



# ASGCT 2019 ANNUAL MEETING PRE-MEETING GENE EDITING WORKSHOP

MORGAN L. MAEDER



# THANKS!

- Co-Chairs: Paula Cannon and Charles Gersbach
- Committee Members: Angelo Lombardo, Pablo Perez Pinera, David Rawlings
- ASGCT: Samantha Kay
- Sponsors: Homology Medicines, Precision Biosciences, Beam Therapeutics, bluebird bio, Casebia Therapeutics, Genethon
- Speakers

# TARGETED GENOME EDITING

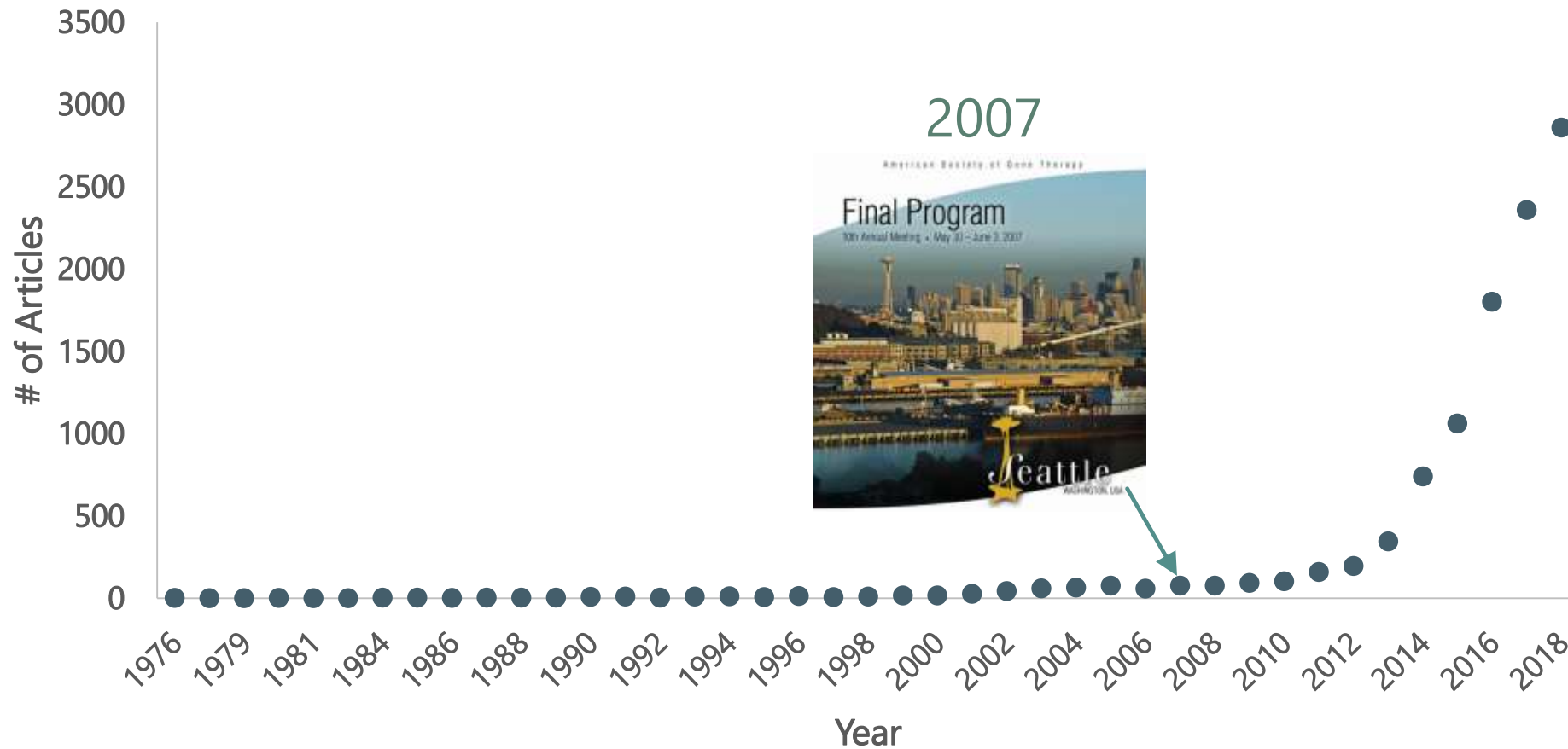


The ability to introduce targeted alterations into any specific gene sequence in any living cell or organism.



# GROWTH OF THE GENE EDITING FIELD

Articles in Pubmed with the term "Gene/Genome Editing/Engineering"



2007



2019

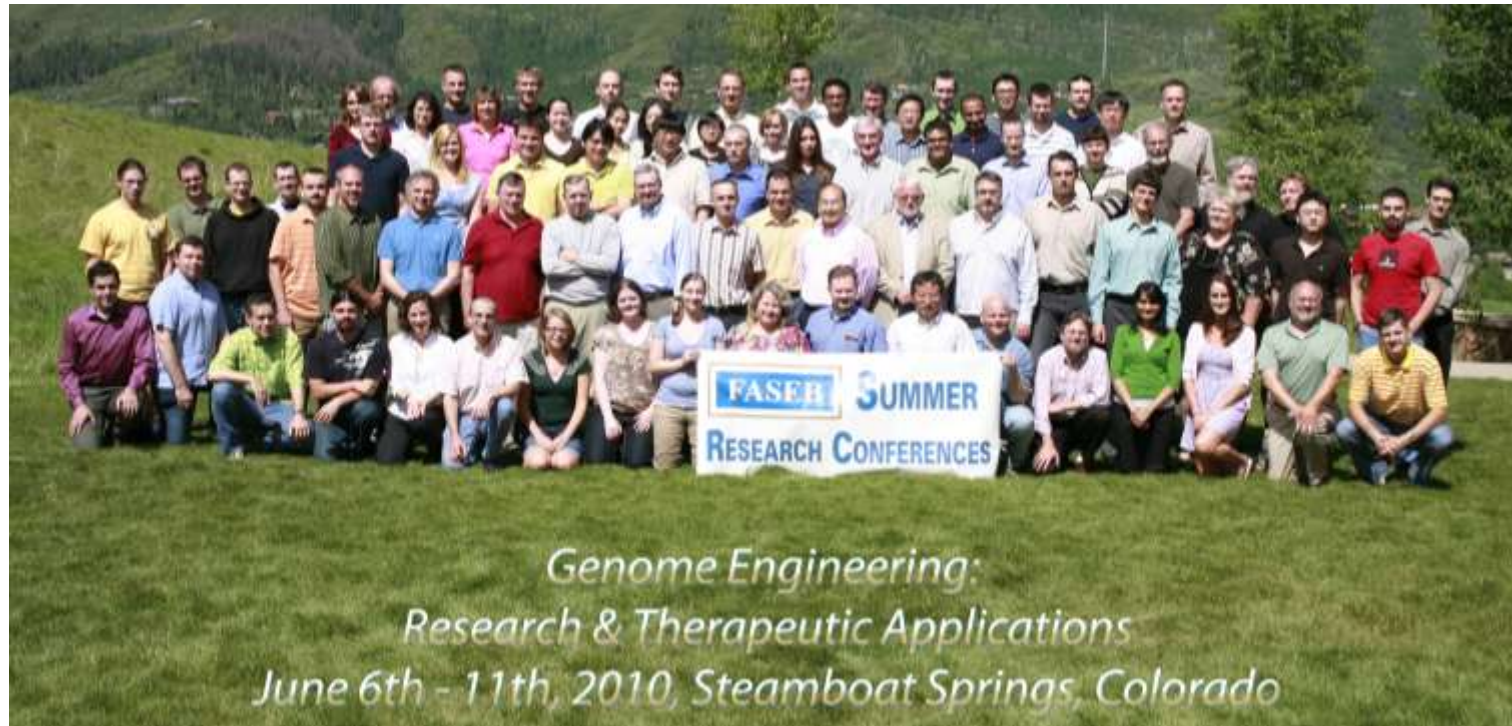


# GENE EDITING PROGRESS FROM 2007 TO 2019

2007



2019





# GENE EDITING PROGRESS FROM 2007 TO 2019

2007



2019



# GENE EDITING PROGRESS FROM 2007 TO 2019

2007



**Number of mentions in  
ASGT Program Book:**

Gene Editing = 1

Genome editing = 0

Zinc finger = 19

Crispr = 0

2019



**Number of mentions in  
ASGCT Program Book:**

Gene Editing = 28

Genome editing = 25

Zinc finger = 3

Crispr = 59

# DEVELOPMENT OF GENE EDITING THERAPEUTICS

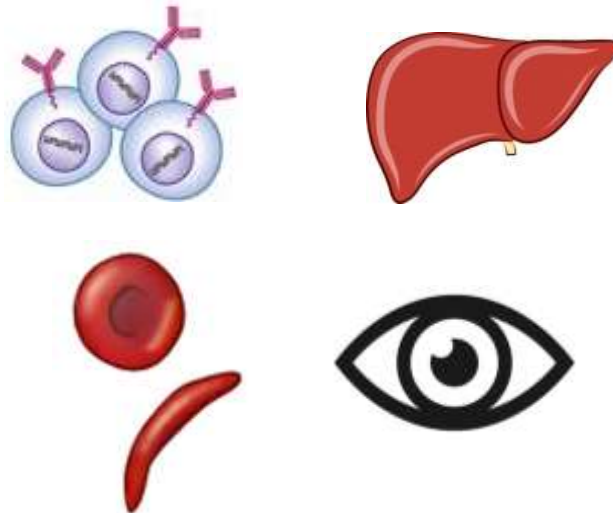
2007



How?



Why?



2019



And then what?





# HOW DO YOU EDIT?

How?



- How will you cut the DNA?
  - Which nuclease platform?
  - How do you engineer targeted nucleases?
- What kind of edit?
  - NHEJ, HDR, Other?
  - What factors influence your ability to do this?
    - Cell cycle?
    - DNA ends?
- How do you prevent off-target editing?
- What if you don't want to cut the DNA?
  - Non-nuclease platforms

# HOW DO YOU EDIT?

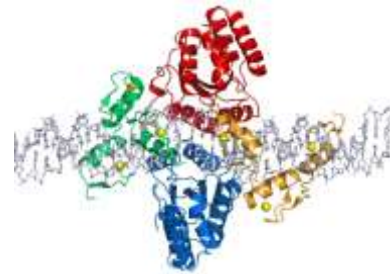
2007



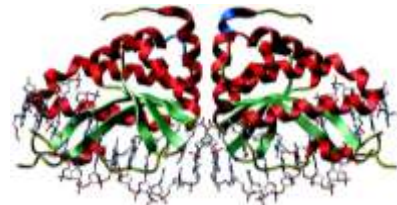
How?



Zinc Finger Nucleases (ZFNs)



Meganucleases



# HOW DO YOU EDIT?

2007



- How to engineer DNA binding nucleases

How?



58

3:15 PM

## **Optimization of Zinc Finger Nucleases for Gene Targeting in Mammalian Cells**

Shondra M. Pruett, Jon P. Connelly, Morgan Maeder, J. Keith Joung, Matthew H. Porteus.

267

## **Gene Targeting Induced by Engineered Endonucleases Derived from the I-CreI Meganuclease**

Jean-Pierre Cabaniols, Sophie Leduc, Cécile Jacquemarcq, Christophe Perez, Julianne Smith, Sylvestre Grizot, Sylvain Arnould, Philippe Duchateau, Frédéric Pâques.

269

## **Flow Cytometric Analysis of DNA Binding and Cleavage by Cell Surface-Displayed Homing Endonucleases**

Petra Volna, Jordan Jarjour, Sarah Baxter, Barry L. Stoddard, Raymond J. Monnat, Jr, Andrew M. Scharenberg.

287

## **An Omega-Based Bacterial Selection System for Engineering Artificial Zinc Finger Proteins**

Marcus B. Noyes, Xiangdong Meng, Joseph C. McNulty, Scot A. Wolfe.

# HOW DO YOU EDIT?

2007



- How to engineer DNA binding nucleases
- Beginning to look at toxicity and specificity

How?



781 12:00 PM

## **The DNA-Binding Specificity of Designer Zinc Finger Nucleases Is a Major Determinant of Activity and Genotoxicity in Human Cells**

Tatjana I. Cornu, Stacey Thibodeau-Beganny, Eva Guhl, Stephen Alwin, Magdalena Eichinger, J. Keith Joung, Toni Cathomen.

288

## **Structure-Based Redesign of the Dimerization Interface Reduces the Toxicity of Zinc Finger Nucleases**

Michal Szczepek, Vincent Brondani, Janine Büchel, Luis Serrano, David J. Segal, Toni Cathomen.

# HOW DO YOU EDIT?

2007



- How to engineer DNA binding nucleases
- Beginning to look at toxicity and specificity
- How to do targeted gene addition

How?



777 11:00 AM

## **Targeted Gene Addition into a Putative Safe-Harbor Locus in the Human Genome Using Engineered Zinc Finger Nucleases**

Russell C. DeKever, Erica A. Moehle, Jeffrey C. Miller, Jeremy M. Rock, David E. Paschon, Igor Rupniewski, Phillip Y. Tam, Edward J. Rebar, Michael C. Holmes, Philip D. Gregory, Fyodor D. Urnov.



# HOW DO YOU EDIT?

2007



- How to engineer DNA binding nucleases
- Beginning to look at toxicity and specificity
- How to do targeted gene addition
- Alternative to cutting – targeted activation

How?



528

## **Modulation of the Human Rhodopsin Expression by Artificial Zinc Finger Transcription Factors To Treat Dominant Retinal Degenerations**

Claudio Mussolino, Daniela Sanges, Valeria Marigo, Germana Meroni, Enrico M. Surace.

585

## **In Vivo Activation of Endogenous, Pigment Epithelial Derived Factor (PEDF) Expression by a Zinc Finger Transcription Factor in Human Lung Cancer Cells**

Gary K. Lee, Yu-An Zhang, Nhu Tran, Andreas Reik, Steve H. Zhang, Philip D. Gregory, Dale Ando, John Nemunaitis, Alex W. Tong.

776

10:45 AM

## **An Engineered Zinc Finger Protein Transcriptional Activator of Pigment Epithelium-Derived Factor Drives Long-Term Inhibition of Choroidal Neovascularization**

H. Steve Zhang, Katsutoshi Yokoi, Shinji Ueno, Naw H. Khu, Qi Yu, Richard Surosky, Liza M. Africa, Philip D. Gregory, Peter A. Campochiaro.

# HOW DO YOU EDIT?

2007



- How to engineer DNA binding nucleases
- Beginning to look at toxicity and specificity
- How to do targeted gene addition
- Alternative to cutting – targeted activation

How?



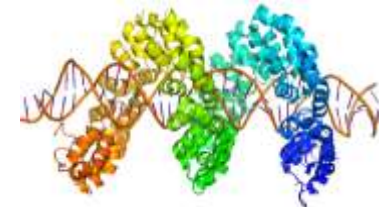
2019



Zinc Finger Nucleases (ZFNs)



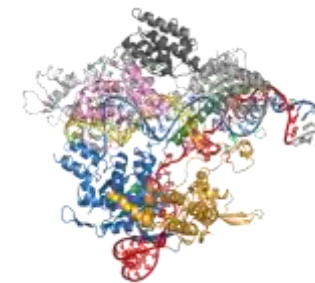
TALE Nucleases (TALENs)



Meganucleases



CRISPR-Cas RNA-Guided Nucleases



# HOW DO YOU EDIT?

2007



- How to engineer DNA binding nucleases
- Beginning to look at toxicity and specificity
- How to do targeted gene addition
- Alternative to cutting – targeted activation

How?



**Oral Abstract Session 424**

**10:15 AM - 12:15 PM**

*Room: International Ballroom East*

**Nuclease Mediated Genome Editing**

*CO-CHAIRS: Shondra Pruett-Miller, PhD and Scot Wolfe, PhD*

2019



- How to optimize nucleases

# HOW DO YOU EDIT?

2007



- How to engineer DNA binding nucleases
- Beginning to look at toxicity and specificity
- How to do targeted gene addition
- Alternative to cutting – targeted activation

How?



## Oral Abstract Session 154

3:30 PM - 5:15 PM

Room: International Ballroom East

**Measuring and Mitigating Genotoxicity of Genome Editing**

CO-CHAIRS: Angela Whatley, PhD and Matthew Porteus, MD, PhD

2019



- How to optimize nucleases
- Advanced investigations of specificity and toxicity

# HOW DO YOU EDIT?

2007



- How to engineer DNA binding nucleases
- Beginning to look at toxicity and specificity
- How to do targeted gene addition
- Alternative to cutting – targeted activation

How?



**Oral Abstract Session 310**

**8:00 AM - 10:00 AM**

*Room: Georgetown*

**Non-Nuclease Mediated Genome Editing**

*CO-CHAIRS: Mark Osborn, PhD and Charles Gersbach, PhD*

2019

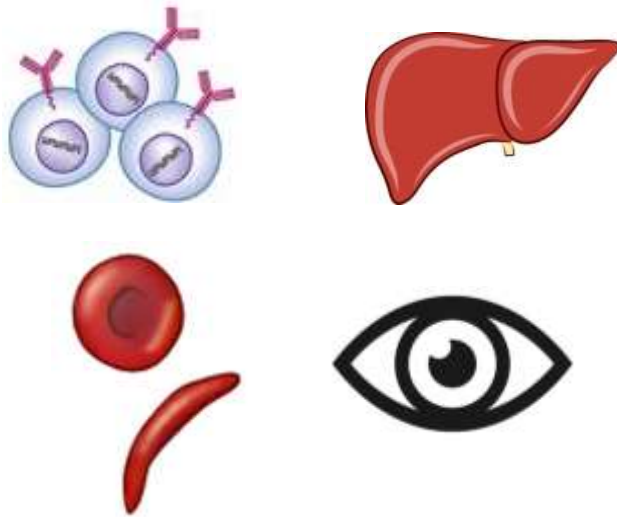


- How to optimize nucleases
- Advanced investigations of specificity and toxicity
- Alternatives to cutting-
  - Activation
  - Repression
  - DNA methylation
  - DNA de-methylation
  - Base Editing
  - RNA editing



# DISEASE TARGETS AND POC

Why?



- What edit do you want to make?
- What is the validation that this edit will have the desired effect?
- What is the target cell type?
- How to deliver nucleases?
- What are the disease models?
  - Cell models
  - Animal models

# DISEASE TARGETS AND POC

2007



- Gene editing in disease-relevant cell types (stem cells, T-cells...)

Why?



373 9:00 AM

**“Designer” Cellular Immunotherapy: Zinc Finger Nucleases Generate Glucocorticoid Receptor Negative IL-13 Zetamine Expressing CD8+ T-Cells**

Andreas Reik, Michael C. Holmes, Yuanyue Zhou, Matthew Mendel, Pei-Qi Liu, Gary K. Lee, Nhu Tran, Philip Tam, David Paschon, Yanhong Kong, Edward J. Rebar, Dale Ando, Philip D. Gregory, Michael C. Jensen.

426 2:30 PM

**Highly-Efficient Genome Modification in Human Mesenchymal Stem Cells Using Engineered Zinc Finger Nucleases**

Shuyuan Yao, Jianbin Wang, Gary Lee, Aleida Perez, Nathaniel Wang, Kenneth Kim, James Li, Fyodor D. Urnov, Philip D. Gregory, Michael C. Holmes.

321 8:00 AM

**Efficient Gene Correction and Targeted Gene Addition in Human Stem Cells Using Engineered Zinc Finger Nucleases and Integrase-Defective Lentiviral Vectors**

Angelo Lombardo, Christian Beausejour, Pietro Genovese, Silvia Colleoni, Cesare Galli, Fyodor D. Urnov, Philip D. Gregory, Michael C. Holmes, Luigi Naldini.

# DISEASE TARGETS AND POC

2007



- Gene editing in disease-relevant cell types (stem cells, T-cells...)
- Disease applications of gene editing
- Gene editing in vivo

Why?



528

## **Modulation of the Human Rhodopsin Expression by Artificial Zinc Finger Transcription Factors To Treat Dominant Retinal Degenerations**

Claudio Mussolino, Daniela Sanges, Valeria Marigo, Germana Meroni, Enrico M. Surace.

580

## **Zinc-Finger Nucleases Inactivating Hepatitis B Virus Genomic DNA**

Thomas J. Cradick, Andrew C. Jamieson, Anton P. McCaffrey.

436

4:56 PM

## **Targeted Disruption of CCR5 Using Engineered Zinc Finger Protein Nucleases Provides *In Vivo* Protection from HIV**

Elena E. Perez, Jianbin Wang, Olga Liu, Kenneth Kim, Nathaniel Wang, Gary Lee, Jeffrey C. Miller, Dmitry Guschin, Victor Bartsevich, Dale Ando, Philip D. Gregory, James L. Riley, Michael C. Holmes, Carl H. June.

# DISEASE TARGETS AND POC

2007



- Gene editing in disease-relevant cell types (stem cells, T-cells...)
- Disease applications of gene editing
- Gene editing in vivo

Why?



2019



- Expansion into all disease areas – many talks!
- Cell and animal disease models

## Oral Abstract Session 140

1:30 PM - 3:00 PM

Room: Heights Courtyard 2

**Gene Editing for Musculo-Skeletal and Skin Diseases**

CHAIR: Scott Harper, PhD

## Oral Abstract Session 425

10:15 AM - 12:15 PM

Room: International Ballroom West

**Gene Editing for Red Blood Cell Disorders**

CO-CHAIRS: Jennifer Gori, PhD and Annarita Miccio, PhD

## Oral Abstract Session 110

8:00 AM - 10:00 AM

Room: Heights Courtyard 2

**Advances in Genome Editing and Hemophilia Gene Therapies**

CO-CHAIRS: Federico Mingozzi, PhD and Ben Kleinstiver, PhD

## Scientific Symposium 302

8:00 AM - 10:00 AM

Room: International Ballroom West

**Genome Editing in the Retina and CNS - Organized by the Neurologic & Ophthalmic Gene & Cell Therapy Committee**

CO-CHAIRS: Caroline E. Bass, PhD and David J. Segal, PhD

# DEVELOPMENT OF GENE EDITING THERAPEUTICS

And then what?



- Pharmacology studies
- IND-enabling studies
- Manufacturing
- Clinical trial design
- Biomarkers



# DEVELOPMENT OF GENE EDITING THERAPEUTICS

2007



- No gene editing in the clinic

And then what?



436

4:56 PM


## **Targeted Disruption of CCR5 Using Engineered Zinc Finger Protein Nucleases Provides *In Vivo* Protection from HIV**

Elena E. Perez, Jianbin Wang, Olga Liu, Kenneth Kim, Nathaniel Wang, Gary Lee, Jeffrey C. Miller, Dmitry Guschin, Victor Bartsevich, Dale Ando, Philip D. Gregory, James L. Riley, Michael C. Holmes, Carl H. June.

nature  
biotechnology

Article | Published: 29 June 2008

## **Establishment of HIV-1 resistance in CD4<sup>+</sup> T cells by genome editing using zinc-finger nucleases**

Elena E Perez, Jianbin Wang, Jeffrey C Miller, Yann Jouvenot, Kenneth A Kim, Olga Liu, Nathaniel Wang, Gary Lee, Victor V Bartsevich, Ya-Li Lee, Dmitry Y Guschin, Igor Rupniewski, Adam J Waite, Carmine Carpenito, Richard G Carroll, Jordan S Orange, Fyodor D Urnov, Edward J Rebar, Dale Ando, Philip D Gregory, James L Riley, Michael C Holmes & Carl H June 

# DEVELOPMENT OF GENE EDITING THERAPEUTICS

2007



- No gene editing in the clinic

And then what?

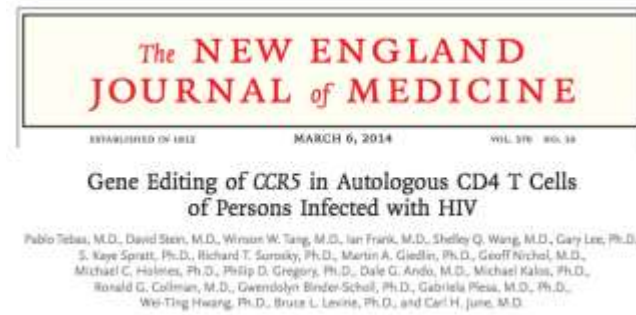


*Science* 2011

2019



- ZFNs for CCR5 KO to treat HIV in clinic since 2009



# DEVELOPMENT OF GENE EDITING THERAPEUTICS

2007



- No gene editing in the clinic

And then what?



The New York Times

*A Cell Therapy Untested in Humans Saves a Baby With Cancer*



2019



- ZFNs for CCR5 KO to treat HIV (2009)
- TALEN-edited T-cells (2015)

# DEVELOPMENT OF GENE EDITING THERAPEUTICS

2007



- No gene editing in the clinic

And then what?



2019



- ZFNs for CCR5 KO to treat HIV (2009)
- TALEN-edited T-cells (2016)
- ZFNs for MPSII – first in vivo gene editing therapy (2017)

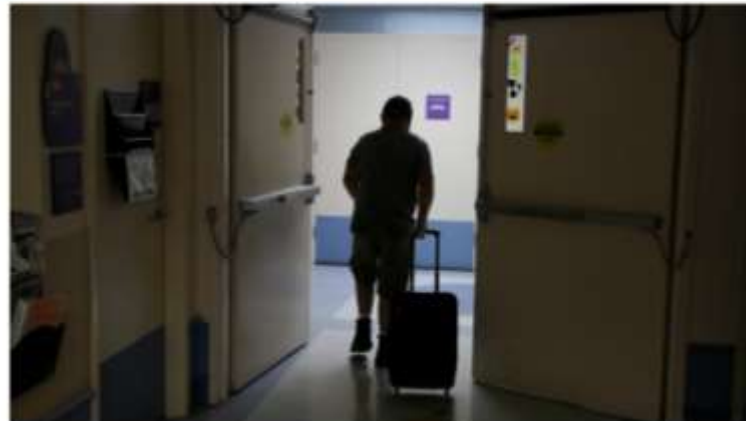
SCIENCE

## The First Man to Have His Genes Edited Inside His Body

A clinical trial for zinc-finger nucleases, a potential new method of curing genetic diseases, kicks off.

SARAH ZHANG NOV 15, 2017

*The Atlantic*



# DEVELOPMENT OF GENE EDITING THERAPEUTICS

2007



And then what?

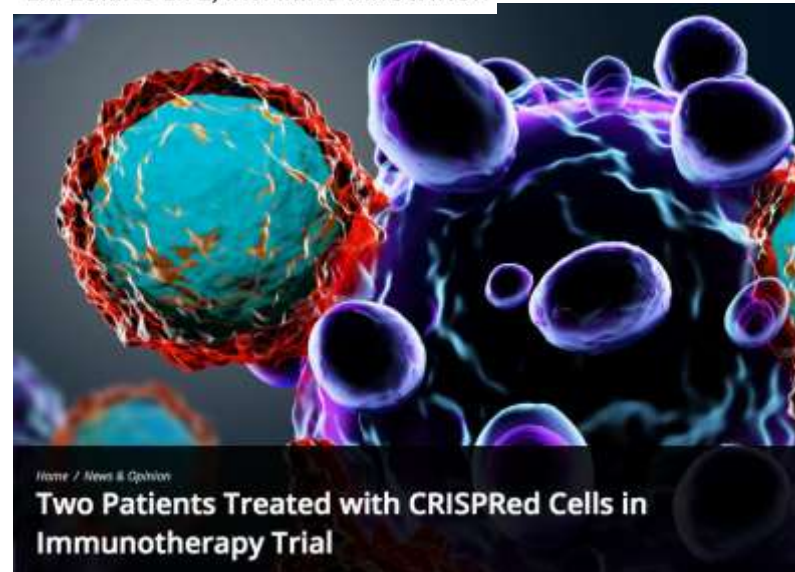


2019



- No gene editing in the clinic

**TheScientist**  
EXPLORING LIFE, INSPIRING INNOVATION



- ZFNs for CCR5 KO to treat HIV (2009)
- TALEN-edited T-cells (2016)
- ZFNs for MPSII – first in vivo gene editing therapy (2017)
- CRISPR-edited T-cells (2019)



# DEVELOPMENT OF GENE EDITING THERAPEUTICS

2007



- No gene editing in the clinic

And then what?



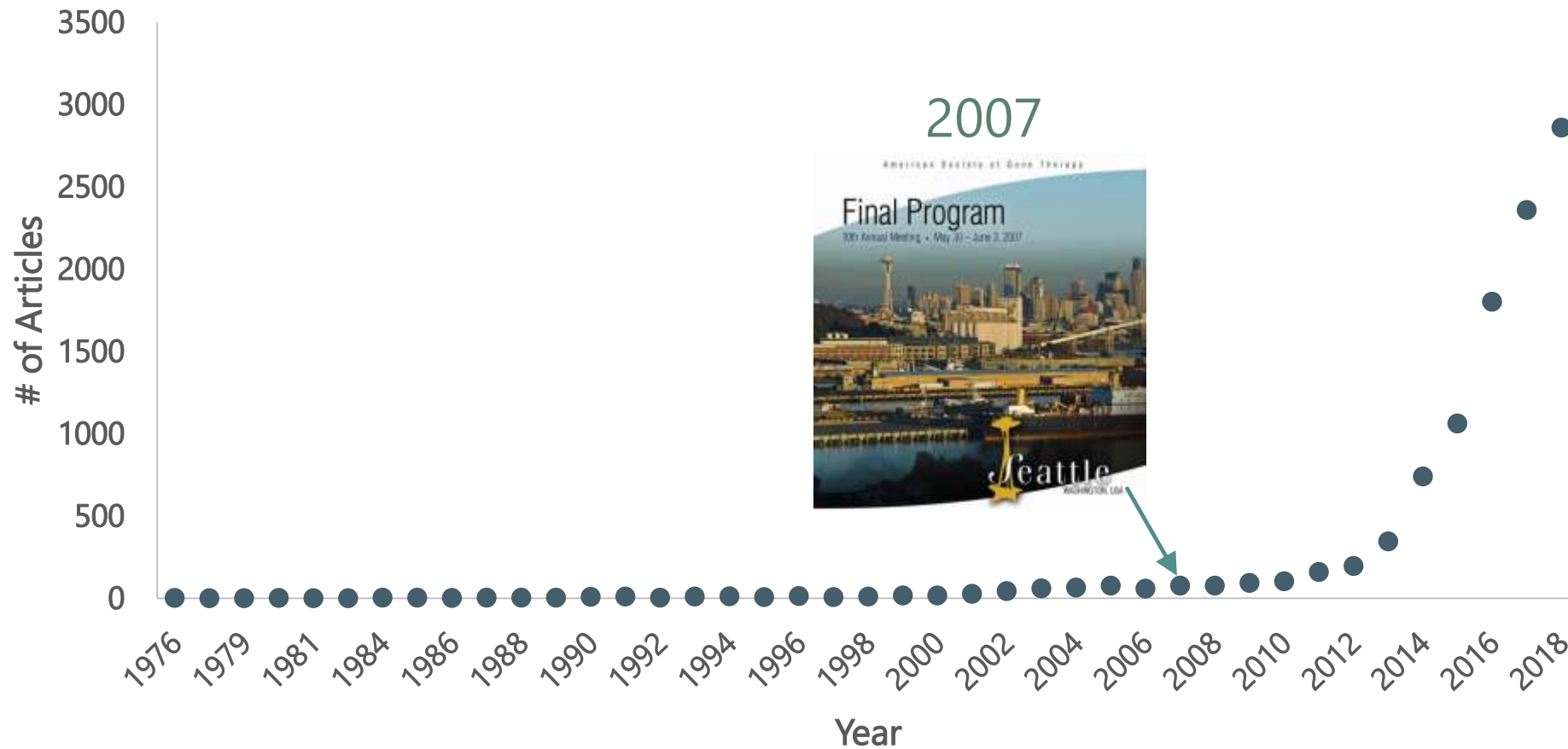
2019



- ZFNs for CCR5 KO to treat HIV (2009)
- TALEN-edited T-cells (2016)
- ZFNs for MPSII – first in vivo gene editing therapy (2017)
- CRISPR-edited T-cells (2019)
- Many more poised to begin FHL trials

# GROWTH OF THE GENE EDITING FIELD

Articles in Pubmed with the term "Gene/Genome Editing/Engineering"



2007



2019



# WORKSHOP SCHEDULE

- NIH Genome Editing Consortium Grant Recipients I (10:20am -12pm)
  - Shengdar Tsai, PhD
  - Guangping Gao, PhD
  - Aravind Asokan, PhD
- Lunch (12–1pm)
- Corporate Review I (1-2pm)
  - Shawdee Eshghi, PhD (Caribou Biosciences)
  - Leonela Amoassi, PhD (Exonics Therapeutics)
  - Derek Jantz, PhD (Precision Biosciences)
  - Charlie Albright, PhD (Editas Medicine)
  - Guiseppe Ciaramella, PhD (Beam Therapeutics)
  - Tony Ho, MD (CRISPR Therapeutics)
- NIH Genome Editing Consortium Grant Recipients II (2-3pm)
  - Eric Sontheimer, PhD
  - Shaoqin Sarah Gong, PhD
  - Zheng-Yi Chen, DPhil
- Coffee Break (3–3:30pm)
- Junior Investigator Session (3:30-5pm)
  - Pietro Genovese, PhD
  - Ben Kleinstiver, PhD
  - Thomas Gaj, PhD
  - Prashant Mali, PhD
  - Pinar Akcakaya, PhD
  - Jennifer Adair, PhD
- Corporate Review II (5-6pm)
  - Edward Rebar, PhD (Sangamo Therapeutics)
  - Julianne Smith, PhD (Cellecris)
  - Philip Gregory, DPhil (Bluebird Bio)
  - Andy Scharenberg, MD (Casebia Therapeutics)
  - Fred Chereau, MBA (Logic Bio)
  - Sean Burns, PhD (Intellia Therapeutics)