Potential Rett Syndrome Therapeutics

Approach	How it works	Development Phase (Discovery = basic science Preclinical = animal work Phase 1&2 = human trials)	Investigators	Advantages	Potential Limitations
Therapies targeted at *MECP2*					
Gene therapy	Introduces a healthy *MECP2* gene into cells	Preclinical	Gene Therapy Consortium (Gail Mandel, Stuart Cobb, Steve Gray, Brian Kaspar) James Eubanks Jean-Christophe Roux	Attacks the underlying cause of Rett so has the potential to profoundly impact symptoms Published animal studies show reversal of some symptoms in aged female mice.	Could result in too much *MECP2* in cells that might be detrimental Gene therapy must be brain penetrant and target large number of cells No FDA approved gene therapy treatment exists yet in US so steeper regulatory pathway is likely
Activating *MECP2* on the inactive X chromosome	Mechanism will likely be unique to each compound	Discovery	Ben Philpot Bryan Roth Terry Magnuson Toni Bedalov Marisa Bartolomei Jeannie Lee Rudolf Jaenisch Michael Green (trying to activate the entire X chromosome)	Attacks the underlying cause of Rett so has the potential to profoundly impact symptoms Should not result in too much *MECP2* so dosage should not be an issue	Drug must be brain penetrant and target a large number of cells Potential for increased expression of other genes on the X chromosome No robust candidates yet identified
Translation read-through drugs	May allow the translation of MeCP2 even though there is a nonsense or stop mutation (mutations that end in X)	Preclinical	Peter Huppke Timor Baasov Jeffrey Neul Carolyn Schanen Andrew Napper	Attacks the underlying cause of Rett so has the potential to profoundly impact symptoms Should not result in too much *MECP2* so dosage should not be an issue	Drug may reduce severity but does not eliminate mutation Drug must be brain penetrant and target a large number of cells Will only work for nonsense mutations (about 1/3 of all *MECP2* mutations) To date, efficacy of this approach in other diseases has been relatively poor

Current as of August 2015

rett syndrome research trust

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Growth Factors and approaches to boost brain neurotrophic factors					
IGF1	Growth factor signaling	Preclinical Phase 1 Phase 2	Mriganka Sur Giorgio Pini Walter Kaufmann Walter Kaufmann	Published Phase 1 results show drug to be well tolerated IGF1 activates signaling pathways that may provide therapeutic benefit Approved drug	Drug does not address underlying cause of disorder so impact may be restricted to subset of symptoms and/or individuals Published Phase 1 results showed modest and inconsistent improvements If approved for Rett will likely only be used for children pre-puberty Injection
Copaxone	Boosts brain-derived neurotrophic factor (BDNF)	Preclinical Phase 2	Andrew Pieper Ruth Arnon Rina Aharoni Sasha Djukic Bruria Ben Zeev	Approved drug	Drug does not address underlying cause of disorder so impact may be restricted to subset of symptoms and/or individuals No published behavioral studies in Rett animal models Injection
Fingolimod	Boosts BDNF	Preclinical Phase 1/2	Yves Alain Barde Peter Weber	Approved drug – but not in children Brain penetrant oral drug	Drug does not address underlying cause of disorder so impact may be restricted to subset of symptoms and/or individuals High doses of drug impact immune system function No data for use in children
LM22A-4	Compensates for reduced BDNF levels by directly activating BDNF receptor	Preclinical	David Katz Frank Longo	Highly specific (may correlate with reduced potential for side effects) Brain penetrant	Drug does not address underlying cause of disorder so impact may be restricted to subset of symptoms and/or individuals Not approved drug yet – longer development timeline
RP103	Boosts BDNF	Preclinical	Laurent Villard Raptor Pharmaceuticals	Published animal studies show modest improvement in lifespan and motor skills.	Drug does not address underlying cause of disorder so impact may be restricted to subset of symptoms and/or individuals Not approved drug yet – longer development timeline

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Small molecule drugs that modulate brain receptor activities					
Low dose Ketamine	Transiently blocks NMDA receptors	Preclinical Clinical trial undergoing IRB approval process	David Katz Michela Fagiolini Dan Sessler/David Katz	Preliminary data indicate brief exposure to ketamine reverses multiple disease symptoms in Rett mouse models Lots of current interest in ketamine because of benefits in depression and other neuropsychiatric disorders Brain penetrant Approved drug	Drug does not address underlying cause of disorder so impact may be restricted to subset of symptoms and/or individuals High doses can cause hallucinations Long term effect of chronic use not known Injection
Dextromethorphan	Blocks NMDA receptors	Open Label trial ended Phase 2	Sakku Bai Naidu	Approved drug Brain penetrant	Drug does not address underlying cause of disorder so impact may be restricted to subset of symptoms and/or individuals Results from open label study reported in ClinicalTrials.gov site show no statistically significant effect on primary outcome measure Weak NMDA blocker No published animal studies Study started in 2004 – no publication yet
SNRM (Subunit-selective NMDA Receptor Modulators)	Blocks particular subtypes of NMDA receptors	Preclinical	Mnemosyne Pharmaceuticals Michela Fagiolini	Highly specific (may correlate with reduced potential for side effects) Brain penetrant	Drug does not address underlying cause of disorder so impact may be restricted to subset of symptoms and/or individuals Not approved drug yet – longer development timeline
Sarizotan	Activates serotonin receptor, 5HT1a	Preclinical Phase 2 – being explored	John Bissonnette Julian Paton Newron Pharmaceuticals	Preclinical studies suggest that activating 5-HT1a receptors improves the breathing pattern in mice Brain penetrant oral drug	Drug does not address underlying cause of disorder so impact may be restricted to subset of symptoms and/or individuals Not approved drug yet – longer development timeline
NLX-101	Activates serotonin receptor, 5HT1a	Preclinical Phase 2 – being explored	John Bissonnette Julian Paton Neurolixis	Preclinical studies suggest that activating 5-HT1a receptors improves the breathing pattern in mice Brain penetrant oral drug	Drug does not address underlying cause of disorder so impact may be restricted to subset of symptoms and/or individuals Not approved drug yet – longer development timeline

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Desipramine	Increases levels of noradrenaline	Preclinical Phase 2	Laurent Villard Gerard Hilaire Josette Mancini	Animal studies suggest increasing noradrenaline helps to maintain a normal respiratory rhythm in Rett mouse models Approved drug (for depression) Brain penetrant oral drug	Drug does not address underlying cause of disorder so impact may be restricted to subset of symptoms and/or individuals Desipramine can cause cardiac dysrhythmias – FDA has issued a warning related to this Study started in 2008 – no publication yet
Vigabatrin	Increases GABA levels, a neurotransmitter critical for brain function and is reduced in Rett mouse models	Preclinical	Huda Zoghbi	Already FDA approved and used for selected forms of epilepsy (more abroad than USA) Brain penetrant	Drug does not address underlying cause of disorder so impact may be restricted to subset of symptoms and/or individuals Retinal toxicity prohibits chronic use
Other Approaches					
NNZ-2566	Anti-inflammatory reduces neuronal degeneration following injury	Phase 2	Jeffrey Neul Alan Percy Arthur Beisang Neuren Pharmaceuticals	Brain penetrant oral drug Unpublished Phase 2 results announced by Neuren show drug to be safe and well tolerated. Neuren indicates preliminary efficacy signals suggestive of benefit. Further studies will be necessary to definitively establish whether or not the drug confers clinical benefit.	Drug does not address underlying cause of disorder so impact may be restricted to subset of symptoms and/or individuals No published animal studies Not approved drug yet – longer development timeline No data for use in children
Statins	Addresses imbalances in cholesterol synthesis that may contribute to Rett symptoms	Preclinical Clinical trial recruiting	Monica Justice Sasha Djukic	Cholesterol pathway is well studied FDA approved and cheap Many drugs that work on cholesterol pathway, beyond statins, are available for testing.	Drug does not address underlying cause of disorder so impact may be restricted to subset of symptoms and/or individuals Unknown whether only a certain age group will benefit Unknown to what degree cholesterol pathway is disrupted in Rett
Topoisomerase inhibitors or other drugs that correct long gene expression	MeCP2 appears to turn down protein production of physically long genes. In Rett where MeCP2 is not working properly long genes are upregulated. A drug that lowers expression of long genes can therefore rebalance the situation.	Preclinical	Michael Greenberg Sacha Nelson	Potentially addresses a root cause of neuronal dysfunction in Rett (altered gene expression), instead of just treating symptoms. Drugs 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 humans, see limitations).	Drug may not replace every critical function of MeCP2 so impact may be restricted to subset of symptoms Topoisomerase inhibitors don't readily cross the blood brain barrier and are chemotherapy drugs and therefore toxic

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REV-003	Information not available	Preclinical	Unknown Revive Therapeutics	Brain penetrant oral drug	Drug does not address underlying cause of disorder so impact may be restricted to subset of symptoms and/or individuals Not approved drug yet – longer development timeline Animal study not published yet.
EPI-743	There is evidence of mitochondrial dysfunction in Rett. EPI-743 is being developed for mitochondrial diseases	Phase 2	Joussef Hayek Edison Pharmaceuticals	Brain penetrant oral drug Phase 2 results show drug to be well-tolerated and increased head circumference.	Drug does not address underlying cause of disorder so impact may be restricted to subset of symptoms and/or individuals Phase 2 results did not improve primary outcome measure of Rett severity scale. No published animal studies Not approved drug yet – longer development timeline
Triheptanoin	There is evidence of mitochondrial and metabolic dysfunction in Rett. Triheptanoin restores metabolic imbalance and enhances energy production.	Preclinical	Gabriele Ronnett	Safe drug already in development for other disorders. Preclinical data looks encouraging.	Drug does not address underlying cause of disorder so impact may be restricted to subset of symptoms and/or individuals
Procedures					
Deep Brain Stimulation	Treatment used for Parkinson's, OCD, depression, dystonia and other neurological disorders that could be applicable for Rett.	Preclinical	Huda Zoghbi James Leiter Qiu Zilong	Approved procedure for many disorders.	Does not address underlying cause of disorder so impact may be restricted to subset of symptoms and/or individuals Invasive procedure
Bone marrow transplants	Microglia may be affected in Rett and a transplant may deliver healthy microglia	Preclinical	Jonathan Kipnis	Approved procedure for many disorders.	Does not address underlying cause of disorder so impact may be restricted to subset of symptoms and/or individuals Reports from several groups did not observe any benefit of transplant in mouse models Improvement in symptomatic female mice after transplantation has not been shown. Procedure is painful, risky and expensive