Connecting the dots of protein aggregation in neurodegenerative and systemic diseases: A review

Shaik Basha[1], Darshan Chikkanayakanahalli Mukunda[1], Jackson Rodgruies[1], Gireesh Gangadharan[2] Nisha N Shenoy[3], Krishna Kishore Mahato[1*]

1. Department of Biophysics, Manipal School of Life Sciences, Manipal Academy of Higher Education, Manipal, Karnataka – 576104, India.
2. Department of Cell and Molecular Biology, Manipal School of Life Sciences, Manipal Academy of Higher Education, Manipal, Karnataka – 576104, India.
3. Department of Neurology, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal, Karnataka – 576104, India.

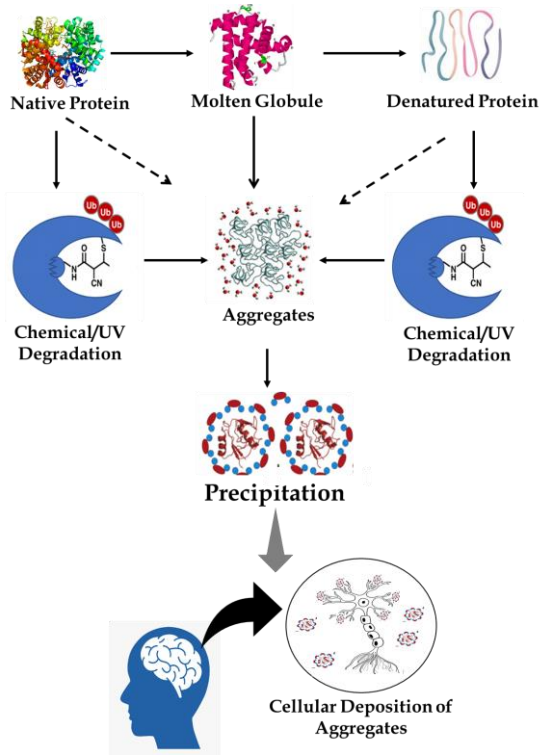
***Corresponding email: mahato.kk@manipal.edu**

Introduction

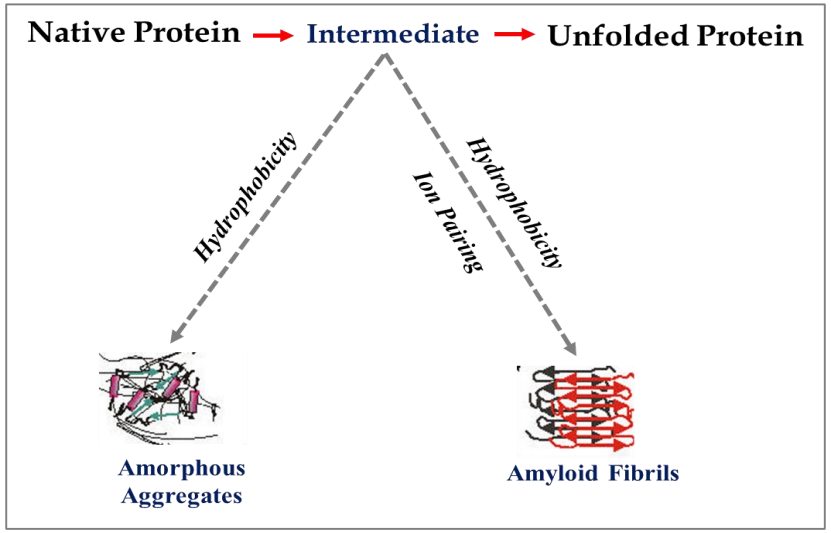
1. Protein Aggregation

- Misfolding of proteins to form oligomers
- Insoluble and highly cytotoxic.
- Can cause neurodegenerative diseases (NDD)

2. Protein Aggregation in NDD



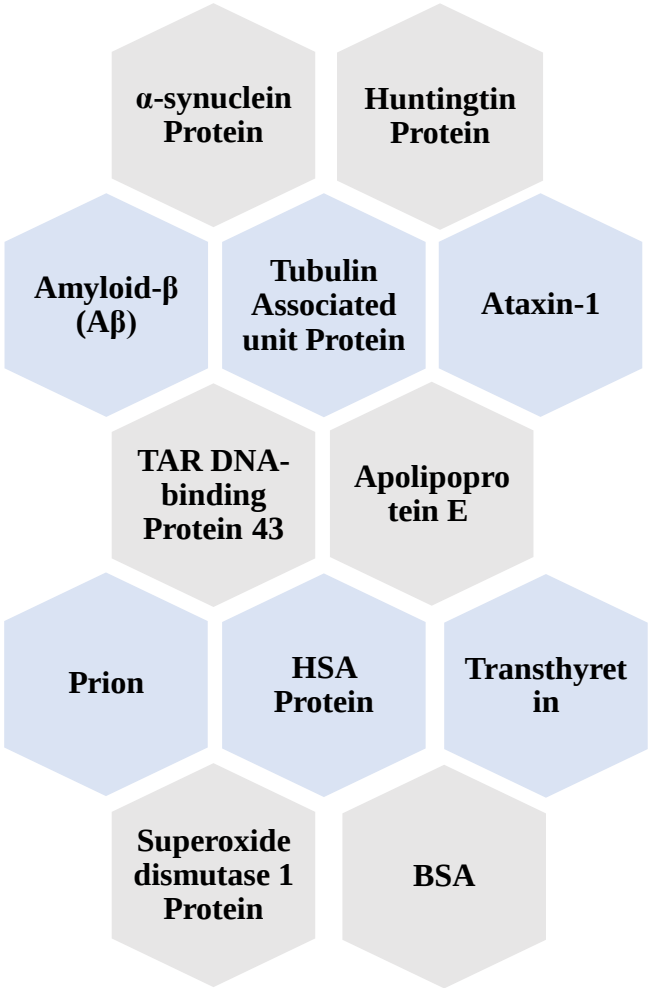
3. Formation of aggregates



4 .Factors causing protein aggregation

Extrinsic Factors	Intrinsic Factors
Temperature	Ageing
Radiation	Oxidative stress
Pressure	Ionic strength
Agitation	Impaired Autophagy
Chemical Exposure	Pathogenic mutations
pH	Over expression of genes

5. Proteins associated with NDD



(Zapadka KL et al., 2017); (Merlini G et al., 2001); (Morozova-Roche L et al., 2017)

Aim

- This review aims to highlight pathological conditions associated with protein aggregation and the underlying mechanisms for developing diseases.

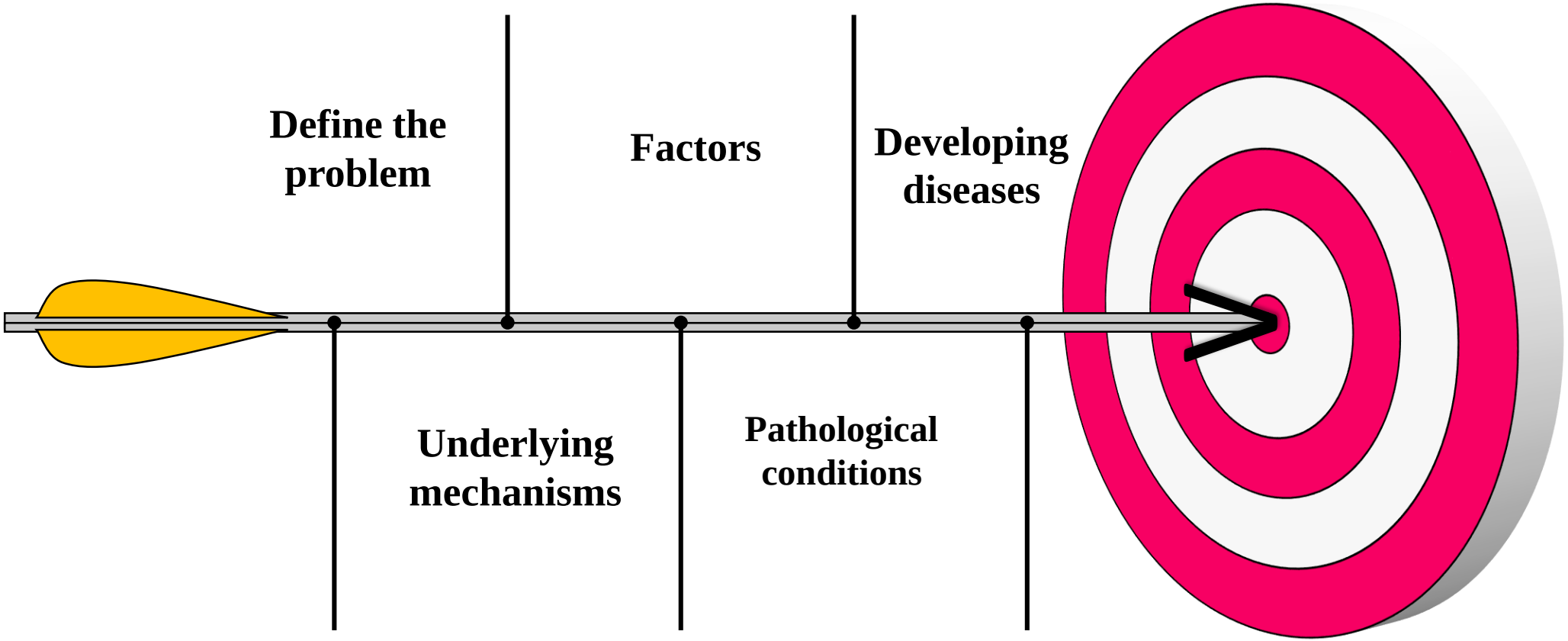
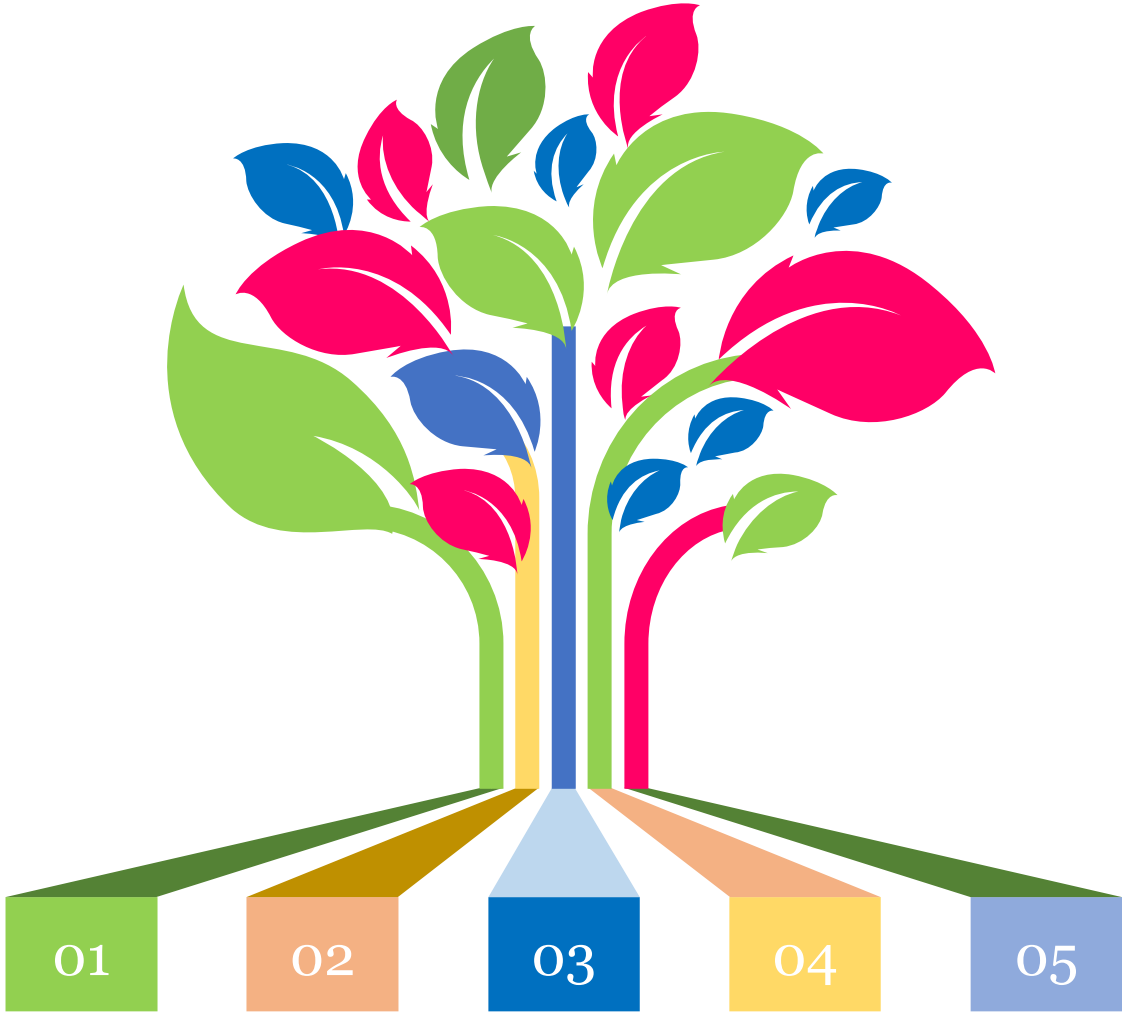


Figure 2. Goal of the review

Objective

- The objective is to highlight the available information on protein aggregation linking to neurodegenerative and specific systemic diseases for better understanding and possible solutions.



Protein aggregation

Mechanism

Neurodegenerative diseases

Systemic diseases

Conventional techniques

Figure 3. Objective of the review

Methodology

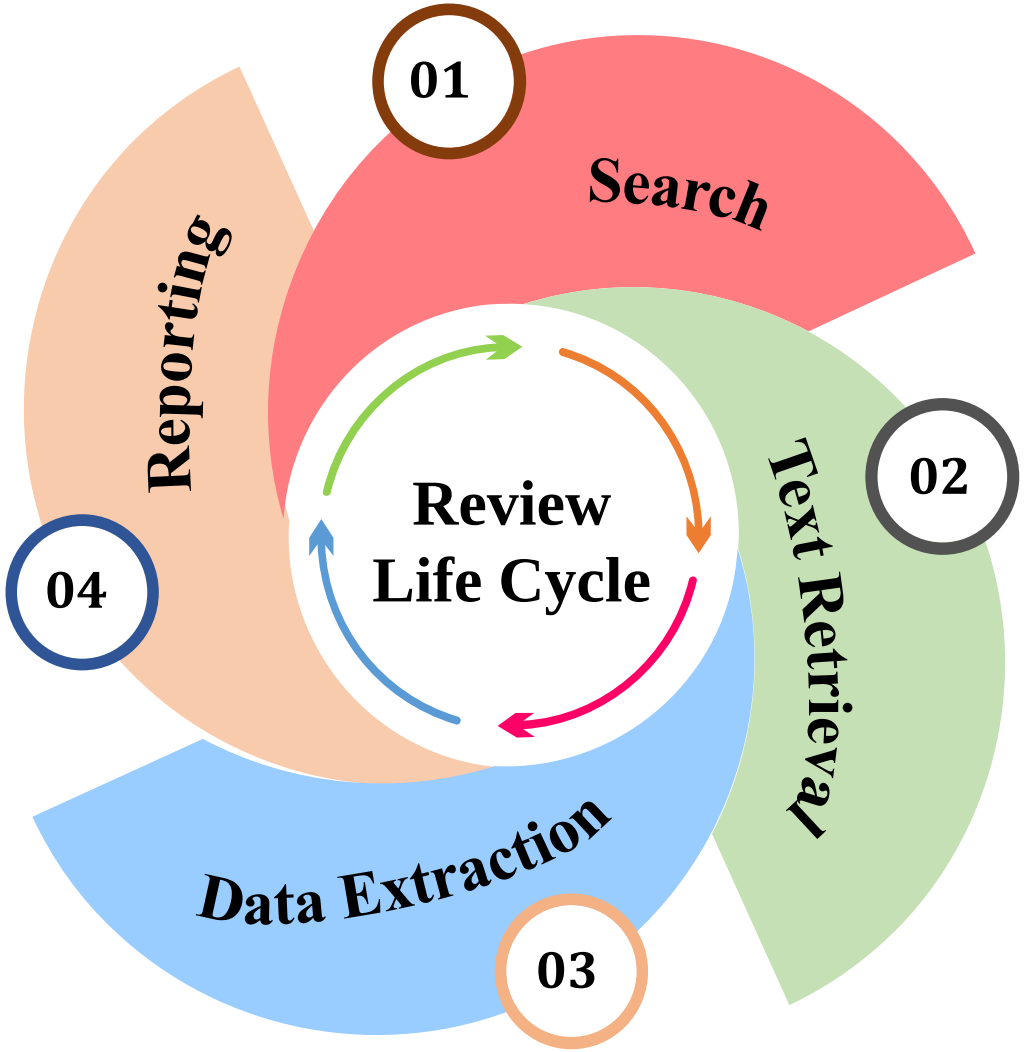


Figure 4. Review Life Cycle

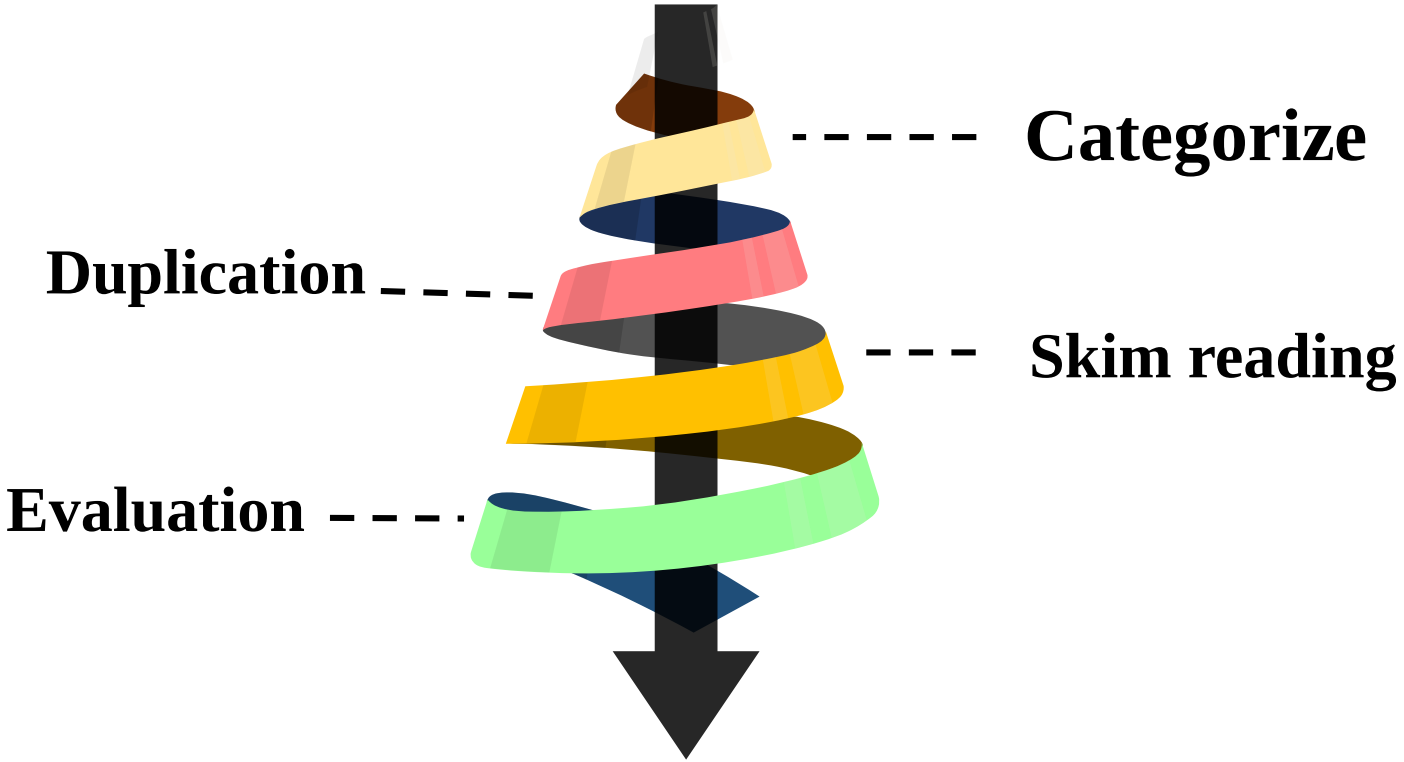


Figure 5. Plan of view

Methodology

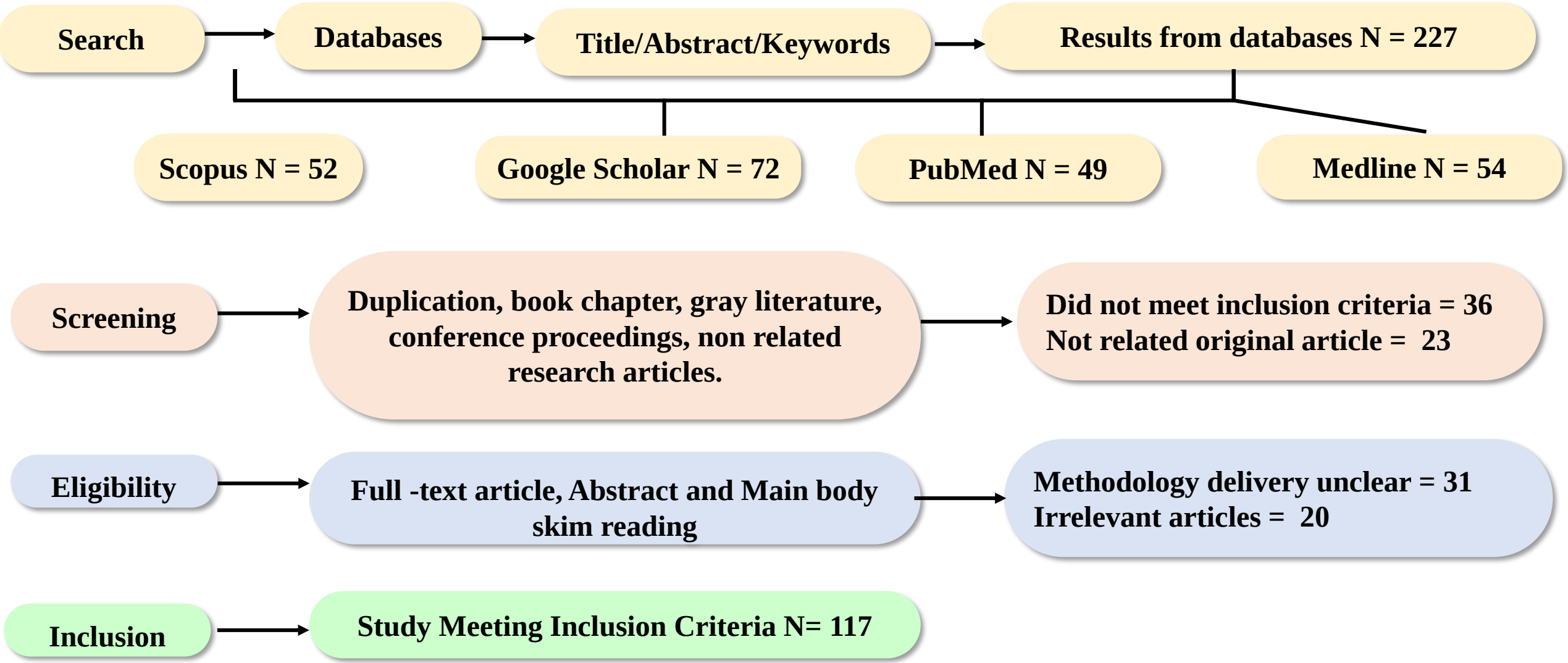
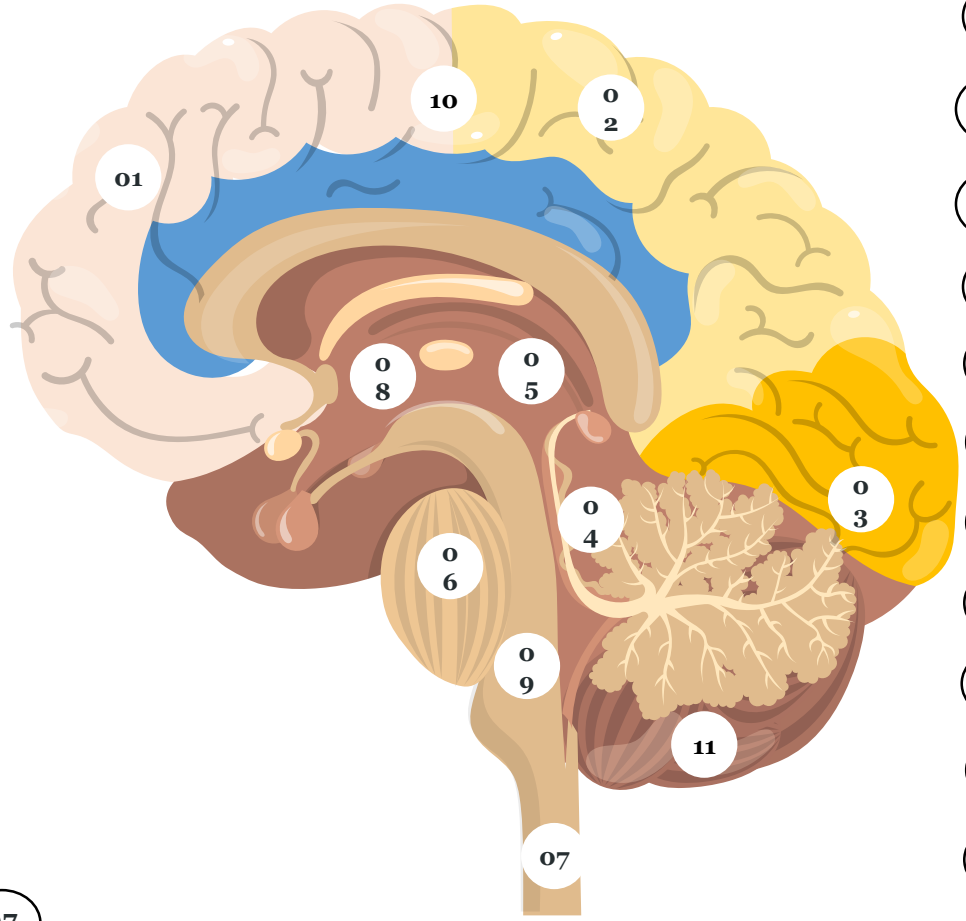


Figure 5. Work plan

Results

- Familial British Dementia N =2 — 01
- Familial Danish Dementia N =2 — 01
- Familial Encephalopathy N =1 — 07
- Neuroferritinopathy N =2 — 08
- Light chain Amyloidosis N =2 — 01
- AH Amyloidosis N =1 — 01
- Transmissible encephalopathies N =2 — 09
- Spinal and Bulbar muscular atrophy N =2 — 06
- Hereditary dentatorubral atrophy N =2 — 03
- Familial amyloidogenic polyneuropathy N =1 — 07



- 06 Charcot – Marie – Tooth N =2
- 05 Multiple Sclerosis N =2
- 10 Creutzfeldt – Jakob disease N =1
- 09 Progressive nuclear palsy N =2
- 11 Machado-Joseph disease N =2
- 01 Frontotemporal Dementia N =4
- 08 Huntington’s disease N =4
- 09 Amyotrophic lateral sclerosis N =6
- 08 Parkinson's disease N =4
- 02 Alzheimer's disease N =4
- 04 Tauopathies N =2
- 11 Spinocerebellar ataxia N =2

Figure 6 . Surface area of brain with affecting the diseases

Results

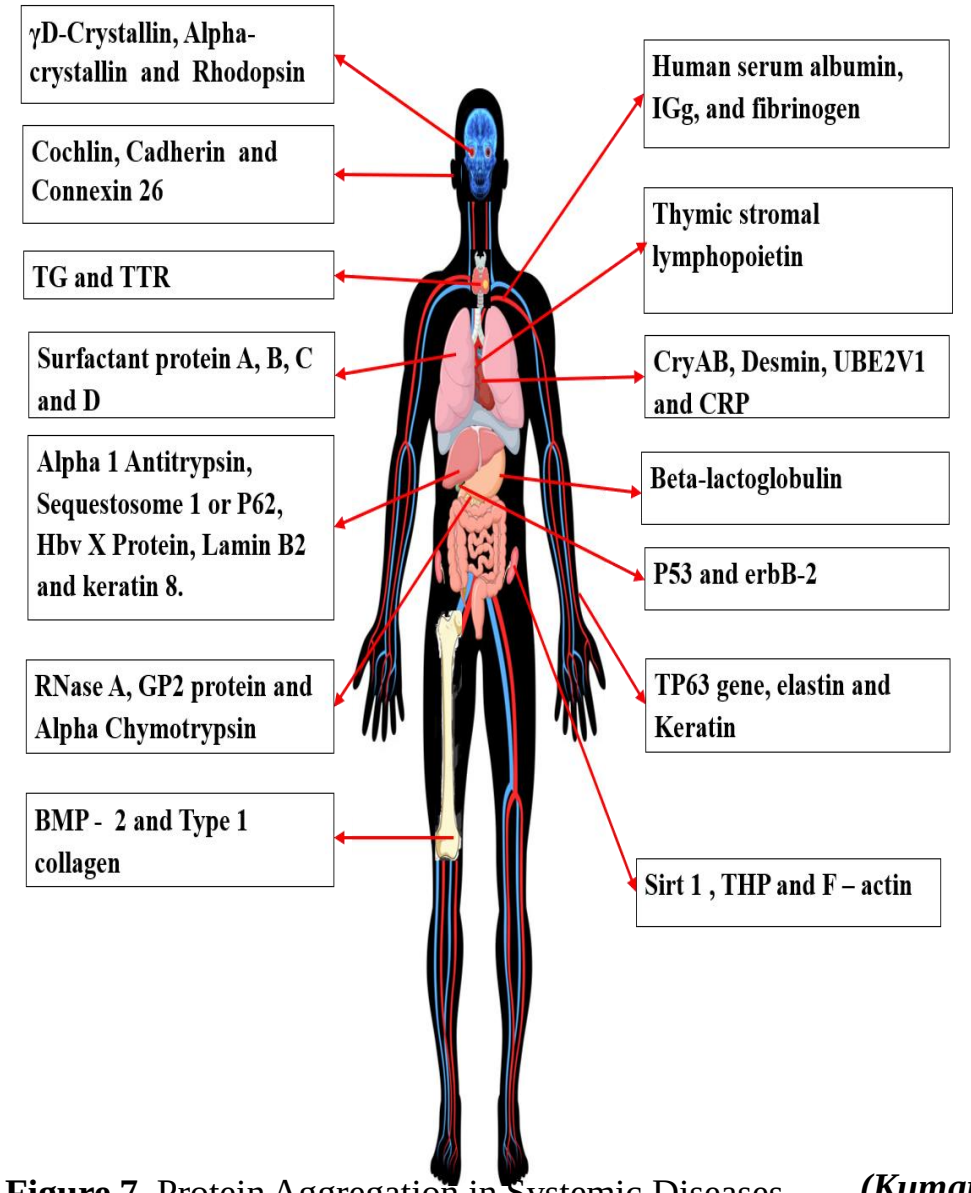


Figure 7. Protein Aggregation in Systemic Diseases. ***(Kumar. A. Bishnoi et al., 2020)***

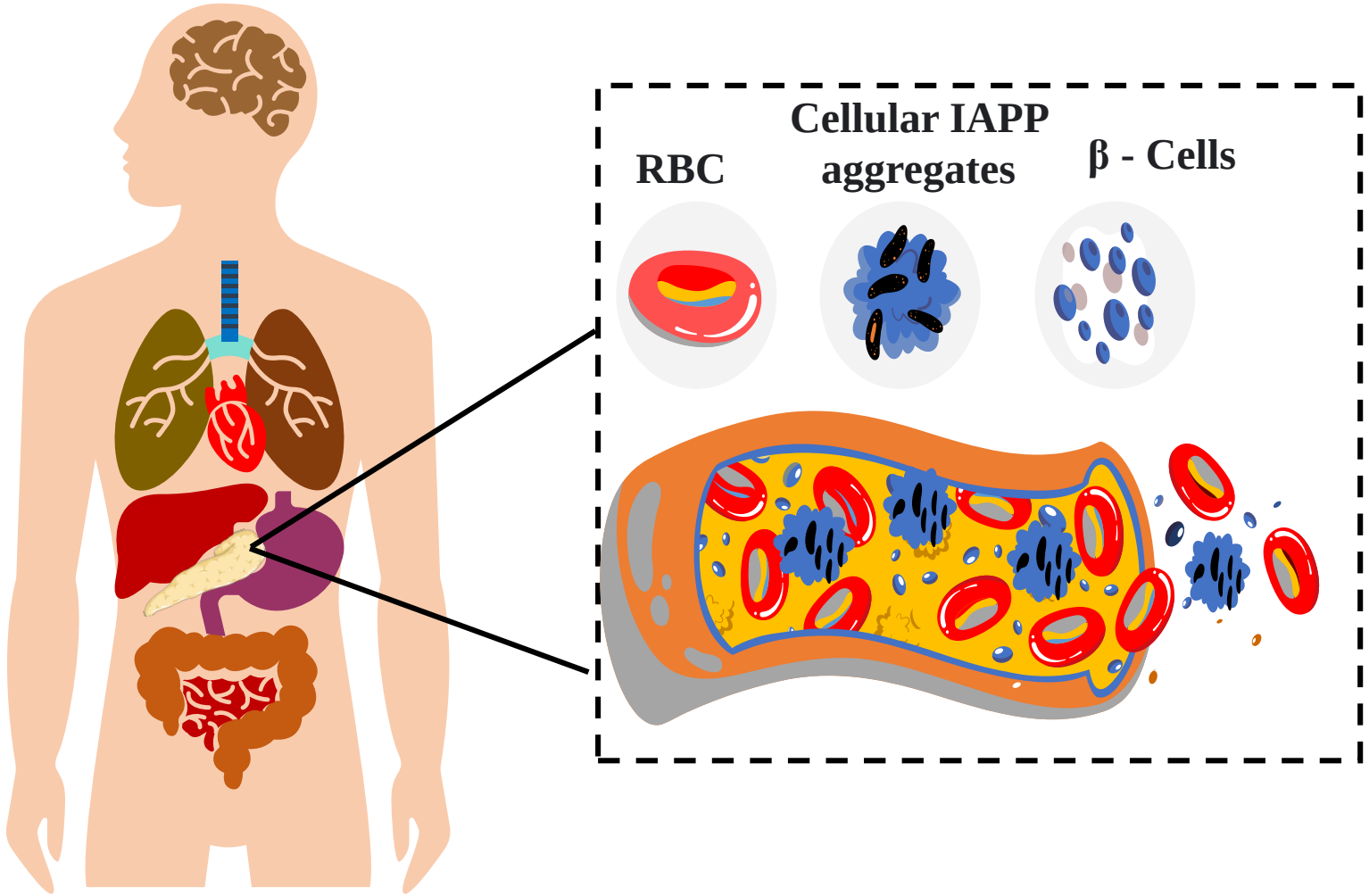


Figure 8. Islet amyloid polypeptide aggregates (IAPP) with vasculature innervation

Results

3D structure determination		Fluorescent protein		Microscopy probing		Spectroscopic techniques	
Solid state NMR	N =22	Green Fluorescence Protein	N =8	Atomic Force Microscopy	N =5	Circular Dichroism	N =27
X-Ray Diffraction	N =9	Yellow Fluorescent Protein	N =7	Fluorescence lifetime microscop	N =4	FTIR	N =13
X-Ray Crystallography	N =11	Reef Coral Fluorescent protein	N =5	Electron Microscopy	N =12	UV - visible absorption	N =8
Enzyme reporters monitor		**Separation techniques**		Fluorescence recovery after photobleaching	N =4	Fluorescence Correlation	
Chloramphenicol acetyltransferase	N =5	SDS or Native Page	N =23	Scanning Electron Microscopy	N =18	Electrospray ionization	N =11
Murine dihydrofolate reductase	N =2	SEC Chromatography	N =18	Cryogenic electron microscopy	N =3	Dynamic Light Scattering	N =27
Human dihydrofolate reductase	N =1	Ultracentrifugation	N =5	Multiphoton Fluorescence Microscopy	N =1	Fluorescence Resonance Energy Transfer	N =8
Imaging		Filed flow fraction	N =2			Raman Spectroscopy	
PET	N =34	**Fluorescent dye-based**				Multiangle Light Scattering	N =5
MRI	N =14	ThT assay	N =32			Atomic spectroscopy	N =11
SPECT	N =9	Congo Red assay	N =9				
Specific antibody		ANS or Bis – ANS assay	N =12				
A11	N =5	NILE – RED	N = 2				
MC1 / Alz50	N =3	DCVJ	N =4				
OC & α – APF	N =7	SYPRO ORANGE	N =6				

Akira et al., 2016 **Table 1.** Analytical Techniques Determination of Protein Aggregation

Conclusion

- The review summarises the protein aggregates associated with neurodegenerative and systemic diseases. This may aid in better understanding of protein misfolding and diagnosing aggregates to the progression of diseases.

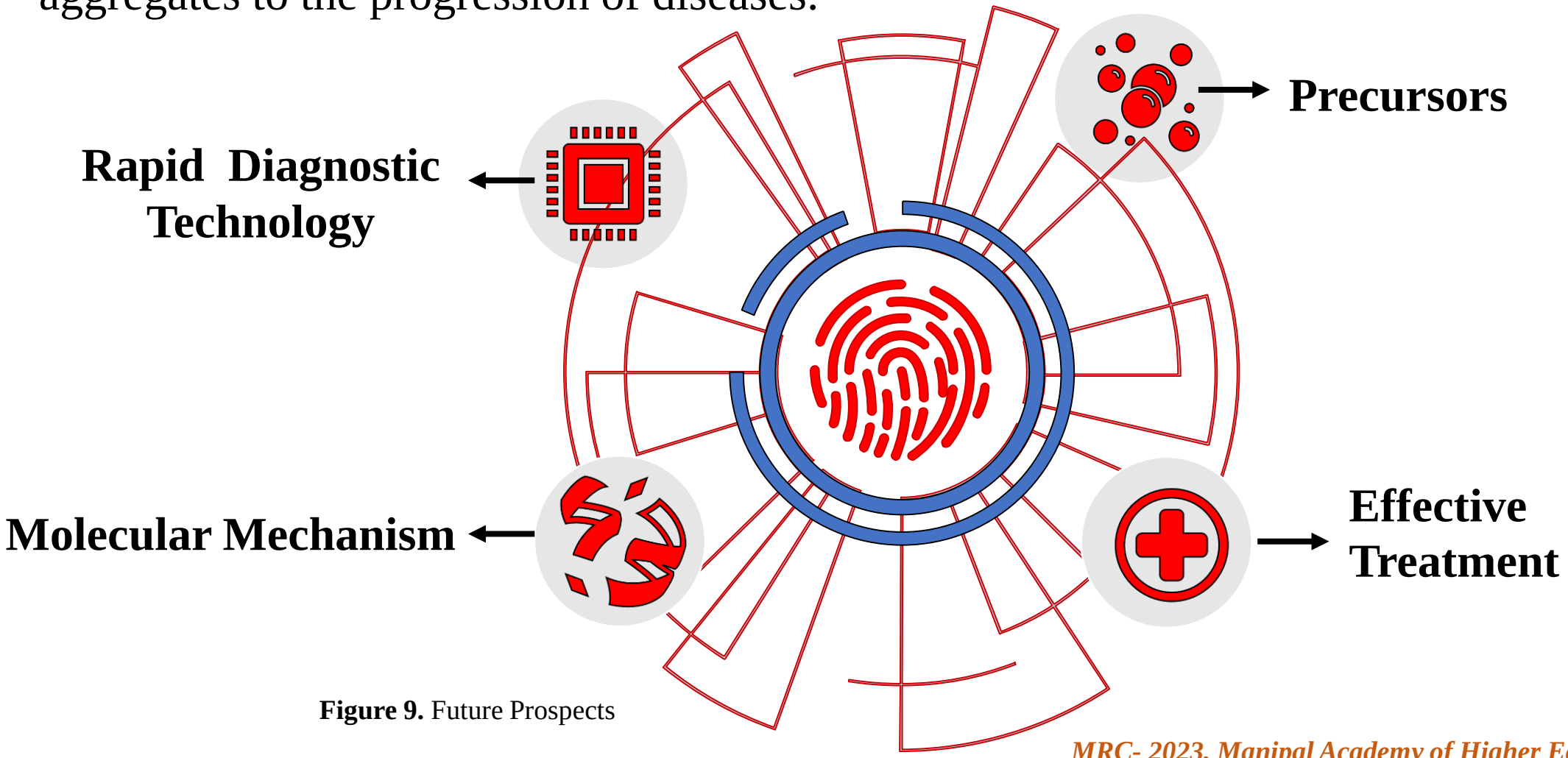


Figure 9. Future Prospects

Key References

- Akira Fricano, Librizzi F, Rao E, Alfano C, Vetri V. Blue autofluorescence in protein aggregates "lighted on" by UV induced oxidation. Biochimica et Biophysical Acta (BBA)-Proteins and Proteomics. 2019 Nov 1;1867(11):140258.
- Huo, F.; Wan, T.; Wang, Y.; Liu, Y.; Karmaker, P. G.; Yang, X. Enhanced Light Emitting Diode Induced Fluorescence Detection System with Capillary Electrophoresis. J. Chromatogr. A. 2020 Jun 11;1619(22): 460935.
- Ji H, Wu Y, Duan Z, Yang F, Yuan H, Xiao D. Sensitive determination of sulfonamides in environmental water by capillary electrophoresis coupled with both silvering detection window and in-capillary optical fiber light-emitting diode-induced fluorescence detector. Electrophoresis. 2017 Feb 2;38(3-4):452-459.
- Kitamura A, Fujimoto A, Kinjo M. Detection of Protein Aggregation using Fluorescence Correlation Spectroscopy. JoVE (Journal of Visualized Experiments). 2021 Apr 25;11(17):e62576.
- Merlini G, Bellotti V, Andreola A, Palladini G, Obici L, Casarini S, Perfetti V. Protein aggregation. Clin Chem Lab Med. 2001 Nov 12;39(11):1065-75.
- Miia Kivipelto, Francesca Mangialasche, Nicola Payton. Strategies for risk reduction and prevention of late-life Alzheimer's disease and dementia based on multidomain approaches. World Alzheimer Report 2022 Jan 11;16(22): 4605.
- Morozova-Roche L, Malisauskas M. A false paradise-mixed blessing in the protein universe: the Amyloid as a new challenge in drug development. Current medicinal chemistry. 2007 May 1;14(11):1221-30.
- Parkinson J. An essay on the shaking palsy. The Journal of neuropsychiatry and clinical neurosciences. 2002 May;14(2):223-36.
- Przedborski S, Vila M, Jackson-Lewis V. Series Introduction: Neurodegeneration: What is it and where are we? The Journal of clinical investigation. 2003 Jan 1;111(1):3-10.
- Ravindranath V, Sundarakumar JS. Changing demography and the challenge of dementia in India. Nature Reviews Neurology. 2021 Dec;17(12):747-58.
- Zapadka KL, Becher FJ, Gomes dos Santos AL, Jackson SE. Factors affecting the physical stability (aggregation) of peptide therapeutics. Interface focus. 2017 Dec 6;7(6):20170030.

Acknowledgement

- **Dr. B.S. Satish Rao,** Professor, Director, Manipal School of Life Sciences, MAHE, Manipal.
- **Dr. Krishna Kishore Mahato, (Guide),** Professor and Head, Dept. of Biophysics, Manipal School of Life Sciences, MAHE, Manipal.
- **Dr. Gireesh Gangadharan**, **(Co –Guide),** Assistant Professor, Dept. of Cell and Molecular Biology, Manipal School of Life Sciences, MAHE, Manipal.
- **Dr. Nisha Shenoy,** Associate Professor, Dept. of Neurology, Kasturba Medical College, MAHE, Manipal.
- **Mr. Subhash,** Asst. Engineer, Dept. of Biophysics, Manipal School of Life Sciences, MAHE, Manipal.
- **Mr. Darshan C. M, Jackson Rodgruies,** Research Scholars, Dept. of Biophysics, Manipal School of Life Sciences, MAHE, Manipal.
- **Department of Biophysics,** Manipal School of Life Sciences, MAHE, Manipal.
- **Staff and Research Scholars,** Manipal School of Life Sciences, MAHE, Manipal.
- **Manipal Academy of Higher Education**, Manipal for providing Dr. T.M.A Pai Structured Ph.D. Scheme.

सत्यमेव जयते
Department of Science & Technology
Government of India

MAHE-SRF
RESEARCH IS CREATING NEW KNOWLEDGE

MANIPAL
ACADEMY of HIGHER EDUCATION
(Institution of Eminence Deemed to be University)

INDIAN COUNCIL OF MEDICAL RESEARCH
Serving the nation since 1911


THANK YOU