Methods to Predict Efficacy of Cancer Stem Cell Targeted Therapy (SD2012-084)

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BACKGROUND

As evidenced by fusions found in leukemia and mutations implicated in a number of myeloproliferative disorders, the JAK2 (Janus Kinase 2) gene figures prominently in blood cell development. In leukemia, it appears that JAK2 activation of Stat5A is required for tumorigenisis. In diseases with aberrant JAK2 expression or mutations, JAK2 inhibitors can be used to modulate the survival or differentiation of the affected cell population. UC researchers have explored the interaction of JAK2 and STAT5A to identify a set of markers that can be used for prognosis and monitoring of patients who may be treated with JAK2 inhibitors.

TECHNOLOGY DESCRIPTION

UC researchers have found that the extent of JAK2 and STAT5A phosphorylation as well as the RNA isoform patterns indicate the extent of response to selective JAK2 inhibition and can also be used to inform the clinician whether this therapeutic approach is likely to succeed.

APPLICATIONS

The pattern of alternatively spliced *JAK2* and *STAT5A* RNA isoforms as well as their protein products can be used to:

- measure the effectiveness of a therapy targeting leukemic stem cells (LSC);
- predict or monitor which patients will be most responsive to targeted agents;
- assess the resistance, or relative resistance, of self-renewing LSC; and
- Distinguish leukemic progenitors from their normal counterparts.

ADVANTAGES

• Compatible with nanofluidic proteomic assays, which enable automated and more sensitive detection of isoform variants

• Novel biomarkers of response in validated primary cancer stem cell populations

• Can confirm mechanism of action and synergistic activity (i.e. JAK2 and BCR-ABL inhibitors)

• Uses both protein and confirmatory nucleic acid readouts to decrease the likelihood of false negative and false positive results.

STATE OF DEVELOPMENT

The invention has been validated in humanized murine models of CML (LSC engrafted RAG2-/-■c-/- mice) using a JAK2 inhibitor (SAR302503), which is currently in clinical trials. Nanoproteomic analysis confirmed that phospho-JAK2 and phospho-STAT5A distinguished leukemic progenitors from their normal counterparts and analysis of isoforms has identified useful RNA biomarkers. Interestingly, synergistic inhibition of self-renewal isoforms was found for combination treatment using SAR302503 and dasatinib (a BCR-ABL inhibitor).

INTELLECTUAL PROPERTY INFO

Worldwide rights available for licensure (See WO2013036867)

RELATED MATERIALS

- Fan, Alice C., et al., (2009) Nanofluidic proteomic assay for serial analysis of oncoprotein activation in clincal specimens, Nature Medicine, 15(5): 566-571 - 07/05/2012
- O'Neill, Roger A., et al., (2006) Isoelectric focusing technology quantifies protein signaling in 25 cells, PNAS, 103(44): 16153-16158 - 07/05/2012

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OTHER INFORMATION

KEYWORDS

JAK-2, Janus kinase, STAT5A, leukemia, chronic myeloid leukemia, cancer, myelofibrosis, myeloproliferative, myoproliferation, hemato, essential thrombocythemia, stem cell, oncology, polycythemia vera, CML, LSC, JAK2, hematopoietic, combination, biomarker, diagnose, oncology

CATEGORIZED AS

- Medical
- Diagnostics
- Disease: Cancer
- Stem Cell

RELATED CASES

2012-037-2, 2012-084-0

- Jiang, Q. et al., (2012) ADAR1 promotes malignant progenitor reprogramming in chronic myeloid leukemia, Proc Natl Acad Sci U S A., (3):1041-6
- also see: http://hem-onc.ucsd.edu/faculty/jamieson.shtml

PATENT STATUS

Country	Type	Number	Dated	Case
United States Of America	Issued Patent	9,611,330	04/04/2017	2012-037

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