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

Case: 2018-372

Donald B. Kohn, Distinguished Professor; Microbiology, Immunology, and Molecular Genetics

Donald B. Kohn

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

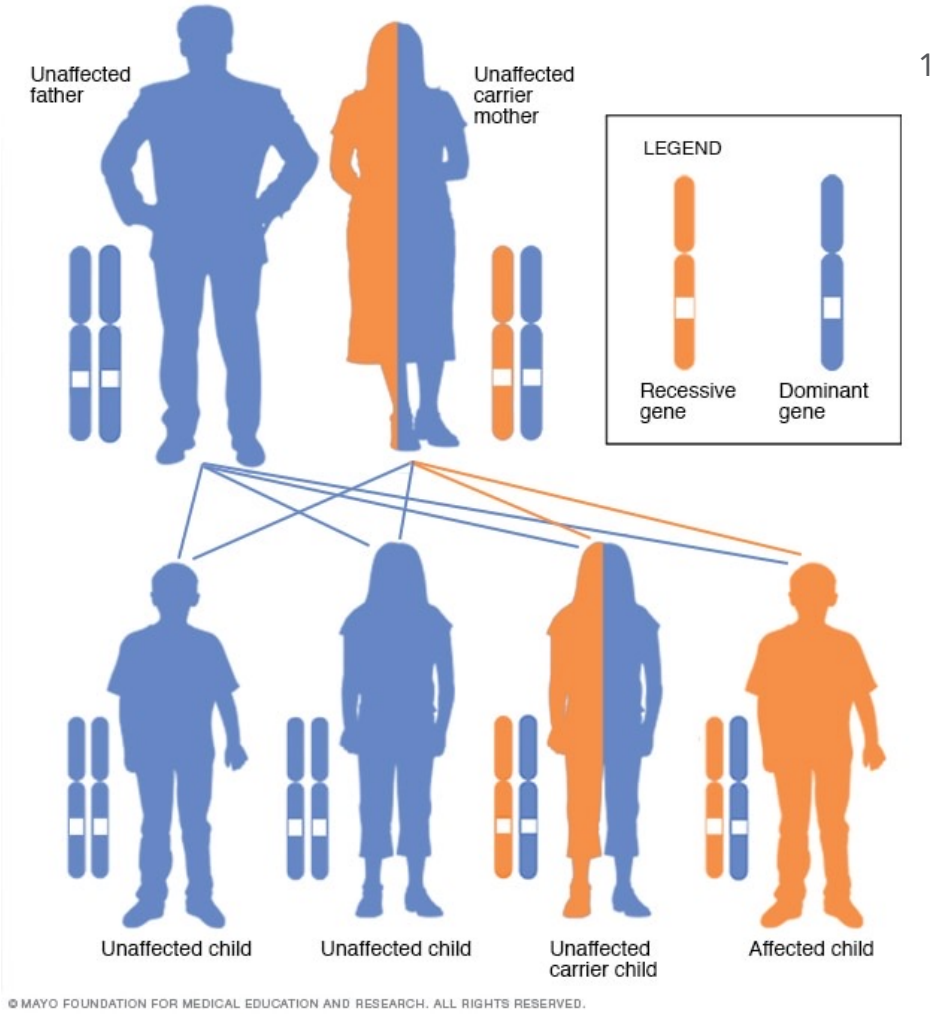
Kohn began working on gene therapy as a fellow at the National Institutes of Health in 1985. After, while practicing at Children's Hospital Los Angeles, he started his own lab focused on stem cell research and has continued this work, advancing new therapies from the lab to the clinic.

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

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.[1]



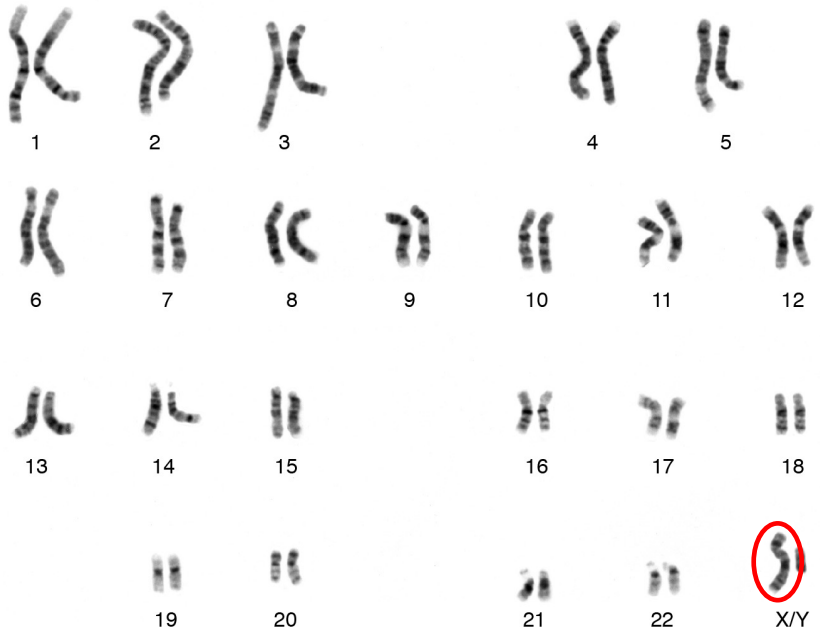
1

[1] Mayo Clinic, X-linked aggamaglobulonemia; https://www.mayoclinic.org/diseases-conditions/x-linked-agammaglobulinemia/symptoms-causes/syc-20361635.

X-Linked Agammaglobulinemia is a Genetic Immunological Disorder

2

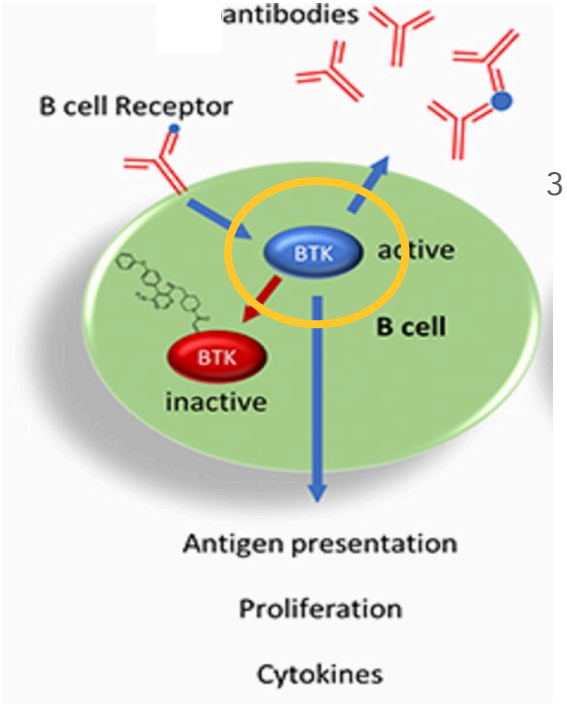
Human Chromosomes



Male X-Chromosome

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

3



- 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.[1]

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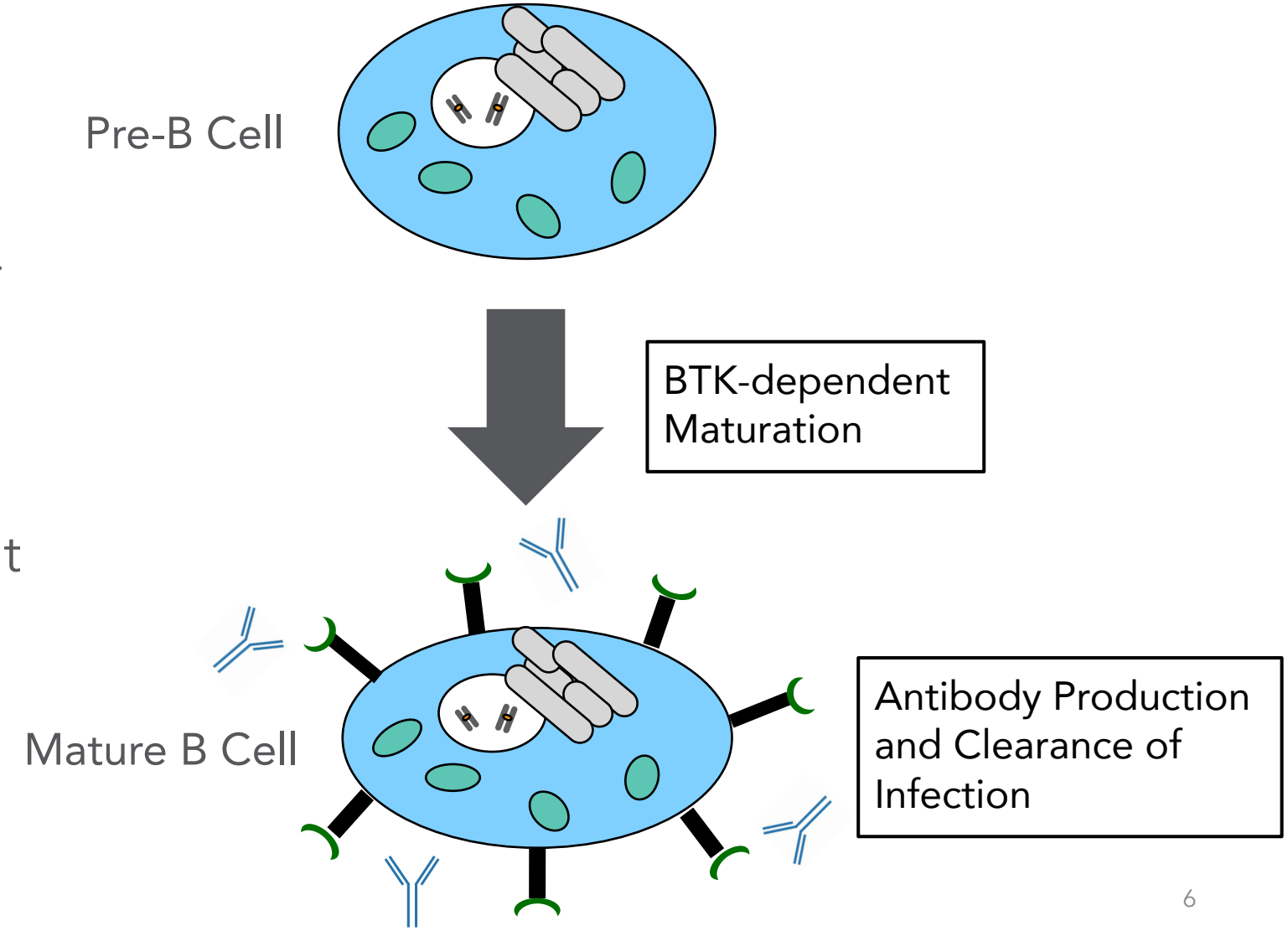
[1] Mayo Clinic, X-linked aggamaglobulonemia; https://www.mayoclinic.org/diseases-conditions/x-linked-agammaglobulinemia/symptoms-causes/syc-20361635.
[2] National Human Genome Research Institute, Karyotype; https://www.genome.gov/genetics-glossary/Karyotype.
[3] Haselmayer, P. *et al.* Efficacy and Pharmacodynamic Modeling of the BTK Inhibitor Evobrutinib in Autoimmune Disease Models. *J.I.* **202**, 2888–2906 (2019).

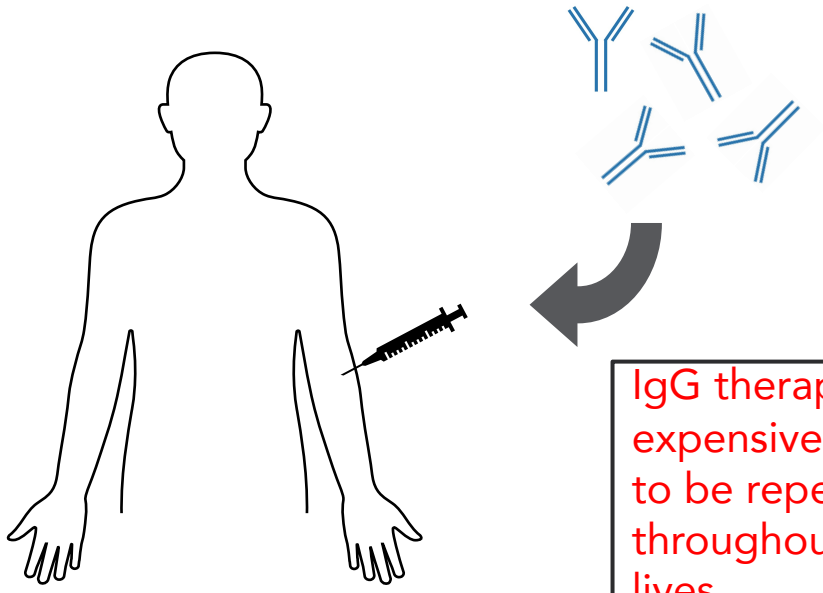
X-Linked Agammaglobulinemia is a Genetic Immunological Disorder

- 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.



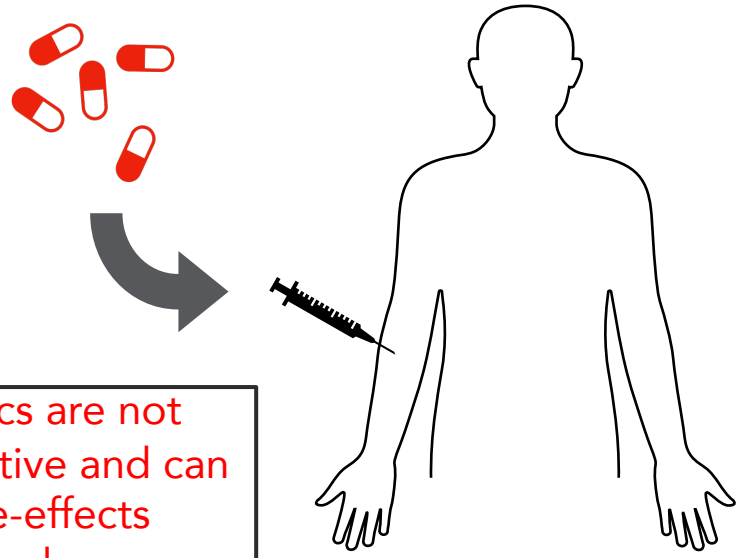
Treatments for XLA are Expensive and Ineffective

IgG Replacement Therapy



IgG therapy is expensive and needs to be repeated throughout patients' lives.

Antibiotic Therapy



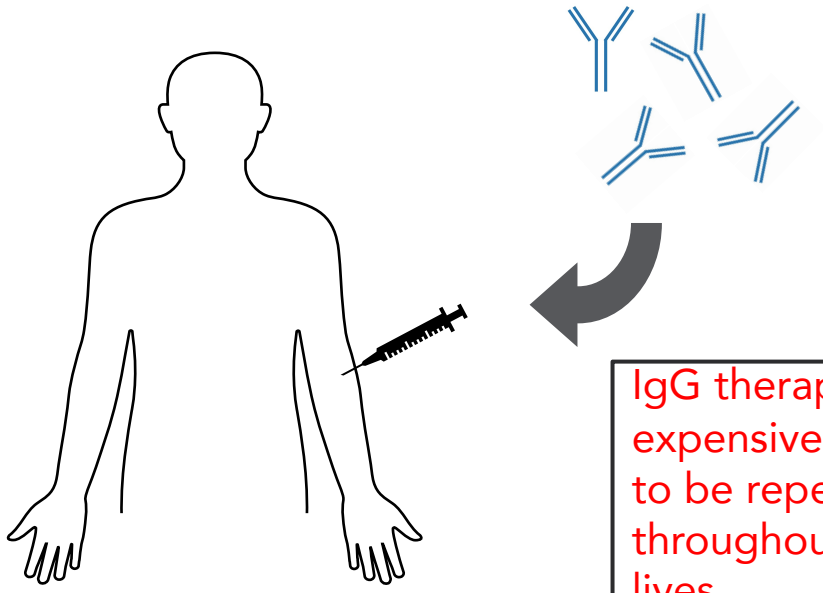
Antibiotics are not preventative and can have side-effects when relied upon.

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

[1] National Organization of Rare Diseases, X-linked aggamaglobulonemia; https://rarediseases.org/rare-diseases/agammaglobulinemia/

Treatments for XLA are Expensive and Ineffective

IgG Replacement Therapy



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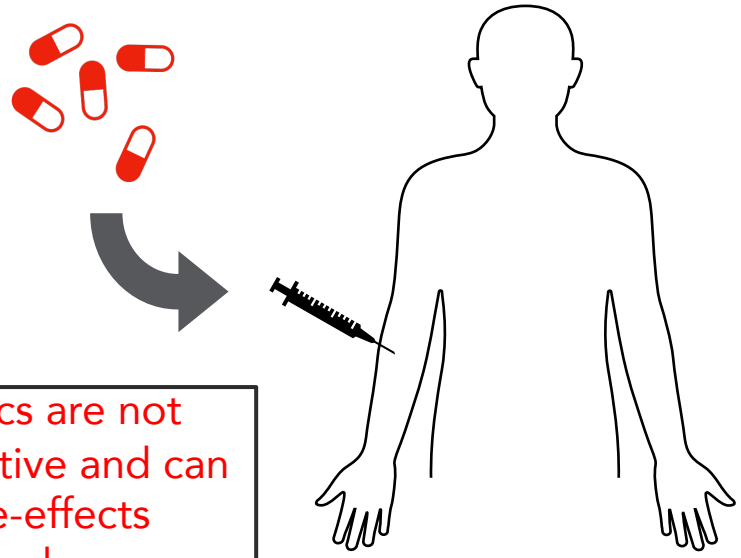


Antibiotics are not preventative and can have side-effects when relied upon.

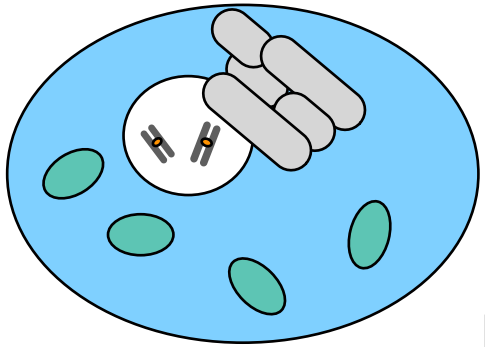
- **There is an urgent need for cost effective, curative treatment for XLA with limited off target effects.**

Technology Overview

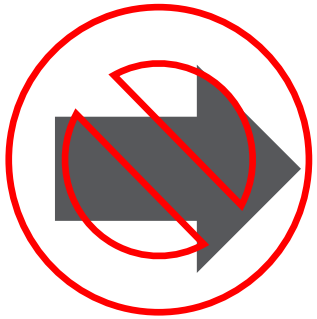
XLA Inhibits Maturation of Immune B Cells

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

XLA – Affected Pre-B Cell

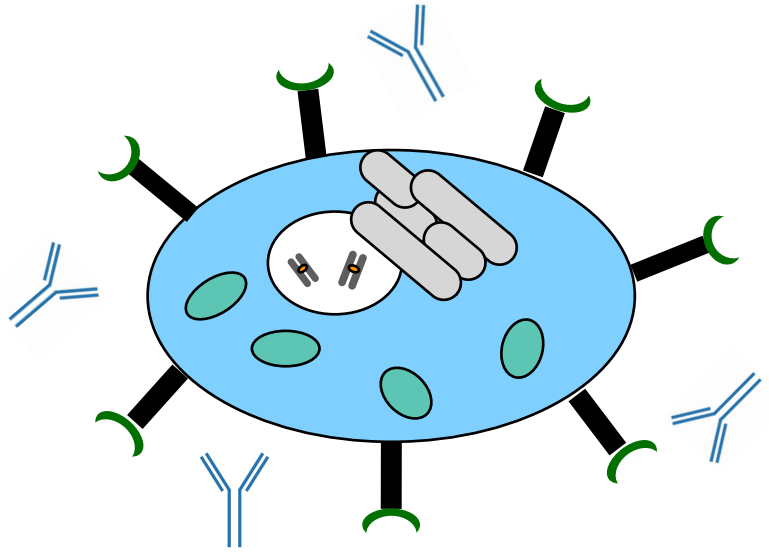


Process Blocked in XLA



BTK-dependent Maturation

Mature B Cell

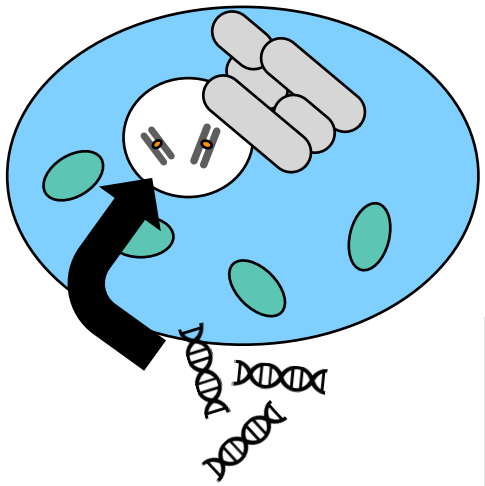


Antibody Production and Clearance of Infection

Gene Therapy Intervention Could Cure XLA

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

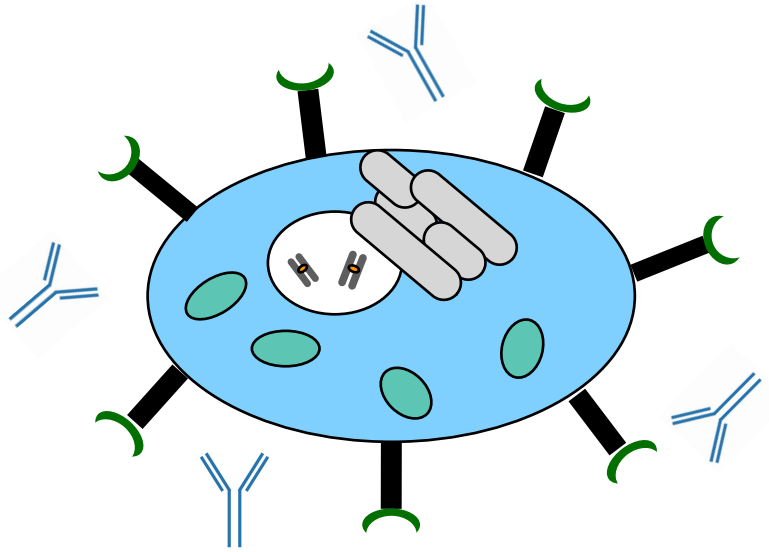
XLA – Affected Pre-B Cell



Gene Therapy Intervention

BTK-dependent Maturation

Mature B Cell



Antibody Production and Clearance of Infection

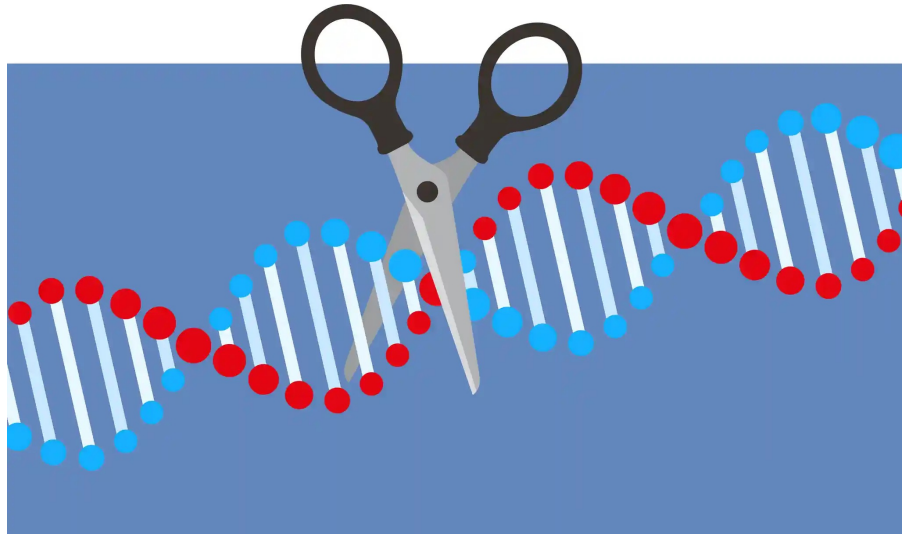
Advantages Over Other Gene Therapy Methods

1

Complications of Gene Therapy
1. Adverse host immune responses
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
2. Insertional Mutagenesis
3. Failure of Transgene Expression
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.**

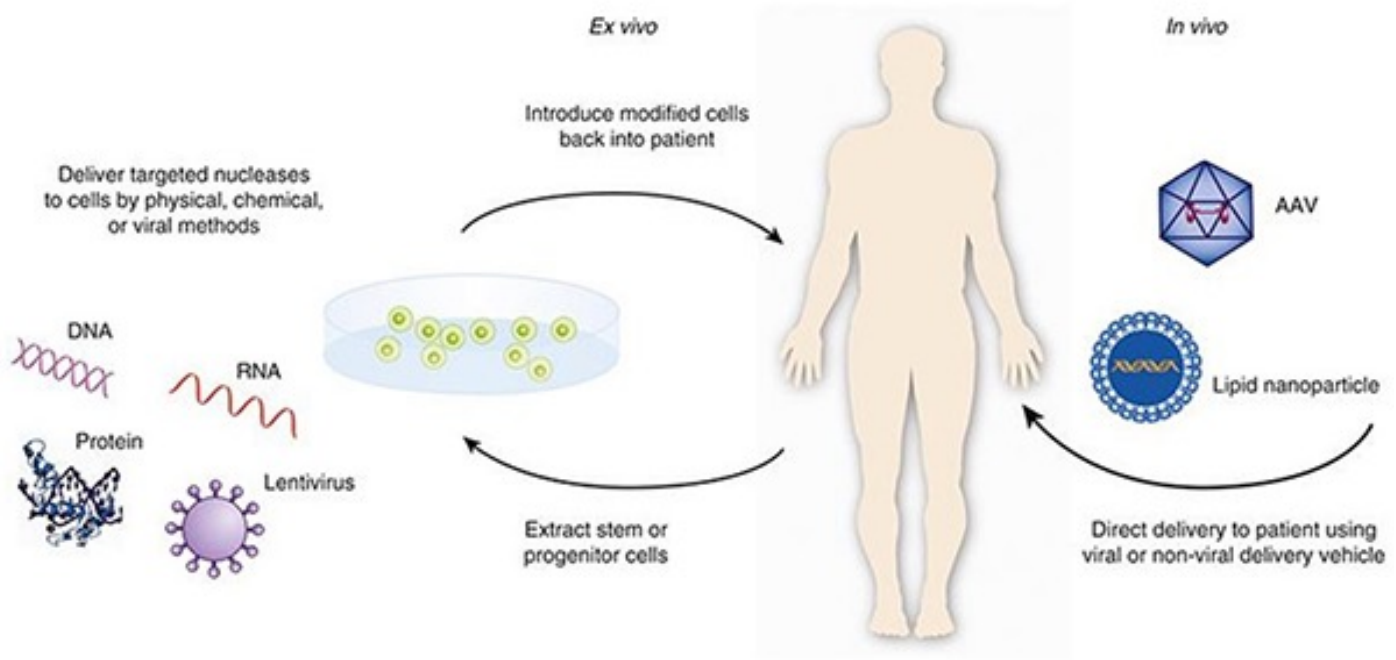


2

[1] Swystun, L. L. & Lillicrap, D. Gene Therapy for Coagulation Disorders. *Circ Res* **118**, 1443–1452 (2016).
[2] The Guardian, After the Novel what's next for Crispr gene-editing therapies?; https://www.theguardian.com/science/2021/feb/21/after-the-nobel-what-next-for-crispr-gene-editing-therapies

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.

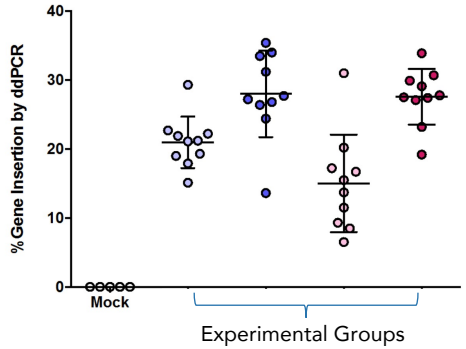


- Novel XLA-treating gene therapy method can be used to modify stem cells *ex vivo* for reintroduction into patient's body.

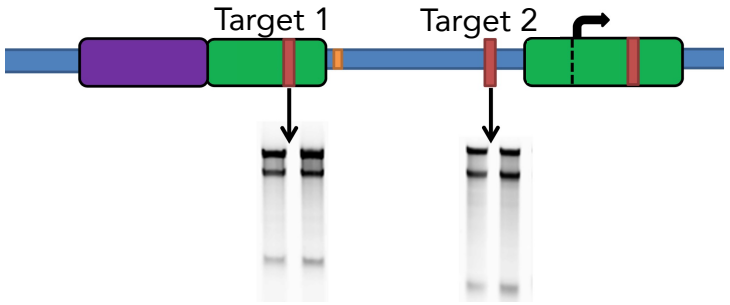
[1] U.S. Food and Drug Administration, Gene Therapy; https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/what-gene-therapy

Developmental Timeline of Technology

July 2015:
Initial Conception.

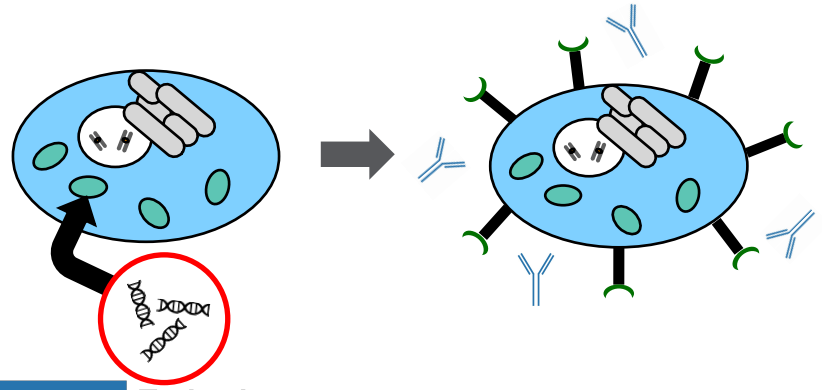


Demonstration of effectiveness at editing gene linked to other X-linked disorders

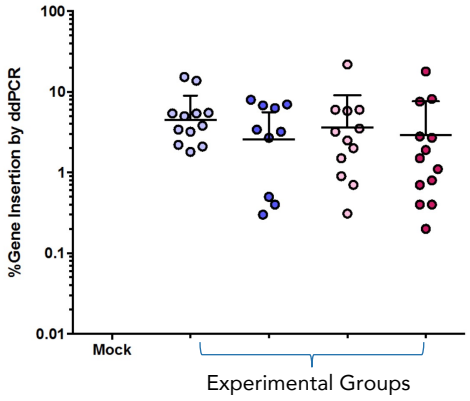


Development of BTK-targeting gene therapy

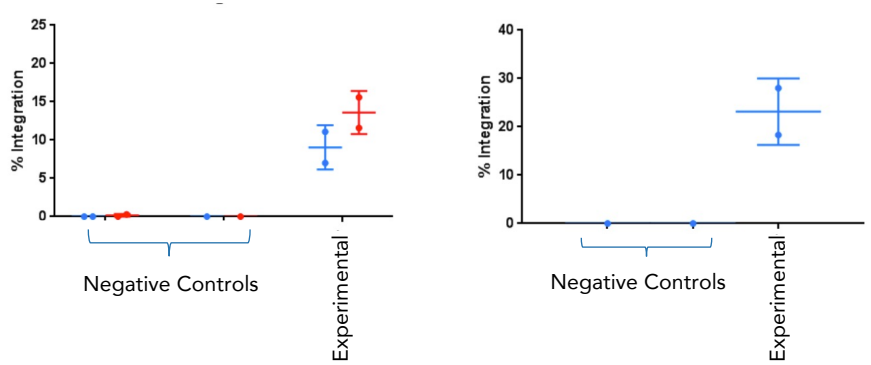
Development of novel gene editing platform



Demonstration of effectiveness of technique *in Vivo*



Demonstrated technology efficiently edits BTK gene



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Market Opportunity

Market Overview: Generalized Market

BCC Research
Report Code: BIO159A

Global Marker 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

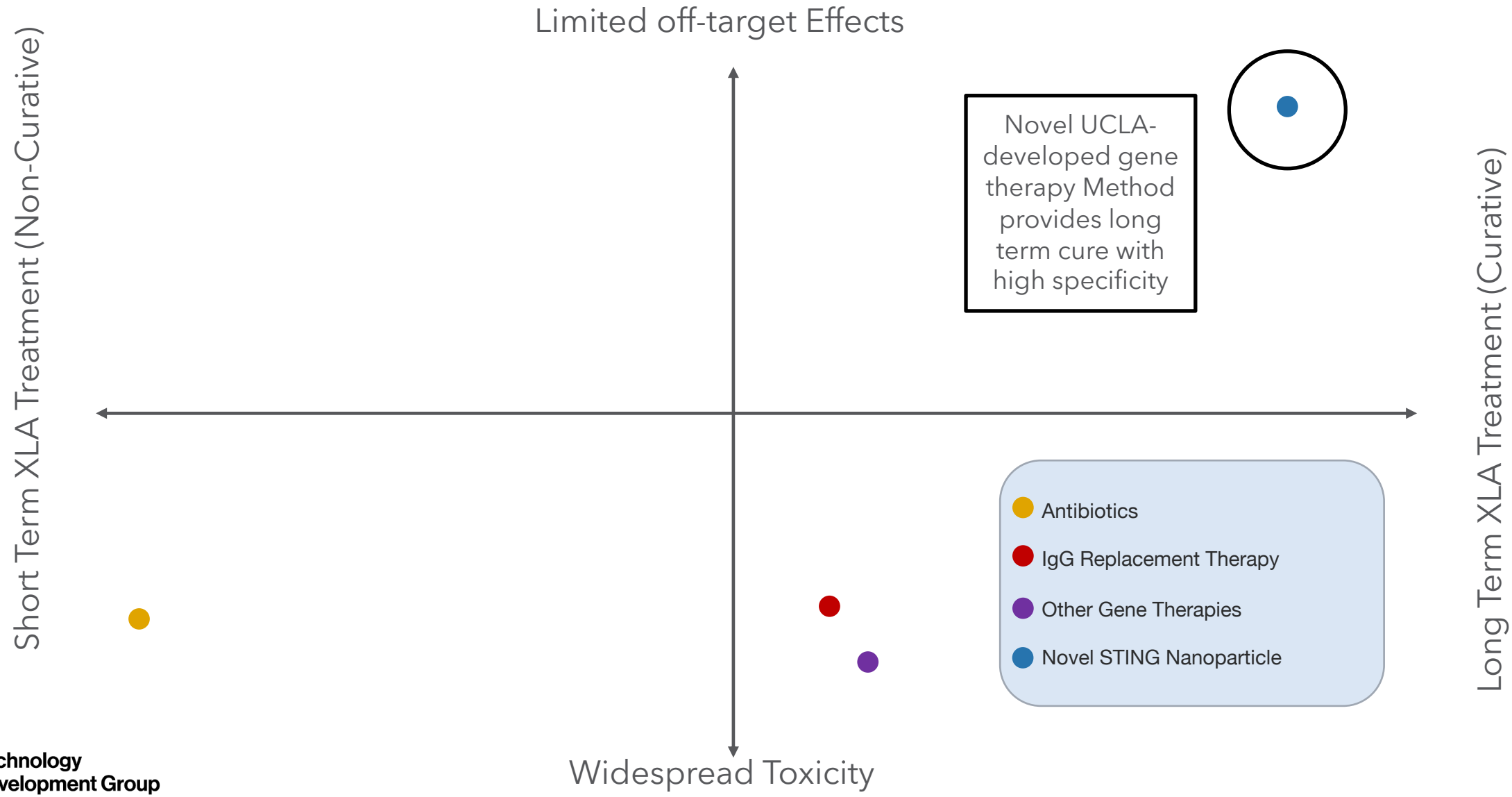
Global Market for Genetic Modification Therapies, by Region, Through 2023

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:

Roche
NOVARTIS
Spark THERAPEUTICS
GILEAD Creating Possible
Johnson & Johnson
MERCK
TaKaRa
SANOFI
Pfizer

Comparisons with Existing Innovations in Cancer Therapeutics



Commercialization Potential

Novel UCLA Gene Therapy Treatment will Revolutionize Clinical Intervention for XLA

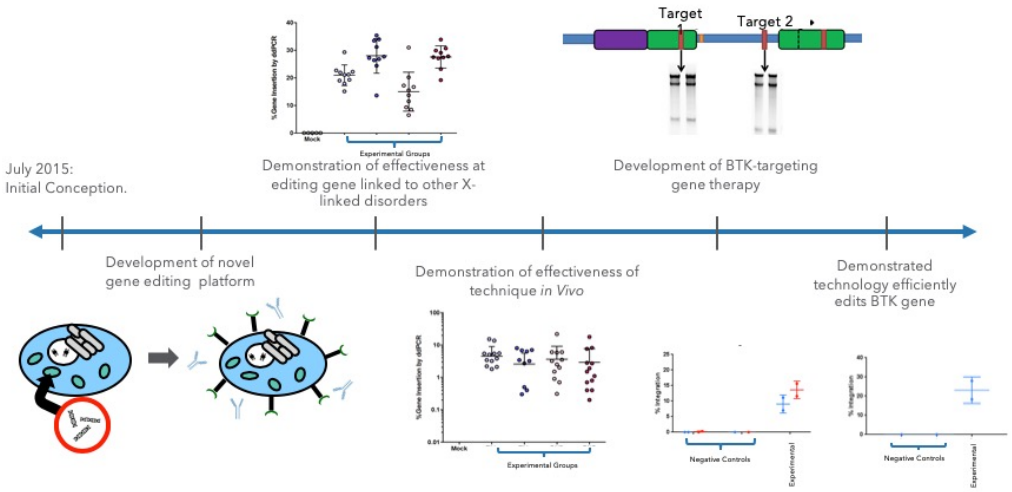
There is a dire need for a drug that cures XLA with high efficiency and low toxicity

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

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Thank You

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