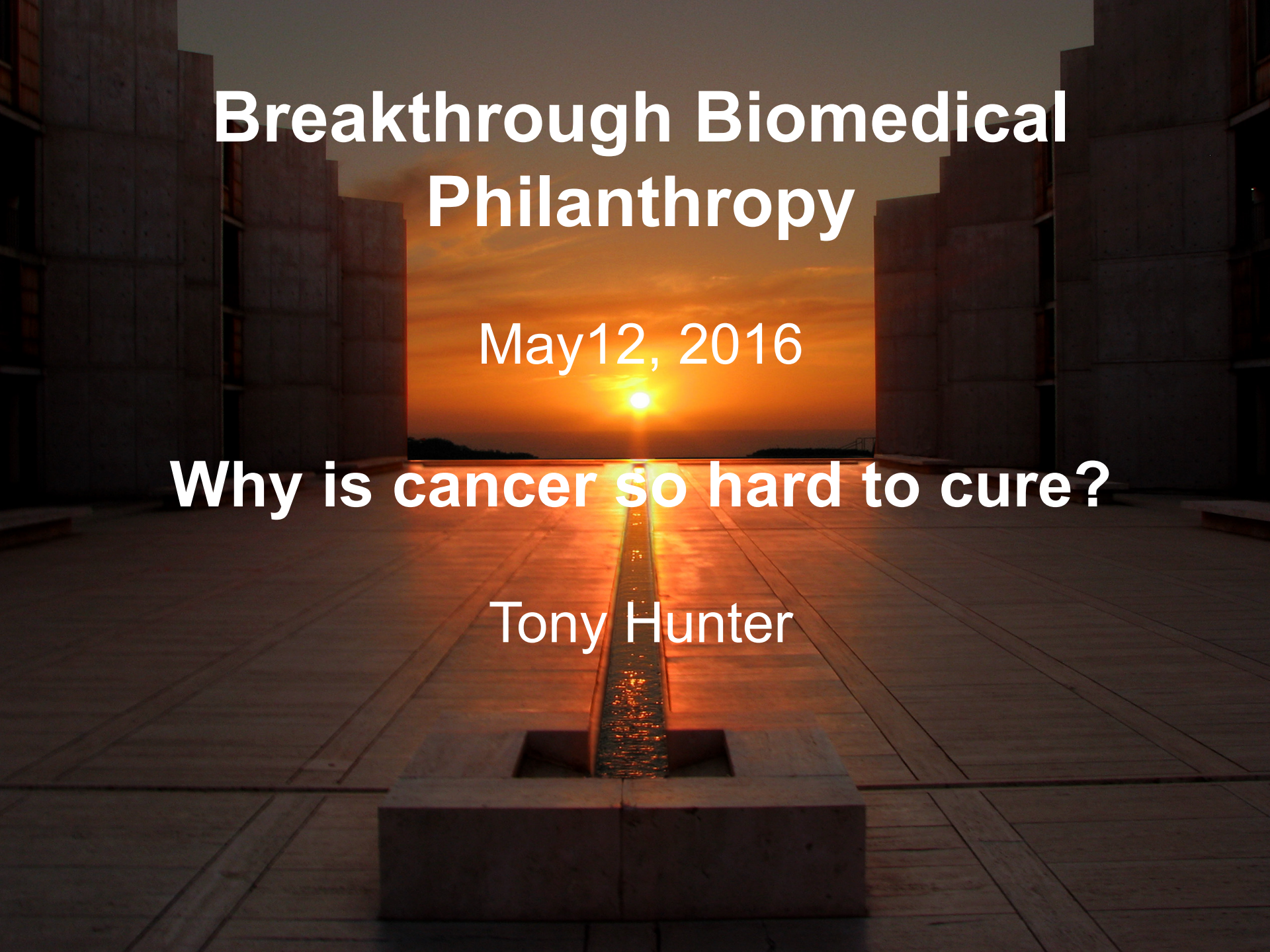


Breakthrough Biomedical Philanthropy

May12, 2016

Why is cancer so hard to cure?

Tony Hunter

1971 National Cancer Act

National Cancer Act
Signed into law by President Nixon
December 23, 1971

The Director of National Cancer Institute was given authorities under the act that included:

- ***Create new Cancer Centers*** *and manpower training programs*
- ities.
- y.
- res,

and disseminates results of cancer research

- ***Award research grants***

Since 1971 the NCI has spent over $140 billion on cancer research

This was Nixon's "moonshot" to cure cancer

Cancer remains a scourge worldwide

- 14 million cancers diagnosed worldwide in 2012 with 8 million deaths, with half of the cancers occurring in underdeveloped countries
- Lung cancer accounts for 20% of all cancers world wide, and breast cancers 10% of all cancers

- In the United States,1,665,540 new cancer cases were diagnosed and 585,720 cancer deaths occurred in 2014

Cancer is about to overtake heart disease as the leading cause of death in the US

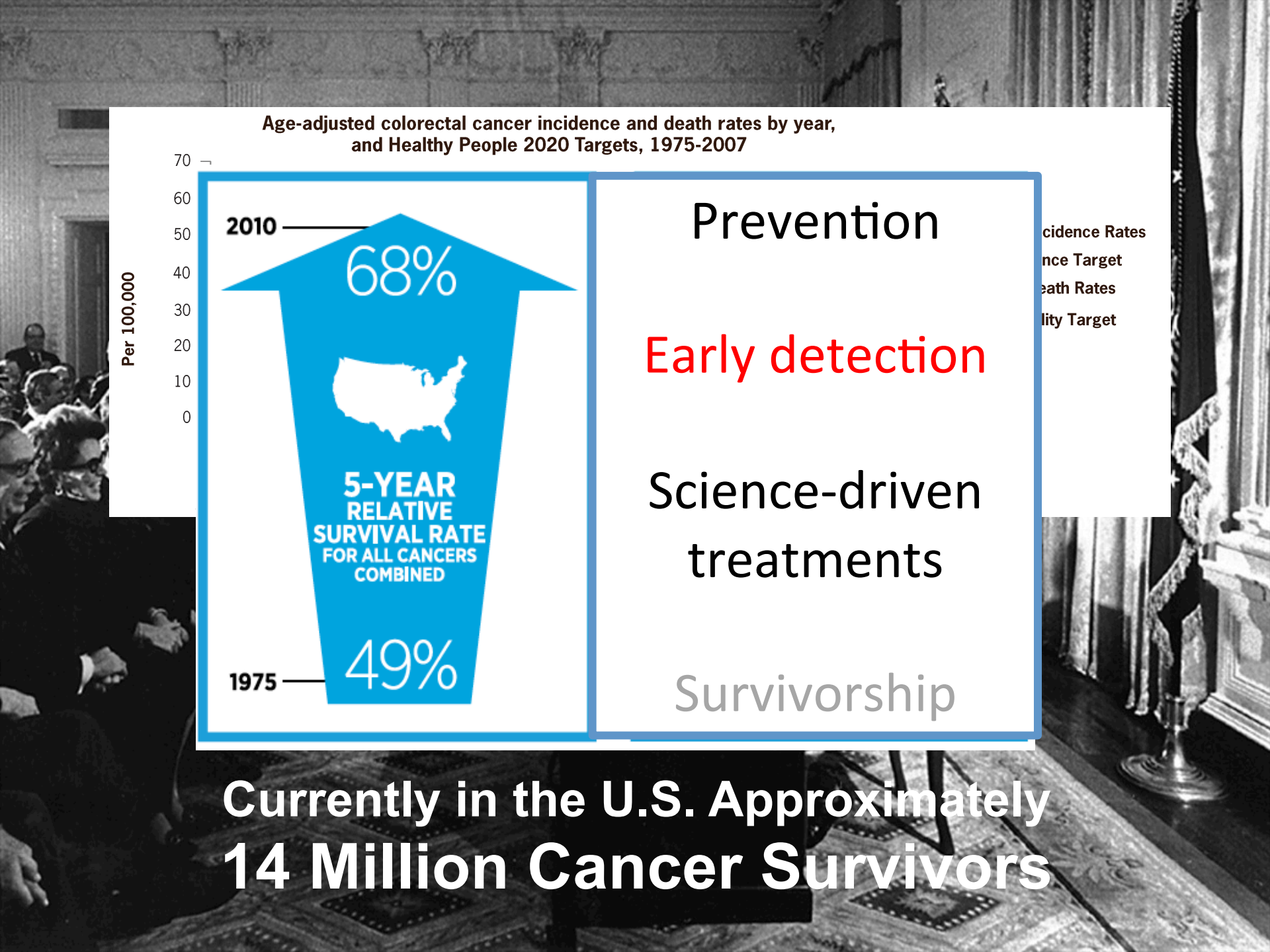
US Mortality Data - 2013

Rank	Cause of Death	No. of deaths	% of all deaths
1.	Heart diseases	611,105	32.6
2.	**Cancer**	**584,881**	**30.9**
3.	Chronic lower respiratory diseases	149,205	7.4
4.	Accidents	130,557	6.8
5.	Cerebrovascular diseases	117,176	6.4
6.	Alzheimer disease	84,767	4.2
7.	Diabetes	75,578	3.7
8.	Influenza and pneumonia	56,979	2.9
9.	Nephritis	47,112	2.6
10.	Suicide	41,149	2.1

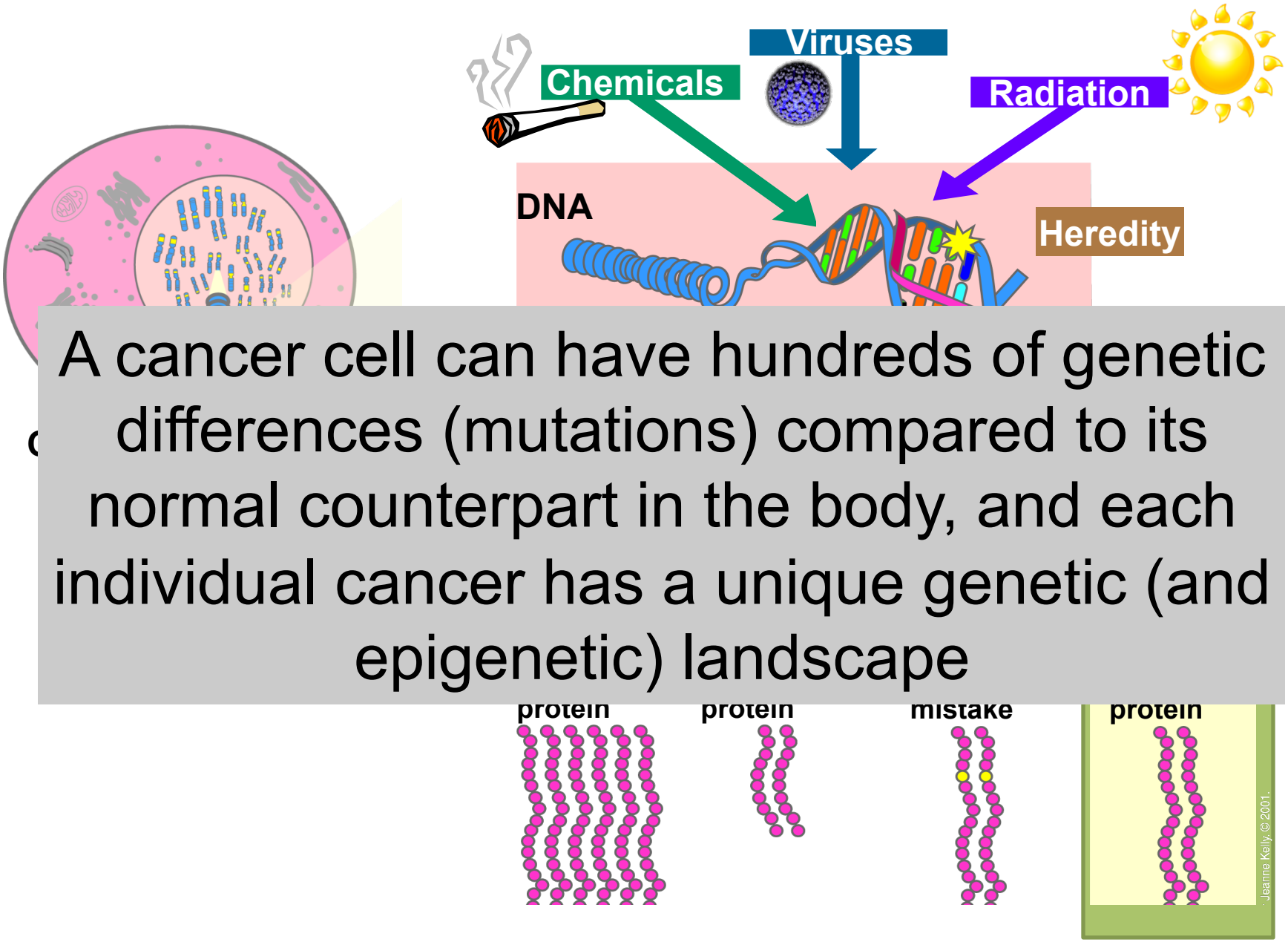
Why is cancer so hard to cure?

- Canc al
  canc here
  are c
- Canc sily
  gene ing
  drug- geneity
- Canc r
  prolif gs
- Canc cells
  and r essel
  cells ribute
  to the
- Canc n
  repo tumor
  cells are killed

Cancer Whack-a-Mole


Age-adjusted colorectal cancer incidence and death rates by year,
and Healthy People 2020 Targets, 1975-2007
Per 100,000
70
60
50
40
30
20
10
0
2010
68%
5-YEAR
RELATIVE
SURVIVAL RATE
FOR ALL CANCERS
COMBINED
1975
49%
Prevention
Early detection
Science-driven
treatments
Survivorship
Currently in the U.S. Approximately
14 Million Cancer Survivors

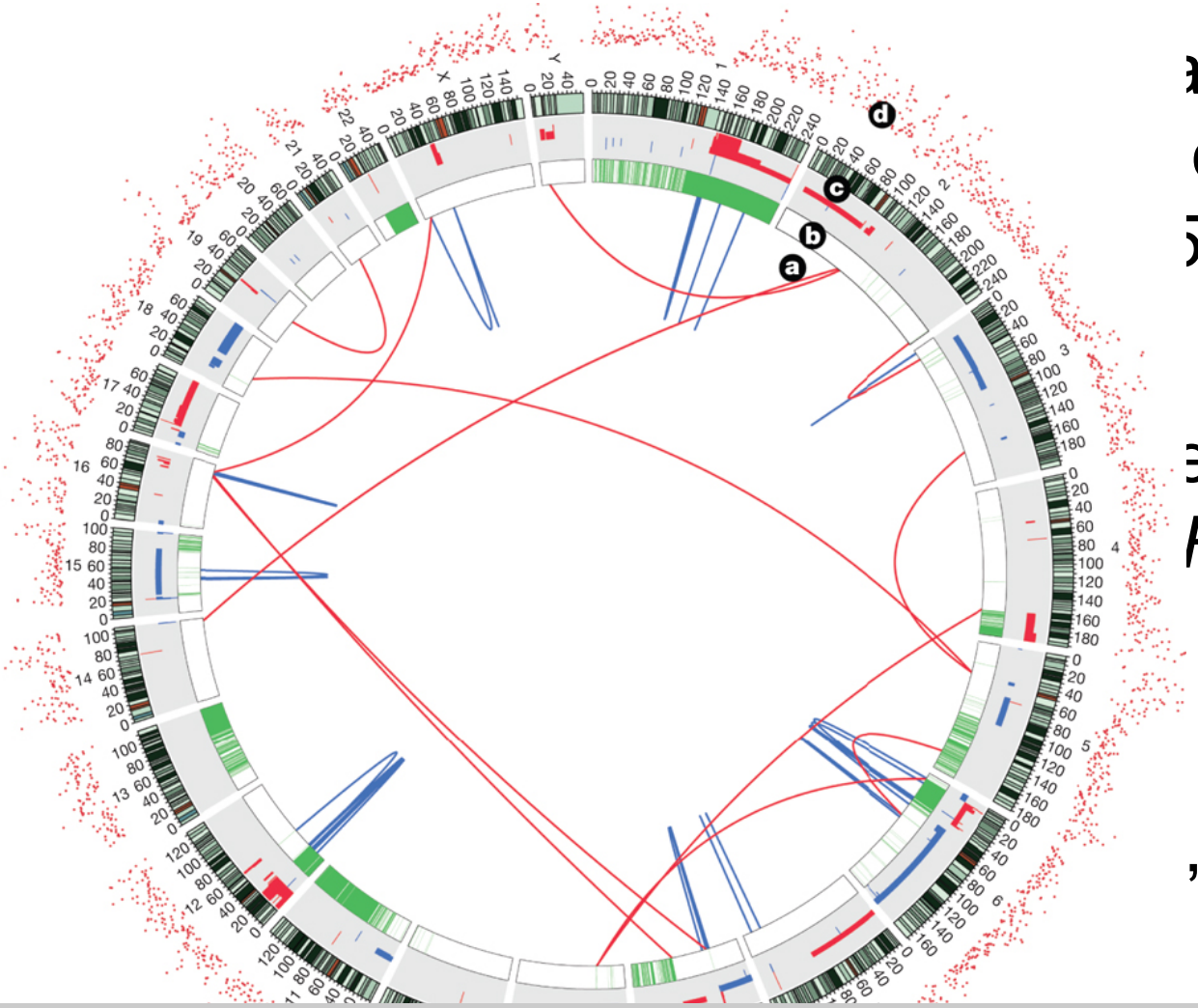
Cancer is a genetic disease



A cancer cell can have hundreds of genetic differences (mutations) compared to its normal counterpart in the body, and each individual cancer has a unique genetic (and epigenetic) landscape

How many mutations are there in an individual cancer?

- Com … a
  nons … ormal
  DNA … 50,000
  muta …
- 530 … ere
  foun … *RAS*
  prot …
- Ove …
  meg … ,000
  Mb (…



Which of these mutations are "driver" mutations and which are passenger mutations?

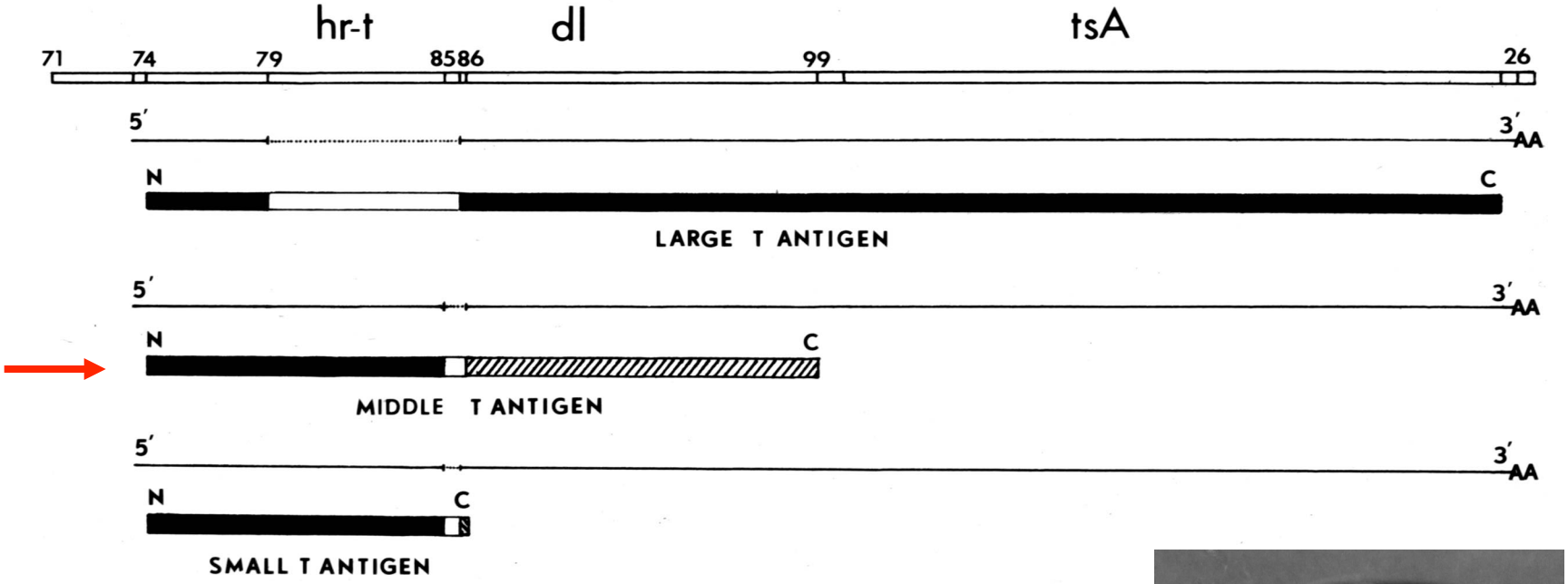
Lee et al. *Nature* **465:**473 (2010)

The Salk has a long legacy in cancer research and has made many landmark discoveries

We are at a turning point in the study of tumor virology and cancer in general. If we wish to learn more about cancer, we must now concentrate on the cellular genome. We are back to where cancer research started, but the situation is drastically different because we have new knowledge and crucial tools, such as DNA cloning. We have two options: either to try to discover the genes important in malignancy by a piecemeal approach, or to sequence the whole genome of a selected animal species.

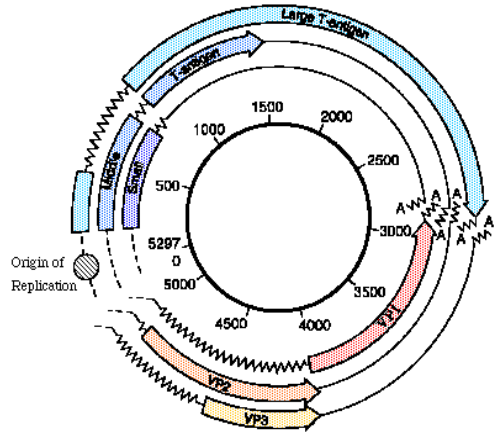
In which species should this effort be made? If we wish to understand human cancer, it should be made in humans because the genetic control of cancer seems to be different in different species. Research on human cancer would receive a major boost from the detailed knowledge of DNA. Humans would become the preferred experimental species for cancer research with cells in culture or in immunodeficient mice. Because cancer could be defined in molecular terms, the agents capable of inducing cancer in humans could be identified by the combination of in vitro and epidemiological studies. Knowledge of the genes involved in progression would open new therapeutic approaches, which might lead to a general cancer cure if progression has common features in all cancers.

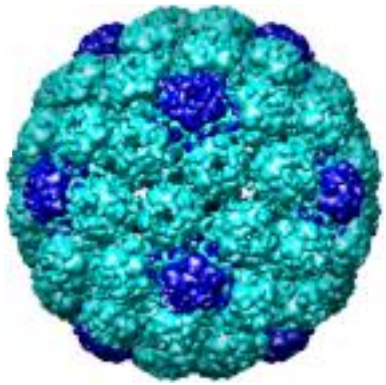
Back in 1979 we were using the small DNA tumor virus polyomavirus as a model for human cancer



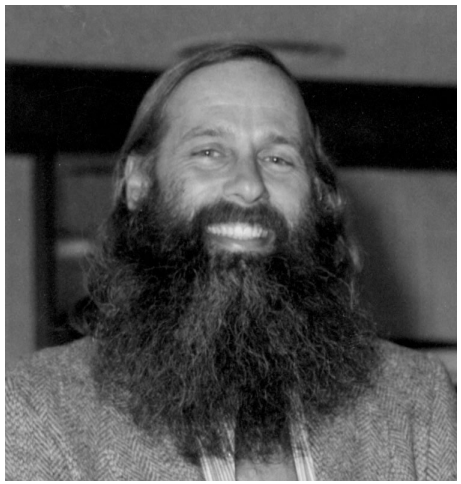
Early

Late



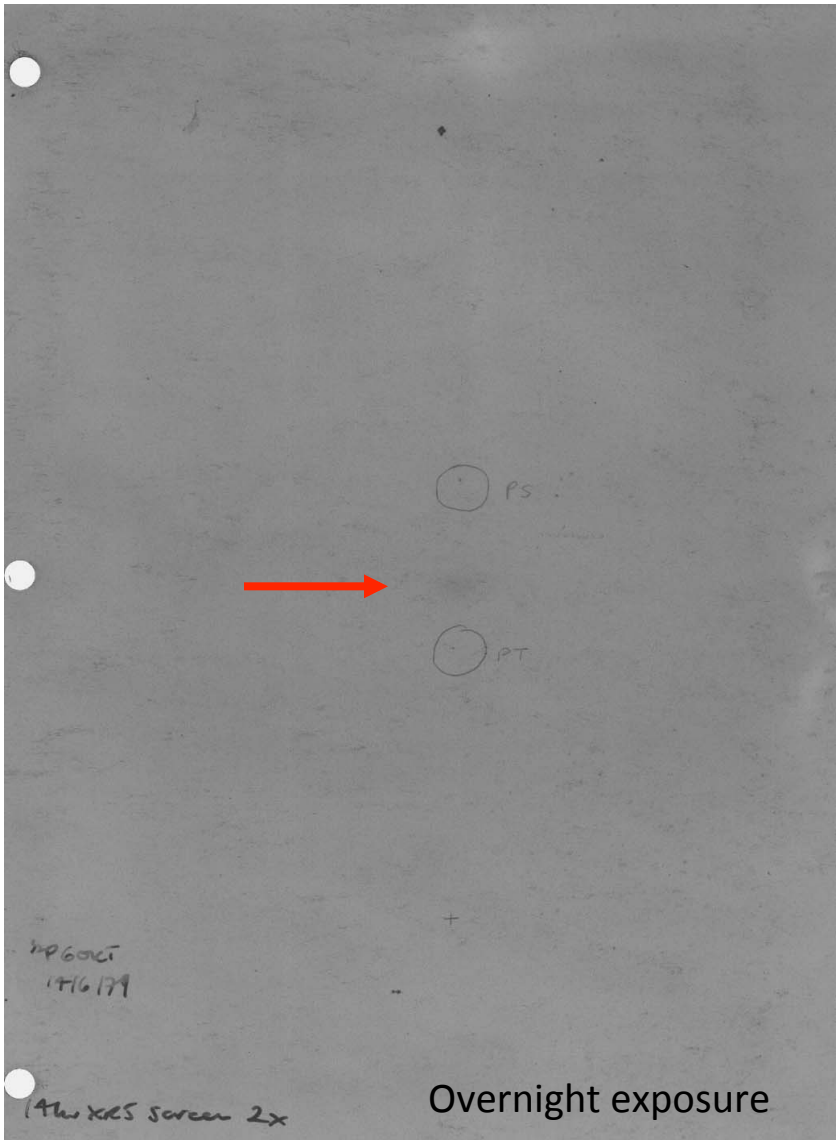


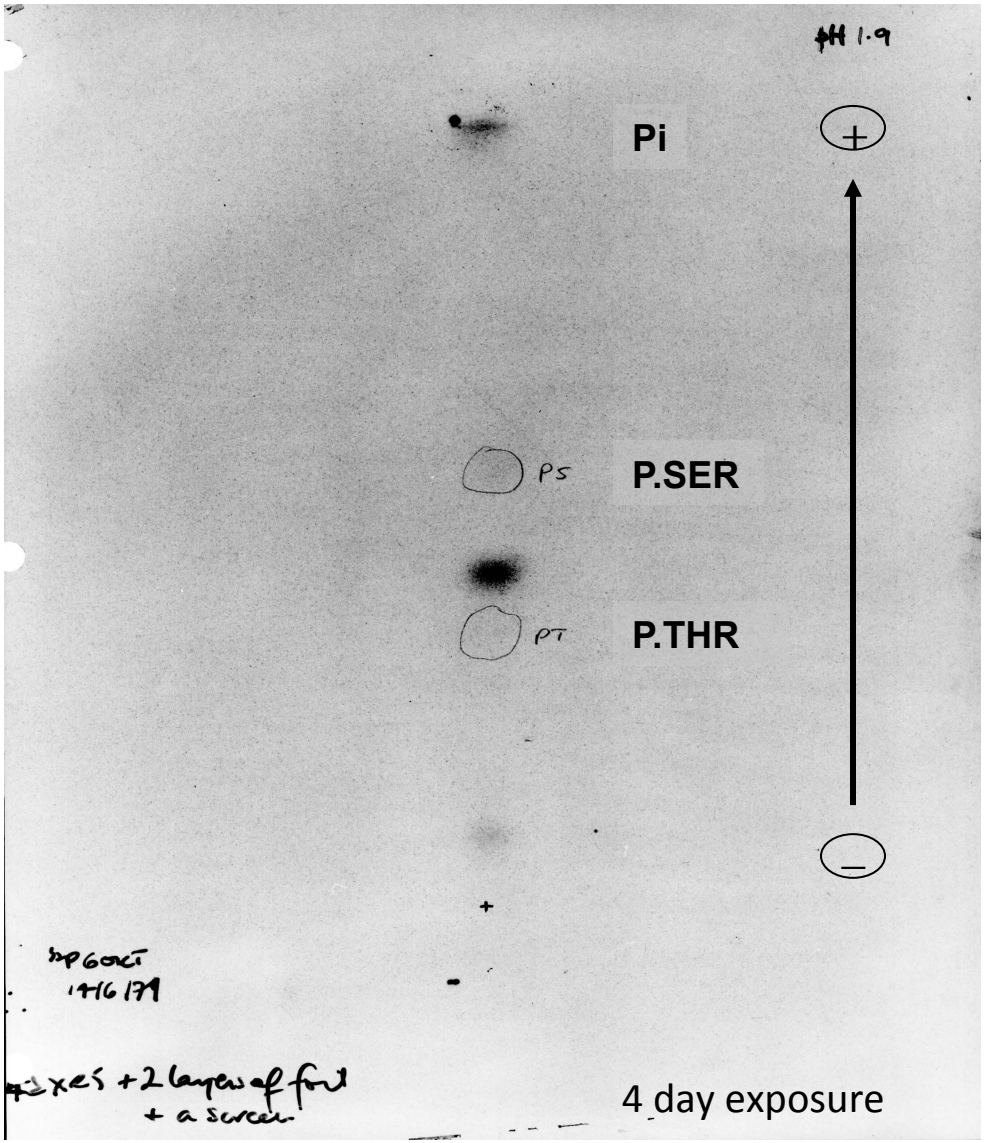
40 nm



~5 kbp circular genome – **only 6 genes**

The first sighting of phosphotyrosine - June 1979
(polyoma middle T kinase assay)





Thin layer electrophoresis at pH “1.9” on June 14, 1979

Current cancer therapies

- Chemotherapy - drugs that damage or block key elements and processes in cancer cells, e.g. doxorubicin; Taxol; AraC

- Radiation - X-rays or gamma rays

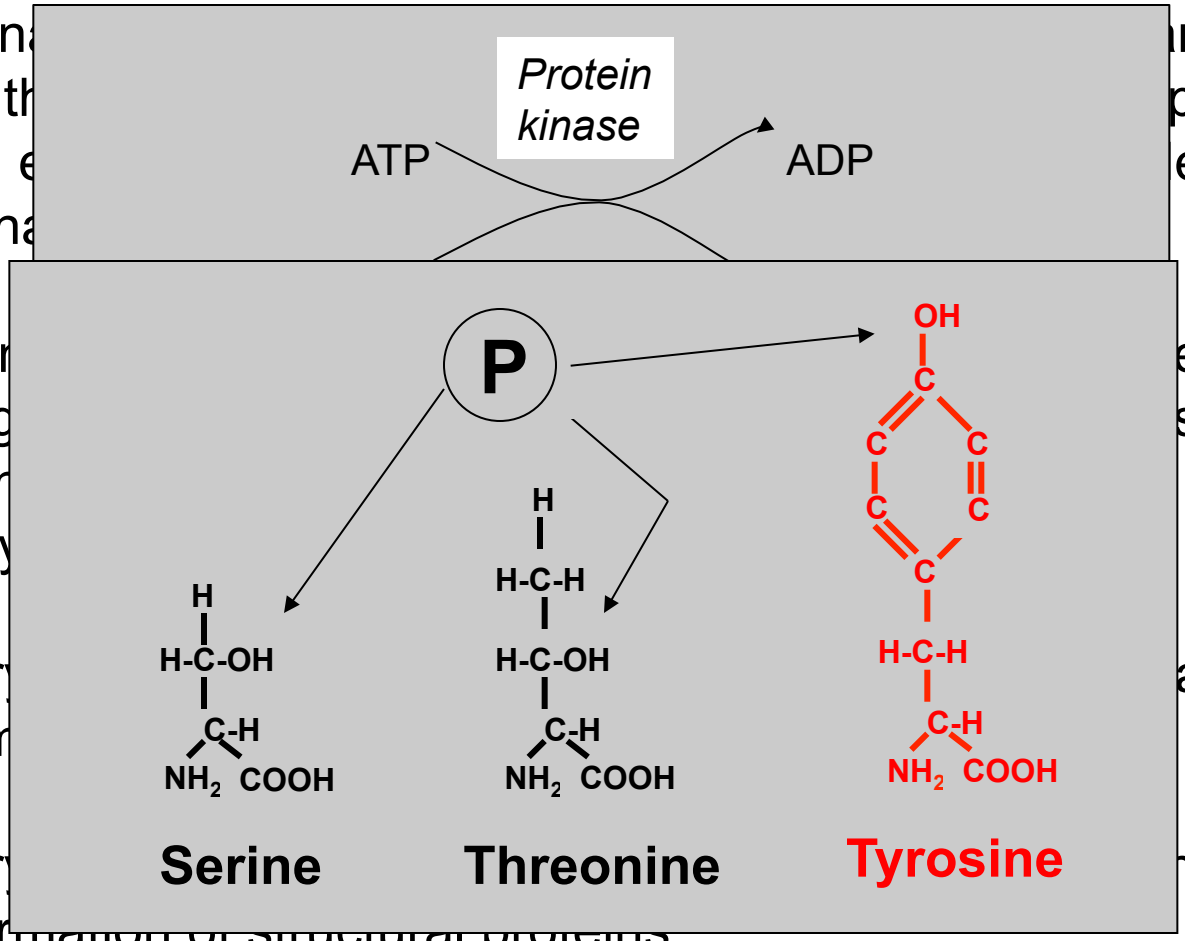
- Targeted therapies
  - *small molecules targeted against a single altered protein target in cancer cells*
  - protein drugs such as monoclonal antibodies targeted against proteins outside cancer cells

- Immune checkpoint therapy - monoclonal antibodies that boost the ability of the body's own immune system to attack tumor cells

- Cancer vaccines and CAR T-cells targeting tumor cells

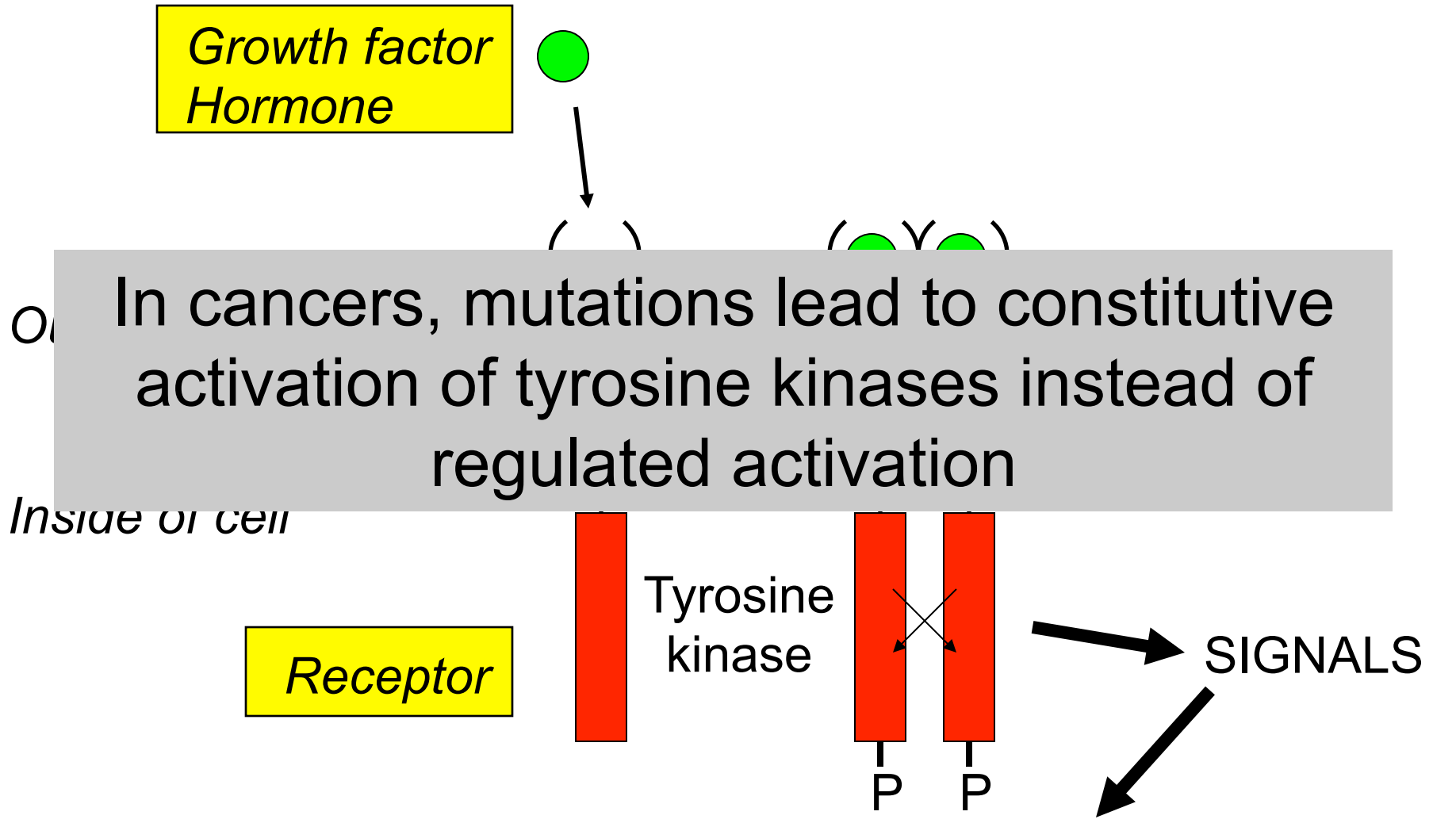
What is a protein kinase?

- Protein kin… …rds) are enzymes th… …phosphate donor (an e… …ependent protein kina…



- Protein ki… …e to the hydroxyl g… …sine (Y) in proteins ir… phosphory…
- Phosphor… …atases are the enzym…
- Phosphor… …nzymes, and the confor… …
- Phosphate attached to proteins can also act as a binding site for other proteins and this principle is used in signaling pathways leading to the nucleus inside the cell

Tyrosine kinases transmit signals across the cell membrane to drive proliferation



Types of cancer drugs that target tyrosine kinases

- Orally available "small molecule" inhibitors of tyrosine kinases activated in cancer (TKIs) (e.g. Gleevec™, Iressa™, Tarceva™)

- Monoclonal antibodies (protein drugs) that antagonize surface (receptor) tyrosine kinases activated in cancer (e.g. Herceptin™, Erbitux™)

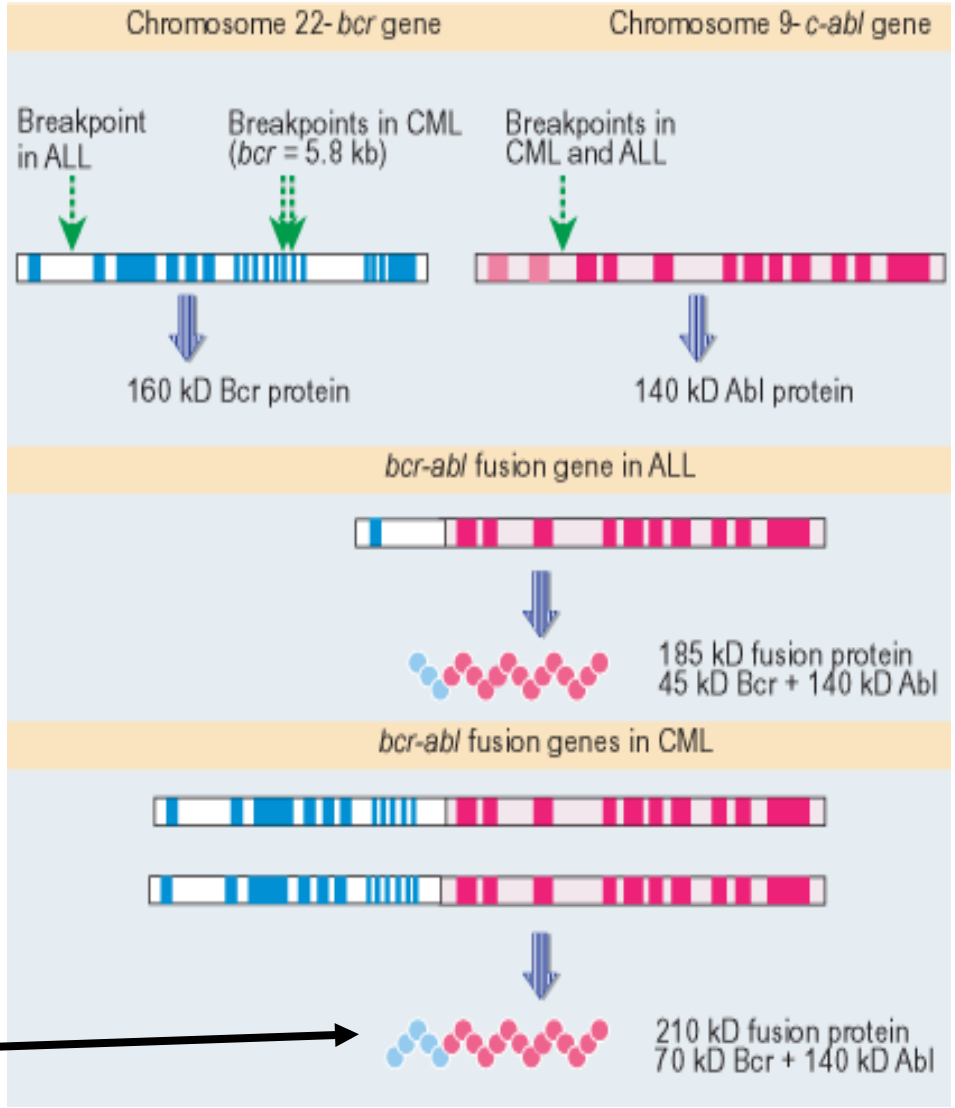
- Neutralizing monoclonal antibodies against growth factors that activate receptor tyrosine kinases needed for tumor growth (e.g. Avastin™)

- siRNA, antisense oligonucleotides and designer DNA-binding proteins (e.g. zinc finger combinations)

CML is caused by BCR-ABL - an oncogenic tyrosine kinase

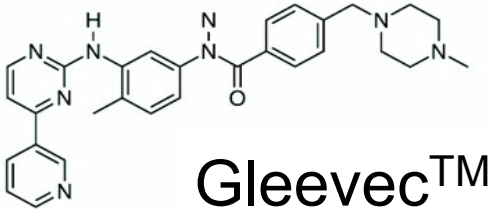
The Philadelphia chromosome fusion found in >95% CML creates a new gene with N-terminal sequences from BCR and C-terminal sequences from the c-ABL tyrosine kinase

Both parts of the fusion protein contribute to oncogenicity, which results from activation of the Ras/ERK MAPK pathway and other pathways

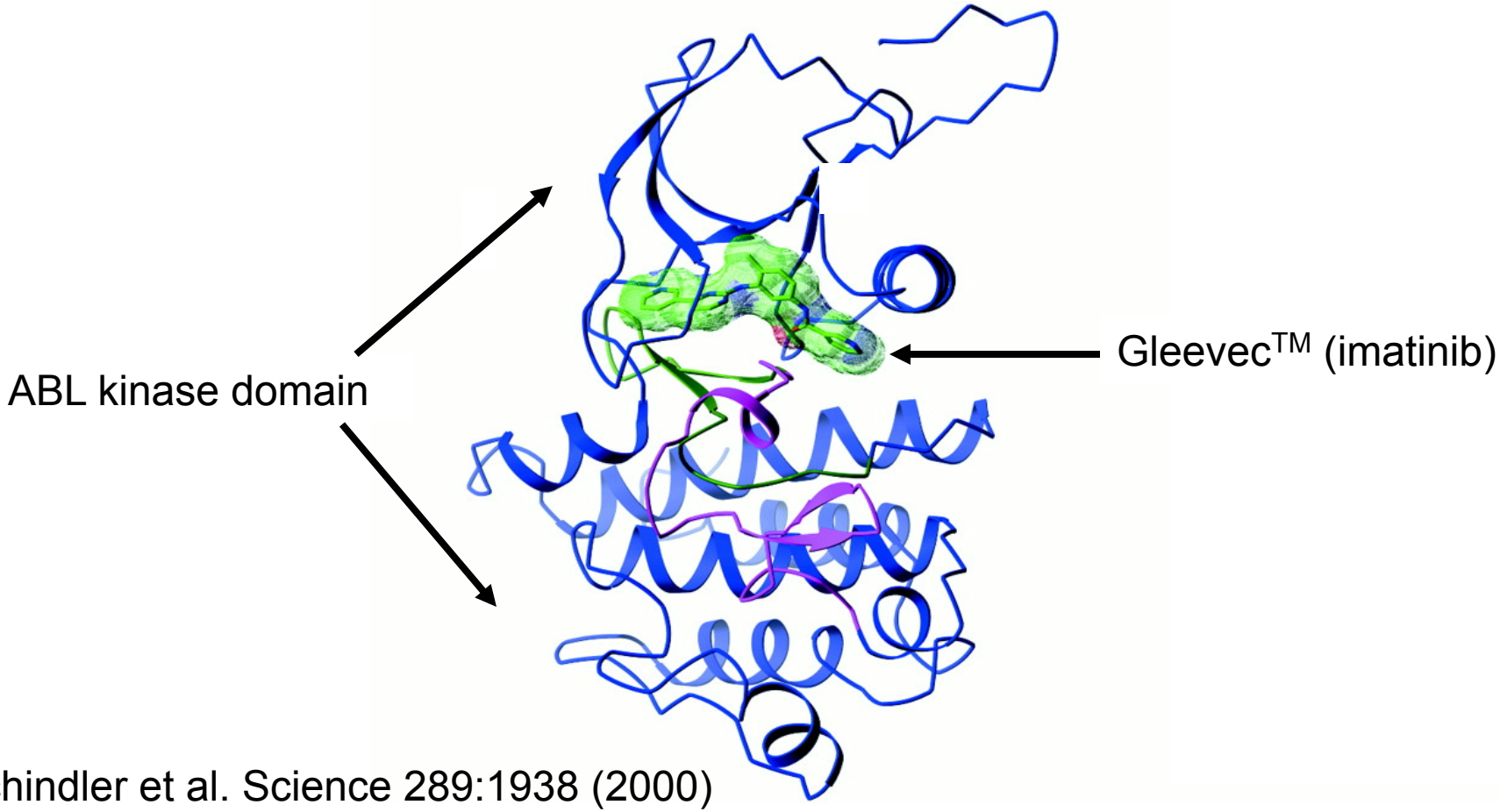


BCR-ABL fusion protein made in the leukemic cells is an activated tyrosine kinase

Structure of ABL tyrosine kinase bound to Gleevec



Gleevec™ (imatinib) - inhibitor of ABL kinase activity



Schindler et al. Science 289:1938 (2000)

Lessons from treating chronic myelogenous leukemia (CML) with imatinib (Gleevec)

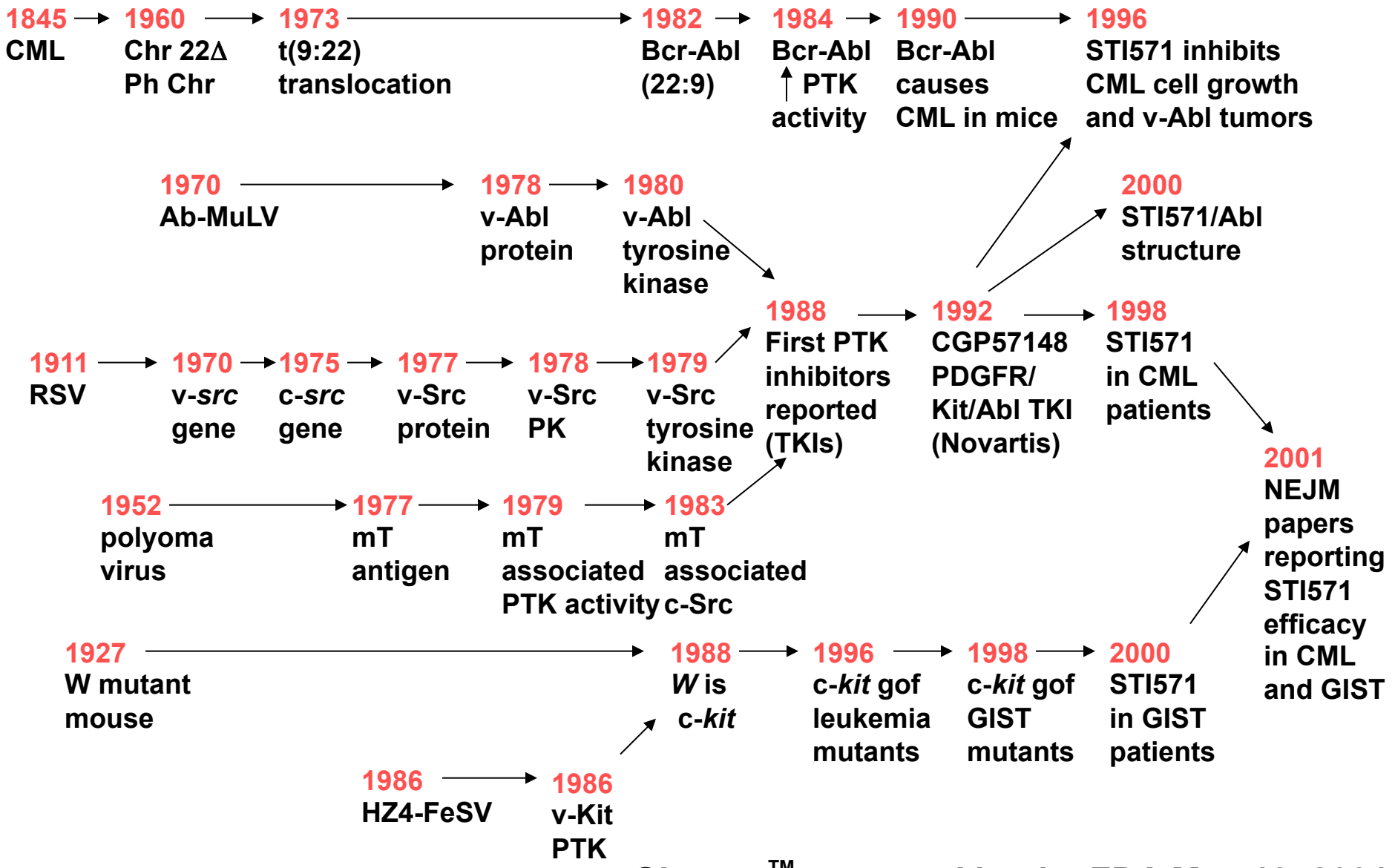
Response to imatinib in chronic phase versus blast crisis CML

	Chronic phase	*Blast crisis*
Ten year survival	70%	30%
Imatinib resistance in <2 years	12%	62%

- Poster child for early detection
- Imatinib resistance is almost always due to mutations in the target kinase BCR-ABL
- Second generation drugs that work on the imatinib-resistant mutant BCR-ABL have been developed and approved, e.g. dasatinib and nilotinib

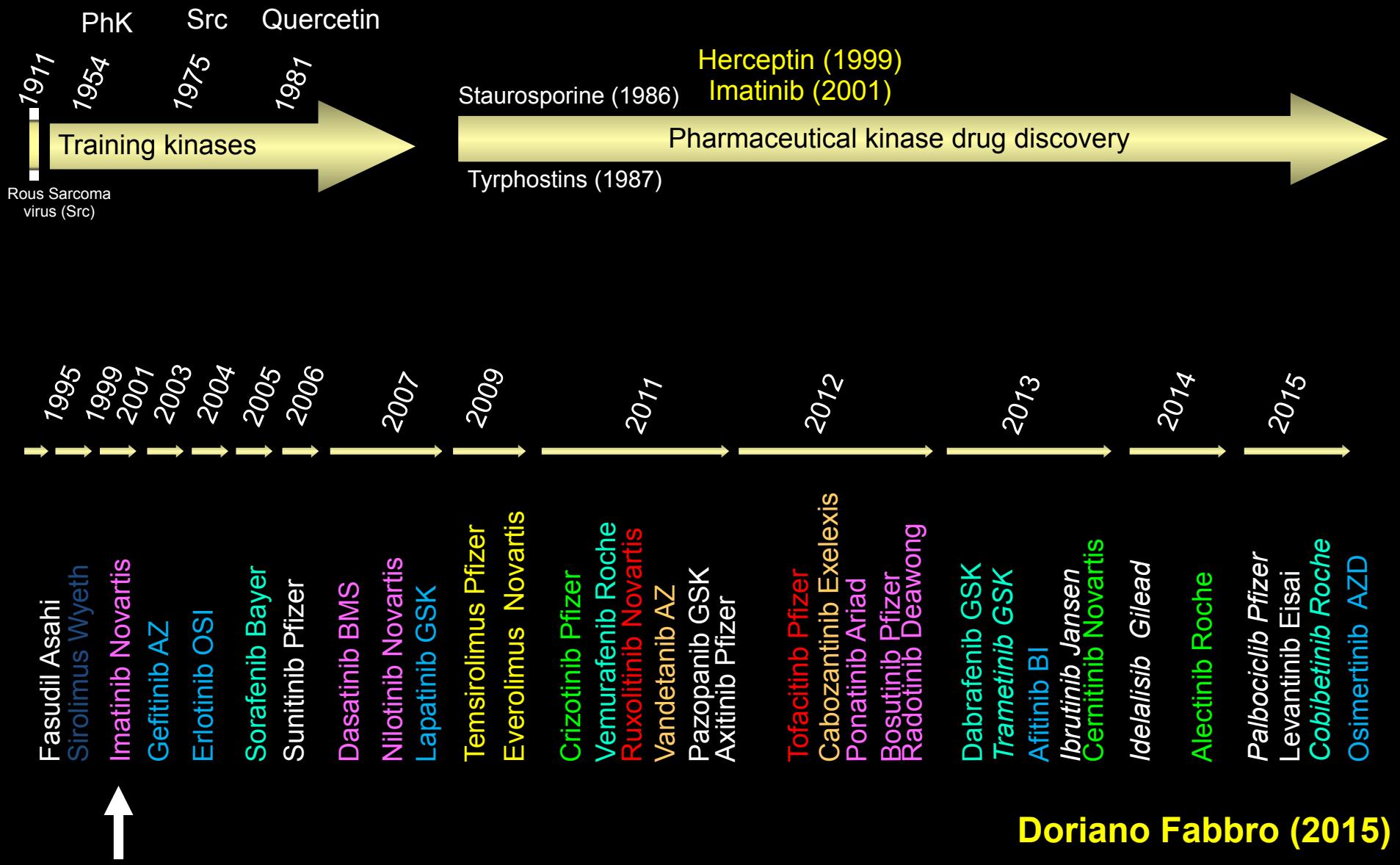

MAY 28, 2001
www.time.com AOL Keyword: TIME
TIME
THERE IS NEW AMMUNITION IN THE WAR AGAINST CANCER.
THESE ARE THE BULLETS.
Revolutionary new pills like GLEEVEC combat cancer by targeting only the diseased cells. Is this the breakthrough we've been waiting for?
May 28, 2001

The long road to the GLEEVEC™ cancer drug



Gleevec™ approved by the FDA May 10, 2001

30 years of kinase drug discovery→36 approved KIs

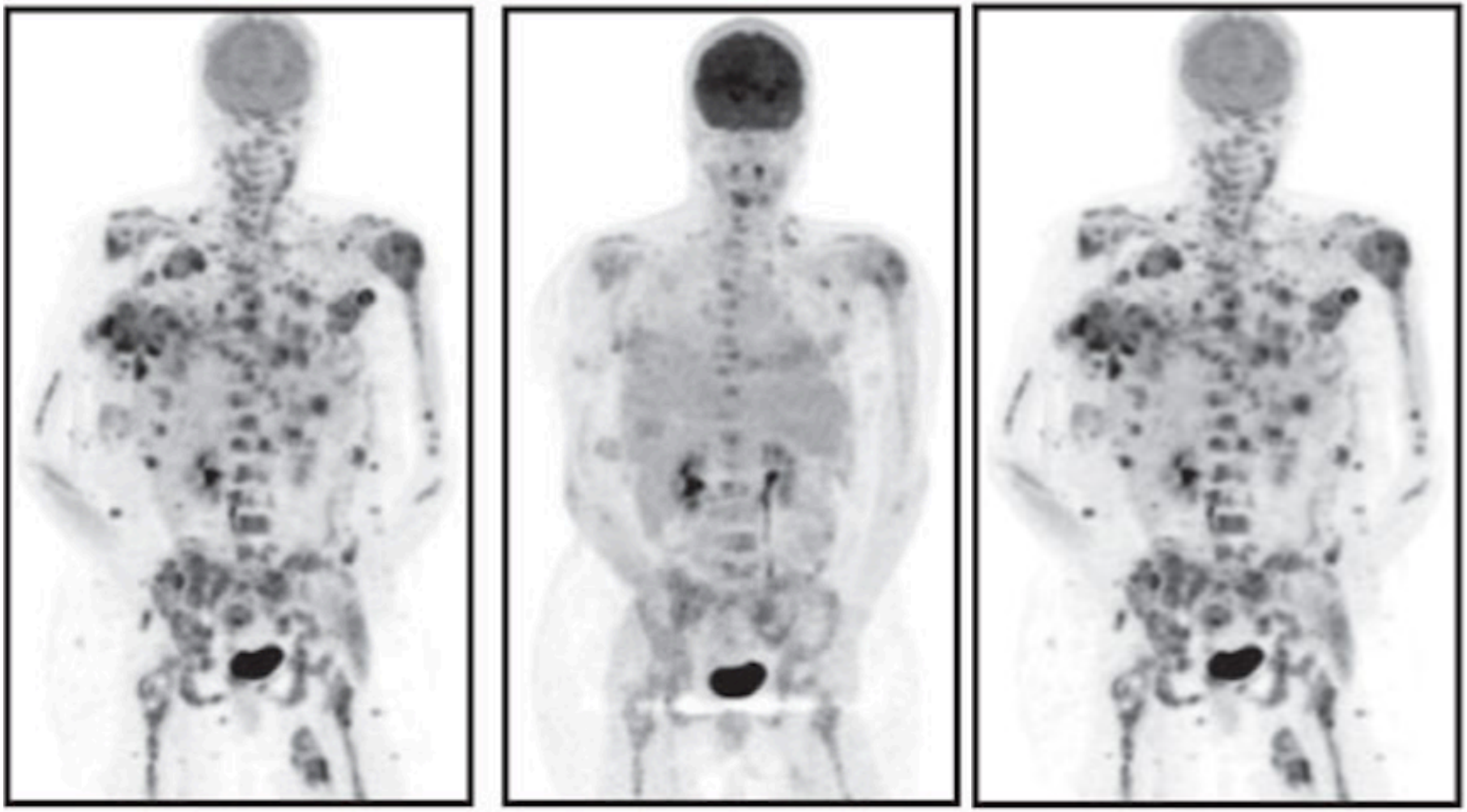


Doriano Fabbro (2015)

Success stories with molecularly targeted cancer treatment

- Breast cancer - Herceptin™ monoclonal antibody for HER2-plus patients and tamoxifen estrogen (HER2 is a tyrosine kinase)
- Follicular B cell lymphoma - Rituxan™ - anti-CD20 monoclonal antibody
- Acute promyelocytic leukemia – all-trans retinoic acid + arsenic trioxide
- Chronic myelogenous leukemia - Gleevec™, Nilotinib™, Dasatinib™
- Lung cancer - Tarceva™ for patients with mutant EGF receptor
- Myeloma - Velcade™ - proteasome inhibitor
- Hairy cell leukemia - Leustatin™ (cladribine/2-CdA)
- Melanoma - vemurafenib/Zelboraf™ for patients whose tumors have a V600E B-RAF kinase mutation
- Melanoma - ipilimumab/Yervoy™ and pembrolizumab/Keytruda™ checkpoint immunotherapy

Success stories with molecularly targeted cancer treatment - Zelboraf and melanoma

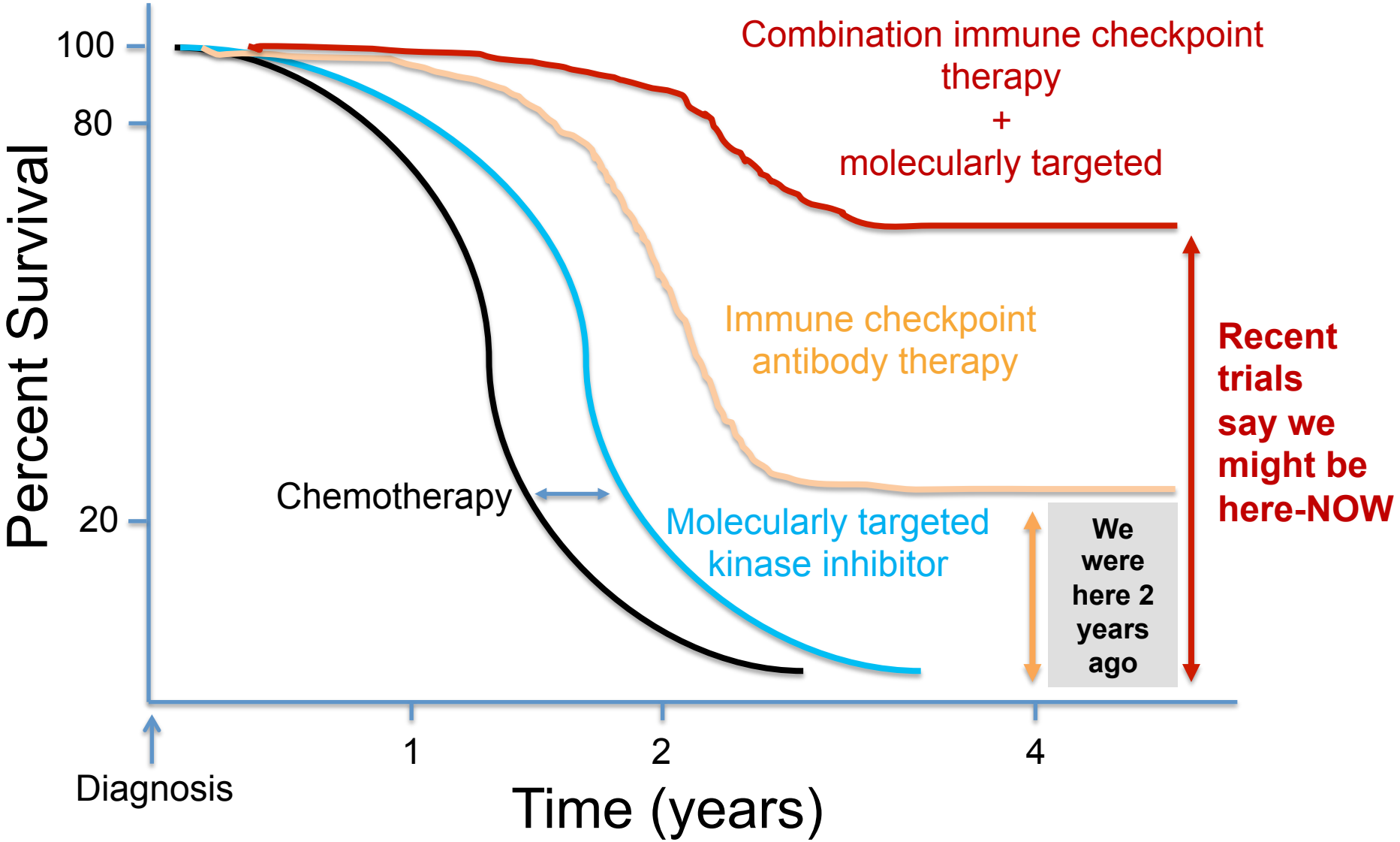


Pretreatment

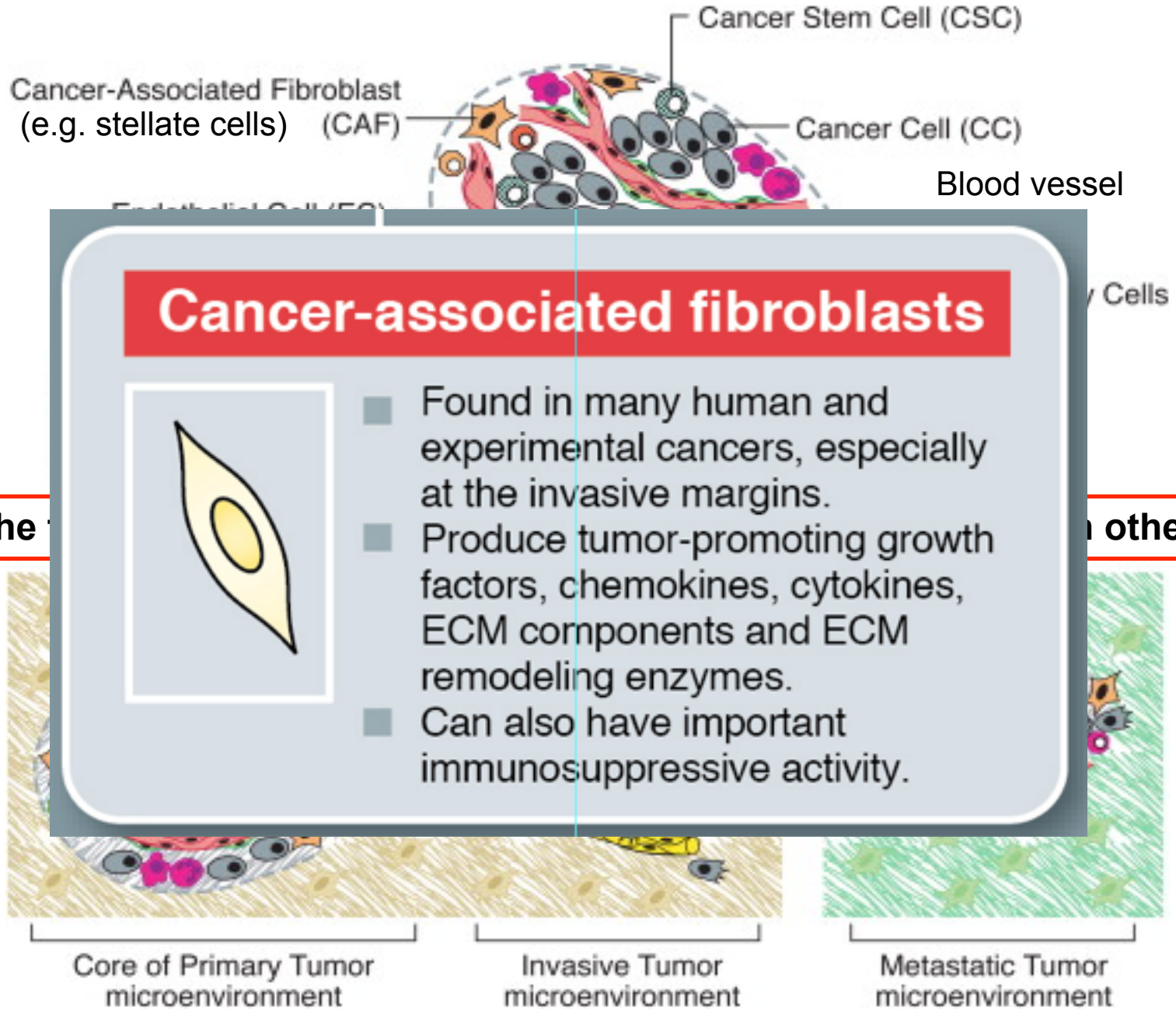
1 month

6 months

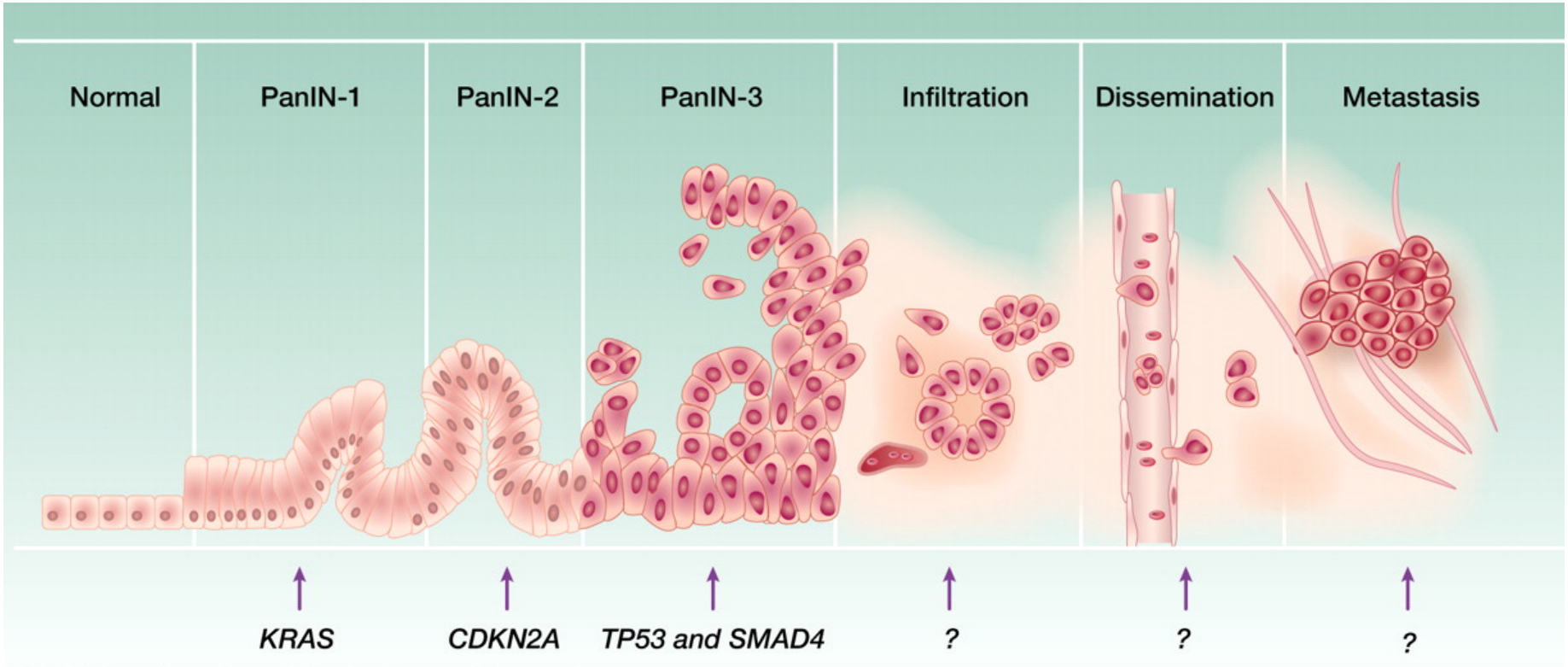
Melanoma: dramatic improvements in cancer treatment enabled by knowledge gained from fundamental (i.e. basic) research



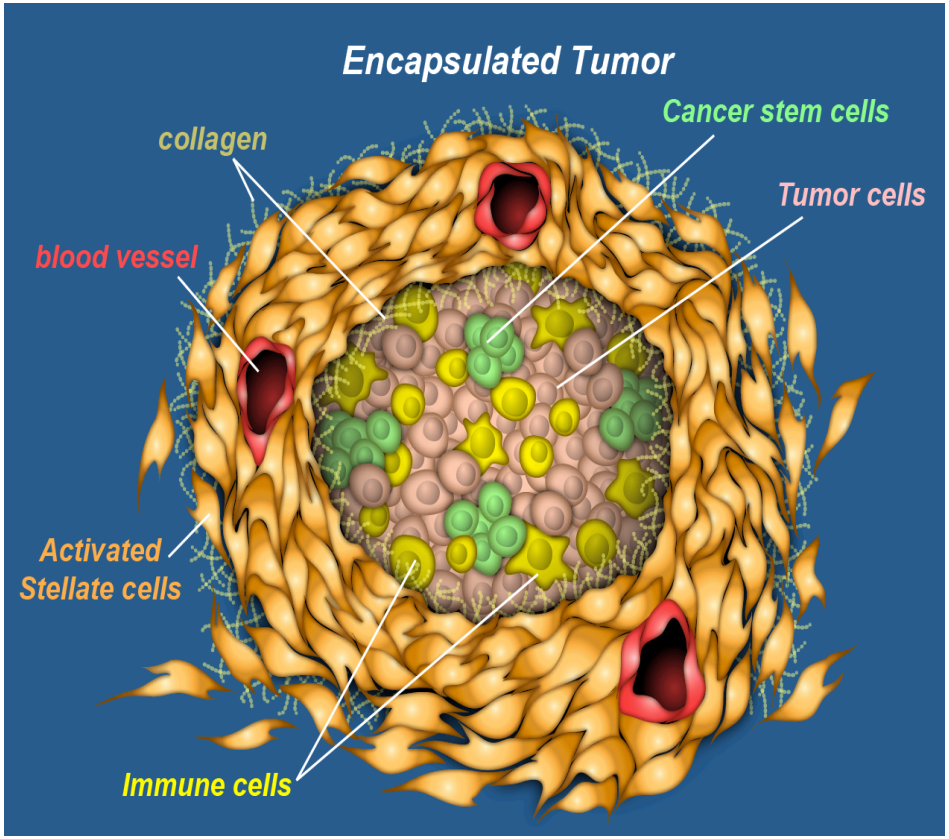
The tumor microenvironment



Pancreatic adenocarcinoma progression



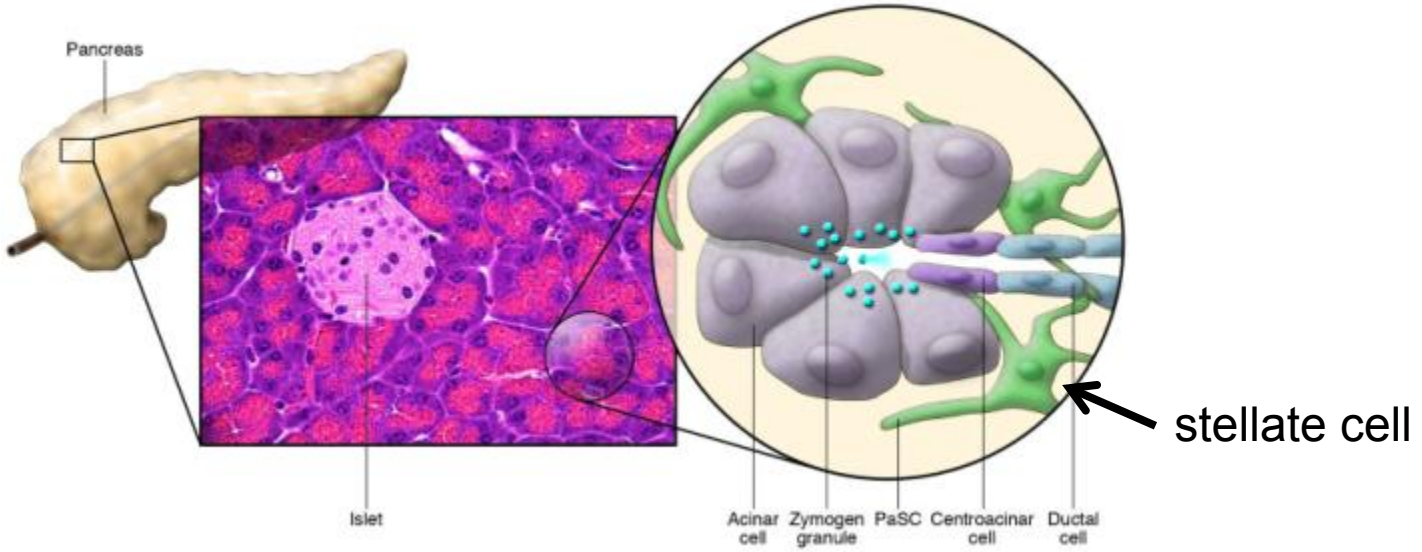
Pancreatic cancer cells are hard to reach



The stroma in pancreatic cancer not only presents a mechanical barrier and restricts blood supply, causing it to be largely impenetrable by drugs, but also constitutes a favorable microenvironment critical for tumorigenesis

Pancreatic stellate cells

- Star-shaped pancreatic stellate cells were isolated and first characterized in the 1990s
- In the healthy organ, stellate cells are about 4% of all pancreatic cells
- In response to tissue injury and tumor-induced inflammation, stellate cells transform from a quiescent state into an activated myofibroblast-like phenotype, which secretes excessive amounts of extracellular matrix (ECM) proteins and a variety of cytokines
- Stellate cells have become a focus of attention for their potential roles in the pathogenesis of pancreatitis and pancreatic cancer



Pancreatic stellate cells

SU2C Pancreatic Cancer Dream Team – Ron Evans, Geoff Wahl, Tony Hunter

- Is it possible to treat pancreatic cancer by targeting the activated stellate cells or the products they make that act on the tumor cells?
- What strategies could one use to switch the activated stellate cells back into a normal quiescent cell?

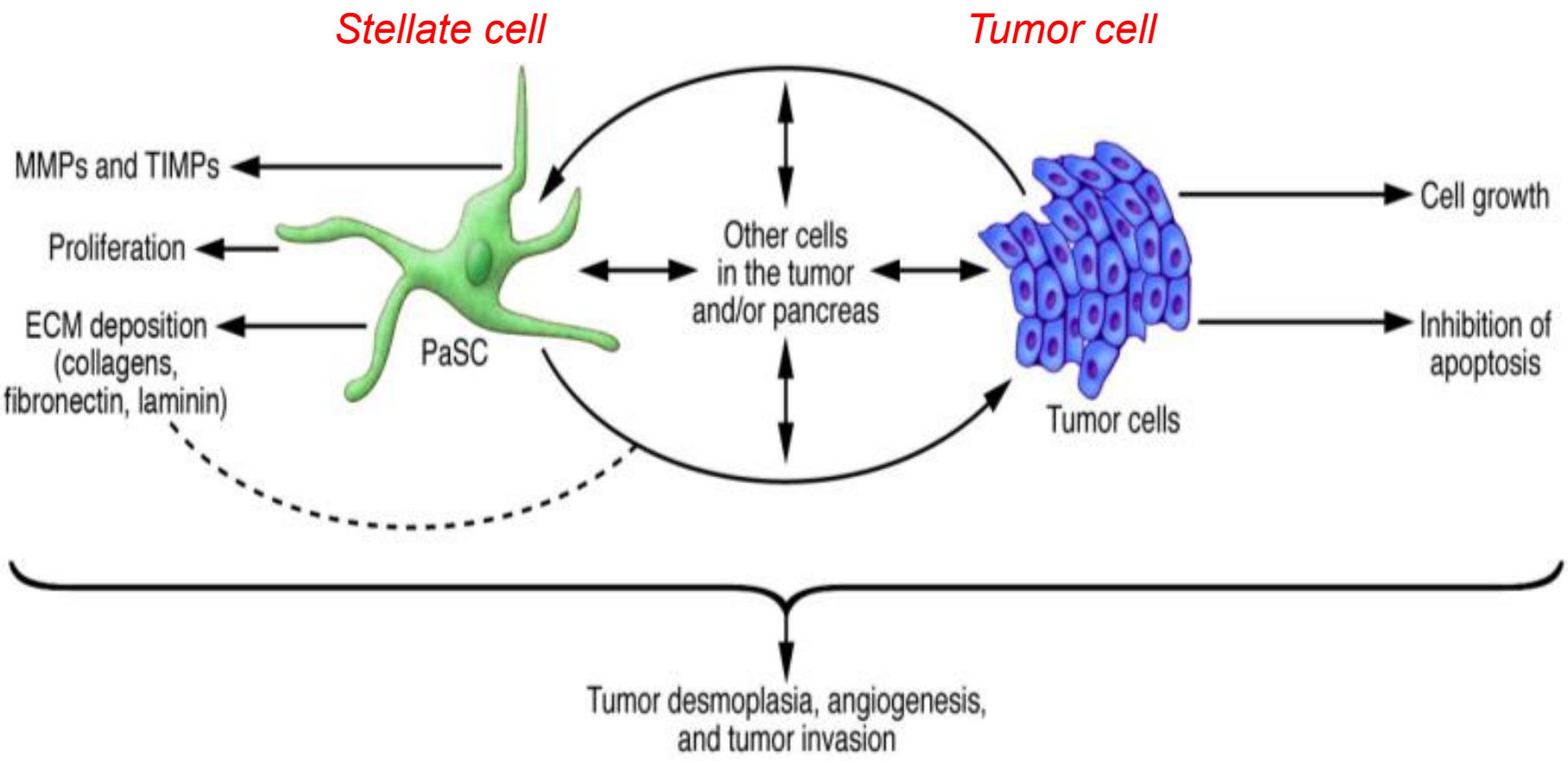
1. Find a drug that switches off the activated stellate cell (vitamin D analogue)

2. Reprogram the stellate gene expression program so that it reverts to a quiescent state (p53 expression)

3. Antagonize the proteins that are made by stellate cells that communicate with the tumor cells

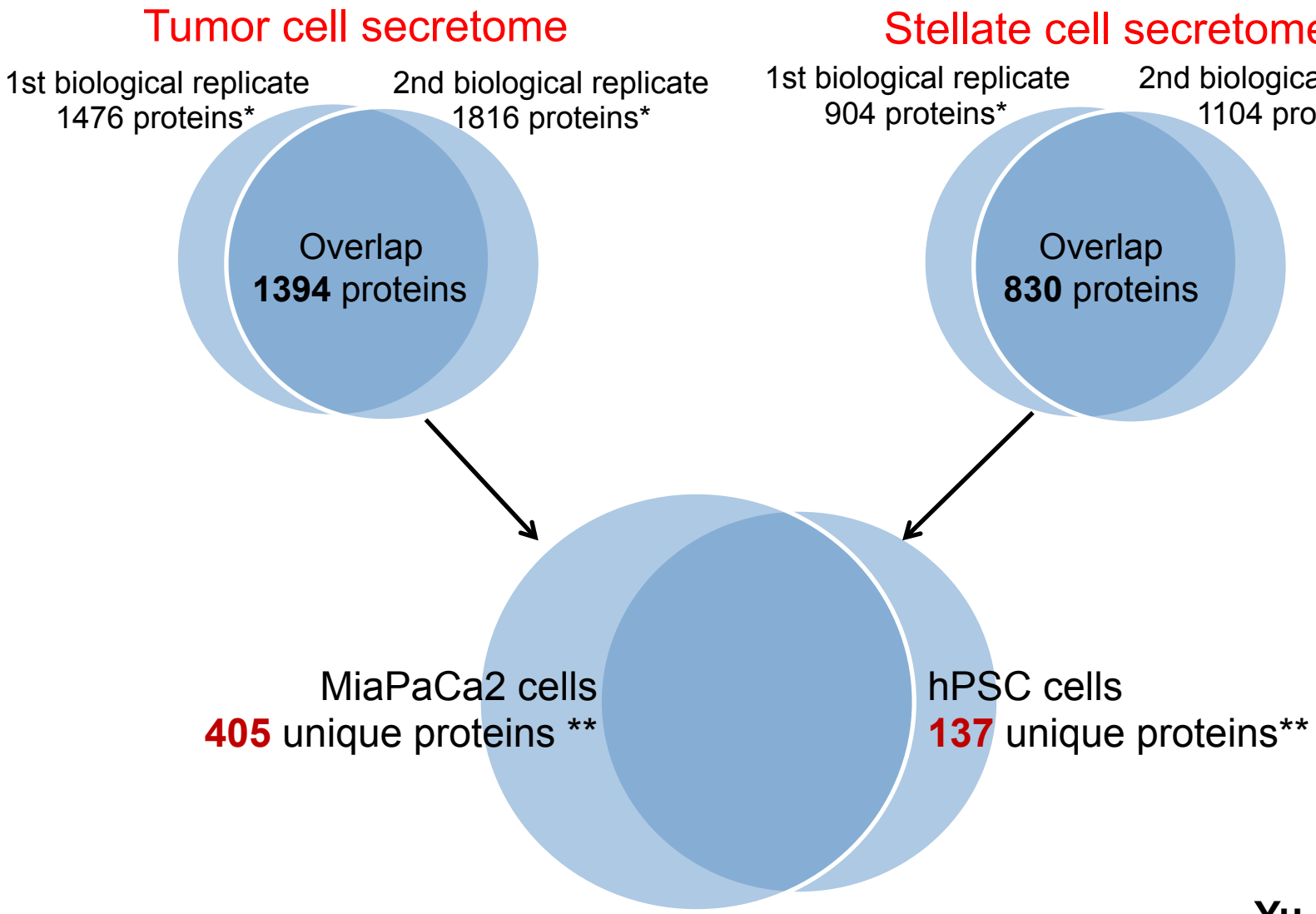
STAND UP TO CANCER

Role of stellate cells in pancreatic carcinogenesis



What factors do stellate cells secrete that can act on pancreatic cancer cells (and vice versa)?

Profiling the secretome of stellate and cancer cells



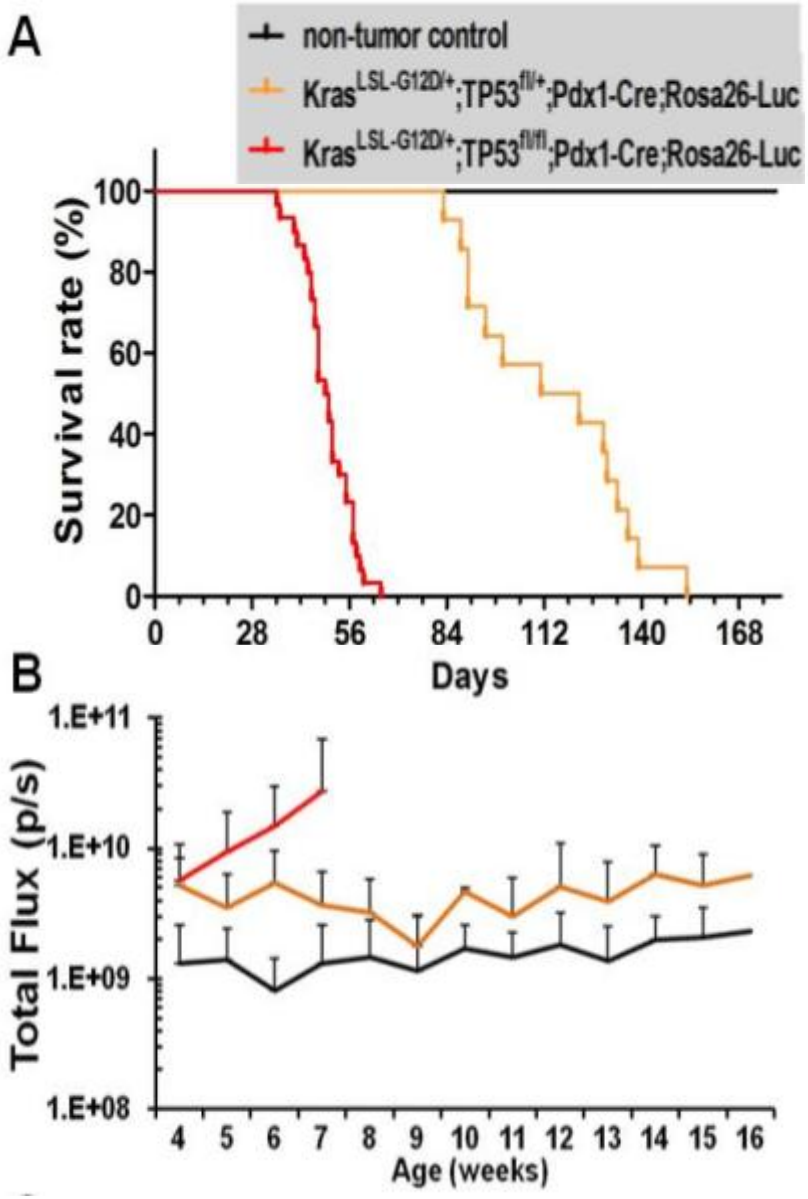
Yu Shi
Ruijun Tian

Proteins secreted uniquely from stellate and tumor cells

	Stellate cells	Tumor cells	Both cells
Growth factors / cytokines / chemokines	CTGF, CCL2, CXCL12, HGF, GDF15, IL-6, IL-11, LIF, Wnt5a, ANGPTL2	AREG, BMP1, CXCL5, CXCL16, M-CSF, G-CSF, PDGFc, b/a(low), PEDF, VEGFa, VGF	CXCL1, CXCL2/3(Low), HDGF, IL-8, TGFβ1, VEGFc,
	Collagen Ia1, IV, XII, XV, COMP, EFEMP1/2	SRRM2	Collagen Ia2, III, IV, V, VI, ECM1, LTBP3
Proteases and inhibitors	MMP1/2/3, ADAMTS1, CST1, MASP1, PAMR1, PLAT, RECK, SERPINs, TFPI2	ADAM10, MBTPS1	ADAMTS5, CTSD, CTSD, CSTB, CST3, CPE, PLAU, SERPINE1, TIMP1/2
Receptors / membrane proteins	CDH2, CDH6, CD248/ Endosialin, CD90, RARRES1	EGFR, Erb2, EphA2, EphA4, DNER, HGFR, IL-27Ra, TGFBR3, TNFR1a	CD44, CD59, NRP1, TNFRSF12A

We decided to test whether LIF or leukemia inhibitory factor, a growth factor specifically made by stellate cells, is important for pancreatic cancer progression

Evaluating the therapeutic efficacy of blocking LIF signaling with an antibody using *KP*C-Luc mice



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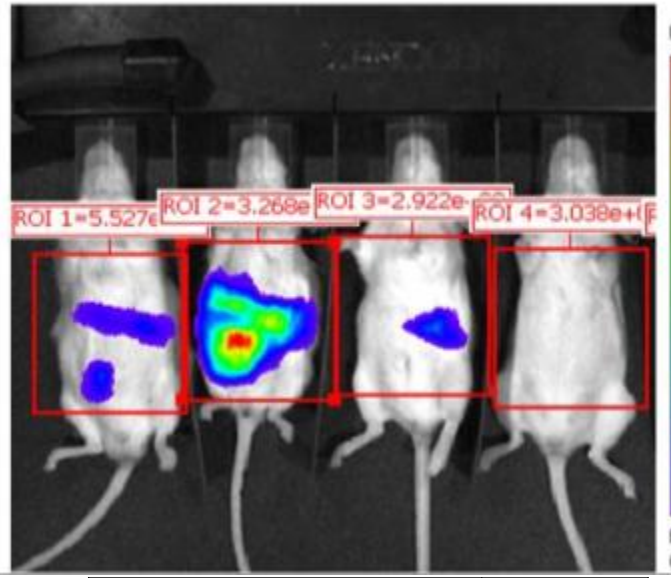
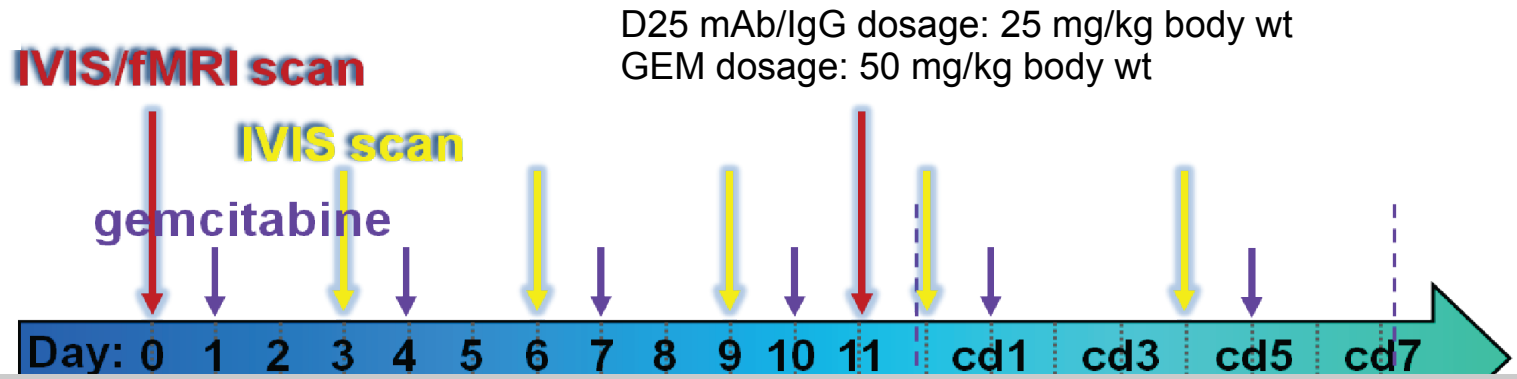
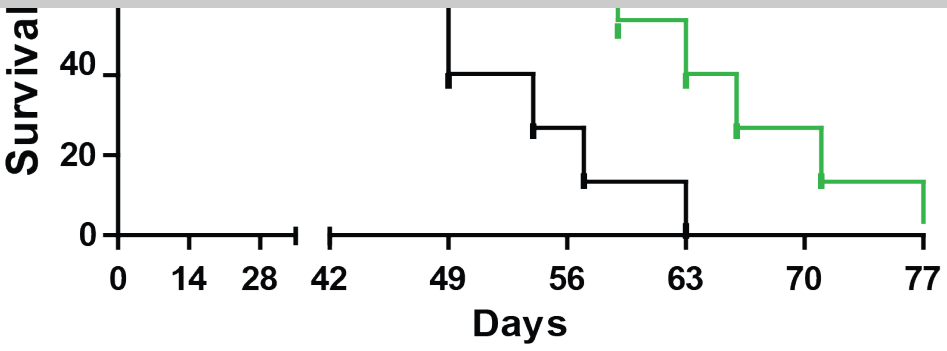


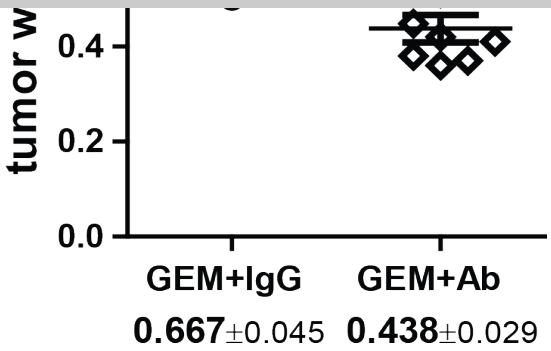
Kras;P/P;Pdx1-Cre;Luc	5.5E+09
Kras;P/P;Pdx1-Cre;Luc	3.3E+10
P/P;Pdx1-Cre;Luc	2.9E+09
Kras;P/P;Luc	3.0E+07

Anti-LIF antibody treatment of KPC mice



Based on these encouraging results we are now testing whether human pancreatic tumors express high levels of LIF, and exploring the possiblity of using a neutralizing anti-LIF mAb in clinical trials in combination with chemotherapy





10 day (19.5%) increase in survival; 34.4% decrease in tumor weight

Looking forward: precision medicine and new therapies for cancer

- Customize treatment based on genetic/RNA fingerprint of the

Advancing these strategies is a goal of Biden's "moonshot" to cure cancer

- Identify and target new vulnerabilities, e.g. metabolic dependencies and DNA repair defects
- Targeting strategies to deliver drugs selectively to tumors, e.g. drug delivery with nanoparticles

Turn cancer into a chronic disease!

- Using oncolytic viruses to selectively kill tumor cells
- Analyze circulating tumor cells - early detection
- Stem cell and epigenetic therapies; anti-metastasis therapy

Acknowledgements

Targeting stellate cells in pancreatic cancer

Yu Shi

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Tony Pawson

Ron Evans

Geoff Wahl

Stand up to Cancer
Lustgarten Foundation