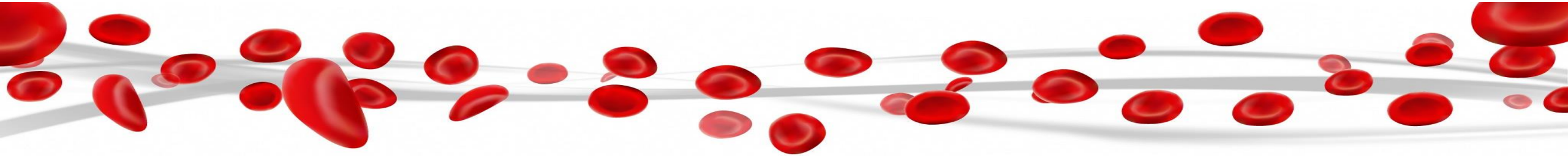


Management of inherited disorders outside transplantation

Francesca Fioredda, MD

Unit of Hematology
IRCCS Ospedale Giannina Gaslini

ERN-EuroBloodNet
Focus on BMF Syndromes
Genova–Italy
22nd February 2022

Co-funded by
the Health Programme
of the European Union

EBMT

European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

Conflicts of interest

DISCLOSURE

Objectives of the webinar

1. Why HSCT is not always indicated in Inherited Bone Marrow Failure
2. Alternative strategies to HSCT
   - “ Old drugs”
   - Growth-factors/Agonists
   - Target molecules
   - Gene therapy

1. Why not always HSCT in Inherited BMF

Comorbidities

Cancer predisposition

Reversion/compensation

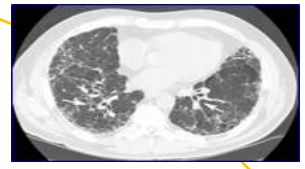
Access and costs

Alternatives strategies

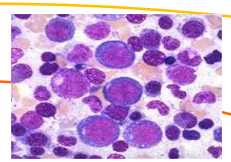
Comorbidities 1

TELOMERS DISEASES

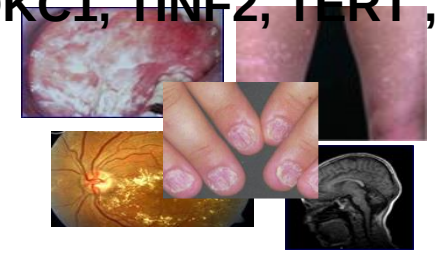
Idiopathic Lung Fibrosis
TERT / TERC
PARN/RTEL1

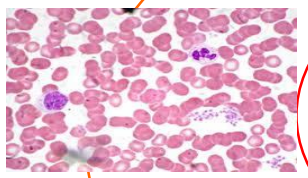


MDS/LA
TERT/TERC
RTEL1

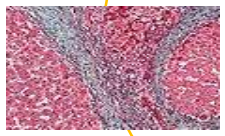


Diskeratosis congenita
DKC1, TINF2, TERT , TERT , TINF2, CTC1,PARN etc

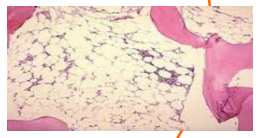




Cytopenias
R-TEL1/TINF2



Cryptogenetic liver cirrhosis
TERC/TERT



Aplastic Anemia
TERT / TERC

Hoyeraal Hreidarsson Syndrome
Revez Syndrome
Plus Syndrome

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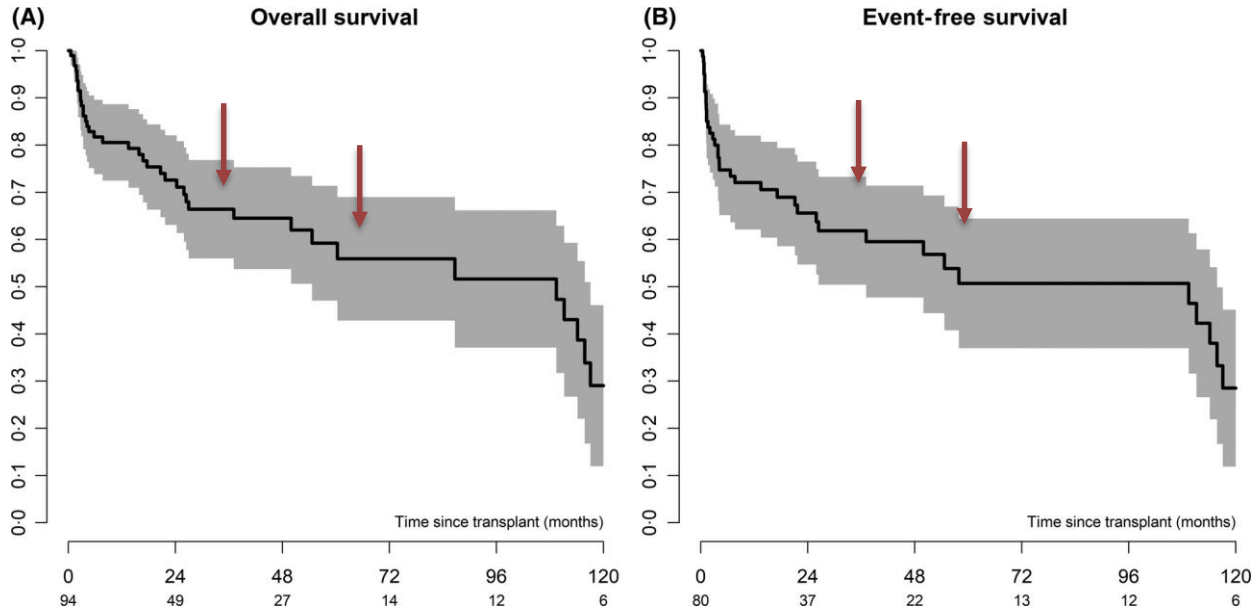
Calado Rt , Hepatology 2011 , Armanios M , Mutat Res 2012

Thursdays Webinars

Comorbidities 2

HSCT Outcome in Diskeratosis congenita



organ failure

T/B cell deficiency

Chronic GVhD

P=0.038

Deaths

p=0.014

Pulmonary Fibrosis

p=0.06

Fioredda F, BJH 2018

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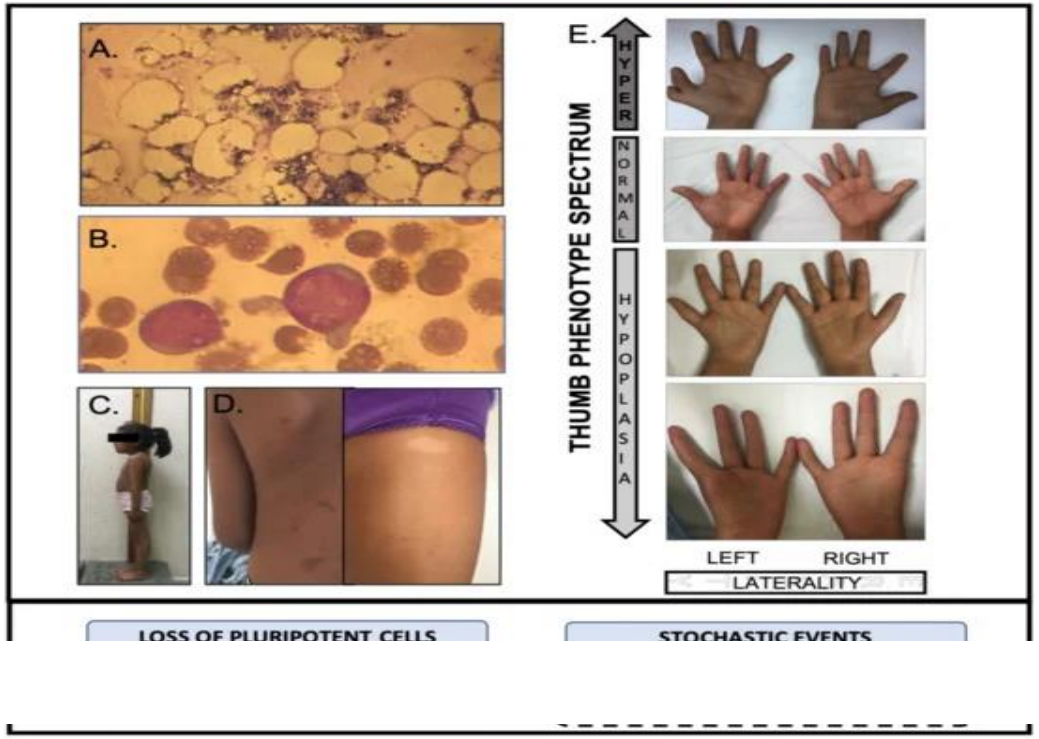
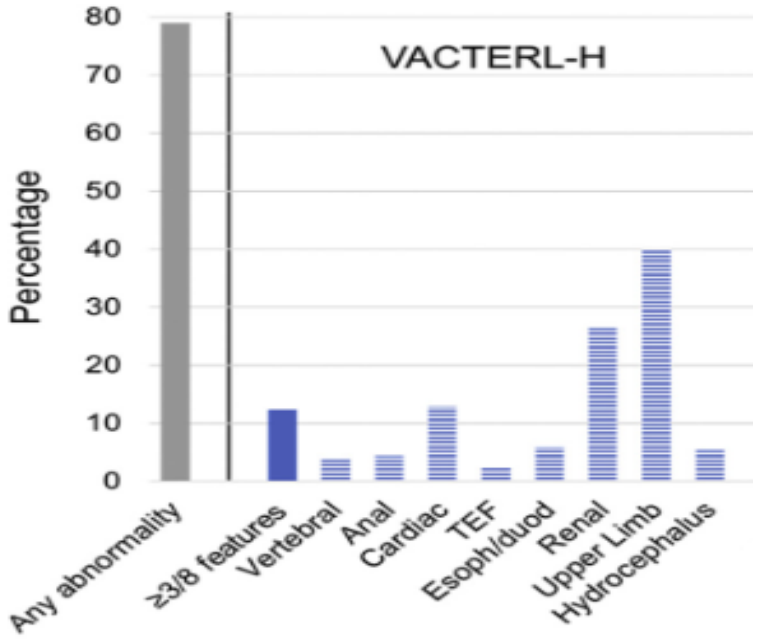
Thursdays Webinars

Comorbidities 3

FANCONI ANEMIA





- developmental alteration
- bone marrow failure
- >risk to develop cancer

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for rare or low prevalence complex diseases
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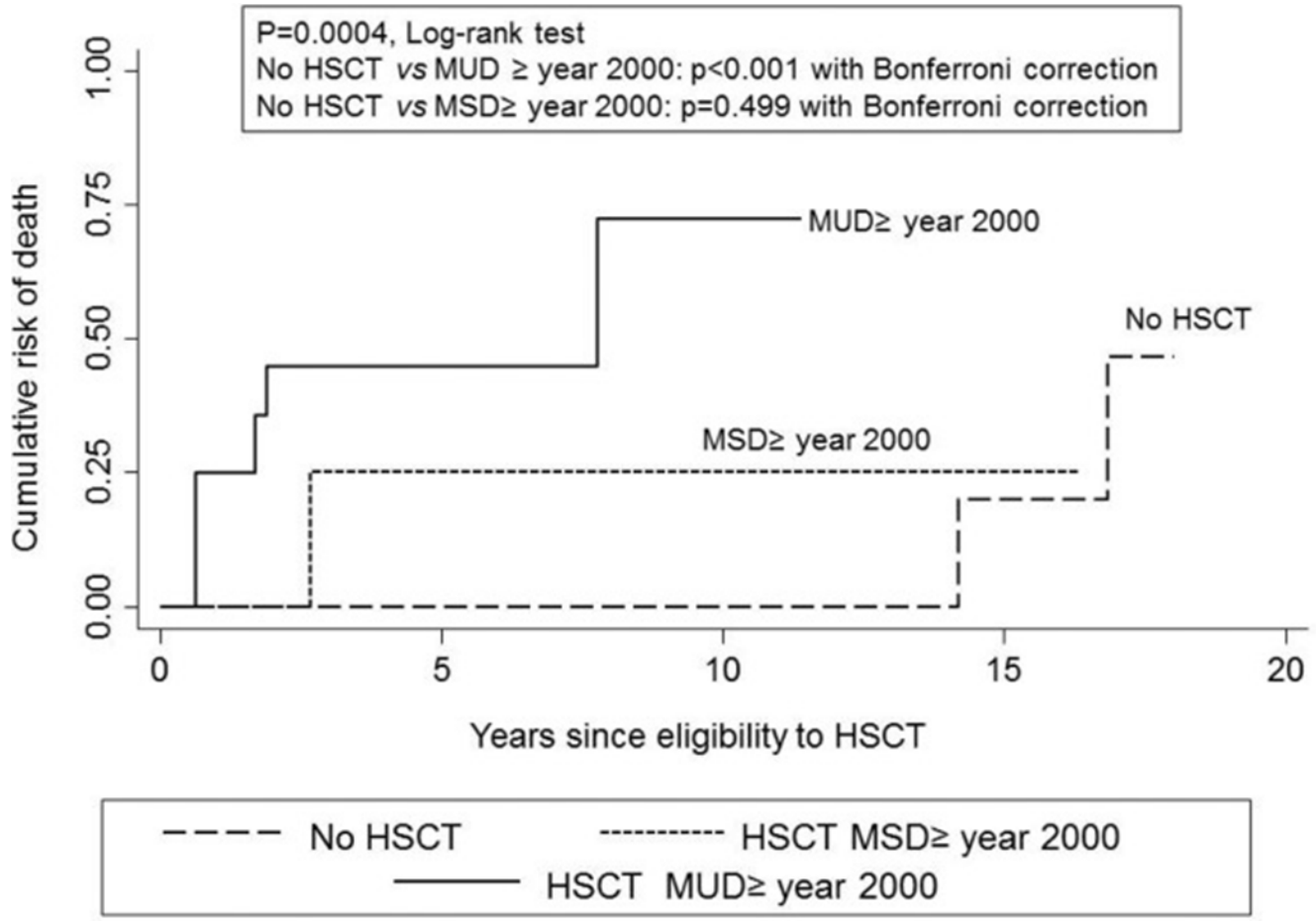
Fiesco Roa MO , Blood Rewiews 2019

Thursdays Webinars

Comorbidities 4

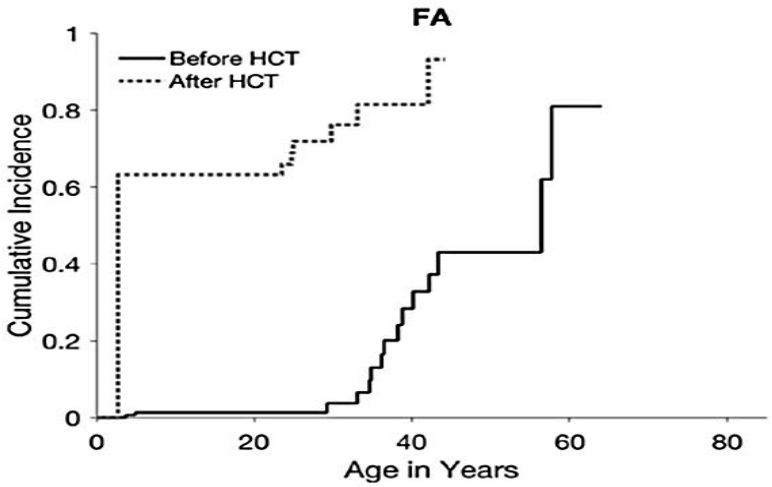
HSCT Outcome in Fanconi Anemia

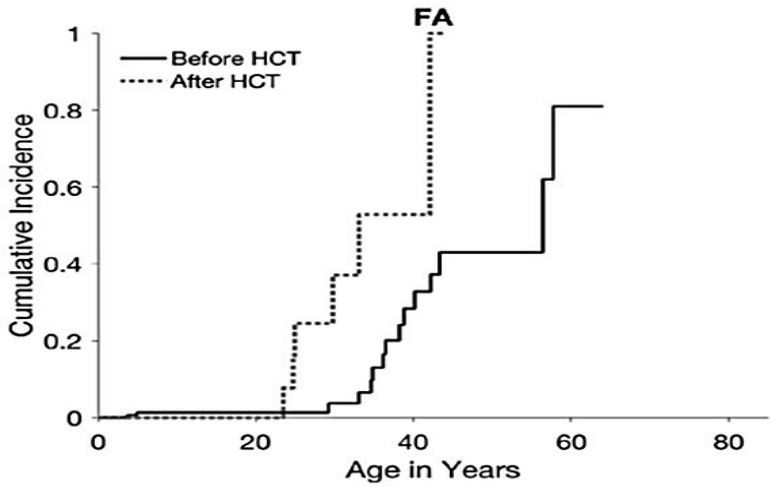


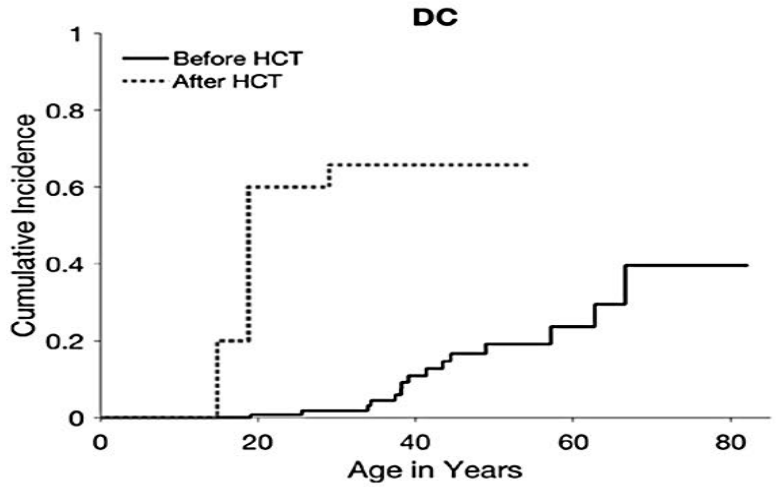
Svahn J Am J Hematol 2016

Cancer predisposition in BFM/HSCT

360 families DBA, DC, FA, SDS
530 affected individuals





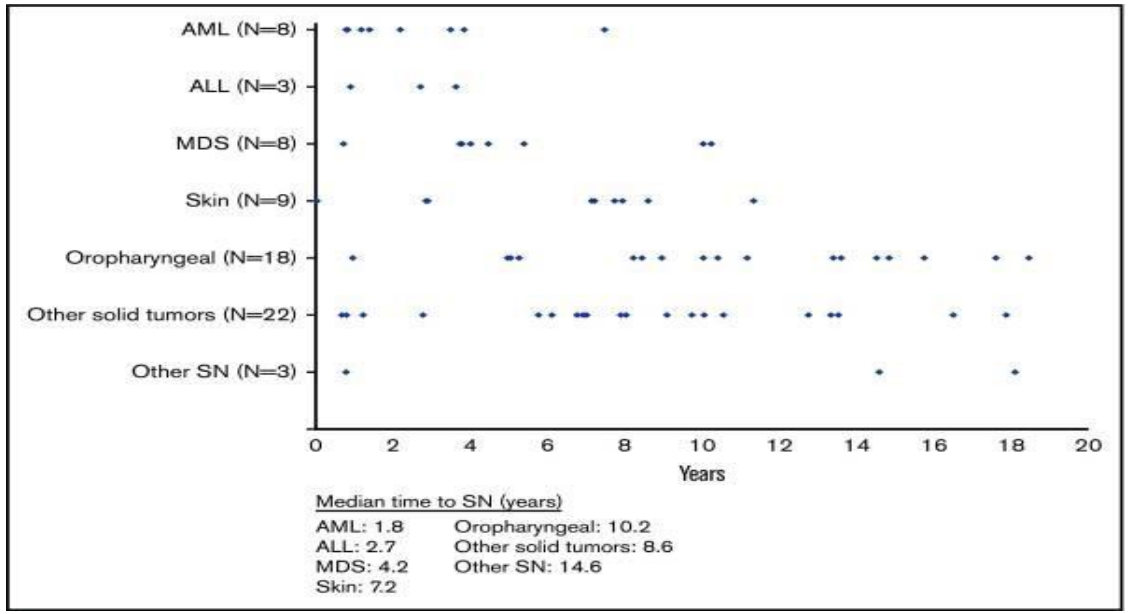


O/E ratio any malignancy in non-transplanted patients
2.5 DBA, 4.2 DC, 19 FA, 8.5 SDS

O/E ratios for the transplanted vs. the non-trans- planted groups
DBA 81 vs. 2.5, DC 30 vs. 4.2, FA 55 vs. 19

Alter B, Hematologica 2018

Cancer predisposition in BFM/HSCT



6028 patients
(2015-2020)

SAA 24%
Fanconi anemia 10%
other marrow failure 6%
hemoglobinopathy 15%
immunodeficiency 23%
metabolic/leukodystrophy syndrome 22%

> AML /ALL

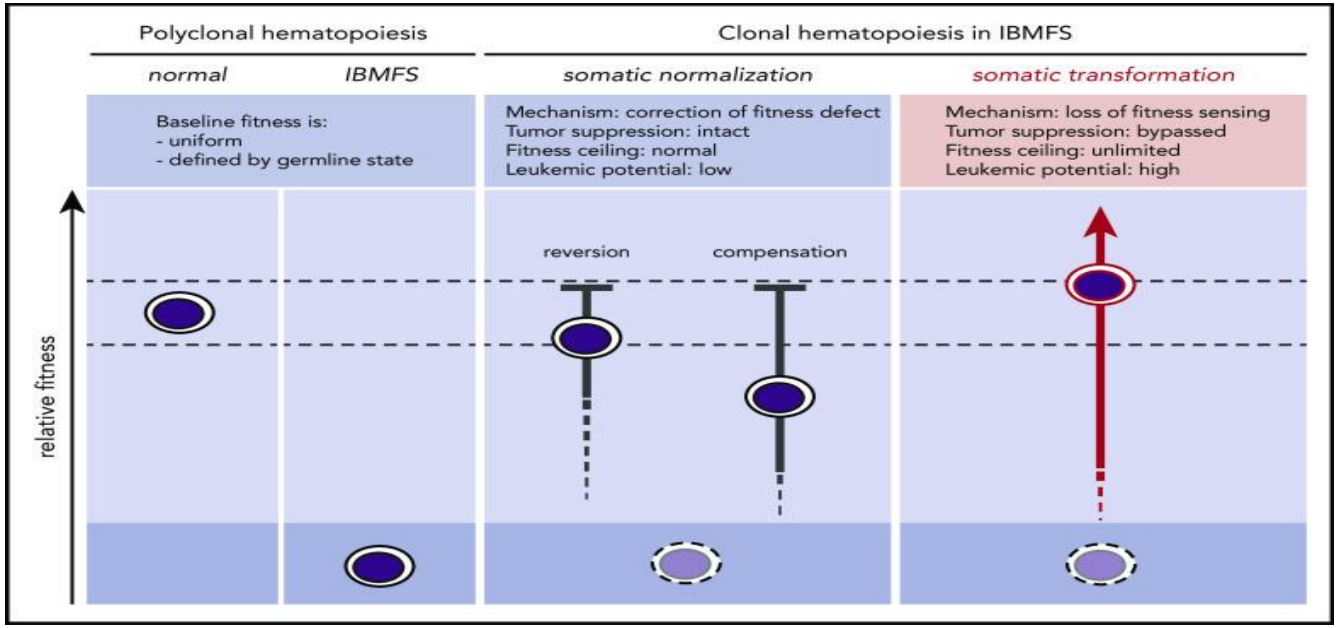
> oropharyngeal, skin, thyroid, liver, and bladder tumors

> tongue and mouth tumors in FA and marrow failure syndromes

TBI-based conditioning regimen and chronic GVHD FA patents :2.5-fold and 4.8 increa
hazard of secondary neoplasia (p<0.001)

Kahn JM , Blood Adv 2020

Reversion/compensation



Reversion/compensation

Some somatic alterations can normalize the underlying germline deficit through direct reversion or indirect compensation

Tsai FD, Blood 2020

Access to allo-HSCT

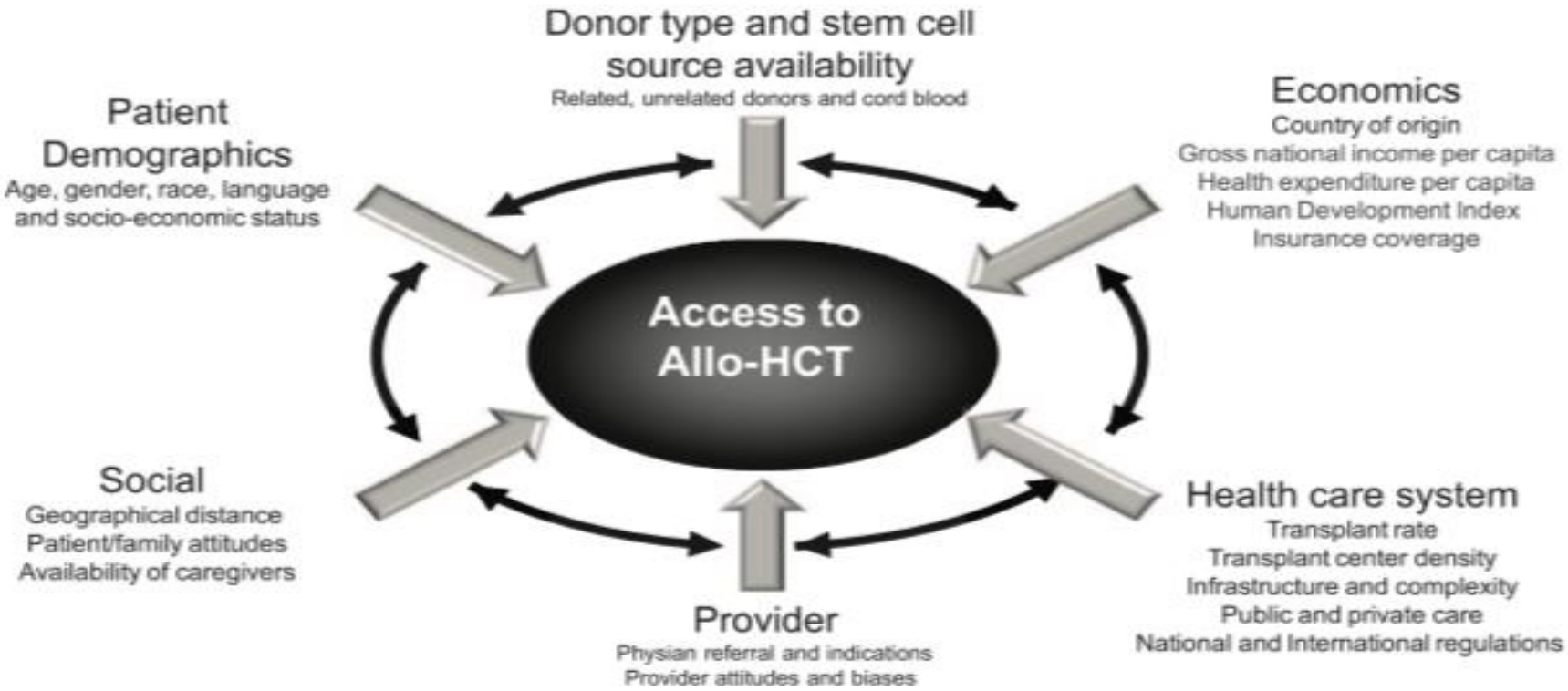
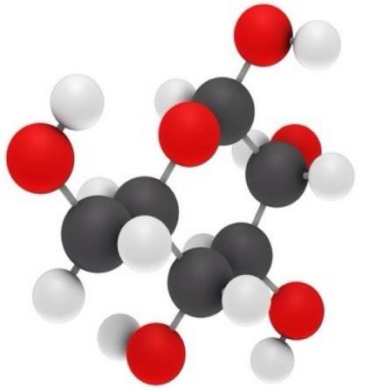


Figure 4. Factors associated with access to allo-HCT: an international perspective.

Rocha V , ASH Educational Programm 2021

2.Alternatives strategies

"Old drugs"
Corticosteroids
Androgens



Growth-factors/agonists
G-CSF
Eltrombopag

Target molecules

Approach to Gene Therapy

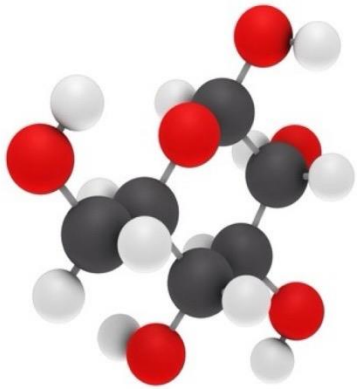
Calado R , Hematology Am Soc Hematol Educ Program. 2017

2.Alternatives strategies

"Old drugs"

Corticosteroids

Androgens



Growth factors/agonists

G-CSF

Eltrombopag

Target molecules

Approach to Gene Therapy

Calado R , Hematology Am Soc Hematol Educ Program. 2017

Old drugs

Corticosteroids in DBA

Corticosteroids (prednisone or prednisolone) 2mg/kg/d
2 weeks > reticulocyte count and Hb

Goal Hb>9 gr/dL

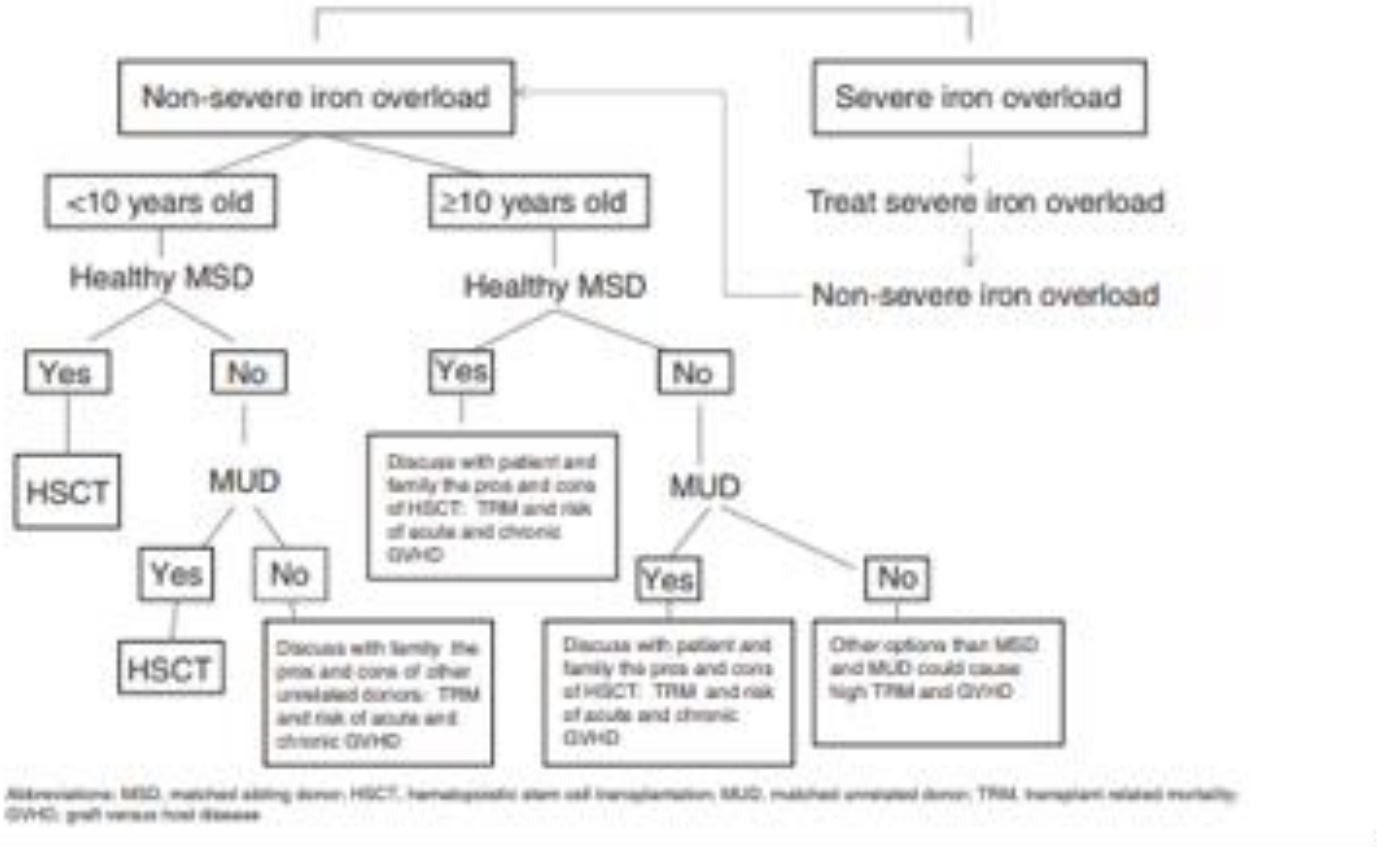
If no response after 1 month stop

Corticosteroids < minimum acceptable dose <0.3mg/kg/d
(<0.5mg/kg/d in difficult or dangerous access to TS

Corticoresistance or corticodependence
transfusions + iron chelation

Da Costa L, Blood 2020

Bone Marrow Transplantation in DBA



HSCT : DBA patients with matched donor/No response to corticosteroids /transfusion dependent.

Diaz-de-Heredia C et al Bone Marrow Transplantation 2021

Old drugs

Androgens

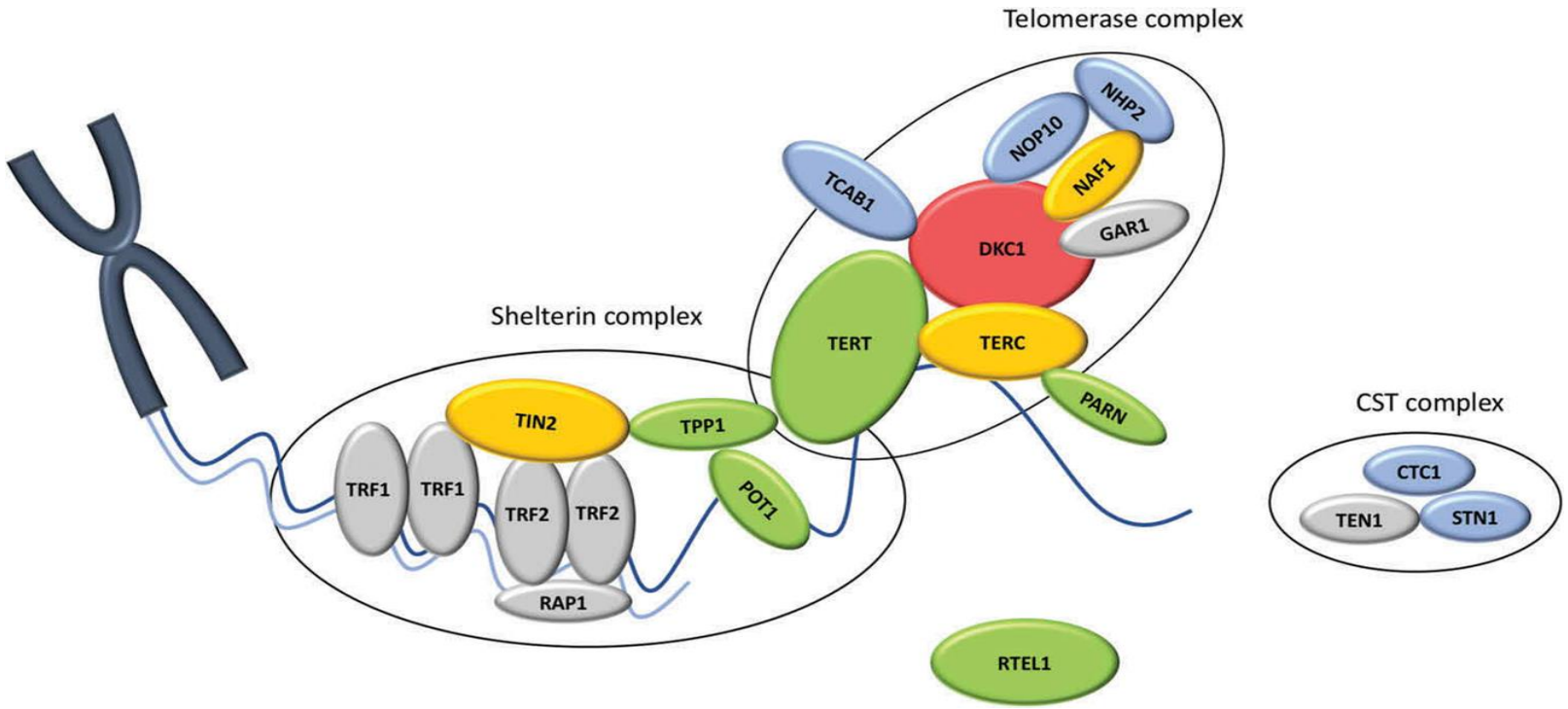
Testosterone propionate
Nandrolone decanoate
Oxymetholone
Oxandrolone
Danazol

Enhance epo production by kidneys

Stimulation of epo receptor on stem cell

Old drugs

Androgens in DC



- Telomers elongation
- Increase telomerase gene expression (TERT) in hematopoietic cells
- Positive effect on marrow microenvironment

Calado R Hematology Am Soc Hematol Educ Program. 2017.Townsley , NEJM 2016, Khincha , BJH 2014 Khincha , Blood Advance 2018,

Old drugs

Androgens in DC

up-regulation of TERT

via the stimulation
intracellular estrogen receptor

enhancement of the enzymatic activity of telomerase

elongation of prematurely shortened telomeres

improvement of peripheral blood counts

Androgens in DC

Oxymetholone 0.5-1 mg/kg

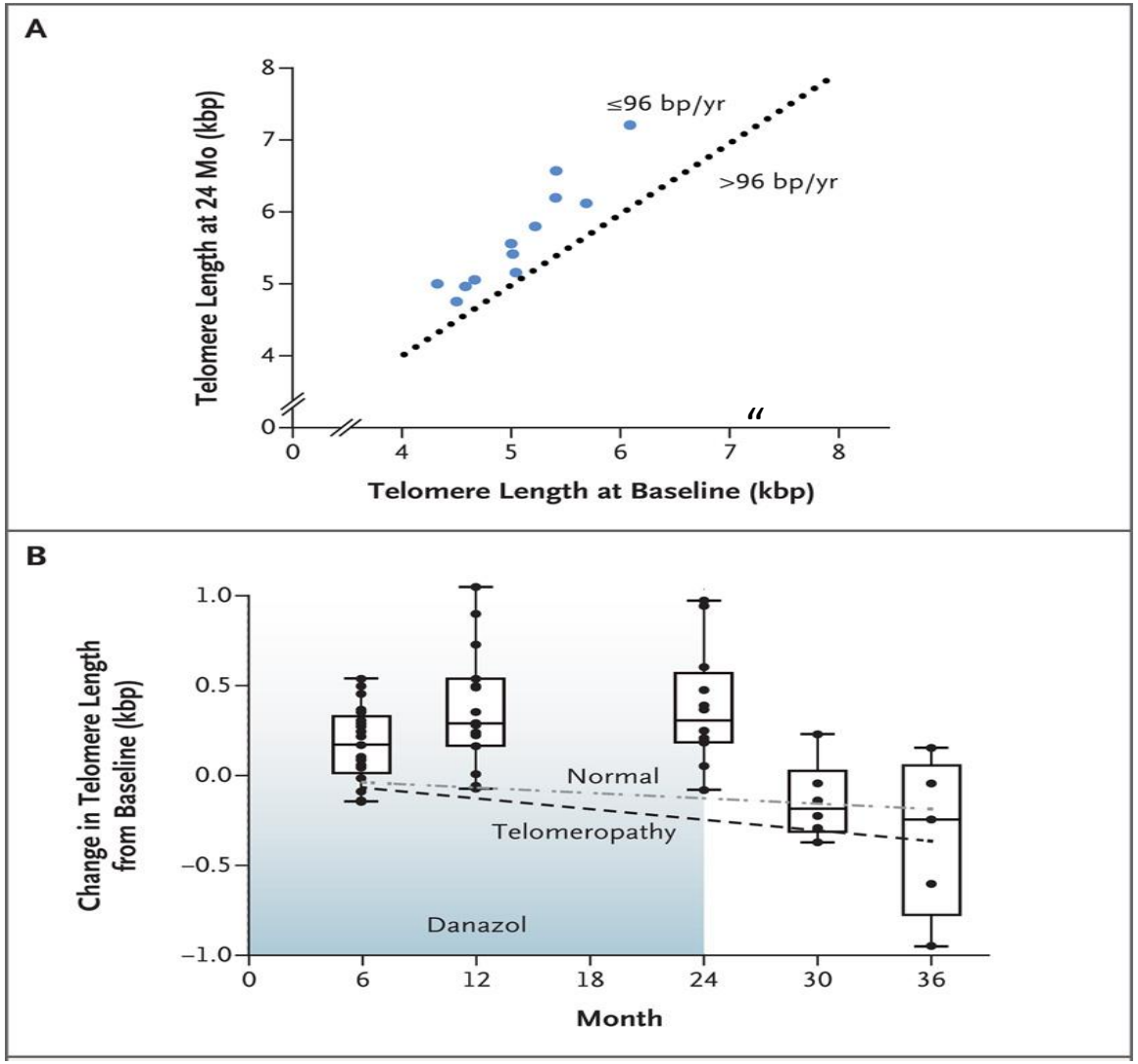
16 subjects
median age of 16 years
Median follow-up 22 months

Hematologic response 69%
Non substantially telomer elongation

Khincha PP BJH 2014

Old drugs

Androgens in DC



29 subjects-danazol 800 mg/die

Median age of 40 years
Median follow-up 24 months

Hematological response 80%
Telomer elongation

Stability of lung disease

Townsely D NEJM2016

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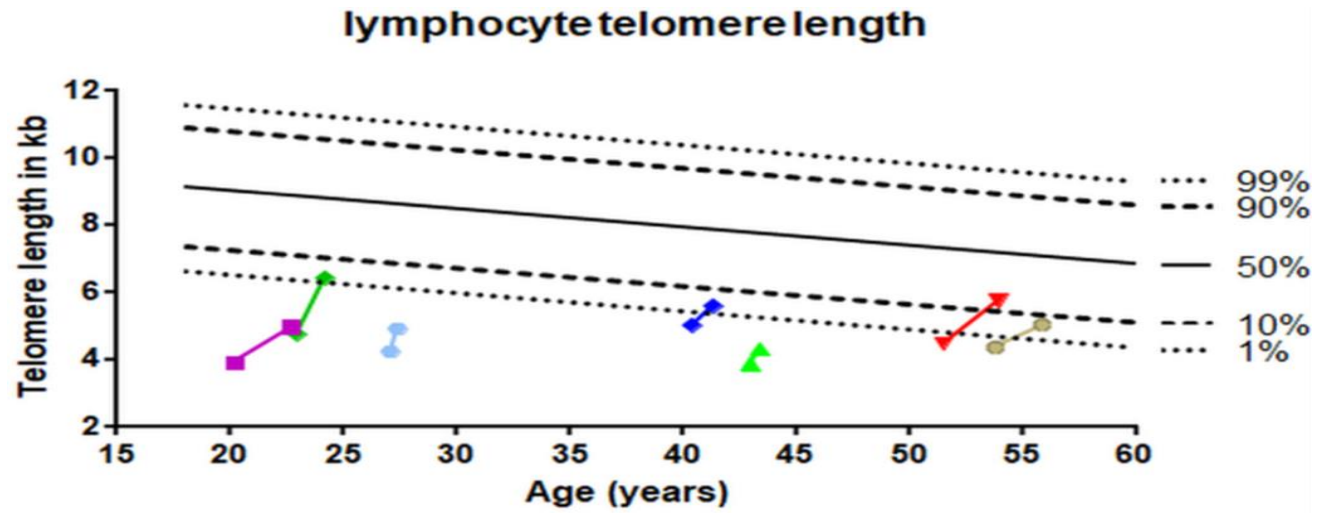
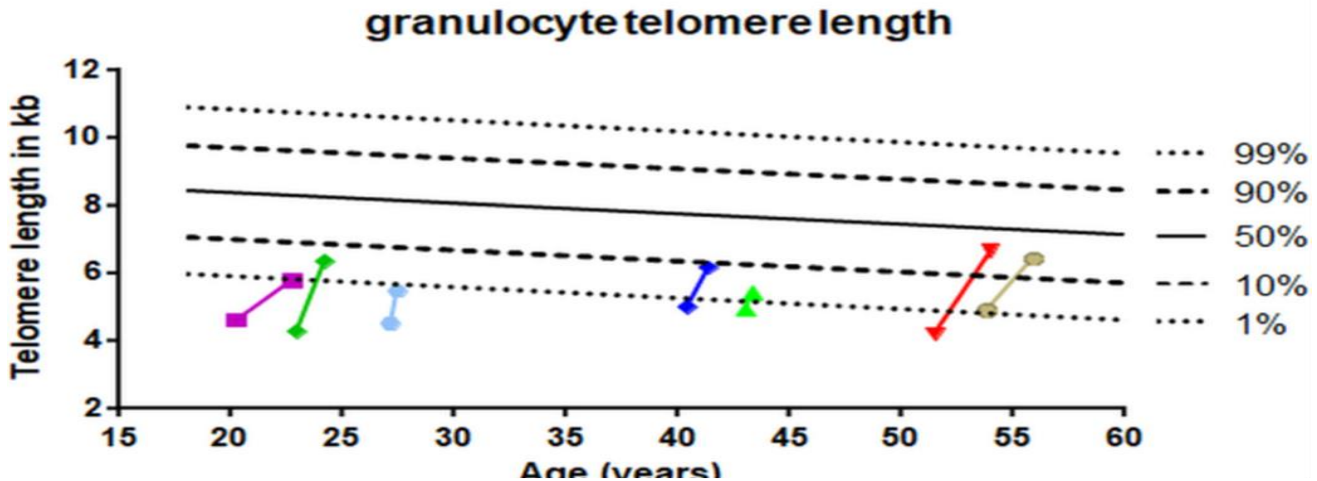
Elongation of prematurely shortened telomeres





7 patiens – Danazol 600 mg /die
median age of 40 years (range: 21–53 years)
Median follow-up during treatment was 14 months
(range: 3–29 months

Flow fish
Absent clonal malignant hemopoiesis

Kirschner M , BJH2021

Androgens in Fanconi Anemia

Study	Reference	Patients, N	Disease	Androgen	Median age, years	Median duration of therapy, years	Response, %	Toxicity
Scheckenbach et al.	14	8	Fanconi anemia	Danazol	11	3	87	—
Rose et al.*	15	10	Fanconi anemia	Oxandrolone	9	2	70	Virilization, liver, MDS
Paustian et al.	6	37	Fanconi anemia	Various	8.8	4.2†	68	Virilization, MDS, hepatic adenoma
Ribeiro et al.	16	66	Fanconi anemia	Oxymetholone, danazol	10.5	1.5	78	Virilization, liver
Khincha et al.	8	16	Dyskeratosis congenita	Oxymetholone, fluoxymesterone, nandrolone decanoate	11	2.2	69	Bone fractures, virilization, splenic peliosis, liver
Townsley et al.*	7	27	Telomeropathy	Danazol	41	2	83	Liver, muscle

MDS, myelodysplastic syndrome.
*Prospective study.
†For responders.

Paustian L, et al Pediatr Hematol 2016, Rose SR Ped Blood and Cancer 2014 , Ribeiro LLN Rev Bras Hematol Hemoter 2015

Androgens toxicity and side effects

Virilization, increased lipid profile

Risk of hepatocarcinoma

Hepatic peliosis/splenic rupture

Townsley , NEJM 2016,
Khincha , BJH 2014
Khincha , Blood Advance 2018

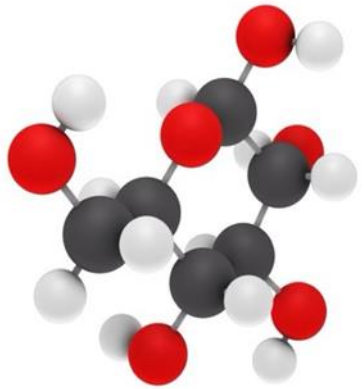
2.Alternatives strategies

"Old drugs"
Corticosteroids
Androgens

Growth factors/agonists
G-CSF
TPO-agonists: Eltrombopag

Target molecules

Gene therapy



Granulokine-Colony Stimulating Factor

Highly proliferative (~1010 cells/day) dynamic process

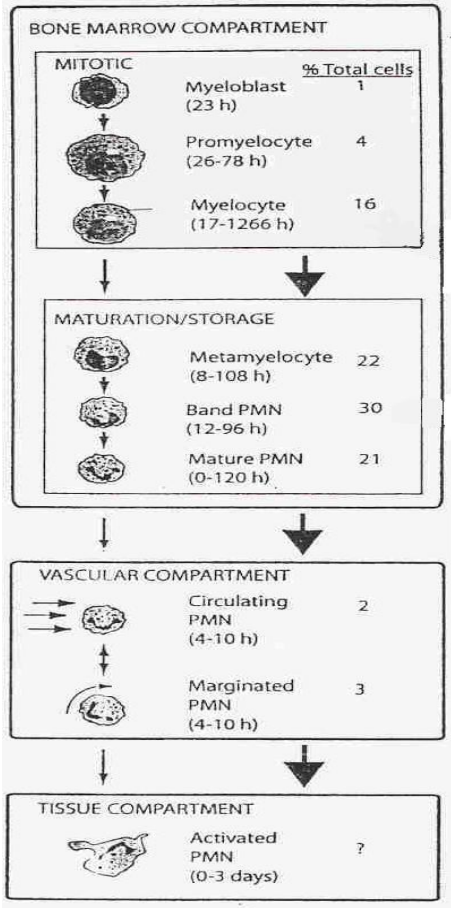
Proliferation and maturation of CFU-GM

Amplification of marrow mitotic pool
(from myeloblast to myelocite)

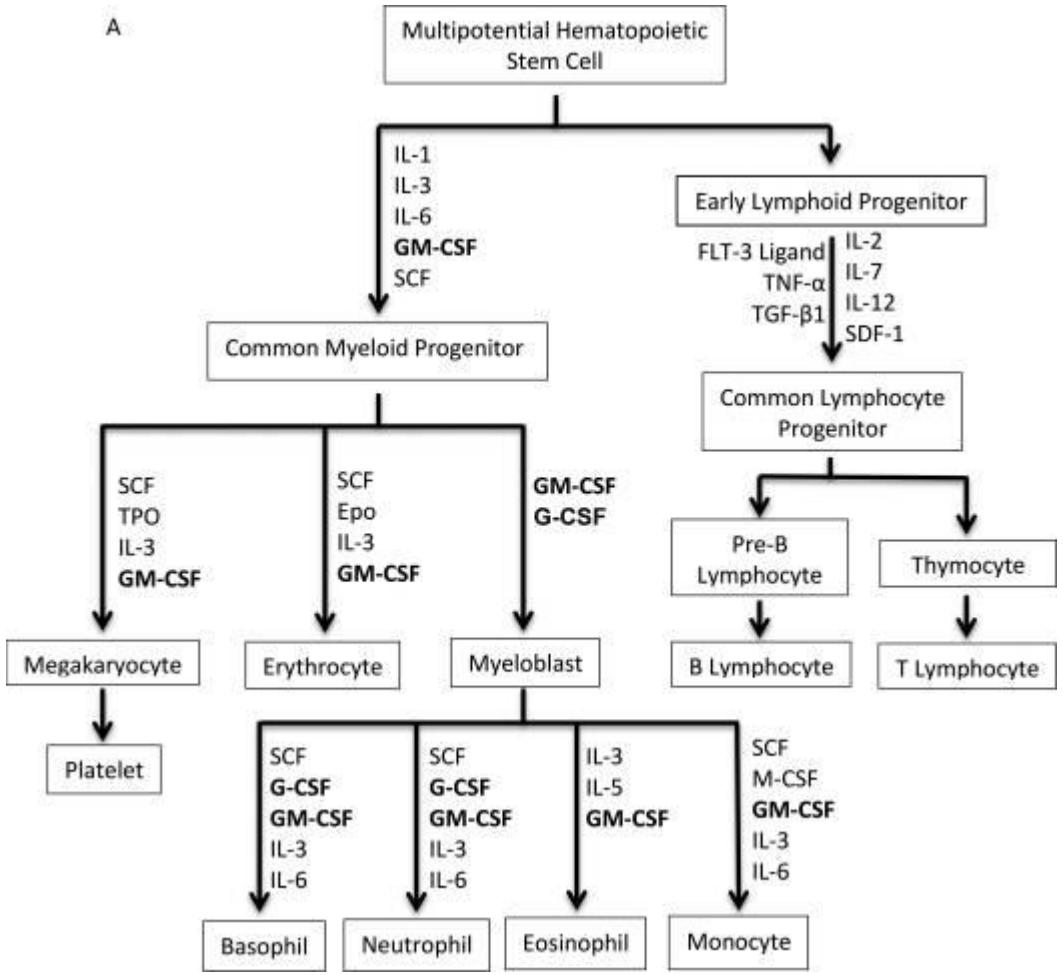
Proliferation of maturative pool
(from metamyelocites to myelocite)

Shortening timing of marrow maturation

Demargination of mature elements



Granulokine-Colony Stimulating Factor
G-CSF



GCSF in Severe Congenital Neutropenia/SDS

Tailored schedule

The least dose for the best effect (standard dose 5 y/kg/die)
SDS 3y/kg/die

Goal: Absolute N count >1.000/mmc <5.000/mmc

Responders: 90% of patients

Responders 15 µg/Kg/d
Poor responders 15-20 µg/Kg/d
Non responders > 20 µg/Kg/d

Donadieu J, Haematologica 2005, Welte K Sem Hematol 2006, Fioredda F , Am J Hematol 2011

GCSF side effects

Hepato/splenomegaly

Thrombocytopenia

Vasculititis

Glomerulonefritis (Shoenlein-Henoch purpura)

Osteoporosis/osteopenia

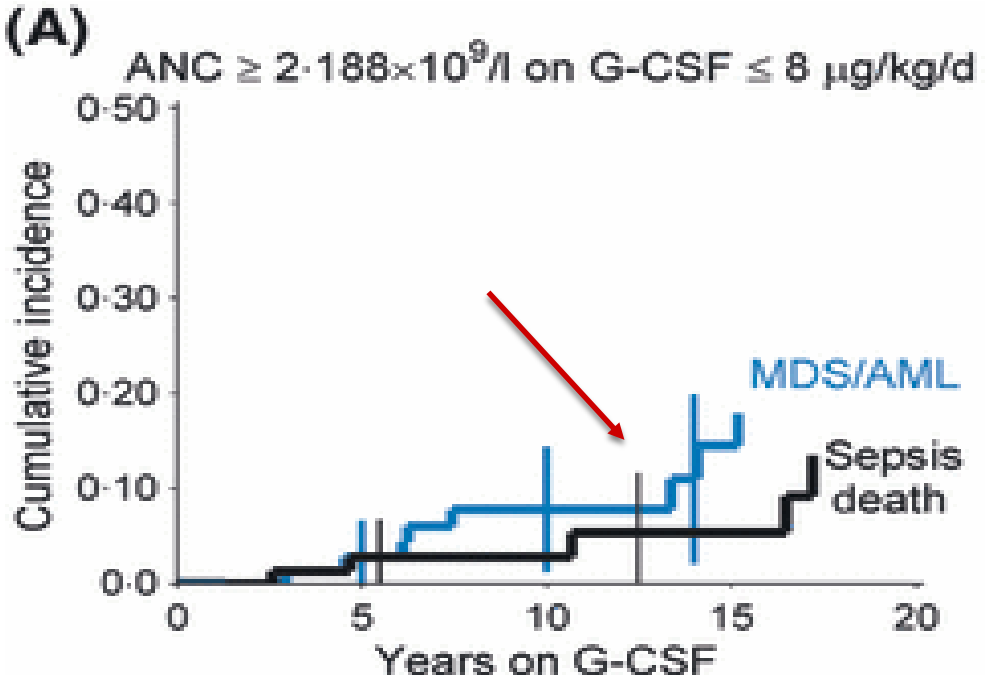
Trasformation to MDS/AL

Dale DC Am J Hematology 2003

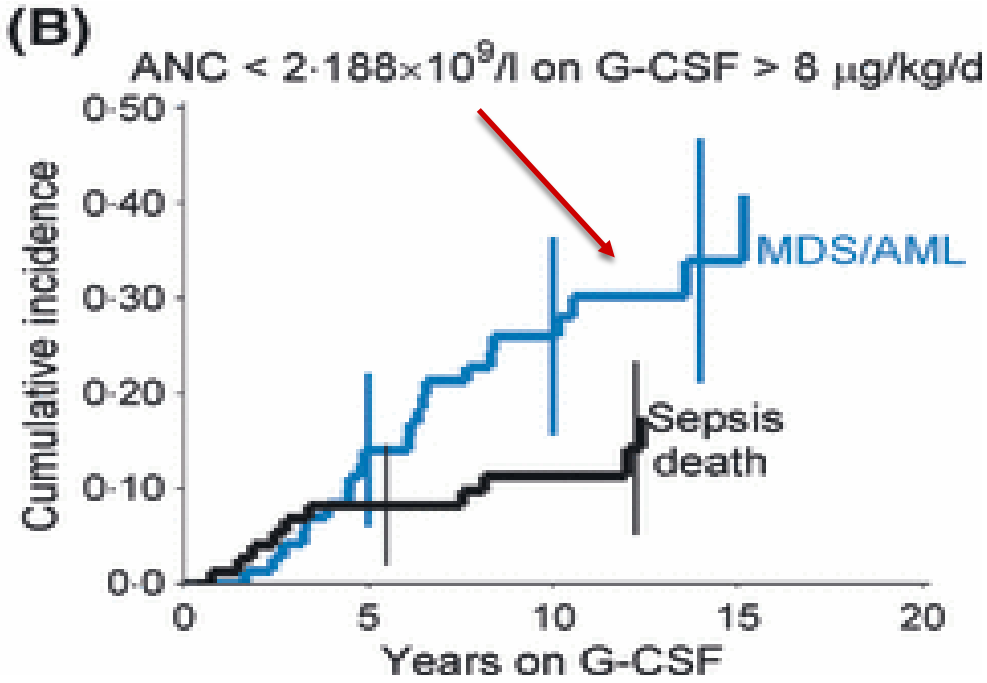
Trasformation to MDS/AL

SCNIR

Low Risk15% ys after G-CSF



High risk 34% ys after G-CSF



«Dose» related risk , higher risk in SDS (SCNFR)

G-CSF in Severe Congenital Neutropenia/SDS

Lifelong G-CSF

- >90% of neutropenic patients respond to G-CSF
- <10% G-CSF treatment does not work/ is not appropriate

Alternative therapy : PEGFILGRASTIM

Dale Dc Blood 1993, Dale Dc Am J hematol 2003

NAMPT e SIRT soppressione di P53, protoncogene FOXO3a, e proteina

Pegfilgrastim in SCN

State of the art

LETTER TO THE EDITOR

Severe congenital neutropenia and pegfilgrastim

Päivi M. Lähteenmäki[1], Kirsi Jahnukainen[1], Tarja-Terttu Pelliniemi[2], Leena Kainulainen[1], Toivo T. Salmi[1]
[1]Department of Paediatrics, Turku University Hospital, Turku; [2]Department of Clinical Chemistry, Turku University Hospital, Turku, Finland

LETTERS TO THE EDITOR

Respiratory distress and sudden death of a patient with GSDIb chronic neutropenia: possible role of pegfilgrastim

Jean Donadieu,[1] Blandine Beaupain,[1] Frédérique Rety-Jacob,[2] and Raphaelle Nove-Josserand[3]
[1]Service d'Hémato-Oncologie Pédiatrique, Registre Français des Neutropénies Chroniques Sévères, Hôpital Trousseau, Paris, France; [2]Service de Radiologie, Hopital Sud, Lyon, France; [3]Service de Médecine Interne, Hopital Sud, Lyon, France.

Pediatr Blood Cancer 2010;54:465–467

BRIEF REPORT

Pegfilgrastim in Children With Severe Congenital Neutropenia

Francesca Fioredda, MD,[1]* Michaela Calvillo, MD,[1] Marina Lanciotti, PhD,[1] Tiziana Lanza, PhD,[1] Laura Giunti, PhD,[2] Elio Castagnola, MD,[3] Ines Lorenzi, PhD,[4] Rossella Tonelli, PhD,[5] Piero Ghezzi, PhD,[5] and Carlo Dufour, MD[1]

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Pediatr Blood Cancer 2009;53:1068–1073

Is Pegfilgrastim Safe and Effective in Congenital Neutropenia? An Analysis of the French Severe Chronic Neutropenia Registry

Blandine Beaupain, MSc,[1] Thierry Leblanc, MD,[2] Oumédaly Reman, MD,[3] Olivier Hermine, MD, PhD,[4] Jean-Pierre Vannier, MD,[5] Felipe Suarez, MD,[4] Patrick Lutz, MD,[6] Pierre Bordigoni, MD,[7] Anne Jourdain, MD,[8] Michele Schoenvald, MD,[9] Marie Ouachee, MD,[10] Sylvie François, MD,[11] Fréderic Kohser, MD,[12] Fabrice Jardin, MD,[13] Gilles Devouassoux, MD,[14] Yves Bertrand, MD,[15] Raphaele Nove-Josserand, MD,[16] and Jean Donadieu, MD, PhD[1]*
for the French SCN Registry, Service d'hémato oncologie Pédiatrique, Hôpital Trousseau, 75012 Paris France

J Am Acad Dermatol
Volume 52, Number 5

Bullous Sweet's syndrome in congenital neutropenia: Association with pegfilgrastim

Bradley K. Draper, MD, PhD, Jason R. Robbins, MD, and George P. Stricklin, MD, PhD
Nashville, Tennessee

blood® 2007 110: 4134

Novel treatment for severe congenital neutropenia with pegfilgrastim

L. Mi Rim Choi, Christine Guelcher and Michael F. Guerrera

LETTERS TO THE EDITOR

Similar favorable outcome of pegfilgrastim overdose in patients with different age and underlying disease

Carlo Dufour,[1] Barbara Cappelli,[2] Michaela Calvillo,[1] Francesca Fioredda,[1] Rossella Tonelli,[3] and Roberto Crocchiolo[4]
[1]Hematology Unit, G. Gaslini Children's Hospital, Genova

rsdays Webinars

Pegfilgrastim protocol in SCN

Phase II, multïcenter, longitudinal, intrasubject open label study (CDF711, EUDRACT code 2005-003096-20)

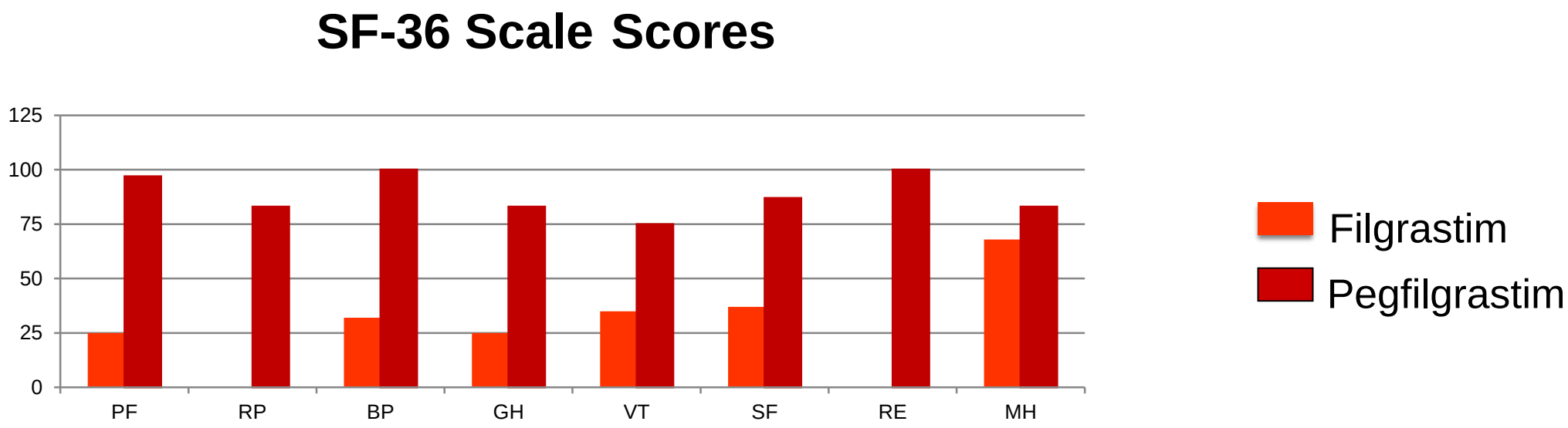
Five patients: 4 ELANE, 1 HAX1 treated G-CSF (median dose 7.5 mcg/kg) after a median follow-up 46 months (7-111 months)

PEGFILGRASTIM 50 mcg/kd every 7-8 days

>Median ANC (1.5 × 10^9/L *vs* 1 × 10^9/L)
<Infectious burden (*10.1 vs* 5.3)
Catch up growth

>>QoL

Quality of life



PF	RP	BP	GH	VT	SF	RE	MH
25	0	32	25	35	37	0	68

PF	RP	BP	GH	VT	SF	RE	MH
97	83	100	83	75	87	100	83

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Fioredda F, Blood 2016

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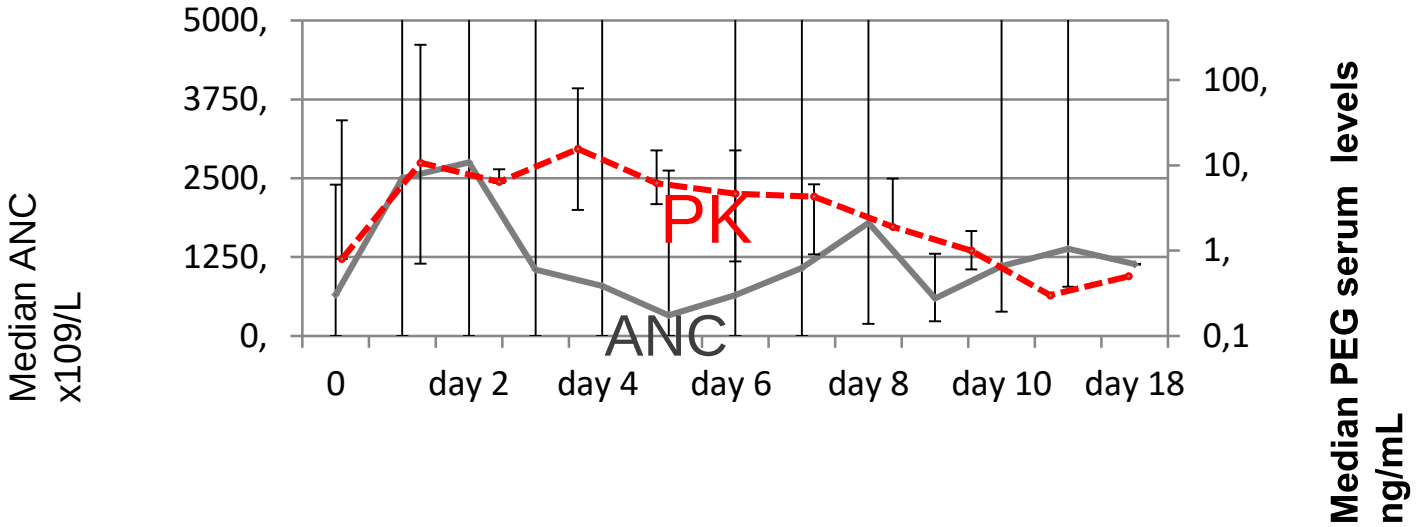
ANC & Peg serum concentrations



ANC

First peak after 24-48 h from inoculum
Decline after 2-5 days
Second rise on days 6-7 without any further administratio

PK
Peak serum concentration after 24-72 hours from inoculum
Decline towards start levels
No cumulative drug concentration effect

Basal Pegfilgrastim
Peak Pegfilgrastim concentrations comparable to values on classical G-CSF

Fioredda F , Blood 2016

Peg filgrastimToxicity and side effects

Neither local nor generalized reactions

No cytogenetic abnormalities

Osteoporosis

Acquisition of CSFR3 mutations

(c.2384C>T, c.2425T>G)

No trasformation to leukemia

Pegfilgrastim

Reduced injections

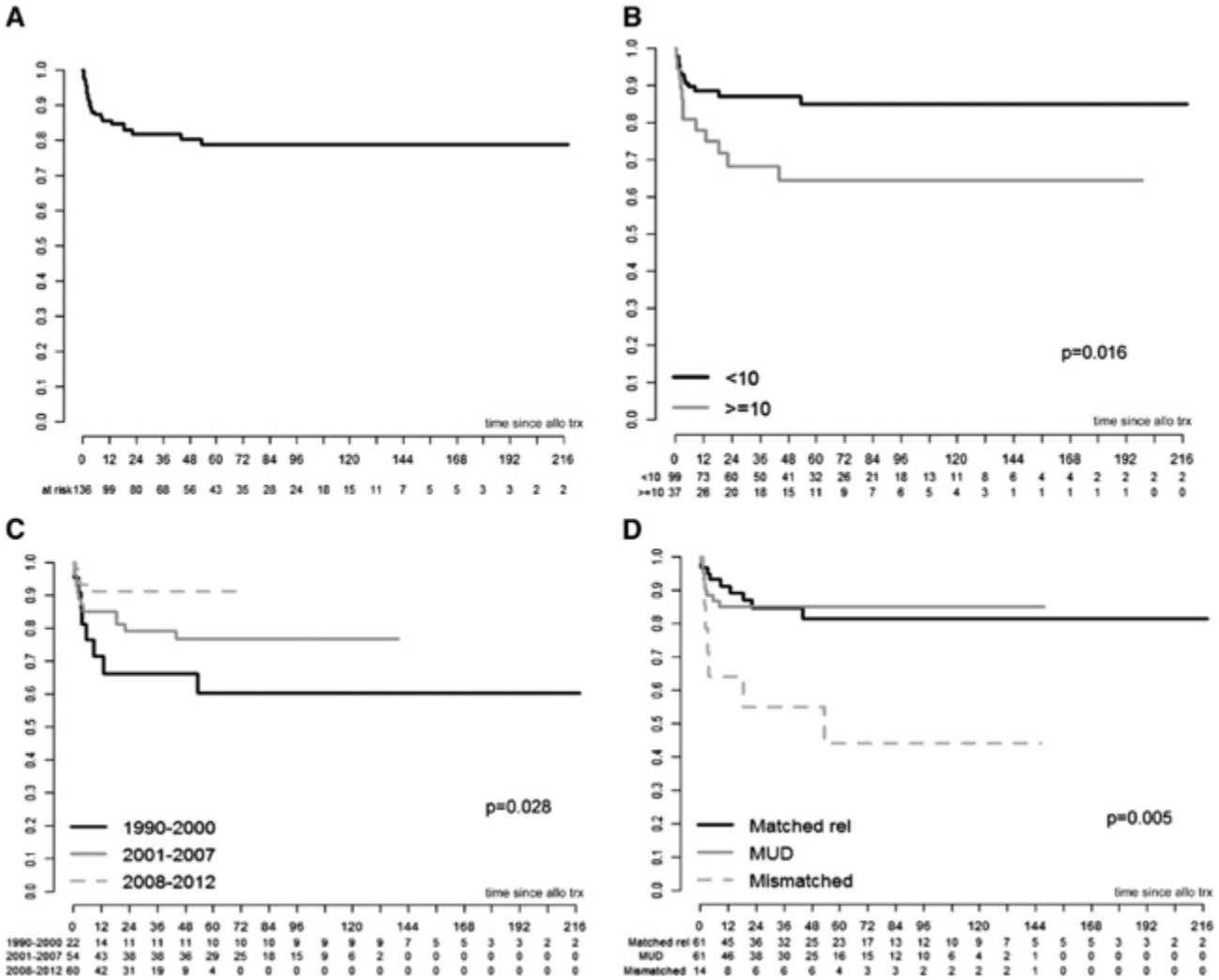
Improved compliance and Qol

Efficacy in rising neutrophils

Defence against infections

Wendelin G JPHO 2005; te Poele EM JPHO 2005; Andre' N Anticancer Drugs 2007; Dallorso S BMT 2008 , Lyman Gh Ann Oncol2015, Spunt SL J Clin Oncol 2010

HSCT Outcome in Severe Congenital neutropenia



136.SCN pts

5y-0S 82%

TRM 17%

Fioredda F Blood 2015

European Reference Network
for rare or low prevalence complex diseases

Network Hematological Diseases (ERN EuroBloodNet)

Thursdays Webinars

2.Alternatives strategies

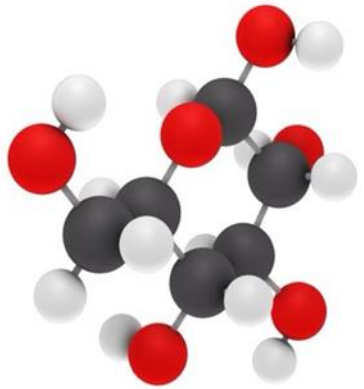
"

"Old drugs"
Corticosteroids
Androgens

Growth factors/agonists
G-CSF/pegfilgrastim
TPO agonists: Eltrombopag

Target molecules

Approach to Gene Therapy



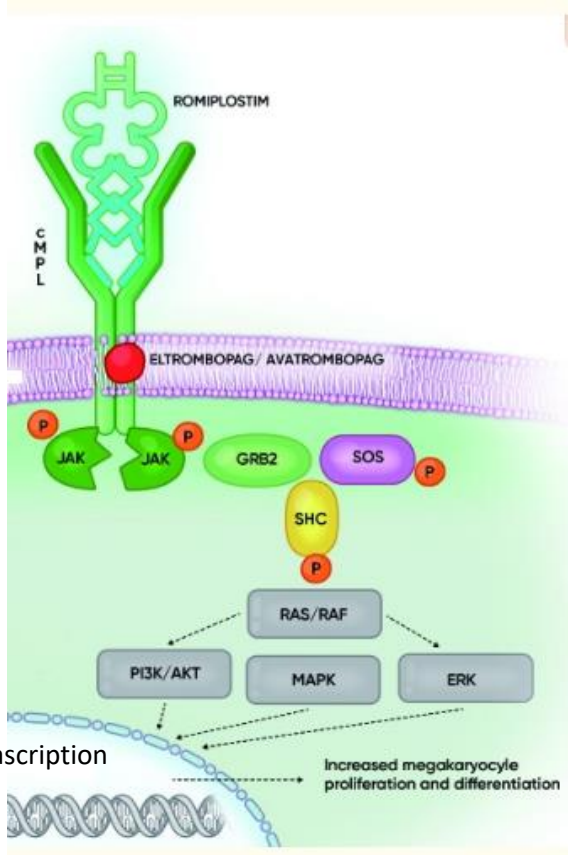
Eltrombopag

ITP- AA- Hepatitis +ITP

TPO agonist stimulates cMPL → JAK/STAT and MAPK

Stabilization of the c-MPL membrane receptor

> platelets production



Ghanima W , Haematologica, 2019

Eltrombopag

- Immunomodulatory effect
- Chelator of ions: extra-and intra-cellular calcium and iron and can shuttle iron out of cells
- Enhancememt of DNA Repair in Stem Cells
- Anti-proliferative effects on leukemic cells (down regulation of Akt)

Vlachodimitropoulou E Blood 2017 , Roth M Blood 2012, Bao W Blood 2010 Kacey L. Guenther, Exp Hematol. 2020, Schmitt N Leukemia 2022

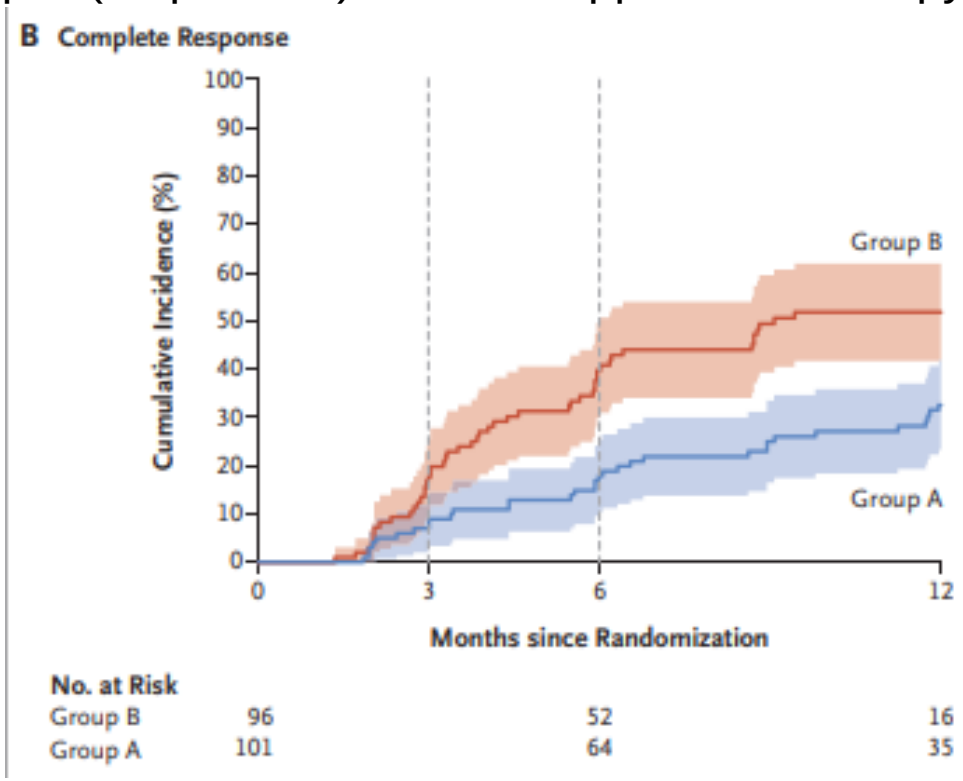
Eltrombopag in AAA

Hematological response

Group A (101 patients) immunosuppressive therapy

vs

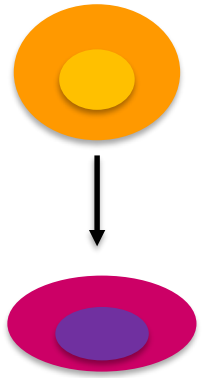
Group B (96 patients) immunosuppressive therapy plus eltrombopag



Peffault Delatour R, NEJM 2022

Eltrombopag in DBA

DBA induced pluripotent stem cell (iPSC) with inactivating mutations in RPS19



DBA Patients' iPSCs

Eltrombopag+ Fe chelation

markedly improved erythroid maturation

HYPOTHESIS iron-chelating properties of EPAG could restrict iron availability and limit heme synthesis in DBA erythroid progenitors, thereby reestablishing the heme-globin ratio and promoting erythroid maturation

.

Ribosomal dysfunction → globin synthesis delay

Excess toxic free heme (erythroid progenitors)

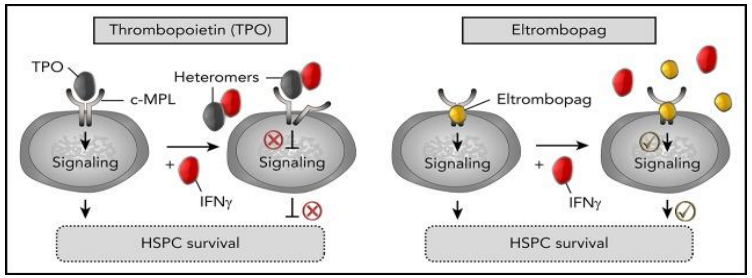
Early differentiation arrest → pure red cell aplasia

trial of phase 1-2
Drug: Eltrombopag
150 mg/day starting dose (titration and adjustments for age and ethnicity)

Eltrombopag in Fanconi Anemia

EPAG PROMOTED DNA REPAIR

actvating the classical non-homologous end joining (C-NHEJ) DNA repair mechanism
displacing IFN-γ action on c-MPL receptor



Phase I/II study → endopoint hematological response at 6 mo (FUP 25 mo)

>>CD34 in the majority

Half of the cohort > peripheral count

Bone Marrow Biopsy < 5% → 20%

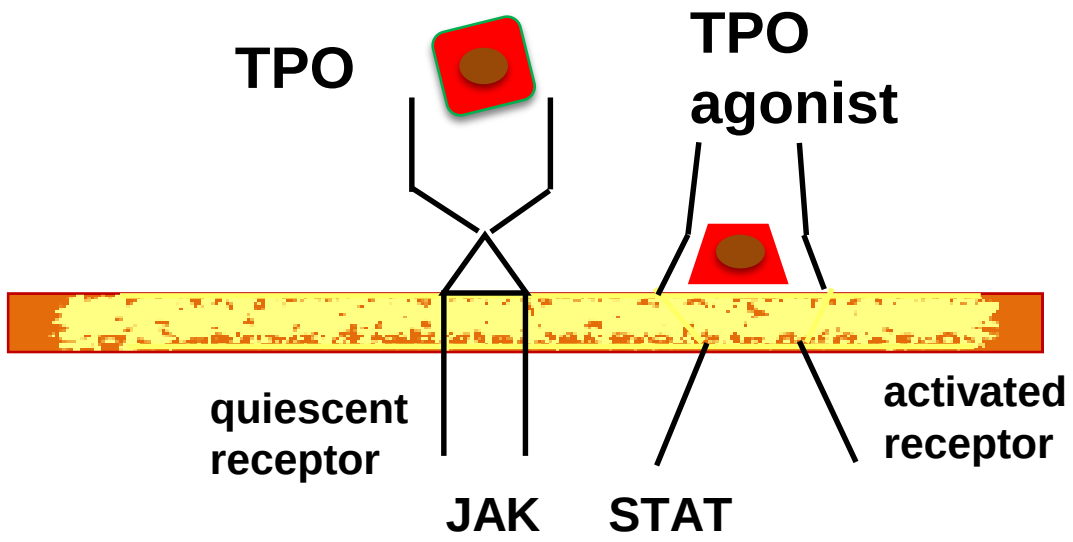
No marrow fibrosis
No solid malignancies/clonal evolution

Boost Marrow CD34+ prior Gene therapy?

Alvarado Blood 2019, Guenther Exp Hematol 2019, La Rochelle ASH Abs 2177

Eltrombopag in Diskeratosis Congenita

> levels of TPO before start of treatment



Trautmann K Thrombosis and Hemostasis, 2012

Eltrombopag Toxicity and side effects

- Bone marrow fibrosis ↓↓↓
- Risk of clonal evolution ↓↓↓
- Thromboembolic events > adults than in children

  No higher dose of TPO-RA
  TEE in the first year of treatment

- Cataracts
- Transaminitis

2.Alternatives strategies

"Old drugs"
Corticosteroids
Androgens

Growth factors/agonists
G-CSF
TPO agonists: Eltrombopag

Target molecules

TARGET THERAPIES : ASSUMPTIONS

1. Knowledge of diseases' mechanism

2. Availability of biological models

3. Choice of targets

Target therapies: Fanconi Anemia

CANONICAL and NON CANONICAL functions of Fanconi proteins

- repair of cross-linked DNA
- prevent aneuploidy and aberrant centrosome accumulation
- response to oxidative stress
- response to inflammation
- mitophagy/viropaghy
- promotion of function and survival of stem cells

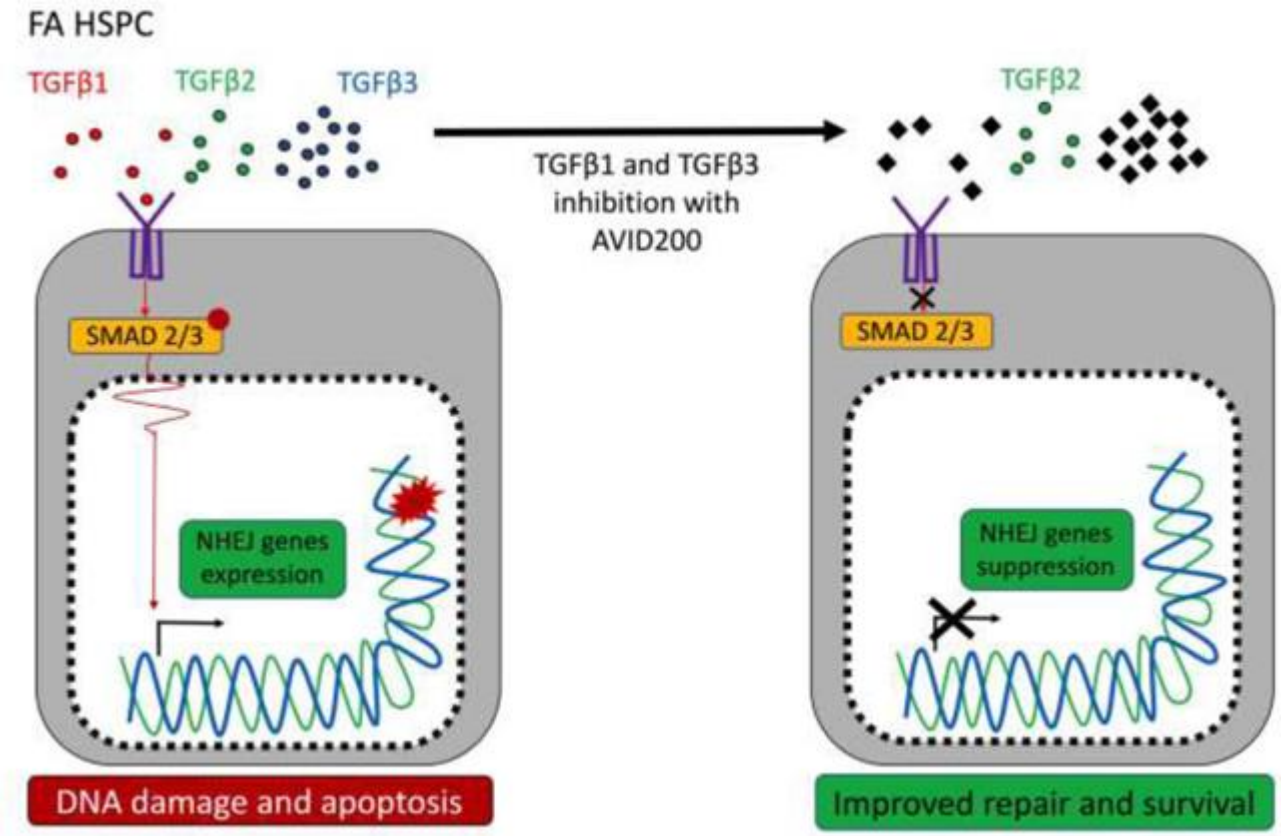
SMALL- MOLECULES
Antagonists of hyperactive signaling pathways in mutant cells
p53/p21/PKR/ TLR pathway (p38MAPK, MK2)

INHIBITION of Transforming Growth Factor beta (TGFβ)

Bagby G, F1000 Research 2018

TGF beta in Fanconi Anemia/SDS/DBA

Inhibition of the TGF-β pathway rescues hematopoiesis in iPSCs model

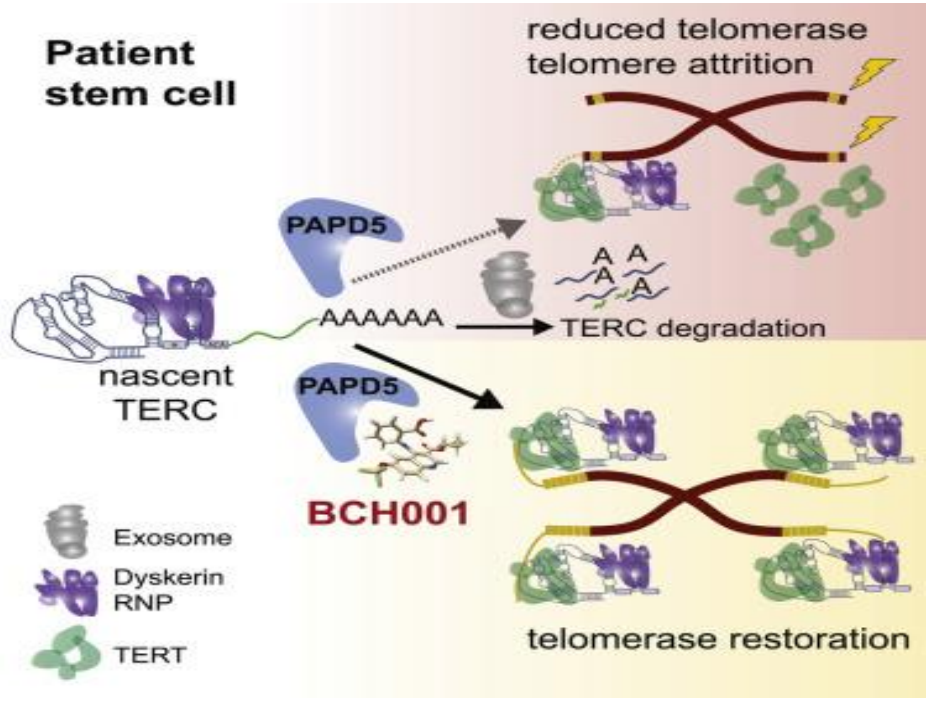


Rodriguez A , Exp Hematol 2021

Target therapies: DSK

PAPD5 inhibitors

Pharmacological manipulation of cRNA biogenes throught micromolecules
BCH001, Rg7834 (dihydroquinolizizinones)



Nagpal n Cell Stem Cell 2020

Target therapy: Blackfan Diamond Anemia

>>>> activity of p53 in
RPS19-deficient cell line model

Calmodulin inhibitors (Trifluoperazine) <<<<< activity of p53
zebrafish model

FDA-approved drug with a favorable safety profile

(registered at www.clinicaltrials.gov as #NCT03966053)

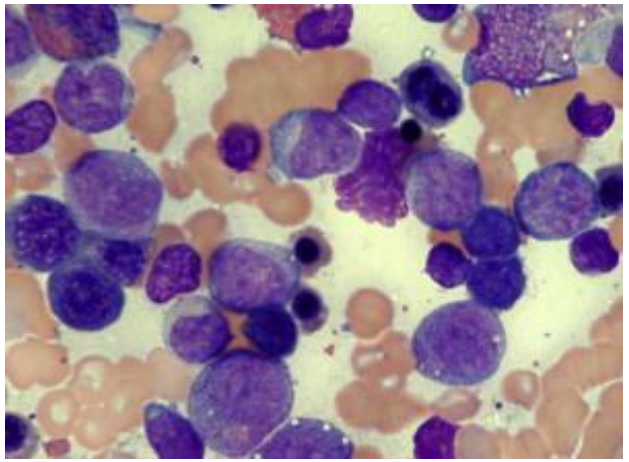
Target Therapy in SevereCongenital Neutropenia

ELANE

ELASTASE

30-kDA/serin-proteasis

Inside granules



NE mislocalization activation of unfolded protein response (UPR)

ER “Stress”

Apoptosis of promyelocytes

Sivelestat (ELANE- Q97P eI118N)

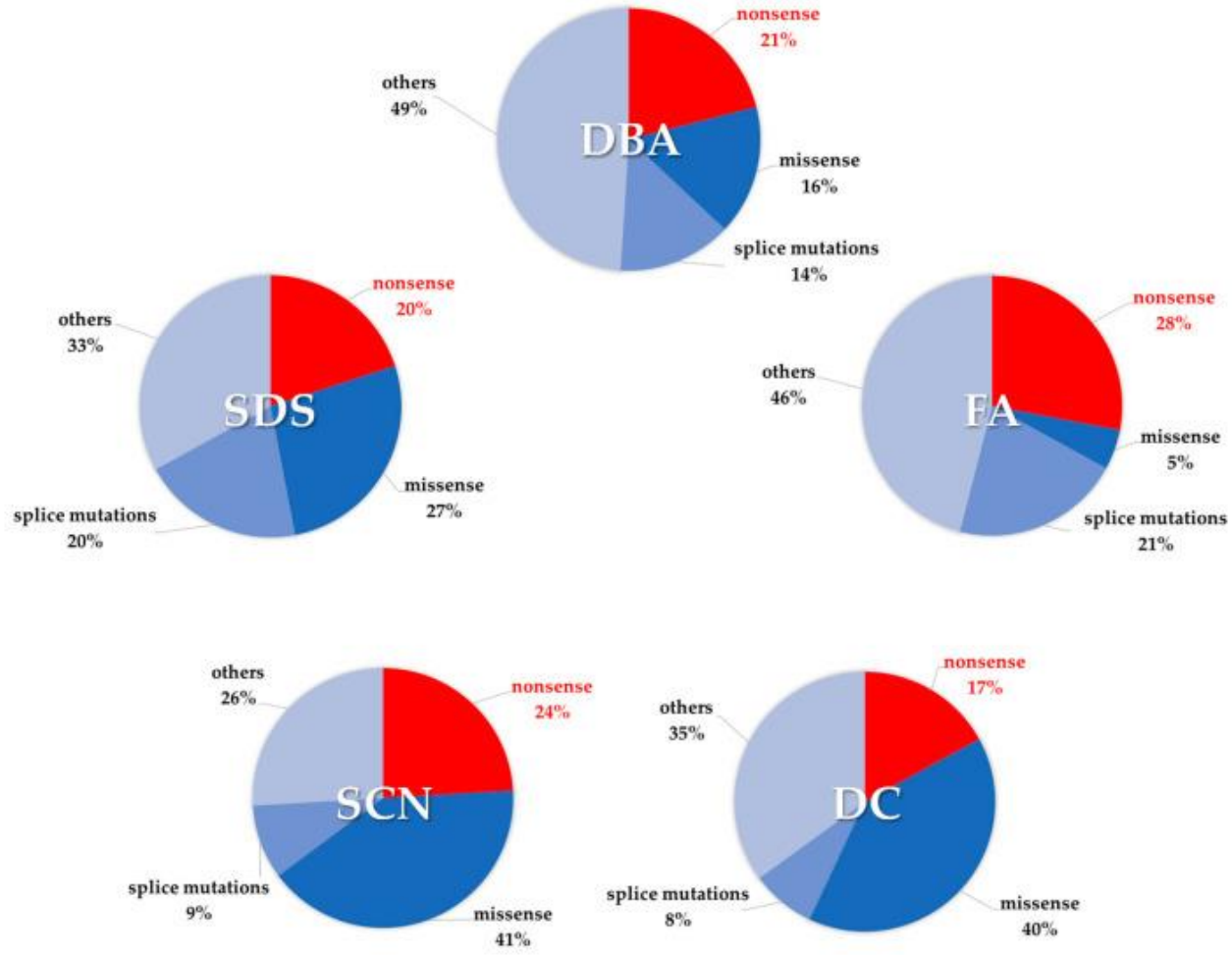
Restores Neutrophil Elastase
promylocyte survival
in iPSC

Nayak RC J Clin Invest 2015, Makaryan V J Leukoc Biol 201

ATALUREN (PTC-124): a new perspective

non sense suppressor drug

non sense mutations causes premature termination codon (PTC) causing PROTEIN DISRUPTION



ATALUREN : a new perspective

THERAPEUTIC STRATEGY
regenerates the read through of PTC

restore a full length protein synthesis

ATALUREN tested o SDS RESTORATION OF FULL LENGHT PROTEIN
in bone marrow mesenchimal cells, stroll cells , lymphoblasts
in hematopoietic colony assay

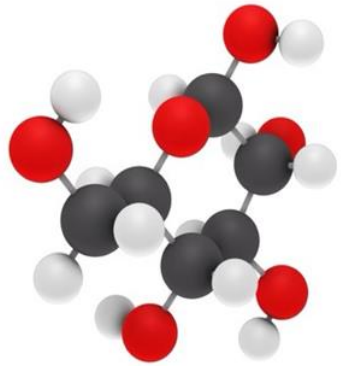
ataluren inhibit m-TOR and apoptotic rate in SDS cells

myeloid differentiation

Bezzerri V Intern J Mole Science 2020, Cancer 2020

3. Gene Therapy: What's up?

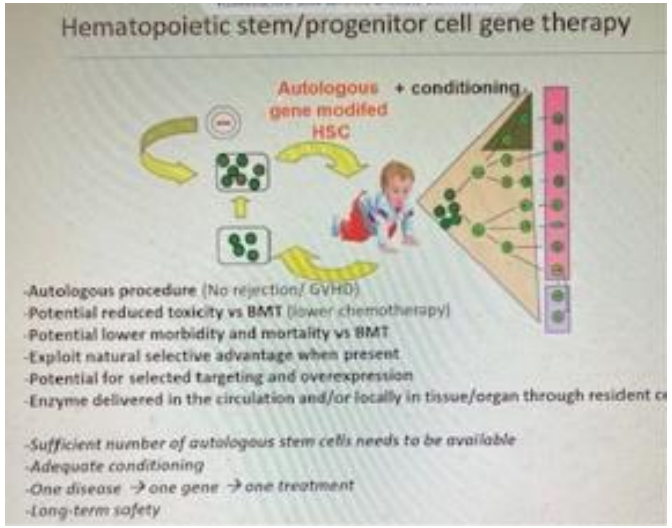
1. Knowledge of diseases' mechanism
2. Availability of biological models
3. Choice of targets
4. Choice of vectors
5. Delivery (biological and immunological barriers)
6. Gene transfert in target cells/specificity
7. Espression of «therapeutic gene»



3. Gene Therapy: What's up?

Replacement of diseased cells

AUTOLOGUS INFUSION OF « CORRECTED STEM CELLS» by
Lentivirus vector
γ-retrovirus vector
Gene Editing



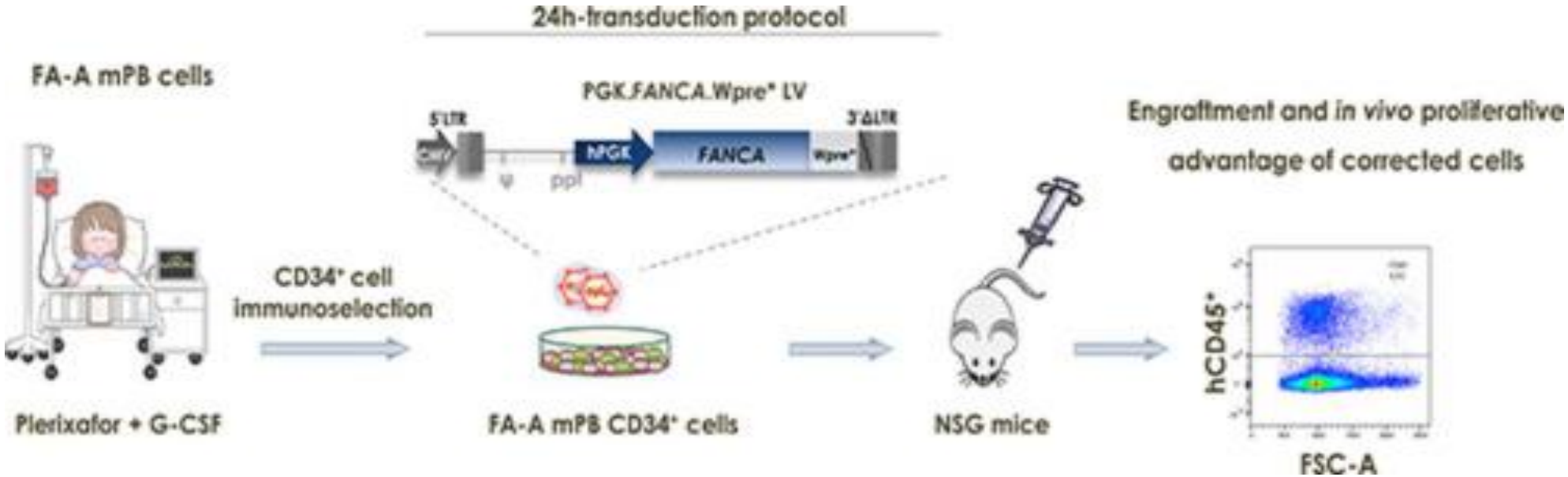
Approved drugs (EMA)

ADA-SCID (gRV)
MLD (LV)
X-ALD (LV)
Beta thalassemia (LV)

Under investigation in Clinical trial

SCID –X1
WAS
ADA-SCID (LV)
X-CGD
ARTEMIS
LAD
Beta thalassemi a (LV and editing)
Sickle Cell Disease (LV and editing)
Fanconi Anemia

GENE THERAPY in FA



low number of gene-corrected autologous FA HSPCs
replace FA patients' hematopoiesis with functionally competent cells

Critical points : low number and accelerated decrease of HSPCs in the bone marrow (BM) of FA
detrimental effect of transduction protocols upon the repopulating FA cells

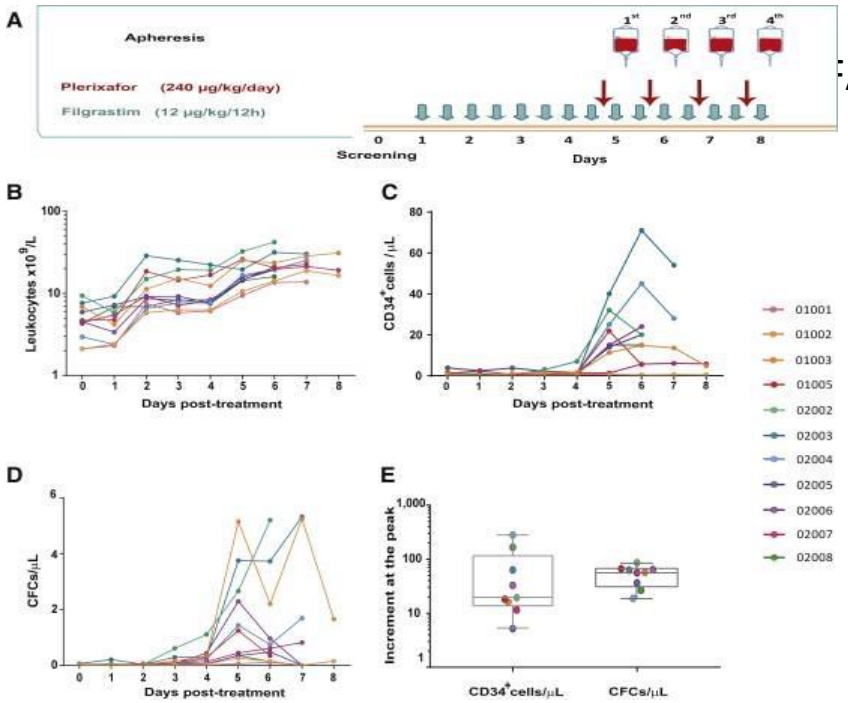
Rio P , Blood 2017

GENE THERAPY in FA

LOW number of CD34+ collection

Combination of plerixafor + G-CSF

Inhibition of the binding of stroma-cell-derived factor 1 to the chemokine receptor CXCR4.



FANCOSTEM-I clinical trial

Plerixafor + G-CSF combination is more effective than G-CSF alone

SevillaJ , Mol Ther Methods Clin Dev. 2021

European Reference Network for rare or low prevalence complex diseases

Network Hematological Diseases (ERN EuroBloodNet)

Webinars EuroBloodNet

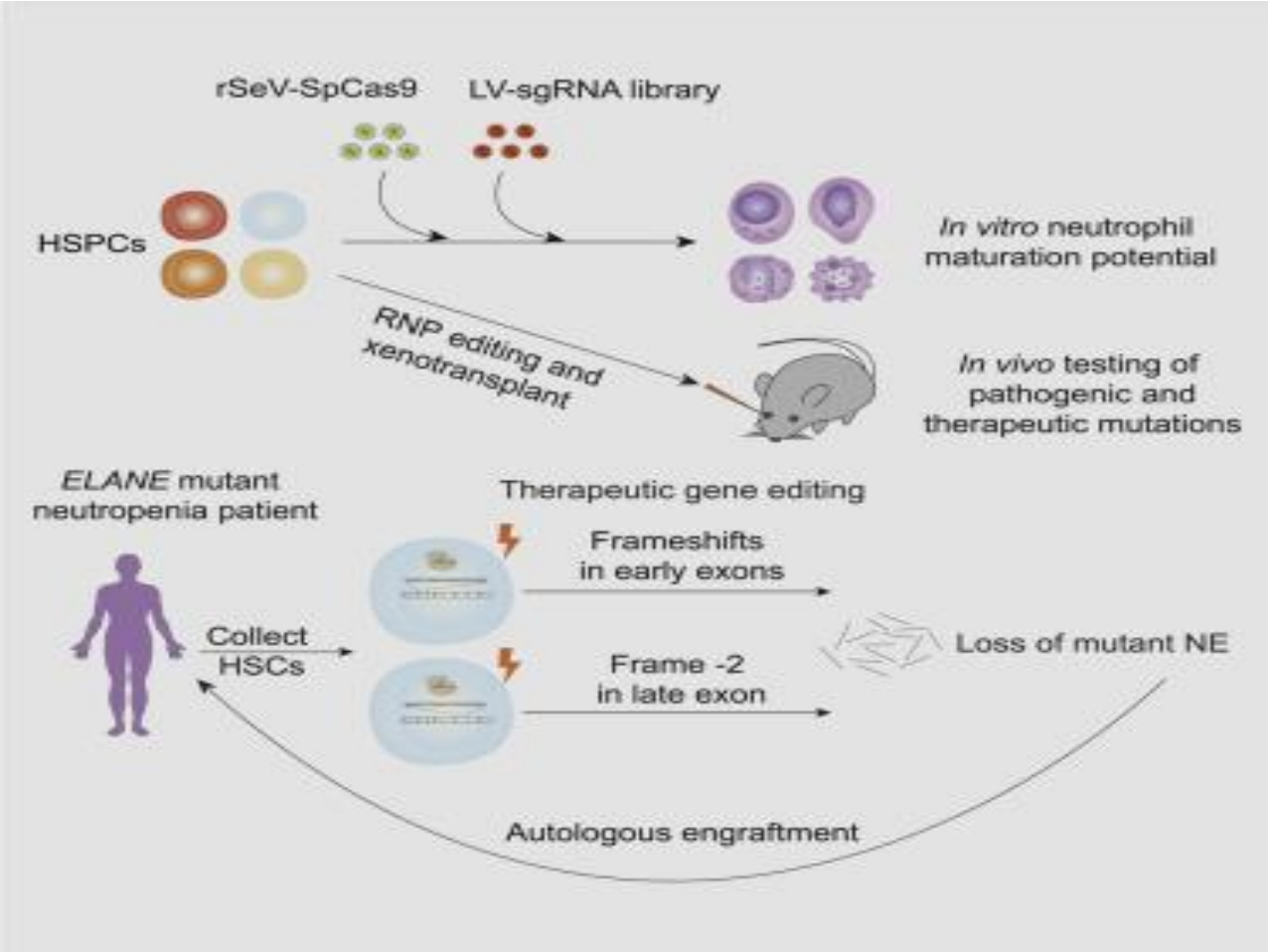
GENE THERAPY in FA

Variables	Study 1	Study 2	Study 3
Title	Successful engraftment of gene-corrected hematopoietic stem cells in nonconditioned patients with Fanconi anemia	Stem cell collection and gene transfer in Fanconi anemia	Gene therapy for Fanconi anemia in Seattle: clinical experience and next steps
Study design	Clinical trial	Clinical trial	Clinical trial
Sample size	4	3	2
Mean age (y)	5.85 ± 1.6	13.7 ± 1.6	16.0 ± 8.5
Cryopreservation	Yes (2 patients)	Yes (1 patient)	No
Cell mobilization	Yes (all; G-CSF and Plerixafor)	Yes (1 patient; G-CSF)	No
Baseline mean			
Hb (g/dL)	11.3 ± 0.9	10.7 ± 2.5	NP
Neutrophils (/μL)	1,235 ± 472	1,423 ± 672	710 ± 56.7
Plts (×103/μL)	48.0 ± 21.8	76.0 ± 40.1	61.0 ± 29.7
CD34+ cells (106/kg)	0.833 ± 0.3	0.183 ± 0.2	NP
CFC survival to 10 nM MMC (%)	0.025	0.0	NP
Vector used	Lentiviral	Lentiviral	Lentiviral
CD34+ cells (105/kg)	2.6 ± 1.07	NP	NP
Mean CFC survival after MMC administration after gene therapy (10 nM) (%)	31.0	44.7	NP
Follow-up period	18–30 mo	12 mo	NP
Follow-up cytogenetic abnormalities	None	None	NP
Serious adverse effects of investigational therapy	None	None	None

Rio P Nat med 2019.Kelly T mol gen therapy 2017. Adair K ASH 2016

GENE THERAPY IN SCN

Autologous infusion in SCN



Tran NT Mol Ther 2020

Take home messages

1. Very careful monitoring of BFM affected subjects to tailor the "best strategy"
2. Conservative management in case of organ compromision
3. Promoting translational research in target therapy/gene therapy

THANKS

European Reference Network
for rare or low prevalence complex diseases

Network Hematological Diseases (ERN EuroBloodNet)

Webinars
EuroBloodNet