J M M **Journal of Molecular Medicine**

Springer International

MDC, Max-Delbrück-Center, Robert-Rössle-Strasse 10, 13122 Berlin

Dr. Kiel
Amselweg 12
93437 Forth im Wald

November 21, 1994

Detlev Ganten
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Dear Dr. Kiel,

Thank you for your inquiry regarding the *Journal of Molecular Medicine (JMM)*. Enclosed, please find the instructions to authors which you requested.

We look forward to receiving your manuscript.

Sincerely,

Chris E. Talsness
Assistant Editor

← Anf: 22.12.

Please note that the form you used was sent to Springer Verlag. You may also receive a copy from them.

J M M Journal of Molecular Medicine

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Dr. R. Kiehl
Research Department
Spezialklinik Neukirchen
Krankenhausstr. 9
93453 Neukirchen b. Hl. Blut

December 6, 1994
kiehl6.12/et

Manuscript No.: 4G 19
Author(s): R. Kiehl

Dear Dr. Kiehl,

Thank you for the submission of your work entitled, "Transport and ATP Synthesis in Mitochondria: Parts 1-4". Your manuscripts have been reviewed and discussed by members of the editorial board. We feel that the biochemical orientation of your manuscripts is not of sufficient interest for clinicians. Therefore, we would like to suggest that you condense your work into one paper and invite you to submit a review article on this topic incorporating the clinical implications of your work.

A review article for *JMM* should be no longer than 30 manuscript pages and any appropriate figures or tables may be included.

We look forward to your positive response and would be grateful if you would inform us regarding a possible date of submission.

Yours sincerely,

Detlev Ganten

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Journal of Molecular Medicine

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February 1, 1995

Manuscript no.: 5G 11
Author(s): R. Kiehl
Title: Glutathione: The essential factor for mitochondrial energy linked functions

Dear Dr. Kiehl,

I am pleased to acknowledge the receipt of your manuscript. The inclusion of the above mentioned manuscript number with all future correspondence regarding your paper would be greatly appreciated.

Thank you for submitting your work to the *Journal of Molecular Medicine (JMM)*. I will notify you as soon as the review process is complete.

Yours sincerely,

Detlev Ganten

Thank you, Please note that this manuscript will now be considered under a new number.

Journal of Molecular Medicine

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93437 Furth im Wald

February 1, 1995

Manuscript no.: 5G 11
Author(s): R. Kiehl
Title: Glutathione: The essential factor for mitochondrial energy linked functions

Dear Dr. Kiehl,

Your manuscript has been forwarded to one of the associate editors and further correspondence regarding possible revisions will be conducted by him. In the case that your paper is returned for revisions, please note the following marked item(s) regarding the instructions to authors.

___No changes necessary
___Manuscript length
___Nucleotide sequence data
___Title page
___Abbreviations
___Abstract
___Key words
___Order of references (we are currently accepting both alphabetical and numerical sequences)
___Introduction
___Citation of references
_X_Tables and figures

I have included a copy of the instructions to authors and have indicated the pertinent section.

I wish you every success in your scientific work and thank you for submitting your paper to the *Journal of Molecular Medicine (JMM)*.

Sincerely,

Chris E. Talsness
Assistant Editor

It is not necessary to submit originals at this point in time.

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October 12, 1995

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Manuscript No.: 5G 11
Author: R. Kiehl
Title: Glutathione: The essential factor for mitochondrial energy linked functions

Elektrophysiology and Thermod...

Dear Dr. Kiehl,

Your manuscript entitled "Glutathione: The essential factor for mitochondrial energy linked functions" has been examined. The reviewer feels that the topic is of interest, however, concerns were expressed that many points in the article are of a speculative nature. In addition, experimental designs which would be useful to demonstrate that glutathione could be an essential factor were not described. I refer you to the more elaborate comments provided by the referee. According to the recommendations of the reviewer, the paper cannot be published in its present form.

1.) 2.) 3.)

bei H. Michel, R. Huber
Paper I–IV:
1) Keine Spekulation
2) is proven!
3) Comment were answered!

Thank you for the submission of your work and I hope you will find the reviewer's comments helpful.

Inzwischen viel weitere Ergebnisse in der Arbeit

Sincerely,

Detlev Ganten

M/G

R. Kiehl

J
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M

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FULL REVIEW FOR AUTHORS

Please fax your comments to: Editorial Office Fax: +49-30 9406 2266
Do not recommend for acceptance or rejection on this sheet.

Reviewer: 1
Manuscript no.: 5G 11
Author(s): R. Kiehl
Title: Glutathione: The essential factor for mitochondrial energy linked functions

The basis of the article in many points is rather speculative. There is a lack of data which could really demonstrate that glutathione is the essential factor for mitochondrial energy linked functions, which is already suggested in the title. The title is only a hypothesis, and the approach for evaluation of the role of glutathione for mitochondrial energy linked functions is not useful for showing that this hypothesis is true. Other factors which could be the essential factor too were not discussed or compared with the suggested essential factor glutathione. The interrelationships between cytosolic and mitochondrial glutathione (GSH; GSSG) are without experimental basis in the article (data on flux rates, not only concentrations for that purpose would be necessary). There is no close connection between the different parts/subtitles of the article. Concerning the hypothesis/ suggestion some parts of the article are without any importance: see Thermoregulation in men; Other systems. The subtitle Therapeutics would be an own topic. Some subtitles contain mechanisms important for mitochondrial functions, other subtitles contain cell types, such as ascites tumor cells. The comparison of different cell types, even some cell types were described in the text, was not carried out. The experimental design for those points which would be useful for the demonstration that glutathione could be the essential factor was not described. The conclusions sometimes are formulated in a general manner - "the whole system is dependent on oxidized and reduced glutathione" (see page 14) - which is true, but superficial from the point of view of molecular basis. Several citations are unpublished/submitted (beginning at the title page with "further results may be obtained on request or from the submitted manuscript for publication in Eur. J. Biochem.") or conference proceedings; contrary some important references should be added.

To some details:
Title - Why did the author combine the detailed point that glutathione should be the essential factor for mitochondrial energy linked functions combine with the aim to give an introduction into the global field of electrophysiology and thermodynamics? It is complicate enough to demonstrate that glutathione is really the essential factor.
The key words which were selected underline the aim to generalize data from the own group and from literature and to apply the hypothesis to all/many fields from basis science to therapy rather than to demonstrate in detail that the hypothesis is true.
page 2: "The modulation of the mitochondrial glutathione concentrations (among others) by active phosphate transport ..." Which other factors are modulated? Why they are not essential in contrast/comparison with glutathione? - Fig. 1 is followed by Fig. 5 (page 3).
To the second subtitle: Glutathione as endogenous regulatory factor for P_i/H^+ symport: (page 3/4) How one can understand that at the applied conditions, most of the glutathione is associated with the mitochondrial membrane and that no free reduced glutathione could be found? (see also Table II) For that important point the detailed description of analytical methods would be useful.

page 4: the phosphate/proton symport and other carriers are regulated by glutathione - Where are the two neighbored disulfide bridges localized in the carrier enzyme (ref.)? What argues for the liberation of GSSG from the receptor side?
page 5: Which experimental data exist for the conclusion that decoupled mitochondria either lack GSSG itself or otherwise the ability to bind available GSSG at the 30 kDa polypeptides incl. phosphate carrier and that only mitochondria with "activated bound glutathione" will be acetylated? Did the author measure GSSG levels to be zero in decoupled mitochondria? page 5: A rough calculation ... would lead in at least 2.1 nmol GSSG/mg ... What about the fact, that the GSSG produced can be reconverted rapidly to GSH using reducing equivalents because mitochondria have an NADPH-specific glutathione reductase (already known from Flohé and Schlegel 1971 and from Jocelyn 1975; Jocelyn and Dickson 1980) which should be highly active in coupled mitochondria preventing such accumulation of GSSG? The facts written under "in summation" at page 5/6 are interesting but should be documented as Table or Figure (see experimental changes by NTU: GSH, GSSG, RCR, etc.).
page 6: This could be shown for most compounds by performing competition experiments - Where are the data?
page 6: "This mechanism would imply new pharmacological treatments of diseases, may help in understanding the functions of our brain and could give even a hint to an explanation for the effects of acupuncture." This sentence is a typical example in the manuscript for leaving the molecular basis, for generalization of (sometimes lacking) facts to explain questions which are itself valid to supply material for different review articles ("functions" of our brain, mechanisms of acupuncture).
page 7"The functions of the human body are dependent on a certain "sulfur status", which disturbance is accompanied by serious disfunctions of the body". That may be true, but does not say anything on causes or results or on the causal chain of damages, functional disturbances. One can even substitute the word sulfur status in the sentence by calcium, or by balance between reactive oxygen species and antioxidants and by many other important "essential factors" and the sentence would be rigth, too.
The part ATP synthesis on the phosphate/proton symport system with oxidized glutathione as catalyst really presents the trial to fulfill the combination of the two points (glutathione as essential factor; introduction into the electrophysiology and thermodynamics of mitochondria) in the title of the review. Nevertheless, the pages 7-11 are completely hypothetically, and even the author refers to the results to this hypothesis in references 6, 13, 18, 26, 31, 38, 39, 45 incl. (end of page 11) the reader needs to get the most important results/demonstrating original data and the logical demonstration of hypothesis on the basis of data directly in the review.
page 14 "the whole system is dependent on oxidized and reduced glutathione": Obviously, that is true without any doubt, but that does not demonstrate that other factors are not of equal or even higher importance for energy linked mitochondrial functions than glutathione.
page 16 "Thermoregulation in men" What is glutathione dependent in Fig. 7? How does this part of the manuscript underline the fact that glutathione is the essential factor for energy linked functions? The changes of glutathione metabolism during initiation of pain were not described, also not the interrelationships between acetylsalicylic acid and glutathione metabolism.
page 17 "glutathione functions in the cells"/"in mitochondria" (page 18-19): here articles from Meister and from Orrenius and Bellomo should be included into the reference list. Especially in Orrenius and Bellomo different metabolic factors are discussed in relation to mitochondrial energy linked functions. There was also written, that pyridine nucleotide oxidation does not seem to require GSH oxidation to induce Ca^{2+} release. In fact, experiments by Richter's group (Frei et al. 1985) have demonstrated that the glutathione reductase inhibitor BCNU, although potentiating t-BH induced oxidation of mitochondrial GSH, delays Ca^{2+} release, which correlates well with the more slowly occurring pyridine nucleotide oxidation observed in the presence of BCNU. Those facts, indeed, relativate the role of glutathione for mitochondrial energy linked functions.
page 21 "Ascites tumor mitochondria" Why did'nt the author compare mitochondria from different cell types with the aim to find out general mechanisms on the one side and specificities on the other side?
page 21 "psychogenic factors play an important role for certain diseases including cancer development". Everyone who combines experimental and clinical work can understand that also from practical experience, but everybody also knows that there is a lack in the understanding of detailed mechanisms. Therefore, the sentence does not say anything.
Part Therapeutics should be deleted, because it makes the article more superficial and does not contribute to the concentration of the topic, that glutathione could be the essential factor for mitochondrial energy linked functions.
Tables and Figures: It seems that there is a disbalance between documentation of original data (own and from others) and hypothetical suggestions.

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November 29, 1995

Manuscript No.: 5G127

Dear Dr. Kiehl,

Enclosed, please find another copy of your manuscript returned by one of the reviewers.

Yours sincerely,

Chris E. Talsness

BIOLOGICAL CHEMISTRY
HOPPE-SEYLER

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Herrn
Dr. R. Kiehl
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17. Mai 1995

FAX (1 Seite)

Sehr geehrter Herr Dr. Kiehl,

Herr Prof. H. Fritz, München, hat die Manuskripte an mich weitergeleitet, die Sie versehentlich bei ihm eingereicht hatten. Leider kommen die Arbeiten für eine Publikation in **Biological Chemistry Hoppe-Seyler** nicht in betracht. Auf dem normalen Postwege werden die Manuskripte an Sie retourniert - von weiteren Einsendungen desselben, dieser Zeitschrift schon wiederholt vorgelegten Materials bitte ich Abstand zu nehmen.

Freundliche Grüße,

H.-J. Fritz

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