ΚΑΤΑΝΟΗΣΗ ΤΗΣ ΛΕΥΧΑΙΜΟΓΕΝΕΣΗΣ ΓΙΑ ΤΗΝ ΠΡΟΛΗΨΗ ΤΗΣ ΟΞΕΙΑΣ ΛΕΜΦΟΒΛΑΣΤΙΚΗ ΛΕΥΧΑΙΜΙΑΣ ΤΗΣ ΠΑΙΔΙΚΗΣ ΗΛΙΚΙΑΣ

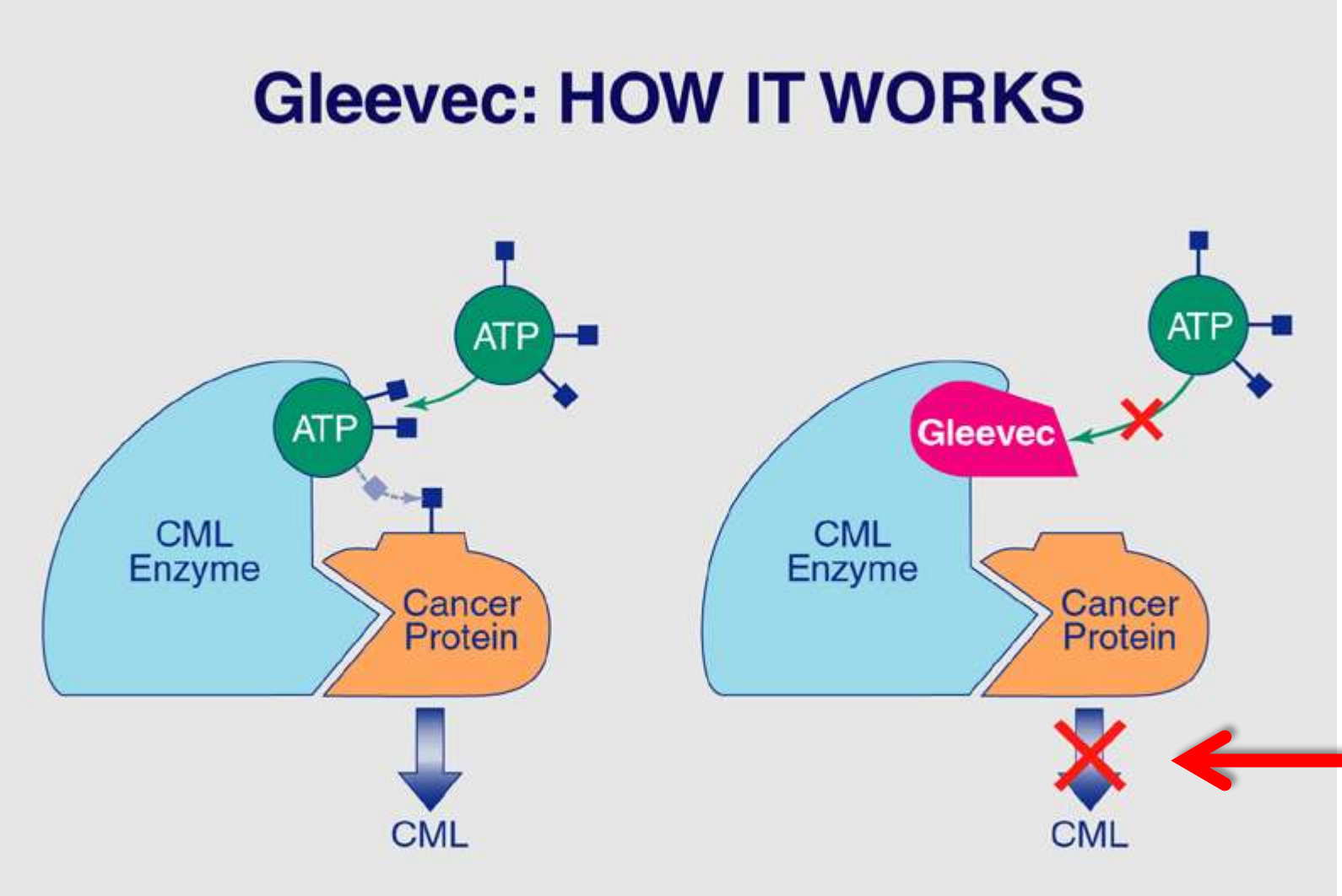
Βασίλειος Παπαδάκης MD PhD

Διευθυντής
Τμήμα Παιδιατρικής Αιματολογίας- Ογκολογίας
Ογκολογική Μονάδα Μαριάννα Β. Βαρδινογιάννη – ΕΛΠΙΔΑ
Νοσ. Παίδων «Η Αγία Σοφία»

Λευχαιμογένεση

- Η διαδικασία της ανάπτυξης της λευχαιμίας
- Πολλαπλές οι κατηγορίες των λευχαιμιών
  - Και οι υποκατηγορίες
- ΧΜΛ, ΧΛΛ, ΟΜΛ, ΟΛΛ,
- ΟΜΛ M1 - -- -- --- M7

Χρόνια Μυελογενής Λευχαιμία Philadelphia Chr. t(9;22) bcr- abl



Οξεία Μυελογενής Λευχαιμία

- FLT-3 30%
- Προγνωστικός παράγοντας
- Θεραπευτικός στόχος

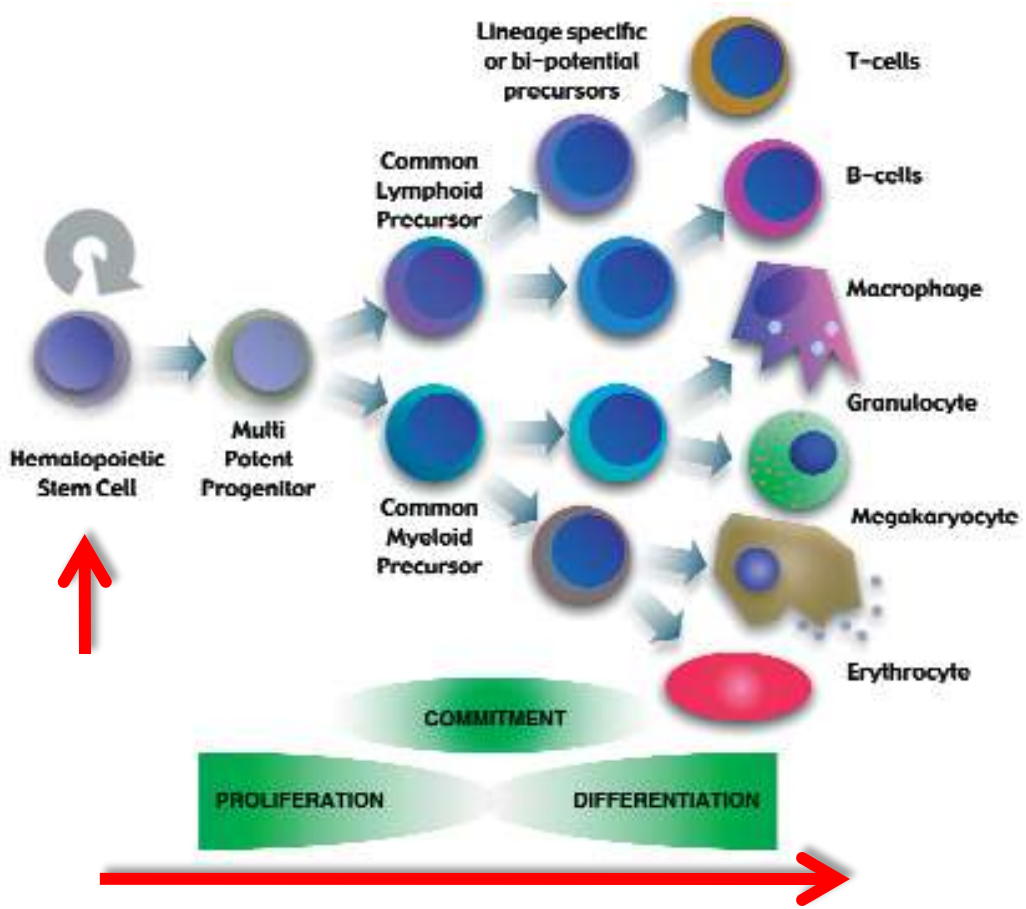
Οξεία Λεμφοβλαστική Λευχαιμία

- Μία νόσος ή περισσότερες
- Μία αιτιολογία ή περισσότερες

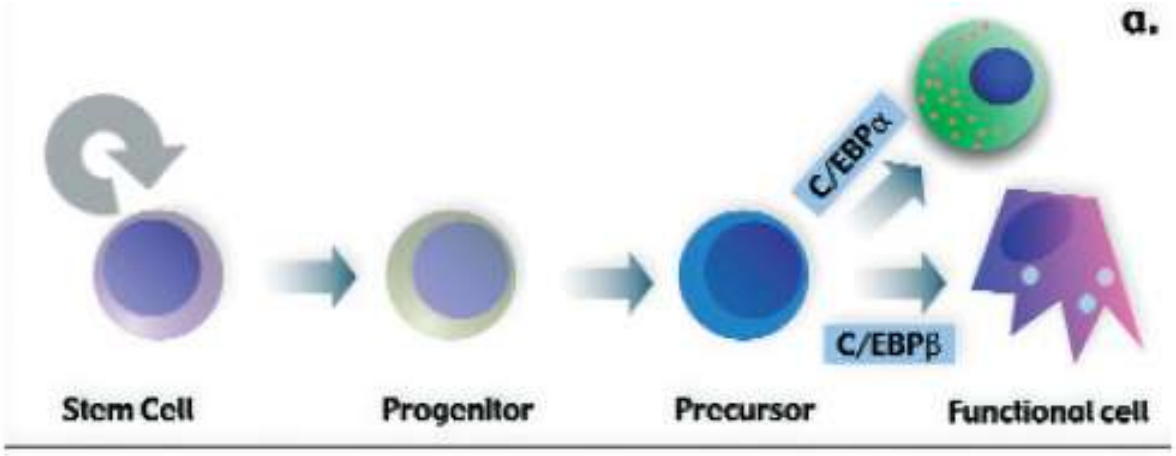
- L1 L2 μορφολογία
- B vs T- cell
- CD10+ CD10 –
- Αριθμός χρωμοσωμάτων

- Έκφραση μεταβολικών οδών
  PHARMACOGENOMICS

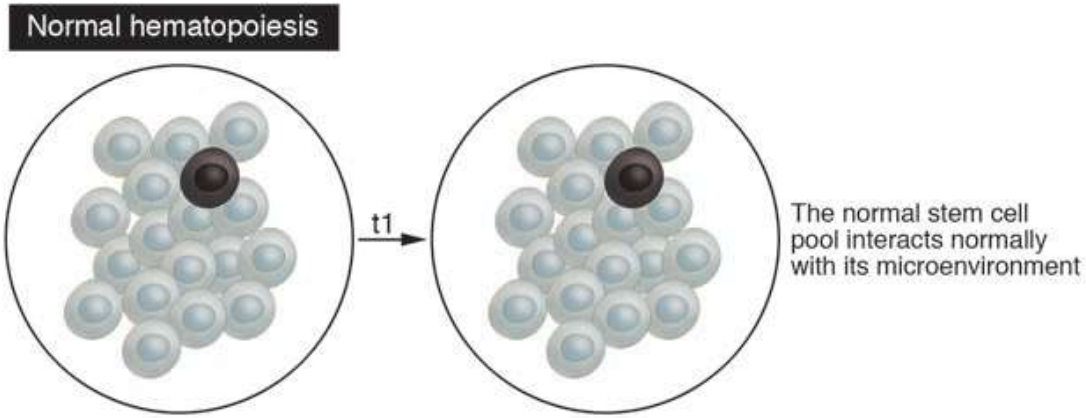
Αιμοποίηση


Lineage specific
or bi-potential
precursors
T-cells
Common
Lymphoid
Precursor
B-cells
Macrophage
Granulocyte
Hematopoietic
Stem Cell
Multi
Potent
Progenitor
Common
Myeloid
Precursor
Megakaryocyte
Erythrocyte
COMMITMENT
PROLIFERATION
DIFFERENTIATION

Λευχαιμογένεση

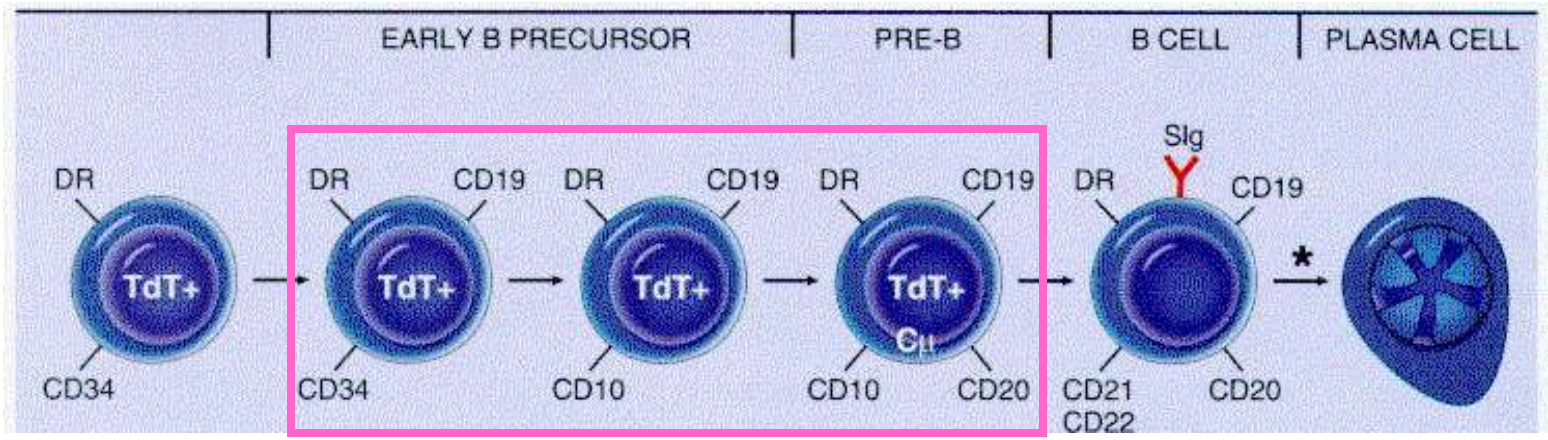


TWO HIT MODEL

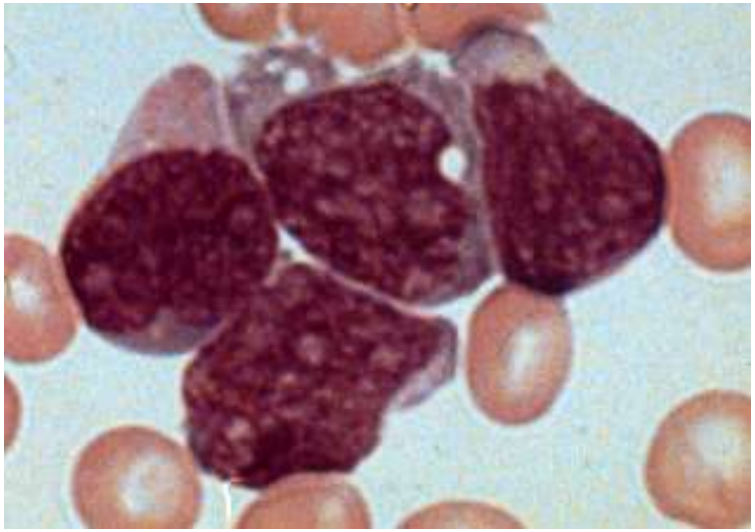


B-Lineage Lymphopoiesis

Morphology / Immunophenotyping / Molecular Studies



"Blasts"



Ποιός ο μηχανισμός ---

- ***BCR-ABL***
- ***E2A-PBX1***
- ***FLT3***
- ***HOX***
- ***MLL-AF4***
- ***MLL-ENL***
- ***NOTCH1***
- **NUP214-ABL1**
- ***TEL-AML1***
- ***TTK***

BCR-ABL: A reciprocal t(9;22) fuses the *BCR* (breakpoint cluster region) gene from chromosome 22 to the *ABL* (Abelson) gene from chromosome 9. The fusion protein is a constitutive protein kinase that alters signaling pathways that control the proliferation, survival, and self-renewal of hematopoietic stem cells.

E2A-PBX1: In the t(1;19), the N-terminal transactivation domain of E2A (a helix–loop–helix protein-coding gene on chromosome 19) fused to the C-terminal DNA-binding homeodomain of *PBX1* (pre-B-cell transforming) gene on chromosome 1. The chimeric protein interferes with hematopoietic differentiation by disrupting patterns of gene expression that are normally regulated by HOX-PBX1 complexes.

FLT3: This class 3 receptor tyrosine-kinase (fms-related tyrosine kinase 3) gene plays an important role in normal hematopoiesis. Constitutive activation of the gene contributes to the abnormal growth of leukemic cells.

HOX: Homeobox genes, master transcriptional regulators of early development, play a critical role in regulating hematopoietic stem-cell survival and proliferation.

MLL-AF4: The t(4;11) results in a chimeric protein consisting of the N-terminal portion of MLL (mixed-lineage leukemia) encoded by the gene on chromosome 11 and the C-terminal portion of AF4 (ALL1 fused gene from chromosome 4). The fusion protein disrupts the normal expression pattern of homeobox genes, causing a change in the self-renewal and growth of hematopoietic stem cells and committed progenitor cells.

MLL-ENL: The fusion of the *MLL* gene with the *ENL* (eleven nineteen leukemia) gene.

NOTCH1: This gene (Notch homologue 1, translocation-associated [Drosphila]) encodes a member of the transmembrane protein family, which plays a role in the developmental processes of a variety of tissues. Constitutive Notch signaling in hematopoietic progenitors disrupts both normal T-cell and B-cell development and leads to T-cell cancers.

NUP214-ABL1: This fusion between *NUP214* (nucleoporin of 214 kD) and *ABL1* is associated with increased *HOX* expression and contributes to the multistep pathogenesis of T-cell ALL.

TEL-AML1: The t(12;21) creates a fusion gene that includes the 5′ portion of *TEL* (translocation-ETS-leukemia) gene on chromosome 12, which encodes a nuclear phosphoprotein that is a member of the ETS family of transcription factors, and almost the entire coding region of *AML1*, another transcription-factor gene that encodes the alpha subunit of core-binding factor, a master regulator of the formation of definitive hematopoietic stem cells. The fusion protein inhibits normal *AML1*-mediated transcriptional activity, resulting in the alteration of self-renewal capacity and the differentiation capacity of hematopoietic stem cells.

TTK: The tramtrack gene encodes a protein kinase detectable in all proliferating cells and tissues; its expression is markedly reduced or absent in normal resting cells and in tissues with a low proliferative index.

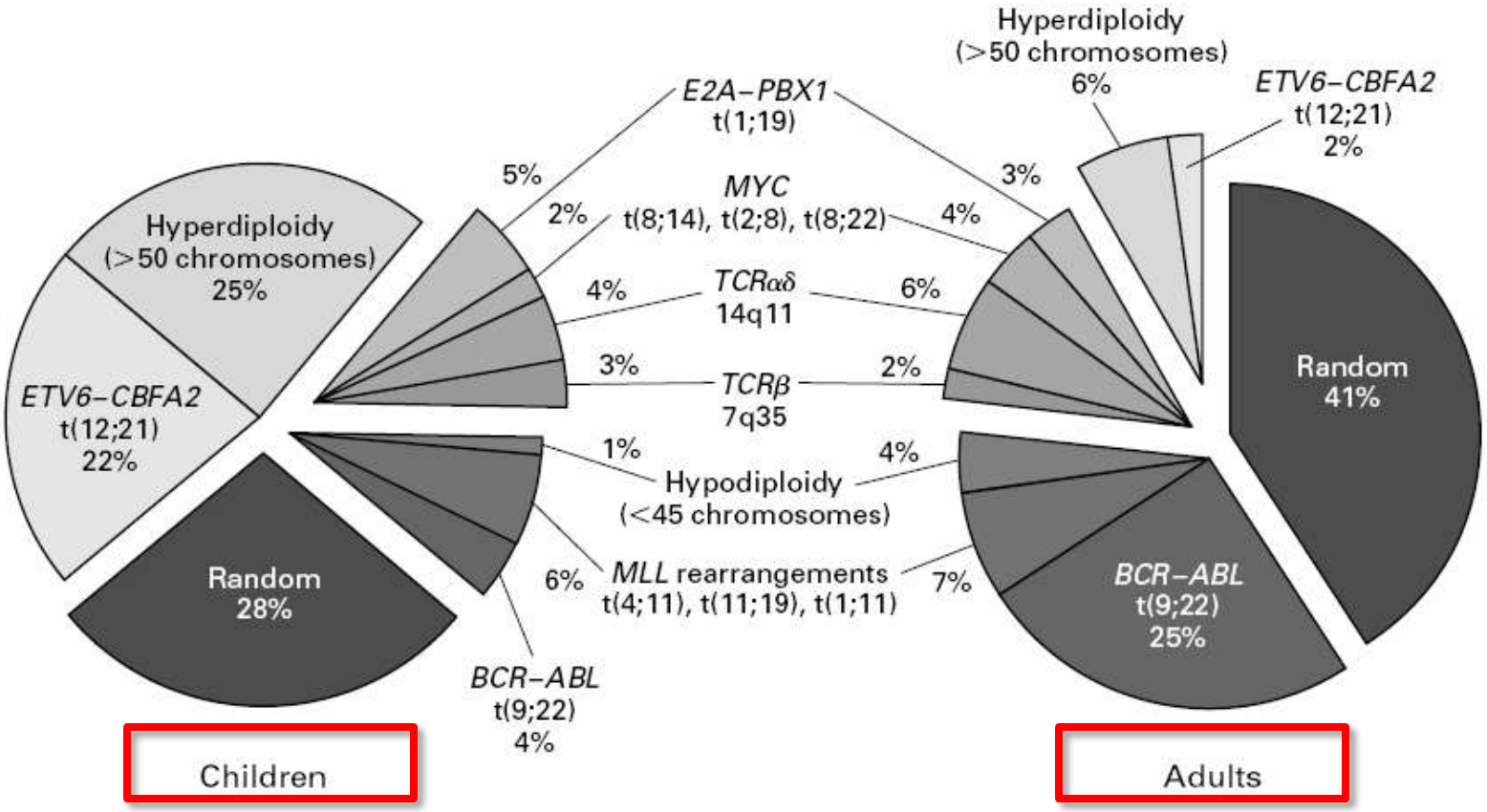
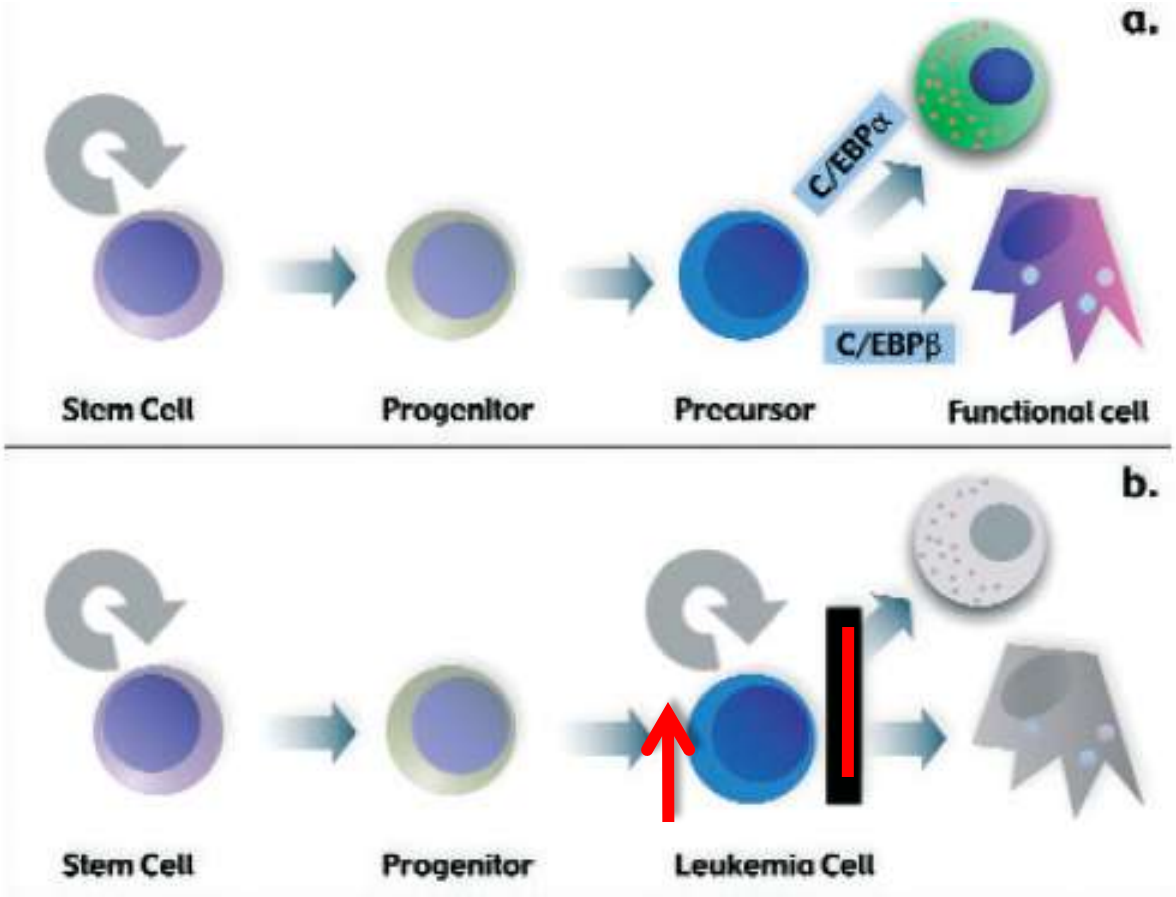


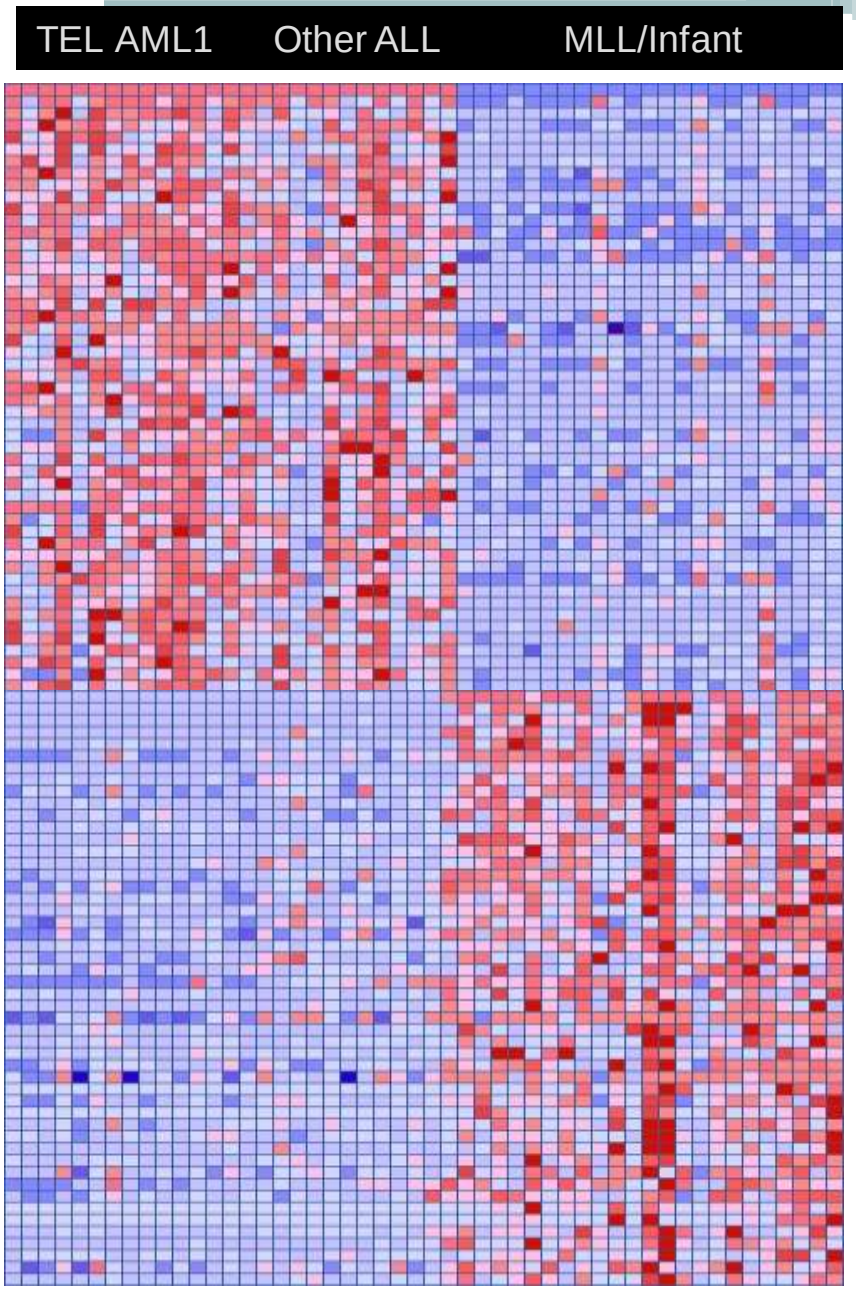
Figure 2. Estimated Frequencies of Specific Genotypes among Children and Adults with ALL.

Λευχαιμογένεση



ΔΙΑΦΟΡΕΣ ΕΚΦΡΑΣΗΣ ΓΟΝΙΔΙΩΝ ΣΤΟΥΣ ΒΛΑΣΤΕΣ ΟΛΛ

cALL vs. infant ALL

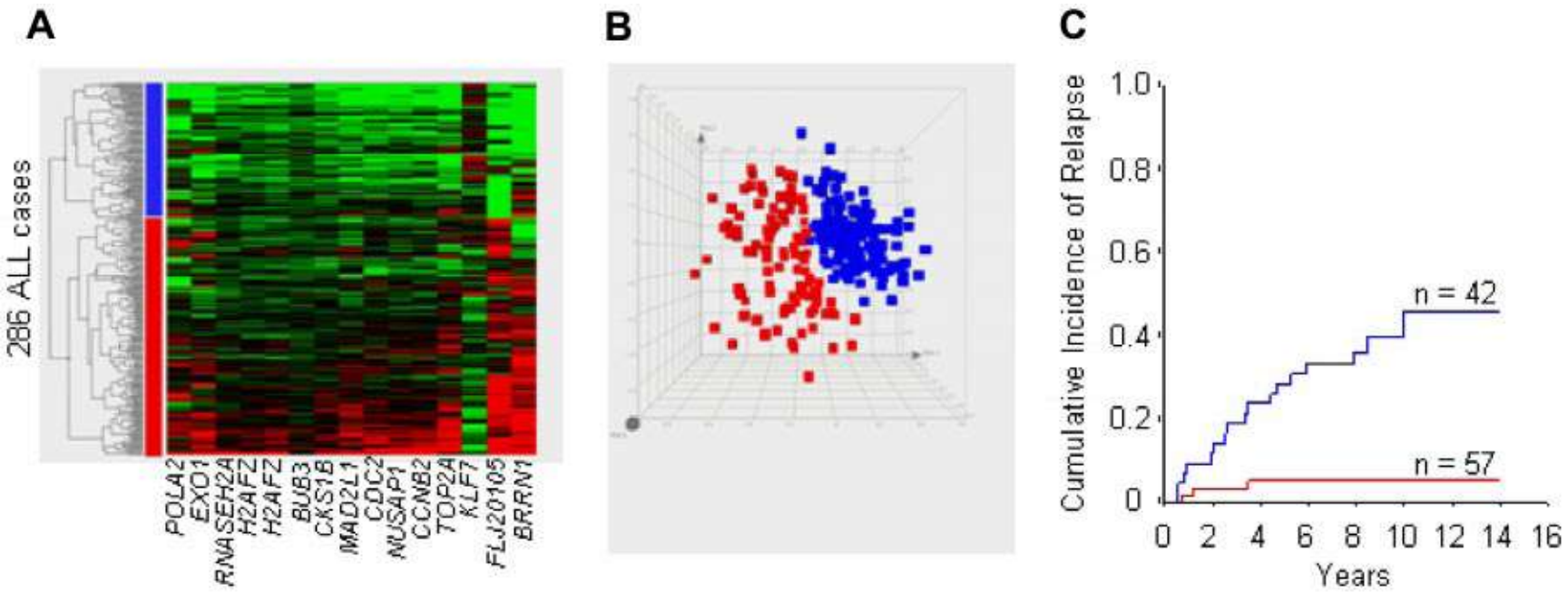


Armstrong,
Nature Genetics 2002

A set of genes that regulate cell proliferation predicts treatment outcome in childhood acute lymphoblastic leukemia

Christian Flotho,[1] Elaine Coustan-Smith,[2] Deqing Pei,[3] Cheng Cheng,[3] Guangchun Song,[1] Ching-Hon Pui,[1,2,4] James R. Downing,[1,4] and Dario Campana[1,2,4]

Departments of [1]Pathology, [2]Oncology, and [3]Biostatistics, St Jude Children's Research Hospital, Memphis, TN; [4]University of Tennessee College of Medicine, Memphis



Clustering by gene-expression profiling and principal component analysis of 286 diagnostic samples of childhood ALL in relation to risk of relapse. Signals represent the 15 probe sets (14 genes) that were associated with MRD on day 19, and independently predicted outcome. (A,B) Heat map and principal component analysis. Clusters are indicated in blue and red. (C) Cumulative incidence of relapse among the 99 patients enrolled on Total XIII belonging to each cluster (*P .001*).

FLOTHO et al BLOOD, 15 AUGUST 2007

ΑΞΙΟΠΟΙΗΣΗ

Βιολογική αξία αυτών των γονιδίων

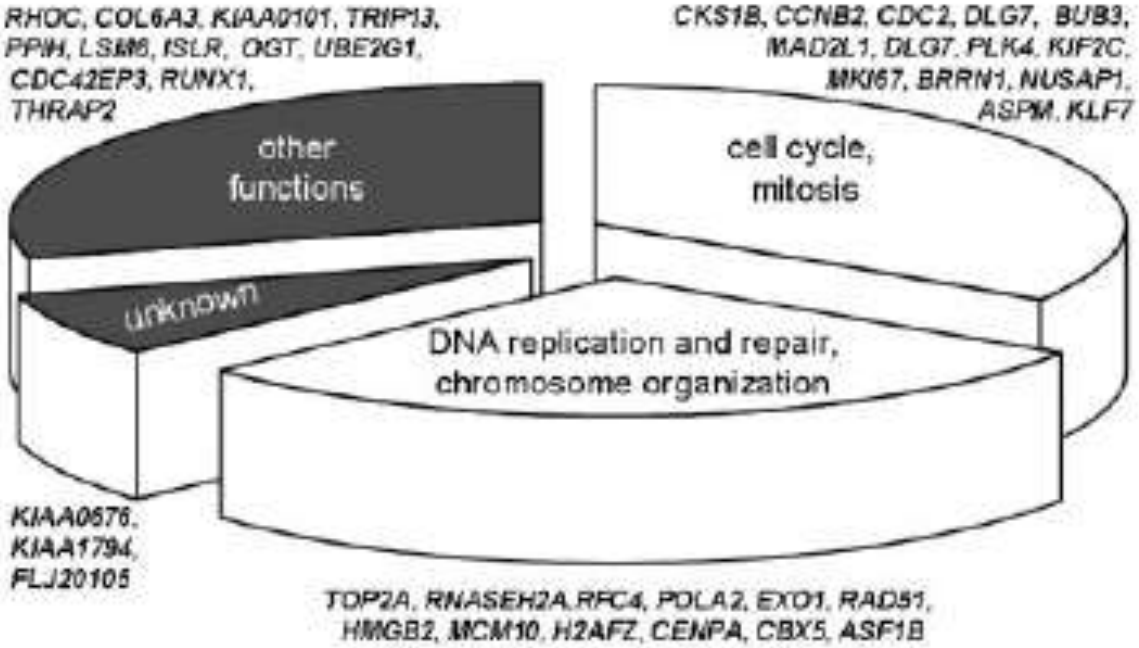


Figure 6. Biologic processes influenced by the 40 gene products associated with MRD on day 19 and with leukemic relapse

Πότε ξεκινά η λευχαιμογένεση στη παιδική ΟΛΛ ;

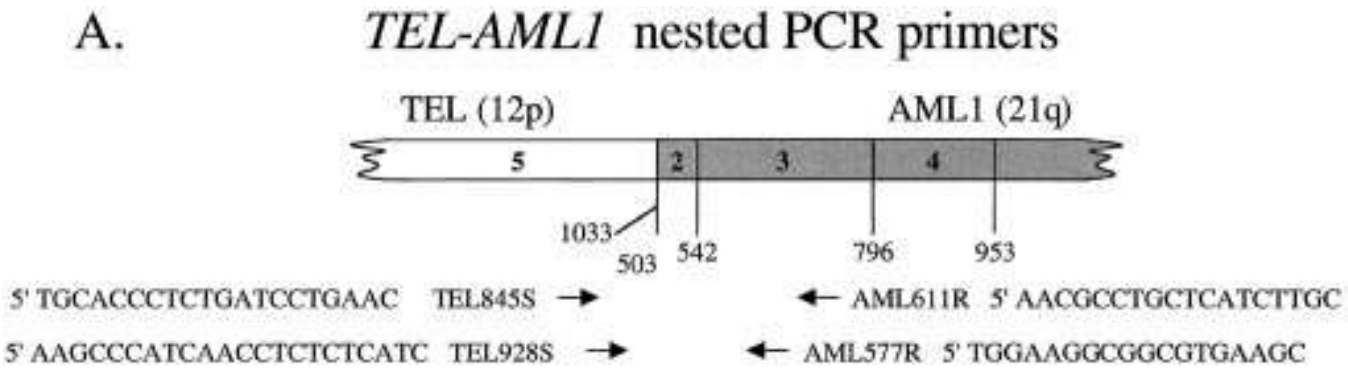
- Υπάρχουν εκ γενετής ;
- Ξεκινούν κατά τη διάρκεια της εμβρυϊκής ζωής ;
- Ή είναι μεταγενέστερο γεγονός ;

High frequency of leukemic clones in newborn screening blood samples of children with B-precursor acute lymphoblastic leukemia

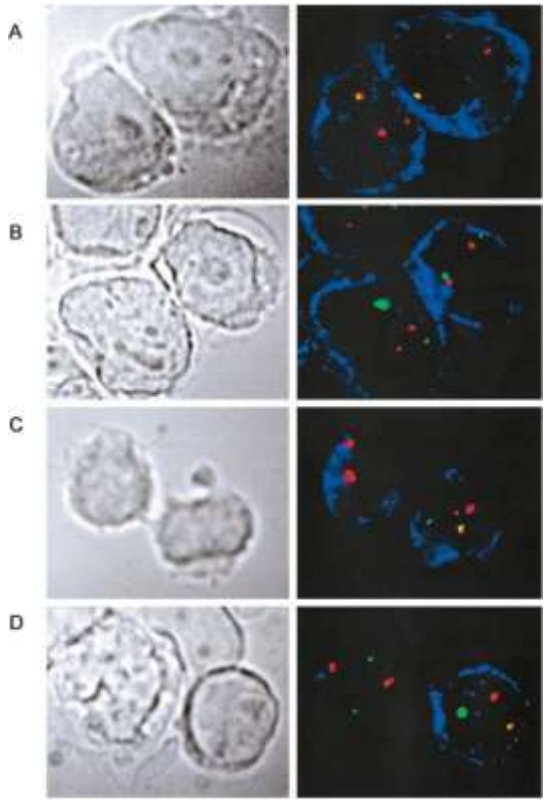
Jeffrey W. Taub, Mark A. Konrad, Yubin Ge, John M. Naber, Jackie S. Scott, Larry H. Matherly, and Yaddanapudi Ravindranath

The detection of leukemia cells on newborn genetic screening cards ("Guthrie cards") of a small group of patients and several sets of identical twins developing acute lymphoblastic leukemia (ALL) with identical phenotypic and chromosomal markers has provided evidence that childhood ALL cases may arise in utero. We conducted a retrospective study of a randomly selected group of childhood B-precursor ALL patients to determine the frequency of the presence of "leukemic" clones prenatally in ALL cases by testing newborn screening cards. The 17 ALL patients analyzed had a median age of 46 months (range, 18 months to 13 years) and had median presenting white blood cell (WBC) counts of 10 950/μL (range, 2900-70 300/μL) at diagnosis. A clonal rearrangement of the immunoglobulin heavy chain (IgH) gene was identified in diagnostic lymphoblasts and sequenced and patient-specific primers were used to amplify DNA from blood samples on the patient's newborn screening cards. Twelve of the 17 (71%) analyzed newborn cards had detectable IgH rearrangements amplified by seminested polymerase chain reaction. DNA sequencing confirmed that the IgH rearrangements detected matched the IgH sequences identified from diagnostic leukemia cells, indicating the presence of a "leukemic" clone at birth. There were no differences in age or presenting WBC counts between the cases with or without positive newborn screening cards. All 6 patients with hyperdiploid ALL had detectable "leukemic" clones on their cards. The results of our study support the notion that a high proportion of childhood B-precursor ALL cases arise in utero, although postnatal events are also important factors in leukemogenesis. (Blood. 2002;99:2992-2996)

TEL-AML1

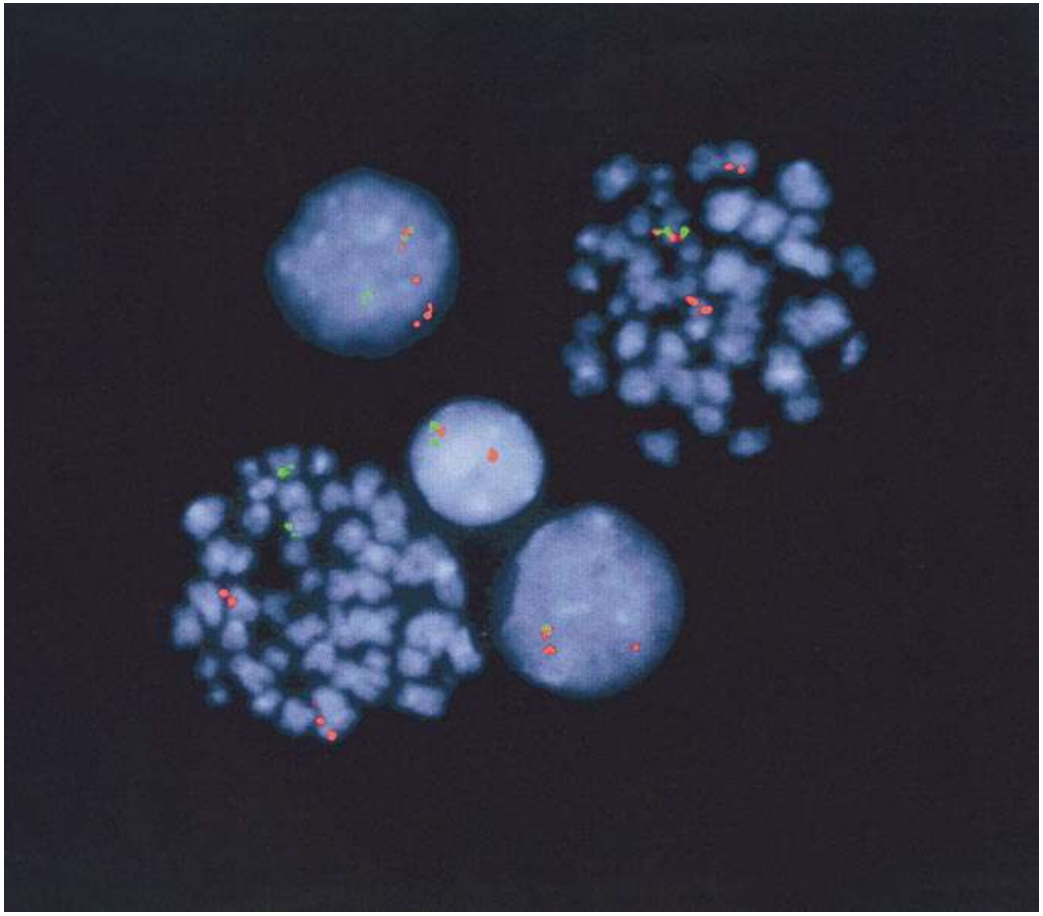

A.
TEL-AML1 nested PCR primers
TEL (12p)
AML1 (21q)
5
2
3
4
1033
503
542
796
953
5' TGCACCCTCTGATCCTGAAC TEL845S →
← AML611R 5' AACGCCTGCTCATCTTGC
5' AAGCCCATCAACCTCTCTCATC TEL928S →
← AML577R 5' TGGAAGGCGGCGTGAAGC

Γέννηση



- Ανίχνευση TEL-AML1 CD10+ κυττάρων στη γέννηση, με απώτερη ανάπτυξη TEL-AML1+/ CD10+ λευχαιμίας

Molecular tracking of leukemogenesis in a triplet pregnancy



The occurrence of childhood acute lymphoblastic leukemia (ALL) in 2 of 3 triplets provided a unique opportunity for the investigation of leukemogenesis and the natural history of ALL. The 2 leukemic triplets were monozygotic twins and shared an identical, acquired TEL-AML1 genomic fusion sequence indicative of a single-cell origin in utero in one fetus followed by dissemination of clonal progeny to the comonozygotic twin by intraplacental transfer. In accord with this interpretation, clonotypic TEL-AML1 fusion sequences could be amplified from the archived neonatal blood spots of the leukemic twins. The blood spot of the third, healthy, dizygotic triplet was also fusion gene positive in a single segment, though at age 3 years, his blood was found negative by sensitive polymerase chain reaction (PCR) screening for the genomic sequence and by reverse transcription–PCR. Leukemic cells in both twins had, in addition to TEL-AML1 fusion, a deletion of the normal, nonrearranged TEL allele. However, this genetic change was found by fluorescence in situ hybridization to be subclonal in both twins. Furthermore, mapping of the genomic boundaries of TEL deletions using microsatellite markers indicated that they were individually distinct in the twins and therefore must have arisen as independent and secondary events, probably after birth. These data support a multihit temporal model for the pathogenesis of the common form of childhood leukemia.
(Blood. 2001;98: 478-482)

Molecular tracking of leukemogenesis in a triplet pregnancy

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- The 2 leukemic triplets were monozygotic twins and shared an identical, acquired TEL-AML1 genomic fusion sequence indicative of a single-cell origin in utero in one fetus followed by dissemination of clonal progeny to the comonozygotic twin by intraplacental transfer.
- In accord with this interpretation, clonotypic TEL-AML1 fusion sequences could be amplified from the archived neonatal blood spots of the leukemic twins.
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- These data support a multihit temporal model for the pathogenesis of the common form of childhood leukemia. (Blood. 2001;98: 478-482)

Etiology of common childhood acute lymphoblastic leukemia: the adrenal hypothesis

Schmiegelow K, Vestergaard T, Nielsen SM, Hjalgrim H

- Περισσότερες λοιμώξεις κατά τα πρώτα χρόνια της ζωής, σχετίζονται με μικρότερη πιθανότητα εμφάνισης ΟΛΛ.
- Γιατί ;
- Με τις λοιμώξεις επάγονται ποιοτικές και ποσοτικές αλλαγές στον άξονα υποθαλάμου – υπόφυσης – επινεφριδίων με αποτέλεσμα της αύξηση των επιπέδων κορτιζόλης στο αίμα.
- Η αυξημένη κορτιζόλη μπορεί άμεσα να εξαλείψει τα προλευχαιμικά και λευχαιμικά κύτταρα που πιθανά να προϋπάρχουν
- **Η λοίμωξη ως ενδογενής θεραπεία της προ-λευχαιμικής κατάστασης - επαγωγή αυξημένων επιπέδων στεροειδών**

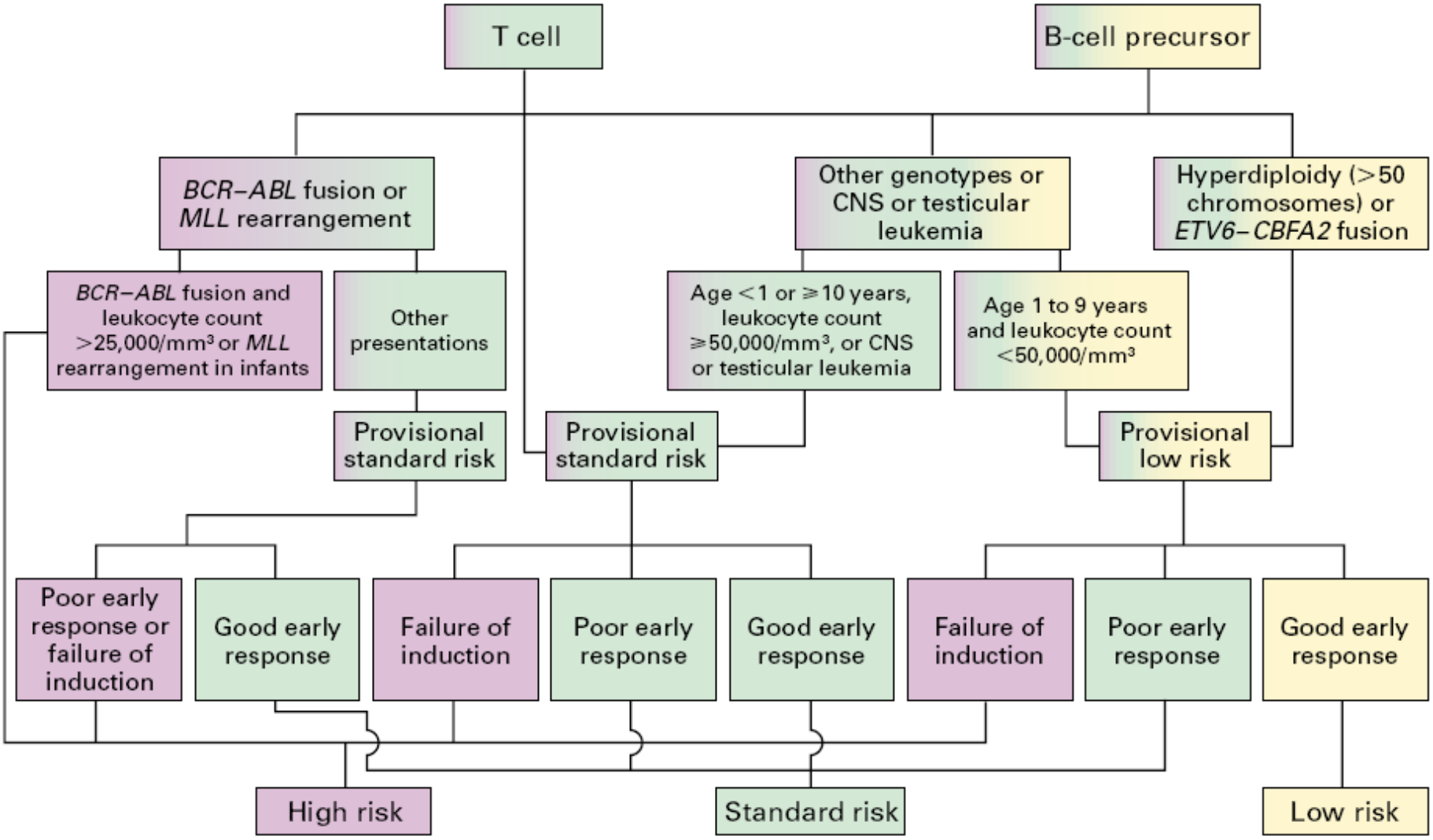
Leukemia. 2008 Dec

Λευχαιμογένεση

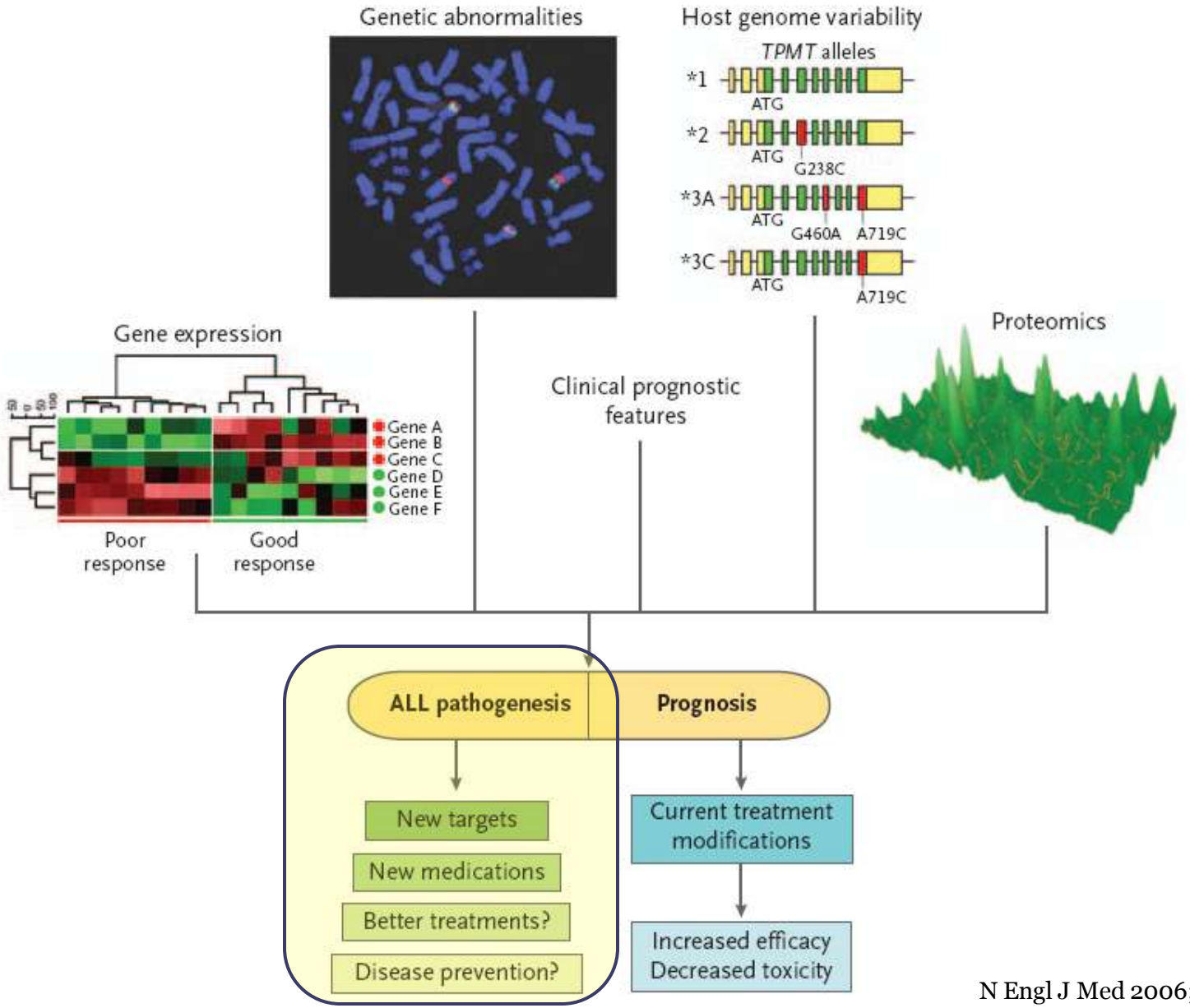
- Η ΟΛΛ της παιδικής ηλικίας δεν είναι ένα ομοιογενές νόσημα
- Gene expression profiling 5 υποτύποι
- Συνδυασμός
  - Γενετικού υποστρώματος
  - Αλλαγών στο γονιδίωμα
  - Λοιμώξεων
  - Επιπρόσθετων βλαβών στο γενετικό υλικό
  - Έκφραση/ συνέκφραση των ανωτέρω παραγόντων
  - Ιδιοσυγκρατικοί παράγοντες του ατόμου
  - .....
- Αιτιολογία
- Επιφαινόμενα

Λευχαιμογένεση

- Κύτταρα με γενετικές βλάβες, όπως BCR-ABL-1, TEL-AML1, μπορεί να ανιχνεύονται στην γέννηση;
- Οι βλάβες αυτές δεν υποδηλώνουν απαραίτητα τη σύγχρονη παρουσία λευχαιμίας
- ΟΛΛ μπορεί να διαγνωσθεί σε απώτερο χρόνο, με συνύπαρξη της γενετικής βλάβης που ανιχνεύθηκε κατά την γέννηση
- Κατά τη κλινική διάγνωση της ΟΛΛ ανιχνεύονται και πρόσθετες γενετικές βλάβες.
- Συνεπώς, η εκδήλωση ΟΛΛ σχετίζεται με αρχικές και πρόσθετες, σε δεύτερο χρόνο γενετικές μεταβολές, οι οποίες μπορούν να επάγονται από περιβαλλοντολογικούς και επιγενετικούς παράγοντες.

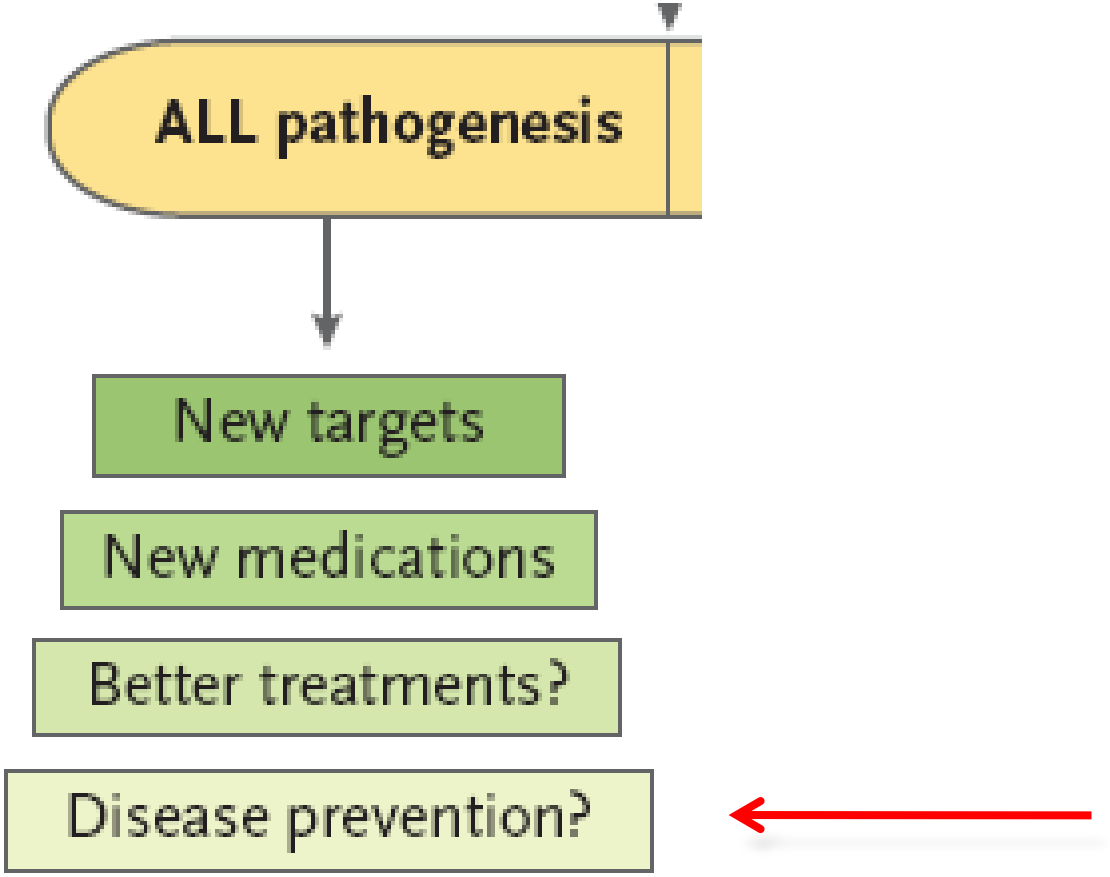


Pui, Evans N Engl J Med 1998



N Engl J Med 2006;354:166-78

Κατανόηση της παθογένειας, των προγνωστικών παραγόντων, των χαρακτηριστικών γενετικών αλλαγών και βιοχημικών οδών



LYMPHOID NEOPLASIA

STAT3 mediates oncogenic addiction to TEL-AML1 in t(12;21) acute lymphoblastic leukemia

Maurizio Mangolini,[1] Jasper de Boer,[1] Vanessa Walf-Vorderwülbecke,[1] Rob Pieters,[2] Monique L. den Boer,[2] and Owen Williams[1]

Key Points

- STAT3 activity is necessary for TEL-AML1 leukemia maintenance.
- TEL-AML1 induces STAT3 activation via RAC1 and leading to induction of MYC expression.

Blood. 2013;122(4):542-549

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Discussion

In this study, we describe a new signaling pathway operating in t(12;21) leukemia, actively regulated by TEL-AML1 and for the first time susceptible to pharmacological inhibition in primary leukemia cells. In this pathway, TEL-AML1 activates RAC1, in turn, that induces STAT3 activation. STAT3 activation is necessary for the survival, proliferation, and self-renewal of TEL-AML1$^+$ leukemia through transcriptional induction of *MYC* expression (Figure 7).

Key Points

- STAT3 activity is necessary for TEL-AML1 leukemia maintenance.
- TEL-AML1 induces STAT3 activation via RAC1 and leading to induction of MYC expression.

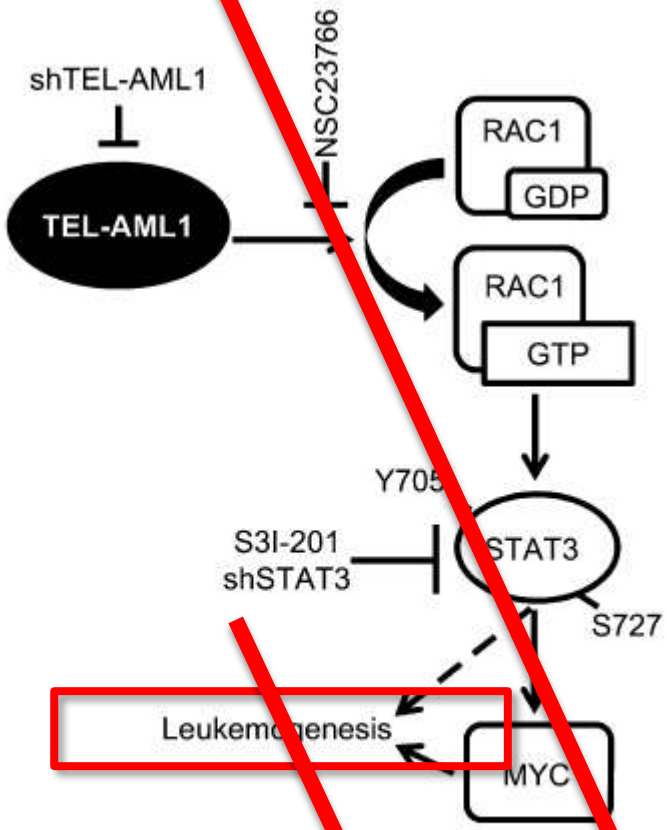

Figure 7. Model of TEL-AML1–induced leukemogenesis. TEL-AML1 induces RAC1 activation that, in turn, promotes STAT3 phosphorylation and consequently the induction of MYC transcription. Active STAT3 is necessary for the survival, proliferation, and self-renewal of TEL-AML1expressing ALL cells.

Blood. 2013;122(4):542-549

Ευχαριστώ πολύ …