EXHIBIT 3

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IN THE HIGH COURT OF JUSTICE
CHANCERY DIVISION
PATENTS COURT

Royal Courts of Justice
Strand, London, WC2A 2LL

Date: 11th April 2001

Before:

THE HONOURABLE MR JUSTICE NEUBERGER

CH 1993 -K-No. 937
CH 1993-B-No.4552

In the matter of European Patents (UK) Nos. 148,605 and 411,678 and in the matter of actions for infringement and counterclaims for revocation thereof by inter alia Kirin-Amgen Incorporated, Janssen-Cilag Limited and Roche Diagnostics GmbH

HC 1999 No. 02916
HC 1999 No. 02917
HC 1999 No. 03241

In the matter of European Patents (UK) Nos. 148,605 and in the matter of a claim for revocation and for a declaration of non-infringement thereof by inter alia Transkaryotic Therapies Inc. and an action for infringement by inter alia Kirin-Amgen Inc.

Mr Anthony Watson QC, Mr Andrew Waugh QC and **Mr Colin Birss** (instructed by Messrs. Taylor Joynson Garrett) appeared on behalf of the Amgen parties.

Mr Simon Thorley QC, Mr Michael Tappin and **Miss Iona Berkeley** (instructed by Messrs. Herbert Smith) appeared on behalf of the Roche Parties.

Mr David Kitchin QC and **Mr Richard Meade** (instructed by Messrs. Bird & Bird) appeared on behalf of the TKT parties.

JUDGMENT
(As approved by the Court)

This is an approved judgment of the Court and I direct that no further note or transcript be made.

The Honourable Mr. Justice Neuberger

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

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

The procedural history

184. As I have mentioned, the application for the grant of 605, which I shall call 605A, was filed on 12th December 1984 at the European Patent Office. In its original form, which I shall call 605B, the patent was granted on 25th July 1990. It was then subject to opposition proceedings which came before the Technical Board of Appeal ("the Board") who gave a decision on, as I have mentioned, 21st November 1994. As is not unusual, some changes were made between filing and initial grant, and other changes were made as a result of the arguments before, and the decision of, the Board.

185. There are three significant differences between (i) the application for the grant of 605, namely 605A and/or the patent granted in its original form, 605B, before the hearing before the Board, and (ii) 605 in its present form. First, there is a paragraph contained in Example 10, which was subsequently deleted. Then there are two relevant amendments to the Claims.

186. The paragraph which was included in Example 10 in 605A and 605B, but was not followed through into the patent in its present form, namely 605, is to be found immediately after the first paragraph, and immediately before the second paragraph, of Example 10 in the passage I have quoted from earlier in this Judgment. The paragraph in question which was deleted (and which I shall refer to as "the deleted matter") was on page 65 of 605A (and on page 29 of 605B). It was in these terms:

"Purified human urinary EPO and a recombinant, CHO cell-purified, EPO according to the invention were subjected to carbohydrate analysis according to the procedure of Ledeen, et al. *Methods in Enzymology*, 83 (Part D), 139-191 (1982) as modified through use of the hydrolysis procedures of Nesser, et al., *Anal.Biochem.*, 142, 58-67 (1984). Experimentally determined carbohydrate constitution values (expressed as molar ratios of carbohydrate in the product) for the urinary isolate were as follows: Hexoses, 1.73; N-acetylglucosamine, 1; N-acetylneuraminic acid, 0.93; Fucose, O; and N-acetylgalactosamine, O. Corresponding values for the recombinant product (derived from CHO pDSVL-gHuEPO 3-day culture media at 100 nM MTX) were as follows: Hexoses, 15.09; N-acetylglucosamine, 1; N-acetylneuraminic acid, 0.998; Fucose, O; and N-acetylgalactosamine, O. These findings are consistent with the Western blot and SDS-PAGE analysis described above."

187. The second significant difference is to be found in Claim 3. In 605A, Claim 3 is in these terms:

"A polypeptide according to Claim 1 [which was in fairly similar terms to Claim 1 of 605] wherein the exogenous DNA sequence is a cDNA sequence."

In 605B Claim 3 was to:

"A cDNA sequence according to Claims 1 [which was in fairly similar terms to Claim 1 of 605] or 2 [which was a claim to a DNA sequence within Claim 1 encoding for human EPO]."

188. The third significant difference is between 605B and 605. In 605B Claim 20 on page 37 was the equivalent of Claim 19 in 605. While it differed from Claim 19 in a number of respects, the only relevant feature was that, unlike Claim 19, it

patent as originally granted. Accordingly, references in this part of the judgment to 605A also extend to 605B .

573. As I have explained, when construing Claim 19, it appears to me that, particularly when one reads the Claim through the eyes of the appropriately skilled man, the requirement, that the rEPO has "higher molecular weight by SDS-PAGE" than uEPO, is satisfied if, on SDS-PAGE, the uEPO band, viewed as a whole, runs ahead of the rEPO band, even if there is a substantial degree of overlap between the two bands. Mr Thorley on behalf of Roche (with the support of Mr Kitchin on behalf of TKT) contends that, with the benefit of the deleted matter in Example 10 in 605A, the skilled addressee would have read the patent as indicating a much more substantial difference between the respective apparent molecular weights by SDS-PAGE of uEPO and rEPO, so that, in particular, he would expect there to be no overlap between the bands. In other words, with the benefit of the deleted matter in Example 10, he would expect the uEPO band to be running so much faster than the rEPO band that there would be no overlap between the trailing edge of the uEPO band and the leading edge of the rEPO band.

574. This argument is entirely based on the proposition that the skilled man, reading 605A, and in particular the deleted matter in Example 10, would appreciate that the high hexose ratio reported for rEPO, when compared with that reported for uEPO (namely 15.09 against 1.73), meant that there was a substantial difference in the actual, and therefore the apparent, respective molecular weights of rEPO and uEPO. This would have been on the basis that they would both have the same amino acid sequence (and therefore the same "bare" protein molecular weight) but the rEPO would be, to put it simply, more heavily glycosylated, and hence would have a much higher molecular weight.

575. In my judgment, the argument that 605 is invalid on the grounds of added matter should be rejected. I consider that the appropriately skilled team (and in particular the post doctoral biochemist with experience of glycoproteins) would have appreciated that the analysis reported in the deleted matter was inaccurate. The

suggestion of a hexose ratio of 15.9 (using the N-acetylglucosamine - GlcNAc - as the base 1 level) for rEPO would have been far too high to be believable. In this connection, the evidence of the expert witnesses was virtually unanimous. In the US proceedings, Dr Fritsch described "the carbohydrate composition" described in the deleted matter as "plainly inaccurate". In his evidence before me, Dr Robbins said that one "could really give... no weight at all" to what was reported in the deleted matter. He also confirmed what he said in his deposition in the US proceedings, namely that "any person of ordinary skill in the art of glycobiology in 1984 would understand [the information in the deleted matter] to be grossly inaccurate". Professor Cummings stated that he thought that he "would have probably found it difficult to convince anybody in the field, who [had] analysed glycoproteins, that [he] had found one [sc. a glycoprotein] that had that ratio [sc. namely hexose 15.09] even if I had repeated the analyses". Professor Clausen said that he would have been highly suspicious of the 15.09 figure, and I infer from his evidence that he would not have given the contents of the deleted matter any significant weight. Accordingly, at least if the notional addressee is to be equated with any or all of these witnesses, he would not have believed this figure, and would therefore have effectively discounted the results contained in the deleted matter.

576. However, Mr Thorley contends that Dr Fritsch, Professor Robbins, Professor Cummings and Professor Clausen were substantially more skilled, and indeed more specialised in the field of glycosylation of proteins, than any member of the notional team of ordinarily skilled people to whom 605 would have been addressed. He suggests that the notionally skilled team of addressees would not have included someone sufficiently well informed about glycoproteins in 1984 to take this view. He draws support from what was said by Professor Clausen and by Professor Cummings, and also by the reaction of those working for Amgen who commissioned and reported on the work which resulted in the information contained in the deleted matter. Professor Clausen said that he would have had problems with the deleted matter because, as at 1984, he had had two years of training in the world's best carbohydrate laboratory, but he would not expect

someone with experience in cell biology, as opposed to an expert in carbohydrate biochemistry, to spot the difference. Professor Cummings accepted that expression of proteins in mammalian cells was in its infancy in 1984 and the kind of glycans that one might see on proteins was unpredictable and had not been the subject of substantial publication. It also is apparent from Amgen's disclosure that none of the people working for Amgen on this project, including Dr Yu, who was accepted by Professor Cummings as a "reasonably respectable carbohydrate chemist", and who performed the analysis which resulted in the information in the deleted matter, raised any question about the 15.09 hexose figure.

577. These points all have force, but in the end I am not persuaded by them. Resolving an argument as to whether or not the notional skilled team includes someone with a particular expertise is difficult, not least because most of the arguments appear to me to involve a degree of circularity. In my judgment, one of the members of the notional team to whom 605 was addressed would have had sufficient knowledge of glycoproteins to have serious concerns about the accuracy of the contents of the deleted matter, and that concern would have been sufficiently great to discount its effect. There is no reason to think that Dr Yu, who carried out, and reported to Amgen on, the experiments which resulted in the information contained in the deleted matter, was asked to advise on or consider, the effect of the evidence that he apparently obtained.

578. In any event, it appears to me that Roche's argument on added matter faces a number of difficulties. First, subject to one possible point, such a high figure as 15.09 for hexose ratio in rEPO (compared with the unexceptionable level of 1.73 in the case of uEPO) would have resulted in the rEPO having a much larger molecular weight than the uEPO. Professor Cummings estimated that such a high hexose level would roughly double what would otherwise be the molecular weight of the EPO: he said it would increase it by over 30kDa; this can be compared to its actual molecular weight of around 36 kDa. Yet at the end of the immediately preceding paragraph of 605A the rEPO is described as having a "slightly larger" molecular weight than the uEPO. Mr Thorley's argument involves assuming that,

while the addressee of 605A will not be sufficiently skilled in glycosylation of proteins to appreciate that the deleted matter is inaccurate, he will be sufficiently skilled in glycosylation of proteins to appreciate that the reported hexose ratio of 15.09 means that rEPO has a substantially greater molecular weight than uEPO, as otherwise he will merely note what is in the preceding passage, and conclude that the difference in apparent molecular weight is not very great. In my view, Mr Thorley's argument therefore faces a squeeze. If the addressee is sufficiently well informed to appreciate that the figure of 15.09 in the deleted matter results in rEPO having a very much higher molecular weight, then he will also have sufficient knowledge to appreciate from his general knowledge and from the previous paragraph that the figure is unreliable. On the other hand, if he does not appreciate that the figure is unreliable, he will not be sufficiently skilled to appreciate that the 15.09 means that rEPO has a much higher molecular weight than uEPO, and will therefore rely on the reference to the difference being "slight". I do not think that Mr Thorley's argument is sustainable in light of this squeeze. In any event, as I have indicated, it appears to me that this notional addressee will appreciate the inaccuracy of the contents of the deleted matter.

579. Quite apart from this, even if Mr Thorley's argument can avoid this "squeeze", and the addressee thinks that the deleted matter results in rEPO having a substantially higher molecular weight than uEPO, he will appreciate that there is a clear inconsistency between the two successive paragraphs of Example 10 in 605A. The first expressly states that there is a "slight" difference between the two molecular weights, whereas the second merely implies that there is a large difference between the two molecular weights. Faced with an inconsistency between express and an implied teaching, I would have thought that the reader would either assume that the express teaching is correct, or would regard both statements as being unreliable for obvious reasons. Whichever view he took, the deleted matter could not affect his interpretation of Claim 19.

580. That is not the end of the difficulties faced by Roche in its added matter argument. First, it appears to me that the whole basis of the argument falls foul of