



University of Hyderabad

Department of Biochemistry

School of Life Sciences

No.UH/SLS/DOB/SK/2025/01

Date: 5th March 2025

Applications are invited from eligible candidates (Indian Nationals only) on a plain paper or in the attached format (*Form B*) for the following position in the ICMR funded research project "**Targeting CRL4Cdt2 complex as a Therapeutic prospect in Breast Cancers by Proteomics-based identification of its Regulators and Substrates.**"

(1)	Name of the Post	Project Technical Support III
(2)	Number of positions	One (1)
(3)	Fellowship/Honorarium/ Stipend in Rs.	Rs 28000 (Consolidated excluding HRA) per month
(4)	HRA if applicable	30 % per month (+Rs 8400)
(5)	Tenure of the Post	1 year (can be extended for further period subject to review)
(6)	Essential Qualifications	Masters in any stream of life sciences with minimum 60% marks. <i>OR Bachelor plus 3 years Lab research experience.</i>
(7)	Desirable Qualifications	Experience in molecular biology and mammalian cell culture.
(8)	Experience	0 - 2 years
(9)	Age Limit	Less than <u>35</u> years

- (1) Applicants should note that the appointment to be made is purely temporary and they have no right for claiming for any regular appointment in the University.
- (2) Applicants selected for the post should be committed towards achieving the projects' goal. Insufficient progress/commitment can lead to termination of the position at any time with a one month notice period.
- (3) No TA/DA will be paid for attending the written test / skill test or at the time of joining.
- (4) Self-Attested copies of all certificates in support of the information furnished in the application should be enclosed.
- (5) Last date for receipt of filled-in applications is: **25th March 2025**
- (6) Hard-copy of duly filled application along with essential documents should be sent to the following person by in-person/registered post/speed post/courier.

Dr Shashi Kiran

Room no. – F10

School of Life Sciences, University of Hyderabad

Gachibowli, Pin Code: 500 046

- (6) The University of Hyderabad will not be responsible for any postal delay
- (7) Only the candidates selected for an interview will be intimated through email on/before **25th March 2025** along with information such as interview date, time and mode (on-line/off-line).

To

1. Web Master, UoH - with a request to place in the University website
2. All Notice Boards in the University of Hyderabad
3. All reputed research institutions in related area of the Project—for display on notice boards

S. J-

अध्यक्ष / Head
जीवरसायनविभाग / Department of Biochemistry
शोला गांव / School of Life Sciences
University of Hyderabad
Hyderabad-500 046. (T.S.)

Name & Signature of **Dr. P. SHASHI KIRAN**

Assistant Professor
Department of Biochemistry
School of Life Sciences
University of Hyderabad
Hyderabad-500 046. (T.S.)

TITLE: Targeting CRL4^{Cdt2} complex as a Therapeutic prospect in Triple Negative Breast Cancers by Proteomics-based identification of its Regulators and Substrates.

SUMMARY

Preface: CRL4^{Cdt2} is an E3 ubiquitin ligase composed of the Cullin4 (4A/4B) scaffold, RBX1 ring, DDB1 adaptor and Cdt2, that recognizes CRL4^{Cdt2} specific substrates for ubiquitination. It is unique among ubiquitin ligases in linking DNA replication to cell cycle and maintenance of genome integrity [1].

- I. Rationale:** (1) Breast tumors, especially Triple Negative Breast Cancers (TNBCs) are oncogenically addicted to very high CRL4^{CDT2} expression and inhibiting CRL4^{Cdt2} blocks proliferation of such tumors [2–5]. (2) Mechanism of stabilization of the CRL4^{CDT2} complex in cancers is not known and is an attractive target to inhibit TNBCs . (3) Cancer specific regulators and substrates of CRL4^{CDT2} in hypoxia, DNA damage and cell cycle can reveal therapeutic targets and clarify oncogenic mechanisms (4) Specific inhibitors for CRL4^{Cdt2} inhibition are required to replace Pevonedistat, general cullin inhibitor [6–8].
- II. Objectives:** (O1) Endogenous tagging of the Cdt2 protein in immortalized, MCF 10A and TNBC cell line, MDA-MB-231, with a Cdt2 tagging protocol established in MCF-7. (O2) Isolate endogenous CRL4^{Cdt2} complex from these cells in hypoxia, DNA damage and cell cycle. (O3) Validation and characterization of interactors for therapeutic targeting of TNBCs (O4) Test the role of CRL4^{Cdt2} as an independent oncogene or not in TNBCs.
- III. Methods:** Genetic tagging of Cdt2 by CRISPR-HDRT followed by immunoprecipitation of the interacting protein complex in cell cycle and DNA damage and their identification by LC/MS.
- IV. Novelty:** (i) Despite of being an oncogenic dependence in breast cancers[9–11], the interaction repertoire of CRL4^{Cdt2} is being explored for the first time. (ii) The intrinsic cellular stoichiometry of CRL4^{CDT2} complex is maintained by genetic tagging thereby ensuring the isolation of genuine interaction repertoire.

REFERENCES:

- 1 Panagopoulos A, Taraviras S, Nishitani H & Lygerou Z (2020) CRL4Cdt2: Coupling Genome Stability to Ubiquitination. *Trends Cell Biol.* **30**, 290–302.
- 2 Pan WW, Zhou JJ, Yu C, Xu Y, Guo LJ, Zhang HY, Zhou D, Song FZ & Fan HY (2013) Ubiquitin E3 ligase CRL4CDT2/DCAF2 as a potential chemotherapeutic target for ovarian surface epithelial cancer. *J. Biol. Chem.* **288**.
- 3 Kiran S, Dar A, Singh SK, Lee KY & Dutta A (2018) The Deubiquitinase USP46 Is Essential for Proliferation and Tumor Growth of HPV-Transformed Cancers. *Mol. Cell* **72**, 823–835.e5.
- 4 Olivero M, Dettori D, Arena S, Zecchin D, Lantelme E & Di Renzo MF (2014) The stress phenotype makes cancer cells addicted to CDT2, a substrate receptor of the CRL4 ubiquitin ligase. *Oncotarget* **5**, 5992–6002.
- 5 Baraniskin A, Birkenkamp-Demtroder K, Maghnouj A, Zöllner H, Munding J, Klein-Scory S, Reinacher-Schick A, Schwarte-Waldhoff I, Schmiegel W & Hahn SA (2012) MiR-30a-5p suppresses tumor growth in colon carcinoma by targeting DTL. *Carcinogenesis* **33**, 732–739.
- 6 Adès L, Girshova L, Doronin VA, Díez-Campelo M, Valcárcel D, Kambhampati S, Viniou NA, Woszczyk D, De Paz Arias R, Symeonidis A, Anagnostopoulos A, Munhoz EC, Platzbecker U, Santini V, Fram RJ, Yuan Y, Friedlander S, Faller D V. & Sekeres MA (2022) Pevonedistat plus azacitidine vs azacitidine alone in higher-risk MDS/chronic myelomonocytic leukemia or low-blast-percentage AML. *Blood Adv.* **6**, 5132–5145.
- 7 Swords RT, Coutre S, Maris MB, Zeidner JF, Foran JM, Cruz J, Erba HP, Berdeja JG, Tam W, Vardhanabhuti S, Pawlikowska-Dobler I, Faessell HM, Dash AB, Sedarati F, Dezube BJ, Faller D V. & Savona MR (2018) Pevonedistat, a first-in-class NEDD8-activating enzyme inhibitor, combined with azacitidine in patients with AML. *Blood* **131**, 1415–1424.
- 8 Shah JJ, Jakubowiak AJ, O'Connor OA, Orlowski RZ, Harvey RD, Smith MR, Lebovic D, Diefenbach C, Kelly K, Hua Z, Berger AJ, Mulligan G, Faessell HM, Tirrell S, Dezube BJ & Lonial S (2016) Phase I study of the novel investigational NEDD8-activating enzyme inhibitor pevonedistat (MLN4924) in patients with relapsed/refractory multiple myeloma or lymphoma. *Clin. Cancer Res.* **22**, 34–43.
- 9 Ueki T, Nishidate T, Park JH, Lin ML, Shimo A, Hirata K, Nakamura Y & Katagiri T (2008) Involvement of elevated expression of multiple cell-cycle regulator, DTL/RAMP (denticleless/RA-regulated nuclear matrix associated protein), in the growth of breast cancer cells. *Oncogene* **27**, 5672–5683.
- 10 Perez-Peña J, Corrales-Sánchez V, Amir E, Pandiella A & Ocana A (2017) Ubiquitin-conjugating enzyme E2T (UBE2T) and denticleless protein homolog (DTL) are linked to poor outcome in breast and lung cancers. *Sci. Rep.* **7**, 1–8.
- 11 Ueki T, Nishidate T, Park JH, Lin ML, Shimo A, Hirata K, Nakamura Y & Katagiri T (2008) Involvement of elevated expression of multiple cell-cycle regulator, DTL/RAMP (denticleless/RA-regulated nuclear matrix associated protein), in the growth of breast cancer cells. *Oncogene* **27**, 5672–5683.

You may send the PDF of completed application along with required documents to following email address:

shashi_sls@uohyd.ac.in

Please don't use bots for submitting the application. They will be automatically deleted.

Application for Position in the Project

<p style="text-align: center;">UNIVERSITY OF HYDERABAD P.O. Central University Campus, Gachibowli Hyderabad 500 046, Telangana, INDIA</p>		
Post Applied for: 		
Notification No & Date: 		Paste Recent Photograph

Personal Details:			Proof enclosed Sl. No.
1	Full Name (as in SSC certificate)		
2	Gender (Male / Female)		
3	Date of Birth & Age (as on last date of the Notification)		
4	Father's Name		
5	Nationality		
6	Community (General / OBC / SC / ST / PWD)		
7	Married / Unmarried		

Candidate's Name & Address for correspondence :		
	Mailing address	Permanent address
Name		
Address with PIN Code		
Email:		
Phone No.		
Mobile No.		
Fax No.		

Present position held, if any:			
Name of the University / Institution	Name of the Position and Salary Details	Nature of Job	Proof encl. no.

Educational Qualifications							
Name of the Examination passed	Name of the Board / University	Month & Year passed	Division /Class	% of Marks	CGPA (if grading is applicable)	Subjects studied	Proof Encl. No.
(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)

Experience (Including present position / employment)						
Designation & scale of pay	Name & Address of the Employer	Period of Experience			Nature of work	Proof encl. Sl.no.
		From date	To date	No. of years/ Months/days		
(a)	(b)	(c)	(d)	(e)	(f)	(g)

Names & complete postal addresses of 2 referees :											
Email:			Email:								
Phone (Landline) with STD Code :			Phone (Landline) with STD Code :								
Mobile Ph:			Mobile Ph:								

Declaration: I hereby declare that all the entries made by me in this application are true to the best of my knowledge and belief. If anything is found false at any stage, my candidature may be canceled without assigning any reason thereof.

Date: _____

Signature of the applicant