Therapies targeted at MECP2
针对 MECP2 基因的标靶治疗方法

Approach 治疗方法	How it works 工作原理	Investigators 研究者	Advantages 优势	Potential Limitations 潜在局限性
Gene Therapy 基因治疗	Introduces a healthy MECP2 gene into cells 引入健康的 MECP2 基因进入细胞	Gene Therapy Consortium (P) (Gail Mandel, Stuart Cobb, Steven Gary, Brain Kaspar) James Eubanks (P) Jean-Christophe Roux (P)	Attacks the underlying cause of Rett so has the potential to profoundly impact symptoms 触及雷特根本的致病原因，因此可能会彻底治愈雷特病 Published animal studies show reversal of some symptoms in aged female mice. 已经发表的动物实验证明在成年小鼠身上实现了一些症状的逆转	Could result in too much MECP2 in cells that might be detrimental 可能造成细胞内太多 MECP2 基因，可能对人体有害 Gene therapy must be brain penetrant and target large number of cells 治疗基因必须是通过脑血屏障并作用于大量脑细胞 No FDA approved gene therapy treatment exists yet in US so steeper regulatory pathway in likely 现阶段基因治疗还没有得到美国食品及药物管理局批准，因此审批途径可能遇到困难

Activating MECP2 on the inactive X Chromosome 激活沉默的 MECP2 基因	Mechanism likely be unique to each compound 每个化合物的作用原理都不同	Ben Philpot, Bryan Roth, Terry Magnuson (D) Toni Bedalov Marisa Bartolomei (D) Jeannie Lee (D) Rudolf Jaenisch (D) Michael Green (D) (trying to activate the entire X chromosome) (试图激活整个 X 染色体)	Attacks the underlying cause of Rett so has the potential to profoundly impact symptom 触及雷特根本的致病原因，因此可能会彻底治愈雷特病 Should not result in too much MECPT2 so dosage should not be an issue 不造成过多的 MECP2 基因，因此计量不是问题	Drug must be brain penetrant and target a large number of cells 治疗药物必须是通过脑血屏障并作用于大量脑细胞 Potential for increased expression of other genes on the X chromosome 可能会增强 x 染色体或其他基因的表达 No robust candidates yet identified 还没有找到理想的备选药物
Translation Read-Through Drugs 通读转换药物	May allow the translation of MECP2 even though there is a nonsense or stop mutation (mutations that end in X) 可能容许 MECP2 的转换，即使是无意或终止突变（突变终止在 X 染色体内）	Peter Huppke Timor Baasow (P) Jeffrey Neul, Carolyn Schanen, Andrew Napper (P)	Attacks the underlying cause of Rett so has the potential to profoundly impact symptom 触及雷特根本的致病原因，因此可能会彻底治愈雷特病 Should not result in too much MECPT2 so dosage should not be an issue 不造成过多的 MECP2 基因，因此计量不是问题	Drug may reduce severity but does not eliminate mutation 药物可以减轻但无法消除突变 Drug must be brain penetrant and target a large number of cells 治疗药物必须是通过脑血屏障并作用于大量脑细胞 Will only work for nonsense mutations (about 1/3 of all MECP2 mutations) 将只作用于无意类突变（大约站所有 MECP2 突变的 1/3）

Development Phase Legend: Discovery (D) Preclinical (P) Phase 1 (P1) Phase 2 (P2)
开发阶段说明：发现（D）临床前期（D）一期临床（P1）二期临床（P2）

GROWTH FACTORS AND APPROACHES TO BOOST BRAIN NEUROTROPHIC FACTORS
生长因子和促进大脑神经营养因子的方法

Approach 治疗方法	How it works 工作原理	Investigators 研究者	Advantages 优势	Potential Limitations 潜在局限性
IGF 1 胰岛素样生长因子	Growth factor signaling 生长因子发信号	Mriganka Sur (P) Giorgio Pini (P1) Walter Kaufmann (P2) Walter Kaufmann (P2)	Published Phase 1 result show drug to be well tolerated 已发布一期临床结果显示药物具备良好的耐受性 IGF 1 activates signaling pathways that may provide therapeutic benefit 胰岛素样激活信号通路可以提供有益的治疗 Approved drug 药物已获批	Drug does not address underlying cause of disorder so impact may be restricted to subset of symptoms and/or individuals 药物无法解决神经紊乱的根本问题，因此效果仅限于小部分或个别症状 Published Phase 1 result showed modest and inconsistent improvements 一期临床试验结果显示较小的和不一致的症状提高 If approved for Rett will likely only be used for children pre-puberty 如果获批针对雷特病症将很可能仅适用于青春期以前的儿童 Injection 注射

Copaxone 克帕松	Boosts brain-derived neurotrophic factor (BDNF) 增加脑源性神经元营养因子	Andrew Pieper (P) Ruth Arnon (P) Rina Aharoni (P) Sasha Diukic (P2) Bruria Ben Zeev (P2)	Approved drug 药物已获批	Drug does not address underlying cause of disorder so impact may be restricted to subset of symptoms and/or individuals 药物无法解决神经紊乱的根本问题，因此效果仅限于小部分或个别症状 No published behavioral studies in Rett animal models 未发布在雷特动物模型上进行行为研究 Injection 需要注射
Fingolimod 芬戈莫德	Boosts BDNF 增强脑源性神经营养因子	Yves Alain Barde (P) Peter Weber (P1) (P2)	Approved drug – but not in children 药物已获批，但不能用于儿童 Brain penetrant oral drug 可通过血脑屏障口服药物	Drug does not address underlying cause of disorder so impact may be restricted to subset of symptoms and/or individuals 药物无法解决神经紊乱的根本问题，因此效果仅限于小部分或个别症状 High doses of drug impact immune system function 大剂量药物影响免疫系统功能 No data for use in children 没有作用于儿童的数据
LM22A-4 药物代号，不必翻译	Compensates for reduced BDNF level by directly activating BDNF receptor	David Katz Frank Longo (P)	Highly specific (may correlate with reduced potential for side effects)	Drug does not address underlying cause of disorder so impact may be restricted to subset of symptoms and/or

	补偿通过直接激活脑源性神经营养因子受体减少脑源性神经营养因子水平		高度明确（可以找出减少潜在副作用的对应关系） Brain penetrant 可通过血脑屏障	individuals 药物无法解决神经紊乱的根本问题，因此效果仅限于小部分或个别症状 No approved drug yet – longer development timeline 药物还未获批，开发时间较长
RP 103	Boosts BDNF 增强脑源性神经营养因子	Laurent Villard (P) Raptor Pharmaceuticals (P)	Published animal studies show modest improvement in lifespan and motor skills 已发布动物研究显示在寿命和运动技巧方面适度的提高	Drug does not address underlying cause of disorder so impact may be restricted to subset of symptoms and/or individuals 药物无法解决神经紊乱的根本问题，因此效果仅限于小部分或个别症状 No approved drug yet – longer development timeline 药物还未获批，开发时间较长

Development Phase Legend: Discovery (D) Preclinical (P) Phase 1 (P1) Phase 2 (P2)
开发阶段说明：发现（D）临床前期（D）阶段 1（P1）阶段 2（P2）

SMALL MOLECULE DRUGS THAT MODULATE BRAIN RECEPTOR ACTIVITIES
小分子药物调节大脑受体的活动性

Approach 治疗方法	How it works 工作原理	Investigators 研究者	Advantages 优势	Potential Limitations 潜在局限性
Low dose Ketamine 低剂量氯胺酮	Transiently blocks NMDA receptors 仅持续短暂阻碍天门冬氨酸受体	David Katz (P) Michela Fagiolini (P) Dan Sessler/David Katz (P1)	Preliminary data indicate brief exposure to ketamine reverses multiple disease symptom in Rett mouse models	Drug does not address underlying cause of disorder so impact may be restricted to subset of symptoms and/or individuals 药物无法解决神经紊

		(Clinical trial undergoing IRB approval process) （临床试验正在进行评级机构的审批过程）	初始数据表明在小鼠模型上短暂接触氯胺酮可逆转多种雷特疾病症状 Lots of current interest in ketamine because of benefits in depression and other neuropsychiatric disorders 许多当前对氯胺酮的研究兴趣基于其在抗抑郁和其他方面的功效 Brain penetrant 可通过血脑屏障 Approved drug 药物已获批	乱的根本问题，因此效果仅限于小部分或个别症状 High doses can cause hallucinations 大剂量可导致幻觉 Long term effect of chronic use not known 长期使用的慢性影响还不明 Injection 需要注射
Dextromethorphan 右美沙芬	Blocks NMDA receptors 阻碍天门冬氨酸受体	Sakku Bai Naidu (P2)	Approved drug 药物已获批 Brain penetrant 可通过血脑屏障	Drug does not address underlying cause of disorder so impact may be restricted to subset of symptoms and/or individuals 药物无法解决神经紊乱的根本问题，因此效果仅限于小部分或个别症状 Result from open label study reported in ClinicalTrials.gov site show no statistically significant effect on primary outcome measure 从临床试验政府网站-ClinicalTrials.gov 公开标注的研究报告结果

				显示在主要的成果衡量中没有统计意义上显著效果 Weak NMDA blocker 天门冬氨酸阻碍效果弱 No published animal studies 没有发布动物试验 Study started in 2004 – no publication yet 自 2004 年研究开始还没有出版研究成果
SNRM (Subunit – selective NMDA Receptor Modulators) (附属-选择性的天门冬氨酸受体调制器)	Blocks particular subtypes of NMDA receptors 阻碍特别的附属类天门冬氨酸受体	Mnemosyne Pharmaceuticals Michela Fagiolini (P)	Highly specific (may correlate with reduced potential for side effects) 高度特异性（可以减少潜在副作用） Brain penetrant 可通过血脑屏障	Drug does not address underlying cause of disorder so impact may be restricted to subset of symptoms and/or individuals 药物无法解决神经紊乱的根本问题，因此效果仅限于小部分或个别症状 Not approved drug yet – longer development timeline 药物还未获批，开发时间较长
Sarizotan 沙立佐坦	Activates serotonin receptor, 5-HT 激活受体，5HT1a	John Bissonnette Julian Paton (P) Newron Pharmaceuticals (P2)	Preclinical studies suggest that activating 5-HT1a receptors improves the breathing pattern in mice 临床前试验建议激活 5-HT1a 受体以提高试验白鼠的呼吸方式	Drug does not address underlying cause of disorder so impact may be restricted to subset of symptoms and/or individuals 药物无法解决神经紊乱的根本问题，因此效果仅限于小部分或个别症状 Not approved drug yet

			Brain penetrant oral drug 可通过血脑屏障口服药物	– longer development timeline 药物还未获批，开发时间较长
NLX – 101 纳洛酮-101	Activates serotonin receptor, 5HT1a 激活 5-羟色胺受体，5HT1a	John Bissonnette Julian Paton (P2 being explored) (正处于二期临床阶段) Neurolixis (P)	Preclinical studies suggest that activating 5-HT1a receptors improves the breathing pattern in mice 临床前试验建议激活 5-HT1a 受体以提高试验小鼠的呼吸节奏 Brain penetrant oral drug 可通过血脑屏障口服药物	Drug does not address underlying cause of disorder so impact may be restricted to subset of symptoms and/or individuals 药物无法解决神经紊乱的根本问题，因此效果仅限于小部分或个别症状 Not approved drug yet – longer development timeline 药物还未获批，开发时间较长
Desipramine 去郁敏	Increases levels of noradrenaline 提高去肾上腺素的水平	Laurent Villard (P) Gerard Hilaire Josette Mancini (P2)	Animal studies suggest increasing noradrenaline helps to maintain a normal respiratory rhythm in Rett mouse models 动物试验显示在雷特小鼠身上提高了去肾上腺素有助于帮助正常的呼吸节奏 Approved drug (for depression) 药物已获批（抗抑郁作用） Brain penetrant oral drug 可通过血脑屏障口服药物	Drug does not address underlying cause of disorder so impact may be restricted to subset of symptoms and/or individuals 药物无法解决神经紊乱的根本问题，因此效果仅限于小部分或个别症状 Desipramine can cause cardiac dysrhythmias – FDA has issued a warning related to this 去郁敏可导致心率障碍 – 美国食品及药物管理局就此已发出了警告 Study started in 2008 – no publication yet 自 2008 年研究开始还没有出版研究成果

Vigabatrin 氨己烯酸	Increases GABA levels, a neurotransmitter critical for brain function and is reduced in Rett mouse models 提高伽马氨基丁酸水平，作为重要的抑制性神经递质，和正常小鼠相比，其含量在雷特小鼠脑中较低。	Huda Zoghbi (P)	Already FDA approved and used for selected forms of epilepsy (more abroad than USA) 已获得美国食品和药物管理局的批准，针对某些特定的癫痫症（更多在美国之外的地区） Brain penetrant 可通过血脑屏障	Drug does not address underlying cause of disorder so impact may be restricted to subset of symptoms and/or individuals 药物无法解决神经紊乱的根本问题，因此效果仅限于小部分或个别症状 Retinal toxicity prohibits chronic use 对视网膜的毒性，禁止长期使用

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开发阶段说明：发现（D）临床前期（D）一期临床（P1）二期临床（P2）

OTHER APPROACHES
其他方法

Approach 治疗方法	How it works 工作原理	Investigators 研究者	Advantages 优势	Potential Limitations 潜在局限性
NNZ-2566	Anti-inflammatory reduces neuronal degeneration following injury 抗炎药减轻神经元的退化和次生损伤	Jeffrey Neul Alan Percy Arthur Beisang Neuren Pharmaceuticals (P2)	Brain penetrant oral drug 可通过血脑屏障口服药物 Unpublished Phase 2 result announced by Neuren show drug to be safe and well tolerated 未公开发表二期临床的研究结果，Neuren 宣布研究显示药物的安全性和良好的耐受性 Neuren indicates	Drug does not address underlying cause of disorder so impact may be restricted to subset of symptoms and/or individuals 药物无法解决神经紊乱的根本问题，因此效果仅限于小部分或个别症状 No published animal studies 未公开发表动物研究 Not approved drug yet – longer development timeline

			preliminary efficacy signals suggestive of benefit. Further studies will be necessary to definitively establish whether or not the drug confers clinical benefit.	药物还未获批，开发时间较长 No data for use in children 无在儿童身上使用的数据
Statins 他汀类降低胆固醇的药物	Addresses imbalances in cholesterol synthesis that may contribute to Rett symptoms 强调胆固醇合成的不平衡，因此可有助于改善雷特症状	Monica Justice (P) Sasha Djukic (P2)	Cholesterol pathway in well studied 已有良好的胆固醇研究路径 FDA Approved and cheap 已获美国食品和药物管理局批准和廉价 Many drugs that work on cholesterol pathway, beyond statins, are available for testing. 许多胆固醇路劲药物，除他汀类降低胆固醇的药物以外均可进行测试	Drug does not address underlying cause of disorder so impact may be restricted to subset of symptoms and/or individuals 药物无法解决神经紊乱的根本问题，因此效果仅限于小部分或个别症状 Unknown whether only a certain age group will benefit 不知是否只有一定年龄的病患群体将受益于此 Unknown to what degree cholesterol pathway is disrupted in Rett 不知胆固醇路径治疗在雷特患者身上的破坏程度
Topoisomerase inhibitors or other drugs that correct long gene expression 拓扑异构酶抑制剂或纠正长基因表达的药物	MECP2 appears to turn down protein production of physically long genes. In Rett where MECP2 is not working properly long genes are	Michael Greenberg Sacha Nelson	Potentially addresses a root cause of neuronal dysfunction in Rett (altered gene expression), instead of just treating symptom.	Drug may not replace every critical function of MECP2 so impact may be restricted to subset of symptoms 药物不可能取代每一个 MECP2 基因的重要功能，因此效果仅限

	upregulated. A drug that lowers expression of long genes can therefore rebalance the situation MECP2 基因可下调长基因编码的蛋白质表达。雷特患者 MECP2 基因不能正常工作从而导致长基因被上调。药物可降低长基因的表达最终重新回到平衡状态		潜在揭示雷特神经元功能紊乱的根本原因（改变基因表达） Drug are already available to facilitate pilot studies testing feasibility and efficacy of treatment in mice (toxicity of these drugs are likely an issue that will have to be addressed before use in human, see limitations). 药物已经可以容宜地用于初步研究在小鼠身上测试治疗的可行性和功效（这些药品的毒性很可能成为问题，将不得不在人身上使用之前解决）	于小部分症状 Topoisomerase inhibitors don't readily cross the blood brain barrier and are chemotherapy drugs and therefore toxic 拓扑异构酶抑制剂不宜通过血脑屏障，其为化疗药物，因此具有毒性
REV-003	N/A	Unknown (P) 未知 Revive Therapeutics (P)	Brain penetrant oral drug 可通过血脑屏障口服药物	Drug does not address underlying cause of disorder so impact may be restricted to subset of symptoms and/or individuals 药物无法解决神经紊乱的根本问题，因此效果仅限于小部分或个别症状 Not approved drug yet – longer development timeline

				药物还未获批，开发时间较长 Animal study not published yet 动物研究还未发表
EPI – 743 表阿霉素	There is evidence of mitochondrial dysfunction in Rett. EPT-743 is being developed for mitochondrial diseases 有证据显示雷特病人有线粒体的功能紊乱。EPT-743 作为针对线粒体的疾病的药物正在进行研发	Joussef Hayek Edison Pharmaceuticals (P)	Brain penetrant oral drug 可通过血脑屏障口服药物 Phase 2 results show drug to be well-tolerated and increased head circumference. 二期临床的研究结果显示药物具有良好的耐受性以及增加了头围	Drug does not address underlying cause of disorder so impact may be restricted to subset of symptoms and/or individuals 药物无法解决神经紊乱的根本问题，因此效果仅限于小部分或个别症状 Phase 2 results did not improve primary outcome measure of Rett severity scale. 二期临床的研究结果没能改善雷特症状严重程度的衡量结果 No published animal studies 未发表动物研究成果 Not approved drug yet – longer development timeline 药物还未获批，开发时间较长
Triheptanoin 三庚酸甘油脂	There is evidence of mitochondrial and metabolic dysfunction in Rett. Triheptanoin restores metabolic imbalance and enhances energy production. 有证据说明在雷特	Gabriele Ronnett (P)	Safe drug already in development for other disorders. 安全药物已用于其他紊乱病症 Preclinical data looks encouraging. 临床前的数据看	Drug does not address underlying cause of disorder so impact may be restricted to subset of symptoms and/or individuals 药物无法解决神经紊乱的根本问题，因此效果仅限于小部分或个别症状

	患者的线粒体和新陈代谢功能性紊乱。三庚酸甘油脂起到回复新陈代谢平衡以及提高能量的产出的作用。		上去令人鼓舞。	

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开发阶段说明：发现（D）临床前期（D）一起临床（P1）二期临床（P2）

PROCEDURES
治疗程序

Approach 治疗方法	How it works 工作原理	Investigators 研究者	Advantages 优势	Potential Limitations 潜在局限性
Deep Brain Stimulation 深度大脑刺激	Treatment used for Parkinson's OCD, depression, dystonia and other neurological disorders that could be applicable for Rett . 治疗用于帕金森强迫性神经官能症，抑郁症，肌张力障碍和其他神经紊乱可应用于雷特综合征。	Huda Zoghbi (P) James Leiter (P) Qiu Zilong (P)	Approved procedure for many disorders. 许多治疗程序已获批准。	Does not address underlying cause of disorder so impact may be restricted to subset of symptom and/or individuals 无法解决神经紊乱的根本问题，因此效果仅限于小部分或个别症状 Invasive procedure 需要进行开颅手术，对病人损伤大
Bone Marrow Transplants 骨髓移植	Microglia may be affected in Rett and a transplant may deliver healthy microglia 小神经胶质细胞可能作用于雷特病症以及骨髓移植可传送健康的小神经胶质细胞。	Jonathan Kipnis (P)	Approved procedure for many disorders. 许多治疗程序已获批准。	Does not address underlying cause of disorder so impact may be restricted to subset of symptom and/or individuals 无法解决神经紊乱的根本问题，因此效果仅限于小部分或个别症状。 Report from several group did not observe

				any benefit of transplant in mouse models 报告显示在实验小鼠身上的移植没有观察到症状的好转 Improvement in symptomatic female mice after transplantation has not been shown. 雌性实验鼠移植之后并没有显现出症状的提高 Procedure is painful, risky and expensive 治疗程序有疼痛，有风险以及昂贵