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Our ref.: S 808 EP

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Ba/Fr

The following observations are made by the Patentee in response to the oppositions filed by Boehringer (Opponent I) on December 23, 1993 and the opposition filed by Biotest (Opponent II) on January 3, 1994:

1. The references cited during the opposition proceedings

The following references were cited by Opponent I (O1 to O12) and Opponent II (D1 to D6):

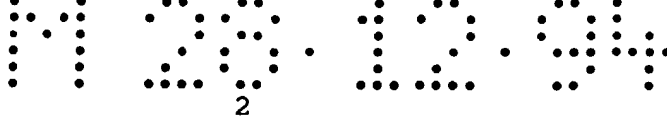
U.S. Patent No. 4,358,535 (01)

Clinica Chimica Acta 81: 1-40 (1977) (02)

Proc. Natl. Acad. Sci USA vol. 78, pp. 6633-6637,
November 1981 (03)

Proc. Natl. Acad. Sci. USA. vol. 79, pp. 7331-7335,
December 1982 (04)

Proc. Natl. Acad. Sci. USA vol., 79, pp. 4381-4385, July
1992 (05)



Proc. Natl. Acad. Sci. USA, vol. 80, pp. 4045-4049, July 1983 (06)

EP-A-0 063 879 (07)

DE-A-29 15 082 (08)

DE-A-27 24 486 (09)

US-A-4,271,140 (010)

Journal of Histochemistry and Cytochemistry Vol. 27, 8, 1131-1139 (1979) (011)

Biochemie 1972, 54, 837-842 (012)

EPA-82301804.9 (D1)

EPA-82303701.5 (D2)

US-Patent No. 4,358,535 (D3)

Exp. Cell Res. 128 (1980), pp. 485-490, J. Bauman et al., "A new method for fluorescence microscopical localization of specific DNA sequences by in situ hybridization of fluorochrome-labeled RNA" (D4)

GB-A-2,019,408 (D5)

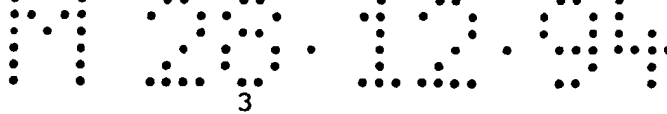
GB-A-2,026,690 (D6)

O1 is identical to D3 and O7 is identical to D1.

2. The subject matter of EP-B-117 440

2.1. The technical problem underlying the present invention is to provide a method for detecting a polynucleotide sequence.

The solution is achieved by a method whereby the sequence is fixed to a solid support in a non-porous, transparent or translucent system, a hybrid is formed between the sequence and a polynucleotide probe having a chemical label which comprises a signalling moiety capable of generating a soluble signal, directly or indirectly, and the soluble signal is generated and



detected. The essential features of the claimed process are outlined in claim 1 which reads as follows:

"A method for detecting a polynucleotide sequence which comprises:

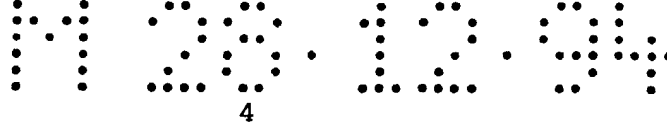
- fixing said polynucleotide sequence to a solid support which comprises or is contained within a transparent or translucent system, such that the polynucleotide is in a single-strand form and is capable of hybridizing to complementary nucleic acid sequences;
- forming an entity comprising said polynucleotide sequence hybridized to a polynucleotide or oligonucleotide probe, said probe having attached thereto a chemical label comprising a signalling moiety capable of generating a signal; and
- generating and detecting a signal, characterized in that the transparent or translucent system is a non-porous system and the generated signal is a soluble signal."

Dependent claims 2 to 16 and 20 to 25 are directed to specific embodiments of features of claim 1.

Claims 17 to 19 are directed to a device and a kit, respectively, to be used in the method of claim 1.

Claim 26 is directed to a transparent or translucent solid, non-porous substrate, and reads as follows:

"A transparent or translucent solid, non-porous substrate having fixed thereto a double-stranded polynucleotide, one of the strands of said double-stranded polynucleotide being a non-radioactive chemically labelled polynucleotide or comprising a non-radioactive chemically-labelled nucleotide as a nucleotide component of said one strand, wherein said



chemically labelled polynucleotide comprises or has attached thereto a chemical label comprising a signalling moiety which generates a soluble signal which is detected spectrophotometrically."

Claims 27 to 28 are specific embodiments of the subject matter of claim 26.

Claim 29 is also directed to a method for detecting a polynucleotide sequence and comprises the following steps:

- fixing a polynucleotide or oligonucleotide probe which has attached thereto a chemical label comprising a signalling moiety capable of generating a signal to a solid support which comprises or is contained within a transparent or translucent system such that said probe is in single-stranded form and is capable of hybridizing to complementary nucleic acid sequences;
- forming an entity comprising said probe hybridized to said polynucleotide sequence, and,
- generating and detecting a signal, characterized in that the transparent or translucent system is non-porous and the generated signal is a soluble signal.

3. The patentability of the subject matter of the patent in suit

3.1. The Opponents, Boehringer (Opponent I) and Biotest (Opponent II), maintain that the present patent is unpatentable over the prior art for the same reasons that were considered and dismissed during the prosecution of the present patent and its corresponding US Patent. The references cited by the Opponents are either identical to or less relevant than the

references cited and considered by the Examining Division during substantive examination. The references were overcome by Patentee's arguments and amendments to the claims and found not to stand in the way of the patentability of the invention. Essentially, Opponents are re-raising and re-arguing prior art work that was distinguished to the satisfaction of the European and US Patent Examiners.

Specifically, both opponents cited the work of David Ward and rely heavily on articles published by him and his colleagues to support their arguments that the claimed invention is unpatentable. In fact, Opponent's I entire argument is based on David Ward's work since all the primary references cited by this Opponent for both lack of novelty and inventive step were authored or co-authored by David Ward. See Opponent's I opposition papers and cited references 03, 04, 05, 06 and 07. Likewise, Opponent II cites the European patent application wherein David Ward is named as an inventor, see D1 of Opponent's II enclosures, as does Opponent I (see reference 07); a reference that was considered repeatedly during prosecution of the contested patent.

David Ward's work led to the discovery that nucleic acids could be labelled in positions that do not interfere with the hybridization ability of the acids. The inventive aspects of this work are best described by European patent EP 63,879[✓] and U.S. Patent No. 5,328,824, of which patentee is the exclusive licensee. Patentee's licensee status as to the Ward patents give it a thorough and unique understanding of the work and the cited Ward, et al., publications.

The Ward articles teach nucleic acid probes labelled in non-destructive positions which can be used to hybridize to specific target sequences of nucleic

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