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Award Number: DAMD17-03-1-0057

TITLE: Pharmacological and Nonpharmacological Methods of
Treatment for Fragile X Syndrome

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REPORT DATE: February 2005

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
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20050621 048

REPORT DOCUMENTATION PAGEForm Approved
OMB No. 074-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503

1. AGENCY USE ONLY (Leave blank)		2. REPORT DATE February 2005	3. REPORT TYPE AND DATES COVERED Annual (1 Feb 2004 - 31 Jan 2005)	
4. TITLE AND SUBTITLE Pharmacological and Nonpharmacological Methods of Treatment for Fragile X Syndrome			5. FUNDING NUMBERS DAMD17-03-1-0057	
6. AUTHOR(S) David H. Perlmutter, M.D.				
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Children's Hospital of Pittsburgh Pittsburgh, PA 15213 E-Mail: David.Perlmutter@Chp.Edu			8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012			10. SPONSORING / MONITORING AGENCY REPORT NUMBER	
11. SUPPLEMENTARY NOTES				
12a. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited				12b. DISTRIBUTION CODE
13. ABSTRACT (Maximum 200 Words) Fragile X (FX) syndrome causes behavioral disturbances such as labile mood, anxiety, hyperactivity, and aberrant behavioral responses to stress. Affected males may suffer from learning disabilities, attention deficit disorders, mental retardation, or autism spectrum disorders. We seek to address the most effective methods of treatment (pharmacological and behavioral) for the symptoms and behavioral problems associated with FX syndrome. During the past year, we have established a comprehensive FX syndrome clinic and we continue to refine our treatment protocol. Collaborative relationships have been established with genetics, speech/language, psychiatry, and dental so that families can obtain these services from specific professionals with an interest in FX syndrome. School liaison services for school aged youth with FX syndrome have been established. Community education programs, in the form of a website, a parent advisory group, and newsletters have been established. We continue to refine our database to track the frequency of the disease and specific symptoms with the goal of guiding future treatment through evidence based medicine.				
14. SUBJECT TERMS Learning disabilities; attention deficit disorder; mood liability; Anxiety states, hyperactivity, behavioral response to stress				15. NUMBER OF PAGES 9
				16. PRICE CODE
17. SECURITY CLASSIFICATION OF REPORT Unclassified	18. SECURITY CLASSIFICATION OF THIS PAGE Unclassified	19. SECURITY CLASSIFICATION OF ABSTRACT Unclassified	20. LIMITATION OF ABSTRACT Unlimited	

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ANNUAL REPORT: DAMD 17-03-1-0057

Pharmacological and Nonpharmacological Methods of Treatment of
Fragile X Syndrome
02/01/04 – 01/31/05

INTRODUCTION:

The Child Development Unit, Center for Neurosciences, and Division of Genetics of the Children's Hospital of Pittsburgh (CHP) are seeking to address the most effective methods of treatment – both pharmacological and nonpharmacological -- for the symptoms and behavioral problems associated with Fragile X (FX) syndrome.

This program will feature the recruitment of children with this disorder in order to conduct physiological and behavioral testing, with the goal of early intervention.

An intervention study will supply groundbreaking data on the behavioral phenotype of children with FX syndrome for a national registry database.

This initiative will establish a basic research program including development of genetically engineered mouse and primate models of the syndrome to determine the mechanism of, and potential novel treatments for symptoms of FX syndrome.

STATEMENT OF HYPOTHESIS

FX syndrome causes behavioral disturbances such as labile mood, anxiety states, hyperactivity, and aberrant behavioral responses to stress. Affected males may suffer learning disabilities, attention deficit disorders, mental retardation, and autism spectrum disorder. The Child Development Unit, Center for Neurosciences, and Division of Genetics at the Children's Hospital of Pittsburgh (CHP) now seek to address the most effective methods of treatment – both pharmacological and nonpharmacological – for the symptoms and behavioral problems associated with FX syndrome. This initiative features the recruitment of children with this disorder to conduct physiological and behavioral testing, with the goal of early intervention. The resulting “interventional study” will supply groundbreaking data on the behavioral phenotype of children with FX syndrome for a national registry database. Finally, this initiative will establish a basic research program including development of genetically engineered mouse and primate models of the syndrome to determine the mechanism of, and potential novel treatments for symptoms of FX syndrome. Because the behavioral symptoms occurring in youth with FX syndrome also occur commonly in non-FX subjects and may affect the behavioral responses to stressful conditions, the overall program will have an impact on military personnel as well as children and families affected by FX syndrome.

OBJECTIVES

1. To establish a clinical center for diagnosis and treatment of individuals with FX syndrome
2. Provide community service and professional education about FX syndrome
3. To develop a registry for FX patients and their families
4. To establish a basic research laboratory dedicated to studies on the pathobiology of neurobehavioral disturbances in FX syndrome, with a particular focus on new genetically engineered animal models of the syndrome

ACCOMPLISHMENTS (Year 2/1/04 – 1/31/05)

Objective 1: To establish a clinical center for diagnosis and treatment of individuals with FX syndrome

- Dr. Robert Noll was hired and became the co-principal investigator. Dr. Noll is the Division Chief of Developmental and Behavioral Pediatrics at the Child Development Unit, Assistant Medical Director of Behavioral Health at Children's Hospital, and Professor of Pediatrics, Psychiatry, and Psychology at the University of Pittsburgh. Dr. Noll is an internationally recognized NIH funded investigator with considerable experience in studies of behavioral outcome and conducting randomized trials of behavioral interventions within pediatrics. He is currently seeing all referred patients with FX syndrome and their families during comprehensive care visits.
- Dr. Dena Hofkosh was appointed Clinical Medical Advisor of the FX Center following the departure of Dr. Carol Delahunty who accepted a position at Children's Hospital Akron. Dr. Delahunty's resignation was effective 6/30/04.
- Rebecca Kronk, CRNP was appointed Clinical Coordinator. Ms Kronk is a board certified nurse practitioner who completed her MSN from the University of Pittsburgh and is currently pursuing a doctorate in Applied Development Psychology in the School of Education at the University of Pittsburgh. She has been in the field of pediatric nursing for 26 years. She is adjunct faculty at the School of Nursing at the University of Pittsburgh and has been actively involved in leadership training for health care professionals to work with families with children with disabilities.
- The FX Syndrome clinic established clinic time to occur the first Tuesday of each month.
- We have a protocol for the clinical care of FX patients in the Center.

Neurobehavioral Assessment:

Children with Fragile X and their families are seen by a psychologist for a comprehensive evaluation. The evaluation depends on the age of the child, developmental level, and behavioral differences. It also focuses on parent distress and parent child interactions.

Behavioral Consultation:

Children seen in the FX Center receive behavioral consultation services by Dr. Robert Noll at the initial visit and ongoing as needed for subsequent visits. Educational evaluations done by outside sources are being reviewed for input and recommendations. School consultation services are now available for parents along with educators.

Comprehensive Medical Evaluation:

Children will be seen as needed but not less frequently than annually by the Clinical Coordinator, a board certified pediatric nurse practitioner with expertise in FX syndrome. On site consultation is available as needed by a CDU Developmental Behavioral Pediatrician along with input from Dr. Noll. Individuals manifesting specific medical problems are referred to appropriate specialists.

Psychopharmacology Evaluation:

For those children with FX who are possible candidates for psychopharmacologic treatment, a consultation is available. Medication management is available for those families if distance is prohibitive. A collaborative relationship has been established with Western Psychiatric Institute as a primary resource for consultations and medication management.

- We continue to develop an interdisciplinary clinic for ongoing evaluation and treatment. Disciplines working collaboratively with the FX Center include communication disorders, psychology, developmental pediatrics, dental, and genetics.
 - The goals of the above disciplines working collaboratively is to facilitate family referrals for evaluation and treatment in the FX clinic, as well as referrals to ancillary disciplines when needed, to improve functional outcomes, and to keep families abreast of most current information including research studies that might be of interest.
 - Speech/language Therapists:
 - Kristine Campbell (CHP South satellite)
 - Joyce O'Keefe (CHP East satellite)
 - Genetics:
 - Ellen Sowry (CHP main site)
 - Dental:
 - Brian Martin, DDS
 - Developmental-Behavioral Pediatrician
 - Dena Hofkosh, M.D.
- Dr. Robert Noll and Rebecca Kronk, CRNP have established a relationship with the National Fragile X Foundation and keep them informed about the FX clinic at Children's Hospital of Pittsburgh. The FX Foundation newsletter, soon going to press, will feature an announcement about the FX Center at Children's Hospital. Persons calling the National FX Foundation to find

resources in Western Pennsylvania or the surrounding areas will be provided information about the CHP FX Clinic.

- We have established a community education program for FX syndrome. FX clinic interdisciplinary team members are offered the quarterly newsletter about research, tips on behavioral management, and information about upcoming educational events such as web casts. A set of educational materials, donated to the FX clinic at CHP by the National FX Foundation, forms the basis for the ongoing development of a lending library. This library is available to FX clinic interdisciplinary team members and families of children seen in the clinic.
- A parent handbook of information, including a quick reference of useful resources, electronic resources, and frequently called phone numbers as well as extensive information provided by the National FX Foundation, has been developed as a resource guide for families. This parent handbook is given to all families of children with FX syndrome who are followed at our Center.
- We have developed a brochure which has been reviewed by Michael Tranfaglia, MD, Medical Director of FRAXA Research Foundation, parent representatives, and Public and Government Affairs. This brochure is being distributed to parents, health care providers, and other community members involved in the coordination of care of children with FX syndrome. The purpose of the brochure is to increase awareness of the incidence of FX syndrome; provide and quickly disseminate information to families seeking the services of the FX clinic; primary care physicians; and other providers of service.
- With Public and Government Affairs of CHP, we are developing the CHP FX Clinic website. This website will enhance access to information about the clinic and provide links to other Local and National resources. Beta testing is currently underway.

Objective 2: Provide community service and professional education about FX syndrome

- Dr. Noll and Rebecca Kronk attended the 9th National FX Conference. Extensive networking has resulted in a working relationship with individuals at the local, state, and national level.
 - Locally -- Two meetings have been held with parents of children with FX syndrome to discuss how the FX Clinic might better address the needs and concerns they have for their children. The group decided to form a parent advisory group to work collaboratively with the staff of the FX Clinic and the ancillary interdisciplinary team members of the Clinic. The group discussed the need for web site development for the FX Clinic and reviewed the proposed draft brochure and the parent handbook to be offered to each family seen through the FX Clinic.

- State --- Dr. Noll has established contact with Mr. William Parker in Harrisburg. The Parkers (William and Debra) are interested in establishing a parent support network in Pennsylvania as well as securing funding sources for FX clinical services. Dr. Noll has been working with this family to facilitate their goals and ensure that the CHP clinic is providing necessary support.
- Nationally --- A meeting facilitated by the local parent advisory group, was held at the Child Development Unit with Dr. Michael Tranfaglia, Medical Director of FRAXA Research Foundation. Dr. Tranfaglia offered the support of FRAXA as well as his own support of the establishment of the clinic.
- We are planning the following goals for next year.
 - We are developing a primary care physician packet of information which will include the CHP FX clinic brochure; information about the recommended lab protocol for diagnostic testing when there is a suspicion of FX syndrome; and the American Academy of Pediatric Practice Guidelines of Care for patients with FX syndrome. CHP Public and Government Affairs will assist us in the distribution of these packets to primary care physicians. The purpose will be to increase awareness of the primary care physician of the frequency and incidence of FX syndrome within their practice, inform them about current updates on FX syndrome, and about services offered to families through our center and the collaborating interdisciplinary team members.
 - A regional FX syndrome conference is being planned for an audience of parents and professionals involved in the health care of patients with FX syndrome. We are hopeful that Dr. Michael Tranfaglia, Medical Director of FRAXA Research Foundation, will be available as our keynote speaker.
 - A parent advisory group will be finalized and a working relationship maintained between the parent advisory group and the FX syndrome Clinic.

Objective 3: To develop a registry for FX syndrome patients and their families

- We have developed a database to assess the frequency of different medical, psychological, and developmental disorders in individuals with FX syndrome. The database includes mutation status and IQ test results. During the next year this will be expanded to include psychometric behavioral data from primary caregivers and for older children, teachers.

This will allow further refining of the recommendations set forth by the American Academy of Pediatrics in "Health Supervision for Children with Fragile X syndrome:" (*Pediatrics* Vol. 98, No. 2, 1996, pp. 297-300). This would improve quality of care by primary care physicians for individuals with FX syndrome.

Systemic evaluation of responses to interventions (medical, developmental, and behavioral) to guide future treatment through evidence based medicine. Evaluation of responses of individuals with FX syndrome treated for medical, behavioral, or developmental disorders will help clarify if response is similar to that of individuals without FX syndrome.

We are now planning the following goals for next year.

- To facilitate inclusion of our families in ongoing clinical research programs for individuals with FX syndrome. This would be made possible by increases in the number of individuals with FX syndrome served by the clinic.
- To disseminate information about existing research studies, endorsed, and supported, in progress at other institutions to increase the fund of knowledge about FX syndrome.
- To collect, interpret, and publish data
 - Individuals with premutation, i.e., present symptomatology of children with permutation
 - Carrier status, i.e., FRAXTA, FX syndrome, tremors, ataxia, and premature ovarian failure, examining its trans-generational effects.

Objective 4: To establish a basic science research laboratory

- A search committee of Dr. Perlmutter, PI, Chair of Pediatrics, Dr. Robert Noll, Chief of Child Development Unit, Dr. Jerry Vockley, Chief of Genetics, Dr. Nina Schor, Chief of Neurology, and Dr. Ron Dahl, WPIC, continues its search in recruiting a senior scientist.

REPORTABLE OUTCOMES

There have been no publications or grant applications this year.

CONCLUSIONS

The CHP FX syndrome center is continuing to emerge as an entity gaining recognition locally as well as nationally and addressing the needs families and children with a diagnosis of FX syndrome.