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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Scientific Aspect

Two major principles of aging

1. **High turnover tissues/cells are not properly eliminated any more, they accumulate non-repairable mutations and develop disease**

2. **Tissues/cells are lost from our body because they die (due to mutations or injury, etc.) and cannot be replaced**

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

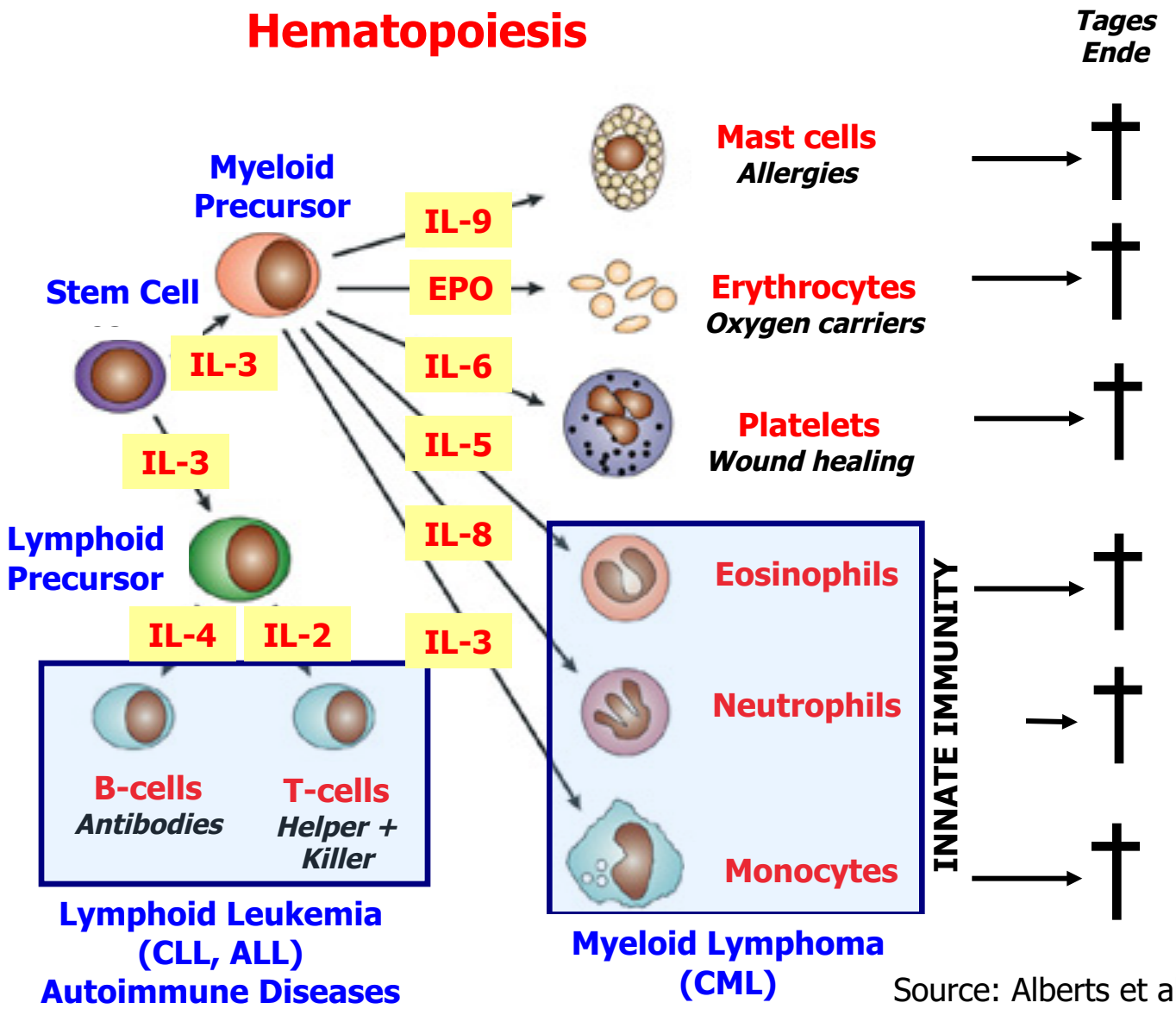
Not or only in limited amounts

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

Average cell turnover in humans

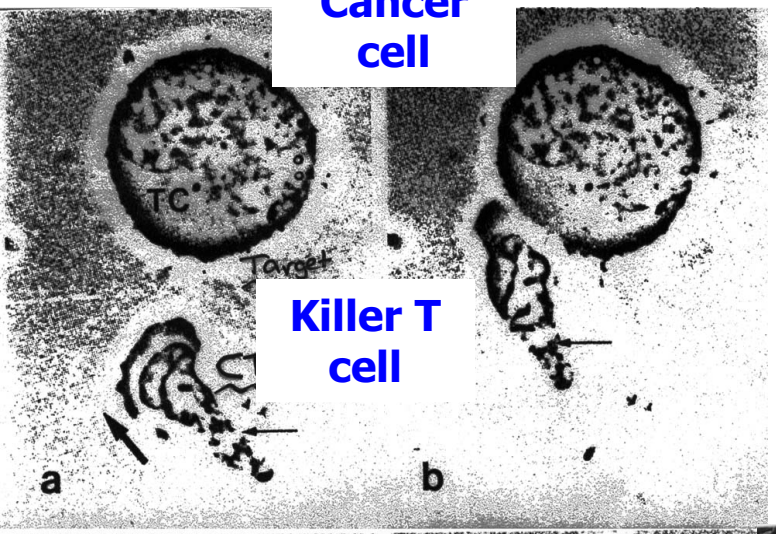
$\sim 1 \times 10^{14}$ cells
$\sim$ 200 cell types
$\geq 1 \times 10^{6}$ turnover/sec

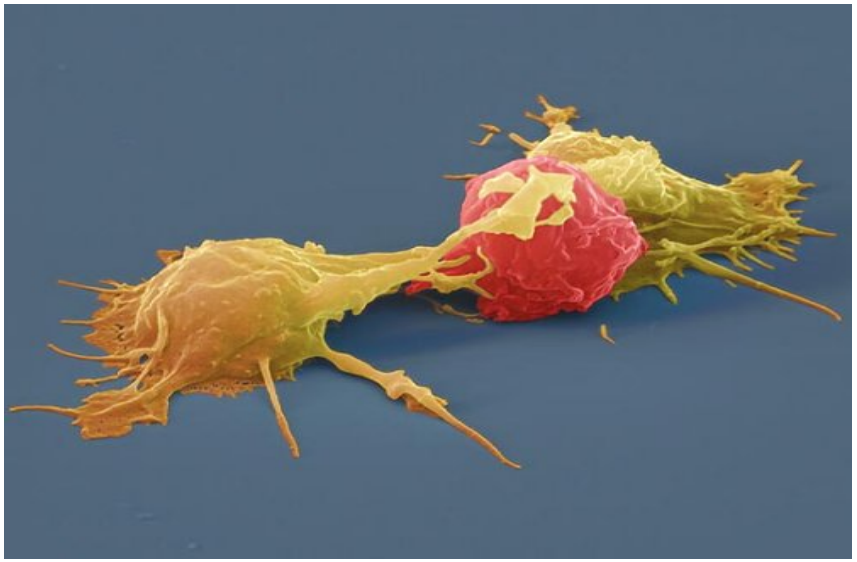
Programmed cell death is essential to correctly regenerate blood cells

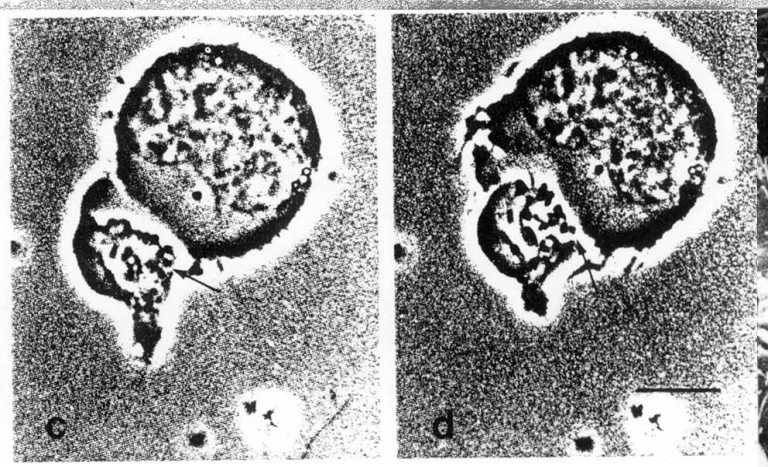


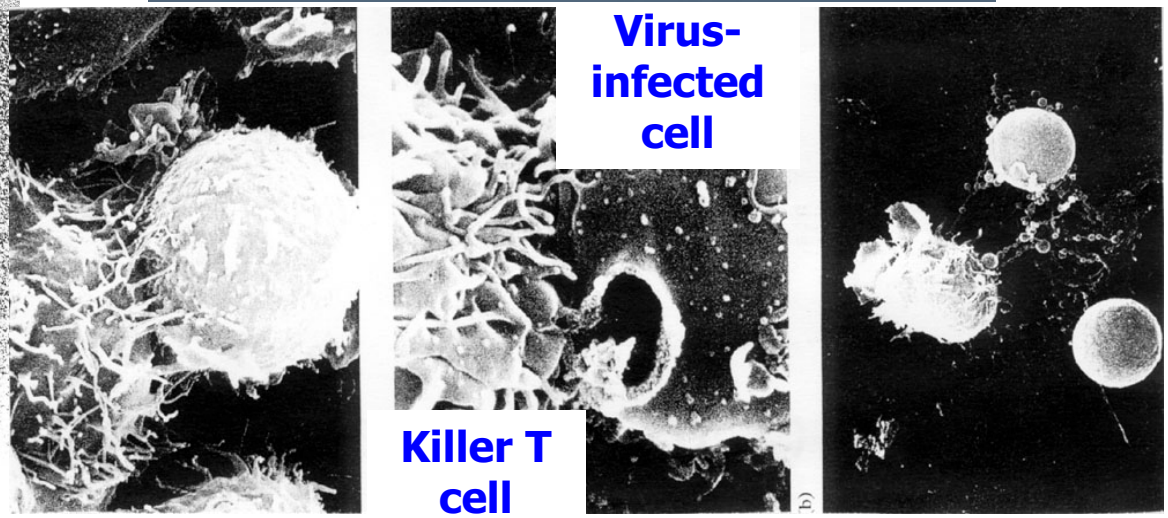
Source: Alberts et al. 2013

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







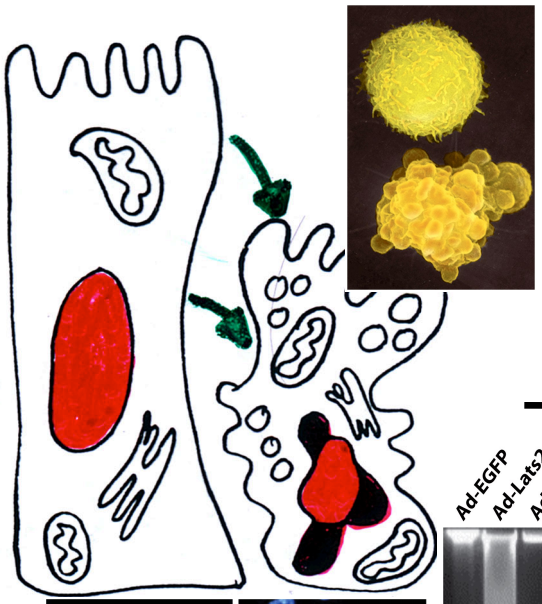


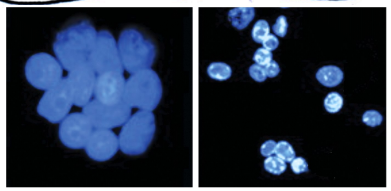
Source: Alberts et al. 2013

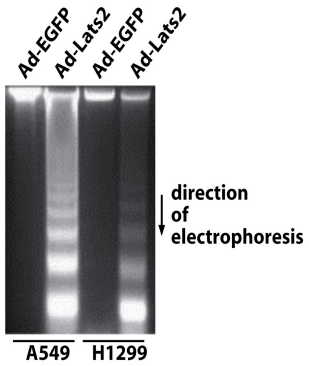
Programmed cell death of epithelia
(surface of the skin, intestine, organs, etc.)

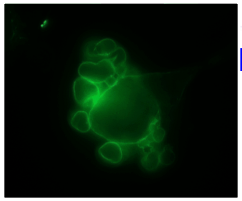
- Outer cell layer of the skin (keratin packed flakes cornea, horny layer)
- Differentiated cells at the tip of intestine villi
- Breast epithelial cells after lactation

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



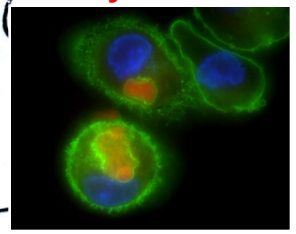






Phosphatidyl serine

Inhibition of the production of pro-inflammatory cytokines



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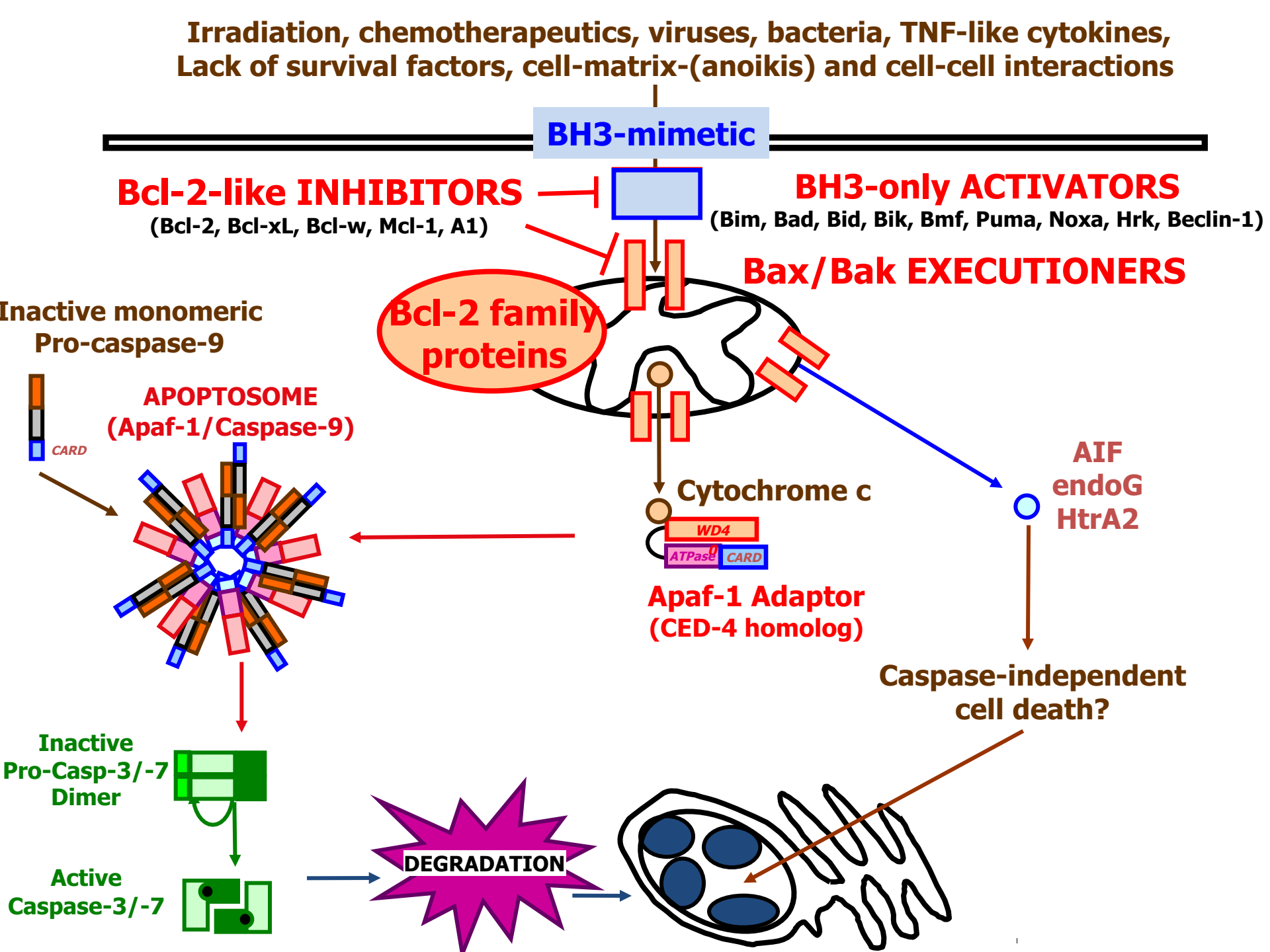
Phagocytosis


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!!!

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

But some mutations accumulate and may fall into relevant genes
and this happens over 90-100 years of our life
The older we get, the more mutations accumulate
(Cancer = disease of the old)

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

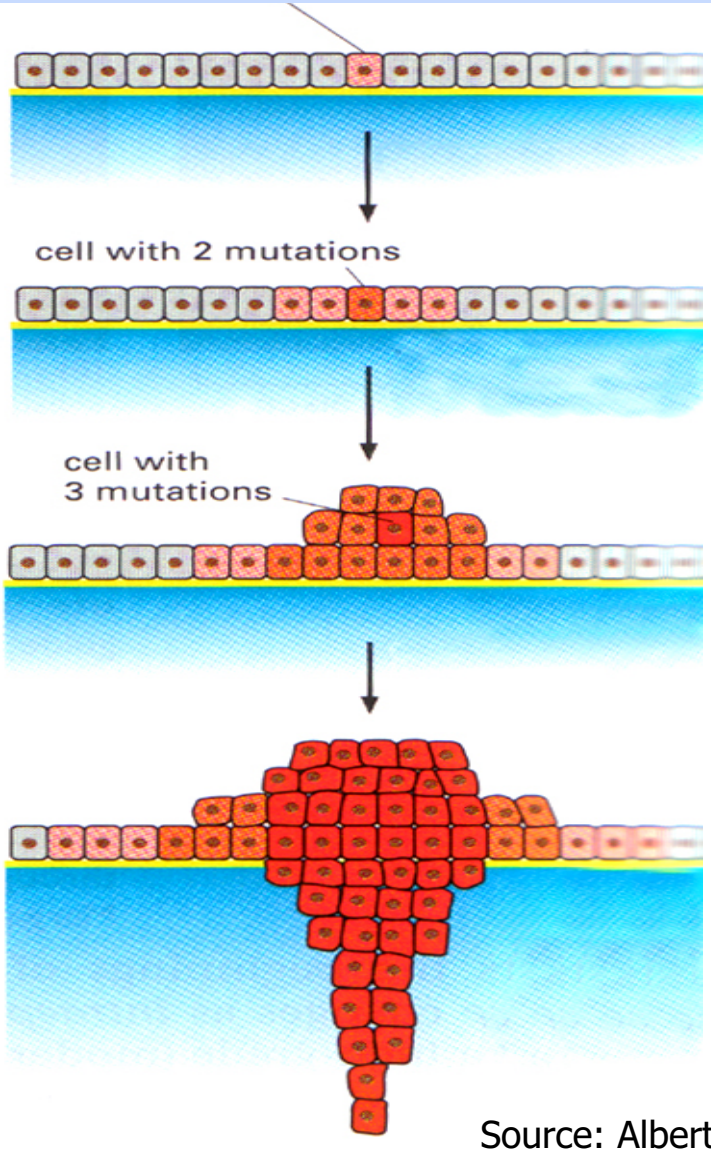
Uncontrolled cell division and lack of cell death of damaged, used-up cells

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

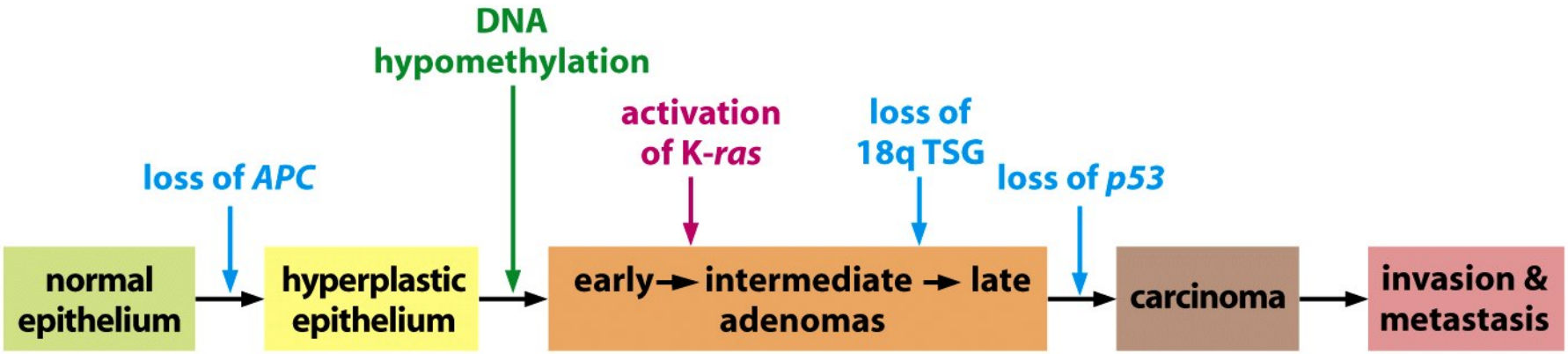
3 genetic changes (mutations) trigger uncontrolled cell division, but still benign tumor

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)

70%

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

20%

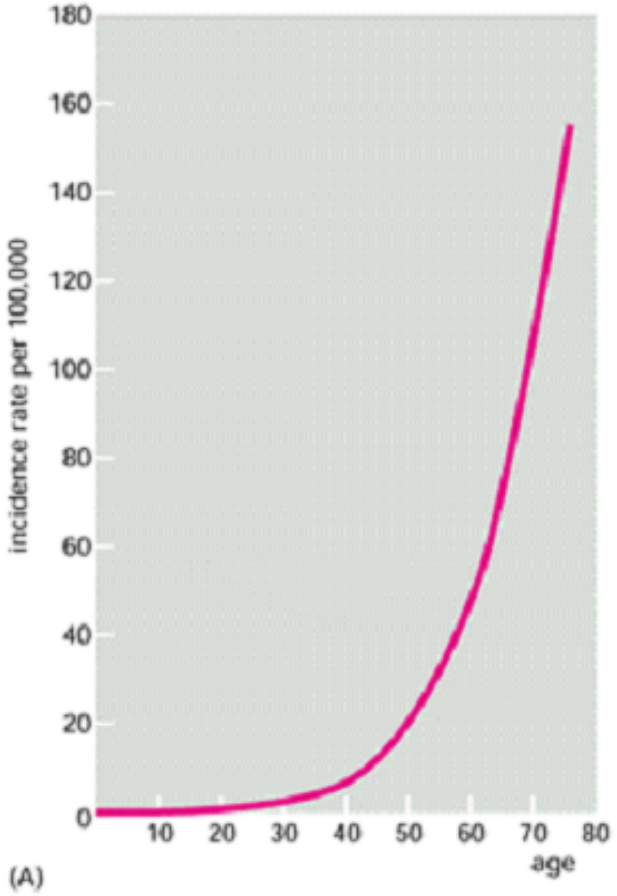
Prophylaxis Genetic screening Check-ups

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?

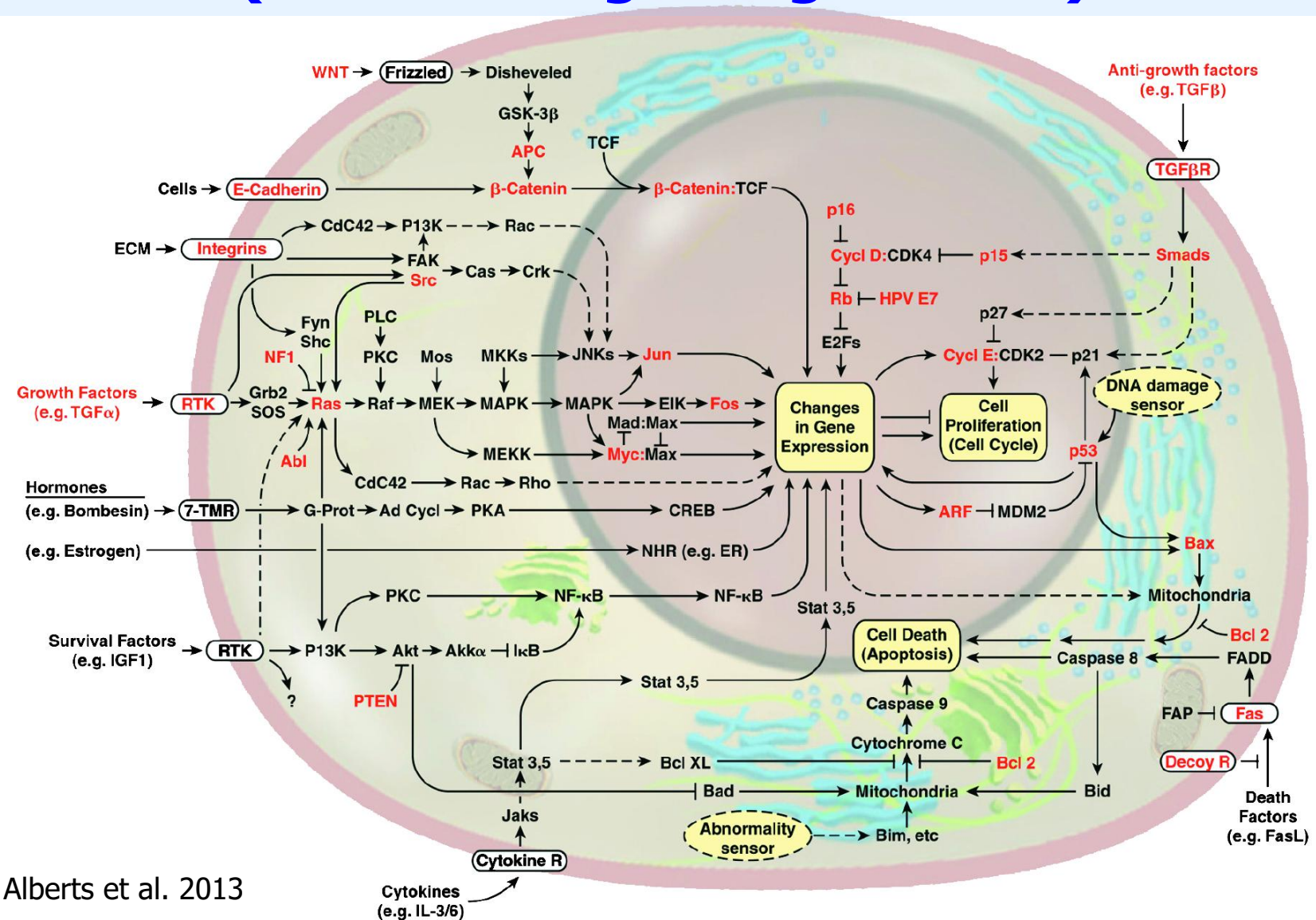
In the past and still ongoing

- 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

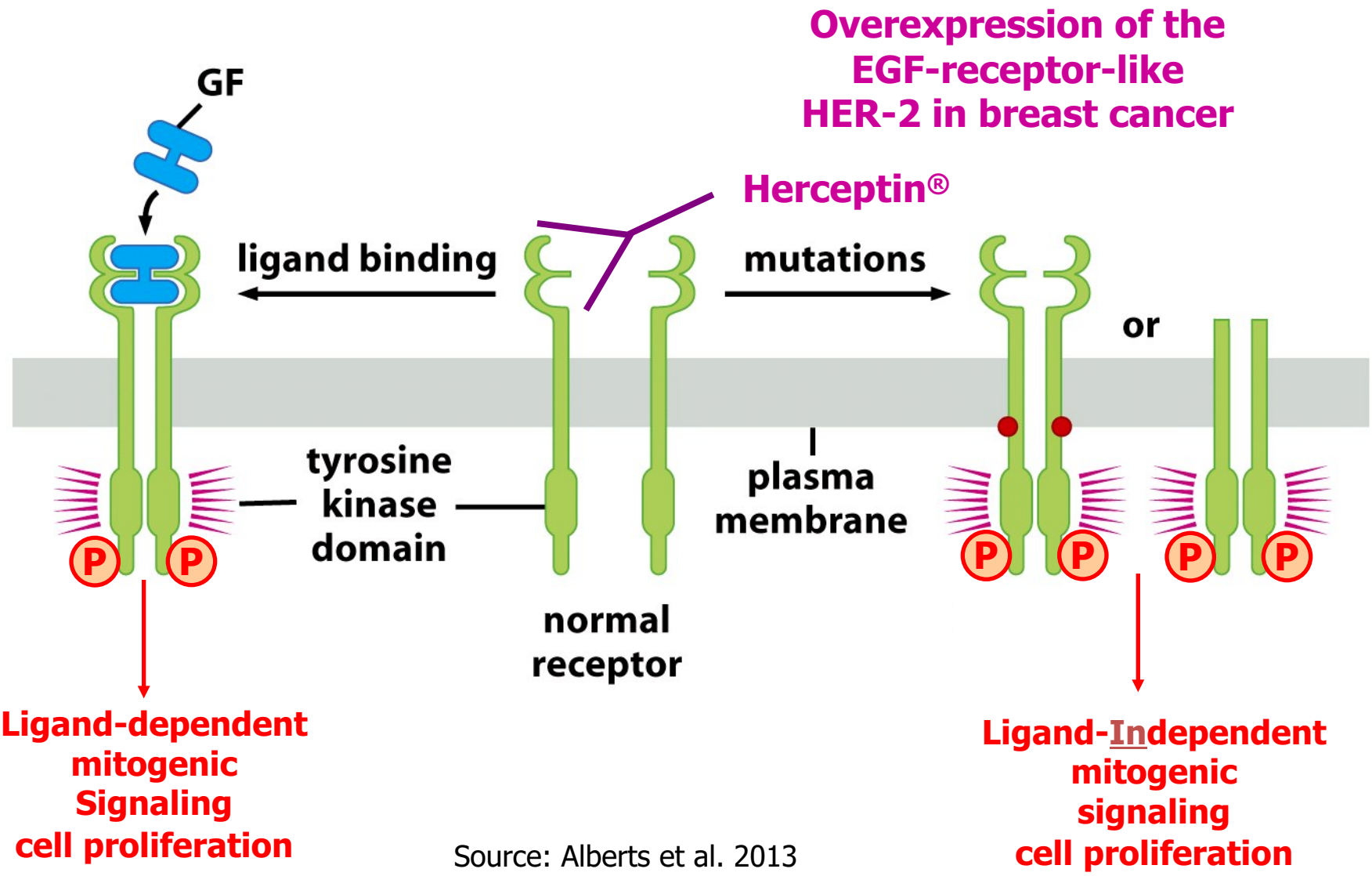
How does precision therapy look like?

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

But

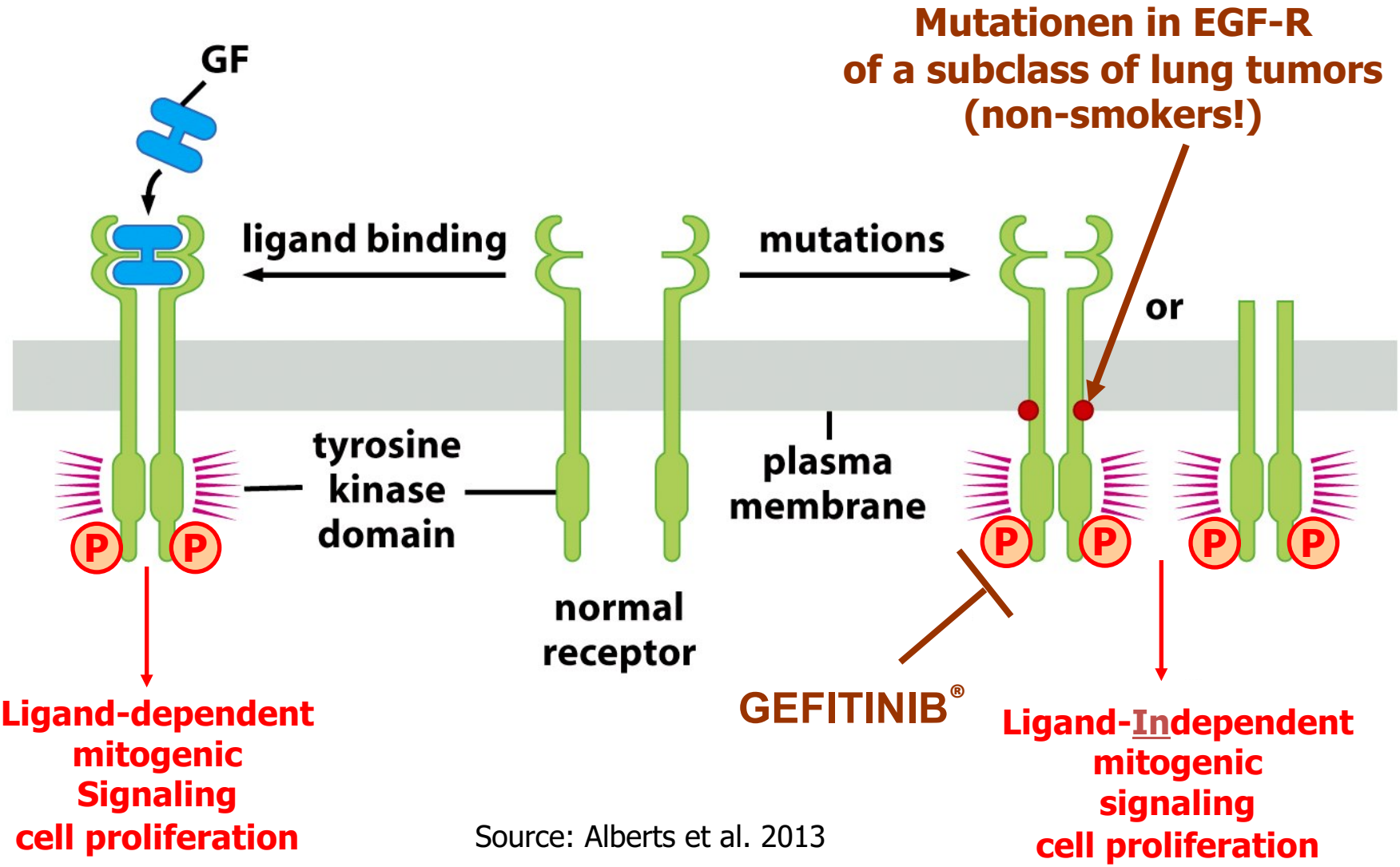
This is not always the case, as cancers have mutations in several genes which contribute to carcinogenesis requiring combination therapies

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



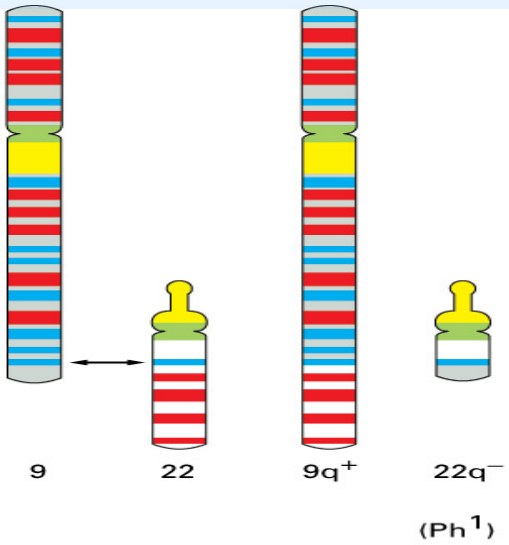
Source: Alberts et al. 2013

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

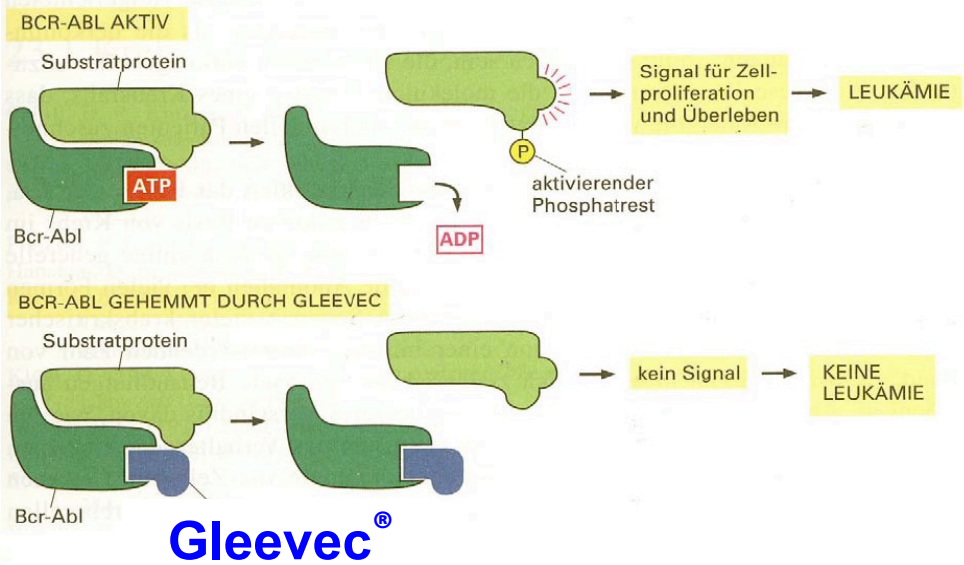


Source: Alberts et al. 2013

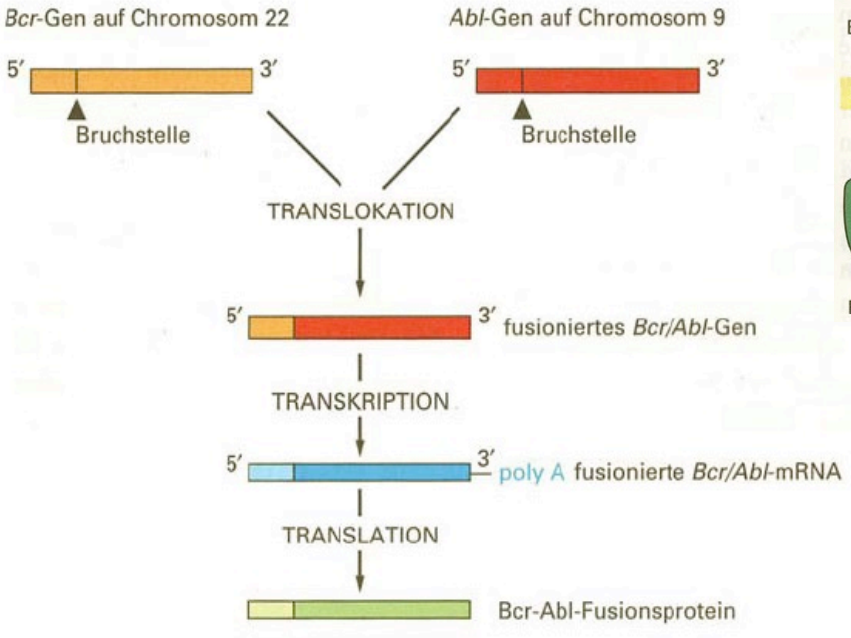
Inhibit constitutively active BCR-ABL protein kinase with small molecule inhibitor in CML (Gleevec, Imatinib)



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



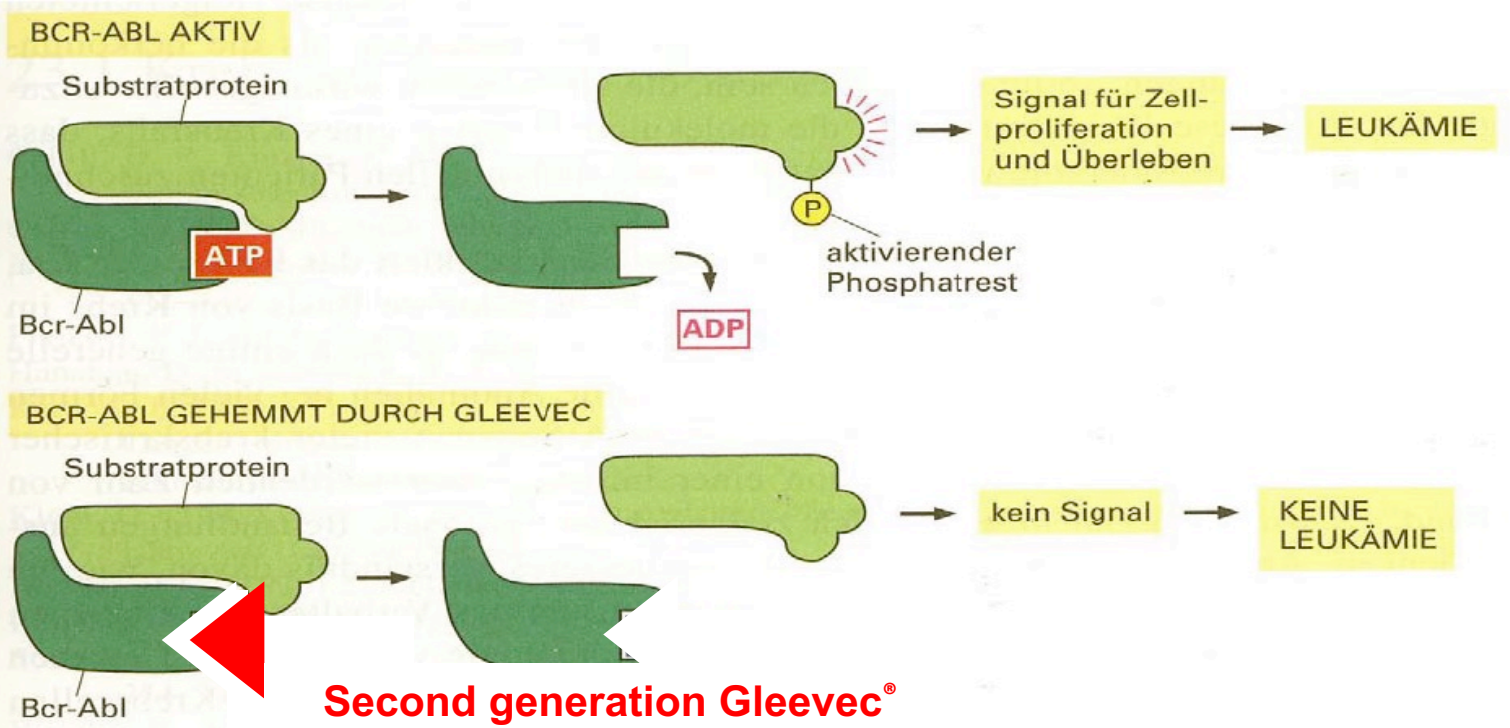
Gleevec®



Source: Alberts et al. 2013

Development of treatment resistance

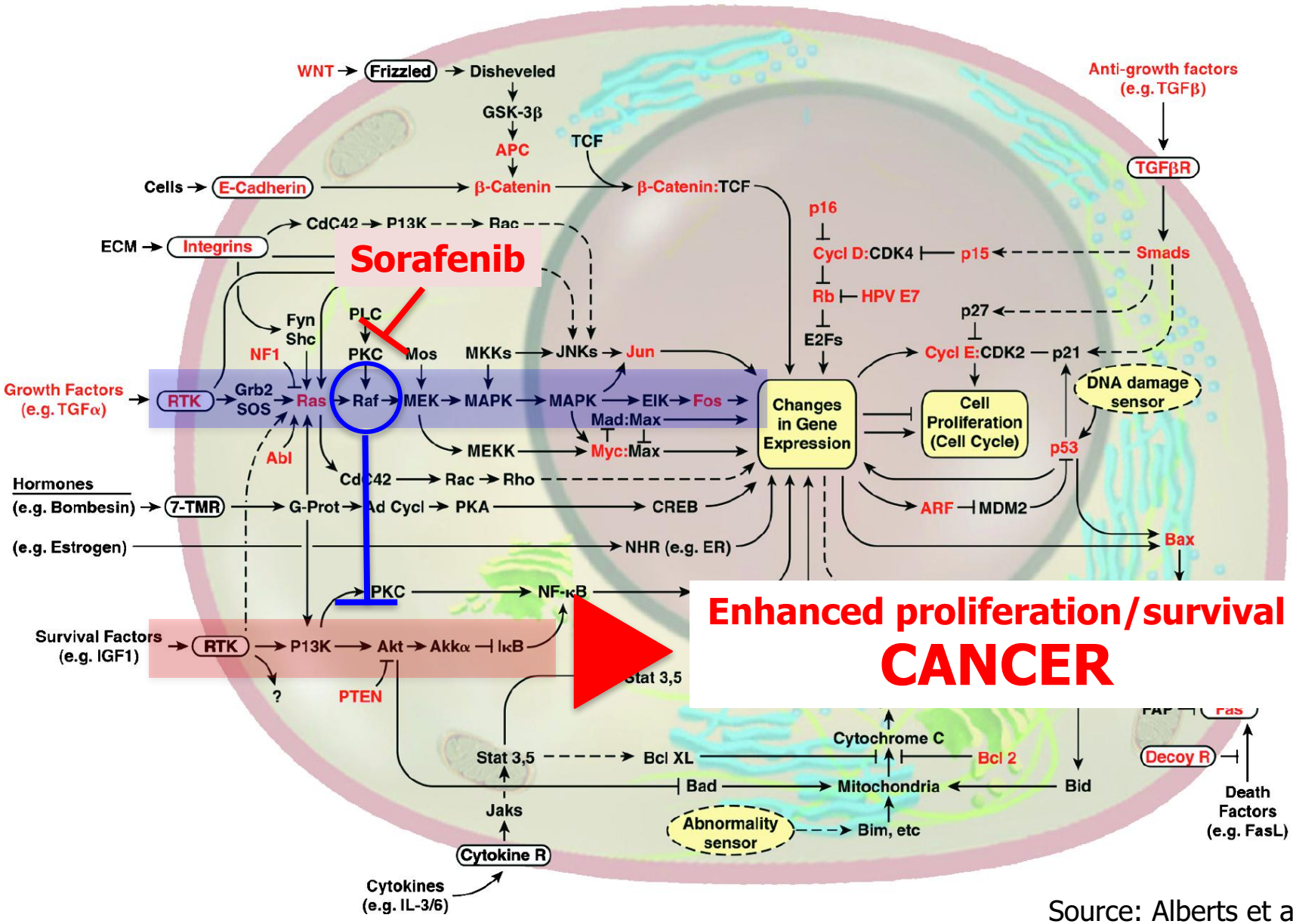
Mutated BCR-ABL protein kinase is not inhibited by Gleevec anymore
Second generation drug is needed



Source: Alberts et al. 2013

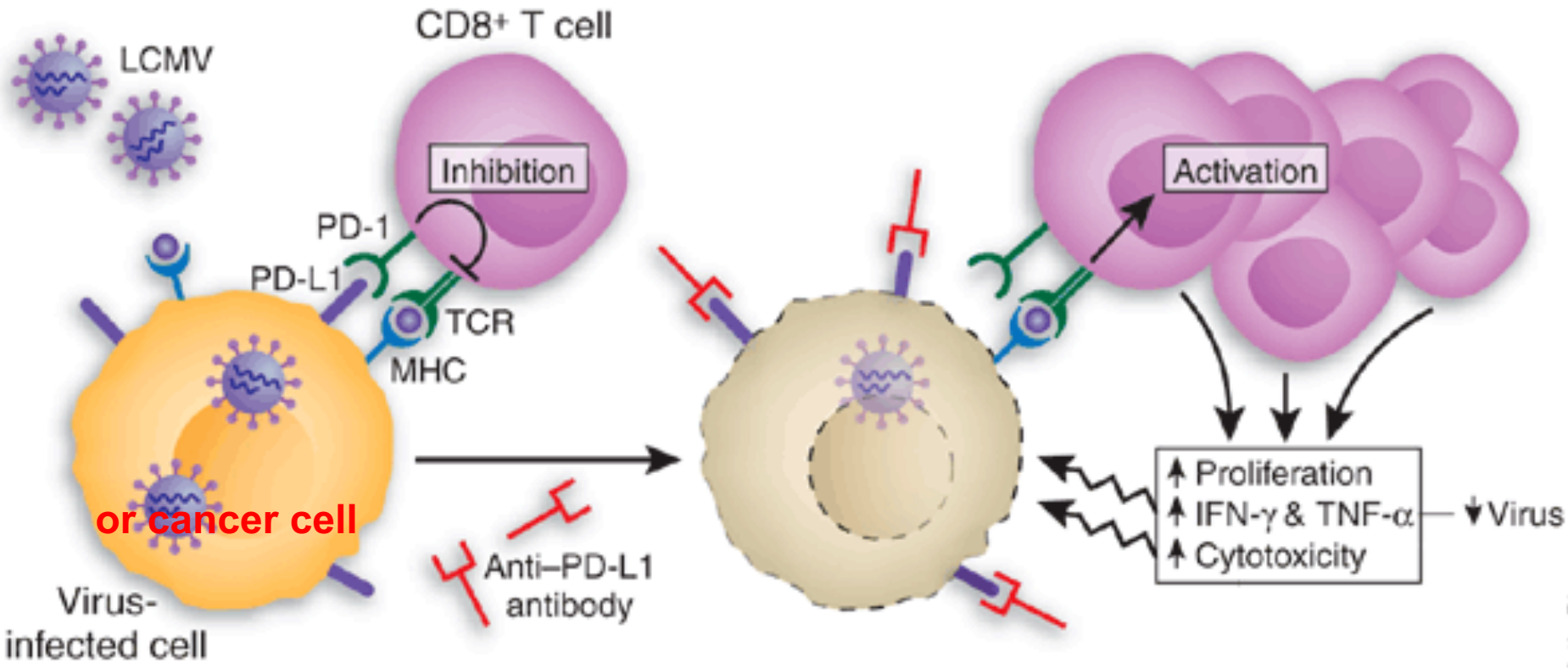
Survival/mitogenic pathways have negative feedback loops to shut down parallel pathways

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



Source: Alberts et al. 2013

Cancer immunotherapy using anti-PD-L1



Very nice but with time (aging) the immunsystem accumulate mutations as well, becomes weak and non-functional
People who live longer have a very good immunsystem

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 strategies

Nature is so fascinating that humans will never understand it completely

Christoph Borner, PhD thesis 1988

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 (for example already in newborns)

- **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

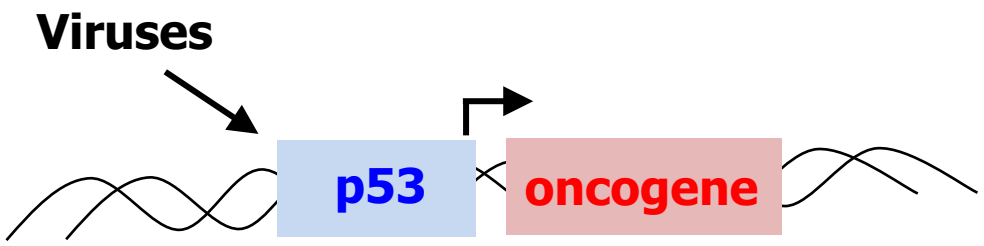
- **How are we going to do that? Overexpress a specific repair gene?**
- **Giving a pill that improves repair?**
- **Even if it worked, how can we prevent mutations in repair genes?**

Ethical Aspects

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

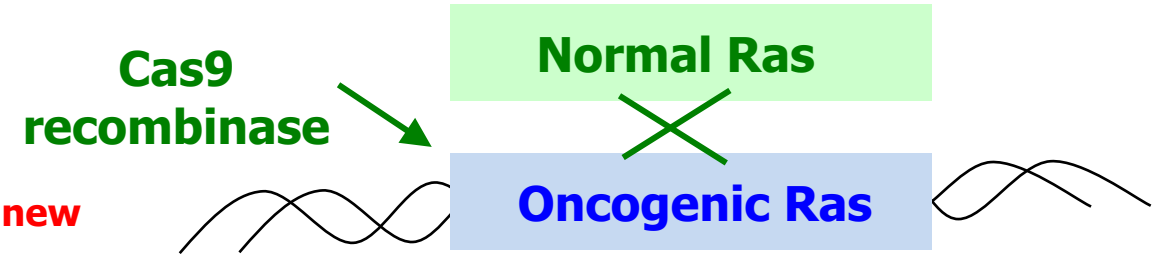
Non-drugged treatment (Playing God)

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
Cannot prevent the occurrence of new cancer-prone mutations
Pharma does not make money anymore



Ethical Aspects

In worms, flies and mice

Prolong life by caloric restriction, lack of movement or lack of sexual reproduction

Problems for humans:

They would starve with the caloric restriction necessary

And who wants to refrain from moving and sexual reproduction?

Solution:

Longevity pathways have been identified (mTOR, insulin, etc.)

Single mutations in the TOR pathway are known to extend the lifespan of C. elegans by 30 per cent, while insulin-signalling mutations could double the amount of time they lived.

But there would be severe side-effects by applying a pill that blocks the insulin and/or mTOR signaling pathways

Summary

We should try to improve early diagnosis and targeted treatment regimens to make the life of elderly people more bearable and enjoyable

But we have to accept that at one point, our life ends and we have to give over our spirit and achievement to the next generation (having children is very important)

Hunde wollt Ihr ewig leben?

(Friedrich des Großen, battle at Kolin, his fleeing Prussian soliders when they lost against Austria)

Enjoy every second of your life

Carpe Diem („Pflücke den Tag")

(Roman poet Horaz 65 v. Chr)

If you want to save lives, you should remove from every person in this world his/her driver's licence