Review Article

Advancing Neurofibromatosis Type 1 Therapies through Basic Research Translation

.

ABSTRACT

Neurofibromatosis type 1 (NF1) is a genetic disorder characterized by the growth of both benign and malignant tumors in neural crest cells. Despite extensive research, only one medication has been approved for plexiform neurofibroma treatment, and no specific drugs exist for other associated tumors. Recent studies suggest targeting cellular signaling pathways (Hippo, Janus kinase/signal transducer and activator of transcription, and mitogen-activated protein kinase) and the microenvironment (nerve cells, macrophages, mast cells, and T cells) as potential therapeutic approaches. Several clinical trials are investigating agents that inhibit specific kinases or target signaling molecules in the microenvironment. Despite significant progress, more effective treatments are needed. This paper reviews previous strategies, ongoing clinical trials, and recent advances in basic research related to NF1 and its associated tumor. Data collected from scientific databases and literature highlight the potential of novel therapeutics, including kinase inhibitors, signaling molecule modulators, and microenvironment-targeting drugs. Understanding the underlying mechanisms of tumor development and progression in NF1 is crucial for developing effective therapies. This review provides insights into current strategies, ongoing trials, and recent basic research, aiming to improve treatment outcomes and address unmet needs in NF1 management. By bridging the gap between basic research and clinical translation, this work paves the way for advancing NF1 therapies and bringing novel treatments to patients.

Keywords: NF1, tumor, signaling, therapies, cell

1. INTRODUCTION

Neurofibromatosis type 1 (NF1) is a genetic disorder characterized by nerve and skin tumor. Despite its high prevalence, effective treatments for NF1 have been limited due to a lack of understanding of the disease biology. However, recent advances in NF1 research have opened doors for therapeutic development. Key progress has been made through basic research translation, applying findings to treatment development. Improved genetic techniques and mouse models have enhanced our understanding of NF1's biology. Human induced pluripotent stem cells (iPSCs) have also provided valuable insights [1].

NF1 research has revealed dysregulated RAS/MAPK signaling as a key factor in tumor development. Mouse models with NF1 mutations have been crucial in studying disease biology and identifying potential therapies. Inhibiting the RAS/MAPK pathway has shown promise in reducing tumour growth. The use of iPSCs has furthered our understanding of NF1, enabling the study of NF1 gene mutations and the testing of novel treatments. These advancements offer new prospects for NF1 therapy development. Basic research translation serves as a crucial link between research findings and treatment innovation. The combination of improved genetic techniques, mouse models, and iPSC research has paved the way for deeper insights into NF1 biology and the exploration of new therapies. The ultimate goal is to develop effective treatments for patients with NF1.

2. MAPPING THE LANDSCAPE OF NEUROFIBROMATOSIS: A HISTORICAL OVERVIEW

The condition was first described in the medical literature over a century ago and has since been the subject of much research and investigation.

The first description of a condition that is now known as NF1 can be traced back to the late 19th century. In 1882, German physician Friedrich Daniel von Recklinghausen first described the condition as a “disorder of the skin and peripheral nerves” characterized by the growth of tumor on nerves and the presence of café-au-lait spots [2]. This description marked the first recognition of a condition that would come to be known as NF1. The recognition of NF1 as a distinct disorder marked a major milestone in the understanding of the disease. However, it was not until the late 20th century that the genetic basis of NF1 was discovered. The condition was later described in detail by several other physicians, including French neurologist Paul Marie Louis Pierre Broca, who described a similar condition in 1886 [3]. These early descriptions laid the foundation for further study and investigation into the condition, and helped to establish NF1 as a distinct disorder.

During the early 20th century, advances in medical science and technology led to a greater understanding of NF1 and the underlying genetic causes of the condition. In 1910, the first case of NF1 was reported in the United States by American physician George Pack [4]. In 1987, the genetic basis of NF1 was discovered when the gene responsible for the condition was identified and located on chromosome 17 [5]. The discovery of the genetic basis of NF1 was made possible by advances in genetic technology and the study of families with multiple cases of the disease. In 1987, the NF1 gene was identified and cloned, marking a major step forward in the understanding of the disease [6]. The identification of the NF1 gene allowed researchers to study the underlying biology of the disease and to develop new treatments. Over the past few decades, there have been many advances in our understanding of NF1 and its underlying mechanisms. In 2003, the complete sequencing of the human genome allowed for the identification of several other genes associated with NF1 [7]. This discovery has helped to shed light on the complex genetic basis of the condition and has provided new avenues for research and investigation.

In recent years, there has been growing interest in the development of personalized therapies for NF1. With the advent of new technologies and techniques, researchers are now able to study the disease at a molecular level and develop new treatments that target the underlying genetic causes of the condition [8]. This research holds great promise for those affected by NF1, as it offers the potential for more effective treatments and improved quality of life.

The history of NF1 is a testament to the progress made in our understanding of the condition over the past century. From the initial descriptions of the disorder by von Recklinghausen and Broca to the current advances in our understanding of the underlying genetic causes of NF1, the history of this condition is marked by a steady progression of knowledge and understanding. With continued research and investigation, it is likely that our understanding of NF1 will continue to grow, leading to the development of new treatments and improved outcomes for those affected by this debilitating condition.

3. CLINICAL MANIFESTATIONS OF NEUROFIBROMATOSIS TYPE 1

Neurofibromatosis type 1 is a genetic disorder that affects multiple systems in the body, including the nervous system, skin, bones, and eyes. The clinical features of nf1 can vary widely from person to person, but there are some common manifestations of the condition (table 1).

One of the hallmark features of nf1 is the presence of café-au-lait macules (figure 1), which are flat, light brown patches on the skin. These macules are present in up to 99% of people with nf1, and their number and size increase with age [9,10].

The presence of six or more café-au-lait macules that are larger than 5 mm in diameter is a diagnostic criterion for NF1 [11].

Another common feature of NF1 is the development of neurofibromas (Figure 2), which are benign tumor that arise from Schwann cells in the peripheral nervous system [12]. Neurofibromas can be classified into two types: cutaneous neurofibromas and plexiform neurofibromas. Cutaneous neurofibromas are small, flesh-colored bumps on or under the skin, while plexiform neurofibromas are larger and involve multiple nerves [13].

In addition to café-au-lait macules and neurofibromas, people with NF1 may also develop other skin findings, such as freckling in the axillary or inguinal regions, and skin-fold freckling [13,14]. Skeletal abnormalities, including scoliosis and bone dysplasia, are also common in NF1 [15].

NF1 can also affect the eyes (Figure 3), with up to 50% of people with NF1 developing optic pathway gliomas. Other eye findings that can occur in NF1 include Lisch nodules, which are benign tumor on the iris, and strabismus (misaligned eyes) [16].

Finally, NF1 can cause neurological problems, such as learning disabilities, attention deficit hyperactivity disorder (ADHD), seizures, and peripheral neuropathy [16-18].

Table 1. **Types of tumors that individuals with NF1 have a lifetime risk of developing [19]**.

Tumour type	Lifetime risk
Glioma of the optic pathway	15–20%
Other brain tumour	More than fivefold increase
Malignant peripheral nerve-sheath tumour	8–13%
Gastrointestinal stromal tumour	4–25%
Breast cancer	About fivefold increase

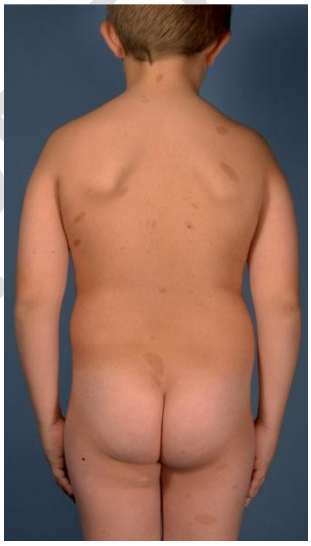

Figure 1. **Multiple (n ≥ 6) café-au-lait macules in a 9-year-old boy with NF 1** [18]

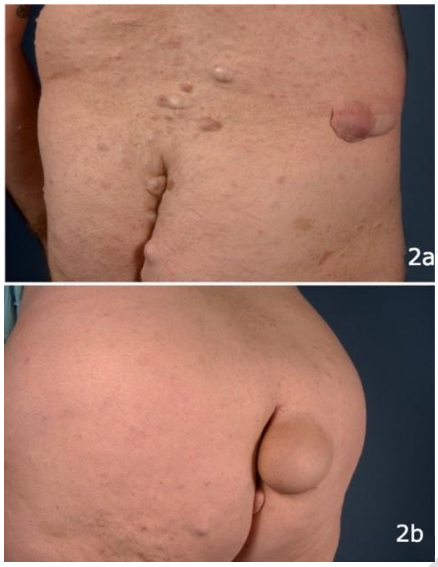

Figure 2a. **A 46-year-old man with NF1 with numerous neurofibromas with a maximum diameter of 4 cm on his back and gluteal area**. **2b**. **A 51-year-old lady with NF1 a tumour in her gluteal area that is 6 cm in diameter and is incapacitating** [18]

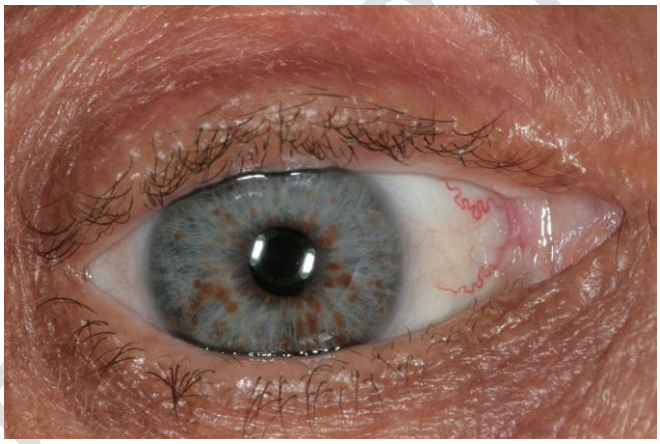

Figure 3. **Lisch nodules: Lisch nodules are clusters of dendritic melanocytes that appear as raised papules with a round shape and brown-yellow coloration when examined with a slit lamp** [18].
They are typically found in the iris of patients with Neurofibromatosis type 1, which is present in over 90% of cases, along with other symptoms such as café au lait pigmented skin lesions and superficial or deep neurofibromas in the skin or other organs

4. THE PAST: RETROSPECTIVE EXAMINATION OF PAST THERAPEUTIC STRATEGIES

The NF1 genetic etiology, the cellular function of the neurofibromin protein, and the identification of cellular elements that contribute to the tumor that grow in NF1 are all areas where the field of neurofibromatosis research has made significant strides. Clinical studies of potential therapeutic targets have been conducted using this knowledge in an effort to create novel NF1 therapies (Figure 4).

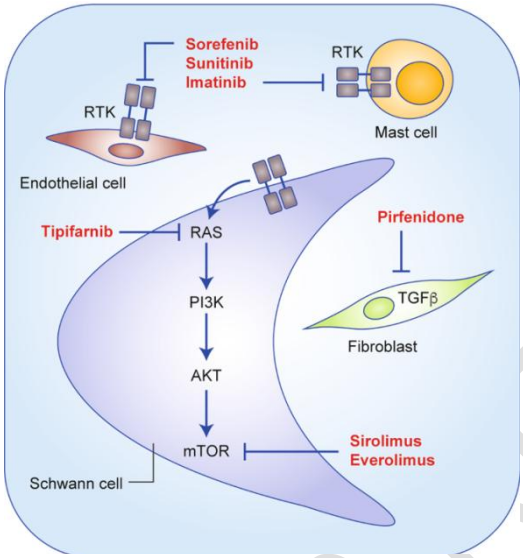

Figure 4. **Overview of the treatments that have been tried in the past for the most prevalent cancers linked to NF1** [19].
The farnesyltransferase inhibitor ipifarnib, RTK inhibitors of the pathway upstream of RAS (imatinib, sunitinib, sorafenib) and mTOR inhibitors (sirolimus, everolimus)

4.1 Targeting Receptor Tyrosine Kinases: Inhibitors Upstream of Ras

The Ras signaling pathway is a key regulator of cell proliferation, differentiation, and survival. Aberrant activation of Ras signaling is implicated in the development and progression of many types of cancer. Ras proteins are activated by receptor tyrosine kinases (RTKs), which are frequently overexpressed or mutated in cancer cells. Therefore, targeting RTKs is a promising therapeutic approach for inhibiting Ras signaling.

RTK inhibitors are a class of drugs that target the extracellular or intracellular domains of RTKs to prevent their activation or downstream signalling. Several RTK inhibitors have been developed and tested in preclinical and clinical studies for the treatment of cancer. Here, we discuss some of the most promising RTK inhibitors that target the upstream of Ras.

One of the most extensively studied RTK inhibitors is erlotinib, which targets the epidermal growth factor receptor (EGFR). Erlotinib has been approved by the US Food and Drug Administration (FDA) for the treatment of non-small cell lung cancer (NSCLC) and pancreatic cancer [20]. In preclinical studies, erlotinib has been shown to inhibit Ras signalling and suppress tumour growth in various types of cancer [21].

Another RTK inhibitor that has shown promising results in preclinical and clinical studies is lapatinib, which targets both EGFR and HER2 (human epidermal growth factor receptor 2) [22-24]. Lapatinib has been approved by the FDA for the treatment of HER2-positive breast cancer [23]. In preclinical studies, lapatinib has been shown to inhibit Ras signalling and induce apoptosis in cancer cells [24].

Sorafenib is another RTK inhibitor that has been approved by the FDA for the treatment of advanced renal cell carcinoma and hepatocellular carcinoma. Sorafenib targets multiple RTKs, including VEGFR (vascular endothelial growth factor receptor) and PDGFR (platelet-derived growth factor receptor), which are frequently overexpressed in cancer cells. Sorafenib has been shown to inhibit Ras signalling and induce apoptosis in cancer cells [25].

In addition to these drugs, several other RTK inhibitors, such as gefitinib, sunitinib, and imatinib, have been approved or are in clinical development for the treatment of cancer [19]. While these drugs have shown efficacy in clinical trials, their efficacy can be limited by the development of resistance or toxicity.

4.2 Targeting the Downstream of Ras: The Promising Role of mTOR Inhibitors in NF1 Therapy

Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic disorder caused by mutations in the NF1 gene. This gene encodes for the protein neurofibromin, which functions as a tumour suppressor and regulates several signalling pathways, including the Ras signalling pathway. Dysregulation of the Ras pathway is a hallmark feature of NF1, and activation of this pathway is believed to contribute to the development of tumours in patients with NF1.

The Ras signalling pathway plays an important role in regulating cell growth and proliferation, and dysregulation of this pathway can lead to the development of various types of cancer. The mammalian target of rapamycin (mTOR) is a key downstream effector of the Ras pathway. The mammalian target of rapamycin (mTOR) is a downstream effector of the Ras pathway that plays a critical role in cell growth and proliferation. Inhibition of the mTOR pathway has emerged as a potential therapeutic strategy for the treatment of NF1-associated tumours. mTOR inhibitors, such as rapamycin and its analogy, have shown promising results in preclinical studies and early-phase clinical trials [26]

Several studies have investigated the use of mTOR inhibitors for the treatment of various types of NF1-associated tumours. For example, studies have shown that the mTOR inhibitor everolimus is effective in reducing the size of plexiform neurofibromas, a type of tumour commonly associated with NF1, in preclinical models and in early-phase clinical trials. Other studies have demonstrated the effectiveness of mTOR inhibitors in treating optic pathway gliomas, which are benign tumours that can cause vision loss in patients with NF1 [27].

mTOR is a serine/threonine kinase that forms two distinct protein complexes, mTORC1 and mTORC2, which are involved in different cellular processes. The mTORC1 complex plays a central role in regulating protein synthesis, cell growth, and autophagy, while the mTORC2 complex is involved in the regulation of cell survival, proliferation, and metabolism. The mTOR pathway is activated by various upstream signalling molecules, including Ras, and is frequently dysregulated in cancer cells.

The mTOR pathway can be targeted by inhibitors such as rapamycin, which inhibits mTORC1 signalling by binding to a cytoplasmic protein called FKBP12 and then binding to and inhibiting mTORC1. Rapamycin and its analogs, collectively known as rapalogs, have been shown to be effective in the treatment of a variety of cancer types, including neurofibromatosis, renal cell carcinoma and breast cancer.

In addition to rapamycin and its analogs, several other mTOR inhibitors have been developed that target different components of the mTOR signalling pathway. For example, the ATP-competitive mTOR inhibitor, Torin1, inhibits both mTORC1 and mTORC2 signalling by directly binding to the ATP-binding site of mTOR. Other mTOR inhibitors include AZD8055 and INK128, which inhibit both mTORC1 and mTORC2 signalling [28].

5. THE PRESENT: EMERGING THERAPEUTIC APPROACHES FOR THE TREATMENT OF NF1

The availability of mice models for NF1 has created previously unheard-of chances to gain crucial insights into the biology of the illness and to establish preclinical models that direct the creation of successful treatments for NF1 (Figure 5).

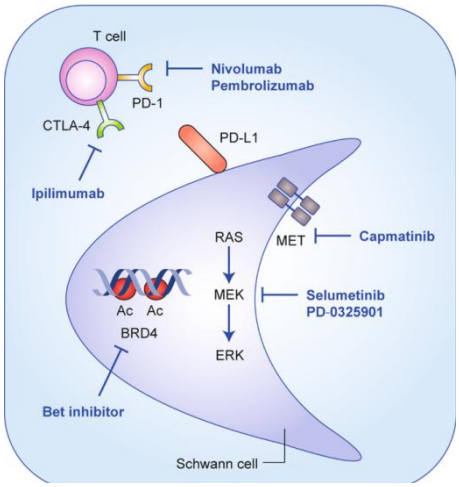

Figure 5. **Overview of the current treatments being researched for the most prevalent cancers linked to NF1, including immune-checkpoint inhibitors (ipilimumab, nivolumab, pembrolizumab), inhibitors of receptor tyrosine kinases (RTKs) upstream of RAS (capmatinib), components of the pathway downstream of RAS (MEK inhibitors), and BET inhibitors [19].**

5.1 The Role of MEK Inhibition in Managing Symptomatic and Progressive Tumours in NF1

Mitogen-activated protein kinase kinase (MEK) inhibitors are a promising therapeutic approach for NF1-related tumours, which are characterized by hyperactivation of the extracellular-signal regulated kinase/mitogen-activated protein kinase (ERK/MAPK) signalling pathway downstream of Ras activation. In a mouse model of NF1, MEK inhibition effectively controlled tumour size. Unlike other therapeutic strategies tested so far, MEK inhibition using selumetinib has yielded unprecedented results in the clinic for peripheral neurofibromas (pNF) [29]. In fact, almost all selumetinib-treated patients showed no tumour progression while being treated with the drug, with 72% showing a partial response and 24% showing stable disease in the SPRINT trial. Based on these promising results, the FDA recently approved selumetinib for children with symptomatic, progressive, and inoperable pNFs. While MEK inhibition has also shown promise in a small cohort of children with optic pathway gliomas (OPG) [30], equivalent strategies in the malignant context of malignant peripheral nerve sheath tumours (MPNST) have so far shown only moderate efficacy in mouse models [31]. However, it has been reported that the RTK MET is activated in some MPNSTs and that a mouse model recapitulating MET activation in MPNST is sensitive to MET inhibition. Therefore, testing a variety of MEK combination therapies, such as dual MET-MEK inhibition, in the context of MPNSTs would be interesting.

6.2 T-Cell Therapy

The discovery of checkpoint strategies that enable cancer to evade the cytotoxic effects of T cells has the potential to revolutionize cancer therapeutics. Despite the clinical success of immune checkpoint inhibitors, T cells have received little attention in the context of NF1. Immune profiling of neurofibromas and MPNSTs has revealed significant variation in the extent of CD8+ T cell infiltration as well as in the expression level of the T-cell inhibitory ligand PD-L1 [32,33], with 50% of gliomas containing a high number of T cells. Although the role of T cells in NF1-related tumorigenesis has not been directly evaluated, they are emerging as essential components of the tumour stroma that support tumour growth [33].

Clinical trials targeting T cells using a combination of antibodies against the receptor for PD-L1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA4) are currently ongoing in a Phase 2 trial for patients with rare tumours, including NF1-related tumours. However, reliable markers predicting the response to immunotherapies remain to be identified in NF1 preclinical models [33, 34].

Immunocompromised (T-cell-deficient) mouse models are commonly used in cancer biology to perform xenograft studies. Interestingly, malignant glioma cells successfully graft in immunocompromised mice whereas benign glioma cells fail to engraft [35]. This failure is due to impaired microglia function, including reduced expression of the chemokine receptor Ccr2 and its ligand Ccl5 in the immunocompromised mice. Mice deficient in Ccl5 phenocopy T-cell-deficiency, as gliomas also fail to engraft in Ccl5 knockout mice. T cell exposure restores Ccr2 and Ccl5 expression in athymic microglia [35].

These observations suggest that T cells support benign glioma growth but impair malignant transformation. It is possible that a similar mechanism occurs in humans, as human MPNST cells can be grown in athymic mice [36] but a xenograft model with human neurofibroma cells has not been reported. Therefore, dampening T-cell function can restrain benign tumour development, while enhancing T-cell function can be used to prevent malignant transformation.

7. THE FUTURE: THE CUTTING-EDGE OF BASIC RESEARCH – UNLEASHING NEW POTENTIALS FOR THERAPEUTIC INTERVENTION

7.1 Gene Therapy

Gene therapy has emerged as a promising strategy for restoring normal function of the NF1 gene. Gene therapy involves the introduction of a functional copy of the gene into the affected cells to restore normal protein expression and function. Several preclinical studies have explored the potential of gene therapy for NF1, with promising results.

One approach to gene therapy for NF1 involves the use of viral vectors to deliver a functional copy of the NF1 gene to the affected cells. Adeno-associated virus (AAV) vectors are commonly used for gene therapy due to their safety profile and ability to integrate into the host genome. In a preclinical study, AAV-mediated delivery of the NF1 gene to Schwann cells in a mouse model of NF1 resulted in a significant reduction in tumour burden and improved survival compared to untreated mice [37]. Another study demonstrated the feasibility of AAV-mediated gene therapy in non-human primates with NF1-related optic gliomas, showing long-term transgene expression and a reduction in tumour size [37, 38].

In addition to AAV vectors, lentiviral vectors have also been explored for NF1 gene therapy. Lentiviral vectors have a larger capacity for gene transfer and are able to integrate into the host genome, allowing for stable and long-term expression of the therapeutic gene. In a preclinical study, lentiviral-mediated delivery of the NF1 gene to Schwann cells in a mouse model of NF1 resulted in a significant reduction in tumour burden and improved survival compared to untreated mice [38, 39].

While gene therapy holds great promise for the treatment of NF1-related tumours, several challenges must be addressed before it can be widely adopted in the clinic. One major challenge is the delivery of the therapeutic gene to the affected cells in a safe and efficient manner. Another challenge is ensuring long-term expression of the therapeutic gene without inducing an immune response. However, advances in vector technology and gene editing techniques have brought us closer to realizing the potential of gene therapy for the treatment of NF1.

7.2 Neuron Therapy

One promising avenue of treatment is nerve cell therapy, which involves the transplantation of healthy nerve cells to replace damaged or dysfunctional cells in the nervous system.

One potential application of nerve cell therapy in NF1 is the treatment of plexiform neurofibromas (PNs), which are benign tumours that can cause significant morbidity in NF1 patients. These tumours are composed of a variety of cell types, including Schwann cells, fibroblasts, and mast cells. Previous studies have suggested that Schwann cells may play a critical role in the growth and maintenance of PNs [40]. Therefore, one approach to nerve cell therapy in NF1 is to transplant healthy Schwann cells to replace damaged or dysfunctional cells within PNs.

In recent years, there has been growing interest in the use of induced pluripotent stem cells (iPSCs) for nerve cell therapy in NF1. iPSCs are generated by reprogramming adult cells, such as skin cells, to a pluripotent state, where they can differentiate into any cell type in the body, including Schwann cells [40, 41]. This approach has several advantages over traditional nerve cell transplantation methods, including the ability to generate an unlimited supply of cells and the avoidance of immune rejection.

Several studies have investigated the potential of iPSC-derived Schwann cells for the treatment of PNs in NF1. In one study, iPSC-derived Schwann cells were transplanted into mice with NF1-associated PNs, resulting in a significant reduction in tumour size and an improvement in nerve function [42]. The transplanted cells were able to integrate into the existing nerve tissue and differentiate into functional Schwann cells. In another study, iPSC-derived Schwann cells were transplanted into rats with sciatic nerve injuries, resulting in significant improvements in nerve function and regeneration [43].

While nerve cell therapy holds promise as a potential treatment for NF1, there are still several challenges that need to be overcome. One major challenge is the development of safe and effective methods for delivering the transplanted cells to the affected areas of the nervous system. Another challenge is the potential for the transplanted cells to undergo malignant transformation and form tumours. Despite these challenges, the potential benefits of nerve cell therapy for the treatment of NF1 make it a promising avenue for future research.

7.3 CRISPR-based Therapeutic Approaches

CRISPR/Cas9 technology is a revolutionary tool in the field of molecular biology that has opened up new possibilities for the treatment of genetic diseases. It is a genome-editing technology that uses a guide RNA to target specific DNA sequences and a Cas9 enzyme to cut and modify the DNA. The potential of CRISPR/Cas9 technology in the treatment of genetic diseases, including NF1, has generated considerable excitement in the scientific community.

CRISPR/Cas9 technology offers the possibility of correcting the genetic mutations that cause NF1 by precisely targeting and repairing the defective genes. In preclinical studies, researchers have used CRISPR/Cas9 technology to correct mutations in the NF1 gene in vitro and in animal models of the disease. For example, a study published in 2018 demonstrated successful correction of the NF1 gene mutation in Schwann cells, the cells that produce the myelin sheath that surrounds and protects nerve fibres [44]. The researchers used CRISPR/Cas9 to insert a functional copy of the NF1 gene into the cells, which resulted in increased levels of neurofibromin protein and improved myelination.

Another study published in 2018 demonstrated the potential of CRISPR/Cas9 to treat pains cause by NF1 [45]. By editing the Nf1 gene using CRISPR/Cas9, CRMP2 has been identified as a potential target for treating pain associated with neurofibromatosis type 1. The researched used of (S)-Lacosamide to reverse this pain.

Despite the promising results of these preclinical studies, there are still significant challenges to overcome before CRISPR/Cas9 technology can be used as a safe and effective therapy for NF1 patients. One of the major concerns is the potential for off-target effects, in which the guide RNA and Cas9 enzyme may inadvertently target and modify unintended genes, leading to unintended consequences. Another concern is the potential for immune responses to the CRISPR/Cas9 components, which could limit the effectiveness and safety of the therapy.

Nonetheless, the potential of CRISPR/Cas9 technology in the treatment of NF1 is significant, and ongoing research is focused on addressing these challenges and developing safe and effective CRISPR/Cas9-based therapies for NF1 and other genetic diseases.

7.4 Exploring the potential of miRNAs and lncRNAs as therapeutic targets

Recent studies have shown that non-coding RNA molecules, particularly microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), may play a crucial role in the development and progression of NF1, and could potentially serve as therapeutic targets for the disease.

MiRNAs are small RNA molecules that regulate gene expression by binding to messenger RNA (mRNA) and preventing their translation into proteins. Several studies have identified dysregulated miRNAs in NF1, including miR-155, miR-10b, and miR-150, among others. These miRNAs have been implicated in various cellular processes, including inflammation, cell proliferation, and differentiation, which are crucial for the development of neurofibromas. For instance, miR-155 has been shown to promote the growth of neurofibromas by regulating the expression of several genes involved in cell proliferation and survival, such as c-Myc and Bcl-2.

In addition to miRNAs, lncRNAs have also emerged as potential therapeutic targets for NF1. LncRNAs are longer RNA molecules that do not code for proteins but play crucial roles in gene regulation and cellular processes. Recent studies have identified several dysregulated lncRNAs in NF1, including HOTAIR, MALAT1, and ANRIL, among others [46]. These lncRNAs have been shown to regulate the expression of genes involved in various cellular processes, such as cell proliferation, apoptosis, and differentiation, which are crucial for the development and progression of neurofibromas.

The dysregulation of miRNAs and lncRNAs in NF1 suggests that these non-coding RNA molecules may play a critical role in the pathogenesis of the disease and could potentially serve as therapeutic targets. Several approaches have been proposed for targeting miRNAs and lncRNAs in NF1, including the use of antisense oligonucleotides, small molecule inhibitors, and gene therapy. For instance, a study demonstrated the therapeutic potential of antisense oligonucleotides targeting miR-10b in a mouse model of NF1 [46,47]. The treatment led to a significant reduction in neurofibroma growth and improved neurological function in the mice.

7.5 Macrophage Therapy

The focus of research in the neurofibroma tumour microenvironment has turned towards pNF-associated macrophages. In fact, macrophages are abundant in neurofibromas and MPNSTs, and their recruitment is stimulated by macrophage colony-stimulating factor (M-CSF). Studies have shown that inhibiting macrophages can slow down pNF progression, making them a potential therapeutic target for neurofibroma and glioma in addition to tumorous glial cells.

In the case of OPG, microglia have been investigated to determine their role in the growth of the tumour. Results indicate that microglia promote the growth of OPG, making stromal cells such as microglia a potential target for treatment strategies [48]. Researchers discovered that the expression of numerous cytokines, chemokines, and their receptors is altered in microglia in the context of OPG, including the chemokine ligand CX3CL1 and Ccl5 [49]. However, the mechanism by which CCL5 promotes tumorigenic activity in the context of OPG remains to be demonstrated.

Although the presence of macrophages is abundant in pNF and MPNSTs in both mice and humans, their absolute role in tumorigenesis in the NF1 context is not yet clear. Inhibiting the receptor for macrophage M-CSF successfully decreased macrophage density and promoted tumour regression in mice, but only once pNFs had been established [50]. It is uncertain which cells and pathways within the tumour contribute to the reduced growth of pNFs in response to treatment, and a better understanding of the downstream effectors of ccl5 is needed. The Cxcl10–Cxcr3 chemokine axis appears to play a critical role in macrophage recruitment for neurofibroma formation, and pegylated IFN-α2b has been shown to slow down neurofibroma growth in some NF1 patients, warranting further investigation [51].

8. CONCLUSION

Neurofibromatosis type 1 (NF1) affects one in every 3,000 individuals worldwide, leading to benign tumour growth on nerves and various complications. Although there is no cure and current treatments are limited, recent breakthroughs in basic research offer hope for new therapeutic approaches.

Historically, surgery and symptom management were primary treatments. However, targeting molecular mechanisms like Ras and mTOR signalling has emerged as a promising strategy. MEK inhibitors, mTOR inhibitors, and immunotherapy have shown encouraging results in preclinical and clinical trials. Combining targeted therapies with personalized precision medicine, tailored to individual genetic alterations, holds potential for improved outcomes.

Further basic research is crucial for understanding NF1 pathogenesis, including the roles of microenvironmental cells like macrophages and microglia. Identifying new therapeutic targets through this research is essential for enhancing patient outcomes. The translation of basic research findings has driven significant progress in NF1 therapy. Ongoing efforts in this direction hold tremendous promise for enhancing the lives of individuals affected by NF1.

REFERENCES

1. Maertens O, Johnson B, Hollstein P, et al. Elucidating distinct roles for NF1 in melanomagenesis. Cancer Discovery. 2013;3(3):338-349. doi:10.1158/2159-8290.
2. Canale DJ, Bebin J. von Recklinghausen disease of the nervous system. In: Vinken PJ, Bruyn GW, eds. Handbook of Clinical Neurology. Vol 14. Holland Publishing Company; 1972:132-162.
3. Broca P. Sur un cas de dégénérescence musculaire progressive avec anomalies de la peau et des os sous-cutanés [A case of progressive muscular degeneration with anomalies of the skin and subcutaneous bones]. Bull Soc Anat Paris. 1886;61:123-126.
4. Pack GT. Heredity in Neuro-Fibromatosis (von Recklinghausen's Disease). Am J Med Sci. 1910;140(3):359-366.
5. Roach ES, Gorsky M. Neurofibromatosis 1: Clinical findings in 111 patients. Neurology. 1987;37(1):121-127.
6. Weinberg JM, Aylsworth AS, Carey JC, et al. The neurofibromatoses: A review of the clinical and genetic aspects of neurofibromatosis 1 and neurofibromatosis 2. J Pediatr. 1987;111(2):181-189.
7. International Human Genome Sequencing Consortium. Initial sequencing and analysis of the human genome. Nature. 2003;409(6822):860-921.
8. Chaivorapol C, Garg S, Gutmann DH. NF1 microdeletions: Clinical and molecular characterization. Am J Med Genet Part A. 2017;173(12):3234-3242.
9. Adil A, Koritala T, Munakomi S. Neurofibromatosis Type 1. In: StatPearls [Internet]. StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459358/
10. Ferner RE, Huson SM, Thomas N, et al. Guidelines for the diagnosis and management of individuals with neurofibromatosis 1. J Med Genet. 2007;44(2):81-88. doi:10.1136/jmg.2006.045906.
11. Gutmann DH, Aylsworth A, Carey JC, et al. The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2. JAMA. 1997;278(1):51-57.
12. Dombi E, Solomon J, Gillespie AJ, et al.,. NF1 plexiform neurofibroma growth rate by volumetric MRI: Relationship to age and body weight. Neurology. 2007;68(9):643-647. doi: 10.1212/01.wnl.0000250332.89420.e6
13. Wolkenstein P, Zeller J, Revuz J, et al. Quality-of-life impairment in neurofibromatosis type 1: A cross-sectional study of 128 cases. Arch Dermatol. 2001;137(11):1421-1425.
14. Ferner RE. Neurofibromatosis 1 and neurofibromatosis 2: A twenty-first century perspective. Lancet Neurol. 2007;6(4):340-351. doi:10.1016/S1474-4422(07)70075-3.
15. Upadhyaya M, Huson SM, Davies M, et al. An absence of cutaneous neurofibromas associated with a 3-bp inframe deletion in exon 17 of the NF1 gene (c.2970-2972 delAAT): Evidence of a clinically significant NF1 genotype-phenotype correlation. Am J Hum Genet. 2007;80(1):140-151. doi:10.1086/510781.
16. Ferner RE, Gutmann DH. International consensus statement on malignant peripheral nerve sheath tumors in neurofibromatosis. Cancer Res. 2002;62(5):1573-1577.
17. Zudek J, Birch P, Riccardi VM, Evans DG, et al. Associations of clinical features in neurofibromatosis 1 (NF1). Genet Epidemiol. 2000;19(4):429-439.doi:10.1002/1098-2272(200012)19:4<429:AID-GEPI1>3.0.CO;2-A.
18. Gerber PA, Antal AS, Neumann NJ, et al. Neurofibromatosis. Eur J Med Res. 2009;14(3):102-105. doi:10.1186/2047-783X-14-3-102.
19. Brosseau JP, Liao CP, Le LQ. Translating current basic research into future therapies for neurofibromatosis type 1. Br J Cancer. 2020;122(2):178-186. doi:10.1038/s41416-020-0903-x
20. Pao W, Miller V, Zakowski M, et al. EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. Proc Natl Acad Sci U S A. 2004;101(36):13306-13311.
21. Yap TA, Vidal L, Adam J, et al. Phase I trial of the irreversible EGFR and HER2 kinase inhibitor BIBW 2992 in patients with advanced solid tumors. J Clin Oncol. 2010;28(25):3965-3972.
22. Ritter CA, Perez-Torres M, Rinehart C, et al. Human breast cancer cells selected for resistance to trastuzumab in vivo overexpress epidermal growth factor receptor and ErbB ligands and remain dependent on the ErbB receptor network. Clin Cancer Res. 2007; 15,13(16):4909-19. doi: 10.1158/1078-0432.CCR-07-0701.
23. Liang W, Guan KL. MAPK and mTOR signaling pathways converge on eIF4B to control its phosphorylation and activity. EMBO J. 2021;40(3):e105142. doi:10.15252/embj.2020105142
24. Al-Lazikani B, Banerji U, Workman P. Combinatorial drug therapy for cancer in the post-genomic era. Nat Biotechnol. 2012;30(7):679-692. doi:10.1038/nbt.2284
25. Nakanishi Y, Akiyama N, Tsukaguchi T, et al. Mechanism of Oncogenic Signal Activation by the Novel Fusion Kinase FGFR3-BAIAP2L1. Mol Cancer Ther. 2015;14(3):704-12. doi: 10.1158/1535-7163.
26. Philpott C, Tovell H, Frayling IM, et al. The NF1 somatic mutational landscape in sporadic human cancers. Hum Genomics. 2017;11(1):13. doi:10.1186/s40246-017-0109-3
27. Weiss B, Widemann BC, Wolters P et al. Sirolimus for progressive neurofibromatosis type 1-associated plexiform neurofibromas: a neurofibromatosis Clinical Trials Consortium phase II study. Neuro Oncol. 2015 Apr;17(4):596-603. doi: 10.1093/neuonc/nou235. Epub 2014 Oct 14. Erratum in: Neuro Oncol. 2015;17(6):905.
28. Mao B, Zhang Q, Ma L, et al. Overview of Research into mTOR Inhibitors. Molecules. 2022;27(16):5295. doi: 10.3390/molecules27165295.
29. Dombi E, Baldwin A, Marcus LJ, et al. Activity of Selumetinib in Neurofibromatosis Type 1-Related Plexiform Neurofibromas. N Engl J Med. 2016, 29;375(26):2550-2560. doi: 10.1056/NEJMoa1605943.

30. Kondyli M, Larouche V, Saint-Martin C, et al. Trametinib for progressive pediatric low-grade gliomas. J Neurooncol. 2018;140:435-444. doi:10.1007/s11060-018-2994-y.
31. Malone CF, Fromm JA, Maertens O, et al. Defining key signaling nodes and therapeutic biomarkers in NF1-mutant cancers. Cancer Discov. 2014;4:1062-1073. doi:10.1158/2159-8290.CD-14-0349.
32. Shurell E, Singh AS, Crompton JG, et al. Characterizing the immune microenvironment of malignant peripheral nerve sheath tumor by PD-L1 expression and presence of CD8+ tumor infiltrating lymphocytes. Oncotarget. 2016;7(39):64300-64308. doi: 10.18632/oncotarget.11734.
33. Fletcher JS, Wu J, Jessen WJ et al. Cxcr3-expressing leukocytes are necessary for neurofibroma formation in mice. JCI Insight. 2019;4(3):e98601. doi: 10.1172/jci.insight.98601.
34. Havel JJ, Chowell D, Chan TA. The evolving landscape of biomarkers for checkpoint inhibitor immunotherapy. Nat Rev Cancer. 2019;19:133-150. doi:10.1038/s41568-019-0116-x.
35. Pan Y, Xiong M, Chen R, et al. Athymic mice reveal a requirement for T-cell-microglia interactions in establishing a microenvironment supportive of Nf1 low-grade glioma growth. Genes Dev. 2018;32:491-496. doi:10.1101/gad.310625.118.
36. Patel AJ, Liao CP, Chen Z, et al. BET bromodomain inhibition triggers apoptosis of NF1-associated malignant peripheral nerve sheath tumors through Bim induction. Cell Rep. 2014;6:81-92. doi:10.1016/j.celrep.2013.11.028.
37. Wu J, Keng VW, Patmore DM, et al. Insertional mutagenesis identifies a STAT3/Arid1b/β-catenin pathway driving neurofibroma initiation. Cell Rep. 2016;14:1979-1990. doi:10.1016/j.celrep.2016.01.074.
38. Kim YS, Shin S, Jung SH, et al. Pathogenic NF1 truncating mutation and copy number alterations in a dedifferentiated liposarcoma with multiple lung metastasis: a case report. BMC Med Genet. 2020;21(1):200. doi: 10.1186/s12881-020-01137-4.
39. Bai RY, Esposito D, Tam AJ, et al. Feasibility of using NF1-GRD and AAV for gene replacement therapy in NF1-associated tumors. Gene Ther. 2019;26(6):277-286. doi: 10.1038/s41434-019-0080-9.
40. Lehmann HC, Höke A. Schwann cells as a therapeutic target for peripheral neuropathies. CNS Neurol Disord Drug Targets. 2010;9(6):801-6. doi: 10.2174/187152710793237412.
41. Aboul-Soud MA, Alzahrani AJ, Mahmoud A. Induced Pluripotent Stem Cells (iPSCs)-Roles in Regenerative Therapies, Disease Modelling and Drug Screening. Cells. 2021;10(9):2319. doi: 10.3390/cells10092319.
42. Patritti Cram J, Wu J, Coover RA, et al. P2RY14 cAMP signaling regulates Schwann cell precursor self-renewal, proliferation, and nerve tumor initiation in a mouse model of neurofibromatosis. Elife. 2022;11:e73511. doi: 10.7554/eLife.73511.
43. Cooney DS, Wimmers EG, Ibrahim Z, et al. Mesenchymal Stem Cells Enhance Nerve Regeneration in a Rat Sciatic Nerve Repair and Hindlimb Transplant Model. Sci Rep. 2016;6:31306. doi: 10.1038/srep31306.
44. Jung M, Pfeifer GP. CRISPR/Cas9 editing of the NF1 gene to characterize the functional significance of missense mutations found in human melanoma. Genes Chromosomes Cancer. 2018;57(5):238-246. doi: 10.1002/gcc.22534.
45. Moutal A, Yang X, Li W, et al. CRISPR/Cas9 editing of Nf1 gene identifies CRMP2 as a therapeutic target in neurofibromatosis type 1-related pain that is reversed by (S)-Lacosamide. Pain. 2017;158(12):2301-2319. doi: 10.1097/j.pain.0000000000001002.
46. Zhang H, Chen Z, Wang X, et al. Long non-coding RNA: a new player in cancer. J Hematol Oncol. 2013;6:37. doi: 10.1186/1756-8722-6-37.
47. Teplyuk NM, Uhlmann EJ, Gabriely G, et al. Therapeutic potential of targeting microRNA-10b in established intracranial glioblastoma: first steps toward the clinic. EMBO Mol Med. 2016;8(3):268-87. doi: 10.15252/emmm.201505495.
48. Daginakatte GC, Gutmann DH. Neurofibromatosis-1 (Nf1) heterozygous brain microglia elaborate paracrine factors that promote Nf1-deficient astrocyte and glioma growth. Hum Mol Genet. 2007;16:1098-1112.
49. Solga AC, Pong WW, Kim KY, et al. RNA sequencing of tumor-associated microglia reveals Ccl5 as a stromal chemokine critical for neurofibromatosis-1 glioma growth. Neoplasia. 2015;17:776-788.
50. Prada CE, Jousma E, Rizvi TA, et al. Neurofibroma-associated macrophages play roles in tumor growth and response to pharmacological inhibition. Acta Neuropathol. 2013;125:159-168.
51. Jakacki RI, Cohen KJ, Buxton A, et al. Phase 2 study of concurrent radiotherapy and temozolomide followed by temozolomide and lomustine in the treatment of children with high-grade glioma: A report of the Children's Oncology Group ACNS0423 study. Neuro Oncol. 2016;18:1442-1450.