

Are the Authors of Scientific Articles Protected Against Plagiarism?



27 Years of Experience Shows that Rather Plagiarists are Protected in the Peer Review System

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Abstract

The Author of this article in 1990 submitted for publishing a manuscript describing the split-mix combinatorial synthesis and the invention was expropriated and published by the Editor in Chief of International Journal of Peptide and Protein Research and all the three reviewers are suspected to do so. The Author tried to seek justice but it was refused by the Editor in chief of Nature (where the expropriated invention was published), by the Office of Research Integrity at NIH and by the Munksgaard International Publishers, Copenhagen, publisher of the International Journal of Peptide and Protein Research. Since the plagiarists continued to publish misleading papers the Author sent 10 correction letters to the journals but only three were published. The Committee on Ethics of the American Chemical Society also refrained from acting. In order to avoid happening again of the mentioned type of plagiarism, introduction of new rules is suggested by the Author.

Keywords: Split-Mix Combinatorial Synthesis; Research Integrity; Ethics; Scientific Plagiarism; Editors; Combinatorial Chemistry; Peptides; Drug Research; Reviewers

Introduction

Wikipedia defines plagiarism as follows: "Plagiarism is the wrongful appropriation and stealing and publication of another author's language, thoughts, ideas, or expressions and the representation of them as one's own original work. Plagiarism is considered academic dishonesty and a breach of journalistic ethics. It is subject to sanctions such as penalties, suspension, and even expulsion from school or work" [1]. By this definition one expects that the peer reviewing system is organized so to prevent plagiarism and if necessary, apply the sanctions. The scientific plagiarism may be committed by colleagues, other researchers and by those who have access to manuscripts: editors in chiefs of the journals and the reviewers of the manuscripts. The Author's case will show that much remains to be done in this respect.

Invention and Notarization of the Principles of Combinatorial Chemistry

The Author in 1964/65 participated in elucidation of the amino acid sequence of a protein containing 245 amino acid residues [2]. Later, wondered how many different sequences may have such a protein. The exact number proved to be enormous: 20^{245} ($= 5.65 \times 10^{318}$). The calculated number of peptides in peptide families depending on their number of amino acid

residues of course proved much lower: dipeptides 400, tripeptides 8,000, tetrapeptides 160,000, pentapeptides 3,200,000 and so on. The Author began to speculate how all these peptides could be prepared. The solution (the "split-mix" method) was found in early 1982. The method was in two ways radically new:

- i. It made possible to prepare millions of peptides in a single short process
- ii. The peptides formed were available as mixtures.

A patent attorney advised to describe the method and before publishing notarize it then publish it in steps. The document written in Hungarian was notarized on 15 June 1982. The English version of the original Hungarian text can be found in a later published article [3] (Figure 1). Since until that time the peptide drug researchers dealt only with single pure peptides, finding a biologically active peptide in a multicomponent mixture seemed to be like finding a needle in a haystack. For this reason, a deconvolution strategy was developed (named "back searching") that ensured the identification of the active peptide if an assay method was at hand.

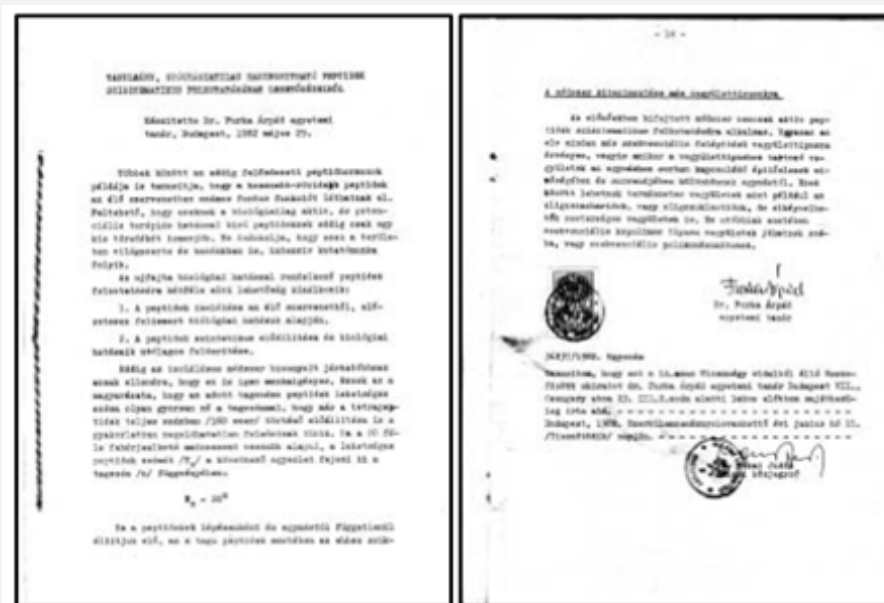


Figure 1: The first and last page of the notarized document

Publication



Figure 2: Copies of the two 1988 posters.

The synthetic method was first published on two international congresses: 14th International Congress of Biochemistry, Prague, 1988 [4] and 10th International Symposium of Medicinal Chemistry, Budapest in the same year [5]. Both publications were posters. Their copies are shown in Figure 2. On 12 February 1990 our manuscript was sent to Professor Victor Hruby University of Arizona, the Editor in Chief of the International Journal of Peptide and Protein Research in order to publish the split-mix method in print. On May 15 professor Hruby sent his decision: the article is unacceptable without major revision. After doing the requested

HPLC experiments the manuscript was accepted on November 21 and finally, after nearly one and a half year of delay appeared in print in June 1991 [6].

After taking appropriate precautions in the publishing process to exclude the chance to expropriate the invention (notarization, long period before the first publishing and additional two years before the publishing in print) we felt safe so what happened in the evaluation period of our manuscript was a very big surprise and a source of much bitterness and hundreds of unslept nights.

The Significance of the Split-Mix Synthesis

Since the split-mix synthesis made possible to prepare a practically unlimited number of peptides and other kinds of organic compounds it gave rise to enormous expectations. Dozens of new companies were founded to exploit the promises. It even led to a new discipline in chemistry: combinatorial chemistry. Its name comes from one of the properties of the split-mix synthesis. In such a synthesis all structural combinations of compounds are formed that can be deduced from the building blocks used in the process. Although the original expectations were not immediately fulfilled combinatorial chemistry remained one of the most important technologies in drug research, material science and other disciplines. In the recent years it is revitalized by using DNS [7] for encoding that made possible to synthesize billion or even trillion component libraries that are applied in drug research [8].

Events and Evidences of Plagiarism in the Evaluation Period of the Manuscript

As described in detail in a recent article [9], in the evaluation period of our manuscript sent to Professor Hruby, other articles were published, patent applications were filed, and a company was founded all based on the Author's invention:

- a. A lecture of Dr. Kit S. Lam and his co-workers, including the editor in chief of the Int. J. Peptide Protein Res. and S. Salmon the founder of the Arizona Cancer Center, on the 12th American Peptide Symposium, Boston, USA, 1991 [10].
- b. A lecture of Dr. Richard A. Houghten on the Innovation & Perspectives in Solid Phase Synthesis & Related Technologies, Second International Symposium, Canterbury, 1991 [11].
- c. An article of Lam et al. including professors Hruby and Salmon among the authors in Nature [12].
- d. An article of Houghten et al. in Nature [13].
- e. A book chapter of Hruby et al. [14].
- f. A patent application of Lam et al. including professor Hruby among the authors [15].
- g. A patent application of Houghten et al. [16] Torrey Pines Institute for Molecular Studies, San Diego, Calif.
- h. A patent application of Di Marchi and Geshellchen [17]. Eli Lilly and Company, Indianapolis Ind.
- i. A patent application of Huebner and Santi [18]. San Francisco Cal.
- j. Foundation of the Selectide Corporation Tucson Arizona.

What one can read above seems unbelievable, but the citations prove its reality. A closer look into the documents convinced the Author that what happened must have been a multi personal intentional plagiarism. In the followings, evidences will support this conclusion.

Patent Applications

Let's mention first the patent applications. The content of the four patent applications and patents prove that they are based on our split-mix synthesis. The persons who had opportunity to read our manuscript are the editor in chief of the journal, professor Hruby and the three reviewers. Their number is four and exactly four patent applications were filed. In the opinion of the Author this can't be incidental. In the applications (except the Huebner and Santi application) one of our 1988 poster publications were cited. This allows presuming that three applications were filed by the reviewers since the posters were cited in our manuscript.

The fact that the patent applications were not filed earlier but just after submitting our manuscript supports the supposition that three of the patent applicants were reviewers. Concerning the fourth application, no question professor Hruby also read the manuscript. Later the Author asked professor Hruby about the reviewers. He answered that he has forgotten the names. The patent applications in which the 1988 publications were cited substantially differ from the articles and conference papers of the next paragraph. In the applications the original invention is not expropriated but - if as supposed - the applicants that is the reviewers, "only" violated the privacy of the manuscript and used the information for their own purposes.

Conference Papers, Articles, Grant Applications

The inventions described in the Hruby-Salmon-Lam group and Houghten et al. group in the above-mentioned conference papers and Nature articles are neither original nor even independent ones since the split-mix synthesis was published in 1988, three years earlier than their Nature papers. As shown below they knew about our 1988 publications well before their manuscripts were submitted to Nature since they cited our 1988 publications in their earlier filed patent applications.

- i. The patent application of Lam et al. was filed on July 2, 1990.

The manuscript of the Lam et al. Nature paper was submitted nearly one year later May 30, 1991.

- ii. The filing date of the patent application of Houghten et al. is November 21, 1990.

Submission of the Houghten et al. Nature paper occurred on July 31, 1991 seven months later.

This supports the supposition that omission of the citation our invention from their articles was intentional. Not even mentioning the fact that professor Hruby certainly new about our 1988 publications from our submitted manuscript. It also seems worthwhile to mention that the Author was invited by Selectide Corporation to Tucson and on April 2, 1991 and gave a seminar in the Arizona Cancer Center speaking about the split-mix synthesis and the back searching deconvolution strategy in the presence of the authors of the Lam article. This was also before the Lam manuscript was submitted.

It also needs mentioning that the Selectide Corporation was founded in 1990 in Tucson Arizona also in the evaluation period of our manuscript. The company at present is a subsidiary of Aventis Pharmaceuticals Inc. The Lam-Salmon-Hruby group also applied for grants based on the invention of the split-mix synthesis. One of their successful proposals to National Institutes of Health had the title "Discovery of Peptide Anticancer Drugs," grant No. CA57723. This grant lasted from 1992 to 1995 and brought more than 3 million dollars to the applicants. A copy of the grant application was in the hands of the Author who saw no reference in it to our publications.

Protesting Actions

What can do an individual person after such trauma?

- First, a correction letter was sent to Nature.
- Sent protesting letter to Selectide and asked correction in Nature.
- Sent protesting letter to Dr. Houghten also asking to publish correction in Nature.
- Contacted the Office of Research Integrity of National Institute of Health.
- Contacted the Publisher of the International Journal of Peptide and Protein Research.

Results of the Protesting Actions

The correction letter sent to Nature was shortly rejected by Dr. Maddox the Editor in Chief of Nature at that time. The Author does not think that the intention of Dr. Maddox was protection of plagiarists, but the result was in fact a clear protection of the committed plagiarism. What else can do a victim of plagiarism than publishing about his complain? Or if he has a lot of money can choose litigation.

The results of the protesting letter sent to Selectide were apologetic letters written by Professor Hruby and Dr. Lam. The letters stated that they included reference to our publication in their original manuscript, but they had to shorten it and in this process the reference was lost. Taking into consideration, however, that the references to our earlier publications were also omitted from Dr. Lam's conference lecture, from Prof. Hruby's book chapter and from Lam-Salmon-Hruby's grant application the Hruby-Lam interpretation of the omission of the references can be safely rejected. Nevertheless, both Prof. Hruby and Dr. Lam promised to publish correction in Nature and that really appeared in 1992 with the following content: [19]

"In this paper we inadvertently omitted to cite the work of Fukura and colleagues (A. Fukura, F. Sebestyen, M. Asgedom and G. Dibo 14th Int. Congr. Biochem. FR3,1988), who independently described a similar synthetic method for producing multiple peptide sequences (which we called „split synthesis“). However, Fukura et al. did not describe the concept of 'one bead, one peptide' which was central to our approach"

The Author's name is misprinted: Fukura instead of Furka. There is good reason to believe that misprinting was intentional. After a request the name was corrected [20]. In addition to misprinting the name there is an even bigger problem with the above text. Lam says that "Fukura-Furka" described independently a similar synthesis. The independent invention and description of the split-mix synthesis by Furka does not need to be acknowledged by Lam since it was notarized almost ten years earlier in 1982 and published three years earlier in 1988. What is involved in the above correction written by Lam et al. is, their independent inventor status. This must be absolutely rejected since, as shown above, his publication was 3 years late to be considered independent.

Protesting letter was also sent to Dr. Houghten and asked to publish correction. He answered that he did not know about our publication but citation of our 1988 poster in his earlier filed patent application contradict this. He also promised to correct his Nature article and even sent the content of his planned correction but, as far as the Author is aware, it was never published.

The contact to the Office of Research Integrity resulted in several exchange of letters with Dr. Alan Price of Investigations Branch A, Division of Research Investigations at NIH. At the end he saw no problems to solve.

Finally, the Munksgaard International Publishers, Copenhagen, publisher of the International Journal of Peptide and Protein Research was contacted with the hope that they help to solve the problems caused by the editor in chief of the journal. This action, however, led to disappointment: absolutely no action was taken. Taking into consideration of all that is described above one can ask: is it acceptable that the peer reviewing system can be maintained if it is not capable to correct such a plagiarism?

Actions and Results After 27 Years

In the later years the split-mix method was named by Dr. Lam as Selectide Technology and the combinatorial libraries One Bead One Compound (OBOC) libraries while in fact formation of OBOC libraries is the intrinsic feature of our split-mix method. Formation of such libraries in the synthetic process is not even avoidable. Later the name Selectide technology was replaced by OBOC Technology. This technology has two parts:

- Synthesis of OBOC libraries.
- Screening the peptides while are attached to the solid support.

Although the OBOC name was probably created by Professor Lam neither part is his invention. As mentioned, the synthetic method is our split-mix procedure and screening of the peptides in anchored form was pioneered by Smith et al. [21]. Despite all these Professor Lam referred to OBOC Technology as his invention and placed himself among the inventors of combinatorial chemistry. At the same time the Author was completely excluded. He wrote the followings in 2017 in an article published in the Current Opinion in Chemical Biology: [22]

"The concept of combinatorial chemistry was developed in the mid 1980's, with Geysen's multi-pin technology [1] and Houghten's tea-bag technology [3] to synthesize hundreds of thousands of peptides on solid support in parallel. In 1991, Lam et al. [4] introduced the one-bead one-compound (OBOC) combinatorial peptide libraries and Houghten et al. [5] described the solution-phase mixtures of combinatorial peptide libraries."

This was more than could be tolerated and steps were taken to stop the untruthful statements and misleading references. It was also considered that the attitude towards plagiarism must have changed in the past 26 years. Since misleading statements and citations were published in quite few articles appearing in different journals corrections were prepared and sent to the following journals in the form of Letter to Editor (publishers in brackets).

- A. Current Opinion in Chemical Biology
(Elsevier)
- B. Advanced Drug Delivery Reviews
(Elsevier)
- C. Cellular & Molecular Immunology
(Springer Nature)
- D. ACS Combinatorial Scienc 2
(Am. Chem. Soc.)
- E. Analytical Chemistry
(Am. Chem. Soc.)
- F. ACS Chemical Biology
(Am. Chem. Soc.)
- G. Molecular Cancer Therapy 2
(Amer. Assoc. for Cancer Research)
- H. Nature
(Springer Nature)

At the first three journals took the Letters seriously, and after considering the evidences published them [23-25]. As far as the Author knows in the first two cases even the representative of the publisher, Elsevier was involved in decision making.

Both letters sent to ACS Combinatorial Science were rejected by the editor in chief professor M.G. FINN. The editor in chief of Analytical Chemistry, professor Jonathan V. Sweedler as well as the editor in chief of ACS Chemical Biology also refused to publish the Letters. It seems that for the ACS journals is not important to help the victim of plagiarism. The two letters sent to the Molecular Cancer Therapy were not even answered.

This year a second correction letter was sent to Nature shortly describing the evidences with the hope that the attitude towards plagiarism has changed during the last 27 years. The sad reality again was rejection of publishing the correction by Dr. Karl

Ziemelis the Physical Sciences Editor. At University of California Park Davis Professor Lam has several web sites in which the OBOC method is described as his invention. In one of them one can

Read: *"Dr. Lam invented the "one-bead-one-compound" (OBOC) combinatorial library method, filed the patents (the basic patents on the OBOC technology was issued in 1996, 1997, and 1999 by the US patent office), and published the technique in Nature in 1991."*

A request was sent to the vice provost Prof. Philip Kass asking to remove the misleading content from the sites. He forwarded the material to the Interim Dean of the UC Davis School of Medicine but there was no answer and the content of the web sites remained unchanged. Since all the correction letters submitted to ACS journals were rejected a letter was sent to Ms. Judith Currano chair of the Committee on Ethics of the American Chemical Society describing the fate of the invention 27 years ago and attached all documents proving the plagiarism including the Letters accepted at other journals and the rejections at the ACS journals. Ms. Currano answered the followings:

"The best advice we can provide for authors in this situation is to contact the editors of the journals in question to request a correction, including the omitted citation. It sounds like you have done this. Unfortunately, it is not within the purview of the ACS Committee on Ethics to intervene under such circumstances (even with ACS Publications); the committee is not an adjudicatory body in any way, and it cannot force editors to change the scholarly record. If you feel that your complaints to publishers have been mishandled, you might want to consider contacting COPE (<https://publicationethics.org/>), the Committee on Publications Ethics."

Since the ACS Committee on Ethics proved to be impotent to act the advice of Ms. Currano was followed and contacted COPE and asked to help publishing the Letter to Editor at ACS Combinatorial Science. The request is still under consideration.

The Main Participants

The persons in this list described the procedure of combinatorial synthesis as their own invention and omitted citation of the three years earlier publications [4,5].

Professor Victor J Hruby [10,12,14], grant CA57723

In 1990-91 when the Author's manuscript was submitted and was under consideration, Professor Hruby was Regents Professor at University of Arizona, President of the American Peptide Society and Editor in Chief of the International Journal of Peptide Protein Research. At present he is Regents Professor emeritus and has a long list of awards and honors. At present he is also member of the ACS Committee on Ethics. Nothing else that this fact characterizes the present relation of the peer review system to plagiarism.

Dr. Kit S Lam [10,12], grant CA57723

In 1990-91 Dr. Lam belonged to the Arizona Cancer Center led by Professor Sydney E. Salmon cooperation partner of Professor Hruby. At present he is Professor and Chair at University of

California Davis and member of the Editorial Board of ACS Combinatorial Science!!! One can reasonably think that his career is based on the expropriated invention.

Dr. Richard A Houghten [11,13]

In 1990-91 Dr. Houghten was and at present is the founder and Chief Executive Officer of Torrey Pines Institute for Molecular Studies San Diego CA and Port St. Lucie FL and recipient of different awards. In 2007-2008 he was president of the American Peptide Society.

Verena D Huebner and D V Santi [18]

Chiron Corporation, Emeriville, CA USA

Conclusion

If the researchers wish to share their results with the scientific community the main possibility is to publish articles in scientific journals. In order to do this, they must make available their results to the editor in chief of the journal and to the reviewers. The editor in chief decides about publishing or rejection. This ensures the good scientific level of publications. The editor in chief is designated by the publisher of the journal and the reviewers are selected by the editor in chief. The content of the manuscript is supposed to be kept confidential. The whole peer review system is based on the honesty of the editor in chief and of the reviewers. No question this works in many of the cases.

The above discussed case shows however, that exceptions may occur. It is a highly aggravating circumstance that all those are suspects who had access to the manuscript and the publishing system at present has no means to protect the victim or do appropriate correction. No question the main responsibility lies on the publisher who failed to check up the case immediately after the complaint. The editor in chief of Nature at that time is also responsible because of rejecting the correction. This led to more citation of the Lam and Houghten articles [12,13] than to that of the Furka et al. paper [6] not mentioning the hundreds of unslept nights. Since similar cases can't be excluded in the future several rules are needed to be implemented to avoid them and protect the authors.

- The editor in chief of a journal and the reviewers of a manuscript are prohibited to submit their own manuscript for publication before publishing date of the original article that has the same subject as that of the original one or is based on it except the authors of the original article give written permission to do so.
- The publisher is obliged to immediately investigate complain or accusation for violating rule No 1.
- If complain turns out to be true, the article of the editor in chief or the reviewers must be retracted and let the original author to publish his correction or complain.

Exclusion plagiarists from the scientific community and showing them that they can't escape punishing is very important.

Unveiling them will not erode but rather increase the prestige of the cooperating journals and publishers.

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