Novel RAS inhibitors for NF1 disease

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Introduction

Neurofibromatosis type 1 is a genetic disease that results from either heritable or spontaneous autosomal dominant mutations in the NF1 gene. Neurofibromatosis type 1 individuals frequently suffer benign tumors known as Plexiform Neurofibromas which develop from cranial and peripheral nerve sheaths. Plexiform Neurofibromas have the potential to develop into a highly deadly malignant peripheral nerve sheath tumor (MPNST). MPNST exhibit a low overall 5 year survival rate of less than 40%, and there is no effective treatment or cure.

The NF1 gene encodes the protein Neurofibromin. Neurofibromin is a negative regulator (a "brake") for the notorious RAS oncoprotein. Thus, inactivation of NF1 leads to a constitutive increase in the active form of RAS. This is a transforming event that drives the disease.

In an attempt to combat the problem of a lack of a therapeutic treatment for Neurofibromatosis Type 1, and indeed, RAS driven cancer in general, we have performed in silico screening of two million compounds followed by bioassy to identify a small molecule, referred to as F3, that binds and inhibits active RAS. The compound is effective against models of mutant RAS driven tumor formation in vitro and in vivo. We have subsequently developed enhanced derivatives (F3F60).

Here, for the first time, we test the compounds against a disease driven by hyper-activation of the wild type RAS protein, rather than the mutant form. We find the compound has little effect on the growth of MPNST cells cultured in 2D but exhibits a striking inhibition of their ability to proliferate in 3D culture. We observe specific inhibition of RAS driven signaling pathways and suppression of tumor formation in vivo models of RAS mediated transformation, with no detectable toxicity. We propose this approach may lead to novel therapeutics for NF1 disease.

Discussion

NF1 disease is largely caused by deregulation of RAS due to loss of function of NF1. We have developed a RAS binding small molecule (kd ~70uM) that inhibits the ability of RAS to interact with downstream effectors. Designated F3, the ~490kd compound has little effect at low concentrations on 2D cell growth but is a potent inhibitor of 3D growth of MPNST cells. This is likely due to the suppression of RAS signaling pathways leading to anoikis. The compound is effective at suppressing tumor formation by RAS driven lung tumor cell lines without inducing detectable in vivo toxicity. We have developed several enhanced activity derivatives by Medicinal Chemistry, which we are in the process of characterizing and optimizing further. We intend to test the compounds against in vivo models of MPNST, as well as in vitro models of PFN to determine if they have the potential to be developed into targeted therapy for NF1 disease. As at least some of the cognitive issues associated with NF1 patients also appear to be due to aberrant RAS activity, and as our compounds can pass the blood brain barrier, we also hypothesize they may have utility in treating neurological defects caused by excess RAS activity.

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Results

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