



Gene Therapy for Rare Diseases Using Modification of HSCs

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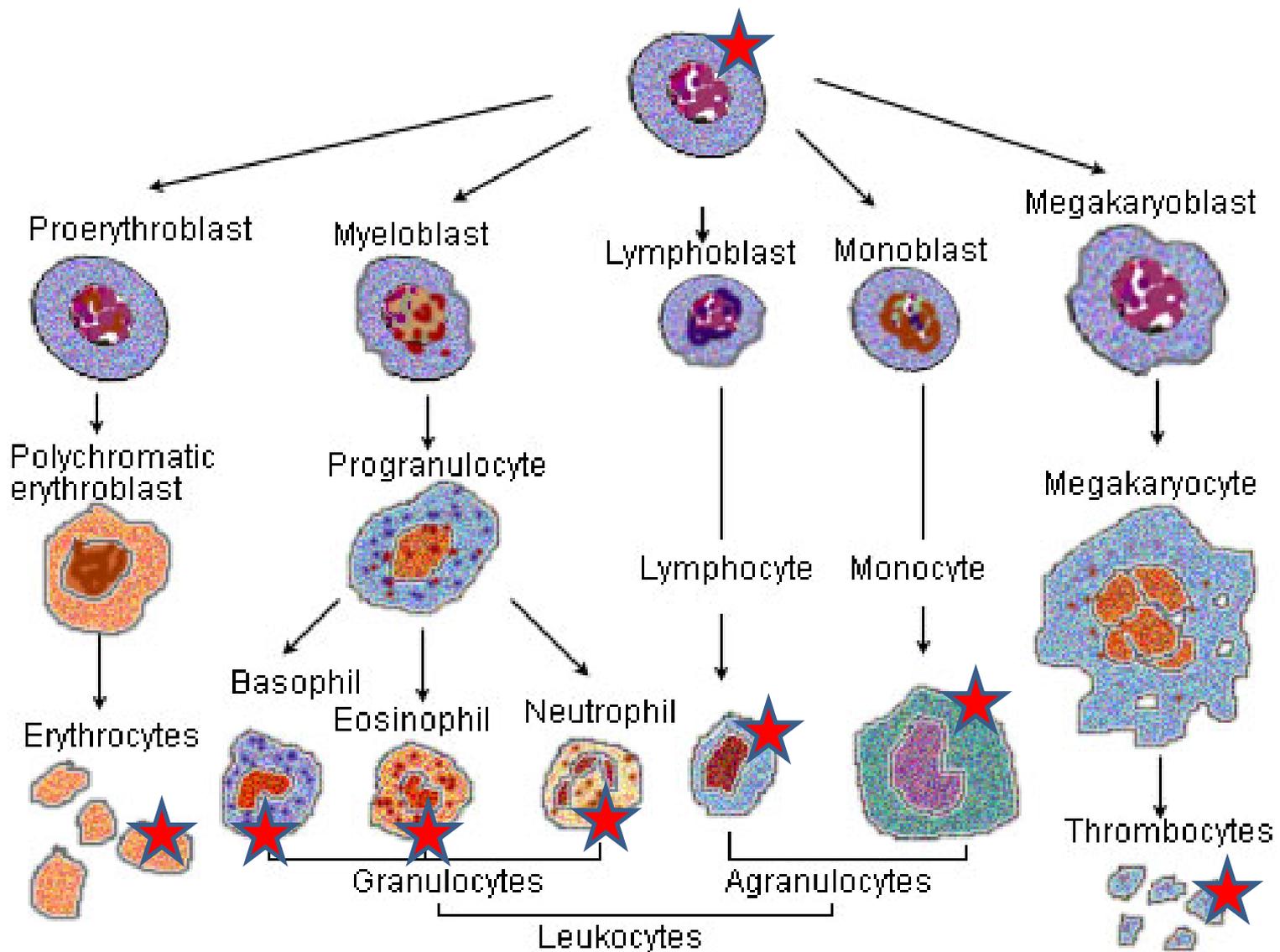
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Outline

- 1. Therapeutic Approach**
- 2. Drug Definition**
- 3. Current Target Diseases**
- 4. Gene Therapy for ADA- SCID**
- 5. Challenges**
- 6. Valuable Resources**



Strategy:

modification of hematopoietic stem and progenitor cells
for transgene delivery

Drug Definition

**autologous bone marrow (BM) CD34+ cells
transduced *ex vivo* with a transgene-carrying vector**

Current Target Diseases

- **ADA- SCID**
- **X-SCID**
- **X-ALD**
- **Sickle Cell, β -Thalassemia**
- **Cancer Immunotherapy**
 - **Exogenous TCR**
 - **Chimeric Antigen Receptors**

ADA-deficient SCID

- Inherited immunodeficiency caused by deficiency of adenosine deaminase enzyme
- T-, B-, NK-
- Incidence: 1 in 200,000 live births
- Approximately 15-20% of all SCID cases
- Treatment:
 - Allogeneic or haploidentical HSCT
 - MSD: >90% successful
 - MUD or haplo: 55-75%
 - Enzyme Replacement Therapy
 - Gene Therapy

Gene Therapy for ADA-SCID

Year	Site	Cell Type	PEG-ADA	Pre-transplant Conditioning	Clinical Benefit (#benefited/#treated)
1990	Bethesda, U.S.	T	Continued	N/A	No (0/2)
1993 1995	Milan, Italy	T + BM	Continued	No	No (0/6)
1993	Netherlands/UK	BM	Continued	No	No (0/3)
1993	L.A./Bethesda, U.S.	UCB	Continued	No	No (0/3)
1996	Hokkaidō, Japan	T	Continued	N/A	No (0/1)
2000	Milan, Italy	BM	No	Busulfan (4 mg/kg)	Yes (15/18)
2003 2004	Hokkaidō, Japan	BM	No	No	?/2
2002	London, UK	BM	No	Melphalan (n=5, 140 mg/m ²) Busulfan (n=1, 4 mg/kg)	Yes (3/6)
2001	L.A./Bethesda, U.S.	BM	Continued	None	No (0/4)
			No	Busulfan (75-90 mg/m ²)	Yes (3/6)
2009	L.A./Bethesda, U.S.	BM	No	Busulfan (90 mg/m ²)	Yes (8/10)

Challenges for gene therapy

- **Vector Design**
 - Persistence of gene modification
 - Efficiency
 - Minimal genotoxicity
- **Selection of optimal cell target**
- **Production of clinical grade vector**
 - Expertise
 - Regulatory steps
 - Expensive
- **Toxicity evaluation of vector**
 - Pharmacological
 - Genotoxicity
- **Large-scale production**

Challenges for clinical trials in rare diseases

- **Experimental disease models**
- **Access to subjects**
- **Evaluation of response/efficacy**
- **Comparison to current therapies**
- **Follow-up**



- **14 centers in the US**
- **Centralized computerized registry**
- **Data collection and management**
- **Design, coordination and execution of clinical trials**





- **Multi-institutional pediatric BMT organization**
- **Includes over 100 centers in the US, Canada, New Zealand, Australia, Thailand and the Czech Republic and over 600 individual members**

Summary

- Gene therapy for rare diseases using modification of HSCs is feasible and can be effective
- Multiple challenges require
 - Continued research in HSC biology and transplantation, gene transfer and regulation, DNA repair
 - Development of large-scale technology for gene transfer
 - Team Science
 - Multi-phase, milestone-driven research support



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