Current State of the Science on Aplastic Anemia Care

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Outline and Objectives

- Aplastic Anemia:
  - Review recent studies on ATG
  - Where does bone marrow transplant fit in the treatment plan?
  - Review newer treatments in refractory AA: Alemtuzumab, Eltrombopag
- Dyskeratosis Congenita
  - Reduced Intensity Conditioning regimens for bone marrow transplant
- Diamond-Blackfan Anemia:
  - Appraise the rationale for Leucine treatment in DBA
  - Explore other possible therapeutic interventions?

1. Aplastic Anemia

ATG therapy

- Standard therapy is still horse ATG over 4 days with Cyclosporine

- Consistent recovery rates across multiple studies in different countries using different horse ATG preparations
  - Response rates of 60-77%
  - Overall survival 80-93%
- Slower Cyclosporine taper reduces relapse rate

Rabbit ATG

- Generally used in children with AA who fail to respond to hATG or who relapse after hATG
  - 60-70% response
- Can it be used as first line ATG choice?
  - hATG not available in Europe, Japan, Latin America
  - More potent immune suppressor – more efficiently depletes peripheral lymphocytes
  - Induces regulatory T cells in tissue culture – beneficial in suppressing harmful immune response

Comparative ATG Study

- Scheinberg et al. NEJM 2011; 365:430-8
- Randomized 120 patients to either hATG or rATG
- 30 children (12 got hATG, 18 got rATG)

	Response (3 mo)	Response (6 mo)	Overall Survival
hATG	62% (49-74)	68% (56-80)	96% (90-100)
rATG	33% (21-46)	37% (24-49)	76% (61-95)
p-value	0.002	<0.001	0.04

Comparative ATG Study

- Unexpected result given rATG effectiveness in relapsed and refractory situations
- rATG may be too potent in depleting lymphocytes?
  - Deplete the cells that may play a role in hematologic recovery and immune tolerance
  - While more regulatory T cells were present compared to hATG, the absolute number was still quite low

How is ATG Generally Used?

- hATG + Cyclosporine is first line therapy if no full sibling match is available for bone marrow transplant
- Better likelihood of response if:
  - Younger age
  - Male
  - Higher number of young red blood cells and lymphocytes pre-treatment
  - Treating as soon as possible after diagnosis

How is ATG Generally Used?

- In children with relapse following initial response
  - 60-70% response to rATG

- Third course of ATG generally not successful and not recommended

Bone Marrow Transplant

What we know

- Transplant with a matched sibling donor is the first treatment of choice in children
  - 85-97% survival rate

- But…..
  - Graft rejection – 5%
  - Acute graft vs host disease – 10%
  - Chronic graft vs host disease – 30%
  - Not available in many parts of the world

Samarasinghe & Webb, Br J Haematol 2012; 157:26-40

What about Unrelated Donor BMT?

- Considered in children who fail IST
- Improved outcomes over time due to:
  - Use of leukodepleted blood products
  - Improved tissue typing techniques
  - Using bone marrow as stem cell source (rather than peripheral blood stem cells)
  - Better conditioning regimens

What about Unrelated Donor BMT?

- Outcomes approaching those seen in sibling match BMT
  - Overall survival approaching 95%
  - Low acute and chronic GVHD rates using conditioning with alemtuzumab base

Socie G, Hematology 2013 2013:82-86
Marsh & Kulasekararaj, Hematology 2013 2013:87-94
Kennedy-Nasser et al. Biol Blood Marrow Transplant 2006; 12:1277-1284
Kosaka et al. Blood 2008; 111:1054-1059

Newer agents in refractory AA

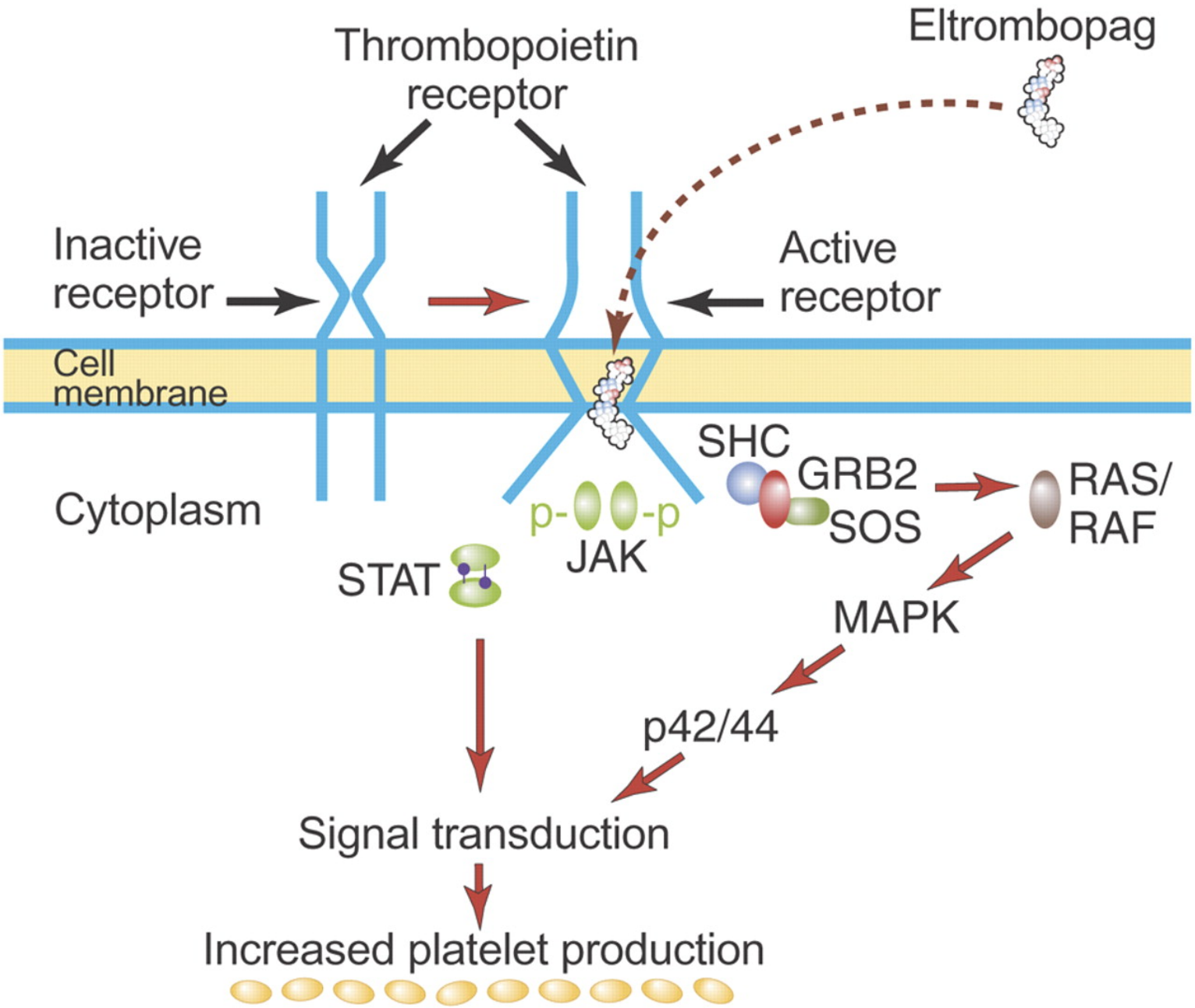
Alemtuzumab

- Comparable outcomes to rATG in recent randomized trial
  - Hematologic response in 30-40%
  - May have role in those with cyclosporine toxicities who need further therapy
  - Long term data needed

Scheinberg et al. Blood 2012; 119:345-354

Eltrombopag

- Small molecule that binds to platelet precursor cells in the bone marrow
  - Via cell receptor involved in stimulating platelet production
- Oral medication
- Used in immune thrombocytopenia
- No major side effects


Eltrombopag
Thrombopoietin receptor
Inactive receptor
Active receptor
Cell membrane
Cytoplasm
SHC
GRB2
SOS
RAS/ RAF
p- -p
JAK
STAT
MAPK
p42/44
Signal transduction
Increased platelet production

Eltrombopag

- Growth factors for all 3 cell lines elevated in AA
  - Why erythropoietin doesn't help anemia substantially
  - Why GCSF not overly beneficial

- But pilot study shows response!

Eltrombopag Pilot

- Olnes et al. NEJM 2012; 367:11-19
- 25 adult patients with refractory AA (ages 18-77)
- 11 (40%) responded at 12 week evaluation based on peripheral blood counts
- 3 of 4 followed past 8 months had normalization of bone marrow cellularity

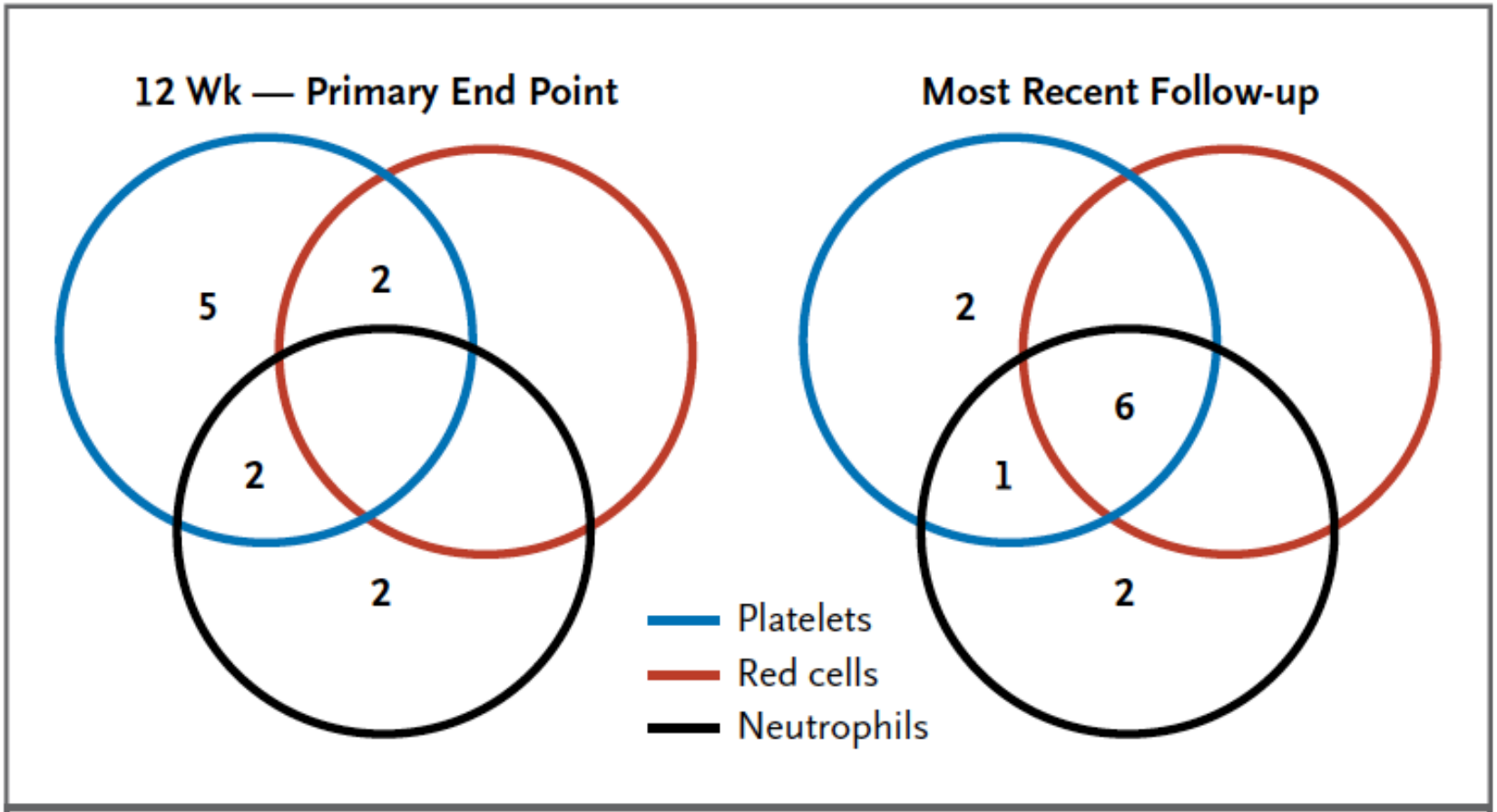
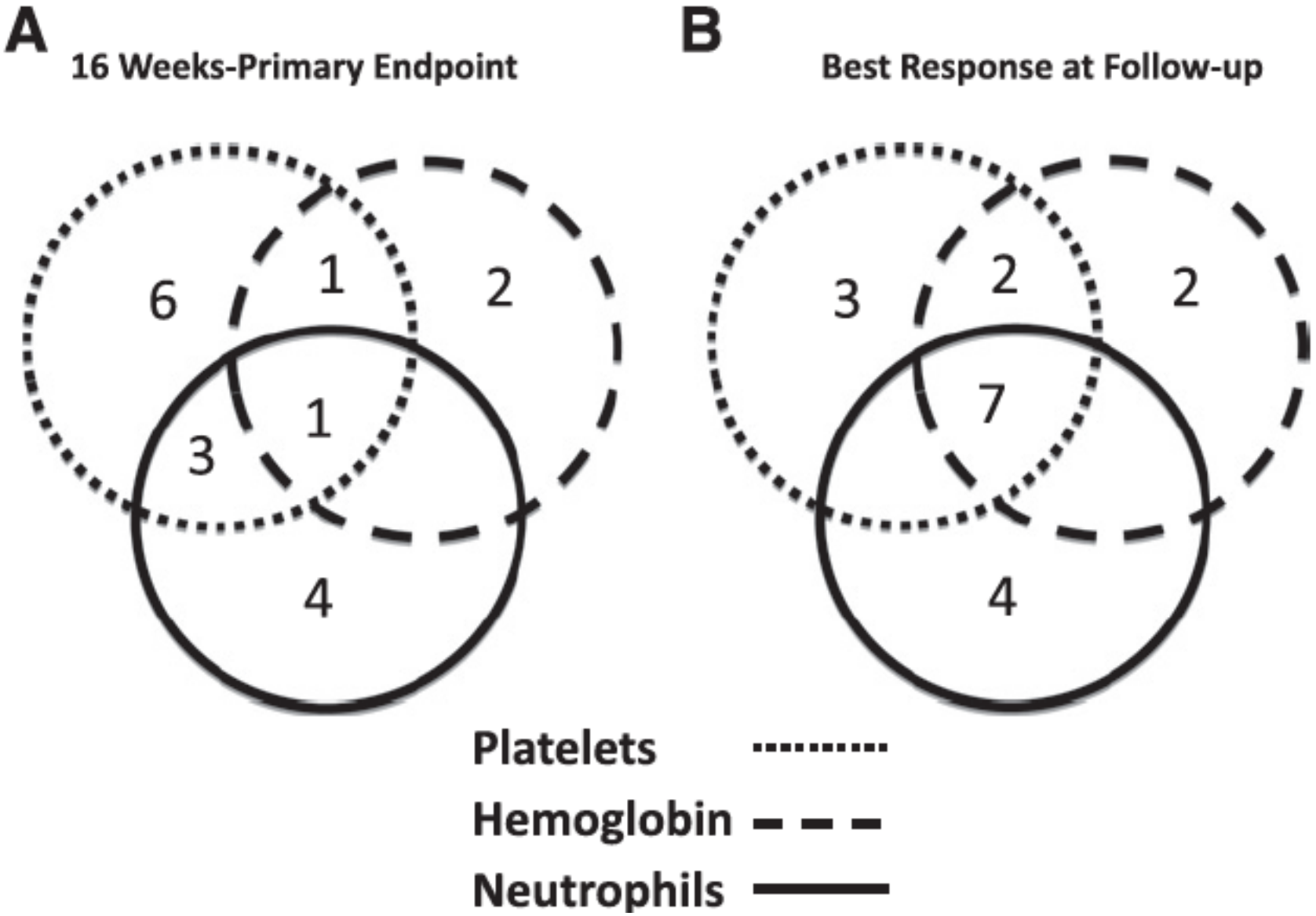


Figure 1. Lineage Characteristics of Responses to Eltrombopag.

The Venn diagrams show the numbers of patients with unilineage, bilineage, and trilineage hematologic responses. The numbers of patients with a response and their response pattern at 12 weeks are shown on the left. The numbers of patients who met the response criteria at the most recent follow-up assessment are shown on the right.

Extension Study

- Desmond et al. Blood 2014; 123:1818-1825
- 43 patients, 17 responses (40%) at 3-4 months
- 5 of the responders discontinued drug after being transfusion independent for 8 weeks
  - Taper over 9-37 months, median 28.5 months
  - Counts remained stable off drug (follow up 1-15 months, median 13 months)
  - Normal bone marrow cellularity


A
16 Weeks-Primary Endpoint
6
1
2
3
1
4
B
Best Response at Follow-up
3
2
2
7
4
Platelets
Hemoglobin
Neutrophils

Extension Study

- Clonal evolution in 8 patients
  - 2 responders
  - Concerning
- Low toxicity profile
- Higher baseline reticulocyte count found to be predictive of response

Why does Eltrombopag work in AA?

- TPO receptor also on hematopoietic stem cells and progenitor cells
- Stimulation of receptor with Eltrombopag may expand the pool of stem cells and lead to marrow regeneration
- Does it stimulate abnormal clones as well?

Ongoing Eltrombopag Trials

- Moderate aplastic anemia
- Treatment-naïve aplastic anemia
  - Combined with ATG and CSA

Young NS, Hematology 2013
2013: 76-81

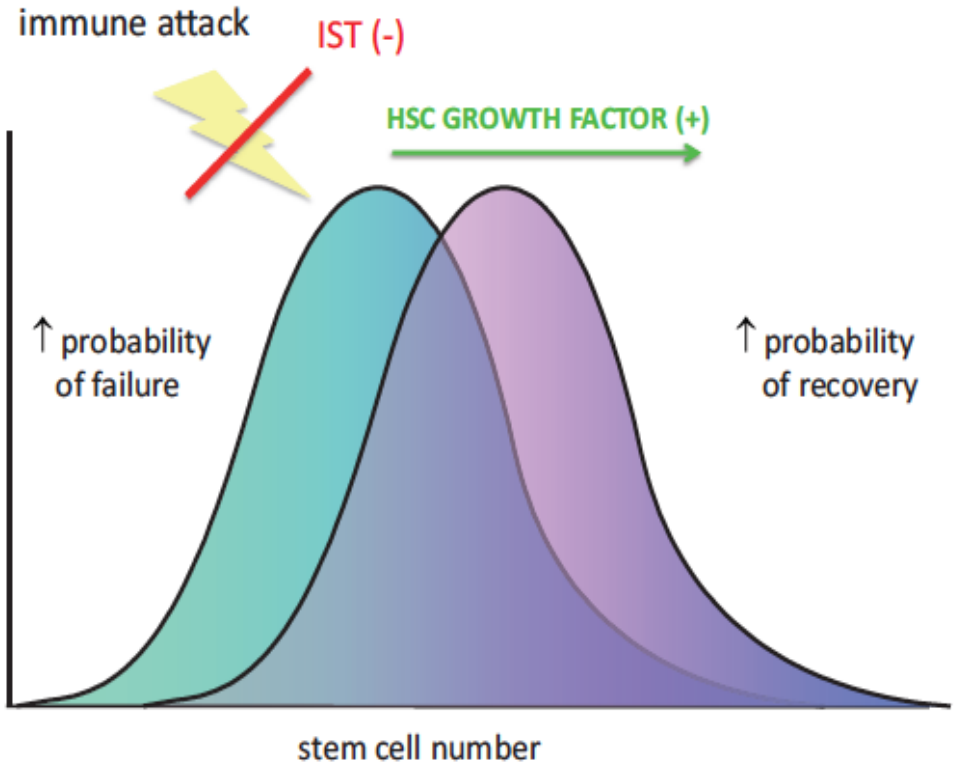
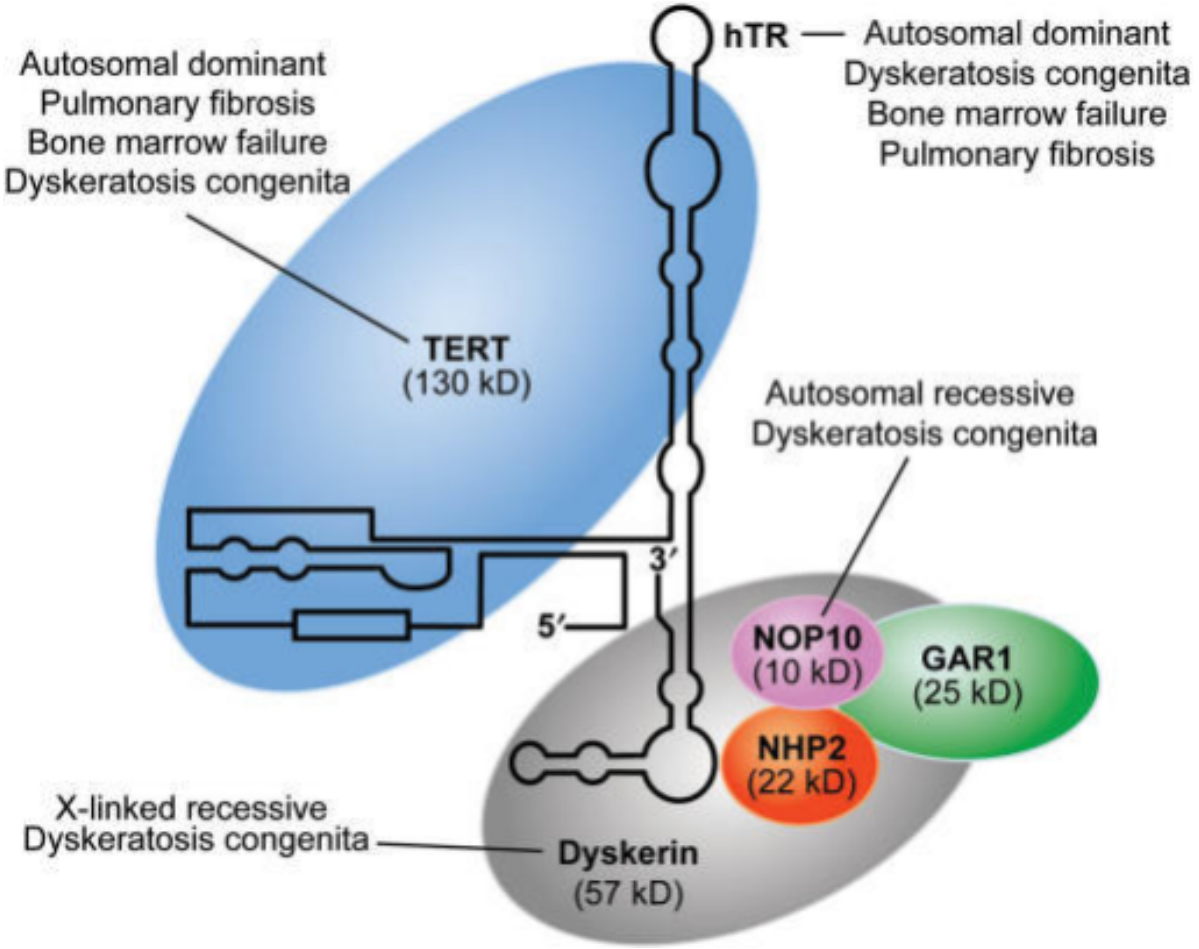
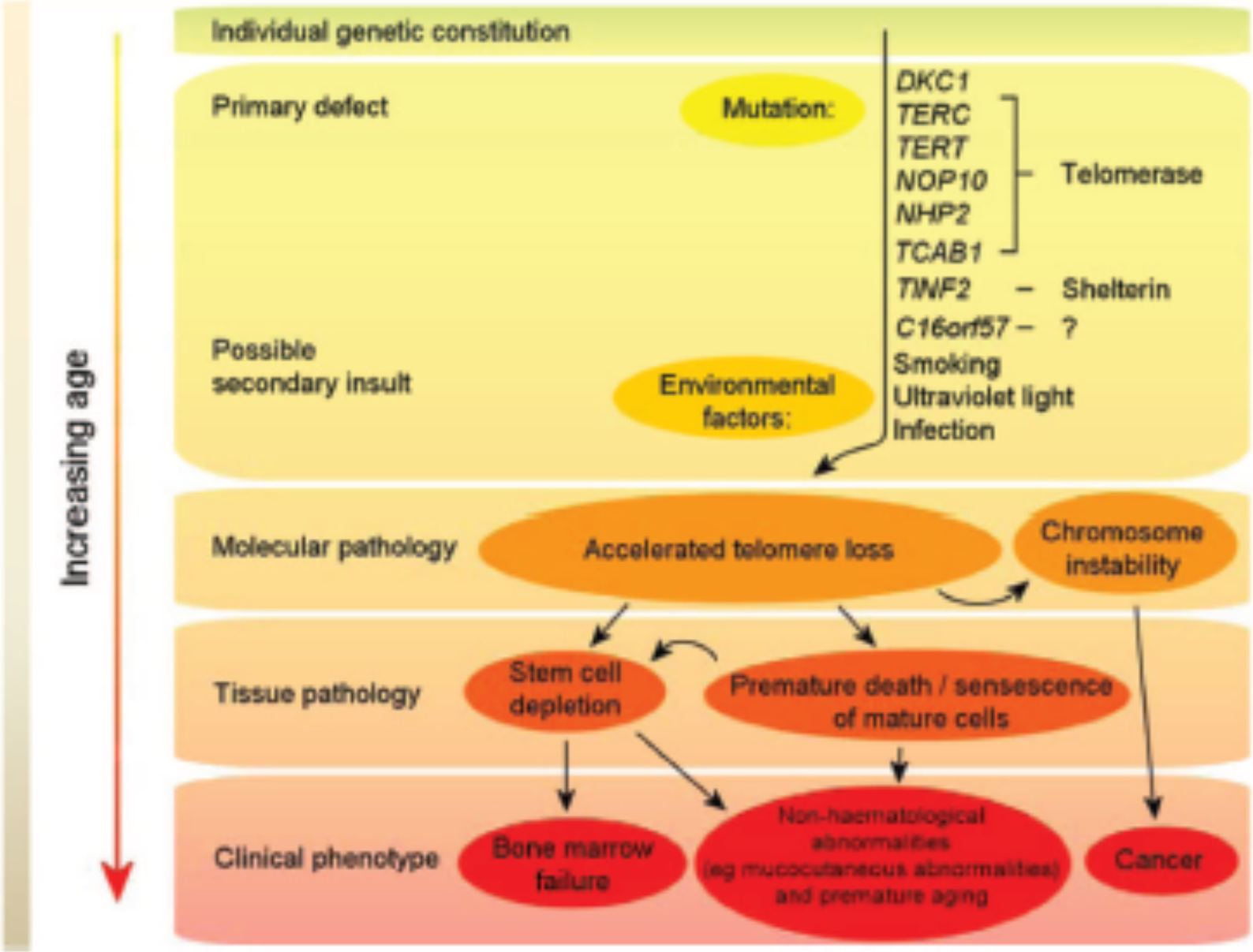


Figure 3. Stem cells as limiting in the response to immunosuppressive therapy. Combining immunosuppressive therapy with a factor that increases stem cell proliferation and/or self-renewal might overcome this limit.



2. Dyskeratosis Congenita


Increasing age
Individual genetic constitution
Primary defect
Mutation:
DKC1
TERC
TERT
NOP10
NHP2
TCAB1
Telomerase
TWF2 – Shelterin
C16orf57 – ?
Possible secondary insult
Environmental factors:
Smoking
Ultraviolet light
Infection
Molecular pathology
Accelerated telomere loss
Chromosome instability
Tissue pathology
Stem cell depletion
Premature death / senescence of mature cells
Clinical phenotype
Bone marrow failure
Non-haematological abnormalities (eg mucocutaneous abnormalities) and premature aging
Cancer

Bone Marrow Transplant

- Only curative therapy for individuals with DC who have bone marrow failure
- PROBLEM: high risk of organ toxicity using:
  - traditional conditioning regimens that completely clear out the bone marrow (myeloablative conditioning)
  - Alternative donor transplant (unrelated, umbilical cord, haploidentical)
- SOLUTION: Reduced Intensity Conditioning
  - Decreased tissue damage and decreased inflammatory response

RIC in DC

- Dietz et al. Bone Marrow Transplantation 2011; 46: 98-104
  - 6 patients transplanted with fludarabine-based RIC
  - Ages 2-25, 5 of 6 received unrelated donor
  - 2 septic deaths early after transplant
  - 4 alive at 12-45 months post-BMT, full donor chimerism
  - Grade II skin aGVHD, Grade IV GI aGVHD, Grade II skin cGVHD
- Nishio et al. Pediatr Transplantation 2011; 15: 161-166
  - 3 patients transplanted with fludarabine-based RIC
  - Ages 9-18, alternate donor sources used
  - All alive with no chronic complications

Conclusions

- Feasible
- Promising
- Needs further exploration, larger numbers

3. Diamond-Blackfan Anemia

Leucine

- Evidence that leucine upregulates components of translational machinery in muscle cells
  - Including ribosomal proteins
- Can the same occur in red cell precursor cells of DBA patients?
  - One published case report of complete response
  - Multiple reports from DBA conferences – steroid reduction, increased time between transfusion
- Ongoing clinical trial to evaluate this in a controlled fashion