Tumor Biology

and Precision Medicine

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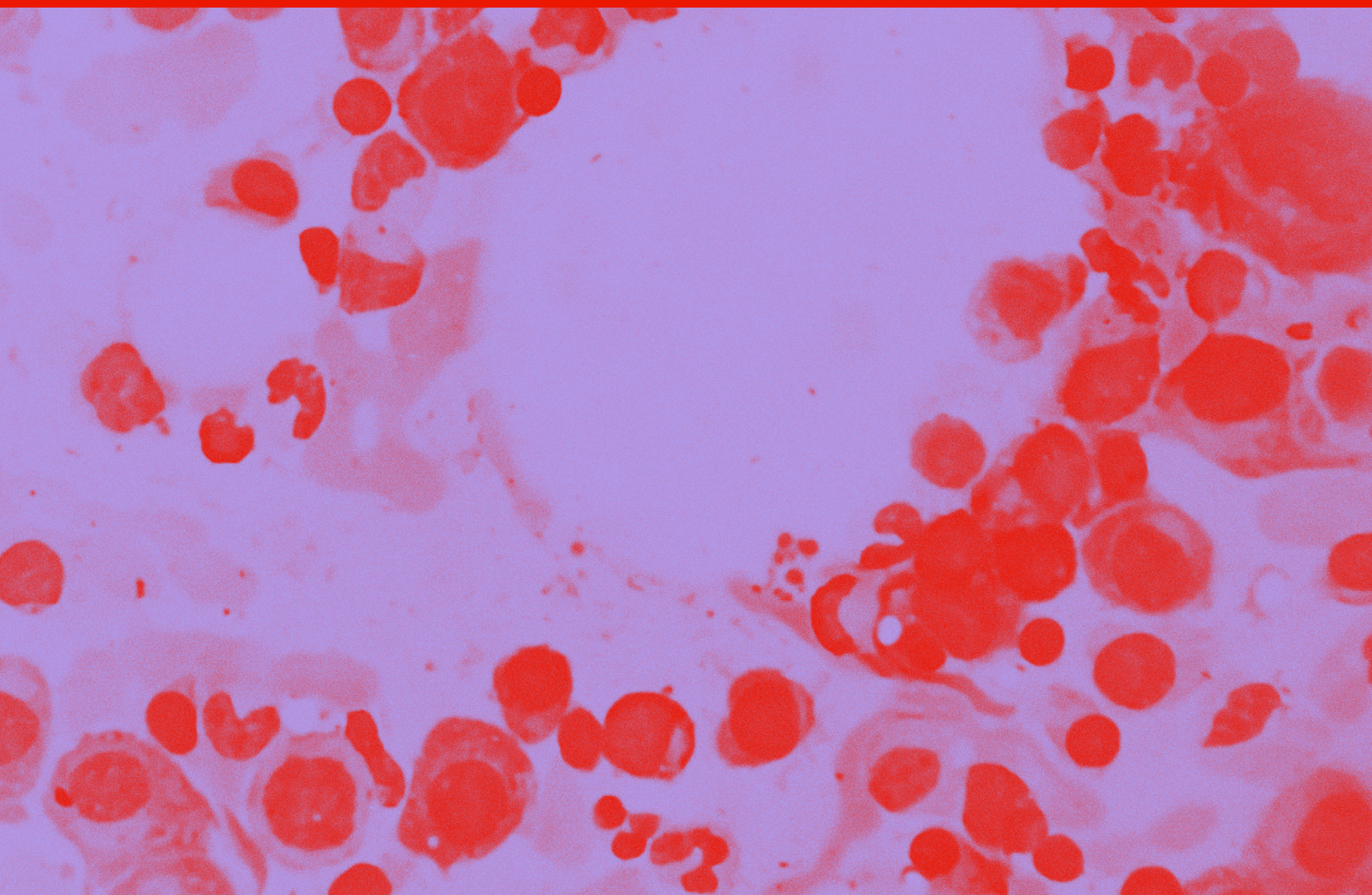
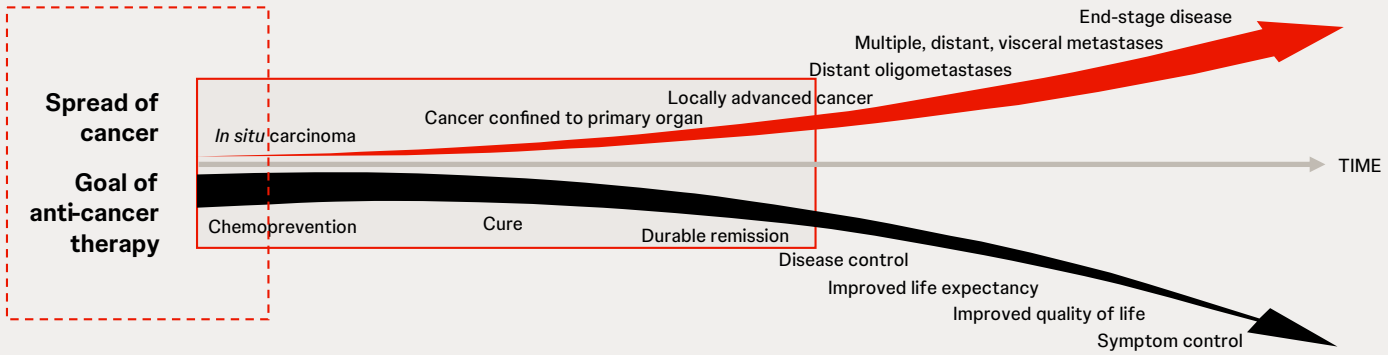
Precision Medicine



For some patients with cancer, it is a chronic disease that recurs[1–4]

- Survival after cancer has improved due to screening, facilitating earlier diagnosis[2,5,6]
- Currently, treatments with **curative intent are only available for early-stage** disease[7,8]
- For patients with cancer treated with curative intent, **recurrence rates range from 8.5% to ~85%**[2,8,9]
- Treatment planning is rooted in our understanding of tumor biology[10]

Relationship between cancer spread and goal of therapy[7]



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Mechanisms for recurrence may include evolutionary pressure from anti-cancer therapies[11]

Targeted therapy may cause **development of specific mutation(s) that lead to resistance**[12–14]

Immunotherapy is associated with **changes in tumor microenvironment (TME)** composition and expression of inflammatory genes in tumor cells[15]

Cytotoxic chemotherapies are linked to **increased mutation burden** throughout the genome, with platinum chemotherapy having the greatest mutagenic effect[12,13]

Opportunity to optimize

In cancers in which on-target evolution may be relevant for clinical decision-making, comprehensive genomic profiling at recurrence may provide insight into resistance mechanisms, identify new predictive biomarkers, and inform treatment decisions[13,14,16]

The hallmarks of cancer have evolved with our improved understanding of cancer biology, as has our understanding of driver alterations and tumor characteristics[17–19]

2000 | **2011** | **2022**

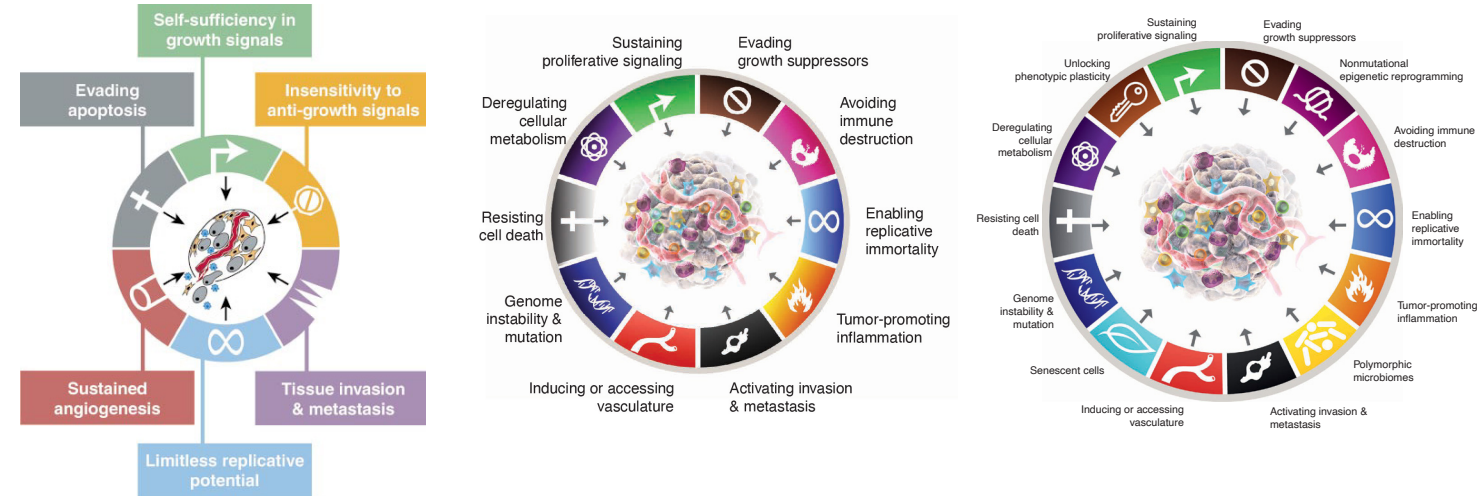


Image adapted from: Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell*. 2000;100(1):57–70; Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144(5):646–674; Hanahan D. Hallmarks of cancer: new dimensions. *Cancer Discov*. 2022;12(1):31–46.

Theoretical framework identified **6 core capabilities** involved in all cancers[17]

Greater understanding of the importance of the immune system drove **the addition of 2 core capabilities and 2 enabling characteristics**[17–19]

New insights into cancer complexity led to **addition of 4 core capabilities, bringing the total to 14**[17,19]

- Most hallmarks may be targeted with a biomarker-informed therapy[17,18]
- Many of the hallmarks of cancer are associated with **driver alterations**[17–21]
  - **Driver alterations** are any genetic alterations that directly or indirectly confer a growth advantage to the cells in which they occur, are selected, and are implicated in the development of cancer[20,21]
- Other hallmarks of cancer can be primarily defined by **tumor characteristics** or phenotypes (eg, expression of PD-L1)[18,19,22]

Comprehensive genomic profiling gives insight into the tumor biology of the cancer of your patient, and is recommended by ASCO for patients with advanced or metastatic disease[16,17,23]

Biomarkers may be used to identify patients most likely to respond to different therapies[24]

Diagnostic, prognostic, and predictive biomarkers[24]*	
	Diagnostic biomarkers identify if a patient has a particular medical condition for which treatment may be indicated
	Prognostic biomarkers provide information on the likely course of a disease, indicating a patient's risk of recurrence or progression
	Predictive biomarkers suggest which patients are likely to respond to specific treatments

Therapy	**Targeted therapy**[16,25]	**Targeted drug delivery**[26]	**Immunotherapy**[22,27]
MOA assumption	Most cancer cells have the same driver alteration	Target overexpressed on tumor cells	Immune cells can access tumor cells; neoantigen diversity
Therapy	*ROS1* TKI	ADC targeting HER2	Immune checkpoint inhibitor (ICI)
Predictive biomarker	*ROS1* fusions	HER2 overexpression	PD-L1, TMB
Assay	**PCR or NGS**	**IHC and/or FISH**	**IHC, NGS or PCR**
Turnaround time (median)[28,29†]	6–15 days for PCR 17.5–24.5 days for NGS	2–3 days for IHC 5–7 days for FISH	2–3 days for IHC 17–24.5 days for NGS 6–15 days for PCR
Estimated cost[30,31]	$875 per PCR test $438 to $3,700 per NGS test	$600 per IHC test $1,400 per FISH test	$600 per IHC test $438 to $3,700 per NGS test $875 per PCR test

*Therapy types and biomarker testing assays are representative and may not include the full spectrum of anti-cancer therapies or biomarker testing assays.
†The number of calendar days between the date of sample receipt/initial test requisition and the date test results are made available for biomarkers in lung cancer, breast cancer, or melanoma.[28]

Comprehensive biomarker testing supports clinical decision-making across various cancer types[32–35]

mNSCLC
~44%–71%

of patients with *EGFR* mutations are also positive for PD-L1 expression[36,37]

Patients with *EGFR*+ and PD-L1+ mNSCLC may not benefit when treated with IO instead of targeted therapy[38–40]

mCRPC
~37% & ~34%

of *BRCA*+ patients have co-occurring alterations in *TP53* or *PTEN*, respectively[41]

TP53 alterations are associated with a **worse prognosis**[32]

Breast cancer
~93%

of patients tested for actionable and emerging biomarkers are eligible for a biomarker-informed therapy[33]

For patients with mBC, ASCO guidelines recommend **testing for at least 10 biomarkers to** guide therapeutic decisions[34,35]

mCRC
43.9%

of patients with mCRC have both *RAS* and *TP53* mutations[42]

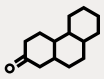
Co-mutation of *RAS* and *TP53* in patients with mCRC was associated with a **higher risk of chemotherapy resistance and inferior outcomes**[42]

ASCO recommends comprehensive biomarker testing in patients with advanced or metastatic disease[42]

Cancer is a dynamic process[18,43]

Cancer cells integrate signals from and utilize multiple distinct cellular circuits during tumorigenesis[18,43]

Key pathways include (but are not limited to):

	**Proliferation receptor signaling like EGFR and MAPK pathway[17,43]**
	**DNA damage-response proteins like BRCA1/2[44]**
	**Motility and adhesion molecules like E-cadherin[18,43]**
	**Cell cycle regulation like CDK4/6[17]**

Tumor evolution: from driver mutations to clonal heterogeneity

Genomic analysis of >35,000 unique tumors revealed that most driver alterations occur earlier in cancer evolution[45,46]

Over time, tumors **accumulate** mutations, including:

- Additional driver mutations[45,46]
- Co-mutations[46]
- Mutations facilitating metastasis[47]

Some primary cancers contain multiple clones capable of forming metastases through different routes, termed **evolutionary signatures**[46,47]

- In one study, evolutionary signatures were associated with different prognoses[46]
- Further study is needed to see if evolutionary signatures can be used to generate personalized risk assessment[46]

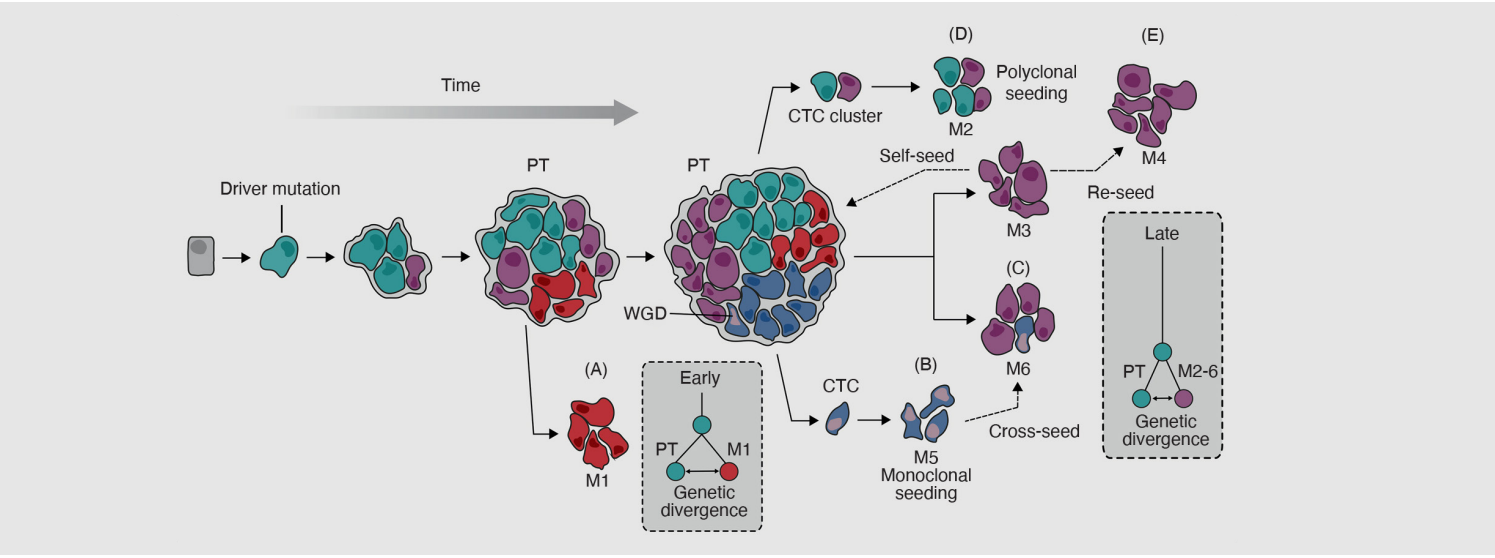


Image adapted from: Patel SA, Rodrigues P, Wesolowski L, et al. Genomic control of metastasis. *Br J Cancer*. 2021;124(1):3–12. https://creativecommons.org/licenses/by/4.0/

Opportunity to optimize

Most key driver mutations occur decades before diagnosis.[45] Comprehensive biomarker testing upfront may inform therapeutic choices, now and in the future[16]

Co-mutations may impact clinical outcomes[48]

Computational modeling based on multiple large datasets reveals co-mutations affect one another and impact clinical outcomes[46]

Co-mutations can influence disease course via:

- Complementary cellular mechanisms[46,49]
- Changing tumor immune microenvironment composition[48]
- Altering therapeutic vulnerabilities[46,48,49]
- **Enabling drug resistance[48]**

Patients with *EGFR*+ mNSCLC and *TP53* mutations have shorter progression-free survival following first-/second-generation TKIs compared with patients without the mutation[48]

TP53 co-mutations:
Impact the natural history of *EGFR*-mutant NSCLC[48]

Allow tolerance of greater genomic instability[48]

Result in larger numbers of[48]:

- Co-occurring truncal drivers[48]
- Late subclonal diversification[48]
- High-amplitude amplifications and deletions in mediators of therapeutic resistance[48]

Current understanding of the interplay between different co-mutations is limited. This active area of research may uncover key relationships that inform future clinical decision-making[48]

The importance of the tumor microenvironment (TME)

The **TME** is the temporal-spatial organization of cancer cells, immune cells, and other cells within the tumor[50,51]

The TME changes in response to multiple factors, including tumor genetics and environmental stimuli[50,51]

- **Driver alterations** influence the composition of the TME cell-cell interactions and cytokine/chemokine signaling[50,52]
- **Cancer-associated fibroblasts (CAFs)** remodel the extracellular matrix, which impacts tumor invasion and ability for different immune cells to access the tumor[53]
- **Clonal evolution** responds to and reshapes the TME[54]
- **Anti-cancer therapies** like ICIs can alter immune cell signaling, which may lead to TME remodeling and acquired therapeutic resistance[55]

Assessing the TME with biomarker testing may play a future role in clinical care[50,51]

Molecular drivers, tumor evolution, and the TME may give greater insight into cancer management[11,16,48,50,51]

Biomarker testing at diagnosis or recurrence may identify therapeutically actionable alterations and co-mutations to identify patients most likely to respond to a specific therapy[16,48]

Understanding tumor evolution and heterogeneity through biomarker testing may inform prognosis[11,50]

Biomarker testing to define the spatial composition of the TME may inform treatment decisions at diagnosis and recurrence[51]

An integrated framework of biomarker testing considering all these factors could one day better aid in clinical decision-making[11,16,48,50,51]

Our knowledge of tumor biology has grown and is now being utilized to develop novel anti-cancer agents[17,18]

Complexities of cancer are beginning to be understood and may translate to clinical decisions[11,16,48,50,51]

Results from comprehensive biomarker testing can:

- **Identify patients with actionable driver alterations**[16,24]
- **Find co-mutations and resistance mutations**[48]
- **Identify emerging predictive biomarkers**[13,16]

ADC, antibody-drug conjugates; ASCO, American Society of Clinical Oncology; BRCA1/2, breast cancer gene 1/2; CAFs, cancer-associated fibroblasts; CDK4/6, cyclin-dependent kinases 4 and 6; CTC, circulating tumor cells; DNA, deoxyribonucleic acid; EGFR, epidermal growth factor receptor; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; ICI, immune checkpoint inhibitor; IHC, immunohistochemistry; IO, immuno-oncology; M, metastases; MAPK, mitogen-activated protein kinase; mBC, metastatic breast cancer; mCRC, metastatic colorectal cancer; mCRPC, metastatic castration-resistant prostate cancer; mNSCLC, metastatic non-small cell lung cancer; MOA, mechanism of action; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; PCR, polymerase chain reaction; PD-L1, programmed death-ligand 1; PT, primary tumor; *PTEN*, phosphatase and tensin homolog gene; *RAS*, rat sarcoma; *ROS1*, ROS proto-oncogene 1, receptor tyrosine kinase; TKIs, tyrosine kinase inhibitors; TMB, tumor mutational burden; TME, tumor microenvironment; *TP53*, tumor protein 53 gene; WGD, whole-genome doubling.

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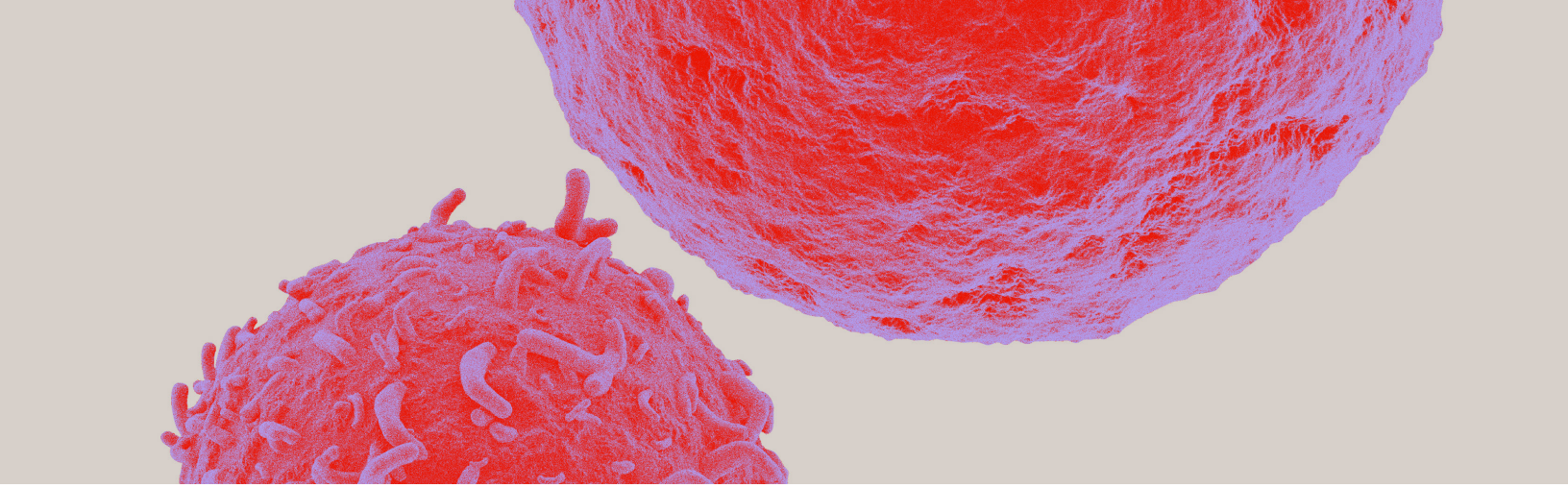

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