IRICoR
COMMERCIALIZATION OF RESEARCH
Institute for Research in Immunology and Cancer

AmorChem

NOVEL IMMUNODOMINANT MINOR HISTOCOMPATIBILITY ANTIGENS PROGRAM

THERAPEUTIC AREA - Hematologic cancers - Cancer immunotherapy

INDICATION - Hematologic cancers (Leukemia, lymphoma, myeloma)

OBJECTIVES - To discover immunodominant minor histocompatibility antigens (MiHAs) to be used as targets for cancer immunotherapy:

+ To discover MiHAs presented by the most common HLA molecules using a high-throughput mass spectrometry approach
+ To determine the best targets for cancer immunotherapy

CURRENT STAGE - Clinical studies

IP STATUS - Patent application Family 1: #US 14/421,310 - #CA 2,880,331 - #EP 13829855.9 - #JP 2015-526842 – Family 2: #PCT/CA2016/050116

PRINCIPAL INVESTIGATORS - ***Claude Perreault*** (Immunogenetics), ***Pierre Thibault*** (Proteomics) ***and Denis-Claude Roy*** (Clinical)

COMPETITIVE ADVANTAGES

Recently awarded a major multi-year funding from Genome Canada in collaboration with Genome Quebec in the 2012 Personalized Medicine national competition:

+ Complementary expertise of investigators and their infrastructure

+ Novel and well-validated high throughput (HT) mass spectrometry (MS)-based method for MiHA discovery

+ Novel strategy for selection of human immunodominant MiHAs

+ Ready access to more than 500 HLA-genotyped specimens at Hôpital Maisonneuve-Rosemont (HMR) and to extensively characterized samples from the Quebec Leukemia Cell Bank (at HMR)

+ Affiliation with the Center of Excellence for Cellular Therapy (HMR) with GMP environment for clinical trials

SCIENTIFIC BACKGROUND AND RATIONALE

Two types of Ags can be targeted for T-cell based cancer immunotherapy: tumor-specific Ags (TSAs) and minor histocompatibility Ags (MiHAs). MiHAs are polymorphic peptides presented by HLA molecules; in other words, they are genetic polymorphisms that can be seen by T cells. MiHAs are the best targets for treatment of hematologic cancers (HCs) because:

+ All types of HCs express MiHAs (that is not the case for TSAs),
+ MiHAs are very immunogenic,
+ Since they result from germline polymorphisms (rather than somatic mutations), MiHAs are present on all HC cells (obviating the risk of intratumoral heterogeneity).

Furthermore, MiHAs are convenient targets for personalized immunotherapy because they are shared by many subjects (they are not unique to a given leukemia). We have shown that injection of T cells specific for a single MiHA can cure leukemia in mice without causing any form of toxicity. Translation of this approach in humans has been hampered by the paucity of molecularly defined MiHAs in humans.

COMPLETED WORK

Identification of proprietary human MiHA peptide sequences:

+ We have developed a novel high-throughput proteogenomic method for MiHA discovery. Our method leverages on next-generation sequencing to perform genomically informed mass spectrometry.
+ We have studied the repertoire of MiHAs presented by HLA-A*02:01 and-B*44:03 allotypes which compose the most common HLA haplotype in European Americans. Based on proteogenomic analyses of cells from 13 subjects, we have discovered 420 novel MiHAs. Of these MiHAs, 39 possess all the features required for HC immunotherapy : each of these optimal MiHAs is present on at least 10% of patients, is well expressed in HC cells and is expressed only at low levels or not at all on non-hematopoietic cells.
+ We found that with our 39 optimal MiHAs, we could treat practically all HLA-A*02:01 B*44:03 subjects. Extending our approach to four other HLA haplotypes will enable us to treat almost all patients.
+ We have developed a protocol for *in vitro* expansion of MiHA-specific T cells that generates therapeutic amounts of MiHA-specific T cells in 33 days under GMP conditions. Implementation of MiHA-targeted therapy in the context of allogeneic hematopoietic cell transplantation requires two steps: i) sequencing the 39 MiHA coding genes in donor and recipient peripheral bone marrow cells in order to determine which MiHAs are present in the recipient but absent in the donor; ii) *in vitro* priming and expansion of donor T cells specific for the selected MiHAs for injection into the recipient.

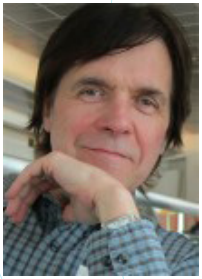
NEXT STEPS

+ Following our pre-CTA meeting with Health Canada on February 3, 2015, we plan to launch a phase I-II clinical trial in October 2016. GLIDE-201/44 (Guided Lymphocyte Immunopeptide Derived Expansion against MiHAs expressed on HLA-A201 and HLA-B44-03) is an exploratory, open-label, multicenter study to evaluate the safety and efficacy of anti-MiHA T-lymphocytes expanded *ex vivo*, in patients with HC presenting a molecular or clinical relapse after hematopoietic stem cell transplantation from a matched donor.
+ Further proteogenomic studies to discover MiHAs presented by four common HLA haplotypes, in order to enable treatment of all patients with refractory HCs.

LEAD SCIENTIST

Claude Perreault, M.D., F.R.C.P. (C)

+ Head of the Immunobiology Laboratory, IRIC
+ Full Professor, Dept of Medicine, Faculty of Medicine, UdeM
+ Hematologist, Maisonneuve-Rosemont Hospital (HMR)



Trained as a hematologist, Claude Perreault is one of the founding members of the Institute for Research in Immunology and Cancer (IRIC), the ranks of which he joined as a Principal Investigator in 2005. In addition to his research and training activities at IRIC, Dr. Perreault is a clinical practitioner at Maisonneuve-Rosemont Hospital where he set up both the Histocompatibility Laboratory and the Bone Marrow Transplant Unit. Before joining IRIC, Dr. Perreault worked at the Maisonneuve-Rosemont Hospital Research Center, which he also directed from 1992 through to 2001. Since 2004, he holds the Canada Research Chair in Immunobiology and has recently received the Murray Margarit Memorial Award, Leukemia and Lymphoma Society of Canada in 2009. He has been nominated Fellow of the Canadian Academy of Health Sciences in 2010 and has received the Léo-Pariseau Award from ACFAS in 2011. Claude Perreault and his team at IRIC focus their research initiatives on: 1- The mechanisms responsible for the development of T-lymphocytes; 2- The molecular definition of the immune self and how it is influenced by neoplastic transformation; and 3- The mechanisms of tolerance induction and maintenance by the TGF-beta pathway.

CO-LEAD SCIENTIST

Pierre Thibault, Ph.D.

+ Head of the Proteomic and Bioanalytical Mass Spectometry Laboratory, IRIC
+ Full Professor, Dept of Chemistry, UdeM
+ Accredited Member, Dept of Biochemistry, UdeM
+ Adjunct Professor, Dept of Anatomy, McGill Universitytomy, McGill University

Prior to joining IRIC in 2004 as a founding member, Pierre Thibault was an executive director of the protein analysis department at Caprion Pharmaceuticals (2001-2004) where he developed an industrial scale proteomics platform and novel approaches to the identification of trace-level protein targets for cancer immunotherapy resulting in numerous R&D contracts and partnerships with companies such as Biogen Idec, Abbott and Wyeth. Pierre Thibault was also Research Officer with the National Research Council of Canada's Institute of Marine Biosciences in Halifax (1990-1996) and Institute of Biological Sciences in Ottawa (1996-2002) respectively. He won the National Research Council of Canada (NRC) President's Award for his exceptional contribution to bioanalytical mass spectrometry, as well as the NRC's Outstanding Merit Award for his innovative work in the development of separation techniques coupled with electrospray ionization methods and their applications in protein chemistry and cell biology. Since 2004, he holds the Canada Research Chair in Proteomics and Bioanalytical Spectrometry. He brings his combined expertise in chemometrics, bioanalytical MS and protein chemistry to the development and implementation of new technologies in proteomics and cell biology.

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