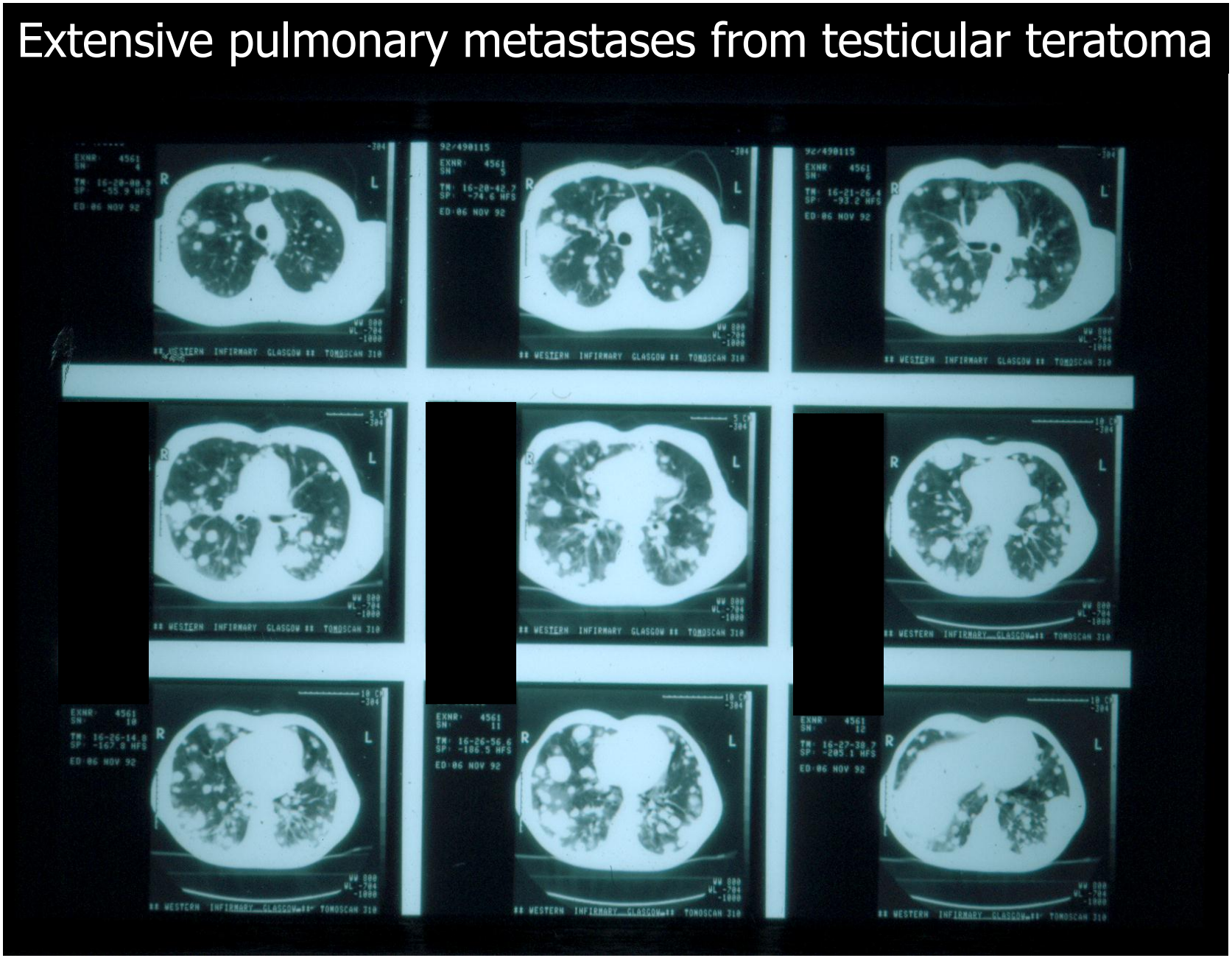
New Therapeutic Targets in Cancer

Duncan Jodrell,
Professor of Cancer Therapeutics,
http://www.oncology.cam.ac.uk/research/groupleaders/jodrell.html

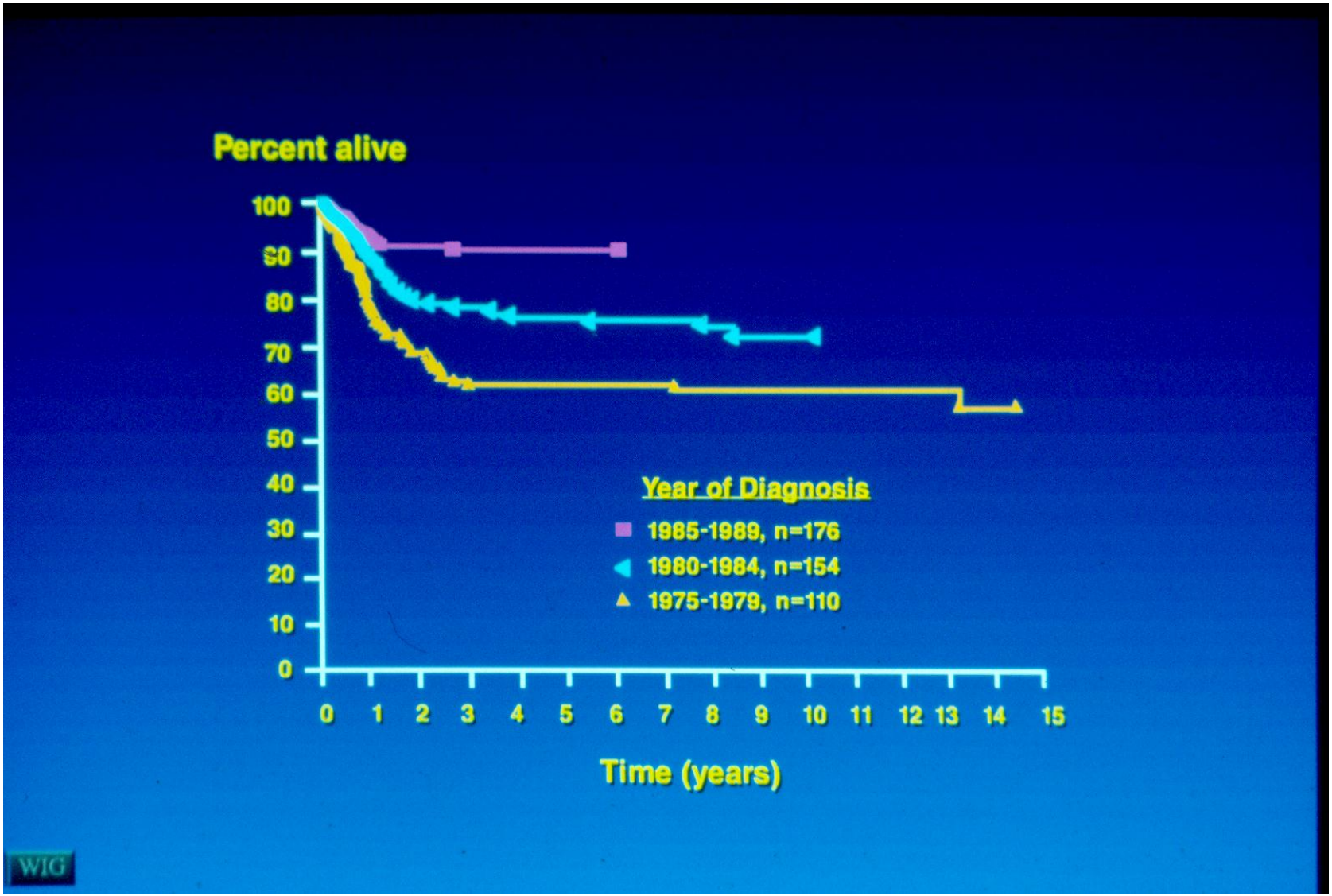
Do "drugs" alone have a curative role in the treatment of patients with cancer?

- Metastatic disease:
  - lymphoma
  - Hodgkin's disease
  - Wilm's, rhabdomyosarcoma
  - testicular tumours - seminoma, teratoma

Extensive pulmonary metastases from testicular teratoma



Drug related improvements in outcome over time
(with apologies for an old slide!)



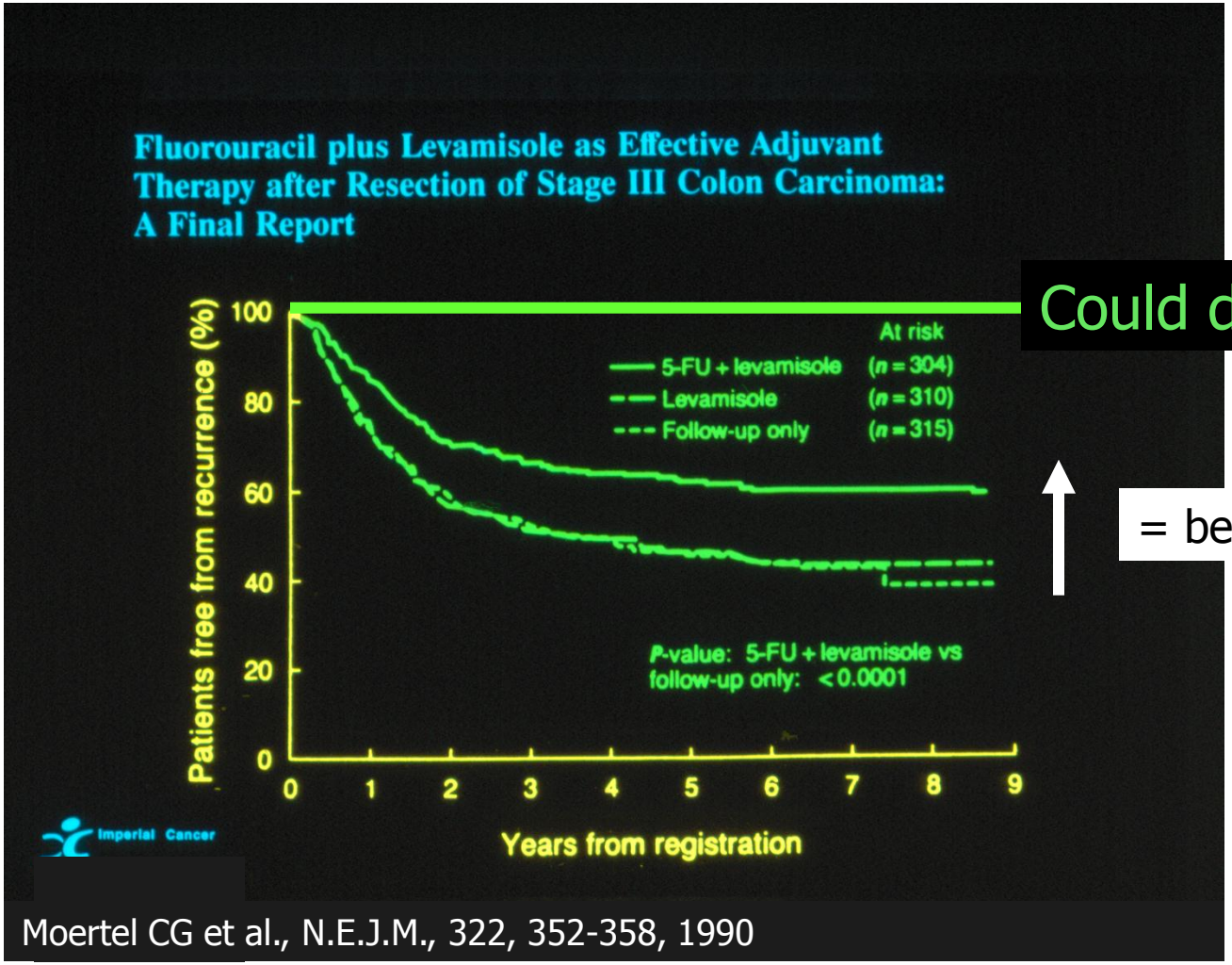
Do "drugs" alone have a curative role in the treatment of patients with cancer?

- Metastatic disease:
  - lymphoma
  - Hodgkin's disease
  - Wilm's, rhabdomyosarcoma
  - testicular tumours - seminoma, teratoma

} Yes .....
..... but these are rare cancers

+ an established role as palliative therapy

Chemotherapy administered after surgery leads to a survival advantage in patients with bowel cancer

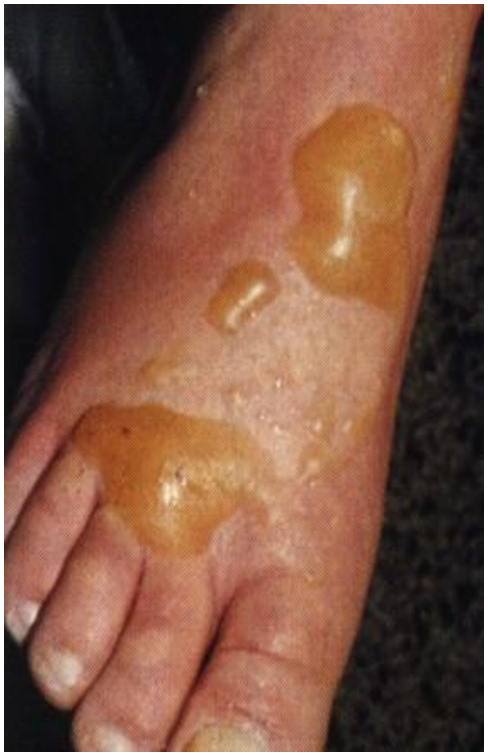


Could do better!!

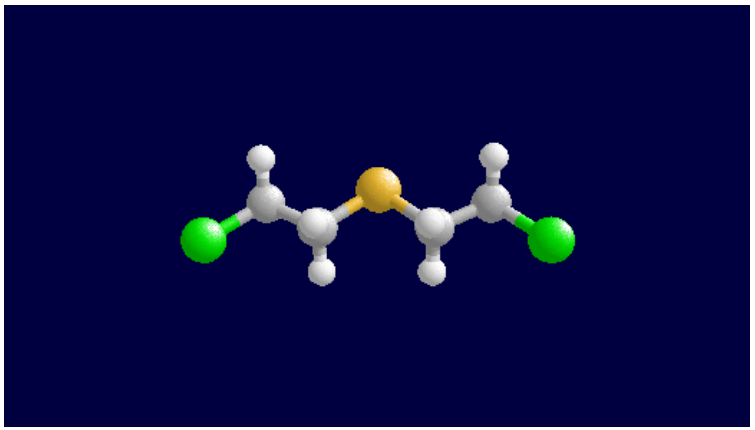
= better survival

Moertel CG et al., N.E.J.M., 322, 352-358, 1990

The first cancer chemotherapies came from a serendipitous observation

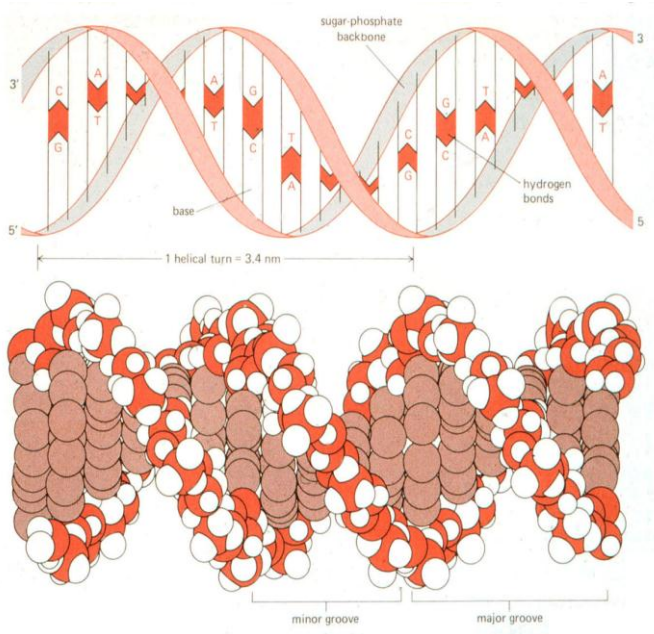


Mustard Gas (Sulphur Mustard)



- Sulphur mustard – Potent vesicant agent that burns eyes, skin and respiratory tract
- Caused leucopenia, bone marrow aplasia and destruction of lymphoid tissue
- The precursor for curative therapies for leukaemia and lymphoid malignancies

DNA: The classical target



- "alkylators" (mustards)
- platinum derivatives (covalent binding)
- anti-metabolites
  - inhibit nucleotide synthesis
  - mis-incorporation into DNA
- DNA intercalators
- DNA topoisomerase inhibitors

Chemotherapy related toxicities:

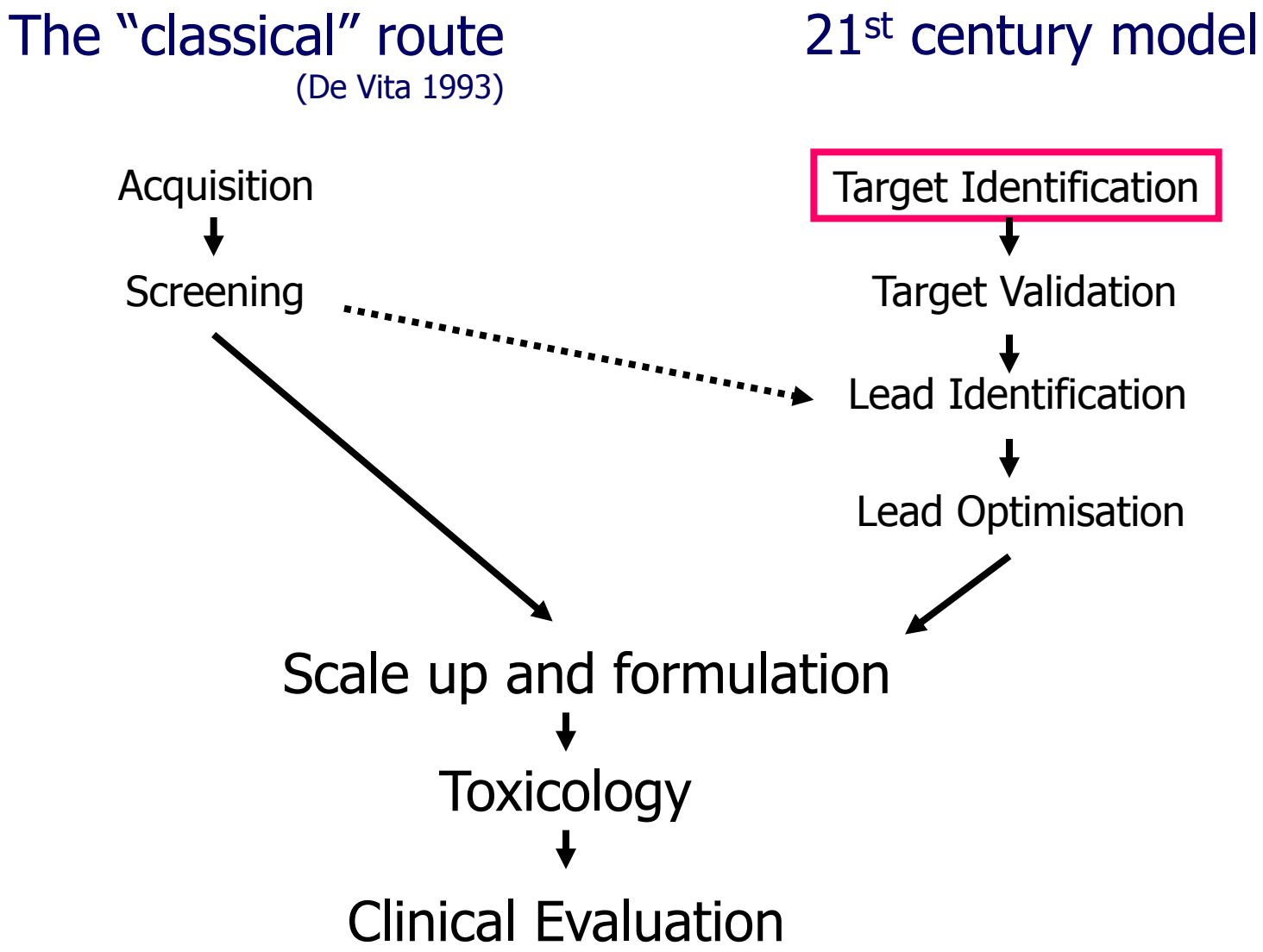
- Anti-proliferative effects:
  - alopecia … can vary from drug to drug
  - myelosuppression
    - red cells
    - white cells … lymphopenia, neutropenia
    - platelets … carboplatin
  - GI mucosal damage
    - Mucositis (pain and ulceration of mucous membranes)
    - Diarrhoea
    - N+V … (may also be due to central chemical effects)
  - fertility

- Conventional cytotoxic chemotherapy has modest (but, often useful) activity in common solid tumours

- Conventional cytotoxic chemotherapy causes damage to normal tissues

Conclusion: We need new, smarter drugs!

New Small Molecule Drug Development



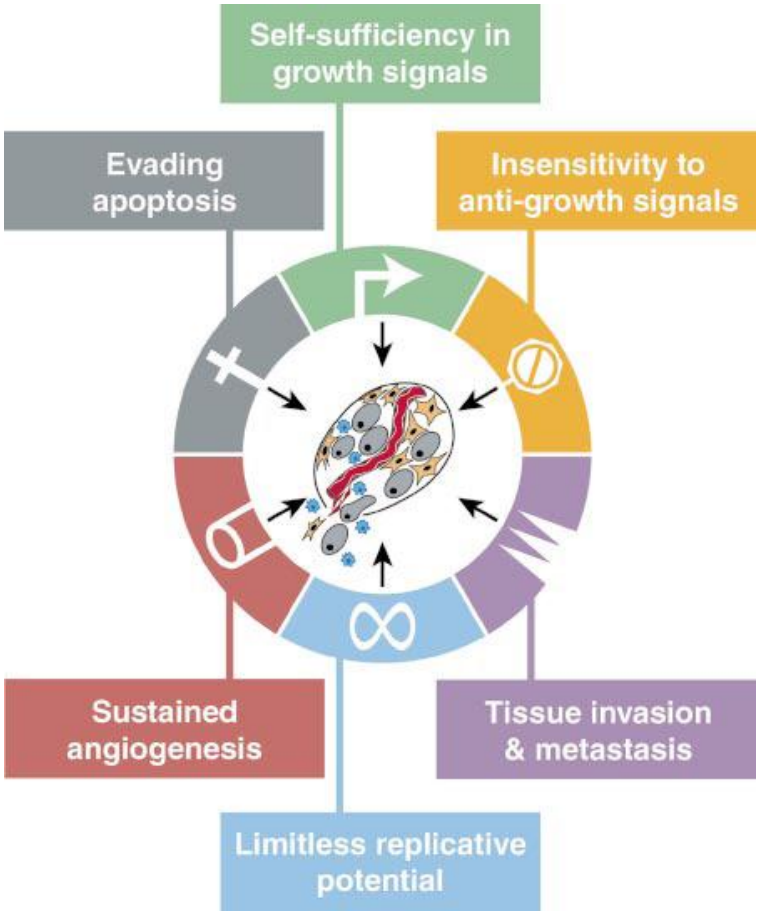
Strategies for new drug design

- Acquisition based
  - screening of novel chemical entities against cell lines
    - often natural products – taxanes, camptothecins
    - likely to be cytotoxic
  - analogues/pro-drugs of existing agents

- Target based
  - the way forward? .... but maybe not as new as people think!
    - analogues of naturally occurring substrates for DNA synthesis
      - e.g. anti-metabolites from the 1950s
    - endocrine therapies (e.g. tamoxifen, initially synthesised in 1962)
  - design a target specific, in vitro assay
  - perform High Through-put Screening (HTS) using compound libraries or fragments to identify chemical leads

Examples of target areas for drug development

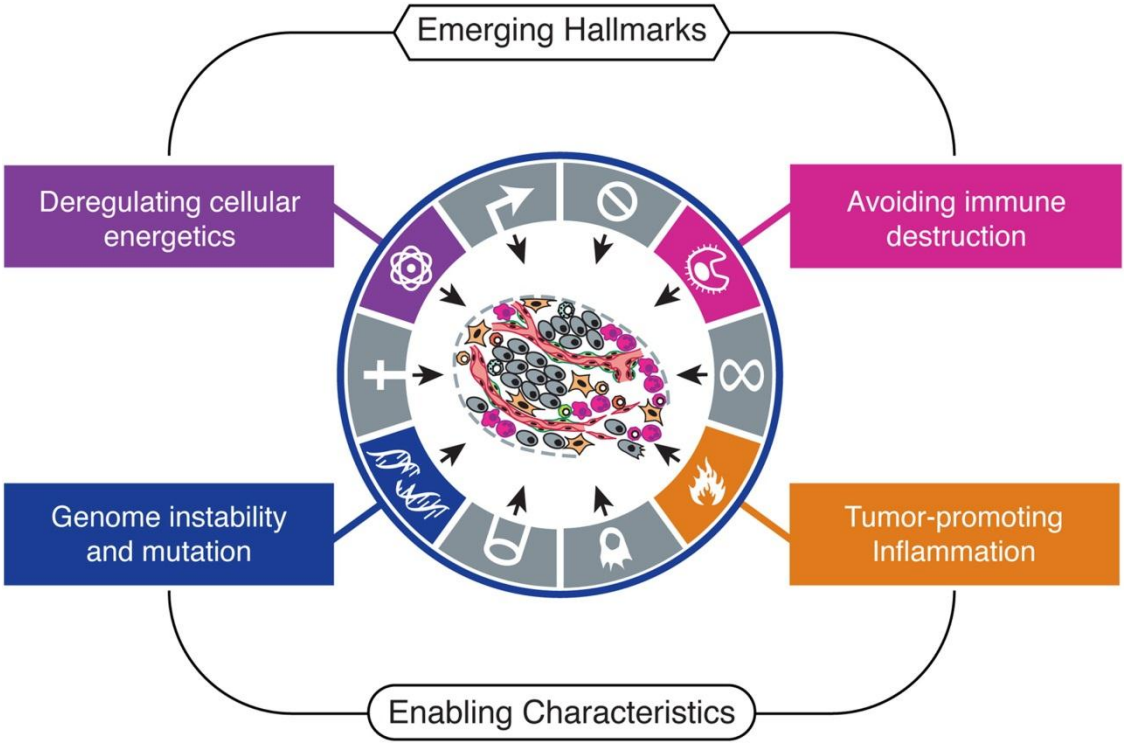
- Growth factors/signal transduction
- Angiogenesis
- Invasion/metastasis
- Telomerase
- Cell cycle regulators
- Control of apoptosis
- Oncogene silencing



Hanahan and Weinberg Cell, Vol. 100, 57–70, 2000

Examples of target areas for drug development

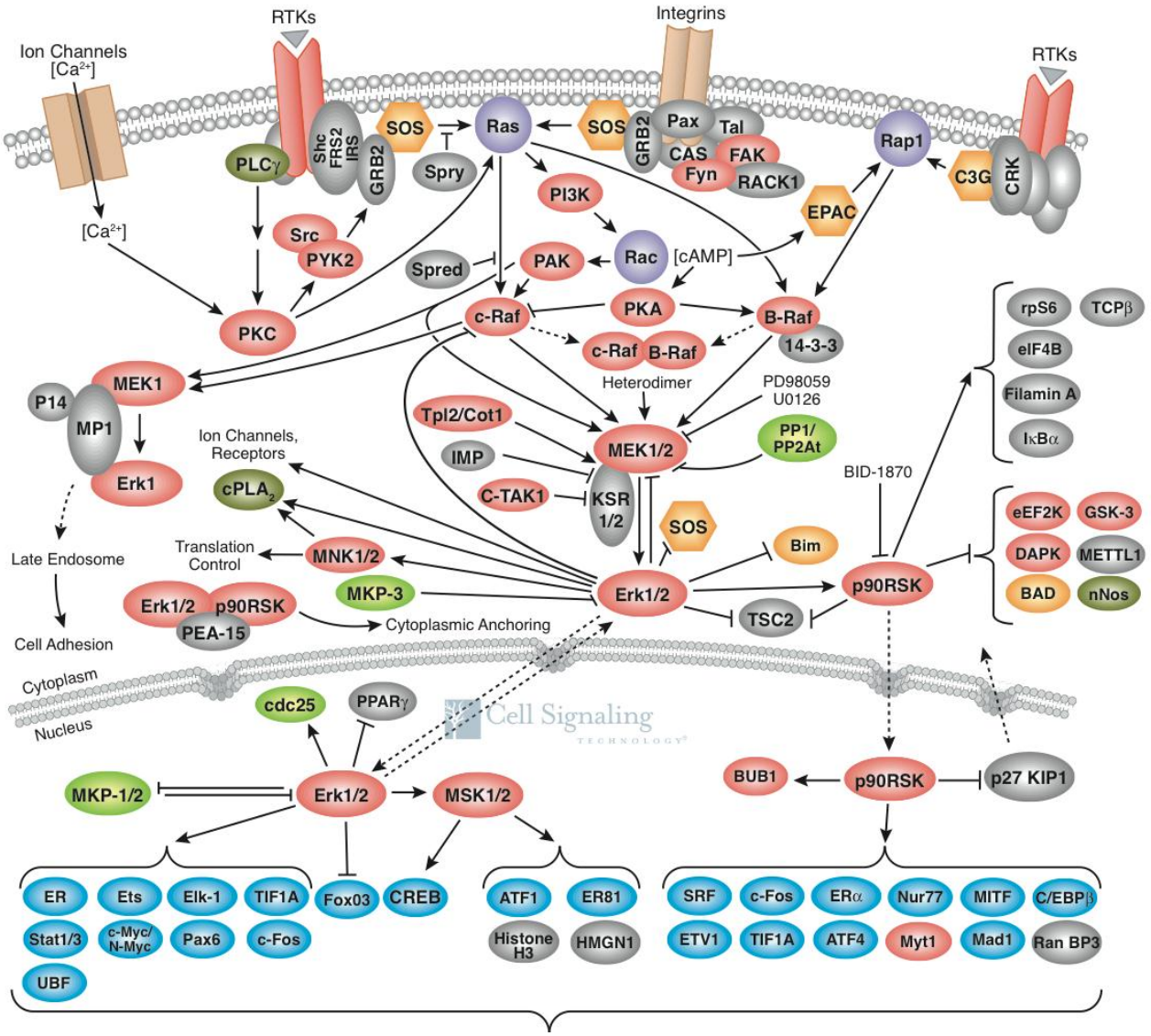
- DNA damage recognition and repair
- Immunotherapy
- Metabolism



Hanahan and Weinberg Cell, Vol. 100, 57-70, 2000
Cell, Vol. 144, 646-74, 2011

CANCER RESEARCH UK

MAPK/Erk in Growth and Differentiation



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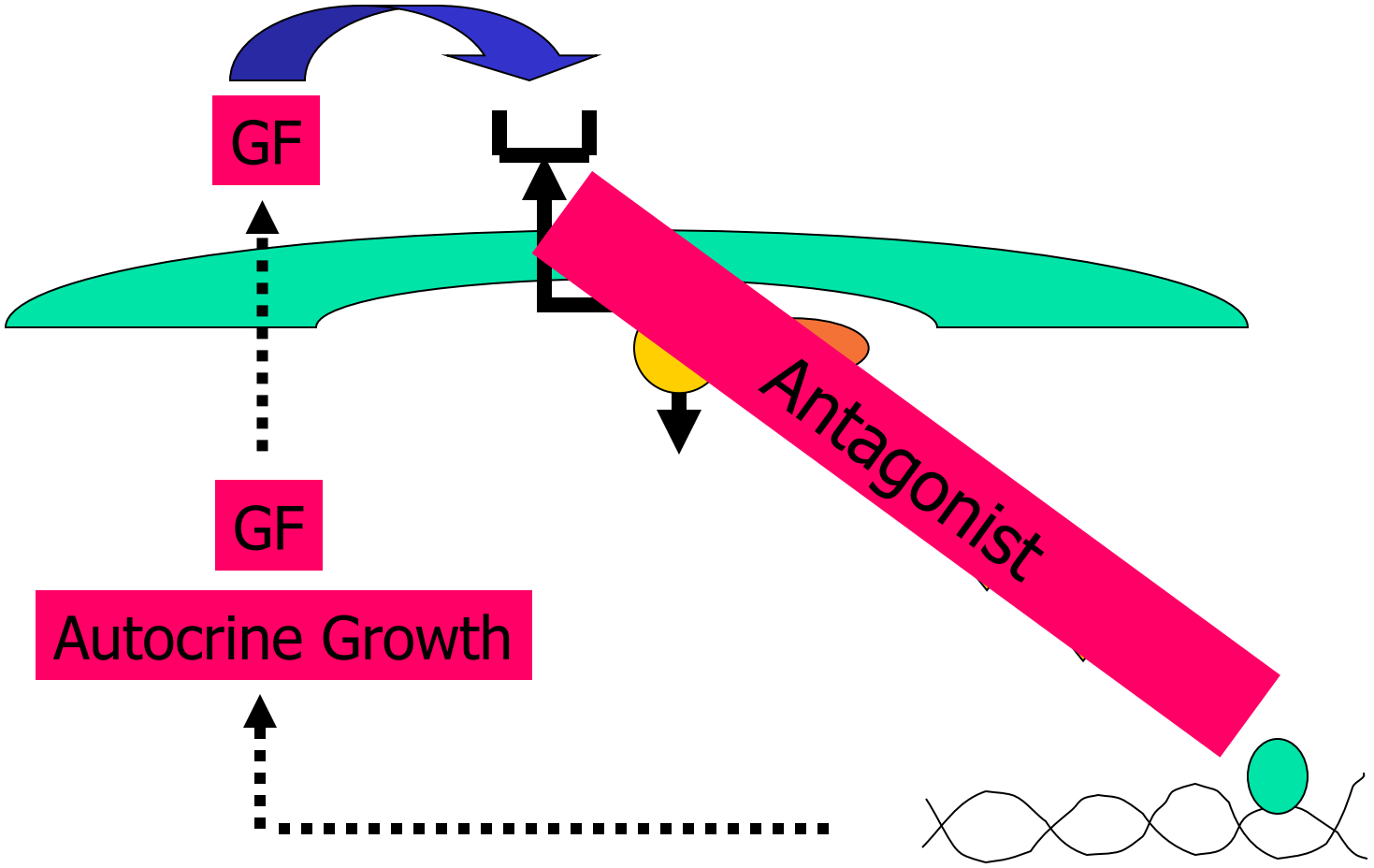
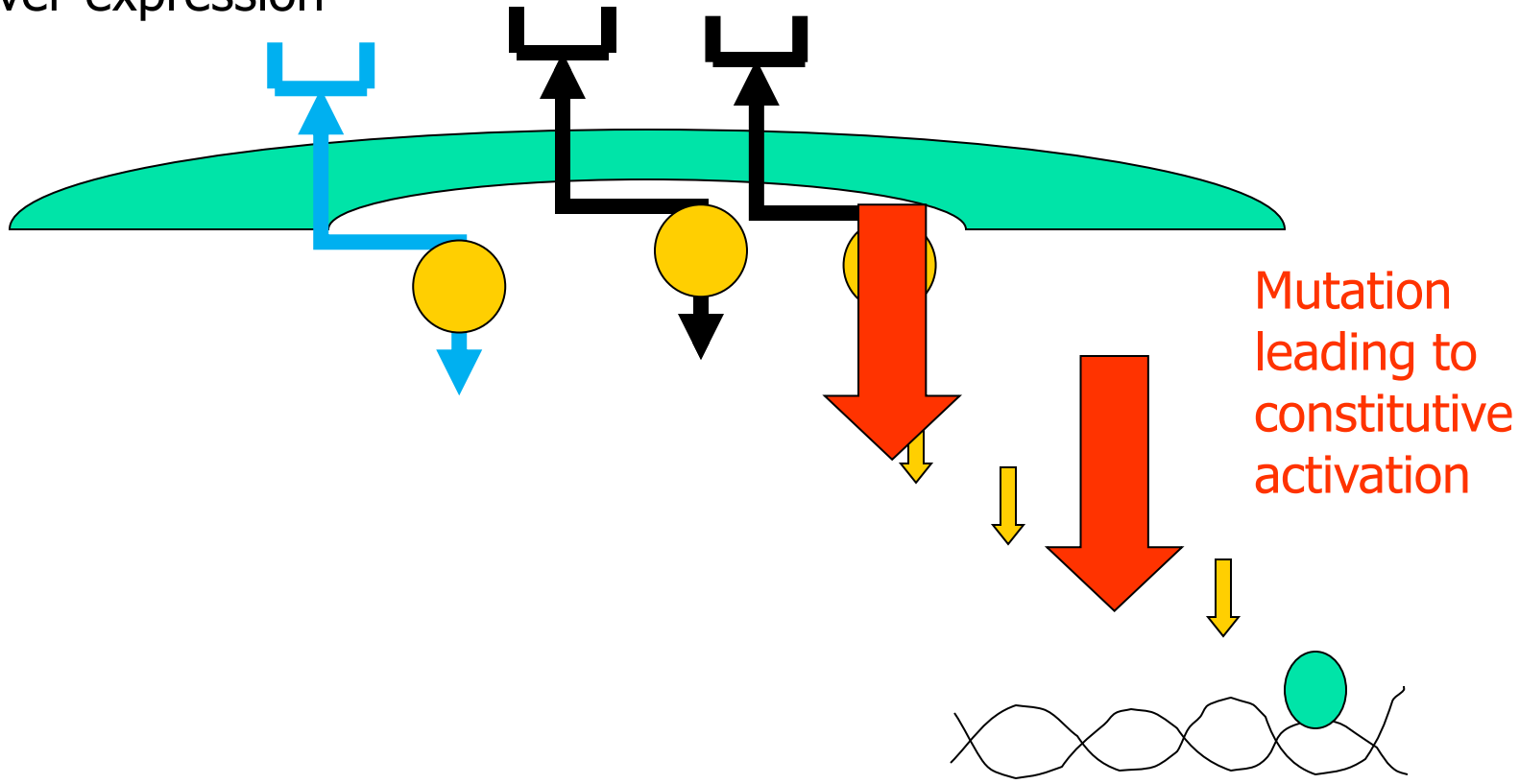
Cell Signalling Technology

Growth factor antagonism/signal transduction: a target for anti-cancer drug design

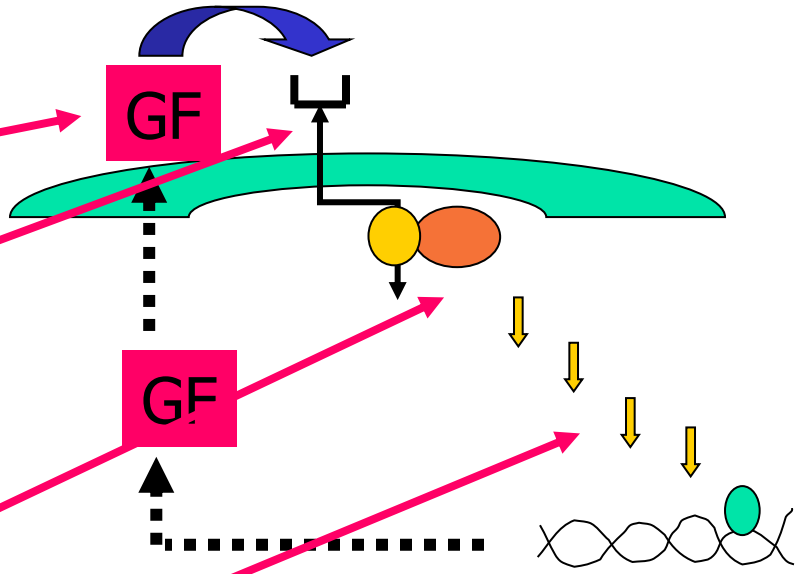


Growth factor antagonism/signal transduction: a target for anti-cancer drug design

Receptor
- mutation
- over-expression

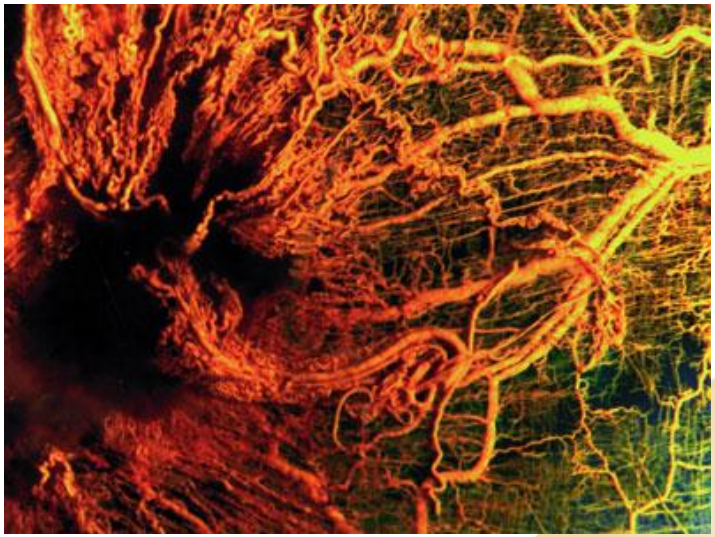


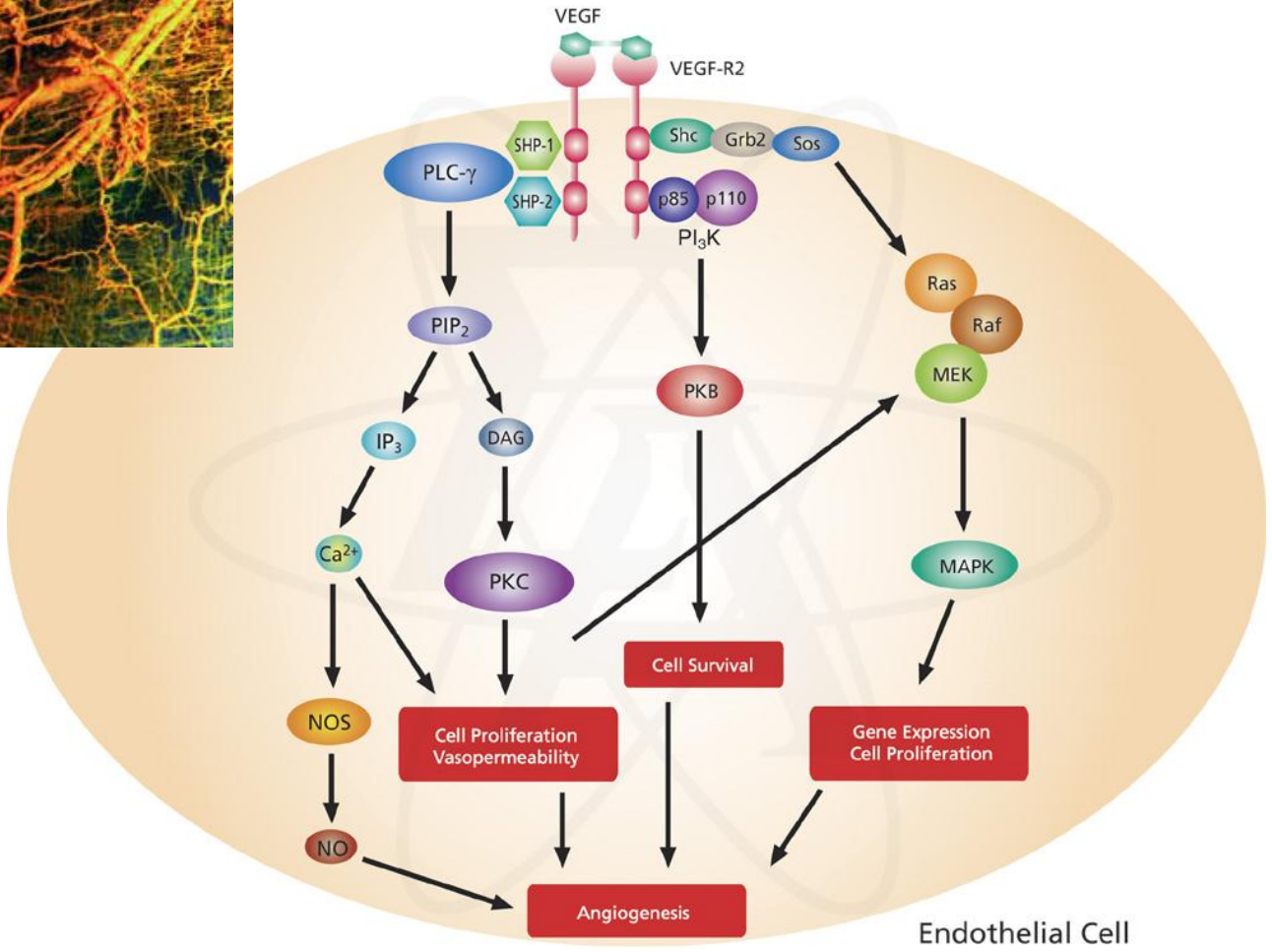
Growth/Survival Factor Pathways: Molecularly Targeted Agents (MTAs)



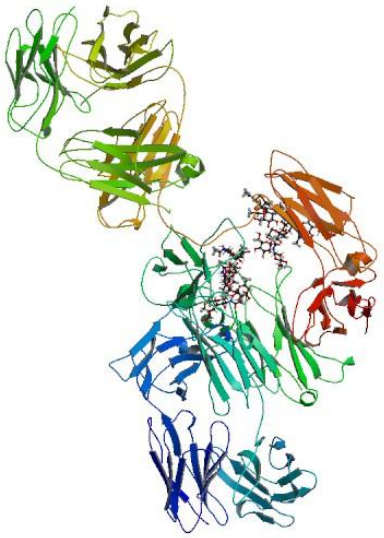
- Antibody targeting circulating factor
  - VEGF: bevacizumab (Avastin)
- Antibody targeting receptor
  - EGFR: cetuximab (Erbitux)
  - Erb B2: trastuzamab (Herceptin)
- Small molecule targeting receptor
  - EGFR TK inhibitor: gefitinib (Iressa), erlotinib (Tarceva)
  - Pan Erb TK inhibitor: lapatinib, afatinib
- Small molecules targeting the signal transduction pathway
  - RAF inhibitors are used in clinical practice (melanoma)
  - MEK and ERK inhibitors are in development

Angiogenesis and VEGF



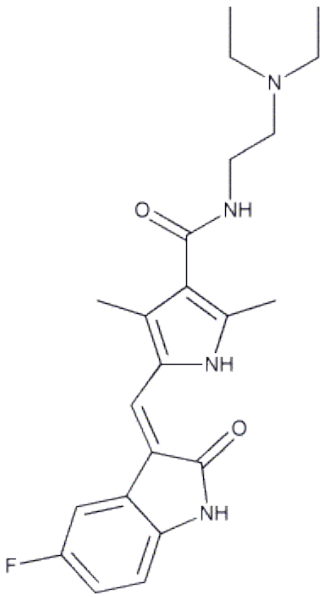


Bevacizumab; established in the treatment of patients with colorectal cancer



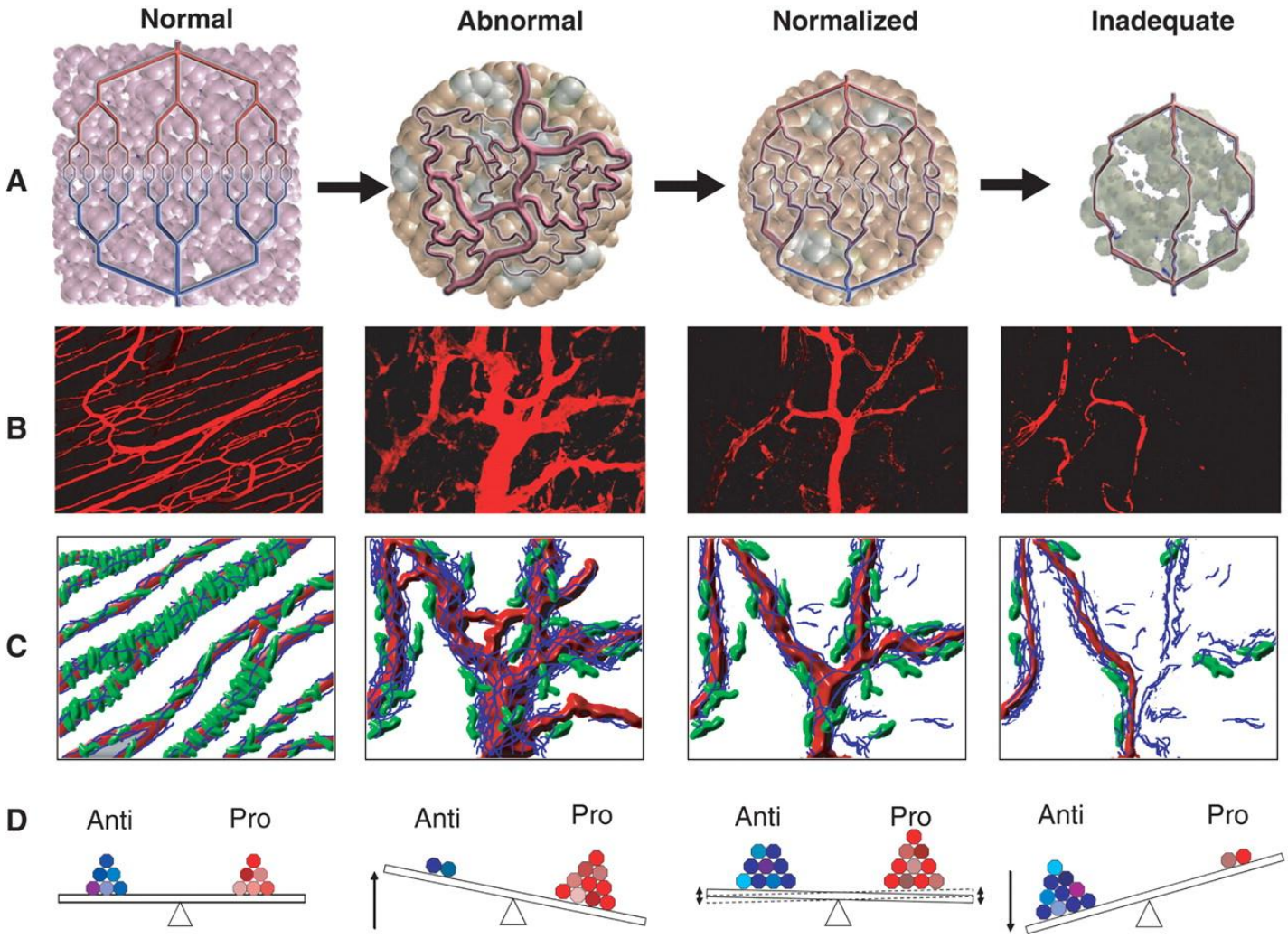
- Recombinant, humanised monoclonal Ab targeting VEGF-α
- Pivotal paper published in NEJM in June 2004 (Hurwitz et al)
- Median overall survival of 20.3 months (IFL + bevacizumab) versus 15.6 months (IFL alone)in patients with metastatic colorectal cancer
- Hypertension (a class effect), thromboses and bleeding events

Sunitinib; changed practice in patients with kidney cancer, a disease refractory to conventional chemotherapy



- Small molecule inhibitor of VEGFR (1,2), FLT3, KIT and PDGFR (α,β) tyrosine kinases
- Pivotal paper published in NEJM in January 2007 (Motzer et al)
- Progression free survival of 11 months versus 5 months with interferon-α in patients with metastatic kidney cancer
- Fatigue, stomatitis (sore mouth), hand-foot syndrome, hypertension (a class effect)

Proposed role of vessel normalisation in the response of tumours to anti-angiogenic therapy



Jain RK, Science 2005; 307:58-62

Science
AAAS

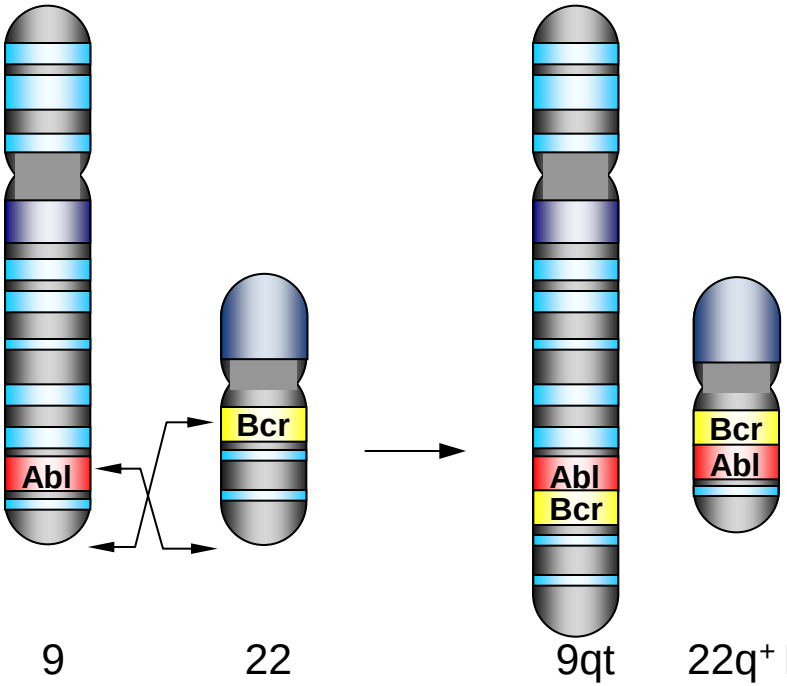
Seeking the magic bullet

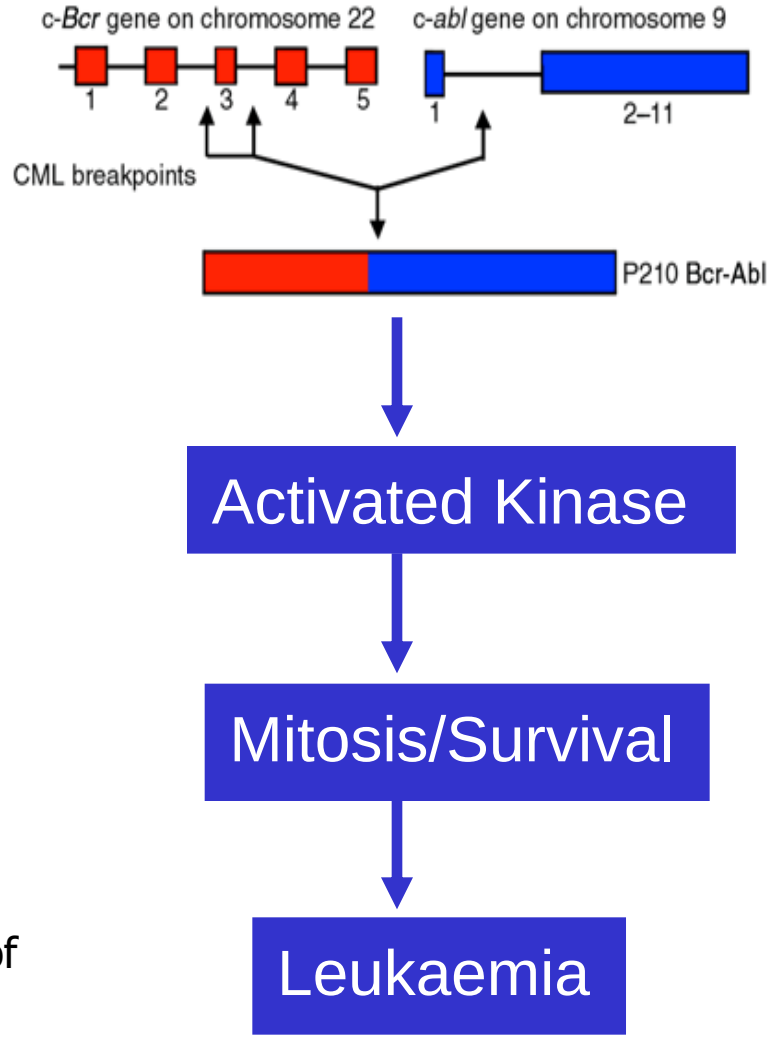
Efficacy with minimal toxicity

Hitting a truly cancer specific target, where the cancer is driven by a single "oncogene"

Philadelphia Chromosome and Leukaemia

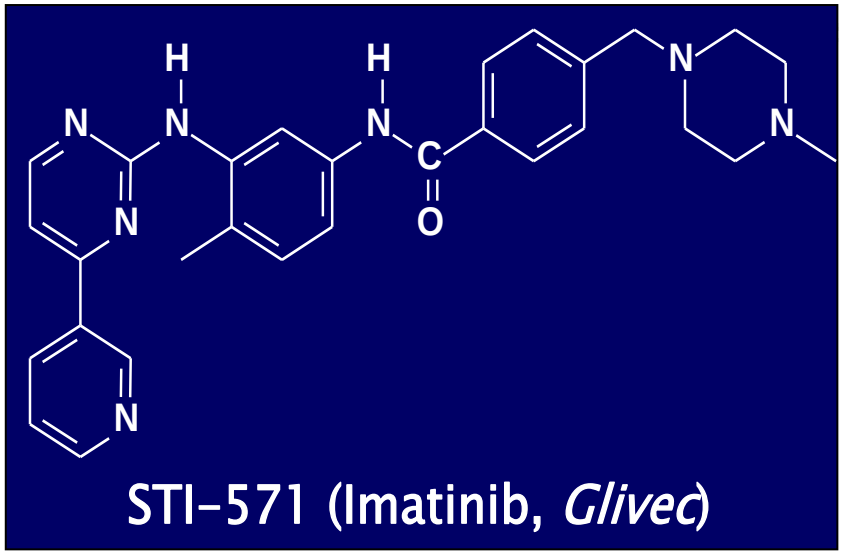
Chronic Myeloid Leukemia (CML)

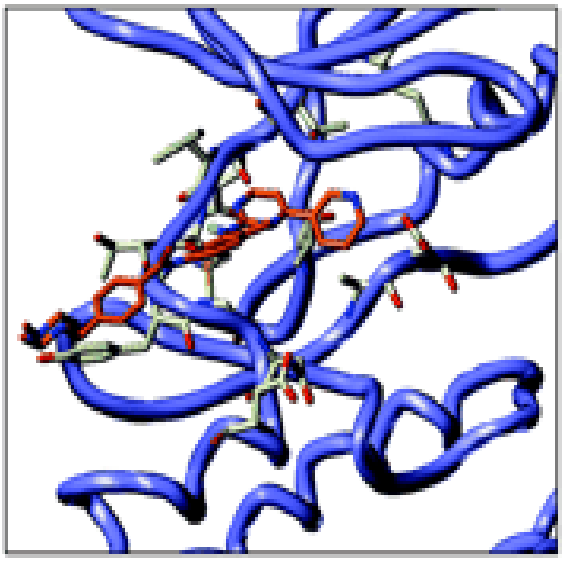




Philadelphia chromosome present in cells in 95% of patients with Chronic Myeloid Leukaemia (CML)

Imatinib (Glivec): A Selective Bcr-Abl Tyrosine Kinase Inhibitor





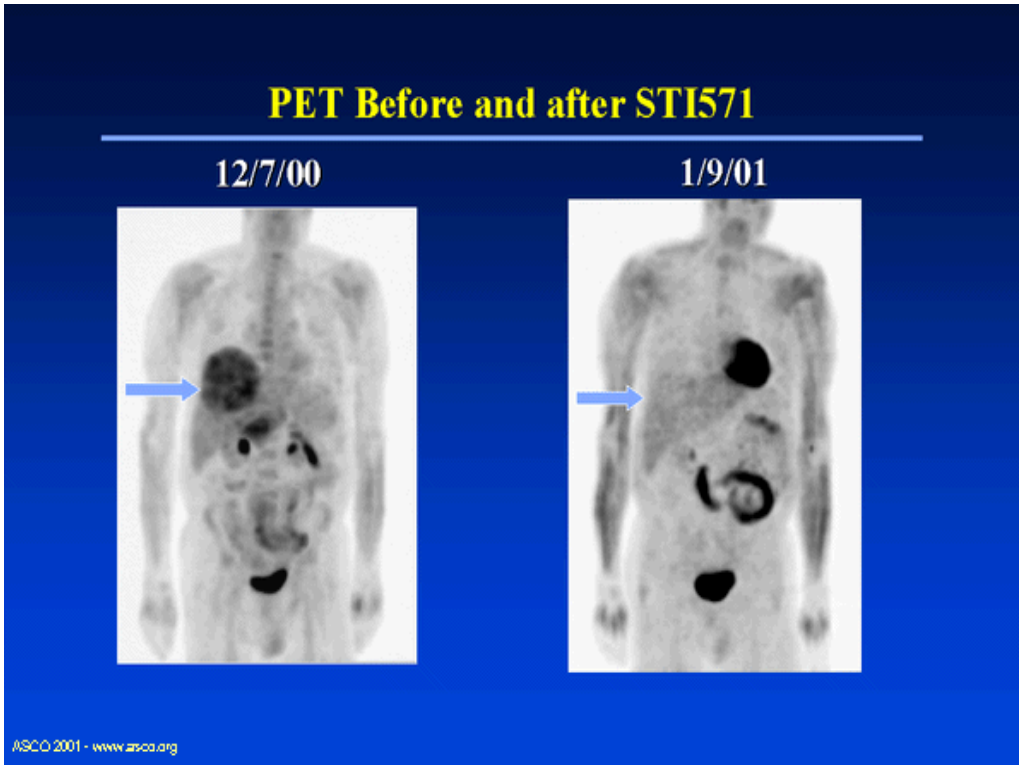
- STI-571 – a small molecule ATP-competitive inhibitor of the Bcr-abl tyrosine kinase
- Pivotal (Phase I) paper published in the NEJM in 2001 (Druker BJ et al)
- Druker, Lydon and Sawyers received the Lasker-DeBakey Clinical Medical Research Award in 2009 for "converting a fatal cancer into a manageable chronic condition"

"Collateral damage"?

Imatinib demonstrates "good" specificity for bcr-abl kinase, although it also inhibits c-kit.

C-kit is over-expressed Gastro Intestinal Stromal Tumour (GIST), a highly chemo-refractory tumour

FDG-PET scans before and after imatinib in a patient with GIST



Synthetic lethality

Two genes are synthetic lethal if mutation of either gene alone is compatible with viability but mutation of both leads to death.

Inhibiting the products of genes that are synthetic lethal to cancer-causing mutations should, by definition, kill cells that harbour such mutations, while sparing normal cells.

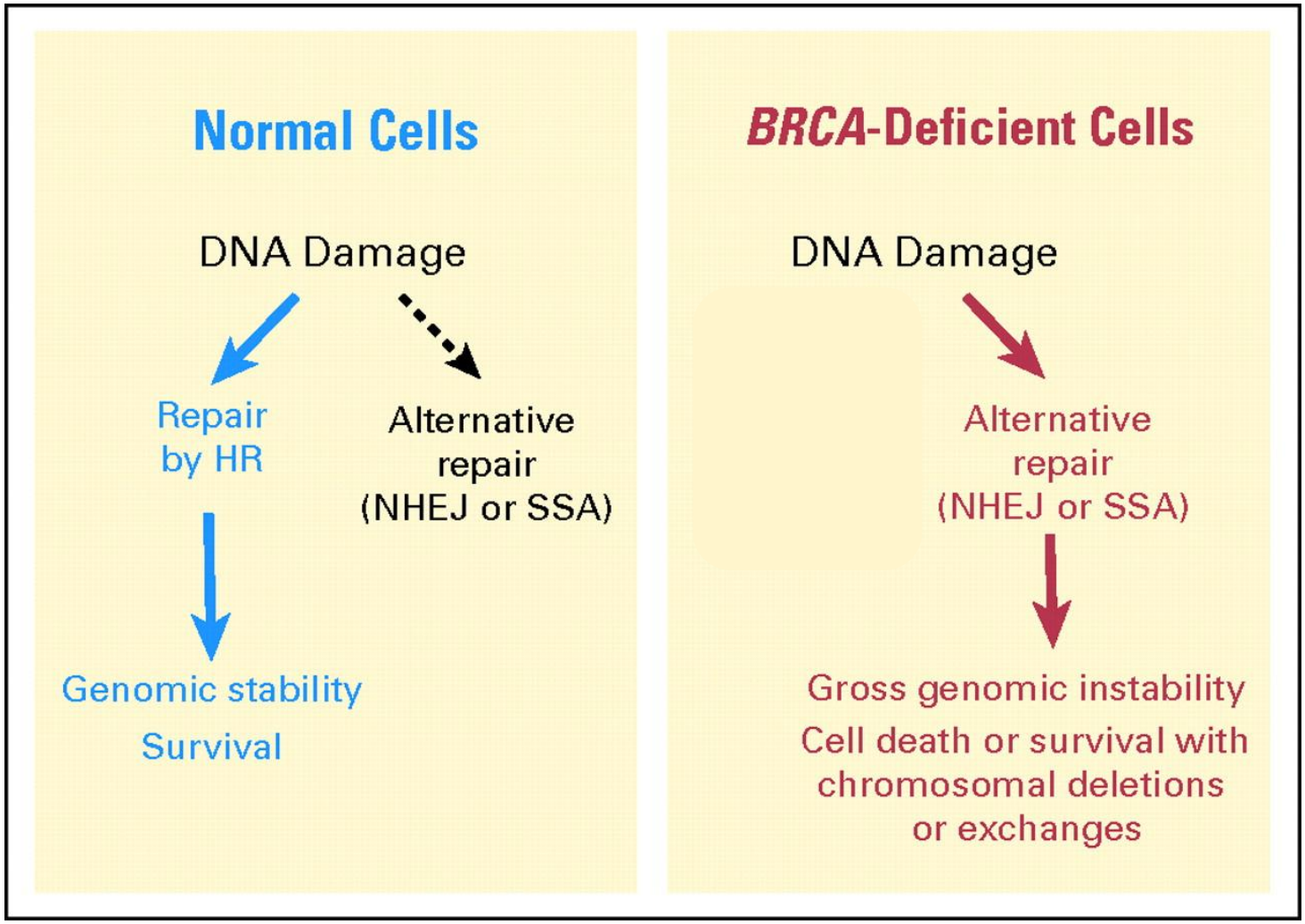
William Kaelin, Nature Reviews Cancer, 5, 689-698, 2005

Gene *X*	Gene *Y*	
+	+	No effect
–	+	No effect
+	–	No effect
–	–	Death

Ashworth A JCO 2008; 26: 3785-3790

JOURNAL OF CLINICAL ONCOLOGY

Synthetic lethality: PARP inhibition in patients with BRCA mutations



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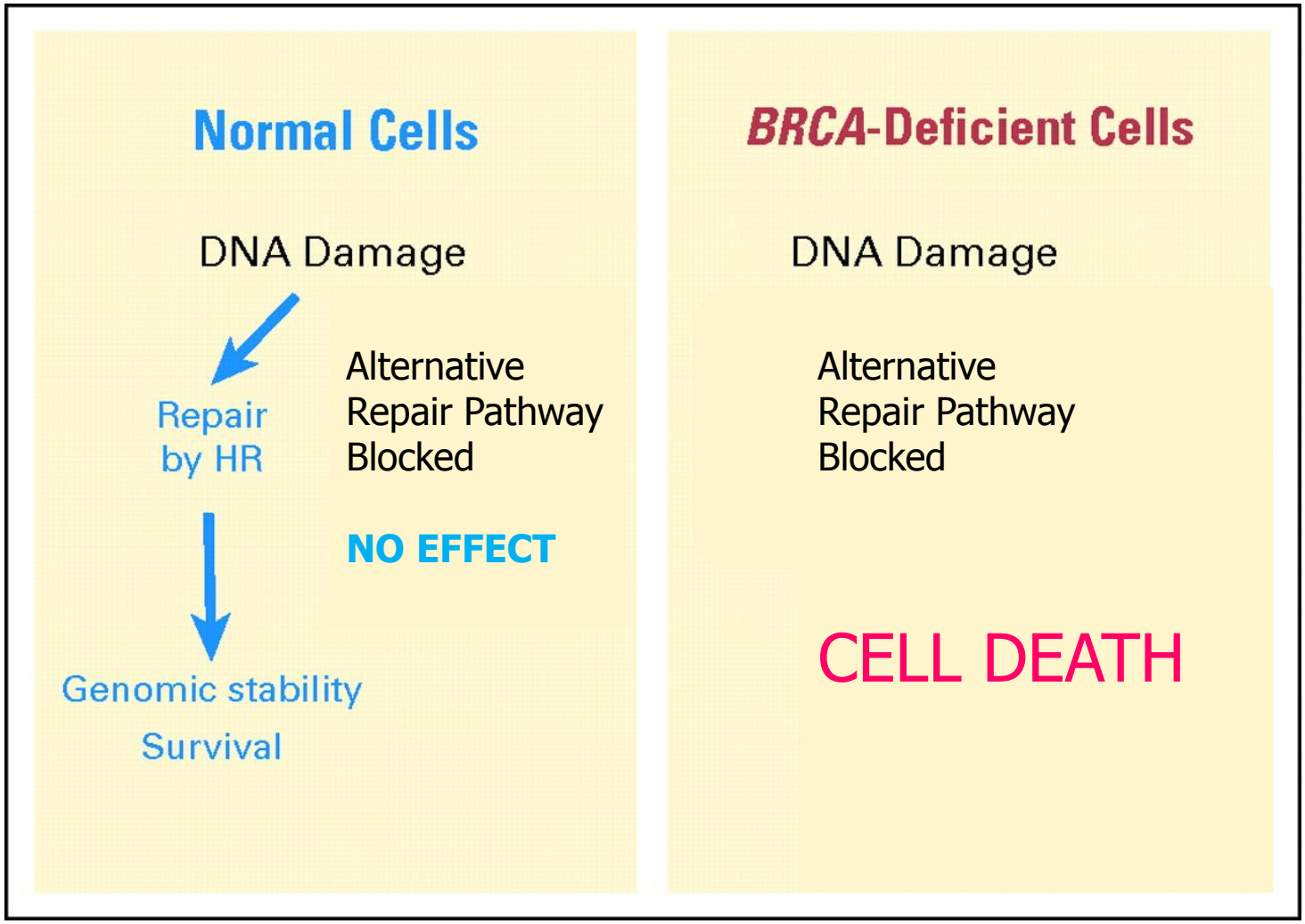

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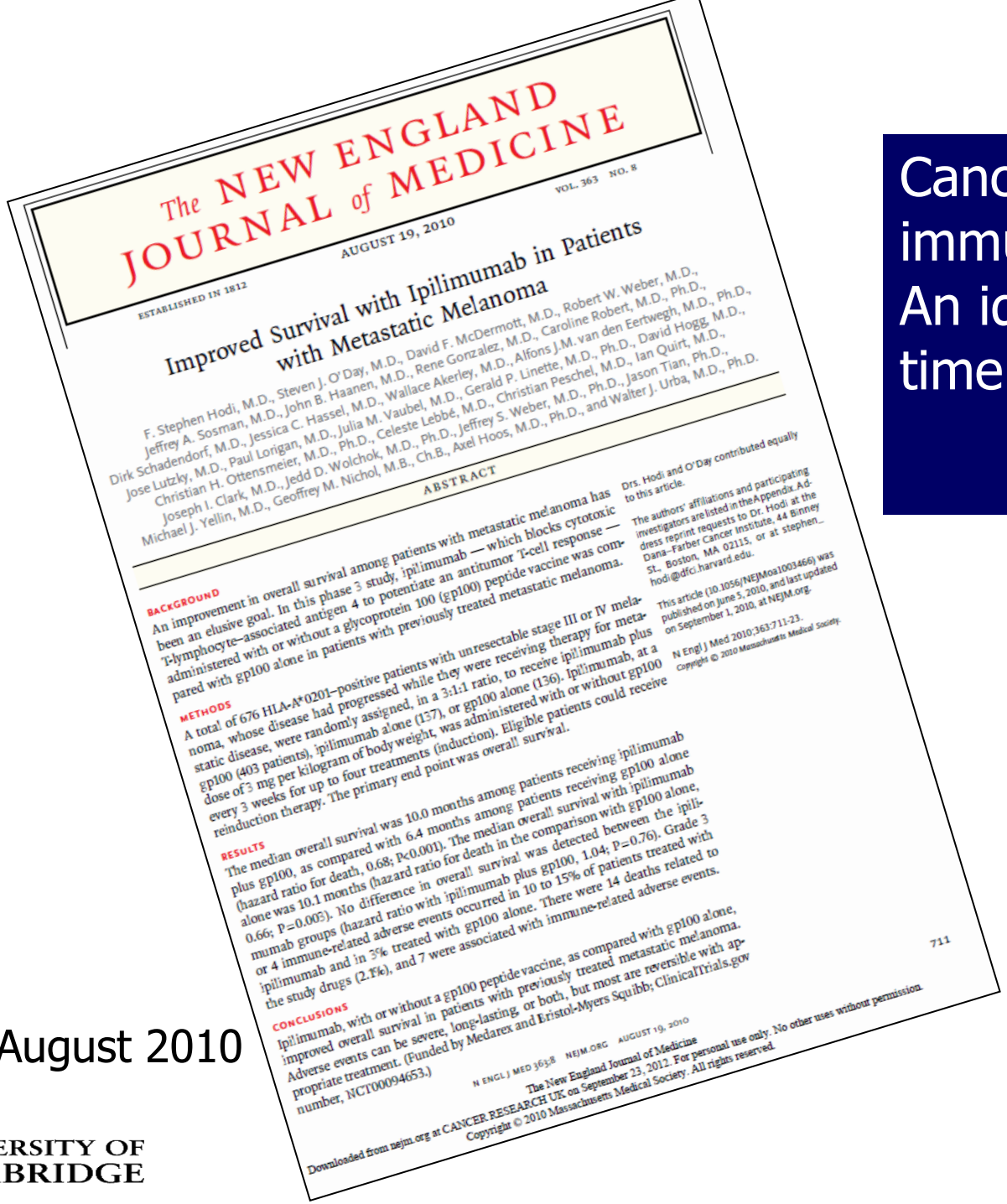
Poly ADP Ribose Polymerase (PARP) inhibition

- Role in DNA single strand break repair
- Important in NHEJ and BE repair pathways
- 41% response rate in women with breast cancer and confirmed BRCA1 or BRCA2 mutations treated with the PARP inhibitor olaparib following the failure of previous chemotherapy
  - Tutt et al, Lancet. 2010; 376(9737): 235-44
- Potential as a sensitiser to conventional chemotherapy

CANCER RESEARCH UK

Cancer immunotherapy: An idea whose time has come?



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 19, 2010 VOL. 363 NO. 8

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wallace Akerley, M.D., Alfons J.M. van den Eertwegh, M.D., Ph.D., Jose Lutzky, M.D., Paul Lorigan, M.D., Julia M. Vaubel, M.D., Gerald P. Linette, M.D., Ph.D., David Hogg, M.D., Christian H. Ottensmeier, M.D., Ph.D., Celeste Lebbé, M.D., Christian Peschel, M.D., Ian Quirt, M.D., Joseph I. Clark, M.D., Jedd D. Wolchok, M.D., Ph.D., Jeffrey S. Weber, M.D., Ph.D., Jason Tian, Ph.D., Michael J. Yellin, M.D., Geoffrey M. Nichol, M.B., Ch.B., Axel Hoos, M.D., Ph.D., and Walter J. Urba, M.D., Ph.D.

ABSTRACT

BACKGROUND

An improvement in overall survival among patients with metastatic melanoma has been an elusive goal. In this phase 3 study, ipilimumab — which blocks cytotoxic T-lymphocyte–associated antigen 4 to potentiate an antitumor T-cell response — administered with or without a glycoprotein 100 (gp100) peptide vaccine was compared with gp100 alone in patients with previously treated metastatic melanoma.

METHODS

A total of 676 HLA-A*0201–positive patients with unresectable stage III or IV melanoma, whose disease had progressed while they were receiving therapy for metastatic disease, were randomly assigned, in a 3:1:1 ratio, to receive ipilimumab plus gp100 (403 patients), ipilimumab alone (137), or gp100 alone (136). Ipilimumab, at a dose of 3 mg per kilogram of body weight, was administered with or without gp100 every 3 weeks for up to four treatments (induction). Eligible patients could receive reinduction therapy. The primary end point was overall survival.

RESULTS

The median overall survival was 10.0 months among patients receiving ipilimumab plus gp100, as compared with 6.4 months among patients receiving gp100 alone (hazard ratio for death, 0.68; P<0.001). The median overall survival with ipilimumab alone was 10.1 months (hazard ratio for death in the comparison with gp100 alone, 0.66; P=0.003). No difference in overall survival was detected between the ipilimumab groups (hazard ratio with ipilimumab plus gp100, 1.04; P=0.76). Grade 3 or 4 immune-related adverse events occurred in 10 to 15% of patients treated with ipilimumab and in 3% treated with gp100 alone. There were 14 deaths related to the study drugs (2.1%), and 7 were associated with immune-related adverse events.

CONCLUSIONS

Ipilimumab, with or without a gp100 peptide vaccine, as compared with gp100 alone, improved overall survival in patients with previously treated metastatic melanoma. Adverse events can be severe, long-lasting, or both, but most are reversible with appropriate treatment. (Funded by Medarex and Bristol-Myers Squibb; ClinicalTrials.gov number, NCT00094653.)

Drs. Hodi and O'Day contributed equally to this article.

The authors' affiliations and participating investigators are listed in the Appendix. Address reprint requests to Dr. Hodi at the Dana–Farber Cancer Institute, 44 Binney St., Boston, MA 02115, or at stephen_hodi@dfci.harvard.edu.

This article (10.1056/NEJMoa1003466) was published on June 5, 2010, and last updated on September 1, 2010, at NEJM.org.

N Engl J Med 2010;363:711-23.

NEJM, August 2010

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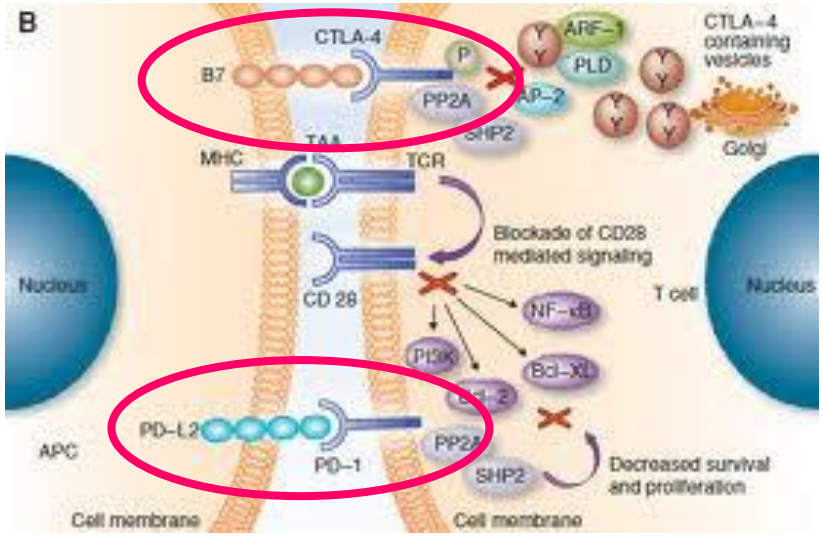
Ipilimumab

- Ipilimumab is an anti-CTLA4 monoclonal antibody
- "T cell stimulatory" effect
- Common side effects:
  - A **skin reaction** occurs in 4 out of 10 people (40%) – acneiform or just dry and itchy skin. This can be very severe. Steroids may be required to help control this or may be treatment limiting
  - **Vitiligo and sensitivity to sunlight**, also recorded
  - **Diarrhoea** occurs in ~30% – this can be life-threatening (immune-related colitis).
  - **Fatigue** (50%) during and after treatment – but most people find their energy levels are back to normal within 6 months to a year
  - **Nausea and/or vomiting** (30%) but is usually well controlled with anti emetics

Immune checkpoints: CTLA-4 and PD-1



Anti PD-1 antibody therapy

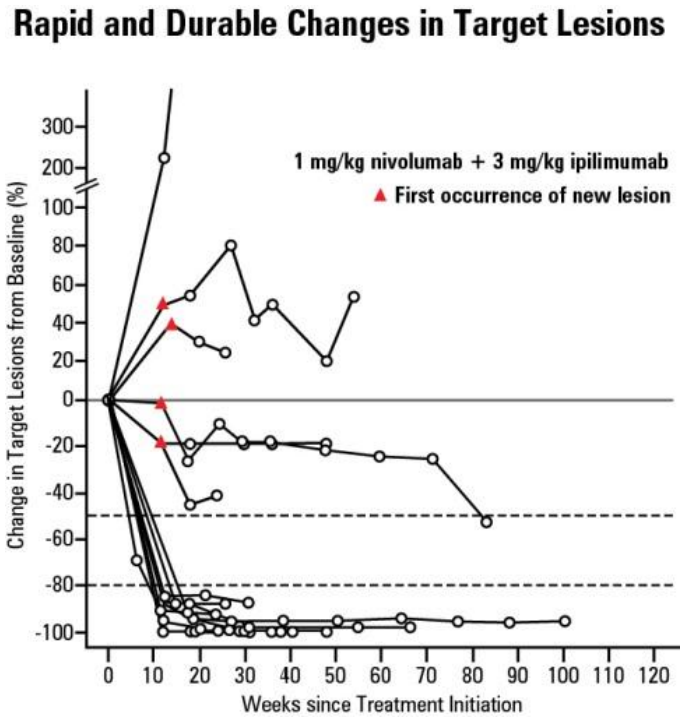
- Nivolumab (anti PD-1) acts as an immunomodulator, by blocking ligand activation of the programmed cell death 1 (PD-1) receptor on activated T cells.
- Common adverse events with nivolumab included fatigue, rash, diarrhea, decreased appetite, nausea, and pruritus.
- Grade 3-4 toxicity occurred in 41 of 296 patients (14%), with 3 deaths attributed to treatment-related pneumonitis.
- Phase III clinical trials are ongoing (kidney, lung and melanoma)

Stop Press: ASCO 2013

A combination of a CTLA-4-blocking antibody (ipilimumab) and the PD-1–blocking antibody (nivolumab) appears to provide deep, rapid, and durable tumor responses in patients with advanced melanoma ….

….. according to results of a phase I study (17 patients).

Presented by Jedd D. Wolchok, MD, PhD, at a Clinical Science Symposium at the American Society of Clinical Oncology (ASCO) meeting in 2013



Failure of immune checkpoint antagonists in pancreatic ductal adenocarcinoma

JUNE 28, 2012
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer

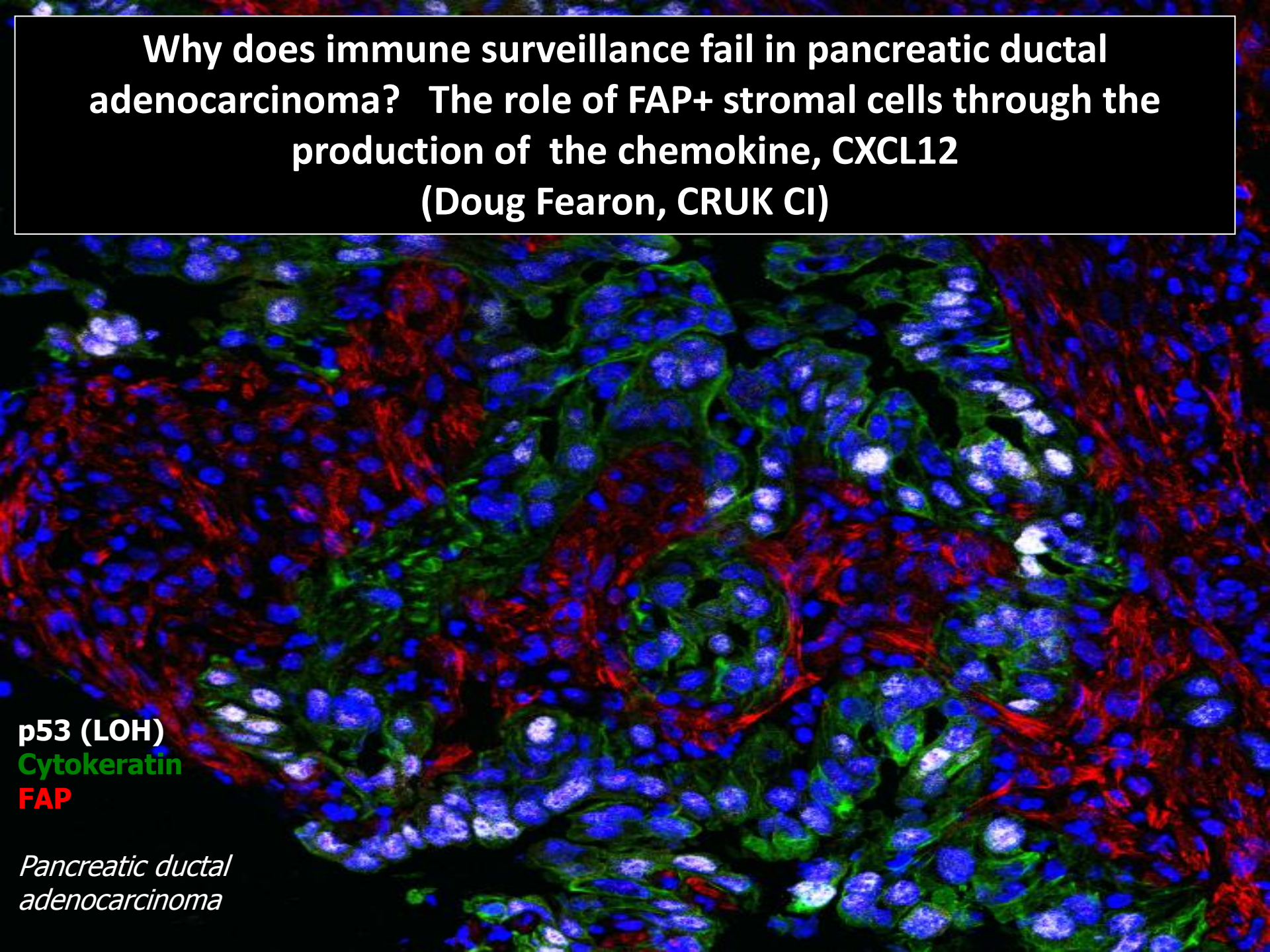
Cancer	Patients	Responders
Melanoma	52	9
Renal-cell	17	2
NSCLC	49	5
Ovarian	17	1
Colorectal	75	0
Pancreatic	*14*	*0*

Royal RE, et al. Phase 2 trial of single agent Ipilimumab (anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. J Immunother. 2010;33:828-33.

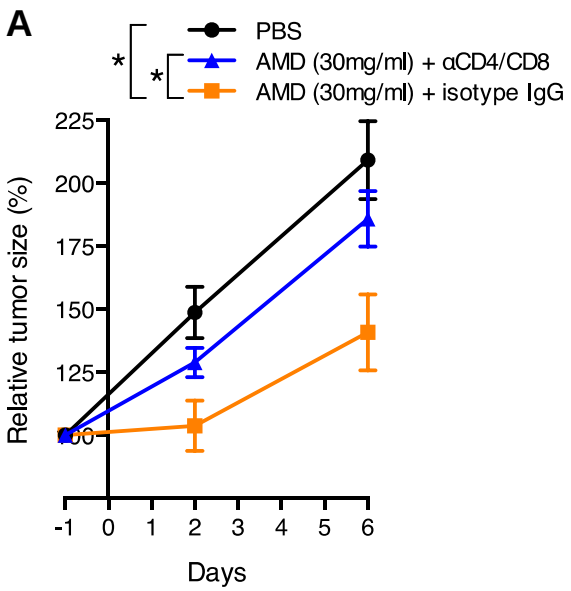
"Single agent Ipilimumab, is ineffective for the treatment of advanced pancreas cancer."

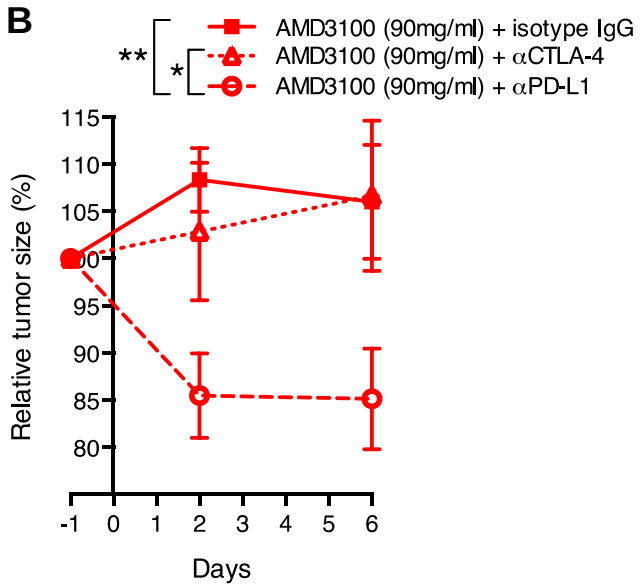
Why does immune surveillance fail in pancreatic ductal adenocarcinoma? The role of FAP+ stromal cells through the production of the chemokine, CXCL12

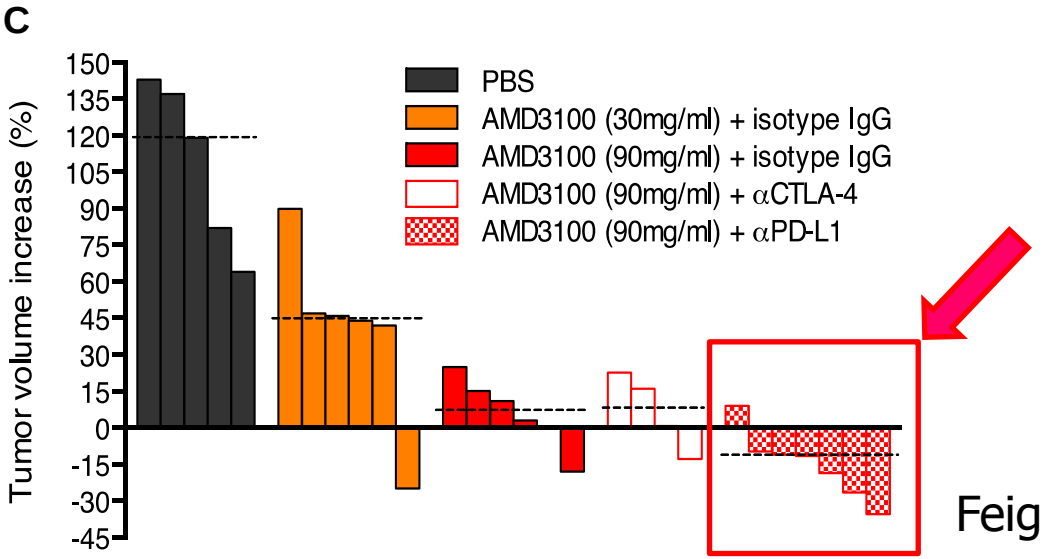
(Doug Fearon, CRUK CI)



Blocking the CXCR4/CXCL12 interaction, using the small molecule CXCR4 inhibitor AMD3100, leads to sensitivity to αPD-L1







Feig et al, PNAS 2013

The phases of clinical drug development

- Phase 0 — Single, sub-therapeutic doses (microdoses)
- Phase I — Dose finding/toxicity/definition of dose for efficacy testing

} pharmacokinetics and pharmacodynamics

- Phase II — Preliminary assessment of efficacy
- Phase III — Comparative studies
- Phase IV — Post marketing

What do I mean by PK/PD?

- Pharmacokinetics:
  - What the body does to the drug:
    - A=Absorption
    - D=Distribution
    - M=Metabolism
    - E=Elimination
- Pharmacodynamics:
  - What the drug does to the body
    - Mechanistic effect
    - Therapeutic effect
    - Toxicity

PK PD questions to be answered:

Does the agent get absorbed (oral therapies)?	PK
Do we achieve relevant plasma concentrations?	PK
How long does it hang around for?	PK
Does the agent reach its target IN THE TUMOUR?	PK
At achievable concentrations, does the agent inhibit its target? (Proof of Mechanism)	PD
Does inhibiting the target, block the pathway?	PD
Does blocking the pathway arrest growth and/or kill cells? (Proof of Concept)	PD
Does blocking the pathway cause toxicity in normal tissues (Selectivity)	PD

CANCER RESEARCH UK

UNIVERSITY OF CAMBRIDGE

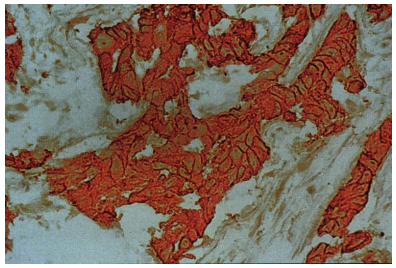
Biomarkers and Experimental Cancer Therapeutics

- Pharmacological biomarkers
  - drug target interaction
    (pharmacodynamics – proof of mechanism)
  - phenotypic effects (pharmacodynamics – proof of concept)

- Predictive biomarkers
  - Patient enrichment to maximize likely benefit from individual therapies
  - The dawn of "personalised medicine"

Predictive biomarkers in cancer therapy

- Oestrogen receptor status and hormonal therapy for patients with breast cancer
- c-ErbB2 (Her-2) gene amplification and trastuzumab therapy for breast cancer



- k-ras mutation and EGF receptor expression/mutation guiding targeted therapies for colorectal cancer and lung cancer
- B-RAF kinase mutation (V600E) in melanoma (vemurafenib)
- Bcr-Abl translocation (CML) and c-Kit mutation (GIST) for imatinib therapy
- ALK translocation in lung cancer (crizotinib)

The future of cancer treatment

- Cancer will be managed as a chronic illness
- Molecularly targeted therapies:
  - lower (hopefully), different (definitely) toxicity
  - cytostasis – long term exposure will be needed
- oral therapies will facilitate the long term exposure required for newer molecular targets
- Individualisation based on genotype or expression profile
- New therapies based on emerging "Hallmarks":
  - Immunotherapy, tumour metabolism, DNA damage recognition and repair