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APPLICATION OF PRIONS AND PRION PROTEIN IN BIOMEDICAL SCIENCES

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ABSTRACT
Prion proteins are normal proteins (PrP) found on the cell membranes of majorly the brain, spinal cord, heart, muscle and in selected lymphoid and myeloid cells. They play a key role in the development of prion diseases, and the sole determinant of it. A Prion disease (also known as Transimissible Spongiform Encephalopathy, TSE) is a rapidly progressive and sever neurodegenerative disorder that results from conversion of PrP^{C} into a conformational altered isoform, PrP^{Sc} in the CNS (Garrity *et al*., 2010). Prion disease is classified into infectious, familial or sporadic. They are considered as attractive target for therapeutic intervention in biomedical sciences. Prion disease is of major public health concern because of its rising prevelance and outburst epidemics in some geographical areas, for example, Paupa New Guinean and United Kingdom. This seminar is intended to explain Prion Protein, its applications and how the idea will help to understand the disease state.

KEYWORDS: Encephalopathy, Isoform, Sporadic & Glycosylation.

1.0 INTRODUCTION
Prion proteins are normal proteins (PrP) found on the cell membranes of majorly the brain, spinal cord, heart, muscle and in selected lymphoid and myeloid cell. In adults, they are expressed at highest levels in neurons of the brain and spinal cord and in lowest level in glial of the CNS and in some peripherial cells. They play a key role in cellular processes, neural development and in mature mammalian central nervous system (Steel *et al*., 2006). The misfolding of prion protein in healthy individuals and animals is what results to prion disease. Prion diseases also know as transmissible spongiform encephalopathies (TSEs), are family of rare, fatal neurodegenerative diseases or disorders of humans and animals which originates spontaneously, genetically or by infection (Kavacs *et al*.,2008). Human prion associated disease causes: fatal familial or sporadic insomnia, Gerstmann-straussler-scheinker syndrome, sporadic, genetic, iatrogenic and variant Creutzfeldt-Jakob disease (CJD) and kuru, passed by ritual cannibalism in the force tribe of New Guinea. Animal counterpart are Scrapie in sheep and goats known as (transmissible mink encephalopathy), bovine spongiform encephalopathy (BSE, also known as "mad cow disease"), and chronic wasting disease of mule deer and elk (Moosawi et al., 2009). These diseases have long incubation periods, and cause characteristic spongiform changes, neuronal loss and gliosis without provoking an inflammatory reaction. This leads to death within one year after onset of illness. This misfolding property of Prion proteins is a central event in prion disease. Thus, confers stable changes in biological states that are of great interest biomedical and evolutionary.

1.1 Overview of Prion disease
Prion disease known as transmissible spongiform encephalopathy is a neuro-degenerative disorder, characterized by long incubation period, rapidly progressive and severe neurological dysfunction and specific pathogenical lesion of the CNS. This prion disease is said to be different from other neuro-degenerative disorders, by its transmissibility through inoculation of pathological tissue into healthy recipients (Aucouturier and Carnaud., 2002). The term prion is derived from the phrase "proteinaceous infectious particle. Prions are infectious or pathogenic disease as a result of post-translational modification process whereby a portion of its α-helical and coil structure is refolded into β-sheet rich fibrile (Lysek *et al.*, 2005, Pan *et al.*, 1993). This misfolding and aggregations of these abnormal isoform give rise to highly structured amyloid fibers which are propagated and spread within the body by carrier cells before transferred into the nerve tissue (Burthem *et al*., 2015). Protein misfolding can result as native protein changes their comformations or newly synthesized polypeptide failing to fold properly, thus

exposes the hydrophobic aminoacid chains on the surfaces (interior amino acids) as result become prone to self association. The normal or cellular isoform (PrP^{C}) converted into abnormal scrapies isorform (PrP^{SC}) causes profound changes in the physicochemical properties such as an increase in the β-sheet content, insoluble in many detergents, and resistance to proteolytic digestion. Also, the abnormal PrP^{Sc} isoform has a different secondary and tertiary structure from PrP^{C}, but identical primary sequence. Prions are devoid of nucleic acid or virus-like particles and seem to be composed exclusively of protein. Also, they are resistant to routine physical and chemical sterilization measures (Moosawi *et al*., 2009).

1.1.1 Prion strains

Their exist different prion strains with identical amino acid sequences observed in 1961 by pattison and millson; these include N2a, C_{57}BL, 129 /SV, 139 A, 263 K, 22A-H Yeast sup_{35p} , hyper (HY), RML, ME7-H and drowsy (DY).

These strains differ among themselves in many ways; they may have different incubation periods in a given host, different clinical manifestation, biochemical characteristics such electrophoretic mobility and glycosylation of PrP^{Sc}, or its resistance to detergents and proteases, different histopathological localization and expression in the CNS. However, the difference in prion strain is not the only factor that leads to variation in incubation period of a given host, rather dose of inoculum, route of injection, age and genetic background of the host. This prion inoculation occurs through peritoneal, cutaneous or venous route which leads to lymph node and spleen invasion first, intestinal mucosa and spinal cord before neuro-invasion. Strain properties appear the same upon serial passage in the same host species.

1.2 Normal Funtioning Of Prion Protein

Prion Proteins are formed through instructions from *PRNP* gene of the family of CD molecule, active in neurons of the brain, spinal cord and other tissues (Westergard *et al.,* 2007).There exists different forms of Prion-Proteins (PrP):Cellular Prion Protein (PrP^{C}) and the Scrapie Prion Protein (PrP^{Sc}) . The normal version is often designated PrP^{C} to distinguish it from abnormal forms of the protein, which are generally designated PrP^{Sc}. More prion protein sequence is highly conserved in evolution, which suggests biological importance. Since, alteration of prion protein can play a role in disease process, investigating the biological activity of prion protein is necessary for understanding the pathogenesis of prion disease. According to westergard *et al.,* (2007). The functions of normal prion proteins includes: transport of copper into cells and protection of brain cells (neurons) from injury (neuroprotection); formation and maintaining of synapses, which are the junctions between nerve cells (neurons) where cell-to-cell communication occurs; protection against apoptotic, oxidative stress, and adhesion to the extracellular matrix.

1.3 Prion a Molecular Disease

PrP^{C} is a highly conserved 32 kDa glycophosphotidylinositol anchored sialoglycoprotein of 253 amino acids in human (stahl *et al*., 1987). The first 22 N-terminal amino acid are removed from PrP^{c} after its transport to endoplasmic reticulum, while the last 23 C-terminal amino acid are cleaved off after the addition of glycosylphosphatidylinositol (GPI) anchor, which helps the protein to attach to the outer surface of cell membranes (Imaran and saqib, 2011).The ultimate destination is then the plasma membrane where PrP^{C} can be released by phospholipase or protease treatment. Spectroscopic studies demonstrated that PrP^{C} contains 40% a-helix only that is soluble in detergents, and sensitive to Proteolytic digestion (Westargard *et al*., 2007). In contrast, PrP^{SC} has a high (43% β-sheet content, which correlates with scrapie infectivity (Stahl *et al*., 1993). During infection, PrP^{sc} is thought to derive from PrP^{c} after exposure to the plasma membrane. PrP^{c} can bind to a putative ‘‘protein X’’ that may function as a molecular chaperone in the formation of PrP^{sc}. PrP^{Sc} molecules do not differ from PrP^{C} at the level of an amino acid substitution and also no difference in primary structure rather it seems likely that PrP^{Sc} differs from PrP^{C} in its secondary and tertiary structure and numerous modifications including two N-linked carbohydrate moieties, removal of an amino-terminal signal sequence, and alternative COOH termini (stahl et al., 1993).

2.0 CAUSES OF PRION DISEASE

2.1 Mode of infection

The prion mode of action is very different to bacteria and viruses as they are simply proteins, devoid of any genetic material. Prion disease can be naturally (inherited), artificially (acquired) and sporadically. The large amount of infectivity in the blood of humans and animals occurred naturally and sporadically while the rare cases of human prion disease are acquired. Natural or inherited prion disease occurs mainly through inherited point mutation in PRNP gene resulting to conformational change (without any detectable difference in primary structure) of normal prion protein to abnormal contaminated form. This conformational change could be template directed refolding eg: glutamic acid-200 is replaced by lysine in Familial Jakob Diseases in human, change in codon 102 from proline to leucine in Gerstmann-Sträussler-Scheinker syndrome and aspartic acid-178 is replaced by asparagine in fatal familial insomnia. In the other case, acquired prion disease occur through consumption of contaminated cattle products (BSE) and iatrogenic transmission which are rarely acquired through medical procedures from neurosurgical instrument, transplanted human-derived pituitary hormones, dura mater, corneal graft and blood transfusion eg variant creuzfedlt Jakob disease. (Hunter *et al.,* 2002). Also, the Spontenous /Sporadic mode of infection occurs without evidence of transmission or familial origin eg: Cruetzfeldt-Jacob disease (CJD), fatal insomnia and variably protease-sensitive prionopathy (Imaran and saqib., 2011) . Once a misfolded prion

enters a healthy human or animal through acquired means, the correctly folded protein is converted into disease-associated form (valleron *et al*., 2001). A build up of misfolded prions in the brain causes progressive death of neuron, for which the cure is still in progress. Prion diseases of humans are not transmitted through casual or intimate person to person contact, animal to animal and animal to human.The following diseases are caused by prions in both animals and humans : In animals**:** Scrapie in sheep and goats, Bovine spongiform encephalopathy (BSE) in cattle ("mad cow disease"),Transmissible mink encephalopathy (TME) in mink ,Chronic wasting disease (CWD) in North American cervids (mule deer, white-tailed deer, elk and moose), Feline spongiform encephalopathy in cats an, Exotic ungulate encephalopathy (EUE) in nyala, oryx and greater kudu; In humans**:** Sporadic forms: Sporadic Creutzfeldt-Jakob disease (sCJD), Sporadic Fatal Insomnia (sFI); Genetic forms: Familial Creutzfeldt-Jakob disease (fCJD), Gerstmann-Sträussler-Scheinker syndrome (GSS), Fatal Familial Insomnia (FFI); Acquired forms: Iatrogenic Creutzfeldt-Jakob disease (iCJD),Variant Creutzfeldt-Jakob disease (vCJD) and Kuru. Numerous studies have shown that infectious prions can enter the environment through saliva, feces, urine, blood, or placenta from infected animals, as well as by decaying carcasses (Haley et al., 2009; Maddison et al., 2010; Terry et al., 2011). Research has shown that infectious prions bind tightly to soil and remain infectious for years, indicating that environmental contamination of soil may play a role in TSE spreading (Johnson et al., 2006, ; Seidel et al., 2007).

Table 1: Classification of human prion disease Prion disease are classified into Sporadic, inherited and acquired factor.

Aetiology	Phenotype	Frequence
Sporadic (1–2 per million per annum)	sub-acute myoclonic form and range of atypical multiple distinct prion strains associated with distinct clinicopathological phenotypes (eg:sFFI)	~85%
Inherited Autosomal dominantly inherited conditions; a germline PRNP coding mutations (1 in 100 million population)	Extremely variable: readily mimics familial Alzheimer's disease which as follows Includes GSS, fCJD. and FFI	~10-15%
(3) Acquired (a) Iatrogenic infection with human prions via medical or surgical procedures: human grafts, and contaminated neurosurgical instruments	Iatrogenic CJD: ataxic onset when peripheral infection and	~ 5%,
(b) Exposure to human prions endocannibalism Kuru Unique to small area of Papua New Guinea; major epidemic in 1950s with gradual decline since cessation of cannibalism.		
(c) Enviromental exposure (presumed diatary) to BSE prion strain. Transmission via Blood transfusion and Enviromental prion contamination: grass plants bind prions from contaminated brain and Excreta, Prions from different strains and species remain bound to living plants,Hamsters fed with prion-contaminated plant samples, Stems and leaves from grass plants grown in infected soil.		

2.1.1 Prion Replication and Propagation

According to Brandner *et al*. (1996), neurografting brain tissue from wild-type mice brains revealed that prion protein gene tissue grafts replicated prions with accompanying damage to neurons while nearby PrP-deficient tissue was unharmed. This showed that the main principal of prion replication is the requirement of a host protein which is cellular prion protein (PrP^{C}) (Steele *et al*., 2007).Prions must transit through the lymphoreticular system before invading the central nervous system. The coordinated network cells that support replication and propagation of prion from the sites of penetration to sites of neuroinvasion are the follicular dendritic cells (FDC), dendritic cells (DCs), B-cells and the T-cell and alternatively the macrophages. These agents migrate from a peripheral site of exposure for instance, the digestive tract or skin to the sites of invasion. Here, the involvement of peripheral lymphoid tissue helps in early infectivity of lymphoid tissues and progressive increase of titres well before infectivity in the CNS, accumulation and effect of targeted immune impairments on host susceptibility to peripheral inoculation.FDC have long been demonstrated as major sites of prion accumulation in the germinal center of the spleen, lymph nodes, and mucosa-associated lymphoid tissue following either acquired or natural mode of

contamination (Mabbott *et al*., 1997). FDCs do not migrate widely and the natural history of prion disorders suggests that other cells may be required for the transport of abnormal prion protein from the site of ingestion to lymphoid organ and the central nervous system. Futhermore, FDCs network in germinal center of a healthy animal are strongly decorated with PrP^{c}. This major feature is responsible for their proneness to capture prions and to become infected. Also, DCs can propagate prions directly from the periphery to the CNS in the absence of any additional lymphoid elements and with no need of PrP replication in the sites. The unique migration properties of DCs could be essential for prions spreading to the site of neuroinvesion. Notwithstanding, the real purpose of lymphoidinvasion in the pathogenesis of TSEs are as follows; to transport prions from where they enter to sites of neuroinvasion, to show the necessity for prions to replicate, to reach a critical mass before invading the brain and to show that qualitative modifications of TSE agents occur in the cells of the lymphoidreticular system (Aucouturier and Carnaud., 2002).

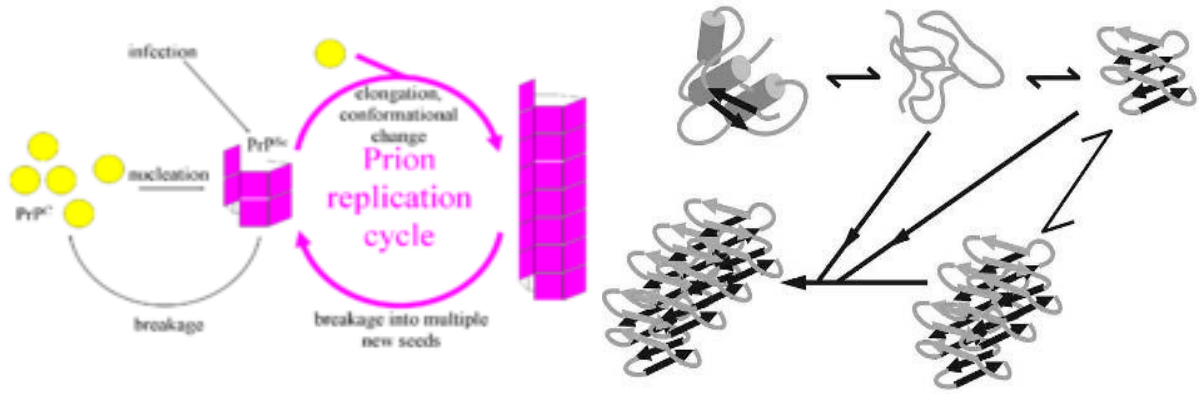

Fig 1: A schematic representation of a prion replication cycle and propagation Sourced: (Wikipedia.org & www.innp.com).

2.1 Symptoms of Prion Protein

These are some challenges experienced from individuals suffering from prion diseases:

(1) Cerebellar signs of CJD may include: (a) Ataxia (failure of muscular coordination) which causes postural and balance problems early in the disease process and as the disease progresses, severe ataxia leads to loss of ability to walk, (b) Movement tremor (involuntary trembling/quivering) such as termination or terminal tremor would be included in CJD signs, however "tremor" alone is not necessarily a cerebellar or CJD sign,(c) Dementia (cognitive decline) is very pronounced over a short period of time (weeks) unlike dementia associated with Alzheimer's disease

(2) Progressive neuropsychiatric disorder: Abnormalities in the nervous system and in mental processes. In the variant form of CJD, the first symptoms are psychiatric and patients experience a progressive neuropsychiatric disorder lasting at least 6 months. In the sporadic form, if neuropsychiatric disorders are present, they usually are concurrent with the physical manifestations of the disease.

(3) Pyramidal signs refer to disorders of the upper motor neuron pathway going from the motor cortex through the brainstem and down to the spinal cord. Pyramidal signs would include things such as:Upper motor neuron weakness such as Hemiplegia (paralysis of one side of the body), Spastic (limb) paralysis / paresis , Presence of Babinski's sign / "upgoing toes" and Clonus (alternate muscular contraction and relaxation in rapid succession).

(4) Extrapyramidal signs refer to disorders of brain structures controlling movement, mainly with reference to the basal ganglia and related structures. The most commonly recognized extrapyramidal signs are those associated with Parkinson's disease. Extrapyramidal signs of CJD may include: Bradykinesia / hypokinesia (slowness of movement), Rigidity (limb or neck) ,Tremor, Postural instability.

(5) Visual Deficits: The visual abnormalities in CJD most commonly are complex visual disturbances, such as hallucinations or cortical blindness, Hemianopsia (defective vision or blindness in half of the visual field), Blindness and Diplopia / double vision.

2.3 Diagnosis

The following tests may help determine whether an individual suffer from this prion disease:

Electroencephalogram (EEG): measures the brain patterns of electrical activity, Brain magnetic resonance imaging (MRI) can detect certain brain changes consistent with CJD and Lumbar puncture (spinal tap) tests: spinal fluid for the presence of certain proteins. Also in analyzes of cerebrospinal fluid we use two methods namely: Two-dimensional electrophoresis which could be used to differentiate between Creuzfeldt Jakob diseases and other neurological disorder and Tonsil biopsy dectecting glycoform which is majorly used to detect vCJD. Other diagnostic tests are as

follows: Nueropathology, Electron microscopic Examination, Immunohistochemistry, western blotting and ELISA.

3.0 Functions of Prion Protein

3.1 Prion Protein in the immune system.

Prion Protein plays a major role in co stimulatory function and activation of immunologic cells such as T-cells that protects the body system against invading micro organism (allangmaran *et al*., 2000).These above functions are achieved by colocalization of cellular prion protein with major histocompatibility complex class II (MHC class II) in immature and mature myeloid dendritic cells. Notwithstanding, prion protein with high affinity copper binding site, wide spread tissue distribution are highly expressed in neurological tissue and cells of the immune system. The myeloid dendritic cells are the immune cells, which are the main reservoir of the normal prion protein. They are derived from the bone-marrow or monocytes of peripherial cells which are readily identified within the circulating cell population area (Roberts *et al*., 2015). In humans, the peripherial B and T-Lymphocytes expresses cellular prion protein at low level while the natural killer cells, platelate and monocytes expresses in high level. An individual with a healthy immune system is more susceptible to prion disease than one that lacks a functional immune system (Bradford et al., 2012). The spread of PrP^{Sc} in an infected host must require the conversion of PrP^{C} to PrP^{Sc}. In mice high titers of infectivity occur in the spleen soon after intraperitoneal inoculation with PrP^{Sc}, and subsequent spread to the CNS can be retarded, though not prevented, by splenectomy. PrP^{Sc} has been detected on FDCs, B cells, and T cells in the lymphoid follicles of mice, as it may be the FDCs have been shown to be required for transmission of PrP^{Sc} in mice. However, splenic infectivity can be restored in PrP^{C} knockout mice using transplanted normal bone marrow, suggesting an importance for a rapidly repopulated bone marrow-derived cell population, and in some mouse models spread of PrP^{Sc} from peripheral tissues to the CNS occurs in the absence of functional FDCs or T lymphocytes (Burthem *et al*., 2015). Furthermore, the immune system actually contributes to pathogenesis by amplifying prion 'load' in lymphoid compartments thereby facilitating efficient neuro invasion.

3.2 Prion Protein in Oxidative Stress

Prion protein especially the PrP^{C} is involved in defense against oxidative stress. This was supported by a review done by Steele and Colleague (2007) where it was stated that the superoxide dismutase (SOD) activity significantly decreased in brain and muscles of prp Kos resulting that any deficiency in PrP will result to a pronounced decrease in SOD activity. According to Martin., (1997) he suggested that copper ions bind to the N-terminal sequences in PrP^{c} molecules. Copper analysis showed that cells lacking PrP^{c} are more sensitive to oxidative stress than wild type cells. Binding to copper is important for the catalytic activity of many enzymes involved in oxidative stress, including superoxide dismutase (Brown *et al*., 1997). It has been postulated that PrP^{c} might act as a "shuttle" for copper ions destined to bind to enzymes that prevent oxidative stress (Brown *et.al.*1997,).

3.3 Prion protein in Neuroscience (Learning and memory)

Memories are stored for long term with the help of prion-like protein (normal prion protein) called CPEB. This memory molecules called CPEB aggregates and maintain synapses that record the memory. Also, persistence of memory is achieved by the growth of new synaptic connections that are maintained by local synthesis at the synapse of the CPEB synaptic proteins (Kandel et al., 2014).When CPEB are not present or inactivated the synapses collapse and the memory fades. Mammals express four CPEB isoforms (CPEB1, CPEB2, CPEB3, and CPEB4; Drisaldi *et al.*, 2015). CPEB3 contains a Q/N-rich domain at its N-terminal and is the mammalian homolog Aplysia of CPEB. According to Floriti *et al*., (2015). Aplysia CPEB, mouse CPEB3 also exists in two conformational states: a soluble and an insoluble and aggregated form. The presence of the N-terminal domain is required for the aggregation of CPEB3 and for the maintenance of long-term memory. Various studies have shown that prion proteins are of great interest: Performance in latent learning and passive avoidance was evaluated using water-finding and step-through tests, respectively. *PrP* deficient mice showed impaired performance in the water-finding test, indicating a disturbance in latent learning, at 23 weeks of age. In the step-through test, although the *PrP* deficient mice showed normal learning ability and short-term memory retention, they evidenced a significant disturbance in long-term memory retention. These results indicate that PrP^{c} is needed for certain types of learning and memory.

3.4 prion protein in sleep regulation

Prion protein plays a role in regulating and promoting sleep continuity. The loss of its normal function as a result of certain mutations in PRNP gene causes fatal familial insomnia (inability to sleep).According to Tobler *et al*. (1996) showed that during a normal light/dark cycle (circadian) the PrP Kos had similar patterns of running wheel activity as controls. However, in constant darkness, wild type mice display a shorter circadian period whereas PrP Kos remarkably maintains a normal period as if still suspended by light. Also, the PrP Kos have more fragmented sleep episode than the controls thus, leads in conclusion that PrP^{c} remains essential in promoting continuity.

4.0 Application of prion protein in biomedical sciences

4.1 Immunointervention

Several attempts have been made towards developing therapeutic interventions to circumvent this prion disease. These interventions are achieved by the following: using compounds that specifically bind PrP^{C}

or PrP^{SC} or potentially by gene silencing of PRNP, adopting the host to block prion conversion or clear abnormal protein and vaccination. However self tolerance to PrP remains a hurdle to vaccination attempts. Several groups have nevertheless started to carryout *in vitro* and *in vivo* studies. These studies have shown that anti-PrP antibodies added to the culture medium could cure infected cell lines by preventing the conversion of PrP^{c} to PrP^{sc} . The mechanism on how the conversion occurs is not fully understood. They could possibly hinder physical contact between the two conformers or prevent the docking of an auxillary cofactor catalyzing transformation. In the other way, it is possible that the antibodies redirect PrP^{C} traffic and isolate the protein in subcellular compartment where conversion cannot take place, as it is inaccessible to PrP^{SC}, or make physiochemical conditions not favorable to conversion. Also, with doubtful *in vivo* relevance it is assumed that the antibodies enhance selective pressure against infected cells, allowing uninfected cell to over-grow. However, strategies apart from anti-PrP immunity have to be developed for breaking tolerance and agonizing prion propagation in infected hosts.

4.2 Genetic Engineering

Production of **PrP^{C}**-deficient cattle produced by a Sequential Gene Targeting System. After 20 months of age, the cattle were clinically, physiologically, histopathologically, immunologically and reproductively normal (Richt *et al.*,2007). This **PrP^{C}**-deficient cattle may be useful model for prion research in human disease, and provide product free from prion protein.

Tobler and Colleagues(1996) showed that in constant darkness, wild-type mice display a shorter circadian period (as normally their nature) while the prion deficit mice remarkably display nearly complete inability to sleep.

4.3 Drug development

Drug development is generally based around the desire to up regulate or down regulate a specific activity implicated in disease state. A substantial development has been made in providing potential therapeutic strategy to reverse the comformational changes seen in PrP, either by degrading pre-existing scrapie prion or inhibiting the production (Mccarthay *et al*., 2013). For example, the treatment of prion diseases can be achieved by use of anti-prion protein dendrimers known as maltose modified poly(propylene imine) generation five dendrimers (mPPIg5).This is a synthetic macromolecules with ability of eliminating PrP^{sc} in both in vivo and invitro settings, posses neutral surface on the outer shell with low cytotoxicity and to cross the blood brain barrier (Klajnert *et a*l.,2008). Also P-L-Lysine is an anti-agent used in targeting plasminogen (cellular cofactor) that stimulates PrP conversion.

5.0 CONCLUSION

We have shown from the study that prion protein (in its abnormal form) plays a role in pathogenicity of prion disease such as FFI, GSS, Cerebral angiopathy and CJD. Also, how effective targeting of prion protein can be useful in biomedical sciences (drug design).

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests regarding the publication of this paper.

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