Congenital Neutropenia

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National Neutropenia Network Family Retreat

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Cincinnati Children's
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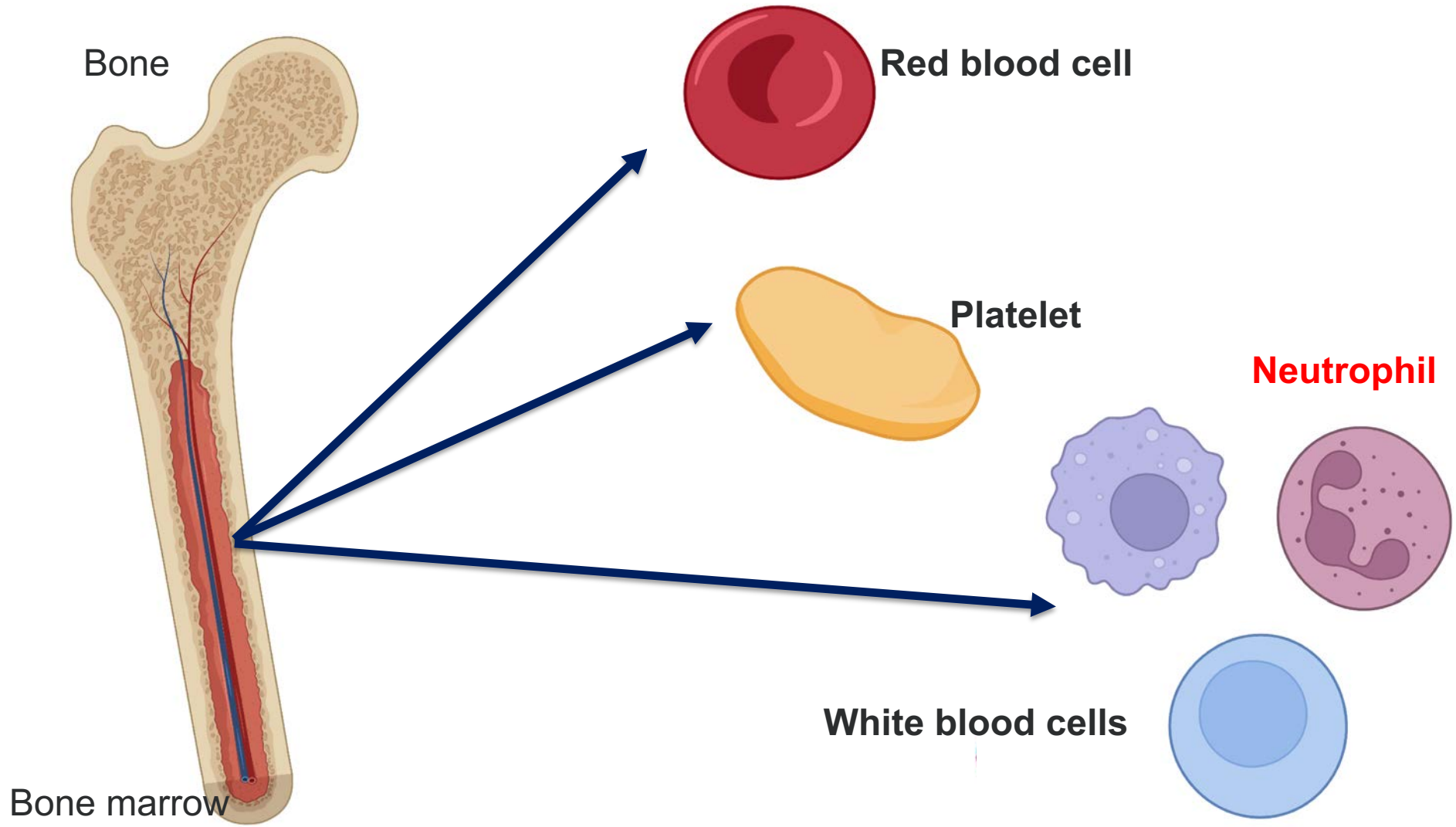
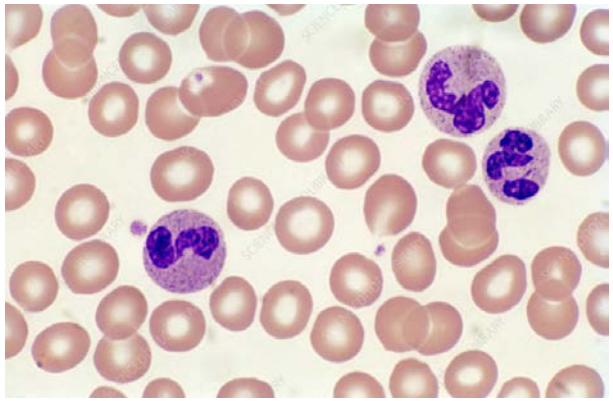
Outline

- Overview of:
  - Severe Congenital Neutropenia
  - Cyclic Neutropenia
- Bone Marrow Transplant for Congenital Neutropenia

The bone marrow is the factory for blood cell production



Neutrophils



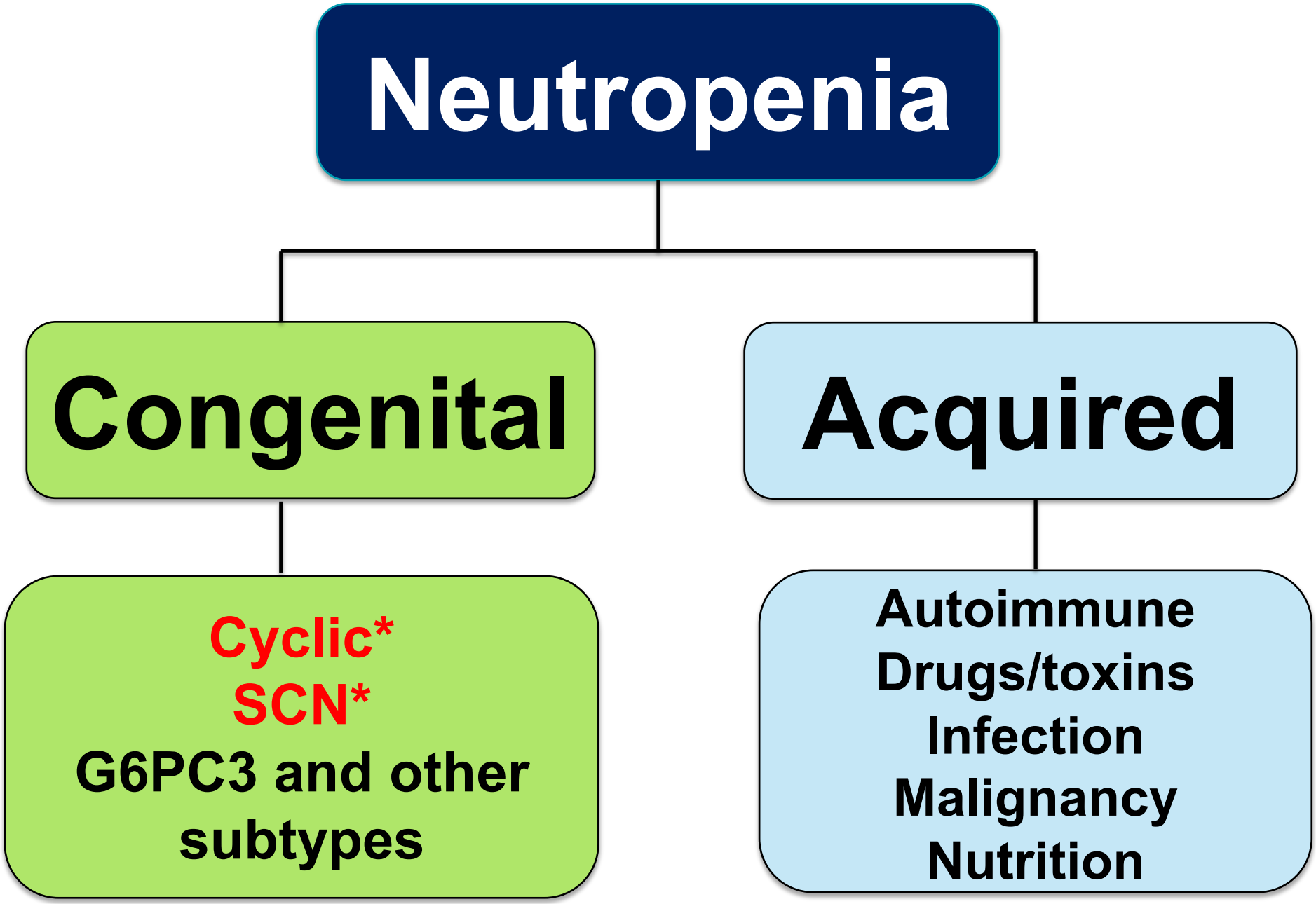
- Make up approximately 60% of the immune cells in our blood
- Act as one of the first responders to migrate toward site of inflammation or infection
- Capable of ingesting microorganisms or particles (phagocytes)
- Because of specific genetic anomalies, some people are born with too few neutrophils or **neutropenia**

Severity of neutropenia is defined by the absolute neutrophil count

Severity of Neutropenia	Absolute Neutrophil Count (ANC)
Mild	Between 1000-1500/uL
Moderate	Between 500-1000/uL
Severe	<500/uL

Symptoms of neutropenia

- **Symptoms and infection depend on the severity and duration of neutropenia (may include):**
  - Middle ear infections (otitis media)
  - Tonsillitis
  - Gingivitis and/or periodontitis
  - Ulcers of the oral mucosa (aphthous stomatitis)
  - Skin abscesses
  - Respiratory infections (pneumonia)


Neutropenia
Congenital
Acquired
Cyclic*
SCN*
G6PC3 and other subtypes
Autoimmune
Drugs/toxins
Infection
Malignancy
Nutrition

Severe Congenital Neutropenia

Neutropenia

Types of SCN

Multisystem diseases

- Shwachman-Diamond Syndrome
- Glycogen Storage Disease
- Barth syndrome

Congenital neutropenia

- **Severe congenital neutropenia**
- Cyclic neutropenia
- G6PC3 and other subtypes

Immune disorders

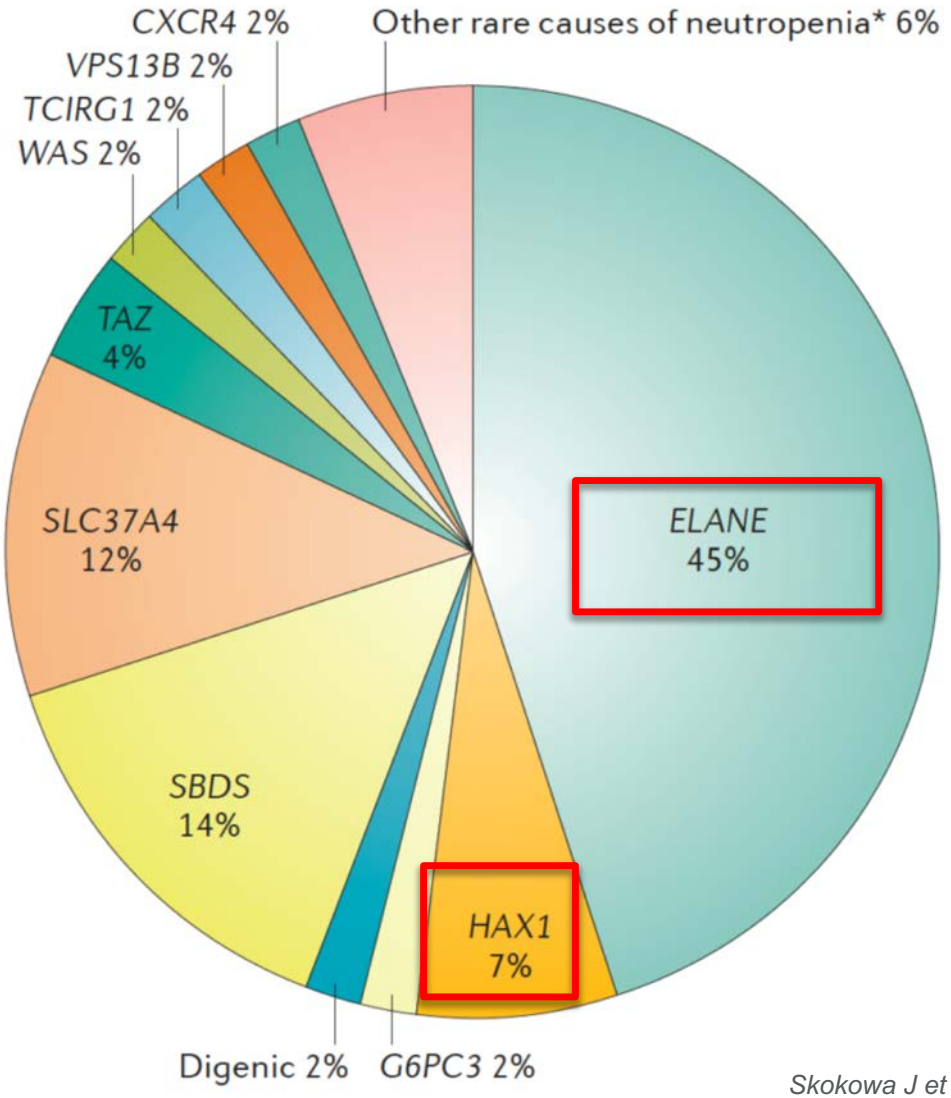
- WHIM syndrome
- Wiskott-Aldrich Syndrome

Gene defects in congenital neutropenia

Category	Diagnosis	Genetic defects	Inheritance
Isolated neutropenia	**ELANE deficiency**	*ELANE*	Autosomal dominant
	HAX1 deficiency	*HAX1*	Autosomal recessive
	GF1 deficiency	*GF1*	Autosomal dominant
	JAGN1 deficiency	*JAGN1*	Autosomal recessive
	VPS45 deficiency	*VPS45*	Autosomal recessive
	CSF3R deficiency	*CSF3R*	Autosomal recessive

****Does not include multisystem diseases with neutropenia, neutropenia with other marrow failure and other syndromes associated with congenital neutropenia**

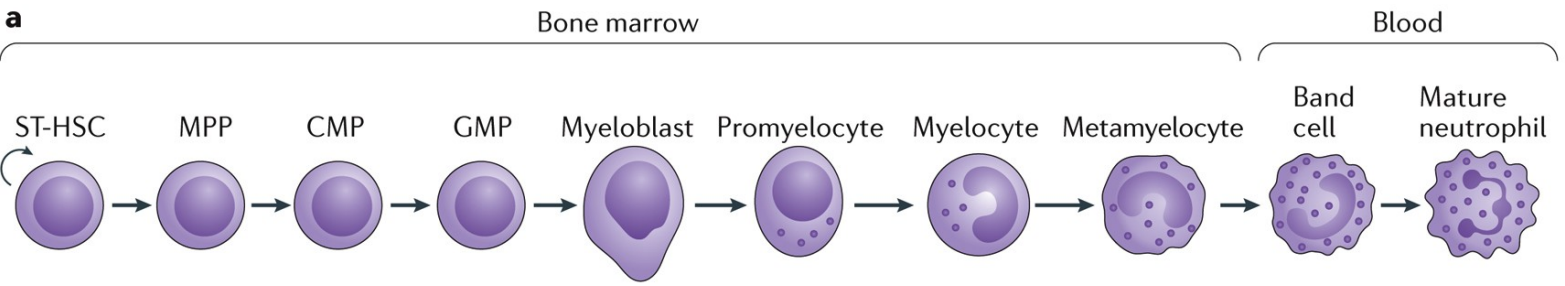
Germline mutations associated with congenital neutropenia

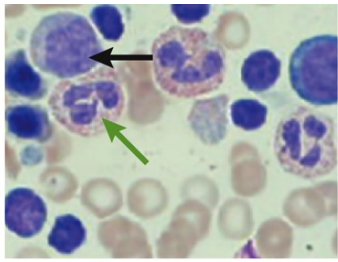


Skokowa J et al. Nature Disease Review Primers. 2017

Congenital neutropenia occurs due to maturational arrest in the bone marrow

Normal neutrophil development →





Skokowa J et al. Nature Disease Review Primers. 2017

Neutropenia

Types of SCN

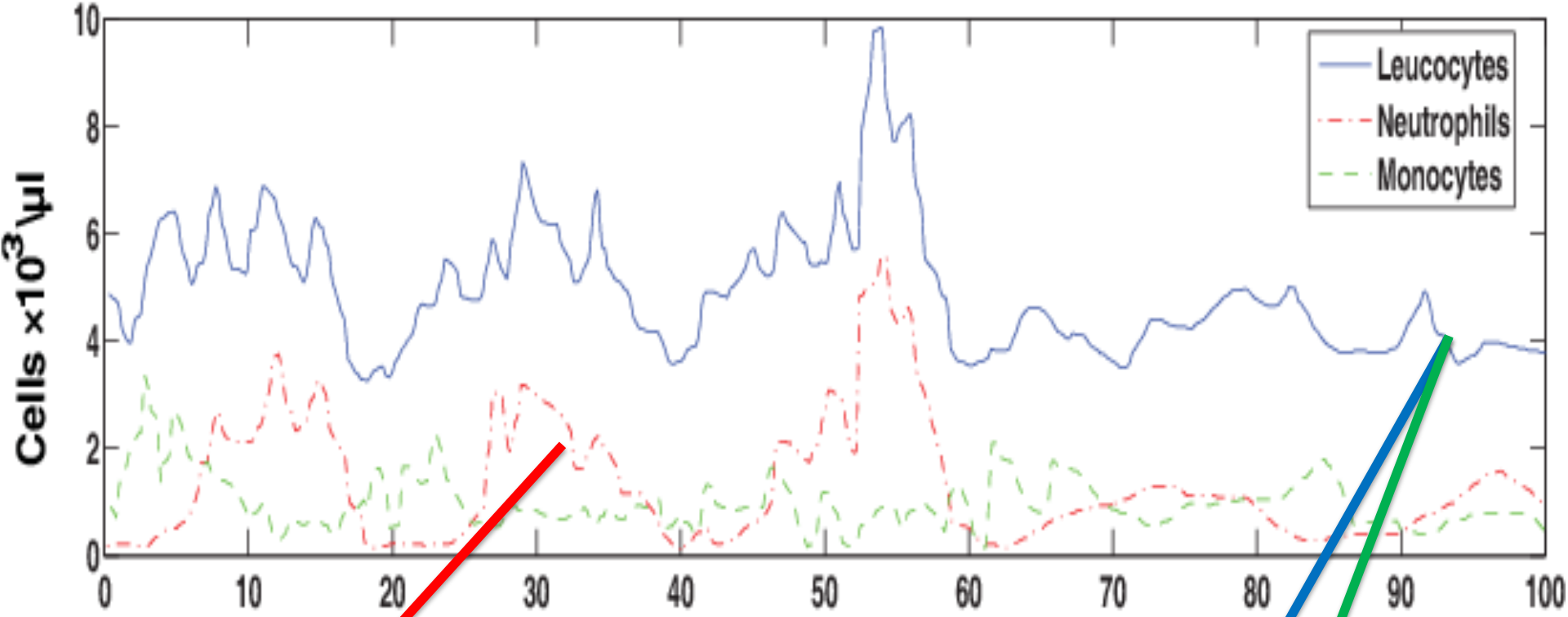
Congenital neutropenia

- Severe *congenital* neutropenia
- **Cyclic neutropenia**
- G6PC3 and other subtypes

Cyclic neutropenia

- Occurs from mutations in the *ELANE* gene (neutrophil elastase)
- Exact pathophysiology is unknown, likely secondary to interrupted cell production in the bone marrow
- Fevers, mouth ulcers and at times infection can occur in approximately three-week intervals

Cyclic neutropenia shows recurrent patterns of low neutrophil counts



Cycling of neutrophils typically average 21 days

Cycling of platelets and red cells can also occur

Diagnosis of cyclic neutropenia

- Diagnosis of cyclical neutropenia:
  - serial complete blood counts 3 times weekly for 6 weeks.
- Fevers, mouth ulcers and at times infection can occur in approximately three-week intervals
- Nearly all patients have periods of *severe neutropenia* every 3 weeks (ANC <200/uL)
- During ANC nadir, serious infections are generally very rare

Management of cyclic neutropenia

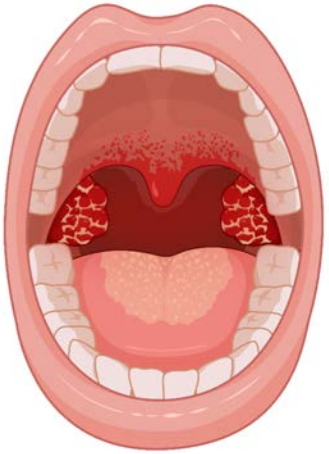
- Routine, regular monitoring of complete blood counts
- Prevention and control of infections
- Clinical course and prognosis of cyclic neutropenia is benign
- For the majority of patients, systemic symptoms (fevers) generally go away by adolescence
  - Some adult patients can experience oral ulcers, gingivitis, periodontitis and other infections

Treatments for congenital neutropenia

- **Supportive treatments**
  - Oral care
  - Bone health
- **Granulocyte-colony stimulating factor (G-CSF)**
- **Hematopoietic stem cell transplant**
  - Dr. Kasiani Myers

Oral issues in congenital neutropenia

- The oral cavity is home to hundreds of species of bacteria
- Mucous membranes lining the mouth and gums are susceptible to infection
- Neutropenic patients are at risk of increased mouth sores/stomatitis and gum inflammation → higher risk of bacterial infections
- Periodontal disease
- Dental plaques
- Tooth decay
- **Excellent oral hygiene is critical**



Recommendations for Oral Care

- **Regular check-ups with a dentist** (usually every 6 months)
- **Good, regular oral hygiene**
- **Mouth rinses**
  - Example: chlorhexidine gluconate

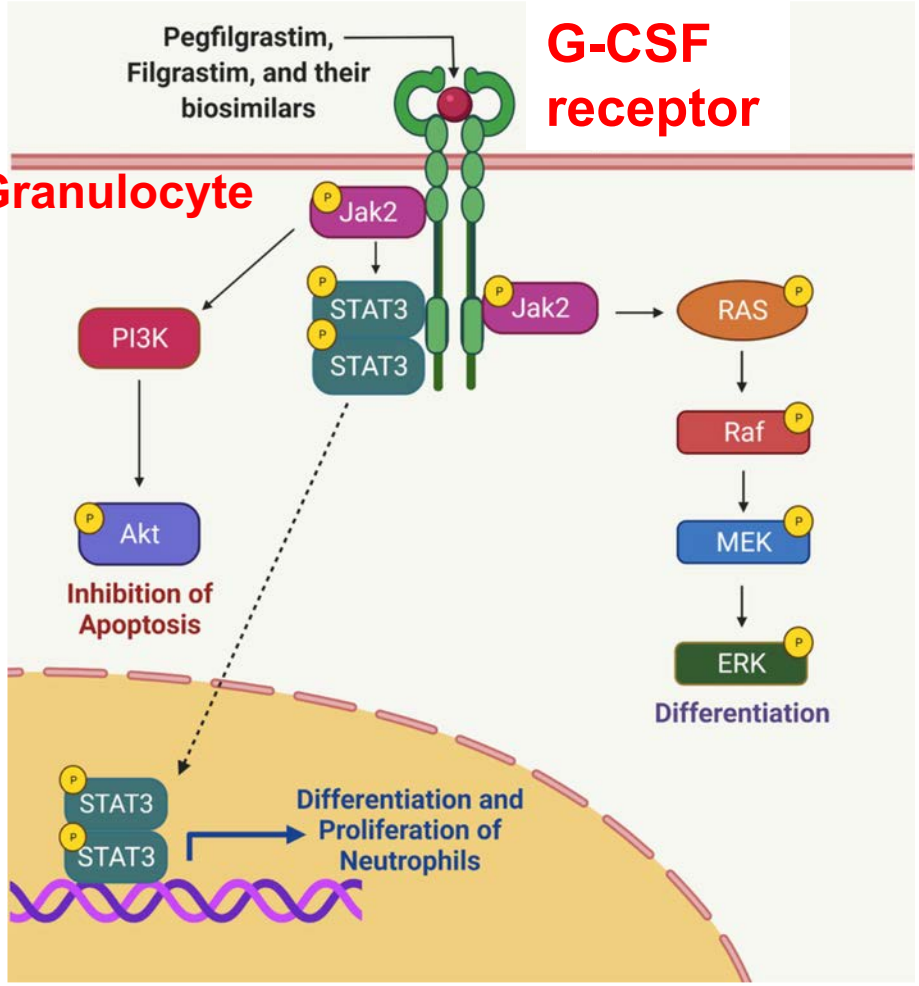
Bone related issues in congenital neutropenia

- **Low bone mineral density (BMD) or osteopenia**
- **Osteoporosis**
- **Bone issues:**
  - Can be seen in up to 20-50% of patients with congenital neutropenia
  - Likely due to both neutropenia and G-CSF therapy
  - Fractures (compression, fragility)

Management of bone issues in congenital neutropenia

- **Assessment with regular DXA scans**
  - Especially after bone marrow transplant
- **Optimize vitamin D levels and nutrition (calcium)**
- **Hormones**
  - Estrogen, thyroid
- **Bisphosphonates** for patients with fractures

G-CSF for the treatment of congenital neutropenias

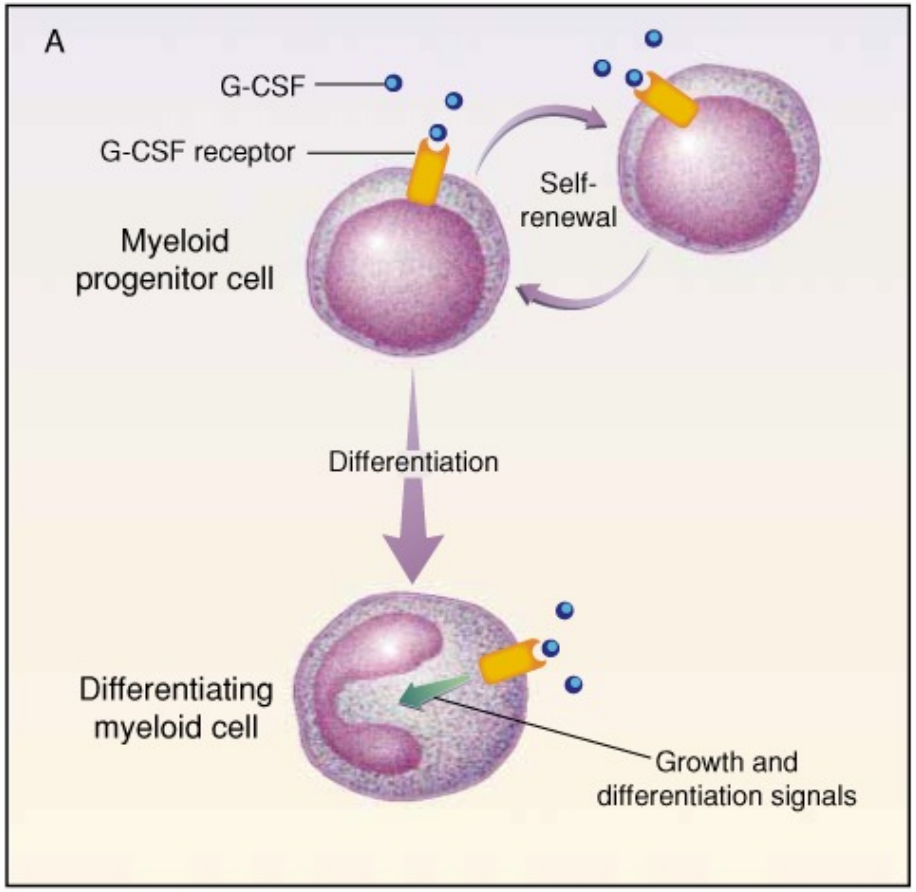


- G-CSF is a cytokine that stimulates neutrophil production and activity
- G-CSF naturally occurs in the human body
- G-CSF operates through the G-CSF receptor found on granulocytes
- Dosing of G-CSF can vary widely

Bachu R et al. Cancer Reports. 2022

G-CSF for the treatment of congenital neutropenias

- SCN patients produce their own G-CSF but can require much higher doses to maintain ANC >1000/uL
- In cyclic neutropenia, G-CSF tends to shorten the intervals between neutropenia nadir



Naperstek E. New England Journal of Medicine. 1995

Side effects from G-CSF

- Muscle or bone pain
- Enlargement of the spleen (splenomegaly)
- Infrequent side effects can include:
  - Injection site reactions (redness, swelling)
  - Protein in the urine
  - Vasculitis
- Transformation to myelodysplastic syndrome (MDS) and leukemia have been described in congenital neutropenias treated with G-CSF
  - But G-CSF therapy does **not cause** MDS/leukemia
  - Close monitoring with regular bone marrow examinations and blood counts is recommended

HSCT for congenital neutropenias