A method to treat JAK2 inhibitor-resistant cancers

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Value Proposition

Myeloproliferative neoplasms (MPN) are a class of hematologic malignancies arising from hematopoietic progenitors and include diseases such as chronic myeloid leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF). In 2005, a recurrent somatic point mutation in the pseudo kinase domain of the Janus kinase 2 (JAK2) gene was discovered to be present in a large proportion of patients suffering from these diseases. Recently, clinical trials have been carried out to evaluate the efficacy of the second generation JAK1 and JAK2 inhibitor ICNB018424 in patients suffering from MPNs. The conclusions of these trials show that, while transiently effective at reducing spleen size and alleviating some symptoms (in about 50% of patients), INCB018424-resistance is a real problem facing the drug moving forward in the clinic. In light of the development of JAK2 inhibitor resistance in the treatment of some cancers, there is a need to understand and develop effective therapies for the treatment of cancers having developed resistance to JAK2 inhibitors.

Technology

Duke researchers have developed a method to treat JAK2 inhibitor resistant cancers. This invention relates to the surprising discovery that in certain cancers conventionally treated with JAK inhibitors, combined inhibition of JAK2 and Ras effector pathways, or the direct, selective inhibition of BCL-XL protein, yields more robust and durable responses than JAK inhibitor monotherapy. In sensitive cells, exposure to a JAK inhibitor resulted in dephosphorylation of BAD, enabling BAD to bind and sequester the prosurvival protein BCL-XL, thereby triggering apoptosis. In resistant cells, RAS effector pathways maintained BAD phosphorylation in the presence of JAK inhibitors, yielding a specific dependence on BCL-XL for survival. In patients with MPNs, activating mutations in RAS co-occur with the JAK2V617F mutation in the malignant cells, suggesting that RAS effector pathways likely play an important role in clinically observed resistance. Therefore, administering a therapeutically effective amount of BCL-XL protein inhibitor with a JAK2 inhibitor is a promising method for treating myeloproliferative neoplasms. This invention has been demonstrated in cellular studies.

Advantages

- Could improve the lives of patients suffering from

Duke File (IDF)

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myeloproliferative neoplasms (MPN)
- Offers a promising strategy for combatting JAK2 inhibitor resistance
- Cell studies demonstrate that the activation of RAS or its effector pathways AKT and ERK can efficiently rescue JAK inhibitor–driven apoptosis in JAK2V617F MPN cells

Publications

- RAS signaling promotes resistance to JAK inhibitors by suppressing BAD-mediated apoptosis (Science Signaling, 2014)

Patents

Patent Number: 10,111,897

Title: COMPOSITIONS AND METHODS FOR TREATING CANCER WITH JAK2 ACTIVITY

Country: United States of America