

**THE PATENTS ACT, 1970**  
**The Patents Rules, 2003**  
**(SECTION 25(1) and RULE 55)**

In the matter of the application for Patent Application. No 8417/CHENP/2012

And

In the matter of representation by way of opposition u/s 25(1) to the grant of patent thereon by

**Applicant:** THE JOHNS HOPKINS UNIVERSITY

**Opponent:** BIOCON LTD

**Present:**

Agents for Applicant: Vikas. J and Dr. Deepa Kachroo Tikku

Agents for Opponent: S. MAJUMDAR, Ms. Amrita Majumdar and  
Dr.Sanchitha Ganguly

**VIDEO CONFERENCE HEARING HELD ON 07/03/2023 BEFORE**

**Ms.RESMI C. SENAN**

**DEPUTY CONTROLLER OF PATENTS & DESIGNS**

**BRIEF HISTORY OF THE CASE**

**THE JOHNS HOPKINS UNIVERSITY** , hereinafter referred as **applicant**, have filed an application on 01/10/2012 for an invention titled “ COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS” was numbered as 8417/CHENP/2012 . As per the provision under Section 11-A of Patents Act, the said application was published on 14/02/2014. A request for examination under Section 11-B was filed on 26/02/2014. The said application was examined under Section 12 and 13 of Patents Act and FER was issued on 18/06/2018 the basis of the 67 claims filed on 03/10/2012 under sections 12 & 13 of the Patents Act, 1970 and the Patents Rules, 2003 with the objections u/s 2(1)ja, 3(d) ,3(e)

3(i), 10(4) (b, d, c) and 10(5). Response to FER was filed on 18/03/2019 with 16 amended claims.

**BIOCON LTD** , hereinafter referred as **opponent** filed Pre-Grant Opposition under Section 25(1) of the Indian Patents Act by on 20/10/2014 through their agent S. Majumdar & Co. within the stipulated time limit. Reply Statement in accordance with Section 25(1), Rule 55(4) of the Indian Patents Act was filed on 02/05/2022.

Hearing u/s 14 of The Patent Act, 1970 was issued on 20/01/2020 with the objections u/s 2(1)j(a) (lack of inventive step was maintained) and was held on 10/02/2020. Response to hearing notice was filed by the applicant on 24/02/2020.

Pregrant hearing was held on 07/03/2023 . The reply was submitted by applicant on 21/03/2023 and by opponent on 22/03/2023.

### **Grounds of Opposition**

Section 25(l)(a): the applicant for the patent or the person under or through whom he claims, wrongfully obtained the invention or any part thereof from him or from any person under or through whom he claims.

### **Documents submitted**

#### **On 16/10/2014**

**Exhibit A** -Complete specification in respect of Patent Application No. 8417/CHENP/2012

**Exhibit B**- license agreement on January 18, 2008

**EXHIBIT 1 to 5**- lab note books and other supporting documents

**EXHIBIT 6**- A copy of the said communication dated November II, 2008

**EXHIBIT 7** - A copy of the email of August 21, 2009

**EXHIBIT 8**- A copy of the email of September 30,2009

**EXHIBIT 8**- A copy of the email of September 30,2009

Notarized evidence in support of the opposition by Mr. Nagaraj Govindappa

**Annexures filed by Applicant**

**On 22/05/2022 & 21/03/2023**

Annexure-A

Copy of originally filed claims

Annexure-B

Copy of Amended claims filed on 18.03.2019

Annexure-C

Comparison table ( Figures depicting Invention 1 and instant application)

Annexure-D

Copies of the communications between Dr. Atul Bedi and representatives of the Opponent on 19 March, 2012

Annexure-E

Email dated Dec 9, 2008 From Atul Bedi to Kedarnath Sastry and Rajani Ravi- regarding the sequences for Tetanus toxin fragment C (TTC) and the subset pDOM fragment (pDOM). Email dated 31 st August 2008 from Atul Bedi to Kedarnath Sastry and Colleagues regarding " the alarmin - LL37 which include the peptide sequence. The peptides with various modifications are available from Innovagen - attached web site.

Annexure-F

Copy of article by Zhang et al, "Targeted and Untargeted CD137L Fusion Proteins for the Immunotherapy of Experimental Solid Tumors", Clinical Cancer Research 2007;13(9)May 1, 2007

Annexure-G

Article by Khawli et al, Cytokine, Chemokine, and CoStimulatory Fusion Proteins for the Immunotherapy of Solid Tumors, Therapeutic Antibodies,

Handbook of Experimental Pharmacology, 2008, vol 181. Springer, Berlin, Heidelberg

Annexure-H

Copy of email of Dr. Bedi 1

Annexure-I

Copy of email of Dr. Bedi

Annexure-J

Copy of Article by Alfthan et al, Properties of a single-chain antibody containing different linker peptides, Protein Engineering, Design and Selection, Volume 8, Issue 7, July 1995, Pages 725-731

Annexure-K

Copy of article by Shan et al, Characterization of scFv-Ig Constructs Generated from the Anti-CD20 mAb 1F5 Using Linker Peptides of Varying Lengths, J Immunol 1999, 162:6589-659

**On 28/05/2022**

Affidavits of Dr. Atul Bedi and Dr. Rajani Rani with copy of labnotes and research analysis

**On 22/03/2023**

Annexure-A - Figures depicting Invention 1 and instant application

Annexure-B- Amended set of claims

Annexure-C- Email dated Dec 9, 2008 From Atul Bedi to Kedarnath Sastry and Rajani Ravi- regarding the sequences for Tetanus toxin fragment C (TTC) and the subset pDOM fragment (pDOM). Email dated 31 st August 2008 from Atul Bedi to Kedarnath Sastry and Colleagues regarding " the alarmin - LL37 which include the peptide sequence. The peptides with various modifications are available from Innovagen - attached web site.

Annexure-D-E-mail dated Feb 11, 2011 From Atul Bedi to Kedarnath Sastry and Rajani Ravi mentioning that Confidential document containing the sequences for 14 products. Also mentioning that the sequences are IP of Johns Hopkins University and cannot be disclosed without a confidentiality agreement.

Annexure-E- Regarding E mails between Dr. Atul Bedi and Bicon regarding the developed molecule. It was specifically mentioned the Biocon has selected three molecules .e. BIOIAT01, BIOIAT02, BIOIAT10

Annexure-F- Zhang et al, "Targeted and Untargeted CD137L Fusion Proteins for the Immunotherapy of Experimental Solid Tumors", Clinical Cancer Research 2007;13(9)May 1, 2007

Annexure-G-L.A. Khawli et al., Cytokine, Chemokine, and Co-Stimulatory Fusion Proteins for the Immunotherapy of Solid Tumors, Springer-Verlag Berlin Heidelberg 2008

Annexure-H- Kaija Alfthan et al, Properties of a single-chain antibody containing different linker peptides , Protein Engineering vol.8 no.7 pp.725-731, 1995

Annexure -I - Daming Shan et al, Characterization of scFv-Ig Constructs Generated from the Anti-CD20 mAb 1F5 Using Linker Peptides of Varying Lengths<sup>1</sup>, The Journal of Immunology, 1999

*Annexures G, H and I were disclosing different conjugates*

Annexure -J- Same as the document of Annexure D mentioning an email dated E-mail dated Feb 11, 2011 From Atul Bedi to Kedarnath Sastry and Rajani Ravi mentioning that Confidential document containing the sequences for 14 products. Also mentioning that the sequences are IP of Johns Hopkins University and cannot be disclosed without a confidentiality agreement.

Annexure -K- US2008/071858

Annexure -L- Document Regarding Wrongful Obtaining from Patent Law by P Narayanan.

### **Grounds of Opposition**

**Section 25(1)(a):** the applicant for the patent or the person under or through whom he claims, wrongfully obtained the invention or any part thereof from him or from any person under or through whom he claims.

### **Field of Invention and Amended claim**

#### **The instant invention is related to**

Fusion proteins comprising a targeting moiety fused to an immunomodulatory moiety, wherein the targeting moiety specifically binds Programmed Death-1 (PD-1) receptor/ligand family i.e., PD1, PD-L1 or PD-L2; and the immunomodulatory moiety specifically binds Transforming growth factor-beta (TGF- $\beta$ ).

#### **Amended claims filed on 22/03/2023 :**

1. A molecule comprising a targeting moiety fused with an immunomodulatory moiety, wherein: (a) the targeting moiety comprises an antibody, antibody fragment, scFv, or Fccontaining polypeptide that specifically binds to Programmed Death-1 (PD-1), Programmed death-1 ligand 1 (PD-L1), or Programmed death-1 ligand 2 (PD-L2), and (b) the immunomodulatory moiety specifically binds to: Transforming growth factorbeta (TGF- $\beta$ ).
2. The molecule as claimed in claim 1, wherein the immunomodulatory moiety comprises an amino acid sequence of the extracellular domain of Transforming growth factor-beta receptor (TGF- $\beta$ R) or Transforming growth factor-beta receptor II (TGF $\beta$ R II) or a fragment thereof.
3. The molecule as claimed in claim 2, wherein the immunomodulatory moiety comprises an amino acid sequence of the extracellular domain of Transforming growth factor-beta receptor selected from the group consisting of SEQ ID NO: 79-91.
4. The molecule as claimed in claim 3, wherein the immunomodulatory moiety comprises the amino acid sequence corresponding to SEQ ID NO:87 or a binding fragment thereof.
5. The molecule as claimed in claim 1, wherein the targeting moiety binds Programmed death1 ligand 1 (PD-L1).

6. The molecule as claimed in claim 1, wherein the targeting moiety comprises an extracellular ligand-binding domain or ectodomain of Programmed Death-1 (PD-1) or a fragment thereof.

7. The molecule as claimed in claim 6, wherein the molecule comprises an immunoglobulin Fc region, and amino acid sequence of TGFβRII ectodomain or a fragment thereof.

8. The molecule as claimed in claim 7, wherein the molecule comprises an amino acid sequence corresponding to SEQ ID NO: 11 or 12. 9. The molecule as claimed in claim 1, wherein said immunomodulatory moiety is fused to the C-terminus or N-terminus of said targeting moiety.

10. The molecule as claimed in claim 1, wherein said targeting moiety and said extracellular ligand-binding domain of a receptor are fused with each other via a linker.

11. The molecule as claimed in claim 10, further comprising a linker at the CH3 region of the Fc.

12. The molecule as claimed in claim 11, wherein the linker is (GGGGS)<sub>n</sub> and wherein n is 1, 2, 3, 4, 5, 6, 7 or 8.

13. The molecule as claimed in claim 12, wherein the linker comprises the amino acid sequence GGGSGGGSGGGGS (SEQ ID NO: 104). 14. The molecule as claimed in claim 1, wherein the targeting moiety is an immunoglobulin IgG of subclass IgG1, IgG2, IgG3 or IgG4

The submissions provided by the applicant and opponent are available in the uploaded documents of the instant case. The arguments provided by opponent and applicant have been taken on record but not detailed here for the sake of brevity.

**My inference from the arguments and explanations are as follows:**

The arguments, explanation, written submissions and annexures by applicant and opponent have been carefully considered.

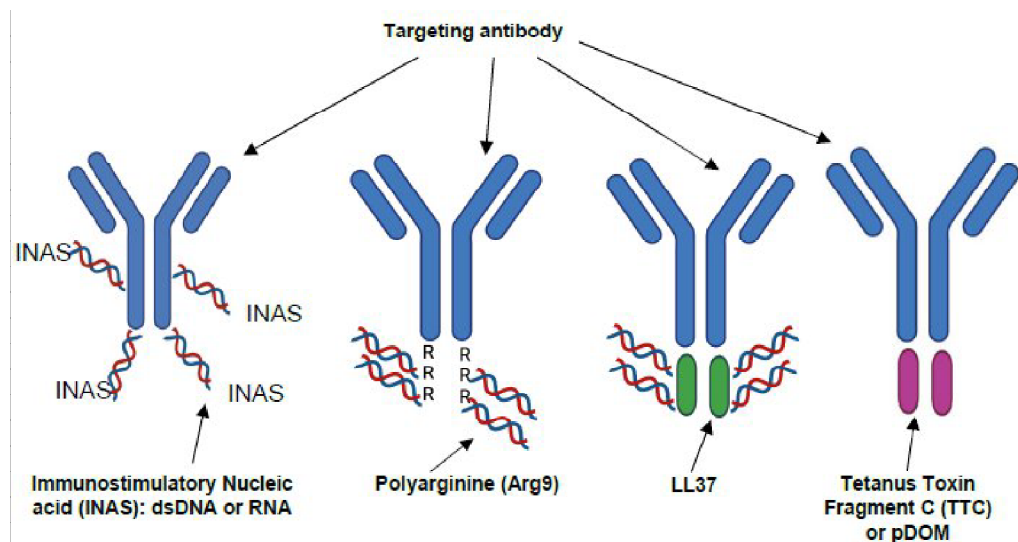
**Regarding Exhibit B-** license agreement on January 18, 2008

The applicant argued that there are Technology 1 and Technology 2. Technology 1 (INAS) is covered under the 2008 agreement and 'Technology 2'

(instant invention) are completely distinct. They had provided a table and pictorial representation to distinguish the two inventions.

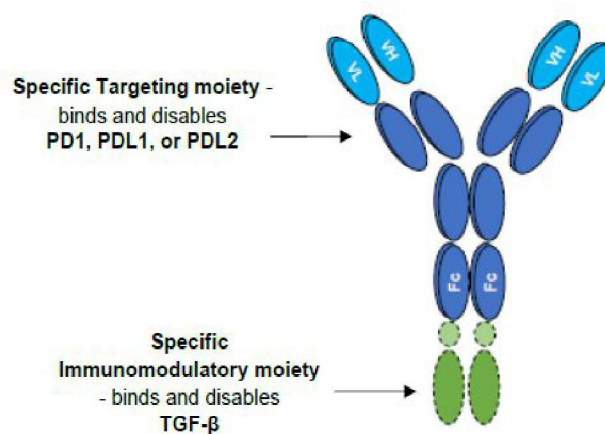
Pictorial representation as submitted by the applicant

INVENTION 1: Tumor targeted antibody conjugated to Immunostimulatory Nucleic acid (INAS) or peptide



PRESENT INVENTION (Protein-Protein fusion): Tumor targeted antibody/moiety

conjugated to Immunomodulatory moiety/peptide



The argument by opponent has not been found persuasive for the following reasons with respect to Exhibit B

- The applicant was unrelated to 2008 agreement . Exhibit B was between **IATRICa** and the **Opponent**.
- Agreement with IATRICa as evidenced by Exhibit B **for sublicensing and co-developing three INAS immunoconjugate molecules**.
- In particular, the IATRICa engaged the opponent for services including **purifying said INAS conjugates**. The opponent was responsible for identifying third party vendors for purifying said conjugates. The opponent accordingly considered Reamatrix and Life Technologies as vendors. The said Reamatrix was chosen in June 2008.
- The invention **covered under the 2008 agreement and the ‘present invention’ are completely different technologies and nowhere related with instant invention as the invention covered under the 2008 agreement is three INAS (immunogenic nucleic acid sequences)** and the instant invention is related with **protein-protein fusion molecules**. **The argument by applicant has been considered and found persuasive.**
- With reference to agreement of both parties, point 4.5 clearly mentioned that **“no rights beyond products”**. So based on this opponents points are void.

#### **Regarding Exhibit 1 and 2 (lab notes)**

The opponent has provided 3 pages of lab notes dated 01/09/2008 as evidence for the generation molecules. Page nos are 192, 193 and 194 of pregrant opposition filed on 20/10/2014.

The applicant argued that there are Technology 1 and Technology 2. Technology 1 (INAS) is covered under the 2008 agreement and ‘Technology 2’ (instant invention) are completely distinct and also argued that the illustrated pages are not at all a part of the instant invention.

In the pregrant opposition documents, the opponent has mentioned that the lab notes books dated between **September 1, 2008 and September 20, 2008** clearly indicate the development of fusion proteins with said

linker/spacer and email dated October 23, 2008 also shows the cooperation for co-developing fusion proteins between the opponent and IATRICa.

**The argument has not been found persuasive for the following reasons:**

Lab notes dated 01/09/2008 has only been submitted. The **authenticity** of the lab notes has not been found valid for the following reasons detailed below:

**Date and Sign:** Every entry should be dated and signed by the researcher. Witness signatures can also add credibility.

**Observation:**

**Pages 192 and 194 are incomplete.**

**Signature of the task person has not been provided. It was signed only by the Supervisor.** The document **lack signature from independent witness** who can attest to the accuracy and authenticity of the entries.

**The opponent has submitted the lab notes on 01/09/2008. Still failed to provide the chronological order of pages of the same.**

**On detail analysis, it was found that there are certain discrepancies in the dates mentioned in Exhibit 2. Exhibit 2 was a lab note signed by the supervisor on 01/09/2008. This document refers to an analysis done 28/10/2008 for an optimized sequence of Pichia pastoris. The authenticity of this document cannot be valid due the discrepancy in the dates mentioned in Exhibit 2.**

**The page is given below: -**

## BRED RECORDS

PROJECT NO.: 1182

EXPERIMENT NO.: 2

PAGE NO.: 003

PRINTED FROM PAGE NO. :

sequence of the construct

[illegible][illegible]

15 SPGERVFSFCRASQSIGNIHMYQQRNGSPRLIKYASESISG  
 20 QSDFTLSINSGVEDIADYQQQNNMWPTTFQAGTKLELKGGGGS  
 25 QSQVOLKSGSPGLVYQSSLSITCTVGFSGSLTNGYVHVSQFGPK  
 30 NGVNGGNTDNTPTFSTRLSINKNSKQVFFKMNSLNDTAYYCRA  
 35 VHYGQGLTVTSAGGGSSLGDFFRKSKEIKGEFKIVQRIKDFLRN

Black color: VL, Pink color: Linker between VL and VH, Blue color: VH,  
Green color: Linker between scFV and LL37 and Red color: LL-37 (Alarmin)

we minimized the above expression at constant temperature in PBCa partition.

Relationships and the Corresponding amino acid sequence

**Blocon - Nagaraj Govindappa**  
**BIOIATCETX1**

Report No. 0834155

Contig length: 881 bp

Optimized for expression in: *Pichia pastoris*

Analysis created: 10/28/2008 (16:36H)

*Xba*I *Xho*I *Hinc*II  
 GGTACCTCGAAGAGAGACATCTGTGTGACTCAGTCCCGAGTTATTTGCTCTTTTCC  
 -----  
 CCATCGACCTCTCTCTCTGTGAGAACAACTGAGTCAGGGGTCAATAAAGCAGACAAGGG  
 K R D I L L T Q S P V F L S V S F  
 1 3 5 7 9 11 13 15 17

61 CAGGTGAAAGAGTTTCATTCTCCTGTAGAGCTTCCCAATCCATCGGAACTAACATCCACT  
-----+-----  
GTCCACTTTTCAAAGTAGAGGACATTCGAAGGGTAGGTAGCCTTGATTTGTAGGTGA  
\_ G E R V S F S C R A S Q S I G T N I H W  
  19   21   23   25   27   29   31   33   35   37

SIGNATURE OF THE TASK PERSON  
NAME :  
DATE :

SIGNATURE OF THE SUPERVISOR  
NAME :  
DATE : 01/09/2008

Continued to Page No. : 4

**Detail:** Include detailed descriptions of experiments, procedures, results, and observations. This helps to demonstrate the inventive process and the progression of the work.

**Observation:** Pages 192 and 194 lacks clarity and these pages are incomplete. The left part of page 1 of Exhibit 1 and exhibit 2 are darkened cannot be read. Moreover these pages are not enough to give details about the invention.

Exhibit 1

Biocore-ATRICAL collaborative project  
The following approaches were considered to develop  
a new method:  
1. Conjugation of DNA oligomer to antibodies  
2. Conjugation of INAS SS DNA oligomer to Receptor  
3. This was carried out by Receptor  
4. Conjugation of CPAA oligo into Receptor  
5. Bion carried out this work.

To develop a second generation molecules  
to establish simple non-covalent conjugation  
system. It was decided to express SCFV fragment  
in *Pichia pastoris*. In this program:-

- ① Cetuximab SCFV
- ② Cetuximab SCFV-LL37
- ③ Cetuximab SCFV-LL37RK (This version is  
designed to avoid any Kozak cleavage).

→ The idea behind inclusion of LL37 is  
LL37 can non-covalently bind to DNA and take  
it into the target along with antibody molecule.

\_\_\_\_\_  
SIGNATURE OF THE SUPERVISOR  
NAME: \_\_\_\_\_  
DATE: 01/09/2008

Continued to Page No.: 2

192

194

**Chronological Order:** The entries in the lab notebook should be in chronological order, providing a timeline of the research and development activities. This helps establish a clear sequence of events leading to the invention.

**Observation:** . There is discrepancy in numbering the pages. Page 1 has not been submitted. The opponent has submitted the lab notes on 01/09/2008. The pages were not in chronological order.

Page no 192 - continued to Page 2

Page No 193- Continued from Page 1. Since the page no 1 is absent in the Exhibit 1, the reliability cannot be determined.

**Legibility:** The handwriting in the lab notebook should be legible, and any corrections or additions should be clearly marked with the date and signature of the person making the changes.

**Observation: Page 1 of Exhibit and Exhibit 2 are not legible. The pictures were illustrated above**

**Originality:** Lab notes should demonstrate the originality of the invention by documenting the problems encountered, the solutions attempted, and the unique aspects of the final invention.

**Observation: Only a part of the lab notes was submitted which is not enough to substantiate the originality of documents due to illegibility, incomplete description and discrepancies in dates mentioned in the submitted pages.**

**Relevance:** The content of the lab notes should be directly relevant to the claims of the patent. They should show the conception and reduction to practice of the invention.

**Observation: In the technical aspect, the illustrated invention is different from the instant application.**

**Illustrated invention is regarding the optimized scFv expression in Pichia pastoris .**

**The instant invention is regarding Fusion proteins comprising a targeting moiety fused to an immunomodulatory moiety, wherein the targeting moiety specifically binds Programmed Death-1 (PD-1) receptor/ligand family i.e., PD1, PD-L1 or PD-L2; and the immunomodulatory moiety specifically binds Transforming growth factor-beta (TGF- $\beta$ ).**

Hence the content of the lab notes are not relevant to the instant application.

Thus Exhibit 1 and 2 are considered invalid .

### **Regarding Exhibit 3, 4,5**

Exhibit 3 is an email from Biocon to Dr. Atul Bedi . This about the LL-37 sequence for making alarmin fusion protein for expression in Pichia.

Exhibits 4 and 5 of the opposition

1) fusion molecules of “antibodies and LL37 cationic peptides

2) fusion molecules of “antibodies and pDOM

The applicant replied that these molecules are not a part of instant invention. The **design and mechanism of action of the specific fusion proteins** of present invention are completely different.

The explanation has been found persuasive. Hence Exhibit 3-5 are considered as invalid.

### **Regarding Exhibit 6**

Exhibit 6 is an email from Biocon to Dr. Atul Bedi **regarding the orientation of oligo to antibody, which is no way related to the instant invention.**

### **Regarding Exhibit 7**

Exhibit 7 is a forwarded email dated 21st August 2009, from Biocon to Dr. Atul Bedi. The original mail was from the Yale University regarding TGF-beta and IL-15 in controlling the number and survival of CD8<sup>+</sup> T- cells in killing tumour cells and cells affected with viruses.

The applicant replied that their work is not based on TGF-beta *per se*.

In my opinion, research papers can be vital sources of information and inspiration that can lead to new inventions since it provide detailed insights into existing problems, current solutions, and gaps in knowledge. In the instant case, **the opponent has not been substantiated how this e mail and research paper mailed by them is leading to the instant invention.**

### **Regarding Exhibit 8 & 9**

Exhibit 8 is an email from Biocon to Dr. Atul Bedi **dated on September 30,2009**. This e mail is regarding the amino acid sequences of:

Fusion construct of cetiximab, BIOMAb- EGFR, trastuzumab and rituximab.

The applicant has explained that the antibody-fusion molecules disclosed in ‘Exhibit 8’ of the Opposition are NOT a part of the instant application. More

particularly, **NEITHER the targeting moiety NOR the immunomodulatory moiety of the claims of present application** have any connection to the molecules disclosed in Exhibit 8 & 9. Also added that the said sequences were publicly well documented.

The applicant's explanation has been found persuasive and Exhibit 8 & 9 are considered as invalid.

The interlocutory petition and the supporting documents have been considered. The applicant's arguments with respect to lab notes and explanations have been taken on account. The arguments provided by the applicant regarding the difference in the molecules of the agreement (INAS immunoconjugate molecules) and instant application has been found persuasive.

Exhibit II filed as a support to interlocutory petition, with regard to Confidentiality and Non-Disclosure Agreement between Biocon limited and Evitria and IATRICa. The applicant is unrelated to this agreement and it is not specifically mentioning to any molecules, not even to INAS immunoconjugates. Protien-protein fusin products are not at all a part of this agreement.

The arguments provided by the applicant has been found persuasive since none of the documents clearly mentioning about the components of the instant invention.

In the technical perspective, the **concept of a targeting moiety is common to both INAS conjugates and fusion proteins, but the** overall structure and mechanism of action differ.

Since the evidence in support of the interlocutory **petition** has been found irrelevant, the same is not allowed.

### **Technical views summarized for Targeting Moieties and Linker**

The arguments, explanation, written submissions and annexures by applicant and opponent have been carefully considered.

### **Targeting Moieties**

A targeting moiety of fusion proteins or drug delivery systems refers to a specific component designed to direct the therapeutic or diagnostic agent to a particular cell type, tissue, or molecular target.

**The concept of a targeting moiety is common to both INAS conjugates and fusion proteins.**

While the targeting moiety serves a similar purpose in both INAS conjugates and fusion proteins, the overall structure and mechanism of action differ:

- INAS Conjugates: Typically involve chemical conjugation of an antibody to a drug, focusing on the targeted delivery and controlled release of the drug.
- Fusion Proteins: Involve genetic fusion of protein domains, often resulting in multifunctional proteins that can simultaneously perform targeting and therapeutic functions.

As per the 2008 agreement, the molecules of Invention is INAS immunoconjugates.

The same targeting moieties can be a part of immuno conjugate as well as for fusion proteins.

While the targeting moiety serves a similar purpose in both INAS conjugates and fusion proteins, the overall structure and mechanism of action differ:

- INAS Conjugates: Typically involve chemical conjugation of an antibody to a drug, focusing on the targeted delivery and controlled release of the drug.
- Fusion Proteins: Involve genetic fusion of protein domains, often resulting in multifunctional proteins that can simultaneously perform targeting and therapeutic functions.

Hence the arguments regarding targeting moieties purposed by the opponent has not been found persuasive.

### **Linker**

The specific linker which is used in the instant application is **GGGSGGGSGGGGS linker.**

In the matter of the instant case, the opponent argue that the linker is optimized by them for invention 1 ( INAS conjugates) and was used by the applicant in invention 2 ((protein protein conjugate)

The repeating units of GGGGS is a **common flexible peptide linker sequence** used in protein engineering. The repeating units of GGGGS in the sequence help to ensure that the linked protein domains maintain their respective functionalities and structures by providing the necessary spatial separation and flexibility. This linker is often used in recombinant protein design, **fusion proteins**, and synthetic biology applications.

The argument by opponent has not been found persuasive for the following reasons with respect to the linker.

- The applicant was unrelated to 2008 agreement ( Exhibit B) between **IATRICa**, the **Opponent**.
- Agreement with IATRICa as evidenced by Exhibit B **for sublicensing and co-developing three INAS immunoconjugate molecules**.
- The invention **covered under the 2008 agreement and the 'present invention' are completely different technologies and nowhere related with instant invention as the invention covered under the 2008 agreement is three INAS (immunogenic nucleic acid sequences)** and the instant invention is related with protein-protein fusion.

***The instant invention does not involve chemical conjugation of oligonucleotides to an antibody but provides specific protein-protein fusion molecules.***

- The GGGGS linker used in the instant application is **already known in the prior art** . The generic concept of fusing a peptide/polypeptide sequence to the C-terminus of a target protein is known in the art. The applicant has submitted **Annexures H & I** to substantiate the same which has been found persuasive.
- The opponent argued that Exhibit 2 has demonstrated the use and optimization of such linkers to attach protein-protein constructs. This research has done as a part of INAS molecules and optimized the expression in *Pichia pastoris*. It was argued that the Opponent optimized its conformation, i.e. point of attachment of the linker to the targeting moiety.

**Selecting and optimizing a linker** by a person skilled in the art involves understanding the requirements of protein engineering, particularly the need for a flexible and minimally invasive connection between protein domains. This can be done by a person skilled in art by both **theoretical considerations and practical results** . **Since the inventor is also a person from the similar field**, the selection of this linker may be based on **empirical data from his studies** that have demonstrated its effectiveness in maintaining the functional and structural integrity of fusion proteins. Since the invention is considered as whole, the inventiveness of the linker cannot be denied. Hence the argument based on Exhibit 2 cannot be accepted.

- The opponent argued to exclude portions of the specification including claims disclosing the linker (GGGGS)<sub>n</sub> since the linker is known in the art. The instant application refers to fusion proteins. For the successful construction of a fusion protein the two essential elements are component proteins and the linkers. The crux of the invention lies in the final product . In the instant application the targeting moiety fused with an immunomodulatory moiety by using a linker. The use of an empirical linker is a part of fusion. Hence the only the use of this flexible empirical linker in this invention cannot be denied.

Exhibit B, 1-7 were discuss about the INAS conjugates. This is very clear from the agreement. The licensing agreement is only for immunostimulatory nucleotide conjugated Targeted Moieties.

**EXHIBIT 1 to 9** - These are disclosing the research details which include certain targeting moieties and constructs used for INAS conjugates.

The instant invention is related to

Fusion proteins comprising a targeting moiety fused to an immunomodulatory moiety, wherein the targeting moiety specifically binds Programmed Death-1

(PD-1) receptor/ligand family i.e., PD1, PD-L1 or PD-L2; and the immunomodulatory moiety specifically binds Transforming growth factor-beta (TGF- $\beta$ ).

In an opposition hearing, objections regarding patentability are directly within the purview of the patent office, which refers to the legal requirements for obtaining a patent, including novelty, non-obviousness, and industrial applicability.

The opponent claims that the patent was wrongfully obtained due to a breach of a licensing agreement. On the basis of this, the specifics of the claim has been examined and found that the **concept of a targeting moiety is common to both INAS conjugates ( as specified in the 2008 agreement) and fusion proteins (instant application).**

**In the technical view it has been found that overall structure and mechanism of action INAS conjugates and Fusion proteins differ:**

- INAS Conjugates: Typically involve **chemical conjugation of an antibody to a drug, focusing on the targeted delivery and controlled release of the drug.**
- Fusion Proteins: Involve **genetic fusion of protein domains, often resulting in multifunctional proteins that can simultaneously perform targeting and therapeutic functions.**

When the patentability criteria is evaluated, the instant application has been met the criteria and hence found that the application can be considered for grant of Patent.

It is evident from Intellectual Property Appellate Board (IPAB), Chennai decision in FDC Ltd. Vs. Sanjeev Khandelwal and Ors. [OA/15/2009/PT/MUM] dated 21.03.2014 where it was held that in para 88” Where an invention has been obtained from an opponent, the novelty of such invention must be considered in the light of prior specification and patents...” In para 89 of the decision “Obtained the invention means obtained the invention which is purported to be patented meaning thereby to refer to the identity of the invention not the right of the person from whom it was obtained to be regarded

as the first and true inventor” In para 90 “ An application for a patent will be refused only if a clear case of obtaining is established. It would appear that when the matter is in doubt, the application will be allowed to proceed on the patent not amended or revoked leaving the question to be decided by the Court in a revocation proceeding.” In para 91 “An opposition upon the ground of obtaining usually involves the credibility of witnesses and will not be decided against the applicant or the patentee unless there is very little doubt on the facts, since the opponent always has an opportunity of having the question tried by the Court or a petition to revoke the patent.” In para 92 “The burden of proof is on the Opponent if the allegation is that the invention is obtained Thus referring to the para 89 of IPAB order above ,for assessing if the invention is wrongfully obtained , it has to be ascertained if it is “identical “ to the evidences submitted by the Opponent. But none of the evidences submitted by the Opponent (Exhibit B, 1-9 ) and interlocutory petition ( Exhibit 1-III) are identical to the present claims as discussed above.

An application for patent will be refused only if a clear case of obtaining is established. In view of the discussion in the preceding paragraphs, considering the relevant oral and written submissions made by both the parties and all the circumstances of the case, the pre-grant opposition filed under section 25(1) (a) of the Patent Act is not considered.

### **Inference with regard to hearing conducted u/s 14**

#### **Clarity and Conciseness**

The explanation provided by the applicant has been found persuasive, hence the objection is considered as met.

#### **Invention u/s 2(1)(ja)**

Upon analysis, it has been found that,

D1 fails to disclose the fusion protein can comprise a targeting moiety that binds to a protein from PD-1 receptor/ligand protein family and an immunomodulatory moiety binding to TGF- $\beta$ .

D2 fails to disclose a moiety that binds any PD1 receptor/ligand family member.

D3 fails to disclose an iota of suggestion or guidance with regard to fusion molecules that bind any PD1 receptor/ligand.

D4 fails to disclose an iota of suggestion or guidance in D4 regarding fusion molecules/proteins.

D5 fails to suggest or hint at a conjugate of IL-2 and TGF $\beta$ RII, or its use in cancer immunotherapy.

The comparative experiments provided by the applicant to show the improved technical efficacy have been found satisfactory. Inventive step is acknowledged for the currently amended claims.

#### **Non-Patentability u/s 3 & Sufficiency of Disclosure u/s 10 (4)**

It was explained that, none of the citations D1-D5 disclose or suggest the fusion molecule as presently claimed. The present invention directed to a fusion molecule comprising a targeting moiety fused with an immunomodulatory moiety.

The Applicant has submitted data for comparative experiments as affidavit.

- i) anti-PDL1 alone (targeting moiety),
- ii) non-targeted anti-TGF $\beta$  alone (immunomodulatory moiety), and
- iii) combination of anti-PDL1 and non-targeted anti-TGF $\beta$

The comparative experimental results submitted by the applicant have been found satisfactory. Hence the objection u/s 3(d) and 10(4) have been considered as met.

#### **Unity of Invention u/s 10 (5)**

Regarding objection u/s 10(5), it was explained that, the fusion molecule comprising targeting moiety binding to PD-1 receptor/ligand protein family (a T cell co-inhibitory molecule) and immunomodulatory moiety binding to TGF- $\beta$ . The common technical feature is the **bispecific fusion molecule** binding to both PD-1 receptor/ligand protein family and TGF- $\beta$  which is inventive over

prior art thereby forming the special technical feature. The explanation provided by the applicant has been found persuasive, hence the objection is considered as met.

### **Decision**

After considering the Applicant's submissions (oral as well as written), and amendments, the requirements of outstanding objections are treated as met. The application is found to be in order for grant of patent with the revised claims 1-14.

Pregrant opposition disposed.

Dated this on 09/08/2024

(Resmi C. Senan)

Deputy Controller of Patents & Designs

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