

## Supplementary

The rationales for the biomarkers selected

### 1. The rational for the choice of TNF- $\alpha$

Surgery activates the innate immune system resulting in release of proinflammatory mediators (TNF- $\alpha$ , IL-1 and IL-6). However, ketamine could suppress nuclear factor- $\kappa$ B expression involved in the transcription of genes encoding the proinflammatory cytokines tumour necrosis factor (TNF- $\alpha$ ). [1]

### 2. The rational for the choice of BDNF

BDNF has a role in increasing synaptic plasticity and synaptic function. Reviews have suggested that brain-derived neurotrophic factor (BDNF) improved memory function, reversed age-related changes in brain and prevented cell death. [2] Furthermore, ketamine requires brain-derived neurotrophic factor (BDNF) signals to exert antidepressant effects. [3]

### 3. The rational for the choice of acetylcholine

Acetylcholine is thought to be involved in the neuroplasticity, and is present in several neural pathways responsible for arousal, attention and memory. [4] However, ketamine could increase cholinergic tone that may contribute to the improvement of cognition. [5]

## References

- [1] Choudhury D, Autry AE, Tolias KF, et al. Ketamine: Neuroprotective or Neurotoxic?. *Front Neurosci.* 2021;15:672526.
- [2] Kotekar N, Shenkar A, Nagaraj R. Postoperative cognitive dysfunction - current preventive strategies. *Clin Interv Aging.* 2018;13:2267-2273.
- [3] Himmelseher S, Kochs EF. Ready for a "breakthrough" with ketamine? A look at recent pharmacological insights!. *Curr Opin Anaesthesiol.* 2021;34(4):393-401.
- [4] Jin Z, Hu J, Ma D. Postoperative delirium: perioperative assessment, risk reduction, and management. *Br J Anaesth.* 2020;125(4):492-504.
- [5] Hambrecht-Wiedbusch VS, Li D, Mashour GA. Paradoxical Emergence: Administration of Subanesthetic Ketamine during Isoflurane Anesthesia Induces Burst Suppression but Accelerates Recovery. *Anesthesiology.* 2017;126(3):482-494.