Adrenergic Receptor Agonists for Treating Cancer

Technology Abstract

The mitogen activated protein kinase Raf-1/Mek-1/Erk1/2 is found aberrantly activated in many human cancers including breast and lung tumors as a result of Ras mutations. The beta 2 adrenergic receptor (β2AR) small molecule, ARA-211 (Pirbuterol), causes tumor regression by blocking the hyperactivated Raf-1/Mek-1/Erk1/2 pathway and has been determined to be a selective β2AR agonist which induces cAMO production, PKA activation, blockade activities, inhibition of tumor growth and human tumor growth in mouse models. Similar results have also been obtained with the well known β2AR agonist, isopreteranol. The hyperactivation of these oncogenic and tumor survival pathways such as Raf-1/Mek-1/Erk1/2 is found in 30% of all human cancers and have been associated with poor prognosis and resistance to chemotherapy in cancer patients. This has prompted drug discovery efforts targeting receptor tyrosine kinases to thwart aberrant signal transduction pathways in tumor cells.

Stage of Development

Pirbuterol is currently FDA approved and has been used for many years to treat symptoms of asthma. As a result, the safety and side affects of Pirbuterol in humans is well known. Pirbuterol is currently in pre-clinical stages for treatment of cancer and has been tested in mouse xenografts of human breast and renal tumors, and in human breast, renal, colon, CNS, and lung cancer cell lines. It has been determined that Pirbuterol has the ability to interfere with the growth and progression of nude mince xenografts of several human cancer cells. After 2 weeks of treatment with Pirbuterol, and an additional 3 weeks of observation of the tumors in the mice models, neither the breast nor renal tumors regrew. Both tumors remained undetectable. Pirbuterol was only able to suppress tumor growth in human tumors of breast and renal cancer (100% in each) where β2ARstimulation occurs, but not in those cells in which it does not (lung cancer, HCT, hematopoietic stem cell transplantation, and central nervous system). Apoptosis was also shown in breast and renal cells (15% and 11.4% induction respectively).

Commercial Opportunity

A large number of cancers harbor genetic alterations that ultimately result in hyperactivation of the Raf-1/Mek-1/Erk1/2 pathway resulting in poor prognosis, resistance to therapy, and shortened patient life. It is estimated that 30% of all human cancers including Leukemias, colon cancer, pancreatic cancer, and lung cancer contain Ras mutations that lead to hyperactivation of this pathway. The hyperactivation of the Raf-1/Mek-1/Erk1/2 pathway is critical to the growth and survival of human tumors. A target inhibitor such as Imatinib (Gleevec) is

currently FDA approved as first line treatment for chronic myeloid leukemia (CML). Other target inhibitors such as Herceptin and Iressa are available as treatments therapies for lung and breast cancers. Pirbuterol would expand the market of target inhibitors, provide more advanced treatment options in breast, renal, and CNS cancers, and reduce the possibilities of poor prognosis, resistance to therapy, and shortened patient life.

Market Summary

There are over 200,000 new cases of breast cancer in both men and women, over 58,000 new cases of renal cancer, and about 20,000 new cases of CNS cancers estimated for 2010. All three cancers will be the cause in over 66,000 deaths in 2010. The targeted drug market is estimated to reach over $58.6 billion in 2010 as well.

Financial Projections

Imatinib (Gleevec) is a target-specific drug, FDA approved for use most commonly in patients with chronic myeloid leukemia. The cost of Gleevec to patients is approximately $3500 per month. Comparing Pirbuterol to Gleevec, assuming 10% of the 278,000 total breast, renal, and CNS patients are prescribed the drug, annual revenues would approximate $1.1 billion.

Tarceva (Erlotinib hydrochloride) is an inhibitor drug used to treat several cancers including non-small cell lung cancer and pancreatic cancer. The cost of Tarceva to patients is approximately $3300 a month. Comparing Pirbuterol to Tarceva, assuming 10% of the target population is prescribed the drug, annual revenues would approximate $1.1 billion.

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