Towards identifying therapeutic targets of MECP2 deficiency

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The postnatal re-introduction of a Mecp2 functional allele into a mouse mutant and the concomitant rescue of key aspects of the neurodevelopmental phenotype raised hope (and expectation) for the discovery of tenable therapeutics, not only for Rett syndrome (RTT), but also for other similar neurodevelopmental disorders. However, progress towards that goal has remained frustratingly slow. Some excitement is garnered by possible gene therapy trials, whereas recent reports of antisense-oligonucleotide driven suppression of MECP2 in duplication cases has likewise shown some promise. The Center for Human Disease Modeling (CDHDM) at Duke is focused on the development of physiologically-relevant animal models of human disorders and their implementation for the acceleration of biological mechanism and therapeutics. As part of that effort, we have built scalable screening tools to harness the power of the zebrafish embryo, a vertebrate with high similarity to many aspects of human anatomy and physiology, to test the effect of mutations in patients and to launch novel drug screening platforms. Here, we propose to use a series of robust in vivo assays: a) to explore the pathomechanism of the neurodevelopmental pathology of RTT; and b) to use our state-of-the-art in vivo tools to identify chemical targets that can rescue RTT pathology.