Forskning på B-cellekreft - KLL

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IR Centre for Immune Regulation

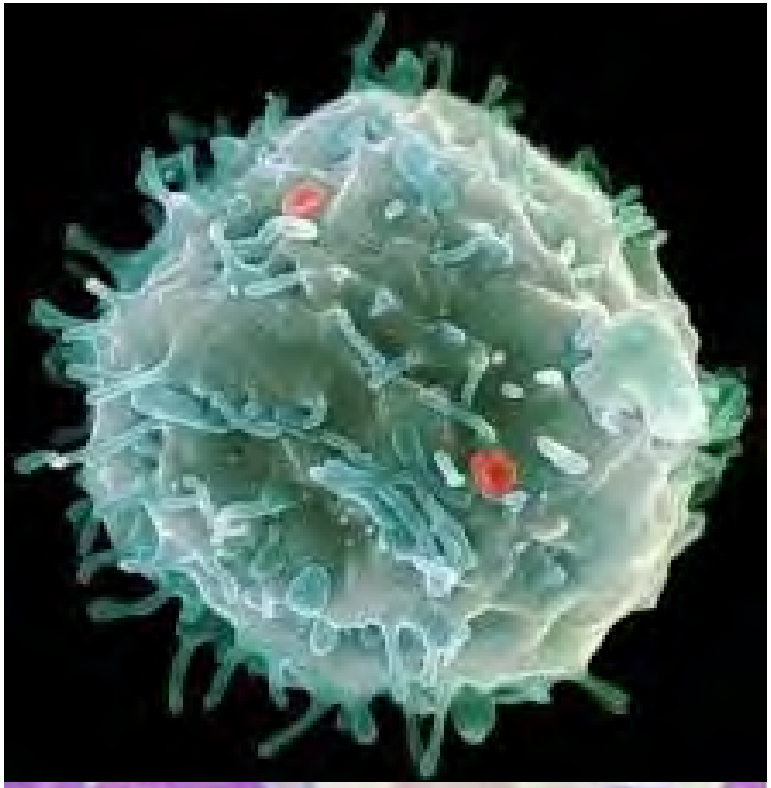
UiO : Institutt for klinisk medisin
Det medisinske fakultet

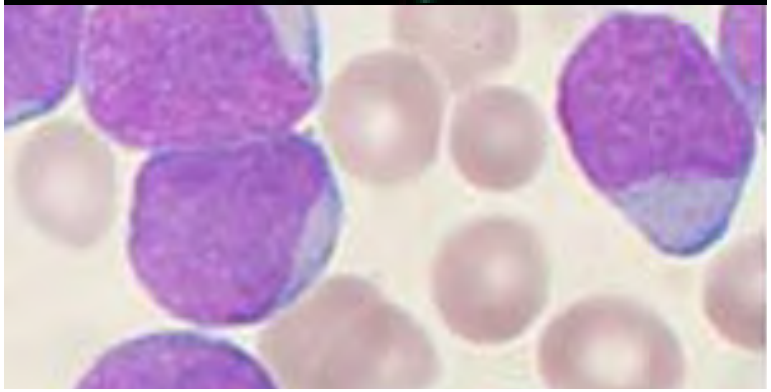
UiO : Universitetet i Oslo

Plan

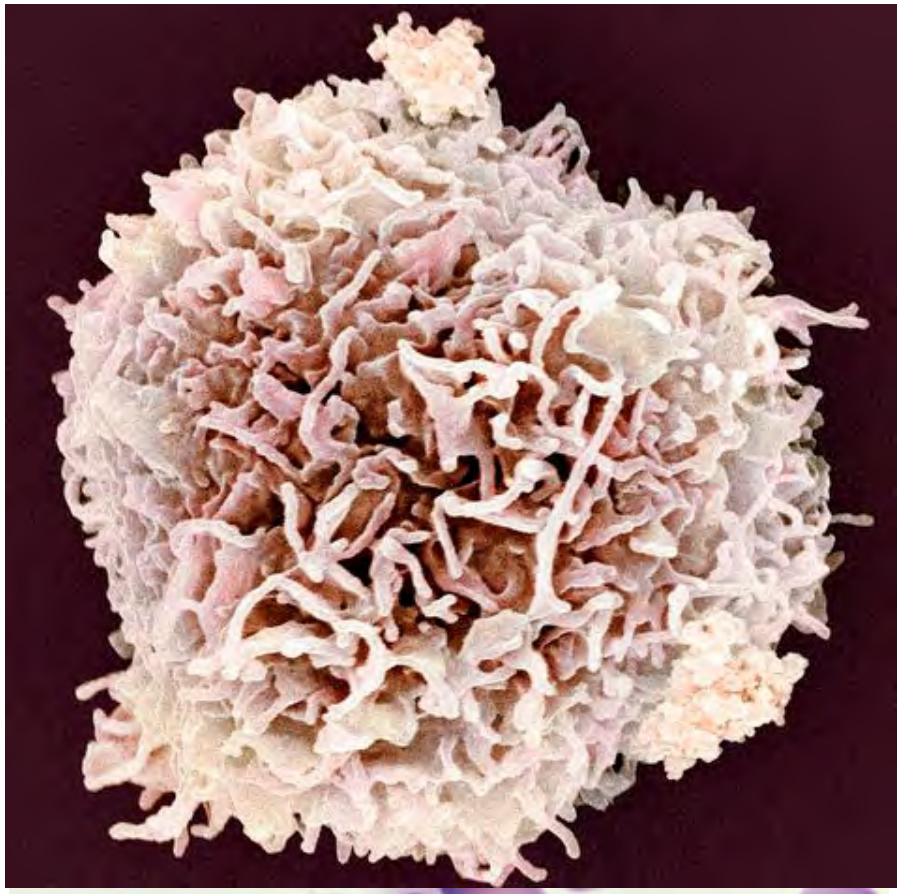
- Innledning om B-cellekreft
- Kreftceller vokser ikke av seg selv
- Persontilpasset medisin
- Analyser av mikromiljøet i som omkranser kreftcellene
- Sammendrag

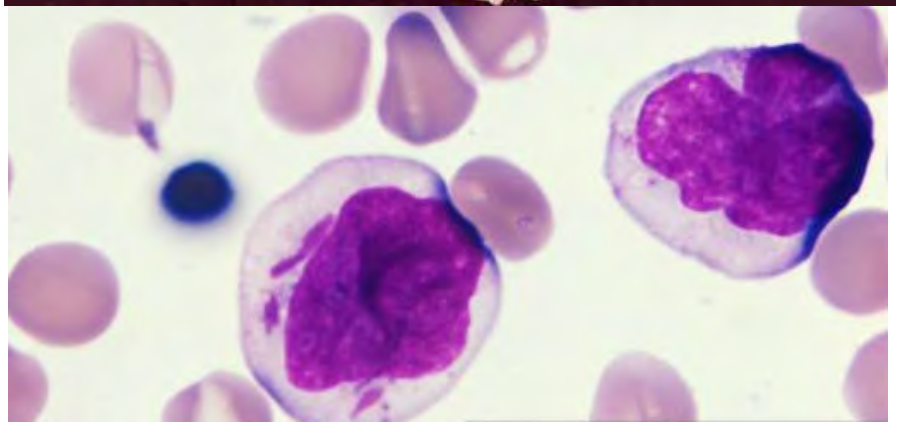
L(ymfocytt)





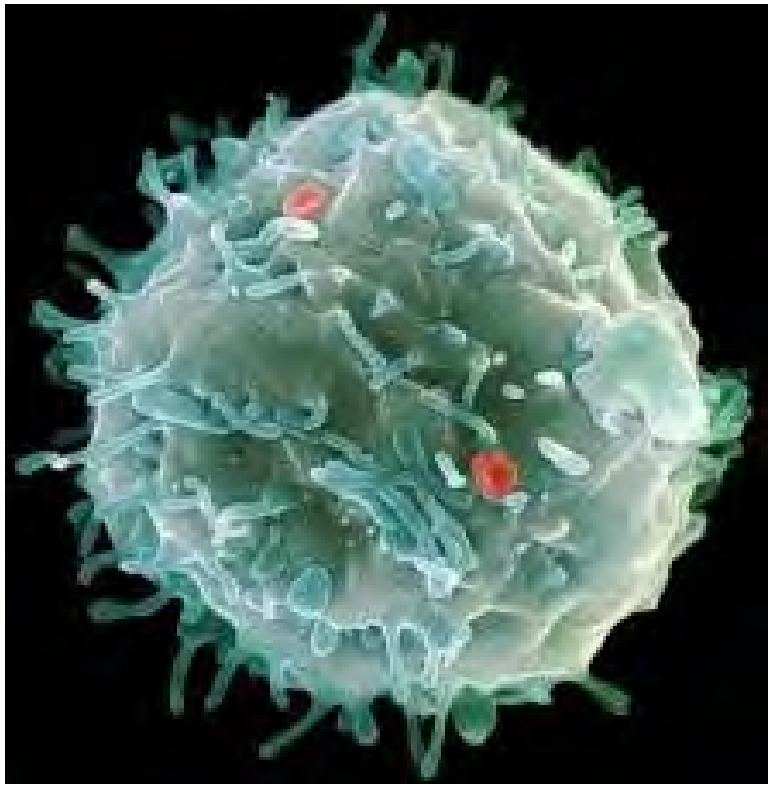
M(yeloid)

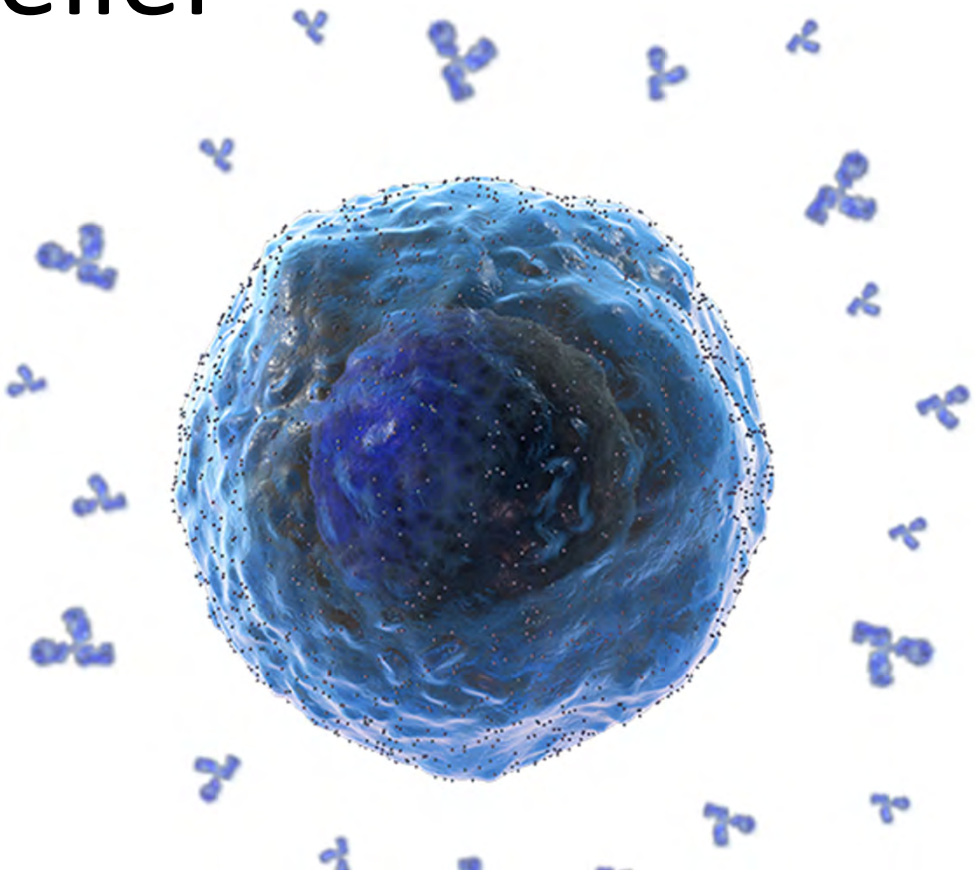




Non-Hodgkins lymfom: 1 av 50 mennesker utvikler i løpet av livet. De aller fleste av disse NHL (>90%) er B-cellekreftformer.
KLL: 1 av hundre og 1% av dødsfall som skyldes kreft
Benmargskreft (Myelomatose): 1 av 150
Hodgkins lymfom: 1 av 200

B-celler





B-cellestadier

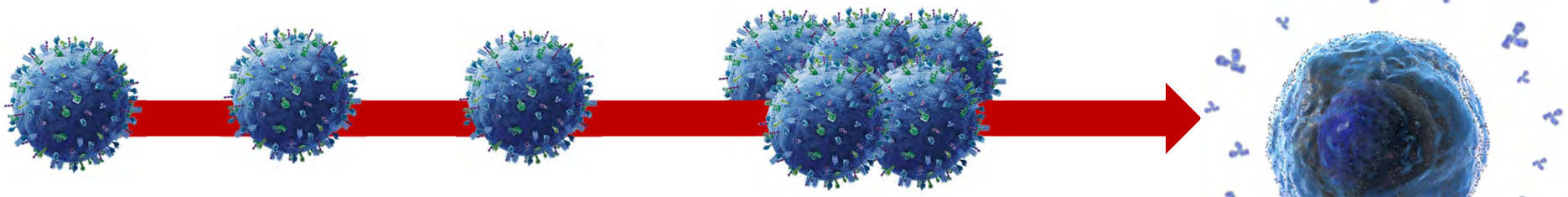
Umoden

Overgang

naiv

Hukommelses-celle

Plasmaceller

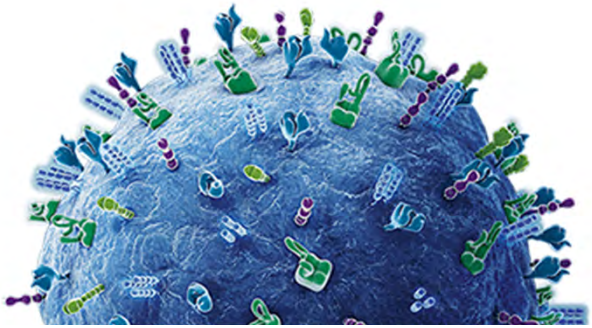


B-akutt lymfoblastisk leukemi (ALL)

Follikulært lymfom
Diffus storcellet lymfom
Hodgkinlymfom
Mantelcellelymfom

Benmargskreft (myelomatose)

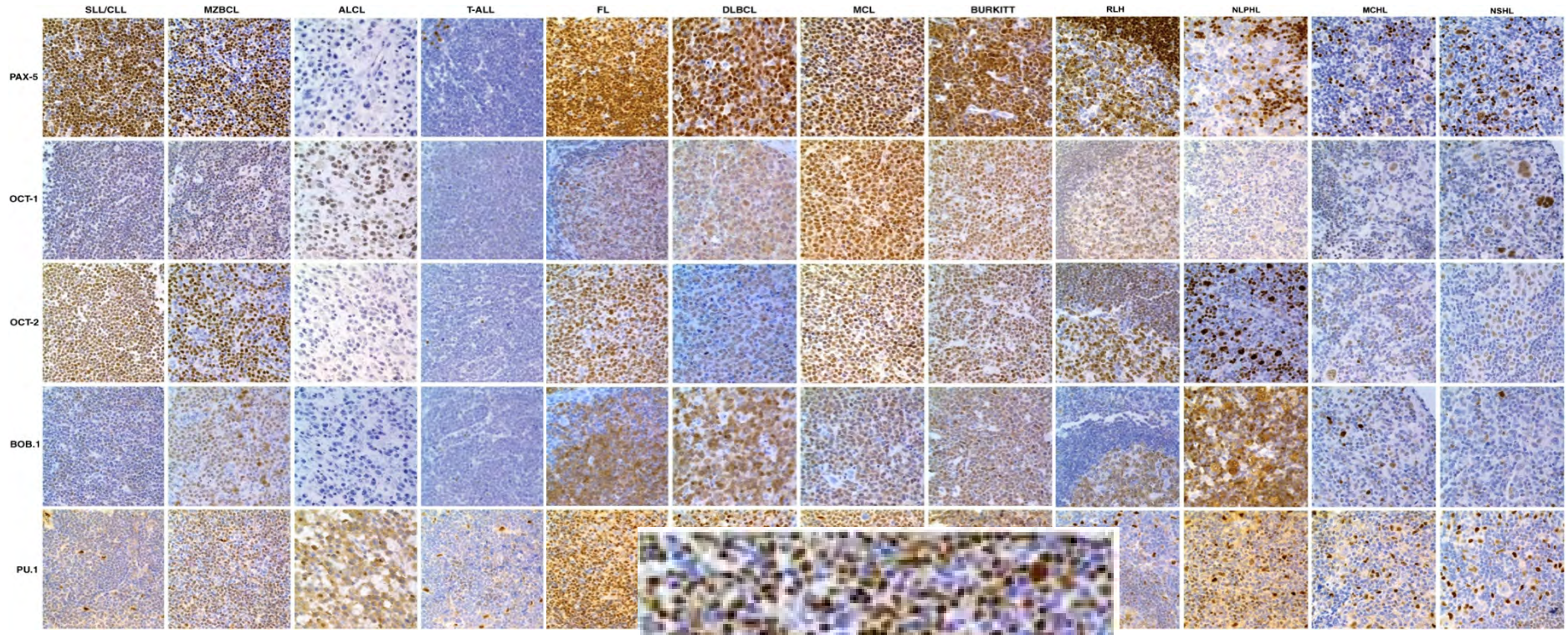
Kronisk lymfatisk leukemi (KLL), SLL

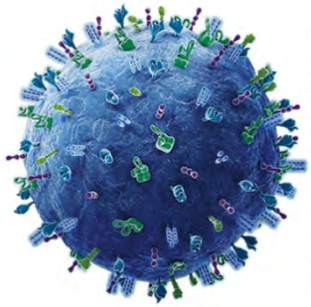


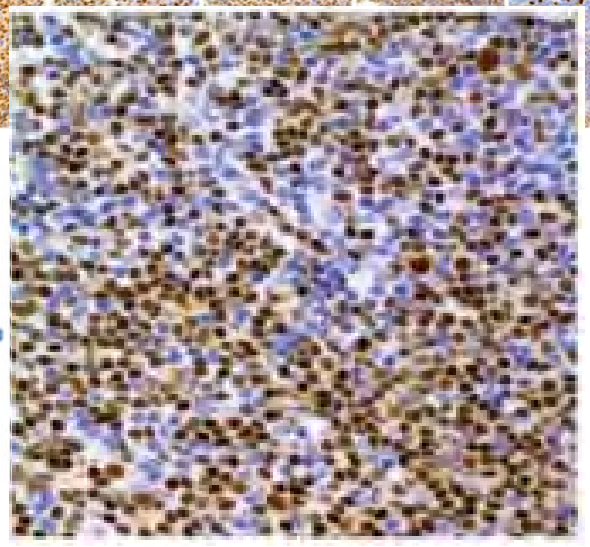
Overflaten har helt spesielle kjennetegn
Antistoffreseptor
Receptorer for regulerende signaler

B-cellekreftcellene lever i spesialisete lommer i vevet

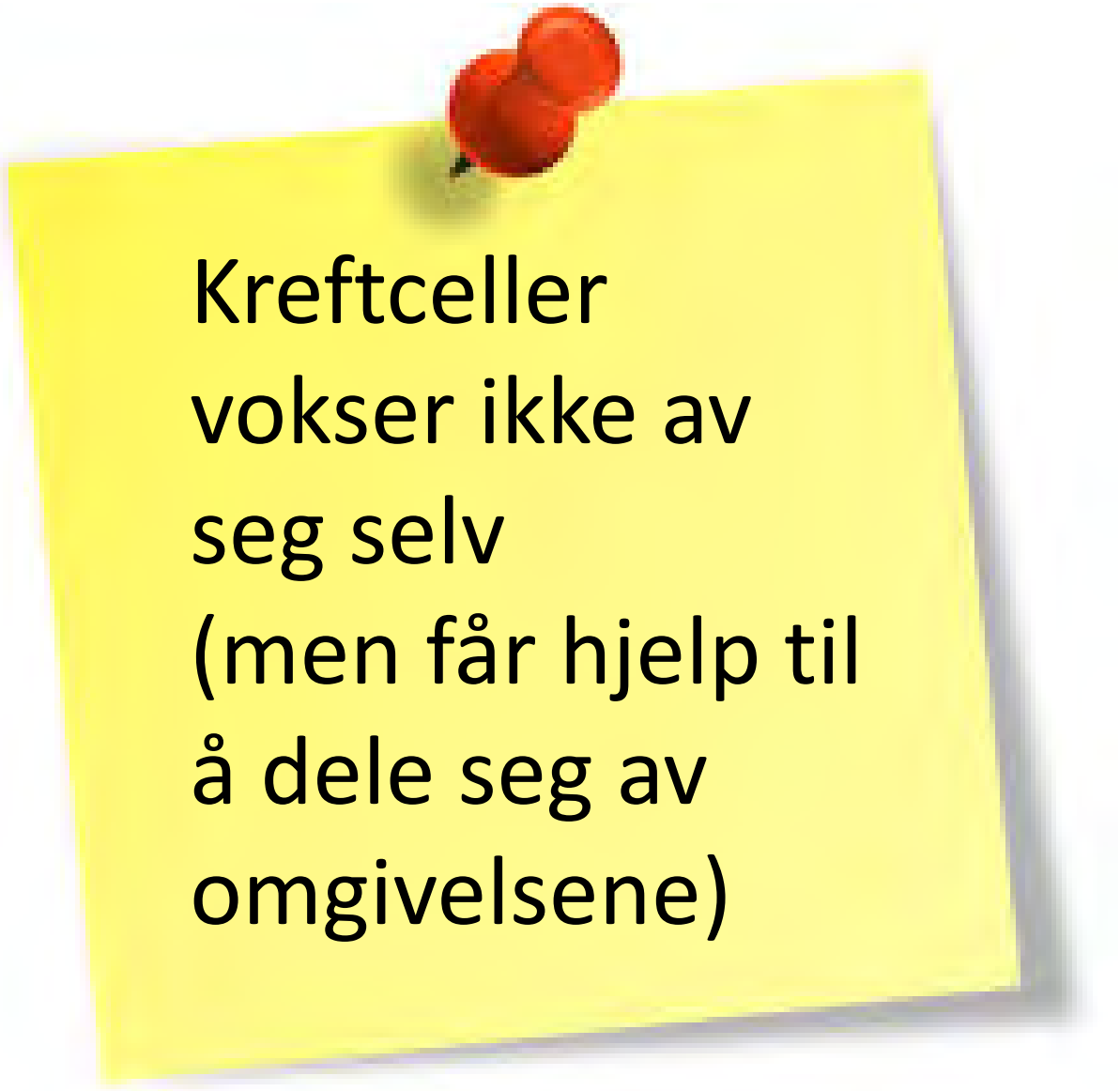
Det kan her være like mange (eller flere) normale celler enn kreftceller



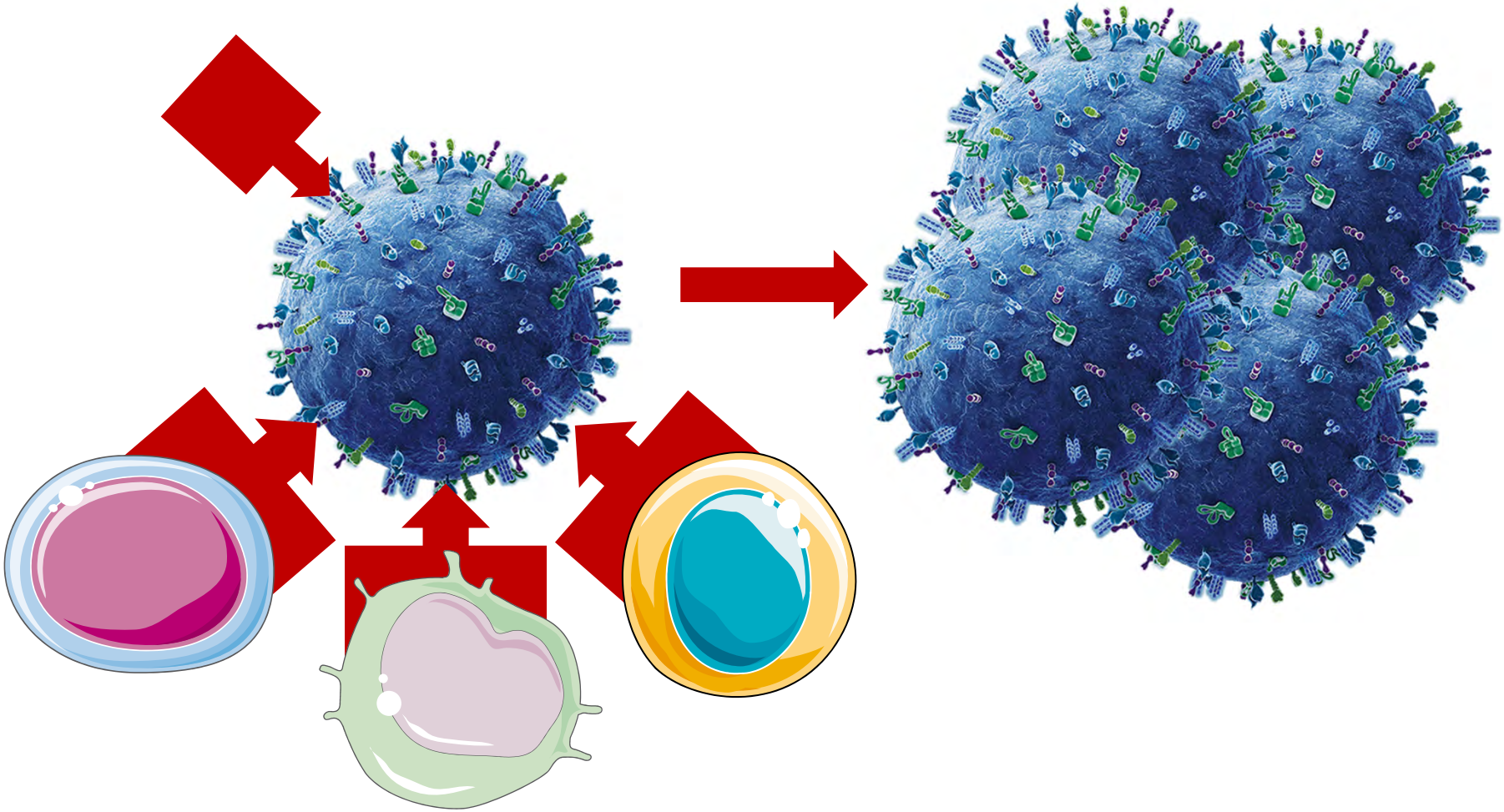




Huskelapp: 1)

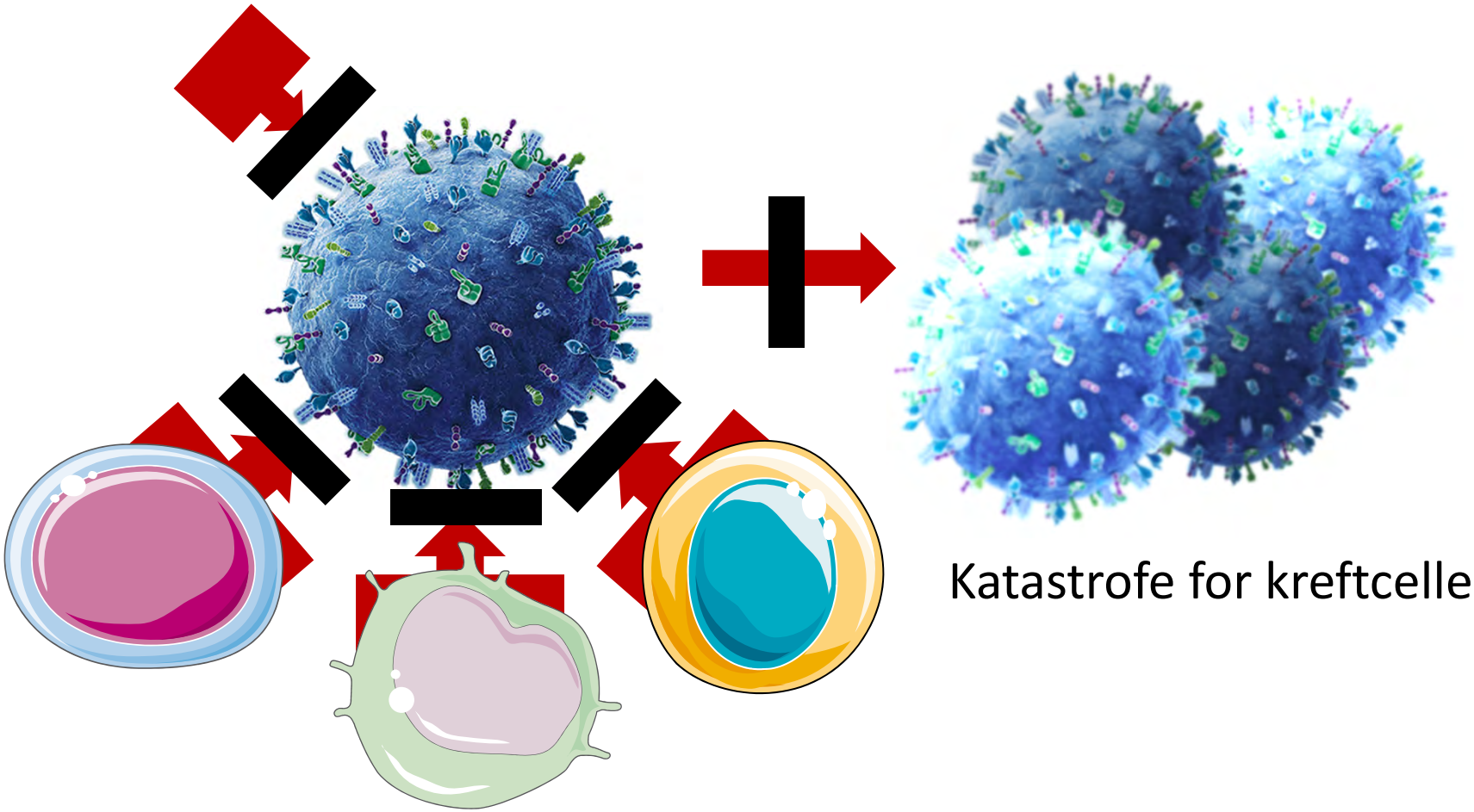

Kreftceller
vokser ikke av
seg selv
(men får hjelp til
å dele seg av
omgivelsene)

Det er ukjent hva som opprettholder kreftcelledelingen, men forskere er nå på sporet



Drømmeforhold for kreftcellene

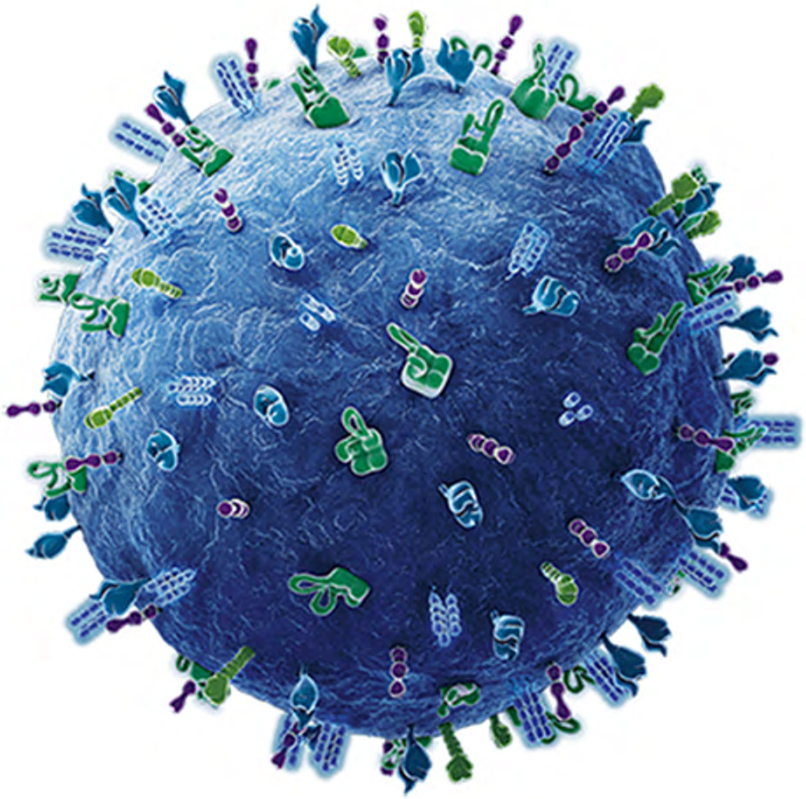
Kretcellene dør dersom de frarøves stimulerende signaler fra omgivelsene



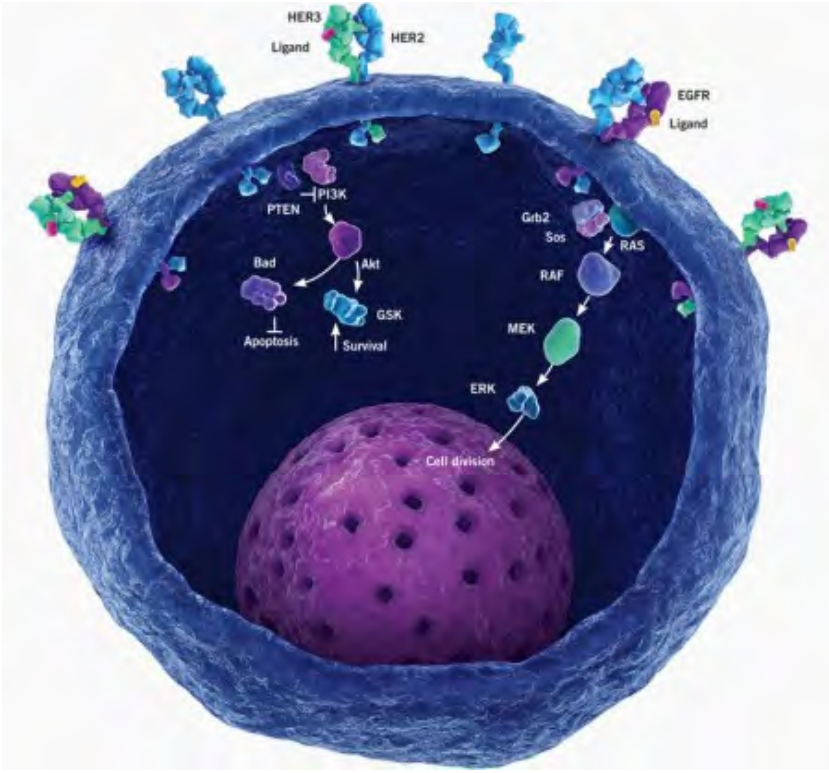
Katastrofe for kreftcellene

Intenst forskningsfelt: Hva trenger kreftcellene for å vokse?

Reseptorer på overflaten – for vekstfaktorer



Signaleringsveier inn i cellen – for vekstfaktorer

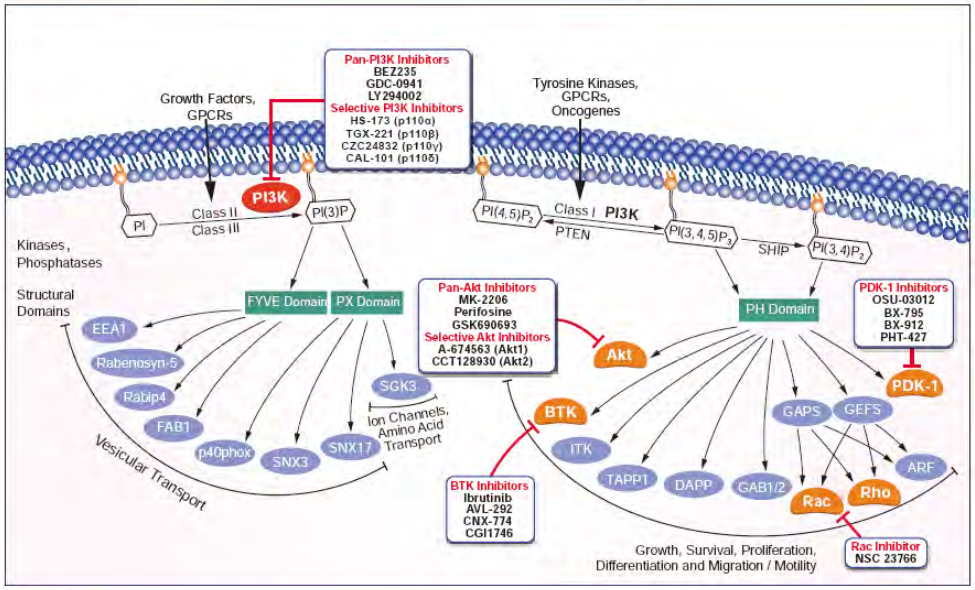


Kappløpet for å finne en pille som virker

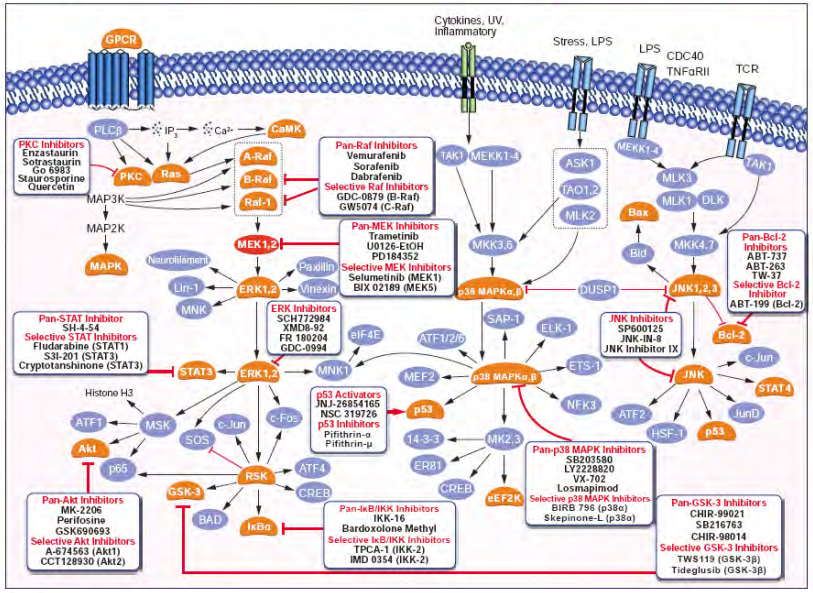
Merkelapp: 2)


Det utvikles en lang rekke nye legemidler, nye kommer hver måned – men det tar tid å teste disse skikkelig

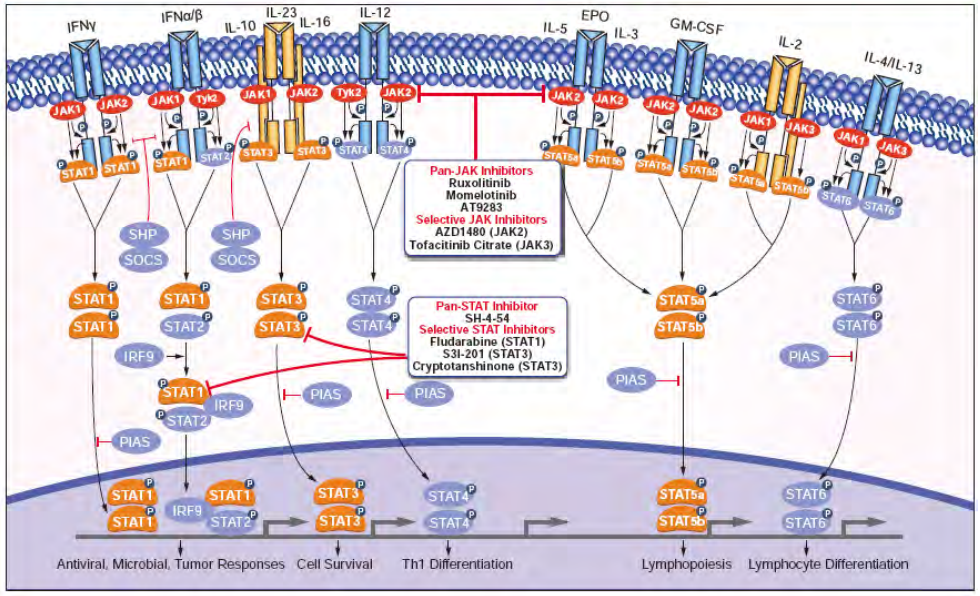
PI3K



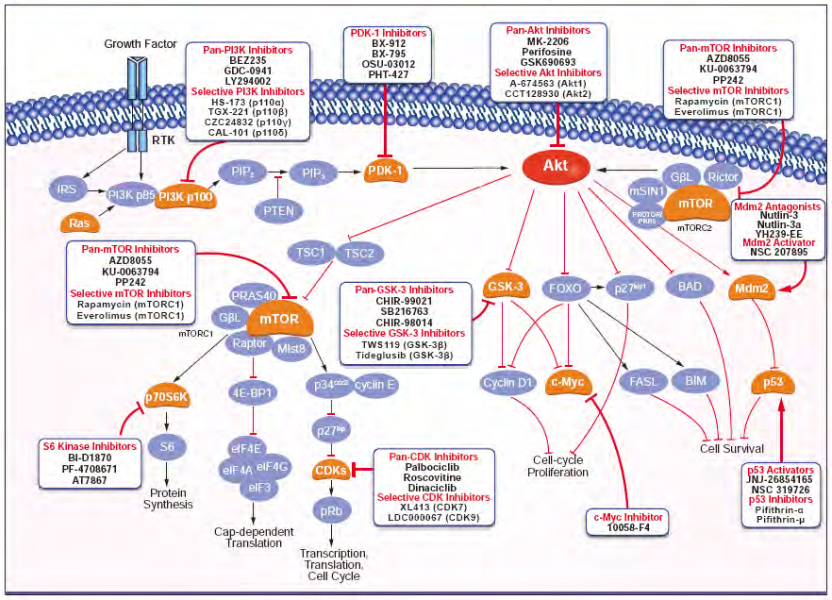
MEK



JAK

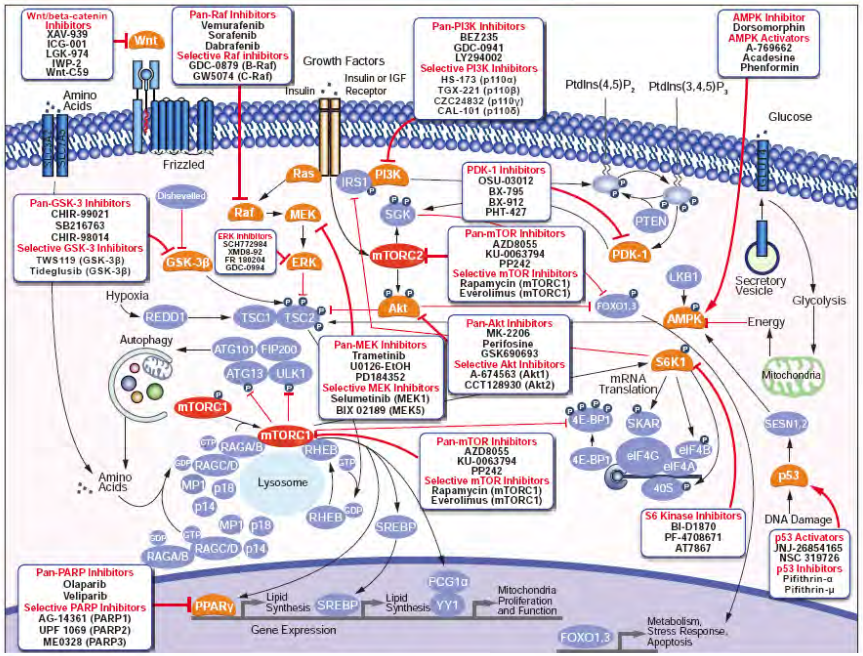


Akt

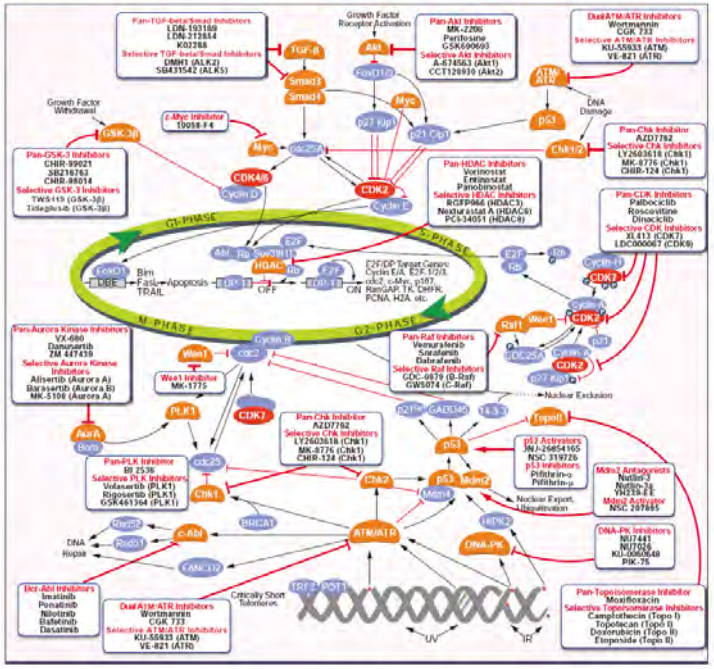


http://file.selleckchem.com/img_test/Inhibitors-of-Signaling-Pathways.pdf

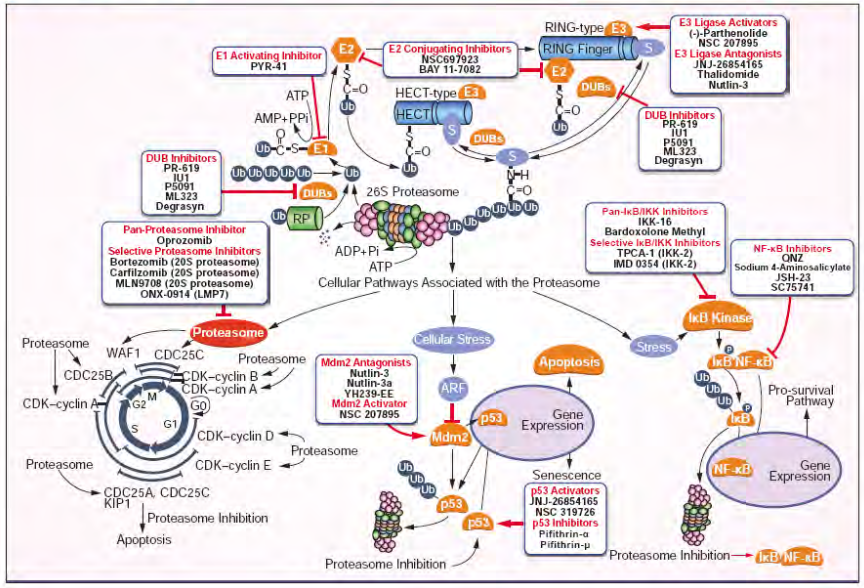
mTOR



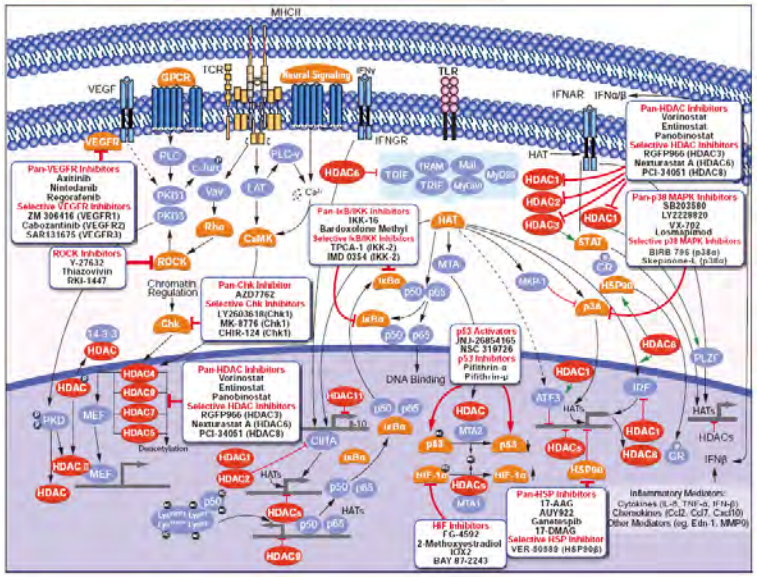
CDK



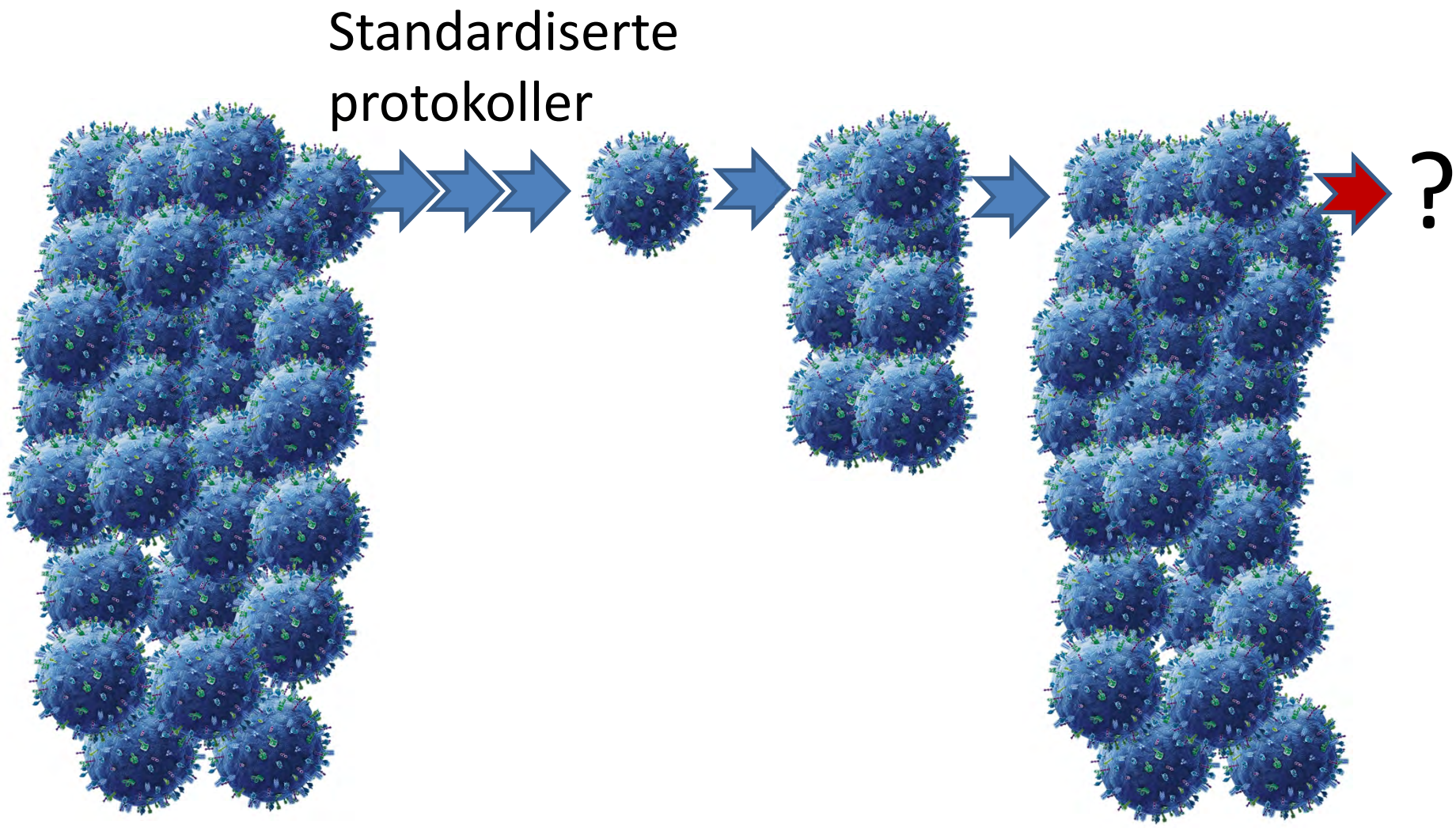
Proteasome



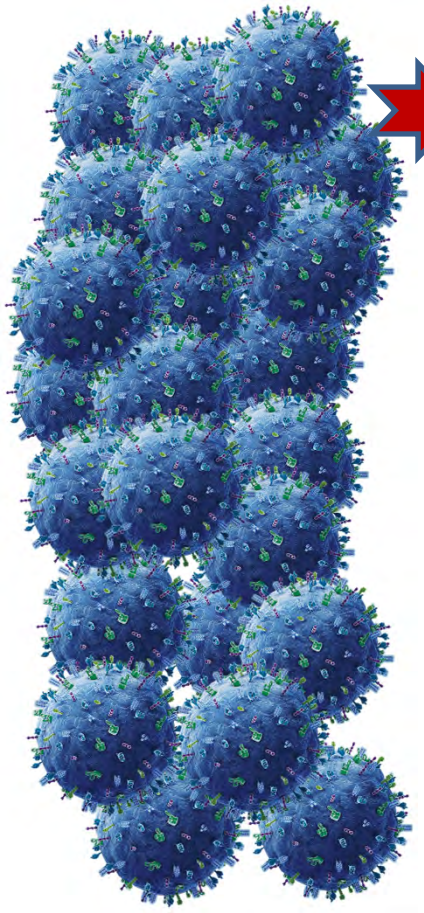
HDAC



Det er rett og slett for mange legemiddelmuligheter: vanskelig å spå om hva som kan bite på kreftcellene



Alternative midler når standardterapi ikke kommer i mål?



?

Ibrutinib (Btk)?
Idelalisib(PI3K)?
Fostamatinib (Syk)?
Venetoclax (Bcl2)?
Lenalidomide (Ikaros)?
Bendamustine (alkylerende)

Ved flere B-cellekreftformer kommer kreften nesten alltid tilbake

- Men det rapporteres likevel om at enkeltpasienter ble kurert ved et eller annet legemiddel. Men, det har vært umulig å spå hvilket som passer for hver enkelt pasient.

- Hos de aller fleste ved slike kreftformer kommer likevel sykdommen tilbake, hvilke nye midler skal man velge da – når de forrige ikke fungerer?

GOP Makeover / Drone Morality / The Marriage Test By Joel Stein

TIME

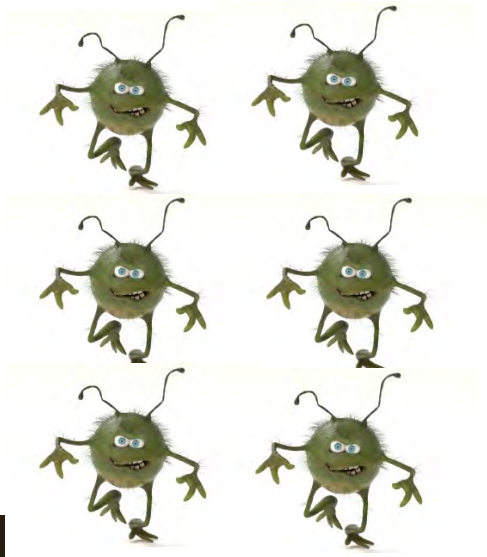
HOW TO CURE CANCER*

*Yes, it's now possible—thanks to new cancer dream teams that are delivering better results faster

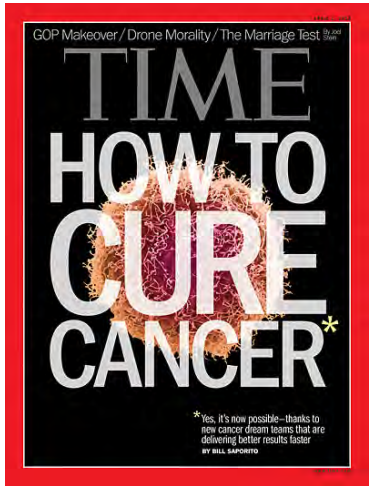
BY BILL SAPORITO

Persontilpasset medisin: Urinveisinfeksjon

Melkesjokoladeparadis!



Persontilpasset medisin: Kreftbehandling



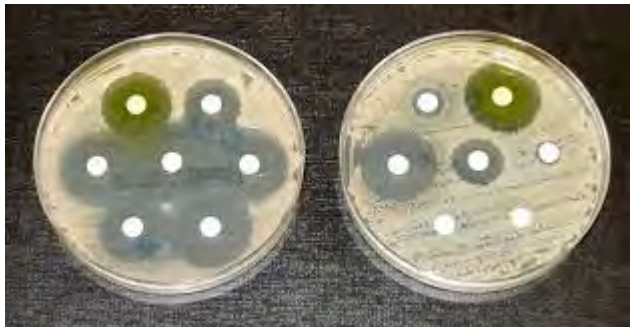
RESEARCH ARTICLES

CANCER THERAPY

Patient-derived models of acquired resistance can identify effective drug combinations for cancer

Adam S. Crystal,[1] Alice T. Shaw,[1] Lecia V. Sequist,[1] Luc Friboulet,[1] Matthew J. Niederst,[1] Elizabeth L. Lockerman,[1] Rosa L. Frias,[1] Justin F. Gainor,[1] Arnaud Amzallag,[1] Patricia Greninger,[1] Dana Lee,[1] Anuj Kalsy,[1] Maria Gomez-Caraballo,[1] Leila Elamine,[1] Emily Howe,[1] Wooyoung Hur,[3,4] Eugene Lifshits,[1] Hayley E. Robinson,[2] Ryohei Katayama,[1] Anthony C. Faber,[1] Mark M. Awad,[1] Sridhar Ramaswamy,[1] Mari Mino-Kenudson,[2] A. John Iafrate,[2] Cyril H. Benes,[1*] Jeffrey A. Engelman[1*]

Targeted cancer therapies have produced substantial clinical responses, but most tumors develop resistance to these drugs. Here, we describe a pharmacogenomic platform that facilitates rapid discovery of drug combinations that can overcome resistance. We established cell culture models derived from biopsy samples of lung cancer patients whose disease had progressed while on treatment with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors and then subjected these cells to genetic analyses and a pharmacological screen. Multiple effective drug combinations were identified. For example, the combination of ALK and MAPK kinase (MEK) inhibitors was active in an *ALK*-positive resistant tumor that had developed a *MAP2K1* activating mutation, and the combination of EGFR and fibroblast growth factor receptor (FGFR) inhibitors was active in an *EGFR* mutant resistant cancer with a mutation in *FGFR3*. Combined ALK and SRC (pp60c-src) inhibition was effective in several ALK-driven patient-derived models, a result not predicted by genetic analysis alone. With further refinements, this strategy could help direct therapeutic choices for individual patients.



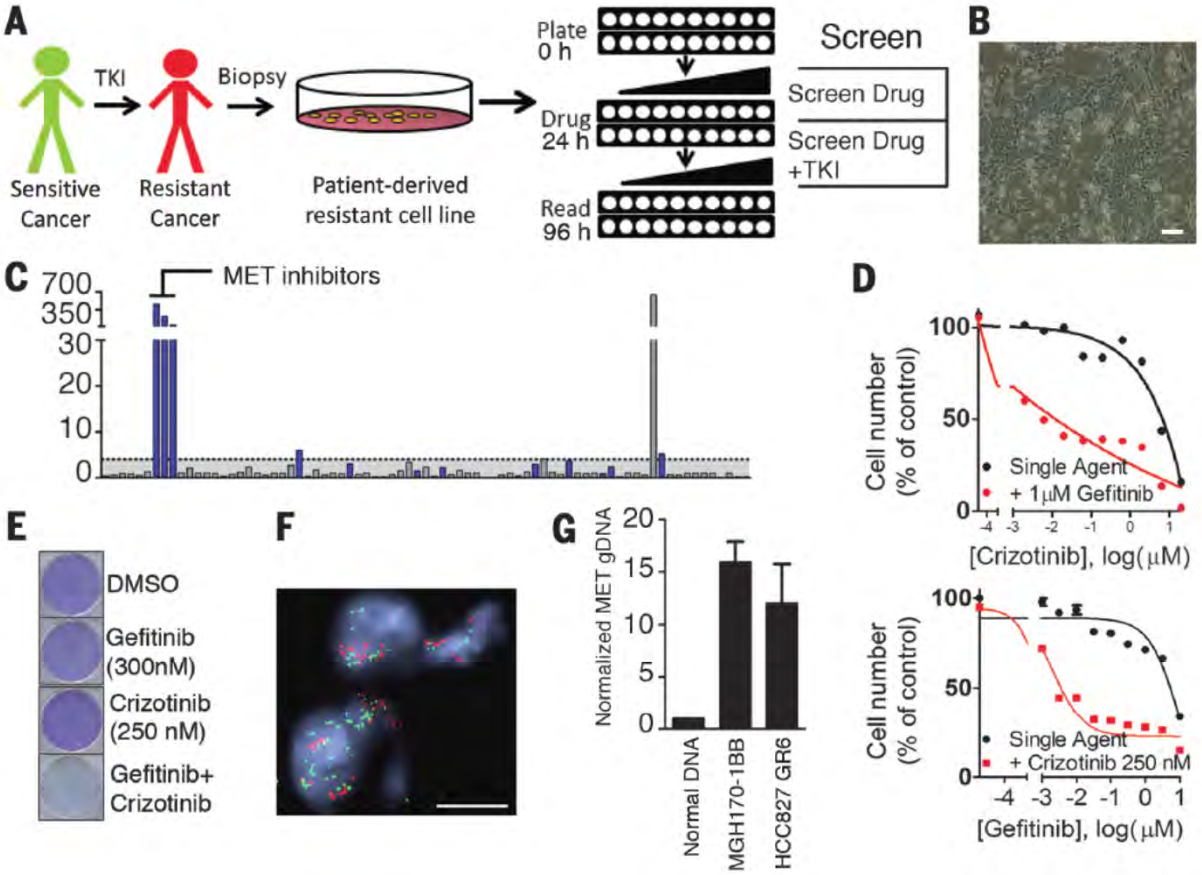
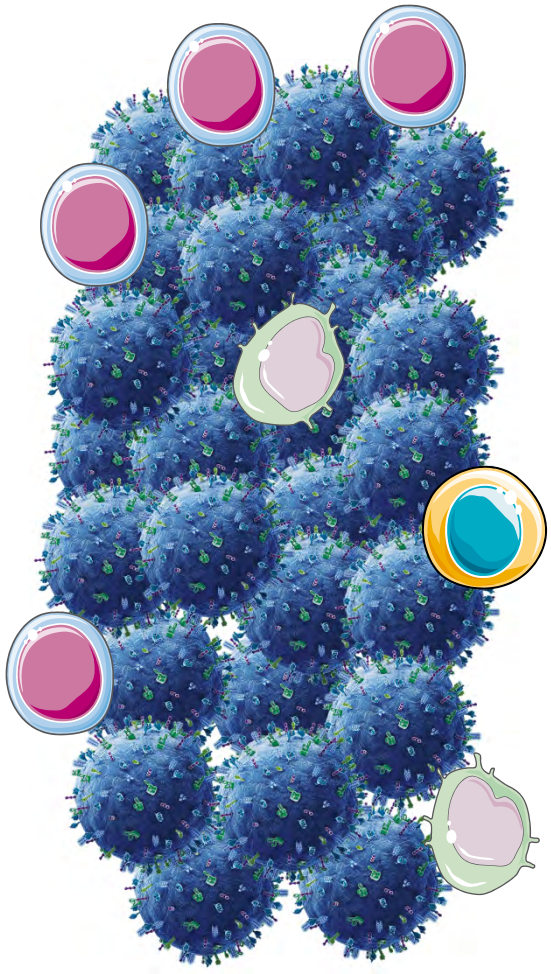
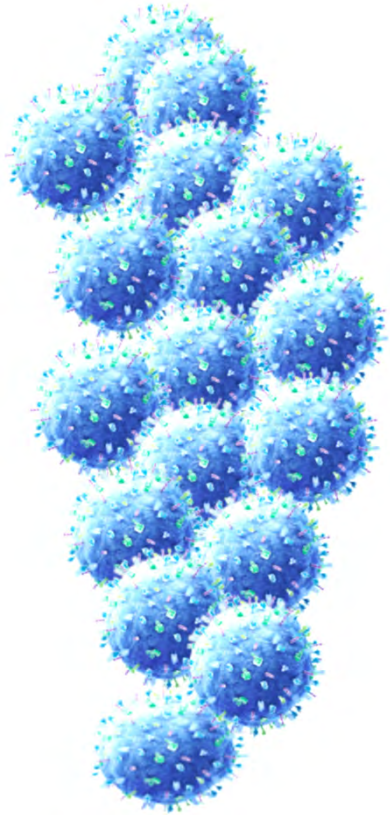


Fig. 1. Screen schematic and proof of concept in a patient-derived cell line. (**A**) Schematic of the screen workflow. Cell line models of acquired resistance were obtained directly from biopsies of patients after the development of acquired resistance to either EGFR inhibitor or ALK inhibitor in the clinic. Screen drugs were tested as a single agent and in the presence of a single fixed concentration of the primary TKI across 10 concentrations encompassing a 10,000-fold dilution range. After 72 hours, cell viability was determined with CellTiter-Glo. (**B**) Phase-contrast microscopy of cell line MGH170-1BB, derived from an *EGFR* mutant lung cancer metastatic lesion with acquired resistance to EGFR inhibitors. Scale bar, 100 μm. (**C**) Representation of screen data for the MGH170-1BB cell line. The *y* axis represents the fold-change GI50 that resulted with the addition of gefitinib (GI50 single agent/GI50 combination). Each bar is the result for an individual drug. The bars are color-coded blue when the percentage of decrease in AUC from single agent to combination was greater than 10%. Drugs were defined as "hits" when the GI50 shift was > 4 and the AUC change > 10% (see Materials and Methods). (**D**) (Top) The MET

Pasienttilpasset medisin, B-cellekreft?





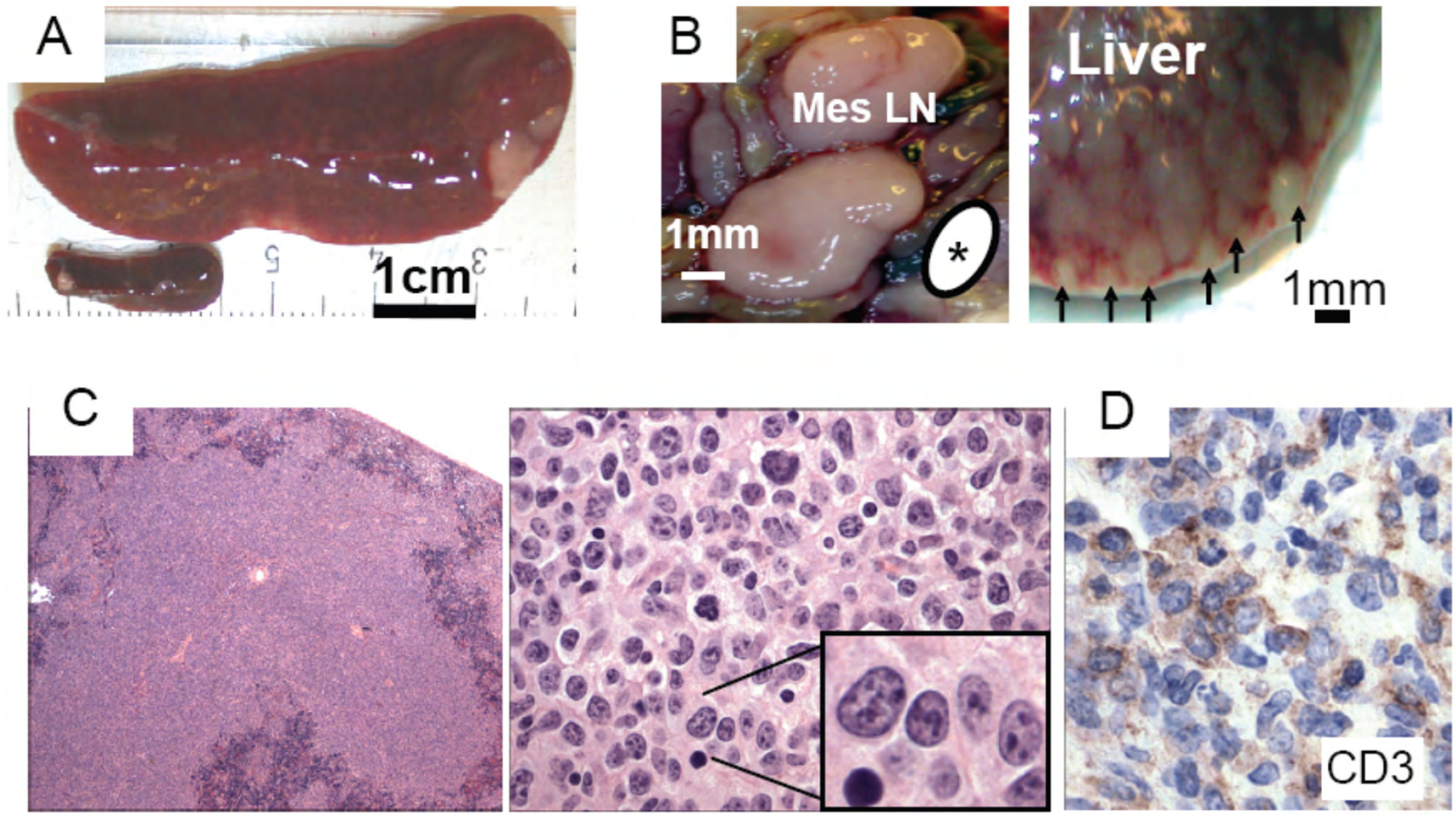
Kreftceller begynner straks å dø når de tas ut av kroppen

Legemiddel-testing har ikke vært lett

Merkelapp: 3)

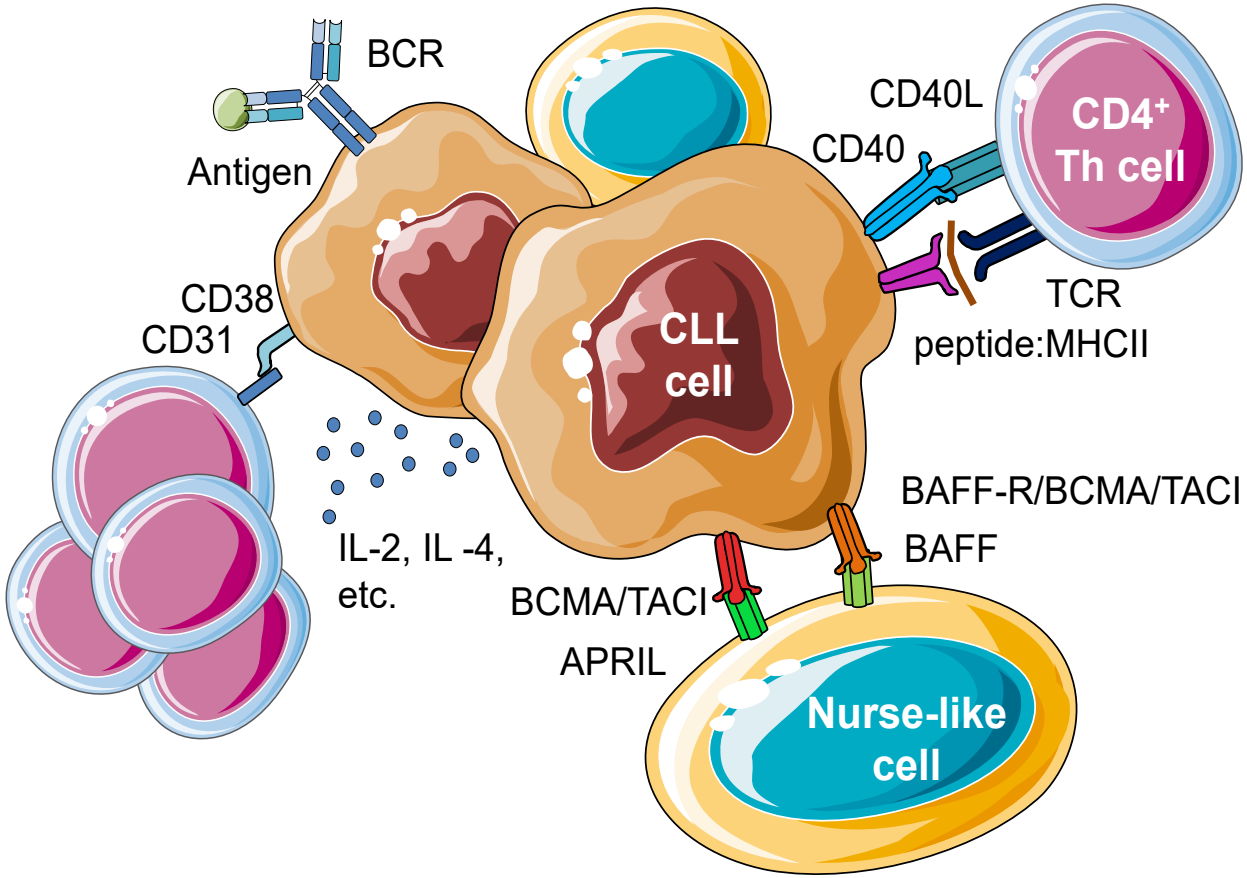

Det er et mål å lage drømmeforhold for lymfekreftcellers vekst for nettopp å teste legemiddel-effekt for enkelt-pasienter

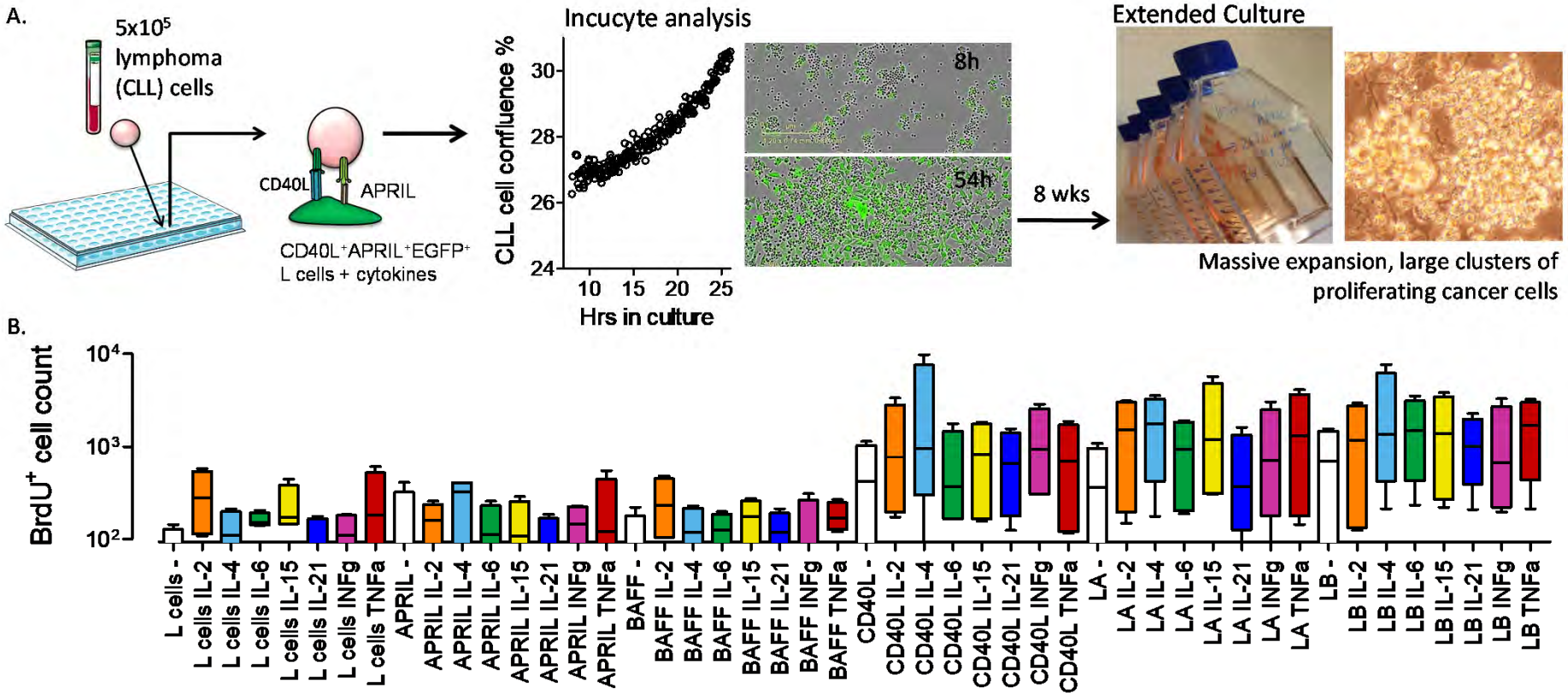
Lymphomagenesis in mice, JEM 2007



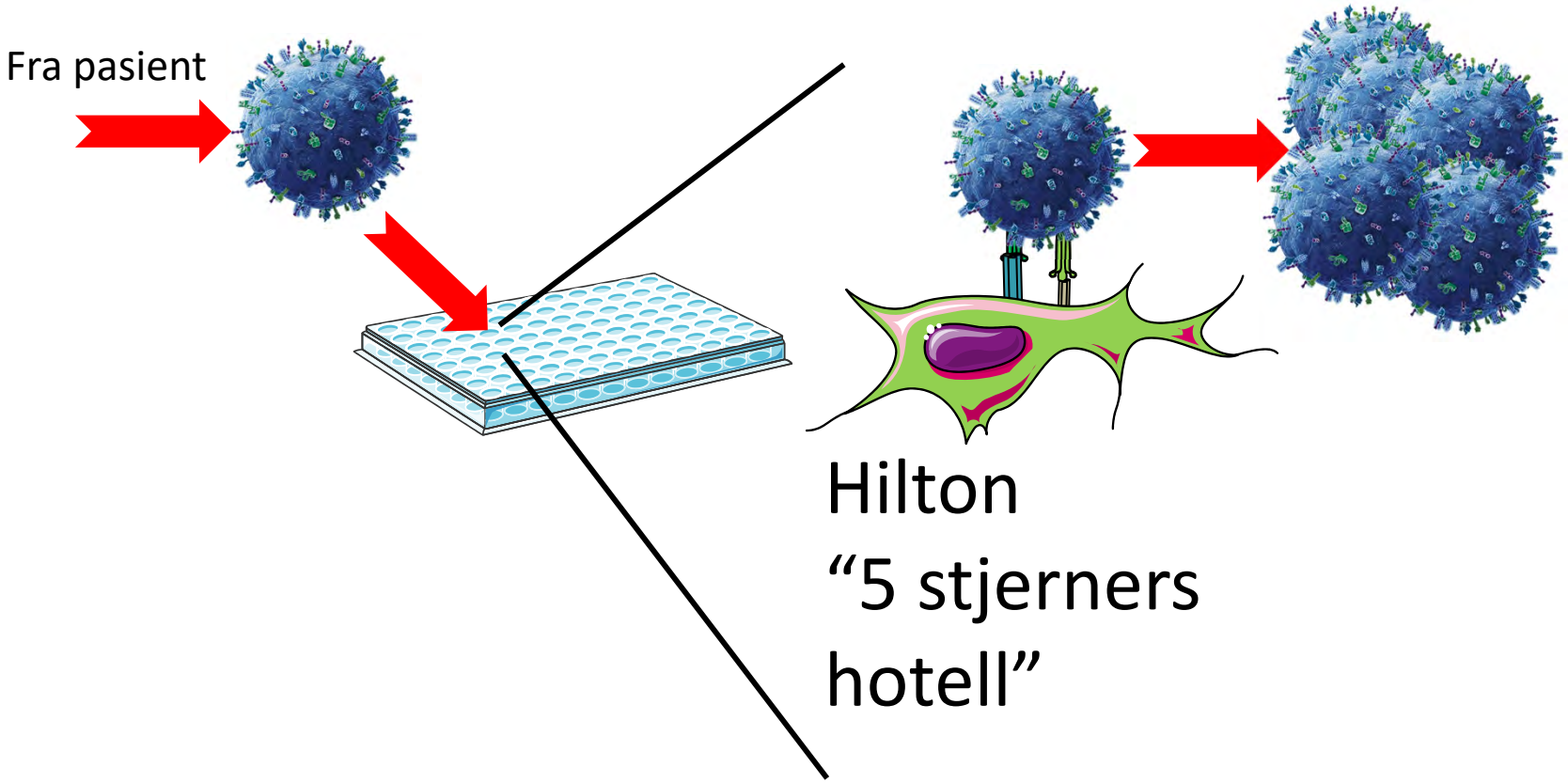
Large cell lymphoma, cytogenetically abnormal (copy number abberations CGH)

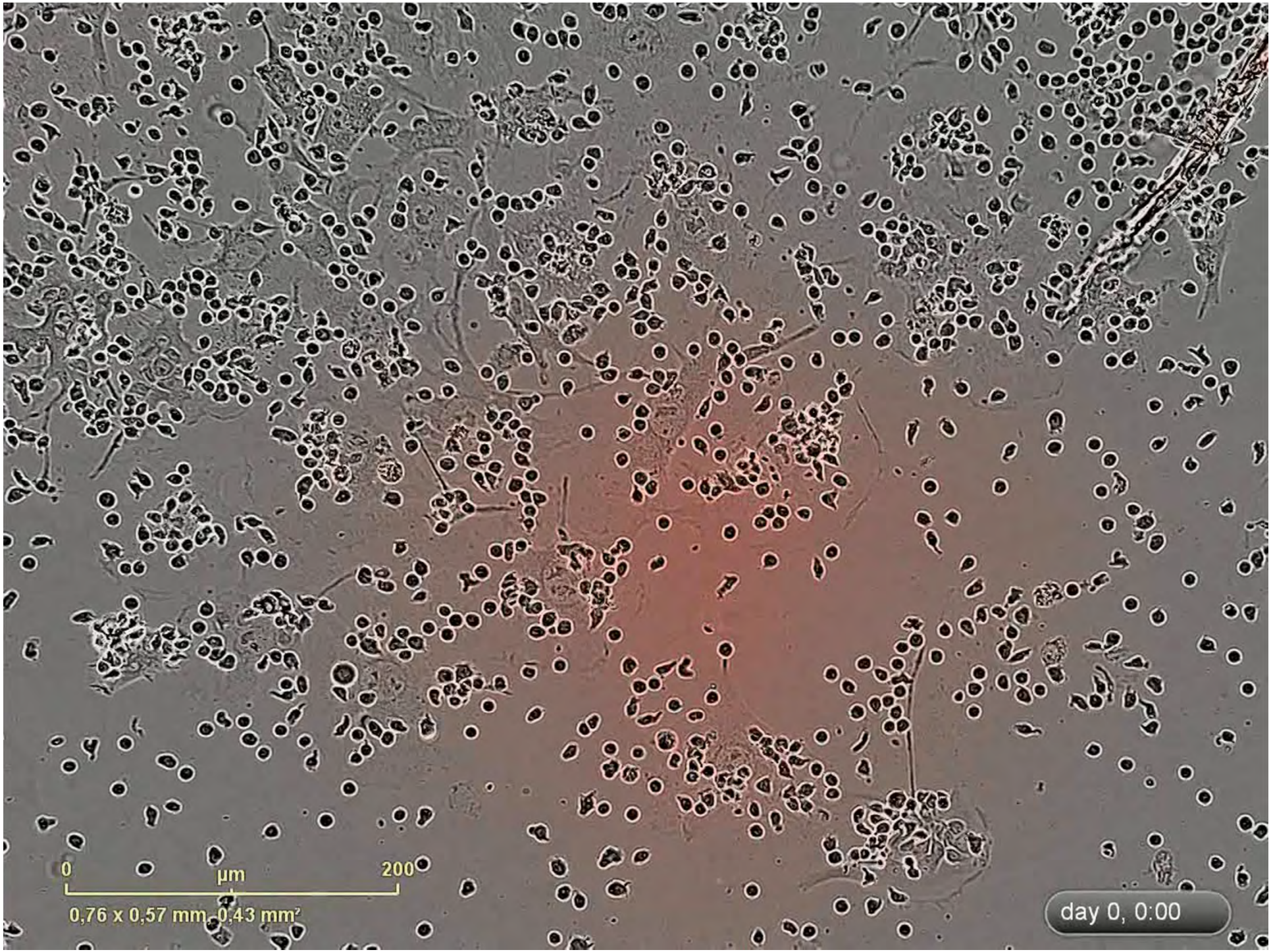
Zangani et al JEM 2007


BCR
Antigen
CD38
CD31
IL-2, IL -4,
etc.
CLL
cell
CD40L
CD40
CD4+
Th cell
TCR
peptide:MHCII
BAFF-R/BCMA/TACI
BAFF
BCMA/TACI
APRIL
Nurse-like
cell


A.
5x10^5
lymphoma
(CLL) cells
CD40L
APRIL
CD40L+APRIL+EGFP+
L cells + cytokines
Incucyte analysis
CLL cell confluence %
30
28
26
24
10
15
20
25
Hrs in culture
8h
54h
8 wks
Extended Culture
Massive expansion, large clusters of
proliferating cancer cells
B.
BrdU+ cell count
10^4
10^3
10^2
L cells -
L cells IL-2
L cells IL-4
L cells IL-6
L cells IL-15
L cells IL-21
L cells INFg
L cells TNFa
APRIL -
APRIL IL-2
APRIL IL-4
APRIL IL-6
APRIL IL-15
APRIL IL-21
APRIL INFg
APRIL TNFa
BAFF -
BAFF IL-2
BAFF IL-4
BAFF IL-6
BAFF IL-15
BAFF IL-21
BAFF INFg
BAFF TNFa
CD40L -
CD40L IL-2
CD40L IL-4
CD40L IL-6
CD40L IL-15
CD40L IL-21
CD40L INFg
CD40L TNFa
LA -
LA IL-2
LA IL-4
LA IL-6
LA IL-15
LA IL-21
LA INFg
LA TNFa
LB -
LB IL-2
LB IL-4
LB IL-6
LB IL-15
LB IL-21
LB INFg
LB TNFa

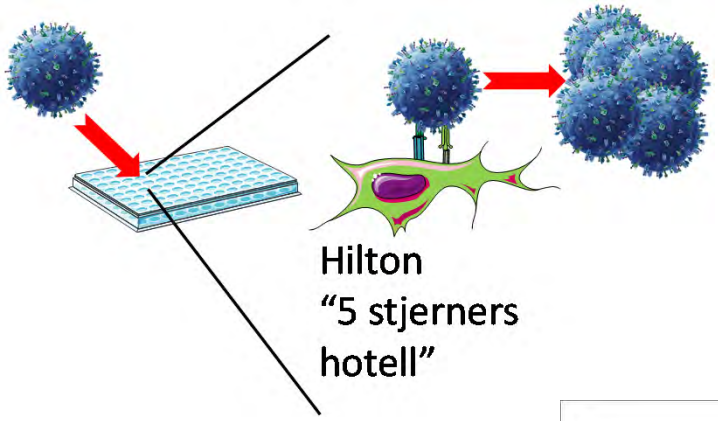
Kunstige stimuleringsceller gjenskaper **drømmeforhold** for kreftcellene



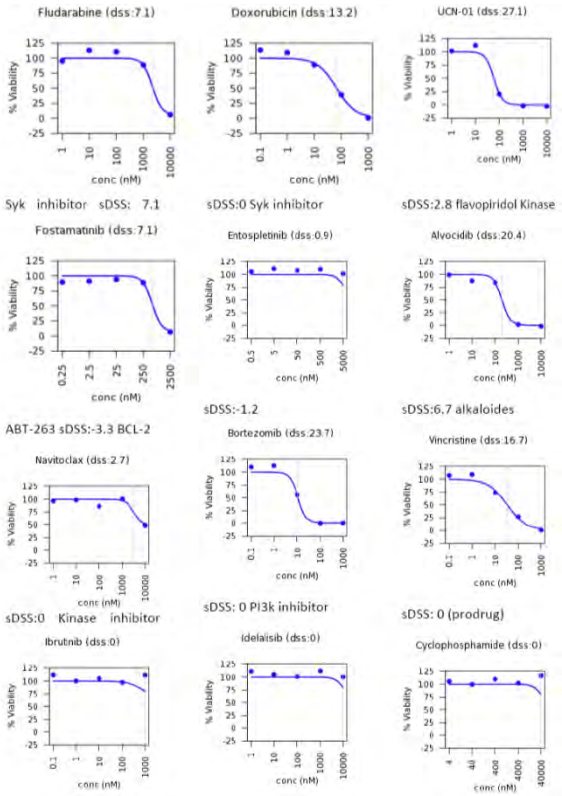

0
µm
200
0,76 x 0,57 mm, 0,43 mm²
day 0, 0:00

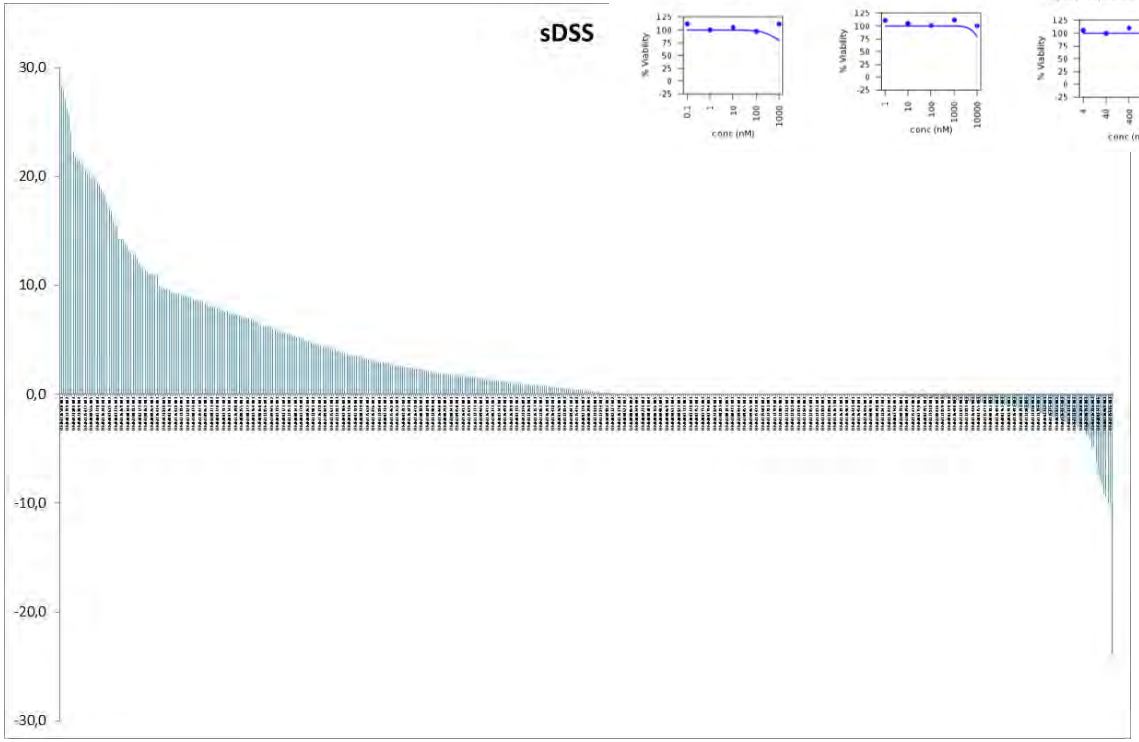
Utvikling av storskalatesting

Kreftceller: sensitivitetstesting for legemidler



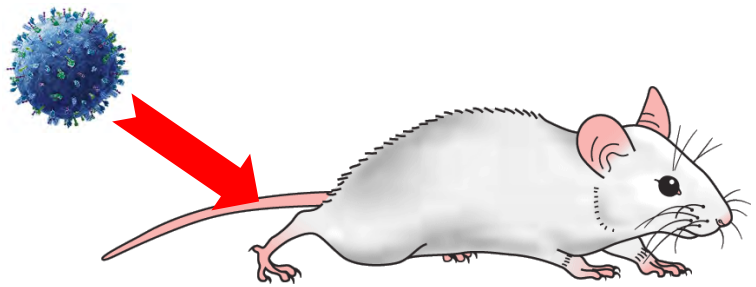
740 forskjellige legemilder: hvilke fungerer best



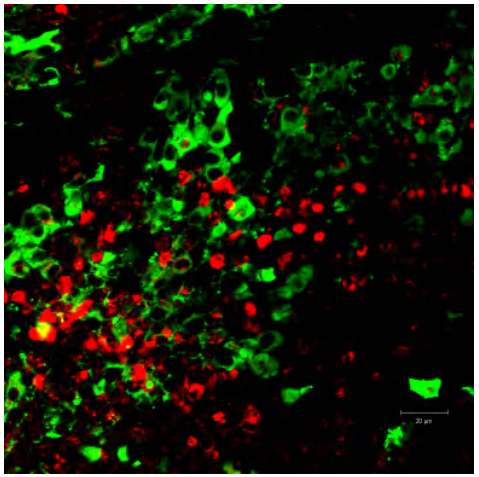


Validering av sensitivitetsresultater ved å behandle mus

Fra pasient

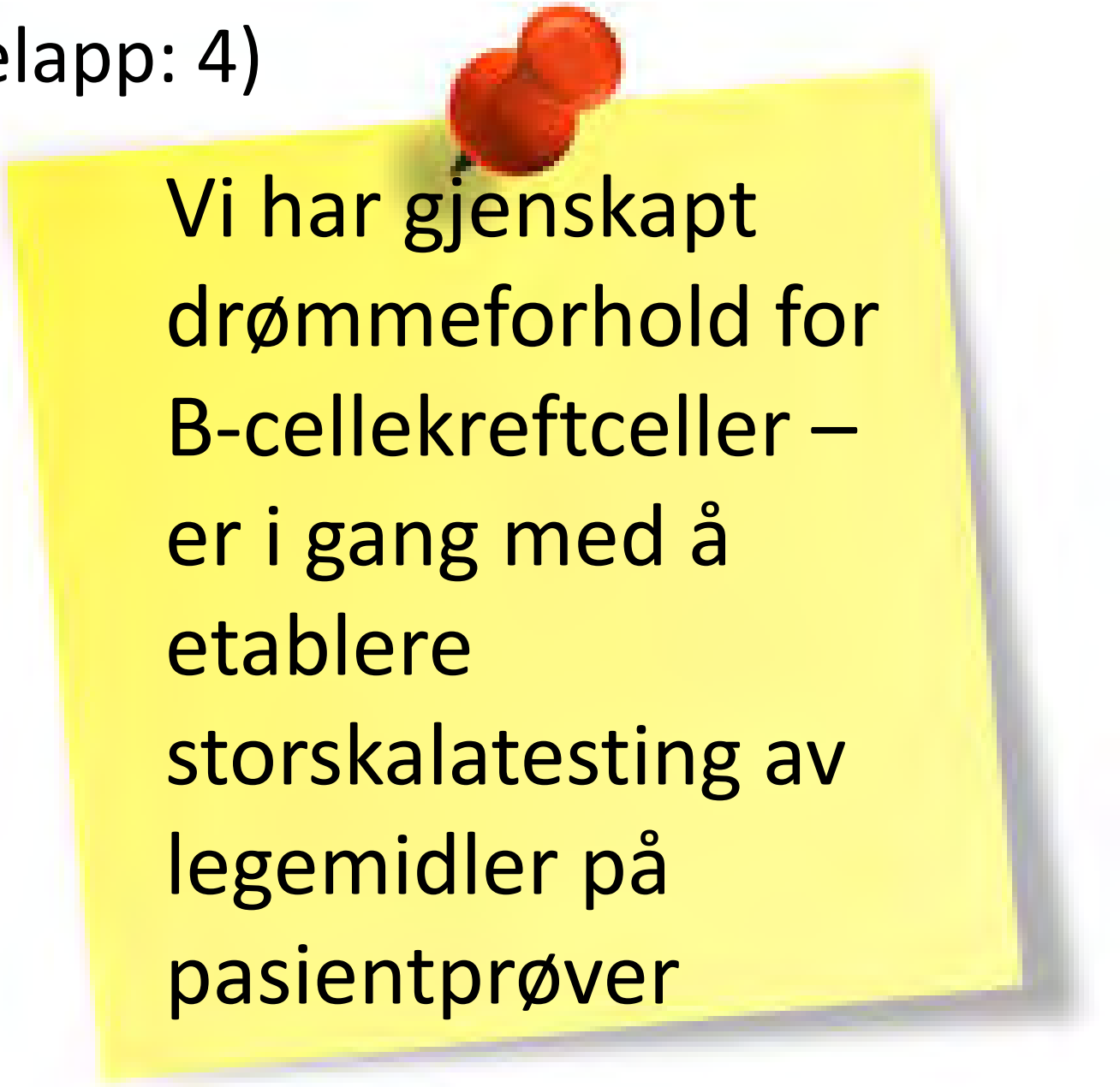


KLL
Myelomatose
(benmargskreft)



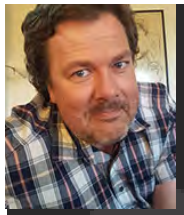
Har testet biologiske legemidler og småmolekylære signalhemmere

Merkelapp: 4)


Vi har gjenskapt drømmeforhold for B-cellekreftceller – er i gang med å etablere storskalatesting av legemidler på pasientprøver

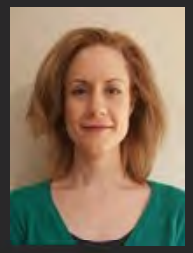
Sammendrag

- Kreftceller vokser ikke av seg selv – de stimuleres av omkringliggende celler
- Det er viktig å kartlegge hva som er drømmeforhold for kreftcellene for å definere angrepspunkter for behandling
- Det er viktig å etablere laboratorieteter som kan si noe om hva som har effekt på enkeltpasienters celler
- Dyrkning utenfor kroppen: det viser seg at det er celler som angriper kreftcellene, men at disse ikke har sluppet til. Viktig å følge opp.



Camilla Myklebust

Sandra Espada Serrano



CLL/MM

Simone Bürgler

Anna Parente Ribes

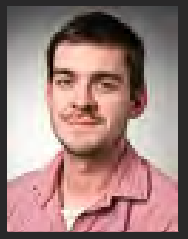
Ine Jørgensen

CLL

Wang Dong

MM

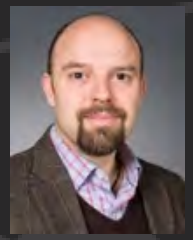
Anders Tveita



CLL/MM

Britt Nakken

Peter Szodoray

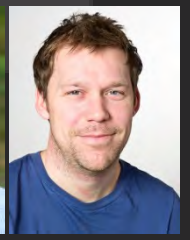


Geir Tjønnfjord

Yngvar Fløisand

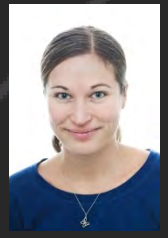
Jakob Dalgaard

Fredrik Schjesvold



CLL/MM MM MM MM

Sigrid Skånland



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