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LIST OF PUBLICATIONS

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1. **Talukdar, A.**, and Doley, R. (2024). Identification of poorly immunodepleted phospholipase A_2 (PLA_2) proteins of *Bungarus fasciatus* venom from Assam, India and evaluation of Indian polyvalent antivenom using third-generation antivenomics. *Toxicon, 239.* doi: https://doi.org/10.1016/j.toxicon.2024.107617

2. **Talukdar, A.**, Malhotra, A., Lalremsanga, H. T., Santra, V., and Doley, R. (2023). Bungarus fasciatus venom from eastern and north-east India: venom variation and immune cross-reactivity with Indian polyvalent antivenoms. *Journal of Proteins and Proteomics*, *14*(1), 61-76. doi: https://doi.org/10.1007/s42485-022-00104-2

3. **Talukdar, A.**, Maddhesiya, P., Namsa, N. D., and Doley, R. (2023). Snake venom toxins targeting the central nervous system. *Toxin Reviews*, *42*(1), 382-406. doi: https://doi.org/10.1080/15569543.2022.2084418

LIST OF CONFERENCES

1. **Amit Talukdar** and Robin Doley (2024) "Venom Unmasked: A Journey into the Immuno-Secrets of North_East India's Banded Krait." at *SnakeSymp 2024 (From Venom Pharmacology to Drug Discovery: National and International Perspective)* organized by IASST, Guwahati, Assam on 9th to 10th February, 2024. ***(Poster Presentation: Best Poster Award, 2nd Rank)***

2. **Amit Talukdar** and Robin Doley (2022) "A study on *Bungarus fasciatus* venoms of India and their immuno-crossreactivity with Indian polyvalent antivenoms." at the *27th-ISCB International Conference (ISCB-2022),* jointly organized by ISCB & Department of Chemistry, Birla Institute of Technology, Mesra, Ranchi, Jharkhand, 16th Nov, 2022. ***(Poster Presentation)***

3. **Amit Talukdar** and Robin Doley (2022) "Snake venom toxins: Their role in the central nervous system." at *One Day National Symposium on Snake and Scorpion Envenomation and Therapy: National and International Perspectives*, organized by IASST, Guwahati, Assam, 16th July, 2022. ***(Poster Presentation)***

4. **Amit Talukdar** and Robin Doley (2022) "A comparative study on the venoms of *Bungarus fasciatus* from Eastern India and their immuno-crossreactivity with Indian polyvalent antivenoms." at *National level Seminar "Biology is Fascinating"*, jointly organized by Department of Molecular Biology and Biotechnology in association with inSCIgnis'22, Tezpur University, Napaam, Assam, 1st March, 2022. ***(Poster Presentation)***

APPENDIX I

Permissions and Approvals

DATE: 8.06.2012

CERTIFICATE

THIS IS TO CERTIFY THAT THIS SNAKE VENOM RELEASED ONLY FOR RESEARCH PURPOSE AND THIS PARCEL CONTAINS THE FOLLOWING SNAKE VENOMS.

1. COBRA SNAKE VENOM	1.000 gm
2. KRAIT SNAKE VENOM	1.000 gm
3. RUSSELL'S VIPER SNAKE VENOM	1.000 gm
4. SAW SCALED VIPER SNAKE VENOM	1.000 gm

SNAKE VENOMS WEIGHED BY

C.V. 8.6.12

Special Officer
IRULA SNAKE CATCHERS ICS LTD.,

SNAKE VENOM WEIGHMENT INSPECTED

8.6.12

FOREST RANGE OFFICER,
WILDLIFE ENFORCEMENT RANGE.
CHENNAI – 32.

FOREST RANGE OFFICER HEAD QUARTERS RANGE (WILD) Date: 8.6.12

SNAKE VENOM PARCEL DESPATCH

TO
Dr. Dr. D.Velmurugn,
Professor,
University of Madras,
Dept. of Crystallography and Biophysics,
Guindy Campus,
Chennai - 25.

GOVERNMENT OF ASSAM
OFFICE OF THE PRINCIPAL CHIEF CONSERVATOR OF FORESTS:: WILDLIFE
BASISTHA:: GUWAHATI-29.

O.O.No. 450 Dt. 01/10/11

On submission of the undertaking to abide all the stipulations laid down and communicated vide this Office letter No. WL/FG.27/ Tissue Collection/09 dtd. 18.08.11 (copy enclosed), fulfilling provisions of the clause 10 and having deposited an amount of Rs. 10,000/- vide the Union Bank of India deposit No. EM/COM/A026337 dtd. 26-09-2011 in the form of "fixed deposit" pledged In favour of the Chief Wildlife Warden, Assam, Guwhati-29, towards security deposit and special purpose permit fee Rs. 1000/- vide receipt No.9967 dtd.1.10.11, permission under section 12 of the Wildlife (Protection) Act, 1972 is hereby accorded to Dr. Robin Doley to collect snake venom samples from Assam during 2010-2011.

Encl: As stated.

PCCF (WL) & Chief Wildlife Warden, Assam.

WL/FG.27/ Tissue Collection/09, Dt. 07/10/11.

Copy for information and necessary action to:
1. The DFOs, all Wildlife Divisions of Assam,
2. The DFOs, all Territorial Divisions of Assam.
3. Dr. Robin Doley, Asstt. Prof., Dept. of Molecular Biology and Biotechnology, Tezpur University, Naapam, Tezpur.

PCCF (WL) & Chief Wildlife Warden, Assam.

GOVERNMENT OF ASSAM
OFFICE OF THE PRINCIPAL CHIEF CONSERVATOR OF FORESTS: :WILDLIFE::
BASISTHA:: GUWAHATI-29.

No. WL/FG.27/Tissue collection/09. Dt. 19/08/11.

To, Dr. Robin Doley, Asstt. Prof., Deptt. of Molecular Biology & Biotechnology, Tezpur University, Tezpur.

Sub: Grant of special purpose permit.

Sir,

The permission to collect snake venom samples from Assam can be accorded under Sec. 12 of Wildlife(Protection) Act, 1972 under the following terms & conditions during 2011-12.

1. All the provisions, relating to the National Parks, Sanctuaries and NTCA under the Wildlife (Protection) Act, 1972 shall be strictly adhered to.
2. No boundary mark of the Protected Area will be damaged, altered, destroyed, moved or defaced.
3. No other wild animal will be teased, molested or disturbed.
4. No damage to any flora or fauna and snake venom samples will be allowed to collect inside and outside the PAs.
5. The ground of the Park/Sanctuary will not be littered.
6. A Project Monitoring Officer authorized by the PA authority and the Research Officer, O/o PCCF(WL), Assam will monitor the activities to ensure the adherence of all the conditions stipulated herein.
7. The Park Authority will not take responsibility for arrangement of the food, lodging and conveyance.
8. The Park Authority will reserve the right to cancel/ terminate this permission at any time, whenever it is considered that the activities resulting from this permission is affecting the flora and fauna adversely or the permit holder is not abiding by the stipulations contained herein.
9. A copy of annual progress report with a soft copy may be submitted for the extension of the project and three copies of final report shall be furnished to the Research Officer, O/o the PCCF (WL), Assam for office record.
10. An amount of Rs.1,000/- as special purpose permit fees and Rs. 10,000/- will have to be deposited in the form of a "Fixed Deposit" pledged in favour of the Chief Wildlife Warden, Assam, Basistha, Ghy-29, as a security deposit which will be released immediately after fulfilling the Clause 9 and also on receipt of the NOC about satisfactory compliance of all the above stipulations.
11. Entry to the Protected Area would be as per the convenience of the local forest Authority and a register will have to be maintained by the researcher for entering in to the PA and equipment used with authentication of the local forest authority.

If agreed to all the above stipulations and on furnishing the documents and security deposit an undertaking as below will have to be signed by you before obtaining the permission for entering into the Protected Area for implementing the abovestated research.

Please take the necessary steps accordingly.

Yours faithfully,

PCCF (WL) & Chief Wildlife Warden, Assam.

Undertaking

I do hereby undertake that I shall abide by all the stipulations contained in this permission and I shall enter in to the PA at my own risk and in case of any violation of any of the stipulations, I shall be liable to be prosecuted under the relevant provisions of law.

26/9/11

Signature of the applicant.

GOVERNMENT OF WEST BENGAL
DIRECTORATE OF FORESTS
Office of the Principal Chief Conservator of Forests, Wildlife
& Chief Wildlife Warden, West Bengal.
Bikash Bhavan, North Block, Third Floor, Saltlake City, Kolkata-700 091.
Tel.No.033- 2334-6900/2358-3208, Fax. 033-2334-5946
Website - www.wildbengal.com e-mail wbwildlife@gmail.com

Memo No. 5141 /WL / 4R-6/ 2017 Dated : 27 / 11 / 2017

To : Dr. Dayal Bandhu Majumdar,
Task Force Member, Indian Snakebite Management Protocol,
State Resource person for Snakebite Training , W.B.
Senior MO, (Grade-II), Calcutta National Medical College & Hospital,
Kolkata- 700014.

Sub: Permission to access to Biological Resources in West Bengal for Snake Venom Research- reg.
Ref: Your proposal no. Nil, dated 17.08.2017

Permission is hereby accorded as per approval of the PCCF, WL & CWLW, W.B. to collect snake venom in West Bengal for Research under Section 12(b) & (d) as proposed in your letter quoted under reference subject to following terms and conditions.

a) No other survey /study shall be carried out without prior approval of the competent authority.
b) The approval is for the period 1 (One) year from the date of issue of this letter.
c) Dr. Dayal Bandhu Majumdar is the only authorized person for the research.
d) Permission is given only for snakes, not included in Schedule I of Wildlife (Protection) Act, 1972. (No collection of Colubridae). Venom Collection is limited to 10 ml. from each species as follows: Elapidae-Kraits (*Bungarus*), Indian Cobra (*Naja*), King Cobra (*Ophiophagus*) & Viperidae–Vipers.
e) Permission is not granted for collection of scales or buccal scrapes .
f) Permission is restricted for collection of snakes only from Canning, Gosaba (South24Pgs), Saltora (Bankura) & Chandannagar (Hooghly).
g) All snakes are to be released immediately after milking / venom collection.
h) Entry to the forest is prohibited before Sunrise and after Sunset.
i) All movements inside forest areas should be performed with assistance of local staff only.
j) Prior to entry into the forest, necessary permission should be sought from the competent authority and all activities to be reported to the nearest Range Office prior to commencement and after the work is completed.
k) The team will abide by the provisions of Wildlife (Protection) Act, 1972, Indian Forest Act, 1927 and any other directive issued by the competent authority. All restrictions/Rules in vogue are to be followed.
l) On completion of work, 2 (two) copies of the work report to be submitted to the Forest Department for record & the list of all publication arising out of the study shall be furnished to the Principal Chief Conservator of Forests, Wildlife & Chief Wildlife Warden, West Bengal.
m) Failure to comply with the condition and violation of Wildlife (Protection) Act, 1972 would amount to withdrawal of permission & subsequent punitive action.
n) The Forest Department will not be responsible for any damage or loss suffered by the researcher / surveyor during the course of his fieldwork.
o) A complete Project Report in Hard and Soft copy is to be submitted to the Principal Chief Conservator of Forests, Wildlife & Chief Wildlife Warden, W.B. You may have to give presentation on the research, if required.

Addl. Principal Chief Conservator of Forests
Wildlife, West Bengal &
ex-officio Addl. Chief Wildlife Warden, West Bengal

Memo No. 5142 (10)/WL / 4R-6/ 2017 Dated : 27 / 11 / 2017

Copy along with copy of proposal submitted forwarded for information and taking necessary action to :
1) The Principal Secretary, Department of Forests, Govt. of West Bengal
2) The Principal Chief Conservator of Forests & Head of Forest Force, West Bengal.
3) The Addl. PCCF & Director, Sundarban Bio-sphere Reserve, West Bengal.
4) The Chief Conservator of Forests, Central Circle, West Bengal.

GOVERNMENT OF MIZORAM
OFFICE OF THE CHIEF WILDLIFE WARDEN
ENVIRONMENT, FOREST & CLIMATE CHANGE DEPERTMENT
MIZORAM :: AIZAWL
****

No.A.33011/5/2011-CWLW/305 : Dated Aizawl the 18th July/ 2016

To,

Dr. H.T. Lalremsanga
Assistant Professor
Mizoram University
Aizawl, Mizoram.

Subj : ***Permission to collect biological samples from Medically Significant Venomous snakes of Mizoram for the project titled 'Biodiversity Informatics and Technology Exchange for Snakebite Management'.***

Ref : Your application No: nil dt. 29th June 2016.

Permission is hereby granted to you for non-invasive collection of biological samples from medically significant venomous snakes of Mizoram for the Project titled 'Biodiversity Informatics and Technology Exchange for snakebite Management within Mizoram.

However, you are requested to deposit Rs. 100.00 (one hundred) only as per the provision of Mizoram State Biodiversity Rule, 2010 Claused (1) of Rule 17 to Chief Wildlife Warden by Bank Draft or IPO

Further it will be obligatory on your part to share all the information and research findings with this department, whatever collected through this permit.

18/7/16
(LIANDAWLA)
Chief Wildlife Warden
Mizoram :: Aizawl

Memo No.A.33011/5/2011-CWLW/305 : Dated Aizawl the 18th July/ 2016
Copy to:-

1) All CFs viz, SC Lunglei, CC Aizawl, NC Aizawl, Wildlife for information.

Chief Wildlife Warden
Mizoram :: Aizawl

APPENDIX II

Reprints of Publications

Toxicon 239 (2024) 107617

Contents lists available at ScienceDirect

Toxicon

journal homepage: www.elsevier.com/locate/toxicon

Identification of poorly immunodepleted phospholipase A_2 (PLA_2) proteins of *Bungarus fasciatus* venom from Assam, India and evaluation of Indian polyvalent antivenom using third-generation antivenomics

Amit Talukdar, Robin Doley *

Molecular Toxinology Laboratory, Department of Molecular Biology and Biotechnology, Tezpur University, Assam, 784028, India

ARTICLE INFO

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Keywords:
Bungarus fasciatus
Snakebite
Snake venom toxins
Third-generation antivenomics
Indian polyvalent antivenom
Maximal binding capability

ABSTRACT

Bungarus fasciatus also referred to as the Banded krait is a snake which possesses venom and belongs to the Elapidae family. It is widely distributed across the Indian subcontinent and South East Asian countries and is responsible for numerous snakebites in the population. *B. fasciatus* possesses a neurotoxic venom and envenomation by the snake results in significant morbidity and occasional morbidity in the victim if not treated appropriately. In this study, the efficacy of Indian polyvalent antivenom (Premium Serums polyvalent antivenom) was evaluated against the venom of *B. fasciatus* from Guwahati, Assam (India) employing the Third-generation antivenomics technique followed by identification of venom proteins from three poorly immunodepleted peaks (P5, P6 and P7) using LC-MS/MS analysis. Seven proteins were identified from the three peaks and all these venom proteins belonged to the phospholipase A_2 (PLA_2) superfamily. The identified PLA_2 proteins were corroborated by the *in vitro* enzymatic activities (PLA_2 and Anticoagulant activity) exhibited by the three peaks and previous reports of pathological manifestation in the envenomated victims. Neutralization of enzymatic activities by Premium Serums polyvalent antivenom was also assessed *in vitro* for crude venom, P5, P6 and P7 which revealed moderate to poor inhibition. Inclusion of venom proteins/peptides, which are non-immunodepleted or poorly immunodepleted, into the immunization mixture of venom used for antivenom production may help in enhancing the efficacy of the polyvalent antivenom.

1. Introduction

The venomous snake Banded krait (*Bungarus fasciatus,* Schneider, 1801) belonging to the snake family Elapidae is widely distributed in the continent of Asia. The snake is commonly identified from its yellow (or white) and black-colored alternating bands present on its body along with a triangular body shape and a short and blunt tail (Chanhome et al., 2011; Slowinski, 1994). The length may reach up to 2.25 m. The snake is distributed up to 5000 m above sea level from the Indo-Chinese region to the Indonesian archipelago through the Malay peninsula (Boulenger, 1890; Stuart et al., 2013; Tsai et al., 2007). However, recent data from molecular phylogenetics and comparative morphology has indicated that three distinct taxonomic entities (clades) may exist with distinct Indo-Myanmar, Sundaic and East Asian Sundaland lineages (including Southern China) (Fig. 1). As a result, the distribution of *B. fasciatus, sensu stricto,* may be restricted to only the Indo-Myanmar region (Biakzuala et al., 2023). In India, the snake has been reported from various states such as Assam, Arunachal Pradesh, Meghalaya, Manipur, Mizoram, Nagaland, Tripura, Odisha, Bihar, Jharkhand, West Bengal, Chhattisgarh, Maharashtra, Uttar Pradesh, Uttarakhand, Andhra Pradesh and Telangana (Chandra et al., 2013; Majumder et al., 2012; Prakash, 2016; Stuart et al., 2013).

B. fasciatus inhabits diverse environments, ranging from deciduous, temperate and mixed forests to plains, grasslands, termite moulds and agricultural fields as well as areas near human habitats and water bodies like canals and ponds (Knierim et al., 2019; Stuart et al., 2013). They are generally timid and not aggressive and mostly active at night. Snakebites from kraits generally occur in farmers and labourers working in paddy fields, forests and farms or in poor families which sleep on the floor without using any protective barrier like a mosquito net (Chappuis et al., 2007; Hia et al., 2020). The Red List of Threatened Species by IUCN has categorized *B. fasciatus* as a Least Concern (LC) species (Stuart et al., 2013). *B. fasciatus* possess neurotoxic venom and envenomation in human victims is associated with substantial morbidity or even death if

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Journal of Proteins and Proteomics (2023) 14:61–76
https://doi.org/10.1007/s42485-022-00104-2

RESEARCH

Bungarus fasciatus venom from eastern and north-east India: venom variation and immune cross-reactivity with Indian polyvalent antivenoms

Amit Talukdar[1] · Anita Malhotra[2] · H. T. Lalremsanga[3] · Vishal Santra[4,5] · Robin Doley[1]

Received: 8 September 2022 / Revised: 2 December 2022 / Accepted: 30 December 2022 / Published online: 16 January 2023

Abstract

Bungarus fasciatus is one of the medically important elapid snakes of South and South-eastern Asia and is responsible for several snakebite incidents some of which were fatal. In this study, the venom compositional variation of *Bungarus fasciatus* from three different geographical locations in eastern and north-east India: two adjacent villages of Hooghly (West Bengal), Aizawl (Mizoram) and Guwahati (Assam) are reported. In vitro biochemical assays exhibit variation in phospholipase A_2 activity, fibrinogenolytic activity, caseinolytic activity and anti-coagulation activity. The immunoreactivity of three Indian polyvalent antivenoms against the venoms revealed incomplete recognition. Bharat Serums antivenom demonstrated that at a venom–antivenom ratio of 1:16, the antivenom exhibited different immunocapturing abilities for all the venom samples. The percentage of non-retained fractions was highest for Guwahati (60.00%) and lowest for Hooghly 1 (18.91%). The study demonstrates intra-population (or inter-individual) variation of *B. fasciatus* venom from two nearby locations of Hooghly (West Bengal), intra-specific variation of *B. fasciatus* from three geographical locations and also inter-specific venom variation with *B.* caeruleus from Tamil Nadu. Thus, the venom variation leads to partial immune cross-reactivity by Indian polyvalent antivenoms. Inclusion of non-recognized venom proteins in the immunization mixture during antivenom production would help to improve the efficacy of the antivenom. Further study of the neutralizing ability of Indian polyvalent antivenoms against medically important snakes from different geographical regions would help to understand the effectiveness of the antivenoms and would invariably assist in the designing and development of safe and effective antivenoms.

Keywords *Bungarus fasciatus* · Snake venom toxins · Venom variation · Snakebite management · Indian polyvalent antivenoms

Introduction

Venomous snakes have attracted the curiosity and attention of mankind since ancient times due to their venom. This unique feature helps this limbless creature to incapacitate as well as kill its prey. They have been regarded with both fear and fascination throughout the ages and have secured a distinct position among various cultures and civilizations. Venomous snakes belong to one of the three snake families, namely Atractaspididae, Elapidae and Viperidae (Tasoulis and Isbister 2017). The venom of elapids is mostly neurotoxic and that of viperids is mostly hemotoxic, however, this distinction is not strict and there are exceptions in both families. Snakebite is an occupational hazard that affects mostly the marginalized communities of society such as farmers, labourers, plantation workers, fishermen, herdsmen and hunters (Warrell 1999). Open habitation and sleeping

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4 Society for Nature Conservation, Research and Community Engagement (CONCERN), Hooghly 1, Hooghly, West Bengal, India

5 Captive and Field Herpetology, 13 Hirfron, Anglesey, Wales, UK

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REVIEW ARTICLE

Snake venom toxins targeting the central nervous system

Amit Talukdar[a], Priya Maddhesiya[b], Nima Dondu Namsa[a] and Robin Doley[a]

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ABSTRACT

Snake venom is a blend of bioactive proteins, polypeptides, and various other substances with toxic and lethal properties that are known to modulate varied physiological and biological systems. During envenomation, venom toxins primarily target the hemostatic and nervous system for effective immobilization or death of the prey. The central (CNS) and the peripheral nervous system (PNS) are targeted through neuroreceptors, synaptic membranes, and critical ion channels, and some of these toxins also penetrate the blood-brain barrier. Despite its vital role and influence on the central nervous system, there exist limited information on the role of venom proteins and peptides associated with the manifestations of neurotoxicity. This review attempts to update the reader on the mechanism of direct and indirect interactions of snake venom protein (s) in the central nervous system as well as its effects on the physiology and behavior of the envenomated prey. Further, the role of these snake venom peptides in the field of neuropathic pain and neurodegenerative diseases has been reviewed for their therapeutic potential. Future investigations may provide valuable information to study the detailed mechanisms of such interactions to identify novel targets for the development of therapeutic interventions.

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KEYWORDS
Snake venom toxins; central nervous system; neurotoxins; blood-brain-barrier; neurotransmitters; snakebite management

Introduction

Snake venom is a mixture of proteins, polypeptides, and other substances which have diverse biological functions. The bioactive proteins and peptides consist of about 90–95% of the venom and the rest are non-proteinaceous contents such as nucleic acids, amino acids, carbohydrates, metal ions, lipids, citrate, organic molecules, and metal ions (Iwanaga and Suzuki 1979, Freitas *et al*. 1992, Mackessy 2016). Venom components possess high degrees of selectivity and affinities toward the receptors of the biological system and hence a small volume of venom can lead to severe physiological manifestation in the prey (Osipov and Utkin 2012). Venomous snakes belong to one of the four snake families, namely Atractaspididae, Elapidae, Viperidae, and Colubridae (Zaher *et al*. 2019). In general, the venom of Viperids and Elapids are considered hemotoxic and neurotoxic respectively. However, this distinction between hemotoxic and neurotoxic venom is not restricted to snake families, as neurotoxic venoms may contain hemotoxic compounds and vice-versa. However, the composition, delivery system, and physiological targets may markedly vary among different species of venomous snakes (Lewis and Gutmann 2004, Rossetto *et al*. 2006). Based on amino acid sequences and three-dimensional (3 D) structures, the snake venom components are classified into enzymatic and non-enzymatic superfamilies (Ménez 1998, Kordiš and Gubenšek 2000, Tasoulis and Isbister 2017). The enzymatic components of snake venom include the superfamilies such as phospholipase A_2 (PLA_2), snake venom metalloprotease (SVMP), snake venom serine protease (SVSP), nucleases, nucelotidases ($5^{/}$-NUC), acetylcholinesterase (AChE), L-amino acid oxidases (LAAO), hyaluronidases and phosphodiesterases. The non-enzymatic components of snake venom include the superfamilies such as three-finger toxin (3FTx), Kunitz-type serine protease inhibitor, sarafotoxins, cysteine-rich secretory proteins (CRiSP), disintegrins, snake C-type lectins (Snaclecs), vascular nerve growth factors (VNGF). The functions and biological activities of each snake venom superfamily that have been previously described by various authors are summarized in Tables 1 and 2.

One of the main targets of the venom components (toxins) is the nervous system of the prey. Receptors, ion channels, enzymes, or elements of muscles are targeted by neurotoxins for impairment of the normal functioning of the nerves such as neuromuscular

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Amit Talukdar

Studies on *Bungarus fasciatus* venom from Eastern and North-East India and characterization of poorly immunodepleted PLA_2 enzymes

A thesis submitted in part fulfilment of the requirements
for the degree of
Doctor of Philosophy

AMIT TALUKDAR
Registration No. TZ201043 of 2019

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MARCH, 2024

Amit Talukdar