

Center for Cell and Developmental Biology



Principal Investigators

John A. Barnard, MD, Center Director

Carlton M. Bates, MD

David Brigstock, PhD

Kirk McHugh, PhD

Wenyan Mei, PhD

Christopher Phiel, PhD

Jing Yang, PhD

Research scientists in the Center for Cell and Developmental Biology at Nationwide Children's Hospital study fundamental processes in growth factor biology, cellular signaling, and vertebrate development.

State-of-the-art research models are used, ranging from simple cell culture systems to zebrafish, Xenopus, and genetically modified mice generated in The Research Institute's Transgenic and Embryonic Stem Cell Core.

By establishing a basic scientific foundation for understanding human health, the Center for Cell and Developmental Biology is working to improve diagnosis, treatment and prevention for pediatric diseases such as cancer, cirrhosis, polyposis disorders, neurological disorders and kidney diseases.

Clinical, Teaching And Research Interests

John A. Barnard, MD, is President of The Research Institute at Nationwide Children's Hospital, Vice Chair for Research in the Department of Pediatrics and a Professor of Pediatrics at The Ohio State University College of Medicine. Dr. Barnard's National Institutes of Health (NIH)-funded research program focuses on regulation of intestinal epithelial growth by TGF β (transforming growth factor beta). Generally, in vitro cell culture models and genetically modified mice are used in the lab to dissect out signaling pathways involved in Smad-dependent and Smad-independent signaling, and tumor suppressive signaling from pro-oncogenic signaling. Currently the lab is also characterizing the role of the ZAS transcription factor family in Smad-dependent signaling and characterizing a phenotype observed in transgenic

mouse lines expressing mutant, constitutively active TGF β 1 under direction of the intestine-specific villin promoter. The mice will be used to study pro-oncogenic and tumor suppressive TGF β activities in mouse models of intestinal neoplasia. Dr. Barnard is president of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, a member of the Gastrointestinal Cell and Molecular Biology study section at the NIH and was named among the "Best Doctors in America" in 2007.

Carlton M. Bates, MD, is a member of the Section of Nephrology at Nationwide Children's Hospital, an investigator in the Center for Cell and Developmental Biology at The Research Institute at Nationwide Children's Hospital and an Associate Professor of Pediatrics at The Ohio State University College of Medicine. He is also a member of the Institutional Animal Care and Use Committee at The Research Institute at Nationwide Children's Hospital. Dr. Bates received his medical degree from The Ohio State University College of Medicine. His research emphasis is on the molecular mechanisms of kidney development using the mouse as a model.

David Brigstock, PhD, is Director of the Pediatric Surgery Research Laboratory and a member of the Center for Cell and Developmental Biology at The Research Institute at Nationwide Children's Hospital and an Associate Professor in the Departments of Surgery and Molecular & Cellular Biochemistry of The Ohio State University College of Medicine. He is also a faculty member in the Molecular, Cellular and Developmental Biology Program at The Ohio State University. His laboratory is studying the role of connective tissue growth factor (CTGF) in fibrotic diseases, which are characterized by excessive production and deposition of insoluble collagen matrix, resulting in loss of tissue structure and organ dysfunction. His main research efforts are currently focused on liver and pancreatic fibrosis and collaborative efforts that focus on other organ systems such as the lung, intestine, heart and skin. Using molecular, cellular and biochemical approaches, both in vitro and in vivo, his lab's goals are to understand the mechanisms by which CTGF stimulates collagen production by fibrogenic cells types. In this manner, the therapeutic value of targeting pathways of CTGF biosynthesis or action to treat a variety of fibrotic disorders will be determined.

Kirk McHugh, PhD, is the Director of the Nephrology and Urology Research Affinity Group at The Research Institute at Nationwide Children's Hospital and an

Associate Professor of Pediatrics at The Ohio State University College of Medicine. His current research efforts focus on the development and pathogenesis of the urogenital system. Urinary tract malformations, obstructive nephropathy and renal hypoplasia/dysplasia comprise more than 50 percent of the children with end-stage renal disease worldwide. These defects are extremely important in the terms of pediatric health care costs with end-stage renal disease estimated to cost 1.5 billion dollars annually in the United States alone. Laboratory studies focus on congenital defects in bladder smooth muscle development as well as the resulting pathologies associated with the development of obstructive nephropathy including chronic renal failure and kidney disease. We have identified a highly unique mouse model, designated *mgb* for megabladder, which permits the study of the development of obstructive nephropathy in utero, and are currently using a wide range of genetic and molecular approaches to identify the genes responsible for the developmental defects and subsequent pathologies observed in *mgb* mice. The identification and characterization of the factors responsible for the pathogenic changes in renal function following the development of congenital bilateral obstructive nephropathy in *mgb* mice will provide a platform for the evaluation of pharmacological, surgical and gene therapy strategies designed to prevent and treat the pathogenic processes associated with the development of progressive renal failure in utero.

Wenyan Mei, PhD, is an investigator in the Center for Cell and Developmental Biology at The Research Institute at Nationwide Children's Hospital. Laboratory interests include how RNA binding protein controls cell differentiation and development through post-transcriptional regulation. Zebrafish (*Danio rerio*) are used as a research model system. Specifically, the lab uses a zebrafish mutant called *brom bones*, to study how RNA binding protein hnRNP I, controls oogenesis, egg activation and intestinal development.

Christopher Phiel, PhD, is an investigator in the Center for Cell and Developmental Biology at The Research Institute at Nationwide Children's Hospital and an Assistant Professor of Pediatrics at The Ohio State University College of Medicine. His laboratory is interested in the post-translational modification of proteins, with a focus on how these modifications affect neurodegeneration. Currently, their main project involves understanding how glycogen synthase kinase-3 (GSK-3) isoforms contribute to the amyloid plaques and neurofibrillary tangles, which

are pathological hallmarks of Alzheimer's disease. This effort is being approached through the development of novel transgenic mice and cell lines. Dr. Phiel's long-term goal is to define the molecular mechanism underlying the role for GSK-3 in plaque and tangle formation, with the eventual hope of developing alternative therapeutic strategies for the prevention of Alzheimer's disease.

Jing Yang, PhD, is an investigator in the Center for Cell and Developmental Biology at The Research Institute at Nationwide Children's Hospital and an Assistant Professor of Pediatrics at The Ohio State University College of Medicine. The Yang laboratory has been studying signaling pathways involved in stem cell proliferation and differentiation. Recent studies have identified several signaling pathways that play critical roles in many stem cell lineages. These include the PI3K/Akt pathway, the Wnt pathway, the Notch pathway, and the Hedgehog pathway, et al. The Yang's lab has found that the B56 epsilon regulatory subunit of the protein phosphatase 2A (PP2A:B56ε) is involved in several signaling pathways, including the Wnt pathway, the Hedgehog pathway, and the PI3K/Akt pathway. To better understand the function of PP2A:B56ε, we performed a screen for downstream targets of B56ε. This leads to the identification of a novel glycosyltransferase (XGALNT), which plays essential roles in the neural and retinal stem cell lineage. In addition, we have recently found that hnRNP I plays critical roles in turning off the Notch pathway during intestinal stem cell differentiation. Currently, we try to understand: the functions of PP2A:B56ε in Wnt, Akt, and Hedgehog signaling; the mechanism through which XGALNT regulates retinal and neural stem cells; and the mechanism through which hnRNP I inhibits the Notch pathway.

Research Funding (Over \$50,000)

John A. Barnard, MD

TGF-beta Regulation of Intestinal Epithelial Cells, National Institute of Diabetes & Digestive & Kidney Diseases, \$296,212

Carlton M. Bates, MD

Role of FGF Receptors in the Developing Kidney, National Institute of Diabetes & Digestive & Kidney Diseases, \$304,556

David Brigstock, PhD

Connective Tissue Growth Factor in Hepatic Fibrosis, National Institute on Alcohol Abuse and Alcoholism, \$343,125

Mechanisms of CTGF-induced Liver Disease, National Institute on Alcohol Abuse and Alcoholism, \$324,000

CTGF in Pancreatic Stellate Cell-Mediated Fibrogenesis, National Institute on Alcohol Abuse and Alcoholism, \$319,500

Targeting Connective Tissue Growth Factor in Fibrotic Liver Disease, Anonymous, \$55,000

Kirk McHugh, PhD

A Genetic Model of Urogenital Development and Obstruction, National Institute of Diabetes & Digestive & Kidney Diseases, \$296,212

Co-regulatory Model of Smooth Muscle Myogenesis, National Institute of Diabetes & Digestive & Kidney Diseases, \$269,910

Publications

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