ErbB4 Inhibitors and Methods of Use

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Technology description

ErbB4 is a receptor tyrosine kinase member with roles in several key pathways associated with cell proliferation, death and differentiation. ErbB4 overexpression is associated with several types of cancers as well as psychiatric and cardiovascular disorders. Currently there are no drugs available for ErbB4-driven pathologies, or methods of identifying patients which can be treated with ErbB4 inhibitors. Ibrutinib is a, recently FDA approved, kinase inhibitor used in treating Mantle Cell Lymphoma. It is a specific inhibitor of Bruton’ s tyrosine kinase (BTK) with few other known/reported targets. Researchers at the Biodesign Institute of Arizona State University have developed novel methods for treating ErbB4-driven pathologies and a gene expression profile to identify potentially responsive patients. Using a novel protein microarray platform that was optimized for screening kinase inhibitors they identified ErbB4 as a target (in the nM range) for Ibrutinib. The microarray data were validated in vitro using gold-standard methodologies such as solution-based and bead-based kinase assays. In vivo, Ibrutinib inhibited cell proliferation in a number of cell lines expressing ErbB4. Further studies evaluating responsive and non-responsive cell lines identified a link between the ErbB4 pathway and the Wnt pathway, providing a gene signature that predicted drug responsiveness in cell lines.

Application area

• Treatment of ErbB4-driven diseases
o Cancers: breast, lung, colon, gastric, prostate, ovarian, melanoma, glioma, etc.
o Psychiatric disorders
o Cardiovascular disorders
• Identification of ErbB4 inhibitor-responsive patients

Advantages

• Inhibition of ERBB4 by Ibrutinib is dose-dependent and occurs at the same lower nM range as the canonical target BTK
• Gene profile differences between sensitive and resistance cell lines can predict Ibrutinib response in ErbB4 positive/BTK negative samples, personalizing the treatment and maximizing drug efficacy
• Optimized arrays provide low background signal during the kinase assay allowing the measurement of the kinase activity in the presence/absence of drugs

• Drug-response curves were successfully obtained and the microarray data correlates with classical solution-based and bead-based kinase assays.

Institution

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