

Unravelling the patenting of biotechnology inventions -

The European Perspective

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Patenting Biotech in EP

- *Nucleic Acids: DNA, RNA, SNP, EST*
- *Polypeptides (Proteins): Epitopes, Antigens, Peptides*
- *(Medical) Uses: 1st medical use, 2nd and further medical uses*
- *Microorganisms: bacteria, viruses, cells*
- *Vectors: plasmids, viruses, transposons,...*

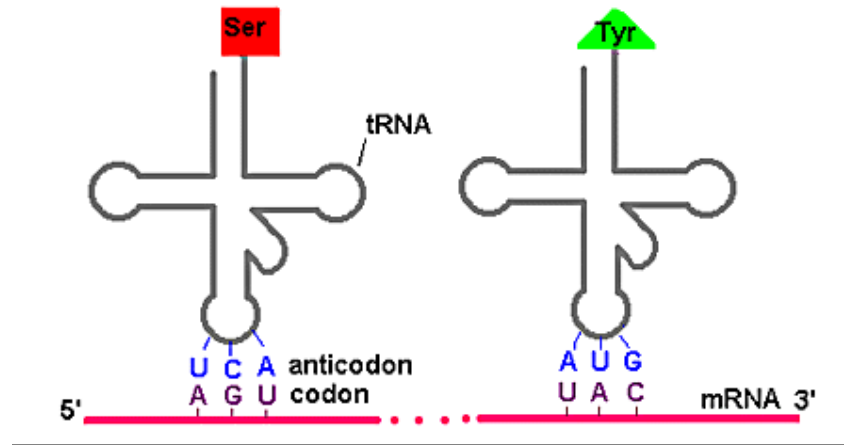


Patenting Biotech in EP

- *Nucleic Acids: molecules containing A, G, C and T residues (DNA); molecules containing A, G, C and U residues (RNA)*
- *DNA is transcribed into RNA*
- *RNA is translated into **Proteins***
- ***Proteins** are molecules containing up to 20 different amino acid residues: **A (ala), C (cys), D (asp), E (glu), F (phe), G (gly), H (his), I (ile), K (lys), L (leu), M (met), N (asn), P (pro), Q (gln), R (arg), S (ser), T (thr), V (val), W (trp)***
- *3 nucleic acid residues code for one **amino acid residue**:*



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2nd base in codon

	U	C	A	G	
U	Phe Phe Leu Leu	Ser Ser Ser Ser	Tyr Tyr STOP STOP	Cys Cys STOP Trp	U C A G
C	Leu Leu Leu Leu	Pro Pro Pro Pro	His His Gln Gln	Arg Arg Arg Arg	U C A G
A	Ile Ile Ile Met	Thr Thr Thr Thr	Asn Asn Lys Lys	Ser Ser Arg Arg	U C A G
G	Val Val Val Val	Ala Ala Ala Ala	Asp Asp Glu Glu	Gly Gly Gly Gly	U C A G

3rd base in codon

The Genetic Code



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- *Nucleic Acid: Example: Molecules with 33 residues (bases): 4^{33} possibilities = 7.4×10^{19}*

1 TTTATTTGTCCTATTTAACCTCGTGCTCATGCT

2 TTCATCTGCCCCATCTAGCCCCGCGCCACGCC

- *Grouped by three residues:*

1 TTT ATT TGT CCT ATT TAA CCT CGT GCT CAT GCT

2 TTC ATC TGC CCC ATC TAG CCC AGC GCC CAC GCC

- *21 of 33 residues identical; 12 different:
63 % identity*



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➤ 1 TTT ATT TGT CCT ATT TAA CCT CGT GCT CAT GCT

➤ *encodes for a polypeptide with 11 amino acid residues:*

1 TTT ATT TGT CCT ATT TAA CCT CGT GCT CAT GCT

phe ile cys pro ile stp pro arg ala his ala

F I C P I * P R A H A

2 TTC ATC TGC CCC ATC TAG CCC AGC GCC CAC GCC

1 TTT ATT TGT CCT ATT TAA CCT CGT GCT CAT GCT

C C C C C AG C C C C C

A A GA A A A A A A A

G G G G G G G G G

A C

A G



Patenting Biotech in EP

1 TTT ATT TGT CCT ATT TAA CCT CGT GCT CAT GCT
 phe ile cys pro ile stp pro arg ala his ala
F I C P I * P R A H A

1 TTT ATT TGT CCT ATT TAA CCT CGT GCT CAT GCT
 C C C C C AG C C C C C
 A A A GA A A A A A
 G G G G G
 A C
 A G

2 x 3 x 2 x 4 x 3 x 3 x 4 x 6 x 4 x 2 x 4 =

➤ 331776 possibilities to encode the
FICPI*PRAHA peptide in DNA

➤ CLAIMS ?



Patenting Biotech in EP

- *331776 possibilities to encode the **FICPI PRAHA** peptide in DNA*
- *CLAIMS:*
 - *List all 33-mers in claim 1*
 - *Chemical Formula: „ X_1 - X_2 -...- X_{33} , wherein X_1 is T, X_2 is T, X_3 is T or C, ... X_{33} is A, C, T or G.“*
 - *Functional Terms I: „Nucleic acid molecule encoding **FICPI*PRAHA** Peptide.“*
 - *Functional Terms II: „DNA molecule encoding our meeting.“*



Patenting Biotech in EP

- *331776 possibilities to encode the **FICPI PRAHA** peptide in DNA*
- *CLAIMS:*
 - *% identity: „Nucleic acid molecule with at least 63 % identity to Seq.ID.no 1“*
 - *„DNA with at least 63 % identity to Seq.ID.no 1 and encoding our meeting“*
 - *„DNA with at least 63 % identity to Seq.ID.no 1 and encoding **FICPI*PRAHA**“*



Patenting Biotech in EP

1 TTT ATT TGT CCT ATT TAA CCT CGT GCT CAT GCT

F I C P I * P R A H A

2 TTC ATC TGC CCC ATC TAG CCC AGC GCC CAC GCC

63 % identity; identical function

3 GCT ATC CCT CCT ATT TAA CCT CGT GCT CAT GCT

85 % identity; no identical function

3 GCT ATC CCT CCT ATT TAA CCT CGT GCT CAT GCT

A I P P I * P R A H A

➤ *The 17th AIPPI Congress*

➤ *6th to 11th June*

➤ *1938*



Patenting Biotech in EP

➤ *The Legal Basis (I)*

➤ *European Patent Convention (EPC)*

➤ *Art. 52(1), 52(2)a, 52(4), 53, 54, 56, 57, 83, (84)*

➤ *Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the Legal Protection of Biotechnological Inventions („Biotech-Directive“)*

➤ *Judgement of the European Court of Justice (ECJ) in Case C-377/98*

➤ *Application of the NL (supported by and NO) for annulment the Biotech-Directive*

➤ *Art.27 TRIPs*



Patenting Biotech in EP

➤ *The Legal Basis (II)*

➤ *European Patent Convention (EPC) Implementing Regulations*

➤ *Rules 23b-e, 27a, 28, 28a*

➤ *Guidelines for the Examination before the European Patent Office (EPO)*

➤ *Part C, Chapter II: 4.12, 6*

➤ *Part C, Chapter IV: 2a, 3.3b,
3.4 - 3.6, 4.2 - 4.4., 4.6*



Patenting Biotech in EP

➤ *The Legal Basis*

- *Is the Directive applicable to the EPC ?*
- *What are biotechnological inventions ?*
- *Are biotechnological inventions patentable ?*
- *Are (human) genes patentable or (non-patentable) discoveries?*
- *Are methods for cloning human beings patentable ?*
- *Which other biotechnological inventions are excluded from patentability ?*
- *What are the other issues of the Directive ?*
- *Is the Directive valid ?*

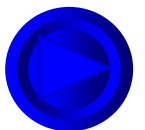
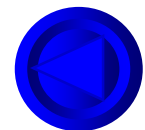


Patenting Biotech in EP

- *Is the Directive applicable to the EPC ?*
- *Rule 23b EPC*

General and definitions

*(1) For **European patent applications** and patents concerning biotechnological inventions, the relevant provisions of the Convention shall be applied and interpreted in accordance with the provisions of this chapter. **Directive 98/44/EC** of 6 July 1998 on the legal protection of biotechnological inventions **shall be used as a supplementary means of interpretation.***



Patenting Biotech in EP

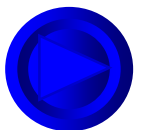
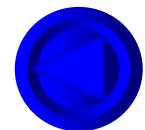
- *What are biotechnological inventions ?*
- *Rule 23b EPC*

General and definitions

(1)

(2) “Biotechnological inventions” are inventions which concern a product consisting of or containing biological material or a process by means of which biological material is produced, processed or used.

(3) “Biological material” means any material containing genetic information and capable of reproducing itself or being reproduced in a biological system. [Directive, Art.3.2]



Patenting Biotech in EP

- *Are biotechnological inventions patentable ?*
- *Directive: Article 3.1*
 - *1. For the purposes of this Directive, inventions which are **new**, which involve an **inventive step** and which are susceptible of **industrial application** shall be patentable*
***even if** they concern a product consisting of or containing **biological material** or a process by means of which biological material is produced, processed or used.*

Art. 52(1), 54, 56, 57 EPC
EPO-Guidelines C-IV, 2a.1



Patenting Biotech in EP

➤ *Are (human) genes patentable or (non-patentable) discoveries ?*

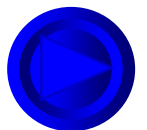
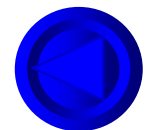
➤ *Directive Article 3.2*

2. Biological material which is isolated from its natural environment or produced by means of a technical process may be the subject of an invention even if it previously occurred in nature.

➤ *EPC Rule 23c Patentable biotechnological inventions:*

Biotechnological inventions shall also be patentable if they concern:

a) biological material which is isolated from its natural environment or produced by means of a technical process even if it previously occurred in nature;



Patenting Biotech in EP

➤ *Are (human) genes patentable or (non-patentable) discoveries ?*

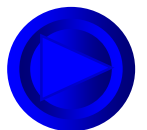
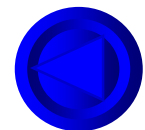
➤ *Directive Article 5*

1. 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.

2. An element isolated from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene, may constitute a patentable invention, even if the structure of that element is identical to that of a natural element.

3. The industrial application of a sequence or a partial sequence of a gene must be disclosed in the patent application.

➤ *Rule 23e EPC*



Patenting Biotech in EP

➤ *Are methods for cloning human beings patentable ?*

➤ *Art. 53a EPC*

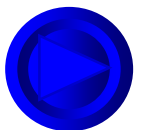
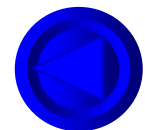
European patents shall not be granted in respect of:

(a) inventions the [publication or] exploitation of which would be contrary to “ordre public” or morality, provided that the exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation in some or all of the Contracting States;

➤ *Directive Article 6*

1. Inventions shall be considered unpatentable where their commercial exploitation would be contrary to ordre public or morality; however, exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation.

*2. On the basis of paragraph 1, the following, in particular, shall be considered unpatentable: (a) processes for **cloning human beings**;*



Patenting Biotech in EP

➤ *Which other biotechnological inventions are excluded from patentability ?*

➤ *Directive Article 6*

1. Inventions shall be considered unpatentable where their commercial exploitation would be contrary to ordre public or morality; however, exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation.

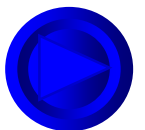
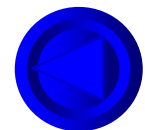
2. On the basis of paragraph 1, the following, in particular, shall be considered unpatentable:

*(a) processes for **cloning** human beings;*

*(b) processes for **modifying the germ line** genetic identity of human beings;*

*(c) **uses of human embryos** for industrial or commercial purposes;*

*(d) processes for modifying the genetic identity of animals which are likely to cause them **suffering without any substantial medical benefit** to man or animal, and also animals resulting from such processes.*



Patenting Biotech in EP

➤ *Which other biotechnological inventions are excluded from patentability ?*

➤ *Article 53b EPC*

European patents shall not be granted in respect of: (a) ...

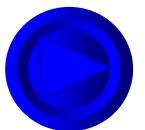
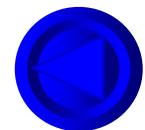
(b) plant or animal varieties or essentially biological processes for the production of plants or animals; this provision does not apply to microbiological processes or the products thereof.

➤ *Directive Article 4 (Rule 23c EPC)*

1. The following shall not be patentable: (a) plant and animal varieties; (b) essentially biological processes for the production of plants or animals.

*2. Inventions which concern plants or animals **shall be patentable** if the **technical feasibility** of the invention is **not confined to a particular plant or animal variety**.*

3. Paragraph 1(b) shall be without prejudice to the patentability of inventions which concern a microbiological or other technical process or a product obtained by means of such a process.



Patenting Biotech in EP

- *What are other issues of the Directive ?*
- *Scope of Protection*
 - *extends to any biological material derived, as long as it possesses the same (inventive) characteristics*
 - *Farmer's privilege (for propagation or multiplication by the farmer on his own farm)*
- *Compulsory cross-licensing with plant variety rights*
- *Deposit, access and re-deposit of a biological material*
- *(Informed consent)*



Patenting Biotech in EP

- *Is the Directive valid ?*
- *Yes, ECJ decision C-377 of 9 October 2001*
- *NL filed suit with Six Pleas:*
 - *incorrect legal basis*
 - *breach of the principle of subsidiarity*
 - *breach of the principle of legal certainty*
 - *breach of obligations in international law*
 - *breach of the fundamental right to respect for human dignity*
 - *breach of procedural rules in the adoption of the Commission's proposal.*
- *All pleas rejected*



Patenting Biotech in EP

➤ *The (current) EP Practice*

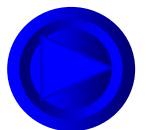
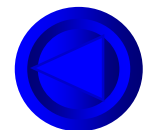
- *The Practice: Patentability*
- *The Practice: Novelty*
- *The Practice: Claiming Priority*
- *The Practice: Inventive Step*
- *The Practice: Industrial Application*
- *The Practice: Enabling Disclosure*
- *The Practice: Clarity of Claims*
- *The Practice: Claim Examples*



Patenting Biotech in EP

➤ *The (current) EP Practice*

- *Running Example: „Novel V28 seven transmembrane receptor“ OD EPO 20. June 2001 (OJ EPO 2002, 293)*
- *EP 0 630 405 B1 (“V28-Receptor”)*
- *Subject Matter: Purified and isolated polynucleotide encoding the amino acid sequence of V28 seven transmembrane receptor set out in SEQ ID NO:28 or a fragment thereof possessing at least one ligand/antiligand binding activity or immunological property specific to said V28 seven transmembrane receptor (sequences given in patent)*
- *All further data: in silicio computer predictions*
- *No “wet biochemistry” in examples*
- *V28 is member of a known protein family*



Patenting Biotech in EP

- *The Practice: Patentability (or pure discovery ?)*
- *“V28-Receptor“: “Although nucleic acid encoding V28 protein exists as a segment of the human genome and thus is a part of nature, the **purified and isolated** nucleic acid having that sequence **does not exist in nature** and thus **cannot be discovered**. The purified and isolated polynucleotide encoding V28 protein is, de facto, **not a discovery**.“*
- *T 292/85 “Polypeptide expression/GENENTECH”; OJ EPA 1989, 275*
- *“Relaxin“ OD decision (OJ EPO 1995, 388)*



Patenting Biotech in EP

- *The Practice: Patentability: plants and animals*
- *T 19/90 “Oncomouse/HARVARD”; OJ EPA 1990, 476*
- *G 1/98 “Transgenic plants/NOVARTIS II; OJ EPO 2000, 111)*
- *A claim to a (genetically modified) plant or animal is not excluded from patentability even if this claim encompasses a plant (animal) variety, provided that the invention is not restricted to a single plant (animal) variety.*



Patenting Biotech in EP

- *The Practice: Novelty*
- *“photographic novelty”*
- *at least one novel structural feature*
- *“even a change in one amino acid can dramatically change the properties of a protein molecule” (T838/97)*
- *recombinant vs. natural*
- *genomic DNA libraries*
- *electronic DNA library ??*
- *oral disclosures (T 400/97)*
- *Entry in database (T 91/98)*



Patenting Biotech in EP

➤ *The Practice: Claiming Priority*

➤ *G2/98:*

*„The requirement for claiming priority of "the same invention", referred to in Article 87(1) EPC, means that priority of a previous application in respect of a claim in a European patent application in accordance with Article 88 EPC is to be acknowledged only if the skilled person can derive the subject-matter of the claim **directly and unambiguously**, using common general knowledge, from the previous application as a whole.”*



Patenting Biotech in EP

- *The Practice: Inventive Step*
- *EPO: problem-solution-approach*
- *closest prior art ?*
- *object to be solved ?*
- *inventive or not ?*
- *V28-receptor: closest prior art (D1): review of 74 proteins of 7 TM-Receptors (also called G-protein coupled receptor; GPR), wherein structural features, binding domains, signal transduction coupling, homologies have been disclosed*



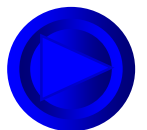
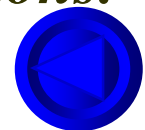
P a t e n t i n g B i o t e c h i n E P

- *The Practice: Inventive Step*
- *V28-receptor: object to be solved: providing additional 7 TM receptor*
- *inventive or not ?*
- *OD: “Consequently, the disclosure of the primary structure of an **additional** 7TM protein which is **arrived** at by following the **well established methods** disclosed in the prior art is not considered inventive and fails the requirements of Article 56 EPC.”*



Patenting Biotech in EP

- *The Practice: Industrial Application*
- *V28-Receptor: The specification disclosed how to make the V28 protein and disclosed also uses (e.g. as receptor involved in immunological processes).*
- *OD: “Thus, the potential uses disclosed in the application are **speculative**, ie are **not specific, substantial and credible** and as such are not considered industrial applications.”*
- *“However, the **evidence in the present specification** does not explicitly or implicitly indicate the involvement of V28 protein in immunological processes and thus it does not indicate that said invention is capable of exploitation in relevant industrial applications.”*



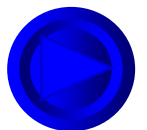
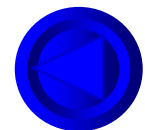
Patenting Biotech in EP

- *The Practice: Enabling Disclosure*
- *Scope of granted patent should correspond to its technical contribution to the state of the art*
- *Disclosure should enable invention (claims) to be performed without undue burden or application of inventive skill*
- *T 188/97 NANBV/CHIRON CORPORATION*
 - *Hepatitis C Virus (HCV); approx 10000 nucleic acid residues*
 - *77 % sequenced, 100 % deposited*
- *Claims to (whole) isolated HCV-polynucleotide ?*
 - *enabled*
- *Claims to polypeptide epitopes ?*
 - *non-enabled*



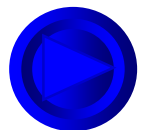
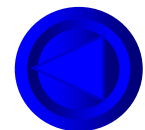
Patenting Biotech in EP

- *The Practice: Enabling Disclosure: V28-Receptor*
- *sequence and function as a receptor disclosed*
- *no ligands (not even antibodies) disclosed, only several methods for finding such ligands*
- *V28 protein was verified to be a receptor in later publications (co-receptor for HIV-2)*
- *OD: “... the opposition division concludes that disclosure of the amino acid sequence of V28 protein and prediction of a function as a receptor in combination with the method disclosed for identification of the respective ligand does not suffice to disclose a receptor protein with SEQ ID NO:28.”*



P a t e n t i n g B i o t e c h i n E P

- *The Practice: Enabling Disclosure: V28-Receptor*
- *Claims to V28-Receptor-Antibodies:*
- *OD: “Although it is conceivable that a number of antibodies (including known antibodies) recognise and bind to V28 protein, an antibody that **specifically recognises V28 protein**, is not disclosed. Furthermore, the assertion of the patentee that generation of such antibodies is routine matter in the art is not followed by the opposition division. An antibody that specifically recognises V28 is understood to mean an antibody that does not recognise any other protein. **The generation of such antibodies is not considered a routine matter given the labour intensive exclusion of cross reactivity of the candidate specific antibody with any other protein.**“*



Patenting Biotech in EP

- *The Practice: Clarity of Claims*
- *often interconnected with Art. 83: no undue burden or inventive skill*
- *claims must contain all features necessary to obtain the desired technical result*
- *the wording of a claim should not leave the addressee guessing as to whether something falls within its terms*
- *functional language possible, if not only wishful thinking*



Patenting Biotech in EP

➤ *The Practice: Claim examples*

➤ ***FICPI*PRAHA peptide** and DNA*

➤ *List all 33-mers in claim 1*

➤ *Chemical Formula: „ X_1 - X_2 -...- X_{33} , wherein X_1 is T, X_2 is T, X_3 is T or C, ... X_{33} is A, C, T or G.“*

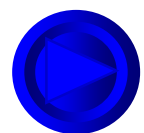
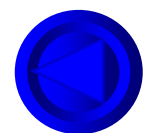
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➤ *Functional Terms II: „DNA molecule encoding our meeting“*

➤ *% identity: „Nucleic acid molecule with at least 63 % identity to Seq.ID.no 1“*

➤ *„DNA with at least 63 % identity to Seq.ID.no 1 and encoding our meeting“*

➤ *„DNA with at least 63 % identity to Seq.ID.no 1 and encoding **FICPI*PRAHA**“*

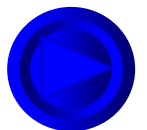
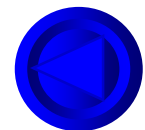


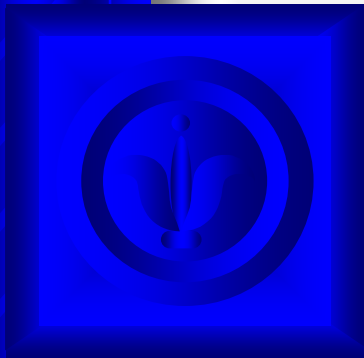
Patenting Biotech in EP

➤ *The Practice: Claim examples*

➤ ***FICPI*PRAHA** peptide and DNA*

- *? Chemical Formula: „ X_1 - X_2 -...- X_{33} , wherein X_1 is T, X_2 is T, X_3 is T or C, ... X_{33} is A, C, T or G.“ ?*
- *Functional Terms I: „Nucleic acid molecule encoding **FICPI*PRAHA** Peptide.“*
- *„DNA with at least 63 % identity to Seq.ID.no 1 and encoding **FICPI*PRAHA**.“*





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The European Perspective

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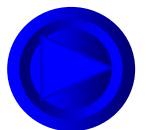
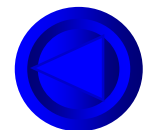
- *The Practice: Claim examples*
- *T 412/93 Erythropoietin/KIRIN-AMGEN*
- *T 636/97 Erythropoietin II/KIRIN-AMGEN*



Patenting Biotech in EP

➤ *The Practice: Erythropoietin/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 [sic] of that of erythropoietin to allow possession of the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells and to increase hemoglobin [sic] synthesis or iron uptake, said DNA sequence selected from the group consisting of:*
 - *(a) the DNA sequences set out in Tables V and VI or their complementary strands;*
 - *(b) DNA sequences which hybridize under stringent conditions to the protein coding regions of the DNA sequences defined in (a) or fragments thereof; and*
 - *(c) DNA sequences which, but for the degeneracy of the genetic code, would hybridize to the DNA sequences defined in (a) and (b).”*



Patenting Biotech in EP

➤ *The Practice: Erythropoietin/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.”*

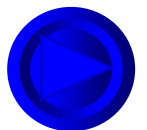
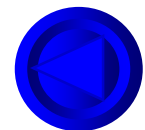


Patenting Biotech in EP

➤ *The Practice: Claim examples*

➤ *T 188/97 NANBV/CHIRON CORPORATION*

"31. A polynucleotide in substantially isolated form comprising a contiguous sequence of nucleotides which is capable of selectively hybridising to the genome of hepatitis C virus (HCV) or the complement thereof, wherein HCV is characterized by: a positive stranded RNA genome; said genome comprising an open reading frame (ORF) encoding a polyprotein; and the entirety of the said polyprotein having at least 40% homology to the entire polyprotein of a viral isolate from the genome of which was prepared cDNAs deposited in a lambda gt-11 cDNA library with the American Type Culture Collection (ATCC) under accession n. 40394."

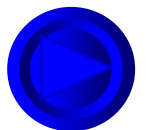
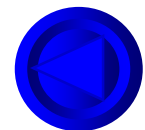


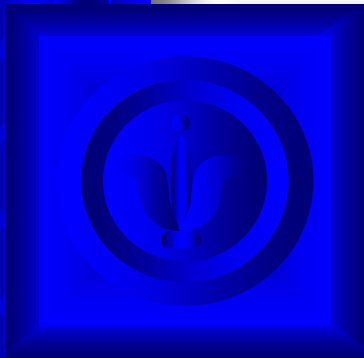
Patenting Biotech in EP

➤ *The Practice: Claim examples*

➤ *T 188/97 NANBV/CHIRON CORPORATION*

"1. A polypeptide in substantially isolated form comprising a contiguous sequence of at least 10 amino acids encoded by the genome of hepatitis C virus (HCV) and comprising an HCV antigenic determinant wherein HCV is characterized by:
a positive stranded RNA genome;
said genome comprising an open reading frame (ORF)
encoding a polyprotein;
and the entirety of the said polyprotein having at least 40% homology to the entire polyprotein of a viral isolate from the genome of which was prepared cDNAs deposited in a lambda gt-11 cDNA library with the American Type Culture Collection (ATCC) under accession n. 40394."





Unravelling the patenting of biotechnology inventions -

The European Perspective

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Patenting Biotech in EP and US

➤ *Written Disclosure*

Uni.Calif/Eli Lilly (US) vs. NANBV/CHIRON CORPORATION (EP)

➤ *Industrial Applicability (EP) vs. Utility (US)*

➤ *Morality*

➤ *Novelty*

➤ *“Grace Period” (US) vs. no Grace Period (EP)*
Inventive Step

➤ *Priority Claiming*

G 2/98 (EP) vs. “First to invent” and “Hilmer-Doctrine” (US)

“problem-solution-approach” (EP) vs. Graham/John Deere (US)

