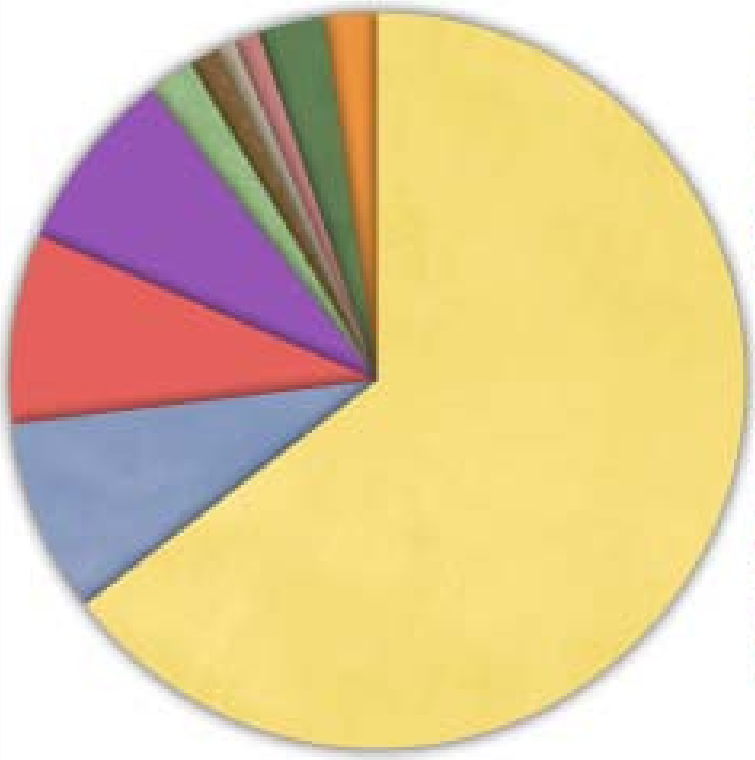
Lecture 13

Gene therapy for cancer

16th January 2012

Indications Addressed by Gene Therapy Clinical Trials



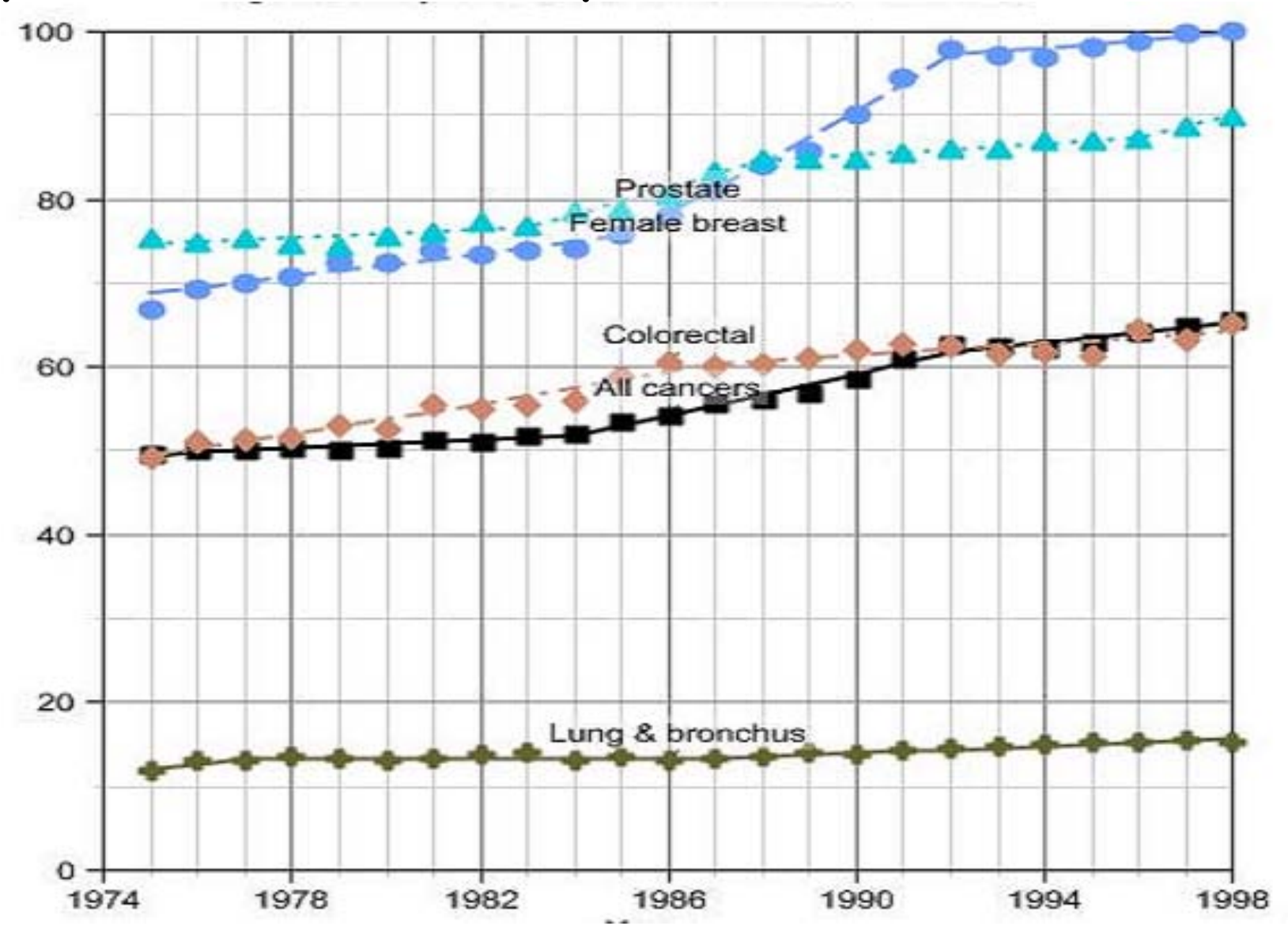
- Cancer diseases 64.6% (n=1107)
- Cardiovascular diseases 8.5% (n=146)
- Monogenic diseases 8.3% (n=143)
- Infectious diseases 8.1% (n=138)
- Neurological diseases 2% (n=35)
- Ocular diseases 1.3% (n=23)
- Inflammatory diseases 0.8% (n=13)
- Other diseases 1.1% (n=19)
- Gene marking 2.9% (n=50)
- Healthy volunteers 2.3% (n=40)

www.wiley.co.uk/genmed/clinical

Aim of cancer gene therapy

Effective killing of most (if not all) cancer cells without serious damage to normal cells and tissues

Why there is a need for cancer gene therapy?
- 5-years survival rates of patients with different cancer

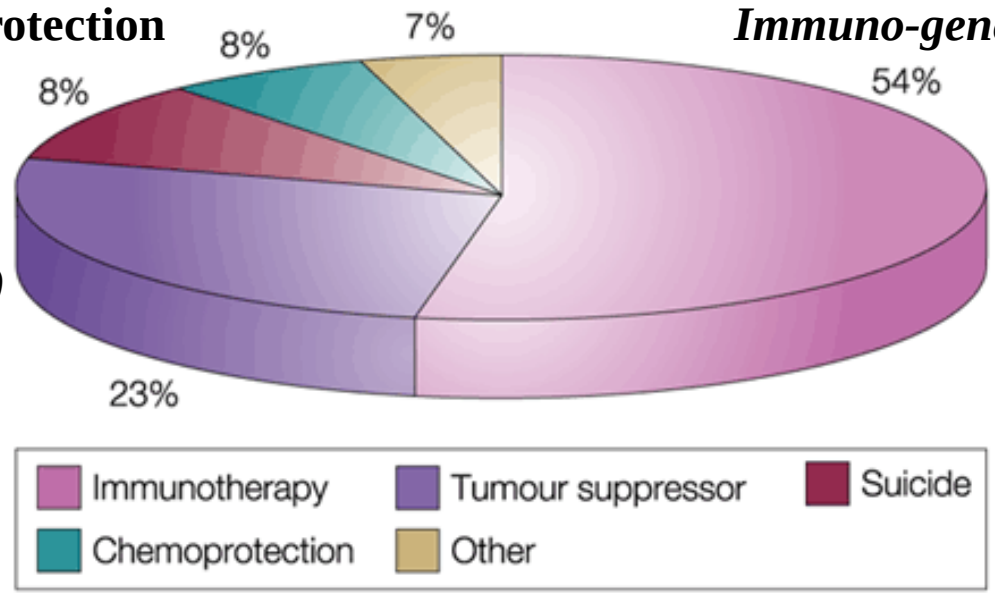


chemoprotection

Immuno-gene therapy

Suicide gene therapy

Tumor suppressor (p53)



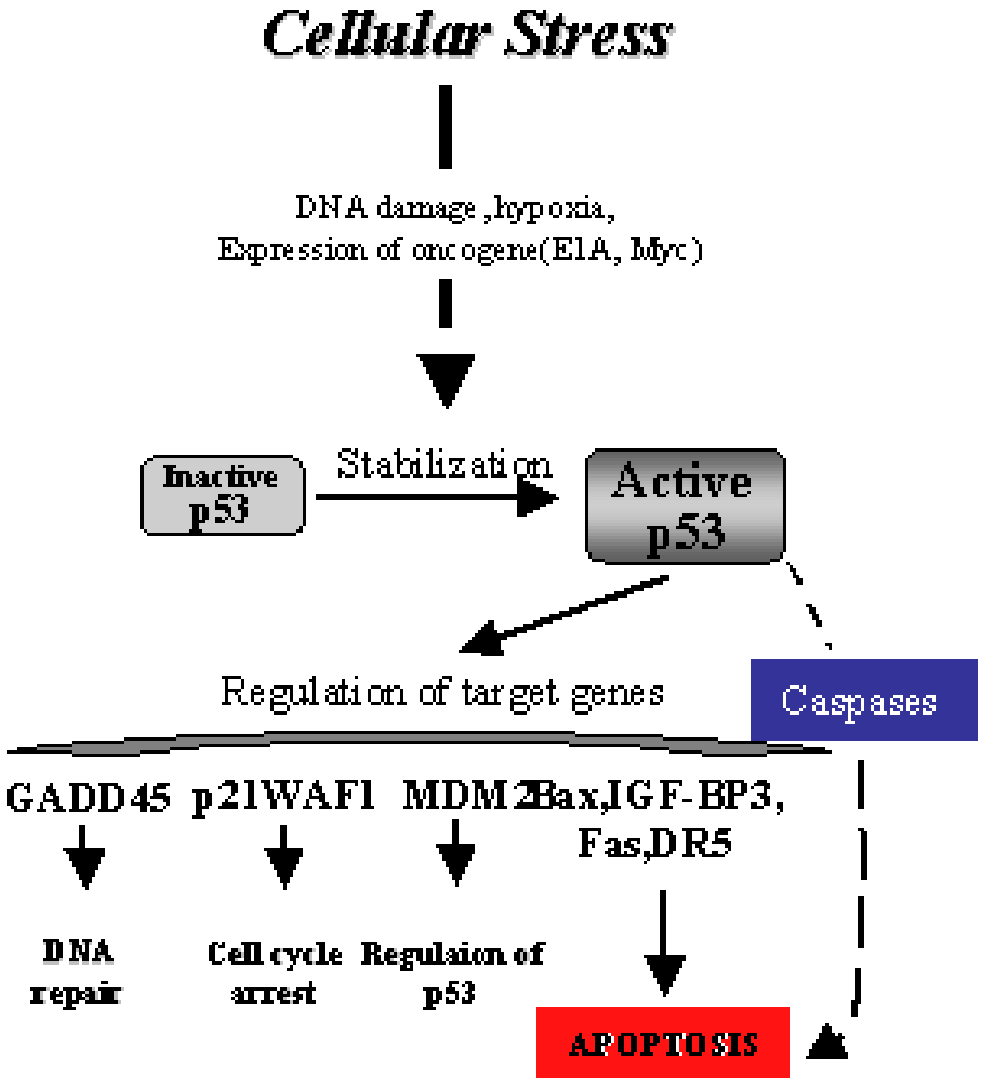
Nature Reviews | Cancer

Figure 1 | **Cancer gene therapy and immunotherapy trials currently listed as open by the US Recombinant Advisory Committee.** Over half of all gene-therapy-based protocols in the United States (113 currently open) are aimed at boosting the immune response to tumour antigens. Trials in melanoma alone account for 54% of immunotherapy trials. Delivery of the tumour-suppressor gene *TP53* accounts for the next largest group, followed by suicide gene delivery, in which viral vectors deliver enzymes that activate prodrugs to toxic products that kill tumour cells and their neighbours. Most of these use herpes simplex virus thymidine kinase (HSV-tk), which activates the prodrug ganciclovir. Chemoprotection is an indirect approach in which bone marrow cells are infected with viruses that protect them from the toxic effects of chemotherapy, by expressing drug-resistance genes.

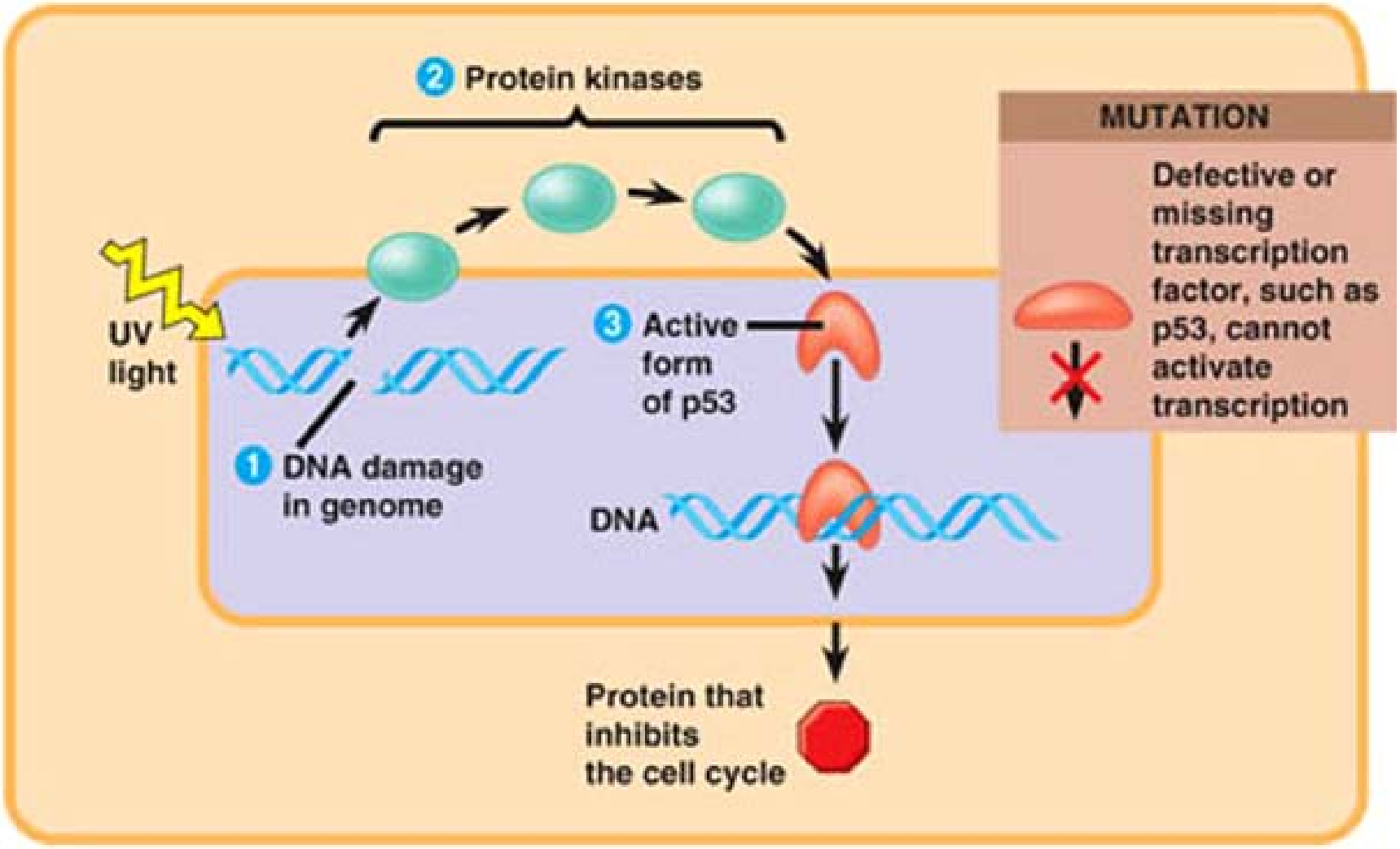
Cancer gene therapy

1. Direct attack on tumor cells
    - **a) transfer of tumor suppressor gene**
    - b) inhibition of oncogenes
    - c) suicide genes
    - d) oncolytic viruses (replication-competent viruses)
2. Harnessing immune response to tumor antigens
3. Chemoprotection
4. Anti-angiogenic therapy

p53 – the guardian of the genome

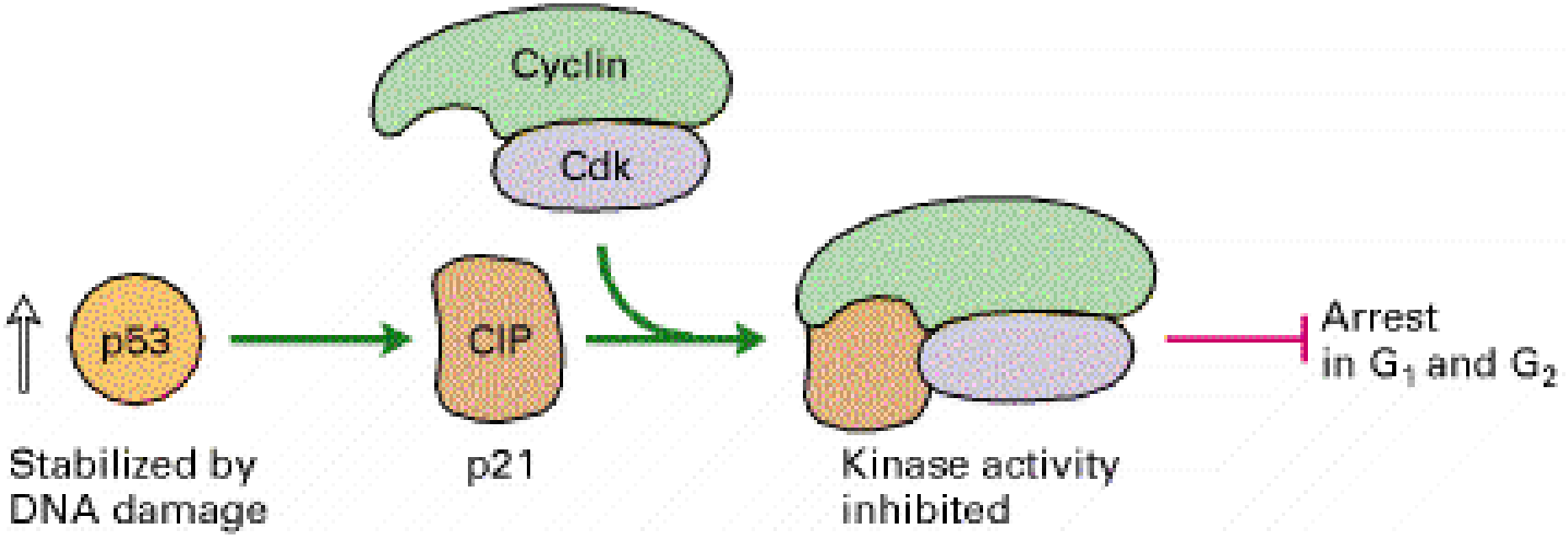


p53 – a guardian of the genome

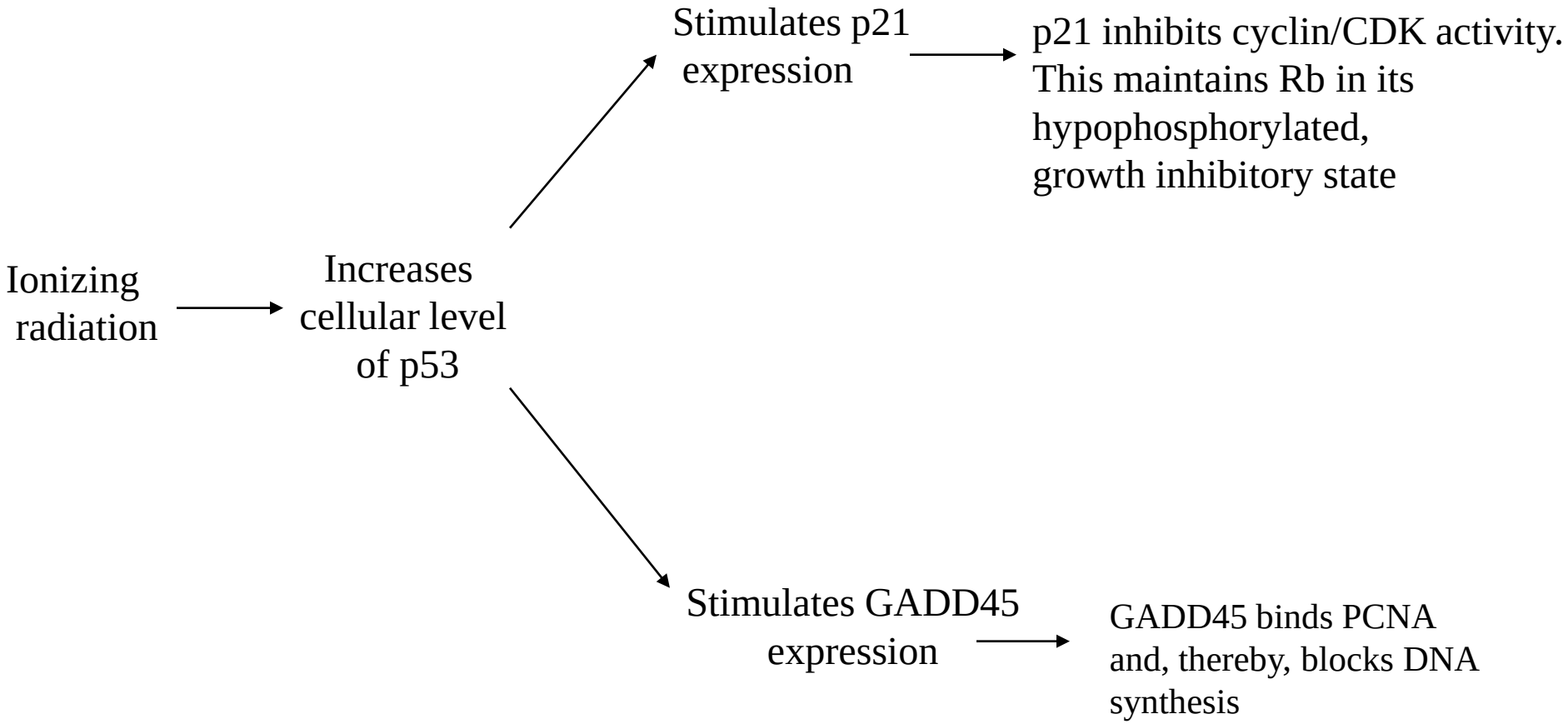


p53-induced cell-cycle arrest in response to DNA damage.

The normally unstable p53 protein is stabilized by damaged DNA, so its concentration increases. Acting as a transcription factor, p53 induces expression of $p21^{CIP}$, a cyclin-kinase inhibitor that inhibits all Cdk1-, Cdk2-, Cdk4-, and Cdk6-cyclin complexes. Binding of $p21^{CIP}$ to these Cdk-cyclin complexes leads to cell cycle arrest in G_1 and G_2



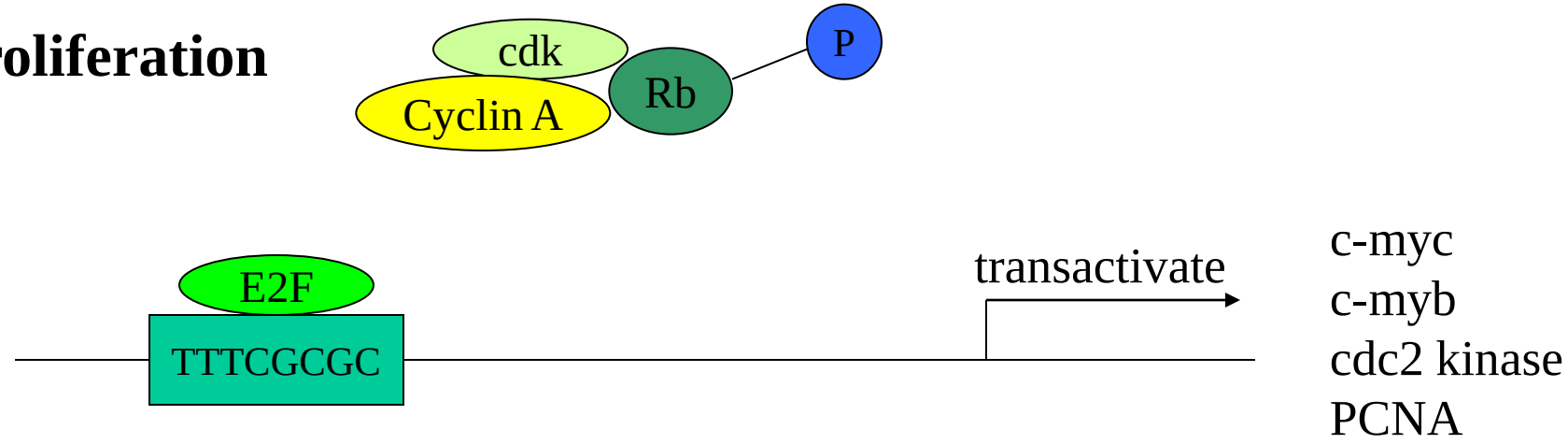
p53 and cell arrest



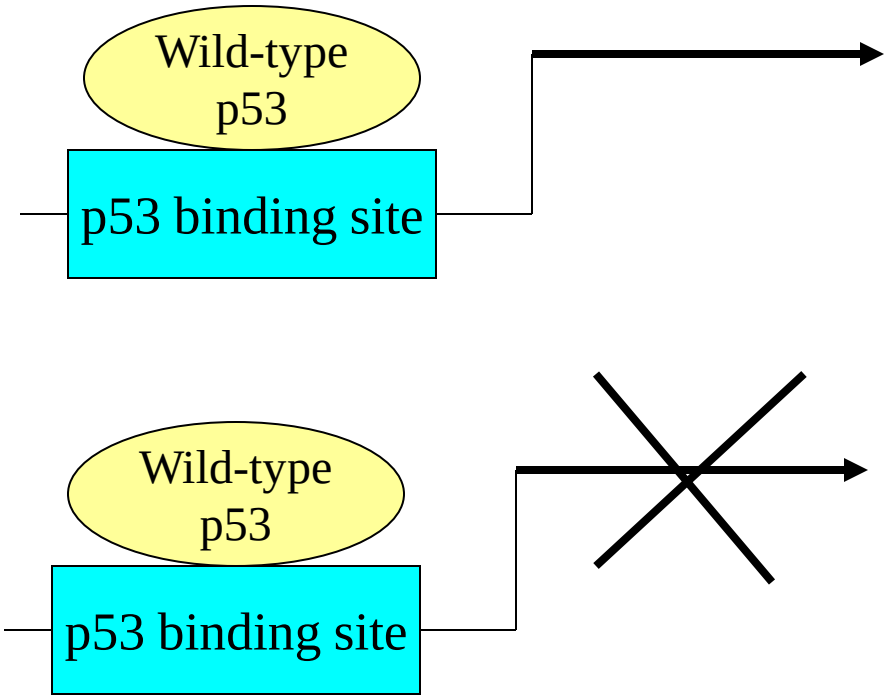
Transcription factor E2F

Quiescence

Proliferation



Mann MJ, Mol Med. Today 2000



The ability of p53 to stimulate transcription is essential for tumor suppression

p53 and gene therapy of cancer

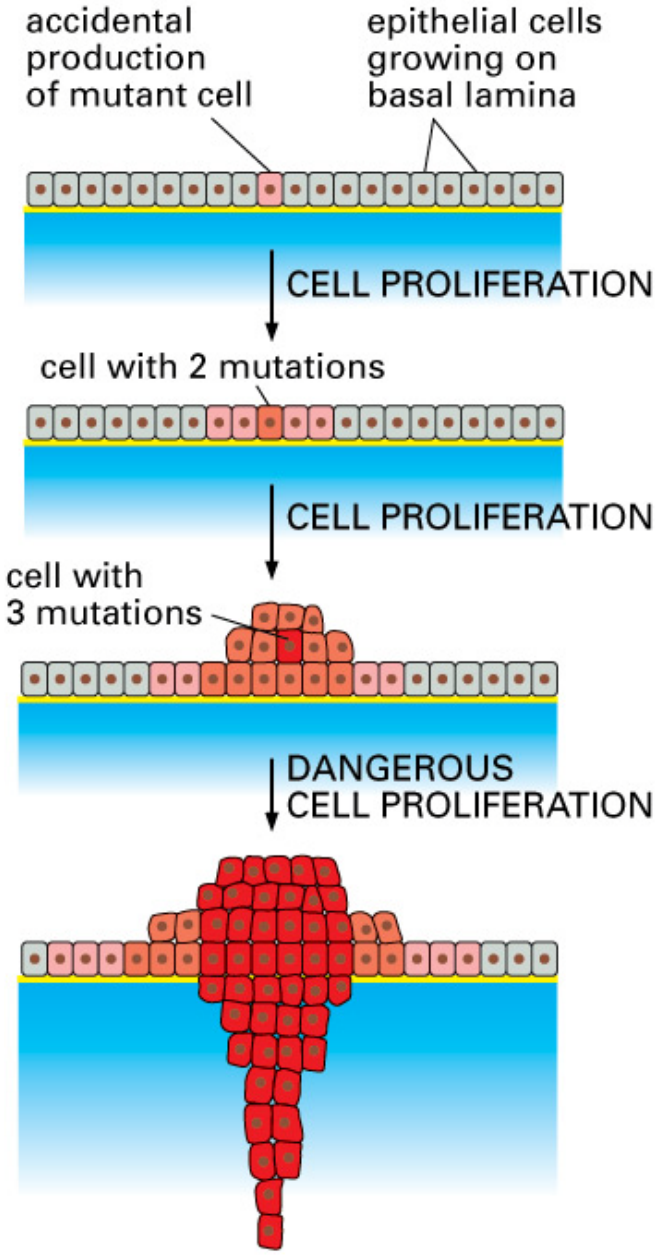


Figure 23–11. Molecular Biology of the Cell, 4th Edition.

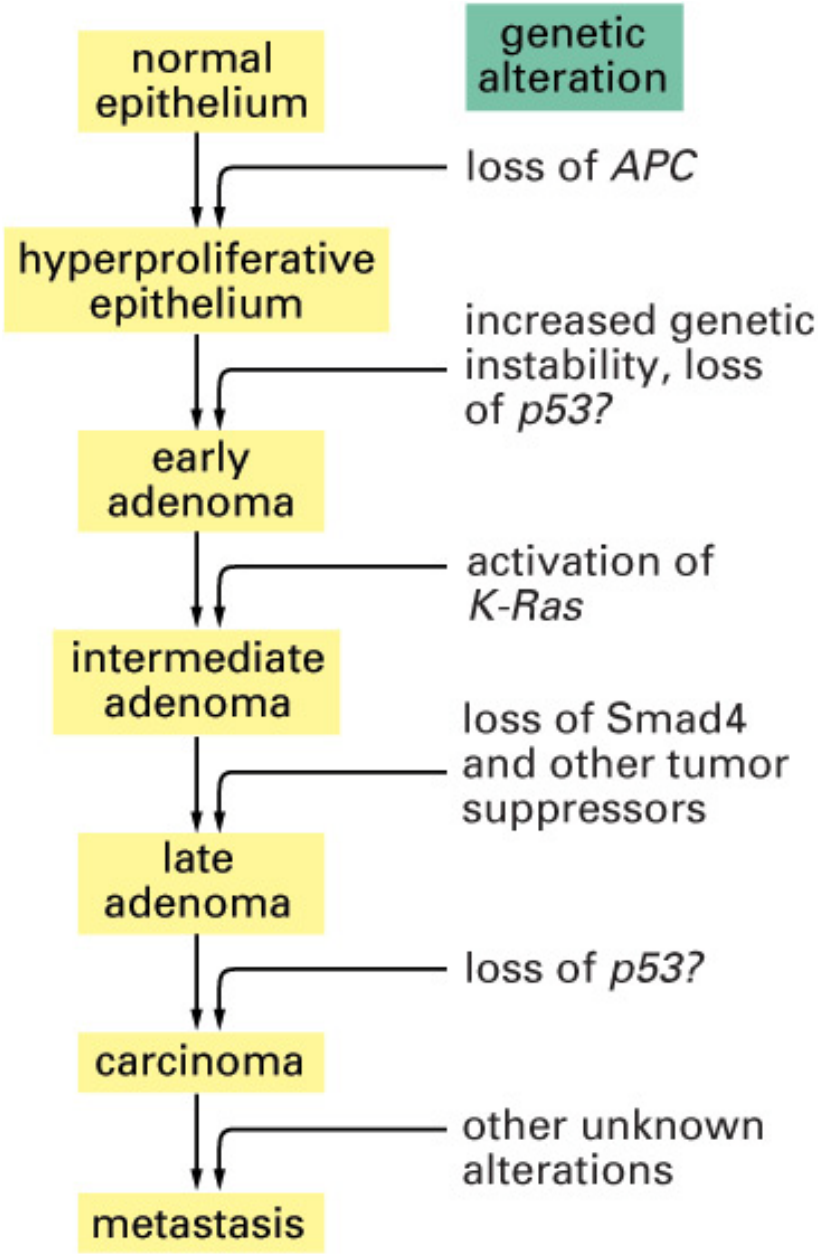
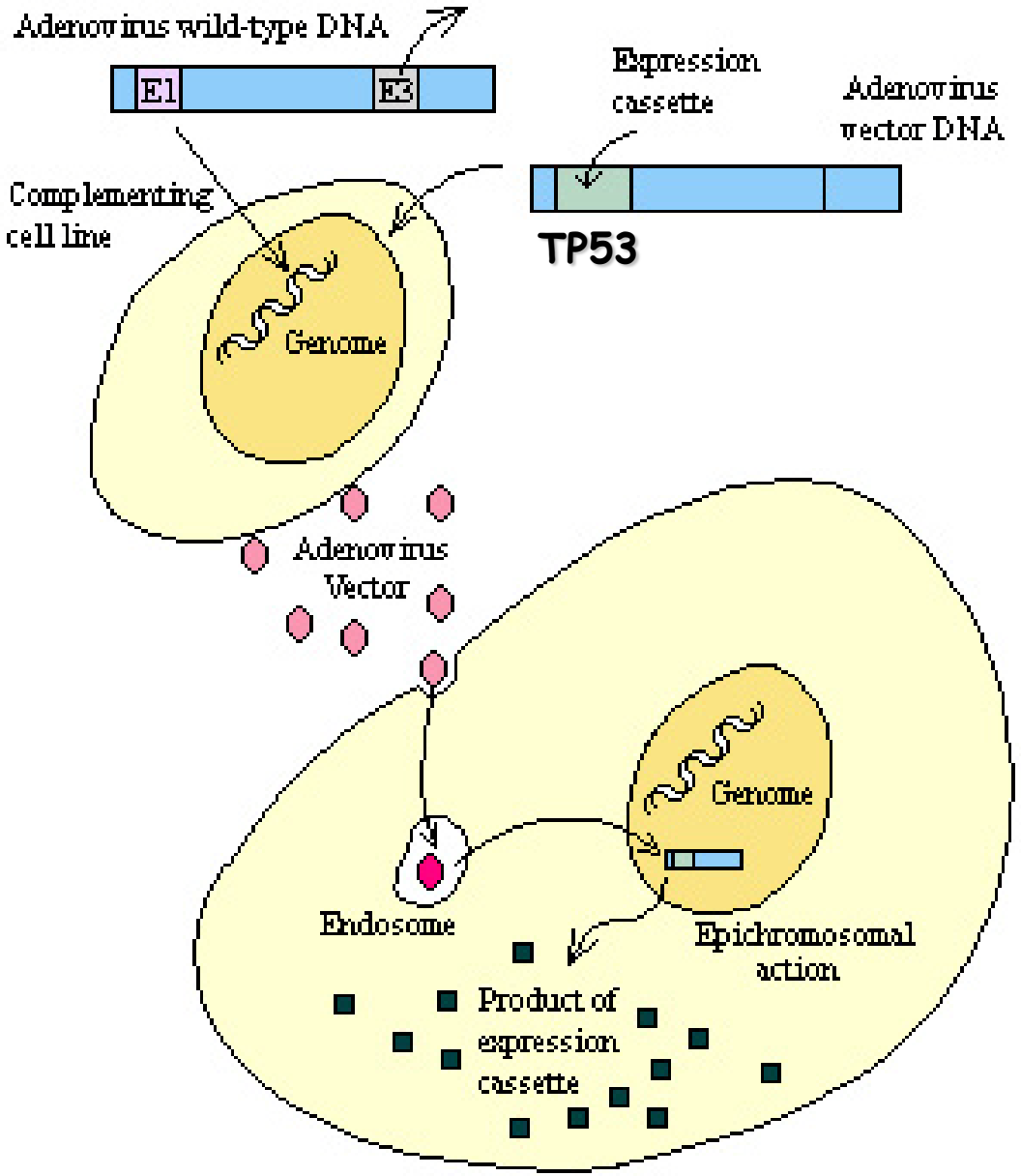


Figure 23–41. Molecular Biology of the Cell, 4th Edition.

Adenoviral delivery of p53 gene

DMB



Adenoviral vector
With correct p53 gene

↓

Cancer cell

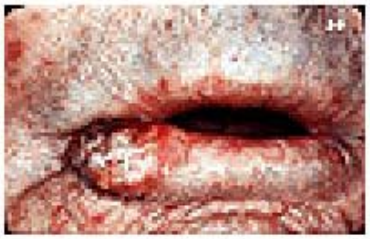
↓

expression of p53 in cancer cell

↓

apoptosis

Head and Neck Cancer



Overview

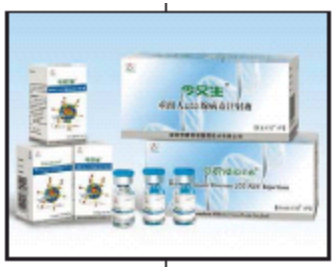
Head and neck cancer is the term given to a variety of malignant tumors that develop in the

- oral cavity (mouth);
- pharynx (throat);
- paranasal sinuses (small hollow spaces around the nose lined with cells that secrete mucus);
- nasal cavity (airway just behind the nose);
- larynx ("Adam's apple" or voice box); and
- salivary glands (parotid, submanidular, sublingual glands that secrete saliva).

Many authorities also include skin tumors of the face and neck and tumors of the cervical lymph nodes.

Excluding superficial skin cancers, but including cancer of the larynx and thyroid, it is conservatively estimated that about 60,000 people are diagnosed with head and neck cancer annually - about 5% of all cancers diagnosed in the United States. There are more than half a million survivors of oral, head, and neck cancer living in the United States today.

First officially registered therapeutic nucleic acid



Gendicine (SiBiono GeneTech, Chiny*)*

Adenoviral vector with a correct p53 gene

Efficient in patients with head and neck cancers

Claimed to be 3 x more efficient than radiotherapy alone

Registered on 16. X. 2003, after 5 years of clinical trials

Advexin – adenoviral vector expressing p53 gene

effective in patients with head and neck cancer

Alfredo and Elena Gonzalvo enjoyed visiting relatives recently in the Philippines.

Research nurse supervisor Marcelo Dolormente helps Bernis Teaters celebrate her fifth anniversary after gene therapy.

Examples of the most advanced clinical trials of cancer gene therapy

Table 1 Biotech firms with gene therapy products for cancer in phase 2 or later of clinical development

Company or research institute	Indication	Delivered gene	Vector	Phase of clinical development
Shenzhen SiBiono Gene Technologies (Shenzhen, China)	HNSCC	Tumor protein p53	Adenovirus	Approved
Shanghai Sunway Biotech (Shanghai, China)	HNSCC	HAdv5 oncolytic virus	Adenovirus	Phase 3
AnGes MG (Osaka, Japan)	Arteriosclerosis obliterans	Hepatocyte growth factor	Plasmid	Phase2
GenVec, Inc. (Gaithersburg, MD, USA)	Pancreatic, esophageal and rectal cancers	Human tumor necrosis factor-?	Adenovirus	Phase 2
Introgen (Austin, TX, USA)	Head and neck, lung, breast, esophageal, ovarian, bladder, brain, prostate and bronchoalveolar cancers	Tumor protein p53	Adenovirus	Phases 1–3
Transgene (Strasbourg, France)	Cervical cancer	Human papilloma virus type 16 E6 and E7 antigens and interleukin 2	Vaccinia virus	Phase 2
Transgene (Strasbourg, France)	Breast, lung, prostate and renal cancers	Human mucin 1 antigen and interleukin 2	Vaccinia virus	Phase 2

Nature Biotechnology, January 2004

ADVEXIN®

p53 tumor suppressor therapy

ADVEXIN therapy combines the p53 tumor suppressor with a non-replicating, non-integrating adenoviral delivery system we have developed and extensively tested. The p53 gene is one of the most potent members of a group of naturally-occurring tumor suppressors, which act to kill cancer cells, arrest cancer cell growth and protect cells from becoming cancerous. Introgen's clinical trial strategy for ADVEXIN is to test it in a variety of life-threatening cancers for which there are no effective treatments. Introgen is seeking to register ADVEXIN for the treatment of head and neck cancer and Li-Fraumeni Syndrome. Additional late stage clinical trials in breast and lung cancers will enable Introgen to add follow-on indications.

ADVEXIN® -- Clinically advanced, late-stage oncology product development program. Phase I through Phase 3 trials currently ongoing.

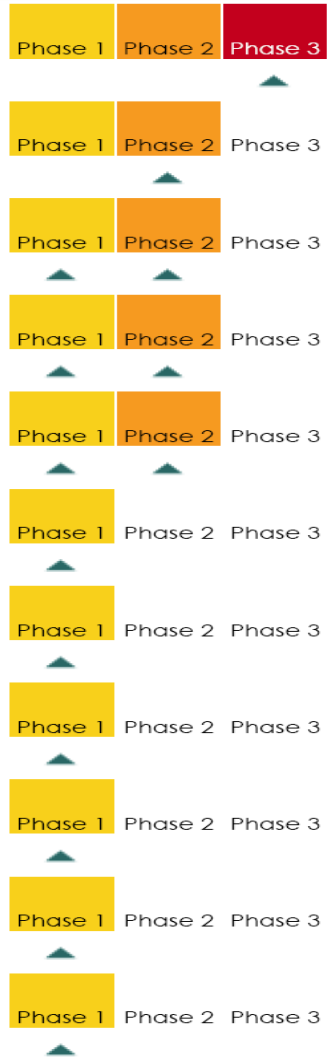
FDA designated Fast Track Drug Product Development program

FDA and EMEA designated Orphan Drug status for ADVEXIN® in head and neck cancer.

ADVEXIN® therapy well tolerated and clinically active.

ADVEXIN® Clinical Trials**

Cancer Type	Status
Head and Neck (both monotherapy and combined with chemotherapy)	Phase 1, Phase 2, Phase 3
Non-Small Cell Lung (combined with radiation therapy)	Phase 1, Phase 2, Phase 3
Breast (combined with chemotherapy)	Phase 1, Phase 2, Phase 3
Perioperative (and surgery)	Phase 1, Phase 2, Phase 3
Esophageal	Phase 1, Phase 2, Phase 3
Prostate	* Phase 1, Phase 2, Phase 3
Intravenous Administration	Phase 1, Phase 2, Phase 3
Ovarian	* Phase 1, Phase 2, Phase 3
Bladder	* Phase 1, Phase 2, Phase 3
Bronchoalveolar	* Phase 1, Phase 2, Phase 3
Brain (glioblastoma)	* Phase 1, Phase 2, Phase 3



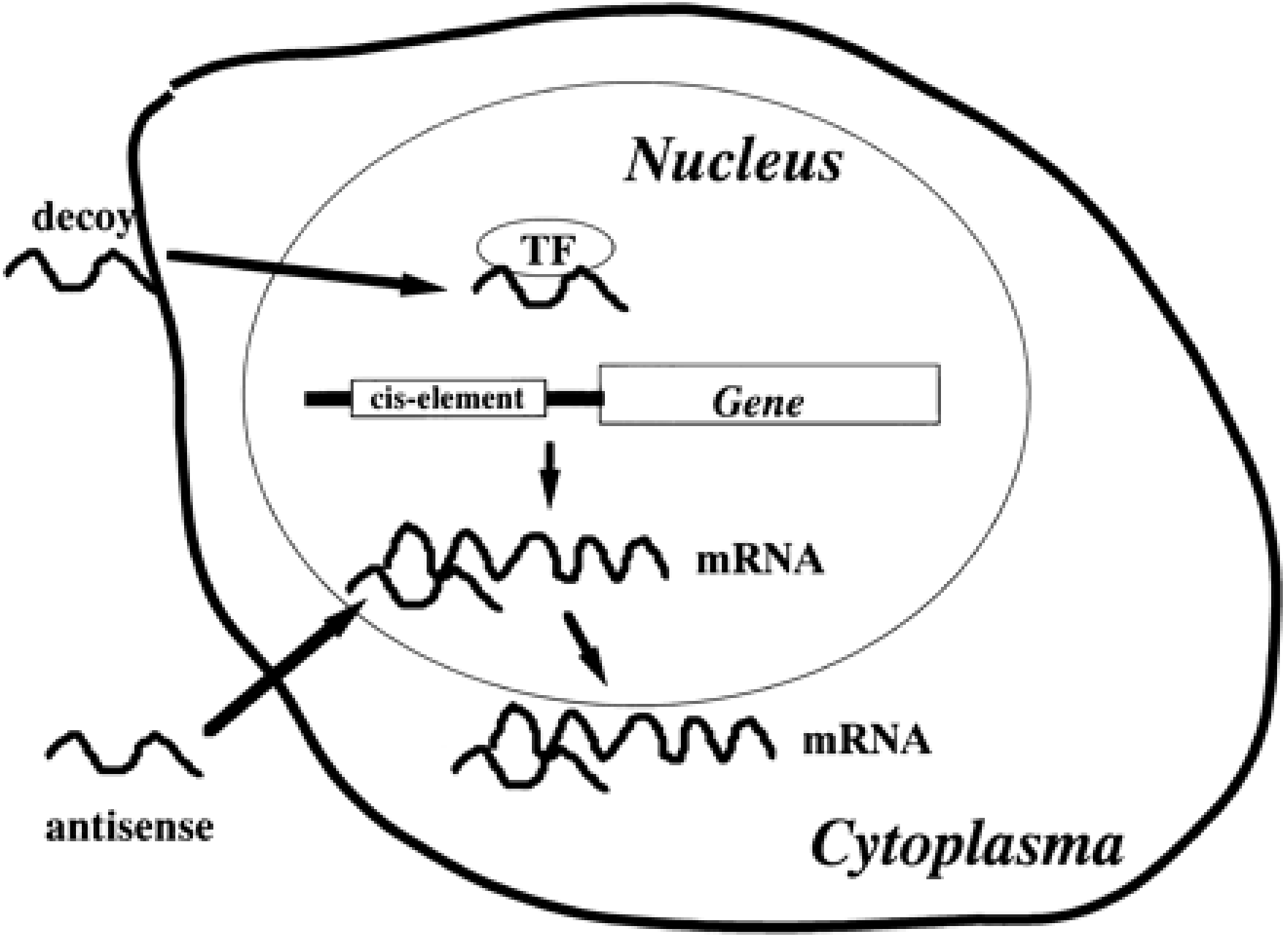
* Conducted in conjunction with the National Cancer Institute.

** We hold the worldwide commercial rights to the product candidates related to each of these programs.

Advexin finally was not registered by FDA…

Cancer gene therapy

1. Direct attack on tumor cells
    a) transfer of tumor suppressor gene
    b) **inhibition of oncogenes**
        - antisense therapy
        - ribozymes
    c) suicide genes
    d) oncolytic viruses (replication-competent viruses)
2. Harnessing immune response to tumor antigens
3. Chemoprotection
4. Anti-angiogenic therapy


Nucleus
decoy
TF
cis-element
Gene
mRNA
mRNA
antisense
Cytoplasma

Blocking oncogenes in tumors

Sis - growth factor

erB-2

abl

ras

jun

myc

DNA decoys for cancer gene therapy

Will they be effective?

Remember the story of Edifoligide

When Bad Gene Transfer Is Good...

Cancer gene therapy

1. Direct attack on tumor cells
    a) transfer of tumor suppressor gene
    b) inhibition of oncogenes
        - antisense therapy
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Suicide gene therapy –pro-drug activation

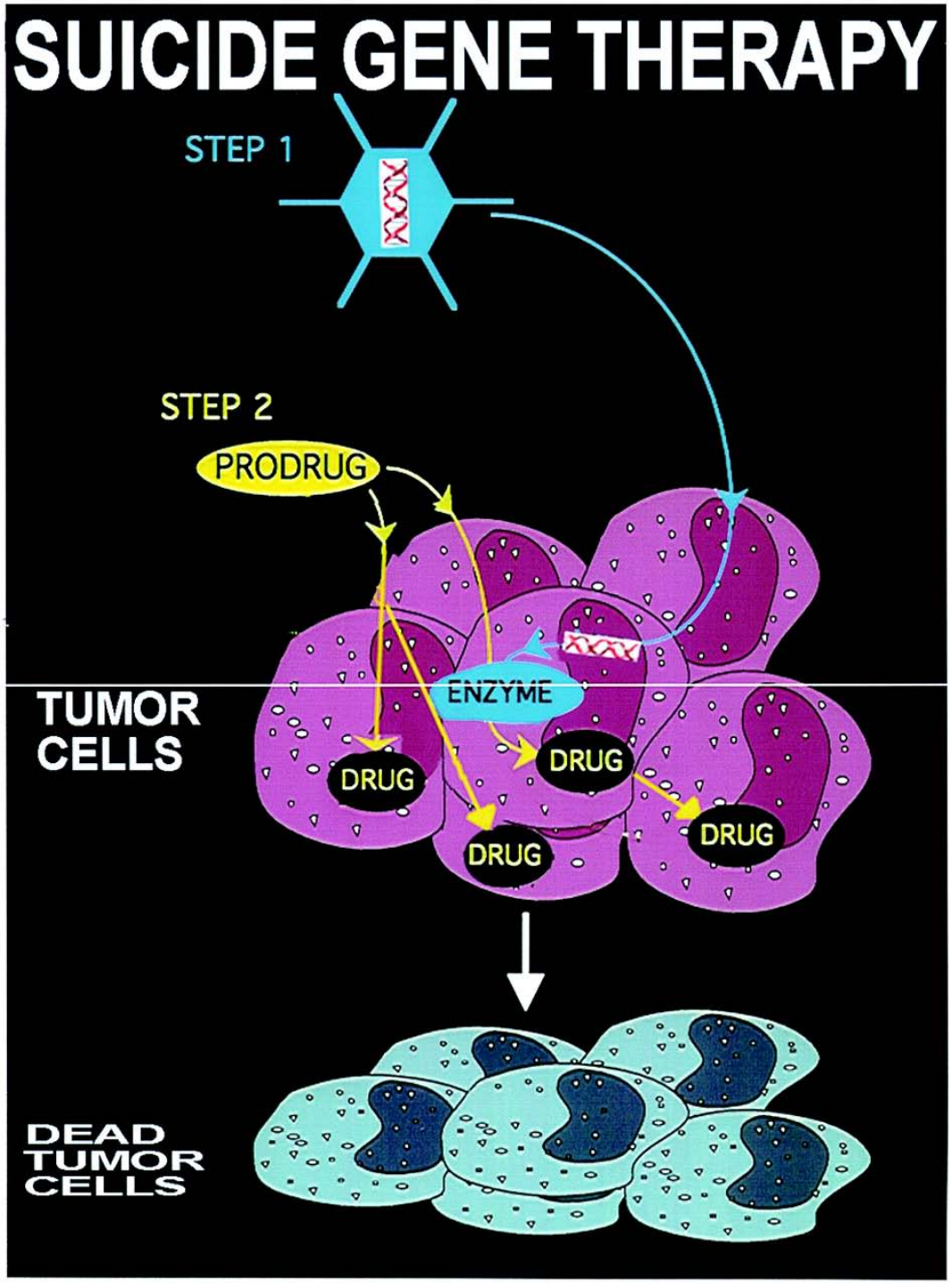
Gene-directed enzyme prodrug therapy

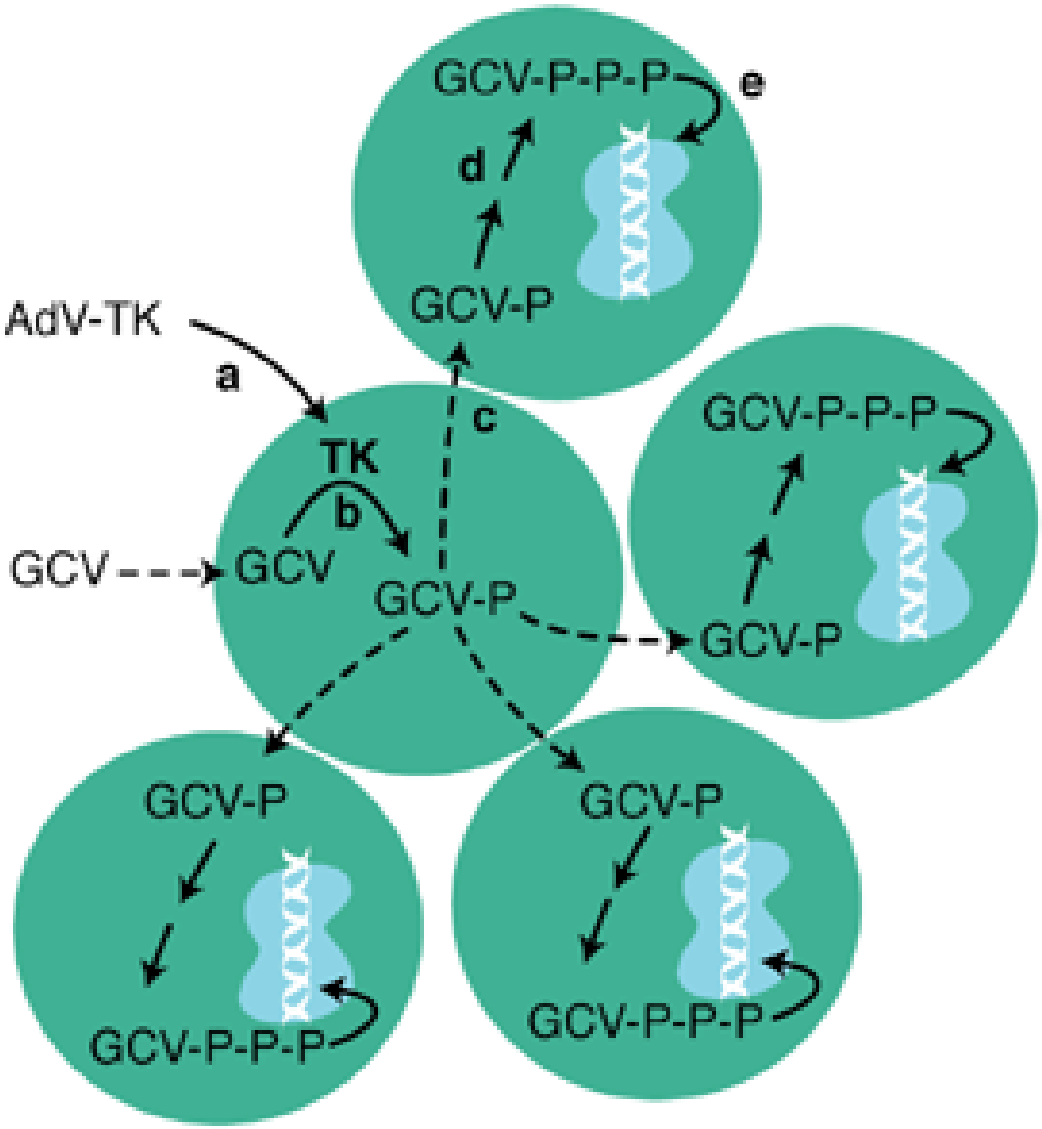
The objective of pro-drug activation therapy is to express an activating enzyme within the tumor, which will then activate a systemically delivered, inactive pro-drug at the target site only

Enzyme-prodrug combination for suicide gene therapy

Enzyme	Prodrug	Product	Mechanism
HSV-tk	ganciclovir acyclovir valacylcovir	ganciclovir triphosphate	blocks DNA synthesis
cytosine deaminase	5-fluorocytosine	5-fluorouracil (5-FU)	blocks DNA and RNA synthesis (pyrimidine antagonist)
cytochrome P450	cyclophosphamide	phosphoramide mustard	DNA alkylating agent; blocks DNA synthesis

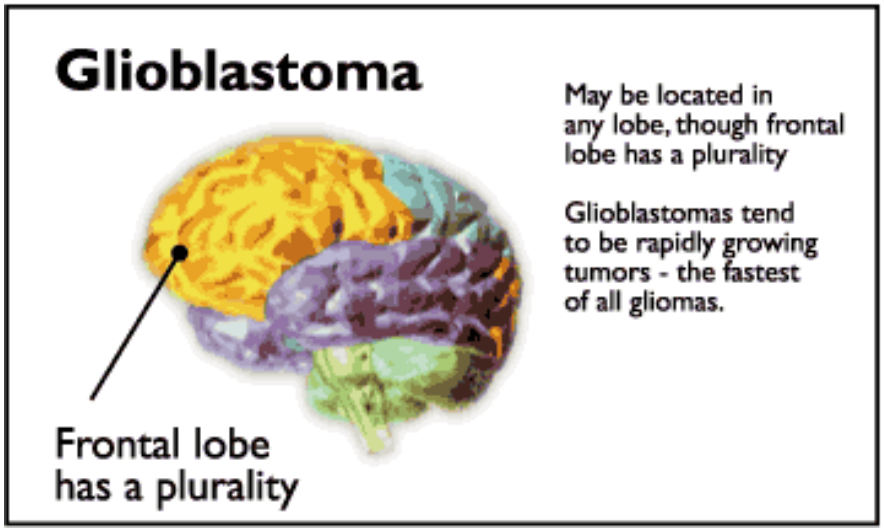
Bystander effect
(efekt sąsiedztwa)



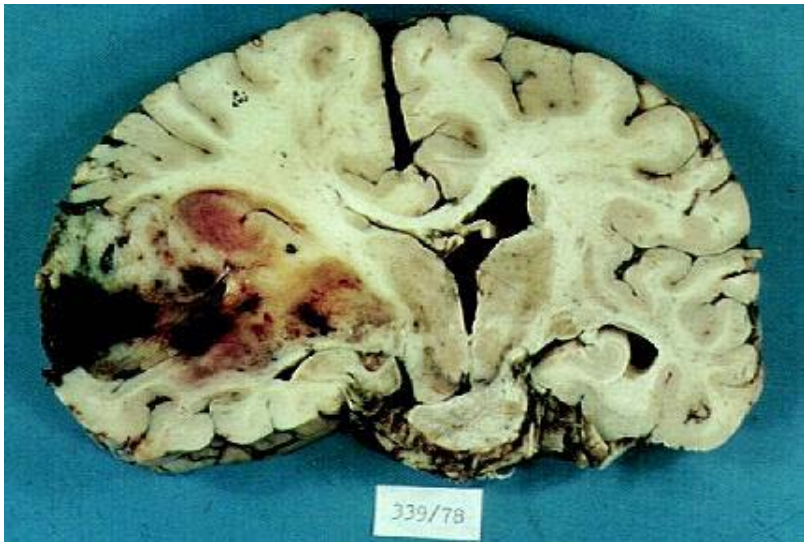


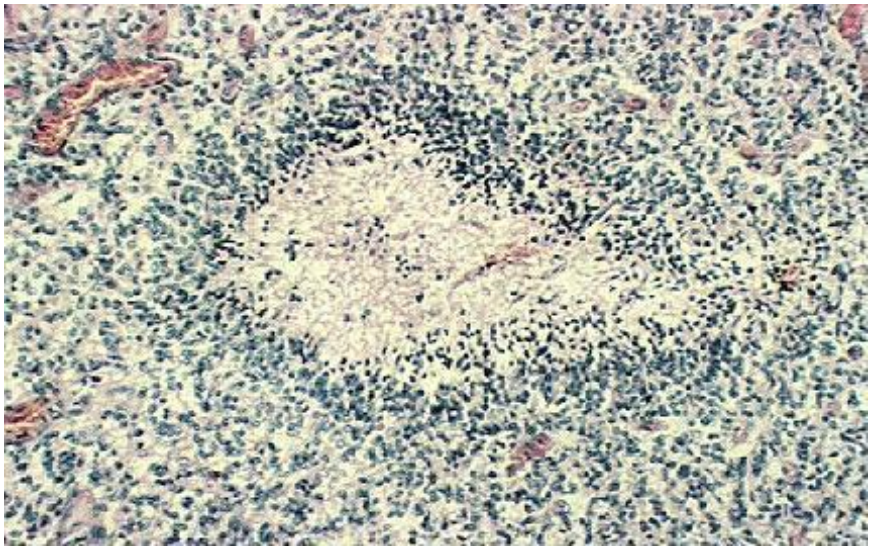
Suicide gene therapy

Expert Reviews in Molecular Medicine



Glioblastoma multiforme - Infiltrative; rapid-growing; occurs: most frequently in mid-aged; apt to involve both cerebral hemispheres via the corpus callosum; Average Survival: 1 year





Gene therapy for glioblastoma multiforme

Kuopio University

Mol Ther. 2004 Nov;10(5):967-72

- surgical resection of tumor followed by radiotherapy – all patients

- delivery of AdvHSV-tk (3 x 10(10) pfu) by local injection into the wound bed after tumor resection, followed by intravenous ganciclovir 5 mg/kg twice daily for 14 days

AdvHSV-tk treatment produced a clinically and statistically significant increase in mean survival from 39.0 +/- 19.7 (SD) to 70.6 +/- 52.9 weeks (P = 0.0095, log-rank regression vs. randomized controls). **The median survival time increased from 37.7 to 62.4 weeks.**

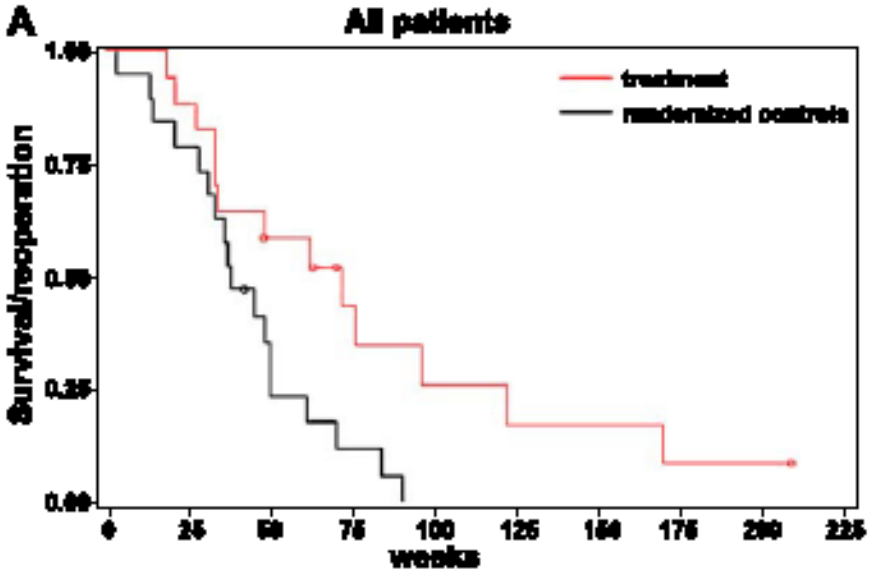
Mol Ther. 2004 Nov;10(5):967-72

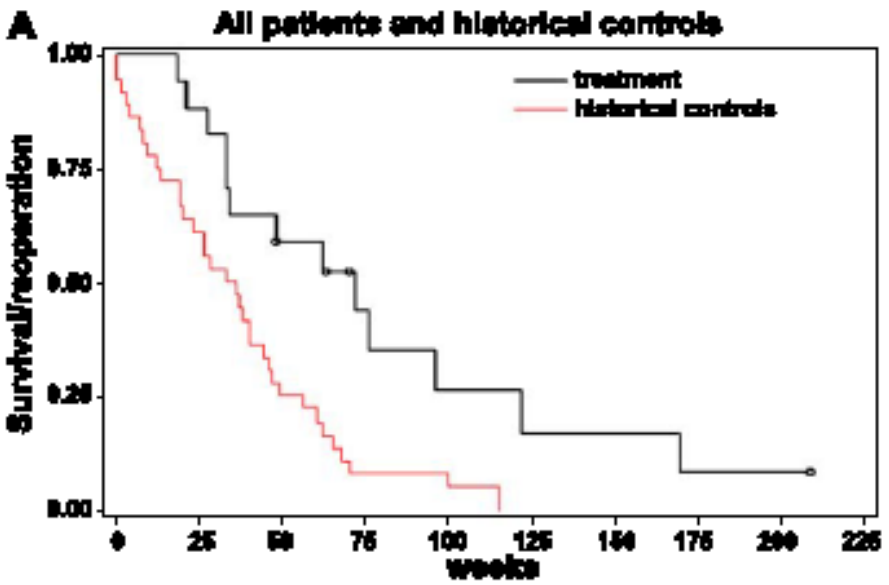
AdvHSV-tk gene therapy with intravenous ganciclovir improves survival in human malignant glioma: a randomised, controlled study.

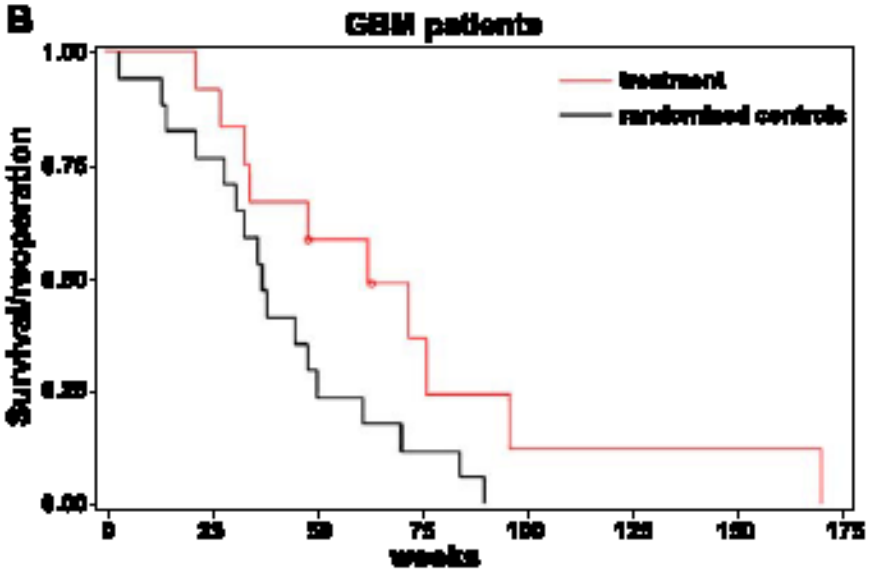
Immonen A, Vapalahti M, Tyynela K, Hurskainen H, Sandmair A, Vanninen R, Langford G, Murray N, Yla-Herttuala S.
Department of Neurosurgery, University of Kuopio, A.I. Virtanen Institute, Finland.

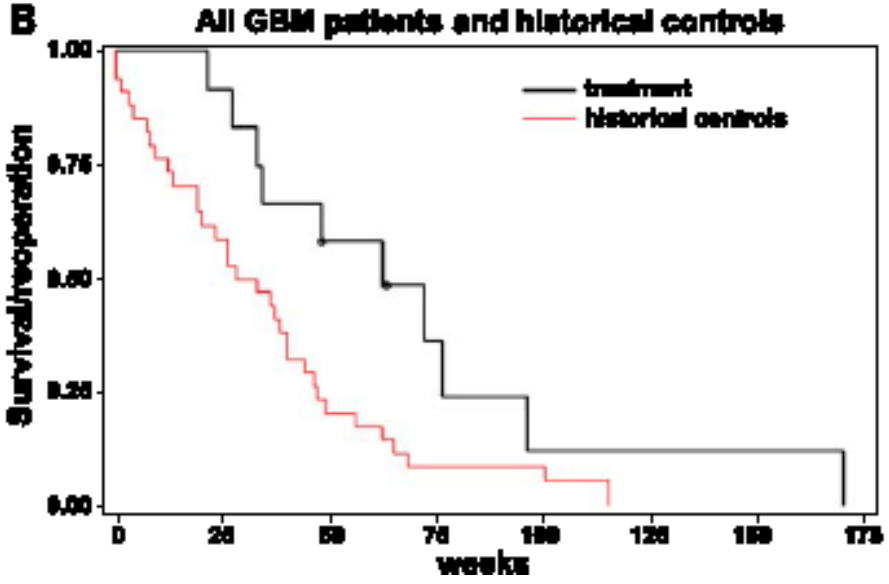
Malignant glioma is a devastating brain tumor with no effective treatment. This randomised, controlled study involved 36 patients with operable primary or recurrent malignant glioma. Seventeen patients were randomized to receive AdvHSV-tk gene therapy (3 x 10(10) pfu) by local injection into the wound bed after tumor resection, followed by intravenous ganciclovir (GCV), 5 mg/kg twice daily for 14 days. The control group of 19 patients received standard care consisting of radical excision followed by radiotherapy in those patients with primary tumors. The primary end-point was survival as defined by death or surgery for recurrence. Secondary end-points were all-cause mortality and tumour progression as determined by MRI. Overall safety and quality of life were also assessed. Findings were also compared with historical controls (n = 36) from the same unit over 2 years preceding the study. AdvHSV-tk treatment produced a clinically and statistically significant increase in mean survival from 39.0 +/- 19.7 (SD) to 70.6 +/- 52.9 weeks (P = 0.0095, log-rank regression vs. randomized controls). **The median survival time increased from 37.7 to 62.4 weeks.** Six patients had increased anti-adenovirus antibody titers, without adverse effects. The treatment was well tolerated. **It is concluded that AdvHSV-tk gene therapy with GCV is a potential new treatment for operable primary or recurrent high-grade glioma.**

AdvHSV-tk gene therapy with intravenous ganciclovir improves survival in human malignant glioma: a randomised, controlled study



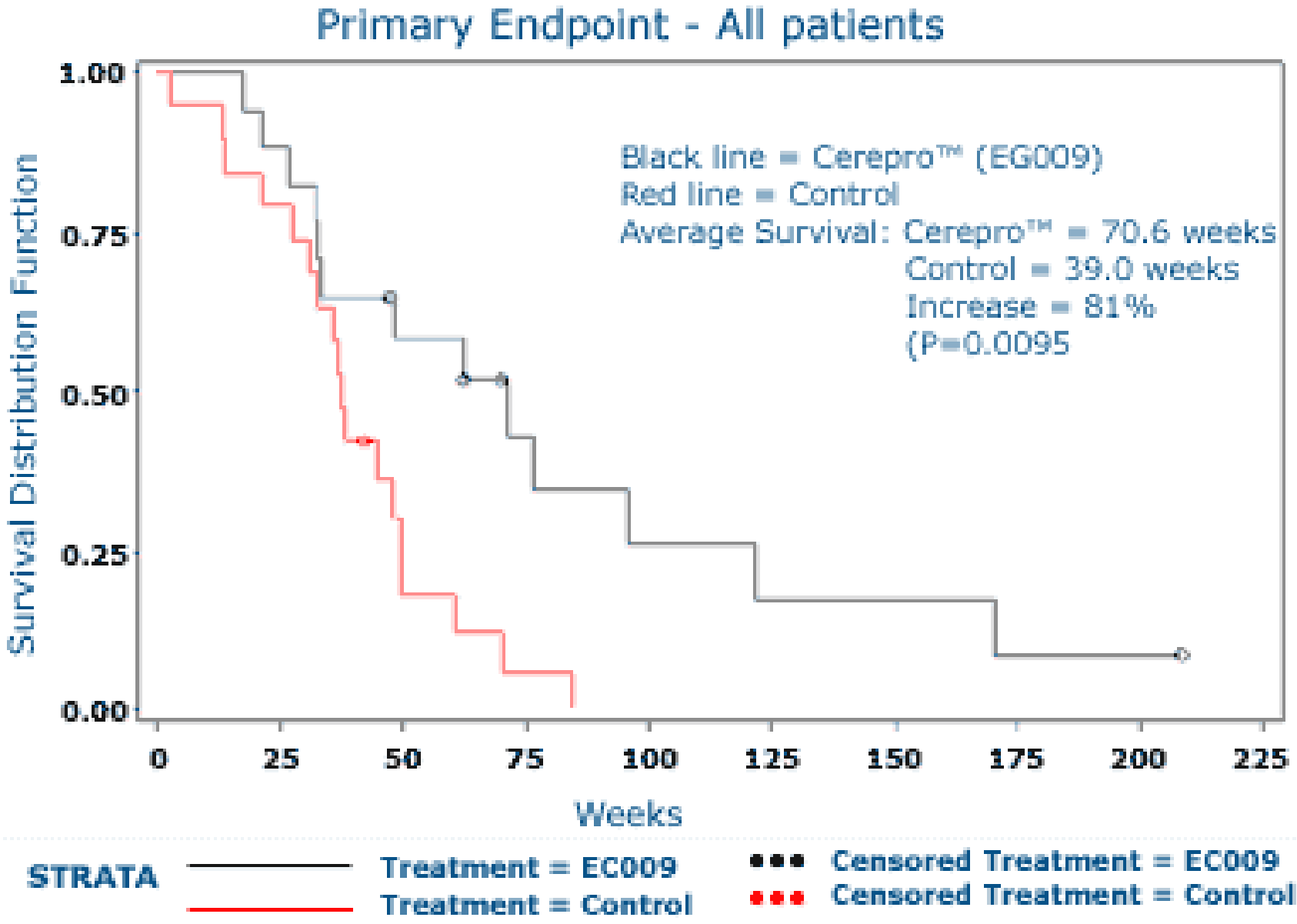






Immonen et al.., Mol Therapy 2004

RESULTS - KAPLAN-MEIR SURVIVAL PLOT FOR PRIMARY ENDPOINT



The Cerepro™ development programme has completed three clinical trials to date. The first, published **in Human Gene Therapy in 1998,** established the dose and method of administration. Results of the second, an open label efficacy and safety study, were published in **Human Gene Therapy in 2000** and showed that Cerepro™ doubled mean survival time and was well tolerated.

The results of the third study were presented at the American Society of Gene Therapy (ASGT) meeting in Minneapolis on 5 June 2004, and **published in Molecular Therapy in 2004**. This was the second study to be performed which investigated the efficacy and safety of Cerepro™ for the treatment of patients with operable malignant glioma. It was a 36 patient randomised, controlled study, blinded to the point of treatment allocation and enrolled both primary and recurrent cases of malignant glioma. All patients received standard care which involved surgical removal of the tumour followed by radiotherapy (primary tumours only) or chemotherapy. On the primary survival endpoint (death or re-operation to prevent death), Cerepro™, administered after surgical removal of the solid tumour mass, demonstrated an 81% increase in mean survival (from 39 weeks to 71 weeks) compared to standard care. The difference between the groups was statistically significant

Cerepro™ has been granted Orphan Drug Status by the European Committee for Orphan Medicinal Products and by the Office of Orphan Products Development, FDA

LONDON, Jan. 5, 2007 - **Ark Therapeutics Group plc** (LSE: AKT) ("Ark" or the "Company) today provides an update on the Phase III trial (Study 904) being undertaken on its lead product, CereproTM, for the treatment of high grade glioma (malignant brain tumour).

The independent Data and Safety Monitoring Board (DSMB) met on December 13th 2006 to review the data from the first 130 patients entered into the trial. Ark has now been notified by the DSMB that the side effect profile observed to date in Study 904 is in line with that previously reported, giving the DSMB no cause for concern nor requiring any alteration in the design and architecture of the trial. The DSMB has unanimously recommended that the Company continue the study without modification.

Recruitment into Study 904 has now passed 160 patients, in line with the Company's previous guidance.

Trials completed to date have shown that Cerepro™ treatment produces an average extension of 7.5 months of life, giving around 15.5 months survival in a disease where most patients will only live for around 8 months

Next step for suicide gene therapy in glioblastoma multiforme

Results presented by Prof. Seppo Yla-Herttuala from
AI Virtanen Institute, Kuopio, Finland at Gene & Cell Therapy Conference,
Brugge, November 2008

Phase III trial – Adv-Tk - 3 x 10^{10} pfu/ml

Vector injected into tumor cavity at the depth of 10 mm

250 patients from Germany, France, Belgium, UK, Poland, Finalnd, Czech, Hungary, Israel

1) Standard therapy:	*mean survival – 308 days*
2) + temodar (temozolamide)	*- 307 days*
3) Standard therapy + gene therapy	*- 300 days*
4) + temodar + gene therapy	*- 350 days*

Cancer gene therapy

1. Direct attack on tumor cells
    a) transfer of tumor suppressor gene
    b) inhibition of oncogenes
        - antisense therapy
        - ribozymes
    c) suicide genes
    d) oncolytic viruses (replication-competent viruses)
2. Harnessing immune response to tumor antigens
3. Anti-angiogenic therapy

Oncolytic viruses

Unhindered by interferon-mediated antiviral defence, which is compromised in many tumours, these viruses **specifically attack** cancer cells by:

1. gaining entry through receptors that are overexpressed in these cells and/or
2. exploiting molecular pathways associated with malignant transformation for their replication

Replication competent viruses

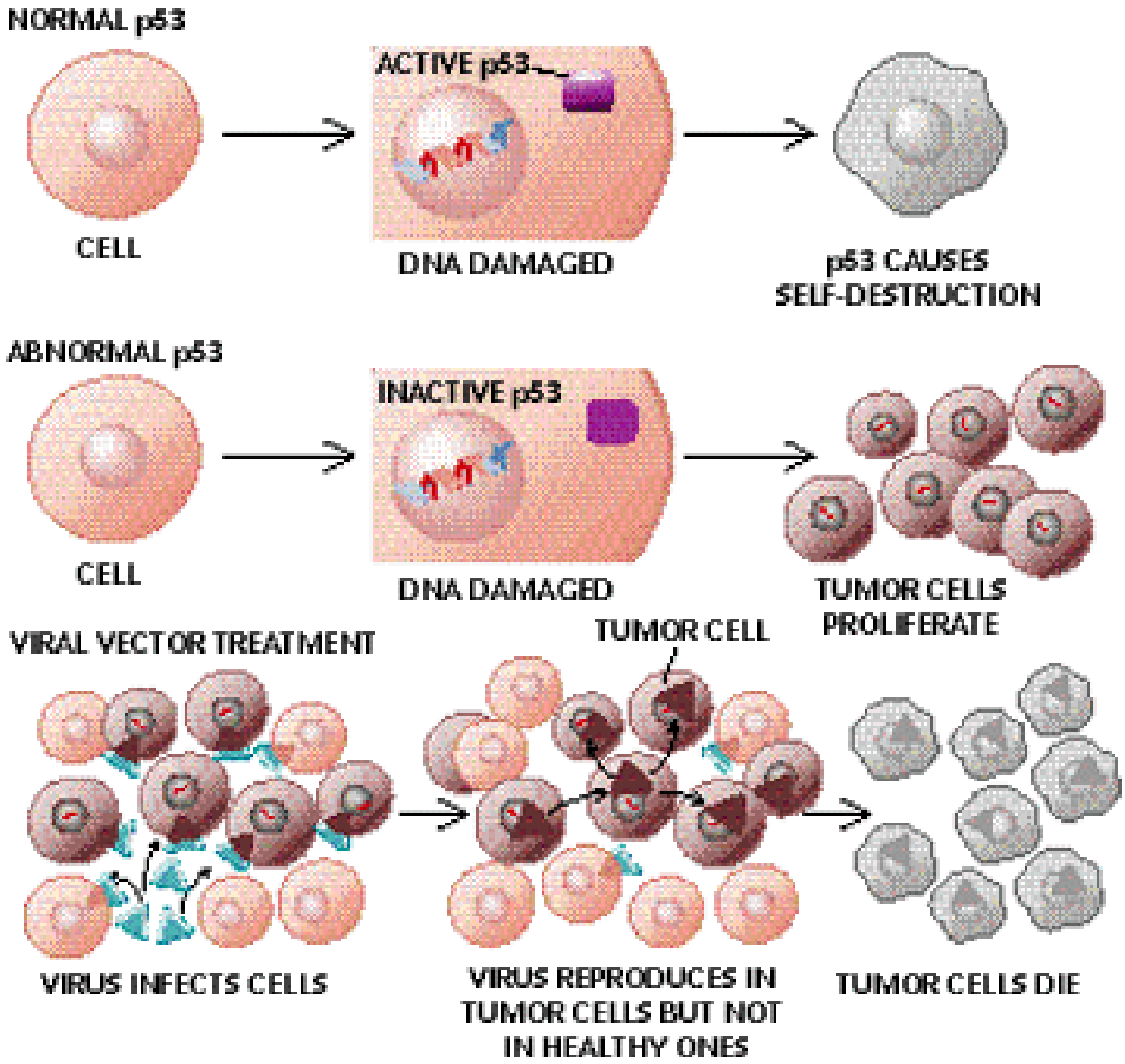
Naturally occuring viruses

- autonomously replicating parvoviruses
- human reoviruses
- vesicular stomatitis virus
- Newcastle disease virus

Engineered oncotropic viruses

- conditionally replicating adenoviruses (such as ONYX-15)

Oncolytic viruses replicate in cells deficient of p53

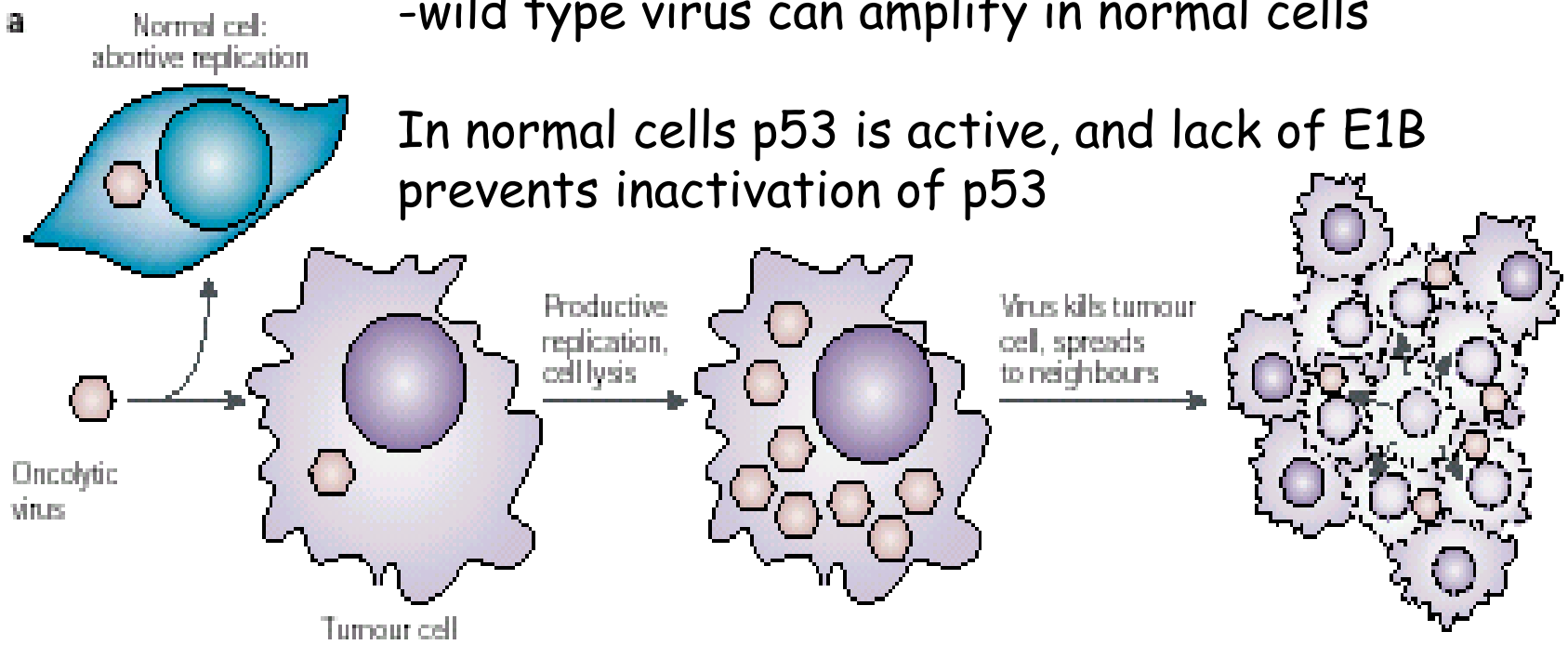


Oncolytic viruses

Lyse only tumor cells,
Adenovirus ONYX-015 , with deletion in E1B gene, may amplify only in cells with mutated p53 gene

E1B 55K protein binds to p53 and blocks its function
-wild type virus can amplify in normal cells

In normal cells p53 is active, and lack of E1B prevents inactivation of p53



JX-594

JX-594 is a proprietary, engineered oncolytic virus that is designed to selectively target and destroy cancer cells. JX-594 is designed to attack cancer through three diverse mechanisms of action:

1)the lysis of cancer cells through viral replication,
2) the reduction of the blood supply to tumors through vascular targeting and destruction,
3) the stimulation of the body's immune response against cancer cells.

JX-594 exploits a specific genetic feature in cancer cells to become activated and lyse the cells, including the **EGFR-ras signaling pathway, the cell cycle activation and the loss of cellular interferon defenses**. JX-594 is a Wyeth vaccinia virus with a disruption of the viral thymidine kinase (tk) gene and expression of the immunostimulatory cytokine, GM-CSF (granulocyte macrophage colony-stimulating factor)

Phase 1 and Phase 2 clinical trials in multiple cancer types have shown that JX-594, delivered either directly into tumors or intravenously, induces tumor shrinkage, necrosis and is well-tolerated by patients. Multiple JX-594-treated patients have survived for over one year and up to four years

http://www.jennerex.com/

JX-594

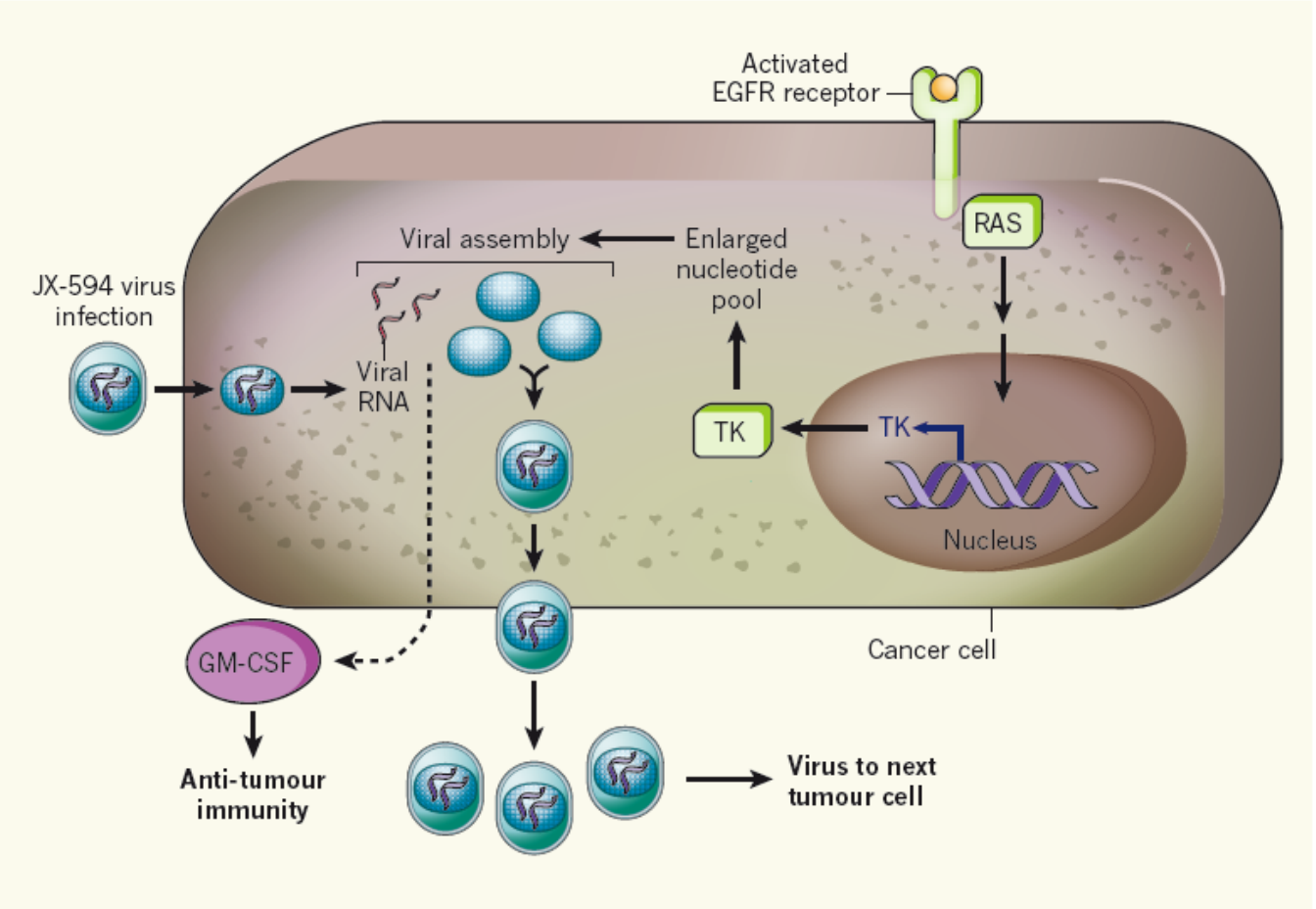


Figure 1 | Common oncogenic mutations in cancer cells encourage replication of the genetically engineered oncolytic JX-594 virus[1]. The virus takes advantage of a cancer cell's uncontrolled epidermal growth factor receptor (EGFR)–RAS signalling pathway. To replicate, this thymidine kinase (TK)-deficient virus relies on expression of TK by cancer cells. The newly assembled viruses then leave the cell to infect other tumour cells. These viruses also secrete GM-CSF, a factor that stimulates anti-tumour immunity. In normal cells, however, viral replication is blocked because this virus cannot efficiently exploit the cell's replication machinery.

E.Galanis, Nature 1st Sept 2011

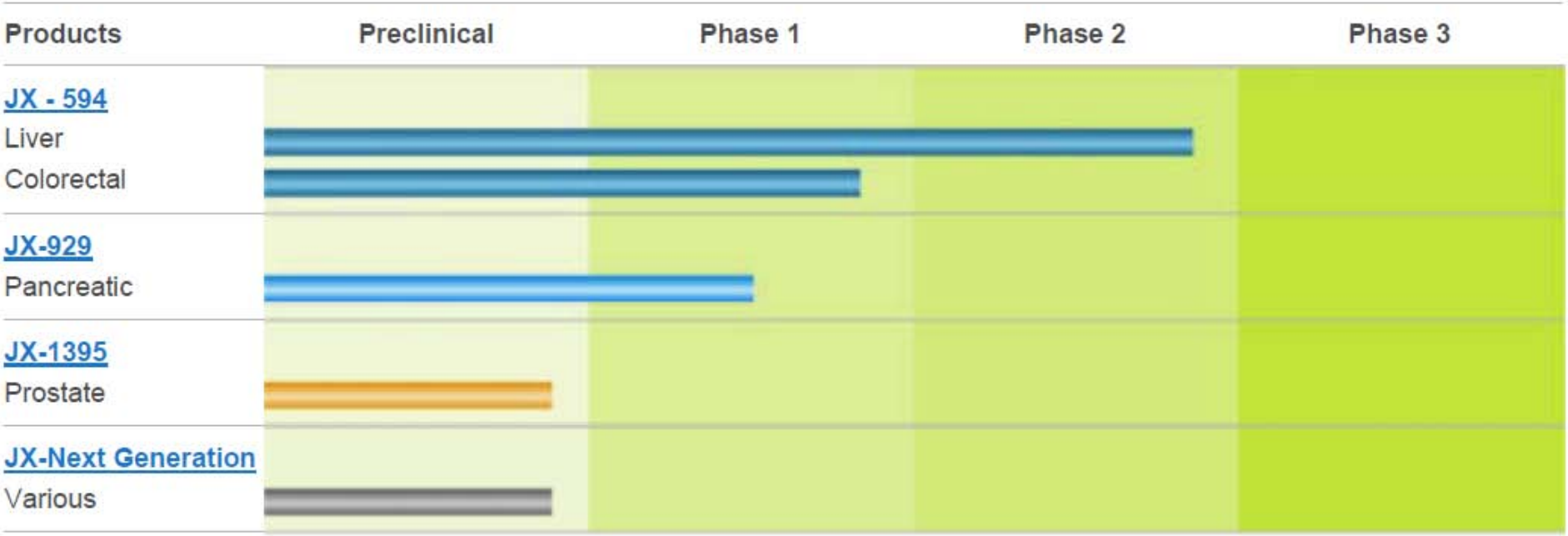
JX-594

In November 2011, Jennerex presented final data from a randomized dose-ranging Phase 2 clinical trial of JX-594 in patients with advanced liver cancer showing a statistically significant benefit in overall survival for the high JX-594 dose group versus the low dose group. The final data from the HEP007 trial demonstrated that the risk of death for patients who received JX-594 at the high dose was markedly reduced (by nearly 60 percent; hazard ratio = 0.41) when compared to patients randomized to a low dose control (one-tenth of the high dose). **The median overall survival for high and low dose groups was 13.8 months versus 6.7 months**, respectively (p = 0.029 for superiority of the high dose). **The percent of patients alive at one year was 66 percent versus 23 percent in high- and low-dose groups, respectively** (Kaplan-Meier estimate). JX-594 was well-tolerated with patients experiencing transient flu-like symptoms that generally resolved within 24 hours. A Phase 2b multinational trial (TRAVERSE) is now underway and is designed to enroll 120 patients with advanced liver cancer who have failed sorafenib therapy

http://www.jennerex.com/

Other oncolytic viruses

Pipeline



Ongoing trials with oncolytic viruses

1. soon-to-be-completed phase III trial of an attenuated strain of herpes simplex virus-1 that encodes GM-CSF in patients with metastatic melanoma;
2. the recently activated phase III trial testing addition of reovirus to paclitaxel/carboplatin chemotherapy in patients with recurrent head and neck cancer;
3. and a randomized phase II trial comparing JX-594 with the best supportive care in patients with hepatocellular carcinoma for whom treatment with the drug sorafenib has failed.

Nature, 1st September 2012

Cancer gene therapy

1. Direct attack on tumor cells
    a) transfer of tumor suppressor gene
    b) inhibition of oncogenes
        - antisense therapy
        - ribozymes
    c) suicide genes
    d) oncolytic viruses (replication-competent viruses)
2. Harnessing immune response to tumor antigens
    - overexpression of cytokines genes
    - tumor vaccines
3. Anti-angiogenic therapy

Genetically modified tumor vaccines

- Immune system may play a role in controlling tumor growth and development
- However, antigens present on tumor cells are not sufficient to boost immune response:
  - they are weak
  - lack the co-stimulatory molecules necessary for full recruitment of cellular immunity
- Many tumors also employ active immune evasion strategies

hence

Modification of tumor cells – i.e, overexpressing certain genes, may stimulate immune system to respond to tumor cells

Strategy of genetically modified tumor vaccines

1. Isolate tumor cells from a patient – however, it is often not possible to use autologic cells

2. Alternative – culture other tumor cells- eg, cell line of the same type – i.e. allogeneic cell line

3. Transduce such cells with vector – eg. retroviral vector harboring cytokine gene

4. Inject such modified cells into patients

5. Antigens present on allogeneic tumor cells stimulate immune system, which respond to the same antigens present on patient's tumor
   - Cytokines enhance the response

TABLE 3 Cytokine gene therapy trials

Cytokine	Vector	Malignancy	Immune response	Clinical response	Reference
IL-12	Vaccinia	Mesothelioma	T cell infiltrate	0/6	78
GM-CSF	Retrovirus	Melanoma	Infiltrate at vaccine site	1/ 5 CR	79
IFN-γ	Retrovirus	Melanoma	Antibodies to tumor antigens	5/8 SD 3/8 CR/PR	80

CR, complete response; PR, partial response; SD, stable disease.

IL-6 and sIL-6R retrovirus melanoma (allogeneic)

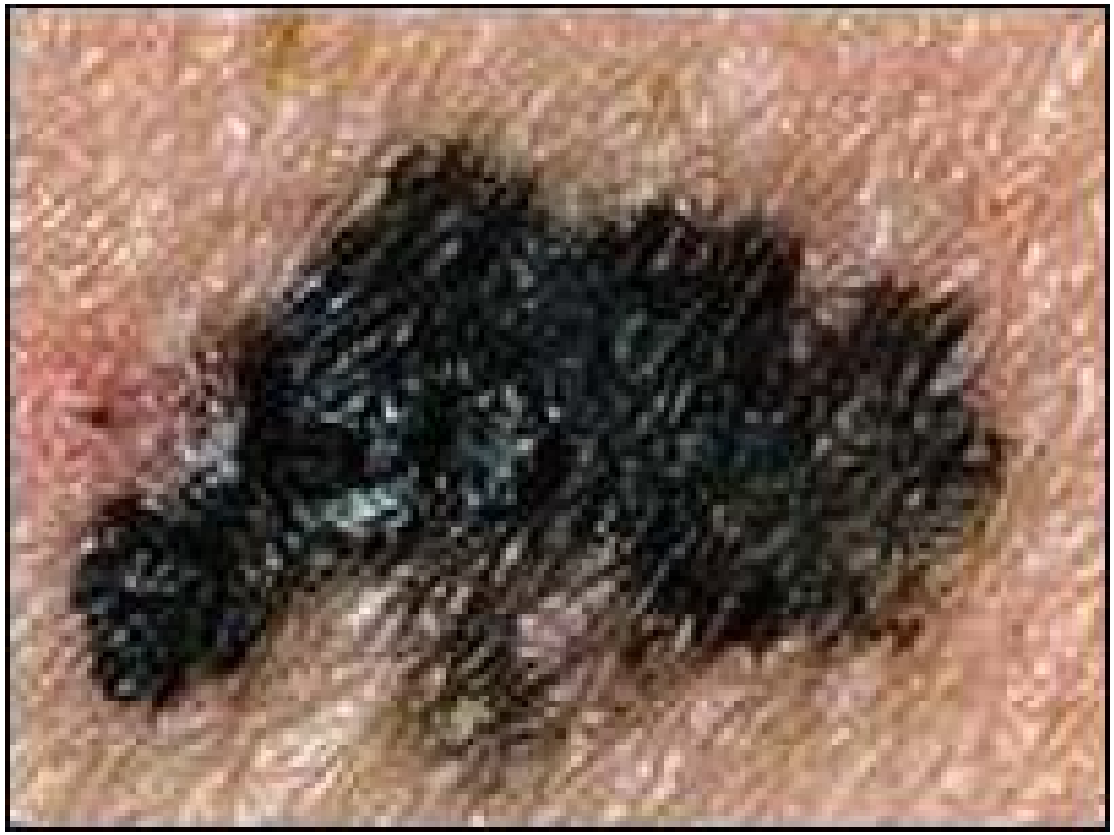
A. Mackiewicz et al., - Poznań

Wadhwa et al., Ann Rev Med. 2002

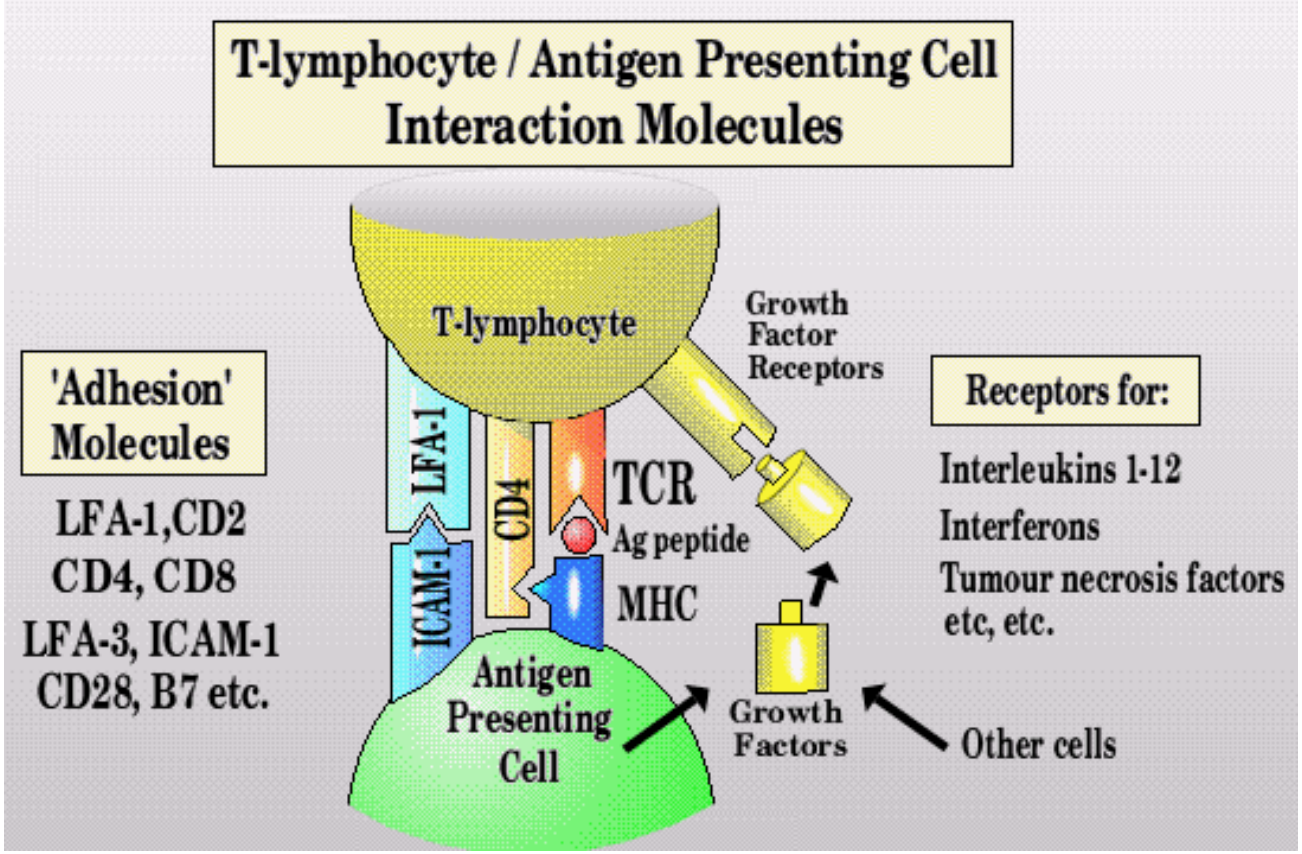
Gene therapy for treatment of melanoma

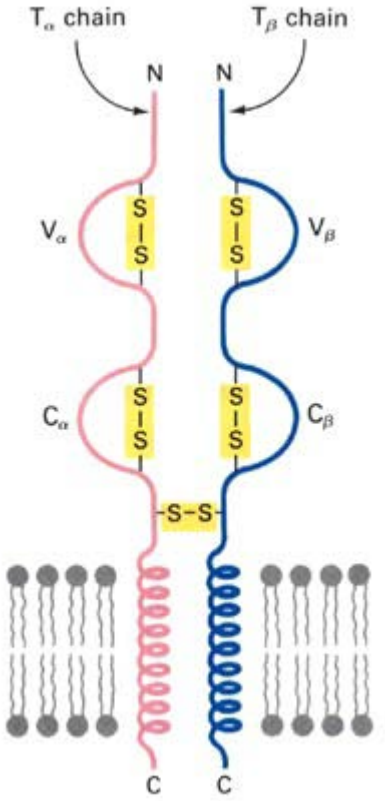
Cancer Regression in Patients After Transfer of Genetically Engineered Lymphocytes.

Morgan at al.. (Rosenberg), Science, 31 August 2006



Tumor associated antigens (TAA) are recognized by T cell receptor (TCR) on the T lymphocyte surface, which is composed of the TCR α and β-chains





Genes encoding TCR specific for a variety of TAA have now been cloned and these include:

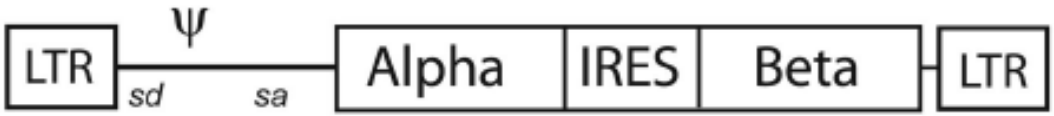
1) the MART-1 and gp100 melanoma/melanocyte differentiation antigens
2) the NY-ESO-1 cancer-testis antigen present on many epithelial cancers
3) the epitope from the p53 molecule, expressed on the surface of approx. 50% of cancers of common epithelial origin

Cancer Regression in Patients After Transfer of Genetically Engineered Lymphocytes

Morgan at al.. (Rosenberg), Science, 31 August 2006

Peripheral blood lymphocytes (PBL) of the patients with refractory melanoma were transduced ex vivo with retroviral vector encoding T cell receptor (TCR), recognizing:

1) the MART-1 and gp100 melanoma/melanocyte differentiation antigens



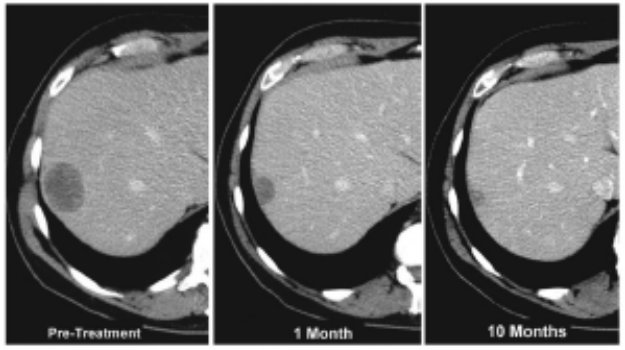
Transduction with these TCR encoding retroviral vectors converted normal PBL to cells capable of specifically recognizing and destroying both fresh and cultured cells from multiple common cancers

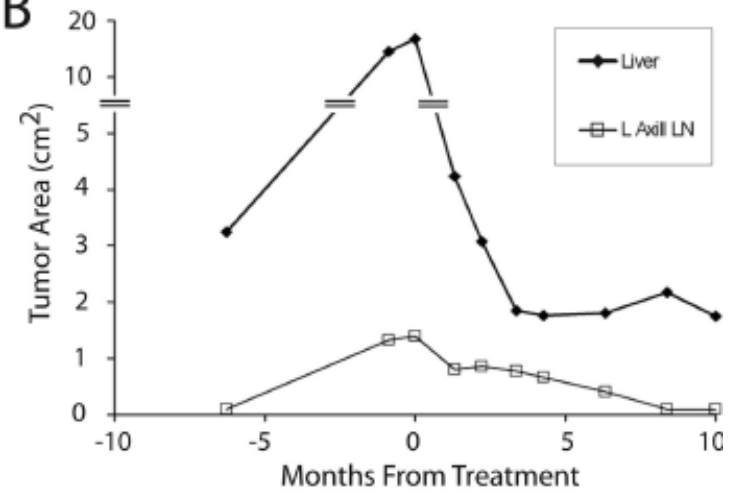
Those TCR transduced T cells secreted IFN-γ following co-culture with melanoma cells

Cancer Regression in Patients After Transfer of Genetically Engineered Lymphocytes

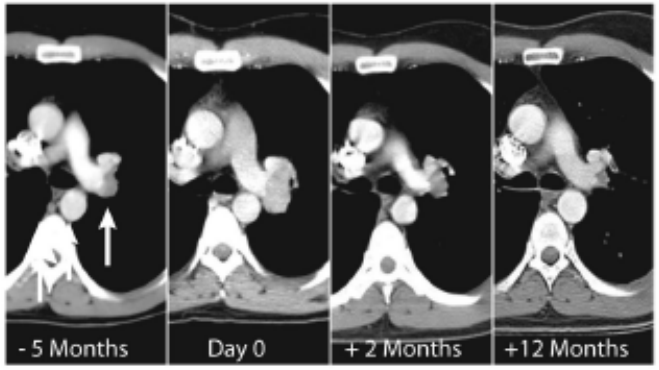
Morgan at al.. (Rosenberg), Science, 31 August 2006

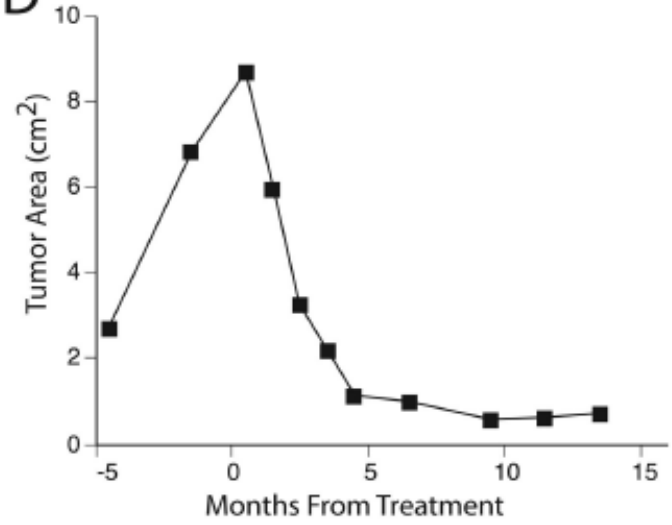
Patient 4 liver metastasis





Patient 14 lymph node metastasis





Cancer gene therapy

1. Direct attack on tumor cells
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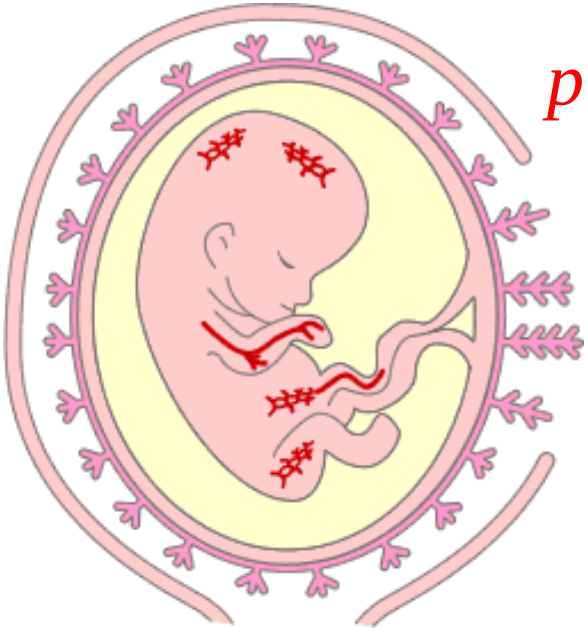
        - ribozymes
    c) suicide genes
    d) oncolytic viruses (replication-competent viruses**)**
2. Harnessing immune response to tumor antigens
3**. Anti-angiogenic therapy**

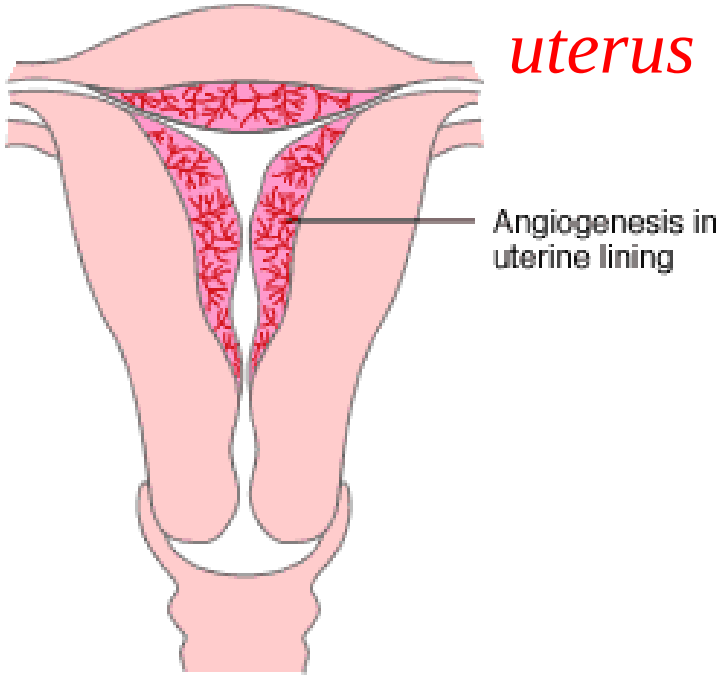
How to starve tumor to death...

Anti-angiogenic gene therapy

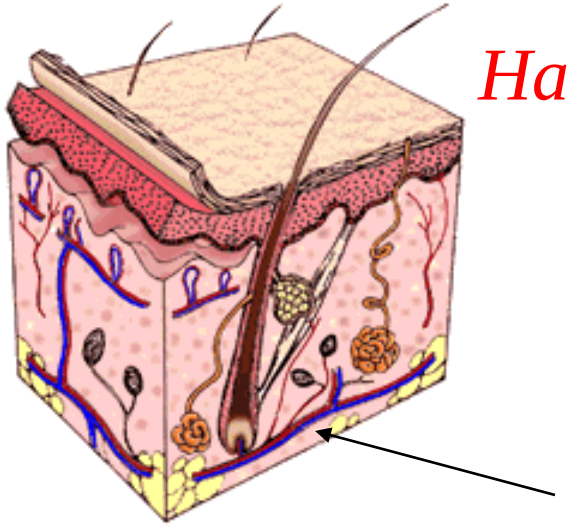
Physiological angiogenesis in adults is restricted



placenta

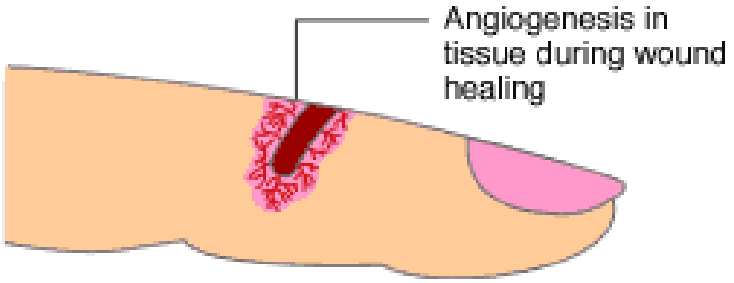


uterus

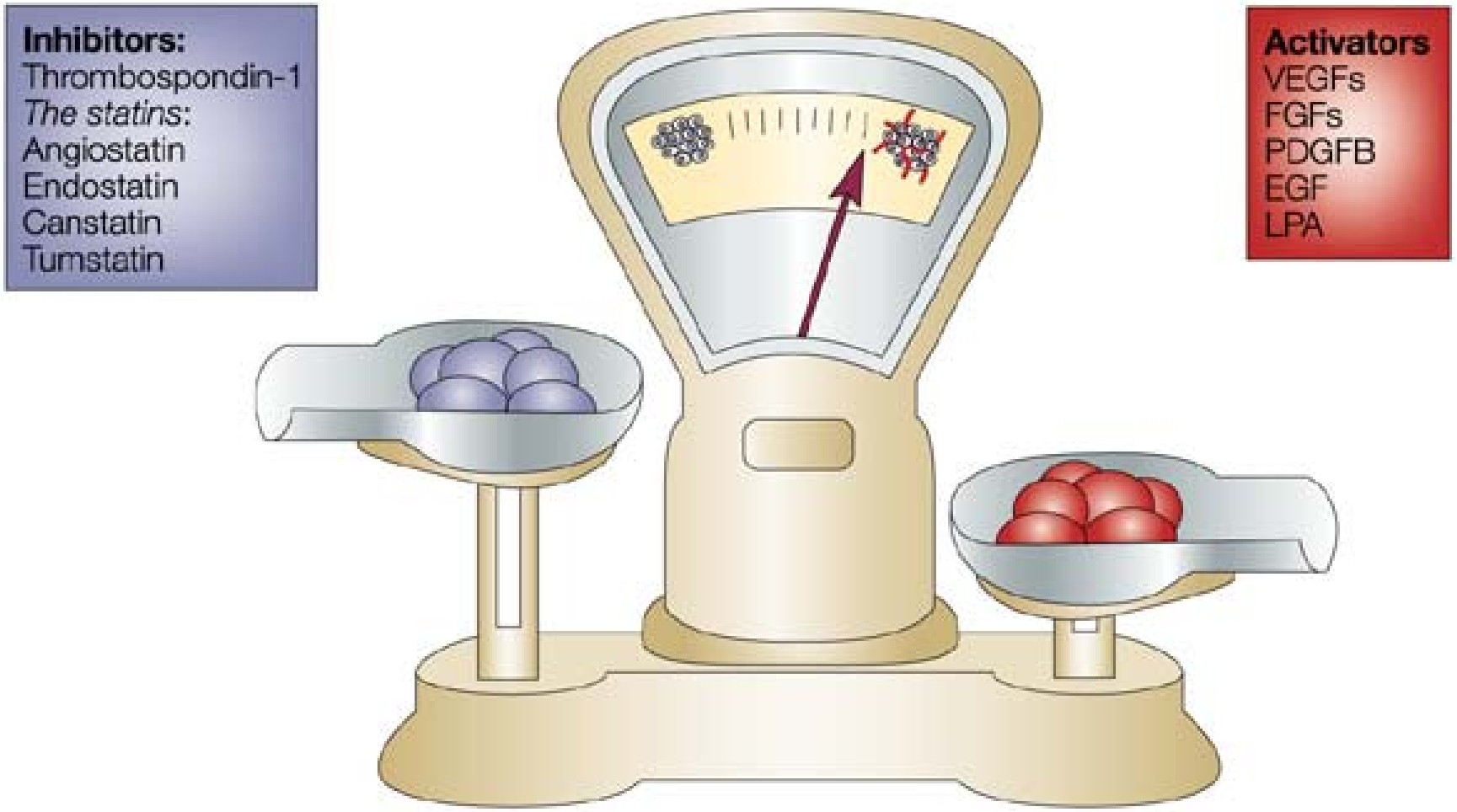


Hair growth

Wound healing

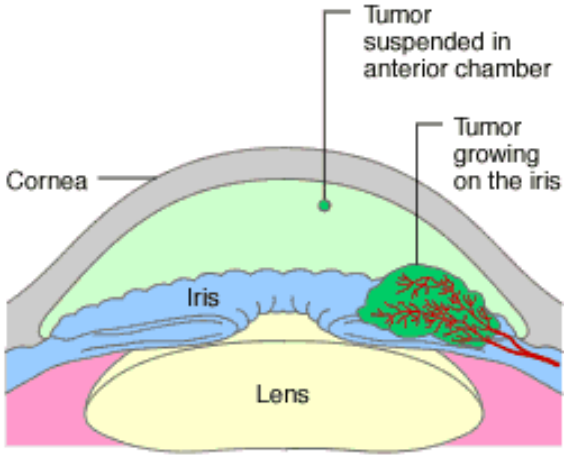


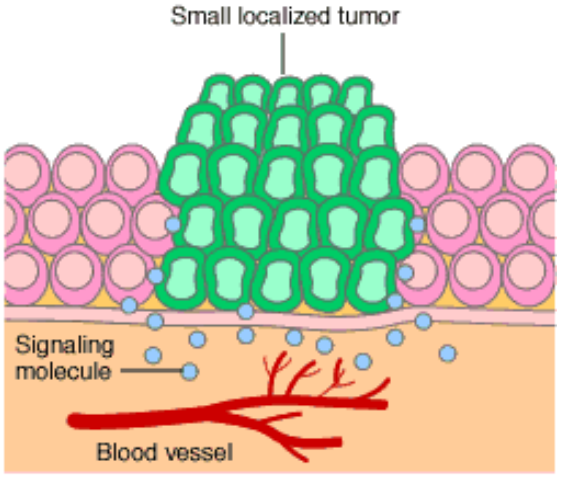
In healthy organism the action of activators and inhibitors of angiogenesis is balanced

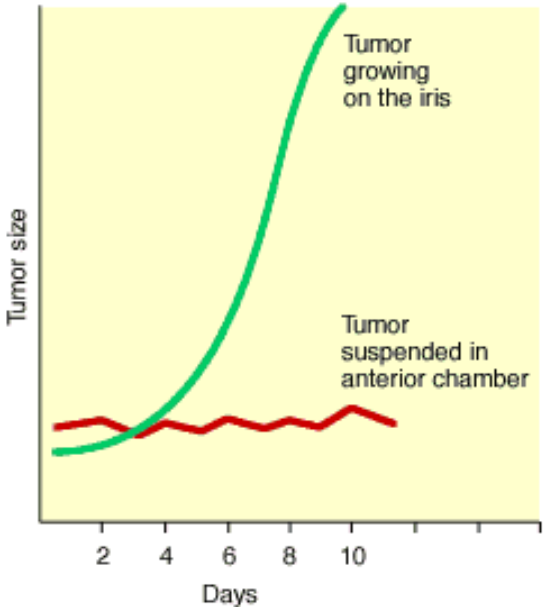


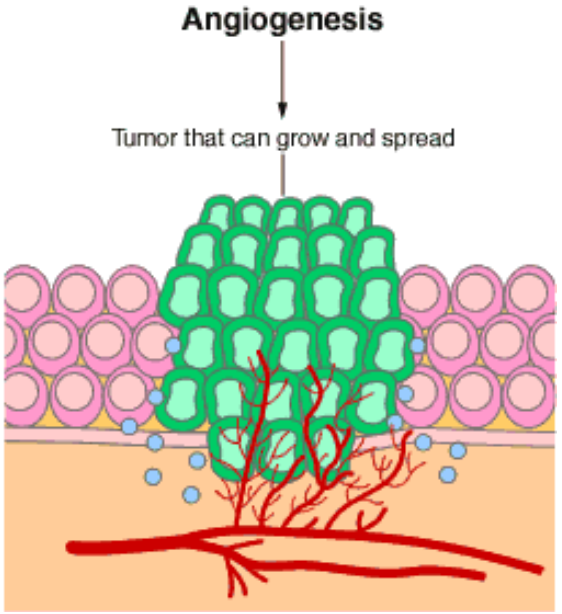
Nature Review Cancer

Tumor growth is dependent on angiogenesis

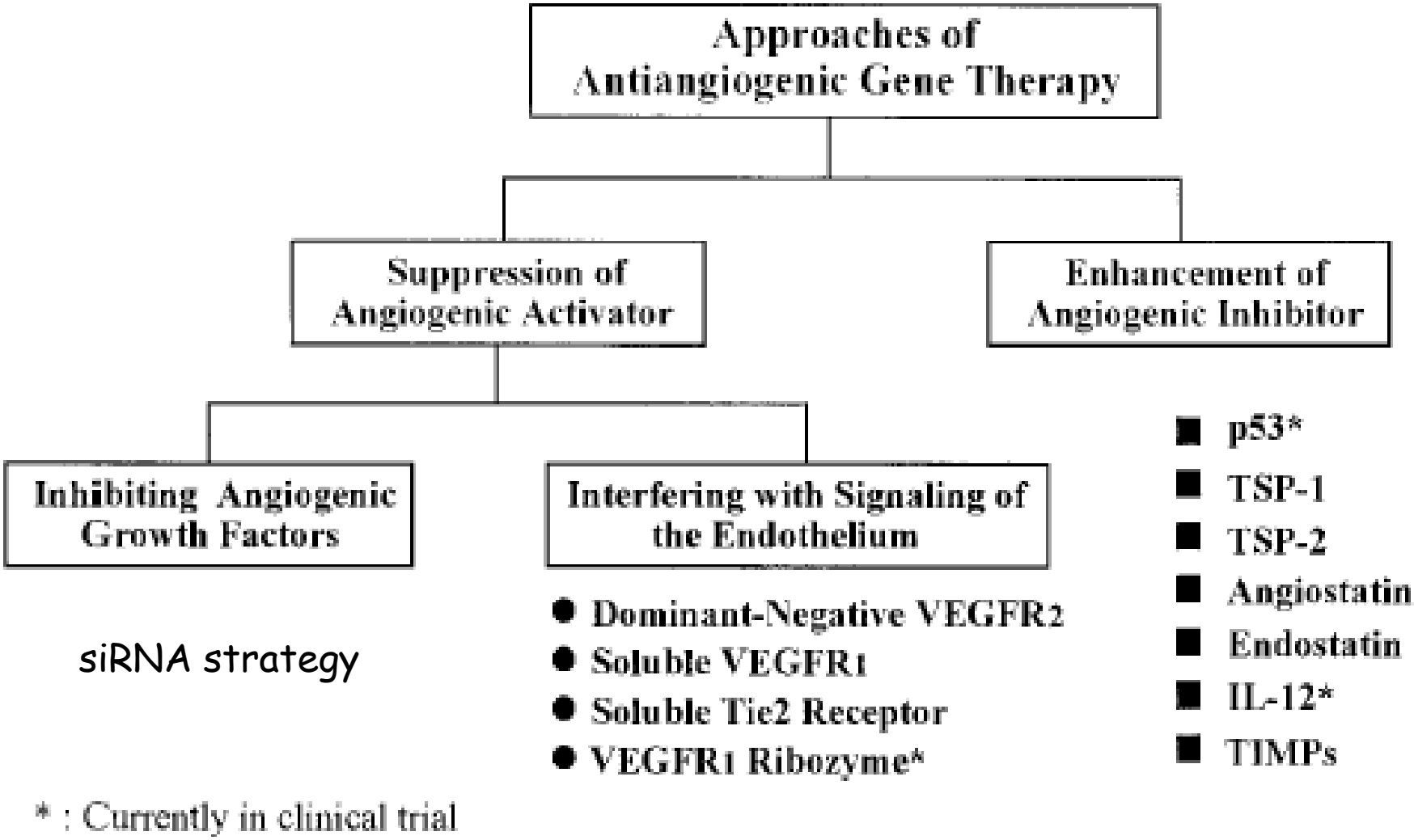






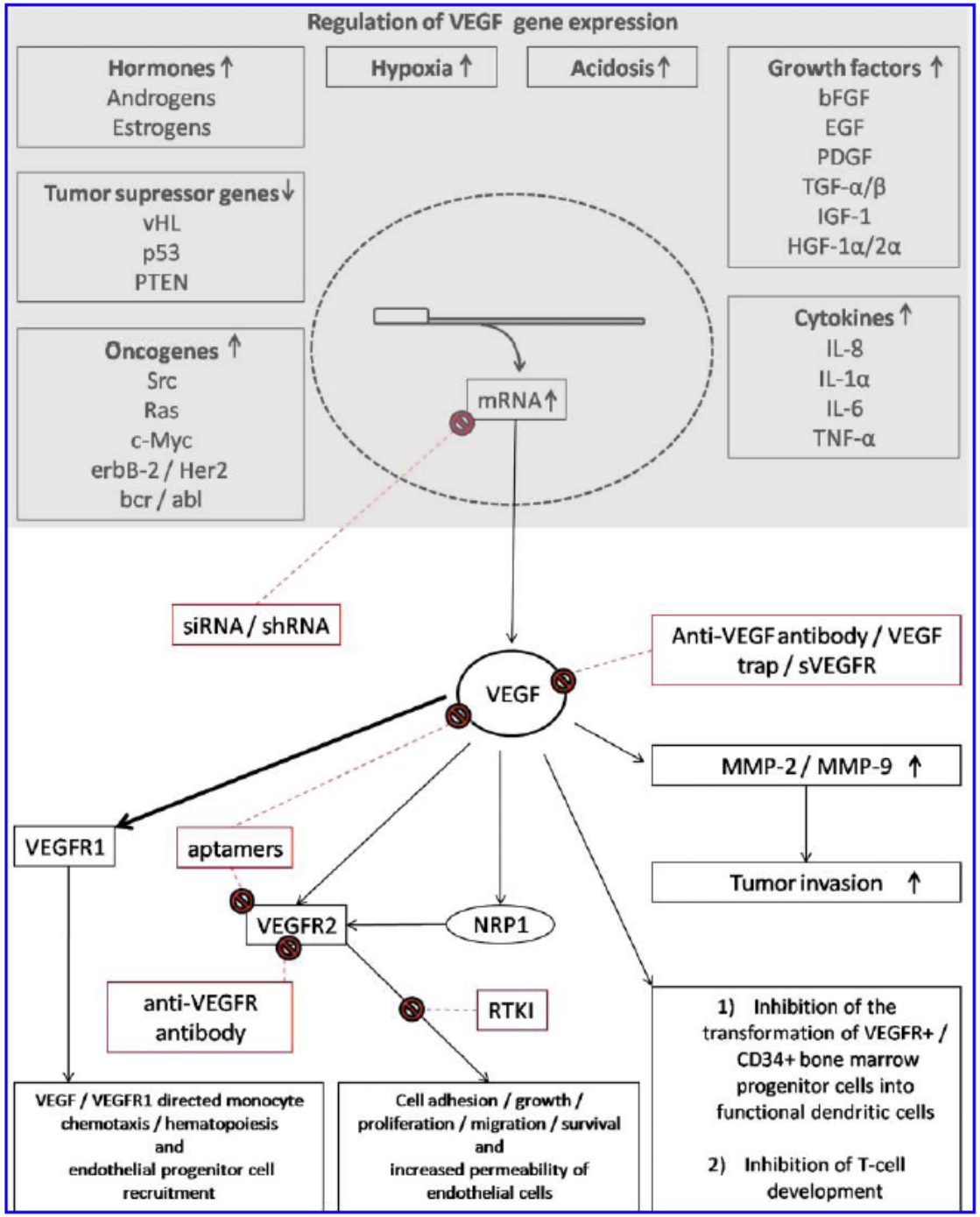


Strategies of anti-angiogenic gene therapy



* : Currently in clinical trial

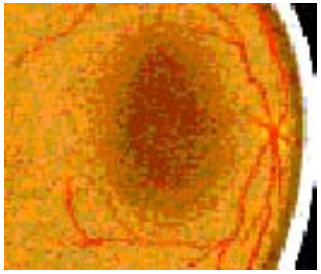
Rationale and targets for anti-angioegnic therapy



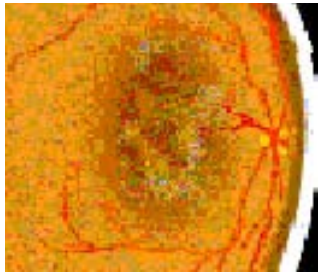
H. Samaranayake et al., Hum gene Ther, 2010

siRNA against mRNA VEGF

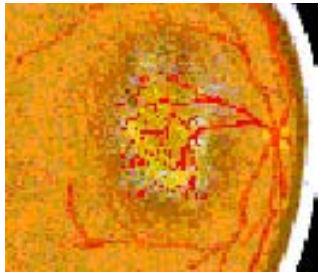
Acuity Pharmaceuticals



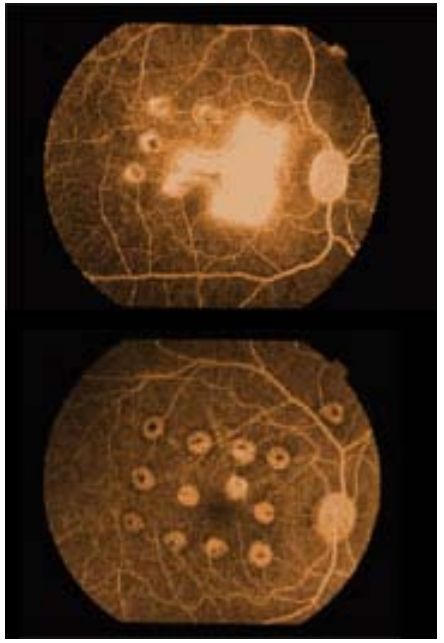
Normal Macula



Dry AMD:Drusen formation under the Macula



Wet AMD:Macula with abnormal blood vessels



+ siRNA

Gene therapy of cancer: anti-cancer vs anti-angiogenic

Anti-cancer cells- introduction of genes that:

1. Permit tumor cells to express toxic molecules
2. Prevent or correct genetic defects
3. Increase the immunogenecity of tumor cells
4. Increase the sensitivity of tumor cells to drugs

Anti-angiogenic - anti-endothelial cells: introduction of genes that:

1. Specifically target tumor endothelial cells
2. Block tumor-derived angiogenic activity

They may be employed together or separately

Cancer gene therapy

1. The largest number of clinical trials in gene therapy are for cancer

2. Different strategies are employed

3. Experiemntal and early clinical trials indicate for the potential benefit of this type of therapy

4. Unfortunately, the large clincial trials have not yet supported strongly the anti-cancer gene therapy