Expression of Interest (EOI) from Eligible Contract Research Organizations (CROs)

TO

Plan and perform detailed toxicological preclinical evaluation of NHEJ inhibitors

EoI Number: BC/SCR/EOI-1/2025

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BACKGROUND

The Indian Institute of Science (IISc), established in 1909 in Bangalore, stands as one of India's foremost institutions for advanced research and education. Renowned for its pioneering contributions in science and technology, IISc has consistently pushed the frontiers of knowledge through cutting-edge research, innovation, and academic excellence. Its stellar reputation is built on a foundation of rigorous academic programs, globally recognized faculty, and state-of-the-art research infrastructure. With a vibrant and diverse student community, IISc continues to shape India's scientific landscape and remains a beacon of the nation's commitment to progress and intellectual growth.

The Department of Biochemistry at IISc, founded in 1921, has a distinguished legacy of excellence in research and education. Over the past century, the department has made significant contributions to molecular biology, genetic engineering, and metabolic biochemistry. Several of its pioneering discoveries have been successfully translated into advances in human health, exemplifying IISc's unwavering focus on bridging fundamental science with real-world medical applications.

In this context, we are pleased to invite Expressions of Interest (EoI) from qualified vendors with proven expertise in preclinical drug development to collaborate with us in advancing novel NHEJ inhibitors—specifically, DNA Ligase IV inhibitors—through critical stages of drug development. The objective is to ensure rigorous scientific validation and adherence to regulatory standards.

DNA double-strand breaks (DSBs) are among the most severe forms of genomic damage, and the nonhomologous end joining (NHEJ) pathway is one of the primary repair mechanisms in mammalian cells. DNA Ligase IV is a core component of this pathway, making it an attractive therapeutic target. Inhibition of Ligase IV can compromise DSB repair, promoting apoptosis in cancer cells.

Our team previously identified SCR7, the first known NHEJ inhibitor, which showed potential in cancer therapy and precision genome editing (*Srivastava et al., Cell, 2012; Vartak et al., 2015; Ray and Raghavan, 2020*). Building on this foundation, we have recently developed two novel derivatives, SCR116 and SCR132, which demonstrate several fold improved efficacy (nanomolar IC50) and specifically inhibit NHEJ in a Ligase IV-dependent manner, as confirmed in preliminary studies. By performing preclinical toxicity studies of NHEJ inhibitors, we aim to deliver an indigenously developed DNA repair inhibitor, with strong preclinical validation, poised for entry into clinical trials. We are committed to a fair and transparent selection process that ensures equal opportunity for all eligible vendors. This EoI document outlines the scope of work, eligibility criteria, evaluation methodology, and submission guidelines. We encourage all qualified vendors to submit their Expression of Interest and join us in this exciting initiative to advance next-generation cancer therapeutics developed in India.

ELIGIBILITY CRITERIA

- The vendor must be accredited by relevant regulatory authorities (e.g., OECD GLP, AAALAC) and demonstrate a clear understanding of the regulatory requirements for non-rodent preclinical studies.
- The vendor should have state-of-the-art facilities and equipment required for conducting PK/PD and toxicity and genotoxicity studies.
- The vendor must employ a qualified and experienced team of scientists, including toxicologists, pharmacologists, and bioanalytical experts, with a track record of delivering similar studies within the agreed timelines and budgets.
- They should have executed ≥ 10 projects of a similar nature that has been deployed in a large academic campus and should attach a copy of the purchase order/work completion certificate from clients as proof.

SCOPE OF WORK

The selected Contract Research Organization (CRO) will be responsible for conducting following studies for 2 compounds

- Bioanalytical Method Development and Validation using LC-MS for quantification of one analyte in Rat Plasma, GLP
- 10-day Tox Study in Rats, GLP
- 28 Day or Repeated Dose Subchronic Toxicology study (along with TK arm) in Rats, GLP
- Ames Test, GLP
- In vitro Micronucleus Test, GLP
- In vivo Micronucleus Test, GLP
- In vitro Chromosomal Aberration Test, GLP

These preclinical studies are critical to determining the safety, efficacy, and dosing parameters necessary for advancing NHEJ inhibitors into clinical trials. By gaining a comprehensive understanding of compounds ADME (Absorption, Distribution, Metabolism, and Excretion) characteristics, pharmacological impact, and potential toxicities, we aim to establish a solid foundation for future regulatory submissions and clinical development, ultimately contributing to the development of effective cancer therapies.

PROJECT DETAILS

S.No.	STUDY DETAILS
1	Bioanalytical Method Development and Validation using LC-MS for quantification of one analyte in Rat Plasma, GLP (for 2 compounds)
2	10-day Tox Study in Rats, GLP (for 2 compounds)
3	28-Day Toxicity Study in Rats with 14-day Recovery with TK (for 2 compounds)
4	Ames (including Dose Formulation), GLP (for 2 compounds)
5	In vitro Micronucleus Test, GLP (for 2 compounds)
6	In vivo Micronucleus Test, GLP (for 2 compounds)
7	In vitro Chromosomal Aberration test, GLP (for 2 compounds)

1. Bioanalytical Method Development and Validation using LC-MS (Quantification in Rat Plasma)

CDSCO (aligns with USFDA/EMA): Follow USFDA (2022) or EMA (2011) guidelines.

Parameters: Selectivity, sensitivity, accuracy, precision, linearity, recovery, matrix effects, stability.

Validation required before TK/PK sample analysis in GLP studies.

2. GLP - 10-day Toxicity Study in Rats (Repeated Dose Toxicity)

CDSCO Guideline:

Objective: Identify target organs and determine Maximum Tolerated Dose (MTD).
Species: One rodent species (rat).

Dosing: Daily for 10 days via proposed clinical route.

Group Design: Minimum 4 dose groups including control.

Each group: At least 5 males and 5 females.

Observations: Clinical signs, body weight, lab parameters.

Gross necropsy and histopathology of affected organs.

Regulatory Reference: Based on CDSCO Schedule Y guidance

3. 28-Day Repeated-Dose Toxicity Study (Rodents)

OECD Guidelines: TG 407 (Rodents)

Design: Rodents: 6–10/sex/group;

3 dose levels (high with observable toxicity, mid, and low) + vehicle control and reversal groups

Route: Same as intended for humans.

Parameters: Clinical signs, body weight, food/water intake.

Hematology, clinical biochemistry. Full gross and microscopic evaluation.

4. Ames Test (Bacterial Reverse Mutation Assay)

OECD Guideline: TG 471

Bacterial Strains: Salmonella typhimurium: TA98, TA100, TA102, TA1535, TA97
E. coli: WP2 uvrA or WP2 uvrA (pKM101)

Design: At least 5 dose levels in log intervals.

± S9 metabolic activation.

Solvent and positive controls (e.g., 9-aminoacridine, sodium azide).

At least 3 replicates per group.

Criteria: ≥2.5-fold increase in revertants over control = positive.

5. In Vitro Micronucleus Assay

OECD Guideline: TG 487

Cells: Human lymphocytes or mammalian cell lines (e.g., CHO).

Design: ≥3 dose levels ± S9 activation.

Target toxicity: >50% cytotoxicity or mitotic inhibition.

Controls: Solvent + Positive (e.g., Mitomycin C, Cyclophosphamide).

Evaluation: Increase in micronucleated binucleated cells across ≥3 replicates.

6. In Vivo Micronucleus Assay

OECD Guideline: TG 474

Species: Rodent (preferably mouse).

Design: Route: Same as clinical. ≥3 dose levels + solvent + positive control.

5 animals/sex/group.

Dose on Day 1 and 2; sacrifice 6 hrs post final dose.

Evaluation: Bone marrow smears from femur.

Giemsa-May-Grünwald staining.

Score ≥1000 polychromatic erythrocytes (PCEs) for micronuclei.

7. In Vitro Chromosomal Aberration Test

OECD Guideline: TG 473

Cells: Human lymphocytes or CHO/CHL cells.

Design: ≥3 dose levels ± S9 mix.

Solvent and positive controls: Mitomycin C (–S9), Cyclophosphamide (+S9).

≥3 replicates.

Evaluation: ≥50% mitotic index inhibition = adequate cytotoxicity.

Count metaphase cells; assess for structural/numerical aberrations.

DELIVERABLES

The vendor is expected to deliver the results within a specific timeline of 6-8 months from the date of initiation of the project including, progress reports provided on a monthly basis to ensure transparency and track milestones.

SELECTION CRITERIA

The shortlisting of CROs will be done by a committee set up by Competent Authority, IISc. The criteria for evaluation would be:

S.No.	Criteria
1.	**Experience**
1.1.	Number of years in providing preclinical services
1.2.	GLP and AAALAC accreditation
1.3.	Past Assignments-experience in dealing with similar projects listed under Project Details
2.	**Technical Aspects**
2.1.	Expertise and experience of key personnel
2.2.	Quality of past projects relevant to the current project listed under Project Details
3.	**Quotation**
3.1.	Evaluation will be based on the bids submitted by the shortlisted vendors.
3.2.	Final selection will not only be based on the overall

	cost of the project, but also by considering the cost of resources per month and the total effort required within the appropriate time unit, such as weeks or months.

This comprehensive evaluation will ensure that the total cost for delivering the scoped phase of the project can be accurately calculated. Therefore, vendors are expected to provide the project efforts and associated costs for resources required. This will enable a fair and transparent evaluation process, leading to the selection of a vendor who can provide the best value for money while meeting the necessary project requirements.

Documents Required for Validating Eligibility Criteria

- Certificate of incorporation or registration of the company.
- Certificate of Good Laboratory Practices (GLP) Compliance.
- PAN (Permanent Account Number) card of the company.
- GST (Goods and Services Tax) registration of certificate.
- References or testimonials from previous clients or projects.
- Technical proposal outlining the experimental blueprint for performing preclinical studies, including details of the methodology, number of animals, and bioanalytical equipments to be used.
- Financial proposal specifying the cost of the project, including a breakdown of the costs as per the objectives of the project.

How to Submit the EoI

EoI with all enclosures should be emailed to sathees@iisc.ac.in or posted to Dept. of Biochemistry, Division of Biological Sciences, Sir CV Raman Road, Bengaluru – 560012 on or before 5.00 PM on May 20, 2025.

Late submissions will not be considered.

In case of queries, Vendors may contact 080-2293-2674 between 9AM-5PM on working days.

IISc reserved the right to reject any/or all the EoIs without assigning any reasons whatsoever.

REFERENCES

Srivastava, M., Nambiar, M., Sharma, S., Karki, S. S., Goldsmith, G., Hegde, M., Kumar, S., Pandey, M., Singh, R. K., Ray, P., Natarajan, R., Kelkar, M., De, A., Choudhary, B., & Raghavan, S. C. (2012). An inhibitor of nonhomologous end-joining abrogates double-strand break repair and impedes cancer progression. *Cell*, *151*(7), 1474–1487.

Ray, U., Gopinatha, V. K., Sharma, S., Goyary, L., Choudhary, B., Mantelingu, K., Rangappa, K. S., & Raghavan, S. C. (2023). Identification and characterization of mercaptopyrimidine-based small molecules as inhibitors of nonhomologous DNA end joining. *The FEBS journal*, *290*(3), 796–820.

Ray, U., Vartak, S. V., & Raghavan, S. C. (2020). NHEJ inhibitor SCR7 and its different forms: Promising CRISPR tools for genome engineering. *Gene*, *763*, 144997.

Gopalakrishnan, V., Sharma, S., Ray, U., Manjunath, M., Lakshmanan, D., Vartak, S. V., Gopinatha, V. K., Srivastava, M., Kempegowda, M., Choudhary, B., & Raghavan, S. C. (2021). SCR7, an inhibitor of NHEJ can sensitize tumor cells to ionization radiation. *Molecular carcinogenesis*, *60*(9), 627–643.

John, F., George, J., Vartak, S. V., Srivastava, M., Hassan, P. A., Aswal, V. K., Karki, S. S., & Raghavan, S. C. (2015). Enhanced efficacy of pluronic copolymer micelle encapsulated SCR7 against cancer cell proliferation. *Macromolecular bioscience*, *15*(4), 521–534.

Vartak, S. V., Swarup, H. A., Gopalakrishnan, V., Gopinatha, V. K., Ropars, V., Nambiar, M., John, F., Kothanahally, S. K. S., Kumari, R., Kumari, N., Ray, U., Radha, G., Dinesh, D., Pandey, M., Ananda, H., Karki, S. S., Srivastava, M., Charbonnier, J. B., Choudhary, B., Mantelingu, K., … Raghavan, S. C. (2018). Autocyclized and oxidized forms of SCR7 induce cancer cell death by inhibiting nonhomologous DNA end joining in a Ligase IV dependent manner. *The FEBS journal*, *285*(21), 3959–3976.

Annexure I

Self-Declaration Format

Ref. No.: Date:

To,

The Chair,

Dept. of Biochemistry, Indian Institute of Science

With reference to my/our expression of interest to IISc, it is hereby declared that I/ (name of firm) was not declared ineligible for corrupt & fraudulent practices either indefinitely or for a particular period by any Govt or other agency.

I/ (name of firm) also declare that there are no contractual restrictions or legal disqualifications or other obligations which will prohibit from me/us entering this bid and each and every one of the statement and particulars contained herein are correct.

Signature of the Applicant

Date:

Place:

Seal