Antibody-mediated gene editing and DNA/RNA delivery

Peter Glazer
Departments of Therapeutic Radiology and Genetics
Yale University

Application for a Blavatnik Development Grant

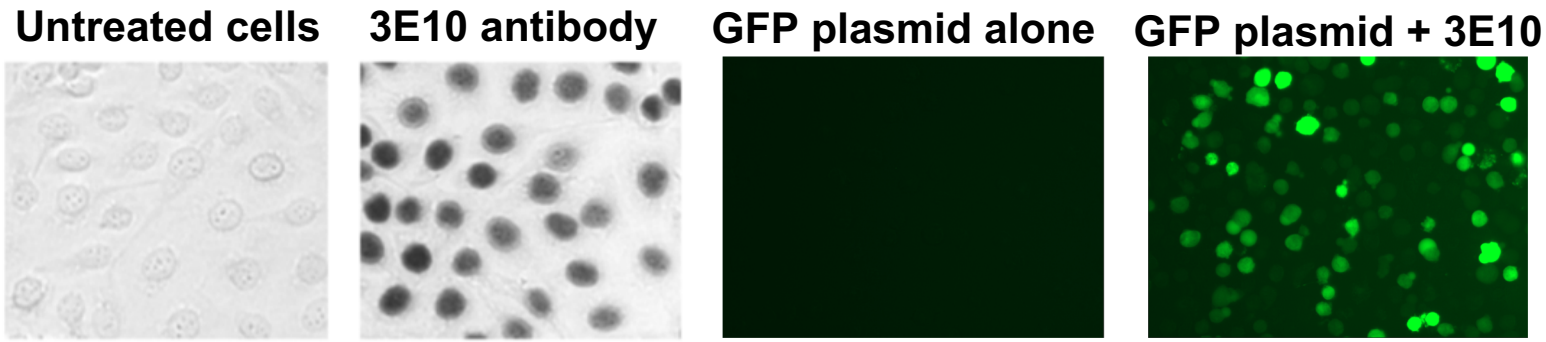
Team

- Peter Glazer:
  - Professor and Chair of Therapeutic Radiology, Professor of Genetics, Yale
  - Founder, Cybrexa Therapeutics, New Haven, CT
  - Co-inventor of foundational IP
  - Inventor on more than 20 licensed patents

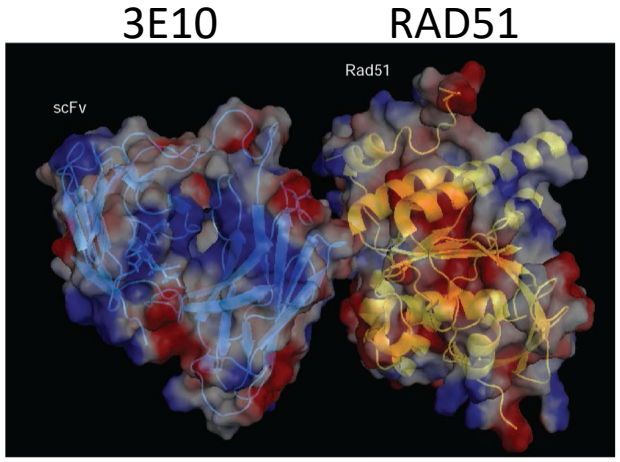
- Elias Quijano
  - MD/PhD student, Yale
  - Co-inventor of foundational IP

3E10: a gene editing Monoclonal antibody (geMab)

3E10 is a cell-penetrating antibody that transports DNAs and RNAs into cells and tissues in vivo



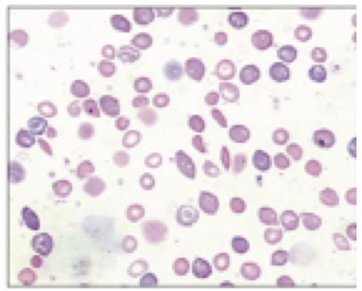
3E10 modulates DNA repair pathway to promote gene editing



A cell-penetrating antibody inhibits human RAD51 via direct binding

Audrey Turchick[1], Denise C. Hegan[2], Ryan B. Jensen[2,3] and Peter M. Glazer[1,2,*]

Antibody mediated gene editing of the sickle cell disease mutation in mice: IV injection of 3E10 antibody with donor DNA

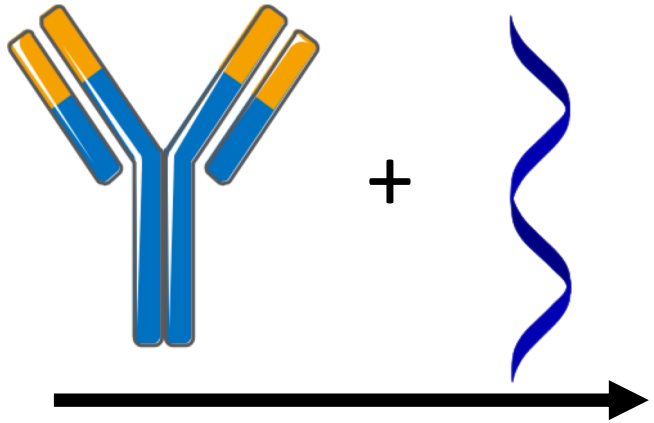


Knockout-Transgenic Mouse Model of Sickle Cell Disease

T. M. Ryan, D. J. Ciavatta, T. M. Townes*

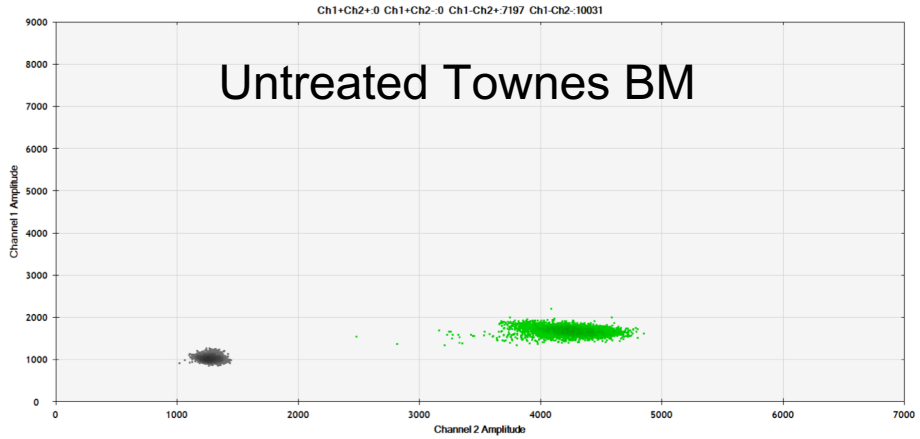
Antibody 3E10

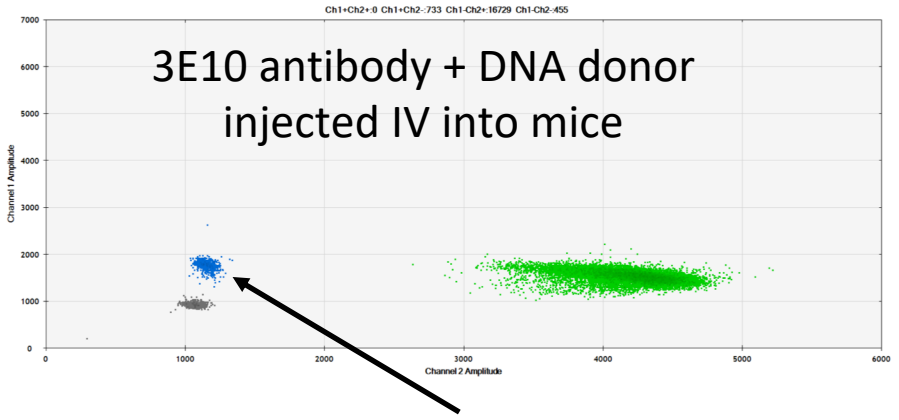
60 nucleotide donor DNA



IV injection

Droplet digital PCR assay for gene editing





Blue dots represent corrected genes

Business opportunity

- Antibody gene editing: a clinically translatable gene editing platform with broad application
- Scalable to multiple diseases:
  - sickle cell, cystic fibrosis, lysosome storage diseases
- The disease targets are already established
- Exclusive IP: "Compositions and Methods For Enhancing Donor Oligonucleotide-Based Gene Editing" – pending, Yale University application

Pricing Precedents

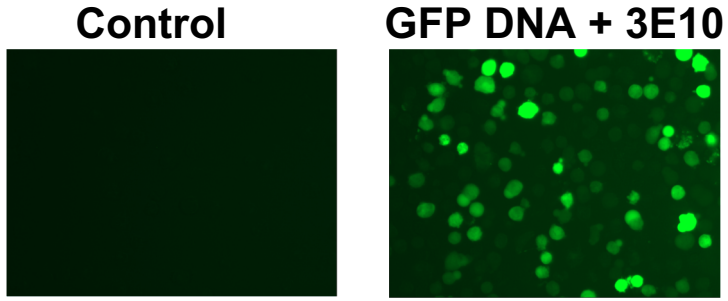
Bluebird Bio set a price of $1.8 million for gene therapy Zynteglo

Spark Therapeutics' Luxturna will cost $850,000 ($425,000 / eye)

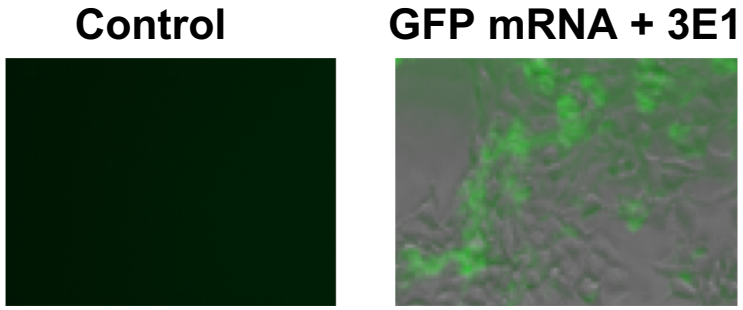
Novartis / AveXis set a price of $2.1M for Zolgensma

Broader applications: DNA and RNA delivery in vivo

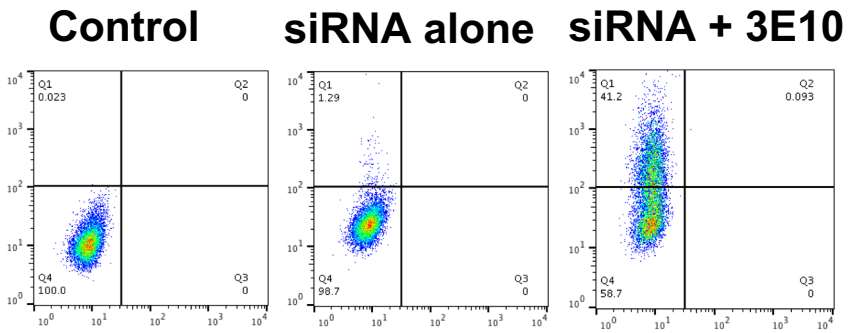
- Delivery of large DNAs
  - Gene replacement and gene therapy
  - Generate CAR-T cells in vivo and simplify CAR-T production



- Delivery of mRNAs
  - Alternative technology to Moderna



- Delivery of siRNAs
  - Alternative technology to Alnylam



Fluorescein labeled siRNA

Differentiating benefits

Technology	Virus?	Nuclease?	Immunogenic?	IV treatment?	Established CMC methods
CRISPR	YES	YES	YES - people have pre-existing antibodies to Cas9	mostly ex vivo	under development
Viral gene therapy	YES	NO	YES - history of adverse events	YES	yes but high cost of goods
3E10 antibody	NO	NO	Not after antibody is humanized	YES	yes- clinical antibody production well established

Unmet need: 3E10 as a gene therapy delivery platform

IN THE LAB

STAT+

Gene therapy pioneer says the field is behind — and that delivery technology is 'embarrassing'

By REBECCA ROBBINS @rebeccadrobbins / NOVEMBER 21, 2019

Use of Blavatnik funds

- Determine scope of DNA and RNA delivery in vivo
- Determine size maximum of DNA
  - T cell receptor expression construct?
- Evaluate gene editing capabilities
- Generate antibody variants to optimize activity
- Scale up antibody production for pre-clinical studies