


RELEASE ORDER

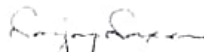
Subject: Release from BIRAC under **ACADEMIC INNOVATION RESEARCH (AIR)** under Promoting Academic Research Conversion to Enterprise (PACE) for the project entitled " **Echis carinatus venom induced sustained tissue necrosis and validating the therapeutic potential of DNase enzyme time kinetics in mammalian models**"

1. In continuation of BIRAC's **Grant-In-Aid Letter Agreement (GIA)** Ref. No. **BT/AIR0607/PACE-16/18** of even no. dated **2nd July, 2019** the approval of the competent authority is hereby accorded to release an amount of **Rs. 14.502 Lakhs (Rupees Fourteen Lakhs Fifty Thousands Two Hundred Only)** as Grants-in aid to **University of Mysore, Mysuru**, the Applicant, being the **first instalment** for implementation of the project entitled " **Echis carinatus venom induced sustained tissue necrosis and validating the therapeutic potential of DNase enzyme time kinetics in mammalian models**" with **Dr. K. Kemparaju, Professor, University of Mysore, Department of Studies in Biochemistry, Manasagangotri, Karnataka, Mysuru - 570 006**, the Project Investigator from the Academia.
2. The State Bank of India is being separately instructed to disburse the amount of **Rs. 14.502 Lakhs (Rupees Fourteen Lakhs Fifty Thousands Two Hundred Only)** in the bank account of **University of Mysore, Mysuru**, as per the bank details of the recipient given below:

Name of the Bank	State Bank of India
Branch Address	University Campus Branch, Crawford Hall, Mysore -570005
Account Number	54007591437
Account Holder's Name	Finance officer, University of Mysore, Crawford Hall, Mysore -570005
PAN Number	AAAGU0083N
MICR Number (on Cheque)	570002056
NEFT/IFSC Code	SBIN0040059


Dr. K. KEMPARAJU, M.Sc., Ph.D
Professor
Dept. of Studies in Biochemistry
University of Mysore
Mysore - 570 006, INDIA.

3. The other terms and conditions governing this financial release will remain the same as mentioned in the GLA dated 2nd July, 2019.
4. The Expenditure is debitable to PACE scheme under BIRAC Head of Accounts B.04 for the financial year 2019-20.
5. This issues with the concurrence of BIRAC Finance Division (BFD) and approval of the Competent Authority vide BFD No ~~BFD(R.O/B:04/0156)2019-20~~ dated ... ~~26.7.2019~~.
6. The Release order has been noted at Serial No. 56 in the Grants Register.

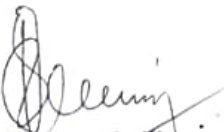

Dr. Sanjay Saxena
(GM & Head Investment, BIRAC)

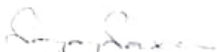
To,

Dr. K. Kemparaju, Professor, University of Mysore, Department of Studies in Biochemistry, Manasagangotri, Karnataka, Mysuru - 570 006
Email: kemparajuom@gmail.com

Copy to,

1. BIRAC Finance folder.
2. Sh. Nand Kishore, Senior Finance Officer, Biotechnology Industry Research Assistance Council, New Delhi. E-mail: nkishore.birac@nic.in
3. Sanction Folder


Dr. K. KEMPARAJU, M.Sc., Ph.D.
Professor
Dept. of Studies in Biochemistry
University of Mysore
Mysore - 570 006, INDIA


Dr. Sanjay Saxena
(GM & Head Investment, BIRAC)

To,
Dr. K. Kemparaju
Professor,
University of Mysore
Department of Studies in Biochemistry
Manasagangothri, Karnataka.
Mysuru - 570 006
Email: kemparajuom@gmail.com

2.7.2019

Ref: PACE Project Title "*Echis carinatus* venom induced sustained tissue necrosis and validating the therapeutic potential of DNase enzyme time kinetics in mammalian models"

Dear Dr. Kemparaju.

With reference to your above, mentioned PACE proposal, we are pleased to inform that your proposal has been approved by BIRAC at a total cost of Rs. 48.34 Lakhs (Rupees Fourty-Eight Lakhs and Thirty-Four Thousands only) The contribution of BIRAC is Rs. 48.34 Lakhs (Rupees Fourty-Eight Lakhs and Thirty-Four Thousands only) as Grant-in-aid to the University of Mysore for 18 Months as per the terms of the Grant in Aid Letter Agreement (GLA) enclosed.

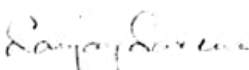
If you are in acceptance with the terms of funding support as mentioned in the Gil A, the following documents should be executed within a time period of **TWO WEEKS** from the date of issue of this communication

- Grant-in-aid Letter Agreement (GLA) including all the Schedules: All pages to be clearly initialled with proper stamp by the Fund Recipient.
- Letter of Authorization from the institute in the prescribed format of BIRAC
- Bank Details

The Grant-in-Aid Letter agreement has been executed by BIRAC, kindly take a colour printout of this GLA and the schedules; and execute the same from your end.

The first instalment of fund release will be made only after completion of all these formalities and upon submission of above mentioned documents as per norms.

For Biotechnology Industry Research Assistance Council


Dr. Sanjay Saxena
(GM & Head - Investment)



Ref. No. BT/AIR0607/PACE-16/18

Dated : 27.7.2019

Sub: Funding of Project entitled "Echis carinatus venom induced sustained tissue necrosis and validating the therapeutic potential of DNase enzyme time kinetics in mammalian models" for funding under ACADEMIC INNOVATION RESEARCH (AIR) under Promoting Academic Research Conversion to Enterprise (PACE)

GRANT-IN-AID LETTER AGREEMENT

This Grant-in-aid Letter Agreement (hereinafter called as "GLA") is between Biotechnology Industry Research Assistance Council, a Government of India enterprise, incorporated under the Companies Act, 2013 having its office at 1st Floor, MTNL Building, 9, CGO Complex, Lodhi Road, New Delhi- 110003 (the "BIRAC") and the entities mentioned below for research **proposal entitled " Echis carinatus venom induced sustained tissue necrosis and validating the therapeutic potential of DNase enzyme time kinetics in mammalian models"**

1. Recipient(s) and Designated Project Investigator(s):

S. No.	Recipient(s)	Designated Project Investigator
1	University of Mysore, an Institute having its office at Department of Studies in Biochemistry, Manasagangotri, Karnataka a. Mysuru - 570 006, hereinafter referred to as the "Institute" (which expression shall wherever the context so admits include its successors in interest, liquidators, administrators and permitted assignees).	Dr. K. Kemparaju Professor, Department of Studies in Biochemistry, University of Mysore, Manasagangotri, Karnataka. Mysuru - 570 006 Email: kemparajuom@gmail.com

2. Aims & Objectives:

The detailed aims and the objectives that are to be executed by the aforesaid are as per the detailed Project document, submitted including revisions/modifications incorporated therein hereinafter called as "Project") and appended herein as Schedule 3.

The main objectives proposed to be achieved from the project are enumerated hereunder:

- To establish the time and dose kinetics of Ec venom induced tissue necrosis at the snake bite site using two mammalian model systems
- To establish the therapeutic use of DNase-1 to prevent further tissue necrosis of Ec venom induced post necrotic animal models.
- To evaluate the effect of Ec venom on the Extracellular Traps ETs using blood cells other than neutrophils.

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3. **Project Duration:** The Recipients shall complete the Project within the stipulated period of 18 months from the date of acceptance of the GLA by all the recipients. In the event the Parties affix their signatures to this GLA on separate dates, the GLA shall be effective from the date on which the last set of signature is affixed thereto "**Effective Date**". Project Duration is subject to the Change order(s) issued by the BIRAC from time to time.

4. **Project Implementation Site:**
 Department of Studies in Biochemistry,
 University of Mysore,
 Manasagangothri, Karnataka-570 006

5. **Project Cost and Contribution:** The total estimated cost of the Project is **Rs. 48.34** Lakhs (Rupees Forty-Eight Lakhs and Thirty-Four Thousands only). The contribution of BIRAC is **Rs. 48.34** Lakhs (Rupees Forty-Eight Lakhs and Thirty-Four Thousands only) as Grant-in-aid to the **University of Mysore** on the terms and conditions detailed in this GLA.

6. **BIRAC Budget break-up (Year Wise): (Rs In Lakhs)**

Details	Support under PACE to University of Mysore	Total
Non-recurring	5.00	5.00
Recurring	43.34	43.34
Total	48.34	48.34

BUDGET Break-up Non-Recurring (Rs. In Lakhs)

Non Recurring items	Contribution by BIRAC to University of Mysore	Total
Equipment's	4.00	4.00
Accessories	1.00	1.00
Total	5.00	5.00

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 Professor
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 University of Mysore
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BUDGET Break-up Recurring (Rs In Lakhs)


Recurring items	Contribution by BIRAC to University of Mysore	Total
Manpower	2.56 ₹	2.56 ₹
Consumables	36.78 ₹	36.78 ₹
Travel	1.50 ₹	1.50 ₹
Outsourcing	1.00 ₹	1.00 ₹
Contingency & Other Costs	1.50 ₹	1.50 ₹
Total	43.34 ₹	43.34 ₹

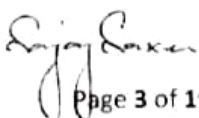
Details Of Equipment Proposed To Be Acquired Through BIRAC Contribution For Applicant Institute

S.No	Infrastructure/Equipment	Capacity	Quantity	Specific Requirement In The Project	Estimated Value (Rs.In Lakhs)
1	Bio-rad Western Blotting and electrophoresis Unit	NA	1	Identification of NETosis marker and DNA Analysis, Protein and Antibody Interactions, Testing Antibiotics	4.00 ₹
Accessories To Be Acquired (Rs in Lakhs):					1.00 ₹
Total:					5.00 ₹


7. Milestones/Timelines

S.No.	Milestones	Month of end of activity	Required financial input (Rs. In Lakhs)
1	Acceptance of Undertaking under GLA And Fulfilment of fund release requirements	0	14.502 ₹ (30% of BIRAC contribution)


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BUDGET Break-up Recurring (Rs in Lakhs)

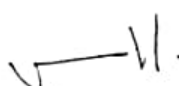
Recurring items	Contribution by BIRAC to University of Mysore	Total
Manpower	2.56	2.56
Consumables	36.78	36.78
Travel	1.50	1.50
Outsourcing	1.00	1.00
Contingency & Other Costs	1.50	1.50
Total	43.34	43.34

Details Of Equipment Proposed To Be Acquired Through BIRAC Contribution For Applicant Institute

S.No	Infrastructure/Equipment	Capacity	Quantity	Specific Requirement In The Project	Estimated Value (Rs.In Lakhs)
1	Bio-rad Western Blotting and electrophoresis Unit	NA	1	Identification of NEIosis marker and DNA Analysis,Protein and Antibody Interactions,Testing Antibiotics	4.00
Accessories To Be Acquired (Rs in Lakhs):					1.00
Total:					5.00

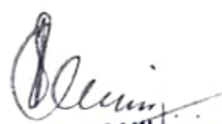
7. Milestones/Timelines

S.No.	Milestones	Month of end of activity	Required financial input (Rs. In Lakhs)
1	Acceptance of Undertaking under GLA <i>And</i> Fulfilment of fund release requirements	0	14.502 (30% of BIRAC contribution)


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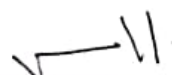
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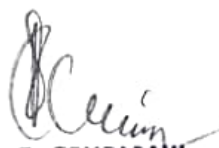




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2	<p>Status report on Completion of at least one <i>in vivo</i> study to establish the time and dose kinetics of Ec venom induced tissue necrosis at the snake bite site</p> <p style="text-align: center;"><i>And</i></p> <p>Submission of UC/SOE for the corresponding milestone certified by internal finance.</p>	6	<p>9.668 ₹ (20% of BIRAC contribution)</p>
3	<p>Status report on Completion of time and dose kinetics of Ec venom induced tissue necrosis at the snake bite site in the other animal model and Establishment of efficacy of DNase-1 in post necrotic animal models</p> <p style="text-align: center;"><i>And</i></p> <p>Submission of UC/SOE for the corresponding milestone certified by internal finance.</p>	12	<p>9.668 ₹ (20% of BIRAC contribution)</p>
4	<p>Status report on Establishing the mechanism of action of Ec venom on Extracellular Traps formation leading to necrosis</p> <p style="text-align: center;"><i>And</i></p> <p>Submission of UC/SOE for the corresponding milestone certified by internal finance.</p>	17	<p>9.668 ₹ (20% of BIRAC contribution)</p>
5	<p>Submission of final completion report and consolidated Utilization Certificate (UC) and Statement of Expenses (SOE)</p>	18	<p>4.834 ₹ (20% of BIRAC contribution)</p>
Total			<u>48.34</u> ₹

Note:- Utilization Certificate (UC) and Statements of Expenses (SOE) duly audited by a chartered accountant for the expenditure incurred towards the Project for every half year period, ending 30th September and 31st March, to BIRAC, within a month of closure of the accounts for the respective half year should be submitted by the Fund Recipient till completion of Project Duration.


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8. Periodic Payment/Release Arrangements of the project support based on milestones

Instalment	Contribution by BIRAC under PACE to University of Mysore	Total (Rs. in Lakhs)
First	14.502	14.502
Second	9.668	9.668
Third	9.668	9.668
Fourth	9.668	9.668
Fifth	4.834	4.834
Total	48.34	48.34

9. The recipient of the fund should convey their acceptance to the terms and conditions of this GLA within four (4) weeks of the issue of GLA failing which the present offer of the funding support will be considered as infructuous and the project will be treated as withdrawn.

10. Inclusion by Reference:

This GLA includes and incorporates by this reference:

- Terms and Conditions (Schedule 1)
- Acceptance and Undertaking (Schedule 2)
- Project document (Schedule 3)
- Intellectual Property Governing Framework (Schedule 4)

11. The Expenditure is debitable to B.04 - Head of Accounts for the financial year 2019 - 20.

12. This issue with the approval of competent authority vide BFD No.

BFD/RO/18.04/036/2019-20 dated 28/06/2019

13. The GLA has been noted at Serial No. 13 in the Reg.

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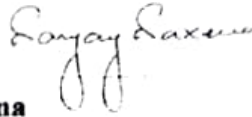


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This GLA is between Biotechnology Industry Research Assistance Council ("BIRAC") and University of Mysore, and is effective as of the date of last signature. Each party to this GLA may be referred to individually as a "Party", University of Mysore as "Fund Recipient" and all Party together as the "Parties". As a condition of this grant, the Parties enter into this GLA by having their authorized representatives sign below:

I) For and on behalf of BIRAC

Signature



Name: **Dr. Sanjay Saxena**

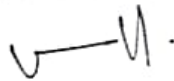
Designation : **GM & Head – Investment**

Official Seal



II) For and on behalf of University of Mysore, the "Fund Recipient" duly authorized vide letter dated by its concerned authority. duly authorized vide letter dated by its concerned authority.

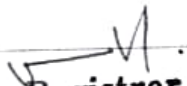
Signature



Name

Designation

Institute Seal



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The terms and conditions for Project support under Grant-in-aid Letter Agreement (hereinafter called as "GLA") are as follows;

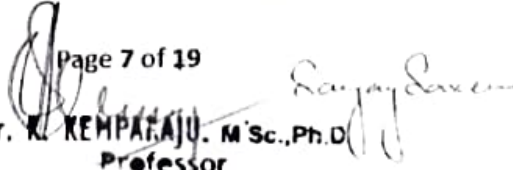
1. FUND DISBURSEMENT

- a. First installment of the Grant-in-aid will be released after issue of the GLA subject to fulfillment of the terms and conditions for such release by the relevant Parties. Further release of funds shall be subject to satisfactory progress against the objectives, outputs, milestones and targets specified in the Project which progress shall be determined by BIRAC and on submission of audited/certified statements of accounts and utilization certificates as provided for in Point 2 (a).

2. FUND UTILISATION AND ACCOUNTING

- a. The Fund Recipient shall submit the Utilization Certificate (UC) and Statements of Expenses (SOE) duly audited by a Chartered Accountant (CA) for the expenditure incurred towards the Project for every half year period, ending 30th September and 31st March, to BIRAC, within a month of closure of the accounts for the respective half year, in the format provided by BIRAC.
- b. The Fund Recipient shall submit UC and SOE duly certified by Internal finance personnel to BIRAC in the format provided on the completion of the respective milestones.
- c. The input credit for the expenditures incurred under the project out of Grant-in-aid shall be reported to BIRAC as a part of utilization certificate against the corresponding entry- "Amount of GST Input credit". Such amount, if any, will be considered accordingly at the time of the release of the next instalment.
- d. The Fund Recipient shall submit audited Annual reports along with the audited balance sheets and profit & loss accounts to BIRAC within seven months of the completion of the financial year ending 31st March till the completion of the Project Duration.
- e. The Fund Recipient shall keep the Grant-in-aid assistance in an interest bearing account with a Scheduled Bank (as defined under the RBI Act, 1934), the withdrawals and payments from which account shall be subject to verification by BIRAC. The interest earned on the Grant-in-aid should be


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reported to BIRAC. The interest thus earned on the grant in aid will be adjusted towards further instalment of the fund.

- f. The Fund Recipient shall ensure that the funds released for the Project are actually utilized only for the purposes of the Project and as expressly provided for in this GLA. Re-appropriation of BIRAC funds from one budget head to another shall not be effected without the specific written approval of BIRAC;
- g. The Fund Recipient shall refund such part of Grant-in-aid funds disbursed to it that remains unutilized with it upon completion of all the responsibilities, duties and functions specified in connection with the Project, within one month of such completion, to BIRAC along with consolidated accounts of the funds received and utilized and of the unutilized balance returned (UC & SOE);
- h. The Fund Recipient at their own cost shall take adequate care to maintain the capital assets acquired for the Project through BIRAC's Grant-in-aid. The capital assets acquired through BIRAC's Grant-in-aid shall not be disposed of or hypothecated without the specific approval of BIRAC till full and final settlement of all dues to the satisfaction of BIRAC.

3. PROJECT MONITORING

A Project Monitoring Committee (PMC) comprising of eminent experts from the relevant field(s) will be constituted by BIRAC to monitor the progress of the objective

(s) of the Project. BIRAC shall have at least one representative in the PMC.

The functions of the PMC shall be as follows:

- a. To monitor the progress of the Project in conformity with the outputs, milestones, targets objectives and other terms and conditions as contained in the GLA
- b. To keep track of funding from any other source for the Project.
- c. To assess the global developments impacting the domain of the Project.
- d. Based on the foregoing, to assess and recommend:
 - i. the release of next installment or part release thereof by the BIRAC.
 - ii. revision of Project Duration
 - iii. closing, dropping or modifying any of the components of the Project, within the overall approved objectives, budget and time-frame,
 - iv. inclusion of additional industrial/institutional partner(s), if the Institute requests involvement of such partner(s), in the overall interest of the Project; and
 - v. revision of the financial assistance.
- e. To advise on issues related to securing of IPR and mentor to over

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technological problem faced in the Project implementation; and

- f. To advise on any other matter as referred to it by BIRAC and/or otherwise reasonably necessary for effective discharge of its duties and/or achievement of aims and
- g. objectives of the Schemes.

4. INDEMNIFICATION

- a) The Fund Recipient shall, at all times, indemnify and keep indemnified BIRAC against any claims or suits in respect of any losses, damages or compensation payable in consequences of any accident, death or injury sustained by their employees or by any other third party resulting from or by any act, omission or operation conducted by or on their behalf;
- b) The Fund Recipient shall, at all times, indemnify and keep indemnified BIRAC against all claims/damages etc. by any infringement of any Intellectual Property Rights (IPR) while carrying out their responsibilities/work under the Project and this GLA.
- c) The provision of Grant-in-aid funds by BIRAC does not create any liability, explicit or implicit, on BIRAC in respect of the manpower engaged in the Project.
- d) The Parties shall not be held responsible for non-fulfilment of their respective obligations in successful completion of the Project under this GLA due to the exigency of one or more force majeure events such as but not limited to acts of God, war, flood, earthquakes etc.

5. CHANGE OF CONTROL:

BIRAC shall reserve the right to reconsider further funding assistance, governance of the New Intellectual Property and consider refund of the amount of Grant-in-aid in such circumstances of change of control as mentioned the following paragraphs;

- a. The Fund Recipient and the Institutes shall notify BIRAC of any material change in its entity status, entity name, Project Coordinator, implementation site, registered office or any such change that would impact on performance of its obligations under the Project and this GLA.

6. FORECLOSURE AND TERMINATION

- i. In case, during the tenure of the Project, it is found that the Project or any Project component is not likely to lead to successful completion, BIRAC

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decide to foreclose the Project or the Project component as warranted. The decision of the BIRAC shall be final in all respects. The Fund Recipient shall immediately refund any grant-in-aid unutilized out of BIRAC's disbursements, along with detailed accounts of funds received, utilized and unutilized. If Fund Recipient like to continue the Project at its own cost, it would be able to do so without restrictions from BIRAC after complying with these provisions.

- ii. The Fund Recipient may, before the completion of the Project, terminate this Agreement by giving three months' notice in writing to BIRAC. BIRAC may also terminate this Agreement by written notice to "Fund Recipient" committing breach of any term of this Agreement and either not rectifying it to the satisfaction of BIRAC or not satisfying

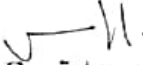
BIRAC about its inevitability within a specified period. In the event of termination of the Agreement, no further disbursement shall be made by BIRAC. The Fund Recipient shall be liable to return immediately the amount of Grant-in-aid already availed of from BIRAC with additional simple interest at the rate of 12 (twelve) per cent per annum within 30 (thirty) days of termination of the GLA. Interest on the quantum of funding assistance shall accrue from the date of release of the grant in aid assistance. In case of failure to repay, without prejudice to any other rights under this Agreement, the amount can be recovered by initiating any procedure available in Law.

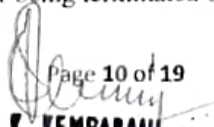
7. DISPUTE RESOLUTION AND ARBITRATION

In the event of any dispute or difference whatsoever arising between the Parties out of or relation to the construction, meaning, scope, operation or effect of this agreement or the validity the breach thereof shall be resolved amicably by mutual consultation or through the good offices of the Chairman, BIRAC.

If such resolution is not possible, then the unresolved dispute or difference whatsoever arising between the Parties out of or relation to the construction, meaning, scope, operation or effect of this GLA or the validity the breach thereof or in respect of any defined legal relationship associated therewith or derived there from dispute shall be submitted for arbitration to International Center for Alternate Dispute Resolution (ICADR), an autonomous organization working under the aegis of the Ministry of Law & Justice, Department of Legal Affairs, Government of India. The Authority to appoint the arbitrator(s) shall be the ICADR. The Arbitration under this Clause and provision of administrative services by ICADR shall be in accordance with the ICADR Arbitration Rules, 1996. The award made in pursuance thereof shall be binding on the Parties. The venue of arbitration shall be New Delhi and the arbitration proceedings shall be conducted in English Language.

The provision of this Clause shall not become inoperative notwithstanding the GLA expiring or ceasing to exist or being terminated or foreclosed.


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6. EFFECT AND AMENDMENTS TO THE GLA


- i. GLA shall remain in force for whichever of these is the longest time unless suspended sooner:
 - a. For **18 Months** from the above Effective Date subject to the Change Order(s) issued by the BIRAC from time to time;
 - b. As long as any part of the amount disbursed for the Project remains unspent; or
 - c. For as long as any monitoring or recording or IP governance is required under any relevant laws and regulations.
- ii. No amendment or modification of this GLA shall be valid unless the same is made in writing by the Parties or their authorized representatives specifically stating the same to be an amendment of this GLA. The modifications / changes shall be effective from the date on which they are made / executed unless otherwise agreed to.

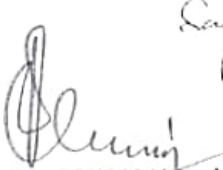
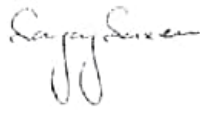
9. SEVERABILITY

In case any one or more of the provisions or parts of a provision contained in this GLA shall, for any reason, be held to be invalid, illegal or unenforceable in any respect, such invalidity, illegality or unenforceability shall not affect any other provision or part of a provision of this GLA; and this GLA shall, to the fullest extent lawful, be construed as if such invalid or illegal or unenforceable provision, or part of a provision, had never been contained herein.

10. GOVERNING LAW

This GLA and the associated undertaking shall be governed and interpreted in accordance with the laws of India subject to the exclusive jurisdiction of the Courts at New Delhi.


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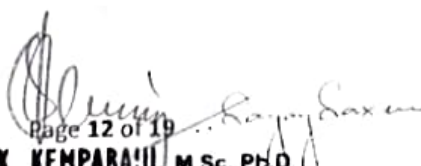
Acceptance & Undertaking

In consideration of the foregoing, the fund recipient, intending to be admittedly bound by the terms set forth above, undertake as stated below:

The recipient of the Grant shall;

1. Execute the activities as set out in the Project document and shall conform to the specified objectives, outputs, milestones, and targets therein at Schedule 3.
2. Submit periodic Progress report to BIRAC as per the Project milestones, details of activities involved in performing the Project activities, Utilization Certificate (UC) and Statements of Accounts Expenses (SOE) as per Schedule 1.
3. Comply with the fund utilization and accounting requirements as per Schedule 1.
4. Obtain all the necessary requisite approvals, clearance certificates, permissions and licenses from the Government/local authorities for conducting its activities/ operations in connection with the Project.
5. Abide by the decisions of BIRAC to modify the objectives, outputs, milestones, targets, Project Grant-in-aid as also the foreclosure of the Project or any of its components as may be arrived at after mutual discussion.
6. Subject themselves to Project monitoring of the Project Monitoring Committee (PMC).
7. Maintain strict confidentiality and refrain from disclosure thereof, of all or any part of such information and data exchanged/generated from the Project which is not in the public domain by use and/or publication at the time of its disclosure except for purposes in accordance with this Project or is required by public authority, by law or decree.
8. Shall verify the completion of the milestone and the utilization of the funds as stated which will be a pre requisite for the next fund release.
9. Complete the Project within the stipulated period subject to the Change Order(s) issued by the BIRAC from time to time.
10. The Fund Recipient shall not sub-delegate or outsource the obligations under this GLA without express permission of BIRAC except as provided for in the Project Document.


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11. Adhere to this GLA and the Conditions of Grant, as, violation of any provision of which shall be the reason for suspension of the Grant.
12. Consider any changes to the provisions of this GLA when made in writing only and shall consider any notice duly served if the same shall have been delivered electronically through the official mail of the Project Coordinator or delivered by post at the addresses mentioned in the GLA.
13. Acknowledge the assistance of BIRAC while publishing or presenting in any manner the details of the Project, its progress or its success or commercialization of the Product.

Sajjan



K. Kemparaju

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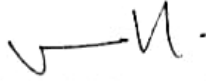
V. W.
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University of Mysore
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IN ACCEPTANCE WHEREOF the fund recipient hereto through their duly authorized representatives have signed this undertaking as set below:

For and on behalf of **University of Mysore**, the "Institute"

Date and Place:

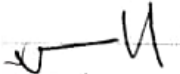
Signature



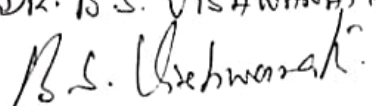
Name

Designation

Seal


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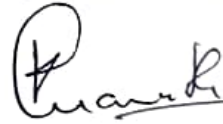
Witness

Name: **DR. B.S. VISHWANATH**


Signature:

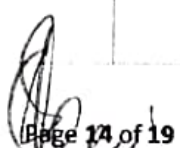
Chairman
Dept. of Studies in Biochemistry
University of Mysore
Manasagangotri, MYSORE-570 006
INDIA


Name: **PROF. GOPAL MARATHE K.**



Signature:

Dr. GOPAL MARATHE. K. M.Sc., Ph.D.
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Project Document:

OBJECTIVE AND TIMELINES**PROPOSAL OBJECTIVES & WORK PLAN**

Objective1: To establish the time and dose kinetics of Ec venom induced tissue necrosis at the snake bite site using two mammalian model systems

Methodology/Experimental Design To Accomplish The Stated Objective:

E. carinatus venom-induced mouse tail tissue necrosis Pre-necrosis followed for 12 hours. E. carinatus venom LD50/LD dissolved in 50 µl PBS is subcutaneously administered to the groups of mice n=4, 3 cm distal to the base of the tail. The severity of the tail injury is judged visually and scored according to a 10 point scale 0=no injury, 1=oedema, 2=oedema with minor haemorrhage, 4=oedema with haemorrhage causing less than 25 percent tail discolouration, 6=oedema and major haemorrhage or wound causing 25%–50 percent tail discolouration, 8=oedema and major haemorrhage or wound causing 50%–75 percent tail discolouration, 10=oedema and major haemorrhage or wound causing more than 75 percent tail discolouration. The tail injury observations are recorded every day for 15 days after venom injection. To assess the time and dose dependent effects of DNase-1 on tail hemorrhage, DNase-1 is injected for every 1 hour of intervals until 12 hours. To determine dose dependent effect of DNase-1 100 – 500 units of DNase-1 is injected. It is also important to explore the possible therapeutic potential of DNase-1 injection after the tail detachment. Histopathology: The venom-induced tail tissue destruction and the presence of NETs in the venom-injected tail tissues and were examined in H&E-stained tissue sections. The respective tissues are dissected from the venom injection site, fixed overnight in buffered formalin and subjected to dehydration with different grades of alcohol and chloroform mixture. The processed tissues are embedded in molten paraffin wax, and 10-mm-thick sections were prepared using a microtome. The sections are stained with H&E, observed under an Axio Imager.A2 microscope Zeiss and photographed.

Alternate Strategies: NA

Objective2: To establish the therapeutic use of DNase-1 to prevent further tissue necrosis of Ec venom induced post necrotic animal models.

Methodology/Experimental Design To Accomplish The Stated Objective:

Post necrosis study: E. carinatus venom-induced mouse tail tissue/rabbit tissue necrosis: E. carinatus venom LD50/LD dissolved in 50 ml PBS was subcutaneously administered to the groups of mice 3 cm distal to the base of the tail. The tail injury observations were recorded every day for 5 days after venom injection. The severity of the tail injury is judged visually and scored according to a 10 point scale 0=no injury, 1=oedema, 2=oedema with minor haemorrhage, 4=oedema with haemorrhage causing less than 25 percent tail discolouration, 6=oedema and major haemorrhage or wound causing 25%–50 percent tail discolouration, 8=oedema and major haemorrhage or wound causing 50%–75 percent tail discolouration, 10=oedema and major haemorrhage or wound causing more than 75 percent tail discolouration. To assess time dependent response, DNase-1 is injected on 1st, 2nd and 5th day after venom injection. Histopathology: The venom-induced tail tissue destruction and the presence of NETs in the venom-injected tail tissues are examined in H&E-stained tissue sections. The respective tissues were dissected from the venom injection site, fixed overnight in buffered formalin and subjected to dehydration with different grades of alcohol and chloroform mixture. The processed tissues are embedded in molten paraffin wax, and 10-mm-thick sections were prepared using a microtome. The sections are stained with H&E, observed under an Axio Imager.A2 microscope Zeiss and photographed.

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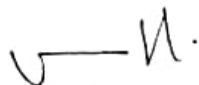
Alternate Strategies: NA

Objective3: To evaluate the effect of Ec venom on the Extracellular Traps ETs using blood cells other than neutrophils.

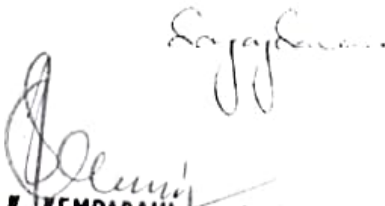
Methodology/Experimental Design To Accomplish The Stated Objective:

10/23 Isolation of human PMNs and PBMCs: Human polymorpho nuclear leukocytes PMNs and peripheral blood mononuclear cells PBMCs are isolated from healthy donors. Whole blood is collected and mixed with acid citrate dextrose citric acid: sodium citrate: dextrose, 3:6:4 in a 5:1 volume ratio followed by dextran sedimentation and hypotonic lysis to remove red blood cells. Upon complete lysis of red blood cells, the cell pellet is suspended in 2 ml PBS and subjected to density gradient centrifugation using Histopaque-1077 for 30 min, $210\text{Å}-g$ at $4\text{Å}^\circ\text{C}$. The opaque layer of PBMCs is collected from PBS-Histopaque-1077 interphase whereas PMNs are settled at the bottom as cell pellets. The subsequent pellets of PMNs and PBMCs are washed twice with PBS and re-suspended in HBSS buffer without cation containing 0.2 human serum albumin HSA. Cells are counted using a Neubauer chamber and required cell density is adjusted. Wright and Giemsa stain is used to determine the purity of cells. The number of viable cells is determined using trypan blue exclusion assay. Preparation of washed platelets: Platelet-rich plasma PRP is obtained by mixing fresh blood sample with acid citrate dextrose solution ACD 85 mM sodium citrate 71 mM citric acid 111 mM dextrose in a 6:1 blood: ACD volume ratio followed by centrifugation at $90\text{Å}-g$ for 15 min in a polypropylene tube. The PRP is further centrifuged at $1700\text{Å}-g$ for 15 min at $37\text{Å}^\circ\text{C}$ to obtain the platelet pellet. The platelet pellet is washed in Tyrodes albumin buffer 145 mM NaCl, 5 mM KCl, 10 mM HEPES, 0.5 mM Na_2HPO_4 , 1 mM MgCl_2 , 6 mM glucose, and 0.3 BSA pH 6.5, containing 10 U/ml heparin and $0.5\text{Å}^\circ\text{C}$ prostacyclin. After 10 min of incubation at $37\text{Å}^\circ\text{C}$, the platelets are again washed using the same buffer. Finally, the platelets are resuspended in Tyrodes albumin buffer, pH 7.4. Platelets are counted using a Neubauer chamber and required number of platelets density is adjusted using Tyrodes albumin buffer, pH 7.4. NETosis assay: The neutrophils $2\text{Å}-105$ cells/ml in 500Å HBSS with 2 HSA are seeded on 13 mm round coverslips placed in 24 well culture plates and allowed to adhere to the coverslips by incubating for 30 min at $37\text{Å}^\circ\text{C}$ and 5 CO_2 . Then, the cells are stimulated with E. carinatus venom $50\text{Å}^\circ\text{C}$ for 180 min and PMA 50 nm served as a positive control. The cells are then fixed with 4 paraformaldehyde, followed by Hoechst 33342 staining 1:10,000. The images are acquired by fluorescence and confocal microscope

Alternate Strategies: NA



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TIME LINES

Activities	Month Of End Of Activity	Indicators Of Progress
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OBJECTIVE : To establish the time and dose kinetics of *Ec* venom induced tissue necrosis at the snake bite site using two mammalian model systems

Induction of tissue necrosis in mouse and rabbit/guinea pig models

1

Hemorrhage or wound causing more than 75 percent discoloration of tail

Testing the tissue necrosis, histopathological studies, dose and time kinetics of DNase-1 in mouse models


3

The mice are euthanized and sacrificed. the affected tail tissue section are observed under fluorescent/confocal microscope for necrosis and NETs markers. Cellular burst without releasing DNA fibers is the indicator of necrosis.the release of DNA fibers coated with myeloperoxidase and neutrophil elastase or citrulinated histone formation are the indicators . The tail tissue section after treatment with DNase1 normally do not show the accumulation of neutrophils nor the NET markers however after treatment with DNase1 its expected to protect the tail from undergoing the necrosis and thus the recovery to be normal.

Testing the tissue necrosis, histopathological studies, dose and time kinetics of DNase-1 in rabbit/guinea pig models

4

The Guinea pig/rabbit are euthanized and sacrificed. the affected tail tissue section are observed under fluorescent/confocal microscope for necrosis and NETs markers. Cellular burst without releasing DNA fibers is the indicator of necrosis.the release of DNA fibers coated with myeloperoxidase and neutrophil elastase or citrulinated histone formation are the indicators .


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Completion of in vivo studies to establish the time and dose kinetics of Ec venom induced tissue necrosis at the snake bite site	6	Not applicable
Activities	Month Of End Of Activity	Indicators Of Progress

OBJECTIVE : To establish the therapeutic use of DNase-I to prevent further tissue necrosis of Ec venom induced post necrotic animal models

Inducing tissue necrosis, testing the effect of DNase-I after 6 hours of Ec venom dose (dose/time) and histopathological studies	9	Disappearance of tail tissue necrosis.
Establishment of efficacy of DNase-1 in post necrotic animal models	12	Complete recovery from tissue necrosis
Activities	Month Of End Of Activity	Indicators Of Progress

OBJECTIVE : To evaluate the effect of Ec venom on the Extracellular Traps (ETs) using blood cells other than neutrophils.

Isolation of PBMCs monocytes, lymphocytes and platelets.	16	Microscopic examination
Testing the effect of Ec venom (dose and time) on ETs formation	16	ETosis markers
Effect of established on endothelial cell lines.	16	Ejection of DNA by endothelial cells
I In vitro induction of ETosis by snake venoms (Ec and other snake venoms)	16	Ejection of DNA by other cells than neutrophils

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INTELLECTUAL PROPERTY GOVERNING FRAMEWORK

a. Background IP Rights:

All rights, title and interest in or to any information, data, reports, documents, procedures, forecasts, technology, know-how, and inventions, including any patents, designs, copyrights, trademarks and any applications for patents, designs, copyrights or trademarks, in India and anywhere else in the world, that are owned by or vest in any Party before execution of this Agreement ("Background IP") shall remain the property of such Party.

b. New IP:

For the purpose of PACE, New IP means intellectual property generated during the conduct of the Project by the Fund Recipient excluding the intellectual property generated by the Institute before execution of this Agreement and any New IP generated by the Fund Recipient outside the scope of this Agreement even during the term of this Agreement. All rights, title and interest in New IP in India and anywhere else in the world, shall be owned by or vest in the applicant academia unless agreed otherwise between the parties.

The fund recipient will not publish in any manner with regard to the results of the Project which will be in derogation to the creation and protection of IP and related rights as stated above.

NOTE: For the purpose of this GLA, New IP means intellectual property generated during the conduct of the Project by the Fund Recipient, but excluding the intellectual property generated by the Fund Recipient before execution of this GLA and any IP generated outside the scope of this GLA even during the term of this GLA.

1. The background Intellectual Property (IP) generated by the Fund Recipient before execution of this GLA are as provided hereunder;

I.	Background IP of the Fund Recipient
The applicant does not own any IP related to the proposal.	

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