EDITING LIFE

# COMMITMENT TO A CURE

Cellectis Innovation Days
Episode 4

# FORWARD-LOOKING STATEMENTS

This presentation contains "forward-looking" statements within the meaning of applicable securities laws, including the Private Securities Litigation Reform Act of 1995. Forward-looking statements may be identified by words such as "at this time," "anticipate," "believe," "expect," "on track," "plan," "scheduled," and "will," or the negative of these and similar expressions.

These forward-looking statements, which are based on our management's current expectations and assumptions and on information currently available to management, include statements about our research and development projects and priorities, our pre-clinical project development efforts, the timing and progress of clinical trials (including with respect to patient enrollment and follow-up), the timing of our presentation of data, the adequacy of our supply of clinical vials, the timing of completion of construction of our Raleigh, North Carolina manufacturing facility, and operational capabilities at our manufacturing facilities, and the sufficiency of cash to fund operations.

These forward-looking statements are made in light of information currently available to us and are subject to numerous risks and uncertainties, including with respect to the numerous risks associated with biopharmaceutical product candidate development as well as the duration and severity of the COVID-19 pandemic and governmental and regulatory measures implemented in response to the evolving situation.

With respect to our cash runway, our operating plans, including product development plans, may change as a result of various factors, including factors currently unknown to us. Furthermore, many other important factors, including those described in our Annual Report on Form 20-F and the financial report (including the management report) for the year ended December 31, 2020 and subsequent filings Cellectis makes with the Securities Exchange Commission from time to time, as well as other known and unknown risks and uncertainties may adversely affect such forward-looking statements and cause our actual results, performance or achievements to be materially different from those expressed or implied by the forward-looking statements.

Except as required by law, we assume no obligation to update these forward-looking statements publicly, or to update the reasons why actual results could differ materially from those anticipated in the forward-looking statements, even if new information becomes available in the future.

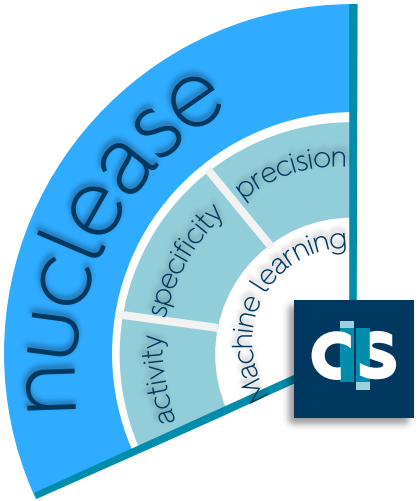
# It Takes More Than One Tool To Make A CAR

FROM

TO

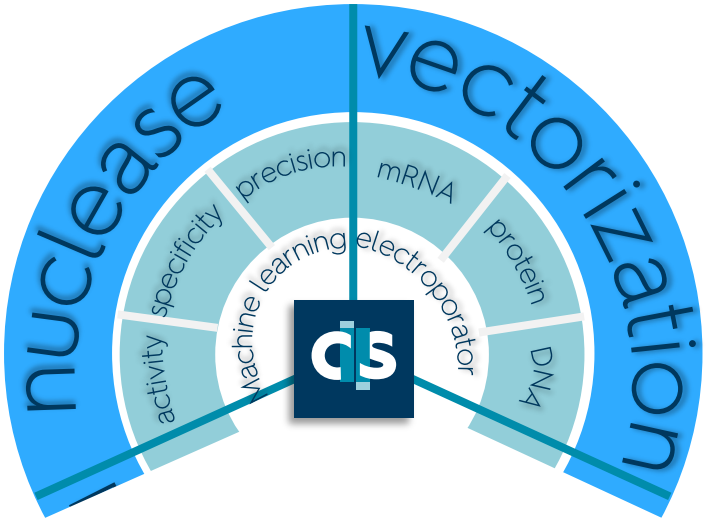
The one-stop shop for next generation cell and gene therapy

# The Cell And Gene Therapy Toolbox



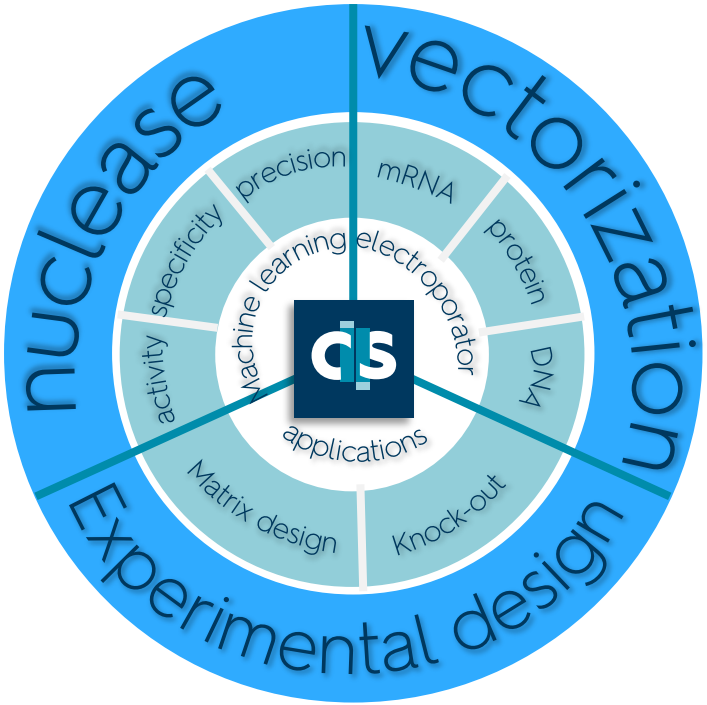

Mastering this element is a critical success factor

# The Cell And Gene Therapy Toolbox




Mastering this element is a critical success factor

# The Cell And Gene Therapy Toolbox




Mastering these elements are critical success factors

# The Cell And Gene Therapy Toolbox


Mastering these elements are a critical success factors

Part 1

# Gene Editing Technologies

# Our Gene Editing story

**21 years**
of expertise in gene editing

**12 years**
of expertise with TALEN®

**10 years**
of expertise with MegaTAL and compact TALEN®

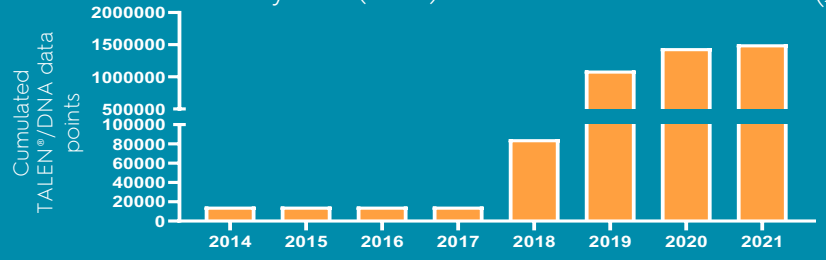
**8 years**
of expertise with CRISPR

High throughput Gene Editing platform

PIONEERS OF GENE EDITING

>15'500 unique TALEN®/DNA cleavage profiles in yeast (2014)

**>1'500'000** on/off sites data points in primary human cells (2021)



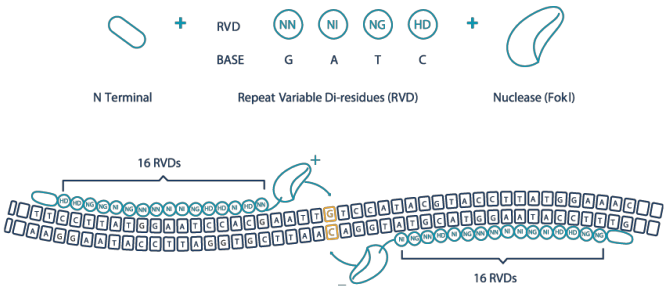
# Cellectis Patents Global Overview

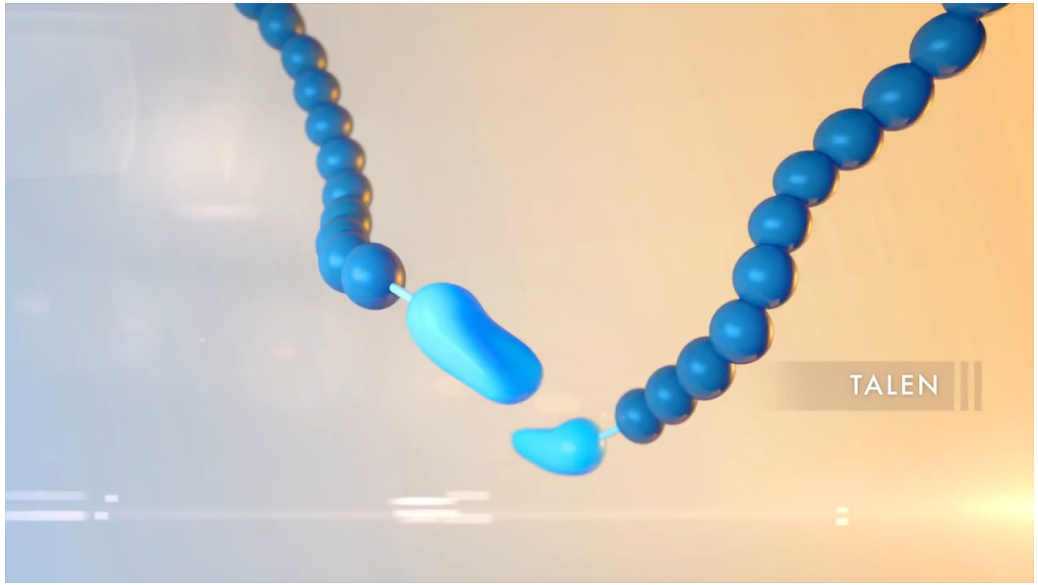
| CELLECTIS PATENT PORTFOLIO (124 patent families) | | | | | | |
|---|---|---|---|---|---|---|
| | Granted patents (278) | | | Pending patent applications (316) | | |
| | **US** | **EP** | **Other territories** | **US** | **EP** | **Other territories** |
| **Cellectis** | 60 | *52* | 127 | 56 | 43 | 178 |
| **Excusive In-Licensing** | 17 | 6 | 16 | 6 | 6 | 27 |

# Cellectis Patents Global Overview

| | Meganucleases | TALEN® | Compact TALEN® | MegaTAL | CRISPR | Gene editing applications | Cellectis Total Portfolio |
|---|---|---|---|---|---|---|---|
| **Patent families** | 9 | 8 | 2 | 2 | 4 | 18 | 105 |
| **Delivered patents** | 34 | 37 | 13 | 10 | 16 | 42 | 239 |
| **Pending applications** | 1 | 15 | 4 | 2 | 9 | 117 | 277 |
| **Latest Expiration date** | 2031 | 2035 | 2034 | 2034 | 2034 | 2038 | 2041 |

# TALEN® For Gene Editing



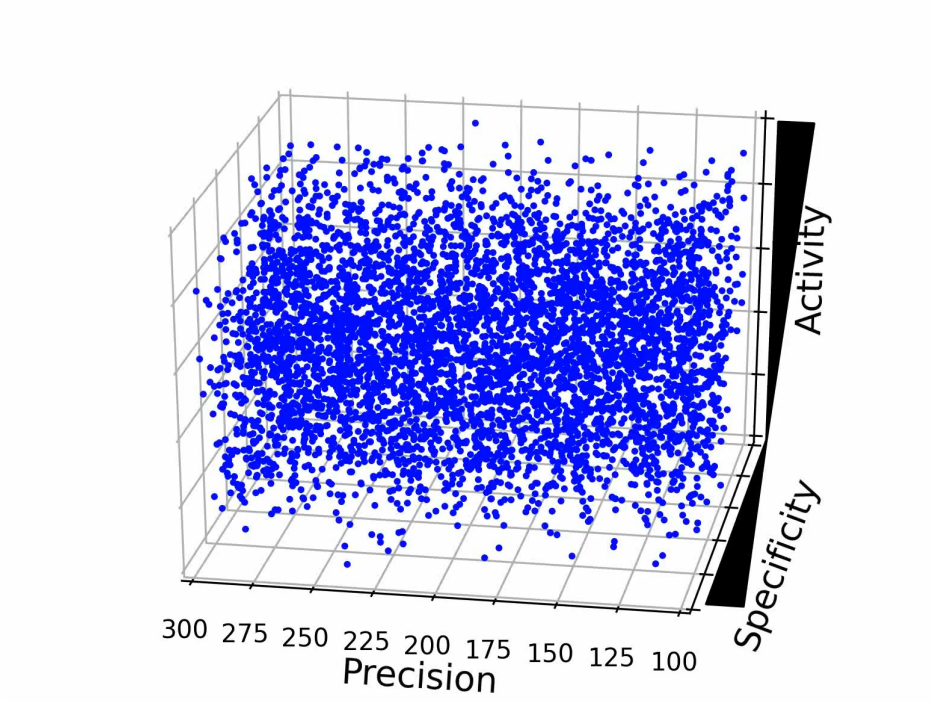




Best-in-class gene editing platform

# The Three Pillars Of Gene Editing For Therapeutic Applications

Capacity to induce efficiently a double strand break in the genome

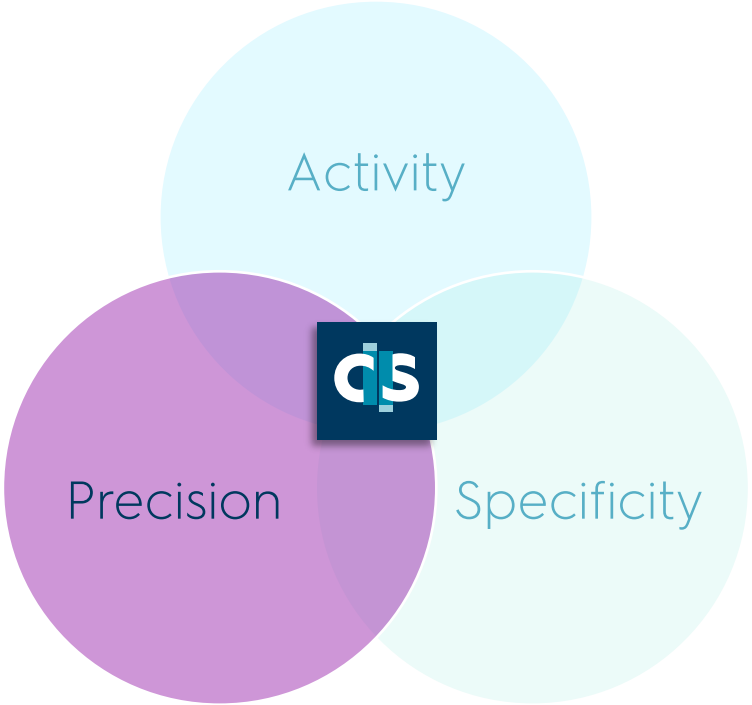
Capacity to target as close as possible to the desired site



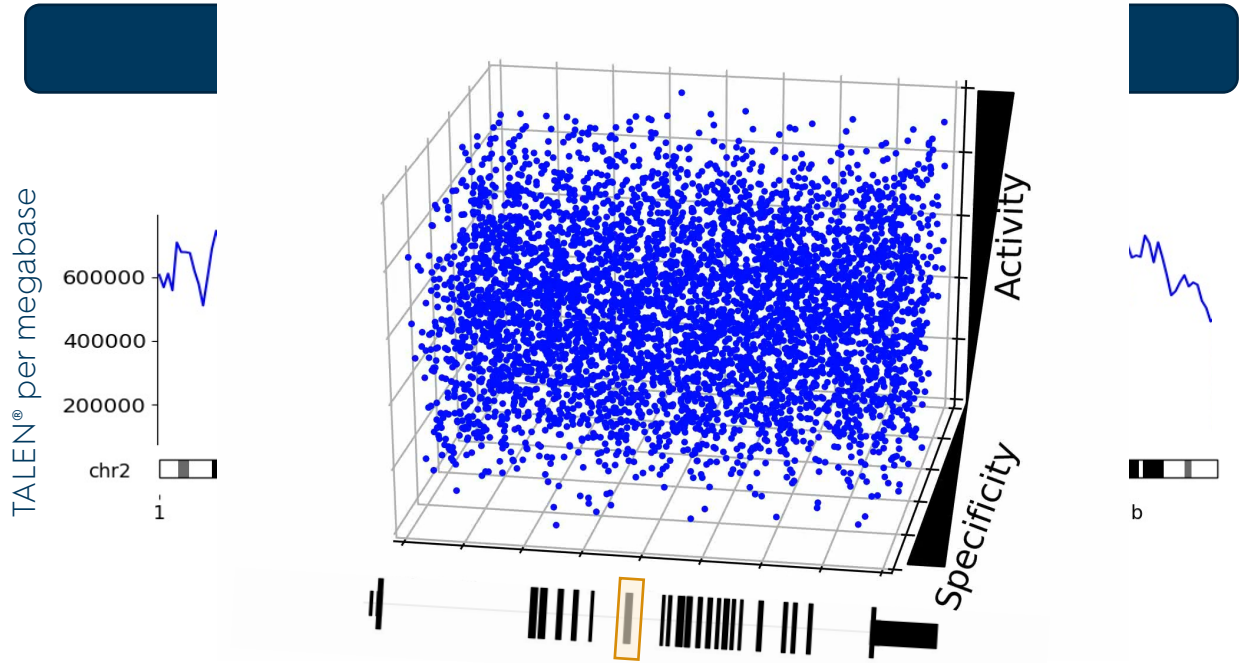

Capacity to avoid unintended genetic modifications

# The Three Pillars Of Gene Editing: Precision

Capacity to target
as close as possible
to the desired site



# TALEN®: Unmatched Targeting Precision

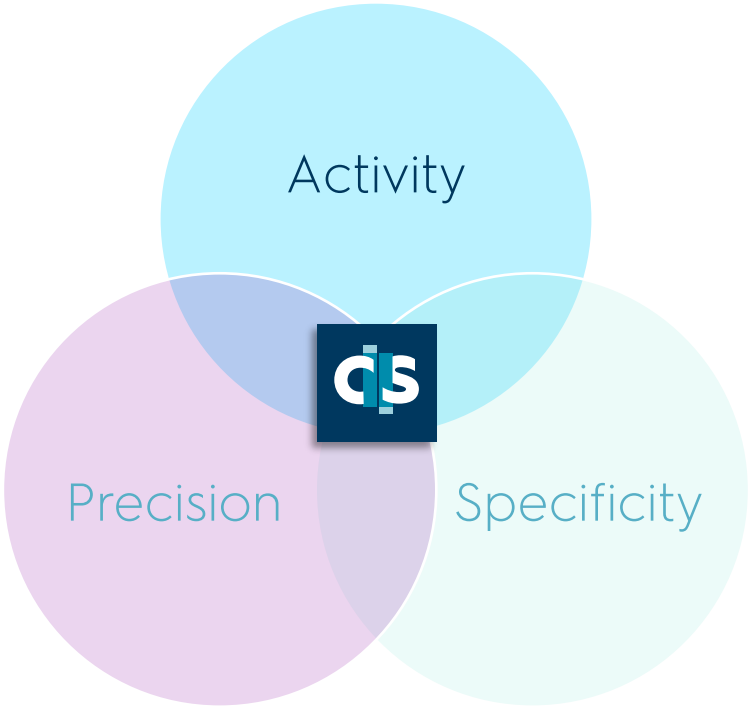



The whole genome is targetable with a high density of TALEN®

- Mean distance between 2 TALEN® sites **< 7 bp**

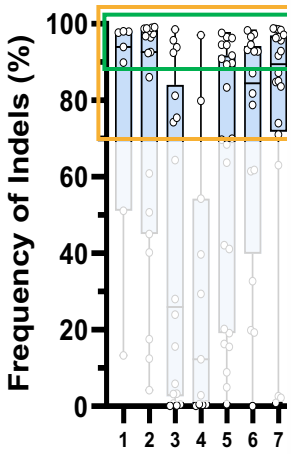
# The Three Pillars Of Gene Editing: Activity

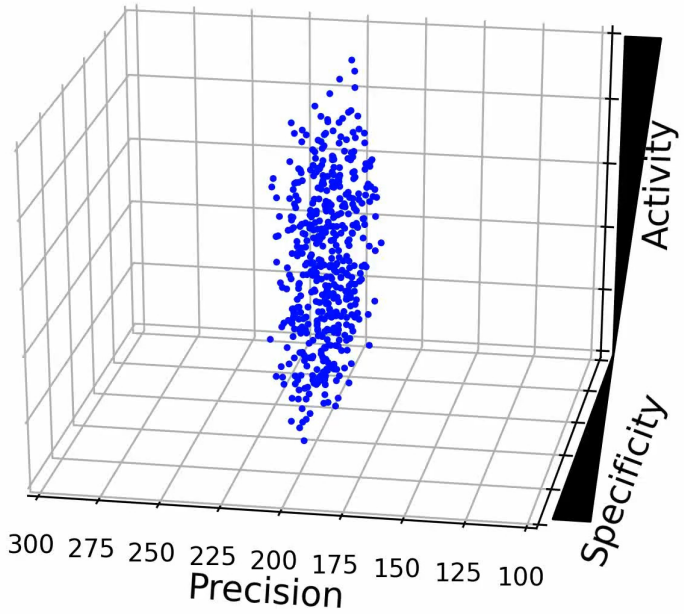
Capacity to induce efficiently a double strand break in the genome



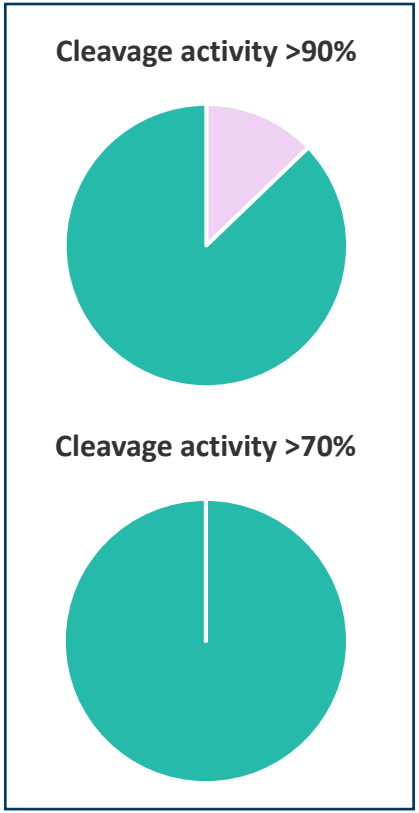
# TALEN®: High Editing Efficiency

Id



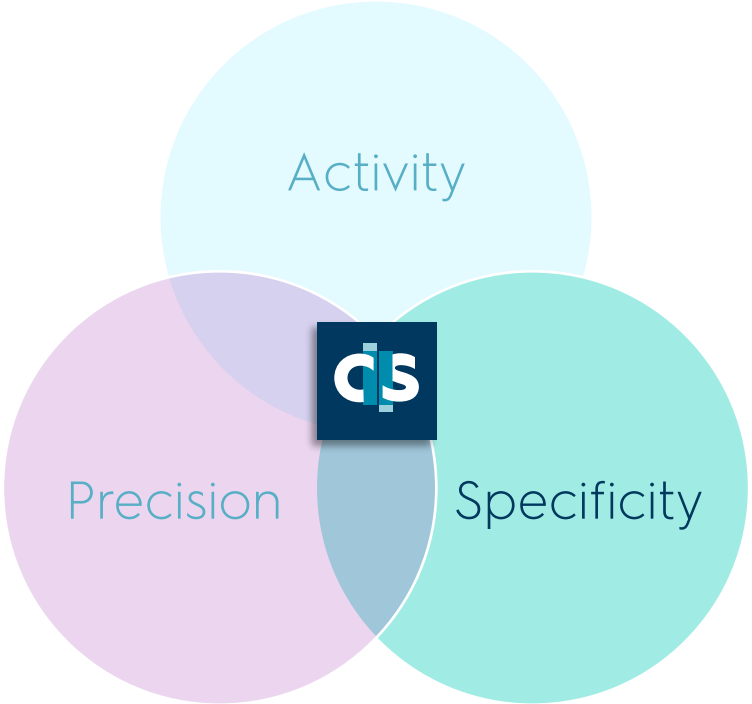




Success rate




- Proprietary algorithm (Machine learning)
- Pipeline to identify lead candidates TALEN®

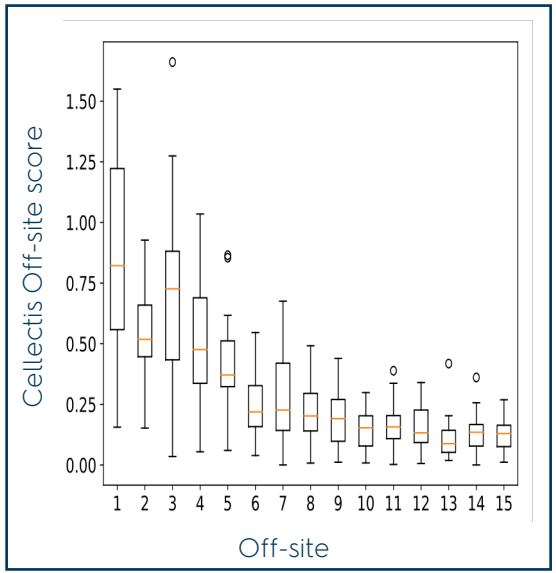
# The Three Pillars Of Gene Editing: Specificity



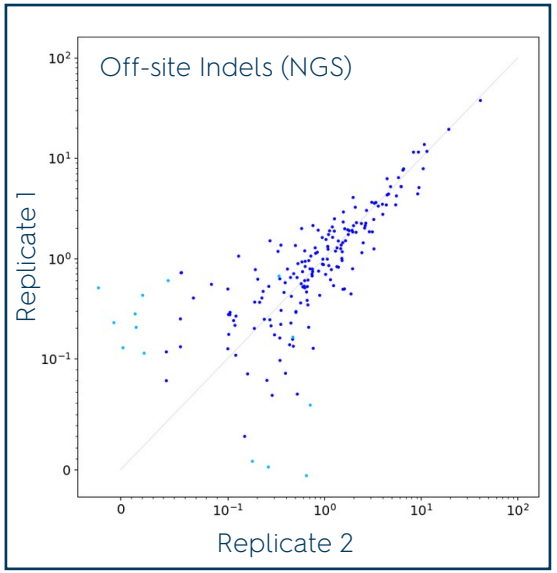

Capacity to avoid unintended genetic modifications

# TALEN® Specificity: State-of-the-art Off-site Validation Process

## Robust off-site identification

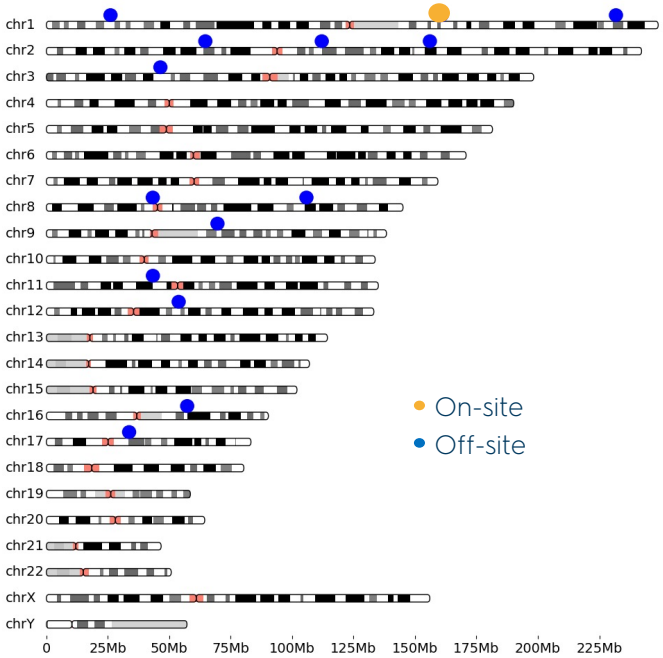



## High throughput off-site assessment

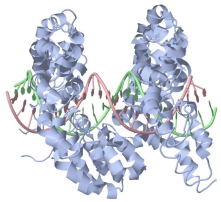



- Genome wide identification of potential off-sites
- Hundreds to thousands of site assessed simultaneously

# TALEN®: Exquisite Specificity




Rational Design

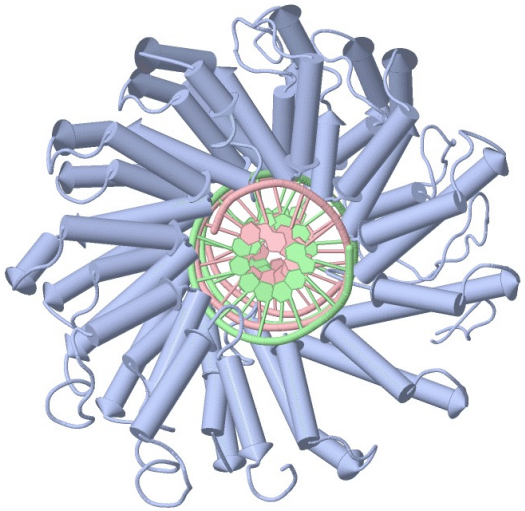



Cellectis proprietary TALEN® design

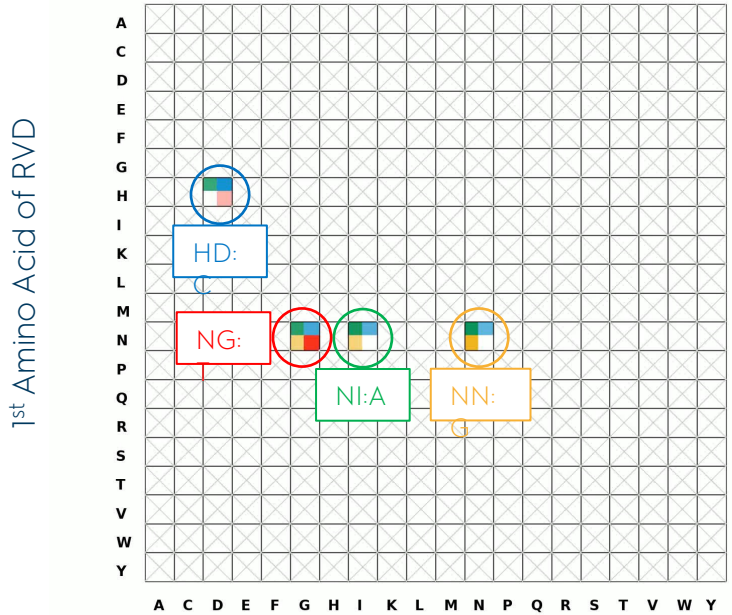

Protein engineering to reach perfect specificity for therapeutic applications

# TALEN® Specificity: Protein Engineering To Expand The Recognition Code

## Direct Protein: DNA contact



## Extending the TALE Code

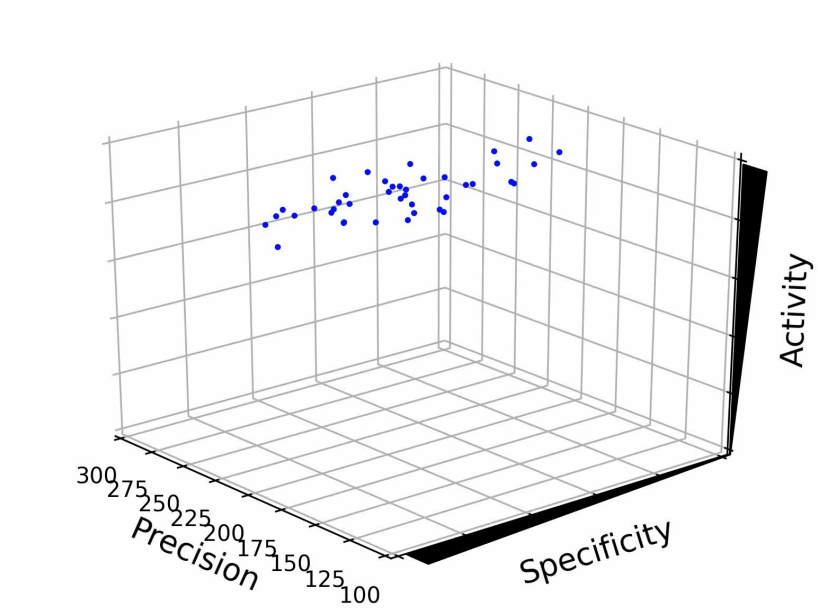



Targeted nucleotide

A C
G T

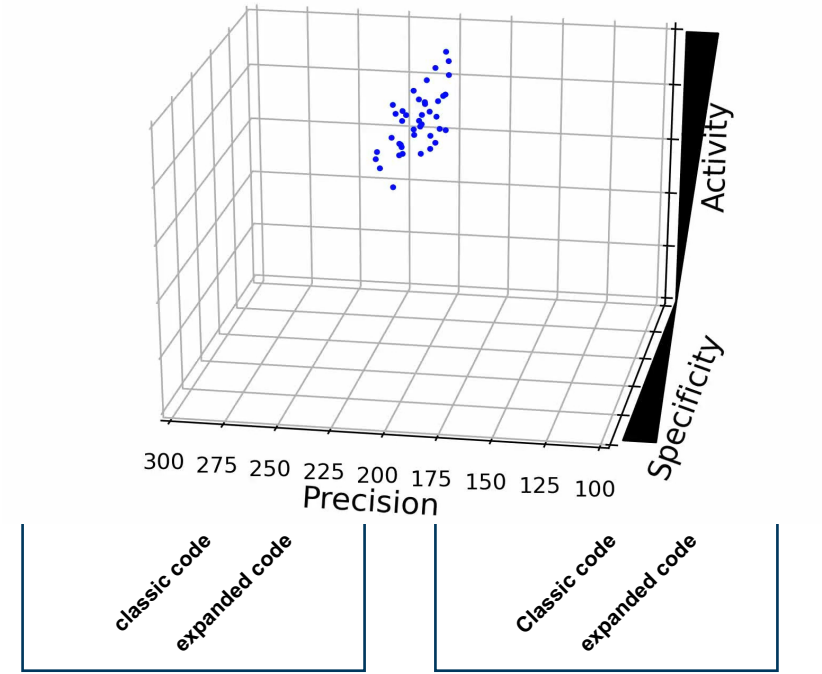
From a 4 RVD code to >200 targeting modules allow exquisite control of targeting

# Controlling TALEN® Specificity By Expanding The Recognition Code



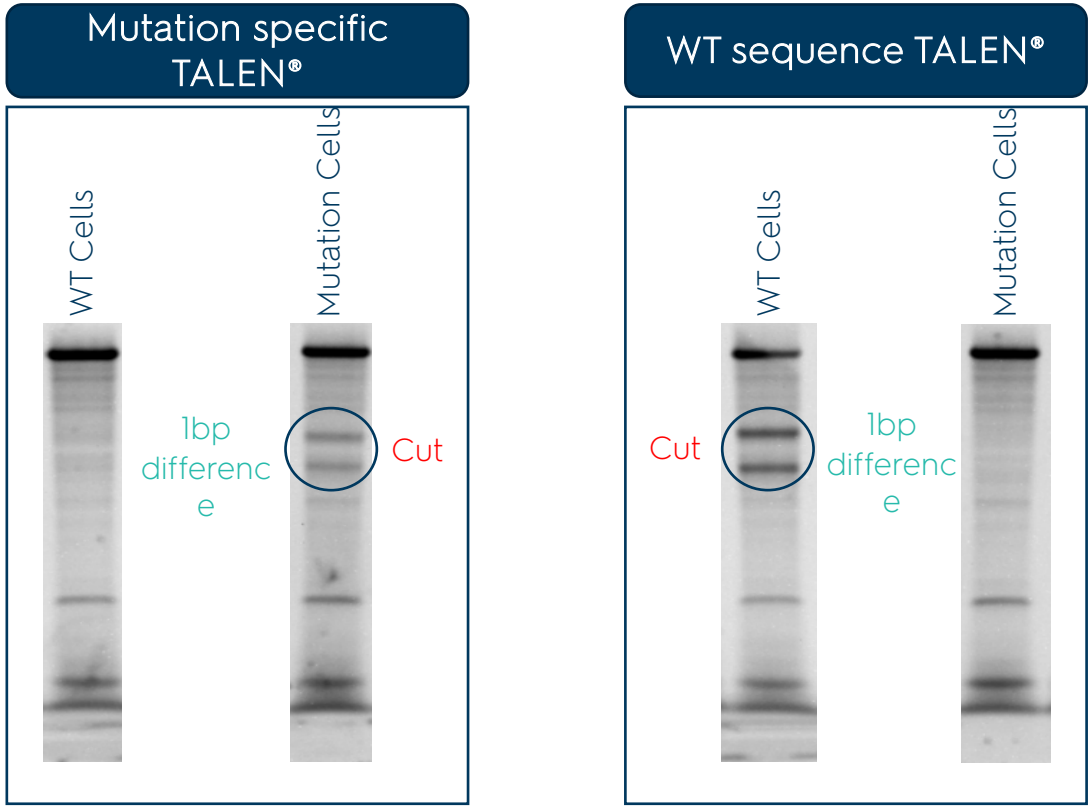
# Controlling TALEN® Specificity By Expanding The Recognition Code

## Expanding the “targeting code”




Targeting specificity is defined by design

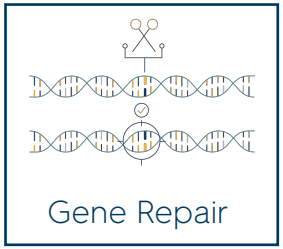
# TALEN® Specificity: Design Of An Allele-specific TALEN®

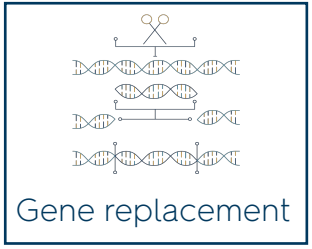


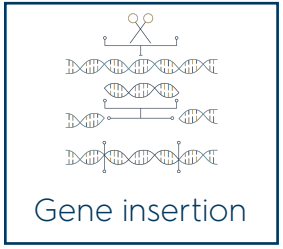

TALEN® can be designed to discriminate to a single base pair resolution

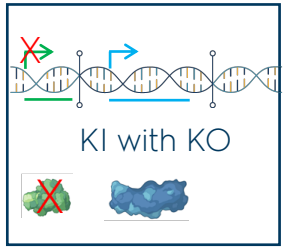
# Experimental considerations

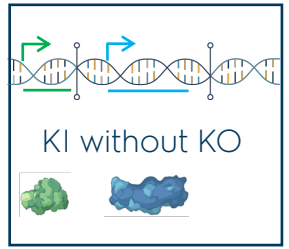
# TALE: A Versatile Gene Editing Platform

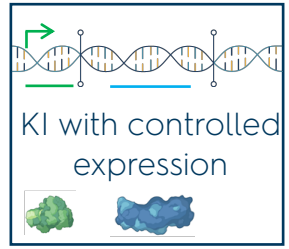



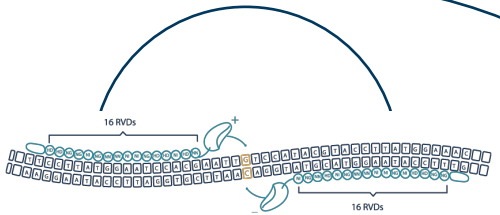



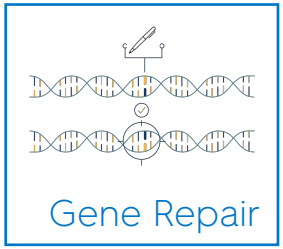




Nuclease

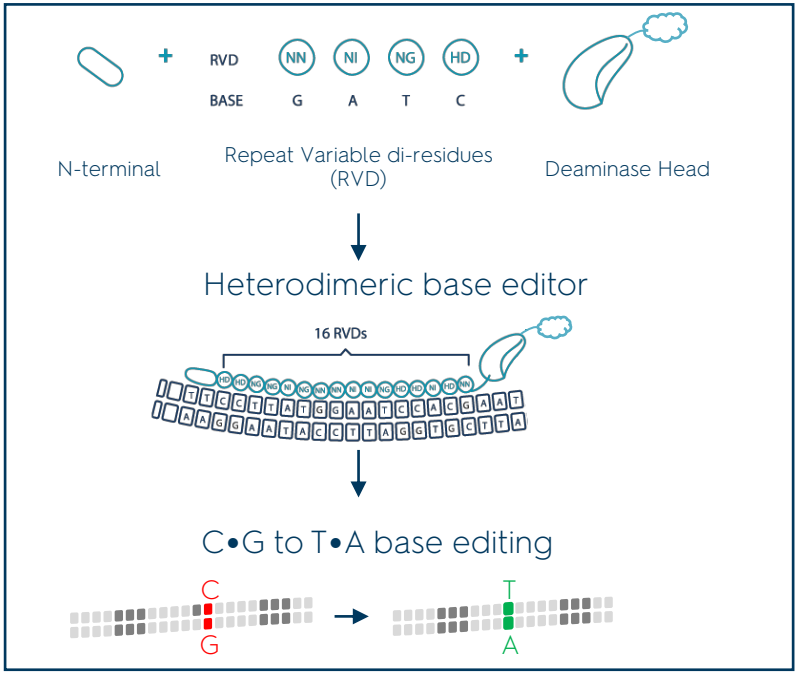



Base editor

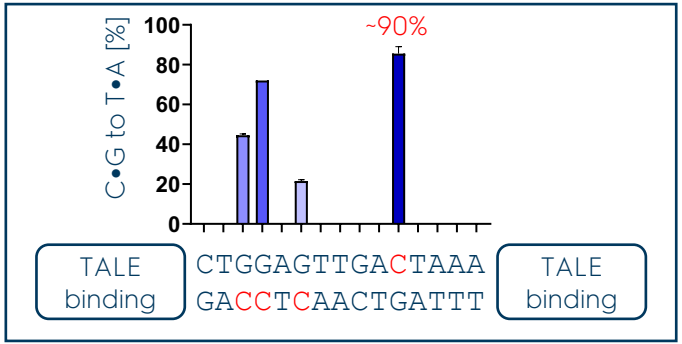



# TALE: A Versatile Scaffold For Efficient Base Editing

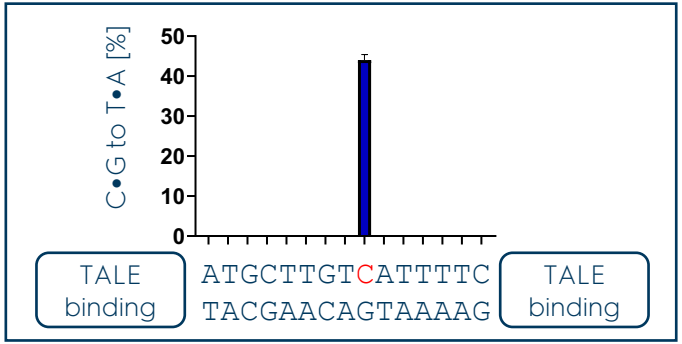
## TALE Base Editors




## High editing efficiency

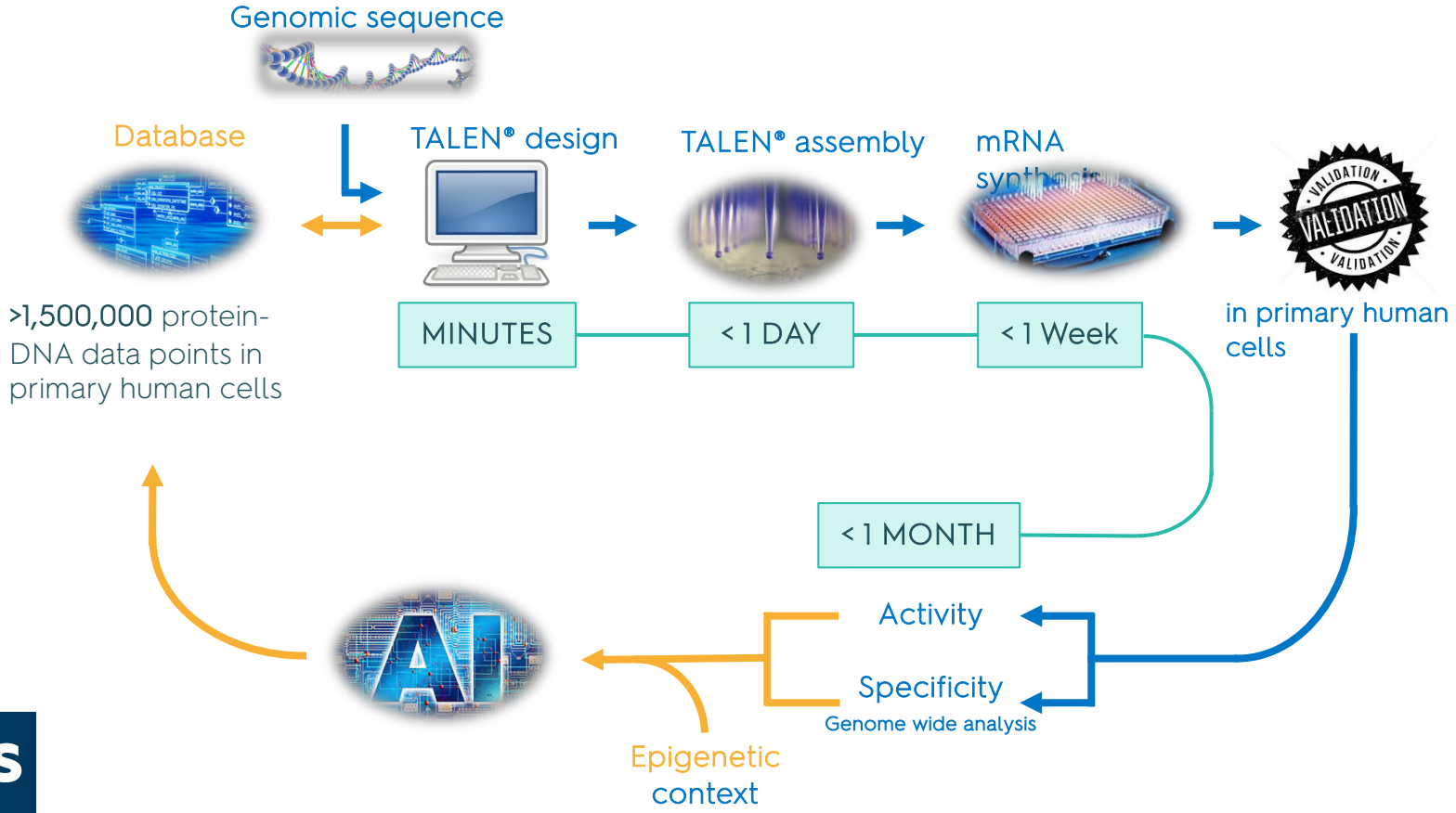



## High editing precision



# A fully Integrated Gene Editing platform

# TALEN®: Best-in-class Gene Editing Platform



# Part 2

# Gene Editing Technologies

# Introduction

Key Messages:

- The future of cell therapy lies in smart cells that will do what normal cells cannot.
- It's all going to be about genome engineering : programming cells to execute predetermined scenarios once infused in patients

- At Cellectis, we are already in the era of genome design.
- We developed a unique genome engineering technological platform:
  - ✓ Best in class DNA modification tools, with the potential to make precise changes in cells' genomes.
  - ✓ Powerful technologies developed to engineer billions of cells of any type at industrial scale for the clinic
  - ✓ (optional if Novo's in): Clinical-ready stem cells technologies to manufacture potentially any cell/tissue type >

# Genome Engineering Is Transforming Cell Therapies

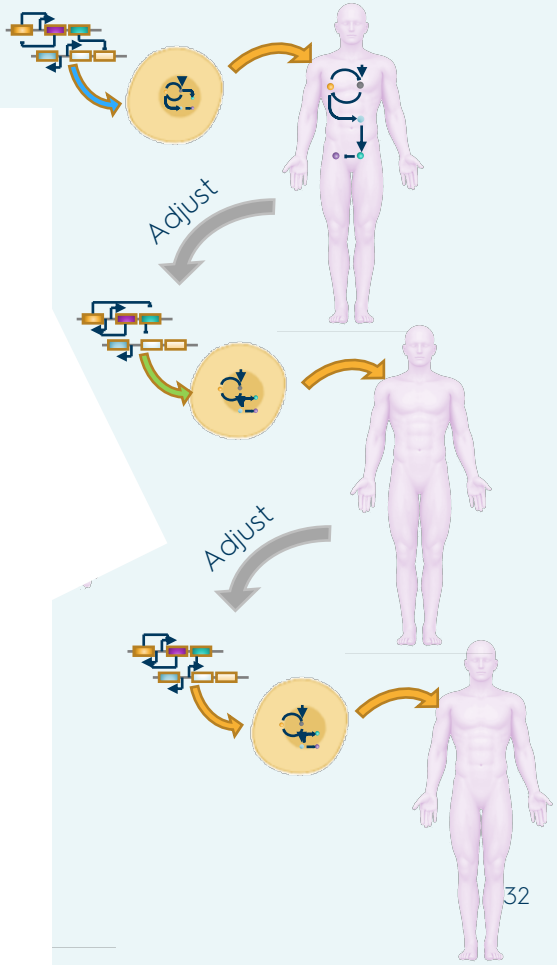
Smart cells industrial platform

✓ Genome design

✓ Programming scenarios

Strategic capability for

- multiple cell types (T-cells, stem cells, etc.)
- fast versioning (key to incremental development for complex indications)

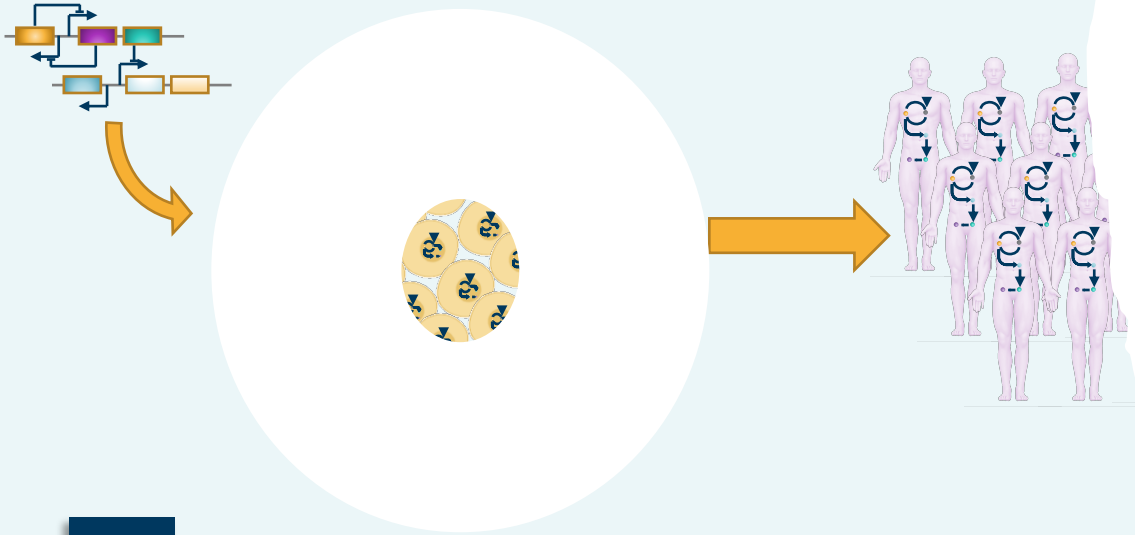


# Robust Delivery Is Key For Yield

Genome engineering relies on

- brief DNA surgery
- long-lasting effects,
- in billions of primary cells

⇒ Deliver messenger RNA, DNA, vectors.



High and robust yields allow clinical & commercial deployment

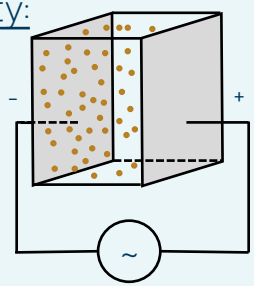
# A Platform Based On Electroporation

- Delivery with electroporation: versatile (DNA, mRNA, proteins) with any cell type, scalable, robust
- High electric fields open pores in the outer cell membrane.
- low voltage electric pulses drag macromolecules into the cells through the pores.
- It takes a few minutes for the cells to close those open holes.

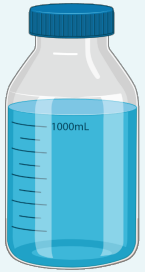
20 ms

# Controlling Gene Delivery From End To End

Cellectis acquired the Cytopulse technologies in 2010
and built upon it its own electroporation capability:




- ✓ devices




- ✓ reagent and buffers

- ✓ process and electrical wave forms

⇒ for each cell and payload types

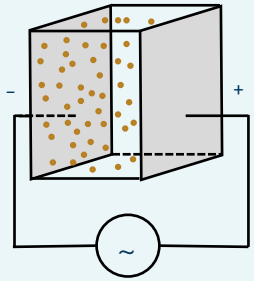
# PulseAgile: Wholly Owned Industrial Gene Editing Delivery Platform

Mastering and controlling genome engineering from end to end

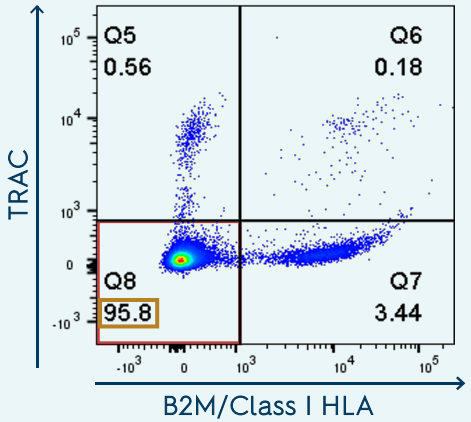
- PulseAgile:  electric wave form generator deliver precise, controlled and flexibly adjustable pulses

# Electroporation Of Billions Of Cells

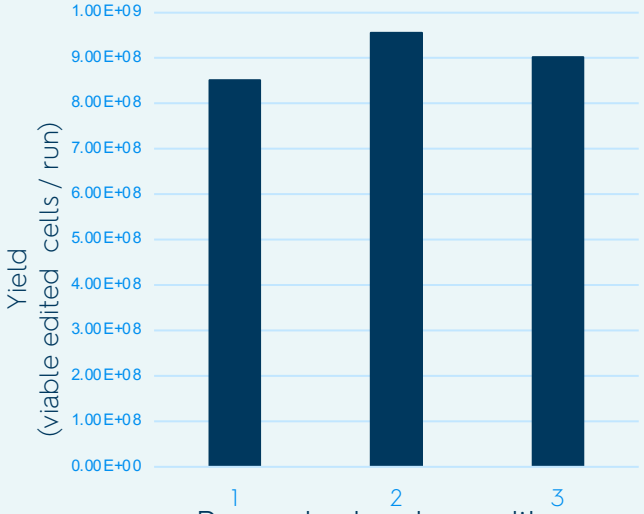
Proprietary electroporation chamber designed for billions of cells








Single pulse multiple edits

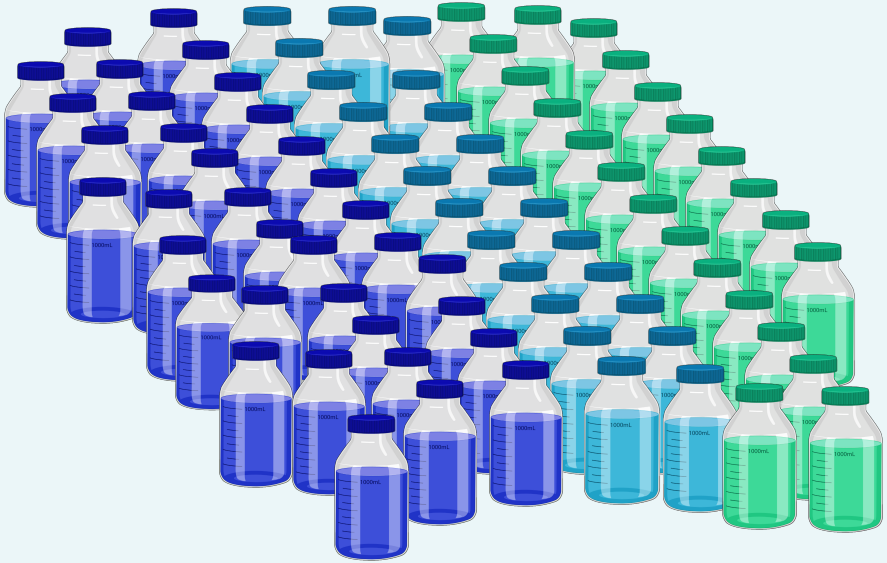


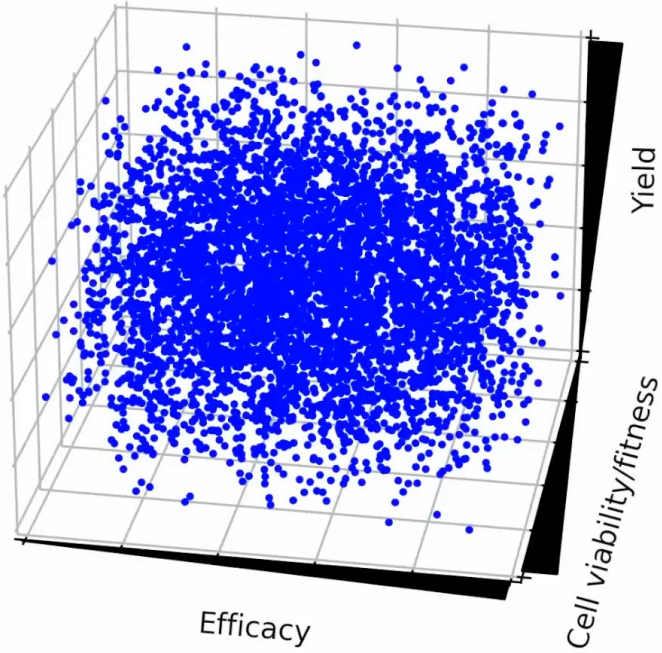

Repeated pulse edits

# Proprietary Chemically Designed Buffers

Making proprietary electroporation buffers for each cell and payload types.

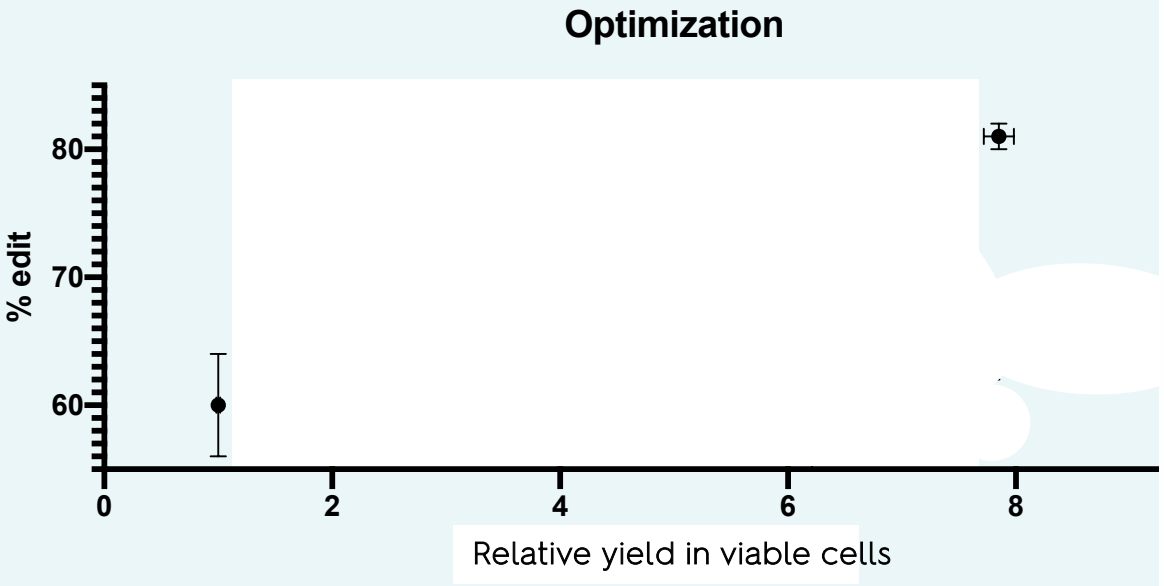
Screening vast chemical space along critical buffer properties

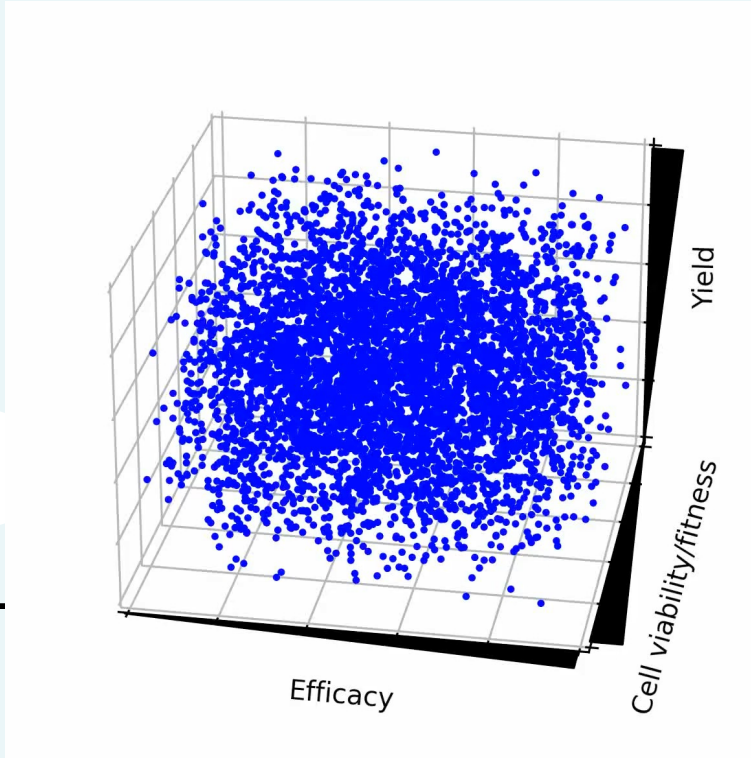




# Optimizing Electroporation For Any Application

Example for hemopoietic stem cells

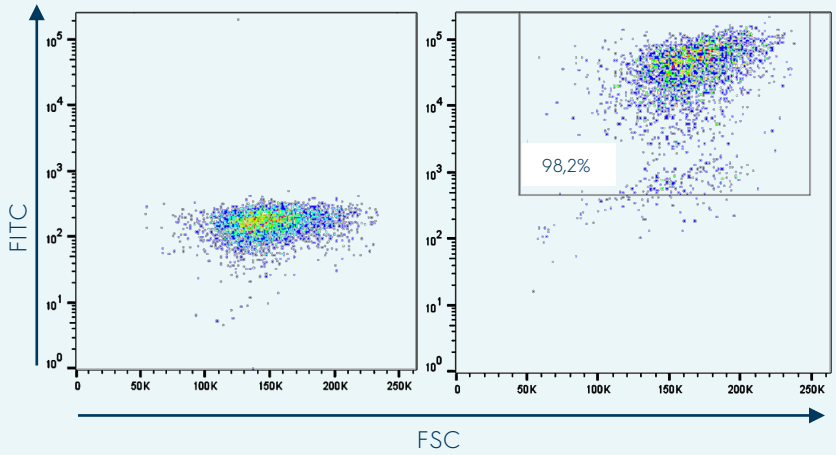


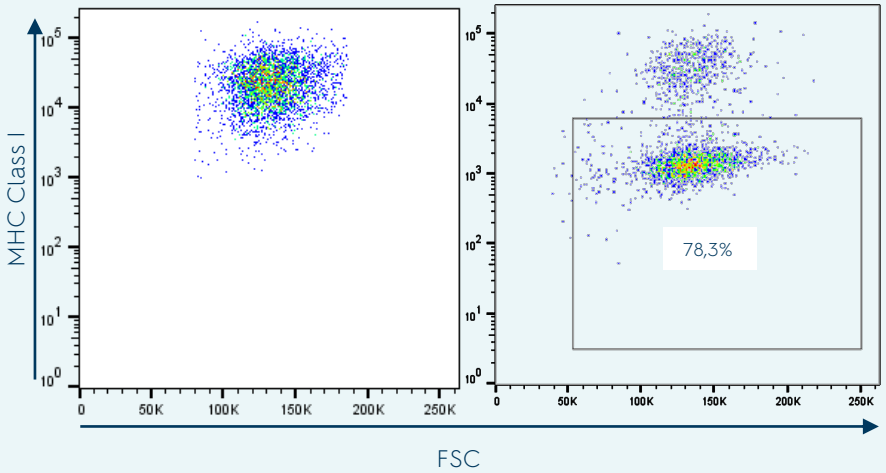
# Edits With Yield And Accuracy

Examples in hemopoietic stem cells (HSC)

## HSC transfection




## HSC gene editing




Hundred millions cells scale

# Scaling to hundred billions of cells : GeneEngine™

# GeneEngine™ For Hundreds Of Billions Of Cells

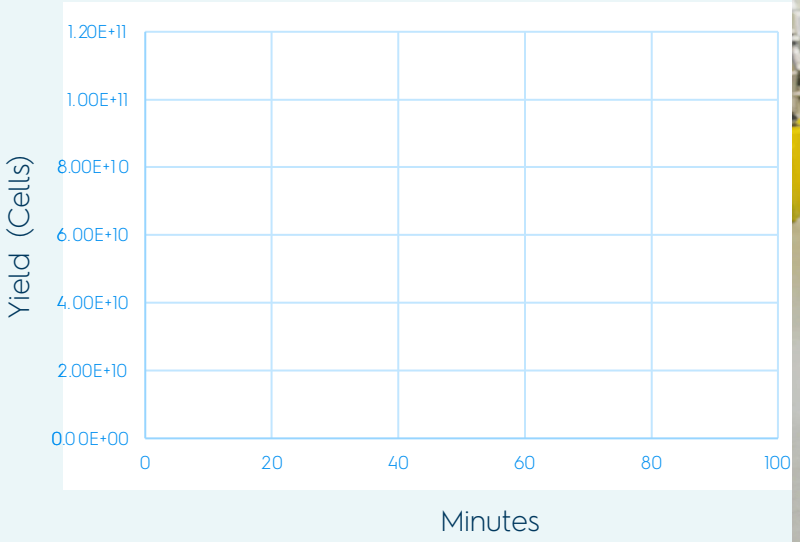
Expanding to hundreds of billions of cells

GeneEngine™ provides

- ✓Versatility : any cell type
- ✓Scalability
- ✓Robustness: closed system
- ✓Yield

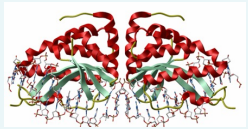
# Robustness At Industrial Scale

## Examples in T-cell



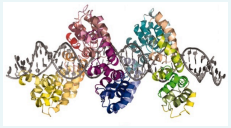

# Era Of Genome Design

First nuclease-based gene knockout



1999

TALEN®-enabled single knock-in



2011

Genomic engineering for simple functions


2017

Genome design for industrial deployment


2021

# A Unique Smart Cell Technological Platform

Unique position: short time from genomic design to bed side and rapid versioning

- ✓ TALEN® for therapeutics: exquisite precision, activity and specificity
- ✓ Fast target to therapeutic TALEN® turnaround
- ✓ End to end controlled versatile and scalable vectorization : electroporation
- ✓ Comprehensive smart cell engineering platform from concept to GMP and bedside

⇒ Strategic to foster the transformative power of genome engineering in cell therapy

# THANK YOU

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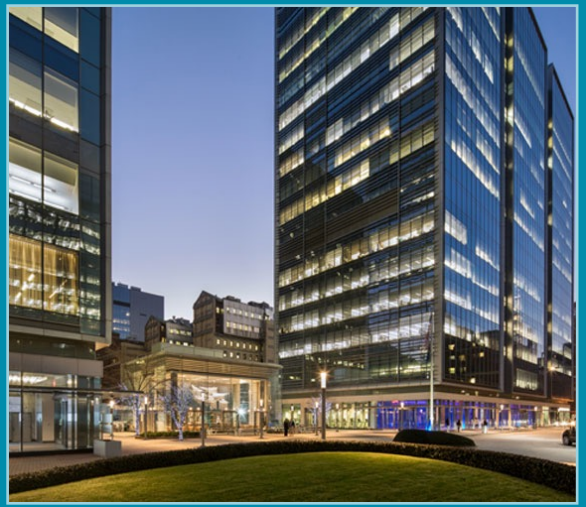

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