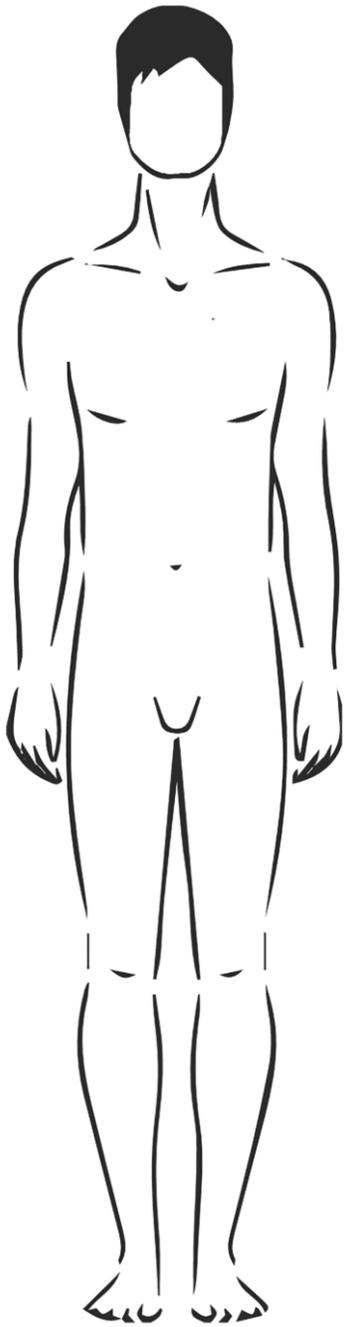


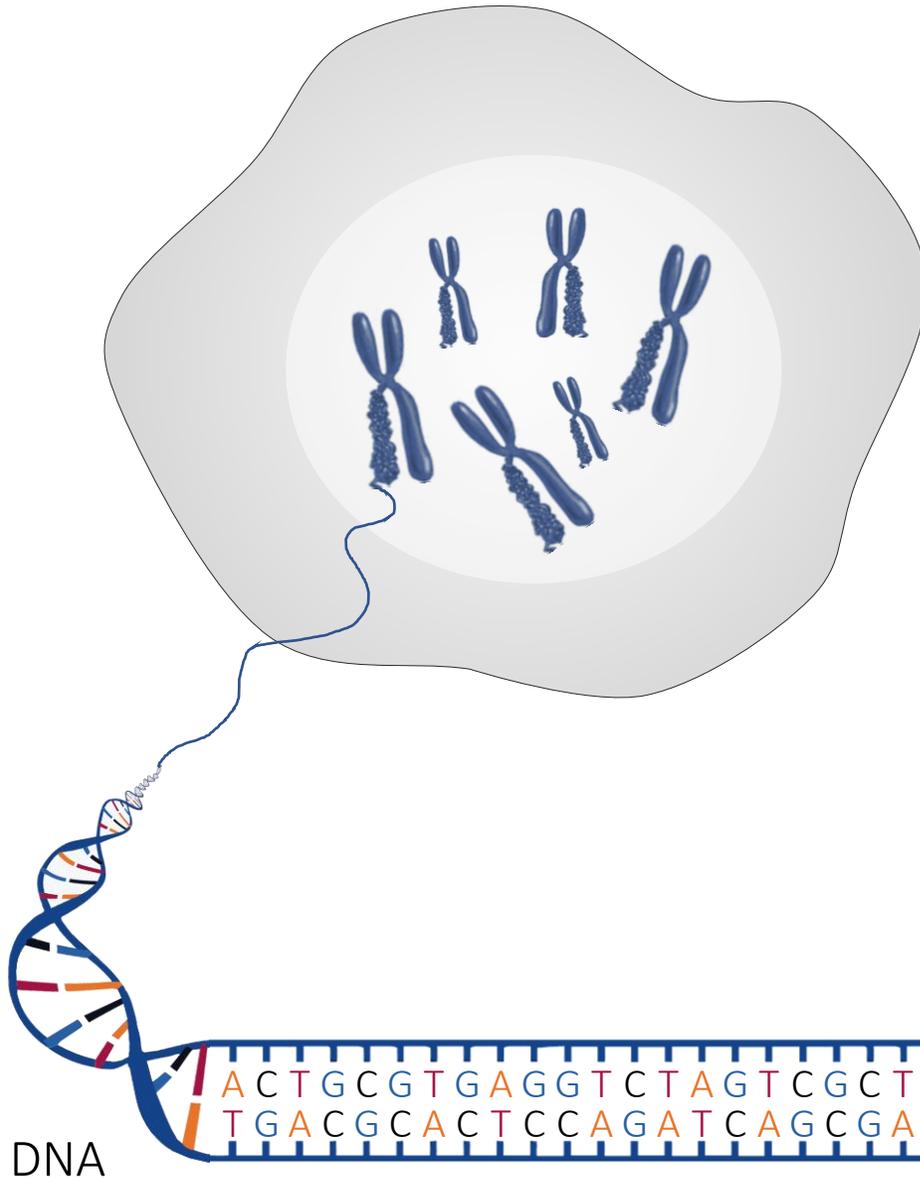
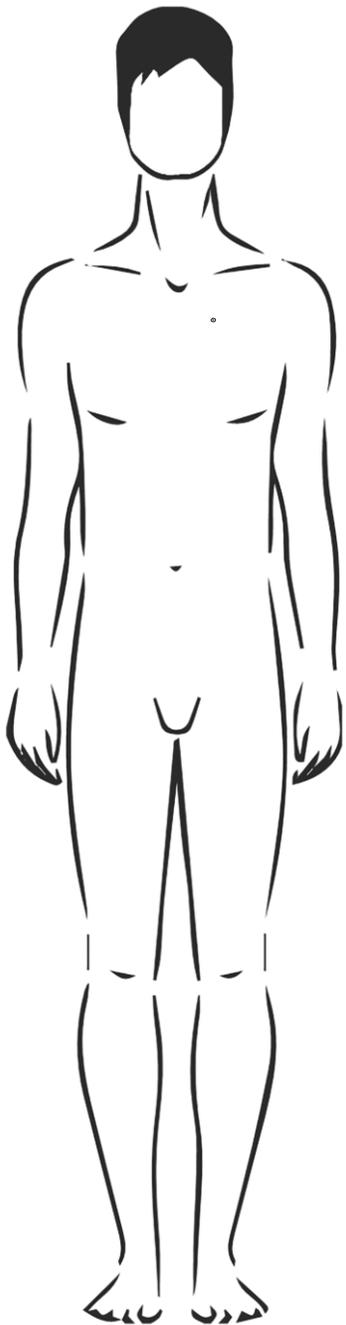
Dem Krebs auf der Spur: Mechanismen der Metastasierung und neue Therapien

Anna Obenauf





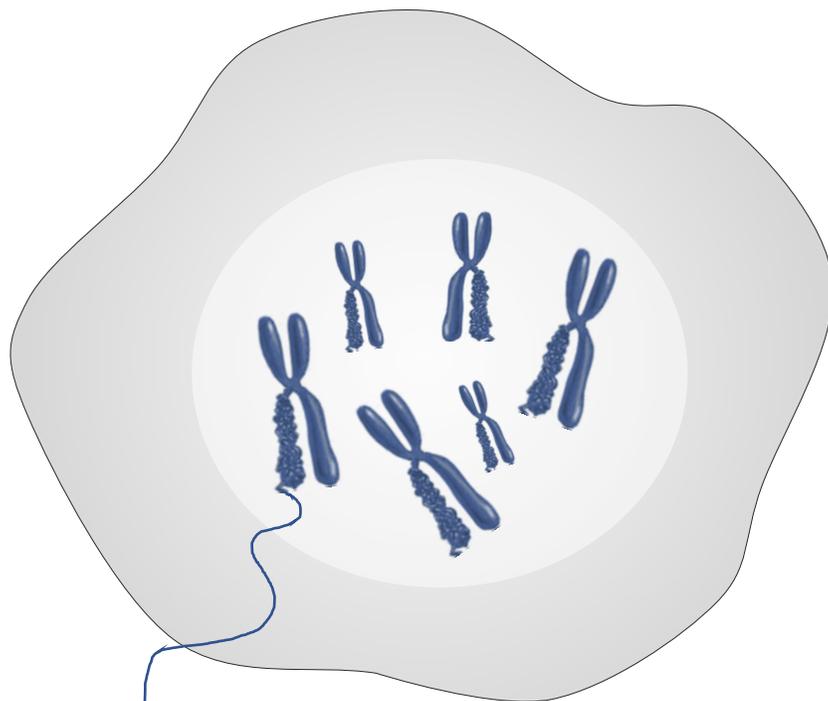
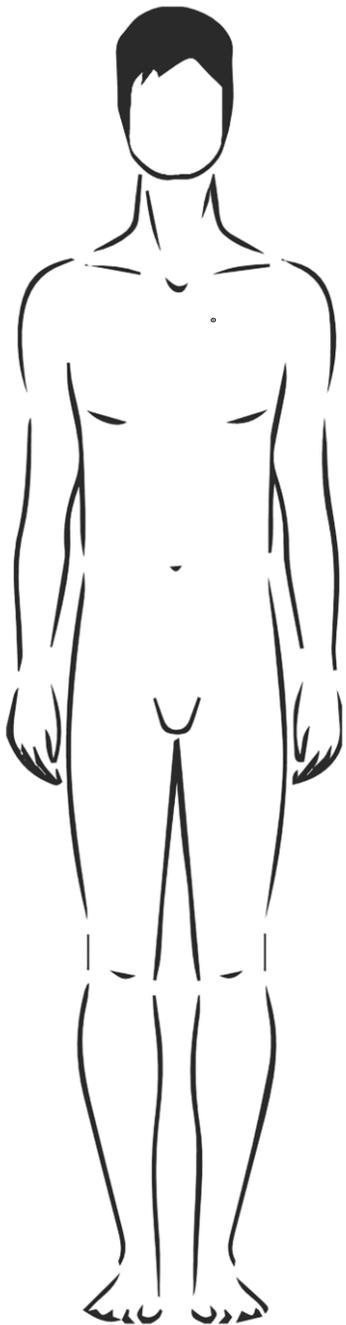
Cells in the human body: **35 Trillion**



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Length of DNA per cell: **2 m (6.5 ft)**

Cell divisions per second: **5 Million**



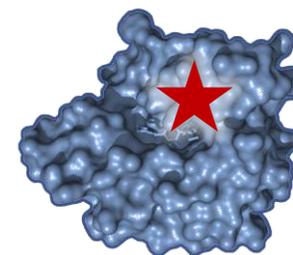
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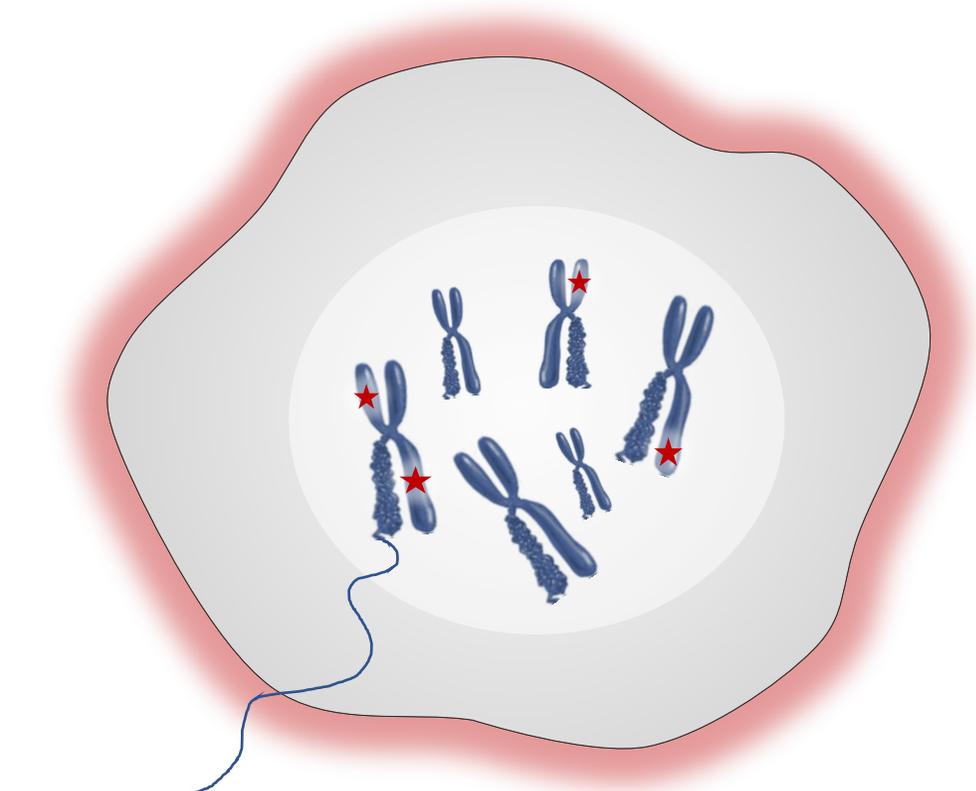
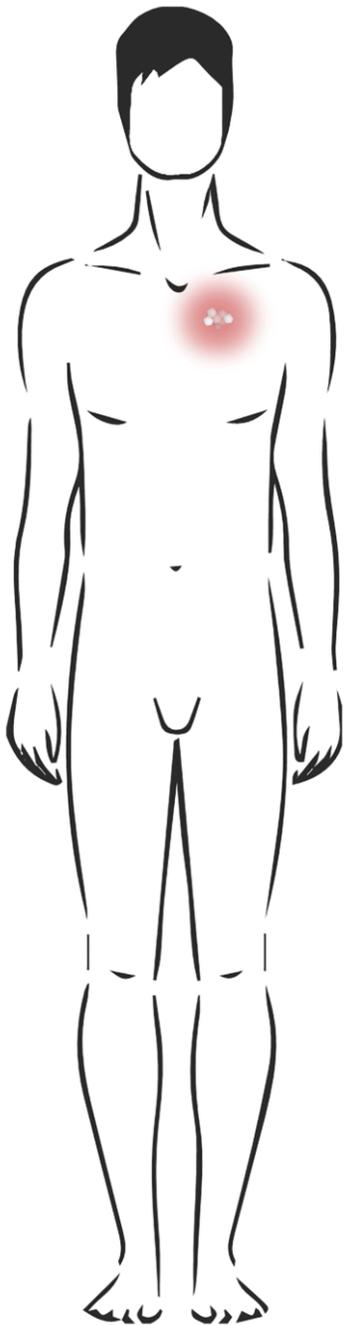
Cell divisions per second: **5 Million**

DNA

ACTGCGTGAAGGTCTAGTCGCTGATCTGCCAGTAAGCA
TGACGCACCTCCAGATCAGCGACTAACGGTCATTCGT



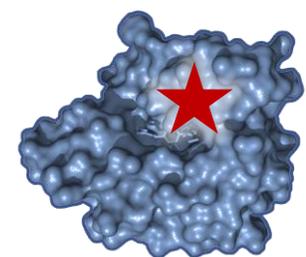
Protein



Cancer cell



ACTGCGTGAGGTCCTAGTCGCTGATTGCCAGTAAGCA
TGACGCACCTCCAGATCAGCGACTAACGGTCATTCGT

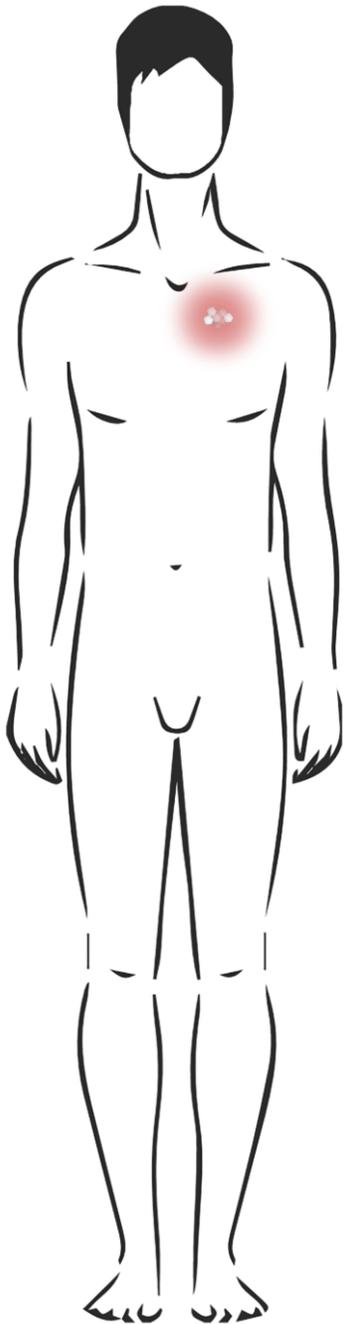


Protein

1 von 2 Männern
1 von 3 Frauen

entwickelt einen Tumor
im Laufe des Lebens.

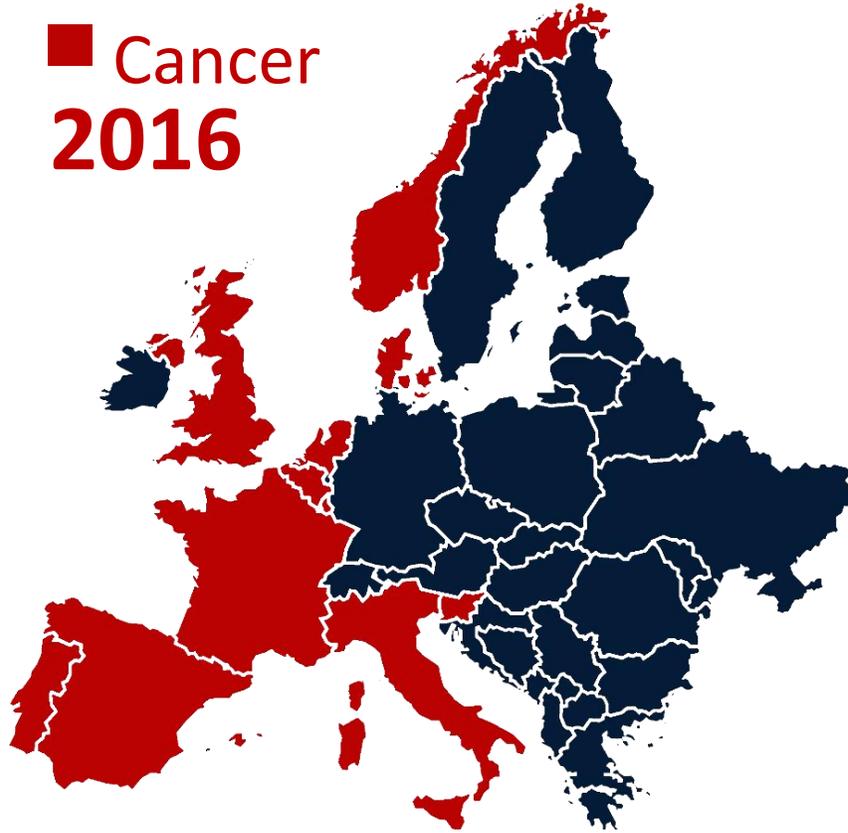
Krebs ist in vielen Laendern die Haupt-Todesursache



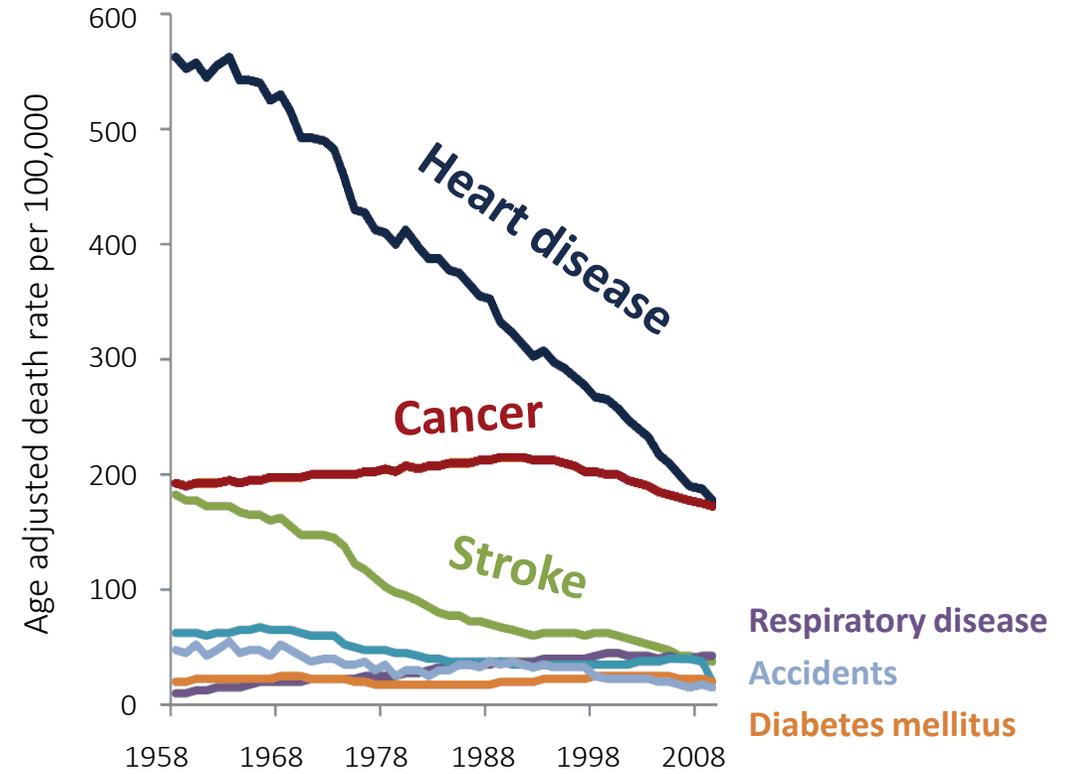
■ Cardiovascular

■ Cancer

2016

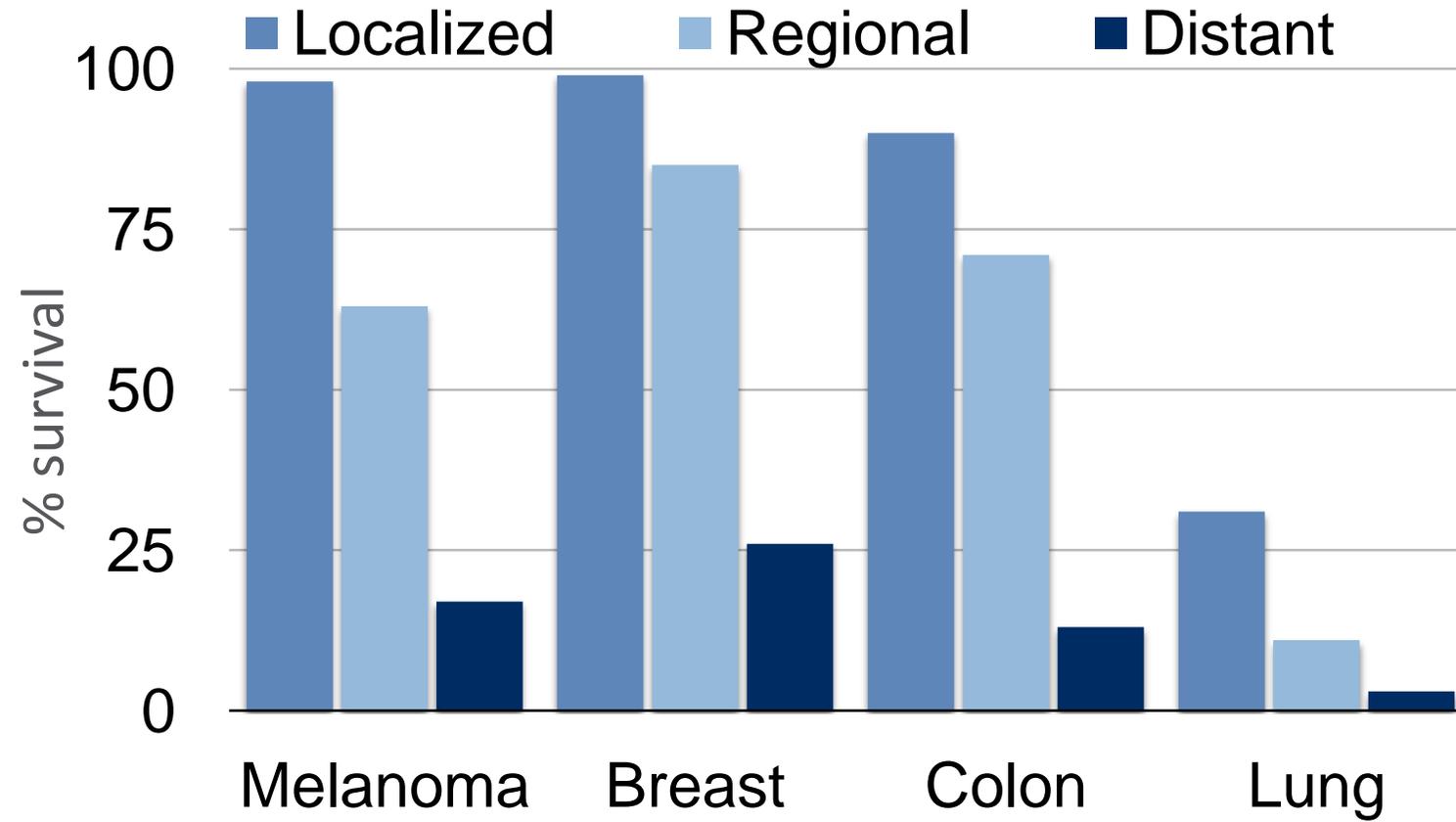
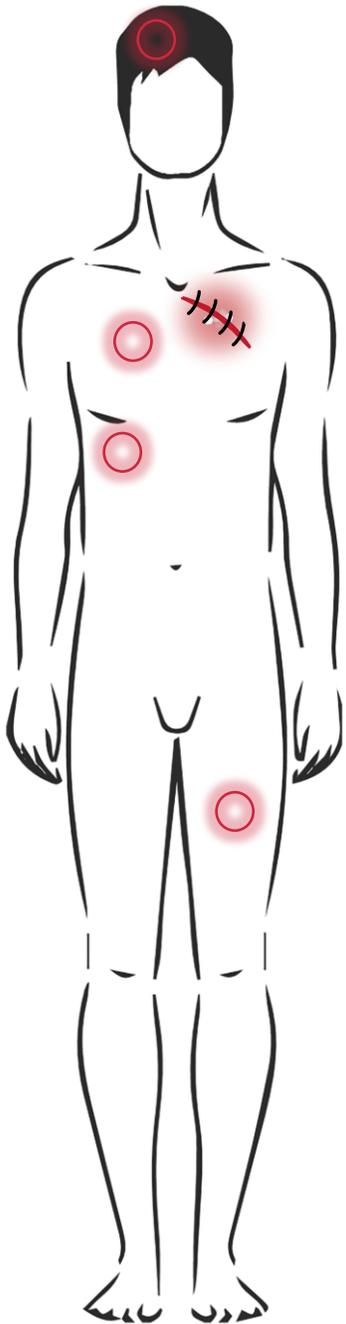


Townsend et al., Eur Heart J (2016)

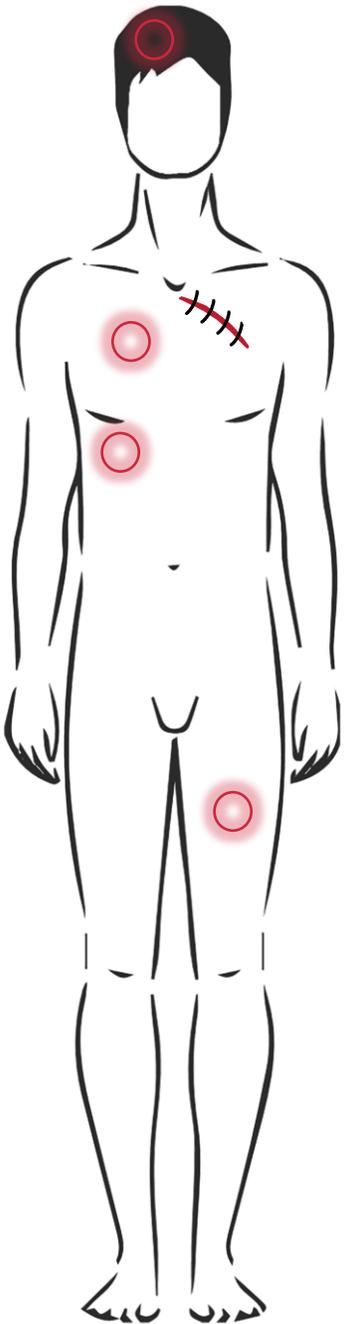


Source: WHO, 2017

Metastasierung in lebenswichtige Organe ist für 90% der Krebs-assoziierten Todesfälle verantwortlich



Metastasierung in lebenswichtige Organe ist für 90% der Krebs-assoziierten Todesfälle verantwortlich

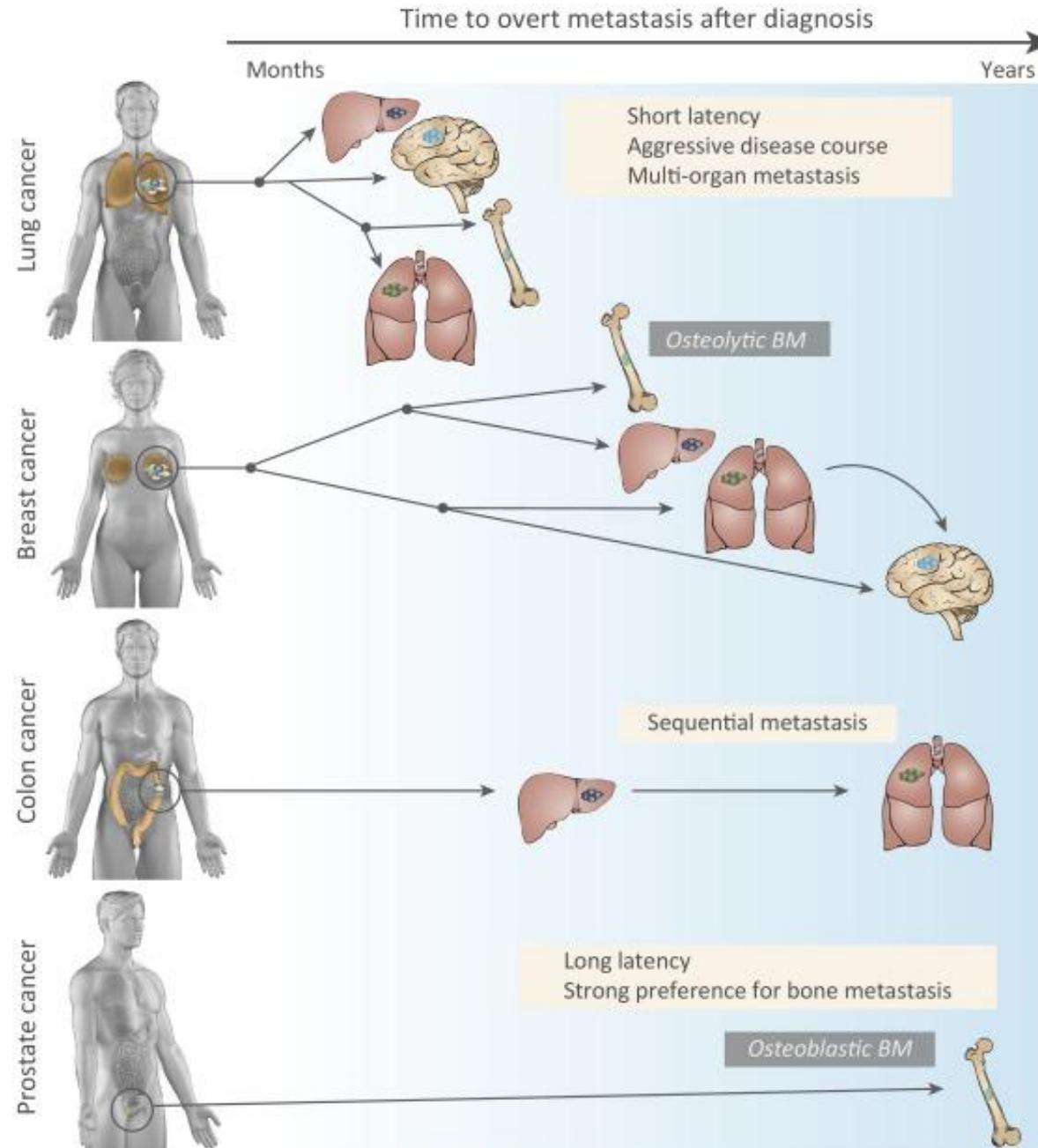


WICHTIGES KLINISCHES PROBLEM

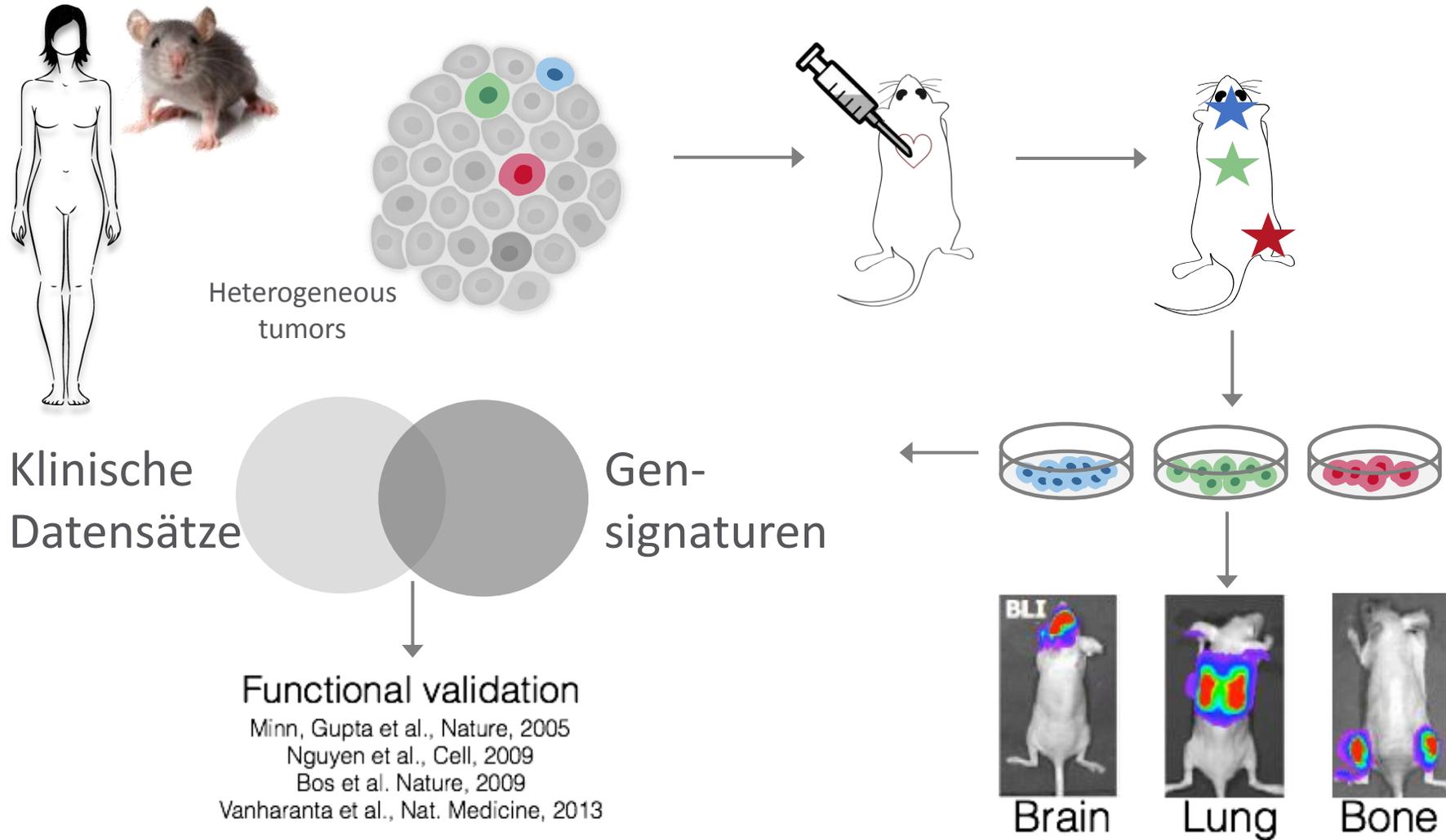
FASZINIERENDER BIOLOGISCHER PROZESS

SYSTEMISCHE THERAPIE

Klinische Präsentation variiert zwischen verschiedenen Entitäten



Funktionelle Modelle zur Studie der Metastasierung

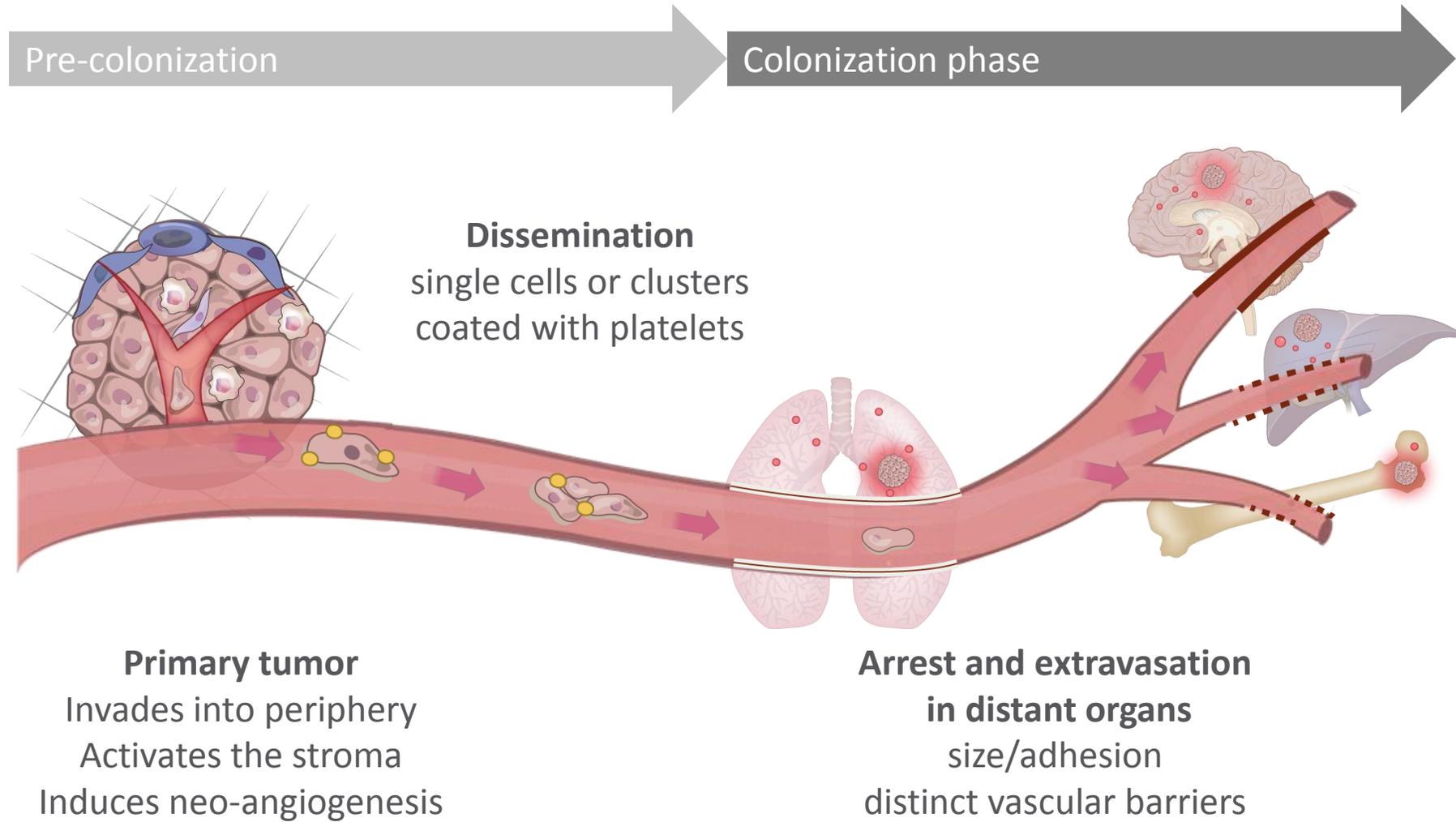


MMTV-ERBB2 brain metastasis model (immunocompetent)

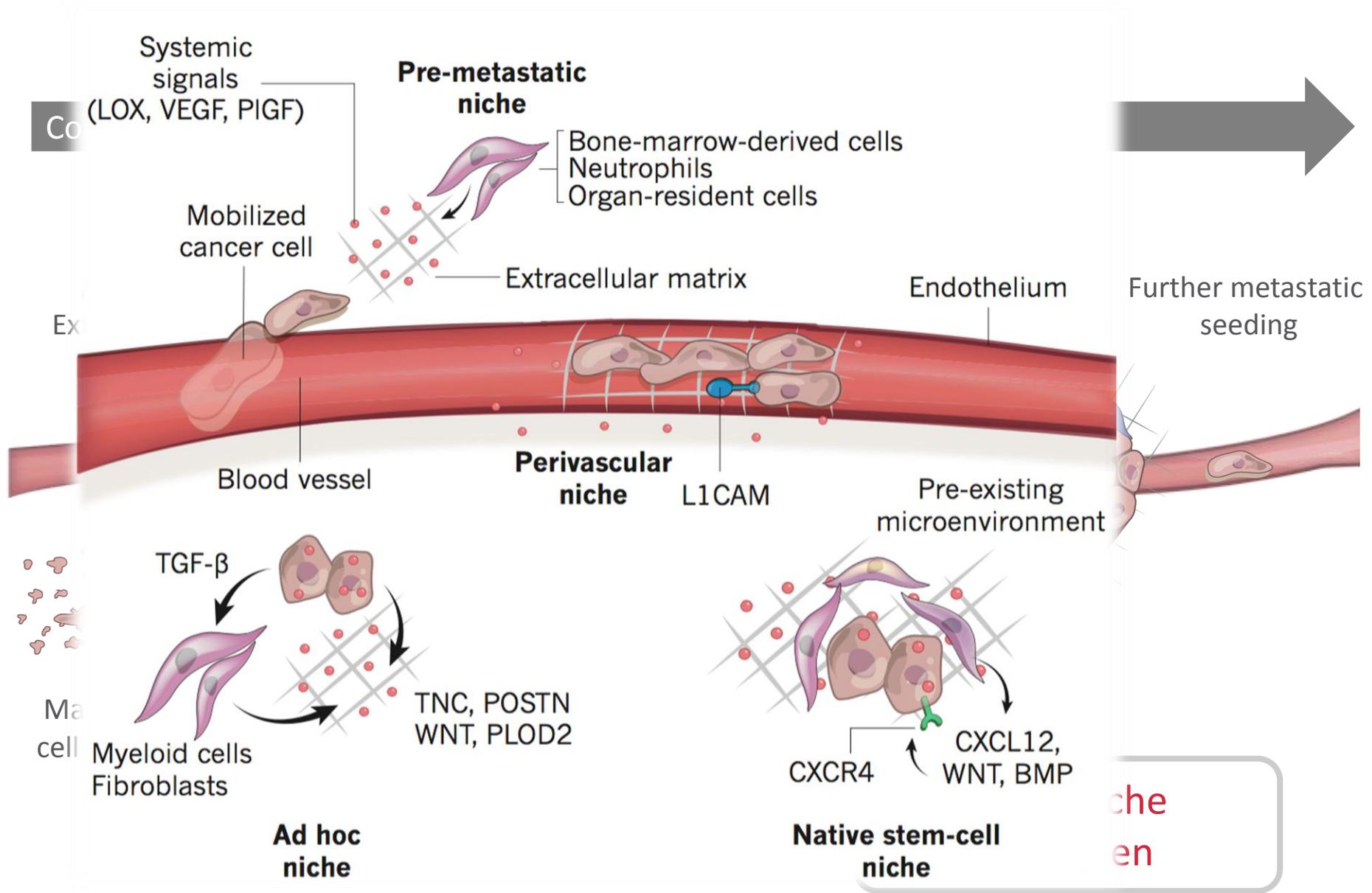
Serpins promote cancer cell survival and vascular co-option in brain metastasis.

Valiente M, Obenauf AC, et al., Cell, 2014

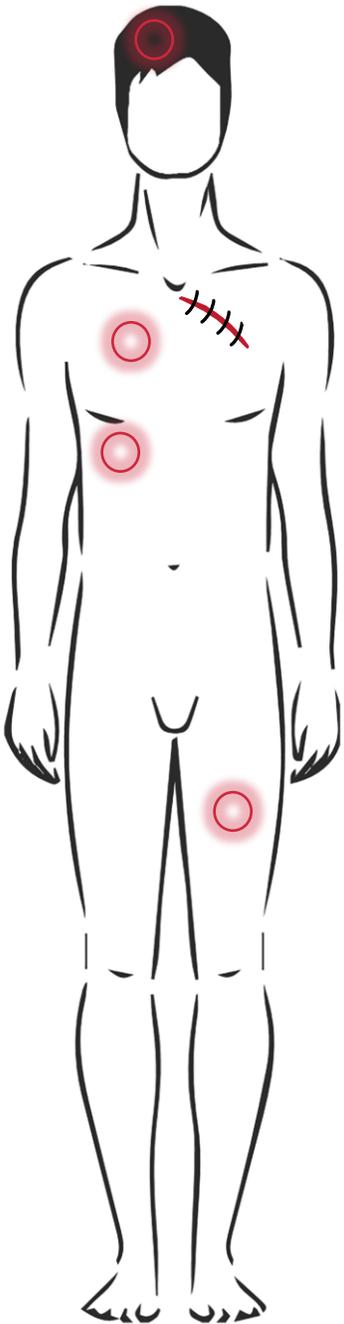
Die Metastasierungskaskade



Die Metastasierungskaskade



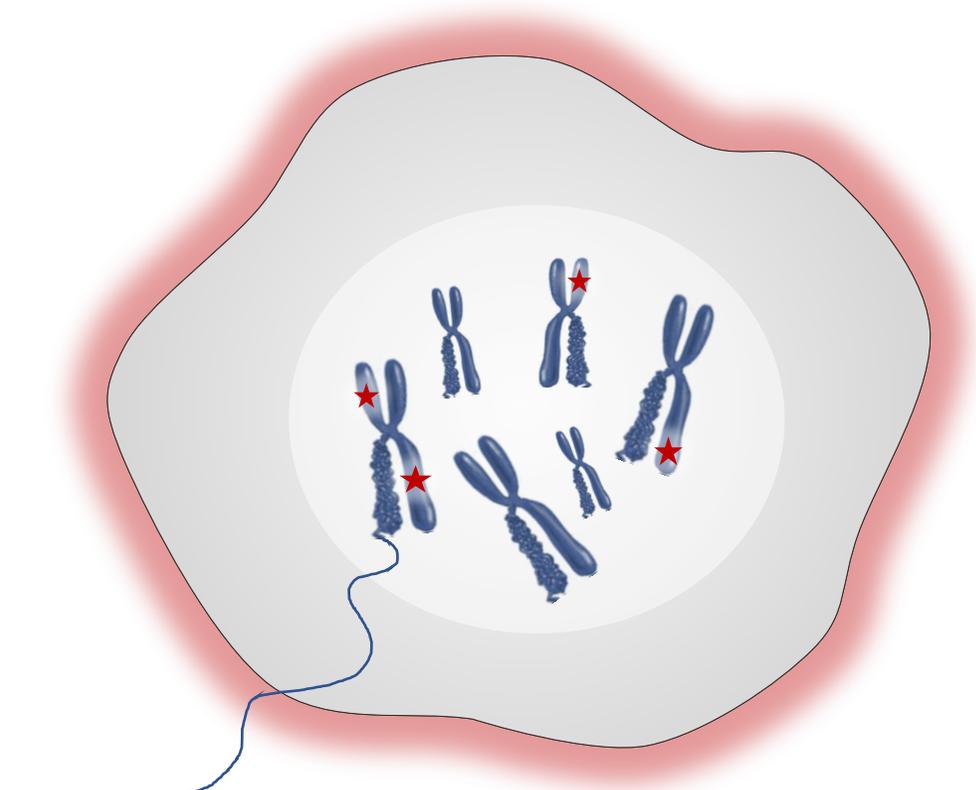
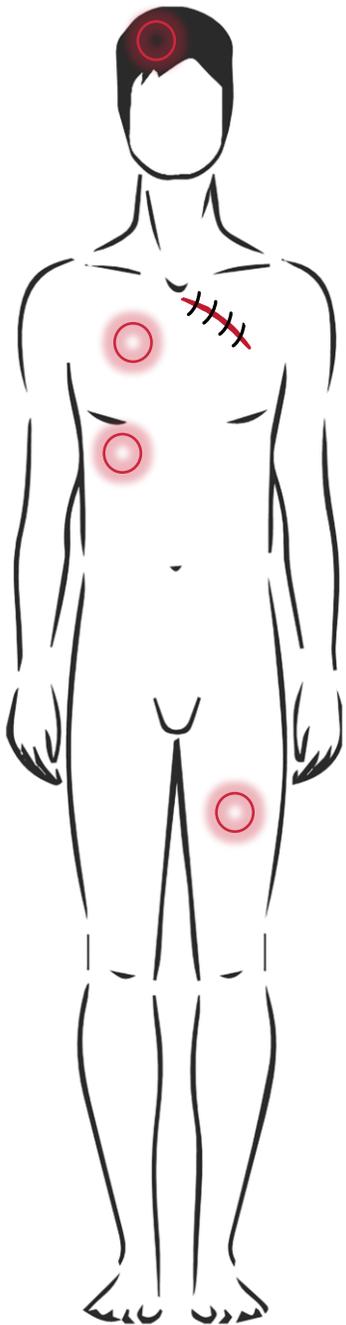
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Cancer cell

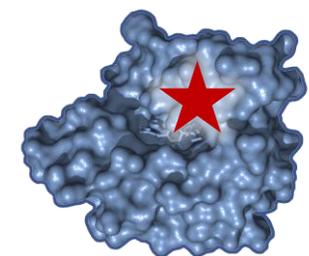
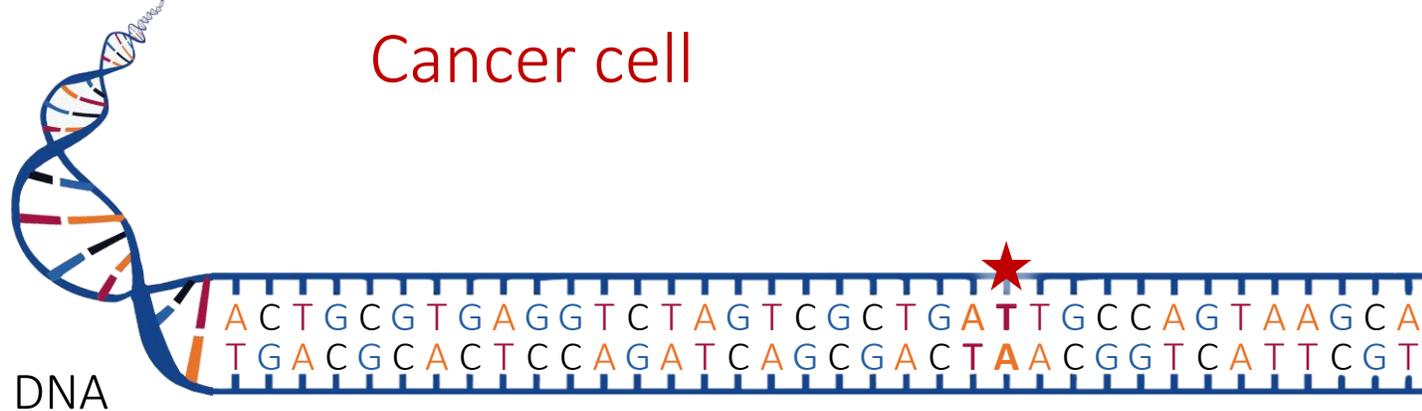
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Driver mutations: **5**

Druggable mutations: **5%**

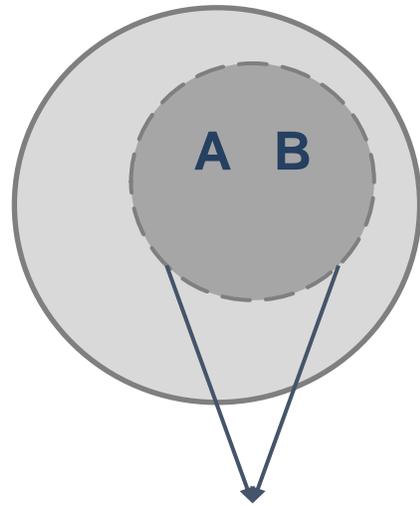


Targeted Therapy

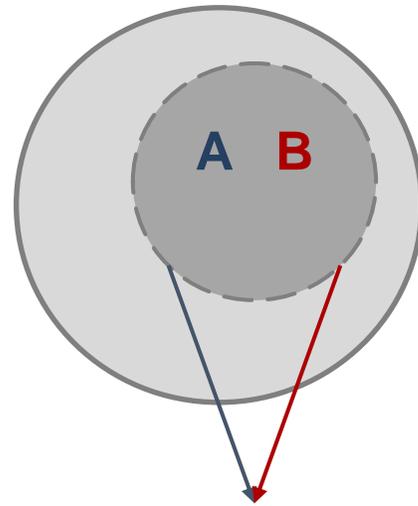


Protein

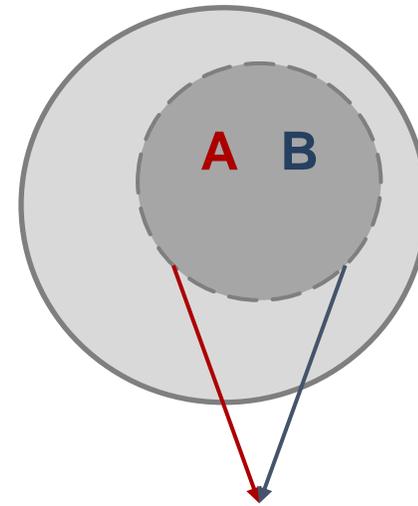
Synthetische Lethalität



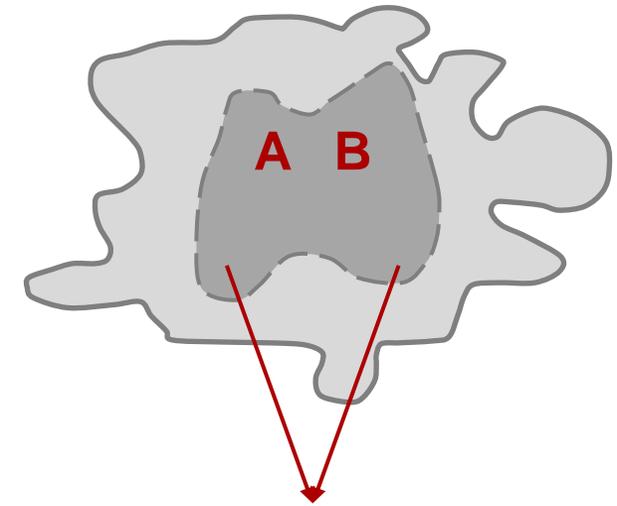
überlebt



überlebt



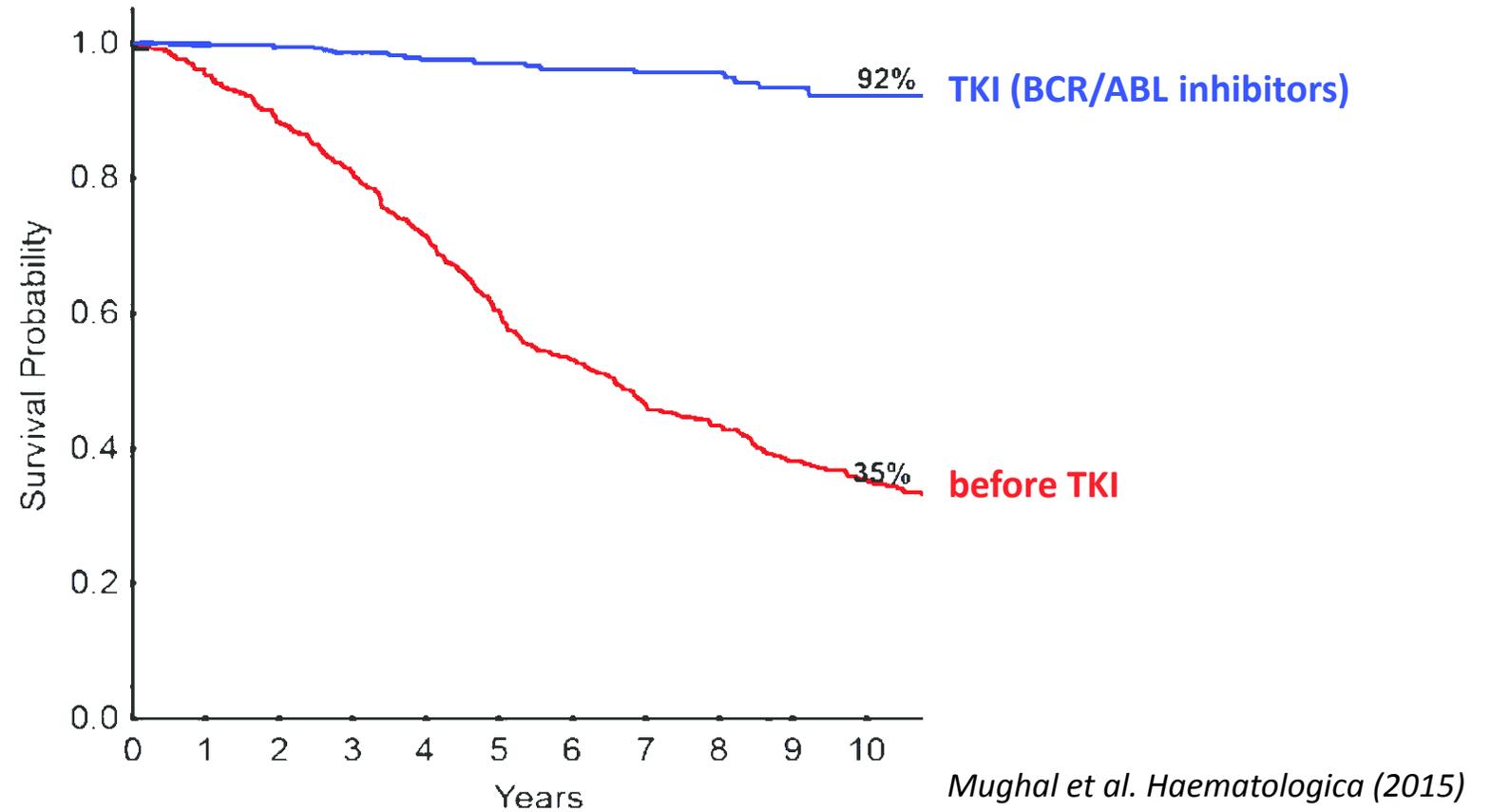
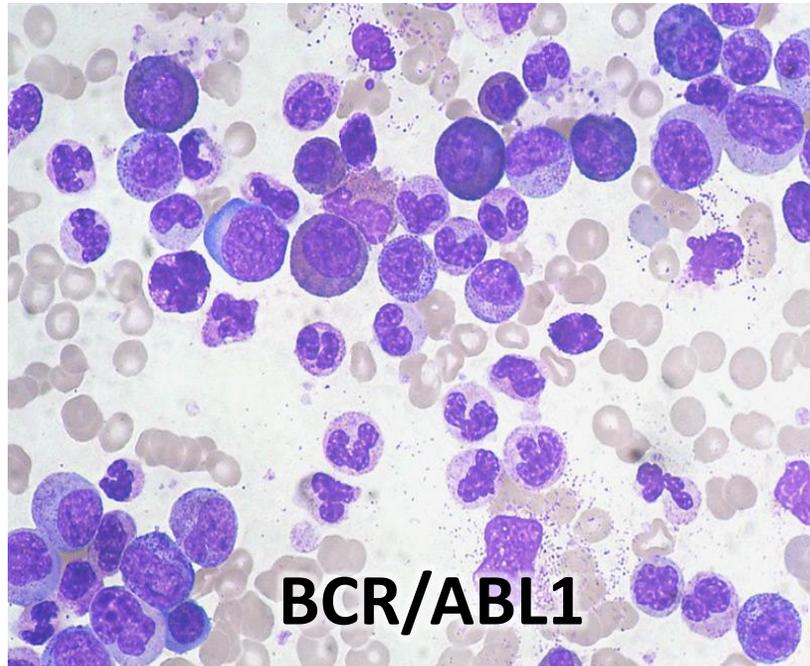
überlebt



stirbt

Eine Erfolgsgeschichte: Zielgerichtete Therapie in Chronisch myeloider Leukemie

Chronic myeloid leukemia (CML)

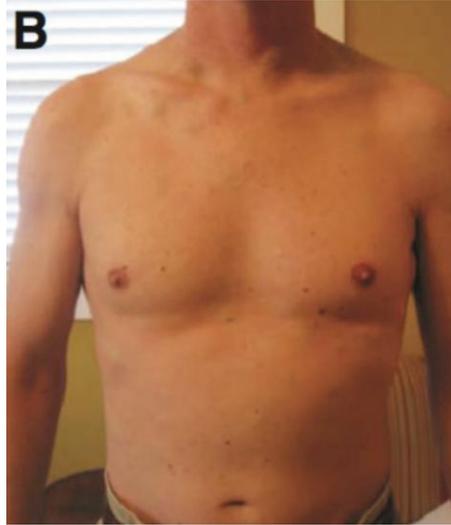


Zielgerichtete Therapie beim Melanom: neue Herausforderungen für die Zukunft

38 year-old patient with melanoma (BRAF^{V600E})



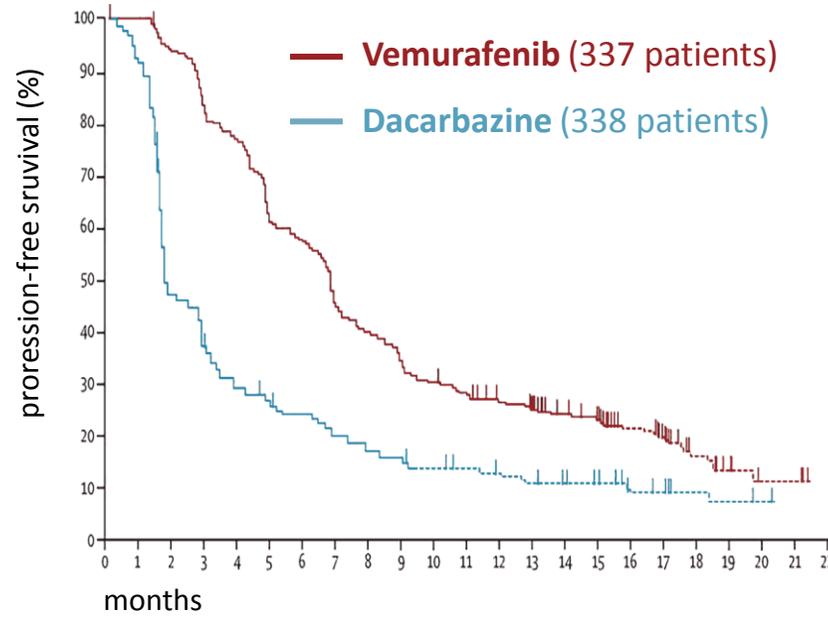
Vemurafenib (PLX4032)
15 weeks



Vemurafenib (PLX4032)
23 weeks



Wagle et al., *J Clin Oncol.* (2011)



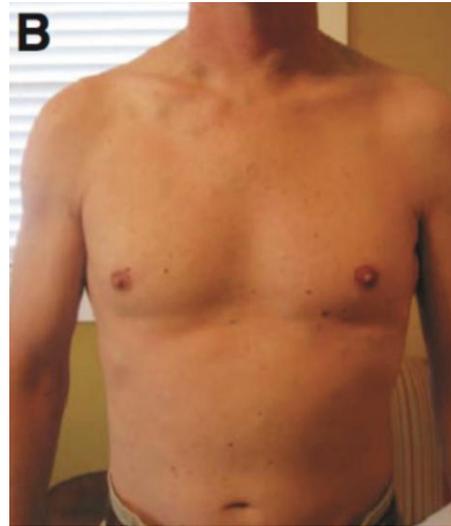
McArthur et al., *Lancet* (2014)

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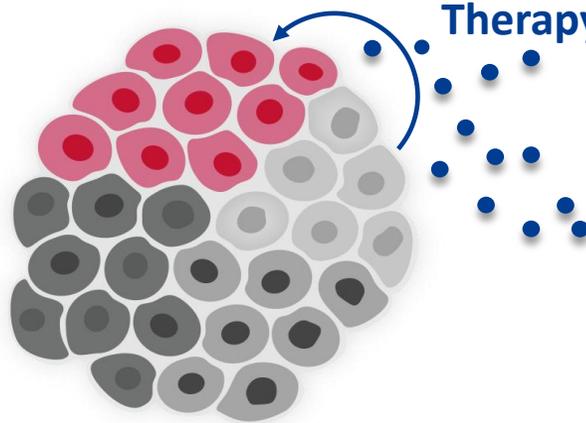
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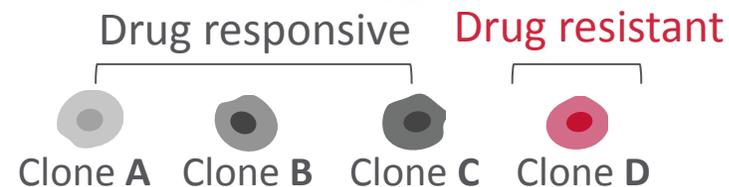


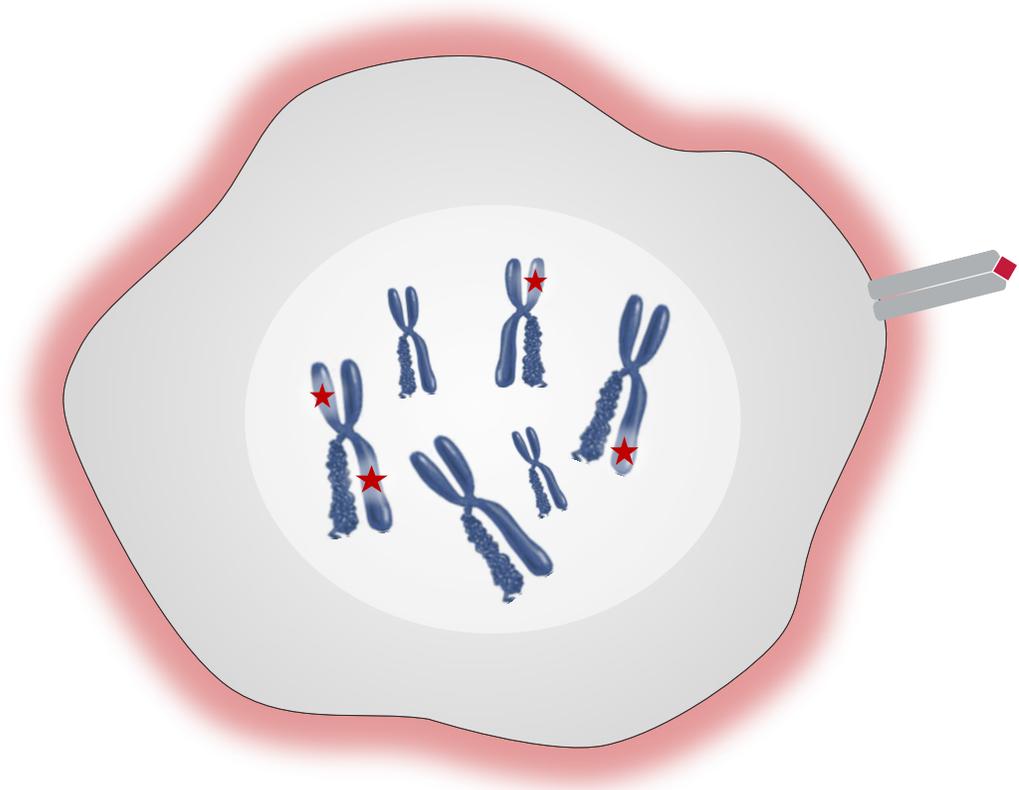
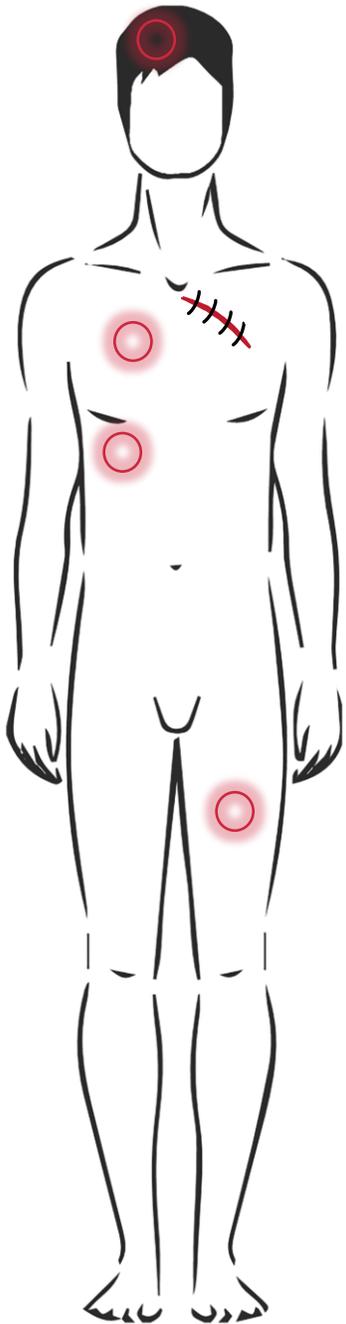
Therapy-induced secretome

Therapy-induced tumour secretomes promote resistance and tumour progression

Anna C. Obenauf¹, Yilong Zou^{1,2*}, Andrew L. Ji^{1*}, Sakari Vanharanta^{1,3}, Weiping Shu¹, Hubing Shi⁴, Xiangju Kong⁴, Marcus C. Bosenberg^{5,6}, Thomas Wiesner⁷, Neal Rosen⁸, Roger S. Lo⁴ & Joan Massagué¹

Nature, 2015



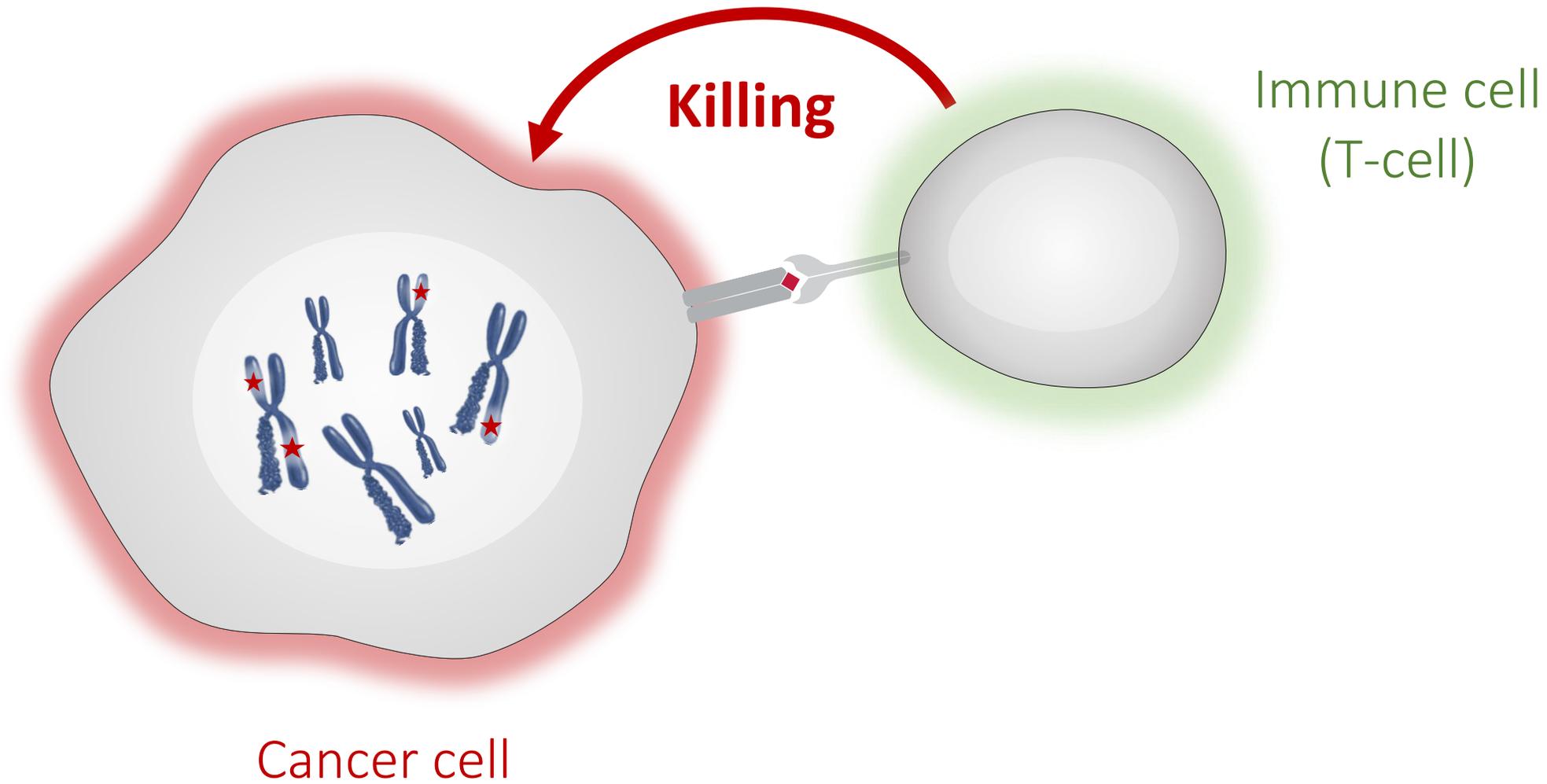
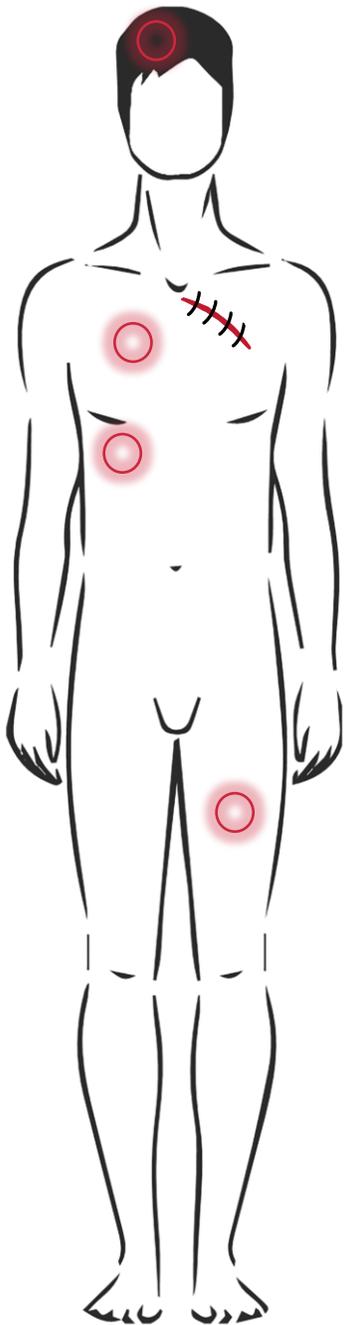


Cancer cell

Total mutations: **5000**

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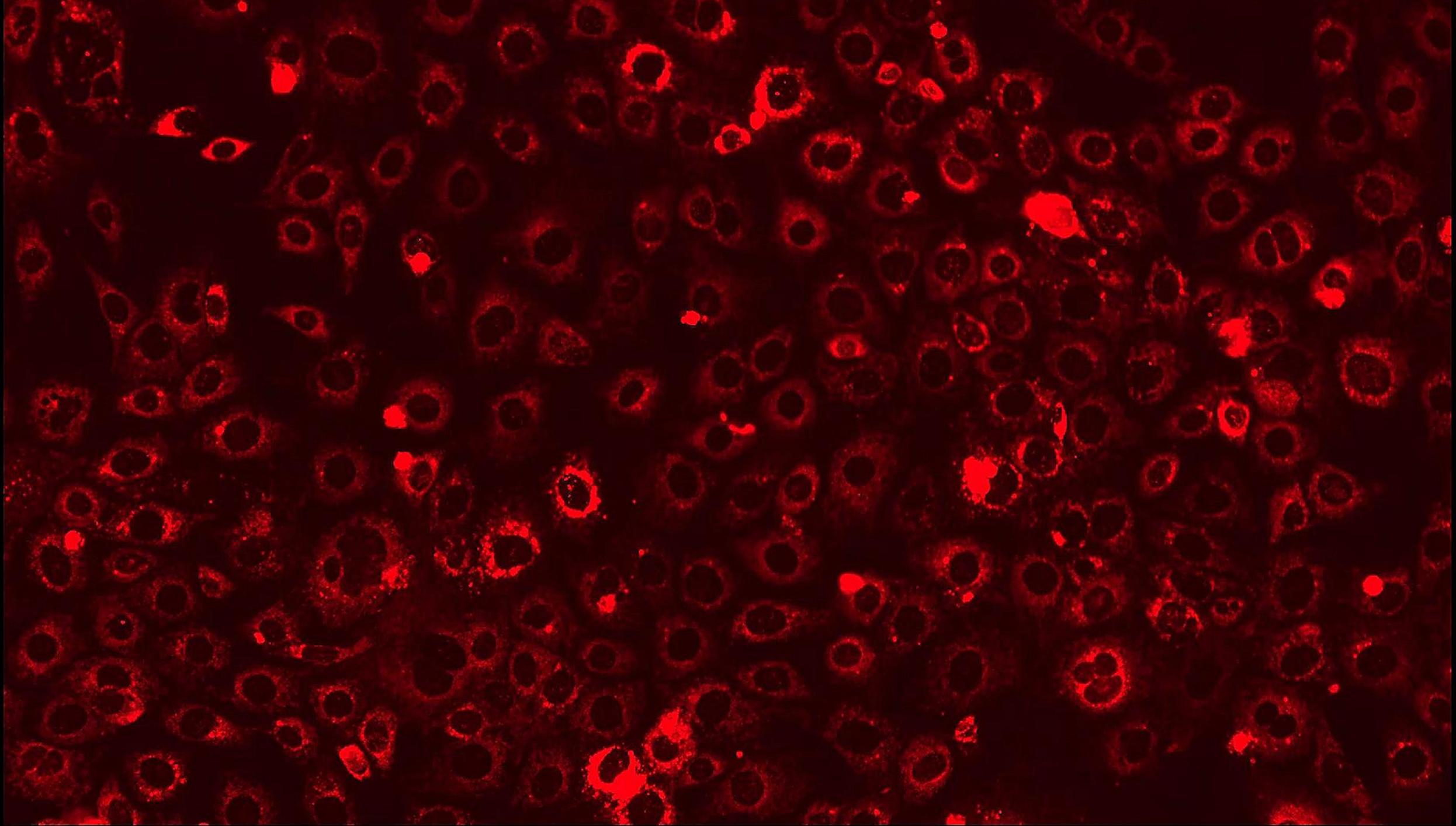
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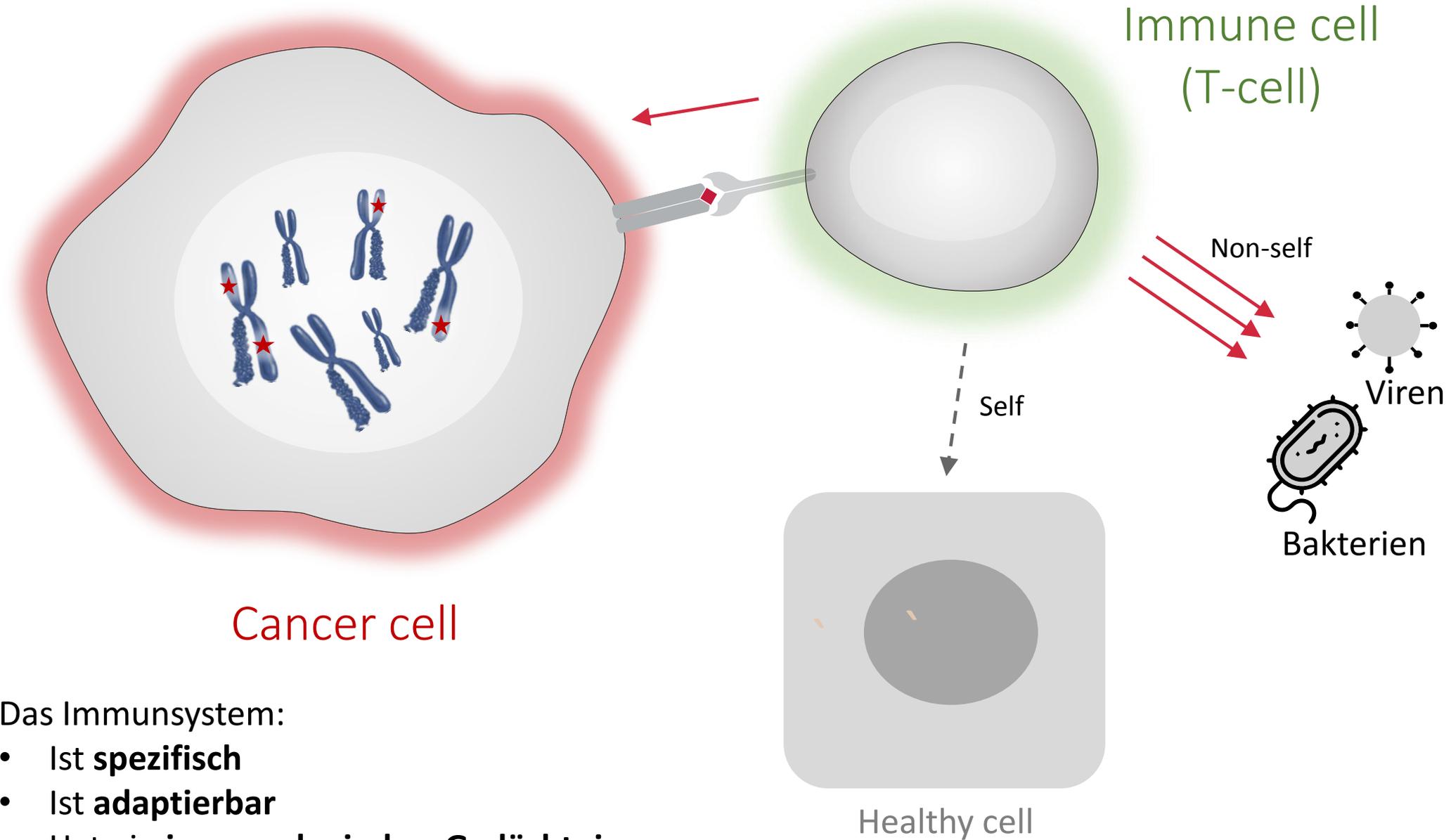
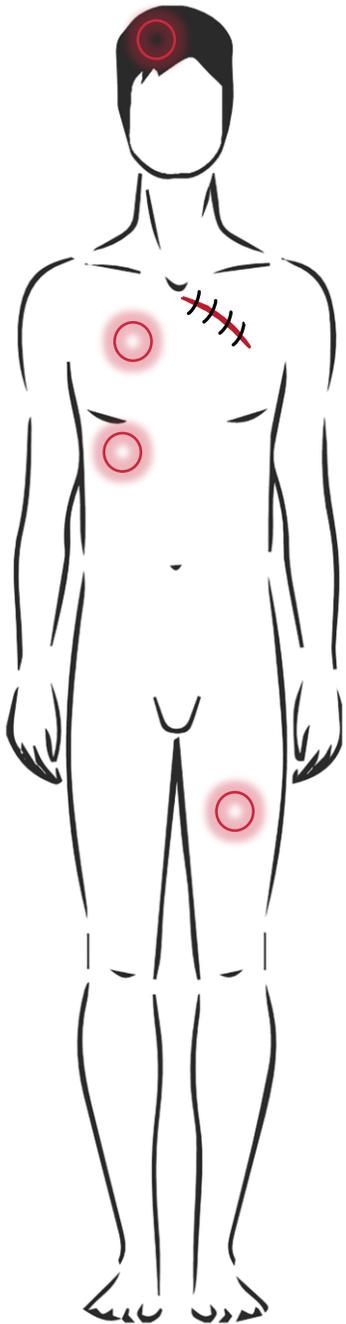


Cancer cell

Killing

Immune cell
(T-cell)





Das Immunsystem:

- Ist **spezifisch**
- Ist **adaptierbar**
- Hat ein **immunologisches Gedächtnis**

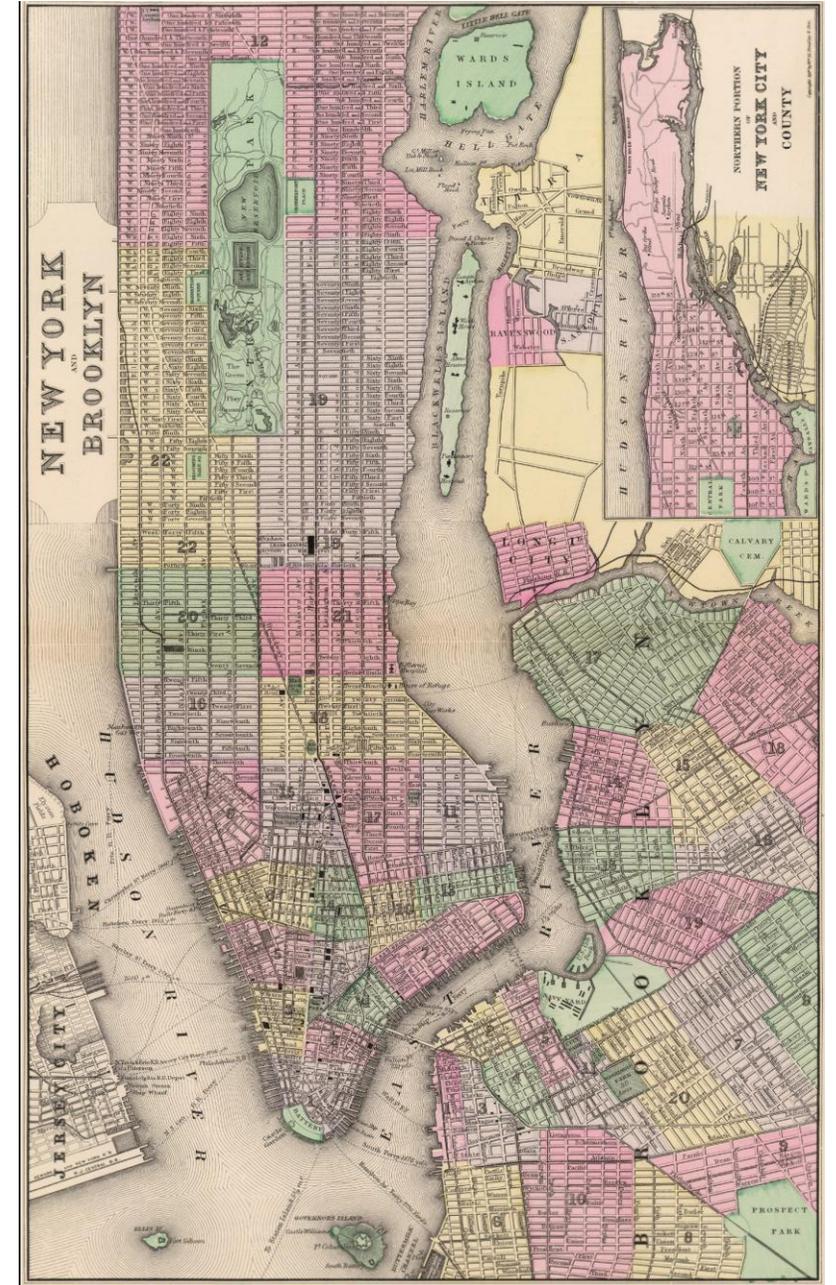
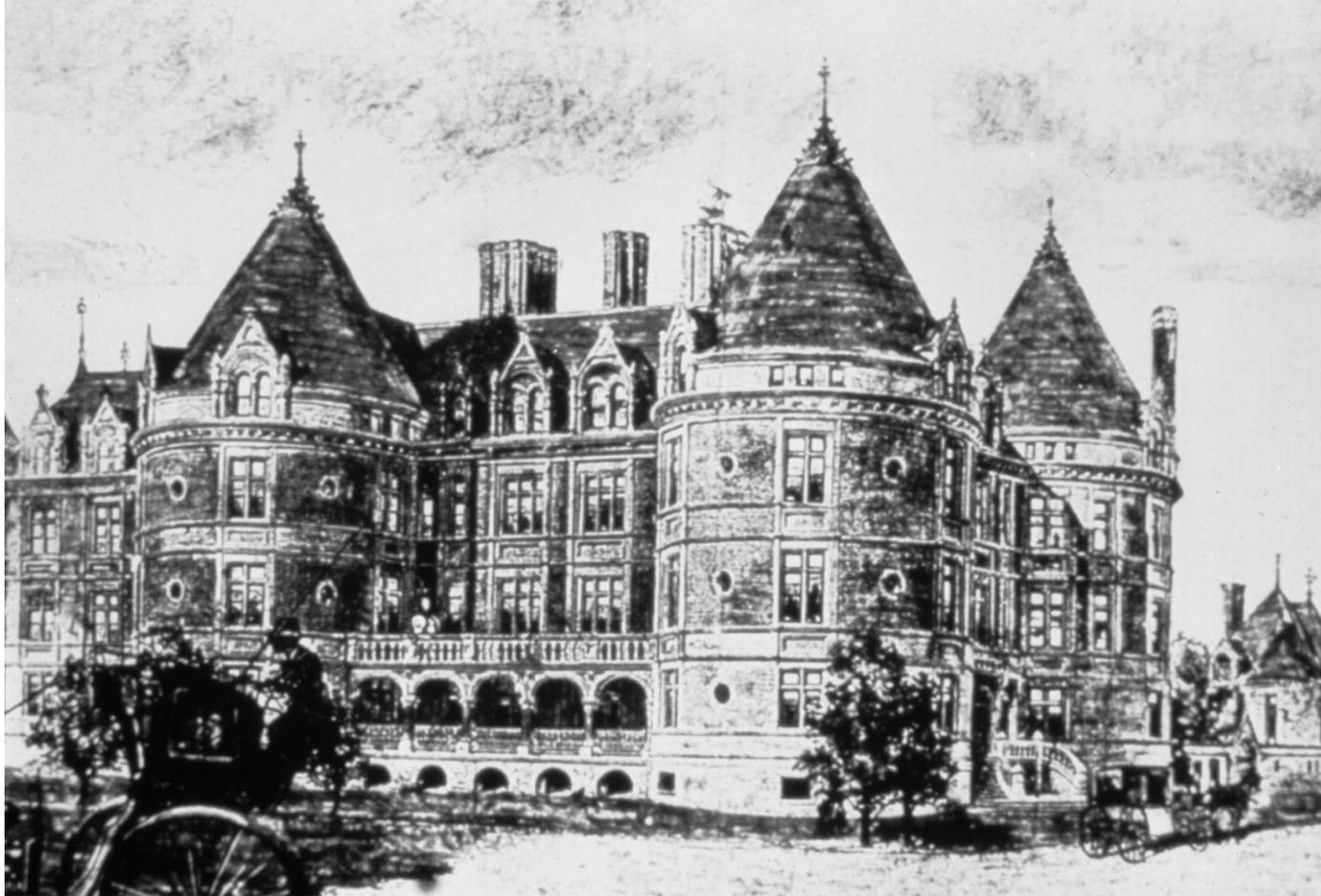
Paul Ehrlich erkannte bereits früh die Signifikanz des Immunsystems



In the 19th century Paul Ehrlich proposed

- The concept of **immune surveillance**
(immune system constantly eradicates malignant cells)
- That we may **use the immune system** to fight cancer

William Coley - Chirurg am Memorial Sloan Kettering in NY



William Coley heilte Krebs mit der Injektion von toten Bakterien

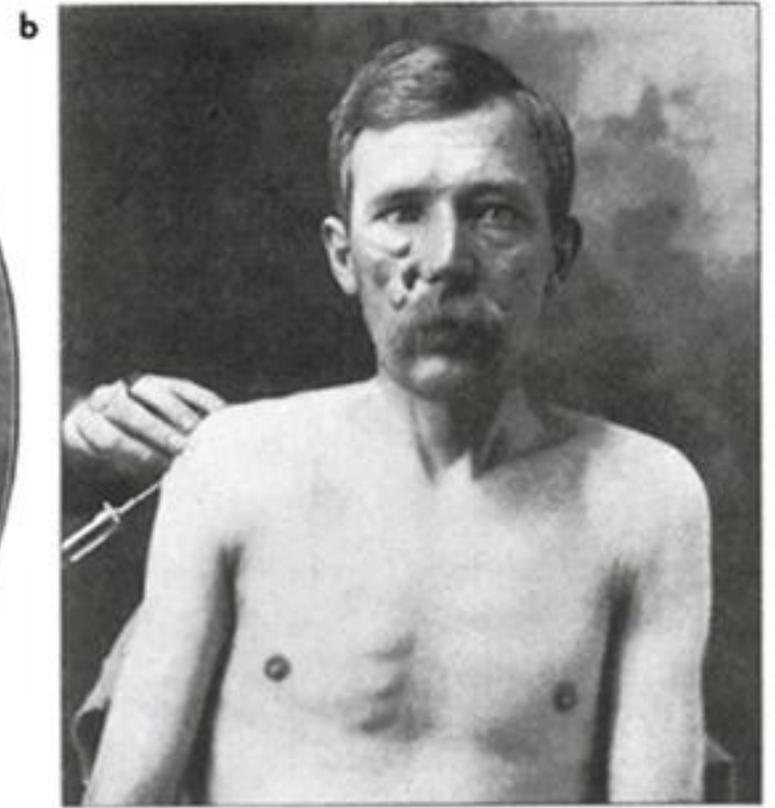
DIE GEBURT DER KREBS-IMMUNOTHERAPIE

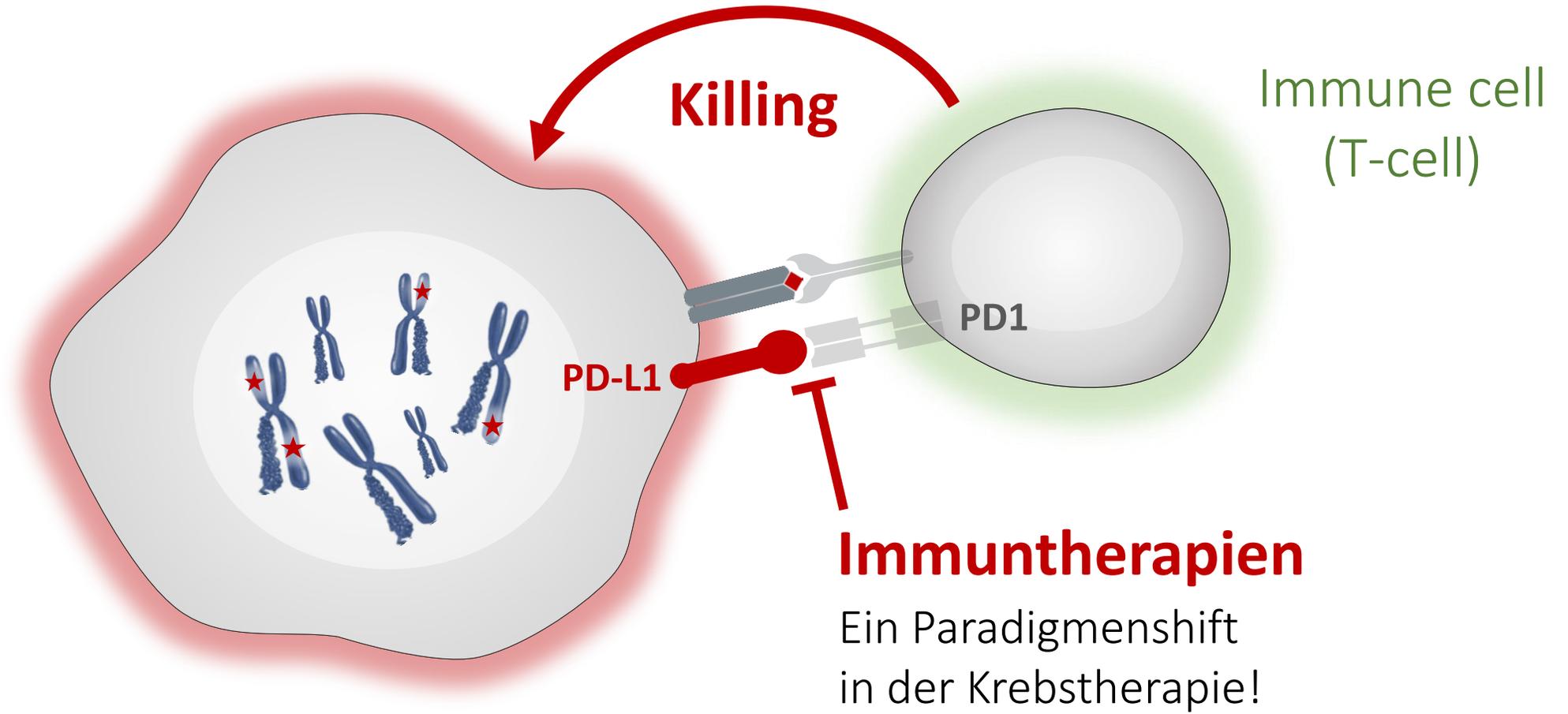
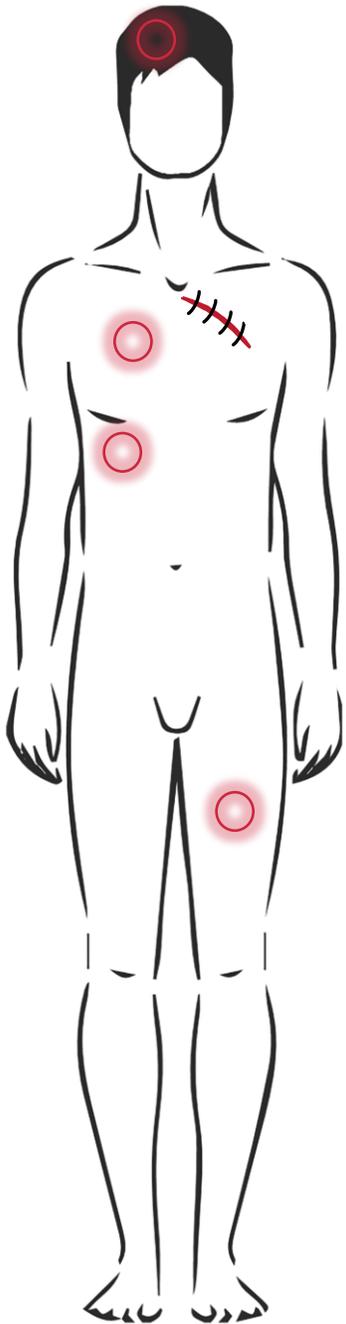


Patient with rapid response

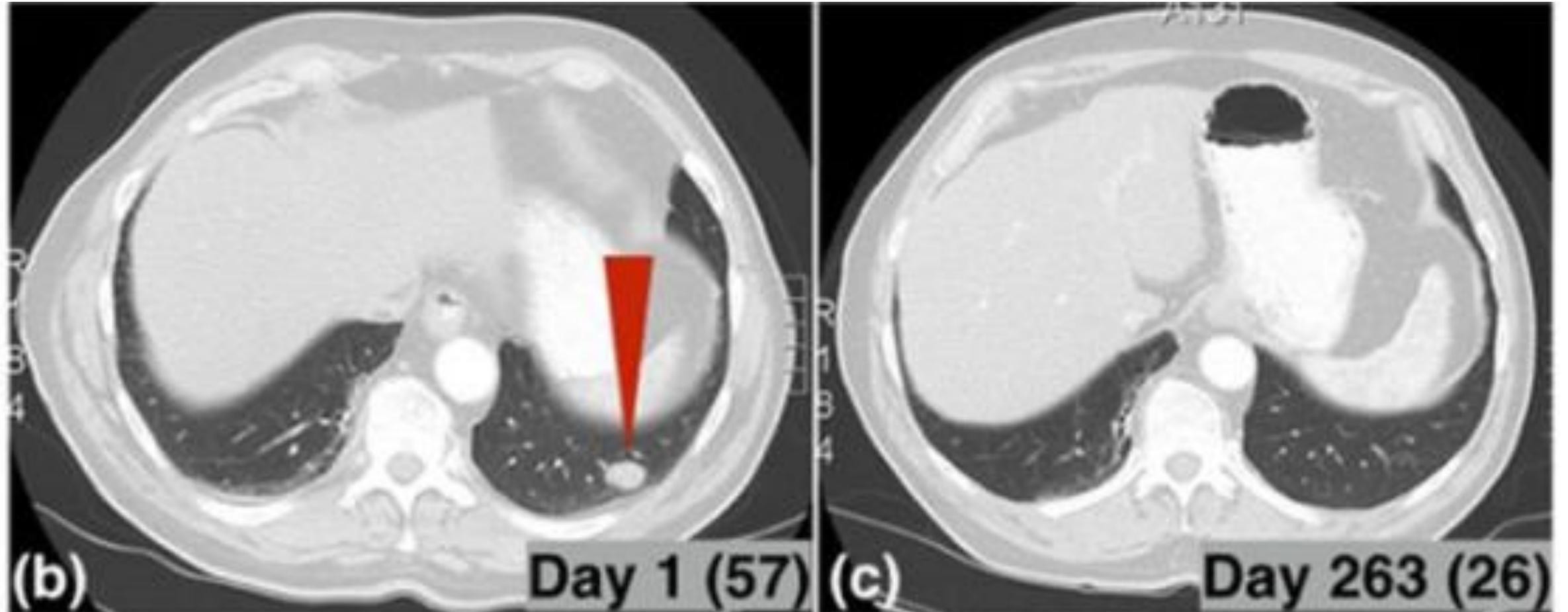


Patient responded after 63 injections





Ergebnisse nach Immuntherapie

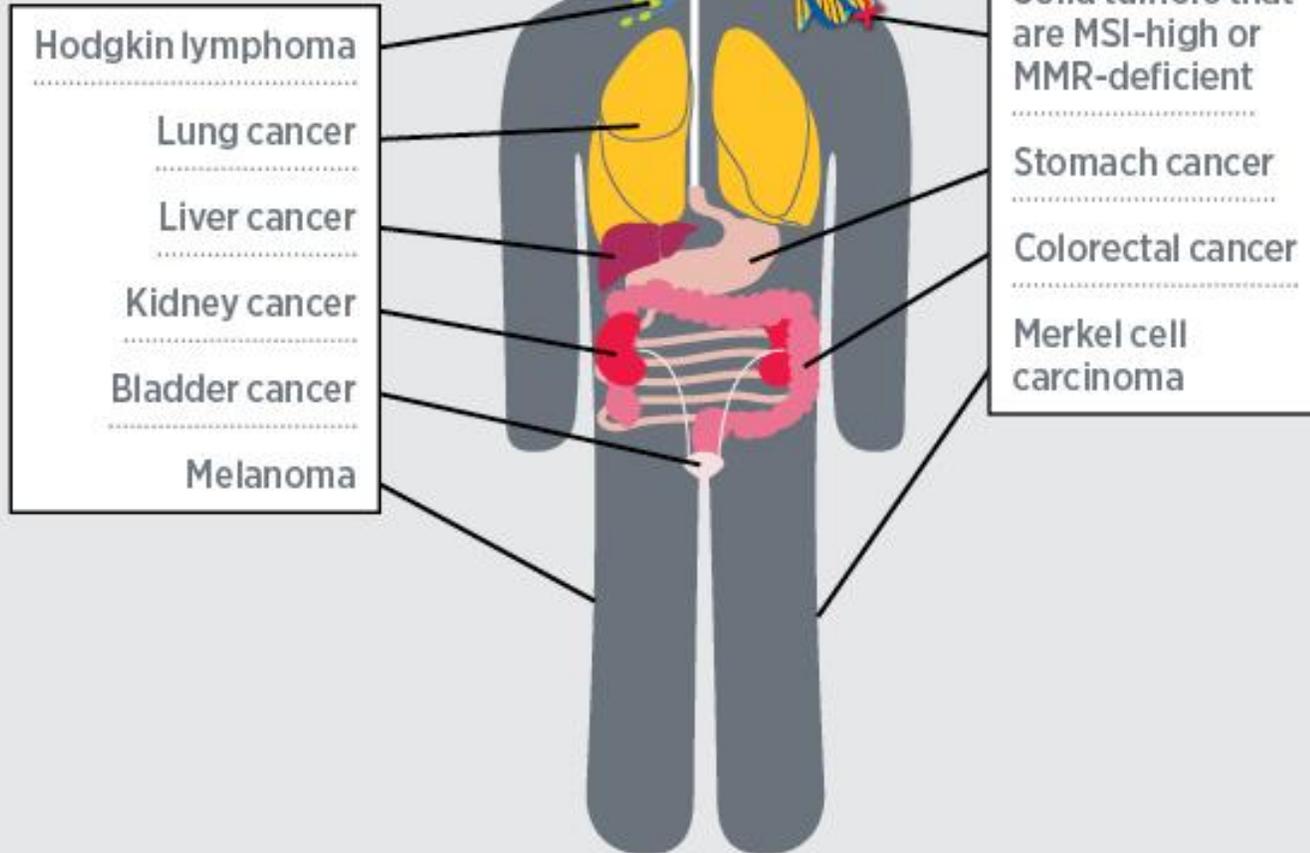


These are not isolated patient cases any more:

A large fraction of melanoma patients responds and the responses are durable.

Immuntherapien werden in der Klinik für verschiedene Tumortypen verwendet

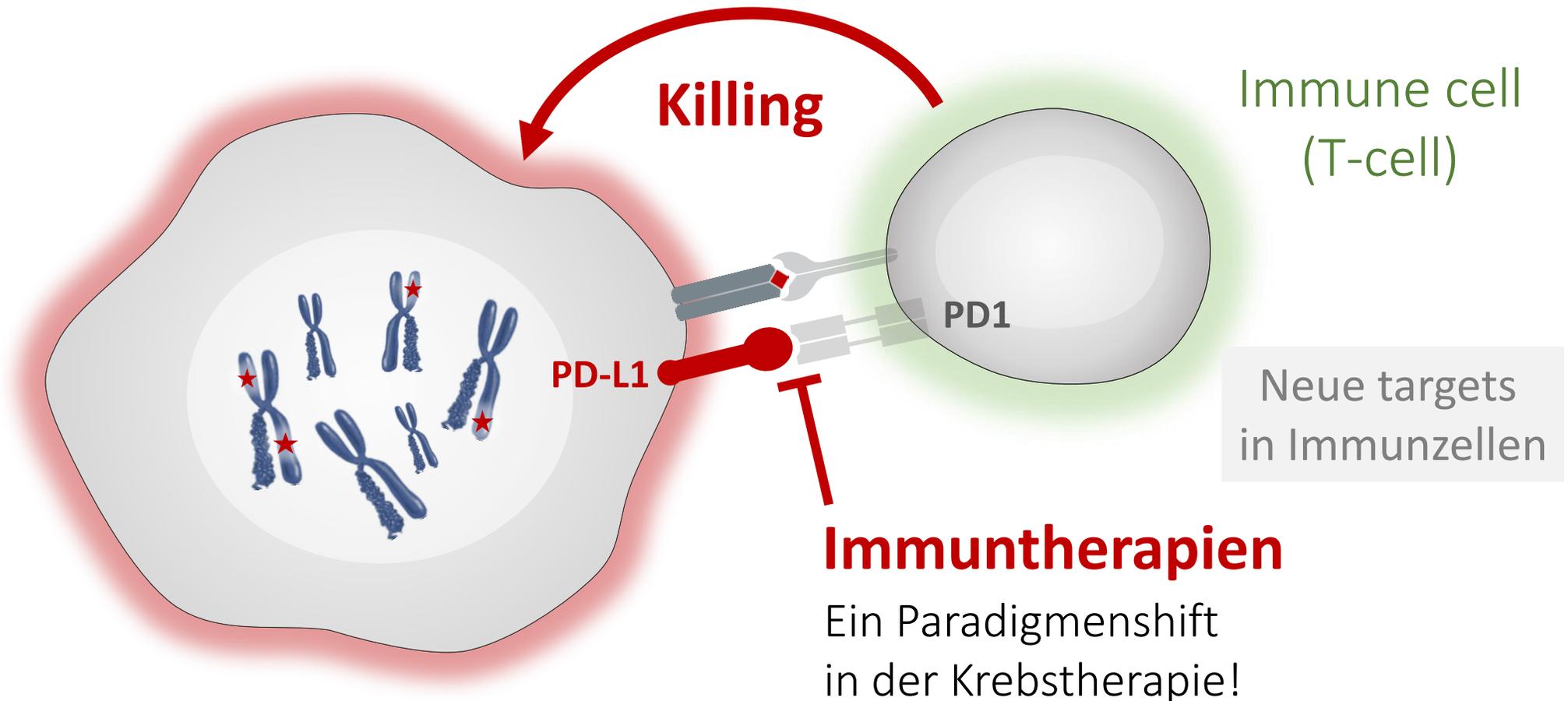
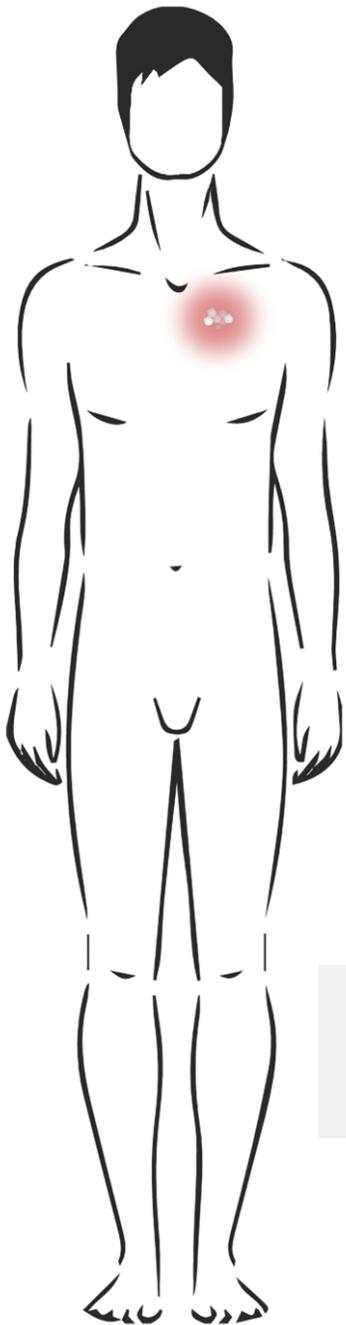
As of 2017,
immunotherapies
were FDA approved
for certain patients with:



American Association for Cancer Research (AACR)

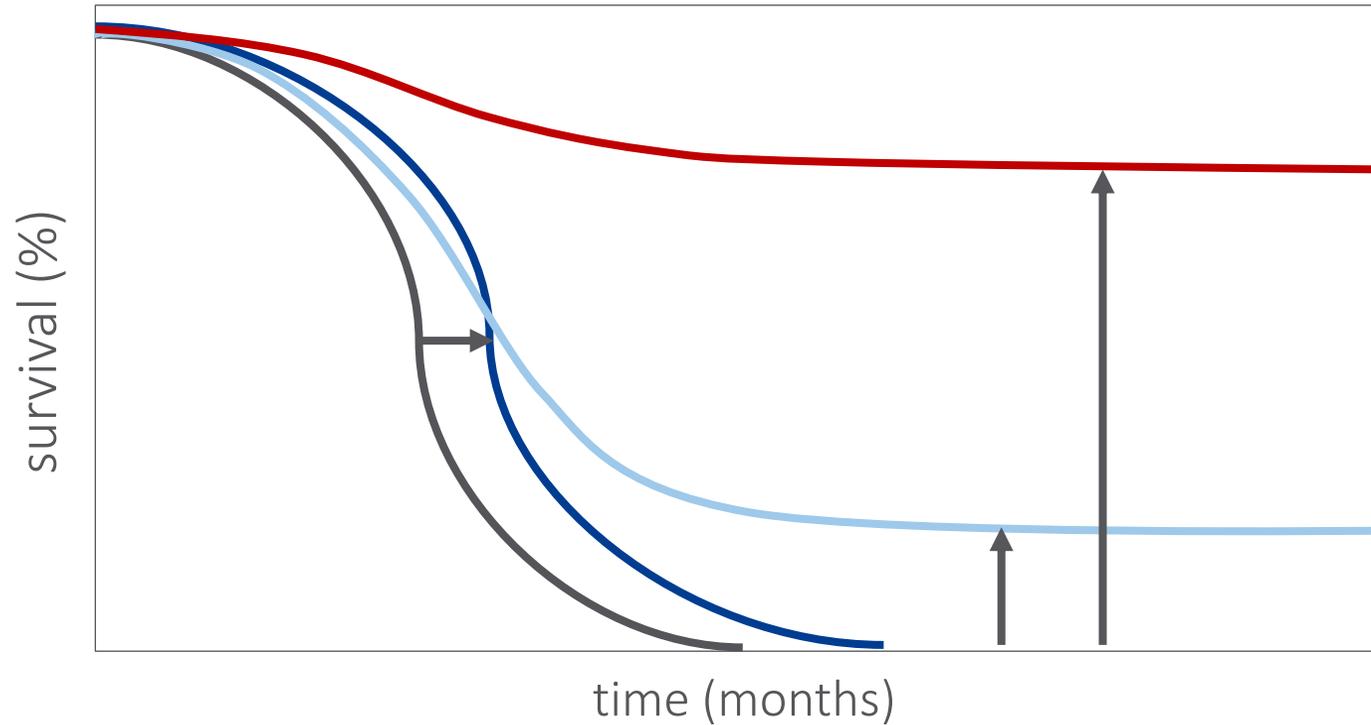
Challenges remain:

- About half of patients from these (in principal responsive) cancer types do not respond
- In many cancer types immunotherapies are ineffective



Inhibierung von Tumor-spezifischen Signalen, die das Immunsystem paralisieren.

Ziel: Mittels Kombinationstherapien die Überlebenskurven verschieben



Chemotherapy: cytotoxic, systemic inhibition of proliferating cells

Targeted therapy: inhibition of specific oncogenic signaling pathways, lack of durable responses

Immunotherapy: unleashing immune system to fight cancer, durable but only in fraction of patients

Combination therapy: the future of cancer treatment

Adapted from Sharma and Allison, Cell, 2015

Mein Team am IMP



Find out more @

www.obenauf lab.com

www.imp.ac.at

www.training.vbc.ac.at

Looking for motivated
students/**postdocs**/
bioinformaticians.

Funding:



Technical support:



Some of our collaborators:

Thomas Wiesner

Johannes Zuber

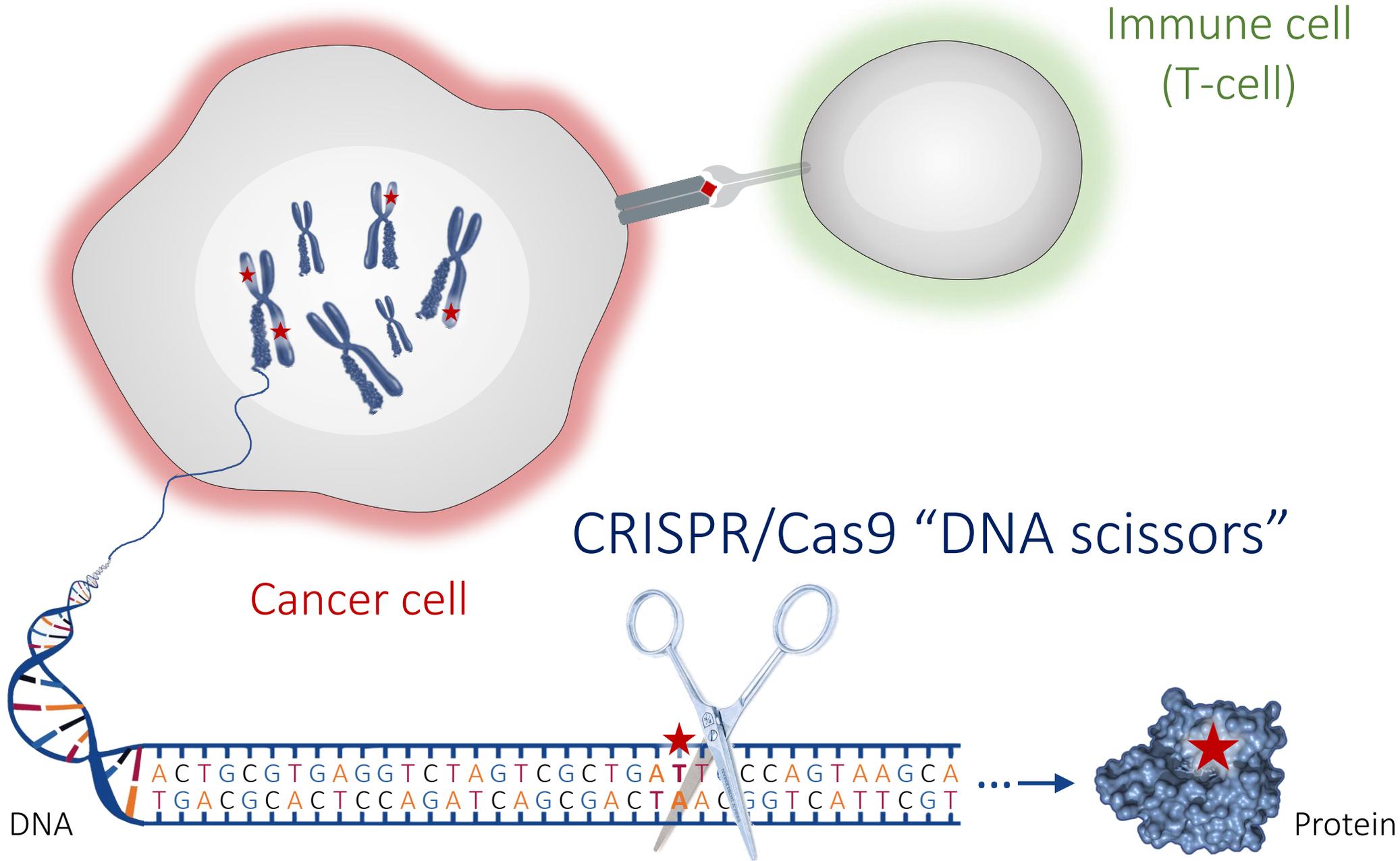
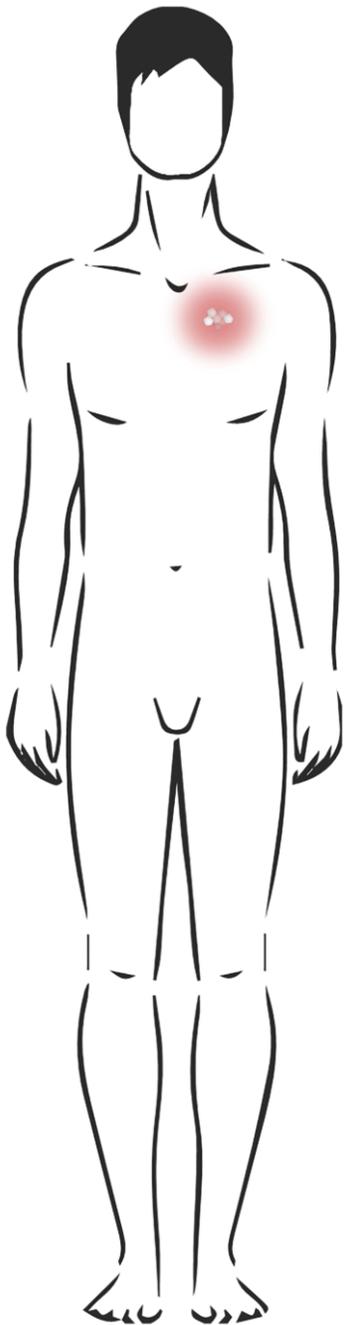
Iris Helfrich/Dirk Schadendorf

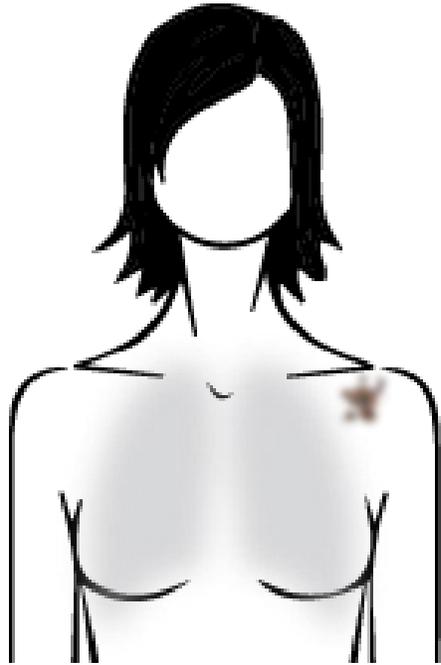
Marcus Bosenberg

Michael Speicher

Flavio Solca

Ulrike Weyer-Czernilofsky





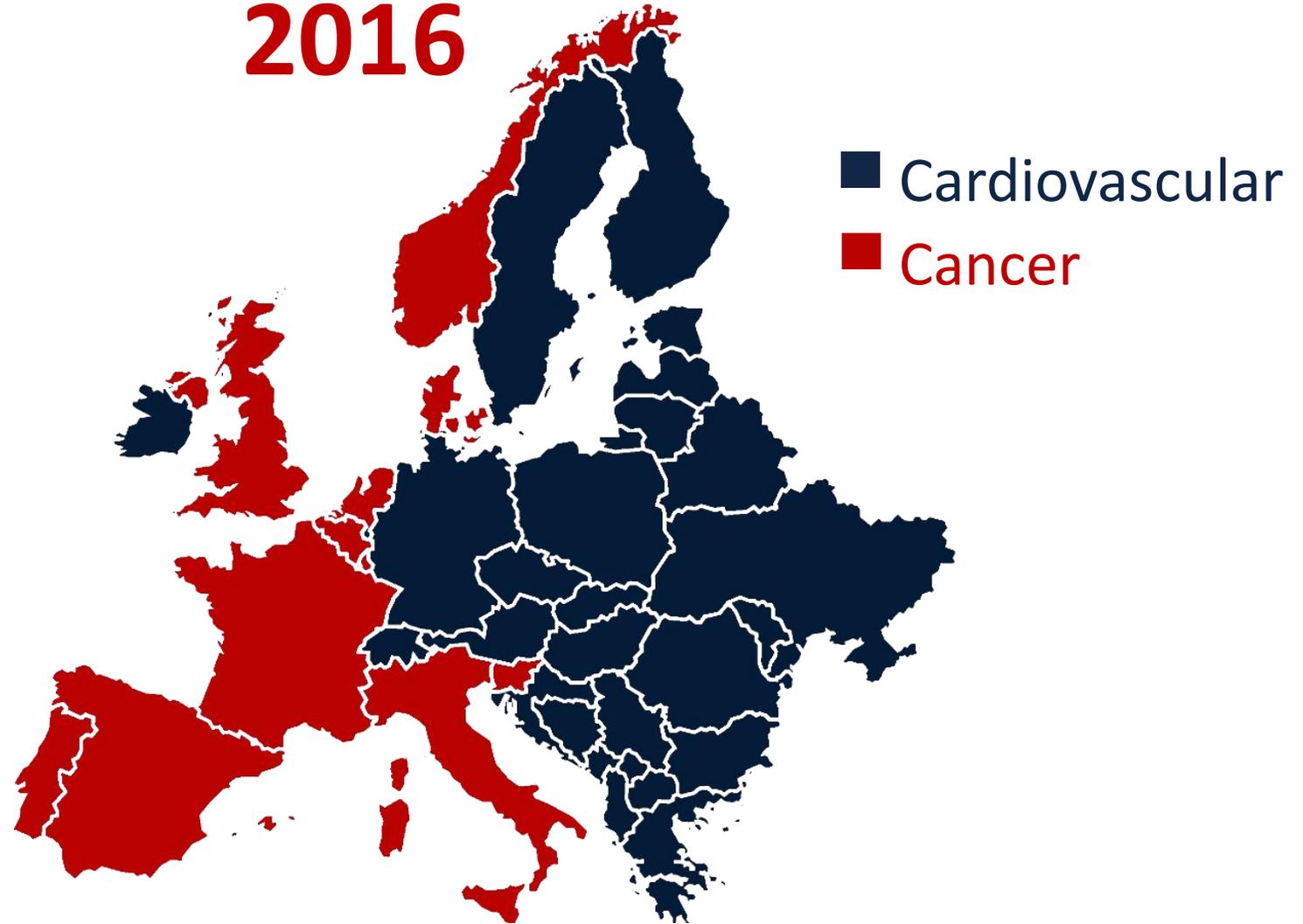
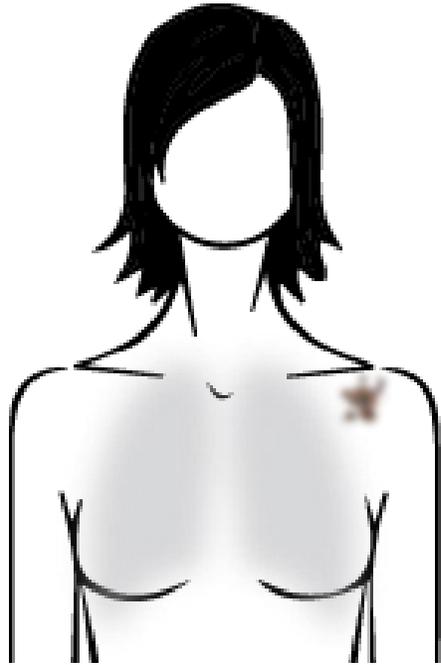
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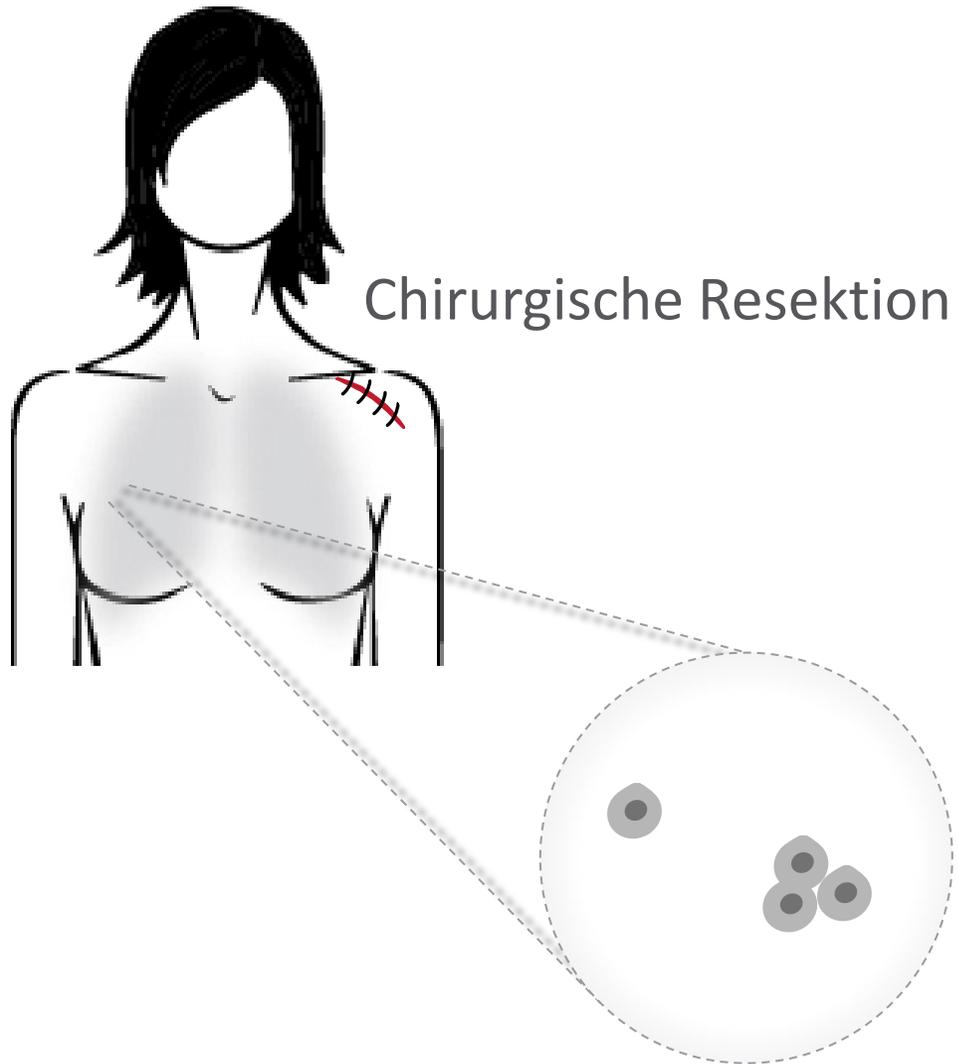
entwickelt einen Tumor
im Laufe des Lebens.

Hauptursache der Sterblichkeit

2016

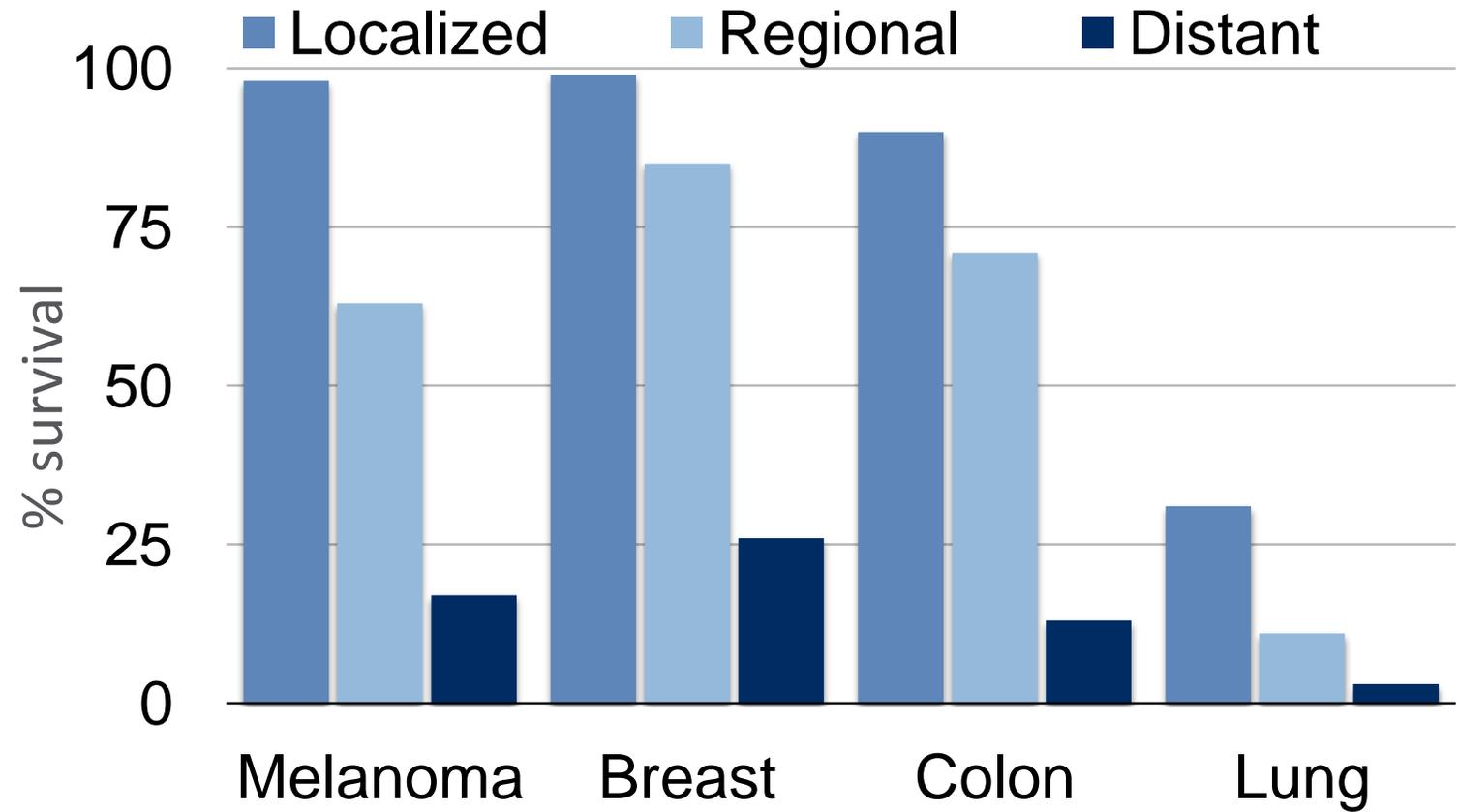
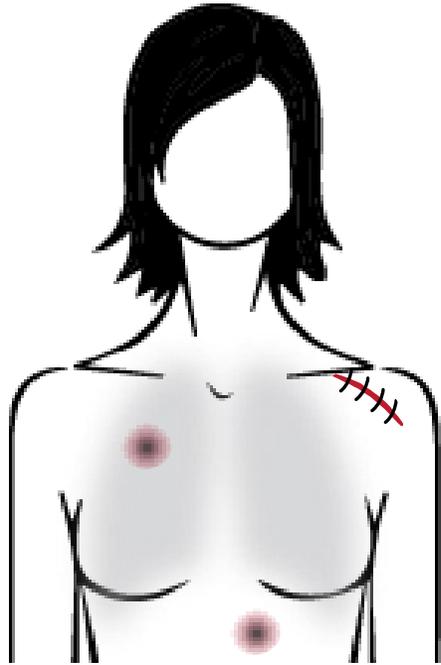


Chirurgische Resektion des Primärtumors ist in vielen Fällen kurativ

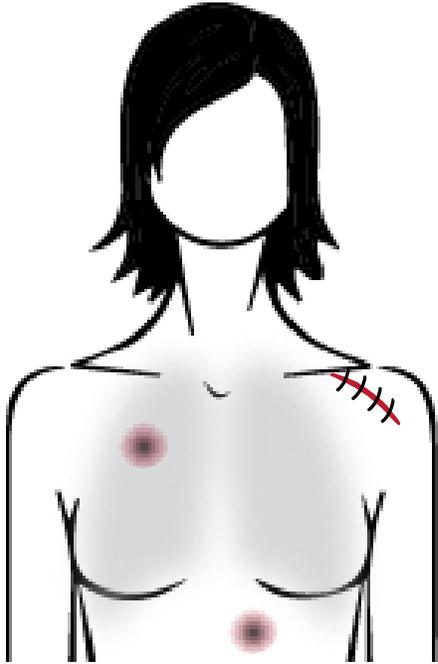


Tumorzellen können den Tumor früh verlassen und in einem **“schlafenden Zustand”** überleben

Metastasis is responsible for more than 90% of cancer related deaths and requires systemic therapy



Metastasis is responsible for more than 90% of cancer related deaths
and requires systemic therapy

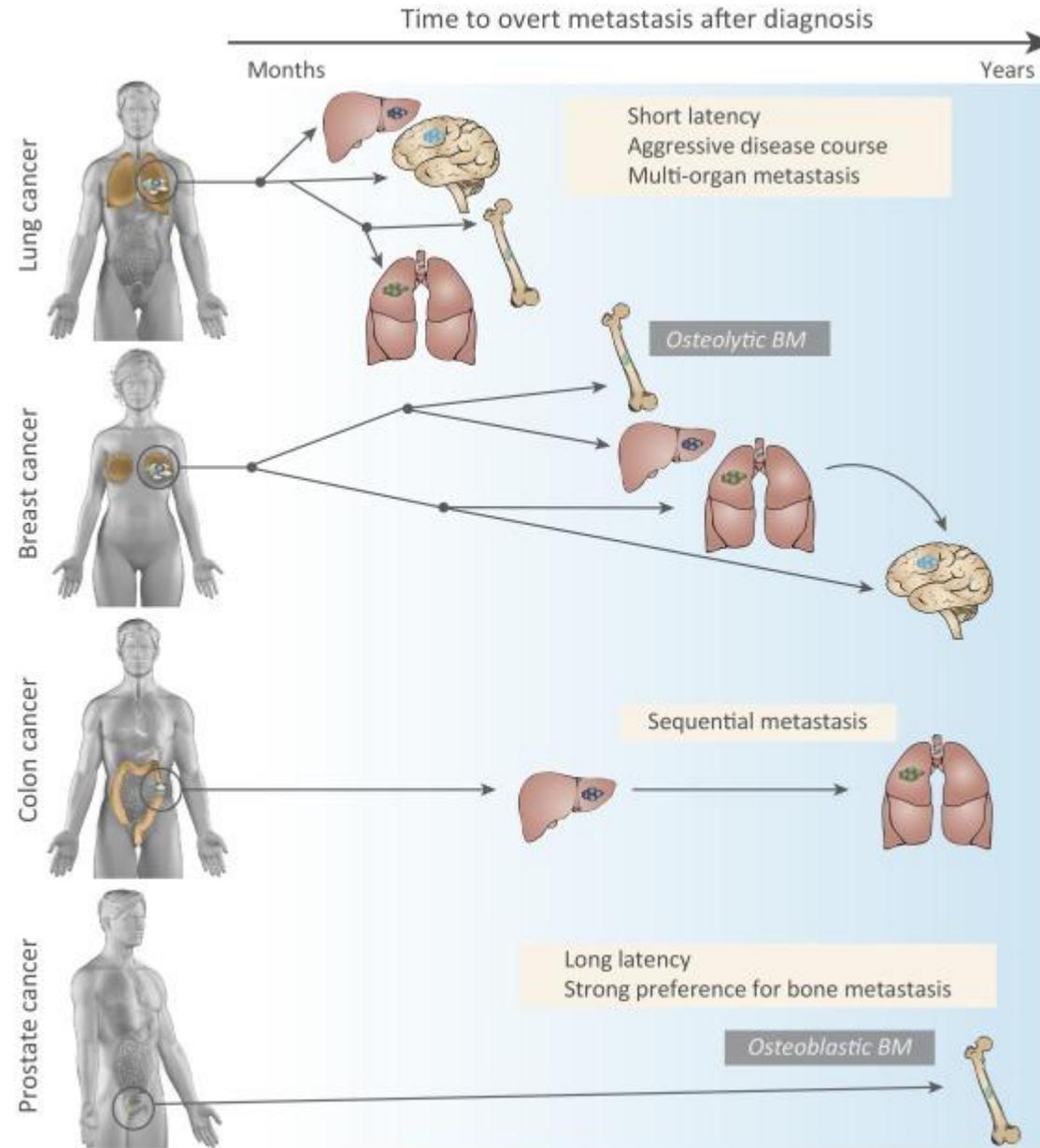


IMPORTANT CLINICAL PROBLEM

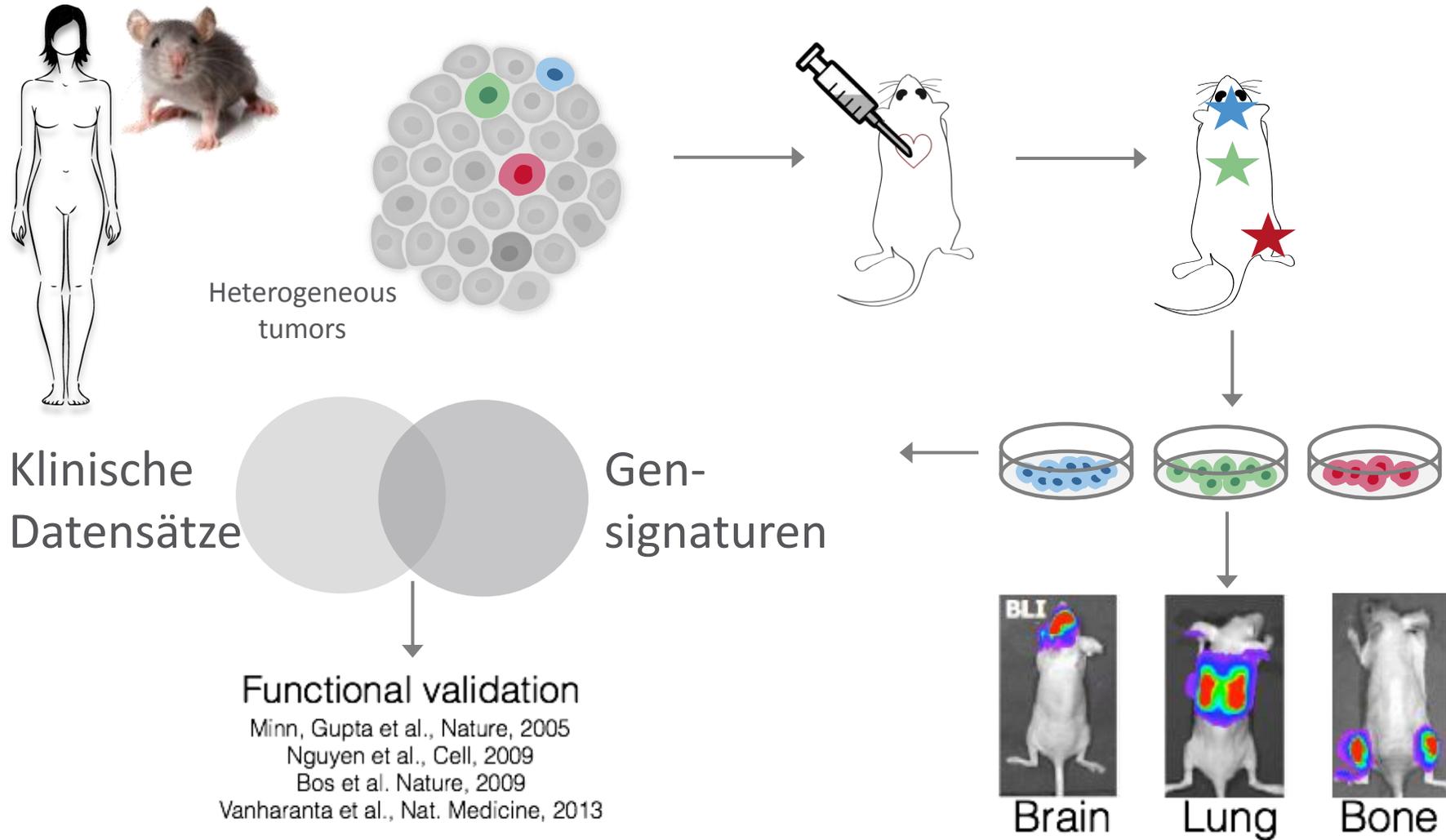
FASCINATING BIOLOGICAL PROCESS

REQUIRES SYSTEMIC THERAPY

Clinical presentation of metastasis varies dramatically



Funktionelle Modelle zur Studie der Metastasierung

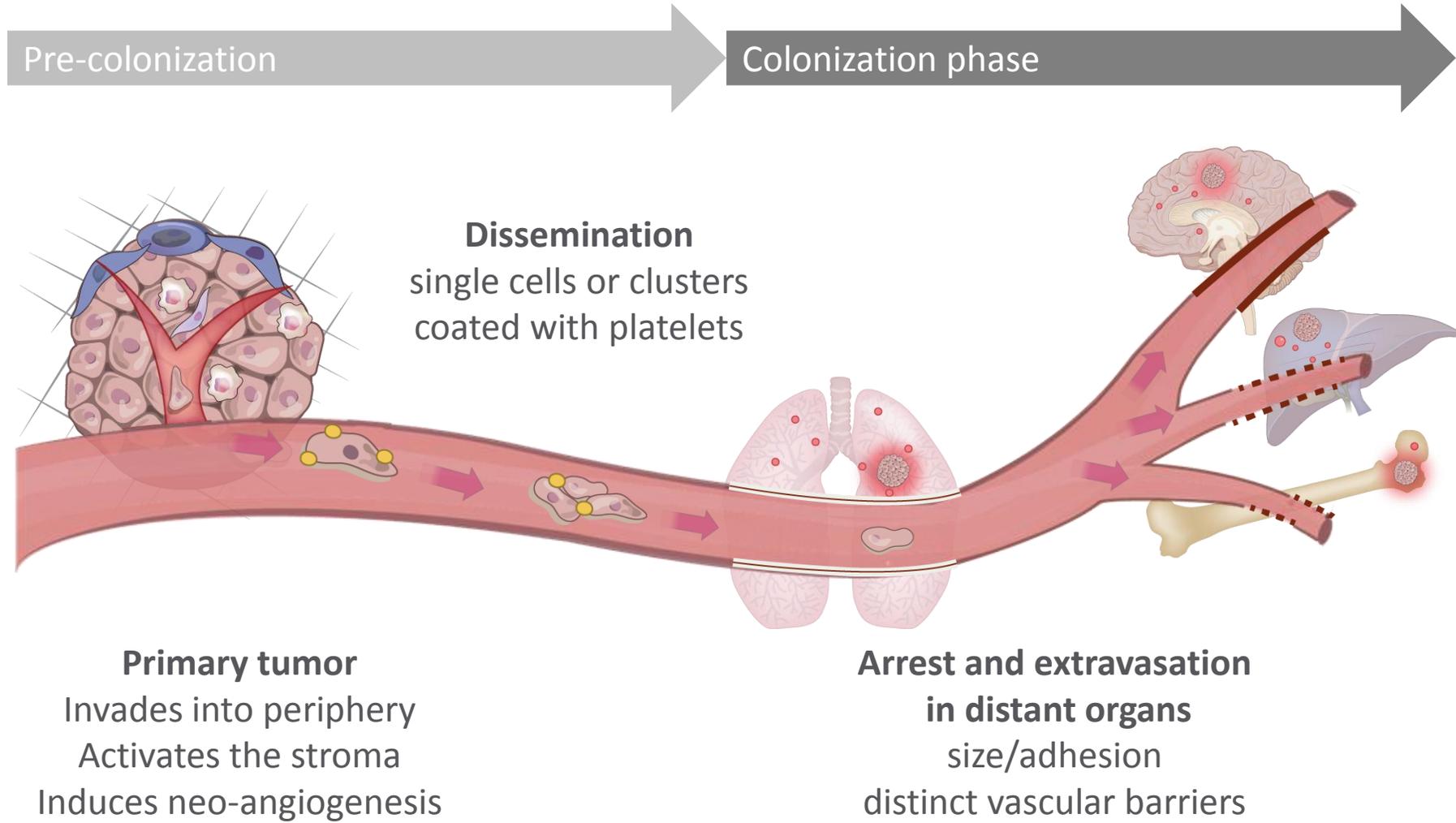


MMTV-ERBB2 brain metastasis model (immunocompetent)

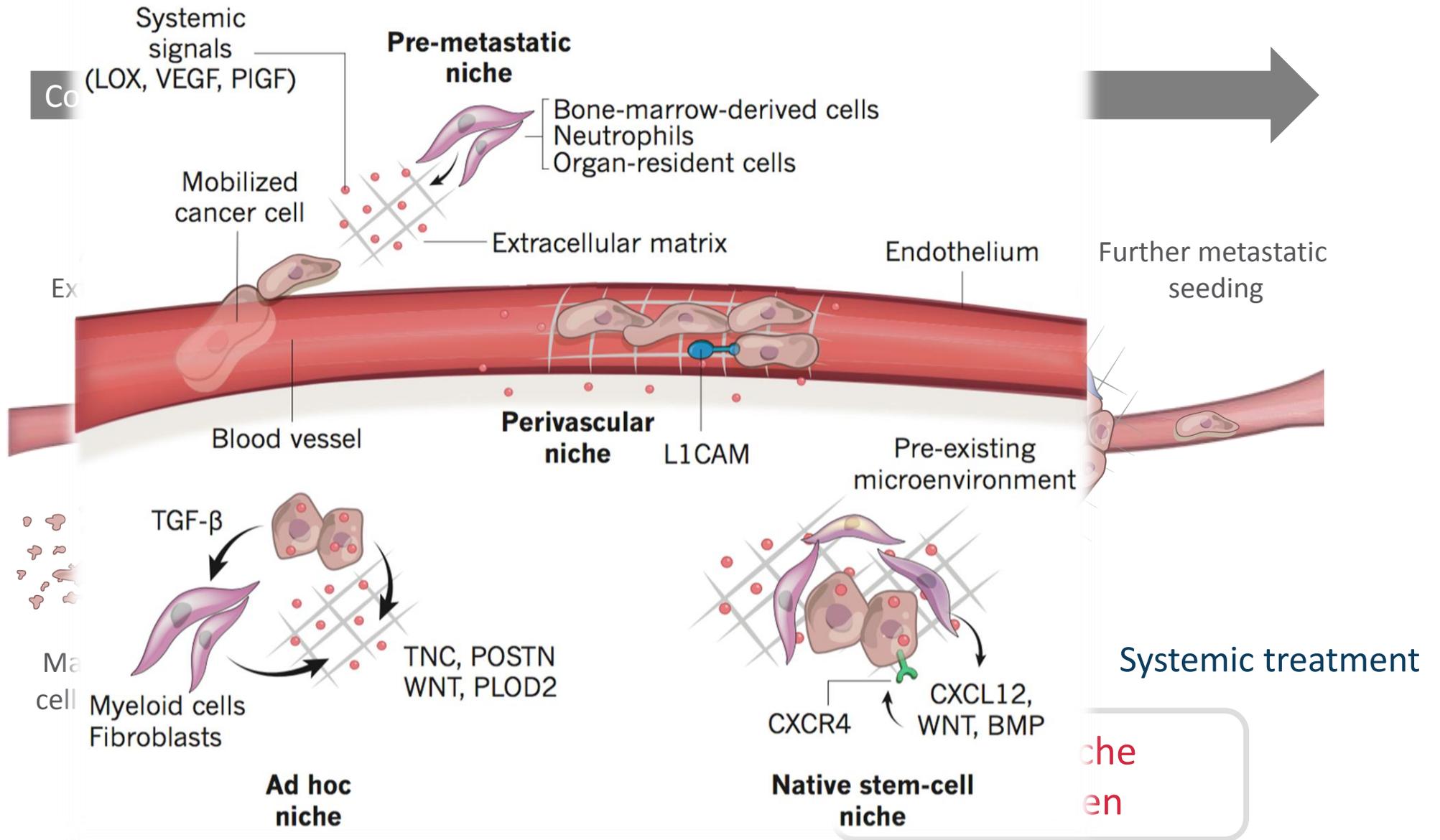
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Die Metastasierungskaskade

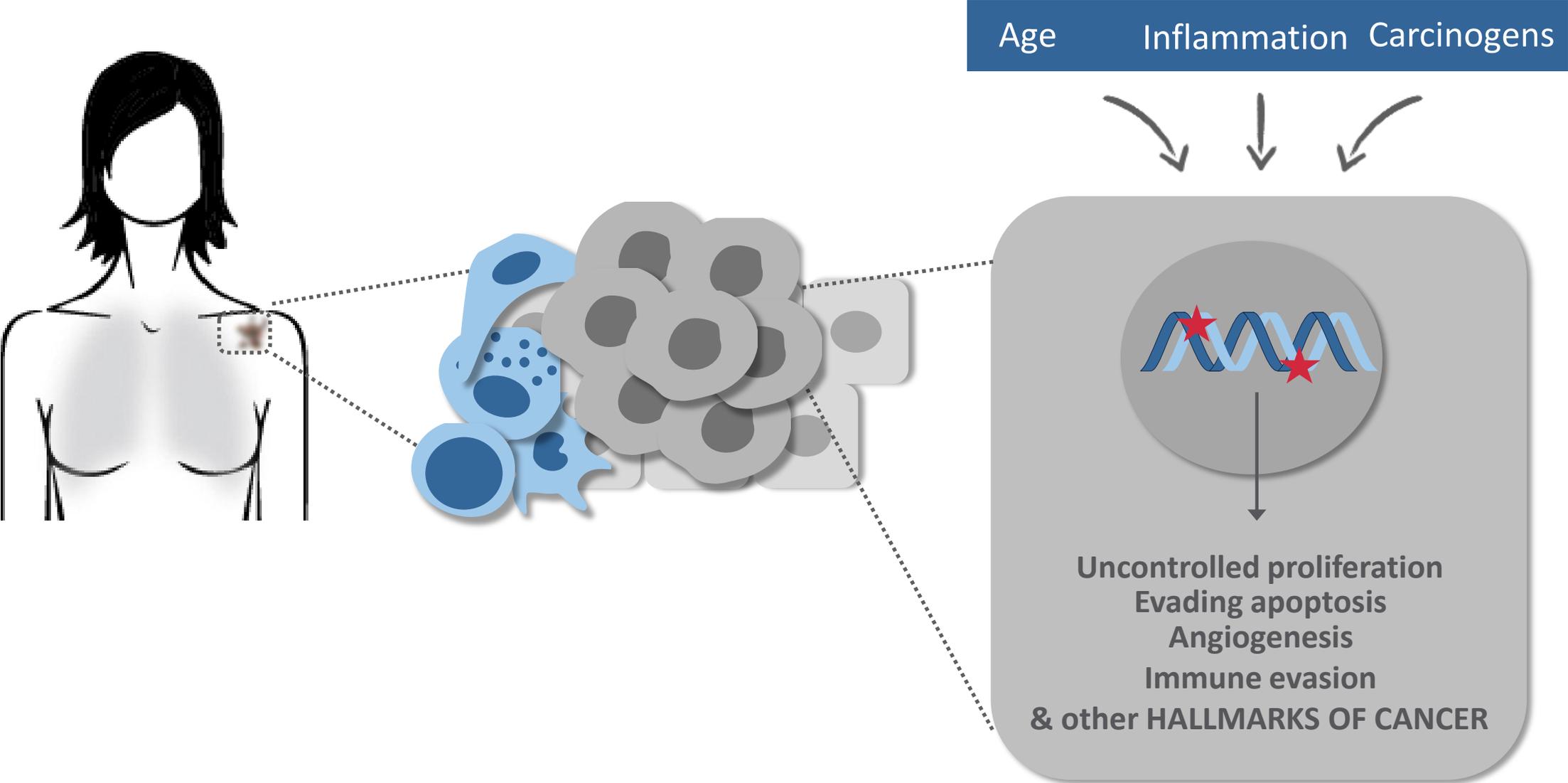


Die Metastasierungskaskade



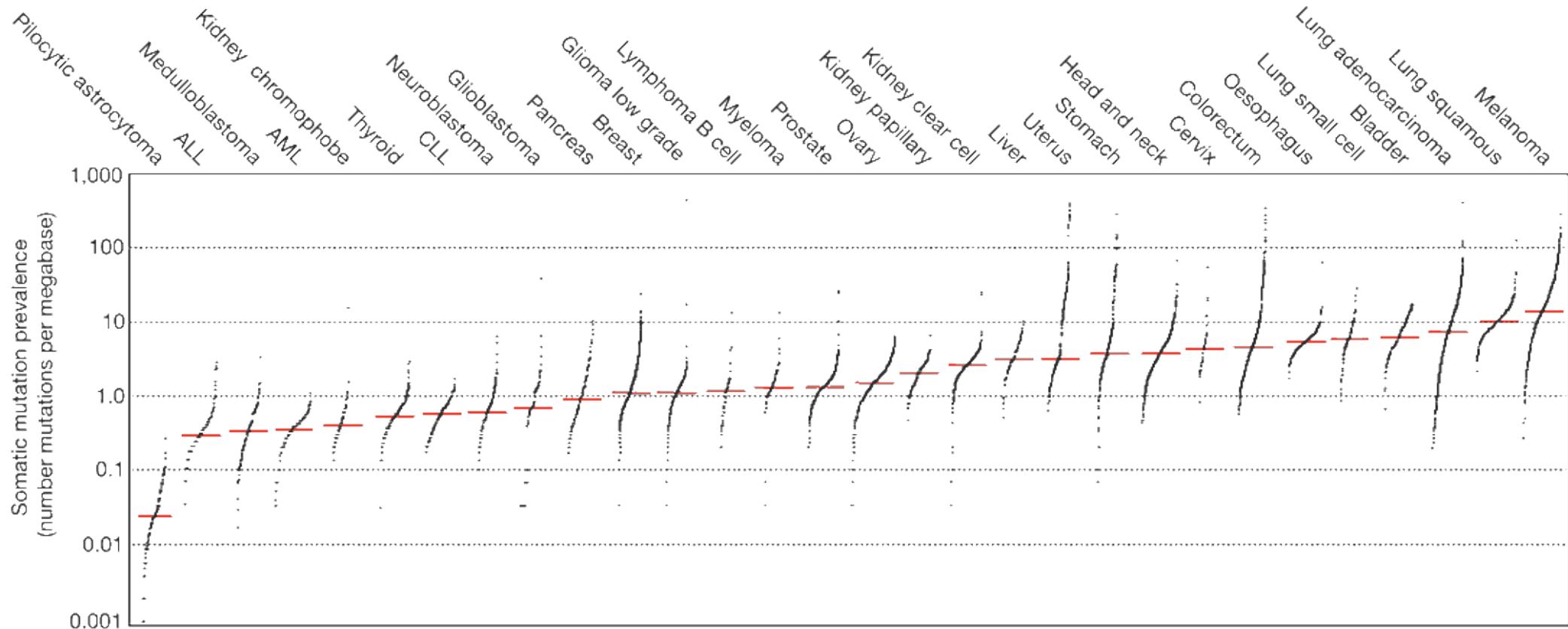
Therapie-Optionen
für Patienten
mit metastasierten Tumoren

Zielgerichtete Therapien richten sich gegen spezifische Veränderungen in den Krebszellen

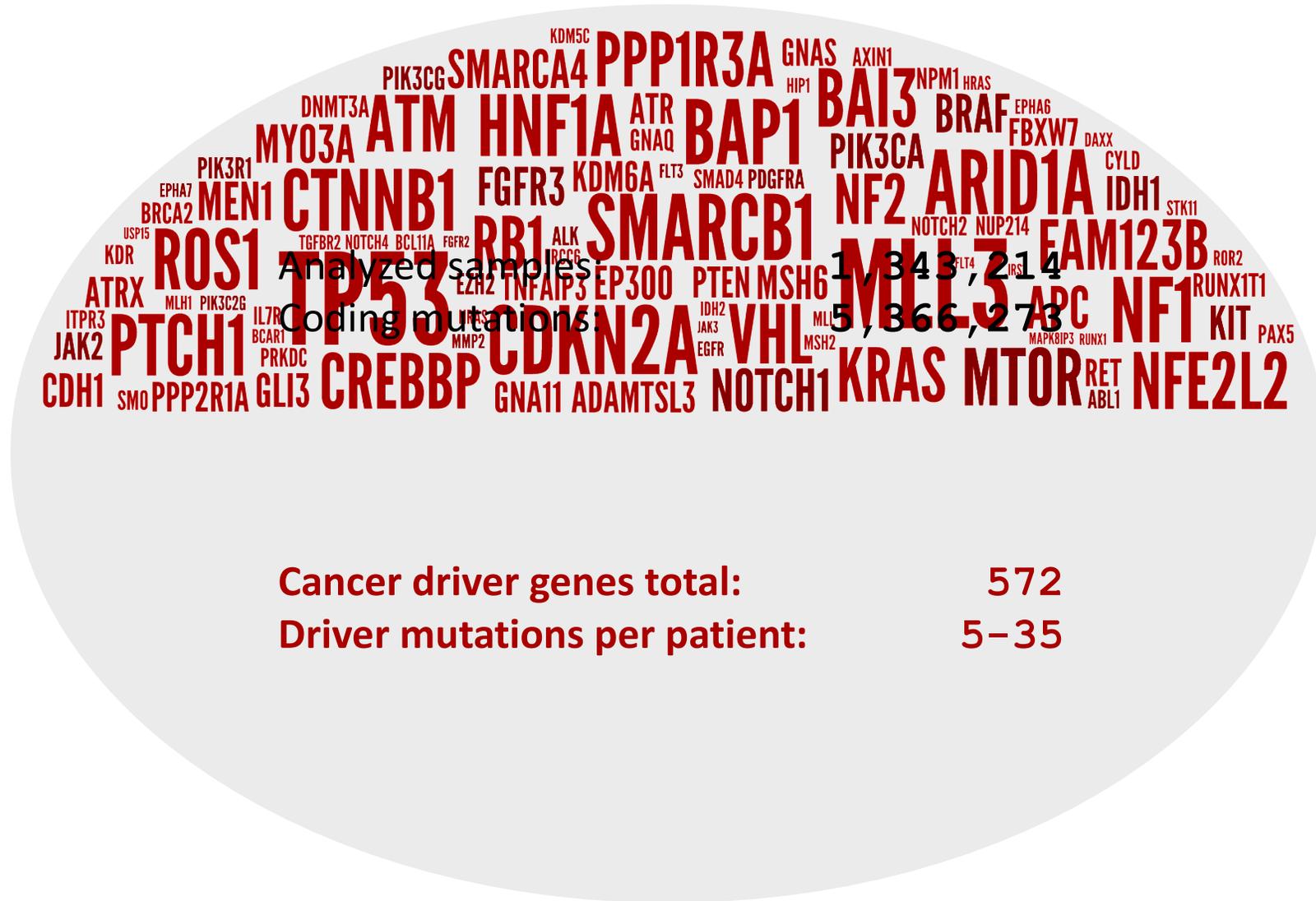


Tumore zeichnen sich durch komplexe genetische Veränderungen und viele Mutationen aus

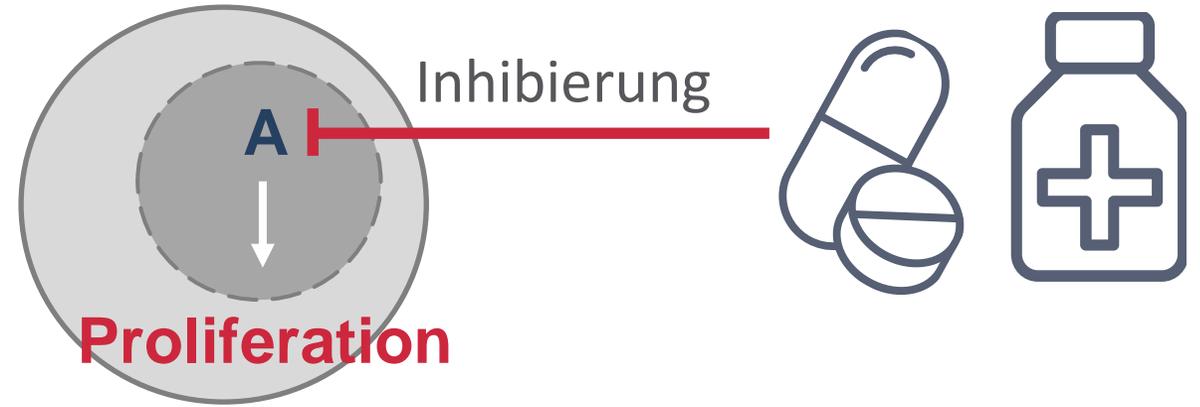
Analyzed samples: **1,343,214**
Coding mutations: **5,366,273**



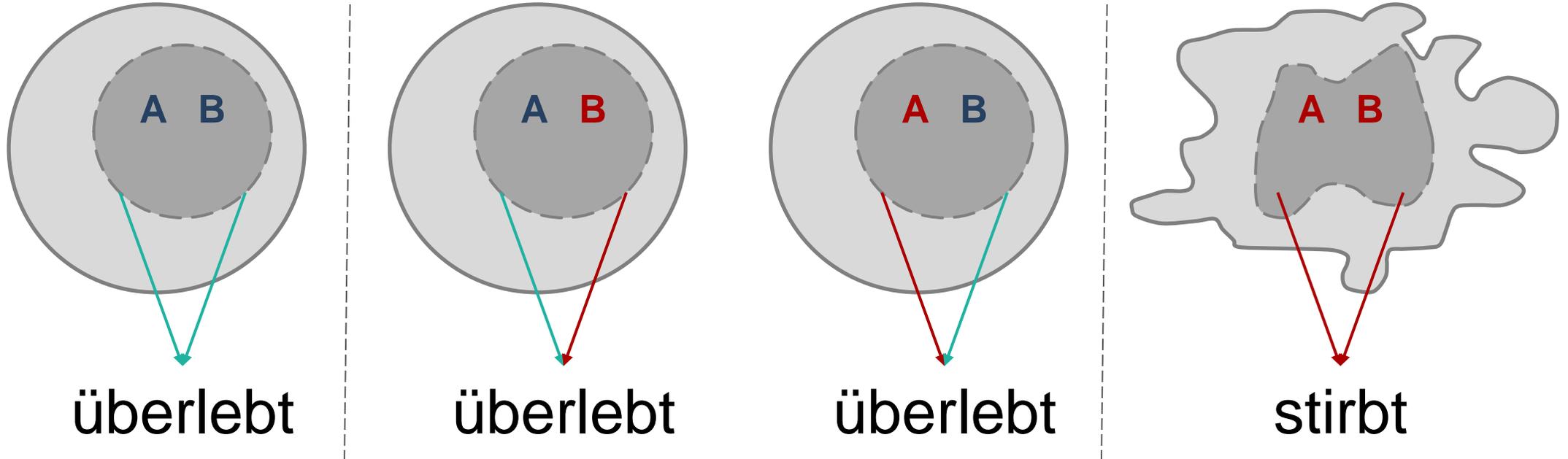
Zielgerichtete Therapien richten sich gegen spezifische Veränderungen in den Krebszellen



1. Direkte Inhibierung eines Onkogens

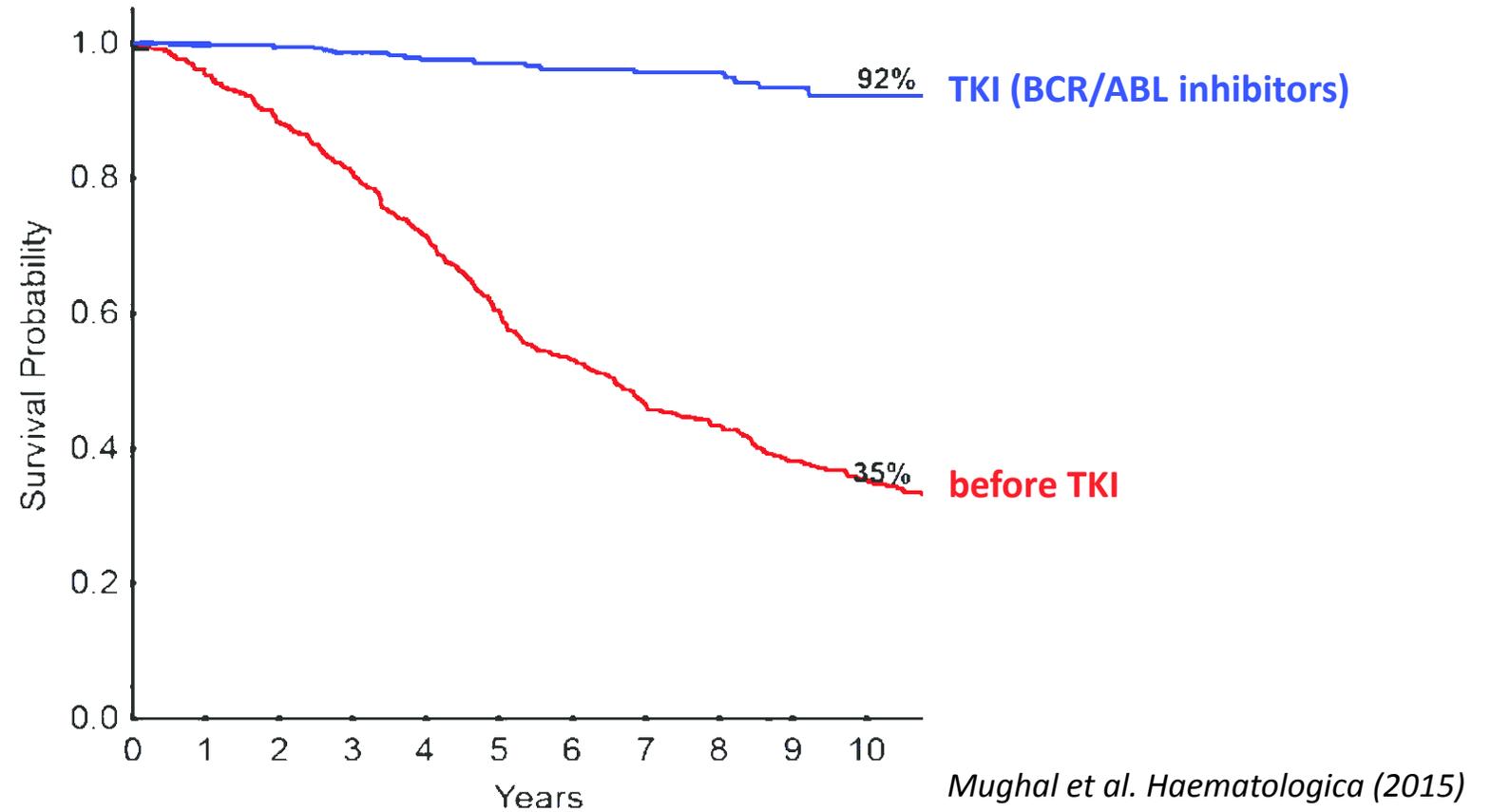
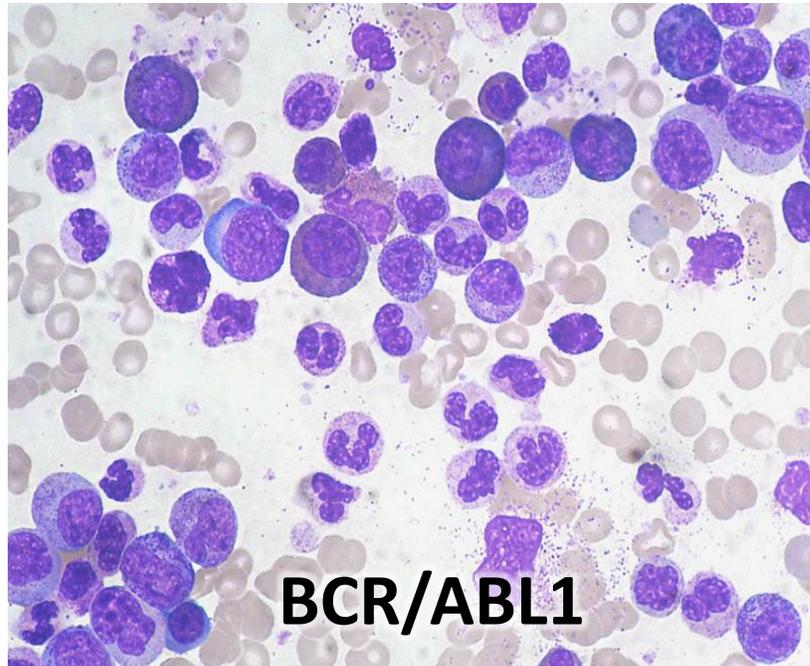


2. Synthetische Lethalität



Eine Erfolgsgeschichte: Zielgerichtete Therapie in Chronisch myeloider Leukemie

Chronic myeloid leukemia (CML)

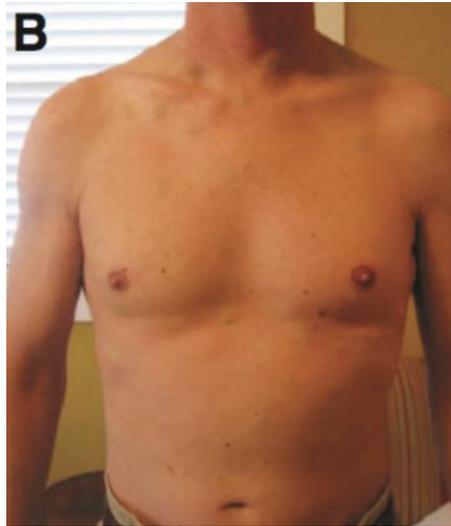


Zielgerichtete Therapie beim Melanom: neue Herausforderungen für die Zukunft

38 year-old patient with melanoma (BRAF^{V600E})



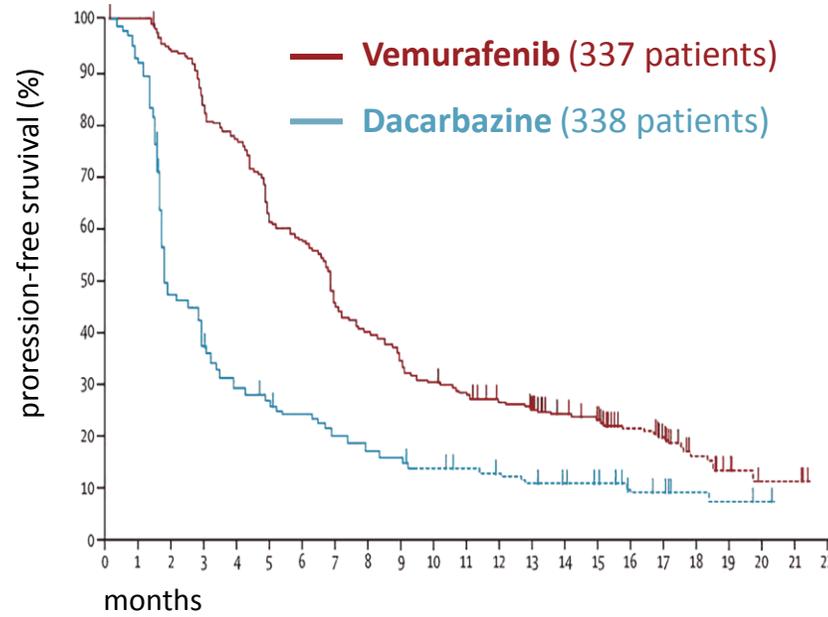
Vemurafenib (PLX4032)
15 weeks



Vemurafenib (PLX4032)
23 weeks



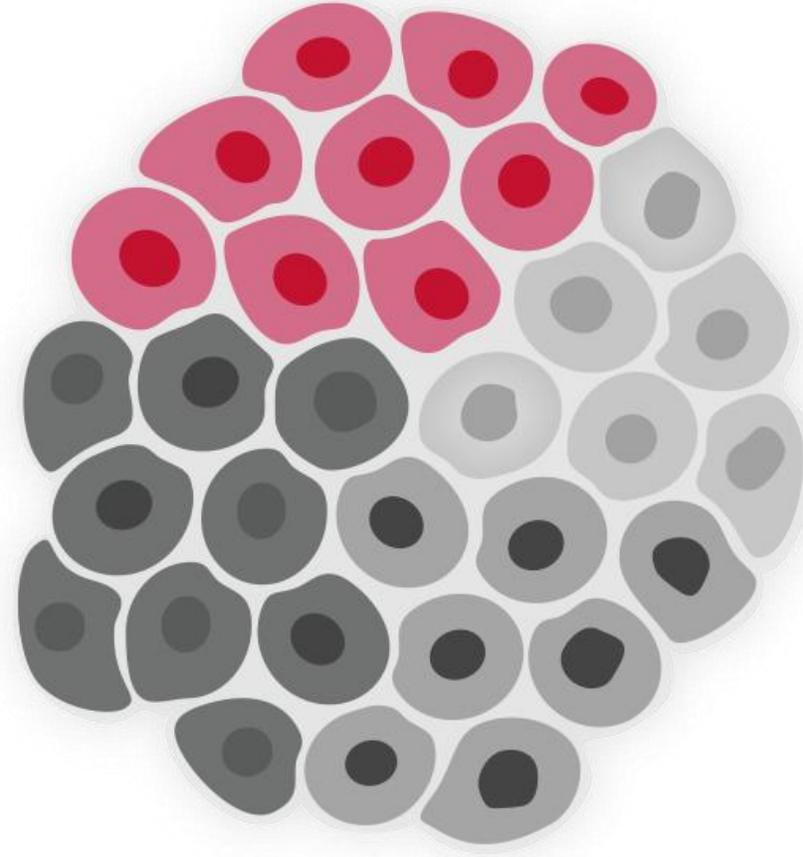
Wagle et al., *J Clin Oncol.* (2011)



McArthur et al., *Lancet* (2014)

Herausforderungen: Tumore sind komplexe Gewebe

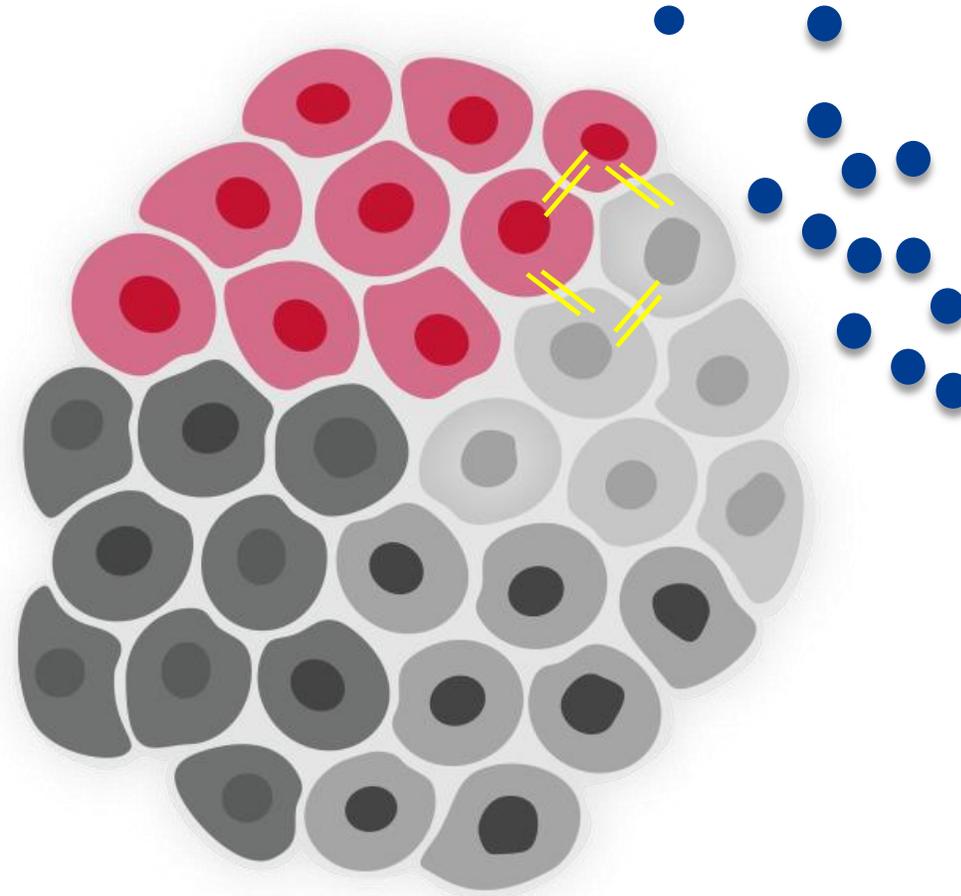
Tumor heterogeneity



Herausforderungen: Tumore sind komplexe Gewebe

Tumor heterogeneity

Cellular crosstalk



Drug responsive

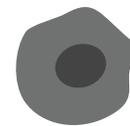
Drug resistant



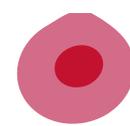
Clone A



Clone B



Clone C



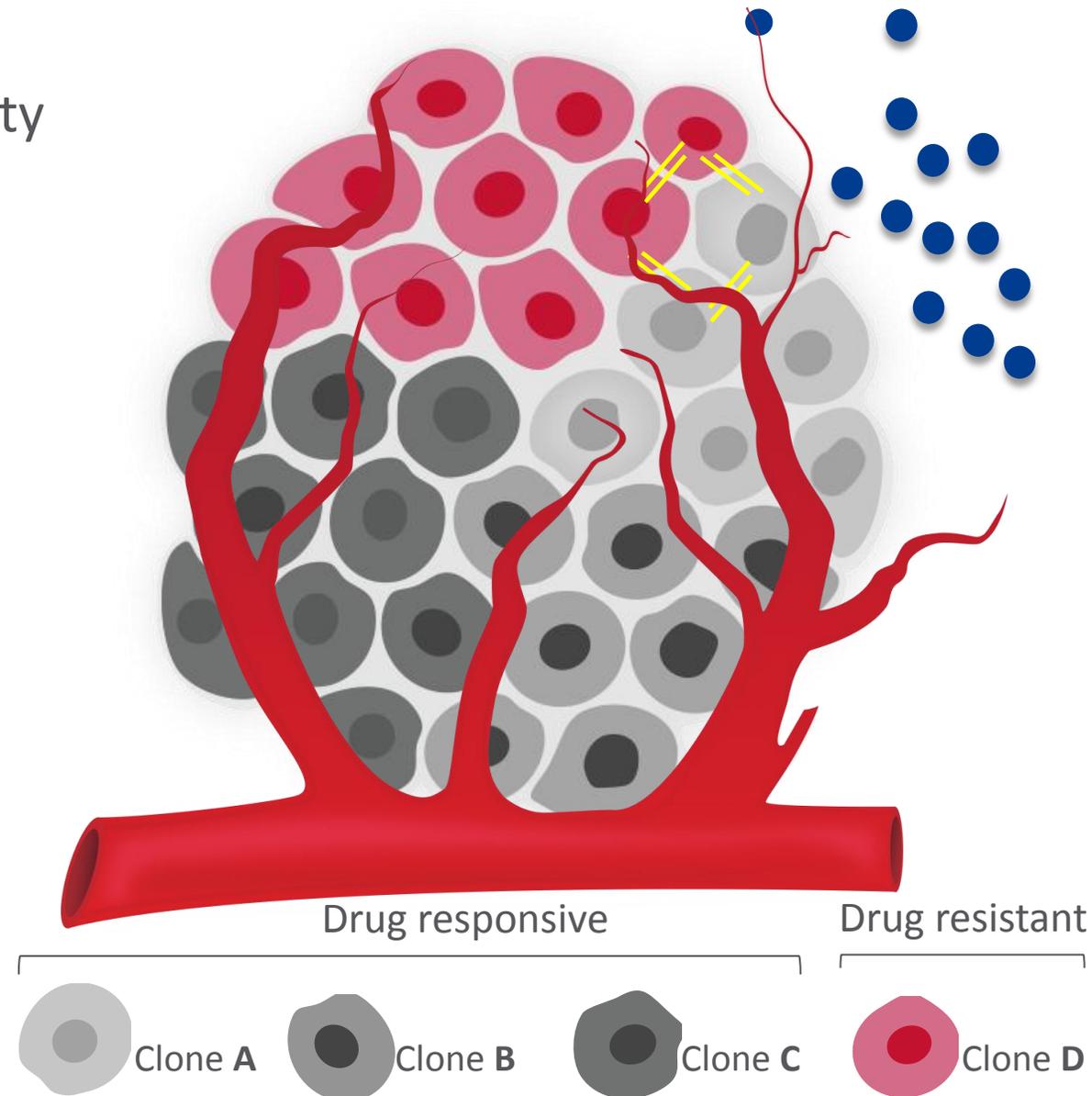
Clone D

Herausforderungen: Tumore sind komplexe Gewebe

Tumor heterogeneity

Cellular crosstalk

Vasculature



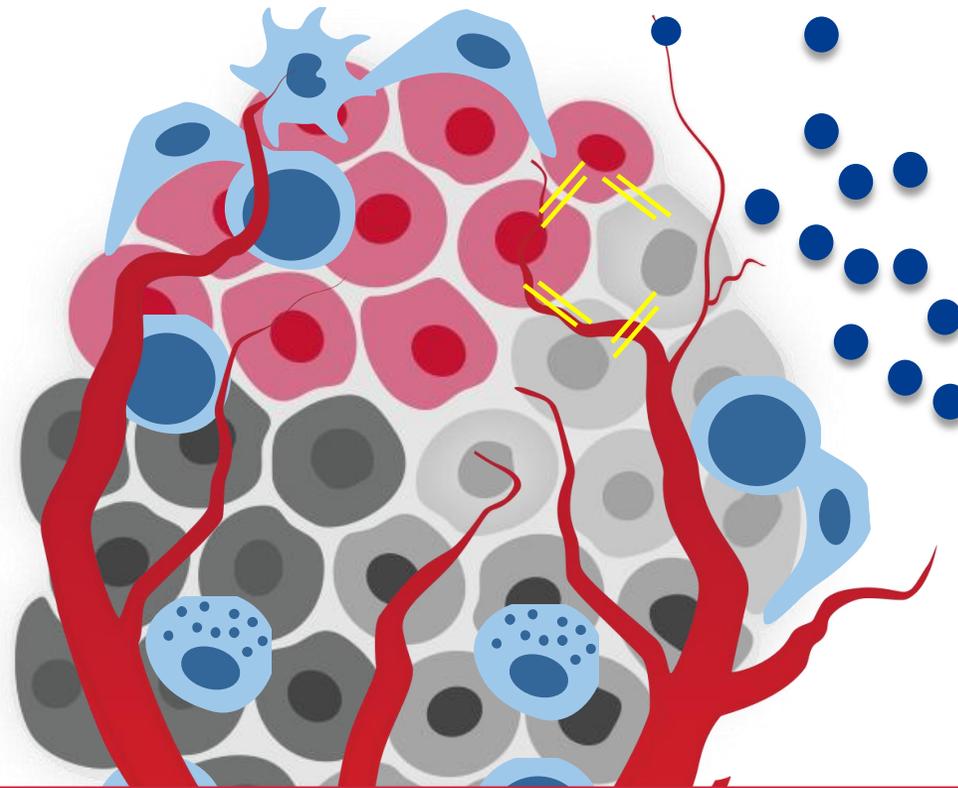
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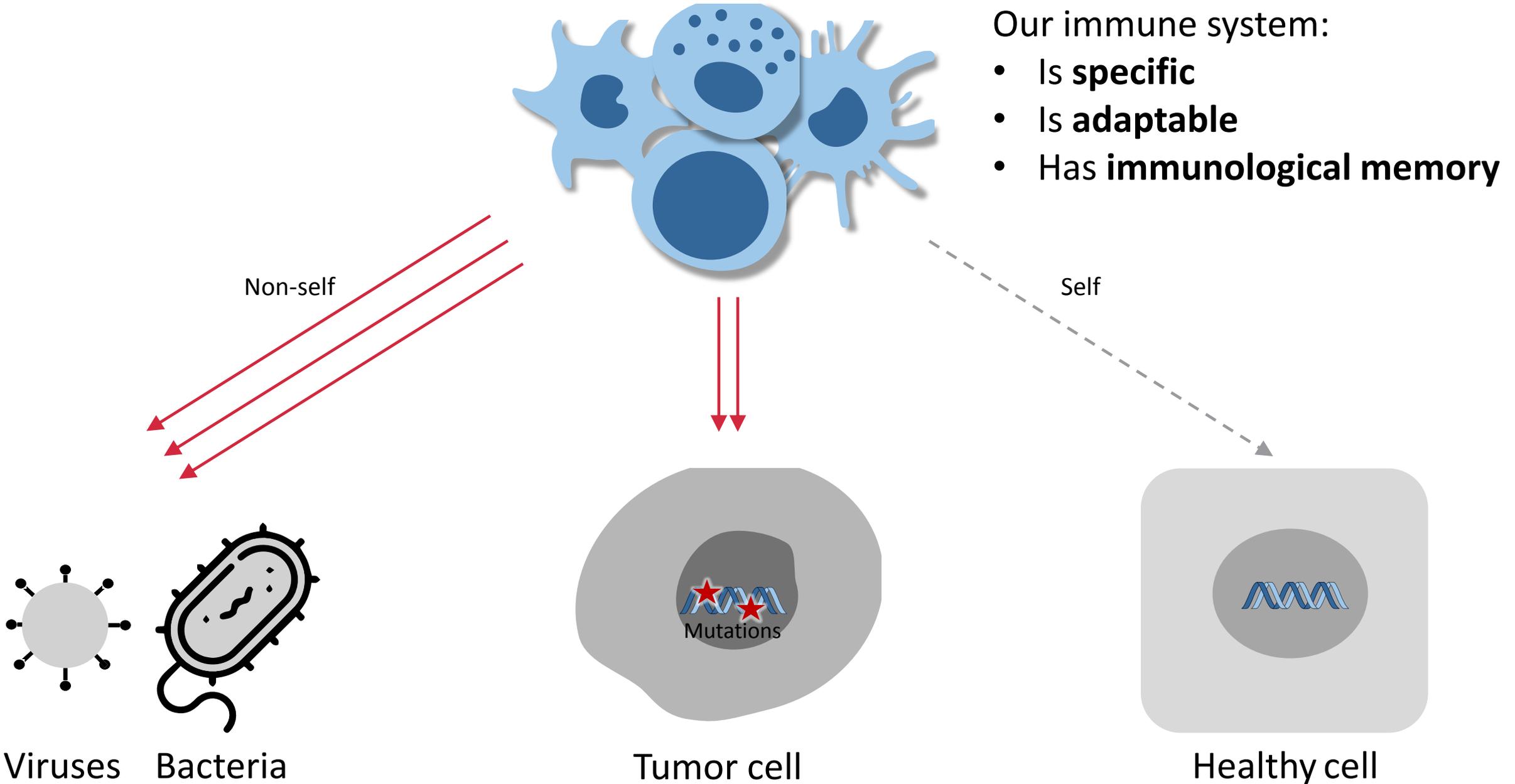
Vasculature

Immune/stromal cells



Immunonkologie:
Ein Paradigmenshift

Unser Immunsystem: beschützt uns gegen Bakterien, Viren, Wuermer,... und Krebs



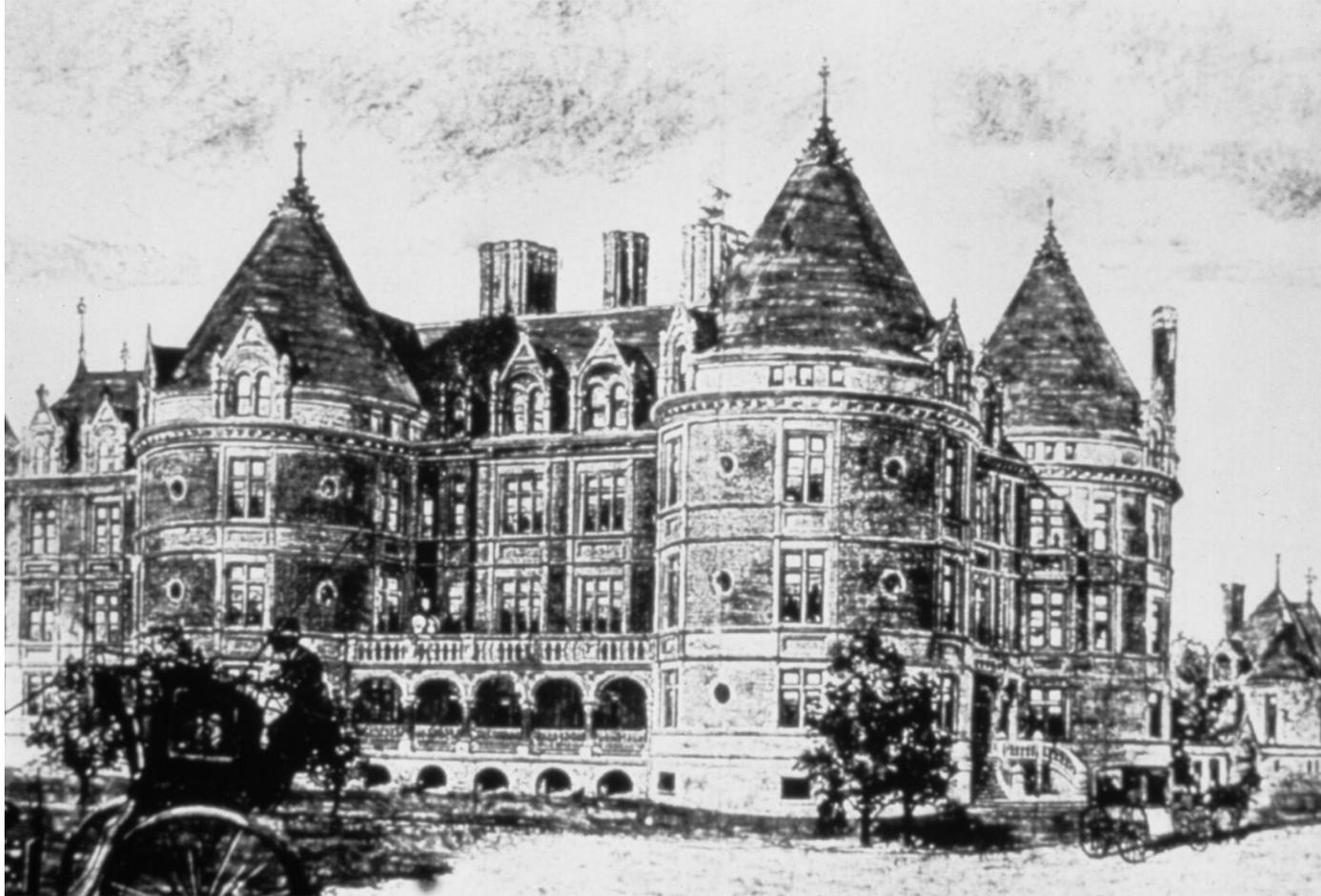
Paul Ehrlich erkannte bereits früh die Signifikanz des Immunsystems



In the 19th century Paul Ehrlich proposed

- The concept of **immune surveillance**
(immune system constantly eradicates malignant cells)
- That we may **use the immune system** to fight cancer

William Coley - Chirurg am Memorial Sloan Kettering in NY



William Coley heilte Krebs mit der Injektion von toten Bakterien

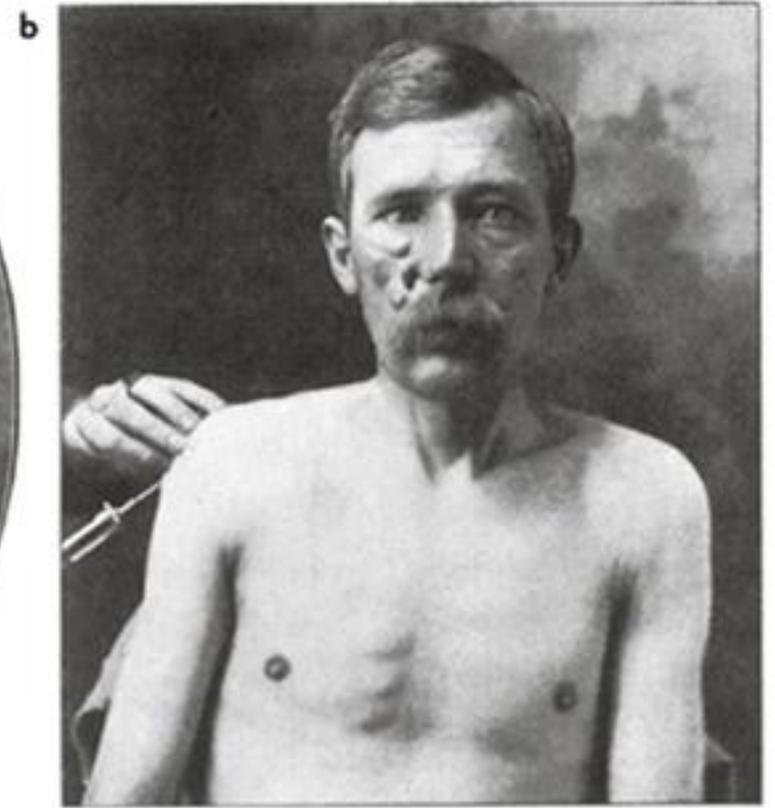
DIE GEBURT DER KREBS-IMMUNOTHERAPIE



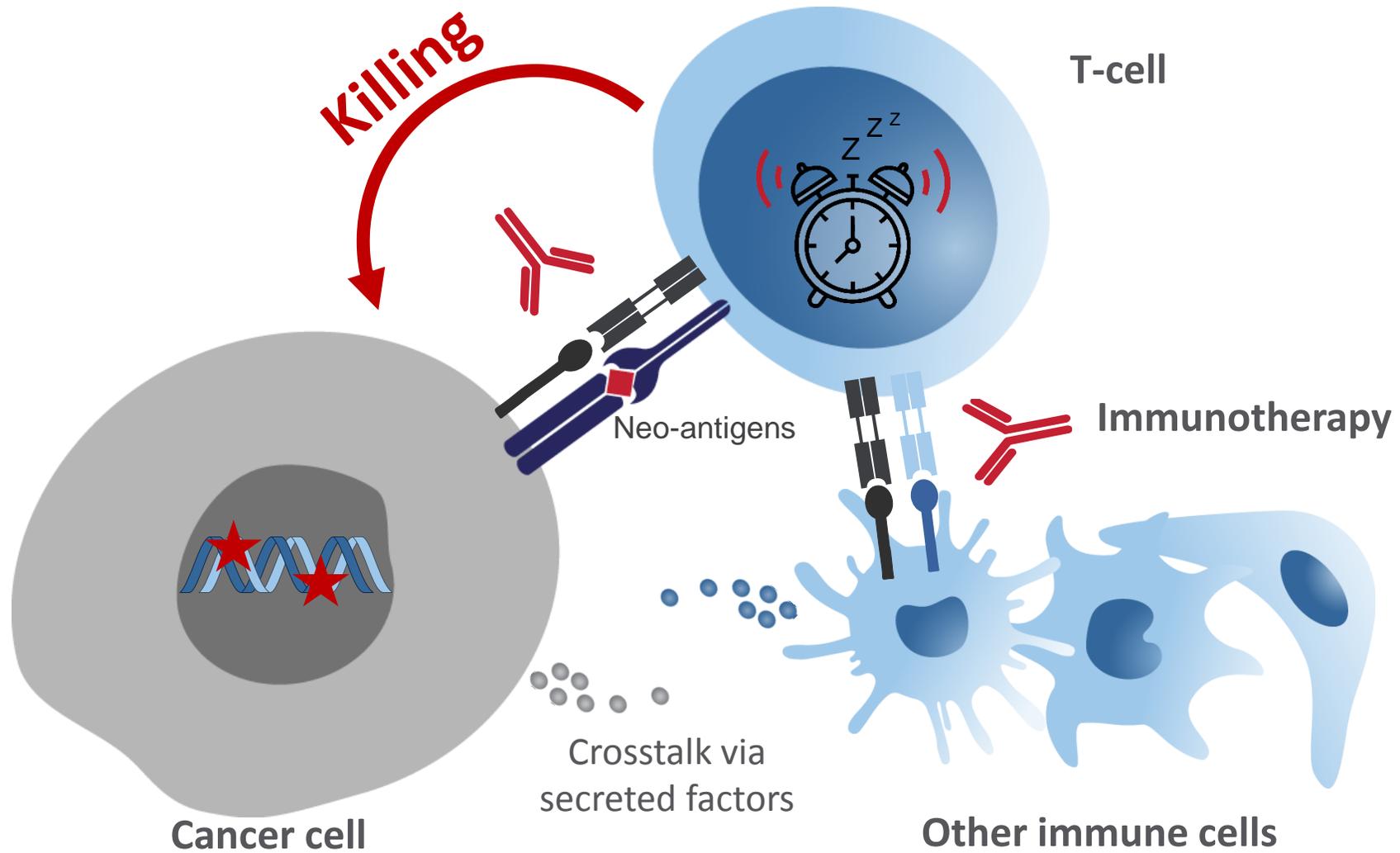
Patient with rapid response



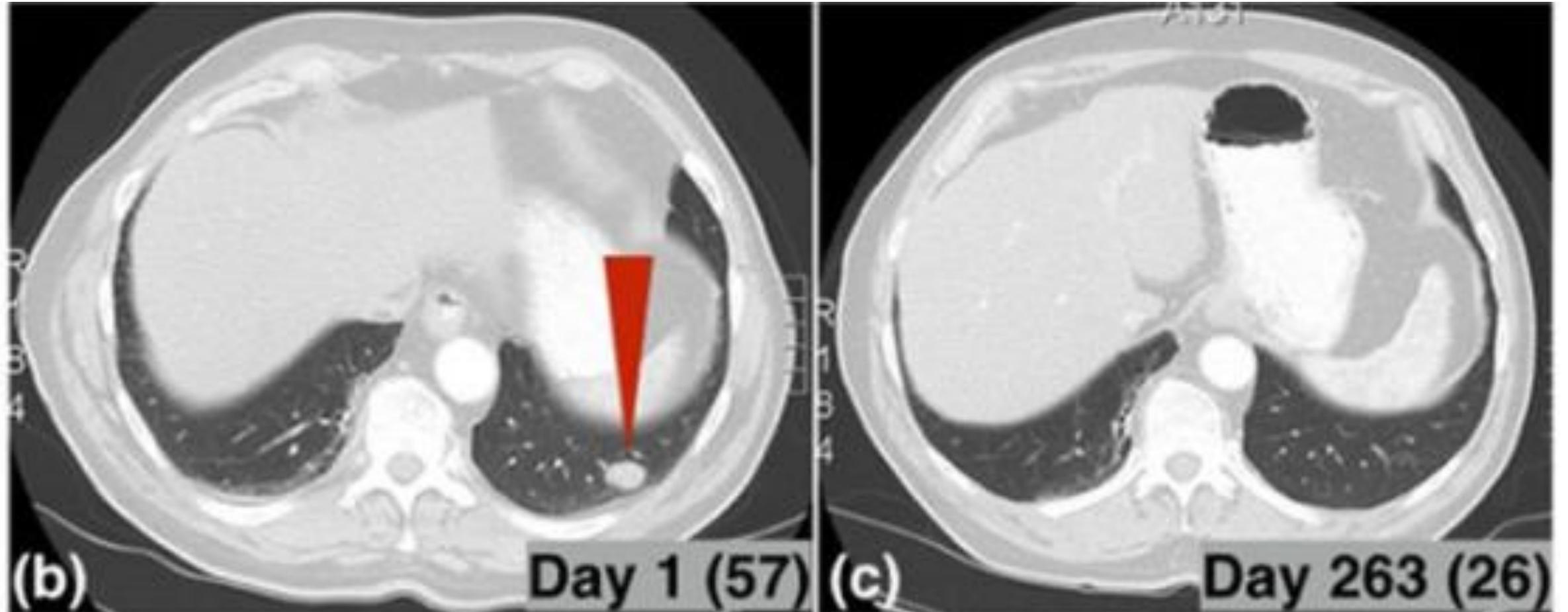
Patient responded after 63 injections



Krebszellen legen T-Zellen schlafend, Immunotherapy weckt sie wieder auf



Ergebnisse nach Immuntherapie

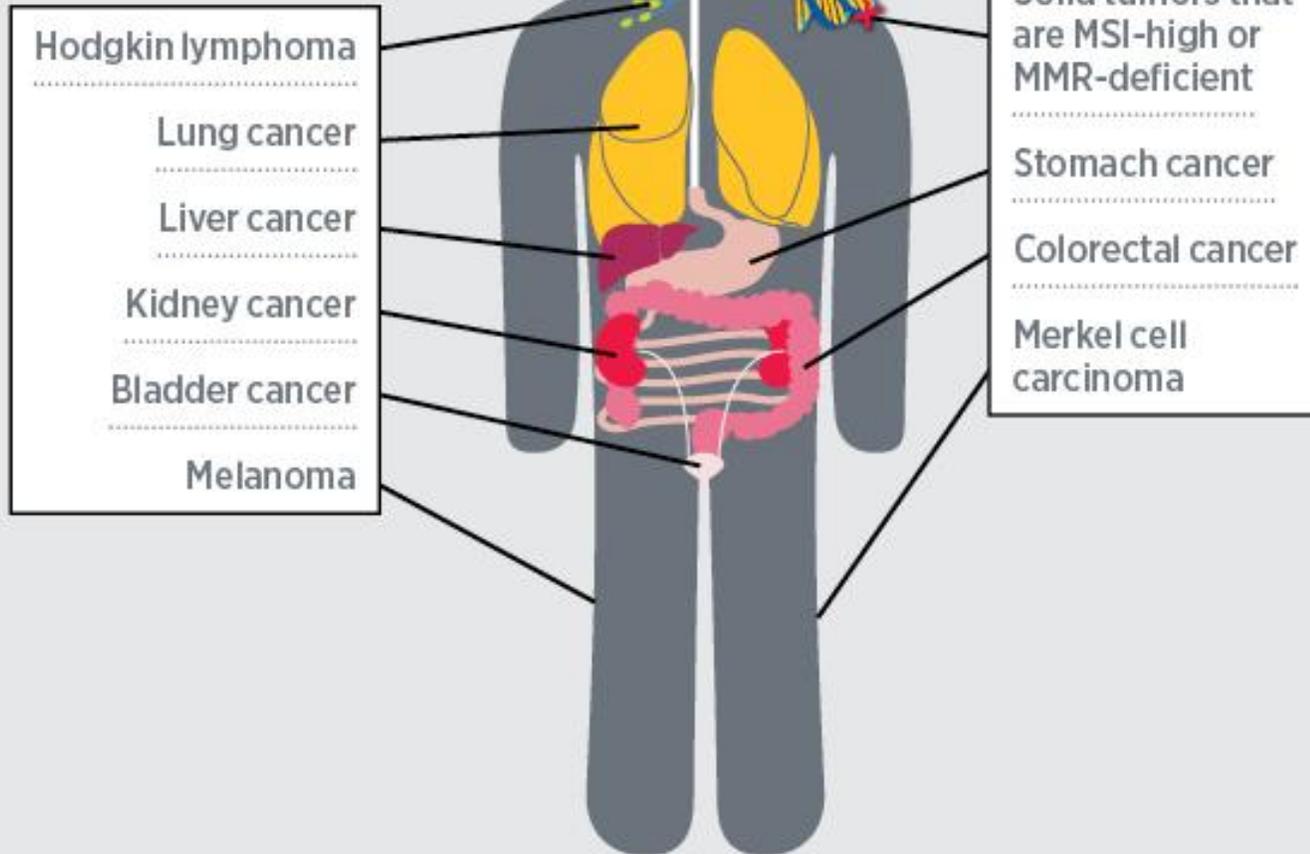


These are not isolated patient cases any more:

A large fraction of melanoma patients responds and the responses are durable.

Immuntherapien werden in der Klinik für verschiedene Tumortypen verwendet

As of 2017,
immunotherapies
were FDA approved
for certain patients with:

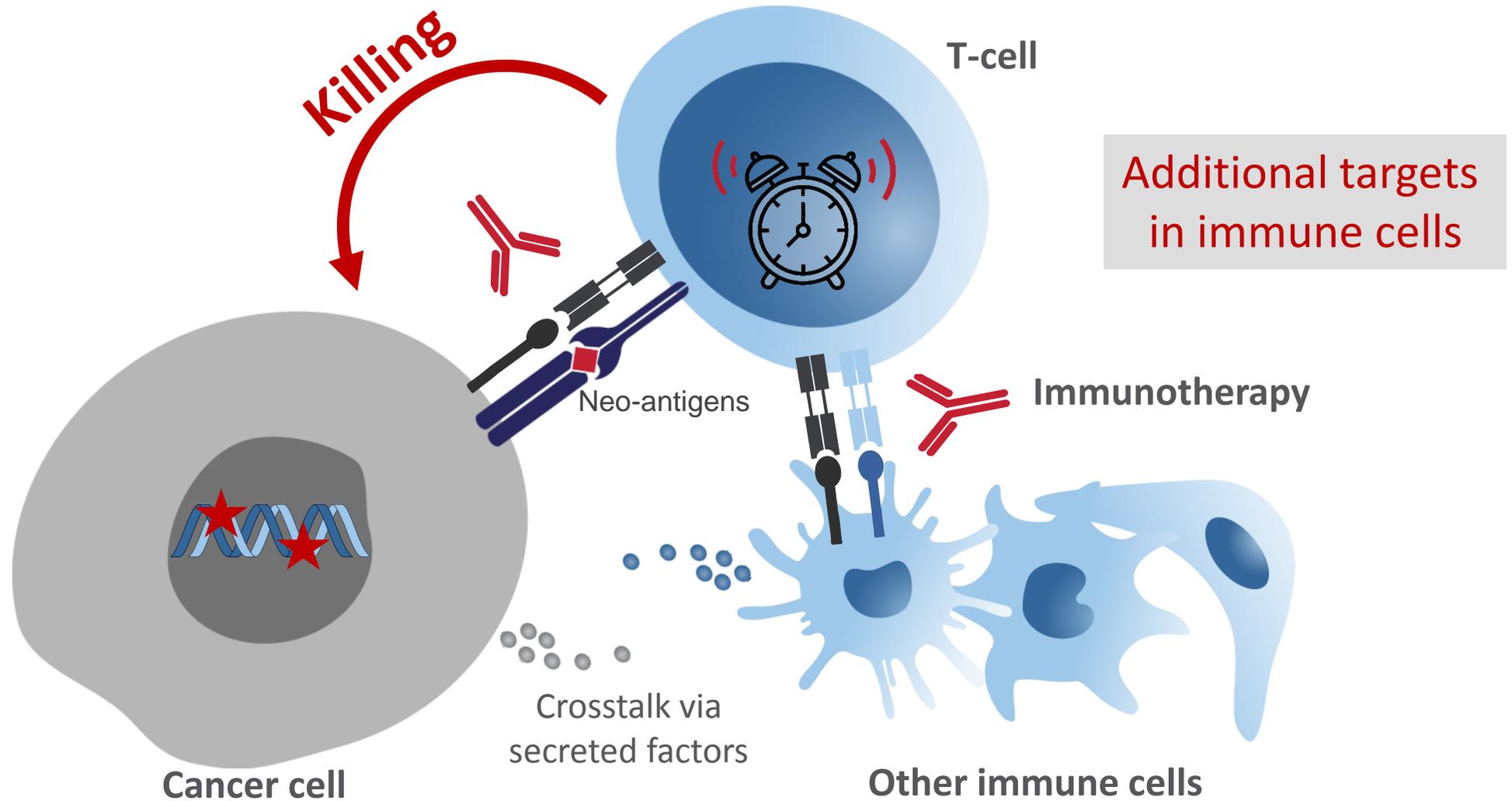


American Association for Cancer Research (AACR)

Challenges remain:

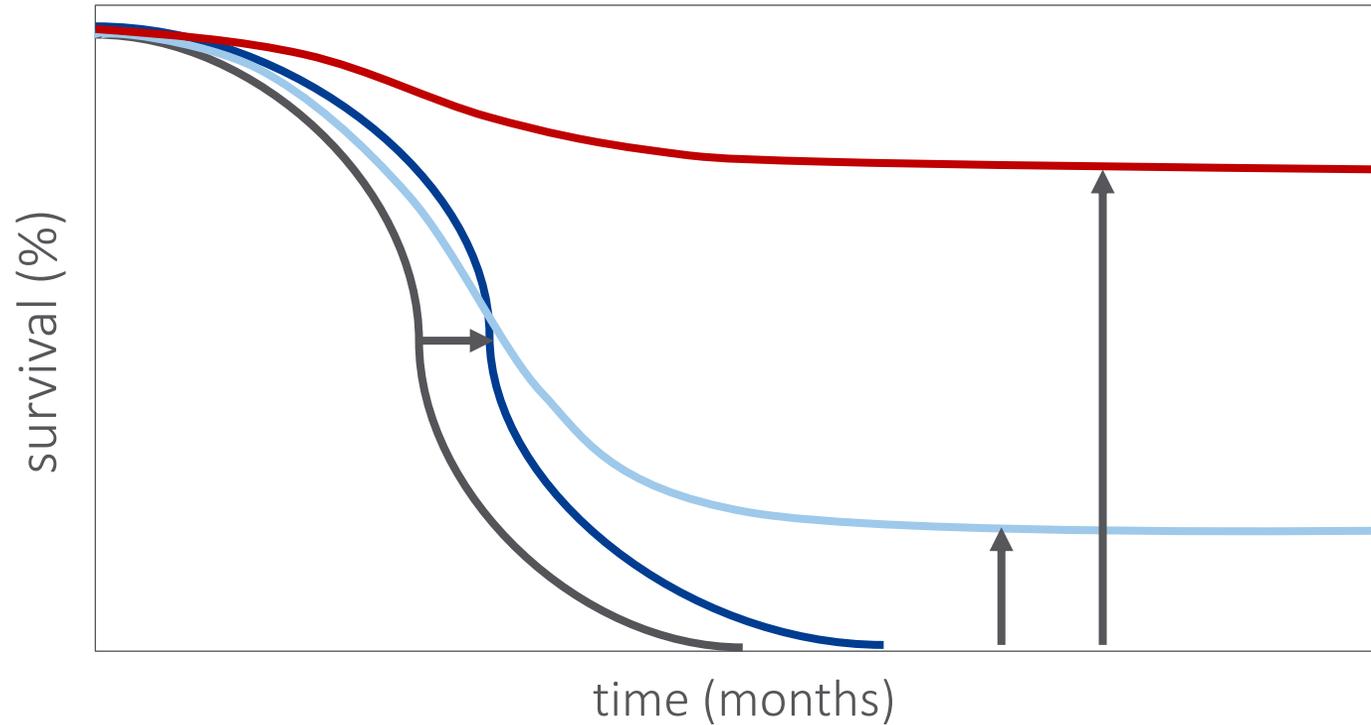
- About half of patients from these (in principal responsive) cancer types do not respond
- In many cancer types immunotherapies are ineffective

Erweiterung des Repertoires von immunmodulierenden Therapien



**Tumor specific (oncogenic) pathways
instructing the immune microenvironment**

Ziel: Mittels Kombinationstherapien die Überlebenskurven verschieben



Chemotherapy: cytotoxic, systemic inhibition of proliferating cells

Targeted therapy: inhibition of specific oncogenic signaling pathways, lack of durable responses

Immunotherapy: unleashing immune system to fight cancer, durable but only in fraction of patients

Combination therapy: the future of cancer treatment

Adapted from Sharma and Allison, Cell, 2015

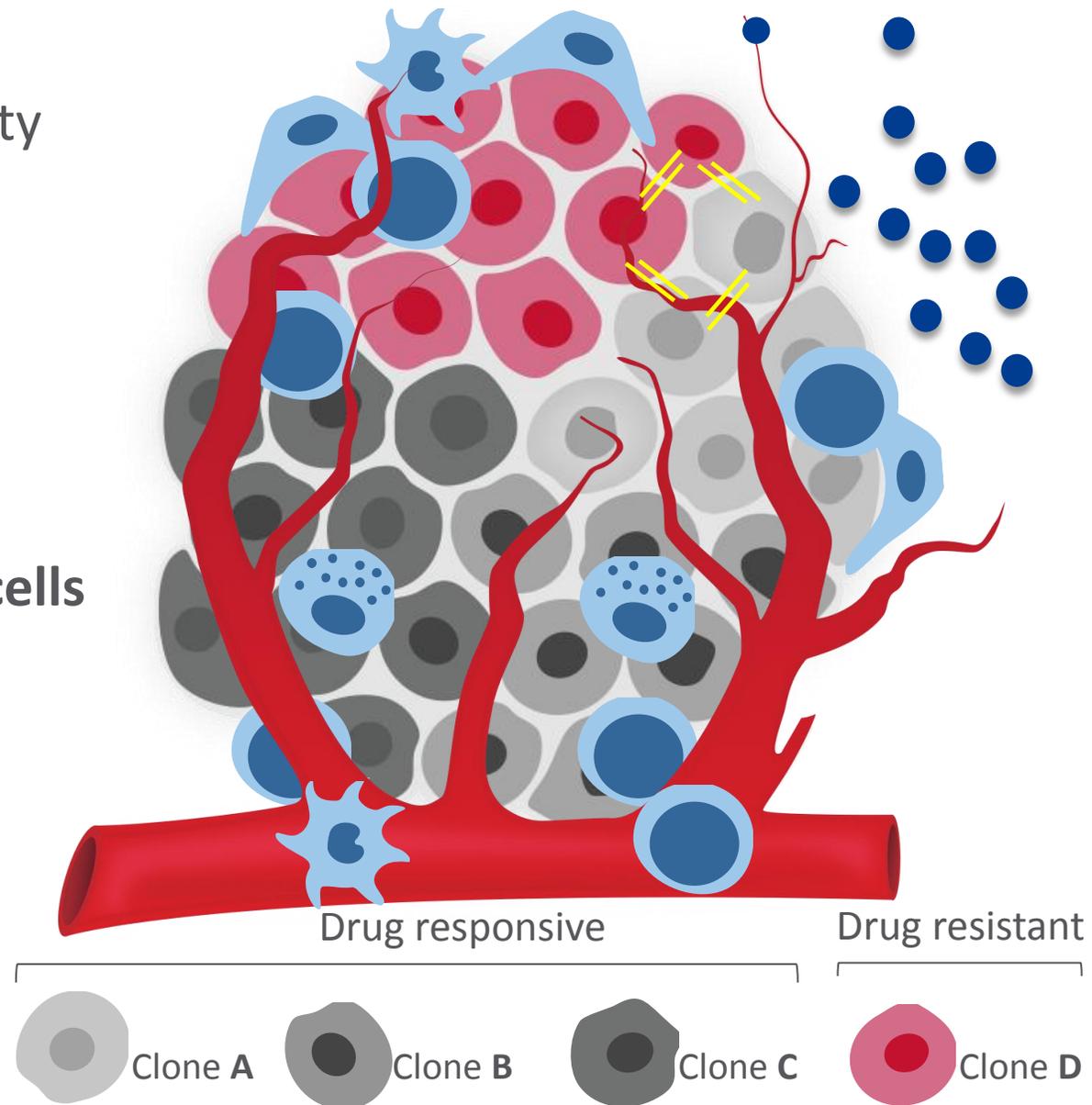
Woran wir arbeiten:

Tumor heterogeneity

Cellular crosstalk

Vasculature

Immune/stromal cells



Mein Team am IMP



Find out more @

www.obenauf lab.com

www.imp.ac.at

www.training.vbc.ac.at

Looking for motivated
students/**postdocs**/
bioinformaticians.

Funding:



Technical support:



Some of our collaborators:

Thomas Wiesner

Johannes Zuber

Iris Helfrich/Dirk Schadendorf

Marcus Bosenberg

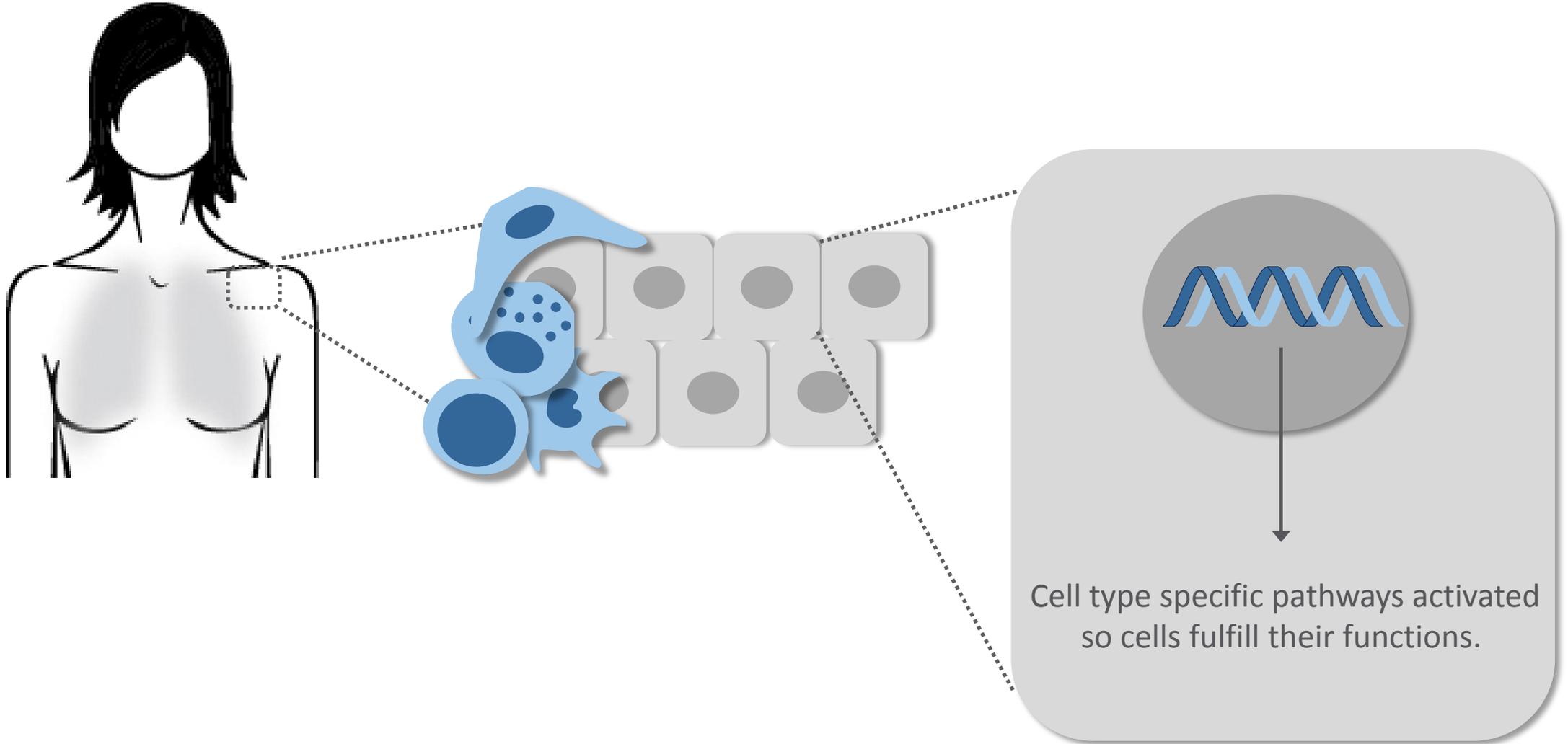
Michael Speicher

Flavio Solca

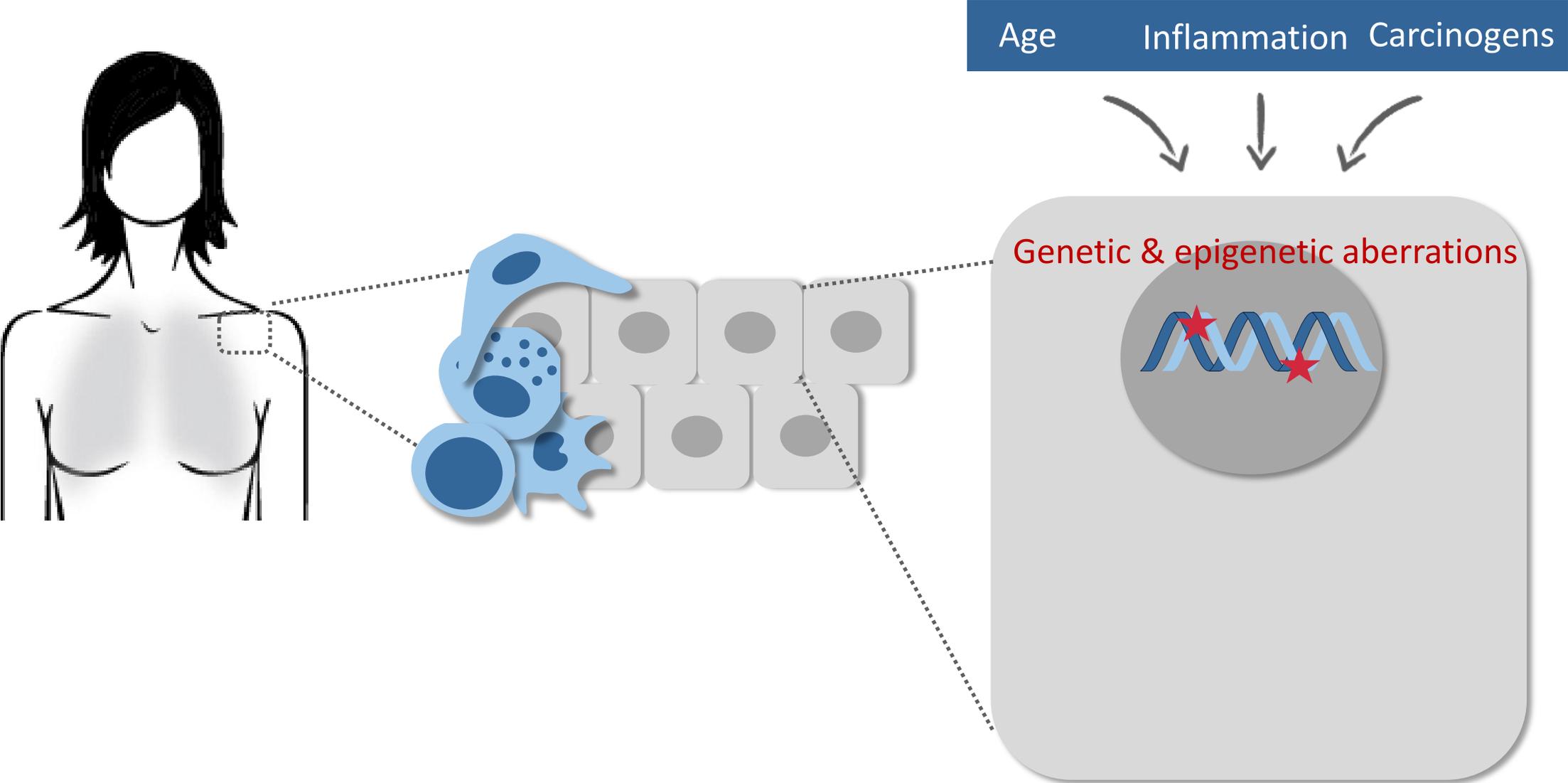
Ulrike Weyer-Czernilofsky

Cellular processes are tightly regulated

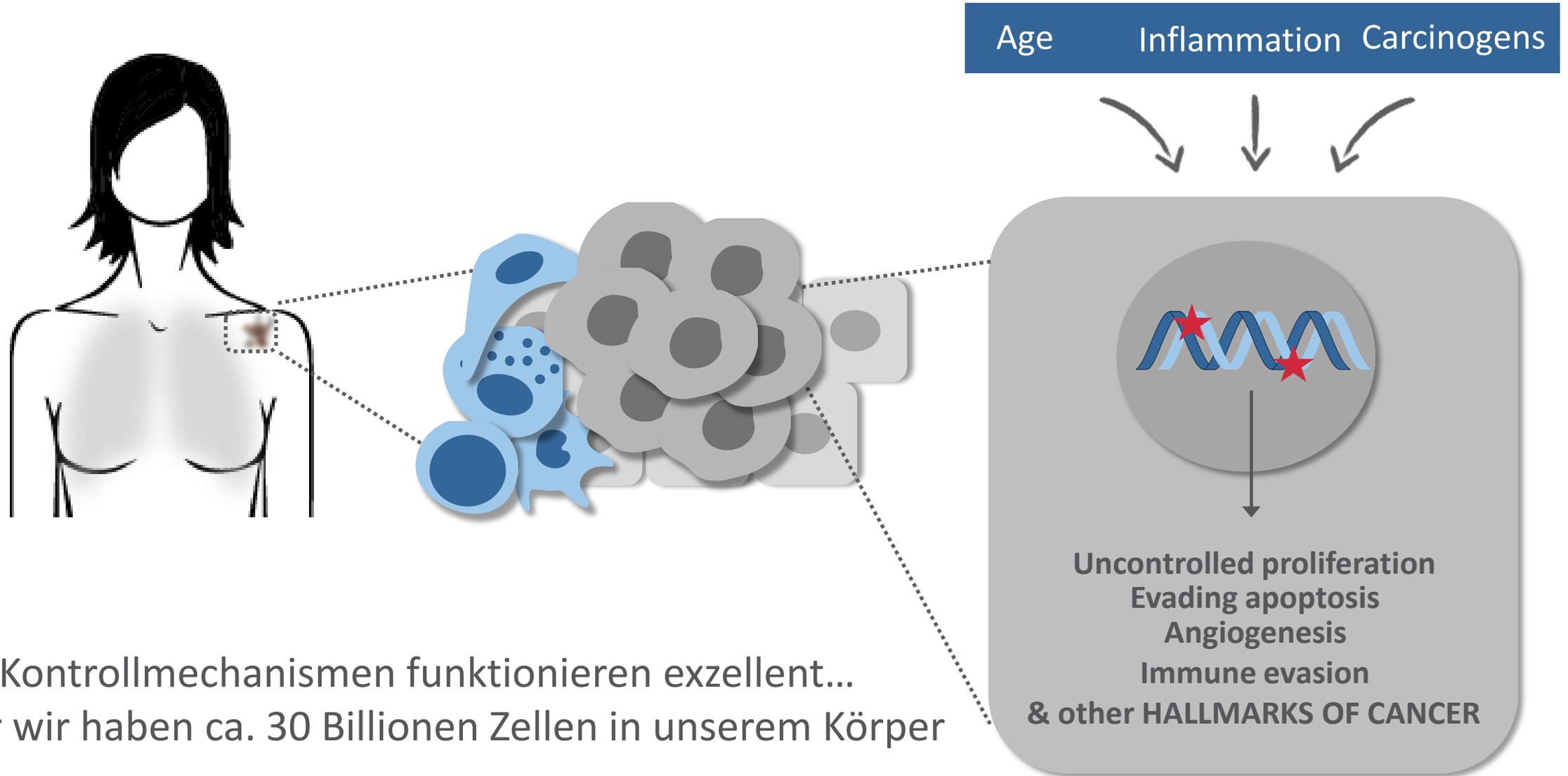
Multiple layers of **regulation** and **control mechanisms** ensure cells function properly or are eliminated (e.g via programmed cell death).



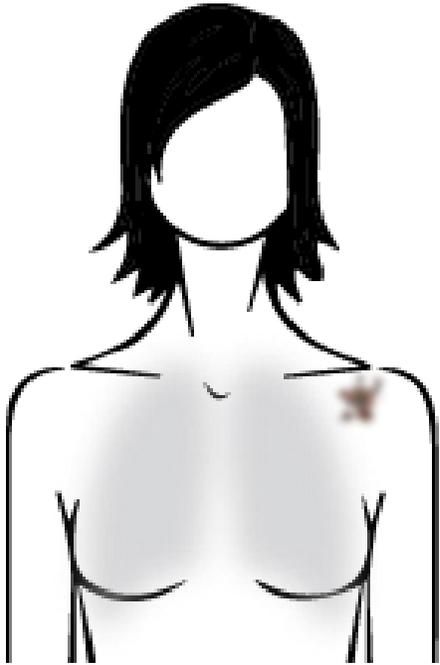
Cellular processes are de-regulated during cancer development



Cellular processes are de-regulated during cancer development



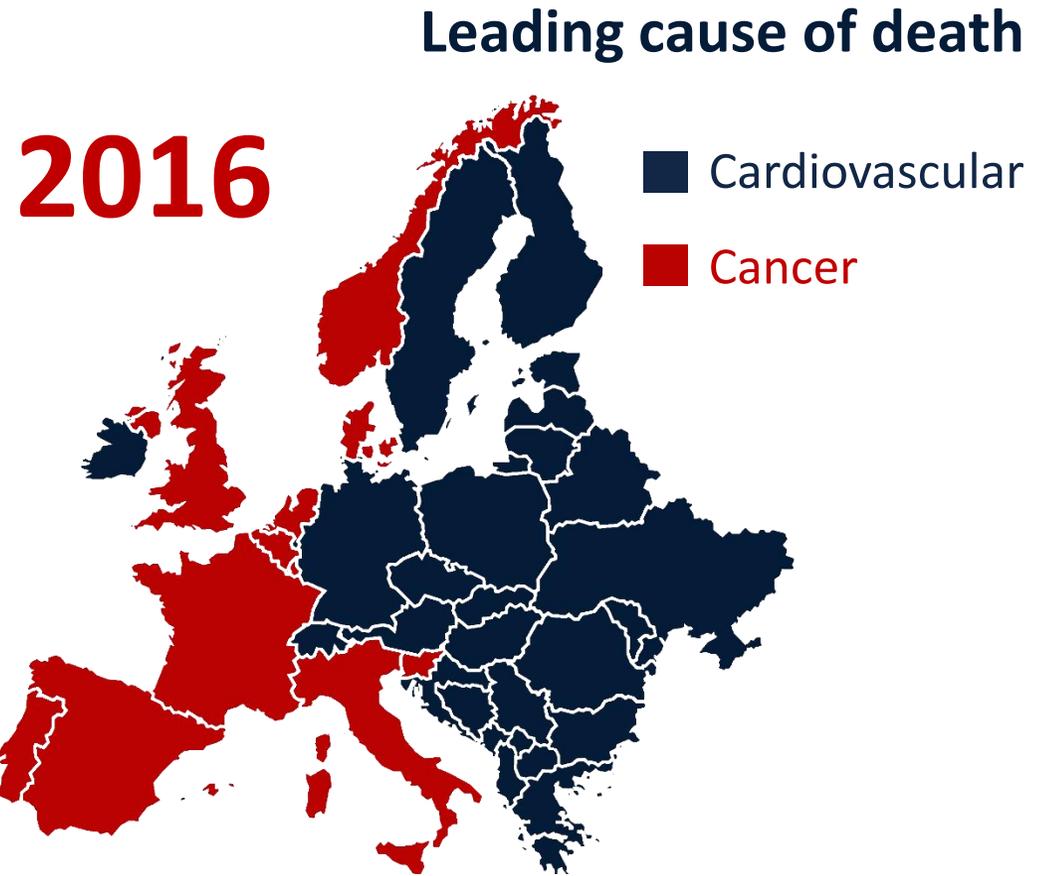
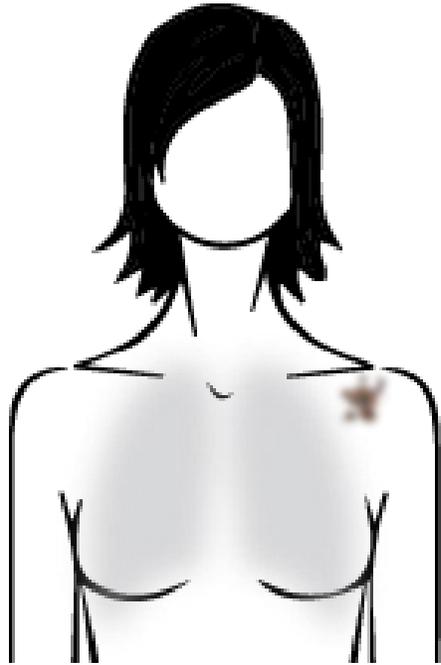
Diese Kontrollmechanismen funktionieren exzellent...
...aber wir haben ca. 30 Billionen Zellen in unserem Körper



1 in 2 men

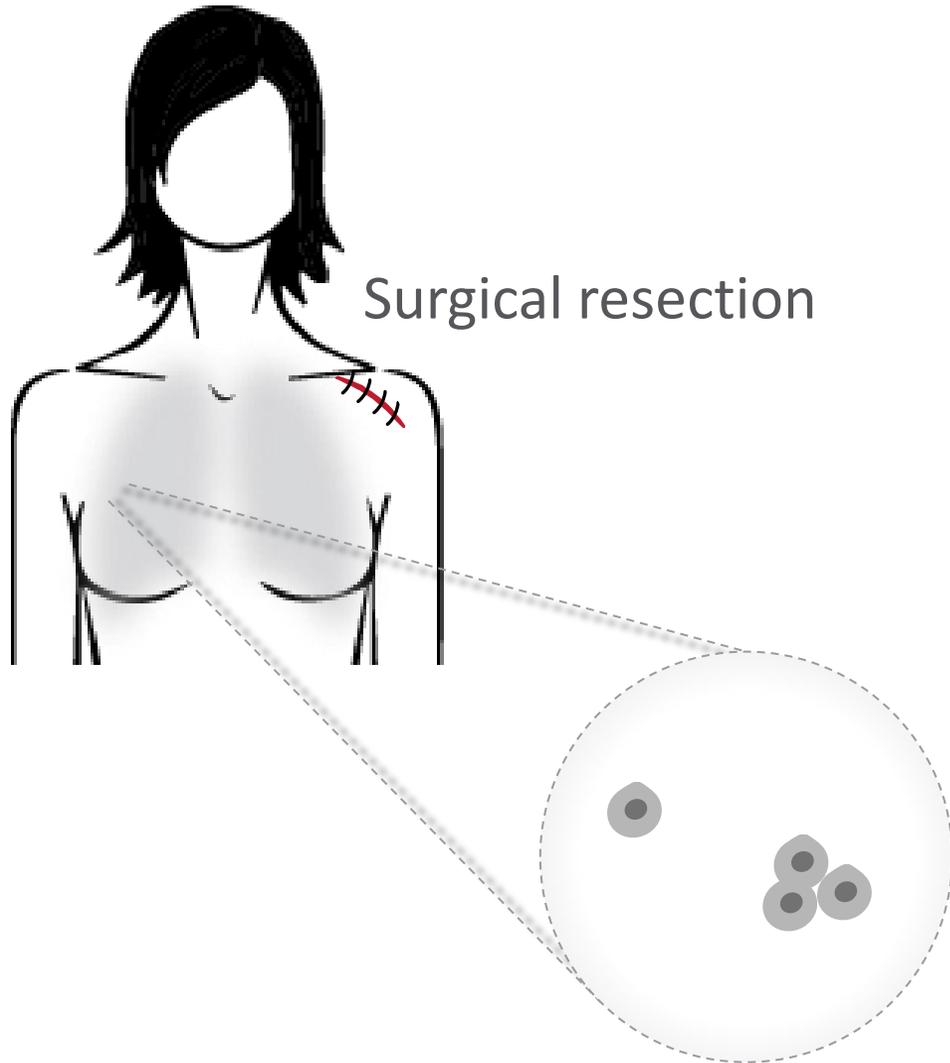
1 in 3 women

will develop cancer.



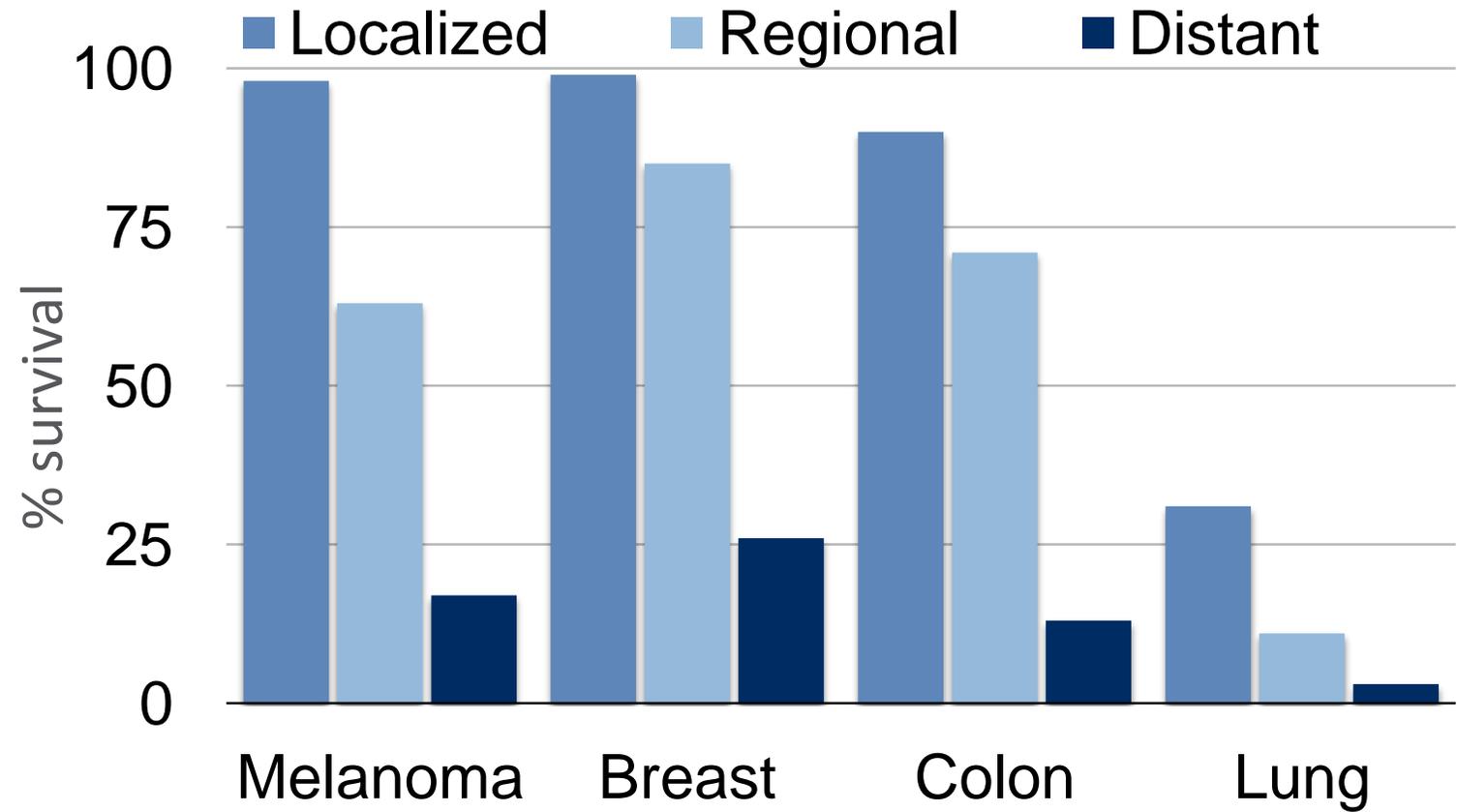
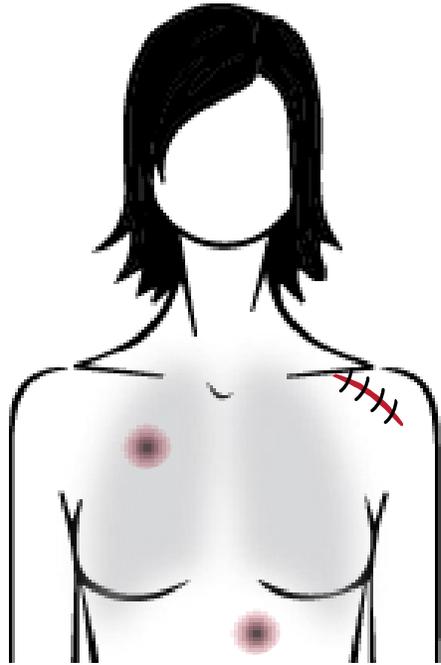
Townsend et al., Eur Heart J (2016)

Surgical resection of the primary tumor can be curative if the tumor has not yet spread

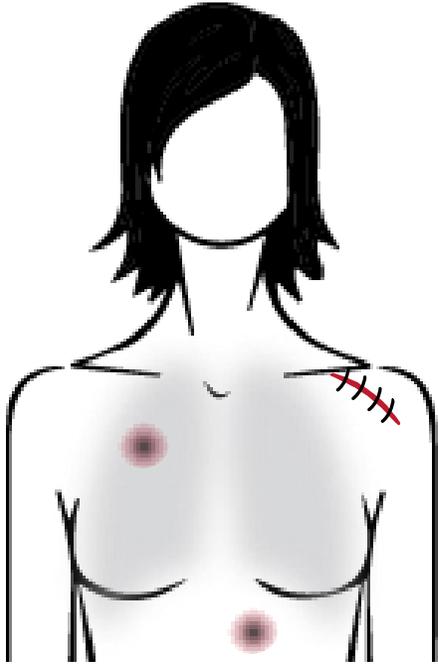


Cancer cells leave the primary tumor early and survive in a dormant state.

Metastasis is responsible for more than 90% of cancer related deaths and requires systemic therapy



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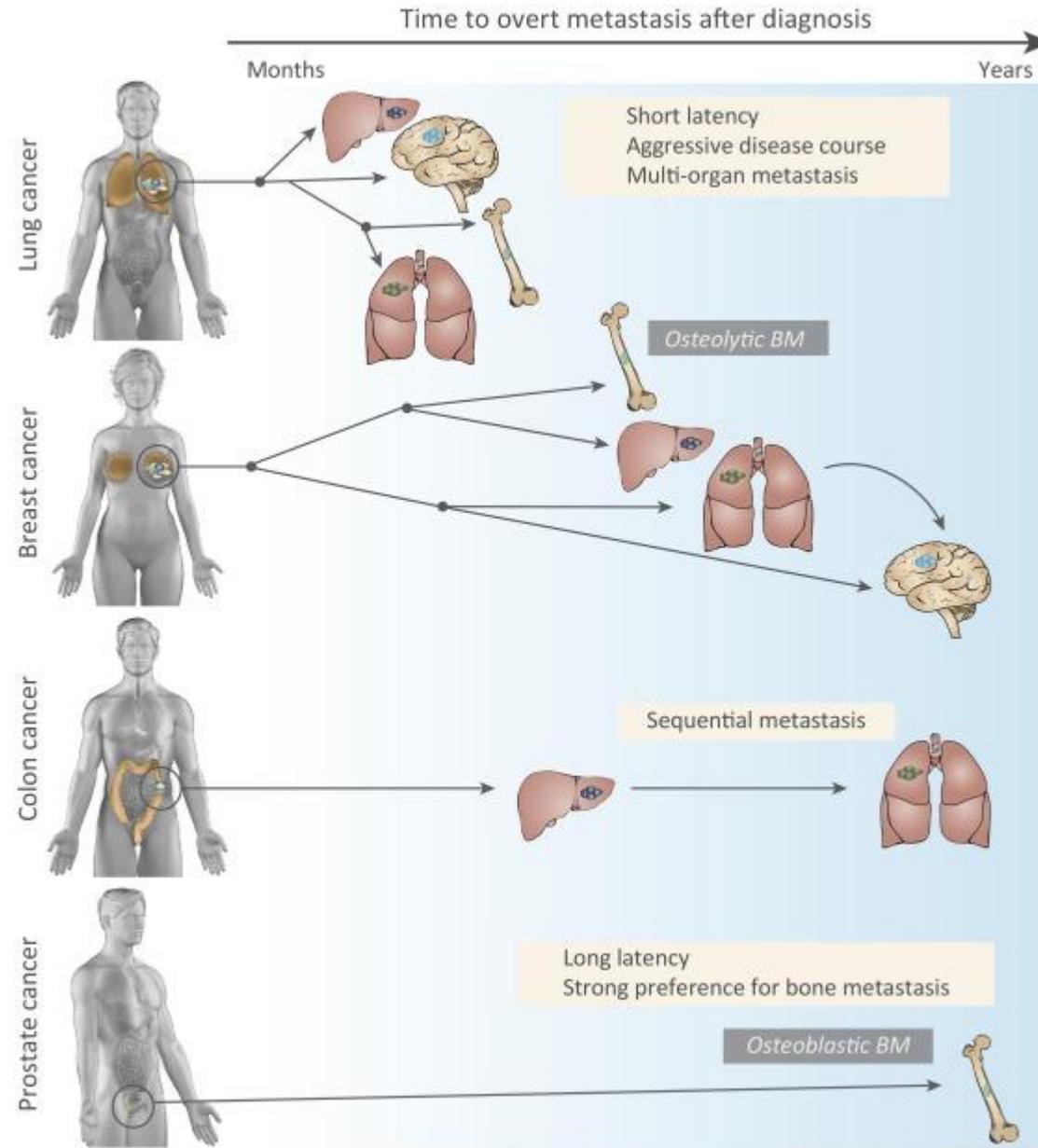


IMPORTANT CLINICAL PROBLEM

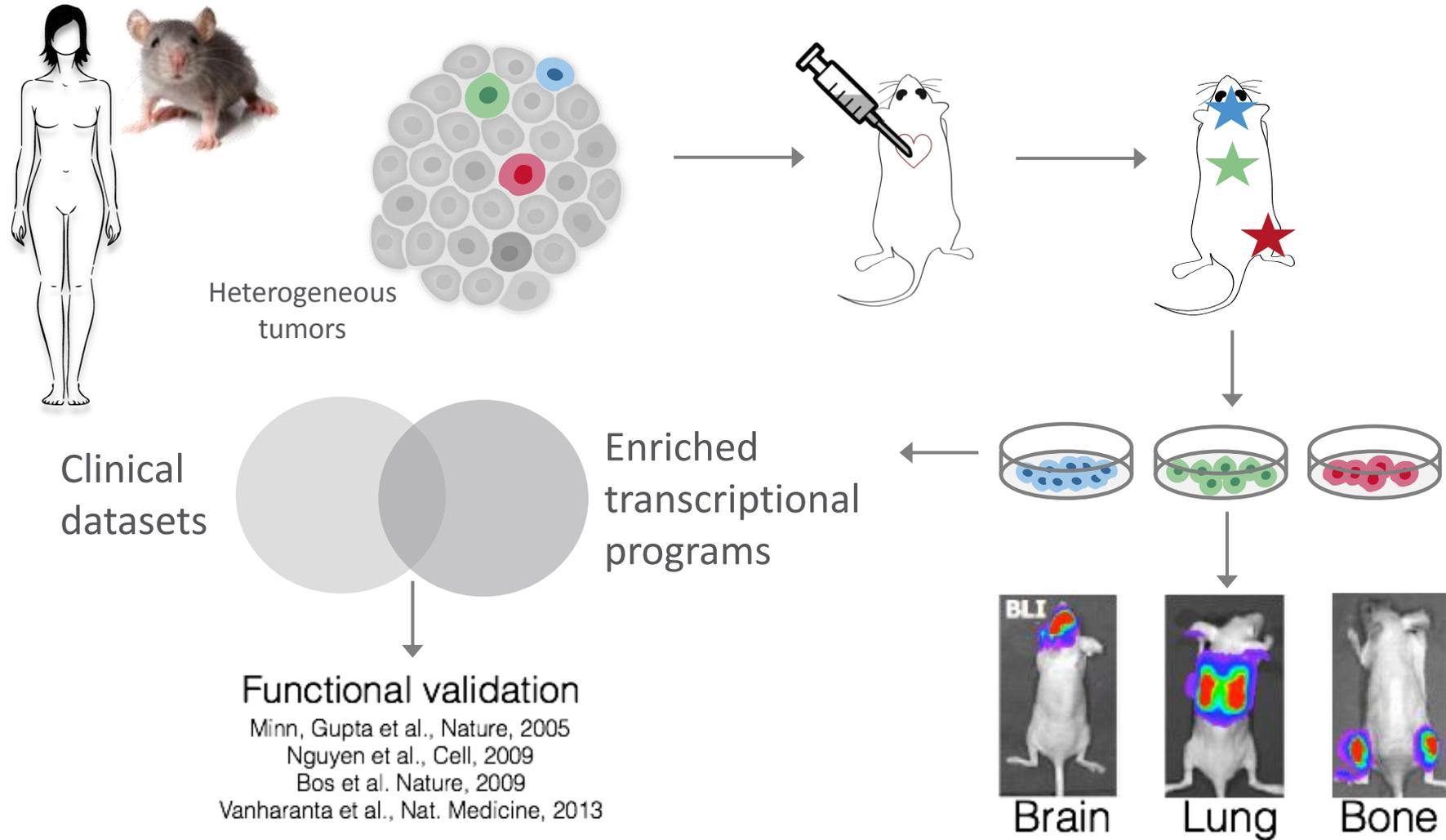
FASCINATING BIOLOGICAL PROCESS

REQUIRES SYSTEMIC THERAPY

Clinical presentation of metastasis varies dramatically



Experimental metastasis models

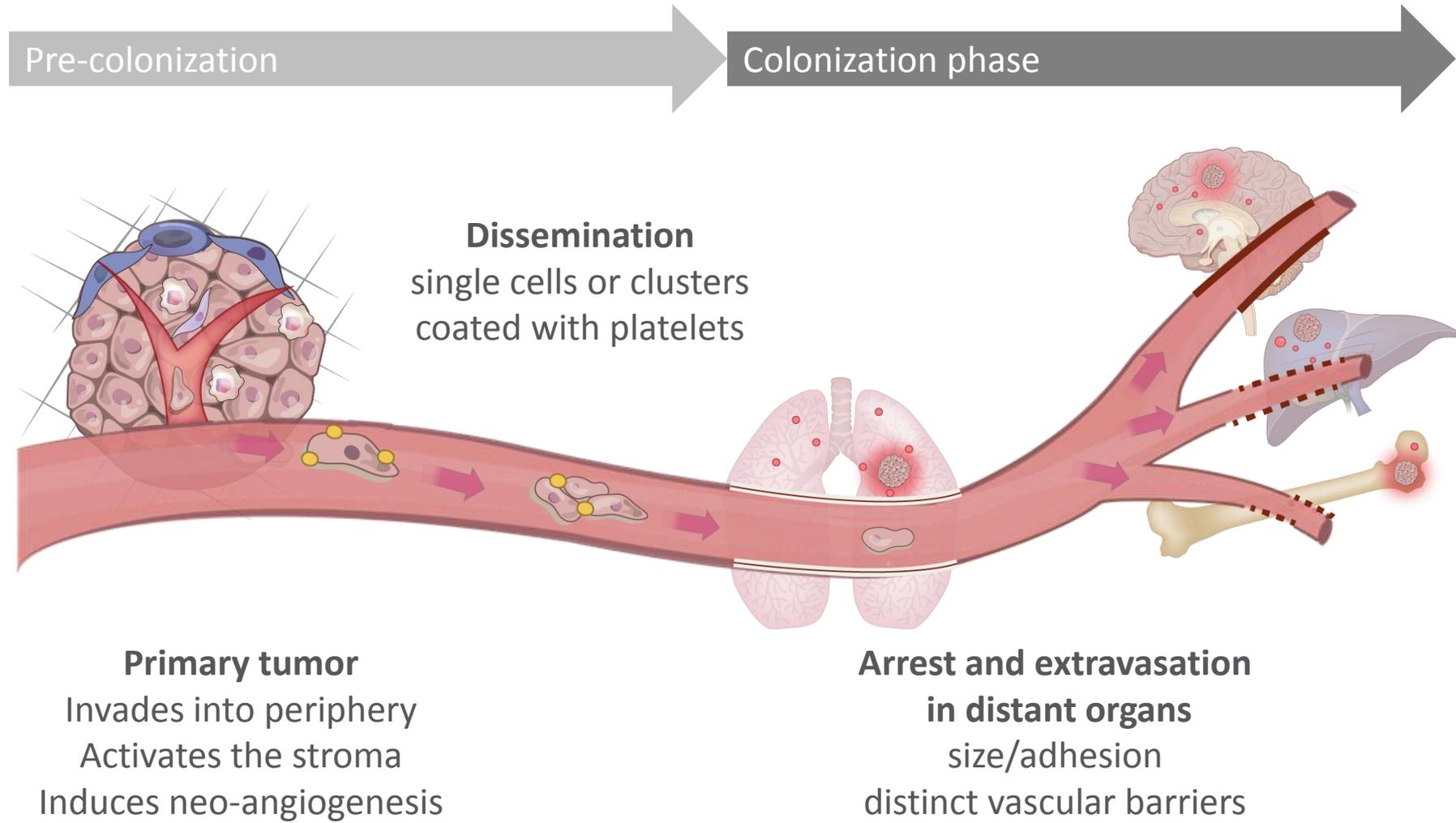


MMTV-ERBB2 brain metastasis model (immunocompetent)

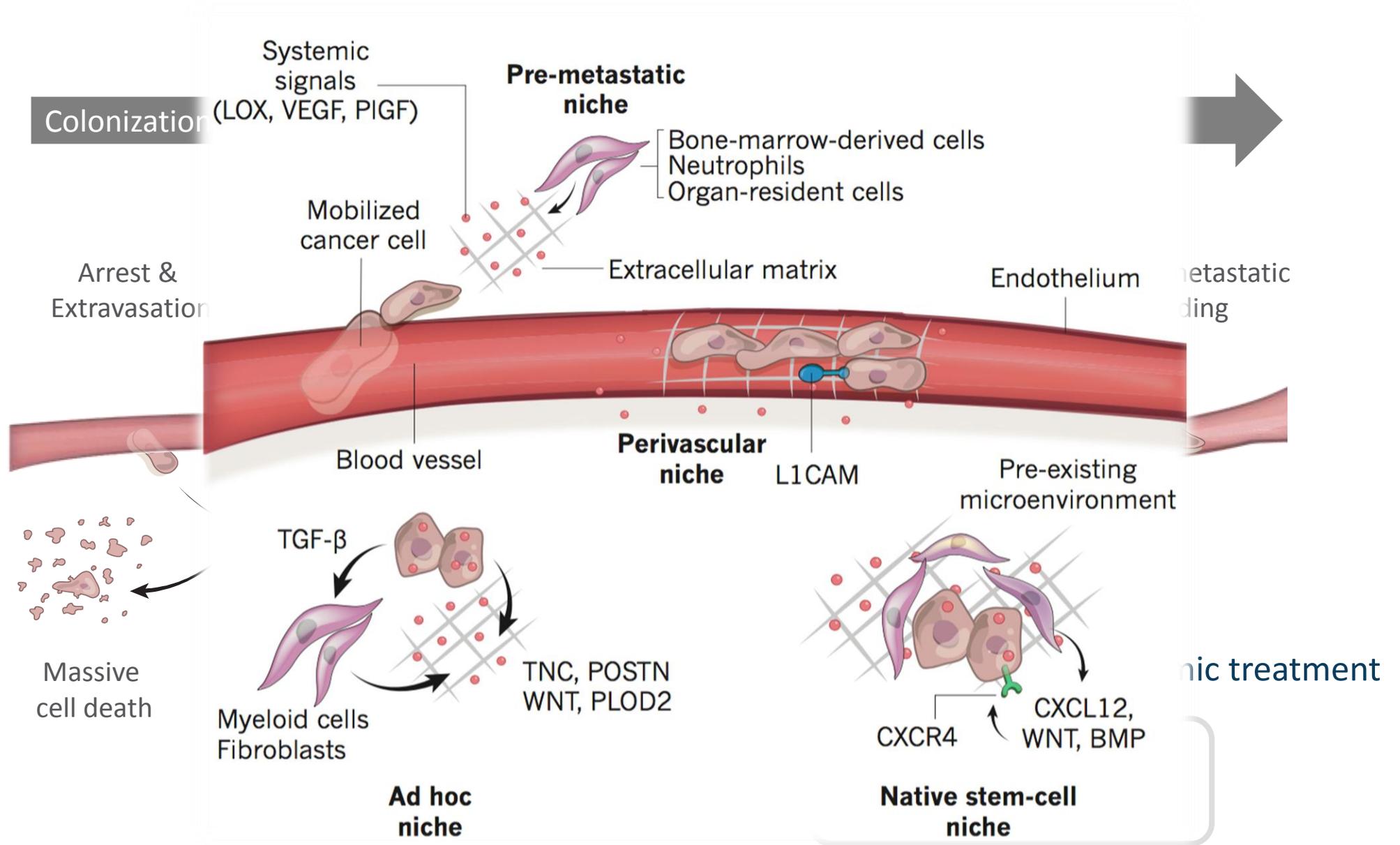
Serpins promote cancer cell survival and vascular co-option in brain metastasis.

Valiente M, Obenauf AC, et al., Cell, 2014

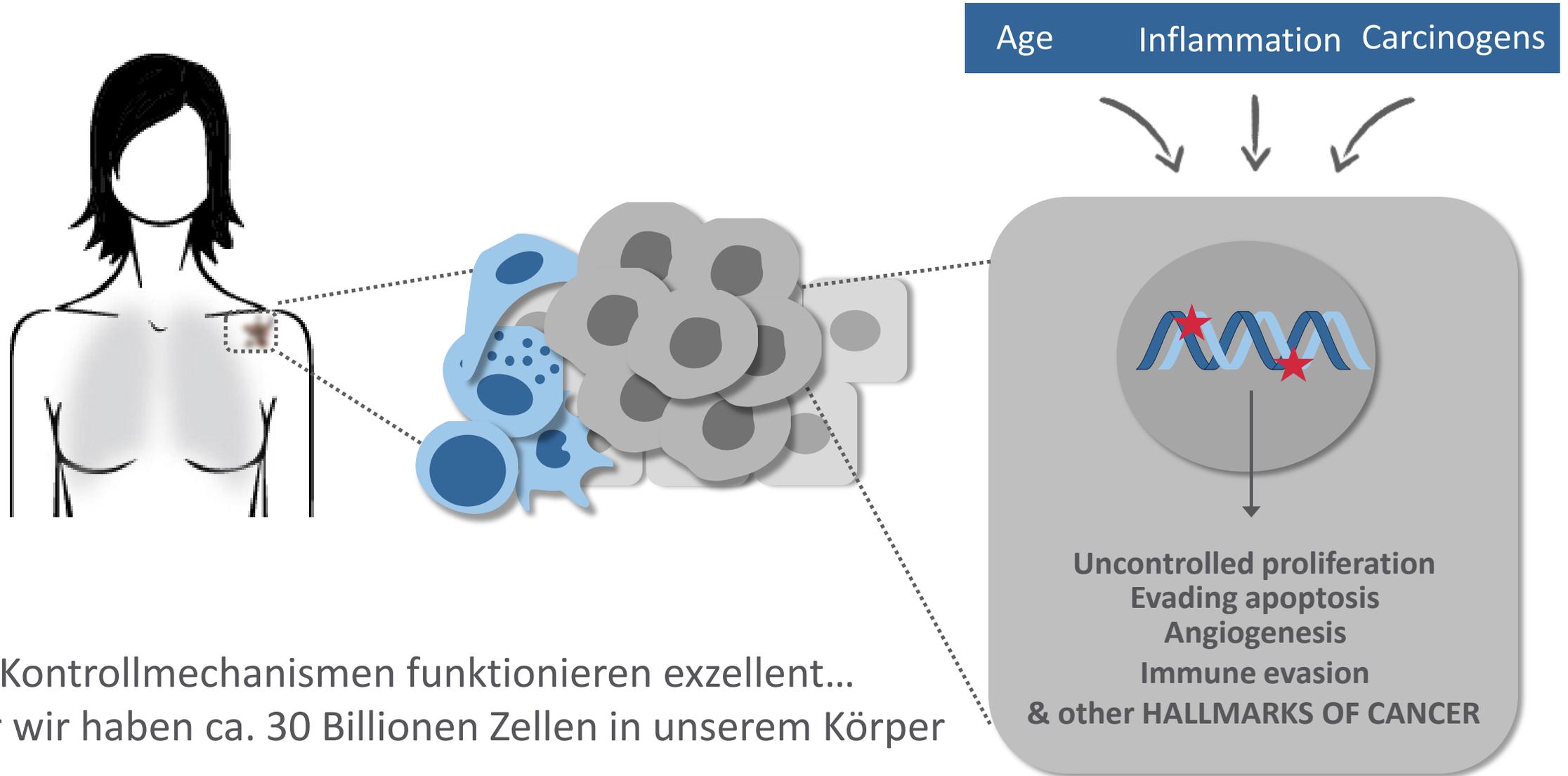
The metastatic cascade



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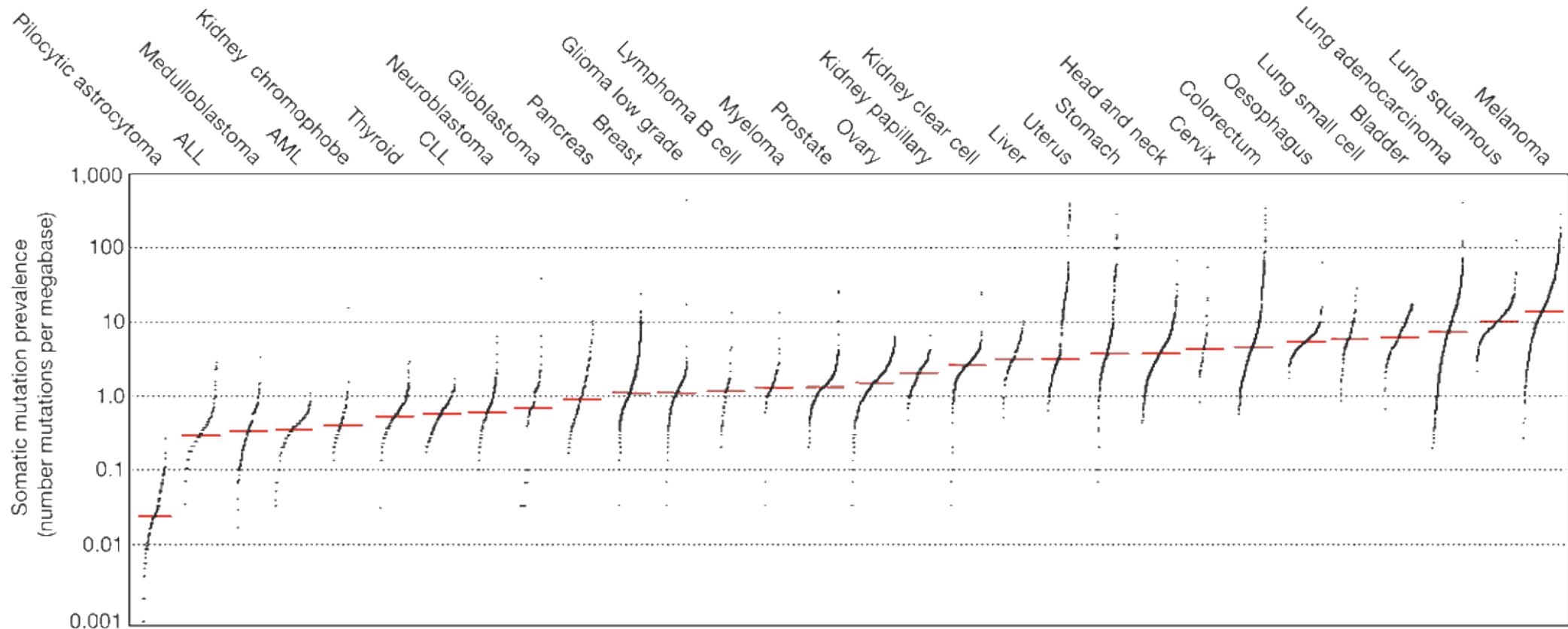
Zielgerichtete Therapien richten sich gegen spezifische Veränderungen in den Krebszellen



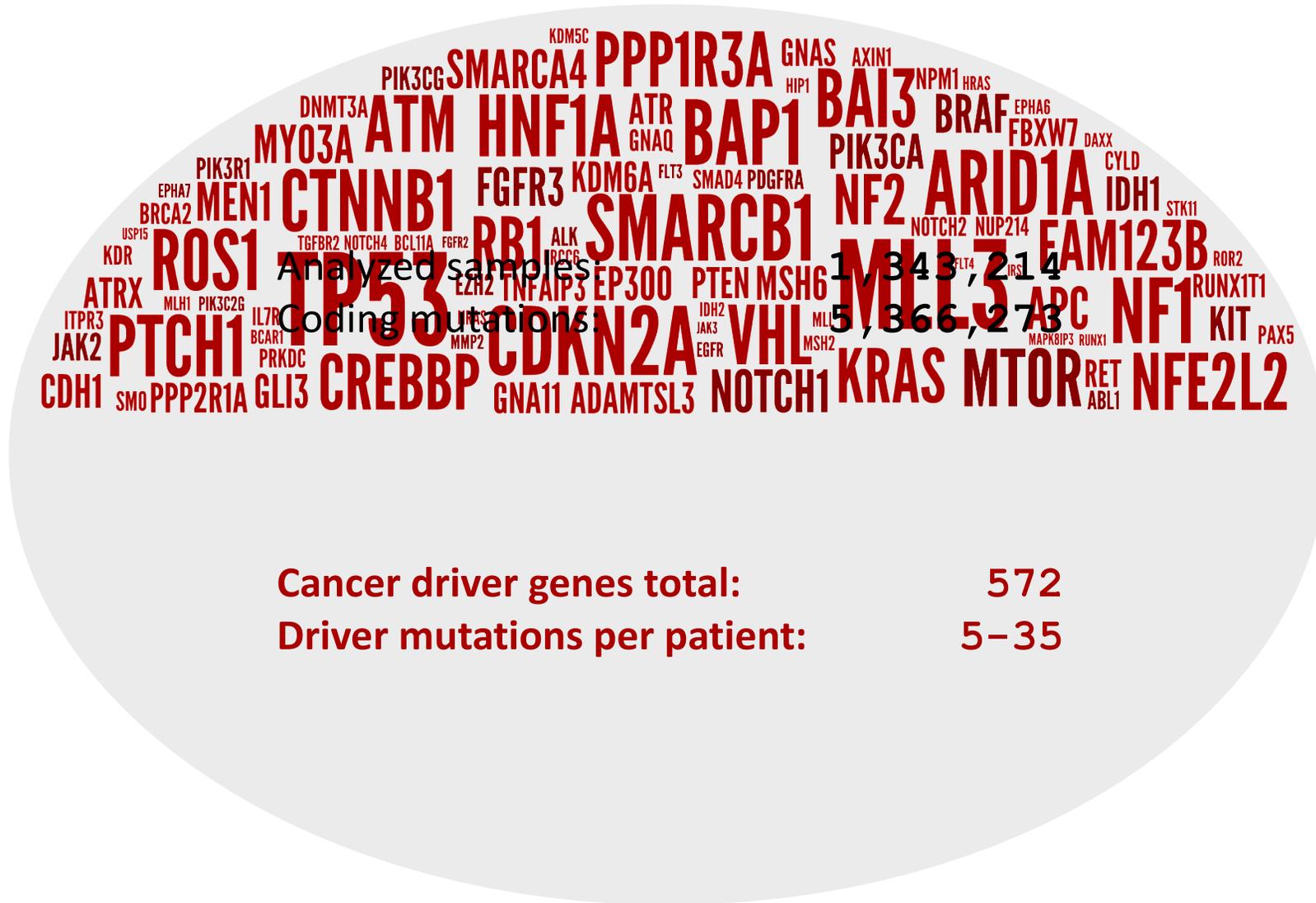
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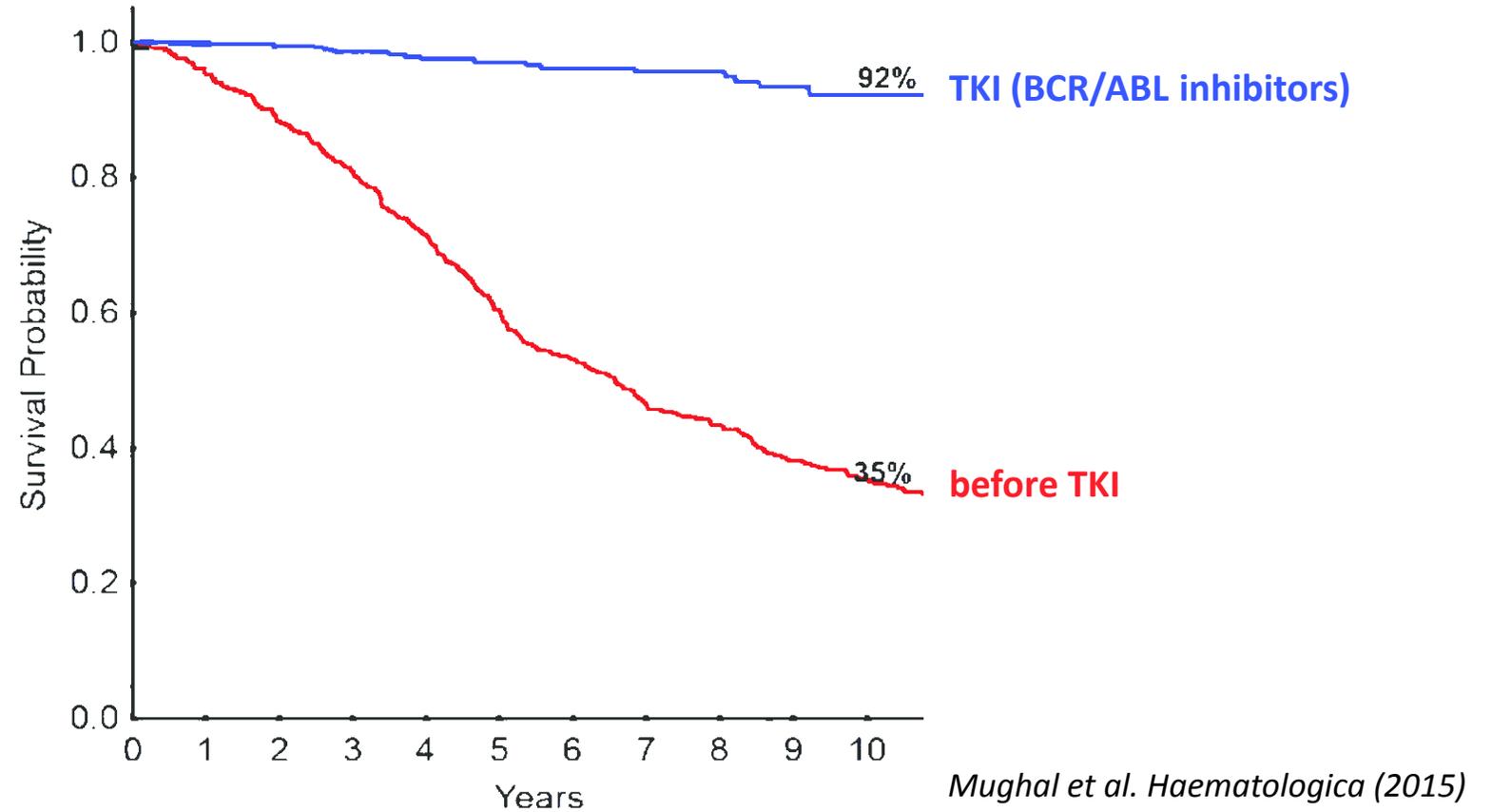
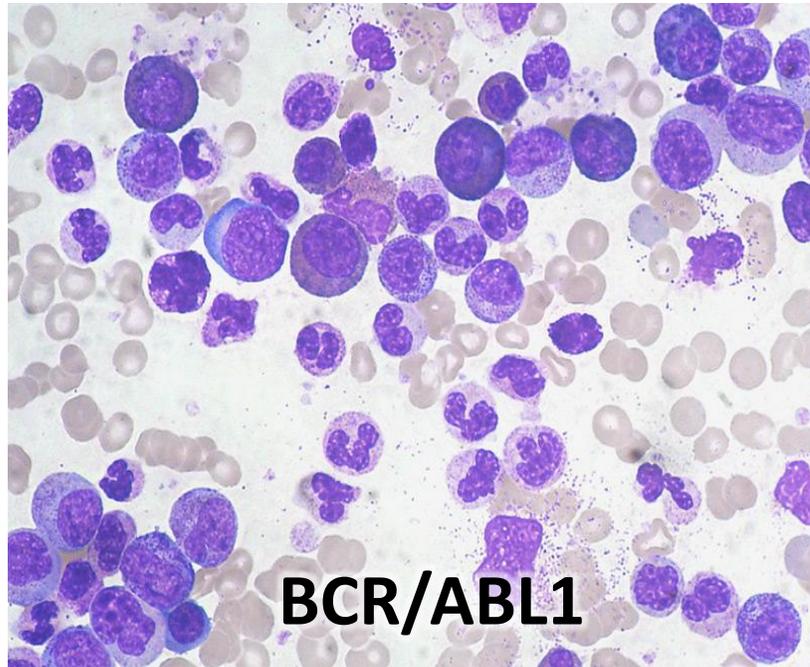


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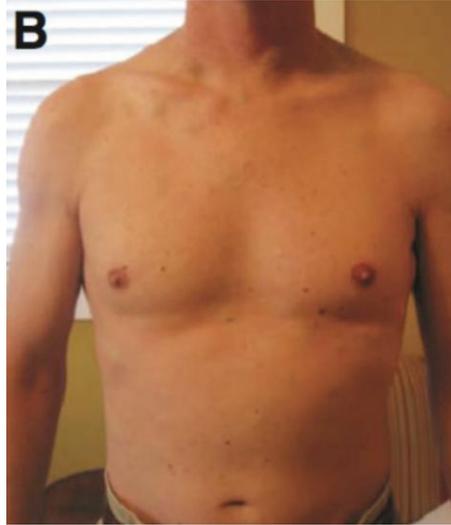


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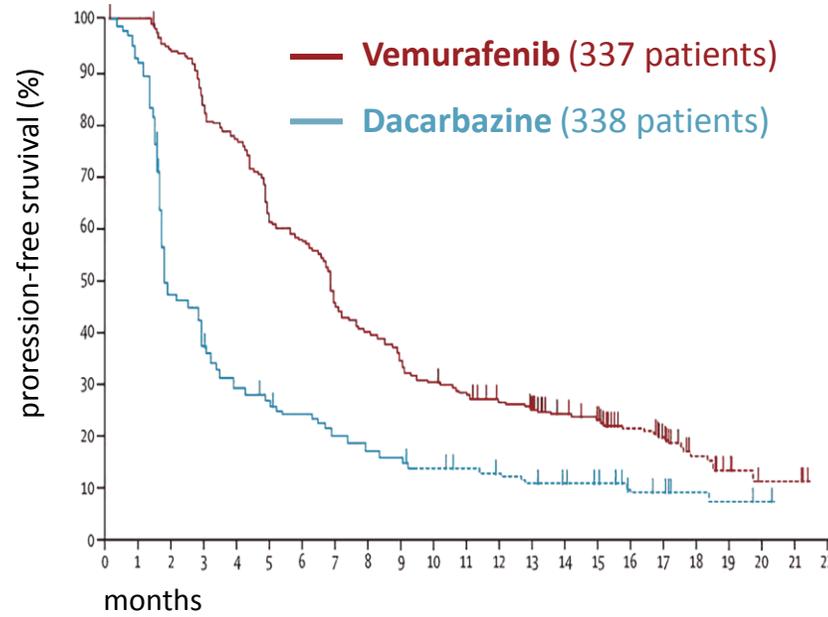
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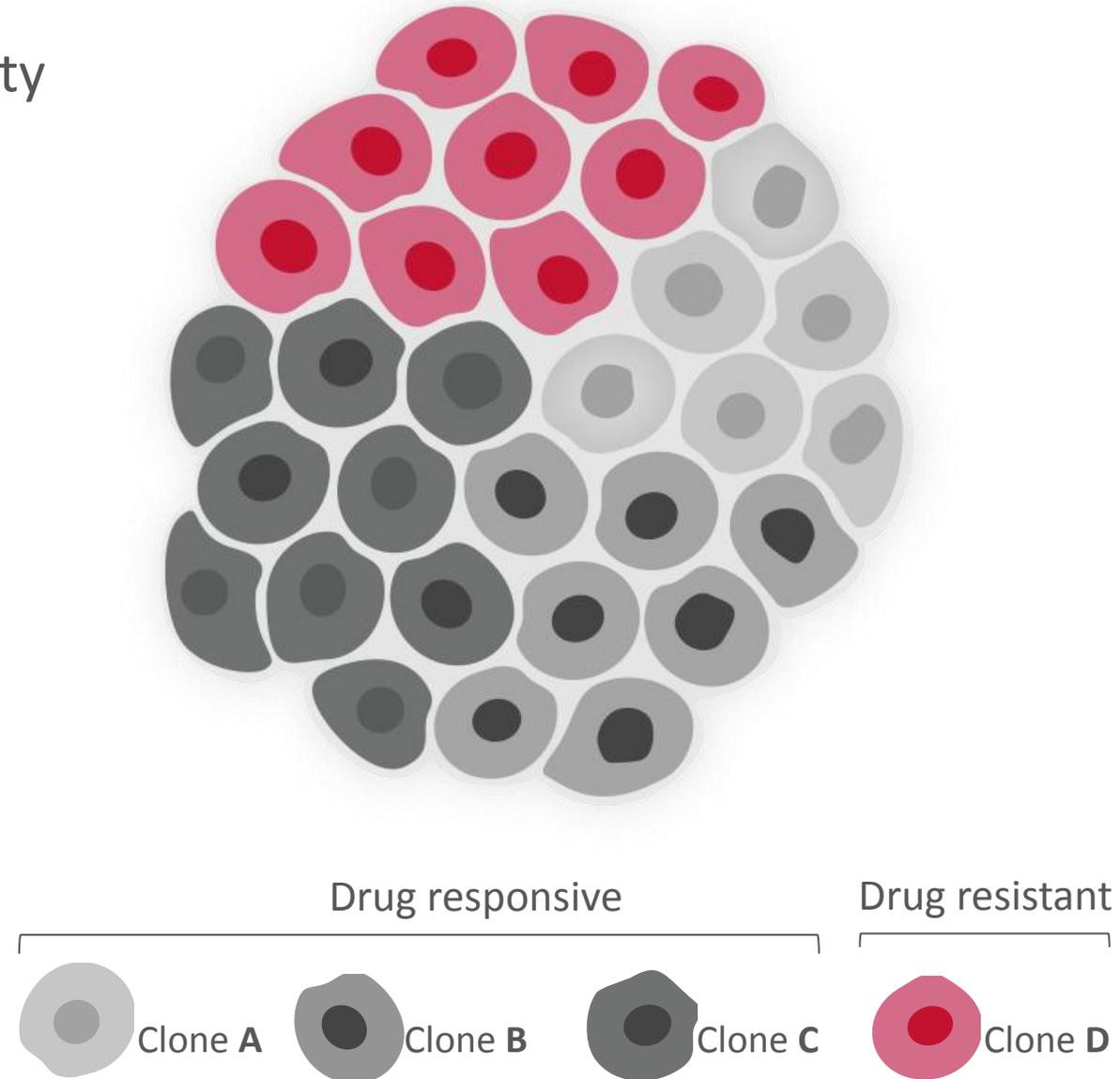
Wagle et al., *J Clin Oncol.* (2011)



McArthur et al., *Lancet* (2014)

Additional layers of complexity for the design of rational therapeutic combinations
– tumors are complex tissues

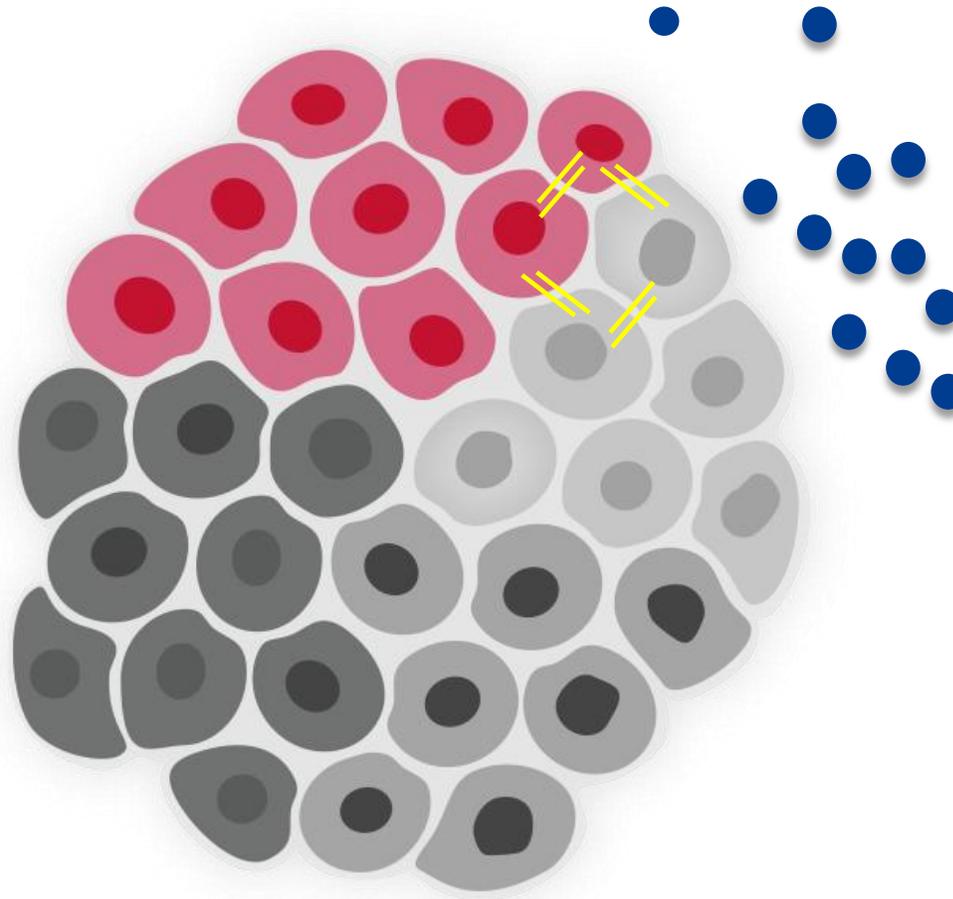
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Tumor heterogeneity

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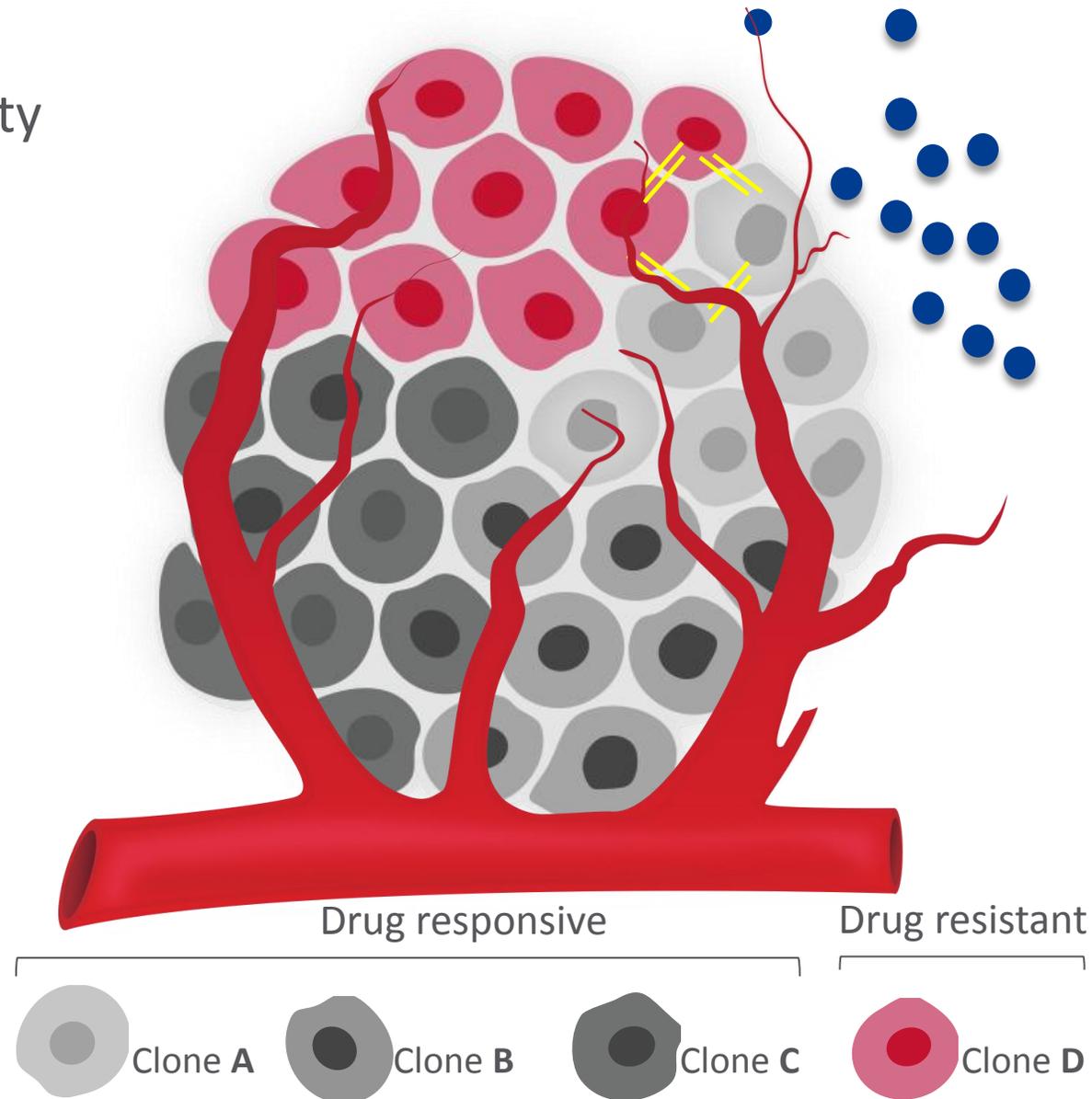


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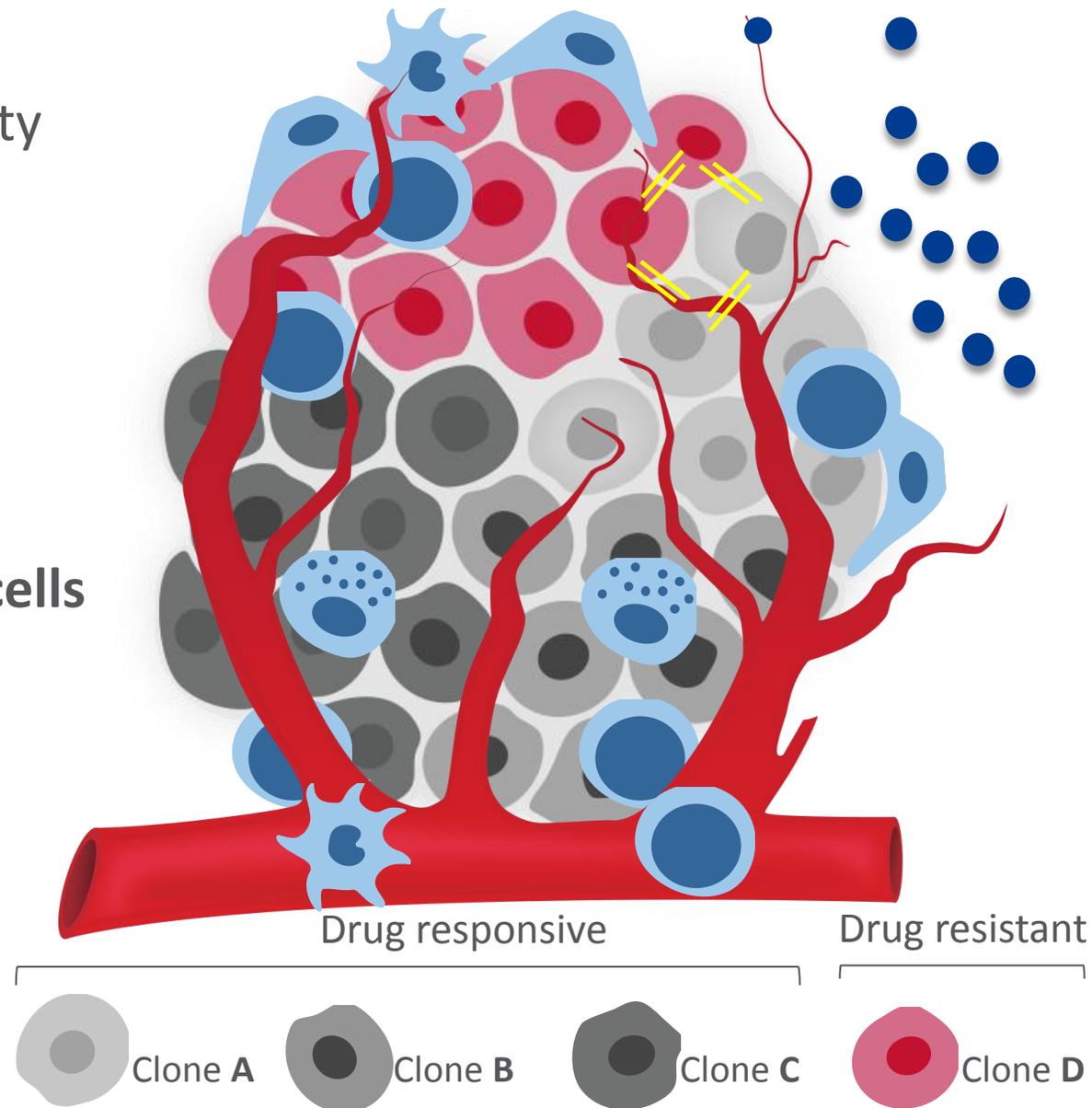
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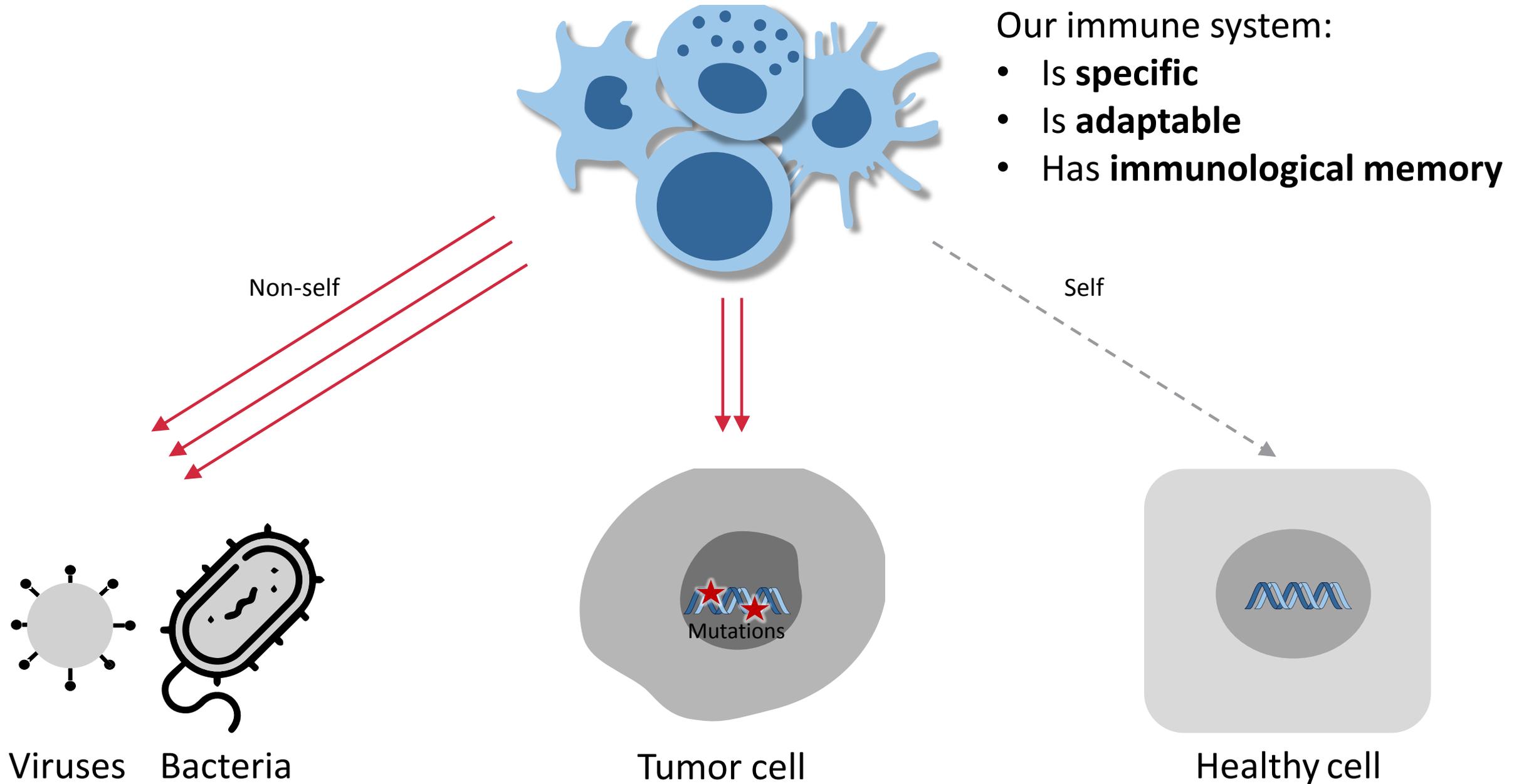
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Immune/stromal cells



Our immune system: protection against bacteria, viruses, worms, and cancer





In the 19th century Paul Ehrlich proposed

- The concept of **immune surveillance**
(immune system constantly eradicates malignant cells)
- That we may **use the immune system** to fight cancer

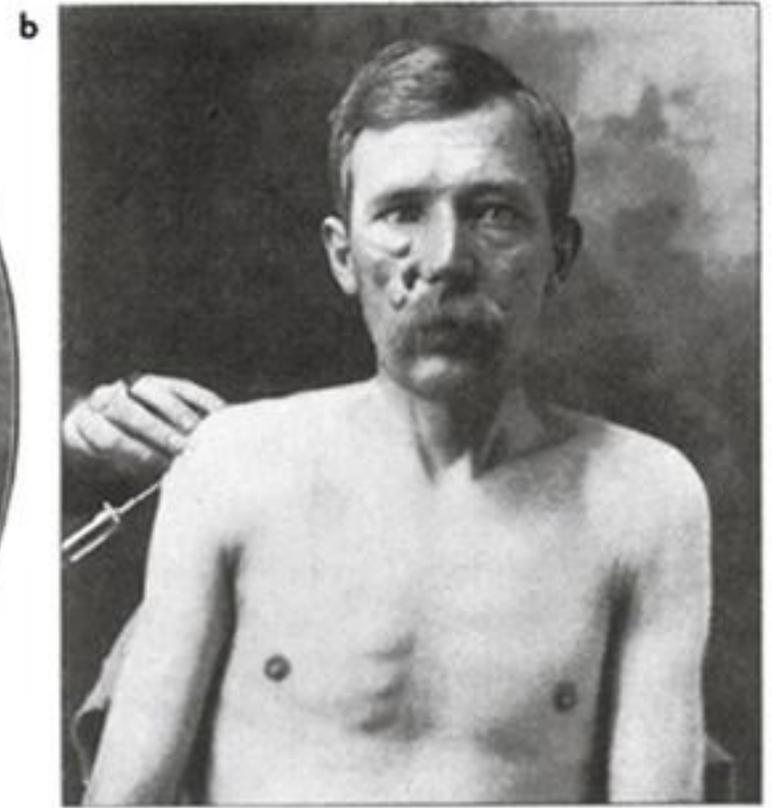
William Coley – cures cancer with injections of dead bacteria



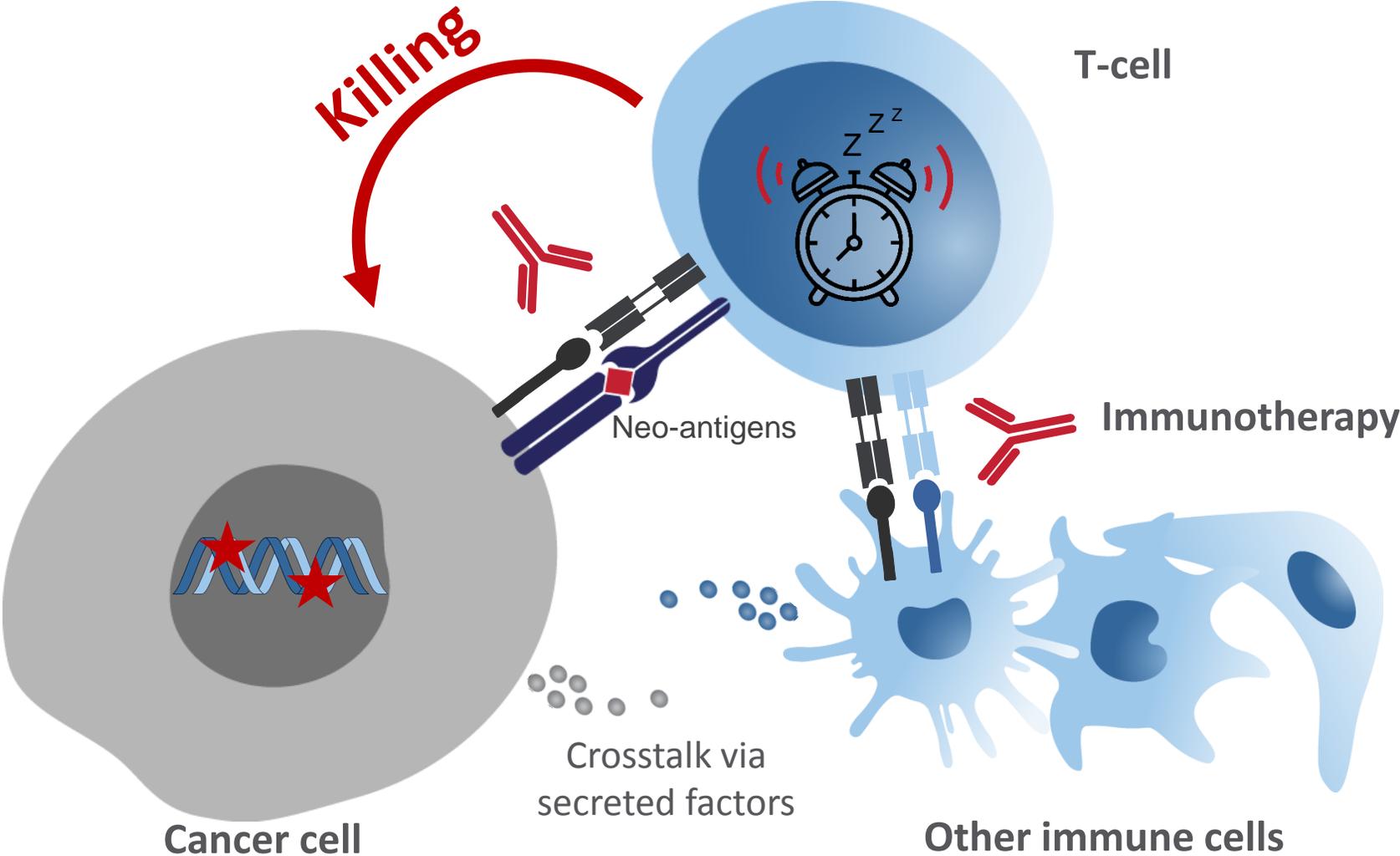
Patient with rapid response



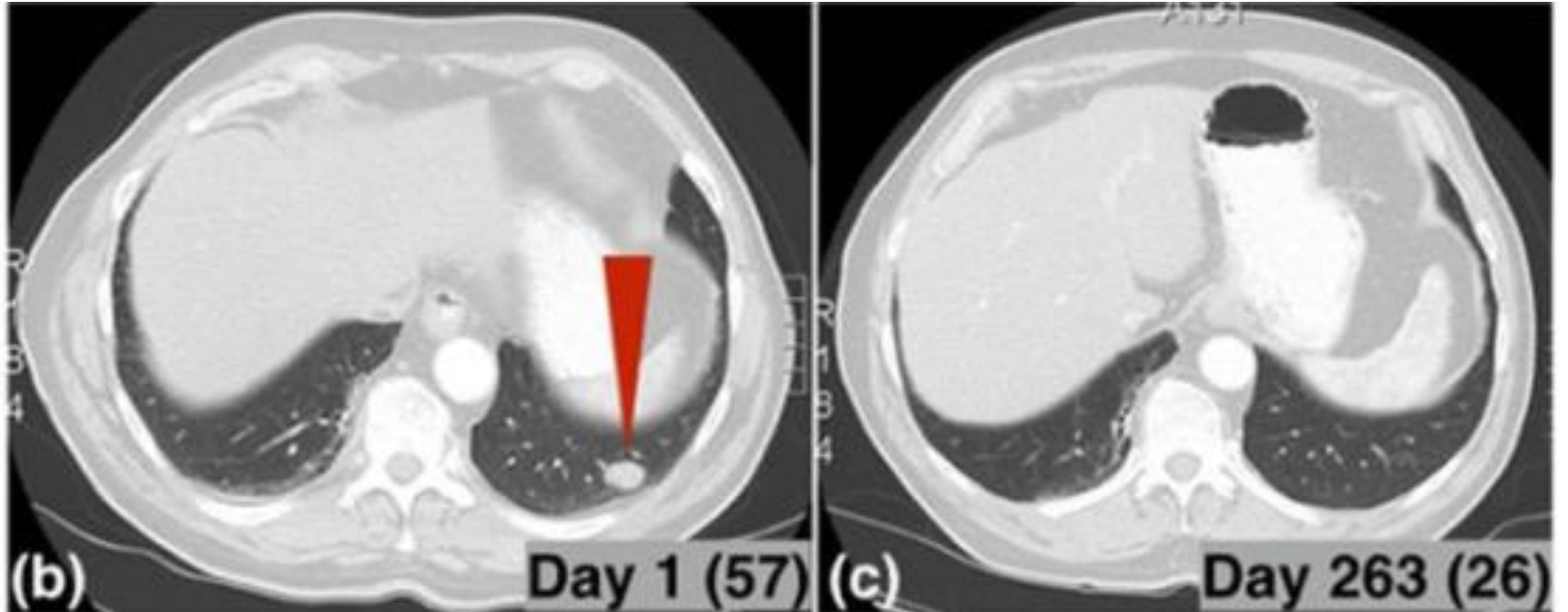
Patient responded after 63 injections



Cancer cells put T-cells to sleep, immunotherapy can wake them up again



Patient responding to immunotherapy

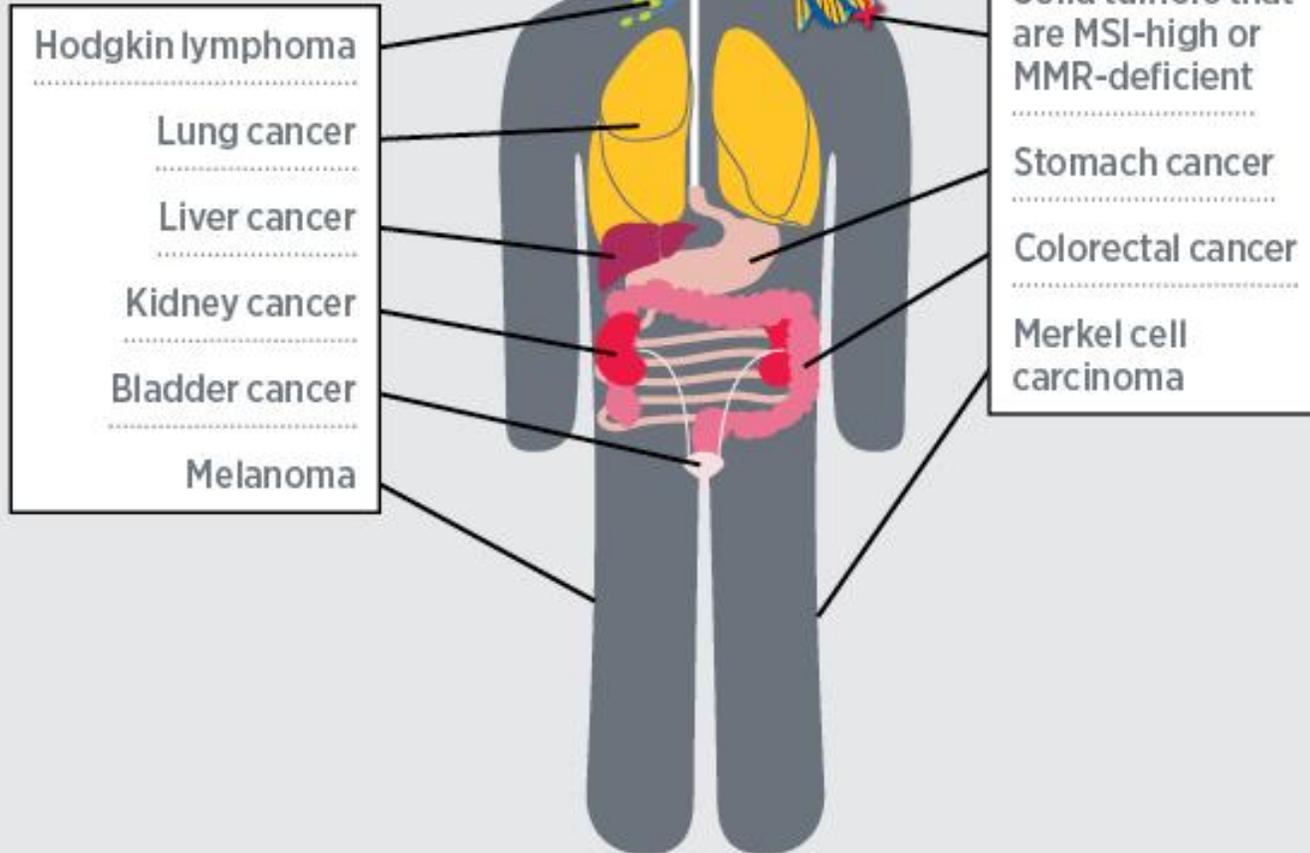


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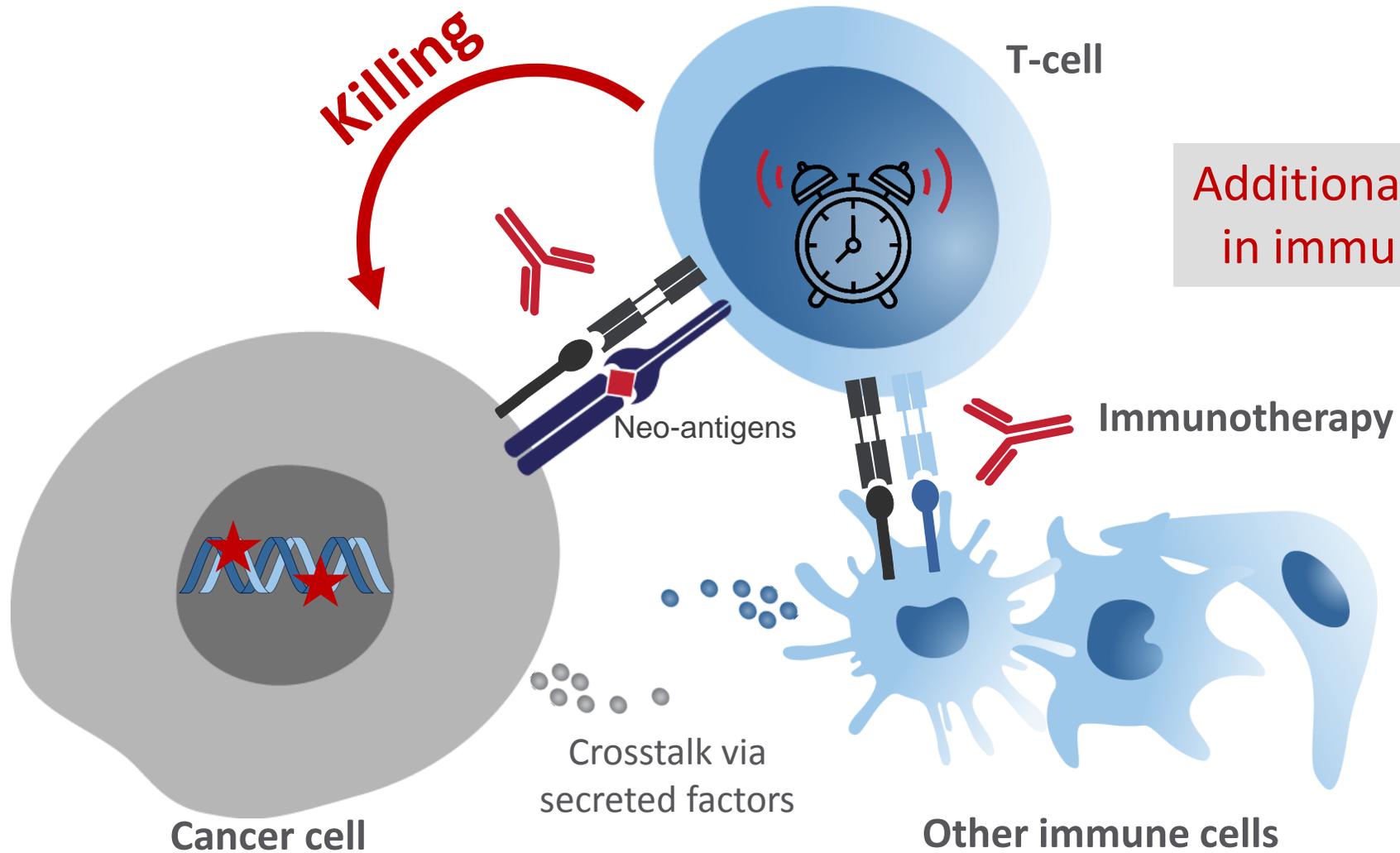


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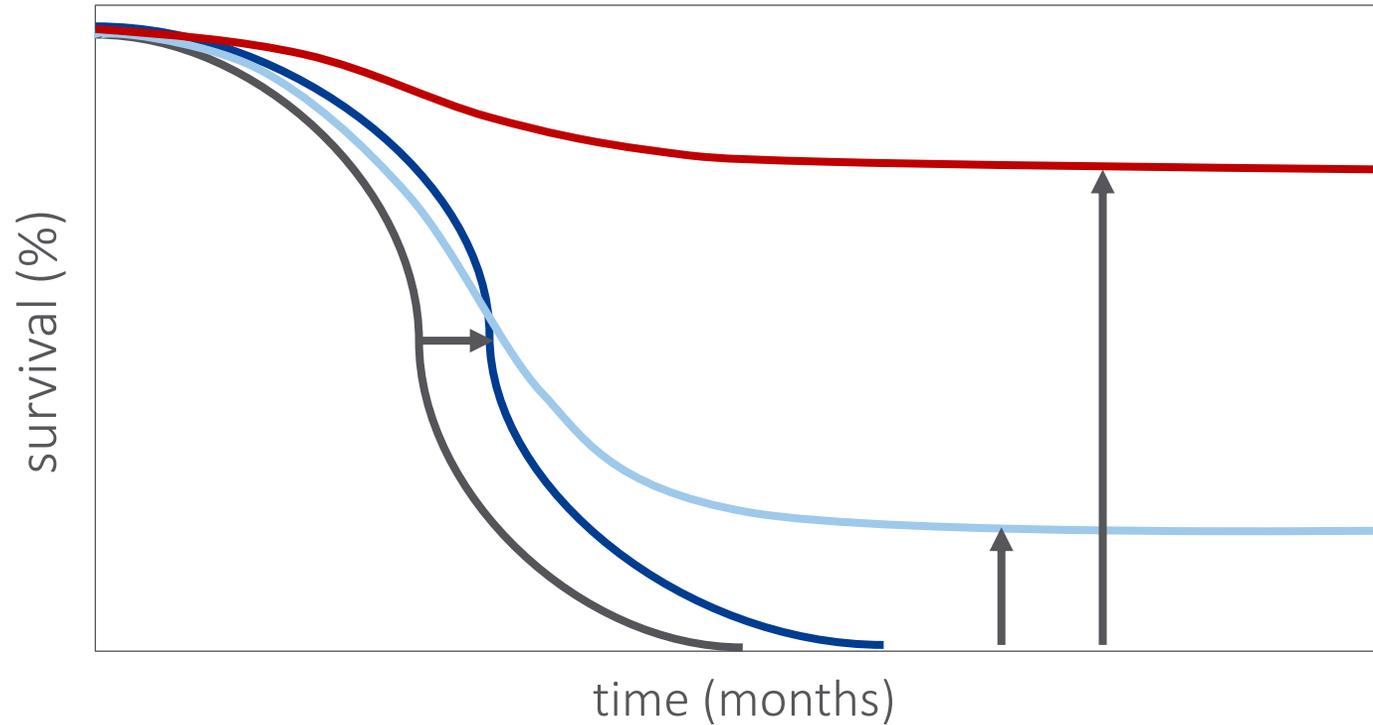
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Expanding the repertoire of immune-modulating agents



**Tumor specific (oncogenic) pathways
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Chemotherapy: cytotoxic, systemic inhibition of proliferating cells

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Immunotherapy: unleashing immune system to fight cancer, durable but only in fraction of patients

Combination therapy: the future of cancer treatment