คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล
FACULTY OF MEDICINE SIRIRAJ HOSPITAL

# *Bone marrow failure*

Jane Jianthanakanon, MD
Siriraj Hospital

# Bone marrow failure in ASH 2017

Old and new tools in the clinical diagnosis of inherited bone marrow failure syndromes

*Allison H. West[1] and Jane E. Churpek[1,2]*

Inherited bone marrow failure syndromes: considerations pre- and posttransplant

*Blanche P. Alter*

Treatment of inherited bone marrow failu beyond transplantation

*Rodrigo T. Calado and Diego V. Clé*

Chronic neutropenia in LGL leukemia and rheumatoid arthritis

*Tal Gazitt[1] and Thomas P. Loughran, Jr.[2]*

New monogenic disorders identify more pathways to neutropenia: from the clinic to next-generation sequencing

*Seth J. Corey and Usua Oyarbide*

Clinical implications of somatic mutation and myelodysplastic syndrome in genom

*Jaroslaw P. Maciejewski and Suresh K. Balasubramanian*

Non–chemotherapy drug–induced neutropenia: key points to manage the challenges

*Brian R. Curtis*

Acquired ribosomopathies in leukemia and solid tumors

*Adrianna Vlachos*

Aging, hematopoiesis, and the myelodysplastic syndromes

*Stephen S. Chung[1] and Christopher Y. Park[2]*

# Old and new tools in the clinical diagnosis of inherited bone marrow failure syndromes

*Allison H. West[1] and Jane E. Churpek[1,2]*

*[1]Section of Hematology/Oncology, The University of Chicago Comprehensive Cancer Center, Chicago, IL; and [2]Center for Clinical Cancer Genetics, The University of Chicago, Chicago, IL*

# Bone marrow failure (BMF)

- Inability of hematopoiesis to meet physiologic demands for the production of a sufficient number of functional blood cells
  - Inherited
  - Secondary
  - Idiopathic

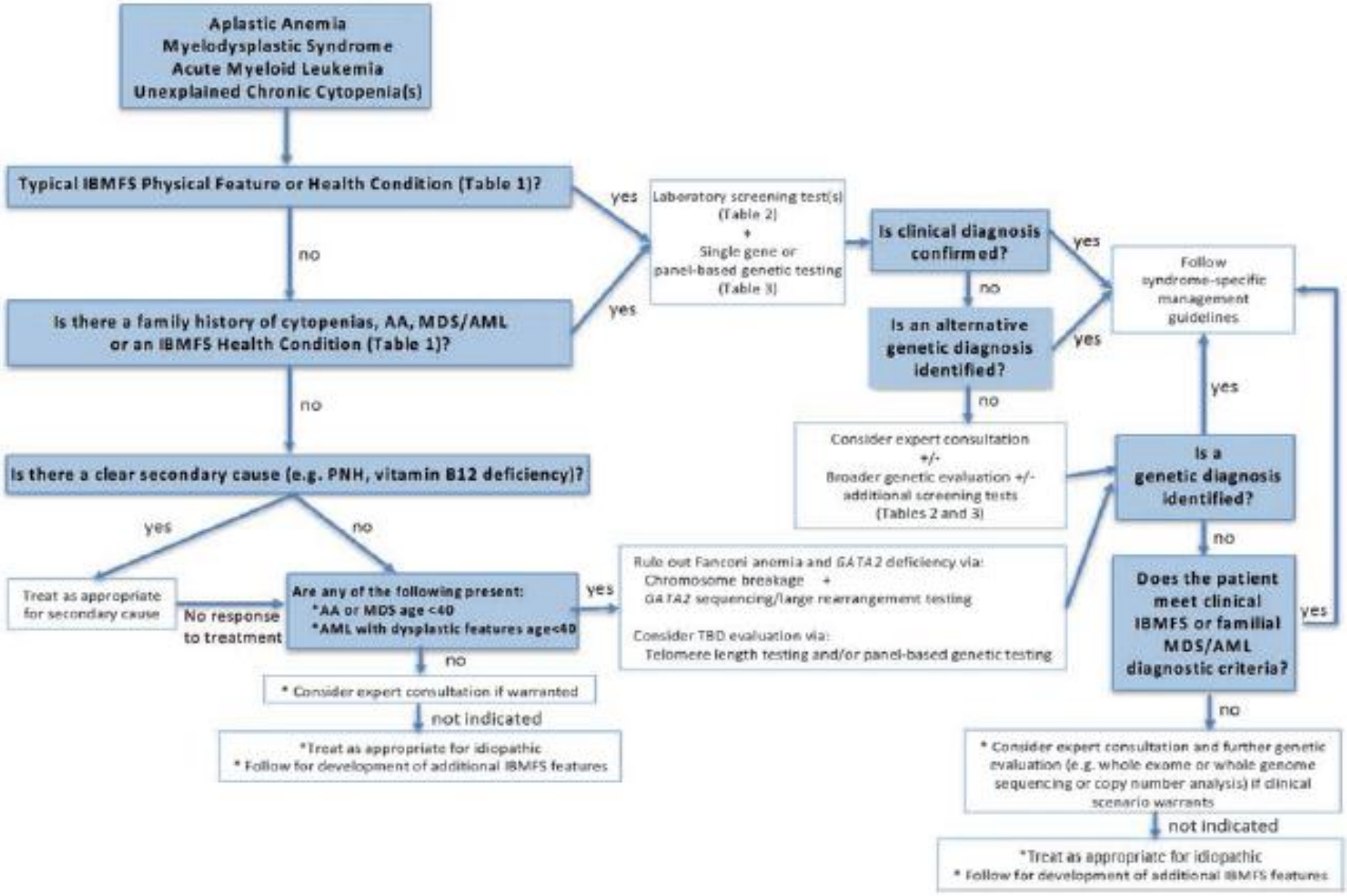
# *Inherited BMF syndromes*

- Clinical features and laboratory tests provide accurate diagnoses for most patients.
- Similar genomic investigations have also been performed in patients with apparently sporadic aplastic anemia (AA) and myelodysplastic syndrome (MDS) to determine how often IBMFSs are overlooked in clinical diagnosis.

# Clinical features of IBMFS

| | Macrocytosis | | | | | |
|---|---|---|---|---|---|---|
| Thrombocytopenia | | | Anemia | Neutropenia | | |
| **TAR** | **TBD** | **FA** | **DBA** | **SDS** | **GATA2 deficiency** | **SCN** |
| Absent radii with thumbs present | -Oral leukoplakia<br>-Pulmonary fibrosis<br>-Lacy reticulated skin pigmentation<br>-Dysplastic nails | -Renal/GU tract anomalies<br>-Short stature<br>-Thumb/ radii anomalies<br>-Café au lait spots<br>-Hypo-/hyperpigmantation | -Short stature<br>-Thumb anomalies | -Pancreatic dysfunction<br>-Short stature<br>-Metaphyseal dysostosis | -Pulmonary dysfunction<br>-HPV-related warts<br>-Lymphedema<br>-DVT/PE<br>-Mycobacterial,fungal, viral infections<br>-MDS/AML | Recurrent infections |

# Approach for IBMFS



# *Whom to evaluate for IBMFS*

- All patients presenting with AA, MDS, acute myeloid leukemia (AML), and chronic unexplained cytopenias
- Patients with excess hematologic or other toxicities during treatment of an early-onset solid tumor characteristic of the IBMFSs

# Screening test for IBMFS

| | Macrocytosis | | | | | |
|---|---|---|---|---|---|---|
| Thrombocytopenia | | | Anemia | Neutropenia | | |
| **TAR** | **TBD** | **FA** | **DBA** | **SDS** | **GATA2 deficiency** | **SCN** |
| Arm X ray | Decresed lymphocyte telomere lengths | Spontaneous and DEB/MMC induced chromosome breaks and radial configurations | Elevated red cell adenosine deaminase | Decreased pancreatic isoamylase and/or trypsinogen | Increased FLT3 ligand | None |

# IBMFS genetics and inheritance patterns

| Syndrome | Gene | Inheritance pattern |
|---|---|---|
| **FA** | FANCA | AR |
| | FANCB | XLR |
| | FANCC | AR |
| **TBD** | DKC1 | XLR |
| | TERT | AD or AR |
| | ACD | AD or AR |
| **DBA** | RPS19 | AD |
| | GATA1 | XLR |
| **GATA2 deficiency** | GATA2 | AD |
| **SDS** | SBDS | AR |
| | DNAJC21/HSP40 | AR |
| **SCN** | ELANE | AD |
| | CSF3R | AR |
| **TAR** | RBM8A | AR |

# *Conclusions*

- Clinical diagnosis still critical
- > 90% of the time accurate in classical presentations
- Those without identifiable genetic diagnosis
- Combination of clinical features, screening tests, genetics together most likely to provide accurate diagnosis

# Inherited bone marrow failure syndromes: considerations pre- and posttransplant

*Blanche P. Alter*

*Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD*

# *HSCT in IBMFS*

- Hematopoietic stem cell transplantation (SCT) may cure some problems, prevent others, and introduce new ones.
- Important to distinguish an SCT-related late effect from a feature of aging in a person with an IBMFS to offer appropriate counseling, surveillance, and treatment.

# *Fanconi anemia*

- Hemato: AA, MDS, AML
- Onco:
  - H&N SCC (tongue, pharyngeal, laryngeal), esophagus
  - Anogenital SCC vulvar
  - Brain
  - Skin SCC and basal cell
  - HCC

Relative risk of cancer : 20-40 fold increased compared with general population

# *Fanconi anemia after SCT*

- Hemato: ~~AA, MDS, AML~~ chronic GVHD
- Onco:
  - H&N SCC (tongue, pharyngeal, laryngeal), esophagus
  - Anogenital SCC vulvar
  - Brain
  - Skin SCC and basal cell
  - HCC
  - PTLD

Relative risk of cancer : ~~20-40~~ >50 fold increased compared with general population

# *Fanconi anemia*

- Indication for SCT : Pancytopenia (Hb <8 g/dL, ANC < 500 /$mm^3$ , plt < 20,000 $mm^3$
  - Considered in patients who have developed clonal cytogenetics ( gain of chromosome 1q or 3q26q29, deletion 7q, or abnormal RUNX1, or deletions of 5q, 13q, and 20q)
- Optimal recipient : Fewer than 20 units of rbc or plt transfusions

# *Fanconi anemia*

- Preparative regimens : reduced intensity conditioning, with low-dose cyclophosphamide, fludarbine, and busulfan, or low-dose irradiation, as well as T-depletion to reduce GVHD
- The patient must be reminded that although the bone marrow is “cured” of FA, the nonhematopoietic organs remain at the same or even increased risk of FA complications.

# *Dyskeratosis congenita*

- Hemato : AA, MDS, AML, Lymphomas
- Onco:
  - H&N SCC (tongue), esophagus
  - Anogenital SCC
  - Stomach, rectal adenoCA
  - Lung
  - Skin SCC and basal cell
  - HCC

  Relative risk of cancer : 5 fold increased compared with general population

# *Dyskeratosis congenita after SCT*

- Hemato : ~~AA, MDS, AML~~, Lymphomas chronic GVHD
- Onco:
  - H&N SCC (tongue), esophagus
  - Anogenital SCC
  - Stomach, rectal adenoCA
  - Lung
  - Skin SCC and basal cell
  - HCC
  - PTLD

Relative risk of cancer : 5 30 fold increased compared with general population

# *Dyskeratosis congenita*

- Indication for SCT : Marrow failure
- Preparative regimens : RIC
- Major post-SCT late effects
  - Pulmonary and liver disease (fibrosis)
  - Arteriovenous malformations

# *Diamond Blackfan anemia*

- Hemato: Anemia, MDS, AML
- Onco:
  - Colon, stomach
  - Lung
  - Osteosarcoma
  - HCC

Relative risk of cancer : 5 fold increased compared with genreal population

# Diamond Blackfan anemia after SCT

- Hemato: ~~Anemia, MDS, AML~~ Chronic GVHD
- Onco:
  - Colon, stomach
  - Lung
  - Osteosarcoma
  - HCC
  - PTLD

  Relative risk of cancer : ~~5~~ 32 fold increased compared with genreal population

# *Diamond Blackfan anemia*

- Indication for SCT :
  - Failure to respond to corticosteroids
  - Parental or patient preference to avoid potential toxicities from steroids or to avoid chronic transfusions and iron chelation
- Preparative regimens : Myeloablative regimens with fludarabine and busulfan or treosulfan
- No published data on the use of RIC

# *Shwachman Diamond syndrome*

- Hemato: Neutropenia, AA, MDS, AML
- Onco:
  - Ovarian cancer

  Relative risk of cancer : 8 fold increased compared with general population

# Shwachman Diamond syndrome after SCT

- Hemato: ~~Neutropenia, AA, MDS, AML~~ Chronic GVHD
- Onco:
  - Ovarian cancer

  Relative risk of cancer : ~~8~~ No report fold increased compared with general population

# *Shwachman Diamond syndrome*

- SCT may be recommended for patients with progressive pancytopenia.
- SCT experience in SDS is too small.

# Treatment of inherited bone marrow failure syndromes beyond transplantation

*Rodrigo T. Calado and Diego V. Clé*

*Department of Internal Medicine, University of São Paulo at Ribeirão Preto School of Medicine, Ribeirão Preto, SP, Brazil*

# Treatment of IBMFS

- Aim to restore hematopoiesis, prevent other organ damage, and reduce cancer risk
- Monitoring BMF :
  - Bone marrow biopsy, aspirate analysis, and cytogenetics should be performed annually to identify malignant clonal evolution.
  - Marrow function should be assessed every 4 to 6 months for patients with decreasing peripheral blood counts, those who are transfusion dependent, and those with abnormal cytogenetics.

# Treatment of IBMFS

- Antithymocyte globulin and cyclosporine
- Androgens
- Corticosteroids
- Growth factors and agonists

# *Androgens*

- Increase the red blood cell mass by stimulating the production of erythroid progenitors in the bone marrow
- Increase telomerase (TERT) gene expression in hematopoietic cells → Telomerase activity
- Danazol treatment led to telomere elongation in humans with telomeropathies.

# Androgens

| Study | Patients, N | Disease | Androgen | Median age, yrs | Median duration of therapy,yrs | Response, % | Toxicity |
|---|---|---|---|---|---|---|---|
| Scheckenbach et al. | 8 | FA | Danazol | 11 | 3 | 87 | - |
| Rose et al. | 10 | FA | Oxandrolone | 9 | 2 | 70 | Viril, liver, MDS |
| Paustian et al. | 37 | FA | Various | 8.8 | 4.2 | 68 | Viril, MDS, hepatic adenoma |
| Ribeiro et al. | 66 | FA | Oxy, danazol | 10.5 | 1.5 | 78 | Viril liver |
| Khincha et al. | 16 | DC | Oxy, fluoxy, nan | 11 | 2.2 | 69 | Bone fracture, viril, splenic peliosis, liver |
| Townsley et al. | 27 | Telomeropathy | Danazol | 41 | 2 | 83 | Liver, muscle |

# Corticosteroids

- Restricted for the treatment of Diamond-Blackfan anemia (DBA)
- Major aim of treatment :
  - maintain a stable hemoglobin concentration sufficient for adequate growth and development in children and for daily activities with minimal anemic symptoms in adults

# Corticosteroids

- Prednisolone : starting dose of 2 mg/kg per day
- Up to 80 % achieve response
- Increase in hemoglobin should be expected within 4 weeks.
- Steroids should be deferred until the age of 1 year to avoid potential effects on growth and neurocognitive development.

# Growth factors and agonists

- EPO
  - Small clinical trials failed to demonstrate any clinical benefit of EPO in DBA.
  - In other inherited marrow failures, EPO only produces transient and unsustainable hemoglobin responses.

# Growth factors and agonists

- G-CSF
  - Increase neutrophil counts in severe congenital neutropenia (SCN) and Shwachman-Diamond syndrome at 3-20 mcg /kg/day
  - Aim of long term use : prevent infections
  - G-CSF should be instituted when severe neutropenia develops or recurrent infections are present.
  - Long-term use of G-CSF in congenital neutropenia is associated with a risk of progression to MDS and AML. (mutant clonal expansion CSF3R, RUNX1)

# Growth factors and agonists

- Thrombopoietin receptor agonists
  - Eltrombopaq
    - restore trilineage hematopoiesis in refractory acquired aplastic anemia
    - hematologic response of 94%
    - considerably restored the number of $CD34_1$ cells in the bone marrow
  - Patients with inherited bone marrow failure syndromes should not receive eltrombopag outside the context of a clinical trial.

# Nonhematopoietic complications

- Nonhematologic cancers are not prevented by transplantation.
  - Should be screened for head and neck cancers every 6 months after age 10 years
- Pulmonary fibrosis and liver cirrhosis are common manifestations of telomere diseases with no effective available therapy.

# Nonhematopoietic complications

- Iron overload
  - Chelation should be started when the volume of transfused red cells reaches 200 mL/kg, the hepatic iron level is >5 mg/g dry weight, or the serum ferritin level is persistently >1000 mg/L.

# Oral presentation

**Paper No: 776**

**Eltrombopag Promotes DNA Repair in Human Hematopoietic Stem and Progenitor Cells: Implications for the Treatment of Fanconi Anemia**

Kacey Linnea Guenther, BS, NIH

**Paper No: 777**

**Eltrombopag for Refractory Severe Aplastic Anemia: Dosing Regimens, Long-Term Follow-up, Clonal Evolution and Somatic Mutation Profiling**

Thomas Winkler, MD, NHI

**Paper No: 776**

**Eltrombopag Promotes DNA Repair in Human Hematopoietic Stem and Progenitor Cells: Implications for the Treatment of Fanconi Anemia**

Kacey Linnea Guenther, BS, NIH

- Thrombopoietin (TPO) was shown to specifically increase the efficiency of non-homologous end joining (NHEJ), the predominant repair mechanism for DNA double strand breaks(DSBs) in hematopoietic stem/progenitor cell(HSPC)

- Can Eltrombopaq (epaq) promote NHEJ DSB repair in human HSPCs ?
- Potential new therapeutic modality for patients with Fanconi anemia ?

- Epaq and TPO increase the kinetics of DSB repair in FA HSPCs.
- Phase II clinical trial is in development to assess safety and efficacy of epaq in the treatment of hematological manifestations of FA.

**Paper No: 777**

**Eltrombopag for Refractory Severe Aplastic Anemia: Dosing Regimens, Long-Term Follow-up, Clonal Evolution and Somatic Mutation Profiling**

Thomas Winkler, MD, NHI

- Elthrombopaq (EPAG) – FDA approval for treatment of refractory severe aplastic anemia in 2014
- Further investigation :
  - Extended administration of EPAG at a fixed dose of 150 mg could speed and improve response rates.
  - New cytogenetic abnormalities on EPAG patients ,raising concerns that EPAG might promote progression to MDS/AML.

- Phase II study
- EPAG 150 mg daily for 6 months in patients with refractory SAA
- 39 patients between July 2013 and April 2017
- Primary endpoint : hematologic response at 6 months
- Secondary endpoint : response at 3 months and the rate of clonal cytogenetic evolution

- 19/39 (49%) – hematologic response at 6 months
  - 5/19 (26%) non responders at 3 months
  - 18/19 extension arm
  - EPAG was discontinued for robust response in 13/18 (72%) (median duration of drug use 12 months)
  - EPAG was reinitiated for relapse in 3/13.
  - 3/3 recovered response.

- At median follow up of 6 months , 6/39 (15%) developed marrow cytogenetic abnormalities.
- In summary:
  - EPAG at a fixed dose of 150 mg daily for 6 months induces additional responses in rSAA.
  - After EPAG was discontinued, most patients maintained durable robust responses.
  - EPAG may promote expansion of dormant pre-exist clones with and an aberrant keryotype.
  - No clinical or laboratory findings prior to therapy predicted response or risk of clonal evolution.

คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล
FACULTY OF MEDICINE SIRIRAJ HOSPITAL

# New monogenic disorders identify more pathways to neutropenia: from the clinic to next-generation sequencing

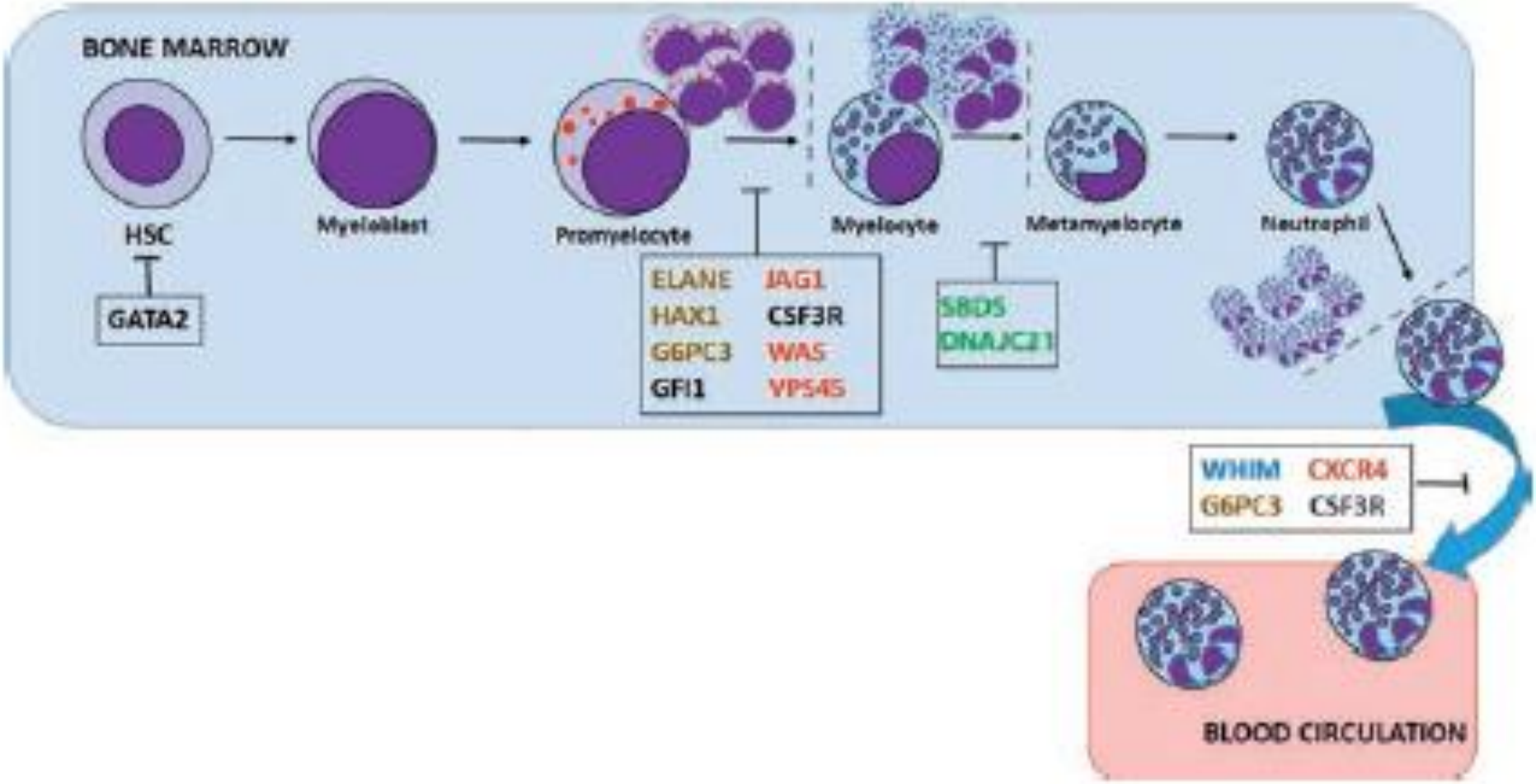
*Seth J. Corey and Usua Oyarbide*

*Department of Pediatrics, Massey Cancer Center, Virginia Commonwealth University, Richmond, VA*

# *Neutropenia*

- Reduction from a normal range in the number of circulating neutrophils
- Mild – ANC 1,000-1,500 /$mm^3$
- Moderate – ANC 500-1,000 /$mm^3$
- Severe – ANC < 500 /$mm^3$

# Mutations and neutropenia



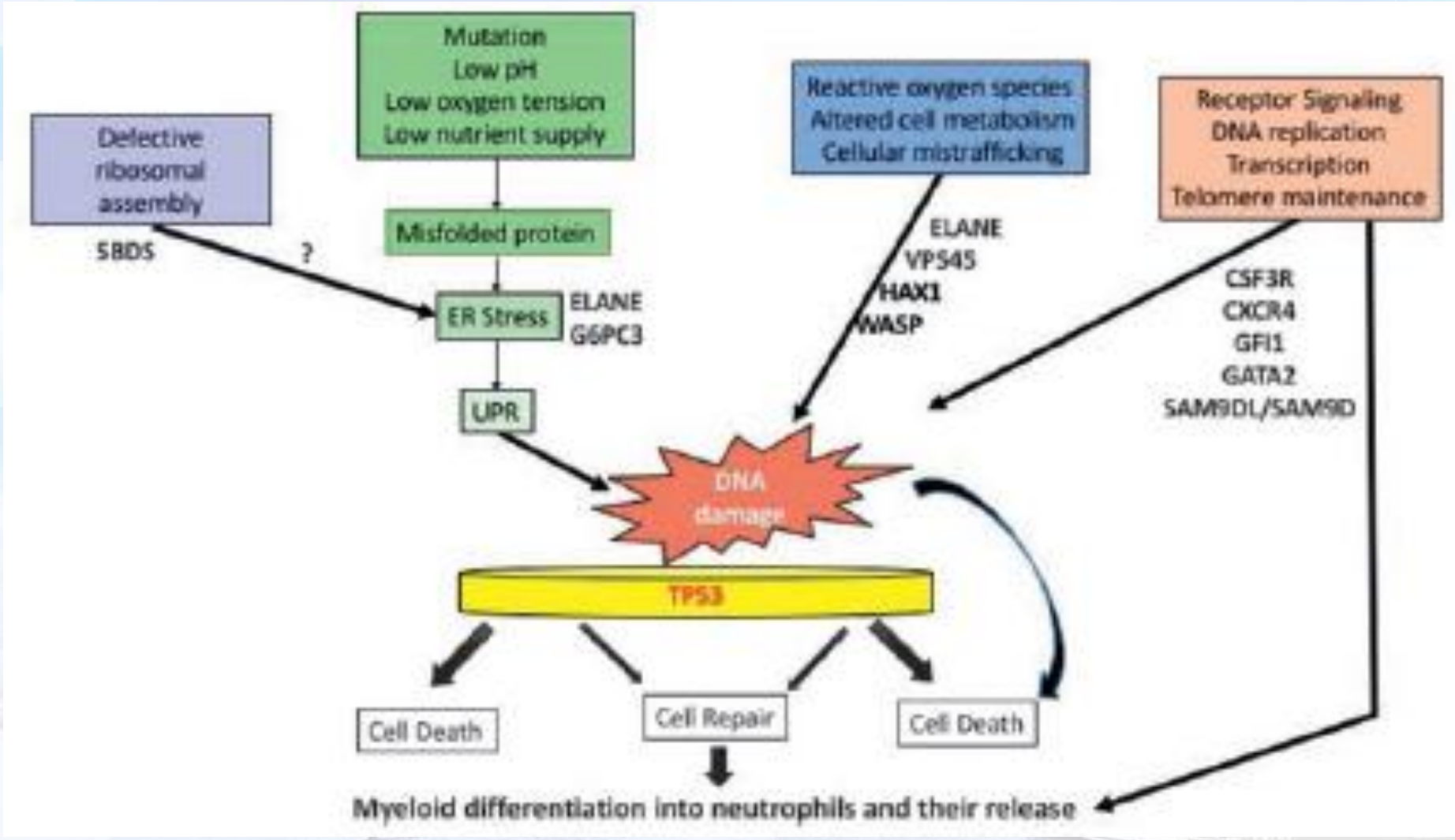
# Monogenic disorders associated with severe neutropenia

| Disease | Gene | Function | Incidence | Inheritance | Clinical features |
|---|---|---|---|---|---|
| SCN and CyN | ELANE | Serine protease | 40-60% | AD | Isolated neutropenia |
| Kostmann syndrome | HAX1 | Mitochondrial protein | 10% | AR | Neurologic |
| G6PC3 deficiency | G6PC3 | Glucose metabolism | multiple | AR | Cardiac, urogenital, thrombocytopenia , bone defects |
| Wiskott-Aldrich syndrome | WAS | Actin cytoskeletal activator | multiple | X linked | Monocytopenia and T activation |
| CSF3R deficiency | CSF3R | GCSF receptor | Multiple | AD | Resistance to G-CSF |

# Monogenic disorders associated with moderate neutropenia

| Disease | Gene | Function | Incidence | Inheritance | Clinical features |
|---|---|---|---|---|---|
| Shwachman-Diamond syndrome (SDS) | SBDS | Ribosomal protein | 90% | AR | Pancreatic insufficiency |
| | DNAJC21 | Heat shock protein | <10% | AR | Pancreatic insufficiency |
| GATA2 deficiency | GATA2 | Transcription factor | Unknown | AD | Monocytopenia , MDS |
| WHIM syndrome | CXCR4 | Chemokine receptor | Unknown | AD | Warts, hypogammaglobulinemia, infections ,neutropenia |

# Proposed pathways of neutropenia



# *Next-generation sequencing (NGS)*

- Evaluation for a wide range of mutations and quantification of variant alleles (useful in determining mosaicism)
- Early identification of cancer/leukemia predisposition syndromes
- Identification of genetic disorders that confer increased toxicity in chemotherapy and/or myeloablative transplantation regimens
- Better scrutiny of related stem cell donors
- More accurate family planning and genetic counseling

# *Treatment of neutropenia*

- Patients without an underlying syndrome or history of recurrent infections are unlikely to benefit from filgrastim.
- Filgrastim is highly effective in SCN and moderate neutropenia associated with conditions such as SDS.

# *Treatment of neutropenia*

- Some patients will not respond to filgrastim (>10 mcg/kg per day), and they need to be evaluated for CSF3R mutations.
- Prophylactic antibiotics and/or antifungal therapy should be used only for those with documented infections.

# Treatment of neutropenia

- Indications for an allogeneic stem cell transplant
  - filgrastim nonresponsive patients
  - requiring high doses of filgrastim
  - presence of a mutated CSF3R
  - frank myelodysplasia or increased bone marrow or peripheral blasts

# Non–chemotherapy drug–induced neutropenia: key points to manage the challenges

*Brian R. Curtis*

*Blood Research Institute, BloodCenter of Wisconsin, Milwaukee, WI*

# Neutropenia

- Reduction of neutrophils (segmented and band cells) in the blood
  - absolute neutrophil count (ANC) < 1,500 /$mm^3$
  - ANC < 500 /$mm^3$ is considered severe neutropenia
  - ANC < 100 /$mm^3$ are at severe risk of morbidity and mortality from infections

# Causes of neutropenia

- Myeloid suppression :decreased production or direct cytotoxicity
  - IBMFS
  - MDS
  - Other marrow infiltrative malignacies and disorders
  - Chemotherapy
  - Alcohol use disorder
  - Idiopathic neutropenia in adults
  - Vitamin B12 deficiency
  - Copper deficiency
  - Metabolic disorders (Pearson syndrome, Gaucher syndrome, acidemias)

# Causes of neutropenia

- Infection induced
  - Viral infections : Hepatitis A, B,C , HIV, EBV, CMV, HHV6
  - Lyme disease
  - Malaria
  - Salmonella infection
  - Mycobacterial infection
  - Fungal infection
  - sepsis

# Causes of neutropenia

- Neutrophils destruction : immune mediated
  - Secondary to autoimmune disorders : RA, SLE
  - Drug induced : antibiotics , antithyroid drugs, clozapine and others
  - Hypersplenism
  - Autoimmune neutropenia
  - Neonatal alloimmune neutropenia : maternal Ab against human neutrophil alloAg destroy fetal and neonatal neutrophils

# *Drug induced neutropenia*

- Decreased production of neutrophils
  - Frequently a consequence of chemotherapeutic drugs that cause suppression of bone marrow myeloid progenitor cells
- Increased destruction of neutrophils – Idiosyncratic drug-induced neutropenia (IDIN)
  - Commonly caused by adverse idiosyncratic reactions to nonchemotherapy drugs

# *Idiosyncratic drug-induced neutropenia (IDIN)*

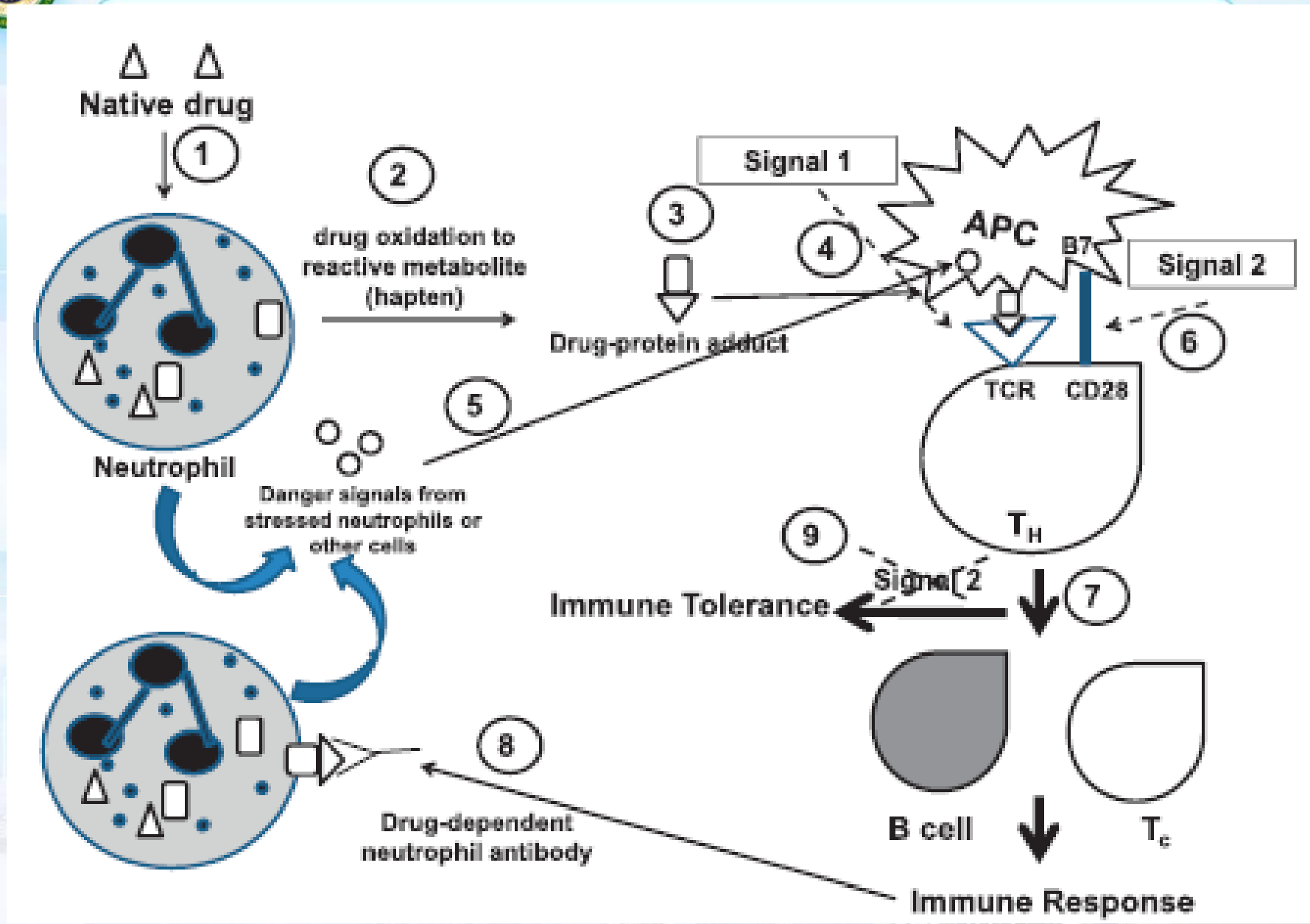
- Annual incidence of IDIN 2.4 -15.4 cases per year per million population
- Increases with age and polypharmacy
- Mortality associated with IDIN 5 %
  - Increase with age (esp. aged > 65 years) , ANC < 100 /$mm^3$ , concomitant renal disease, septicemia and shock

# Drugs most frequently reported to cause IDIN

| Huber et al. | Medrano-Casique et al. | Andres et al. | Curtis |
|---|---|---|---|
| Carbamazepine | Benzylpenicillin | Amoxicillin | Ceftriaxone |
| Clozapine | Cefepime | Carbimazole | Ciprofloxacin |
| Metamizole(dipyrone) | Meropenem | Clozapine | Piperacillin-tazobactam |
| Sulfasalazine | Piperacillin-tazobactam | Cotrimoxazole | sulfamethoxazole /trimethoprim |
| thiamazole | vancomycin | Ticlopidine | vancomycin |

# Proposed mechanisms for IDIN

- Immune- mediated mechanism
  - Hapten hypothesis
  - Danger hypothesis


Native drug
1
2
drug oxidation to reactive metabolite (hapten)
Signal 1
3
4
APC
B7
Signal 2
Drug-protein adduct
6
TCR
CD28
5
Neutrophil
Danger signals from stressed neutrophils or other cells
$T_H$
9
Signal 2
Immune Tolerance
7
B cell
$T_c$
8
Drug-dependent neutrophil antibody
Immune Response

# *Hapten hypothesis*

- Hapten
  - low-molecular-weight (usually < 5000 Da) molecules
  - not capable of eliciting an immune response by themselves but can when coupled to a large carrier molecule, usually a protein
- Neutrophil glycoprotein–drug complexes on the cell membrane surface leading to neutrophil clearance/destruction

# *Danger hypothesis*

- Danger signal produced by injured cells that leads to co-stimulation of APC and TH cells, culminating in production of specific antibodies and cytotoxic T cells.

# *Testing for drug-dependent neutrophil antibodies*

- Testing for drug-dependent neutrophil antibodies is rarely performed.
- Due to the daily requirement to use freshly isolated cells, because neutrophils cannot be stored for long periods.

# Treatment

- Discontinuation of the offending drug
- Treatment of patients with severe neutropenia using G-CSF is controversial.
  - Some reports show shortened duration of neutropenia,antibiotic therapy, and hospital length of stay
  - Only prospective, randomized trial to date did not confirm the benefit of G-CSF therapy.

# Treatment

- Patients with a neutrophil count < 100 /$mm^3$ have been reported to have more infections and fatal complications than those with a higher nadir.
- Patients with a neutrophil nadir < 100 /$mm^3$ should therefore receive G-CSF 300 mg/d regardless of the presence of infection.

คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล
FACULTY OF MEDICINE SIRIRAJ HOSPITAL

# Chronic neutropenia in LGL leukemia and rheumatoid arthritis

*Tal Gazitt[1] and Thomas P. Loughran, Jr.[2]*

*[1]University of Washington, Seattle, WA; and [2]University of Virginia, Charlottesville, VA*

# *Large granular lymphocyte (LGL) leukemia*

- 3 categories
  - T-cell large granular lymphocytic leukemia (T-LGLL)
  - Chronic lymphoproliferative disorder of NK cells (NK-LGLL )
  - Aggressive NK-cell leukemia (ANKL)

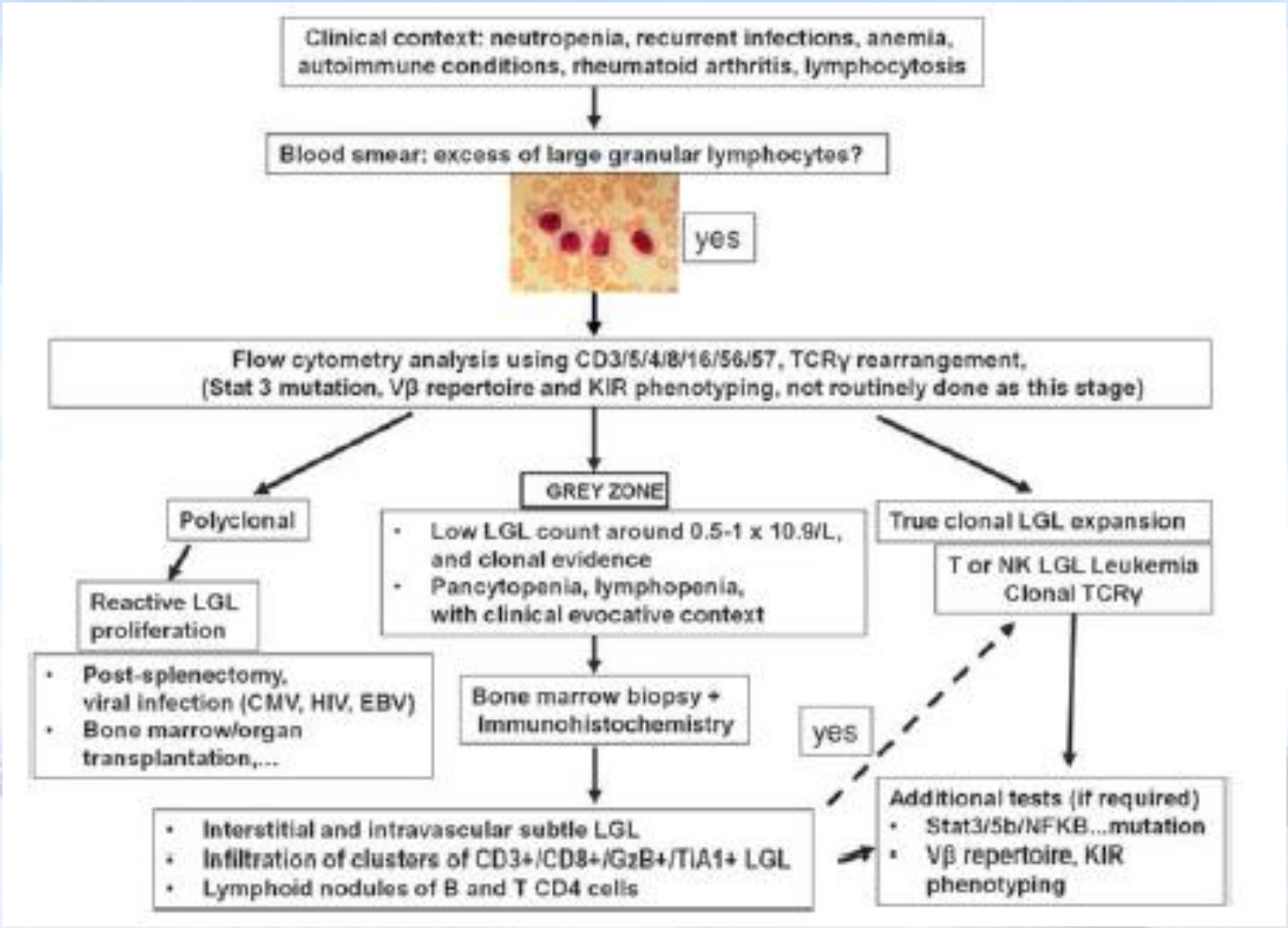
# *LGL leukemia*

- Presenting features : cytopenias or autoimmune diseases
- Excess large granular lymphocytes > 500 /$mm^3$ on peripheral blood smear
- Flow cytometry :
  - T cell form CD3+, CD8+, CD57+
  - NK cell form CD3-, CD8+, CD16+, CD56+

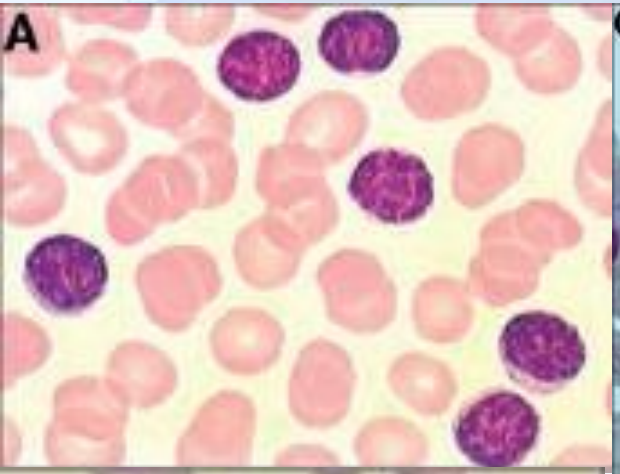
# Clinical features of LGL leukemia

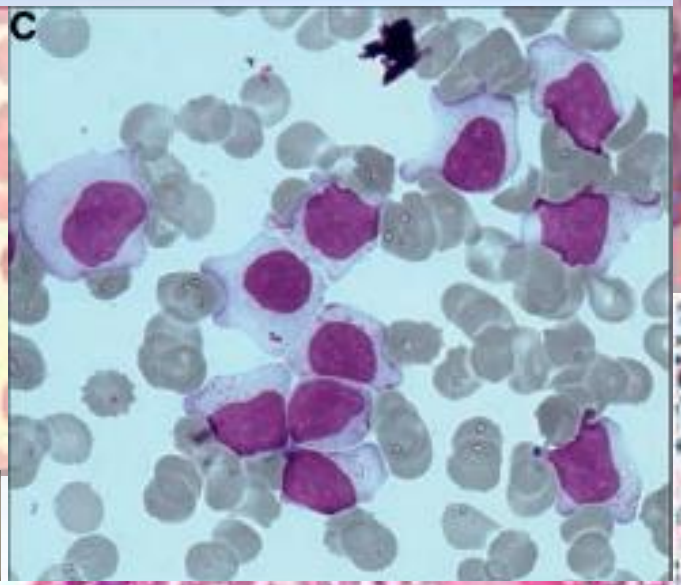
- Chronic neutropenia
  - Bacterial infection at skin, oropharynx and perirectal regions
- Anemia
- Hepatosplenomegaly
- B symptoms
- Autoimmune diseases (most frequently rheumatoid arthritis)

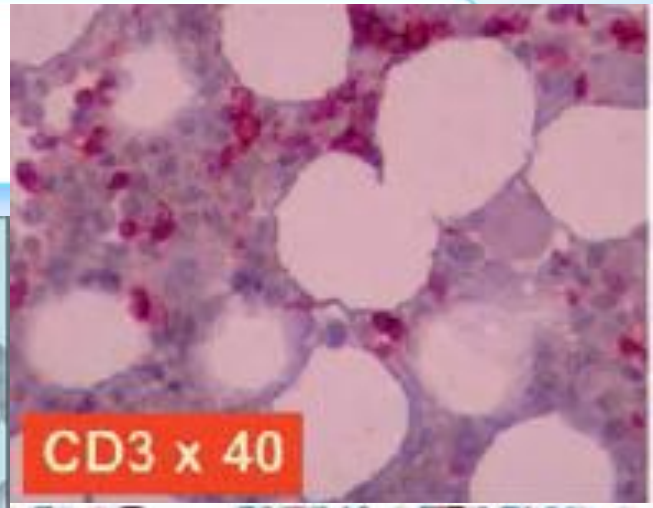
# Diagnosis of LGL leukemia

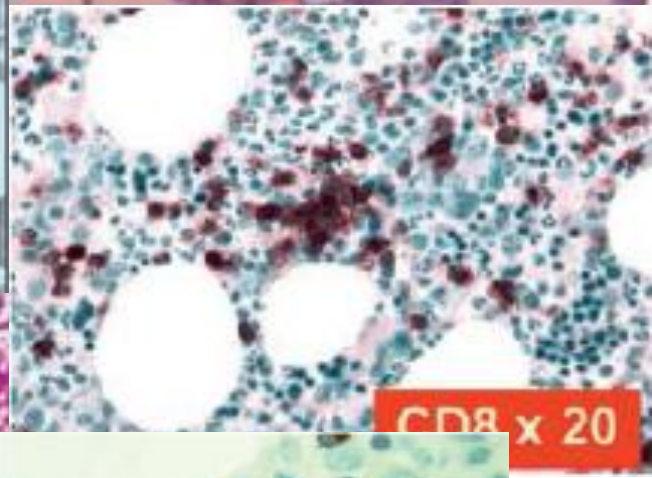


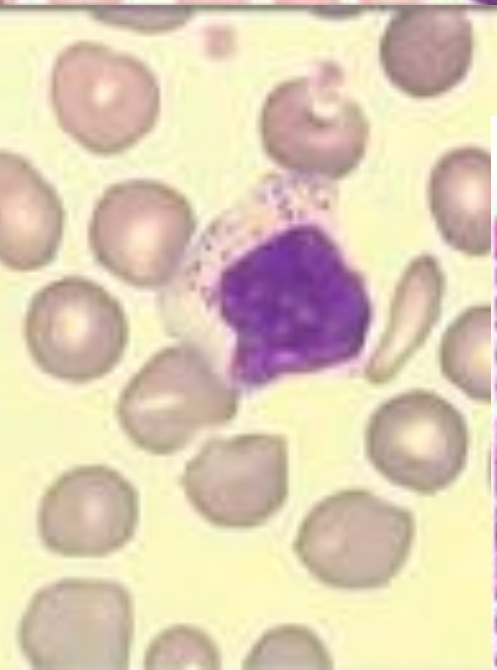
# LGL leukemia

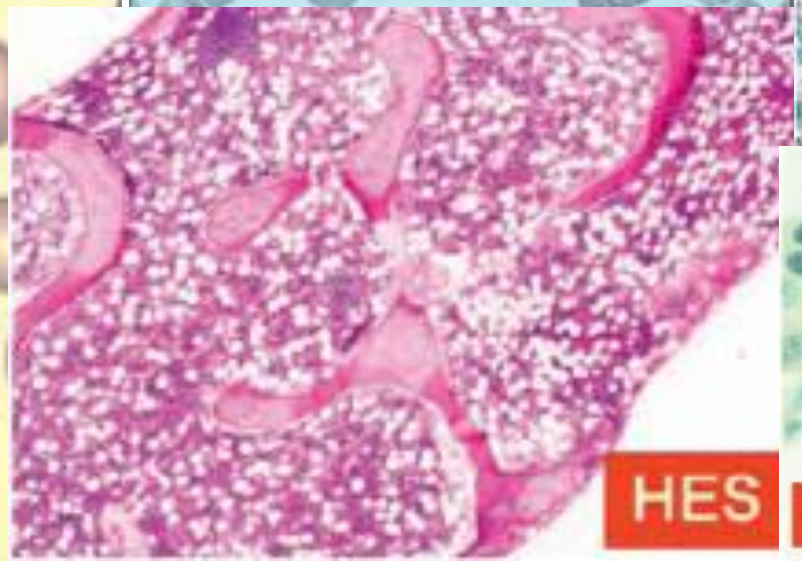


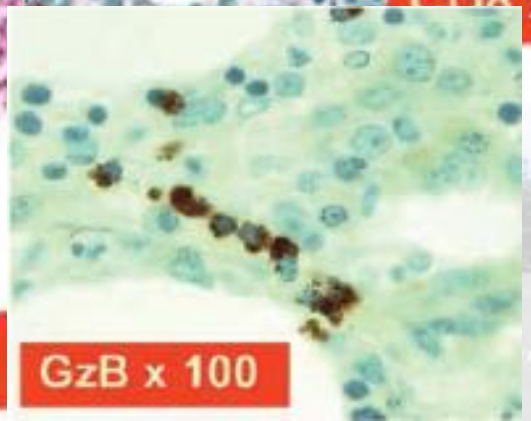



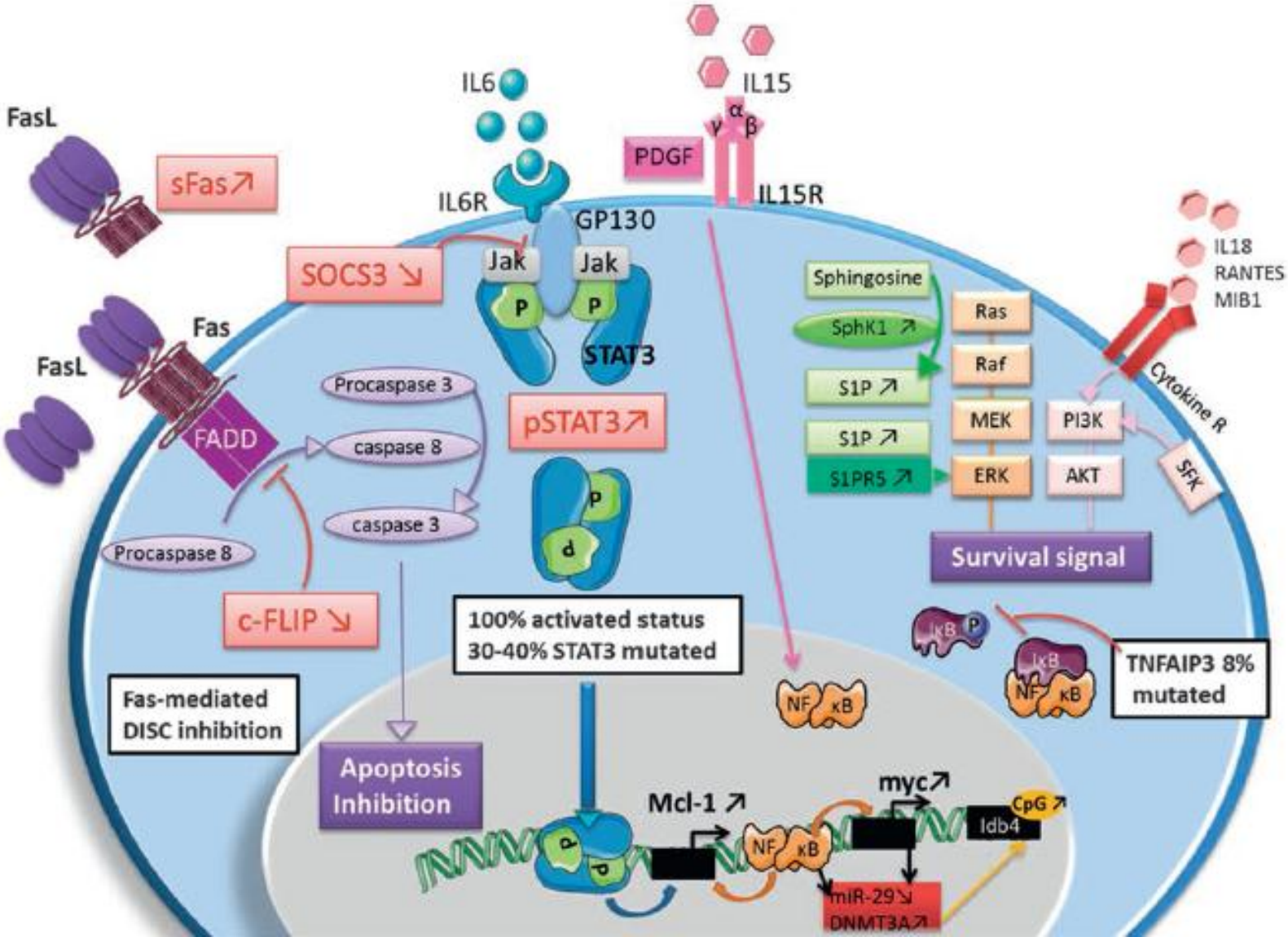


# *Felty's syndrome (FS)*

- Triad of RA, splenomegaly and neutropenia
- 20% of T-LGLL patients have RA.
  - Clinically indistinguishable from FS
  - Shared predilection for HLA-DR4
  - Spectrum of a similar disease process (proposed)

# Mechanism of neutropenia



# *Mechanisms of neutropenia in LGL and RA*

- Anti-neutrophil Ab (Immune complexes)
- Soluble Fas Ligand

# Treatment of LGL leukemia

- Indications for treatment
  - Persistent severe neutropenia (< 500 /$mm^3$ )
  - Symptomatic or transfusion dependent anemia
  - RA requiring immunomodulatory therapy
- Immunosuppressive regimens
  - Methotrexate
  - Cyclophosphamide
  - Cyclosporin A
  - Prednisolone

# Treatment recommendations

- Standard therapy :
  - Methotrexate 10 mg/$m^2$ PO once weekly in divided doses
  - Cyclophosphamide 100 mg PO daily
  - Cyclosporine 3-5 mg/kg PO daily in divided doses
- Clinical trials

How I treat LGL leukemia :
Blood 117;2764, 2011

# *Treatment of LGL leukemia*

- In the prospective Eastern Cooperative Oncology Group trial, the median overall survival for patients with anemia was 69 months, whereas median overall survival for patients with neutropenia had not been reached 13 years

คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล
FACULTY OF MEDICINE SIRIRAJ HOSPITAL

# Acquired ribosomopathies in leukemia and solid tumors

*Adrianna Vlachos*

*Feinstein Institute for Medical Research, Cohen Children's Medical Center, Division of Hematology/Oncology and Stem Cell Transplantation, Zucker School of Medicine, Hofstra/Northwell, Manhasset, NY*

- In 1997 : Diamond-Blackfan anemia (DBA) (defect in the gene encoding the small subunit- associated ribosomal protein RPS19)
  - Predisposed to a variety of solid tumors , MDS and AML
- Shwachman-Diamond syndrome (SDS) (mutations in SBDS leading to faulty ribosome subunit joining)
  - Predisposed to MDS and AML
- In 2006 : 5q- syndrome (acquired somatic RPS14 deletion)

- Somatic mutations in genes encoding RPs seem to be a common feature of many cancers, suggesting their importance in oncogenesis.

# Cancer types and associated RP mutations or deletions

| Cancer type | RP mutation/deletion |
|---|---|
| T-cell ALL | RPL5,RPL10,RPL11,RPL22 |
| Chronic lymphoblastic leukemia | RPS15,RPSA,RPS20 |
| 5q- syndrome | RPS14 |
| Glioblastoma multiforme | RPL5 |
| Gastric adenocarcinoma | RPSA, RPS5, RPL22 |
| Endometrial carcinoma | RPS20, RPL22 |
| Melanoma | RPL5, RPL11, RPS27 |
| Breast cancer | RPL5 |

- Overexpression of RPs that results in disrupted translation can be an oncogenic driver that confers malignant growth potential to tissues with such acquired mutations.
- RP haploinsufficiency, both germline (DBA) and somatic (5q– syndrome and other cancers), creates a selective pressure predisposing to malignancy.

# Role of RP mutations in Oncogenesis

- Proposed mechanisms for oncogenesis :
  - Germline or somatic RP mutations create nucleolar stress and mediate the HDM2-p53 tumor suppressor mechanism leading to apoptosis and cell cycle arrest.
  - Some ribosomal proteins behave as classical tumor suppressors.

# *Thank you*