

20th & 21st October 2021 - Pullman Paris Tour Eiffel Tower

Particles & Health 2021

An International conference addressing issues in science and regulation

In vivo Processing of Nanoparticles – Influence on Toxicity

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Manufactured Particles

Environmental Particles

In vivo Processing of Nanoparticles – Influence on Toxicity

and a second

OBJECTIVE Differentiate Translocated Nanoparticle Types in Brain of Humans with Neurodegeneration

Inhalation Pathway to OB ••

Pollution AEROSOL

Do inhaled NPs translocate to the OB?
Which types of NPs?
Do translocated NPs interact with specific cells in OB?
Are NPs undergoing bioprocessing?
More NPs cause more neurodegeneration?

Pollution Nanoparticle Uptake

Tissue Interactions In vivo Processing HEALTH EFFECTS ? TOXICITY?

Exposure - Dose - Response

....



High Resolution TEM for Characterization of Nanoparticle-Cell Interactions

In vivo Processing?

HR-TEM

Human OB – Tissue of select Cohort Subjects

- Titan produce a spatial image and achieves ultra high-resolution using aberration correction and can produces extremely narrow electron beam.
- Seeing ~1-10 nm NPs inside tissue without destroying the OB section.
- TALOS for fast elemental mapping over larger tissue regions.

AIR POLLUTION

Multi-disciplinary TEAM

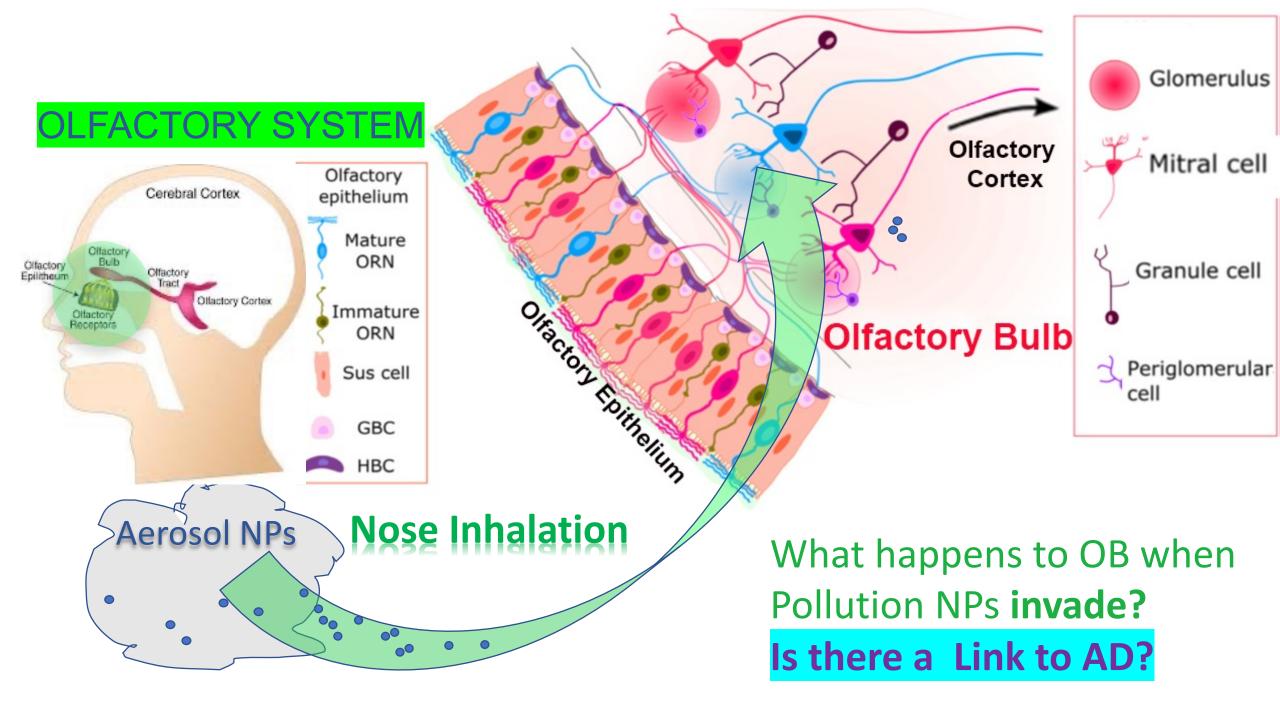
Air Pollution and Alzheimer's Dementia: Neuropathologic and Olfactory Mechanisms in Multi-Ethnic Longitudinal Cohorts

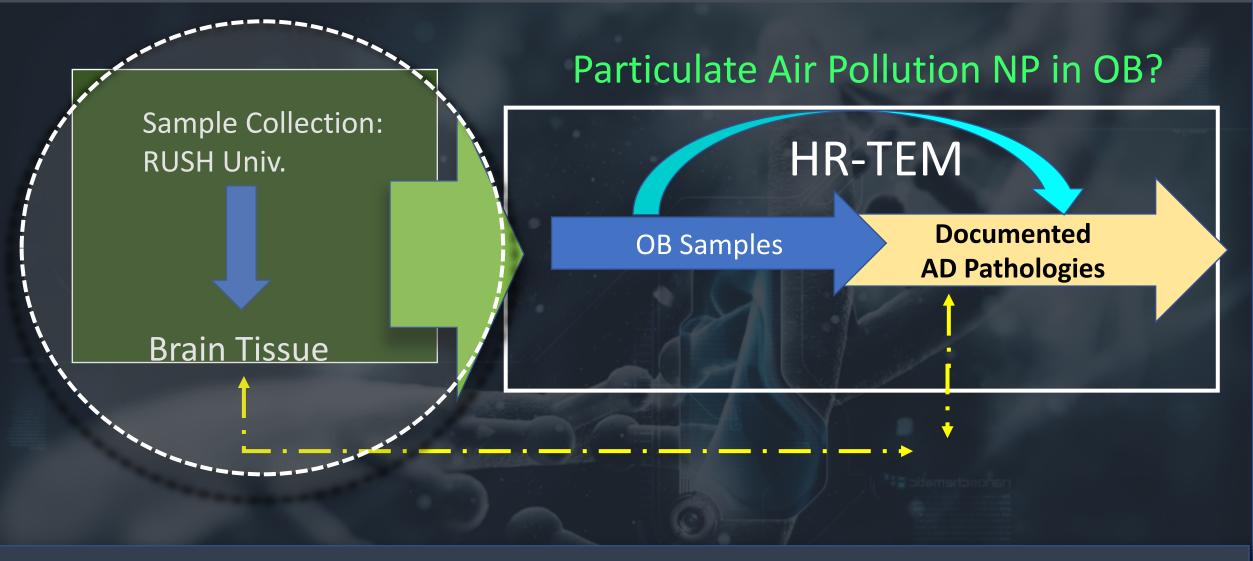


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EXPOSURE

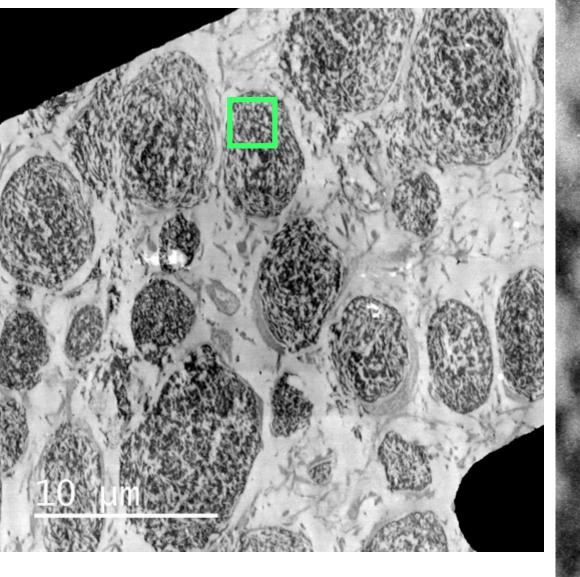
Epidemiology	Surgery	Neurology	Pathology	Nanotoxicology	Nanotechnology	
J Weuve	JJ Pinto	DA Bennett	J Schneider	G Oberdorster	UM Graham	
BOSTON UNIVERSITY	CHICAGO	€ RUSH	⑦ RUSH	ROCHESTER MEDICAL CENTER	Kentucky	





<u>Religious Order Study and Rush Memory and Aging Projects</u> Subjects with different progression of AD.

OB-STEM-F1

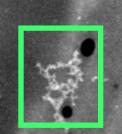


Amorphous Silica NPs

In vivo processing

Ferritins

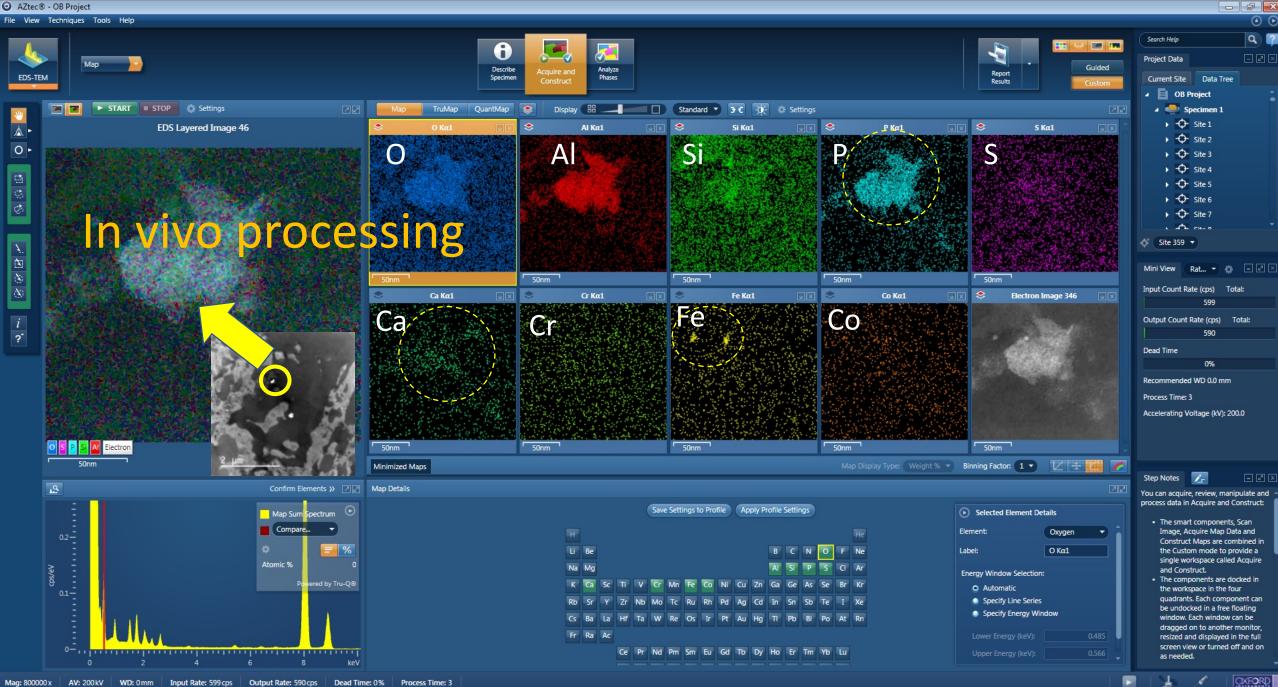
SiO₂ Amorphous Silica





μm





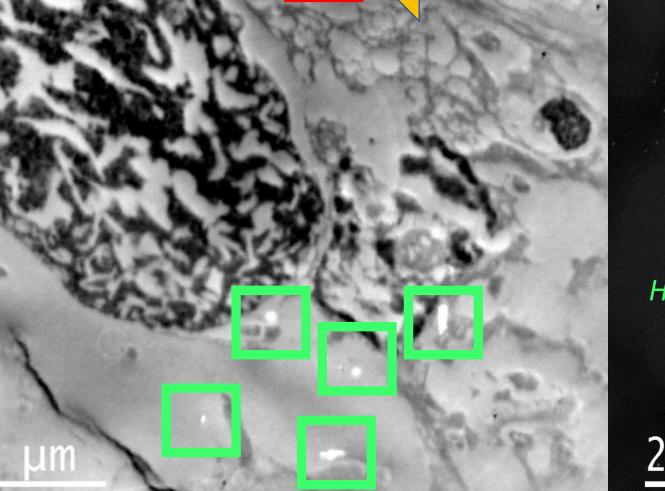
Mag: 800000 x AV: 200 kV WD: 0mm Input Rate: 599 cps Output Rate: 590 cps Dead Time: 0% Process Time: 3

2

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OB-Tissue



HOST: Amorphous Zn; Cr SiO₂ Pb; Zn; Cr Heavy metals

200 nm

Zn; Cr

Heavy Metal Uptake to the OB and potentially Deeper Brain via a Trojan Horse Nanoparticle Transport Mechanism



200

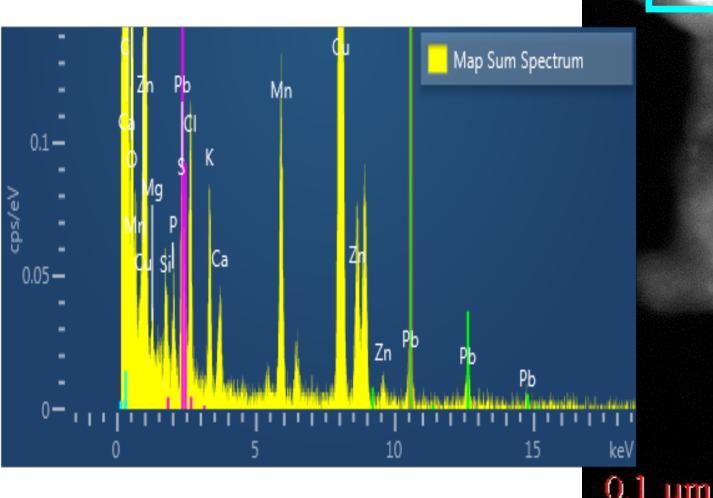


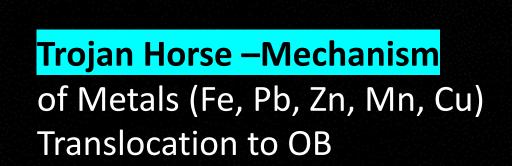
Trojan Horse –Mechanism of Metals (Fe, Pb, Zn, Mn, Cu) Translocation to OB MM

um

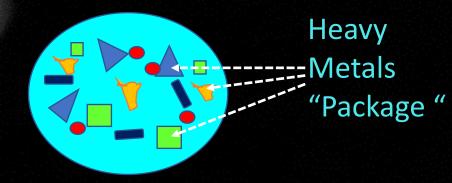
OB Sample: 20794261 - M1---A

Translocated Si/Al NPs with heavy metal inclusions.





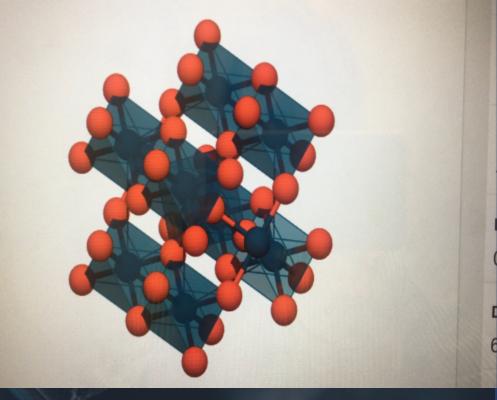
Si/Al



In vivo Processed NP

- Metallic Pb
- Nano-crystallites of PbO₂

Catalytic Properties



Olfactory Uptake of Lead (Pb) PM

Glomerulus

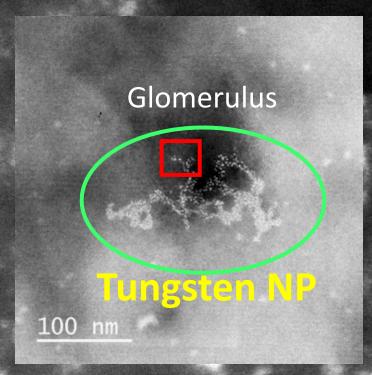
Abundant Ferritins!

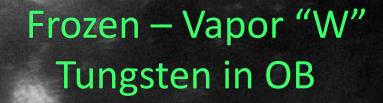




Ferritins

Tungsten NP

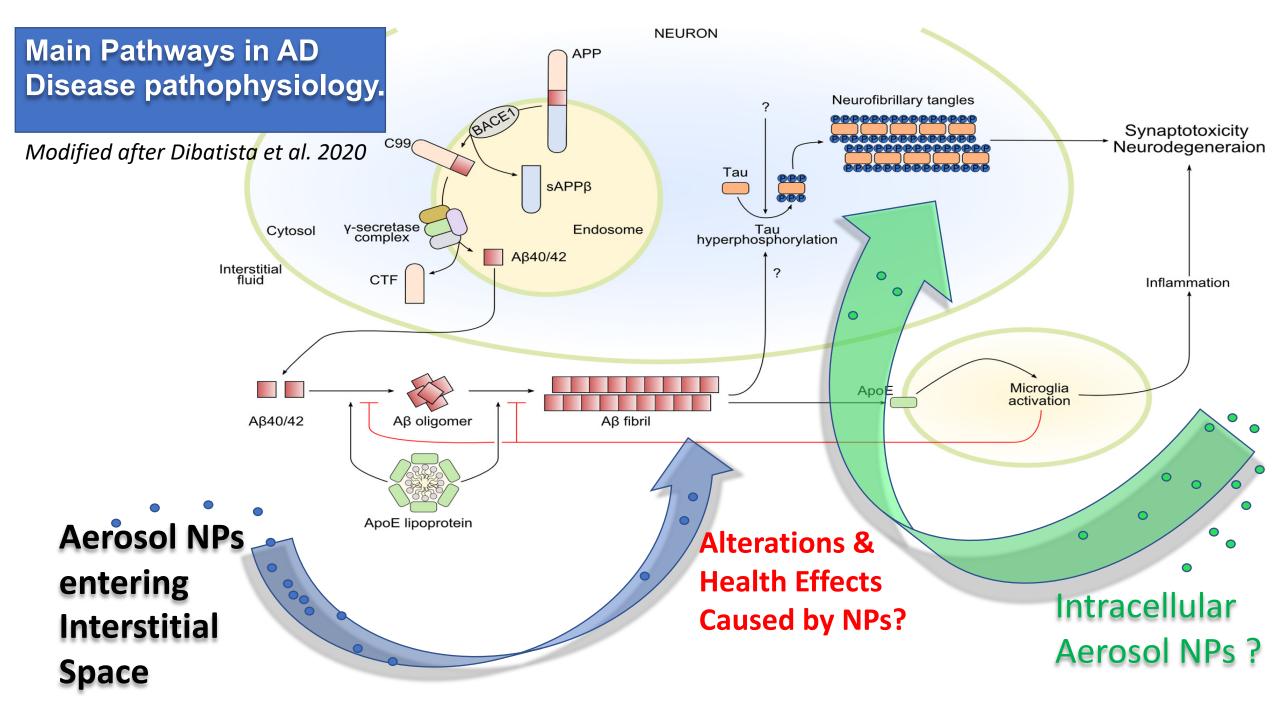




ATOMIC DISPERSION of W - NP







Olfactory Bulb Tissue

NP – induced inflammation

Ferritins

Pollution Particles

200 nm

Olfactory Bulb Tissue

Pb/Zn/Ni-Pollution Particles

NP – induced inflammation

Ferritins

In vivo Processing of NPs

200 nm ^{Iron Phosphate} "Crust"

AZtec® - 0		AZtec® - OB F				
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	Viewed Data: Spectrum 422	2	Confirm Elements »	Map Details		
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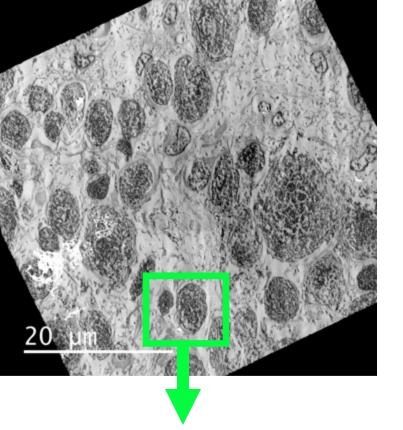
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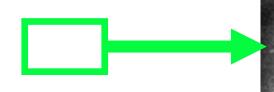
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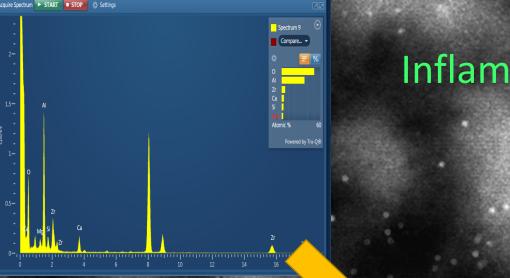
Nanoparticles in OB

Exogenous vs. Endogenous Fe

In vivo processing and toxicity







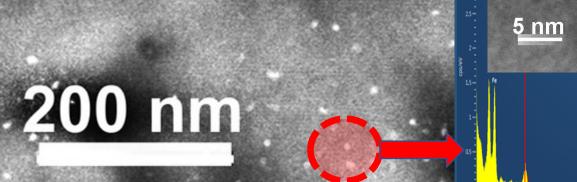
Inflammatory Response



FERRITIN

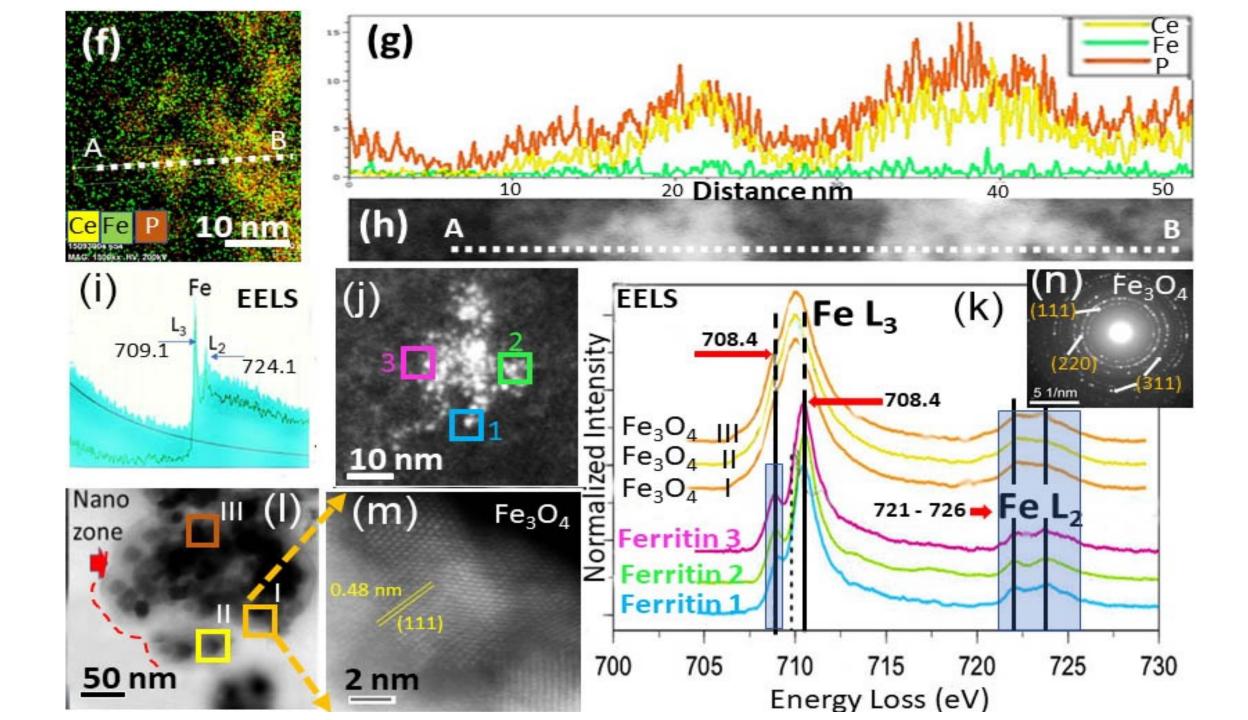
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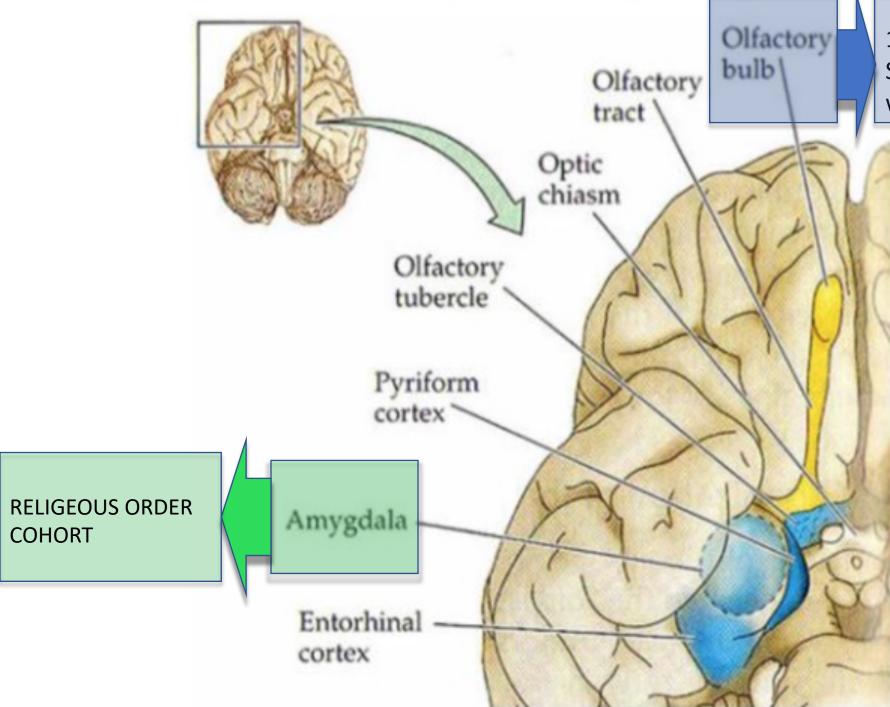






Ferritins





12 OBs from RELIGEOUS ORDER STUDY COHORT with different progression of AD

- NP Locations
- NP size, morphologies,
- Quantification
- Association of NP with cellular features
- NP association with ferritin enrichment

NEXT

Examine neuronal pathways from the OB glomeruli along the Olfactory tract to the amygdala and deeper brain regions.

SUMMARY: In vivo Processing of Pollution Particles in OBs: Influence on Toxicity

- In vivo processing of translocated NPs in OB cells involves Fe-phosphate crust formation
- Heavy metals embedded in Al-Si particles in OB and inside Fe-phosphate crusts
- Fe-phosphate crust formation mechanism is same for different Cohort-Subjects
- Trojan Horse transport mechanism is same for different Cohort Subjects.
- Abundance of Ferritin NP (*acute phase protein*) and Fe-phosphate "crusts" due to Febiomineralization as indicator of inflammation.
- DOES ASSOCIATION MEAN CAUSALITY?
- Heavy metal NPs in OB as indicator of environmental and occupational exposure (Pb;W) ?
- Need for studying NP in vivo processing mechanisms in context with histopathology and molecular biology mechanisms

•Although very high numbers of exogenous NPs in OB tissue, what does it mean in terms of toxicity potential?

•To be determined: Degree of association/correlation with pathology; plaques; A-β: Tau; and other marker proteins; activated microglial and oligodendrocytes, etc.

Acknowledgements

1R01AG067497-01

ROS Cohort

Religious Orders Study and Rush Memory and Aging Project Bennett DA, Buchman AS, Boyle PA, Barnes LL, Wilson RS, Schneider JA. *J Alzheimers Dis.* 64(s1):S161-S189. PubMed PMID: 29865057 Published date: 2018 Jun 12

MAP Cohort

Overview and findings from the Rush Memory and Aging Project. Bennett DA, Schneider JA, Buchman AS, Barnes LL, Boyle PA, Wilson RS. *Curr Alzheimer Res.* 9(6):646-63. PubMed PMID: 22471867 Published date: 2012 Jul

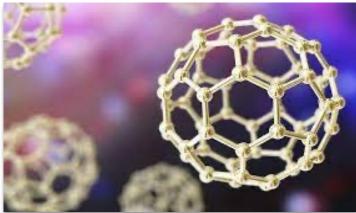
The Minority Aging Research Study: ongoing efforts to obtain brain donation in African Americans without dementia. Barnes LL, Shah RC, Aggarwal NT, Bennett DA, Schneider JA. *Curr Alzheimer Res.* 9(6):734-45 PubMed PMID: 22471868 Published date: 2012 Jul Instrumentation:

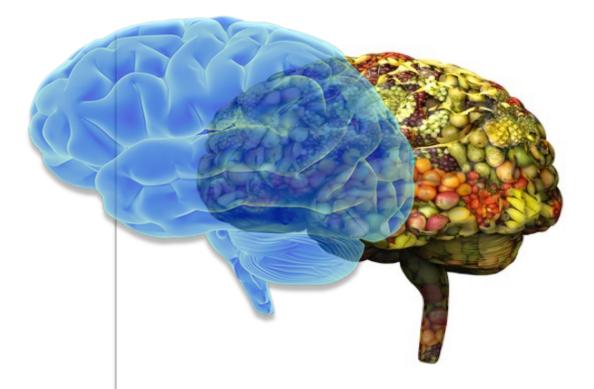
NIOSH, Cincinnati OH Advanced Electron Microscopy Center Dr. Alan K Dozier

AFRL Wright Patterson Air Force Base Titan and Talos Dr. Larry Drummy: Group Leader In 1826, the French lawyer Anthelme Brillat-Savarin wrote, in *Physiologie du Gout, ou Meditations de Gastronomie Transcendante*:

"Dis-moi ce que tu manges, je te dirai ce que tu es." Tell me what you eat and I will tell you what you are.







Particles & Brain Health

"Tell us what you **breathe** ---------- and we will tell you what happens in your brain."

Image Credit: 'The Martian'