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Neurofibromatosis as a gateway to better treatment for a variety of malignancies

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ABSTRACT

The neurofibromatoses (NF) are a group of rare genetic disorders that can affect all races equally at an incidence from 1:3000 (NF1) to a log unit lower for NF2 and schwannomatosis. Since the research community is reporting an increasing number of malignant cancers that carry mutations in the NF genes, the general interest of both the research and pharma community is increasing and the authors saw an opportunity to present a novel, fresh approach to drug discovery in NF.

The aim of the paper is to challenge the current drug discovery approach to NF, whereby existing targeted therapies that are either in the clinic or on the market for other disease indications are repurposed for NF. We offer a suggestion for an alternative drug discovery approach. In the new approach, selective and tolerable targeted therapies would be developed for NF and later expanded to patients with more complex diseases such as malignant cancer in which the NF downstream pathways are deregulated.

The Children's Tumor Foundation, together with some other major NF funders, is playing a key role in funding critical initiatives that will accelerate the development of better targeted therapies for NF patients, while these novel, innovative treatments could potentially be beneficial to molecularly characterized cancer patients in which NF mutations have been identified.

Contents

Abbreviations: NF, neurofibromatoses; NF1, neurofibromatosis type 1; NF2, neurofibromatosis type 2; WHO, World Health Organization; PN, plexiform neurofibromas; MPNST, malignant peripheral nerve sheath tumors; FTase, farnesyl transferase; TTP, time-to-progression; OPG, optic pathway gliomas; LGG, low grade glioma; PoC, Proof-of-Concept.

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1. Introduction

The neurofibromatoses (NF) consist of three genetically distinct disorders (NF1, NF2 and schwannomatosis). All three disorders are characterized by the growth of peripheral nerve sheath tumors despite the fact that their pathogenesis is driven by distinct genetic aberrations. As of today, the course of these diseases is mainly unpredictable and variable amongst individuals. NF1 affects 1/3000 people across all genders, races and ethnicities and can either be inherited or arise from a spontaneous mutation. The incidence of NF2 and Schwannomatosis is much lower (estimated at 1:25,000 and 1:30,000, respectively). Overall, approximately 120,000 U.S. citizens are afflicted with NF.

Although the NF research community has made major breakthroughs in understanding the biology that drives NF1, NF2 and schwannomatosis, there are as of yet no approved therapies for these diseases. The identification of disease-modifying therapies for NF that shrink tumor volume, improve neurological function (hearing, vision, mobility) and quality of life or even prevention of tumor initiation and growth can be considered an urgent and high unmet medical need. Funding entities such as the Children's Tumor Foundation, the Neurofibromatosis Research Program from the Congressionally Directed Medical Research Program (CDMRP) and the Neurofibromatosis Therapeutics Acceleration Program (NTAP) are currently funding multiple ongoing clinical trials.

Agents currently being assessed in the clinic for NF are mostly oncology drugs. These drug candidates can be used because the pathways that are hyperactivated in NF1, NF2 and schwannomatosis are typically the same pathways activated in malignant cancers such as Ras, the epidermal growth factor receptor (EGFR), the vascular endothelial growth factor receptor (VEGFR), the Wnt pathway and others. Therefore, we observe that the most frequently used research and development (R&D) approach in the NF field today is the 'oncology to NF' approach: drug candidates that were originally developed or are being developed as oncology assets are being repurposed for NF.

The current paper is aimed at reviewing the history of this approach as well as suggesting that the inverse R&D approach, NF to oncology, should also be considered. In this case, the initial intent of the R&D projects would be to develop and even market targeted therapies that specifically affect pathways that are activated in NF tissues or tumors only. Because of the overlap between the NF-activated pathways and the pathways that are activated in malignant cancer, the market of the specific and tolerable targeted therapies for NF could be expanded to the malignant cancer field. A perfect example could be the use of ultra-specific tolerable Ras pathway inhibitors developed in NF1, and then later used for the treatment of non-small cell lung cancer or drug resistant melanoma.

This novel approach in NF is modeled on the R&D experience with Gorlin syndrome. Gorlin syndrome, also known as nevoid basal cell carcinoma syndrome (NBCCS), is an autosomal dominant tumor predisposition disorder. Gorlin syndrome is characterized by a hyperactivated Hedgehog signaling pathway, mostly due to loss of the natural Hedgehog inhibitor Ptch. A few pharmaceutical companies were able to rapidly bring to market a group of Hedgehog inhibitors thanks to the very efficient clinical proof-of-concept testing in Gorlin syndrome patients. Following the initial 'Gorlin syndrome validation', the same compounds were tested in a variety of malignant cancers in which Hedgehog signaling was observed to be activated. Today, a long list of clinical trials of these Hedgehog inhibitors in malignant cancers where Hedgehog activation was described, is ongoing. We argue that a similar approach could be used for NF. This approach will not only offer safe, tolerable targeted drugs for a chronic condition such as NF, it will also allow the malignant cancer field to gain access to specific, tolerable drugs that can be combined with other safe and efficacious drugs.

Finally, the paper will conclude by summarizing some of the major NF-focused scientific initiatives that are designed, developed and coordinated by the major funding organizations including CDMRP, the Children's Tumor Foundation, the National Institutes of Health (NIH), NTAP and others and how resources from each agency are advancing bench-to-bedside initiatives that could benefit NF patients.

2. Neurofibromatosis type 1 (NF1)

2.1. Diagnostic criteria and clinical manifestations

NF1 (MIM 162200), the most common NF variant, is usually diagnosed very early in childhood.

The National Institutes of Health published formal diagnostic criteria in 1987.

According to these criteria, an individual must meet at least two of the following to be diagnosed with NF1: (http://consensus.nih.gov/1987/1987Neurofibromatosis064html.htm).

- Six or more café-au-lait macules over 5 mm in greatest diameter in pre-pubertal individuals and over 15 mm in greatest diameter in post-pubertal individuals. These café au lait spots are generally one of the first signs of neurofibromatosis 1 and can be identified in babies of only a few weeks of age.
- Two or more neurofibromas of any type *or* one plexiform neurofibroma.
- Freckling in the axillary or inguinal region.
- Optic pathway glioma.
- Two or more Lisch nodules (iris hamartomas).
- A distinctive osseous lesion such as sphenoid dysplasia or thinning of long bone cortex with or without pseudarthrosis.
- A first-degree relative (parent, sibling, or offspring) with NF1 by the above criteria.

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