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A Call for Discovery and Therapeutic Development for Cutaneous Neurofibromas

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Skin is the calling card of humanity—the body's first line of defense against external threats and a major part of a person's identity. Diseases of the skin are common and a leading cause of nonfatal disease burden in humans (Hay et al., 2014). Effectively addressing skin diseases not only halts or prevents physical illness, it often treats or prevents the common comorbidities of skin disease: depression, anxiety, and suicidal ideation (Hay et al., 2014; Misery et al., 2018). Such mental health diagnoses carry their own substantial disease burden and dramatically impact QOL for both the person and the community affected by chronic skin diseases (Dalgard et al., 2015). Accordingly, an important aspect of effectively treating or preventing skin disease is improving mental health comorbidities and QOL through therapeutic discovery (Kaundinya et al., 2022; Renert-Yuval et al., 2022). Of course, to achieve that critical step, we must first understand disease pathophysiology, develop therapies on the basis of established biologic mechanisms, know the natural history of the disease, and validate meaningful outcome measures for therapeutic interventions. Successful generation of this enormous dataset can result in incredible benefits for people living with skin disease. Indeed, there has been a recent explosion of new drug therapies (including a raft of new biologic agents targeting specific mediators of disease pathobiology) for conditions such as atopic dermatitis, psoriasis, and vitiligo (Arkwright and Koplin, 2023; Chovatiya and Paller, 2021; Malik and Guttman-Yassky, 2018). Such developments give inspiration and direction for another skin condition that has been without therapeutic advance: cutaneous neurofibromas (cNFs).

cNFs are the most common tumor in people with the autosomal dominant neurocutaneous condition, neurofibromatosis type 1 (NF1) (Guiraud et al., 2019). Nearly all adults with NF1 are afflicted with cNFs ranging in number from a handful to several thousand tumors involving the skin of all regions of the body (Cannon et al., 2018; Ehara et al., 2018). cNFs are intermittently painful and itchy and can compromise skin integrity. In all cases, cNFs are disfiguring, negatively impacting mental health and QOL (Guiraud et al., 2019; Maguiness et al., 2021).

NF1 is the most common autosomal dominant neurocutaneous disease (estimated incidence of 1:3,000), and nearly 100% (roughly 2.5 million people worldwide) develop cNFs. Indeed, people living with NF1 report that cNFs are the manifestation that they find most distressing (Guiraud et al., 2019; Maguiness et al., 2021). Yet, historically, there has been a lack of dedicated effort to understand the pathophysiology, relevant preclinical and clinical endpoints, and potential therapies to prevent and treat cNFs. A committed effort to understanding and effectively treating NF1-associated cNFs will benefit not only people with NF1 but all people with dermal lesions that are associated with neuropathic irritation, itch, and disfigurement because the core elements of cNFs (Schwann cells, fibroblasts, mast cells, and macrophages) are shared across many skin conditions. The time is optimal for multidisciplinary investment in unraveling the elemental factors that contribute to cNF formation, their associated symptoms, and the many opportunities to prevent and treat these tumors and their comorbidities.

The articles presented in this "Spotlight on Cutaneous Neurofibroma" reflect the work undertaken by a community of invested stakeholders (patients and caregivers, basic scientists, clinical scientists, dermatologists, neuro-oncologists, and regulatory experts) to explore key questions pertaining to developing effective therapeutics for cNFs in people with NF1. Individuals with expertise in various areas participated

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in the 2022 cNF symposium organized by the Neurofibromatosis Therapeutic Acceleration Program. Four teams focused on addressing core concepts in cNF Pathology and Biology, Therapeutic Targets for cNF Treatment, Preclinical Testing and Assays, and Human Clinical Trials: Therapeutic Strategy and Development. Through a review of published and unpublished data and leveraging the recent therapeutic advances for other NF1-associated tumors such as plexiform neurofibromas (pNFs) and optic pathway gliomas (Fangusaro et al., 2021; Gross et al., 2020) and positive outcomes for other skin conditions such as vitiligo and alopecia areata that were previously without meaningful therapeutic advance (Chovatiya and Paller, 2021; Sheikh et al., 2022), the teams addressed what is known as well as the knowledge gaps needing to be filled to support meaningful therapeutic development for NF1-associated cNFs.

cNF biology and pathophysiology

NF1 results from inactivating pathogenic variants in the *NF1* gene, which is located on chromosome 17q11.2 (Brosseau et al., 2018; Carey et al., 1986; Upadhyaya et al., 1997). The gene product, neurofibromin, is widely expressed in almost all tissues but is most abundant in the central and peripheral nervous systems (Brosseau et al., 2018; Daston and Ratner, 1992; Upadhyaya et al., 1997). NF1 can result from a de novo or familial pathogenic variant and is transmitted in an autosomal dominant inheritance pattern. Roughly 50% of patients with NF1 have a spontaneous pathogenic variant since the *NF1* gene has one of the highest rates of spontaneous variation (Carey et al., 1986).

Absence of functional neurofibromin contributes to the constitutive activation of RAS (Bollag et al., 1996). *RAS* is a commonly mutated oncogene that is implicated in most human cancers. Altered RAS regulation is also associated with a range of conditions affecting multiple organs termed the RASopathies (Matthews et al., 2022). NF1 is one such Rasopathy because variants in the gene *NF1* lead to reduced function of neurofibromin and dysregulation of RAS. This results in highly variable clinical manifestations ranging from the nearly universal cNFs (including the various forms of the most common, discreet cNFs or the rarer diffusely infiltrating dermal neurofibromas [Ortonne et al., 2018]) to the uncommon but potentially fatal sarcomas and gliomas in people with NF1. The contribution of altered regulation of RAS to cNF formation, growth, and maintenance is explored in detail in the article "RAS signaling gone awry in skin: the complex role of RAS in cutaneous neurofibroma pathogenesis, emerging biological insights" (Rhodes et al., 2023). Although the specific RAS isoforms activated in cNF development have yet to be defined, RAS and its down and upstream effectors are leading targets for cNF therapeutic development (Figure 1a). Furthermore, there are compelling developments highlighting the relatively protective role of germline loss of *NF1* against malignancy versus the causative role of somatic *NF1* alterations in common cancers, including melanoma (Brosseau et al., 2018). These observations indicate that there may be a complex balance in RAS regulation between benign and malignant tumors that, once understood, can be therapeutically harnessed (Figure 1a).

Key challenges in the treatment or prevention of cNFs are their multiplicity and variability in clinical and molecular features across people with NF1 and even across tumors in a single individual. There are many factors that contribute to the regulation of cNF multiplicity addressed in the article "Cutaneous Neurofibroma Heterogenetity: Factors that Influence Tumor Burden in Neurofibromatosis Type 1" (Jiang et al.,2023). First, biallelic inactivation of the *NF1* gene in Schwann cells is critical for cNF formation (and indeed, the formation of all peripheral nerve tumors in people with NF1) (Brosseau et al., 2018; Chen et al., 2019; Radomska et al., 2019; Staser et al., 2012). The cell of origin of cNFs is defined as a boundary cap cell (Radomska et al., 2019) or a skin-derived precursor cell (Chen et al., 2019) derived from the embryonic dorsal nerve root and the dorsal root ganglion (DRG) (Figure 1b). These recent discoveries link *NF1* loss and RAS regulation with neural and skin development and homeostasis; both helping to identify new targets and experimental endpoints for cNFs and highlighting the important interaction between skin and the peripheral nervous system (Figure 1b). Work is ongoing to define the spatial and temporal loss of somatic *NF1* and how *NF1* variants influence cNF behavior in skin and pNF in deep nerves.

Another hallmark of cNFs is the infiltration of inflammatory cells. Recent efforts revealed that cNF development in murine models is a multistep process, involving a number of intersecting cellular and inflammatory processes (Chen et al., 2019; Radomska et al., 2019). Mast cells play a key role in the development of pNFs (infiltrating tumors of the peripheral nerve) where they are recruited by the chemoattractant stem cell factor secreted by *NF1* null Schwann cells (Liao et al., 2018; Staser et al., 2012). Early studies indicate that there is also increased mast cell density in cNFs versus in uninvolved skin (with relatively higher density in small cNFs, cNFs removed from people in early adulthood, and symptomatic cNFs), but their role in tumorigenesis is still unclear (Kallionpää et al., 2022). Macrophages are also abundant in cNFs compared to unaffected skin, and there is a proposed relationship between the recruitment and proliferation of macrophages in human cNFs and the expression of YAP and TAZ, core effectors in the Hippo pathway (Jia et al., 2020). Chen et al. (2019) showed that the HOXB7 lineage–derived cells were the source cells for both cNFs and pNFs in a *Hoxb7-Cre;Nf1*$^{f/fl}$ genetically engineered mouse model and that the Hippo pathway is a key modulator of both the (more common) discrete and (rarer) diffuse cNFs. They also showed that Hippo and MAPK pathway dysregulation interact in the setting of *Nf1* loss to support both cNF and pNF development (Chen et al., 2019). Finally, in 36 cNF samples from 10 patients, genetic variation was observed in genes within the Hippo pathway (Faden et al., 2017; Gosline et al., 2017). The specific relationship between *NF1*, Ras, cNF formation, and alterations in the Hippo pathway is yet to be elucidated. This is of particular interest for cNFs because there are several therapeutics (systemic and topical) that are effective for regulation of altered Jak–signal transducer and activator of transcription (STAT) signaling in skin conditions such as atopic dermatitis and psoriasis (Chovatiya and Paller, 2021; Papp et al., 2021). The Jak–STAT pathway interacts with the Hippo pathway and may be a promising area of investigation

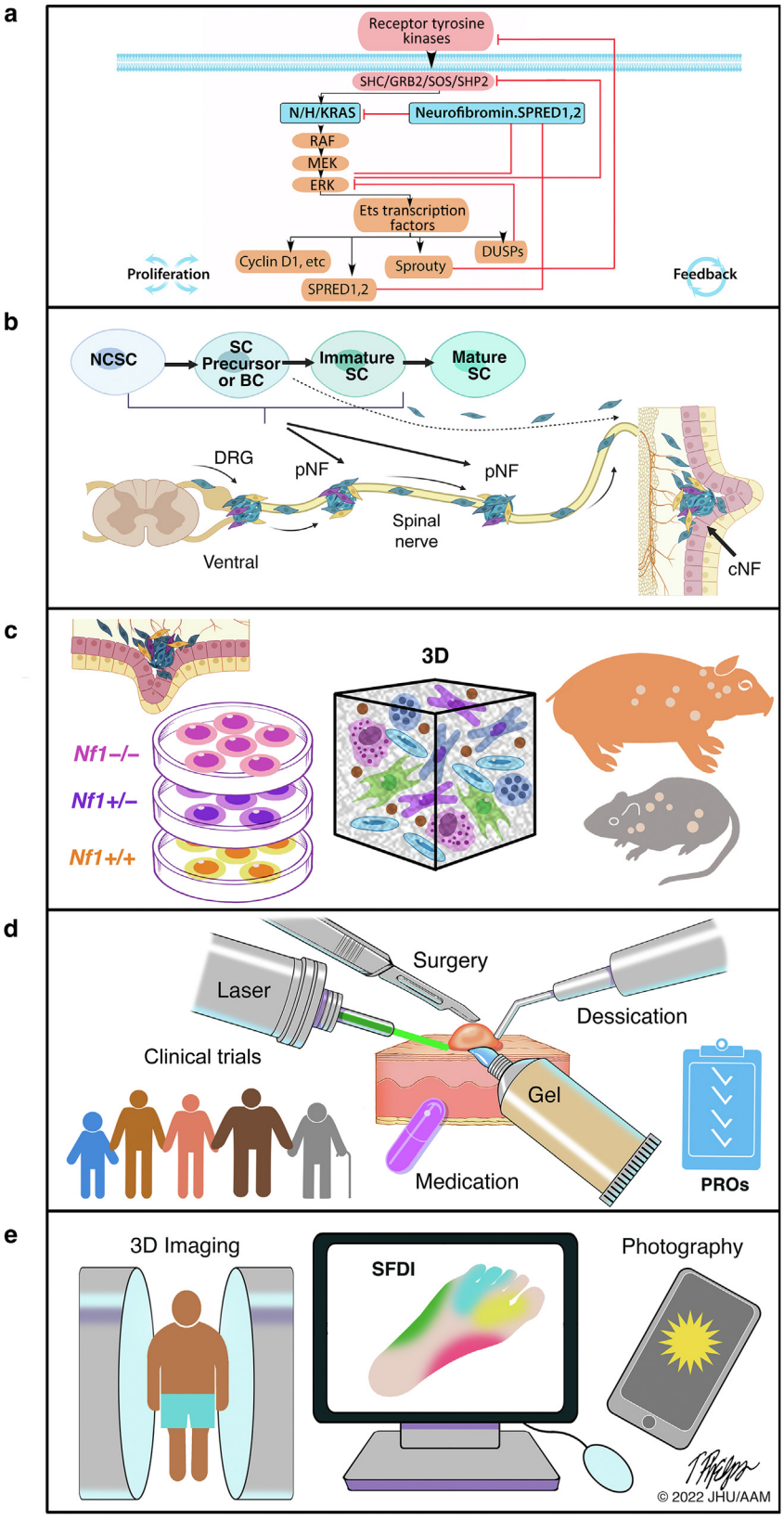

Figure 1. Cellular pathways, cell types, therapeutic approaches, and diagnostic imaging for human cNFs. In this edition, the *Journal of Investigative Dermatology* shines a spotlight on cNFs in the context of neurofibromatosis type 1, the most common neurocutaneous tumor–predisposition syndrome and a field that has seen remarkable scientific progress in the last two decades. With the hope to inform and accelerate research, five articles delve into (**a**) the current state of knowledge of RAS signaling in cNF pathogenesis and therapeutic development for cNF as well as the molecular mechanisms that remain to be elucidated. (**b**) The concept of cNF multiplicity, which is the vast heterogeneity of cNF presentation and evolution, and the growing evidence that a myriad of factors are implicated in cNF development. Understanding the underpinnings of this variability is critical in the development of innovative and targeted

for cNFs (Guo et al., 2021; Rosmarin et al., 2020; Wang et al., 2018).

Finally, there are emerging data about the relationship between neuronal tissue and other cell components in cNFs such as Schwann cells and the cells of the microenvironment. This includes potential contributions of neurturin and artemin signaling between aberrant C-fiber terminals and Schwann cells in the dermis contributing to both the initiation and propagation of early-stage cNFs (Rice et al., 2019). This finding is reminiscent of the critical role of cells derived from the DRG in cNF development in preclinical models of cNF (Chen et al., 2019; Radomska et al., 2019) (Figure 1b). As addressed by Jiang et al. (2023), an improved understanding of the factors that contribute to cNF heterogeneity (cell specific, tissue intrinsic, and systemic) will enable therapeutic development for both prevention and treatment of cNFs.

An important element in a functional pipeline for therapeutic discovery and development for cNFs is the availability of feasible and informative model systems relative to human disease. Fortunately, tremendous progress has been made in the development and validation of preclinical models and their use for therapeutic assessment. These models range from two-dimensional semi-immortalized cell cultures to three-dimensional cocultures, human induced pluripotent stem cells harboring *NF1* gene sequence variations, and multiple in vivo models (fly, mouse, pig) (Figure 1c) (Chen et al., 2019; King et al., 2020; Li et al., 2016; Mazuelas et al., 2020; Mo et al., 2021; Radomska et al., 2019; Stemmer-Rachamimov et al., 2004). The applicability of each of the models to specific questions pertinent to cNF therapeutic development is addressed in the article by Staedtke et al. (2023), "Existing and Developing Preclinical Models for Neurofibromatosis Type 1-related Cutaneous Neurofibromas." One important role of these models is to enable the investigation of the temporal and spatial influence of *Nf1* variants on the behavior of the various cells that make up cNFs. As such, these models enable therapeutic discovery for the condition NF1 (cNFs and other manifestations) as well as skin conditions influenced by the RAS–MAP kinase pathways.

cNF epidemiology

Despite the nearly universal presence of cNFs in people with NF1, the natural history of cNFs is not fully elucidated. It is well-documented that cNFs become apparent later in life than pNFs and increase in number and perhaps size over decades (Cannon et al., 2018; Ehara et al., 2018). Specific patterns have also been observed: cNFs have a greater propensity to develop and grow on the trunk than on the head and neck or extremities, with tumors typically being apparent in late childhood (Ehara et al., 2018). However, some may appear and progress as late as the third or fourth decade of life. The evolution of cNFs over time, across different age groups and sex and in people with different skin types, has not been adequately studied. A prospective natural history study of 22 adults with NF1 and cNFs monitored a region of the back over an 8-year period to quantify cNF size and number (Cannon et al., 2018). The investigators utilized calipers to measure cNFs at baseline and then every 4 months for 2 years and finally, in 14 of 22 participants, at 8 years. The data showed that both the size and the number of cNFs increased slowly over time.

Others groups have attempted to elucidate the natural history of cNFs and identify prognostic features. For example, the role of systemic hormones has been addressed in a series of studies. In in vitro studies, the proliferation of *NF1* nullizygous Schwann cells (but not *NF1* heterozygous cells) was significantly increased by estradiol, testosterone, and human chorionic gonadotropin (Pennanen et al., 2018). However, these findings have not been confirmed in clinical studies, and data in humans are conflicting. In a study of 80 participants with NF1, over 92% of cNFs expressed progesterone receptor and GPER-1, but an association with clinical behavior was not assessed (Rozza-de-Menezes et al., 2021). In a retrospective study, 60% of 105 women with NF1 recalled new cNFs during pregnancy, and 52% recalled enlargement of existing cNFs (Dugoff and Sujansky, 1996). However, a recent study of 13 women examined during pregnancy found no difference in cNF growth between pregnant and nulliparous women, although pregnant women were noted to have an increase in the size of individual cNFs during pregnancy (Well et al., 2020).

Current landscape of treatments for cNFs

The current standard of care for cNFs is either observation (with symptomatic management of pain or itch), surgical resection, or destruction through instrumental dermatology (Chamseddin and Le, 2020; Verma et al., 2018) (Figure 1d). However, both surgery and device-based treatments are limited in efficacy owing to the number of cNFs needing treatment, associated scarring, and the limited access to cNF skin experts for many people with NF1 around the world. Various forms of laser therapies are also used for cNF destruction, but there is an absence of prospective data specific to cNFs and concern about scarring and pigmentary changes when treating large swaths of skin (Kriechbaumer et al., 2014; Verma et al., 2018). In addition, standardized therapeutic guidelines have not been established, and selection of treatment varies widely between providers. A better understanding of the natural history of cNFs as well as a systematic and prospective assessment of outcomes of current treatment options across different cNF subtypes, skin

therapeutics. (**c**) A review of the currently available preclinical models that have allowed progress in our understanding of cNF pathogenesis; this article highlights the uses and limitations of these models as well as future avenues for discovery. (**d**) The current landscape of therapeutic options for cNFs, which includes a review of clinical trials completed thus far and others that are actively accruing participants. In addition, this article explores regulatory considerations specific to cNF therapeutic development and strategies to improve cNF clinical trial design. (**e**) The current techniques available in dermatology to identify and monitor cNFs, with a focus on novel imaging techniques under investigation for better characterization and prospective tracking of cNFs. This article also describes emerging technologies that enable the detection of early cNFs that are not yet clinically apparent to enable prevention and early-intervention strategies. Illustration was provided by Tim Phelps courtesy of 2022 JHU AAM Department of Art as Applied to Medicine The Johns Hopkins University School of Medicine. 3D, three-dimensional; BC, boundary cap; CNF, cutaneous neurofibroma; DRG, dorsal root ganglion; ERK, extracellular signal–regulated kinase; MEK, MAPK/extracellular signal–regulated kinase kinase; NC, neural crest; pNF, plexiform neurofibromas; SC, stem cell.

phototypes, and age groups are required to improve therapeutic discovery and assessment of therapeutic efficacy. The article "Target product profile for cutaneous neurofibromas (cNFs): clinical trials to prevent, arrest, or regress cNFs" (Ly et al., 2023) provides an outline of treatment options ranging from excision and localized treatments to systemic options that are in current clinical use or under investigation (Figure 1d). The authors highlight development opportunities for each of these approaches and provide recommendations for the minimum set of criteria required to advance experimental treatments into efficacy clinical trials. In addition, the paper offers insights into the regulatory considerations for cNF clinical trials such as development and selection of appropriate clinical trial endpoints. This includes further investigation and incorporation of professional, caregiver, and patient perspectives into clinical trial measures.

Evaluation and monitoring of cNFs

The final article in this series, "Current and emerging imaging techniques for Neurofibromatosis Type 1-associated cutaneous neurofibromas" (Li et al., 2023), explores another important aspect in therapeutic development: the need for a consistent set of measurement techniques and endpoints to reliably and objectively document the biologic or clinical benefit of treatment. Through a comprehensive search of the literature and the presentation of early-stage results from ongoing evaluations of new techniques, including optical coherence tomography, spatial frequency domain imaging, and application of hand-held and whole-body stereoscopic optical imaging devices to cNFs, the authors present the available sensitivity, specificity, and applicability of various measures for assessing response to therapy in cNFs.

Published measurement approaches include calipers, digital photography, and high-frequency ultrasound sonography (Figure 1e). These tools enable a more accurate and nuanced understanding of the natural history of cNFs and enable quantification of change with treatment. In addition, they aid in identifying nascent or latent tumors not visible to the eye. Detecting these incipient cNFs opens the possibility for prevention and early therapeutic interventions. However, ongoing optimization of these techniques and evaluation of new modalities is required to accurately identify cNFs at different developmental stages, differentiate them from other skin lesions, establish reliability and reproducibility, and establish the clinically significant change to fuel therapeutic trials.

The convergence of an incredible period of development of effective therapies for a range of common and rare skin diseases, the maturation and expansion of data explaining foundational elements underlying NF1-associated cNF formation, and the existence of tools and resources that enable (even encourage) multidisciplinary collaboration to solve clinical problems that were once deemed unsolvable highlight the opportunity to accelerate meaningful discovery and therapies for NF1-associated cNFs. Now is the ideal time for the specialists in skin, nerve, and therapeutic development to bring forward the next revolution in therapeutics for skin disease, this time for NF1-associated cNFs.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

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Disclaimer

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COMMENTARY

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