Methods for Detection and Elimination of Dormant Cancer Stem Cells (SD2012-080, 2012-081)

Tech ID: 23555 / UC Case 2012-037-2

BACKGROUND
Mounting evidence suggests that dormant leukemia stem cells (LSC) evade therapies that target cycling cells. On the basis of the observation that sonic hedgehog (Shh) signaling pathways modulate cell cycle regulation in normal hematopoiesis, inventors hypothesized that forcing dormant refractory cells back into the cell cycle might also make them vulnerable to drugs that target actively dividing cells.

TECHNOLOGY DESCRIPTION
UC inventors found that by inhibiting the Shh pathway (validated for Smo inhibition), dormant cancer stem cells could be forced back into the cell cycle where they again become susceptible to BCR-ABL tyrosine kinase inhibitors (e.g., imatinib and dasatinib). And, because the stages of disease are characterized by predictable RNA isoform patterns, the levels of specific RNA isoforms and downstream gene products comprise companion indicators of CML progression and the likelihood of response to current therapeutic options.

APPLICATIONS
Various agents that inhibit the Shh pathway may revive the ability to use classic tyrosine kinase inhibitors to treat patients that have become refractory to this standard of care. In addition, while validation is for CML, this may be useful for any cancer with an etiology based in changes in Shh signaling and may be used to sensitize patients to radiation therapy in addition to chemotherapeutic agents.

ADVANTAGES
To inhibit the dormancy of therapeutically resistant LSC, methods:
- Identify and functionally characterize LSC based on RNA isoform patterns, and
- Treat patients via a novel therapeutic strategy that sensitizes LSC to tyrosine kinase inhibitors and spares normal hematopoietic progenitors.

Specifically, this approach may revive the ability to use classic BCR-ABL inhibitors to treat patients that are refractory to this standard of care.

STATE OF DEVELOPMENT
In humanized, murine models of CML, inventors have identified RNA isoforms and levels of specific gene products that correlate with the stage of disease progression (chronic, blast crisis) and have found that these characteristic profiles reflect the physiologic changes that accompany treatment with a Smoothened (Smo) inhibitor. These findings are supported by studies that showed that dormant blast crisis CML stem cells re-entered the cell cycle when treated with a Smo inhibitor.

INTELLECTUAL PROPERTY INFO
Worldwide rights available for licensure (See WO2013036867)

RELATED MATERIALS

PATENT STATUS

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