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DECISION
of 29 October 2003

Case Number: W 0012/01 - 3.3.4
Application Number: PCT/GB 00/00740
Publication Number: WO 0052203

Language of the proceedings: EN

Title of invention: Identification of bacteria

Applicant: KING'S COLLEGE LONDON GUY'S & ST. THOMAS'S NATIONAL HEALTH TRUST

Opponent: -

Headword: Identification of bacteria/KING'S COLLEGE et al

Relevant legal provisions:
PCT Art. 17(3)(a), 34(3), 34(3)(a)
PCT R. 13.1, 13.2, 13.3, 40.1, 68.2, 68.3(c)

Keyword: "Lack of unity a posteriori (no)"

Decisions cited:
G 0001/89, W 0013/87, W 0011/89, W 0004/94

Catchword: -
Case Number: W 0012/01 - 3.3.4

DECISION
of the Technical Board of Appeal 3.3.4
of 29 October 2003

Applicants: KING'S COLLEGE LONDON
GUY'S & ST. THOMAS'S NATIONAL HEALTH TRUST

Representative: Tollett, Ian
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Decision under appeal: Protest according to Rule 40.2(c) of the Patent Cooperation Treaty made by the applicants against the invitation (payment of additional fees) of the European Patent Office (International Searching Authority) dated 17 July 2000.

Composition of the Board:
Chairwoman: U. M Kinkeldey
Members: R. G. Gramaglia
B. Günzel
Summary of Facts and Submissions

I. The Applicant filed international patent application PCT/GB00/00740 on 1 March 2000. The application contained 27 claims:

"1. A method for identifying bacteria in a sample which comprises amplifying a portion of the 23S rDNA present in the sample using, as one primer, a degenerate primer set comprising one or more DNA molecules consisting essentially of DNA having the sequence(s)

5'GCGATTTTCYGAAYGGGGRAACCC

the other primer consisting essentially of DNA having the sequence

5'TTCGCCTTTCCCTCACGGTACT

and testing the resulting amplicon by hybridisation to one or more oligonucleotide probes designed to identify one or more bacteria likely to be present in the sample.

2. Method according to claim 1, in which at least 8 bacterial species are tested for.

3. Method according to claim 2, in which the organisms tested for comprise at least one of Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, Enterococcus spp., Klebsiella spp., Enterobacter spp., Proteus spp, Pneumococci, and coagulase negative Staphylococci.
4. Method according to claim 1, in which at least 10 bacterial species are tested for.

5. Method according to claim 4, in which the organisms tested for comprise at least one of Pseudomonas aeruginosa, Proteus mirabilis, Enterococcus faecium, Enterococcus faecalis, Staphylococcus aureus, coagulase negative Staphylococcus, Listeria species, Stenotrophomonas maltophilia, Burkholderia cepacia, and Escherichia coli.

6. A method according to claim 1, in which the oligonucleotide probe or probes has/have a sequence(s) selected from the group consisting of

7. A method according to claim 1, in which the oligonucleotide probe or probes has/have a sequence(s) selected from the group consisting of
SEQ ID Nos 8, 14, 20, 29, 33-38, 42, 43, 50, 52, and 59.

8. A method according to claim 1, in which the oligonucleotide probe or probes has/have a sequence(s) selected from the group consisting of
SEQ ID Nos 3-59.

9. A method according to claim 1, in which the oligonucleotide probe or probes has/have a sequence(s) selected from the group consisting of
SEQ ID Nos 60-63.
10. A method according to any of claims 1 to 9, in which amplification is carried out by the polymerase chain reaction (PCR).

11. A method according to any of claims 1 to 9, in which amplification is carried out by transcription mediated amplification.

12. A method according to any of the preceding claims, in which a plurality of oligonucleotide probes are used attached to a support material.

13. A degenerate primer set essentially comprising DNA having the sequences 5'GCGATTTCYGAAYGGGRAACCC

14. A primer consisting essentially of DNA having the sequence 5'TTCGCCCTTTCCCTCACGGTACT

15. A DNA sequence according to claim 13 or 14, being a labelled sequence.

16. A Digoxigenin-labelled DNA sequence according to claim 15.

17. One or more oligonucleotides consisting essentially of one or more DNA molecules having sequences specified in claim 6.

18. One or more oligonucleotides consisting essentially of one or more DNA molecules having sequences specified in claim 7.
19. One or more oligonucleotides consisting essentially of one or more DNA molecules having sequences specified in claim 8.

20. One or more oligonucleotides consisting essentially of one or more DNA molecules having sequences specified in claim 9.

21. One or more oligonucleotides according to any of claims 17 to 20, immobilised on a solid carrier.

22. A solid support material carrying one or more oligonucleotide probes as specified in claims 6, 7, 8, or 9.

23. A support material according to claim 22, in which some or all of the probes are attached to the substrate by means of chemically modified or additional bases.

24. A support material according to claim 23, in which additional thymine bases have been attached to the 3 prime end of the probe to increase hybridization intensity.

25. A diagnostic kit for the identification of bacteria comprising one or more amplification primers specified in claim 1.

26. A diagnostic kit for the identification of bacteria comprising one or more oligonucleotide probes as specified in claim 6, 7, 8, or 9.
27. A diagnostic kit for the identification of bacteria comprising a solid support material carrying one or more oligonucleotide probes as specified in claim 6, 7, 8, or 9."

II. On 17 July 2000, the EPO, acting as International Searching Authority (ISA), issued to the Applicant an invitation to pay twenty four additional search fees in accordance with Article 17(3)(a) and Rule 40.1 PCT because it considered that the international application covered the twenty five groups of inventions below:

1. Claims: 13-16, 25 (complete); 1-6, 8, 10-12, 17, 19, 21-24, 26, 27 (partial)

INVENTION 1:

A primer set, suitable for amplification of bacterial 23S rRNA comprising such a sequence, an oligonucleotide probe according to SEQ ID Nos. 3 to 4, suitable for detecting Proteus species, a solid support material carrying such probe(s), a diagnostic kit comprising such primers and/or probe(s), as well as a method of identifying bacteria using such primers and probe(s).
2. Claims: 1 to 8, 10 to 12, 17 to 19, 21 to 24, 26, 27 (partial)

INVENTION 2:

An oligonucleotide probe according to SEQ ID Nos. 5, 8, 10, 37, 48, suitable for detecting E. coli species, a solid support material carrying such probes, a diagnostic kit comprising such probe(s), as well as an amplification method of identifying bacteria using such probe(s).

3. Claims: 1 to 4, 6, 8, 10 to 12, 17, 19, 21 to 24, 26, 27 (partial)

INVENTION 3:

An oligonucleotide probe according to SEQ ID Nos. 6, 7, suitable for detecting Klebsiella species, a solid support material carrying such probes, a diagnostic kit comprising such probe(s), as well as an amplification method of identifying bacteria using such probe(s).

4. Claims: 1 to 8, 10 to 12, 17 to 19, 21 to 24, 26, 27 (partial)

INVENTION 4:

An oligonucleotide probe according to SEQ ID Nos. 9, 38, 49, suitable for detecting Enterobacter species, a solid support material carrying such probes, a diagnostic kit comprising such probe(s), as well as an amplification method of identifying bacteria using such probe(s).
5. Claims: 1, 2, 4, 6, 8, 10 to 12, 17, 19, 21 to 24, 26, 27 (partial)

INVENTION 5:

An oligonucleotide probe according to SEQ ID No. 11, suitable for detecting Salmonella species, a solid support material carrying such probe, a diagnostic kit comprising such probe, as well as an amplification method of identifying bacteria using such probe.

6. Claims: 1, 2, 4, 6 to 8, 10 to 12, 17 to 19, 21 to 24, 26, 27 (partial)

INVENTION 6:

An oligonucleotide probe according to SEQ ID Nos. 12, 15, 18, 30 to 35, suitable for detecting Streptococcus species, a solid support material carrying such probes, a diagnostic kit comprising such probe(s), as well as an amplification method of identifying bacteria using such probe(s).

7. Claims: 1 to 6, 8, 10 to 12, 17, 19, 21 to 24, 26, 27 (partial)

INVENTION 7:

An oligonucleotide probe according to SEQ ID No. 13, suitable for detecting Pseudomonas species, a solid support material carrying such probe, a diagnostic kit comprising such probe, as well as an amplification method of identifying bacteria using such probe.
8. Claims: 1, 2, 4, 7, 8, 10 to 12, 18, 19, 21 to 24, 26, 27 (partial)

INVENTION 8:

An oligonucleotide probe according to SEQ ID No. 14, suitable for detecting Haemophilus species, a solid support material carrying such probe, a diagnostic kit comprising such probe, as well as an amplification method of identifying bacteria using such probe.

9. Claims: 1 to 6, 8, 10 to 12, 17, 19, 21 to 24, 26, 27 (partial)

INVENTION 9:

An oligonucleotide probe according to SEQ ID Nos. 16, 19, suitable for detecting Enterococcus species, a solid support material carrying such probes, a diagnostic kit comprising such probe(s), as well as an amplification method of identifying bacteria using such probe(s).

10. Claims: 1, 2, 4, 6, 8, 10 to 12, 17, 19, 21 to 24, 26, 27 (partial)

INVENTION 10:

An oligonucleotide probe according to SEQ ID No. 17, suitable for detecting Aeromonas species, a solid support material carrying such probe, a diagnostic kit comprising such probe, as well as an amplification method of identifying bacteria using such probe.
11. Claims: 1 to 6, 8, 10 to 12, 17, 19, 21 to 24, 26, 27 (partial)

INVENTION 11:

An oligonucleotide probe according to SEQ ID Nos. 20 to 26, suitable for detecting Staphylococcus species, a solid support material carrying such probes, a diagnostic kit comprising such probe(s), as well as an amplification method of identifying bacteria using such probe(s).

12. Claims: 1, 2, 4 to 6, 8, 10 to 12, 17, 19, 21 to 24, 26, 27 (partial)

INVENTION 12:

An oligonucleotide probe according to SEQ ID No. 27, suitable for detecting Burkholderia species, a solid support material carrying such probe, a diagnostic kit comprising such probe, as well as an amplification method of identifying bacteria using such probe.

13. Claims: 1, 2, 4, 6, 8, 10 to 12, 17, 19, 21 to 24, 26, 27 (partial)

INVENTION 13:

An oligonucleotide probe according to SEQ ID No. 28, suitable for detecting Stenotrophomonas species, a solid support material carrying such probe, a diagnostic kit comprising such probe, as well as an
amplification method of identifying bacteria using such probe.

14. Claims: 1, 2, 4, 5, 7, 8, 10 to 12, 18, 19, 21 to 24, 26, 27 (partial)

INVENTION 14:

An oligonucleotide probe according to SEQ ID No. 29, suitable for detecting Listeria species, a solid support material carrying such probe, a diagnostic kit comprising such probe, as well as an amplification method of identifying bacteria using such probe.

15. Claims: 1, 2, 4, 7, 8, 10 to 12, 18, 19, 21 to 24, 26, 27 (partial)

INVENTION 15:

An oligonucleotide probe according to SEQ ID No. 36, suitable for detecting Acinetobacter species, a solid support material carrying such probe, a diagnostic kit comprising such probe, as well as an amplification method of identifying bacteria using such probe.

16. Claims: 1, 2, 4, 6 to 8, 10 to 12, 17 to 19, 21 to 24, 26, 27 (partial)

INVENTION 16:

An oligonucleotide probe according to SEQ ID Nos. 38, 39, suitable for detecting CNS species, a solid support material carrying such probes, a diagnostic kit
comprising such probe(s), as well as an amplification method of identifying bacteria using such probe(s).

17. Claims: 1, 2, 4, 6, 8, 10 to 12, 17, 19, 21 to 24, 26, 27 (partial)

INVENTION 17:

An oligonucleotide probe according to SEQ ID No. 41, suitable for detecting Plesiomonas species, a solid support material carrying such probe, a diagnostic kit comprising such probe, as well as an amplification method of identifying bacteria using such probe.

18. Claims: 1, 2, 4, 7 to 12, 18 to 24, 26, 27 (partial)

INVENTION 18:

An oligonucleotide probe according to SEQ ID Nos. 42, 43, 60, 61, suitable for detecting Neisseria species, a solid support material carrying such probes, a diagnostic kit comprising such probe(s), as well as an amplification method of identifying bacteria using such probe(s).

19. Claims: 1, 2, 4, 6, 8, 10 to 12, 17, 19, 21 to 24, 26, 27 (partial)

INVENTION 19:

An oligonucleotide probe according to SEQ ID Nos. 44, 45, suitable for detecting Campylobacter species, a solid support material carrying such probes, a
diagnostic kit comprising such probe(s), as well as an amplification method of identifying bacteria using such probe(s).

20. Claims: 1, 2, 4, 6, 8, 10 to 12, 17, 19, 21 to 24, 26, 27 (partial)

INVENTION 20:

An oligonucleotide probe according to SEQ ID No. 46, suitable for detecting Helicobacter species, a solid support material carrying such probe, a diagnostic kit comprising such probe, as well as an amplification method of identifying bacteria using such probe.

21. Claims: 1, 2, 4, 6, 8, 10 to 12, 17, 19, 21 to 24, 26, 27 (partial)

INVENTION 21:

An oligonucleotide probe according to SEQ ID No. 47, suitable for detecting Ralstonia species, a solid support material carrying such probe, a diagnostic kit comprising such probe, as well as an amplification method of identifying bacteria using such probe.

22. Claims: 1, 2, 4, 6 to 12, 17 to 24, 26, 27 (partial)

INVENTION 22:

An oligonucleotide probe according to SEQ ID Nos. 50 to 52, 62, 63, suitable for detecting Chlamydia species, a solid support material carrying such probes,
a diagnostic kit comprising such probe(s), as well as an amplification method of identifying bacteria using such probe(s).

23. Claims: 1, 2, 4, 6, 8, 10 to 12, 17, 19, 21 to 24, 26, 27 (partial)

INVENTION 23:

An oligonucleotide probe according to SEQ ID No. 53, suitable for detecting Coxiella species, a solid support material carrying such probe, a diagnostic kit comprising such probe, as well as an amplification method of identifying bacteria using such probe.

24. Claims: 1, 2, 4, 6, 8, 10 to 12, 17, 19, 21 to 24, 26, 27 (partial)

INVENTION 24:

An oligonucleotide probe according to SEQ ID Nos. 54, 55, suitable for detecting Rhodococcus species, a solid support material carrying such probes, a diagnostic kit comprising such probe(s), as well as an amplification method of identifying bacteria using such probe(s).

25. Claims: 1, 2, 4, 6, 8, 10 to 12, 17, 19, 21 to 24, 26, 27 (partial)

INVENTION 25:

An oligonucleotide probe according to SEQ ID Nos. 56 to 58, suitable for detecting Mycobacterium species, a solid support material carrying such probes, a
diagnostic kit comprising such probe(s), as well as an amplification method of identifying bacteria using such probe(s).

III. The ISA reasoned their invitation to pay the additional fees that oligonucleotide primers suitable for amplifying "universal" or "consensus" parts of bacterial rRNA genes, especially deriving from bacterial 23S genes, species-specific oligonucleotide detection probes, as well as (multiplex) methods combining such primers and probes for the purpose of identifying bacterial species within a sample were already known in the prior art represented by:

(D1) EP-A-0395292;

(D2) Lew. A.E. et al., J. Clin. Microbiol., Vol. 32, No. 5, pages 1326 o 1332 (1994); and

(D3) W0-A-96/00298.

Document (D1) disclosed "universal" primers for amplifying conserved genomic 16S- and 23S-rDNA regions of numerous phylogenetically related microorganisms, followed by species identification via the use of species-specific probes. Likewise, document (D2) disclosed detection of Pseudomonas species by PCR using primers directed against conserved parts of the 23S rDNA gene, followed by hybridization with strain-specific probes, whereas document (D3) described multiplex detection of microorganisms within a sample by amplification of the 16S-23S rRNA spacer region, followed by detection with taxon-specific probes.
IV. In the ISA's view, the problem solved by the application vis-à-vis this prior could be defined as the provision of further alternative consensus oligonucleotide amplification primers (SEQ ID Nos. 1, 2) and oligonucleotide detection probes (SEQ ID Nos. 3 to 63), suitable within a method for (multiplex) detection of bacterial species within a sample. However, each of the 61 detection probes having each a different primary structure and a different species specificity in combination with the disclosed primer set represented an independent solution concerning the problem of the underlying application, taking into account the fact that no other technical features could be distinguished which, in the light of the prior art, could be regarded as special technical features common to these solutions, pursuant to Article 17(3)(a) PCT.

V. Nevertheless, taking into account the balance between necessary search effort and the levying of additional fees, the ISA decided to combine probes referring to the same bacterial species (Proteus, E. coli, Klebsiella, Enterobacter, Salmonella, Streptococcus, Pseudomanas, Haemophilus, Enterococcus, Aeromonas, Staphylococcus, Burkholderia, Stenotrophomonas, Listeria, Acinetobacter, CNS (coagulase negative Streptococcus), Plesiomonas, Neisseria, Campylobacter, Helicobacter, Ralstonia, Chlamydia, Coxiella, Rhodococcus and Mycobacterium) into one group of invention, so that the application comprised a plurality of 25 (groups of) inventions.

VI. With its response of 16 August 2000, the Applicant paid under protest nine additional search fees for the search of the inventions identified by the ISA as 2, 3,
4, 7, 9, 11, 12, 13 and 14 and presented arguments that the inventions identified as 1 to 25 (see Section II supra) were unitary, because, inter alia, all the probes hybridized to the particular portions of the 23S rDNA defined by the primers according to SEQ ID Nos. 1 and 2.

VII. With a communication dated 12 October 2000, a review board within the meaning of Rule 68.3(c) PCT confirmed the ISA’s opinion regarding lack of unity. It was pointed out by the review board that the "down" primer with SEQ ID No. 156 disclosed on page 64 of document (D3) primed at the same site as the "second" primer with SEQ ID No. 2 referred to in present claim 1 and that, therefore, the specific probes according to document (D3) originated from the same region as in the present application. Furthermore, the review panel reconsidered the number of additional search fees to be requested, reducing it to three. Consequently, refund of six of the nine additionally paid search fees was ordered.

VIII. The Applicant requested reimbursement of the additional search fees, and of the protest fee.

Reasons for the Decision

1. The protest is admissible.

2. According to Rule 13.1 PCT, the international patent application shall relate to one invention only or to a group of inventions so linked as to form a single inventive concept. If the ISA considers that the claims
lack this unity, it is empowered, under Article 17(3)(a) and Rule 40.2 PCT, to invite the Applicant to pay additional fees.

3. Lack of unity may be directly evident *a priori*, ie before the examination of the merits of the claims in comparison with the state of the art revealed by the search (cf., for example, decision W 13/87 of 9 August 1988). Alternatively, having regard to decision G 1/89 of the Enlarged Board of Appeal (EBA) (OJ EPO 1991, 155), the ISA is also empowered to raise an objection *a posteriori*, ie after having taken the prior art revealed by the search into closer consideration. This practice is laid down in the PCT/International Search Guidelines, Chapter VII: 9. (PCT Gazette Special Issue 66/1998) which are the basis for a uniform practice of all International Searching Authorities. The Enlarged Board of Appeal indicated that such considerations represent only a provisional opinion on novelty and inventive step which are in no way binding upon the authorities subsequently responsible for the substantive examination of the application (point 8.1. of the reasons). In point 8.2 of the reasons, the EBA mentioned that such invitation to pay additional fees should always be made "with a view to giving the Applicant fair treatment" and should only be made in clear cases.

4. According to Rule 13.3 PCT, the determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim.
5. The ISA has based its finding of lack of unity upon *posteriori* considerations (see sections III and IV above). They found that "the common inventive concept" underlying the present claims, in the light of the prior art, could only be seen in the provision of further alternative consensus oligonucleotide amplification primers (SEQ ID Nos. 1, 2) and oligonucleotide detection probes (SEQ ID Nos. 3 to 63), suitable within a method for (multiplex) detection of bacterial species within a sample. However, firstly the ISA came to the conclusion that each of the 61 detection probes (SEQ ID Nos. 3 to 63) having each a different primary structure and a different species specificity in combination with the disclosed primer set represented an independent solution concerning the problem of the underlying application, resulting in 61 separate inventions. The ISA "has taken the decision to combine probe referring to the same bacterial species into one group of invention" (see invitation of 17 July 2000, point 5) resulting in 25 inventions. The Review panel finally used its discretion (PCT International Search Guidelines IV-VII-12) to reduce the number of fees to three.

6. In order to define the underlying technical problem to be solved by the present application the disclosure of documents (D1) to (D3) has to be taken into consideration.

7. Document (1) relates, inter alia, to a method as that of the application, however, the two "universal" primers, distant about 100 to 120 bp, flank either the V2 (primers R1 and R2) or the V6 (primers U1 and U2) variable regions of the 16S rDNA (see page 9, line 37
to page 10, line 6). Apparently, the "V2 system" (primers R1 and R2) enables amplification of the DNA of (only) seven bacteria species, as does the "V6" one (primers U1 and U2) (see page 10, lines 8 to 22), compared with the 80 bacteria species of the present application (see Table 1 on pages 19 to 20) involving only two primers.

8. Primers PPMA and PPMC disclosed in document (2) are distant 1,550 bp and have been chosen from the 23S rDNA region (see Figure 1 and legend thereto). However, they have been designed by comparing the 23S rRNA sequences of Pseudomonas cepacia with that of Pseudomonas aeruginosa, ie only two bacteria of the same species (see page 1327, left-hand column). There is no disclosure, however, that these primers are "universal" in the sense that they enable amplification of DNAs from bacterial species different from Pseudomonas.

9. As for document (3), it relates to a method for identifying bacteria in a sample. The review board concluded (see section VII supra) that the "down" primer with SEQ ID No. 156 disclosed on page 64 of document (D3) primed at the same site as the "second" primer with SEQ ID No. 2 referred to in present claim 1 and that, therefore, the specific probes according to document (D3) originated from the same region as in the present application. The board agrees that the "lower" primer with SEQ ID No. 156 5'CCTTTCCCTCACGGTACT (see page 64, line 20) almost coincides with the "second" primer 5'TTCGCCTTTCCCTCACGGTACT of claim 1 of the present application. However, the following two differences are worth to be noted: (i) the "upper" primer with SEQ ID No. 155 hybridizes in the 16S-23S


The present application describes a method for identifying bacteria in a sample which comprises amplifying a portion of the 23S rDNA region of bacteria present in the sample by means of two "universal" primers distant about 390 to 420 bp (see page 14, lines 11 to 12) and testing the resulting amplicon by hybridisation to one or more oligonucleotide probes designed to identify one or more bacteria likely to be present in the sample. In view of the above, the board can agree neither to the finding by the ISA that the prior art already discloses "universal" or "consensus" oligonucleotide primers deriving from bacterial 23S genes, nor to the ISA's conclusion that the technical problem solved by the claimed subject-matter lies with the provision of further alternative consensus oligonucleotide amplification primers (SEQ ID Nos. 1, 2) and oligonucleotide detection probes (SEQ ID Nos. 3 to 63), suitable for (multiplex) detection of bacterial species within a sample. Rather, these consensus oligonucleotide amplification primers (SEQ ID Nos. 1, 2)
being a specific sequence of the 23S rDNA region and the oligonucleotide detection probes (SEQ ID Nos. 3 to 63) (the latter all bind to the 390-420 bp long 23S rDNA region delimited by the two primers 5'GCGATTTCYGAAYGGGGRAACCC and 5'TTCGCCTTTCCCTCACGGTACT recited in present claim 1) represent the solution to the problem set out in the present application (see page 2, lines 14 to 17) of finding a region of the rDNA gene which enables identifying a large number of different bacteria by means of only two primers.

11. Given the novelty of the solution defined in the claims, in order to conclude that there is nevertheless a lack of feature linking the solutions defined in the claims justifying the finding of non-unity of the invention, an examination of the inventive step would be necessary. However, the board only has to examine whether considering the reason given by the ISA retaining the additional fees as justified and it cannot investigate ex officio whether an objection of lack of unity would have been justified for reasons other than those given (see W 4/94, OJ EPO 1996, 74, point 5.5 of the reasons). Since the reasons given in the ISA's invitation for finding non-unity were only based on lack of novelty, the protest is justified to the full extent and the remaining additional search fees and the protest fee must be refunded.
Order

For these reasons it is decided that:

Refund of the additional search fees and of the protest fee paid by the Applicant is ordered.

The Registrar: The Chairwoman:

P. Cremona U. M. Kinkeldey