Therapeutic Approach Targeting Malignant Reprogramming in CML Stem Cells

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OTHER INFORMATION

KEYWORDS

therapy, therapeutic, cancer, oncology, malignant, stem cell, Chronic Myeloid Leukemia, CML, leukemia, myelodysplastic syndromes, MDS, myeloproliferative neoplasm, MPN, RNA editing, ADAR1, diagnose, diagnosis, prognosis, isoform, signature, biomarker

CATEGORIZED AS

- **Medical**
  - Diagnostics
  - Disease: Cancer
  - Stem Cell

RELATED CASES

2012-037-0, 2014-199-0

BACKGROUND

The early (Chronic) form of Chronic Myeloid Leukemia (CML) is most commonly treated with Bcr-Abl tyrosine kinase inhibitors (e.g., imatinib and dasatinib). These drugs effectively counteract the constitutive activation of a BCR-ABL kinase, which derives from a chromosomal transposition of part of the BCR region of chromosome 22 to the ABL gene on chromosome 9. However, the Chronic phase of CML is followed by two progressively more aggressive phases and current therapies are marginally effective in the later Accelerated and Blast Crisis stages of the disease. To prevent and treat refractory forms of CML, there is a need for alternative means targeting molecular processes that fuel progression.

TECHNOLOGY DESCRIPTION

RNA editing is a post-transcriptional process that yields diversified RNA products, which can also have distinct functions. UC inventors have defined a novel target for CML therapeutics. Recent studies have highlighted the importance of ADAR1, which is one of a family of enzymes responsible for A-to-I RNA editing and normal hematopoiesis. Inventors have found that the editing process yields modified cellular RNAs, which have characteristic patterns through the progression of CML from Chronic to Blast Crisis forms of the disease. The crucial role of ADAR1 in both cell differentiation fate and self-renewal of malignant progenitor cells suggests that ADAR1 may provide a potential target for development of therapeutics as well as for diagnosing and monitoring CML patients during therapy.

APPLICATIONS

Methods of use cover inhibiting the expression or functional activity of ADAR1 in order to:

- Treat or prevent CML and its progression;
- Inhibit or ablate cancer stem cells;
- Treat CML that is refractory to standard therapies;
- Assessing ADAR transcript signatures as a means of diagnosing and monitoring disease status; and
- Similiarly useful for myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPN) as an acute leukemic transformation switch.

In summary, ADAR1 may provide a target for development of therapeutics as well as directly help physicians effectively treat their CML patients.

ADVANTAGES

Traditional CML treatment, such as hydroxyurea and imatinib, do not efficiently eradicate leukemia stem cells, which often lead to disease progression and relapse. This approach:

- Provides a completely new approach to targeting cancer stem cells;
- Focuses on RNA modifications rather than DNA mutations; and
- Provides a new avenue for epigenetic regulation at the RNA level.

New drugs that target cancer stem cells are vital for improving patient outcomes and quality of life as well as reducing the cost of care.

STATE OF DEVELOPMENT

Support for the crucial role for ADAR1 in disease stage-specific RNA editing as well as cell differentiation and self-renewal of hematopoietic stem cells is confirmed by a number of *in vivo* and *in vitro* studies:

- ADAR1 expression (protein and RNA) in samples derived from human normal and cancer stem cells (CSC) at various times during CML progression have identified ADAR1 isoform expression patterns that indicate disease status and efficacy of treatment.
- Normal and chronic phase progenitors can be biased to a stem cell profile by induced ADAR1 expression; conversely, ADAR1knockdown replicates blast and chronic phase profiles.

Together these data indicate that ADAR1 may provide a useful target for development of therapeutics as well as for diagnosing and monitoring CML patients.

INTELLECTUAL PROPERTY INFO

US rights available for licensure (See WO2013036867)

RELATED MATERIALS

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PATENT STATUS

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

ADDITIONAL TECHNOLOGIES BY THESE INVENTORS

▶ Compositions and Methods for Determining Cancer Stem Cell Self-Renewal Potential

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