Send Orders for Reprints to reprints@benthamscience.ae

Current Neuropharmacology, **2016**, *14*, **155-164**

LPS-induced Murine Neuroinflammation Model: Main Features and Suitability for Pre-clinical Assessment of Nutraceuticals

Miryam Nava Catorce and Goar Gevorkian*

Instituto de Investigaciones Biomedicas, Universidad Nacional Autonoma de Mexico (UNAM), Mexico DF, Mexico

G. Gevorkian

Abstract: Neuroinflammation is an important feature in the pathogenesis and progression of neurodegenerative diseases such as Alzheimer´s disease (AD), Parkinson´s disease (PD), frontotemporal dementia and amyotrophic lateral sclerosis. Based on current knowledge in the field, suggesting that targeting peripheral inflammation could be a promising additional treatment/prevention approach for neurodegenerative diseases, drugs and natural products with anti-inflammatory properties have been evaluated in animal models of neuroinflammation and neurodegeneration. In this review, we provide an extensive analysis of one of the most important and widely-used animal models of peripherally induced neuroinflammation and neurodegeneration - lipopolysaccharide (LPS)-treated mice, and address the data reproducibility in published research. We also summarize briefly basic features of various natural products, nutraceuticals, with known anti-inflammatory effects and present an overview of data on their therapeutic potential for reducing neuroinflammation in LPS-treated mice.

Keywords: Astrocytes, LPS, microglia, neurodegeneration, neuroinflammation, nutraceuticals.

INTRODUCTION

Neuroinflammation is an important feature in the pathogenesis and progression of neurodegenerative diseases such as Alzheimer´s disease (AD), Parkinson´s disease (PD), frontotemporal dementia and amyotrophic lateral sclerosis [1-8]. Brains from patients with neurodegenerative diseases are characterized by marked astrocytosis, activation of microglia and elevated levels of pro-inflammatory cytokines [8, 10-12].

Epidemiological studies indicate that AD and PD risk positively correlates with pro-inflammatory conditions such as diabetes mellitus, metabolic syndrome, hypercholesterolemia and atherosclerosis suggesting that chronic inflammation may influence the development of neurodegenerative diseases (for detailed reviews see Refs. [13-17]). In addition, it has been recently reported that peripheral infections accompanied by inflammation represent major risk factors for the development of sporadic AD and PD [18-20].

Based on current knowledge in the field, suggesting that targeting peripheral inflammation could be a promising additional treatment/prevention approach for neurodegenerative diseases, drugs and natural products with anti-inflammatory properties have been evaluated in animal models of neuroinflammation and neurodegeneration (for a review see Ref. [21]). In this review, we will first provide an extensive analysis of one of the most important and widely-used animal models of peripherally induced neuroinflammation and neurodegeneration - lipopolysaccharide (LPS)-treated mice. We will address data reproducibility as well as different experimental approaches in analyzed literature. LPS, an endotoxin from the outer membrane of bacteria, is known as a potent trigger of inflammation. It has been demonstrated that peripheral administration of LPS in mice induced astrocyte and microglia activation, as well as cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS) and pro-inflammatory cytokine expression in the brain [22-25]. In addition, intracellular accumulation of amyloid precursor protein, amyloid β peptide and hyperphosphorylated tau as well as exacerbation of memory deficits were observed in LPS-treated APP transgenic mice [26, 27].

We will also provide an overview of studies on anti-inflammatory properties of various natural products, nutraceuticals, tested in LPS-treated mice.

NEUROINFLAMMATION AND NEURODEGENERATION INDUCED BY PERIPHERAL ADMINISTRATION OF LPS

Activated Microglia and Pro-inflammatory Cytokines

It is widely accepted that microglia, the principal effector cells of the immune system in the brain, in addition to being key actors for host defense in brain injury and disease (for comprehensive reviews see Refs. [28-31]), play an important role in the healthy brain physiology and synaptic remodeling associated with learning and memory probably by releasing neurotrophic factors like BDNF [32]. During an inflammatory response, activation of microglia leads to retraction of their processes and swelling of the cell bodies with subsequent loss of brain monitoring, and this may induce neuronal damage, disruption of relevant circuits and,

*Address correspondence to this author at the Instituto de Investigaciones Biomedicas, Universidad Nacional Autonoma de Mexico (UNAM), Apartado Postal 70228, Cuidad Universitaria, Mexico DF, CP 04510, Mexico; Tel: 5255-56223151; Fax: 56223369; E-mail: gokar@unam.mx

1570-159X/16 $58.00+.00

in the case of uncontrolled or chronic neuroinflammation, functional decline (for a review, see Ref. [32]).

After single or multiple peripheral treatment of mice with LPS, the increase in the numbers of F4/80-, CD11-, CD45- or Iba-1-positive cells as well as morphological changes characteristic for activated microglia were observed in numerous studies [22, 26, 27, 33-36]. However, there are also reports where authors did not observe microglia activation after single i.p. injection of LPS, although after multiple administration activated microglia were detected [37, 38].

It has been well documented that peripherally-injected LPS induced a variety of central effects mediated, in part, by pro-inflammatory cytokines released mainly from microglia. Although it is generally accepted that cytokines released in periphery do not diffuse across the blood-brain barrier (BBB), but they may transfer the signal to the brain [39-41], numerous studies in animals demonstrated that LPS is capable of stimulating from periphery the synthesis of pro-inflammatory cytokines in the brain [42-45]. However, despite the abundant literature available, the data on the presence of the main pro-inflammatory cytokines in the brain after LPS challenge differ according to different authors. The discrepancies in the results reported could be due to the numerous experimental details that are differing in all available reports: LPS or mouse strain used, site of injection, quantity of LPS applied, time after the challenge mice were sacrificed *etc*.

First studies reported robust and transient expression of interleukin-1β (IL-1β), IL-6 and TNF-α mRNA in various brain regions assessed by the reverse transcription polymerase chain reaction (RT-PCR) [42, 44, 46-49]. Different strains of mice (both males and females) were used in these studies: CH3/He, B6C3F1, C57BL/6J and CD-1. Intravenous or intraperitoneal injection of LPS at doses ranging from 0.02 mg/kg to 3 mg/kg was another variable in these studies. Moreover, mice were sacrificed at different time after the challenge, and this may explain, in part, different outcome seen because at certain concentrations LPS induces transient disease.

Subsequently, more studies were performed in wild type mice as well as in murine models of different neuro-degenerative diseases (AD, PD, ALS *etc*) using animals of different ages and, again, elevated and prolonged expression of IL-1β, IL-6 and TNF-α mRNA as well as proteins was documented in various brain regions after single or multiple peripheral administration of LPS. In the Tables **1** and **2** we are summarizing most frequently used protocols and their

Table 1. Summary of single LPS administration protocols and results.

Mouse Strain and Treatment Protocol	Results and Methods Applied	Refs.
BALB/c, young adult* or old*; LPS-0127:B8; i.p.0.33mg/kg. Sacrificed at 4h	Elevated IL-1β and IL-6 mRNA (RT-PCR) and protein (ELISA)	[50]
Same protocol; Sacrificed at 24 h	Elevated IL-1β mRNA and IL-6 protein	[50]
BALB/c, old; same protocol; Sacrificed at 24 h	Elevated IL-1β and IL-6 mRNA and IL-6 protein	[50]
C57BL/6J, ME7-infected (prion-disease model); i.p. 0.5mg/kg. Sacrificed at 6 h	Elevated IL-1β, IL-6 and TNF-α mRNA (RT-PCR) and IL-1β protein (ICH)	[37]
C57BL/6J; LPS-0111:B4; i.p.5mg/kg. Sacrificed at 1 h, 14 and 21 days, 10 months	Elevated TNF-α mRNA and protein (ELISA)	[22]
BALB/c, young adult and old; LPS-0127:B8; i.p.0.33mg/kg. Sacrificed at 4 h	Elevated IL-1β, IL-6 and TNF-α mRNA (RT-PCR)	[51]
BALB/c, young adult and old; LPS-0127:B8; i.p. 0.33mg/kg. Sacrificed at 4 h or 8 h	Elevated IL-1β mRNA (RT-PCR) and protein (FACS)	[52]
C57BL/6J, young adult; LPS-026:B6; i.p.2mg/kg. sacrificed at 4 h or 24 h	No effect observed	[53]
C57BL/6J, young adult; LPS-Salmonella Typhimurium; i.p.1mg/kg. Sacrificed at 4 days	Elevated IL-1β protein (ELISA)	[35]
ICR, young; LPS-Salmonella Typhimurium; i.p.5mg/kg. Sacrificed at 24 h	Elevated IL-6 protein (WB)	[54]
C57BL/6J, young; LPS-0111:B4; i.p. 2mg/kg. Sacrificed at 24 h	Elevated IL-1β, IL-6 and TNF-α mRNA and protein	[55]
B6C3F1, young adult; LPS-0111:B4; i.p. 10mg/kg. Sacrificed at 3 h	No statistically significant production of IL-1β, IL-6 and TNF-α protein (ELISA)	[56]
Same protocol. Sacrificed at 4,6 and 12 h	Elevated IL-6 protein (ELISA)	[56]

*young mice: 2 months of age; young adult mice: 3-4 months of age; adult mice: 12-13 months of age; old or aged mice: 20 or more months old.

Table 2. Summary of multiple LPS administration protocols and results.

Mouse Strain and Treatment	Results and Methods Applied	Refs.
3xTg-AD, young adult*; LPS-055:B5; i.p. 0.5mg/kg; twice per week/6 weeks. Sacrificed at 24h	Elevated IL-1β but not IL-6 or TNF-α mRNA (RT-PCR)	[27]
3xTg-AD, adult*; same protocol. Sacrificed at 48 h	Elevated IL-6 protein (ELISA)- statistically significant Elevated IL-1β protein (ELISA)- no statistical significance achieved	[33]
C57BL/6J, young adult; LPS-026:B6; i.p. 2mg/kg; dual injection at 0 and 16 h. Sacrificed at 4 h or 24 h	Elevated IL-1β, IL-6 and TNF-α mRNA	[53]
C57BL/6J; LPS-N/A; i.p. 0.25mg/kg; daily for 7 days. Sacrificed at 24 h	Elevated TNF-α and IL-1β mRNA	[34]
B6C3F1, young adult; LPS-0111:B4; i.p. 10mg/kg; 2 or 3 injections during 24 h. Sacrificed at 24 h	Elevated IL-1β, IL-6 and TNF-αprotein	[56]
B6C3F1, young adult; LPS-0111:B4; i.p. 0.5mg/kg; every 3 days during 3 months.	Elevated IL-1β and decreased TNF-α protein No changes in IL-6 protein (ELISA)	[56]

*young mice: 2 months of age; young adult mice: 3-4 months of age; adult mice: 12-13 months of age; old or aged mice: 20 or more months old.

outcome published recently. Cited papers, in turn, contain extensive review of previous work.

As can be seen, even in the case of the same mouse and LPS strain and almost similar experimental procedure, some authors observed elevated pro-inflammatory cytokines in the brain while others did not. Some authors measured both mRNA and protein levels while others evaluated (or reported) only mRNA or protein data. In some cases, it is not clear if the absence of a given cytokine is because authors measured it and obtained negative results or they did not perform the evaluation. Another important issue to be considered is the psychological stress that may lead to a pro-inflammatory status of the brain and to exaggerated microglia activation, and differences in animal management and care in the different laboratories may explain, in part, heterogeneity of results [57, 58]. However, certain reproducibility among different laboratories exists, and one may conclude that 1) peripheral administration of LPS leads to exacerbated neuroinflammation in old vs adult mice; 2) high doses as well as multiple administration of LPS increase the expression of pro-inflammatory cytokines in the brain. In biomedical research, the convergence of different methods for evaluating the same phenomena is another important issue, and, as can be seen below in Tables **1** and **2**, the elevated expression of pro-inflammatory cytokines was documented using different experimental approaches, like RT-PCR, ELISA, WB, FACS and immunocytochemistry.

An important point to be considered when using this model should be the mouse strain. Thus, C57BL/6J and FVB/NL mice were shown to be highly susceptible to systemic LPS challenge while A/J, C3H/HeJ and 129S1/SvImJ were reported to be resistant [59-61]. However, in another study from Yang's group, C57BL/6J mice were found to be resistant [62]. The great majority of APP-Tg mice as well as mouse models for Parkinson disease have mixed C57BL/6Jx129S1/Sv, C57BL/6JxSJL or C57BL/6JxC3H/HeJ background, and it is difficult to guess their susceptibility to systemic LPS [63-72].

Some unique observations were also reported. Thus, while the majority of studies in this model pointed to destructive role of activated microglia and molecules released and demonstrated M-1 (pro-inflammatory) cytokine profile, Chen and collaborators reported that one or multiple i.p. injections of 1mg/kg LPS prime microglia toward M2 (anti-inflammatory) phenotype and may lead to neuroprotection, and suggested LPS preconditioning for therapeutic applications to benefit patients who suffer from neurodegenerative diseases or brain trauma [38]. One likely reason for these contradictory results may be slightly different experimental conditions used. Also, it is also important to mention that in the latter study authors did not include (or did not report) in microarray analysis of M-1-related genes two important pro-inflammatory cytokines, IL-6 and IL-1β, known to be expressed in the brain of i.p. LPS-treated mice. Instead, they observed no changes in iNOS and TNF-α genes, in agreement with some previous research.

In conclusion, whether i.p. LPS injection in mice will have neurotoxic or neuroprotective effect, will depend on experimental conditions, and there are examples included in Tables **1** and **2**.

Astrogliosis

Astrocytes, the most abundant cell type in the CNS, have many essential functions in the healthy brain and respond to different forms of damage through a process called astrogliosis (for extensive recent reviews see Ref. [73-75]). Although the astrogliosis was shown to be a beneficial process to protect neurons and repair the tissue after CNS insult, under specific conditions reactive astrocytes can exacerbate neuroinflammation and tissue damage (for detailed reviews see Ref. [75-77]).

In LPS-treated mice an increase in the number of glial fibrillary acidic protein (GFAP)-positive cells and up-regulation of GFAP expression at different time points after challenge as well as astrocyte hypertrophy were reported by

some laboratories [25, 26, 34, 35, 58] while others did not observe such an increase [78].

iNOS and COX-2

Two pro-inflammatory effector enzymes, iNOS and COX-2, are induced and up-regulated upon inflammation and known to contribute to neurodegeneration. There is no detectable iNOSgene expression in the brain at baseline, while COX-2 was found to be expressed under normal conditions too and to participate in fundamental brain functions such as synaptic plasticity and memory consolidation (for a review see Refs. [79-81]). Enhanced expression of iNOS during an inflammatory response can increase the local production of NO which has been suggested to be involved in neurodegenerative processes, including the inhibition of mitochondrial respiration, axonal and synaptic damage, and the induction of neuronal apoptosis [82-85]. Genetic ablation and pharmacological inhibition of iNOS has been shown to protect mice from spatial memory dysfunction and depressive-like behavior [86, 87].

Numerous studies demonstrated increased levels of iNOS and COX-2 mRNA and protein in the brains of i.p. LPS-treated mice using RT-PCR, WB or immunohistochemistry [24, 49, 88-90]. While levels of mRNA picked between 3 and 6 h and then decreased to basal levels at 12-24 h after LPS treatment, elevated iNOS and COX-2 protein were detected by WB and immunohistochemistry at 6, 24 h and 3 days [35, 88, 91, 92]. Interestingly, induction of COX-2 occurred mainly in brain endothelia [89, 91, 93] and was not significantly region-specific [89]. However, Okuyama and collaborators detected COX-2 in activated astrocytes but not microglia after i.p. LPS injection [35]. COX-2 immuno-reactivity was observed mainly around the nuclear envelope as well as in dendritic and axonal domains [88, 93].

Up-regulation of iNOS was also evaluated by measuring the activation of the NO pathway after peripheral administration of LPS [94].

Synaptic Failure and Cognitive Dysfunction

It has been demonstrated that neuroinflammation impaired synaptic plasticity in the hippocampus, disrupted hippocampal-dependent learning and memory and increased neuronal death [37, 95-97]. These phenomena were also addressed in mice after single or multiple peripheral LPS administration. Authors detected increased neuronal apoptosis, progressive loss of dopaminergic neurons, reduced expression of brain-derived neurotrophic factor (BDNF), reduced serotonin release by serotonergic neurons, decreased levels of autophagy markers, reduced social behavior and locomotor activity as well as impaired performance in various learning and memory tasks, including two-way active avoidance conditioning test and the Morris water maze [22, 35, 37, 50, 51, 54-56, 96, 98-101]. Young and old C57BL/6J and BALB/c mice were used, and, as expected, greater cognitive dysfunction was observed in old animals reflecting higher neuroinflammation in elderly [51, 99]. However, it is noteworthy to mention findings reported by Sparkman and collaborators that old mice given repeated LPS injections had significantly longer latencies compared with controls, but authors contributed these results to reduced swim speed as well as anxiety-like symptoms and not necessarily to learning and memory dysfunction [99]. On the other hand, in a recent study by Ormerod and collaborators, swim speeds in C57BL/6J female mice (7-8 weeks-old) were unaffected one week after single intraperitoneal challenge with 5mg/kg LPS [102]. In addition, no statistically significant effect of LPS on learning and memory on hidden platform trials was observed one week later in these animals. Four weeks after challenge LPS-treated mice manifested latent spatial memory impairment but their ability to either learn a novel hidden platform location or locate a visible platform was similar to control group [102]. Finally, authors demonstrated that peripheral LPS compromises hippocampal neurogenesis [102].

Exacerbation of AD-like Pathology in APP-transgenic Mice

Few studies were performed in APP-transgenic mice to evaluate the effect of peripherally administered LPS [26, 27, 33, 103]. In the first study, Sheng and collaborators treated with LPS adult APPswe Tg mice intraperitoneally once a week for 12 weeks and observed microglia activation as determined by the increase in F4/80(+) cells [26]. In addition, LPS treatment increases brain levels of APP, APP C-terminal fragments and Aβ1-40/42 as determined by immunohistochemical analysis and western blotting [26]. Subsequently, the effect of a systemic challenge with LPS on brain was assessed in three studies in 3xTg-AD mice that develop both Aβ and tau pathology [27, 33, 103]. All three studies used the same LPS strain, but other experimental conditions were not similar. In summary, i.p. LPS treatment of young adult (4-month-old) 3xTg-AD mice twice per week for 6 weeks induced microglial activation, IL-1β expression and tau phosphorylation, but unlike in the previous report by Sheng and collaborators [26], did not affect APP processing and Aβ deposition [27]. No significant effect of LPS on the onset and progression of Aβ pathology was observed in 12-month-old 3xTg-AD mice treated by using the same protocol [33]. However, in the latter study authors also observed exacerbation of tau pathology as well as learning and memory impairments in LPS-treated mice [33]. Finally, Valero and collaborators demonstrated that a single i.p. injection of LPS in 3xTG-AD mice has a long-term impact on adult neurogenesis and lead to the development of memory deficits [103].

All these studies suggested that systemic LPS-induced inflammation may trigger neuroinflammation with subsequent Aβ and/or tau pathology, neurodegeneration and cognitive decline.

NUTRACEUTICALS: PRECLINICAL STUDIES IN LPS-INDUCED NEUROINFLAMMATION MODEL

As an important and widely-used animal model of peripherally induced neuroinflammation and neuro-degeneration, LPS-treated mice were also widely used to screen synthetic drugs and natural products. This review will focus on natural products with therapeutic properties known

as nutraceuticals and used to reduce LPS-induced neuro-inflammation in mouse brain. Comprehensive review on nutraceuticals with anti-inflammatory and neuroprotective properties in other models as well as possible multiple mechanisms of their action may be found elsewhere [104-108].

Resveratrol

Resveratrol is a polyphenol found mainly in grapes and red vine and shown to confer protection *in vitro* and *in vivo* against oxidative stress, inflammatory and cardiovascular diseases, cancer as well as neuropathology associated with neurodegenerative diseases, brain trauma and cerebral ischemia (see excellent recent reviews Refs. [109-111]).

It has been shown that dietary supplementation of resveratrol during four weeks reduced IL-1β mRNA in the hippocampus of aged (22-24 months) male BALB/c mice treated intraperitoneally with LPS [112]. Interestingly, in this study resveratrol did not affect LPS-induced sickness behavior in young adult mice (3-6 months) at any time post-injection, however, ameliorated LPS-induced locomotor deficits in aged (22-24 months) mice beginning at 8 h [112]. In addition, resveratrol completely blocked LPS-induced inhibition of working memory in aged mice [112]. In another study, adult male Swiss Albino mice were daily i.p. injected with resveratrol during 7 days and then challenged by a single i.p. administration of LPS (4mg/kg) [113]. Authors showed that resveratrol increases the survival rate, abolished NO elevation to near control levels and counteracted all LPS-induced iron disturbances in the brain [113]. Protective effects of resveratrol on memory decline were also observed in mice first treated i.p. with LPS to induce neuroinflammation and then injected with resveratrol for 7 days, suggesting possible therapeutic application [114].

Curcumin

Curcumin, the main ingredient of the Indian spice turmeric, was shown to display anti-inflammatory, anti-oxidant, anti-cancer and anti-bacterial properties by multiple mechanisms (see comprehensive recent reviews Refs. [115-119]). In mouse model of neuroinflammation induced by i.p. LPS injection, curcumin was able to reduce iNOS and IL-1β levels in the brain [120]. Wang and collaborators demonstrated that pretreatment with curcumin (50 mg/kg, i.p.) for 7 consecutive days reverses i.p. LPS-induced alterations in the forced swimming, tail suspension and sucrose preference tests and attenuates microglial activation and overproduction of pro-inflammatory cytokines (IL-1β and TNF-α) as well as levels of iNOS and COX-2 mRNA in the hippocampus and prefrontal cortex of adult male Kun-Ming mice [121]. Because of its insolubility in water, poor bioavailability and difficulty to cross blood-brain barrier, curcumin has to be used with new delivery systems. One of these strategies was tested in LPS-treated mice [122]. Authors demonstrated that intranasally administered exosome encapsulated curcumin is rapidly transported to the brain and inhibits i.p. LPS-induced increase in brain IL-1β as detected by FACS and RT-PCR analysis in C57BL/6J mice [122].

Ginsenosides and Glycyrrhizin

Ginsenosides are ginseng saponins shown to modulate inflammatory processes, as well as to inhibit neuron death, mitochondrial dysfunction and tumor growth [123-126]. In LPS-induced neuroinflammation model ginsenoside Rg_3 has been demonstrated to attenuate pro-inflammatory cytokines (TNF-α, IL-1β and IL-6) mRNA expression in the brain[24]. In addition, inhibition of microglia activation (evaluated by Western blot and immunohistochemistry using anti-Iba 1 antibody) and iNOS and COX-2 expression (evaluated by immunohistochemistry) in the brain of i.p. LPS-treated C57BL/6J adult male mice was observed after oral administration of Rg_3 [24]. In another study, Lee and collaborators demonstrated that ginsenoside Rb1 reduced microglia activation and pro-inflammatory cytokines (TNF-α, IL-1β and IL-6) and COX-2 mRNA expression in the brain following single i.p. administration of 3 mg/kg of LPS [127]. In this study, COX-2 reduction was also observed by IHQ [127].

Glycyrrhizin (GRZ), a triterpenoid saponin compound composed of one molecule of glycyrrhetinic acid and two molecules of glucuronic acid, was shown to have anti-inflammatory and neuroprotective effects *in vitro* and *in vivo* [128-130]. In peripherally LPS-treated C57BL/6J mice, orally administered GRZ significantly reduced brain expression of TNF-a, IL-1β, iNOS and COX-2 as determined by RT-PCR, immunohistochemical analysis and western blotting [92]. Also, authors demonstrated that GRZ ameliorates the memory deficits as observed in Morris water maze test [92].

Oenothein B

Oenothein B, a dimeric macrocyclic ellagitannin, was shown to have anti-inflammatory, anti-oxidant and anti-tumor activity both *in vitro and in vivo* [131-133]. Okuyama and collaborators showed that oenothein B suppresses microglial activation and COX-2 production in the hippocampus and striatum of i.p. LPS-treated mice [35].

Flavonoids

A group of dietary polyphenols, known as flavonoids, has been shown to inhibit inflammatory processes and to prevent age-related neurodegeneration and cognitive decline (reviewed in Refs [107, 108, 134, 135]). Their potential to attenuate neuroinflammation may be explained by inhibition of microglial activation and pro-inflammatory cytokines, as well as iNOS and COX-2 expression [107, 108].

Acacetin, the active compound of the crude extract of the leaves of Robinia pseudoacacia, has been shown to suppress microglia activation in i.p.LPS-treated adult male C57BL/6J mice after oral administration for 3 days [136].

It has been demonstrated that orally administered epigallocatechin-3-gallate (EGCG), the most abundant biologically active compound in tea, prevented memory impairment in 5-week-old male IcrTacSam:ICR mice caused by 7daily i.p. LPS injections, as determined by water maze and passive avoidance performance tests [137]. Moreover,

authors observed inhibition of LPS-induced iNOS, COX-2 and GFAP expression in the brains of EGCG-administered mice, as determined by immunohistochemical analysis and Western blotting [138].

Purple sweet potato color (PSPC), a natural anthocyanin from the flavonoid family, has been shown to suppress iNOS, COX-2, TNF-α, IL-1β and IL-6 expression in LPS-treated mouse brain and to reverse the impairment of motor and exploration behavior induced by LPS [138].

CONCLUSIONS

Neuroinflammation is now known to contribute to and exacerbate the pathology of neurodegenerative diseases. Better understanding of the mechanisms of neuro-inflammation induced by peripheral infection may lead to discovery of new therapeutic targets as well as new treatment approaches. The strategy of reducing inflammation in neurodegenerative disease has attracted increasing attention in recent years, and numerous synthetic and natural compounds are being tested in pre-clinical models as well as in clinical trials. However, more studies are needed to define which immune pathways or molecules, participating in inflammatory events leading to neurodegeneration, should be targeted. Importantly, we should always keep in mind that phenomena observed in mice may not occur in the same way in humans because of differences between mouse and human immune system (for a review see Ref. [139]). A systemic comparison of gene expression patterns in three inflammatory conditions – trauma/hemorrhage, burn and endotoxemia- showed poor correlation between mouse and human immune responses [140]. However, in the latter study LPS was administered to mice in very low concentrations and it is not possible to compare their results with observations summarized and discussed in this review. Also, authors studied gene expression using blood samples and did not address neuroinflammation [140]. Nevertheless, we completely agree that although peripheral LPS-induced mouse model of neuroinflammation is an important tool for deciphering pathological mechanisms involved in neurodegeneration as well as for testing potential therapeutic molecules, caution is warranted when translating results to human studies.

Importantly, combination of strategies targeting simultaneously different pathological pathways, "systems therapeutics", may be more appropriate for a range of multifactorial neurodegenerative diseases with a known neuroinflammatory component.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Funding provided by DGAPA-UNAM (IN200713) and CONACyT, MEXICO (177269) to G.G. MNC is recipient of a doctoral scholarship from CONACyT and Doctorado en Ciencias Bioquimicas, UNAM, MEXICO.

REFERENCES

[1] Philips, T.; Robberecht, W. Neuroinflammation in amyotrophic lateral sclerosis: role of glial activation in motor neuron disease. *Lancet Neurol.,* **2011**, *10*(3), 253-263. http://dx.doi.org/10.1016/S1474-4422(11)70015-1

[2] Eikelenboom, P.; Hoozemans, J.J.; Veerhuis, R.; van Exel, E.; Rozemuller, A.J.; van Gool, W., A. Whether, when and how chronic inflammation increases the risk of developing late-onset Alzheimer´s disease. *Alzheimers Res. Ther.,* **2012**, *4*(3), 15. http://dx.doi.org/10.1186/alzrt118

[3] Blandini, F. Neural and immune mechanisms in the pathogenesis of Parkinson's disease. *J. Neuroimmune Pharmacol.,* **2013**, *8*(1), 189-201. http://dx.doi.org/10.1007/s11481-013-9435-y

[4] Evans, M.C.; Couch, Y.; Sibson, N.; Turner, M.R. Inflammation and neurovascular changes in amyotrophic lateral sclerosis. *Mol. Cell. Neurosci.,* **2013**, *53*, 34-41. http://dx.doi.org/10.1016/j.mcn.2012.10.008

[5] Krstic, D.; Knuessel, I. Deciphering the mechanism underlying late-onset Alzheimer disease. *Nat. Rev. Neurol.,* **2013**, *9*(1), 25-34. http://dx.doi.org/10.1038/nrneurol.2012.236

[6] Murta, V.; Ferrari, C.C. Influence of peripheral inflammation on the progression of multiple sclerosis: evidence from clinic and experimental animal models. *Mol. Cell. Neurosci.,* **2013**, *53,* 6-13. http://dx.doi.org/10.1016/j.mcn.2012.06.004

[7] Amor, S.; Peferoen, L.A.; Vogel, D.Y.; van der Valk, P.; Baker, D.; van Noort, J.M. Inflammation in neurodegenerative diseases – an update. *Immunology,* **2014**, *142*(2), 151-166. http://dx.doi.org/10.1111/imm.12233

[8] Heneka, M.T.; Kummer, M.P.; Latz, E. Innate immune activation in neurodegenerative disease. *Nat. Rev. Immunol.,* **2014**, *14*(7), 463-477. http://dx.doi.org/10.1038/nri3705

[9] Pasqualetti, G.; Brooks, D.J.; Edison, P. The role of neuroinflammation in dementias. *Curr. Neurol. Neurosci. Rep.,* **2015**, *15*(4), 17. http://dx.doi.org/10.1007/s11910-015-0531-7

[10] Luterman, J.D.; Haroutunian V.; Yemul, S.; Ho, L.; Purohit, D.; Aisen, P.S.; Mohs, R.; Pasinetti, G.M. Cytokine gene expression as a function of the clinical progression of Alzheimer disease dementia. *Arch. Neurol.,* **2000**, *57*(8), 1153-1160. http://dx.doi.org/10.1001/archneur.57.8.1153

[11] Serrano-Pozo, A.; Mielke, M.L.; Gomez-Isla, T.; Betensky, R.A.; Growdon, J.H.; Frosch, M.P.; Hyman, B.T. Reactive glia not only associates with plaques but also parallels tangles in Alzheimer´s disease. *Am. J. Pathol.,* **2011**, *179*(3), 1373-1384. http://dx.doi.org/10.1016/j.ajpath.2011.05.047

[12] McGeer, P.L.; McGeer, E.G. The amyloid cascade-inflammatory hypothesis of Alzheimer disease: implications for therapy. *Acta Neuropathol.,* **2013**, *126*(4), 479-497. http://dx.doi.org/10.1007/s00401-013-1177-7

[13] Exalto, L.G.; Whitmer, R.A.; Kappele, L.J.; Biessels, G.J. An update on type 2 diabetes, vascular dementia and Alzheimer´s disease. *Exp. Gerontol.,* **2012**, *47*(11), 858-864. http://dx.doi.org/10.1016/j.exger.2012.07.014

[14] Ledesma, M.D.; Dotti, C.G. Peripheral cholesterol, metabolic disorders and Alzheimer´s disease. *Front. Biosci.,* **2012**, *4,* 181-194. http://dx.doi.org/10.2741/E368

[15] Misiak, B.; Leszek, J.; Kiejna, A. metabolic syndrome, mild cognitive impairment and Alzheimer´s disease – the emerging role of systemic low-grade inflammation and adiposity. *Brain Res. Bull.,* **2012**, *89*(3-4), 144-149. http://dx.doi.org/10.1016/j.brainresbull.2012.08.003

[16] Polidori, M.C.; Pientka, L.; Mecocci, P. A review of the major vascular risk factors related to Alzheimer´s disease. *J. Alzheimers Dis.,* **2012**, *32*(3), 521-530.

[17] Spielman, L.J.; Little, J.P.; Klegeris, A. Inflammation and insulin/IGF-1 resistance as the possible link between obesity and neurodegeneration. *J. Neuroimmunol.,* **2014**, *273*(1-2), 8-21. http://dx.doi.org/10.1016/j.jneuroim.2014.06.004

[18] Holmes, C.; Cotterell, D. Role of infection in the pathogenesis of Alzheimer´s disease: implications for treatment. *CNS Drugs,* **2009**, *23*(12), 993-1002. http://dx.doi.org/10.2165/11310910-000000000-00000

[19] Holmes, C. Review: systemic inflammation and Alzheimer´s disease. *Neuropathol. Appl. Neurobiol.,* **2013**, *39*(1), 51-68. http://dx.doi.org/10.1111/j.1365-2990.2012.01307.x

[20] Su, X.; Federoff, H.J. Immune responses in Parkinson´s disease: interplay between central and peripheral immune systems. *Biomed. Res. Int.,* **2014**, *2014,* 275178.

[21] Magrone, T.; Marzulli, G.; Jirillo, E. Immunopathogenesis of neurodegenerative diseases: current therapeutic models of neuroprotection with special reference to natural products. *Curr. Pharm. Des.,* **2012**, *18*(1), 34-42. http://dx.doi.org/10.2174/138161212798919057

[22] Qin, L.; Wu, X.; Block, M.L.; Liu, Y.; Breese, G.R.; Hong, J.S.; Knapp, D.J.; Crews, F.T. Systemic LPS causes chronic neuroinflammation and progressive neurodegeneration. *Glia,* **2007**, *55*(5), 453-462. http://dx.doi.org/10.1002/glia.20467

[23] Erickson, M.A.; Banks, W.A. Cytokine and chemokine responses in serum and brain after single and repeated injections of lipopolysaccharide: multiplex quantification with path analysis. *Brain Behav. Immun*., **2011**, *25*(8), 1637-1648. http://dx.doi.org/10.1016/j.bbi.2011.06.006

[24] Park, S.M.; Choi, M.S.; Sohn, N.W.; Shin, J.W. Ginsenoside Rg_3 attenuates microglia activation following systemic lipopolysaccharide treatment in mice. *Biol. Pharm. Bull*., *35*(9), 1546-1552. http://dx.doi.org/10.1248/bpb.b12-00393

[25] Biesmans, S.; Meert, T.F.; Bouwknecht, J.A.; Acton, P.D.; Davoodi, N.; De Haes, P.; Kuijlaars, J.; Langlois, X.; Matthews, L. J.; Ver Donck, L.; Hellings, N.; Nuydens, R. Systemic immune activation leads to neuroinflammation and sickness behavior in mice. *Mediators Inflamm.,* **2013**, *2013*, 271359.

[26] Sheng, J.G.; Bora, S.H.; Xu, G.; Borchelt, D.R.; Price, D.L.; Koliatsos, V.E. Lipopolysaccharide-induced neuroinflammation increases intracellular accumulation of amyloid precursor protein and amyloid β peptide in APPswe transgenic mice. *Neurobiol. Dis.,* **2003**, *14,* 133-145. http://dx.doi.org/10.1016/S0969-9961(03)00069-X

[27] Kitazawa, M.; Oddo, S.; Yamasaki, T.R.; Green, K.N.; LaFerla, F.M. Lipopolysaccharide-induced inflammation exacerbates tau pathology by a cyclin-dependent kinase 5-mediated pathway in a transgenic model of Alzheimer´s disease. *J. Neurosci.,* **2005**, *25*(39), 8843-8853. http://dx.doi.org/10.1523/JNEUROSCI.2868-05.2005

[28] Schwartz, M.; Kipnis, J.; Rivest, S.; Prat, A. How do immune cells support and shape the brain in health, disease, and aging? *J. Neurosci.,* **2013**, *33*(45), 17587-17596. http://dx.doi.org/10.1523/JNEUROSCI.3241-13.2013

[29] Nayak, D.; Roth, T.L.; McGavern, D.B. Microglia development and function. *Annu. Rev. Immunol.,* **2014**, *32,* 367-402. http://dx.doi.org/10.1146/annurev-immunol-032713-120240

[30] Casano, A.M.; Peri, F. Microglia: multitasking specialists of the brain. *Dev. Cell,* **2015**, *32*(4), 469-477. http://dx.doi.org/10.1016/j.devcel.2015.01.018

[31] Benakis, C.; Garcia-Bonilla, L.; Iadecola, C.; Anrather, J. The role of microglia and myeloid immune cells in acute cerebral ischemia. *Front. Cell. Neyrosci.,* **2015**, *8,* 461. http://dx.doi.org/10.3389/fncel.2014.00461

[32] Tremblay, M.E.; Stevens, B.; Sierra, A.; Wake, H.; Bessis, A.; Nimmerjahn, A. The role of microglia in the healthy brain. *J. Neurosci.,* **2011**, *31*(45), 16064-16069. http://dx.doi.org/10.1523/JNEUROSCI.4158-11.2011

[33] Sy, M.; Kitazawa, M.; Medeiros, R.; Whitman, L.; Cheng, D.; Lane, T.E.; LaFerla., F.M. Inflammation induced by infection potentiates pathological features in transgenic mice. *Am. J. Pathol.,* **2011**, *178*(6), 2811-2822. http://dx.doi.org/10.1016/j.ajpath.2011.02.012

[34] Ifuku, M.; Katafuchi, T.; Mawatari, S.; Noda, M.; Miake, K.; Sugiyama, M.; Fujino, T. Anti-inflammatory/anti-amyloidogenic effects of plasmalogens in lipopolysaccharide-induced neuro-inflammation in adult mice. *J. Neuroinflamm.,* **2012**, *9,* 197. http://dx.doi.org/10.1186/1742-2094-9-197

[35] Okuyama, S.; Makihata, N.; Yoshimura, M.; Amakura, Y.; Yoshida, T.; Nakajima, M.; Furukawa, Y. Oenothein B suppresses lipopolysaccharide (LPS)-induced inflammation in mouse brain. *Int. J. Mol. Sci.,* **2013**, *14*, 9767-9778. http://dx.doi.org/10.3390/ijms14059767

[36] Jin, M.; Jang, E.; Suk, K. Lipocalin-2 acts as a neuroinflammatogen in lipopolysaccharide-injected mice. *Exp. Neurobiol.,* **2014**, *23*(2), 155-162. http://dx.doi.org/10.5607/en.2014.23.2.155

[37] Cunningham, C.; Wilcockson, D. C.; Campion, S.; Lunnon, K.; Perry, V. H. Central and systemic endotoxin challenges exacerbate the local inflammatory response and increase neuronal death during chronic neurodegeneration. *J. Neurosci.,* **2005**, *25*(40), 9275-9284. http://dx.doi.org/10.1523/JNEUROSCI.2614-05.2005

[38] Chen, Z.; Jalabi, W.; Shpargel, K.B.; Farabaugh, K.T.; Dutta, R.; Yin, X.; Kidd, G.J.; Bergmann, C.C.; Stohlman, S.A.; Trapp, B.D. Lipopolysaccharide-induced microglial activation and neuroprotection against experimental brain injury is independent on hematogenous TLR4. *J. Neurosci.,* **2012**, *32*(34), 11706-11715. http://dx.doi.org/10.1523/JNEUROSCI.0730-12.2012

[39] Elmquist, J.K.; Scammell, T.E.; Saper, C.B. Mechanisms of CNS response to systemic immune challenge: the febrile response. *Trends Neurosci.,* **1997**, *20*(12), 565-570. http://dx.doi.org/10.1016/S0166-2236(97)01138-7

[40] Vallieres, L.; Rivest, S. Regulation of the genes encoding interleukin-6, its receptor, and gp130 in the rat brain in response to the immune activator lipopolysaccharide and proinflammatory cytokine interleukin -1beta. *J. Neurochem.,* **1997**, *69*(4), 1668-1683. http://dx.doi.org/10.1046/j.1471-4159.1997.69041668.x

[41] Lacroix, S.; Rivest, S. Effect of acute systemic inflammatory response and cytokines on the transcription of the genes encoding cyclooxygenase enzymes (COX-1 and COX-2) in the rat brain. *J. Neurochem.,* **1998**, *70*(2), 452-466. http://dx.doi.org/10.1046/j.1471-4159.1998.70020452.x

[42] Laye, S.; Parnet, P.; Goujon, E.; Dantzer, R. Peripheral administration of lipopolysaccharide induces the expression of cytokine transcripts in the brain and pituitary of mice. *Brain Res. Mol. Brain Res.,* **1994**, *27*(1), 157-162. http://dx.doi.org/10.1016/0169-328X(94)90197-X

[43] Brugg, B.; Dubreuil, Y.L.; Huber, G.; Wollman, E.E.; Delhaye-Bouchaud, N.; Mariani, J. Inflammatory processes induce beta-amyloid precursor protein changes in mouse brain. *Proc. Natl. Acad. Sci. USA,* **1995**, *92*(7), 3032-3035. http://dx.doi.org/10.1073/pnas.92.7.3032

[44] Gabellec, M.M.; Griffais, R.; Fillion, G.; Haour, F. Expression of interleukin 1 alpha, interleukin 1 beta and interleukin 1 receptor antagonist mRNA in mouse brain: regulation by bacterial lipopolysaccharide (LPS) treatment. *Brain Res. Mol. Brain Res.,* **1995**, *31*(1-2), 122-130. http://dx.doi.org/10.1016/0169-328X(95)00042-Q

[45] Pitossi, F.; del Rey, A.; Kabiersch, A.; Besedovsky, H. Induction of cytokine transcripts in the central nervous system and pituitary following peripheral administration of endotoxin to mice. *J. Neurosci. Res.,* **1997**, *48*(4), 287-298. http://dx.doi.org/10.1002/(SICI)1097-4547(19970515)48:4%3C287::AID-JNR1%3E3.0.CO;2-7

[46] Ban, E.; Haour, F.; Lenstra, R. Brain interleukin 1 gene expression induced by peripheral lipopolysaccharide administration. *Cytokine,* **1992**, *4*(1), 48-54. http://dx.doi.org/10.1016/1043-4666(92)90036-Q

[47] Takao, T.; Culp, S.G.; De Souza, E.B. Reciprocal modulation of interleukin-1 beta (IL-1beta) and IL-1 receptors by lipopolysaccharide (endotoxin) treatment in the mouse brain-endocrine-immune axis. *Endocrinology,* **1993**, *132*(4), 1497-1504.

[48] Kishikawa, H.; Lawrence, D.A. Differential production of interleukin-6 in the brain and spleen of mice treated with lipopolysaccharide in the presence and absence of lead. *J. Toxicol. Environ. Health A.,* **1998**, *53*(5), 357-373. http://dx.doi.org/10.1080/009841098159222

[49] Brochu, S.; Olivier, M.; Rivest, S. Neuronal activity and transcription of proinflammatory cytokines, IkappaBalpha, and iNOS in the mouse brain during acute endotoxemia and chronic infection with Trypanosoma brucei brucei. *J. Neurosci. Res.,* **1999**, *57*(6), 801-816. http://dx.doi.org/10.1002/(SICI)1097-4547(19990915)57:6%3C801::AID-JNR5%3E3.0.CO;2-B

[50] Godbout, J.P.; Chen, J.; Abraham, J.; Richwine, A.F.; Berg, B.M.; Kelley, K.W.; Jphnson, R.W. Exaggerated neuroinflammation and sickness behavior in aged mice following activation of the peripheral innate immune system. *FASEB J.,* **2005**, *19*(10), 1329-1331.

[51] Chen, J.; Buchanan, J.B.; Sparkman, N.L.; Godbout, J.P.; Freund, G.G.; Johnson, R.W. Neuroinflammation and disruption in working memory in aged mice after acute stimulation of the peripheral

innate immune system. *Brain Behav. Immun.,* **2008**, *22,* 301-311. http://dx.doi.org/10.1016/j.bbi.2007.08.014

[52] Henry, C.J.; Huang, Y.; Wynne, A.M.; Godbout, J.P. Peripheral lipopolysaccharide (LPS) challenge promotesmicroglial hyperactivity in aged mice that is associated with exaggerated induction of both pro-inflammatory IL-1β and anti-inflammatory IL-10 cytokines. *Brain Behav. Immun.,* **2009**, *23,* 309-317. http://dx.doi.org/10.1016/j.bbi.2008.09.002

[53] Ip, J.P.; Nocon, A.L.; Hofer, M.J.; Lim, S.L.; Muller, M.; Campbell, I.L. Lipocalin 2 in the central nervous system host response to systemic lipopolysaccharide administration. *J. Neuroinflammation,* **2011**, *8*, 124. http://dx.doi.org/10.1186/1742-2094-8-124

[54] Fu, Y.Y.; Zhang, F.; Zhang, L.; Liu, H.Z.; Zhao, Z.M.; Wen, X.R.; Wu, J.; Qi, D.S.; Sun, Y.; Du, Y.; Dong, H.Y.; Liu, Y.H.; Song, Y.J. Mangiferin regulates interleukin-6 and cystathionine-b-synthase in lipopolysaccharide-induced brain injury. *Cell. Mol. Neurobiol.,* **2014**, *34*(5), 651-657. http://dx.doi.org/10.1007/s10571-014-0039-8

[55] Cazareth, J.; Guyon, A.; Heurteaux, C.; Chabry, J.; Petit-Paitel, A. Molecular and cellular neuroinflammatory status of mouse brain after systemic lipopolysaccharide challenge: importance of CCR2/CCL2 signaling. *J. Neuroinflamm.,* **2014**, *11*, 132. http://dx.doi.org/10.1186/1742-2094-11-132

[56] Francois, A.; Terro, F.; Quellard, N.; Fernandez, B.; Chassaing, D.; Janet, T.; Rioux-Bilan, A.; Paccalin, M.; Page, G. Impairment of autophagy in the central nervous system during lipopolysaccharide-induced inflammatory stress in mice. *Mol. Brain,* **2014**, *7*(1), 56. http://dx.doi.org/10.1186/s13041-014-0056-z

[57] Wohleb, E.S.; Fenn, A.M.; Pacenta, A.M.; Powell, N.D.; Sheridan, J.F.; Godbout, J.P. Peripheral innate immune challenge exaggerated microglia activation, increased the number of inflammatory CNS macrophages, and prolonged social withdrawal in socially defeated mice. *Psyconeuroendocrinology,* **2012**, *37*(9), 1491-1505. http://dx.doi.org/10.1016/j.psyneuen.2012.02.003

[58] Biesmans, S.; Acton, P.D.; Cotto, C.; Langlois, X.; Donck, L.V.; Bouwknecht, J.A.; Aelvoet, S.A.; Hellings, N.; Meert, T.F.; Nuydens, R. Effect of stress and peripheral immune activation on astrocyte activation in transgenic bioluminescent Gfap-luc mice. *Glia,* **2015**, *63,* 1126-1137. http://dx.doi.org/10.1002/glia.22804

[59] Hopkins, W.; Gendron-Fitzpatrick, A.; McCarthy, D.O.; Haine, J.E.; Uehling, D.T. Lipopolysaccharide-responder and nonresponder C3H mouse strains are equally susceptible to an induced Escherichia coli urinary tract infection. *Infect. Immun.,* **1996**, *64*(4), 1369-1372.

[60] De Maio, A.; Mooney, M.L.; matesic, L.E.; Paidas, C.N.; Reeves, R.H. Genetic component in the inflammatory response induced by bacterial lipopolysaccharide. *Shock,* **1998**, *10*(5), 319-323. http://dx.doi.org/10.1097/00024382-199811000-00002

[61] Yang, I.V.; Rutledge, H.R.; Yang, J.; Warg, L.A.; Sevilla, S.D.; Schwartz, D.A. A locus on chromosome 9 is associated with defferential response of 129S1/SvlmJ and FVB/NJ strains of mice to systemic LPS. *Mamm. Genome,* **2011**, *22*(9-10), 518-529. http://dx.doi.org/10.1007/s00335-011-9340-8

[62] Yang, I.V.; Alper, S.; Lackford, B.; Rutledge, H.; Warg, L.A.; Burch, L.H.; Schwatrz, D.A. Novel regulators of the systemic response to lipopolysaccharide. *Am. J. Respir. Cell. Mol. Biol.,* **2011**, *45*(2), 393-402. http://dx.doi.org/10.1165/rcmb.2010-0342OC

[63] Hsiao, K.; Chapman, P.; Nilsen, S.; Eckman, C.; Harigaya, Y.; Younkin, S.; Yang, F.; Cole, G. Correlative memory deficits, Abeta elevation, and amyloid plaques in transgenic mice. *Science,* **1996**, *274*(5284), 99-102. http://dx.doi.org/10.1126/science.274.5284.99

[64] irizzary, M.C.; McNamara, M.; Fedorchak, K.; Hsiao, K.; hyman, B.T. APPSwe transgenic mice develop age-related A beta deposits and neuropil abnormalities, but no neuronal loss in CA1. *J. Neuropathol. Exp. Neurol.,* **1997**, *56*(9), 965-973. http://dx.doi.org/10.1097/00005072-199709000-00002

[65] Johnson-Wood, K.; Lee, M.; Motter, R.; Hu, K.; Gordon, G.; Barbour, R.; Khan, K.; Gordon, M.; Tan, H.; Games, D.; Leiberburg, I.; Schenk, D.; Seubert, P.; McConlogue, L. Amyloid precursor protein processing and A beta42 deposition in a transgenic mouse model of Alzheimer disease. *Proc. Natl. Acad. Sci. USA,* **1997**, *94*(4), 1550-1555. http://dx.doi.org/10.1073/pnas.94.4.1550

[66] Masliah, E.; Rockenstein, E. Genetically altered transgenic models of Alzheimer´s disease. *J. Neural. Transm. Suppl.,* **2000**, *59,* 175-183. http://dx.doi.org/10.1007/978-3-7091-6781-6_20

[67] Oddo, S.; Caccamo, A.; Shepherd, J.D.; Murphy, M.P.; Golde, T.E.; Kayed, R.; Metherate, R.; Mattson, M.P.; Akbari, Y.; LaFerla, F. M. Triple-transgenic model of Alzheimer´s disease with plaques and tangles: intracellular Abeta and synaptic dysfunction. *Neuron,* **2003**, *39*(3), 409-421. http://dx.doi.org/10.1016/S0896-6273(03)00434-3

[68] German, D.C.; Nelson, O.; Liang, F.; Liang, C.L.; Games, D. The PDAPP mouse model of Alzheimer´s disease: locus coeruleus neuronal shrinkage. *J. Comp. Neurol.,* **2005**, *492*(4), 469-476. http://dx.doi.org/10.1002/cne.20744

[69] Meredith, G.E.; Totterdel, S.; Potshkin, J.A.; Surmeier, D.J. Modelling PD pathogenesis in mice: advantages of a chronic MPTP protocol. *Parkinsonism Relat. Disord.,* **2008**, *14*(Suppl. 2), S112-115. http://dx.doi.org/10.1016/j.parkreldis.2008.04.012

[70] Crews, L.; Rockenstein, E.; masliah, E. APP transgenic modeling of Alzheimer´s disease: mechanisms of neurodegeneration and aberrant neurogenesis. *Brain Struct. Funct.,* **2010**, *214*(3-4), 116-126.

[71] Bove, J.; Perier, C. Neurotoxin-based models of Parkinson´s disease. *Neuroscience,* **2012**, *211,* 51-76. http://dx.doi.org/10.1016/j.neuroscience.2011.10.057

[72] Chesselet, M.F.; Richter, F.; Zhu, C.; Magen, I.; Watson, M.B.; Subramanian, S.R. A progressive mouse model of Parkinson´s disease: the Thy1-aSyn ("Line61") mice. *Neurotherapeutics,* **2012**, *9*(2), 297-314. http://dx.doi.org/10.1007/s13311-012-0104-2

[73] Chaboub, L.S.; Deneen, B. Developmental origins of astrocyte heterogeneity: The final frontier of CNS development. *Dev. Neurosci.,* **2012**, *34*(5), 379-388. http://dx.doi.org/10.1159/000343723

[74] Sofroniew, M.V. Astrocyte barriers to neurotoxic inflammation. *Nat. Rev. Neurosci.,* **2015**, *16*(5), 249-263. http://dx.doi.org/10.1038/nrn3898

[75] Sofroniew, M.V. Astrogliosis. *Cold Spring Harb. Perspect. Biol.,* **2015**, *7,* a020420. http://dx.doi.org/10.1101/cshperspect.a020420

[76] Kang, W.; Hebert, J.M. Signaling pathways in reactive astrocytes, a genetic perspective. *Mol. Neurobiol.,* **2011**, *43,* 147-154. http://dx.doi.org/10.1007/s12035-011-8163-7

[77] Burda, J.E.; Sofroniew, M.V. Reactive gliosis and the multicellular response to CNS damaga and disease. *Neuron,* **2014**, *81*(2), 229-248. http://dx.doi.org/10.1016/j.neuron.2013.12.034

[78] Camara , M.L.; Corrigan, F.; Jaehne, E.J.; Jawahar, M.C.; Anscomb, H.; Baune, B.T. Effects of centrally administered etanercept on behavior, microglia, and astrocytes in mice following a peripheral immune challenge. *Neuropsycopharmacology,* **2015**, *40,* 502-512. http://dx.doi.org/10.1038/npp.2014.199

[79] Dubois, R.N.; Abramson, S.B.; Crofford, L.; Gupta, R.A.; Simon, L.S.; van de Putte, L.B.A.; Lipsky, P.E. Cyclooxygenase in biology and disease. *FASEB J.,* **1998**, *12,* 1063-1073.

[80] Heneka, M.T.; Feinstein, D.L. Expression and function of inducible nitric oxide synthase in neurons. *J. Neuroimmunol.,* **2001**, *114*(1-2), 8-18. http://dx.doi.org/10.1016/S0165-5728(01)00246-6

[81] Minghetti, L. Cyclooxygenase-2 (COX-2) in inflammatory and degenerative brain diseases. *J. Neuropathol. Exp.Neurol.,* **2004**, *63*(9), 901-910. http://dx.doi.org/10.1093/jnen/63.9.901

[82] Brown, G.C. Mechanisms of inflammatory neurodegeneration: iNOS and NADPH oxidase. *Biochem. Soc. Trans.,* **2007**, *35,* 1119-1121. http://dx.doi.org/10.1042/BST0351119

[83] Doherty, G.H. Nitric oxide in neurodegeneration: potential benefits on non-steroidal anti-inflammatories. *Neurosci. Bull.,* **2011**, *27*(6), 366-382. http://dx.doi.org/10.1007/s12264-011-1530-6

[84] Lassmann, H. Mechanisms of neurodegeneration shared between multiple sclerosis and Alzheimer´s disease. *J. Neural. Transm.,* **2011**, *118*(5), 747-752. http://dx.doi.org/10.1007/s00702-011-0607-8

[85] Drechsel, D.A.; Estevez, A.G.; Barbeito, L.; Beckman, J.S. Nitric oxide-mediated oxidative damage and the progressive demise of motor neurons in ALS. *Neurotox. Res.,* **2012**, *22*(4), 251-264. http://dx.doi.org/10.1007/s12640-012-9322-y

[86] Nathan, C.; Calingasan, N.; Nezezon, J.; Ding, A.; Lucia, M.S.; La Perle, K.; Fuortes, M.; Lin, M.; Ehrt, S.; Kwon, N. S.; Chen, J.; Vodovotz, Y.; Kipiani, K.; Beal, M.F. protection from Alzheimer´s-like disease in the mouse by genetic ablation of

inducible nitric oxide synthase. *J. Exp. Med.,* **2005**, *202*(9), 1163-1169. http://dx.doi.org/10.1084/jem.20051529

[87] Tomaz, V.S.; Cordeiro, R.C.; Costa, A.M.; de Lucena, D. F.; Nobre Junior, H.V.; de Sousa, F.C.; Vasconcelos, S.M.; Vale, M.L.; Quevedo, J.; Macedo, D. Antidepressant-like effect of nitric oxide synthase inhibitors and sildenafil against lipopolysaccharide-induced depressive-like behavior in mice. *Neuroscience,* **2014**, *268,* 236-246. http://dx.doi.org/10.1016/j.neuroscience.2014.03.025

[88] Sapirstein, A.; Saito, H.; Texel, S.J.; Samad, T.A.; O´Leary, E.; Bonventre, J.V. Cytosolic phospholipase $A_2\alpha$ regulates induction of brain cyclooxygenase-2 in a mouse model of inflammation. *Am. J. Physiol. Regul. Integr. Comp. Physiol.,* **2005**, *288,* R1774-R1782. http://dx.doi.org/10.1152/ajpregu.00815.2004

[89] Dunn, A.J.; Swiergiel, A.H.; Zhang, H.; Quan, N. Reduced ingestion of sweetened milk induced by interleukin-1 and lipopolysaccharide is associated with induction of cyclooxygenase-2 in brain endothelia. *Neuroimmunomodulation,* **2006**, *13*(2), 96-104. http://dx.doi.org/10.1159/000096291

[90] Czapski, G.A.; Gajkowska, B.; Strosznajder, J.B. Systemic administration of lipopolysaccharide induces molecular and morphological alterations in the hippocampus. *Brain Res.,* **2010**, *1356,* 85-94. http://dx.doi.org/10.1016/j.brainres.2010.07.096

[91] Chung, D.W.; Yoo, K.Y.; hwang, I.K.; Kim, D.W.; Chung, J.Y.; Lee, C.H.; Choi, J.H.; Youn, H.Y.; Lee, I.S.; Won, M.H. Systemic administration of lipopolysaccharide induces cyclooxygenase-2 immunoreactivity in endothelium and increases microglia in the mouse hippocampus. *Cell. Mol. Neurobiol.,* **2010**, *30*(4), 531-541. http://dx.doi.org/10.1007/s10571-009-9477-0

[92] Song, J.H.; Lee, J.W.; Shim, B.; Lee, C.Y.; Choi, S.; Kang, C.; Sohn, N.W.; Shin, J.W. Glycyrrhizin alleviates neuroinflammation and memory deficit induced by systemic lipopolysaccharide treatment in mice. *Molecules,* **2013**, *18,* 15788-15803. http://dx.doi.org/10.3390/molecules181215788

[93] Laflamme, N.; Lacroix, S.; Rivest, S. An essential role of interleukin-1β in mediating NF-kappaB activity and COX-2 transcription in cells of the blood-brain barrier in response to a systemic and localized inflammation but not during endotoxemia. *J. Neurosci.,* **1999**, *19*(24), 10923-10930.

[94] Zinetti, M.; Benigni, F.; Sacco, S.; minto, M.; Galli, G.; Salmona, S.; Andreoni, G.; Vezzni, A.; Ghezzi, P.; Fratelli, M. Regional production of nitric oxide after peripheral or central low dose of LPS in mice. *Neuroimmunomodulation,* **1996**, *3*(6), 364-370. http://dx.doi.org/10.1159/000097297

[95] Palin, K.; Bluthe, R.M.; Verrier, D.; Tridon, V.; Dantzer, R.; Lestage, J. Interleukin-1β mediates the memory impairment associated with delayed type hypersensitivity reponse to bacillus Calmette-Guerin in the rat hippocampus. *Brain Behav. Immun.,* **2004**, *18*(3), 223-230. http://dx.doi.org/10.1016/j.bbi.2003.09.002

[96] Sparkman, N.L.; Buchanan, J.B.; Heyen, J.R.R.; Chen, J.; Beverly, J.L.; Johnson, R.W. Interleukin-6 facilitates lipopolysaccharide-induced disruption in working memory and expression of other proinflammatory cytokines in hippocampal neuronal cell layers. *J. Neurosci.,* **2006**, *26*(42), 10709-10716. http://dx.doi.org/10.1523/JNEUROSCI.3376-06.2006

[97] Mandolesi, G.; Grasseli, G.; Musumeci, G.; Centonze, D. Cognitive deficits in experimental autoimmune encephalomyelitis: neuro-inflammation and synaptic degeneration. *Neurol. Sci.,* **2010**, *31*(Suppl. 2), S255-S259. http://dx.doi.org/10.1007/s10072-010-0369-3

[98] Jain, N.K.; Patil, C.S.; Kulkarni, S. K.; Singh, A. Modulatory role of cyclooxygenase inhibitors in aging- and scopolamine or lipopolysaccharide-induced cognitive disfunction in mice. *Behav. Brain. Res.,* **2002**, *133,* 369-376. http://dx.doi.org/10.1016/S0166-4328(02)00025-6

[99] Sparkman, N.L.; Martin, L.A.; Calvert, W.S.; Boehm, G.W. Effects of intraperitoneal lipopolysaccharide on Morris maze performance year-old and 2-month-old female C57BL/6J mice. *Behav. Brain Res.,* **2005**, *159,* 145-151. http://dx.doi.org/10.1016/j.bbr.2004.10.011

[100] Schnydrig, S.; Korner, L.; Landweer, S.; Ernst, B.; Walker, G.; Otten, U.; Kunz, D. Peripheral lipopolysaccharide administration transiently affects expression of brain-derived neurotrophic factor, corticotropin and proopiomelanocortin in mouse brain. *Neurosci. Lett.,* **2007**, *429*(1), 69-73. http://dx.doi.org/10.1016/j.neulet.2007.09.067

[101] Kohman, R.A.; Tarr, A.J.; Sparkman, N.L.; day, C.E.; paquet, A.; Akkaraju, G.R.; Boehm, G.W. Alleviation of the effects of endotoxin exposure on behavior and hippocampal IL-1b by a selective non-peptide antagonist of corticotropin-releasing factor receptors. *Brain Behav. Immun.,* **2007**, *21,* 824-835. http://dx.doi.org/10.1016/j.bbi.2007.01.009

[102] Ormerod, B.K.; Hanft, S.J.; Asokan, A.; Haditsch, U.; Lee, S.W.; Palmer, T.D. PPARg activation prevents impairments in spatial memory and neurogenesis following transient illness. *Brain Behav. Immun.,* **2013**, *29,* 28-38. http://dx.doi.org/10.1016/j.bbi.2012.10.017

[103] Valero, J.; Mastrella, G.; Neiva, I.; Sanchez, S.; Malva, J.A. Long-term effects of an acute and systemic administration of LPS on adult neurogenesis and spatial memory. *Front. Neurosci.,* **2014**, *8,* 83. http://dx.doi.org/10.3389/fnins.2014.00083

[104] Choi, D.K.; Koppula, S.; Suk, K. Inhibitors of microglial neurotoxicity: focus on natural products. *Molecules,* **2011**, *16*(2), 1021-1043. http://dx.doi.org/10.3390/molecules16021021

[105] Ray, B.; Chauhan, N.B.; Lahiri, D.K. The "aged garlic extract": (AGE) and one of its active ingredients S-allyl-L-cysteine (SAC) as potential preventive and therapeutic agents for Alzheimer´s disease (AD). *Curr. Med. Chem.,* **2011**, *18*(22), 3306-3313. http://dx.doi.org/10.2174/092986711796504664

[106] Essa, M.M.; Vijayan, R.K.; Castellano-Gonzalez, G.; memon, M.A.; Braidy, N.; Guillemin, G.J. Neuroprotective effect of natural products against Alzheimer´s disease. *Neurochem. Res.,* **2012**, *37*(9), 1829-1842. http://dx.doi.org/10.1007/s11064-012-0799-9

[107] Spencer, J.P.; Vafeiadou, K.; Williams, R.J.; vauzour, D. Neuroinflammation: modulation by flavonoids and mechanisms of action. *Mol. Aspects Med.,* **2012**, *33*(1), 83-97. http://dx.doi.org/10.1016/j.mam.2011.10.016

[108] Vauzour, D. Effect of flavonoids on learning, memory and neurocognitive performance: relevance and potential implications for Alzheimer´s disease pathophysiology. *J. Sci. Food Agric.,* **2014**, *94,* 1042-1056. http://dx.doi.org/10.1002/jsfa.6473

[109] Rege, S.D.; Geetha, T.; Griffin, G.D.; Broderick, T.L.; Babu, J.R. Neuroprotective effects of resveratrol in Alzheimer disease pathology. *Front. Aging Neurosci.,* **2014**, *6,* 218. http://dx.doi.org/10.3389/fnagi.2014.00218

[110] Poulsen, M.M.; Fjeldborg, K.; ornstrup, M.J.; Kjaer, T.N.; Nohr, M.K.; Pedersen, S.B. Resveratrol and inflammation: challenges in translating pre-clinical findings to improved patient outcomes. *Biochim. Biophys. Acta,* **2015**, *1852, 6,* 1124-1136. http://dx.doi.org/10.1016/j.bbadis.2014.12.024

[111] Bhullar, K.S.; Hubbard, B.P. Lifespan and healthspan extension by resveratrol. *Biochim. Biophys. Acta,* **2015**, *1852, 6,* 1209-1218. http://dx.doi.org/10.1016/j.bbadis.2015.01.012

[112] Abraham, J.; Johnson, R.W. Consuming a diet supplemented with resveratrol reduced infection-related neuroinflammation and deficits in working memory in aged mice. *Rejuvenation Res.,* **2009**, *12*(6), 445-453. http://dx.doi.org/10.1089/rej.2009.0888

[113] Sebai, H.; Sani, M.; Ghanem-Boughanmi, N.; Aouani, E. Prevention of lipopolysaccharide-induced mouse lethality by resveratrol. *Food Chem. Toxicol.,* **2010**, *48,* 1543-1549. http://dx.doi.org/10.1016/j.fct.2010.03.022

[114] El-Sayed, N.S.; Bayan, Y. Possible role of resveratrol targeting estradiol and neprilysin pathways in lipopolysaccharide model of Alzheimer disease. *Adv. Exp. Med. Biol.,* **2015**, *822,* 107-108. http://dx.doi.org/10.1007/978-3-319-08927-0_12

[115] Noorafshan, A.; Ashkani-Esfahani, S.A review on therapeutic effects of curcumin. *Curr. Pharm. Des.,* **2013**, *19*(11), 2032-2046. http://dx.doi.org/10.2174/1381612811319110006

[116] Lee, W.H.; Loo, C.Y.; Bebawy, M.; Luk, F.; Mason, R.S.; Rohanizadeh, R. Curcumin and its derivatives: their application in neuropharmacology and neuroscience in the 21st century. *Curr. Neuropharmacol.,* **2013**, *11*(4), 338-378. http://dx.doi.org/10.2174/1570159X11311040002

[117] Furst, R.; Zundorf, I. Plant-derived anti-inflammatory compounds: hopes and disappointments regarding the translation of preclinical knowledge into clinical progress. *Mediators Inflamm.,* **2014**, *2014,* 146832.

[118] Shanmugam, M.K.; Rane, G.; Kanchi, M.M.; Arfuso, F.; Chinnathambi, A.; Zayed, M.E.; Alharbi, S.A.; Tan, B.K.; Kumar, A.P.; Sethi, G. The multifaceted role of curcumin in cancer

prevention and treatment. *Molecules,* **2015**, *20*(2), 2728-2769. http://dx.doi.org/10.3390/molecules20022728

[119] Vallianou, N.G.; Evangelopoulos, A.; Schiraz, N.; Kazazis, C. Potential anticancer properties and mechanisms of action of curcumin. *Anticancer Res.,* **2015**, *35*(2), 645-651.

[120] Begum, A.N.; Jones, M.R.; Lim, G.P.; Morihara, T.; Kim, P.; Heath, D.D.; Rock, C.L.; Pruitt, M.A.; Yang, F.; Hudspeth, B.; Hu, S.; Faull, K.F.; Teter, B.; Cole, G.M.; Frautschy, S.A. Curcumin structure-function, bioavailability, and efficacy in models of neuroinflammation and Alzheimer´s disease. *J. Pharmacol. Exp. Ther.,* **2008**, *326*(1), 196-208. http://dx.doi.org/10.1124/jpet.108.137455

[121] Wang, Z.; Zhang, Q.; Yuan, L.; Wang, S.; Liu, L.; Yang, X.; Li, G.; Liu, D. The effects of curcumin on depressive-like behavior in mice after lipopolysaccharide administration. *Behav. Brain Res.,* **2014**, *274,* 282-290. http://dx.doi.org/10.1016/j.bbr.2014.08.018

[122] Zhuang, X.; Xiang, X.; Grizzle, W.; Sun, D.; Zhang, S.; Axtell., R.; Ju, S.; Mu, J.; Zhang, L.; Steinman, L.; Miller, D.; Zhang, H.G. Treatment of brain inflammatory diseases by delivering exosome encapsulated anti-inflammatory drugs from the nasal region to the brain. *Mol. Ther.,* **2011**, *19*(10), 1769-1779. http://dx.doi.org/10.1038/mt.2011.164

[123] Nah, S.Y. Ginseng ginsenoside pharmacology in the nervous system: involvement in the regulation of ion channels and receptors. *Front. Physiol.,* **2014**, *5,* 98. http://dx.doi.org/10.3389/fphys.2014.00098

[124] Chen, W.Z.; Liu, S.; Chen, F.F.; Zhou, C.J.; Yu, J.; Zhuang, C.L.; Shen, X., Chen, B.C.; Yu, Z. prevention of postoperative fatigue syndrome in rat model by ginsenoside Rb1 *via* down-regulation of inflammation along NMDA receptor pathway in the hippocampus. *Biol. Pharm. Bull.,* **2015**, *38*(2), 239-247. http://dx.doi.org/10.1248/bpb.b14-00599

[125] Guan, N.; Huo, X.; Zhang, Z.; Zhang, S.; Luo, J.; Guo, W. Ginsenoside Rh2 inhibits metastasis of glioblastoma multiforme through Akt-regulated MMP13. *Tumor Biol.,* **2015**, DOI 10.1007/s13277-015-3387-1.

[126] Miao, H.H.; Zhen, Y.; Ding, G.N.; Hong, F.X.; Xie, Z.C.; Tian, M. Ginsenoside Rg1 attenuates isoflurane-induced caspase-3 activation *via* inhibiting mitochondrial dysfunction. *Biomed. Environ. Sci.,* **2015**, *28*(2), 116-126.

[127] Lee, J.S.; Song, J.H.; Sohn, N.W.; Shin, J.W.Inhibitory effects of Ginsenoside Rb1 on neuroinflammation following systemic lipopolysaccharide treatment in mice. *Phytother. Res.,* **2013**, *27,* 1270-1276. http://dx.doi.org/10.1002/ptr.4852

[128] Ni, Y.F.; kuai, J.K.; Lu, Z.F.; Yang, G.D.; Fu, H.Y.; Wang, J.; Tian, F.; Yan, X.L.; Zhao, Y.C.; Wang, Y.J.; Jiang, T. Glycyrrhizin treatment is associated with attenuation of lipopolysaccharide-induced acute lung injury by inhibiting cyclooxygenase-2 and inducible nitric oxide synthase expression. *J. Surg. Res.,* **2011**, *165,* e29-e35. http://dx.doi.org/10.1016/j.jss.2010.10.004

[129] Ming, L.J.; Yin, A.C. therapeutic effects of glycyrrhizic acid. *Nat. Prod. Commun.,* **2013**, *8*(3), 415-418.

[130] Akman, T.; Guven, M.; Aras, A.B.; Ozkan, A.; sen, H.M.; Okuyucu, A.; Kalkan, Y.; Sehitoglu, I.; Silan, C.; Cosar, M. The neuroprotective effect of glycyrrhizic acid on an experimental model of focal cerebral ischemia in rats. *Inflammation,* **2015**, DOI: 10.1007/s10753-015-0133-1. http://dx.doi.org/10.1007/s10753-015-0133-1

[131] Schepetkin, I.A.; Kirpotina, L.N.; jakiw, L.; khlebnikov, A.I.; Blaskovich, C.L.; Jutila, M.A.; Quinn, M.T. Immunomodulatory activity of oenothein B isolated from Epilobium angustifolium. *J. Immunol.,* **2009**, *183*(10), 6754-6766. http://dx.doi.org/10.4049/jimmunol.0901827

[132] Kiss, A.K.; bazylko, A.; Filipek, A.; Granica, S.; Jaszewska, E.; Kiarszys, U.; kosmider, A.; Piwowarski, J. Oenothein B´s contribution to the anti-inflammatory and antioxidant activity of Epilobium sp. *Phytomedicine,* **2011**, *18*(7), 557-560. http://dx.doi.org/10.1016/j.phymed.2010.10.016

[133] Azimi, H.; Khakshur, A.A.; Aghdasi, I.; Fallah-Tafti, M.; Abdollahi, M. A review of animal and human studies for management of benign prostatic hyperplasia with natural products: perspective of new pharmacological agents. *Inflamm. Allergy Drug Targets,* **2012**, *11*(3), 207-221. http://dx.doi.org/10.2174/187152812800392715

[134] Suk, K. Regulation of neuroinflammation by herbal medicine and its implications for neurodegenerative diseases. *Neurosignals,* **2005**, *14,* 23-33. http://dx.doi.org/10.1159/000085383

[135] Vafeiadou, K.; Vauzour, D.; Spencer, J.P. Neuroinflammation and its modulation by flavonoids. *Endocr. Metab.Immune Disord. Drug Targets,* **2007**, *7*(3), 211-224. http://dx.doi.org/10.2174/187153007781662521

[136] Ha, S.K.; Moon, E.; Lee, P.; Ryu, J.H.; Oh, M.S.; Kim, S.Y. Acacetin attenuates neuroinflammation *via* regulation the response to LPS stimuli *in vitro* and *in vivo*. *Neurochem. Res.,* **2012**, *37,* 1560-1567. http://dx.doi.org/10.1007/s11064-012-0751-z

[137] Lee, Y.J.; Choi, D.Y.; Han, S.B.; Oh, K.W.; Hong, J.T. Epigallocatechin-3-gallate prevents systemic inflammation-induced memory deficiency and amyloidogenesis *via* its anti-neuroinflammatory properties. *J. Nutr. Biochem.,* **2013**, *24,* 298-310. http://dx.doi.org/10.1016/j.jnutbio.2012.06.011

[138] Wang, Y.J.; Zheng, Y.L.; Lu, J.; Chen, G.Q.; Wang, X.H.; Feng, J.; Ruan, J.; Sun, X.; Li, C.X.; Sun, Q.J. Purple sweet potato Color suppresses lipopolysaccharide-induced acute inflammatory response in mouse brain. *Neurochem. Int.,* **2010**, *56,* 424-430. http://dx.doi.org/10.1016/j.neuint.2009.11.016

[139] Mestas, J.; Hughes, C.C.W. Of mice and not men: differences between mouse and human immunology. *J. Immunol.,* **2004**, *172,* 2731-2738. http://dx.doi.org/10.4049/jimmunol.172.5.2731

[140] Seok, J.; Warren, H.S.; Cuenca, A.G.; Mindrinos, M.N.; Baker, H.V.; Xu, W.; Richards, D.R.; McDonald-Smith, G.P.; Gao, H.; Hennesy, L.; Finnerty, C.C.; Lopez, C.M.; Honari, S.; Moore, E.E.; Minei, J.P.; Cuschieri, J.; Bankey, P.E.; Johnson, J.L.; Sperry, J.; Nathens, A.B.; Billiar, T.R.; West, M.A.; Jeschke, M.G.; Klein, M.B.; Gamelli, R.L.; Gibran, N.S.; Brownstein, B.H.; Miller-Graziano, C.; Calvano, S.E.; Mason, P.H.; Cobb, J.P.; Rahme, R.G.; Lowry, S.F.; Maier, R.V.; Moldawer, L.L.; Herndon, D.N.; Davis, R.W.; Xiao, W.; Tompkins, R.G.; the Inflammation and Host Response to Injury, Large Scale Collaborative Research Program. Genomic responses in mouse models poorly mimic human inflammatory diseases. *Proc. Natl. Acad. Sci. USA*, **2013**, *110*(9), 3507-3512. http://dx.doi.org/10.1073/pnas.1222878110

Received: June 04, 2015 Revised: November 02, 2015 Accepted: December 04, 2015