Combinatorial Therapies for Neurofibroma and MPNST Treatment and Prevention

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12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

14. ABSTRACT
We hypothesize that tamoxifen, trifluoperazine or combined tamoxifen-trifluoperazine therapy will effectively treat established neurofibromas and MPNSTs and prolong survival. We also hypothesize that prophylactic treatment with these drugs will prevent neurofibroma and MPNST pathogenesis. To test these hypotheses, we will: 1) determine whether tamoxifen, trifluoperazine or tamoxifen-trifluoperazine therapy effectively inhibits tumor cell proliferation and survival in established neurofibromas and MPNSTs and prolongs the survival of mice with these tumors and 2) determine whether prophylactic therapy with tamoxifen and/or trifluoperazine will prevent the pathogenesis of neurofibromas and MPNSTs. These preclinical trials will be performed using robust mouse models of neurofibroma (Krox20-Cre;Nf1floxflox/mice) and MPNST (P0-GGFβ3;Trp53+/-mice) pathogenesis. In Aim 1, mice with established neurofibromas and MPNSTs will be challenged with vehicle, tamoxifen, trifluoperazine or combined tamoxifen-trifluoperazine therapy and we will establish which of these treatments maximally inhibits tumor cell proliferation and survival and improves long term survival. In Aim 2, we will begin treatment of Krox20-Cre;Nf1floxflox/- and P0-GGFβ3;Trp53+/- mice with vehicle, tamoxifen, trifluoperazine or tamoxifen-trifluoperazine prior to the development of tumors and continue this treatment to 15 months of age. We will then determine if these prophylactic therapies prevent neurofibroma and MPNST pathogenesis or reduce the number and size of tumors in our mice.

15. SUBJECT TERMS
Nothing listed
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INTRODUCTION
We hypothesize that tamoxifen, trifluoperazine or combined tamoxifen-trifluoperazine therapy will effectively treat established neurofibromas and MPNSTs and prolong survival. We also hypothesize that prophylactic treatment with these drugs will prevent neurofibroma and MPNST pathogenesis. To test these hypotheses, we will: 1) determine whether tamoxifen, trifluoperazine or tamoxifen-trifluoperazine therapy effectively inhibits tumor cell proliferation and survival in established neurofibromas and MPNSTs and prolongs the survival of mice with these tumors and 2) determine whether prophylactic therapy with tamoxifen and/or trifluoperazine will prevent the pathogenesis of neurofibromas and MPNSTs. These preclinical trials will be performed using robust mouse models of neurofibroma (Krox20-Cre;Nf1^flox/- mice) and MPNST (P0-GGFβ3;Trp53^+/+ mice) pathogenesis. In Aim 1, mice with established neurofibromas and MPNSTs will be challenged with vehicle, tamoxifen, trifluoperazine or combined tamoxifen-trifluoperazine therapy and we will establish which of these treatments maximally inhibits tumor cell proliferation and survival and improves long term survival. In Aim 2, we will begin treatment of Krox20-Cre;Nf1^flox/- and P0-GGFβ3;Trp53^+/+ mice with vehicle, tamoxifen, trifluoperazine or tamoxifen-trifluoperazine prior to the development of tumors and continue this treatment to 15 months of age. We will then determine if these prophylactic therapies prevent neurofibroma and MPNST pathogenesis or reduce the number and size of tumors in our mice.

KEYWORDS: NF1; neurofibroma; malignant peripheral nerve sheath tumor; calmodulin inhibitor; estrogen receptor inhibitor; therapeutic targets.

ACCOMPLISHMENTS:
Our progress is on track with our original approved Statement of Work. Below, I will first indicate the two Specific Aims of our project and the tasks within each Aim. I will then break out the tasks that were planned for the current funding period and describe the progress we have made in each of these tasks.

Specific Aims and Studies in Approved Statement of Work

Specific Aim 1: Test the hypothesis that tamoxifen, trifluoperazine or tamoxifen-trifluoperazine therapy effectively inhibits tumor cell proliferation and survival in established neurofibromas and MPNSTs and prolongs the survival of mice with these tumors.

Specific Aim 2: Test the hypothesis that prophylactic therapy with tamoxifen and/or trifluoperazine will prevent the pathogenesis of neurofibromas and MPNSTs.

Task 1. To determine whether tamoxifen, trifluoperazine or combined tamoxifen/trifluoperazine therapy inhibits tumor cell proliferation and survival in MPNST bearing P0-GGFβ3;Trp53^+/+ mice (months 1-36):
   a. Obtain regulatory review and approval for these studies (months 1-2)
   b. Perform studies with tamoxifen and trifluoperazine to establish maximum tolerated doses of these agents in C57BL/6 mice (months 2-4)
   c. Establish cohorts of P0-GGFβ3;Trp53^+/+ mice, identify MPNST bearing mice with PET scans and randomize mice into cohorts for treatment with vehicle, tamoxifen, trifluoperazine or tamoxifen and trifluoperazine (months 3-18)
   d. Evaluate the effectiveness of the therapeutic regimens described in c (months 12-18)
   e. Perform diagnostic, histochemical and immunohistochemical analyses of proliferation and cell death in tumor cohorts (months 18-36)
Task 2. To determine whether tamoxifen, trifluoperazine or combined tamoxifen/trifluoperazine therapy inhibits tumor cell proliferation and survival in neurofibroma bearing Krox20-Cre;Nf1flox−/− mice (months 1-36):
   a. Obtain regulatory review and approval for these studies (months 1-2)
   b. Establish cohorts of Krox20-Cre;Nf1flox−/− mice, identify neurofibroma bearing mice with MRI scans and randomize mice into cohorts for treatment with vehicle, tamoxifen, trifluoperazine or tamoxifen and trifluoperazine (months 3-18)
   c. Evaluate the effectiveness of the therapeutic regimens described in c (months 12-18)
   d. Perform diagnostic, histochemical and immunohistochemical analyses of proliferation and cell death in tumor cohorts (months 18-36)

Task 3. To determine whether tamoxifen, trifluoperazine or combined tamoxifen/trifluoperazine therapy extends the survival of MPNST bearing P0-GGFβ3;Trp53+/− mice (months 1-36):
   a. Obtain regulatory review and approval for these studies (months 1-2)
   b. Establish cohorts of P0-GGFβ3;Trp53+/− mice, identify MPNST bearing mice with PET scans and randomize mice into cohorts for treatment with vehicle, tamoxifen, trifluoperazine or tamoxifen and trifluoperazine (months 3-18)
   c. Evaluate the effectiveness of the therapeutic regimens described in c (months 12-18)
   d. Perform diagnostic, histochemical and immunohistochemical analyses of proliferation and cell death in tumor cohorts (months 18-36)

Task 4. To determine whether tamoxifen, trifluoperazine or combined tamoxifen/trifluoperazine therapy inhibits tumor cell proliferation and survival in neurofibroma bearing Krox20-Cre;Nf1flox−/− mice (months 1-36):
   a. Obtain regulatory review and approval for these studies (months 1-2)
   b. Establish cohorts of Krox20-Cre;Nf1flox−/− mice, identify neurofibroma bearing mice with MRI scans and randomize mice into cohorts for treatment with vehicle, tamoxifen, trifluoperazine or tamoxifen and trifluoperazine (months 3-18)
   c. Evaluate the effectiveness of the therapeutic regimens described in b (months 12-18)
   d. Perform diagnostic, histochemical and immunohistochemical analyses of proliferation and cell death in tumors (months 18-36)

Task 5. To determine whether prophylactic therapy with tamoxifen, trifluoperazine or combined tamoxifen/trifluoperazine therapy prevents neurofibroma and MPNST pathogenesis in Krox20-Cre;Nf1flox−/− and P0-GGFβ3;Trp53+/− mice, respectively (months 18-36):
   a. Obtain regulatory review and approval for these studies (months 1-2)
   b. Establish cohorts of Krox20-Cre;Nf1flox−/− and P0-GGFβ3;Trp53+/− mice (months 18-22)
   c. Treat cohorts with vehicle, tamoxifen, trifluoperazine or tamoxifen and trifluoperazine (months 22-36)
   d. Evaluate the effectiveness of the therapeutic regimens described in b (months 22-36)
   e. Perform diagnostic, histochemical and immunohistochemical analyses of proliferation and cell death in tumors, if tumors are present (months 30-36)

All five of the Tasks delineated above shared a common initial subtask, which was:

Task 1. To determine whether tamoxifen, trifluoperazine or combined tamoxifen/trifluoperazine therapy inhibits tumor cell proliferation and survival in MPNST bearing P0-GGFβ3;Trp53+/− mice (months 1-36):
   a. Obtain regulatory review and approval for these studies (months 1-2; completed)
Task 2. To determine whether tamoxifen, trifluoperazine or combined tamoxifen/trifluoperazine therapy inhibits tumor cell proliferation and survival in neurofibroma bearing Krox20-Cre;Nf1^{lox/-} mice (months 1-36):
   a. Obtain regulatory review and approval for these studies (months 1-2; completed)

Task 3. To determine whether tamoxifen, trifluoperazine or combined tamoxifen/trifluoperazine therapy extends the survival of MPNST bearing P_0-GGFβ3;Trp53^{+/+} mice (months 1-36):
   a. Obtain regulatory review and approval for these studies (months 1-2; completed)

Task 4. To determine whether tamoxifen, trifluoperazine or combined tamoxifen/trifluoperazine therapy inhibits tumor cell proliferation and survival in neurofibroma bearing Krox20-Cre;Nf1^{lox/-} mice (months 1-36):
   a. Obtain regulatory review and approval for these studies (months 1-2; completed)

Task 5. To determine whether prophylactic therapy with tamoxifen, trifluoperazine or combined tamoxifen/trifluoperazine therapy prevents neurofibroma and MPNST pathogenesis in Krox20-Cre;Nf1^{lox/-} and P_0-GGFβ3;Trp53^{+/+} mice, respectively (months 18-36):
   a. Obtain regulatory review and approval for these studies (months 1-2; completed)

We received approval for this animal protocol from the Medical University of South Carolina’s IACUC on June 25, 2015. Please note, however, that ACURO did not approve this protocol until November 16, 2015. This research project exclusively involves experiments utilizing genetically engineered mouse models. Consequently, we were not allowed to start actual experimental work towards the goals of this project until we had obtained ACURO approval; likewise, we did not start personnel effort on this project until December 1, 2015.

Task 1. To determine whether tamoxifen, trifluoperazine or combined tamoxifen/trifluoperazine therapy inhibits tumor cell proliferation and survival in MPNST bearing P_0-GGFβ3;Trp53^{+/+} mice (months 1-36):
   b. Perform studies with tamoxifen and trifluoperazine to establish maximum tolerated doses of these agents in C57BL/6 mice (months 2-4; completed)

We recognize that the maximal tolerated dose (MTD) for a specific drug may differ in mice with different genetic backgrounds. Consequently, before beginning the full study, it was necessary that we first determine the MTD for tamoxifen and trifluoperazine in C57BL/6 mice (the genetic background of the Krox20-Cre;Nf1^{lox/-} and P_0-GGFβ3;Trp53^{+/+} mice that are to be used for our preclinical trials) and, if necessary, adjust the doses that will be used in our studies following the guidelines outlined in our preliminary studies. We began by determining the MTD for tamoxifen and trifluoperazine when administered via intraperitoneal injection to C57BL/6J mice, following a “3 + 3” regimen. Under this regimen, groups of three mice were treated with each agent for 1 month, following a dosing regimen in which animals received 5 consecutive days of intraperitoneally injected drug, with 2 days rest in between. This dose was increased in a step-wise fashion until adverse effects such as weight loss, alterations in grooming behavior, or death were observed. At this point, 3 additional mice were treated with the same dose to verify its effect on these animals; if it has the same effect, the dose immediately below the dose producing toxic effects is considered to be the maximum tolerated dose. For all mice, blood was collected via cardiac puncture, centrifuged to separate the cells from the serum and the serum was frozen in aliquots at -80°C if needed in the future to measure levels of markers of the function of key organs [e.g., liver (ALT and AST enzyme levels) and kidney (blood urea nitrogen (BUN) and creatinine)]. Complete necropsies were performed on all
mice and detailed histologic analyses were performed on organs most commonly affected by therapeutic agents (brain, liver, kidney, small and large intestine, lung). We found that tamoxifen administered at the maximum dose we tested primarily had negative effects on small and large intestine, which was evident as blunting of intestinal villi. We did not see any overt histologic changes in any of the tissues we examined from mice receiving the MTD of trifluoperazine. We established that the maximal tolerated dose of tamoxifen in C57BL/6J mice was 30mg/kg and that for trifluoperazine was 20mg/kg.

The next subtasks in each of the tasks likewise shared the common goal of establishing the large cohorts of genetically engineered mice with the appropriate genotype in months 3-18 of the project and, for Tasks 1-4, evaluating the effectiveness of these regimens (months 12-18, which will occur in the upcoming funding year of this project):

**Task 1.** To determine whether tamoxifen, trifluoperazine or combined tamoxifen/trifluoperazine therapy inhibits tumor cell proliferation and survival in MPNST bearing $P_0$-GGFβ3; $Trp53^{+/−}$ mice (months 1-36):
   c. Establish cohorts of $P_0$-GGFβ3; $Trp53^{−/−}$ mice, identify MPNST bearing mice with PET scans and randomize mice into cohorts for treatment with vehicle, tamoxifen, trifluoperazine or tamoxifen and trifluoperazine (months 3-18; **in progress**)
   d. Evaluate the effectiveness of the therapeutic regimens described in c (months 12-18; **upcoming funding period**)

**Task 2.** To determine whether tamoxifen, trifluoperazine or combined tamoxifen/trifluoperazine therapy inhibits tumor cell proliferation and survival in neurofibroma bearing Krox20-Cre; $Nf1^{flox/−}$ mice (months 1-36):
   b. Establish cohorts of Krox20-Cre; $Nf1^{flox/−}$ mice, identify neurofibroma bearing mice with MRI scans and randomize mice into cohorts for treatment with vehicle, tamoxifen, trifluoperazine or tamoxifen and trifluoperazine (months 3-18; **in progress**)
   c. Evaluate the effectiveness of the therapeutic regimens described in c (months 12-18; **upcoming funding period**)

**Task 3.** To determine whether tamoxifen, trifluoperazine or combined tamoxifen/trifluoperazine therapy extends the survival of MPNST bearing $P_0$-GGFβ3; $Trp53^{+/−}$ mice (months 1-36):
   b. Establish cohorts of $P_0$-GGFβ3; $Trp53^{−/−}$ mice, identify MPNST bearing mice with PET scans and randomize mice into cohorts for treatment with vehicle, tamoxifen, trifluoperazine or tamoxifen and trifluoperazine (months 3-18; **in progress**)
   c. Evaluate the effectiveness of the therapeutic regimens described in c (months 12-18 **upcoming funding period**)

**Task 4.** To determine whether tamoxifen, trifluoperazine or combined tamoxifen/trifluoperazine therapy inhibits tumor cell proliferation and survival in neurofibroma bearing Krox20-Cre; $Nf1^{flox/−}$ mice (months 1-36):
   b. Establish cohorts of Krox20-Cre; $Nf1^{flox/−}$ mice, identify neurofibroma bearing mice with MRI scans and randomize mice into cohorts for treatment with vehicle, tamoxifen, trifluoperazine or tamoxifen and trifluoperazine (months 3-18; **in progress**)
   c. Evaluate the effectiveness of the therapeutic regimens described in b (months 12-18; **upcoming funding period**)

For the interim analysis, our biostatistician recommended that we look for an effect size of at least 2 (following the measures outlined below) in the treatment versus control groups. One-way ANOVA with a Dunnett test for adjustment of pair-wise comparisons (compared to the
control group) will be used for sample size calculation. We determined that 20 mice per group would give us 95% power to detect at least an effect size of 2 between the treatment groups and the control (vehicle) group, given 5% type I error. We also recognize NIH’s recent recommendation that animal experiments include both male and female animals to avoid a sex bias. Consequently, our original experimental design was that each cohort would include 20 male and 20 female mice; male and female mice will be analyzed both independently and in a stratified fashion. In accordance with these goals, we have established the full cohort of $P_0$-GGFB3; $Trp53^{+/c}$ mice necessary for Tasks 1 and 3 and are currently following them, using clinical examination and PET scans, to identify MPNST-bearing mice which are then randomized into treatment cohorts. We have established a portion of the Krox20-Cre; $Nf1^{floox/-}$ mice necessary for Tasks 2 and 4; the generation of these cohorts is still ongoing because the genotype of these animals is more complicated than that of $P_0$-GGFB3; $Trp53^{+/c}$ mice and thus takes longer to generate. Krox20-Cre; $Nf1^{floox/-}$ mice are being followed, using clinical examination and MRI scans, to identify neurofibroma-bearing mice which are then randomized into treatment cohorts.

**Task 5.** To determine whether prophylactic therapy with tamoxifen, trifluoperazine or combined tamoxifen/trifluoperazine therapy prevents neurofibroma and MPNST pathogenesis in Krox20-Cre; $Nf1^{floox/-}$ and $P_0$-GGFB3; $Trp53^{+/c}$ mice, respectively (months 18-36):

b. Establish cohorts of Krox20-Cre; $Nf1^{floox/-}$ and $P_0$-GGFB3; $Trp53^{+/c}$ mice (months 18-22)

In our original grant application, we had proposed to establish the cohorts of Krox20-Cre; $Nf1^{floox/-}$ and $P_0$-GGFB3; $Trp53^{+/c}$ mice required for this Task in the latter half of this project. However, in light of the delay in getting our animal protocol approved by ACURO, we have gone ahead and begun to establish these cohorts.

The subtasks indicated below are planned for the later phases of this project and thus were not addressed during the just completed funding period:

**Task 1.** To determine whether tamoxifen, trifluoperazine or combined tamoxifen/trifluoperazine therapy inhibits tumor cell proliferation and survival in MPNST bearing $P_0$-GGFB3; $Trp53^{+/c}$ mice (months 1-36):

--Perform diagnostic, histochemical and immunohistochemical analyses of proliferation and cell death in tumor cohorts (months 18-36)

**Task 2.** To determine whether tamoxifen, trifluoperazine or combined tamoxifen/trifluoperazine therapy inhibits tumor cell proliferation and survival in neurofibroma bearing Krox20-Cre; $Nf1^{floox/-}$ mice (months 1-36):

--Perform diagnostic, histochemical and immunohistochemical analyses of proliferation and cell death in tumor cohorts (months 18-36)

**Task 3.** To determine whether tamoxifen, trifluoperazine or combined tamoxifen/trifluoperazine therapy extends the survival of MPNST bearing $P_0$-GGFB3; $Trp53^{+/c}$ mice (months 1-36):

--Perform diagnostic, histochemical and immunohistochemical analyses of proliferation and cell death in tumor cohorts (months 18-36)

**Task 4.** To determine whether tamoxifen, trifluoperazine or combined tamoxifen/trifluoperazine therapy inhibits tumor cell proliferation and survival in neurofibroma bearing Krox20-Cre; $Nf1^{floox/-}$ mice (months 1-36):

--Perform diagnostic, histochemical and immunohistochemical analyses of proliferation and cell death in tumors (months 18-36)
Task 5. To determine whether prophylactic therapy with tamoxifen, trifluoperazine or combined tamoxifen/trifluoperazine therapy prevents neurofibroma and MPNST pathogenesis in Krox20-Cre;Nf1\textsuperscript{flov/} and P\textsubscript{0}-GGF\textbeta 3; Trp53\textsuperscript{+/} mice, respectively (months 18-36):
--Treat cohorts with vehicle, tamoxifen, trifluoperazine or tamoxifen and trifluoperazine (months 22-36)
--Evaluate the effectiveness of the therapeutic regimens described in b (months 22-36)
--Perform diagnostic, histochemical and immunohistochemical analyses of proliferation and cell death in tumors, if tumors are present (months 30-36)

Opportunities for Training and Professional Development
Nothing to Report

Dissemination of Results to Communities of Interest
Nothing to Report

Plan during the Next Reporting Period to Accomplish Goals
As indicated by the research plan outlined above, the experiments we have begun are relatively long term (15-18 month) experiments. Consequently, during the next reporting period, we will continue to follow the cohorts that we have established and assess the effectiveness of the therapeutic regimens that we are testing. We anticipate that we will be able to obtain information as to whether these regimens have effects on animal survival and tumor mass; more detailed assessments of parameters such as the impact these regimens have on tumor cell proliferation and survival are planned for the later stages of this project. We will also be beginning the prophylactic regimens that are proposed as Task 5. Since we will need to follow these mice for an extended period to determine whether we have successfully prevented tumorigenesis, we do not anticipate completing the prophylactic regimen studies during the next reporting period.

IMPACT
Impact on the development of the principal discipline(s) of the project
Nothing to Report

Impact on other disciplines
Nothing to Report

Impact on technology transfer
Nothing to Report

Impact on society beyond science and technology
Nothing to Report

CHANGES/PROBLEMS
Changes in approach and reasons for change
Nothing to Report

Actual or anticipated problems or delays and actions or plans to resolve them
As noted above, we did experience a delay in getting ACURO to approve our animal protocol. As a result of this delay, we have moved up our schedule for Task 5, which will ensure that we complete this task during the funding period of this grant.
Changes that had a significant impact on expenditures
Our expenditures during the last reporting period are lower than expected. This is because the delay in getting ACURO approval meant that we could not perform any animal work until that approval was received; this included purchasing and beginning to breed the mice needed for the tasks planned for this project and beginning personnel effort on this project. As the scope of the animal work required for this project is unchanged, this will not impact overall expenditures for this project—it simply puts off some of the expenditures that were planned for the initial funding period to the upcoming funding period.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Nothing to Report

PRODUCTS
MANUSCRIPTS, ABSTRACTS and PRESENTATIONS
Manuscripts


Abstracts
Nothing to Report

Presentations
Nothing to Report

LICENSES APPLIED FOR AND/OR ISSUED
Nothing to Report

DEGREES OBTAINED THAT ARE SUPPORTED BY THIS AWARD
Nothing to Report

DEVELOPMENT OF CELL LINES, TISSUE OR SERUM REPOSITORIES
Nothing to Report

DATABASES AND ANIMAL MODELS
Nothing to Report

FUNDING APPLIED FOR BASED ON WORK SUPPORTED BY THIS AWARD
Nothing to Report
### EMPLOYMENT OR RESEARCH OPPORTUNITIES APPLIED FOR AND/OR RECEIVED BASED ON EXPERIENCE/TRAINING SUPPORTED BY THIS AWARD

Nothing to Report

### PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

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### Suraj Dixit

**Project Role:** Post Doc  
**Nearest person month worked:** 8  
**Contribution to Project:** No Change  
**Funding Support:**

### Jody Longo

**Project Role:** Scientist  
**Nearest person month worked:** 8  
**Contribution to Project:** No Change  
**Funding Support:**

**Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**  
Nothing to Report

**What other organizations were involved as partners?**  
Nothing to Report

**Partner’s contribution to the project**  
Nothing to Report

**Financial support:**

- In-kind support  
- Facilities  
- Collaboration  
  Nothing to Report

**Personnel exchanges**  
Nothing to Report

**Other**  
Nothing to Report
APPENDICES