ment) occlusion in the hours following intravenous (i.v.) tPA treatment.

Endovascular reperfusion therapies are currently considered fully implemented meaning that acute stroke patients are now consistently undergoing a complete vascular evaluation (computed tomography angiography and CT perfusion [CTA/CTP]) and those presenting LVO undergo EVT that ensures recanalization rates as high as 85-90%. Moreover, several studies show the greater therapeutic window of EVT (up to 24h after stroke onset in some specific cases) compared with 4.5h in the case of tPA. However, even though EVT has shown to consistently achieve substantial recanalization grades in 85-90% of the cases, more than 50% of the treated patients will develop a moderate to severe disability.

Despite this known inherent risk of reperfusion therapies, the benefit-risk ratio favors their use. In this context, it is of great interest to find new drugs with potential neuroprotective effects to improve stroke outcomes while reducing intracranial hemorrhages, in parallel with reperfusion treatments.

ApTOLL, an anti-inflammatory drug with proven neuroprotective effects in preclinical models, is an aptamer targeting the extracellular domain of TLR-4, a receptor involved in innate immune responses that also responds to tissue damage-associated molecular patterns (DAMPs) and which is directly involved in a large number of diseases such as ischemic stroke. Specifically, the inflammatory component triggered in the acute phase of stroke is considered an interesting target to enhance the recovery of patients, and ApTOLL offers a potential high therapeutic effect in this area. WO2015197706A1 (AptaTargets SL) describes nucleic acid aptamers, particularly ApTOLL, with the capability of binding specifically to and inhibiting TLR-4 and uses thereof, including stroke.

In fact, the efficacy of ApTOLL has been demonstrated at the preclinical level in experimental models of cerebral and myocardial ischemia. Particularly, WO2020230108A1 (AptaTargets SL) discloses methods and compositions for the treatment of ischemic stroke and demonstrates the efficacy of ApTOLL in rodent models of stroke (Example 2). In addition, a First-in-Human study showed the safety and defined the pharmacokinetics of ApTOLL in healthy subjects, described in Example 3.1 of WO2020230108A1 and in Hernández-Jiménez M, et al., 2022.

SUMMARY

One problem to be solved by the present invention is to provide new uses and methods that improve functional outcomes of patients, e.g., reduction of neurological damage, while reducing hemorrhagic complications associated to an ischemic stroke and to reperfusion techniques.

The solution is based on the administration of ApTOLL molecules (e.g., ApTOLL, SEQ ID NO: 1 at 0.2 mg/kg) to a subject in need thereof for reducing neurological damage and intracranial hemorrhages among other effects explained hereinafter, associated to an ischemic stroke and to reperfu-

(1) the delayed administration was set at the time still safe in humans;
(2) the protective effect of TLR-4 absence requires to be studied in future long-term outcome experiments; and
(3) TLR-4 involvement in thrombectomy-induced HT remains to be studied.

In brief, this study was carried out in mouse models that have a total knock-out of TLR-4 receptor and therefore the mechanisms are not the same as in a normal scenario, e.g., these mice do not undergo an inflammatory response in the TLR-4 pathway when a stroke is triggered. Instead, the APRIL study uses ApTOLL in AIS patients: thus, in the first place, the aptamer partially inhibits TLR-4 and thus does not have the same effects as a complete absence of TLR-4 in all tissues; and secondly, patients experience inflammation in the TLR-4 pathway in brain and have multiple complications in clinical practice, contrary to the mouse model of García-Culebras A et al., 2017.

In a first aspect, the present disclosure provides use of an aptamer comprising SEQ ID NO: 1 for the manufacture of a medicament for reducing the risk of intracranial hemorrhages after an acute ischemic stroke in a subject, wherein the aptamer is to be administered after the acute ischemic stroke at a dose of at least about 0.2 mg/kg, and wherein the administration of the aptamer reduces the risk of intracranial hemorrhages in at least about a 14% with respect to a subject not treated with the aptamer.

In a second aspect, the present disclosure provides use of an aptamer comprising SEQ ID NO: 1 for the manufacture of a medicament for improving the neurological recovery after an acute ischemic stroke in a subject, wherein the improvement of neurological recovery is mediated by a reduction of the risk of intracranial hemorrhages, wherein the aptamer is to be administered after the acute ischemic stroke at a dose of at least about 0.2 mg/kg, and wherein the aptamer: (i) reduces the NIHSS score, and (ii) reduces the mRS score to 0-2, with respect to a subject not treated with the aptamer.

Accordingly, a first example of the invention relates to ApTOLL molecules for use in reducing the risk of intracranial or secondary hemorrhages (or preventing intracranial hemorrhages or reducing the occurrence of intracranial hemorrhages) after an acute ischemic stroke in a subject, wherein the ApTOLL molecules are administered after the acute ischemic stroke (i.e., after stroke onset).

Another example relates to ApTOLL molecules for use in reducing the risk of intracranial or secondary hemorrhages (or preventing intracranial hemorrhages or reducing the occurrence of intracranial hemorrhages) after a thrombotic disorder in a subject, wherein the ApTOLL molecules are administered after the thrombotic disorder.

An example of the invention is related to ApTOLL molecules for use in reducing the neurological damage and in improving the neurological recovery an after acute ischemic stroke in a subject, wherein the ApTOLL molecules are administered after the acute ischemic stroke.

In another example, the present invention relates to ApTOLL molecules for use in increasing survival and/or reducing brain edema after an acute ischemic stroke in a subject, wherein the ApTOLL molecules are administered after the acute ischemic stroke.

Other aspects of the invention relate to ApTOLL molecules for use in improving anxiety/depression complications, performance of usual activities, mobility and/or self care after an acute ischemic stroke in a subject, wherein the ApTOLL molecules are administered after the acute ischemic stroke.

Throughout the description and claims the word "comprise" and its variations are not intended to exclude other technical features, additives, components, or steps. Additional objects, advantages and features of the invention will become apparent to those skilled in the art upon examination of the description or may be learned by practice of the invention. Furthermore, the present invention