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# Amyloid, A Jekyll and Hyde Molecule, Induces Neuronal Decline and Cognitive Dysfunction but is also a Unique Molecular Template used in Nano-Electronics, Light Capture Photovoltaics, Biosensors and in Neuromorphic Computing

**Margaret M Smith[1,2] and James Melrose[1,3,4*]**

[1]*Raymond Purves Bone and Joint Research Laboratory, Kolling Institute, St. Leonards, NSW 2065, Australia*

[2]*Arthropharm/Sylvan Scientific Pty Ltd, Bondi Junction,Sydney, NSW 2022, Australia*

[3]*School of Medical Sciences, Faculty of Medicine and Health, The University of Sydney at Royal North Shore Hospital, St. Leonards, NSW 2065, Australia*

[4]*Graduate School of Biomedical Engineering, Faculty of Engineering, University of New South Wales, Sydney, NSW 2052, Australia*

**[*]Corresponding Author**

Prof. James Melrose, Raymond Purves Laboratory,Level 10, Kolling Institute of Medical Research B6,Royal North Shore Hospital, St. Leonards, NSW 2065, Australia.

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**Abstract**

*This study, examined the self-assembly of amyloid peptides β-40 or β-42 to form neurotoxic plaque and neurofibrillary tangles, neuronal dysfunction and diseases of cognitive decline (e.g. Alzheimer's, Parkinson's and Huntington's disease). However, not all amyloids are toxic, functional amyloids are non-toxic ordered structures that have been used in tissue engineering applications. Long and hollow amyloid fibres and flattened tube and spiral ribbon-like structures are diverse self-assembling structures that have found application in the development of next generation computers and biosensors, ultracapacitors, memristors, actuators, molecular switches, artificial synapses and in photoelectric photon capture light harvesting technologies in nano-photoelectronics, photovoltaics and photo-pharmacological drug regulation. Hybrid Aβ(16–22)-α-synuclein amyloid fibrils also exhibits light-harvesting and electron-transfer properties. Engineered amyloid assemblies are thus driving futuristic developments in nano-technology. With a better understanding of amyloid fibril assembly clues are also being uncovered as to how the toxic build up of amyloid deposits in brain tissues and resultant diseases of cognitive decline may be prevented. The elevated incidence of neurological diseases in the ageing general global population, points to a clear need to find a remedy for these debilitating conditions.*

**Keywords:** Amyloid Fibrils, Nano-Electronics, Memristors, Bio-Sensors, Actuators, Molecular Switches, Photovoltaics, Artificial Synapses, Functional Amyloids, Neuromorphic Computing

## 1. Introduction

The aim of this study was to review the roles of amyloid protein aggregates in neurodegeneration and contrast this with beneficial aspects of its structural organization which have found application in nanobiology in several innovative areas of tissue engineering.

### 1.1. Definition of Amyloid

Amyloid is an insoluble protein aggregate formed from misfolded proteins containing β-pleated sheets and can be stained with Congo red, exhibiting a characteristic green-yellow birefringence under polarized light [1-6]. These misfolded proteins exhibit specific features that facilitate auto-assembly of ordered repeat structures in insoluble amyloid deposits [2-4]. Aβ peptides released from

appican (APP) in brain tissues are assembled into dimers, trimers, oligomers and distinctive fibrillar structures. Amyloid deposits occur in many tissues in the human body other than the brain, leading to organ and tissue dysfunction [7,8]. Amyloid refers to the insoluble protein aggregates that accumulate in the aging brain in diseases of cognitive decline such as Alzheimer's (AD) and Parkinson's (PD). Amyloid can arise from over 36 proteins in various parts of the body in different human diseases [7-9]. Amyloid deposits in the brain display distinctive morphologies formed by β-40 or β-42 peptides. Amyloid plaques are visible by light microscopy using a variety of staining procedures, including silver stains, Congo red, Thioflavin, cresyl violet and periodic acid-Schiff (PAS) procedures which stain different components of amyloid plaques, with variable sensitivity [7-10]. Immunolocalization of amyloid plaques with specific antibodies to Aβ epitopes and to other amyloid-associated components has also been used to visualize amyloid formations [11]. Examination of human autopsy samples and tissues from experimental models of AD have identified the biochemical, cytological, and inflammatory processes involved in the generation of these amyloid plaques [7]. Amyloid fibrils are diverse molecular structures, ENTAIL and PARROT are two information systems developed for the classification of amyloid fibril biodiversity [12-14]. Ultrasensitive, new generation amyloid biosensors have also been developed for the detection of amyloid peptides in tissues, plasma and cerebrospinal fluid [15-22]. These show amyloid plaque formation may be linked to trauma of the brain microvascular and immune system [23]. Chronic brain inflammation and immune dysfunction may accelerate amyloid deposition [24,25].

Aβ40 and Aβ42 oligomers of Aβ peptides in AD only differ by two C-terminal residues, however Aβ42 aggregates assemble much faster than Aβ40 structures and is more toxic, forming pore-like structures in cell membranes [26-28]. The additional C-terminal residues in Aβ42 allow electrostatic interactions which stabilize the β-hairpin promoting dimer formation and oligomerization through intermolecular β-bridge formation [29,30]. A combination of hydrophobic and charged amino acids in Aβ peptides contribute to aggregate formation; glycosaminoglycans (GAGs) also act at the earliest stages of fibril formation, namely during amyloid-beta nucleation [31]. The amyloid plaques in Alzheimer's brains consist mainly of Aβ42 and some plaques contain only Aβ42, even though Aβ40 concentrations in cerebrospinal fluids is several-fold higher than Aβ42 in the brain.

### 1.2. Amyloid Aggregates Promote Neurodegeneration and Cognitive Decline, However Functional Amyloids are Non-Toxic and have Beneficial Properties

The amyloid cascade hypothesis proposes that dysfunctional metabolism of amyloid precursor protein (APP) initiates the pathogenesis of AD [32]. This results in aggregation of Aβ, formation of neuritic plaques which cause pathological changes through formation of neurofibrillary tangles that disrupt normal synaptic connections and compromised neuronal synaptic activity, neuronal cell death, cognition, memory problems and development of dementia and cognitive decline in AD and PD [32,33-36]. However, not all amyloids are toxic nor do they disrupt normal organ functions [37]. So-called functional amyloids have beneficial properties through unique structural features and have been receiving considerable attention in tissue engineering applications in highly innovative areas of nanobiology [38]. From an engineering perspective, the self-assembling regular and tight packing structure of amyloids provides strength, and are useful molecular templates amenable to structural modification and application in tissue engineering. Such self-assembled networks are highly suited to biomaterial scaffold developments [39-42]. Amyloids are some of the strongest protein structures ever identified in nature [43,44]. Spider-web drag-line silk is composed of repeat peptide modules with a high β-sheet content on a weight for weight basis web silk has a strength exceeding that of high quality structural steel [45-47].

## 2. Amyloid Precursor Protein and Its Bioactive Fragments

Appican is a transmembrane chondroitin sulfate-proteoglycan precursor, containing an embedded amyloid precursor protein (APP) module within its core protein and is a 110-130kDa type 1 transmembrane glycoprotein [48,49]. APP is also a component of APP-like proteins 1 and 2 (APLP-1, 2) and these constitute a family of mammalian membrane proteins. However, unlike APP, the APLPs lack the Aβ sequence, and do not give rise to the AD [50]. APP and APLP regulate synaptic transmission, plasticity, and calcium homeostasis, and are important cell messengers and regulators of neural activity in neurotransduction and are neuroprotective, soluble sAPPα counteracts the deleterious effects of the APP-derived Aβ 40 and 42 peptides that lead to amyloid deposition [51-54].

### 2.1. The Enigmatic and Perplexing Story of APP Processing in Brain Tissues

APP is a type I transmembrane glycoprotein notorious for its involvement in the pathogenesis of AD through βA40 and βA42 peptides generated by an amyloidogenic protease pathway in the brain involving β-secretase (BACE-1, β-site APP cleaving enzyme, mepapsin 2) and γ-secretase [55]. βA40 and βA42 peptides self-assemble to form insoluble plaques and neurofibrillary tangles which detrimentally impact on synaptic function, neuron viability and cognitive processes in the brain, leading to dementia [56-58]. APP, however, is also processed by α-secretase via a non-amyloidogenic pathway, generating the soluble amyloid precursor sAPPα peptide [55]. sAPPα promotes neuroprotection, synaptic plasticity, memory formation, neurogenesis, neuritogenesis, and reduces amyloid and tau pathology [59-61]. Several studies also suggest that sAPPα regulates the trafficking of APP and its processing by proteases and may decrease the risk of developing AD [62]. Aβ monomers share similar properties to sAPPα however, when self-assembled into Aβ oligomers, they become neurotoxic [61]. The precise physiological functions of full length APP and its proteolytic fragments is thus a complex story, Aβ production is not deleterious per se but when assembled into oligomers βA is toxic [63-66].

## 3. Identification of Proteins with Amyloid Aggregative Potential

The propensity of a peptide to form an amyloid fibril is dependent on factors such as polypeptide charge, sequence, hydrophobicity and peptide secondary structure and not by a specific "amyloid" amino-acid sequence per se [67-73]. Amyloidogenic peptides self-assemble into repetitive stacked structures that attract further proteins to propagate fibril formation [74]. Predictive algorithms have been developed to assess peptides that display a propensity to form amyloid fibrils in web-based software that predicts aggregation-prone protein sequences [75-77]. AMYLPRED2 (http://biophysics.biol.uoa.gr/AMYLPRED2) is a public web tool for the prediction of amyloidogenic determinants in 'aggregation-prone' peptide sequences within proteins [76]. Development of methods to produce controlled amyloid fibrils in vitro is an important innovation and opens the door for the design of new biomaterials exploiting the superior structural properties of amyloid fibrils and the inherent diversity of peptide sequences [78]. A number of bioinformatics and computational studies have examined the peptide sequences of amyloid proteins to better understand the aggregation process and to determine peptide sequences that initiate and propagate assembly of fibrillar material [79-97].

## 4. The Attributes of Functional Amyloids

In nature, amyloids have a range of functions across mammals, bacteria, fungi and marine organisms in beneficial physiological processes such as regulation of pigment formation, storage and controlled release of peptide hormones, memory, fertilization of oocytes by sperm, antimicrobial responses, regulated necrosis, cellular responses to stress and powerful adhesive properties [98-103]. Naturally occurring amyloids are also associated with a number of disease processes (Table 1A). Amyloid fibrils are found in barnacle and mussel bioadhesives with powerful adhesive properties that have inspired the development of tissue adhesives of potential application in highly specialized surgical procedures [104]. The unique architectural assembly processes and exceptional mechanical strength of amyloid fibrils makes these structures of interest in innovative applications in organic micro-circuitry in nano-electronics, in the development of actuators, molecular switches, memristors and microcomputers [105-114]. The low power requirements and ultra-high speed signal transmittance capability of memristors is revolutionising development of neuromorphic circuits that are used in synthetic neural networks, switching devices and low-power sensors in microcomputing [115-117]. Nano-wires prepared in hollow amyloid fibril casting templates have been used in bio-sensing, optoelectronics and photovoltaics and show potential in the development of synthetic synapses in highly innovative bio-nanotechnological applications [118-120]. Amyloid fibrils have found a number of applications in tissue engineering (Table 1B) [121]. Photobiomodulation therapy, using near infra-red 700-1400 nm low-level laser phototherapy, reduces the deposition of βA in the AD brain, ameliorating neuroinflammation and oxidant stress, supporting mitochondrial homeostasis to elicit a healing or regenerative response 122. The surface chemistry of engineered amyloid fibrils can be modified depending on the amino acids used and bacterial expression systems used in their assembly; fibrils can also be coated with chemicals that modify their responsiveness to specific chemical microenvironments and their light capture properties [123-125]. Amyloid fibrils can also be coated with gold nanomaterials modified with peptides or other chemicals. Gold is chemically inert but highly conductive and, when modified with additional components, can fine-tune the surface interactivity of amyloid fibrils. Some chemicals (PEDOT-S, Poly(3,4-ethylenedioxythiophene) polystyrene sulfonate; PPF, luminescent polyfluorene; APFO, Ammonium pentadecafluorooctanoate) can improve the light harvesting and electron transfer properties of fibrils to improve the efficiency of photobiomodulation therapy [126]. Amyloid fibrils have UV–visible–near-infrared optical light capture properties that have been applied in pharmaceutical healthcare applications [127,128]. Light capture technologies can be used to activate photoswitchable drugs in the regulation of neural pain generation. Systemic pharmacotherapeutic neuroinhibitory medications like antiseizure drugs, used to treat epilepsy and neuropathic pain also have unwanted side-effects, there is an urgent need to develop pain alleviating drugs that do not display such unwanted side-effects. Photopharmacology uses light-activated drugs illuminated locally at specific tissue target sites to provide specificity of action. Photoswitchable derivatives (carbazopine-1, carbadiazocine) of the antiseizure drug carbamazepine (tegretol) are used to treat tonic-clonic seizures and bipolar disorder and to relieve intense, stabbing, electric shock-like pain caused by trigeminal neuralgia (douloureux, Fothergill disease). Light emitting semi-conductor diodes (LEDs) that deliver light of 400-590nm can be used to activate carbadiazocine, the photo-switched drug has been shown to provide specific analgesic mechanical and thermal pain relief profiles in a rat model of neuropathic pain [129]. Amyloid fibril optical biosensors and smart Trojan-horse technology has improved tissue light delivery precision to photoactivate pain alleviating drugs in photomedicine and have also been examined for the eradication of □-amyloid fibril deposition in tissues [128,130-135].

| Disease process | Amyloid precursor protein | Amyloid monomer |
|---|---|---|
| AD | APP | Aβ |
| Atrial amyloidosis | Atrial natriuritic protein | Amyloid ATF |
| Spongiform encephalopathy | Prion protein PrPc | PrPsc |
| Primary systemic amyloidosis | Ig L and H chains | AL, AH |
| Secondary systemic amyloidosis | Apo serum amyloid A | SAA |
| Familial amyloid polyneuropathy I | Transthyretin | ATTR |
| Familial amyloid polyneuropathy II | ApoA | AApoA |
| Haemodialysis amyloidosis | β2-microglobulin | Aαβ2M |
| Hereditary systemic amyloidosis | Lysozyme | ALys |
| Diabetes type II | ProIAPP | APP/amylin |
| Insulin injection amyloidosis | Insulin | AIns |
| Cerebral amyloid angiopathy | Cystatin C | ACys |
| Finnish hereditary systemic amyloidosis | Gelsolin | AGel |
| Age associated pituitary prolactinomas | Prolactin | APro |
| Familial amyloidosis | Fibrinogen αA chain | AFib |

**Table 1 A: Naturally occurring amyloids associated with specific disease processes [9,38,136]**

| Amyloid | Applications | Reference |
|---|---|---|
| Transthyretin peptide (105-115) | Cell adhesive properties | 137 |
| Gonadotropin releasing hormone | Long acting peptide/protein drug depot/delivery | 138 |
| *Candida albicans* Killer decapeptide | Auto-delivery of therapeutic peptides | 139 |
| Yeast Sup35p NM prion domain | Nanowire development | 140 |
| α-synuclein fibrils | Enzyme entrapment hydrogel | 141 |
| insulin fibril semi-conductor oligoelectrolyte | Optoelectronic nanowire assembly | 142 |
| PPF coated Insulin fibrils | Polymer light emitting diode fibrils | 143 |
| APFO-12 coated Insulin fibrils | Optical nanowires | 144 |
| PEDOT-S coated Insulin fibrils | Conductive nanowires | 145 |
| β2-microglobulin | Nanoporous cell support matrix | 146 |

**Table 1B: Functional Amyloids used in bio-nanotechnology applications**
**Abbreviations:** PEDOT-S, Poly(3,4-ethylenedioxythiophene) polystyrene sulfonate; PPF, luminescent polyfluorene; APFO, Ammonium pentadecafluorooctanoate.

## 5. Amyloid Fibrils as Building Blocks for Innovative Biomaterials

Protein assemblies based on amyloid core structures display diverse biological functions with potential application in futuristic self-assembling biomaterials [41,126,136,147-150]. The roles of amyloid fibrils in a range of human diseases of cognitive decline are well known, however, so-called functional amyloids have low toxicity and beneficial properties in a range of physiologic processes (eg, long-term memory formation, gradual release of stored peptide hormones) and roles in cell fate and cell-signalling cascades in mammals, bacteria and fungi [74,151-154]. Functional amyloids display many features that make them attractive candidates for tissue engineering forming self-assembled regularly organised structures with impressive biophysical properties in extended straight filaments, tapes, twisted ribbons, and hollow tubes [45,121,155]. Fibrils are typically 5–20 nm in diameter with a length in the micron size range irrespective of the many different proteins from which they are assembled. Fibrillar assembly occurs over a wide range of temperature, pH and solvent conditions providing flexibility in the procedures that may be utilised in the laboratory in engineering applications to assemble fibrils. Introduction of point mutations in fibrillar structures can be used to design fibrils with variable chemical surface and electrostatic characteristics with diverse binding properties and unique environmental responsiveness [150,156]. Amyloid fibrils possess a Young's Modulus in the GPa scale and a strength comparable to steel. High-resolution data gathered from X-ray diffraction and

NMR images, demonstrate the presence of extensive cross β-sheet structure within the core of the fibril which forms an expansive hydrogen-bonding network spanning the length of the fibril. It is this cooperative intermolecular hydrogen-bonding network in the fibril that confers stability and unique material properties [43,157].

Hollow ~100 nm nanotubes have been developed using self-assembly of amyloid-like fibrillar structures to form templates within which silver nanowires can be cast of 10-nm width and lengths ranging from 60 to 100 microns with the central nanowire recovered by proteolytic dissolution of the peptide shell [109,110,158]. Multi-layered co-axial nano-wire assemblies have also been prepared decorated on the exterior of the nanowire with metallic gold, nanowire structures have been confirmed by TEM and energy dispersive X-ray analysis [108]. Gold or silver nanowires with widths of ~100 nm have demonstrated high conductivities and low resistances (~80 Ω), their use in the microcircuitry of nano-electronics have revolutionised development of next generation computers and biosensors [159]. Ultracapacitors have also been developed using an external magnetic field to orient horizontal and vertical arrangements of nanotubes which display enhanced capacitance relative to carbon and carbon nanotube–modified electrodes [107].

### 5.1. Amyloid Cell Attachment Matrices and Hydrogels for Cell Delivery in Tissue Repair Strategies

The ECM has important instructive properties over cellular activity. Instructive communication between the cells and ECM is encoded in peptide epitopes of structural and signaling components that act as molecular directors of cellular activity [160]. Peptide epitopes can be incorporated into synthetic biomatrices to mimic the specific communication that occurs between cells and tissues to control cell adhesion, differentiation, immunomodulation and ECM turnover to achieve tissue homeostasis. Self-assembled amyloid peptide biomatrices have been prepared with RGD motifs to improve cellular attachment [161]. Lysozyme amyloid micronetworks support chondrocyte viability and ECM deposition, while α-synuclein and β-lactoglobulin matrices maintain cell viability [160]. Synthetic amyloid biomatrices with specific added proteins hold promise in cartilage regeneration [162]. Amyloid scaffolds represent versatile biomaterials for cell adhesion and tissue engineering applications [41].

In tissues, amyloid fibrils also promote neural proliferation and neurite outgrowth through interaction with ECM components [65,163]. Amyloid fibril 3D scaffolds have been used to culture neurons and used to develop a model of AD [164]. Amyloid fibril bioscaffolds have been used to culture neural progenitor cells to assess if an Aββ sheet environment could be used to guide differentiation of cultured neural progenitor cells simulating conditions found in brain tissues in which amyloid deposition was evident producing neural progenitor cells of a phenotype evident in amyloid containing AD tissues [165].

Amyloid fibril hydrogels have also been prepared and shown to be suitable as cell delivery vehicles for cultured stem cells which have undergone cellular differentiation [166,167]. Such hydrogels are smart materials capable of transitioning to altered rheological properties in response to spatiotemporal changes in temperature, pH, ionic strength, and external stresses and are also suitable for drug delivery and stem cells in regenerative procedures [137,168].

### 5.2. Application of Amyloid Fibrils in Nanobiology and Organic Microelectronics

Amyloid fibrils have found application in photoelectric and light harvesting technologies [169]. A peptide fragment of transerythritin (TTR 105-115) spontaneously forms highly aligned uniform fibrils in which fluors can be incorporated with little disruption in fibril structure to provide an amyloid fibril with the ability to capture photons and harvest light [170]. Aβ (16–22)-α-synuclein hybridised amyloid fibrils also exhibit light-harvesting and electron-transfer properties [171].

While naturally occurring amyloids are robust self-assembled nanometer-sized fibril biomaterials, it is now possible using in-vitro methods to assemble large 10-20 μm diameter amyloid fibers several mm in length [172]. Using a short, hydrophobic director α-helical template peptide and mixtures of peptides it is possible to self-assemble large amyloid fibers, encoded by micron-sized self-assembled structures at the genetic level, with tailored rectangular or cylindrical cross-sectional morphologies and robust material properties (modulus 0.1-2.5 GPa) [173,174]. A template peptide expressed in E. coli has been used to grow customized 200-500 nm amyloid fibrils and 7-20 μm wide fibers for tissue engineering.

### 5.3. Amyloid Fibrillar Assemblies and Neuromorphic Computing

Quantum computers offer the computational power required to drive neuromorphic hardware in neural network dynamic simulations [175]. Machine learning and artificial intelligence algorithms running on neuromorphic hardware by quantum computers are being developed to assist in data analysis in artificial synapse modular supercomputing developments. Self-assembling amyloid fibrillar structures can be modeled to provide neuromorphic hardware due to varied fibril surface chemistry and their responsiveness to specific electrochemical microenvironments. This may be useful in the development of electrochemical random-access memory using ionic neurotransistors, leading to neuromorphic computing networks that drive sensory intelligent perception systems [176,177].

### 5.4. HS-Amyloid Interactions in Pathological Neuronal Tissue

While deposition of amyloid as neuritic plaques and fibrillary tangles in AD is a self-assembly process an ongoing debate over the last 30 years over whether HSPGs also have roles to play in amyloid aggregation has finally been resolved and it is now accepted that HSPGs also promote the amyloid aggregation process and this affects the functional status of brain tissues [178-180]. HS has multiple roles in the regulation of amyloidogenesis, a range of synthetic HS oligosaccharides have been prepared to examine amyloid-HS interactions [181-185]. HS from porcine

mucosa has also been shown to promote amyloid-beta clearance in APP/PS1 mice alleviating the pathological features of AD in the mouse [186]. Brain HSPGs are differentially expressed in AD and a HS code has been established for neurodegenerative changes that accompany amyloid deposition [187,188]. Dystroglycan-HSPG interactions also regulate synaptic plasticity and specificity maintaining normal neuronal functional activity [189]. A further HS code has been shown to independently regulate synuclein aggregation dynamics [190]. 6-O-Phosphorylated HS oligosaccharides have also been synthesized and shown to inhibit amyloid β aggregation suggesting the charge status of GAGs are important in such regulatory processes [191]. KS is another highly charged instructive GAG in neuronal tissues and has neuroregulatory instructive properties however it is not known if it regulates amyloid aggregative processes or specifically regulates neuronal activity in pathological tissues in AD [192-194].

GAGs have been proposed as attractive platforms for energy devices and flexible electronics and may be particularly relevant to the electro-responsive neuron [195]. A range of proteoglycans and hyaluronan organize the neuronal micro-environment ensuring that ion fluxes, gradients and micro-niches are maintained in brain tissues ensuring optimal neuronal activity and viability [196,197].

## 6. Application of Engineered Amyloid Polymers in Biomedicine

A number of studies have reviewed the diverse range of biomedical applications that have been developed using functional amyloids in biomedicine [198-201]. These applications range from development of cell-culture bioscaffolds and hydrogels for tissue engineering, real-time bidirectional control systems between living brains and actuators of motor and sensory neuromorphic drug delivery systems, immune therapies, biosensor development and Aβ bio-imaging applications, anti-cancer therapies, photopharmacology, light-capture photovoltaics, nano-electronics, nano-photoelectronics, ultracapacitators, memristors, artificial synapses, molecular switches and implantable neural communication interface technologies [198-201].

## 7. Concluding Remarks and Future Studies

This review has illustrated the toxic features of amyloid plaques and neurotangles in brain tissues which lead to neurodegeneration, impaired neuron synaptic function and consequential diseases of cognitive decline. The beneficial properties of functionalamyloids are also reviewed and engineering applications that have been developed using the amyloid fibril as a molecular template which can be manipulated in a number of innovative applications in significant advancements in nano-technology. These have made important contributions to neuro-signaling in neural repair strategies and in areas of bio-regulation using nano-electronics. Development of biosensors, actuators, ultracapacitors, memristors, molecular switches and next generation micro-computing technologies are examples of these innovative applications that have been applied in bioregulation. The high conductance of nano-wires cast in hollow amyloid fibril molecular templates, low resistance and ultra-high signaling capability of such structures makes them particularly useful in nano-electronic applications. Furthermore, engineered amyloid fibril assemblies have also found application in photoelectric and photon capture light harvesting technologies of application in innovative nano-photoelectronics and photovoltaic applications which promise to revolutionise specific areas of optical neuro-regulatory processes. The application of AI and quantum computer methodologies in brain-interface technologies offers particularly exciting possibilities in the improvement of real-time bidirectional control systems between living brains and actuators in motor and sensory neuromorphic applications and have had notable clinical success in the treatment of paralyzed patients' and expanded the mobility of disabled patients [202]. We have entered an exciting era in bioregulation of neuroregulatory processes.

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