

Advances in understanding glioblastoma genetics: towards better treatments?

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Overview

1. Cancer genetics

2. Targeted cancer therapy

3. Improving the treatment of glioblastoma

- biomarkers

- new drug targets

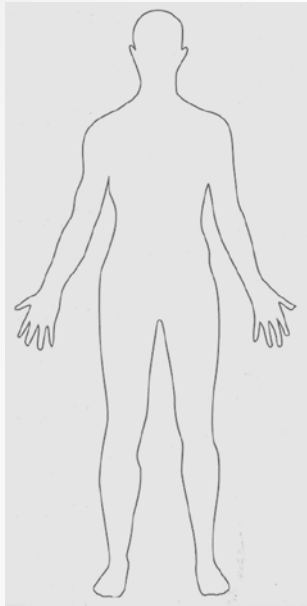
- molecular subtyping of glioblastoma

- process of developing a new treatment

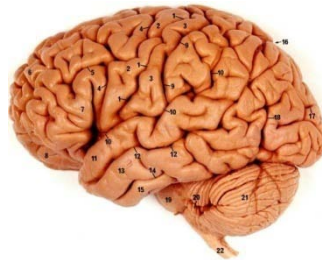
4. Glioblastoma stem cells

Cancer genetics

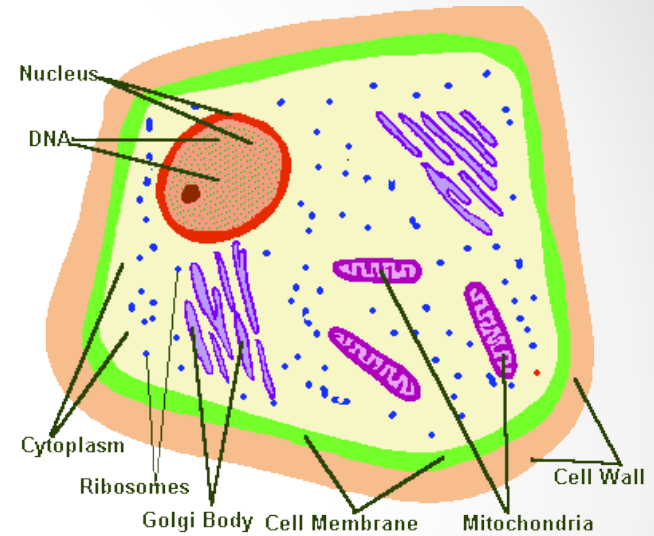
What is molecular biology?



organism



organ

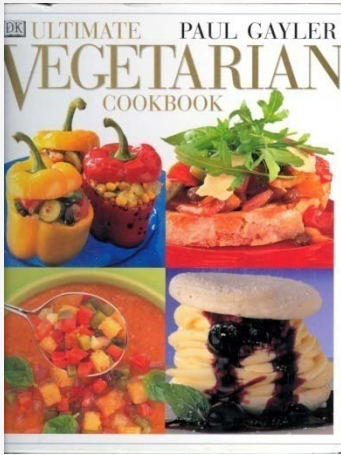


cell



**molecules:
DNA, RNA, proteins**

How genes cause disease



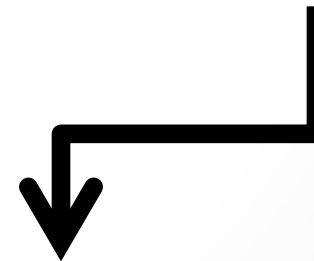
**DNA
(genes)**



RNA



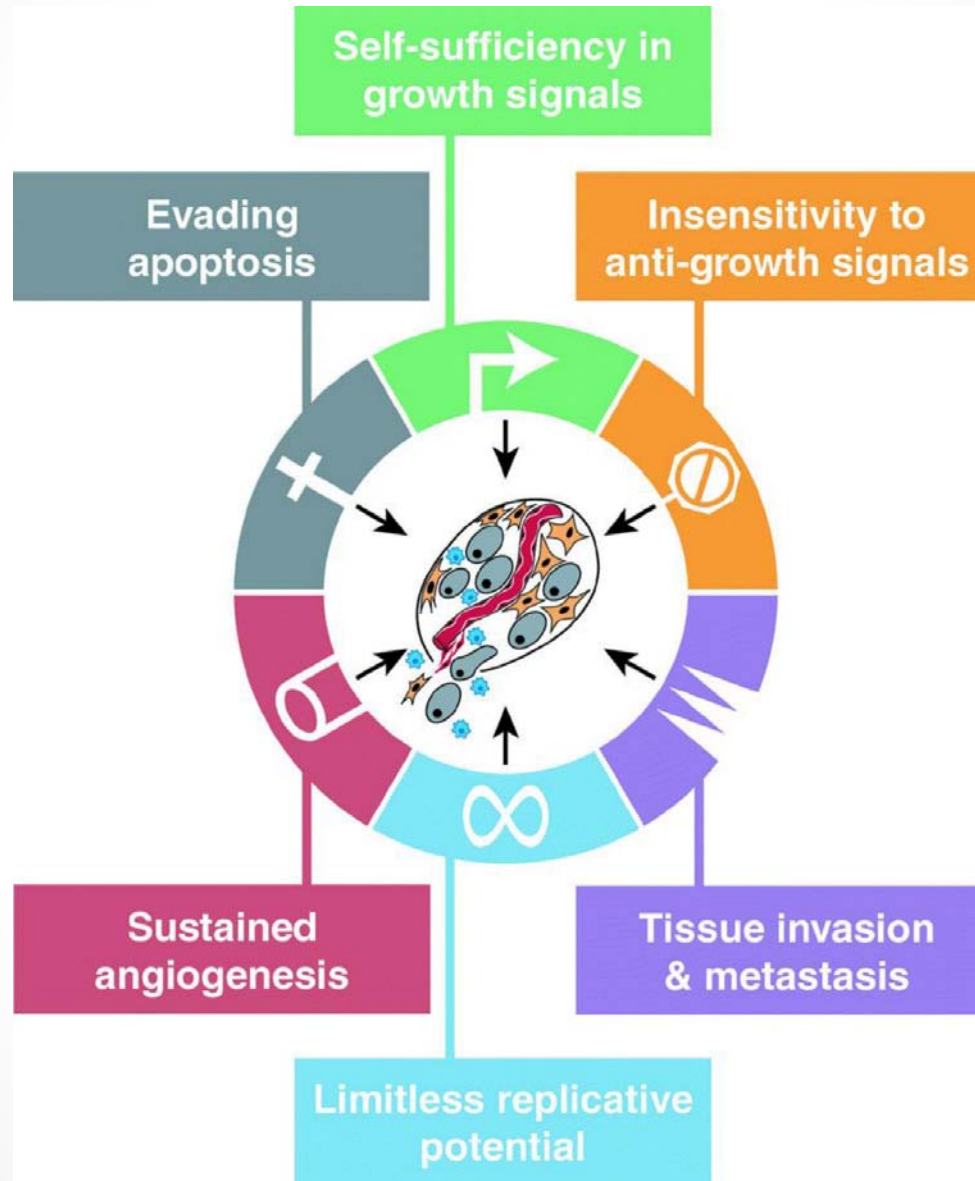
Protein



Disease ←.....

**Structure &
function of cells**

The hallmarks of cancer cells

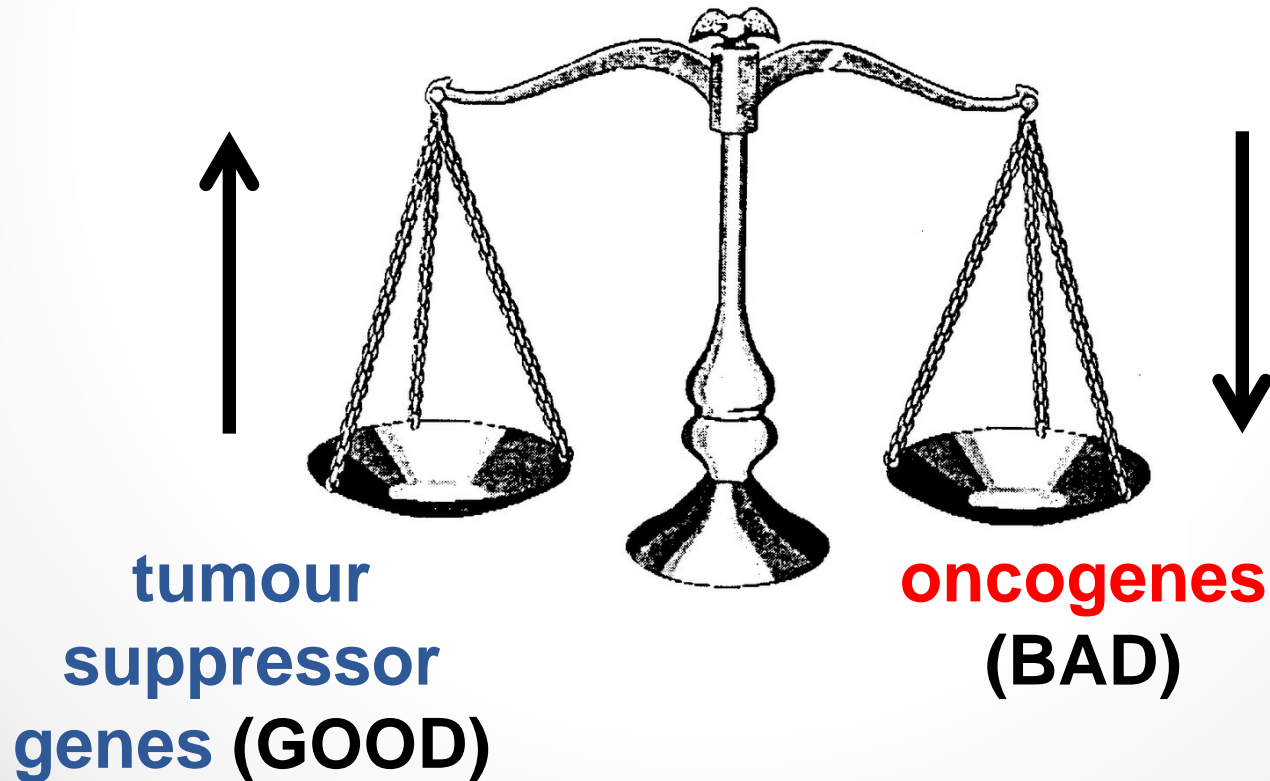


Genes control cancer

Mutations (errors) may cause cancer:

-by activating **oncogenes**

- by silencing **tumour suppressor genes**



Gene mutations in cancer

Cancers originate as the result of accumulated changes (**mutations**) in genes that control critical processes in cells

*DNA
sequence*

G A C T A A T C G G

Normal gene

G A C T A **G** T C G G

Single base change

G A C T A A **C C A** T C G G

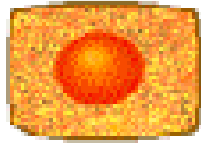
Insertion

G A C T C G G

Deletion

Altered gene expression in cancer

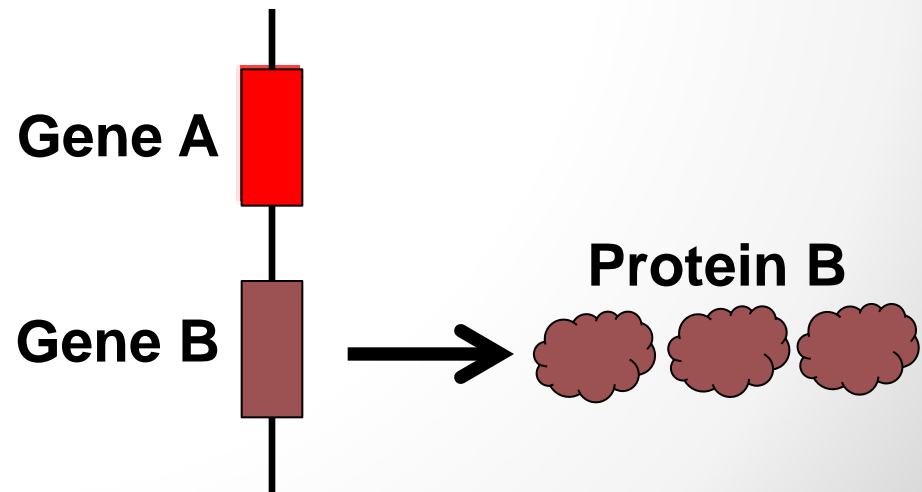
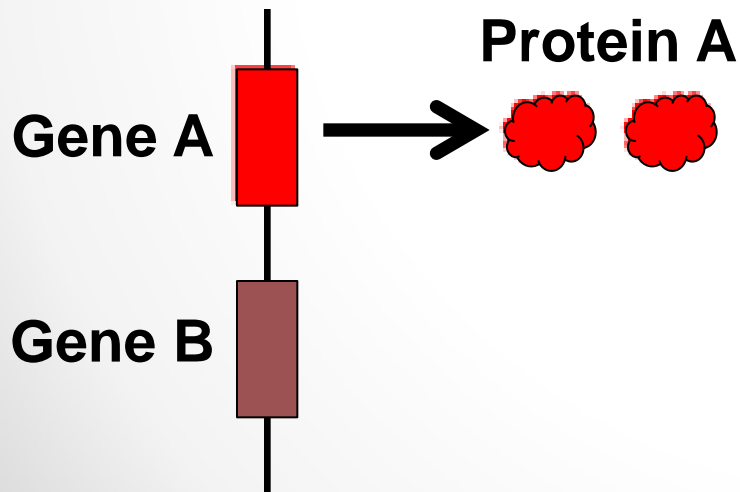
There is **increased** or **decreased** expression of specific genes in cancer cells (= more or less of a given protein)



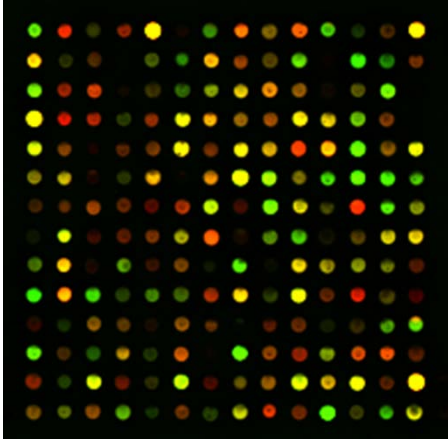
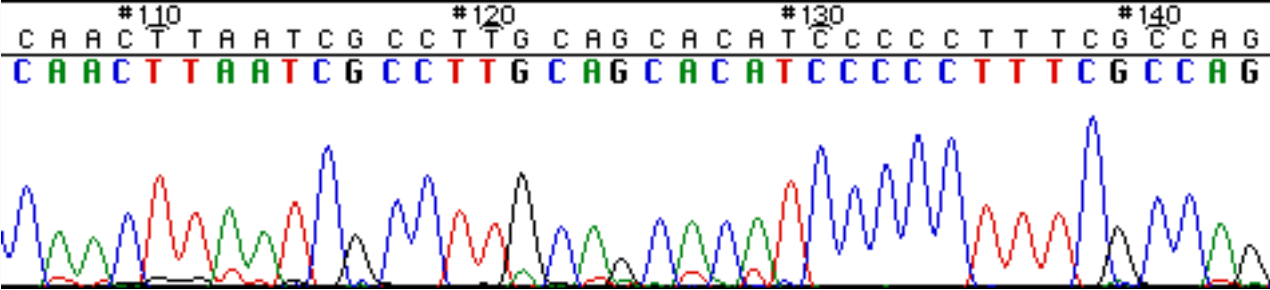
Normal cell



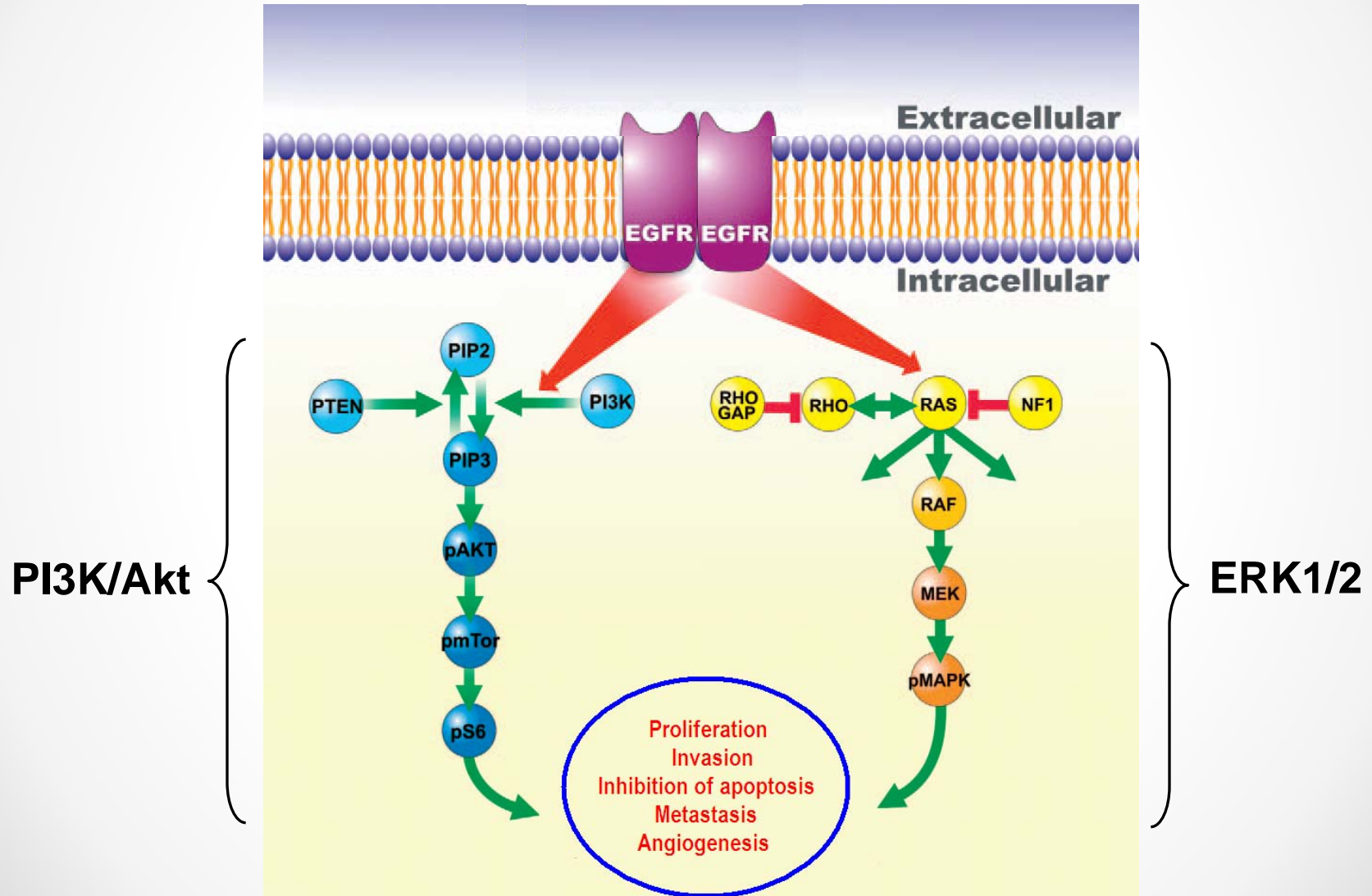
Cancer cell



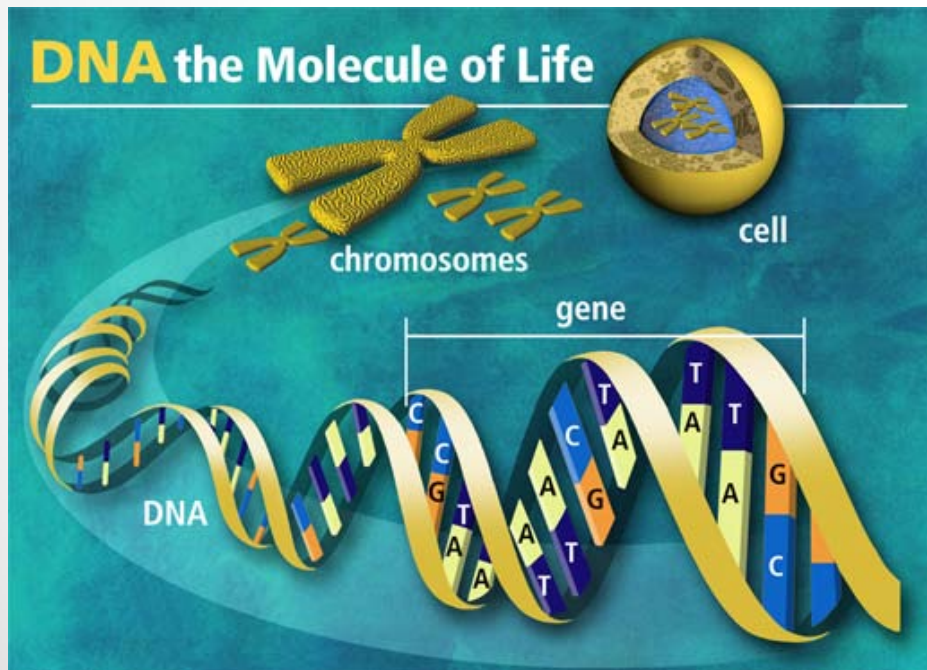
Gene expression and mutations can be studied in the laboratory using sophisticated genetic analysis methods



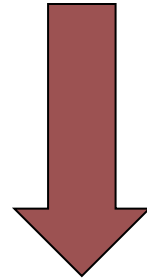
Altered signaling pathways in cancer cells promote tumour growth and progression



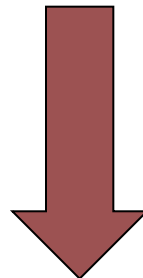
How can understanding the genetics of cancer cells (glioblastoma) help to develop new treatments?



**Understand what has “gone wrong”
in glioblastoma cells
(what mutations “drive” their growth?)**



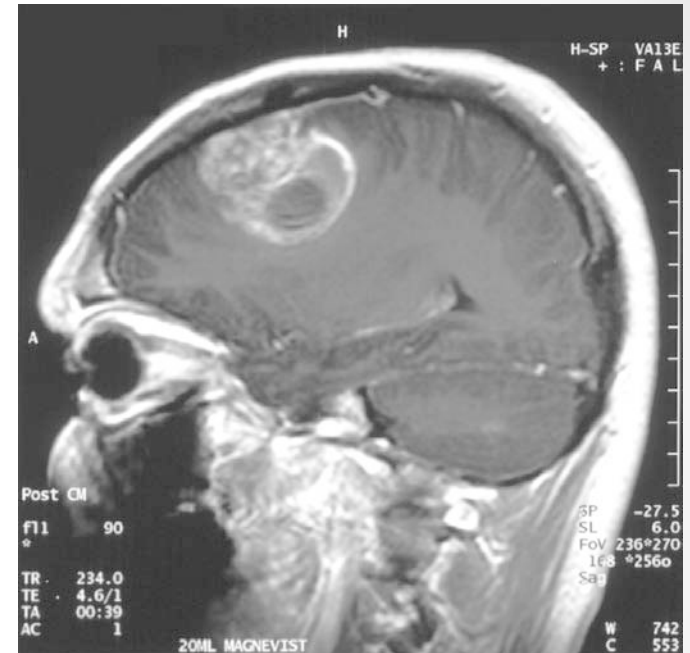
**Design a drug to target the protein created by this
mutation (normal cells lack the mutation and
should be unaffected)**



**Preclinical studies and clinical trials
new drugs to treat glioblastoma**

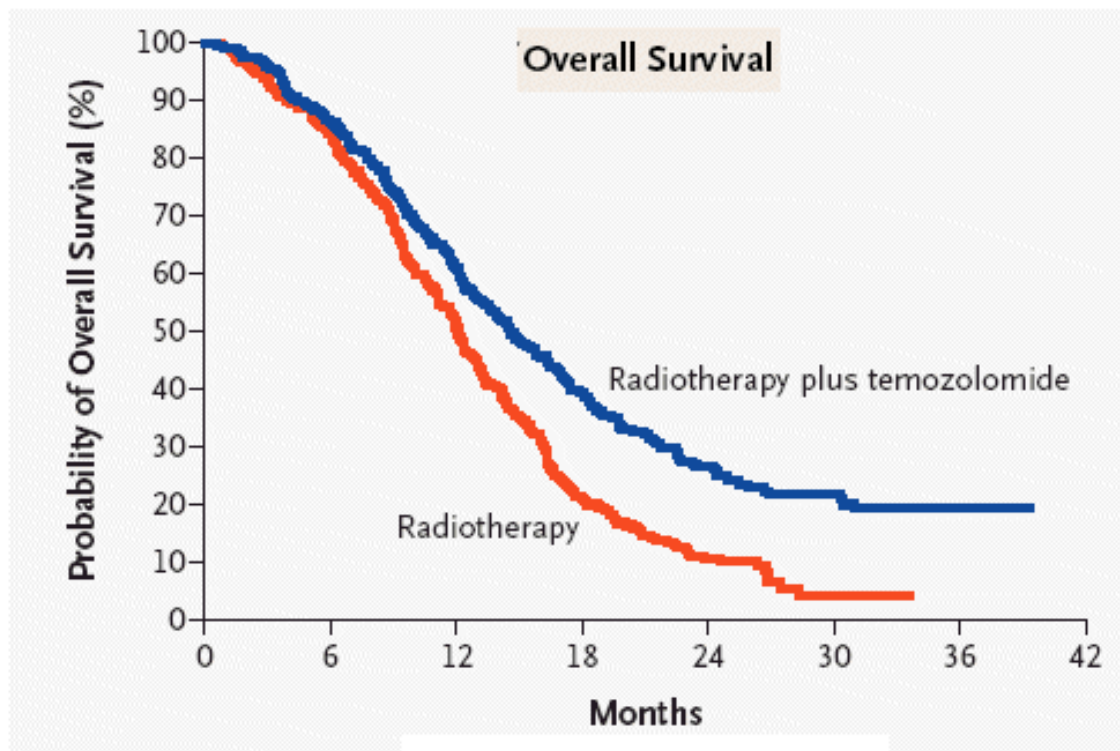
Glioblastoma

- Most common adult primary brain tumour
- Poor prognosis
- Standard treatment before 2005: Maximal surgical resection, radiation therapy, chemotherapy (survival benefit?)
- Urgent need for better treatment options to improve patient survival

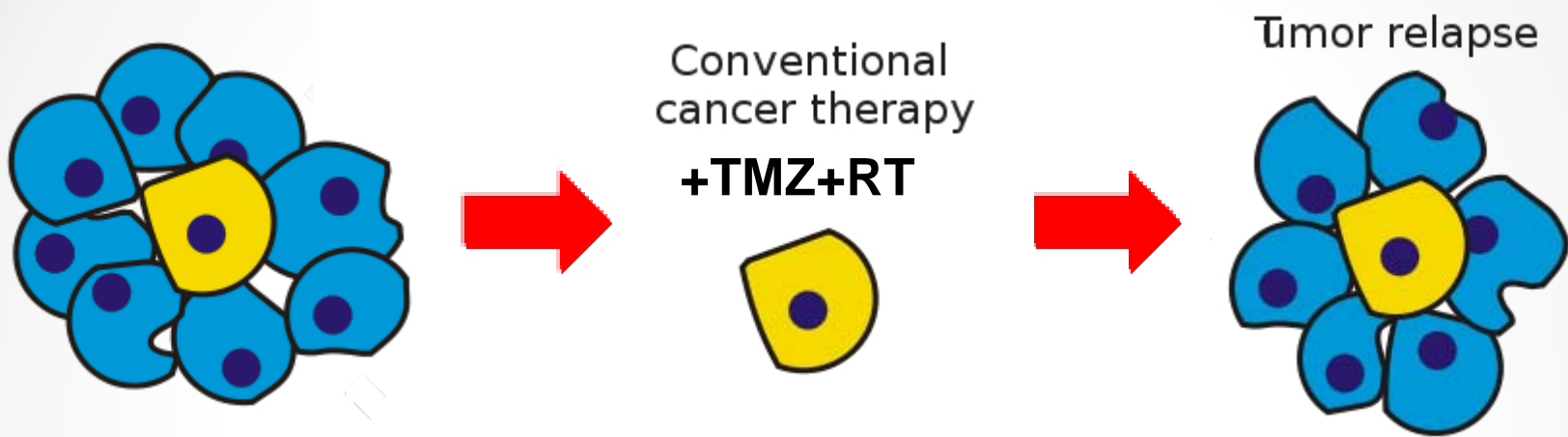


Glioblastoma in the temozolomide era

- Temozolomide (Temodar): oral alkylating chemotherapeutic
- Temozolomide + radiotherapy (**BLUE**): significantly improves survival in glioblastoma patients vs radiotherapy only (**RED**)



The problem of tumour relapse



Relapsed glioblastomas are extremely challenging to treat: median survival after recurrence may be as little as a few months (Brandes et al 2001).

Treatment of recurrent glioblastoma

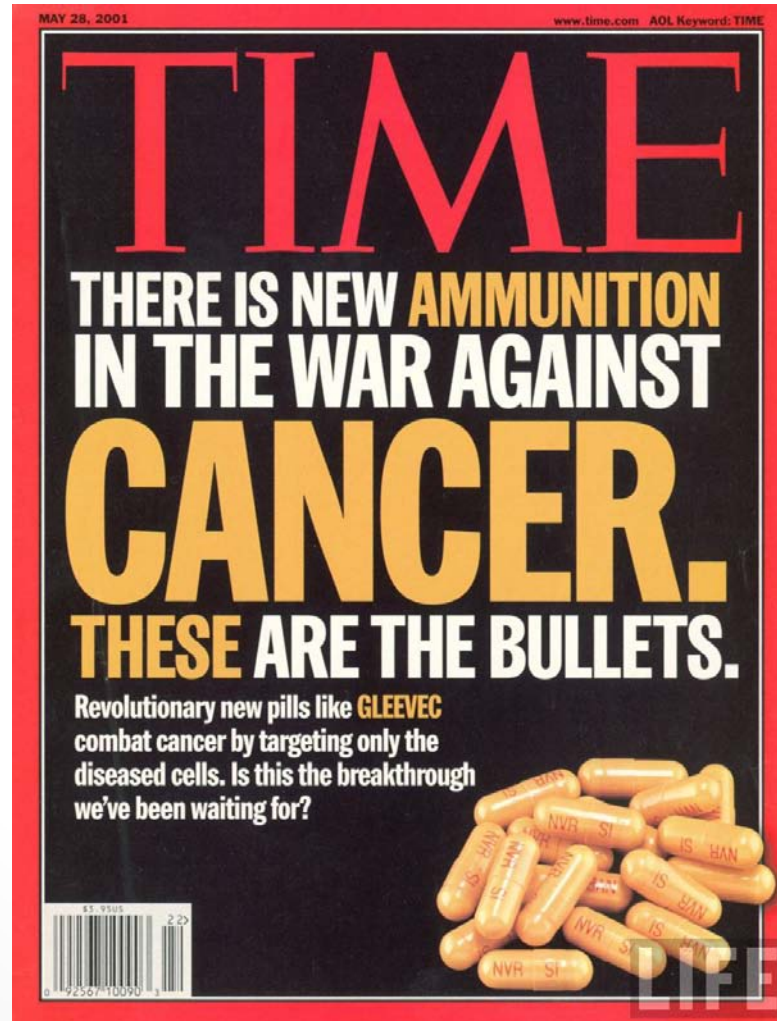
- **Poor prognosis, no standard treatment**
- **Rechallenge with TMZ, or change to an alternative TMZ dosing regimen (trials underway)**
- **Other chemotherapeutic agents trialled for recurrent glioblastoma... “Targeted agents”**

enzastaurin, anti-EGFRvIII antibodies, cilengitide, gefitinib, imatinib, irinotecan, bevacizumab, & more...

“Targeted cancer therapy”

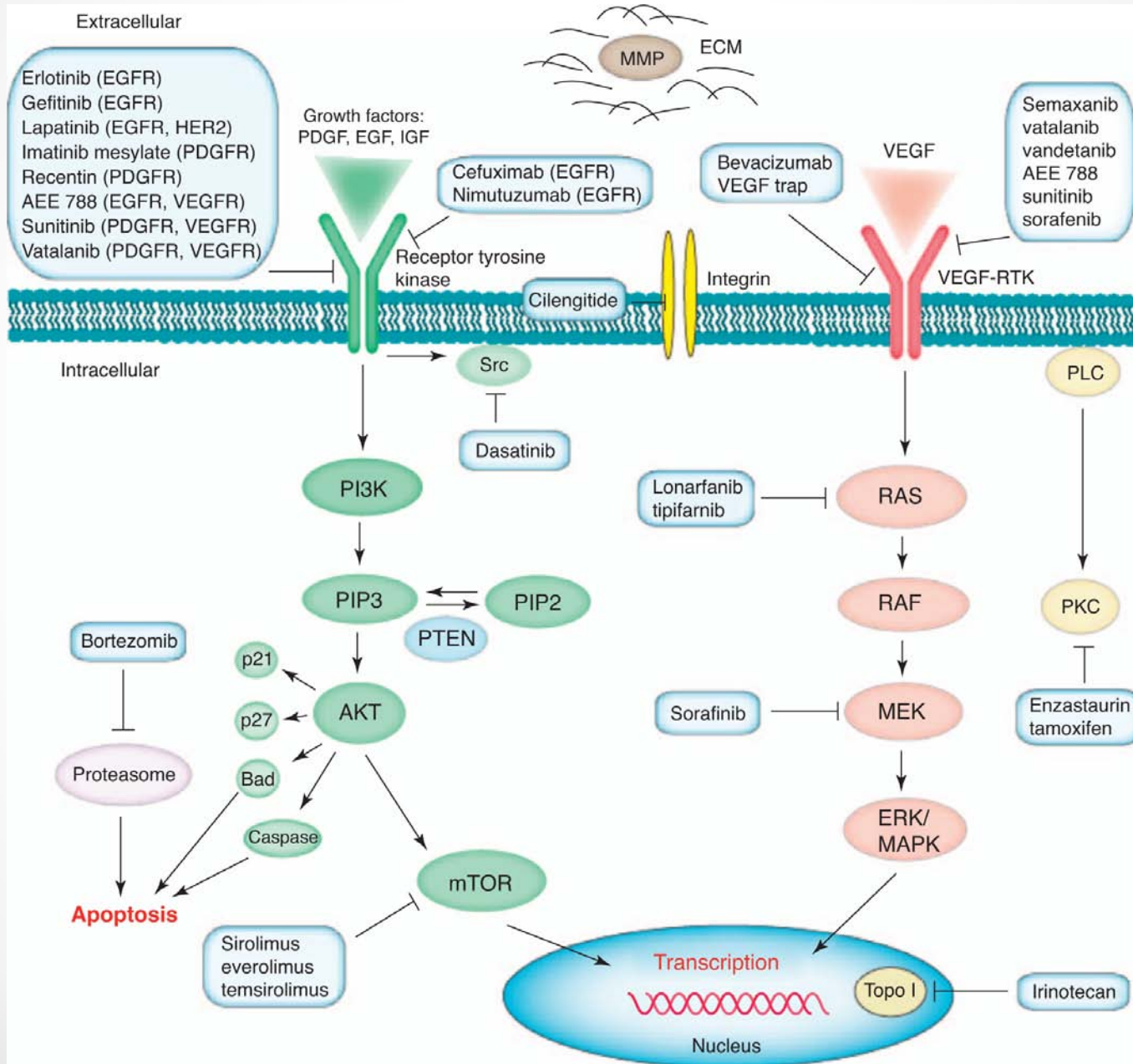
“Personalised medicine”

Gleevec & chronic myelogenous leukaemia (CML)



(TIME magazine,
May 2001)

Targeted therapies for recurrent glioblastoma

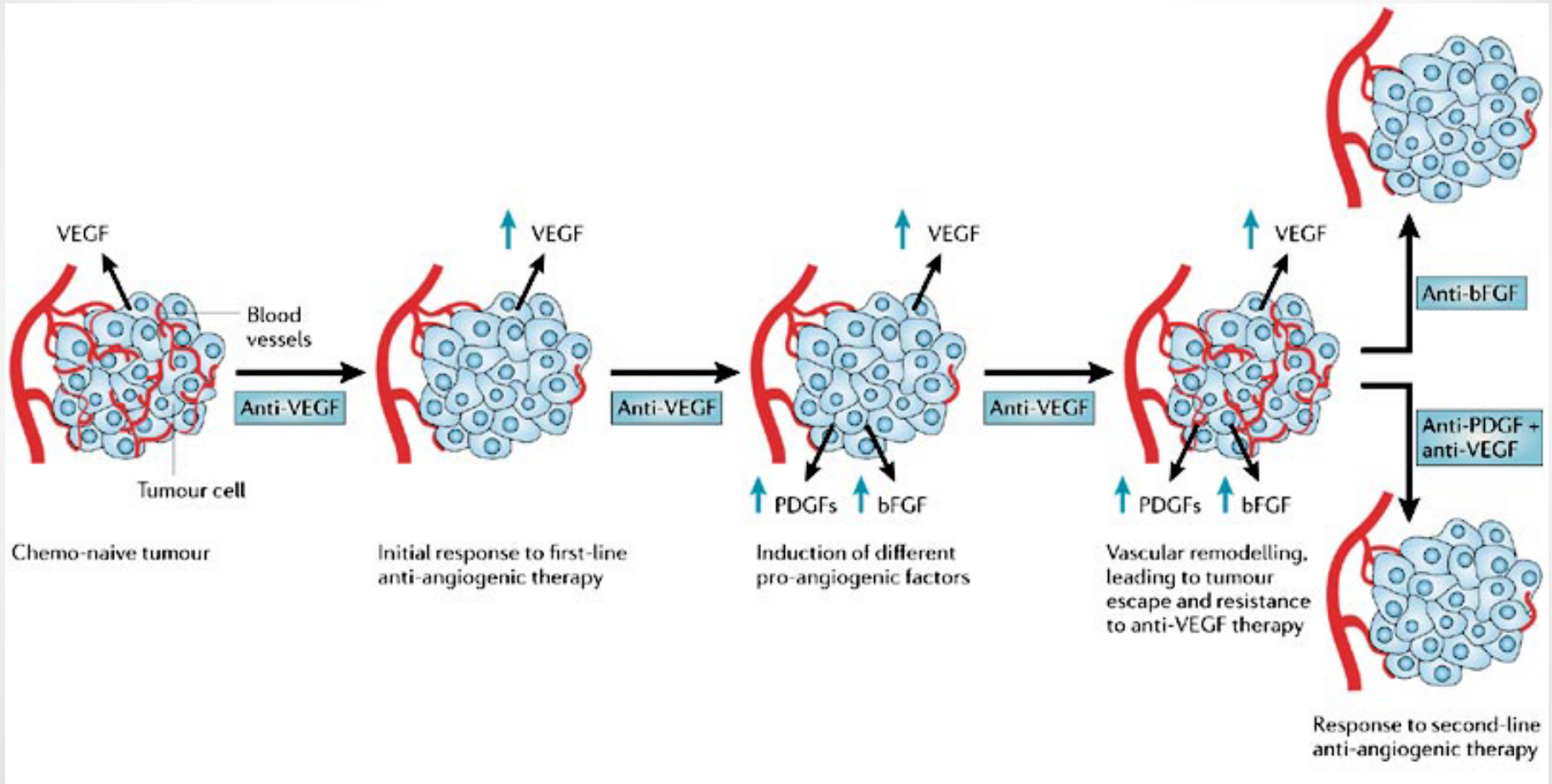


Bevacizumab (Avastin): anti-angiogenic therapy for recurrent glioblastoma

- **Bevacizumab (Avastin): humanised monoclonal antibody targeted against vascular endothelial growth factor (VEGF)**
- **High response rates in trials - proof of principle for targeted therapy in glioblastoma... survival benefit?**
- **Other anti-angiogenesis drugs are in clinical trials...**



Why does existing anti-angiogenesis therapy ultimately fail?



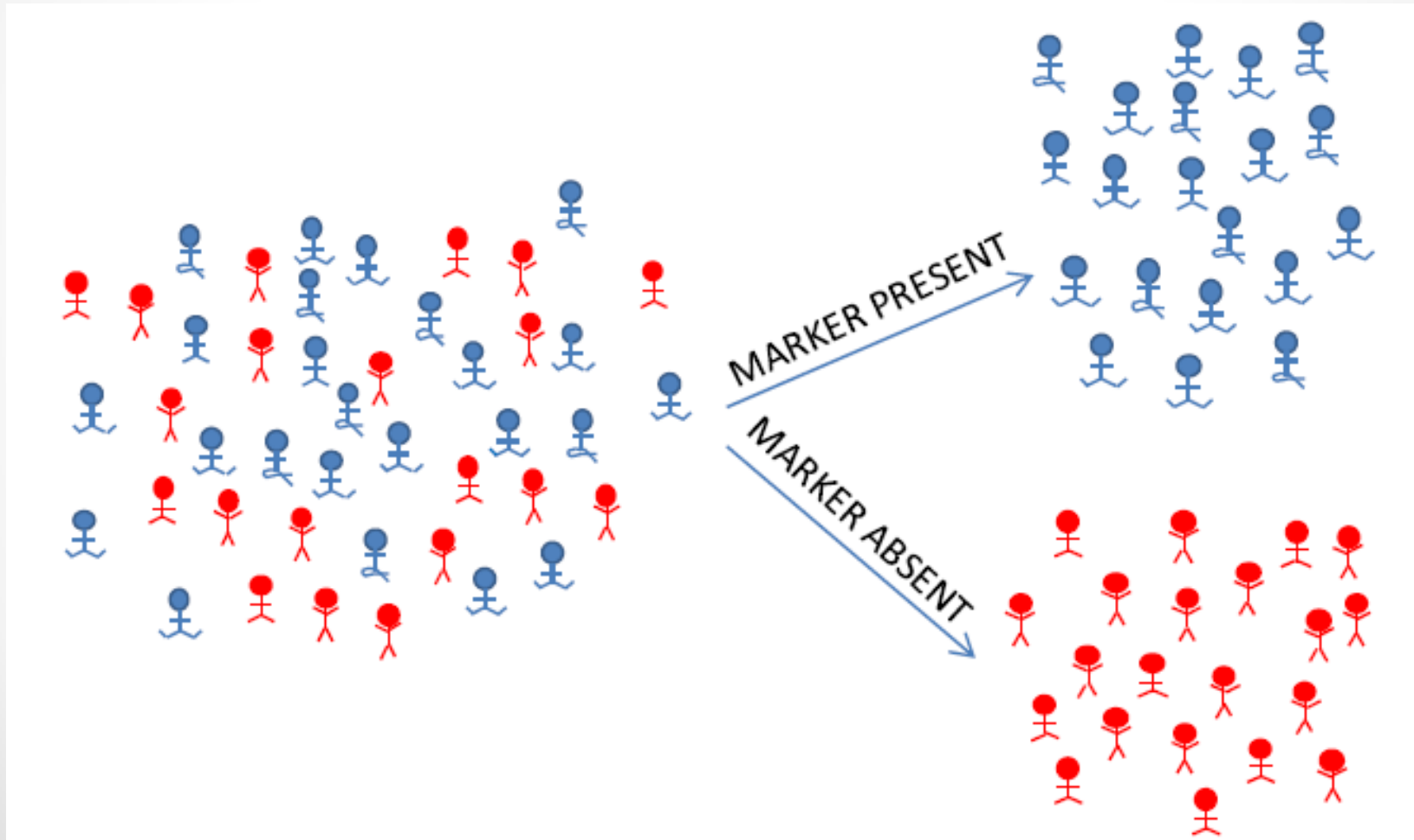
Target angiogenic factors other than VEGF!

How to improve the treatment of glioblastoma?

Find biomarkers of treatment response

- Treat patients likely to benefit most from a particular treatment**
- Avoid unnecessary toxicity in patients that fail to respond to the particular treatment**
- Reduce the healthcare cost associated with targeted therapy**
- Better understand drug resistance mechanisms**

Biomarkers may allow patients to be stratified into responders & non-responders



MGMT gene methylation dictates the response of gliomas to temozolomide

- Temozolomide: damages DNA, triggers tumour cell death
- Glioma cells express MGMT enzyme (repairs DNA) to different levels:

Unmethylated
MGMT gene



MGMT
protein 

Glioma cells express
MGMT, can repair damage caused
by temozolomide:
less tumour response

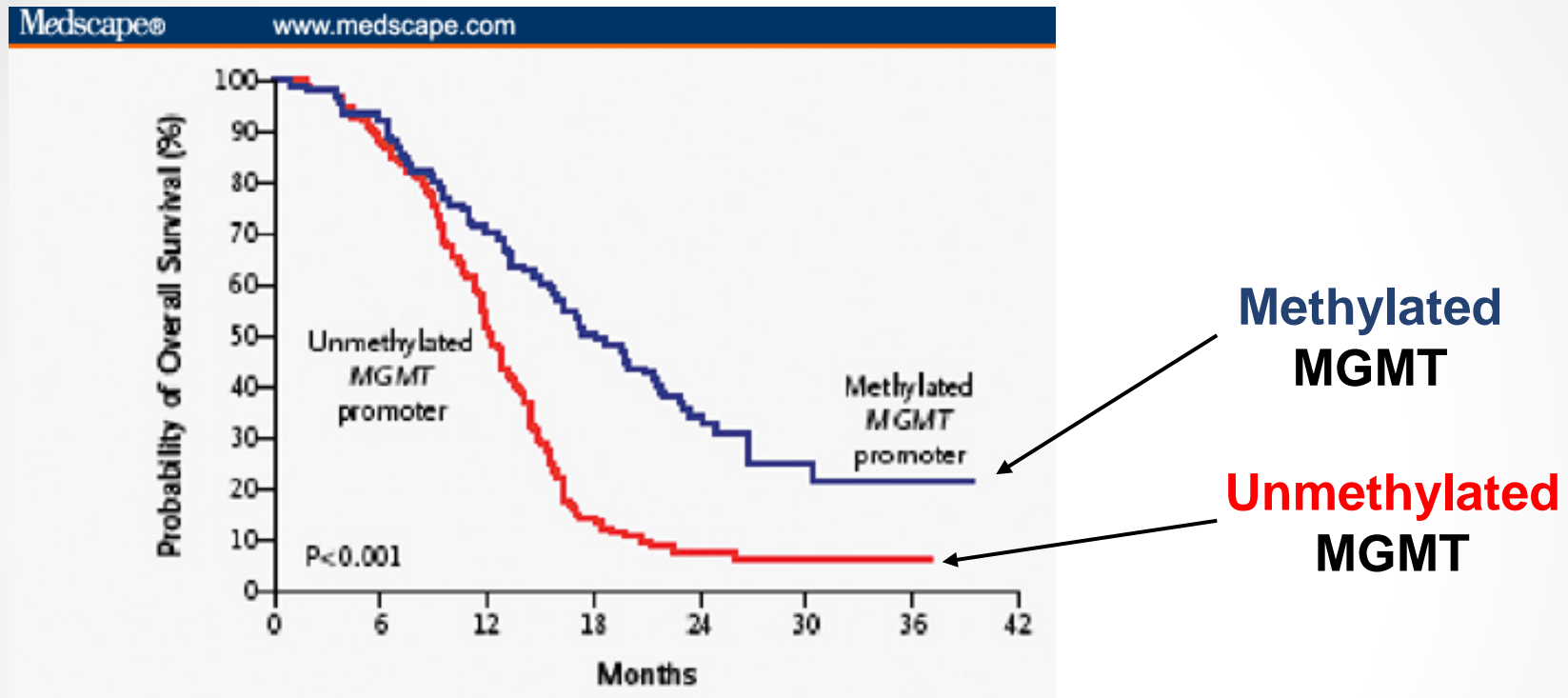
Methylated
MGMT gene



No MGMT protein

Glioma cells do not express
MGMT, can't repair damage caused by
temozolomide:
more tumour response

- **MGMT gene methylation (ie. level of MGMT enzyme in glioma cells) may predict tumour response to temozolomide**



- **MGMT methylation might determine response to radiotherapy (Wick et al 2009)**
- **Strategies to inhibit MGMT in glioma cells might increase efficacy of temozolomide or radiotherapy? (MGMT as a drug target?)**

While MGMT gene methylation may be used to predict glioblastoma response to temozolomide...

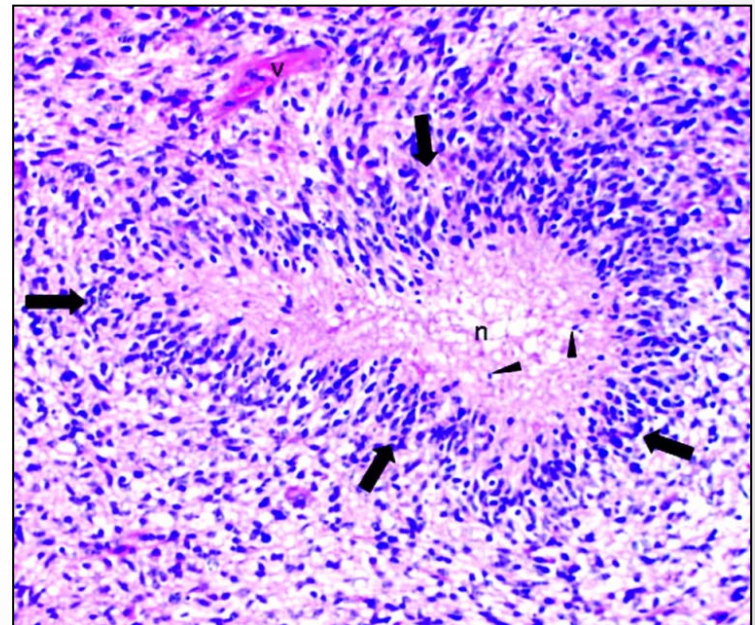
There is as yet no alternative treatment strategy available for patients with unmethylated MGMT gene (ie. high tumour MGMT enzyme expression)

Find new biomarkers and drug targets

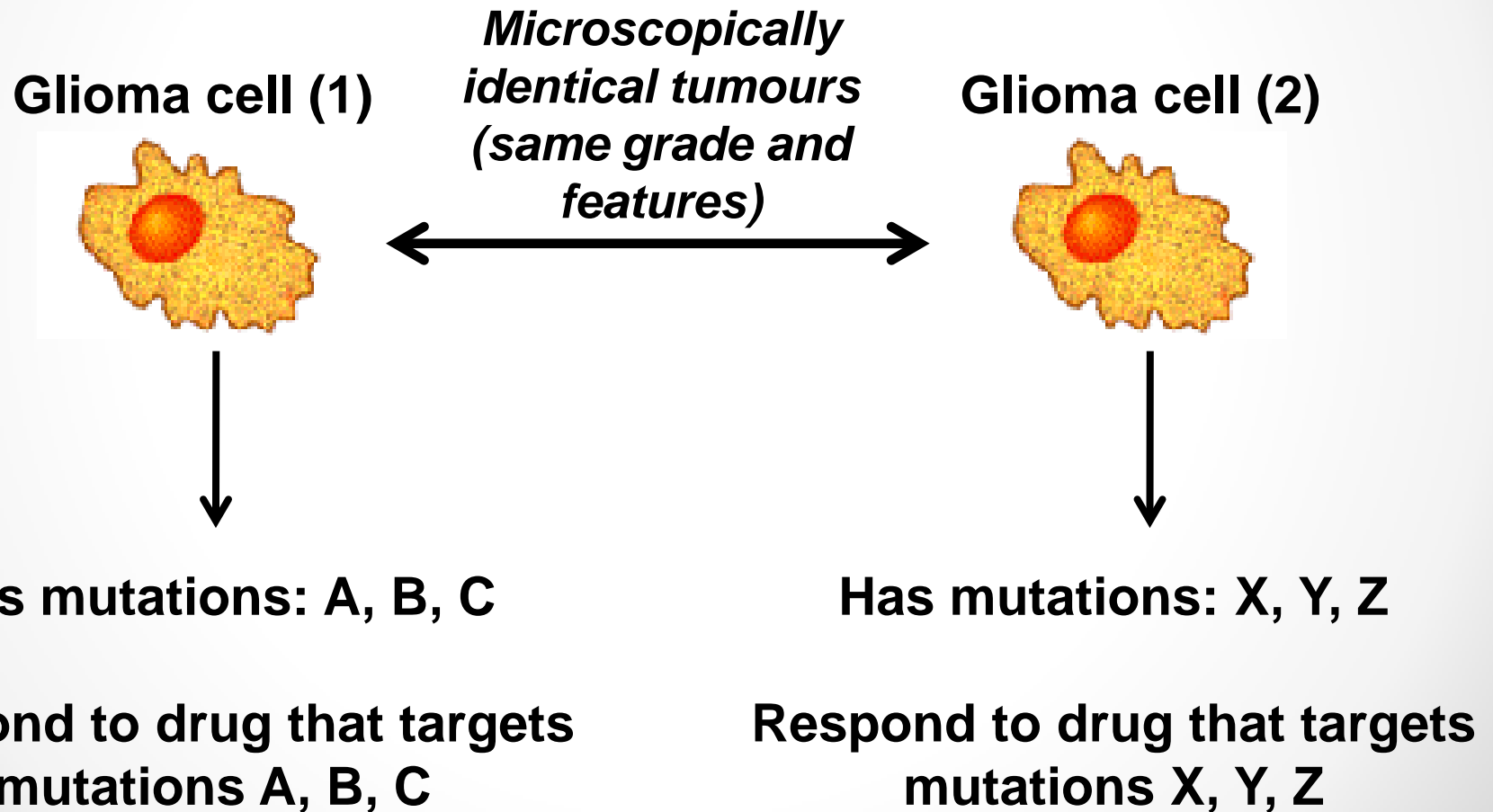
- Existing classification of gliomas is inadequate:

WHO grading (I-IV) based on *macroscopic & microscopic* features:

- Necrosis
- Atypia (nuclear)
- Mitosis
- Endothelial proliferation



Microscopic features do not detect functional differences between gliomas at the subcellular (genetic) level



Gliomas are different

Gliomas carry different mutations

**Gliomas carry different sets
(combinations) of mutations**

**Drug treatment must take relevant
mutations into account**

**A finer level of resolution is required to
better classify gliomas**

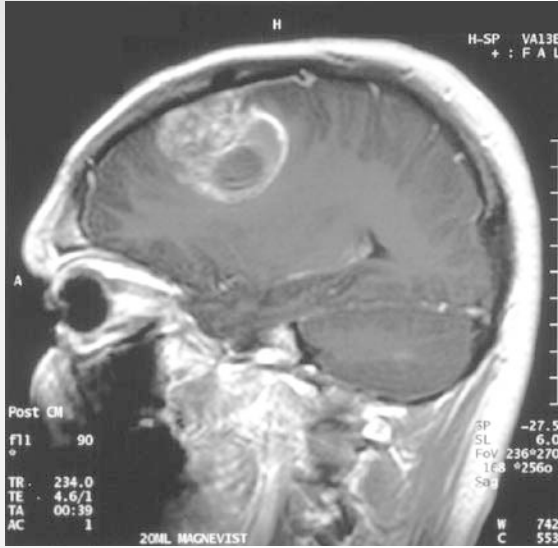
**(To catalogue individual mutations in
each glioma)**

The Cancer Genome Atlas



*Understanding genomics
to improve cancer care*

(2008)



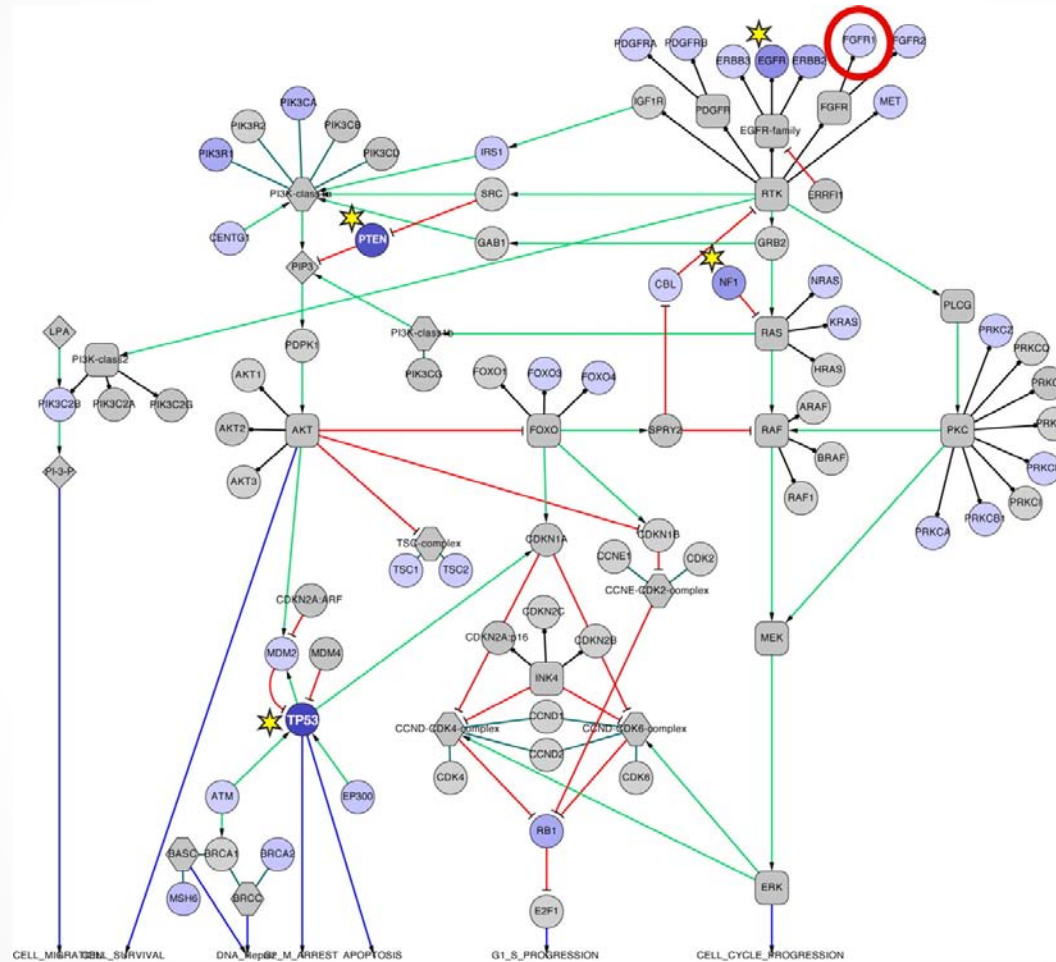
Tumour samples

Gene analysis



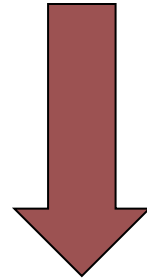
**Gene signatures and DNA mutations for
a large number of glioblastoma samples**

New mutations in glioblastoma have been identified

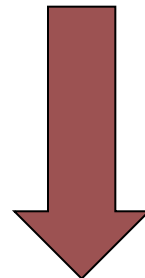


Targets for new treatments?

**Understand what has “gone wrong”
in glioblastoma cells
(what mutations “drive” their growth?)**

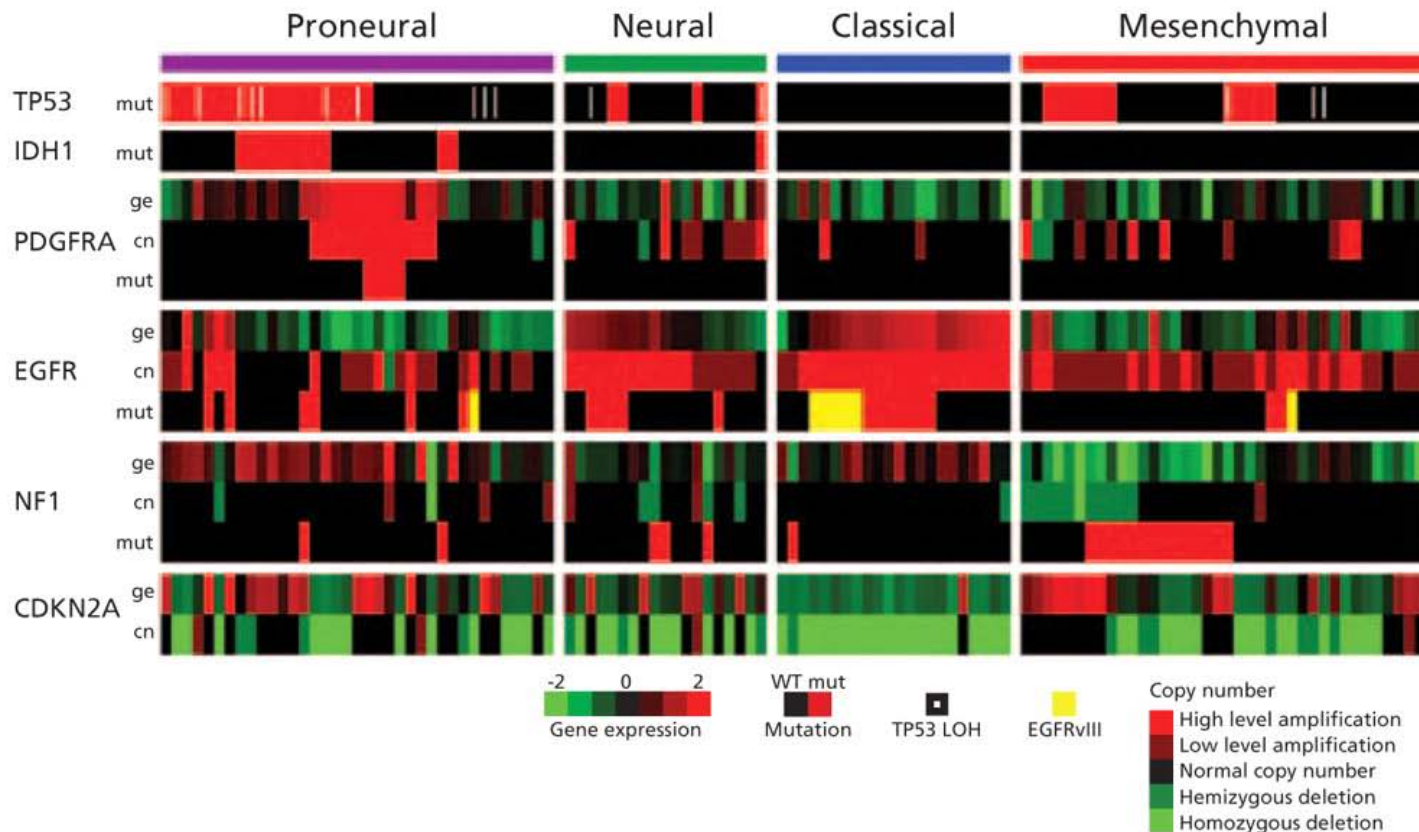


**Design a drug to target the protein created by this
mutation (normal cells lack the mutation and
should be unaffected)**



**Preclinical studies and clinical trials
new drugs to treat glioblastoma**

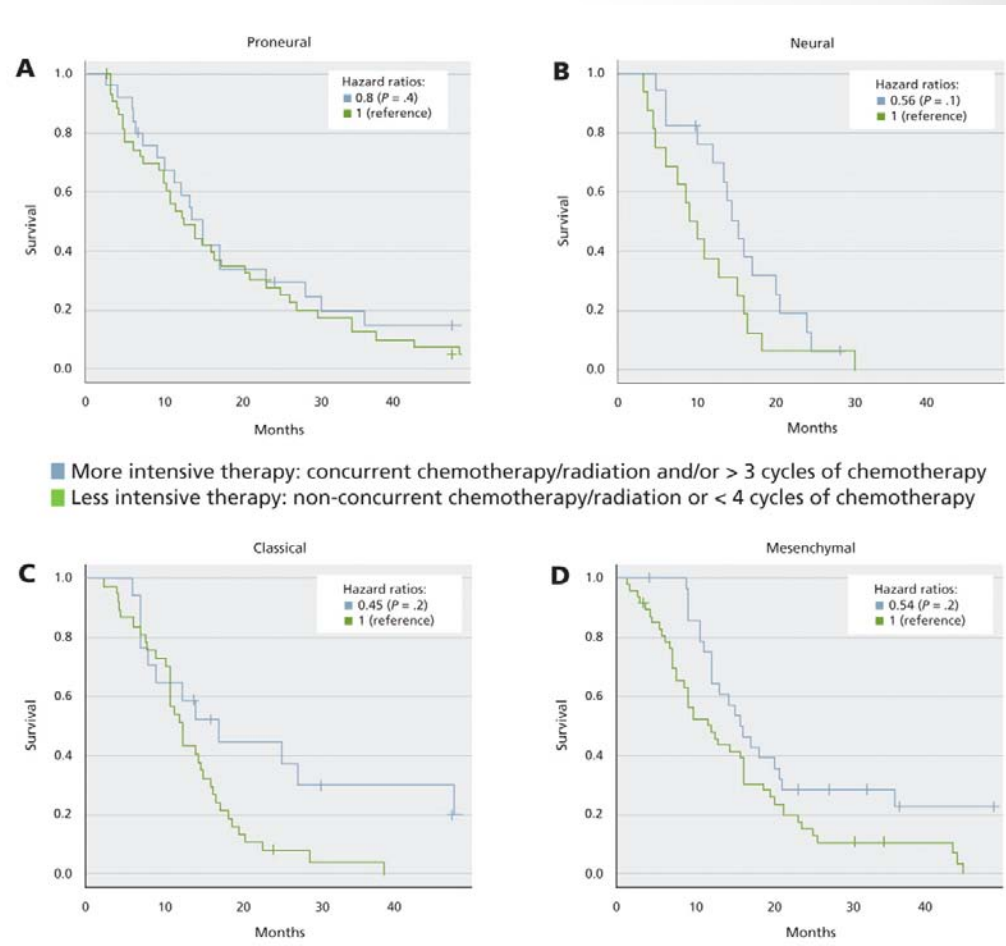
Glioblastomas have been subdivided into molecular subtypes



Molecular subtype determines outcome and treatment response

- **Mesenchymal subtype: associated with genes involved in angiogenesis and cell invasion: more responsive to bevacizumab (Avastin)**

- **Correlation between subtypes and chemotherapy response? Temozolomide may be less effective in proneural subtype? (Verhaak & Valk 2010)**



Development of new treatments for glioblastoma

1. Identify drug targets (The Cancer Genome Atlas, etc)

PI3K-AKT and RAS pathways, p53 pathway, RB and cell cycle pathways, IDH1/IDH2 metabolic pathways, DNA repair defects, tumour hypoxia, tumour invasion, etc.

Development of new treatments for glioblastoma

2. Perform drug screening assays

A compound library (>millions) is tested in the lab to assess for impact on target protein.

Results confirmed in cell-based assays.

Development of new treatments for glioblastoma

3. Preclinical animal models

Glioblastoma cell lines implanted into mice/rats.

Subcutaneous vs intracranial tumours.

Test drug candidates.

Development of new treatments for glioblastoma

4. Human clinical trials

Phase I, II, III clinical trials.

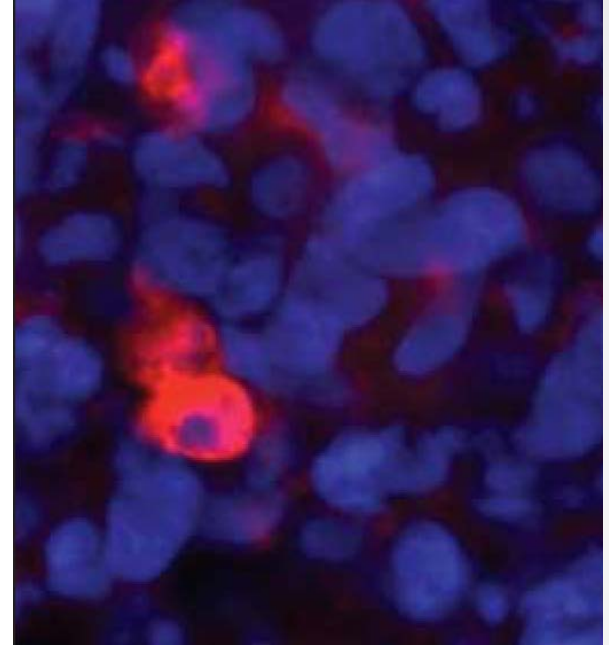
Prior to Phase I (first in-human study): mechanism of action, pharmacodynamics, pharmacokinetics, toxicology must be determined.

High cost and extensive regulatory procedures.

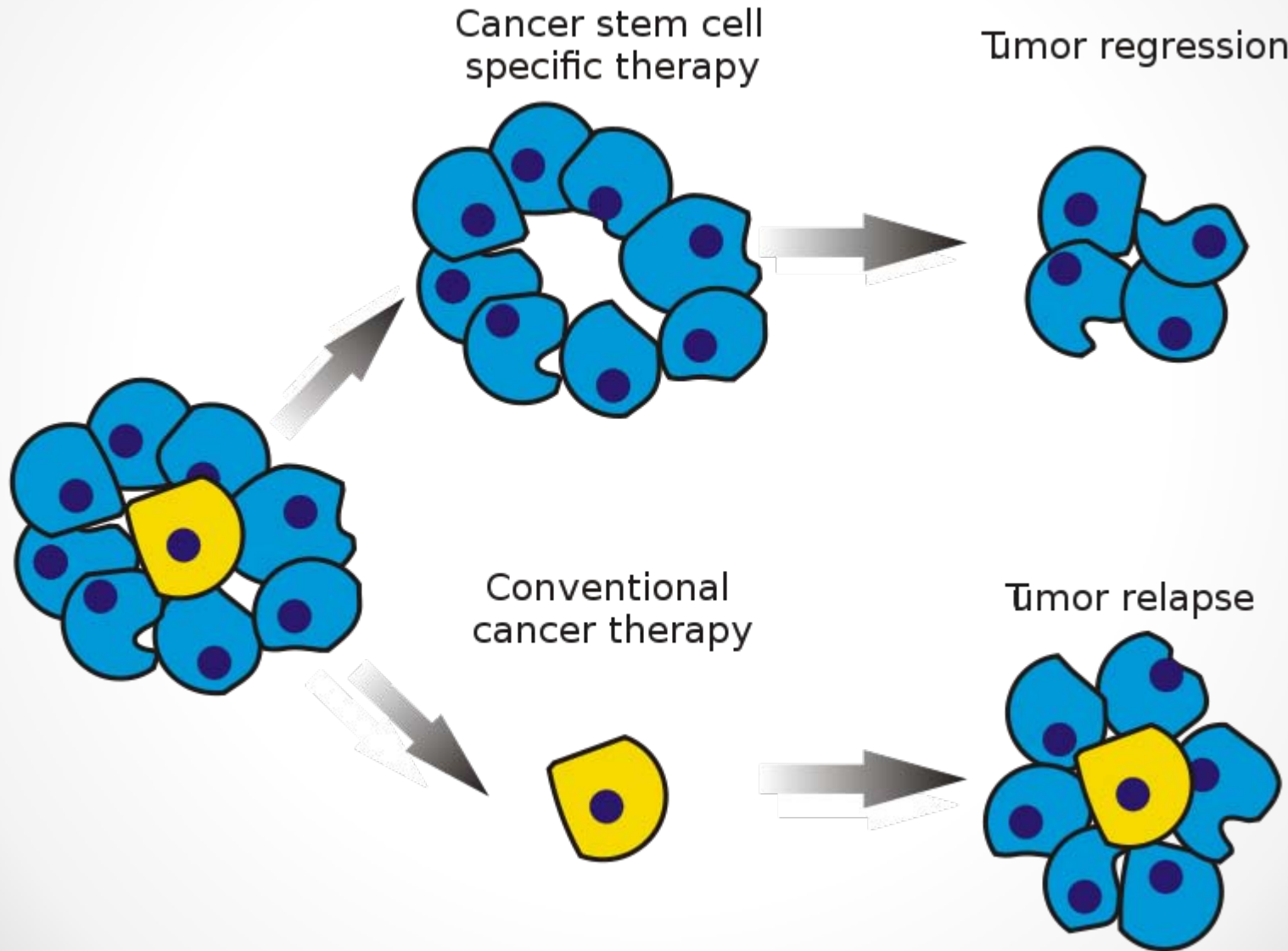
Identification of biomarkers for response.

Glioblastoma stem cells

- **Growing evidence that a subset of glioblastoma tumour cells have stem cell properties (eg. unlimited self-renewal)**
- **Stem cell markers have been used to isolate glioblastoma stem cells from tumours**
- **Glioblastoma stem cells are highly resistant to temozolomide and radiation (& may drive treatment resistance?)**



Targeting glioblastoma stem cells



Main points

- **A new generation of anti-glioblastoma drugs in preclinical and clinical development are targeted against specific mutated proteins that drive glioblastoma growth (“Targeted therapy”).**
- **Improving treatment of glioblastoma requires use of predictive biomarkers, discovery of new biomarkers and new drug targets, and development and testing of new drugs against these targets.**
- **Targeting glioblastoma stem cells may be an effective strategy to treat the disease.**

Questions?

“New and novel treatments... may offer additional ways to control glioblastoma.”

**Eric Wong (Brain Tumour Centre and Neuro-Oncology Unit,
Beth Israel Deaconess Medical Centre, Boston, USA)
- in a 2011 review of treatment advances for glioblastoma.**