In the 50 plus years since Rett syndrome was first described, a tremendous amount of fundamental – “basic” – research has driven forward our understanding of this developmental disorder. However, do we know all we should to discover a cure or even an effective treatment? We think there is still much more to learn about Rett syndrome from the genetic level, molecular interactions, and cellular interactions all the way to the neural networks that receive and integrate all the sensory information and drive the behaviors that make us humans.

To understand how a genetic disease manifests, allowing information-based therapies to be designed, the gene responsible for the condition must be first identified and the function(s) of the protein it encodes be clearly defined. The identification of MECP2 as the primary causal gene for Rett syndrome provided a quantum leap for seeking such rationale-based treatment strategies for Rett syndrome. The list of research advances that were enabled by the identification of MECP2 as the causal gene is long and has set the stage for many of the current clinical trials that are either underway or working their way through regulatory approval processes.

When MECP2 was originally identified as the primary Rett syndrome gene we knew virtually nothing about what it did in the brain. What was known about the MeCP2 protein stemmed from work in non-neuronal systems, many of which geared towards cancer biology rather than neurobiology. We have learned much about what MeCP2 does in the brain since then, but to this day we have not yet identified clearly all of what MeCP2 does in the cells that make up the nervous system.

We often use the structure of a large oak tree as an illustration for trying to envision what MeCP2 does – MeCP2 would be found within the trunk of the tree and play a role in regulating everything that moves from the roots of the tree out to its furthest branches. Each branch of the tree represents a site that one could potentially target for therapies - but only the part of the tree connecting to that specific branch would benefit from targeting that site. You can imagine that the closest to the trunk you target, the better the overall effect of the intervention could be, or a combinatorial strategy that targets multiple tree branches could be effective. For this to occur, a great deal of fundamental scientific research remains to be done.

Using this same oak tree analogy, one can appreciate that targeting the trunk of the tree would represent the best therapeutic intervention site. This type of intervention would restore MECP2 function, and gene therapy, protein replacement therapy, silent X chromosome re-activation, and nonsense mutation “read-through” drug therapies represent strategies that could achieve this goal. There is very good evidence that restoring normal MECP2 function would be beneficial, as dramatic improvements were seen in experimental Rett syndrome mice when a previously silent Mecp2 gene was re-activated (i.e. turned back on), even when mice showed all the neurological symptoms of Rett syndrome. The same was done in human neurons derived from Rett syndrome patients. To date, there is great interest in each of these prospective treatment areas, although only initial preclinical gene therapy studies in Rett syndrome mouse models have been published. This again highlights the need for more fundamental scientific research to unveil the possibilities and limitations of novel prospective therapies.

With respect to gene therapy, indeed, the initial outcomes have been encouraging. But such encouraging preclinical outcomes in mice or cells in a dish remain a long way from implementation in humans. We have to get it right, or be as close to right as possible, because gene therapy is not reversible. We know that restoring MECP2 too quickly increases the risk of sudden death in mice, and that putting back too much MECP2 can be problematic. We know that recovering only small amounts of MECP2 function does little for neurological symptoms, but administering too much MECP2 virus can harm the liver. Ten years ago, few felt these hurdles could be overcome. Now there is reason for optimism – but more work must be done in experimental animal models to define the best balance for likelihood of success with the lowest risk of complications.
So where do we stand in 2018? Have we reached the place where we know enough to focus efforts on clinical implementation, or do we still need more work to refine our knowledge towards best clinical strategies? From our perspective, this is not an either/or scenario. We do arguably know enough to move forward with some of the experimental translational knowledge and test them in patients. This is a type of research project, as all clinical trials are experiments being done in patients. And today, we celebrate that science has moved research from the bench to advanced phases of clinical trials testing different drugs that target different branches of that oak tree.

However, we continue to strive towards identifying new therapeutic targets that effectively treat or even cure Rett syndrome. We will find out which branches of the oak tree are closest to the trunk. The consensus amongst scientists in this field is that there are more targets to be found, and that they will emerge only through hard work in fundamental scientific research. We all know this is not a fast process, nor one that can be done without significant financial backing. Moving from “bench-to-bedside” has been frequently viewed as a pipeline. Rather, we posit it is a staircase that, even though is hard to climb, reveals new views at every step, information that will never again be hidden.