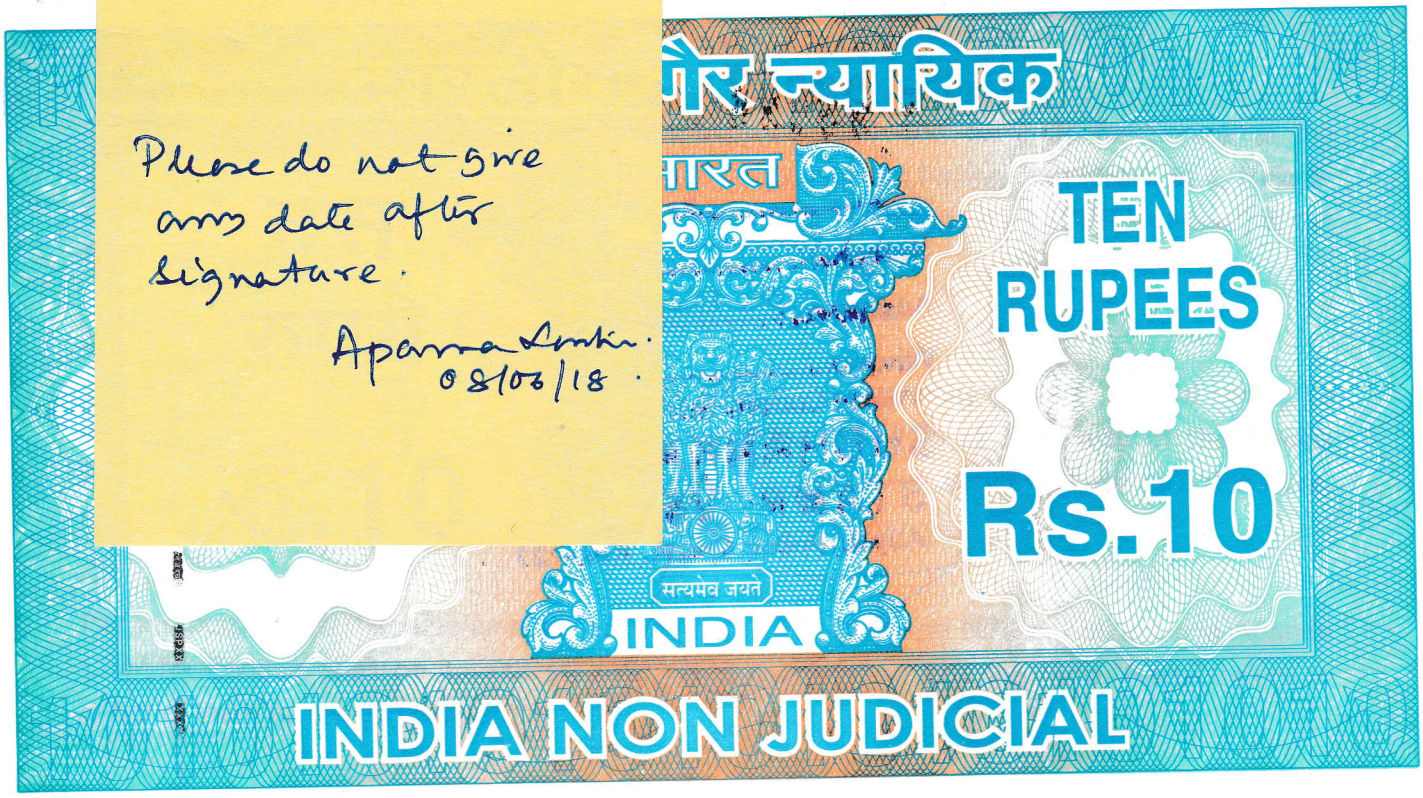
Please do not give any date after signature.

Aparna Sinha.
08/06/18.




पश्चिमबङ्ग पश्चिम बंगाल WEST BENGAL 08AB 637551

## AGREEMENT FOR COLLABORATIVE RESEARCH

### CL.1. THE AGREENENT

**THIS AGREEMENT** made and entered into on this 8th day of June, Two thousand and Eighteen between

CL.1.1. **COUNCIL OF SCIENTIFIC AND INDUSTRIAL RESEARCH (CSIR)**, a Society registered under the Societies Registration Act (XXI of 1860), having its registered office at Anusandhan Bhawan, 2, Rafi Marg, New Delhi - 110 001 THROUGH its constituent laboratory, **CSIR-Indian Institute of Chemical Biology**, having its address at 4, Raja S. C. Mullick Road, Jadavpur, Kolkata - 700 032 India (herein after referred to as **CSIR IICB** for the sake of brevity and convenience which expression shall where the context so admits include the successors and permitted assigns), of the **FIRST PART**

And

CL.1.2. **NATIONAL INSTITUTE OF PHARMACEUTICAL EDUCATION & RESEARCH - KOLKATA**, an Institute of National Importance established by the Department of Pharmaceuticals, Ministry of Chemicals & Fertilizers, Government

Md. Abdur Razzaque

C. Mullick Road, Jadavpur, Kolkata -700 032 (hereinafter referred to as "**NIPER Kolkata**") of the **SECOND PART**

And

CL.1.3. **Ananda Chandra College**, a College affiliated to University of North Bengal having its office at Jalpaiguri, West Bengal 735101 hereinafter referred to as the **Party of the THIRD PART** (which term or expression shall wherever the context so admits include its successors, executors, administrators, legal representatives and/or assigns).

For the purpose of this supplemental **agreement**, CSIR-IICB and NIPER Kolkata and Ananda Chandra College shall be collectively referred to as "**Parties**" and the term "**Party**" refers to either of them as the context permits.

**CL.2. PREAMBLE**

CL.2.1. WHEREAS the Department of Biotechnology (DBT), Govt. of West Bengal, has sanctioned a project entitled "Synthesis of Novel Imipramine derivatives targeting *Leishmania donovani.*" among Dr. Sanjay Datta of CSR-IICB (as PI), Dr. Syamal Roy of NIPER, Kolkata and Dr. Bikramjit Roy Chaudhuri of Ananda Chandra College, Jalpaiguri, west Bengal (as Co PIs), vide letter No.12(Sanc)/BT/P/Estt/RD-53/2015.

CL.2.2. WHEREAS CSIR at its constituted unit, Indian Institute of Chemical Biology, Kolkata – 700 032 as the party of the First part is working in the field of leishmaniasis. The laboratory will synthesize potential antileishmanial compounds and the testing of the compounds will be carried out by the 2nd and 3rd parties.

CL.2.3. WHEREAS Dr. Syamal Roy at the above National Institute of Pharmaceutical Education and Research has the expertise in culturing of leishmanial parasites and host-pathogen interactions.

CL.2.4. WHEREAS Dr.Bikramjit Roy Chaudhuri at the above Ananda Chandra College has the expertise in the animal model development and determination of parasite load in the infected organs.

CL.2.6. WHEREAS Dr Dr. Syamal Roy and Dr.Bikramjit Roy Chaudhuri are desirous of collaborating with Dr. Sanjay Datta of CSIR IICB for the study as mentioned in clause CL.2.1 (hereinafter called the PROJECT) as per the scope of work detailed in Annexure-I to this agreement.

Now, therefore, in consideration of the premises and mutual covenants hereinafter contained, the parties hereto agree as follows:

**CL.3. SCOPE OF THE AGREEMENT**

The agreement details the terms and conditions financial arrangements, modalities of collaboration, intellectual property rights, responsibilities, and obligations of the PARTIES and CSIR IICB pertaining to the DBT-Govt. of west Bengal PROJECT.

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(i) A research proposal (summary laid down in Annexure-I) has been sanctioned by DBT-Govt. of West Bengal for funding. The Parties of the Second and Third Part, and CSIR-IICB shall have their own share of money as sanctioned by the DBT, Govt. of West Bengal. The proposed budget sanctioned by DBT for the first year is shown in Annexure-II. There will be no other financial obligation in the part of any of the parties. CSIR-IICB will not have any financial obligation in relation to the said project.

(ii). All expenditures related to the personnel deputed outside their place of work in connection with work pertaining to the PROJECT, travel charges, TA/DA, boarding & lodging and local transportation etc, shall be borne by the respective parties.

**CL.5. MODALITIES OF COLLABORATION**

CL.5.1. The respective responsibilities of CSIR- IICB and the other PARTIES and schedule of fulfillment thereof shall be as per Annexure-III.

CL.5.2. There will be a joint Monitoring Group for the PROJECT. The monitoring Group shall consist of two members each from the CSIR IICB and the PARTIES. The monitoring Group will fix/identify the work to be done by the PARTIES, the targets/milestones and criteria for completion of the PROJECT. It shall also review every six months the progress of the PROJECT.

CL.5.3 CSIR-IICB will draw up protocols for such studies. The parties shall jointly identify centers for carrying out the assay and monitoring of patients and draw up protocols for such studies if envisaged in the project.

**CL.6. RESPONSIBILITY OF CSIR-IICB**

CL.6.1. CSIR IICB shall undertake the work on the Project as per schedule of work detailed on Annexure-III at IICB, Kolkata for the Project as described in **Annexure-I**.

CL.6.2. CSIR IICB shall carry out the DBT funded project as per the protocol drawn up and agreed to between the parties as per schedule of work detailed in **Annexure-II**.

CL.6.3. CSIR IICB shall complete the work as per schedule of work as detailed in Annexure -III. This period of completion of work could however be extended to such further periods as may be mutually agreed to between the parties without any financial or other liability on the part of CSIR IICB and only if agreed upon by DBT, Govt. of West Bengal.

CL.6.4. CSIR IICB shall submit progress reports annual and detailed final report for forward transmission to the funding agency. CSIR IICB should complete the work as per schedule of work as detailed in **Annexure-III**.

CL.6.5. CSIR IICB shall submit a yearly statement of expenditure incurred by it against the amount paid by the DBT,Govt. of West Bengal.

CL.6.6. In case the superannuation of the Principal Investigator, the responsibility of caring out the PROJECT will be on the senior most Co-Project Investigators. In the absence of a Co-PI, shall be appointed by the competent authority.

CL.6.7. CSIR IICB shall not be responsible for any damage to the property/plant/material of the PARTIES by its personnel during or consequent to the work if any carried out under the PROJECT in PARTY's premises.

**CL.7. RESPONSIBILITY OF THE PARTIES**

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described in **Annexure-I**.

CL.7.2. The PARTIES shall supply the PRODUCT/research material to the CSIR IICB for the work envisaged at CSIR IICB as provided for the **Annexure-III**.

CL.7.3. The PARTIES shall co-operate with CSIR-IICB to carry out the evaluation of antileishmanial properties studies of the product as detailed In Annexure-I and mutually agreed, to carry out toxicity/bio-efficacy studies of the PRODUCT as per the protocol detailed in Annexure-III.

CL.7.4. The PARTIES shall undertake and complete the work as per schedule of work detailed in Annexure-III. This period of completion of work could, however, be extended to such further periods as may be mutually agreed to between the parties without any liability on the part of the PARTY and only if DBT, Govt. of West Bengal agrees to extend such period.

CL.7.5. The PARTIES shall submit a yearly statement of expenditure incurred by the PARTIES against the amount paid by the DBT, Govt. of West Bengal.

CL.7.6. The PARTIES shall not be responsible for any damage to the property/plant/material of the CSIR-IICB by its personnel during or consequent to the work if any carried out under the PROJECT in the CSIR-IICB premises.

**CL.8. COMPLETION**

CL.8.1. The work envisaged to be done by the IICB/CSIR LABORATORY/PARTIES shall be deemed to have been successfully completed by the CSIR IICB and the PARTIES on submission of the Final Report as per requirement of the DBT, Govt. of West Bengal sponsored project as detailed in Annexure-I and satisfaction of criteria fixed by the Monitoring Group or any other criteria mutually agreed by the parties hereto, and after final approval from DBT, Govt. of West Bengal.

**CL.9. RESULTS OF PROJECT**

CL.9.1. Any intellectual property rights [patents] obtained by the IICB/CSIR hereto pertaining to the PROJECT or related to the project prior to signing of the agreement shall remain as absolute the property of CSIR-IICB. The PARTIES shall have no IPR or financial right for such compounds /products and to commercially exploit/use the intellectual property. \

CL.9.2. CSIR IICB will have absolute right to patent such processes of knowhow/knowledge /compounds here to pertaining to the project or merely related to the project, those are already developed /being developed by CSIR IICB of its own before singing this agreement.

CL.9.3. The intellectual property that is patents generated in the PROJECT shall be jointly owned by CSIR IICB, and the PARTIES; the extent of ownership shall be decided mutually depending upon the relative inputs [intellectual/technical/financial/physical] made by the parties hereto to the PROJECT.

CL.9.4. The procedural formalities for securing and maintaining the intellectual property rights shall be the responsibility of CSIR IICB and the expenditure incurred thereof shall be borne by each party equally. The question of whether or not intellectual property right should be secured and the territory where these shall be secured shall be decided by Director, CSIR IICB.

CL.9.5. The parties shall consult each other for any publication in respect of the PROJECT. These publications (papers, reports etc.) shall be in the names of research workers, wherein it will be dully acknowledged that the work has been carried out under the collaborative program between the parties with financial support from DBT, Govt. of West Bengal.

PARTIES undertake on their behalf and on behalf of their subcontractors/employees /representatives/associates to maintain strict confidentiality and prevent disclosure thereof, of all the information and data exchanged/generated pertaining to work under this agreement for any purposes other than in accordance with this agreement. The parties, however, retain the rights to use their own R&D results generated at their respective laboratories during the PROJECT for its own R&D programmes without any obligation to the other.

## CL.11. UTILIZATION OF INTELLECTUAL PROPERTY DEVELOPED

CL.11.1. CSIR-IICB shall have the exclusive right to license the intellectual property generated in the project. The PARTIES on the second and third shall have the first option to commercially exploit the intellectual property generated in the PROJECT provided such option is exercised by the PARTY within 6 months of completion of the PROJECT as per Clause 8. In such an event the fee and or royalty and other terms and conditions for licensing the PRODUCT shall be settled mutually between CSIR IICB and PARTIES (depending on relative financial and intellectual inputs), for which a separate agreement shall be entered into.

CL.11.2. CSIR IICB shall have the right to license the intellectual property generated in the PROJECT to others if the parties on the second and third part fails to exercise the option within stipulated period or having exercised the option fails to commercialize the intellectual property within 6 months from date of exercise of such option. In such an event the terms and conditions for licensing to others shall be settled mutually between CSIR IICB and the PARTIES.

CL.11.3. The PARTIES shall have the right on non-exclusive basis on fulfillment of criteria as mentioned in CL.11.1 to commercially exploit the intellectual property generated in the PROJECT for a period of 5 years from the date of agreement for commercial use between the concerned parties as per Clause 11.1. After the expiry of the exclusive period, CSIR-IICB shall have the right to license the intellectual property to others. In such an event the terms and conditions for licensing to others shall be settled mutually between CSIR IICB and the PARTIES.

CL.11.4. The premia/royalty accrued from licensing of the intellectual property to other party(ies) shall be shared between IICB/CSIR, and the PARTIES in a ratio to be mutually decided depending upon the relative financial and intellectual inputs to the PROJECT.

CL.11.5. During the work envisaged under the agreement in the event of CSIR IICB scientist exploring, inventing or discovering results other than the specific objectives of the PROJECT, CSIR-IICB shall retain absolute rights on such results. CSIR-IICB shall first offer such results to the PARTIES on negotiated terms by entering into a separate agreement. In case the PARTIES does not accept the offer, CSIR IICB shall be free to release such results to other parties without any obligations to the PARTY(s).

## CL.12. FORCE MAJEURE

CL.12.1. Neither party shall be held responsible for non-fulfillment of their respective obligations under the agreement due to the exigency of one or more of the force majeure events such as but not limited to Acts of God, war, flood, earthquakes, strike, lockouts, epidemics, riots, civil commotion, etc. provided on the occurrence and cessation of any such events, the party affected thereby shall give a notice in writing to the other party within one month of such occurrence or cessation. If the force majeure conditions continue beyond six months, the parties shall then mutually decide about the future course of action.

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Bengal.

CL13.2. The agreement shall terminate on the expiry of the period, as in clause CL.13.1 unless extended by DBT, Govt. of West Bengal and agreed by the parties.

CL.13.3. During the tenure of the agreement, parties hereto can terminate the agreement either for breach of any the terms and conditions of this agreement or otherwise by giving a THREE months notice in writing to the default party. Failure of either party to terminate the agreement on account of breach or default by the other shall not constitute a waiver of that party's right to terminate this agreement subject to fulfillment of DBT, Govt. of West Bengal terms and conditions.

CL.13.4. In the event of termination of the agreement vide clause 13.3 the rights and obligations of the parties shall be settled by mutual discussion; the financial settlement shall take into consideration not only the expenditure incurred but also the expenditure committed by the parties hereto.

CL.13.5. The agreement arrived at between the parties hereto for the utilization of the intellectual property shall survive the termination of the agreement.

**CL.14. NOTICE**

CL.14.1. All notices and other communications required to be served on the PARTIES under the terms of this agreement shall be considered to be duly served if the same shall have been delivered to, left with or posted by registered mail to the PARTIES at its last known address of business. Similarly, any notice to be given to the CSIR-IICB shall be considered duly served if the same shall have been delivered to, left with or posted by registered mail to the CSIR-IICB at its address at Kolkata.

**CL.15. AMENDMENTS TO THE AGREEMENT**

CL.15.1. No amendment or modification of this agreement shall be valid unless the same is made in writing by the parties or their authorized representatives and specifically stating the same to be an amendment of this agreement. The modifications/changes shall be effective from the date on which they are made/executed, unless otherwise

**CL.16. ASSIGNMENT OF THE AGREEMENT**

CL.16.1. The rights or/and liabilities arising to any party to this agreement shall not be assigned except with the consent of the other party and subject to such terms and conditions as may be mutually agreed upon.

Md. Abdur Razzaque

**CL.17. ARBITRATION**

CL.17.1. In the event of any dispute or difference between the parties hereto, such disputes or differences shall be resolved amicably by mutual consultation or through the good offices of empowered agencies of the Government of India. If such resolution is not possible, then, the unresolved dispute or difference shall be referred to arbitration of an arbitrator to be nominated by Secretary, Department of Legal Affairs ("Law Secretary"), Government of India, in terms of the Office Memorandum No.55/3/1/75-CF dated the 19th November, 1975 issued by the Cabinet Secretariat (Department of Cabinet Affairs) Government of India, as modified from time to time. The Arbitration Act. 1940 (10 of 1940) shall not be applicable to the arbitration under this clause. The award of the Arbitrator shall be binding upon parties to the dispute. Provided, however, any party aggrieved by such award may make a further reference for setting aside or revision of the award to Law Secretary whose decision shall bind the parties finally and conclusively].

End of MoU. Signature page follows

Md. Abdus Razzaque

**SEAL OF THE PARTIES**

In witness whereof the parties hereto have signed this agreement on the day, month and year mentioned hereinbefore.

Parties

For and on behalf of First Part (CSIR-IICB)

Dr. Arun Bandyopadhyay
Head, Business Development and IPM Division

Witness:

1. Dr. Sanjay Datta
Senior Scientist

2. Dr. Aparna Laskar
Principal Technical Officer,
Business Development and IPM Division

For and on behalf party of the Second Part (NIPER, Kolkata)

Witness:

1. Dr. Syamal Roy

2. (Dr S.R. Sarkar)

Dr. S. R. Sarkar
REGISTRAR (I/C)
National Institute of Pharmaceutical Education & Research, Kolkata
4, Raja S.C. Mullick Road, Jadavpur, Kolkata- 700 032

For and on behalf party of the Third Part (Ananda Chandra College)

Dr. Bikramjit Raychaudhury, Ph.D
Assistant Professor
Department of Physiology
Ananda Chandra College, Jalpaiguri

Md. Abdur Razzaque

Principal
Ananda Chandra College
Jalpaiguri

## SCOPE OF WORK

The project title: **Synthesis of Novel Imipramine derivatives targeting *Leishmania donovani.***

The disease visceral leishmaniasis or Kala-azar is caused by the protozoan parasite *Leishmaniadonovani*(LD) and is widening its base in different parts of the world (*J Glob Infect Dis* 2010 2: 124–26.;*Clin Infect Dis* 2000 31: 1104–1107.). Pentavalent antimonial ($Sb^V$) has long been the first line drug, is no longer recommended for use as high levels of resistance in the Indian subcontinent have been reported (Trop Med Int Health 2001 6: 849–854.). Other drugs like miltefosine (hexadecylphosphocholine, a polyene antibiotic) and amphotericin B (an anti-fungal agent) are in current clinical use. As miltefosine is orally active, it offers advantages in terms of reduced hospitalization but cannot be used during pregnancy and lactation (*Clin Infect Dis* 2000 31: 1104–1107.). Amphotericin B and its liposomal form are to be administered as an infusion and therefore the patients require hospitalization (*J ClinOncol*2000 18: 2476–2483.). Unfortunately, treatment failure cases to miltefosine (*Am J Trop Med Hyg* 2000 80: 580–582.) and amphotericin B (*J ClinMicrobiol* 2011 49: 3088–3091.) are emerging, which raises serious concerns for their future use. There is a genuine need for an orally active and affordable drug for the treatment of relapsed Kala-azar cases.

"New use of old drug" is now a day's looming concept of the researchers and pharmaceutical sector because it saves the huge time and cost to bring a molecule as drug. There are evidences of using old drugs in the therapy of different diseases successfully (*J Health Econ* 2003 22, 151-185; Drug Discov Today, 2011 16, 298-310). For example diclofenac sodium is normally used for pain management, but now a day it is also use as anti-bacterial agent. Similarly dicyclomine, dobutamine, methyl-L-dopa, trimeprazineetc are used as antibacterial agent apart from their normal and previous uses. Imipramine, N-(γ-dimethylaminopropyl)-iminodibenzylHCl, is a tricyclic antidepressant and belongs to the broad class of cationic amphiphilic drugs. The tricycle consists of two benzene rings fused with a seven member heterocycle. Imipramine is FDA (Food and Drug Administration) approved drug for treating depression and paediatric nocturnal enuresis (Can Med Assoc J 1969 101:65–68), and is sometimes used off-label to treat chronic pain in combination with other pain medications (Gut 1998 42: 807–813.). The dose range for treating depression is 100–200 mg daily and the recommended use for enuresis is 10–75 mg daily (Peragmon Press. 1990 pp. 383–435.).

The selection of imipramine for therapy of experimental visceral leishmaniasis is based on the following past observations by others: (i) the drug alters the proton motive force of LD's membrane (BiochemPharmacol 1990 39: 935–940.), (ii) inhibits trypanothionereductase, an enzyme upregulated in SSG resistant LD parasites (Biochem J 1992 286 (Pt 1): 9–11.), (iii) an effective immunomodulator as it induces the production of TNF-α, an important cytokine for antileishmanialdefense (IntImmunopharmacol 2004 4: 185–192), (iv) cationic properties favor its absorption by phagocytic cells and accumulation in phagolysosomal bodies (Toxicol Pathol 1997 25: 53–60.), and (v) its metabolite desipramine is as effective as the parent drug *against* LD promastigotes (Biochem Pharmacol 1994 48: 613–616.). These compelling attributes of imipramine towards *Leishmania*parasites led us to test its efficacy directly on LD and also in experimental infection induced by recent clinical isolates of SbS and SbR LD parasites with miltefosine as a reference oral drug.

It was shown that the drug is highly active against antimony sensitive and resistant *Leishmaniadonovani* (LD) in both promastigotes and intracellular amastigotes and in LD infected hamster model (*PLoSNegl. Trop. Dis.* 2012 6: e1987.). The drug was found to decrease the mitochondrial transmembrane potential of LD promastigotes and purified amastigotes after 8 h of treatment, whereas miltefosine effected only a marginal change even after 24 h. The drug restores defective antigen presenting ability of the parasitized macrophages. The status of the host protective factors TNF-α, IFN-γ and iNOS activity increased with the concomitant decrease in IL-10 and TGF-β level in imipramine treated infected hamsters and evolution of matured sterile hepatic granuloma. The 10-day therapeutic window as a monotherapy, showing about 90% clearance of organ parasites in infected hamsters regardless of their SSG sensitivity (*PLoS Negl. Trop. Dis.* 2012 6: e1987.). Imipramine was found to inhibit IL-10 production from antimony resistant LD infected macrophages and therefore favors accumulation of surrogates of antimonials (J Immunol, 2014, 193: 4083–4094.). The drug upregulates histone deacetylase 11, which inhibits acetylation of IL-10 promoter, leading to a decrease in IL-10 production from antimony resistant LD infected macrophages. Oral treatment of infected BALB/c mice with imipramine in combination with sodium stibogluconate cleared organ $Sb^R$LD parasites and caused an expansion of the antileishmanial T cell repertoire where sodium stibogluconate alone had no effect (J Immunol, 2014, 193: 4083–4094).

We are proposing to synthesize novel Imipramine derivatives which can have antileishmanial properties.

**Specific Aims**:

1) Design and Synthesis of Novel Imipramine molecules.

2) To test its efficacy directly on Leishmania parasites LD and also in experimental infection induced by recent clinical isolates of SbS and SbR LD parasites with miltefosine as a reference oral drug.

## ANNEXURE-II

The financial input (1st year) and different heads in the research project sanctioned by DBT. are as follows:

### A. CSIR-IICB (Dr. Sanjay Datta)

| Head | Amount (in Rs) |
|---|---|
| Equipment | Nil |
| Salary | Nil |
| Consumables | 5,00,000 |
| Travel | 25,000 |
| Contingency | 25,000 |
| Overhead | 55,000 |
| TOTAL | 6,05,000 |

Ist Year release for CSIR-IICB is Rs 6,05,000 (Six lakhs, five thousand only)

B. PARTIES

(1) NIPER (Dr. Syamal Roy)

| Head | Amount (in Rs) |
|---|---|
| Equipment | Nil |
| Salary | Nil |
| Consumables | 4,00,000 |
| Travel | 25,000 |
| Contingency | 25,000 |
| Overhead | 45,000 |
| TOTAL | 4,95,000 |

Ist Year release for NIPER is **Rs 4,95,000 (Four lakhs, ninety five thousand only)**

**(2) Ananda Chandra College (Dr.Bikramjit**

| Head | Amount (in Rs) |
|---|---|
| Equipment | Nil |
| Salary | Nil |
| Consumables | 2,00,000 |
| Travel | 15,000 |
| Contingency | 25,000 |
| Overhead | 24,000 |
| TOTAL | 2,64,000 |

Ist Year release for Ananda Chandra College, Jalpaiguri is **Rs, 2,64,000 (Two lakhs, sixty four thousand only)**

The respective responsibilities of the parties and the schedule and criteria for fulfillment of their responsibilities shall be as follows:

**A. CSIR-IICB** shall carry out the work as mentioned below:

a) Design and Synthesis of Novel Imipramine molecules.

b) Structure activity relationship after getting the *in-vitro* and *in-vivo* results.

**B. NIPER-KOLKATA** shall carry out the work as mentioned below:

a) To test Imipramine-triazole efficacy directly on *Leishmania* parasites *in vitro* (PLoSNegl. Trop. Dis. 2012 6: e1987.)

Determination of drug efficacy on promastigotes and intracellular amastigotes: $IC_{50}$ and $EC_{50}$:

LD promastigotes will be maintained in M199 medium supplemented with 10% heat inactivated FBS (Gibco), 100 IU/mL of penicillin and 100 mg/mL of streptomycin (Gibco) in a 22$^0$C room (Int J Parasitol 2011 41: 1311–1321). Day 5 culture of parasites will be used to determine the drug efficacy (IC50) to kill promastigotes using MTT (J Immunol Methods 65: 55–63.). The LD parasites will be harvested on the 96-well cell culture plates at a density of $10^5$ cells/well and incubated in presence of drugs for 48 h.

Results will be expressed as the concentration that inhibited parasite growth by 50% (IC50).

In order to determine EC50 (Efficacy against intracellular amastigote), different drugs will be serially diluted in RPMI complete medium over six concentrations in triplicate at each concentration. Macrophages will be harvested from BALB/c mice by lavage, 48 h after i.p. injection of 2% (w/v) soluble starch. In chambered slide at a density of 105/cover slip in RPMI 1640 medium supplemented with 10% heat inactivated FBS, 100 IU/mL of penicillin, and 100 mg/mL of streptomycin, i.e. RPMI complete medium. The cells will be left to adhere for 48 h at 37$^0$C under 5% $CO_2$ before infection. The Macrophages were infected with stationary phase promastigotes at a ratio of 1:10 (PLoS Negl. Trop. Dis. 2012 6: e1987.). Infected macrophages will be incubated with drug dilutions for another 24 h at 37$^0$C and under 5% $CO_2$. Untreated macrophages received medium alone and intracellular parasites will be enumerated. The average of three untreated cultures will be 100% control against which the percentage inhibition of infected macrophages in treated cultures will be calculated. The 50% effective concentration (EC50) of imipramine for each of the isolates was estimated as described elsewhere (Antimicrob Agents Chemother 2010 54: 5257–5268.).

**C. Ananda Chandra College** shall carry out the work as mentioned below:

a) To test Imipramine-triazole efficacy directly on *Leishmania* parasites *in-vivo* (PLoSNegl. Trop. Dis. 2012 6: e1987.)

*In vivo* parasite clearance

Hamsters will be infected with LD amastigotes (Arch BiochemBiophys 1996 334: 1–8.) and inoculated ($10^7$ parasites in 200 mL) via intracardiac routes as described previously (J Immunol 2005 174: 7160–7171). The 8-week infected hamsters will be randomly divided into several groups and will be treated with the synthesized drug as required. Two days after the completion of treatment, hamsters will be sacrificed to determine splenic and hepatic parasite burdens by stamp smear method as described elsewhere (J Immunol 166: 1912–1920.).

## ANNEXURE-IV

Sharing of Fee, Premia and royalty and other terms and conditions for commercial exploitation/use of the Intellectual Property by the PARTIES.

Separate agreement shall be signed between CSIR-IICB, NIPER-Kolkata and Ananda Chandra College, and the sharing/distribution will be decided mutually on the basis of proportionate input pertaining to the project. A separate agreement shall be signed for this purpose with full details.