IRICoR
COMMERCIALIZATION OF RESEARCH
Institute for Research in Immunology and Cancer

INHIBITION OF AN E2 UBIQUITIN-CONJUGATING ENZYME AS A NOVEL APPROACH TO CANCER THERAPY

THERAPEUTIC AREA - Oncology

INDICATION - Multiple solid tumors

OBJECTIVE - To identify first-in-class small molecule inhibitors of novel E2 target as novel approach to cancer therapy

CURRENT STAGE - Hit-to-lead

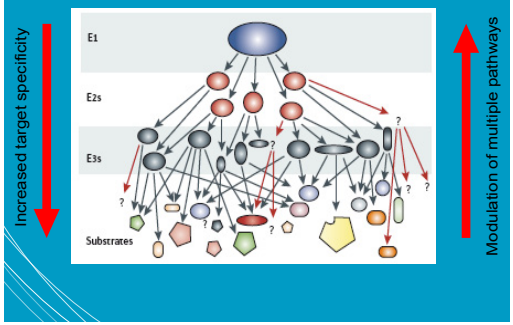
IP STATUS - Pending patent applications

TYPE OF TARGET - E2 ubiquitin-conjugating enzyme

PRINCIPAL INVESTIGATOR - ***Sylvain Meloche***

COMPETITIVE ADVANTAGES

+ Novel drug target identified and validated.
+ Pharmacologically tractable E2 target.
+ Potential for inhibitors of the program to be combined to other anti-cancer drugs for increased potency.
+ Biochemical assays readily available.
+ E2 target amenable to structural studies to guide future SAR activities.



SCIENTIFIC BACKGROUND AND RATIONALE

The project aims at developing small molecule drugs blocking more specific components of the UPS than the currently used proteasome inhibitors. Proteasome inhibitors have been shown to lack selectivity, induce side effects, and present an ill-defined mechanism of action in the treatment of multiple myeloma. Proteasome inhibitors have so far failed to show clinical benefit in solid tumors. In 2008, proteasome inhibitor Velcade generated annual sales of about $1B, with a YoY growth of over 20%. There is still strong potential for market expansion given the potential link between the UPS and many other human diseases. There is a significant need for novel compounds targeting specific UPS elements which are ideally orally available, cancer cell-specific, with increased specificity and decreased risk of off-target effects, in comparison with Velcade and the standard of care treatments.

COMPLETED WORK

+ Development of a robust HTS-compatible cell-based assay using a p21-Rluc fusion protein reporter as surrogate marker to identify small molecule inhibitors of p21 degradation and cancer cell proliferation. Screening of IRIC library of 112,000 compounds leading to identification of 6 chemotypes with confirmed activity. Initial SAR optimization of one chemotype series: synthesis of UM129480 which markedly induces p21 accumulation and inhibits proliferation of a panel of cancer cell lines with IC50 values in the low M range.
+ Use of a chemoproteomic strategy to identify the cellular target of UM129480: identification of the ubiquitin-conjugating enzyme XX E2.
+ Confirmation by immunoblot analysis that UM129480 selectively and reversibly binds to XX E2 in cells and binds to recombinant XX E2.
+ Genetic validation that RNAi depletion of XX E2 phenocopies the effect of UM129480 in up-regulating p21 expression and inhibiting cancer cell proliferation.
+ Bioinformatics analyses show that XX E2 is up-regulated in various cancers.
+ Development of an *in vitro* biochemical assay of XX E2 ubiquitin-conjugating activity based on autoubiquitination of XX E2.
+ Demonstration that UM129480 directly inhibits XX E2 activity *in vitro*.
+ Implementation of XX E2 biochemical assay in HTS format and screening of a Diversity Set of 3,200 compounds using XX E2 biochemical assay. Identification of 18 hits in primary XX E2 biochemical screen. Reconfirmation of 8 hits out of 8 molecules retested.
+ Demonstration of the *in vivo* activity of one confirmed hit: UM011500 inhibits HCT 116 cell proliferation with IC50 value comparable to that for inhibition of XX E2 activity. Cellular evidence of on-target effect (*in vivo* testing of other confirmed hits ongoing).
+ Identification of 4 chemical fragments that bind to XX E2 by NMR fragment-based screening.

NEXT STEPS

+ Pursuing hit-to-lead optimization of initial hits.
+ Hit profiling on human solid cancer cell lines.
+ MOA studies of the hits to confirm on target effects.

LEAD SCIENTIST

Sylvain Meloche, Ph.D.

+ Head of the Signalling and Cell Growth Laboratory, IRIC
+ Full Professor, Dpt of Pharmacology, Faculty of Medicine, UdeM

Dr. Meloche is a renowned expert in cell signaling. He is Professor in the Departments of Pharmacology and Molecular Biology of UdeM and principal investigator at IRIC. He is one of the founding members of IRIC. Research in Dr. Meloche's laboratory focuses on the signaling pathways that control thel proliferation of normal and cancer cells. Since 2004, Dr. Meloche holds the Canada Research Chair in Cellular Signaling. After his doctoral studies in molecular pharmacology at UdeM, Dr. Meloche did his postdoctoral training in immunology at the Clinical Research Institute of Montreal, and in biochemistry at the Université de Nice, in France. Among his main achievements is the demonstration of the key role of the MAP kinases ERK1 and ERK2 in cell proliferation control. This discovery had a major impact on the understanding of the biological roles of the MAP kinase signaling pathway. In functional genomics, Drs Lamarre and Meloche have obtained $7.3M from Sigma-Aldrich and Génome Québec (PRIVAC initiative) to set up the first genome-wide mouse and human lentiviral shRNA HTS platform, a project that uniquely positions IRICoR in the field of genome-wide RNAi screens and therapeutic target identification. This project has earned Drs Lamarre and Meloche the GENESIS Award in 2009 – category Biotechnology Award of Tomorrow.

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