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TITLE: Screening Trial for Pain Relief in Schwannomatosis (STARFISH)

PRINCIPAL INVESTIGATOR: Scott Plotkin, MD, PhD

CONTRACTING ORGANIZATION: Massachusetts General Hospital

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1. REPORT DATE	**2. REPORT TYPE**	**3. DATES COVERED**
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4. TITLE AND SUBTITLE

Screening Trial for Pain Relief in Schwannomatosis (STARFISH)

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6. AUTHOR(S)

Scott Plotkin, MD, PhD

E-Mail:

5d. PROJECT NUMBER

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Massachusetts General Hospital

8. PERFORMING ORGANIZATION REPORT NUMBER

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12. DISTRIBUTION / AVAILABILITY STATEMENT

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13. SUPPLEMENTARY NOTES

14. ABSTRACT:

Schwannomatosis (SWN) is a rare tumor suppressor syndrome (estimated prevalence of 1/126,315) characterized by the predisposition to develop non-intradermal schwannomas. Chronic pain is the most common symptom of SWN and usually persists despite aggressive surgical and medical management. The etiology of pain in SWN is not clear, and the development of novel treatments for SWN and related pain has been extremely slow and inefficient. To date, virtually no agents have passed through the development pathway to enter clinical trials for SWN patients. Recognizing that one of the biggest challenges in basic and translational SWN research is the lack of clinically-relevant models, we successfully established five patient-derived SWN cell lines and an orthotopic patient-derived xenograft (PDX) tumor mouse model. In SWN patient samples and in PDX tumors, we found evidence of elevated neuroinflammatory signaling – SWN tumor cells prime macrophages to produce inflammatory cytokines. These inflammatory cytokines, including interleukin-6 (IL-6), induce calcitonin gene-related peptide (CGRP) in dorsal root ganglia sensory neurons, therebycontributing to the development of pain. Our proposed study will leverage these exciting findings and utilize state-of-the-art molecular and genetic approaches and our clinically relevant SWN models to improve treatment of SWN. Hypothesis: We hypothesize that erenumab-aooe, an anti-CGRP receptor monoclonal antibody, will be

15. SUBJECT TERMS

NONE LISTED

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			USAMRDC
U	U	U	UU	**15**	**19b. TELEPHONE NUMBER** *(include area code)*

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1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

STARFISH is a placebo-controlled, multi-arm phase 2 platform screening trial designed to test the safety, pain responses, and pharmacodynamic activity of multiple experimental therapies simultaneously in patients with schwannomatosis (SWN) and moderate-to-severe pain. Up to 20 subjects with SWN and moderate-to-severe pain will be enrolled and randomized to each of several experimental treatment arms. Periodic assessments of pain intensity will be assessed by subject self -report. Clinical will be assessed by measuring changes in quality of life (QOL).

2. **KEYWORDS:** *Provide a brief list of keywords (limit to 20 words).*

Schwannomatosis; chronic pain; interleukin-6; calcitonin gene-related peptide; CGRP;

3. **ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

What were the major goals of the project?
List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

The Specific Aims of this study include:

Aim 1: To determine the analgesic effect of erenumab-aooe, an inhibitor of the CGRP receptor, in SWN patients with moderate-to-severe pain and to determine if the drug is worthy of further study.

Aim 2. To determine the safety and tolerability of erenumab-aooe in SWN patients with moderate-to-severe pain.

Aim 3: To identify circulating and imaging biomarkers that correlate with pain response to erenumab-aooe.

What was accomplished under these goals?
For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

1) Major activities: The major activities accomplished during this report period include progress in approval of regulatory protocols. The STARFISH protocol describes a platform clinical trial including a master study and two drug substudies (for siltuximab and erenumab). In addition, the erenumab sub-study is a decentralized clinical trial with a goal of increasing enrollment for a rare disease. For this reason, the STARFISH protocol is extremely complex and has required more regulatory work than a typical clinical trial with a single drug. To date, the protocol for the platform trial (master protocol, siltuximab sub-study, and erenumab sub-study) has been developed, submitted/approved by the Scientific Review Committee, and approved by the local Institutional Review Board on 12/21/2022. The Food and Drug Administration provided a Study May Proceed letter for IND152079 on 8/31/2020. HRPO provided initial approval for the study on 5/25/2023. Currently, the protocol is undergoing activation at Mass General Hospital. This process is expected to be complete in July, 2023, after which time enrollment of subjects can begin.
2) Specific objectives: To date, no scientific objectives have been accomplished.
3) Significant results/key outcomes: As noted above, the significant results to date include approval of the protocol by the local Institutional Review Board, FDA, and HRPO.
4) Other achievements: None

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

To date, this project has not provided any opportunities for training or professional development.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these

project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

No results have been generated and thus, none have been disseminated to communities of interest.

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

During the next reporting period, we hope to complete activation of the protocol at Mass General Hospital and to begin enrollment into the clinical trial.

4. **IMPACT:** D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Nothing to report.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to report

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to report.

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to report.

5. **CHANGES/PROBLEMS:** *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are*

significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them

Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

To date, no unexpected problems have been encountered. However, progress in approval of the STARFISH protocol has been slower than expected due to the complexity of approving a platform trial that includes a decentralized clinical trial. Currently, we are running about 6 months behind our projected time line. However, we hope to have the protocol fully activated in the next reporting period and will focus on accrual into the clinical trial.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

Nothing to report.

Significant changes in use of biohazards and/or select agents

Nothing to report.

6. PRODUCTS: *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to reprot

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report.

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Nothing to report.

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to report.

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

Nothing to report.

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to report.

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:
  - *data or databases;*
  - *physical collections;*
  - *audio or video products;*
  - *software;*
  - *models;*
  - *educational aids or curricula;*
  - *instruments or equipment;*
  - *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
  - *clinical interventions;*
  - *new business creation; and*

- *other.*

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

Example:

Name: *Mary Smith*
Project Role: *Graduate Student*
Researcher Identifier (e.g. ORCID ID): *1234567*
Nearest person month worked: *5*

Contribution to Project: *Ms. Smith has performed work in the area of combined error-control and constrained coding.*
Funding Support: *The Ford Foundation (Complete only if the funding support is provided from other than this award.)*

Name: Scott Plotkin
Project Role: Principle Investigator
Researcher Identifier (e.g. ORCID ID): 0000-0002-6109-6419
Nearest person month worked: 1.8
Contribution to Project: Dr. Plotkin has written and edited the STARFISH protocol and guided submission of the protocol to the institutional review board, FDA, and HRPO.

Name: Lei Xu
Project Role: Co-PI
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 1.2
Contribution to Project: Dr. Xu has edited the STARFISH protocol for submission to the IRB, FDA, and HRPO.

Name: Alona Muzikansky
Project Role: Statistician
Researcher Identifier (e.g. ORCID ID): 0000-0001-7585-8181
Nearest person month worked: 0.6
Contribution to Project: Ms. Muzikansky has provided statistical support during the development of the protocol.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Project title and project #: NF Variant Curation Expert Panel (VCEP)
Percent effort (time commitment): 0.26 CM
Funding agency: Hospital Universitari Germans Trias i Pujol (originating sponsor: Children's Tumor Foundation)
Period of performance: 12/31/21-12/31/23
Level of funding: $12,000
Brief description of project goals: To create an infrastructure for the NF community to create a variant curation expert panel (VCEP).
Specific aims: The specific aims of this project include to create the NF variant curation expert panel (VCEP) approved by ClinGen, to develop and validate the variant classification rules following ACMG/AMP scheme for the five NF genes (NF1, NF2, SMARCB1, LZTR1, and SPRED1), and to create an internal database with all variants detected in the different laboratories to prepare them to be uploaded to ClinVar/LOVD or a specific NF database in the following years.
Areas of potential overlap: None

Project title and project #: Implementing an Online Platform to Promote Evidence-Based Care for Children and Adults with Neurofibromatosis 1 / TBD
Percent effort (time commitment): 0.36 CM
Funding agency: Department of Defense-Congressionally Directed Medical Research Programs
Period of performance: 06/1/23-05/30/26
Level of funding: $603,000
Brief description of project goals: The goal of this study is to tailor materials for and pilot the implementation of an online platform to disseminate NF1 clinical care guidelines to children and adults with NF1 and their primary care providers.
Specific aims:

- Aim 1. To characterize gaps in NF1 care during annual primary care visits for people with NF1 who do not attend specialty clinics through qualitative interviews (n=50) with adults with NF1, parents of children with NF1, and PCPs caring for people with NF1
- Aim 2. To create the initial NF Guidelines to You platform via participatory co-design methods with advisory board members (including NF1 patients, parents, PCPs, and medical/scientific experts) and determine the platform's usability in an open pilot study (n=10 adults/parents)

Aim 3. To determine the feasibility, acceptability, and preliminary effectiveness of the final NF Guidelines to You platform for adults with NF1 (n=50) and parents of children with NF1 (n=50) across the U.S. in a feasibility study randomizing participants to immediate access to the platform or a waitlist control group

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*

Organization: EUSA Pharma/Recordati
Location: Italy
Partner's contribution to the project:

- In-kind support including siltuximab for drug sub-study A

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to* ***https://ebrap.org/eBRAP/public/index.htm*** *for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on https://www.usamraa.army.mil/Pages/Resources.aspx) should be updated and submitted with attachments.*

9. APPENDICES: *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.*

No appendices.