BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Becker, Mara L

eRA COMMONS USER NAME (credential, e.g., agency login): mlbecker1

POSITION TITLE: Senior Medical Director, Professor of Pediatrics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Pennsylvania State University, State College, PA	BA	12/1994	Liberal Arts
Jefferson Medical College, Philadelphia, PA	MD	06/1999	Medicine
DuPont Hospital for Children/Thomas Jefferson University Hospital, Philadelphia, PA		06/2002	Pediatrics
DuPont Hospital for Children/Thomas Jefferson University Hospital, Philadelphia, PA		06/2003	Chief Resident
DuPont Hospital for Children/Thomas Jefferson University Hospital, Philadelphia, PA		06/2006	Fellow: Pediatric Rheumatology
University of Pennsylvania, Philadelphia, PA	MSCE	01/2007	Clinical Epidemiology
Children's Mercy- Kansas City		06/2012	Clinical Pharmacology

A. Personal Statement

My long term research goal is to identify factors that enhance response and minimize toxicity to drugs used for the treatment of rheumatic diseases in children, focusing on a personalized therapeutic strategy. My research training and experience over the last several years, including my M.S.C.E. degree from the University of Pennsylvania, as well as completion of a formal clinical pharmacology fellowship, has provided a solid foundation from which to advance this work. I have led a team of inter-disciplinary researchers and clinicians in the investigation of intracellular methotrexate (MTX) polyglutamates and erythrocyte folate as biomarkers of MTX response in JIA patients. Over the last several years, I have developed a collaborative relationship with Dr. Sue Thompson through our mutual interest in the effect of genetics upon JIA and drug response, and this work is currently funded by the NICHD (1R01 HD089928). I have also maintained a solid and productive working relationship with my mentee, Dr. Ryan Funk to expand our translational research interests in drug response in JIA to include a mouse model for experimental validation of our work, novel cytokine biomarkers including Nicotinamide Phosphoribosyltransferase (NAMPT), metabolomics as exploratory analyses, evaluation of Down syndrome patients who are particularly vulnerable to immune modulating treatments, and biologic therapeutic drug monitoring in JIA and IBD.

1. **Becker ML**, van Haandel L, Gaedigk R, et al. (2010). Analysis of Intracellular Polyglutamates in Juvenile Idiopathic Arthritis: effect of Route of Administration upon Intracellular Methotrexate Polyglutamate Variability. Arthritis Rheum, June 62 (6): 1803-1812.
2. **Becker ML**, Gaedigk R, van Haandel L, et al. (2011). The Effect of Genotype on Methotrexate Polyglutamate Variability in Juvenile Idiopathic Arthritis and Association with Drug Response. Arthritis Rheum, 63 (1): 276-285
3. **Becker ML**, vanHaandel L, Gaedigk R, et al. (2012). Red Blood Cell Folate Concentrations and Polyglutamate Distribution in JIA: Predictors of Folate Variability. Pharmacogenetics and Genomics, 22(4): 236-246

4. Funk RS, Singh R, Pramann L, Gigliotti N, Islam S, Heruth D, Ye S, Chan M, Leeder, JS, **Becker, ML**. Nicotinamide Phosphoribosyltransferase Attenuates Methotrexate Response in Juvenile Idiopathic Arthritis and In Vitro. Clinical and Translational Science 2016, Jun; 9(3):149-57. PMID:27166432

B. Positions and Honors

Positions and Employment

2006-2011 Assistant Professor of Pediatrics, UMKC School of Medicine, Children's Mercy-Kansas City
2011-Pres. Associate Professor of Pediatrics, UMKC School of Medicine, Children's Mercy-Kansas City
2013-2018 Division Director, Rheumatology Children's Mercy-Kansas City
2016-2018 Associate Chair, Department of Pediatrics, Children's Mercy-Kansas City
2017-Pres. Professor of Pediatrics, UMKC School of Medicine, Children's Mercy-Kansas City
2018-Pres. Senior Medical Director, Ambulatory Services, Children's Mercy-Kansas City
2018-Pres. Interim Medical Director for Office of Faculty Development, Children's Mercy-Kansas City

Selected Experience and Professional Memberships

2001-Pres. Member, American Academy of Pediatrics, FAAP
2003-Pres. Member, American College of Rheumatology
2007-Pres. Member, Childhood Arthritis and Rheumatology Research Alliance (CARRA)
2007-2013 Co-director BRNSTRM, CMH
2009-Pres. Member, American Society for Clinical Pharmacology and Therapeutics
2009-2015 Executive Committee of AAP Section on Rheumatology, Membership Chair
2010-2011 ARHQ reviewer for "Comparative Effectiveness of disease-modifying anti-rheumatic drugs (DMARDs) in children with juvenile idiopathic arthritis (JIA)
2010-2013 MWSPR Council
2010-2013 ASCPT Scientific Program Committee
2011-2014 American College of Rheumatology (ACR) Special Pediatric Committee
2011-Pres. Member, Localized Scleroderma subcommittee of CARRA
2012-2013 ACR Task Force Panel for JIA treatment guidelines
2012-Pres. Member, Pediatric Rheumatology Collaborative Study Group (PRCSG)
2012 Co-chair, BPCA Rheumatology working group
2014-Pres. Society for Pediatric Research (SPR)
2015-2018 SPR Council member representing Allergy, Immunology, and Rheumatology
2015 Strategic Planning Task Force, Rheumatology Research Foundation (RRF)
2015 Co-moderator CARRA Pediatric Rheumatology Fellows' conference, Austin, TX
2015-Pres FDA Arthritis Advisory Committee
2016-Pres ACR Committee of Education, Chair Educational Meetings Subcommittee
2016 RRF Peer Reviewer for the Disease Targets Research Initiative Grants
2016-Pres ACR JIA Treatment Guidelines Task Force
2018-Pres ACR PRYSM Planning Subcommittee

Select Honors

1994 Invited into Phi Beta Kappa National Honor Society
2005 Paula de Merieux Rheumatology Fellowship Award
2006 American College of Rheumatology Distinguished Fellow Award
2008 Midwest Society for Pediatric Research Southerland Award for Young Investigators
2010 Presidential Trainee Award from the American Society for Clinical Pharmacology and Therapeutics
2010 David J. Goldstein Trainee Award from the American Society for Clinical Pharmacology and Therapeutics
2012 Kreamer Research Excellence Award, Children's Mercy Hospitals and Clinics
2014 Rheumatology Research Foundation Pediatric Rheumatology Visiting Professorship
2015 Selected as one of 30 influential rheumatologists who made an impact through their work with RRF
2018 Children's Mercy Faculty Award, Senior Research Achievement Award

C. Contribution to Science

1. Clinical utilization of methotrexate in JIA: During my fellowship I was intrigued in the variability of initial dosing strategies for methotrexate (MTX) in JIA. My master's thesis revolved around investigating two pediatric rheumatology clinics in close proximity that had vastly different dosing practice for MTX in JIA. I performed a retrospective cohort study that revealed that using higher initial doses of MTX in JIA increased the risk of side effects, but was not always more effective in treating arthritis. This finding has supported starting children on moderate doses of MTX. As I develop my expertise in this area, I have been asked to contribute to several publications that have reviewed the use of MTX in JIA and the mechanisms of action of MTX in JIA.I have contributed to the ARHQ review of DMARD use in children with JIA, the Choosing Wisely recommendations for Pediatric Rheumatology which include guidelines for MTX toxicity monitoring, and the ACR JIA treatment guidelines taskforce.
    a. **Becker, ML**, Rosé CD, Cron RQ et al. (2010). Effectiveness and Toxicity of Methotrexate in Juvenile Idiopathic Arthritis: Comparison of Two Initial Dosing Regimens. J Rheum, April 37 (4): 870-875
    b. **Becker ML**. (2013). Role of Methotrexate in Juvenile Idiopathic Arthritis: where we have been and where we are going. International Journal of Clinical Rheumatology, Feb 8(1):123-135
    c. Hashkes PJ**, Becker ML**, Cabral D, Laxer RM, Pallor A, Rabinovich E, et al. (2014). Methotrexate: New Uses for an Old Drug. Journal of Pediatrics,164(2): 231-236
    d. Rouster-Stevens KA, Ardoin SP, Cooper AM, **Becker ML**, et. al. (2014). Choosing Wisely: The American College of Rheumatology's "Top Five" for Pediatric Rheumatology. Arthritis Rheum, 66 (5): 649-657

2. MTX metabolites and biomarkers: After joining the faculty at Children's Mercy-Kansas City, I began more translational investigation into the mechanism of action of MTX and why we clinically observe so much variability in response. I partnered with pharmaceutical chemists, clinical pharmacologists, and molecular geneticists in the development of improved methods to quantify stable cellular MTX metabolites (MTX polyglutamates (MTXGlu)). In fact, our group was the first to report more sensitive HPLC/MS/MS methods for MTXGlu measurement, and meaningful measurement of MTXGlu and JIA, the effect of route of administration and genotype upon MTXGlu distribution and associations with clinical outcomes in JIA. We have also investigated novel biomarkers of response that are affected by MTX. In addition to the publications listed in my personal statement above, we have contributed the following in this area:
    a. van Haandel L, **Becker ML**, Leeder JS et al. (2009). A Novel HPLC Mass Spectrometry Method for Improved Selective and Sensitive Measurement of Methotrexate Polyglutamation Status in Human Red Blood Cells. Rapid Communications in Mass Spectrometry, Dec;23(23):3693-702
    b. van Haandel L, **Becker ML**, Williams TD, et al. (2011). Measurement of Methotrexate Polyglutamates in Human Erythrocytes by Ion Pair UPLC-MS/MS. Bioanalysis, Dec 3(24) 2783-96
    c. Funk RS, van Haandel L, **Becker ML**, Leeder JS. (2013). Low-dose Methotrexate Results in the Selective Accumulation of Aminoimidazole Carboxamide Ribotide in an Erythroblastoid Cell Line. J Pharmacol Exp Ther, Oct;347: 154-163
    d. Funk, RS, Chan MA, **Becker, ML**. Cytokine Biomarkers of Disease Activity and Therapeutic Response in Juvenile Idiopathic Arthritis, Pharmacotherapy 2017 May 5th doi: 10.1002/phar.1938 PMID 28475276

3. The effect of MTX upon the folate pathway: Investigating MTX without an understanding of the folate pathway is only knowing part of the story, as MTX exerts effects upon the endogenous folate pathway and likely vice versa. I was asked to participate with the PharmGKB group to update its report on the folate pathway and the effect that MTX has upon this pathway in addition to the currently known effects of MTX upon folate pathway enzymes. Our team has published methods on quantifying intracellular folate concentrations and folate polyglutamate concentrations via similar sensitive methods as MTXGlu. We are the first group to publish the folate phenotype in JIA, and we have reported these initial data in JIA patients both on and off MTX in a cross sectional study as well as *in vitro* to show the effect that MTX and baseline genotype have upon folate homeostasis.
    a. Mikkelsen TS, Thorn CF, Yang JJ, Ulrich C, French D, Zaza G, Marsh S, McLeod HL, Giacomini K, **Becker ML**, et al. (2011). PharmGKB summary—Methotrexate Pathway, Pharmacogenetics and Genomics, e pub Feb, 2011

b. van Haandel L, **Becker ML**, Williams,TD, Stobaugh JF, Leeder JS. (2012). Comprehensive Quantitative Measurement of Folate Polyglutamates in Human Erythrocytes by Ion Pair UPLC-MS/MS. Rapid Communications of Mass Spectrometry, 26(14): 1617-1630
c. **Becker ML**, vanHaandel L, Gaedigk R, et al. (2012). Red Blood Cell Folate Concentrations and Polyglutamate Distribution in JIA: Predictors of Folate Variability. Pharmacogenetics and Genomics, 22(4): 236-246
d. Funk RS, van Haandel L, Leeder JS, **Becker ML**. (2014). Folate Depletion and Increased Glutamation in Juvenile Idiopathic Arthritis Patients Treated with Methotrexate. Arthritis Rheum,66;12:3476-3485

4. Pharmacology in Rheumatology: As one of the few pediatric rheumatologists formally fellowship trained in clinical pharmacology in the world, I have become a bridge between the two disciplines. I help disseminate the principles of clinical pharmacology to rheumatologists as well as educate clinical pharmacologists about the therapeutic challenges faced specifically by pediatric rheumatologists- including the paucity of biomarkers, rare patient populations, and ontogeny. This unique perspective has allowed me to be a resource and leader in therapeutic initiatives in pediatric rheumatology as evidenced by my involvement in the BPCA rheumatology working group, the task force for JIA treatment guidelines, updating the Pharmacology chapter in the Textbook of Pediatric Rheumatology, the signature textbook in the field, and invited manuscripts as noted below in both disciplines
    a. **Becker ML** and Leeder JS. (2010). Developmental Pharmacogenetics in Pediatric Rheumatology: Utilizing a New Paradigm to Effectively Treat Patients with Juvenile Idiopathic Arthritis with Methotrexate. *Human Genomics and Proteomics*, vol. 2010, Article ID 257120, 9 pages. doi:10.4061/2010/257120
    b. **Becker ML.** (2012). Optimization of Pediatric Rheumatology Therapeutics. *Clinical Pharmacology and Therapeutics*, Apr 91(4): 597-606
    c. **Becker, ML**. (2012). Pharmacogenomics in Pediatrics. Pediatrics and Heritable Disorders. Curr Opin Rheumatol, 24(5):541-547
    d. **Becker ML** Methotrexate Metabolites to Make Clinical Decisions in JIA. Current Treatment Options in Rheumatology, 2015; 1 (4), pp 381-395

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1v1ZFrn8mz95u/bibliography/46642876/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support (For the Past Three Years)

1R01 HD089928-01A1 Becker (Co-PI) 09/01/2017- 08/31/2022
RFA PAR-14-274 Pharmacogenetics, Pharmacoepigenetics and Personalized Medicine in Children
Identifying Pharmacogenomic Predictors of Methotrexate Response and Metabolite Biotransformation in JIA

KU Frontiers CTSA KL2 Funk (PI) 01/2018-01/2020
(KL2TR002367)
Metabolic Markers of methotrexate Response in Autoimmune Arthritis
Role: Mentor

PhRMA Foundation
Research Starter Grant in Pharmacology/Toxicology Funk (PI) 01/2018-01/2019
A Biochemical Strategy to Mitigate Methotrexate Toxicity in Patients with Down Syndrome
Role: Mentor

Young Investigator Award Funk (PI) 09/15/16-09/14/17
American College of Clinical Pharmacy Research Institute
Etanercept Trough Level Monitoring and Therapeutic Response in Juvenile Arthritis

This project seeks to evaluate the relationship of serum trough levels of etanercept and circulating TNFα levels with therapeutic response in juvenile arthritis as the basis for an individualized approach to drug therapy.
Role: Mentor

Completed Research Support (Selected For the Past Three Years)

CARRA Small Grant Award Becker (PI) 02/2017-02/2018
Pharmacogenomic Predictors of MTX Polyglutamation
This grant is to fund sample collection for $MTXGlu_{(n)}$ at 6 months within the CARRA and PCORI funded STOP JIA cohort

ACR RRF R Bridge Award Becker (PI) 08/15/2014-08/15/2016
Integrated Approach to Individualizing therapy with MTX in JIA
This project integrates clinical and non-clinical approached to understand the mechanistic basis for difference in response to MTX.

2 PO1 AR048929-06 Thompson (PI) 2013-Present
Gene Expression in Pediatric Arthritis
Project 2- Advanced Therapies in JIA towards Predictive Treatment
This project investigates gene expression profiling for predictive biomarkers of response with initiation or discontinuation of therapy in JIA.
Role: Site PI

IM101-301-0012 Brystol Myers Squibb (PI) 2013-2016
Phase 3 Multi-center, Open-Label Study to Evaluate Pharmacokinetics, Efficacy and Safety of Abatacept Administered Subcutaneously (SC) in Children and Adolescents with Active Polyarticular Juvenile Idiopathic Arthritis (pJIA) and Inadequate Response (IR) to biologic or non-biologic Disease Modifying Anti-Rheumatic Drugs (DMARDs)
This project is an open label phase 3 study of subcutaneous Abatacept in the pediatric population.
Role: Site PI

NIH U34 Clinical Trial Planning Grant IIowite/Beukelman (PI) 09/2014-08/2015
PREVENT: Prospective Randomized Trial of the Effectiveness of Methotrexate to Prevent Extension of Limited JIA
The purpose of this grant was to plan the randomized double blind placebo controlled clinical trial to study oral methotrexate as an effective agent to prevent extension or uveitis in limited JIA.
Role: Advisor/Trial Design/biospecimens

ACR REF Rheumatology Investigator Award Becker (PI) 07/01/2011-06/30/2014
Signature of Response to Methotrexate in JIA
The goals of this project are to incorporate folate concentrations and folate polyglutamation patterns into the observed variability of response to methotrexate seen in JIA in a prospective study of patients newly prescribed methotrexate.

MC-MTX. 16/HF Children Medac/PPD 2013-2014
Human Factors Study for the Evaluation of the Penmet Prefilled Pen for Subcutaneous Injection in Pediatric and Adolescent Patients with Juvenile Idiopathic Arthritis
The purpose of this grant was to study the ease of administration and usability of the pre-filled methotrexate injection pen.
Role: Principal Coordination Investigator