Final Progress Report for Research Projects Funded by Health Research Grants

Instructions: Please complete all of the items as instructed. Do not delete instructions. Do not leave any items blank; responses must be provided for all items. If your response to an item is "None", please specify "None" as your response. "Not applicable" is not an acceptable response for any of the items. There is no limit to the length of your response to any question. Responses should be single-spaced, no smaller than 12-point type. The report **must be completed using MS Word**. Submitted reports must be Word documents; they should not be converted to pdf format. Questions? Contact Health Research Program staff at 717-783-2548.

1. **Grantee Institution:** Drexel University

2. **Reporting Period (start and end date of grant award period):** 1/1/2009- 12/31/2010

3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** Anne Martella

4. **Grant Contact Person's Telephone Number:** (215) 895-6471

5. **Grant ME Number or SAP Number:** 4100047631

6. **Project Number and Title of Research Project:** 9 – Somatostatin Signaling in Alzheimer's Disease

7. **Start and End Date of Research Project:** 1/1/2009 - 12/31/2009

8. **Name of Principal Investigator for the Research Project:** Melanie K. Tallent, PhD

9. **Research Project Expenses**.

   9(A) Please provide the amount of health research grant funds spent on this project for the entire duration of the grant, including any interest earned that was spent:

   $ 112,500

   9(B) Provide the last names (include first initial if multiple individuals with the same last name are listed) of **all** persons who worked on this research project and were supported with health research funds. Include position titles (Principal Investigator, Graduate Assistant, Post-doctoral Fellow, etc.), percent of effort on project and total health research funds expended for the position. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name	Position Title	% of Effort on Project	Cost
Tallent	Assistant Professor	10%	$ 10,416
Reddi	Research Assistant	50%	$ 21,648

9(C) Provide the names of **all** persons who worked on this research project, but who *were not* supported with health research funds. Include position titles (Research Assistant, Administrative Assistant, etc.) and percent of effort on project. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name	Position Title	% of Effort on Project
None		

9(D) Provide a list of **all** scientific equipment purchased as part of this research grant, a short description of the value (benefit) derived by the institution from this equipment, and the cost of the equipment.

Type of Scientific Equipment	Value Derived	Cost
None		

10. Co-funding of Research Project during Health Research Grant Award Period. Did this research project receive funding from any other source during the project period when it was supported by the health research grant?

Yes_____ No_____X___

If yes, please indicate the source and amount of other funds:

11. Leveraging of Additional Funds

11(A) As a result of the health research funds provided for this research project, were you able to apply for and/or obtain funding from other sources to continue or expand the research?

Yes__X___ No__ _____

If yes, please list the applications submitted (column A), the funding agency (National Institutes of Health—NIH, or other source in column B), the month and year when the application was submitted (column C), and the amount of funds requested (column D). If you have received a notice that the grant will be funded, please indicate the amount of funds to be awarded (column E). If the grant was not funded, insert "not funded" in column E.

Do not include funding from your own institution or from CURE (tobacco settlement funds). Do not include grants submitted prior to the start date of the grant as shown in Question 2. If

you list grants submitted within 1-6 months of the start date of this grant, add a statement below the table indicating how the data/results from this project were used to secure that grant.

A. Title of research project on grant application	B. Funding agency (check those that apply)	C. Month and Year Submitted	D. Amount of funds requested:	E. Amount of funds to be awarded:
Targeting somatostatin receptors to treat Alzheimer's disease	☑NIH ☐ Other federal (specify:_____) ☐ Nonfederal source (specify: _____)	April 2009	$686,140	Not funded
Targeting somatostatin receptors to treat Alzheimer's disease	☐NIH ☐ Other federal (specify) ☑ Nonfederal source (specify: American Health Association Foundation)	Oct 2009	$150,000	Not funded
Somatostatin receptors as a therapeutic target for Alzheimer's Disease	☑NIH ☐ Other federal (specify:_____) ☐ Nonfederal source (specify: _____)	Oct 2009	$424,250	$ Not funded

11(B) Are you planning to apply for additional funding in the future to continue or expand the research?

Yes __X___ No_____

If yes, please describe your plans:

We have applied for an Alzheimer's Foundation grant and will continue to seek NIH funding for this project at the R21 or R01 level.

12. Future of Research Project. What are the future plans for this research project?

To continue to seek additional funding to explore the relationship of somatostatin and SST_3 dysfunction to Alzheimer's disease etiology.

13. New Investigator Training and Development. Did students participate in project supported internships or graduate or post-graduate training for at least one semester or one summer?

Yes__X___ No_____

If yes, how many students? Please specify in the tables below:

	Undergraduate	Masters	Pre-doc	Post-doc
Male	1			
Female	1			
Unknown				
Total	**2**			

	Undergraduate	Masters	Pre-doc	Post-doc
Hispanic				
Non-Hispanic	2			
Unknown				
Total	**2**			

	Undergraduate	Masters	Pre-doc	Post-doc
White	2			
Black				
Asian				
Other				
Unknown				
Total	**2**			

14. Recruitment of Out-of–State Researchers. Did you bring researchers into Pennsylvania to carry out this research project?

Yes_____ No__X_____

If yes, please list the name and degree of each researcher and his/her previous affiliation:

15. Impact on Research Capacity and Quality. Did the health research project enhance the quality and/or capacity of research at your institution?

Yes____x_____ No_____

If yes, describe how improvements in infrastructure, the addition of new investigators, and other resources have led to more and better research.

This project provided training for two undergraduate students.

16. Collaboration, business and community involvement.

16(A) Did the health research funds lead to collaboration with research partners outside of your institution (e.g., entire university, entire hospital system)?

Yes_____ No____X___

If yes, please describe the collaborations:

16(B) Did the research project result in commercial development of any research products?

Yes_____ No____X___

If yes, please describe commercial development activities that resulted from the research project:

16(C) Did the research lead to new involvement with the community?

Yes_____ No___X_____

If yes, please describe involvement with community groups that resulted from the research project:

17. Progress in Achieving Research Goals, Objectives and Aims.

List the project goals, objectives and specific aims (as contained in the grant application's strategic plan). Summarize the progress made in achieving these goals, objectives and aims for the entire grant award period. Indicate whether or not each goal/objective/aim was achieved; if something was not achieved, note the reasons why. Describe the methods used. If changes were made to the research goals/objectives/aims, methods, design or timeline since the original grant application was submitted, please describe the changes. Provide detailed results of the project. Include evidence of the data that was generated and analyzed, and provide tables, graphs, and figures of the data. List published abstracts, poster presentations and scientific meeting presentations at the end of the summary of progress; peer-reviewed publications should be listed under item 20.

This response should be a DETAILED report of the methods and findings. It is not sufficient to state that the work was completed. Insufficient information may result in an unfavorable performance review, which may jeopardize future funding. If research findings are pending publication you must still include enough detail for the expert peer reviewers to evaluate the progress during the course of the project.

Health research grants funded under the Tobacco Settlement Act will be evaluated via a performance review by an expert panel of researchers and clinicians who will assess project work using this Final Progress Report, all project Annual Reports and the project's strategic plan. After the final performance review of each project is complete, approximately 12-16

months after the end of the grant, this Final Progress Report, as well as the Final Performance Review Report containing the comments of the expert review panel, and the grantee's written response to the Final Performance Review Report, will be posted on the CURE Web site.

There is no limit to the length of your response. Responses must be single-spaced below, no smaller than 12-point type. If you cut and paste text from a publication, be sure symbols print properly, e.g., the Greek symbol for alpha (α) and beta (ß) should not print as boxes (□) and include the appropriate citation(s). DO NOT DELETE THESE INSTRUCTIONS.

Original Research Goals

The purpose of our research plan was to examine the function of the somatostatin (SST) receptor SST_3 in a mouse model of Alzheimer's disease (AD). SST depletion in the brain is associated with cognitive decline in AD, and we have shown that SST_3 mediates the major actions of this peptide in regulating cognitive function. Thus we hypothesized that hypofunctional SST_3 could contribute to cognitive dysfunction in AD.

Experiment 1) Examine whether a specific form of synaptic plasticity, forskolin evoked long-term potentiation (LTP), is dysfunctional in the AD mouse model.

Experiment 2) Determine whether activation of SST3 can restore LTP deficits in AD mice.

Experiment 3) Examine whether cognitive deficits in AD mice can be restored by intracerebroventricular injection of SST or its analogs.

Experiment 4) Examine whether neuronal cilia are abnormal in the AD mouse.

Most of the progress was made in Experiments 1, 3, and 4. Initial success in experiment 1 motivated us to expand the scope of this experimental aim to begin to examine the cellular mechanism of SST_3. Further, since we ended up testing several different LTP paradigms in 3x-tg mice before we discovered a consistent deficit, we did not have the opportunity to explore whether activation of SST_3 can restore forskolin LTP deficits in 3x-tg mice. In experiment 3, we made much progress in characterizing the object recognition memory deficits in 3x tg mice. Further, we have been able to discriminate the site of action of SST_3, which is dorsal hippocampus and have data showing that an SST_3 agonist can restore cognitive function in an AD mouse model. Experiment 4 was largely completed as originally written.

Completed Research

Long-term potentiation in 3x-tg Alzheimer's mice

Synaptic plasticity is a phenomenon where the history of a synapse changes its response to synaptic input. This is a much studied process since synaptic plasticity in different forms is thought to be required for learning and memory. Activation of SST_3 is required for a specific type of synaptic plasticity in CA1 hippocampus of young adult wild type mice. This form of long term potentiation (LTP) is evoked with forskolin (F-LTP), a direct activator of adenylyl cyclase. LTP evoked with high-frequency trains (HFTs) of stimulation does not appear to require, although it can be modulated, by SST_3 activation (not shown; n =5).

We first examined CA1 LTP induced by HFTs, to confirm a previously reported deficit in the 3x-tg mouse model. Surprisingly, we found that this form of LTP was normal in our hands, even in 3x-tg mice over 12-14 month old (Fig. 1A; n = 6-8; ANOVA $p > 0.05$). We varied different conditions to determine whether the normal LTP that we observed was related to a specific condition in our lab. But even after varying slicing protocols and train paradigms we still did not observe a deficit in CA1 LTP. We next examined LTP in the dentate gyrus region of aged AD 3x-tg mice, reasoning that perhaps we could observe a deficit since LTP is not as robust in this region as in CA1. LTP in the dentate gyrus was also not impaired in the AD mouse model (Fig. 1B; n = 4-6; ANOVA $p > 0.05$).

We next examined F-LTP in the AD 3x-tg mouse. As seen in Fig. 1C, non-Tg mice, at age 9-12 months, display robust LTP induced by forskolin. However, in the AD 3x-tg mice, no LTP is evoked by forskolin (n = 3-4; ANOVA; $p < 0.05$). This suggest cAMP-mediated signaling may be impaired in these mice.

Signaling mechanisms of SST3 in hippocampus

Since LTP deficits in 3x-tg mice are remarkably similar to our findings in SST3 knockout mice, we further explored the requirement of SST3 activation for F-LTP. This type of LTP is generated by direct activation of adenylyl cyclase, an enzyme that when activated produces the important signaling molecule cyclic adenosine monophosphate (cAMP). Therefore we examined the role of SST3 in modulating cAMP levels in mouse hippocampus.

We found that cAMP levels in *sst3* knockout mice were 41.5 ± 13% of wild type when extracted directly from hippocampus (n = 6 each; $p < 0.05$). We also examined forskolin-induced increases in cAMP in a homogenized hippocampal preparation (lysate) from wild type and *sst3* knockout mice. Unstimulated cAMP levels in lysates were also significantly lower in *sst3* knockout mice (820 ± 312 pmol/mg protein) compared to wild type (1299 ± 144 pmol/mg protein). However, forskolin induced a similar relative increase in cAMP in hippocampal lysates from wild type (5.1 ± 1.7 fold increase; n = 5) and *sst3* knockout mice (4.8 ± 0.4 fold increase; n = 5). We also examined the effect of the SST3 agonist and antagonist in hippocampal lysate (n = 5) and in hippocampal slices (n = 5; Fig. 2). In hippocampal lysate, blockade of SST3 with ACQ090 (1 µM) did not significantly affect forskolin-stimulated cAMP levels (91 ± 15% of control; $p = 0.6$). However, in hippocampal slices, ACQ090 reduced forskolin-stimulated cAMP levels to 48.6 ± 8% of control levels ($p = 0.03$). Similarly, SST3

activation with L-796,779 (1 µM) did not affect basal cAMP levels in hippocampal lysate (90 ± 11%; n = 0.4), but in hippocampal slices increased basal cAMP levels to 130 ± 7% of control levels (p = 0.03). These results suggest that intact cilia and/or neuronal structure may be required for SST3 signaling.

The next question we wished to address was how does activation of cAMP lead to signaling events in the neuronal soma. Our findings suggested that cAMP signaling within the tiny cilia must be amplified in order to produce such large changes in overall cellular cAMP levels. Interestingly, neuronal cilia in hippocampus and elsewhere specifically express adenylyl cyclase type 3 (AC3). This same AC isoform mediates olfactory transduction in olfactory cilia. Therefore we proposed a model of signaling based on analogies to olfactory signaling, in which increases in cAMP activate cyclic nucleotide gated (CNG) ion channels. We therefore tested whether blockers of CNG channels impaired F-LTP. We used two different blockers, dicholorobenzamil (DCB; 30 µM) and L-cis-diltiazem (DTZ; 30 µM). Interestingly, both blockers inhibited F-LTP to a similar degree as the SST3 antagonist ACQ090 (Fig. 3). This supports our hypothesis that signaling in hippocampal cilia shares common mechanisms with olfactory transduction.

Our major hypothesis is that dysfunction in somatostatinergic systems contributes to cognitive decline in AD. Although decreases in brain SST levels reported in humans have been observed in several mouse models of AD, SST levels in the 3x-tg mouse had not been examined. Therefore we examined SST staining in hippocampus of aged 3x-tg mice. We found that SST-positive neurons were decreased in number in 3x-tg mice compared to age-matched non-Tg mice (18-24 months old). This decrease was apparent in both CA1 (Fig. 4A) and dentate gyrus (Fig. 4B). We examined whether SST deficits were found in younger 3x-tg mice using Western blotting that allows for better quantification. We found a reduced level of SST in 6 mos old 3x-tg mice compared to aged matched non-tg mice (Fig.5).

We next examined expression of SST_3 and cilia morphology in aged 3x-tg mice (the mouse model we are using, which expresses 3 transgenes associated with familial AD and have pathological and cognitive phenotypes associated with the human disease). Throughout early development up until young adulthood, SST_3 is specifically expressed on neuronal cilia. Many neurons express single primary (non-motile) cilia of unknown function but are likely signaling organelles. We first established our immunohistochemistry protocols in young wild type mice. Shown in Fig. 6 is adenylyl cyclase type 3 (AC3), a cilia marker, labeling in young adult C57Bl/6J mice and SST_3 knockout mice. Note normal cilia number and structure in SST_3 knockout mice, demonstrating knockout of SST_3 does not grossly affect cilia morphology.

We labeled cilia in aged brain of AD 3x-tg mice and non-transgenic littermates using the cilia marker adenylyl AC3. Cilia structure and number did not obviously differ between non-TG and AD 3x-tg mice in hippocampus or cortex (Fig. 7; top panels). However, SST_3 expression was dramatically different between the strains. In both strains, a reduction in CA1 SST_3 expression was observed compared to young adult mice (not shown). In CA3 hippocampus, in non-TG mice, SST_3 was localized to cilia as in younger mice, but nuclear and perinuclear staining was also present (Fig. 7; bottom panels). In the AD 3x-tg mice, the SST_3 antibody did

not label cilia, but the non-cilia labeling was present and similar to the non-Tg mice (Fig. 7; bottom panels). In the dentate gyrus, AC3 staining was normal in both mouse strains (Fig. 8; top panel). SST_3 appeared to be expressed mostly on neuronal cilia in non-Tg mice; however, in the age-matched AD 3x-tg no SST_3 expression was apparent in the dentate (Fig. 8; bottom panels). Our results show that SST_3 is abnormally expressed in hippocampus of aged AD 3x-tg mice, and suggest that dysfunction of this receptor could play a role in the etiology of AD. We also wanted to determine at what age SST3 expression and targeting began to show changes in 3x-tg mice. We found that at 9 mos of age, SST3 expression appears normal in 3x-tg mice (Fig. 9). These results suggest that SST3 may be a valid therapeutic target for AD until late stages of the disease.

Object recognition memory in 3x-tg mice

We have demonstrated that the major cognitive impairment in SST3 knockout mice is in object recognition memory (ORM). Mice have an innate preference for novel vs. familiar objects which can be utilized to test ORM. SST3 knockout mice show no discrimination between novel and familiar objects. Acute blockade of SST3 via IP injection of the systemically active SST3 antagonist ACQ090 leads to a similar impairment. Since ORM in the 3x-tg mice had not been examined, we determined whether these mice could discriminate novel objects. We found that 3x-tg mice as young as 5 mos (n = 12), with a 1 hr delay, showed no preference for a novel object (Fig. 10). Non-transgenic (non-tg) control mice as old as 11 mos showed significant preference for the novel object at the 1 hr retention interval (n = 10). Thus ORM represents an early cognitive deficit in the 3x-tg mice, and demonstrates another similarity between this AD mouse model and SST3 knockout mice.

To further define the role of SST3 in ORM, we needed to determine its site of action. ORM involves both the hippocampus and perirhinal cortex (PRC). We examined whether SST3 blockade with ACQ090 could affect F-LTP in the PRC, as it does in CA1. Interestingly, although we were able to induce stable LTP with forskolin, it was not impaired by ACQ090 (1 μM). In control slices, 60 min following washout of forskolin cocktail, fEPSP slopes were 158 ± 9.9% of baseline (n = 8). When ACQ090 was superfused beginning 15 min prior to and during the 15 min forskolin application, fEPSP slopes were 155 ± 15% of baseline 60 min following washout of drugs. (n = 4). Thus although SST3 is expressed in PRC, it may have a function distinct from that in CA1 hippocampus.

We next wanted to examine whether SST3 blockade in hippocampus was sufficient to block ORM. We have established a protocol to inject drugs into hippocampus using bilateral cannulae in mice. The original stereotaxic coordinates we used resulted in hippocampal damage and nonspecific functional deficits in some wild type mice. After altering our coordinates, we were able to show no impairment of ORM after saline injection in mice 30 min prior to the test phase in our ORM paradigm (Fig. 4; n = 5). However, the SST3 antagonist ACQ090 (20 ng; n = 5) impairs ORM when injected into hippocampus 30 min prior to the ORM test (30 min after training; Fig. 11). Thus blockade of SST3 in hippocampus is sufficient to impair ORM in mice.

These preceding studies allowed us to address the major goal of this aim, whether activation of SST_3 can rescue the deficits in ORM in the 3x-tg mice. As shown in Fig. 12, bilateral hippocampal injection of 350 ng of the SST_3 agonist L-796,778, 30 min prior to testing, restores ORM in 3x-tg mice aged 7-8 mos (n = 3). These results validate that SST_3 warrants further investigation as a therapeutic target for treatment of cognitive deficits associated with Alzheimer's disease.

Published abstracts, poster presentations and scientific meeting presentations

Abstracts and presentations

Melnikoff, David and Tallent, M. K. Somatostatin Signaling in Neuronal Cilia Is Critical for Object Recognition Memory, Drexel Discovery Day poster 2009 (3rd place undergraduate poster).

D. E. Melnikoff, E. B. Einstein, C. A. Patterson, K. A. Regan[1] M. J. Mateer, M. K. Tallent, Somatostatin signaling in neuronal cilia is critical for object recognition memory and cAMP-dependent LTP, 2009 Society for Neuroscience meeting, Chicago, IL.

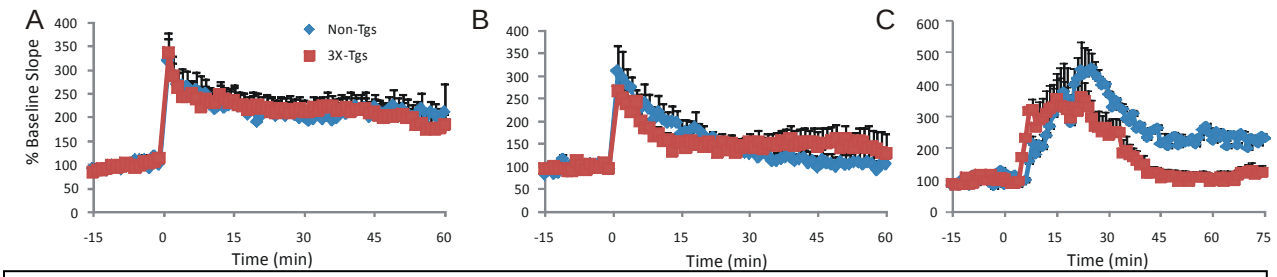

Figure 1. LTP in 3x-tg mice vs. non-transgenic littermates. In CA1 (**A**) and dentate gyrus (**B**), LTP induced by 2 high frequency trains in normal in the AD 3x-tg mice. **C.** LTP induced by forskolin is impaired in 3x-tg mice. In all 3 graphs, trains or forskolin application begins at the 0 timepoint.

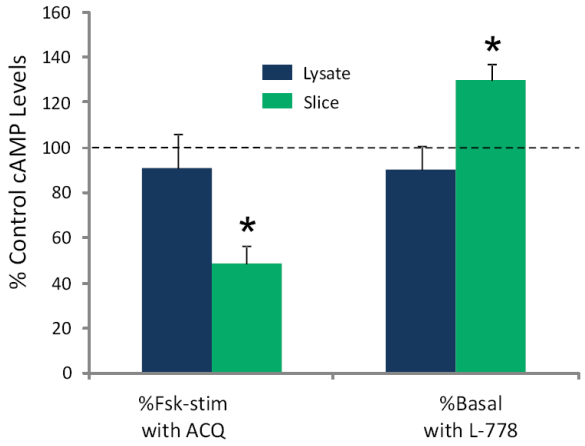

Figure 2. *Effects of SST3 agonist and antagonist in hippocampal lysate and slices*. Forskolin (Fsk) stimulation of cAMP is inhibited by 1 µM ACQ090 in hippocampal slices but not hippo-campal lysate (left columns). The SST3 agonist L-796,778 (L-778) increases basal cAMP levels in hippo-campal slices but not hippocampal lysate (right columns). * indicate significant difference from control cAMP levels (basal or forskolin-stimulated in the absence of SST3 ligand; dashed line).

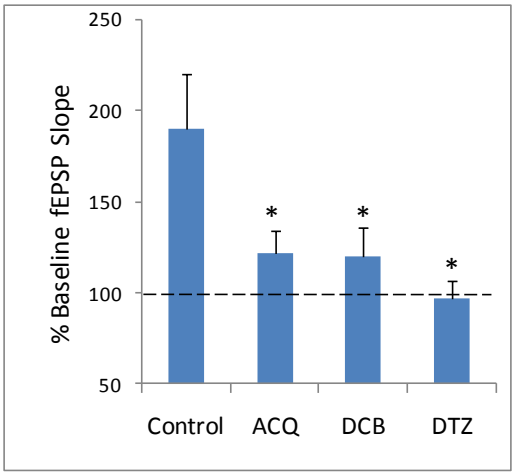

Figure 3. *Blockade of CNG channels impairs F-LTP in hippocampal slices*. Forskolin (Fsk) stimulation of cAMP is inhibited by SST_3 antagonist 1 µM ACQ090, and to a similar degree by CNG channel blockers dichlorobenzamil (DCB) and L-cis-diltiazem (DTZ). * indicate significant difference from control F-LTP.

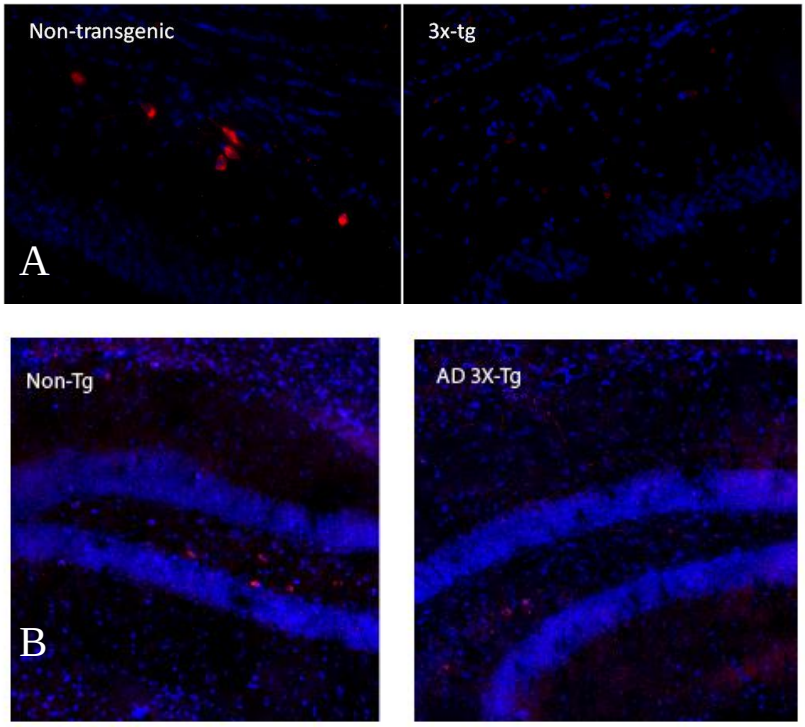

Figure 4. Somatostatin expression is reduced in 3x-tg mice. **A**. SST stains less CA1 interneurons in aged 3x-Tg mice compared to aged-matched non-transgenics. SST-positive neurons are also much more lightly stained in 3x-tg vs. non-Tg mice. **B**. Less SST staining is apparent in dentate gyrus of 3x-tg mice. Note all photo adjustments were the same for each paired figure.

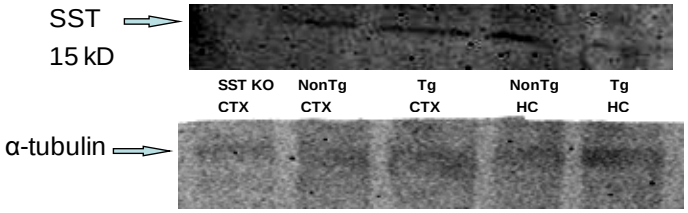

Figure 5. Western blots with anti-SST antibody shows reduction of SST in hippocampus of <u>6 mos old</u> 3x-Tg mice. Antibody specificity is confirmed in SST knockout mouse (lane 1).

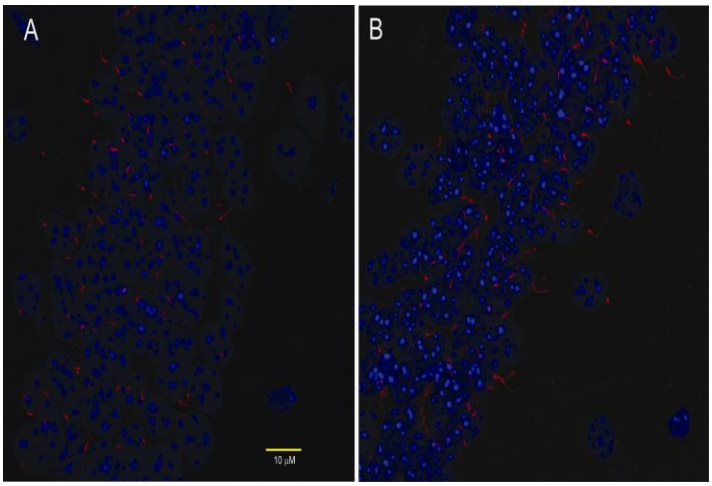

Figure 6. AC3 immunolabeling is normal in SST3 knockout mice. **A.** CA1 hippocampus from wild type mice. **B**. CA1 hippocampus from SST3 knockout mice. Red labeling is AC3 staining (Santa Cruz-Sc-588, 1: 1000).

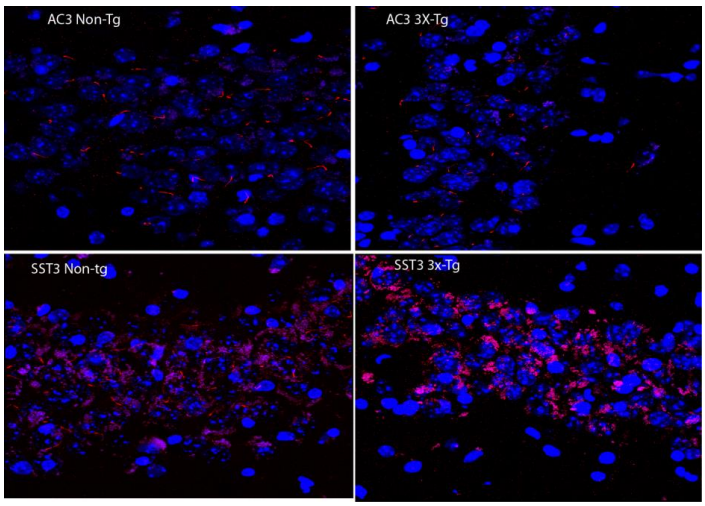

Figure 7. AC3 (*top panels*) and SST_3 (*bottom panels*) labeling in CA3 of aged non-transgenic and 3x-tg mice. Note the normal cilia structure compared to younger mice (see Fig. 3), but the abnormal localization of SST_3 in aged mice. Also note the cilia localization of SST_3 in non-transgenic but not 3x-tg mice.

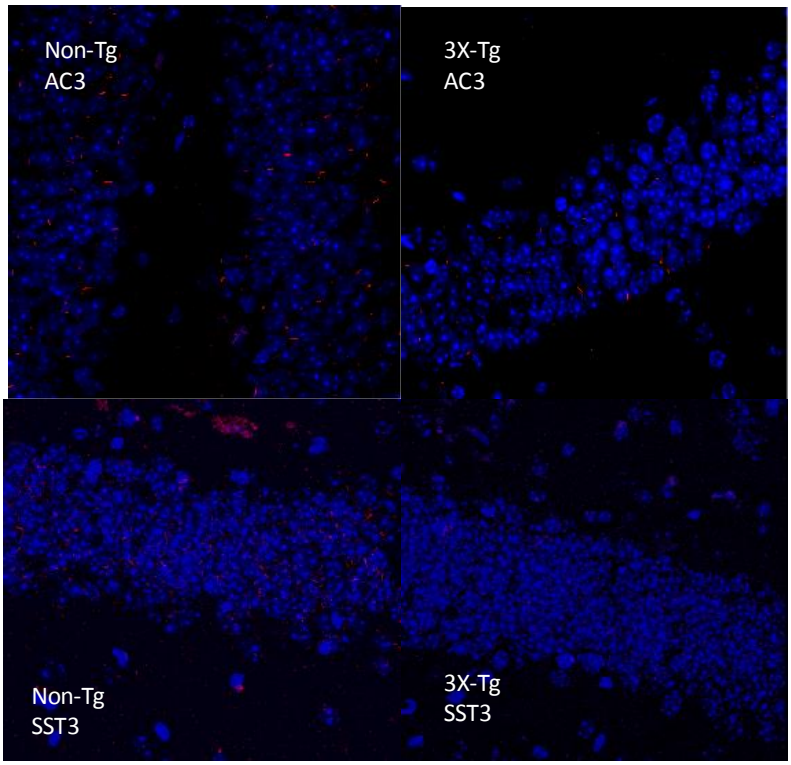

Figure 8. SST_3 staining is absent in dentate gyrus of SST_3 knockout mice. AC3 staining (*top panels*) looks similar in non-Tg and 3x-tg mice. However, no SST_3 staining is present in dentate gyrus of 3x-tg mice, whereas normal cilia staining is present in age-matched non-transgenics (*bottom panels*).

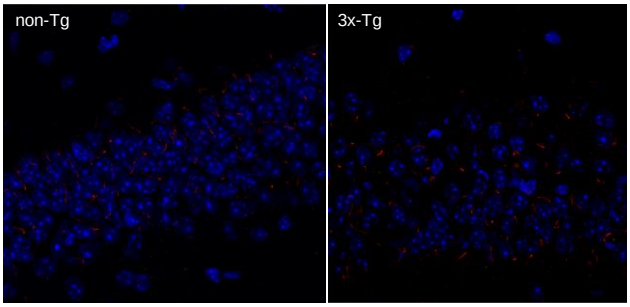

Figure 9. *Normal SST3 staining (red) in CA1 of 9 mos old 3x-Tg mice*. Left panel 9 mos old non-Tg mice; Right panel age-matched 3x Tg mice. Note similar staining pattern and ciliary targeting of SST3 in both mouse strains. Anti-SST3 antibody 7986 gift from S. Schulz, blue staining is DAPI (nuclear).

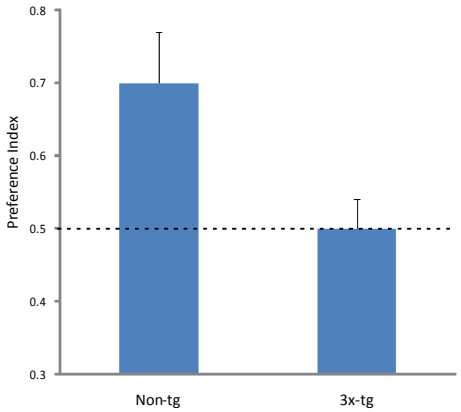

Figure 10: *ORM deficit in 3x-tg mice.* Preference index is number of approaches to the novel object over total number of approaches. Dotted line equals show no preference (0.5).

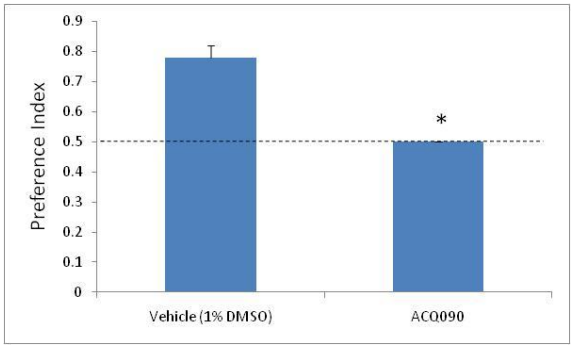

Figure 11. Bilateral intrahippocampal injection of ACQ090 impairs object recognition memory in wild type mice. Injections of vehicle or ACQ090 (20 ng bilaterally) were made 30 min prior to testing using a 1 hr retention interval. Dashed line indicates no preference; asterisk shows significant difference from vehicle injection ($p < 0.05$; paired t-test.)

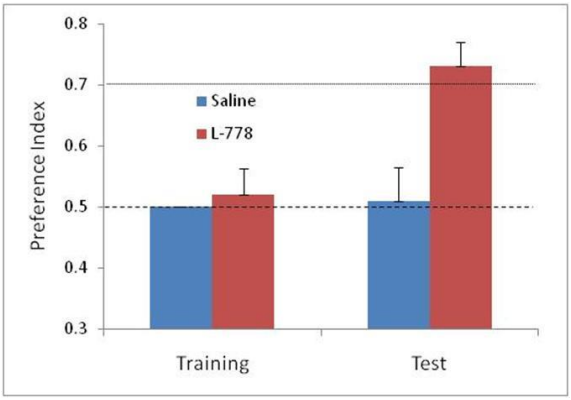

Figure 12. Bilateral intrahippocampal injection of the SST3 agonist L-796,778 rescues ORM deficits in 3x-tg mice. Injections of vehicle or ACQ090 (350 ng bilaterally) were made 30 min prior to testing using a 1 hr retention interval. Dashed line indicates no preference; dotted line shows preference index in non-tg wild type mice (see Fig. 10).

18. Extent of Clinical Activities Initiated and Completed. Items 18(A) and 18(B) should be completed for all research projects. If the project was restricted to secondary analysis of clinical data or data analysis of clinical research, then responses to 18(A) and 18(B) should be "No."

18(A) Did you initiate a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

_____Yes
___X__No

18(B) Did you complete a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

_____Yes
___X__No

If "Yes" to either 18(A) or 18(B), items 18(C) – (F) must also be completed. (Do NOT complete 18(C-F) if 18(A) and 18(B) are both "No.")

18(C) How many hospital and health care professionals were involved in the research project?

_____Number of hospital and health care professionals involved in the research project

18(D) How many subjects were included in the study compared to targeted goals?

_____Number of subjects originally targeted to be included in the study
_____Number of subjects enrolled in the study

18(E) How many subjects were enrolled in the study by gender, ethnicity and race?

Gender:
_____Males
_____Females
_____Unknown

Ethnicity:
_____Latinos or Hispanics
_____Not Latinos or Hispanics
_____Unknown

Race:
_____American Indian or Alaska Native
_____Asian
_____Blacks or African American
_____Native Hawaiian or Other Pacific Islander

_____White
_____Other, specify:_____
_____Unknown

18(F) Where was the research study conducted? (List the county where the research study was conducted. If the treatment, prevention and diagnostic tests were offered in more than one county, list all of the counties where the research study was conducted.)

19. Human Embryonic Stem Cell Research. Item 19(A) should be completed for all research projects. If the research project involved human embryonic stem cells, items 19(B) and 19(C) must also be completed.

19(A) Did this project involve, in any capacity, human embryonic stem cells?
_____Yes
__X___ No

19(B) Were these stem cell lines NIH-approved lines that were derived outside of Pennsylvania?
_____Yes
_____ No

19(C) Please describe how this project involved human embryonic stem cells:

20. Articles Submitted to Peer-Reviewed Publications.

20(A) Identify all publications that resulted from the research performed during the funding period and that have been submitted to peer-reviewed publications. Do not list journal abstracts or presentations at professional meetings; abstract and meeting presentations should be listed at the end of item 17. **Include only those publications that acknowledge the Pennsylvania Department of Health as a funding source** (as required in the grant agreement). List the title of the journal article, the authors, the name of the peer-reviewed publication, the month and year when it was submitted, and the status of publication (submitted for publication, accepted for publication or published.). Submit an electronic copy of each publication, listed in the table, in a PDF version 5.0.5 format, 1,200 dpi. Filenames for each publication should include the number of the research project, the last name of the PI, the number of the publication and an abbreviated research project title. For example, if you submit two publications for PI Smith for the "Cognition and MRI in Older Adults" research project (Project 1), and two publications for PI Zhang for the "Lung Cancer" research project (Project 3), the filenames should be:

Project 1 – Smith – Publication 1 – Cognition and MRI
Project 1 – Smith – Publication 2 – Cognition and MRI
Project 3 – Zhang – Publication 1 – Lung Cancer
Project 3 – Zhang – Publication 2 – Lung Cancer

If the publication is not available electronically, provide 5 paper copies of the publication.

Note: The grant agreement requires that recipients acknowledge the Pennsylvania Department of Health funding in all publications. Please ensure that all publications listed acknowledge the Department of Health funding. If a publication does not acknowledge the funding from the Commonwealth, do not list the publication.

Title of Journal Article:	Authors:	Name of Peer-reviewed Publication:	Month and Year Submitted:	Publication Status (check appropriate box below):
1. Somatostatin Signaling in Neuronal Cilia Is Critical for Object Recognition Memory	Emily B. Einstein, Carlyn A. Patterson, Beverly J. Ho, Kathleen A. Rega, Jyoti Reddi, David E. Melnikoff, Marcus J. Mateer, Stefan Schulz, Brian N. Johnson, and Melanie K. Tallent	Journal of Neuroscience	Oct. 2009	☐Submitted ☐Accepted ☑Published

20(B) Based on this project, are you planning to submit articles to peer-reviewed publications in the future?

Yes___X_____ No_____

If yes, please describe your plans:

We plan to submit an article on SST_3 in the 3x-tg mice, that will include our behavioral data and our immunohistochemistry.

21. Changes in Outcome, Impact and Effectiveness Attributable to the Research Project. Describe the outcome, impact, and effectiveness of the research project by summarizing its impact on the incidence of disease, death from disease, stage of disease at time of diagnosis, or other relevant measures of outcome, impact or effectiveness of the research project. If there were no changes, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

None

22. Major Discoveries, New Drugs, and New Approaches for Prevention Diagnosis and Treatment. Describe major discoveries, new drugs, and new approaches for prevention, diagnosis and treatment that are attributable to the completed research project. If there were no major discoveries, drugs or approaches, insert "None"; do not use "Not applicable."

Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

We have demonstrated that SST_3 is a valid target for treating cognitive deficits in Alzheimer's disease, since activation of this receptor restores cognitive deficits in an AD mouse model. Further, we have shown that neuronal cilia are a novel nonsynaptic signaling compartment in neurons that can be targeted to treat cognitive dysfunction. Our studies are the first to show that signaling in neuronal cilia is critical to learning and memory.

23. Inventions, Patents and Commercial Development Opportunities.

23(A) Were any inventions, which may be patentable or otherwise protectable under Title 35 of the United States Code, conceived or first actually reduced to practice in the performance of work under this health research grant? Yes_____ No___X___

If "Yes" to 23(A), complete items a – g below for each invention. (Do NOT complete items a - g if 23(A) is "No.")

a. Title of Invention:

b. Name of Inventor(s):

c. Technical Description of Invention (describe nature, purpose, operation and physical, chemical, biological or electrical characteristics of the invention):

d. Was a patent filed for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No____

If yes, indicate date patent was filed:

e. Was a patent issued for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No____
If yes, indicate number of patent, title and date issued:
Patent number:
Title of patent:
Date issued:

f. Were any licenses granted for the patent obtained as a result of work performed under this health research grant? Yes_____ No____

If yes, how many licenses were granted?_____

g. Were any commercial development activities taken to develop the invention into a commercial product or service for manufacture or sale? Yes___ No____

If yes, describe the commercial development activities:

23(B) Based on the results of this project, are you planning to file for any licenses or patents, or undertake any commercial development opportunities in the future?

Yes_____ No____X____

If yes, please describe your plans:

24. Key Investigator Qualifications. Briefly describe the education, research interests and experience and professional commitments of the Principal Investigator and all other key investigators. In place of narrative you may insert the NIH biosketch form here; however, please limit each biosketch to 1-2 pages. *For Nonformula grants only – include information for only those key investigators whose biosketches were not included in the original grant application.*

PI: Melanie K. Tallent

A. Education

Tennessee Tech. University, Cookeville, TN	BS	1982-86	Chemistry
University of Tennessee, Knoxville, TN		1987-1989	Physiology
University of Pennsylvania, Philadelphia, PA	Ph.D.	1989-1995	Neuroscience
The Scripps Research Institute, La Jolla, CA		1995-1999	Neuropharm

B. Positions and Honors

Positions:

1/90-5/95: Graduate Research Fellow, Institute of Neurological Sciences, Univ. of Pennsylvania.

6/95-11/95: Postdoctoral Fellow, Dept. of Pharmacology, Univ. of Pennsylvania.

11/95-4/98: Research Associate, Dept. of Neuropharmacology, The Scripps Research Institute.

5/98-9/99: Senior Research Associate, Dept. of Neuropharmacology, The Scripps Research Institute.

9/99-7/03: Assistant Professor, Dept. of Neuropharmacology, The Scripps Research Institute.

8/01/02-present: Assistant Professor, Dept. of Pharmacology and Physiology, Drexel University College of Medicine

Honors:

1989: Science Alliance Award, Univ. of Tennessee and Oak Ridge National Laboratories, Graduate Group in Physiology.

3/00: NINDS Travel Award for "Curing Epilepsy: Focus on the Future", a White House-initiated Conference, Washington, D.C.

NIH study section member

1999—Brain Disorders and Clinical Neurosciences, ad hoc

2002—2006 Special Emphasis Panel F03B, Molecular, Cellular, and Developmental Neurosciences, NRSA review panel, ad hoc (no permanent members because it is not a standing committee).

2004, 2006, 2009— Neurotransporters, receptors, channels and calcium signaling (NTRC), ad hoc.

2005-2006—Brain Disorders and Clinical Neuroscience (BDCN) 11: Pharmacology and Diagnostics for Neuropsychiatric Disorders Small Business, ad hoc.

2007. NCCR COBRE Special Emphasis Panel, ad hoc.

Foundation Grant Reviews

2007—Citizens United for Research in Epilepsy, research grant review, ad hoc.

2008—Wellcome Trust, United Kingdom, Project grants, ad hoc.

2009—Alzheimer's Association, research grants, ad hoc.

C. Selected Peer-reviewed Publications (out of 28)

1. **Tallent, M. K.**, Fabre, V., Qiu, C., Baratta, M. V., Lamp, T., Sánchez-Alavez, M., Suzuki, C., Calbet, M., Criado, J. R., Siggins, G. R., Henriksen, S. J., Roberts, A., and de Lecea, L. (2005) Cortistatin overexpression in transgenic mice produces deficits in synaptic plasticity and learning, Mol. Cell. Neurosci 30:465-475. PMID: 16182561, PMCID Journal-in process.
2. Qiu, C., Johnson, B. N., and **Tallent, M. K.** (2007) K+ M-current regulates the transition to seizures in immature and adult hippocampus. Epilepsia. 48 (11): 2047-2058.
3. **Tallent, M. K.** (2008) Presynaptic inhibition of glutamate release by neuropeptides: use-dependent synaptic modification. *Results Probl Cell Differ*. 44:177-200. PMID: 17554500, PMCID Journal-in process.
4. Qiu, C., Zeyda, T., Johnson, B. N., Hochgenshwender, U., de Lecea, L., and **Tallent, M. K.** (2008) Somatostatin receptor subtype 4 couples to the K+ M-current to regulate seizures and hippocampal excitability. *J. Neurosci*. 28 (14): 3567-3576 (*highlighted paper of the week*). PMID: 18385315, PMCID Journal-in process.
5. Williams, J. H., Schray, R. C., Patterson, C. A., Ayitey, S., **Tallent**, **M. K.** and Lutz, G. J. Oligonucleotide-Mediated SMN Expression and Improved Phenotype in a Mouse Model of Spinal Muscular Atrophy (2009), *J. Neurosci*. 29(24):7633–7638 *(highlighted paper of the week)*. PMID: 19535574, PMCID Journal-in process.
6. **Tallent, M. K**., Varghis, N., Skorobogatko, Y., Hernandez-Cuebas , L., Whelan , K., Vocadlo, D. J., and Vosseller, K. (2009) O-GlcNAc is a novel synaptic signaling component of hippocampal neuronal plasticity, *J. Biol. Chem.* 284(1): 174-181. PMID: 19004831, PMCID Journal-in process.
7. Einstein, E. B., Patterson, C.A., Hon, B. J., Mateer, M. J., Johnson, B. N., and **Tallent, M. K.** (2010) Somatostatin signaling in neuronal cilia is critical for object recognition memory, *J. Neurosci.*30 (12): 4306-4314.

Additional publications of importance to the field (listed chronologically)

8. **Tallent, M. K.** and Siggins, G. R. (1997) Somatostatin depresses excitatory but not
9. **Tallent, M. K.**, Madamba, S. G., and Siggins, G. R. (2001) Nociceptin reduces epileptiform events in CA3 hippocampus through pre- and postsynaptic mechanisms. *J. Neurosci*.21 (17): 6940-6948.
10. Baratta, M. V., Lamp, T., and **Tallent, M. K.** (2002) Somatostatin depresses long-term potentiation and Ca^{++} signaling in mouse dentate gyrus. *J. Neurophysiol.* 88: 3078-3086.
11. Baraban, S. C. and **Tallent, M. K.** (2004) Interneuronal Diversity series: Interneuronal neuropepeptides—endogenous regulators of neuronal excitability. *Trends in Neurosci*. 27 (3): 135-142.
12. **Tallent, M. K**. Somatostatin in the dentate gyrus. (2007) *Prog Brain Res*.163:265-84.