Reactivating the silent MECP2 allele through a synergistic drug mechanism

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Our goal is to treat Rett Syndrome by reactivating the silent copy of MECP2. In the past two years, we made a major breakthrough towards reactivating the inactive X-chromosome (Xi). By defining a comprehensive protein interactome for Xist RNA, we have discovered multiple classes of interactors, including cohesins, condensins, topoisomerases, RNA helicases, chromatin remodelers and modifiers, which synergistically repress Xi transcription. Because Xist is a central molecule that orchestrates the X-chromosome silencing process, our present goal is to perturb the Xi by inhibiting components of the Xist interactome. Preliminary data indicate that this approach can reactivate genes on the Xi, including Mecp2. To translate our discovery to the clinic, we will perform testing in vivo in mouse models as well as patient-specific human cells, with the ultimate goal of partnering with industry to bring the therapeutic to Rett Syndrome patients.