Blood 101 – Introduction Blood and Marrow & Overview of Bone Marrow Failure Diseases

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Normal Marrow

- knee joint
- white is articular cartilage
- Adjacent to this is the red marrow

Structure of bone marrow

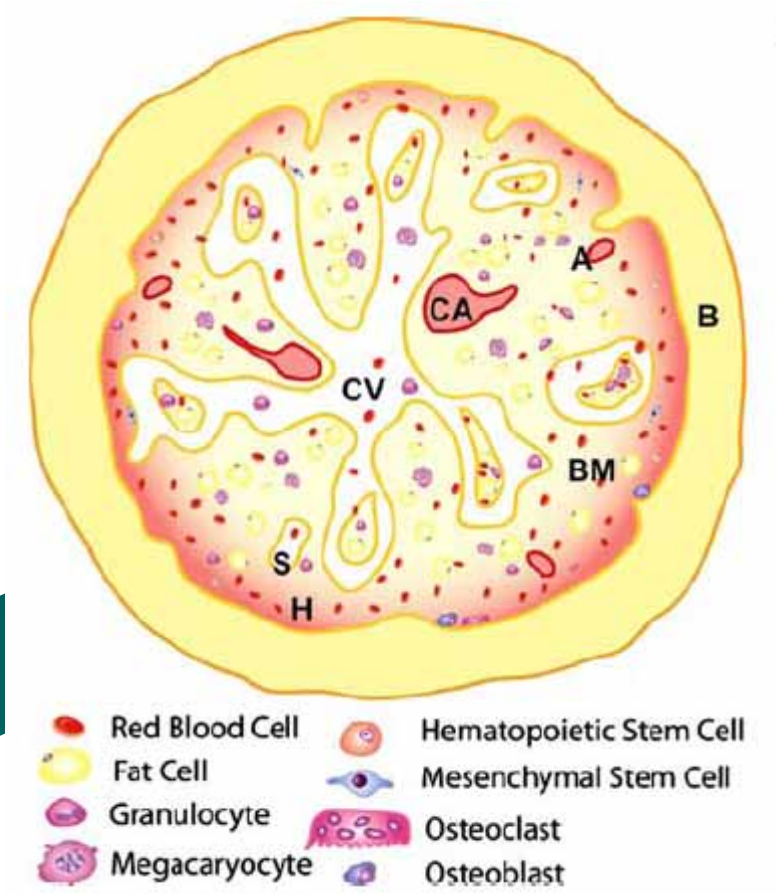
- Contained in
  - Skull, ribs, vertebrae, long bones.
- Divided between
  - fatty tissue (yellow) and blood precusors (red)
- Besides blood precursors other cells
  - Network of support structures (reticular cells)
  - Mesenchymal cells which can produce host of other specialized cells

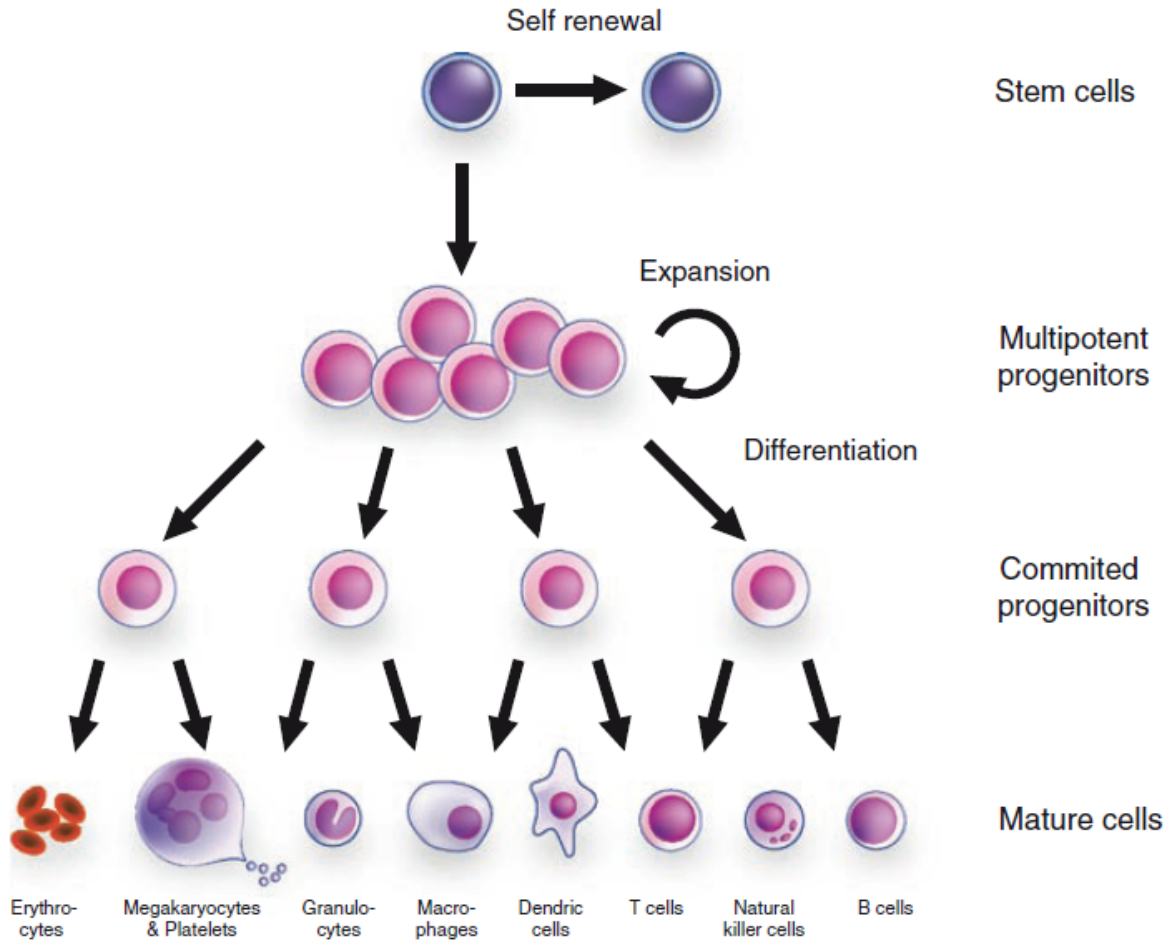
Bone Marrow Structure

- Not organized into uniform layers
- Loosely composed of hematopoietic and mesenchymal (supportive) cells
  - Hematopoietic – can produce all cells of the blood and immune system
  - Mesenchymal - Can produce other supportive cells such as
    - Bone, muscle, fat and nerve cells

Bone Marrow Structure

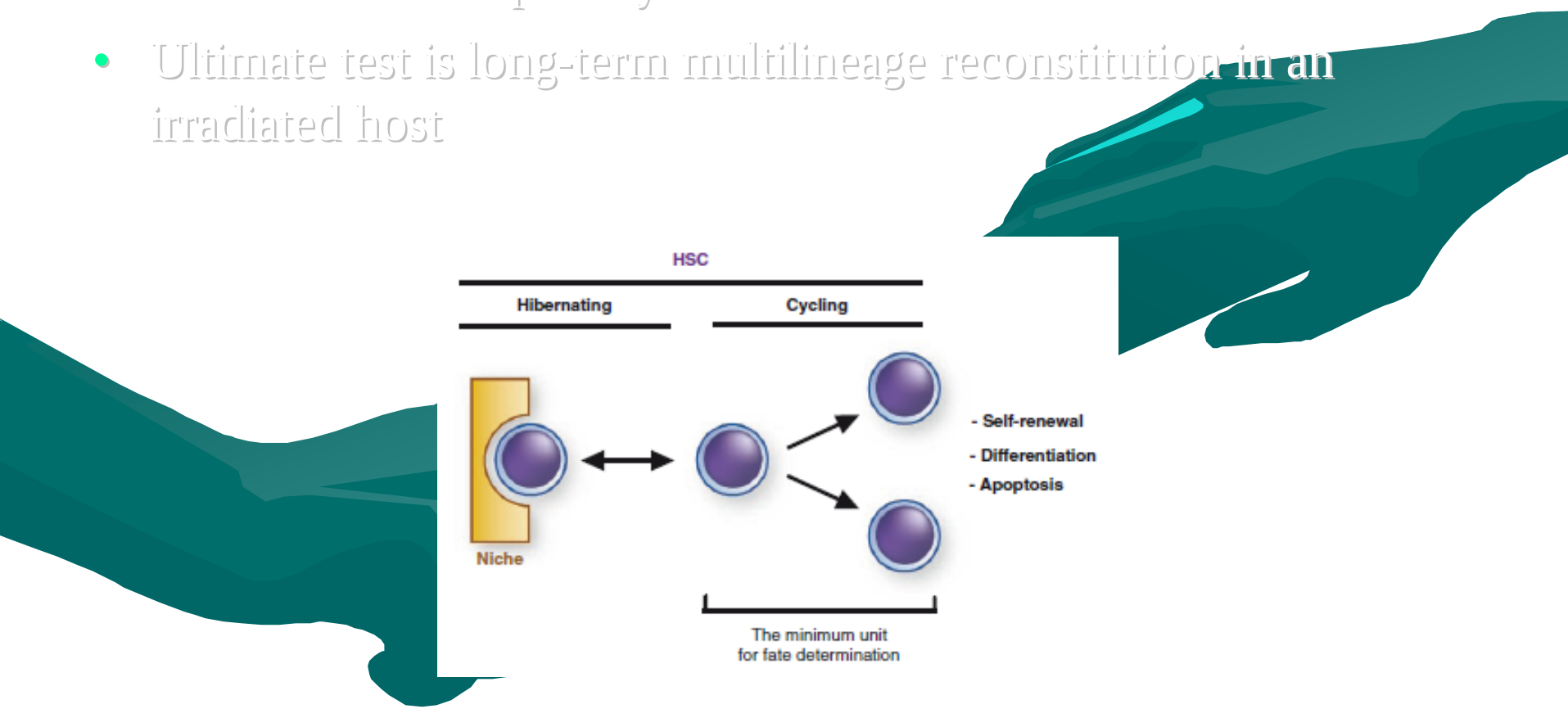
- Main artery runs down center (CV)
- Branches towards bone surface forming sinuses
- Blood then flows back towards the center




Self renewal
Stem cells
Expansion
Multipotent progenitors
Differentiation
Commited progenitors
Mature cells
Erythro-cytes
Megakaryocytes & Platelets
Granulo-cytes
Macro-phages
Dendric cells
T cells
Natural killer cells
B cells

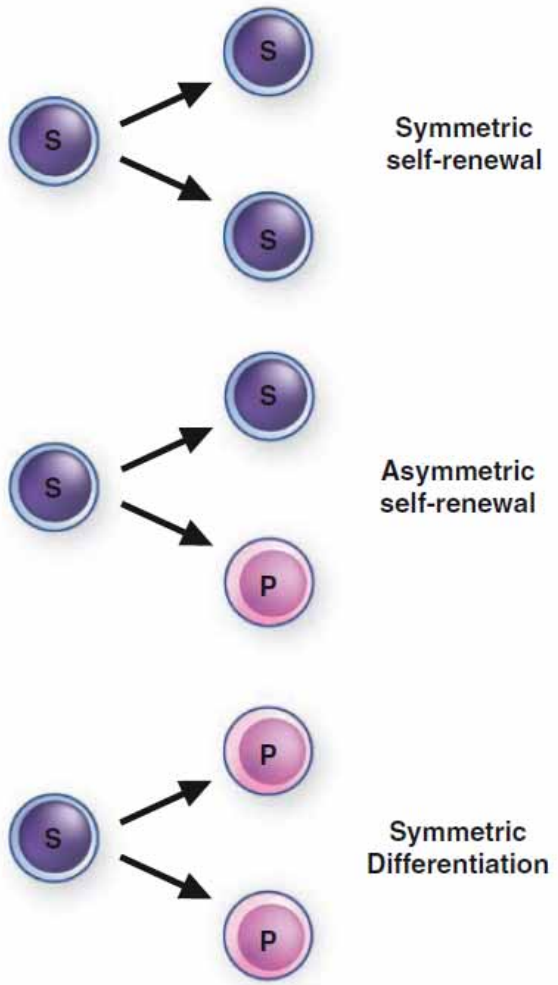
Stem cell

- Self-renewal potential and
- Differentiation capability
- Ultimate test is long-term multilineage reconstitution in an irradiated host



Stem have to make some choices

- Stem cells may have limited number of divisions
- Some have to stay quiescent while others differentiate
- decisions area based on influences outside the cell and within the cell

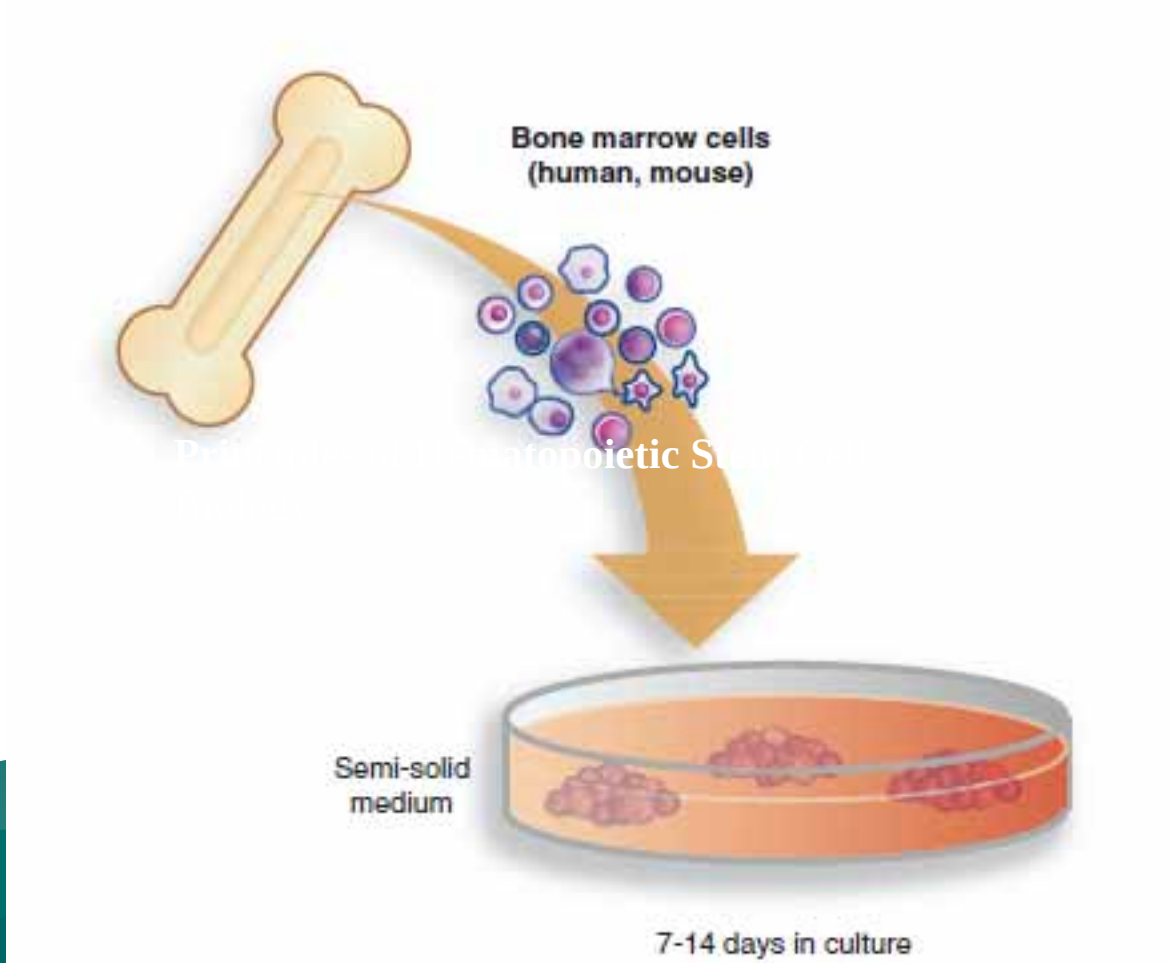


What does this differentiation depend on

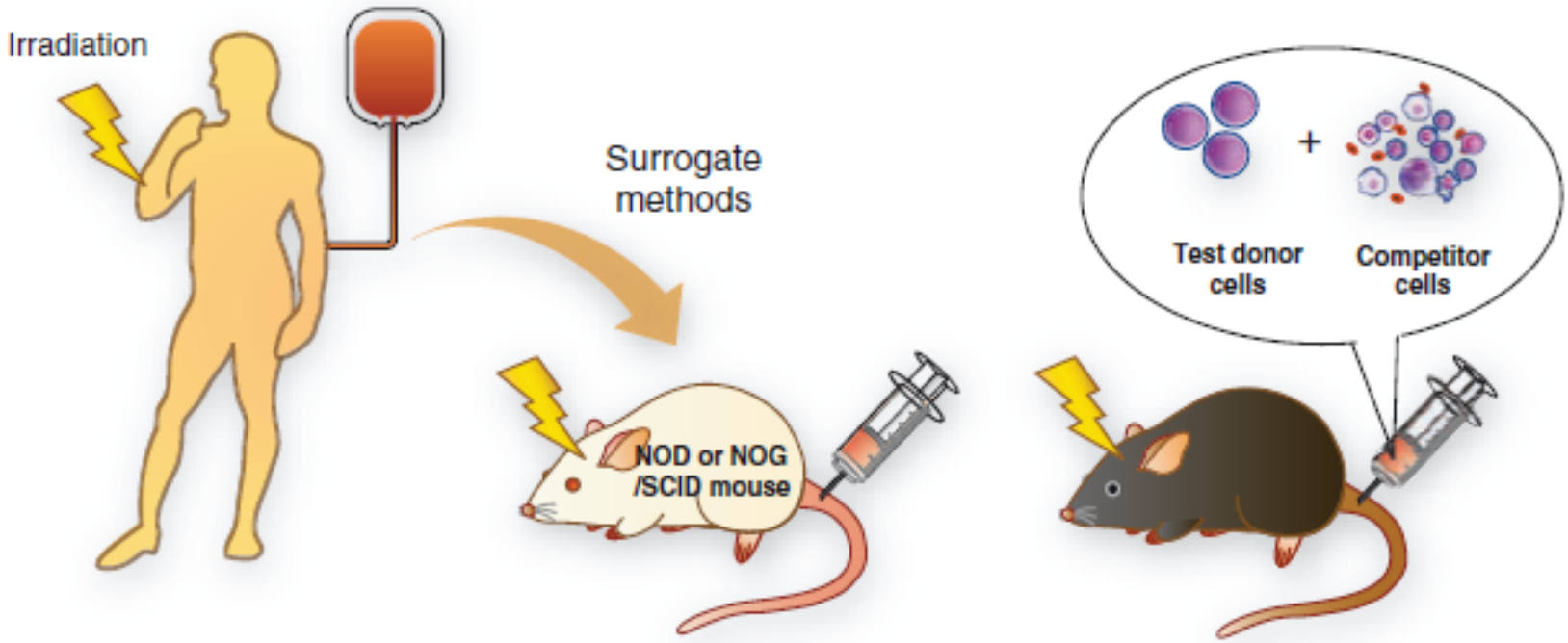
- Genetic material
- Communication tools
- Nutrition support

- How do we know this?
  - In vitro assays
  - Animal models (i.e. mice etc)
  - Human models

In Vitro assays

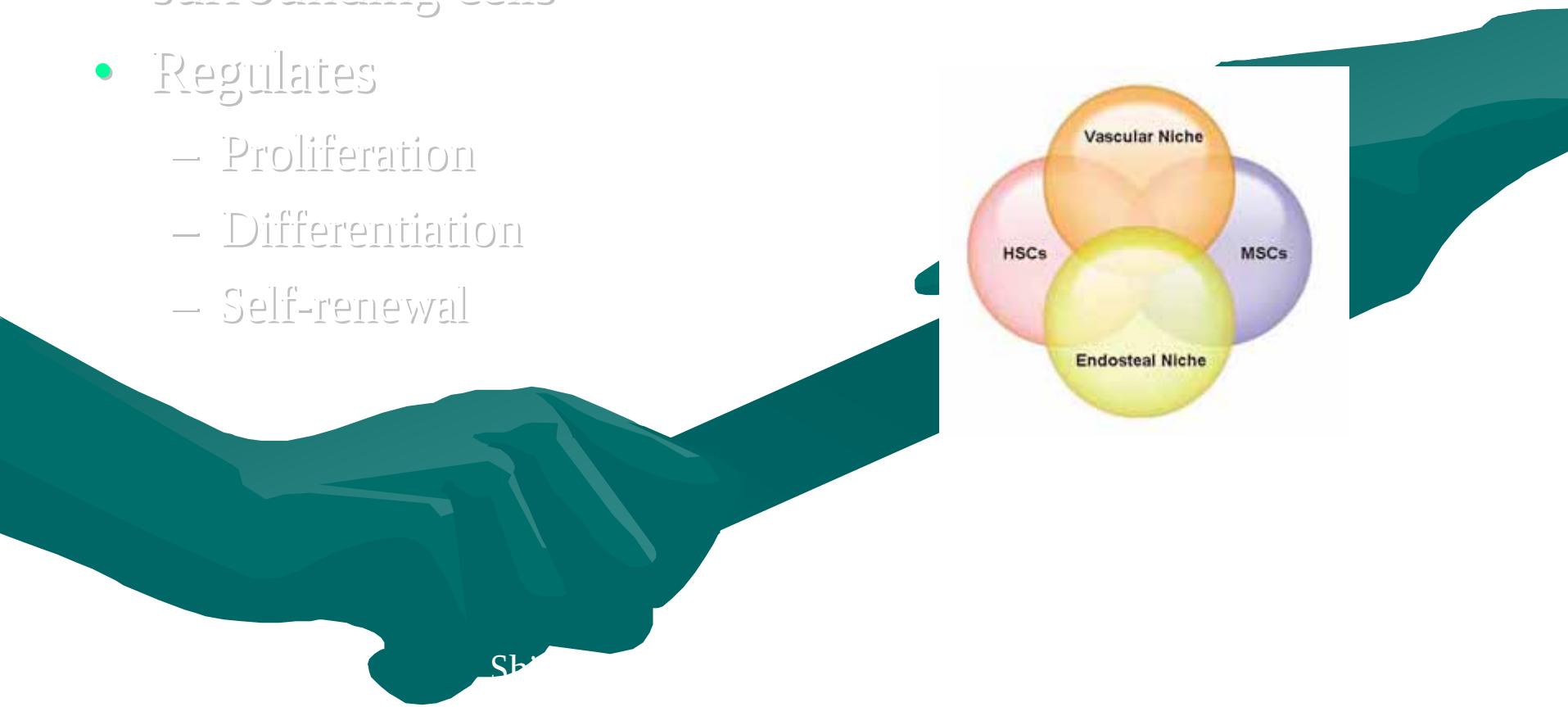


In vivo assays



The niche

- Stem cells influenced by surrounding cells
- Regulates
  - Proliferation
  - Differentiation
  - Self-renewal



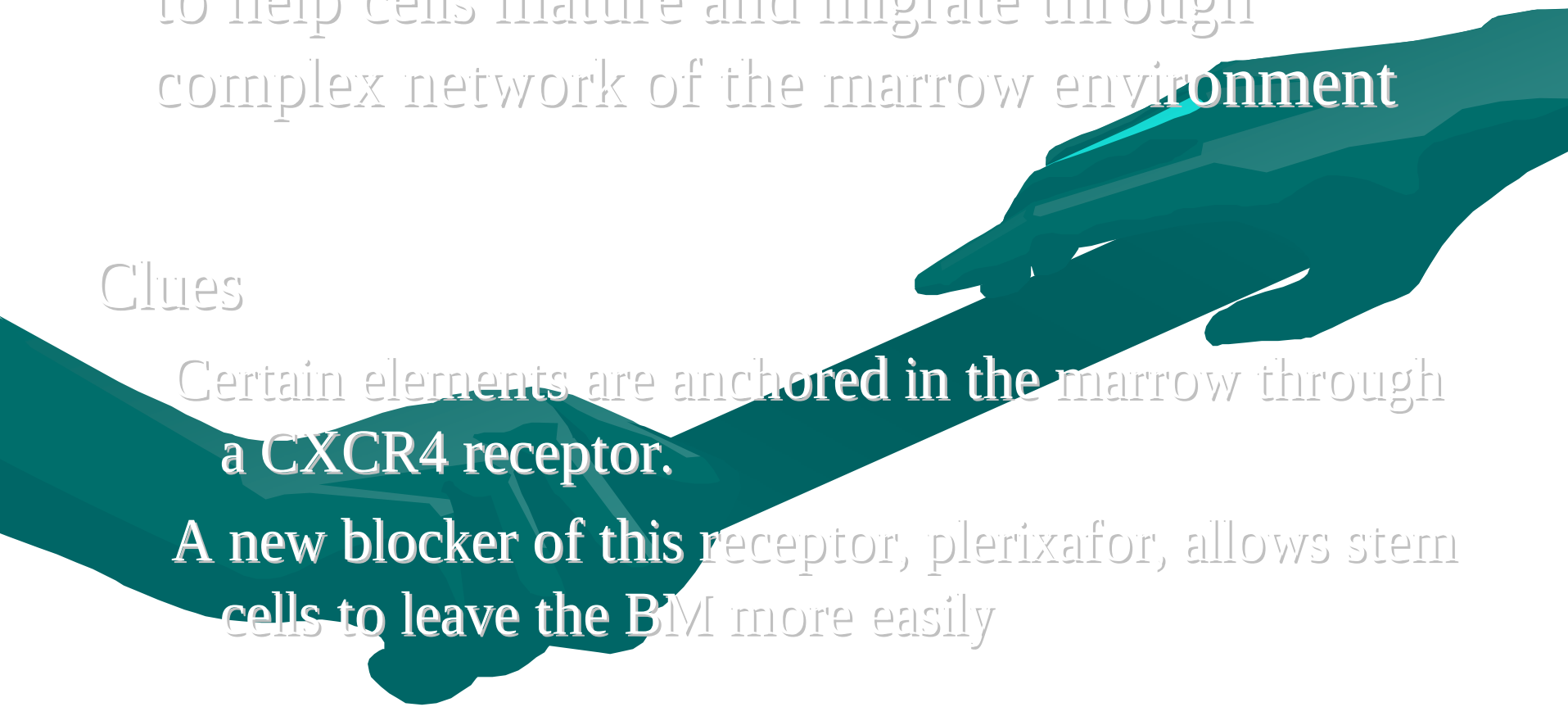
Complex interaction with other cells

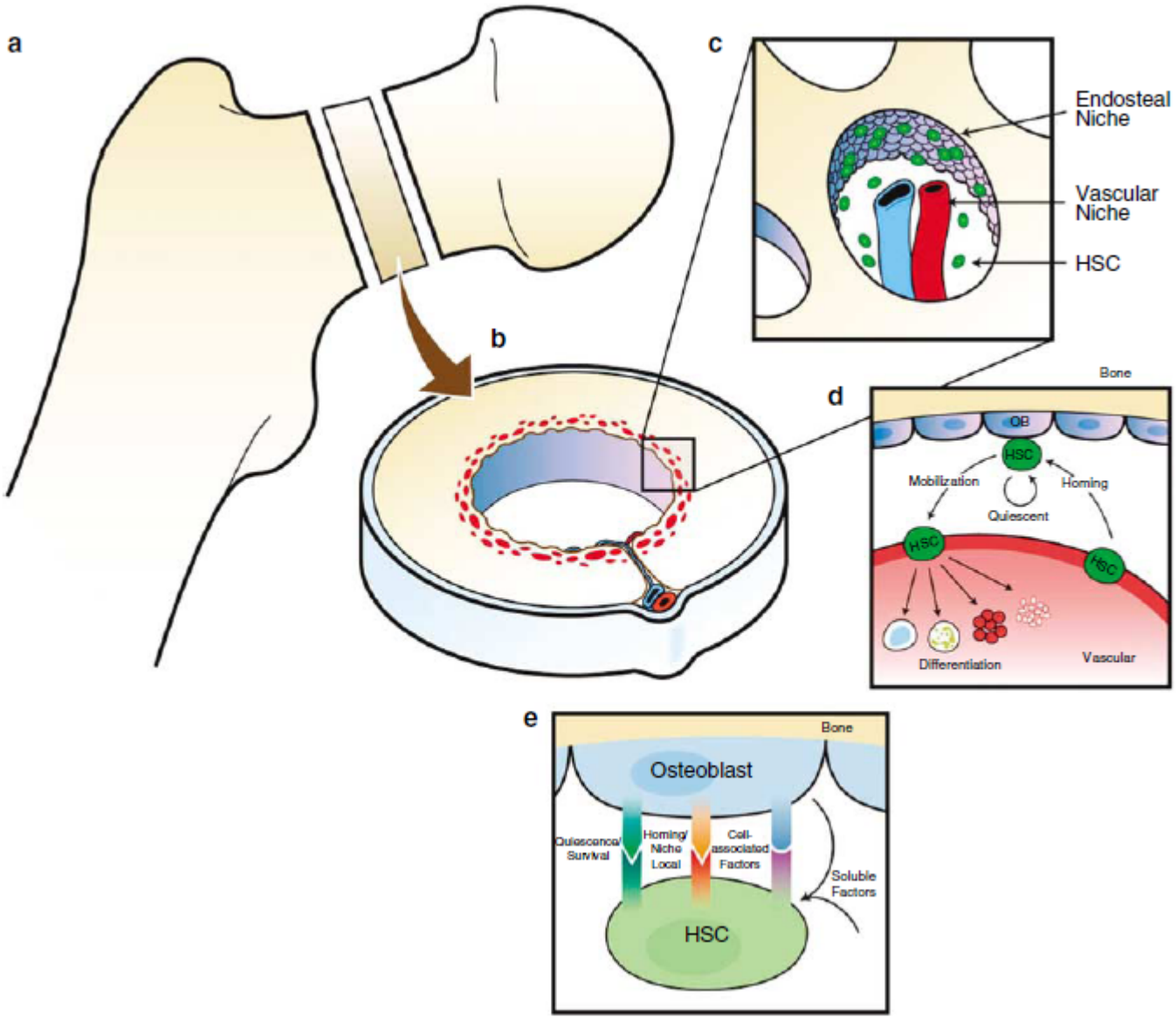
Chemical signals and receptors/antigens combine to help cells mature and migrate through complex network of the marrow environment

Clues

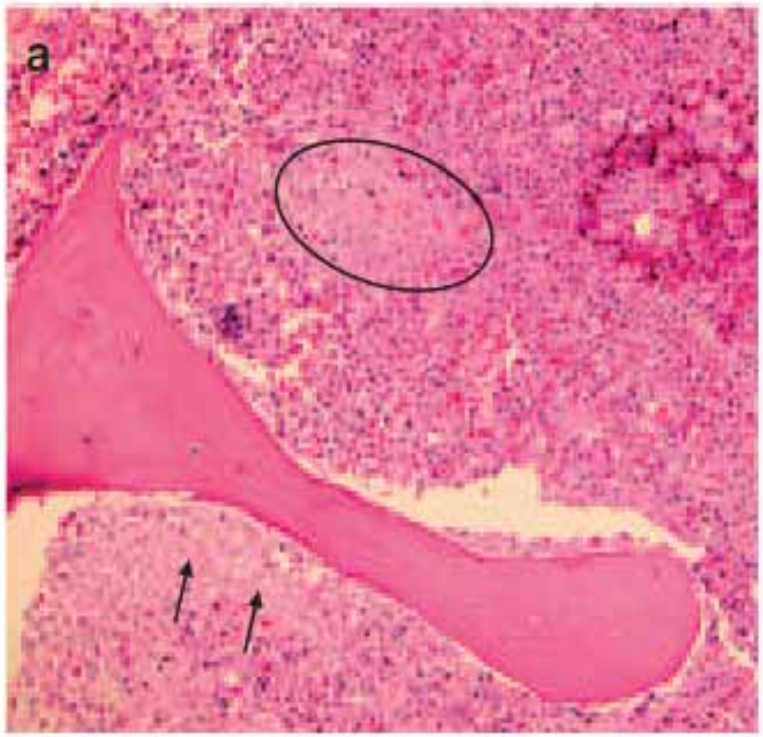
Certain elements are anchored in the marrow through a CXCR4 receptor.

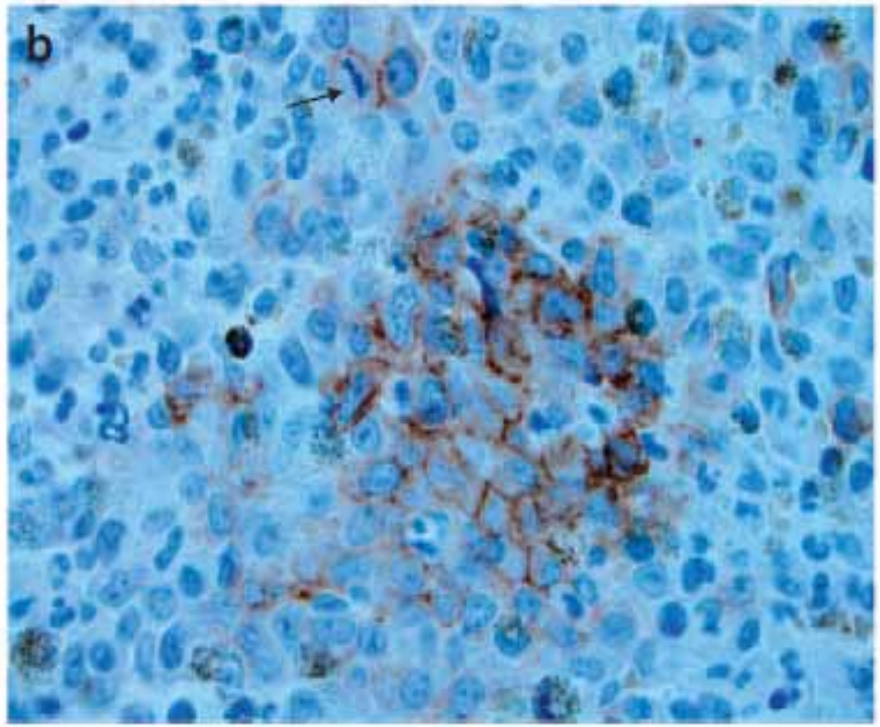
A new blocker of this receptor, plerixafor, allows stem cells to leave the BM more easily




a
b
c
Endosteal Niche
Vascular Niche
HSC
d
Bone
OB
HSC
Mobilization
Homing
Quiescent
HSC
HSC
Differentiation
Vascular
e
Bone
Osteoblast
Quiescence/ Survival
Homing/ Niche Local
Cell-associated Factors
Soluble Factors
HSC

Abnormal localization of myeloid precursors in MDS



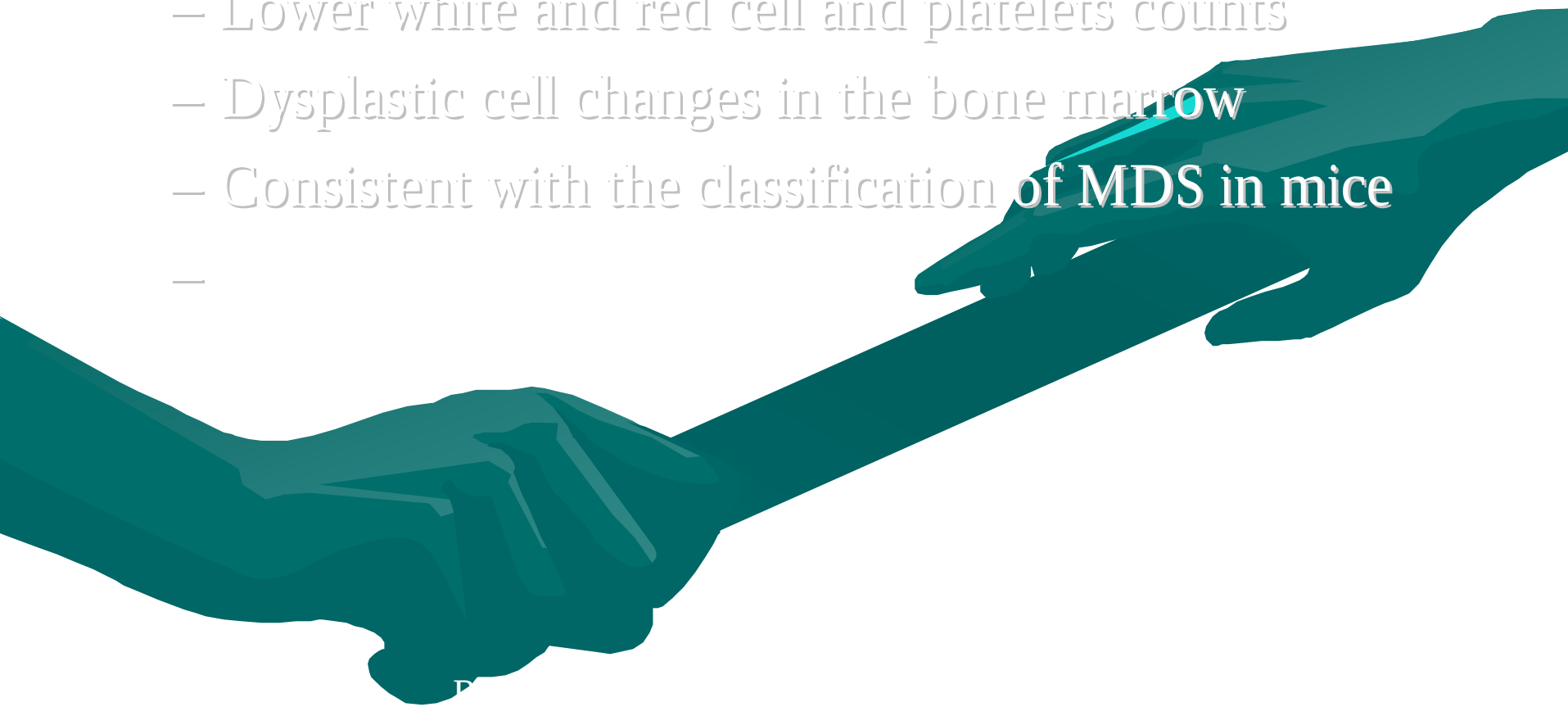


An example of the influence of the supporting structure

- Generated mice missing the gene "dicer1" in osteoprogenitor cells (bone supporting structure)
- Gene was not absent from hematopoietic cells
- results were
  - Impaired bone precursor formation
  - and

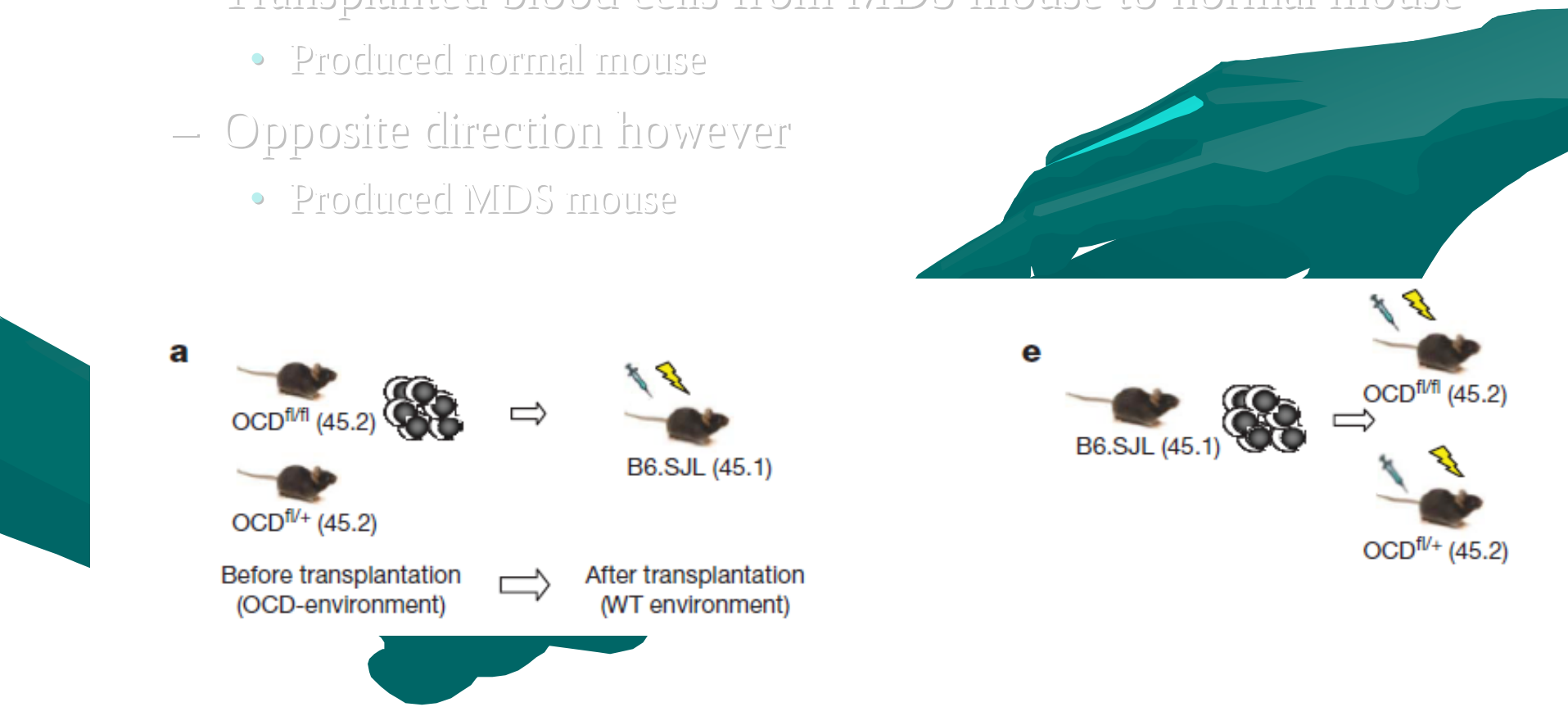
An example of the influence of the supporting structure

- Results
  - Lower white and red cell and platelets counts
  - Dysplastic cell changes in the bone marrow
  - Consistent with the classification of MDS in mice
  -



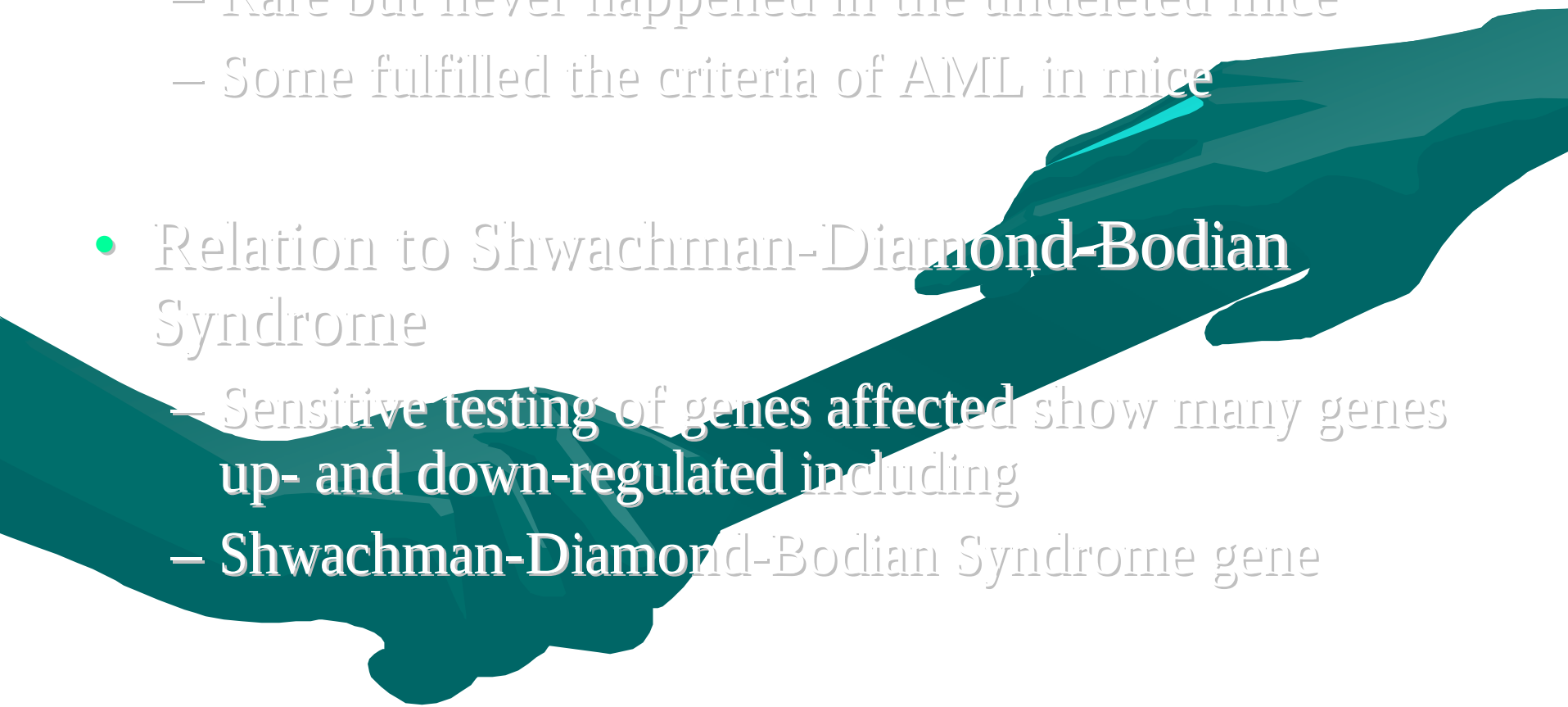
An example of the influence of the supporting structure

- Experiment 2
  - Transplanted blood cells from MDS mouse to normal mouse
    - Produced normal mouse
  - Opposite direction however
    - Produced MDS mouse



An example of the influence of the supporting structure

- Progression to acute leukemia
  - Rare but never happened in the undeleted mice
  - Some fulfilled the criteria of AML in mice
- Relation to Shwachman-Diamond-Bodian Syndrome
  - Sensitive testing of genes affected show many genes up- and down-regulated including
  - Shwachman-Diamond-Bodian Syndrome gene



An example of the influence of the supporting structure

Conclusions

Changes to the bone marrow microenvironment may either help initiate, facilitate or propagate myelodysplasia

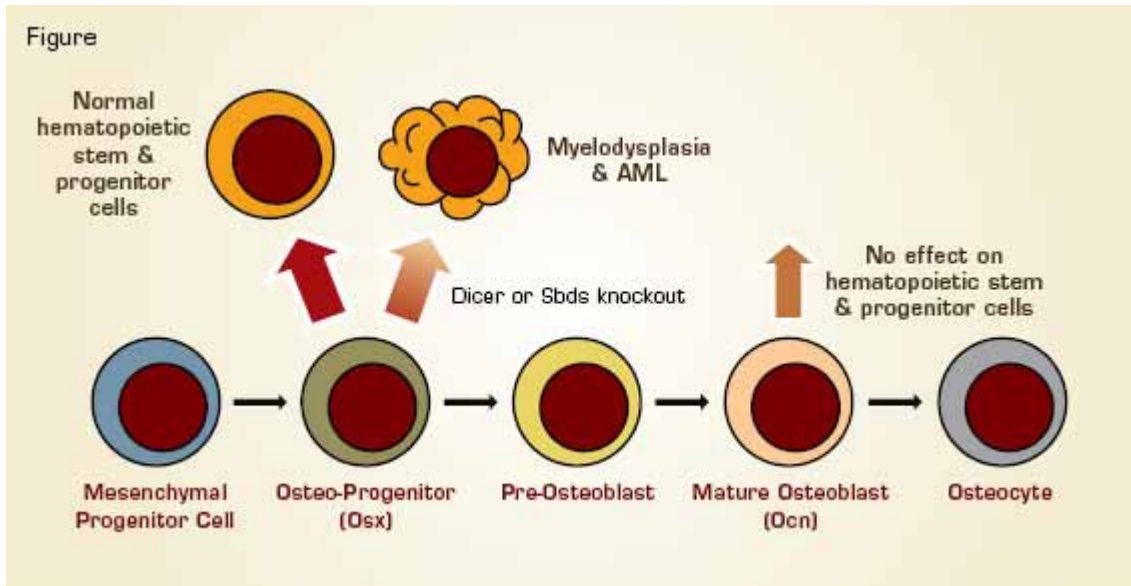
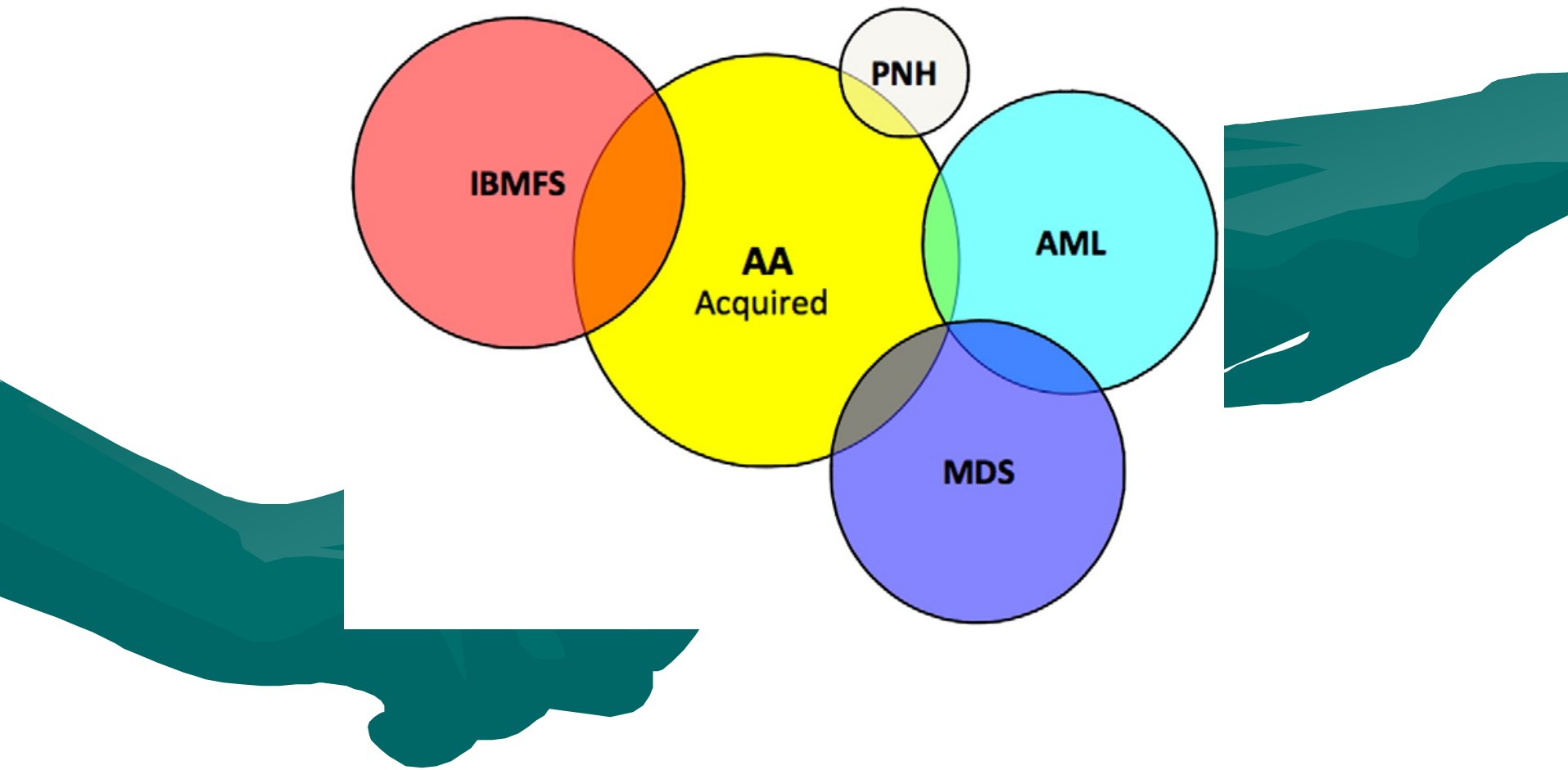


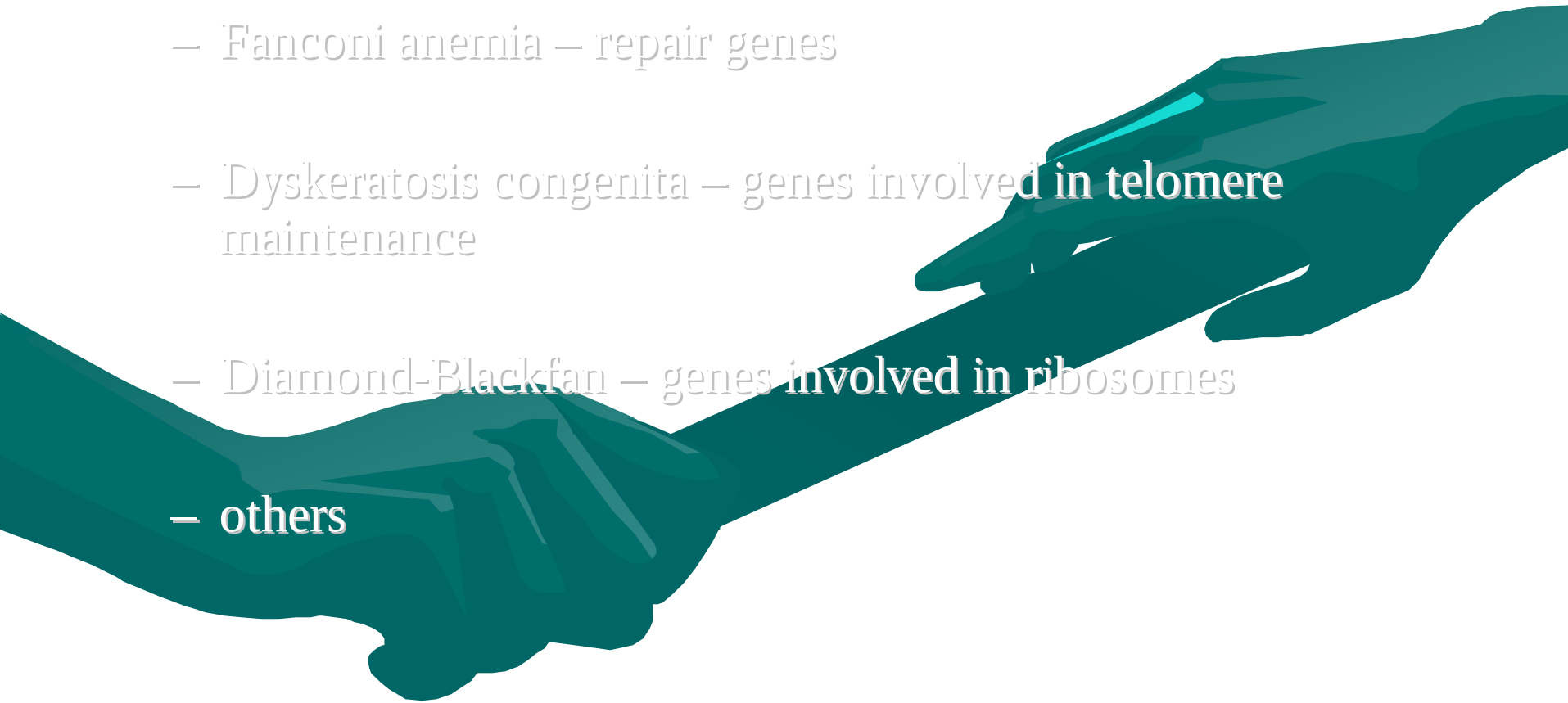
Figure
Normal hematopoietic stem & progenitor cells
Myelodysplasia & AML
Dicer or Sbds knockout
No effect on hematopoietic stem & progenitor cells
Mesenchymal Progenitor Cell
Osteo-Progenitor (Osx)
Pre-Osteoblast
Mature Osteoblast (Ocn)
Osteocyte

What happens when the marrow fails



Genetic disorders

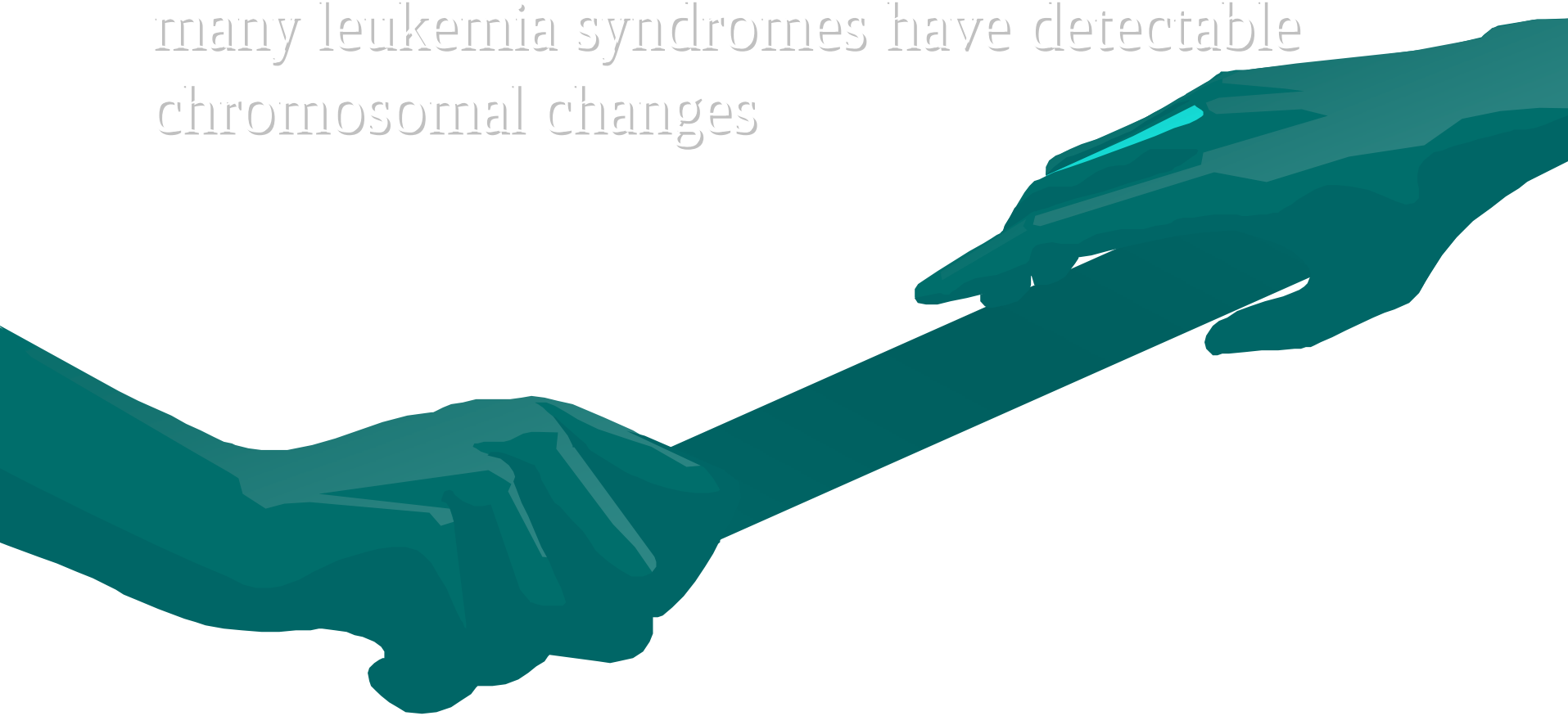
- Most are due to genetic alterations resulting in the manifestation of the disease
  - Fanconi anemia – repair genes
  - Dyskeratosis congenita – genes involved in telomere maintenance
  - Diamond-Blackfan – genes involved in ribosomes
  - others



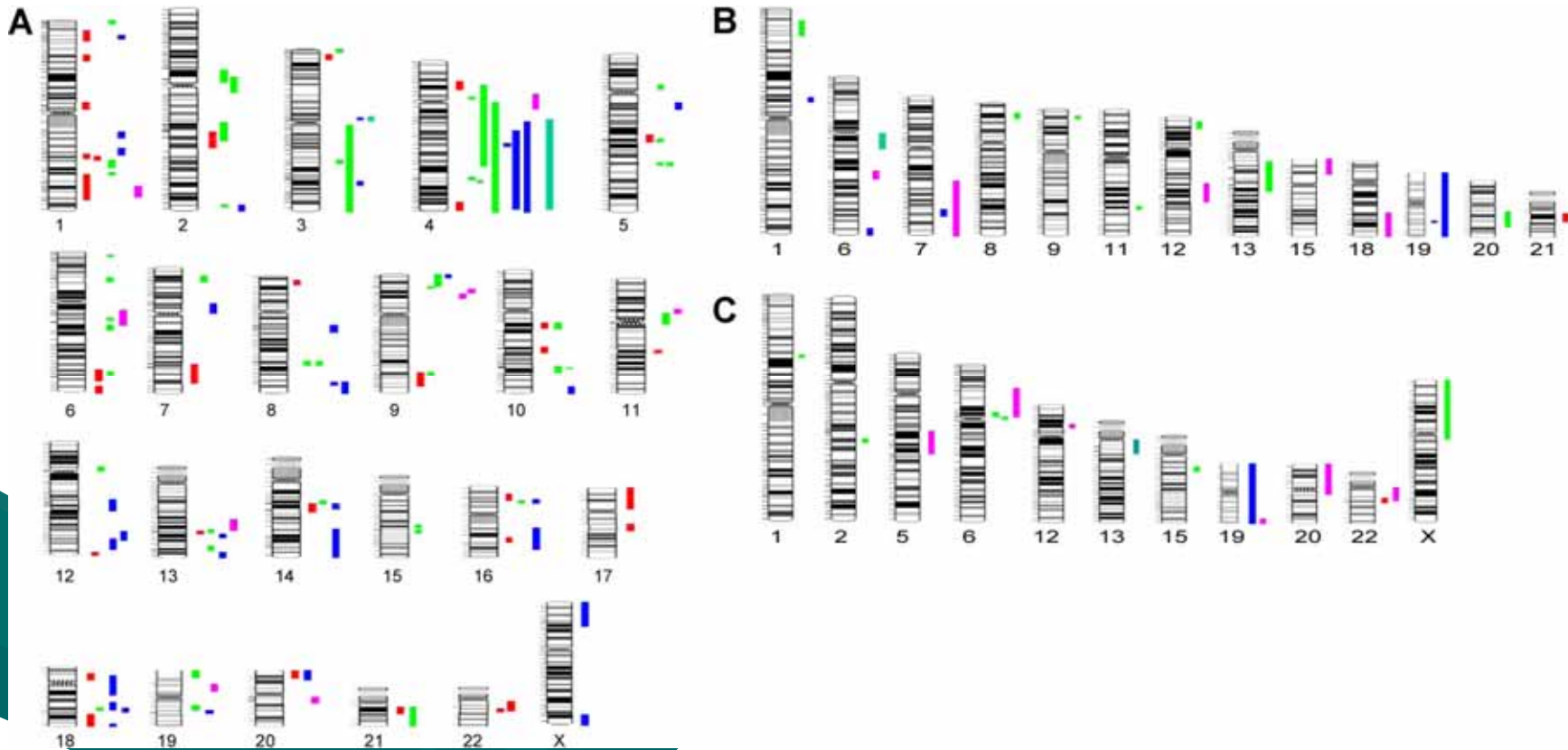
What has gone wrong in MDS/Leukemia

Chromosomal changes

- many leukemia syndromes have detectable chromosomal changes

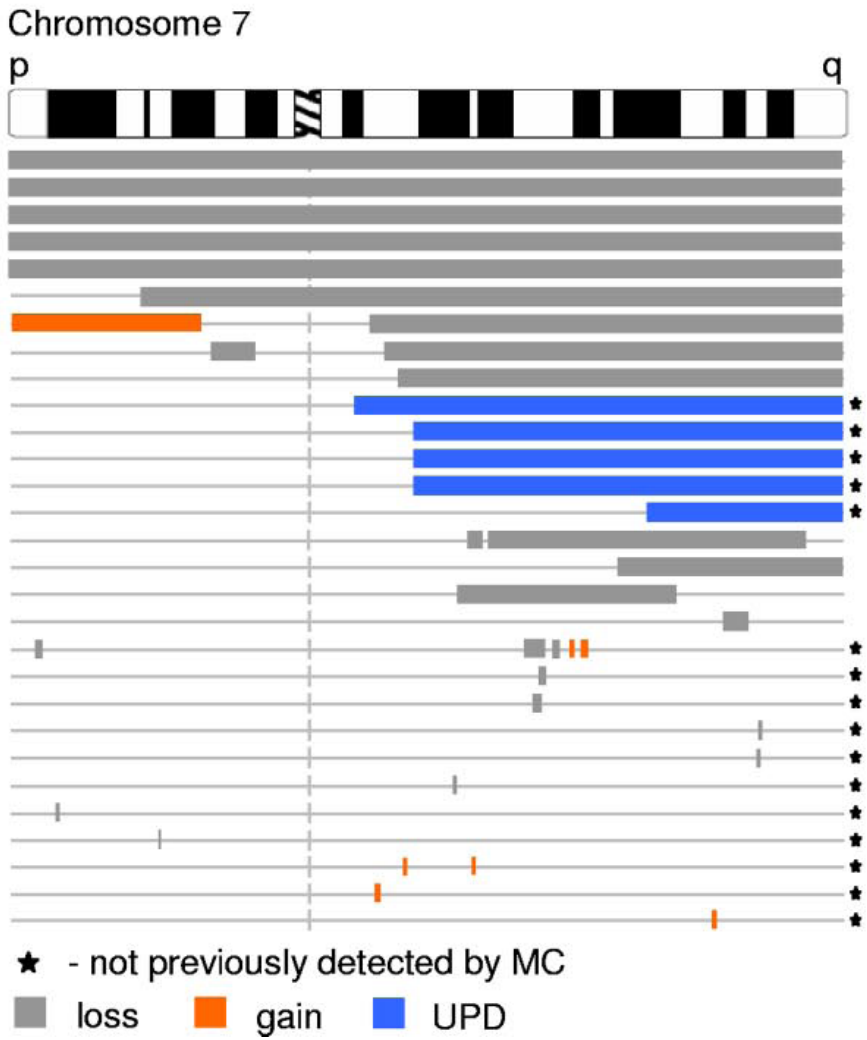


Genetic diversity in MDS



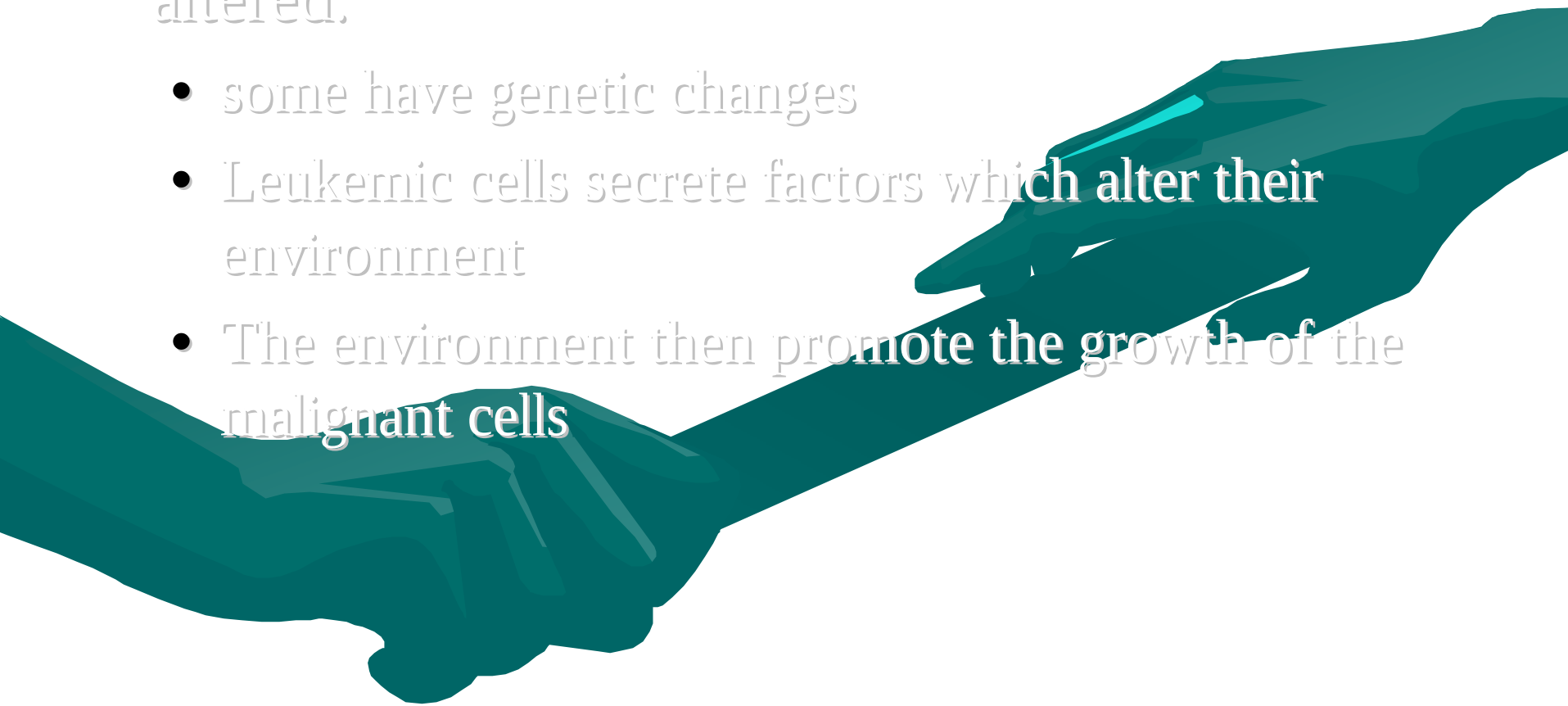
Mohamedali A. Blood. (2007) 110:3365

New genetic lesions in MDS

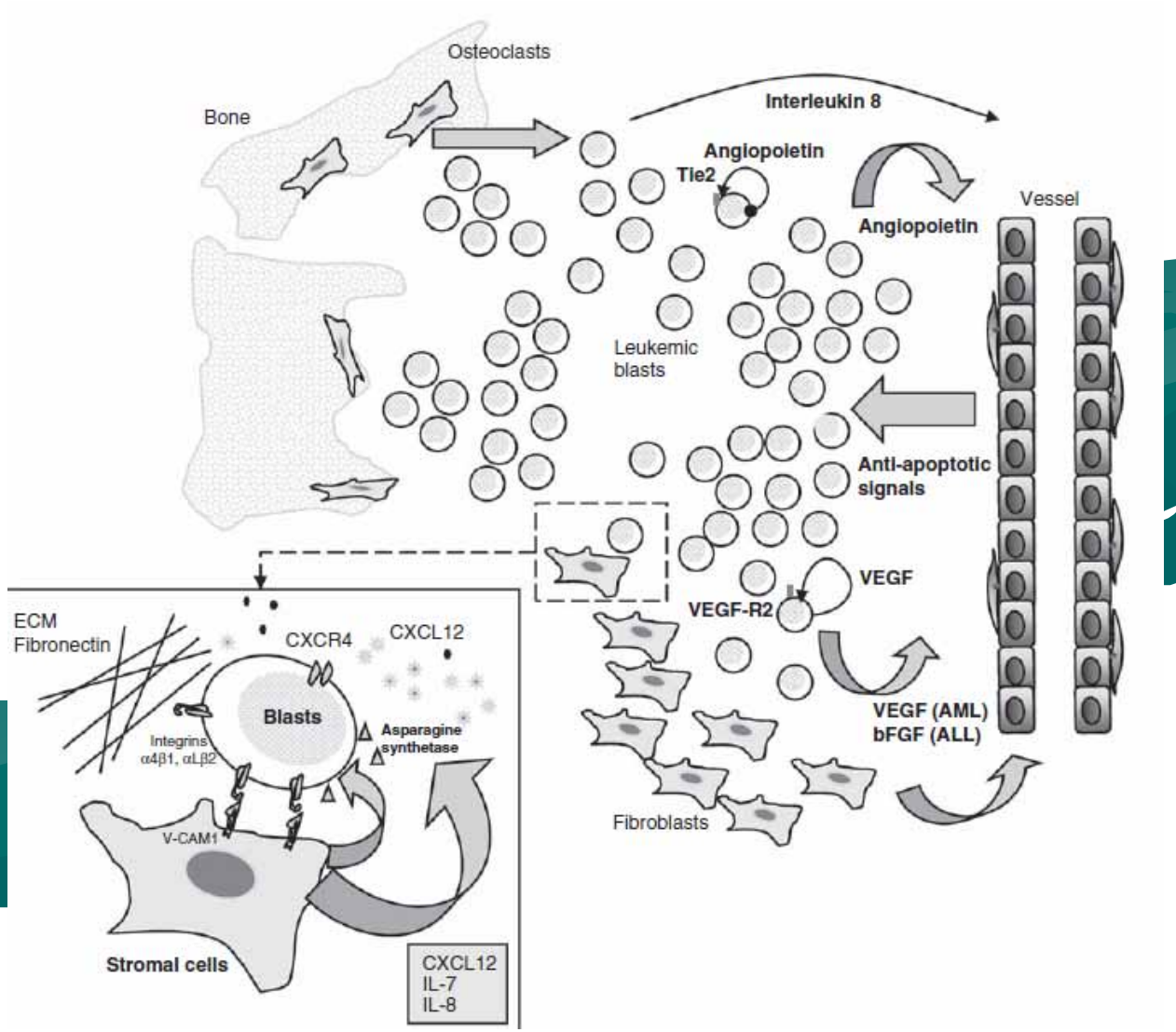


What about the surrounding bone marrow

- In leukemic syndromes supporting structure is altered.
  - some have genetic changes
  - Leukemic cells secrete factors which alter their environment
  - The environment then promote the growth of the malignant cells



Complex cellular interactions



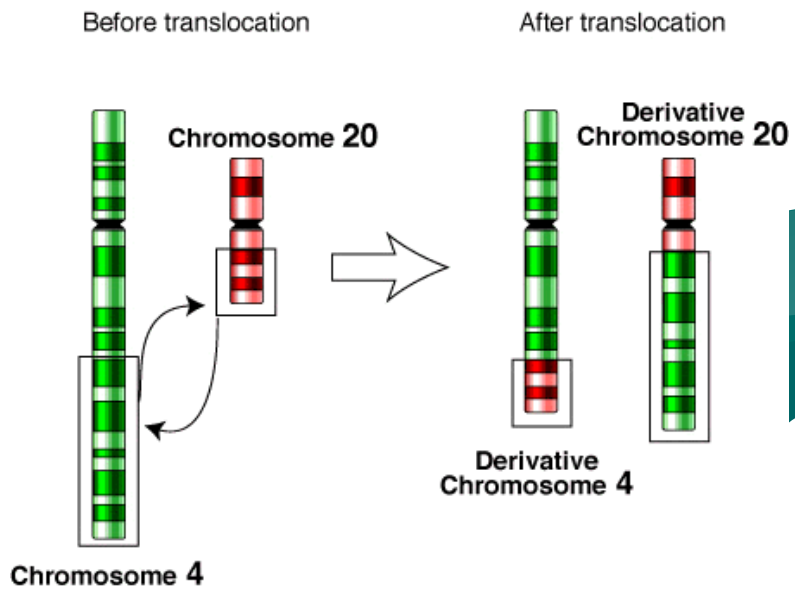
Environmental cues

- one study demonstrated that by exposing leukemic cells to certain chemical signals they could produce AML or ALL.
- There is some investigations into the level of oxygen in the bone marrow where lower oxygen levels might promote leukemia
- Others show that certain factors protect the leukemic cells from the effect of chemotherapy.

Other nuclear changes

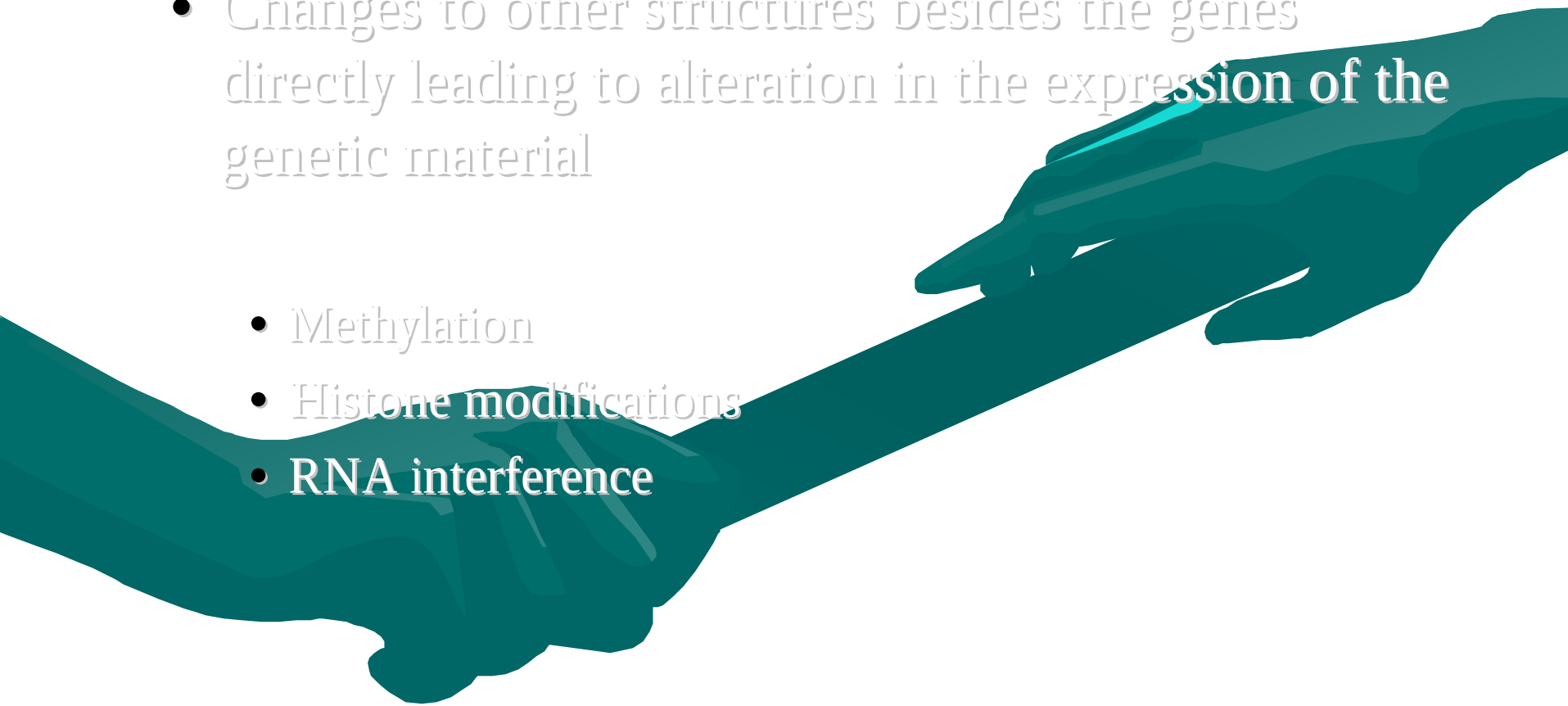
- Direct structural changes
  - Deleted
  - Translocations
  - Amplifications

- But 50% of MDS cases do not have detectable changes



Other nuclear changes

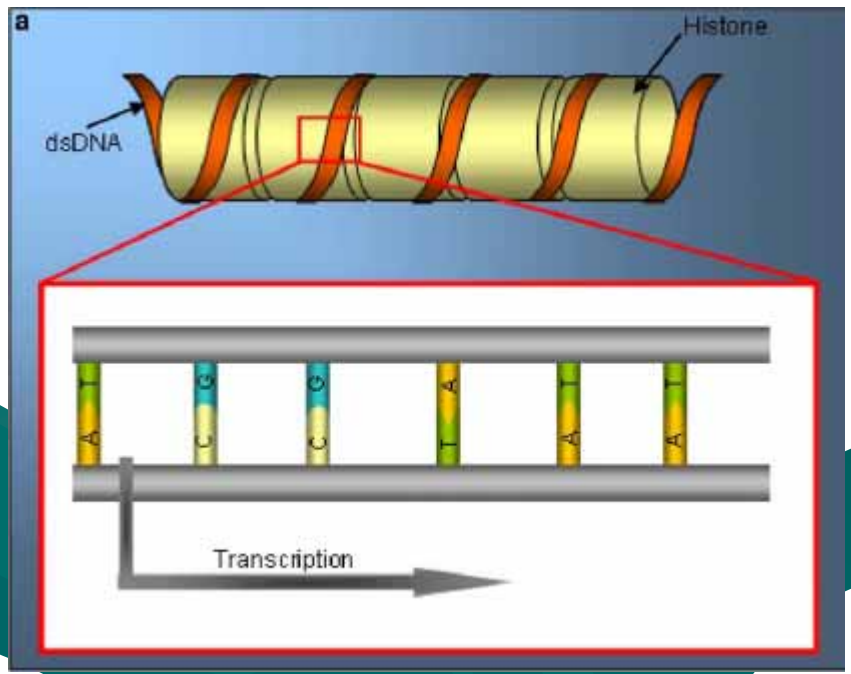
- Epigenetic changes
  - Changes to other structures besides the genes directly leading to alteration in the expression of the genetic material
    - Methylation
    - Histone modifications
    - RNA interference

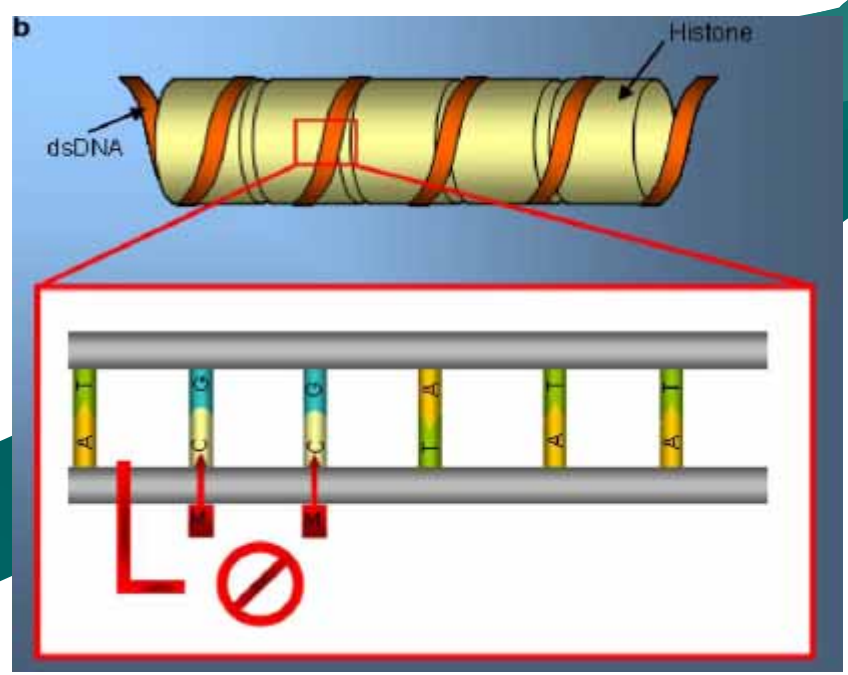


Methylation

UNmethylated

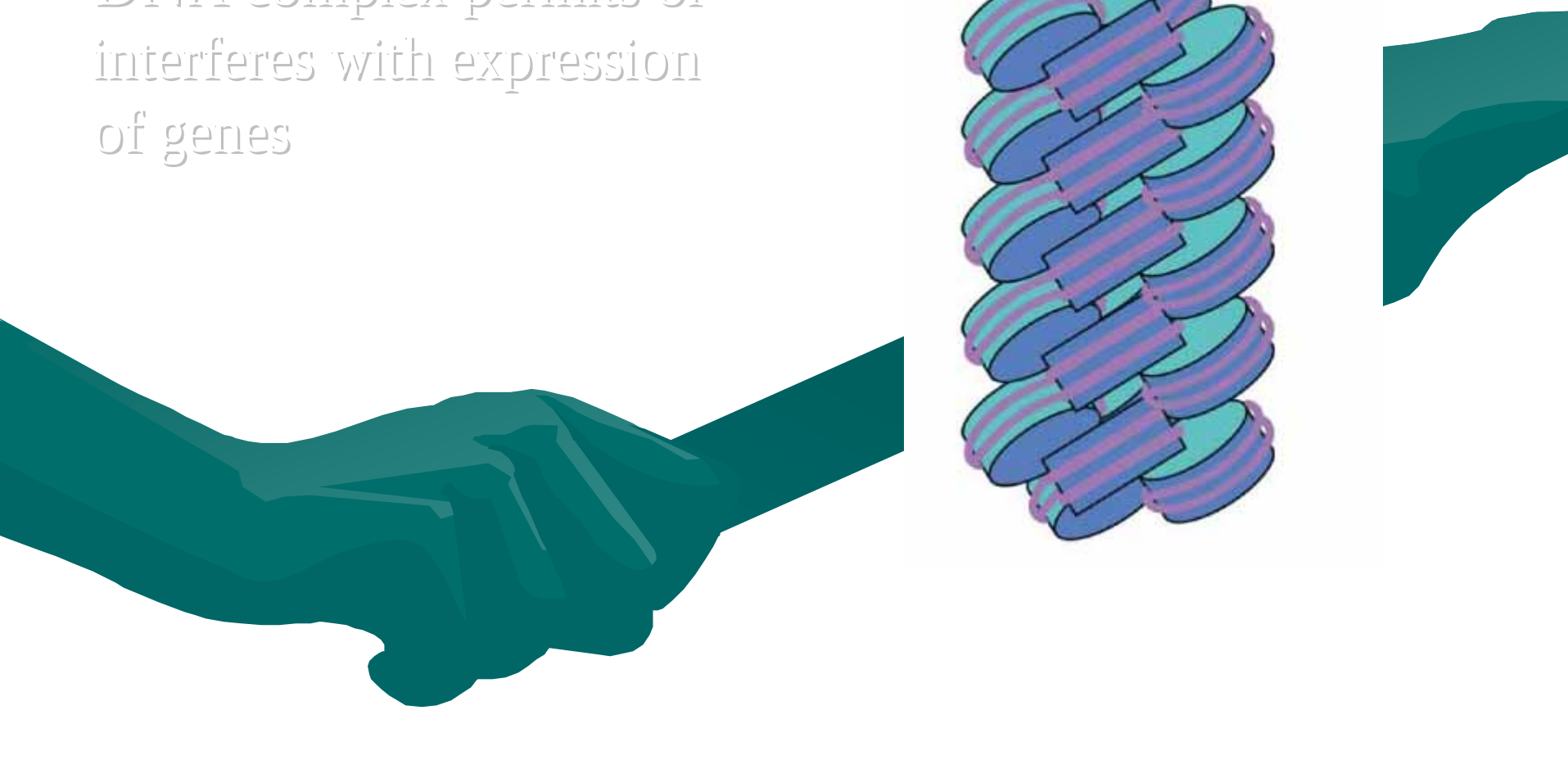
HYPERmethylated





Histone modification

Changes in the histone DNA complex permits or interferes with expression of genes



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