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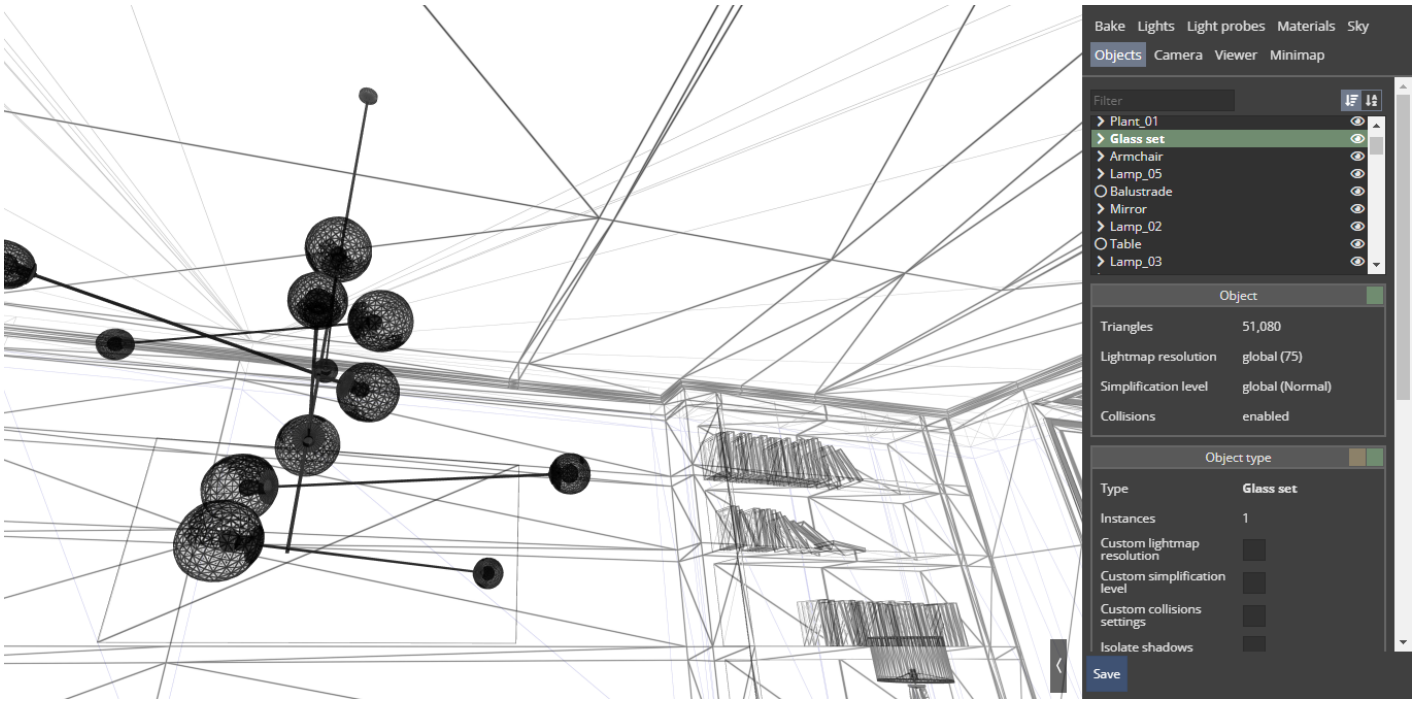

This article illuminates how a next-generation ASO (anti-sense oligonucleotide) screening study has revealed a powerful and precise investigative technique.

At present, four ASO therapies have approval for treating DMD. All four therapies induce exon skipping during pre-mRNA splicing to produce functional dystrophin. However, they do this to a relatively low extent, and thus, there is still a need for new and effective therapies for the disease.

A recent paper by VICO Therapeutics describes an ASO screening study that identifies new ASOs that target novel stretches of dystrophin exon 51 by combining chemical modification screening, in vivo and in vitro models.

In this study, a series of ASOs were screened for their efficacy in DMD patient myotube cultures with ddPCR (digital droplet polymerase chain reaction), and immunoassays were used to identify ASO candidates inducing the highest levels of dystrophin expression in vitro and exon 51 skipping. The process found a new ASO, which was 10 times more effective at exon 51 skipping than an ASO for DMD formally under development at BioMarin (drisapersen).

Following the in vitro testing, the hDMDdel52/mdx mouse model—which lacks any functional dystrophin and displays associated motor deficits and biomarkers, allowing candidate screening at a functional and molecular level—was used to examine the effect of AON-C19.

Tissue profiling demonstrated that AON-C19 penetrated the heart and quadricep muscle in the mouse

model, inducing a reduction in dystrophin levels and a high percentage of exon skipping. CK and LDH, serum biomarkers usually elevated in patients suffering from DMD, were decreased in mdx mice treated with AON-C19.

VICO Therapeutics and Charles River Laboratories worked together to perform a fine kinematic motor analysis of the effects of AON-C19 on motor activity and gait in the mdx mouse model.

This high-precision assay uses the MotoRater system with Charles River's proprietary algorithms to analyze multiple markers to assess gait, whole-body movements, and the movements of individual limbs, resulting in an output of over 100 parameters to investigate the effects of therapeutics.
Fine kinematic motor analysis is more sensitive to therapeutics' effects than traditional motor assays, enabling detection of small changes in mutliple paramaters before they would be evident in traditional assays.

In comparison to wild-type controls, mdx mice show changes in limb swing speed, hip, knee, and ankle angles, stride distance, and ileac crest height. Compared to vehicle-treated mdx mice and following a 20-week treatment with AON-C19, mdx mice displayed improved gait and motor functions.

About Charles River Laboratories
At Charles River, we are passionate about our role in improving the quality of people's lives. Our mission, our excellent science and our strong sense of purpose guides us in all that we do, and we approach each day with the knowledge that our work helps to improve the health and well-being of many across the globe.

Charles River provides essential products and services to help pharmaceutical and biotechnology companies, government agencies and leading academic institutions around the globe accelerate their research and drug development efforts.

As a fully integrated partner, Charles River can support your research at any point along the drug discovery continuum.

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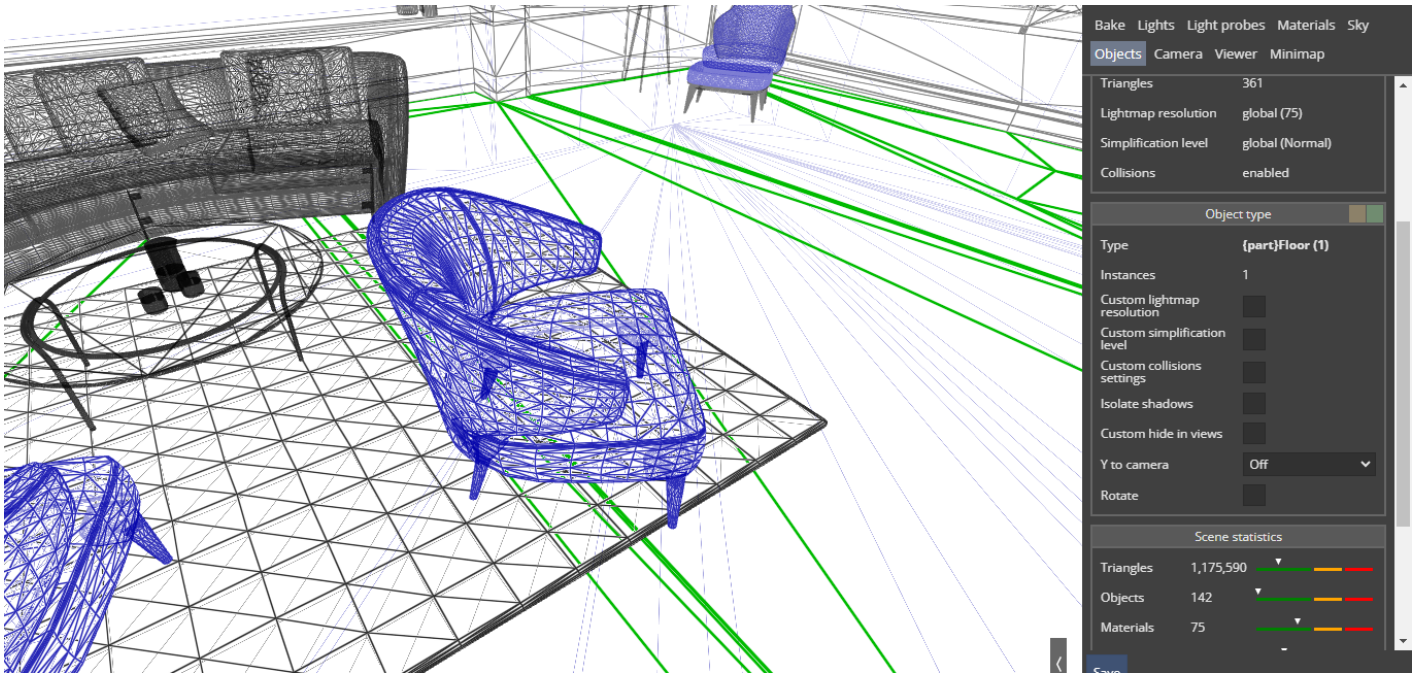

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