Medicamentos Biotecnológicos

Antonio Blázquez
Barcelona, Junio 2011

Hoy nos “importan”

Generic Name	Brands ®	Sales $ billion 2009	2010
Atorvastatin	Lipitor	**12.45** 13.28	**11.8** 12.6
Clopidrogel	Plavix	**9.29** 9.1	**9.4** 8.82
Infliximab	**Remicade**	**6.91** 5.4	**8.0** 6.04
Fluticasone Salmetrol	Advair	**7.764** 8.09	**7.96** 8.47
Etanercept	**Enbrel**	**8.0** 5.8	**7.4** 6.17
Bevacizumab	**Avastin**	**5.92** 5.01	**6.8** 5.53
Aripiprazole	Abilify	**5.5** 4.67	**6.8** 5.43
Rituximab	**Rituxan**	**5.80** 4.68	**6.7** 5.03
Adalimumab	**Humira**	**5.49** 5.03	**6.5** 5.96
Valsartan	Diovan	**6.01** 3.93	**6.1** 4.16

Y seguirán importándonos

2010
19/4 21%

2009
23/4 17%

2008
20/2 10%

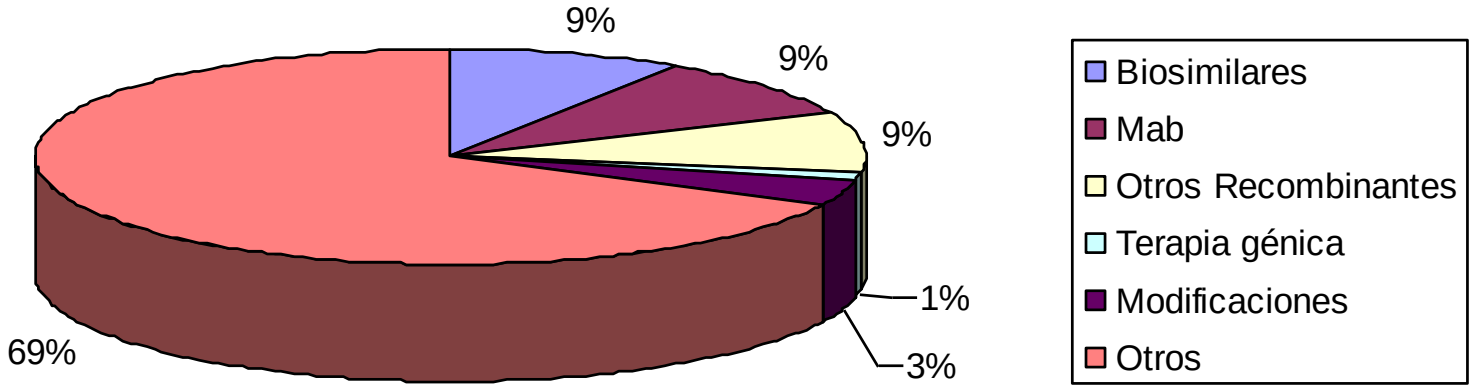
2007
27/7 26%

Tabla I. Grupo y actividad de los "Nuevos Principios activos autorizados en 2010"

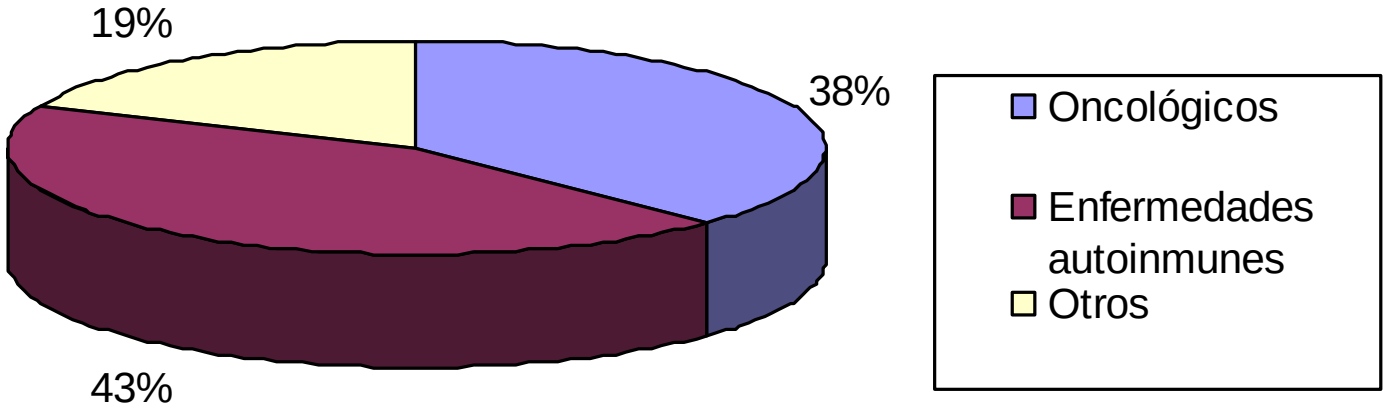
GRUPO A.T.C.	PRINCIPIO ACTIVO	PRESENTACIÓN	ACTIVIDAD/ EFECTO
* A (Tracto Alimentario y Metabolismo)	LIRAGLUTIDA	6 mg plumas	Hipoglucemiante
	SAXAGLIPTINA	5 mg comp	Hipoglucemiante
* B (Sangre y Órganos hematopoyéticos)	ELTROMBOPAG (2,3)	25 y 50 mg comp	Hemostático
* C (Sistema Cardiovascular)	DRONEDARONA	400mg comp	Antiarrítmico
	TOLVAPTAN	15 y 30 mg comp	Diurético
*G (Sistema Genitourinario y Hormonas sexuales)	CORIFOLITROPINA ALFA (1)	100 y 150 mg sol iny	Estimulante ovárico
	SILODOSINA(3)	4 y 8 mg comp	Antagonista dopaminérgico
	TADALAFILO(2)	20 mg comp	Antihipertensivo
* L (Antineoplásicos e Inmunomoduladores)	BENDAMUSTINA (2, 3)	2,5 mg/ml vial	Análogo mostaza nitorgenada
	CANAKINUMAB (2, 3)	150 mg vial	Inhibidor interleucina
	CERTOLIZUMAB PEGOL	200 mg jer	Inhibidor TNFα
	GEFITINIB (1)	250 mg comp	Inhibidor proteín-quinasa
	GOLIMUMAB (2)	50 mg pluma	Inhibidor TNFα
	MIFAMURTIDA (2,3)	4 mg vial	Inmunoestimulante
	PLERIXAFLOR (2, 3)	20 mg/ml vial	Inmunoestimulante
	VINFLUNINA (2)	25 mcg/ml vial	Alcaloide de la vinca
* N (Sistema Nervioso)	ESTIRIPENTOL (1, 3)	250 mg caps	Antiepiléptico
*R (Sistema respiratorio)	INDACATEROL	150 y 300 mcg cáps	Broncodilatador
	ROFLUMILAST	5.000 mcg comp	Inhibidor de la fosfodiesterasa

(1) = Medicamento de Diagnóstico Hospitalario. (2) = Medicamento de Uso Hospitalario. (3) = Medicamento Huérfano.

ADVICES 2011, primeros 5 meses, 174 productos



MAbs



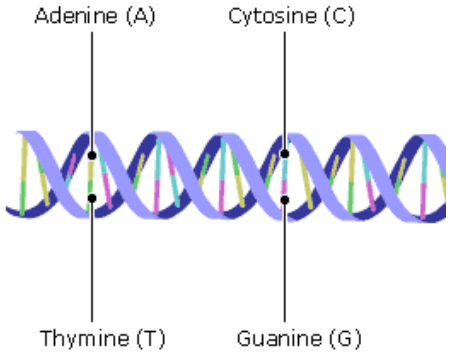
- Peculiaridades
- Biosimilares
- Terapia génica.

Medicamentos obtenidos a partir de tecnología del ADN recombinante, o de la expresión controlada de genes que codifican proteínas biológicamente activas en procariotas o eucariotas, incluyendo las células de mamífero transformadas, u obtenidos a partir de hibridomas o que emplean anticuerpos monoclonales durante su producción.

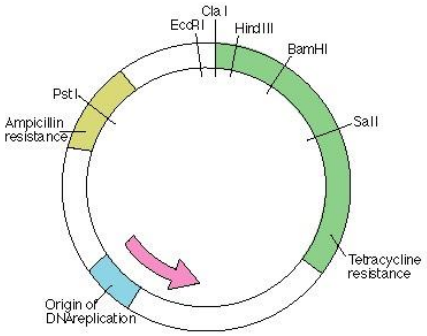
Proteínas Recombinantes

Terapia Génica

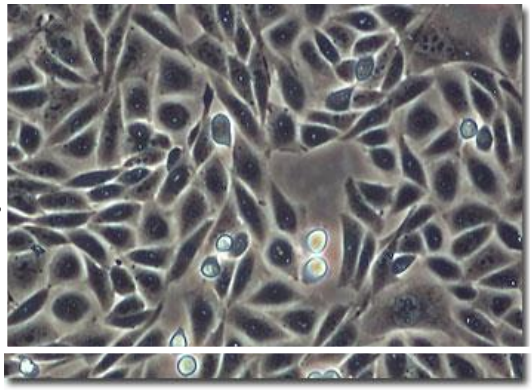
Proceso de producción



Secuencia de ADN



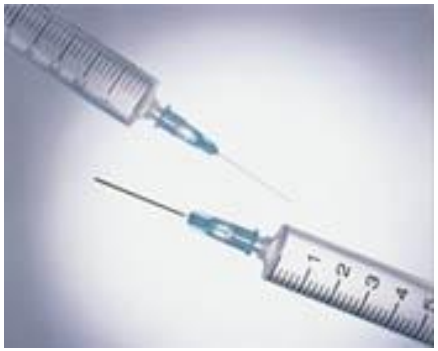
Clonado



Expresión celular

Fermentación

Purificación



Formulación

BACTERIAS

LEVADURAS

- Fácil producción a gran escala
- Producción rápida, costo bajo
- No modificaciones secundarias o ≠

Líneas celulares de mamífero

- Menor antigenicidad
- Producción compleja, costo elevado
- Riesgo de contaminación

Animales TRANSGÉNICOS

- Menor antigenicidad (?)
- Mantenimiento de animales, GMP
- Riesgo de contaminación

BBC NEWS

'Pharmed' goats seek drug license

Imagine you could get life-saving medicines from milking a common farmyard animal.

That idea moves a step closer to becoming a reality this week, as the European Medicines Agency (EMEA) considers the final stages of an application to license a natural human protein extracted from the milk of goats.

22 February 2006

The first recombinant protein produced in goat bioreactor Atryn received a belated approval from the European Union in June after an initial rejection.

NATURE BIOTECHNOLOGY VOLUME 24 NUMBER 8 AUGUST 2006

BBC NEWS

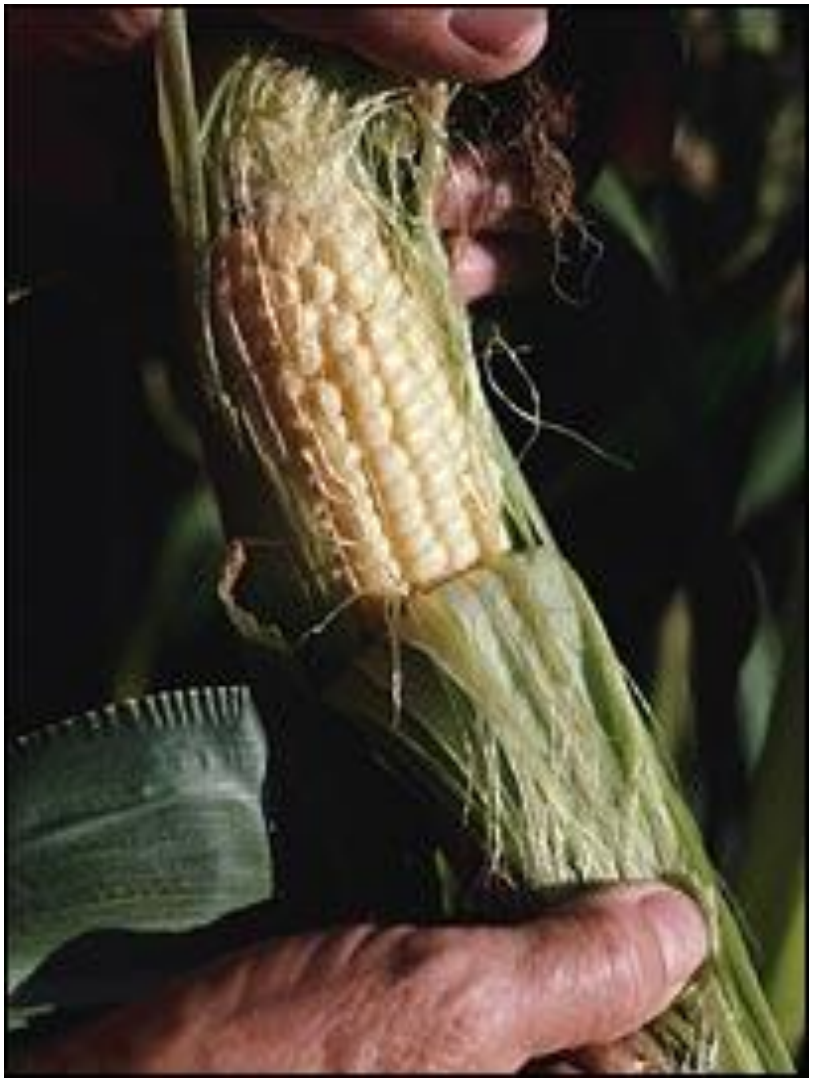
EU funding for GM plant vaccines

European scientists have launched a project to make pharmaceutically useful products in genetically modified crops. The consortium, called Pharma-Planta, wants to produce vaccines and other treatments for major diseases, such as HIV/Aids, rabies and TB.

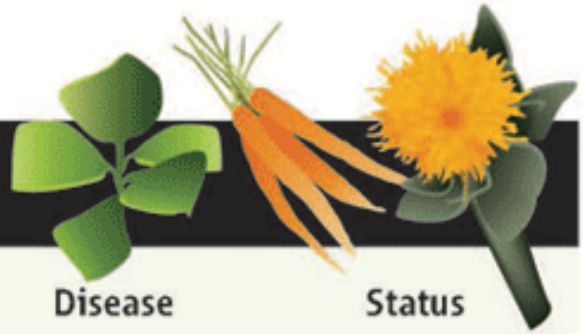
The EU has put 12 million euros (£8m) into the project, which hopes to start clinical trials by 2009.

The first product, possibly grown in maize, is likely to be an antibody that can be used to block HIV transmission.

It would be incorporated into a microbicidal cream that could be used in the vagina.



12 July 2004



Selected Plant-Made Pharmaceuticals

Company	Plant	Grown in	Drug or product	Disease	Status
Human drugs					
Protalix Biotherapeutics	carrot	cell culture	glucocerebrosidase	Gaucher disease	Phase III trial*
Biolex Therapeutics	duckweed	indoor chambers	alpha interferon	hepatitis C	Phase II trial*
SemBioSys Genetics	safflower	field	insulin	diabetes	Phase I/II trial †
Meristem Therapeutics	corn	field	lipase	cystic fibrosis	Phase III trial †
Other products					
Ventria Bioscience	rice	field	lactoferrin, lysozyme	diarrhea	Efficacy trial §
Cobento	*Arabidopsis*	greenhouse	human intrinsic factor	Vitamin B-12 deficiency	Approved ††
Planet Biotechnology	tobacco	field	secretory antibody vaccine	tooth decay	E.U. approved
Dow AgroSciences	tobacco	cell culture	poultry vaccine	Newcastle disease	USDA approved
CIGB, Cuba	tobacco	greenhouse	vaccine purification antibody	hepatitis B	On market

* Ongoing; † Projected late 2008; § Completed; †† In Ukraine.

Science 25 April 2008

Science 25 April 2008

Características proteínas recombinantes

Trastuzumab

- **Caracterización difícil.**
- **Estructura tridimensional compleja.**
- **Microheterogeneidad.**
- **Similares a moléculas endógenas.**
- **Inestables.**
- **Perfil de impurezas característico**
- **pK-pD particular**
- **Inmunogenicidad**

Biosimilitud
Biosimilares / Variaciones

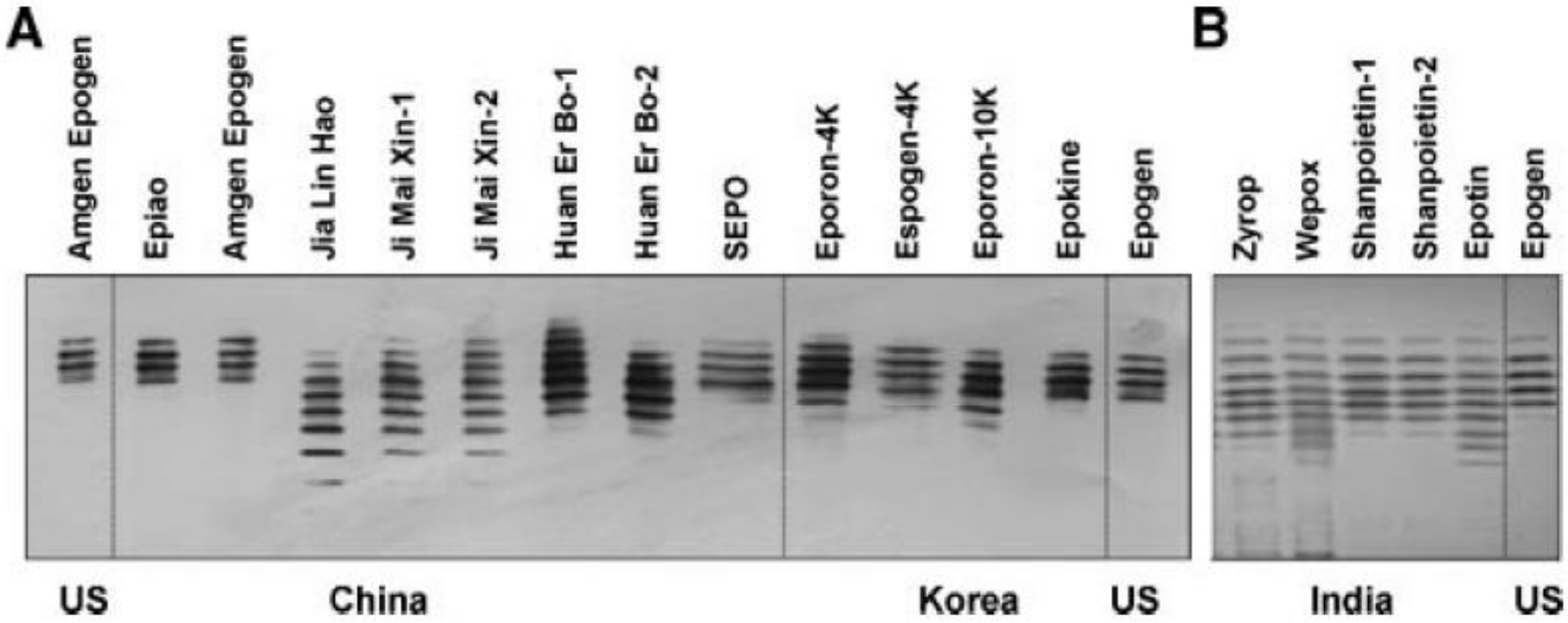
- **Caracterización difícil.**
- **Estructura tridimensional compleja.**
- **Microheterogeneidad.**
- **Similares a moléculas endógenas.**
- **Inestables.**
- **Perfil de impurezas característico**
- **pK-pD particular**
- **Inmunogenicidad**

Caracterización.

Producto de síntesis química.

…Descripción del producto
Identificación por IR, HPLC
Contenido en agua
Metales pesados
Cenizas Sulfatadas
Impurezas por HPLC
Contenido por HPLC
Solventes residuales…

→ **100 % de fiabilidad**



Park., et al., Journal of Pharmaceutical Sciences, 98 (5), **2009**, 1688-1699.

- **Inestables**
- **Perfil de impurezas característico**

  Relacionadas con el proceso productivo (proteínas o DNA de las células empleadas)

  Relacionadas con el producto (agregados, formas truncadas)

- **…Y además agentes adventicios y TSE**

COMPROMETEN SEGURIDAD Y EFICACIA DEL PRODUCTO

➢pK-pD particular

- El tamaño de las moléculas y su inestabilidad condiciona la vía de administración.

- Generalmente sufren el metabolismo propio de las proteínas endógenas, proteolisis inespecífica, dejando a un lado los procesos oxidativos hepáticos por lo que las interacciones farmacológicas propias del citocromo P450 no son aplicables.

- Buen escalado alométrico (en Pk).

- Disposición mediada por unión a receptor, aclaramiento por esta vía puede llegar a ser importante, responsable de no linealidad.

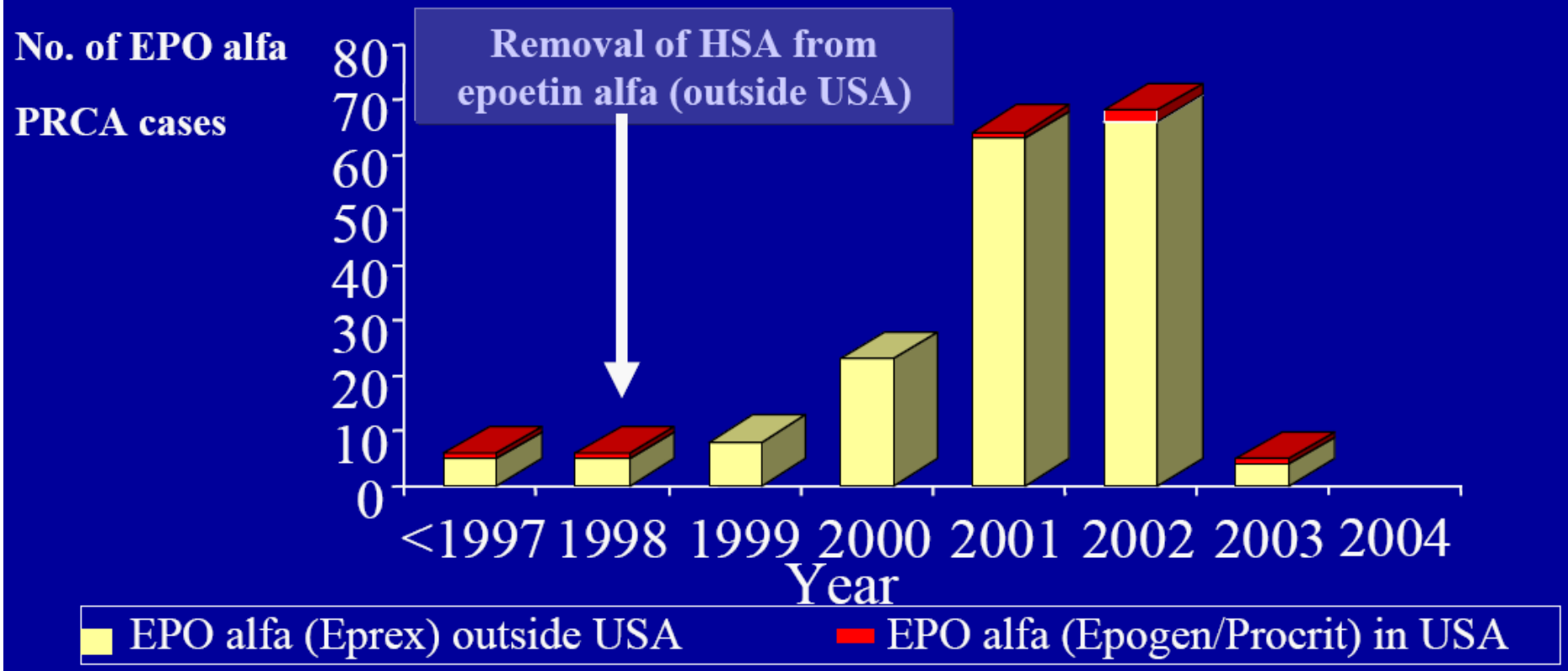
➢Inmunogenicidad

Table 1. Factors that May Impact Immunogenicity of Biotherapeutics

Product-Related Factors	Patient-Related Factors	Treatment-Related Factors
Protein structure (human/non-human, post-translational or chemical modifications, T cell epitopes)	Disease state being treated	Dose
Product quality parameters (isoforms, chemical and physical degradants)	General immune status of patient	Route
Contaminants and impurities	Genetic background (MHC genotype, HLA phenotypes)	Frequency of dosing
Target (cellular or soluble)	Concurrent illnesses and concomitant therapy	Length of treatment

Impact of Product-Related Factors on Immunogenicity of Biotherapeutics
SATISH KUMAR SINGH. Journal of Pharmaceutical Sciences
Volume 100, Issue 2, pages 354–387.

EPO alfa PRCA cases



- Epoetin α formulation in US still contains HSA
  - No increase in EPO-associated PRCA in USA

Immune-response and adverse reactions: PRCA case example - Nicole Casadevall
Disponible en EMA. http://www.ema.europa.eu

PRCA in Thailand

- Epo Ab-mediated PRCA is more common than in other countries

- Most cases reported with Eprex (9 cases) but also with :
  - Recormon®
  - Hemax® (local biosimilar)

Immune-response and adverse reactions: PRCA case example - Nicole Casadevall
Disponible en EMA. http://www.ema.europa.eu

PRCA in Thailand

- Storage and cold chain not guaranteed at out-of-hospital pharmacies
- No traceability substitution is frequent
- 7 marketed biosimilars
- Thai FDA announced that products are illegaly imported
- Counterfeit products

A Thai « loss of effect » registry is set-up run by hematology, nephrology and hospital pharmacy associations

Immune-response and adverse reactions: PRCA case example - Nicole Casadevall
Disponible en EMA. http://www.ema.europa.eu

Lecciones aprendidas de PRCA con EPO.

✓El desarrollo de anticuerpos no se puede anticipar (reacciones muy raras). Con incidencias de 1-3/100.000 no es posible detectarlo pre-autorización en ensayos clínicos.

✓Cuando son detectados es demasiado tarde.

✓Sólo un “risk management plan” sólido es capaz de ver este tipo de efectos.

Lecciones aprendidas de PRCA con EPO.

✓**Modificaciones menores de estos productos pueden alterar puntos clave como la inmunogenicidad.**

✓**No puede asumirse por tanto que todos los productos “similares” tengan el mismo perfil inmunogénico.**

✓**El manejo y almacenaje del producto pueden alterar el producto y por tanto…**

✓**La sustitución debería evitarse o al menos ser lo menos frecuente posible.**

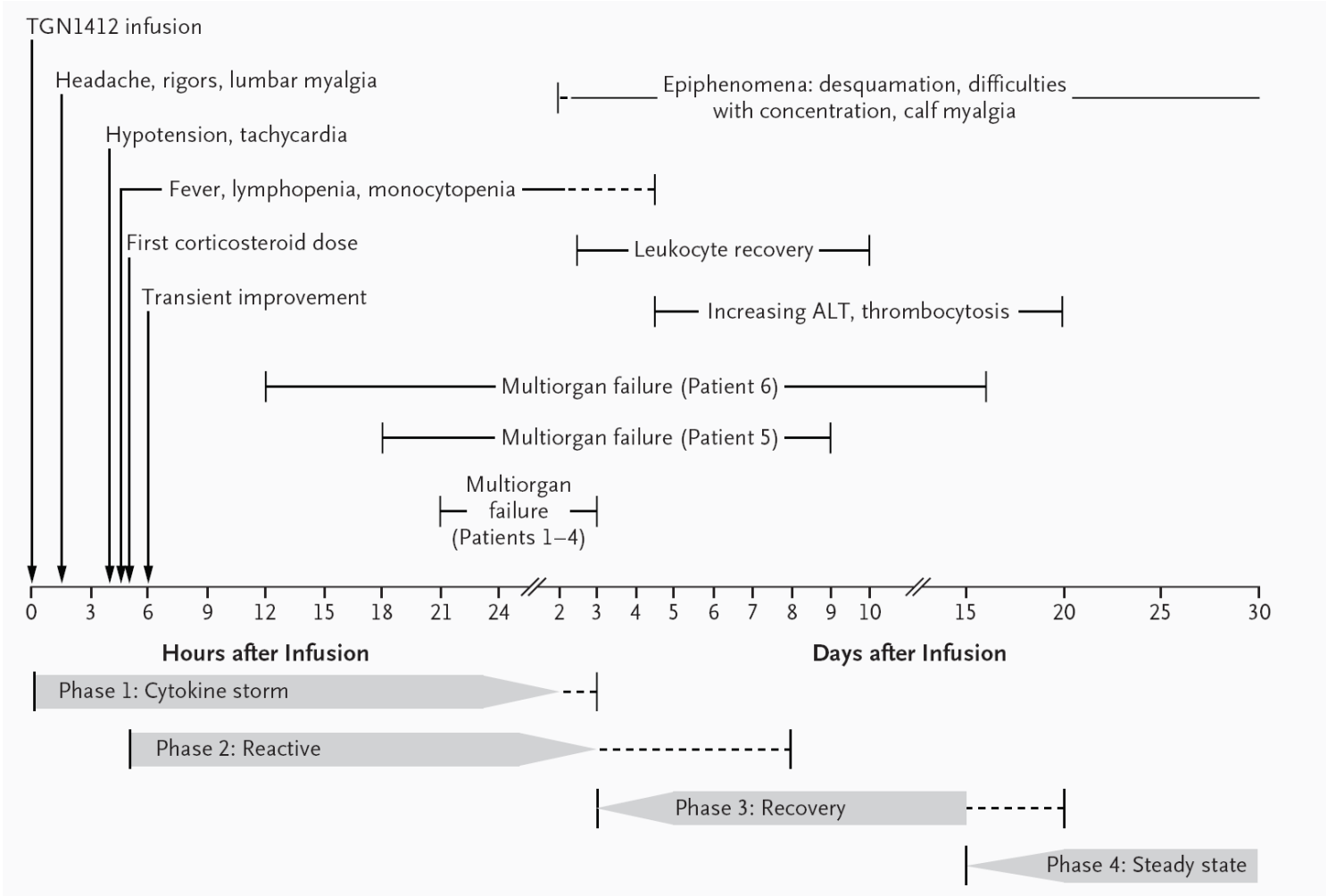
✓**La trazabilidad de estos productos es esencial. Atención a los INN en biosimilares.**

El caso TGN1412

Trial Design

- Mono-centre, double-blind, randomised first-in-man trail on TGN1412
  - TGN1412: CD-28 “super-agonist” antibody
- Trial population: 32 healthy volunteers in 4 cohorts
  - 0.1 mg/kg, 0.5 mg/kg, 2 mg/kg, 5 mg/kg
- First cohort: 8 subjects
  - 6 TGN1412 0.1 mg/kg, 2 Placebo
- Acute cytokine release syndrome in all six subjects treated with TGN1412
  - Life-threatening
  - Requiring ICU treatment

Clinical Course



Suntharalingam et al. NEJM 2006

European Medicines Agency

London, 22 March 2007
Doc. Ref.EMEA/CHMP/SWP/28367/2007

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)

DRAFT

GUIDELINE ON REQUIREMENTS FOR FIRST-IN-MAN CLINICAL TRIALS FOR POTENTIAL HIGH-RISK MEDICINAL PRODUCTS

DRAFT AGREED BY CHMP EXPERT GROUP	6 March 2007
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	22 March 2007
END OF CONSULTATION (DEADLINE FOR COMMENTS)	23 May 2007
AGREED BY	

Biosimilares

EMA:

Biosimilares autorizados hasta 2011

Insulin	GH	Epoetin	G-CSF	IFN-alpha
Marvel Insulins *retirado*	1.Omnitrope	3.HX 575 (Binocrit, Epoetin-alpha Hexal, Abseamed)	5.BiograstimRatiograstimFilgrastim Ratiopharm Tevagrastim	Alpheon (IFN-alpha) *rechazado*
	2.Valtropin	4.SB309 (Silapo, Retacrit)	6.Filgrastim Hexal, Zarzio	
		Epostim *retirado*	7.Nivestim	

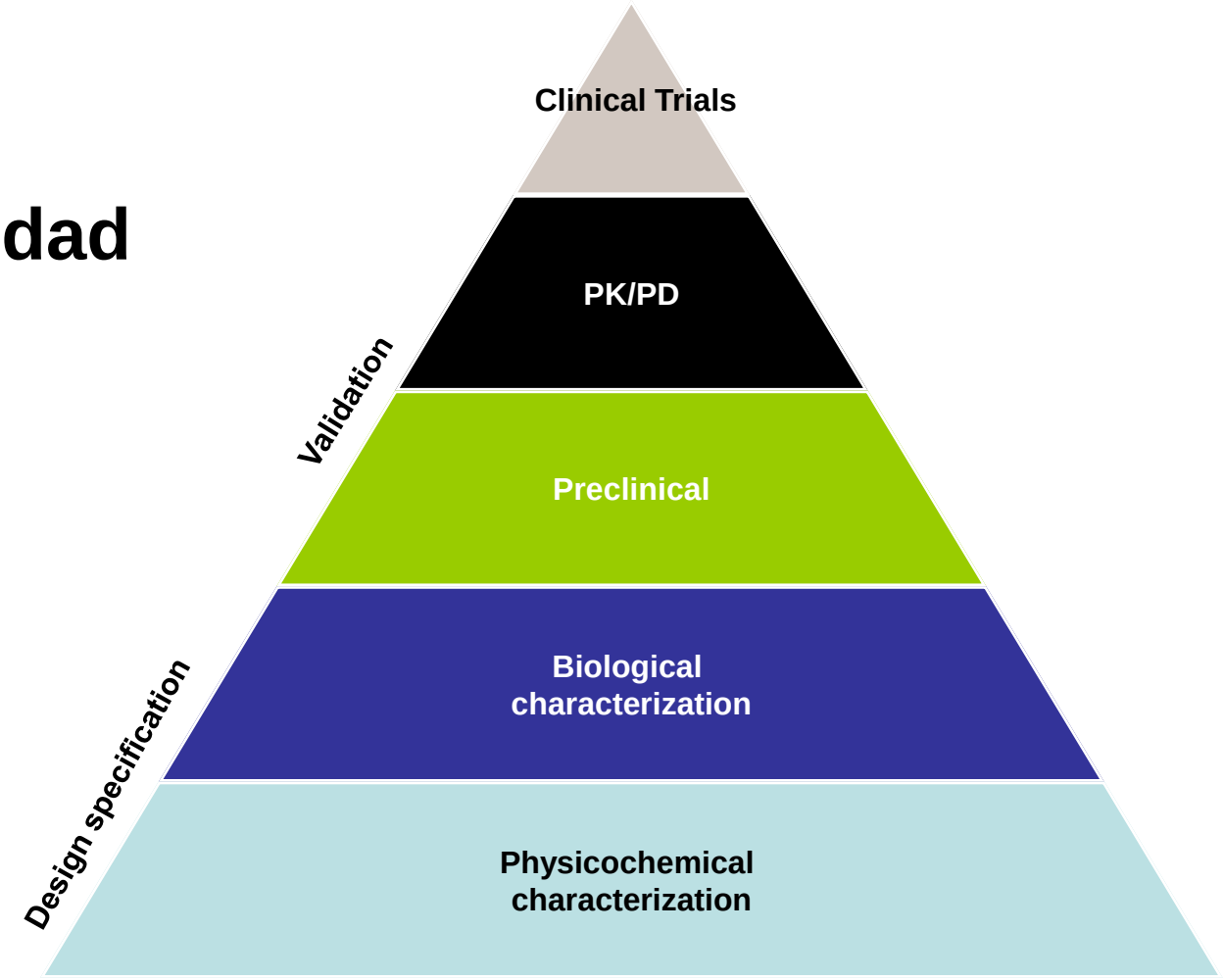
LMWH
Ninguno

Biosimilares Asuntos Importantes

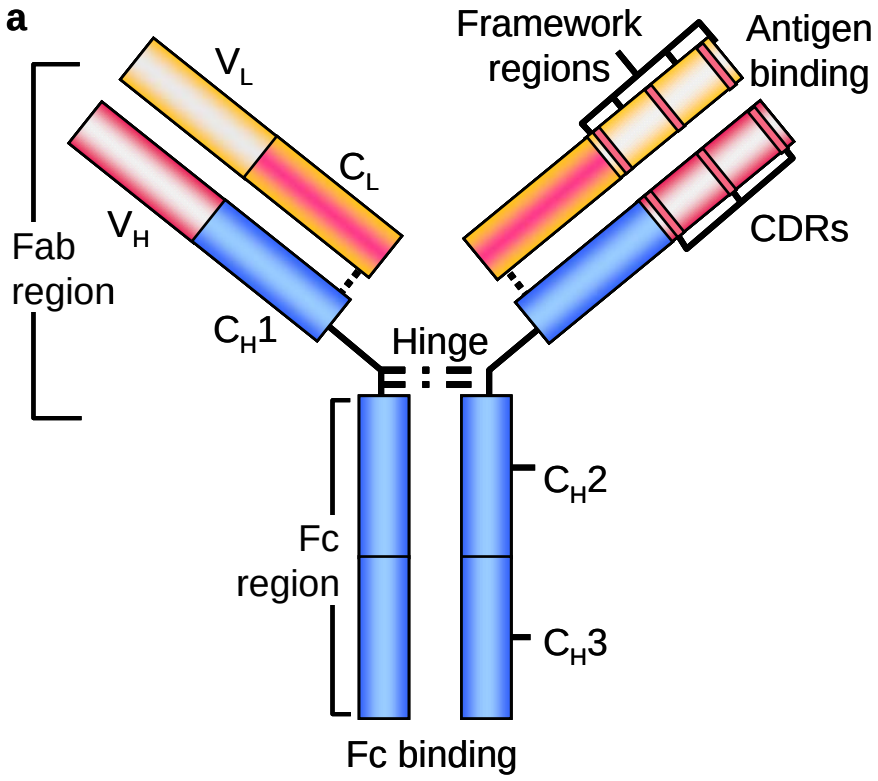
1. Biosimilitud
2. Farmacovigilancia/Identificación
3. Intercambiabilidad
4. Asuntos económicos/innovación

BIOSIMILITUD

Ejercicio de comparatibilidad



mAb Biosimilars



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 November 2010
EMA/CHMP/BMWP/403543/2010
Committee for Medicinal Products for Human Use (CHMP)

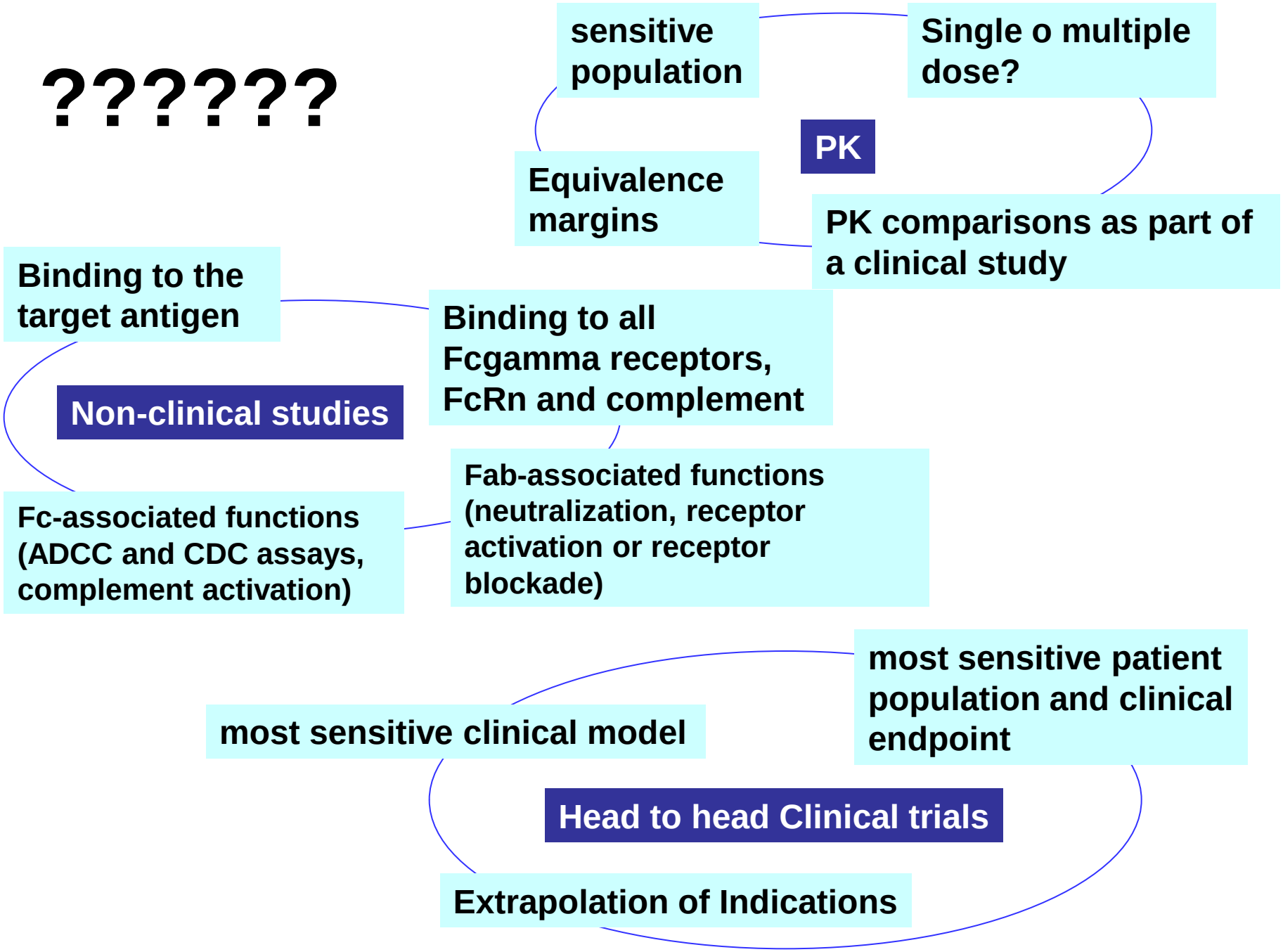
Guideline on similar biological medicinal products containing monoclonal antibodies

Draft

Draft Agreed by Similar Biological Medicinal Products Working Party	October 2010
Adoption by CHMP for release for consultation	18 November 2010
End of consultation (deadline for comments)	31 May 2011

Comments should be provided using this template. The completed comments form should be sent to BMWP.Secretariat@ema.europa.eu

Keywords	*Biosimilars, monoclonal antibodies, similar biological medicinal products, relevant animal model, clinical use, clinical endpoints, extrapolation*


??????
sensitive population
Single o multiple dose?
PK
Equivalence margins
PK comparisons as part of a clinical study
Binding to the target antigen
Binding to all Fcgamma receptors, FcRn and complement
Non-clinical studies
Fab-associated functions (neutralization, receptor activation or receptor blockade)
Fc-associated functions (ADCC and CDC assays, complement activation)
most sensitive patient population and clinical endpoint
most sensitive clinical model
Head to head Clinical trials
Extrapolation of Indications

SUBSTITUTION *vs.* INTERCHANGEABILITY

PRESCRIBABILITY vs.SWITCHABILITY

Prescribability

Drug product is provided to "naïve" subject who has not received yet the drug in any of its forms

Autorización EMA

Switchability

Drug product is provided to a subject who has already received another form of the drug,

- i.e., the patient is "switched" from one formulation to another

Alternating / interchangeability

Repeated switching among reference and various test formulations

- Perhaps without intervention or even information of health-care provider

Different Designs
Crossover studies

En España la intercambiabilidad o sustitución inmediata no está permitida pero otro asunto es la sustitución desde la farmacia del hospital…

TERAPIA GÉNICA

Tabla 2. Enfermedades hereditarias que pueden ser consideradas como primeras candidatas a ser tratadas por medio de la terapia génica

Enfermedad	Producto normal del gen defectuoso	Células a modificar por la TG
Inmunodeficiencia combinada grave (SCID) (niños burbuja)	Enzima adenosin desaminasa (ADA)	Células de la médula ósea o linfocitos T
Hemoglobinopatías (talasemias)	b-globina de la hemoglobina	Células de la médula ósea
Hemofilia A	Factor VIII de coagulación	Células del hígado o fibroblastos
Hemofilia B	Factor IX de coagulación	Células del hígado o fibroblastos
Hipercolesterolemia familiar	Receptor del hígado para lipoproteínas de baja densidad (LDL)	Células del hígado
Enfisema hereditario	a-1-antitripsina (producto hepático que protege los pulmones de la degradación enzimática)	Células del pulmón o del hígado
Fibrosis quística	Producto del gen CFTR que mantiene libre de mucus los tubos aéreos de los pulmones	Células del pulmón
Distrofia muscular de Duchenne	Distrofina (componente estructural del músculo)	Células musculares

Terapia génica en trastornos hematopoyéticos

Inmunodeficiencia Combinada Grave ligada a cromosoma X

Hacein-Bey-Abina, S., et al., Sustained correction of X-linked severe combined immunodeficiency by ex vivo gene therapy.N Engl J Med, 2002. 346(16): 1185–1193.

11 PACIENTES

Hacein-Bey-Abina, S., et al., A serious adverse event after successful gene therapy for X-linked severe combined immunodeficiency. N Engl J Med, 2003, 348(3): 255–256.

4 PACIENTES

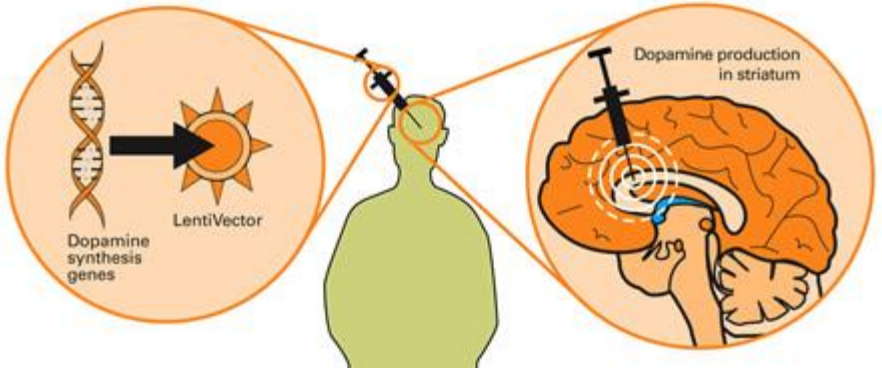
Hacein-Bey-Abina, S., et al., LMO2-associated clonal T cell proliferation in two patients after gene therapy for SCID-X1.Science, 2003, 302(5644): 415–419.

Efficacy of Gene Therapy for X-Linked Severe Combined Immunodeficiency. Hacein-Bey-Abina, S., et al. N Engl J Med 2010; 363:355-364July 22, 2010

Background
The outcomes of gene therapy to correct congenital immunodeficiencies are unknown. We reviewed long-term outcomes after gene therapy in nine patients with X-linked severe combined immunodeficiency (SCID-X1), which is characterized by the absence of the cytokine receptor common γ chain.
Methods
The nine patients, who lacked an HLA-identical donor, underwent ex vivo retrovirus-mediated transfer of γ chain to autologous CD34+ bone marrow cells between 1999 and 2002. We assessed clinical events and immune function on long-term follow-up.
Results
Eight patients were alive after a median follow-up period of 9 years (range, 8 to 11). Gene therapy was initially successful at **correcting immune dysfunction in eight of the nine patients**. However, acute leukemia developed in four patients, and **one died**. **Transduced T cells were detected for up to 10.7 years after gene therapy**. Seven patients, including the three survivors of leukemia, had sustained immune reconstitution; three patients required immunoglobulin-replacement therapy. Sustained thymopoiesis was established by the persistent presence of naive T cells, even after chemotherapy in three patients. The T-cell−receptor repertoire was diverse in all patients. Transduced B cells were not detected. Correction of the immunodeficiency improved the patients' health.
Conclusions
After nearly 10 years of follow-up, gene therapy was shown to have corrected the immunodeficiency associated with SCID-X1. Gene therapy may be an option for patients who do not have an HLA-identical donor for hematopoietic stem-cell transplantation and for whom the risks are deemed acceptable. This treatment is associated with a risk of acute leukemia.

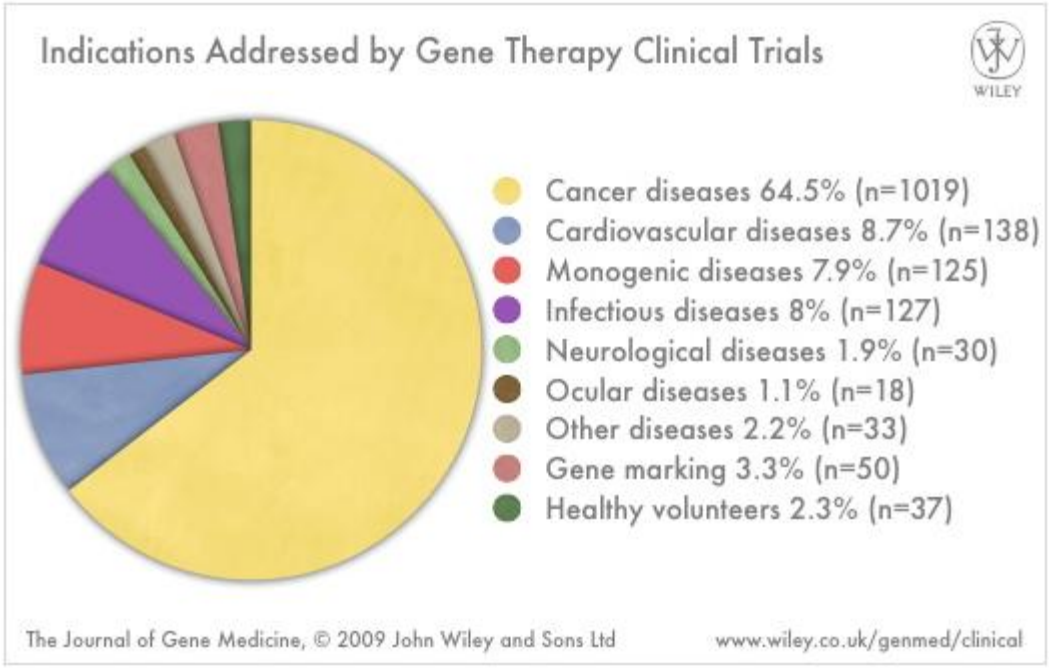
ProSavin®

ProSavin is a gene-based treatment for Parkinson's disease, a progressive movement disorder caused by the degeneration of dopamine producing nerve cells in the brain. In Parkinson's disease, there is degeneration of the cells in the brain that produce dopamine. ProSavin uses the Company's LentiVector system to **deliver the genes for three enzymes that are required for the synthesis of dopamine**. The product is administered locally to the region of the brain called the striatum, converting cells into a replacement dopamine factory within the brain, thus replacing the patient's own lost source of the neurotransmitter.



INVESTIGACION TERAPIA GÉNICA

http://www.nature.com/cgt/index.html



http://www.wiley.co.uk/genetherapy/clinical/

Terapia génica en cáncer. Estrategias.

- Immunomodulation
- Prodrug Converting Enzymes (Suicide Strategy)
- Tumor Suppressor Genes
- Tumor Lysis by Recombinant Viruses
- Antiangiogenic and Antiproteolytic Gene Therapy

Enzimas transformadoras de un profármaco (Gen suicida)

•Timidina quinasa derivada del virus del herpes (HSV-tk), que genera derivados trifosfato del ganciclovir que inhiben la síntesis de ADN

• Citosina deaminasa (CD) derivada de Escherichia coli, que convierte la 5 fluorocitosina (5-FC) en 5-fluorouracilo (5-FU)

No solo muere la célula que recibe el gen sino también las células circundantes

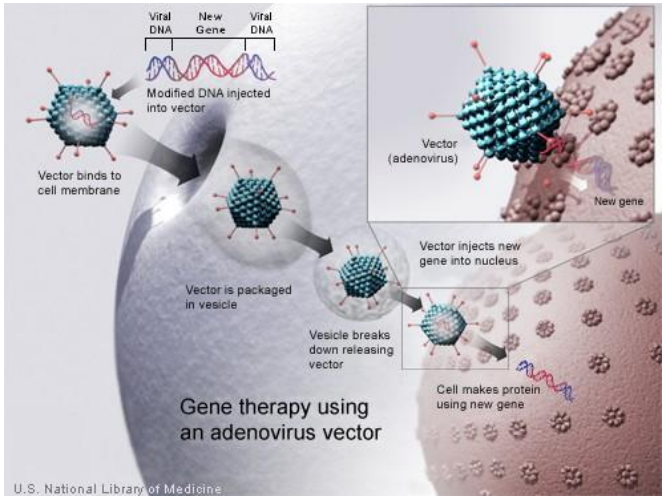
Cerepro®

Producto calificado como Orphan Drug

Mechanism of action

Cerepro® is comprised of a gene encased in a virus 'shell' (a "vector"). Vectors transfer their gene 'payload' into target cells, a process known as transfection, which use this new genetic material as a blueprint for the production of new beneficial proteins.

Cerepro® uses a well-established **adenoviral vector (Ad5)** to introduce the gene that causes cells to express a protein called **thymidine kinase ("TK").** Following the standard surgery to remove the solid tumour mass, Cerepro® is injected through the wall of the cavity left behind by the surgical removal of the solid tumour, into the surrounding healthy brain tissue. In the following days, the healthy cells in the wall of the cavity express TK. Five days after surgery, the drug **ganciclovir ("GCV")** is given to the patient as part of the overall Cerepro® treatment regimen. Neither TK nor GCV is individually active but they react together to produce **a substance which destroys cells when they try to divide**. Since **cell division is a key characteristic of cancer and the normal brain cells are not dividing, cells that try to divide to form a new tumour around the site of the removal of the original tumour are targeted for destruction by the Cerepro® treatment**.



Información página web compañía

Pero….

Taking into account the assessment performed by the CAT, the CHMP concluded that, based on the results of the main study, including the main measure of effectiveness, Cerepro was not shown to be effective. Finally, Cerepro was associated with an increased risk of serious side effects such as hemiparesis (paralysis on one side of the body) and seizures (fits). These side effects were a concern, considering the lack of proven effectiveness.

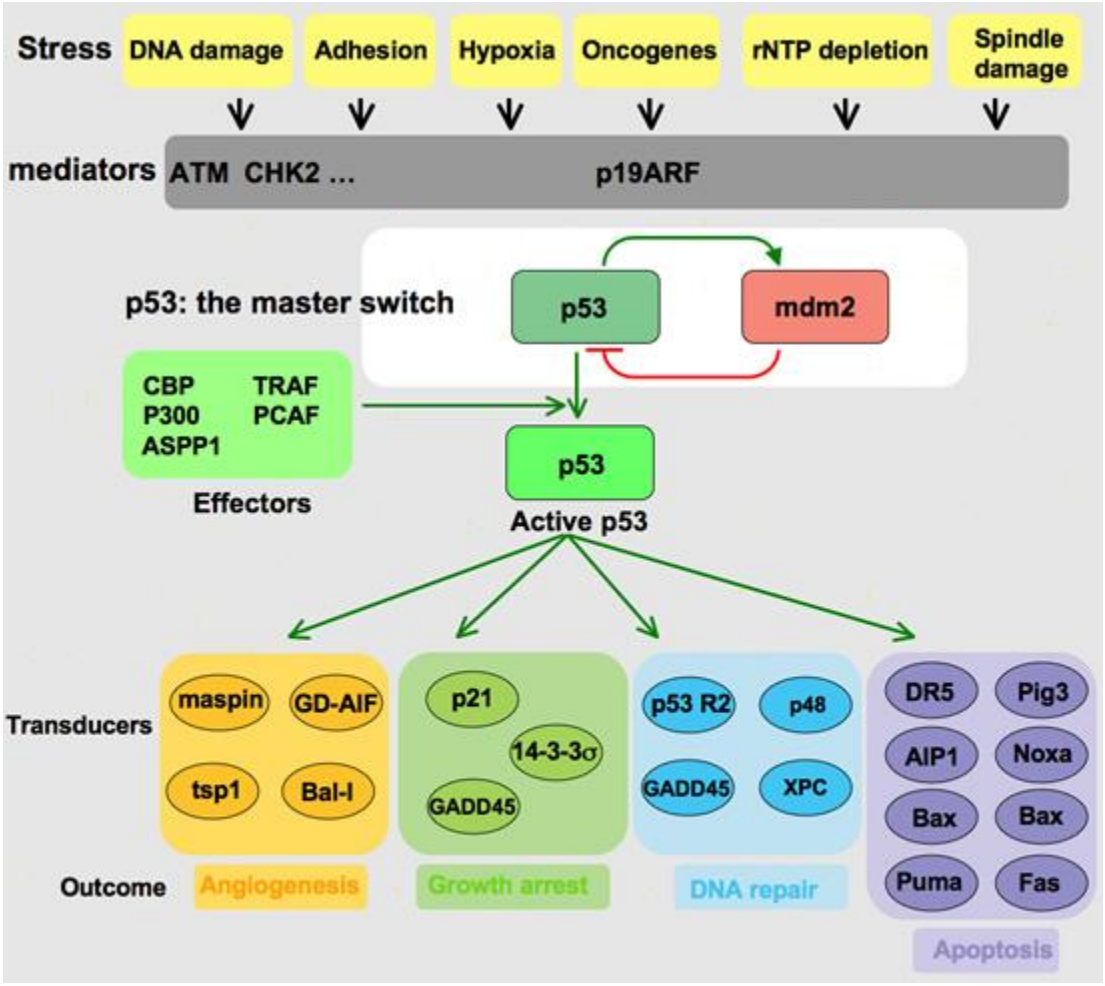
At that point in time, because of lack of proven effectiveness, the CHMP was of the opinion that the benefits of Cerepro did not outweigh its risks and recommended that it be refused marketing authorisation.

Publicado en Marzo de 2010

http://www.ema.europa.eu

Genes supresores de tumores

p53 es el gen supresor tumoral que se ha encontrado alterado con más frecuencia en tumores humanos, es lógico que se haya utilizado muy frecuentemente en protocolos de reemplazamiento genético. Es la pérdida de la función normal de los genes supresores de tumores lo que contribuye al desarrollo neoplásico.


Stress
DNA damage
Adhesion
Hypoxia
Oncogenes
rNTP depletion
Spindle damage
mediators
ATM CHK2 ...
p19ARF
p53: the master switch
p53
mdm2
CBP
P300
ASPP1
TRAF
PCAF
Effectors
p53
Active p53
Transducers
maspin
GD-AIF
tsp1
Bal-I
p21
14-3-3σ
GADD45
p53 R2
p48
GADD45
XPC
DR5
Pig3
AIP1
Noxa
Bax
Bax
Puma
Fas
Outcome
Angiogenesis
Growth arrest
DNA repair
Apoptosis

ADVEXIN

The active substance in Advexin, contusugene ladenovec, is a ‘viral vector’. This is a type of virus that has been altered genetically so that it can carry a gene into the cells of the body. The virus in Advexin is an ‘adenovirus’ that has been engineered so that it cannot make copies of itself and therefore does not cause infections in humans. The gene carried by the virus in Advexin is the normal (non-defective) p53 gene.

Advexin was expected to be injected directly into the tumours, thus allowing the cancer cells to produce normal p53 protein again. The p53 protein, which is produced from the non-defective p53 gene present in the human body, normally contributes to the repair of damaged DNA and causes cell death when the DNA cannot be repaired. Because cancer cells contain damaged DNA, the p53 protein either helps to repair the DNA or causes the cells to die.

In Li-Fraumeni cancer, where the p53 gene is defective, the p53 protein does not work properly and the cancer cells can continue to grow and divide. Advexin was expected to cure or slow down the disease by restoring the normal protective function of the cells.

Sin embargo…

On 17 December 2008, Gendux Molecular Limited officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wishes to withdraw its application for a marketing authorisation for Advexin for the treatment of Li-Fraumeni cancer. Advexin was designated as an orphan medicinal product on 23 October 2006.

The CHMP was concerned that there was not enough evidence to show that the injection of Advexin into Li-Fraumeni tumours led to benefits for patients. The Committee also had concerns over what happens to the medicine in the body, how it should be given and how safe it is. In addition, the company had not supplied enough evidence to demonstrate that Advexin could be made in a reliable manner, or that it would not be harmful to the environment or to people in close contact with the patient.

Virus oncolíticos

Esta estrategia comenzó en 1957 (Smith), 4 años después de descubrirse el método de replicación de los adenovirus. Aunque se postuló por primera vez en 1904 (Dock).

La base de esta estrategia es inyección en el tumor del virus, e infección de las células tumorales muriendo estas y diseminando el virus para infectar otras células tumorales, obviamente sin infectar células sanas.

ONYX adenovirus modificado comercializado en China en 2005 por Shanghai Sunway Biotech Co.

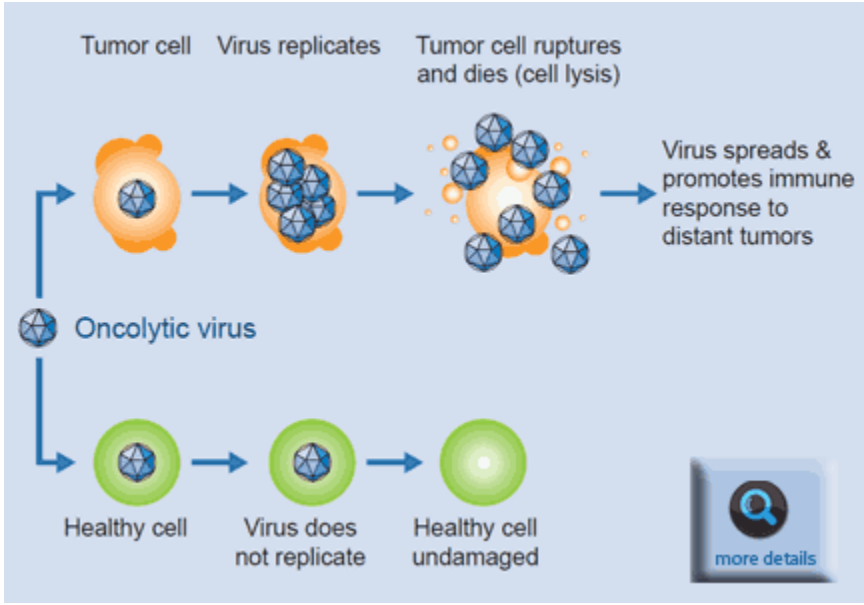


Table 1a Peer reviewed publications on clinical studies with ONYX-015

Author	Indication/ study type	No. of patients	Viral dose	Route of administration	Treatment schedule	Chemo-therapy	Main adverse events	Best response (%)
Ganly (Ganly *et al*, 2000)	Recurrent head and neck cancer Phase I	22	10^7-10^{11} pfu[a]	Intratumoural injection	Single injection	–	Fever, nausea chills	PR[c], 3 (14)
Mulvihill (Mulvihill *et al*, 2001)	Pancreatic carcinoma Phase I	23	10^8-10^{11} pfu	Intratumoural injection	Single injection	–	Flu-like symptoms, fever	MR[d], 6 (26) SD[e], 10 (43)
Nemunaitis (Nemunaitis *et al*, 2001)	Metastatic solid tumours Phase I	10	$2\times10^{10}-2\times10^{13}$ particles[b]	Intravenous injection	Day 1, 8, 15, q 21 days	Carboplatin, taxol	Fever, rigor, LFT[g]↑	MR, 1 (10) SD, 8 (80)
Nemunaitis (Nemunaitis *et al*, 2000)	Recurrent head and neck cancer Phase II	40	10^{10} pfu	Intratumoural injection	Day 1–5, q 21 days[h]	–	Pain at injection site, fever, flu-like symptoms	CR[f], 3 (8) PR, 2 (5)
Khuri (Khuri *et al*, 2000)	Recurrent head and neck cancer Phase II	37	10^{10} pfu	Intratumoural injection	Day 1–5, q 21 days	5-FU cisplatin	Pain at injection site, fever, flu-like symptoms	CR, 8 (27) PR, 11 (36)

[a]Plaque forming units; [b]Viral particles; [c]Partial response; [d]Minor response; [e]Stable disease; [f]Complete response; [g]Liver function tests; [h]Additional 10 patients received 'hyperfractionated' treatment, see text.

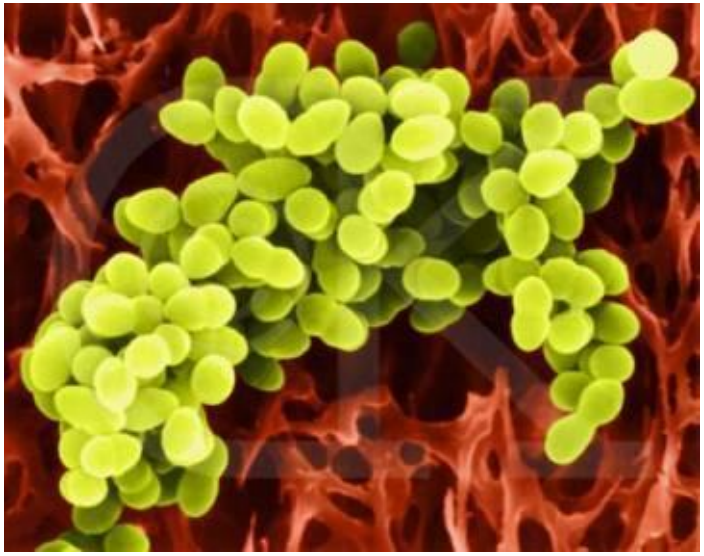
Table 1b Clinical studies with ONYX-015 published as abstracts

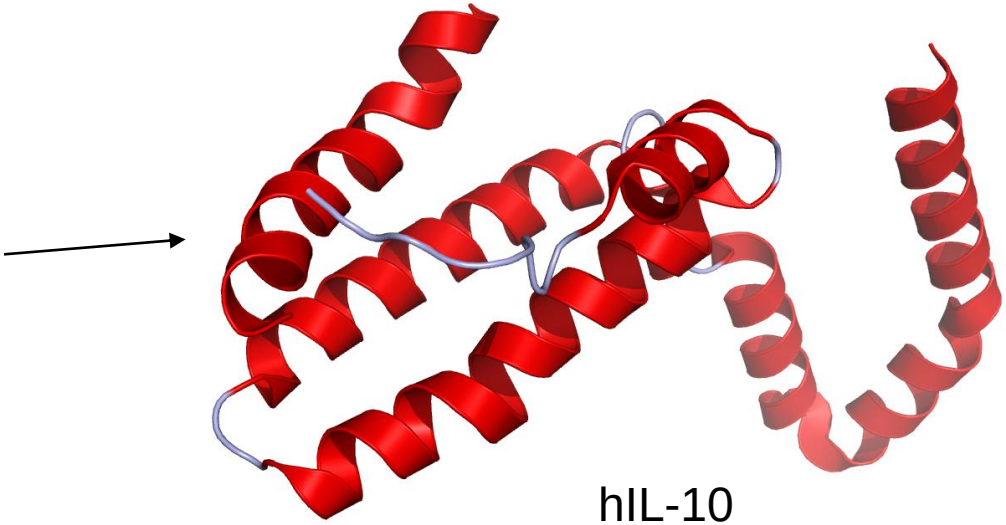
Author	Indication/ study type	No. of patients	Viral dose	Route of administration	Treatment schedule	Chemo-therapy	Main adverse events	Best response (%)
Rudin (Rudin *et al*, 1999)	Oral dysplasia phase II	10	10^{10} pfu	Oral mouthwash	Daily ×5, q 28 days	–	–	CR 3 (67) PR[a] 2 (20)
Reid (Reid *et al*, 2001)	Colorectal cancer liver metastases	25	$2\times10^8-2\times10^{12}$ particles	Infusion into hepatic artery	Day 1, 8, q 28 days	5-FU/ Leucovorin	Fever, flu-like symptoms	CR 0 (0) PR 2 (8)
Hecht (Hecht *et al*, 2000)	Pancreatic carcinoma phase I/II	18	10^9-10^{10} pfu	Intratumoural injection[b]	Weekly ×8	Gemcitabine	Fever, sepsis	PR 2 (11) MR 1 (6)
Bergsland (Bergsland *et al*, 1998)	Liver metastases phase I	16	10^8-10^{11} pfu	Intratumoural injection	Day 1, q 28 days	–	Flu-like symptoms	MR 2 (13) SD 9 (60)
Vasey (Vasey *et al*, 2000)	Ovarian cancer phase I	16	10^9-10^{11} pfu	Intraperitoneal infusion	Daily ×5, q 21 days	–	Abdom. Pain, flu-like symptoms	N/A

[a]Reduction of grade of dysplasia; [b]Endoscopic ultrasound guided.

Otros enfoques

AG011 [technology platform for the genetic engineering of a non-pathogenic bacterium, *Lactococcus lactis* engineered to secrete hIL-10]
Applicant: ActoGenix Indication: treatment of ulcerative colitis





hIL-10

Lactococcus lactis

GRACIAS