"***In silico identification of common proteins involved in crotonylation and acetylation in Alzheimer's disease and drug repurposing***"

A DISSERTATION

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MASTER OF TECHNOLOGY

IN

BIOMEDICAL ENGINEERING

BY

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2K19/BME/04

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DECLARATION

I, Swati Tiwari, 2K19/BME/04 student of M.Tech Biomedical Engineering, hereby declare that the project Dissertation titled "**In silico identification of common proteins involved in crotonylation and acetylation in Alzheimer's disease and drug repurposing**" which is submitted by me to the department of Biotechnology, Delhi Technological University, Delhi in partial fulfillment of the requirement for the award of the degree of Master of Technology, is original and not copied from any source without paper citation. The work has not previously formed the basis for the award of any Degree, Diploma Associateship, Fellowship or other similar title or recognition.

Place: Delhi

Date: 06-07-2021 **Swati Tiwari**

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CERTIFICATE

I hereby certify that the Project Dissertation titled "**In silico identification of common proteins involved in crotonylation and acetylation in Alzheimer's disease and drug repurposing**" which is submitted by Swati Tiwari, 2K19/BME/04, Department of Biotechnology, Delhi Technological University, Delhi in partial fulfillment of the requirement for the award of the degree of Master of Technology, is a record of the project work carried out by the student under my supervision. To the best of my knowledge this work has not been submitted in part of full for any Degree or Diploma to this University or elsewhere.

Place: Delhi

Date: 07.07.2021

Prof. Pravir Kumar

Head of Department

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At the time of submission of my M.Tech Dissertation, I would first like to thank GOD for giving me patience, strength, capability, and willpower to complete my work. Apart from our efforts, the success of this project depends largely on the encouragement and guidelines of many others. I, therefore, take this opportunity to express my gratitude to the people who have been instrumental in the successful completion of this project.

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ABSTRACT

Dementia is one of leading cause of the most common neuronal disorders Alzheimer's Disease (AD) that remains untreated even after decades of research. Post-translational modification (PTMs) plays many roles in protein turnover rate accumulation of aggregate and can also help in the degradation of disease-causing toxic metabolites. In this study we tried to understand the involvement of Crotonylation and acetylation in AD by using computational tools and database and finally identify a possible drug for treatment using Drug Repositioning tools. Through extensive literature analysis we found that P300 and CBP are the common enzymes associated with protein crotonylation and acetylation in Alzheimer's Disease (AD) proving the association between these two PTMs. Using step by step computational analysis we found hub genes associated with the PTMs and AD. With the help of a comprehensive visual drug network gene analysis tool, we identified Arsenic Trioxide as potential drug which interacted with the MAPK1, JUN and MAPK3 genes associated with AD. And finally using DrugNet website tool for drug-disease association and PhospNet tool for disease-gene association studies developed by group of researchers from university of Granada, Spain we validated the results and concluded that Arsenic Trioxide is associated with different form of Dementia including Frontotemporal dementia, vascular Dementia and Dementia associated with lewy bodies.

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LIST OF ABBREVIATIONS

AD	ALZHEIMER'S DISEASE
PTM	POST-TRANSLATIONAL MODIFICATIONS
NDD	NEURODEGENERATIVE DISORDERS
FOXO3	FORKHEAD BOX PROTEIN O3
EP300	HISTONE ACETYLE TRANSFERASE P300
MAPK3	MITOGEN ACTIVATION PROTEIN KINASE 3

CREBBP	**cAMP RESPONSE ELEMENT BINDING -BRINDING PROTEIN**
HDAC1	HISTONE DEACETYLASE 1
MAPK1	MITOGEN ACTIVATION PROTEIN KINASE 1
ESR1	ESTROGEN RECEPTOR1
APP	AMYLOID BETA PRECURSOR PROTEIN
BACE1	BETA SECRETASE 1
Aβ	AMYLOID BETA

1. INTRODUCTION:

Most neurodegenerative diseases (NDDs) are caused by the accumulation, aggregation, and modification of normal host proteins, as well as the effects of viral infections, decreased blood flow, changes in tissue homeostasis, and immunological damask. There have been no studies done to explain the exact mechanism of protein aggregation and its pathogenicity in NDDs. Furthermore, a number of drugs have been tested for NDDs, but their effectiveness has been limited, highlighting the gaps in our understanding of their pathogenic mechanism. There has not been a full-proof medicine to stop the disease from spreading, until now [1]. Drug designing and development is an important area of research for pharmaceutical companies and chemical scientists. However, low efficacy, off-target delivery, time consumption, and high-cost impose a hurdle and challenges that impact drug design and discovery. Further, complex and big data from genomics, proteomics, microarray data, and clinical trials also imposes an obstacle in drug discovery pipeline. Artificial intelligence and machine learning technology play a crucial role in drug discovery and development. In other words, artificial neural networks and deep learning algorithms modernised the area. Machine learning and deep learning algorithms have been implemented in several drug discovery processes such as peptide synthesis, structure-based virtual screening, ligand-based virtual screening, toxicity prediction, drug monitoring and release, and pharmacophore modelling, quantitative structure-activity relationship, drug repositioning, polypharmacology, and physiochemical activity. In this project we In this study we tried to understand the involvement of Crotonylation and acetylation in AD by using computational tools and database and finally identify a possible drug for treatment using Drug Repositioning tools. Through extensive literature analysis we found that P300 and CBP are the common enzymes associated with protein crotonylation and acetylation in Alzheimer's Disease (AD) proving the association between these two PTMs. Using step by step computational analysis we found hub genes associated with the PTMs and AD. With the help of a comprehensive visual drug network gene analysis tool, we identified Arsenic Trioxide as potential drug which interacted with the MAPK1, JUN and MAPK3 genes associated with AD. And finally using DrugNet website tool for drug-disease association and PhospNet tool for disease-gene association studies developed by group of researchers from university of Granada, Spain we validated the results and concluded that Arsenic Trioxide is associated with different form of Dementia including Frontotemporal dementia, vascular Dementia and Dementia associated with lewy bodies.

2. REVIEW OF LITERATURE:

2.1 Alzheimer's Disease and Dementia:

Most neurodegenerative diseases (NDDs) are caused by the accumulation, aggregation, and modification of normal host proteins, as well as the effects of viral infections, decreased blood flow, changes in tissue homeostasis, and immunological damask. There have been no studies done to explain the exact mechanism of protein aggregation and its pathogenicity in NDDs. Furthermore, a number of drugs have been tested for NDDs, but their effectiveness has been limited, highlighting the gaps in our understanding of their pathogenic mechanism. There has not been a full-proof medicine to stop the disease from spreading, until now [1]. Dementia is one of leading cause of the most common neuronal disorders Alzheimer's Disease (AD) that remains untreated even after decades of research. Post-translational modification (PTMs) plays many roles in protein turnover rate accumulation of aggregate and can also help in the degradation of disease-causing toxic metabolites. However, not much is known about the crosstalk between crotonylation and acetylation in AD. mutations in protein-coding genes can also promote abnormal protein aggregation, such as mutations in the presenilin-2 (PSEN2) gene accelerate Aβ aggregation in AD by enhancing the activity of γ-secretase. Similarly, a mutation in the SNCA gene is responsible for causing aggregation of α-synuclein in PD and mutations in the interesting transcript 15 (IT15) gene increases huntingtin aggregation in HD [2].

2.2 ER stress and UPR response:

In eukaryotes, the endoplasmic reticulum (ER) governs the protein translation, production and translocation in secretory pathways and extracellular space to the target locations [3]. Mutations in the secretory proteins result in conformation disorders initiating from metabolic disease to neurological and developmental disorders. Any modification/abnormality in ER functioning due to protein and calcium accumulation results in a perturbed state known as ER stress. The ER stress activates the unfolded protein response (UPR) signaling pathway, which counters the perturbed activity by upregulated expression of molecular chaperons and foldase [4,5]. PTMs are considered as one of the significant factors for protein aggregation, which causes an alteration in three primary UPR sensors- inositol-requiring enzyme 1 α (IRE1α), protein kinase R like endoplasmic reticulum kinase (PERK), activating transcription factor 6 α (ATF6α), and thus, leads to proteostasis dysfunction and elevated ER stress [6]. The UPR response helps in regulating the proteostasis by

modulating the misfolded protein by unfolding and refolding mechanism, but prolonged activation of UPR results in cell death [7]. In normal conditions, PERK, IRE1α and ATF6 elevates protein folding signaling cascades to re-establish protein homeostasis and reduce ER stress, whereas, under chronic ER stress conditions, PERK and IRE1α promote cellular dysfunction and cell death [8]. Further, ATF4 mediated regulation of PERK has been reported in the death receptor 5 (DR5) gene responsible for controlling cell fate via mitochondrial signaling [9]. Under normal conditions, PERK phosphorylation results in eukaryotic initiation factor 2 (elF2α) phosphorylation, eventually leading to ATF4 expression. IRE1α activity recruits X-box binding protein 1 (XBP1), apoptosis signal-regulating kinase 1/ c-Jun N-terminal kinases (ASK1-JNK) and TNF receptor-associated factor 2 (TRAF2) that regulates the PTM gene expression. Finally, ATF6 is released from the Golgi body and undergoes specificity protein 1 (SP1) and specificity protein 2 (SP2) mediated degradation releasing its cytosolic domain. Under perturbed state, decreased UPR signaling has been observed due to the competition between the protein accumulate to ligate to GRP78 receptor that releases the UPR protein [10,11].

ER lumen acetylation is regulated by multiple enzymes, including AT1, ATase1 and ATase2. ER lumen protein acetylation has been associated with the processing of Aβ precursor protein cleaving enzyme BACE1. Any modification results in amassment of juvenile proteins inside the lumen, initiating mild stress, which codes for the autophagic process. Similar results have been reported in ALS and HD, where cross-talk between ER acetylation and neuroprotection has been observed by activation of UPR mediated autophagy that maintains the protein homeostasis [12].

2.3 Predicting Bioactive Agents and Monitoring of Drug Release

Designing and monitoring of drug-likeness is a tedious and time-consuming process. Lately, multiple online tools have been developed to analyze drug release and check accountability of selected bioactive compounds as a carrier. Benchmark datasets are later used to validate the computational analysis. For such evaluation's pharmacophore based on the chemical feature suits the best. These models construct large 3D datasets developed via *in silico* experiments or *in-house* compound collection [13]. To study ligand-based chemical features, various successful experiments have been established using the CATALYST program (www.accelrys.com), and a

group of researchers was successful in predicting 11β-hydroxysteroid dehydrogenase type 1 inhibitors using the VS experiments [14].

Determining bioactive ligands is a crucial step for selecting a potent drug for a specific target. Now, researchers are taking advantage of artificial intelligence in determining bioactive compounds that can be used for specific targets associated with a disease. For instance, Wu et al., 2018 integrated DL and RF methods to devise WDL-RF (https://zhanglab.ccmb.med.umich.edu/WDL-RF/), for determining bioactivity of G protein-coupled receptors (GPCRs) targeting ligands [15]. Likewise, Cichonska et al., 2018 developed pairwiseMKL (https://github.com/aalto-ics-kepaco), a multiple kernel learning-based method, for determining the bioactivity of compounds [16]. To test the efficiency of their model, they used to model to predict the anti-cancerous potency of compounds. Further, Mustapha et al., 2016 developed an Xgboost model to determine bioactive chemical molecules [17]. In addition, Merget et al., 2017 created machine learning models like DNN, RF to determine the bioactivity of more than 280 different kinases[18]. Furthermore, Arshadi et al., 2020 have devised DeepMalaria, a DL-based model for identifying compounds having Plasmodium falciparum inhibitory activity [19]. In addition, Sugaya et al., 2014 created a ligand-efficiency-driven support vector regression model to ascertain the biological activity of various chemical compounds [20]. Moreover, Afolabi et al., 2018 used data from the MLD drug data report (MDDR) repository and applied it to a combination of boosting algorithms in order to identify novel bioactive compounds [21]. Additionally, Petinrin et al., 2018 used the majority voting technique with an ensemble of different machine learning models in order to determine biologically active molecules [22].

Furthermore, adverse drug reactions (ADRs) are unexpected, pernicious, fatal side effects caused by drug administration. ADRs are a major challenge in drug development, and it has become very necessary to identify possible ADRs during the nascent stage of drug development in order to make the drug development process more robust and efficacious. Lately, researchers have taken the help of artificial intelligence to determine possible ADRs associated with different drugs before they are launched in the market for public use. For instance, Dey et al., 2018 used DL based model, which can predict ADRs associated with a drug and even identify chemical substructures responsible for those ADRs [23]. In addition, Liu et al., 2012 integrated chemical, biological, phenotypic properties of drugs to predict ADR associated with it via machine learning

analysis [24]. Similarly, Jamal et al., 2017 combined biological, chemical and phenotypic properties to predict nervous system ADRs linked with drugs through machine learning analysis [25]. The authors also used their model to find out ADRs associated with current Alzheimer's drugs. Furthermore, Xue et al., 2020 integrated biomedical network topology with a DL algorithm in order to predict Drug-ADR correlation [26]. Moreover, Raja et al., 2017 used machine learning analysis in order to predict ADRs, which are a result of drug-drug interactions [27]. They further used their model to predict ADR related to cutaneous disease drugs. Besides screening for an effective bioactive agent, another key area to work with is drug likeliness and its interaction post-release. Recently, a freely accessible, user-friendly graphical interface SwissADME (http://www.swissadme.ch) was developed to evaluate the compatibility of the drug and its pharmacokinetic actions [28]. Mathematical models such as Higuchi, Hixson–Crowell, Ritger–Peppas–Kormeyers, Brazel–Peppas, Baker–Lonsdale, Hopfenberg, Weibull and Peppas–Sahlin has also been applied in drug discovery, one of the most common practice has been the calculation of drug loading capacity of the selected or screened bioactive molecule.

2.4 Prediction of Protein Folding and Protein-Protein Interactions

Analyzing protein-protein interactions (PPIs) is crucial for effective drug development and discovery. Most of the protein annotation methods use sequence homology that has limited scope. High-throughput protein-protein interaction data, with ever-increasing volume, are becoming the foundation for new biological discoveries. A great challenge to bioinformatics is to manage, analyze, and model these data. Hence, computational models were developed that predicts multiple inputs at one place simultaneously [29]. Computational methods are implied to study both PPIs as well as protein-protein non-interactions (PPNIs), although PPIs are considered more informative than PPNIs. PPIs prediction can be identified as direct PPI, direct PPI with indirect functional associations and PPIs for signal transduction in pathways [30]. Machine and statical learning approaches like K-Nearest Neighbor, Naïve Bayesian, SVM, ANN, DT, and RF are used to predict the hindrance in PPIs. Use of Bayesian network was applied to predict PPIs essentially using gene co-expression, gene ontology (GO) biological process similarity. Dataset integration using BN produces precise and accurate PPI networks illustrating comprehensive yeast interactome [31]. Another group also used BN to combine datasets for the yeast to study PPIs [32]. A novel hierarchical model PCA-ensemble extreme learning machine (PCA-EELM) to predict protein-protein interactions only using the information of protein sequences has appeared as a powerful

tool that gives output with accuracy and less duration [33]. Furthermore, DNNs PPIs prediction efficiency was improved by a novel method known as DNN for Protein-Protein Interactions prediction (DeepPPI) (http://ailab.ahu.edu.cn:8087/DeepPPI/index.html) [34]. In mammalian cells, signal transduction is mostly controlled by PPIs between unstructured motifs and globular proteins binding domains (PBDs). To predict these PBDs across multiple protein families bespoke ML tool was developed, known as hierarchical statistical mechanical modelling (HSMM) [35]. Prediction of protein-protein interactions based on ML, domain-domain affinities and frequency tables, a novel tool referred to as PPI-SVM was developed in 2011, which is freely accessible at (http://code.google.com/p/cmater-bioinfo/) [36]. Due to the increased number of solved complex structures, a multimeric threading approach, PROSPECTOR, has been developed. In this method, proteins with known template structures are rethreaded, and their interaction with other proteins, their interfacial energy and Z-score are established [37]. Structure-based threading logistic regression tool Struct2Net (http://struct2net.csail.mit.edu) to evaluate the probability of interaction and is the first structure-based PPI predictor apart from homology modelling [38]. Gene cluster-based methods calculate the co-occurrence probability of orthologs of query proteins encoded from the same gene clusters. This method is also named domain/gene co-occurrence. If two proteins' genes are not close by in the genome, then this method cannot reliably predict an interaction between these two genes [39] [40].

2.5 Implementation of Artificial Intelligence in *De Novo* Drug Designing

The iterative process to design 3D structures of receptors to generate a novel molecule is termed as *de-novo* drug designing, which was intending to produce new dynamics. However, *de-novo* drug designing has not seen a boundless use in medication disclosure. Further, The field has seen some recovery recently because of advancements in the field of AI [41,42]. VS has emerged as a huge tool in the drug improvement measure, as it conducts profitable in silico look in excess of an enormous number of blends, at last, extending yields of potential medicine leads. As a subset of AI, ML is a technique for coordinating VS for drug leads, which generally incorporates gathering a filtered planning set of blends, contained known actives and inactives [43,44]. In the wake of setting up the model, it is tested and, if accurate enough, used on previously unknown database. In this section, we discussed how AI has proved to be a boon for drug designing using the *de-novo* technique.

In one study, the researchers utilized the indolent space portrayal to prepare a model dependent on the quantitative estimate of drug-likeness (QED) drug-similarity score and the manufactured availability score synthetic accessibility score (SAS**)** [45]. In another distribution, the presentation of such a variational autoencoder was contrasted with an antagonistic autoencoder [46]. The ill-disposed autoencoder comprises of a generative model delivering novel compound structures. A second discriminative antagonistic model is prepared to differentiate genuine particles from produced ones, while the generative model attempts to trick the discriminative one [47]. The antagonistic autoencoder created more substantial structures than the variational autoencoder in generation mode essentially. In mix with an in-silico model, novel structures anticipated to be dynamic against the dopamine receptor type, 2 could be gotten. Researches utilized a generative ill-disposed organization (GAN) to propose mixes with putative anticancer properties [48]. RNN has likewise been effectively utilized for de-novo drug design. Since SMILES strings encode substance structures in a grouping of letters, RNNs have been utilized to generate compound structures. It was observed that RNNs have the potential to utilize SMILES strings for drug designing [49]. A similar methodology was likewise effectively utilized for the development of novel peptide structures [50]. Neural network learning was effectively applied to inclination the created mixes towards wanted properties [51]. Similarly, transfer learning was utilized as another system to create novel synthetic structures with an ideal natural action. In the subsequent steps, the organization is prepared to get familiar with the SMILES syntax with a huge preparing set [52,53]. In the subsequent advance, the preparation is proceeded with mixes having the ideal movement. Moreover, additional epochs of training were adequate to reach the stage of novel combinations into a compound space involved by dynamic atoms. In light of such a methodology, five atoms were combined, and the plan action could be affirmed for four particles against atomic, chemical receptors [54]. A few distinct designs have been proposed, which have been equipped for creating legitimate, important novel structures. The novel synthesis has been investigated by these strategies, with the property dissemination of the created molecules or atoms being similar to the large training set used. The forthcoming primary application for this strategy was effective, with 4 out of 5 atoms indicating the ideal action [55]. Optimization of AI and multi-objective has been proved to be a promising solution to bridge the chemical and biological phase. Novel pair of multi-objectives based on RNN for the automated *de-novo* design based on SMILES were developed to find the best possible match between physicochemical properties and their

constrained biological targets. The results indicated that AI and multi-objective optimization allows capturing the latent links joining chemical and biological aspects, thus providing easy-to-use options for customizable design strategies, which proved especially effective for both lead generation and lead optimization [56].

ML models like SVM, RF, DNNs, and many others have been used for drug discovery for analyzing the pharmaceuticals applications from docking to VS [57]. Recently, drug repurposing has emerged as an innovative approach to minimize drug development duration that usually involves data mining and AI [58]. A group proposed a question-answer artificial system (QAAI) that had the capability to repurpose drugs that used google semantic AI universal encoder to compute the sentence embedding in the red brain JSON database. The study validated prediction for the lipoxygenase inhibitor drug zileuton as a modulator of the NRF2 pathway *in-vitro*, with potential applications to reduce macrophage M1 phenotype and reactive oxygen species production. This novel approach has been proved to effective for reposition in NDDs [59]. With the rapid development of systems-based pharmacology and poly-pharmacology, method development for the rational design of multi-target drugs has to become urgent. The first *de-novo* multi-target drug configuration program known as LigBuilder V3 (http://www.pkumdl.cn/ligbuilder3/) has been devised to design ligands for different receptors, numerous coupling locales of one receptor, or different configurations of one receptor. LigBuilder V3 is for the most part relevant in again multi-target drug plan and enhancement, particularly for the plan of compact ligands for protein proteins with varying ligand binding sites [60]. *De-novo* drug design actively seeks to use sets of chemical rules for the fast and efficient identification of structurally new chemotypes with the desired set of biological properties. Moreover, fragment-based *de novo* design tools have been successfully applied in the discovery of noncovalent inhibitors. Herein a new protocol, called Cov_FB3D, which involves the *in silico* assembly of potential novel covalent inhibitors by identifying the active fragments in the covalently binding site of the target protein [61].

2.6 Post Translational Modification Enzymes as Drug Targets in Pathogenesis of NDDs

Emerging evidence suggests the mechanistic involvement of aberrant PTMs in the pathogenesis of NDDs such as AD, PD, ALS, HD, multiple sclerosis, and frontotemporal dementia. Alteration in PTMs causes misfolded protein aggregates, which increases neurotoxicity through disrupted

cell signaling cascades. These impeding cells signaling pathways hamper the biological process such as autophagy and mitophagy, inflammatory response, cell-cycle regulation, and mitochondrial function, which are the major causes of neuronal cell death. Recent studies demonstrated the implications of drug molecules and natural biomolecules targeting different PTM enzymes in the NDDs therapeutics. Drug molecules or natural biomolecules act as either inhibitors or activators of particular PTM enzymes. For example, In AD, Tau's hyperphosphorylation at S396 residue by GSK-3 results in the formation of neural fibrils accumulate, leading to tau aggregation. SAR502250 [62], curcumin [63], 6-hydroxydopamine [64] have been reported to downregulate GSK3 activity, thus reducing tau aggregation. Similarly, BACE1 is an exciting target for AD therapeutics, which phosphorylates Aβ with the help of enzymes such as γ-secretase and β-secretase that cleaves APP, and thus, results in the aggregation and formation of Aβ plaques. Verubecestat, Lanabacestat, and Elenbacestat (E-2609) are considered as BACE1 inhibitors, but their phase-III trial was discontinued due to their respective inefficacy [65,66]. Likewise, palmitoylation of APP leads to enhanced APP cleavage by BACE1, leading to amyloidogenesis. However, inhibition of Sterol O-acyltransferase (ACAT) with CP-113818 reduces the APP palmitoylation level and can be used in AD therapeutics [67,68]. **(Figure1)**

Moreover, TDP-43 deacetylation by histone deacetylase (HDAC) at K154 and K192 leads to hyperphosphorylation of TDP-43, which causes the formation of peptide aggregates that promote ALS pathogenesis [69]. In the SOD1-G93A mouse model, sodium butyrate and trichostatin inhibit HDAC activity promoting neuroprotection [69]. In embryonic mouse model 31B12A, scFv was observed to prompt HSP70 mediated chaperone autophagy activation resulted in TDP-43 aggregates inhibition [70]. Similarly, in a study, it was demonstrated that α-synuclein glycation potentiated aggregation via magnesium oxide-induced oligomerization in mice and *Drosophila* [71]. Further, glycation hampers the ubiquitination of α-synuclein, thereby reducing its degradation, which could be reversed with magnesium oxide inhibitors like aminoguanidine [72]. Furthermore, In AD, it has been reported that AGEs elevate oxygen radicles, thereby increases APP activity [73]. However, increased reactive oxygen species (ROS) activity was suppressed by resveratrol via β-secretase downregulation [73]. Furthermore, Aβ nitration at Y10 is a bit contradictory. An early study reported that Y10 nitration by peroxynitrite enhances aggregate formation, which was found in amyloid plaque core in the AD mice model [74]. However, a recent experiment showed that Y10 nitration notably curbed amyloid aggregation. The

aggregates formed in the former study, when treated with L-NIL, accounted for reduced 3NTyr10-Aβ in APP/PS1 mice [75]. Similarly, in AD, BACE1 SUMOylation at K501 residue escalated its stability, thereby altering the APP that later generates Aβ plaque [76]. BACE1 inhibitors are reported to retard its activity and suppress APP cleavage. SOD-1 SUMOylation enhances protein misfolding that results in the formation of an inclusion body. MIF is observed to reduce inclusion body formation here by curbing aggregate formation [77]. Similarly, ubiquitin sequestering in inclusion bodies retards the proteasomal activity and result in the progression of NDDs.

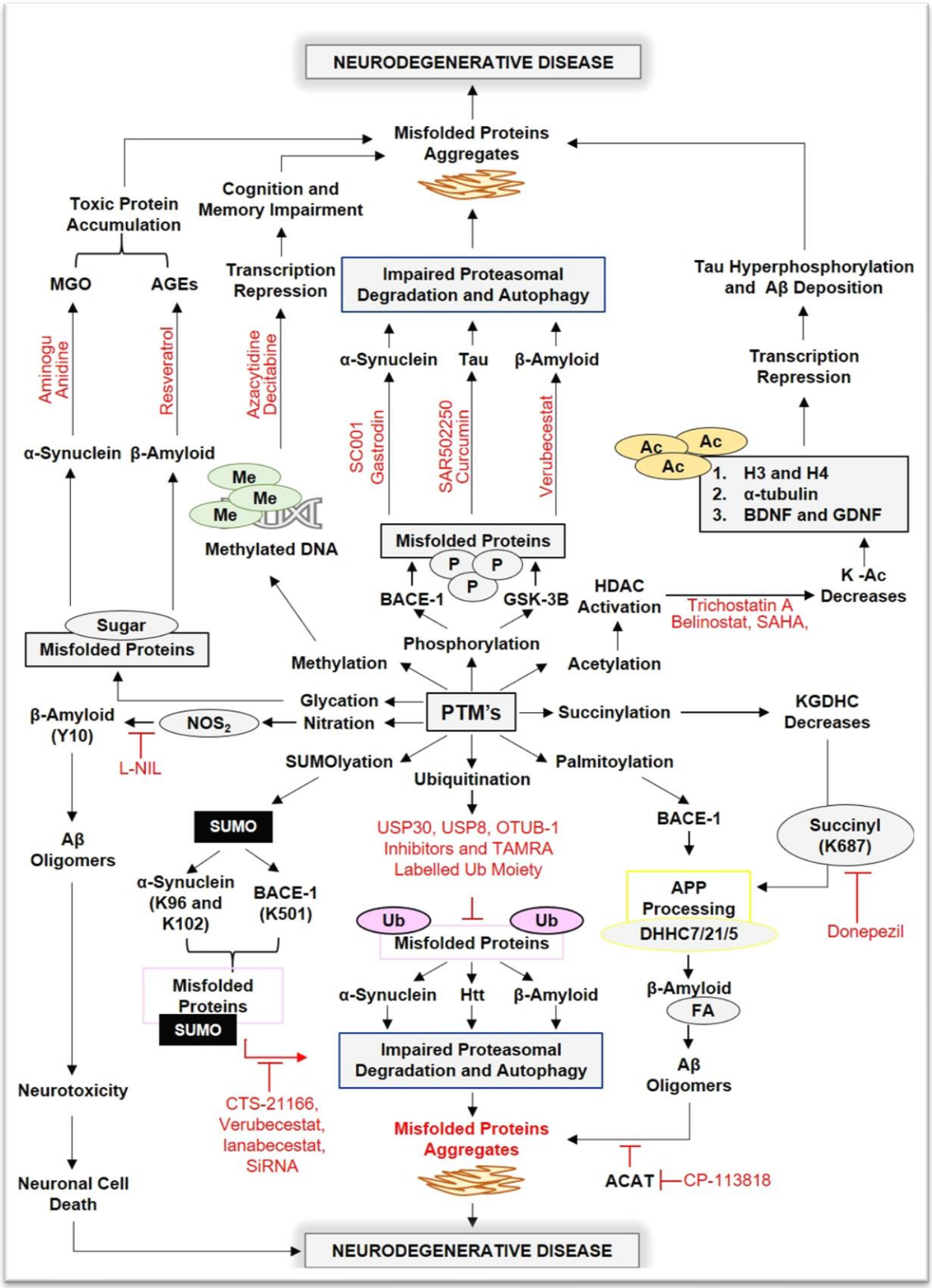

FIGURE 1: THERAPEUTICS TARGET FOR VARIOUS NDDS

Ubiquitination of α-synuclein at K10, K23 downregulates the protein clearance resulting in inclusion bodies in AD. Furthermore, neural precursor cell expressed developmentally down-regulated protein 4 (Nedd4) enhances the α-synuclein clearance as it is reported to interact directly with it by promoting ubiquitination at K63 [78]. α-synuclein SUMOylation at K96 and K102 mediated by phytochrome-interacting ankyrin-repeat protein 2 (PIA2) suppresses the proteasomal degradation and elevated protein aggregate that promote PD, SiRNA can knock out the PIA2 UPS suppression and can enhance monoubiquitination of α-synuclein [79]. Likewise, the succinylation of APP at K687 residue hampers its degradation and escalates Aβ aggregation. It was observed that the succinylated APP, along with Aβ agglomerates, was present in the hippocampus of a transgenic mouse for AD due to diminished brain glucose regulation [80]. In one experiment, inhibition of agglomerates by donepezil was observed in BCCAO rats, and donepezil escalated sorting Nexin 33 (SNX33) level in cortical neurons resulting in reduced agglomerates [81]. Moreover, one carbon methylation can perturb normal DNA; this one carbon manipulation results in AD by generating Aβ agglomerates. DNMTs, ten-eleven translocation methylcytosine dioxygenase 1 (TET-1), were associated with AD onset. The use of EGCG DNMT inhibitors has been shown to curb agglomerate growth [82]

3. METHODOLOGY:

3.1 DATA EXTRACTION

Herein, through extensive literature review we found that CBP and P300 were common enzymes associated with acetylation and crotonylation in AD (REF). A readily accessible database Comparative toxicogenomic database (CTD) http://ctdbase.org/ that contains the information about genes and its activity associated with particular disease has been used for data extraction to retrieve information of genes-interactions of AD, P300 and CBP (REF).

3.2 IDENTIFICATION OF COMMON PROTEINS (VENNY2.0)

Venny 2.0 (https://bioinfogp.cnb.csic.es/tools/venny/) is an online bioinformatics tool that helps frame a Venn diagram. The information retrieved from CTD were then visually interpreted to identify common protein residues between AD, P300 and CBP using Venny 2.0 (**Figure**).

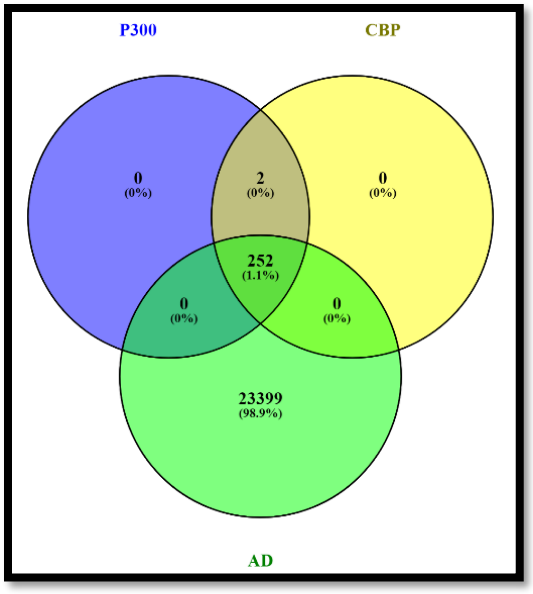

Figure2: Venn diagram for identified common protein

AFP	CENPJ	EPAS1	HIPK2	KLF5	MYC	POLR1E	SERTAD2	TCF12
AKT1	CHUK	ESR1	HLF	KMT2A	MYOD1	POLR2A	SERTAD3	TCF3
ANAPC2	CITED2	ESR2	HNF1A	KMT2D	N4BP2	POT1	SETD1A	TDG
ANAPC7	CITED4	ETS1	HNF1B	LAMP2	NCOA1	POU1F1	SH3GL1	TEAD1
APC	CLOCK	ETS2	HNF4A	LDB2	NCOA2	PPARG	SIRT1	TFAP2B
AR	CNTN2	EWSR1	HNRNPL	LIG4	NCOA3	PPARGC1A	SMAD2	TFDP1
ATF2	COPS2	FBXL19	HOXA10	LYN	NCOA6	PPP1CA	SMAD3	TGS1
ATF3	CPSF4	FGFR1	HOXB6	MAF	NCOR1	PPP1CC	SMAD4	TP53
ATF4	CREB1	FHL1	HOXB7	MAML1	NCOR2	PPP1R13L	SMARCA2	TP53BP1
ATG12	CREBBP	FOS	HSF1	MAP3K5	NEUROG1	PRLR	SMARCA4	TRIM24
ATXN3	CSK	FOXM1	HSPA8	MAPK1	NFATC1	PTMA	SMG7	TRIM25
BMI1	CTBP1	FOXO1	HSPB1	MAPK10	NFE2	PTMS	SNAI1	TRIM28
BRCA1	CTNNB1	FOXO3	HTT	MAPK3	NFE2L2	PTTG1	SNIP1	TRIP4
BRD4	DAXX	FOXO4	IFNAR2	MDC1	NFYA	PYCR1	SOWAHA	TRP53
C3ORF62	DDIT3	GATA3	IKBKB	MED21	NKX2-1	PYGO2	SP1	TSPYL2
CARM1	DDX17	GCM1	IKBKG	MED23	NLK	RAD23A	SPI1	TXNDC11
CCAR2	DDX5	GLI3	ING1	MED25	NPAS2	RARA	SPIB	UBE2I
CCN2	DUX4	GPBP1	IRF3	MEIS1	NR3C1	RB1	SRC	UBE2S
CCNA2	DYRK1A	GRIP1	IRF5	MGA	NR3C2	RBBP4	SRCAP	USP14
CCND3	DYRK1B	GTF2B	IRF7	MIER1	NR5A1	RBCK1	SREBF1	USP7
CDC16	E2F1	H3C1	JUN	MITF	NUP98	REL	SREBF2	VDR
CDC20	E2F3	HBP1	KAT2B	MKNK1	PARP1	RELA	SRF	VIRMA
CDC27	EBF1	HCK	KAT6A	MSX1	PCMT1	RPS6KA3	SS18L1	WRN
CDH1	EGLN3	HDAC1	KDM3B	MTDH	PELP1	RPS6KA5	STAT1	WT1
CDH2	EID1	HDAC2	KHDRBS1	MTF1	PHOX2B	RUNX1	STAT2	XRCC6
CDK2	EIF4ENIF1	HDAC3	KLF1	MUS81	PLAGL1	RUNX2	STAT6	YY1
CEBPB	ELAVL1	HES1	KLF13	MYB	PML	RUVBL1	TBP	
CEBPD	EP300	HIF1A	KLF4	MYBL2	PNKP	SERTAD1	TBX21	

Table1: list of identified common protein

3.3 PROTEIN-PROTEIN INTERACTIONS

To understand the protein- protein interactions between the identified common a functional protein network association biological database STRING (https://string-db.org/) has been been used. The node table and the network are retrieved in cytoscape readable form.

3.4 IDENTIFICATION OF HUB GENES

Once the PPI has been developed the retrieved data is then uploaded on cytoscape and nested network of the common protein is obtained. Thereafter, using MCODE application present in cytoscape clusters of subnetworks were developed. In total seven clusters were obtained based on the association of genes out of which cluster 1 has been considered for our studies. Later using another application present in cytoscape cytohubba hub genes were identified.

3.5 NETWORK ANALYSIS

To analyze the gene-drug interaction online tool network analyst has been used in which gene IDs are uploaded and a comprehensive network is developed. To validate the drug-gene association determined by network analysis an online drug repurposing tool DrugNet & disease-gene prioritization tool ProphNet developed by university of Granada, Spain (http://genome.ugr.es:9000/) has been used. These tools use algorithms on the provided input that can be disease network, protein domain and/or gene network and performs network-based information predictions that aid in drug repurposing.

4. RESULTS AND DISCUSSION

4.1 PROTEIN-PROTEIN INTERACTIONS BETWEEN IDENTIFIES COMMON PROTEINS

PPI network enables to understand the relation between two or more interacting proteins within same or different class. The list common proteins were fed into the database and molecular interactions were visualized. This list was retrieved and uploaded into Cystoscape tool that be downloaded from (https://cytoscape.org/download.html),

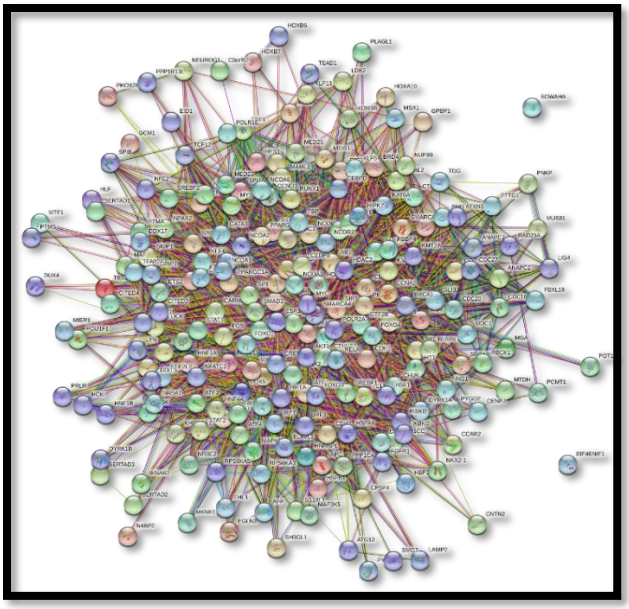

Figure3: Molecular Interaction between common proteins using STRING

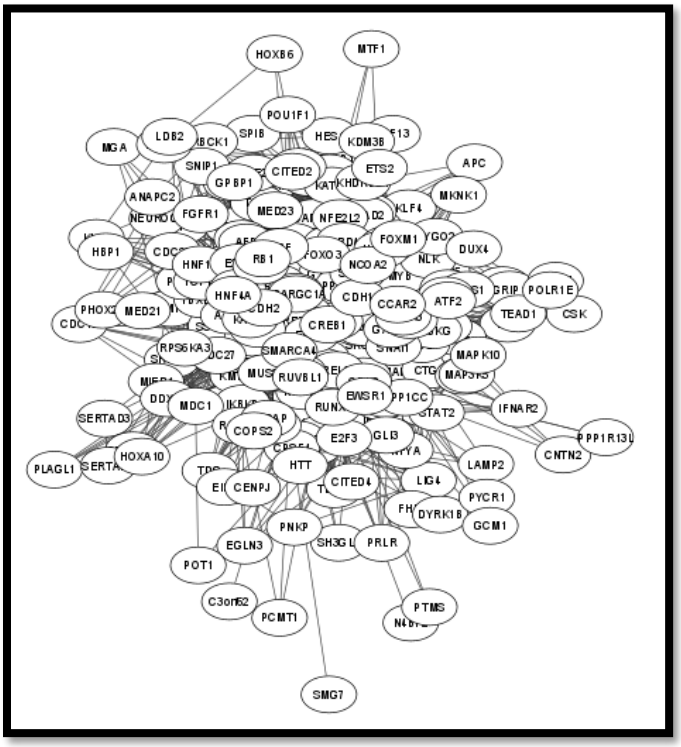

Figure4: Network obtained using Cytoscape

4.2 IDENTIFICATION OF HUB GENES

Using MCODE tool in Cytoscape different set of clutsers were identified. Overall, seven clusters were obtained of which cluster1 was selected due to higher score 28.467, number of nodes and edges 32 and 445 respectively. This cluster contains total 32 genes namely HNF4, CEBPB, EP300, MAPK1, NR3C1, SIRT1, CDK2, CTNNB1, CDH1, SMAD3, SMAD4, SRC, AR, SP1, CREBBP, SNAI1, HDAC1, RELA, NCOR1, SMAD2, FOXO3, HIF1A, CREB1, ESR1, MYC, RUNX2, FOXO1, JUN, AKT1, PARP1, MAPK3 and FOS (see figure). Thereafter, cytohubba another tool available on cytoscape was used to identify the hub genes in the selected cluster. Cytohubba use multiple algorithms to identify the essential nodes that may be a potential drug-targets. We identified 10 HUB genes namely FOXO3, EP300, MAPK3, CREBBP, AR, HDAC1, MAPK1, MYC, JUN, ESR1.

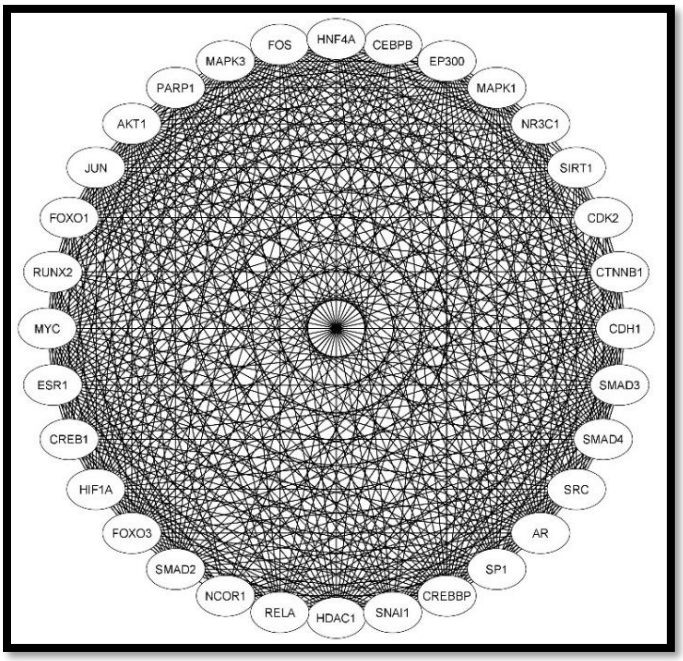

Figure5: cluster network

Top 10 in network 1: Cluster 1 (Score: 28.467) ranked by MCC method		
Rank	**Name**	**Score**
1	FOXO3	2.31E+21
1	EP300	2.31E+21
1	MAPK3	2.31E+21
1	CREBBP	2.31E+21
1	AR	2.31E+21
1	HDAC1	2.31E+21
1	MAPK1	2.31E+21
1	MYC	2.31E+21
1	JUN	2.31E+21
1	ESR1	2.31E+21

Table 2: Rank and Score of Hub genes

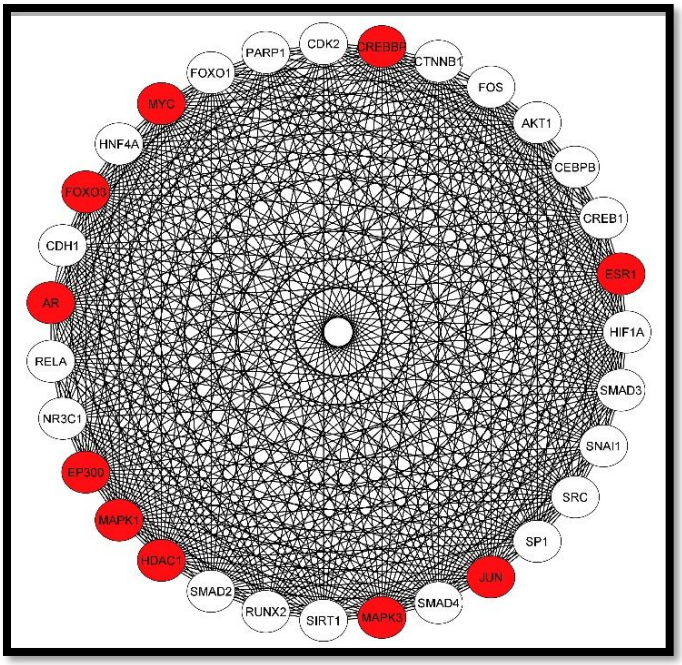

Figure6: Identified HUB genes in cluster

4.3 IDENTIFICATION OF DRUG-GENE INTERACTIONS

After identification of hub genes, network analysis has been performed to identify the drug-gene interaction. The network obtained for a minimum of 3 nodes has been selected which has MAPK1, JUN and MAPK3 as main target nodes. Through visual analysis of the network, we see that MAPK1 has degree of 14 which means it interacts with 14 drugs, JUN has degree of 5 and MAPK3 has 4. Interestingly, MAPK1 and MAPK3 share a common drug purvalanol (DB02733) and all the three main nodes of the genes that includes MAPK1, JUN and MAPK3 share a common drug Arsenic trioxide (DB01169) with highest betweenness among the interacting drugs of 104.5.

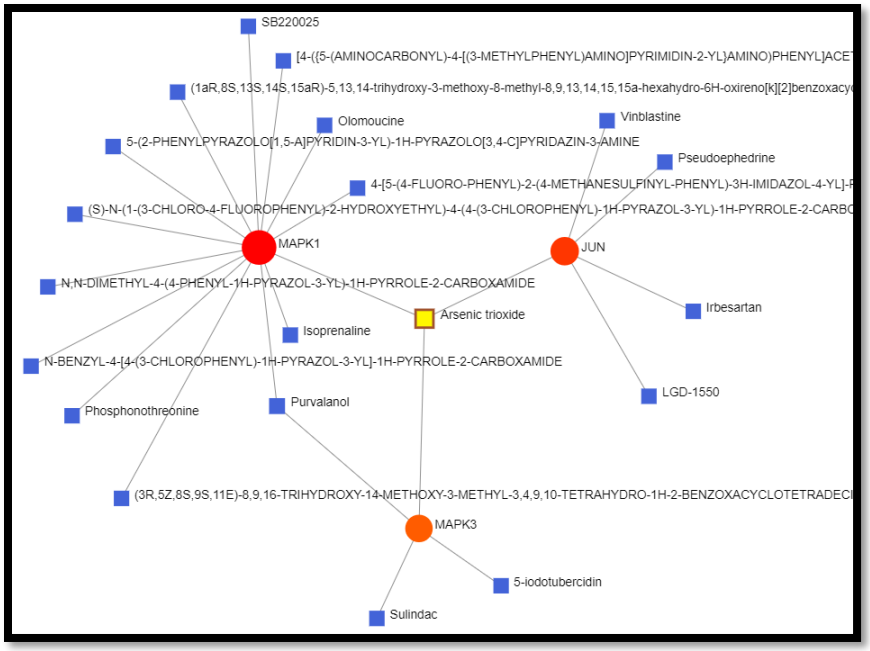

Figure7: Drug- gene interactions

ID	Label	Degree	Betweenness
5594	MAPK1	14	189
3725	JUN	5	78
5595	MAPK3	4	44
DB01169	Arsenic trioxide	3	104.5
DB02733	Purvalanol	2	19.5
DB00570	Vinblastine	1	0
DB00605	Sulindac	1	0
DB00852	Pseudoephedrine	1	0
DB01029	Irbesartan	1	0
DB01064	Isoprenaline	1	0
DB02116	Olomoucine	1	0
DB02482	Phosphonothreonine	1	0
DB04338	SB220025	1	0
DB04604	5-iodotubercidin	1	0
DB05785	LGD-1550	1	0

Table 3: Node Table

4.4 VALIDATION OF THE RESULTS

To validate the drug-gene association determined by network analysis an online drug repurposing tool DrugNet & disease-gene prioritization tool ProphNet developed by university of Granada, Spain (http://genome.ugr.es:9000/) has been used. These tools use algorithms on the provided input that can be disease network, protein domain and/or gene network and performs network-based information predictions that aid in drug repurposing. The identified hub genes were first

uploaded in prophnet tool it has been observed that out of the identified genes ESR1 is involved with Dementia one of the leading causes for AD and Frontotemporal Dementia (FTD). Similar results were observed for drug- gene association Arsenic trioxide has shown to be associated with Dementia and FTD. These results show that Arsenic trioxide has potential to be used as repurposed drug for AD treatment.

5. CONCLUSION

AD is one of the most common prominent neurodegenerative disorders that has no cure. Here in this project, we carried out in silico experiments to establish and understand the correlation between the protein involved in acetylation and crotonylation of proteins in AD. We found that p300 and CBP are involved in both the PTMs. Further investigations shows that there are 254 common proteins associated with genes interacting with AD, P300 and CBP. With the help of these identified common proteins their visual networks have been studied and found that 10 HUB genes namely FOXO3, EP300, MAPK3, CREBBP, AR, HDAC1, MAPK1, MYC, JUN, ESR1 actively interact with the drugs. Further using drug repurposing tools readily available online we found that arsenic trioxide interacts actively with MAPK1 JUN and MAPK3 with highest betweenness of 104.5 finally through validation we concluded that arsenic trioxide is a potential drug for the treatment.

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Review

Post-translational modifications: Regulators of neurodegenerative proteinopathies

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ABSTRACT

One of the hallmark features in the neurodegenerative disorders (NDDs) is the accumulation of aggregated and/or non-functional protein in the cellular milieu. Post-translational modifications (PTMs) are an essential regulator of non-functional protein aggregation in the pathogenesis of NDDs. Any alteration in the post-translational mechanism and the protein quality control system, for instance, molecular chaperone, ubiquitin-proteasome system, autophagy-lysosomal degradation pathway, enhances the accumulation of misfolded protein, which

Abbreviations: PTMs, Post-translational modifications; NDDs, Neurodegenerative diseases; AD, Alzheimer's disease; PD, Parkinson's disease; ALS, Amyotrophic lateral sclerosis; HD, Huntington's disease; TDP-43, Transactivation response DNA binding protein-43; Aβ, β-amyloid; NFTs, Neurofibrils tangles; SNpc, Substantia nigra pars compacta; polyQ, Polyglutamine; LBs, Lewy bodies; htt, Huntingtin protein; SOD1, Superoxide dismutase 1; UPS, Ubiquitin-proteasome system; CMA, Chaperone mediated autophagy; HSPs, Heat shock proteins; PSEN2, Presenilin-2; IT15, Interesting transcript 15; TARDBP, TAR DNA Binding Protein; NO, Nitric oxide; CK1, Casein kinase 1; GSK-3β, Glycogen synthase kinase 3β; PKA, Protein kinase A; CDK5, Cyclin-dependent kinase 5; DYRK1A, Dual Specificity Tyrosine Phosphorylation Regulated Kinase 1A; REP, Repressor element of PARKIN; MTS, Mitochondrial targeting sequence; TM, Transmembrane; FUS, Fused in sarcoma; NLS, Nuclear localization sequence; RRMs, RNA recognition motif; NES, Nuclear export sequence; ER, Endoplasmic reticulum; UPR, Unfolded protein response; IRE1α, Inositol-requiring enzyme 1 α; PERK, Protein kinase R like endoplasmic reticulum kinase; ATF6α, Activating transcription factor 6 α; DR5, Death receptor 5; eIF2α, Eukaryotic initiation factor 2 α; XBP1, X-box binding protein 1; ASK1-JNK, apoptosis signal-regulating kinase 1/ c-Jun N-terminal kinases; TRAF2, TNF receptor-associated factor 2; PAD4, Protein arginase deaminase 4; SP1, Specificity protein 1; SP2, Specificity protein 2; PARP16, poly ADP ribose polymerase 16; Umf1, ubiquitin fold modifier 1; CHOP, C/EBP homologous protein; ERAD, endoplasmic reticulum-associated degradation; APP, Amyloid precursor protein; PSEN1, Presenilin-1; BACE1, Beta-secretase 1; BiP, Binding immunoglobulin protein; PARKIN, E3 ubiquitin-protein ligase parkin; PINK1, PTEN-induced kinase 1; PDI, Protein disulfide isomerase; GADD34, Growth arrest and DNA damage-inducible protein; DJ1, Protein deglycase; ATFS1, Cyclic AMP-dependent transcription factor; PDR1, Pleiotropic drug resistance 1; CSMNs, Corticospinal motor neurons; FOXO1, Forkhead box protein O1; FTLD, frontotemporal lobar degeneration; ASK1, Signal-regulating kinase 1; PI3K, Phosphatidylinositol 3-kinase; PIP2, Phosphatidylinositol 4,5-bisphosphate; PIP3, Phosphatidylinositol (3,4,5)-trisphosphate; PH domain, Pleckstrin homology domain; PDK1, Phosphoinositide dependent kinase 1; mTORC2, Mammalian target of rapamycin complex 2; mTORC1, Mammalian target of rapamycin complex 1; IGF-1, Insulin like growth factor-1; AGEs, Advanced glycation end-product; RAGE, Receptor for advanced glycation end products; MAPK, Mitogen activated protein kinase; ERK ½, Extracellular signal regulated kinase ½; AMPK, Adenosine monophosphate activated protein kinase; CBS, cystathionine-beta-synthase; AMP, Adenosine monophosphate; ADP, Adenosine diphosphate; ATP, Adenosine triphosphate; LKB1, Liver kinase B1; TAK1, Transforming growth factor beta activated kinase 1; CaMKKβ, Calmodulin dependent protein kinase kinase-β; ACC, Acetyl CoA carboxylase; ULK1, Unc-51 like autophagy activating kinase 1; TSC 1/2, Tuberous sclerosis complex ½; SREBP, Sterol regulatory element binding protein; NAD^+, Nicotinamide adenine dinucleotide; PGC-1α, Peroxisome proliferator activated receptor gamma coactivator-1α; BCL-2, B-cell lymphoma 2; APC, Adenomatous polyposis coli; β-TrCP, β-transducin repeats containing proteins; LRP5/6, Low density lipoprotein receptor related protein 5/6; Dsh, Dishevelled; TCF/LEF, T-cell factor/lymphoid enhancer factor; DKK1, Dickkopf related protein 1; AVs, Autophagic vacuoles; PAR, UBE3A: Ubiquitin-protein ligase E3A; TRAF6, Tumor necrosis factor receptor associated factor 6; UBE2D2, Ubiquitin-conjugating enzyme E2 D2; UCH-L1, Ubiquitin carboxy-terminal hydrolase L1; USP14, Ubiquitin carboxyl-terminal hydrolase 14; BCL-xL, B-cell lymphoma-extra-large; LAMP2A, Lysosome-associated membrane protein 2A; LRRK2, Leucine-rich repeat kinase; CNS, Central nervous system; COX2, cyclooxygenase-2; iNOS, Inducible nitric oxide synthase; NF-κβ, Nuclear factor kappa-light-chain-enhancer of activated B cells; IKK, IκB kinase; Cdks, cyclin-dependent kinases; NGF, Nerve growth factor; PPIase, Peptidyl-prolyl cis/trans isomerase; Prx2, Peroxiredoxin-2; 3-NPA, 3-Nitropropionic acid; PLK2, Polo like kinase 2; VDAC1, Voltage-dependent anion-selective channel 1; DLP-1, Dynamin-like protein 1; Drp1, Dynamin-related protein 1; E-2609, Elenbacestat; ACAT, Sterol O-acyltransferase; HDAC, Histone deacetylase; ROS, Reactive oxygen species; NEDD4, Neural precursor cell expressed developmentally down-regulated protein 4; PIA2, Phytochrome-interacting ankyrin-repeat protein 2; SNX33, Sorting Nexin 33; DNMTs, DNA methyltransferases; TET-1, Ten-eleven translocation methylcytosine dioxygenase 1.

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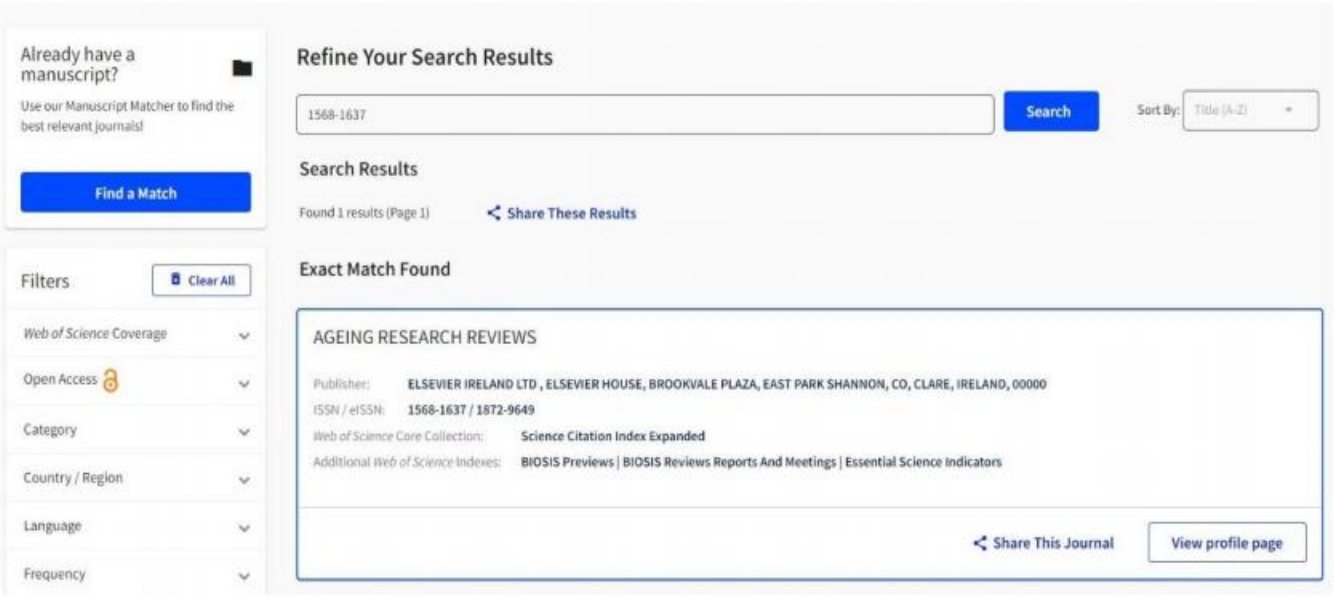
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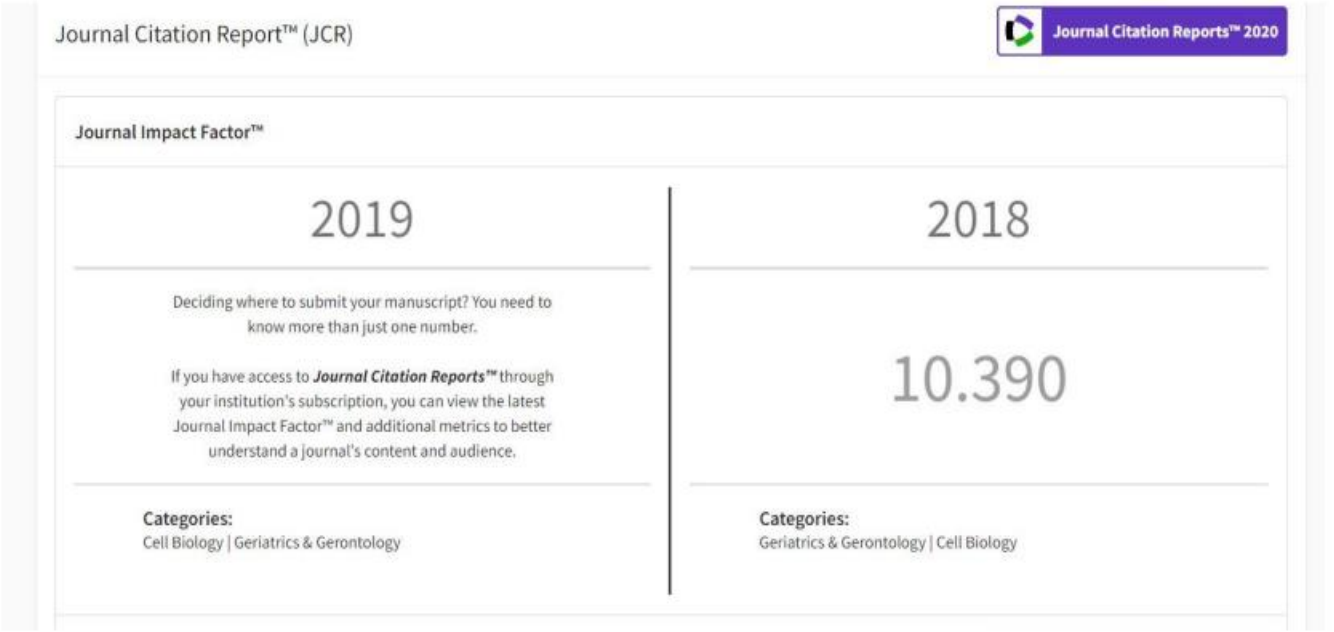
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Artificial intelligence to deep learning: machine intelligence approach for drug discovery

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Abstract

Drug designing and development is an important area of research for pharmaceutical companies and chemical scientists. However, low efficacy, off-target delivery, time consumption, and high cost impose a hurdle and challenges that impact drug design and discovery. Further, complex and big data from genomics, proteomics, microarray data, and clinical trials also impose an obstacle in the drug discovery pipeline. Artificial intelligence and machine learning technology play a crucial role in drug discovery and development. In other words, artificial neural networks and deep learning algorithms have modernized the area. Machine learning and deep learning algorithms have been implemented in several drug discovery processes such as peptide synthesis, structure-based virtual screening, ligand-based virtual screening, toxicity prediction, drug monitoring and release, pharmacophore modeling, quantitative structure–activity relationship, drug repositioning, polypharmacology, and physiochemical activity. Evidence from the past strengthens the implementation of artificial intelligence and deep learning in this field. Moreover, novel data mining, curation, and management techniques provided critical support to recently developed modeling algorithms. In summary, artificial intelligence and deep learning advancements provide an excellent opportunity for rational drug design and discovery process, which will eventually impact mankind.

Graphic abstract

The primary concern associated with drug design and development is time consumption and production cost. Further, inefficiency, inaccurate target delivery, and inappropriate dosage are other hurdles that inhibit the process of drug delivery and development. With advancements in technology, computer-aided drug design integrating artificial intelligence algorithms can eliminate the challenges and hurdles of traditional drug design and development. Artificial intelligence is referred to as superset comprising machine learning, whereas machine learning comprises supervised learning, unsupervised learning, and reinforcement learning. Further, deep learning, a subset of machine learning, has been extensively implemented in drug design and development. The artificial neural network, deep neural network, support vector machines, classification and regression, generative adversarial networks, symbolic learning, and meta-learning are examples of the algorithms applied to the drug design and discovery process. Artificial intelligence has been applied to different areas of drug design and development process, such as from peptide synthesis to molecule design, virtual screening to molecular docking, quantitative structure–activity relationship to drug repositioning, protein misfolding to protein–protein interactions, and molecular pathway identification to polypharmacology. Artificial intelligence principles have been applied to the classification of active and inactive, monitoring drug release, pre-clinical and clinical development, primary and secondary drug screening, biomarker

Rohan Gupta, Devesh Srivastava, Mehar Sahu, and Swati Tiwari contributed equally to this work.

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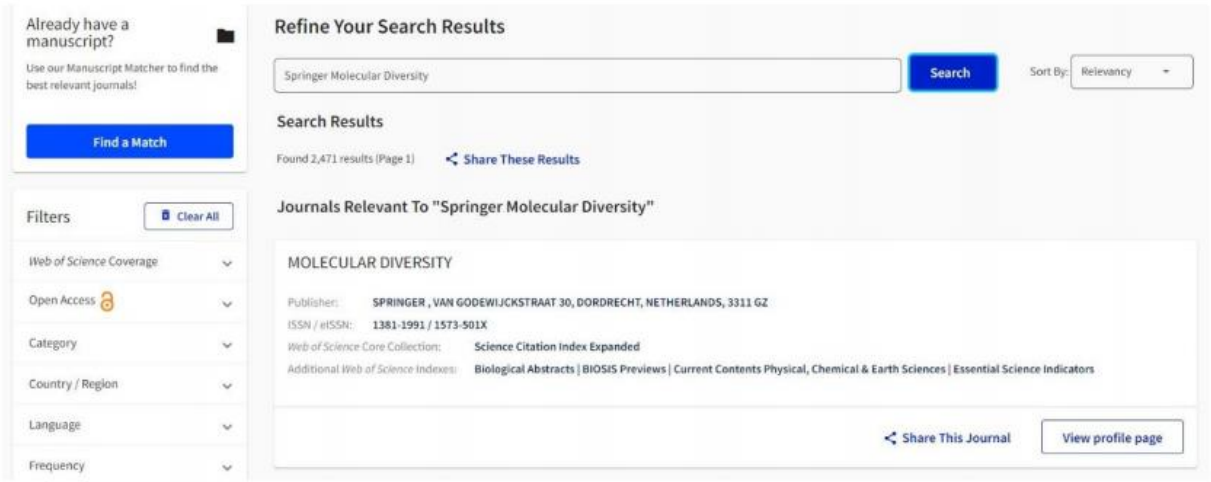
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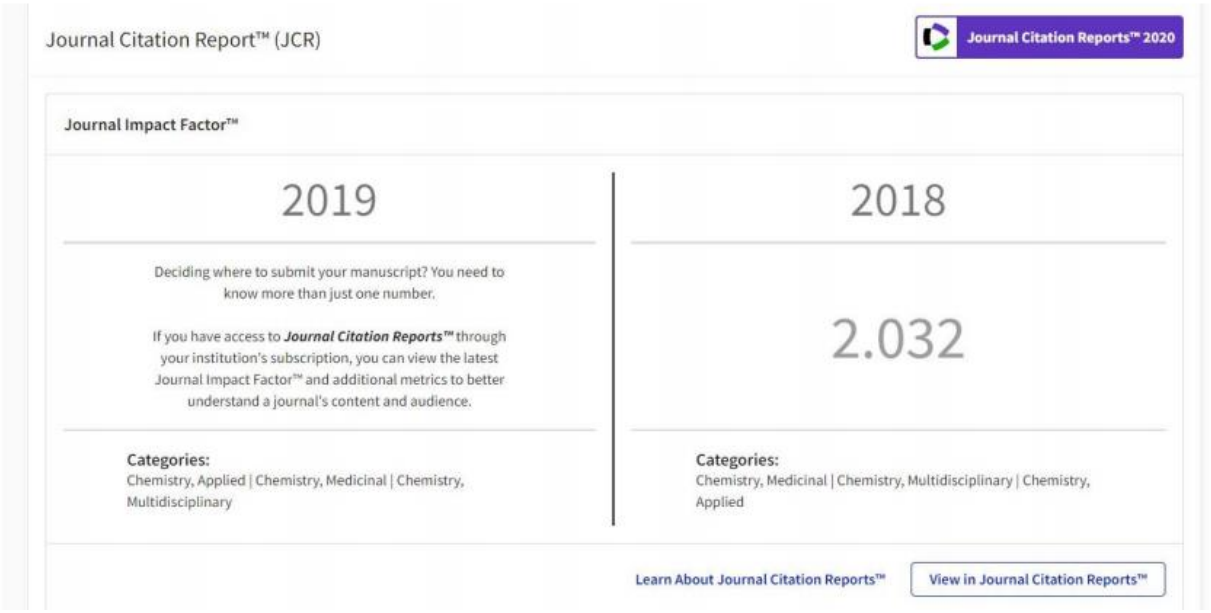
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