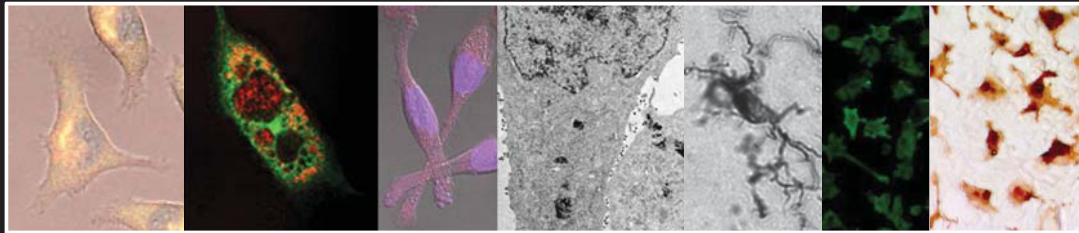


# The Role of Protein Radicals in Neuroinflammation As a Model of GWI & Therapeutic Strategies

## Microglia Activation



Pathogen

Environment

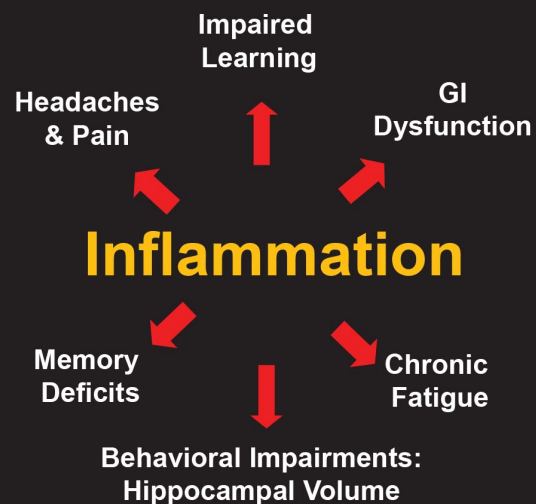
Disease

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Department of Anatomy & Neurobiology  
Virginia Commonwealth University

## Gulf War Illness (GWI)

- Known:**
- ★ Devastating multisymptom illness.
  - ★ Symptoms- delayed & persistent.
  - ★ 1/3 of 1990–1991 Persian Gulf War Veterans affected.
- Unknown:**
- ★ Specific cause(s) unknown.  
*(But we have some good hypotheses.)*
  - ★ Pathobiology - poorly understood.  
*(But we have some good hypotheses.)*
  - ★ Markers & treatments are elusive.

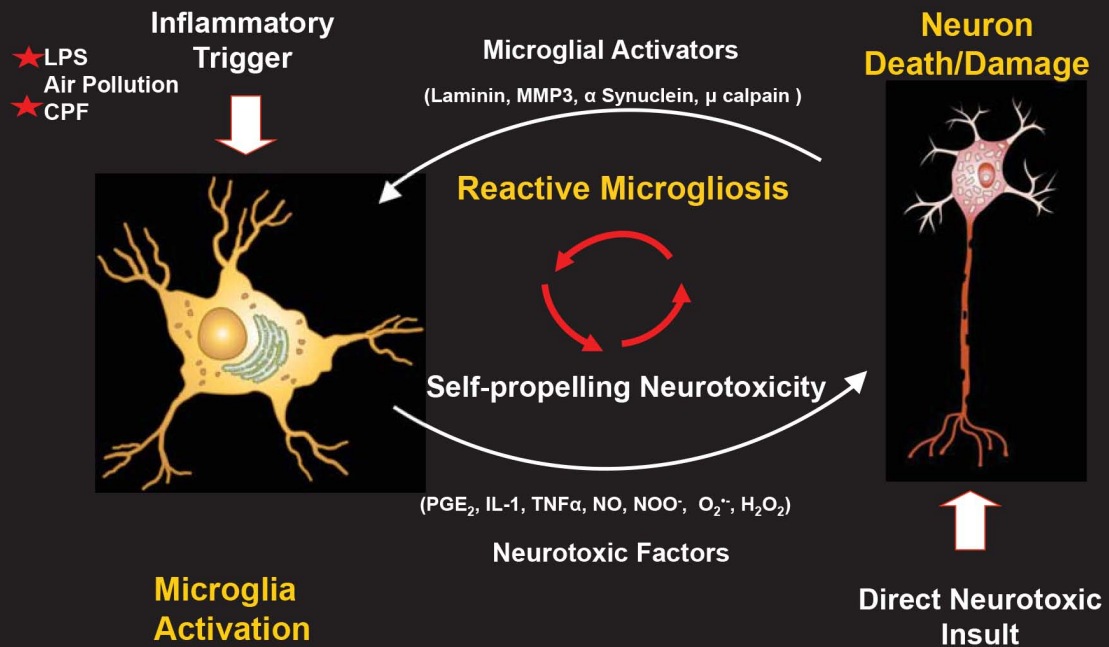
### Many Symptoms Linked to Peripheral & Central Inflammation



**Why is the immune perturbation chronic?**

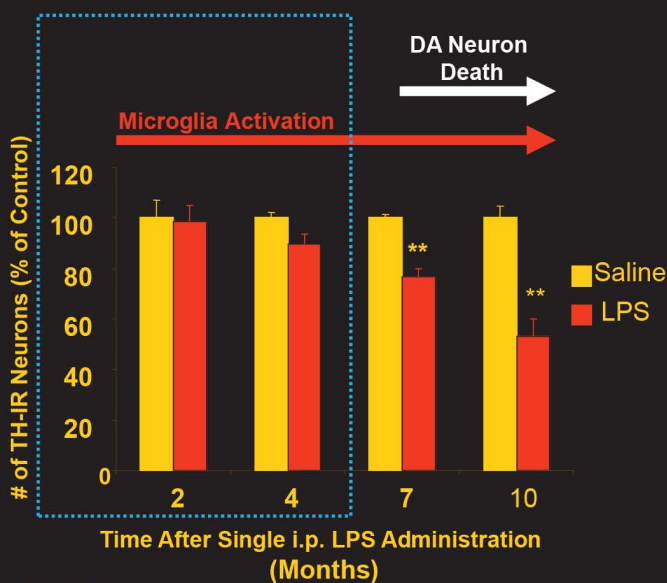


# Microglia are a Source of Chronic Inflammation and Oxidative Stress



(Block et al., 2007, Nature Reviews Neuroscience)

## Lessons from a Parkinson's Disease Model: Inflammation-mediated Neuropathology is Delayed & Progressive



(*in vivo*)  
 (Qin, Wu, Block, et al., 2007, *Glia*)



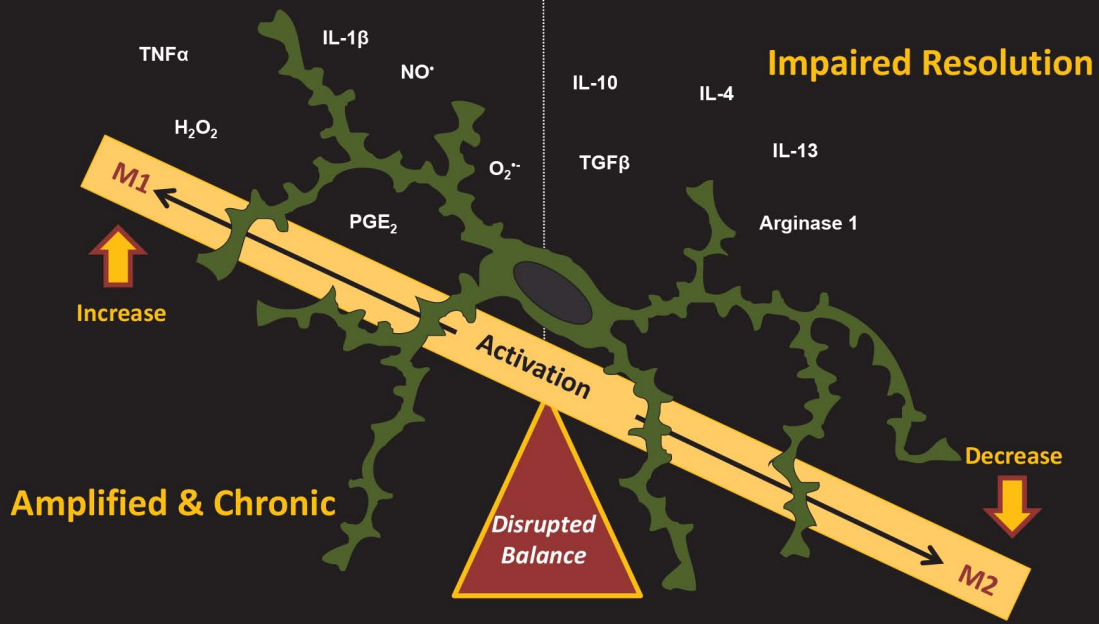
➡ Early time points (0-6 m) – Model of chronic neuroinflammation without overt toxicity.

# M1 Polarization & Dysregulated Activation

(The Deleterious Phenotype: Exaggerated & Chronic)

(M1) Pro-inflammatory Response

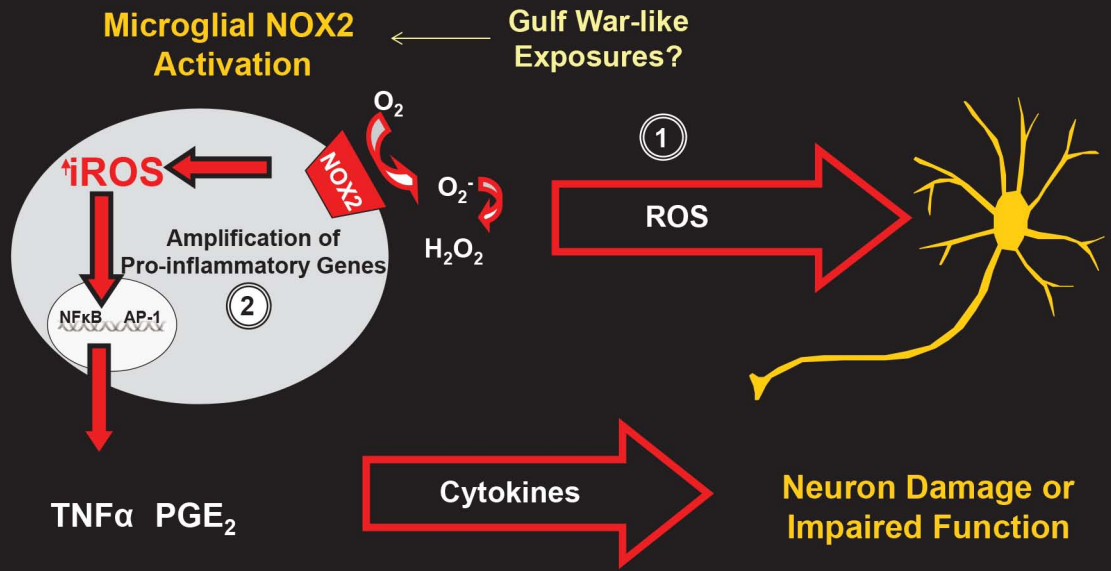
(M2) Wound Healing/Alternative Response



## NOX2: Common Mechanism of Microglia-Mediated Neurotoxicity

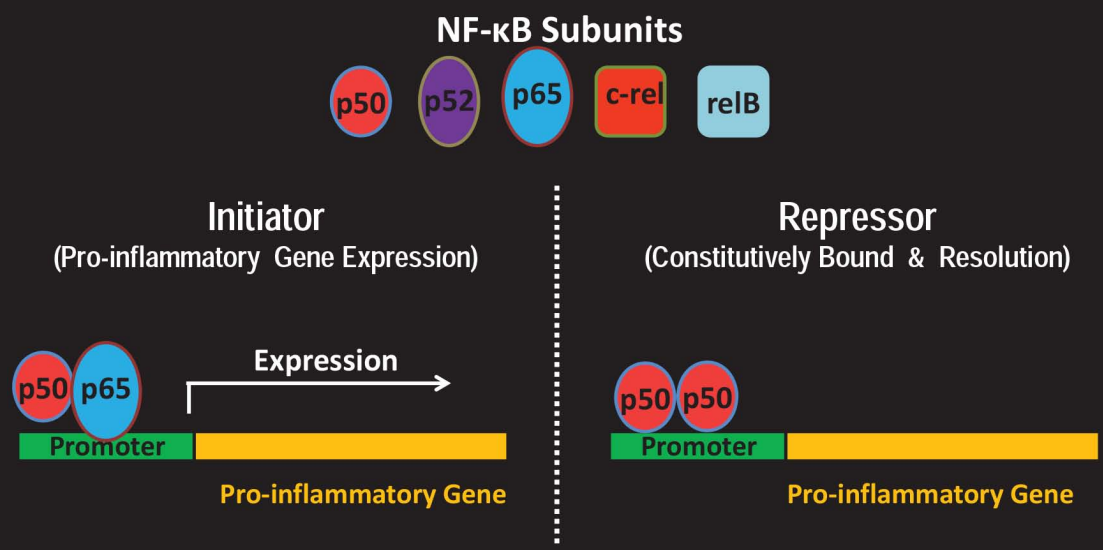
Microglia Activator/Toxin	Extracellular Superoxide	Pro-inflammatory Factor Production	References
Lipopolysaccharide	Yes	Yes	(Qin et al., <i>JBC</i> , 2004)
Diesel Exhaust Particles	Yes	No	(Block et al., <i>FASEB J</i> , 2004) (Levesque et al., <i>JNC</i> , 2013)
Paraquat	Yes	No	(Wu et al., <i>Ant. Red. Sig.</i> , 2005)
$\alpha$ Synuclein	Yes	No	(Zhang et al., <i>FASEB J</i> 2005)
Substance P	Yes	No	(Block et al., <i>FASEB J</i> , 2006)
MMP3	Yes	Yes	(Kim et al., <i>FASEB J</i> , 2006)
$\mu$ Calpain	Yes	No	(Levesque et al., <i>Brain</i> , 2010)

# Microglial ROS are Detrimental Through Two Mechanisms



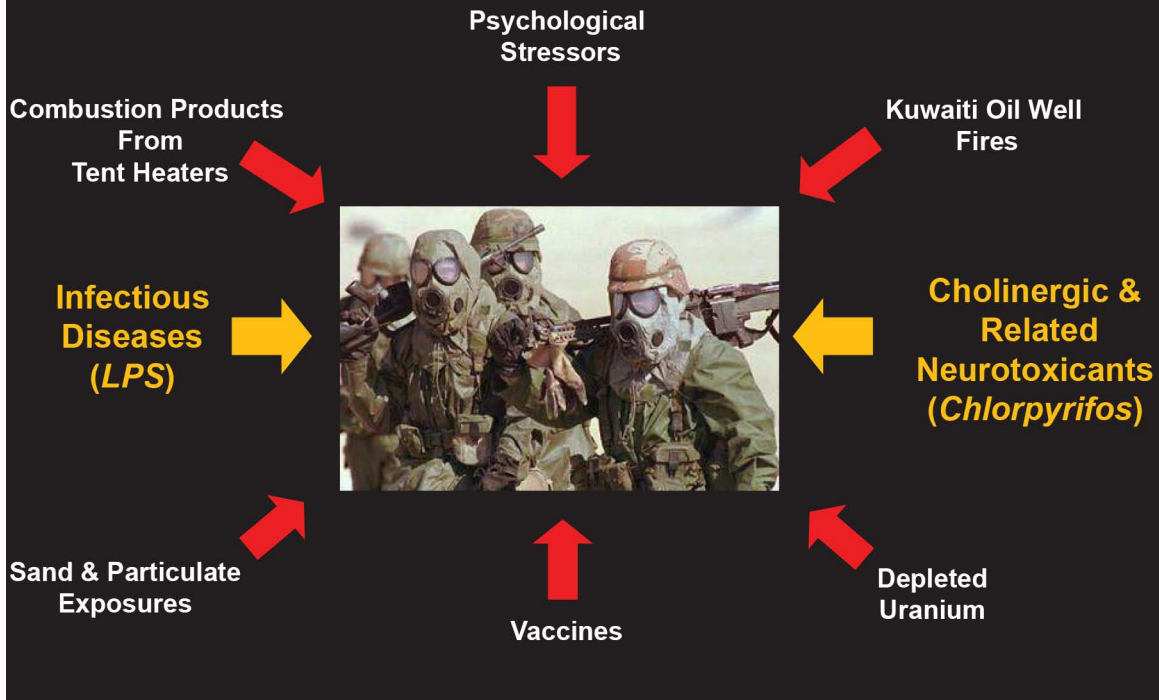
(Block & Hong 2005, Progress in Neurobiology)

# Dual Roles of NF-κB p50 in Inflammation

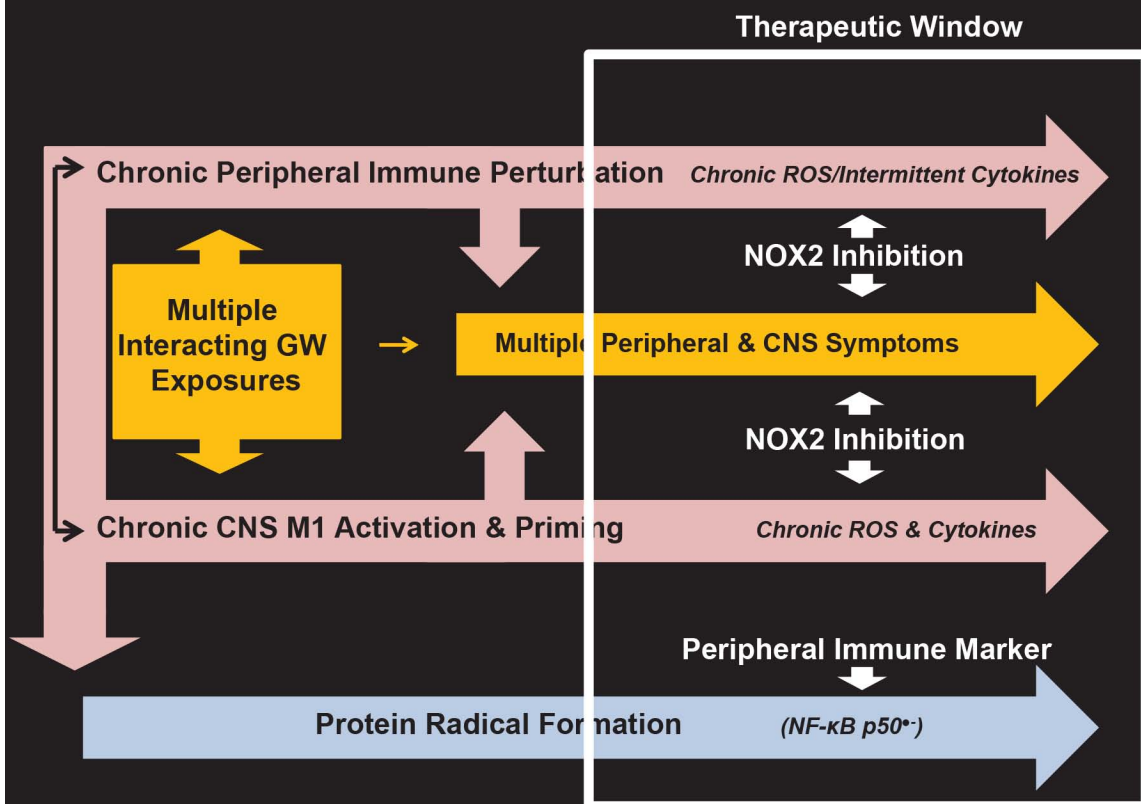


# The Multiple Hit Hypothesis of GWI:

Many Potential Causes/Exposures/Stressors May Act in Synergy for Persistent Impact



# Protein Radicals & the Immune Hypothesis of GWI





# Acknowledgements

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Technician  
Postdoctoral Scientist  
Postdoctoral Scientist

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Marcello Bonini – University of Chicago

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★ **The Persian Gulf War Veterans**  
We are indebted to you.

## The Block Lab

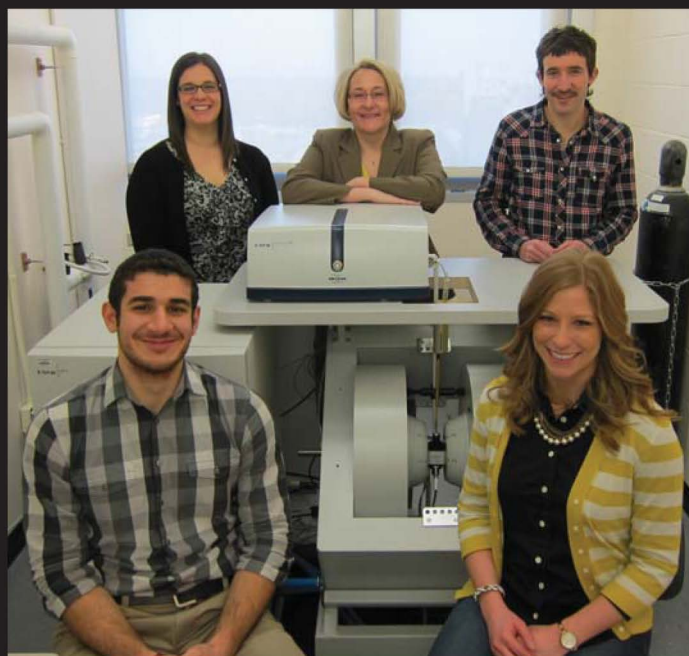
Michelle Block

Shannon Levesque

Tom Taetzsch

Rafy Luqa:

Savanah Brookins



“Big Betty” (EPR Spectrophotometer)