NEW TREATMENTS FOR DISEASE PANEL

February 29, 2020

Sickle-Cell Anemia/Beta-Thalassemia

Cystic Fibrosis

Parkinson’s Disease

MS (PML actually)
Target single sequence in a genome (similar can be bound but less efficiently, and are called “off target.” One of the main technical objections to editing)

Only breaks DNA and then cell repair machinery “fix” but usually in a mutated way
CRISPR IN DISEASE STUDY

- Mimic mutations in cells, tissues, model organisms
- Mutagenesis to discover interacting genes
- Unfortunately, clinical delivery of gene editing components remains a challenge
- Prime editing imparts more control
Sickle cell anemia and Beta thalassemia

CRISPR Therapeutics and Vertex Pharmaceuticals

Blood disorders caused by mutations in the β-globin gene

Reduced Symptoms in β-Thalassemia with Higher Levels of HbF

http://www.crisprtx.com/programs/hemoglobinopathies

Adapted from Musallam, et al. Blood 2017
CRISPR Therapeutics and Vertex Announce Positive Safety and Efficacy Data From First Two Patients Treated With Investigational CRISPR/Cas9 Gene-Editing Therapy CTX001® for Severe Hemoglobinopathies


Cystic Fibrosis as a CRISPR Target


Figure 1. The structure of the human CFTR transcription unit, coding sequence and protein.
Cystic Fibrosis as a CRISPR Target


Table 1. The ten most common CF disease alleles.

<table>
<thead>
<tr>
<th>Allele Frequency</th>
<th>Mutation</th>
<th>DNA Change</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>70%</td>
<td>F508del</td>
<td>delCTT</td>
<td>deletion</td>
</tr>
<tr>
<td>2.50%</td>
<td>G542X</td>
<td>G &gt; T</td>
<td>transversion</td>
</tr>
<tr>
<td>2.10%</td>
<td>G551D</td>
<td>G &gt; A</td>
<td>transition</td>
</tr>
<tr>
<td>1.50%</td>
<td>N1303K</td>
<td>C &gt; G</td>
<td>transversion</td>
</tr>
<tr>
<td>1.30%</td>
<td>R117H</td>
<td>G &gt; A</td>
<td>transition</td>
</tr>
<tr>
<td>1.20%</td>
<td>W1282X</td>
<td>G &gt; A</td>
<td>transition</td>
</tr>
<tr>
<td>0.93%</td>
<td>R553X</td>
<td>C &gt; T</td>
<td>transition</td>
</tr>
<tr>
<td>0.93%</td>
<td>621+1G &gt; T</td>
<td>G &gt; T</td>
<td>transversion</td>
</tr>
<tr>
<td>0.86%</td>
<td>1717-1G &gt; A</td>
<td>G &gt; A</td>
<td>transition</td>
</tr>
<tr>
<td>0.82%</td>
<td>3849 + 10kbC &gt; T</td>
<td>C &gt; T</td>
<td>transition</td>
</tr>
</tbody>
</table>

Spacing is important
As is type of base change
C to T, or A to G
G to A, or T to C are only options
Perturbing Regulatory Interactions by Synthetic Modulators (PRISM) Overview

Validated the target in a human cell line model

Alpha-synuclein aggregates are identified as pathological hallmark in PD


Fatal demyelinating disease of the central nervous system (CNS) caused by reactivation of the human polyomavirus JCV gene expression

Infects 90% of people

Healthy immune systems keep it suppressed

Using Cas9 to mutate and inactivate a viral gene important for replication