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Review

Collaboration in Research for Rare Disease: How Nonprofits can be the Change Makers

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Abstract

The Children's Tumor Foundation (CTF), a nonprofit foundation dedicated to driving research, expanding knowledge, and advancing care for patients living with a rare genetic disorder neurofibromatosis (NF), saw the benefits of piloting a new collaborative initiative that was named "Synodos." Every Synodos project is driven by patients, properly funded, grounded in multidisciplinary global collaboration and data sharing, and managed by the foundation staff. In the current paper, we describe the Synodos networks, share our wins and learnings, and conclude by highlighting the changes that will be made to the next wave of Synodos projects.

Introduction

Problem setting

Historic authorship order and traditional metrics hamper collaboration

Novel innovative treatments for any disease are completely driven by new biological discoveries. The discoveries, generally made by basic academic researchers, are published in peer-reviewed journals (scientific magazines). In the biomedical field, the order of the authors is still of importance. Typically, the most important contributors to the study are the first or last author [1]. Recent studies showed that while the research environment has changed, including the development of some new and better metrics, the evaluation systems to determine the impact of papers, authors and journals has not changed much. Traditional measures based on citations (impact factor, citation numbers) or authorship order are still the base metrics used by the academic publishing world to quantify the researcher's productivity and success [2]. The ever-growing number of scientific publications muddles even more the evaluation of scientific impact, sometimes limiting the scope of research metrics and indicators [3]. Because the research ecosystem is becoming more and more connected and research projects are becoming more collaborative and sometimes multi-disciplinary, the number of authors has also boomed, diluting the efforts of key contributors and instigating unhealthy behaviors to secure incentives and compete for tenure-track positions and access to funding [4,5]. Changes in taxonomies and standardized vocabularies or even revision of the bibliometrics practices may be needed to improve the recognition of the contributors to a research study [6,7].

Lack of incentives to translate discoveries into clinical benefit

To build a career, academic researchers are currently incentivized to build an extensive portfolio of first/ last author publications in top scientific peer-reviewed journals. Researchers with more extensive portfolios increase their access to funding. Therefore, research publications can be considered 'currency' in the academic environment. High-impact journals prefer novel, first-in-class discoveries over reproducibility or translational studies, incentivizing academic researchers to search for new concepts rather than confirmatory studies. In contrast, the translation of these discoveries into potential treatments for patients remains lacking (the typical valley of death).

The power of a movement

Initiatives such as Stand Up to Cancer (SU2C) [8] (https://standuptocancer.org/) and the Cancer Moonshot [9] have ex-

tensively demonstrated that interdisciplinary collaborations are possible and do accelerate patients' access to treatments. What is so different and why would this happen? SU2C and the Cancer moonshot are both movements, driven by patients, and made possible because the funding was provided.

The Synodos Approach

The Synodos initiative sought to support innovation and efficiency in NF research by fostering interdisciplinary collaborations among research partners and patients, and by incorporating elements of the research and development process employed in non-academic industry settings (e.g., deliverables-based payment structure and flexibility in budgeting where needed) into the project infrastructure. Each Synodos team was co-led by both a clinician and a basic scientist, who provided oversight to a team of principal investigators (PIs) and researchers from collaborating institutions. An innovative feature of Synodos is the inclusion of a patient representative on each team, allowing NF patients to have a voice in the research process. All team members were involved in making decisions related to the project implementation. Each team was connected to a project manager from CTF and supported by a steering committee consisting of PIs and CTF staff. The steering committee took responsibility for ensuring that the project kept the interests of patients in mind and for giving input to CTF on scientific matters. Throughout the process, teams had regular check-ins with their CTF project manager. Full teams were encouraged to meet monthly, or at minimum twice per year.

Moreover, data sharing and knowledge dissemination of unpublished data were a contractual obligation within each Synodos team. To support standardized data sharing, CTF partnered with Sage Bionetworks to develop the NF Data Portal [10]. Based on the premise that sharing unpublished data and results would lead to faster translation of research into clinical benefit, the portal was designed to help the research community share datasets, analysis tools, resources, and publications related to neurofibromatosis and Schwannomatosis. By joining the NF Open Science Initiative (NF-OSI) [11], anyone can access and contribute to the portal. All researchers and individuals who wish to use data produced by Synodos project teams may access the research records after an approximately 12-month embargo period. A data manager from Sage Bionetworks provided support in computational biology to each Synodos project team. The data manager worked with the Synodos partners to ensure that data were uploaded and stored according to guidelines and assisted with data curation and analysis.

As part of the governance structure, the Synodos initiative involved an external review board that provided input on the implementation of all Synodos projects. Project teams participated in a formal review process once per year, and any proposed changes to the original project plan were reviewed by the external review board before being ultimately approved by CTF.

The Synodos project teams were supported by leadership and resources from CTF, including regular contact and support from a CTF project manager, oversight from a steering committee including CTF staff, feedback from the external review board, and two in-person convenings. In October 2017, all partners from the Synodos projects and broader collective were invited to convene at the first annual Synodos Network meeting in Palm Beach, Florida. The primary objective of the meeting, which took place over 3 days, was to share ideas and findings among project teams. During the meeting, PIs presented the status of their project to a panel of reviewers and CTF staff and presented emerging results to an audience of peers, reviewers, patient representatives, donors, and board members.

In addition to the network meeting in Florida, an annual review meeting was also held with CTF staff, project leads from each team, and members of the external review board. Together, these participants conducted reviews to ensure that projects were progressing in alignment with their original plans, to revise plans when needed, and to offer technical assistance as necessary.

Outcomes of synodos model

By implementing collaborative interdisciplinary research, increasing the efficiency of the research process in academic environments, and providing support to the funded project teams, CTF intended for several outcomes to be achieved. As a result of Synodos projects, partners from different institutions would be able to collaborate effectively, with high levels of participation and information sharing, yielding a more coherent and intelligent network of NF researchers and practitioners. Including patients' voices would be beneficial for both the researchers and the patient community. Partners would recognize the value of collaboration and, over time, multidisciplinary research teams that incorporate patient input would become typical for the field. Moreover, the benefits of data sharing would become clear, and making data publicly accessible would become the norm for NF researchers.

Utilizing industry tools would accelerate academic progress, by applying a more accurate time and budget allocation process to produce intended results, being the clinical benefit of discoveries, more quickly. Collaborative teams and a vibrant data-sharing community would lead to more innovation, and the time from discovery to clinical benefit would shorten. All of this would improve the lives of patients living with NF.

Description and impact of the first wave of Synodos projects

Since 2014, CTF has funded five Synodos projects which collectively constitute "Wave 1" of the Synodos for NF initiative.

NF2 Synodos

The NF2 Synodos team developed a comprehensive preclinical pipeline that has resulted in the discovery of clinical trial candidates [12]. Moreover, one of the drug candidates, Brigatinib, had a significant effect in both a meningioma [13] and the vestibular schwannoma [14] model. Since the molecular target of Brigatinib (ALK) is not responsible for NF2 -/- tumor growth, extensive proteomic analyses of Brigatinib treated NF2-.- tumors were performed. The studies revealed that the molecular target for Brigatinib in NF2 tumors is FAK [15]. The discoveries made in the Synodos NF2 team resulted in the CTF- Takeda co-funded first-ever NF2 platform/ basket trial, known as INTUITT NF2 (NCT04374305).

Low grade glioma Synodos

The Synodos NF1 Glioma project is the largest and most com-

Table 1. Basic description of the first wave of Synodos NF projects-name, the number of laboratories involved, the overall budget and the duration of the project.

Synodos Project Name	Number of laboratories	Budget ($)	Duration (years)
NF2 preclinical pipeline	12	3,000,000	4
NF1- Glioma	5	2,000,000	3
NF1- Preclinical 1	6	2,000,000	3
NF1- Preclinical 2	4	2,000,000	3
Schwannomatosis-pain	5	1,000,000	2

prehensive analysis to date of the genetic, epigenetic, and immune alterations of gliomas developing in NF1 patients [16,17]. The results from this study provided many previously unknown insights into the biology of these rare tumors. The majority of the pediatric NF1 gliomas, especially those arising in the optic pathway, were pilocytic astrocytomas. Additional non-NF1 mutations, of which FGFR1 mutations were most common, were found only in the pediatric non-pilocytic astrocytomas. High-grade gliomas exhibit frequent mutations of ATRX typically co-occurring with alterations of TP53 and CDKN2A. These analyses identified potential new targets and also new treatment modalities such as immunotherapy for NF1 glioma.

Pig model Synodos

The most important contribution of the two NF1-preclinical Synodoses is the delivery of two genetically modified swine models of NF1 that faithfully recapitulate most aspects of the disease in humans [18,19]. However costly to experiment on, these swine models constitute the closest-to-human animal models of NF1 and are proving valuable tools in both early research and IND-enabling studies.

Importantly, the NF1-preclinical Synodos calls attracted the interest of research groups that previously operated outside of the field of NF, and have since become active contributors to the goal of ending NF, bringing valuable expertise and insights that were missing in the overall NF research hub.

Schwannomatosis

The Synodos Schwannomatosis is the largest initiative to date to establish an extensive molecular analysis of tumors developing in schwannomatosis patients [20] and to understand their association with schwannomatosis-related pain. The study established correlations between specific DNA methylation profiles and tumor location, and identified new chromosomal aberrations that were distinct from sporadic schwannomas. Besides unearthing a wealth of new information about the overall biology of schwannomatosis tumors, the study also pointed in new directions for targeted therapy such as using MEK inhibitors, mTOR agents, and antiangiogenic drugs for managing the tumors and tumor-related pain.

Another success of Synodos can be measured by the amount of follow-on funding that resulted from our initial investment. The NF2 Synodos project has secured the largest amount of funding so far, with some projects still in the process of applying for funding.

Table 2. Follow on funding for each of the project - amount, funding source, number of years follow up funding was or is being provided.

Synodos Project Name	End Year	Follow on funding ($)	Funding source*	Duration of follow on funding (Y)
NF2 preclinical pipeline	2018	$9,244,523	NIH, CDMRP, CTF, pharma	5+
NF1- Glioma	2020	None	None	-
NF1- Preclinical - Iowa	2019	$153,000	CTF	4
NF1- Preclinical - Minn	2020	$3,877,224	NFRI, NIH, GFF	5+
Schwannomatosis- pain	2021	$95,172	CTF	2

NIH: National Institute of Health; CDMRP: Congressionally Directed Medical Research Program; CTF: Children's Tumor Foundation; NFRI: Neurofibromatosis Research Initiative at Boston Children's Hospital; GFF: Gilbert Family Foundation.

The Synodos projects have resulted in an enormous amount of data that is being managed by a dedicated NF community-funded Sage Bionetworks team. The Synodos data can now be queried by the entire research community (https://nf.synapse.org/Explore/Initiatives/DetailsPage?initiative=Synodos) and has led to new research questions.

Evaluation and Key Learnings

In 2020, CTF engaged NPC Research (www.npcresearch.com) to conduct a retrospective study of Wave 1 of Synodos for NF. The primary goal of the evaluation was to gather information from Wave 1 Synodos project partners about the successes and challenges of project implementation, including the feasibility of the collaborative research model. This information will bolster CTF's considerations of possible future Synodos cohorts and will allow CTF to structure any subsequent grants in a way that will maximize success by capitalizing on lessons learned from the first cohort.

Key Learnings

Investigators were motivated to collaborate

Investigators were motivated to apply for a Synodos grant by both the size of the grant and the support for collaboration. Among project leads, 77% reported that the amount of funding was very important to their decision to apply for funding, and 69% reported that the opportunity to collaborate with other NF researchers on a specific project was very important.

Most Synodos projects established healthy collaborations

Overall, project partners described their Synodos teams as healthy collaborations. Across all five projects, most had established sufficient governance structures, workable procedures for administration, appropriate balance of organization and collaboration interests, and solid group norms of trust and reciproci-

ty among partners. However, closer inspection revealed a wide range of individual project scores, indicating that some projects found notable success in these areas while others struggled. Interpersonal dynamics such as norms of trust and reciprocity and the balance between self and shared interests were trickier areas for projects to navigate well. The teams reported that a key component to their success was having a driven, community minded cheerleader, who cared about the team and kept members working together well.

Synodos projects demonstrated a range of successes that were rooted in collaboration

Specific achievements included identifying a drug that moved into clinical trials for NF2, the generation of two first-ever minipig models for NF, performing a first-ever full omics analysis of a set of schwannomatosis tumor samples for study, and generating game-changing findings for low-grade glioma. The Synodos achievements have led to new investigational studies as well as 19 (at time of writing) publications in high-visibility medical journals [12,15–32].

Accomplishments were attributed to the collaborative nature of the projects and the additive power of the multidisciplinary partners. Some projects noted that their main success was the creation of a productive and efficient interdisciplinary team.

Primary challenges pertained to tensions between team success and individual achievement

Academic research environments typically recognize and reward individual achievement.Implementing "team science" in this context created some challenges for projects in ensuring that all investigators would prioritize the team's shared goals above their own individual goals and that all partners felt they would receive sufficient individual credit for accomplishments.

Grant expectations were not always clear initially

At the project start, the majority of partners understood the data-sharing requirement. However, expectations regarding deliverable deadlines and the payment structure were clear for less than half of the partners. Many partners learned these guidelines over the course of the project, often by inadvertent infractions which created some confusion and frustration. Some concern was expressed about a deliverables-based structure being incompatible with academic environments, although 61% of respondents found this structure at least moderately helpful in supporting project implementation. For future Synodos grants, taking time to review the contract with the project leads, in advance of contract execution or work inception, and fully explain the deliverables-based timeline and payment structure may help allay some of this confusion, allow teams to start their Synodos work from a more informed position, and reduce the number of challenges experienced over time. It may also ease the CTF project manager's duties of enforcing the contract requirements and payment schedules.

Synodos partners appreciated the connection with others in the field

Project partners valued the different types of project support offered by CTF. They particularly appreciated the opportunity to convene with other NF researchers and people in the field. Two-thirds found the annual review meetings and the network meeting in Florida very helpful, and they requested additional time for investigators to share findings and ideas with each other.

Collaborative project structure was beneficial, and overall cohesion can be strengthened

Project partners and external review board members agreed that the Synodos model was beneficial for NF research. Forming interdisciplinary research teams and sharing data were important ingredients to accelerate progress in the field. However, results indicated some room for improvement in overall cohesion, within project teams, across projects, and between projects and CTF.

How CTF will apply learnings to the next wave of Synodos projects

Intentionally and explicitly cultivate a culture of collaboration and learning

As the funder and lead of the Synodos for NF initiative, CTF is instrumental in setting this tone. CTF project managers will continue to promote this culture by modeling healthy collaborative engagement and extolling the value of the collective benefit (mutuality). Project leadership and group management training will be offered to the Synodos project leads.

Facilitate agreements among partners regarding credit for project work

During project kickoff meetings, CTF project managers will facilitate discussions about ways in which all project partners can receive credit for project accomplishments. We will clearly state the expectation of Synodos partners to prioritize shared project goals, as well as clarify guidelines around publishing and sharing data.

Set aside specific time to review the contract with project leads

CTF project managers will devote time at the kickoff meeting for reviewing the contract and explaining the grant requirements to ensure that the project leads clearly understand the parameters of the contract.

Continue to provide opportunities for network meetings and cross-project convenings

Partners reported appreciating cross-project and network meetings, particularly if they offer sufficient time for sharing ideas and receiving feedback. CTF will increase the number of Synodos network meetings to stimulate cross-team learnings and collaboration.

Streamline processes for deliverables, payments, and amendments to project plans

Some partners found the steps required for reporting and submitting deliverables cumbersome. Simplifying the processes for submitting deliverables and releasing payments may help to make the process easier to navigate so that partners do not perceive them as a hindrance to progress. CTF is conducting an internal audit to find ways to expedite the review process so that projects do not lose momentum.

Engage projects in contingency planning as part of initial project planning

The foundation will encourage all teams to develop a contin-

gency plan to better prepare the team for navigating unforeseen barriers. Listing specific contingency plans in the initial project plan, and having them approved by the reviewers, may also alleviate the number of separate reviews necessary for later amendments.

Conclusion

The Children's Tumor Foundation and the Children's Tumor Foundation Europe constitute a nonprofit research foundation aimed at funding research, accelerating the path from discovery to clinical benefit and building communities for neurofibromatosis.

With Synodos for NF, CTF has taken bold steps into new territory to make its mission of ending NF a reality. CTF is essentially seeking to build a new field of NF research, one in which interdisciplinary collaboration, data sharing, and patient inclusion are the norm.

Overall, the Wave 1 Synodos projects demonstrated a range of successes. These included specific achievements, such as identifying a drug that is moving into clinical trials, gaining access to rare samples for study, and publishing results in a high-visibility outlet to inform the field. All of these accomplishments were rooted in the collaborative nature of the project and the additive power of the multidisciplinary partners. Some projects noted that their main success was the creation of a productive and efficient interdisciplinary team, highlighting partners' recognition of the strength of the team-science approach. Field building is hard work. However, when successful, it can be utterly transformative.

References

1. Riesenberg D, Lundberg GD. The order of authorship: who's on first? JAMA. 1990 Oct 10;264(14):1857.
2. Fire M, Guestrin C. Over-optimization of academic publishing metrics: observing Goodhart's Law in action. GigaScience. 2019 Jun 1;8(6):giz053.
3. Wilsdon J. The Metric Tide: Independent Review of the Role of Metrics in Research Assessment and Management [Internet]. 1 Oliver's Yard, 55 City Road London EC1Y 1SP: SAGE Publications Ltd; 2015 [cited 2022 Feb 17]. Available from: http://sk.sagepub.com/books/the-metric-tide/
4. Cyranoski D, Gilbert N, Ledford H, et al. Education: The PhD factory. Nature. 2011 Apr;472(7343):276–9.
5. Schofferman J, Wetzel FT, Bono C. Ghost and Guest Authors: You Can't Always Trust Who You Read. Pain Med. 2015 Mar;16(3):416–20.
6. Das N, Das S. 'Author Contribution Details' and not 'Authorship Sequence' as a merit to determine credit: A need to relook at the current Indian practice. Natl Med J India. 2020;33(1):24.
7. Helgesson G. Authorship order and effects of changing bibliometrics practices. Res Ethics. 2020 Jan;16(1–2):1–7.
8. Burki TK. Stand Up To Cancer. Lancet Oncol. 2012 Dec;13(12):1197–8.
9. Agus DB, Jaffee EM, Van Dang C. Cancer Moonshot 2.0. Lancet Oncol. 2021 Feb;22(2):164–5.
10. Allaway RJ, La Rosa S, Verma S, et al. Engaging a community to enable disease-centric data sharing with the NF Data Portal. Sci Data. 2019 Dec;6(1):319.
11. https://sagebionetworks.org/research-projects/nf-open-science-initiative/ [Internet]. Available from: https://sagebionetworks.org/research-projects/nf-open-science-initiative/
12. The Synodos for NF2 Consortium, Allaway R, Angus SP, et al. Traditional and systems biology based drug discovery for the rare tumor syndrome neurofibromatosis type 2. Lebedeva IV, editor. PLOS ONE. 2018 Jun 13;13(6):e0197350.
13. Burns SS, Akhmametyeva EM, Oblinger JL, et al. Histone Deacetylase Inhibitor AR-42 Differentially Affects Cell-cycle Transit in Meningeal and Meningioma Cells, Potently Inhibiting NF2 -Deficient Meningioma Growth. Cancer Res. 2013 Jan 15;73(2):792–803.
14. Gehlhausen JR, Park S-J, Hickox AE, et al. A murine model of neurofibromatosis type 2 that accurately phenocopies human schwannoma formation. Hum Mol Genet. 2015 Jan 1;24(1):1–8.
15. Chang L-S, Oblinger JL, Smith AE, et al. Brigatinib causes tumor shrinkage in both NF2-deficient meningioma and schwannoma through inhibition of multiple tyrosine kinases but not ALK. Dasgupta P, editor. PLOS ONE. 2021 Jul 15;16(7):e0252048.
16. D'Angelo F, Ceccarelli M, Tala, et al. The molecular landscape of glioma in patients with Neurofibromatosis 1. Nat Med. 2019 Jan;25(1):176–87.
17. Fisher MJ, Jones DTW, Li Y, et al. Integrated molecular and clinical analysis of low-grade gliomas in children with neurofibromatosis type 1 (NF1). Acta Neuropathol (Berl). 2021 Apr;141(4):605–17.
18. Isakson SH, Rizzardi AE, Coutts AW, et al. Genetically engineered minipigs model the major clinical features of human neurofibromatosis type 1. Commun Biol. 2018 Dec;1(1):158.
19. White KA, Swier VJ, Cain JT, et al. A porcine model of neurofibromatosis type 1 that mimics the human disease. JCI Insight. 2018 Jun 21;3(12):e120402.
20. Mansouri S, Suppiah S, Mamatjan Y, et al. Epigenomic, genomic, and transcriptomic landscape of schwannomatosis. Acta Neuropathol (Berl). 2021 Jan;141(1):101–16.
21. Meyerholz DK, Ofori-Amanfo GK, Leidinger MR, et al. Immunohistochemical Markers for Prospective Studies in Neurofibromatosis-1 Porcine Models. J Histochem Cytochem. 2017 Oct;65(10):607–18.
22. Moutal A, Dustrude ET, Khanna R. Sensitization of Ion Channels Contributes to Central and Peripheral Dysfunction in Neurofibromatosis Type 1. Mol Neurobiol. 2017 Jul;54(5):3342–9.
23. Moutal A, Sun L, Yang X, et al. CRMP2–Neurofibromin Interface Drives NF1-related Pain. Neuroscience. 2018 Jun;381:79–90.
24. Moutal A, Luo S, Largent-Milnes TM, et al. Cdk5-mediated CRMP2 phosphorylation is necessary and sufficient for peripheral neuropathic pain. Neurobiol Pain. 2019 Jan;5:100022.
25. Moutal A, White KA, Chefdeville A, et al. Dysregulation of CRMP2 Post-Translational Modifications Drive Its Pathological Functions. Mol Neurobiol. 2019 Oct;56(10):6736–55.
26. Khanna R, Moutal A, White KA, et al. Sex-dependent differences in pain and sleep in a porcine model of Neurofibromatosis type 1 [Internet]. Neuroscience; 2018 Dec [cited 2022 Feb 17]. Available from: http://biorxiv.org/lookup/doi/10.1101/495358
27. Ramkissoon A, Chaney KE, Milewski D, et al. Targeted Inhibition of the Dual Specificity Phosphatases DUSP1 and DUSP6 Suppress MPNST Growth via JNK. Clin Cancer Res. 2019 Jul 1;25(13):4117–27.

28. Kohlmeyer JL, Kaemmer CA, Pulliam C, et al. RABL6A Is an Essential Driver of MPNSTs that Negatively Regulates the RB1 Pathway and Sensitizes Tumor Cells to CDK4/6 Inhibitors. Clin Cancer Res. 2020 Jun 15;26(12):2997–3011.
29. Sagers JE, Beauchamp RL, Zhang Y, et al. Combination therapy with mTOR kinase inhibitor and dasatinib as a novel therapeutic strategy for vestibular schwannoma. Sci Rep. 2020 Dec;10(1):4211.
30. Swier VJ, White KA, Meyerholz DK, et al. Validating indicators of CNS disorders in a swine model of neurological disease. Wang W, editor. PLOS ONE. 2020 Feb 19;15(2):e0228222.
31. Uthoff J, Larson J, Sato TS, t al. Longitudinal phenotype development in a minipig model of neurofibromatosis type 1. Sci Rep. 2020 Dec;10(1):5046.
32. Osum SH, Watson AL, Largaespada DA. Spontaneous and Engineered Large Animal Models of Neurofibromatosis Type 1. Int J Mol Sci. 2021 Feb 16;22(4):1954.

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