

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Modeling Amyloid Diseases in Fruit Fly *Drosophila Melanogaster*

Svetlana Sarantseva¹ and Alexander Schwarzman^{1,2}

¹Petersburg Nuclear Physics Institute, Russian Academy of Sciences

²Institute for Experimental Medicine, Russian Academy of Medical Sciences
Russia

1. Introduction

Amyloidoses are a heterogeneous group of diverse etiology diseases. They are characterized by an endogenous production of abnormal proteins called amyloid proteins, which are not hydrosoluble, form depots in various organs and cause functional dysfunctions [Westermarck et al., 2007]. Despite of their different structures, these proteins are probably generated by a common pathological pathway. Twenty-seven such proteins have been identified as amyloid precursors in humans [Sipe et al., 2010]. However, the question how and why these proteins form aggregates and cause disease is not still completely clear. A wide range of common neurodegenerative diseases is associated with amyloidosis such as Alzheimer's disease and Creutzfeldt-Jakob disease, as well as non-neuropathic diseases, such as senile systemic amyloidosis and type II diabetes. At present, there is not an effective treatment to prevent these amyloid diseases.

To understand the pathogenesis and to develop novel therapeutic strategies, it is crucial to generate animal models of amyloid diseases in genetically tractable organisms. During the last decades, the genetically amenable fruit fly *Drosophila melanogaster* was established as a valuable model system for the study of variety of human neurodegenerative disorders including Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis and familial amyloidotic polyneuropathy [Bilen & Bonini., 2005; Lu & Vogel., 2009]. The advantages of using the *Drosophila* model are that flies have a short lifespan, small size, large number of individuals and simplicity in genetic manipulation [Hirth, 2010]. In addition, *Drosophila* represents a useful model for screening and testing chemical compounds. Moreover, *Drosophila* is an ideal model for screening genetic modifiers of pathogenic process due to their potential to prevent or ameliorate the disease [Marsh & Thompson., 2006].

In this review we will summarize recent progress in developing of fly models for amyloid disease. We address the following issues: (1) creating models of human amyloidosis in *Drosophila* (Alzheimer' disease, prion disease, senile systemic amyloidosis, familial amyloidotic polyneuropathy) and (2) screening of chemical and peptide compounds, as well as modifier genes of protein toxicity in the fly model.

2. Advantages in using *Drosophila melanogaster* to model amyloid diseases

One of the most interesting approaches to research of genetic forms of human diseases is their modeling on fruit fly *Drosophila melanogaster*. For these purposes two basic experimental approaches are used: an expression in *Drosophila* of human genes playing the role in development of diseases, and studying of own genes of *Drosophila*, orthologs of human genes involved in development of diseases [Bier, 2005]. The recent sequencing of the human and *Drosophila* genome has shown that more than 50% of genes of *Drosophila melanogaster* have homologs in humans, and at the same time not less than 60%-70% of genes of human hereditary diseases have the *Drosophila* counterparts [Fortini, 2000; Reiter, 2001]. Therefore, when acting with various models of diseases on *Drosophila* direct research of mutant protein can characterize substantially its participation in a pathogenesis of human disease. Moreover, use of transgenic technology allows to create the strains carrying the human genes and to use them for modulation of concrete physiological mechanisms. On the other hand, genetic experiments with gene knockout can be a basis for definition of unknown cellular protein functions involved in the development of pathological process.

Well-established techniques on the *Drosophila* [Rubin & Spradling, 1982] allows receiving transgenic flies not only according to the certain gene, but also to define an expression of this gene in tissues at various stages of an ontogenesis of the *Drosophila*, due to binary system UAS-GAL4 [Brand & Perrimon, 1993]. The system imported from yeast consists of two independent strains one of which carries an investigated gene under promoter UAS control (Upstream Activating Sequence), and the second strain contains its transcription activator – transcription factor GAL4. For the induction of transgenic expression, UAS strain is crossed to the strain expressing GAL4 under control of the endogenous or specially designed promoter that leads to the expression of investigated gene in tissues where GAL4 expresses. Hundreds of different activator-expressing strains have been generated by the *Drosophila* community and are available to other investigators.

Temperature- sensitive character of transgenic expression in UAS-GAL4 system has been used for creation of temporal and regional gene expression targeting (TARGET) [McGuire, 2003]. TARGET system is based on ability of yeast protein GAL80 to suppress the GAL4 expression. Joint expression of UAS-GAL4 strain and temperature-sensitive allele Gal80^{TS} [Matsumoto, 1978], under tubulin 1 α promoter control leads to the greatest suppression of GAL4 expression at 19°C and synthesis depressions of this protein at 30°C.

The other approach for the direct temporary gene expression by using UAS-GAL4 system is based on creation of hormone-inducible chimeric GAL4 variants: Gal4-estrogen receptor [Han, 2000] and GAL4-progesterone receptor (Gene Switch) [Nicholson, 2008; Osterwalder, 2001; Roman, 2001]. The transgenic expression is controlled with addition of ligands in food of flies or larvae during certain time period that allows excluding deleterious effects of the early expression of transgene. However, it imposes restriction on the use of these approaches on embryonal and pupal development stages [Elliott & Brand, 2008].

The method of insertional mutagenesis has been developed on *Drosophila melanogaster* and became widely used, based on application of mobile genetic elements (ME). ME represent the DNA segments capable to independent transpositions inside the genome. The share of mobile elements in human and mammal genome can reach 40% of the nuclear DNA [Kazazian, 2004]. The quantity of copies of mobile elements from various families changes

from one to several hundreds. ME insertion can essentially change the character of gene expression, and it has become the cause for wide ME application in creation of regulated tissue specific expression vectors [Enerly et al., 2002; Rorth P., 1996; Staudt et al., 2005]. The largest extension in *Drosophila* researches belongs to vectors, framed on the basis of mobile P-element [Adams & Sekelsky, 2002; Bellen et al., 2004]; however property of the P-element to be built in only certain genome sites, limits the mutagenesis in the whole genome. Therefore now approaches with use of other mobile elements preferring insertion sites distinct from the P-element, in particular, *hobo* [Huet et al., 20002; Myrick et al., 2009; Smith et al., 1993] and *Minos* [Metaxakis et al., 2005], are developed.

It is necessary to notice that use of *Drosophila* models allows avoiding such restrictions arising in action with human material, as incomplete family pedigrees, genetic heterogeneity of population, duration of the sampling. At the same time, fundamental aspects of cellular biology, such as regulation of gene expression, membrane transport, cell signaling, synaptogenesis, cellular death, neurotransmitter systems are similar enough in humans and *Drosophila* [Sang & Jackson, 2005].

3. *Drosophila* models of Alzheimer's amyloidosis

Alzheimer's disease (AD) is the most frequent reason of a dementia in elderly and senile age [Davis and Samuels, 1998]. Clinically, AD manifests as a gradual decline of cognitive functions such as learning and memory, which significantly correlates with synaptic loss. The main neuropathological features of AD are well known and characterized by the accumulation of aggregated phosphorylated tau in neurofibrillary tangles (NFTs) and amyloid beta peptide (A β) in senile amyloid plaques. A β is the peptide with 39 - 42 *amino acid*, a product of the proteolytic processing of the big transmembrane protein which has received a name of Amyloid Precursor Protein (APP). Normally, A β in nanomolar quantities is found out in the blood flow and cerebrospinal fluid; however, according to modern representations, accumulation of toxic intermediates of amyloid fibril in AD brain is the central link in all neuropathological processes, including dysfunction of synapses, neurodegeneration, neuron loss and dementia development [De Strooper & Annaert, 2001; Hardy & Selkoe, 2002; Selkoe, 1998]. The appreciable part of works specifies that such intermediates may be soluble oligomers of A β [Walh & Selkoe, 2004].

Different membrane proteases known as alpha, beta (BACE) and gamma-secretases, are involved in proteolytic APP processing. The coordinated action of β - and γ -secretases results in the formation of A β . γ -secretase represents the protein complex, in which basic component are transmembrane proteins presenilin 1 (PSN1) or presenilin 2 (PSN2) [De Strooper & Annaert, 2000]. All known familial AD forms are caused by mutations in *APP*, *PSN1*, *PSN2* genes [Selkoe, 1999]. There are a fly homologue of presenilin genes (*Psn*) [Ye & Fortini, 1998] and homologue of *APP* gene (*Appl*) [Luo et al., 1990] in *Drosophila melanogaster* genome.

Appl is characterized by high degree of homology with APP, it is exposed to similar proteolytic processing, but it lacks the A β peptide region and its processing does not lead to neurotoxic effects [Luo et al., 1990; Rosen et al., 1989]. *Appl* knockout didn't lead to lethal effect, but caused change of behavioral reactions which were restored at APP expression. This indicates functional conservatism between *Drosophila Appl* and human APP [Luo et al., 1992]. Many researches specify the key role of *Appl* in formation and maintenance of synapses in *Drosophila* [Ashley et al., 2005; Torroja et al., 1996]. Experiments by definition of *Appl* localization have shown significant *Appl* enrichment in growing axons and synaptic

structures and participation of Appl in formation and differentiations of synapses in neuromuscular junctions of larvae [Torroja et al., 1996, 1999b]. The overexpression both Appl, and human APP caused disturbance of axon transport [Gunawardena and Goldstein, 2001; Torroja et al., 1999a]. At APP human overexpression in *Drosophila melanogaster* it also was transported in the presynaptic terminal of neurons and postsynaptic sites of neuromuscular junctions [Yagi et al., 2000].

Fly models of human A β peptide-induced amyloidosis have been generated employing direct expression A β ₄₀ and A β ₄₂, in nervous system in *Drosophila* strains [Iijima-Ando & Iijima, 2010; Moloney et al., 2010]. Interestingly, diffusive amyloid deposits and neuron loss have been detected only in flies carrying the sequence of more amyloidogenic A β ₄₂ in genome. Amyloid formation was accompanied by progressive age-dependent behavioral defects, and life expectancy reduction. Authors did not detect amyloid accumulation and neuron loss as for flies carrying the sequences of less amyloidogenic A β ₄₀ [Finelli et al., 2004; Iijima et al., 2004]. In other work, flies expressing wild-type A β ₄₂ and Arctic mutant A β ₄₂ (Glu22Gly) showed a decline in climbing behavior, increased intracellular A β accumulation and diffuse plaques prior to signs of neurodegeneration [Crowther et al., 2005]. Late findings demonstrated that expression of the Arctic mutant significantly enhanced formation of A β oligomers and A β deposits, together with a decline of locomotor functions when compared with A β -art (artificial mutation L17P) [Iijima et al., 2008].

It has been proposed that dysfunction and loss of synapses underlie in the basis of cognitive disturbances at AD [Hardy & Selkoe, 2002; Honer, 2003 Sze et al., 1997; Selkoe, 2002; Terry et al., 1991]. At the analysis of sporadic AD form it has been established that the significant reduction (> 25 %) of synapse density in a frontal and temporal cortex and in hippocampus was observed already in the early stage of disease [Masliah et al., 1994]. Thus loss of synapses is not age-dependent and it is the specific characteristic of AD [Masliah et al., 2001]. Moreover, the degeneration of only insignificant part of synapses is caused by neuron death whereas the appreciable share of synapses is lost by living cells [Coleman & Yao, 2003].

In addition, transgenic models clearly show that synapse loss strictly correlates with cognitive disturbances and precedes formation of neurofibrillary tangles (NFTs) and amyloid deposits [Duyckaerts et al., 2008; Mucke et al., 2000; Oddo et al., 2003]. Now the most researchers suggest that accumulation of soluble toxic A β oligomers in neurons lead directly to degeneration of synapses and the neuron loss [Walsh & Selkoe, 2004]. This suggestion, considerably, is based on the data showing correlation between concentration of soluble non-aggregated A β in extracts of cortex and hippocampus, reduction of synapses quantity and degree of cognitive disturbances [Lue et al., 1999]. In summary, despite appreciable number of modeling experiments on the transgenic animals [Haass and Selkoe, 2007; LaFerla et al., 2007; Wirths et al., 2004] it is extremely difficult to prove a hypothesis about causative the role of toxic A β oligomer in synaptic dysfunction *in vivo*. Surprisingly, different A β ₄₂ aggregates had distinctive roles in modulation of synaptic functions. While exogenously prepared small A β ₄₂ oligomers or A β oligomers secreted from neurons lead to a reduction of neurotransmitter release; larger-sized aggregates, possibly fibrils secreted by muscle cells, enhanced neurotransmitter release and synaptic transmission [Chiang et al., 2009].

The A β ₄₂ expression induced depletion of mitochondria in axons and dendrites and their accumulated in the somata without severe mitochondrial damage or neurodegeneration [Iijima-Ando et al., 2009]. In addition, significant depletion of presynaptic mitochondria occurred before changes in synaptic transmission [Zhao et al., 2010].

Greeve et al. (2004) have taken an alternative approach to generating flies with A β deposition. Because BACE activity is very low or not present in *Drosophila* [Carmine-Simmen et al., 2009; Fossgreen et al., 1998;], overexpression of human APP does not lead to secretion of A β leading to the interpretation that all phenotypic effects in these transgenic flies should be attributed to the presence of human APP. When human BACE and APP were expressed in combination in fly eyes A β was secreted and diffuse amyloid plaques and age-dependent neurodegeneration of photoreceptor cells were observed. The neurodegeneration phenotype was enhanced in the flies expressing dPsn carrying early-onset familial AD mutations. Surprisingly, neurodegeneration was even more pronounced in APP transgenic flies than in APP/BACE double transgenic flies [Greeve et al., 2004]. Our data confirm these results. We did not find differences in age-dependent neurodegeneration in transgenic flies expressing full size APP with BACE or without BACE. However, transgenic expressing APP and BACE had lower levels of the presynaptic protein GFP- synaptobrevin or GFP-synaptotagmin than transgenic expressing APP alone [Sarantseva et al., 2009a, 2009b]. These findings raise the question whether the decline of synaptic proteins levels and/or neurodegeneration are caused by different mechanisms. Alternatively, we suggest that A β reflects just a part of a larger pathological process and independently contributes to different neuropathological abnormalities caused by APP overexpression.

3.1 Screening for genetic modifiers

Drosophila represents one of classical tools used to conduct genetic modifiers screens. The main goal of these screens is to identify proteins or pathways that modulate pathological process. One of the most interesting examples is discovery of modifiers of A β pathology. Flies expressing A β ₄₂ in retina have been used for detection of A β phenotype-modifying mutations in *Drosophila* genome. These flies developed so-called «rough eye» phenotype characterized by disorganization of photoreceptor cells and reduction of the eye size [Finelli et al., 2004]. Modifiers (suppressors and enhancers) of rough eye phenotype were identified from screening the collection of nearly 2,000 *Drosophila* strains carrying in genome inserts of EP transposon. The EP transposon has a GAL4 activated promoter and modulates the gene activity depending on site and orientation insertion [Rorth et al., 1998]. All strains of this collection were individually crossed to the flies expressing A β ₄₂. As a result of screening of phenotypes and the subsequent DNA-analysis 23 modifiers gene have been discovered. They included genes participating in various secretory processes, cholesterol homeostasis, the innate immune pathway, control of transcription and chromatin remodeling. Eight mutations change the total A β peptide level, but only one mutation resulted in 70 % decrease of total A β level. This mutation revealed insertion in regulatory zone of neprilysin 2 (nep2) gene [Cao et al., 2008; Finelli et al., 2004]. Neprilysin is one of major neuropeptidases of brain of mammals [Iwata et al., 2001, 2005]. Interestingly, epidemiological studies suggest that reduction in Neprilysin levels may contribute to the onset and/or progression of late-onset AD [Hersh & Rodgers, 2008].

Several studies show that normal cellular presenilin functions and the nature of abnormalities caused by PSN1 and PSN2 mutations in familial AD are not restricted by participation of these proteins in γ -secretase complex and required the further investigations [Baki et al., 2004; Bentahir et al., 2006; Singh et al., 2001; Saura et al., 2004; Schwarzman et al., 1999]. For understanding presenilin functions the search of genetic modifiers modulating Psn-dependent phenotype in *Drosophila* wings and notum has been conducted. 177 modifiers, included the proteins regulating intracellular calcium signaling, stress response and protein folding, components of signal transduction, apoptotic factors and proteins of the cellular cycle. Notably, 58 modifiers interacted with APP, including those involved in calcium signaling. These results provide strong evidence for a link between presenilins, APP, and calcium homeostasis, and suggest that these may play an important role in AD pathogenesis [van de Hoef et al., 2009].

4. *Drosophila* model for transthyretin-associated amyloidosis

Transthyretin (TTR), plasma protein primarily synthesized in the liver, choroid plexus and in retinal pigment epithelium, is the basic transporter of thyroxine and retinol-binding protein in mammals [Goodman, D., 1987; Woeber & Ingbar, 1968]. Three human diseases are characterized by extracellular transthyretin deposits – Familial Amyloidotic Polyneuropathy (FAP), Familial Amyloidotic Cardiomyopathy (FAC) and Senile Systemic Amyloidosis (SSA). SSA is the most widespread form of transthyretin associated amyloidosis, in which the lesion of heart, brain, and pancreas is observed [Westermarck, et al., 1990]. FAP and FAC are hereditary forms caused by mutations in the transthyretin gene. Now it is known more than 100 human genetic TTR variants differing with unique amino-acid replacement, of which the majority is amyloidogenic [Connors et al., 2003]. TTR forms amyloid through a process that is initiated by tetramer destabilization. This process results in accumulation of monomers, which can misfold and aggregate into fibrillar structures [Wiseman et al., 2005]. TTR is involved in A β metabolism, the basic component of amyloid deposits in Alzheimer's disease [Liu & Murphy, 2006; Schwarzman, et al., 1994]. Moreover, binding TTR to A β prevented A β aggregation and formation of an amyloid both *in vitro* and *in vivo* [S.H. Choi et al, 2007; Buxbaum et al, 2008]. Despite the fact that *Drosophila* does not have distinct TTR homolog, the expression of its two clinical forms TTRV30M [Berg, I. et al, 2009] and TTRL55P and mutant form TTR-A [Pokrzywa et al., 2007], with two amino-acid replacements (TTRV14N/V16E) [Olofsson et al., 2001] led to development of the phenotypes partially reminiscent of the human pathology. Expression of TTRV30M in the nervous system resulted in neurodegeneration, reduced lifespan, climbing ability, whereas the expression of wild type TTR (TTRwt) showed a milder phenotype. Congo red staining of the *Drosophila* brain shows positive amyloid binding in aged TTRV30M flies [Berg, I. et al, 2009]. Similar results have been received at TTRL55P and TTR-A expression: shortened lifespan, locomotive dysfunction, including flight ability [Pokrzywa et al., 2007]. Notably, that the expression of all three TTR forms (TTRL55P, TTR-A and TTRwt) caused the unusual “dragged-wing” phenotype. TTR aggregates possessed different toxicity. So, the most toxic were TTR aggregations separated from hemolymph and fat body of aged TTR-A flies [Pokrzywa et al., 2010].

Drosophila strains expressing TTR can address specific questions in transthyretin biology. For instance, a variety of TTR-binding partners have been identified over the years [Liz et al., 2009]. However, the biological significance of these interactions remains obscure. Use of

a tractable genetic system such as *Drosophila* can play a key role for the elucidation of cellular pathways and compartments in which these interactions take place.

5. Modeling prion diseases in *Drosophila*

Prion diseases (transmissible spongiform encephalopathies) are an unusual group of fatal neurodegenerative disease including Gerstmann-Sträussler-Scheinker (GSS) syndrome, familial fatal insomnia (FFI), Creutzfeldt-Jakob disease (CJD) and kuru in human and also scrapie in sheep and goats, bovine spongiform encephalopathy (BSE) in cattle, chronic wasting disease in mule deer and elk, [Prusiner, 1998, Prusiner & Hsiao, 1994]. These diseases may present with sporadic, inherited or infectious origins and lead to dementia, motor dysfunction and death [Aguzzi et al., 2008]. The majority of prion diseases cases in humans are classified as sporadic forms and about 10-15 % are the inherited form caused by mutations in *PRNP* gene. Now it is described more than 30 mutations in *PRNP* gene [Mead, 2006]. According to modern considerations, the central pathogenetic event in prion diseases is the conformational conversion of the normal cellular isoform of prion protein (PrP^C) into its pathological scrapie isoform (PrP^{Sc}) [Prusiner, 1998]. The precise structural differences between the two PrP isoforms remain to be defined, although it is clear that PrP^{Sc} contains significantly more β -sheet and is more protease-resistant regions. The deposition of PrP^{Sc} in the brain is associated with cerebral damage, including spongiform degeneration and neuronal loss. However, increasing evidence argues against the neurotoxicity of PrP^{Sc}. Significant pathology and/or clinical dysfunction develop with little accumulation of PrP^{Sc} [Flechsiger et al., 2000; Manson et al., 1999] and some familial prion diseases are not transmissible, and are not accompanied by the accumulation of protease resistant PrP [Brown et al., 1994; Rodríguez-Martínez et al., 2010; Tateishi & Kitamoto, 1995; Zou et al., 2010]. Thus, it is not clear whether specific conformers are associated with neuronal dysfunction and degeneration [Solomon et al., 2010].

The first attempts to create the model of prion diseases on *Drosophila* were unsuccessful. PrP Syrian hamster (SHaPrP) expression under heat shock promoter Hsp70 did not lead to neuropathology and accumulation of protease-resistant SHaPrP forms [Raeber et al., 1995]. The expression of wild type of the mouse (MoPrP) and human CJD-associated PrP (PG14) [Krasemann et al., 1995] using GAL4-UAS has not also revealed clinical and pathological abnormalities in the flies. Surprisingly, the flies seemed to accumulate very little mutant PrP in the brain compared with the eyes, suggesting that *Drosophila* brain possesses a specific and saturable mechanism that suppresses the accumulation of PG14 [Deleault et al., 2003].

The successes in modeling of prion disease in *Drosophila* was achieved in the expression of wild type mouse prion protein and GSS syndrome-associated mouse prion protein (MoPrP^{P101L}) in cholinergic and dopaminergic neurons. The MoPrP^{P101L} flies showed severe locomotor dysfunction, decreased lifespan and neuronal vacuolization associated to age-dependent accumulation of misfolded PrP molecules and intracellular PrP aggregates [Gavin et al., 2006]. In addition, MoPrP^{P101L} induced altered synaptic architectures in larval neuromuscular junctions and progressive reduction of a synaptic scaffolding protein, Discs large (DLG), in adult brains [J.K. Choi et al., 2010]. Flies expressing wild type prion protein displayed no phenotype [J.K. Choi et al., 2010; Gavin et al., 2006].

Expression of wild type PrP (SHaPrP) in *Drosophila* neurons caused lifespan reduction, locomotive abnormality and spongiform degeneration of brain neurons. This was a first

successful attempt on creation of the sporadic form of prion diseases in *Drosophila*. Notably, PrP underwent conformational changes comparable to those of PrP^{Sc}, however flies did not accumulate proteinase K-resistant PrP, indicating that wild type PrP can induce spongiform degeneration in the absence of its prototypical PrP^{Sc} conformation [Fernandez-Funez et al., 2009].

6. *Drosophila* as a model system for discovery of therapeutic compounds for brain delivery

A major obstacle in the treatment of diseases of the central nervous system is the limited penetration of drugs into the brain. A basic reason for low efficacy of many systemically administered therapeutics is insufficient drug delivery due to the presence of the blood-brain barrier (BBB) [Pardridge, 2005]. The BBB is formed by the complex tight junctions between the endothelial cells of the brain capillaries and their low endocytic activity. This results in capillary walls that behave as a continuous lipid bilayer that prevents the passage of polar and lipid-insoluble substances into the brain [Ballabh et al., 2004; Huber et al., 2001; Reese and Karnovsky, 1967]. The BBB also limits the delivery of protein and peptide-based therapeutics that are highly potent, lack toxicity and may prove extremely efficacious for the treatment of many neurological disorders [Laskowitz et al., 2006].

Limited numbers of investigations of brain delivery of therapeutic compounds described in literature are partially due to the difficulties in evaluating and predicting simultaneously the fate of a compound in a therapeutic intervention and the efficiency with which it crosses the BBB. Current methods such as *in vitro* measurements in cell cultures are insufficient to address problem in modeling of CNS diseases. At the same time present models of neurological diseases using rodents often have serious limitations for repetitive testing of a large number of structural variants of drugs. Therefore, to avoid these difficulties we examined the utility of *Drosophila* and its BBB for neuropharmacological research. Recent studies showing structural and functional similarities between the BBB of *Drosophila* the mammalian BBB suggest that *Drosophila* represents a reasonable model for testing the penetration of drugs and peptide vectors into the CNS [Daneman and Barres, 2005; Genova & Fehon, 2003; Schwabe et al., 2005; Stork et al., 2008; Wu et al., 2004]. We have demonstrated the ability of penetratin (protein transduction domain vector) [Derossi et al., 1994] to carry a cargo (apoE mimetics) across the *Drosophila* BBB into brain cells. These apoE mimetics are peptides derived from the receptor binding region of apoE that mimic the functional anti-inflammatory and neuroprotective effects of the intact apoE protein [Laskowitz et al., 2007; Wang et al., 2007]. Amazingly, penetratin fused with apoE mimetics restored cognitive functions in transgenic *Drosophila*. Moreover, penetratin fused with peptide SH8 (inhibitor of A β amyloidosis) [Schwarzman et al., 2005] decreased size of A β deposits after abdominal injection in *Drosophila* lines secreting A β [Sarantseva et al., 2009a]. These results suggest that *Drosophila* may be a very fruitful model system for the development of CNS drugs and studying drug delivery into the brain.

7. Conclusion

Transgenic *Drosophila* lines reproduce many key signs of Alzheimer's disease, prion diseases, FAP, FAC, SSA. Here it should be noted that although experiments with transgenic *Drosophila* do not faithfully recapitulate all aspects of studied amyloid diseases,

they offer real opportunities for studying disease-related pathology. In particular, these models help to explain the contributions of APP and A β in familial AD pathogenesis. In general, fly models should be surveyed as the sensitive genetic system, which gives possibility to reveal the cellular processes involved in a pathogenesis of diseases, modifiers of these processes. In a very practical view *Drosophila* strains may be also used to test new therapeutic compounds, which would help resolve a variety of fundamental questions. The discovery of genetic modifiers in *Drosophila* will help to reveal the corresponding human genes and therefore new therapeutic targets.

8. Acknowledgment

This study is supported by the Russian Foundation for Basic Research and by the Program of the Presidium of the Russian Academy of Sciences “Fundamental Sciences for Medicine”.

9. References

- Adams, M.D. & Sekelsky, J.J. (2002). From sequence to phenotype: reverse genetics in *Drosophila melanogaster*. *Nat Rev Genet*, Vol.3, No.3, (March 2002), pp.189-98, ISSN 1471-0056
- Ashley, J., Packard, M., Ataman, B. & Budnik, V. (2005). Fasciclin II signals new synapse formation through amyloid precursor protein and the scaffolding protein dX11/Mint. *J Neurosci*, Vol.25, No.25, (June 2005), pp.5943–5955, ISSN 0270-6474
- Aguzzi, A., Baumann, F. & Bremer, J. (2008) The Prion's Elusive Reason for Being. *Annu Rev Neurosci*. Vol.31, pp. 439–477, ISSN 0147-006X
- Ballabh, P., Braun, A. Nedergard, M. (2004). The blood-brain barrier: an overview: Structure, regulation, and clinical implications. *Neurobiol. Dis.*, Vol.16, No.13, (June 2004), pp.1-13, ISSN 0261-4189
- Baki, L., Shioi, J., Wen, P., Shao, Z., Schwarzman, A., Gama-Sosa, M., Neve & R., Robakis, N.K. (2004). PS1 activates PI3K thus inhibiting GSK-3 activity and tau overphosphorylation: effects of FAD mutations. *EMBO J*, Vol.23, No.13, (July 2004), pp.2586–2596, ISSN 0261-4189
- Bellen, H.J., Levis, R.W., Liao, G., He, Y., Carlson, J.W., Tsang, G., Evans-Holm, M., Hiesinger, P.R., Schulze, K.L., Rubin, G.M., Hoskins, R.A. & Spradling, A.C. (2004). The BDGP gene disruption project: single transposon insertions associated with 40% of *Drosophila* genes. *Genetics*, Vol.167, No.2, (June 2004), pp.761 –781, ISSN 0016-6731
- Bentahir, M., Nyabi, O., Verhamme, J., Tolia, A., Horrer, K., Wiltfang, J., Esselmann, H. & De Strooper, B. (2006). Presenilin clinical mutations can affect c-secretase activity by different mechanisms. *J. Neurochem*, Vol.96, No.3, (February 2006), pp. 732–742, ISSN 0022-3042
- Berg, I., Thor, S., & Hammarström, P. (2009). Modeling familial amyloidotic polyneuropathy (Transthyretin V30M) in *Drosophila melanogaster*. *Neurodegener Dis*, Vol.6, No.3, (May 2009), pp. 127-38, ISSN 1660-2854
- Brown, P., Gibbs, C.J., Rodgers-Johnson, P., Asher, D.M., Sulima, M.P., Bacote, A., Goldfarb, L.G., & Gajdusek, D.C. (1994). Human spongiform encephalopathy: the National Institutes of Health series of 300 cases of experimentally transmitted disease. *Ann Neurol*. Vol.35, No.5, (May 1994), pp.513-529, ISSN 0364-5134

- Bier, E. (2005). *Drosophila*, the golden bug, emerges as a tool for human genetics. *Nat Rev Genet*, Vol.6, No.1, (January 2005), pp.9-23, ISSN 1471-0056
- Bilen, J. & Bonini, N.M. (2005). *Drosophila* as a model for human neurodegenerative disease. *Annu Rev Genet*, Vol.39, (December 2005), pp.153-71, ISSN 0066-4197
- Brand, A.H. & Perrimon, N. (1993). Targeted gene expression as a means of altering cell fates and generating dominant phenotypes. *Development*, Vol.118, No.2, (January 1999), pp.401-415, ISSN 0950-1991
- Buxbaum, J.N., Ye, Z., Reixach, N., Friske, L., Levy, C., Das, P., Golde, T., Masliah, E., Roberts, A.R. & Bartfai, T. (2008). Transthyretin protects Alzheimer's mice from the behavioral and biochemical effects of Abeta toxicity. *Proc. Natl. Acad. Sci. USA*, Vol.105, (February 2008), pp. 2681-2686, ISSN 0027-8424
- Cao, W., Song, H.J., Gangi, T., Kelkar, A., Antani, I., Garza, D. & Konsolaki, M. (2008). Identification of novel genes that modify phenotypes induced by Alzheimer's beta-amyloid overexpression in *Drosophila*. *Genetics*, Vol.178. No.3. (March 2008), pp.1457-7, ISSN 0016-6731
- Carmine-Simmen, K., Proctor, T., Tschape, J., Poeck, B., Triphan, T., Strauss, R. & Kretzschmar, D. (2009). Neurotoxic effects induced by the *Drosophila* amyloid-beta peptide suggest a conserved toxic function. *Neurobiol Dis*. Vol.33, No.2, (February 2009), pp.274-281, ISSN 0969-9961
- Chiang, H.C., Iijima, K., Hakker, I. & Zhong, Y. (2009). Distinctive roles of different beta-amyloid 42 aggregates in modulation of synaptic functions. *FASEB J*, Vol.23, No.6, (June 2009), pp. 969-1977, ISSN 0892-6638
- Choi, J.K., Jeon, Y.C., Lee, D.W., Oh, J.M., Lee, H.P., Jeong, B.H., Carp, R.I., Koh, Y.H. & Kim, Y.S. (2010). A *Drosophila* model of GSS syndrome suggests defects in active zones are responsible for pathogenesis of GSS syndrome. *Hum Mol Genet*, Vol.19, No.22, pp. 4474-89, ISSN 0964-6906
- Choi, S.H., Leight, S.N., Lee, V.M., Li, T., Wong, P.C., Johnson, J.A. & Saraiva, M.J. (2007) Accelerated Abeta deposition in APP^{swe}/PS1^{deltaE9} mice with hemizygous deletions of TTR (transthyretin). *J. Neurosci*, Vol.27, No.26, (Jne 2007), pp.7006-7010, ISSN 0020-7454
- Coleman, P.D. & Yao, P.J. (2003). Synaptic slaughter in Alzheimer's disease. *Neurobiol. Aging*, Vol.24, N0.8, (December 2003), pp. 1023-1027, ISSN 0197-4580
- Connors, L.H., Lim, A., Prokaeva, T., Roskens, V.A. & Costello, C.E. (2003). Tabulation of human transthyretin (TTR) variants. *Amyloid*, Vol.10, No.3, (September 2003), pp.160-184, ISSN 1350-6129
- Crowther, D.C., Kinghorn, K.J., Miranda, E., Page, R., Curry, J.A., Duthie, F.A., Gubb, D.C. & Lomas, D.A. (2005). Intraneuronal Abeta, nonamyloid aggregates and neurodegeneration in a *Drosophila* model of Alzheimer's disease. *Neuroscience*, Vol.132, pp.123-135, ISSN0306-4522
- Daneman, R. & Barres, B.A. (2005). The blood-brain barrier lessons from moody flies. *Cell*, Vol.123, No,1, (October 2005), pp.9-12, ISSN 0092-8674
- Davis, K. L. & Samuels, S. C. (1998). Dementia and delirium, In: *Pharmacological Management of Neurological and Psychiatric Disorders*. eds Enna S. J. and Coyle J.T., pp. 267-316, McGraw -Hill, ISBN 0070217645, New York
- Deleault, N.R., Dolph, P.J., Feany, M.B., Cook, M.E., Nishina, K., Harris, D.A. & Supattapone, S. (2003). Post-transcriptional suppression of pathogenic prion

- protein expression in *Drosophila* neurons. *J Neurochem*, Vol.85, No.6, (June 2003), pp.1614–1623, ISSN 0022-3042
- Derossi, D., Joliot, A.H., Chassaing, G., Prochiantz, A., 1994. The third helix of the Antennapedia homeodomain translocates through biological membranes. *J. Biol. Chem*, Vol.269, No.14, (April 1994), pp. 10444– 10450, ISSN 0021-9258
- Duyckaerts, C., Potier, M.C. & Delatour, B. (2008). Alzheimer disease models and human neuropathology: similarities and differences. *Acta Neuropathol*, Vol.115, No.1, (January 2008), pp.5-38, ISSN 0001-6322
- De Strooper, B.D. & Annaert, W. (2001). Presenilins and the intramembrane proteolysis of proteins: facts and fiction. *Nat. Cell Biol*, Vol.3, No.10, (October 2001), pp. 221–25, ISSN 1465-7392
- De Strooper, B. & Annaert, W. (2000). Proteolytic processing and cell biological functions of the amyloid precursor protein. *J. Cell Sci*, Vol.113, No.Pt11, (June 2000), pp. 1857–70, ISSN 0021-9533
- Elliott, D. & Brand H. (2008). The GAL4 System: A Versatile System for the Expression of Genes, In: *Methods in Molecular Biology: Drosophila: Methods and Protocols*. C. Dahmann, pp. 79-96, Humana Press Inc., ISBN 978-1-58829-817-1, Totowa, NJ.
- Enerly, E., Larsson, J. & Lambertsson, A. (2002). Reverse genetics in *Drosophila*: from sequence to phenotype using UAS-RNAi transgenic flies. *Genesis*, Vol.34, No.1, (October 2002), pp.152-5, ISSN 0016-6731
- Fernandez-Funez, P., Casas-Tinto, S., Zhang, Y., Gomez-Velazquez, M., Morales-Garza, M.A., Cepeda-Nieto, A.C., Castilla, J., Soto, C. & Rincon-Limas, D.E. (2009). In vivo generation of neurotoxic prion protein: role for hsp70 in accumulation of misfolded isoforms. *PLoS Genet*, Vol.5, No.6, (June 2009), e1000507, ISSN1553-7390
- Finelli, A., Kelkar, A., Song, H.-J., Yang, H. & Konsolaki, M. (2004). A model for studying Alzheimer's AB42-induced toxicity in *Drosophila melanogaster*. *Mol. Cell. Neurosci*, Vol. 26.No.3, (July 2004), pp. 365–375, ISSN 1044-7431
- Flechsig, E., Shmerling, D., Hegyi, I., Raeber, A.J., Fischer, M., Cozzio, A., von Mering, C., Aguzzi, A., & Weissmann, C. (2000). Prion protein devoid of the octapeptide repeat region restores susceptibility to scrapie in PrP knockout mice. *Neuron*, Vol.27, No.2, (August 2000), pp.399-408, ISSN 0896-6273
- Fortini, M.E., Skupski, M.P., Boguski, M.S. & Hariharan, I.K. (2000). A survey of human disease gene counterparts in the *Drosophila* genome. *J. Cell Biol*, Vol.150, No.2, (July 2000), pp. 23–30, ISSN0021-9525
- Fossgreen, A., Bruckner, B., Czech, C., Masters, C.L., Beyreuther, K. & Paro R. (1998). Transgenic *Drosophila* expressing human amyloid precursor protein show gamma-secretase activity and a blistered-wing phenotype. *Proc Natl Acad Sci USA*, Vol.95, No.23, (November 1998), pp.13703–13708, ISSN 0027-8424
- Gavin, B.A., Dolph, M.J., Deleault, N.R., Geoghegan, J.C., Khurana, V., Feany, M.B., Dolph, P.J. & Supattapone, S. (2006). Accelerated accumulation of misfolded prion protein and spongiform degeneration in a *Drosophila* model of Gerstmann- Straussler-Scheinker syndrome. *J Neurosci*, Vol.26, No.48, (November 2006), pp.12408-14, ISSN 0020-7454
- Genova, J.L. & Fehon, R.G. (2003) Neuroglian, Gliotactin, and the Na/K-ATPase are essential for septate junction function in *Drosophila*. *J. Cell Biol.*, Vol.161, No.5, (June 2003), pp.979-989, ISSN 0021-9525

- Goodman, D. (1987). Retinoids and retinol-binding proteins. *Harvey Lect*, Vol.81, pp.111–132, ISSN 0073-0874
- Greeve, I., Kretschmar D., Tschape, J.A., Beyn, A., Brellinger, C., Schweizer, M., Nitsch, R.M. & Reifegerste, R. (2004). Age-dependent neurodegeneration and Alzheimer-amyloid plaque formation in transgenic *Drosophila*. *J Neurosci*, Vol.24, No. 16, (April 2004), pp.3899–3906, ISSN0020-7454
- Gunawardena, S., Goldstein, L.S. (2001). Disruption of axonal transport and neuronal viability by amyloid precursor protein mutations in *Drosophila*. *Neuron*, Vol.32, No.3, (November 2001), pp.389–401, ISSN0896-6273
- Haass, C. & Selkoe, D.J. (2007). Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid beta-peptide. *Nat Rev Mol Cell Biol*, Vol.8, No.2, (February 2007), pp.101-12, ISSN 1471-0072
- Han, D. D., Stein, D., & Stevens, L. M. (2000). Investigating the function of follicular subpopulations during *Drosophila* oogenesis through hormone-dependent enhancer-targeted cell ablation. *Development*, Vol.127, No.3, (February 2000), pp. 573–583, ISSN 0950-1991
- Hardy, J. & Selkoe, D.J. (2002). The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science*, Vol.297, No. 5580, (July 2002), pp.353–356, ISSN 0193-4511
- Hersh, L.B. & Rodgers, D.W. (2008). Neprilysin and amyloid beta peptide degradation. *Curr Alzheimer Res*, Vol.5, No.2, (April 2008), pp.225-31, ISSN 1567-2050
- Hirth, F. (2010). *Drosophila melanogaster* in the study of human neurodegeneration. *CNS Neurol Disord Drug Targets*, Vol. 9. No. 4, (April 2010), pp.504-23, ISSN 1871-5273
- Honer, W.G. (2003). Pathology of presynaptic proteins in Alzheimer's disease: more than simple loss of terminals. *Neurobiol Aging*, Vol.24, No.8, (December 2003), pp.1047-62, ISSN 0197-4580
- Huber, J.D., Egleton, R.D. & Davis, T.P. (2001). Molecular physiology and pathophysiology of tight junctions in the blood-brain barrier. *Trends Neurosci.*, Vol.24, No.1, (December 2001), ISSN 719 –725.
- Huet, F., Lu, J.T., Myrick, K.V., Baugh, L.R., Crosby, M.A. & Gelbart, W.M. (2002). A deletion-generator compound element allows deletion saturation analysis for genome-wide phenotypic annotation. *Proc Natl Acad Sci U S A*. Vol. 99, No.15. (July 2002), pp.9948-53, ISSN 0027-8424
- Iijima, K., Liu, H.-P., Chiang, A.-S., Hearn, S., Konsolaki, M. & Zhong Y. (2004). Dissecting the pathological effects of human A β 40 and A β 42 in *Drosophila*: A potential model for Alzheimer's disease. *PNAS*, Vol.101, No.17, (April 2004), pp.6623–6628, ISSN 0027-8424
- Iijima, K., Chiang, H.C., Hearn, S.A., Hakker, I., Gatt, A., Shenton, C., Granger, L., Leung, A., Iijima-Ando, K. & Zhong, Y. (2008). Abeta42 mutants with different aggregation profiles induce distinct pathologies in *Drosophila*. *PLoS ONE*, Vol.3, No.2, (February 2008), e1703, ISSN 1932-6203
- Iijima-Ando, K., Hearn, S.A., Shenton, C., Gatt, A., Zhao, L. & Iijima, K. (2009). Mitochondrial Mislocalization Underlies Ab42-Induced Neuronal Dysfunction in a *Drosophila* Model of Alzheimer's Disease. *PLoS ONE*, Vol.4, No.12. (December 2009), e8310, ISSN 1932-6203

- Iijima-Ando, K. & Iijima, K. (2010). Transgenic *Drosophila* models of Alzheimer's disease and tauopathies. *Brain Struct Funct.*, Vol.214, No.2-3, (March 2010), pp.245-62, ISSN 1863-2653
- Iwata, N., Tsubuki, S., Takaki, Y., Shirotani, K., Lu, B., Gerard, N.P., Gerard, C., Hama, E., Lee, H.J. & Saido, T.C. (2001). Metabolic regulation of brain A β by neprilysin. *Science*, Vol.292, No. 292(5521), (May 2001), pp. 1550– 1552, ISSN 0193-4511
- Iwata, N., Higuchi, M. & Saido, T. (2005). Metabolism of amyloid- β peptide and Alzheimer's disease *Pharmacology & Therapeutics*, Vol.108, No. , pp. 129 – 148. ISSN
- Kazazian, H.H. (2004). Mobile elements: drivers of genome evolution. *Science*, Vol.303. No.303(5664), (March 2004), pp.1626-1632, ISSN 0193-4511
- Krasemann, S., Zerr, I., Weber, T., Poser, S., Kretzschmar, H., Hunsmann, G. & Bodemer W. (1995). Prion disease associated with a novel nine octapeptide repeat insertion in the PRNP gene. *Brain Res. Mol. Brain Res*, Vol.34, No.1, (December 1995), pp.173–176, ISSN 0169-328X
- LaFerla, F.M., Green, K.N. & Oddo S (2007). Intracellular amyloid-beta in Alzheimer's disease. *Nat Rev Neurosci*, Vol.8, No.7, (July 2007), pp.499 –509, ISSN 1471-003X
- Laskowitz, D.T., Fillit, H., Yeung, N., Toku, K., & Vitek, M.P. (2006). Apolipoprotein E-derived peptides reduce CNS inflammation: implications for therapy of neurological disease. *Acta Neurol Scand Suppl*, Vol.185, pp.15-20, ISSN 0065-1427
- Laskowitz, D.T. & Vitek, M.P. (2007). Apolipoprotein E and neurological disease: therapeutic potential and pharmacogenomic interactions. *Pharmacogenomics*, Vol.8, No.8, (August 2007) pp.959-969, ISSN 1462-2416
- Liz, M.A., Fleming, C.E., Nunes, A.F., Almeida, M.R., Mar, F.M., Choe, Y., Craik, C.S., Powers, J.C., Bogoy, M. & Sousa, M.M. (2009) Substrate specificity of transthyretin: identification of natural substrates in the nervous system. *Biochem J*, Vol.419, No.2, (April 2009), pp.467-74, ISSN 0264-6021
- Liu, L. & Murphy, R.M. (2006) Kinetics of inhibition of beta-amyloid aggregation by transthyretin. *Biochemistry*, Vol.45, No. 51, (December 2006), pp. 15702–15709, ISSN 0006-2960
- Lu, B. & Vogel, H. (2009). *Drosophila* models of neurodegenerative diseases. *Annu Rev Pathol*, Vol.4, pp. 315-42, ISSN 1553-4006
- Lue, L.F., Kuo, Y.M., Roher, A.E., Brachova, L., Shen, Y., Sue, L., Beach, T., Kurth, J.H., Rydel, R.E., Rogers. J. (1999). Soluble amyloid beta peptide concentration as a predictor of synaptic change in Alzheimer's disease. *Amer. J. Pathol.* Vol. 155, No.3, (September 1999), pp. 853–862, ISSN 0002-9440
- Luo, L.Q., Martin-Morris, L.E. & White, K. (1990). Identification, secretion, and neural expression of APPL, a *Drosophila* protein similar to human amyloid protein precursor. *J. Neurosci*, Vol.10, No.12, (December 1990), pp. 3849–61, ISSN 0020-7454
- Luo, L., Tully, T. & White, K. (1992). Human amyloid precursor protein ameliorates behavioral deficit of flies deleted for *Appl* gene. *Neuron*, Vol. 9, No.4, (October 1992), pp. 595– 605, ISSN 0896-6273
- Manson, J.C., Jamieson, E., Baybutt, H., Tuzi, N.L., Barron, R., McConnell, I., Somerville, R., Ironside, J., Will, R., Sy, M.S., Melton, D.W., Hope, J. & Bostock, C. (1999). A single amino acid alteration (101L) introduced into murine PrP dramatically alters incubation time of transmissible spongiform encephalopathy. *EMBO J*, Vol.18, No.23, (December 1999), pp.6855-6864, ISSN 0261-4189

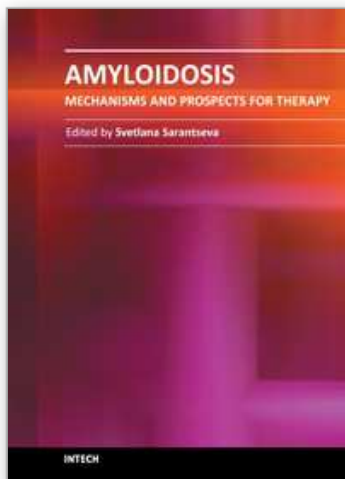
- Marsh, J.L. & Thompson LM. (2006). *Drosophila* in the study of neurodegenerative disease. *Neuron*, Vol.52, No.1, (October 2006), pp.169-78, ISSN 0896-6273
- Maslah, E., Mallory, M., Hansen, L., DeTeresa, R., Alford, M. & Terry, R. (1994). Synaptic and neuritic alterations during the progression of Alzheimer's Disease. *Neurosci. Lett*, Vol.174. No.1, (June 1994), pp. 67-72, ISSN 0306-4522
- Maslah, E., Mallory, M., Alford, M., DeTeresa, R., Hansen, L.A., McKeel, Jr, D.W. & Morris, J.C. (2001). Altered expression of synaptic proteins occurs early during progression of Alzheimer's disease. *Neurology*, Vol.56, No.1, (January 2001), pp.127-129, ISSN 0028-3878
- Matsumoto, K., Toh-e, A., & Oshima, Y. (1978). Genetic control of galactokinase synthesis in *Saccharomyces cerevisiae*: evidence for constitutive expression of the positive regulatory gene gal4. *J. Bacteriol*, Vol.134, No.2, (May 1978), pp.446-457, ISSN 0021-9193
- McGuire, S. E., Le, P. T., Osborn, A. J., Matsumoto, K., and Davis, R. L. (2003). Spatiotemporal rescue of memory dysfunction in *Drosophila*. *Science*, Vol.302, No.5651, (December 2003), pp.1765-1768, ISSN 0193-4511
- Mead, S. (2006). Prion disease genetics. *Eur. J. Hum. Genet*, Vol.14, No. 3, (March 2006), pp.273-281, ISSN 1018-4813
- Metaxakis, A., Oehler, S., Klinakis, A. & Savakis, C. (2005). Minos as a genetic and genomic tool in *Drosophila melanogaster*. *Genetics*, Vol.171, No.12, (October 2005), pp.571-81, ISSN 0016-6731
- Moloney, A., Sattelle, D.B., Lomas, D.A. & Crowther, D.C. (2010). Alzheimer's disease: insights from *Drosophila melanogaster* models. *Trends Biochem Sci*, Vol.35, No.4, (April 2010), pp. 228-35, ISSN 0968-0004
- Mucke, L., Maslah, E., Yu, G.Q., Mallory, M., Rockenstein, E.M., Tatsuno, G., Hu, K., Kholodenko, D., Johnson-Wood, K. & McConlogue, L. (2000). High-level neuronal expression of A₁₋₄₂ in wild-type human amyloid protein precursor transgenic mice: synaptotoxicity without plaque formation. *J Neurosci*, Vol.20, pp.4050-4058, ISSN 0020-7454
- Myrick, K.V., Huet, F., Mohr, S.E., Alvarez-García, I., Lu, J.T., Smith, M.A., Crosby, M.A. & Gelbart, W.M. (2009). Large-scale functional annotation and expanded implementations of the P{wHy} hybrid transposon in the *Drosophila melanogaster* genome. *Genetics*, Vol. 182, No. 3, (July 2009), pp.653-60, ISSN 0016-6731
- Nicholson, L., Singh, G.K., Osterwalder, T., Roman, G.W., Davis, R.L. & Keshishian, H. (2008). Spatial and temporal control of gene expression in *Drosophila* using the inducible GeneSwitch GAL4 system. I. Screen for larval nervous system drivers. *Genetics*, Vol.178, No.1, (January 2008), pp.215-34, ISSN 0016-6731
- Oddo, S., Caccamo, A., Shepherd, J.D., Murphy, M.P., Golde, T.E., Kaye, R., Metherate, R., Mattson, M.P., Akbari, Y. & LaFerla, F.M. (2003). Tripletransgenic model of Alzheimer's disease with plaques and tangles: intracellular Abeta and synaptic dysfunction. *Neuron*, Vol.39, No.3, (June 2003), pp.409-421, ISSN 0896-6273
- Olofsson, A., Ippel, H.J., Baranov, V., Horstedt, P., Wijmenga, S. & Lundgren, E. (2001). Capture of a dimeric intermediate during transthyretin amyloid formation. *J. Biol. Chem.*, Vol.276, No.4, (October 2001), pp. 39592-39599, ISSN 0021-9258

- Osterwalder, T., Yoon, K. S., White, B. H. & Keshishian, H. (2001). A conditional tissue-specific transgene expression system using inducible GAL4. *Proc. Natl. Acad. Sci. USA*, Vol.98, No.22, (October 2001), pp.596–601, ISSN 0027-8424
- Pardridge, W.M. (2005). The blood-brain barrier: bottleneck in brain drug development. *NeuroRx*, Vol.2, No.1, (January 2005), pp.3–14, ISSN 1545-5343
- Pokrzywa, M., Dacklin, I., Hultmark, D. & Lundgren, E. (2007). Misfolded transthyretin causes behavioral changes in a *Drosophila* model for transthyretin-associated amyloidosis. *Eur J Neurosci*, Vol.26, No.4, (August 2007), pp. 913-24, ISSN 0953-816X
- Pokrzywa, M., Dacklin, I., Vestling, M., Hultmark, D., Lundgren, E. & Cantera, R. (2010). Uptake of Aggregating Transthyretin by Fat Body in a *Drosophila* Model for TTR-Associated Amyloidosis. *PLoS ONE*, Vol.5, No.12., (December 2010), e14343. ISSN 1932-6203
- Prusiner, S. B. (1998). Prions. *PNAS*, Vol.95, No.23, (November 1998), pp.13363–13383, ISSN 0027-8424
- Prusiner, S.B. (1998). The prion diseases. *Brain Pathol*, Vol.8, No.3, (July 1998), pp.499-513, ISSN 1015-6305
- Prusiner, S.B. & Hsiao, K.K. (1994). Human prion diseases. *Ann Neurol*, Vol.35, No.4, (April 1994), pp. 385-95, ISSN 0364-5134
- Raeber, A.J., Muramoto, T., Kornberg, T.B. & Prusiner, S.B. (1995). Expression and targeting of Syrian hamster prion protein induced by heat shock in transgenic *Drosophila melanogaster*. *Mech Dev*, Vol. No.2-3, (June 1995), pp.317-27, ISSN 0925-4773
- Reese, T.S. & Karnovsky, M.J. (1967) Fine structural localization of a blood-brain barrier to exogenous peroxidase. *J Cell Biol.*, Vol.34, No.1, (July 1967), pp.207–217, ISSN 0021-9525
- Reiter, L.T., Potocki, L., Chien, S., Gribskov, M. & Bier, E. (2001). A systematic analysis of human disease-associated gene sequences in *Drosophila melanogaster*. *Genome Res*, Vol. 11, No.6, (June 2001), pp.1114–25, ISSN 1088-9051
- Rodríguez-Martínez, A.B., Garrido, J.M., Zarranz, J.J., Arteagoitia, J.M., de Pancorbo, M.M., Atarés, B., Bilbao, M.J., Ferrer, I., Juste, R.A. (2010). A novel form of human disease with a protease-sensitive prion protein and heterozygosity methionine/valine at codon 129: Case report. *BMC Neurol*, Vol. 10, No. 99, (October 2010), ISSN 1471-2377
- Roman, G., Endo, K., Zong, L., and Davis, R. L. (2001). P[Switch], a system for spatial and temporal control of gene expression in *Drosophila melanogaster*. *Proc. Natl. Acad. Sci. USA*, Vol.98, No.12, pp.602–607, ISSN 0027-8424
- Rørth, P. (1996). A modular misexpression screen in *Drosophila* detecting tissue-specific phenotypes. *Proc Natl Acad Sci U S A*, Vol. 93. No.22, (October 1996), pp.12418-22, ISSN 0027-8424
- Rørth, P., Szabo, K., Bailey, A., Laverty, T., Rehm, J., Rubin, G.M., Weigmann, K., Milán, M., Benes, V., Ansorge, W. & Cohen, S.M. (1998). Systematic gain-of-function genetics in *Drosophila*. *Development*, Vol.125, No.6, (March 1998), pp.1049–1057, ISSN 0950-1991
- Rosen, D.R., Martin-Morris, L., Luo, L. & White, K. A. (1989). *Drosophila* gene encoding a protein resembling the human b-amyloid protein precursor. *Proc Natl Acad Sci USA*, Vol.86, No.7, (April 1989), pp. 2478 –2482, ISSN 0027-8424

- Rubin, G.M. & Spradling, A.C. (1982). Genetic transformation of *Drosophila* with transposable element vectors. *Science*, Vol. 218, No.4570, (October 1982), pp.348-53, ISSN 0193-4511
- Sang, T.K., Jackson, G.R. (2005). *Drosophila* models of neurodegenerative disease. *NeuroRx*. Vol. 2, No. 3, (July 2010), pp.438-46, ISSN 1545-5343
- Sarantseva, S., Timoshenko, S., Bolshakova, O., Karaseva, E., Rodin, D., Schwarzman, A.L. & Vitek, M.P. (2009a). Apolipoprotein E-mimetics inhibit neurodegeneration and restore cognitive functions in a transgenic *Drosophila* model of Alzheimer's disease. *PLoS One*, Vol.4, No.12, (December 2009), e8191, ISSN1932-6203
- Sarantseva, S., Bolshakova, O., Timoshenko, S., Vitek, M.P. & Schwarzman, A.L. (2009b). Overexpression of human amyloid precursor protein causes neurodegeneration and loss of synaptic proteins in transgenic *Drosophila*. In: Hanin I., Fisher A., pp.245-248, Medimont, ISBN 978-88-7587-528-2, Prague, Czech Republic
- Saura, C., Choi, S.-Y., Beglopoulos, V., Malkani, S., Zhang, D., Rao, B.S.S., Chattarji, S., Kelleher, R., Kandel, E., Duff, K. Kirkwood A, Shen J. (2004). Loss of presenilin function causes impairments of memory and synaptic plasticity followed by age-dependent neurodegeneration. *Neuron*, Vol.42, No.1, (April 2004), pp.23-36, ISSN 0896-6273
- Schwabe, T., Bainton, R.J., Fetter, R.D., Heberlein, U. & Gaul, U. (2005). GPCR signaling is required for blood-brain barrier formation in *Drosophila*. *Cell*, Vol.123, No.7, (October 2005), pp.133-144, ISSN0092-8674
- Schwarzman, A.L., Gregori, L., Vitek, M.P., Lyubski, S., Strittmatter, W.J., Enghilde, J.J., Bhasin, R., Silverman, J., Weisgraber, K.H. & Coyle, P.K. (1994). Transthyretin sequesters amyloid beta protein and prevents amyloid formation. *Proc.Natl.Acad.Sci.USA*. Vol.91, No.18, (August 1994), pp.8368-8372, ISSN0027-8424
- Schwarzman, A.L., Singh, N., Tsiper, M., Gregori, L., Dranovsky, A., Vitek, M., Glabe, C., St.George-Hyslop, P. & Goldgaber, D. (1999). Endogenous presenilin 1 redistributes to the lamellipodia upon adhesion of Jurkat cells to a collagen matrix. *Proc.Natl. Acad.Sci.USA*, Vol.96, No.14, (July 1999), pp. 7932-7937, ISSN 0027-8424
- Schwarzman, A.L., Tsiper, M., Gregori, L., Goldgaber, D., Fracowiak, J., Mazur-Kolecka, B., Taraskina, A., Pchelina, S. & Vitek, M.P. (2005). Selection of peptides binding to the amyloid Ab-protein reveals potential inhibitors of amyloid formation. *Amyloid*, Vol.12, No.4, (December 2005), pp.1-11, ISSN 1350-6129
- Selkoe, D.J. (1998). The cell biology of β -amyloid precursor protein and presenilin in Alzheimer's disease. *Trends Cell Biol*, Vol.8, No.11, (November 1998), pp. 447-53, ISSN 0962-8924
- Selkoe, D.J. (1999). Translating cell biology into therapeutic advances in Alzheimer's disease. *Nature*. Vol.399, pp. 23-31, No. 6738 Suppl, (June 1999), ISSN 0028-0836
- Selkoe, D.J. (2002). Alzheimer's disease is a synaptic failure. *Science*, Vol.298, No.5594, (October 2002) pp.789 -791, ISSN 0193-4511
- Singh, N., Tsiper, M., Romanov, V., Dranovsky, A., Talalayeva, Y., Colflesh, D., Rudamen, G., Vitek, M.P., Shen, J., Yang, X., Goldgaber, D. & Schwarzman, A.L. (2001). The role of Alzheimer's disease-related presenilin 1 in intercellular adhesion. *Exp.Cell.Res*, Vol.263, No.1. (February 2001), pp.1-13, ISSN 0014-4827
- Sipe, J.D., Benson, M.D., Buxbaum, J.N., Ikeda, S., Merlini, G., Saraiva, M.J. & Westermarck, P. (2010). Amyloid fibril protein nomenclature: 2010 recommendations from the

- nomenclature committee of the International Society of Amyloidosis. *Amyloid*, Vol.17, No.13-14, (September 2010), pp.101-4, ISSN 1350-6129
- Smith, D., Wohlgemuth, J., Calvi, B. R. Franklin I, Gelbart WM. (1993). *hobo* enhancer trapping mutagenesis in *Drosophila* reveals an insertion specificity different from *P* elements. *Genetics*, Vol. 135, No.4, (December 1993), pp. 1063–1076, ISSN 0016-6731
- Solomon, I.H., Schepker, J.A. & Harris, D.A. (2010). Prion neurotoxicity: insights from prion protein mutants. *Curr Issues Mol Biol*, Vol.12, No.2, pp.51-61, ISSN 1467-3037
- Staudt, N., Molitor, A., Somogyi, K., Mata, J., Curado, S., Eulenberg, K., Meise, M., Siegmund, T., Häder, T., Hilfiker, A., Brönnner, G., Ephrussi, A., Rørth, P., Cohen, S.M., Fellert, S., Chung, H.R., Piepenburg, O., Schäfer, U., Jäckle, H. & Vorbrüggen, G. (2005). Gain-of-function screen for genes that affect *Drosophila* muscle pattern formation. *PLoS Genet*, Vol.1, No.4, (October 2005), e55, ISSN 1553-7390
- Stork, T., Engelen, D., Krudewig, A., Silies, M., Bainton, R.J. & Klämbt, C. (2008). Organization and function of the blood-brain barrier in *Drosophila*. *J Neurosci*, Vol.28, No.3, (January 2008), pp.587-97, ISSN 0270-6474
- Sze, C.I., Troncoso J.C., Kawas, C., Mouton, P., Price, D.L. & Martin, L.J. (1997). Loss of the presynaptic vesicle protein synaptophysin in hippocampus correlates with cognitive decline in Alzheimer disease. *J Neuropathol Exp Neurol*, Vol.56, No.8, (August 1997), pp.933–944, ISSN 0022-3069
- Tateishi, J. & Kitamoto, T. (1995). Inherited prion diseases and transmission to rodents. *Brain Pathol*, Vol.5, No.1, (January 1995), pp.53-9, ISSN 1015-6305
- Terry, R.D., Masliah, E., Salmon, D.P., Butters, N., DeTeresa, R., Hill, R., Hansen, L.A. & Katzman, R. (1991). Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. *Ann Neurol*, Vol.30, No.4, (October 1991), pp.572–580, ISSN 0364-5134
- Torroja, L., Luo, L. & White, K. (1996). APPL, the *Drosophila* member of the APP-family, exhibits differential trafficking and processing in CNS neurons. *J Neurosci*, Vol.16, No.15, (August 1996), pp. 4638–4650, ISSN 0020-7454
- Torroja L, Chu H, Kotovsky I, White K (1999a) Neuronal overexpression of APPL, the *Drosophila* homologue of the amyloid precursor protein (APP), disrupts axonal transport. *Curr Biol*, Vol.9, No.9, (May 1999), pp.489–492, ISSN 0960-9822
- Torroja, L., Packard, M., Gorczyca, M., White, K. & Budnik, V. (1999b). The *Drosophila* beta-amyloid precursor protein homolog promotes synapse differentiation at the neuromuscular junction. *J Neurosci*, Vol.19, No.18, (September 1999), pp.7793–7803, ISSN 0020-7454
- van de Hoef, D.L., Hughes, J., Livne-Bar, I., Garza, D., Konsolaki, M. & Boulianne, G.L. (2009). Identifying genes that interact with *Drosophila* presenilin and amyloid precursor protein. *Genesis*, Vol. 47, No.4, (April 2009), pp. 246-60, ISSN 1526-954X
- Wang, H., Durham, L., Dawson, H., Song, P., Warner, D.S., Sullivan, P.M., Vitek, M.P. & Laskowitz, D.T. (2007). An apolipoprotein E-based therapeutic improves outcome and reduce Alzheimer's disease pathology following closed head injury: evidence of pharmacogenomic interaction. *Neuroscience*, Vol.144, No.4, (February 2007), pp.1324–33, ISSN 0306-4522
- Walsh, D.M. & Selkoe, D.J. (2004). Deciphering the molecular basis of memory failure in Alzheimer's disease. *Neuron*, Vol.44, No.1, (September 2004), pp.181-193, ISSN 0896-6273

- Westermarck, P., Sletten, K., Johansson, B. & Cornwell, G.G. 3rd. (1990). Fibril in senile systemic amyloidosis is derived from normal transthyretin. *Proc Natl Acad Sci U S A*, Vol.87, No.7, (April 1990), pp. 2843-5, ISSN 0027-8424
- Westermarck, P., Benson, M.D., Buxbaum, J.N., Cohen AS, Frangione B, Ikeda S, Masters CL, Merlini G, Saraiva MJ, Sipe JD. (2007). A primer of amyloid nomenclature. *Amyloid*, Vol.14, No.3, (September 2007), pp.179-183, ISSN 1350-6129
- Wirths, O., Multhaup, G. & Bayer, T.A. (2004). A modified beta-amyloid hypothesis: intraneuronal accumulation of the beta-amyloid peptide—the first step of a fatal cascade. *J Neurochem*, Vol.91, No.3, (November 2004), pp.513-520, ISSN 0022-3042
- Wiseman, R.L., Powers, E.T. & Kelly, J.W. (2005). Partitioning conformational intermediates between competing refolding and aggregation pathways: insights into transthyretin amyloid disease. *Biochemistry*, Vol. 44, No.50, (December 2005), pp.16612-16623, ISSN 0006-2960
- Woeber, K. A. & Ingbar, S. H. (1968). The contribution of thyroxinebinding prealbumin to the binding of thyroxine in human serum, as assessed by immunoadsorption. *J. Clin. Invest*, Vol.47, No.7, (July 1968), pp.1710-1721, ISSN 0021-9738
- Wu, V.M., Schulte, J., Hirschi, A., Tepass, U. & Beitel, G.J. (2004). Sinuous is a *Drosophila* claudin required for septate junction organization and epithelial tube size control. *J. Cell Biol.*, Vol.164, No.2, (January 2004), pp.313-323, ISSN 0021-9525
- Yagi, Y., Tomita, S., Nakamura, M. & Suzuki, T. (2000). Overexpression of human amyloid precursor protein in *Drosophila*. *Mol. Cell. Biol. Res. Commun*, Vol.4, No.1, (July 2000), pp. 43-49, ISSN 1522-4724
- Ye, Y. & Fortini, M.E. (1998). Characterization of *Drosophila* presenilin and its colocalization with Notch during development. *Mech. Dev*, Vol.79, No.1, (December 1998), pp.199-211, ISSN 0925-4773
- Zhao, X.L., Wang, W.A., Tan, J.X., Huang, J.K., Zhang, X., Zhang, B.Z., Wang, Y.H., YangCheng, H.Y., Zhu, H.L., Sun, X.J., Huang, F.D. (2010). Expression of beta-amyloid induced age-dependent presynaptic and axonal changes in *Drosophila*. *J Neurosci*, Vol.20, No.4, (January 2010), pp.1512-22, ISSN0020-7454
- Zou, W.Q., Puoti, G., Xiao, X., Yuan, J., Qing, L., Cali, I., Shimoji, M., Langeveld, J.P., Castellani, R., Notari, S., Crain, B., Schmidt, R.E., Ge schwind, M., Dearmond, S.J., Cairns, N.J., Dickson, D., Honig, L., Torres, J.M., Mastrianni, J., Capellari, S., Giaccone, G., Belay, E.D., Schonberger, L.B., Cohen, M., Perry, G., Kong, Q., Parchi, P., Tagliavini, F. & Gambetti, P. (2010). Variably protease-sensitive prionopathy: a new sporadic disease of the prion protein. *Ann Neurol*. Vol. 68, No.2, (August 2010), pp.162-72, ISSN 0364-5134



Amyloidosis - Mechanisms and Prospects for Therapy

Edited by Dr. Svetlana Sarantseva

ISBN 978-953-307-253-1

Hard cover, 216 pages

Publisher InTech

Published online 22, September, 2011

Published in print edition September, 2011

Amyloidoses are a heterogeneous group of diverse etiology diseases. They are characterized by an endogenous production of abnormal proteins called amyloid proteins, which are not hydrosoluble, form depots in various organs and tissue of animals and humans and cause dysfunctions. Despite many decades of research, the origin of the pathogenesis and the molecular determinants involved in amyloid diseases has remained elusive. At present, there is not an effective treatment to prevent protein misfolding in these amyloid diseases. The aim of this book is to present an overview of different aspects of amyloidoses from basic mechanisms and diagnosis to latest advancements in treatment.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Svetlana Sarantseva and Alexander Schwarzman (2011). Modeling Amyloid Diseases in Fruit Fly *Drosophila Melanogaster*, *Amyloidosis - Mechanisms and Prospects for Therapy*, Dr. Svetlana Sarantseva (Ed.), ISBN: 978-953-307-253-1, InTech, Available from: <http://www.intechopen.com/books/amyloidosis-mechanisms-and-prospects-for-therapy/modeling-amyloid-diseases-in-fruit-fly-drosophila-melanogaster>

INTech
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2011 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the [Creative Commons Attribution-NonCommercial-ShareAlike-3.0 License](https://creativecommons.org/licenses/by-nc-sa/3.0/), which permits use, distribution and reproduction for non-commercial purposes, provided the original is properly cited and derivative works building on this content are distributed under the same license.

IntechOpen

IntechOpen