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Interactions of Graphene Oxide and Few-Layer Graphene with the Blood–Brain Barrier

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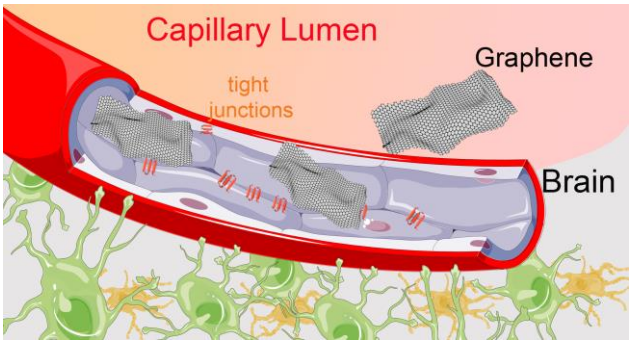

The blood-brain barrier (BBB) is an essential regulatory layer at the neural interface with the brain vasculature, which acts as a selective barrier. The tight junctions forming between adjacent cells prevent molecules from moving paracellularly, forcing them to take a transcellular route for their translocation.[1, 2]

Graphene, either in the form of colloidal suspension or planar substrate, has been considered an exciting biomaterial for biological applications, and its interactions with the central nervous system (CNS) have been widely investigated in the past decade.[3-8] Like all other nano/micro materials, graphene-based materials, when administered systemically, must cross the blood-brain barrier (BBB) in order to access the brain. Thanks to their biocompatibility and high cargo capability, graphene-based materials (GRMs) might represent an ideal brain delivery system. The capability of GRMs to reach the brain was mainly investigated *in vivo*, and has highlighted some controversy.

Herein, we employed two in vitro BBB models of increasing complexity to investigate the bionano interactions with graphene oxide (GO) and few-layer graphene (FLG), so far overlooked. We employed a 2D murine Transwell model, followed by a 3D human multicellular assembloid, to better mimic the complexity of the *in vivo* architecture and inter-cellular crosstalk. We developed specific methodologies to assess the translocation of GO and FLG in a label-free fashion and a methodological platform widely applicable to any nanomaterial type. Overall our results show good biocompatibility of the two GRMs, which did not impact the integrity and functionality of the barrier. Sufficiently dispersed subpopulations of GO and FLG were actively uptaken by the endothelial layer; however, the translocation was identified as a rare event.

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