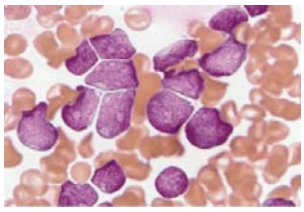
AKUTT LEUKEM HOS BARN



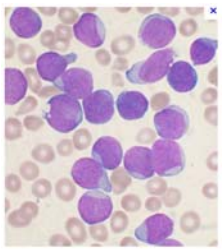
Bendik Lund

Immunologi og immunologiske metoder

Trondheim, 28.nov 2018

Kasuistikk

- 3 år gammel jente
- Svingende feber i 2-3 uker
- Smerter i beina
- Enkelte store blåmerker
- Bleik, god alm tilstand
- Forstørret lever og milt, glandelsvulst
- Hematologi:
  - Hb **6.5** g/dL
  - Trombocytter **45** x 10^9/L
  - Leukocytter **22** x 10^9/L
  - Granulocytter **0.7** x 10^9/L
  - Ferritin **440** µg/L
- **PANCYTOPENI, leukocytose**



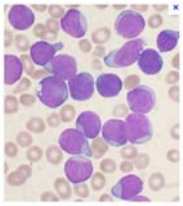
AKUTT LYMFATISK LEUKEMI – ALL

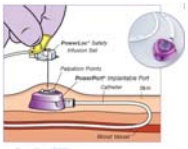
AKUTT MYELOGEN LEUKEMI – AML

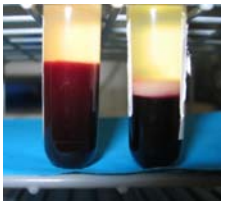
Akutt leukemi hos barn

- Ukjent årsak
- **Modningsstopp** i den myeloide eller lymfoide cellerekke
- Forandringer i gener og kromosomer, enkelte med prognostisk betydning

Leukemi hos barn



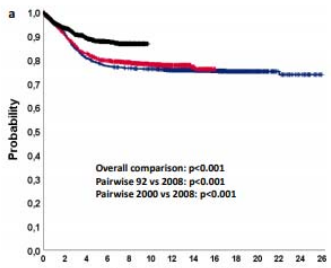




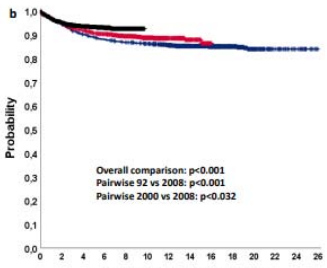
Akutt lymfatisk leukemi – NOPHO 2018

Treatment-results – Survival analyses

Figure 4. NOPHO ALL-92, NOPHO ALL-2000, NOPHO ALL-2008, Non-B cell ALL 1-<15 years at diagnosis. (a) EFS, (b) OS, (c) cum inc of relapse, and (d) DCR1



Cohort	Total n	Events	no Event	pEFS (5yr)	pEFS (at FU)
92	1561	386	1175	0.79	0.74
2000	1056	231	825	0.80	0.76
2008	1747	175	1572	0.88	0.87



Cohort	Total n	Deaths	Alive	pOS (5yr)	pOS (at FU)
92	1561	235	1326	0.89	0.84
2000	1056	119	937	0.91	0.88
2008	1747	107	1640	0.93	0.92

Akutt myelogen leukemi – NOPHO 2018

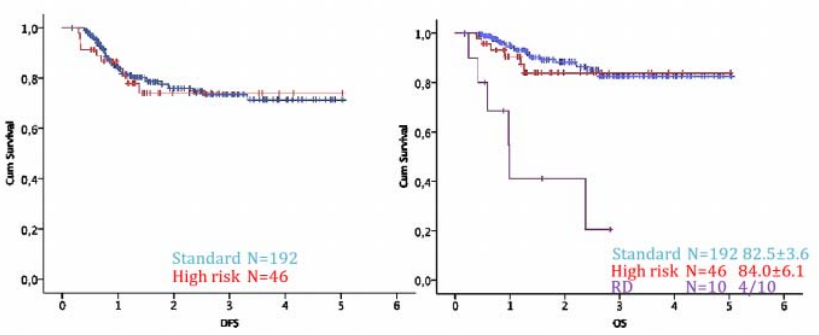
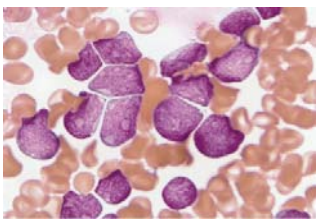


Figure 5. Disease-free survival and overall survival at three years is almost equal in both risk groups. Estimated survival is shown also for patients with resistant disease (RD). Blue curve - standard risk, red - high risk, violet - resistant disease.

Leukemi hos barn

- Utgjør 1/3 av barnekrefttilfellene
- **Ca 40 nye/år <15 år i Norge**
- ALL: 85%
- AML: 15%
- KML: <5% (Ph+)
- Spedbarn: 17%
- 2-3 års alder: 40-50%

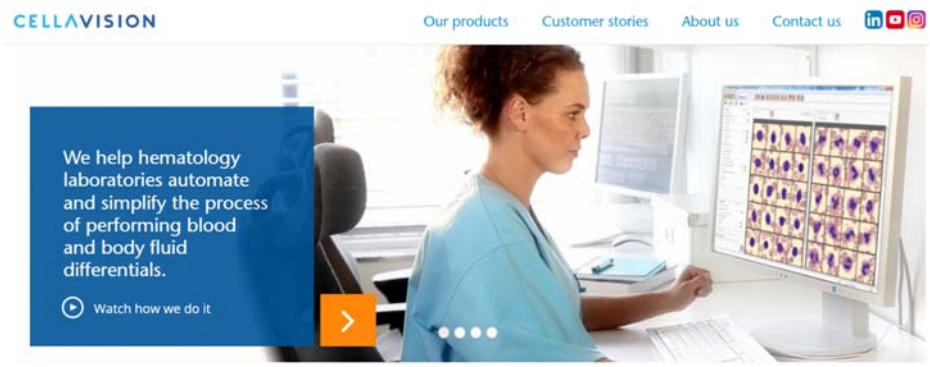


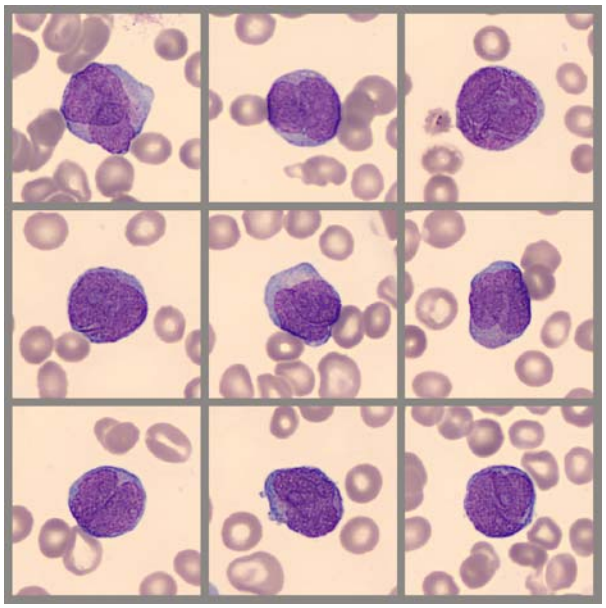
Akutte leukemier

- **Stille diagnosen hurtig, men nøyaktig**
- **Få kontroll over kliniske problemer**
  - metabolske forstyrrelser
  - blødninger
  - infeksjoner
- **Behandling**
- **Langtidsoppfølging**

Mistanke eller nyoppdaget leukemi

- Blodutstryk: **blaster?**





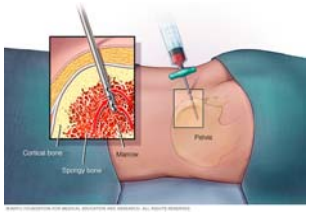
Leukemi-utredning

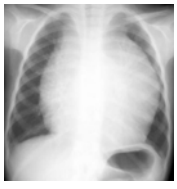
Klinikk:

- symptomer og funn

Utredning:

- Mikroskopi:
  - perifert blodutstryk; blaster?
  - Beinmarg: >25% blaster?
- Beinmarg (perifert blod):
  - FLOWCYTOMETRI (FCM)
  - CYTOGENETIKK (karyotyping/FISH)
  - MOL.PAT. (PCR)
- Spinalvæske:
  - Celletall, Cytospin, (FCM)
- Rtg. Thorax/UL-abdomen





Karakterisering av leukemier

- **Morfologisk**
- **Immunfenotypisk**
- **Cytogenetisk**
- **Molekylærbiologisk**

FAB-kriteriene (morfologi/immun)

Akutt myelogen leukemi

- M0 Udifferensiert leukemi
- M1 Uten modningstegn
- M2 Med modningstegn
- **M3 Promyelocyttleukemi(APL)**
- M4 Myelomonocyttleukemi
- M5 Monoblastleukemi
- M6 Erytroleukemi
- M7 Megacaryoblastleukemi

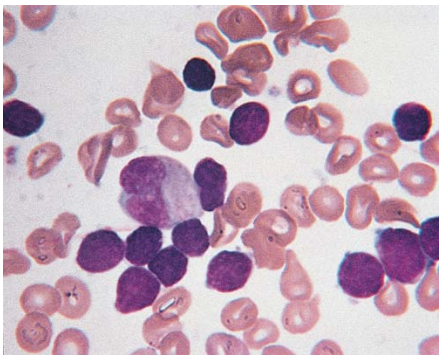
Akutt lymfatisk leukemi

- L1 Cytoplasmafattige, små blaster
- L2 Mer heterogent m.h.t. cytoplasmarikdom og størrelse. Tydeligere nukleoler enn L1
- L3 B-celleblaster med basofilt, vakuolisert cytoplasma

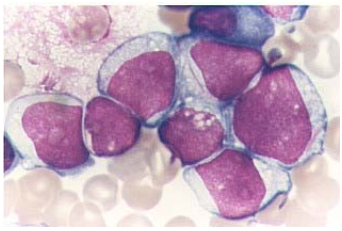
ALL : morfologi

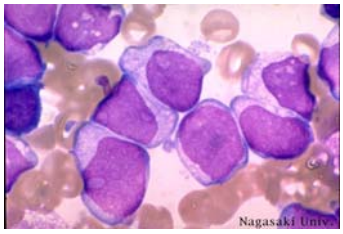
L 1

- små blaster med lite cytoplasma
- runde kjerner (eller "cleft") med 0-1 nukleol

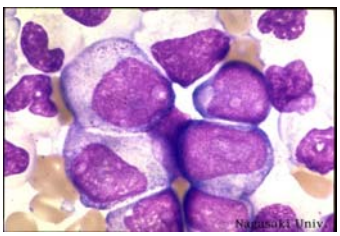


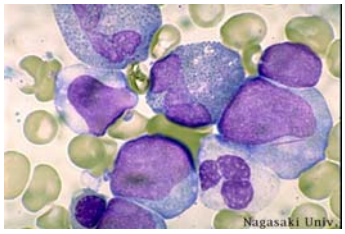
M1





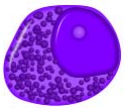
M2

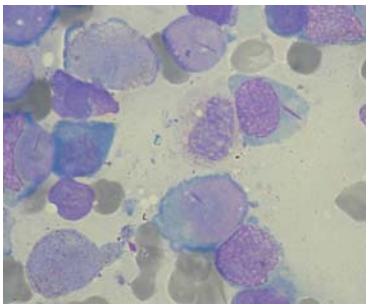




AML M3: Akutt Promyelocytt Leukemi

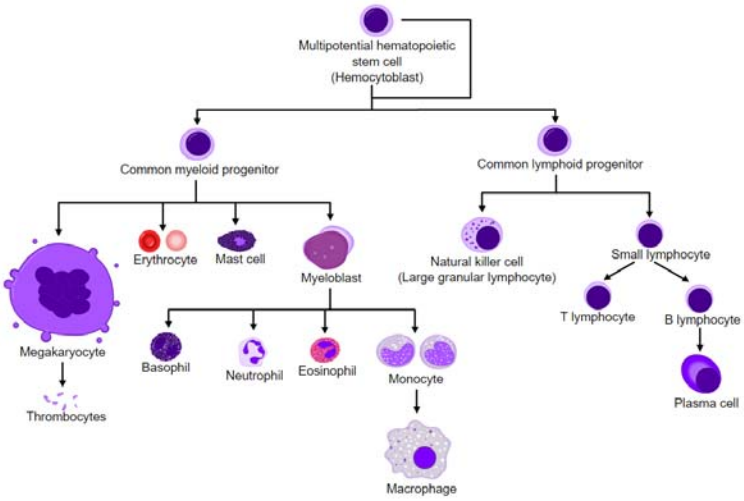
- APL
- Egen AML variant
- Morfologi:
  - Auer-staver (M2/M3)
- Translokasjon:
  - *RARA*
  (retinoic acid receptor)
- Egen protokoll
- Behandles med arsenikk og A-vitamin (ATRA)





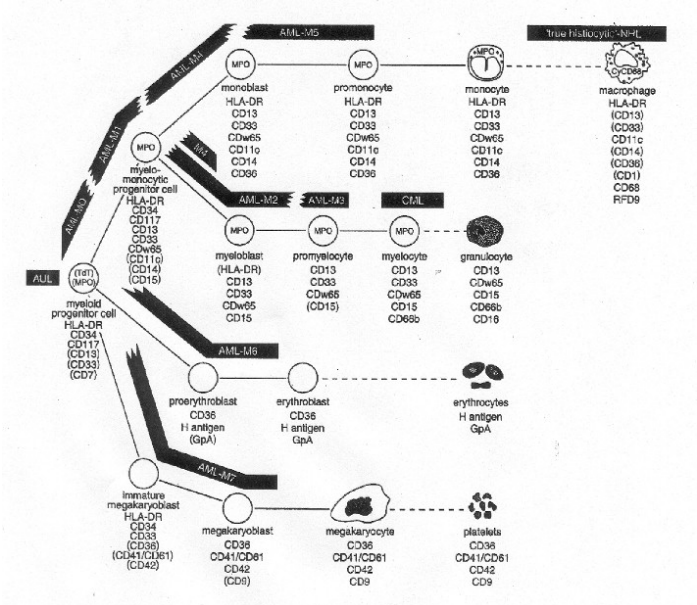
Immunfenotyping av leukemier

- Leukemiceller i forskjellige **modningsstadium** uttrykker forskjellige cellemembranantigener eller cytoplasmatiske antigener.
- Modningsstadiet påvises ved bruk av forskjellige **monoklonale antistoffer.**
- **Immunfenotypen** til leukemicellene bestemmes av mønsteret av **CD-antistoffene** (CD= clusters of differentiation)



Fra Wikipedia

Akutt leukemi: Immunfenotyping



Immunological classification of ALL

Subtype	Profile of antigen expression	Frequency (%)
Pro B ALL	$CD19^{+/-}$ $CD22^{-}$ $CD79a^{+}$ $CD10^{-}$ $CD7^{-}$ $cCD3^{-}$ $clg\mu^{-}$ slg^{-}	5-10
Early pre-B	$CD19^{+}$ $CD22^{+}$ CD 79a^{+} $CD10^{+}$ $CD7^{-}$ $cCD3^{-}$ $clg\mu^{-}$ slg^{-}	55-65
Pre-B	$CD19^{+}$ $CD22^{+}$ CD 79a^{+} $CD10^{+/-}$ $CD7^{-}$ $cCD3^{-}$ $clg\mu^{+}$ slg^{-}	20-25
Transitional	$CD19^{+}$ $CD22^{+}$ CD 79a^{+} $CD10^{-}$ $CD7^{-}$ $cCD3^{-}$ $clg\mu^{+}$ $slg\mu^{+}$ $slg\kappa^{-}$ $slg\lambda^{+}$	2-3
B cell	$CD19^{+}$ $CD22^{+}$ $CD79a^{+}$ $CD10^{+/-}$ $CD7^{-}$ $cCD3^{-}$ $clg\mu^{+}slg\mu^{+}$ $slg\kappa^{-}$ or $slg\lambda^{+}$	2-3
T cell	$CD19^{-}$ $CD22^{-}$ $CD79a^{-}$ $CD10^{+/-}$ $CD7^{+}$ $cCD3^{+}$ $clg\mu^{-}$ slg^{-}	13-15

Cytogenetikk ved leukemi

Abnorm karyotype kan påvises ved ALL hos 70-95 %

Numeriske forandringer

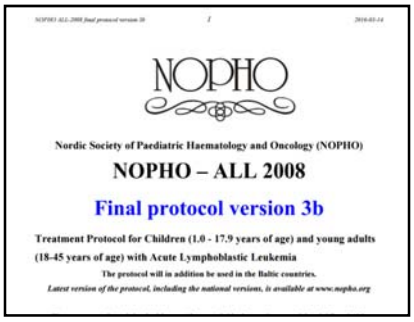
- **Hyperdiploiditet (>46 krom):** god prognose
- **Hypodiploiditet (<45 krom)**: dårlig prognose, HR-behandling

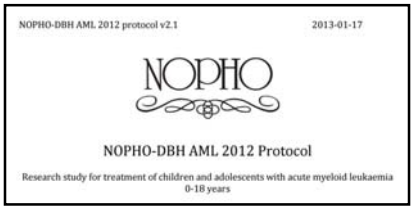
Strukturelle forandringer

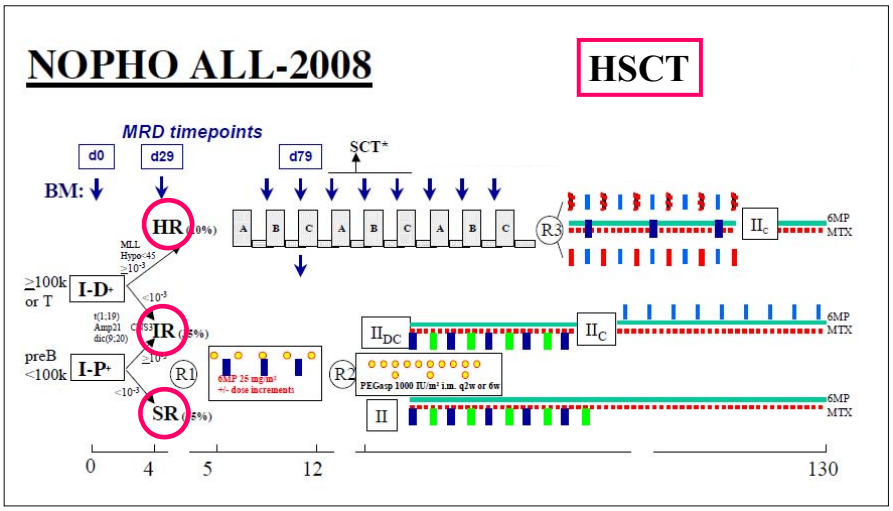
- t(8;14) ved moden B-ALL
- t(1;19)
- ic21amp
- **t(9;22)** (Philadelphia kromosom positiv ALL): dårligere prognose
- ***MLL*-rearrangering** (11q23). Ofte hos spedbarn. Dårligere progn

Protokoller

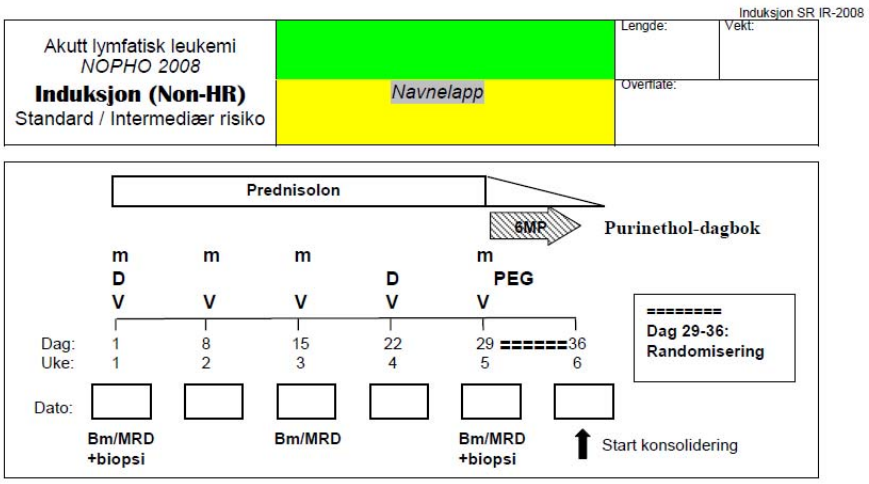
- **NOPHO ALL-2008** (1-18 (45) år)
  - 2,5 år med cellegift
  - Evt HSCT
- **NOPHO-DBH AML 2012** (0-18 år)
  - 4 eller 5 cellegiftkurer
  - ca ½ år







Ref: NOPHO Web-site/ALL group; Toft et al., 2013



Induksjonsbehandling

- Kontroll kliniske problemer
  - **Tumor lyse? Nyresvikt? Infeksjoner? Transfusjoner?**
- Redusere leukemicelletallet for å oppnå "komplett remisjon" (CR)
- (fra 10^{12} celler til 10^{9} celler)
- > 95 % oppnår CR
- Svikt i induksjonsfasen
  - refraktær sykdom
  - dødsfall av komplikasjoner

Prognostiske faktorer ved ALL

- Leukocytt-tall ved diagnosetidspunktet (>100)
- CNS-leukemi
- Testis –leukemi
- Immunfenotype (T-ALL)
- Cytogenetiske forandringer
  - MLL
  - Hypodiploidi
- Respons på behandlingen

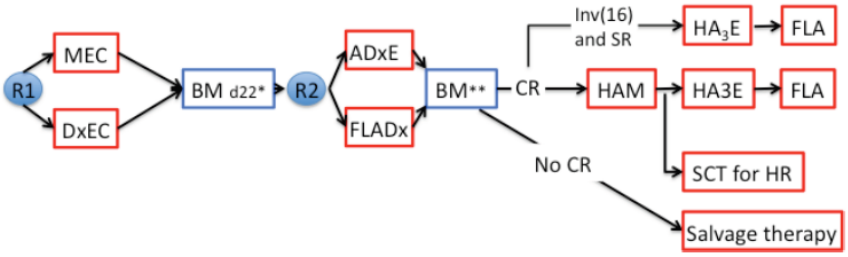
Respons på behandlingen:

- **Morfologi**
  - M1 (<5% blaster)
  - M2 (5-25% blaster)
  - M3 (>25% blaster)

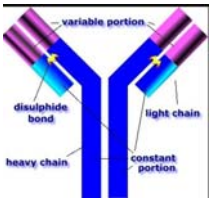
- **MRD-respons**
  - Flowcytometri
  - PCR-basert
  - $<10^{-3}$ (=<0,1%) ?

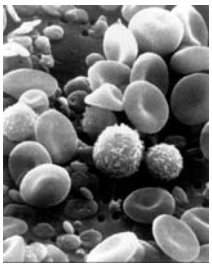
NOPHO-DBH AML 2012 Protokolloversikt

3. Protocol outline



Immunterapi ved barnekreft





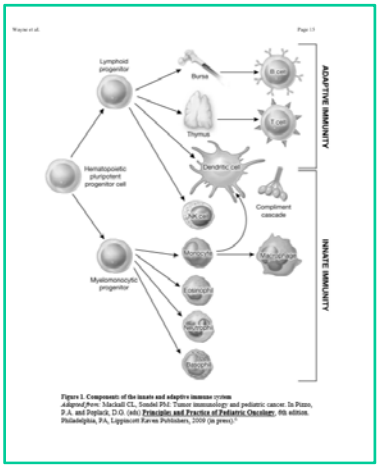
From 80 to 100% of high quality survival

- Standard terapi er toksisk overfor friskt vev
- Kreftceller utvikler resistens mot kjemoterapi
- **Residiv er en hovedårsak til død**

Immunsystemet

To deler

- **Innate –** uspesifikt, medfødt
  - Fagocyterende celler (granulocytter, NK-celler)
- **Adaptive** – tilpasser seg, «skoleres», varig immunitet
  - **Humoral:** B-lymfocytter, antistoffer
  - **Cellulær:** T-lymfocytter

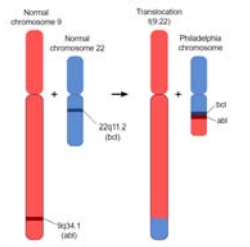


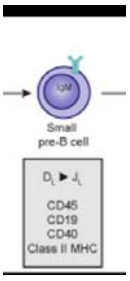
Immunterapi mot cancer

- **Humoral immunitet**
  - Monoklonale antistoffer
- **Cellemediert**
  - BM-transplantasjon
    - «Graft vs leukemi effekt»
  - Kreftvaksiner
  - T-celle terapi

Cancerassosierte antigener er «target» for immunterapi

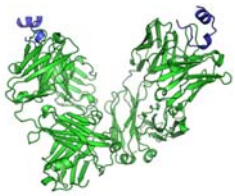
- **Translokasjons proteiner**
  - **Ph+ ALL (t(9;22)); BCR-ABL;**
    - **Glivec, immatinib (Bcr-Abl tyrosinkinasehemmer)**
- **Cellelinje-spesifikke differensieringsantigener**
  - **CD-molekyler (CD19, CD20)**
- **Gen-produkter som er over-uttrykt av kreftcellene**
- **HLA**



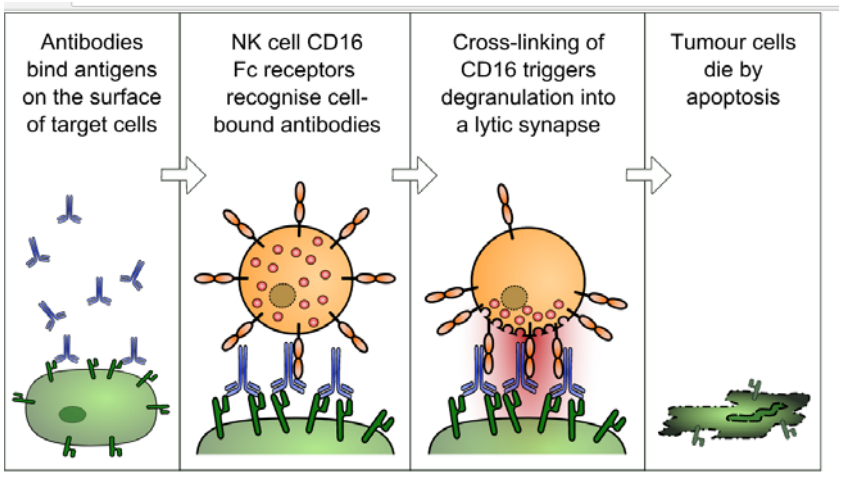


Antistoff-mediert kreftbehandling: monoklonale antistoffer – mab'er

- Mot leukemi/lymfom
  - **Rituximab (Mabtera)**
    - Anti CD20
    - CD20+ leukemier og lymfomer
  - **Epratuzumab**
    - Anti CD22 (B-celler)(IntReALL)
- Mot solide svulster
  - HR Nevroblastom – **anti GD2**



Antistoff-avhengig cellemediert cytotoksisitet



CAR-T
Chimeric antigen receptor

Kimæren

FDA Approves First CAR-T Cell Therapy for Pediatric Acute Lymphoblastic Leukemia

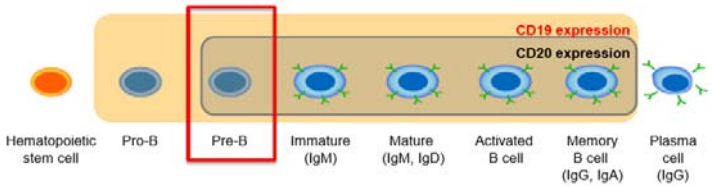
Posted on August 30, 2017 by Dr. Francis Collins

Caption: Cancer survivor Emily Whitehead with her dog Lucy.
Credit: Emily Whitehead Foundation

Tremendous progress continues to be made against the Emperor of All Maladies, cancer. One of the most exciting areas of progress involves immunotherapy, a treatment strategy that harnesses the natural ability of the body's own immune cells to attack and kill tumor cells. A lot of extremely hard work has gone into this research, so I was thrilled to learn that the Food and Drug Administration (FDA) just announced today its first approval of a promising type of immunotherapy called CAR-T cell therapy for kids and young adults with B-cell acute lymphoblastic leukemia (ALL) –the most common childhood cancer in the U.S.

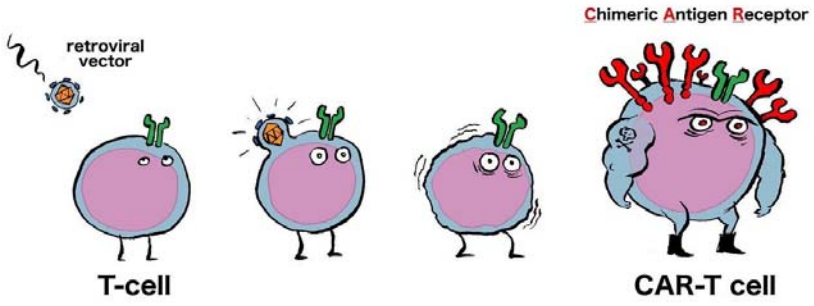
CAR T-cells targeting CD19

- CD19 attractive therapeutic target in pedALL
  - expressed on
    - normal B-cells and B-cell precursors
    - all B-cell malignancies (except myeloma)



  - but not on pluripotent stem cells or non–B-cell tissues

Generating super-soldiers
the production of CAR-T cells



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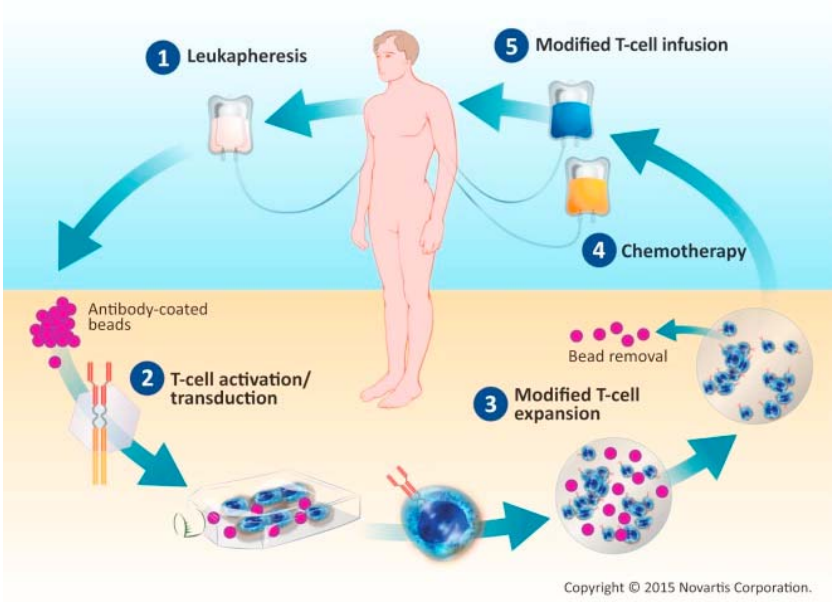


The NEW ENGLAND JOURNAL of MEDICINE

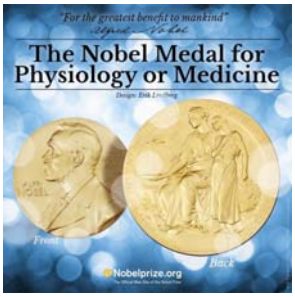
ORIGINAL ARTICLE

Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia

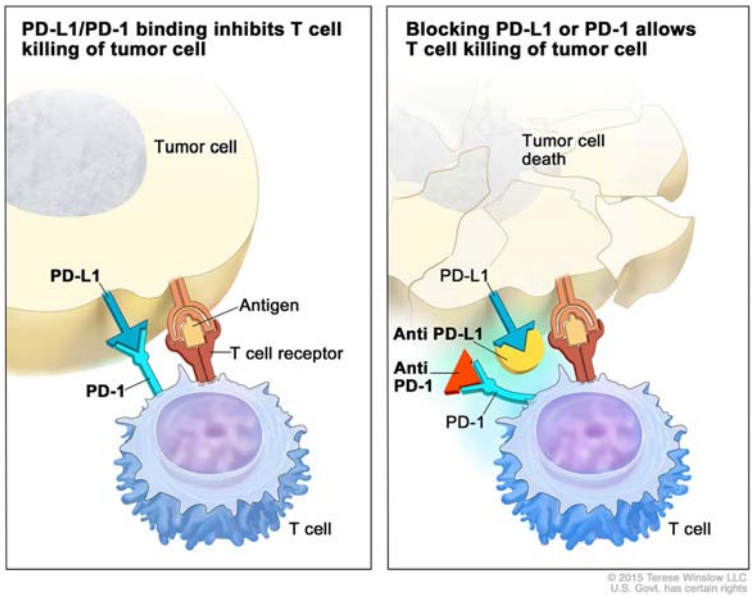
S.L. Maude, T.W. Laetsch, J. Buechner, S. Rives, M. Boyer, H. Bittencourt, P. Bader, M.R. Verneris, H.E. Stefanski, G.D. Myers, M. Qayed, B. De Moerloose, H. Hiramatsu, K. Schlis, K.L. Davis, P.L. Martin, E.R. Nemecek, G.A. Yanik, C. Peters, A. Baruchel, N. Boissel, F. Mechinaud, A. Balduzzi, J. Krueger, C.H. June, B.L. Levine, P. Wood, T. Taran, M. Leung, K.T. Mueller, Y. Zhang, K. Sen, D. Lebwohl, M.A. Pulsipher, and S.A. Grupp

PD1/PDL1 hemmere

- Checkpoint inhibitors
- PD1 – PDL1
  - Undertrykker immunsystemet
- PD1/PDL1 inhibitorer hindrer kreftcellene å unnslippe immunforsvaret



James P. Allison, Tasuku Honjo



SLUTT

Aftenposten ap.no

Mandag 14. mai 2012 | Oslo 10°

Verden Norge Oslopuls Økonomi Kultur Meninger TV Sport A-Å

Siste nytt: 17. mai-vuvuzelaer beslaglagt (kl.14:58) TIPS OSS Søk i på nett og papir Aftenposten

Etter to og et halvt års behandling, er Malin Evensen kvitt kreftsykdommen. Nå driver hun med magedans og zomba, og gleder seg til å bli konfirmert til våren.

FOTO: STIG B HANSEN

Fire av fem barn med leukemi blir friske

Malin Evensen (14) er frisk etter å ha fått diagnosen leukemi som 12-åring. □ Jeg er nok litt mer moden enn mange andre på min alder, sier hun.

Anbefal 54 personer anbefaler dette. Vær den første blant vennene dine.