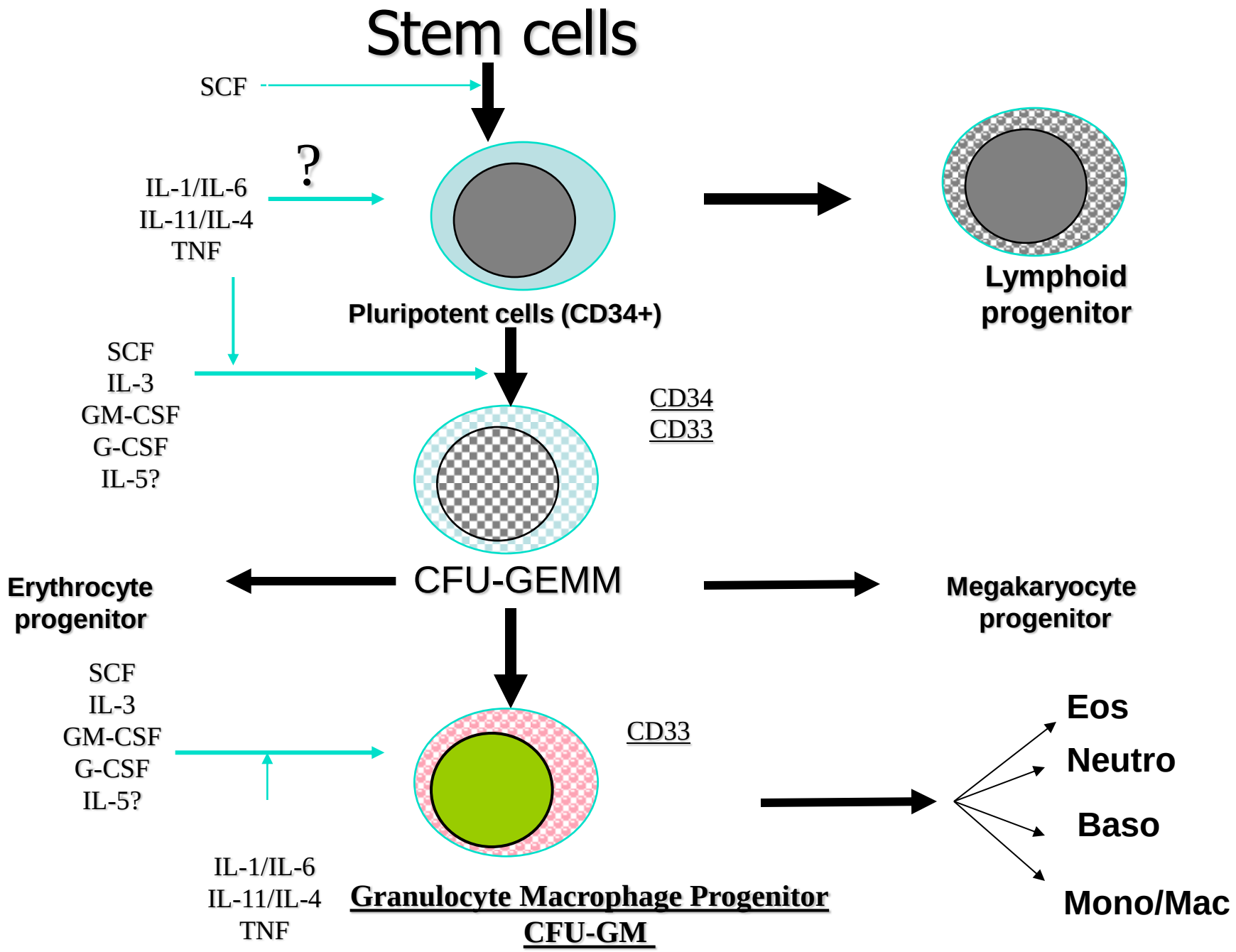
Hypereosinophilic syndromes


Stem cells
SCF
?
IL-1/IL-6
IL-11/IL-4
TNF
Pluripotent cells (CD34+)
Lymphoid progenitor
SCF
IL-3
GM-CSF
G-CSF
IL-5?
CD34
CD33
Erythrocyte progenitor
CFU-GEMM
Megakaryocyte progenitor
SCF
IL-3
GM-CSF
G-CSF
IL-5?
CD33
Eos
Neutro
Baso
Mono/Mac
IL-1/IL-6
IL-11/IL-4
TNF
Granulocyte Macrophage Progenitor
CFU-GM

Control of Myelopoiesis

1-Commitment to myeloid lineage

- **Intrinsic factors: Nuclear transcription factors**
  PU.1
  GATA-1,2 ..

- **Extrinsic factors: Unknown**

2- Differentiation & maturation

Cytokines, chemokines, cell surface receptors
Growth factors

Eosinophilia: what we are talking about ?!

- Primary eosinophilia
  - Abnormality of hematopoietic stem cells

    "Eosinophilic leukemia"

    » differentiation mainly to eosinophil lineage

    » Increase of myeloid lineages cell nbre associated with eosinophilia

- Secondary eosinophilia
  - Hematopoietic stem cells are normal

    » Eosinophilia is cytokine driven process

Hypereosinophilic Syndrome (HES)

- Heterogeneous groups of hematological diseases.
  - ***Diagnosis of exclusion***

  - Eosinophilia more than 6 months (>1500 Eos/μl).

  - Exclusion of other causes.
    - **Parasitic infection**
    - **Allergies**
    - **Eosinophilia associated with neoplasias**

  - Evidence of end organ damage.

  - Leukocytosis: others myeloid lineage: neutrophilia.

Organ Involvement in HES

Organ system	Cumulative frequency from 3 studies, %	Examples of end organ manifestations
Hematologic	100	Leukocytosis with eosinophilia; neutrophilia, basophilia, myeloid immaturity, anemia, immature eosinophils, ..
Cadiovascular	58	Cardiomyopathy, endomyocarditis, valvular dysfunction, ..
Cutaneous	56	Angioedema, urticaria, papules, nodules, plaques, mucosal ulcers, vasculitis
Neurologic	54	Thromboembolism, peripheral neuropathy, encephalopathy, dementia, epilepsy, eosinophilic meningitis
Pulmonary	49	Pulmonary infiltrates, fibrosis, Emboli, ARDS
Splenic	43	Hypersplenism, Infarct.
Liver/gallbladder	30	Hepatomegaly, chronic active hepatitis, hepatic necrosis,
Ocular	23	Microthrombi, retinal arteritis, …..
Gastrointestinal	23	Gastritis, colitis, ascites, diarrhea
Musculoskeletal	NA	Arthritis
Renal	NA	Acute renal failure with Charcot Leyden crystalluria, nephrotic syndrome

Adapted from Gotlib et al, Blood 2004

Epidemiology of HES

- Disease of men; male–female ratio, 9-1.
- Diagnosis: ages 20-50.
- Mean age of onset ~33 years.
- Very rare in infant and children.

Eosinophilic Leukaemia and HES

Table I. WHO criteria for the diagnosis of eosinophilic leukaemia and the idiopathic hypereosinophilic syndromes.

Diagnosis	Eosinophilic leukaemia	Idiopathic hypereosinophilic syndrome*
Eosinophil count	Equal to or greater than $1{\cdot}5 \times 10^9$/l	
Conditions to be excluded	Reactive eosinophilia including reactive eosinophilia in haematological neoplasms, **AND** haematological neoplasms in which eosinophils are part of the leukaemic clone (e.g. Ph-positive chronic myeloid leukaemia, polycythaemia vera, idiopathic myelofibrosis, essential thrombocythaemia, acute myeloid leukaemia and the myelodysplastic syndromes), **AND** systemic mastocytosis (for which it is not known whether or not the eosinophils are part of the neoplastic clone).	
Diagnostic criteria	Blast cells greater than 2% in the blood or between 5% and 19% in the bone marrow **OR** evidence of clonality of myeloid cells	No evidence of the cause, including no aberrant cytokine-secreting T-cell population

*Will inevitably include some patients who really have eosinophilic leukaemia but in whom no firm evidence of this can be found.

From Bain BJ, BJH, 2003

Cytogenetic Abnormalities in Malignancies with Eosinophilia

- 8p11 syndrome.
  - Mutation in **pluripotent** stem cells (myleoid, T and B cells).
    - » T, B cell lymphoblastic lymphoma, bone marrow myeloid hyperplasia and eosinophilia.
    - » Fusion gene FGFR1 to FOP: constitutive activation.
- Chronic myeloid leukaemia associated with t(5;12).
  - Mutation in multipotent myeloid stem cells.
    - » Fusion gene (PGDFRB) to ETV6.
    - » Eosinophil growth factors: IL-5, IL-3, GM-CSF.

HES and CEL

- HES can be classified as chronic eosinophilic leukemia (CEL).
  - if evidence of clonality and elevated of blast cells.

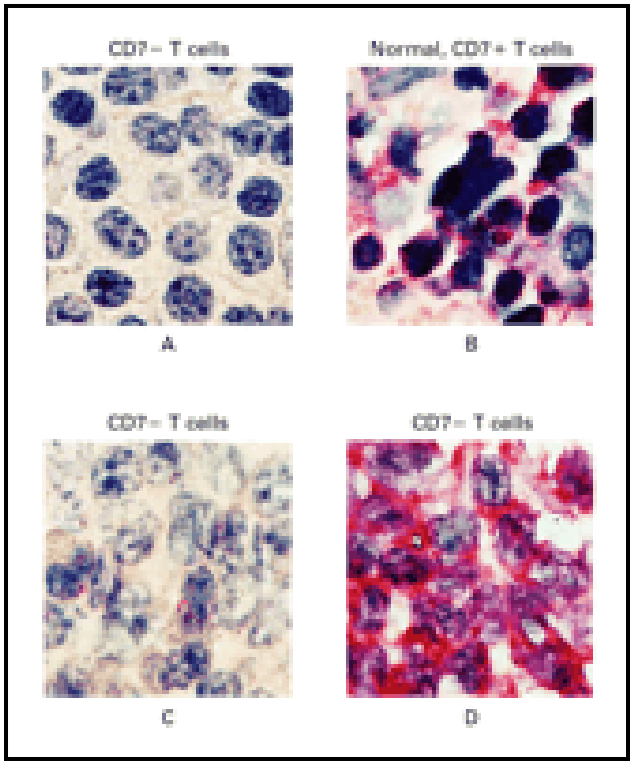
- Splenomegaly, hepatomegaly, anemia suggested to favor a diagnostic of CEL.
    - Markers of clonality !?

T cell mediated “HES”

- Expansion of abnormal T lymphocytes
  - » Immature CD3+ CD4-CD8-.
  - » Absence of T cells CD3- CD4+.
  - » high IgE associated with high IL-5.
  - » Some cases high level of IL-4 and IL-13.

– Simon et al, NEJM, 1999
  - » Abnormal immunophenotype (CD25 and or HLA-DR).
  - » High level of IL-5 *in vitro.*
  - » Some patient T cell lymphoma (Sezary syndrome).

T cell mediated “HES”



Simon et al, NEJM, 1999

Treatment of HES

- **Corticosteroids (1mg/kg/d).**
- **Hydroxyurea, vincristine, cyclophosphamide, etoposide.**
- **Interferon-α.**
- **Cyclosporin A, 2 chlorodeoxyadenosine.**
- **Bone marrow stem cell / alloegenic transplantation (Pb: infections, acute and chronic GVHD).**
- **Cardiac surgery.**
- **Leukapheresis; splenectomy.**
- **Anticoagulants, anti-platelets**

Treatment of HES

- Imatinib (Gleevec, STI-571, Navartis Pharma, Switzerland).

  - **Potent inhibitor of of BCR-ABL kinase associated with Chronic Myelogenous Leukemia (CML)**

  - **Other TKs targeted by imatinib**:

    Kit, ARG (ABL2), PDGFRβ, PDGFRα kinases.

Imatinib and HES

- Schaller and Burckland: 2001
  - » Patient with HES for 8 years.
  - » 100mg/d: eosinophil disappearance within 4weeks
  - » 75mg/d.

- Gleich et al, 2002
  - » Four out of five patient respond
  - » 100mg/d then reduced to 200mg/week