



Trinity College  
The University of Dublin



# Protecting Babies' & Children's Brains

## Lessons from GB Shaw

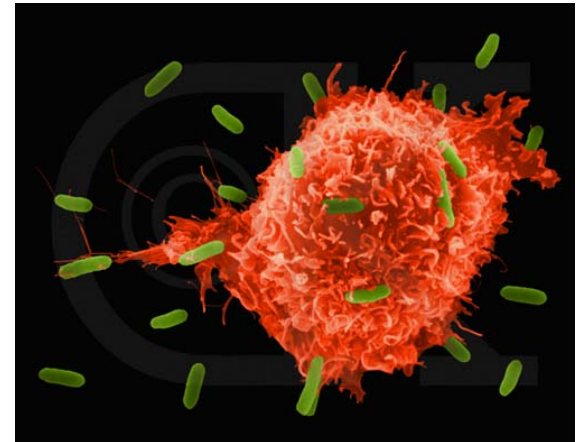
### Child Health Research in Ireland

Eleanor Molloy  
Inaugural lecture 24<sup>th</sup> May 2016

Trinity College Dublin  
NCH, OLCH, CWIUH  
Faculty of Paediatrics, Spring Study day 2016

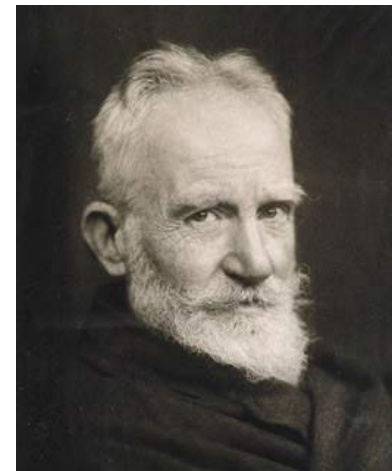
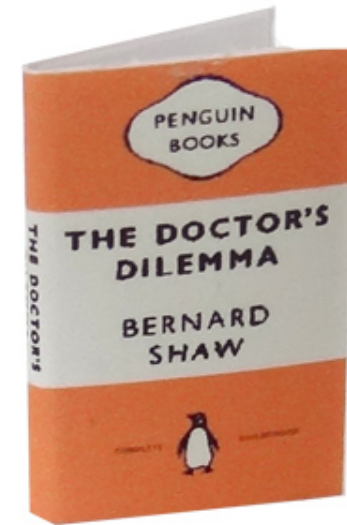
# Overview

- Lessons from GB Shaw
  - Medicine & Immunology
  - Children
- Protecting Babies' and Childrens' Brains
  - Persistent inflammation
  - New therapies
- The Future
  - National Paediatric hospital
  - Personalised medicine
  - International networks



# George Bernard Shaw

- Born 160 years ago in the Coombe
- The Doctor's Dilemma
- Written 1906
- Dilemma
  - “Who to save”
  - Dubedat v Dr. Blenkinsop
- Sir Colenso Ridgeon= Sir Almroth Wright



# AE Wright (1861-1947)

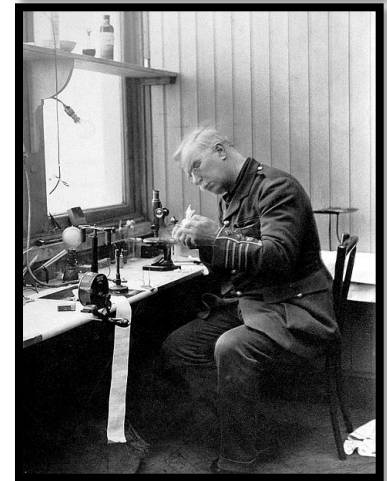
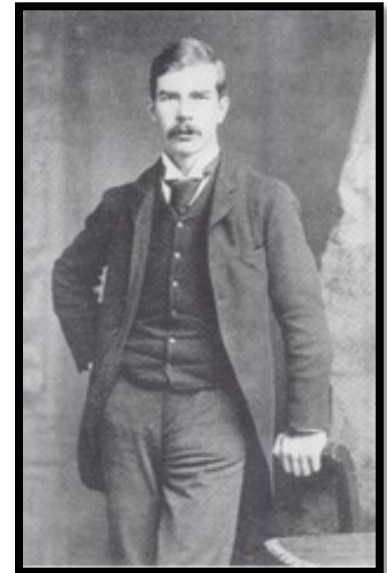
- Bacteriologist & Immunologist
- Trinity College Dublin: Qualified Modern Literature 1882, Medicine 1883
- 1896 :Typhoid
  - Developed first successful vaccine
  - Widely used in World War I saving over 100,000 lives.
- 1902 started inoculation department at St Mary's Hospital
- Leonard Colebrook and Alexander Fleming
- Today, Wright-Fleming Institute.
  - The Plato of Praed Street, the Life and Times of Almroth Wright, by Michael Dunnill; ISBN 1-85315-477-6; London: RSM Press, 2000 .





# AE Wright

- Warned of Antibiotic resistance
- Preventative medicine
- Logic in medical education
- “Renaissance man”
- Discovered opsonins=“butter”
- Pasteur and Fleming had not found cures for the diseases which they had sought cures, but instead had stumbled upon cures for totally unrelated diseases.
- *The Unexpurgated Case against Woman Suffrage* (1913)



# The Doctors Dilemma

## *A Tragedy*

- Shaw, Preface on Doctors: 81 pages
  - Ethics of Private medical practice
  - Equality of health care delivery
  - High-risk therapies
  - Evidence-based practice
- Immunology
  - Individualised medicine

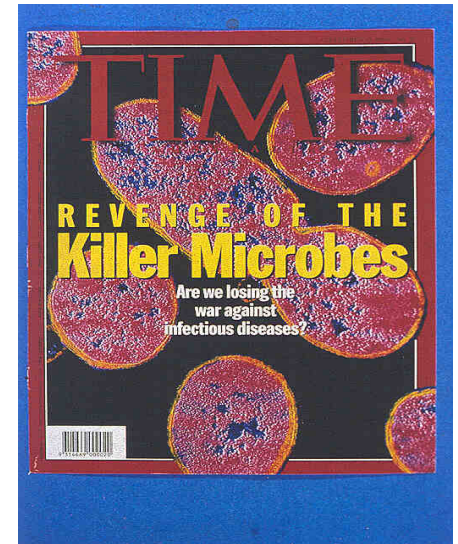
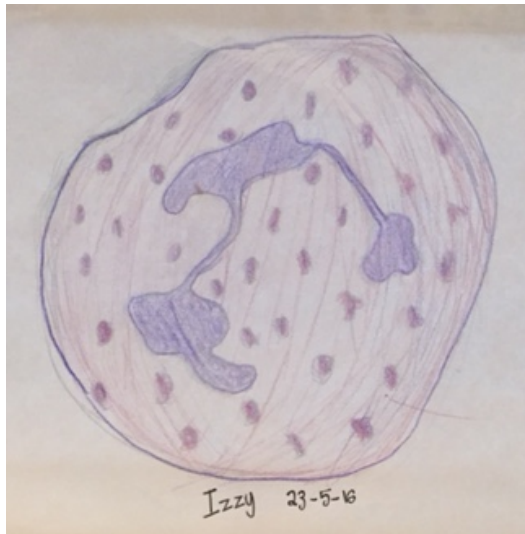


# The Doctor's Dilemma

- In Shaws time (pre-antibiotics)...the only solution was to stimulate the phagocytes
- Immunomodulation still not an exact science
- Sir Almroth Wright
  - Sir Always Wrong
  - Sir Almost Wright



“Stimulate the  
phagocytes...Drugs are a  
delusion”



# Perinatal Inflammation

**PhD**

**Neutrophil  
Apoptosis & function**

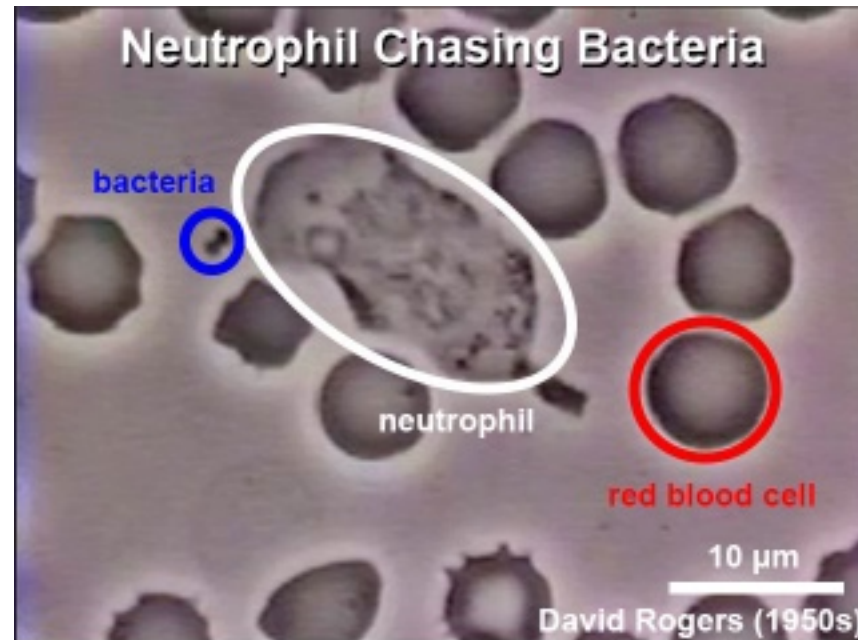
**Prof RW Watson,  
UCD & CWIUH**

Labour  
Gender  
Sepsis  
NE  
G/GMCSF

**Postdoc**

**Endotoxin responses**  
**Prof Claire Doerschuk,  
Rainbow Babies & Childrens  
Hospital, CWRU, Cleveland**

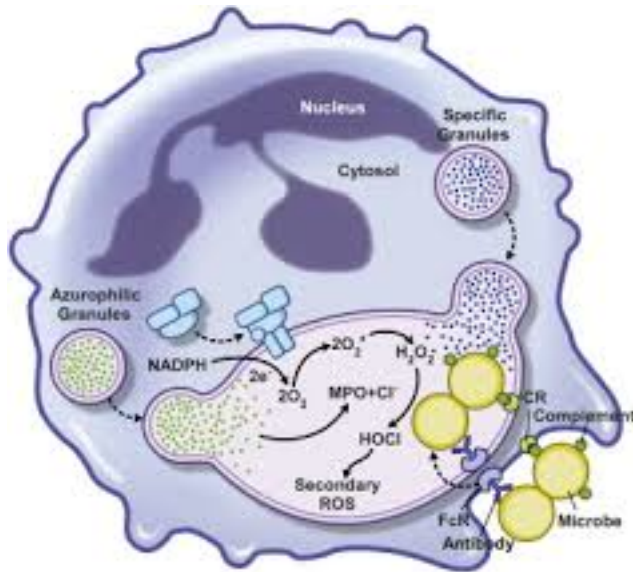
Toll-like  
Receptor  
TREM-1  
pathway



MP4 movie

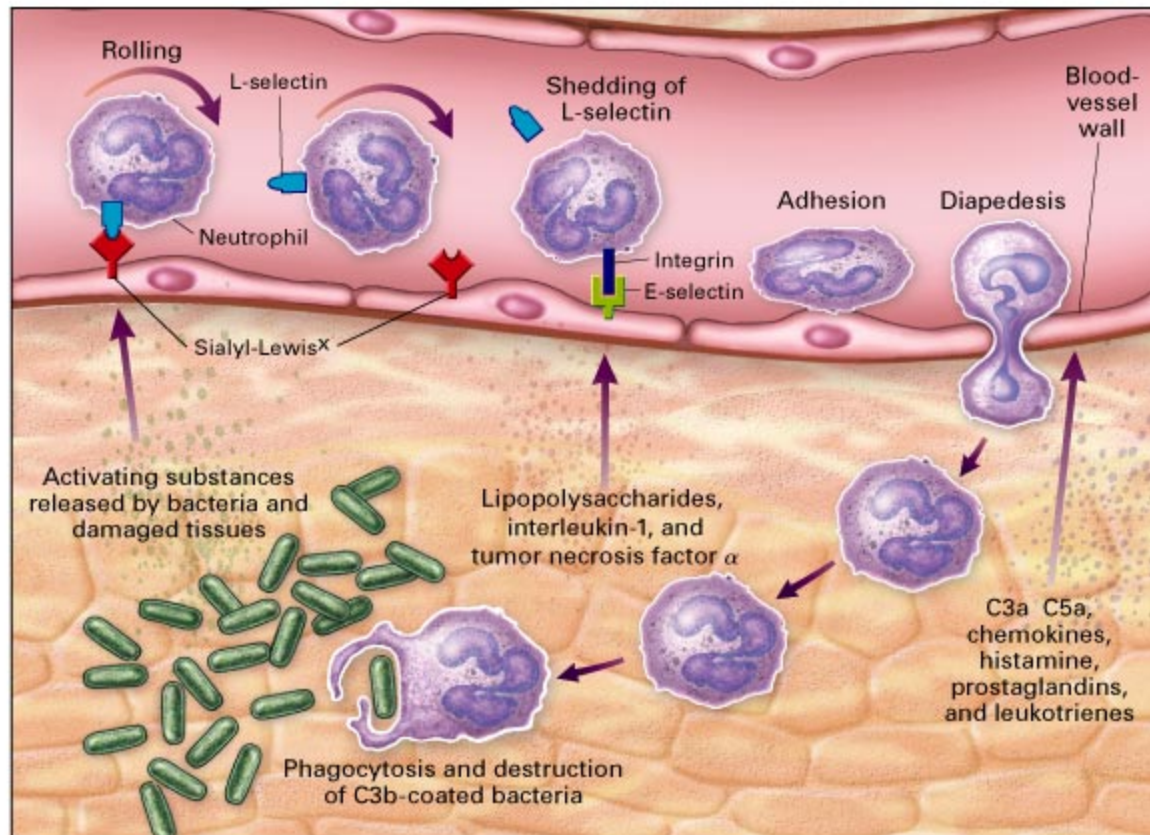
[https://embryology.med.unsw.edu.au/embryology/index.php/Movie\\_-\\_Neutrophil\\_chasing\\_bacteria](https://embryology.med.unsw.edu.au/embryology/index.php/Movie_-_Neutrophil_chasing_bacteria)

# Neutrophils



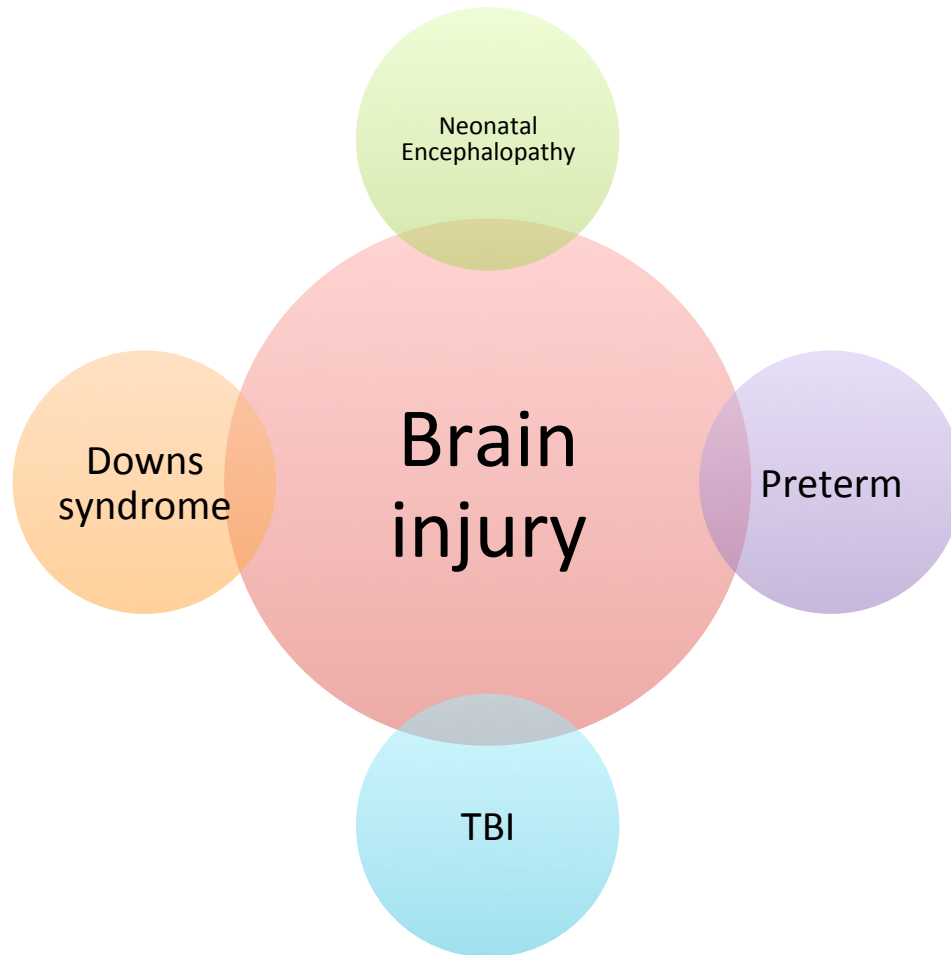
- High Neutrophil count
  - Worse outcome in Neonatal brain injury
  - Stroke
  - MI
- Low neutrophils
  - Improved dev outcome in neonates
  - Increased sepsis



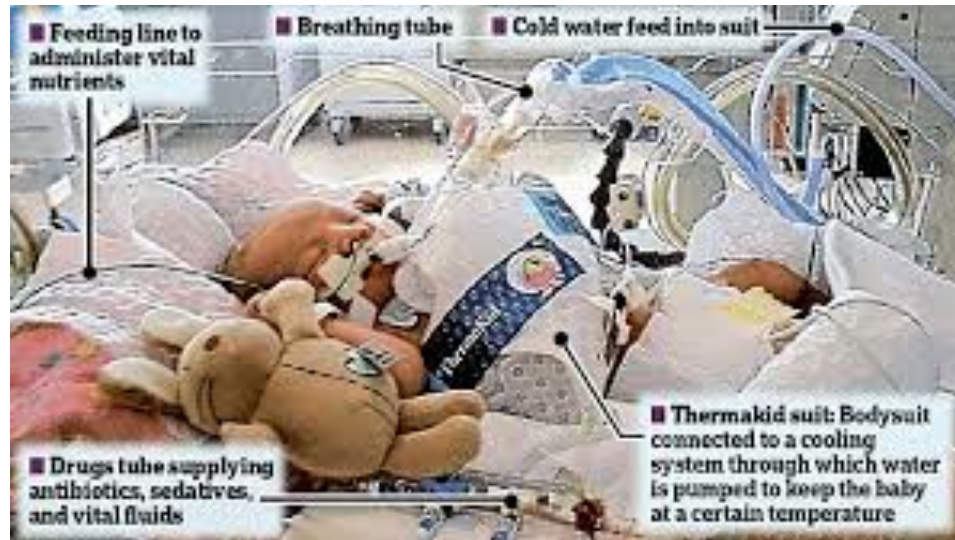




# Brain injury in Babies and Children



# 'Our little miracle' Ella the ice baby, who died in the womb and was stillborn, amazes doctors by coming back to life after 25 MINUTES



<http://www.dailymail.co.uk/health/article-1362132/>



Nearly 750,000 babies born each year in the United Kingdom are at risk of brain damage because of low oxygen during birth.

MRC: Nature News, Wrika Hayden 9 July 2014

# Neonatal Brain Injury

- Full –term
- Neonatal Encephalopathy (NE) ~ 3.0/1,000 live births
  - HIE ~ 1.5/1,000 live births
- Permanent neurological and cognitive impairment
  - Shankaran et al, NEJM, 2005.
- Even NE I :poorer cognitive outcomes
- Leading cause of perinatal brain injury, cerebral palsy and lifelong disability

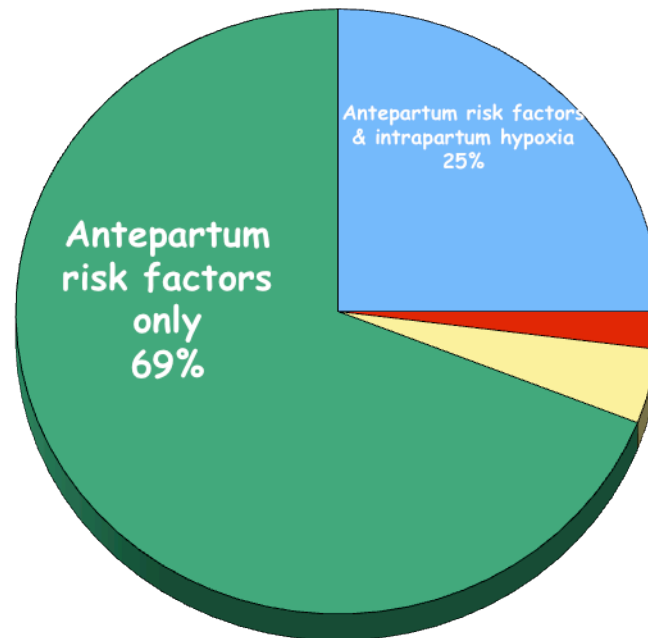


# Multiple factors involved in Brain Injury



# Causes of Neonatal brain injury

- 10% Cerebral Palsy attributed to hypoxia-ischaemia alone
  - Graham EM et al., 2008, ACOG
  - Badawi N et al., 1998



# Preterm Infants

- Preterm infants <32 weeks gestation
- Susceptible to infection and inflammatory diseases.
  - Hornik CP et al., , Early Hum Dev 2012; 88: S69–74.
- Systemic inflammation related to sepsis –
  - implicated in many common neonatal complications: brain, lung and GI injury and can be life threatening.
- Every infection adversely affects neurodevelopmental outcome
  - Marlow N et al and the EPICure Study Group N Engl J Med 2005; 352: 9–19.





# Gender

- Gender disparity
  - Females well recognised survival advantage compared to males throughout the entire lifecycle
  - Male gender :
    - increased risk of neonatal mortality in preterm infants
    - more susceptible to sepsis compared to females throughout life.
- Oestrogen
  - Gender differences are largely attributed to oestrogen levels
  - Need to elucidate the role of sex hormones on immune function.
  - Oestrogen an anti-inflammatory role and increases neutrophil survival.
    - Molloy EJ, Blood, 2003



# Traumatic Brain injury (TBI) in children

- TBI:
  - More common in childhood and adolescence than at any other time of life
  - One of the most common causes of neurological morbidity
    - McKinlay A et al., 2008; Langlois JA et al., 2005; Thornhill S et al., 2000; Maas AIR et al., 2008
- Mild traumatic brain injury (mTBI)=90% of all TBIs
  - Barkhoudarian G et al., 2011; Heads up, CDC
  - Falls (51%) and sports-related activities (25%)
- One in five children will experience mTBI by the age of 10 years
  - McKinlay A et al., 2008; Corrigan JD et al., 2010



# Post concussive syndrome

- Post concussion syndrome (PCS)
  - combines clinical, cognitive and behavioural symptoms
  - 1 in 7 school children sustaining an mTBI > 3 months
    - Barlow KM et al., 2010
- PCS can persist and cause significant disability
  - 2% of mTBI continuing for more than 1 year
    - (Barlow KA et al., 2010).
- No evidence-based medical treatments or diagnostics available
  - McCrory et al., 2009
  - Neurobiological understanding of PCS is lacking
    - Barkoudarian G et al. 2011;McCrory et al., 2009
- Urgent need to develop novel treatment options



# Post-inflammatory brain syndromes (PIBS)

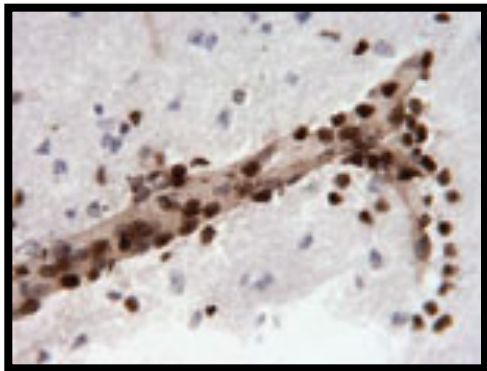
- Rathbone et al have coined the term PIBS
  - neuroinflammation and systemic inflammation in post-concussion syndrome
  - Rathbone AT et 2015
- Systemic inflammation, proinflammatory cytokines Interleukin (IL)-1, IL-6, and TNF and other inflammatory mediators may mediate cognitive impairment and induce sickness behaviour following traumatic brain injury
  - Rehman Y et al., 2014
- CRP:
  - elevated C-reactive protein
  - associated with persistent post-concussive syndrome,
  - psychological problems and cognitive impairment
  - Su SH et al., 2014

<http://www.cortjohnson.org/blog/2014/05/06/>



# Inflammation & Brain injury

- Systemic inflammation & brain injury
  - Stroke
  - Hind-limb ischaemia in neonatal rat
  - Infection/inflammation
    - McColl et al., 2007



Neutrophils (brown) cerebral blood vessel  
=>brain.

Systemic inflammatory challenge markedly  
potentiates this migration.

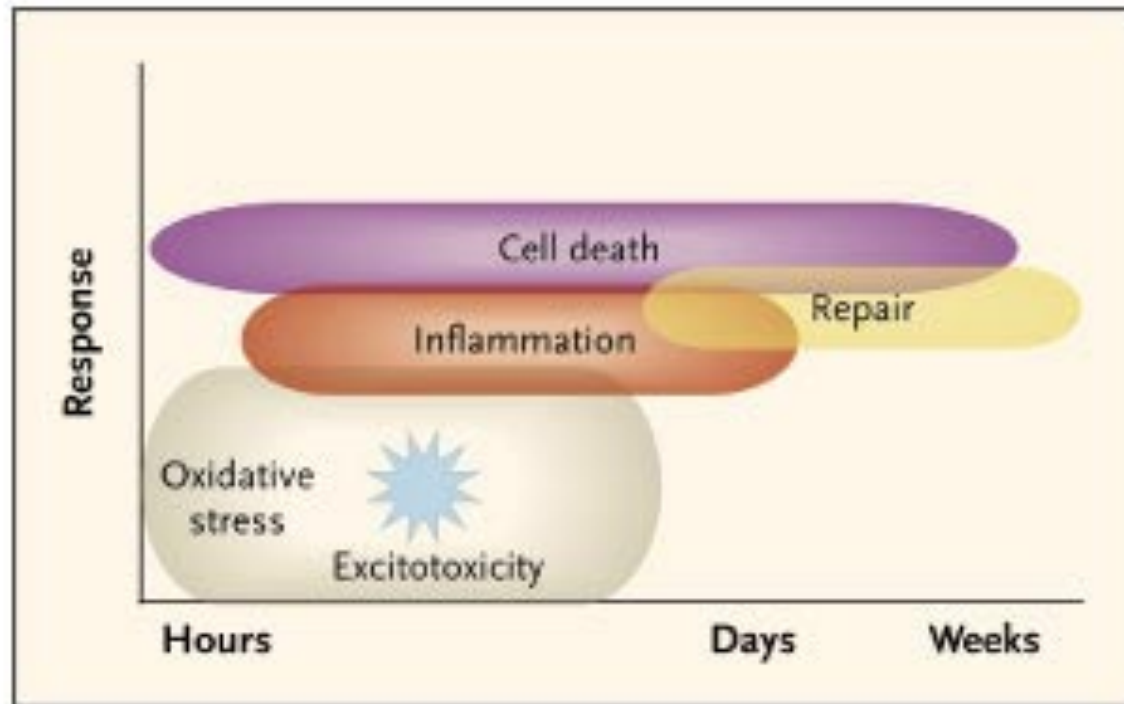
Neutrophils release many toxic molecules  
that damage brain tissue.

# Persistent/sustained inflammation

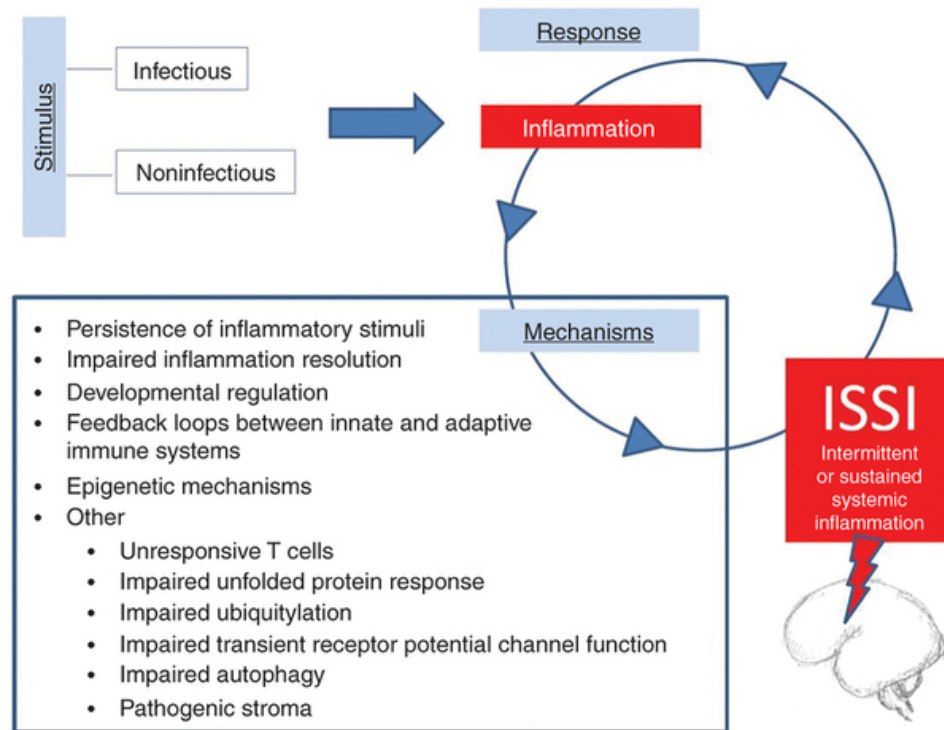


# Mechanisms of Brain injury in the Term Neonate

## Necrosis-apoptosis continuum



# Perinatal inflammation => sustained Preterm infants

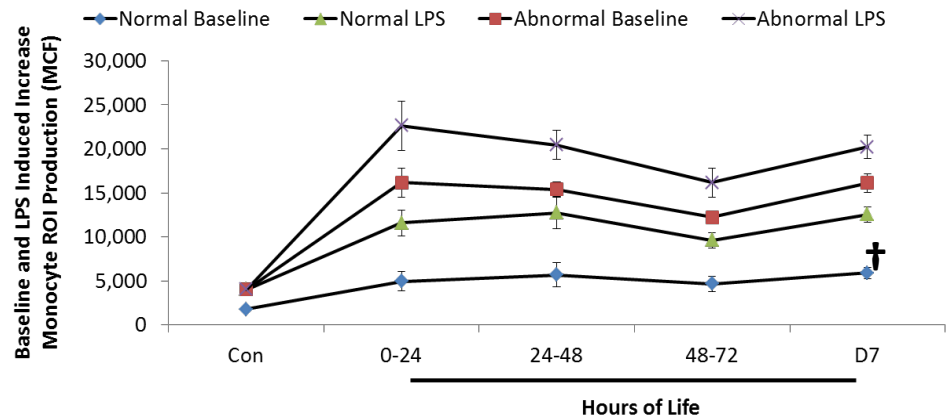
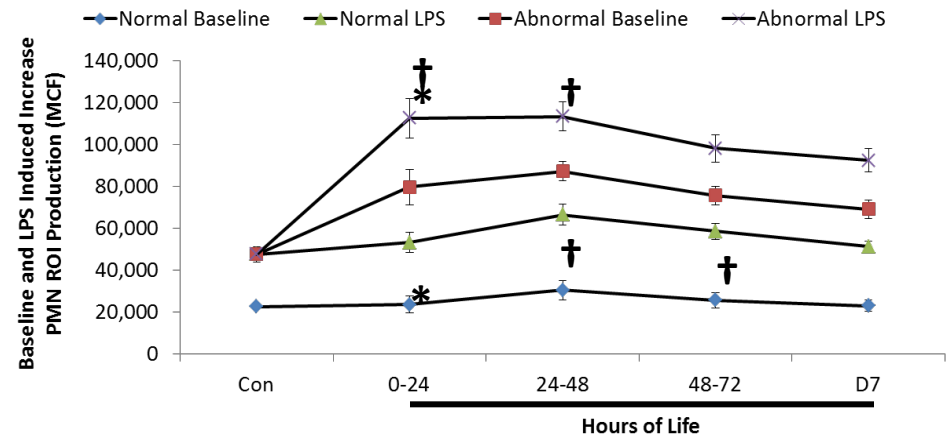


Dammann O & Leviton A, Ped Res 2014

# Persistent inflammation & NE

- Persistent inflammation in NE & Preterm infants correlates with brain injury

- O'Hare FM et al., Ped Res 2015 & J Mat Fet Med 2015
- Molloy EJ et al., Am J Perintol, 2007



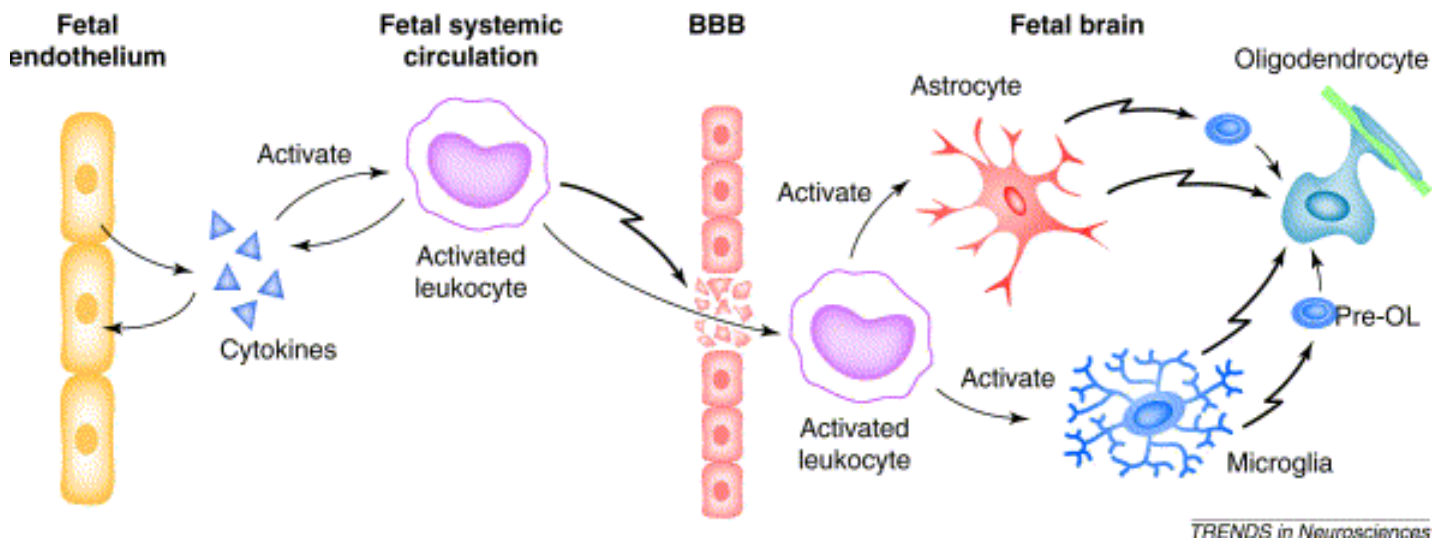


# Persistent inflammation and TBI

- Sustained neuroinflammation after brain or spinal cord trauma
  - described since the 1950s
  - Extensive microglial and astroglial activation
- Chronic traumatic brain inflammation or chronic traumatic inflammatory encephalopathy
  - may be among the most important causes of post-traumatic neurodegeneration in terms of prevalence
    - Faden AI et al., 2015
- Post-concussion syndrome itself has a significant neuroinflammatory component.

# Neuroinflammation:

Activated leukocytes may mediate neonatal brain injury

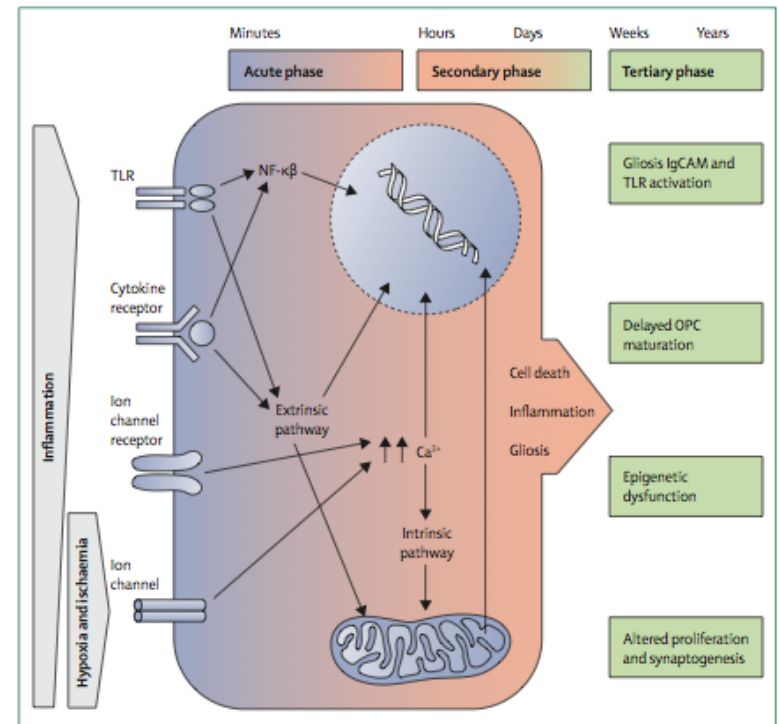


**Dammann O, Durum S, Leviton A. Do white cells matter in white matter damage? Trends Neurosci 2001 Jun;24(6):320-4**

# Persistent Inflammation:

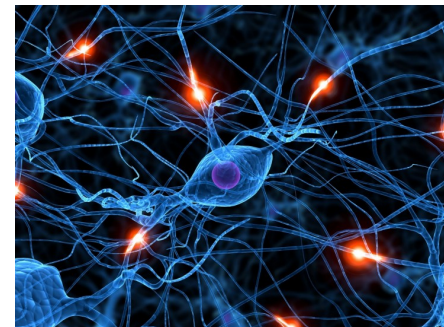
## Altered inflammatory responses persist

- Preterm infants with CP: aged ~5 years
  - Elevated TLR4 mRNA in PBMCs
  - and LPS-induced TNF $\alpha$  levels
    - Lin CY et al., 2010, Ann Neurol
- Tertiary brain injury
  - Fleiss & Gressens, 2012
  - Lancet Neurol



# Tertiary brain injury

- Consider Post-hypothermia intervention in NE which may be required into childhood
- Inflammation during fetal and neonatal life: implications for neurologic and neuropsychiatric disease in children and adults.
  - Hagberg H et al., 2012
  - Fleiss & Gressens, 2012



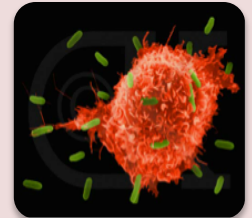
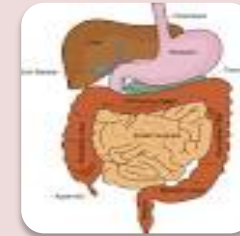
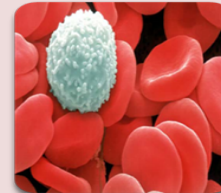
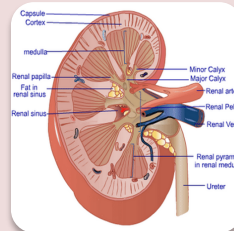
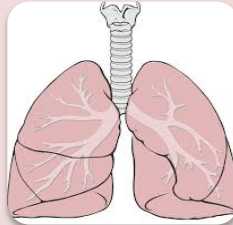
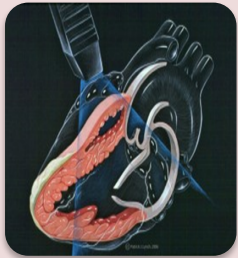
# Perinatal inflammation correlates with adiposity in children

6-month Sum of Skinfolts		B	SE B	p
IL-6 Early Pregnancy		0.111	0.056	0.052
RCT Group		-1.233	1.476	0.407
Weeks of Age		-0.134	0.068	0.052
Birth Weight		0.002	0.002	0.152
Maternal Edu Achievement		-0.392	1.477	0.791
<b>6-month Subscapular/ Triceps Ratio</b>				
TNF- $\alpha$ Early Pregnancy		0.023	0.009	0.017
RCT Group		0.029	0.058	0.619
Weeks of Age		0.006	0.003	0.017
Birth Weight		0.000	0.000	0.991
Maternal Edu Achievement		0.059	0.059	0.324

**PERINATAL INFLAMMATION AND CHILDHOOD ADIPOSITY - THE INFLUENCE OF GENDER (ROLO Kids study)** J M Donnelly, J M Walsh, M Horan, EJ Molloy, F M McAuliffe.

# CHaMplON Study: followup

## Childhood Multlorgan Outcomes after Neonatal encephalopathy



### CVS

HR, BP,  
Bloods: Troponin Pro  
BNP  
ECHO

### NEURO

Clinical Exam  
+/-MRI Brain  
Sleep

Dev followup

### RESP

Sleep studies,  
overnight pulse  
oximetry  
Blood gas analysis

### RENAL

Urine output  
Cr, Ur, U&E  
Renal biomarkers  
e.g. NGAL, cyst

### HAEM

Hb,  
Plt,  
WCC,  
Coag Data

### GI/HEPATIC

GORD Score  
Albumin, LFT  
Nutrition BMI, MUAC

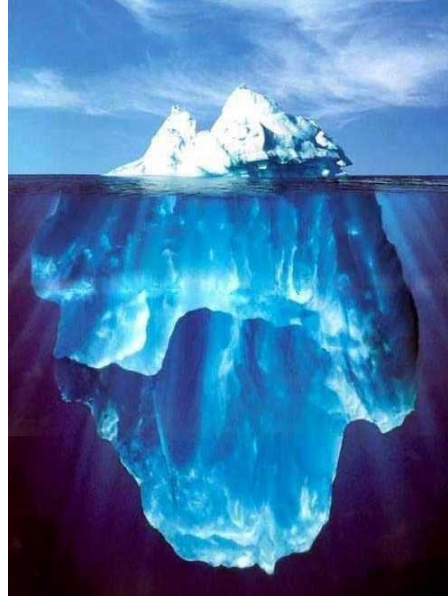
### Inflammation

- Monocyte/PMN fn
- Inflammasome
- HIF1 alpha
- TLR

Drs. Zunera Zareeen, Dee Sweetman & Denise McDonald,  
NMH, Tallaght

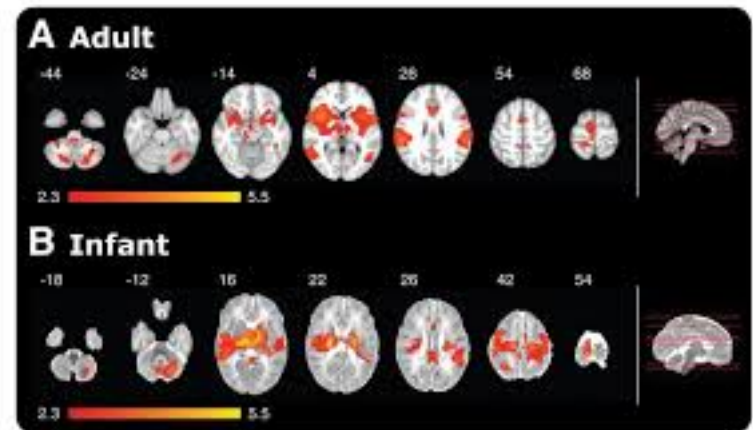
# Biomarkers of Brain Injury

*Using inflammation to predict outcome*



# Use for biomarkers

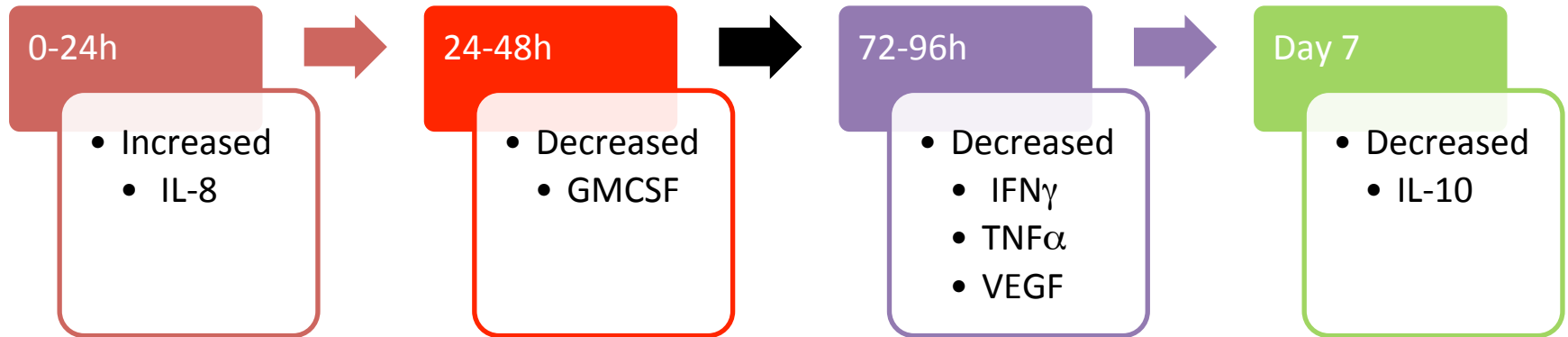
- Early prediction of outcome
- Stratification pre-randomisation for new drug trials and subclinical early response
- Pathogenesis
- Dynamic
- MRI/MRS/EEG
- Blood/CSF/Urine



Goksan et al., 2015

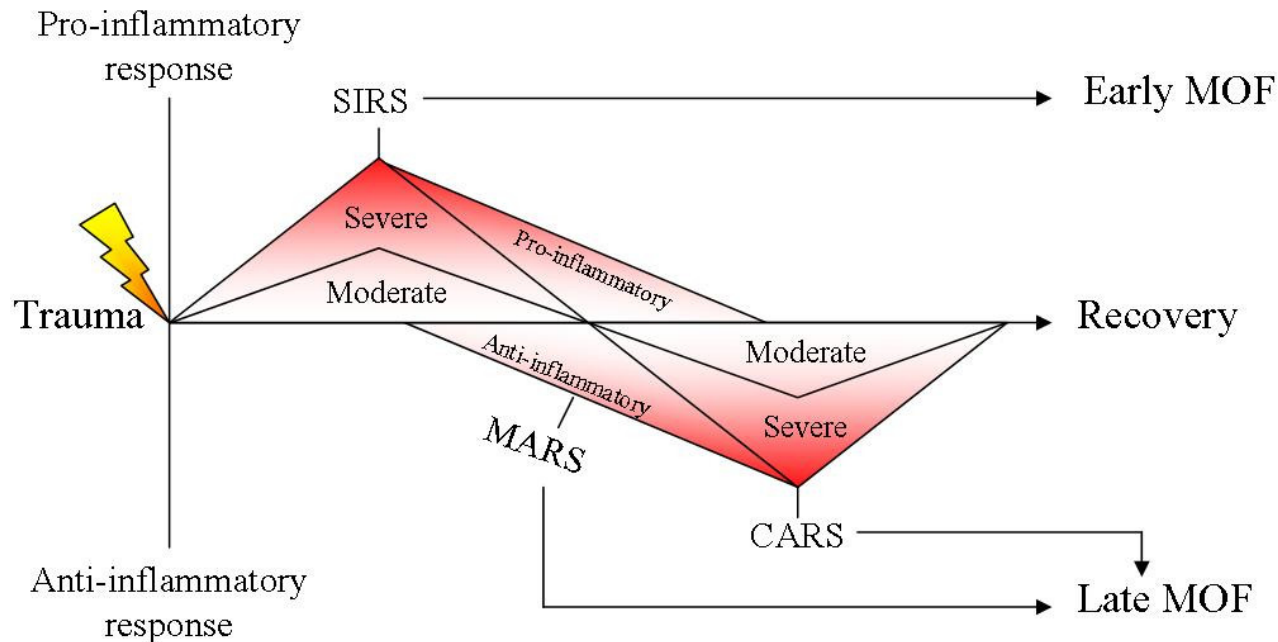


# Cytokine alterations in NE with Abnormal MRI



- **Neurodevelopmental outcome:**
- Systematic review biomarkers of NE and outcome
  - n=110 studies: n=22 >1 year outcome
  - Ramaswamy V et al., 2009
- Best correlation with poor neurodevelopmental outcome in survivors:
  - Serum IL-1 $\beta$  (p=0.04, n=3), serum IL-6 (p=0.04, n=2)
  - CSF NSE (p=0.03, n=3), and CSF IL-1 $\beta$  (p=0.003, n=2)

# Pro- & Anti-inflammatory responses



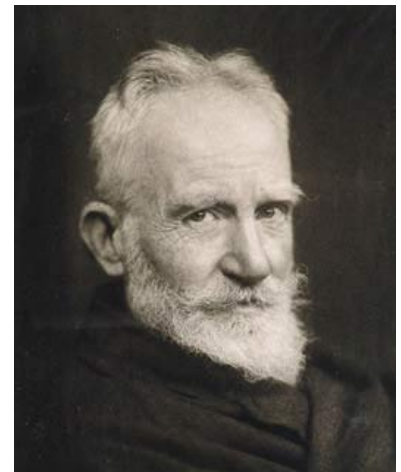
Moore et al.,

+/- Infection/insults

Immunomodulation

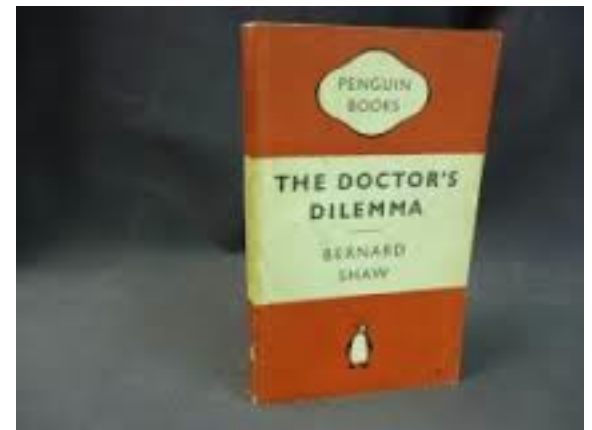
# Systemic Pro & Anti-inflammatory responses

- “Well, the patient manufactures the butter for himself all right; but my discovery is that the manufacture of that butter, which I call opsonin, goes on in the system by ups and downs, Nature being always rhythmical you know, and what the inoculation does is to stimulate the ups or downs as the case may be”.
- The Doctors Dilemma

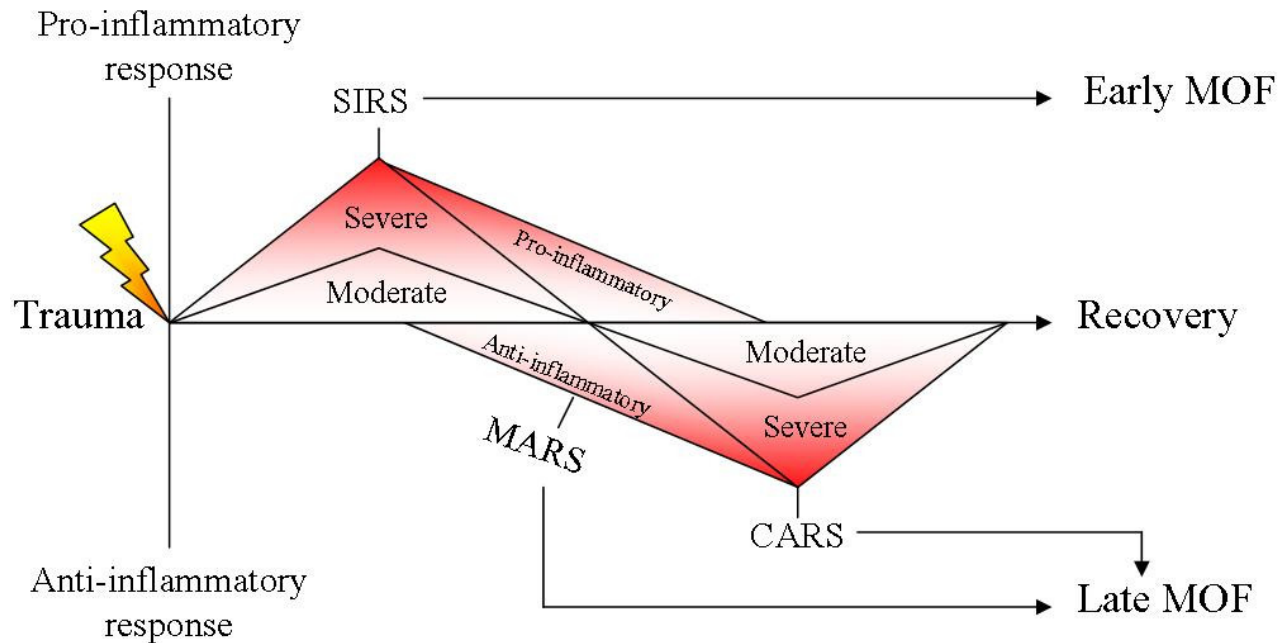


# Immunosuppression

- “... Inoculate when the patient is in the negative phase and you kill; inoculate when the patient is in the positive phase and you cure.”



# Pro- & Anti-inflammatory responses



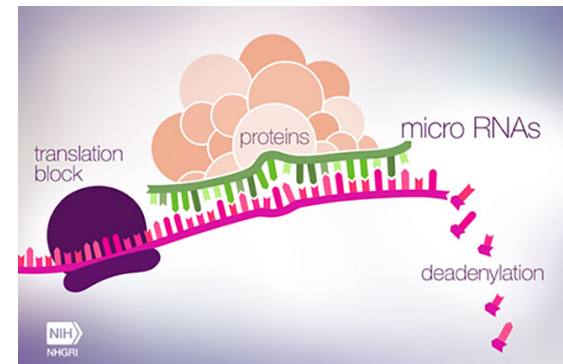
Moore et al.,

+/- Infection/insult

Immunomodulation

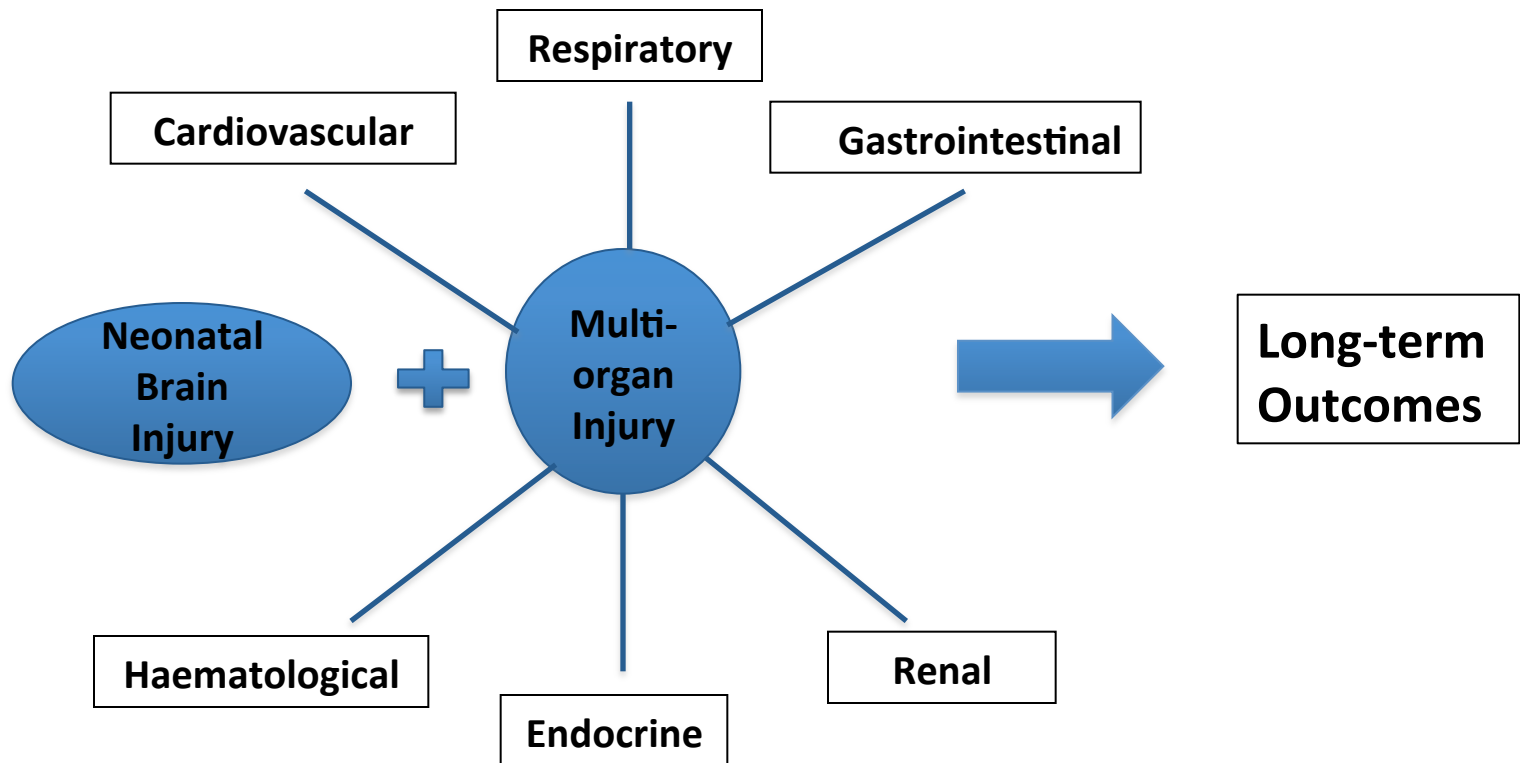
# Novel Biomarkers

- microRNAs (miRNAs)
  - small, noncoding genetic material that regulates gene expression
  - Dr. Eva Jiminez-Mateos, RCSI
  - n=818 miRNA: 15 significantly assoc with seizures in NE
  - miR-16, miR-19b, miR92 and miR451
  - Prof Boylan/Murray: UCC
- Metabolomics
  - Reinke SN et al., 2013
    - Succinate and perinatal asphyxia and NE





# NOT JUST BRAIN INJURY!



# Multiorgan Biomarkers

- Multiorgan biomarkers
  - Aslam S et al., 2015
  - CVS:
    - Sweetman D et al., 2012; Armstrong K et al., 2012
  - Renal:
    - Sweetman D et al., 2013, Acta Paediatrica & Eur J Paed
- Placental biomarkers
  - Hayes B et al., 2013



# Possible treatments: Immunomodulation as an adjunctive therapy in Paediatric brain injury



# Therapeutic Hypothermia

- Standard therapy
- Therapeutic creep: now NE I
- Alters systemic inflammation
- Persistent inflammatory response despite hypothermia
- Some babies still cannot be rescued



Icehotel Sweden