INDEPENDENT PEER-REVIEWED ARTICLES

I. Ischemic Stroke

II. Safety

- **Safety Profile of MLC601 (NeuroAiD) in Acute Ischemic Stroke Patients: A Singaporean Substudy of the Chinese Medicine NeuroaiD Efficacy on Stroke Recovery Study.** Young SHY, et al. *Cerebrovasc Dis 2010.*
- **NeuroAiD Danqi Piantang Jiaonang Does Not Modify Hemostasis, Hematology, and Biochemistry in Normal Subjects and Stroke Patients.** Gan R, et al. *Cerebrovasc Dis 2008.*

III. Hemorrhagic Stroke and Traumatic Brain Injury

- **Case Report on the Use of MLC601 (NeuroAiD) in Neurosurgical Pathologies.** Yeo TT, et al. *Poster WSC Seoul 2010.*

IV. Pharmacology

- **A pharmacogenomic profile of human neural progenitors undergoing differentiation in the presence of the traditional Chinese medicine NeuroAiD.** HYA Chan, et al. *The Pharmacogenomics Journal 2016.*
- **MLC901 Favors Angiogenesis and Associated Recovery after Ischemic Stroke in Mice.** Gandin C, et al. *Cerebrovasc Diseases 2016.*
- **Therapeutic Efficacy of NeuroAiD™ (MLC 601), a Traditional Chinese Medicine, in Experimental Traumatic Brain Injury.** Tsai MC, et al. *J Neuroimmune Pharmacol 2014.*
- **MLC901, a Traditional Chinese Medicine induces neuroprotective and neuroregenerative benefits after Traumatic Brain Injury in rats.** Quintard H, et al. *Neuroscience 2014.*
- **NeuroAiD: Properties for Neuroprotection and Neurorepair.** Heurteaux C, et al. *Cerebrovasc Dis 2013.*
- **Activation of ATP-sensitive potassium channels as an element of the neuroprotective effects of the Traditional Chinese Medicine MLC901 against oxygen glucose deprivation.** Moha Ou Maati H, et al. *Neuropharmacology 2012.*
- **MLC901, a traditional Chinese medicine protects the brain against global ischemia.** Quintard H, et al. *Neuropharmacology 2011.*
- **Neuroprotective and neuroproliferative activities of NeuroAiD (MLC601, MLC901), a Chinese medicine, in vitro and in vivo.** Heurteaux C, et al. *Neuropharmacology 2010.*

V. Ongoing Clinical Trials

- **CHIMES-I: sub-group analyzes of the effects of NeuroAiD according to baseline brain imaging characteristics among patients randomized in the CHIMES study.** Navarro JC et al. *Int J Stroke 2013.*
- **The NeuroAiD II (MLC901) in Vascular Cognitive Impairment Study (NEURITES).** Chen C, et al. *Cerebrovasc Dis 2013.*

VI. Alzheimer's Disease

- **Effectiveness and Safety of MLC601 in the Treatment of Mild to Moderate Alzheimer's Disease: A Multicenter, Randomized Controlled Trial.** Pakdaman, H et al. *Dementia and Geriatric Cognitive Disorders 2015.*
- **NeuroAiD (MLC601) and Amyloid Precursor Protein Processing.** Lim YA, et al. *Cerebrovasc Dis 2013.*
- **Efficacy and Tolerability of MLC601 in Patients with Mild to Moderate Alzheimer Disease Who Were Unable to Tolerate or Failed to Benefit from Treatment with Rivastigmine.** Harandi AA, et al. *Brit Med Med Res 2013.*

VII. NeST Registry

» **The NeuroAiD Safe Treatment (NeST) Registry: a protocol.** Venketasubramanian N, et al. *BJM Open 2015.*

I. Ischemic Stroke

Prognostic Factors and Pattern of Long-Term Recovery with MLC601 (NeuroAiD™) in the Chinese Medicine NeuroAiD Efficacy on Stroke Recovery – Extension Study.
Venketasubramanian N, et al. *Cerebrovascular Diseases 2016.*

This is a sub-analysis of the CHIMES-E study. The researchers aimed to evaluate the recovery pattern and the influence of prognostic factors on treatment effect of NeuroAiD over 2 years. The sustained benefits of NeuroAiD over 2 years were due to more subjects with poorer prognosis improving to functional independence at month 6 and beyond compared to placebo. Selection of subjects with poorer prognosis, particularly those with more severe NIHSS score and longer OTT delay, as well as a long follow-up period, may improve the power of future trials investigating the treatment effect of neuroprotective or neurorestorative therapies.

Durability of the beneficial effect of MLC601 (NeuroAiD™) on functional recovery among stroke patients from the Philippines in the CHIMES and CHIMES-E studies.
Navarro JC, et al. *International Journal of Stroke 2016.*

A pre-specified country analysis of subjects from the Philippines in the CHInese Medicine NeuroAiD Efficacy on Stroke recovery (CHIMES) Study, published in 2014, showed significantly improved functional and neurological outcomes on NeuroAiD at month 3. With this new analysis, the researchers showed that the beneficial effect of NeuroAiD seen at month 3 in the Filipino cohort is durable up to two years after stroke.

The value of patient selection in demonstrating treatment effect in stroke recovery trials: lessons from the CHIMES study of MLC601 (NeuroAiD). Venketasubramanian N, et al. *Journal of Evidence-Based Medicine 2015*.

The authors' purpose was to verify if patient selection based on two prognostic factors (ie, stroke severity and time to treatment) improves detection of a treatment effect with MLC601. Analyses were performed using data from the CHIMES Study (international, randomized, placebo-controlled, double-blind trials comparing MLC601 to placebo in patients with ischemic stroke of intermediate severity in the preceding 72 hours). MLC601 treatment effects were much higher in the subgroups with prognostic factors than for the entire group and the highest treatment effect was seen among patients with both prognostic factors. It can be concluded that patient selection appears to be an important factor for consideration when designing clinical trials in stroke to better reveal the treatment effect and provides new insights for futures trials.

CHInese Medicine NeuroAiD Efficacy on Stroke Recovery – Extension Study (CHIMES-E): A Multicenter Study of Long-Term Efficacy. Venketasubramanian N, et al. *Cerebrovascular Diseases* 2015.

The CHIMES-E study, a planned extension study of the CHIMES study, aimed to evaluate the effects of an initial 3-month treatment with NeuroAiD on long-term outcomes of up to 2 years. This study has showed that NeuroAiD increases significantly the odds of achieving functional independence at 6 months and persisted up to 18 months after a stroke, as measured by mRS dichotomy 0-1. It also provided further long-term safety data on NeuroAiD, even when combined with other stroke treatments. The authors concluded that an initial 3-month treatment with NeuroAiD increased the odds of functional independence after a stroke, "providing level 1 evidence of benefit in ischaemic stroke".*

**Venketasubramanian N, et al. As presented at ESOC Glasgow and ESC Vienna 2015*

Prognostic Factors and Treatment Effect in the CHIMES Study. Chankrachang S, et al. *J. of Stroke and Cerebro Diseases 2015*.

This publication is a post-hoc analysis performed on CHIMES study patients. The authors have identified predictors of poorer mRS at 3 months (Age > 60; Female sex; Baseline NIHSS 10-14; Stroke onset to initiation of MLC601 > 48h) and have shown that NeuroAiD™ treatment effect is statistically significant for patients with 2 or more predictors of poorer outcome. Hence this paper illustrates NeuroAiD™ efficacy at 3 months, which is best demonstrated among patients with poorer prognosis.

NeuroAiD™ (MLC601, MLC901): a new bench-to-bedside approach to the treatment of Ischemic Brain Injury. Dib M, et al. *European Journal of Medicinal Plants* 2014.

This paper reviews the important findings on NeuroAiD™, from pharmacological properties to efficacy and safety data in Stroke recovery. It reminds that NeuroAiD has demonstrated neurorestorative and neuroprotective properties and this justifies its use from the post-acute to chronic phase of stroke. Clinical benefits have shown that it helps achieve functional independence with 63% increase in the odds of achieving independence in patients with established deficits and enhances recovery of motor functions. In addition, NeuroAiD offers a better protection by reducing early cardiovascular events and deaths by 50% after a stroke.

Baseline characteristics and treatment response of patients from the Philippines in the CHIMES study. Navarro J, et al. *Int J Stroke* 2014.

This publication is a pre-planned analysis performed on subjects from the Philippines included in the CHIMES Study. The authors found a statistically significant treatment effect in favour of NeuroAiD™ in the primary outcome of mRS and other secondary outcomes (NIHSS and Barthel Index). This result was likely attributable to the inclusion of patients with more severe stroke and longer delay from stroke onset to treatment initiation in the Philippines cohort. Thus the favourable treatment of NeuroAiD was best demonstrated among post-acute stroke patients with moderate severity.

Effects of MLC601 on Early Vascular Events in Patients After Stroke: The CHIMES study. Chen C, et al. *Stroke* 2013.

This publication is a post-hoc analysis performed on data from subjects included in the CHInese Medicine Neuroaid Efficacy on Stroke recovery (CHIMES) study. The CHIMES study is an academic international double-blind placebo-controlled clinical trial which treated and monitored 1100 patients from several countries who had suffered an ischemic stroke of intermediate severity within 72 hours, for 3 months. Early vascular events were defined as a composite of recurrent stroke, acute coronary syndrome, and vascular death occurring within 3 months of stroke onset. The research concluded that the risk of early vascular events during the 3-month follow-up was significantly reduced by half in the MLC601 group as compared to the placebo group without an increase in nonvascular deaths. Kaplan–Meier survival analysis demonstrated the difference in risk as early as the first 14 days after stroke.

Chinese Medicine Neuroaid Efficacy on Stroke Recovery : A Double-Blind, Placebo-Controlled, Randomized Study. Chen C, et al. *Stroke* 2013.

The CHIMES study is an academic international double-blind placebo-controlled clinical trial which treated and monitored 1100 patients from several countries who had suffered an ischemic stroke of intermediate severity within 72 hours, for 3 months. The research concluded that NeuroAiD is statistically no better than placebo in improving outcomes at 3 months when used among patients with acute ischemic stroke of intermediate severity. However the results of the study confirmed the overall benefit of NeuroAiD in stroke recovery and showed that treatment effect for achieving functional independence was greater among non-acute strokes, consistent with previous studies. In addition the study showed that NeuroAiD had an excellent safety profile.

Efficacy and Safety of MLC601 (NeuroAiD), a Traditional Chinese Medicine, in Poststroke Recovery: A Systematic Review. Siddiqui FJ, et al. *Cerebrovasc Dis* 2013.

This publication updates the 2-study meta-analysis published in Stroke journal in 2009 with all clinical data available since on NeuroAiD and provides an overall assessment of the effects of NeuroAiD in improving functional and motor outcomes by the end of treatment. In a systematic review this paper shows that previous studies on NeuroAiD in ischemic stroke in general were of low risk of bias. The meta-analysis showed a statistically significant beneficial effect in favor of NeuroAiD on functional outcome when assessed at the end of study treatment. Although the results did not reach statistical significance, the overall effects on motor recovery were also in favor of NeuroAiD.

NeuroAiD (Danqi Piantang Jiaonang), a Traditional Chinese Medicine, in Poststroke Recovery. Chen C, et al. *Stroke* 2009.

The paper reports the pooled analysis of two randomized controlled clinical trials (initial stroke trials in China) that included 605 patients recruited between 2 weeks and 6 months after their stroke. The results show that patients on NeuroAiD have 2.4 times more chances of achieving independence after 1 month of treatment, and have a 25% better recovery in motor impairments. No serious adverse event was reported.

Safety and efficacy of MLC601 in Iranian patients after stroke: a double-blind, placebo-controlled clinical trial. Harandi AA, et al. *Stroke Res Treat* 2011.

This study of 150 Iranian patients with a recent ischemic stroke (within 1 month) shows that MLC601 improves motor recovery as early as 4 weeks and persisted up to 12 weeks after stroke. Moreover, good tolerability to treatment was shown and adverse events were mild and transient. No severe adverse event leading to drug discontinuation was reported.

The effect of NeuroAiD (MLC601) on cerebral blood flow velocity in subjects' post brain infarct in the middle cerebral artery territory. Shahripour RB, et al. *Eur Intern Med* 2011.

This randomized double-blind placebo-controlled study recruited 80 patients within 1 week of stroke, of which 40 received 4 capsules of NeuroAiD 3 times a day and 40 others received placebo for 3 months. The subjects were recruited at Ahvaz Golestan Hospital in Iran from April 2009 to March 2010. This study shows that MLC601 improves cerebral blood flow velocity in post-cerebral infarction subjects better than in the control group. This is associated with more improvement in functional outcome (Barthel Index of activities of daily living) as compared to placebo at 3 months.

A Double-Blind, Placebo-Controlled, Randomized Phase II Pilot Study to Investigate the Potential Efficacy of the Traditional Chinese Medicine NeuroAiD (MLC601) in Enhancing Recovery after Stroke (TIERS). Kong KH, et al. *Cerebrovasc Dis* 2009.

The aim of this phase II double-blind placebo controlled study was to investigate the efficacy of NeuroAiD on motor recovery in ischemic stroke patients using rehabilitation endpoints in order to provide predictive information for further larger trials. In this clinical trial, 20 patients within 1 month post-stroke received 4 capsules of NeuroAiD 3 times a day for 4 weeks and 20 other patients received placebo. While no statistical significance was detected for all primary and secondary endpoints due to the small sample size, subgroup analysis show trends for better outcome with NeuroAiD for more severe strokes, posterior strokes, and strokes with potential for recovery at 8 weeks.

NeuroAiD (MLC601) *versus* piracetam in the recovery of post-infarct homonymous hemianopsia. Ghandehari K, et al. *Neural Regen Res* 2011.

In the clinic, the natural recovery rate of homonymous hemianopsia caused by occipital lobe infarction is low. This prospective study compared the effects of NeuroAiD (MLC601) versus piracetam in improving visual field defects in 40 patients matched for age and sex within 1 week of PCA infarction with pure homonymous hemianopsia. After 3 months of treatment, the findings suggest that MLC601 is superior to piracetam for reducing quantitative visual field defects in homonymous hemianopsia patients.

The Use of NeuroAiD (MLC601) in Post ischemic Stroke Patients. Navarro JC, et al. *Rehabil Res Pract* 2012.

This paper aimed to assess the efficacy of MLC601 on functional recovery in patients given MLC601 after an ischemic stroke. This was a retrospective cohort study comparing 30 post-stroke patients given open-label MLC601 for three months and 30 matching patients who did not receive MLC601 from the Stroke Data Bank. There were positive results from this study: NeuroAiD has been shown to improve functional recovery at 3 months post-ischemic stroke.

NeuroAiD in Stroke Recovery. Siow C, *Eur Neurol* 2008.

This case series report deals with 10 patients who received NeuroAiD after an ischemic stroke as confirmed on brain imaging (MRI). Conducted in an outpatient private clinic in Mount Alvernia Hospital in Singapore, the report suggests that NeuroAiD can be considered as an add-on treatment to other medications including anti-platelet, warfarin, lipid-lowering, anti-hypertensive, anti-diabetic, and antidepressant medications.

II. Safety

A Randomized Trial to Assess the Long-Term Safety of NeuroAiD among Caucasian Patients with Acute Ischemic Stroke. Shahripour RB, et al. *Chin J Integr Med* 2014.

This study on 150 patients with acute ischemic stroke within 1 week of onset demonstrates the long-term (up to 6 months) safety of NeuroAiD in a Caucasian population. While mild nausea was more commonly reported in the NeuroAiD group, none of the reported adverse events were serious or required discontinuation of treatment. There was no significant change observed in blood pressure, hematologic, hepatic, and renal functions during treatment with NeuroAid and up to 3 months after completion of a 3-month regimen. These data confirm the excellent safety profile of NeuroAiD in patients with acute ischemic stroke during treatment and long after completion of treatment.

Safety Profile of MLC601 (NeuroAiD) in Acute Ischemic Stroke Patients: A Singaporean Substudy of the Chinese Medicine NeuroaiD Efficacy on Stroke Recovery Study. Young SHY, et al. *Cerebrovasc Dis* 2010.

This study on 114 patients with acute ischemic stroke randomized within 48 hours of onset shows that serious adverse events (SAEs) were similar between the group treated with placebo and the group treated with MLC601. The SAEs reported were those commonly seen in stroke patients. There were neither statistically or clinically significant differences between treatment groups in biochemical, haematological, or electrocardiogram tests at 3 months, nor any statistically or clinically significant differences in the absolute and relative changes of the various parameters between baseline and 3 months. Thus, MLC601 is safe for patients with acute stroke receiving a 3-month treatment.

NeuroAiD Danqi Piantang Jiaonang Does Not Modify Hemostasis, Hematology, and Biochemistry in Normal Subjects and Stroke Patients. Gan R, et al. *Cerebrovasc Dis* 2008.

NeuroAiD does not significantly affect hematological, hemostatic, and biochemical parameters in normal and stroke patients. Clinical parameters and expected effects of aspirin are not altered by co-administration of the drug even when started and maintained at the early stage of acute stroke.

III. Hemorrhagic Stroke and Traumatic Brain Injury

Case Report on the Use of MLC601 (NeuroAiD) in Neurosurgical Pathologies. Yeo TT, et al. *Poster WSC Seoul* 2010.

This case series report of 20 patients treated with MLC601 in the Neurosurgery division of National University Hospital in Singapore. All patients received 4 capsules of MLC601 3 times a day for 3 months started within 3 months of onset of brain injury or stroke. All patients reported some improvements and good tolerance for the drug. Three cases (head injury, hemorrhagic stroke from AVM, and brain abscess) with remarkable outcomes were presented, illustrating how it may not be unreasonable to prescribe MLC601 to selected patients with difficult neurosurgical pathology in the hope that the neurological function outcome would improve.

IV. Pharmacology

A pharmacogenomic profile of human neural progenitors undergoing differentiation in the presence of the traditional Chinese medicine NeuroAiD. HYA Chan, et al. *The Pharmacogenomics Journal* 2016.

This study was designed to learn more about NeuroAiD™II's cellular and molecular mechanisms of action on human neurons and more precisely by investigating the impact of MLC901 on human neural progenitor cells undergoing neural differentiation. Genes having a role in neurogenesis and neural differentiation were found significantly regulated by MLC901 in three independent experiments. The researchers identified genes of functional pathways regulated by MLC901 that could promote neurogenesis and neuroprotection in the human brain, and offered some insights into the possible mechanism of action of MLC901. After extensive studies in cell and animal models previously published, this paper provides the first validation, in human cells of the neuroplasticity mechanism triggered by MLC901, and whose effects are observed in clinical trials on recovery.

MLC901 Favors Angiogenesis and Associated Recovery after Ischemic Stroke in Mice. Gandin C, et al. *Cerebrovasc Diseases* 2016.

NeuroAiD™II (MLC901) has already demonstrated neuroprotective and neuroreparative properties and is also proven to improve long-term post-stroke recovery in human. In humans, vascular remodeling takes place 3 or 4 days after stroke, facilitating the processes of neurorepair. Therapeutic angiogenesis is an approach of regenerative medicine that may help in improving the outcomes of patients after an ischemic stroke. Because the neural and vascular cell cross-talk is important in brain repair, Dr. Catherine Heurteaux and her team at CNRS (National Center for Scientific Research, France) decided to further investigate the effect of MLC901 on vascular remodeling in a model of focal ischemia in mice. This study has provided evidences that MLC901 enhances endothelial cell proliferation and vascular remodeling locally in the ipsilateral infarcted area, but not in the contralateral hemisphere, showing that MLC901 is stimulating only the natural local revascularization process. This key finding highlights the role of MLC901 in stimulating revascularization, neuroprotection and repair of the neurovascular niche after ischemic stroke.

Therapeutic Efficacy of NeuroAiD™ (MLC 601), a Traditional Chinese Medicine, in Experimental Traumatic Brain Injury. Tsai MC, et al. *J Neuroimmune Pharmacol* 2014.

This paper highlights the role of MLC601 in improving recovery as well as affecting microglial activation in a model of rats with induced TBI. Early treatment with MLC601 (1h post-TBI) has shown significantly better benefits in reducing TBI-induced cerebral contusion than a late treatment. Beneficial effects of MLC601 were correlated with reduction in neurological and motor deficits, neuronal apoptosis and microglial activation (microgliosis, morphological transformation of microglia and microglial overexpression of TNF-α). These results are consistent in part with the beneficial effects of MLC901 in a model of rats with induced TBI already published. This work provides further evidence and a rationale to use MLC601 or MLC901 therapy in improving functional recovery in patients with TBI.

MLC901, a Traditional Chinese Medicine induces neuroprotective and neuroregenerative benefits after Traumatic Brain Injury in rats. Quintard H, et al. *Neuroscience* 2014.

This paper demonstrates how NeuroAiD™ can be beneficial in reducing the deleterious consequences induced by Traumatic Brain Injury (TBI) and highlights NeuroAiD™ properties in a rat model of TBI. This is the first publication on the pharmacological actions of NeuroAiD™ in TBI and in which its multimodal mechanisms as well as its time-effect have been demonstrated. Adding to NeuroAiD™ beneficial effects in ischemic stroke recovery, this work provides evidence that NeuroAiD™ has neuroprotective and neurorestorative actions which lead to an improvement in the recovery of cognitive functions in an animal model of TBI, hence providing a rationale for NeuroAiD™ to improve recovery of patients with TBI.

NeuroAiD: Properties for Neuroprotection and Neurorepair. Heurteaux C, et al. *Cerebrovasc Dis* 2013.

This paper reviews the pharmacological effects of NeuroAiD on the normal and ischemic brain and neurons. In vivo and in vitro experiments using mouse model of stroke (focal ischemia), rat model of cardiac arrest (global ischemia) and cortical neurons in culture were reviewed and summarized. In conclusion NeuroAID demonstrated both neuroprotective and neuroregenerative properties in rodent models of focal and global ischemia and in cortical cell cultures.

Activation of ATP-sensitive potassium channels as an element of the neuroprotective effects of the Traditional Chinese Medicine MLC901 against oxygen glucose deprivation. Moha Ou Maati H, et al. *Neuropharmacology* 2012.

This paper highlights the potency of NeuroAid in neuroprotection with the discovery of a key underlying mechanism of action. The activation by NeuroAid of the ATP-sensitive potassium channel located in the suffering neurons of the brain protects them from death. Indeed, the opening of the channel decreases the excitability of neurons (by hyperpolarization) preventing an overload of calcium and release of excitotoxic glutamate. Besides the beneficial effects in neuroplasticity already published, these results strengthen the interest of NeuroAid in stroke recovery.

MLC901, a traditional Chinese medicine protects the brain against global ischemia. Quintard H, et al. *Neuropharmacology* 2011.

The paper describes the results of a series of in vivo experiments demonstrating neuroprotective and neurogenesis effects of MLC901 on hippocampal CA1 region against global ischemia in rodent models of global ischemia. It shows how neuronal protection by MLC901 is likely mediated by the Akt protein (a central mediator in the signal transduction pathway involved in cell survival) and reduction of oxidative stress. MLC901 prevents necrosis and apoptotic cell death induced by global ischemia, enhances neurogenesis, and enhances functional recovery. This makes MLC901 a potential novel therapeutic strategy in treating cognitive and neurological deficits caused by global ischemia from conditions that deprive the brain of oxygen and glucose, such as cardiac arrest.

Neuroprotective and neuroproliferative activities of NeuroAiD (MLC601, MLC901), a Chinese medicine, *in vitro* and *in vivo*. Heurteaux C, et al. *Neuropharmacology* 2010.

The paper describes the results of a series of in vivo and in vitro experiments demonstrating the neuroprotective and neuroproliferative effects of NeuroAiD when given prior to and/or after injury in rodent models of ischemic stroke and neuronal injuries, human embryonic stem cells, and neuronal cell cultures. It shows how NeuroAiD supports neuroplasticity by its effect on neurogenesis, neuritic outgrowth, and synaptogenesis. NeuroAiD provides a better milieu for post-stroke recovery and decreases neurological impairments.

V. Ongoing Clinical Trials

CHIMES-I: sub-group analyzes of the effects of NeuroAiD according to baseline brain imaging characteristics among patients randomized in the CHIMES study. Navarro JC et al. *Int J Stroke* 2013.

This imaging substudy aims to assess the efficacy of NeuroAiD in subgroups of patients randomized in the main CHIMES Study when categorized according to baseline imaging characteristics. Acute stroke lesions on baseline CT or MRI are reviewed in terms of size, location, and extent of involvement by two readers who remain blinded to treatment allocation and outcomes of the subjects. The outcomes, namely modified Rankin Scale, National Institute of Health Stroke Scale, Barthel Index, and Mini-Mental Status Examination, will be analyzed by the sub-groups nonlacunar and lacunar, cortical and sub-cortical, hemispheric vs. brainstem, Alberta Stroke Program Early CT score <7 and 7–10, and score <8 and 8–10.

The NeuroAiD II (MLC901) in Vascular Cognitive Impairment Study (NEURITES). Chen C, et al. *Cerebrovasc Dis* 2013.

The objective of this study is to investigate the effects and tolerability of NeuroAiD II in patients with VCIND (Vascular Cognitive Impairment no Dementia). The NeuroAiD II (MLC901) in Vascular Cognitive Impairment Study (NEURITES) is a 24-week, double-blind, randomized, placebo-controlled phase II study of NeuroAiD II in patients with VCIND. In conclusion NEURITES has the potential to set new standards for the systematic evaluation of Asian traditional medicine for integration into standard medicine practice and establishing a novel therapeutic approach for improving cognition after stroke.

VI. Alzheimer's Disease

Effectiveness and Safety of MLC601 in the Treatment of Mild to Moderate Alzheimer's Disease: A Multicenter, Randomized Controlled Trial. Pakdaman, H et al. *Dementia and Geriatric Cognitive Disorders 2015.*

This publication is a multicenter, nonblinded, randomized controlled trial, which included 264 volunteers with AD to evaluate the effectiveness and safety of MLC601 in the treatment of mild to moderate AD as compared to 3 approved cholinesterase inhibitors (ChEIs) including donepezil, rivastigmine and galantamine. This is the second clinical study of NeuroAiD™ effectiveness and safety in Alzheimer disease. In a previous clinical trial study, NeuroAiD™ has demonstrated a favorable tolerability and encouraging effectiveness on cognitive function in Alzheimer disease patients during 18 months of treatment when compared to rivastigmine. In this study, the authors have shown that NeuroAiD™ has favorable effects on cognitive functions during 16 months of follow-up, with improvements on cognitive function specifically observed in the first 8 months of treatment. NeuroAiD™ is as effective as other commonly used Cholinesterase inhibitors (Donepazil, Rivastigmine, Galantamine) in treating cognitive deficits. Finally, NeuroAiD™ has shown a better tolerability profile compared to the 3 ChEIs, which implies a better compliance for patients.

NeuroAiD (MLC601) and Amyloid Precursor Protein Processing. Lim YA, et al. *Cerebrovasc Dis* 2013.

The purpose of this paper was to investigate the effects of MLC601 (NeuroAiD) on regulation of APP (Amyloid Precursor Protein) processing. Human neuroblastoma cell line SH-SY5Y was used for all experiments. Cells were treated with different concentration of NeuroAiD before assessing changes in the levels of released lactate dehydrogenase (LDH), full-length APP and secreted sAPPα. In conclusion it appears that NeuroAiD is a possible modulator of APP processing and has implications as a putative therapeutic strategy for the treatment of post stroke dementia and AD.

Efficacy and Tolerability of MLC601 in Patients with Mild to Moderate Alzheimer Disease Who Were Unable to Tolerate or Failed to Benefit from Treatment with Rivastigmine. Harandi AA, et al. *Brit Med Med Res* 2013.

The aim of this early stage "proof-of-concept" clinical study was to evaluate the efficacy and tolerability of MLC601 in patients with mild to moderate Alzheimer disease (AD). The results showed that NeuroAiD was well-tolerated even up to 18 months of treatment. This tolerability represents a key improvement compared to current AD treatments, i.e. ChEIs, in which a modest but significant therapeutic effect is often compromised by the occurrence of adverse events and discontinuation of treatment.

VII. NeST Registry

The NeuroAiD Safe Treatment (NeST) Registry: a protocol. Venketasubramanian N, et al. *BJM Open 2015.*

The NeuroAiD Safe Treatment (NeST) Registry works as a product registry to provide information on the use of NeuroAiD and monitor its safety in a real world setting. The NeST Registry is a proactive industry-academic effort designed to be as unobtrusive as possible during its assessment hence an online framework was introduced for easier data entry and retrieval of clinical information. The registry also acts as a complement for more accurate pharmacovigilance, essential for patient care and surveillance. Participation is voluntary and patients' data is anonymous.