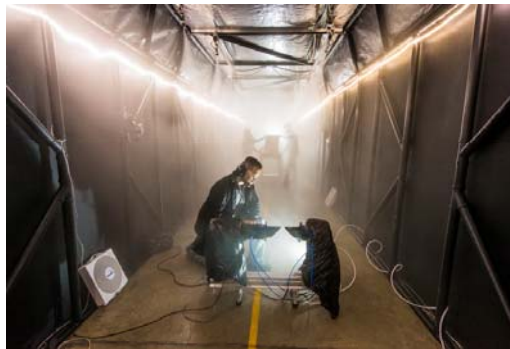


*Exceptional service in the national interest*



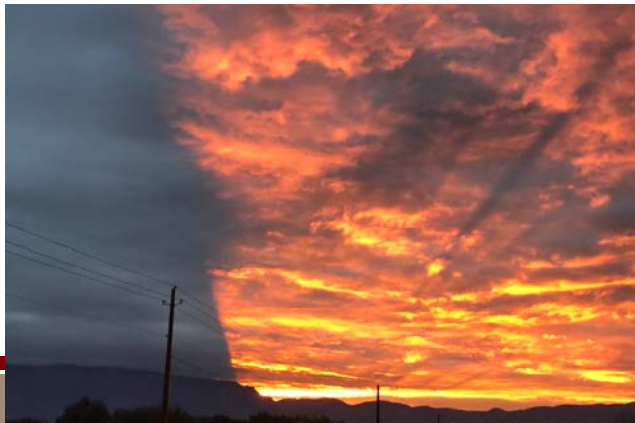
## Who's Behind The Wheel? CRISPR, Gene Drives and Where We're Going

*Jim Carney, Ph.D.*



Sandia National Laboratories is a multimission laboratory managed and operated by National Technology and Engineering Solutions of Sandia, LLC, a wholly owned subsidiary of Honeywell International, Inc., for the U.S. Department of Energy's National Nuclear Security Administration under Contract DE-NA0003525. SAND2017-4391 C

# Welcome to Albuquerque!



## Thank You

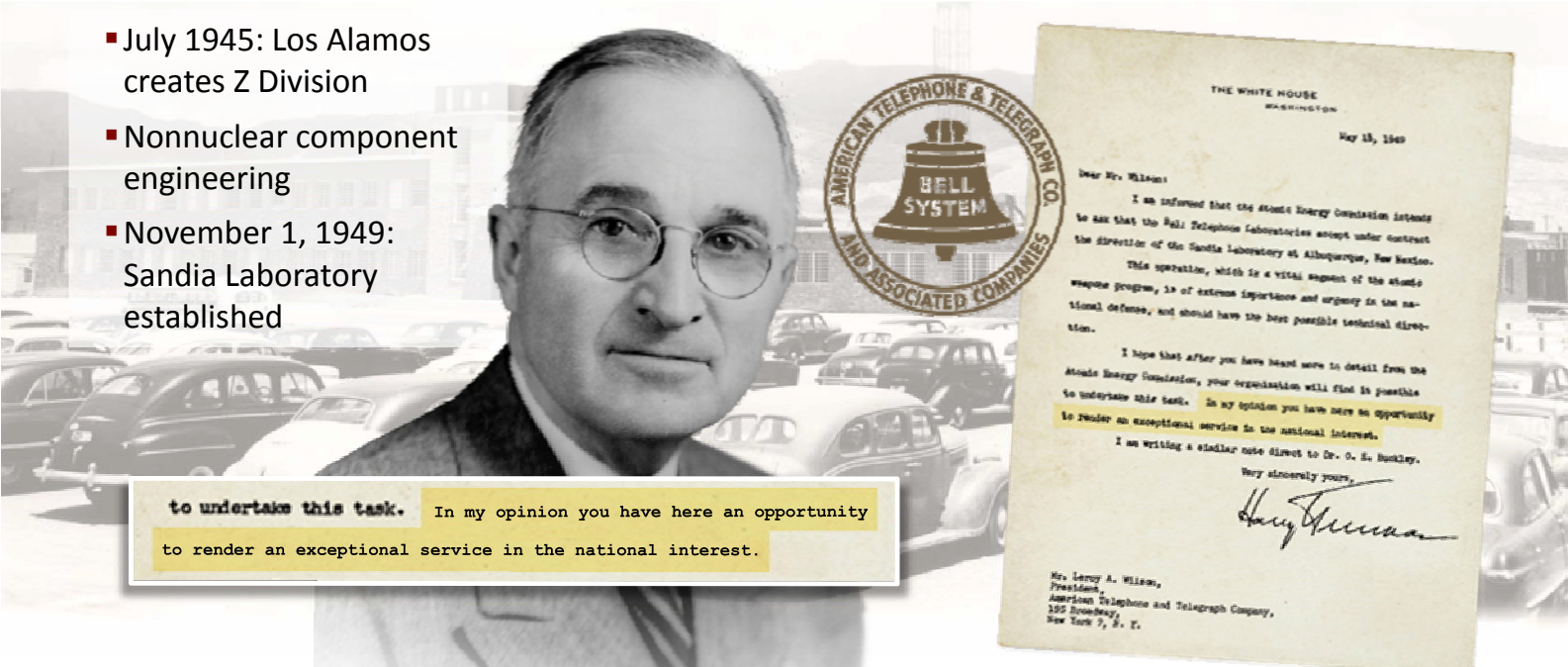
- Jen Gaudioso
  - Ben Brodsky
  - LouAnn Burnett
  - Jeri Timlin
  - Mark Lies
  - Cathy Branda
  - Steve Casalnuovo
  - Anup Singh
  - Duane Lindner
- 
- Everyone within SNL and elsewhere that has helped me to understand how all of this works and the potential it has!



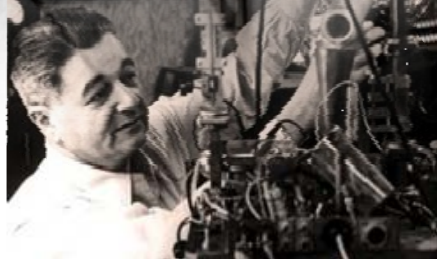
# Sandia's History

*Exceptional service in the national interest*

- July 1945: Los Alamos creates Z Division
- Nonnuclear component engineering
- November 1, 1949: Sandia Laboratory established



to undertake this task. In my opinion you have here an opportunity to render an exceptional service in the national interest.



# Sandia Sites





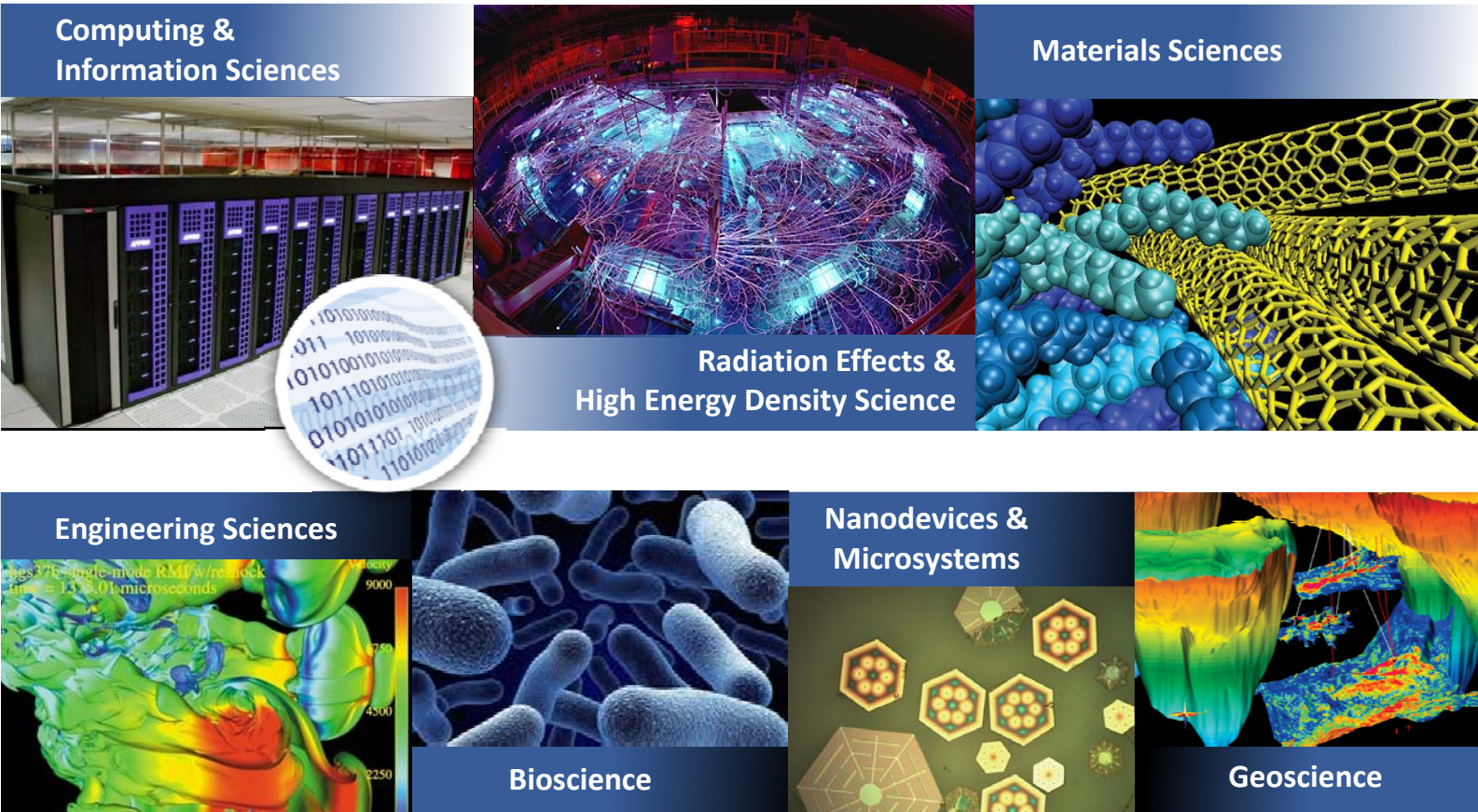
# Purpose Statement

*Sandia develops advanced technologies to ensure global peace*



# Our Research Framework

*Strong research foundations play a differentiating role in our mission delivery*



**Computing & Information Sciences**

**Materials Sciences**

**Radiation Effects & High Energy Density Science**

**Engineering Sciences**

**Bioscience**

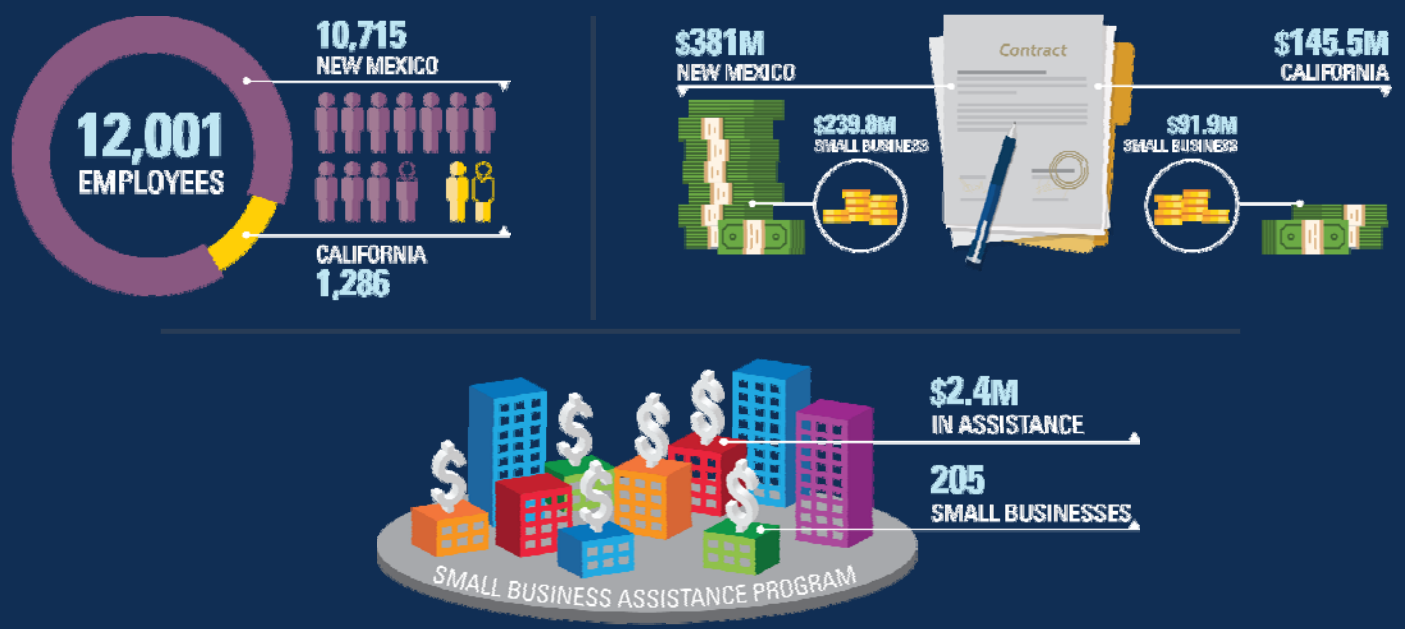
**Nanodevices & Microsystems**

**Geoscience**

The collage features six distinct research areas. 'Computing & Information Sciences' shows server racks and a circular graphic with binary code. 'Materials Sciences' displays a 3D molecular model of a lattice structure. 'Radiation Effects & High Energy Density Science' depicts a glowing, complex network of fibers. 'Engineering Sciences' includes a colorful surface plot with technical text: 'es376 single-mode RM w/re-lock' and 'time = 1.3301 microseconds'. 'Bioscience' shows a microscopic view of blue, rod-shaped bacteria. 'Nanodevices & Microsystems' features a grid of hexagonal patterns. 'Geoscience' shows a 3D topographic map of a landscape.

# FY 2016: Impacting the local economy

Workforce: 12,001 employees (10,715 NM, 1,286 CA)



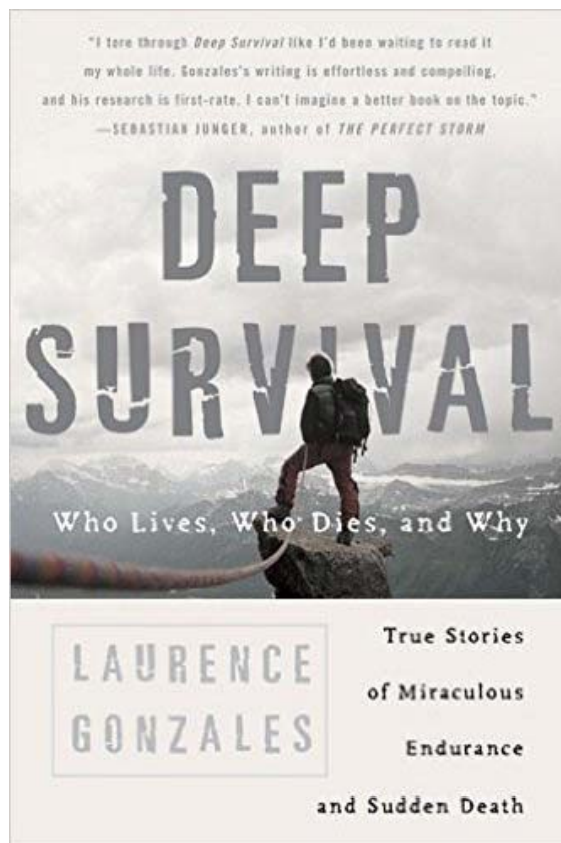


## A Biosafety Journey...

- Young Assistant Professor's know everything
- S/he is always eager to show this skill off
- This typically doesn't go over well...

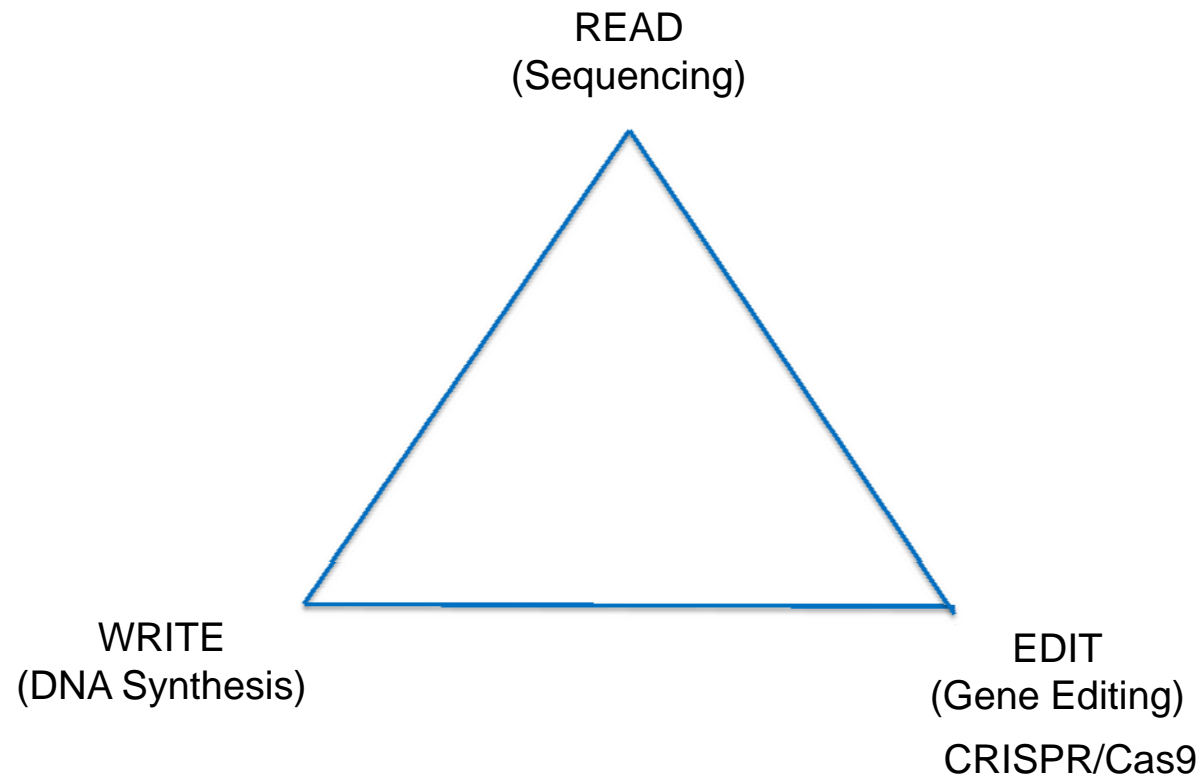
# Deep Survival: Who Lives, Who Dies and Why

## Laurence Gonzales



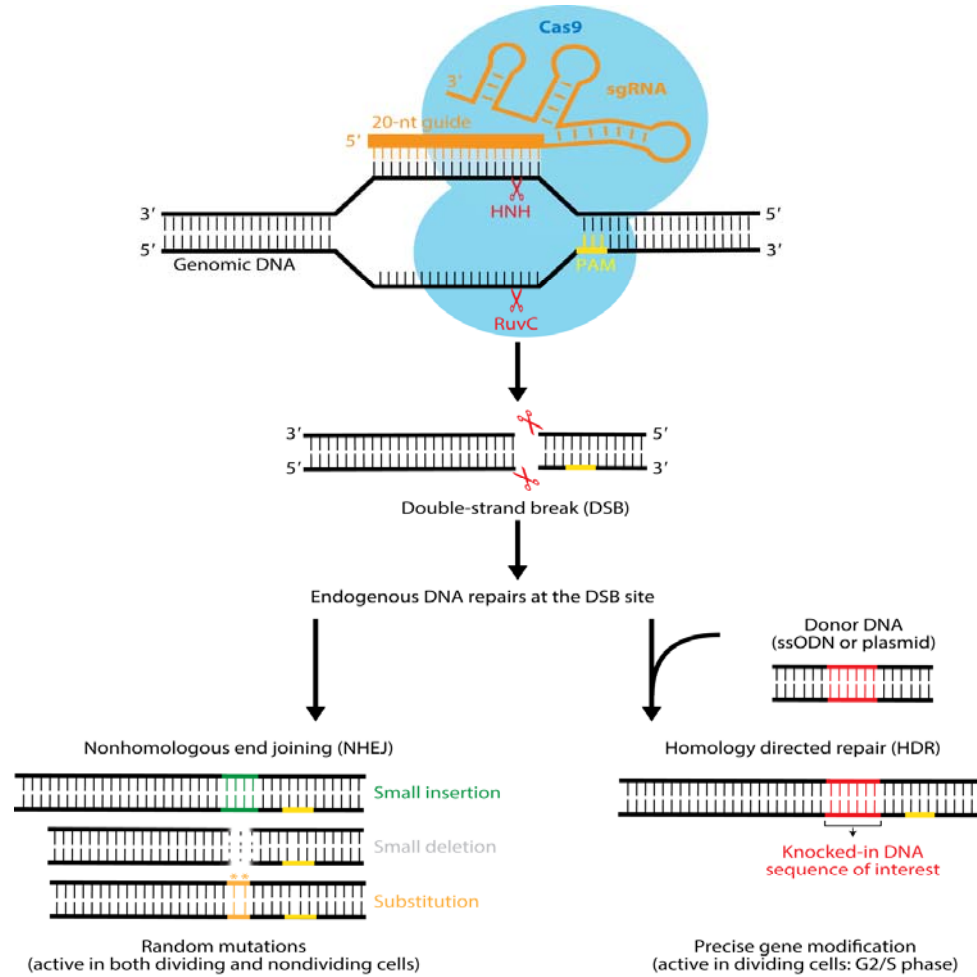
“The word ‘experienced’ often refers to someone who’s gotten away with doing the wrong thing more frequently than you have” p.100

# Engineering Biology

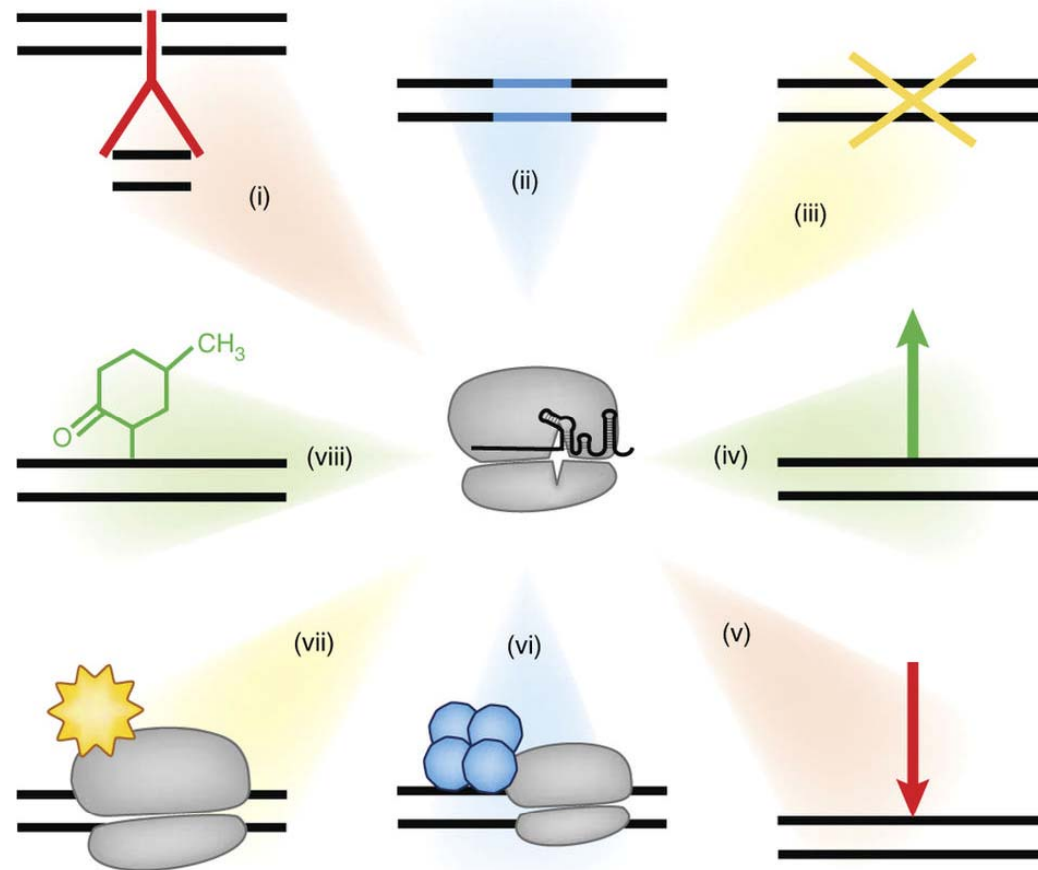




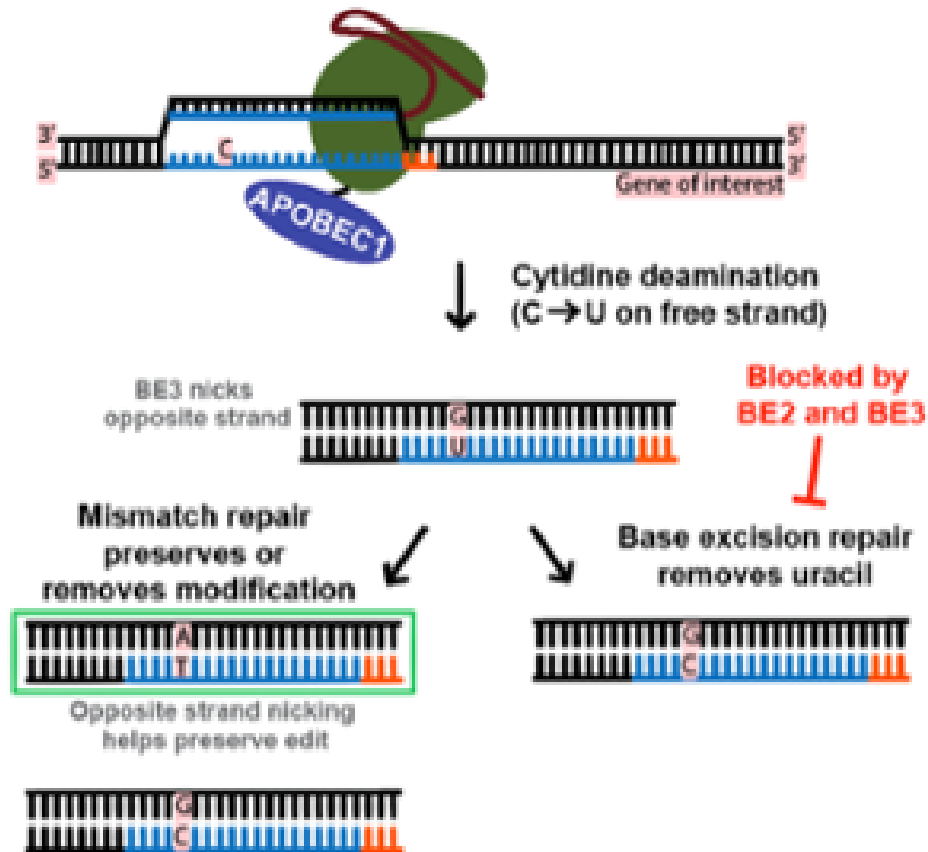
# How Does CRISPR Work?



# CRISPR Applications



# CRISPR-Base Editing

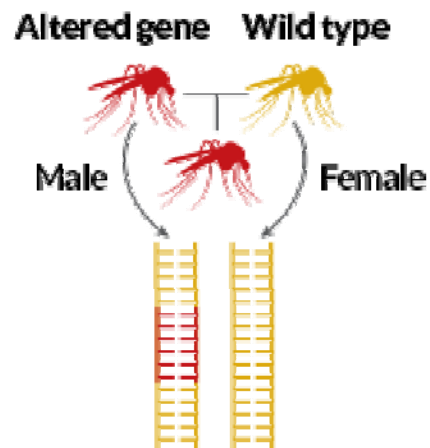




# Gene Drives

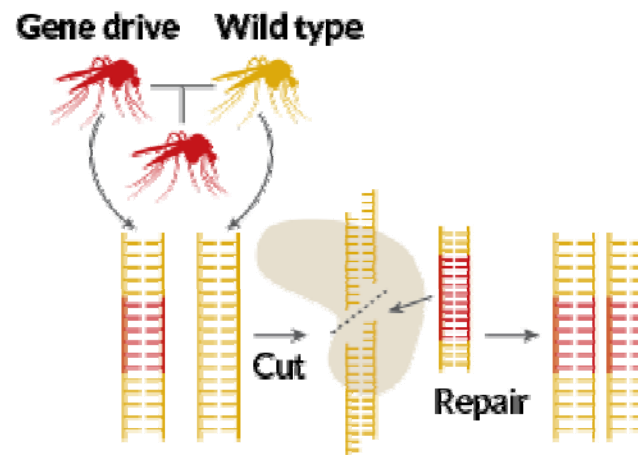
# Mechanism of Gene Drive

## Normal inheritance



Altered gene without gene drive: One copy inherited from one parent. 50 percent chance of passing it on.

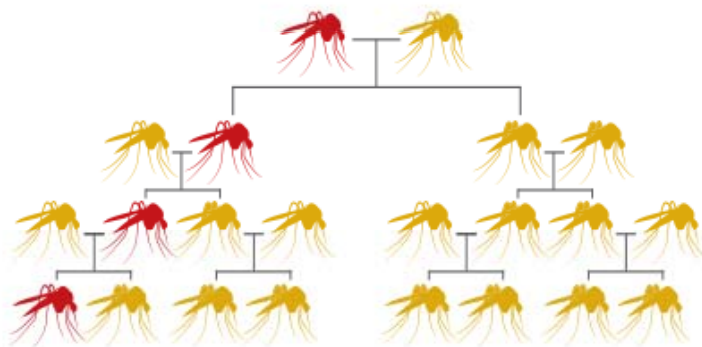
## Gene drive inheritance



Altered gene as gene drive: One copy converts gene inherited from other parent. More than 50 percent chance of passing it on.

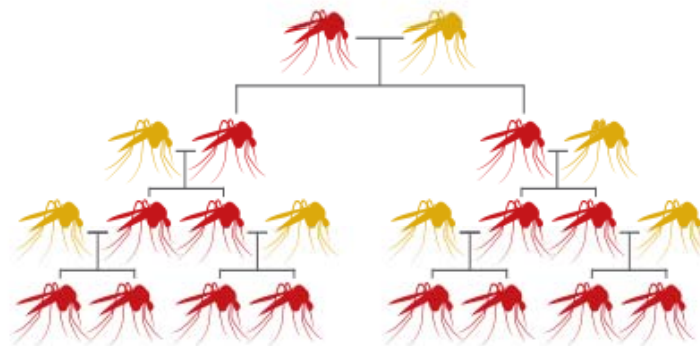
# Genetics of Gene Drive

## Normal inheritance



Altered gene does not spread

## Gene drive inheritance

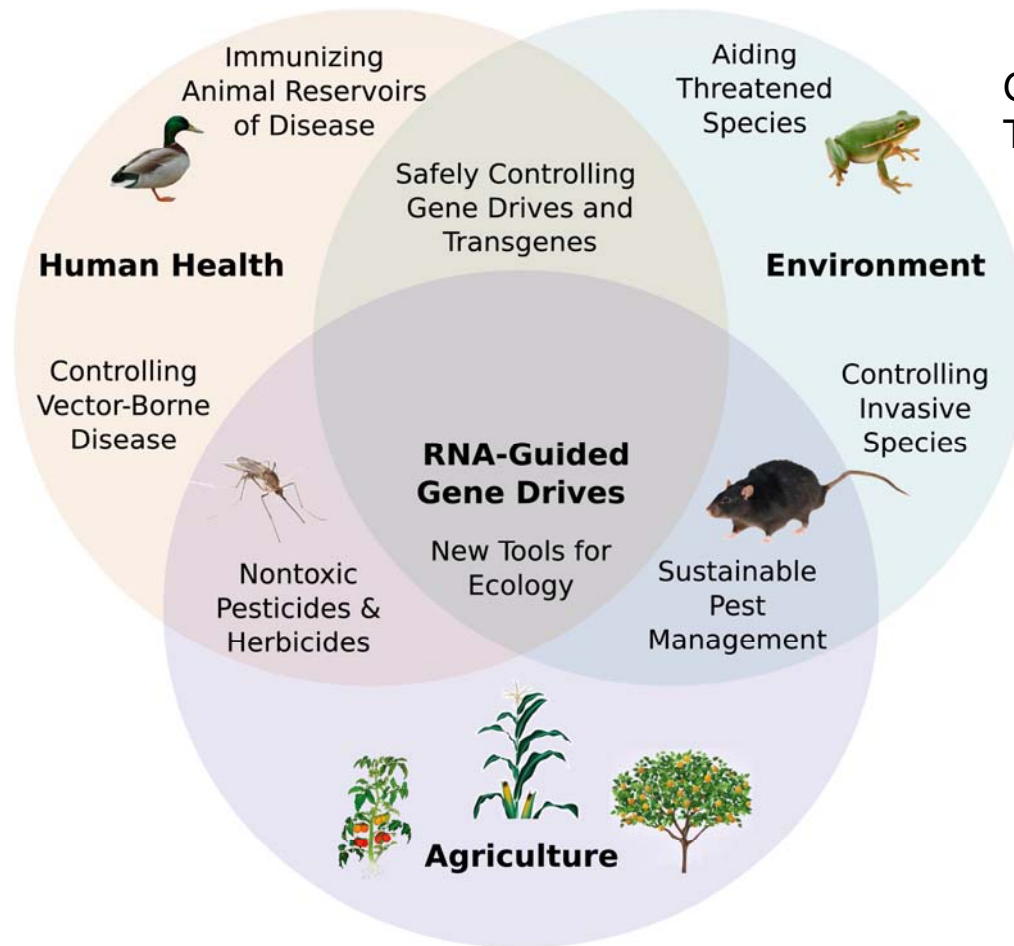


Altered gene is almost always inherited

<https://www.sciencenews.org/blog/science-ticker/gene-drives-aren't-ready-wild-report-concludes>



# Applications of Gene Drives



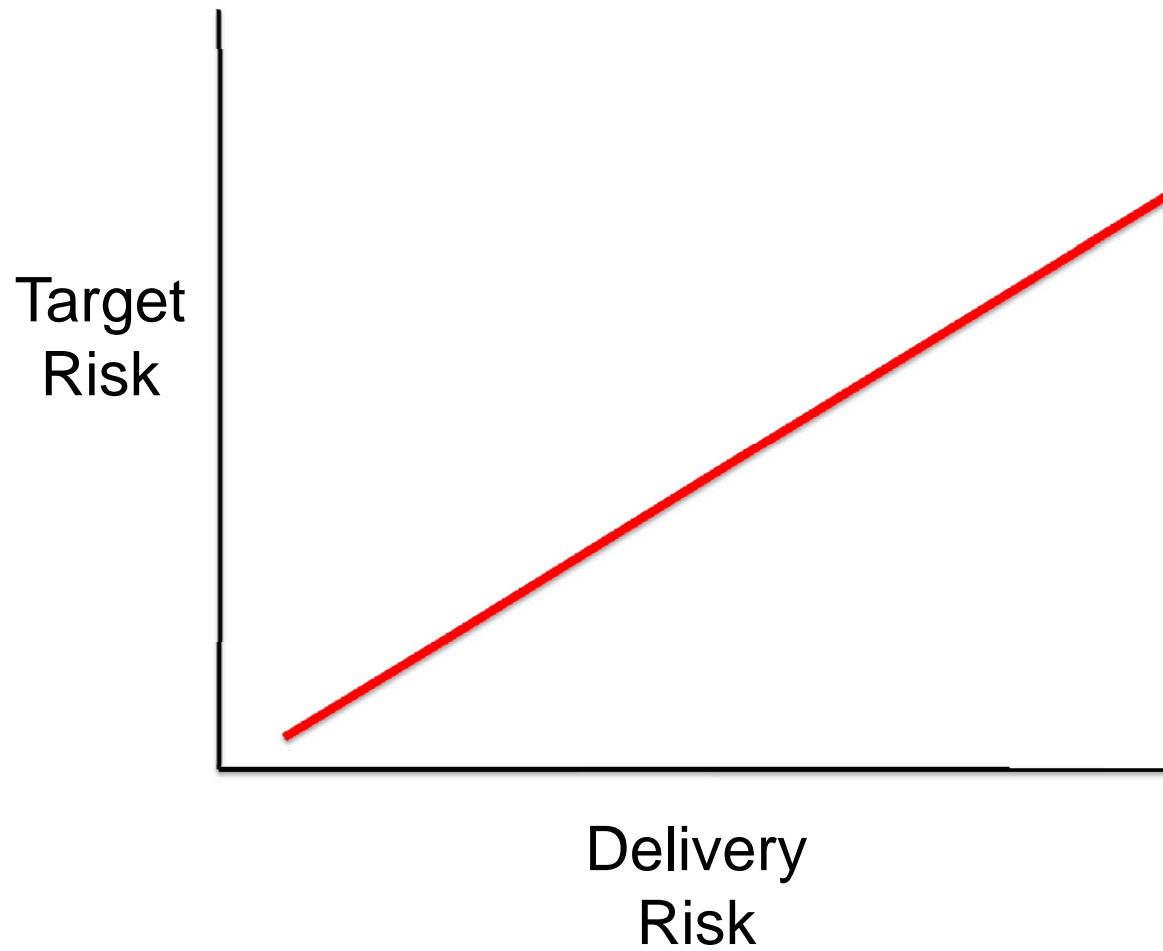
Gates Foundation - \$75M to Target Malaria  
Tata Foundation of India - \$35M to UCSD

Esvelt et al Ecology, Genes and Chromosomes 2014)

## So What Do We Do Now?

- Fortunately all of you are already thinking about this
  - ...and acting on it!
- Approaches for risk assessment...
- How to encourage safe design?

# A Framework for Evaluating Risk of Gene Editing Research



## Target Considerations

- Species-human likely highest risk for exposure
- Targeted gene-increased risk for some (tumor suppressor, others?)
- Design of experiment-knockout, insertion, base edit, others?

## Delivery Considerations

- Delivery mode-DNA, RNA, ribonucleoprotein
- Vector-lipid, viral, nanoparticle
- Persistence-not well characterized, in general
- Physical characteristics-aerosol?

## Known Unknowns

- Biological Amplification
- Biological Effects-arrayed
- Functional Annotation
- Off-Target Effects
- Persistence of Editing Activity



## Whole Genome gRNA Libraries

- Available from several companies
- Two/three gRNAs per gene
- Arrayed in 384 well plates
- **Determine genes required for cell viability**
- Predict this data to become available in the near term

# Unknown Unknowns...

## Human Genome Editing:

Science, Ethics, and Governance (2017)-The National Academies of Science, Engineering and Medicine



- **RECOMMENDATION 3-1. Existing regulatory infrastructure and processes for reviewing and evaluating basic laboratory genome-editing research with human cells and tissues should be used to evaluate future basic laboratory research on human genome editing.**

Thank You!