

Exhibit 6

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Genetics Institute

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of document # ↗

January 16, 1984

Dr. R. Sadahiro
Deputy Senior Manager
Ethical Product Planning Dept.
R&D Division
Chugai Pharmaceutical Co. Ltd.
1-9, Kyobashi 2-chome, Chuo-ku
Tokyo 104
JAPAN

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Dear Dr. Sadahiro,

After receiving your telex of January 11, 1984, we had a serious discussion among the management and scientific staff at Genetics Institute. We came to the conclusion that although we missed the chance to be the first one to clone EPO, we will continue to pursue this project aggressively, for the following two major reasons:

- (1) The patent situation

First we do not know whether patents on naturally-occurring proteins will withstand judicial scrutiny. There are many other incidences that we are not detained from our research work just because other people have cloned the proteins first. One such example is tissue plasminogen activator.

If necessary, we believe that we will be able to modify the protein to make it non-infringing through protein engineering. With the fast pace of technological advancement and our continuing development of proprietary

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Boston, Massachusetts 02115
Telephone 617 232-6886
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know-how, we believe that our chance of developing a proprietary product is extremely high, although there can be no assurance.

In addition, from our experience, it will be several months to a year before we see the technical publication of Amgen's work on EPO if they choose to publish it. It may take several years before the content of the patent is known. Valuable time could be lost if we wait until all the facts are known.

2) Development of commercializable product

It is our business strategy to be among the front runners in all the product areas we choose to work on. Cloning is only part of the research work needed to develop a therapeutic protein drug. Expression, scale-up, process development and purification are all important steps for successful product development. Genetics Institute already has extensive experience in these ~~mid-stream and downstream~~ developmental ~~works~~ technologies.

yeast?

Since EPO is a heavily glycosylated protein, mammalian expression system may be the choice for the production of therapeutically useful EPO. We have a very strong mammalian expression team, which has successfully expressed glycosylated proteins in high yields (50-100 mg/l). Because of these existing in-house technologies, we believe we

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still have a good chance to introduce a EPO product *(at)*
the marketplace ahead of Amgen together with our partners.

Regarding to the specific points in your telex, I have reviewed it with Dr. Fritsch and the management staffs of GI.

Following are Dr. Fritsch's answers:

- 1) To clone EPO Amgen used new sequence information obtained from tryptic fragments of EPO obtained from ^{Dr.}Goldwasser. They also claim to use novel hybridization technology which allowed them to use oligos of high degeneracy. We are using nucleic acid technology which has the same sensitivity. We are currently in the process of purifying more protein. We hope to purify enough to get additional N-terminal sequence and potentially some internal sequence.

We are uncertain as to whether they obtained a baboonⁿ cDNA or a human genomic DNA clone first - we have heard conflicting reports. However, with this information they can certainly predict the human cDNA sequence and synthesize it easily.

- 2) If Amgen obtained a genomic clone first using synthetic oligonucleotides then our approaches could be similar. Whether they are or not depends on the exact nucleic

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acid technology used and the description in the patent. However, our use of a human kidney carcinoma cell line as a source of EPO RNA is different and outside the scope of a process patent which they could file.

- 3) If the Amgen patent holds, the only alternative to commercialization without conflict would be, to try to make a modified EPO with superior properties. Thus we could try to do base specific mutagenesis to change the primary amino acid sequence of EPO and change properties such as stability, antigenicity, or efficacy. This would be a major research effort. However, we suspect the Amgen patent will not present a problem since it is a natural product.
- 4) We have filed no patent on our cloning process for EPO. A patent has been filed on the cell line by the investigator ^(my consultant) who developed it. The original application was rejected but is being considered for refiling.
- 5) It is unlikely Amgen would give license to GI.

Enclosed please find a copy of the announcement made by Amgen and a news report from McGraw-Hill's Biotechnology Newswatch. As you may already be aware, in the biotechnology race there are

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usually many runners going after the same goal. Amgen may be the front runner at this moment, the goal is still miles away and the race far from finished. We sincerely hope Chugai will join us in this race.

Sincerely yours,

Man-chui Yang

enclosure

cc: G. Schmergel

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