



ANGELA RUSSELL, DPhil
 Professor of Medicinal Chemistry
 University of Oxford

“Our Harrington team has been absolutely wonderful in helping us conduct all the right experiments and make progress toward the clinic.”

FROM FAILURE TO POTENTIAL BREAKTHROUGH

FOCUS: Small molecule AhR antagonists for the treatment of Duchenne muscular dystrophy.

Duchenne muscular dystrophy (DMD) is a severe muscle-wasting disorder that primarily affects boys. Muscle weakness usually begins around the age of four, typically in the thighs and pelvis, followed by the arms. It worsens quickly, eventually affecting all muscles. Individuals with this disease don't often reach the age of 30.

DMD is caused by a defect in a particular gene that makes dystrophin, an important protein that acts as a shock absorber in muscles, protecting muscle fibers from damage that would otherwise result from normal contraction and exercise.

Fortunately, there is another protein encoded in one's genome that makes a protein called utrophin, which is similar to the protein that's absent in DMD, dystrophin. Dr. Russell and her team developed a compound, ezutromid, designed to treat DMD by increasing the amount of utrophin in muscle.

“Our clinical trial of ezutromid showed promising results, but wasn't effective over a long period,” Dr. Russell says. “But we then sought to understand just how ezutromid works, and found that it binds to and switches off a protein

called the arylhydrocarbon receptor (AhR), which leads to more utrophin production.”

Since then, Dr. Russell's lab has discovered two new molecules that switch off AhR and increase production of utrophin, both with better efficacy and improved properties compared to ezutromid. She is optimistic that this work will result in a drug candidate for utrophin replacement therapy, which in turn could be applicable to other inflammatory diseases such as cancer and arthritis.

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