Penn Medicine
Center for Orphan Disease
Research and Therapy

CENTER FOR ORPHAN DISEASE RESEARCH AND THERAPY
IMPROVED THERAPIES FOR RARE DISEASES
Postdoctoral Fellowship Application

Cover Page

PI Name: **Annette Bley, MD**
PI Title: **Pediatrician**
PI Institution: **Department of Pediatrics, University Hospital, Hamburg Eppendorf, Germany**

Mentor Name: **Florian Eichler, MD**
Mentor Title: **Associate Professor of Neurology MD**

Project Title: **Quantitative description of the clinical course of Canavan disease**

Rare Disease: **Tay-Sachs and related**

Human Subjects Research: ✓ Yes (Please attach IRB approval letter) ☐ No

Animal Research: ☐ Yes (Please attach IACUC approval letter) ✓ No

Abstract (Up to 250 words):
Canavan disease (CD) is a rare inherited leukodystrophy caused by deficiency of aspartoacylase. It is characterized by progressive spongy degeneration of brain white matter leading to a disturbed psychomotor development, severe disability and early death.
Despite several trials with experimental therapies (gene, drug and metabolic therapies) an effective treatment remains to be developed and proved to be effective. One of the prerequisites for evaluating upcoming therapies is a sufficient body of quantitative data describing the natural course of CD.
As a Referral Center within the European cooperative leukodystrophy research project LEUKOTREAT (http://www.leukotreat.eu) Dr. Bley developed a questionnaire and collected data of 9 patients with CD. In order to obtain meaningful results for CD, extended recruitment is necessary for at least 12 months. Cooperation with Dr. Eichler, MGH, Boston, USA and others with harmonization and aggregation with CD data at U.S. institutions as NeuroBANK™ and GLIA (Global Leukodystrophy Alliance) is intended. We aim to describe the natural history of at least 50 patients with CD for evaluation of experimental therapies including development of a clinical scoring tool that allows quantification of disease progression.
Impact: The project will supply a solid basis of quantitative data describing the disease course of CD. The data will help to establish outcome measures and ultimately trial design of any new treatment modality. Building on the innovative approaches of NeuroBANK™ and collaboration with ALD Connect and PCORnet (half of all centered research networks are rare diseases) we aim to accelerate progress in the field.

Checklist

ATTACH:

☐ **Cover Page/Checklist/Institutional Signature Page [PDF]**

☐ **CV of the Postdoctoral Applicant [PDF]**

☐ **NIH-style Biosketch with Other Support of the Mentor** (4 pages maximum). **[PDF]**
The Mentor must include accurate and complete information regarding all other sources of grant support (current and pending), including title, abstract, annual and total amount of grant, inclusive funding period, and percent effort.

☐ **Detailed Budget and Justification. [combined into one PDF]**
Complete attached Excel budget sheet. Describe justifications in a Word document. Award will be for one year, total cost $35,000 ($31,818 direct costs, plus 10% indirect costs of $3,182, if relevant to your institution). Proposed funding period: Dec 1, 2014 – Nov 30, 2015. Salary and benefit expenses for any individuals other than the grantee, indirect costs, tuition, travel, professional membership dues, general office supplies, institutional administrative charges (e.g., telephone, other electronic communication, IT network, etc.), pre-award charges, and any other expenses not directly related to the project are **not** allowable expenses.

☐ **Personal Statement from the Applicant** (2 pages max). **[PDF]**
Must include Applicant's interest in this research project, as well as future career plans.

☐ **Letter of Reference from Mentor** (3 pages max). **[PDF]**
Must confirm the availability of research facilities to conduct the research project. Should also address plans for supervision, guidance, counseling, or other formal or informal training of the applicant.

☐ **Research Plan** (5 pages max) and **Bibliography** (1 page max). **[combined into one PDF]**
Include the following sections: Specific Aims, Background and Significance, Preliminary Studies/Data, Research Design and Methods.
Text citations should use a numbered format. Include all author names in the reference list.

☐ **Appendix [combined into one PDF]**
Limited to 5 pages of supplemental information pertaining to proposal or preliminary data only; a maximum of 3 relevant reprints are also acceptable. Include IRB and/or IACUC approval letters if relevant.

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IMPROVED THERAPIES FOR RARE DISEASES
INSTITUTIONAL SIGNATURE PAGE

Certification and Acceptance:
We, the undersigned, certify that the statements contained in the attached grant application are true and complete to the best of our knowledge. We agree to conform to the policies and rules governing this award. We agree to openly share final data sets and observations with the full scientific community, and all reagents and/or research tools developed under support by this mechanism will be made accessible upon request. We understand that the University of Pennsylvania makes no claim to rights on these items or intellectual property other than for those faculty employed by the University of Pennsylvania. We understand that indirect costs are limited to 10% of direct costs.

Principal Investigator:

Annette E. Bley
Name (typed)

Signature

Title: **MD**

Institution: University Medical Center Hamburg-Eppendorf, Hamburg, Germany
Department: Department of Pediatrics
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Institutional Official:

Ania Muntau
Name (typed)

Signature

Title: **Professor of Pediatrics, MD**

Institution: University Medical Center Hamburg-Eppendorf, Hamburg, Germany
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CENTER FOR ORPHAN DISEASE RESEARCH AND THERAPY
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Grant Program Award Terms

1. Indirect Costs are limited to 10% of direct costs.

2. Awardees are required to provide updates concerning other support, resulting publications, and research activities, as requested.

3. An interim report is due ~June 1, 2015. A final report is due one month after the close of the project. Each two-page report must contain a synopsis of scientific progress, a list of resulting collaborations, publications and grants, a description of the relationship of the project to the goals of the related-disease research, a financial report, and a statement regarding unspent funds. Any unspent funds must be returned.

4. The following citation must be included in all publications: This work was supported in part by a research grant from the University of Pennsylvania.

5. Appropriate citation of all collaborations must be included in all publications.

6. All final data sets and observations must be shared openly with the full scientific community, and all reagents and/or research tools developed under support by this mechanism must be made accessible upon request. The University of Pennsylvania makes no claim to rights on these items or intellectual property other than for those faculty employed by the University of Pennsylvania.

Personal statement of the applicant

Project: Quantitative description of the clinical course of Canavan disease

My interest in leukodystrophy research was triggered by the limited knowledge about pathogenesis and therapeutic options for leukodystrophies. More importantly I was struck by the dramatic fate of individual patients in my clinic. New insights in neurodegenerative disorders in general and in Canavan disease specifically, will lead to an improved understanding of disease mechanisms, and ultimately a cure of the disease. To understand the natural history, broaden the knowledge about the disease and enable trial design for this devastating disorder motivates this application.

I care for many families with Canavan disease in the Leukodystrophy Outpatient Clinic at the University Hospital Hamburg Eppendorf. Investigation of the natural history of Canavan disease and its variability is a basic prerequisite for evaluation of potential therapies for this rare leukodystrophy. Since 2007, I have been working in the clinic for pediatric degenerative brain diseases at the University Hospital Hamburg Eppendorf, Germany, under the lead of Prof. Dr. Alfried Kohlschütter. My special clinical and research interest focuses on leukodystrophies, inherited and metabolic degenerative diseases of the white matter of the brain. From 2007-2009 I was part of the German leukodystrophy research network Leukonet (www. Leukonet.de). For this German Research network a database for leukodystrophy natural history studies was developed in Hamburg by Prof. Kohlschütter and myself.

In 2008 I completed my doctoral thesis with the title “Analysis of human and rat C3a-Receptor with new monoclonal antibodies” in the Department of Cellular and Molecular Immunology, University of Goettingen, Germany.

In 2009/2010 I joined Dr. Florian Eichler's team at MGH, Harvard Medical School, Boston, USA. During this time I successfully performed and published a natural history study of infantile GM2-Gangliosidosis (Tay Sachs disease etc.).During this time I also directed a workshop for Canavan families at the NTSAD family meeting in St. Petersburg, Florida in April 2010. Many US-Canavan disease families announced their support concerning a study elucidating the natural history of Canavan disease and its variability.

From 2010 to 2013 I was member of the European Leukodystrophy Research network LEUKOTREAT (www. Leukotreat.eu) and was involved in natural history studies of various leukodystrophies, epidemiological analyses of leukodystrophies in Europe as well as the evaluation of bone marrow transplant as a treatment for metachromatic leukodystrophy.
A common leukodystrophy database was developed for European researchers.

I have a strong interest in broadening the knowledge within in the field of inherited neurodegenerative disorders of the brain in childhood. Understanding how to collaborate on a global basis to establish solid outcome measures and disease course is a clear focus of mine. My connection to European and U/.S. based efforts place me in unique position to pursue this. Between the collaborating centers of Boston and Hamburg a wealth of resources are available to me (biostatistics, database managers, neuroradiologists etc.). The application will allow me to continue and foster ongoing relations with Dr. Eichler, Kohlschuetter and many others in the field.
Future career plans include the extension of the already existing vital international network with other leukodystrophy researchers to share insights of this very rare disease together. Harmonization and aggregation of the data with USA networks as NeuroBANK will be an important steps to achieve this aim.

Research Plan: Quantitative description of the clinical course of Canavan disease

State of the art: Canavan disease (CD) is an autosomal recessively inherited leukodystrophy caused by deficiency of the enzyme N-acetyl-L-aspartate aminohydrolase (aspartoacylase) (1). The disease is characterized by progressive degeneration of brain white matter.

After an unremarkable prenatal and perinatal course most affected children lack development of fundamental psychomotor milestones between three and five months of age. Macrocephaly, visual inattentiveness, head lag, generalized muscular hypotonia and/or hypertonia, seizures, swallowing difficulties and early death usually occur. Several therapeutic approaches have been tested in preclinical models, but the lack of natural history and variability in phenotype remain a challenge for trial design (2).

Therapeutic options: Canavan leukodystrophy is presently incurable. Currently a number of promising experimental trials are being performed with animal models, e.g. gene therapy (3) or various pharmacological approaches as usage of lithium (4) or acetate (5). Significant clinical benefit for humans still needs to be proved.

Challenges for development of new therapies: Evaluation of effectiveness and tolerability of new treatments in humans, driven by animal model experiments or theoretical considerations, is impeded by the variability in the disease course. Placebo-controlled trials are not feasible due to the devastating nature and rarity of the disease. An alternative is the comparison with historical controls (6, 7). This method is practical and it is being used in similar neurodegenerative diseases in childhood such as metachromatic leukodystrophy (Shire HGT http://clinicaltrials.gov/show/NCT01510028) and neuronal ceroid lipofuscinosis Type CLN 2 (BioMarin http://clinicaltrials.gov/show/ NCT01907087). A similar approach to advance CD research is feasible. More quantitative tools can be established through retrospective data, and can be used for the evaluation of the clinical course and evolution of MRI findings. Such tools and a corresponding database have been created in other neurodegenerative diseases such as ALS but are currently lacking for leukodystrophies (Sherman 2012).

Preparatory work of the applicant: The applicant, Dr. A. Bley, is a pediatrician and has been working in the field of leukodystrophies since 2007. She is a member of the clinical and research team for neurodegenerative diseases under the lead of Prof. Alfried Kohlschütter at the Department of Pediatrics of the University Medical Center Hamburg. In 2009/2010 Dr. Bley spent a research fellowship at the Massachussetts General Hospital, Harvard Medical School. There she evaluated data on the natural history of infantile GM2-gangliosidoses, in collaboration with NTSAD and Dr. Eichler's team (8). This led to publication of the largest natural history study on GM2 to date.

After participation in the German Leukodystrophy Research network LEUKONET, Dr. Bley became data coordinator for the European LEUKOTREAT project, which was funded by the European Commission (www.leukotreat.eu), from July 2010 until August 2013. Within the latter project the applicant collected and analysed clinical and MRI data from patients with several different types of leukodystrophies. Dr. Bley's responsibility was the collection and analysis of data from Canavan disease patients living in European countries, using a

questionnaire specifically developed by the applicant for this purpose. The study also includes international patients as from the USA and Australia. After obtaining informed consent from the families, patient data was collected and evaluated in a pseudonymised manner, using a database developed for leukodystrophies.

Detailed data from nine Canavan patients have been entered into the database to date. The cooperation with international researchers (Dr. Florian Eichler, MGH, Harvard Medical School, Boston, USA und Dr. Caroline Sevin, Saint-Vincent de Paul Hospital, Paris, France) is expected to lead to information of another 10 patients.

More recently Florian Eichler has made the resources of ALD Connect available to efforts in the field of Canavan disease. ALD Connect is a consortium dedicated to eradicate adrenoleukodystrophy, established with the support of PCORI, the U.S. based Patient Centered Outcomes Research Institute. In particular, ALD Connect is facilitating the use of an international web-based clinical data repository platform, NeuroBANK™, in which clinicians and researchers collect and share their patients' clinical data. This system has been implemented by the Neurological Clinical Research Institute at Massachusetts General Hospital [9]. The European Leukodystrophy Association plans to harmonize data collection with NeuroBANK™.

In a first phase, a collection of detailed patient data was started in the second half of the LEUKOTREAT project, for which financial support ended in August 2013 with finalization of the LEUKOTREAT project. For a systematic description of the course of CD a larger number of patients is necessary. We will therefore in a second phase implement electronic CRFs in NeuroBANK™, and facilitate recruitment in the U.S. and globally using LEUKOTREAT adapted database in Hamburg and NeuroBANK™ together. We assume that in an episode of further 12 months recruitment of data of 50 patients is realistic.

The platform NeuroBANK™ allows clinicians to enter patient data, either a) manually via a Web-based interface, or b) by exporting the data from the electronic health record (EHR). One of the objectives of this platform is to allow clinicians to compare patient and/or site outcomes against the averages calculated from the entire dataset, enabling the rapid identification of important trends. The data captured by the platform are standardized and harmonized based on a set of agreed-upon forms. The platform supports implementation of non-English language case report forms, functional scales, and questionnaires. An enormous advantage of utilization of the NeuroBANK™ platform is that patient-reported information will be aggregated along with the clinicians' and researchers' captured data. This approach alone will add validity of the patient-entered data and the overall repository.

Aims:

1. Continuation and completion of the CD-study that was started within the LEUKOTREAT project. Creating a Canavan-specific database which will facilitate the evaluation of experimental treatments

2. Recruitment of at least 50 CD patients in order to collect sufficient data for a precise description of the clinical course. Development of CD-specific clinical scores for a better quantitative evaluation of the course of the disease. For this purpose more

neuropediatric departments, diagnostic laboratories and patient organisations in Europe and overseas will be contacted and motivated to participate in the study.

3. Create electronic CRFs for CD within NeuroBANK™. As this has been done for other leukodystrophies within ALD Connect and GLIA (Global Leukodystrophy Alliance), we anticipate that we will quickly arrive at a computable phenotype that can be queried across PCORnet (see above).

4. Harmonization and aggregation with CD data of U.S. institutions: NeuroBANK™ will facilitate collaboration with U.S. and international researchers.

5. Future plans: (a) Attempt to create a MRI correlation to the course of the disease. In a first phase we will incorporate descriptions (natural language processing). In a second phase we will de-identify DICOM images and aggregate.

   (b) Evaluation of clinical information on disease modifying factors through web-based survey material.

Importance:

Creation of a suitable database of the clinical course of the disease is the major prerequisite for trial design and implementation.

Building on the innovative approaches of NeuroBANK™ and collaboration with ALD Connect and PCORnet (half of all patient centered research networks are rare diseases), we aim to accelerate progress in the field.

Research plan 1st December 2014 – 30th November 2015:

1st of December - 28th of February:

- Extended recruitment of Canavan patients. Further neuropediatric institutions, diagnostic laboratories and potentially cooperating networks will be contacted through NeuroBANK™.

- Study material will be translated into foreign languages.

1st of March – 31st of August:

Acquisition of clinical data from new Canavan patients (patient surveys, later to be gathered through web-based Patient Portal)

- Acquisition of neuroradiological data from existing brain MRIs

- Create electronic CRFs for CD within NeuroBANK™

1st of September – 30th of November:

- Development of adequate scoring tools (clinical rating systems)

References

(1) Kumar S, Mattan NS, de Vellis J. Canavan disease: a white matter disorder. Ment Retard Dev Disabil Res Rev.2006;12(2):157-165.

(2) Traeger EC, Rapin I, The clinical course of Canavan disease, Pediatr Neurol. 1998;18(3):207-12

(3) von Jonquieres G, Mersmann N, Klugmann CB, Harasta AE, Lutz B, Teahan O, Housley GD, Fröhlich D, Krämer-Albers EM, Klugmann M. Glial promoter selectivity following AAV-delivery to the immature brain. PLoS One.2013;14;8(6)

(4) Janson CG, Assadi M, Francis J, Bilaniuk L, Shera D, Leone P. Lithium citrate for Canavan disease. Pediatr Neurol.2005;33:235–243.

(5) Mathew R, Arun P, Madhavarao CN, Moffett JR, Namboodiri MA. Progress toward acetate supplementation therapy for Canavan disease: Glyceryl triacetate administration increases acetate, but not *N*-acetylaspartate, levels in brain. J Pharmacol Exp Ther.2005;315:297–303.

(6) Steinfeld R, Heim P, Von Gregory H, Meyer K, Ullrich K, Goebel HH, Kohlschütter A. Late infantile neuronal ceroid lipofuscinosis: Quantitative description of the clinical course in patients with CLN2 mutations. Am J Med Genet.2002;112(4):347-354.

(7) Eichler F, Grodd W, Grant E, Sessa M, Biffi A, Bley A, Kohlschuetter A, Loes DJ, Kraegeloh-Mann I . Metachromatic leukodystrophy: a scoring system for brain MR imaging observations. AJNR Am J Neuroradiol.2009;30(10):1893-1897.

(8) Bley AE, Giannikopoulos OA, Hayden D, Kubilus K, Tifft CJ, Eichler FS. Natural history of infantile GM2- gangliosidosis. Pediatrics.2011;128(5):e1233-41.

(9) Ahmed SS, Li H, Cao C, Sikoglu EM, et al. A single intravenous rAAV injection as late as P20 achieves efficacious and sustained CNS Gene therapy in Canavan mice. Mol Ther.2013;21(12):2136-47.

(10) Sherman A, Gubitz A, Al-Chalabi A, Bedlack R, Berry J, Conwit R, Harris B, Horton D, Kaufmann P, Leitner M, Miller R, Shefner J, Vonsattel J, Mitsumoto H. Infrastructure Resources for Clinical Research in ALS Amyotroph Lateral Scler. 2012;13,S1,126-134

(11) PCORnet PPRN Consortium, Daugherty SE, Wahba S, Fleurence R. Patient-powered research networks: building capacity for conducting patient-centered clinical outcomes research. J Am Med Inform Assoc.2014

18th October 2014

MASSACHUSETTS GENERAL HOSPITAL

HARVARD MEDICAL SCHOOL

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Florian Eichler, MD
Associate Professor of Neurology
Massachusetts General Hospital
Harvard Medical School

October 17, 2014

Re: recommendation of Annette Bley for CODRT Postdoctoral Fellowship program.

To the CODRTSelection Committee,

I highly recommend Dr. Annette Bley for the Center for Orphan Disease Research and Therapy Postdoctoral Fellowship program. She is the right kind of energetic, motivated and bright young researcher that would benefit from this support at a crucial stage in her career. As chair of ALD Connect, a consortium dedicated to eradicating adrenoleukodystrophy, we have access to many resources, including an experienced trial repository called NeuroBANK™. I am glad to make these resources available to Annette during her project period.

I met Annette in 2007, when she was a pediatric research fellow at the Pediatric Department of University in Hamburg developing a Leukodystrophy database and caring for families with leukodystrophies. At the time she was part of a very active group within the German Leukodystrophy research network LEUKONET and subsequently funded by the Federal Ministry of Education and Research, Germany, from 2008-2009.

Her analytic approach to medicine combined with professional competence and passion for data integrity impressed me and motivated a collaborative project in the leukodystrophies. We developed an MRI scoring system for patients with metachromatic leukodystrophy which led to a publication in 2009. I was particularly impressed by the work Annette contributed to this project. She was essential in compiling the data from centers in Europe and the U.S. and provided key clinical insights along the way.

Caring for many patients with various leukodystrophies during the past seven years she is a very experienced clinician within the field of rare neurodegenerative diseases. She is keenly aware of diagnostic and treatment options, and works to further establish new opportunities for diseases that currently lack options. Beyond this she studies pediatric palliative care. She is highly motivated to be an excellent researcher, always eager to broaden the knowledge in the field of these diseases.

In 2009/2010 she worked in my laboratory at Massachusetts General Hospital (MGH) gaining first experience in bench science and making new insights into the pathophysiology of inherited neuropathies. A major contribution was her analysis of natural history data of infantile GM2-gangliosidoses that had been collected by the National Tay-Sachs and Allied Diseases association (NTSAD). Her work resulted in a publication in 2011 in the journal *Pediatrics*. During that period I served as her mentor. All of us who worked with her were extremely pleased and delighted at the high standards and great abilities which she brought to this job. As a colleague, her relationship with the other physicians, researchers, students, families, and nurses was outstanding. She was consistently outstanding and certainly ranks among the top postdocs that we see in U.S. medical schools and academic institutions.

During her time at MGH, we were particularly impressed with the thoroughness of her evaluation and her desire to learn more about the pathophysiology of neurodegenerative diseases. From the very beginning it was clear to her that the path to new treatment options was by establishing natural history data. During a NTSAD family meeting, Annette conducted a Canavan disease workshop and was very well received by participating families. The thoughtful care that she provided to families left a lasting impression.

From 2010 to 2013, Annette was part of the European Leukodystrophy network LEUKOTREAT, funded by the European Commission. Within this network of international leukodystrophy researchers Annette developed the Canavan questionnaire, which was used by all LEUKOTREAT partners. She hence is the optimal candidate to carry this international effort forward and enhance our understanding of Canavan Disease.

Annette is an excellent team player with strong collaborations within her institution as well as on a national and international level. Many of these collaborations already led to important publications in the field of neurodegenerative diseases.

I am convinced that Annette will have a successful future career, contributing significantly to progress in the field. As a clinician her dedication to the field is bound to result in new trials and treatment options for patients.

Sincerely,

Florian Eichler, MD

Detailed Budget and Justification.

Proposed funding period: December 1st, 2014 – November 30th, 2015

Financial considerations:
$35 000 will be requested of which $3,182 will be relevant for indirect costs of my institution.
$35 000 - $3 182 = $31 818

$12 672 will be added by the patient organisation Myelin Project Germany for the salary of Dr. Bley for this project "Quantitative description of the clinical course of Canavan disease".

$ 31 818
+ $ 12 672
= $ 44 490 ($44 490 = 35 091 Euro if $1 = 0,789 Euro)

$44 490 for 12 months (1st December 2014 – 30th November 2015) enable to pay salary for a specialized pediatrician (Dr. Annette Bley) for 16 hours per week which is equal to 40% of full time working.

The grant will be administrated by the financial department of the UKE and will exclusively be used for the salary of the Principal Investigator Dr. Annette Bley.

Principal Investigator: Annette Bley MD

Institution: Department of Pedatrics, University Hospital Hamburg Eppendorf, Hamburg Germany

DETAILED BUDGET		FROM: 01.12.2014		TO: 11/31/15
PERSONNEL		**Yr 1**		
NAME	**ROLE ON PROJECT**	**SALARY REQUESTED**	**FRINGE BENEFITS**	**TOTALS**
Bley, Annette Elisabeth	Principal investigator			$ -
				$ -
				$ -
				$ -
				$ -
				$ -
				$ -
				$ -
PERSONNEL TOTAL		$ -	$ -	$31,818
CONSULTANT COSTS				
		$ -		**$ -**
SUPPLIES (Itemize by category)				
		$ -		
		$ -		
		$ -		
		$ -		
		$ -		**$ -**
TRAVEL COSTS				
		$ -		**$ -**
OTHER EXPENSES (Itemize by category)				
		$ -		
		$ -		
		$ -		
		$ -		
		$ -		
		$ -		**$ -**

TOTAL DIRECT COSTS	$31,818
INDIRECT COSTS (at 10%)	$3,182
TOTAL COSTS	35 000

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Annette Bley	Pediatric Neurology Fellow
eRA COMMONS USER NAME (credential, e.g., agency login) abley	

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
University of Goettingen, University of Vienna	MD	2003	Medicine

A. Personal Statement

Dr. Bley is a pediatric neurology fellow at the University Hospital Hamburg Eppendorf. She is trained in Pediatrics and Pediatric Palliative Care. Her clinical and research focus lies in neurodegenerative disorders, especially leukodystrophies. She works in the Leukodystrophy Clinic at University Hospital Hamburg Eppendorf under the direction of Dr. Alfried Kohlschütter. As a member of the German leukodystrophy research network LEUKONET and the European leukodystrophy research network LEUKOTREAT, Dr. Bley contributed to the development of a common German Leukodystrophy database and to a European database for various leukodystrophies. Within the LEUKOTREAT project she was responsible for the development of a questionnaire for Canavan disease and analysis of Canavan data. She is currently involved in studies concerning epidemiological aspects of leukodystrophies in Europa a study analyzing occurrence and treatment options of pain in leukodystrophies. A retrospective study of hematopoietic stem cell transplantation in juvenile metachromatic leukodystrophy (MLD) is almost complete. She spent a year in research fellowship at MassachusettsGeneral Hospital. Under the supervision of Dr. Florian Eichler she established the largest natural history study of infantile GM2 gangliosidoses to date. Dr. Annette Bley has the broad support of both the patient and academic community. After giving birth to three children in 2008, 2011 and 2014, Dr. Bley is now in her 4th postdoctoral research year.

B. Positions

Positions and Employment

2004-2007	Pediatric training, Hospitals of Aschaffenburg and Rosenheim, Germany
2007-2009	Senior pediatric resident, research assistant to Alfried Kohlschuetter, Clinic and Research Group for Degenerative Brain Disorders, Department of Pediatrics, University Medical Center Hamburg-Eppendorf, Germany
2009-2010	Postdoctoral research fellow to Prof. Florian Eichler, Department of Pediatric Neurology, Leukodystrophy clinic and laboratory, Massachusetts General Hospital, Harvard Medical School, Boston, USA
2010-today	Senior pediatric resident, research assistant to Prof. Alfried Kohlschuetter, Clinic and Research Group for Degenerative Brain Disorders, Department of Pediatrics, University Medical Center Hamburg-Eppendorf, Germany
2012	Board-certified pediatrician
2011-2013	Training courses in pediatric palliative care

Other Experience and Professional Memberships

- German Society of Pediatrics and Adolescent Medicine (DGKJ)
- Gesellschaft für Neuropädiatrie (“Neuropediatric society“)
- European Pediatric Neurology Society

C. Selected Peer-reviewed Publications

1. Kehrer C, Groeschel S, Kustermann-Kuhn B, Bürger F, Köhler W, Kohlschütter A, **Bley A**, Steinfeld R, Gieselmann V, Krägeloh-Mann I, German LEUKONET. Language and cognition in children with Metachromatic leukodystrophy: onset and natural course in a nationwide cohort. Orphanet J Rare Dis. 2014;5;9:18 PMID: 24499656

2. Steenweg ME, Ghezzi D, Haack T, Abbink TE, Martinelli D, van Berkel CG, **Bley A**, Diogo L, Grillo E, Te Water Naudé J, Strom TM, Bertini E, Prokisch H, van der Knaap MS, Zeviani M. Leukoencephalopathy with thalamus and brainstem involvement and high lactate 'LTBL' caused by EARS2 mutations. Brain. 2012;135(Pt 5):1387-94 PMID: 22492562

3. Ding XQ, **Bley A**, Ohlenbusch A, Kohlschutter A, Fiehler J, Zhu W and Lanfermann H. Imaging evidence of early brain tissue degeneration in patients with vanishing white matter disease: A multimodal MR study. J Magn Reson Imaging. 2012;35(4):926-32 PMID: 22128017

4. Ding XQ, **Bley A**, Kohlschütter A, Fiehler J, Lanfermann H. Long-term neuroimaging follow-up on an asymptomatic juvenile metachromatic leukodystrophy patient after hematopoietic stem cell transplantation: Evidence of myelin recovery and ongoing brain maturation. Am J Med Genet A. 2012;158A(1):257-60 PMID: 22140054

5. **Bley AE**, Giannikopoulos OA, Hayden D, Kubilus K, Tifft CJ, Eichler FS. Natural history of infantile G(M2) gangliosidosis. Pediatrics. 2011;128(5):e1233-41 PMID: 22025593

6. Groeschel S, Kehrer C, Engel C, I Dali C, **Bley A**, Steinfeld R, Grodd W, Krägeloh-Mann I. Metachromatic leukodystrophy: natural course of cerebral MRI changes in relation to clinical course.J Inherit Metab Dis. 2011;34(5):1095-102 PMID: 21698385

7. Kohlschütter A, **Bley A**, Brockmann K, Gärtner J, Krägeloh-Mann I, Rolfs A, Schöls L. Leukodystrophies and other genetic metabolic leukoencephalopathies in children and adults. Brain Dev. 2010;32(2):82-9 PMID: 19427149

8. Eichler F, Grodd W, Grant E, Sessa M, Biffi A, **Bley A**, Kohlschuetter A, Loes DJ, Kraegeloh-Mann I. Metachromatic leukodystrophy: a scoring system for brain MR imaging observations. Am J Neuroradiol. 2009;30(10):1893-7 PMID: 19797797

9. Kiafard Z, Tschernig T, Schweyer S, **Bley A**, Neumann D, Zwirner J. Use of monoclonal antibodies to assess expression of anaphylatoxin receptors in tubular epithelial cells of human, murine and rat kidneys. Immunobiology. 2007;212(2):129-39 PMID: 17336833

D. Research Support

Ongoing Research Support

Grant of Berlin Will foundation Bley (PI) 10/01/14-09/30/17
"Freunde der Kinderklinik (Friends of Pediatric Department, University Hospital Hamburg Eppendorf)"
Care for leukodystrophy patients and leukodystrophy research projects
Role: PI

Grant of Myelin project Bley (PI) 7/01/14-06/30/16
Quantitative description of the clinical course of Canavan disease
Role: PI

Grant of ELA Germany Kohlschütter and Bley (PI) September 2014
Support for Leukodystrophy Outpatient Clinic at University Hospital Hamburg Eppendorf, Study of pain in Leukodystrophies
Role: PI

Completed:

LEUKOTREAT Health-F2-2010-241622-Project Boespflug-Tanguy (PI) 04/01/2010-09/30/2013
European Commission
Therapeutic challenge in Leukodystrophies: translational and ethical research towards clinical trials
Role: member, Work Package 1

BMBF Dr. Alfried Kohlschütter (PI) 02/02/2007-06/30/2009
Central patient data base and information service for leukodystrophy related issues, German Leukodystrophy Network LEUKONET
Role: Assistant to Dr. Alfried Kohlschütter (PI)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Florian Eichler	Associate Professor in Neurology
eRA COMMONS USER NAME (credential, e.g., agency login) feichler	

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
Rhode Island School of Design	BFA	1988	Painting
University of Vienna	MD	1997	Medicine

A. Personal Statement

Dr. Eichler is an Associate Professor of Neurology at Massachusetts General Hospital (MGH) and Harvard Medical School. He is trained in Neurology and Neurogenetics with a focus in neurodegenerative disorders. He is currently Director of the Leukodystrophy Clinic at Massachusetts General Hospital. Dr. Eichler runs a laboratory at MGH that explores the relationship of mutant genes to specific biochemical defects and their contribution to neurodegeneration. Dr. Eichler was the first to describe microglial apoptosis in adrenoleukodystrophy (ALD). Dr. Eichler is an active member of several consortiums aiming to move gene therapy forward in the leukodystrophies. Currently he is Co-PI of an ex vivo lentiviral gene therapy trial for ALD. He works closely with Dr. Xandra Breakefield, gene therapy expert at MGH. As chair of the national consortium ALD Connect that aims to eradicate adrenoleukodystrophy, Dr. Eichler has the broad support of both the patient and academic community. In addition, he has been the PI of several federal and foundation grants on neurogenetic disorders and serves on the boards of scientific advisors for the United Leukodystrophy Foundation and the National Tay Sachs and Allied Disease Foundation.

B. Positions and Honors

Positions and Employment

11/97 – 11/99	Residency in the Division of Neonatology of the Vienna General Hospital, Austria
11/99 – 08/00	Neurogenetics Staff, Kennedy Krieger Institute, Johns Hopkins Medical Institutions, Baltimore, Maryland
09/00 – 06/01	Postdoctoral Fellow, Department of Neurology, Johns Hopkins School of Medicine, Baltimore, Maryland
07/01 – 06/02	Residency in the Department of Pediatrics, Geisinger Medical Center, Pennsylvania
07/02 – 09/04	Residency in the Partners Neurology Program, Harvard Medical School, Boston, Massachusetts
07/04 - 06/05	Chief Resident in Pediatric Neurology, Partners Neurology Program, Harvard Medical School, Boston, Massachusetts
07/05 – 04/07	Instructor in Child Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts
04/07 – 12/13	Assistant Professor in Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts
1/14 - present	Associate Professor in Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

Other Experience and Professional Memberships

2004	Member of the American Academy of Neurology
2004	Member of the Child Neurology Society
2006	Member of the Scientific Advisory Board of the United Leukodystrophy Foundation

Honors

1999	Stipendium Metabolicum (scholarship awarded for the project "in vivo MR Spectroscopy in pediatric patients with metabolic and neurometabolic disorders")
2000	VIII International Congress of IEM (Inborn Errors of Metabolism) Travel Award
2002	Resident's Award from the American Neurological Association
2004	Top Scholar Fellow at Child Neurology Society
2005	Marine Biological Laboratory Scholarship
2005	William Randolph Hearst Fund Award
2006	Career Development Award, NINDS (K08)
2009	Wolfe Neuropathy Research Prize (American Neurological Association)
2011	MGH Clinical Research Day Departmental Award for Neurology
2013	MGH Teacher of the Year Award in Child Neurology

C. Selected Peer-reviewed Publications

1. **Eichler F**, Barker PB, Cox C, Edwin D, Ulug AM, Moser HW, and Raymond G. Proton MR Spectroscopic Imaging predicts lesion progression on MRI in X-linked Adrenoleukodystrophy. Neurology 2002; 58:901-907.

2. **Eichler F**, Wang P, Wityk RJ, Beauchamp NJ, and Barker PB. Diffuse Metabolic Abnormalities in Reversible Posterior Leukoencephalopathy Syndrome. AJNR Am J Neuroradiol. 2002; 23(5):833-7.

3. **Eichler F**, Itoh R, Barker PB, Mori S, Garrett ES, van Zijl PC, Moser HW, Raymond GV, Melhem ER. Proton MR spectroscopic and diffusion tensor brain MR imaging in X-linked adrenoleukodystrophy: initial experience. Radiology. 2002; 225(1):245-52.

4. Tan WH, **Eichler FS**, Hoda S, Lee M, Baris H, Hanley C, Grant EP, Krishnamoorthy KS, Shih VE. Isolated Sulfite Oxidase Deficiency – A case report with a novel mutation and review of the literature. Pediatrics 2005;116(3):757-66.

5. Smith EE, **Eichler F**. Cerebral amyloid angiopathy and lobar hemorrhage. Archives of Neurology 2006; 63(1):148-51.

6. **Eichler F**, Tan WH, Shih VS et al. Proton MR Spectroscopy and Diffusion Weighted Imaging in Isolated Sulfite Oxidase Deficiency. Journal of Child Neurology 2006; 21:801–805.

7. Liu CH, Kim YR, Ren JQ, **Eichler F**, Rosen BR, Liu PK. Imaging cerebral gene transcripts in live animals. Journal of Neuroscience. 2007; 27(3):713-722.

8. **Eichler F**, Mahmood A, Loes D, Bezman L, Lin L, Moser HW, Raymond G. MRI Lesion Progression in Adult Patients with X-linked Adrenoleukodystrophy. Archives of Neurology. 2007; (64):659-664.

9. Moll NM, Rietsch AM, Ransohoff AJ, Cossoy MB, Huang D, **Eichler FS**, Trapp BD, Ransohoff RM. Cortical demyelination in PML and MS: Similarities and differences. Neurology. 2007: 1-8.

10. **Eichler FS**, Ren JQ, Cossoy M, Rietsch AM, Nagpal S, Moser A, Frosch MP, Ransohoff RM. Is microglial apoptosis an early pathogenic change in cerebral X-ALD? Annals of Neurology. 2008; 63(6):729-42.

11. Ratai E, Kok T, Wiggins C, Wiggins G, Grant E, Gagoski B, O'Neill G, Adalsteinsson E, **Eichler FS**. 7 Tesla proton magnetic resonance spectroscopic imaging in adult X-linked adrenoleukodystrophy. Archives of Neurology. 2008; 65(11):1488-94. NIHMSID: NIHMS173156

12. **Eichler F**, Grodd W, Grant E, Sessa M, Biffi A, Bley A, Kohlschuetter A, Loes DJ, Kraegeloh-Mann I. Metachromatic Leukodystrophy: A Scoring System for Brain MR Observations. AJNR Am J Neuroradiol. AJNR Am J Neuroradiol. 2009; 30(10):1893-7.

13. Han G, Gupta SD, Gable K, Niranjanakumari S, Moitra P, **Eichler F**, Brown RH Jr, Harmon JM, Dunn TM. Identification of small subunits of mammalian serine palmitoyltransferase that confer distinct acyl-CoA substrate specificities. Proc Natl Acad Sci U S A. 2009; 106(20):8186-91. PMCID: PMC2688822

14. **Eichler FS**, Hornemann T, McCampbell A, Kuljis D, Penno A, Vardeh D, Tamrazian E, Garofalo K, Lee HJ, Kini L, Selig M, Frosch M, Gable K, von Eckardstein A, Woolf CJ, Guan G, Harmon JM, Dunn TM, Brown RH Jr. Overexpression of the wild-type SPT1 subunit lowers desoxysphingolipids levels and rescues the phenotype of HSAN1. J Neurosci. 2009; 29(46):14646-51. NIHMSID: NIHMS172541

15. Penno A, Reilly MM, Houlden H, Laura M, Rentsch K, Niederkofler V, Stoeckli ET, Nicholson G, **Eichler F**, Brown RH Jr, von Eckardstein A, Hornemann T. Hereditary sensory neuropathy type 1 is caused by accumulation two neurotoxic sphingolipids. J Biol Chem. 2010; 285(15):11178-87. PMCID: PMC2856995

16. Garofalo K, Penno A, Schmidt BP, Lee H, Frosch MP, von Eckardstein A, Brown RH, Hornemann T, **Eicher FS**. Oral L-serine supplementation reduces production of neurotoxic deoxy-sphingolipids in mice and humans with Hereditary Sensory Autonomic Neuropathy Type 1. Journal of Clinical Investigation. 2011; 121(12): 4735-45.

17. Bley A, Giannikopoulous O, Hayden D, Kubilus K, Tifft CJ, **Eichler FS**. Natural History of Infantile GM2 Gangliosidosis. Pediatrics. 2011; 128(5): 1233-41.

18. Thibert R, Hyland K, Chiles J, Steinberg S, **Eichler F**. Levodopa response reveals sepiapterin reductase deficiency in a female heterozygote with adrenoleukodystrophy. Journal of Inherited Metabolic Disease. 2011.

19. Horvath GA, **Eichler F**, Poskitt K, Stockler-Ipsiroglu S. Failure of Repeated Cyclophosphamide Pulse Therapy in Childhood Cerebral X-linked Adrenoleukodystrophy. Neuropediatrics. 2012; 43(1): 48-52.

20. Friedman J, Roze E, Abdenur JE, Chang R, Gasperini S, Saletti V, Wali GM, Eiroa H, Neville B, Felice A, Parascandalo R, Zafeiriou DI, Arrabal-Fernandez L, Dill P, **Eichler FS**, Echenne B, Gutierrez-Solana LG, Hoffmann GF, Hyland K, Kusmierska K, Tijssen MA, Lutz T, Mazzuca M, Penzien J, Poll-The BT, Sykut-Cegielska J, Szymanska K, Thöny B, Blau N. Sepiapterin Reductase Deficiency: A Treatable Mimic of Cerebral Palsy. Ann Neurol. 2012; 71(4): 520-530.

21. Musolino P, Rapalino O, Caruso P, Caviness VS, **Eichler FS**. Hypoperfusion Predicts Lesion Progression in Cerebral X-linked Adrenoleukodystrophy. Brain 2012; 135(9): 2676-83.

22. Musolino PL, Lund TC, Pan J, Escolar ML, Paker AM, Duncan CN, **Eichler FS**. Hematopoietic Stem Cell Transplantation in the Leukodystrophies: A Systematic Review of the Literature. Neuropediatrics. 2014

23. Patient-powered research networks: building capacity for conducting patient-centered clinical outcomes research. PCORnet PPRN Consortium, Daugherty SE, Wahba S, Fleurence R. J Am Med Inform Assoc. 2014; 21(4):583-6.

24. Krishnamoorthy KS, **Eichler F**, Rapalino O, Frosch MP. Case records of the Massachusetts General Hospital. Case 14-2014. An 11-month-old girl with developmental delay. N Engl J Med. 2014 May 8;370(19):1830-41.

D. Research Support

Ongoing Research Support

Patient-Powered Research Network Eichler (PI) 03/01/14-09/30/15
PCORI
ALD Connect
The goal of this consortium is to empower patients, caregivers, and their affinity groups to move beyond conventional research participation, advocacy, and fundraising efforts to improve care for and ultimately eradicate the debilitating single-gene disorder, X-linked Adrenoleukodystrophy (ALD).
Role: PI

U01NS064096 Sena-Esteves (PI) 09/01/09-08/31/13
AAV-mediated gene therapy for GM2-gangliodoses
The goal of this proposal is to translate results obtained with AAV vectors in animal models of GM2-gangliosidoses into a human clinical trial.
Role: Project Director

R01 NS072446-01 Eichler (PI) 12/01/10-11/30/15
NIH/NINDS
The Role of Desoxysphingoid Bases in HSAN1
The goal of this study is to determine whether desoxysphingoid bases are toxic to nerves and assess dietary means to lower these lipids.
Role: PI

FD-R-004127-01 Eichler (PI) 09/15/12-9/15/16
FDA/NIH
Phase 2 Trial of L-Serine in HSAN1
This is a double-blinded, randomized, placebo controlled clinical trial testing the efficacy of L-serine supplementation as treatment for hereditary sensory and autonomic neuropathy type 1. This proposal was awarded by the FDA as Orphan Products Development Grant (OOPD).

Completed:

1K08NS052550-05 (Eichler) 06/01/06-05/31/2011
NIH/NINDS
Imaging the Pathophysiology of AMN in Mice and Humans
Goal: The project studies the histopathology and biochemistry in relation to advanced MR imaging techniques in patients with adrenomyeloneuropathy and a mouse model of the disease.
Role: PI

ETHICS COMMITTEE of the
MEDICAL ASSOCIATION
OF HAMBURG
a public body

Medical Association of Hamburg - P.O. Box 760109 - 22051 Hamburg
Prof. Dr. med. Alfried Kohlschütter
Clinic and Polyclinic for Paediatric Medicine
University Medical Center Hamburg-Eppendorf
Martinistraße 52
20246 Hamburg

07 Nov. 2011

File No.: PV3782 (please quote in all correspondence!)
Study: Study of the clinical course of leukodystrophies within the framework of a project of the European Union (LEUKOTREAT), realized in part in cooperation with research partners in the U.S.A.

Prof. Kohlschütter
Dear Colleague -

The Ethics Committee has undertaken detailed deliberation of the project you submitted - as mentioned above - for primary consideration.

The project is found to be in keeping with the relevant professional and legal stipulations. The Ethics Committee hereby approves the project.

In the above matter, the Committee hereby informs you that the Committee vote on the project mentioned above has no effect on the responsibility of the Study Director for the research project and realization of same.

You are asked to inform the Ethics Committee in the event of any serious or unexpected events occurring during the study that put the safety of study participants at risk, together with your own assessment.
The Committee assumes that the personal data of the study participants / patients will be processed and handled in accordance with the stipulations of the data protection laws in force.

It is our expectation that an unsolicited Final Report will be sent to the Committee after conclusion of the project (with mention of the File. No.), on the basis of which it can be determined whether the study was a success or failure, whether the study was discontinued or changed and whether compensation claims were made.

Respectfully yours,
By order of the Committee:
[signature]
Prof. Dr. med. Th. Weber
-Chairman-

PS: The work of the Ethics Committee is based on German and professional law as well as on the ICH-GCP

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