

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 717-231-2825.

1. **Grantee Institution:** The Pennsylvania State University
2. **Reporting Period (start and end date of grant award period):** 1/1/2011 - 12/31/2014
3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** John Anthony, MPA
4. **Grant Contact Person’s Telephone Number:** 814 935 1081
5. **Grant SAP Number:** 4100054865
6. **Project Number and Title of Research Project:** 2. *A Trial to Evaluate the Safety and Tolerability of a Novel Oral Iron Supplement for the Treatment of Iron Deficiency Anemia*
7. **Start and End Date of Research Project:** 3/1/2012 – 12/31/2014
8. **Name of Principal Investigator for the Research Project:** James R. Connor, PhD
9. **Research Project Expenses.**

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

\$50,936.95

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, First Name	Position Title	% of Effort on Project	Cost
Langan, Sara	Clinical coordinator	16%	\$7,127

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, First Name	Position Title	% of Effort on Project
Pu, Jeffrey	Medical Director	5%
Connor , James	PI	2%

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 awarded:
<i>Novel Medical Food to Treat Infant Anemia and Iron Deficiency in the CNS</i>	X NIH <input type="checkbox"/> Other federal (specify: _____) <input type="checkbox"/> Nonfederal source (specify: _)	March 2014	\$925, 216 (Subaward on a University of Wisconsin application)	\$744,820
<i>A Novel Medical Food for Management of Iron Deficiency Anemia</i>	NIH X Other federal (specify: <u>STTR application with CHYNA LLC</u>) <input type="checkbox"/> Nonfederal source (specify: _)	8/5/2014	\$90,000	\$ pending with a score of 26 (no percentile)
<i>Novel nutritional treatment for ADHD</i>	XNIH <input type="checkbox"/> Other federal (specify: _____) <input type="checkbox"/> Nonfederal source (specify: _)	2/15/2015	\$49,954 (Subaward on a University of Michigan application)	\$Pending

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 are in the process of preparing a proposal with investigators at Penn State in pediatrics and another in the Department of Nutrition. We are also preparing a NIH application with a neonatologist at University of Washington. We fully expect to pursue funding through small business funding mechanisms at NIH as we await the outcome of our first STTR that received an outstanding score of 26. We have also submitted a proposal to the Gates Foundation.

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

We plan to continue to obtain data in additional clinical studies while initial efforts are made to market the product. A manufacturer has been identified and a business entity has been established to pursue the goal of reaching the market in 2015.

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 _____ No X _____

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

	Undergraduate	Masters	Pre-doc	Post-doc
Male				
Female				
Unknown				
Total				

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

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

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 _____ No X _____

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

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 agreement). Summarize the progress made in achieving these goals, objectives and aims for the period that the project was funded (i.e., from project start date through end date). 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 (β) should not print as boxes (\square) and include the appropriate citation(s). DO NOT DELETE THESE INSTRUCTIONS.

The primary objective of this project is to demonstrate the safety and tolerability of a novel oral iron supplement. The secondary objective is to begin to evaluate efficacy and identify a potential therapeutic dose of this novel oral iron supplement.

Aim: Perform a pilot study on iron deficient human subjects to determine safety, tolerability, and iron absorption rates using our oral iron supplement.

Background: We will test a novel approach to managing iron deficiency. We have a medical food that is composed of nutritional yeast that has been biotechnologically modified to express ferritin. Ferritin is a protein that normally occurs in plants, humans and animals and allows cells in the body to store iron in sufficient levels to meet energy requirements. Dr. Connor's group discovered that ferritin, particularly the form found in human breast milk and used in the nutritional yeast in this study, has the ability to deliver iron and not just store it.

The main function of ferritin is to store iron and make it available in cells so that they can use the oxygen needed for metabolic processes (i.e. generation of energy). Humans, animals and plants share the need to use oxygen so they have evolved a similar strategy of storing iron in ferritin so the iron can be readily available in cells. Plant and animal ferritins are similar in structure in addition to being similar in function. The reason that we cannot simply eat animal products or plants to obtain sufficient ferritin and iron in our diet is that the amounts of ferritin and iron in the plant and animal tissue vary widely because the amount of iron and ferritin they contain is a product of the environment in which the plants and animals are raised.

Connor and collaborators developed a method for delivering ferritin and iron in a safe and economical manner; namely nutritional yeast. Another advantage of the use of nutritional yeast is that it provides ferritin and iron in yeast that are grown in controlled laboratory conditions so that the iron and ferritin content are known and reliable. The manufacturer of the yeast for this study is Vivolac Cultures Corporation/Lyoferm Incorporated (Indianapolis IN). All products are made complying with the Good Manufacturing Practices (GMP) procedures as listed by the FDA in the Code of Federal Regulation CFR 21 110.

The test product is not a dietary supplement. The FDA determined in a pre-IND meeting on February 22, 2010 that the test product is not a drug (IND 103,455). The product meets the regulatory requirements for production and standard set by the FDA as a medical food. That standard is as follows:

FDA considers the statutory definition of medical foods to narrowly constrain the types of products that fit within this category of food. Medical foods are distinguished from the broader category of foods for special dietary use and from foods that make health claims by the requirement that medical foods be intended to meet distinctive nutritional requirements of a disease or condition, used under medical supervision, and intended for the specific dietary management of a disease or condition. . . . medical foods are foods that are specially formulated and processed (as opposed to a naturally occurring foodstuff used in a natural state) for a patient who is seriously ill or who requires use of the product as a major component of a disease or condition's specific dietary management.

-Medical Food Guidance Document: FDA

All of the components in our medical food meet the FDA definition of food, and the product is specially formulated for dietary management of iron deficiency, and the product is taken orally.

The FDA has clearly articulated that a medical food must be specially formulated from components that are food. The definition of food from the FDA is: The term "food" means: (1) articles used for food or drink for man or other animals: (2) chewing gum: and (3) articles used for components of any such article.

The medical food we developed consists of three key elements.

- *Saccharomyces cerevisiae* yeast. This yeast is a widely available nutritional strain. The yeast are biotechnologically modified to produce and contain within its cell body the human protein ferritin and the product undergoes a high heat drying process resulting in inactive yeast.
- Ferritin is a natural protein found in mammals and plants. It is consumed in many diets and is known for its ability to sequester and deliver iron. The H-form of ferritin, used in the medical food, is enriched in human breast milk. Thus ferritin is the natural mechanism for mothers to pass iron to their infants.
- Iron is the element needed for repletion of individuals with iron deficiency. The iron is bound within ferritin which enables the yeast to accumulate therapeutic levels of iron.

To deliver the ferritin, a common strain of yeast already in use as a nutritional product technically known as *Saccharomyces cerevisiae* (the nutritional strain of yeast) is used. Yeast is a food constituent in many products around the world and has a long history of being orally consumed. This strain of yeast has had the gene for human H-ferritin stably inserted into its genome and this is the only alteration to the yeast. Specifically, there is no plasmid in the yeast. Stable insertion of the human H-ferritin gene into the yeast chromosome also permits a consistent level of expression of ferritin by the yeast. The yeast for our novel iron supplement is grown in an iron rich medium and the presence of the H-ferritin allows the yeast to accumulate iron and sequester the iron in ferritin which allows the yeast to safely accumulate the iron and makes the iron more readily bioavailable to humans. The H-ferritin protein is highly conserved in the animal and plant kingdom and is thus consumed in meats and some plant products such as soybeans. Human H-ferritin is given in large doses as part of the blood during blood transfusions with no known reported cases of a reaction or a safety concern. In addition, human ferritin is consumed by babies who nurse as this protein is a component of breast milk. Thus, the test product in this study can be expected to be both safe and effective as indicated by the animal studies.

Approach:

The study design that was approved by the Penn State IRB in 2010 is a standard “3+3” rule-based dose-escalation schemes, which use predetermined dose levels and cohorts of three patients. The scheme consists of the following rules: 1) Enter three patients at the lowest dose level; 2) If none of three patients experiences dose limiting toxicity (DLT), defined as GI discomfort described by the subject as intolerable and adverse event (AE) or side effect classified as severe and related to the novel oral iron supplement after one month, a new cohort of 3 subjects will be enrolled at the next Level dose for 30 days. 2) If one of three patients experiences DLT at the current dose, three more subjects will be enrolled at that dose and an independent evaluation will be made to determine if the AE is directly attributable to the study material. 3) If more than one patient experiences DLT at any dose level, then the trial is stopped to determine if the AEs are directly attributable to the study material. 4) the maximum tolerated dose is declared to be the dose at the level immediately below that at which the trial was stopped.

After the initial approval, we worked with two commercial manufacturers to meet the scale up requirements for the human study. After considerable negotiation with the world’s largest manufacturer of yeast (Lesaffre, France) that lasted over a year, they could not meet our requirements under the conditions that we needed. We then were introduced to Vivolac Inc which has turned out to be an outstanding collaboration. During this time we acquired additional pre-clinical data which showed considerably better efficacy than ferric ammonium sulfate (standard of care) so we modified the proposed dosing schedule in the IRB study to lower the upper level doses. The study design approved by the IRB was:

The study will begin with 3 patients meeting criteria. These individuals will receive 300 mg tablets of the novel oral iron supplement. The iron content of these tablets is 9mg. Our initial dose is set at 18 mg of iron. This dose was chosen as the initial starting dose because it contains the RDA for iron for adult women. Thus this dose is considered the minimum that would be

utilized in any setting for maintenance of a healthy iron status. The dosing increases to a maximum of 108 mg of iron per day which is significantly below the standard amount of iron (165-195mg per day) recommended for an iron deficient individual or the amount of iron given intravenously (1000 mg) for some iron deficient conditions.

When we submitted the request to the IRB for the lower dose, we also requested a change in medical director of the study because the initial director had retired. It was determined that changing the medical director and lowering the dose required a full IRB review. We submitted all the documentation that the IRB had requested when they first approved the study in August of 2013. The IRB had multiple new questions with this review and did not re-approve the study until April of 2014. At that time we immediately had the product shipped to our pharmacy at Penn State Hershey Medical Center. The PI then learned that the pharmacist was not comfortable with the IRB approved bottles that contained the yeast and we reprinted all labels and obtained new bottles. We enrolled the first subject on 6/3/14.

Results:

During the summer of 2014, we had 37 screen failures because they did not meet eligibility criteria. We learned that potential subjects in the hematology/oncology clinic met at least one and usually multiple exclusion criteria so we requested and received approval from the IRB to expand our search to Family and Community Medicine clinics. We were unable to successfully recruit from those clinics unfortunately. We also had fliers approved for posting but they were not posted until October 2014 and our study was not listed among the on-going clinical studies at Penn State Hershey until November of 2014. The PI has an appropriately strict conflict of interest monitoring plan and could not be involved in any type of patient recruitment.

From May 2014 to end of the funded study period (December 31, 2014) 169 subjects were screened. All but two of these were screen failures. The reason for the screen failures (% of those meeting the exclusion criteria shown) are as follows:

- o IBS = 4.3%
- o Chronic, active Auto-immune = 4.9%
- o HIV = 0.5%
- o Tobacco Abuser = 8.1%
- o Iron / Hemoglobin counts too high = 16.2%
- o Hemoglobin counts too low = 0.5%
- o Asthma = 9.7%
- o Other Anemias = 3.8%
- o Serious Heart Condition (CAD, CHF, A Fib, etc) = 16.8%
- o Active GI Bleed = 1%
- o CKD = 4.3%
- o Cancer = 8.6%
- o Pregnant = 0.5%
- o Currently on another clinical trial = 0.5%
- o History of non-compliance/ scanty med records / told not to enroll by PCP or hematologist = 4.9%
- o Chose not to participate = 1% - all chose not to participate due to time

commitment (number and length of clinic visits in particular)

Two subjects were enrolled in the study on the low entry dose and completed 28 days on the test product. A number of analyses were performed on these individuals. The 18mg of iron contained in the entry level dose is significantly below the standard amount of iron (165-195mg per day) recommended for an iron deficient individual and below what our pre-clinical data suggested would be the therapeutic dose but we started at the low dose because this study is for safety and tolerability. Indeed, the two subjects enrolled for 28 days did not report any adverse events or discomfort associated with taking the test product.

In Table 1 are the safety values obtained for the two subjects:

Subject 1	BUN	Creatinine	AST	AST2	Alkaline Phosphatase
Screening	13	0.61	33	32	71
Day 14	14	0.69	32	25	68
Day 28	12	0.74	24	25	73
Subject 2					
Screening	15	0.61	24	30	35
Day 14	13	1.55	31	22	33
Day 28	13	0.66	23	29	32

Table 2: Values associated with iron status:

Subject 1	Hemoglobin	Hematocrit	TIBC	Serum Ferritin	MCV
Screening	9.5	29	481	5.2	80.6
Day 14	8.8	27.8	472	4.8	68
Day 28	9.1	29.3	479	4.8	73
Subject 2					
Screening	10.4	32.5	373	8	35
Day 14	10.6	33.3	380	5.8	33
Day 28	10.0	32.5	389	5.3	32

Conclusions:

Although only two subjects were enrolled we can report no toxicity at the entry dose. It was expected at this low dose that the patients may continue on the course of anemia which was the case as indicated by the decrease in TIBC over the course of the treatment. It is important to note that the hemoglobin and hematocrit levels did not decrease over the course of the treatment indicating there was no suppression of hematopoiesis. The recommendation of the medical director, Dr. Pu, was to enroll the next group of subjects at the Level 2 dose. We approached the IRB with this request but unfortunately time has expired on this project and remaining funds will

be returned. As noted in Question 11, we have been able to leverage this proposal and have a STTR application to the NIH that received a score of 26 (no percentile) and we are awaiting a funding decision. The summary statement on our critique stated : “*The committee’s overall evaluation was that the likelihood would be excellent for the project to exert a powerful, sustained influence on the field of dietary management for iron deficiency anemia*”. This project will continue using other funds.

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
 No

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

Yes
 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?

 2 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?

 15 Number of subjects originally targeted to be included in the study
 2 Number of subjects enrolled in the study

Note: Studies that fall dramatically short on recruitment are encouraged to provide the details of their recruitment efforts in Item 17, Progress in Achieving Research Goals, Objectives and Aims. For example, the number of eligible subjects approached, the number that refused to participate and the reasons for refusal. Without this information it is difficult to discern whether eligibility criteria were too restrictive or the study simply did not appeal to subjects.

18(E) How many subjects were enrolled in the study by gender, ethnicity and race?
Because research is ongoing, PI is unable to answer these questions.

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.)

Dauphin County

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
 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 or paper submitted for publication, listed in the table, in a PDF version 5.0.5 (or greater) format, 1,200 dpi. Filenames for each publication should include the number of the research project, the last name of the PI, and an abbreviated title of the publication. For example, if you submit two publications for Smith (PI for Project 01), one publication for Zhang (PI for Project 03), and one publication for Bates (PI for Project 04), the filenames would be:

- Project 01 – Smith – Three cases of isolated
- Project 01 – Smith – Investigation of NEB1 deletions
- Project 03 – Zhang – Molecular profiling of aromatase
- Project 04 – Bates – Neonatal intensive care

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. None				<input type="checkbox"/> Submitted <input type="checkbox"/> Accepted <input type="checkbox"/> Published

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

Yes _____ No X

If yes, please describe your plans:

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.

None

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 ___ X ___ No _____

If yes, please describe your plans:

Patents (US, EU) have already been awarded for the technology. We have formed a company (CHYNA LLC) to undertake the commercial development of the product. The goal of the company is to obtain a licensing partner for commercialization of the product.

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.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.

NAME James R. Connor, Ph.D.		POSITION TITLE Distinguished Professor	
eRA COMMONS USER NAME (credential, e.g., agency login) James_R_Connor			
EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)			
INSTITUTION AND LOCATION	DEGREE (if applicable)	MM/YY	FIELD OF STUDY
Thomas More College, Ft. Mitchell, KY	B.A.	05/1975	Psychology
Wright State University, Dayton, OH	M.S.	06/1978	Physiology
University of California, Berkeley, CA	Ph.D.	05/1981	Anatomy
Boston University Medical Center, Boston, MA	Postdoc	07/83	Neuroscience

A. Personal Statement

Overall accomplishments, expertise, and contributions to field of iron deficiency. I am an internationally recognized leader in the field of brain iron metabolism. My H-index is 64 with over 1600 citations over the last 2 years. I have been privileged to maintain a continuously funded program with funding from 5 different NIH agencies and numerous foundations. This funding has allowed me to lead investigations into many aspects of brain iron metabolism including, oxidative stress, the role of iron in myelin and oligodendrocyte function, mechanisms and regulation of brain iron transport. My work has led to understanding basic pathophysiology of diseases such as Alzheimer's, Parkinson's, multiple sclerosis and restless legs syndrome. In the course of determining brain iron uptake mechanisms, I discovered that iron could enter the brain in the absence of transferrin. This observation led to a series of investigations resulting in the discovery of a ferritin receptor in the brain. Subsequently, I developed a mechanism for providing ferritin in yeast as a medical food. We have received both US and EU patents for this innovative technology.

B. Positions and Honors

Professional Positions:

1983-1987 Research Biologist, Veteran's Administration Medical Center, Washington, DC
 1983-1987 Assistant Research Professor, Department of Physiology, The George Washington University School of Medicine
 1987-1990 Assistant Professor, Department of Anatomy Pennsylvania State University College of Medicine (PSUCOM) Neuroscience & Anatomy, (PSUCOM)
 1990-1996 Associate Professor, Department of Neuroscience & Anatomy, (PSUCOM)
 1996- Professor, Department of Neuroscience & Anatomy, (PSUCOM)
 1999-2002 Vice Chair Department of Neuroscience & Anatomy, (PSUCOM)
 2002-2003 Interim Chair Department of Neuroscience & Anatomy, (PSUCOM)
 2004- Professor Neurosurgery, (PSUCOM)
 2006 Co-Director, Neuro-oncology Experimental Therapeutic Group (PSU Cancer Institute)
 2007 University Distinguished Professor (PSUCOM)
 2007- CEO and Founder, CHYNA LLC

Grant Review Experience:

NIH, NIEHS, Veterans Administration, Department of Defense USDA, NSF, MRC, Wellcome

Trust, Israel Academy of Science, Alzheimer's Association, Hong Kong Research Council, American Federation for Aging Research, American Heart Association

Honors and Awards:

Samuel Hinkle Society Outstanding Young Investigator Award, Pennsylvania State University College of Medicine (1990);

Mentored two graduate students awarded Marion Kies Award by the American Society for Neurochemistry for outstanding doctoral thesis (Sara Robb, Ph.D., 1999; Bozho Todorich, M.D., Ph.D., 2010);

Elected Chair of the East Coast Iron Club (2000-2002);

Dean's Lecturer Pennsylvania State University College of Medicine/M.S. Hershey Medical Center (2003);

Distinguished Alumni Award, Thomas More College (2007);

Named University Distinguished Professor Penn State University (2007);

Honorary Professor, Department of Neurology, Tianjin First Center Hospital, Tianjin (2008-)

Patents:

US Patent No. 12/021/922 *Use of Ferritin to Treat Iron Disorders*

U.S. Patent No. 13/114,429 *Use of Ferritin to Treat Iron Disorders (CIP)*

Editorial Boards:

Journal of Neuroscience Research (1994-); *GLIA* (2001-); *Fluids and Barriers of the CNS* (2004-); *Current Neurovascular Research* (2004-); *CNS Drug Discovery* (2005-); *Recent Patents on Biotechnology* (2008-); *Journal of Neurochemistry* (Handling Editor, 2011-); *PlosOne* (2012-).

C. Selected Peer-reviewed Publications.

1. Ward LK, Tkac I, Jing Y, Felt B, Beard J, **Connor J**, Schallert T, Georgieff MK, Rao R. Gestational and lactational iron deficiency alters the developing striatal metabolome and associated behaviors in the young rat. *J Nutr*; 137:1043-1049, 2007.
2. Geguchadze RN, Coe CL, Lubach GR, Clardy TW, Beard JL, and **Connor JR**. CSF proteomic analysis reveals persistent iron deficiency-induced alterations in nonhuman primate infants. *J Neurochem*;105(1):127-136, 2008.
3. Mitchell RM, Freeman WM, Randazzo WT, Stephens HE, Beard JL, Simmons Z, **Connor JR**. A CSF biomarker panel for identification of patients with Amyotrophic Lateral Sclerosis. *Neurology*; 72(1):14-19, 2009.
4. Allen RP, **Connor JR**, Hyland, K. Earley CJ: Abnormally increased CSF 3-Orthomethylidopa (3OMD) in untreated restless legs syndrome (RLS) patients indicates more severe disease and possibly abnormally increased dopamine synthesis. *Sleep Med*; 10(1):123-128, 2009. PMID: 2655320
5. Mitchell RM, Beard JL, Stephens HE, Simmons Z, **Connor JR**. Plasma Biomarkers Associated with ALS and their Relationship to iron Homeostasis. *Muscle Nerve*; 42(1):95-103, 2010.

Ferritin:

6. Fisher J, Devraj K, Ingram J, Slagle-Webb B, Madhankumar AB, Klinger M, Simpson IA, **Connor JR**. Ferritin: A novel mechanism for delivery of iron to the brain and other organs. *Am J Physiol Cell Physiol*; 293(2):C641-C649, 2007.
7. Hulet S, Hess EJ, Debinski W, Arosio P, Bruce K, Powers S, and **Connor JR**. Characterization and distribution of ferritin binding sites in the adult mouse brain. *J Neurochem* 72:868-874, 1999.

8. Hulet SW, Heyliger SO, Powers S, and **Connor JR**. Oligodendrocyte progenitor cells internalize Ferritin via Clathrin-dependent receptor mediated endocytosis. *J Neurosci Res*; 61(1):52-60, 2000.
9. Hulet SW, Menzies SL, and **Connor JR**. Ferritin binding in the developing mouse brain follows a pattern similar to myelination and is unaffected by the jimpy mutation. *Dev Neurosci*; 24:208-231, 2002.

Myelin and iron deficiency:

10. Beard JL, Wiesinger JA, Li N and **Connor JR**. Brain iron uptake in hypotransferrinemic mice: Influence of systemic iron status. *J Neurosci Res*; 79(1-2):254-261, 2005.
11. Badaracco ME, Ortiz EH, Soto EF, **Connor JR**, Pasquini JM: Effect of transferrin on hypomyelination induced by iron deficiency. *J Neurosci Res*; 86(12):2663-2673, 2008.
12. Todorich B, Zhang X, Slagle-Webb B, Seaman WE, **Connor JR**: Tim-2 is the receptor for H-ferritin and oligodendrocytes. *J Neurochem*; 107:1495-1505, 2008.
13. Ortiz E, Pasquini JM, Thompson K, Felt B, Gutkus G, Beard J, and **Connor JR**. Effect of manipulation of iron storage, transport or availability on myelin composition and brain iron content in three different animal models. *J Neurosci Res*; 77(5):681-689, 2004.
14. Todorich B, Xhang X, **Connor JR**. H-Ferritin is the major source of iron for oligodendrocytes. *Glia*; 59(6):927-35, 2011.
15. Patton SM, Coe CL, Lubach GR, and **Connor JR**. Quantitative Proteomic Analyses of Cerebrospinal Fluid Using iTRAQ in a Primate Model of Iron Deficiency Anemia. *Dev Neurosci*. 34(4):354-65 2012.

D. Ongoing Research Support

National Institutes of Health R01CA169117091 (Rich/Connor – Multi-PI) 07/01/13 – 04/30/18
Glioblastoma Therapy through Ferritin Targeting

Grant U01NS082151 (Huang PI; Connor-Co-I) 09/30/12 – 08/31/17

National Institute of Neurological Disorders and Stroke

Multimodal MRI Markers of Nigrostriatal Pathology in Parkinson's Disease

Elekta Instrument AB (McInerney PI; Connor Co-I) 02/01/07 – 06/30/15

Gamma Knife Radiosurgery for Aneurysms --- Animal Studies

Woodward Endowment (Connor) 07/01/13 – 06/30/15

Targeted Deliver of a Potent Anti-proliferative Metal Chelator to Brain Tumors

National Institutes of Health (Connor/Simpson – Multi-PI) 09/01/11 – 06/30/16

R01 NS077678 *Mechanisms and Regulation of Brain Iron Uptake*

Judith and Jean Pape Adams Charitable Foundation 01/01/15 – 12/31/15

Genotype Specific Impact of Nuclear Factor E2-Related

Factor 2 (Nrf2) In Animal Models of Amyotrophic Lateral Sclerosis

Albert Einstein College of Medicine (Aschner PI, Connor- Consortium PI) 11/01/13 – 10/31/16

R01 ES010563 NIH Subaward *Mechanisms of Manganese Neurotoxicity*