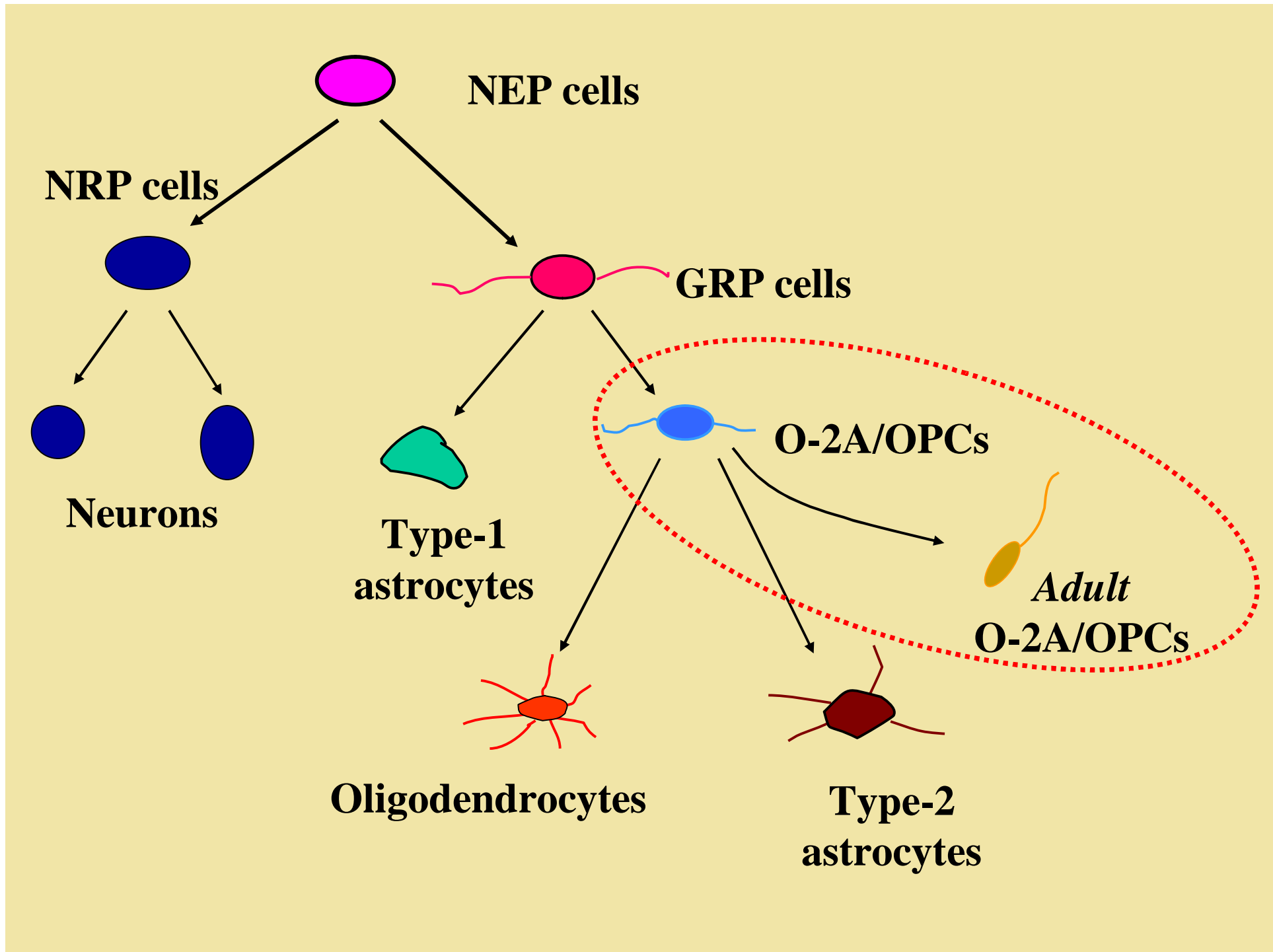


***Redox Modulation of
Cellular Function:
Cellular and
Mechanistic Analyses***

Mark Noble

University of Rochester
Medical Center

M. Chemiakin



Myelination disorders: the largest category of neurological disorder

- thyroid hormone deficiency, iron deficiency, selenium deficiency, nutritional deficiency
 - fetal alcohol syndrome, fetal cocaine syndrome
- traumatic injury, multiple sclerosis
 - stroke (lacunar infarcts)
- leukomalacia in pre-term infants

PML - leukoencephalopathy in AIDS patients

Developmental maladies are diseases of precursor cells

- generation of specific precursor cell populations
- generation of differentiated cell types
- generation of sufficient numbers of cells

E10.5

NEP

E13.5

GRP

TH, Fe

E18

O-2A

TH, Fe

p1



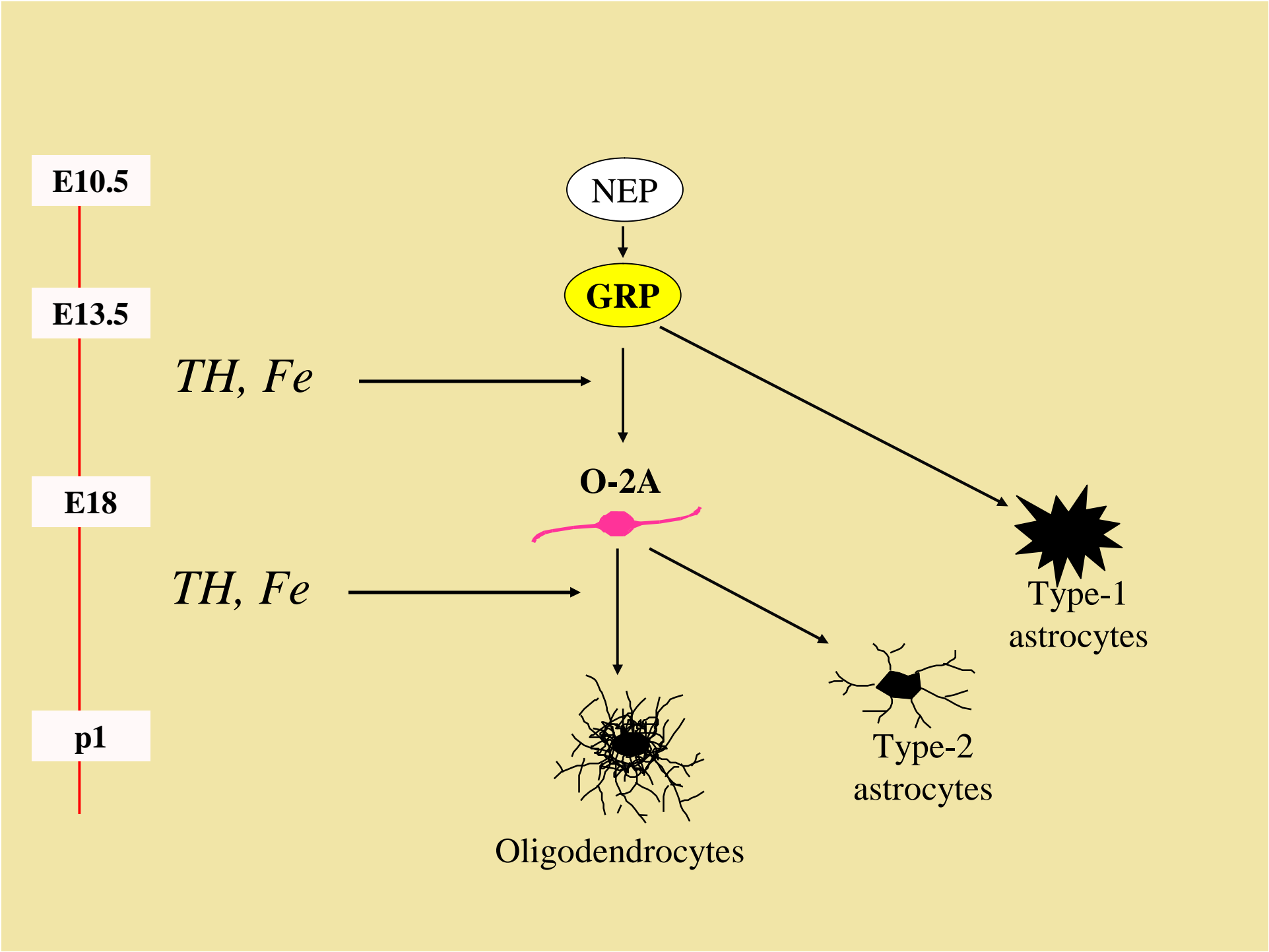
Oligodendrocytes



Type-2
astrocytes



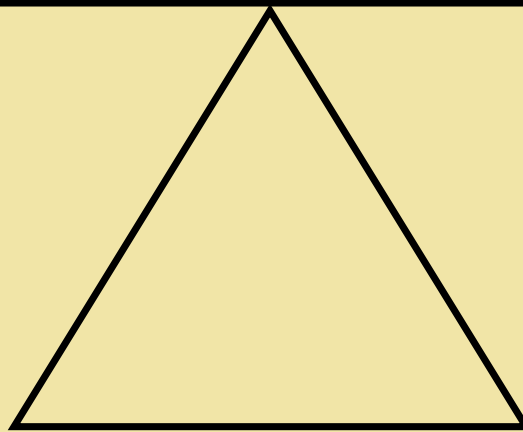
Type-1
astrocytes



**How do you control
precursor cell fate?**

Self-renewal

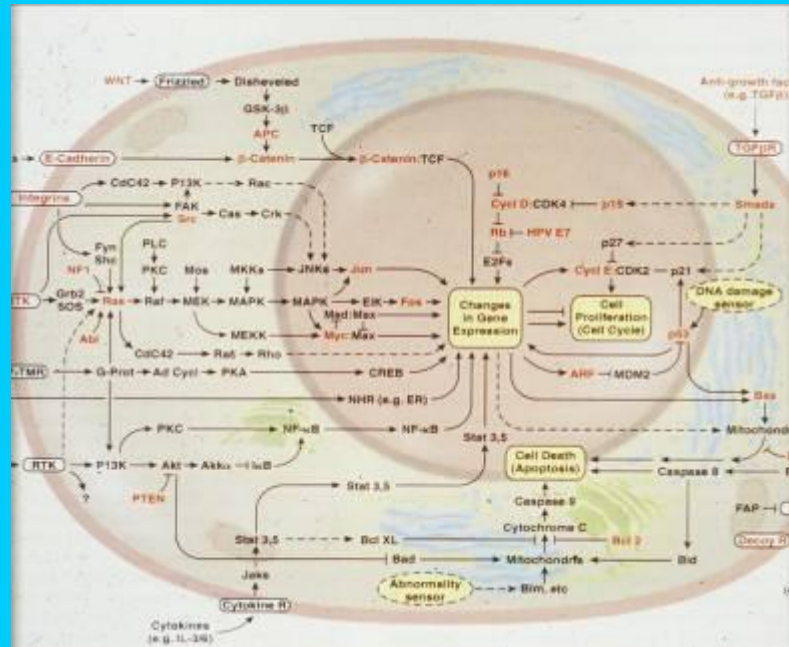
differentiation



Multiple signaling molecules modulate the balance between self-renewal and differentiation as in the O-2A lineage

- PDGF is sufficient to promote division and allow oligodendrocyte generation
 - NT-3 and FGF enhance self-renewal
 - Thyroid hormone and CNTF promote oligodendrocyte generation
 - BMP-4 promotes differentiation into type-2 astrocytes

Physiology



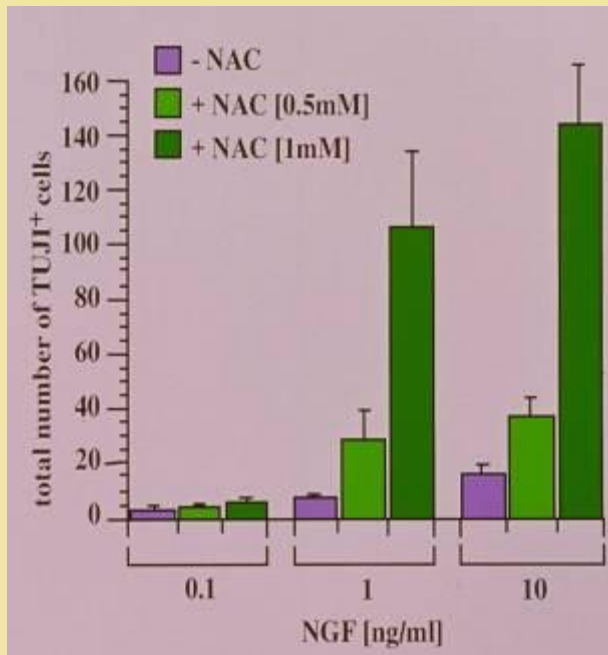
What is redox state?

The balance between reducing and oxidizing equivalents.

Electron transfer = bioenergetics

Not all oxidation is oxidative stress

Cellular redox state modulates responsiveness to environmental signals



Being more reduced protects against cell death from cytotoxic agents and also enhances the response to cell survival signals

Critical point: The extent of redox change required to have large functional consequences is only ~15%.

Redox and cell function: Some general principles

1. Redox state controls precursor cell function.
2. Classical signaling molecules that enhance self-renewal or induce differentiation alter redox state as a necessary component of their mechanism.
3. The organism uses developmental (genetic) regulation of redox state to control precursor cell function.



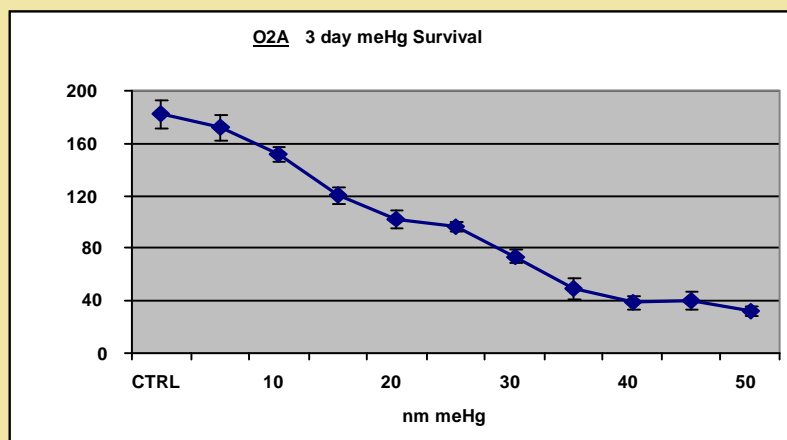
Reduced



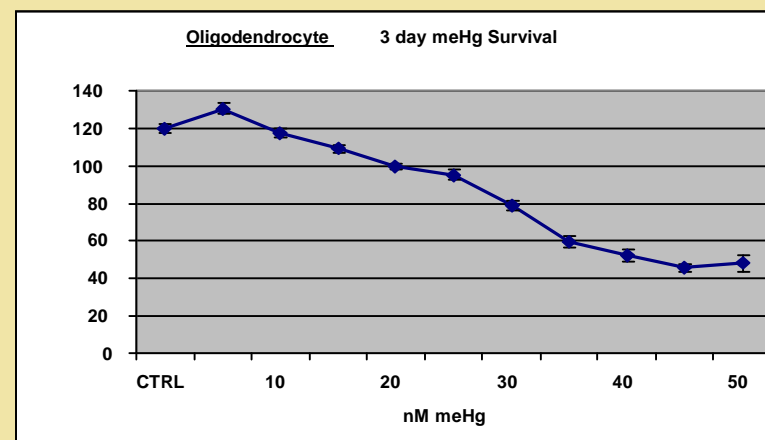
Oxidized

Many environmental toxicants
are potent pro-oxidants

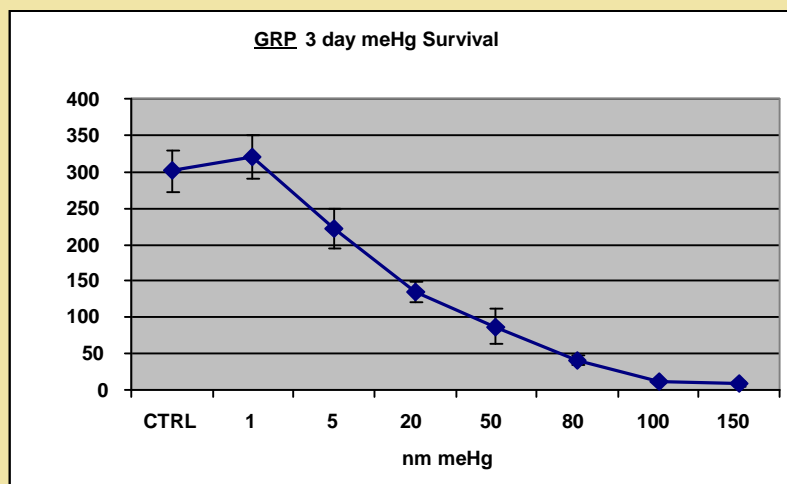
MeHg toxicity for precursor cells and oligodendrocytes is an order of magnitude lower than reported in the literature for other cells.



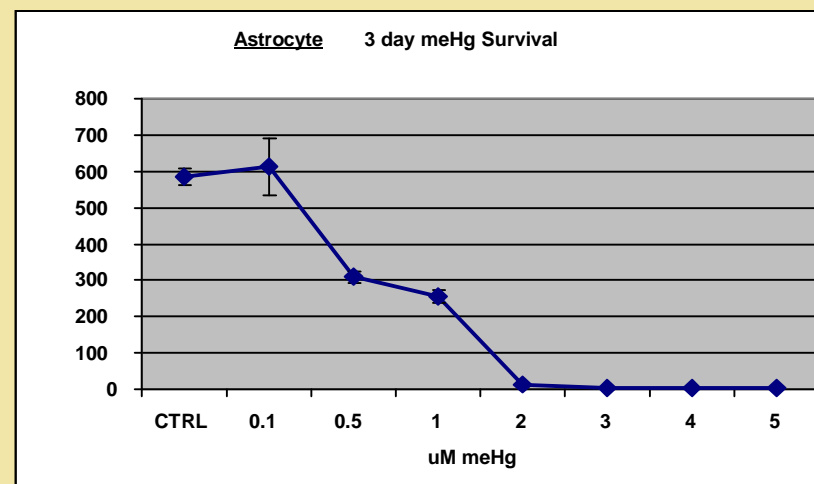
LD50 = 25nM



LD50= 45nM



LD50= 20nM



LD50=500nM

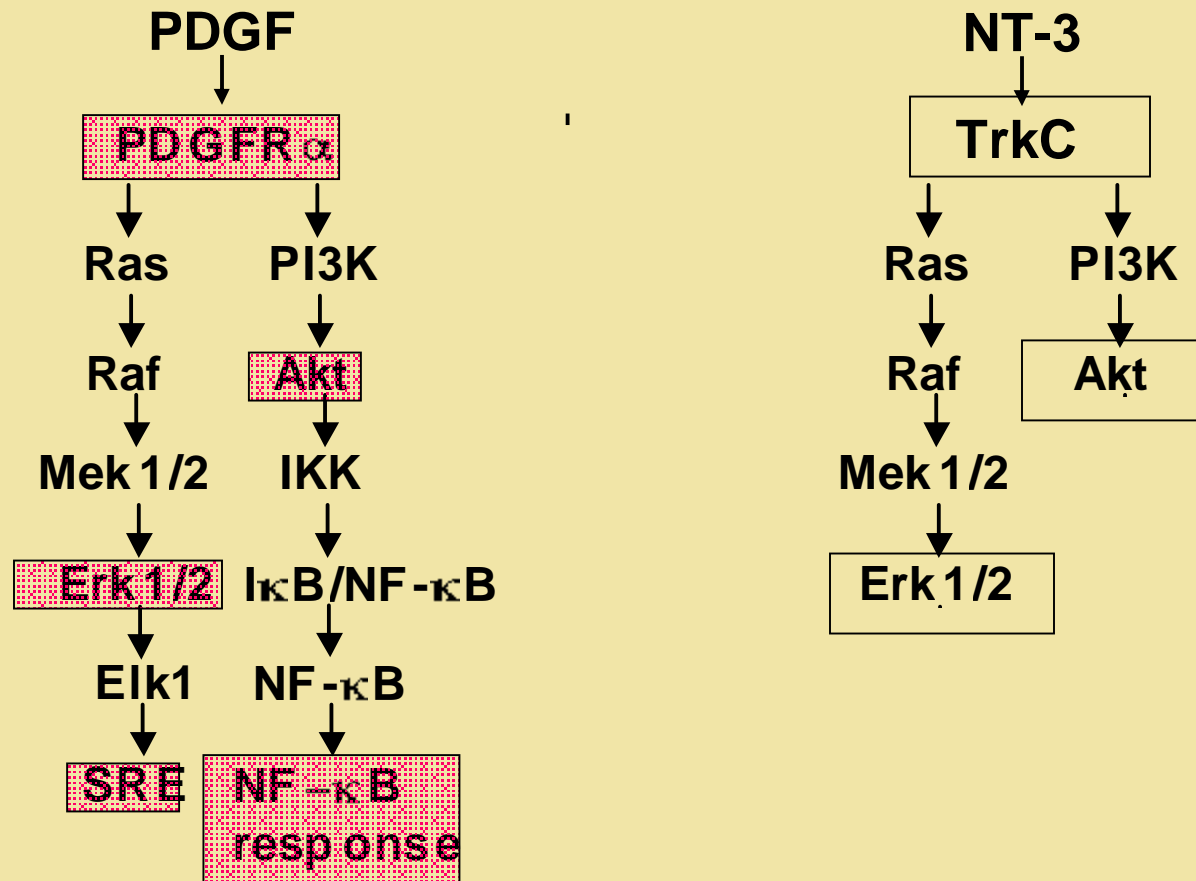
MTT+ Survival Curves

Environmentally relevant levels of toxicants (organic mercurials, lead, et al.) make cells more oxidized in precisely the range that alters the response to the environmental signals.

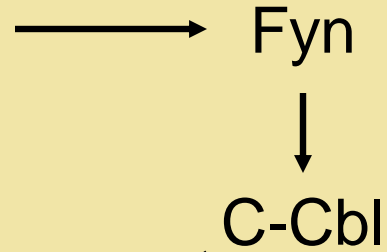
As a consequence:

- **Cell division is suppressed**
- **Cells are made more vulnerable to inducers of cell death**

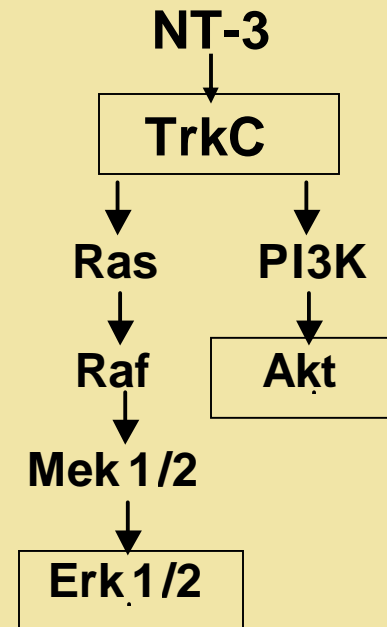
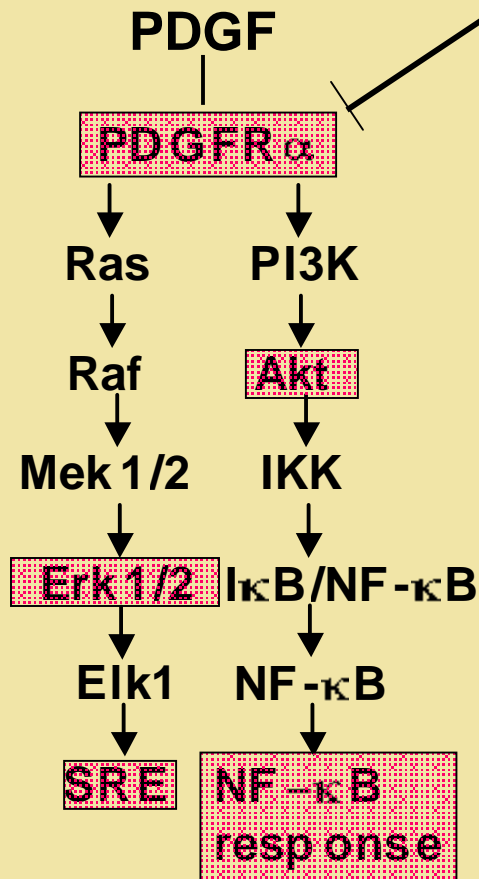
Toxicant-mediated suppression of critical cell signaling functions are pathway specific - *but are not toxicant-specific*



Small increases in oxidative status
(oxidized glutathione?)

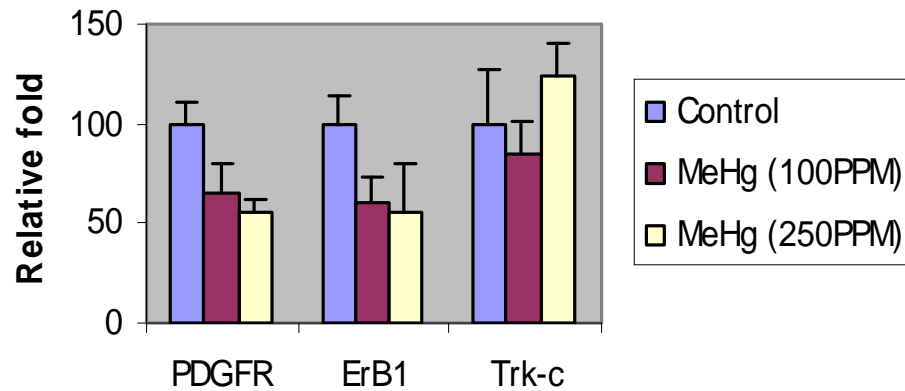


EGFR
c-Met

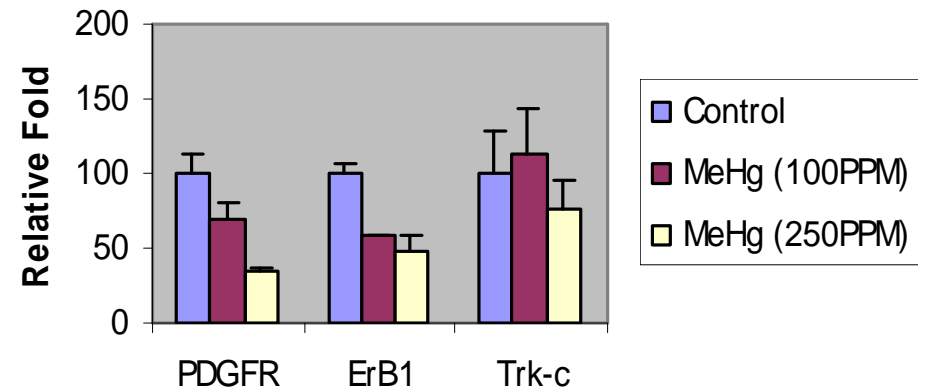


Low-level MeHg exposure reduces RTK levels in vivo in a pathway-specific *and* region-specific manner

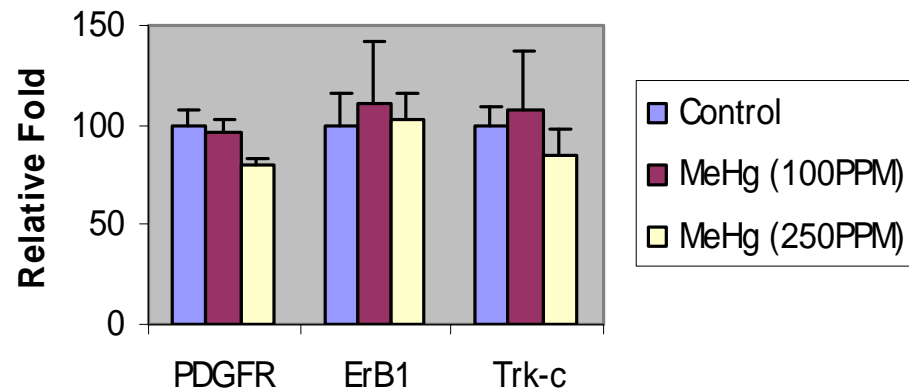
Cerebellum



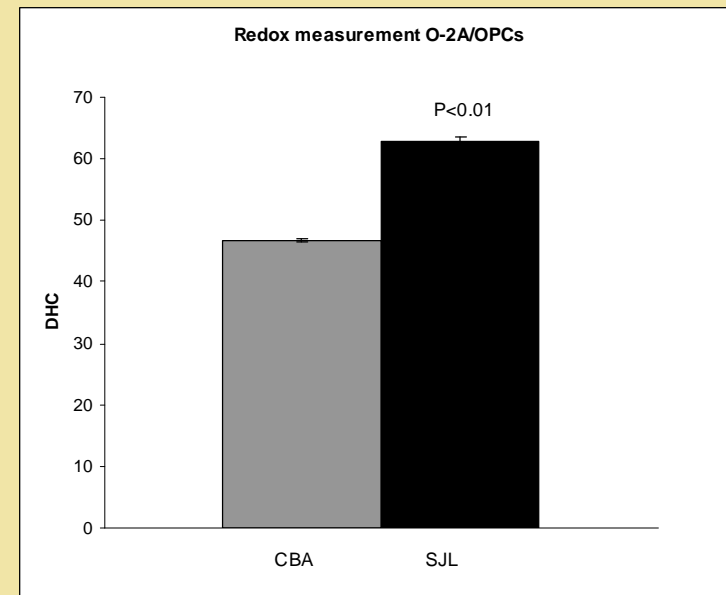
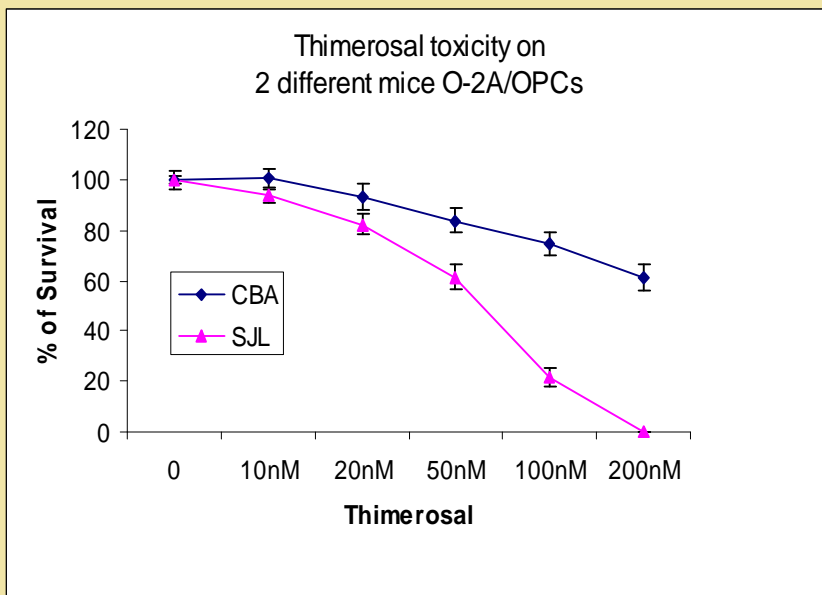
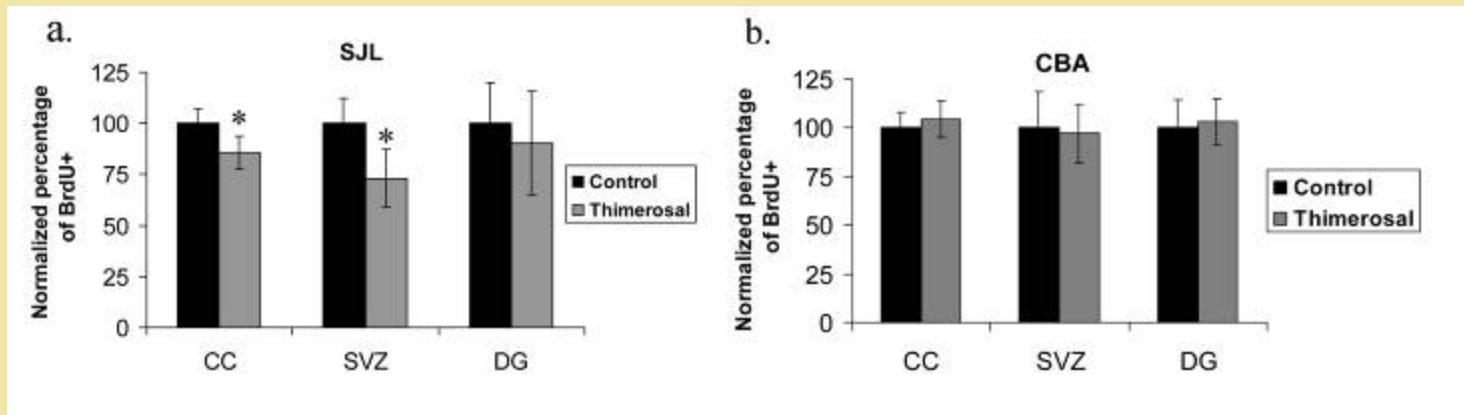
Hippocampus



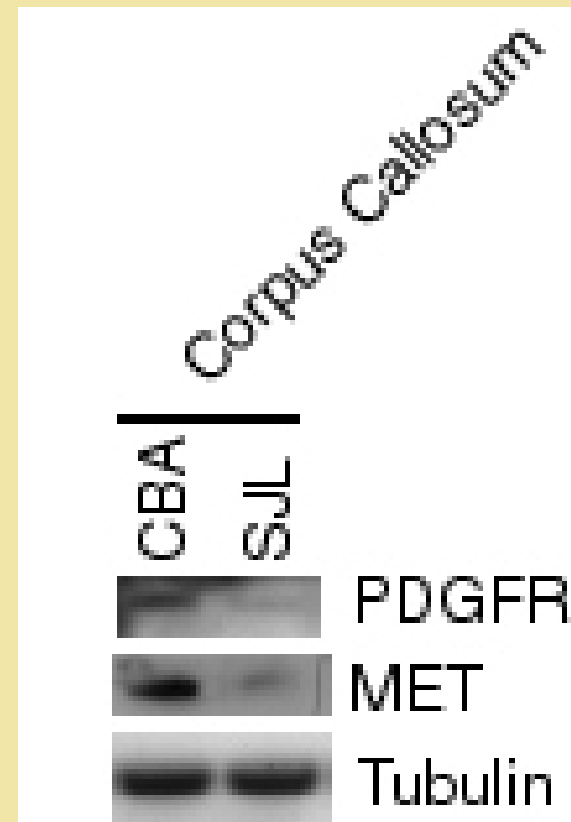
Cortex



Strain-specific vulnerability to toxicants may be redox-dependent

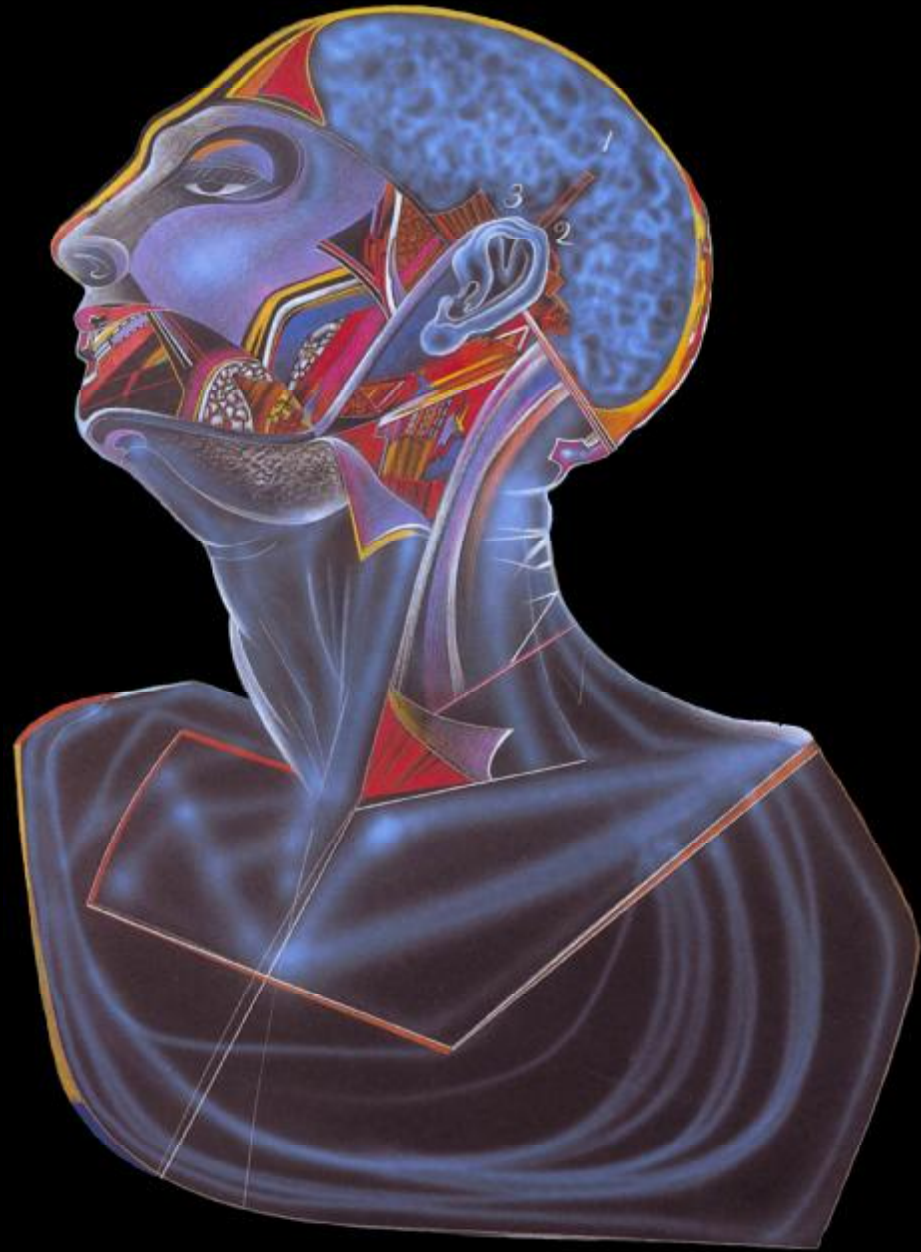


The CNS of SJL mice has lower levels of c-Cbl targeted RTKs than do CBA mice



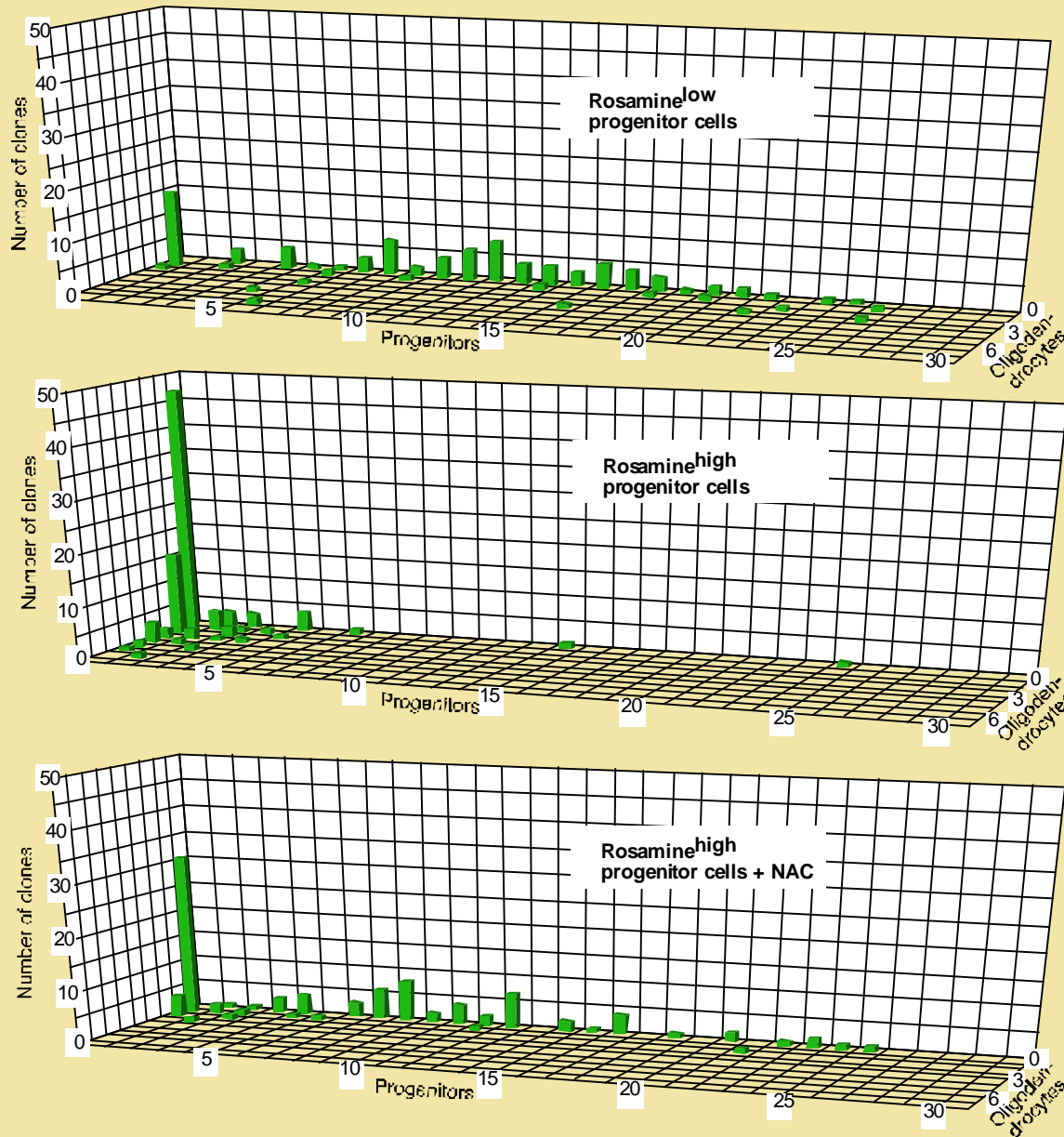
Some thoughts for consideration

- Reconciling the diverse data sets
- The importance of altered redox status
- The cerebellum as a target
- C-Met as a target of the redox/Fyn/c-Cbl pathway
- Effects of environmental toxicants on the developing CNS
- Organic mercurials vs. other toxicants or physiological stressors
- The relationship between susceptibility and outcome of exposure to physiological stressors (i.e., gene-environment interactions)
- Intervention strategies: Prevention, Repair, Re-configuring, Behavioral Adaptation



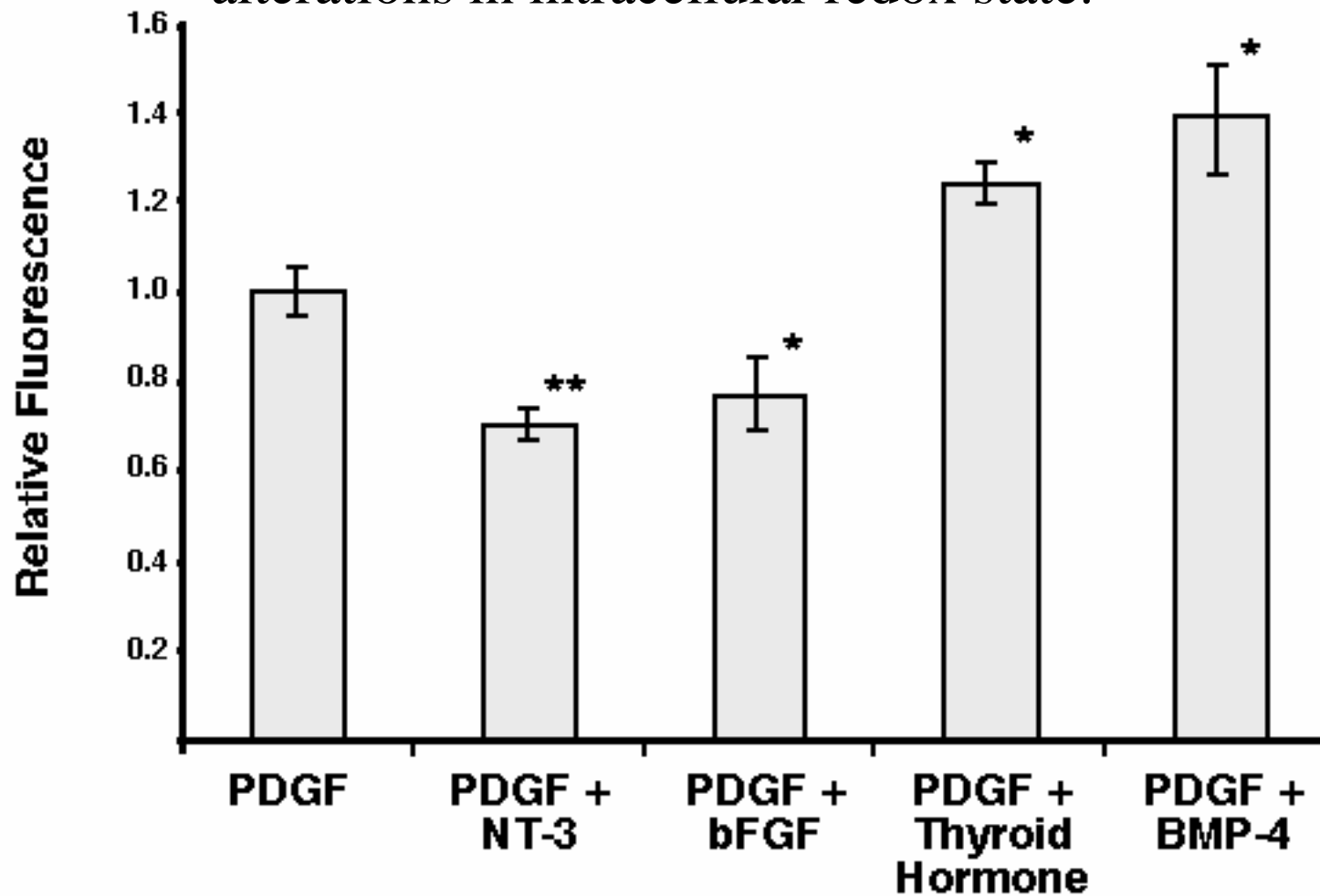
M. Chemiakin

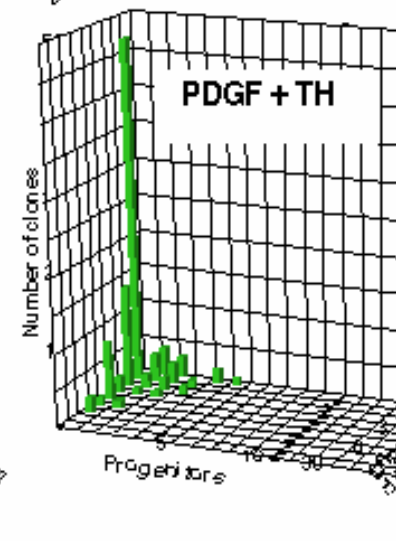
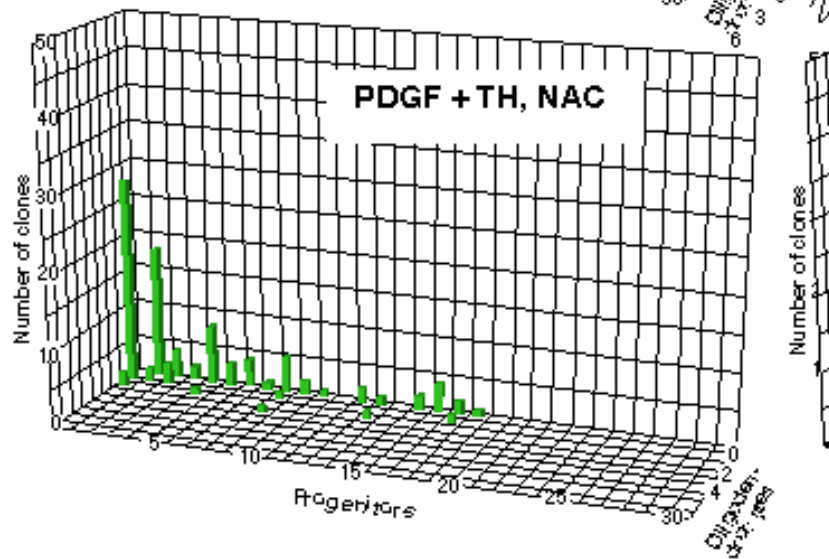
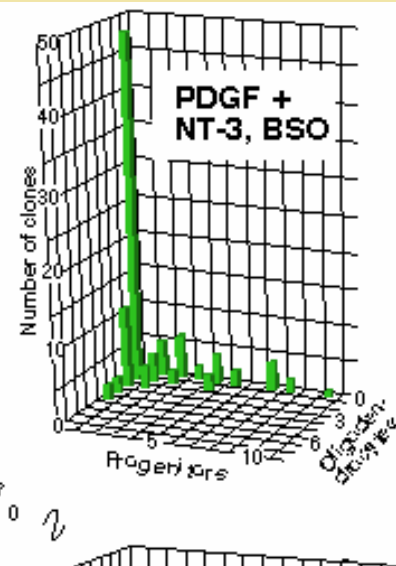
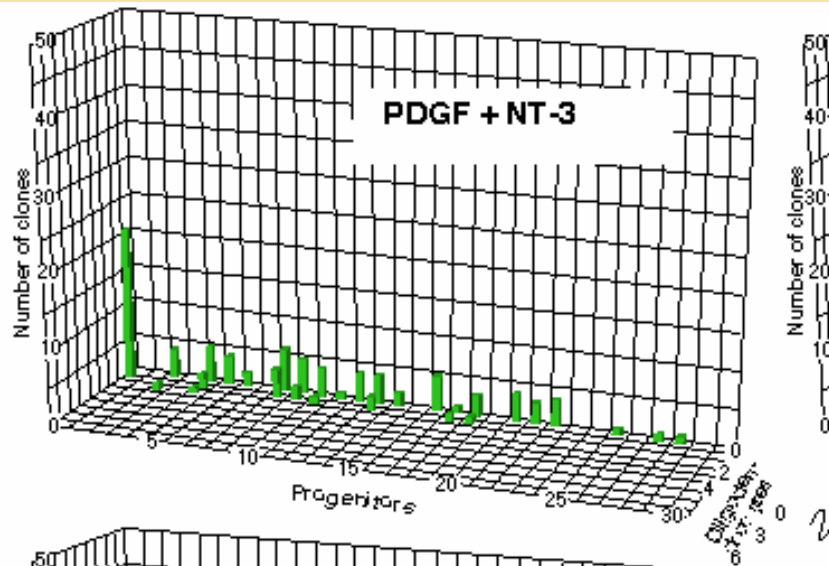
Figure 5



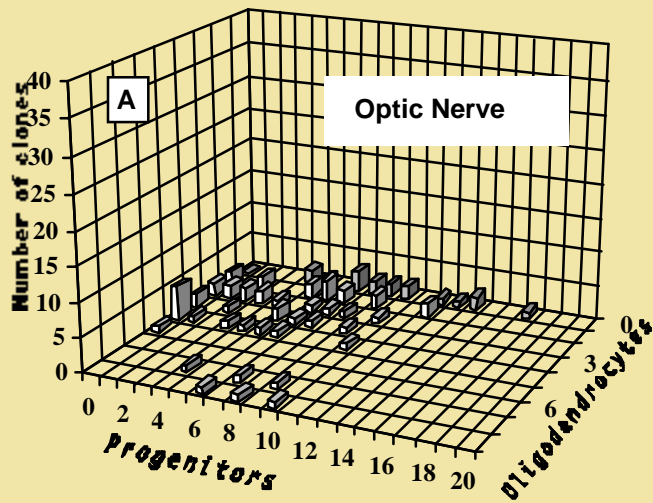
Precursor cells that are more reduced when isolated from the animal undergo more self-renewal in vitro.

Cell-extrinsic signaling molecules cause alterations in intracellular redox state.

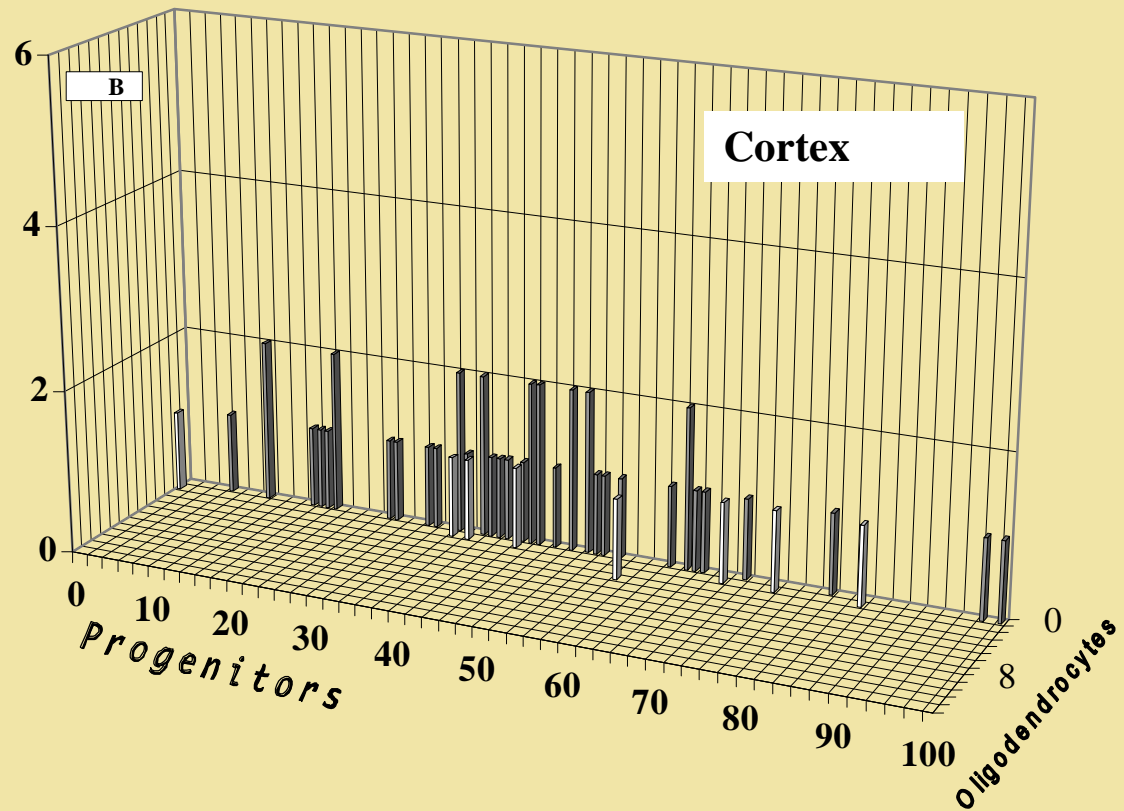


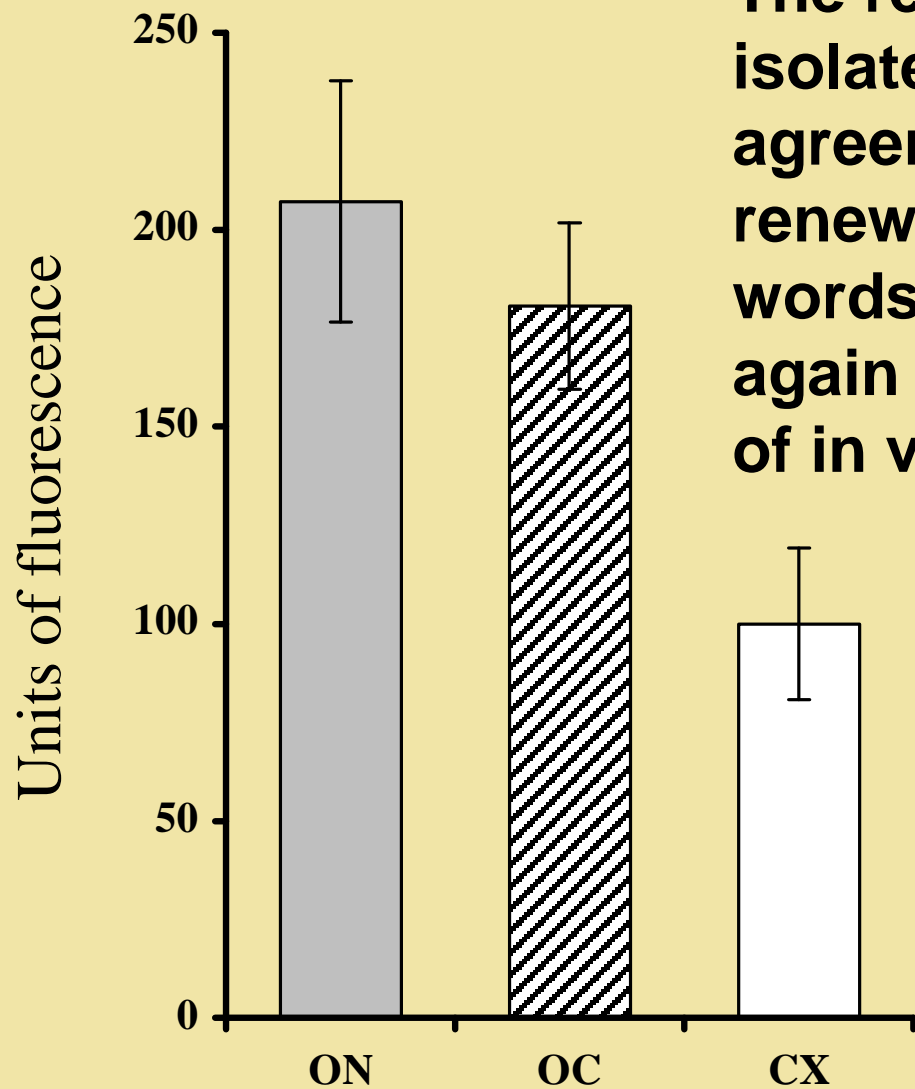


Redox state modulation is a necessary component of the action of signaling molecules that alter the balance between self-renewal and differentiation

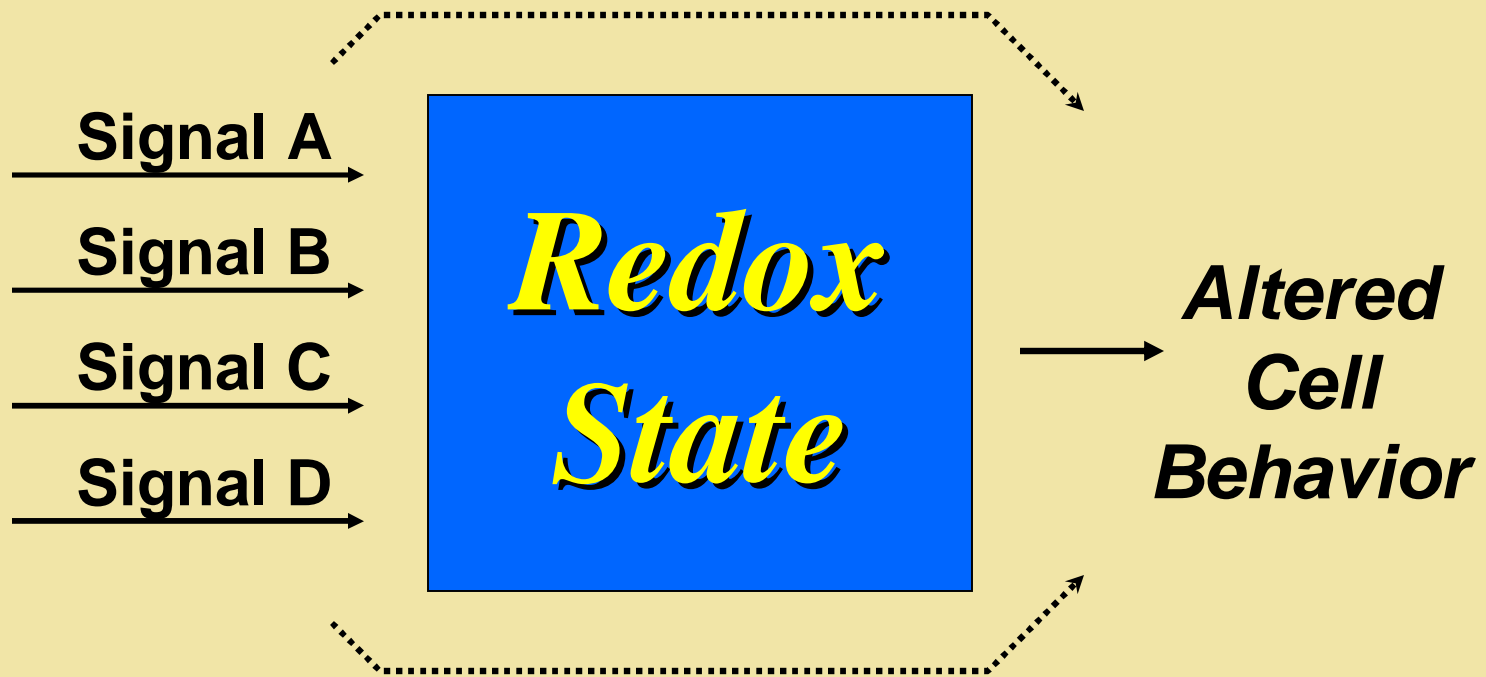


Cortical O-2A/OPCs undergo more self-renewal and generate fewer oligodendrocytes than do optic nerve-derived O-2A/OPCs





The redox state of freshly isolated O-2A/OPCs is in agreement with their self-renewal potential. In other words, redox modulation again appears to be part of in vivo regulation.



Some relevant publications:

[Smith J, Ladi E, Mayer-Proschel M, Noble M.](#) (2000) Redox state is a central modulator of the balance between self-renewal and differentiation in a dividing glial precursor cell. Proc Natl Acad Sci USA 97:10032-10037.

[Noble M, Smith J, Power J, Mayer-Proschel M.](#) (2003) Redox state as a central modulator of precursor cell function. Ann N Y Acad Sci. 991:251-271.

[Dietrich J, Lacagnina M, Gass D, Richfield E, Mayer-Proschel M, Noble M, Torres C, Proschel C.](#) (2005) EIF2B5 mutations compromise GFAP+ astrocyte generation in vanishing white matter leukodystrophy. Nat Med. 11:277-283.

[Davies JE, Huang C, Proschel C, Noble M, Mayer-Proschel M, Davies SJ.](#) (2006) Astrocytes derived from glial-restricted precursors promote spinal cord repair. J Biol. 2006;5(3):7.

[Li Z, Dong T, Proschel C, Noble M.](#) (2007) Chemically diverse toxicants converge on Fyn and c-Cbl to disrupt precursor cell function. PLoS Biol. 5(2):e35