U.S. Department of Health and Human Services
National Institutes of Health

National Heart Lung and Blood Institute

Aplastic Anemia: Current Thinking on Disease, Diagnosis and Non-Transplant Treatment

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National, Heart, Lung and Blood Institute
National Institutes of Health

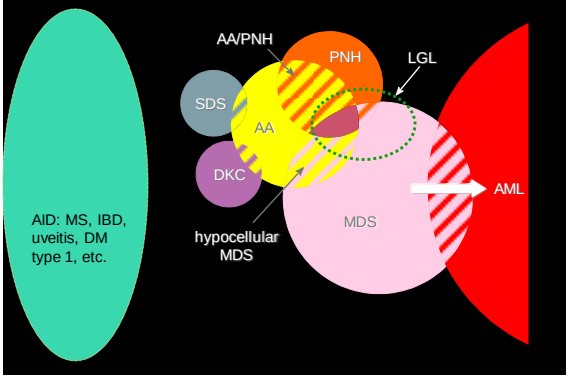
Today's agenda

Aplastic Anemia – general overview

Non-transplant treatment options

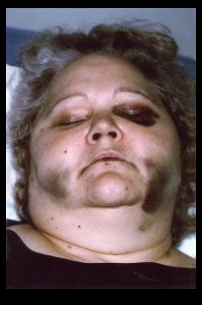
Novel agents and active research

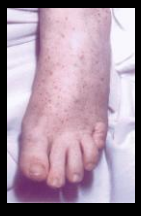
BONE MARROW FAILURE SYNDROMES



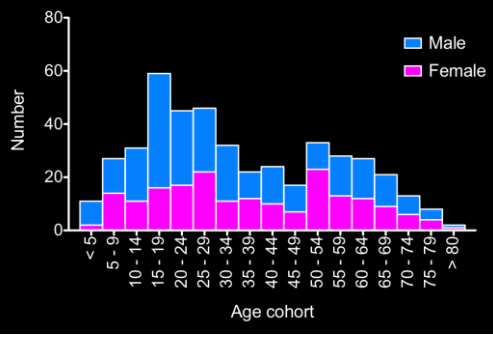
CLINICAL MANIFESTATIONS OF BONE MAROW FAILURE

anemia, bleeding, infection

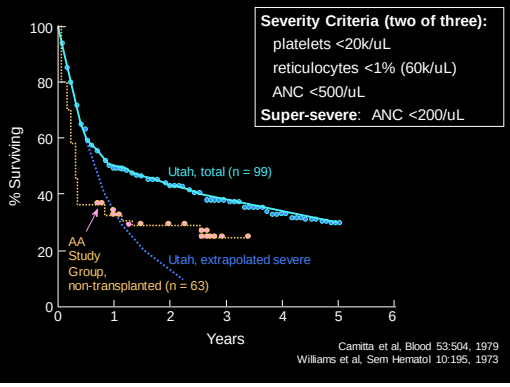




AGE AT DIAGNOSIS
Aplastic Anemia Admissions to NIH Clinical Center



"NATURAL HISTORY" OF APLASTIC ANEMIA



Camitta et al, Blood 53:504, 1979
Williams et al, Sem Hematol 10:195, 1973

Causes of Aplastic Anemia

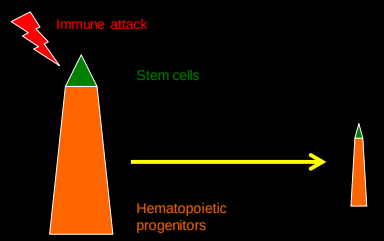
Most of the cases of Aplastic Anemia have no identifiable cause

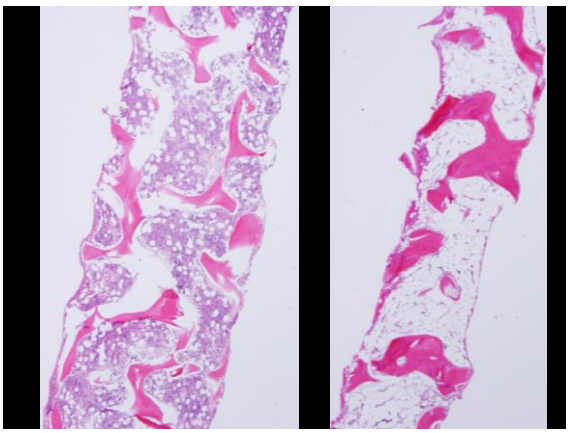
Pregnancy, eosinophilic fasciitis, and seronegative hepatitis are associated with AA

Drugs and chemicals have been reported as well (Benzene, Chloramphenicol)

All identifiable causes explain very few cases of AA

Pathophysiology of Aplastic Anemia





- 1960's → 10% survival in 1 year
- 2010 → 90% survival in 1 year

- Immunosuppressive therapy
- Bone marrow transplantation
- Supportive care
- Novel agents

Immunosuppressive therapy

- Anti-thymocyte globulin (ATG)
  - Horse
  - Rabbit
- Cyclosporine (CsA)
- Campath
- Others

Immunosuppressive therapy

- First line of treatment in adults
- Salvage for treatment-refractory patients
- Treatment for relapsed disease

PROGRESS IN IMMUNOSUPPRESSIVE THERAPIES FOR SEVERE APLASTIC ANEMIA

Era	Drug	Response
1960s	corticosteroids	~10% (occasional)
1970s	ATGs	40-50%
1980s	ATG plus CSA	60-70%

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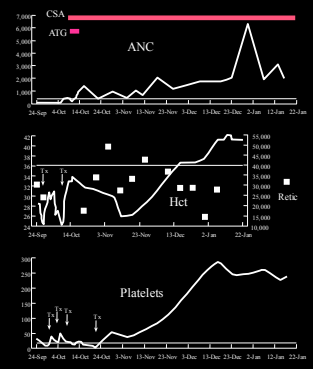
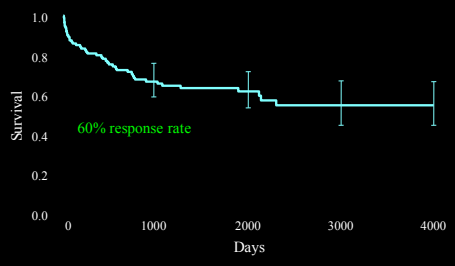
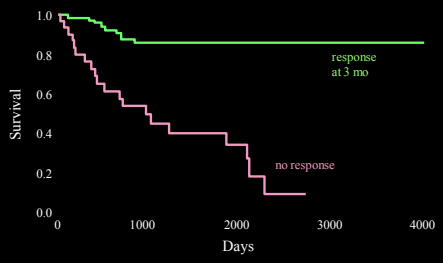
RESPONSE OF SEVERE APLASTIC ANEMIA TO INTENSIVE IMMUNOSUPPRESSION



ATG AND CSA FOR SEVERE APLASTIC ANEMIA
OVERALL SURVIVAL



ATG AND CSA FOR SEVERE APLASTIC ANEMIA
RESPONSE AT 3 MONTHS AND SURVIVAL



INTENSIVE IMMUNOSUPPRESSION FOR SAA
COMPARISON OF RESULTS

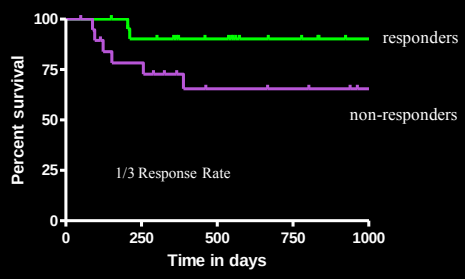
Study	Years	N	Median Age (years)	Response	Relapse	Clonal Evolution	Survival
German	1986-1989	84	32	65%	19%	8%	58% at 11 yrs
NIH	1991-1998	122	35	61%	35%	11%	55% at 7 yrs
EGMBT	1991-1998	100	16	77%	12%	11%	87% at 5 yrs
Japan	1992-1997	119	9	68%	22%	6%	88% at 3 yrs
German/Austrian	1993-1997	114	9	77%	12%	6%	87% at 4yrs
Japan	1996-2000	101	54	74%	42%	8%	88% at 4 yrs
NIH	1999-2003	104	30	62%	37%	9%	80% at 4 yrs
EGBMT	2002-2008	192	46	70%	33%	4%	76% at 6 yrs
NIH	2003-2005	77	26	57%	26%	10%	93% at 3yrs
NIH	2005-2010	120	28	68%	28%	21%	96% at 3 yrs

Young NS, Calado RT, Scheinberg P. *Blood* 2006

NEW DIRECTIONS IN TREATMENT FOR APLASTIC ANEMIA

- Add to horse ATG + CsA platform
  - G-CSF (Neupogen)
  - Mycophenolate mofetil
  - Sirolimus
  - long course immunosuppression
- Augment initial lymphocytotoxicity
  - Horse ATG
  - Rabbit ATG
  - Campath

Survival of refractory SAA following retreatment with rabbit ATG + CsA (salvage)



Scheinberg P, Nunez O, Young NS. *Br J Haematol* 2006

A Randomized Trial of H-ATG vs. R-ATG in SAA
Patients and Methods

- 120 consecutive patients (60 per arm)
- NIH Clinical Center
- 1:1 randomization
- Primary objective –response at 6 months

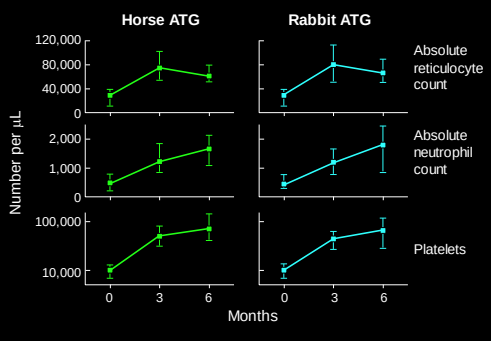
Scheinberg et al. NEJM 2011

A Randomized Trial of H-ATG vs. R-ATG in SAA
Hematologic Responses at 3 and 6 months

	Horse ATG	Rabbit ATG	P-value
3 months	37/60 **(62%)**	20/60 **(33%)**	0.003
6 months	41/60 **(68%)**	22/60 **(37%)**	< 0.001

A Randomized Trial of H-ATG vs. R-ATG in SAA

Blood Count Recovery in Responders



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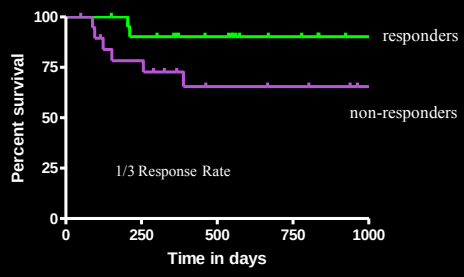
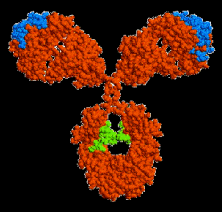


Scheinberg P, Nunez O, Young NS. *Br J Haematol* 2006

Alemtuzumab (Campath-1H)

- Anti-CD52 Antibody
- Murine hypervariable regions fused into human IgG1
- CD52 expressed:
  - B and T cells
  - NK cells, dendritic cells
  - Monocytes, macrophages
  - Plasma cells, Eos
- No CD52 expression on:
  - RBCs, platelets
  - Hematopoietic stem cells

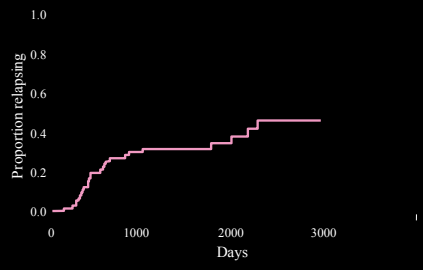


Ravandi and O' Brien, Cancer Invest. 2007 24: 718-725
Hernández-Campo PM, Cytometry B Clin Cytom. 2006 70:71

SECOND IMMUNOSUPPRESSION FOR REFRACTORY SAA

Treatment arm (N=54)	Overall response
rabbit ATG (N=27)	9 (35%)
alemtuzumab (N=27)	10 (37%)

ATG AND CSA FOR SEVERE APLASTIC ANEMIA *RELAPSE*



RELAPSE AFTER ATG + CSA

Cyclosporine-dependence Post-1st relapse

Years post-relapse	1	2	3	4	5	6	7
Patients on CsA	20/22	19/20	14/18	11/17	11/14	7/11	4/7
	(86%)	(91)	(78)	(65)	(79)	(64)	(57)

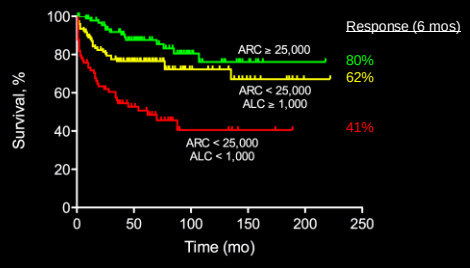
Retreatment with rabbit ATG + CsA Post-1st relapse → 2/3 response

Rosenfeld S, Follmann D, Nunez O, Young NS. *JAMA* 2003
Scheinberg P, Nunez O, Young NS. *Br J Haematol* 2006

CAMPATH IMMUNOSUPPRESSION FOR RELAPSED SAA

Treatment	Overall response
Campath (N=25)	14 (56%)

INITIAL BLOOD COUNTS PREDICT RESPONSE TO IMMUNOSUPPRESSION AND SURVIVAL



Scheinberg P *et al. Br J Haematol* 2009; 144: 206

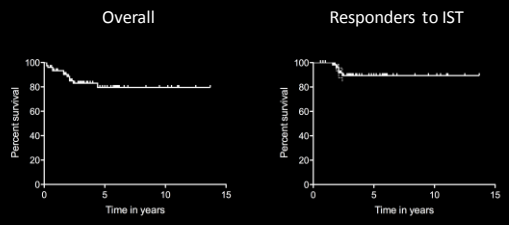
Probability of response according to age

Probability of response according to age

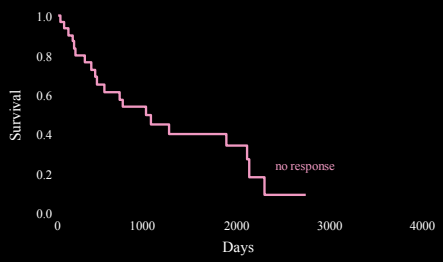
	Number of patients (%)	Response at 6 months			P-value
		Number	Percent	95% CI	
H-ATG	316 (100)	194	61.4	(56.0, 66.8)	-------
Age (years)					
< 18	78 (25)	58	74.4	(64.5, 84.3)	0.0199
18 to 60	187 (59)	109	58.3	(51.2, 65.4)	
> 60	51 (16)	27	52.9	(38.8, 67.1)	

Scheinberg P *et al. J Pediatrics* 2008.

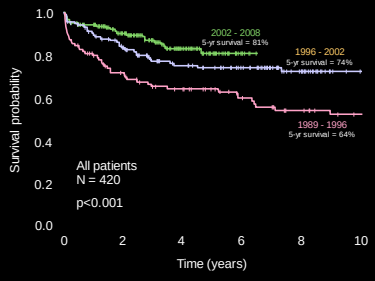
Survival Probability in Children



Survival in refractory SAA 1990s



Improved Survival Over Time



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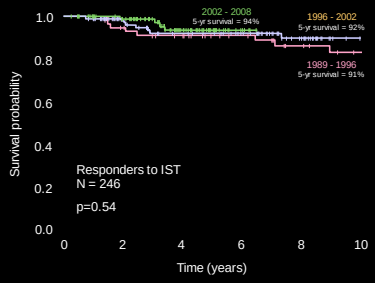

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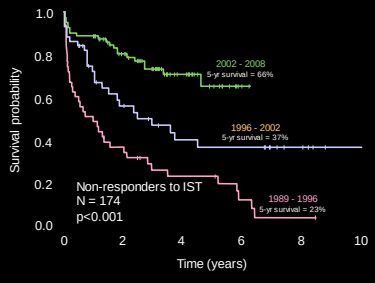


HEMATOPOIETIC GROWTH FACTORS AS THERAPY FOR SAA

Vadhan-Raj S et al, N Engl 1988; 319:1628: GM-CSF pilot
Ganser A et al, Bood 1990; 76;1287: IL-3 pilots
Kojima S et al, Blood 2002;100:786: G-CSF➔monosomy 7
Tichelli A et al, Blood 2011; 117:4434: G-CSF shows no survival benefit

ELTROMBOPAG FOR REFRACTORY SEVERE APLASTIC ANEMIA

- SAA with plts < 30K/uL
- Refractory to ATG/CSA

Non-responders off study

Eltrombopag 50 mg daily

Dose escalation every 2 weeks to 150 mg daily

Hematologic response at 3 months

Responders followed monthly, on drug

Hematologic Response Criteria

- Platelets: >20K/uL increase, or transfusion-independence
- RBCs: > 1.5 g/dL increase in Hb, or transfusion-independence
- ANC: >100% increase if severe neutropenia, or >500/uL increase

NIH Protocol 09-0H0154; ClinicalTrials.gov identifier: NCT00922883

REFRACTORY SAA ELTROMBOPAG STUDY RESULTS

Censure date 11/1/2011

Median follow up 13 months (range 4-28 months)

26 patients enrolled

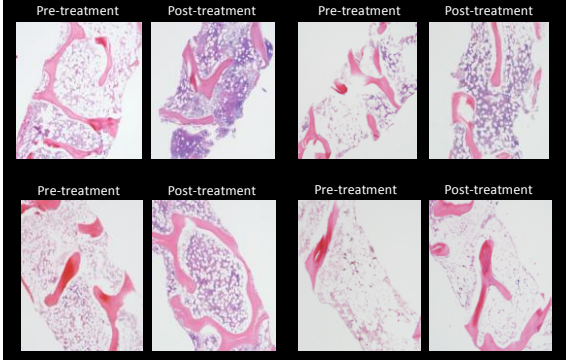
1 patient ineligible, not treated

25 evaluable patients

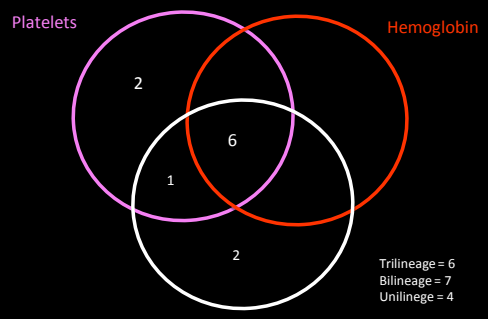
11 responders (44%)
- 9 platelet responses
- 2 hemoglobin responses
  - additional 4 at > 16wks
- 4 neutrophil responses
  - additional 3 at > 16wks

14 non-responders
- 10 stable disease
- 2 died of progression
- 2 clonal evolution to MDS
  - 1 died
  - 1 HSCT

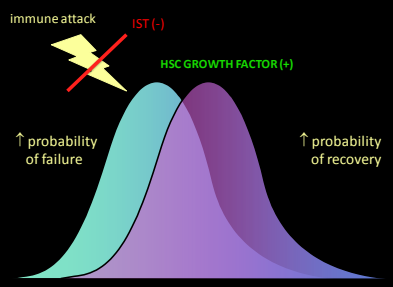
BONE MARROW CELLULARITY AT ONE YEAR



MULTI-LINEAGE HEMATOLOGIC RESPONSES TO ELTROMBOPAG



INSIGHTS INTO SAA PATHOPHYSIOLOGY FROM ELTROMBOPAG RESPONSIVENESS



correlation with blood counts, age, telomere length

SUMMARY

- Eltrombopag can promote tri-lineage hematopoiesis in SAA patients refractory to IST
  - 44% clinical response rate
  - Transfusion independence
  - Well-tolerated
- Eltrombopag stimulation may expand the HSC pool in humans
- Addition of Eltrombopag early in SAA may increase response rate, decrease time to response, prevent HSC depletion, and avoid clonal progression

ELTROMBOPAG FOR MODERATE AA
NHLBI 09-H-0154
clinicaltrials.gov NCT00922883

Eltrombopag, dose escalation to **150 mg QD** by mouth
>18 years old; platelet count <30,000/uL
Assessment by blood counts and BM at 3 and 6 months

Horse ATG + CSA and ELTROMBOPAG for treatment-naïve SAA
NHLBI 12-H-xxxx

Add eltrombopag to existing horse ATG + CSA platform will increase overall response and decrease relapses

TELOMERES AND BONE MARROW FAILURE

TELOMERE STRUCTURE AND BIOLOGY

-Cap chromosome ends

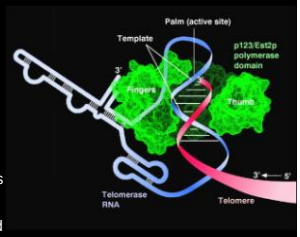
-Tandem TTAGGG repeats

-Bound to array of proteins: telomerase complex

-Forms higher order chromatin T loop

-Shields 3' end to prevent recognition as a DNA "break" by non-homologous end joining machinery

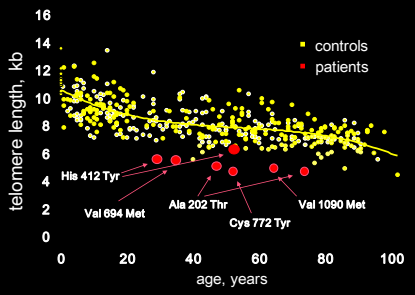
-TTAGGG loss with proliferation: "end replication problem"



TELOMRES AND BONE MARROW FAILURE
DYSKERATOSIS CONGENITA

Courtesy by B. Alter, NCI

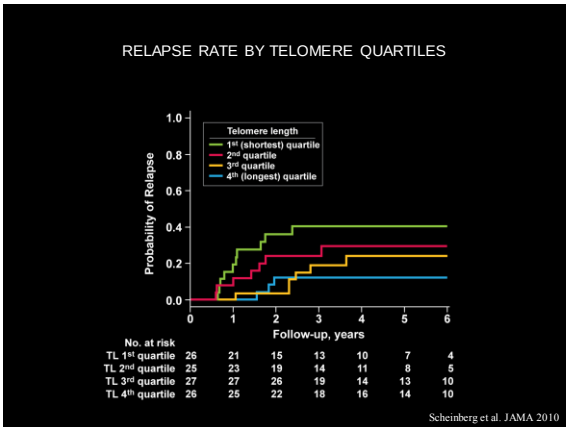
TELOMERE LENGTH IN *TERT* MUTATION LEUCOCYTES

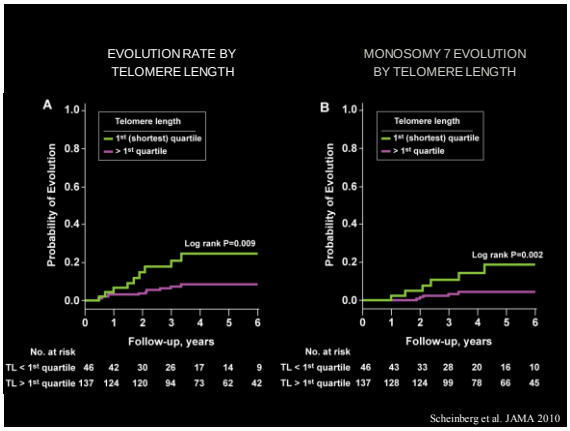


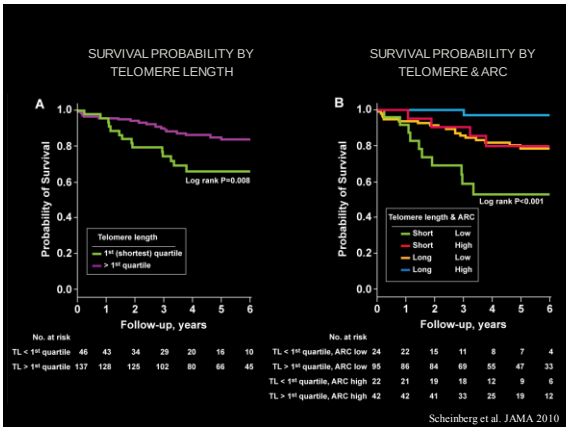
SHORT TELOMERE LENGTH PREDICTS *RELAPSE* AND *EVOLUTION* IN SEVERE APLASTIC ANEMIA

N = 168 consecutive patients on NIH IST protocols
Mean age = 34 years (4-82 years)

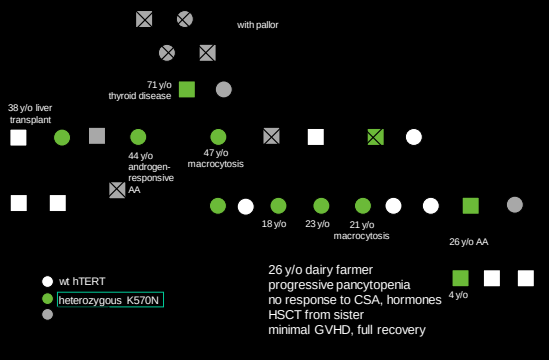
no relationship to *response to treatment* (PR, CR)


RELAPSE RATE BY TELOMERE QUARTILES
Telomere length
1st (shortest) quartile
2nd quartile
3rd quartile
4th (longest) quartile
Probability of Relapse
1.0
0.8
0.6
0.4
0.2
0.0
0 1 2 3 4 5 6
Follow-up, years
No. at risk
TL 1st quartile 26 21 15 13 10 7 4
TL 2nd quartile 25 23 19 14 11 8 5
TL 3rd quartile 27 27 26 19 14 13 10
TL 4th quartile 26 25 22 18 16 14 10
Scheinberg et al. JAMA 2010


EVOLUTION RATE BY TELOMERE LENGTH
MONOSOMY 7 EVOLUTION BY TELOMERE LENGTH
A
B
Telomere length
1st (shortest) quartile
> 1st quartile
Probability of Evolution
Log rank P=0.009
Log rank P=0.002
Follow-up, years
No. at risk
TL < 1st quartile 46 42 30 26 17 14 9
TL > 1st quartile 137 124 120 94 73 62 42
TL < 1st quartile 46 43 33 28 20 16 10
TL > 1st quartile 137 128 124 99 78 66 45
Scheinberg et al. JAMA 2010

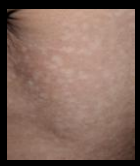

SURVIVAL PROBABILITY BY TELOMERE LENGTH
SURVIVAL PROBABILITY BY TELOMERE & ARC
A
B
Probability of Survival
Log rank P=0.008
Log rank P<0.001
Telomere length
1st (shortest) quartile
> 1st quartile
Telomere length & ARC
Short Low
Short High
Long Low
Long High
Follow-up, years
No. at risk
TL < 1st quartile 46 43 34 29 20 16 10
TL > 1st quartile 137 128 125 102 80 66 45
TL < 1st quartile, ARC low 24 22 15 11 8 7 4
TL > 1st quartile, ARC low 95 86 84 69 55 47 33
TL < 1st quartile, ARC high 22 21 19 18 12 9 6
TL > 1st quartile, ARC high 42 42 41 33 25 19 12
Scheinberg et al. JAMA 2010

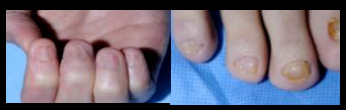
SHANK'S DISEASE" IN A MENNONITE FAMILY

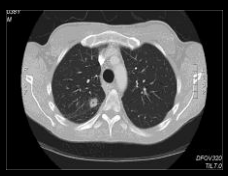


26 y/o dairy farmer
progressive pancytopenia
no response to CSA, hormones
HSCT from sister
minimal GVHD, full recovery

LATE PRESENTATION OF DYSKERATOSIS CONGENITA



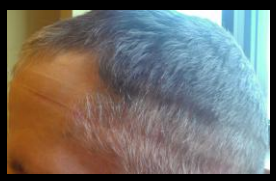


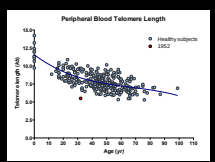


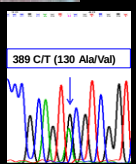
37 y/o US Army officer in Afghanistan
tongue ulcer, diagnosed as squamous cell carcinoma
single round of chemotherapy and radiation resulted in unexpected extreme, persistent pancytopenia. Later, pulmonary metastases
novel Val329Gly mutation in *DKC1*

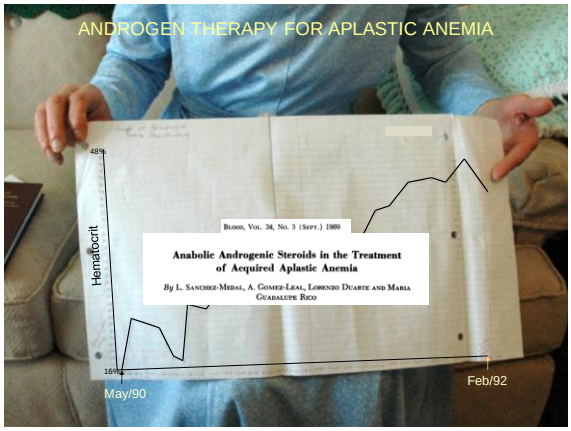
Early onset of graying (20's) and low platelets

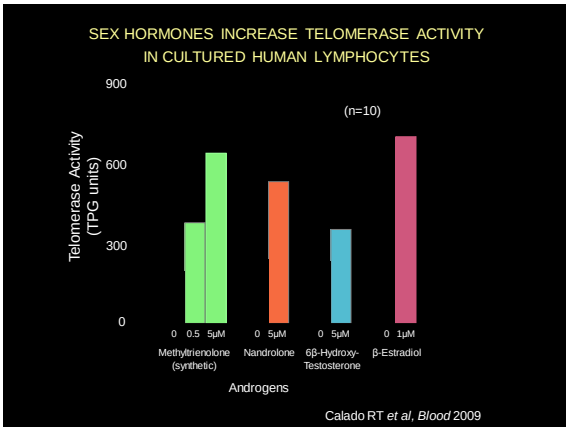
Thrombocytopenia, gray hair, very short telomere, TERT mutation











Danazol for telomeropathy

11-H-0209: "*Danazol for Genetic Bone Marrow and Lung Disorders*"

ClinicalTrials.gov identifier: NCT01441037

http://clinicaltrials.gov/ct2/show/NCT01441037?term=danazol+for+telomere&rank=1

15 patients enrolled in first 6 months.

First patient enrolled on 08/19/2011

First 6 months – no drug-related toxicities.

(Minimal elevation in LFTs in almost all patients and controllable headaches in 4 patients).