BLO /077/88

PATENTS ACT 1977

IN THE MATTER OF Application
No 8424832 for Letters Patent
in the name of Schering Biotech Corporation

STATEMENT OF REASONS

The examiner having objected that the invention claimed in certain claims of the application was not new or inventive having regard to the prior art and moreover that a number of claims were not supported by the description, the case came before me at a hearing on 25 March 1988.

The applicants were represented by their Agent, Mr S D Ritter, and Mr E D Monaghan attended as the examiner in the case. At the hearing I told Mr Ritter that I was going to refuse the application on the basis that it did not comply with the Act. This was confirmed in a letter dated 28 March 1988. The following are the reasons for my decision.

The applicants specification relates to the production of a polypeptide variously known as mammalian multi-lineage cellular growth factor (CSF), mast cell growth factor (MCGF) and interleukin - 3 (IL-3) by recombinant DNA technology. For the purposes of this statement I propose to refer to the polypeptide as IL-3 as a matter of convenience and consistency.

IL-3 is a member of a group of soluble proteins known as lymphokines which apparently mediate cellular activities in the mammalian immune response in a variety of ways. It is produced in minute quantities in vivo by t-lymphocytes and may also be produced by bone marrow cells. IL-3 has a number of biological activities, hence the variety of names, including the regulation of the growth and differentiation of pluripotent stem cells leading to the production of all the major blood cell types and the regulation of the growth of mast cells.

There is no doubt in my own mind, and I was not led to believe otherwise, that at the priority date of the application IL-3 was a known polypeptide. This is confirmed by the prior art found by the examiner, but equally so by the application itself at page 5, lines 7 to 9 where it is disclosed that interleukin-2 (IL-2) and interleukin-3 (IL-3) are two well studied lympokines released by certain stimulated lymphocytes. That description goes on to say that an important characteristic of IL-3 is its ability to support the growth of cell lines having the phenotypic characteristics of mast cells and that a number of other cellular growth properties have been ascribed to IL-3 as well, although its precise relationship with multi-lineage cellular growth factor has been unclear.

In the paragraph commencing at line 21 on page 5 it is disclosed that both mouse IL-2 and IL-3 have been at least partially characterized biochemically and there then follows discussion on the problems surrounding the variously reported molecular weights of MCGF and CSF factors. These problems together with those connected with the study of the biology of mast cells and other cells involved in the immune response may well be overcome if there was the capability of making bulk quantities of a polypeptide exhibiting mammalian MCGF or CSF activity e.g. IL-3, and thus it is that the applicants have turned to recombinant DNA technology to provide this capability.

In summary the provisions of the invention are set out in the paragraph commencing at line 6 on page 7 in the following terms:

> "The present invention provides cDNA clones coding for polypeptides exhibiting mammalian mast cell growth factor (MCGF) activity and/or multi-lineage cellular growth factor activity. A nucleotide sequence for a cDNA and a putative amino acid sequence for an associated polypeptide are shown in Figure 1. The cDNA sequence can be integrated into various vectors, which in turn can direct the synthesis of

the corresponding polypeptides in a variety of hosts, including eukaryotic cells, such as mammalian cells in culture."

I make only one observation at this point and that is that the sequence shown in Figure 1 is a mouse cDNA sequence, although at lines 13 to 18 on page 8 there is the information that this sequence is capable of hybridizing with other DNA sequences, such as DNA coding for other mammalian growth factors from a cDNA or genomic library.

It is appropriate at this stage to turn to the claims, which because they are all the subject of objection by the examiner are set out in full except where it is unnecessary to repeat an amino acid or nucleotide sequence.

CLAIMS:

1. A process for producing a polypeptide exhibiting mammalian multi-lineage cellular growth factor activity, said process comprising the steps of:

a) providing a vector comprising a nucleotide sequence coding for said polypeptide, wherein the nucleotide sequence is capable of being expressed by a host containing the vector and wherein the nucleotide sequence is at least seventy-five percent homologous to a nucleic acid sequence capable of encoding a polypeptide having an amino acid sequence defined by the formula:

Asp - Thr - His - Arg - Leu - Thr - Arg - Thr -
Leu - Asn - Cys - Ser - Ser - Ile - Val - Lys -
Glu - Ile - Ile - Gly - Lys - Leu - Pro - Glu -
Pro - Glu - Leu - Lys - Thr - Asp - Asp - Glu -
Gly - Pro - Ser - Leu - Arg - Asn - Lys - Ser -
Phe - Arg - Arg - Val - Asn - Leu - Ser - Lys -
Phe - Val - Glu - Ser - Gln - Gly - Glu - Val -
Asp - Pro - Glu - Asp - Arg - Tyr - Val - Ile -

Lys - Ser - Asn - Leu - Gln - Lys - Leu - Asn -
Cys - Cys - Leu - Pro - Thr - Ser - Ala - Asn -
Asp - Ser - Ala - Leu - Pro - Gly - Val - Phe -
Ile - Arg - Asp - Leu - Asp - Asp - Phe - Arg -
Lys - Lys - Leu - Arg - Phe - Tyr - Met - Val -
His - Leu - Asn - Asp - Leu - Glu - Thr - Val -
Leu - Ala - Ser - Arg - Pro - Pro - Gln - Pro -
Ala - Ser - Gly - Ser - Val - Ser - Pro - Asn -
Arg - Gly - Thr - Val - Glu - Cys -;

b) incorporating the vector into the host; and

c) maintaining the host containing the vector under conditions suitable for expression of the nucleotide sequence into said polypeptide.

2. A process as claimed in claim 1 wherein the nucleotide sequence is a cDNA sequence derived from an mRNA sequence coding for said polypeptide.

3. A process as claimed in claim 1 or claim 2 wherein the host is a mammalian cell transformed or transfected with the vector.

4. A process as claimed in claim 3 wherein said polypeptide is glycosylated.

5. A process as claimed in any of claims 1 to 4 wherein the vector comprises the nucleotide coding for said polypeptide linked to a second nucleotide sequence, and this second nucleotide sequence comprises a promoter sequence which promotes expression of the nucleotide sequence coding for said polypeptide.

6. A process as claimed in claim 5 wherein the second nucleotide sequence comprises a SV40 virus early region promoter and a SV40 virus late region poly-adenylation sequence.

7. A process as claimed in any of the claims 1 to 6 wherein the nucleotide sequence codes for a polypeptide having hematopoietic cell growth activity.

8. A process as claimed in any of claims 1 to 7 wherein the nucleotide sequence coding for said polypeptide is capable of encoding a polypeptide having an amino acid sequence defined by the formula:

Met - Val - Leu - Ala - Ser - Ser - Thr - Thr -
Ser - Ile - His - Thr - Met - Leu - Leu - Leu -
Leu - Leu - Met - Leu - Phe - His - Leu - Glu -
Leu - Gln - Ala - Ser - Ile - Ser - Gly - Arg -
Asp - Thr - His - Arg - Leu - Thr - Arg - Thr -
Leu - Asn - Cys - Ser - Ser - Ile - Val - Lys -
Glu - Ile - Ile - Gly - Lys - Leu - Pro - Glu -
Pro - Glu - Leu - Lys - Thr - Asp - Asp - Glu -
Gly - Pro - Ser - Leu - Arg - Asn - Lys - Ser -
Phe - Arg - Arg - Val - Asn - Leu - Ser - Lys -
Phe - Val - Glu - Ser - Gln - Gly - Glu - Val -
Asp - Pro - Glu - Asp - Arg - Tyr - Val - Ile -
Lys - Ser - Asn - Leu - Gln - Lys - Leu - Asn -
Cys - Cys - Leu - Pro - Thr - Ser - Ala - Asn -
Asp - Ser - Ala - Leu - Pro - Gly - Val - Phe -
Ile - Arg - Asp - Leu - Asp - Asp - Phe - Arg -
Lys - Lys - Leu - Arg - Phe - Tyr - Met - Val -
His - Leu - Asn - Asp - Leu - Glu - Thr - Val -
Leu - Ala - Ser - Arg - Pro - Pro - Gln - Pro -
Ala - Ser - Gly - Ser - Val - Ser - Pro - Asn -
Arg - Gly - Thr - Val - Glu - Cys -

9. A process as claimed in any of claims 1 to 8 wherein the nucleotide sequence coding for said polypeptide is defined by the formula

ATG - GTT - CTT - GCC - AGC - TCT - ACC - ACC -
AGC - ATC - CAC - ACC - ATG - CTG - CTC - CTG -
CTC - CTG - ATG - CTC - TTC - CAC - CTG - GGA -
CTC - CAA - GCT - TCA - ATC - AGT - GGC - CGG -
GAT - ACC - CAC - CGT - TTA - ACC - AGA - ACG -
TTG - AAT - TGC - AGC - TCT - ATT - GTC - AAG -
GAG - ATT - ATA - GGG - AAG - CTC - CCA - GAA -
CCT - GAA - CTC - AAA - ACT - GAT - GAT - GAA -
GGA - CCC - TCT - CTG - AGG - AAT - AAG - AGC -
TTT - CGG - AGA - CTA - AAC - CTG - TCC - AAA -
TTC - GTG - GAA - AGC - CAA - GGA - GAA - GTG -
GAT - CCT - GAG - GAC - AGA - TAC - GTT - ATC -
AAG - TCC - AAT - CTT - CAG - AAA - CTT - AAC -
TGT - TGC - CTG - CCT - ACA - TCT - GCG - AAT -
GAC - TCT - GCG - CTG - CCA - GGG - GTC - TTC -
ATT - CGA - GAT - CTG - GAT - GAC - TTT - CGG -
AAG - AAA - CTG - AGA - TTC - TAC - ATG - GTC -
CAC - CTT - AAC - GAT - CTG - GAG - ACA - GTG -
CTA - GCC - TCT - AGA - CCA - CCT - CAG - CCC -
GCA - TCT - GGC - TCC - GTC - TCT - CCT - AAC -
CGT - GGA - ACC - GTG - GAA - TGT -.

10. A process as claimed in any of claims 1 to 8 wherein the nucleotide sequence commences with a sequence coding for at least a part of a hydrophobic leader sequence of the polypeptide.

11. A recombinant polypeptide consisting essentially of an amino acid sequence encoded by a nucleic acid sequence that is at least 75% homologous to the sequence defined by the formula

ATG - GTT - CTT - GCC - AGC - TCT - ACC - ACC -
AGC - ATC - CAC - ACC - ATG - CTG - CTC - CTG -
CTC - CTG - ATG - CTC - TTC - CAC - CTG - GGA -
CTC - CAA - GCT - TCA - ATC - AGT - GGC - CGG -
GAT - ACC - CAC - CGT - TTA - ACC - AGA - ACG -
TTG - AAT - TGC - AGC - TCT - ATT - GTC - AAG -
GAG - ATT - ATA - GGG - AAG - CTC - CCA - GAA -

CCT - GAA - CTC - AAA - ACT - GAT - GAT - GAA -
GGA - CCC - TCT - CTG - AGG - AAT - AAG - AGC -
TTT - CGG - AGA - CTA - AAC - CTG - TCC - AAA -
TTC - GTG - GAA - AGC - CAA - GGA - GAA - GTG -
GAT - CCT - GAG - GAC - AGA - TAC - GTT - ATC -
AAG - TCC - AAT - CTT - CAG - AAA - CTT - AAC -
TGT - TGC - CTG - CCT - ACA - TCT - GCG - AAT -
GAC - TCT - GCG - CTG - CCA - GGG - TTT - CGG -
AAG - AAA - CTG - AGA - TTC - TAC - ATG - GTC -
CAC - CTT - AAC - GAT - CTG - GAG - ACA - GTG -
CTA - GCC - TCT - AGA - CCA - CCT - CAG - CCC -
GCA - TCT - GGC - TCC - GTC - TCT - CCT - AAC -
CGT - GGA - ACC - GTG - GAA - TGT - TAA -,

and exhibiting mammalian multi-lineage growth factor activity and/or mammalian mast cell growth factor activity.

12. A recombinant polypeptide as claimed in claim 11 defined by the formula

(the formula which follows defines the same sequence as claim 8)

13. A nucleic acid sequence that is at least seventy-five percent homologous to nucleotide sequences capable of encoding a polypeptide having an amino acid sequence defined by the formula

(the formula which follows defines the same sequence as claim 8).

14. A nucleic acid sequence as claimed in claim 13 that encodes said polypeptide set forth in claim 13.

15. A nucleic acid sequence as claimed in claim 13 or claim 14 and having the formula

ATG - GTT - CTT - GCC - AGC - TCT - ACC - ACC -
AGC - ATC - CAC - ACC - ATG - CTG - CTC - CTG -
CTC - CTG - ATG - CTC - TTC - CAC - CTG - GGA -
CTC - CAA - GCT - TCA - ATC - AGT - GGC - CGG -
GAT - ACC - CAC - CGT - TTA - ACC - AGA - ACG -
TTG - AAT - TGC - AGC - TCT - ATT - GTC - AAG -
GAG - ATT - ATA - GGG - AAG - CTC - CCA - GAA -
CCT - GAA - CTC - AAA - ACT - GAT - GAT - GAA -
GGA - CCC - TCT - CTG - AGG - AAT - AAG - AGC -
TTT - CGG - AGA - CTA - AAC - CTG - TCC - AAA -
TTC - GTG - GAA - AGC - CAA - GGA - GAA - GTG -
GAT - CCT - GAG - GAC - AGA - TAC - GTT - ATC -
AAG - TCC - AAT - CTT - CAG - AAA - CTT - AAC -
TGT - TGC - CTG - CCT - ACA - TCT - GCG - AAT -
GAC - TCT - GCG - CTG - CCA - GGG - GTC - TTC -
AAT - CGA - GAT - CTG - GAT - GAC - TTT - CGG -
AAG - AAA - CTG - AGA - TTC - TAC - ATG - GTC -
CAC - CTT - AAC - GAT - CTG - GAG - ACA - GTG -
CTA - GCC - TCT - AGA - CCA - CCT - CAG - CCC -
GCA - TCT - GGC - TCC - GTC - TCT - CCT - AAC -
CGT - GGA - ACC - GTG - GAA - TGT - TAA -.

16. A nucleic acid sequence that is at least seventy-five per cent homologous to nucleotide sequences capable of encoding a polypetide having an amino acid sequence defined by the formula (the formula which follows defines the same sequence as claim 1).

17. A nucleic acid sequence as claimed in claim 16 that encodes said polypeptide set forth in claim 16.

18. A nucleic acid sequence as claimed in claim 16 or claim 17 and having the formula

GAT - ACC - CAC - CGT - TTA - ACC - AGA - ACG -
TTG - AAT - TGC - AGC - TCT - ATT - GTC - AAG -
GAG - ATT - ATA - GGG - AAG - CTC - CCA - GAA -
CCT - GAA - CTC - AAA - ACT - GAT - GAT - GAA -

GGA - CCC - TCT - CTG - AGG - AAT - AAG - AGC -
TTT - CGG - AGA - CTA - AAC - CTG - TCC - AAA -
TTC - GTG - GAA - AGC - CAA - GGA - GAA - GTG -
GAT - CCT - GAG - GAC - AGA - TAC - GTT - ATC -
AAG - TCC - AAT - CTT - CAG - AAA - CTT - AAC -
TGT - TGC - CTG - CCT - ACA - TCT - GCG - AAT -
GAC - TCT - GCG - CTG - CCA - GGG - GTC - TTC -
ATT - CGA - GAT - CTG - GAT - GAC - TTT - CGG -
AAG - AAA - CTG - AGA - TTC - TAC - ATG - GTC -
CAC - CTT - AAC - GAT - CTG - GAG - ACA - GTG -
CTA - GCC - TCT - AGA - CCA - CCT - CAG - CCC -
GCA - TCT - GGC - TCC - GTC - TCT - CCT - AAC -
CGT - GGA - ACC - GTG - GAA - TGT - TAA -.

19. A vector consisting essentially of the DNA sequences claimed in any of claims 15 to 18.

20. A replicable vector capable of expressing a DNA sequence of any of claims 15 to 18, when said vector is incorporated into a microorganism or cell.

21. A microorganism or cell transformed or transfected with the replicable expression vector of claim 19 or claim 20.

22. A pharmaceutical composition consisting essentially of a polypeptide as claimed in claim 11 of claim 12 having mammalian multi-lineage growth factor activity and/or mammalian mast cell growth factor activity and a therapeutically compatible carrier.

23. A process for enhancing cell growth comprising contacting said cell with a polypeptide as claimed in claim 11 or claim 12 that has a substantial portion of the amino acid sequence of Figure 1.

24. A process as claimed in claim 23 wherein the cell growth is enhanced <u>in vitro</u>.

25. A process for preparing a polypeptide exhibiting mammalian multi-lineage cellular growth factor activity, which comprises cultivating, in an aqueous nutrient medium, a prokaryotic microorganism or eukaryotic cell which has been transfected or transformed with a vector as claimed in claim 19 or claim 20.

26. A transformed organism or cell which contains a gene or other DNA sequence coding for one or more polypeptides having mammalian multi-lineage cellular growth factor activity and/or mammalian mast cell growth factor activity.

27. A protein exhibiting mammalian multi-lineage cellular growth factor activity produced by cultivating the organism or cell of claim 26.

28. A recombinant DNA molecule consisting of segments of DNA from different genomes which have been joined end to end outside of living cells and have the capacity to infect some host and to be maintained therein, and the progeny thereof, comprising a DNA sequence selected from the group consisting of:

a) the DNA sequence of Figure 1;

b) DNA sequences which hybridize to the DNA sequence of Figure 1, which are at least 75% homologous thereto and which code for a polypeptide exhibiting mammalian multi-lineage cellular growth factor activity and/or mammalian mast cell growth factor activity; and

c) DNA sequences which on expression code for a protein exhibiting mammalian multi-lineage cellular growth factor activity and/or mammalian mast cell growth factor activity.

29. A polypeptide exhibiting mammalian multi-cellular growth factor activity and/or human mast cell growth factor activity, whose DNA coding sequence is capable of hybridizing with DNA coding for murine IL-3 and is at least 75% homologous thereto.

30. A polypeptide as claimed in any of Claims 11, 12 and 29

that is capable of acting on a hematopoietic cell line.

31. Recombinant mammalian IL-3 substantially free of other mammalian proteins.

32. Recombinant murine IL-3 substantially free of other murine proteins.

At the hearing Mr Ritter impressed upon me the need to give full weight to the arguments raised by the applicants in the considerable correspondence on the case and to this extent did not forward any substantially new arguments, except in respect of the allowability of the process claims. This matter and those emphasised by Mr Ritter are addressed along with the other matters in the statement below.

As a starting point the Agents letter of 10 December 1987 is to my mind most helpful. Following extensive correspondence this letter categorises the outstanding objections raised by the Examiner and these objections were the ones to be resolved at the date of the hearing. The objections are listed under four categories, (1) lack of Novelty, (2) Obviousness, (3) Breadth of Claim and (4) Miscellaneous, and whilst I could deal with each one in turn I have decided to adopt a slightly different approach to take account of the recent and significant precedent case in the area of recombinant DNA technology namely Genentech Inc's Patent [1987]RPC 553. The Examiner has relied very heavily on this precedent in attacking the majority of the claims of the application but Mr Ritter sought to persuade me at the hearing that since there was an appeal lodged against that decision I ought not to regard it as a binding precedent. Whether that be correct or not, in the absence of any authority it seems to me only right that I should follow the reasoning of that decision if it is applicable to the facts of the present case, it being a decision of a higher court.

I note that in the Genentech case some doubt was raised as to

whether the judge ought to be considering Section 14(5) allegations in a Section 72(1) revocation action and that this may well be a ground of appeal. However in pre-grant hearings before the Office it is beyond doubt that Section 14(5) matters may be raised and so whatever the outcome of the appeal in this particular area I am not precluded from considering the Section 14(5) arguments used by the learned judge in coming to his decision.

As I have indicated above I must first of all consider whether the circumstances of the Genentech case and the present case are such that I should apply the reasoning in that case. If I decide that they are I can then go on to decide which claims are bad on the basis of the Genentech decision. In doing so I will have dealt with objections under categories 1, 2 and 3 referred to in the Agents letter but I shall need to return to a further objection under category 3, namely the reference in several of the claims to the 75% homology feature.

The Genentech case deals with a polypeptide known as t-PA which is an effective agent in the control of blood clotting. It stands admitted that at the priority date of the patent t-PA was a known, naturally occurring substance having known properties, and that the quantity production of t-PA was likely to bring considerable financial rewards to anyone who could establish a monopoly position. In order to achieve quantity production Genentech had turned to recombinant DNA technology and in doing so had discovered the DNA sequence and deduced amino acid sequence of t-PA. It was this discovery that formed the basis of their invention but as was affirmed by Whitford J it is trite law that a discovery cannot be patented. If, however on the basis of that discovery an applicant can show how it may be usefully employed a patentable invention may result. All this is clear from lines 8 to 14 on page 566 of the decision.

Turning to the present case there is no doubt, as I expressed earlier, that at the priority date IL-3 was a known, naturally

occurring substance having known properties i.e. the properties of exhibiting MCGF activity and multi-CSF activity. Although lines 17 to 20 on page 5 of the application appear to indicate that the precise relationship of IL-3 with multi-CSF has been unclear I do not take this to mean that there is doubt about its multi-CSF activity and in support of this I have relied on lines 3 to 12 on page 10 of the application where, by reference to journal articles, it is clearly stated that mouse IL-3 has been shown to exhibit mouse MCGF activity and multi-CSF activity.

Like Genentech, the present applicants have turned to recombinant DNA technology for volume production of a known polypeptide and the discovery of the DNA sequence and deduced amino acid sequence of IL-3 forms the basis of their invention. That being the case I am of the opinion that I can apply similar considerations to those of Whitford J in deciding the allowability of the claims in the present application.

Before addressing myself to the claims of the present application I propose to refer to the Genentech decision to pick out what I consider to be the underlying arguments which led Whitford J to reject the broad claims in that case. After referring to several precedent cases we find this at lines 17 to 33 on page 594:

> "Had Genentech first discovered t-PA, or had they at least been the first to discover its desirable properties as an activator, they having shown the way in which it could be produced by use of recombinant DNA technology might well have been entitled to a broad claim covering the biologically active forms when produced either by the recombinant DNA technology described in the specification or any other recombinant DNA technology.
>
> Claim 3 is a claim to a known product, t-PA and indeed its constituent amino acids were known, if not their sequence, made by any process involving recombinant DNA technology. Only one such route is particularly dealt with in the

patent. Two other routes at the probing stage, though rejected by Genentech on the evidence as being unworkable, are still covered by claim 3.

As a claim to a product, t-PA produced by any known or hereafter discovered route in the field of recombinant DNA technology, is too wide and is bad. There is no basis for it and again, if that were not an objection that is open, the directions outside the particular route followed in the patent must be wholly insufficient. It is a claim to an obviously desirable and potentially possible end reached by routes on which only limited guidance is given."

Then at lines 14 to 31 on page 596:-

"Though it was obvious that recombinant DNA technology might provide a route to the production of t-PA, apparent from the fact that at least five teams embarked upon research headed in this direction, success was not certain. What Genentech did was achieved by what, in my judgement, was rather more than the exercise of proficiency; it involved laborious and costly effort and to deny any monopoly protection to those who are prepared to put as much time, skill and money into research as Genentech did is only too likely to discourage workers in the field from making advances which may be of the greatest public benefit.

Had Genentech, as workers in the field may do, developed some totally new product, they would have been entitled to a monopoly on the product, whatever its process of production. Had they produced some new and valuable variant of t-PA, they might have got protection on that. What they did by way of invention, however, was to discover a particular route to a known end, and to grant them a monopoly which would stop others attempting to discover alternative, possibly wholly unknown and possibly better routes to that end, would be to stifle research which, in the public

interest, it ought to be open to other investigators to pursue and over which other investigators in their turn, if they make valuable contributions might be able to secure better protection."

If I am right in concluding that these are the underlying arguments to be adopted in cases of this type, and I have already indicated that I regard the present application to be of the same type as the Genentech case, then I am not convinced that the largely technical distinctions drawn by the applicants on pages 2 to 5 of their Agents letter of 10 December 1987 are relevant in coming to my decision. It seems to me that in the Genentech case the judge after considering a great deal of technical evidence nevertheless came to his decision out of the background of well-established patent principles and it is reasonable for me to apply those same principles to the present application. Thus, if there is similarity between the form of the claims and the facts in the present application and those in Genentech it is appropriate for me to reject them for the same reasons as given in that case.

Turning now to the claims, these may be broken down into 4 categories, (i) those relating to IL-3 in the form of a polypeptide, (ii) those relating to a nucleic acid sequence or a recombinant DNA molecule, (iii) those relating to a process of preparing IL-3 and (iv) those relating to other matters and I propose to take each category in turn.

i) Polypeptide claims

Specifically these are claims 11, 12, 27 and 29 to 32. Taking claims 31 and 32 first these clearly are on all fours with claim 1 of the Genentech patent and are rejected as being too broad for the reasons given in that case. Claims 11 and 12 are essentially claims to IL-3 with reference to its amino acid sequence encoded by a specific nucleic acid sequence or to its amino acid sequence per se. In so far as IL-3 is a known polypeptide these claims

must be rejected on the grounds that they relate simply to the discovery which underlies any invention contained in the application, namely, the sequence data, and not to how that discovery is employed.

Claims 27, 29 and 30 would be acceptable if the applicants had been the first to discover IL-3 or its desirable properties. In so far as they did not the claims are judged to be too broad and are rejected for the reasons quoted on page 594 of the Genentech decision.

ii) Nucleic acid sequence or recombinant DNA claims

Specifically these are claims 13 to 18 and 28. These claims are based on the discovery of the DNA sequence encoding the polypeptide IL-3 and again, in so far as IL-3 was a known compound of known properties at the priority date, must be rejected. It is clear in recombinant DNA technology that DNA sequences and amino acid sequences are, as it were, different sides of the same coin and even though in the Genentech case there were no claims directed to the DNA encoding t-PA I am in no doubt that if there had been these would have been rejected on the basis of Whitford J's remarks at lines 8 to 16 on page 566.

iii) Claims to the process of preparing IL-3

Claim 1 is the main process claims relating to the preparation of IL-3 and in essence relates to the well known steps of preparing a polypeptide by recombinant DNA technology wherein genetic information in the form of a nucleotide sequence coding for the peptide is integrated into a vector, which is frequently a plasmid or bacteriophage, the vector is incorporated into a host which is a prokaryotic or eukaryotic cell according to the vector used, and the host is maintained under conditions suitable for expression of the nucleotide sequence into the polypeptide. As in the case of the claims to the polypeptide per se, the distinguishing feature of claim 1 relative to the prior art is

the discovery of the amino acid sequence data of IL-3.

There was a time during the examination proceedings when the Examiner regarded claim 1 and the claims dependent thereto as allowable claims but just prior to the Hearing in a telephone conversation dated 23 March 1988 he informed Mr Ritter that objection on the basis of the Genentech decision would be raised against them as being unduly broad in scope.

At the Hearing Mr Ritter questioned whether the subject of the allowability of the process claims in the Genentech patent had been fully addressed by Whitford J in his decision. As I understood Mr Ritter it was his argument that when the learned judge referred to the invalidity of the "broad" claims in that case he was referring to the product claims and not the process claims. Indeed on the basis of the passage at lines 19 to 25 on page 591 of the decision he submitted that there was scope for claims based upon the use of the full sequence information. When it came to be considered as to what was meant by 'broad' claims, said Mr Ritter, it was clear that from the headnote to the decision at page 554, only claims 1, 2 and 3 were intended.

I have fully considered these points and as I told Mr Ritter at the Hearing I cannot agree that his line of argument is the one that I should accept as being correct.

In the Genentech decision the claims being considered in that case, including the process claims numbered 16 to 20, are set out on pages 575 to 576 and there follows a brief summary of the content of each claims until at line 10 on page 577 there is this statement:-

> "The question is, are these claims valid? In my view the majority of them are plainly invalid."

Clearly at this stage of the decision the learned judge was on his way to rejecting most of the claims but whether he was to

include the process claims in this rejection was yet to be made apparent.

The next part of the decision that I find helpful in deciding the validity of the process claims is at lines 19 to 25 on page 591. These read as follows:-

> "I shall start by assuming that there was in truth scope for a claim to a process based upon the use of the full sequence information, as first disclosed by Genentech, and by no means arrived at by a straight forward application of what was obviously the best route to the end which they were seeking to reach, that at the least there might have been scope for a limited process claim (my underlining). I turn to the question as to whether that could justify the broad claims which we find in this patent and, as I have already indicated, in my view it cannot."

In the context I take this to mean that Whitford J was not prepared to allow the broad process claims of Genentech but was prepared to allow a limited process claims based on the route followed by them and I am encouraged in this thinking by what follows later in the decision in the passages on pages 594 and 596 which I have quoted previously, but more particularly by the passage at lines 34 to 37 on page 594 which reads:-

> "The objection to these broad claims, claims 1 and 3, follows through so far as all the broad claims of the patent are concerned and, in consequence, I have reached the conclusion that none of the claims, other than claim 9 and the claims dependent thereon can be supported." (my underlining)

Thus on the basis of these passages I am certain that Whitford J was of a mind to reject all the broad claims of the Genentech patent and not just claims 1 to 3. Indeed it is clear to me that he allowed only claim 9 which is for two specific plasmids used

in the process, and the claim dependent thereon. That being the case I find that claims 1 of the present application stands rejected as do claims 2 to 10 which are dependent thereon and relate to features which are conventional in recombinant DNA technology or at best have as their distinguishing features the discovery of the sequences leading to the application being made. Claim 25 is an independent process claim and this too is rejected on the same grounds as my rejection of claims 1 to 10.

iv) Other claims

Remaining for decision are claims 19 to 24 and 26 and I propose to deal with these briefly. Claims 19 and 20 are broad claims to vectors consisting of the sequences which form the discovery of the present application and claim 21 is a claim to microorganism or cell transformed or transfected with these vectors. Claim 26 is an independent claim to a transformed organism or cell which contains a gene or other DNA sequence coding for one or more polypeptides having mammalian multi-lineage cellular growth factor activity and/or mammalian mast cell growth factor activity. There is a distinct similarity between these claims and claims 7, 8 and 10 of the Genentech patent and therefore I have no hesitation in rejecting them as broad claims for the reasons advanced in that decision.

Claim 22 is a typical pharmaceutical composition - type claim, the composition in this case consisting of the polypeptide of claim 11 or claim 12 and a therapeutically compatible carrier. Having already rejected claims 11 and 12 the mere presence of a carrier brings nothing inventive to claim 22 and therefore in a manner similar to the rejection of clause 13, 14 and 15 in the Genentech case I reject this claim also.

Finally, having regard to claims 23 and 24 the Examiner in the minute of his telephone conversation with Mr Ritter of 3 March 1988 has raised objections of lack of clarity and support and in respect of claim 23 exclusion from patentability under Section

4(2) of the Act. Claim 23 relates to a process of enhancing cell growth comprising contacting a cell with the polypeptide of claims 11 or claims 12 that has a substantial portion of the amino acid sequence of Figure 1 and claim 24 defines that process as being enhanced in vitro. I support the Examiner in these objections and in so far as claims 23 and 24 go to the activity of recombinant IL-3, which activity is known by comparison with that of naturally occurring IL-3, can see no inventive step in the process of these claims.

Although I have at this stage rejected all the claims, mainly on the basis of the Genentech decision, I must come back to what I called earlier the 75% homology feature which occurs in claims 1, 11, 13, 16, 28(b) and 29 of the application.

This feature which occurs largely as a result of an objection raised in paragraph 7 of the Official letter of 15 August 1986 and is based, as far as I can see, on pages 18 to 21 of the application, particularly lines 14 to 15 on page 21, has the effect for the applicants of broadening the claims beyond the single DNA or amino acid sequence described by them. The Agents in their letter of 10 December 1987 have argued that this is a reasonable thing to do for the reason that it would be facile for a competitor to avoid textual infringement by using a vector containing a nucleotide sequence which does not match precisely to one specified in the present application. They further argue that a competitor would know from his own experience that variations in sequence would still be likely to be expressed as polypeptide having multi-CSF activity and the specification itself would tell him that such variant sequences are encompassed by the invention.

It is becoming common in applications relating to recombinant DNA technology to allow claims to nucleotide sequences which are equivalent to the one disclosed by the applicant by virtue of the degeneracy of the genetic code and amendment along these lines was offered to the applicants in the Official Letter of

12 February 1988 and repeated in the telephone report dated 3 March 1988. Clearly however this is not the amendment the applicants are looking for and they have maintained their right to have the 75% feature in the claims.

I have given considerable thought to the allowability of this feature and have come to the conclusion that it should not be allowed. The applicants have made only one disclosure of a nucleotide sequence encoding for IL-3 and have not identified the "active site" which exhibits MCGF or CSF activity. The effect of allowing claims to not only this sequence but to others having at least 75% homology thereto would seem to me to admit a vast number of sequences not explored by the applicants albeit that those sequences would have to encode a polypeptide exhibiting mammalian multi-lineage cellular growth factor activity. It is well known in recombinant DNA technology that the "active site" of a polypeptide may be confined to only a short amino acid sequence of the entire pe ptide chain and had the applicants discovered that active site I might well have been disposed to allow a feature of less than 100% homology in suitable claims. However what they have discovered is the entire sequence of IL-3 and therefore to extend the claims in the manner they desire seems to me to be in the nature of a fishing exercise to draw in other sequences which in themselves may be inventive and therefore the subject of legitimate applications by competitors.

I am further not prepared to countenance the view of Mr Ritter at the interview with the Examiner on 2 March 1988 that the situation is analogous to chemical cases wherein claims are allowed to a wide range of compounds on the basis of only a small number within that range actually being synthesised. It seems to me that if only one compound was synthesised a similar objection to the one raised by the Examiner in this case might result. Even if that were not the situation I consider it to be extremely dangerous to make comparisons between the purely chemical and the more recent and somethat more unpredictable, recombinant DNA arts.

Furthermore I am not convinced that the 75% homology figure is one that can be supported on purely numerical grounds by reference to the description. I say this because the passage which the applicants are relying upon for support lies at lines 9 to 15 on page 21 and refers to technical features of the invention which may well give support to a step in a process claim but not to the definition of a nucleotide sequence in the manner intended by the applicants. The passage on page 21 reads as follows:

> "DNA clones of rodent genes have been used to identify and isolate DNA encoding the homologous human genes. Because of the relatively low degree of homology between human and rodent genes, the stringency of hybridization conditions must be adjusted to allow for cross-hybridization between sequences which are only 75-80% homologous."

and what this passage, together with the following description appears to be describing is how, given that one has a DNA clone of a rodent gene coding for IL-3, a man skilled in the art would be able to probe a human cDNA library to isolate the human multi-CSF cDNA clone. I note though that the only sequence particularly described by the applicants in the application is that in Figure 1 which as I observed earlier is a mouse cDNA sequence. This then is what the applicants have done and I therefore do not think it reasonable for them to isolate the above passage to provide support for a lot of things they have not done. It is my decision therefore that the 75% homology feature should not be allowed to remain in the claims.

To sum up I am of the opinion that largely for the reasons expressed in the Genentech decision, all the claims of the application are either not novel or inventive or are not supported by the description. In addition the 75% homology feature in claims 1, 11,13, 16, 28(b) and 29 is not supported by the description and in my opinion should be deleted.

These are the reasons for my decision to refuse the application on 28 March 1988.

Dated this 18 day of May 1988.

D L WOOD
Principal Examiner, acting for the Comptroller