URVentures

Treatment for Genetic Diseases through Correction of pre-mRNA Splicing

An RNA therapeutic approach based on a “tailor-made” mRNA splice factor to treat genetic diseases that are caused by mRNA splice site mutations, such as muscular dystrophy, β-thalassemia, retinitis pigmentosa, neurofibromatosis, and cancers.

Problem Solved by This Technology

This invention provides a platform technology to treat various genetic diseases through manipulating a single mRNA splicing factor. Due to the heterogeneity of genetic diseases, this technology offers a tailor-made solution to the post-genomic age of personalized medicine.

Applications

Our researchers have reengineered the pre-mRNA splicing factor (U2AF65) to enable specific and correct mRNA transcriptions and functional protein productions. In vitro testing in human retinitis pigmentosa cells has demonstrated that the U2AF65 splicing factor with a single amino acid change was specifically targeted to the desired splice site and enabled fully-spliced mRNAs production. By using RNA-bound structures of U2AF65 as a road-map, a feasible number of U2AF65 variants can be readily screened for further alterations in specificity and affinity for the RNA recognition sites in different gene mutation contexts. The inherent ability of U2AF65 to activate (as opposed to block) splicing offers a complementary tool to existing antisense oligonucleotide approaches. As such, this technology is an attractive strategy to investigate or treat diseases related to mis-regulated splicing, such as retinitis pigmentosa, hepatocellular carcinoma, spinal muscular dystrophy, neurofibromatosis, muscular dystrophy, and hematologic malignancies.

Publications

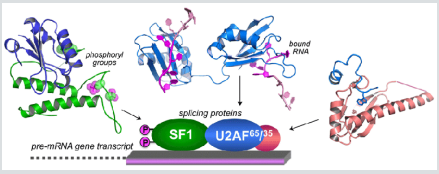
Agrawal, A.A., McLaughlin, K.J., Jenkins, J.L., Kielkopf, C.L. (2014) "Structure-guided U2AF65 variant improves recognition and splicing of a defective pre-mRNA." PNAS 111:17420-5. PMCID: PMC4267390.

Sickmier, E.A., Frato, K.E.*, Paranawithana, S., Shen, H. Green, M.R. and Kielkopf, C.L. (2006) "Structural basis of polypyrimidine tract recognition by the essential splicing factor U2AF65." Mol. Cell 23:49-59. PMCID: PMC2043114.

Jenkins, J.L., Agrawal, A.A.*, Gupta, A.*, Green, M.R., and Kielkopf, C.L. (2013) "U2AF65 adapts to diverse pre-mRNA splice sites through conformational selection of specific and promiscuous RNA recognition motifs. " Nucleic Acids Res. 41:3859-73. PMCID: PMC3616741.

URV Reference Number

6-14073



Inventors

Clara Kielkopf, Ph.D.

Anant Agrawal, Ph.D.

Intellectual Property Status

U.S. and international patent applications pending.

For More Information, Contact

Weimin Kaufman, Ph.D., MBA - Licensing Manager

e: weimin.kaufman@rochester.edu

t: 585.276.6608