

# Gene Editing of Monogenic disorders in Human Hematopoietic Stem Cells (XLA)

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Case: 2018-372

# Donald B. Kohn

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**Distinguished Professor, Microbiology, Immunology and Molecular Genetics; Pediatrics (Hematology/Oncology); Molecular and Medical Pharmacology**

Kohn began working on gene therapy as a fellow at the National Institutes of Health in 1985. After, while practicing at Children's Hospital Los Angeles, he started his own lab focused on stem cell research and has continued this work, advancing new therapies from the lab to the clinic.

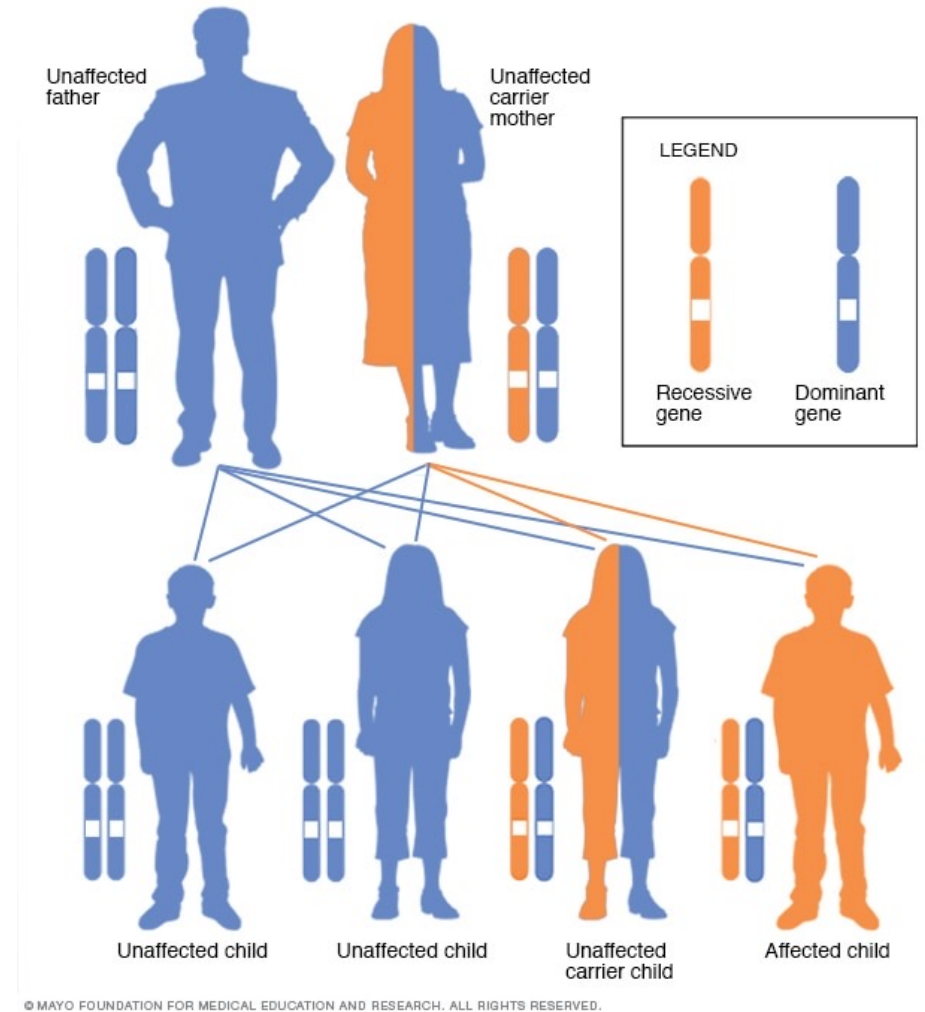
More recently, Donald B. Kohn, M.D., studies the biology of blood stem cells. Over the course of 30 years of research, Kohn has developed new clinical methods to treat genetic blood diseases using blood stem cells that have been modified to remove genetic mutation, focusing especially on gene therapy methods.

# Executive Summary

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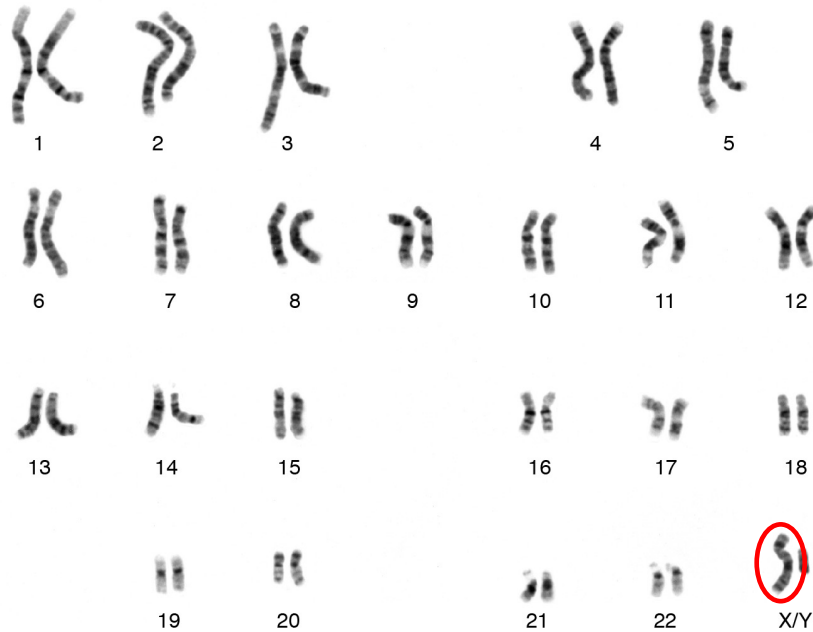
# X-Linked Agammaglobulinemia is a Genetic Immunological Disorder

- X-Linked Agammaglobulinemia (XLA) is a genetic disorder that affects 1/200,000 people worldwide.
- Patients with XLA require lifelong treatment and have reduced life expectancy.<sup>1</sup>



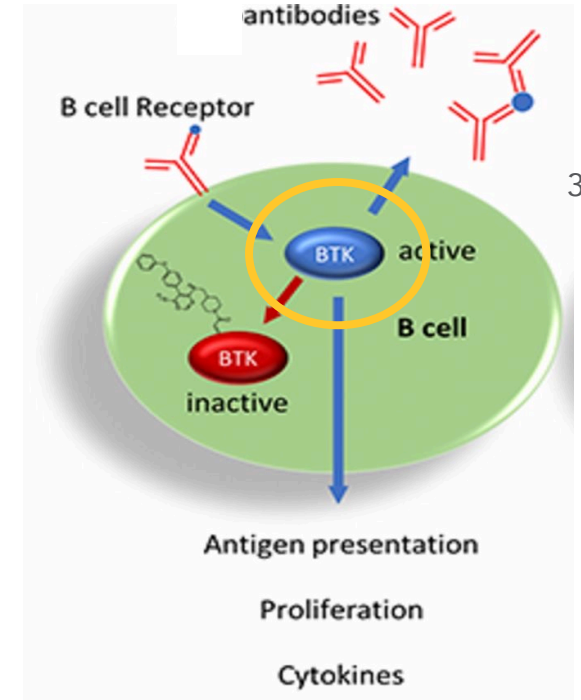
# X-Linked Agammaglobulinemia is a Genetic Immunological Disorder

## Human Chromosomes



## Male X-Chromosome

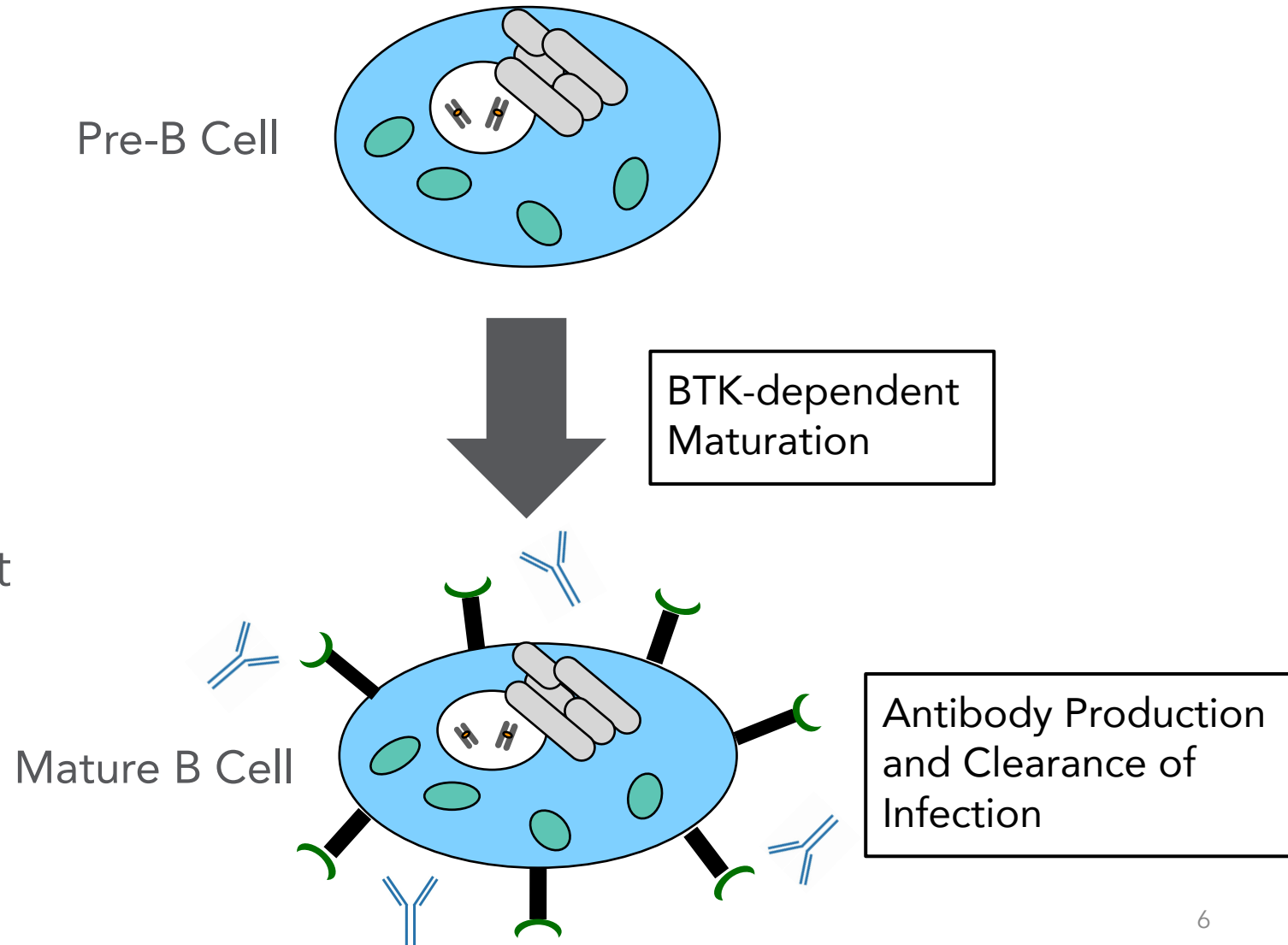
Normal BTK allows proper function of B cells and production of antibodies



- The cause of XLA is a well characterized recessive mutation in the gene encoding Bruton's Tyrosine Kinase (BTK) found on the X-chromosome.
- Mutant/dysfunctional BTK results in a diminished ability to fight off infections.<sup>1</sup>

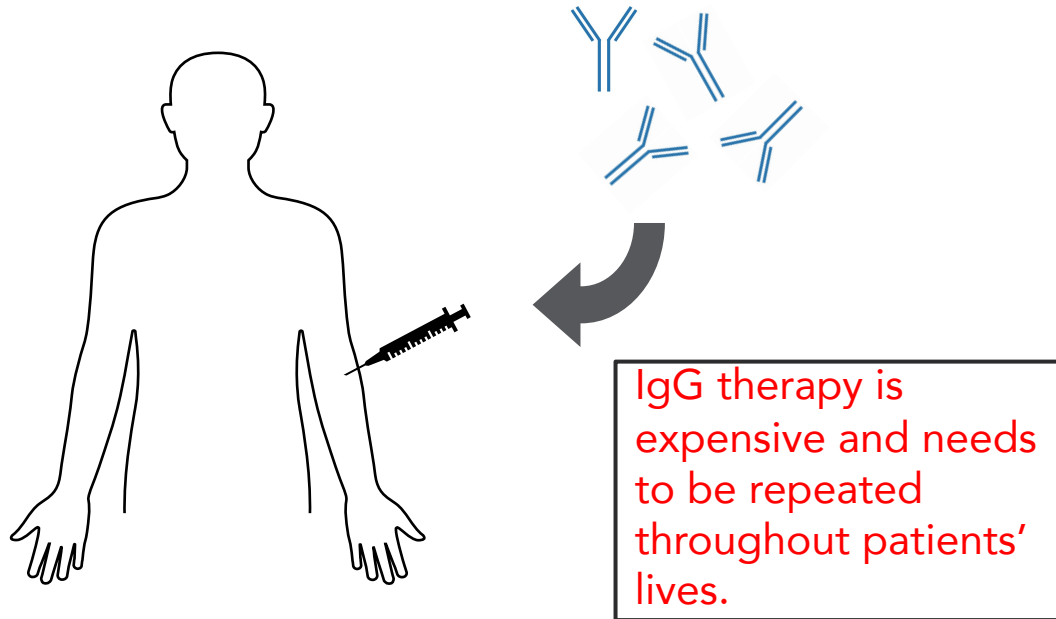
# X-Linked Agammaglobulinemia is a Genetic Immunological Disorder

- Mutant BTK blocks the maturation of B cells to their functional mature state.
- Without a cure, XLA causes patients to have impaired immune function throughout their lives.

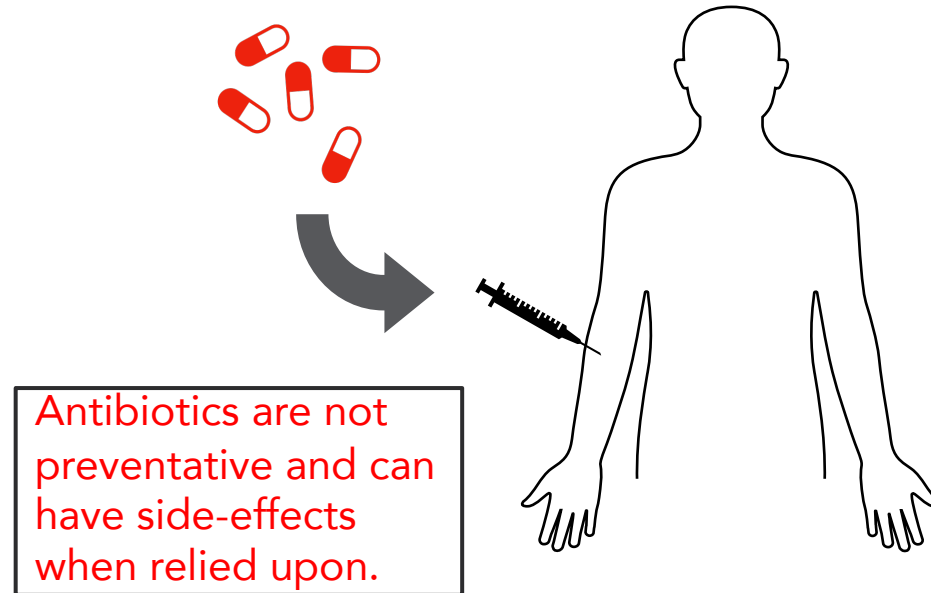


# Treatments for XLA are Expensive and Ineffective

## IgG Replacement Therapy



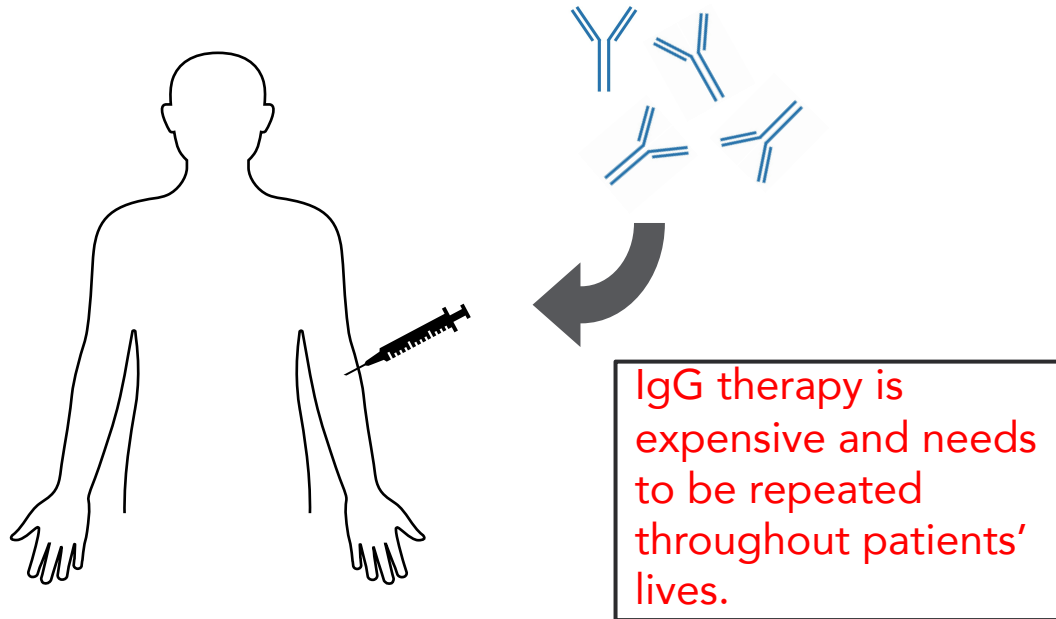
## Antibiotic Therapy



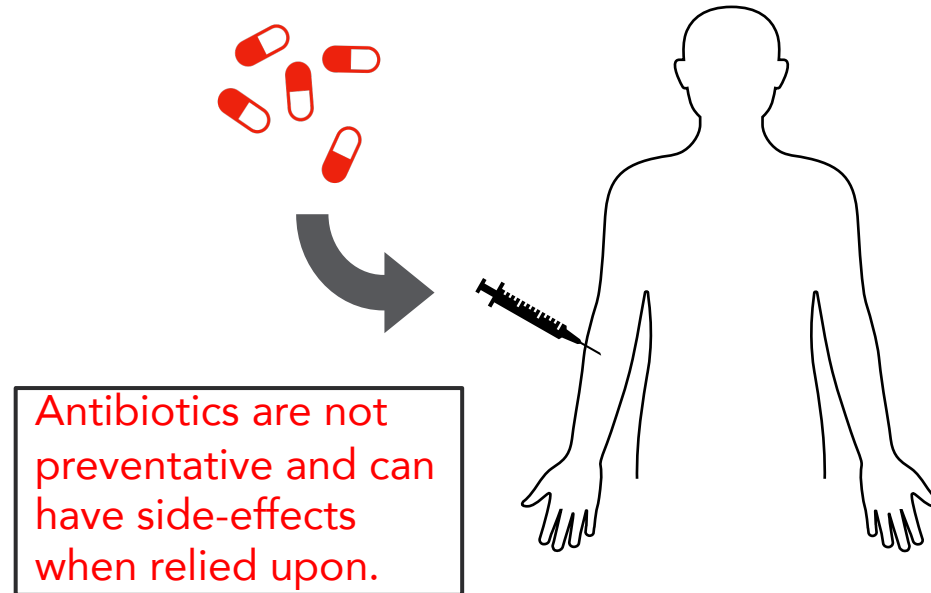
- Current standard of care for XLA is immunoglobulin replacement therapy and frequent antibiotic administration.<sup>1</sup>
- There remains no curative treatment for individuals afflicted with XLA.

# Treatments for XLA are Expensive and Ineffective

## IgG Replacement Therapy



## Antibiotic Therapy



- **There is an urgent need for cost effective, curative treatment for XLA with limited off target effects.**

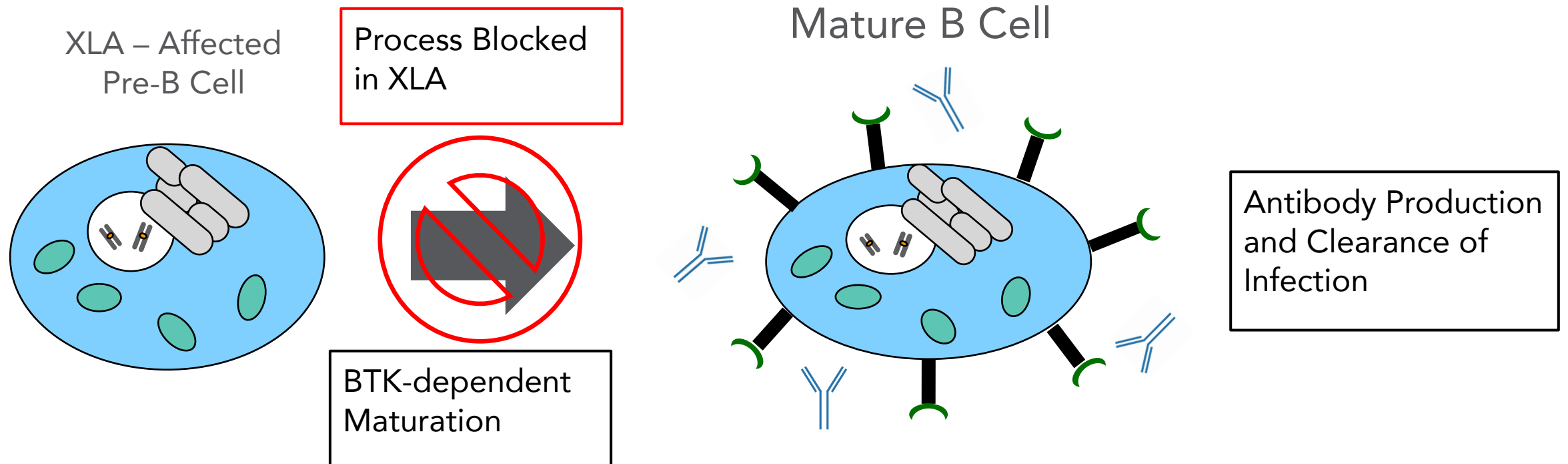


# Technology Overview

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# XLA Inhibits Maturation of Immune B Cells

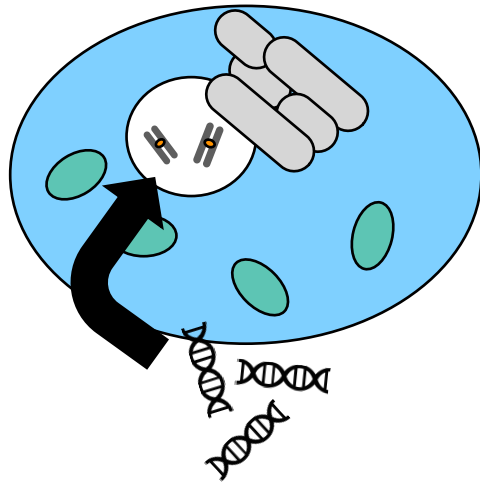
- Restoring functional sequence of BTX protein could produce a cure for XLA.
  - Gene therapy methods provides the potential to provide this cure.



# Gene Therapy Intervention Could Cure XLA

- Restoring functional sequence of BTK protein could produce a cure for XLA.
  - Gene therapy methods provides the potential to provide this cure.

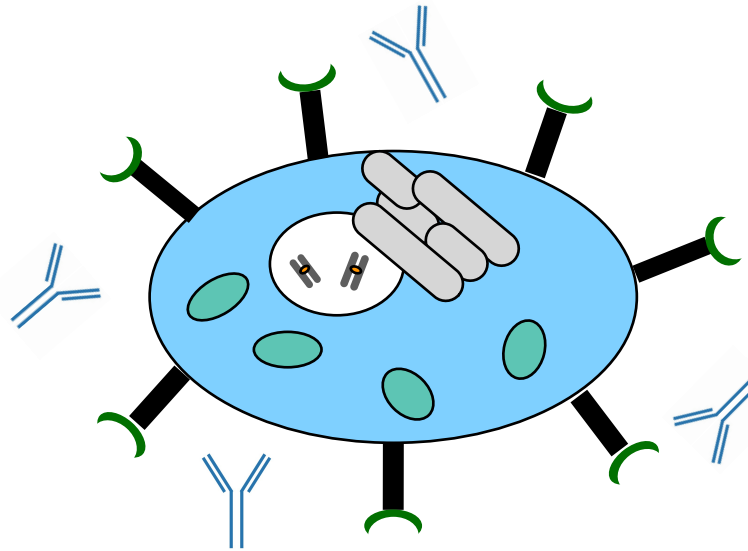
XLA – Affected  
Pre-B Cell



Gene Therapy  
Intervention

BTK-dependent  
Maturation

Mature B Cell



Antibody Production  
and Clearance of  
Infection

# Advantages Over Other Gene Therapy Methods

1

Complications of Gene Therapy	
<b>1. Adverse host immune responses</b>	
o Innate Immunity	Fever, thrombocytopenia, cytokine storm
o Adaptive Immunity	Humoral response eg. Anti-AAV capsid Abs Cell-mediated response eg. Anti-AAV capsid cytotoxic T cells
<b>2. Insertional Mutagenesis</b>	
<b>3. Failure of Transgene Expression</b>	
o Too little	
o Not persistent	

Current available  
treatments struggle with  
efficiency and specificity

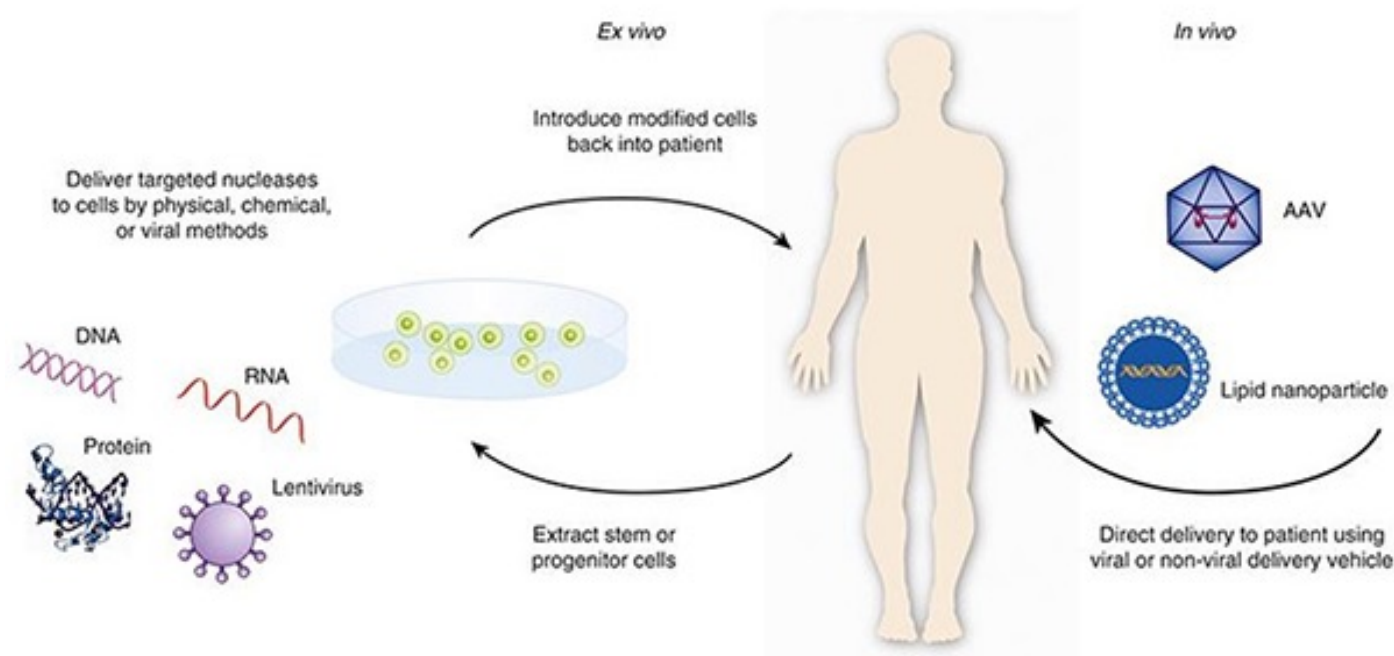
- Existing gene therapy protocols suffer from poor gene editing efficiency, and low expression of inserted gene.
- Novel UCLA-developed method yield high editing efficiency and good expression of inserted transgene.**



2

# Applications of Invention

- UCLA Researchers developed a novel gene therapy method that can efficiently and precisely revert disease causing mutations associated with XLA.
- Unlike other gene therapy methods, novel UCLA method does not suffer from low expression or editing efficiency.



- Novel XLA-treating gene therapy method can be used to modify stem cells *ex vivo* for reintroduction into patient's body.

# Developmental Timeline of Technology

July 2015:  
Initial Conception.

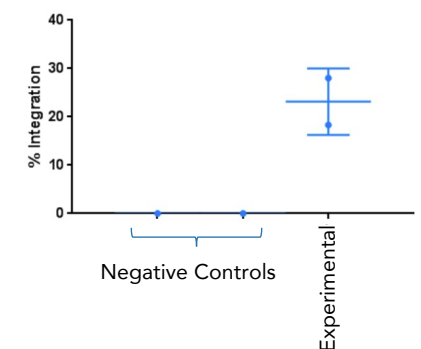
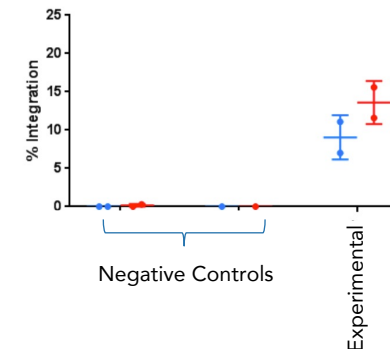
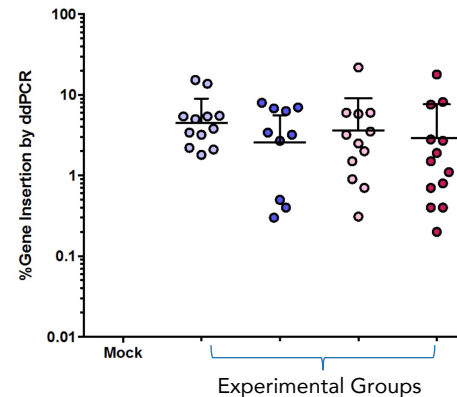
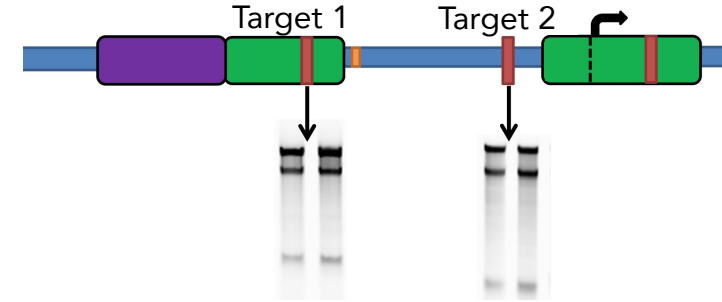
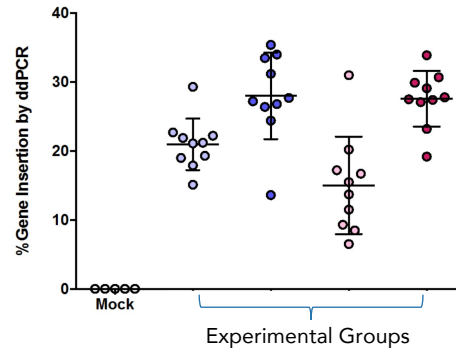
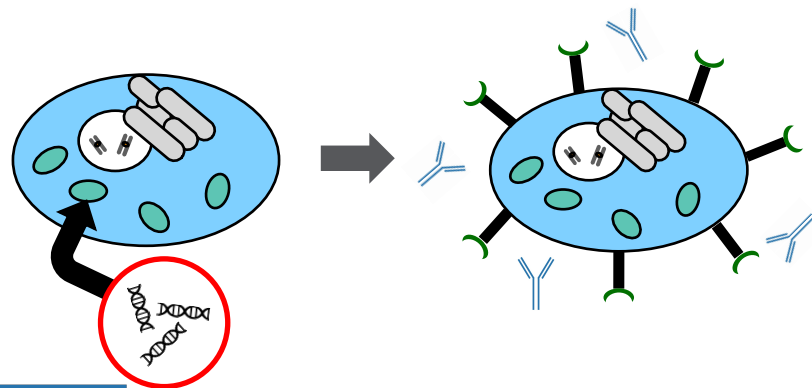
Demonstration of effectiveness at  
editing gene linked to other X-  
linked disorders

Development of BTK-  
targeting gene therapy

Development of novel  
gene editing platform

Demonstration of effectiveness  
of technique *in Vivo*

Demonstrated  
technology  
efficiently edits BTK  
gene



# Market Opportunity

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# Market Overview: Generalized Market

BCC Research  
Report Code: BIO159A

Global Market for Genetic Modification  
Therapies in Rare Diseases, by Indication, Through  
2023 (\$ Millions)

Indication	2017	2018	2023	CAGR % 2018-2023
MPS III (Sanfilippo syndrome)	—	—	1,078.7	—
ATTR	—	47.1	776.2	75.1
HofH	3.8	4.7	366.6	139.0
XLMTM	—	—	135.7	—
MPS I	—	—	82.8	—
ADA-SCID	—	—	73.2	—
MPS II	—	—	33.4	—
Pompe disease	—	—	31.7	—
ADPKD	—	—	25.8	—
CASQ2-CPVT	—	—	23.7	—
Alport syndrome	—	—	19.4	—
Total	3.8	51.8	2,647.2	119.6

- The global market for gene therapy targeting rare diseases:
  - Global Market - \$51.8 million in 2018
  - Projected Growth to \$2.65 billion by 2023
  - CAGR of 119.6%, by 2023
  - Some of the fastest predicted growth rates of any therapeutic market.



# Market Overview (By Region)

BCC Research  
Report Code: BIO159A

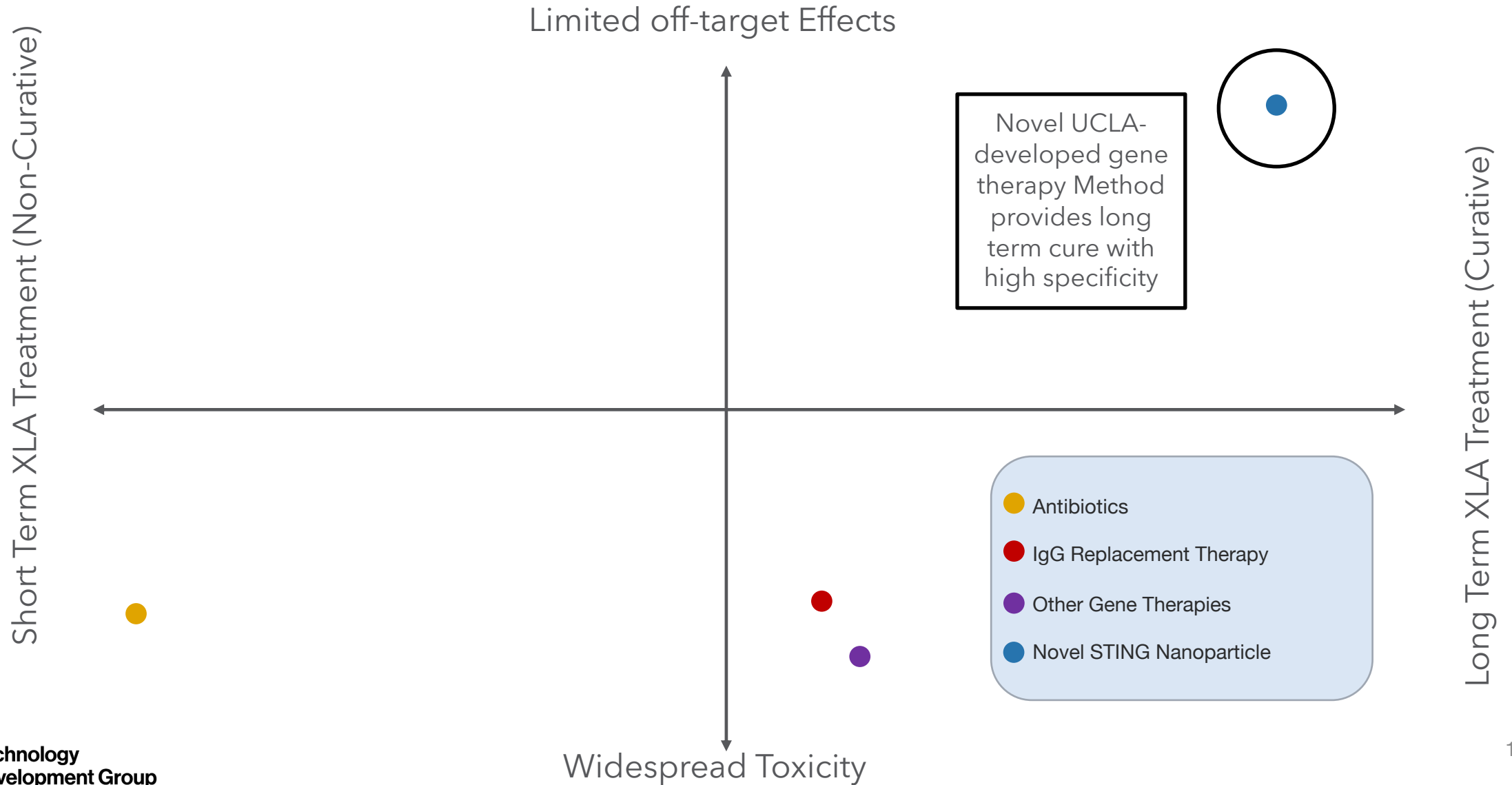
Global Market for Genetic Modification Therapies,  
by Region, Through 2023

Region	2017	2018	2023	CAGR% 2017-2023
North America	908.2	1,609.0	9,330.3	42.1
Europe	15.1	378.8	6,405.8	76.0
Asia-Pacific	47.2	240.1	1,461.1	43.5
ROW	—	72.8	233.3	26.2
Total	970.5	2,300.7	17,430.5	49.9

## Relevant Companies:



# Comparisons with Existing Innovations in Cancer Therapeutics



# Commercialization Potential

# Novel UCLA Gene Therapy Treatment will Revolutionize Clinical Intervention for XLA

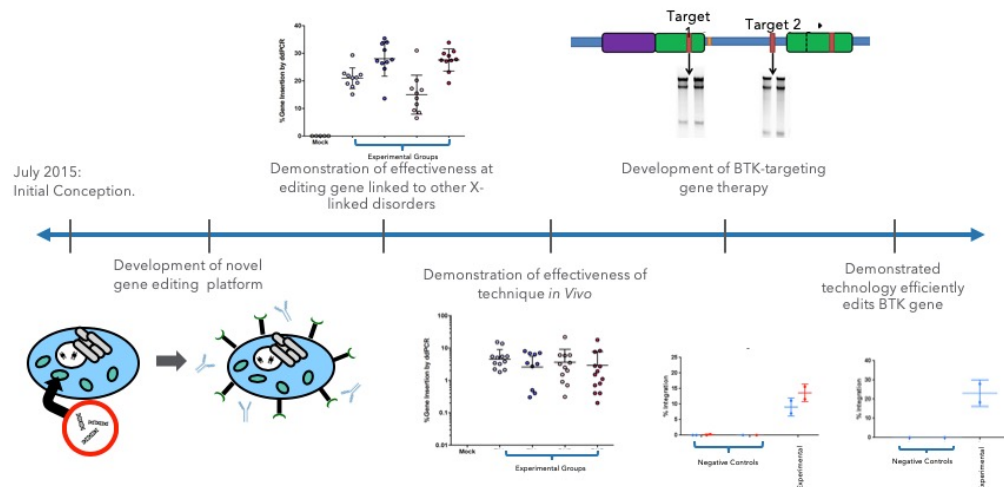
There is a dire need for a drug that cures XLA with high efficiency and low toxicity

Table 38  
Global Market for Genetic Modification Therapies, by Platform Technology, Through 2023  
(\$ Millions)

BCC Research  
Report Code: BIO159A

Platform Technology	2017	2018	2023	CAGR% 2018–2023
Gene therapy	151.7	374.7	9,438.1	90.7
RNA therapy	797.8	1,763.8	4,692.0	21.6
Genetically modified cell therapy	21.0	162.2	3,118.9	80.6
Gene editing	—	—	181.5	—
Total	970.5	2,300.7	17,430.5	49.9

Source: BCC Research



Novel XLA gene therapy efficiently targets BTK gene; Marketing as a **cure** for XLA and a platform for treatment of other X-linked genetic disorders

# UCLA Technology Development Group

# Thank You

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## UCLA® TECHNOLOGY DEVELOPMENT GROUP

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