Zürich, 05/10/92

Dr. Reinhold Kiehl Research Department Spezialklinik Neukirchen Krankenhausstr. 9 DW-8497 NEUKIRCHEN Fed. Rep. Germany

Reference no.: 92-0998

Transport and ATP synthesis in mitochondria 1. I. Evidence for mitochondrial 2,4-dinitrophenol accumulation across the Pi/H+-symport system

Kiehl Reinhold

Reference no.: 92-0999

Transport and ATP synthesis in mitochondria 1. II. Glutathione and endogenous regulatory factor for mitochondrial phosphate/proton symport

Kiehl Reinhold,

Reference no.: 92-1073

Transport and ATP synthesis in mitochondria 1. III. Hypothesis: mitochondrial ATP synthesis of the phosphate/proton symport system with oxidized glutathione as catalyst

Kiehl Reinhold

Editor: Böck

Dear Dr. Kiehl,

Your letter of 09/09/92 was sent to the previous referees. Based upon their negative comments, the Editor has decided to maintain his decision to reject your manuscripts.

Yours sincerely,

Dr. John W. Aitken Editorial manager

Editorial Office:

Apollostrasse 2, Postfach

Tel.: + 41 1 383 00 02 CH-8032 Zürich, Switzerland Fax: + 41 1 383 07 16

PRIVATKLINIK ZUR BEHANDLUNG ALLERGISCHER UND DEGENERATIVER ERKRANKUNGEN GmbH & Co KG Mcd.Leitung: Johannes Müller-Steinwachs, Hautarzt

Spezialklinik Neukirchen - Krankenhauster, 9 - 8497 Neukirchen b. Hl. Blut

Telefon: 09947/28-0 Telefax: 09947/28109 IK: 260 930 595

Prof. Ph. Christen Editorial Office, Eur. J. Biochem. Apollostr. 2 Postfach A 152 8032 Zürich

SCHWEIZ

Unser Zeichen

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Datum

09.10.92

Ref. no.: 92-0998, 92-0999 and 92-1073; my letter dated 9/9/92; letter dated 5/10/92 by Dr. J.W. Aitken

Dear Prof. Christen,

I just got a letter from Dr. J.W. Aitken, dated 5/10/92, concerning my manuscripts (92-0998, 92-0999 and 92-1073) - see

enclosed copy.

He writes that my letter of 9/9/92 was sent to the previous referees!! I don't think that this procedure is the right way to solve the problems I discussed in my letter dated 9/9/92 to you: By this way there is no possibility to obtain neutral comments! As you may have seen without any difficulty my letter is aggressive because I was understandably very angry. It is therefore quite clear, that the referees alone on this reason may have repeated their negative comments (the new comments were missing in Dr. Aitken's letter of 5/10/92).

What is the best way to resolve this dispute? The easiest way is to reject the manuscripts - as I discussed to you in my letter of 9/9/92. The other way would be your decision to publish the manuscripts since there ist no methodical or other mistake in these papers present. To find a neutral referee should be very difficult (may be Hatefi, Hanstein, Lardy, etc. were positive referees).

Yours sincerely

Dr. R. Kiehl

Enclosure

Bankverbindung: Raiffeisenbank Neukirden b. Hl. Blue (BLZ 750 691 10) Kto.-Nr. 977 163

Zürich, 15/10/92

Dr. Reinhold Kiehl Research Department Spezialklinik Neukirchen Krankenhausstr. 9 DW-8497 NEUKIRCHEN Fed. Rep. Germany

Reference no.: 92-0998

Transport and ATP synthesis in mitochondria 1 I. Evidence for mitochondrial 2,4-dinitrophenol accumulation across the Pi/H+-symport system

Kiehl Reinhold

Reference no.: 92-0999

Transport and ATP synthesis in mitochondria 1 II. Glutathione and endogenous regulatory factor for mitochondrial phosphate/proton symport

Kiehl Reinhold,

Reference no.: 92-1073

Transport and ATP synthesis in mitochondria 1 III. Hypothesis: mitochondrial ATP synthesis of the phosphate/proton symport system with oxidized glutathione as catalyst

Kiehl Reinhold

Editor: Böck

Dear Dr. Kiehl,

Your letters of 09/10/92 and 13/10/92 were passed on to the Editor.

He wishes to inform you that it is not possible to change the referees in order to obtain a positive response. Since they were unanimous in their advice to reject your manuscripts, the Editor does not intend to change his original decision.

Yours sincerely,

Dr. John W. Aitken Editorial manager

Copy: Editor

Editorial Office:

Apollostrasse 2, Postfach CH-8032 Zürich, Switzerland Tel.: + 41 1 383 00 02 Fax: + 41 1 383 07 16

PRIVATKLINIK ZUR BEHANDLUNG ALLERGISCHER UND DEGENERATIVER ERKRANKUNGEN GmbH & Co KG Med.Leitung: Johannes Hüller-Steinwachs, Hautarzt

Speziałklinik Neukirchen · Krankenhausstr. 9 · 8497 Neukirchen b. Hl. Blut

Telefon: 09947/28-0 Telefax: 09947/28109 IK: 260 930 595

Prof. Ph. Christen Dr. J. W. Aitken Apollostr. 2 Postfach A 152 8032 Zürich

SCHWEIZ

Unser Zeichen

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Datum

22.10.92

Ref.No.: 92-0998, 92-0999 and 92-1073; your letter of 15/10/92

Dear Prof. Christen, dear Dr. Aitken,

I just got your letter. I am still missing the new negative comments of the referees in your letter dated 5/10/92 in answer to my letter of 9/9/92.

to my letter of 9/9/92. It would be very nice to get comments of the referees to my telefax and letter of 14/10/92.

I don't want other referees: I just like to get correct responses to my manuscripts and letters. This manuscripts contain in the end the results out of some years experimentations.

If you think that it would be helpful in this matter to speak to the Editor in München please let me know.

Yours sincerely

Dr. R. Kiehl

Zürich, 26.10.92

Dr. Reinhold Kiehl Research Department Spezialklinik Neukirchen Krankenhausstr. 9 DW-8497 NEUKIRCHEN Fed. Rep. Germany

Reference no.: 92-0998

Transport and ATP synthesis in mitochondria 1 I. Evidence for mitochondrial 2,4-dinitrophenol accumulation across the Pi/H+-symport system

Kiehl Reinhold

Reference no.: 92-0999

Transport and ATP synthesis in mitochondria 1 II. Glutathione and endogenous regulatory factor for mitochondrial phosphate/proton symport

Kiehl Reinhold,

Reference no.: 92-1073

Transport and ATP synthesis in mitochondria 1 III. Hypothesis: mitochondrial ATP synthesis of the phosphate/proton symport system with oxidized glutathione as catalyst

Kiehl Reinhold

Editor: Böck

Dear Dr. Kiehl,

Thank you for your letter of 22.10.92. Your letter of 09.09.92 was faxed to two referees: report 1 is from a referee who reviewed manuscripts 92-0998 and 92-0999, and report 2 is from a referee who reviewed all three manuscripts. As you can see, both are negative.

The Editor, Prof. Böck, has made it quite clear that he does not intend to alter his decision to reject your manuscripts. However, if you wish to contact him, his telephone number is 089 179 198 56.

Yours sincerely,

Dr. John W. Aitken Editorial manager

Copy: Editor

Apollostrasse 2, Postfach

Editorial Office:

CH-8032 Zürich, Switzerland

Tel.: + 41 1 383 00 02 Fax: + 41 1 383 07 16

Fax:

Phone:

+41 1 383 0716

+41 1 383 0002

30 October 1992

From:

Editorial Office

Postfach

Apollostrasse 2 CH-8032 Zürich Switzerland

erland Date:

Fax to: Dr. Reinhold Kiehl

Number of pages (this one included):

EJB no.: 92 0998, 0999 and 1073

I am sending this fax in response to your telephone call today. Since you now have the referees' comments on your letter of 09.09.92, the only course of action which you can take at this stage is to reply to these comments. Please fax your reply to this office, and I will forward it to the Editor.

Dr. J. Aitken

..... 10.00 15.... SF*TFN =01

PRIVATKLINIK ZUR BEHANDLUNG ALLERGISCHER UND DEGENERATIVER ERKRANKUNGEN GmbH & Co KG Med.Leitung: Johannes Müller-Steinwachs, Hautarzt

TAX: 004113830716

the Zeiden

Speziałklinik Neukirchen + Krankenhausstr, 9 + 8497 Neukirchen b. Hl. Blut

Telefon: 09947/28-0 Telefox: 09947/28109 IK: 260 930 595

Prof. Ph. Christen Dr. J.W. Aitken Apollostr. 2 Postfach A 152 8032 Zürich

SCHWEIZ

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Original (plus changed MS) will follow by inou

October 26th, 1992

Unser Zeichen

Ref.No.: 92-0998, 92-0999 and 92-1073; my letter of 22/10/92

Dear Prof. Christen, dear Dr. Aitken,

I have changed my manuscripts 92-0998, 92-0999 and 92-1073 in order to resolve the dispute with your referees. I added more points and an explanatory figure to clarify better some results.

1. MS 92-0998: I added some more details as well as Figure 3 to clarify the points raised by the referees. I am not using an old fashioned swelling approach, but I am using the normal physiological swelling and contraction cycles of mitochondria, e.g. one more possibility to measure K⁺ (Ca²⁺)-transport (see manuscripts I to IV, some results out of MS IV were sent to you by Fax/Letter of 14/10/92).

There are no artefacts in life, just the explanations are missing. If something has been measured, there are explanations available - one has just to search for!

2. MS 92-0999: The results - and the methology leading to these results - are eminent important to bioenergetics and then of course also to medicine: the description of the way to the right methods leading in finally "only" 1 page results, namely glutathione/modulation by phosphate, are essential for the MS and of interest and also of importance for biochemists.

The finding of glutathione involvement in mitochondrial energy linked functions leads then of course in a discussion as presented. We have now divided this discussion into 3 parts for convenience: 1. glutathione and RCR as well as P_i/H_+ -symport, 2. glutathione RCR/ P_i/H^+ -symport and interfering compounds, 3. glutathione-transport/relation to medicine.

-2-

I rather like to write an <u>extended</u> methodological paper, if someone wishes a paper like this and if enough interest exists.

3. MS 92-1073: In this manuscript I describe a new hypothesis about ATP-synthesis and this hypothesis can be proven in future experiments. This new hypothesis is founded on data out of 20 to 30 years research efforts and much better able to explain these data as present descriptions of ATP formation.

I have changed my English style (K-transport).

Yours sincerely R. U.C.

Dr. R. Kiehl

Enclosure: 2x3 copies of the changed MS

to Rof. Ph. Christer, Dr. J. W. Aither

PRIVATKLINIK ZUR BEHANDLUNG ALLERGISCHER UND DEGENERATIVER ERKRANKUNGEN GmbH & Co KG Hed.Leitung: Johannes Hüller-Steinwachs, Hautarzt

Spezialklinik Neukirchen - Krankenhausstr. 9 · 8497 Neukirchen b. Hl. Blut

Telefon: 09947/28-0 Telefax: 09947/28109 IK: 260 930 595

Prof. Ph. Christen Dr. J.W. Aitken Editorial Office, Eur. J. Biochem. Apollostr. 2 Postfach A 152 8032 Zürich

FAX: 004113830716 Original by mail

SCHWEIZ Unser Zeidien

Ihre Nadiridit vom

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02.11.92

Ref.No.: 92-0998, 92-0999, 92-1073; my letters of 9/10/92 and 26/10/92 plus changed manuscripts; your letter dated 30/10/92 with the referees' comments on my letter of 9/9/92

Dear Prof. Christen, dear Dr. Aitken,

I have just got your letters dated 30/10/92 with the referees' comments on my letter of 9/9/92. A little bit late - as I already told to Dr. Aitken on the phone. I am writing now on Dr. Aitken's suggestion a reply to these comments, although most points raised by the referees are answered by the preliminary results to be reported in the 4th MS sent to you on the 14/10/92 by fax/letter and my letter of 26/10/92 (together with the improved manuscripts).

MS 92-0998: all points raised by the referees were clarified. ERROR: At page 7 line 5 there should correctly be written: "As already suggested...".

MS 92-0999: as I wrote already, the <u>result</u> of glutathione involvement in the mitochondrial energy linked functions, incl. modulation of the membrane bound glutathione concentrations by phosphate - represented by "only" one page description - forces to the presented <u>mechanism</u> in the discussion and the discussion itself. The <u>weight</u> (importance) of the results counts and this fact cannot be expressed in page numbers!

MS 92-1073 (and 92-0998, 92-0999): The comments of the referees make clear, why the manuscripts were rejected - <u>they are not wanted</u> (see my letter of 9/9/92): "The current state of bioenergetics will - <u>in the opinion of the reviewer</u> - not be improved by publishing these papers". I don't agree: the state of bioenergetics will clarify on these papers, this is obvious to everyone standing outside bioenergetics, but the referees rather like to keep the long persisting "state of the art" - or how do they intend to solve the problems in bioenergetics?

In the moment there is one theory and that is Mitchell's but no hypothesis, therefore the field cannot be spoiled with another unproven hypothesis. If one follows the results of the papers and the conclusions out of these results, one ends automatically up in the presented hypothesis:

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 ${\rm F}_0{\rm F}_1$ cannot be the location where ATP is synthesized (remember: which points leaded to ${\rm F}_0{\rm F}_1$ as location for ATP synthesis?)! Realizing our statement may be shocking at first. But just the acceptance of this inference resolves many problems in bioenergetics and clarifies the molecular description of ATP synthesis.

A lot of results imply F_1F_0 as K-pump (as partly described), it needs just a few further experiments to prove this assumption directly. There are also good experiments possible for a direct proof of the proposed ATP synthesis on the P_1/H^+ -symporter. That means the hypothesis may be proven in a relative short time and the mechanism for ATP synthesis could then be settled. This has not been possible for ATP synthesis on F_1F_0 for about 30 years! Another point: Almost all data obtained during the last decades are able to be explained by the presented hypothesis — this is not the case with the current descriptions of mitochondrial energy linked functions. Also, the long persisting discussions about Mitchell's theory are in the formulated hypothesis on the best way resolved.

I'd like to remember mitochondria are embedded into cells and they interact therefore with other organelles as well as with the cellular membranes. Physiological conditions have to be used to find the existant interactions. These interactions (and new functions) are able to be found and described with the presented hypothesis, but not in the current description of bioenergetics. I have pointed toward the relation of the molecular formulated mitochondrial energy linked functions to medical functions. The technical realization of bioenergy production (molecular biotechnology) is with the formulated molecular mechanism of ATP synthesis possible.

One more point: As "Ultima ratio", the editor could publish the comments of the referees together with this reply as discussion at the end of the papers.

An answer to the second "comment" as well as the statement that two negative comments are proof for bad manuscripts is at our state of discussion without any doubt unnecessary. I'd like also to ask the Editor: How is it possible for him under the impression of all the data and arguments to say "he does not intend to change his original decision to reject the papers?"

Please send copies of this reply and copies of all the remaining correspondence, including preliminary data and corrected papers as well as the letter of 9/10/92 as answer to the style of my argumentation to the Editor Prof. Böck and the referee(s).

Yours sincerely

R. Well

Dr. R. Kiehl

Zürich, November 4, 1992

Dr. Reinhold Kiehl Research Department Spezialklinik Neukirchen Krankenhausstr. 9 DW-8497 NEUKIRCHEN Fed. Rep. Germany

Reference no.: 92-0998

Transport and ATP synthesis in mitochondria 1 I. Evidence for mitochondrial 2,4-dinitrophenol accumulation across the Pi/H+-symport system

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Kiehl Reinhold,

Reference no.: 92-1073

Transport and ATP synthesis in mitochondria 1 III. Hypothesis: mitochondrial ATP synthesis of the phosphate/proton symport system with oxidized glutathione as catalyst

Kiehl Reinhold

Editor: Böck

Dear Dr. Kiehl,

Your letter of 02.11.92 was passed on to the Editor.

He asked me to inform you that he has considered the points in your letter, and finds that there are no grounds for reopening the file, because you have still not addressed the fundamental criticisms of the referees.

-

He has also suggested that it may be advisable to submit your manuscripts to a different journal.

Yours sincerely,

Dr. John W. Aitken Editorial manager

Copy: Editor

Editorial Office: Apollostrasse 2, Postfach

CH-8032 Zürich, Switzerland

Tel.: + 41 1 383 00 02 Fax: + 41 1 383 07 16