# DEDICATION

*This work is completely dedicated to my Dad (बुवा), my late Mom (मुमाँ), and Bipul (**मुस-मुस**), who constantly inspired me.*

*Also, towards all the women excelling in research to achieve their dreams.*

*"On days I hate being myself,*
*days I want to disappear forever*
*Let's make a door in your heart*
*Open the door and this place will await*
*It's okay to believe,*
*the Magic Shop will comfort you*
*While drinking a glass of hot tea*
*And looking up at the Milky Way*
*You'll be alright, oh,*
*this here is the Magic Shop"*
***-Jimin & Jin, Magic shop, BTS***

*"Who cares where happiness comes from?*
*We're all a little weird,*
*We're all a little wacky.*
*Some more than others.*
*But if it works, it works."*
***-Dean Winchester, Supernatural***

*"The only person you are destined to become*
*is the person you decide to be."*
***– Ralph Waldo Emerson***

# DECLARATION

I, hereby declare that the thesis entitled ***"Computational insights into the central role of Xeroderma pigmentosum group A (XPA) protein in nucleotide excision repair (NER)"*** has been submitted to Tezpur University in the Department of Molecular Biology and Biotechnology under the School of Sciences for partial fulfillment for the award of the degree of Doctor of Philosophy in Molecular Biology and Biotechnology.

I am the sole author of this thesis.

This is a true copy of an original work carried out by me including any required final revisions, as accepted by my examiners.

Further, I declare that no part of this work has been reproduced elsewhere for the award of any other degree.

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# CERTIFICATE OF THE PRINCIPAL SUPERVISOR

This is to certify that the thesis entitled ***"Computational insights into the central role of Xeroderma pigmentosum group A (XPA) protein in nucleotide excision repair (NER)"*** submitted to the School of Sciences, Tezpur University in partial fulfillment for the award of the degree of Doctor of Philosophy in Molecular Biology and Biotechnology is a record of original research work carried out by **Ms. Sushmita Pradhan** under my supervision and guidance.

All help received by her from various sources have been duly acknowledged. No part of this thesis has been reproduced elsewhere for award of any other degree.

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# CERTIFICATE OF THE EXTERNAL EXAMINER

# AND ODEC

This is to certify that the thesis entitled "***Computational insights into the central role of Xeroderma pigmentosum group A (XPA) protein in nucleotide excision repair (NER)***" submitted by Ms. Sushmita Pradhan to Tezpur University in the Department of Molecular Biology and Biotechnology under the School of Sciences in partial fulfillment of the requirement for the award of the degree of Doctor of Philosophy in Molecular Biology and Biotechnology has been examined by us on 27/01/2023 and found to be satisfactory.

The committee recommends for the award of the degree of Doctor of Philosophy.

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**सुष्मिता प्रधान**

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# LIST OF ABBREVIATIONS

| | | |
|---|---|---|
| 6-4PP | : | 6-4 photoproducts |
| Å | : | Angstrom |
| ACE | : | Atomic contact Energy |
| AMBER | : | Assisted Model Building with Energy Refinement |
| ATR | : | ataxia telangiectasia and Rad3-related protein |
| BFE | : | Binding free energy |
| CHARMM | : | Chemistry at HARvard Macromolecular Mechanics |
| COM | : | Centre of Mass |
| CPD | : | Cyclobutane pyrimidine dimer |
| CPPTRAJ | : | A rewrite of PTRAJ in C++ |
| CS | : | Cockayne syndrome |
| CSP | : | Chemical shift perturbation |
| 3-D | : | 3-Dimensional |
| DBD | : | DNA-binding domain |
| DDB2/XPE | : | Damaged DNA binding protein 2 |
| DNA | : | Deoxyribonucleic Acid |
| DPC | : | DNA-protein complex |
| DPI | : | DNA-protein interaction |
| FF99SB | : | Force-field 99 Stony Brook |
| ERCC1/XPF | : | Excision-repair cross-complementing group 1 |
| FFT | : | Fast Fourier Transform |
| GAFF | : | General Amber force field |
| GB | : | Generalized Born |
| GG-NER | : | Global-genome NER |
| HA | : | Hydrogen acceptor |
| HD | : | Hydrogen donor |
| IDP | : | Intrinsically Disordered Protein |

# LIST OF ABBREVIATIONS

| | | |
|---|---|---|
| I-TASSER | : | Iterative Threading ASSembly Refinement |
| KoBaMIN | : | Knowledge-based minimization |
| MD | : | Molecular Dynamics |
| MM | : | Molecular Mechanics |
| NAMD | : | Nanoscale Molecular Dynamics |
| NER | : | Nucleotide excision repair |
| ns | : | nanosecond |
| NMR | : | Nuclear Magnetic Resonance Spectroscopy |
| PARP-1 | : | Poly [ADP-ribose] polymerase 1 |
| ps | : | picosecond |
| PB | : | Poisson-Boltzmann |
| PBC | : | Periodic boundary conditions |
| PCNA | : | Proliferating cell nuclear antigen |
| PDB | : | Protein Data Bank |
| PIC | : | Pre-incision complex |
| PISA | : | Proteins, Interfaces, Structures and Assemblies |
| PLC | : | Protein-lipid complex |
| PME | : | Particle Mesh Ewald |
| PPC | : | Protein-protein complex |
| PPI | : | Protein-protein interaction |
| PRED | : | Per-residue energy decomposition |
| ProSA | : | Protein structure assessment |
| PTRAJ | : | Short for Process TRAJectory |
| Rg | : | Radius of Gyration |
| RMSD | : | Root Mean Square Deviation |
| RMSF | : | Root Mean Square Fluctuation |
| RPA | : | Replication protein A |
| SASA | : | Solvent-accessible surface area |

# LIST OF ABBREVIATIONS

| | | |
|---|---|---|
| SV40 | : | Simian vacuolating virus 40 |
| TC-NER | : | Transcription-coupled NER |
| TFIIH | : | Transcription factor II H |
| TM | : | Template modeling |
| TPPI | : | Transient PPI |
| TTD | : | Trichothiodystrophy |
| TIP3P | : | Transferable Intermolecular Potential Three-point |
| UCSF | : | University of California, San Francisco |
| UniProt | : | Universal Protein Resource |
| UVr | : | Ultraviolet radiation |
| VMD | : | Visual Molecular Dynamics |
| XAB | : | XPA binding proteins |
| XP | : | Xeroderma pigmentosum |
| XPA | : | Xeroderma pigmentosum complementation group A |
| XPB | : | Xeroderma pigmentosum complementation group B |
| XPC | : | Xeroderma pigmentosum complementation group C |
| XPD | : | Xeroderma pigmentosum complementation group D |
| XPE | : | Xeroderma pigmentosum complementation group E |
| XPF | : | Xeroderma pigmentosum complementation group F |
| XPG | : | Xeroderma pigmentosum complementation group G |
| XPV | : | Xeroderma pigmentosum complementation group V |

# LIST OF PUBLICATIONS

**This thesis is partly based on the following original communications:**

1. Pradhan, S., Das, P., and Mattaparthi, V. S. K. Characterizing the binding interactions between DNA binding proteins, XPA and XPE: A molecular dynamics approach. *ACS Omega*, 3: 15442-15454, 2018. (Impact factor: 4.132)
2. Pradhan, S., Sarma, H., and Mattaparthi, V. S. K. Investigation of the probable homo-dimer model of the Xeroderma pigmentosum complementation group A (XPA) protein to represent the DNA binding core. *Journal of Biomolecular Structure and Dynamics*, 37: 3322-3336, 2019. (Impact factor 3.392)
3. Pradhan, S. and Mattaparthi, V. S. K. Structural dynamics and interactions of Xeroderma pigmentosum complementation group A (XPA98–210) with damaged DNA. *Journal of Biomolecular Structure and Dynamics*, 36: 3341-3353, 2018. (Impact factor 3.392)

**Other publications:**

1. Pradhan, S., Sarma, H., Bharadwaz, B., and Mattaparthi, V. S. K. Comparative Study on the Binding Affinity of Methimazole and Propylthiouracil to Thyroid Peroxidase as an Anti-Thyroid Drug: An *in silico* Approach. Journal of Molecular Imaging and Dynamics, 7(131), 2017. DOI: doi.org/10.4172/2155-9937.1000131 (Impact factor 2.8)

**Book chapter:**

1. Sarma, H., Pradhan, S., Kaushik, S., and Mattaparthi, V. S. K. Phylogenetic analysis: Early evolution of life. In Encyclopedia of Bioinformatics and Computational Biology. Elsevier, ISBN: 9780128114148, 3: 938-952, 2019.

**Communicated manuscripts**

1. Pradhan, S., and Mattaparthi, V. S. K. Investigation on the DNA binding property of Xeroderma pigmentosum complementation group A (XPA) homodimer protein. PROTEINS: Structure, Function, and Bioinformatics, 2022. (Manuscript submitted)

2. Pradhan, S., Das, P., Borah, P., and Mattaparthi, V. S. K. Computational Investigation of R207G mutation in Xeroderma pigmentosum complementation group A (XPA) on its interaction with Xeroderma pigmentosum complementation group E (XPE). Current Science, 2022 (Manuscript submitted)

**In addition, this thesis also contains unpublished data.**

# CONFERENCE PROCEEDINGS

1. Pradhan, S., Das, P., and Mattaparthi, V. S. K. Characterizing the binding interactions between DNA binding proteins, XPA and XPE: A molecular dynamics approach. Assam Science Festival 2019, March 23rd-25th, 2019, Assam Science, Technology and Environment Council in collaboration with Tezpur University, Tezpur, Assam, India. (Poster Presentation).
2. Participated in the National Workshop on "Whole Genome Data Analysis using Computational Framework and Tools" organized by DBT supported Bioinformatics Infrastructure Facility Department of Molecular Biology and Biotechnology, Tezpur University, Tezpur, Assam, India on 24th-25th January, 2019.
3. Participated in the Institutional Biotech Hub seminar on "Careers in Science and Biotechnology" sponsored by DBT, GoI and was held on 27th March, 2018 at Tezpur University, Tezpur, Assam, India.
4. Participated in the National Workshop on "Whole Genome Data Analysis using Computational Framework and Tools" organized by DBT supported Bioinformatics Infrastructure Facility Department of Molecular Biology and Biotechnology, Tezpur University, Tezpur, Assam, India on 24th-25th January, 2019.
5. Pradhan, S. and Mattaparthi, V. S. K. "Structural Dynamics and Interactions of Xeroderma Pigmentosum complementation group A (XPA) with UV-Damaged DNA". International conference on "Emerging Trends in Chemical Sciences" (ETCS-2018) held at Department of Chemistry, Dibrugarh University, Assam, India, held on 26th -28th February, 2018. (Poster presentation)
6. Participated as a core committee member and attended lecture series and hands-on training on International Seminar cum Workshop on "Computer Aided Drug Design for Human Pathogen" at Department of Molecular Biology and Biotechnology, Tezpur University, Tezpur, Assam, India, held on 12th-17th February, 2018.
7. Pradhan, S. and Mattaparthi, V. S. K. "Structural Dynamics and Interactions of Xeroderma Pigmentosum complementation group A

(XPA) with UV-Damaged DNA". Research conclave on "Recent Innovations in Science and Engineering 2017" at NIT Silchar, Assam, India held on 24th - 26th March 2017. (Oral Presentation)

8. Attended a National workshop on "Basic Bioinformatics Tools and Techniques in Structural Biology" held on March 18-19th, 2017 at Tezpur University, Tezpur, Assam, India.
9. Attended a National workshop on "Networks in Biological Systems" held on February 18-19th, 2017 at Tezpur University, Tezpur, Assam, India.
10. Sarma, H., Pradhan, S., and Mattaparthi, V. S. K. Unveiling the transient Protein-Protein interactions that modulate the activity of Estrogen Receptor (ER)-α by Human Lemur Tyrosine Kinase-3 (LMTK3) domain: An *in silico* study, *9th North-East Bioinformatics Network (NEBInet) Annual Meet*, Tezpur University, Tezpur, Assam, India held on 17th 19th January, 2017. (Poster Presentation)