The Scientific, Social and Ethical Aspects of Prolonging Human Life

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The Scientific, Social and Ethical Aspects of Prolonging Human Life

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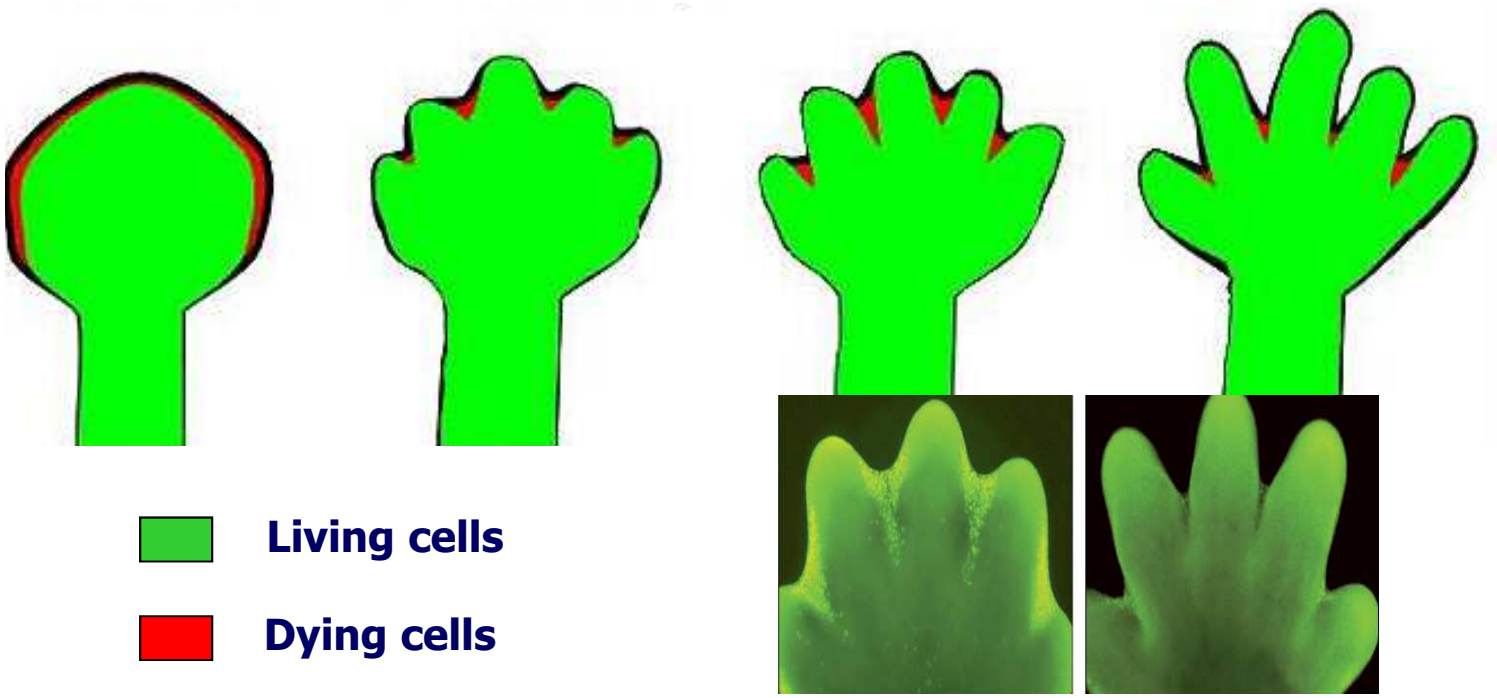
Symposium Science, Ethics and Society, Freiburg, 14.8.2015

No (Cell) Life
without
(Cell) Death

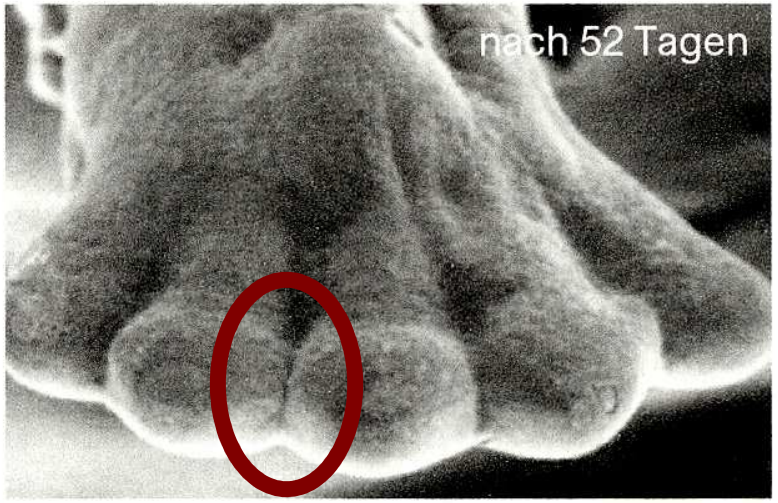
Formation of fingers and toes (digits) during embryonic, fetal development is programmed

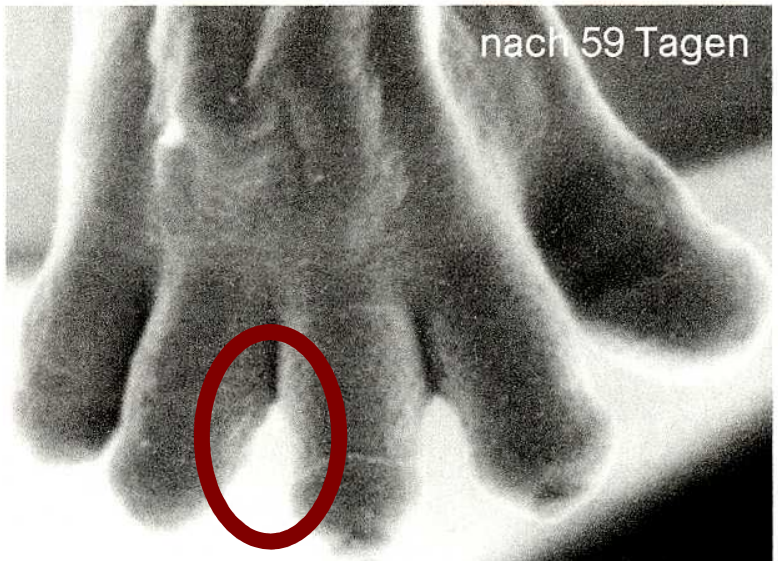
Cells die specifically between fingers and toes (interdigital cells) at a particular time



Source: Alberts et al. 2013

Interdigital cell death occurs exactly between day 52 and 59 in a human embryo



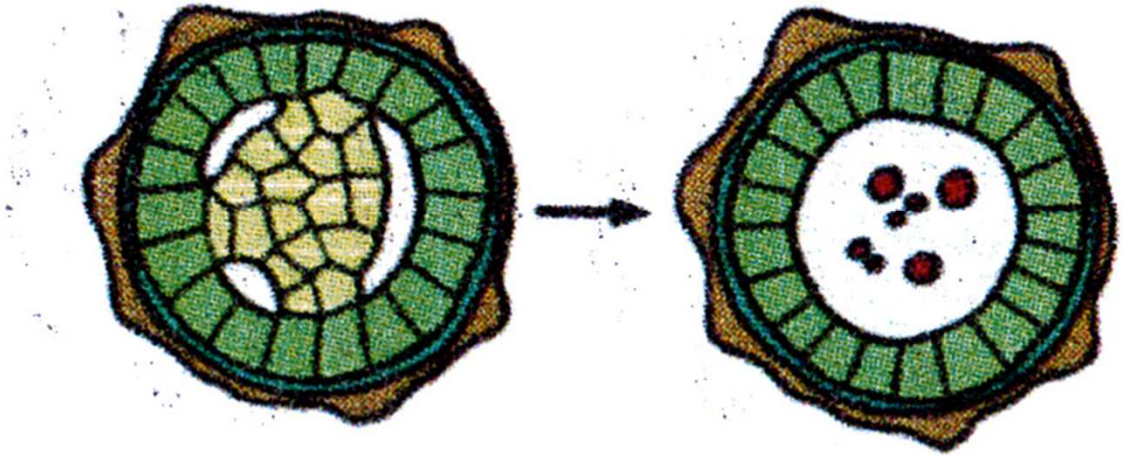


Interdigital cell death is not needed for ducks

Source: Alberts et al. 2013

Programmed cell death ensures the formation of hollow, tubular structures

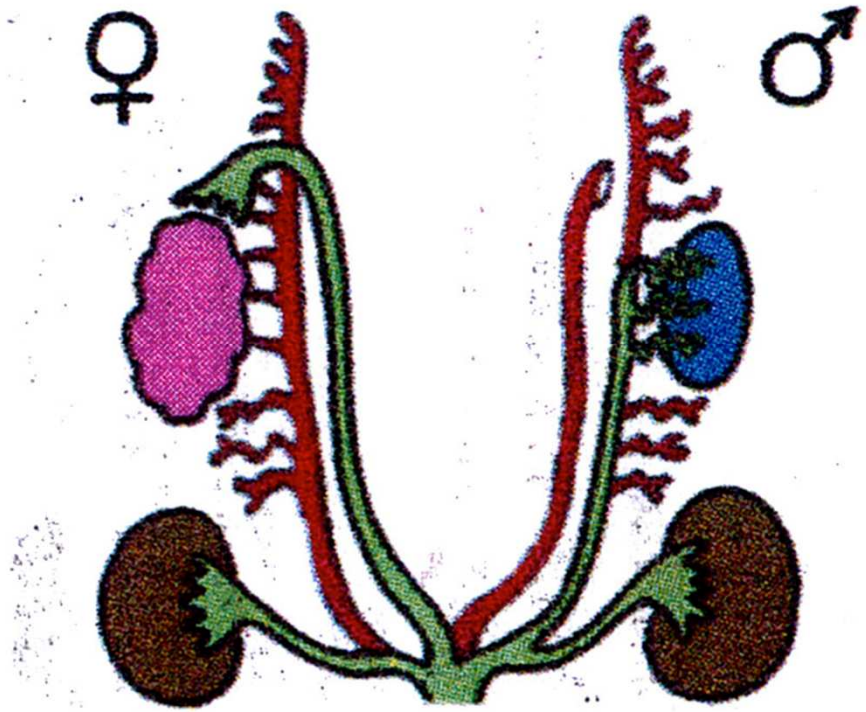
Blood vessels, peritoneum, digestive tract, glands, etc.



Source: Alberts et al. 2013

Programmed cell death is crucial for the formation of reproductive organs

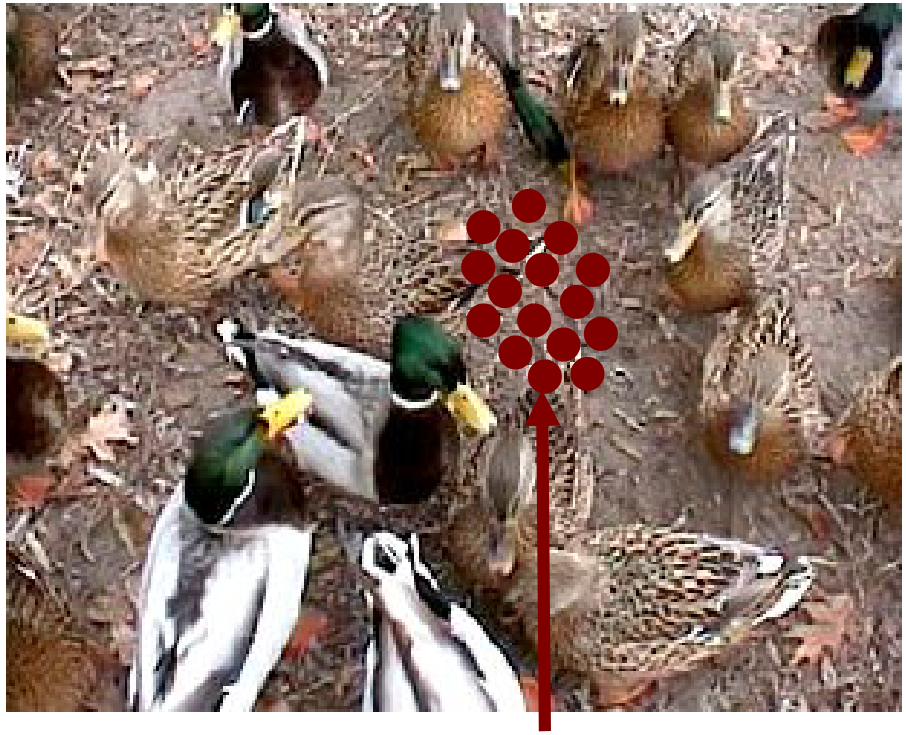
Initially both systems are formed, but during the development one of them degenerates due hormonal regulation



Source: Alberts et al. 2013

Only those cells („ducks") survive, which get enough nutrients/survival factors.
The rest has nothing to eat and dies

20 ducks

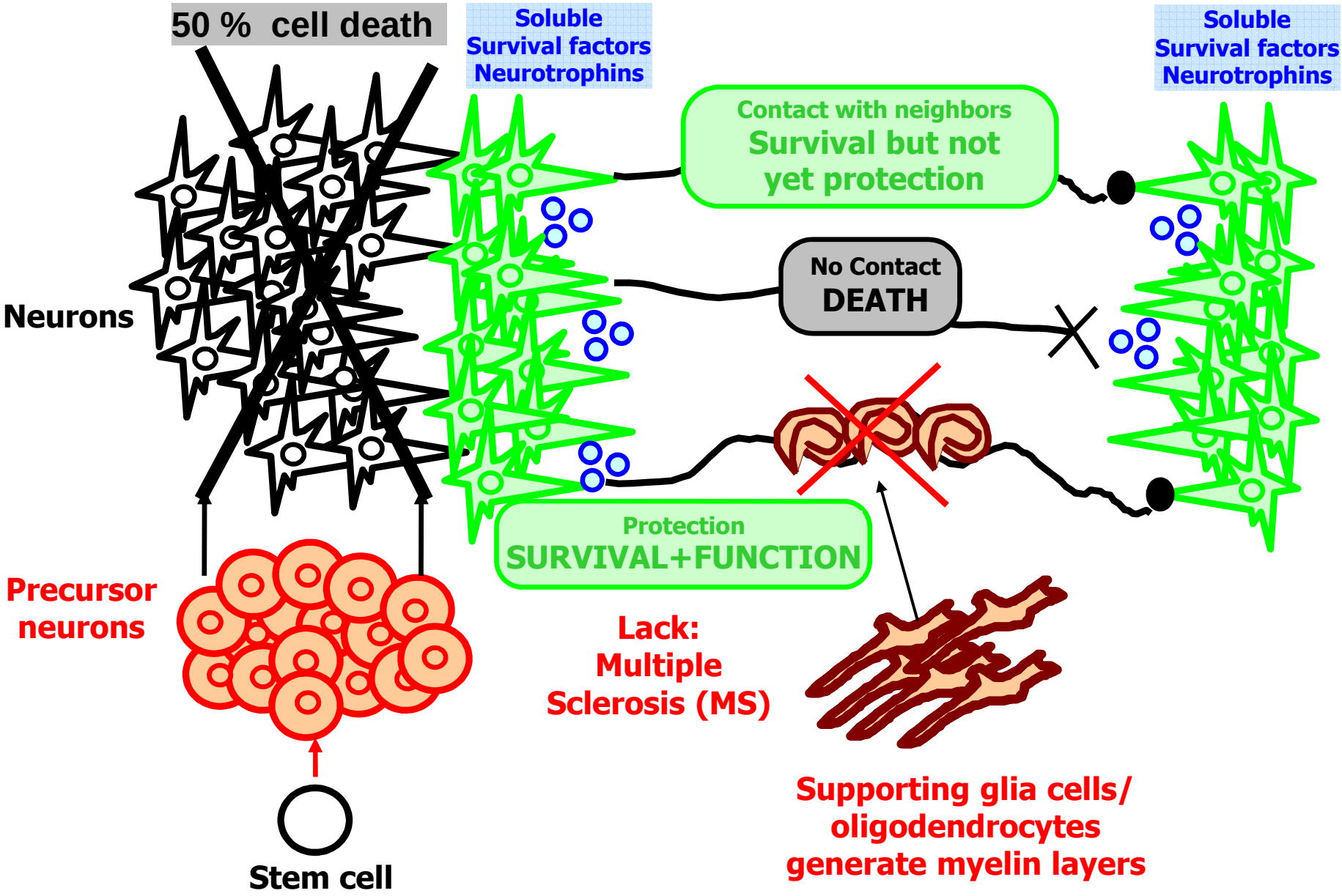


Limited amount of bread pieces

Only 8 ducks left

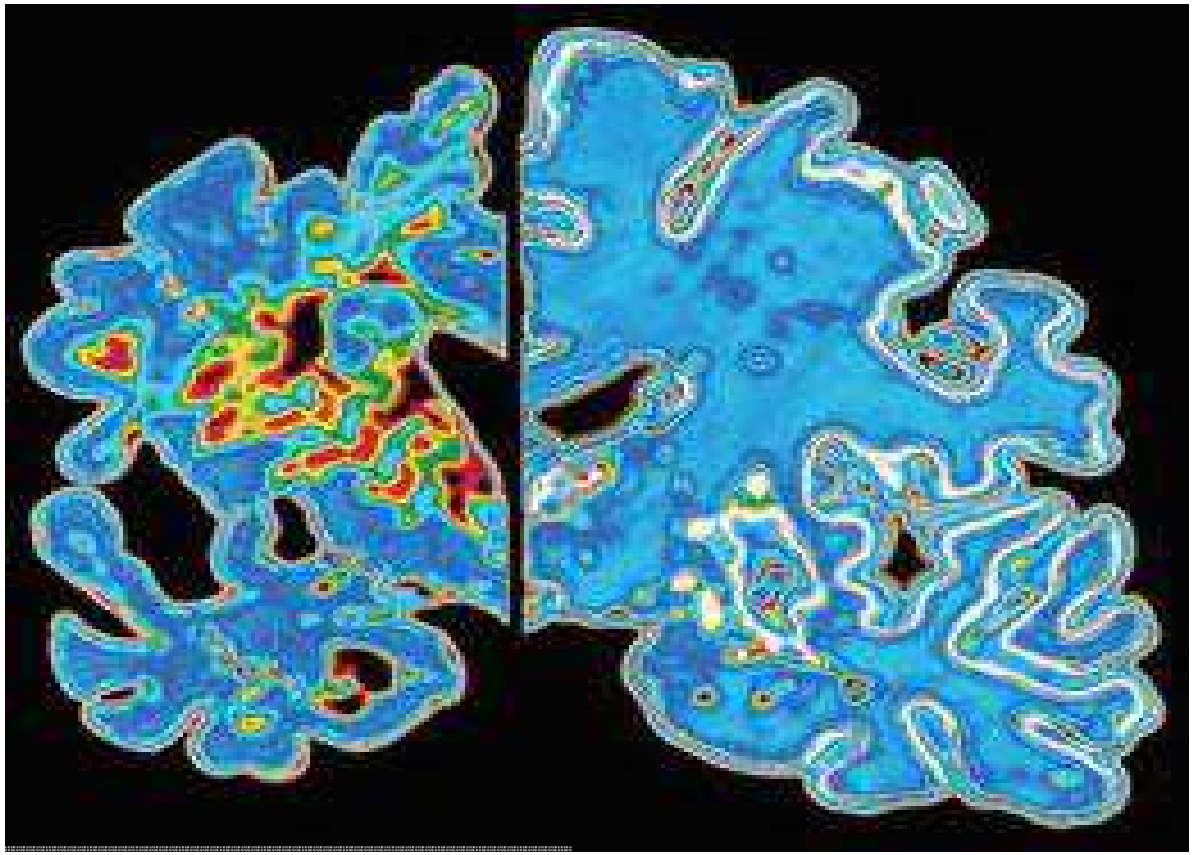
Survivors interact with each other and build a social network

Programmed cell death is essential to form the neuronal network



But can also go beserk if uncontrolled

Too much neuronal cell death leads to neurodegenerative diseases such as Alzheimer, Parkinson, Huntington, ALS, etc.



Alzheimer Patient
Shrunk brain half due to neuronal cell death

Healthy Individual

Where does programmed cell death occur in our adult body on a daily basis?

In regenerating tissues/cells:

- Blood/hematopoietic system
- Epithelia (skin, digestive tract, lung, liver, kidney)
- Blood vessels (endothelium)
- Peripheral nerves

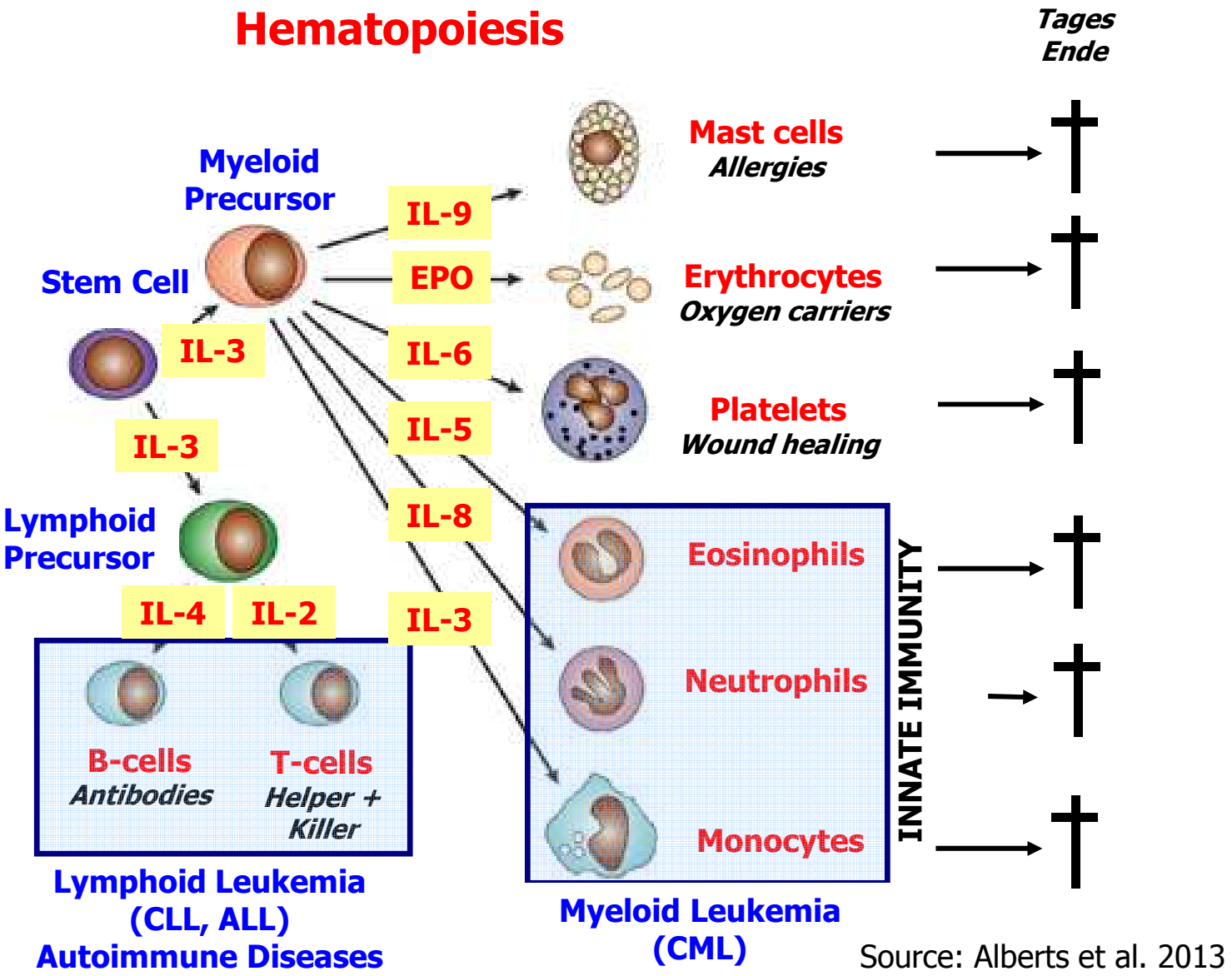
Not or only in limited amounts

- Central nervous system (brain, spinal cord)
- Muscles (skeletal, heart)

Average cell turnover in humans

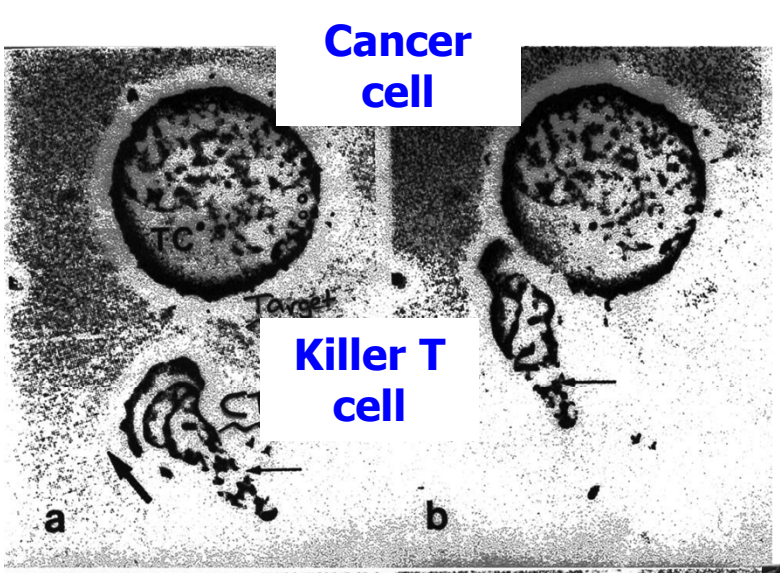
~ 1×10^{14} cells
~ 200 cell types
$\geq 1 \times 10^{6}$ turnover/sec

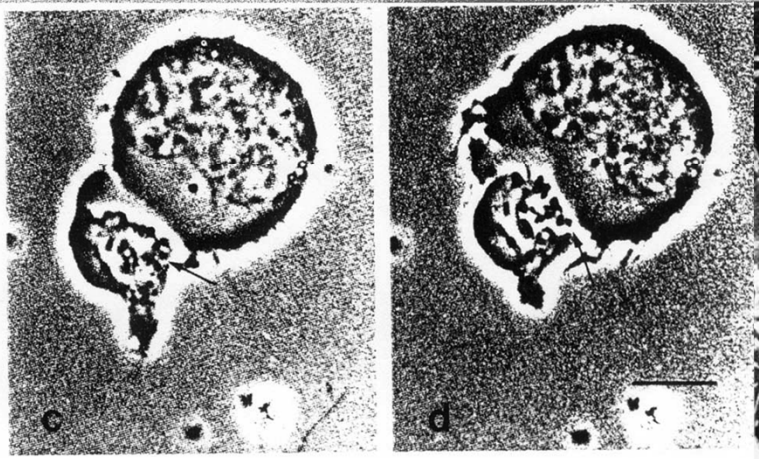
Programmed cell death is essential to correctly regenerate blood cells

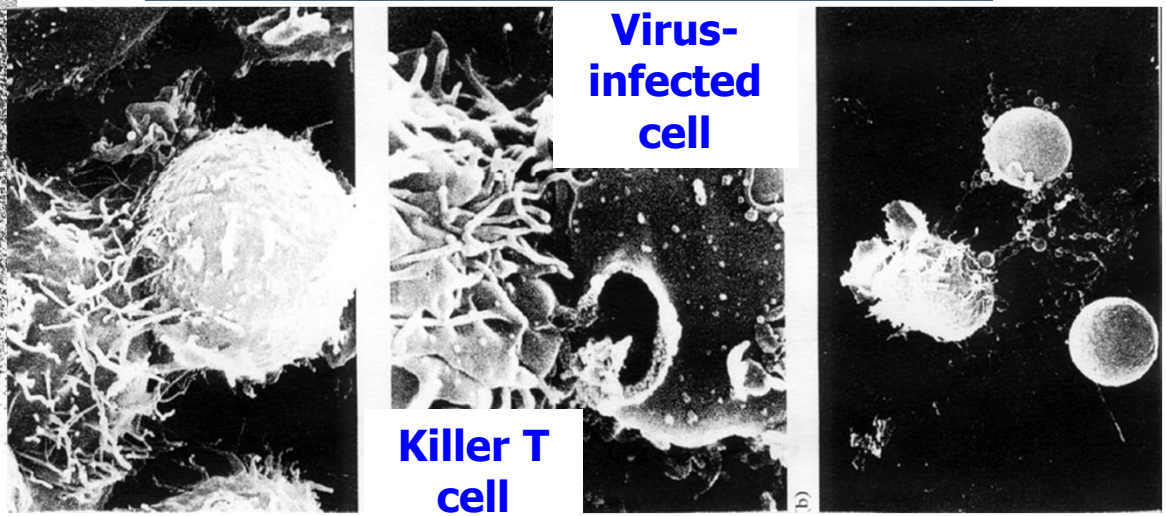


Source: Alberts et al. 2013

Interaction of killer T cell with infected cell: A fatal "KISS"





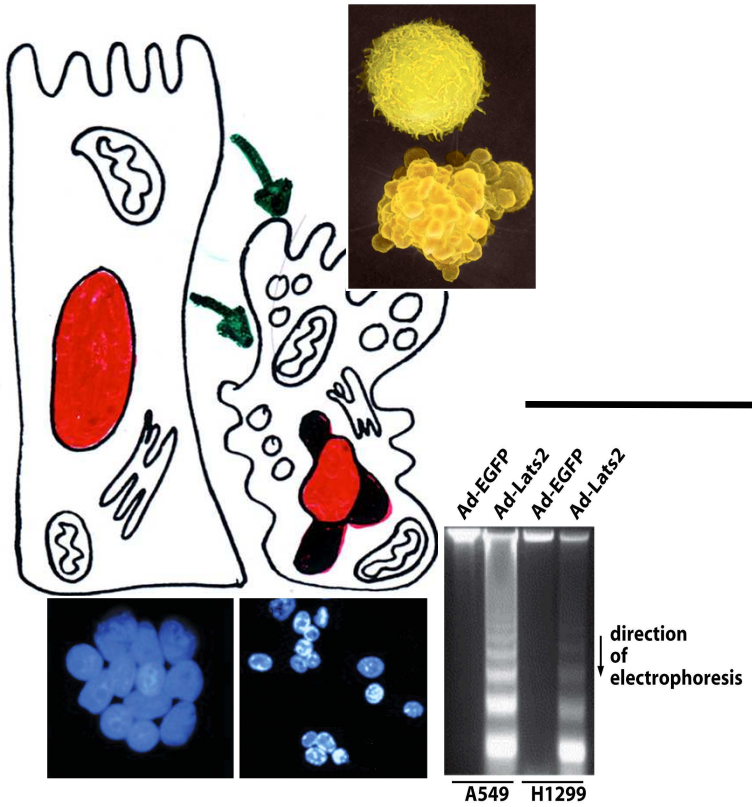


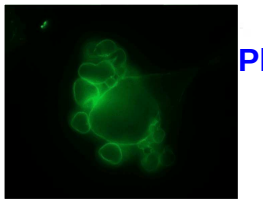
Source: Alberts et al. 2013

Programmed cell death of epithelia
(surface of the skin, intestine, organs, etc.)

- Outer cell layer of the skin (keratin packed flakes cornea, horny layer)
- Differentiated cells at the tip of intestine villi
- Breast epithelial cells after lactation

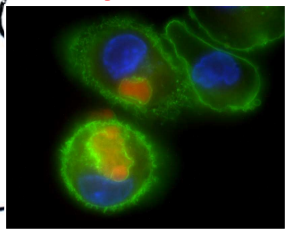
Most damaged, used-up or misplaced cells in our body die by APOPTOSIS





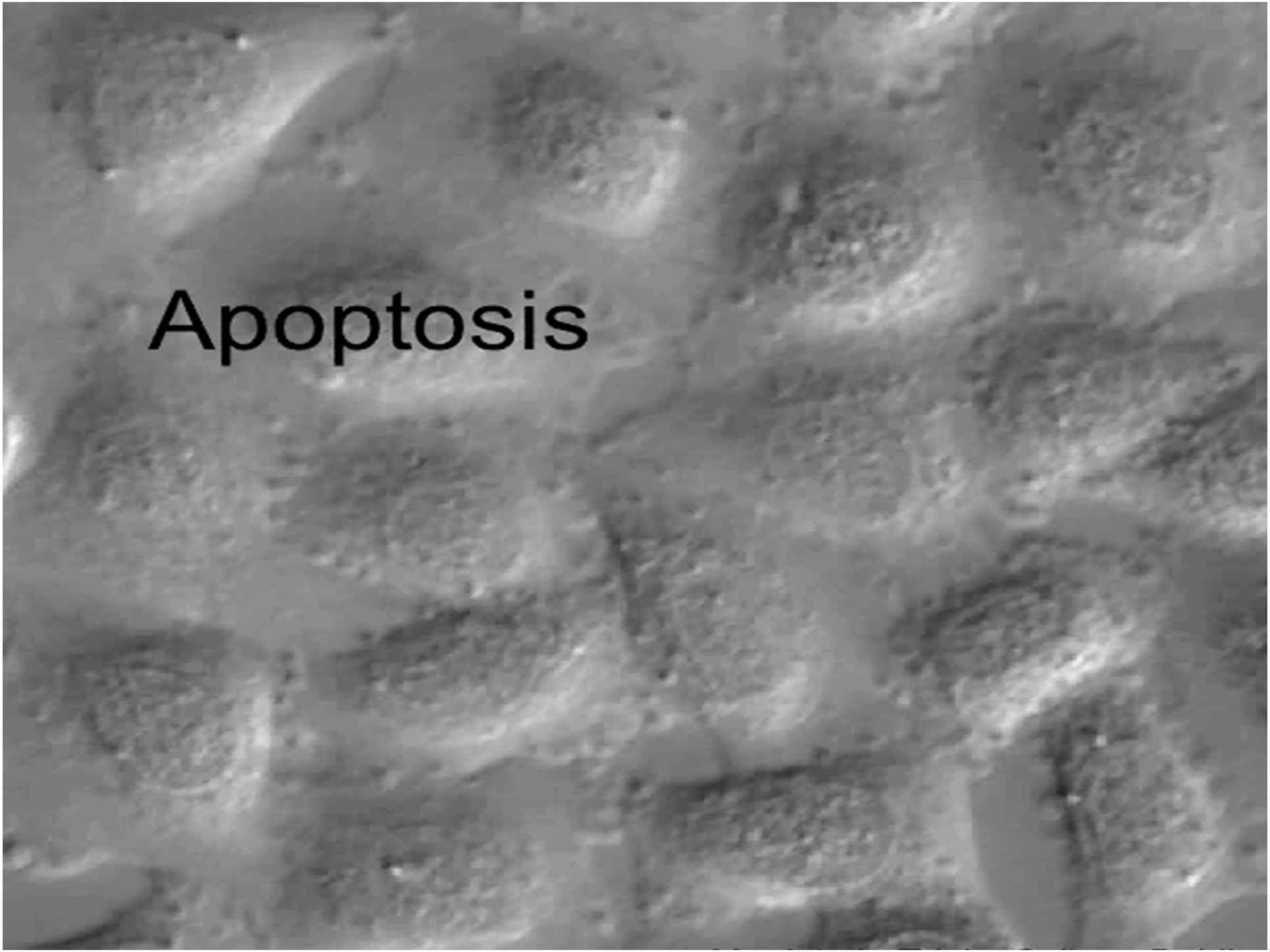
Phosphatidyl serine

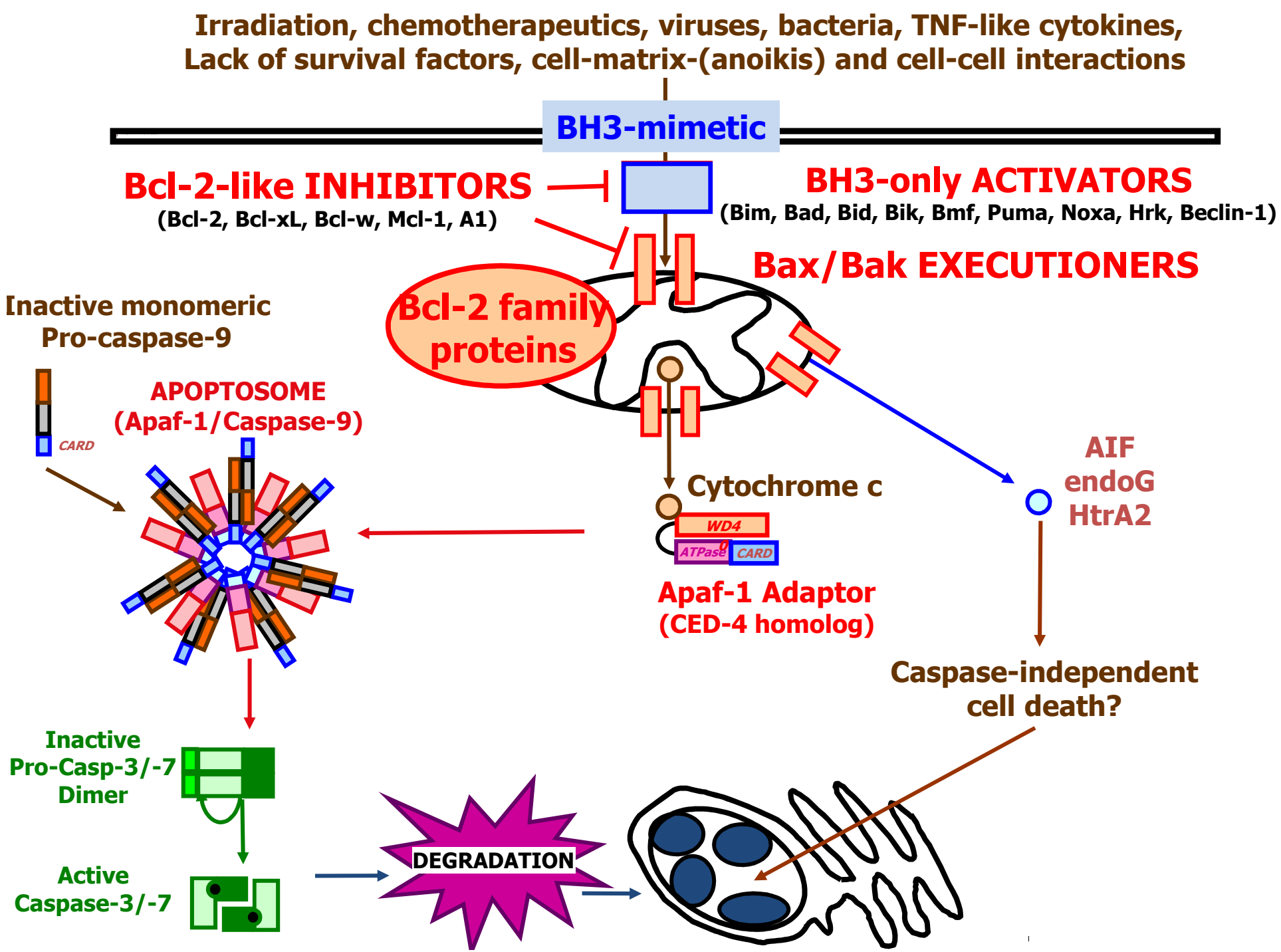
Inhibition of the production of pro-inflammatory cytokines



MØ

Phagocytosis


Apoptosis


Irradiation, chemotherapeutics, viruses, bacteria, TNF-like cytokines,
Lack of survival factors, cell-matrix-(anoikis) and cell-cell interactions
BH3-mimetic
Bcl-2-like INHIBITORS
(Bcl-2, Bcl-xL, Bcl-w, Mcl-1, A1)
BH3-only ACTIVATORS
(Bim, Bad, Bid, Bik, Bmf, Puma, Noxa, Hrk, Beclin-1)
Bax/Bak EXECUTIONERS
Bcl-2 family proteins
Inactive monomeric
Pro-caspase-9
CARD
APOPTOSOME
(Apaf-1/Caspase-9)
Cytochrome c
WD4
ATPase
CARD
Apaf-1 Adaptor
(CED-4 homolog)
AIF
endoG
HtrA2
Caspase-independent
cell death?
Inactive
Pro-Casp-3/-7
Dimer
Active
Caspase-3/-7
DEGRADATION

Is it possible and/or does it make any sense to prolong human life beyond 120 years?

Short answer is: NO!!!

Scientific Aspect

Accumulation of genetic defects/mutations with every cell cycle, even in quiescent cells

Regeneration Rate

~ 1×10^{14} Cells
~ 200 Cell types
$\geq 1 \times 10^{6}$ regenerate/sec

Error Rate for Mutations

~ 3×10^{9} Basepairs
Precision of repair: 10^{-9}
Per cell cycle: 3 bp mistakes
d.h. per sec 3×10^{6} mistakes

But: Most mutated cells die, mutations do not cause negative effects for the cells or fall into irrelevant genomic areas (introns, non-functional regions, wobble of the codon etc.) or aberrant cells are effectively eliminated by the immune system

In the end we may end up with one mutation per sec that is fix
But these mutations accumulate over 90-100 years of our life
and we can follow them now by rapid, whole genome
("next generation" or "deep" sequencing)

So when does it get dangerous, detrimental for us to develop diseases such as cancer

Only a small group of genes are crucial for carcinogenesis:

Oncogenes (gas pedal) and tumor suppressor genes (breaks)
Allelic mutations in tumor suppressor genes can be inherited

MUTATIONS IN THOSE GENES PROVIDE TO THE CELLS
A SELECTION ADVANTAGE
FOR CELL PROLIFERATION AND/OR SURVIVAL

Like DARWIN: Mutation – Selection – Evolution (of Tumors)

Tumor formation: Several genetic changes

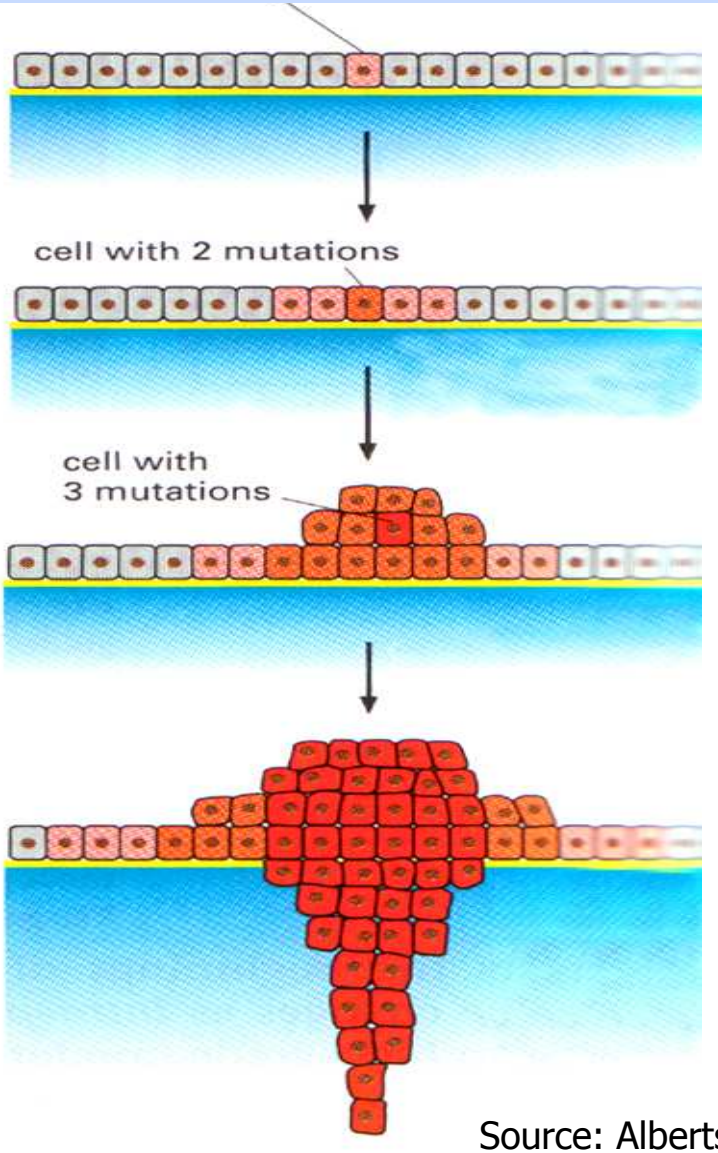
Uncontrolled cell division and lack of cell death of damaged, used-up cells

Accidentially a damaged, used-up cell does not die anymore due to a genetic change (mutation)

A second genetic change (mutation) leads to enhanced cell division of the damage cell but still controlled

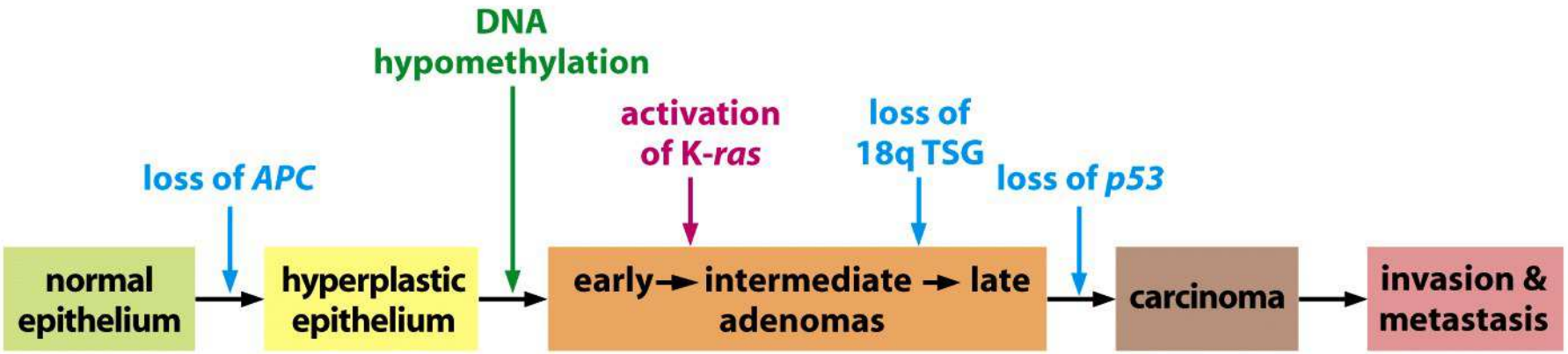
3 genetic changes (mutations) trigger uncontrolled cell division, but still benign tumor

4-6 or more genetic changes leads to malignant tumor; it breaches the barrier, emigrates into the blood and spreads to other tissues (metastasis)



Source: Alberts et al. 2013

Several Genetic Changes Characterize a Multistep Carcinogensis Process



Leukemia: ca. 3 mutagenic events

Carcinoma: ca. 7 mutagenic events

Newest Studies on Breast Cancer Profiliing (Gene Arrays):

178 Genetic Changes

11 Carcinogenic

Source: Alberts et al. 2013

Origin of genetic changes (mutations) which lead to tumor formation

i.e. that cells survive and divide in uncontrolled ways

Chemicals, toxins, asbest, smoking, alcohol
bad nutrition
(high in fat, nitrates, salt, fried, grilled food low in vegetables and fibres)

Irradiation
(UV, gamma, X-ray, radioactivity)

80%

Caused by life style i.e. mostly PREVENTABLE

Tumor Viruses
Papilloma (cervical cancer)
Hepatitis (liver cancer)
Epstein Barr (lymphoma)

10%

Regular check-ups Vaccination

Inheritance
Transmission parent-child

10%

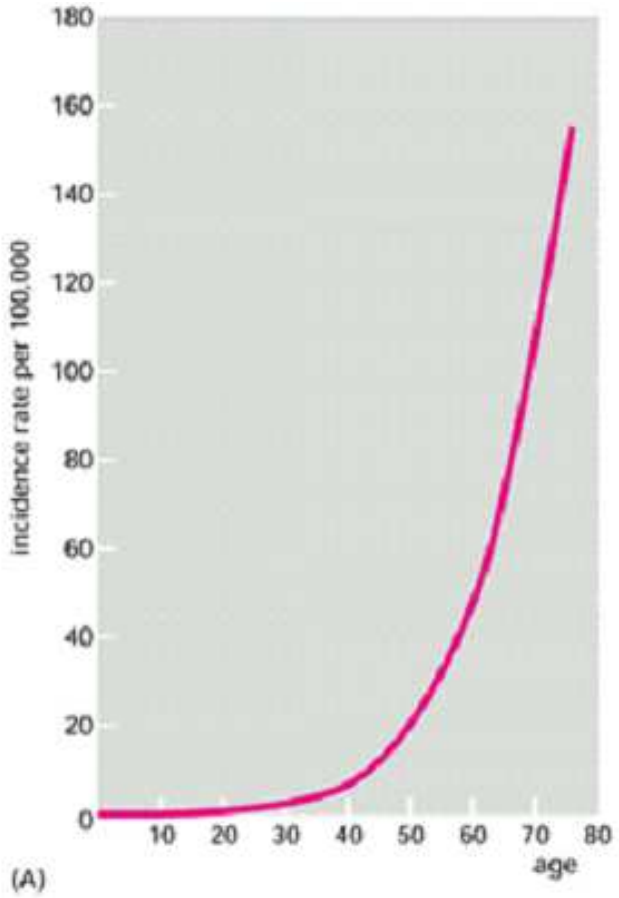
Prophylaxis Genetic screening Check-ups

Tumorincidence and Mortality

Absolute number of tumor diseases is **increasing!**
But....

The age-adjusted/-standardized tumorincidence
remains constant !!!

The age-adjusted/-standardized tumor mortality
is slowly decreasing !!!



Source: Weinberg 2011

Anti-cancer treatments

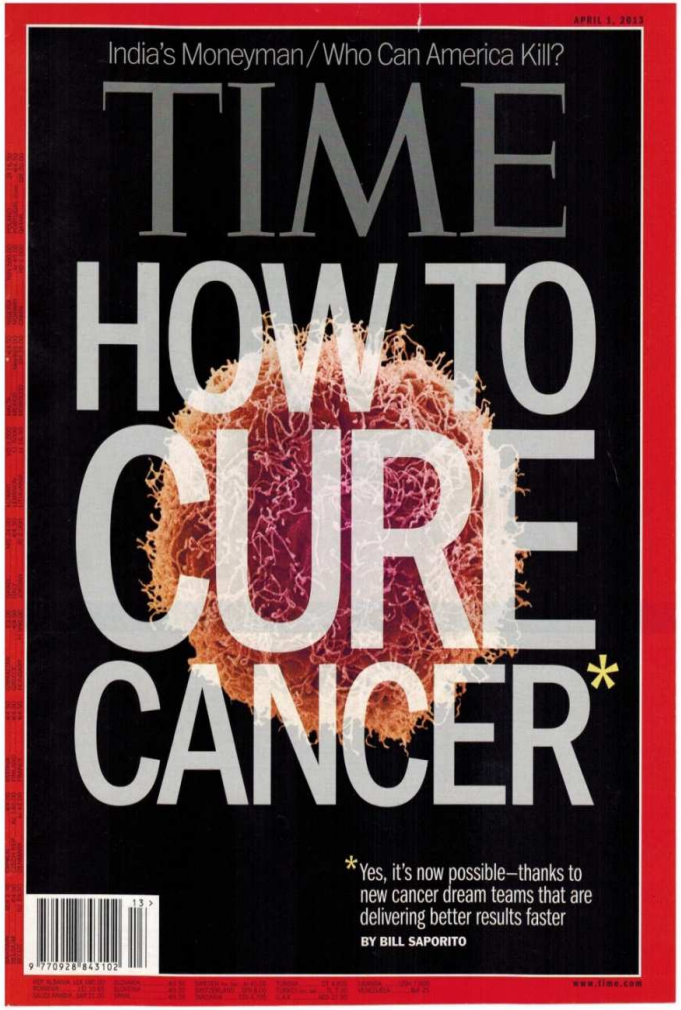
We can and will be able to save more young and older people from cancer with better targeted, precision therapy

But

Cancer cells will always find ways around, activate other constitutive proliferation and survival pathways and accumulate more mutations which confer treatment resistance

The older we get, the more likely this is
We will never outrace cancer completely, never win the war against it entirely if we want to live longer

How do we treat cancer today?



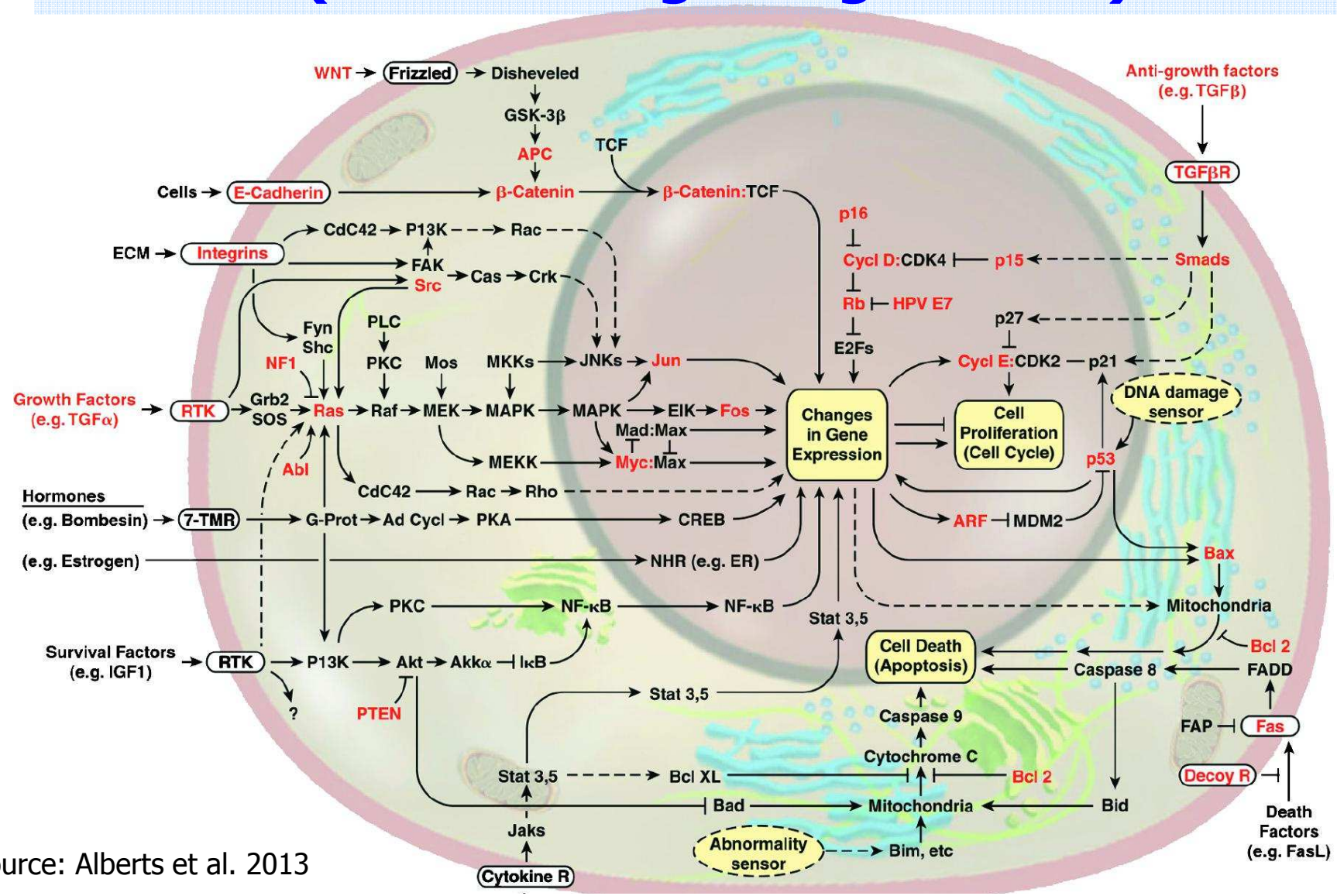
In the past and still ongoing

- Cytotoxic drugs

Now and in the future

- Targeting the "hallmark" pathways by
  - monoclonal antibodies
  - small molecule (e.g. kinase inhibitors)
- "Liberating" endogenous immunity
- Transgenic T cells
- Gene therapy?
- Supportive drugs and care

Targets for precision therapy are components of survival and proliferation pathways (Cancer = signaling disease)



Source: Alberts et al. 2013

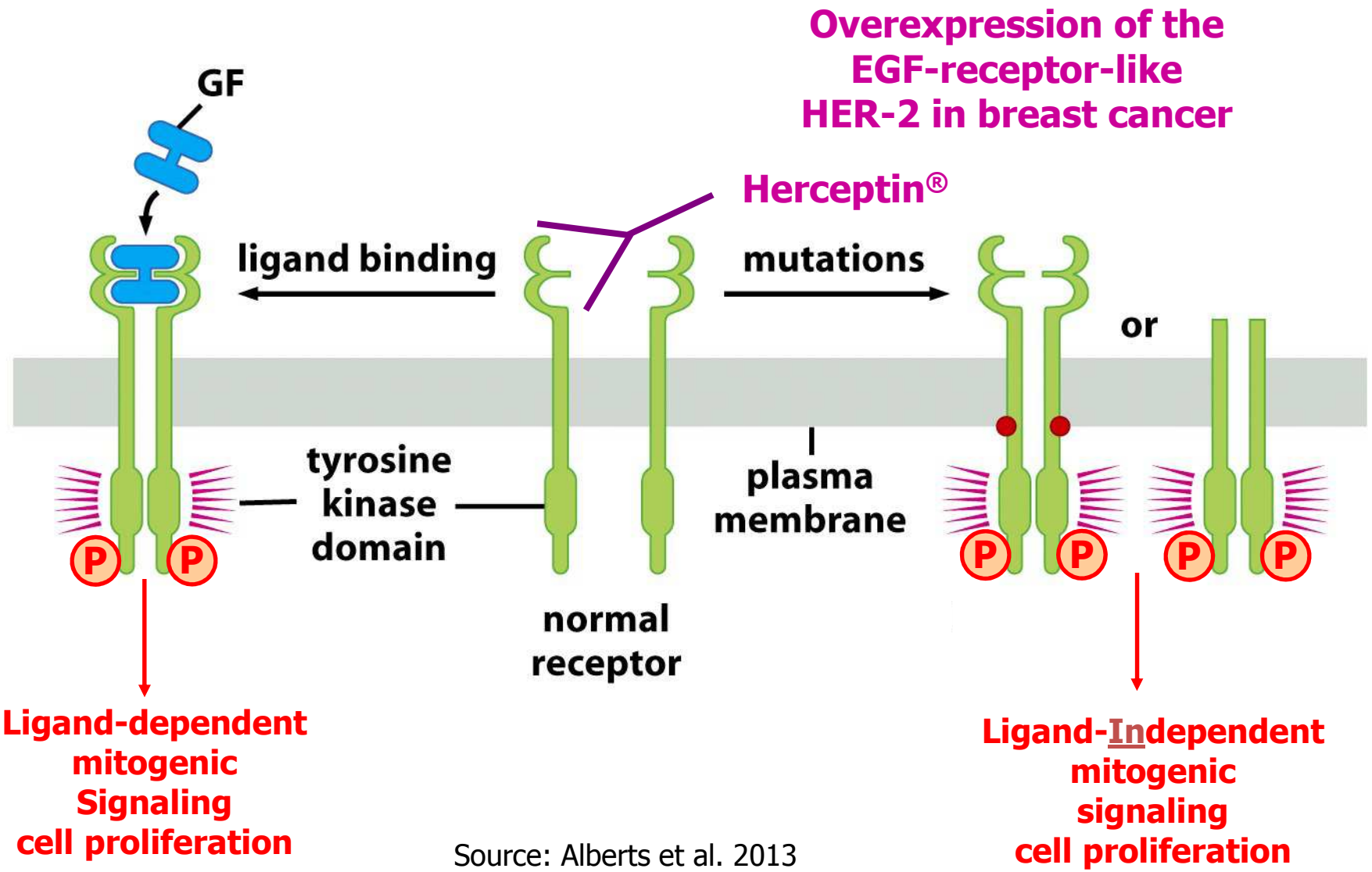
How does precision therapy look like?

Hit the target which the cancer cells entirely depends on (are „addicted" to) The most robust nodule in the pathway

But

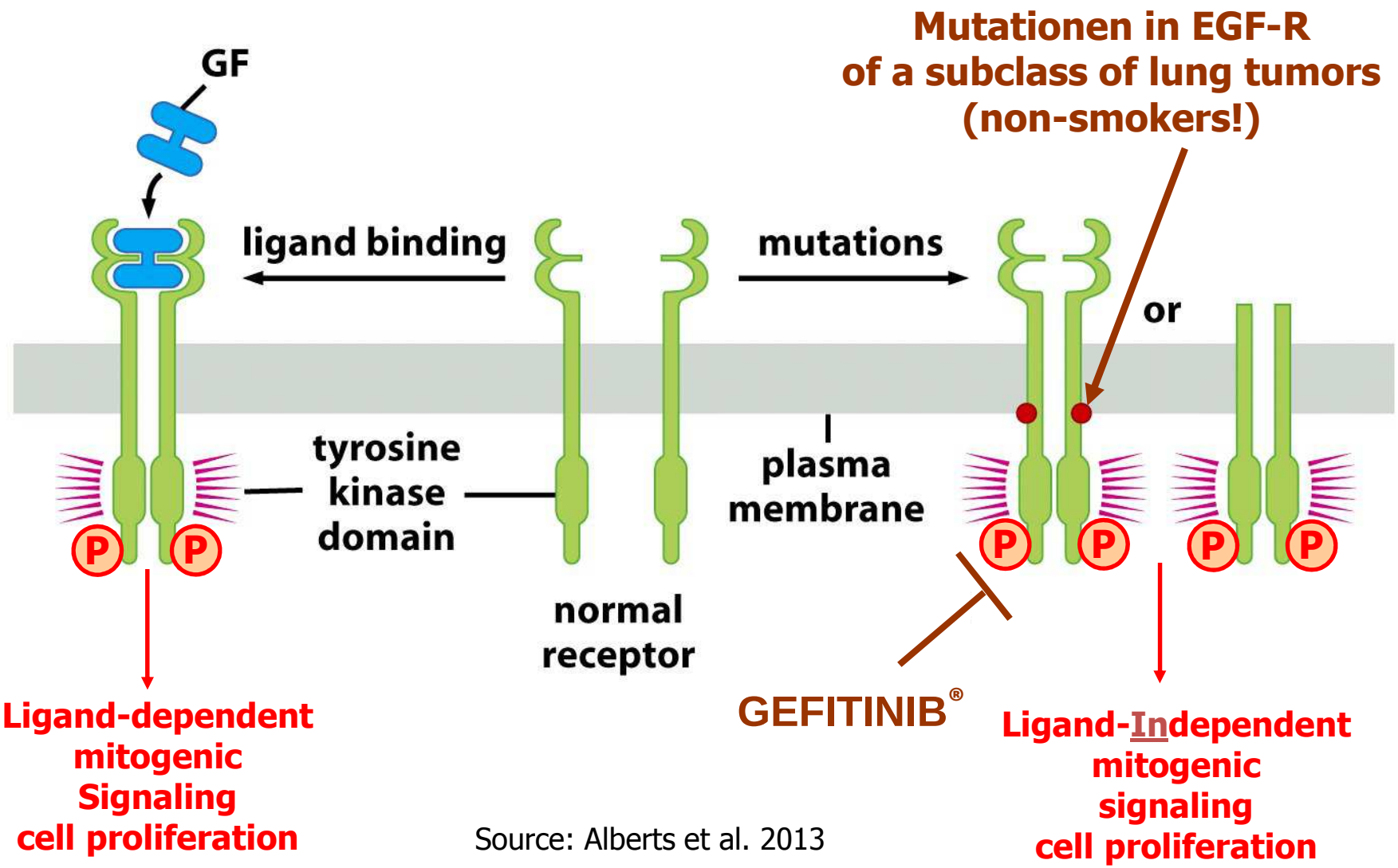
This is not always the case, as cancers have mutations in several genes which contribute to carcinogenesis requiring combination therapies

Block overexpressed, constitutively active, dimerized HER2 receptors with antibodies in breast cancer
(Herceptin, Trastuzumab)



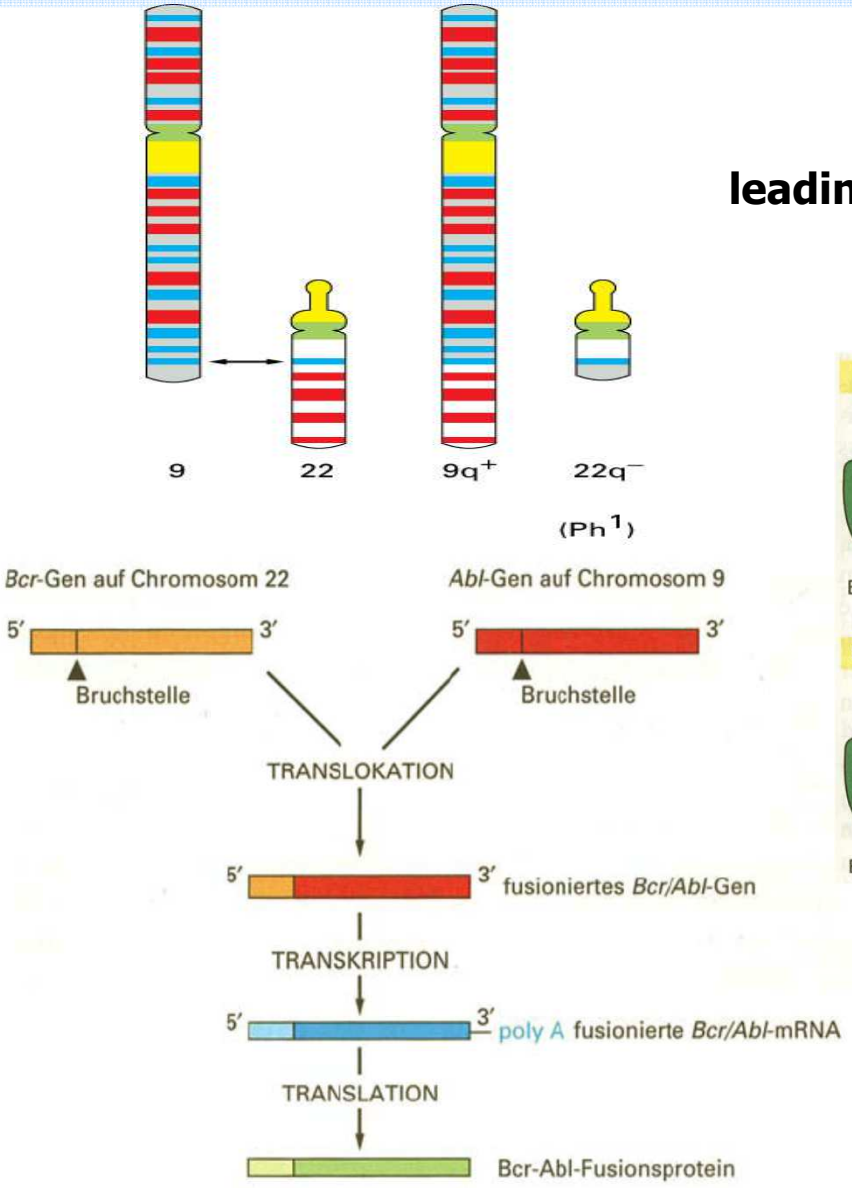
Source: Alberts et al. 2013

Inhibit constitutively active, mutated EGF receptors with small molecule inhibitor in lung cancer
(Iressa, Gefitinib)

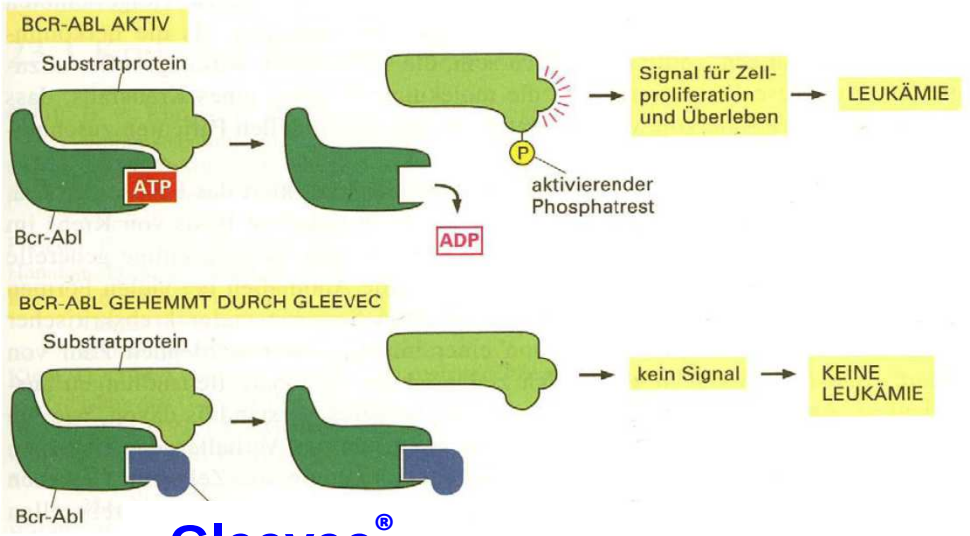


Source: Alberts et al. 2013

Inhibit constitutively active BCR-ABL protein kinase with small molecule inhibitor in CML (Gleevec, Imatinib)



Translocation t(9;22)
(Philadelphia chromosome)
leading to a BCR-ABL fusion and the generation of chronic myeloid leukemia (CML)

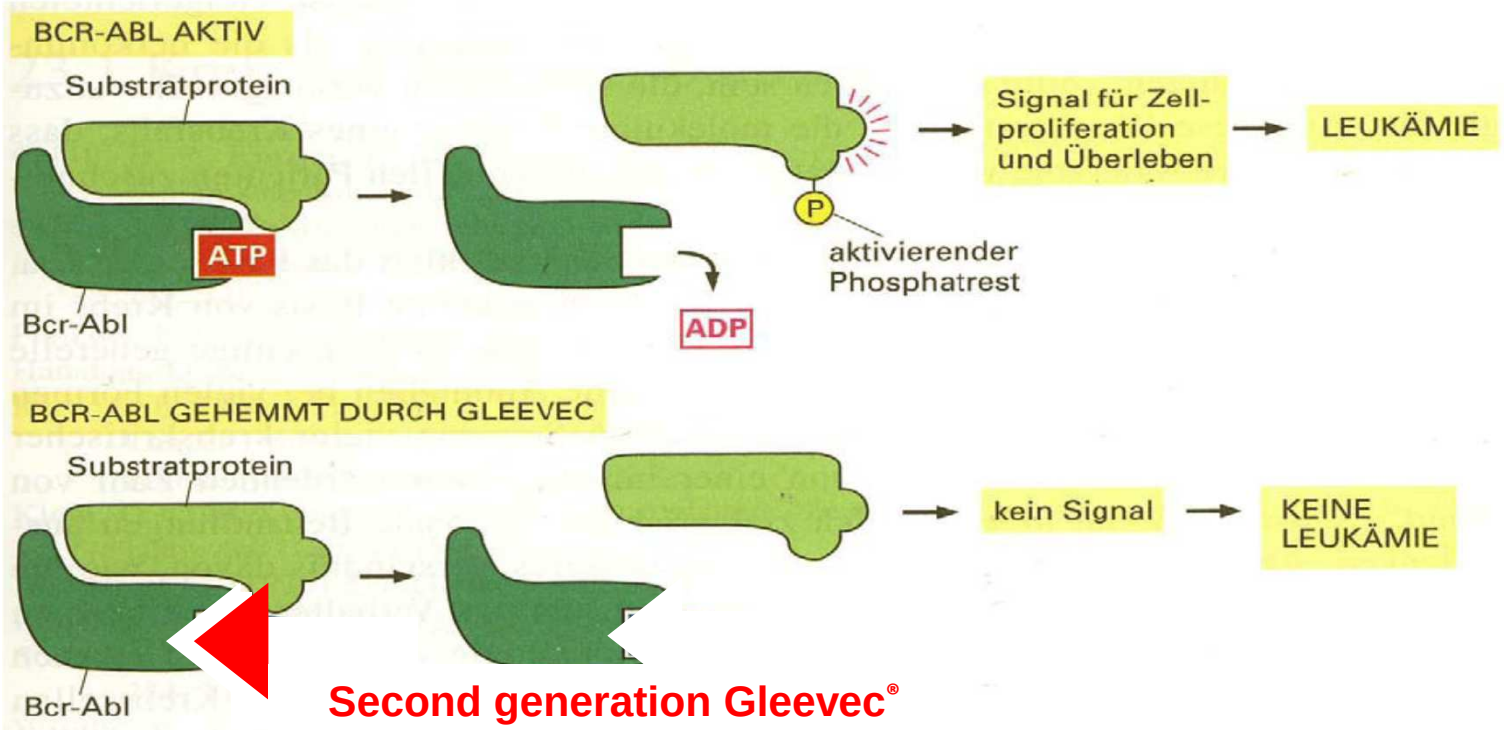


Gleevec®

Source: Alberts et al. 2013

Development of treatment resistance

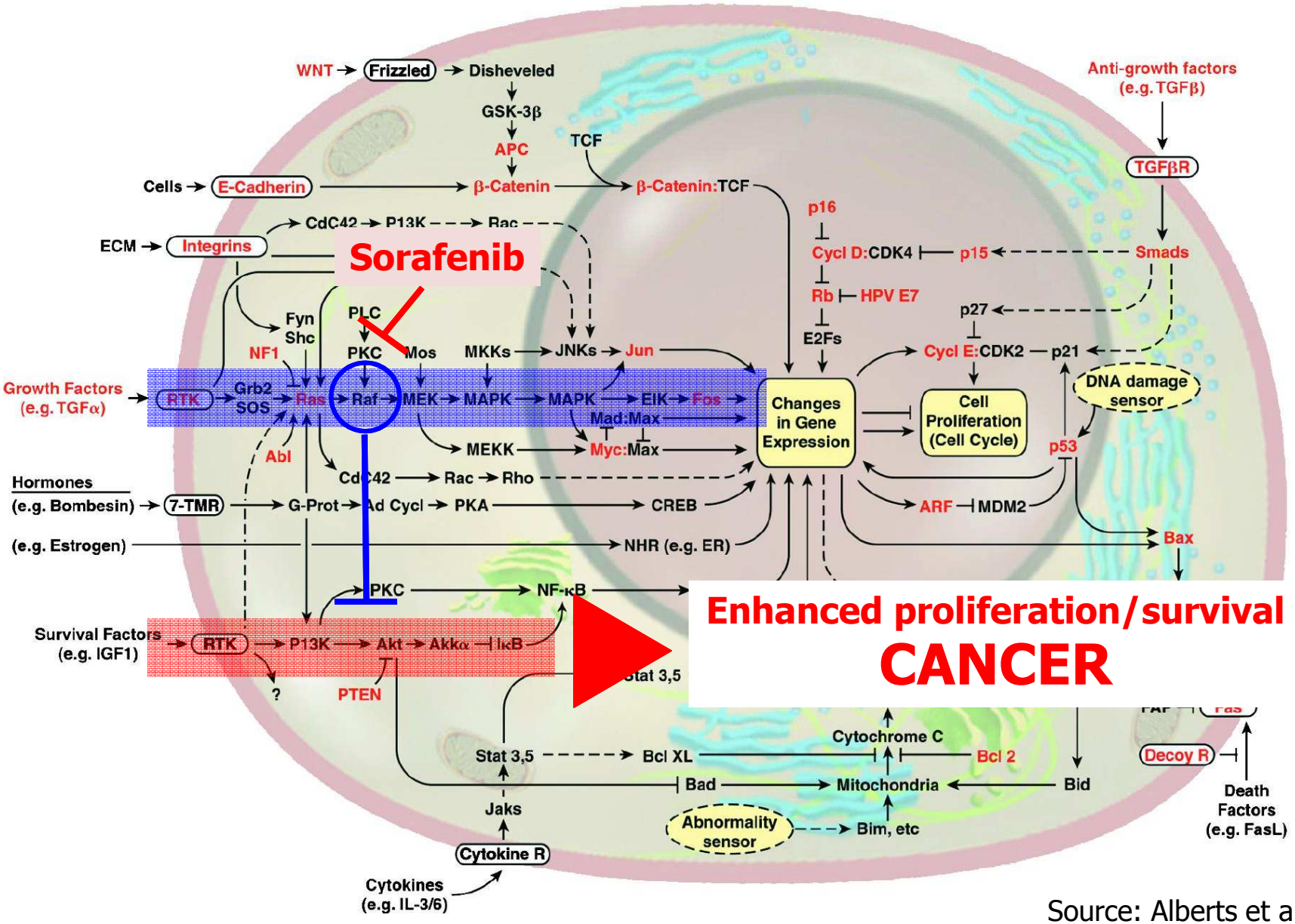
Mutated BCR-ABL protein kinase is not inhibited by Gleevec anymore
Second generation drug is needed



Source: Alberts et al. 2013

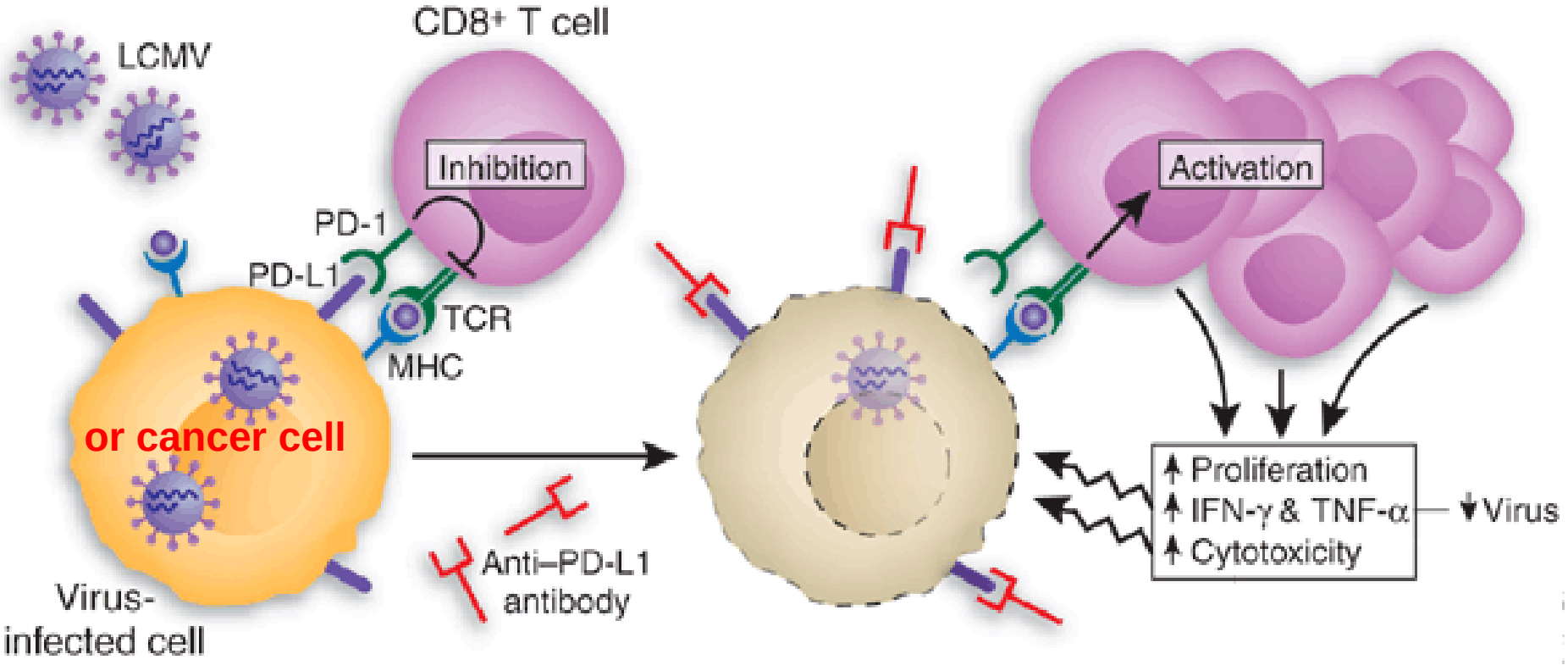
Survival/mitogenic pathways have negative feedback loops to shut down parallel pathways

If you block the former
the latter becomes active (Vemurafenib, B-Raf inhibitor)



Source: Alberts et al. 2013

Cancer immunotherapy using anti-PD-L1



Nature Medicine **12**, 276 - 277 (2006)

We are prone to die because we are not perfect and nature is so complex that it will always find a way around our treatment impact

Nature is so fascinating that humans will never understand it completely

Christoph Borner, PhD thesis 1988

Almost a bit theological, spiritual

Social Aspects

- Overpopulated earth
- Not enough resources to feed all people
- Not enough resources to provide jobs for all people
- Problem of financing the elderly
- Increased health costs

Ethical Aspects

Whole genomes sequencing to find errors – the bad genes

- **Surge of information that we cannot (yet) understand**
- **Problems of counseling, do we tell everything?**
- **Who has the right to know what?**
- **How are the data stored and distributed?**
- **How can we prevent that data get into wrong hands?**
- **What about defects for which we do not have any medicine?**

Ethical Aspects

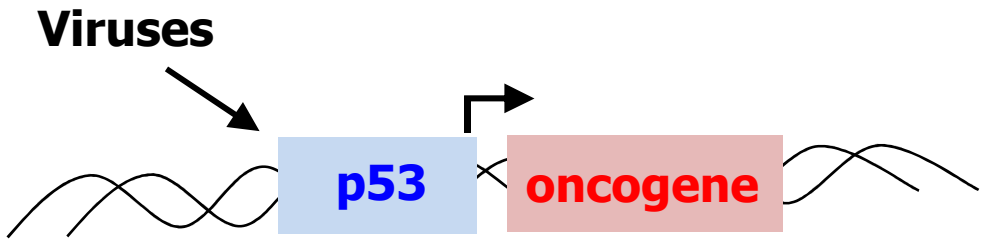
Improve repair system so that less mutations accumulate

- **How are we going to do that? Overexpress a specific repair gene?**
- **Giving a pill that improves repair?**
- **Even if it worked, how can we prevent mutations in repair genes?**

Ethical Aspects

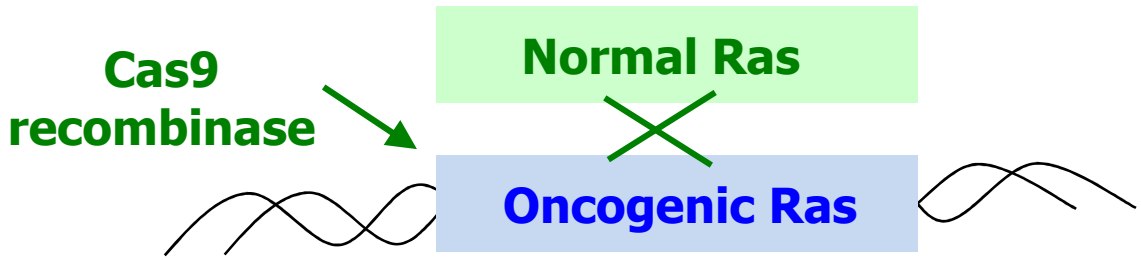
Insert good genes by viral-mediated gene therapy or replace bad genes by good genes by homologous recombination (CRISPR/Cas)

Viruses insert into genome randomly
Danger to activate an oncogene



Homologous recombination via CRISPR/Cas9 faithfully replaces defective gene

Problems: Off-target effects, Transfer to next generation
Playing God



Ethical Aspects

Prolong life by caloric restriction or use a pill which activates longevity signaling pathways

Caloric restriction in worms, flies and mice prolongs their lives

Could humans live to 500 years old? Scientists believe genetic tweaks could significantly extend our lifespan
(Mail Online Dec. 2013)

Single mutations in the TOR pathway were known to extend the lifespan of C. elegans by 30 per cent, while insulin-signalling mutations could double the amount of time they lived.
Adding the two together might have been expected to extend longevity by 130 per cent, but the combined impact turned out to be much greater.
(Pankaj Kapahi, Buck Institue of Age Research, Novato, California)

Problems: Humans would starve with the caloric restriction necessary
Side-effects of blocking the insulin/mTOR pathways

2015: 10 Rules to prevent Cancer

1. Do not smoke.
2. Do not smoke.
3. Do not smoke.
4. Avoid carcinogens: asbestos, UV-light, aflatoxine.
5. Diet: moderate in calories, salt, fat, little alcohol. .
6. 3 x daily fresh fruit and vegetable
7. Exercise and watch your weight.
8. Vaccination (Hepatitis B, HPV) and treatment of (*H. pylori*) chronic infections.
9. Good genes.
10. Good luck!!

Paul Kleihues 2007