BTG2012

3rd International Hematologic Malignancies Conference

Hong Kong, February 23-25, 2012

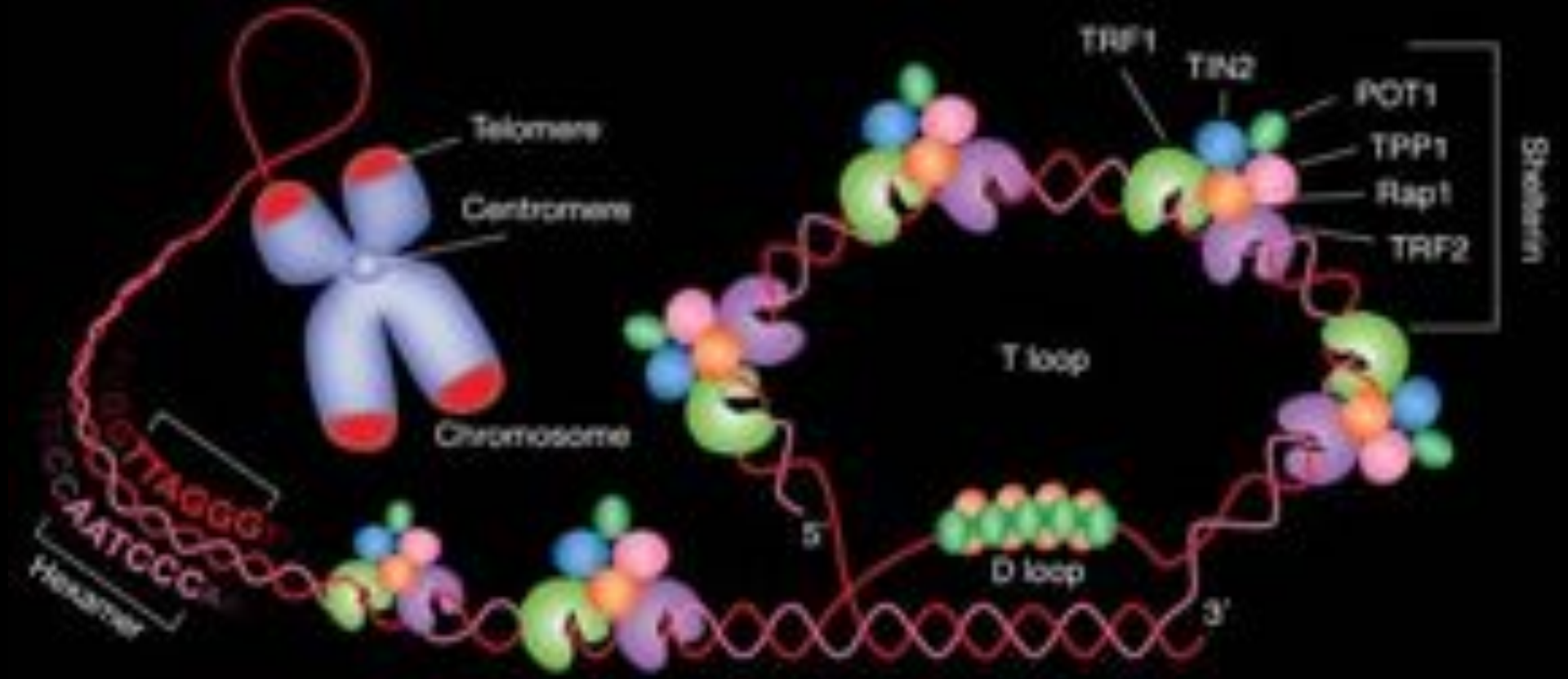
TELOMERE LENGTH AND MALIGNANT TRANSFORMATION IN APLASTIC ANEMIA

Rodrigo T. Calado, MD/PhD

University of São Paulo at Ribeirão Preto Medical School

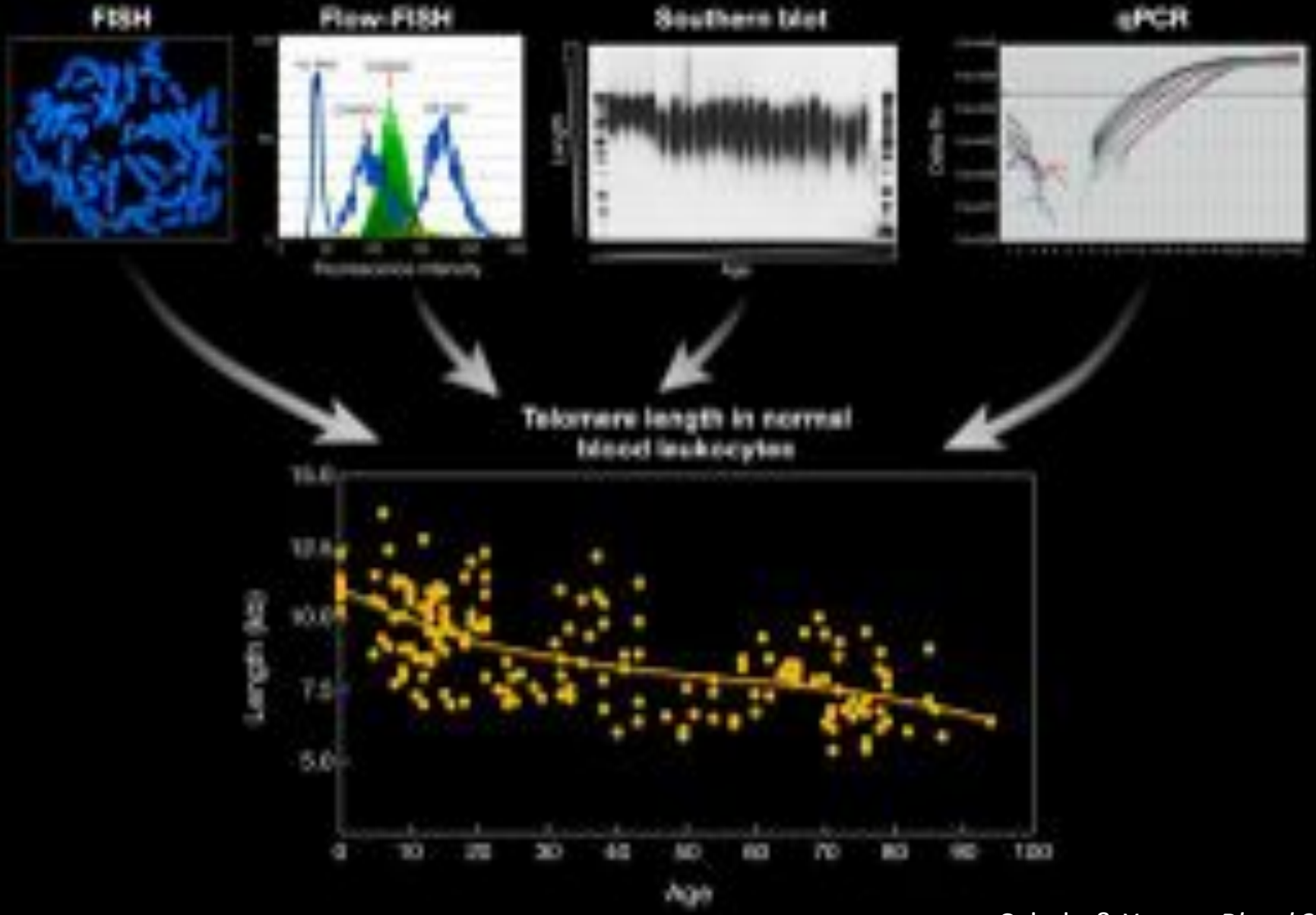
Ribeirão Preto, São Paulo, Brazil

TELOMERE STRUCTURE

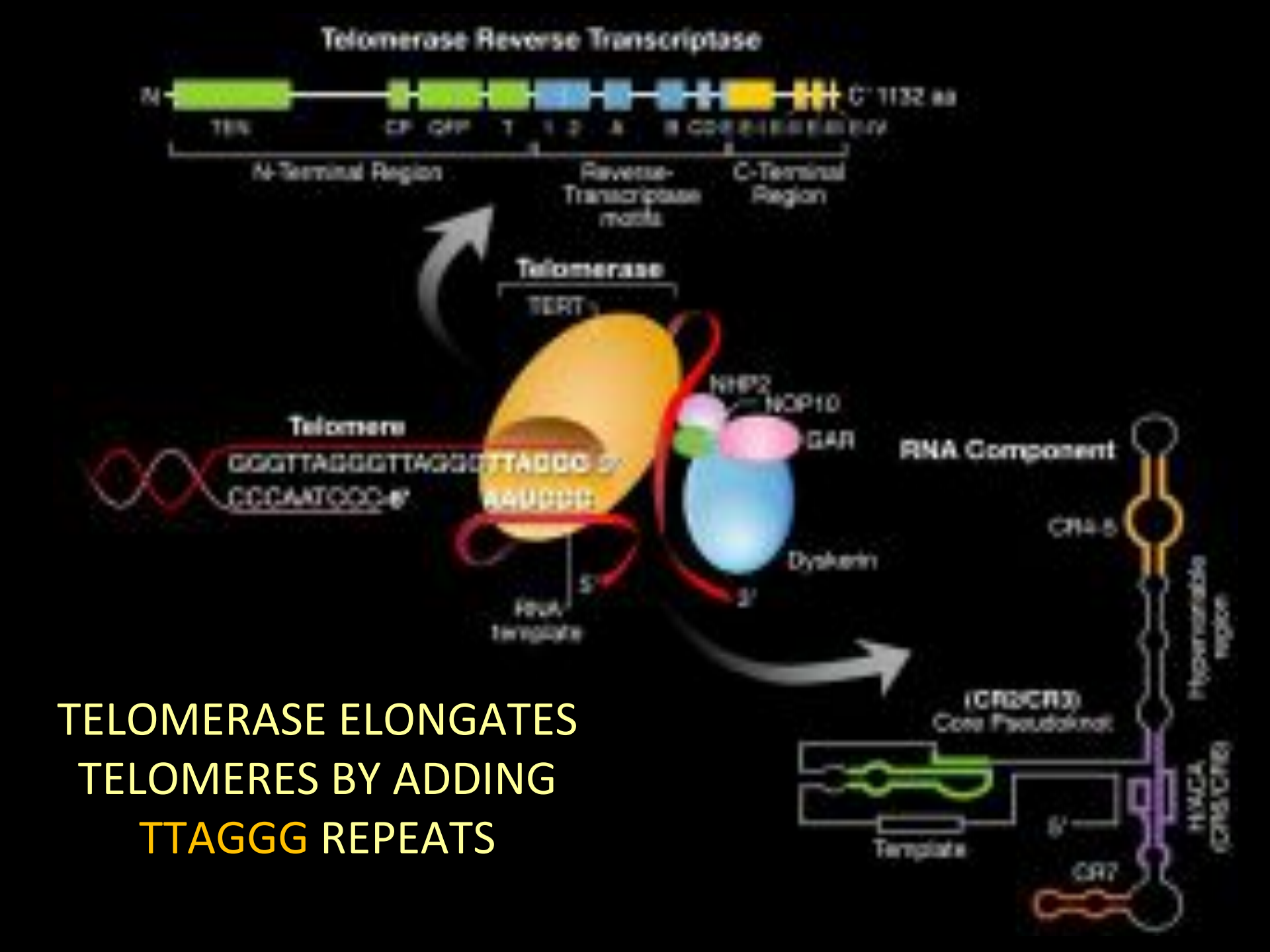


Calado & Young, *Blood* 2008

TELOMERE LENGTH MEASUREMENT



Calado & Young, *Blood* 2008



TELOMERASE ELONGATES TELOMERES BY ADDING TTAGGG REPEATS

TELOMERES ARE SHORT IN ACQUIRED APLASTIC ANEMIA

RAPID COMMUNICATION

Blood, Vol 91, No 10 (May 15), 1998: pp 3582-3592

Progressive Telomere Shortening in Aplastic Anemia

By Sarah E. Ball, Frances M. Gibson, Siân Rizzo, Jennifer A. Tooze, Judith C.W. Marsh, and Edward C. Gordon-Smith

BLOOD, 15 FEBRUARY 2001 • VOLUME 97, NUMBER 4

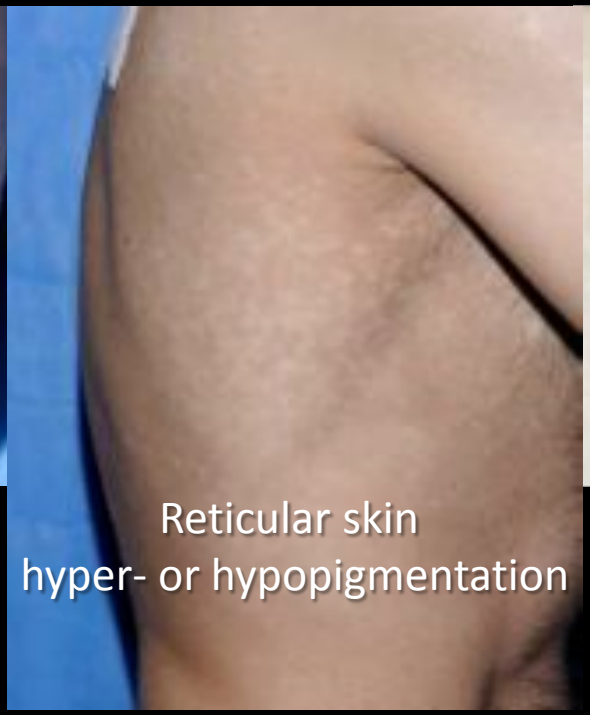
Telomere length in leukocyte subpopulations of patients with aplastic anemia

Tim H. Brümmendorf, Jaroslaw P. Maciejewski, Jennifer Mak, Neal S. Young, and Peter M. Lansdorp

DYSKERATOSIS CONGENITA

Bone Marrow Failure Associated with Mucocutaneous Triad

Nail dystrophy



Reticular skin
hyper- or hypopigmentation

Courtesy of B. Alter, NCI

Leukoplakia

X-linked dyskeratosis congenita is caused by mutations in a highly conserved gene with putative nucleolar functions

Nina S. Heiss[1], Stuart W. Knight[2], Tom J. Vulliamy[2], Sabine M. Klauck[1], Stefan Wiemann[3], Philip J. Mason[2], Annemarie Poustka[1] & Inderjeet Dokal[2]

nature genetics volume 19 may 1998

NATURE | VOL 402 | 2 DECEMBER 1999 | letters to nature

A telomerase component is defective in the human disease dyskeratosis congenita

James R. Mitchell, Emily Wood & Kathleen Collins

ACQUIRED APLASTIC ANEMIA

Telomerase Mutations in Patients without Clinical Features of DKC

The NEW ENGLAND JOURNAL of MEDICINE

Cohort of 205 patients with acquired aplastic anemia:

Mutation	Patient	Diagnosis	Family History
Ala			
Ala			
His			
His 412 Tyr	31 yr Male Hispanic	Severe AA	--
Val 694 Met	34 yr Male White	Moderate AA	sister MDS/AML
Tyr 772 Cys	53 yr Male White	Moderate AA	sister “anemia”
Val 1090 Met	64 yr Female Hispanic	Severe AA	--

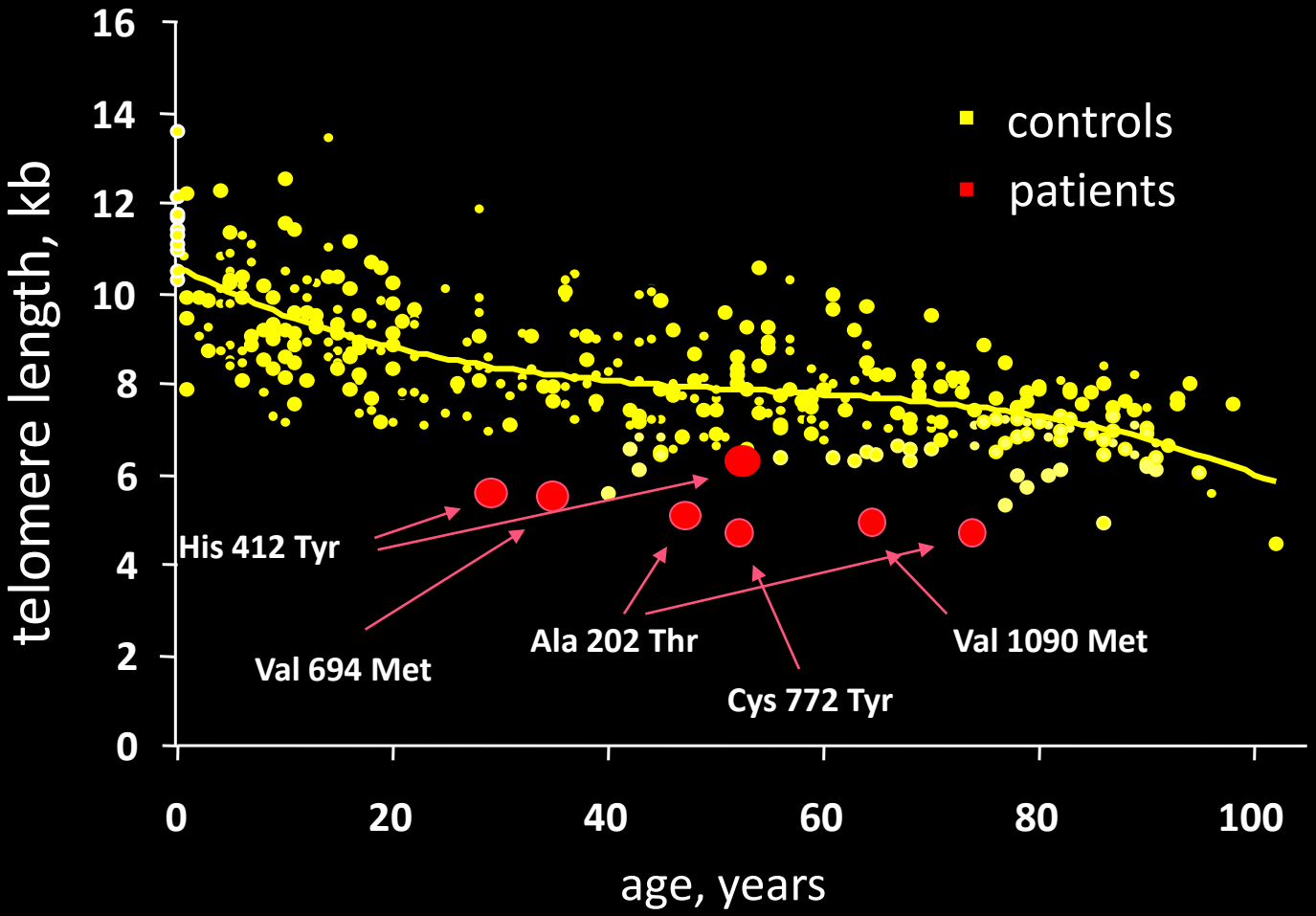
Mutations in TERT, the Gene for Telomerase Reverse Transcriptase, in Aplastic Anemia

Hiroki Yamaguchi, M.D., Rodrigo T. Calado, M.D., Ph.D., Hinh Ly, Ph.D., Sachiko Kajigaya, Ph.D., Gabriela M. Baerlocher, M.D., Stephen J. Chanock, M.D., Peter M. Lansdorp, M.D., Ph.D., and Neal S. Young, M.D.

Yamaguchi *et al.*, *NEJM* 2005

ACQUIRED APLASTIC ANEMIA

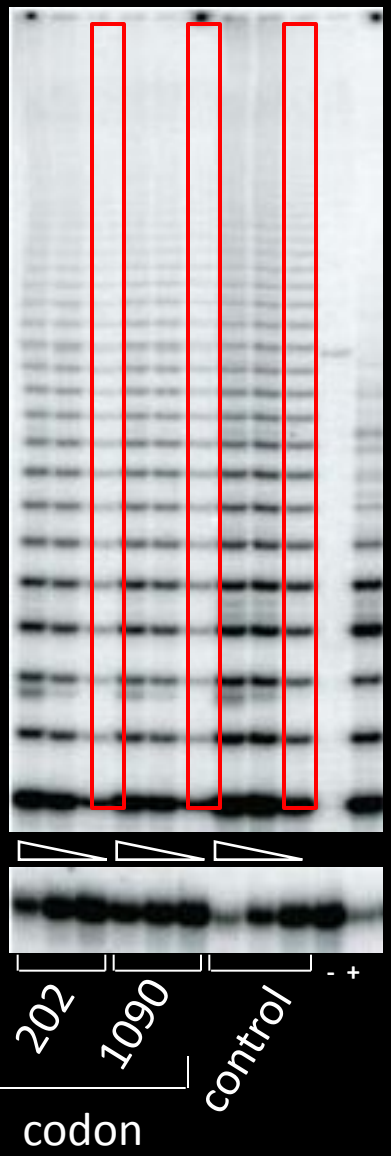
Telomeres Are Short in Patients in with Telomerase Mutations



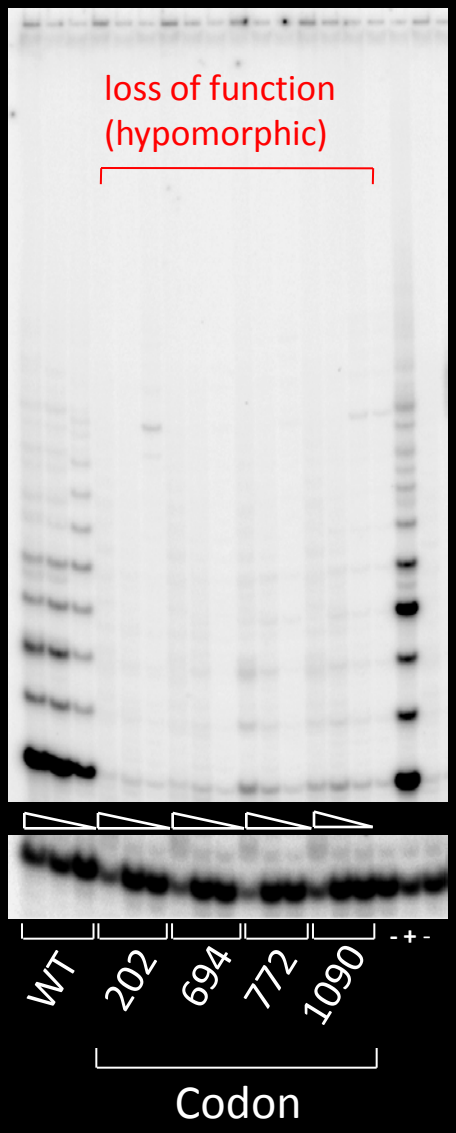
Yamaguchi *et al.*, *NEJM* 2005

FUNCTIONAL ASSAYS OF TELOMERASE ACTIVITY

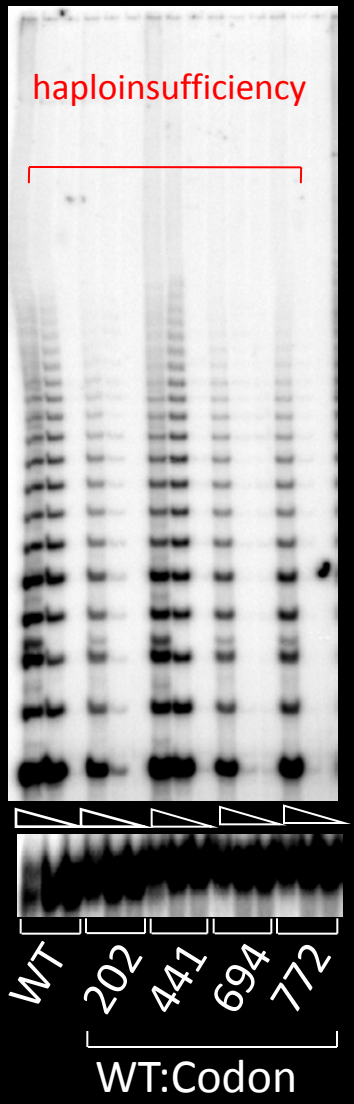
Primary cells



Transfection of *TERT* Mutants



Co-transfection



Yamaguchi *et al.*, *NEJM* 2005

HEMATOPOIESIS IN "NORMAL" RELATIVES WITH *TERC* MUTATIONS

Hematology:

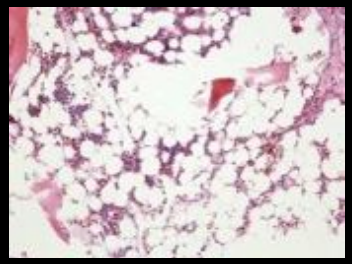
normal peripheral blood counts
mild anemia with macrocytosis
mild thrombocytopenia

Hematopoiesis:

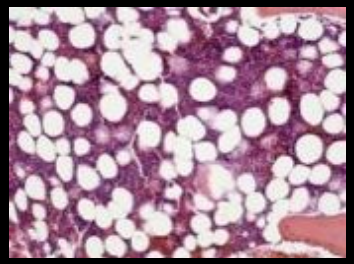
severely hypoplastic
↓CD34 number
↓colony formation
↑erythropoietin, thrombopoietin

proband

affected sister



affected niece

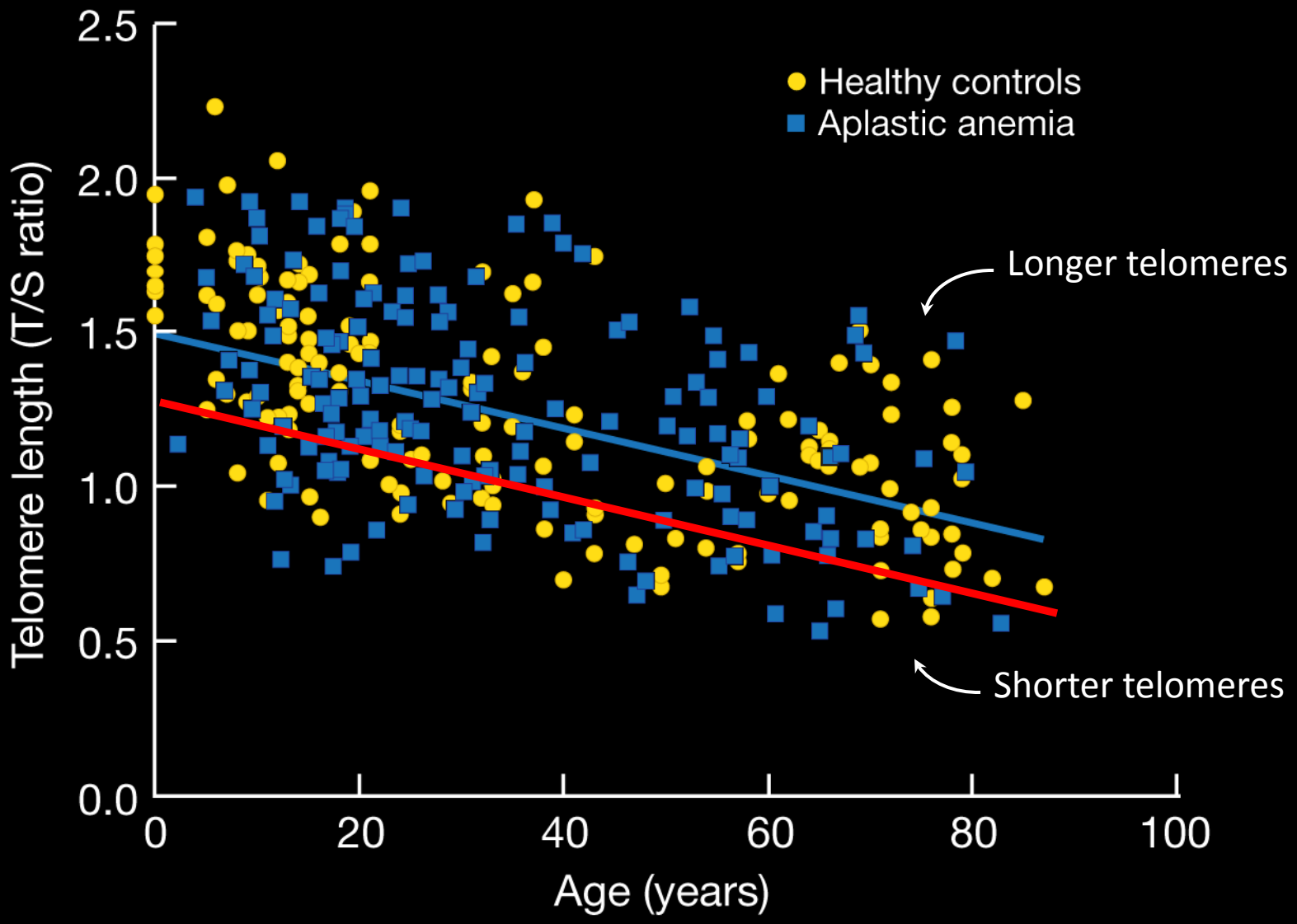


unaffected brother

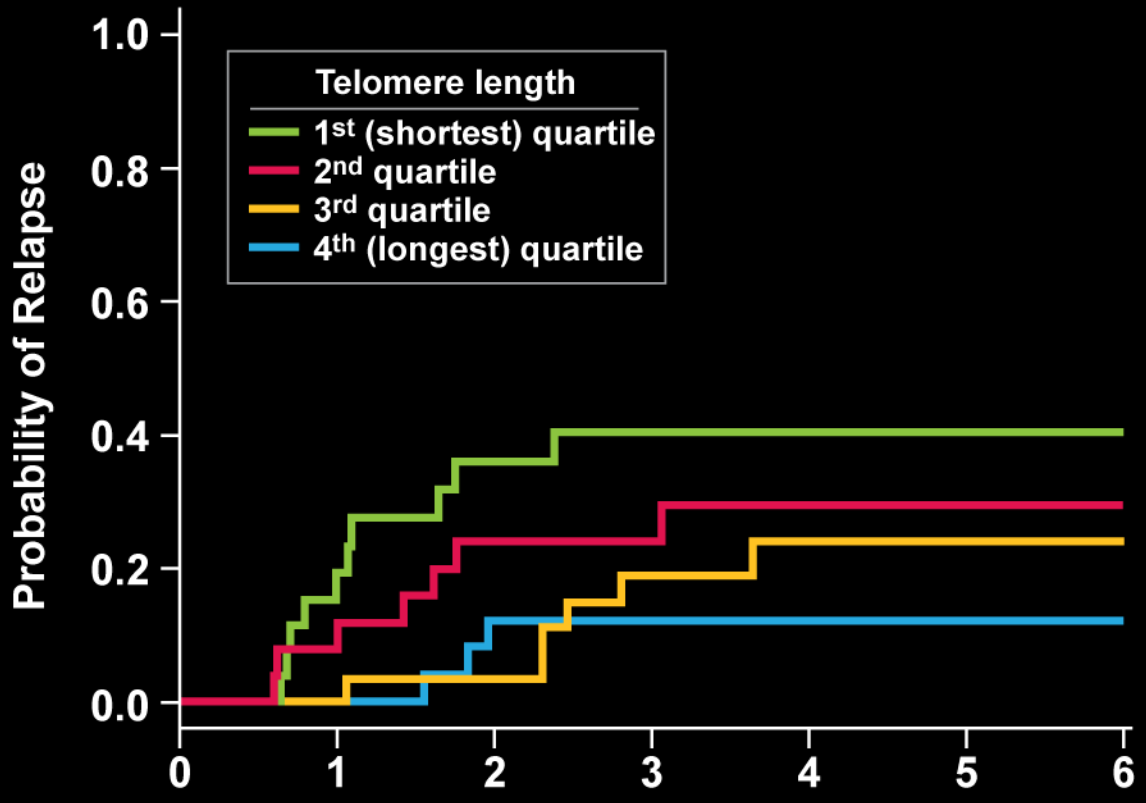
Fogarty *et al.*, *Lancet* 2003

TELOMERE LENGTH IN PATIENTS WITH ACQUIRED APLASTIC ANEMIA

183 Consecutive Patients Treated with IST



Telomere Length and Relapse



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

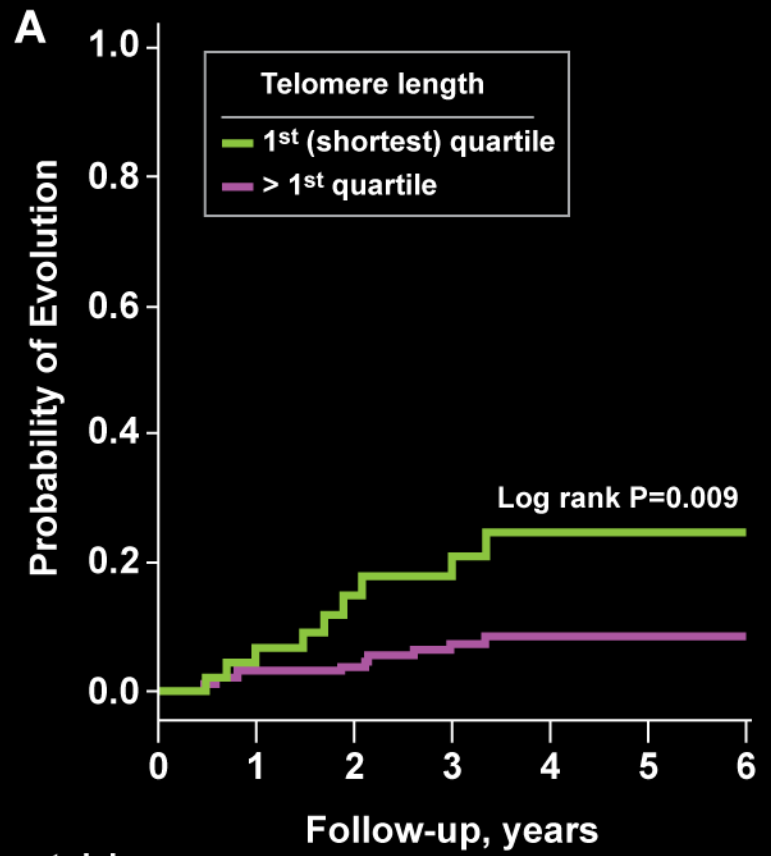
Scheinberg et al. *JAMA* 2010

Telomere Length and Clonal Evolution
Multivariate Analysis

	Coefficient	SD	Relative risk	P-value
Telomere length	-1.475	0.539	0.229	0.006
Age	0.020	0.011	1.020	0.078
ARC	0.192	0.374	1.211	0.610
ALC	0.083	0.428	1.087	0.850
ANC	-0.446	0.326	0.640	0.170
Platelet	-0.262	0.283	0.769	0.35

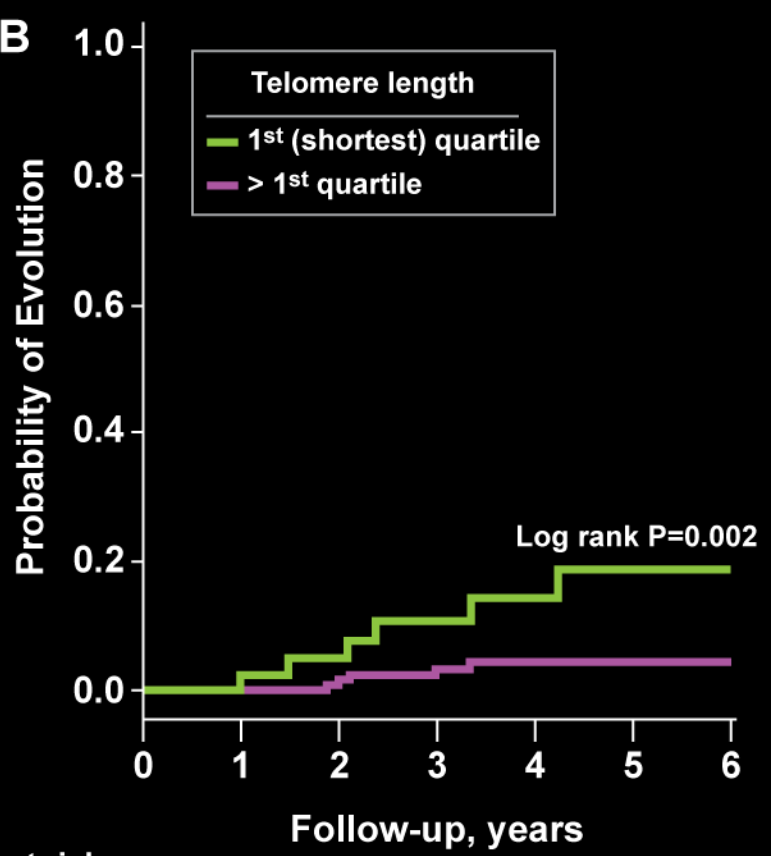
Scheinberg et al. *JAMA* 2010

EVOLUTION RATE BY TELOMERE LENGTH



No. at risk							
TL < 1st quartile	46	42	30	26	17	14	9
TL > 1st quartile	137	124	120	94	73	62	42

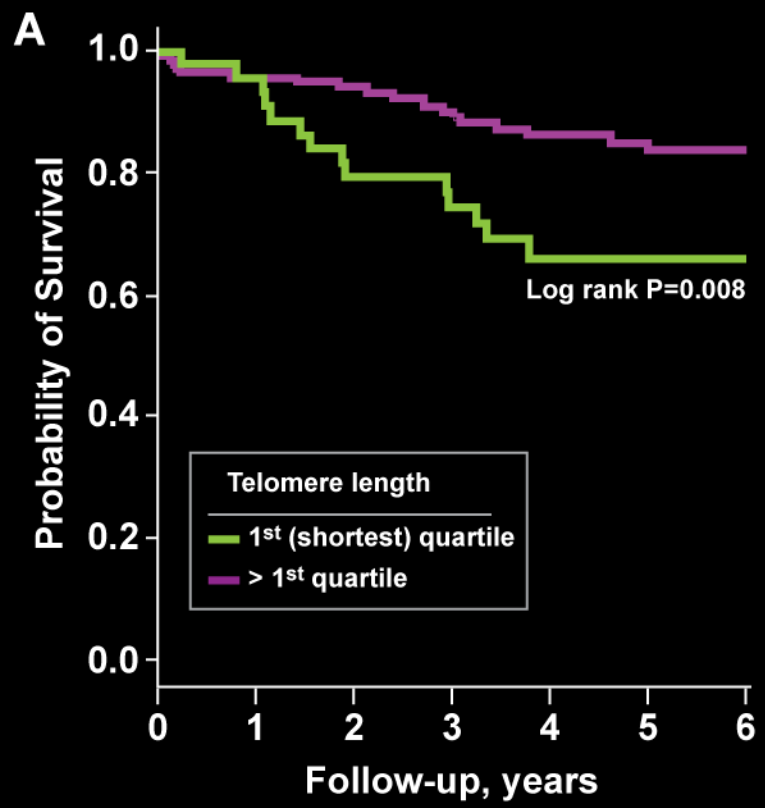
MONOSOMY 7 RATE BY TELOMERE LENGTH



No. at risk							
TL < 1st quartile	46	43	33	28	20	16	10
TL > 1st quartile	137	128	124	99	78	66	45

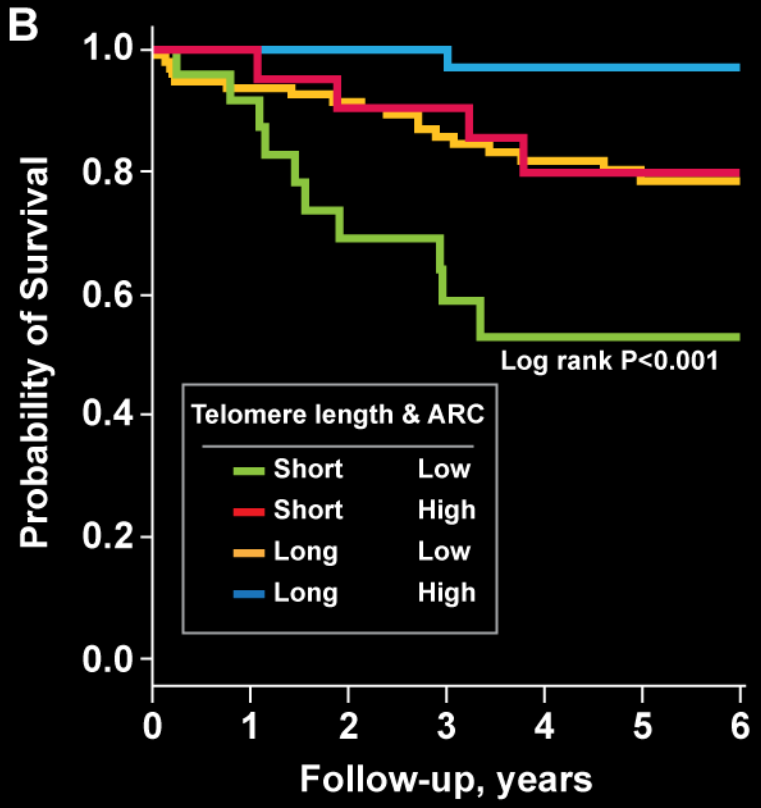
Scheinberg et al. *JAMA* 2010

SURVIVAL PROBABILITY BY TELOMERE LENGTH



No. at risk							
TL < 1st quartile	46	43	34	29	20	16	10
TL > 1st quartile	137	128	125	102	80	66	45

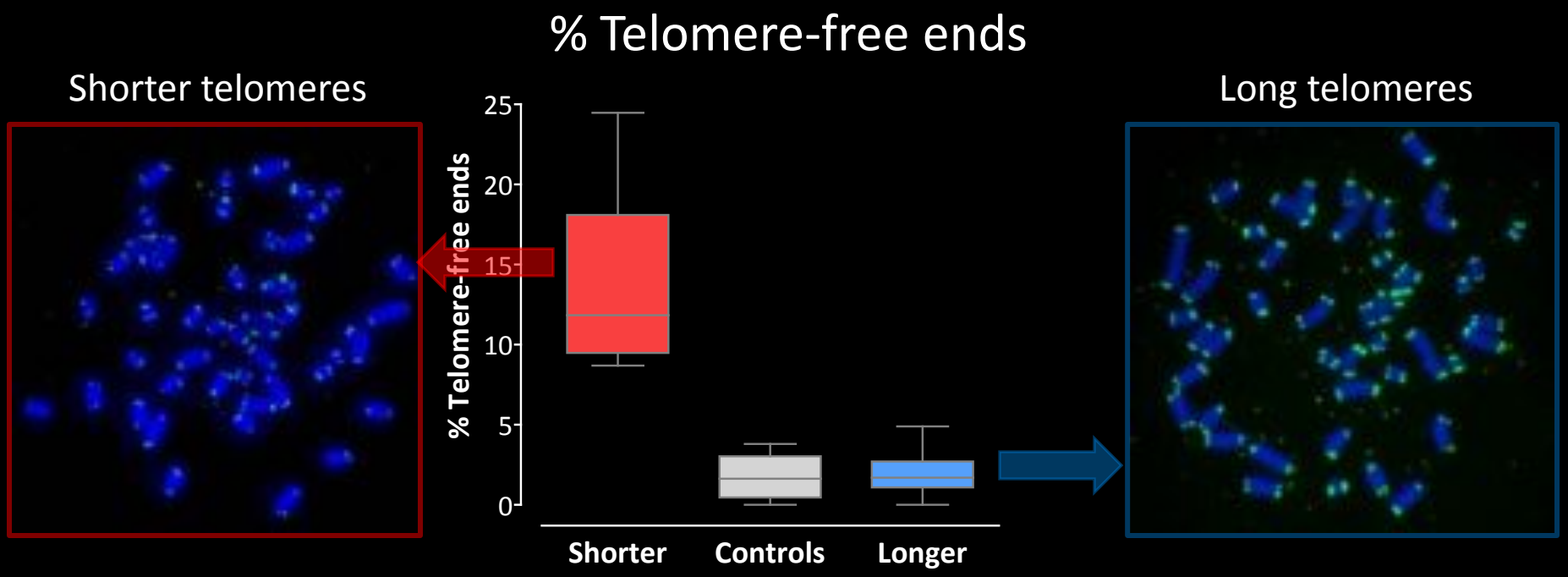
SURVIVAL PROBABILITY BY TELOMERE LENGTH & ARC



No. at risk							
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

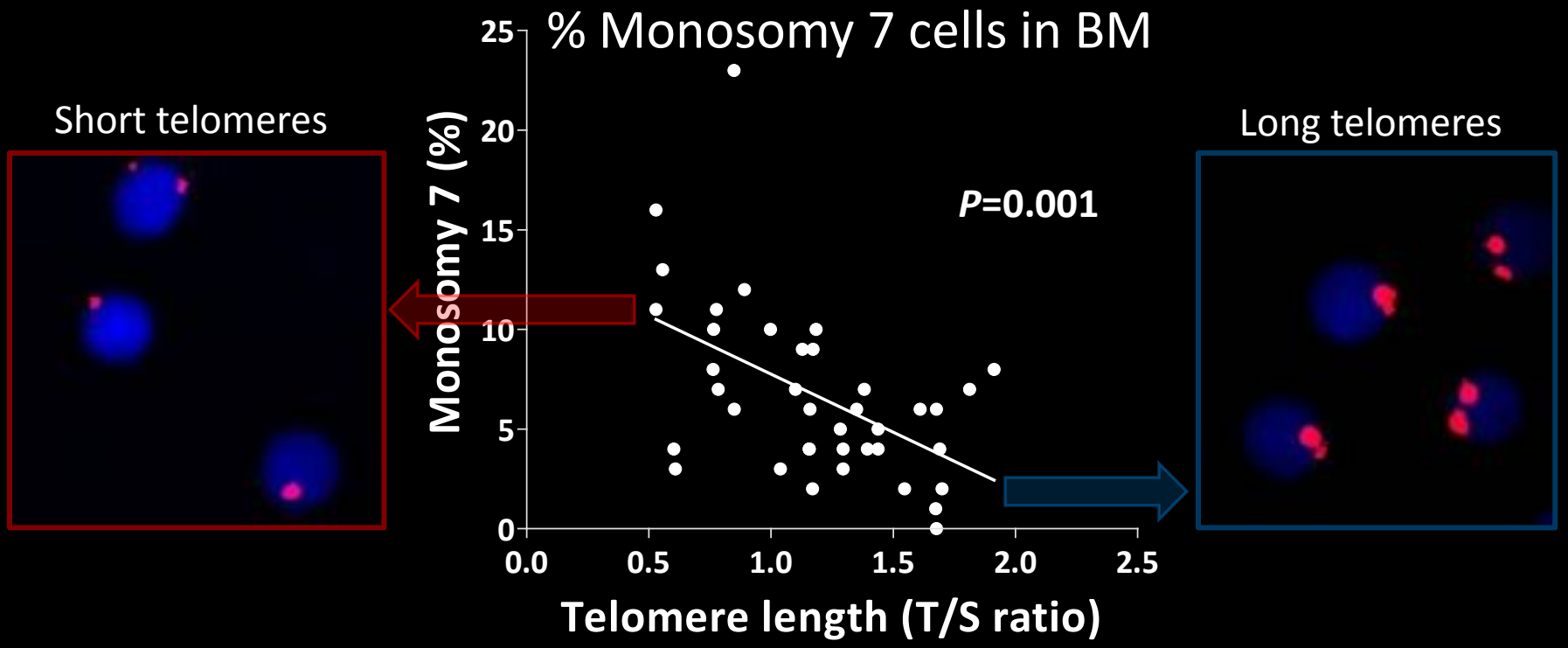
Scheinberg et al. *JAMA* 2010

INCREASED TELOMERE-FREE ENDS IN MARROW CELLS OF AA PATIENTS WITH SHORTER TELOMERES



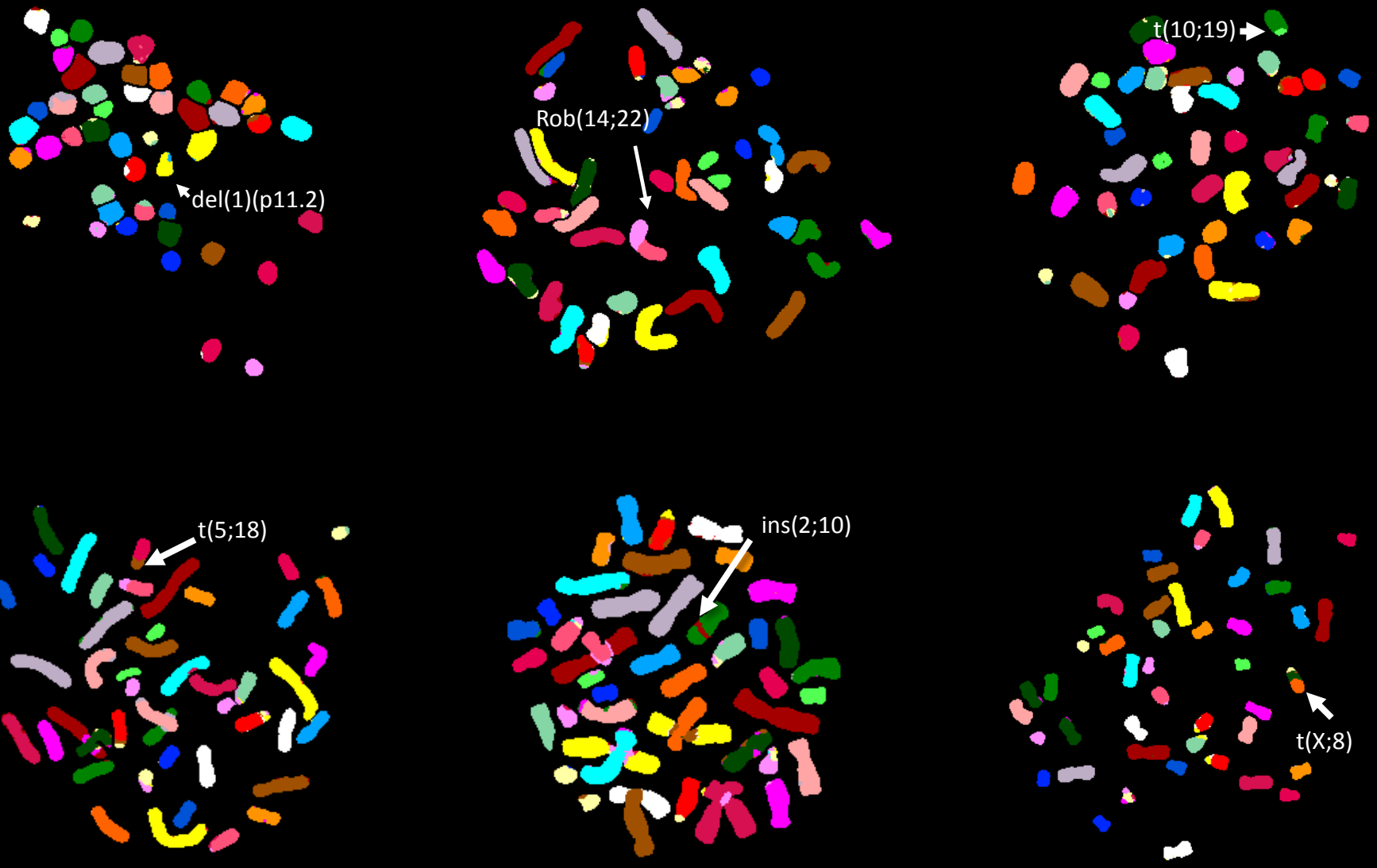
Calado et al. Leukemia 2012 in press

APLASTIC ANEMIA PATIENTS WITH SHORTER TELOMERES AT DIAGNOSIS ALSO DISPLAY MORE ANEUPLOIDY



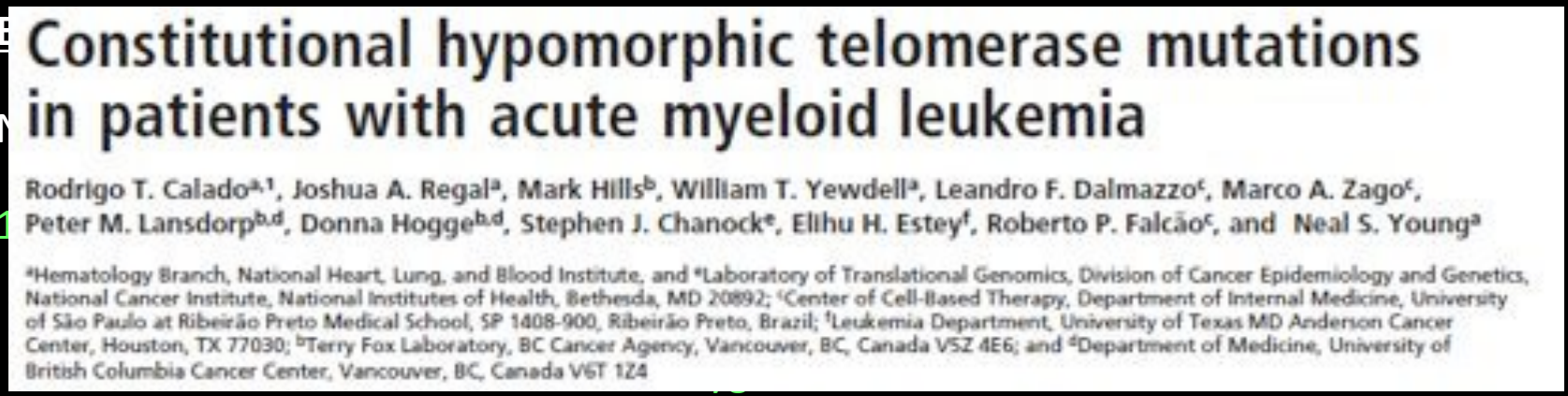
Calado et al. Leukemia 2012 in press

CHROMOSOMAL INSTABILITY IN APLASTIC ANEMIA PATIENTS WITH SHORTER TELOMERES



Calado et al. Leukemia 2012 in press

TERT MUTATIONS IN ACUTE MYELOID LEUKEMIA



Constitutional hypomorphic telomerase mutations in patients with acute myeloid leukemia

Rodrigo T. Calado[a,1], Joshua A. Regal[a], Mark Hills[b], William T. Yewdell[a], Leandro F. Dalmazzo[c], Marco A. Zago[c], Peter M. Lansdorp[b,d], Donna Hogge[b,d], Stephen J. Chanock[e], Elihu H. Estey[f], Roberto P. Falcão[c], and Neal S. Young[a]

[a]Hematology Branch, National Heart, Lung, and Blood Institute, and [e]Laboratory of Translational Genomics, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892; [c]Center of Cell-Based Therapy, Department of Internal Medicine, University of São Paulo at Ribeirão Preto Medical School, SP 1408-900, Ribeirão Preto, Brazil; [f]Leukemia Department, University of Texas MD Anderson Cancer Center, Houston, TX 77030; [b]Terry Fox Laboratory, BC Cancer Agency, Vancouver, BC, Canada V5Z 4E6; and [d]Department of Medicine, University of British Columbia Cancer Center, Vancouver, BC, Canada V6T 1Z4

TERT- AML: 2 inv(16), 1 complex, t(5;11)(q35;q13) + del(10)(p15), 3 t(15,17)

MD Anderson Cohort

N= 89 *selected* AML by cytogenetics (528 healthy controls; P=0.028)

4 *TERT* mutations: 2 heterozygous for A1062T
1 *homozygous* for 411E deletion
1 heterozygous for V299M

Mutations associated with trisomy 8 and inv(16)

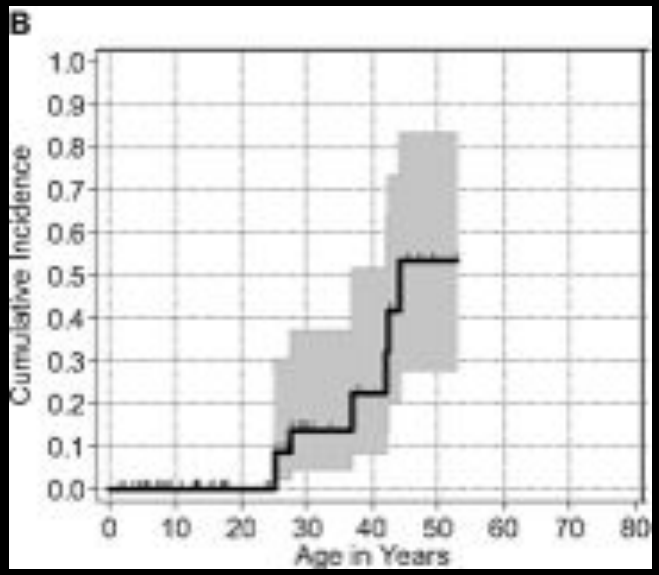
TERT mutations are constitutional and dominant loss-of-function.

Calado *et al.*, *PNAS 2009*

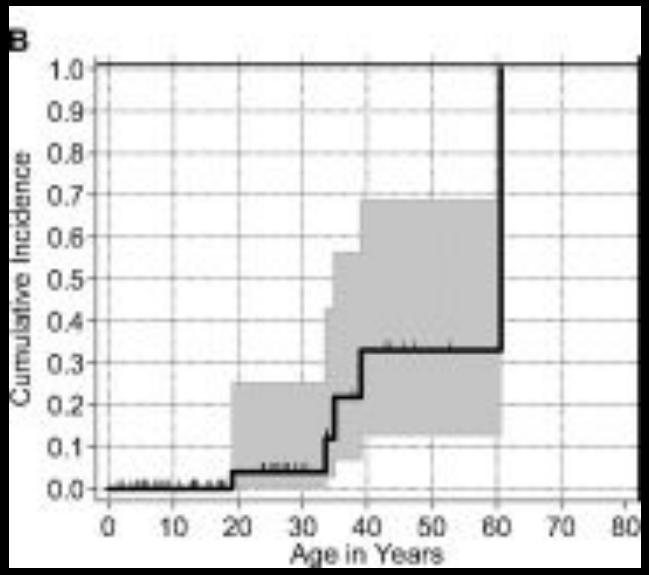
DYSKERATOSIS CONGENITA

Predisposes to Cancer

Cumulative incidence of cancer



Cumulative incidence of MDS



Types of cancers and observed/expected (O/E) ratio

Cancer	O/E	95% C.I.
All sites	11*	4-23
Tongue	1154*	232-3372
AML	196*	22-707
Cervical SCC	43*	0.6-236

*P<0.05

Alter *et al.*, *Blood* 2009

TERT LOCUS AND CANCER

Genome-Wide Association Studies (GWAS)

VOLUME 40 | NU

Lung ca
at 5p15.

James D McKay
Paolo Boffetta[1],
David Zaridze[3],
Jolanta Lissowsk
Dana Mates[8], V
Vladimir Janout
Alexandre Mont
Frank Skorpen[1
Inger Njølstad[17
Gary Goodman
Jan Lubiński[20],
Dorota Oszutov
George Xinarian
Diana Zelenika[2
Mario Foglio[22],
Helene Blanche
Paul Brennan[1]

Lung Cancer 66 (2009) 157–161

Genetic variation in telomere maintenance genes, telomere length, and lung cancer susceptibility

H. Dean Hosgood III[a,*], Richard Cawthon[b], Xingzhou He[c], Stephen Chanock[a,d], Qing Lan[a]

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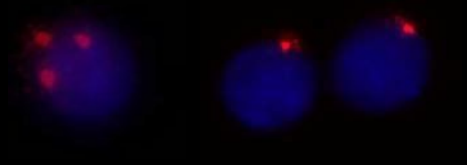
NATU

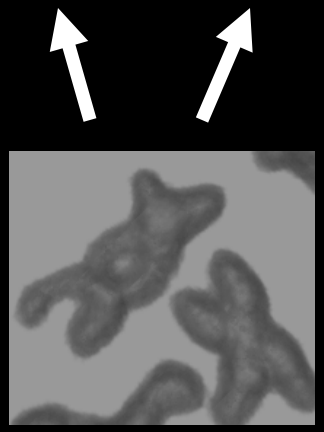
REPORT

A Genome-wide Association Study of Lung Cancer Identifies a Region of Chromosome 5p15 Associated with Risk for Adenocarcinoma

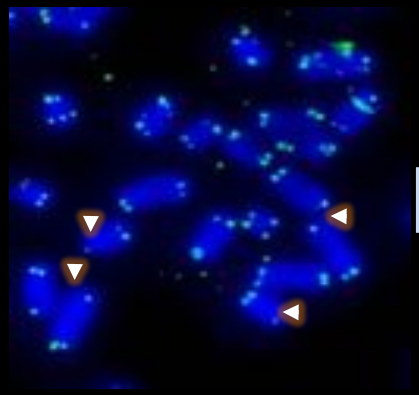
Maria Teresa Landi,[1,*] Nilanjan Chatterjee,[1] Kai Yu,[1] Lynn R. Goldin,[1] Alisa M. Goldstein,[1] Melissa Rotunno,[1] Lisa Mirabello,[1] Kevin Jacobs,[1] William Wheeler,[2] Meredith Yeager,[1] Andrew W. Bergen,[3] Qizhai Li,[1,4] Dario Consonni,[5] Angela C. Pesatori,[5] Sholom Wacholder,[1] Michael Thun,[6] Ryan Diver,[6] Martin Oken,[7] Jarmo Virtamo,[8] Demetrius Albanes,[1] Zhaoming Wang,[1] Laurie Burdette,[1] Kimberly F. Doheny,[9] Elizabeth W. Pugh,[9] Cathy Laurie,[10] Paul Brennan,[11] Rayjean Hung,[12] Valerie Gaborieau,[11] James D. McKay,[11] Mark Lathrop,[13] John McLaughlin,[12] Ying Wang,[12] Ming-Sound Tsao,[14] Margaret R. Spitz,[15] Yufei Wang,[16] Hans Krokan,[17] Lars Vatten,[17] Frank Skorpen,[17] Egil Arnesen,[18] Simone Benhamou,[19] Christine Bouchard,[20] Andres Metsapalu,[21] Tonu Vooder,[21] Mari Nelis,[21] Kristian Välk,[21] John K. Field,[22] Chu Chen,[23] Gary Goodman,[23] Patrick Sulem,[24] Gudmar Thorleifsson,[24] Thorunn Rafnar,[24] Timothy Eisen,[25] Wiebke Sauter,[26] Albert Rosenberger,[29] Heike Bickeböller,[29] Angela Risch,[30] Jenny Chang-Claude,[30] H. Erich Wichmann,[26,27,28] Kari Stefansson,[24] Richard Houlston,[16] Christopher I. Amos,[15] Joseph F. Fraumeni, Jr.,[1] Sharon A. Savage,[1] Pier Alberto Bertazzi,[5] Margaret A. Tucker,[1] Stephen Chanock,[1] and Neil E. Caporaso[1]



Telomere Erosion



Chromosomal Instability



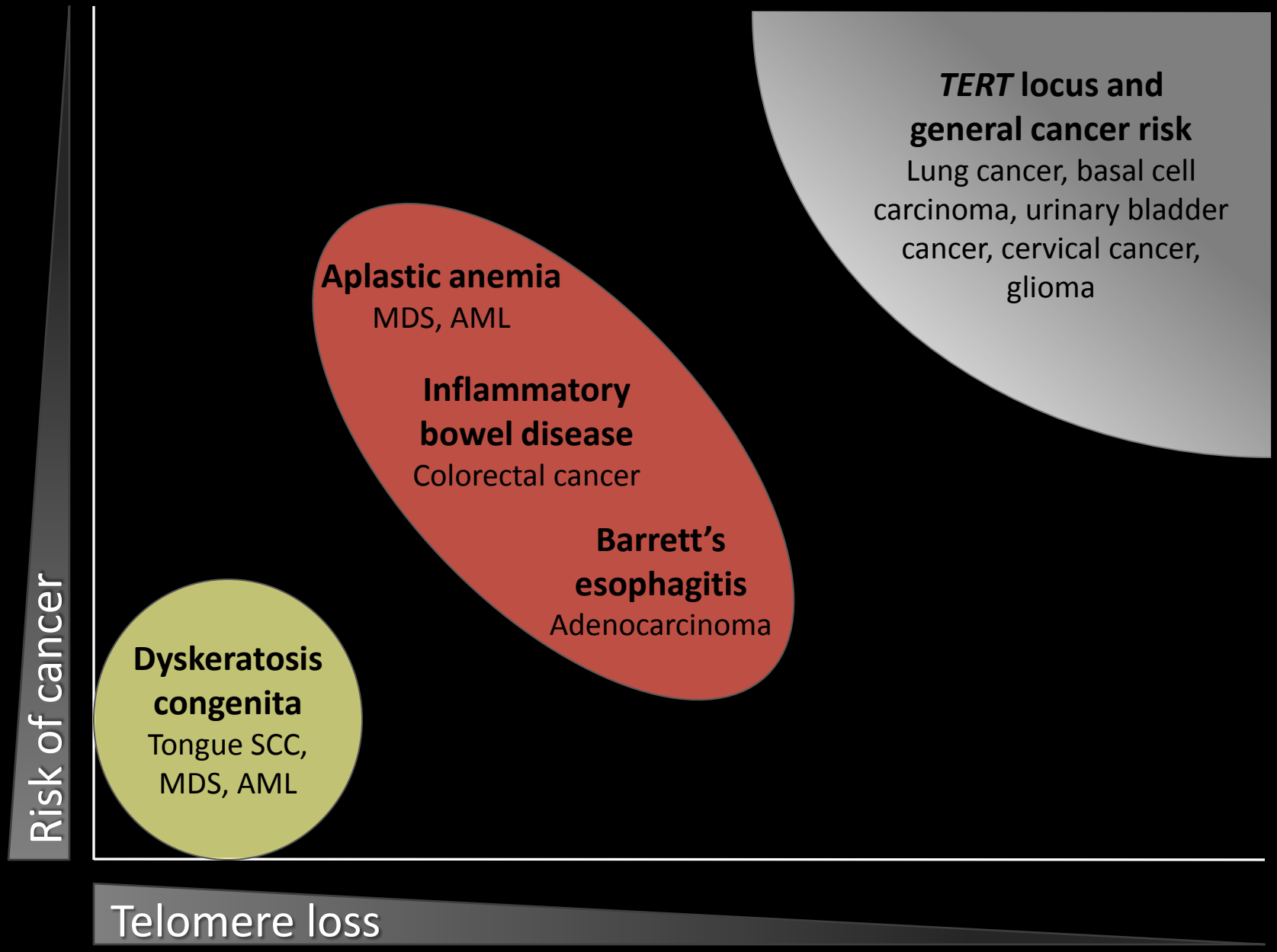
↑p53

Senescence
Apoptosis

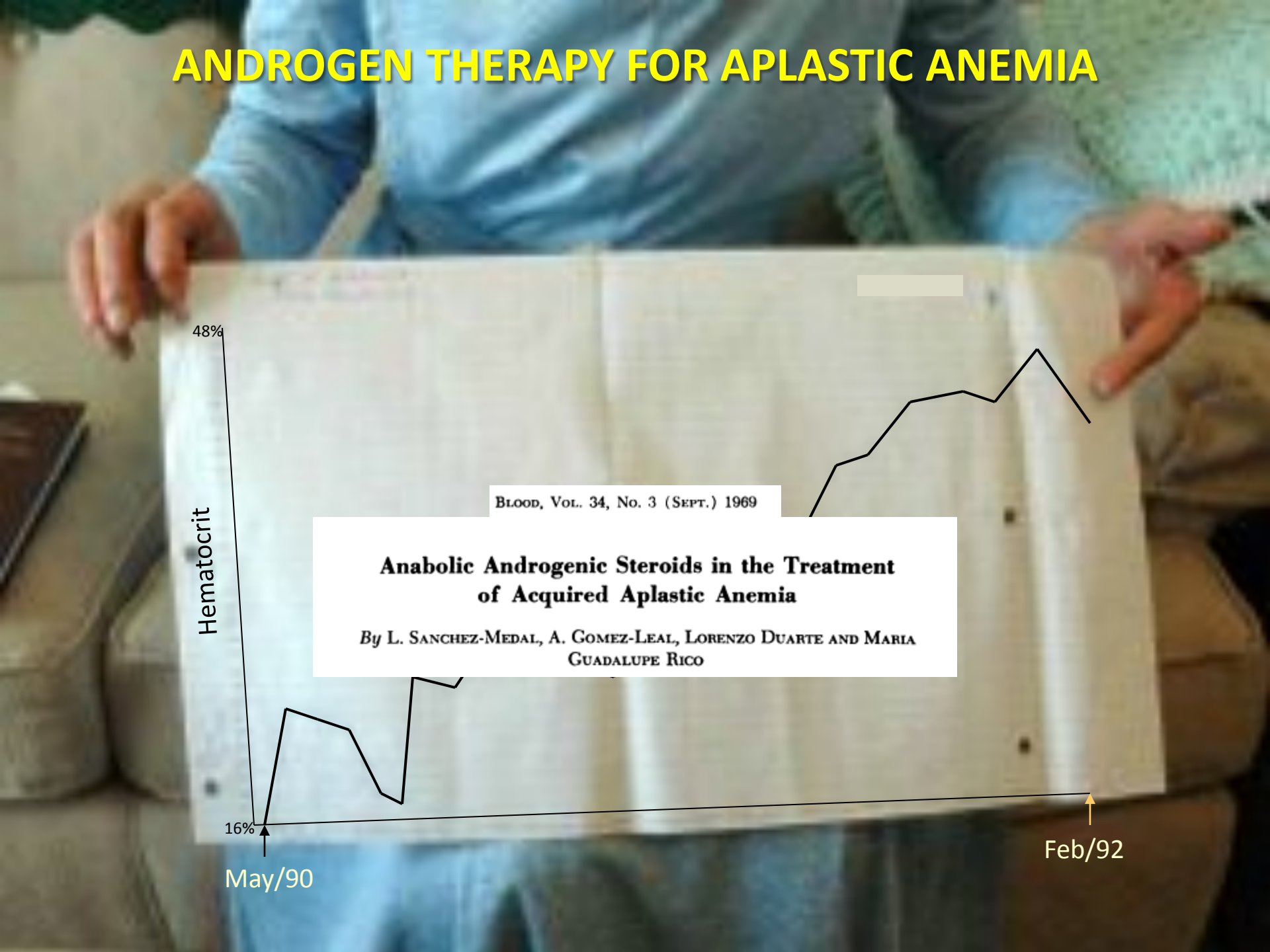
Marrow Failure

Malignant Transformation

TELOMERE EROSION AND CANCER RISK



ANDROGEN THERAPY FOR APLASTIC ANEMIA

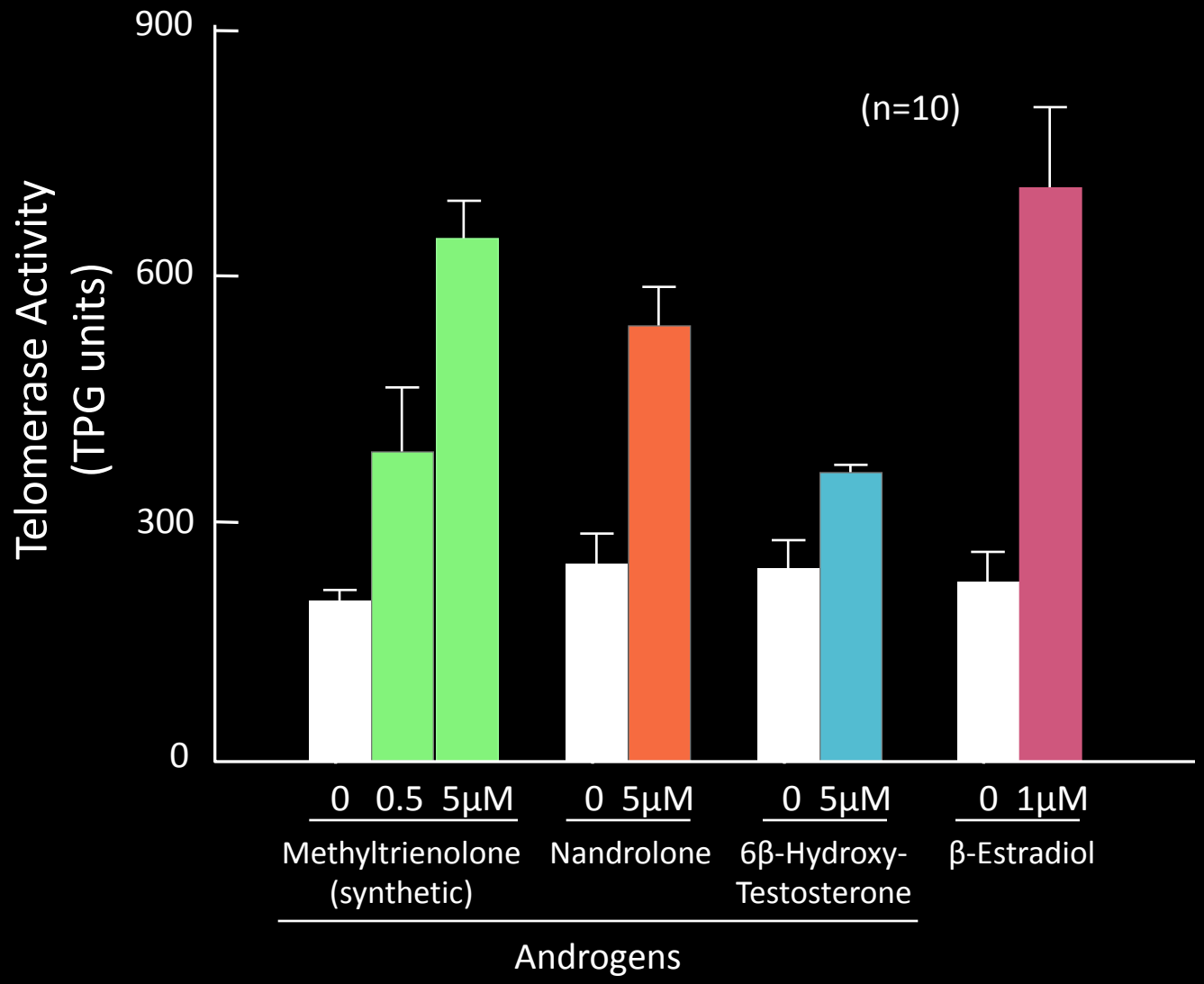


BLOOD, VOL. 34, NO. 3 (SEPT.) 1969

Anabolic Androgenic Steroids in the Treatment of Acquired Aplastic Anemia

By L. SANCHEZ-MEDAL, A. GOMEZ-LEAL, LORENZO DUARTE AND MARIA GUADALUPE RICO

SEX HORMONES INCREASE TELOMERASE ACTIVITY IN CULTURED HUMAN LYMPHOCYTES



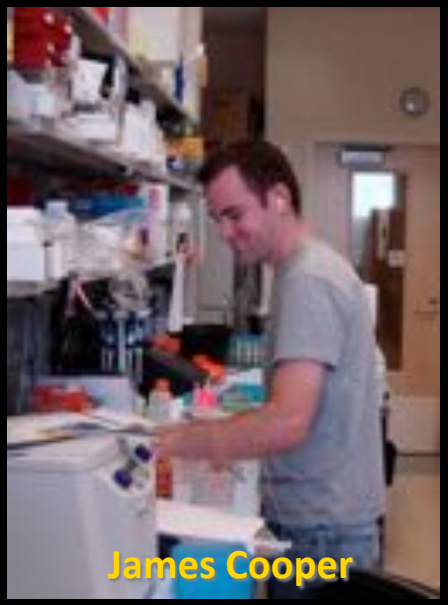
Calado *et al*, *Blood*, 2009

CONCLUSIONS IV

Clinical Implications: Treatment

- Selection of sibling donors for HSCT: mutation status
  - Telomere length measurement (silent carrier)
  - Mutation screening

- Androgens as potential therapy for aplastic anemia patients with telomerase mutations
  - Response in 60% of dyskeratosis congenita patients
  - Response in some AA patients
  - *Androgens in pulmonary fibrosis, cirrhosis?*
  - *Androgens for iatrogenic telomere shortening (Post-HSCT)?*



Genetics Group
Hematology Branch

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Sharon Savage
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NICHD:
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Courtney Prince

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Marco Zago

M.D. Anderson Cancer Center:
Elihu Estey

Emory University:
Hinh Ly

University of Arizona:
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