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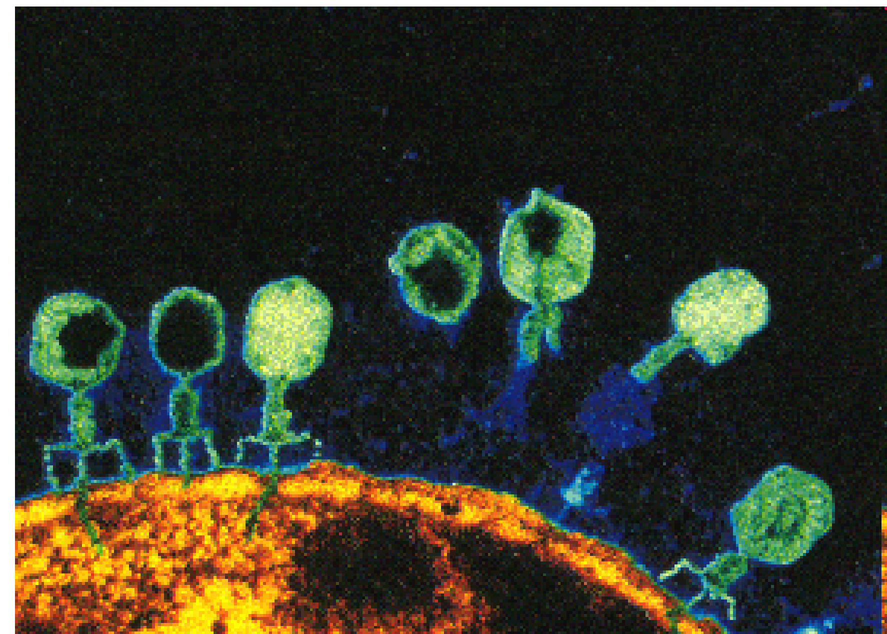
MINISTERIO DE INDUSTRIA, TURISMO Y COMERCIO

Oficina Española de Patentes y Marcas

La biotecnología a través de las patentes

Los Lunes de Patentes
Barcelona, 28 de septiembre de 2009

Lídia Casas
Centre de Patents de la
Universitat de Barcelona



Bacteriófagos infectando a una bacteria

Esquema

Invenciones en biotecnología, tecnologías clave

Patentabilidad. Qué se protege

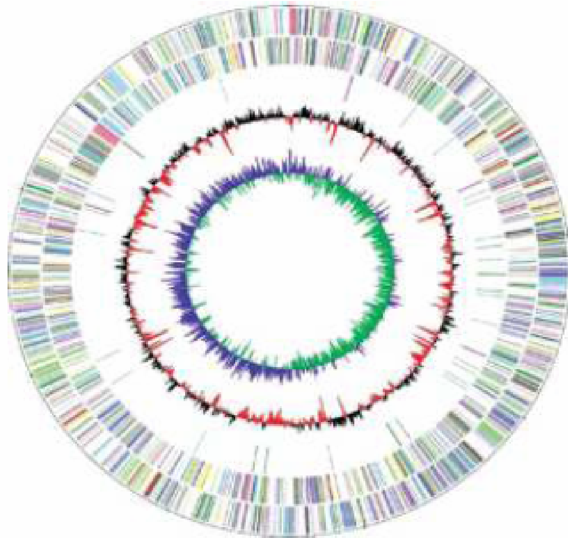
Ejemplos en patentes. “Blockbusters” de la biotecnología

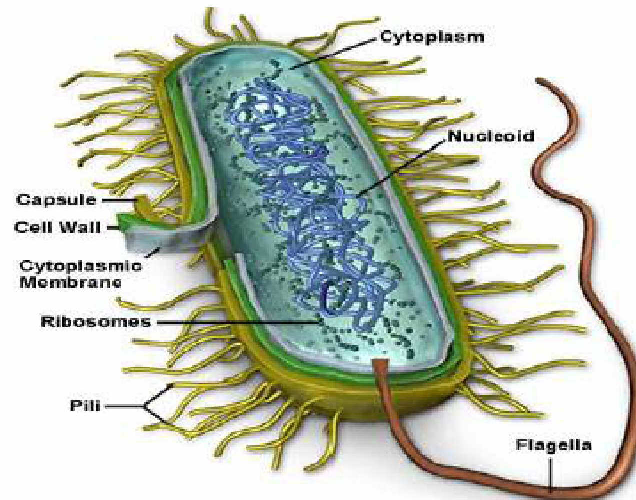
Cuestiones de patentabilidad que están abiertas

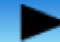
Synthetic Organism Designer 1.0

Design | **Codon Opt.** | **Oligo Synthesis**

Organism	Cell Membrane	Division Type	Form of Metabolism	Structural Genes	Control & Safety
Archaea	Gram +	Meiosis	Photosynthesis	Rubisco (30,000)	Auxotrophic Marker
Bacteria	Gram -	Mitosis	Methanogenesis	Ferredoxin (82,000)	Suicide Gene
Single Cell Euk	Archaeal	Cellular Septation	Glycolysis	Plastocyanin (9,000)	
Virus	Euk		Calvin Cycle	ATP Synthase (100,000)	
Multicellular Euk			Pentose Phosphate		

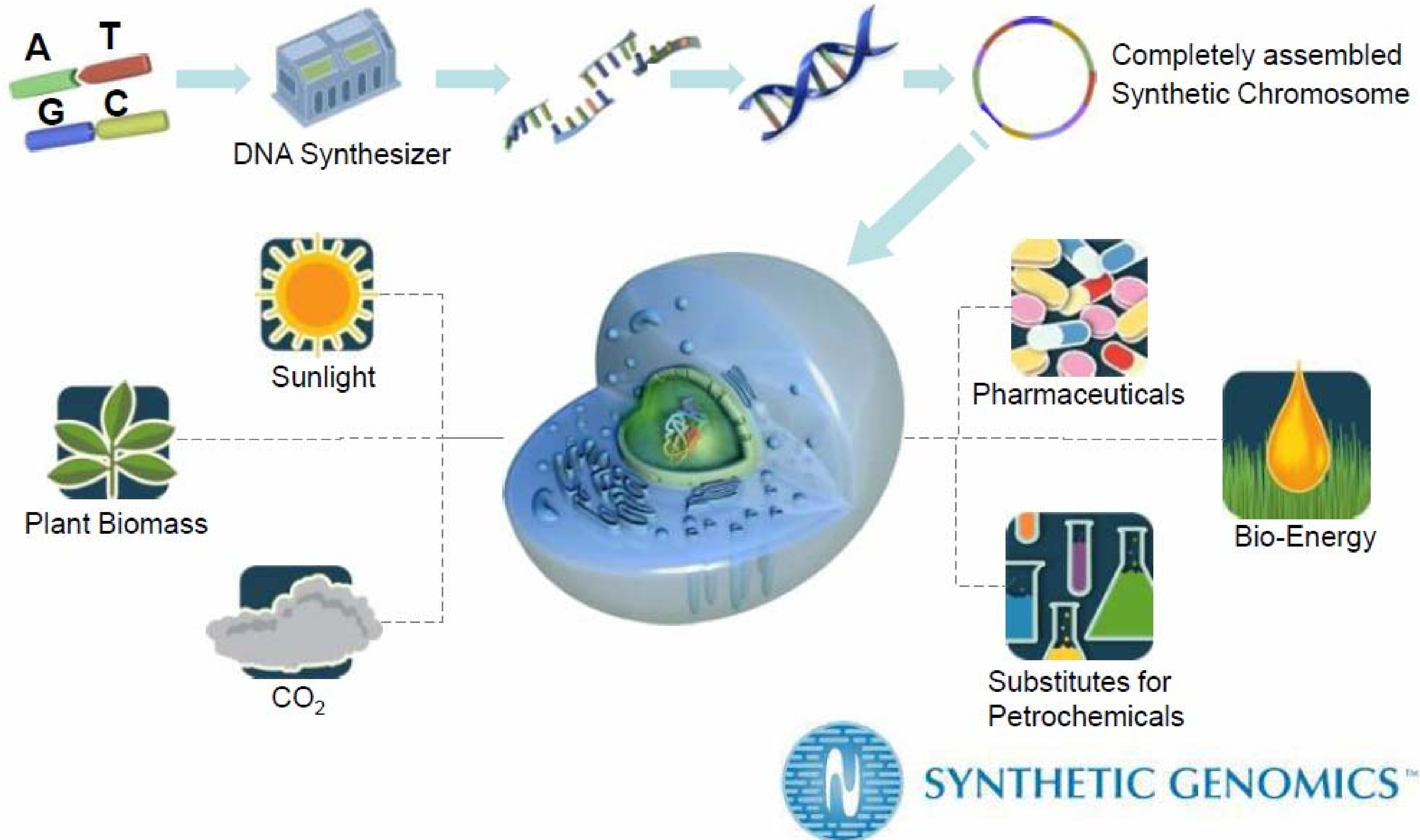




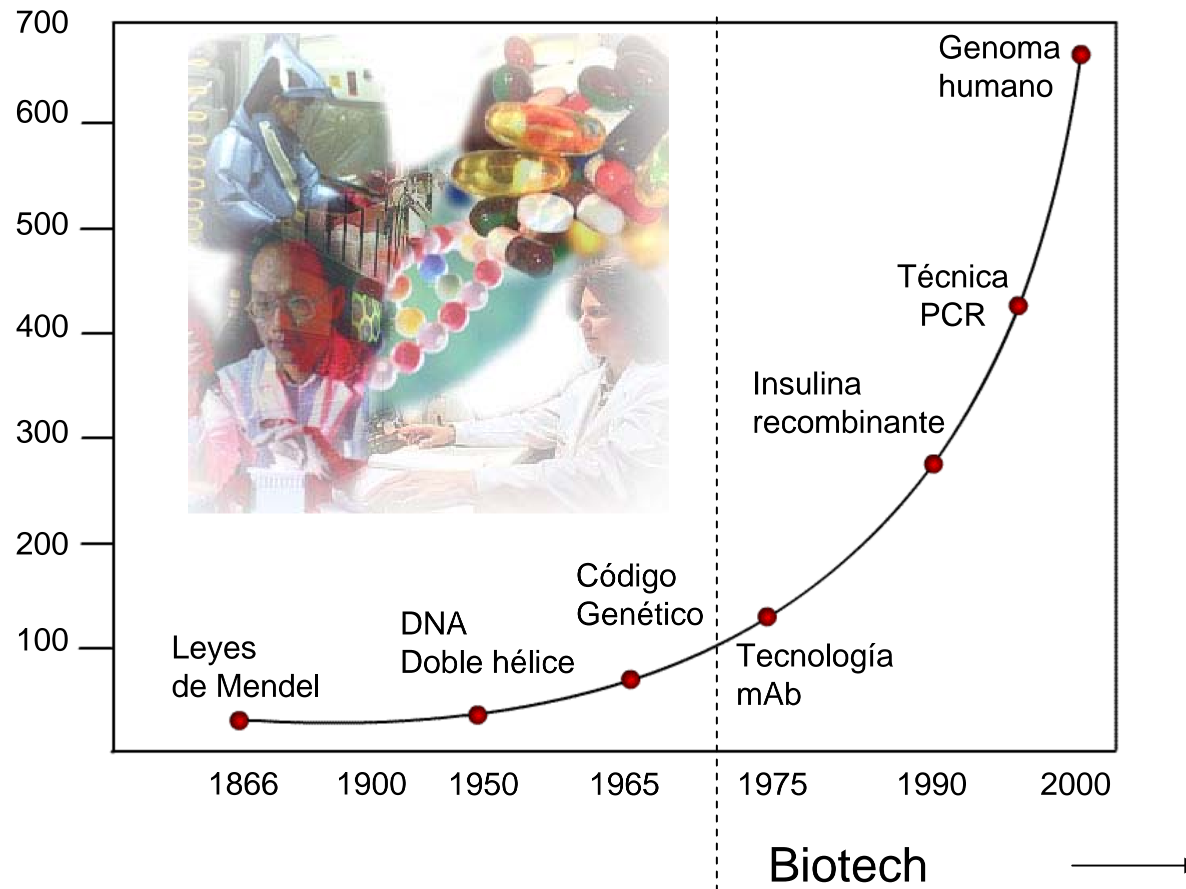


The Potential of Synthetic Genomics

From reading to writing the genome code
…and synthesizing cells that make useful products

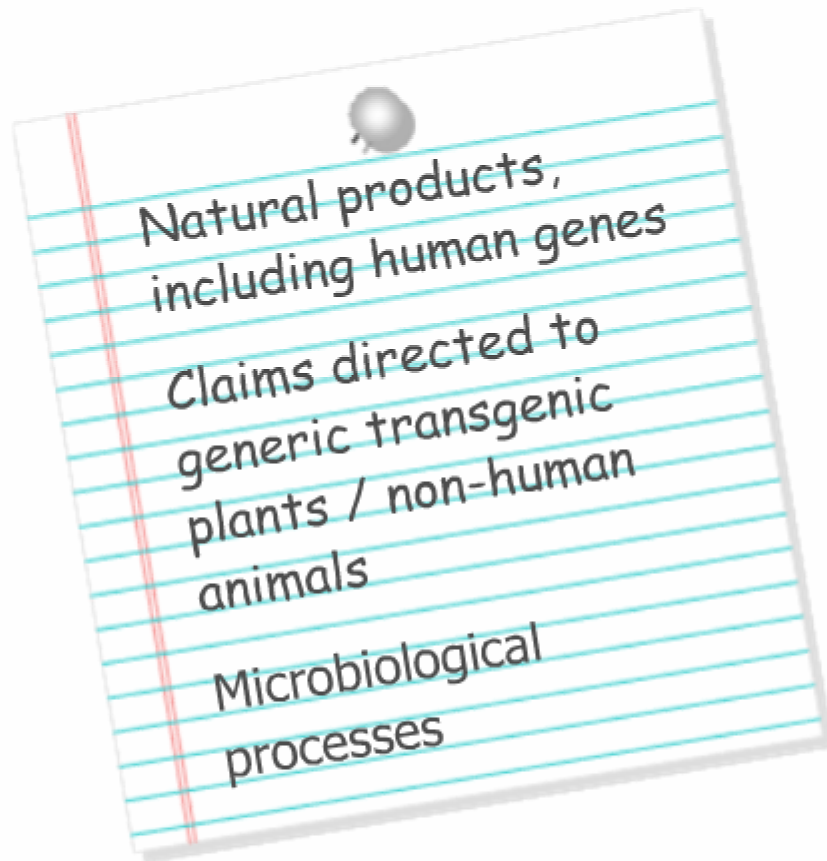


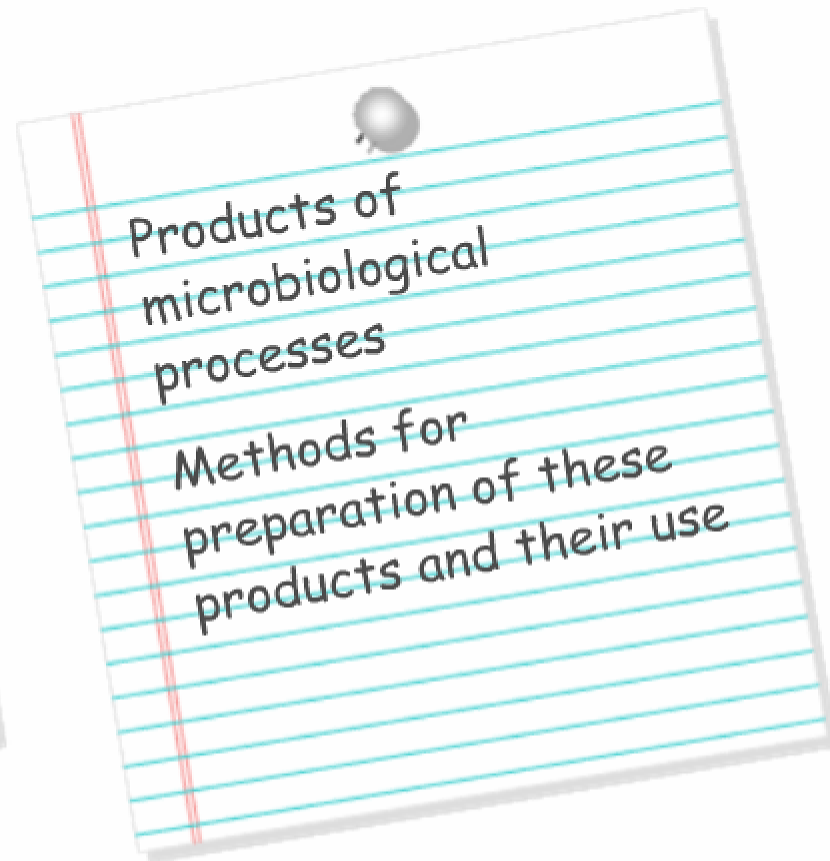
Evolución de la biotecnología



Directive 98/44/EC confirms patentability of:

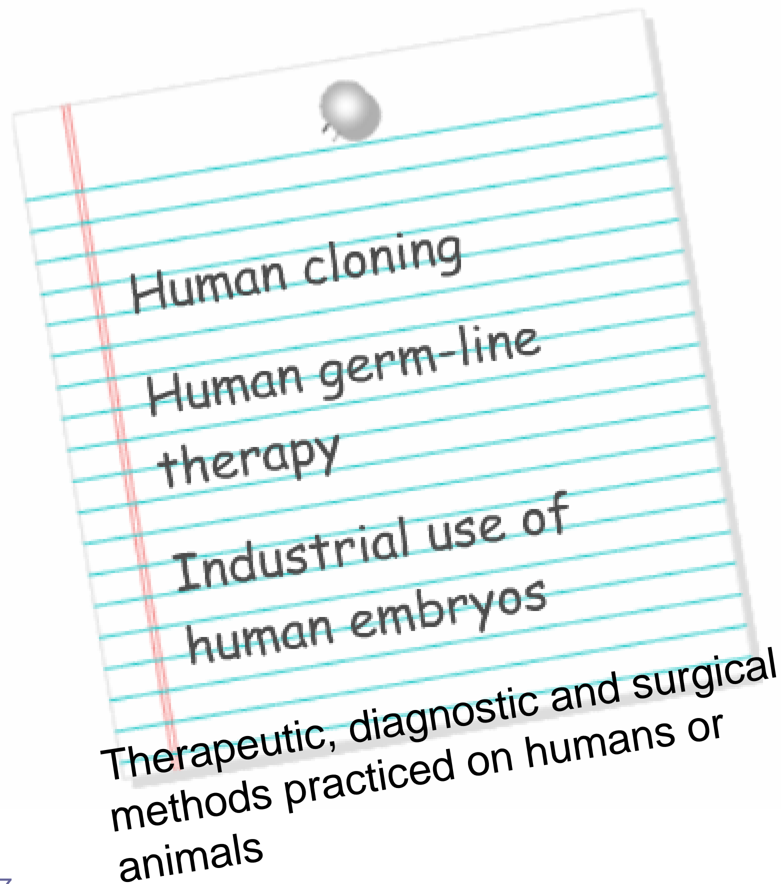
Patentable subject-matter



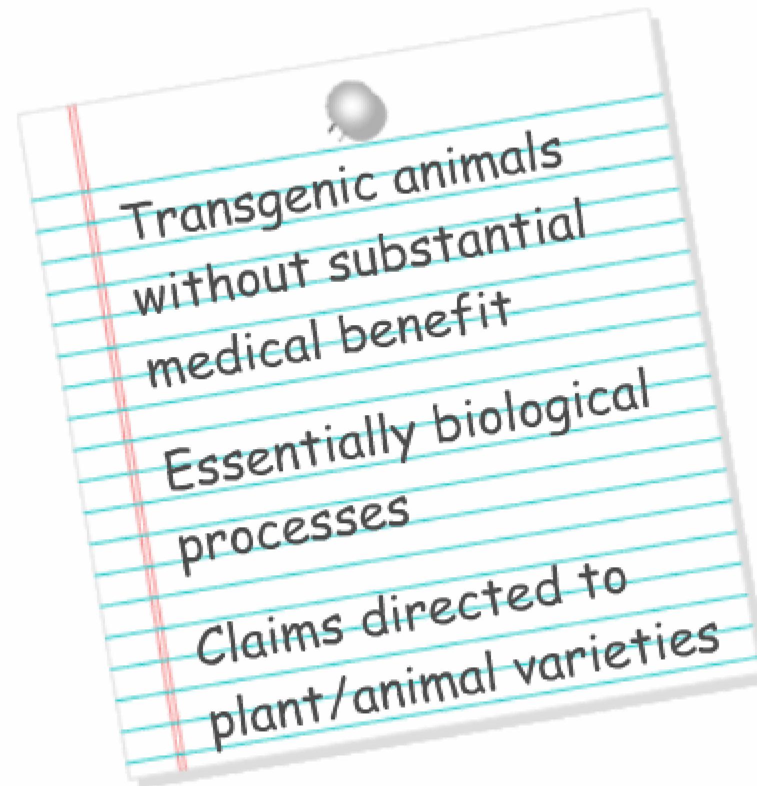


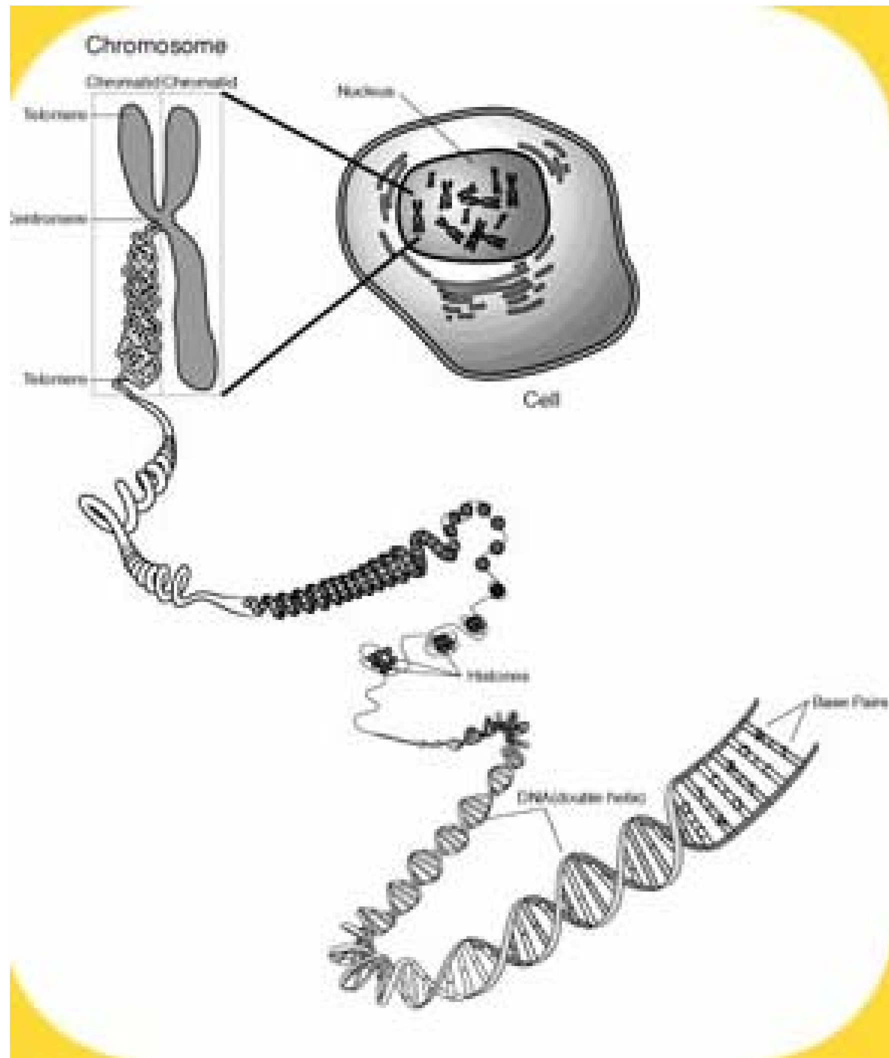
Directive 98/44/EC:

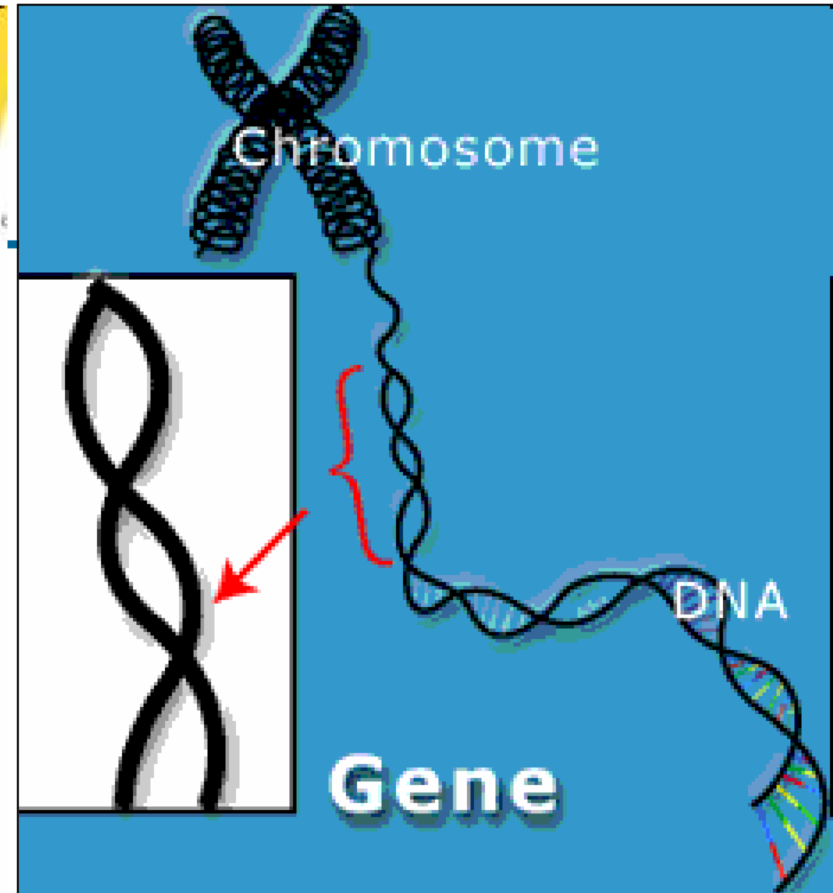
Not Patentable subject-matter



Therapeutic, diagnostic and surgical methods practiced on humans or animals







Genoma: conjunto de genes de un organismo

Gen: segmento de DNA que codifica un producto (proteína) de función definida y que se encuentra localizado en un cromosoma concreto.

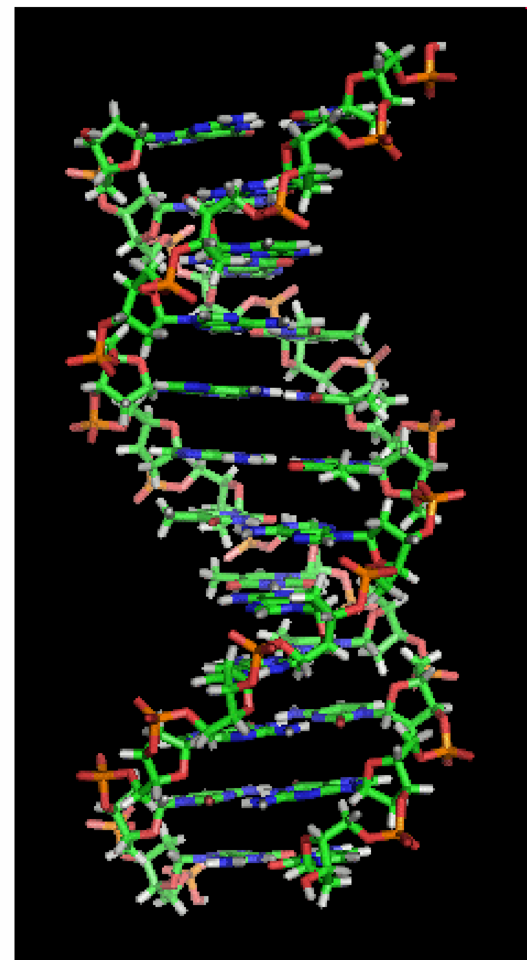
Thymine

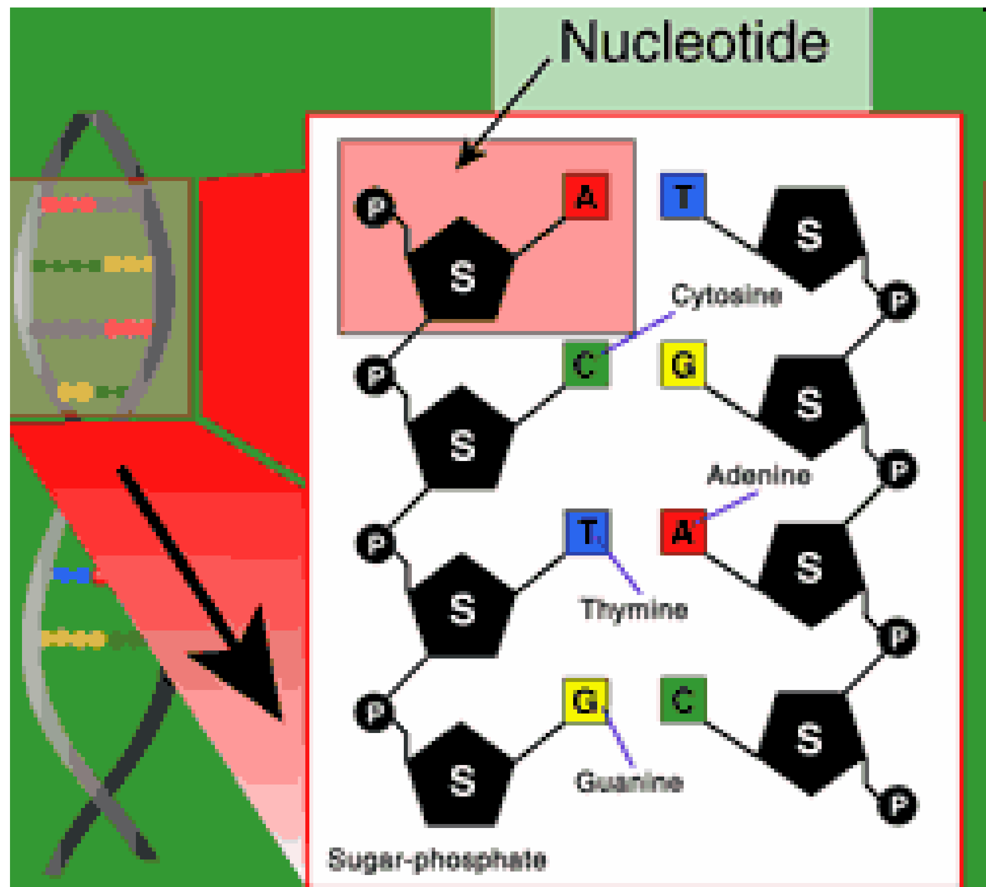
Adenine

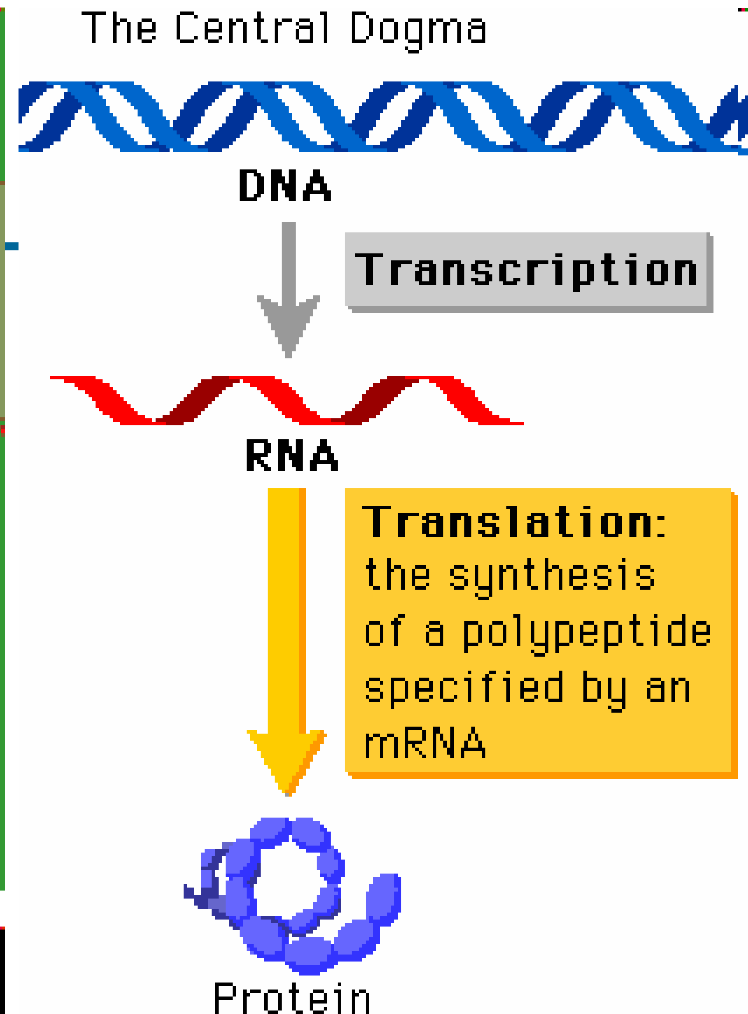
Phosphate-
deoxyribose
backbone

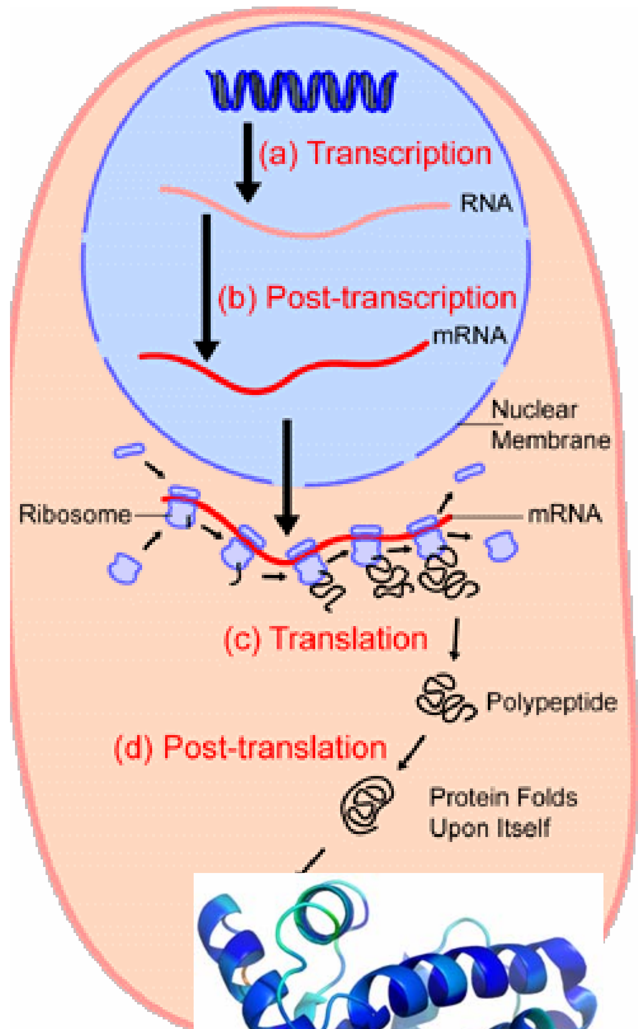
Guanine

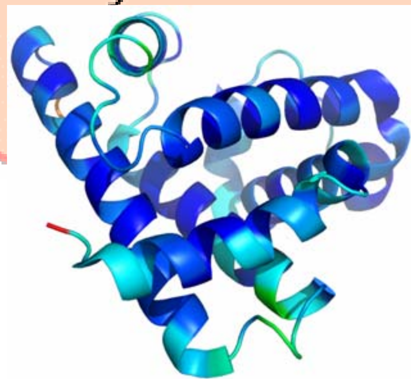
Cytosine




Nucleotide
P
S
A
T
C
G
Cytosine
Adenine
Thymine
Guanine
Sugar-phosphate
AGTCCGCGAATACAGGCTCGGT

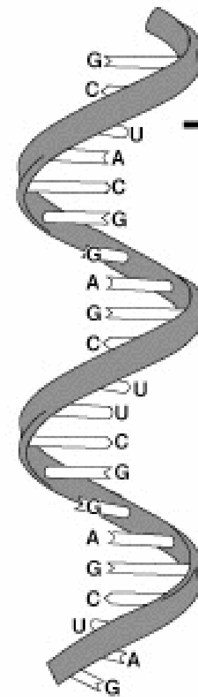

The Central Dogma
DNA
Transcription
RNA
Translation: the synthesis of a polypeptide specified by an mRNA
Protein



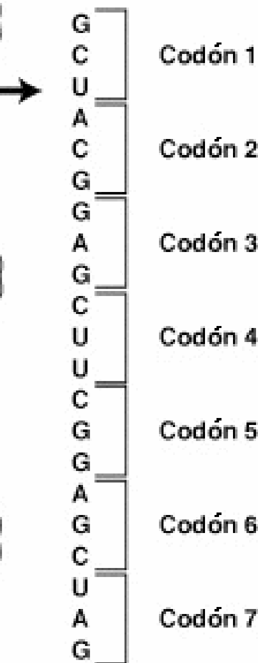


proteína

DNA

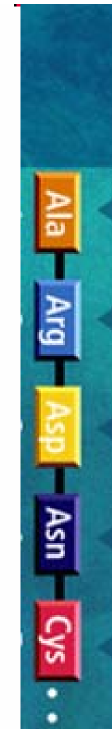


RNA

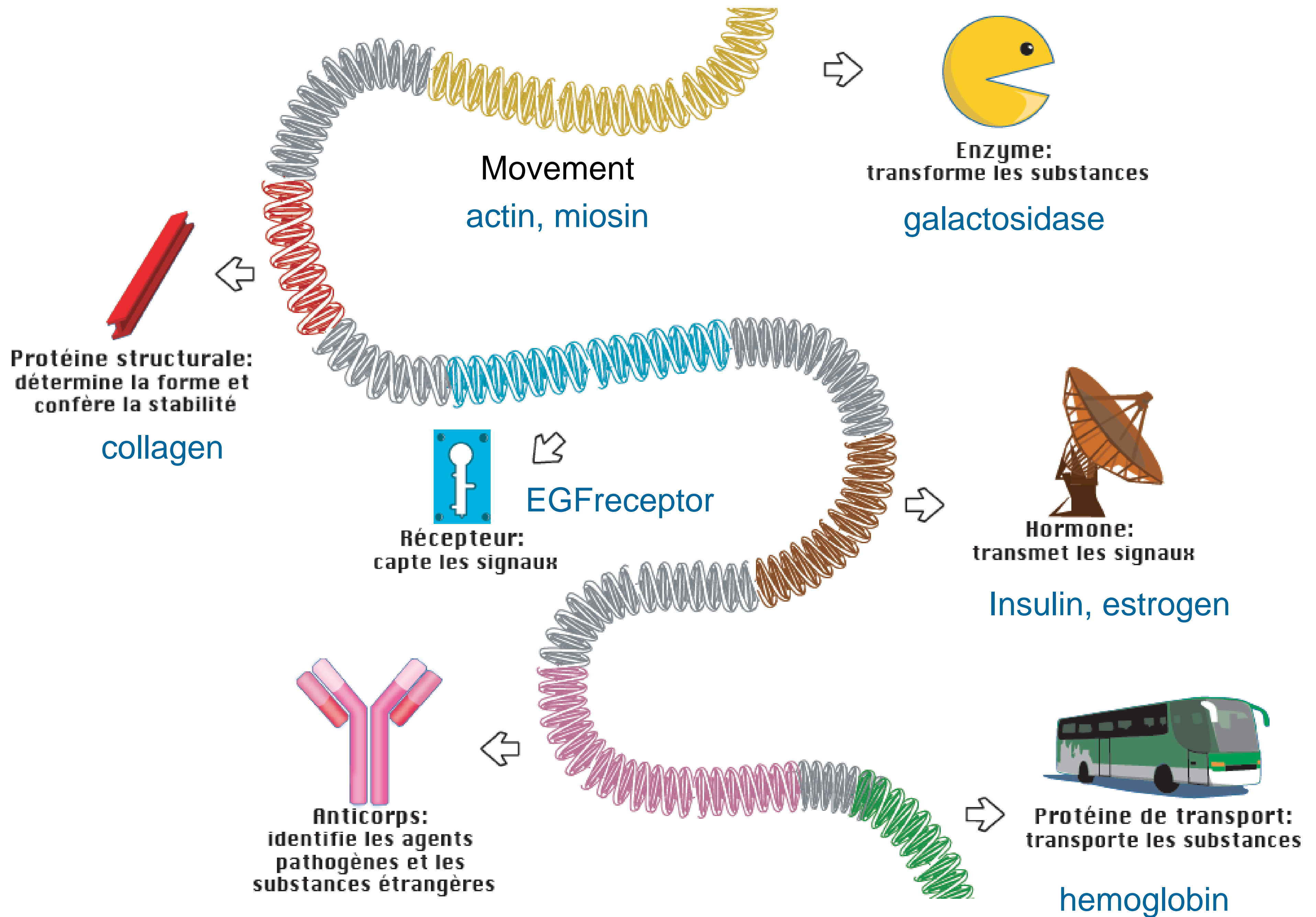


codones

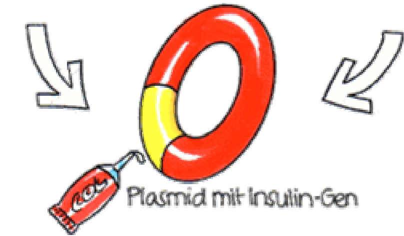
código genético



aminoácidos


Movement
actin, miosin
Enzyme:
transforme les substances
galactosidase
Protéine structurale:
détermine la forme et
confère la stabilité
collagen
EGFreceptor
Récepteur:
capte les signaux
Hormone:
transmet les signaux
Insulin, estrogen
Anticorps:
identifie les agents
pathogènes et les
substances étrangères
Protéine de transport:
transporte les substances
hemoglobin

Invenciones relacionadas con DNA



Categorías de invenciones:

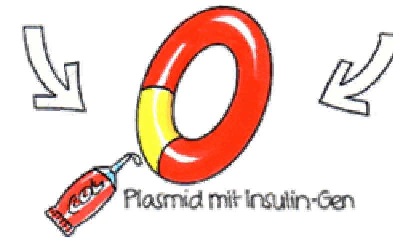
"genes" y las correspondientes "proteínas".
- "genes" (cDNA, fragmentos de genes, DNA antisense, RNA interferencia, PNA, etc)
- "proteínas" (hormonas, enzimas, anticuerpos, etc)

→ referencia: invenciones DNA/proteína

procedimientos de ingeniería genética y elementos para llevar a cabo los procedimientos: construcción de vectores de expresión, sistemas promotores, enzimas de restricción, ligasas, células hospedadoras, síntesis del DNA, selección, transformación y aislamiento del producto de interés.

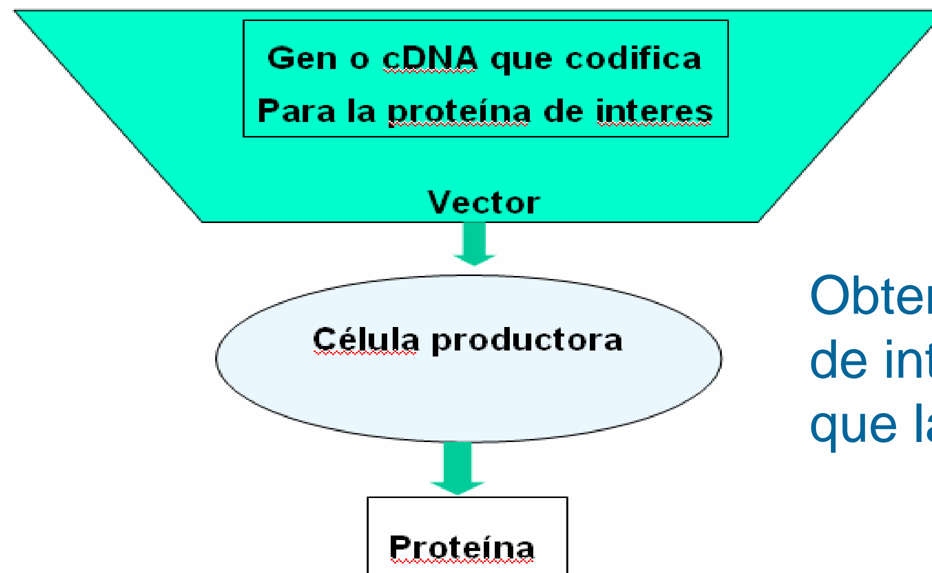
→ referencia: invenciones biología molecular

Invenciones biología molecular



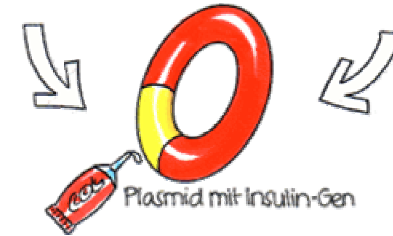
Son las herramientas básicas en cualquier laboratorio de biología molecular. Los principios básicos los veremos en todas las aplicaciones:

- Investigación, genómica, proteómica, etc.
- Producción de compuestos: proteínas, enzimas, anticuerpos, vacunas, etc
- Producción de plantas y animales transgénicos



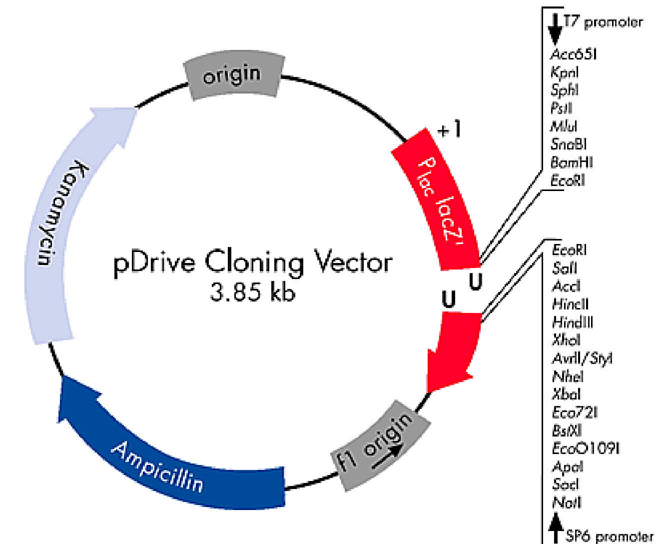
Obtención de una proteína de interés a partir del gen que la codifica

definiciones

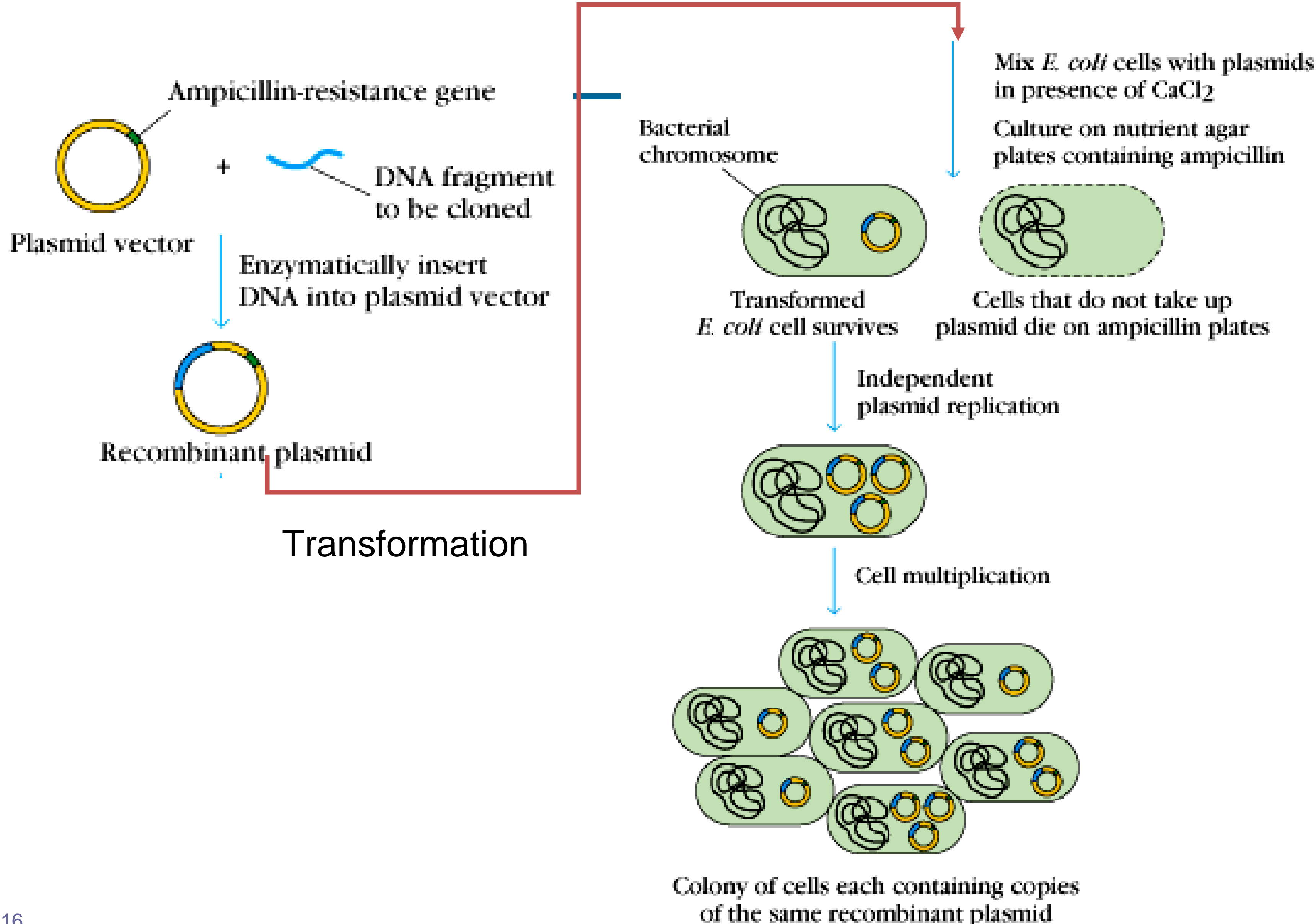


Clonaje (cloning): insertar un fragmento de DNA en un vector de clonaje con el fin de poder propagar este DNA una vez se ha introducido dentro de una célula huésped mediante una transformación.

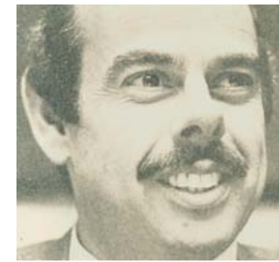
Vector de expresión: Vector utilizado para propagar el DNA recombinante que además tiene los elementos necesarios (promotores) para que este DNA sea traducido a proteína por parte de la célula huésped.



Construcción de un sistema recombinante



DNA recombinante. Cohen y Boyer



Stanley Cohen (Univ. Standford) y Herbert Boyer (Univ. California) estaban en una conferencia sobre plásmidos bacterianos en Hawaii, en 1972. Hablaron de una posible colaboración durante la cena.

Al poco tiempo consiguieron producir moléculas de DNA combinando DNA de diferentes plásmidos, creando así DNA recombinante.

Es la base de la ingeniería genética: se creó un sector completamente nuevo.

La técnica se publicó en una revista (PNAS 1973, vol. 70, p. 3240). Stanford solicitó patentes pero sólo en EEUU, por la existencia de un año de gracia.

DNA recombinante. Cohen y Boyer

Es un ejemplo de cómo puede combinarse la investigación académica con licencias no exclusivas a precio modesto. Es un caso que no se ha vuelto a repetir desde entonces.

El rDNA era una plataforma tecnológica que, gracias a la política de licencias, dio lugar a un gran número de empresas que utilizaron y desarrollaron la tecnología. No hubieron conflictos de patentes.

Funcionó porque:

Era una tecnología no cara y fácil de usar

En ese momento no había alternativa en biología molecular

El rDNA estuvo en el lugar, tiempo y en las manos adecuadas.

DNA recombinante. Cohen y Boyer

Las patentes caducaron en 1997, habiendo producido enormes royalties a las dos universidades (468 licenciatarios, $300 millones de ingresos).

Boyer fue uno de los fundadores de Genentech, la 1ª empresa biotec del mundo. Cohen se quedó en la universidad.

3 patentes cubren el rDNA: US4237224, US4468464, y US4740470.

La primera cubre un 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.

1. A method for replicating a biologically functional DNA, which comprises:

transforming under transforming conditions compatible unicellular organisms with biologically functional DNA to form transformants; said biologically functional DNA prepared in vitro by the method of:

(a) cleaving a viral or circular plasmid DNA compatible with said unicellular organism to provide a first linear segment having an intact replicon and termini of a predetermined character;

(b) combining said first linear segment with a second linear DNA segment, having at least one intact gene and foreign to said unicellular organism and having termini ligatable to said termini of said first linear segment, wherein at least one of said first and second linear DNA segments has a gene for a phenotypical trait, under joining conditions where the termini of said first and second segments join to provide a functional DNA capable of replication and transcription in said unicellular organism;

growing said unicellular organisms under appropriate nutrient conditions; and

isolating said transformants from parent unicellular organisms by means of said phenotypical trait imparted by said biologically functional DNA.

2. A method according to claim 1, wherein said unicellular organisms are bacteria.

3. A method according to claim 2, wherein said transformation is carried out in the presence of calcium chloride.

US4237224

US4237224

4. A method according to claim 3, wherein said phenotypical trait is resistance to growth inhibiting substance, and said growth is carried out in the presence of a sufficient amount of said growth inhibiting substance to inhibit the growth of parent unicellular organisms, but insufficient to inhibit the growth of transformants.

5. A method according to claim 1, wherein said unicellular organism is *E. coli*.

6. A method according to claim 1, wherein said predetermined termini are staggered and cohesive.

7. A method according to claim 6, wherein said joining conditions includes enzymatic ligation.

8. A method according to claim 6, wherein said cohesive ends are formed by staggered cleavage of said viral or circular plasmid DNA and a source of said second segment with a restriction enzyme.

9. A method according to claim 6 wherein said cohesive termini are formed by addition of nucleotides.

10. A method according to claim 1, wherein said predetermined termini are blunt end and said joining conditions include enzymatic ligation.

11. A method for replicating a biologically functional DNA comprising a replicon compatible with a host unicellular organism joined to a gene derived from a source which does not exchange genetic information with said host organism, said method comprising:

isolating said biologically functional DNA from transformants prepared in accordance with claim 1;

transforming unicellular microorganisms with which said replicon is compatible with said isolated DNA to provide second transformants; and

growing said second transformants under appropriate nutrient conditions to replicate said biologically functional DNA.

12. A method for producing a protein foreign to a unicellular organism by means of expression of a gene by said unicellular organism, wherein said gene is derived from a source which does not exchange genetic information with said organism, said method comprising:

growing transformants prepared in accordance with any of claims 1 and 11 under appropriate nutrient conditions, whereby said organism expresses said foreign gene and produces said protein.

13. A method according to claim 12, wherein said protein is an enzyme.

14. A method according to claim 11, wherein said method is repeated substituting said biologically functional DNA from transformants prepared in accordance with claim 1 with second or subsequent transformants to produce additional transformants.

* * * * *

US4237224

PCR – polymerase chain reaction

Técnica indispensable en biología molecular. Permite producir millones de copias de una secuencia de DNA.

Inventor: Kary Mullis (premio nobel), trabajaba en Cetus Corporation, 1983. Cetus recompensó a Mullis con 10000$.

Patentes US4683195, US4683202 y US4965188 / EP201184 y EP200362.

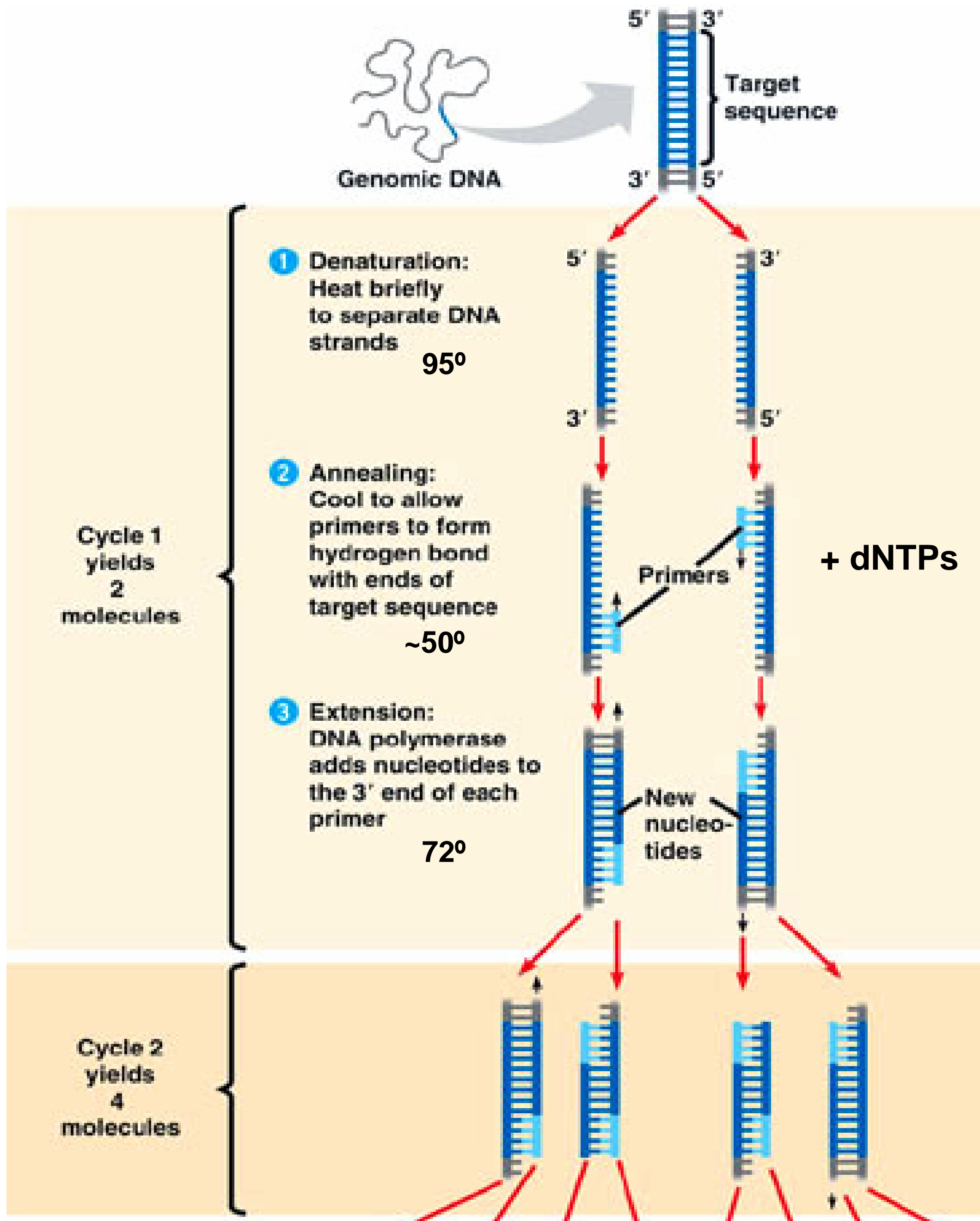
En 1991 Hoffman La Roche compró las patentes a Cetus por $300 millones. Roche creó Roche Molecular Systems (or Diagnostics) para desarrollar tests utilizando la tecnología de la PCR.

En este caso las licencias eran caras y es un ejemplo de “bloqueo” de un sector. La PCR es la base de los análisis de un laboratorio de biología molecular. Hubieron conflictos de patentes en US y EP.

PCR:
http://www.sumanasinc.com/webcontent/animations/molecularbiology.html

Electroforesis

http://www.dnalc.org/resources/animations/



+ dNTPs

1. A process for detecting the presence or absence of at least one specific double-stranded nucleic acid sequence in a sample, or distinguishing between two different double-stranded nucleic acid sequences in said sample, which process comprises first exponentially amplifying the specific sequence or sequences (if present) by the following steps, and then detecting the thus-amplified sequence or sequences (if present):

(a) separating the nucleic acid strands in the sample and treating the sample with a molar excess of a pair of oligonucleotide primers for each different specific sequence being detected, one primer for each strand, under hybridizing conditions and in the presence of an inducing agent for polymerization and the different nucleoside triphosphates such that for each of said strands an extension product of the respective primer is synthesized which is complementary to the strand, wherein said primers are selected so that each is substantially complementary to one end of the sequence to be amplified on one of the strands such that the extension product synthesized from one primer, when it is separated from its complement, can serve as a template for synthesis of an extension product of the other primer of the pair;

(b) treating the sample resulting from (a) under denaturing conditions to separate the primer extension products from their templates;

(c) treating as in (a) the sample resulting from (b) with oligonucleotide primers such that a primer extension product is synthesized using each of the single strands produced in step (b) as a template; and, if desired,

(d) repeating steps (b) and (c) at least once;

whereby exponential amplification of the nucleic acid sequence or sequences, if present, results thus

permitting detection thereof; and, if desired,

(e) adding to the product of step (c) or (d) a labelled oligonucleotide probe capable of hybridizing to said sequence to be detected; and

(f) determining whether said hybridization has occurred.

2. A process of Claim 1, wherein a sequence to be amplified and detected is contained within a larger sequence.

3. A process of Claim 1 or Claim 2, wherein the agent for polymerization is E. coli DNA polymerase I, Klenow fragment of E. coli DNA polymerase I, T4 DNA polymerase, reverse transcriptase, or a heat-stable enzyme.

13. A kit for the detection of at least one specific nucleic acid sequence in a sample, which kit comprises, in packaged form, a multicontainer unit having:

(a) each of two oligonucleotide primers for each different sequence to be detected, wherein

(i) if the specific nucleic acid sequence to be detected is single-stranded one primer is substantially complementary to one end of the strand so that an extension product of said one primer formed under hybridizing conditions and in the presence of an inducing agent for polymerization and the different nucleoside triphosphates is substantially complementary to said strand, and the other primer is substantially complementary to one end of said extension product and can be used under hybridizing conditions and in the presence of an inducing agent for polymerization and the different nucleoside triphosphates to synthesize another extension product employing said extension product of said one primer as a template thereby providing a nucleic acid consisting of two strands; or

Invenciones DNA/proteína

Algunos productos biofarmacéuticos comerciales

Tissue plasminogen activator (tPA)

Insulina

Interferón a, b y g

Interleucina-2 (IL-2)

Granulocyte colony-stimulating factor (G-CSF)

Hormona humana del crecimiento (hGH)

Hormona estimulante del folículo (FSH)

Eritropoyetina

Glucocerebroridasa

Factor VIIa

Eritropoyetina – Kirin Amgen

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.

Treatment of anemia. Epo stimulates the production of red blood cells.

Epogen (erythropoietin-α) → without this product (and the patents) there would be no Amgen.

The patents behind erythropoietin (Epo) provide $2.5 billion a year in revenues.

Eritropoyetina – Kirin Amgen

Dr. Fu-Kuen Lin joined Amgen (established at 1980). By the end of 1983 Lin had isolated the gene of Epo and it can be produced in a form and quantity that made its therapeutic use possible.

At around the same time Japanese beer manufacturer Kirin Brewery approached Amgen and offered to help in the development of Epo in the fermentation process. Deal Amgen-Kirin.

Amgen filed a large portfolio of patents, the first containing DNA sequences encoding Epo (filed at the USPTO in 1984 and granted in 1987). US4703008

It was approved by the FDA in 1989.

Eritropoyetina – Kirin Amgen

In 1985 Amgen licensed exclusive international (non-US) marketing rights to Ortho Biotech, a subsidiary of Johnson & Johnson.

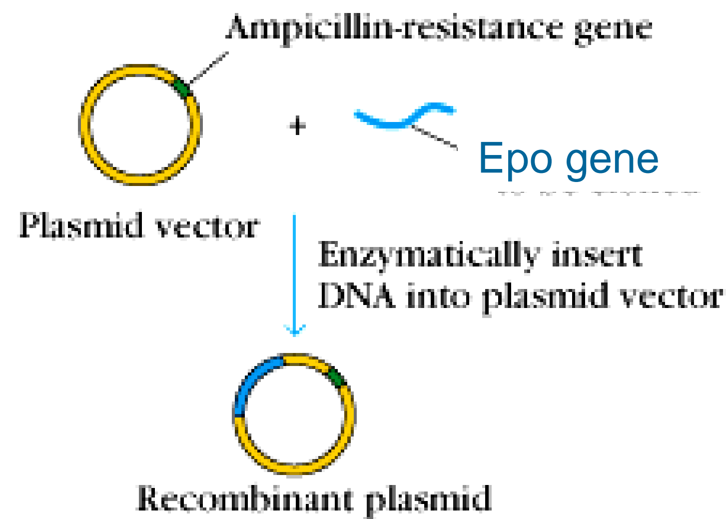
One of the most heavily litigated patents of the last two decades.

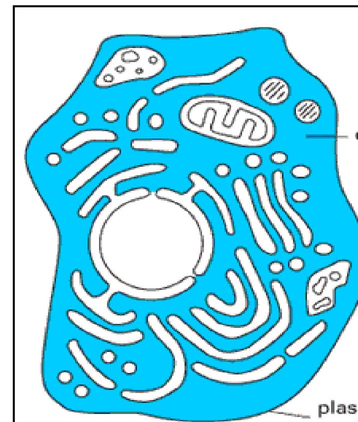
Maybe because Amgen, having invented the process for making Epo, tried to patent the protein itself but it was not new.

The European patent expired in 2004 and it is still in force in US.

Litigation with Johnson & Johnson, Roche (for a pegylated version of Epo) and now for analogues of Epo with many companies.

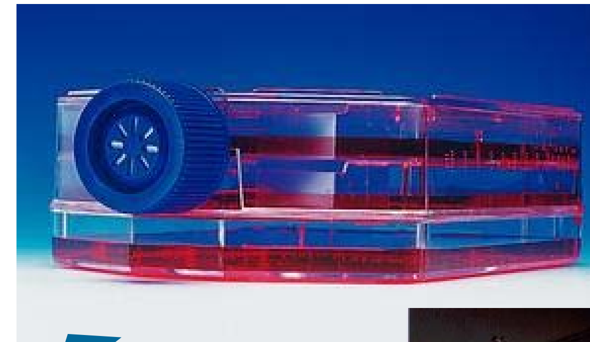
Ejemplo: producción de hEpo recombinante





transformación/

Transfección de células CHO



selección celular

producción

EP148605 - Kirin Amgen

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 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 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).

EP148605 - Kirin Amgen

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

3. A cDNA sequence according to point 1 being a monkey species erythropoietin coding DNA sequence.

4. A DNA sequence according to point 3 and including the protein coding region set forth in Table V.

5. A genomic DNA sequence according to point 1 or 2.

6. A human species erythropoietin coding DNA sequence according to point 5.

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

8. A DNA sequence according to point 1 or 2, covalently associated with a detectable label substance.

9. A DNA sequence according to point 8, wherein the detectable label is a radiolabel.

10. A single-strand DNA sequence according to point 8 or 9.

EP148605 - Kirin Amgen

11. A DNA sequence according to point 1, coding for $[Phe^{15}]$hEPO, $[Phe^{49}]$hEPO, $[Phe^{145}]$hEPO, $[His^{7}]$hEPO, $[Asn^{2}$ des-Pro^{2} through $Ile^{6}]$hEPO, [des-$Thr^{16}]$ through $Arg^{166}]$hEPO, or$[\Delta 27\text{-}55]$hEPO.

12. A procaryotic or eucaryotic host cell transformed or transfected with a DNA sequence according to any one of points 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 point 12 which host cell is capable of glycosylating said polypeptide.

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

15. A transformed or transfected COS cell according to point 13.

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

17. A biologically functional circular plasmid or viral DNA vector including a DNA sequence according to any one of points 1, 2, 3, 5, 6, 7, or 11.

18. A procaryotic or eucaryotic host cell stably transformed or transfected with a DNA vector according to point 17.

EP148605 - Kirin Amgen

19. A recombinant polypeptide having part or all of the primary structural conformation of human or monkey erythropoietin as set forth in Table VI or Table V or any allelic variant or derivative thereof possessing the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells to increase hemoglobin synthesis or iron uptake and characterized by being the product of eucaryotic expression of an exogenous DNA sequence and which has higher molecular weight by SDS-PAGE from erythropoietin isolated from urinary sources.

20. A glycoprotein polypeptide according to point 19 having an average carbohydrate composition which differs from that of human erythropoietin isolated from urinary sources.

21. A polypeptide according to point 19 or 20 wherein the exogenous sequence is a cDNA sequence.

22. A polypeptide according to point 19 or 20 wherein the exogenous DNA sequence is a genomic DNA sequence.

23. A polypeptide according to point 19 or 20 wherein the exogenous DNA sequence is carried on an autonomously replicating circular DNA plasmid or viral vector.

24. A polypeptide according to any one of points 19 to 23 further characterized by being covalently associated with a detectable label substance.

25. A polypeptide according to point 24, wherein said detectable label is a radiolabel.

EP148605 - Kirin Amgen

26. A polypeptide product of the expression in a eucaryotic host cell of a DNA sequence according to any of points 1, 2, 3, 5, 6 and 7.

27. A process for production of a polypeptide having at least part of the primary structural conformation 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 synthesis or iron uptake, which process is characterized by culturing under suitable nutrient conditions a procaryotic or eucaryotic host cell transformed or transfected with a DNA sequence according to any of points 1, 2, 3, 5, 6 and 7 in a manner allowing the host cell to express said polypeptide; and optionally isolating the desired polypeptide product of the expression of the DNA sequence.

28. A process according to point 27, characterized by culturing a host cell of any one of points 12 to 16.

29. A process according to point 27 or 28 for production of a polypeptide of any one of points 19 to 23 and 26.

30. A pharmaceutical composition comprising a polypeptide produced in accordance with the process of point 27, 28 or 29 and a pharmaceutically acceptable diluent, adjuvant or carrier.

31. A pharmaceutical composition according to point 30, comprising a polypeptide of any one of points 19 to 23 and 26.

Patentabilidad de invenciones DNA/proteína.

Situación

DNA is not an ordinary molecule.

DNA itself is not the effector molecule within the cell: it is an information vector. Before it can have effect, DNA must be transcribed into mRNA and then this one translated into the corresponding protein (and the protein suffers modifications to be effective). So the DNA has no structural relationship with the effector molecule, but contains all the information needed by the cell to create it.

So it differs markedly from new chemical entities that exhibit pharmaceutical activity itself.

This unique nature of DNA raises a number of questions in patent law:

- If a valuable effect is identified, what protection should be given and what conditions should be attached to providing this protection?

- Should a patent protect DNA molecule itself?

Patentabilidad de invenciones DNA/proteína.

Situación

-It is justified to treat claims to DNA molecules any different to claims to new chemical entities?

Some of these questions have been addressed by Directive 98/44/EC but questions remain about the implementation of the directive.

Patents have been granted or patent applications have been filed for nearly 20% of human genes.

Ex. major genes for monogenic disorders (Huntington's disease, Cystic fibrosis) and some common predisposition genes (breast cancer BRCA1 and BRCA2).

However, after the publication of the human genome in 2001, there was a clear decrease in patent filings, and gradually the bar on patentability has also been elevated.

Invenciones DNA/proteína

Are genes and proteins patentable?

Yes, if a number of criteria are fulfilled (Rule 26, 27, 29 EPC, EU Directive 98/44/EC, Art. 5 LP):

- Gene/protein is not a mere discovery (= nucleic acid/protein sequence as such)

- A nucleic acid/protein sequence becomes patentable if a specific application or function of the gene and/or protein (e.g. biological, medical, therapeutic...) is described in the application as filed. Ex:

    - medicament (insulin, growth hormone)
    - association with cancer (diagnosis)

- use of a gene for "fishing" similar genes in, for example, a library is not sufficient to fulfill the requirements of industrial applicability

Inventive step

DNA considered inventive if (Rule 23e3 EPC)

- isolation required inventive skill
- surprising/unexpected effect (function, activity) disclosed in application as filed

- Further members of known gene families (T255/05)
- Species homologues (T111/00, T1306/04)

→ Not inventive unless unexpected effect

Later filed supportive data – T1329/04

T1329/04 (Factor-9/JOHN HOPKINS), 2005. Art. 56 (inventive step).

EP Appl. No. 94907259.9

The invention relates to a new member of the transforming growth factor beta (TGF-ß) superfamily, which is denoted growth differentiation factor-9 (GDF-9).

Claim directed to a polynucleotide encoding a polypeptide having GDF-9 activity.

The DNA sequence identified is predicted to encode a polypeptide with the function “causes growth and differentiation of oocytes”.

The application as filed explains the computer prediction.

No evidence in the application that GDF-9 plays a role similar to that of the transforming factor-ß.

Applicant filed post-published evidence establishing that GDF-9 was indeed a growth differentiation factor.

Later filed supportive data – T1329/04

Based on the structural differences between GDF-9 and other members of this superfamily, GDF-9 cannot be clearly and unambiguously identified as a member of the TGF-ß superfamily by only using the „structural approach“:

the computer prediction was not plausible since the claimed sequence did not have the important structural feature (“presence of the seven cysteine residues”) characterizing the known proteins of the TGF-ß superfamily.

BA rejected the claim for lack of inventive step since problem of the claim was not plausible solved. This case is also important because BA rejected to accept late filed evidence as support for inventive step.

Decision: The definition of an invention as being a contribution to the art, i.e. as solving a technical problem and not merely putting forward one, requires that it is at least made plausible by the disclosure in the application that its teaching solves indeed the problem it purports to solve. Therefore, even if supplementary post-published evidence may in the proper circumstances also be taken into consideration, it may not serve as the sole basis to establish that the application solves indeed the problem it purports to solve.

Allowable DNA claim

An isolated nucleic acid molecule encoding a caspase, selected from the group consisting of

a) a nucleic acid molecule comprising a sequence which is at least 60% identical to the nucleotide sequence of SEQ ID NO: 1

b) ... hybridising to SEQ ID NO: 1...

c) ... encoding a naturally occurring allelic variant of a polypeptide...

Allowable DNA terms (cover analogues, not only the specific sequence):

- Hybridisation
    - T301/87; T1074/00: "stringent hybridisation"
- Indentity/ homology
    - T610/01: 60% homology – EPO prefers % identitty for clarity!

Only with functional limitation!

Further possible claims

- Vector comprising SEQ ID NO: 1
- Host cell comprising SEQ ID NO: 1
- Method for producing proteing having SEQ IQ NO: 2 comprinsing culturing host cell and recovering protein
- Pharmaceutical composition comprising protein having SEQ IQ NO: 2

Purpose bound protection

How claims will be interpreted and what protection they will offer?

Different national approaches have been chosen in implementing the Biotech Directive into the national law.

Full product protection:

Absolute, protects the product for any use of the product and for all processes to make it.

Applied to DNA:

- All uses of the DNA sequence, present and future
- All processes to produce the patented DNA sequence

Purpose bound protection

DNA can have various functions:

- Can code for more than one protein (e.g. spliced genes)
- Can be uses for different purposes (e.g. diagnosis and drug targeting)

Subsequent inventors can obtain patent protection for new function but depending on the first product protection.

Purpose bound product protection:

Invention for DNA sequences → protection will be limited to the specific function disclosed

Subsequent inventors can obtain patent protection for new function.

Purpose bound protection

Justified a novel regime of protection in the field of biotechnology?

Countries that have implemented the directive into their laws in a way which limits the scope of a patent to the purpose(s) disclosed in the claim:

France	Switzerland
Luxemburg	Germany
Italy	

The European Commission decided in 2005 not to take a position on the validity of these different national approaches due to the different contravening arguments and the current uncertainty relating to the economic consequences of respective laws (Commission report 2005/312).

Casos relevantes en US - *In re Kubin (2009)*

The isolation and sequencing of a gene is sufficiently non-obvious to be patentable?

The Federal Circuit has long been friendly to patents claiming polynucleotides sequences. Until now, 14 years, with:

In re Bell, 991 F.2d 781 (Fed. Cir. 1993)
In re Deuel, 51 F.3d 1552 (Fed. Cir. 1995)

Even when the sequence of the protein was known, the court held that the nucleotide sequence was not obvious because it could not be derived from the protein sequence.

The obvious methods of isolating a DNA molecule say nothing about the DNA nucleotide sequence.

Casos relevantes en US – *In re Kubin (2009)*

In re Kubin, 561 F.3d at 1351 (Fed. Cir. April 2009):

In re Kubin rejects the *In re Deuel* approach to obviousness.

The board said that the recent decision on "obvious to try" of KSR v Teleflex 2007 appeared to weaken the *Deuel* decision.

The patent: US2008081043 Amgen.

Describes the isolation and amino acid and nucleotide sequence of NAIL (the natural killer cell activation inducing ligand ("NAIL"), a receptor on the surface of NK cells implicated in the activation of the NK cells of the immune system).

Claim to polynucleotide sequences that encode NAIL.

Claims rejected by USPTO as obvious in view of prior art.

Casos relevantes en US – *In re Kubin (2009)*

Prior art:

1. Valiante patent

The NAIL protein had been discovered and disclosed by the prior art Valiante patent, but Valiante did not describe how to purify NAIL and amino acid and nucleotide sequence of NAIL.

Valiante had identified NAIL with a monoclonal antibody and disclosed that the NAIL protein and specified that gene could be obtained by conventional cloning methods.

(here is a bigger gap than in cases *Bell* and *Deuel* because in those cases the prior art disclosed at least partial protein sequences: thus *Kubin* appears to be less obvious than *Bell* and *Deuel*)

2. Sambrook manual

3. An article (Mathew et al) describing the cloning and characterization of the mouse 2B4 gene product which is the mouse homolog of human NAIL.

Casos relevantes en US – *In re Kubin (2009)*

Appeal against USPTO rejection. The Board uphelp de decision.

The Board: a person ordinary skill in the art would have had reasonable expectation of success in cloning NAIL by following the theoretical example of Valiante and using conventional procedures as described in Sambrook and Mathew.

When there is a need to solve a problem and there are a finite number of identified and predictable solutions to a problem, there is a good reason to pursue the known options. KSR

Problem: isolating a NAIL cDNA

A limited number of methods were available to do so.

And there was a reasonable expectation that at least one of the methods would be successful.

Isolating NAIL cDNA was the product of ordinary skill and common sense not of innovation, so the claims were obvious.

Casos relevantes en US – *In re Kubin (2009)*

CAFC maintained the Board's decision.

Future

- *Kubin* will govern polynucleotide claims.
- This brings into question the patentability of polynucleotide inventions and the validity of issued patent claims to polynucleotides.
- The isolation of genes now represents and advanced art and is no longer to be automatically regarded as unpredictable.
- in a higher level, it brings into question every invention involving biotechnology, a highly developed field with many established methods.
- CACF has rejected formalistic rules for determining obviousness after *Kubin.*

Guidance from *Kubin* to what inventions might be non-obvious:

- A polynucleotide is obvious if a limited number of known methods can be used to isolate it and those methods are reasonable expected to work.

Casos relevantes en US – *In re Kubin (2009)*

- *Kubin* clarifies that (as in *In re O'Farrel* 1988) sometimes "obvious to try" does not imply obviousness. Thus it would be no obvious "to vary all parameters or try each of numerous possible choices until one possible arrived at a successful result".

- Biotechnology is full of variable parameters and numerous possibles of choice. So:

  - advisable to avoid characterizing the methods used to arrive at an invention as "standard biochemical methods".
  - describe all the failed attempts and all the adjustments needed to achieve success
  - think twice about mentioning manuals like Sambrook and incorporating it by reference, and instead make an effort to describe the actual method for enablement requirement. Balance.
  - describe the failure of others to make the invention.

Casos relevantes en UK

- Directive implemented in July 28 2000 and applies only to patent applications filed after that date.

- No patents covering biotechnological inventions which the directive applies have yet been considered by the UK Courts today.

- In many cases outside the scope of the directive, claims have been interpreted in line with it.

- The number of cases considering pure claims to DNA-based inventions in the UK is relatively small.

Casos relevantes en UK – *Biogen v Medeva (1997)*

Biogen v Medeva (1997)

Expression of Hepatitis B viral antigens

The claim in issue was to a recombinant DNA molecule.

In the priority inventors described that HBV consisted of an outer protein envelope (use as antigens), but the DNA had not been sequenced. The inventors did not know where to find the genes for the surface and core antigens on the HBV genome and didn't know the sequences of these genes.

In appeal it was considered an speculative idea. There must be support at the priority.

The claim was held to be insufficient because it claimed more than the patent's technical contribution to the field.

Casos relevantes en UK – *Amgen v TKT (2005)*

Amgen v TKT (2005)

There is no mention in the House of Lords decision of the directive but the decision is consistent with it.

(Amgen) Claim 1 was to a DNA sequence for use in securing expression of erythopoietin in a host cell.

Amgen had sequenced the gene for Epo and claim 1 covered its expression in a host cell to produce the Epo protein (claim 26 covering the product of this expression).

TKT made use of a process called homologous recombination to insert a promoter in front of the endogenous Epo gene which cause overexpression of the protein and allowed increased yield.

Casos relevantes en UK - *Amgen v TKT (2005)*

Amgen’s Epo was made by and exogenous DNA sequence in a host cell and TKT’s Epo by an endogenous sequence coding for Epo.

The court: Epo in Amgen patent must be exogenous.

Whilst claim 1 itself was not infringed because TKT made Epo outside UK, its interpretation was important because Amgen alleged infringement of claim 26 which claimed Epo produced by the DNA sequence of claim 1. It was necessary to understand claim 1 in order to understand claim 26.

The court was clear that the sequence of Epo contained in Table VI could not be an invention as it was a mere discovery. It was considered information as such (Lord Hoffmann)

Casos relevantes en UK - *Amgen v TKT (2005)*

Therefore, protection was not given to the DNA sequence *per se*.

TKT process no doubt made use of the same sequence. Protection was given instead to the method of producing Epo

Homologous recombination was not contemplated in the patent and Amgen could not have a monopoly over the information.

Casos relevantes en UK – *Monsanto v Cargill (2007)*

Monsanto v Cargill (2007). EP546090

Monsanto has a patent to the gene sequence that conferred to a plant resistance to the herbicide glyphosate (Round up)

Claim 1 was to a isolated DNA sequence encoding a Class II EPSPS enzyme.

Cargill imported soymeal from genetically modified soya beans into UK.

The judge found as a fact that the gene sequence was present in the allegedly infringing material.

Casos relevantes en UK – *Monsanto v Cargill (2007)*

However because of the construction of the claim, the patent was not infringed:

Pumfrey J held that the term “isolated” was a technical term that applied to DNA sequences that had been removed from a genome and were in a form ready for further processing. The DNA within the soymeal was not in such a state, so there is no infringement.

Case example of differences in implementation and interpretation of directive in different countries.

Case also in Spain (Sestroris) and in the Netherlands (Cefetra).

Casos relevantes en UK – *Monsanto v Cargill (2007)*

Important: The directive applies in these countries, so applies Art. 9:

(Art. 50.4 LP, Art. 9 Directive)

Cuando la patente tenga por objeto un producto que contenga información genética o que consista en información genética, los derechos conferidos por la patente se extenderán, sin perjuicio de lo dispuesto en el apartado 4 del artículo 5 a toda materia a la que se incorpore el producto y en la que se contenga y ejerza su función la información genética".

Soymeal is highly processed and contains no viable cells. In these circumstances the inserted gene even if present, is not performing its function because in order to perform its function ot would need to be transcribed into mRNA and then translated into protein, and this can only be performed in viable cells.

Casos relevantes en UK – *Monsanto v Cargill (2007)*

If the directive applies in this situation, there would be arguably be no infringement due to art 9. → case in Spain (last decision March 2009).

This situation may have been avoided by including a claim to soymeal to the claim set!!

In UK, Cargill did not infringed because of the construction given to "isolated". The Dutch court also adopted this construction and as a result found no infringement.

Some people criticise this interpretation because of the convention of the use "isolated" in US to distinguish the claimed sequence from that in nature.

Casos relevantes en UK – *Lilly v HGS (2008)*

Eli Lilly v Human Genome Science, HGS (2008)

Example of validity of patents covering genes identified using bioinformatics techniques such as homology screening (using data bases).

HGS had identified a new member of the TNF ligand superfamily called neutrokine-α by homology screening and had filed a patent application claiming the nucleic acid and amino acid sequences of neutrokine-α.

As well as claims to the sequences, there were claims to the therapeutic and diagnostic application of the protein and antibodies to the protein.

Although the patent proposed activities of neutrokine-α based on its membership of the TNF ligand superfamily, (inflammation activity) the patent did not include any data which precisely identified neutrokine's biological activities.

The patent was granted, Lilly started opposition in the EPO and revocation proceedings in the UK.

Casos relevantes en UK – *Lilly v HGS (2008)*

The attack was that HGS had filed a wholly speculative application as at the time of filing, HGS did not know for sure what biological activity or function neutrokine-α had.

The claim was to an isolated nucleic acid molecule encoding neutrokine-α polypeptide.

“isolated” was a defined term within the specification of the patent and the parties did not dispute this interpretation so its meaning was not considered.

Kitchin J considered that:

- the directive did not apply but considered the requirements of the directive at least as regards industrial applicability.

Casos relevantes en UK – *Lilly v HGS (2008)*

- reviewed the judisprudence in UK, EPO and US on industrial application. He summarizes the industrial applicability in 9 points.

-in case of inventions with gene sequences and proteins found in nature, industrial applicability requirement should be higher than other inventions.

- used as starting point: the industrial application of a gene must be disclosed in the application and if it encodes a protein, then the protein or its function must be specified.

- accepted that HGS had identified a novel member but it was not sufficient to confer industrial applicability.

Casos relevantes en UK – *Lilly v HGS (2008)*

The patent was also found to be insufficient and obvious:

lack of inventive step because it provided no more than speculation about how neutrokine-α might be useful and

did not teach the skilled person how to solve any technical problem.

The judge provided the first comprehensive review in the UK of how industrial applicability should be considered for biotechnological inventions. High influence in future cases.

After the trial took place but before the judgement was issued, the patent was found to be invalid in opposition proceedings before the EPO. The EPO held lack of inventive step and considered it was a claim to an arbitrary member of the TNF ligand superfamily without a known function.

Resumen

- Genes and proteins may represent patentable matter
- Genes and proteins are usually structurally defined by sequences (not if they are well known, e.g. p53)
- Industrial applicability: Function must be credible and specific
- No possible later filing to demonstrate inventive step
- Elements like % identity but not so broad and with functional limitation
- Absolute protection of product or purpose bound protection?
- Interpretation of the directive?

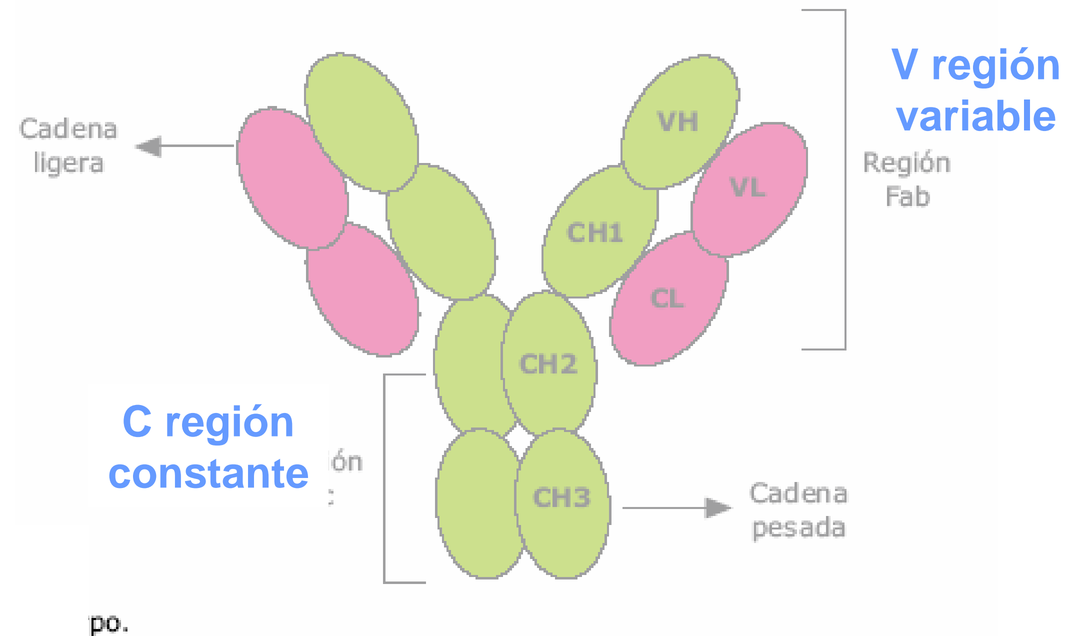
Anticuerpos (inmunoglobulinas)

glucoproteínas empleadas por el sistema inmunitario para identificar y neutralizar elementos extraños tales como bacterias, virus o parásitos. Producidos por los linfocitos B.

Estructura básica de una inmunoglobulina:

- 2 **cadenas pesadas** (**H** o *Heavy*)
- 2 **cadenas ligeras** (**L** o *Light)*

Los dominios N-terminales de las cadenas H y L forman la región variable o V (su secuencia aminoacídica varia según el determinante antigénico reconocido).



Dibujos Genoma España

Anticuerpos

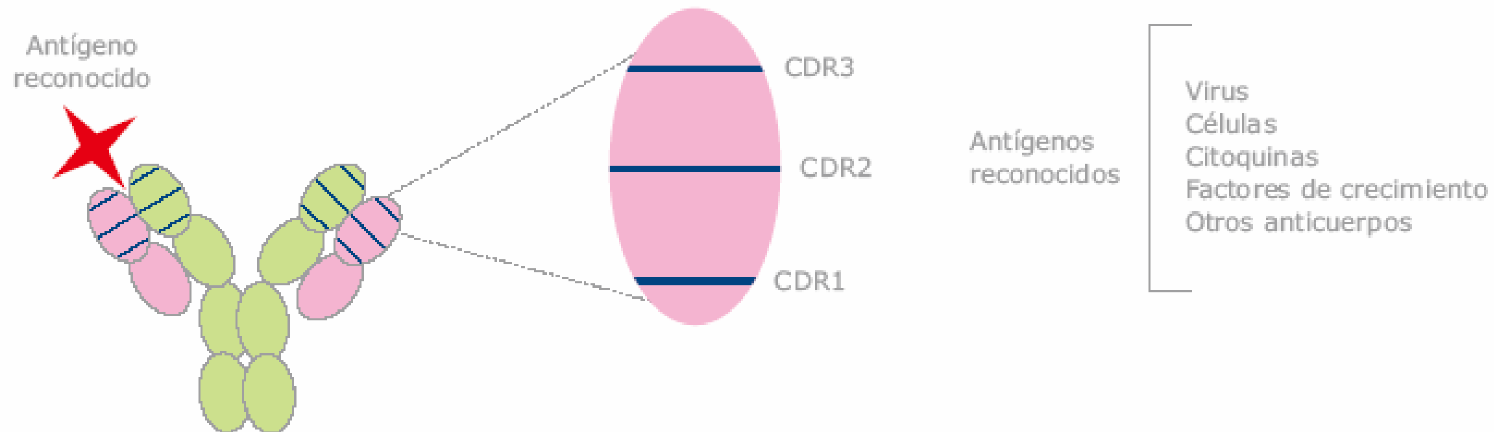


Fig. 3. Regiones CDR de un anticuerpo responsables del reconocimiento de antígenos.

La combinación de la región variable cadena pesada (VH) y de la cadena ligera (VL) forma el punto de unión al antígeno (antigen binding site) y determina la especificidad antigénica que es capaz de reconocer.

Las regiones V de las Ig contienen 3 **zonas hipervariables** llamadas **regiones determinantes de la complementariedad o CDR (*complementarity-determining regions*).** Son las zonas que tienen contacto con el Ag.

Aplicaciones de los anticuerpos. Especificidad

Investigación

Diagnóstico (detección)

Terapia

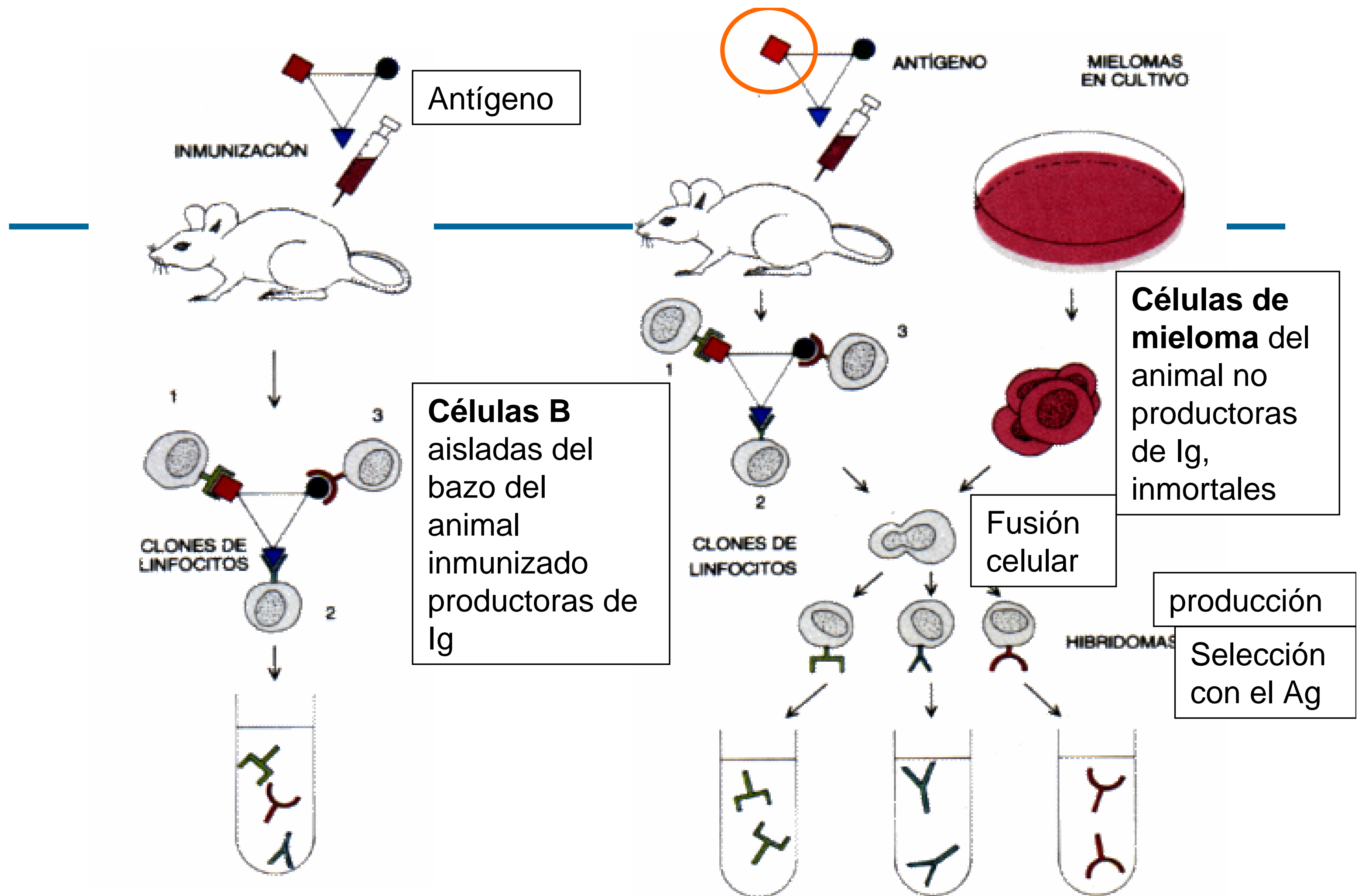
Purificación proteínas

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

Murine	-omab
Chimeric	-ximab
Humanized	-zumab
Fully human	-umab

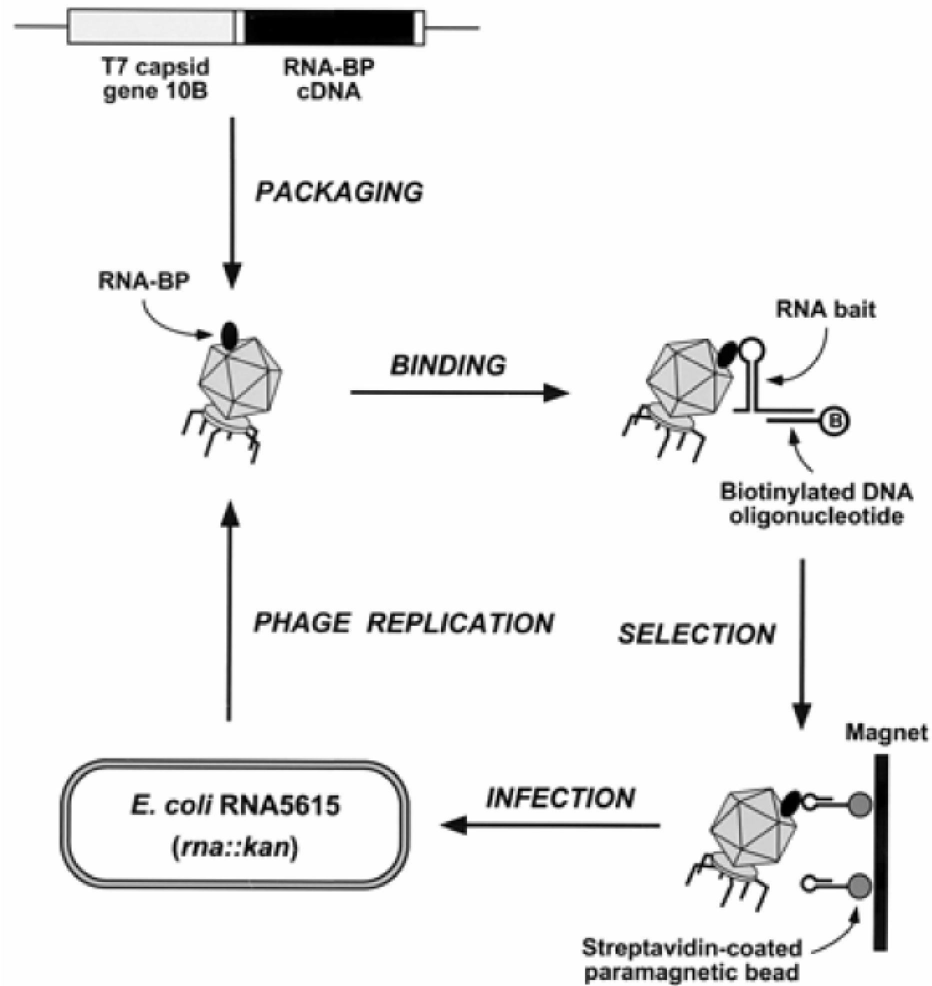


anticuerpos policlonales
o anti-serum

anticuerpos monoclonales.
Kohler and Milstein 1975

Dibujos Jaume Piulats

Phage display technology



mAbs key patents

Medical Research Council, MRC (UK) and Cambridge Antibody Technology, CAT (later MedImmune, now subsidiary of AstraZeneca) (UK)

Patents:

US5969108, US5885793, (expire 2016) and US6248516

Antibody libraries and method of displaying parts of antibodies on phages (phage display technology).

Revolution in the field of mAbs to produce fully human mAbs.

One of the first fully human mAb approved, developed by CAT and Abbott: Humira for the treatment of rheumatoid arthritis.

Claims to antibodies

Application discloses for the first time the antigen X. The antigen X is found novel and inventive (and has industrial applicability).

"An antibody directed (reactive) against protein X".

Is the antibody novel? / inventive?

Answer (T0542/95): YES.

(claimed by the antigen)

If the antigen is well defined -> claim is clear,

even in the absence of working examples

Claim often included in patent applications for protein (antigen) and DNA encoding the protein.

The so-called "imaginary antibody (imAb)".

Claims to antibodies

Application discloses for the first time an antibody to antigen X. The antigen X is known in the art.

"An antibody directed (reactive) against protein X".

Is the antibody novel? / inventive?

Answer:

YES, the antibody is novel.

NO, the antibody is not inventive. The preparation of an antibody to a known target is merely a measure of routine. An inventive step is only present if the antibody has
- unexpected properties
- failures to produce that antibody

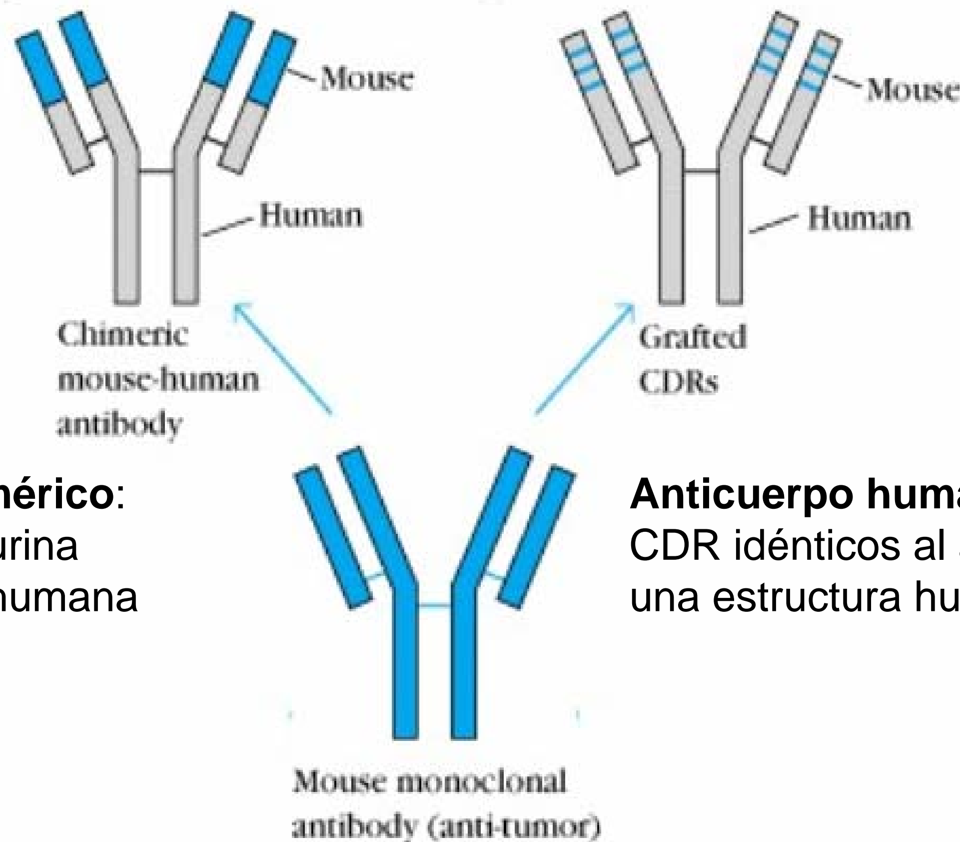
Claims to antibodies

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)

Claims to antibodies

Genetic engineering permits obtention of modified antibodies with advantages:



Anticuerpo quimérico:
Parte variable murina
Parte constante humana

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

Claims to antibodies

"An antibody which binds to protein X, but not to protein Y"

"mAb that binds to human breast adenocarcinoma cells, but not to normal human breast epithelial cells"

"A mAb demonstrating positive reaction to hexon trimer; inability to immunoprecipitate intact adenovirus 3 virions; nuclear immunofluorescence in cells where adenoviruses are present; reactivity with…"

(claimed by functional or immunogenic properties)
Allowability case by case: problems of lack of clarity may arise.
Function and claimed features must be easily be tested by the skilled person with an assay (T877/03, T505/00, T0716/01)

Claims to antibodies

The antigen is not new, then antibodies directed to specific epitopes with particular properties can be claimed (if known antibodies are not directed to those epitopes):

"The antibody of claim 2, wherein the epitope is within the sequence Ala-Met-Lys-Gln-Pro-Ser-Ser-Leu-Phe-Arg-His (SEQ ID NO:…)"

A mAb capable of specific binding to human Mcm3, in which the mAb reacts with the same epitope of human Mcm3 as the mAb obtainable from a hybridoma cell line with deposit number ACC2388 (EP1165615)

(claimed by epitope)

Claims to antibodies

If the invention relates to a specific mAb produced by an hybridoma:

“A monoclonal antibody or antigen-binding fragments thereof produced by the clone deposited with the ATCC as PTA-2700”

“The isolated clone deposited with the ATCC as PTA-2700”.

(claimed by the hybridoma)

The antibody is clearly defined!

Claims to antibodies

Example WO02/092017:

"An antibody or an antigen-binding fragment thereof that specifically binds the capsular polysaccharide of *Streptococcus pneumoniae* serotype 3, wherein said antibody or fragment comprises a heavy chain amino acid sequence comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence encoded by the DNA sequence set forth in SEQ ID NO: 1;

…

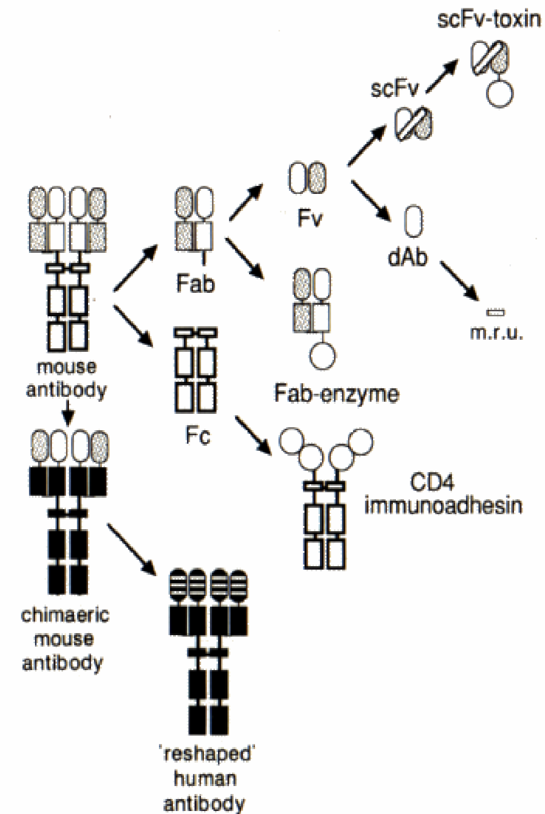
(c) the CDR1, CDR2 and CDR3 amino acid sequences encoded by the DNA sequence set forth in SEQ ID NO:1"

(claimed by sequence)

It is generally sufficient to claim a fragment comprising the variable regions or the specific CDRs.

Claims to Antibodies

Polyclonal
Monoclonal (1975)
Chimeric (1983)
CDR-Grafted (1986)
Humanized (1988)
PCR-cloned (1989)
Human Antibodies
Fragments of Antibodies
Synthetic / Semi-synthetic
Nanobodies
Avimers
Antibody Libraries

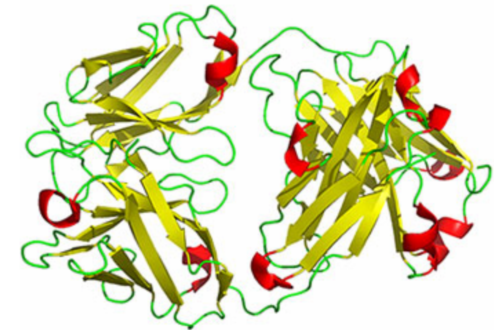


Hybridoma cell line per se
Methods of making antibodies
Methods of using antibodies: screening, therapeutics, purification, detecting
Kits incorporating antibodies (immunoassays)

Trastuzumab

EGFR Inhibition Via Monoclonal Antibodies Blocking Ligand Binding

Anti-EGFR MAb
ligand
ligand
Ligand binding blocked
ligand
Extracellular domain
EGFR
Receptor-MAb internalization
Cell membrane
Tyrosine kinase
Intracellular domain
Other enzyme or adaptor
Signal transduction cascade blocked
Gene activation, Cell cycle progression



Chiron v Genentech. Litigation in Germany

EP0153114 B1 Chiron (Cetus)

- Monoclonal anti-human Breast Cancer Antibody from Genentech: Trastuzumab (Herceptin®)
- Patent granted on 19.07.1989
- No opposition filed
- Patent amended in Nullity Action before German Patents Court / Appeal. Upper Regional Court Dusseldorf decides on Infringement (Oberlandersgericht Düsseldorf, I-2 U 80/02; 10.02.2005)

EP153114B1

1. A murine monoclonal antibody which:

(a) binds a human breast cancer antigen that is also bound by a reference antibody selected from those produced by the hybridomas obtainable from ATCC HB8488, HB8490, HB8486, HB8484, HB8697, HB8485, HB8696 and HB8662.

(b) has a G or M isotype; and

(c) when conjugated to ricin A chain, exhibits a TCID 50% against at least one of MCF-7, CAmA-1, SKBR-3, or BT-20 cells of less than about 10 nM.

2. A monoclonal antibody according to claim 1 which binds to a protein of approximately 210,000 daltons found in cancerous breast tissue.

3. A monoclonal antibody according to claim 1 and which is produced by one of the following hybridomas:

(a) HB8488;	(e) HB8484;
(b) HB8490;	(f) HB8485;
(c) HB8486;	(g) HB8696;
(d) HB8697;	(h) HB8662;

or a monoclonal antibody which is functionally equivalent to any one of the aforesaid antibodies.

EP153114B1

4. A murine × murine hybridoma which produces a monoclonal antibody according to claim 1 or claim 2, and progeny thereof capable of producing the monoclonal anti-human breast cancer antibody of the parent cells.

5. A hybridoma which is:

(a) HB8488;	(e) HB8484;
(b) HB8490;	(f) HB8485;
(c) HB8486;	(g) HB8696;
(d) HB8697;	(h) HB8662;

or progeny thereof, capable of producing the monoclonal anti-human breast cancer antibody of the parent cells.

6. A immunotoxin which is a conjugate of a monoclonal antibody according to any one of claims 1 to 3 and a cytotoxic moiety.

7. A method of in vitro killing human breast cancer cells comprising contacting the cells with a cytocidally effective amount of an immunotoxin as defined in claim 6.

8. A monoclonal antibody according to any one of claims 1 to 3 and labelled with a detectable label.

9. A method of in vitro diagnosing whether a human cell is a breast cancer cell comprising:

(a) incubating a human cell with an antibody as defined in claim 8; and

(b) determining the presence of labelled binary immune complexes on the human cell.

10. A method of preparing a hybridoma as defined in claim 4 comprising fusing murine tumor cells with murine splenocytes obtained from a mouse immunized with human breast cancer immunogen and selecting for hybridomas producing antibody as defined in claim 1.

Chiron v Genentech

Claims amended in Nullity proceedings Claim 3:

"A murine monoclonal antibody according to claim 1 which

is produced by hybridoma ATCC HB 8696, or

which is functionally equivalent to said antibody or to antibodies of claim 2"

Infringing Embodiment:

- Humanized Monoclonal Antibody (Trastuzumab)

Main Issue: Murine vs. Humanized

- Literal Infringement Denied
- Equivalent Infringement?

Chiron v Genentech

Is "humanized" equivalent to "murine"?

Court acknowledges that it might have been possible for the skilled person to find humanized Trastuzumab without inventive effort as an equivalently effective variant of claimed murine antibody, but ...

Chiron v Genentech

Is "humanized" equivalent to "murine"?

… Skilled person would derive from patent specification – as far as it concerns human beings - that the claimed antibodies would be useful for in-vitro purposes only (i.e. for diagnosis) !

When used to kill human breast cancer cells *in vitro* for diagnostic purposes, the conjugates will

Functional equivalence mentioned in claim 3 refers only to variants of murine Antibodies!

Patent specification does not provide any guidance towards the variant, rather teaches against it! (no indication in the specification on how to obtain monoclonal antibodies different from murine)

Decision: No equivalent infringement!

Case in US, 2004

Chiron claim:

"a monoclonal antibody that bind to human c-erbB-2 antigen"

Therapeutic humanized monoclonal antibody marketed by Genentech

No written description, no enablement found for chimeric, humanized Abs in 1984, 85 and 86 filings (nascent technology)

Decision of US CAFC: Chiron patent invalid

Resumen

Antibodies can be claimed by:

- reference to their antigen/target
- structural, sequence features
- functional features
- reference to a hybridoma deposit

If a functional feature is used to define an antibody, then it must be clear and testable

If the antibody has a particular property and was obtained by chance, then a deposit or detailed sequence information is necessary in order to ensure reproducibility

A (generic) antibody to a new and inventive antigen (and has industrial applicability) is always also new and inventive

An antibody to a know target can only be considered inventive if the antibody has:

- unexpected properties
- it was unexpected that an antibody could be produced at all (due to failure in the past)

Individual human genomes that have been published and made publicly available

OPEN ACCESS Freely available online — PLoS BIOLOGY

The Diploid Genome Sequence of an Individual Human

Samuel Levy, Granger Sutton, Pauline C. Ng, Lars Feuk, Aaron L. Halpern, Brian P. Walenz, Nelson Axelrod, Jiaqi Huang, Ewen F. Kirkness, Gennady Denisov, Yuan Lin, Jeffrey R. MacDonald, Andy Wing Chun Pang, Mary Shago, Timothy B. Stockwell, Alexia Tsiamouri, Vineet Bafna, Vikas Bansal, Saul A. Kravitz, Dana A. Busam, Karen Y. Beeson, Tina C. McIntosh, Karin A. Remington, Josep F. Abril, John Gill, Jon Borman, Yu-Hui Rogers, Marvin E. Frazier, Stephen W. Scherer, Robert L. Strausberg, J. Craig Venter

http://huref.jcvi.org

PLoS Biology 5:e254 (2007)

nature — Vol 452 | 17 April 2008 | doi:10.1038/nature06884

The complete genome of an individual by massively parallel DNA sequencing

David A. Wheeler[1*], Maithreyan Srinivasan[2*], Michael Egholm[2*], Yufeng Shen[1*], Lei Chen[1], Amy McGuire[3], Wen He[2], Yi-Ju Chen[2], Vinod Makhijani[2], G. Thomas Roth[2], Xavier Gomes[2], Karrie Tartaro[2]†, Faheem Niazi[2], Cynthia L. Turcotte[2], Gerard P. Irzyk[2], James R. Lupski[4,5,6], Craig Chinault[4], Xing-zhi Song[1], Yue Liu[1], Ye Yuan[1], Lynne Nazareth[1], Xiang Qin[1], Donna M. Muzny[1], Marcel Margulies[2], George M. Weinstock[1,4], Richard A. Gibbs[1,4] & Jonathan M. Rothberg[2]†

http://jimwatsonsequence.cshl.edu

Nature 452:872 (2008)

Looks can be deceiving

Gene	Examples of Some Drugs	James Watson	Craig Venter	Known Effects
CYP2D6	Beta-blockers, Antiarrhythmics, Antipsychotics, Tricyclic antidepressants	Mother: *10 variant Father: *10 variant	Mother: Common variant Father: Common variant	*10 has decreased activity

***10 is really rare in Caucasians (<1% frequency)**

Dr. Watson and Dr. Venter respond differently to drugs

A doctor probably would have never guessed this based on appearances

Demonstrates the utility of sequencing

Clinical Pharmacology & Therapeutics 84:306

Diagnosis, prognosis, personalyzed medicine

From a polymorphism in DNA → to personalized medicine.

Medicina personalizada/individualizada/a medida. Aplicación o uso de medidas específicas de prevención, tratamiento y seguimiento en función de la información genética de cada individuo.

Medicina convencional:

Paciente → diagnóstico convencional de la enfermedad (síntomas, pruebas) → localización del tumor, histología → tratamiento decisión 1 → tratamiento alternativo

Medicina a medida:

Permite la administración a cada individuo del medicamento adecuado para la patología que padece, en la dosis adecuada y en el tiempo adecuado para salvaguardar la eficacia y seguridad del mismo.

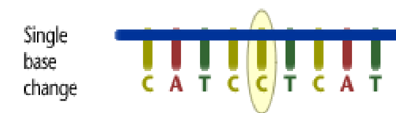
definiciones

Biomarcador. Característica biológica que puede medirse de manera objetiva y que puede ser utilizada como indicador de un proceso biológico normal, de un proceso patológico, así como de la respuesta farmacológica a una intervención terapéutica.

Ejemplos: parámetro bioquímico (colesterol, creatinina, ácido úrico, etc), mutación de un gen, sobreexpresión de un gen, ausencia de una proteína. Dentro de los biomarcadores:

Polimorfismo genético. Variantes de un gen que alcanzan al menos una frecuencia del 1% en la población general. Pueden afectar a la secuencia codificante o reguladora, produciendo cambios en el fenotipo o no.

SNP. Variación en la secuencia de ADN que afecta a una única base, que se observa en la población con una frecuencia superior al 1%.



aplicaciones

Un biomarcador nos dará información sobre:

- la predisposición o riesgo a padecer una enfermedad
- el diagnóstico de la enfermedad, detección precoz
- el grado de malignidad de la enfermedad (p.ej. un tumor más agresivo), clasificación del paciente
- una buena o mala prognosis (evolución)
- la posible respuesta a un determinado tratamiento, y por lo tanto tratamiento a medida

Otros usos de los biomarcadores:

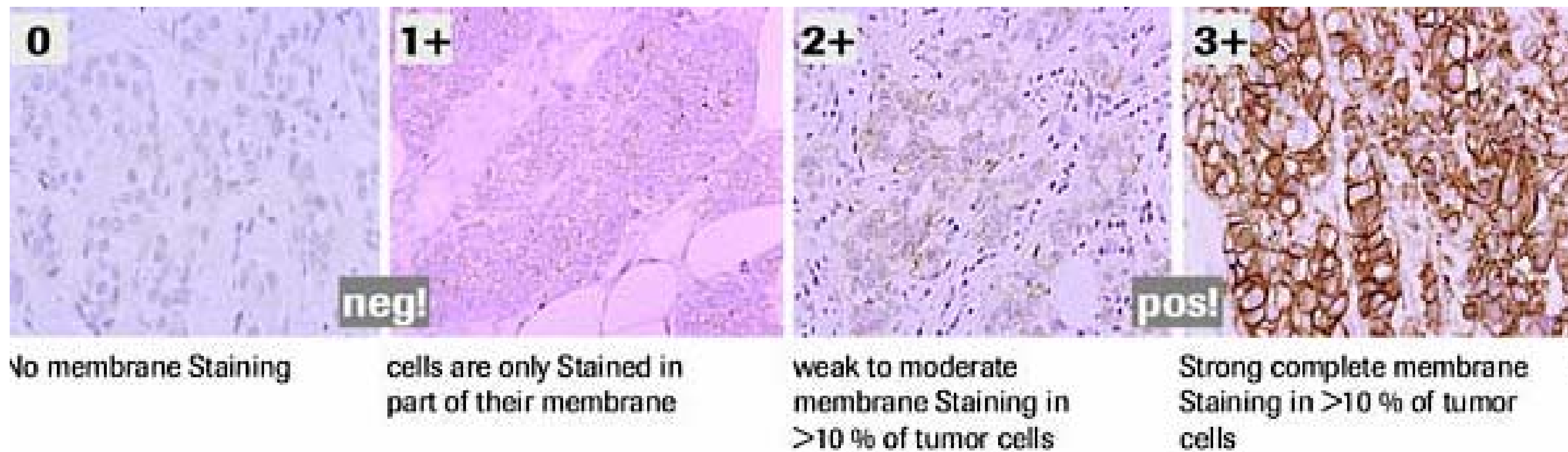
- screening de fármacos
- eficiencia en el desarrollo de fármacos (p.ej. identificación de efectos secundarios en un estadio temprano usando marcadores de toxicidad / estratificación de pacientes que permite testar el fármaco en una población más pequeña y adecuada).

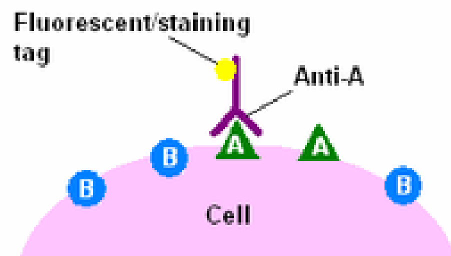
TABLA DE BIOMARCADORES GENÓMICOS VALIDOS EN EL CONTEXTO DE LAS ETIQUETAS DE FÁRMACOS APROBADOS EN ESTADOS UNIDOS

Marcador	Fármaco	Etiquetado
EGFR	Cetuximab	Obligatorio
Sobre-expresión Her2/neu	Trastuzumab	Obligatorio
CCR-5	Maraviroc	Obligatorio
Cromosoma Phl	Dasatinib	Obligatorio
Variantes CYP2C9	Warfarina	Recomendado
Variantes VKORC1	Warfarina	Recomendado
Proteína C	Warfarina	Recomendado
TPMT Actividad baja e intermedia	Azatioprina	Recomendado
Alelo UGT1A1*28	Irinotecán	Recomendado
LDL-R	Atorvastatina	Recomendado
HLA-B*1502	Carbamazepina	Recomendado
HLA-B*5701	Abacavir	Recomendado
UCD	Ácido valproico	Recomendado

Genoma España 2009. Farmacogenómica: Medicina Personalizada y Predictiva. Informe de Prospectiva Tecnológica Sectorial

Determination of HER2-protein overexpression by immunohistochemistry (semiquantitative DAKO Hercep Test™)





WO2004008099A2 Genentech

(57) Abstract: Tumors are identified as responsive to treatment with anti-HER2 antibodies by detecting the presence of a HER2/HER3 and/or HER2/HER1 protein complex or for HER2 phosphorylation in a sample of tumor cells. Patients suffering from a tumor comprising HER/2/HER1 and/or HER2/HER3 heterodimers and/or HER2 phosphorylation are treated with anti-HER2 antibodies, such as rhuMAb 2C4.

1. A method of identifying a tumor as responsive to treatment with an anti-HER2 antibody comprising:

fármaco

a) detecting the presence of a HER2/HER3 and/or HER2/HER1 protein complex in a sample of said tumor;

c) identifying a tumor as responsive to treatment with anti-HER2 antibody when a complex is detected.

2. The method of claim 1 wherein the anti-HER2 antibody blocks ligand activation of an ErbB heterodimer comprising HER2.

3. The method of claim 1 wherein the anti-HER2 antibody is monoclonal antibody 2C4.

…claims to how to identify the marker -> use of kits/reagents

futuro

No todas las indicaciones son aptas para la personalización. Cáncer, enfermedades inmunes y SNC.

Del blockbuster para toda la población → tratamiento + marcador personalizados

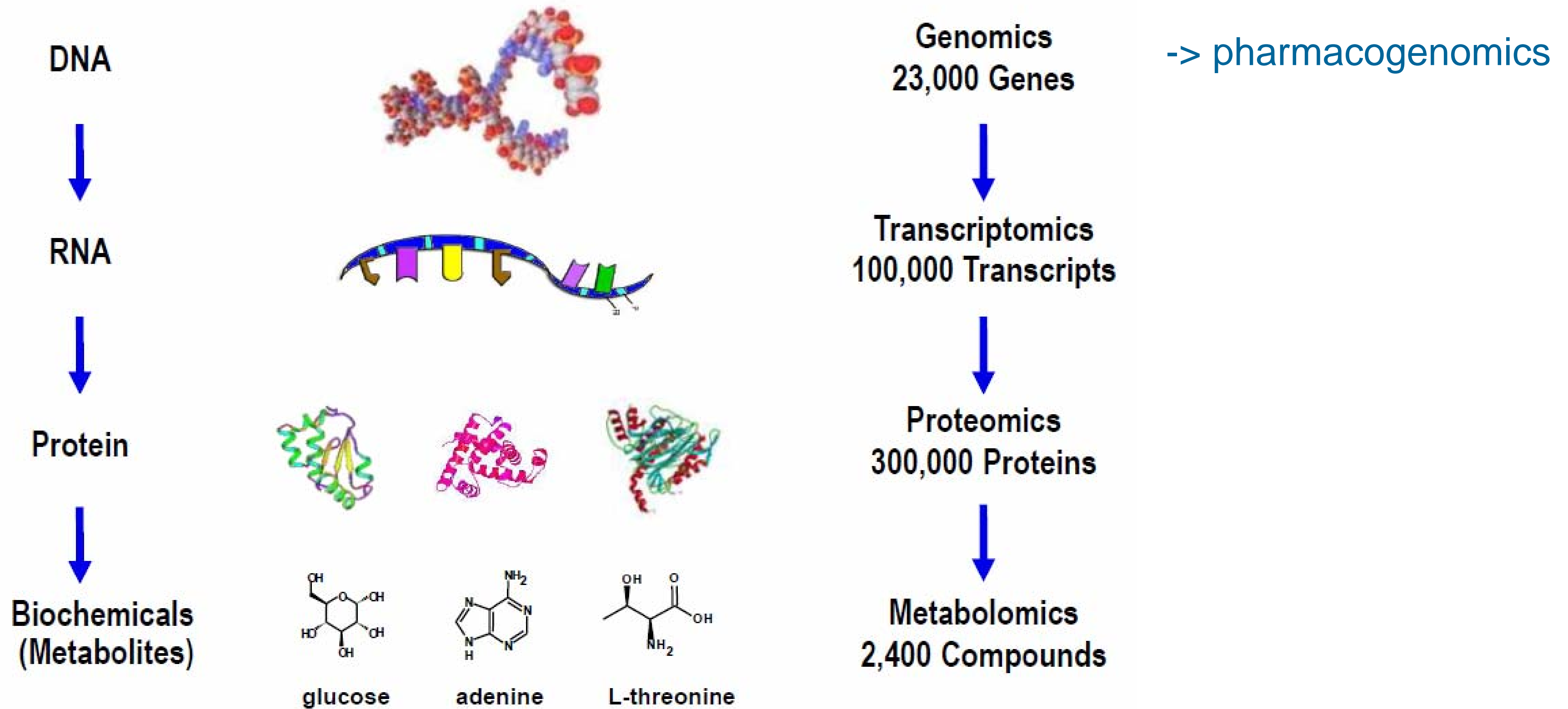
Esto implica nuevos roles en la industria:

Joint-ventures, agreements biotechs con la gran farma, proveedores de diagnóstico integrales (muchas facetas del diagnóstico: molecular, por imagen, etc)

Combinar los dos mundos (terapia y diagnóstico) en una estrategia de negocio coherente.

Farmacogenómica: Medicina Personalizada y Predictiva.
Informe de Prospectiva Tecnológica Sectorial. Genoma España 2009.
Conferencia de Thomas Reiss “Implications of personalized medicine for the health economy”.
Symbiosis, Barcelona, 14 septiembre 2009

OMICs



-> pharmacogenomics

and Metagenomics (also Environmental Genomics, Ecogenomics or Community Genomics) = the study of genetic material recovered directly from environmental samples

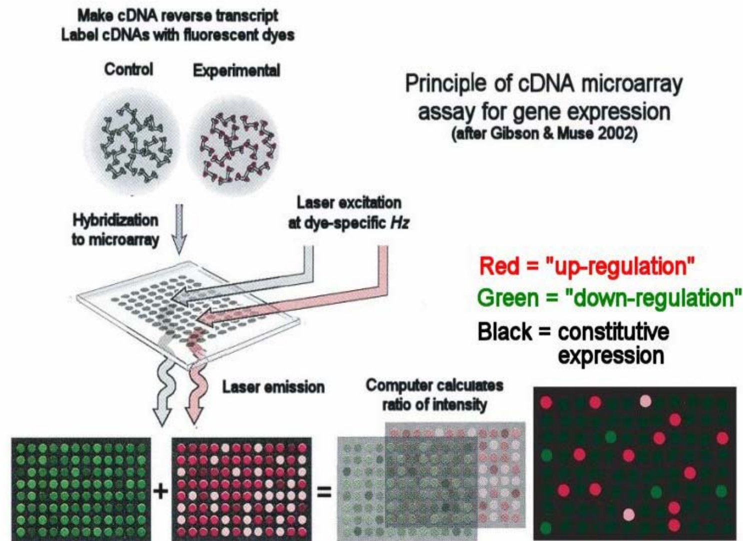
definiciones

Genoma. Conjunto total de genes de un organismo o una especie.

Genómica. Estudio de la estructura y función de todos los genes de un organismo en base al conocimiento de todo el genoma del organismo.

Farmacogenómica. Influencia de la variabilidad genética en la respuesta a fármacos

Microarrays



Principle of cDNA microarray assay of gene expression

http://www.bio.davidson.edu/Courses/genomics/chip/chip.html

http://www.dnalc.org/resources/animations/dnaarray.html

the industry-standard tool for analyzing complex genetic information (analysis of a lot of genes simultaneously).

Microarrays (gene chips or DNA chips)

- Opened a new chapter for the biotech business in the mid 1990s.
- Human Genome Project (2001) specially dependent on this tool.
- the first, invented in 1989, sold in 1994. Called the GeneChip.
- integration of semiconductor fabrication techniques, solid phase chemistry and molecular biology.
- Affymetrix's high density microarray patents: good example of how a pioneering technique helped to develop the industry, but also like other patents, disputes over royalties led to high-stakes litigation for Affymetrix. Known as the Intel of biochips.
- Long patent disputes with Oxford Gene Technologies and Illumina.
- Development of protein arrays, etc.

Materia patentable

- Biomarcadores:

Marcadores genéticos, de expresión, proteínas, metabolitos

- Usos de los biomarcadores en:

Diagnóstico, terapia, investigación

(asociáción del biomarcador con el riesgo a padecer una enfermedad / diagnóstico, pronóstico / respuesta a un fármaco)

    - nuevas poblaciones de pacientes
    - terapia combinada con diagnóstico

- Método para la detección del biomarcador

- Reactivos, herramientas soporte para el estudio (arrays, geles, aparatos de espectrometría de masas, PCR, etc)

Requisitos de patentabilidad de DNA y proteínas / Métodos de diagnóstico / métodos de screening

Métodos de diagnóstico

Art 52(4) EPC, Art 4.6 LP. 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."

→ **G1/04** (16.12.2005)

To be excluded from patentability, a treatment or diagnostic method must actually be carried out on the living human or animal body. A treatment of

Una de las patentes sobre BRCA (“breast cancer”):

BRCA1 EP699754-B1 (Myriad Genetics)

Diagnosis of breast cancer predisposition

- screening for mutations in BRCA1 gene

Claim 1 B1

A method for diagnosing a predisposition for breast and ovarian cancer in human subject which comprises determining in a tissue sample whether there is a germline alteration in the sequence of the BRCA1 gene coding for a BRCA1 polypeptide having the amino acid sequence SEQ ID NO:2 **or a sequence with at least 95% identity to that sequence**, said alteration **being indicative of a predisposition to said cancer**

BRCA1: opposition

Filed 1995, granted 2001, revoked in opposition 2004, appeal decision 2009.

Ethical objections:

- patentee's refusal to license tests
- tests must be done by patentee
- cost of patentee's test higher

Ethical objections rejected

- **exploitation** of invention not unethical
- objections connected with licensing issues

Not EPO's task to consider economic effects of patent and limit the claims accordingly **(G1/98)**

Patent revoked for technical reasons

BRCA1: revocation and appeal

- no basis for 95% at amino acid level, only DNA
- 9 sequencing errors - loss of priority

Appeal by the patentee requesting patent maintained in a amended form (T0666/05, 17.02.09)

B2: No 95%, frameshift mutation (cambio de base en el DNA que da un cambio en la traducción, y por lo tanto sale una proteína diferente)

1. A method for diagnosing a predisposition for breast and ovarian cancer in a human subject which comprises determining in a tissue sample of said subject whether there is a germline alteration that is a frameshift mutation in the sequence of the BRCA1 gene coding for a BRCA1 polypeptide altering the open reading frame for SEQ ID NO: 2, said alteration being indicative of a predisposition to said cancer.

WO2005/015236 Roche diagnostics

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.

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

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.

T558/03 (2005) The Johns Hopkins University

Allowed: “A method of diagnosing a neoplastic tissue of a human, comprising: detecting loss of wild-type p53 genes or their expression products in isolated human tissue suspected of being neoplastic, wherein said loss leads to non-functional p53 gene products, loss of expression of p53 mRNA or diminution of expression of p53 mRNA, said loss indicating neoplasia of the tissue,

wherein the wild-type p53 gene sequence is shown in Zakut-Houri et al., EMBO J., 4, 1251-1255, 1985.

Definition of wild type.

Resumen

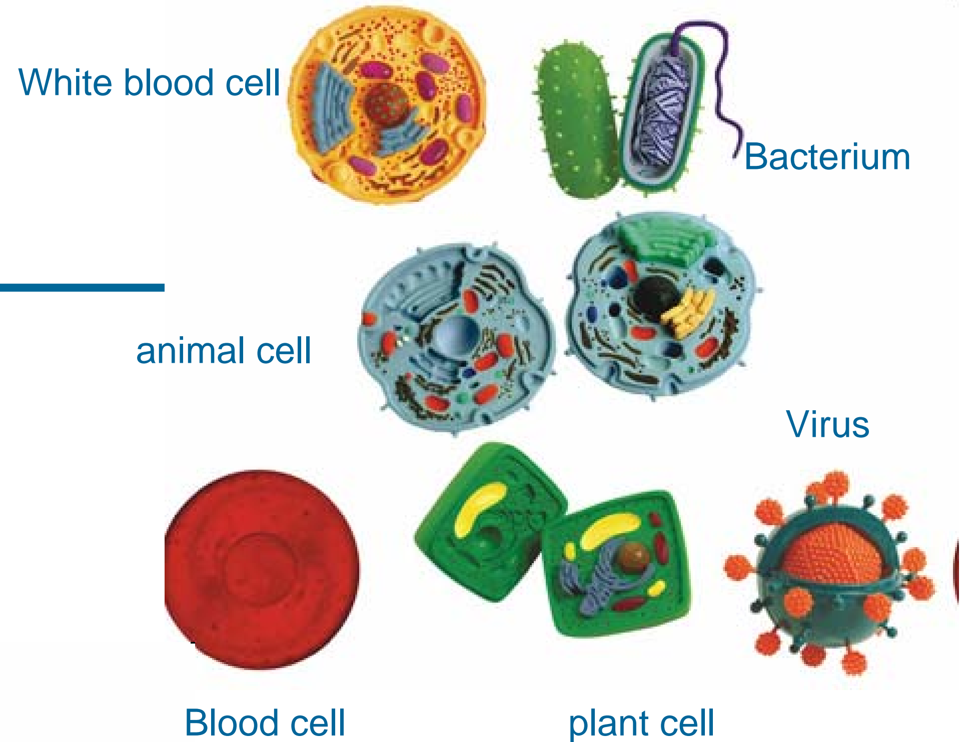
- Patentabilidad “convencional” para DNA/proteínas y métodos de diagnóstico/pronóstico.
- Patentabilidad “convencional” para reactivos y herramientas para llevar a cabo estos métodos.

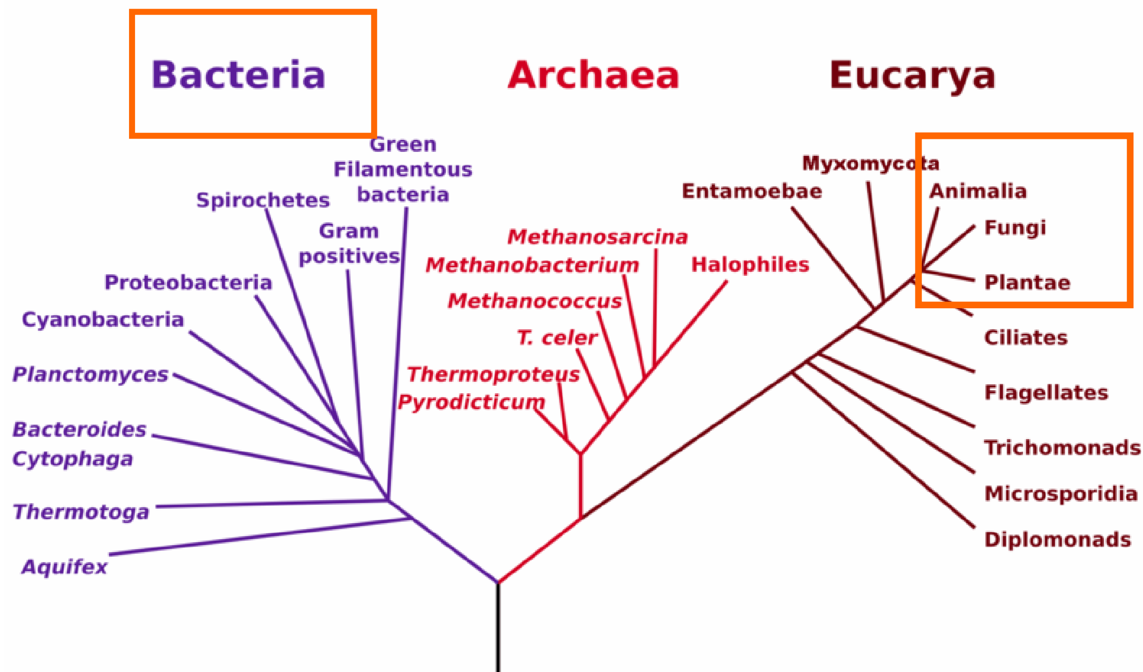
- Aparición de nuevas invenciones basadas en el uso de un biomarcador para determinar la respuesta a un fármaco / combinación terapia-marcador → de momento no causan problemas de patentabilidad.

- Problemática principal está en la explotación de estas invenciones / política de licencias.

- Caso G1/07 pendiente: method excluded from patent protection as a "method for treatment of the human or animal body by surgery" Art. 52(4)

Organismos vivos

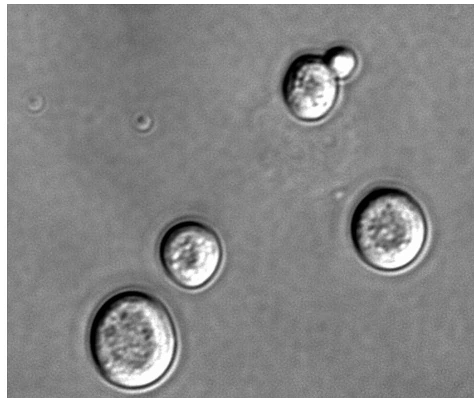


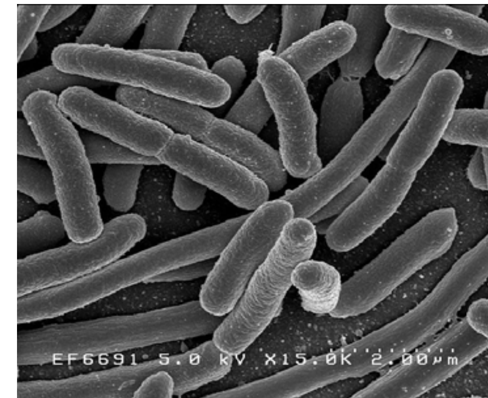


“Microorganismos”

Invenciones relacionadas con microorganismos:

- Uso de microorganismo para producir un producto químico (metabolito) nuevo o producir mejor un metabolito conocido.
- “Microorganismo” como carrier y hospedador.





Penicillium roqueforti *Saccharomyces cerevisiae* *Escherichia*
coli (fungi)
(proteobacteria)

“Microorganismos”

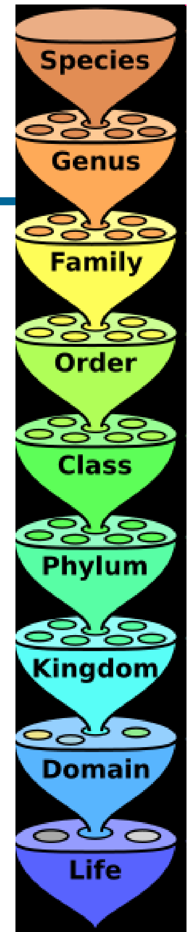
Aunque quedan excluidos de la patentabilidad los procedimientos esencialmente biológicos de obtención de vegetales o de animales que consistan íntegramente en fenómenos naturales como el cruce o la selección,

la exclusión no alcanza a los procedimientos microbiológicos u otros procedimientos técnicos ni a los productos obtenidos mediante los mismos (Art. 5.3 LP).

¿Por qué las comillas? Guidelines EPO 4.7.1.

microbiological process (see IV, 2.3.1). The term "microorganism" includes bacteria and other generally unicellular organisms with dimensions beneath the limits of vision which can be propagated and manipulated in a laboratory (see T 356/93, OJ 8/1995, 545), including plasmids and viruses and unicellular fungi (including yeasts), algae, protozoa and, moreover, human, animal and plant cells.

“Microorganismos”



Podrá constituir materia patentable:

- microorganismo *per se*
- sustancia producida *per se* si es nueva
- procedimiento para obtener la sustancia a partir del microorganismo

El microorganismo reivindicado *per se* tiene que ser nuevo e inventivo. Debe demostrarse un efecto de este microorganismo. Aplicabilidad industrial

Puede ser aislado de la naturaleza (p.ej.por *screening* de heces de bebés para encontrar microorganismos probióticos) u obtenido en el laboratorio por mutación inducida, ingeniería genética, etc. (Art. 4.2 LP)

Suficiencia de la descripción. Depósito del microorganismo bajo el Tratado de Budapest (Art. 25.2 LP).

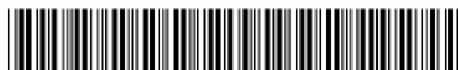
Microorganismo *per se*

En Estados Unidos, a pesar del precedente de la patente de Pasteur sobre levaduras, no se aceptaron reivindicaciones sobre organismos vivos hasta el caso Chakrabarty (Tribunal Supremo, 1980).

Diamond vs Chakrabarty (US 4259444): La invención trata de microorganismos del género *Pseudomonas* que contienen plásmidos que permiten la degradación de hidrocarburos.

En Europa ya se permitían desde antes sobre fermentaciones con microorganismos para obtener sustancias.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets



(11) **EP 0 794 707 B1**

(12) **FASCICULE DE BREVET EUROPEEN**

(45) Date de publication et mention de la délivrance du brevet:
11.11.1998 Bulletin 1998/46

(21) Numéro de dépôt: **95943553.8**

(22) Date de dépôt: **29.12.1995**

(51) Int. Cl.[6]: **A23C 9/123**, C12R 1/225, C12R 1/46

(86) Numéro de dépôt international:
PCT/FR95/01761

(87) Numéro de publication internationale:
WO 96/20607 (11.07.1996 Gazette 1996/31)

(54) **FERMENT LACTIQUE, ET SON UTILISATION POUR LA PREPARATION DE PRODUITS ANTI-DIARRHEIQUES**

MILCHSÄUREFERMENT, UND IHRE VERWENDUNG ZUR HERSTELLUNG VON ANTIDIARRHÖEPRODRUKTEN

MILK STARTER CULTURE AND USE THEREOF FOR PREPARING ANTIDIARRHOEAL PRODUCTS

(84) Etats contractants désignés:
AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE

(30) Priorité: **02.01.1995 FR 9500003**
13.10.1995 FR 9512032

(43) Date de publication de la demande:
17.09.1997 Bulletin 1997/38

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(56) Documents cités:
FR-A- 2 073 279
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FR-A- 2 335 157
GB-A- 1 110 977
GB-A- 2 228 494

- **ANNALS OF AGRICULTURAL SCIENCE., vol. 31, no. 2, CAIRO, EGYPT., pages 1279-1289, XP000568695 M.A. EL-NAWAWY ET AL.: "Production of new type of yoghurt."**

EP validada en España:
ES2126962 T3

Centre de Patents de la UB

Claims

1. A lactic ferment, characterised in that it is a ferment of yogurt constituted by a mixture of the three lactic bacteria *Streptococcus thermophilus* DN-001 147, *Streptococcus thermophilus* DN-001 339 and *Lactobacillus bulgaricus* DN-100 182.

2. A lactic ferment, characterised in that it comprises a yogurt ferment according to claim 1 and further comprises one or a plurality of other species of lactic bacteria.

3. A lactic ferment according to claim 2, characterised in that it comprises a mixture of the lactic bacteria *Streptococcus thermophilus* DN-001 147, *Streptococcus thermophilus* DN-001 339, *Lactobacillus bulgaricus* DN-100 182 and *Lactobacillus paracasei subsp. paracasei* DN-114 001.

4. A method of preparing a fermented milk product and which is characterised in that it comprises the use of a lactic ferment according to any one of claims 1 to 3.

5. A preparation of fermented milk characterised in that it is capable of being obtained by the method according to claim 4.

6. A lactic ferment according to any one of claims 1 to 3 for use as an anti-diarrheic.

7. A preparation of fermented milk according to claim 5 for use as an anti-diarrheic.

8. A strain of lactic bacteria selected from the group consisting of *Streptococcus thermophilus* DN-001 147, *Streptococcus thermophilus* DN-001 339, *Lactobacillus bulgaricus* DN-100 182 and *Lactobacillus paracasei subsp. paracasei* DN-114 001.

L. Casei DN-114 001

Otras patentes y solicitudes

EP1178730 B1- Use of lactic acid bacteria in the preparation of fermented milks for the treatment of depressed immunity levels.

Claims

1. Use of *Lactobacillus casei* in the preparation of a fermented milk for the prevention and treatment of temporarily depressed immune levels associated with a decrease in blood NK cells in individuals subjected to physiological stress.

2. Use of claim 1, wherein said physiological stress results from intense physical effort.

3. Use of any of claims 1 or 2, wherein said fermented milk comprises more than 1×10^5 c.f.u. per millilitre of *Lactobacillus casei.*

4. Use of claim 3, wherein said fermented milk comprises more than 1×10^7 c.f.u. per millilitre of *Lactobacillus casei.*

5. Use of any of claims 1 to 4, wherein said *Lactobacillus casei* is strain CNCM I-1518.

L. Casei DN-114 001

6. Use of any of claims 1 to 5, wherein said fermented milk further comprises at least another lactic acid bacterium selected among *Lactobacillus helveticus, Lactobacillus delbrueckii* subspecies *bulgaricus, Lactobacillus paracasei, Lactobacillus acidophilus, Lactococcus lactis, Streptococcus thermophilus, Bifidobacterium longum* and/or *Bifidobacterium breve.*

Otras patentes y solicitudes

EP1268808 B1 - Mutants of *Lactobacillus casei* defective in carbon catabolism regulation and their use in improving aroma and texture of fermented dairy foods

1. Use of a mutant of *L. casei* having at least a mutation in the ptsH gene, wherein said mutation impairs the regulation of a carbon catabolite repression (CCR) mechanism involving the PTS protein HPr, for the preparation of a food product.

2. The use of claim 1, wherein said mutant has at least a mutation selected in the group consisting of:

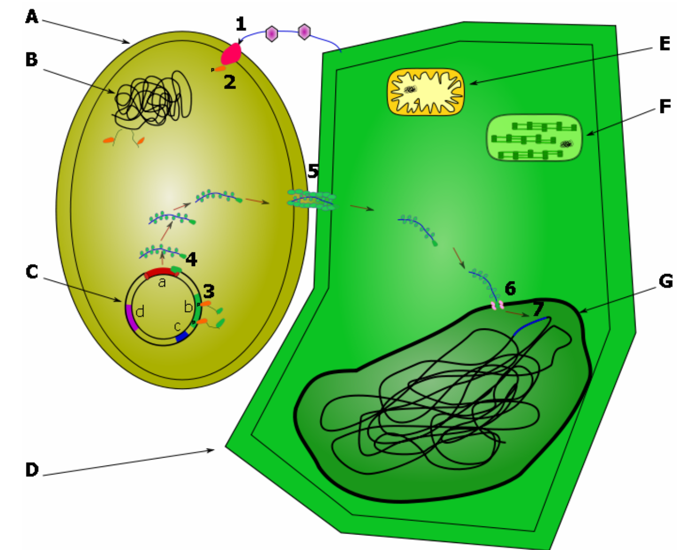
- any mutation in the ptsH gene impairing the ability of HPr to be phosphorylated at His-15, or to phosphorylate EIIA; and
- any mutation in the ptsH gene, impairing the ability of HPr to be phosphorylated at Ser-46.

“Microorganismos”

Otro tipo de invención: “Microorganismo” como carrier y hospedador.

Ejemplos:

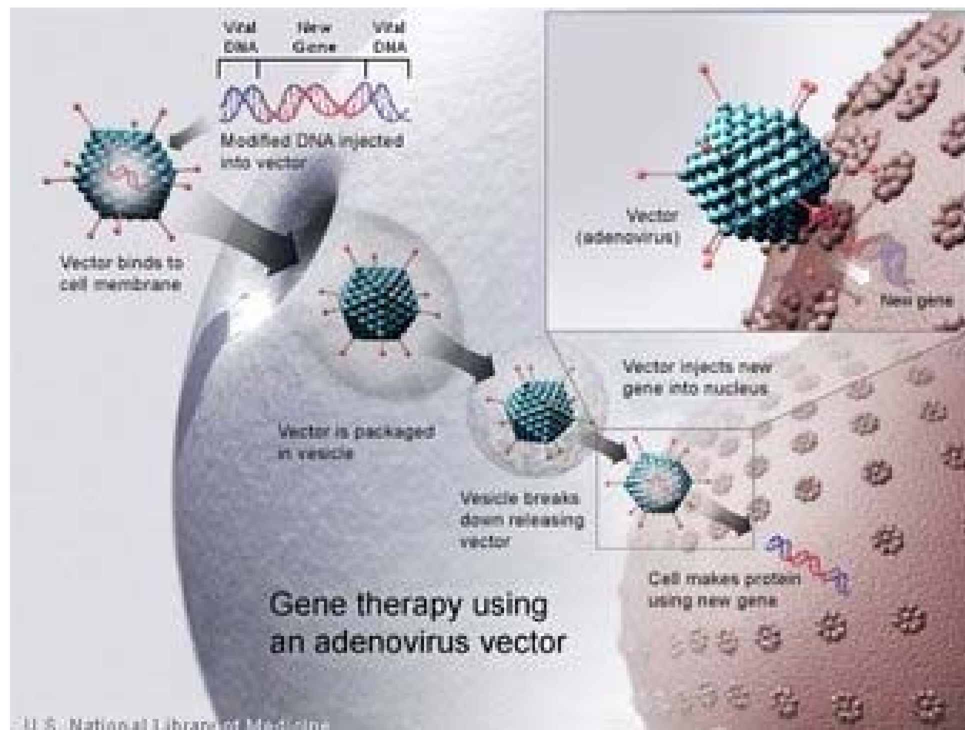
- *Agrobacterium tumefaciens* para infectar células de planta e insertar un gen de interés a la planta
- Nueva cepa de *E. coli* para producir una proteína recombinante
- Vector viral para terapia génica
- Vacunas

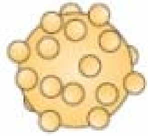


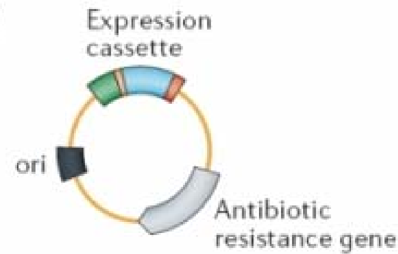
Vector viral para terapia génica

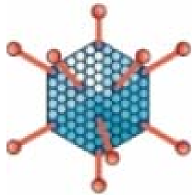
Inserción de genes en las células de los tejidos de un individuo para tratar una enfermedad. Tiene como objetivo suplir un gen defectuoso mutado por uno funcional.

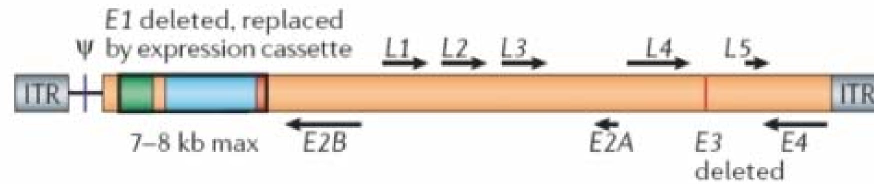
Vectores: adenovirus, retrovirus, vectores no virales (liposomas, etc)

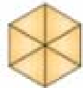


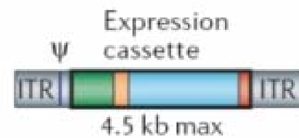


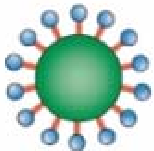












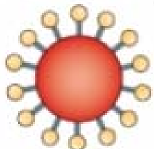


Figure 1 : Gene-transfer vectors that are used to treat hereditary disorders.

Part a depicts a prototypical gene expression cassette, while parts b–f depict five classes of gene-transfer vectors used in the treatment of hereditary disorders.

Copyright 2006 Nature Publishing Group, O'Connor, T. P., & Crystal, R. G., Genetic medicines: Treatment strategies for hereditary disorders, Nature Reviews Genetics 7, 261–276

Vacunas

Son composiciones que provocan la estimulación del sistema inmune de un organismo. Ejemplos de estas composiciones son antígenos, DNA que codifica un antígeno, células muertas y células vivas atenuadas.

Ej. de reivindicaciones:

- A bacterium Z cell that lacks a viable gene encoding a vilurence factor A.

- A live bacterial cell vector that
    (a) infects a human and
    (b) is stably transformed with, and expresses, a heterologous DNA encoding antigen X.

Animales y plantas

Aplicaciones de la biotecnología en animales y plantas:

- modelos para investigar (knock-out, transgénicos, sistemas vegetales modelo –*Arabidopsis thaliana*-)

- productores de sustancias terapéuticas

- desarrollo de plantas mejoradas para p.ej. tener mayor resistencia a las enfermedades, una mejor adaptación a condiciones extremas de climatología, o a un mayor contenido nutricional.

Plants are not only for food

Challenges of agriculture:

- Food security
- Decrease environmental footprint of industry (chemical)
- Plants for fuel production (biomass)
- Increase crop productivity:
  - CO_2 assimilation eficiency
  - pest & disease resistance
  - sun use efficiency
  - nutrient use efficiency
  - shelf life

Plants are not only for food

Solution:

Biotech: GM (genetically modified) plants and MAS (marker assisted selection)

No adverse effects reported with the approved GM crops for health

Barriers:

- delays in commercialization and high costs due to overregulation and unnecessary testing.

    Consequence: only big companies can do it. No SMEs.

- public against.

    Solution: educating people with science, explaining the consequences of not using GM plants

Marc Van Montagu. Chairman of Institute for Plant Biotechnology for Developing Countries (IPBO), Gent University, Belgium.
Symbiosis 15.09.09. El padre de la biotecnología verde.

Animales y plantas, excluido de patentabilidad:

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.

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.

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, Art. 53(a-c) EPC

Animales transgénicos no humanos, el oncomouse de Harvard

1ª solicitud de patente europea sobre un animal

EP169672, Universidad de Harvard

ratón genéticamente modificado (introducción de un oncogen) para tener una predisposición a desarrollar cáncer para utilizarlo en ensayos.

1. A method for producing a transgenic non-human mammalian animal having an increased probability of developing neoplasms, said method comprising chromosomally incorporating an activated oncogene sequence into the genome of a non-human mammalian animal.

19. A transgenic non-human mammalian animal whose germ cells and somatic cells contain an activated oncogene sequence as a result of chromosomal incorporation into the animal genome, or into the genome of an ancestor of said animal, said oncogene optionally being further defined according to any one of claims 3 to 10.

20. An animal as claimed in claim 19 which is a rodent.

el oncomouse de Harvard

Priority date: 1984	
Refusal by ED: 1989	Based on art. 53 and 83 EPC: animals not patentable and method of generating transgenics not sufficiently disclosed for the whole kingdom of animals. No morality issues raised
Decision T19/90: 1990	Balancing test developed between suffering of animals and benefit for human to assess morality. Applications complies with art 53 and 83 because exceptions to patentability are generally applied narrowly and transgenic technology was considered generally aplicable
Grant: 1992	Patent granted to transgenic non-human animals
Oppositions: 1995-2001	Patent limited to rodents (art 53). 17 opponents
Appeals: 2003	
Final decision (T0315/03): 2004	Patent limited to mice: rodents considered too broad with the balancing test: it requires 3 matters to be evaluated: whether animal suffering is likely, whether likely substantial medical benefit has been established and whether the suffering and the medical benefit both exist in relation to the use of the same animals

Plantas

No son patentables 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.

→ G1/98 confirma lo anterior. Pueden patentarse variedades vegetales si no están específicamente reivindicadas.

NO: Rose cultivar cv3145 characterised by resistance to glyphosphate

YES: Rose plant comprising a gene conferring glyphosphate resistance

Protección para variedades vegetales: Obtención de variedades vegetales

Transgenic plants and morality

T356/93. Plant Genetic Systems. EP242236

Opposition and Appeal (Greenpeace)

Herbicide resistant plant:

The invention relates to a DNA fragment containing a determined gene (acetyl-transferase), the expression of which inhibits the antibiotic and herbicidal effects of Bialaphos (glutamine-synthetase inhibitors – herbicide-). It also relates to recombinant vectors, containing such DNA fragment, which enable this protective gene to be introduced and expressed into cells and plant cells.

Arguments for appellant:

- Public opinion was against patenting of transgenic plants
- treated plants could become weeds
- herbicide resistance could spread to other plants
- Ecosystems could be damaged

Transgenic plants and morality

(T356/93) Conclusions:

Patents on transgenic plants cannot be rejected for morality reasons since:

(a) genetic engineering methods *per se* only provide a more powerful tool than traditional breeding methods, which are clearly not contrary to morality

(b) if a clear evidence is not presented at the time of granting the application that the environment is severely damaged (e.g. spreading of a herbicide resistance)

Procedimientos para obtener plantas

A partir de que son patentables “invenciones que tengan por objeto vegetales…”, la pregunta es:

¿Qué métodos para obtenerlas son patentables?

Exclusiones (Art 5.3 LP):

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. → “transgénico”, OK

Procedimientos esencialmente biológicos

Pero, qué se entiende por “procedimiento esencialmente biológico”?

Pueden considerarse como los procedimientos tradicionalmente realizados por agricultores, pero no existe una definición clara…

A process for the production of plants or animals is essentially biological if it consists entirely of natural phenomena such as crossing or selection. To take some examples, a method of crossing, inter-breeding, or selectively breeding, say, horses involving merely selecting for breeding and bringing together those animals having certain characteristics would be essentially biological and therefore unpatentable. On the other hand, a process of treating a plant or animal to improve its properties or yield or to promote or suppress its growth e.g. a method of pruning a tree, would not be essentially biological since although a biological process is involved the essence of the invention is technical; the same could apply to a method of treating a plant characterised by the application of a growth-stimulating substance or radiation. The treatment of soil by technical means to suppress or promote the growth of plants is also not excluded from patentability (see also IV, 4.8.1).

Guidelines EPO

Procedimientos esencialmente biológicos

…y el cruze y la selección no necesariamente son fenómenos naturales:

EP044723 (T320/87)

A process for […] producing hybrid seeds, comprising:

(a) selecting parent plants and selecting a second parent plant;

(b) crossing parent plants to obtain phenotypically uniform hybrids;

(c) cloning said first parent plant to produce a first cloned parental line;

(d) crossing cloned parental line with second parent plant to obtain […] phenotipycally uniform hybrids […], and

(e) repeating steps (c) and (d) as required to obtain hybrid seed that yields phenotipycally uniform hybrid plants.

Procedimientos esencialmente biológicos

(T320/87)

"Essentially biological" has to be judged on the basis of the essence of the invention taking into account the totality of human intervention and its impact on the result achieved".

"Human intervention" may only mean that the process is not a "purely biological" process, without constributing anything beyond a trivial level.

The question is: how much intervention is needed? (mutagenesis, induction by chemical compounds, radiation?)

How much intervention is needed?

EP572412

Method of producing corn grain with enhanced quality grain traits, comprising randomly interplanting two specified types of corn seed, permitting pollination and harvesting the corn grain.

Revoked in opposition (Art. 53 EPC; essentially biological process)

Appeal withdrawn

Questions to be answered:

Is interplanting a sufficient intervention?

Is a corn grain” a plant?

How much intervention is needed? The broccoli case

EP 1069819, Plant Bioscience Limited

Method for the production of Brassica oleracea, comprising steps of crossing and selection, wherein molecular markers used to identified desired hybrids.

Se refiere a métodos para producir nuevas plantas de *Brassica,* en particular brócoli, con niveles elevados de glucosinolatos anticarcinogénicos. El método reivindicado implica la reproducción asistida por marcadores moleculares selectivos.

Opposition: not an essentially biological process of producing plants

Appeal pending (T83/05). Questions referred to Enlarged Board of Appeal (**G2/07**)

Lo que se plantea es si el procedimiento que se reivindica es esencialmente biológico, aunque comprenda pasos de intervención del hombre.

¿Qué grado y naturaleza de la intervención técnica humana se requiere para que el procedimiento se escape de ser esencialmente biológico y por lo tanto, se considere patentable?

How much intervention is needed? The wrinkled tomato case

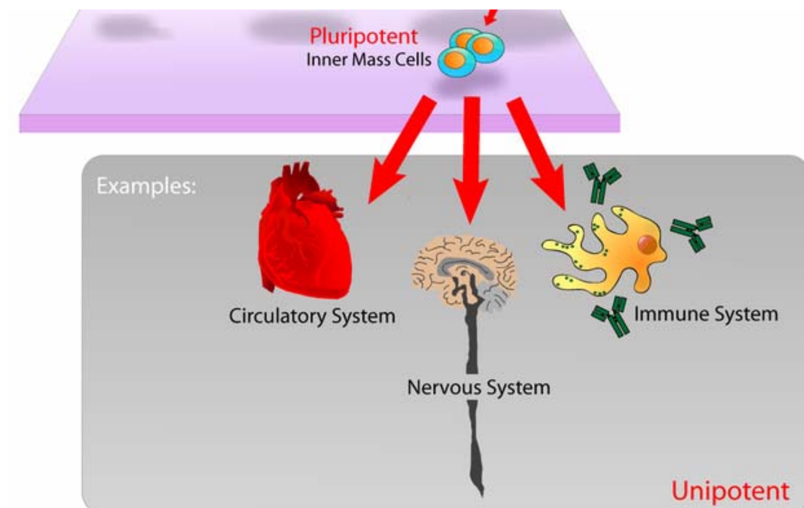
Similar referral to the Enlarged Board of Appeal pending: **G1/08**
The so-called “wrinkled tomato case” (tomato with reduced water content)
It involves also a non-microbiological process for the production of plants.

Cases G 2/07 and G 1/08 will be considered in consolidated proceedings.

Stem cells (“sc”)

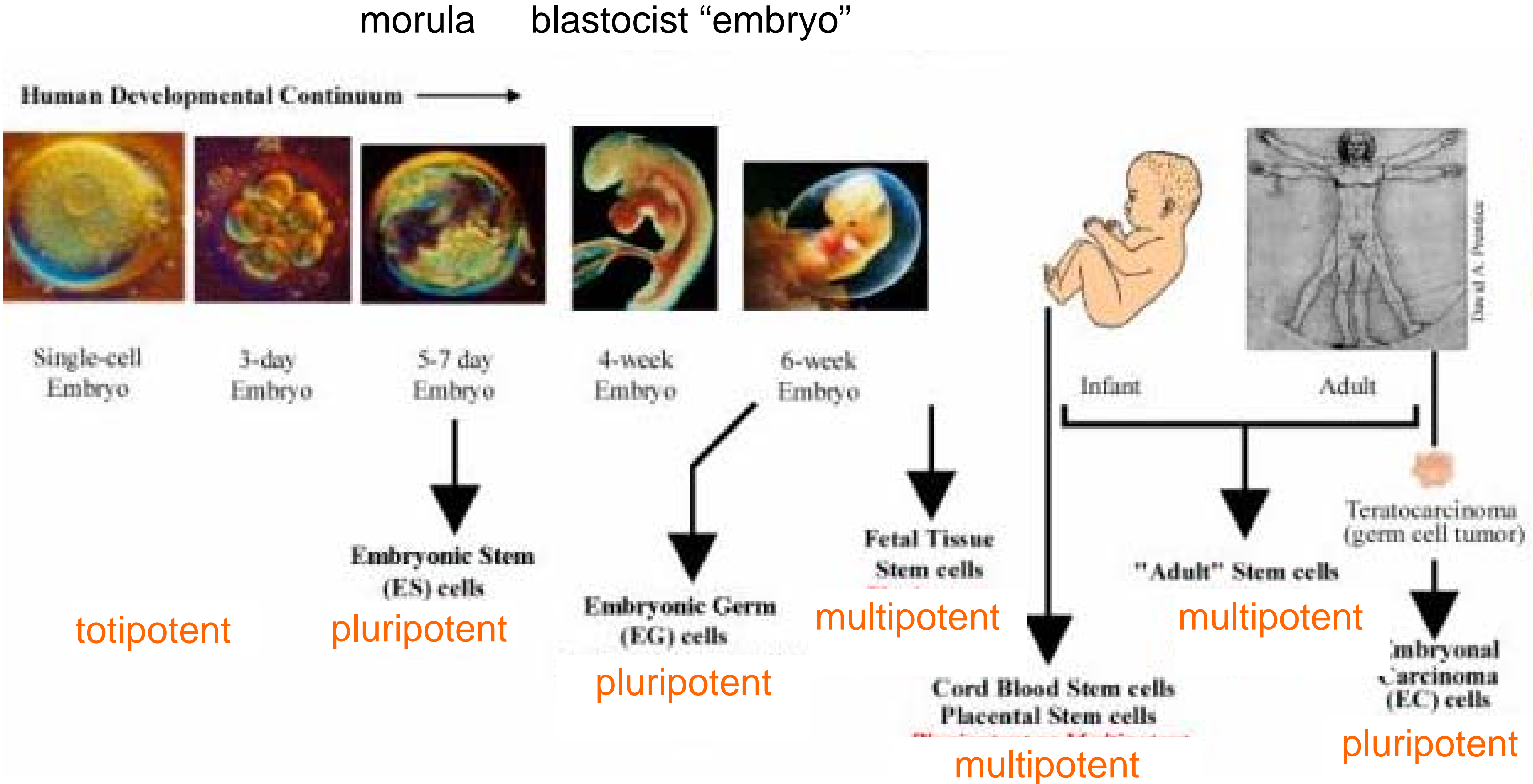
Uses of stem cells:

- transplantation and tissue repair
- study of specific disease, modifying the cells – “disease in a dish”
- pharmacology, toxicology studies
- drug discovery
- regenerative medicine: inducing the body to innate self-healing processes, using own adult stem cells niches



Stem cells

morula blastocist “embryo”



Stem cells

No es patentable (Art. 5.4.LP):

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.

→ Por lo tanto, las sc general y otras células (no sc), en tanto que son elementos aislados del cuerpo humano, pueden constituir una invención patentable.

→ exclusión de patentabilidad de las sc totipotentes y las células germinales porque son "un estadio de desarrollo del cuerpo humano"

Stem cells

In addition, the human body, at the various stages of its formation and development, and the simple discovery of one of its elements, including the sequence or partial sequence of a gene, cannot constitute patentable inventions (see, however, IV, 3.2). Such stages in the formation or development of the human body include germ cells (EU Dir. 98/44/EC, rec. 16).

Also excluded from patentability under Art. 53(a) are processes to produce chimeras from germ cells or totipotent cells of humans and animals (EU Dir. 98/44/EC, rec. 38).

Guidelines EPO

Stem cells

Si se profundiza en el tipo de sc, entran en juego otros Art. relacionados con las excepciones por motivos de moralidad (Art. 5.1 LP y 53a EPC):

No son patentables los procedimientos de clonación de seres humanos, considerando por procedimiento de clonación de seres humanos, cualquier técnica, incluida la de división del embrión, diseñada para crear un ser humano.

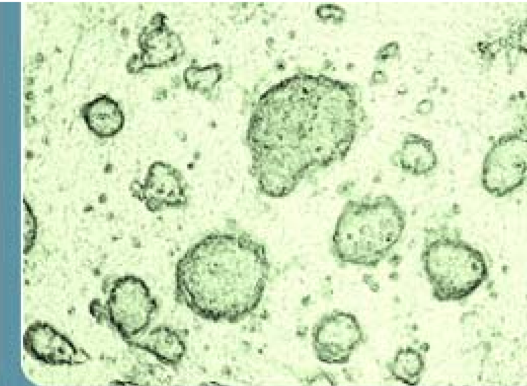
No son patentables las utilizaciones de embriones humanos con fines industriales o comerciales. Esta prohibición no afecta a las invenciones técnicas que tengan un objetivo terapéutico o de diagnóstico que se aplican al embrión y que le son útiles.

Stem cells

→patentables sc de embriones no humanos, y las sc humanas de origen no embrionario (fetal o adulto). No plantean cuestiones éticas pues se obtienen por clonación de las aisladas.

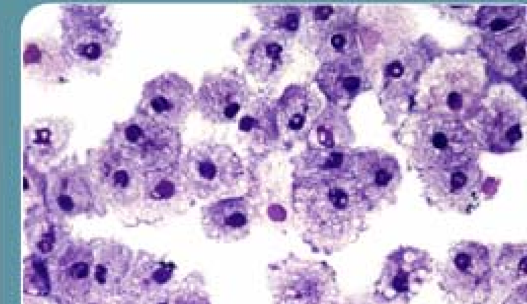
Non-patentable subject-matter

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



Depósito para la suficiencia de la descripción.

qué significa "utilización de embriones humanos"

Possible interpretations:

- Narrow interpretation: Only uses of embryos *per se* prohibited.

→ Embryo-derived products, such as embryonic stem cells and stem cell lines, as well as processes and uses thereof would be patentable.

- Broad interpretation: Embryo-derived products, such as embryonic stem cells, as well as processes and uses thereof, preclude the use of human embryos, without which they would not have been obtained.

“no wood without trees”.

→ Embryonic stem cells, cell lines, and processes and uses thereof would not be patentable.

La patente de Edinburgo EP695351

Se refiere a un método para separar sc de otras células con varios pasos de cultivo y utilizando marcadores selectivos. El tipo de sc era muy amplio – reivindicación 1 referida a mammalian stem cells (que incluye sc embrionarias humanas).

14 oponentes, manteniendo que la patente violaba el Art. 53(a) del EPC (orden público o a la moralidad) y Art. 83 del EPC (sólo suficiencia de la descripción para células de ratón).

1ª vez que se interpreta Rule 28 – use of human embryos…- por la división de oposición.

La patente de Edinburgo EP695351

Decision of Opposition (T1079/03):

- "Use of embryos" in Rule 28c EPC is to be interpreted broadly to avoid redundancy with Rule 29(1) EPC which prohibits patenting of the human body at any stage of its formation.

- Under a broad interpretation, methods for producing/isolating human embryonic stem cells are unpatentable.

La patente fue restringida a "animal stem cell other than human embryonic stem cells"

El caso WARF

Wisconsin Alumni Research Foundation's (EP770125A1)

Claim 1: "A cell culture comprising primate embryonic stem cells…"
(including human)

Filed 1995

2004: refusal by the examining division based on Rule 23dc EPC and Art. 53a EPC (destruction of human embryos for commercial or industrial purposes)

- description provides no source of starting material other than preimplantation embryos
- it is irrelevant that the claimed subject matter related to cell cultures and not to a method of production of said cultures.
- the generated cell cultures do not serve any therapeutic or diagnostic purpose useful to the embryo.

El caso WARF

2004: Appeal filed by the Applicant. Oral proceedings (T1374/04)

Technical Board of Appeals referred case to EBoA (**G2/06**).

Decision (November 2008):

- No es posible conceder una patente para una invención que conlleva exclusivamente y necesariamente el uso y destrucción de embriones humanos, sin importar si estos pasos están reivindicados o no.

- Es irrelevante que después de la fecha de solicitud los mismos productos podían obtenerse sin necesariamente pasar por la destrucción de embriones.

- La decisión no aborda la cuestión directa de si las células madre embrionarias humanas son por si mismas patentables

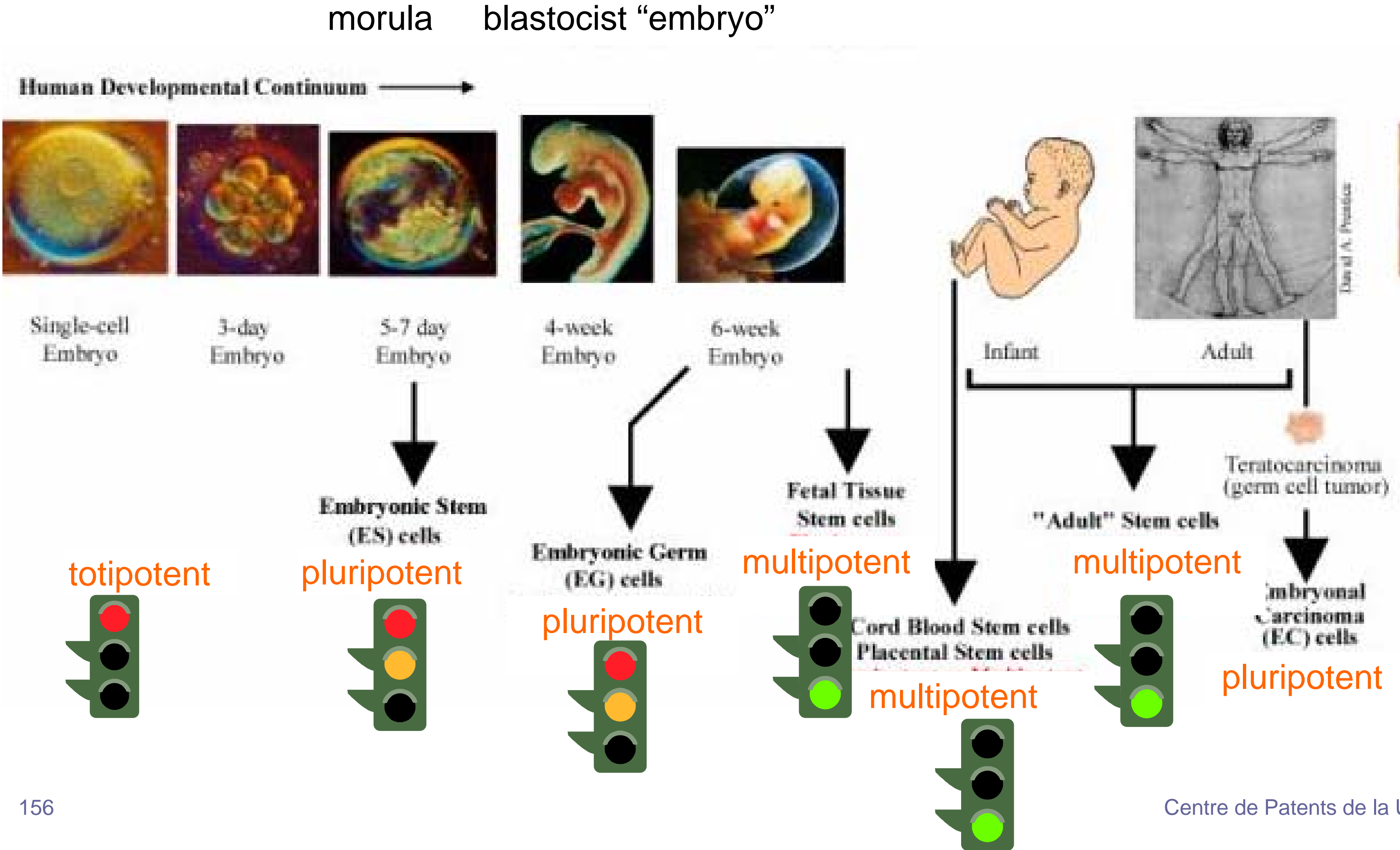
El caso WARF

Por lo tanto células madre embrionarias humanas no obtenidas de la destrucción de embriones (por otros métodos) podrían ser patentables…¿?

Algunos dicen que “given that stem-cell science has moved on considerably — for example, with the generation of induced pluripotent stem cells — the impact of this decision on future stem-cell patents is unlikely to be significant.

También se está cuestionando la definición de “embrión” y el “cuerpo humano en sus diferentes estadios de desarrollo”.

Stem cells (human)



Cuestiones abiertas

Are human embryonic stem cell cultures patentable (if not prepared by destroying human embryos)? (after G2/06)

What is meant by “essentially biological processes for the production of plants”? (open G2/07 and G1/08)

Trends in patents for human genes:

- less speculative, narrower claims, plausible inventions
- number of DNA patent filings declines
- Interpretation of claim scope?

…y la biotecnología no para nunca: biología sintética, nanotecnología, etc

http://www.youtube.com/watch?v=dmTnaN0dykw

Gracias por vuestra atención !!