Clinical Trials & Studies

临床试验和研究

Triheptanoin (UX007) | Treatment of Mitochondrial Dysfunction in Rett Syndrome
三庚酸甘油脂（UX007）| 雷特综合征中线粒体功能紊乱的治疗

Daniel Tarquinio, DO, MS | Emory University | Children's Pediatric Neurology Practice
丹尼尔·奎尼奥|埃默里大学|儿童神经病学科

$51,600 AWARDED
51600 美元奖励

Dr. Daniel Tarquinio, the director of the Rett Syndrome Clinic in Atlanta will soon be recruiting for a 10 person, open label trial (everyone gets the drug) testing triheptanoin. The drug, also called UX007, is a colorless oil which is broken down in the body to help fuel specific chemical reactions that produce energy. Administration of UX007 has shown improvements in both metabolism and mortality in disorders with impaired energy production (for example, mitochondrial disorders). Treatment with UX007 improved longevity, motor function, and social interaction in the mouse model of Rett Syndrome, and may have improved metabolic dysfunction as well. Additionally, in general acute and chronic mouse models of epilepsy, UX007 acts as an anticonvulsant, although the mechanism for this is unclear.

位于美国亚特兰大的雷特综合征临床研究主任 Daniel Tarquinio 博士宣布将很快在亚特兰大招募 10 名药物试验志愿患者，进行三庚酸甘油脂的开放式标签试验（测试者和受试者都知道其测/受试的药物）。该药物也被称为 UX007，为无色油脂，其在体内被分解从而为产生能量的化学反应供给燃料。UX007 药物改善了由于能量产生障碍（例如，线粒体功能障碍）而引起的新陈代谢紊乱并降低了相关疾病的死亡率。在雷特综合征试验小鼠模型上，UX007 的治疗提高了受试鼠寿命、 运动和社交功能，并改善了模型小鼠的新陈代谢。此外，虽然机理尚不明确，UX007 对急性和慢性癫痫老鼠模型具有抗惊厥作用。

The primary objective of the study is to evaluate the safety and tolerability of UX007 in subjects with Rett Syndrome using laboratory values, electrocardiogram, rate of adverse events (AE), and physical exam

这次试验的主要目的是评估 UX007 在雷特综合症患者上的安全性和耐受性，其中包括监测患者的心电图，不良反应比率（AE）以及常规的身体检查。

The secondary objectives are to evaluate the efficacy of UX007 in improving overall seizure frequency and dystonia.

这次试验的第二个目的是评估 UX007 药物在改善整体惊厥频率和肌张力障碍的功效。

The study will enroll 10 pediatric, adolescent, and adult participants with Rett who have seizures (at least four seizures per month), dystonia (at least four dystonic episodes per month), or both. They must be on a stable medication regimen, defined as having had no medications added, taken away or dose adjustments for 30 days prior to the start of the study.
Pediatric participants must be at least 2 years old at the time of consent, and must be in the post-regression period, defined as having had no clear loss of language or hand use in the 6 months prior to the study.

这项研究将招募 10 名儿童、 青少年和成年雷特综合症患者。 受试者要求有癫痫发作 （每月至少四次癫痫发作）或/和肌张力障碍 （每个月的至少四次肌张力障碍发作）的病史。此外受试者还必须有稳定的用药规律，即在试验开始前 30 天没有新增、停用药物或是药物剂量调整。儿童的参与者必须至少 2 周岁，并且在开始试验前 6 个月内没有明显的语言和手部行为丧失。

Participants will be evaluated for inclusion during a screening/baseline period of 2 months. Eligible participants will begin UX007 after 2 months using a 2-week titration schedule until the subject has reached age-specific target dosing. Once the maximum dose is reached, the participant will continue to receive UX007 for 4 months. Participants will be monitored for an additional 2-month period.

受试者将首先通过两个月的筛选和基本标准评估。合格者将在两个月之后开始服用 UX007 药物，通过逐渐测加药量达到特定年龄群的目标计量，一旦确定最大剂量，参与者将连续服用四个月的 UX007 并接受额外两个月的观察。

The trial is funded by Ultragenyx and RSRT.

该临床试验由 Ultragenyx 和 RSRT 提供资金

For more information about the trial please contact Dr. Tarquinio.

关于试验的更多信息请联系 Tarquinio 博士

Outcome Measures and Biomarkers Development: An Ambitious Project To Advance Clinical Trial Methodology for Rett Syndrome
结果评估和生物标志物的开发： 促进雷特综合征临床试验方法的项目

$4,500,000 AWARDED
450 万美元奖励

In the last decade, researchers have made remarkable progress in the Rett research field, yielding a number of potential drugs and procedures (eg. brain stimulation) with undoubtedly many more to come. For each drug or procedure proposed, doctors must conduct a clinical trial to determine if the drug or procedure is actually effective in reducing Rett symptoms. This rigorous testing, called a clinical trial, can take years and millions of dollars to conduct. One key to conducting efficient and effective trials is the identification and validation of reliable outcome measures and biomarkers.

在过去十年中，研究人员在雷特综合症研究领域取得了非凡的进展， 开发出了多种潜在的药物和治疗手段(例如：大脑刺激)。对于每一种可能的药物或治疗手段，医生必须进行一个临床试验以确定药物或治疗方法是否在减轻雷特症状方面具有实际的效果。这种严格的测试，称作临床试验，它的进行可能花费几百万美元和多年的时间。进行高效和有效的临床试验的一个关键是确定和证明可靠的结果评估指标和生物标志物。

Outcome Measure – A measurement or assessment used to objectively determine particular aspects of symptoms, function, or health condition of a patient at the beginning of a clinical trial, during and after treatment

结果评估指标 – 一个用于客观地确定特定的症状，功能或在一项临床试验开始，治疗期间和治疗结束后对病人健康状况的测量或评估

Biomarkers – Characteristics that are objectively measured and evaluated as indicators of normal biological processes, abnormal processes, or responses to therapeutic intervention. A biomarker (e.g., a molecule found in blood) can become an outcome measure if it is closely associated with how well the body responds to a treatment.

生物标志物 – 能够客观地测量和评价正常或异常生物过程的指标或对治疗干预的反应。与身体反应程度密切相关，因此生物标志物 （例如，在血液中发现的分子） 可以成为一个结果评估指标。

TIMOTHY BENKE

蒂莫西 本克

Dr. Benke is Associate Professor in the Department of Pediatrics, Neurology and Pharmacology at the University of Colorado School of Medicine. He runs the Rett Syndrome Clinic at Children's Hospital Colorado.

Benke 博士是科罗拉多医学院神经学和药理学小儿科的副教授。他在科罗拉多儿童医院从事雷特综合症的临床研究。

SASHA DJUKIC

萨沙 德祐尅可

Dr. Djukic is Professor of Neurology at Albert Einstein College of Medicine. She started the Rett Syndrome Center at Children's Hospital at Montefiore in 2007. The clinic now follows hundreds of patients.

Djukic 博士是阿尔伯特 爱因斯坦医学院神经病学教授。她于 2007 年开始在蒙蒂菲奥里儿童医院雷特综合征中心从事研究工作。现在正对几百个患者做临床跟踪治疗。

ALAN PERCY

艾伦 珀西

Dr. Percy is an authority on Rett Syndrome having seen his first patient with the disorder in 1984. He is a Professor of Neurology at the University of Alabama Birmingham School of Medicine and directs the Sparks Clinics Rett Syndrome Research program.

珀西博士是一位雷特综合征研究方面的专家，早于 1984 年就接触了第一个神经紊乱的患者。他是阿拉巴马州伯明翰医学院的神经学教授，并指导斯帕克斯雷特综合征研究项目。

DANIEL TARQUINIO

丹尼尔·塔尔奎尼奥

Dr. Tarquinio is a child neurologist and epileptologist who trained with Dr. Percy. After spending several years at the Rett Clinic in Boston he recently started his own Rett clinic Chilren's Healthcare of Atlanta. He is Assistant Professor of Neurology at Emory University.
塔尔奎尼奥博士一个神经学家和癫痫学家，他曾与珀西博士一起学习过。他在波士顿从事雷特临床研究几年之后，现在在亚特兰大儿童健康保健中心从事雷特临床研究。他是埃默里大学神经学系的助理教授。

Every single conversation with a pharmaceutical company, biotech or investor starts off with the same questions: What outcome measures would we use to test our drug in Rett? What would the clinical trial look like and what is the FDA's view on meaningful symptomatic improvements? These questions starkly highlight the fact that currently there is no consensus on the optimal suite of clinical outcome measures or biomarkers.
每一次与制药公司、 生物技术或投资者单独的会谈均开始于同样的问题： 我们会用什么结果评估指标去测试我们治疗雷特症状的药物？临床试验将会怎样以及美国食品药品管理局对于有意义的症状改善的观点是什么？这些问题强调的事实是当前在临床结果评价指标或生物标志物上尚无共识。

Companies want to ensure that if they invest time and money to develop a drug for Rett, that a reliable path to test it appropriately in patients exists.
制药公司想要确保如果他们投入时间和金钱来开发一种治疗雷特的药物，他们需要一种可靠的评价手段。

Many features of Rett syndrome are difficult to quantify accurately. Abnormal gait, stereotypical hand movements, and anxiety are some of the core diagnostic features of Rett, yet no reliable method exists to quantify them. Additionally, seizures are often reported inaccurately; in one study, 62% of electrographic (EEG) seizures were not recognized clinically by parents, and 82% of events identified by parents as "seizures" were not associated with EEG seizure. Moreover, autonomic function and associated features, such as breathing dysregulation, skin temperature changes, and cardiac conduction abnormalities are all of interest but difficult to monitor continuously.
许多雷特综合症的特征难以被准确地量化。反常的步态，刻板的手部动作，以及焦虑是雷特的主要诊断特征，不幸的是到目前为止还没有现存可靠的方法去量化它们。此外，癫痫经常不能被准确地报告；在一项研究中，62%的脑电癫痫并没有被家长意识到， 还有82%被家长认为的"癫痫"并没有得到脑电图的证实。而且，自主神经功能以及一些其他相关联的特征，例如呼吸调节异常，皮肤温度变化，以及心脏传导异常等情况虽令人感兴趣，但难以被连续不断地监测。

> *"The OMBD Consortium is a prime example of RSRT's leadership in seeking breakthroughs for therapy of Rett Syndrome. This project will serve as a landmark effort to define the optimal means of studying investigational drugs in clinical trials for Rett Syndrome and will help all those who are developing drugs in this field."*
> *"OMBD 财团是领导的 RSRT 在寻求突破雷特综合征治疗的一个主要例子。 这个项目致力于寻求治疗雷特综合征的有效药物，并将帮助所有正在开发这一领域药物研究者。*
>
> ***DAVID SCHEER***
> *大卫 希尔*
> *RSRT Advisor and Biotech Entrepreneur*
> *RSRT 顾问和生物技术企业家*

The OMBD Consortium is designed to be nimble, allowing the pursuit of outcomes that look encouraging while quickly discarding those that don't. RSRT will manage the infrastructure to properly curate this ambitious project including a cutting edge data management system that will make anonymized data available to clinicians, scientists, industry and investors, thereby maximizing its potential use.

Alan Percy, Daniel Tarquinio, Tim Benke and Sasha Djukic, each directors of a Rett Syndrome Clinic, will collaborate on this ambitious project to explore a variety of outcome measures and biomarkers. The scales will be tested on 250 patients while the other tests will be first piloted on a smaller number of patients and then if validated will move to testing in larger number of patients. OMBD 联盟秉承追求效果的同时也迅速放弃那些不令人满意的成果。RSRT 将全力以赴以妥善实施每个雄心勃勃的项目，包括建立全球领先的数据管理系统，这一系统的建立将使匿名资料的数据可用于临床医生、 科学家、 行业和投资者，从而使它的潜在用途最大化。艾伦 珀西, 丹尼尔 • 塔尔奎尼奥, 蒂姆 本克 和萨沙 德祐兎可每个雷特综合症临床研究的主任在这个项目上相互合作，探索各种各样的结果评估指标和生物标志物。其规模将达到在 250 名患者身上做实验，首先在少数患者身上进行测试，一旦通过验证将用于更多的患者。

Study	*Study Type*	*Domain*
Severity Scales	*Outcome Measure*	Global
Dystonia Scales	*Outcome Measure*	Dystonia
Biometric Watches	*Outcome Measure*	Motor function Stereotypies Autonomic function
Gait Analysis	*Outcome Measure*	Gait
Eye Tracking	*Outcome Measure*	Eye-tracking Recognition and Memory
fNIRS	*Biomarker*	Frontal lobe function
Autonomic Function	*Outcome Measure*	Respiratory function
Pupillometry	*Outcome Measure*	Autonomic function
Cortisol Measurements	*Biomarker*	Metabolite measurement
Metabolic Assays	*Biomarker*	Metabolite measurements
Whole Genome Sequencing	*Biomarker*	Genomic status

Study 研究	Study Type 研究类型	Domain 领域
Severity Scales 严重程度	Outcome Measure 结果评估指标	Global 总体

Dystonia Scales 肌张力障碍	Outcome Measure 结果评估指标	Dystonia 肌张力障碍
Biometric Watches 生物计量	Outcome Measure 结果评估指标	Motor function 运动机能 Stereotypies 刻板行为 Autonomic function 自主神经功能
Gait Analysis 步态分析	Outcome Measure 结果评估指标	Gait 步态
Eye Tracking 眼睛跟踪	Outcome Measure 结果评估指标	Eye Tracking 眼睛跟踪 Recognition and Memory 识别和记忆
fNIRS 功能近红外光谱成像技术，是一种无创的大脑皮层功能活动检测手段	Biomarker 生物标志物	Frontal lobe function 大脑额叶功能
Autonomic Function 自主神经功能	Outcome Measure 结果测量	Respiratory function 呼吸功能
Pupillometry 瞳孔测量法	Outcome Measure 结果测量	Autonomic function 自主神经功能
Cortisol Measurement 皮质醇测量	Biomarker 生物标志物	Metabolite measurement 代谢物测量
Metabolic Assays 新陈代谢测量	Biomarker 生物标志物	Metabolite measurement 代谢物测量
Whole Genome Sequencing 基因组测序	Biomarker 生物标志物	Genomic Status 基因组状态

From Sensory-Perceptual Representations to Cognitive Processing in Rett Syndrome
从雷特综合症的感知表现到认知过程

John Foxe, PhD., University of Rochester, Albert Einstein College of Medicine | Sophie Molholm, PhD, Albert Einstein College of Medicine
约翰 福克斯博士，罗契斯特大学，阿尔伯特 爱因斯坦医学院 / 索菲 摩郝母博士，阿尔伯特 爱因斯坦医学院

$533,607 AWARDED
533，607 美元奖励

Most individuals with Rett Syndrome have lost the ability to speak or use their hands. It is therefore often difficult to assess just how much information is being processed and understood. Modern brain mapping techniques can be of enormous utility in these situations. The emergence of easily applied high-density electrode systems over the past decade, and the development of specialized probes of auditory and cognitive processing, allow clinical scientists to monitor the workings of the brain as children process the things they hear. That is, we no longer have to rely on a child being able to tell us what they can hear and understand; rather, we can ask their brain directly by monitoring its ongoing activity.

大部分雷特综合征患者失去了说话的能力或手部功能。因此经常难于判定有多少信息被处理和理解。这样的情况下现代脑电图技术就体现出其优势。在过去的十年里出现了容易应用的高密度电极系统，以及在听觉和认知过程方面认知的进展，使临床科学家们可以在患儿处理听到的信息同时监测大脑的活动。就是说，我们不再只是依赖患儿能够告诉我们他们所听到的和理解的；不如说，我们能够直接对大脑活动进行的监测。

In the first major aim of this project, we take advantage of these cutting-edge electrical brain mapping techniques to ask some basic questions about the auditory processing abilities of individuals with Rett. We begin by assessing the building blocks of auditory perception. 1) We ask if the auditory system of Rett patients can represent a source of constant auditory input in a noisy ever-changing acoustic background. This is a crucial ability because understanding auditory inputs relies on the listener being able to segregate the most relevant input from extraneous background noise. 2) We then ask if they can represent more abstract auditory patterns (e.g. melodies). 3) Finally, we ask whether their auditory systems can adequately separate two sources of competing sound input (e.g. two different speakers).
这个项目最主要的目的：我们利用这些先进的脑电图技术，以探询雷特患者听觉处理能力的几个基本问题。我们首先评估听觉感知的组成因素。1）我们探询雷特患者的听觉系统是否在嘈杂千变万化的声音背景下可以分辨出听觉输入信号来源。这是关键的能力，因为理解听觉输入信号依赖于从外部背景噪声中能够分离出最相关信息的输入信号。2）我们之后探询他们是否可以表现出更抽象的听觉模式 （例如旋律）。3）最后，我们探询他们的听觉系统是否可以充分分离出两个相互竞争的声音的输入来源（例如两个不同的发声者）。

Then, in the second major aim, we build on this work by asking whether heard information is being processed to the level of cognition. It is one thing to have a functioning auditory system that can sense and analyze the information arriving in the brain, but it is another thing altogether to ask whether this information can be acted upon and understood. Put another way, does the auditory input reach awareness? Again here, we can use brain mapping to objectively ask whether the brains of Rett children register surprise when unpredictable auditory events occur.
In summary, using these brain mapping techniques, we intend to build a much better understanding of the fundamental auditory processing abilities of individual with Rett syndrome. In doing so, we will also establish a set of biomarkers that will have potential utility as outcome measures in clinical trials.
第二个目的：这项研究通过探询听到的信息是否被处理到认知的水平。听觉系统能够感觉和分析到达大脑的信息是一回事，但是能否能够理解信息又是另外一回事。换言之，听觉输入信号能够影响意识吗？此外，我们能够通过使用脑电图客观地评价雷特患儿的大脑是否会对无法预测的听觉刺激产生令人意想不到的反应。总之，使用这些脑电图技术，我们会更好的理解个体雷特综合症患者基本听觉的处理能力。这样做，我们还将建立一套具有潜在实用性的生物标记，作为在临床试验中的结果评估指标。

Fifty non-ambulatory and fifty ambulatory individuals with Rett will be tested as well as fifty age-matched controls. The individuals with Rett will be grouped into two age groups, 7 to 12 and 13 to 18. Patients will be recruited from the Rett Syndrome Clinic in the Bronx run by Dr. Sasha Djukic.
50 个不能走动的和 50 个能走动的雷特患者连同 50 个年龄匹配的对照将被测试。雷特患儿将被分成 7 到 12 岁和 13 到 18 岁的两个年龄组。Sasha Djukic 博士将在位于 Bronx 的雷特综合症诊所招募患者。

Treatment of Rett Syndrome with Lovastatin
雷特综合症治疗-洛伐他汀

Aleksandra Djukic, MD, PhD Albert Einstein College of Mediciingne, Children's Hospital at Montefiore
阿尔伯特 爱因斯坦医学院亚历山德拉 德祐尅可博士，蒙蒂菲奥里儿童医院

$403,000 AWARDED
403000 美元奖励

Aleksandra Djukic, MD, PhD, medical director of the Tri-State Rett Syndrome Center at the Children's Hospital at Montefiore is currently recruiting patients for a Phase 2 dose escalating open label clinical trial of lovastatin, a cholesterol lowering medication. The scientific basis for this trial stems from experiments conducted in the lab of mouse

geneticist, Monica Justice, PhD, who identified the cholesterol pathway as a potential avenue to improve Rett symptoms. The trial will determine the effect of lovastatin on gait, respiratory function, cognition, EEG and severity of the disease.

Montefiore 儿童医院雷特综合症中心主任 Aleksandra Djukic 博士正在招募患者进行洛伐他汀（一种胆固醇降低药物治疗）的二期临床试验。该临床试验为药物剂量逐步上升的公开标签试验。试验的科学基础为试验鼠基因学家- Monica Justice 博士的实验室进行的一项实验，她鉴定了胆固醇治疗途径可以作为一种潜在的改善雷特综合症的治疗方法。试验将确定洛伐他汀在行走步态，呼吸功能，脑电波和疾病严重程度的功效。

Treatment of Rett Syndrome with Copaxone
雷特综合症治疗-克帕松

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阿尔伯特 爱因斯坦医学院亚历山德拉 德祐尅可博士，蒙蒂菲奥里儿童医院

$487,000 AWARDED
487，000 美元奖励

There is a multitude of data suggesting that mice models of Rett have low levels of a neurotrophic factor called BDNF (brain derived neurotrophic factor). BDNF is a very important and complex protein that is implicated in a variety of disorders. Increasing BDNF in the Rett mice models, either genetically or pharmacologically is beneficial. An FDA approved drug for multiple sclerosis called copaxone (or Glatiramer Acetate) is known for increasing BDNF and therefore of interest in treating Rett. It's important to note that copaxone will not be a cure for Rett. The goal is symptom(s) improvement.

大量的数据显示雷特试验鼠模型具有低水平的称作 BDNF(脑源性神经营养因子)的营养因子。BDNF 是非常重要和复杂的蛋白质，其涉及到各种各样的神经紊乱。在雷特试验鼠模型上增加 BDNF 神经营养因子，从遗传基因学角度或药理学角度都可受益。美国食品药品管理局核准的用于多发性硬化症的药物---克帕松（或醋酸格拉替雷），可以增加 BDNF 神经营养因子，因此可能对治疗雷特有益。重要的是克帕松不是治愈雷特的而只能改善症状。

RSRT has funded an open label study of copaxone in two centers, the Tri-State Rett Syndrome Center at Children's Hospital at Montefiore in the Bronx, under the supervision of Dr. Aleksandra Djukic, and at Sheba Medical Center in Ramat Gan in Israel under the supervision of Dr. Bruria Ben Zeev (budget of $200,000).

RSRT 在两个研究中心给公开标签临床试验提供资金，其中一个在 Bronx 的 Montefiore 儿童医院雷特综合症治疗中心，该中心由 Aleksandra Djukic 博士领导，另外一个位于以色列拉马特干的示巴医疗中心，该中心由 Bruria Ben Zeev 博士领导（20 万美元的预算）

The trial in NY has finished and the results are encouraging. A paper has been submitted. A larger placebo controlled trial will need to be planned. The trial in Israel encountered some difficulties with several girls having allergic reactions and trial was stopped.

在纽约的试验已经结束，结果令人鼓舞，报告也已经递交。此外还需要作一个规模较大的安慰剂对照试验。而在以色列的临床试验遇到了一些困难，几个患儿发生了过敏反应导致试验被中断。

Low-dose Ketamine for the Treatment of Rett Syndrome
低剂量氯胺酮治疗雷特综合症

David M. Katz, PhD, Case Western Reserve University & Dan Sessler, MD, Cleveland Clinic
大卫 卡茨博士，凯斯西储大学和丹赛斯勒马里兰州克利夫兰诊所

$1,295,131 AWARDED
129 万美元奖励

Case Western Reserve University and the Cleveland Clinic are recruiting for a Phase 2 dose escalating, placebo controlled clinical trial of low-dose ketamine for the treatment of Rett Syndrome. The study is being led by David Katz, Ph.D., Professor of Neurosciences and Psychiatry at Case Western and Daniel I. Sessler, M.D., Michael Cudahy Professor and Chair, Department of Outcomes Research at the Cleveland Clinic.

Case Western Reserve 大学和克利夫兰诊所正在招募二期临床的志愿者，该临床试验包括低剂量氯胺酮的安慰剂对照组。Case Western Reserve 大学神经学和精神病学 Dvid Katz 教授和克利夫兰临床效果评价中心的主任 Daniel I. Sessler 教授共同领导了此项研究。

Studies undertaken by Dr. Katz have shown that low-dose ketamine can reverse deficits in brain activity in mouse models of Rett Syndrome in conjunction with significant improvements in neurological function, including breathing. Ketamine, a drug that has historically been used for sedation and anesthesia, has recently generated much enthusiasm for its ability to rapidly reverse major depression at low, sub-anesthetic, doses. This trial will determine the effect of single doses of ketamine on breathing abnormalities and overall clinical severity, as well as EEG abnormalities and repetitive behaviors.

Katz 博士从事的研究显示低剂量氯胺酮不仅可以逆转实验鼠的大脑功能的不足，还能改善神经系统功能，包括呼吸。氯胺酮以往用于镇静和麻醉，现在则使用其低剂量用于治疗抑郁症。试验将确定单次剂量氯胺酮在呼吸异常和整体临床上的评价，以及脑电图异常和强迫行为上的效果。

Co-investigators include Tom Frazier, Ph.D, Director of the Cleveland Clinic Center for Autism; Sumit Parikh, M.D., Director of the Cleveland Clinic Neurogenetics, Metabolic & Mitochondrial Disease Program; and Edward J. Mascha, Ph.D., Senior Biostatistician in the Department of Outcomes Research at the Cleveland Clinic.

合作研究者包括克利夫兰孤独症临床医疗中心的 Tom Frazier 博士；克利夫兰临床神经遗传学的 Sumit Parikh 博士，他是新陈代谢和线粒体疾病研究项目的主任；以及来自克利夫兰医学院效果评价中心的资深生物统计学家 Edward Mascha 博士。

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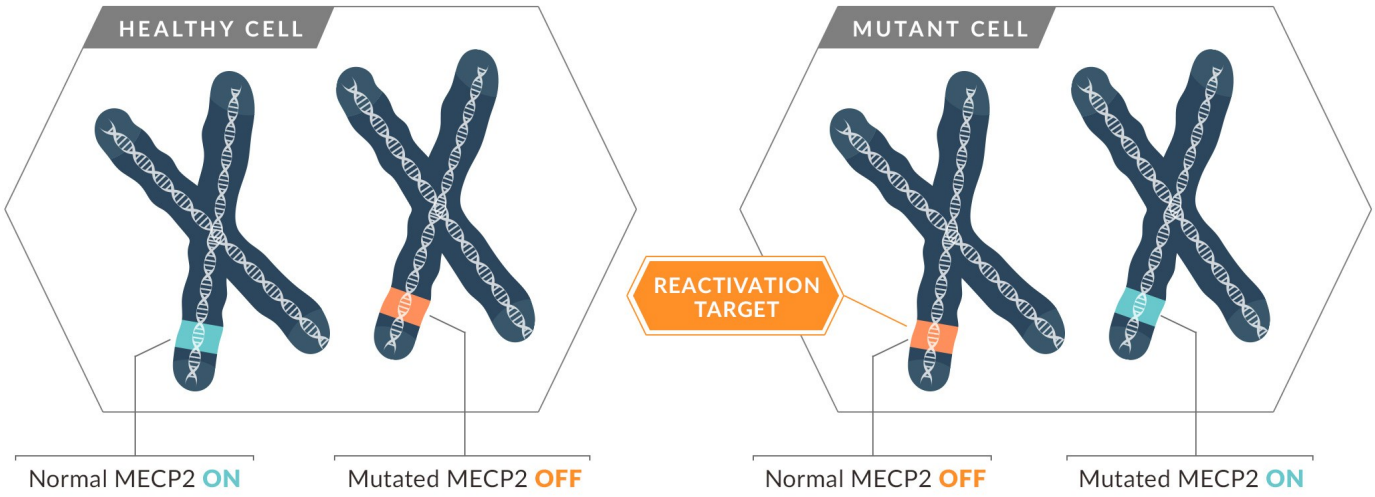
Consortia

联合合作

Reactivating MECP2 Consortium
MECP2 基因再复活联盟

$4,600,000 AWARDED
4，600，000 美元奖励

There is no mystery about why a girl suffers from Rett Syndrome. The cause is the mutated copy of the MECP2 gene inhabiting her cells. But since MECP2 is on the X chromosome and all females have two X's, beside each active mutated gene rests a healthy but silenced twin. What if we could mitigate the flawed gene by reawakening its silenced counterpart? If we could wake up MECP2 in enough cells we could conceivably reverse Rett symptoms. This is an approach that RSRT has championed since our launch in 2008.



关于为什么女孩会患有雷特综合症已经不是秘密了。人有两条等位基因，发病的女孩体内往往只有一条突变的 MECP2 基因，但是因为 MECP2 基因位于 X 染色体上，而所有女性均有两个 X 染色体，那么每个活跃的突变基因旁边都有一个静默的健康基因。假使我们能够通过唤醒静默的健康基因减少缺陷基因的影响将会怎么样？如果我们在脑细胞里唤醒足够多的正常 MECP2 基因我们就可以逆转雷特症状。自从 2008 年启动 RSRT 已经开始支持这项研究了。

We are currently funding a number of labs that are pursuing this line of work. At the University of North Carolina at Chapel Hill we are supporting a collaboration between Benjamin Philpot, Bryan Roth and Terry Magnuson; Jeannie Lee at Harvard; Antonio Bedalov at the Fred Hutchinson Cancer Research Institute; Michael Green at University of Massachusetts Medical School and Joost Gribnau at Erasmus MC in the Netherlands.

当前我们给一些实验室提供基金用以从事此项研究。其中我们支持的一个项目就由北卡罗来纳大学教堂山分校的 Ben Philpot, Bryan Roth 和 Terry Magnuson 教授；哈弗大学的 Jeannie Lee 教授；Fred Hutchinson 癌症研究所的 Antonio Bedalov 教授；马萨诸塞州医学院的 Michael Green 教授以及荷兰医疗中心的 Joost Gribnau 教授。

You may ask why do we need multiple labs working on the same goal. Isn't that a waste of effort and money? The answer is a resounding "NO". While the end game is the same each lab is using a different strategy to get there.

你也许会问为什么要多个实验室研究同样的课题。不是浪费精力和金钱吗？回答当然是"不"。每个实验室采取不同的策略以达到同样的目标。

> *"Our MECP2 reactivation consortium has been another bright spot in the work that we do with the RSRT. Our consortium consists of laboratories from all over the US and abroad. We share the goal and urgency of bringing much needed treatment to patients. The level of sharing and the resulting progress towards reactivating the silent copy of MECP2 are heartening to see. The consortium is making a real difference."*
>
> *"我们重新激活 MECP2 基因的联盟是我们跟 RSRT 合作的另一个亮点。我们联盟包括美国本土和世界各地的实验室。我们分享目标并给病人带来急需的治疗。我们实现了资源共享并取得了重新激活 MECP2 沉默基因的重要进展。联盟使我们的研究与众不同"。*

JEANNIE LEE
珍妮李
Harvard Medical School
哈弗大学医学院

Why it Works
可行性

For example, the types of cells that labs are utilizing are different. Ben Philpot and colleagues at UNC are working with mouse neurons, Toni Bedalov and Jeannie Lee are using fibroblast cells, others still are using human cells. Each cell type has its own set of **advantages and disadvantages.**
The labs are also using different "reporters" – meaning how the cells are designed to detect activation of MECP2. Different compound libraries at different concentrations are being screened. Compounds are also being screened at various degrees of high and low throughput.
Unlike the *MECP2 Consortium* and *Gene Therapy Consortium* this group of researchers did not start out as a consortium. However through conference calls and in person meetings this group of researchers has evolved into an effective and productive collaboration.
One immediate advantage of the consortium approach is that any "hits" identified in any of the labs can immediately be validated in the other labs.
举一个例子，各实验室利用的细胞的类型是不同的。Ben Philpot 实验室和其在北卡罗来纳大学教堂山分校的同事们使用的是小鼠的神经元，Toni Bedalov 和 Jeannie Lee 使用的是成纤维细胞，其他人仍在使用人体细胞。每个细胞类型有其自己的优点和缺点。实验室也在使用不同的"报告方式"— 细胞是如何被设计用于检测激活的 MECP2 基因。不同化合物在不同浓度被一一筛查。化合物也根据各种高低不同的通量被筛选。不像 MECP2 治疗联盟和基因治疗联盟，这组研究人员一开始并没有作为一个联盟。然而通过电话会议和面对面的交谈这组研究人员已经演变成一个富有成效的合作团体。一个直接的好处就是任何试验室的任何突破发现会立即被其他试验室验证确认。

MECP2 Consortium
MECP2 联盟
$5,500,000 AWARDED
5，500，000 美元奖励

As parents will attest to the symptoms of Rett Syndrome are numerous and devastating. Whatever *MECP2* is doing, it's acting globally on many systems in the body. While a repurposed drug may partially treat a symptom(s), to achieve the kind of dramatic improvement that parents yearn for will likely require **attacking the problem at its very root.**
雷特症患儿的父母直接见证了雷特合症繁多的症状和破坏性。MECP2 会影响人体的许多系统反应。虽然一些药物可能改善症状，但父母都渴望能**解决根本问题**。

There are multiple ways to achieve this end goal: gene and/or protein therapy, activating the silent *MECP2*, potentially modifier genes. These are all areas in which RSRT is financially and intellectually engaged with. In parallel, however, it is also imperative to understand what*MeCP2* does. We are trying to cure disorders caused by faulty *MeCP2* so it goes without saying that understanding what MeCP2 does is likely to greatly aide in this endeavor. Elucidating the function of *MeCP2* has occupied labs around the world for years. Yet, explaining in molecular terms just why the absence of*MeCP2* brings about Rett's particular

constellation of symptoms still eludes us. Business as usual was not an option. So in 2011 we shook the conventional practice of laboratories working in isolation and instead convened three powerhouse scientists to work collaboratively: **The MECP2 Consortium.**
We gave them the necessary financial resources and provided infrastructure including in-person meetings. **The results surprised us all.**

有多种方法来实现这一最终目标： 基因和/或蛋白治疗，激活沉默 MECP 基因。这些都是 RSRT 组织在财力上和技术上所支持的领域。同时理解 MECP2 的工作原理也是必要的。我们试图治愈引起 MECP2 缺损的神经紊乱病症，理解 MECP2 的工作原理将带来很大的帮助。多年来在世界各地的实验室全力阐明 MECP2 的功能。然而，我们至今我们仍然无法在分子层面上解释为什么 MECP2 的缺失带来了雷特独特的系列症状。所以在 2011 年我们改变了实验室在孤立工作的常规做法，取而代之的是召集三个有实力的科学家合作研究：结成 **MECP2 联盟**。我们给他们必要的资金支持，提供基础设施，包括面对面会议。**结果令我们惊喜**。

> *"Being able to thrash out ideas and explore different ways of looking at Rett with top class scientists from different backgrounds has sharpened up everybody's research. All the partners have fully committed to the Consortium idea and as a result no one feels inhibited about robustly questioning the others. This kind of free and frank exchange keeps us on our toes and always makes research better."*
>
> *"能够通过讨论解决问题，与不同的背景的顶级科学家探索不同的雷特研究方法从而增强了每个人的研究水平。所有合作伙伴完全都致力于联盟的理念，给彼此提出建设性的意见。这种自由、 坦率地交换意见使我们充满活力，最终使研究更好开展。*
>
> **ADRIAN BIRD**
> **阿德里安博得**
> *University of Edinburgh*
> *爱丁堡大学*

Advancements
进展

GENE THERAPY PROVEN TO WORK
基因治疗证明可行

The Consortium quickly reported significant progress. The Mandel and Bird labs showed, for the first time, a dramatic reversal of symptoms in fully symptomatic Rett mice using gene therapy techniques that could be utilized in people. Video

联盟很快向外界报告了最新取得的重大进展。曼德尔和博得实验室第一次用基因治疗技术对雷特症状的实验鼠产生了显著性地症状逆转，并可以利用于人体。**点击视频**

NOVEL BINDING PARTNER IN MECP2
最新发现的 MECP2 绑定蛋白

The Bird lab discovered that the function of the Rett protein, MeCP2, depends on its ability to recruit a novel binding partner, NCoR/SMRT to DNA. Disrupt that ability and the symptoms of Rett ensue. Video

博得实验室发现了雷特蛋白质 MECP2 的功能取决于它可以绑定并运送一个名为 NCoR/SMRT 的蛋白质到达 DNA。但如果抑制二者的结合对雷特症状并无缓解作用。**点击视频**

LONG GENE MISREGULATION DISCOVERED
长基因错误调节的发现

The Greenberg lab built on the work of the Bird lab and discovered that adding a phosphate group to MeCP2 alters its ability to interact with NCoR/SMRT and affects the expression of downstream genes. They also found that MeCP2 deficiency leads to the misregulation of numerous very long genes. The lab is now using pharmacologic and genetic approaches to reverse this long gene misregulation in mouse models of Rett syndrome with the goal of advancing a therapeutic candidate. Video

格林伯格实验室以博得实验室的工作为基础，发现添加磷酸基团可改变 MECP2 与 NCoR/SMRT 相互作用的能力并影响下游基因的表达。他们还发现 MECP2 缺馅导致很多长基因的错误调节。实验室现在在雷特综合征的试验鼠模型上使用药理学和遗传学的方法来逆转长基因的错误调节从而最终发现治疗的潜在药物。**点击视频**

RETT PROTEIN IS MORE TIGHTLY COMPACTED IN DNA
雷特蛋白质更加紧密的融合在 DNA（脱氧核糖核酸）里

The Mandel is lab showing that the Rett protein, MeCP2, plays a role in how DNA is packaged into the nucleus and that cells that are missing MeCP2 have DNA that is more tightly compacted.

曼德尔的实验室显示雷特蛋白质 MECP2 在 DNA 如何被包装入核起到重要作用，缺少 MECP2 的细胞其 DNA 包装更紧密。

THE GROWING TOOLBOX OF RETT MOUSE MODELS
发展中的雷特试验鼠模型

The Bird lab created mouse models of *three common human mutations* (T158M, R133C, R306C) and found correlations between mutation and severity and protein stability.

博得实验室在试验鼠身上创建了三个常见的人类突变 （T158M、 R133C、 R306C），以及发现突变和严重性以及蛋白质稳定性之间的相关性。

THE PATHOPHYSIOLOGY OF RETT
雷特的病理生理学

The Greenberg lab recently discovered sites on MeCP2 that are modified in response to neuronal activity. Because neuronal activity is critical for normal neurodevelopment and function, the lab is investigating how these activity-dependent modifications of MeCP2 are relevant to the pathophysiology of Rett.

格林伯格实验室最近发现 MECP2 上位点变化对神经元活动有响应。因为神经元活动是神经发育和行使正常功能的关键，实验室正在研究这些 MECP2 功能活动依赖性修改是如何影响雷特的病理生理学。

> *"The MECP2 Consortium is a model for something much bigger: how neuroscience overall needs to operate so that we can find therapies and cures for disease. The rigor and pace of scientific progress is much greater with the three labs working together than would be possible if each lab were working alone. Monica has been essential to keeping the Consortium on target and helping make sure the scientists in the Consortium continue to work together effectively over time."*
>
> *"MECP2 联盟是一个更大模式： 需要整体神经系统科学协同运作以便我们可以找到治疗和治愈疾病方法。三个实验室在一起工作的科学进展的严谨性和速度要比每个实验室单独工作好的多。莫妮卡一直以保持联盟的必要性为目标，并且帮助确保随着时间的推移在联盟中的每一位科学家都能继续有效地一起工作。*
>
> ***MICHAEL GREENBERG***
> ***迈克尔 格林伯格***
> *Harvard University*
> *哈佛大学*

In Their Own Words
用他们自己的话说

The Consortium works in large part due to the commitment of the three principal investigators. However that commitment is also required of all the lab members – the people who actually are in the lab day in day out executing experiments.
该联盟工作很大一部分是由于来自三个主要研究人员的承诺。然而这一承诺也需要所有实验室成员 — — 那些在实验室每天执行实际实验操作的人的参与。

Harrison Gabel (Greenberg lab)
哈里森 加贝尔（格林伯格实验室）
It is truly unprecedented to have three powerhouse labs that work on the mechanism of MeCP2 get together for meetings and share their most recent data. The reality is that under any other circumstances we would be competing and largely keeping secrets from one another until the data were published. This Consortium breaks down these walls and as a result the science moves much faster. Our group meetings are essential to critically assessing our work. Each lab group has its own "world view," and having that view shaken up every six months is very constructive.
我们前所未有的拥有三个具有实力的实验室，他们在 MECP2 的工作机制上一起举行会议分享他们最新数据。现实上，在任何其他情况下他们会互相竞争，很大程度上相互之间保守秘密，直到数据被发表。该联盟打破这些阻碍，因此科学研究进展更快。我们的联盟会议对严谨地评价我们的工作不可或缺。每组实验室有其自己的"世界观"，持有这样的观点，然后每六个月碰撞产生的成果是非常具有建设性的。

Matt Lyst (Bird lab)
马特 李斯特（博得实验室）
Sharing current data between labs means we all receive input from people in the field but outside of our own labs at a much earlier stage than would normally happen.
当前实验室之间共享数据意味着我们可以比在正常情况下更早的收到从我们自己实验室之外关于雷特研究领域的信息。

John Sinnamon (Mandel lab)
约翰 西纳蒙 （曼德尔实验室）
Attending the RSRT Consortium meetings is a wonderful experience. There is a collaborative atmosphere you don't see at large scientific meetings and everyone is focused on understanding the biology of MeCP2 so that we can understand Rett Syndrome. For me personally, it's very powerful to meet parents of girls with Rett and to talk to them about my research. It provides a reminder of what I am working towards and gives the families an opportunity to talk one on one with the scientists they support.
参加 RSRT 联盟会议是一个奇妙的经历。有你在大型科学会议上看不到的合作气氛，每个人都致力于对 MECP2 的生物学理解，以便我们能更好了解雷特综合征。就个人而言，见到雷特女孩的父母，跟他们谈我的研究具有强大的作用。它提供了患者家庭与他们支持的科学家一对一沟通的机会，也再一次提醒我们一直为之奋斗的目标。

Gene Therapy Consortium
基因治疗联盟
$1,603,341 AWARDED
1，603，341 美元奖励
The videos below are perhaps the most well known in the Rett community. If you love a child with Rett then chances are you've watched them obsessively. This work published in 2007 by Adrian Bird, declared to the world that Rett is reversible, but did not tell us how this could

be done in people. Fast-forward six years and the video below from the RSRT-funded labs of Gail Mandel and Adrian Bird may have given us an answer: gene therapy.
下面的视频也许是在雷特社交圈里最广为人知的。如果你爱一个雷特患儿，那么你一定一直注视着他们。2007 年由阿德里安 博得发表的工作向世界宣告：雷特是可逆转的。但没有告诉我们如何在人体上实现。 飞逝的六年和下面的视频中从 RSRT 得到资助的盖尔曼德尔和阿德里安 博得的实验室给了我们答案：基因治疗。

Mouse Before Reversal | Bird Lab
基因逆转之前的实验鼠
Mouse After Reversal | Bird Lab
基因逆转之后的实验鼠
Mouse With Gene Therapy
实验鼠基因治疗

But how do we make the giant leap from recovered mice to recovered children?
但是怎样才能做到从实验鼠到患儿的巨大飞跃呢？
To move us towards this goal as rapidly as possible, RSRT launched the Gene Therapy Consortium, a bold international collaboration between four laboratories who together bring all the necessary skills to determine if gene therapy is a feasible approach. The advantages gained by labs working collaboratively are clear: speed (four labs contributing to the work that has to be done), real time sharing of information means more brainpower and broader perspectives for problem solving. This is an obvious example of more heads are better than one.
为了尽可能迅速地向前推进这一目标，RSRT 推出了基因疗法联盟合作，大胆的国际协作模式在四个实验室之间展开，结合所有必要的技术，以确定基因疗法是否可行。实验室协作模式获得的优势十分明显： 迅速 （四个实验室有助于工作的实施），实时共享信息意味着更多的智囊和更广泛的角度来解决问题。俗话说的好：三个臭皮匠顶个诸葛亮。

Meet the Consortium Members
联盟合作成员
The Consortium is comprised of two gene therapy labs, Brian Kaspar and Steven Gray, and two labs with expertise in the Rett gene and mouse models, Gail Mandel and Stuart Cobb.
联盟合作由两个基因治疗实验室组成，布莱恩 卡斯帕和史蒂文 格雷，以及两个实验室在雷特基因和实验鼠模型方面的专家，盖尔 曼德尔和斯图尔特 柯布。

STEVEN GRAY
史蒂文 格雷
Steven Gray is part of one of the best gene therapy centers in the world located at UNC Chapel Hill. His lab focuses on gene therapy platforms for neurological diseases. He has made enormous strides using existing vectors (the Trojan horses that deliver genes into cells) to their full potential, and also leading the way to develop newer and better vectors.
史蒂文 • 格雷来自 UNC 教堂山分校---世界上最好的基因治疗中心之一。他的实验室主要研究神经系统疾病的基因治疗。他取得了巨大的进步，使用现有载体并充分发挥了他们的潜能（特洛伊木马方式将基因传递到细胞）。他们还在尝试着开发更新更好的载体。

BRIAN KASPAR
布莱恩 卡斯帕
Brian Kaspar is at Nationwide Children's Hospital where is has successfully navigated two programs from bench research to human clinical trials. His recently helped to launch a trial in Spinal Muscular Atrophy that included two "firsts" – the first time that an AAV vector was used in people and the largest amount of vector that had ever been injected into a person.

布莱恩 • 卡斯帕来自 Nationwide 儿童医院,其成功地进行了从实验室研究到人体临床实验的两个项目。 他最近帮助发起了一个试验:脊髓性肌萎缩症，其中包括两个"第一"- 第一次把 AAV 载体用于人体以及到目前为止最大数量的载体注射。

STUART COBB

斯图尔特 科布

Stuart Cobb is at the University of Glasgow and was one of the authors of the reversal paper published in 2007. His lab brings neurobiology expertise with regards to accurately mapping out Rett syndrome-like features in mice and within the brain and being able to assess in detail the ability for gene therapy to improve aspects of the disorder.

斯图亚特 • 科布来自格拉斯哥大学，他是 2007 年出版逆转论文的作者之一。他的实验室拥有神经生物学专业支持从而准确地在实验鼠大脑内绘制出雷特综合症的症状特征并能够详细评估基因疗法的治疗结果。

GAIL MANDEL

盖尔 曼德尔

Gail Mandel, from OHSU, has been involved in Rett Syndrome research for over a decade and has made seminal discoveries. Her lab applies state of the art molecular tools to questions related to gene therapy and histology of the brain.

盖尔 • 曼德尔，来自 OHSU，十多年来一直参与雷特综合征的研究，并取得了重大发现。她的实验室将最先进的分子工具用于有关大脑的基因治疗和组织学研究的问题。

Why Gene Therapy?

为什么基金治疗?

While there have been major advances in understanding the molecular actions of the MeCP2 protein, it is still difficult to conceive of a small 'traditional' drug molecule being able to mimic its function. While traditional drug approaches will likely be restricted to correcting specific aspects of what goes wrong, it's conceivable that gene therapy can correct the cause of Rett at its source and thus provide a profound recovery of function.

虽然 MECP2 蛋白质的分子功能的研究取得重大进展，但仍然难以想象‘传统’药物分子能够模拟其功能。而传统的药物疗法可能会局限于纠正错误的具体细节，可想而知基因治疗可以纠正雷特源头的病因，从而提供显著的功能恢复。

There are several major advantages that Rett offers:

雷特综合症提供了几个主要的优势：

1. ***The genetic target is known: MeCP2***
1. ***基因标靶已知：MECP2***
2. ***Rett is not neurodegenerative – neurons don't die***
2. ***雷特不是神经退化性的 – 神经元没有死***
3. ***We know that restoring the proper level of MeCP2, even later in life, at least in a mouse, results in dramatic improvements.***

3.我们知道恢复适度水平的 MECP2, 即使在较晚的时期，至少在实验鼠身上的实验结果显示了显著的症状改善。

Why Now?

为什么是现在?

Following several decades of rocky ups and downs the gene therapy field is coming into its own due to major advances in molecular biology and viral technologies. Europe and Asia recently approved the first gene therapy products. Worldwide there are hundreds of clinical trials ongoing. Industry is investing enthusiastically in this area resulting in numerous gene therapy biotech startups.

经过几十年跌宕起伏的基因治疗领域在分子生物学和病毒技术取得重大进展的推动下即将进入自身的发展周期。欧洲和亚洲最近核准了第一个基因治疗产品。世界范围内有数百个临床试验正在进行。行业在这一领域积极热情地投资,正在造就许多基因疗法生物科技的创业公司.

> *"When Dr. Cobb visited our lab recently he provided critical expertise in a short visit that saved us an enormous amount of time and effort if we had been working alone. This is a small example of the many benefits we have had from working together in a collaborative fashion."*
> "科布博士最近参观了我们实验室，他提供了重要的专门知识，短暂的访问节约了大量时间，这是我们一直单独研究无法完成的。这是我们以协同的方式一起工作得到收益的一个小例子。
> ***PHEN GRAY***
> ***彭格雷***
> *University of North Carolina Chapel Hill*
> *北卡莱罗纳州大学教堂山分校*

What have we learned thus far about Gene Therapy for Rett?
到现在为止有关基因治疗我们已经学到了什么？

Multiple labs have shown that a single one-time administration of a gene therapeutic can have a clinically meaningful result in the workhorse rodent model of this disease, even when delivered later in life. The studies have also shown that the level of MeCP2 protein produced by the gene therapy is not producing any obvious defects in its own right and it therefore seems possible to deliver protein within limits that are tolerable to cells.
多个实验室证实一次基因治疗可以在实验鼠模型上取得重要的具有临床意义的成果，即使在它们生命中的晚些时候。研究还表明，基因治疗产生的 MECP2 蛋白质的水平没引发任何明显的缺陷，似乎因此有可能在耐受限度内为脑细胞提供蛋白质。

We have also learned that it is not necessary to 'hit' all cells with the virus, this is never going to be achievable in practice anyway. Fortunately, a substantial therapeutic impact may be achieved by delivering the gene to a subset of cells.
我们也知道并没有必要用病毒去攻击所有细胞，实际上是永远不会实现的。幸运的是，只要将基因在一小部分细胞内表达就可以产生显著的效果。

Finally, the studies tell us that we have to be very careful how we target the MeCP2 gene, to make sure too much isn't delivered to a particular organ, such as the liver.
最后，研究告诉我们，把 MECP2 基因作为标靶要十分小心，以确保在特定的器官，如肝脏内不会表达过量的基因。

What are the Challenges?
挑战是什么？

There are several hurdles to overcome. There is a requirement for MECP2 in every part of the brain so the gene will need to be broadly delivered. Also, the MECP2 Duplication Syndrome suggests that too much MECP2 is bad. It is difficult in gene therapy to regulate how many copies of a gene enter a cell and how much protein is made so the issue of MECP2 dosage must be carefully explored. We know that having too much MECP2 from conception and through early development causes serious symptoms. But does the same hold true if extra MECP2 is delivered later in life? Also, is it possible that females tolerate greater amounts of this protein than males? These questions must be answered before a clinical trial can be proposed.
有几个障碍必须克服。由于 MECP2 在大脑内广泛表达，因此基因将需要在其中广泛地传递。此外，MECP2 重复综合症提示太多的 MECP2 也是有害的。在基因治疗中很难调节一个基因的多少个复制进入单个细胞，以及产生多少蛋白质使 MECP2 剂量问题必须仔细探究。我们知道，理论上及早期实验证实太多的 MECP2 会导致严重的不良反应。但是在某些情况下也不一定适用，比如在生命的晚些时候进行基因治疗是不是颗星或是女性比男性可能耐受更大数量的这种蛋白质？在计划一项临床试验前必须回答这些问题。

"It is very stimulating to be part of such a focused group of experts on gene therapy approaches towards Rett. The openness of the investigators propels our studies and makes for a productive venture that would not be possible by any one individual laboratory. Additionally, it saves time because we can move on from doing obvious experiments that were done already in another laboratory."
"成为雷特基因治疗专家小组中的一员是非常令人兴奋的。研究者的开放性推动我们的研究和有助于生产企业，任何一个实验室都无法单独实现。此外，它可以节省时间，因为我们可以继续别的实验室已经完成的实验进展。"

GAIL MANDEL
盖尔 曼德尔
Oregon Health & Science University
俄勒冈健康与科学大学

What We're Working On
我们正在致力于什么

- **Vector Optimization** – The vector is the Trojan horse that delivers the working copy of the gene into a cell. Together, members have tested multiple different permutations. There is one particular version that is looking very encouraging.
优化载体 — — 载体就像是特洛伊木马，它传递基因的工作副本到细胞中。同时，研究成员已经检测了多个不同的载体。有一个特别的载体非常令人鼓舞。

- **Optimizing how much Gene Therapy to Deliver** – Related to the above, the scientists have delivered different dosages of vectors in an attempt to see how much is needed to get an effect versus at what point toxicity develops. The work reported at the meeting suggests that there is a rather narrow "therapeutic window". Present efforts are being directed towards enlarging the gap between doses producing the beneficial actions and those producing adverse actions.
优化到提供多少基因治疗 — — 如上所述，科学家们已将不同剂量的载体做传输的尝试，以确定有效剂量和最小毒性计量之间的治疗区间。而研究报告提出的治疗区间十分狭窄。我们正在致力于扩大产生有益结果的剂量和生产不利结果的剂量之间的差距。

- **Delivery Route Optimization** – Gene therapy can be delivered via the blood stream, directly into the brain, or into the solution that bathes the brain (like an epidural injection). Each route has its own advantages and disadvantages and each route has been used in clinical trials for other disorders.
传递路线的优化 — — 基因治疗能够通过血液传递，直接进入大脑，或深入沐浴大脑的解决方案（像硬膜外注射）。每条路线有其自己的优点和缺点以及每个路线已被用于其他疾病的临床试验中。

- **Spliceosome-Mediated RNA Trans-Splicing Therapy in Rett Syndrome** - Targeting MeCP2 can be done either at the DNA, mRNA or protein level. Both the DNA and protein approaches have a complication due to potential dosage problems (too much MeCP2 may be harmful). An alternative approach is to use a technology called Spliceosome-Mediated RNA Trans-Splicing (SMaRT). This technology allows a mutation to be spliced out and repaired in RNA. The advantage is that this approach avoids any potential overexpression issues. RSRT ***recently awarded*** funding to Stuart Cobb to explore this novel route to RNA correction.
剪接体介导的核糖核酸反式剪接对雷特综合症患者的治疗 – – 靶向 MECP2 可以在 DNA、 mRNA 或蛋白水平中完成。DNA 和蛋白质的治疗方法由于潜在剂量问题可能引发并发症（太多 MECP2 可能是有害的）。另一种方法是使用一种叫做剪接体介导的核糖核酸反式剪接（简称 SMaRT）技术。这种技术允许在核糖核酸中拼接合并修复突变。这种方法的优点是避免了过度表达的任何潜在问题。 RSRT 组织**当前奖励** 提供基金给斯图尔特科布以探索修正核糖核酸的新的路线。

DNA/RNA/Protein Therapy

脱氧核糖核酸/核糖核酸/蛋白质疗法

Protein Replacement for Rett Syndrome
雷特综合症蛋白质替换

Armagen
阿马根
$125,000 AWARDED
125，000 美元奖励
While the Gene Therapy Consortium is working to overcome the challenges of gene therapy for Rett (for example, the overexpression issue) RSRT is also supporting synergistic genetic strategies in parallel.
虽然基因疗法研究联盟正在努力克服雷特基因治疗的挑战 （例如，过度表达问题） RSRT 组织还在支持协同遗传研究。

One such strategy is protein replacement. Rather than delivering genes, this approach delivers the protein that the gene encodes. In order to deliver the MeCP2 protein to the brain we must penetrate the blood brain barrier (BBB), the protective dynamic interface that separates the brain from the circulatory system and protects the central nervous system from potentially harmful chemicals while regulating transport of essential molecules and maintaining a stable environment.
ArmaGen's platform technology takes advantage of the body's natural system to non-invasively deliver drugs across the BBB. The BBB selectively allows vital nutrients to pass from the bloodstream to the brain, through the presence of receptors that enable the entry of compounds such as insulin, transferrin (protein that transports iron) and low-density lipoproteins (LRP1, proteins that transport fat). ArmaGen's approach targets the same receptors that transport these compounds to the brain.
这种策略之一是蛋白质替换。与基因疗法不同，这种方法可传递该基因编码的蛋白质。为了将 MECP2 蛋白质传送到大脑我们必须穿透血脑屏障（简称 BBB），血脑屏障以保护的动态界面是大脑从循环系统中分离，同时调节基本分子的运输和维持一个稳定的环境，保护潜在的有害化学品的危害中枢神经系统。ArmaGen 阿马根公司的平台技术充分利用了人体的自然系统，用无创性的方法把药物穿过血脑屏障传送给大脑。BBB 血脑屏障有选择性地允许重要的营养素从血液中传递到大脑，通过存在的受体，使化合物，如胰岛素，转铁蛋白 （运输铁的蛋白质） 和低密度脂蛋白（简称 LRP1，运输脂肪的蛋白质）进入大脑。ArmaGen 阿马根公司的方法是针对运输这些化合物的受体。

Armagen's scientists will fuse molecules to the MeCP2 protein that will allow it to be recognized and pumped across the blood brain barrier.The advantage to this approach is that protein can be titrated to a much greater degree than gene therapy.
Armagen 阿马根公司的科学家将融合 MECP2 蛋白质分子使其能够被特定受体识别并协助其穿过血脑屏障。这种方法的优点是，与基因疗法相比蛋白质可以精确控制。

Spliceosome-Mediated RNA Trans-Splicing Therapy and Protein Replacement in Rett Syndrome
雷特综合症 – 剪接体介导的核糖核酸反式剪接与蛋白质替换的治疗

Stuart Cobb, PhD | University of Glasgow
斯图尔特 科布博士/格拉斯哥大学
$300,000 AWARDED
300，000 美元奖励
Targeting MeCP2 can be done either at the DNA, mRNA or protein level. Stuart Cobb is working on all of these approaches in parallel. His work with gene therapy is being done as part of the Gene Therapy Consortium.

靶向 MECP2 可以在 DNA、 mRNA 或蛋白水平中完成。斯图亚特 科布正致力于所有这些方法的同时研究。他的基因治疗工作是作为基因治疗联盟的一部分。

We know that both the DNA and protein approaches have a complication due to potential dosage problems (too much MeCP2 may be harmful). So Dr.Cobb is also pursuing an alternative technology called Spliceosome-Mediated RNA Trans-Splicing (SMaRT). This technology allows a mutation to be spliced out and repaired in RNA. The advantage is that this approach avoids any potential overexpression issues.

我们知道，DNA （脱氧核糖核酸） 和蛋白质的治疗方法由于潜在剂量问题会引发并发症（太多 MECP2 可能是有害的）。所以科布博士还从事着一种叫剪接体介导的核糖核酸反式剪接（简称 SMaRT）的替代技术。这种技术允许在核糖核酸中拼接和修复突变。优点是这种方法避免了任何潜在的过度表达问题。

Modifier Genes

基因修正

Systems Genetics Approach toward Understanding Regulation of MECP2 Expression
系统遗传学方法对理解 MECP2 表达调控的研究

Terry Magnuson, PhD | University of North Carolina at Chapel Hill
特里 马格努森博士/北卡莱罗纳大学教堂山分校

$200,000 AWARDED
200，000 美元奖励

Mutations in the *MECP2* gene, located on the X chromosome, are responsible for Rett Syndrome. A possible avenue to treat Rett patients is by directing its expression from the normal copy or by modulating the expression from the mutant copy. The scientists propose to identify the regulatory elements that control *MECP2* expression with a focus on those elements that are functionally variable within natural populations and, thus, amenable to both genetic analysis and to putative manipulation. The proposed work will be conducted in two novel mouse resources specifically designed to maximize the number of genes with regulatory variants and the ability to map the causal regulatory elements.

位于 X 染色体上 MECP2 基因突变造成雷特综合症。一种治疗雷特可能的途径是通过引导其从正常基因复制中表达或者通过调节从突变的基因复制表达。 科学家们建议，认同调整 MECP2 表达的元素，重点放在自然种群内的这些功能上的变量，因此，经得起基因分析和假定操作的检测。计划研究工作将利用两种新型实验鼠资源，以期对基因量和调控因子以及定位致病因素的能力进行优化。

Identification of Genetic Modifiers in Rett Syndrome
发现雷特综合症的遗传修饰因子

Jeffrey Neul, MD, PhD | University of California San Diego
杰弗里 尼奥博士/加利福尼亚桑迭戈大学

$315,000 AWARDED
315,000 美元奖励

This project was awarded in late 2013 and will run in parallel with Dr. Justice's mouse project. Dr. Neul will sequence the exomes (the protein producing portion of the genome) of high-functioning kids/adults in the hopes that some common variables may point to modifiers which can then become drug targets. Importantly, the sequencing and phenotypic data will be a valuable resource as it will be deposited into the National Database for Autism Research and available to the scientific community.

这个项目于 2013 年年底被资助,并与贾斯蒂斯博士的实验鼠项目同时进行. 尼奥博士将按顺序排好高功能患儿/成年患者的外显子组(蛋白质产生基因组的一部分), 希望能使一些常见的变量可以指向之后能成为药物标靶的修饰因子。重要的是，排序和表型数据将是宝贵的资源，因为它会被存放到自闭症研究的国家数据库，并提供给科学界。

Identification of Gene that Ameliorate Rett Symptoms
发现可以改善雷特综合症的基因

Monica Justice, PhD | Hospital for Sick Children (Toronto)
莫妮卡 扎斯泰斯博士/儿童医院（多伦多）
$2,300,000 AWARDED
2，300，000 美元奖励

Individuals with Rett display a broad spectrum of symptom severity. Some girls can run, have a degree of hand use and can speak in short sentences while others cannot even sit or hold their head up. One reason for this variation is the child's own unique genetic makeup – in other words, variations in other genes that impact the severity of the Rett mutation. Monica Justice, Head and Senior Scientist in the Genetics & Genome Biology program at The Hospital for Sick Children in Toronto, has undertaken a mutagenesis screen to identify these modifying genes with a focus on suppressors of symptoms, hoping that they might suggest a therapeutic pathway. The first suppressor she identified, squalene epoxidase, has led to a clinical trial of lovastatin.

Dr. Justice has identified several dozen modifiers to date. We will keep you informed on her progress on the screen.

雷特患者表现出广泛的症状严重程度。有些女孩可以行走，有一定程度手的使用还可以讲简短句子的而其他人甚至不能坐或抬头。这种变异一个原因是孩子自身独特的基因构成 — — 换句话说，变异是在影响雷特突变严重程度的其他基因里。莫妮卡 贾斯蒂斯是多伦多遗传学与基因组生物学项目的领军人物和资深科学家，她已经开始进行突变形成的筛查，以识别这些修改基因，重点放在症状的抑制因子，希望它们可能提示一个治疗途径。第一次她认定的抑制因子，角鲨烯环氧化酶，最终促成了洛伐他汀的临床试验。贾斯蒂斯博士至今为止已经鉴别出几十种修饰基因。我们将对她研究的最新进展进行跟踪报道。

Downstream Targets

下游标靶

Reversal of Rett Phenotype: A screen for compounds that enhance KCC2 expression
雷特表型的逆转：筛查可加强 KCC2 表达的化合物

Rudolf Jaenisch, MD | Whitehead Institute
鲁道夫 耶尼施医学博士/怀特海德学院
$180,000 AWARDED
180，000 美元奖励

There are numerous strategies to target Rett Syndrome. Curative strategies target *MECP2* itself through gene therapy or protein replacement or by activating the backup copy of *MECP2*. An alternative treatment strategy is to activate or stimulate a molecular pathway that is disrupted in Rett but that does not involve *MECP2*.

现在有许多针对雷特综合征的治疗策略。针对 MECP2，包括通过基因疗法或蛋白替换或通过激活 MECP2 的备份副本。替代的治疗策略则是激活或刺激一个在雷特中被扰动的分子途径，而不会涉及 MECP2。

K+/Cl- cotransporter-2 (KCC2), an essential gene for proper brain function, is one such pathway. Dr. Jaenisch's previous published work has demonstrated that restoration of the decreased KCC2 expression level in Rett Syndrome mouse model neurons leads to the recovery of impaired neuronal functions. They have developed a robust in vitro human Rett

neuron screening platform based on KCC2 expression that will allow the identification of compounds that rescue the cellular phenotypes. The lead hit compounds from the screening will be tested on Mecp2 mutant mice for their therapeutic effectiveness. They propose that KCC2-enhancing compounds identified from human reporter neuron screening and further validated in animal model of RTT, may provide the basis for a novel therapeutic strategy for symptom improvement.

钾离子氯离子协同转运蛋白-2（简称 KCC2)是一个大脑功能基本基因。德耶施博士以前发表的论文表明恢复雷特 综合征鼠模型神经元减少的 KCC2 表达水平,可使受损神经元功能恢复。基于 KCC2 的表达，他们已经开发了一个稳定的人体外雷特神经元筛选平台，将对挽救细胞表型的化合物进行鉴别。有效的化合物将在 MECP2 基因突变鼠上进行治疗测试。他们建议利用人类基因报告神经元筛选并在雷特动物模型中进一步验证来提高 KCC2 化合物的鉴别，其可能为症状改善的新治疗策略提供依据。

Modeling MECP2 Dosage in Human Cerebral Organoids

在人类大脑中建立 MECP2 剂量的模型

Alysson Renato Muotri, PhD | University of California San Diego

阿利松 雷纳托 茂垂 博士/加利福尼亚圣迭戈大学

$209,000 AWARDED

209，000 美元奖励

Levels of MeCP2 protein are tightly controlled in the brain. Too little leads to Rett Syndrome, whereas too much leads to another neurodevelopmental disorders. How exactly the correct levels of MeCP2 maintain the proper function of neuronal networks is an important and fundamental question. With RSRT support, Dr. Muotri and his team will genetically engineer human pluripotent stem cells to control MeCP2 levels in “mini-brains” in a dish. The team will perform a comprehensive gene expression analyses to relate molecular pathways to cellular phenotypes. The work has the potential to reveal novel therapeutic opportunities for Rett Syndrome and will also be informative for future gene therapy/protein replacement, where the amount of MeCP2 to be delivered to the brain is critical.

大脑中 MECP2 蛋白质水平被严格的调控着。太少会导致雷特综合征，然而太多会导致另一种神经发育障碍疾病。究竟怎样的 MECP2 的标准水平可以维持神经元网络的正确功能是个重要和基本的问题。在 RSRT 支持下，茂垂博士和他的团队将在一小盘"微型脑髓"里以基因工程人类干细胞来控制 MECP2 水平。团队将进行全面的基因表达分析，其中将会涉及细胞表型的分子途径。此项工作将揭示了对雷特综合症新的治疗可能，也将有益于未来的基因治疗/蛋白置替换疗法，而传送到大脑的 MECP2 数量是关键。

Exploration of the Impact of Cyclodextrin on Lifespan and Brain Cholesterol Metabolism in Male Rett Mice

环糊精对寿命和雄性雷特试验鼠脑胆固醇代谢影响的探索

Stephen Turley, PhD & Adam Lopez, PhD | University of Texas Southwestern Medical Center

斯蒂芬 特利博士和亚当 洛佩兹博士/德克萨斯西南医学中心大学

$156,180 AWARDED

156，180 美元奖励

Recent studies from Monica Justice and Stephen Turley have showed that Rett mice have increased levels of cholesterol in their brains. Cyclodextrin is currently in clinical trials for Nieman Pick Disease where cholesterol becomes trapped in the brain. Through a mechanism(s) that is not well understood, Cyclodextrin facilitates the release of cholesterol. There is now an expanding literature attesting beneficial effects of Cyclo in mouse models for other neurological disorders such as Alzheimer’s disease. Drs. Turley and Lopez will test Cyclodextrin in Rett mice to see if any improvements can be seen.

从莫妮卡 贾斯蒂斯和斯蒂芬 • 特利最近的研究表明雷特鼠大脑中的胆固醇水平高于正常鼠。环糊精目前处于尼曼皮克疾病（脑中胆固醇升高）的临床试验。通过还不很清楚的机制，环糊精可使胆固醇的释放更容易。现在医学文献证明环糊精在其他神经系统疾病试验鼠模型上有有益的效果，如阿尔茨海默氏病。特利和洛佩兹博士将在雷特试验鼠身上测试环糊精，看是否可以看到一些症状改善。

Discovery of Compounds Promoting MECP2 Read-Through
化合物的发现促进 MECP2 的通读

Andrew Napper, PhD | Nemours/A.I. duPont Hospital for Children
安德鲁 纳珀博士/内穆尔/人工智能杜邦儿童医院

$268,452 AWARDED
268，452 美元奖励

Many of the most severely afflicted children with Rett Syndrome have nonsense mutations in the gene for the protein MeCP2. Genes provide a precise instruction code that directs cells to make proteins. Mutations are changes in the genetic code that often result in the production of protein that cannot function normally. Nonsense mutations are like a period in the middle of a long sentence, together with deletion of the words that should have followed. Nonsense mutations in the gene for MeCP2 introduce a "stop codon" prematurely, so that the code for MeCP2 is not read through to the end, and an entire portion of the protein is missing. A potential approach to reverse the effects of a premature stop codon is to discover drugs that "read-through" the stop signal and allow completion of intact MeCP2.

许多被最严重症状折磨的雷特综合征儿童，具有蛋白质 MECP2 基因的无义突变。基因提供精确的指令代码，指示细胞来制造蛋白质。基因突变是蛋白质的基因代码中的改变，往往会导致蛋白质不能正常生产。无义突变就像在一个长句中的一个句号，连同应该后面跟着的单词也被删除。MECP2 基因的无义突变过早地引入了一个"终止密码"，使 MECP2 的代码在没有在结束之前就读完，致使整个蛋白质缺掉。一种扭转造成过早终止密码影响的潜在治疗方法是找出"通读"停止信号并帮助完整的 MECP2 完成表达的药物。

There is much interest in compounds that promote read-through, however, despite considerable effort, read-through compounds have not yet been shown to reverse the pathology of Rett syndrome. To date, aminoglycoside antibiotics have shown the most promise, but their use is limited by significant systemic toxicity. Conversely, the compound ataluren (PTC Therapeutics) is structurally different from the aminoglycosides and is much less toxic; unfortunately, it is also less potent, and numerous labs have had difficulty reproducing its activity.

Dr. Napper has developed innovative methods to discover novel "read-through" compounds for the 30% of kids with Rett who have nonsense mutations.

虽然促进通读的化合物吸引了很多科学家的注意力，然而，尽管付出相当大的努力，通读化合物尚未显示扭转雷特综合征的病理。到目前为止，氨基糖苷类抗生素表现最有前景，但其使用受到重大的全身毒性的限制。相反地，化合物 ataluren （PTC 经皮肝穿刺胆管造影疗法） 在结构上不同于氨基糖甙类抗生素，毒性更小;不幸的是，它的效力也相应减少，以及许多实验室很难再现它的活性度。纳珀博士已经开发了创新的方法，将为 30%的无异突变雷特患儿找出新的通读化合物。

Outlining the Autonomic Signature of Rett Syndrome
描绘雷特综合症的自主症状

Debra Weese-Mayer, MD & Michael Carroll, PhD | Ann & Robert H. Lurie Children's Hospital of Chicago
黛布拉 维斯-马耶尔, 医学博士和迈克尔 卡罗尔博士/安和罗布特 H 卢里芝加哥儿童医院

$157,000 AWARDED
157，000 美元奖励

Though a substantial effort has been made to understand the autonomic phenotype in Rett through the lens of aggregate measures of heart rate variability, cardiac repolarization and cardiorespiratory coupling, a deep understanding of the dysregulation has been elusive. For these reasons these investigators will apply modern computational tools to a data set of ambulatory physiological measures on a large cohort of young girls with Rett and their matched controls. Evaluation of metrics in fine temporal detail will allow us to define the autonomic signature of Rett syndrome at a level that will help understand the underlying

mechanisms, allow clarification of genotype-phenotype correlations and provide a basis for evaluating ongoing clinical interventions.

通过大量的努力，我们通过心率变化、心室复极和心肺功能结合的综合测量已经了解了雷特的自主症状表型，但对功能失调仍一无所知。由于这些原因，研究者们将应用现代计算工具，对一大群同类雷特年轻女性及对照患者进行评估。评价指标最后时间细节将使我们能够定义在一定水平的雷特综合征自主信号，这将有助于理解根本的病症机理，可使基因型和表型相关性得到澄清，为评价正在进行的临床干预措施提供依据。

High-Content Phenotypic Screening of Existing Drugs for the Treatment of Rett Syndrome
对雷特综合征现有治疗药物的高通量表型筛选

Christopher Gibson, PhD & Dean Li, MD, PhD | Recursion Pharmaceuticals
克里索多夫 吉布森博士和迪恩 李医学双博士/Recursion 制药
$50,000 AWARDED
50，000 美元奖励

Recursion combines experimental biology and bioinformatics in a unique drug screening platform. Recursion creates human cellular models of disease and establishes a disease profile based on identifying changes in thousands of structural (morphological) and functional (activity) parameters. These structural and functional changes are then used as the basis of a chemical suppressor screen to identify compounds with strong potential for efficacy in the disease model. For this project RNA interference will be used to genetically manipulate *MECP2* in four human cell lines. The resulting assay will be screened.

Recursion 是结合实验生物学和生物信息学独特的药物筛选平台。Recursion 创建人类疾病的细胞模型，建立了疾病类型清单，其基于识别数以千计的结构 （形态） 的变化和功能 （活动） 参数。这些结构和功能的变化作为化学抑制基因筛选的基础，用于识别在疾病模型中带有强大功效潜力的化合物。对于本项目将使用核糖核酸干扰，从基因方面在四个人类细胞系中控制 MECP2。实验结果将被进一步筛选。

Exploring the Link Between MeCP2 and Gut Physiology to Test a Novel Probiotic Therapy for Rett Syndrome
探讨 MECP2 和胃肠道生理之间环节以测试一种新型针对雷特综合症的益生菌疗法

Ali Khoshnan, PhD & Sarkis K. Mazmanian, PhD | California Institute of Technology
阿里 考施南博士和萨尔基斯 K 马兹玛尼恩博士/加利福尼亚科技学院
$200,000 AWARDED
200，000 美元奖励

This project will test the novel concept that neurodevelopmental and behavioral abnormalities in Rett may be linked to GI defects and/or disruption in the homeostasis of gut microbiota. We will further determine if simple and safe biotherapies directed to the gut of Rett mice ameliorate symptoms, advancing both knowledge of potential etiologies and possible new treatments for Rett Syndrome.

这个项目将测试新的概念，雷特的神经发育和行为异常可能与血糖生成指数缺陷和/肠道菌群体内平衡有关系。我们是进一步将确定针对雷特试验鼠肠道使用简单和安全的生物疗法可改善症状，提高这两种潜在病因知识以及可能成为雷特综合症的新治疗方法，。

Testing NR2A and NR2B NAMs in the mouse models of Rett Syndrome
在雷特试验鼠上测试 NR2A 和 NR2B NAMs

Michela Fagiolini, PhD | Boston Children's Hospital
米凯拉 法吉奥李妮博士/波士顿儿童医院
$464,336 AWARDED
464,336 美元奖励

Work from a variety of labs has identified the excitatory NMDA receptor as a possible target for intervention in Rett. The NMDA receptor is made of various components, including GluN2B and GluN2A. In previous work, Dr. Michela Fagiolini found that decreasing the activity of GluN2A rescues certain neuronal defects and symptoms. Furthermore, past studies identified age and region dependent abnormalities in the NMDA receptor system in young girls with Rett. Together these findings raise the possibility that administration of NMDA receptor modulators may improve Rett symptoms.

很多实验室的研究已经认定兴奋性 NMDA 受体，可能成为雷特干预治疗标靶。NMDA 受体由各种组件组成，包括 GluN2B （Glu-谷氨酸）和 GluN2A。从以往的研究中，米凯拉 法吉奥李妮博士发现，降低 GluN2A 的活性可以挽救某些神经元缺陷和症状。此外，过去的研究发现在雷特年轻女患者中 NMDA 受体系统中所属的年龄和地区出现异常情况。这些发现进一步验证了 NMDA 受体调节剂可改善雷特症状的可能性。

Another drug that blocks the NMDA receptor is ketamine. Dr. Fagiolini's lab recently also began testing ketamine and found that chronic treatment significantly improves symptoms and extends lifespan in mice. Ketamine however can cause psychiatric side effects such as hallucinations. While the dosages used in Rett will be very small and below what should cause problems it is nevertheless prudent to explore other potential ketamine-like drugs in parallel.

The new funding to the Fagiolini laboratory will allow testing of two novel and selective GluN2 modulators.

另一种阻断 NMDA 受体药物是氯胺酮。 法吉奥李妮博士的实验室最近也开始测试氯胺酮，发现长期治疗明显改善症状和延长试验鼠的寿命。但是氯胺酮可以导致精神副作用，例如幻觉。 针对雷特所用剂量将会很小，虽然如此谨慎但仍将导致问题的产生，同时进行探索其他潜在的类氯胺酮等药物。 法吉奥李妮实验室的新拨款将允许两个新型和选择性的 GluN2 调制器的检验。

Therapeutic Approaches to Reversing Forebrain and Brainstem Abnormalities
逆转前脑和脑干异常情况的治疗方法

David Katz, PhD | Case Western Reserve University
大卫 卡兹博士/凯斯西储大学

$150,000 AWARDED
150，000 美元奖励

This project will seek to determine whether NMDA receptor antagonists can reverse the imbalance of excitation vs inhibition present in the forebrain and brainstem of Rett mice. If so, certain drugs could be quickly moved into clinical trials.

此项目将寻求确定是否 NMDA 受体拮抗剂是否可以重新平衡雷特试验鼠前脑和脑干中的兴奋性和抑制性。如果是这样，某些药物能迅速进入临床试验。

Testing Whether LM22A-4 Improves Hippocampal Function in Female MECP2 Heterozygous Mice
测试是否 LM22A 4 可以改善雌性 MECP2 杂合试验鼠的海马功能

Lucas Pozzo-Miller, PhD | University of Alabama Birmingham
卢卡斯 波佐-米勒博士/阿拉巴马州伯明翰大学

$110,000 AWARDED
110,000 美元奖励

Work in the lab of David Katz showed that both acute and chronic administration of LM22A-4 improved respiration in symptomatic female Rett mice. The Pozzo-Miller will test whether this same compound will stabilize the impaired hippocampal network thereby improving synaptic plasticity. The hypothesis is that enhancing TrkB signaling via this drug will improve Rett symptoms.

在大卫 • 卡茨实验室的研究表明，急性和慢性的 LM22A-4 给药可以改善雌性雷特试验鼠的呼吸症状。 波佐-米勒将测试这一化合物是否可以稳定受损的海马网络，从而提高突触可塑性。 假设这种药物是通过加强 TrkB 信号改善雷特症状。

Preclinical Studies of LM22A-4 in Mouse Models of Rett Syndrome
雷特综合征试验鼠模型上的 LM22A-4 临床前研究

David Katz, PhD | Case Western Reserve University
大卫 卡兹博士/凯斯西储大学

$272,000 AWARDED
272,000 美元奖励

Studies have identified Brain Derived Neurotrophic Factor (BDNF) and its receptor, TrkB, as promising therapeutic targets for the treatment of Rett.
Studies in the Katz laboratory demonstrated that respiratory abnormalities are reversed in the Rett animal model following systemic treatment with LM22A-4, a compound that boosts TrkB activity. As a next step towards a potential clinical development path for LM22A-4 for the treatment of Rett, RSRT is supporting the generation of a robust preclinical package of PK/PD (pharmacokinetic/pharmacodynamic), efficacy and safety data in support of a subsequent application for funding of Investigational New Drug (IND) – enabling studies.
研究认定脑源性神经营养因子（简称 BDNF）和它的受体 TrkB 可作为有希望的雷特治疗标靶。卡兹实验室研究证明，在雷特动物模型上进行的 LM22A-4 系统性治疗，逆转了呼吸道异常症状，一种化合物大大增强了 TrkB 活性度。 作为下一步 LM22A 4 雷特治疗潜在的临床发展路径，RSRT 支持新一代的打包式 PK/PD （药动学/药效学）临床前研究，研究的疗效和安全性数据支持了随后在申请临床研究性新药物(简称 IND)的资金申请。

Screening for drugs that can rebalance long gene misexpression
筛选的药物，可以平衡长基因嵌入

Mark Zylka, PhD | University of North Carolina at Chapel Hill
马克 仔奥卡博士/北开来罗那大学教堂山分校

$400,000 AWARDED
400,000 美元奖励

In March of 2013, the lab of Michael Greenberg at Harvard Medical School published data showing that the *MECP2* gene lowers the expression of genes that are physically long. The scientists found that the MeCP2 protein acts as a dimmer switch, dampening the expression of long genes. When the MeCP2 protein is absent, as in the case of Rett, with no dimmer switch to regulate it, long gene expression goes up. This work suggests that drugs that can rebalance the expression of long genes might have therapeutic benefit in Rett.
Mark Zylka from the University of North Carolina at Chapel Hill, working independently on a non-Rett project, discovered that a class of drugs called topoisomerase inhibitors reduces the expression of long genes. Almost by accident, this raised the possibility that this class of drugs could be clinically relevant for Rett. One such drug is topotecan which is FDA approved for cancer. The Greenberg lab is now testing Topotecan in Rett mice models. However, Topotecan may not be the ideal drug since it doesn't get into the brain easily and would be toxic for long term use. As a result, RSRT has awarded Mark Zylka $400,000 to screen for other compounds that can rebalance expression of long genes safely.
在 2013 年 3 月，哈佛大学医学院的迈克尔 • 格林伯格实验室发布数据显示 MECP2 基因降低生理上长基因的表达。科学家们发现，MECP2 蛋白质充当着调节因子，抑制长基因的表达。当 MECP2 蛋白质缺失的时候，没有调节因子来控制它，致使长基因表达上升。这项研究工作表明可以平衡的长基因表达的药物可能对雷特有治疗效果。马克 仔奥卡来自北卡罗来纳大学教堂山分校，独立在非雷特项目进行研究工作，发现一类的药物称为拓扑异构酶抑制剂可以减少长基因的表达。偶然的是这类药物可能很快用于雷特临床，因为其中一种药物拓扑替康是美国食品和药物监管局批准治疗癌症药物。格林伯格实验室现在正在雷特实验鼠模型上测试拓扑替康。
然而，拓扑替康可能不是理想的药物，因为它不容易进入大脑，长期使用会有毒负作用。因此，RSRT 已授予马克 仔奥卡博士 400,000 美元 用以筛选其他可以安全地重新平衡长基因的表达的化合物。

Clinical Development of NLX-101 in Rett Syndrome; estimated costs for filing an IND application

用于雷特综合症的纳络酮 101 的临床发展; IND 申请的费用估算

Mark Varney, PhD | Neurolixis

马克 瓦尼博士/ Neurolixis 公司

$585,000 AWARDED

585，000 美元奖励

Neurolixis is a biotech company developing a drug (NLX-101) to treat breathing problems in Rett Syndrome. John Bissonnette, Ph.D. of OHSU, previously tested the drug in mouse models of Rett. These mice exhibit severe breathing difficulties, including apneas and respiratory irregularity, similar to those seen in girls with Rett syndrome. NLX-101 treatment reduced the occurrence of apneas and normalized the irregular breathing patterns without interfering with other behaviors. These data suggest that NLX-101 may represent a promising strategy for treating breathing disturbances in Rett.

Neurolixis 是一家生物技术公司，它开发一种药物（纳络酮 101）治疗雷特综合征患者呼吸问题。俄勒冈健康与科学大学的约翰 比索博士先前在雷特试验鼠模型上测试过药物。这些试验鼠表现出严重的呼吸困难，包括呼吸暂停、 呼吸不规则，与所见雷特综合征的女孩相似。纳络酮 101 的治疗减少了呼吸暂停的发生和使不规则的呼吸模式正常化，而不会干扰其他的行为。这些数据表明纳络酮 101 可能成为雷特治疗呼吸紊乱的新策略。

MECP2 DUPLICATION

MECP2 基因重叠

A Drug-Screening Platform for the MECP2 Duplication Syndrome Using Human Neurons

人类神经元 MECP2 重叠综合征的药物筛选平台

Alysson Renato Muotri, PhD | University of California San Diego

阿利松 雷纳托 茂垂博士/加利福尼亚圣迭戈大学

$792,000 AWARDED

792，000 美元奖励

The unavailability of live human brain cells for research has blocked progress toward understanding mechanisms behind neurological disorders. A human stem cell model, using reprogrammed patient cells offers an attractive alternative as it captures the patient's genome in the relevant neural cell types. In 2010, Dr. Muotri's group has shown that neurons derived from Rett Syndrome patients displayed several morphological and functional abnormalities that could be reversed using candidate drugs. Last year, they generated stem cell-derived "mini-brains" from patients with *MECP2* duplication syndrome and found a candidate drug that could rescue altered neuronal network activity. With RSRT support, the team will now engineer human stem cells with different *MECP2* doses to screen a larger library of drugs and perform pre-clinical studies in animal models to validate potential candidates.

用于研究的活体脑细胞的缺乏已阻止神经系统疾病背后对理解病症机制的进展。用重组病人细胞组建的人类干细胞模型为科学家们提供了选择。2010 年，茂垂博士的小组研究表明来自雷特综合征患者的神经元显示出几个形态和功能的异常，使用候选药物可能会使症状逆转。去年，他们用 MECP2 重叠综合征患者生成干细胞"迷你-大脑"，并发现一种候选药物能挽救变异的神经元网络活动。在 RSRT 的支持下，团队将设计建造人类干细胞，结合不同的 MECP2 剂量以筛选较大量的药物，并在动物模型上进行临床前研究以验证潜在的候选药物。

Gene Therapy Approach to Treating MECP2 Duplication Syndrome

治疗 MECP2 重叠综合征的基因治疗方法

Kevin Foust, PhD | Ohio State University

凯文 福斯特博士/俄亥俄州立大学

$40,000 AWARDED

40，000 美元奖励

The duplication syndrome is caused by having an extra copy (or two) of the *MECP2* gene and sometimes other genes in the vicinity. In theory, reducing the amount of MeCP2 protein should improve the disease. Dr. Foust will use adeno-associated virus (AAV) to deliver RNA interference to lower the amount of MeCP2 protein. If successful the project will provide proof-of-concept data showing that MeCP2 reduction is a therapeutic option for patients.

重叠综合征是由附近有的一个额外复制的 （或二个） MECP2 基因以及其他可能基因引起的。理论上讲，减少 MECP2 蛋白质的量应该可以改善这种疾病。福斯特博士将使用腺相关病毒 （简称 AAV） 以传送核糖核酸的干涉因子，从而降低 MECP2 蛋白质的量。如果成功该项目将提供证明概念的数据，显示 MECP2 的减少是一种治疗选择。

Investigating the Potential of Antisense Oligonucleotide Therapy for MECP2 Duplication Syndrome

MECP2 重叠综合征反义寡核苷酸治疗的可能性研究

Huda Zoghbi, MD | Baylor College of Medicine

胡达 祖比医学博士/贝勒医学院

$230,000 AWARDED

230，000 美元奖励

MECP2 duplication syndrome is a neurological disorder caused by the duplication of genetic material on chromosome X, spanning the *MECP2*gene. As a result of the duplication, the MeCP2 protein is excessively produced at two times the normal levels. This proposal will explore the use of a drug-like molecule to reverse the symptoms of *MECP2*duplication syndrome, first in an animal model and later in cells derived from patients.Recent data show that MeCP2, at the normal level, is required for proper postnatal neurological functions. Reversibility of symptoms has been demonstrated in a mouse model of Rett syndrome upon normalization of MeCP2 levels, highlighting the surprising potential plasticity of the adult brain upon correction of the molecular mechanisms underlying these disorders. In collaboration with ISIS Pharmaceuticals Inc., we developed an antisense drug that can specifically reduce the levels of MeCP2. We will first screen for the most effective *MECP2*-specific drugs *in vivo* using our MeCP2-Tg1 mice and then test the ability of the selected drugs to reverse symptoms in the mice at the behavioral, molecular and electrophysiological level. We will next test the effectiveness of the drugs in reversing the cellular and molecular phenotype of neural cells derived from *MECP2* duplication patients. In order to generate *MECP2* duplication syndrome neural cells, skin biopsies have been taken from patients and skin cells (fibroblasts) have been derived and cultured in our laboratory. In collaboration with the Human Stem Cell Core at Baylor, we will reprogram the human fibroblasts to generate stem cells that could be then re-differentiated into neurons.If we establish that normalization of MeCP2 levels by treatment with the selected drugs rescues the duplication traits, this would be very exciting for the*MECP2* duplication families. In addition, the establishment of a new patient-specific cellular model of the disease will open a new area of research and a new pre-clinical tool to screen for modulators of MeCP2 levels.

MECP2 重叠综合征是一种由生成 MECP2 基因的 X 染色体上基因物质的重叠复制引起的神经疾病。由于重复，MECP2 蛋白质过度产生达到正常水平的两倍。这项建议将探索使用一种分子药物扭转 MECP2 基因重叠综合征，首先用在动物模型上，然后在来源于患者的细胞上。最近的数据表

明 MECP2 在正常的水平对神经功能的发挥起到重要作用。在雷特症状的实验鼠模型上已证明可逆转到 MECP2 的正常水平。显示一旦这些下游病症分子机制得到修正，成人大脑都可以表现出令人惊讶的潜在可塑性。与 ISIS 制药公司合作，我们开发了专门可以减少 MECP2 的反义药物。我们将在 MECP2-Tg1 活体试验鼠身上首先筛选最有效的 MECP2 特殊药物，然后测试所选药物逆转试验鼠行为、 分子和电生理等症状的能力。我们接下来将在来自 MECP2 重复病人的细胞和分子表型的神经细胞上测试药物逆转的有效性。为了生成 MECP2 重叠综合征神经细胞，我们先对病人进行生物检测，然后在我们的实验室里培养皮肤细胞 （成纤维细胞）。与贝勒医学院人类干细胞核心合作，我们将重编人类成纤维细胞生成干细胞使其可以之后重新分化为神经元。如果我们实现了以所选的药物可以使 MECP2 水平正常化，这将为 MECP2 重叠综合征家庭带来非常令人兴奋消息。此外，新的疾病患者特异性细胞模型的建立将会打开一个新的研究领域和新的临床前工具以筛选出对 MECP2 水平有调节作用的药物。

A Forward Genetic Screen to Identify Druggable Modulators of MECP2 Levels
促进遗传筛选，以鉴定 MECP2 水平的调节药物

Huda Zoghbi, MD | Baylor College of Medicine

胡达 祖比医学博士/贝勒医学院

$733,000 AWARDED

733,000 美元奖励

Dr. Zoghbi will screen compounds in search of any that can reduce levels of MeCP2 for the duplication/triplication syndrome. Any positive “hits” could form the foundation for drug discovery efforts.

祖比博士将筛选寻找任何可以减少 MECP2 重复/三倍重复综合征的化合物药物。任何积极的"突破点"都可以成为发现药物的起点。

Is MECP2 Duplication/Triplication Syndrome Reversible?
MECP2 重复/三倍重复可逆转吗？

Huda Zoghbi, MD | Baylor College of Medicine

胡达 祖比医学博士/贝勒医学院

$236,000 AWARDED

236,000 美元奖励

The dramatic reversal of Rett symptoms in mice described by Adrian Bird in 2007 opened the field to questions that must now also be explored in the *MECP2* Duplication Syndrome. We know that in Rett, restoration of proper MeCP2 function in mice only days away from death brought them back to health. Would elimination of the influence of excess MeCP2 in the Duplication Syndrome have a similarly dramatic effect? The first project funded by the Fund will answer this question. The lab of Huda Zoghbi at Baylor College of Medicine is conducting experiments to answer whether restoring proper amounts of Mecp2 in an animal model of the syndrome will reverse symptoms. If symptoms can be reversed is there a time period or can reversal also occur in adults, as in Rett?

2007 年由阿德里安 • 伯德发现在雷特症状试验鼠试验上出现了症状的显著性逆转，是大家重新审视 MECP2 重叠综合征和相关的问题。我们知道，在雷特综合征领域，恢复试验鼠正常的 MECP2 功能，将它们从死亡的边缘带回到健康的状态。消除多余 MECP2 重叠综合征的影响会有同样的戏剧性的效果吗？ 由基金资助的第一个项目将回答这个问题。 胡达 祖比贝勒医学院的实验室正在进行实验，以回答是否恢复动物模型中的适当数量的 MECP2 将扭转症状。如果雷症状可以扭转，那么会不会有一个特定时间段的限制或者逆转是不是也可以在成年人上实现，就如雷特症那样？