



**Mount  
Sinai** *The Mindich Child Health  
and Development Institute*

# MCHDI Developmental Outcomes

Fall 2015

## Research Advancements: Neurodevelopment

### Reconstructing the Exposome: Implications for Children's Environmental Health

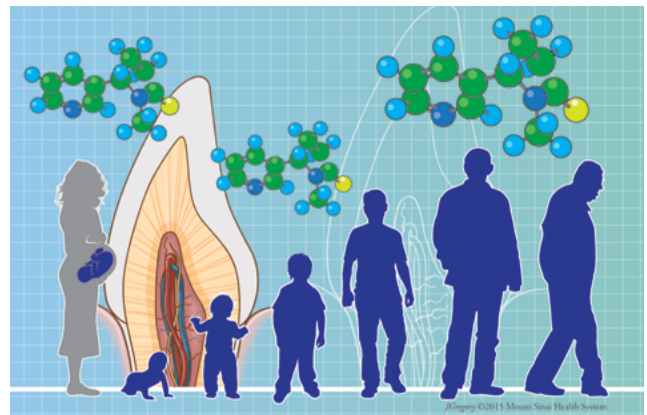
Environmental exposures are recognized as major determinants of life-long health trajectories and are believed to play important roles in childhood disorders such as autism. The array of pollutants, their routes of exposure, and the physiologic pathways that metabolize these chemicals change drastically as we transition from a fetal environment to early postnatal life. Because of this, perturbations during vulnerable periods in early life, called 'windows of susceptibility', when an individual's regulatory mechanisms for handling specific chemicals are immature and crucial developmental processes are underway, can cause life-long dysfunction.

In addition to the growth of the 'windows of susceptibility' model, researchers recognize that the thousands of environmental chemicals that humans are exposed to may exert joint effects distinct from their individual effects. The "Exposome" concept addresses this issue and encompasses lifelong environmental exposures, from the prenatal period onwards. Beyond the large number of environmental chemicals that humans are exposed to routinely, it is also important to recognize the exposome is highly dynamic, changing over short periods of time.

Epidemiologic studies that investigate developmental programming of long-term health trajectories face major challenges when trying to estimate the fetal exposome, especially when studying lower frequency health outcomes. Longitudinal birth cohort studies that collect biomarkers of environmental chemical exposure during pregnancy and then follow offspring into childhood provide the highest evidence study design to assess the impact of exposures during key developmental windows. However,

the large sample sizes and time required for such studies are major barriers to investigating lower frequency conditions with long latency periods. For example, to determine the fetal origins of a disorder that occurs at a frequency of 1:100 live births, 10,000 pregnant women would need to be recruited to obtain 100 cases and biomatrices repeatedly collected from the offspring prospectively until a stable clinical diagnosis could be made many years later.

To overcome these limitations, Manish Arora, Associate Professor of Preventive Medicine and his colleagues, Syam Andra and Christine Austin, have proposed the development of a 'retrospective temporal exposome' that relies on novel biomatrices that store exposure information from the prenatal period onwards. One such matrix is teeth, which have growth rings (similar to rings in trees). The archival nature of tooth dentine, which captures and preserves important aspects of developmental history, can be used to retrospectively study health outcomes in response to early life environmental stressors including chemicals. Recently, Dr. Arora's team at the Senator Frank R Lautenberg Environmental Health Sciences Laboratory has shown that a surprisingly large number of chemical signatures can be recovered from teeth, ranging from metals to organic compounds, some of which have very short half-lives in blood and urine. Dentine, which undergoes very limited remodeling, preserves both the timing and intensity of



*Depiction of various stages of development from fetal life to adulthood, with changing chemical exposures from a highly dynamic environment. Novel tooth matrix biomarkers can be used to retrospectively uncover temporal variations in the exposome.*

*Illustration by Jill Gregory, ISMMS Department of Academic Medical Illustration; jill.gregory@mssm.edu*

chemical signatures over the second and third trimesters, and this property has allowed them to reconstruct trimester-specific information for more than 12,000 unique signatures. Most importantly, it was possible to analyze the deciduous/baby teeth 7 to 10 years after the exposure event. The team is applying this technology to study the environmental determinants of disorders including autism and amyotrophic lateral sclerosis (Lou Gehrig's disease), and also to better understand the role that environmental exposures play in shaping neurodevelopmental trajectories in children.



**Manish Arora, PhD,  
BDS, MPH**

Associate Professor  
of Preventive Medicine  
Associate Professor  
of Dentistry

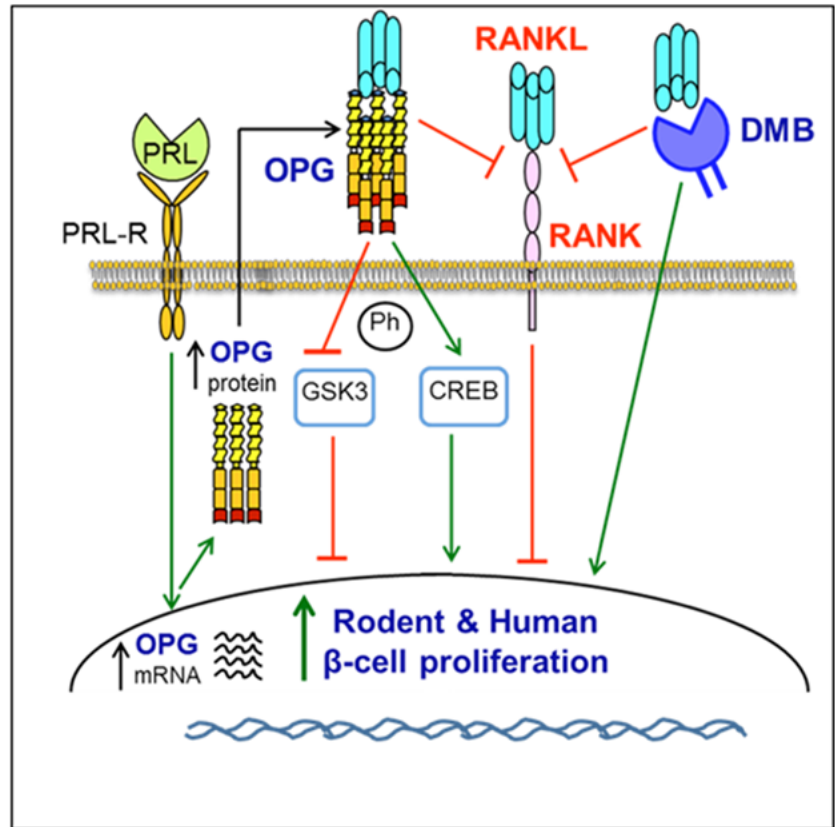
## Bone-related Pathway Stimulates Pancreatic Beta Cell Proliferation

Diabetes mellitus is a metabolic disease of insulin insufficiency leading to high blood sugar levels. If left untreated, chronic hyperglycemia causes tissue damage, leading to secondary complications of diabetes, which include diabetic neuropathy, nephropathy, retinopathy, cardiovascular disease, and eventually increased mortality. Diabetes is one of the fastest growing diseases worldwide, with a steep rise in the health and economic burdens placed by the disease and its complications.

The two major forms of diabetes are type 1 diabetes (T1D) and type 2 diabetes (T2D). T1D is an autoimmune disease in which the body's immune system attacks and destroys the pancreatic beta-cell, causing severe insulin deficiency and hyperglycemia. T2D, the more prevalent form of the disease, results from a combination of insulin resistance, inability of the body to properly sense and respond to insulin, and insufficient insulin production. Unfortunately, there has been a rise in both T1D and T2D in children.

Inadequate insulin arises from a deficiency in endogenous functional pancreatic beta-cell mass. The loss of functional beta-cells in diabetes can occur for several reasons, including improper beta-cell differentiation from precursor cells, defects in beta-cell function, increased beta-cell loss due to cell death, and/or inability of the beta-cell to compensate through increased proliferation. A major focus in the laboratory of Rupangi Vasavada, PhD, Associate Professor of Medicine, is to reverse these processes in diabetes, by enhancing regeneration, replication, function, and survival of beta-cells using naturally occurring peptides, including Prolactin (PRL) and Placental Lactogens, members of the lactogenic hormone family.

Nagesha Guthalu Kondegowda, PhD, Research Assistant Professor and long-standing member of Dr. Vasavada's group, took an unbiased approach to uncover novel downstream targets of lactogens. This led to the identification of a bone-related peptide, Osteoprotegerin (OPG) that is increased by lactogens in the beta-cell. OPG, a soluble decoy receptor, inhibits receptor-ligand interactions between Receptor Activator of NF- $\kappa$ B (RANK) and RANKL, thereby affecting bone turnover, lactation, and a variety of other processes. Interestingly, OPG



Schematic representation of the regulation of beta-cell proliferation by PRL and OPG. Prolactin (PRL) induces expression of Osteoprotegerin (OPG), a bone-related molecule, in pancreatic beta-cells. OPG stimulates beta-cell proliferation in young and aged mice by binding to RANKL, thereby inhibiting the interaction of RANKL with its receptor, RANK, which acts as a brake in beta-cell replication. OPG and Denosumab (DMB), an anti-RANKL antibody and an FDA-approved drug for osteoporosis, enhance human beta-cell replication in vitro and in humanized mice. Kondegowda NG, et al *Cell Metab.* 2015 Jul 7;22(1):77-85.

expression increases in pancreatic islets under conditions that promote beta-cell expansion, such as pregnancy and obesity, suggesting that OPG may be directly involved in beta-cell growth.

Dr. Vasavada's group found that indeed, OPG-treatment enhanced rodent beta-cell replication in young, old, and diabetic mice by 7-14 days, leading to an increase in beta-cell mass with longer treatment. OPG was required for PRL-induced proliferation of rodent beta-cells in vivo, implying that it is a functional downstream target of lactogens in the beta-cell. Importantly, OPG induced replication of adult human beta-cells, which are normally highly refractory to proliferation. Competition and genetic approaches to understand the mechanism of OPG action identified RANKL/RANK as a molecular brake in rodent and human beta-cell replication. OPG was found to promote beta-cell proliferation by binding RANKL and preventing its

interaction with its receptor, RANK, thus inhibiting the brake. Denosumab (DMB), an antibody specific to human RANKL, and an FDA-approved osteoporosis drug, also counteracts this brake to induce human beta-cell proliferation in vitro and in vivo in humanized mice.

Thus, a pathway originally characterized in bone may be manipulated to normalize beta-cell homeostasis in diabetes, and there may be potential to repurpose an osteoporosis drug for diabetes treatment in the future.



**Rupangi Vasavada, PhD**  
Associate Professor  
of Medicine

## New Extramural Faculty

### Nadia Micali, MD, MRCPsych, PhD, FAED

Nadia Micali, MD, MRCPsych, PhD, FAED, is an Associate Professor of Psychiatry and a clinician-scientist who will be developing a research and clinical program within the Center of Excellence for Eating and Weight Disorders under the direction of Tom Hildebrandt, PhD. Most recently, Dr. Micali was a Senior Lecturer in the Brain and Behavior Sciences Unit at the University College of London Institute of Child Health and an Honorary Child Psychiatrist in feeding and eating disorders at Great Ormond Street Hospital.

Dr. Micali received her MD from the University of Messina School of Medicine in Italy, and her PhD from the Institute of Psychiatry, King's College London. She trained in Child and Adolescent Psychiatry, with a specialty in Eating Disorders at the Maudsley Hospital and Institute of Psychiatry, London, UK. She is also a trained epidemiologist. Over the course of her career, Dr. Micali has written over 80-peer reviewed papers and has given over 50 lectures and presentations around the world. She serves as an elected executive member of several societies, including the Eating Disorders Faculty, Royal College of Psychiatrists, the Child and Adolescent Psychiatry Surveillance System, and the Eating Disorders Research Society (of which she is currently President). Dr. Micali is also an active member of the Academy of Eating Disorders.

Dr. Micali's research focuses on understanding biological and intergenerational risk for eating disorders using a developmental perspective. Her research has investigated the epidemiology

#### Recent Publications:

**Micali, N.,** Solmi, F., Horton, NJ, Crosby, RD, Eddy, KT, Calzo, JP, Sonnevile, KR., Swanson, SA., Field, AE. Adolescent eating disorders predict psychiatric, high-risk behaviors and weight outcomes in young adulthood. *Journal of the American Academy of Child and Adolescent Psychiatry.* 2015 Aug;54(8):652-659.

**Micali, N.,** Field, AE., Treasure, J., Evans, D. Are obesity-risk genes associated with binge-eating in adolescence? *Obesity.* 2015 Aug;23(8):1729-36.

**Micali, N.,** De Stavola, B., Ploubidis, G., Simonoff, E., Treasure, J., Field, A.E. Eating disorders behaviours and cognitions in adolescence: gender-specific patterns in the prospective effect of child, maternal and family risk factors. *British Journal of Psychiatry.* 2015 Jul 23.

Sonneville KR, Calzo JP, Horton NJ, Field AE, Crosby RD, Solmi F, **Micali N.** Childhood hyperactivity/inattention and eating disturbances predict binge eating in adolescence. *Psychological Medicine.* 2015 Jun 22:1-10.

Rhind C, Bonfioli E, Hibbs R, Goddard E, Macdonald P, Gowers S, Schmidt U, Tchanturia K, **Micali N\***, Treasure J.\* (\*joint senior authors) An examination of autism spectrum traits in adolescents with anorexia nervosa and their parents. *Molecular Autism.* 2014 Dec 20;5(1):56.

of adolescent eating disorders and behaviors and their etiology, including biological and intergenerational risk; the biological and neuropsychological basis of 'at risk' status; and pregnancy and reproductive outcomes. The impact of Dr. Micali's research is underscored by her role on editorial boards of top journals in the field, including *European Child and Adolescent Psychiatry*, the *European Eating Disorders Review*, and *Advances in Eating Disorders: Research, Therapy and Practice*.

Dr. Micali's contributions to the field of eating disorders have been recognized by several awards, most notably a prestigious fellowship by the Academy of Eating Disorders and her election as 2015 President of the Eating Disorders Research Society. She has also been appointed as a special advisor on the UK National

Institute of Clinical Excellence Antenatal Mental Health Guideline Development Group that developed guidelines for the identification and treatment of eating disorders in pregnancy. Dr. Micali is also extremely committed to training and education and helped establish a Master's Degree in Eating Disorders at University College London, the only such degree in the world.



**Nadia Micali, MD, MRCPsych, PhD, FAED**  
Associate Professor of Psychiatry

### Allan Just, PhD

Allan Just, PhD is an Assistant Professor of Preventive Medicine at the Icahn School of Medicine at Mount Sinai. Dr Just is an environmental epidemiologist with interests in children's environmental health, computational methods for epigenomics, environmental epigenomics, endocrine disrupting compounds, and air pollution modeling using satellite data. He received his PhD in Environmental Health Sciences from Columbia University in 2012. Since 2012 he completed a postdoctoral fellowship in Environmental Epigenetics at the Harvard T.H. Chan School of Public Health. Dr Just is a past recipient of an EPA STAR graduate fellowship for his

dissertation work on phthalate mixtures and children's respiratory health and was awarded a K99/R00 grant from the National Institute of Environmental Health Sciences entitled "Prenatal Exposure to Endocrine Disrupters, DNA Methylation, and Childhood Obesity" (R00ES023450). His R00 grant is based in the Mexico City cohort of the Programming Research in Obesity, Growth, Environment, and Social Stressors (PROGRESS) study as well as the Programming of Intergenerational Stress Mechanisms (PRISM) study. He is collaborating with the National Institute of Public Health, Mexico and the Mexican Center for Research in Geography and Geomatics on a grant from the Mexican National Council of Science and Technology (CONACyT) that

addresses air pollution and health using the Mexican National Health and Nutrition Examination Survey (ENSANUT). He is also in the coordinating groups for several epigenomic meta-analyses as part of the Prenatal and Childhood Epigenetics (PACE) consortium and the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium.



**Allan Just, PhD**  
Assistant Professor of Preventive Medicine

## New Intramural Faculty

### Dani Dumitriu, MD, PhD

Dani Dumitriu, MD, PhD, is an Assistant Professor in Neuroscience and Resident in Pediatrics. Following the completion of the MD/PhD Program at Mount Sinai, she matched into the Pediatrics residency and successfully negotiated a custom-tailored residency program with significant protected research time. She is currently a PGYIII and devotes approximately 50% effort to her medical training and 50% effort to running her lab. Her research focuses on understanding the neurobiological basis for resilience, i.e. the

brain wiring that gives some individuals the ability to withstand adversity. Her lab currently uses on a mouse model of social defeat in order to elucidate the pre-existing neural networks that render roughly one third of the population immune to this type of stress. This question is being addressed with a combination of behavioral tasks, identification of neuronal subnetworks using anterograde and retrograde viruses, high resolution confocal microscopy of dendritic spines, resting state fMRI, quantitative whole-brain immunohistochemistry, graph theory analysis of network dynamics, electrophysiology and

optogenetics. Following identification of resiliency networks, she plans to study developmental interference of these circuits by psychological and toxicological stressors. Her ultimate goal is to pioneer *developmental neuroprevention* by creating tools that will protect and enhance resiliency in children.



**Dani Dumitriu, MD, PhD**  
Assistant Professor in Neuroscience

## Faculty Highlights

### Joseph Buxbaum, PhD Elected to National Academy of Medicine

Joseph D. Buxbaum, PhD, Professor and Vice Chair for Research in the Department of Psychiatry at the Icahn School of Medicine at Mount Sinai, has been elected as one of 70 new members to the prestigious National Academy of Medicine (NAM), formerly known as The Institute of Medicine (IOM). A world-renowned molecular geneticist and neurobiologist, he is also the Director of the Seaver Autism Center for Research and Treatment at Mount Sinai.

“Election to the National Academy of Medicine is considered one of the highest honors in medicine,” says Dennis S. Charney, MD, the Anne and Joel Ehrenkranz Dean of the Icahn School of Medicine at Mount Sinai. “Dr. Buxbaum’s election is a notable achievement and well-deserved recognition of his leadership and important contributions to uncovering the genetic and molecular basis of autism spectrum disorder.”

Dr. Buxbaum’s research focuses on using techniques of molecular genetics and neuroscience to identify and characterize genes that contribute to autism susceptibility. His laboratory has identified common and rare genetic variants that underlie autism and has developed model systems in which novel therapeutics can be tested. This work has led to novel clinical trials in rare genetic disorders associated with autism. As the founder and co-leader of the Autism Sequencing Consortium, he heads an international group of scientists who share autism samples, data and ideas in order to accelerate our understanding of the causes of and treatments for autism.

Recruited in part to establish a molecular genetics program in autism, Dr. Buxbaum joined Mount Sinai in 1997 as Director of Molecular Genetics at the Seaver Autism Center. He took over Directorship of the Center in 2008. Dr. Buxbaum also leads Mount Sinai’s Laboratory of Molecular Neuropsychiatry, which has taken the findings of the causes of neuropsychiatric disorders and translated them into animal models where therapeutic approaches can be evaluated.

Dr. Buxbaum earned his PhD from the Weizmann Institute of Science in Rehovot,

Israel, and completed a post-doctoral fellowship in the Laboratory of Molecular and Cellular Neuroscience at the Rockefeller University. He is the author of more than 200 publications, and he is co-editor in chief of the journal *Molecular Autism*.

New members to the NAM are elected by current active members through a selective process that recognizes people who have made major contributions to the advancement of the medical sciences, health care, and public health. Established in 1970 by the National Academy of Sciences, the National Academy of Medicine is a national resource that provides independent, objective analysis and advice on health issues.



**Joseph D. Buxbaum, PhD**  
Vice Chair for Research, Department of Psychiatry  
Vice Chair for Mentoring, Department of Psychiatry  
Director, Seaver Autism Center for Research and Treatment  
Professor, Psychiatry, Neuroscience and Genetics & Genomic Sciences

***“Election to the National Academy of Medicine is considered one of the highest honors in medicine. Dr. Buxbaum’s election is a notable achievement and well-deserved recognition of his leadership and important contributions to uncovering the genetic and molecular basis of autism spectrum disorder.”***

***—Dennis S. Charney, MD, Anne and Joel Ehrenkranz Dean of the Icahn School of Medicine at Mount Sinai***

## Faculty Highlights

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### Awards/Honors

**Manish Arora**, PhD, BDS, MPH, International Association of Exposure Sciences (ISES), “Joan Daisey Award”

**Jia Chen**, ScD, Chairperson MEG Chairperson-Elect Nominating Committee Molecular Epidemiologic Group American Association of Cancer Research

**Hirofumi Morishita**, MD, PhD, **Manish Arora**, PhD, BDS, MPH, Icahn School of Medicine at Mount Sinai, “Inaugural Faculty Innovative Collaborations-Idea Prize”

### New York Magazine's 2015 “Best Doctors”

**Bruce Gelb**, MD  
Pediatric Cardiology

**Hugh Sampson**, MD  
Pediatric Allergy & Immunology

**Scott Sicherer**, MD  
Pediatric Allergy & Immunology

**Julie Wang**, MD  
Pediatric Allergy & Immunology

**Barbara Coffey**, MD  
Child & Adolescent Psychiatry

**Jeffrey Saland**, MD  
Pediatric Nephrology

**Birte Wistighausen**, MD  
Pediatric Hematology-Oncology

### Grants

**Supinda Bunyavanich**, MD, MPH, NIH/NIAID, R01 grant, “Nasal Biomarkers of Asthma”

**Joseph Buxbaum**, PhD, Human Frontier Science Program, “Deciphering brain oxytocin circuits controlling social behavior”

**Ross Cagan**, PhD; **Bruce Gelb**, MD; Arvin Dar, PhD; Carlos Cordon-Cardo, PhD, NIH/NHLBI, U54 grant, “A New Disease Platform Leveraging Complex Drosophila and Mammalian Models”

**Chenleng Cai**, PhD, American Heart Association, “Isl1 Transcriptional Program in SHF Cardiac Progenitor Cell Development”

**Chenleng Cai**, PhD, NIH/NHLBI, R56 grant, “Tbx1 and canonical Wnt signaling in the second heart field”

**Chris Gennings**, PhD; Susan Teitelbaum, PhD, NIH/NIEHS, Child Health Environmental Assessment Resource grant (Data Center)

**Robert Krauss**, PhD, NIH/NIDCR, R01 grant, “Molecular and developmental analysis of holoprosencephaly”

**Hirofumi Morishita**, MD, PhD, NIH/NEI, R01 grant, “Regulation of adult visual cortex plasticity by endogenous nicotinic modulators”

**Lisa Satlin**, MD, NIH/NIDDK, R01 grant, “Maturation of K Transport in the Distal Nephron”

**Andrew Sharp**, PhD; Patricia Kovatch, Claudio Luz, PhD, NIH/NHGRI, Community Research Education and Engagement for Data Science (CREEDS)

**Shanna Swan**, PhD, EU, Horizon 2020, “European Joint Doctorate in Biology and Technology of Reproductive Health”

**Rupangi Vasavada**, PhD, JDRF, “Therapeutic Potential of Osteoprotegerin and Denosumab in Diabetes”

**Robert Wright**, MD, MPH; **Manish Arora**, PhD, BDS, MPH, NIH/NIEHS, Child Health Environmental Assessment Resource grant (Laboratory network hub)

**Rosalind Wright**, MD, MPH, NIH/NICHHD, R01 grant, “Early life stress, telomere attrition, and child prefrontal cortex functioning”

## Faculty Highlights

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### Publications

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Kidd BA\*, Wroblewska A\*, Boland MR, Agudo J, Merad M, Tatonetti NP, **Brown BD**^, Dudley JT^ . Systematic integrative analysis of immune pharmacology. *Nature Biotechnology*. 2015. [In press] \*Equal contribution ^Co-corresponding authors.

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## Save the Date: MCHDI 3rd Annual Retreat

# SAVE THE DATE

## 3<sup>rd</sup> Annual MCHDI Retreat

**Date: November 18, 2015**

**Time: 8:30AM-3:30PM**

**Location: New York Academy of Medicine**

**Library Reading Room, 3<sup>rd</sup> Floor**

**1216 Fifth Avenue, New York, NY 10029**



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and Development Institute*



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and Development Institute*

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