	End Date
Full Professor, CRC Tier 1, Concordia University	Biology	01/2017	-
Adjunct Professor, McGill University	Computer Science/Biochemistry	06/2017	-
Full Member, Centre for Structural and Functional Genomics	Concordia University	01/2017	-
Associate Professor, McGill University	School of Computer Science	2006	2017
Associate Member, McGill University	Biochemistry	2003	2017
Associate Member, McGill University	Goodman Cancer Centre	2011	2015
Full Member, McGill University	Goodman Cancer Centre	2009	2011
Visiting Scientist, German Cancer Research Centre	German Cancer Research Centre	2007	2008
Director, McGill University	Centre for Bioinformatics	2006	2012
Interim Director, McGill University	Centre for Bioinformatics	2000	2006
Assistant Professor, McGill University	School of Computer Science	2000	2006
Oberassistant, Swiss Federal Institute of Technology	Computer Science	1998	2000

Honours & Awards

2017 Canadian Research Chair Tier 1, Algorithmic Bioinformatics

2008 Alexander von Humboldt Fellow, Germany

Personal Statement

My lab has a long-standing interest in the development of bioinformatics/systems biology methodology for breast cancer with over 40 publications in the area. Of relevance to this proposal, one of our main focuses has been on the development of gene set predictors. Gene set predictors use, for example, mRNA levels for a (small) set of genes in a multivariate fashion to classify or stratify patients relative to a clinical end-point eg prognosis or benefit from a therapy. The majority of predictors in breast cancer (eg. Oncotype DX, MammaPrint and Prosignia) have focused on predicting whether an estrogen receptor positive breast tumors should receive chemotherapy in addition to Tamoxifen, or whether the Tamoxifen alone would suffice. Our projects have taken gene set predictors in new and novel bioinformatic directions. As one example, we attempted to predict the likely site of metastases (eg bone, liver, kidney, brain) from an expression profile of the primary tumor. For some cites such as bone, there are drugs that can inhibit colonization. If we know patient is at high risk for a specific type of metastasis, then she can be given the prophylactic treatment (this area of work has received 1883 citations).

Several of my most significant research contributions stem from my breast cancer project funded by Genome Quebec. Of relevance to this proposal, this project sequenced the DNA and RNA for a sizeable cohort (n=500 invasive breast cancers). We then compared 110 previously reported prognostic set predictors in the literature led to a concept we call *inherent prognostic difficulty* (Tofigh et al. (2014) Cell Reports). Essentially, we observe that the prognosis of some

patients are very easy to predict, while other patients appear very difficult), using molecular profiles from the primary tumor at time of diagnosis. In other words, almost every reported prognostic gene set predictor (which poll a wide range of cancer hallmarks) correctly estimates the easy patients, but none of the existing prognostic signatures is capable of predicting outcome for the difficult cases.

Our lab has also introduced new approaches for patient subtyping that address some of the "real world" clinical constraints associated with personalized medicine. In research settings, we typically have access to a large cohort of profiled samples. Using this cohort, we have the "luxury" of classifying patient subtype using comparative analysis. Essentially, approaches in the literature estimate the subtype of a new sample as the subtype of the sample's closest neighbor in the cohort. In clinical applications, a tumor must often be examined "in isolation" without recourse to relativistic approaches. We presented an approach entitled AIMS (Paquet and Hallett 2014 Journal of the National Cancer Institute) that accurately assessed subtype in an absolute manner, only looking at the target sample and without the use of a comparative group. The manuscript was the subject of two editorials (Staaf, Ringner, JNCI and Kim JY, Kim S-I, Paik S (2015) JAMA Oncology) underscoring perhaps their promise of clinical utility. A second article predicts activation of all molecular pathways in an analogous absolute (AIPS) recently appeared in Breast Cancer Research. We also recently introduced our framework entitled BreSAT (Breast Signatures Analysis Tool). The mathematics and computational framework (based on linear orders and extremal probability) was supported by my previous NSERC Discovery grant. To date, the tool has been used in 14 manuscripts with our collaborators including a Science article, a Nature Methods article and four PNAS articles.

Also of relevance to this proposal, we have a history of developing predictors for early, pre-invasive forms of breast cancer in collaboration with the famous Oslo group led by Sorlie and Borressen-Dale, and now this propoal with E Rakovitch at Sunnybrooke. In 2010, we published a manuscript (Muggerud et al.) that studies ductal carcinoma in situ (DCIS), a non-obligate precursor to invasive breast cancer that affects approximately one in five women. However, only a small fraction (estimated at less than ½) will ever progress to a life-threatening form of the disease. Unfortunately we currently have no means of differentiating between the DCIS that are likely to progress, and those that are likely to remain indolent. Therefore, an enormous number of women are being over-treated, sometimes with mastectomy. In Muggerud et al. (2012) and a follow up manuscript Lesurf et al. (2015), we identified a set of genes that could differentiate between those instances of ductal carcinoma in situ (DCIS) that are likely to progress to an invasive form of the disease from those likely to remain indolent. This work has served as a stepping-stone to projects with Norway, Sweden and now Toronto with larger cohorts of DCIS patients to explore clinically relevant signatures that ablate over-treatment of this disease.

Additional Activities and Contributions

With respect to international leadership, I am one of three founding members of the Computational Cancer workshop, a satellite of RECOMB (Research on Computational Molecular Biology; http://www.recomb.org). This bi-annual meeting was the first to focus specifically on the use of computational biology to study cancer. I have been a co-organizer of large conferences including RECOMB '01 in Montreal, and several smaller bioinformatics workshops. I have organized 17 workshops at McGill's Bellairs research station in Barbados, covering a wide range of topics from fundamental computational biology to cancer immunology http://www.bci.mgill.ca/home/barbados. Nationally, I have served on several CIHR steering committees related to new programs (2010), priority reviews (2012) and the recent funding reforms (2014). I served on the program committees of the Canadian Society for Biochemistry and Molecular Cell Biology in 2008 and the Canadian Cancer Research Conference in 2013. In the latter conference, I designed and chaired the first systems biology session in this venue that attracts both clinical and molecular oncologists. I have also served on the steering committee to build a national centre of excellence for bioinformatics (CBIN), and as an advisor to training programs in systems biology/bioinformatics at the University of Ottawa (Regulomics program 2006) and Universite de Montreal (Robert Cedegren program 2008). Lastly, I supported (co-applicant or collaborator) almost 200 individual research grants to various agencies by different researchers at McGill. As the director of the McGill Centre for Bioinformatics, I helped hire five professors in this area, and developed intellectual support services for many groups spread across the Faculty of Medicine and the MUHC hospitals.

[Hallett, MT]

Over the past 18 years, I have maintained an inter-disciplinary lab with 10-15 researchers who have backgrounds in either the quantitative or life sciences. Five of the 11 research associates/postdocs are now professors at universities (Nebraska, Ottawa, Laval, Bristol, McGill). The lab has also produced 10 PhDs, of which two are now professors in bioinformatics (Sherbrooke, USC), one is completing his postdoctoral training, six have found positions as senior bioinformatic scientists at major research institutes or companies (Sage Bionetworks Inc, Hutchinson Cancer Centre, Princess Margaret Hospital, Sequenta Inc., Google). Of the 20 MSc students, 11 have now received their Ph.d. (9 in bioinformatics), and three have bioinformatic related jobs. I have consistently supported two undergraduate students per year in his lab with typically summer research projects. Every one of the 12 since 2012 has gone on to graduate or medical school.

The highly inter-disciplinary nature of the research group presents many challenges for training. My goal is to form students who are true researchers in a particular area of biology but for whom bioinformatics is their primary assay. I have developed and taught various types of graduate courses in bioinformatics and systems biology including two advanced courses within the School of Computer Science but also courses geared towards undergraduate students in the life sciences. In 2003, I created a graduate program in Bioinformatics at McGill that spanned three faculties and 11 departments involving quantitative, life science and clinical researchers. I was the principle applicant for, and directed, the CIHR-STIHR funded systems biology training program at McGill entitled Integrative Approaches to Human Health (\$1.7M over 5 years). The program offered many *de novo* training events including workshops, courses, roundtables, retreats, and student-run symposia to help in cross-training and supported 44 Ph.D.

I have been an active reviewer for most federal granting agencies including NSERC (Biosciences as panel member and reviewer for the Discovery and Chair programs), CFI, Genome Canada and CRC. For the CIHR, I have served on four different panels as a member including Genomics (6 years). I also chaired the Genomics committee for two years and I continue to serve as a virtual chair in the reformed system. I contributed to many of the provincial agencies throughout Canada (eg FRSQ, Michael Smith Foundation, Alberta Heritage Fund) and served as a member on some panels (eg Ontario Genomics Research Council). I also served as a committee member on cancer panels for the Canadian Cancer Research Initiative (CCSRI) and Prostate Canada and served as a reviewer for other non-profit agencies such as the Terry Fox Research Initiative and Quebec Breast Cancer Foundation.

Service on panels for granting agencies (last 5 years)

2010, 11, 13, 18	Ontario Genomics Research Council
2017	Prostate Canada
2012-2014	Canadian Cancer Society Research Institute, Gene Regulation
2012-2016	Canadian Institute of Health Research (CIHR) Genomics, Chair
2011-2012	Terry Fox Cancer Research Society, Panel Member
2014-2018	CIHR, Foundation Grants Competition, Virtual Chair.
2002-2018	8 additional CIHR panels

Research Support

Awarded

Computational infrastructure for transcriptional signature networks, 2017/11 - 2018/11 Canada Foundation for Innovation (CFI), Equipment Grant (37083) Principal Applicant. Total Funding - 250,000

Algorithmic bioinformatics: Transcriptional signature networks 2017/11 - 2024/10 Canada Research Chairs (CRC) Tier 1, Operating Grant Principal Applicant. Total Funding - 900,000

DCIS-Precise: A Genomics-Driven Model for Predicting DCIS Response to Radiation, 2018/4 - 2022/3 Canadian Institutes of Health Research (CIHR) Operating Grant Principal Applicant. Total Funding - 1,350,000 Co-applicants: Anne Martel; Lawrence Paszat; Lincoln Stein; Rinku Sutradhar; Sharon Nofech-Mozes; Tim Whelan;

[PROGRAM SHORT TITLE] Torsten Nielsen; Vanessa Dumeaux.

Completed

Interactions between the tumor-microenvironment and the systemic response of breast cancer patients 2014/8 - 2017/7 Canadian Cancer Society Research Institute (CCSRI) Innovation 2014 Total Funding - 199,860 Co-principal applicant: Vanessa Dumeaux

Signature Analysis Tools for the Life Sciences 2011/4 - 2016/3 NSERC Discovery Principal Applicant. Total Funding - 200,000

Genetic Analysis of the Breast Tumor Microenvironment, 2012/4 - 2017/3 National Cancer Institute (USA) 2P01CA097189-06 Co-applicant. Total Funding - 7,870,825 (United States dollar) (Hallett 2.5%) Principal Applicant: Michael Ostrowski

Integrative Approaches to Human Health 2009/4 - 2015/3 Canadian Institutes of Health Research (CIHR) STIHR Principal Applicant. Total Funding - 1,790,000 (Canadian dollar) Co-investigator: 40 researchers at McGill

Development of integrated tumor-microenvironmental classifiers for personalized therapy targeting 2012/1 - 2014/12 Québec Consortium for Drug Discovery (CQDM), Operating grant Co-applicant. Total Funding - 1,312,507 (Canadian dollar)

Principal Investigator: Park, Morag

Next Generation Predictive Signatures for Breast Cancer 2010/7 - 2013/7 Genome Quebec - Genomics Research in Human Health Principal applicant. Total Funding - 1,449,560 (Canadian dollar) (Hallett 17%) Portion of Funding Received - 255,000 Co-investigators: Avard, D; Basik, M; Batist, G; Muller, W; Nepveu, A; Park, M; Siegel, P; Ursini-Siegel, J; Collaborator: Dumeaux, V

Pre-clinical models and therapeutic targets for metastatic breast disease 2009/4 - 2014/4 National Cancer Institute of Canada (NCIC) Program Project Grant Co-applicant. Total Funding - 5,153,424 (Hallett 5%) Co-applicants: Giguere, V; Park, M; Siegel, P; Principal Investigator: Muller W (Italics denote students in my lab.)

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Additional Creative outputs

MIxT, Matched Interactions across Tissues. [maintained 2016-] A web-based software platform for the analysis and visualization of cross-tissue comparisons eg between primary tumor, lymph node metastasis, and/or blood based expression profiles. <u>http://mixt-blood-tumor.bci.mcgill.ca/</u>

Stroma 4. [maintained 2016 -] An R package that facilitates subtyping of triple negative breast cancers based on our subtyping scheme (Stroma4) identified in gene expression profiles obtained via laser capture microdissection of the tumor microenvironment. <u>https://github.com/smisaleh/STROMA4</u>

AIPS, Absolute Inference of Patient Signatures. [maintained 2017 -] A R package containing several thousand classifiers that estimate the activation status of different molecular processes and cell types in invasive breast cancers. The classifiers operate in an "absolute" manner and can be applied to single patients without a reference cohort. https://github.com/meoyo/AIPS

AIMS, Absolute Inference of breast cancer Molecular Subtype. [maintained 2014 -] A R package that attempts to mimic PAM50 breast cancer (intrinsic) molecular subtypes using our "absolute" methodology. AIMS allows the subtype of a invasive breast cancer to be determined in isolation without recourse to a reference cohort. http://www.bci.mcgill.ca:8080/AIMS/

BreSect. [maintained 2014 -] Web-bases software that allows for the examination of prognostic gene signatures across a large compendium of gene expression profiles for invasive ductal breast carcinoma. <u>http://www.bci.mcgill.ca/bresect/</u>

BreSAT, Breast Signatures Analysis Tool. [maintained 2013 -] This is a set of R based functions that compute linear orderings of samples based on gene expression signatures, and computes various related statistics. <u>http://www.bci.mcgill.ca/bresat/</u>