Attacking Rett Where it Lives | More Funding Awarded

攻克雷特/更多基金奖励

by RSRT | May 24, 2016

Anyone who follows Rett research knows that the devastating disorder is caused by mutations in the *MECP2* gene. The mutations then cause a poorly understood cascade of downstream effects that result in the symptoms that we associate with the disorder. All of the current clinical trials as well as the numerous recent industry announcements are for drugs that target one of the downstream targets illustrated in the graphic below (dark blue)

雷特综合症是由编码 MECP2 蛋白的基因突变造成的。然而对于由 MECP2 基因突变造成的一系列和疾病相关的下游信号改变我们目前还不是十分清楚。下图列举了目前所有临床试验和药物研究报告所涉及到的治疗靶点（深蓝色）。

Targeting downstream targets is very important to developing potential treatments for Rett symptoms, and numerous RSRT projects and clinical trials take this approach. But the downstream target approach is unlikely to produce the type of profound symptom improvement that we hope would come from attacking the very root of the problem: *MECP2*.

靶向治疗对雷特病的潜在药物开发非常重要，许多 RSRT 资助的研究项目和临床试验均采用这一途径。但是寻找下游靶点可能不会产生显著的症状改善，我们还是希望能够攻克导致雷特病最根本的问题：致病基因 MECP2。

We are fortunate with Rett Syndrome that we *can* target *MECP2.* In fact, this can be achieved in a number of ways. One way is by activating the healthy but silent copy of *MECP2* that is dormant on the inactive X chromosome. Another way is via delivering healthy copies of *MECP2* via gene therapy. RSRT has two *Consortia* that are dedicated to advancing these approaches.

幸运的是我们可以把 MECP2 作为目标基因而最终实现对雷特综合症的治愈。事实上，我们可以通过许多方法实现这一目标。其中之一便是激活沉默的 X 染色体中处于静默状态的 MECP2 基因。另一种则是通过基因疗法向病人体中注射可以表达 MECP2 的基因，以期在病人体内表达其编码的功能蛋白。RSRT 目前拥有两个合作组织从事与推进这些治疗方法的研究。

But there is also another way to target *MECP2*—at the RNA level. A novel technology called Spliceosome-Mediated RNA Trans-Splicing (SMaRT) allows a mutation to be spliced out and repaired in RNA. It's an exciting new way to approach the genetic crux of Rett Syndrome, and it's why Stuart Cobb of the University of Glasgow has received a **$300,000** award from RSRT to work on SMaRT as well as protein replacement which is yet another potentially curative strategy. 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.

但是还有另一种方法也可以在核糖核酸（RNA）层面靶向 MECP2。一种新的技术，称为剪接体介导的 RNA 反式剪接 （简称 SMaRT） 可以修复 RNA 突变。这一振奋人心的新技术引起了广泛的关注，其中来自英国格拉斯哥大学从事 SMaRT 和蛋白替代研究的 Stuart Cobb 教授就得到了 RSRT 提供的三十万美元的研究资助。与基因疗法不同，其中蛋白替代研究以期直接向病人体内注射 MECP2 基因编码的功能蛋白质。但是保护我们大脑的血脑屏障可能会阻碍治疗蛋白的传送。

RSRT has also made a **$125,000** award to a biotech firm, ArmaGen, whose 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.

RSRT 还向 ArmaGen 生物技术公司提供了十二万五千美元的研究基金，其技术充分利用了人体系统，使用无创性的方法穿过血脑屏障传送药物。研究人员发现通过特定的受体，血脑屏障有选择性地允许重要的营养元素从血液中传递到大脑，如胰岛素，转铁蛋白 （运输铁的蛋白质） 和低密度脂蛋白 (LRP1，运输脂肪的蛋白质)。ArmaGen 就是想利用这些受体将 MECP2 蛋白传递至大脑。

Armagen's scientists will fuse certain specific molecules to the MeCP2 protein that will allow it to be recognized and pumped across the blood brain barrier. One advantage to this approach is that it would provide the opportunity to adjust the dose of MeCP2 protein to optimize benefit for each individual.

Armagen 的科学家将某些特定的分子链接到 MECP2 蛋白质上，使其能够被特定受体识别并协助其穿过血脑屏障。这种方法的一个优点是它可以精确控制和调整 MECP2 蛋白质的剂量从而优化每个个体的受益程度。

Since we do not yet know which of these approaches will work best, it is imperative to drive them forward in parallel. We are very fortunate at RSRT that our donors and the families that hold events and raise funds make it possible for us to attack Rett Syndrome from multiple front-lines. As always, we are indebted to all who support our work.

由于目前我们还不知道什么是最好的治疗方法，我们将同时研究所有可能的治疗手段。 作为 RSRT 的成员，我们非常幸运有这么多的捐助者以及患者家庭举办的多种募捐活动使我们能够从多个领域攻克雷特综合征。在此，我们向所有支持我们工作的人表示由衷的感谢。