Title of the research: *High fat diet-associated neuroinflammation and brain aging prevention by Bioactive Compounds*

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Summary

High-Fat Diet (HFD)-induced obesity is increasingly recognized as a major driver of cognitive decline and unhealthy brain aging, largely through metabolic dysfunction and chronic neuroinflammation. The hippocampus, a brain region essential for learning and memory, is particularly vulnerable to these alterations, which disrupt neural stem cell (NSC) activity and impair neurogenesis. This project aims to evaluate the therapeutic potential of two bioactive compounds, D-Pinitol and Oleoylethanolamide (OEA), in restoring hippocampal homeostasis by targeting microglial activation and metabolic imbalance.

D-Pinitol, a natural insulin sensitizer, is expected to improve impaired insulin signaling, thereby enhancing the metabolic environment of the neurogenic niche. OEA, an endogenous lipid mediator and PPAR-α agonist, is known for its potent anti-inflammatory properties and is anticipated to suppress microglial reactivity and improve mitochondrial efficiency. Both compounds can cross the blood-brain barrier, supporting their potential as systemic therapeutic agents.

Using complementary *in vivo* and *in vitro* approaches, including hippocampal slices from HFD-fed mice, transcriptomic profiling of human microglial cells, and functional co-culture systems with NSCs and astrocytes, this study will define how these compounds modulate microglial states and their downstream effects on neurogenesis. Additionally, direct effects on NSC proliferation, differentiation, and survival will be investigated to distinguish niche-mediated from cell-autonomous mechanisms.

By integrating molecular, cellular, and functional analyses, this project will provide novel insights into microglia-driven neurogenic impairment and assess innovative strategies to preserve hippocampal plasticity and cognitive resilience under metabolic stress. These findings may support the development of targeted interventions to mitigate neuroinflammation-associated cognitive decline during aging.

Pertinent Publications of the proponent (last 5 years)

Morandell J, Schwarz LA, Basilico B, Tasciyan S, Dimchev G, Nicolas A, Sommer C, Kreuzinger C, Dotter CP, Knaus LS, Dobler Z, **Cacci E,** Schur FKM, Danzl JG, Novarino G. Cul3 regulates cytoskeleton protein homeostasis and cell migration during a critical window of brain development. Nat Commun. 2021 May 24;12(1):3058. doi: 10.1038/s41467-021-23123-x

Giuliani A, Licursi V, Nisi PS, Fiore M, D'Angelo S, Biagioni S, Negri R, Rugg-Gunn PJ, **Cacci E**, Lupo G. Dbx2, an Aging-Related Homeobox Gene, Inhibits the Proliferation of Adult Neural Progenitors. Stem Cell Rev Rep. 2023 Nov;19(8):2837-2851. doi: 10.1007/s12015-023-10600-7. Epub 2023 Aug 22.

Glucocorticoids rescue cell surface trafficking of R451C Neuroligin3 and enhance synapse Diamanti T, Trobiani L, Mautone L, Serafini F, Gioia R, Ferrucci L, Lauro C, Bianchi S, Perfetto C, Guglielmo S, Sollazzo R, Giorda E, Setini A, Ragozzino D, Miranda E, Comoletti D, Di Angelantonio S, **Cacci E***, De Jaco Aformation. Traffic. 2024 Jan;25(1):e12930. doi: 10.1111/tra.12930. ***co-corresponding author**

Gioia R, Seri T, Diamanti T, Fimmanò S, Vitale M, Ahlenius H, Kokaia Z, Tirone F, Micheli L, Biagioni S, Lupo G, Rinaldi A, De Jaco A, **Cacci E.** Adult hippocampal neurogenesis and social behavioural deficits in the R451C Neuroligin3 mouse model of autism are reverted by the antidepressant fluoxetine. J Neurochem. 2023 May;165(3):318-333. doi: 10.1111/jnc.15753. Epub 2023 Jan 9.

Stronati E, Biagioni S, Fiore M, Giorgi M, Poiana G, Toselli C, **Cacci E**. Wild-Type and Mutant FUS Expression Reduce Proliferation and Neuronal Differentiation Properties of Neural Stem Progenitor Cells. Int J Mol Sci. 2021 Jul 15;22(14):7566. doi: 10.3390/ijms22147566.