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Review Article

Facts from the Early Years of the History of Combinatorial Chemistry

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Abstract: Looking into the combinatorial chemistry literature one can see that it is still mostly believed that the first combinatorial synthesis was invented by several groups exactly at the same time. In fact the principles of combinatorial chemistry, that is, synthesis of large number, even millions, of compounds and then by applying a proper deconvolution method identify the useful components, was invented, first described and notarized as early as 1982 by the Author of this article. The first publication of the synthetic method was in 1988. In February 1990 the manuscript of an article also describing the combinatorial split-mix synthesis was submitted to the International Journal of Peptide and Protein Research that appeared after a one and a half year delay. In this period four patent applications were filed, two conference lectures, two Nature papers and a book chapter were submitted then published. The editor in chief of the mentioned journal was among the authors of one patent application, one lecture, one Nature article and a book chapter. The evidences described below will hopefully convince the readers that the inventions in the patent submissions and in the mentioned publications were all 2-3 years earlier described in our 1988 publications and these publications were known by the authors.

Keywords: Combinatorial Chemistry, Split-Mix Synthesis, OBOC Libraries, Deconvolution, Peptides, Plagiarism

1. Introduction: the Invention and Notarization

During 1964–1965, the Author of this article was a postdoctoral fellow at the University of Alberta, Canada and participated in the determination of the amino acid sequence of a pro-enzyme, chymotrypsinogen-B [1]. This protein has 245 amino acid residues and the Author wondered how many sequence variations may have such a molecule. It turned out that the number of possible sequences is an enormously high number 20^{245} (= 5.65×10^{318}). The number of possible sequences in peptide families was also calculated:

Table 1. *Number of peptide sequences in the peptide families.*

Peptide families	Number of peptides
Dipeptides	400
Tripeptides	8,000
Tetrapeptides	160,000
Pentapeptides	3,200,00
Hexapeptides	64,000,000

The Author began to speculate how all components of the peptide families could be synthesized, for example all the 3.2 million pentapeptides. It was clear that this task could not be accomplished by using the conventional synthetic procedures. An easy solution seemed reasonable: to apply the Merrifield's solid phase method [2] and use equimolar mixture of amino acids in each coupling step. Such a synthesis would produce:

1. A mixture of thousands or even millions of peptides instead of individual ones.

2. As a consequence of differences in the coupling rates of amino acids, in multistep couplings the peptides would be formed in widely different molar quantities.

In early 1982 the problem was solved the following way: before each coupling step the solid support is divided into equal portions then each portion is coupled with a single amino acid. This way each coupling step can be driven to completion like in the synthesis of individual peptides. After couplings the portions are mixed then divided again into portions before the new couplings. By these operations millions of peptides can be prepared in very short time and in equal molar quantities. This procedure that was the first

published real combinatorial synthesis later was named the "split-mix" method.

A problem, however, remained: what to do with the mixtures? To find a biologically active component in the mixture seemed to be something like finding a needle in a haystack. This was also solved very soon. A deconvolution strategy was developed that ensured finding the biologically active component if a proper assay method was at hand. This was an iterative procedure named "back searching" and an example below demonstrates how the two amino acid residues closest to the N-terminus of the bioactive peptide can be identified.

1. In each step of the synthesis before mixing, a small part of the resin mixture is taken aside for later use.

2. The samples are not mixed after the last coupling step. The N-terminal amino acid residue of all peptides of a sample is the last coupled amino acid but this differs from sample to sample. If all of the mixtures are tested and one of the mixtures shows activity the active peptide has to be in this mixture. The N-terminal amino acid of the active peptide like that of all other peptides within the mixture is the last coupled amino acid.

3. Then the identified amino acid is coupled to the samples taken aside before the last coupling step. As a result the N-terminal residue of all peptides is the same as that of the active peptide. The amino acid second from the N-terminus is the same in all peptides of a sample but differs from sample to sample. So by testing the peptide mixtures cleaved from the resin samples the amino acid second from the N-terminus in the active peptide can be determined. Continuing the same way the full amino acid sequence of the active peptide can be identified.

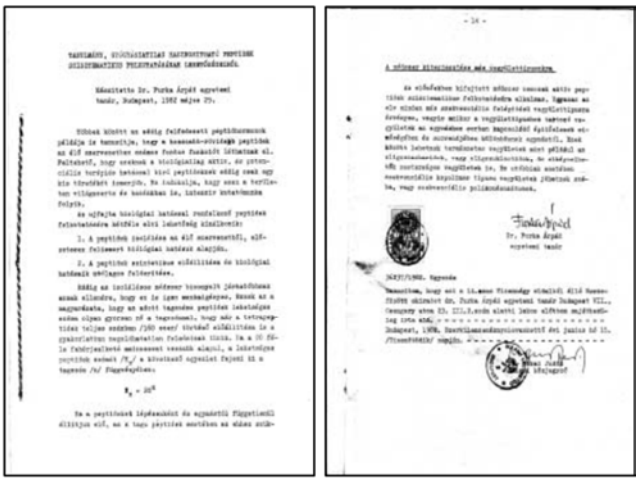


Figure 1. *The first and last page of the notarized document.*

A patent attorney advised to be careful in publishing the method: first describe the procedure, notarize it then publish it in steps. Following her suggestion the method was notarized in June 1982. The copy of the first and last page of the document is seen in Figure 1. In the notarized document written in Hungarian language both the split-mix synthesis and the back searching deconvolution strategy is described. The English version of the original Hungarian text can be found in a later published article [3].

2. The First Publication

The first publication of the split-mix synthetic method occurred 30 years ago on two international congresses: the 14th International Congress of Biochemistry, Prague, 1988 [4] and the 10th International Symposium of Medicinal Chemistry, Budapest in the same year [5]. Both publications were posters. Their copies are shown below in Figure 2.

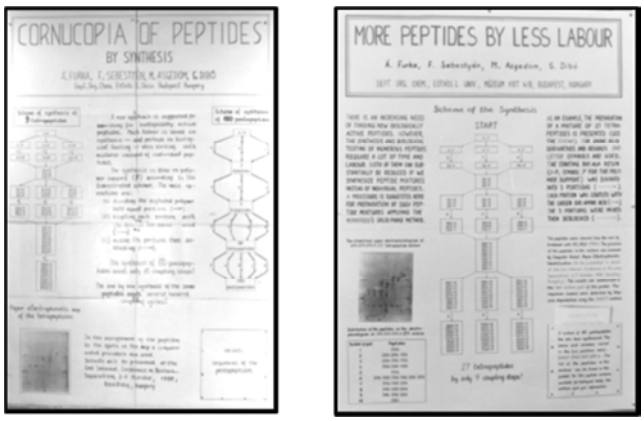


Figure 2. *Copies of the two 1988 posters.*

In the first two publications our purpose was to show that by following the described stepwise operations the expected peptides are really formed and are present in the mixture. This could be carried out by synthesizing only a limited number of peptides in one run. The components of the peptide mixtures were identified by computer-assisted high voltage paper electrophoresis. This method was based on the relation proposed by Offord [6] between the electrophoretic mobility of peptides, their molecular weight and electric charge. A computer program was developed that generated the amino acid sequences of the expected peptides, among them for example the 64 million hexapeptides, and showed their predicted position in the two dimensional electrophoretic map [7] (Figure 3).

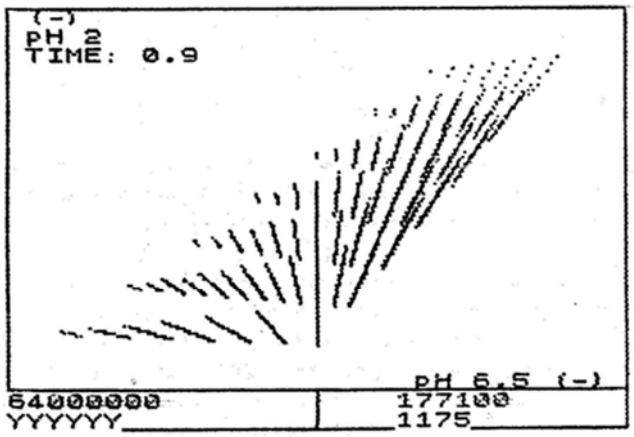


Figure 3. *Predicted two dimensional electrophoretic map of 64 million hexapeptides.*

The synthetic method was clearly described in both posters and made it quite understandable in the abstracts, too. You can read for example in the abstract of the Prague poster:

"*The principle of the method can be illustrated by brief description of the synthesis of a mixture of 9 tetrapaptides: a sample of aminoacyl (Ala) resin is divided into 3 equal parts. One part is coupled with Glu, the other with Lys and the last one with Phe. The resultant samples are then thoroughly mixed and again divided into 3 parts. These are coupled with Glu, Lys and Phe, respectively. Finally the samples are mixed, then coupled with Glu. After processing the following peptides are present in the mixture: GluGluGluAla, GluGluPheAla, GluGluLysAla, GluPheGluAla, GluPhePheAla, GluPheLysAla, GluLysGluAla, GluLysPheAla, GluLysLysAla.*"

3. Publication in Print

Two years later, in 1990 came the time to publish the method in print. Our manuscript describing the split-mix method was sent on 12 February 1990 to Professor Victor Hruby the Editor in Chief of the International Journal of Peptide and Protein Research. The same year on May 15, a letter came from professor Hruby sending the opinions of the three reviewers and his decision. One of the reviewers suggested rejection and the other two major revision and minor revision, respectively. The radical novelty of our method is well reflected in the note added by the reviewer who suggested minor revision: "Having spent years endeavoring to prepare peptides in the pure state, manuscripts like this 'compromising with mixtures' cause me some anxiety". Professor Hruby decided that the article is unacceptable without major revision. The identity of the synthesized peptides had to be proved by HPLC. On 31 October, after the requested HPLC experiments were done, the revised manuscript was sent to Professor Hruby. On November 21 the manuscript was accepted and finally, after nearly one and a half year of delay it appeared in print in June 1991 [8]. In this period and shortly after that a number of totally unexpected and even unbelievable events happened that caused much bitterness to Author and hundreds of unslept nights.

4. Events in the Evaluation Period of the Manuscript

In 18 January 1991 a letter came from Selectide Corporation (Tucson, Arizona, USA) proposing a visit by Dr. Kaubish (executive vice president of Selectide) to talk about potential cooperation and financing our research. On February 27-28 Dr. Kaubish visited our laboratory and invited the Author to Tucson to give a seminar. The seminar was on April 2 at the Arizona Cancer Center with an audience of about ten and talking about the split-mix synthesis and the deconvolution strategy. After the seminar Selectide offered a consultancy ($5000 per year). Professor Hruby also offered cooperation that was, however, absolutely not connected with the split-mix synthesis. He proposed to take part in synthesis of non-natural amino acids. This was unacceptable, and neither the cooperation nor the consultancy was realized. He also asked the Author whether he will be present on the forthcoming peptide symposium in Boston. The answer was no, but the reason behind the question was only later realized.

After returning to Budapest one of his former students visited the Author. She attended the lectures of the 12th American Peptide Symposium in Boston and told that Kit S. Lam in his lecture described the split-mix method as his own invention [9]. This was particularly painful since Kit Lam was present in the seminar in Tucson. Professor Hruby, the Editor in Chief of the Int. J. Peptide Protein Res. was also a member of the audience in the seminar and he also appeared among the authors of the Lam lecture like professor Sydney E. Salmon founder of the Arizona Cancer Center, Tucson. But this was only the first one of the bad news. In August a colleague participated on the Innovation & Perspectives in Solid Phase Synthesis & Related Technologies, Second International Symposium Canterbury. The colleague told that Dr. Richard Houghten had a lecture and like Lam, he also described the synthesis of millions of peptides as his own invention [10].

5. Continuation of the Bad News

In the 7 November 1991 issue of Nature, two papers appeared that need to be mentioned:

1. Lam, Hruby and others: A new type of synthetic peptide library for identifying ligand-binding activity [11] and
2. Houghten et al. Generation and use of synthetic peptide combinatorial libraries for basic research and drug discovery [12].

One can read in the Lam et al paper:

"Our method involves creating a large peptide library consisting of millions of beads…. Our solution was to use a 'split synthesis' approach. The first cycle consisted of distributing a pool of resin beads into separate reaction vessels each with a single amino acid, allowing the coupling reactions to go to completion, and then repooling the beads. This cycle was repeated several times to extend the peptide chain. In this fashion, each bead should contain only a single peptide species."

This was exactly our split-mix method but without any reference to our publications. It may be interesting to note that in this case formation of millions of peptides was not proved at all while in our case proving the presence of the expected peptides by two dimensional high voltage paper electrophoresis was not enough for professor Hruby. He required additional HPLC proof.

Houghten et al. also described preparation of millions of peptides without citing our publications:

Existing methods for the synthesis and screening of large numbers of peptides are limited by their inability to generate and screen the requisite number (millions) of individual peptides….. We have circumvented these limitations by developing synthetic peptide combinatorial libraries composed of mixtures of free peptides in quantities which can

be used directly in virtually all existing assay systems."

As they described, equimolar mixtures of amino acids were used in the elongation steps of the synthesis of the combinatorial libraries.

Professor Hruby and his colleagues also published a book chapter claiming the invention of the split-mix method for themselves [13]. Professors Hruby, Salmon and their colleagues also had grant applications. The Author had opportunity to read these applications. All of them were based on the split-mix synthesis that was indicated in their proposals as their own invention. Our publications were not mentioned.

6. Patent Applications

Later it turned out that four patent applications were filed all based on the split-mix synthesis. The earliest patent application (Lam et al.) was filed on July 2, 1990 and the last one (Di Marchi et al.) on June 18, 1991. Since the submission date of our manuscript was February 12, 1990 and the appearance of the article was in June 1991, no question, that all the four patents were filed within this period.

K. S. Lam and S. E. Salmon RANDOM BIO-OLIGOMER LIBRARY, A METHOD OF SYNTHESIS THEREOF, AND A METHOD OF USE THEREOF.

Filed: Continuation-in-part of Ser. No. 546,845, Jul. 2, 1990

One can read in the patent:

In particular. the present invention provides a method for generating the library comprising repeating the steps….

(i) providing at least two aliquots of a solid phase support for the random subunit sequences;

(ii) separately introducing a set of subunits to the aliquots of the solid phase support; (iii) completely coupling the subunits to substantially all the sites of the solid phase support to form a solid phase support/new subunit combination; (iv) assessing the completeness of coupling

(v) thoroughly mixing the aliquots of the solid phase support/new subunit combination; and. after repeating steps (i)-(v) the desired number of times…

No question this is our split-mix procedure published in 1988 and both publications [4] and [5] are cited in the patent.

The original application was filed with more inventors:

K. S. Lam, S. E. Salmon, V. J. Hruby, E. M. Hersh, F. Al-Obeidi Random bio-oligomer library, a method of synthesis thereof, and a method of use thereof.

R. A. Houghten, J. H. Cuervo, C. Pinilla J. R. Appel, Jr., S. Blondelle EQUIMOLAR MULTIPLE OLIGOMER MIXTURES, ESPECIALLY OLIGOPEPTIDE MIXTURES.

Filed: continuation-in-part of Ser. No.617,023, Nov. 21, 1990, abandoned.

The synthesis of combinatorial libraries begins with the followings:

(a) a plurality of solid supports is provided, each solid support comprised of a particle linked to reactive functional groups. The functional groups of the solid support react with a functional group of each of the monomeric repeating unit compounds to be reacted. In a preferred embodiment, each of the solid supports is within a porous container, the solid support is of a size that is larger than the pores of the container, and both the container and solid support are substantially insoluble in a liquid medium used during the stepwise synthesis.

The coupling cycle continues with coupling a different amino acid to the enclosed solid samples then the containers (plastic bags) are opened then mixed. The procedure continues with repeating the above cycle. This is again the split-mix procedure and our Prague poster [4] as expected appears among the references.

R. D. DiMarchi, P. D. Geshellchen, R. A. Owens RAPID SYNTHESIS AND SCREENING OF PEPTIDE MIMETICS.

Filed: Continuation of Ser. No. 717,184, Jun. 18, 1991 abandoned.

The following text copied from the patent and citation of our two 1988 publications [4] and [5] prove that what is described is our split-mix synthesis:

The new process is based on the repeated mixing, dividing, and coupling of resin-coupled amino acids or peptides. The first step requires the dividing of solid support resin into aliquots having equal amounts of attachment sites. This is followed by coupling to completion of individually selected amino acids to each aliquot, each aliquot of resin being coupled to a different amino acid. As a result, the resin in each aliquot will be coupled to the same molar amount of amino acid as other aliquots which are coupled to different amino acids. The resins are thoroughly mixed to produce an equimolar mixture of resin-coupled am/no acids. The mixture is then divided into equal aliquots followed by further coupling of individually selected amino acids to the resin-coupled amino acids in each aliquot. Repeated stepwise mixing, dividing, and coupling steps result in peptide mixtures…

V. D. Huebner, D. V. Santi CONTROLLED SYNTHESIS OF PEPTIDE MIXTURES USING MIXED RESINS.

Filed: May 15, 1990

Although there is no reference to our 1988 publications, the text copied from the patent clearly shows that the procedure described is our split-mix method.

The method involves three essential steps. First a given amount of a mixture of amino acyl or peptide derivatized resin is divided into a number of pools with each pool containing an equal molar amount of the resin mixture. Second a different single amino acid is coupled to the resin mixture in each of the pools and the coupling reaction is driven to completion. The peptide mixtures in each of the pools are then mixed together to obtain a complex peptide mixture containing each peptide in retrievable and analyzable amounts. The steps can be repeated to lengthen the peptide chains.

7. Questions That Need Answers

The split-mix procedure is very simple, easily understood and realized by any chemist. The idea, however, was radically new in two respects:

1. As never before, made possible to easily synthesize millions of peptides**.**

2. Instead of a single pure substance the synthesis produced a solution of peptide mixtures.

One may ask: is it possible that this radically new idea occurred in four different heads (of those who filed the patents) and not earlier not later but just in the reviewing period of our article? The reader can also consider the funny coincidence: the number of patents and the number of those who had access to our manuscript, the Editor in Chief ant the three reviewers, is the same.

The following question also seems justifiable: is it normal that an important invention described in a manuscript sent to a journal for publication appears in a paper of the editor in chief of the journal and of his colleagues?

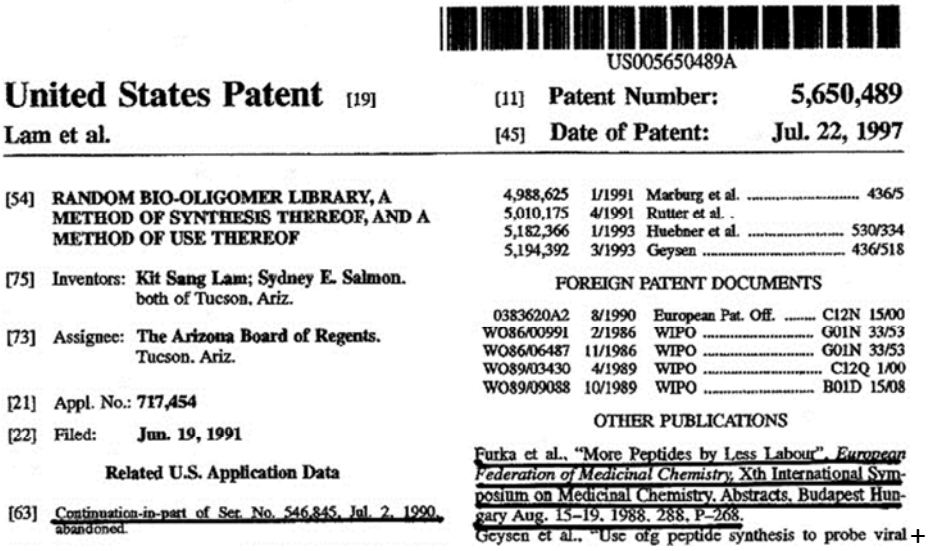
After getting informed about the publications mentioned above, a correction article was sent to Nature but it was rejected. Protesting letters were also sent to Selectide and Dr. Houghten asking them to publish correction. Apologizing letter came from both Professor Hruby and Dr. Kit S. Lam. The letters 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. The reader can judge whether this statement is acceptable or not, taking into consideration that in the Lam's Boston lecture, in Professor Hruby's book chapter and in their grant applications the reference to our work was also omitted.

Nevertheless, both Professor Hruby and Dr. Kit Lam promised to publish a correction in Nature. In this correction, however, as the cited text shows the name of the Author was misprinted [14]:

"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"

New protest letter was needed to correct at least the name [15]. The reader can decide to believe or not the original or even the independent status of the Lam et al. paper since it was submitted three years later than our two original 1988 publications and two months later than the seminar given in Tucson. It seems worthwhile to add that the Nature paper[11] was never cited together with the correction. In the references of further Lam publications his independent inventor status was maintained even till today.

Lam and his colleagues followed a quite different referencing approach in their patent application. As Figure 4 shows they referred to our 1988 publication in their patent application filed on 2 July 1990.



US005650489A

United States Patent [19]

Lam et al.

[11] **Patent Number: 5,650,489**

[45] **Date of Patent: Jul. 22, 1997**

[54] **RANDOM BIO-OLIGOMER LIBRARY, A METHOD OF SYNTHESIS THEREOF, AND A METHOD OF USE THEREOF**

[75] Inventors: **Kit Sang Lam; Sydney E. Salmon.** both of Tucson, Ariz.

[73] Assignee: **The Arizona Board of Regents.** Tucson. Ariz.

[21] Appl. No.: **717,454**

[22] Filed: **Jun. 19, 1991**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 546,845, Jul. 2, 1990, abandoned.

4,988,625	1/1991	Marburg et al.	436/5
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5,182,366	1/1993	Huebner et al.	530/334
5,194,392	3/1993	Geysen	436/518

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OTHER PUBLICATIONS

Furka et al., "More Peptides by Less Labour", *European Federation of Medicinal Chemistry*, Xth International Symposium on Medicinal Chemistry, Abstracts, Budapest Hungary Aug. 15–19, 1988. 288, P–268.

Geysen et al., "Use ofg peptide synthesis to probe viral +

Figure 4. *Part of the patent of Lam et al (copied from US Patent No. 5,650,489).*

They omitted, however, this reference from their Nature paper submitted considerably later on 30 May 1991 and from the other publications and grant applications mentioned above. As already mentioned the invitation to give a seminar at the Arizona Cancer Center came from a company named Selectide Corporation. Later it turned out that the company was founded in 1990 that is while our manuscript was under consideration by Professor Hruby. At the time of the Author's Tucson seminar our method was already used in their laboratories without asking permission.

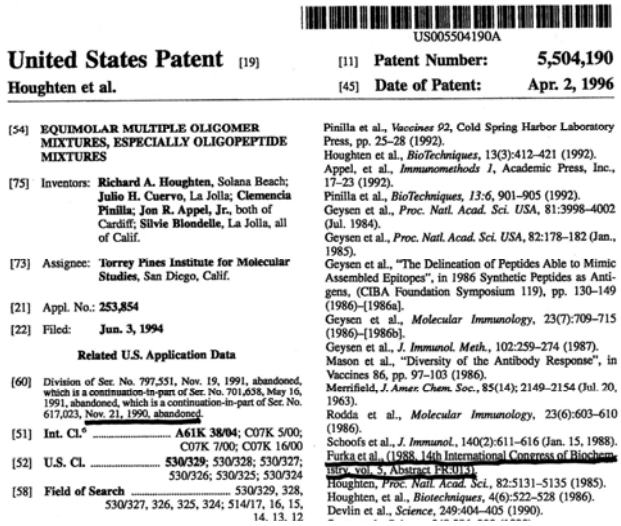
Dr. Houghten also answered the protesting letter saying that he did not know about our publication and promised to send to Nature a correction letter. He even attached the content of the promised letter but it was never published.

Like Dr. Lam, Dr. Houghten also followed a different referencing attitude in his patent and in his Nature article. As Figure 5 shows our 1988 Prague poster is cited in the patent application filed on 21 November 1990. This reference, however, is omitted from the Nature[12] article submitted 8 month later on 31 July 1991.

It seems justified to write a few notes about a different aspect of the Houghten patent. Earlier Dr. Houghten published a method that considerably increased the productivity of the parallel synthesis of peptides [16]. He used the solid phase

synthesis of Merrifield [2] (like the split-mix method) but enclosed each portion of resin assigned for a peptide into a solvent permeable bag and kept it enclosed till the end of the synthetic process. Before the coupling operations all bags that needed coupling with the same amino acid were grouped into the same coupling vessel. This way the needed coupling operations could be considerable reduced.

In the patent application the split-mix synthesis is described but the divided solid support portions are enclosed into bags instead of putting them directly into the coupling vessels. It has to be noted, however, that while the inclusion of the resin into bags in parallel synthesis resulted in a considerable advantage, doing the same in the split-mix procedure is definitely disadvantageous. In order to be able to mix the resin, all bags have to be opened after each coupling step and filled again before the next coupling step. This means that the advantage of the bags is not only completely lost but inserts unnecessary operations into the procedure. It is a question: why Dr. Houghten patented a procedure that is much less advantageous that the referenced original split-mix method?



US005504190A

United States Patent [19]
Houghten et al.

[11] **Patent Number: 5,504,190**
[45] **Date of Patent: Apr. 2, 1996**

[54] **EQUIMOLAR MULTIPLE OLIGOMER MIXTURES, ESPECIALLY OLIGOPEPTIDE MIXTURES**

[75] Inventors: **Richard A. Houghten**, Solana Beach; **Julio H. Cuervo**, La Jolla; **Clemencia Pinilla**; **Jon R. Appel, Jr.**, both of Cardiff; **Silvie Blondelle**, La Jolla, all of Calif.

[73] Assignee: **Torrey Pines Institute for Molecular Studies**, San Diego, Calif.

[21] Appl. No.: **253,854**

[22] Filed: **Jun. 3, 1994**

Related U.S. Application Data

[60] Division of Ser. No. 797,551, Nov. 19, 1991, abandoned, which is a continuation-in-part of Ser. No. 701,638, May 16, 1991, abandoned, which is a continuation-in-part of Ser. No. 617,023, Nov. 21, 1990, abandoned.

[51] **Int. Cl.**[6] **A61K 38/04**; C07K 5/00; C07K 7/00; C07K 16/00

[52] **U.S. Cl.** **530/329**; 530/328; 530/327; 530/326; 530/325; 530/324

[58] **Field of Search** 530/329, 328, 530/327, 326, 325, 324; 514/17, 16, 15, 14, 13, 12

Pinilla et al., *Vaccines 92*, Cold Spring Harbor Laboratory Press, pp. 25–28 (1992).
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Houghten, et al., *Biotechniques*, 4(6):522–528 (1986).
Devlin et al., *Science*, 249:404–405 (1990).

Figure 5. *Part of the patent application of Houghten et al (copied from US Patent No. 5,504,190).*

It seems worthwhile to devote a few words to the Nature paper of Houghten et al. too. As above cited, they say in their paper that they circumvented the inability to synthesize millions of peptides. As his patent shows he knew about our split-mix procedure published three years earlier that does make possible the synthesis of millions of peptides. What was then that they circumvented? They used for "circumvention" an equimolar mixture of amino acids in their synthesis. It is known, however, that the rate of coupling depends on the reactivity amino acids. As already mentioned, in multistep couplings, this may cause huge differences in the molar quantities of the formed peptides. As a consequence, a biologically active peptide present in low concentration in multicomponent mixtures would not be found. It is a question why this very uncertain procedure was described in the paper of Houghten et al. when a much better solution, our split-mix method was in his hands?

8. The Remaining 27 Years

In their later publications both Drs. Lam and Houghten maintained their enounced independent (sometime the original) inventor status concerning the combinatorial libraries. There are, however, a few publications of Lam and his collaborators in which they clearly admit our priority by citing our 1988 papers. In the article of Lebl et al. [17] one can read:

"The split synthesis method for generating libraries of this type was first described by Furka et al., who applied this method for synthesis of equimolar peptide mixtures. This synthetic method was later used to generate iterative libraries or one-bead-one-peptide libraries."

Similarly, Stankova et al. [18] state in their paper:

"The synthesis of libraries with a unique compound on each solid-phase particle employs a simple principle for the generation of equimolar mixtures of peptides in solution that was first described by Furka. This principle was later applied to the construction of soluble libraries for iterative screening and to bead-based libraries screened with solid-phase-binding protocols."

This is admitting that the Lam's libraries were synthesized by our method.

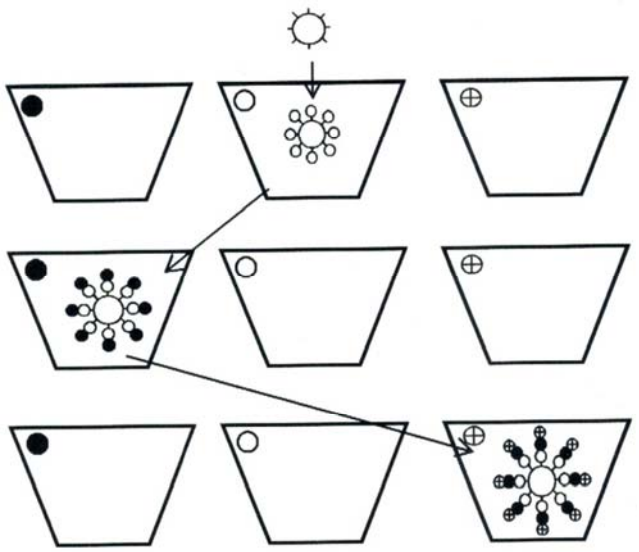

Figure 6. *The fate of a randomly selected bead in the split-mix synthesis.*

The concept of OBOC (One Bed One Compound) library and OBOC Technology was introduced by Dr. Lam as his invention. In fact formation of OBOC libraries is the intrinsic feature of our split-mix procedure. In the split-mix synthesis as Figure 5 shows, in every coupling vessel coupling is done with a single amino acid (denoted by different circles in the left upper corner). As a consequence, as Figure 5 demonstrates, all peptide sequences formed on a bead are the same. The sequence of the formed peptide on each randomly selected bead depends on the route the bead incidentally travels through the coupling vessels in the synthetic process.

Once, meeting on a conference, Dr. John A. Smith complained to the Author that the method used by Lam et al.

in their Nature paper [11], that is screening of peptides while they are attached to the solid support, was first described by he and his colleagues in 1977 [19] but citation of their method was also omitted. If the synthesis used in the OBOC Technology was our split-mix method and the screening approach was described by Smith et al. it seems justifiable to ask: what was invented by Dr. Lam?

Dr. Lam began to cite his Nature paper [11] as the source of the split-mix synthesis and the OBOC libraries and in addition replaced the Author by himself among the founders of combinatorial chemistry [20]. This was more than can be tolerated. Letters to Editor were sent to three journals criticizing his misleading citations and statements. The three articles were accepted and published after the editors and the publisher seriously examined the evidences [21-23]. Dr. Lam responded to one of the letters [21] writing among others the following:

"I independently conceived the split-mix synthesis idea around 1988, recognized the OBOC concept, and spent two years to complete a series of proof of concept experiments…" [24].

It is easy to say anything but is there any evidence to prove this statement? As the result of the second letter [22] Dr. Lam had to correct what he wrote about the OBOC libraries in his criticized article as follows:

"Standard solid phase peptide synthesis employing Fmoc-chemistry and split-mix strategy [Furka et al.] are commonly used for the synthesis of OBOC libraries..." [25].

This is in accordance with what was written above about the OBOC Technology.

Despite of all the documents cited in this article and the published corrections, the misleading referencing continues even these days.

9. Conclusions

The experiences in the past 27 years are very disappointing. The Author thinks that in the present peer reviewing system the confidentiality of the manuscripts is not ensured. It is almost impossible for a victim to make the plagiarism public and to seek justice. Generally rather the plagiarists are protected. It is concluded that introduction of new rules are needed that better protect the authors of scientific articles against plagiarism.

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