COL.LEGI DE QUÍMICS DE CATALUNYA
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Qué se puede patentar en biotecnología y biomedicina

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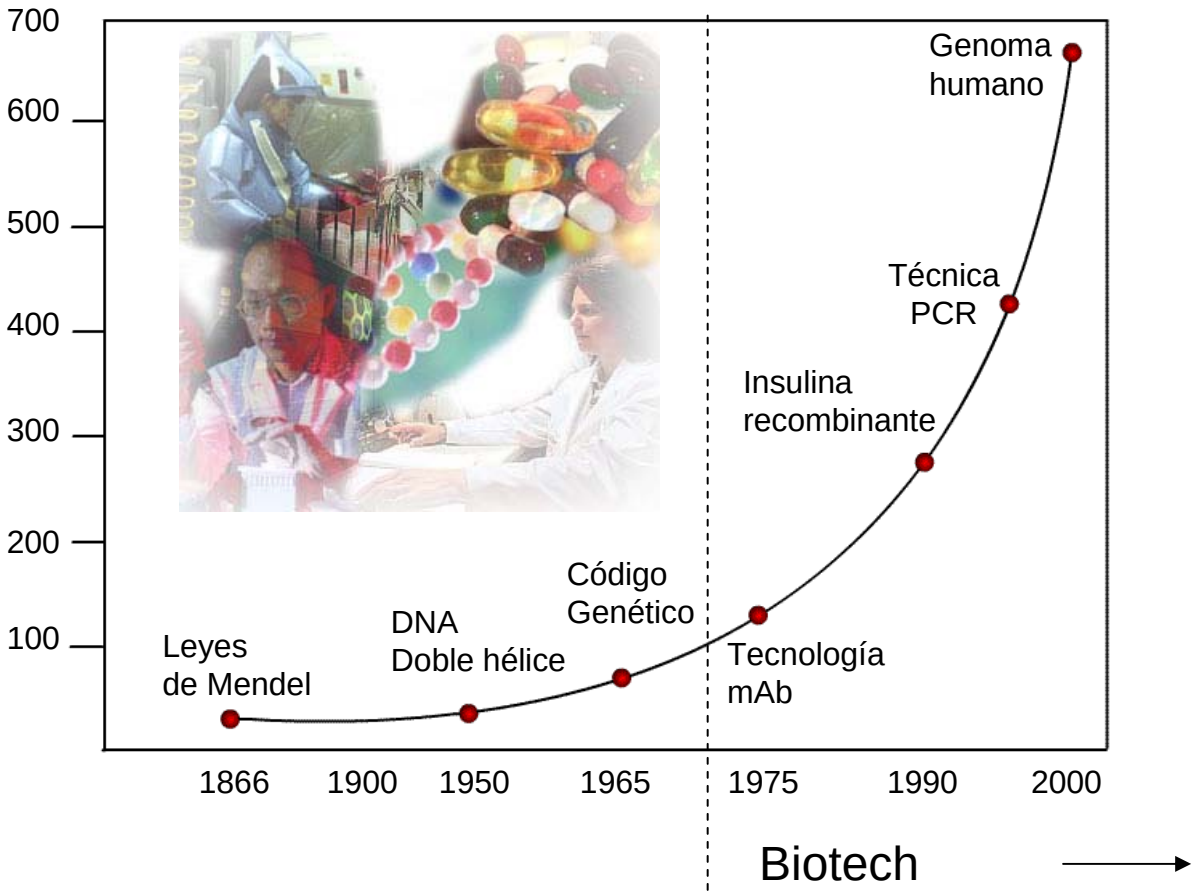
Evolución de la biotecnología



Brief history in patents

Inventors have been filing applications for biotechnological patents for over a hundred years.

* 8 November 1843, Patent No. 3, granted in Finland on **novel method for producing yeast cultures**.

* 29 July 1873, microbiologist Louis Pasteur patented his improved **yeast-making method** at the French Patent Office.

* 1869, BASF patents **alizarin made by a biotechnological process**. The substance the scientists were able to synthesise – a red dye – was used in textile manufacturing.

* In recent years, researchers have succeeded in better understanding the functioning of the human body and its immune system. Biotechnology has already provided life-saving medicaments such as human **insulin, erythropoietin and Herceptin**, and it appears to promise cures for conditions currently regarded as untreatable.

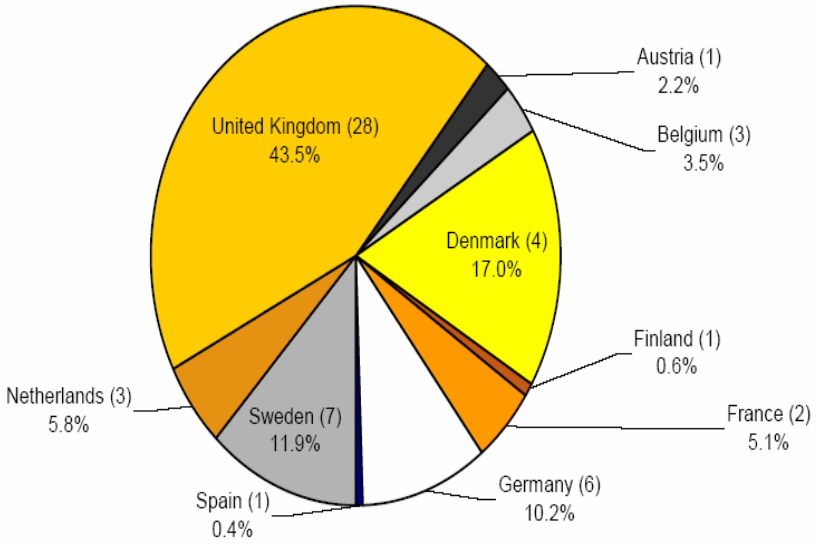
* In agriculture, biotechnology is used to modify the physiology of plants with a view to introducing specific desirable features, such as **resistance to disease and herbicides, or achieving higher yields**.

* However, the debate about possible risks to individuals, society and the environment continues unabated. It affects all levels of political, economic and scientific decision-making.

European Patent Office

United Kingdom leads in EU biotechnology R&D investment

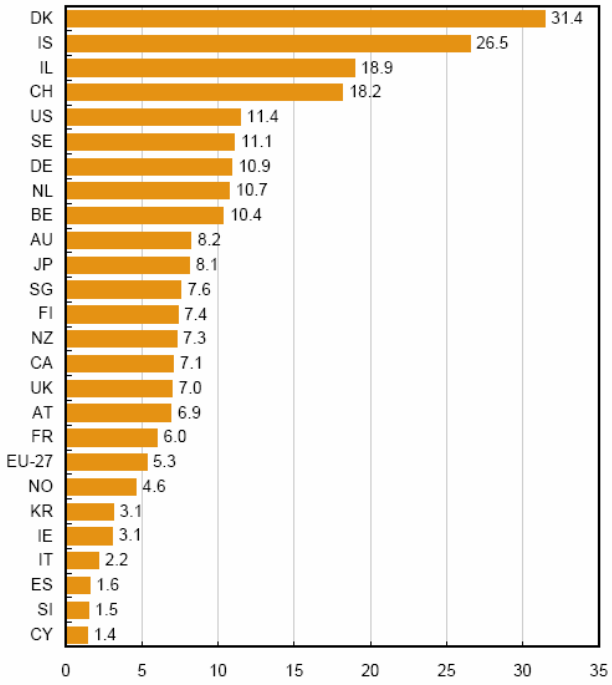
Figure 7: Biotechnology R&D investment of EU companies by country, EU-27 Member States, 2005



In brackets: number of companies

Source: based on 2006 EU industrial R&D investment scoreboar

Figure 1: Biotechnology patent applications to the European Patent Office (EPO) by country, per million inhabitants, EU-27 Member States and selected countries[(1)], 2003



Source: Eurostat, Patent Statistics

[(1)] Countries with less than one biotechnology patent application per million inhabitants are not shown.

Eurostat 2007

Patentes de Biotecnología. Dificultades derivadas de la tecnología

La protección por patentes de invenciones biotecnológicas es de una importancia comercial grande y creciente.

Contrariamente a algunas opiniones, se decidió adaptar el sistema de patentes para proteger las invenciones biotecnológicas, adaptación que ha tenido serias dificultades:

- implica materia viva (autoreplicable)

- enorme velocidad de progreso (lo que origina muchos conflictos de patentes por la dificultad de decidir el estado de la técnica que conoce el experto en la materia).

- problemas especiales respecto algunos requisitos de patentabilidad: actividad inventiva, suficiencia de la descripción, aplicabilidad industrial, grado de generalización permitido en la redacción de las reivindicaciones...

- desinformación y cierta oposición a cualquier patente en el campo de productos naturales o que tengan que ver con seres vivos.

Actividad inventiva

Lo que comenzó siendo revolucionario, pronto se convirtió en una práctica estándar.

Ej. patente de Genentech sobre TPA, que reivindicaba *"Human tissue plasminogen activator as produced by recombinant DNA technology"*

- considerada válida por la Cámara de Recursos de la EPO tras una oposición por falta de actividad inventiva (Decisión T 923/92; EP 93.619 B1);

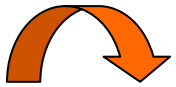
-considerada nula por falta de actividad inventiva en GB, diciendo que, "puesto que la sustancia era conocida, era obviamente deseable obtenerla por ADN recombinante, y los métodos estándar para ello ya eran conocidos" (1989 RPC 147 CA).

- Esto ya en 1989! -

Dificultades derivadas de la tecnología

Invenciones en las que:

- DNA Proteína

- Antígeno  Anticuerpo

se consideran en general, obvias.

Paso que se basa en una información intrínseca de la molécula y la tecnología para llevar a cabo el paso se considera estándar (tecnología de DNA recombinante y tecnología de hibridomas).

Pero, al revés no es tan obvio:
Conocida la estructura primaria de una proteína, la redundancia del código genético hace que sean muchas las secuencias de DNA que la codifiquen, por lo que a veces se decidió que no era obvia la selección de una o varias de estas secuencias (USPQ2d 1529, Fed. Cir. 1993).

Aplicabilidad industrial

Es necesario que sea específica
Decir que un compuesto es útil para el “tratamiento de enfermedades” y es una “sustancia antitumoral” es insuficiente. Se necesitan pruebas, que generalmente serán *in vitro*, pero en algunos casos también *in vivo*.

Revised Interim Utility Guidelines de la USPTO (1999) define qué pruebas se necesitan en cada caso.

P.ej. ESTs, Una secuencia de DNA sin más utilidad que usarla como sonda para obtener el gen completo no tiene utilidad específica de acuerdo con la USPTO y será rechazada

Suficiencia de la descripción

Saber qué es lo adecuado describir requiere poner atención a los cambios en el campo de la técnica, ya que conocimientos que se consideraban experimentales e impredecibles rápidamente se han convertido en estándares y bien conocidos.

Requisitos:
- Depósito de microorganismos / líneas celulares, bajo el Tratado de Budapest
- Lista de secuencias nuevas y conocidas (aminoácidos y DNA) que se describen en la memoria de patente.

Entorno legal y herramientas

Sector de la técnica todavía difuso en cuanto a la protección que puede llegar a tenerse. Hay muchos documentos de patente de materia biotecnológica que lo piden todo (documentos de 200 páginas con 100 reivindicaciones!)

Guía:

- Directiva de Biotecnología 98/44/EC y transposición a la Ley española 10/2002

- Convenio de la Patente Europea y decisiones de las Cámaras de Recursos de la EPO

- Trilateral projects

(existen direferencias entre lo que se puede patentar en biotech entre EEUU y Europa).

Hay una extensa cooperación en patentabilidad biotecnológica USPTO-EPO-JAPIO

Trilateral website: www.uspto.gov/web/tws
(Statistics and reports > Comparative study on biotechnology patent practices / Trilateral Studies)

Trilateral Project 24.1
Biotechnology Comparative Study on Biotechnology Patent Practices

Trilateral Project B3b
Comparative study on biotechnology patent practices
- Update of study 24.1. Theme: Patentability of DNA fragments (2000)
- Theme: Nucleic acid molecule-related inventions whose functions are inferred based on homology search

Trilateral Project WM4
- Comparative studies in new technologies (biotechnology, business methods, etc). Report on comparative study on protein 3-dimensional (3D) structure related claims (2002)
- Report on comparative study on Examination Practice relating to Single Nucleotide Polymorphisms (SNPs) and Haplotypes (2003)

Categorías de invenciones (i.e. de reivindicaciones)

entitades ("productos")

- físicas (mecánicas, eléctricas...)
- químicas (sustancias puras, mezclas...)
- biológicas (microorganismos, animales, plantas...)

actividades ("procedimientos o métodos")

- procedimientos de preparación (obtención, manufactura...)
- métodos para ... (cualquier actividad industrial)
- usos (procedimientos de utilización) en general
- métodos de terapia-cirugía-diagnosis
- uso para la preparación de un producto para terapia-cirugía diagnosis

Representative Subject Matter for Biotechnology Claims

DNA: genes, promoters, vectors, antisense
Protein, fragments, enzymes, antibodies

Living Organisms: Host Cells; Transformed Cell Lines, bacteria, viruses, “animals, plants”

Methods of producing proteins, PCR-related methods, in vitro diagnosis and kits, preparation of plants and animals, making foods, medicines.

Productos biotecnológicos de interés en farmacia:
Anticuerpos monoclonales
Citocinas
Factores hematopoyéticos
Vacunas
Proteínas
Oligonucleótidos, RNA interferencia, etc

Early and famous European biotech patents

EP 32134 (Biogen, 1984):
DNA encoding an alpha interpheron.
First EPO patent on human gene sequence

EP 148605 (Kirin Amgen, 1990):
Human recombinant erythropoietin, DNA encoding it

EP 200362 (1993): PCR
Most cited patent in Chemical Abstracts in 2001
Sold for $300 million in 1991

EP 318216 (1993): hepatitis C virus

EP 849990 (2001): method for cloning animals –Dolly the sheep-

Transposición a la Ley española 10/2002 de la Directiva de Biotecnología 98/44/EC Art. 4 LP

1. Son patentables las invenciones nuevas, que impliquen actividad inventiva y sean susceptibles de aplicación industrial, aún cuando tengan por objeto un producto que esté compuesto o que contenga materia biológica, o un procedimiento mediante el cual se produzca, transforme o utilice materia biológica.

2. La materia biológica aislada de su entorno natural o producida por medio de un procedimiento técnico podrá ser objeto de una invención, aun cuando ya exista anteriormente en estado natural.

3. A los efectos de la presente Ley, se entenderá por "materia biológica" la materia que contenga información genética autorreproducible o reproducible en un sistema biológico y por "procedimiento microbiológico", cualquier procedimiento que utilice una materia microbiológica, que incluya una intervención sobre la misma o que produzca una materia microbiológica.

Diferenciación del producto reivindicado del que existe en la naturaleza con términos como:

biologically pure / substantially pure / purified / isolated

Ex. A biologically pure culture of microorganism X.

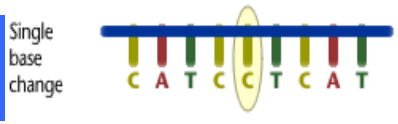
Ha habido un método de selección (presión ambiental) para llegar al producto (posibilidad de reivindicar el método de selección también).

Art. 4 LP

6. No se considerarán como invenciones susceptibles de aplicación industrial en el sentido del apartado 1, los métodos de tratamiento quirúrgico o terapéutico del cuerpo humano o animal ni los métodos de diagnóstico aplicados al cuerpo humano o animal. Esta disposición no será aplicable a los **productos**, *especialmente a las sustancias o composiciones ni a las invenciones de aparatos o instrumentos para la puesta en práctica de tales métodos."*

Decisión G1/04 (16.12.2005)

Ej: un SNP está relacionado con una enfermedad



1. A method of prognosis or diagnosis of DISEASE in a human, comprising the detection of the presence or the absence of a polymorphism on the X gene, in a sample separated from said human, said polymorphism causing an amino acid substitution of E (glutamic acid) by K (lysine) at POSITION' of the corresponding encoded polypeptide.

2. The method according to claim 1, wherein the polymorphism is a single nucleotide substitution of the G in POSITION of the X sequence gene.

44. A kit for performing the method defined in any of the claims 1-3, comprising appropriate reagents for detecting the presence of the absence of the polymorphism.

45. A kit for performing the method defined in claim 4, comprising one or more oligonucleotides defined in any of the claims 22-27.

- Lo que interesa es el kit, el producto comercial, para poder hacer valer los derechos de patente. El método se describe para entender el uso del kit. -

Gene expression profiling

17 February 2005 (17.02.2005) PCT WO 2005/015236 A2

(51) **International Patent Classification**[7]: **G01N 33/579**, C12Q 1/68

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(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2005/01

(54) **Title:** A METHOD FOR PREDICTING THE PROGRESSION OF ADENOCARCINOMA

(57) **Abstract:** The present invention is related to a method for predicting the progression of adenocarcinoma, in particular colorectal cancer, after surgery whereby the level of expression of one or several gene markers is compared to a sample serving as control. Another method according to the invention is related to identifying an agent which will inhibit the progression of adenocarcinoma. The invention is further related to kits and arrays comprising the marker genes according to the invention.

1. A method of evaluating the progression of cancer of a patient who is afflicted with an adenocarcinoma, the method comprising comparing:

   a) the level of expression of one or several marker genes in a patient sample, and
   b) the level of expression of one or several of said marker genes in a sample from a control subject afflicted with an adenocarcinoma which did not recur within 5 years after surgical removal of the adenocarcinoma,

   wherein at least one of said marker genes is selected from the group consisting of the marker genes listed in Table 3, a significant difference between the level of expression of one or several of said marker genes in the patient sample and the level of one or several of said marker genes in a sample from a control subject is an indication that the patient carries the risk of progression of cancer.

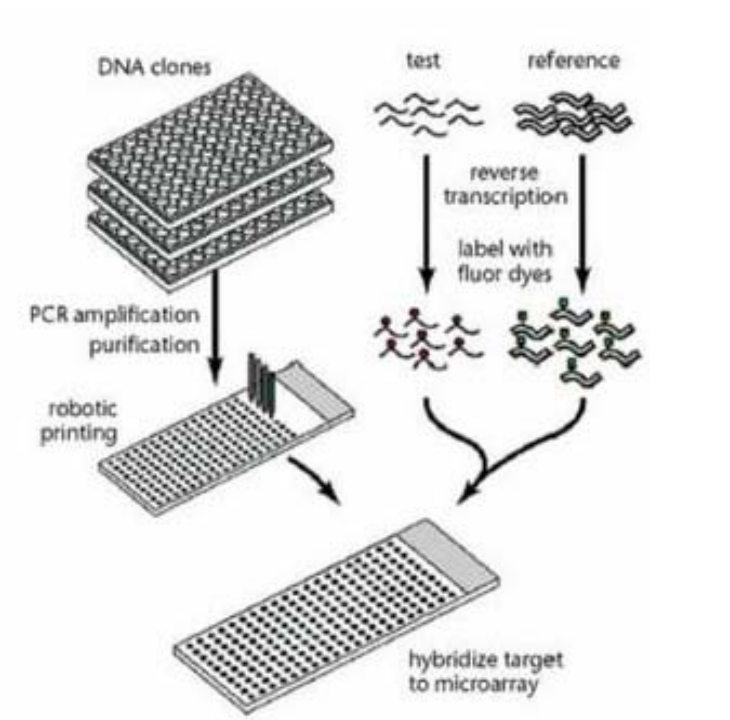
2. The method according to claim 1, wherein the adenocarcinoma is a colorectal cancer.

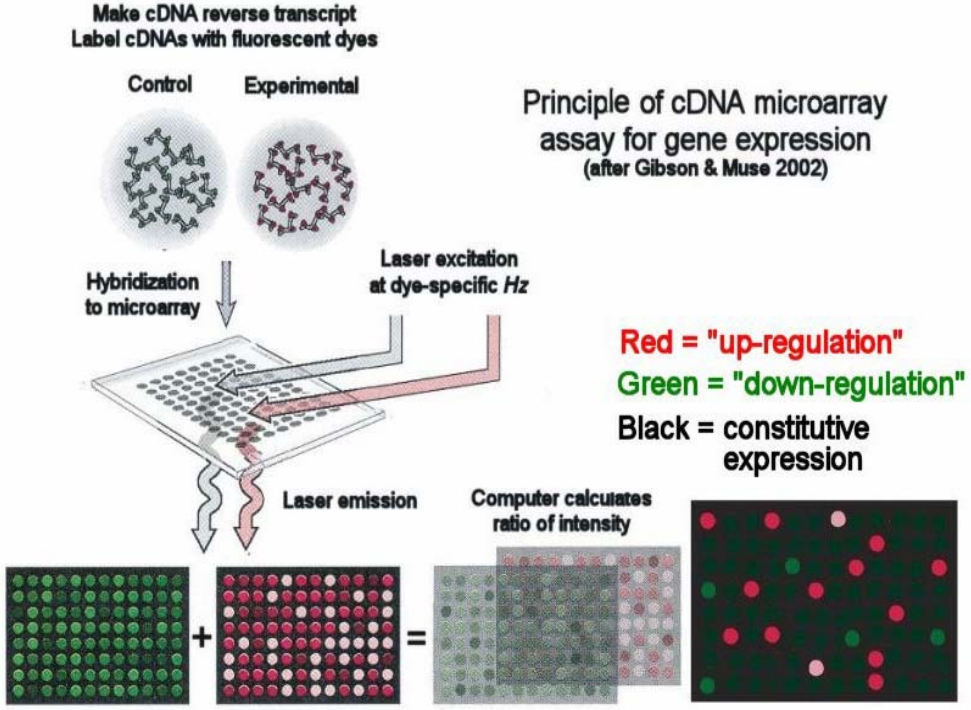
20. A kit for assessing whether a patient carries a risk of progression of adenocarcinoma, particularly colorectal cancer, the kit comprising reagents for assessing expression of one or several marker genes, wherein at least one of said marker genes is selected from the group consisting of the marker genes listed in Table 3.

Table 3:

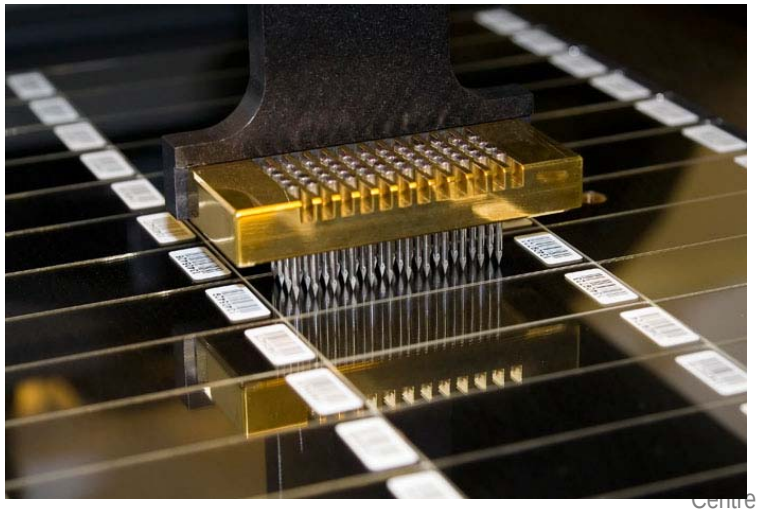
SEQ ID NO	GENE	AFFYMETRIX_ID
1	SFRS protein kinase 1	1031_at
2	replication factor C (activator 1) 4 (37kD)	1054_at
3	interleukin 1, alpha	1076_at
278	((Ubiquitin-Conjugating Enzyme Ubch5))	1164_at
279	((Dihydrofolate Reductase, Alt. Splice 6))	1178_at
4	protein tyrosine phosphatase type IVA, member 2	1241_at
5	protein geranylgeranyltransferase type I, beta subunit	1275_at
6	RNA-binding protein gene with multiple splicing	1276_g_at
280	((Tyrosine Kinase, Receptor Axl, Alt. Splice 2))	1278_at
7	discoidin domain receptor family, member 2	1319_at
8	transforming growth factor, beta-induced, 68kD	1385_at
9	splicing factor, arginine/serine-rich 10 (transformer 2 homolog)	140_s_at
10	ubiquitin-conjugating enzyme E2G 1 (UBC7 homolog, C. elegans)	1423_at
11	MAD, mothers against decapentaplegic homolog 3 (Drosophila)	1433_g_at
12	epidermal growth factor receptor pathway substrate 8	1467_at
13	v-myb myeloblastosis viral oncogene homolog (avian)	1473_s_at
14	Hypothetical protein CG003	1529_at
15	insulin-like growth factor binding protein 3	1586_at
152		37319_at

Centre de Patents de la UB





Principle of cDNA microarray assay of gene expression



Microarray printing

Art. 5 LP

No podrán ser objeto de patente:

1. Las invenciones cuya explotación comercial sea contraria al orden público o a las buenas costumbres, sin poderse considerar como tal a la explotación de una invención por el mero hecho de que esté prohibida por una disposición legal o reglamentaria.

1. En particular, no se considerarán patentables en virtud de lo dispuesto en el párrafo anterior:

a) Los procedimientos de clonación de seres humanos.

b) Los procedimientos de modificación de la identidad genética germinal del ser humano.

c) Las utilizaciones de embriones humanos con fines industriales o comerciales.

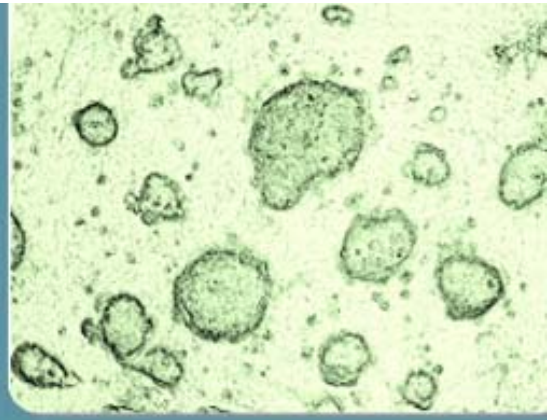
d) Los procedimientos de modificación de la identidad genética de los animales que supongan para éstos sufrimientos sin utilidad médica o veterinaria sustancial para el hombre o el animal, y los animales resultantes de tales procedimientos.

Art. 5 LP

No obstante, la prohibición de utilización de embriones humanos con fines industriales o comerciales, no afecta a las invenciones técnicas que tengan un objetivo terapéutico o de diagnóstico que se aplican al embrión y que le son útiles.

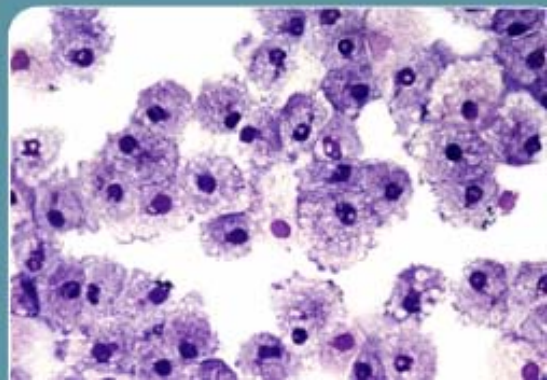
Non-patentable subject-matter

Human embryonic stem cells and further products obtainable only by destruction of human embryos



Patentable subject-matter

Non-human embryonic stem cells, foetal stem cells and adult somatic stem cells



Stem cells

Informe de la Comisión al Consejo y al Parlamento Europeo (13.10.2005):

"Las disposiciones de la Directiva son inequívocas en cuanto a las células madre totipotentes, ya que cada célula puede por sí misma dar origen a un ser humano, y con arreglo al artículo 5, apartado 1, el cuerpo humano en los diferentes estadios de su constitución y de su desarrollo no puede constituir una invención patentable."

"La situación de las células madre embrionarias pluripotentes es más compleja. No es posible dar una respuesta inmediata a la cuestión…La Comisión seguirá atenta a la evolución que se produzca en este ámbito."

Art. 5 LP

… No podrán ser objeto de patente:

d) Los procedimientos de modificación de la identidad genética de los animales que supongan para éstos sufrimientos sin utilidad médica o veterinaria sustancial para el hombre o el animal, y los animales resultantes de tales procedimientos.

The „naked mouse"

A transgenic mouse used to test hair cosmetic products

→ NO

The „Harvard Oncomouse"

Used as a model for studying cancer

→ YES

Art. 5 LP

2. Las variedades vegetales y las razas animales. Serán, sin embargo, patentables las invenciones que tengan por objeto vegetales o animales si la viabilidad técnica de la invención no se limita a una variedad vegetal o a una raza animal determinada.

3. Los procedimientos esencialmente biológicos de obtención de vegetales o de animales. A estos efectos se considerarán esencialmente biológicos aquellos procedimientos que consistan íntegramente en fenómenos naturales como el cruce o la selección.

Lo dispuesto en el párrafo anterior no afectará a la patentabilidad de las invenciones cuyo objeto sea un procedimiento microbiológico o cualquier otro procedimiento técnico o un producto obtenido por dichos procedimientos.

Art. 5 LP

G1/98
(Anti-pathogenically effective compositions; Novartis)

Plant defined by single recombinant DNA sequence are neither expressly nor implicitly defines a single plant variety.

A claim wherein specific plant varieties are not individually claimed is not excluded from patentability.

NO: Rose cultivar cv3145 characterised by resistance to glyphosphate

YES: Rose plant comprising a gene conferring glyphosphate resistance

Microorganismos

Generalmente implican el uso de una nueva cepa de microorganismo (bacterias, hongos y levaduras, pero también virus y células) para producir un producto químico (metabolito) nuevo o producir mejor un producto químico conocido. El microorganismo puede ser aislado de la naturaleza u obtenido en el laboratorio (mutación inducida, ingeniería genética...).

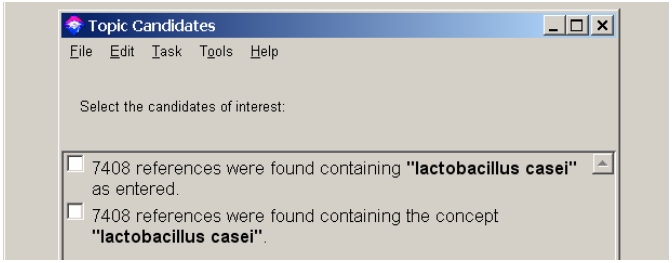
Tipos de reivindicaciones:

- Del producto *per se,* obtenido por el microorganismo (si el producto es nuevo).
- Del procedimiento de obtención del producto, pero esta protección suele ser débil.
- Del microorganismo como tal

Depósito del microorganismo para la suficiencia de la descripción.

Si el microorganismo es de origen natural hay que reivindicarlo como cepa aislada o purificada, para que tenga novedad.

Ej. Protección de una nueva cepa de microorganismo, aislado natural, como probiótico para incluir en productos lácteos



Búsqueda en Hcaplus y Medline (artículos y patentes)

Depósito de la cepa en el CECT. En el Informe de búsqueda de la EPO, el examinador dice:

considered as being identical to the strains disclosed in D1. A different deposit number alone is not sufficient to prove a difference between deposited organisms. Consequently, the subject-matter of claims 1-57 cannot be considered as being novel in view of D1. ➔ El examinador pensará ¿Por qué no utilizas una de las tantas conocidas?

- ¿Problema técnico a plantear? Probiótico, propiedades inmunes, adherencia a mucosa gástrica, etc.
- Búsqueda de antecedentes exhaustiva inviable
- Protección concretada a cepa y alguna variante (por propiedad: secreción de sustancia activa, etc).

Cepa que se va a vender. Estrategia secreto-patente.

- Ejemplo de la complejidad de patentar en biotech -

Art. 25 LP. Tratado de Budapest

Para cumplir el requisito de suficiencia de la descripción, y dado que es prácticamente imposible definir una cepa de micoorganismo de forma no ambigua mediante una descripción escrita, hay que depositar el microorganismo para que éste sea posteriormente accesible al público.

La mayoría de países desarrollados han adoptado el Tratado de Budapest (en vigor desde 1980), que regula las formalidades y exige una viabilidad mínima de 30 años desde el depósito original.

Para cumplir con los requisitos de todos los países, debe citarse el número de depósito en la solicitud de patente, e incluir también una descripción escrita del microorganismo.

En muchos países se permite que el público (potencial competidor) tenga acceso a la cepa depositada desde el momento de la publicación de la solicitud (en la EPO a través de un experto y con condiciones).

Por esto, en los casos en los que se pueda controlar el acceso físico a la cepa, será aconsejable que la empresa mantenga la invención (y la cepa) en secreto, sin patentarla.

Animales y plantas transgénicos

Animales:

- modelos para investigación (p.ej. el oncoratón de Harvard / ratones 'knock-out')

- fuente de productos biológicos (proteínas)

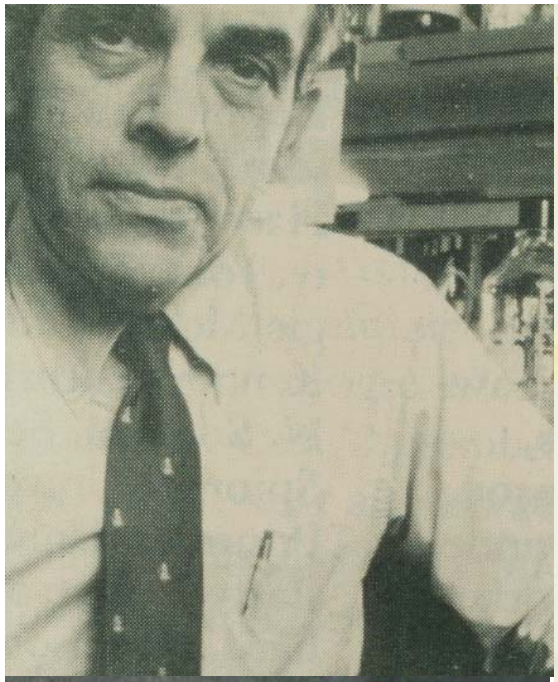
- posible fuente de órganos para transplantes en el futuro (cerdos).

Plantas:

- Propiedades mejoradas: P.ej. el tomate de Calgene, que se podía madurar en la planta: se introdujo en 1994, pero fue retirado por una combinación de problemas de patentes, técnicos (la maquinaria recolectora de tomates verdes no servía), de marketing y de aceptación por el consumidor.

- Resistencia a un herbicida (p.ej. glifosato o *Round-up*® de Monsanto), para poder usar éste contra las otras especies dañinas.

- Resistencia a una plaga



[45] Date of Patent: Apr. 12, 1988

United States Patent [19]

Leder et al.

[54] TRANSGENIC NON-HUMAN MAMMALS

[75] Inventors: Phillip Leder, Chestnut Hill, Mass.; Timothy A. Stewart, San Francisco, Calif.

[73] Assignee: President and Fellows of Harvard College, Cambridge, Mass.

[21] Appl. No.: 623,774

[22] Filed: Jun. 22, 1984

[51] Int. Cl.[4] C12N 1/00; C12Q 1/68
C12N 15/00; C12N 5/00

[52] U.S. Cl. 800/1; 435/6
435/172.3; 435/240.1; 435/240.2; 435/320
435/317.1; 935/32; 935/59; 935/70; 935/76

OTHER EMBODIMENTS

Other embodiments are within the following claims. For example, any species of transgenic animal can be employed. In some circumstances, for instance, it may be desirable to use a species, e.g., a primate such as the rhesus monkey, which is evolutionarily closer to humans than mice.

We claim:

1. A transgenic non-human mammal all of whose germ cells and somatic cells contain a recombinant activated oncogene sequence introduced into said mammal, or an ancestor of said mammal, at an embryonic stage.

* * *

11. The mammal of claim 1, said mammal being a rodent.

12. The mammal of claim 11, said rodent being a mouse.

En US se quedaron con non-human mammal. En EP solicitaron eucariota!:

1. A method for producing a transgenic eucaryotic animal having an increased probability of developing neoplasms, said method comprising introducing into an animal embyro an activated oncogene sequence.

Technical Board of Appeal restricts "Oncomouse" patent

Munich, 6 July 2004-- *As a result of an appeal decision, European patent* **EP 0 169 672**, *better-known as the "Oncomouse" patent, has been further restricted.*

In 1985 the President and Fellows of Harvard College, Cambridge, Massachusetts, USA, applied for a European patent entitled "Method for producing transgenic animals". The patent was granted in May 1992 in respect of "non-human mammalian animals" for eleven member states of the European Patent Organisation.

Seventeen oppositions against the patent, filed in 1992 and 1993, led to the decision in November 2001 to maintain the patent in respect of "transgenic rodents". Several appeals against that decision lodged in March 2003 were heard by the Technical Board of Appeal which decided to restrict the patent further to "transgenic mice".

The full reasons for the appeal decisions will be given later in writing.

Ejemplo que muestra que no todo lo que se pide inicialmente se concede. Diferencia US-EPO

Art. 5 LP

No es patentable…

4. El cuerpo humano, en los diferentes estadios de su constitución y desarrollo, así como el simple descubrimiento de uno de sus elementos, incluida la secuencia o la secuencia parcial de un gen.

Sin embargo, un elemento aislado del cuerpo humano u obtenido de otro modo mediante un procedimiento técnico, incluida la secuencia total o parcial de un gen, podrá considerarse como una invención patentable, aún en el caso de que la estructura de dicho elemento sea idéntica a la de un elemento natural.

La aplicación industrial de una secuencia total o parcial de un gen deberá figurar explícitamente en la solicitud de patente.

Informe de la Comisión al Consejo y al Parlamento Europeo (13.10.2005):

Análisis de “protección en función del objetivo” (purpose-bound protection): “entre las secuencias de ADN y las sustancias químicas no existen diferencias que justifiquen un tratamiento diferente del alcance de la protección conferida por la patente”.

Patenting of genes
(discovery or invention?)

Examples of claims:

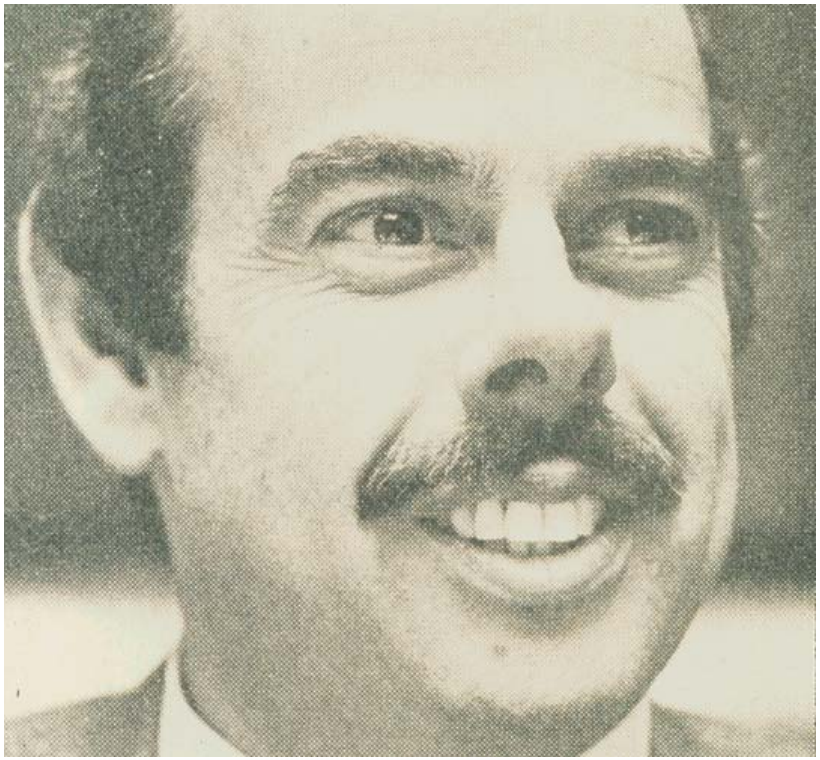
1. DNA sequence coding for IL-35 (SEQ. ID. NO:1)
2. A nucleic acid sequence 70% homolgous/identical to SEQ. ID. NO:1.
3. A nucleic acid sequence hybridizing with SEQ. ID. NO:1.

According to the Directive 98/44/EC:

The simple discovery of a sequence or partial sequence of a gene is not patentable.

Sequences or partial sequences of a gene may be patentable if they have been isolated from the human body or have been produced by a technical process.

The industrial application of a sequence must be disclosed in the patent application



[54] **PROCESS FOR PRODUCING BIOLOGICALLY FUNCTIONAL MOLECULAR CHIMERAS**

[75] Inventors: **Stanley N. Cohen**, Portola Valley; **Herbert W. Boyer**, Mill Valley, both of Calif.

[73] Assignee: **Board of Trustees of the Leland Stanford Jr. University**, Stanford, Calif.

Ingeniería genética:

¿Éxito o fracaso comercial?

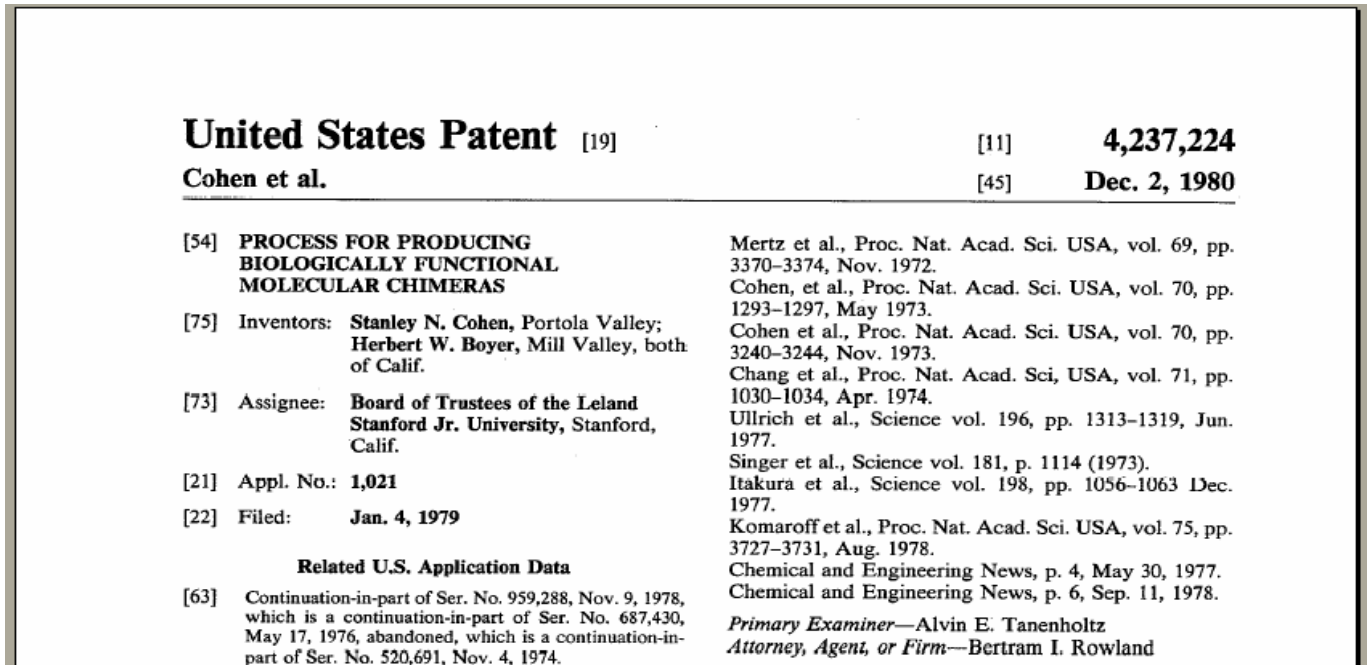
¿y de patentes?

Patente US 4.237.224 (1980)

La técnica básica de ADN recombinante de **Cohen** (Univ. Stanford) y **Boyer** (Univ. California SF) se publicó en una revista (PNAS 1973, vol. 70, p. 3240). Stanford solicitó patentes pero sólo en EEUU, por la existencia de un periodo de gracia de un año.

La patente US 4.237.224, concedida en 1980, reivindicó el método/procedimiento de producción de una proteína por expresión de un gen insertado en cualquier hospedante unicelular, lo que **cubría la mayoría de procedimientos de ingeniería genética**. La patente caducó en diciembre de 1997, habiendo producido enormes royalties a las dos universidades (que tuvieron más de 100 licenciatarios, pagando royalties modestos de 10.000 $/año).

para el titular un gran fracaso de su política de patentes



United States Patent [19]

Cohen et al.

[11] **4,237,224**

[45] **Dec. 2, 1980**

[54] **PROCESS FOR PRODUCING BIOLOGICALLY FUNCTIONAL MOLECULAR CHIMERAS**

[75] Inventors: **Stanley N. Cohen**, Portola Valley; **Herbert W. Boyer**, Mill Valley, both of Calif.

[73] Assignee: **Board of Trustees of the Leland Stanford Jr. University**, Stanford, Calif.

[21] Appl. No.: **1,021**

[22] Filed: **Jan. 4, 1979**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 959,288, Nov. 9, 1978, which is a continuation-in-part of Ser. No. 687,430, May 17, 1976, abandoned, which is a continuation-in-part of Ser. No. 520,691, Nov. 4, 1974.

Mertz et al., Proc. Nat. Acad. Sci. USA, vol. 69, pp. 3370–3374, Nov. 1972.
Cohen, et al., Proc. Nat. Acad. Sci. USA, vol. 70, pp. 1293–1297, May 1973.
Cohen et al., Proc. Nat. Acad. Sci. USA, vol. 70, pp. 3240–3244, Nov. 1973.
Chang et al., Proc. Nat. Acad. Sci, USA, vol. 71, pp. 1030–1034, Apr. 1974.
Ullrich et al., Science vol. 196, pp. 1313–1319, Jun. 1977.
Singer et al., Science vol. 181, p. 1114 (1973).
Itakura et al., Science vol. 198, pp. 1056–1063 Dec. 1977.
Komaroff et al., Proc. Nat. Acad. Sci. USA, vol. 75, pp. 3727–3731, Aug. 1978.
Chemical and Engineering News, p. 4, May 30, 1977.
Chemical and Engineering News, p. 6, Sep. 11, 1978.

Primary Examiner—Alvin E. Tanenholtz
Attorney, Agent, or Firm—Bertram I. Rowland

L5 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2003 ACS
AN 1981:61591 HCAPLUS Full-text
DN 94:61591
TI Biologically functional molecular chimeras
IN Cohen, Stanley N.; Boyer, Herbert W.
PA Stanford University, USA
SO U.S., 10 pp. Cont.-in-part of U.S. Ser. No. 959,288, abandoned.
CODEN: USXXAM
DT Patent
LA English
IC C12P021-00
NCL 435068000
CC 10-4 (Microbial Biochemistry)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 4237224	A	19801202	US 1979-1021 <--	19790104
	US 4468464	A	19840828	US 1978-959288	19781109
	US 4740470	A	19880426	US 1984-602294	19840420
PRAI	US 1974-520691		19741104		
	US 1976-687430		19760517		
	US 1978-959288		19781109		

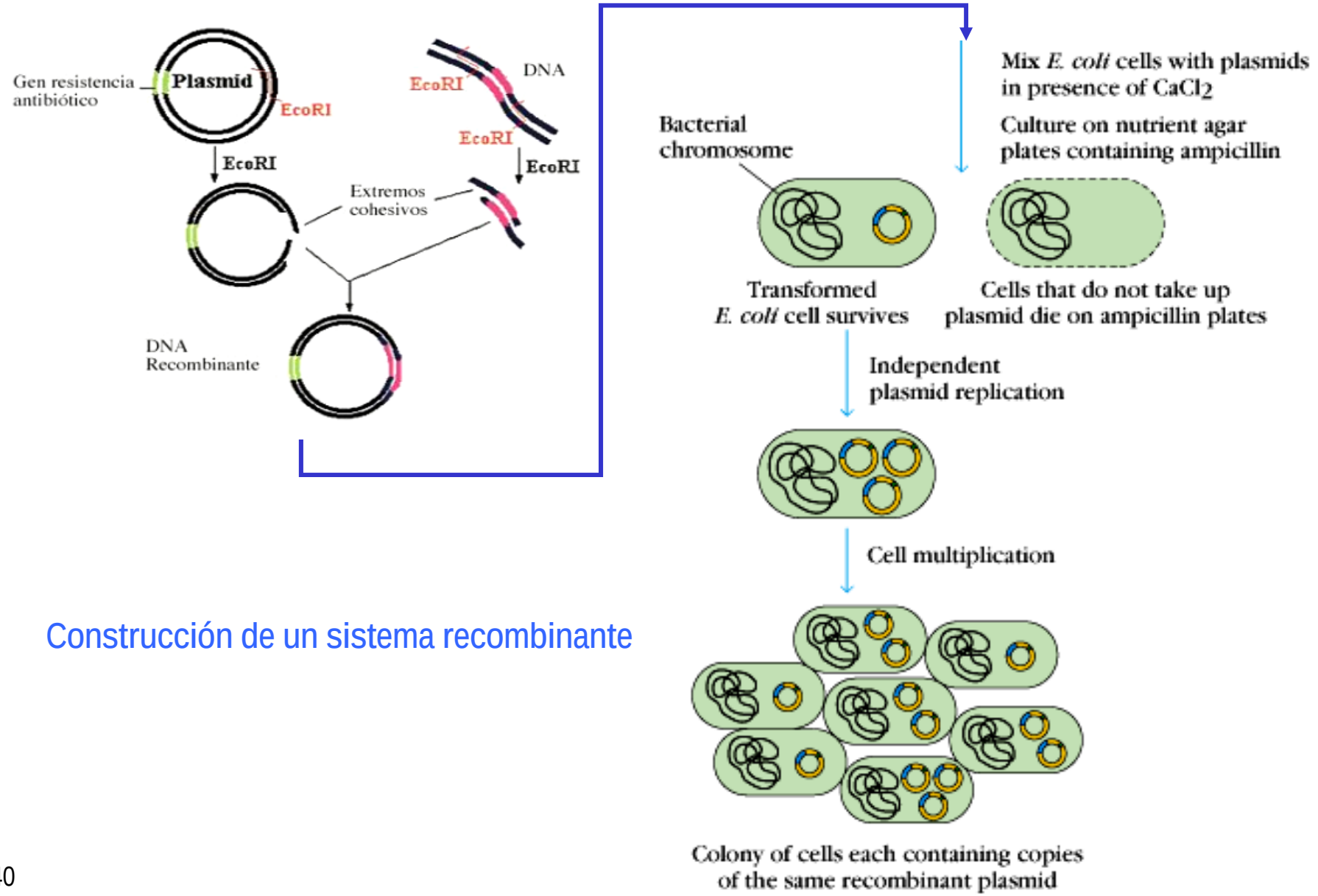
AB Exogenous genes are replicated in microorganisms by recombinant DNA technol. Thus, plasmid ColE1 is used as a vehicle for

Sólo se protegió en EE.UU.

Tecnología de DNA recombinante

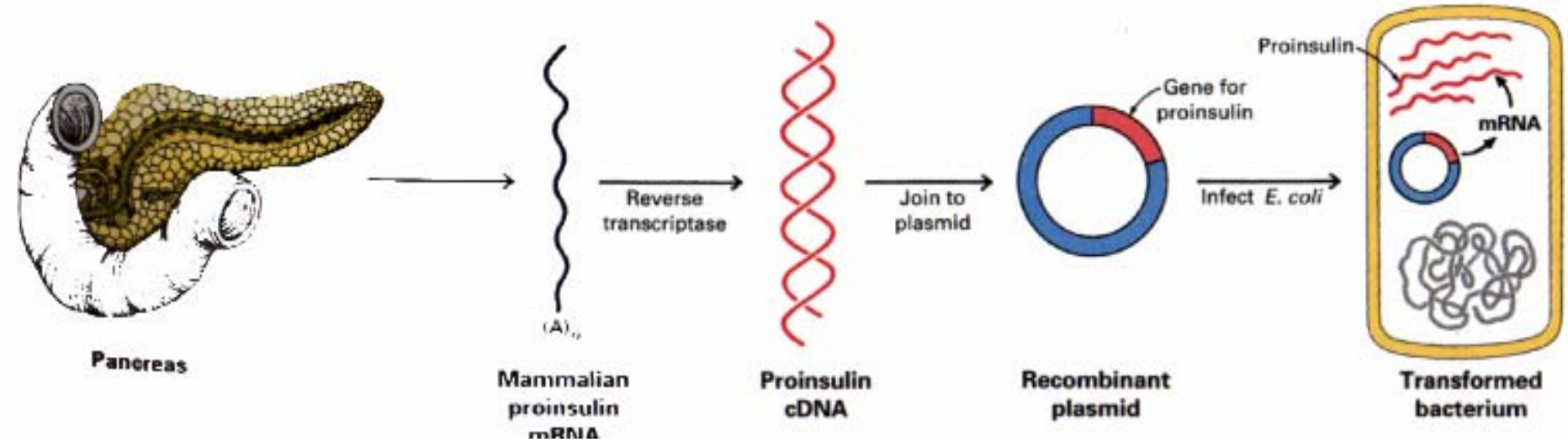
Clonaje: Uso de la tecnología de recombinación del DNA para insertar un fragmento de DNA en un vector de clonaje con el fin de poder propagar este DNA una vez se ha introducido dentro de una célula huésped mediante una transformación.

Vector de expresión: Vector utilizado para propagar el DNA recombinante que además tiene los elementos necesarios (promotores) para que este DNA sea traducido a proteína por parte de la célula huésped.



Construcción de un sistema recombinante

Ejemplo de producción de insulina



DNA y proteínas

Elementos en juego:

genes o fragmentos de genes, las correspondientes proteínas, construcción de vectores de expresión, sistemas promotores, enzimas de restricción, ligasas, células hospedadoras, síntesis del DNA, selección, transformación y aisladamiento del producto de interés.

Categorías de invenciones:

- relacionadas con los procedimientos de ingeniería genética y elementos para llevar a cabo los procedimientos

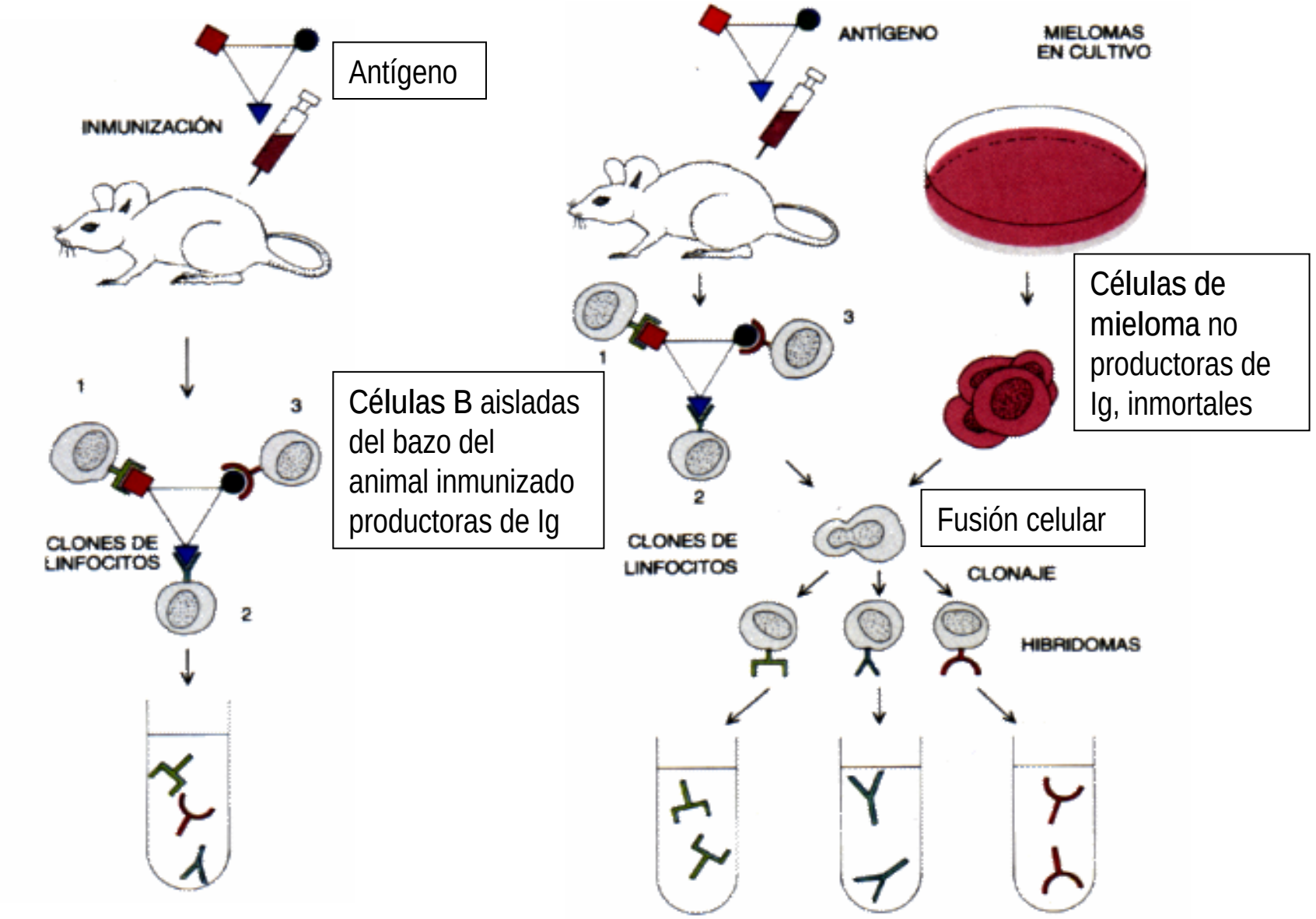
La tecnología básica (Cohen/Boyer 1980, US 4237224) se aplica de manera rutinaria. Se podrán patentar mejoras de los procedimientos.

- relacionadas con DNA y proteínas per se

Ej. proteínas recombinantes patentadas y comercializadas

Tanto de estructura previamente conocida como de estructura previamente desconocida o sólo parcialmente conocida:

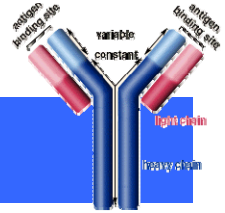
- insulina humana
- TPA (*tissue plasminogen activator)*
- somatrotopina u hormona humana del crecimiento
- interferones alfa-2a, alfa-2b, alfa n-3
- interleucina-2
- Factor VIII anticoagulante
- Factor G-CSF
- eritropoyetina (EPO)



anticuerpos policlonales
o anti-serum

anticuerpos monoclonales

Anticuerpos



Novedad y actividad inventiva:

Antígeno nuevo e inventivo → se permite reivindicar el Anticuerpo (e.g. T542/95)

Antígeno conocido → hacer el anticuerpo policlonal o monoclonal es rutinario, no inventivo

Para tener actividad inventiva:

- efecto sorprendente de mAb
- dificultades en el aislamiento requieren una solución inventiva (e.g. T510/94)
- propiedades inesperadas de mAb.

Procedimiento de obtención de hibridomas, Milstein y Köhler (Medical Research Council, Cambridge, GB), 1975, no patentado. La inmadurez del método al inicio hacía que no fuera obvio obtener el hibridoma y el mAb correspondiente.

Anticuerpos. What are “unexpected properties?

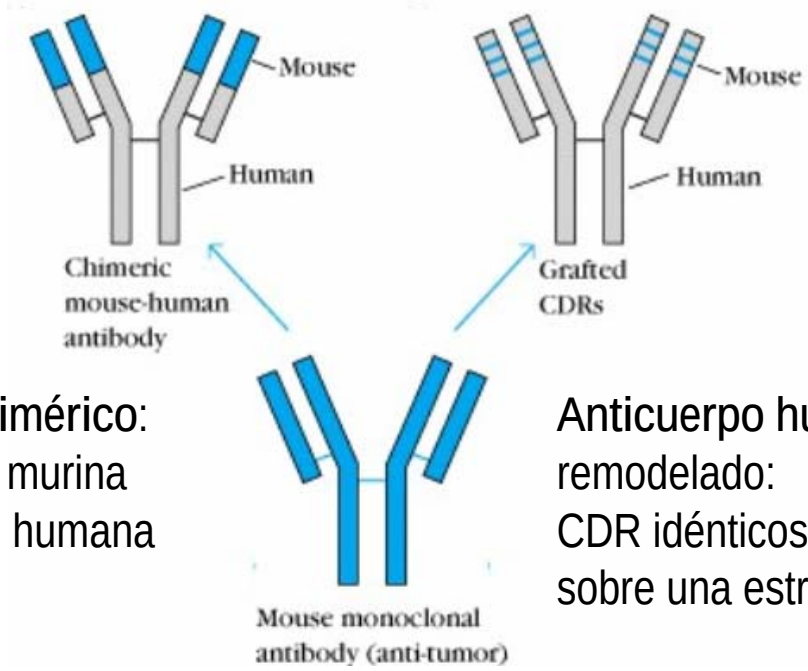
Specificity for a new epitope

Unexpected physiological activity

Unusually low cross-reactivity

Unexpected high affinity (e.g. as achieved for a humanized antibody)

Modification of mAbs:



Anticuerpo quimérico:
Parte variable murina
Parte constante humana

Anticuerpo humanizado o remodelado:
CDR idénticos al anticuerpo murino sobre una estructura humana

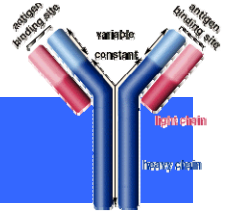
Algunos ejemplos de anticuerpos en clínica

Monoclonal antibodies approved by the US Food and Drug Administration

Box 5 Monoclonal antibodies approved by the US Food and Drug Administration

Product	Type	Target of action	Condition	Approved
Muronomab-CD3 (Orthoclone OKT3)	Mouse	CD3 antigen on T cells	Transplant allograft rejection	1986
Abciximac (ReoPro)	Chimeric	Glycoproteins IIb and IIIa on activated lymphocytes	Cardiovascular disease	1994
Daclizumab (Zenapax)	Humanized	CD25 (IL-2Rα, Tac) on activated lymphocytes	Transplant allograft rejection	1997
Rituximab (Rituxan)	Chimeric	CD20 on B lymphocytes	Non-Hodgkin lymphoma	1997
Basiliximab (Simulect)	Chimeric	CD25 (IL-2Rα) on activated lymphocytes	Transplant allograft rejection	1998
Palivizumab (Synagis)	Humanized	F protein on respiratory syncytial virus	Respiratory syncytial virus	1998
Infliximab (Remicade)	Chimeric	TNF-α	Rheumatoid arthritis, Crohn disease	1998
Trastuxumab (Herceptin)	Humanized	HER2 oncoprotein	Metastatic breast cancer	1998
Gemtuzumab ozogamicin (Mylotarg)	Humanized, toxin-linked	CD33 on leukemic blasts	Acute myelogenous leukemia	2000
Alemzutumab (Campath 1H)	Humanized	CD52 on B, T and NK cells and monocytes	Chronic lymphocytic leukemia	2001
Ibritumomab tiuxetan (Zevalin)	Chimeric, radionuclide-linked	CD20 on B lymphocytes	Non-Hodgkin lymphoma	2002

Anrticuerpos



Protección para:

- Línea celular hibridoma
- MAb secretado por el hibridoma; fragmentos, derivatizaciones, MAb marcado
- Procedimiento de obtención del MAb
- Procedimiento de utilización del MAb, incluyendo inmunoensayos
- Kits de inmunoensayo que incorporan el Mab

Redacción de las reivindicaciones equivalente a la de proteínas.

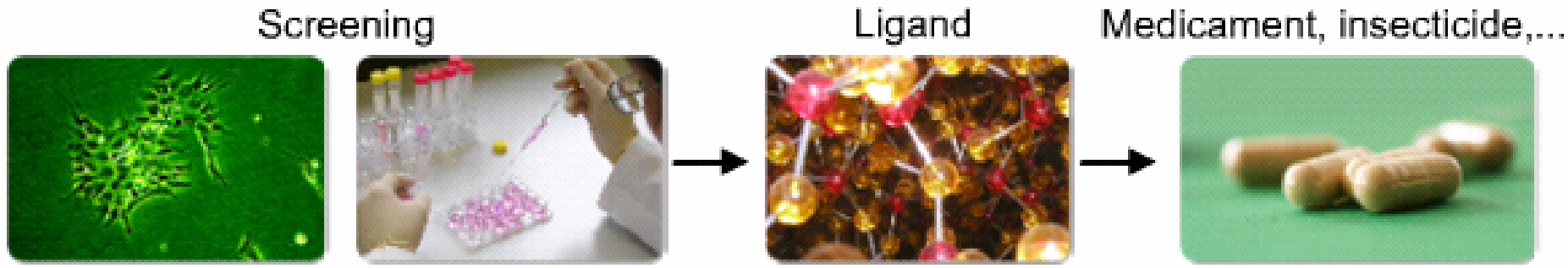
Suficiencia de la descripción:
Procedimientos de producción de los MAbs; cómo usar los MAbs; muchas veces, depósito del hibridoma.

Reach through scenario

Patentee discovers a fundamental mechanism of action
Mechanism is associated with a (known) disease state
Drug target involved in the mechanism of action is identified

Screening Assay is provided to identify potential pharmaceutical compounds using the drug target as a research tool

Claims are drafted to assay, compound and use



Admissibility of reach-through claims

Current Position of Patent Offices (Trilateral Project EPO, JPO, USPTO):

A valid claim must not impermissibly reach through its boundaries to cover products that are the invention of another or even not yet made.

Utility, enablement and description are fundamental requirements of patentability. If these conditions are not met, the claim reaches through to an extent that is not permissible

Patents should not be construed to cover subject matter beyond the scope of what is contributed by the inventor to the art -> claims must be restricted to particular embodiments

Claims can not be properly assessed for novelty –incomplete, no search (because the characteristic is the ability of binding to the target).

Admissibility of reach-through claims

Screening method claim:
A method of identifying a modulator of a defined target comprising
contacting a candidate substance with said target …., and
determining whether said candidate substance is a modulator of the target

Reach-Through Type of Claim:
A modulator of a defined target identifiable by a screening method comprising contacting a candidate substance with said target ….. and determining whether said candidate substance is a modulator of the target.

Se puede patentar:
Patente de método de screening (¿secreto?)
Patente de compuestos *per se*, uso para enfermedad (independientemente del mecanismo de acción, el target).

Art. 52 EPC. Patentable inventions

Exclusions:

discoveries, scientific theories and mathematical methods

(b) aesthetic creations

(c) schemes, rules and methods for performing mental acts, playing games or doing business, and programs for computers

(d) presentations of information

Art. 52(2)(c)

Program for computers patentable, if

it has a further technical effect

it acts on physical data or technical data

method acting on scientific data

it has an effect on the way the computer operates,

effect on the functioning of a computer or its interfaces (T769/92)...

A bioinformatics program (if not mere scientific theory or mathematical method) has (almost always) a technical effect, since it acts on physical or technical data:

Image processing

Computer simulation

Computer aided design or prediction of biological data

Exclusions: Art. 52(2)(d)

Presentation of information:

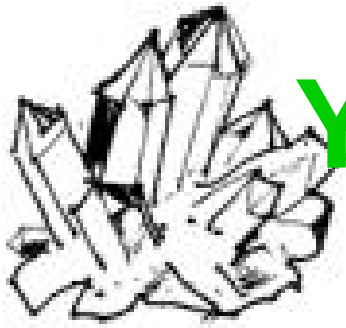
Any (re)presentation of information characterized solely by content of information

Exclusions: Art. 52(2)(d) Crystal structures

No technical effect for 3D model or crystal structure coordinates as such not being a substance / product, process or apparatus

ATOM 145 N VAL A 25 32.433 16.336
57.540 1.00 11.92 A1 N
ATOM 146 CA VAL A 25 31.132 16.439
58.160 1.00 11.85 A1 C
ATOM 147 C VAL A 25 30.447 15.105
58.363 1.00 12.34 A1 C
ATOM 148 O VAL A 25 29.520 15.059
59.174 1.00 15.65 A1 O
ATOM 149 CB AVAL A 25 30.385 17.437
57.230 0.28 13.88 A1 C
ATOM 150 CB BVAL A 25 30.166 17.399
57.373 0.72 15.41 A1 C
ATOM 151 CG1AVAL A 25 28.870 17.401
57.336 0.28 12.64 A1 C
ATOM 152 CG1BVAL A 25 30.805 18.788
57.449 0.72 15.11 A1 C
ATOM 153 CG2AVAL A 25 30.835
18.826 57.661 0.28 13.58 A1 C
ATOM 154 CG2BVAL A 25 29.909 16.996
55.922 0.72 13.25 A1 C

NO



YES

Crystal structures claims:

Abstract: NO

Real: YES

Crystal structures - claims

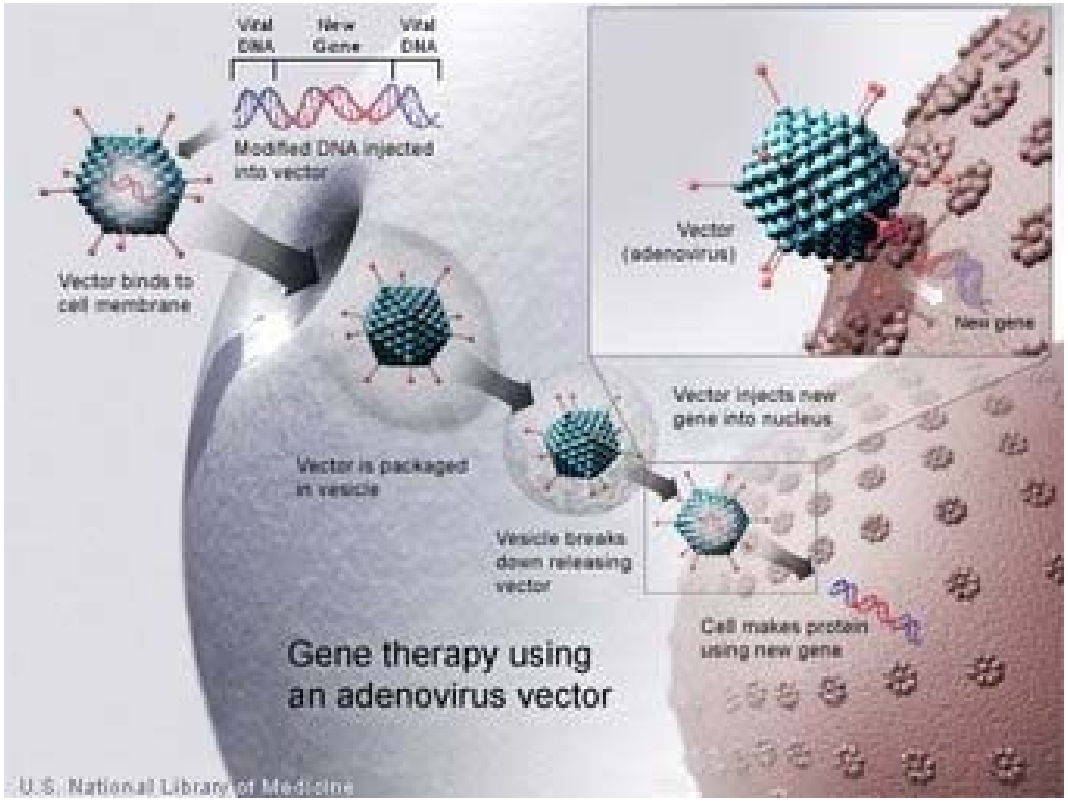
1. The atomic coordinates of protein P as listed in Figure 1 -> NO
2. A data array comprising the atomic coordinates of protein P as listed in Figure 1 -> NO
3. A model of protein P generated with the atomic coordinates of protein P as listed in .. -> NO
4. A secondary or three dimensional structure or model of protein P -> NO

1. A ribosome crystal -> YES
2. A crystalline polypeptide, said polypeptide comprising … -> YES
3. The protein domain D obtained by proteolytic cleavage with enzyme E. -> YES
4. A method for identifying an inhibitor comprising applying rational drug design to the crystal structure of protein P. -> YES

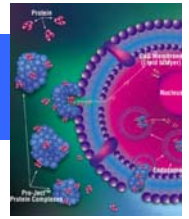
Terapia génica

Inserción de genes en las células de los tejidos de un individuo para tratar una enfermedad en general, y enfermedades hereditarias en particular. Tiene como objetivo suplir un alelo defectuoso mutado por uno funcional.

Vectores: adenovirus, retrovirus, vectores no virales (liposomas, etc)



Terapia génica



No se acepta la terapia génica en la línea germinal, sólo en la línea somática.

Aproximación *in vivo:* administración directa del material genético, que requiere direccionarlo al sitio de interés con un sistema adecuado) → En EP los métodos de terapia génica, siendo métodos de tratamiento médico, están excluidos de patentabilidad.

Son patentables los vectores y las construcciones para llevarlos a cabo.

Pasos *ex vivo:* extirpación de células target del cuerpo, introducción del gen y transplante → patentables en EP si no se reivindica el último paso de administración de las células transformadas al paciente.

En Estados Unidos se reivindicará el procedimiento completo.

Reivindicaciones dirigidas a:
- Técnicas de transferencia de genes
- Vectores mejorados
- Tipos celulares (regeneración de tejidos dañados en ciertas enfermedades, terapia celular, y como vehículos para terapia génica).

Evolving case law

The EPC contains ample provisions for dealing with any issues regarding biotechnology patents. The implemented EU directive is a solid basis for sound decision-making, while the Enlarged Board of Appeal – the department of final instance under the European Patent Convention (EPC) – reviews new appeals.

Some areas in which case law continues to evolve:

* Stem cell cultures – Are human embryonic stem cell cultures which can only be prepared by destroying human embryos to be regarded as immoral?

* Patents for plant production – What is meant by “essentially biological processes for the production of plants”?

* Patents for human genes – The EPO's technical boards of appeal are continuing to build up case law on the criteria for patenting a human gene sequence.

The total number of DNA patent filings has steeply declined. Because the EPO has raised the threshold for DNA patents, applicants are much less likely to file "speculative, broad claims in hope of obtaining what many would view as undue rewards". "That's why patents that go through are more valuable".

European Patent Office

¿Por qué se ataca al sistema de patentes?

Es difícil de entender, pues si se considera que algo es socialmente indeseable, lo lógico es concentrarse en la legislación que impida su experimentación o su explotación, y no tanto en impedir su patentamiento.

Una razón es que es mucho más simple y más barato oponerse públicamente a una patente (cuya tramitación es totalmente transparente), que propiciar una campaña para implementar una legislación.

Otra razón es que resulta mucho más fácil exagerar ante una opinión pública (desinformada) la importancia del sistema de patentes como símbolo de la explotación comercial, que explicar que en realidad el derecho de patente es algo limitado y condicionado.

EMPRESAS

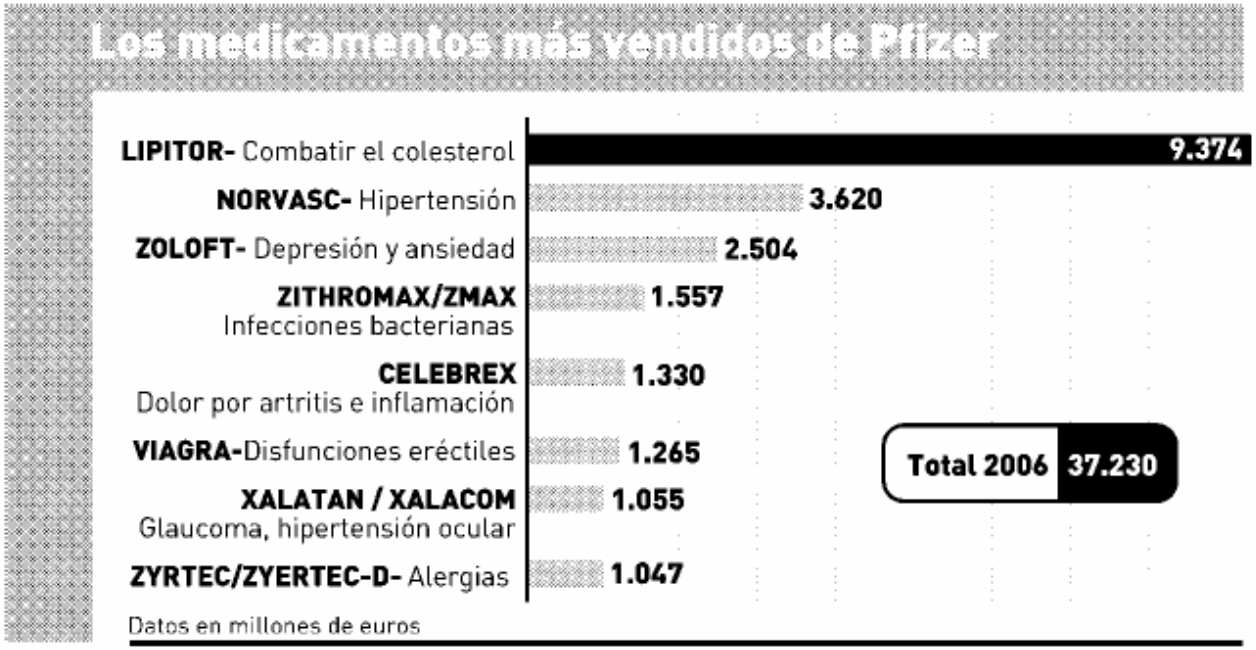
Pfizer, **la mayor farmacéutica del mundo,** perderá el 50% de beneficios cuando en el 2011 finalice la protección de su **patente** del **medicamento Lipitor**, el más rentable de la historia de la medicina. El grupo ha presentado un plan de **reducción del 10% de la plantilla** y nuevas estrategias para afrontar la competencia de **genéricos**

Lipitor = atorvastatina Ca (ES: Cardyl, Zarator, Prevencor-AP)

INDUSTRIA FARMACÉUTICA

Pfizer sufre el mal de las patentes

El desarrollo creciente de los genéricos amenaza las ventas de las grandes farmacéuticas



rol. Pfizer invirtió más de mil millones de euros para desarrollar un nuevo medicamento para potenciar el colesterol bueno, el Torcetrapib, con la intención de crear una combinación de ambos medicamentos con gran potencial. Pero el resultado de las pruebas clínicas en pacientes el pasado mes de diciembre, de la que se obtuvieron un índice de fallecimientos demasiado elevado, obligó a Pfizer a poner fin al desarrollo del nuevo medicamento. Pfizer se ha quedado sin el producto que debía proteger la caída de ventas de Lipitor, y sin el único producto en su *pipeline*

La Vanguardia, 28.01.2007 (Suplemento Dinero)

Biogenerics scenario

The biotech industry is 30 years old and patent expirations are just a few years away.

Difficult to say when the first patents expire on a product, because there are multiple patents for each drug.

No regulatory system exists to approve generic versions of biotech drugs.

It's difficult to make generic versions of biotech drugs because they're based on complex biological organisms, rather than simple molecular compounds like the more traditional pharmaceutical drugs.

"There's no way to 100 percent accurately reproduce the host that these compounds grow off of".
"Therefore it can never be functionally identical."

The only way for a biogeneric company to produce an exact copy of a brand-name biotech drugs is to "sneak into the factory and to steal the host, which is illegal."

Missing the $20 billion biogeneric boom. Aaron Smith, CNNMoney.com, August 15 2006

Brand	Active substance	Marketer	Approval date	1999 Sales US$ million	Generics under development
Epogen	Epoetin alfa	Amgen Inc	1989	1,760.0	+
Procrit	Epoetin alfa	Ortho Biotech Inc	1990	1,505.0	+
Neupogen	Filgrastim	Amgen Inc	1991	1,260.0	+
Humulin	50% human insulin isophane suspension and 50% human insulin (recombinant DNA origin)	Eli Lilly & Co	1992	1,088.0	+
Intron A	Interferon alpha-2b, recombinant	Schering Oncology Biotech	1986	650.0	+
Avonex	Interferon beta-1a	Biogen Inc	1996	621.0	+
Engerix-B	Hepatitis B vaccine, recombinant	SmithKline Beecham	1989	540.0	+
Rebetron	Ribavirin and interferon alpha-2b, recombinant	Schering Corp	1998	530.0	-
Ceredase	Alglucerase	Genzyme Corp	1991	500.0	-
Cerezyme	Imiglucerase	Genzyme Corp	1991	479.0	-
Genotropin	Somatotropin	Pharmacia Corp	1995	460.8	+
ReoPro	Abciximab	Eli Lilly & Co and Centocor Inc	1994	447.3	-
Betaseron	Interferon beta-1b	Berlex Labs Inc	1993	413.0	+
Kogenate	Antihaemophilic factor, recombinant	Bayer Corp	1993	403.4	-
Enbrel	Etanercapt	Immunex Corp and Wyeth-Ayerst Labs	1998	366.9	-

Table 1. Several active substances out of the top 15 biopharmaceuticals will come off patent over the next five years.

Filgrastim (human granulocyte colony stimulating factor, G-CSF)
ReoPro (abciximab), monoclonal antibody

Human recombinant Erytropoietin (rhEPO)

- hEPO, initially isolated and purified from urine in 1977.

- hEPO is a glycoprotein with a molecular mass of about 30,000 Daltons. It has a 165 amino acid chain with four oligosaccharide side chains and a leader peptide of 27 amino acid residues. EPO circulates in the blood plasma at a very low concentration of around about 5 pmol/L.

- In 1983, identified the gene coding for EPO by a team headed by Fu-Kuen Lin at Amgen.

-The Genetics Institute (now part of Wyeth) independently discovered the gene at approximately the same time. The resulting patent dispute to determining whether Amgen or Genetics Institute was actually first to conceive the method of isolating the EPO gene, led to Amgen gaining exclusive marketing rights for EPO in the U.S.

- Recombinant DNA technology was used to express the protein in Chinese hamster ovary cells, which allowed a synthetic form of EPO (rEPO) to be produced in commercial quantities for the first time.

- rEPO was launched as a pharmaceutical product by Amgen for treatment of anemia resulting from chronic renal failure in 1989 under the brand name Epogen. In 1991 it was also approved for treating anemia resulting from cancer chemotherapy.

… (rhEPO)

- Johnson & Johnson markets EPO under license from Amgen for cancer chemotherapy under the brand name **Procrit**.

- In Europe, where there was only one patent, competition is beginning to flourish. But in the US, Amgen received **seven patents** on the same work by Mr. Lin. Because some patents were not granted until years after Amgen applied, the patent protection could extend until 2015, longer than the 20 years contemplated by patent law.

- A longer-acting EPO analogue, darbepoetin (dEPO), also known as novel erythropoiesis-stimulating protein (NESP), was launched by Amgen under the brand name **Aranesp** in 2001.

Mircera: EPO-PEG, longer half-life. Roche:

Amgen won a patent infringement lawsuit against Roche.

A jury in the Federal District Court in Boston ruled that Roche's new drug, Mircera infringed 11 Amgen patent claims. It also ruled that several Amgen patents were valid.

Mircera got the FDA approval on Novemder 2007, but it is stopped in the US by patents. Mircera has the approval in Europe.

Amgen Wins a Crucial Patent Ruling, By ANDREW POLLACK

Published: October 23, 2007

EP0148605B2 Kirin Amgen

EPO produced in genetically engineered hamster cells. Filed on 1984, expired in EP at the end of 2004

Claims:

1. A DNA sequence for use in securing expression in a procaryotic or eucaryotic host cell of a polypeptide product having at least part of the primary structural confirmation [sic] of that of erythropoietin to allow possession of the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells and to increase hemoglobin [sic] synthesis or iron uptake, said DNA sequence selected from the group consisting of:

    (a) the DNA sequences set out in Tables V and VI or their complementary strands;

    (b) DNA sequences which hybridize under stringent conditions to the protein coding regions of the DNA sequences defined in (a) or fragments thereof; and

    (c) DNA sequences which, but for the degeneracy of the genetic code, would hybridize to the DNA sequences defined in (a) and (b).

2. A DNA sequence according to Claim 1 encoding human erythropoietin.

7. A DNA sequence according to Claim 6 and including the protein coding region set forth in Table VI.

12. A procaryotic or eucaryotic host cell transformed or transfected with a DNA sequence according to any one of Claims 1, 2, 3, 6, 7 and 8, in a manner allowing the host cell to express said polypeptide product.

13. A transformed or transfected host cell according to Claim 12 which host cell is capable of glycosylating said polypeptide.

14. A transformed or transfected mammalian host cell according to Claim 13.

16. A transformed or transfected CHO cell according to Claim 13.

EP00205564B2 Genetics Institute, Inc.

cloning of hEPO obtained from human fetal liver and its expression in vitro to produce active hEPO. Filed on 1985 and expired in December 2005.

Claims

1. A method for the production of human erythropoietin comprising culturing in a suitable medium eukaryotic host cells containing the DNA sequence as shown in Table 3 from the sequence ATG encoding initial Met through AGA encoding the terminal Arg operatively linked to an expression control sequence, and separating the erythropoietin so produced from the cells and the medium.
2. A method of claim 1, wherein the culture medium contains fetal serum.
3. A method of one of the preceding claims, wherein the host cells are mammalian cells.
4. A method of claim 3, wherein the mammalian host cells are COS, CHO, C127 or 3T3 cells.
6. A method of claim 3, wherein the mammalian cells are Chinese hamster ovary (CHO) cells.

Taken together the sequences set out EP0148605 and in EP00205564 which comprise the full length 193 amino acid residues EPO protein sequence including the 27 amino acid residues leader sequence, there can today be no valid broad patent protection in Europe on recombinantly expressed wild type EPO as such.

... (rhEPO)

Other patents related to:

Other forms of EPO protein (sequence)
Polypeptide sequence modifications, glycosilations
Expression vector and host cells to express the protein
Culture medium
Purification steps
Final pharmaceutical composition / Form of administration (stabilizers, etc)
Therapeutic applications

Semantics: Generic biopharmaceutical? Biogeneric? Follow-on protein? Biosimilar? Follow-on biologic?

Biopharmaceuticals: pharmaceuticals that are inherently biological in nature due to their manufacture using live organisms / genetic engineering (recombinant proteins and mAbs).

Biogeneric-related concepts and terms are based on relationships (e.g., similarity, comparability, equivalence), taxonomies, and classifications concerning biopharmaceutical finished products and/or their active agents.

The basic presumption underlying (bio)generics is that (bio)pharmaceutical active agents and/or finished products **can be considered to be similar or even identical** (for all practical purposes), **allowing extrapolations of activity, safety, and efficacy among agents or products based on shared characteristics or similarities**.

To date, there are no precedents for biopharmaceuticals in major Western countries approved with formal designation of equivalence/substitutability similar to that granted to many generic drugs.

Proposed Biogenerics and Related Terms

biocomparable: a common synonym for *biogeneric*; best avoided due to comparability guidelines that apply to manufacturing changes (see *comparability* below)

biogeneric: refers to any biopharmaceutical considered generic, based on any criteria (which should be stated or clear in context)

biologic(s): a type of FDA approval for biopharmaceuticals and other associated products (best used only to refer to products approved or on track for approval by this mechanism); generally includes all but the simplest biopharmaceuticals regulated as drugs by the FDA; the official definition is complex, unwieldy, developed decades ago, and based on analogies to terms and concepts at the time (e.g., viruses analogous to toxins, vaccines to serums, etc.)

biological product: an official synonym for *biologic* and best reserved for this use

biopharmaceutical: a pharmaceutical product or active agent that is biological in nature and manufactured using living organisms (biotechnology); note — this does not include small molecule or other drugs that are inherently chemical, not biological, in their nature and manufacture

biosimilar: short name (never actually officially defined) for "similar biotechnology medicinal product," a new type of generic biopharmaceutical approval in the European Union and associated products; best used to refer only to products approved or on track by this mechanism

comparability: refers to similarities, regulatory acceptability, and supplemental approvals of products incorporating a change in the manufacturing process by the product's current manufacturer or contractor (judgments of similarities between the same products, presumably, from the same manufacturer, incorporating a change in the manufacturing process; best used only in this context, not to refer to biogenerics

drugs: chemical, not biological pharmaceutical agents, and products manufactured using chemical, not biological methods, and including the vast majority of pharmaceuticals

follow-on: a synonym for *biogeneric*; often used to describe a later biopharmaceutical and often involving a more technologically advanced version of an innovator product; see also *later generation*; best avoided because the FDA has adopted the term *follow-on protein*

follow-on protein (FOP): a biopharmaceutical approved or on track for approval by the FDA as a generic drug, usually under section 505(b)(2), generally restricted to relatively simple proteins, including those with prior versions approved as natural products (best reserved for this use)

follow-on biologic (FOB): a biopharmaceutical approved or on track for approval by the FDA as a generic biopharmaceutical, a regulatory track that does not yet exist (best reserved for this use)

innovator: refers to original products, usually the first product to receive approval, and associated companies; such products are presumed to have involved original and extensive research and development (R&D) and full (not abbreviated) phase 3 type safety and efficacy testing

later generation: a biopharmaceutical similar to a prior product; it often involves technological advances or other modifications such that it may not actually be similar to prior innovator product(s); term recommended for adoption in place of *follow-on*

pharmaceutical: any medical product, particularly those products with therapeutic or in vivo uses; two major subsets are drugs and biopharmaceuticals

therapeutic biological product: a term adopted by the FDA for those simpler biologics regulated by the Center for Drug Evaluation and Research (CDER), not by the Center for Biologics Evaluation and Research (CBER, which regulates more complex biologics)

Omnitrope, a human growth hormone for children with growth problems from the Novartis-owned generics maker Sandoz. This FDA approval is recognized by some analysts as the first biogeneric, because the Sandoz-drug was based on the Pfizer biotech drug Genotropin.

But Omnitrope was approved based largely on comparisons with Genotropin from Pfizer derived from Hatch-Waxman Act–505(b)(2) generic drug regulations. The European Union approved Omnitrope and another recombinant *E. coli*-expressed somatropin (Valtropin) under its new biosimilar regulations based on comparisons with Genetropin and Humatrope (from Eli Lilly), respectively.

The FDA has denied that Omnitrope is a biogeneric, calling it a "follow-on protein product," of Genotropin and said that the drug was approved through a separate process that has nothing to do with biogenerics. FDA stated:

> *Follow-on protein products generally refers to protein and peptide products that are intended to be sufficiently similar to a product already approved or licensed to permit the applicant to rely for approval on certain existing scientific knowledge about the safety and effectiveness of the approved protein product. Follow-on protein products may be produced through biotechnology or derived from natural sources.*

Meanwhile, Rep. Henry Waxman of the 30th district of California, who helped establish the current regulatory system for generic drugs, is planning to introduce regulation on biogenerics this fall.

Table 2: Some biopharmaceutical approvals as 505(b)(2) generic drugs

Entry	Name (Descriptive and Trade)	Companies
107	Calcitonin, rDNA (Forical)	Unigene, Upsher-Smith
152	Glucagon, rDNA (GlucaGen)	Novo Nordisk
171	Hyaluronidase, rDNA (Hylenex)	Halozyme Therapeutics; Baxter
527	Hyaluronidase, bovine (Amphadase)	Amphaster Pharmaceuticals
529	Hyaluronidase, ovine (Vitrase)	ISTA Pharmaceuticals
235	Somatropin, rDNA (Omnitrope)	Sandoz/Novartis

Recent examples of biogeneric-like FDA drug approvals. None of those has included formal recognition of equivalence and/or substitutability, forcing each to be marketed as branded products - by trade name rather than by generic name. For people taking a restrictive Western (US, EU)- and regulatory-centric view, these are the only current biogeneric products.

From the molecule and regulatory point of view (not taking into account patents):

In the US:

No regulations exist in the US for approval of biologics as generics based on comparative, abbreviated applications.

The FDA has approved thousands of generics, nearly all of them drugs (chemical substances), based on comparison with and knowledge of earlier innovator products. But in terms of biopharmaceuticals, this has been restricted to smaller, simpler, or other active agents (including most peptide hormones, e.g., insulin, somatropin, and calcitonin) that in the US, due to regulatory history, natural sources, and/or small-molecule nature, have already been regulated as drugs (under the Food, Drug, and Cosmetic Act) not as biologics regulated under the Public Heath Service Act of 1946 for which no generic approval mechanisms yet exist.

A bill proposing generic biologics regulations was recently introduced in Congress (2008), and other proposals are likely.

The FDA has avoided issuing guidelines for even the simplest biopharmaceuticals regulated as drugs (follow-on proteins). Only after years of delay did the agency grant approval of Omnitrope, and only after being forced to act after having lost a lawsuit brought by Sandoz in federal court.

In Europe:

Unlike the US, the European Union (EU) has developed a new class of approvals for "similar biotechnology medicinal products" (biosimilars, primarily recombinant proteins and monoclonal antibodies); issued related guidelines for a few classes of biopharmaceuticals (e.g., insulins and somatropins); and approved two "biosimilar" somatropin products.

However, as in the US, the EU has yet to issue guidance concerning the great majority of more complex biopharmaceuticals, and it has avoided issues of therapeutic equivalence and official nomenclature to be used with biosimilars (whether to adopt unique or generic names for the products).

Even though not approved as biogenerics, many current US and EU biopharmaceuticals, including blockbusters (> $1 billion/year sales) are very similar -such that they would be labeled as biogenerics if currently in development - and a number of biopharmaceuticals are commonly considered therapeutically equivalent and/or substitutable.

Ronald A. Rader. BioProcess International March 2007

For most successful biopharmaceuticals developed and marketed in the United States and European Union, there are multiple copies in lesser-developed countries (where lack of granted patents and/or their enforcement allows).

Ex:
In the People's Republic of China alone, there are 17 or more manufacturers of recombinant granulocyle-colony stimulating factor (G-CSF; copies of Leukine from Amgen) and many other biopharmaceuticals. And more than 180 insulin products are reported to be in the world market.

Gràcies per la vostra atenció! …Preguntes?