MoDRN: Rational Design and Development of the Next Generation Chemicals

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Yale University

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Fourth Principle of Green Chemistry

Chemical products should be designed to preserve efficacy of function while reducing toxicity.

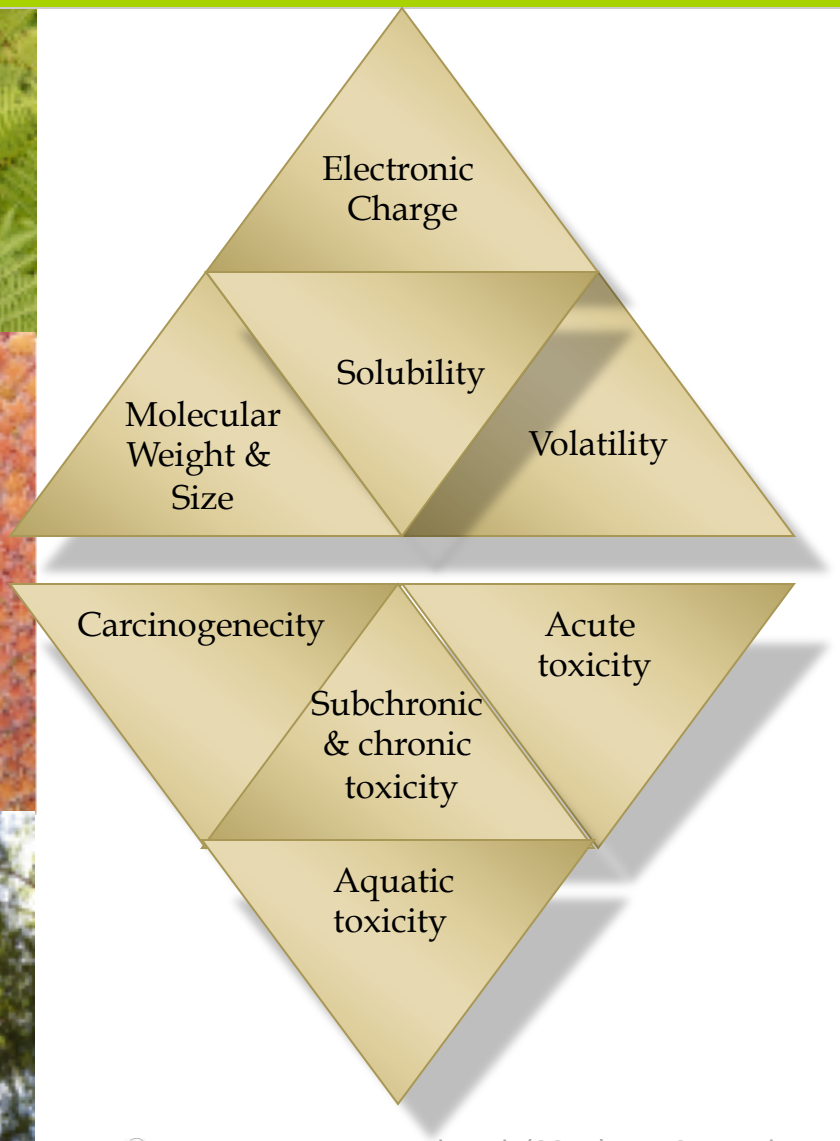
Need for Strategies to Reduce Toxicity

Advancements in toxicology and computational chemistry allow development of *in silico* predictive methods.

QSARs –
Quantitative Structure Activity Relationships
allow toxicity prediction from chemical structures, but have their limitations.

Need for tools to predict toxicity.

Physicochemical Properties and Toxicity



Physicochemical properties can predict toxicity.

Linkages are complex

Seeking guidelines for safer chemicals.

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Kostal et al. (2014) *PNAS*, March 17
Voutchkova-Kostal et al. (2012) *Green Chemistry*, 14:1001-1008
Kostal et al. (2012) *Chemical Research in Toxicology*, 25:2780-2787
Wang & Gallagher (2013) Toxicology & Applied Pharmacology, 266:177-186

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Proof of concept: statistical analysis and partitioning

Statistical comparison of chemicals with known toxicity endpoints designated by EPA's Toxic Release Inventory (TRI) and commercial chemicals.

Physicochemical properties distribution of TRI chemicals is significantly different from commercial chemicals.

Partitioning analysis based on physicochemical properties can differentiate between toxic and non-toxic chemicals.

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Voutchkova, A., Ferris, L., Zimmerman, J., Anastas, P. *Tetrahedron* **2010**, *66*, 1031

Molecular Design Research Network (MoDRN)

Baylor University, George Washington University, University of Washington, Yale

Biology	Computational Chemistry
Engineering	Toxicology

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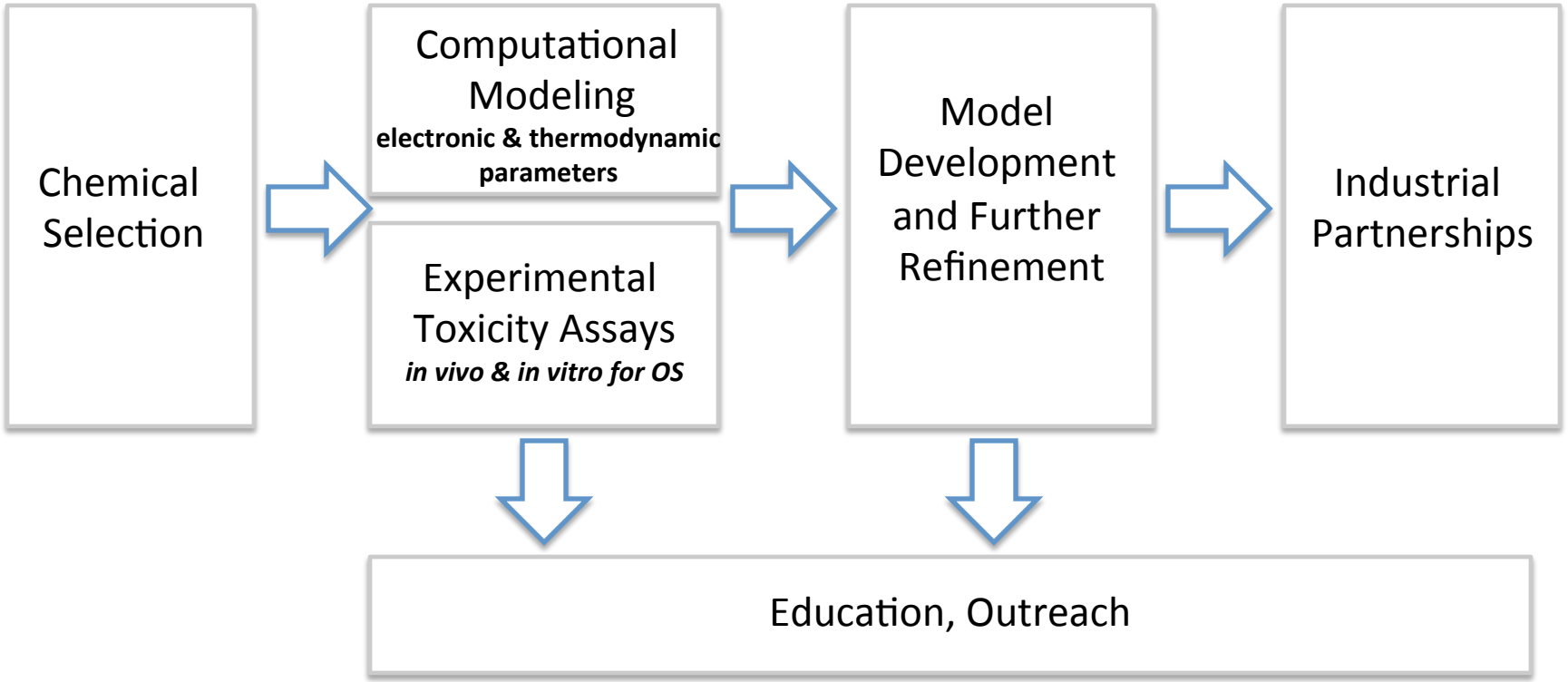
Framework Structure



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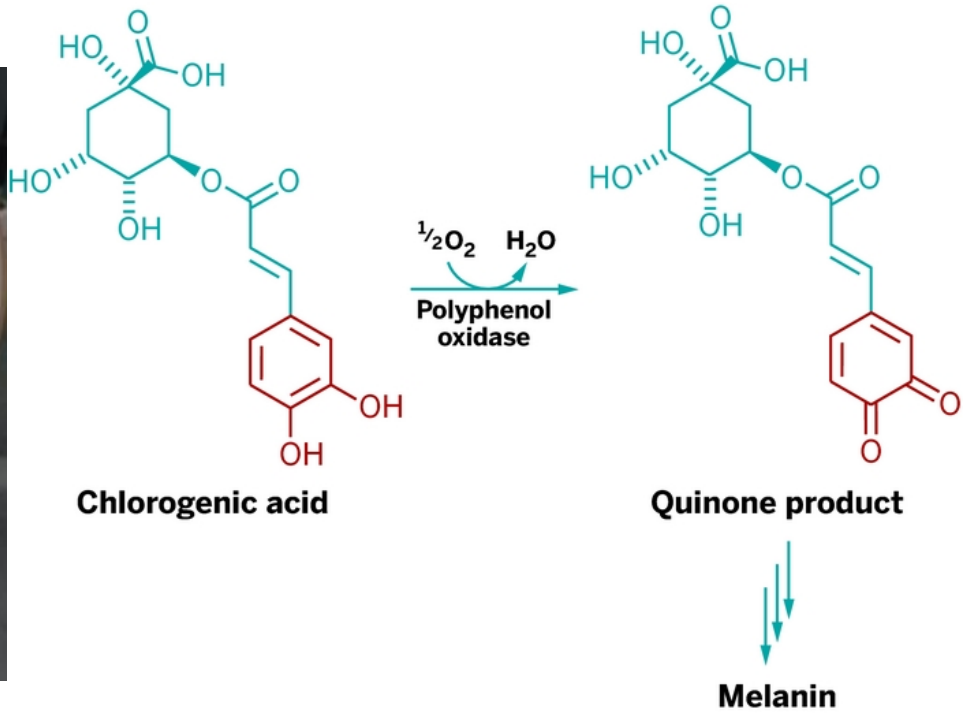
Oxidative Stress : What is it?



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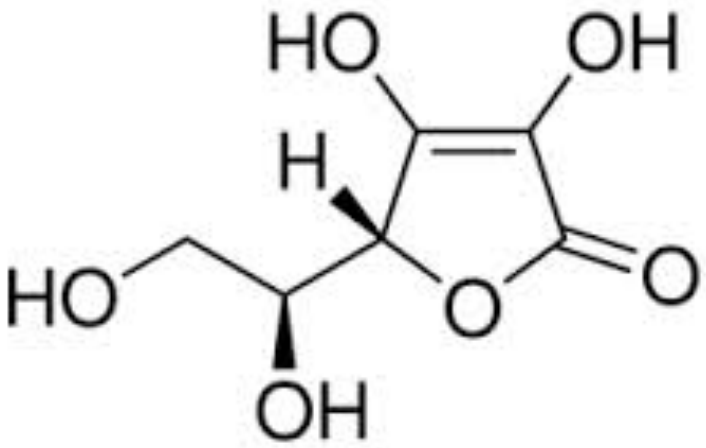
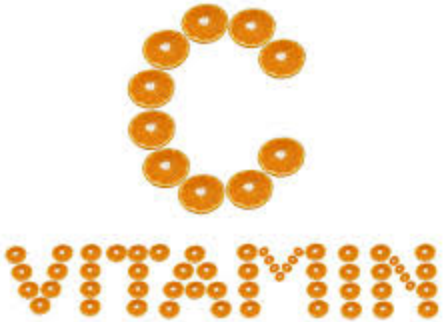
Biosci Biotechnol Biochem. 2011;75(5):829-32.

Oxidative Stress : What is it?





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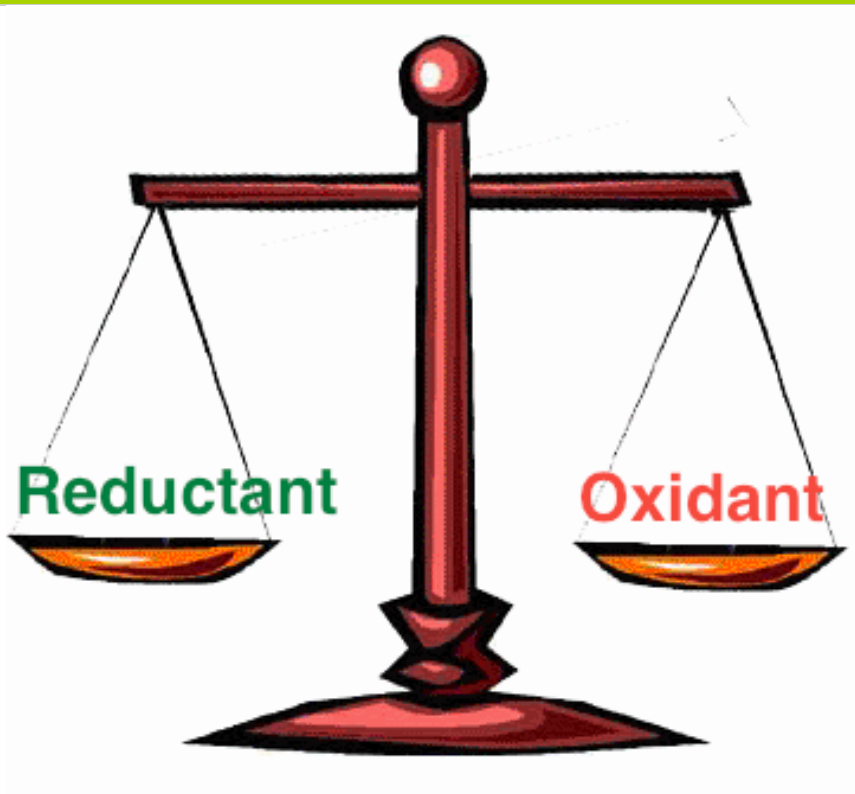

Disruption of the **balance** between prooxidants and antioxidants that leads to potential damage

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http://www.redoxbalance.com/

Oxidative Stress : Why do we care

Oxygen : Life dependent substance

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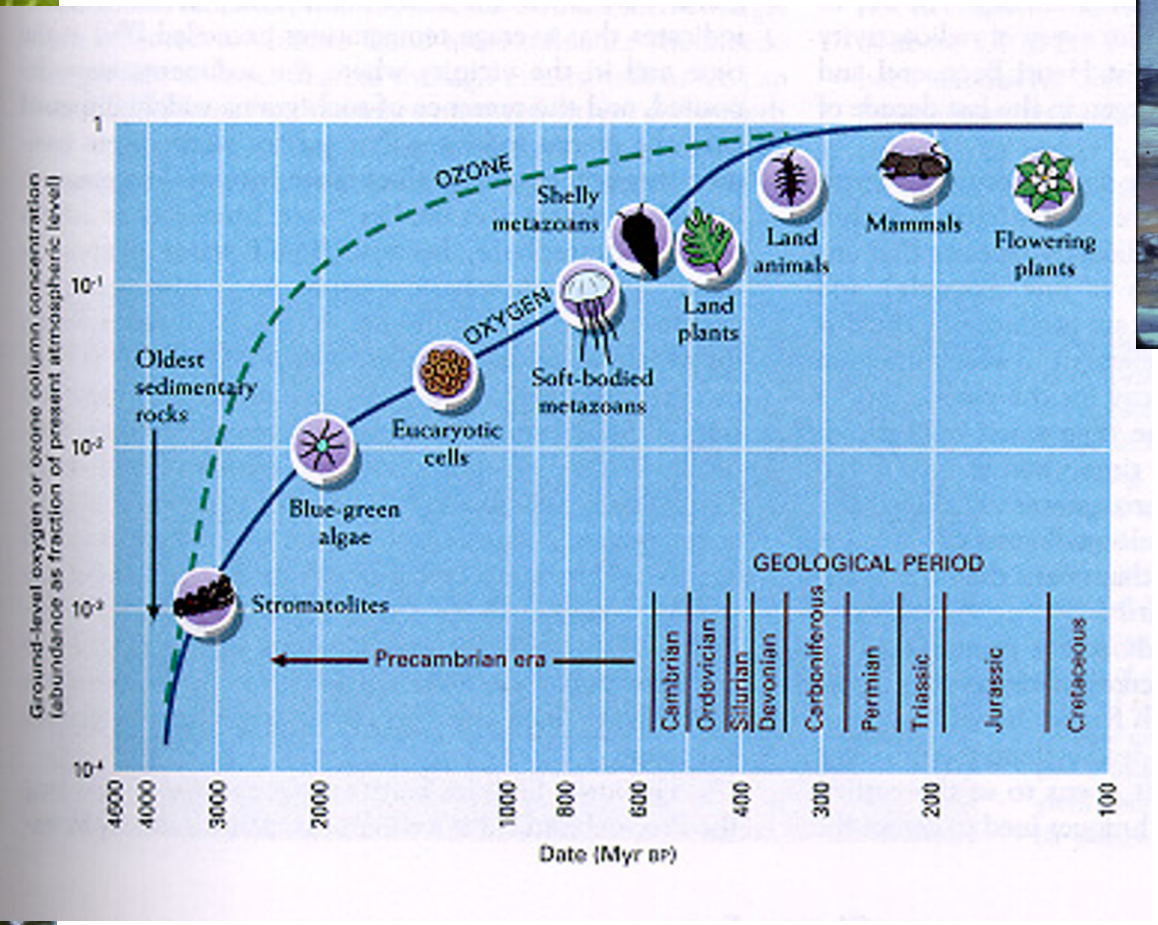
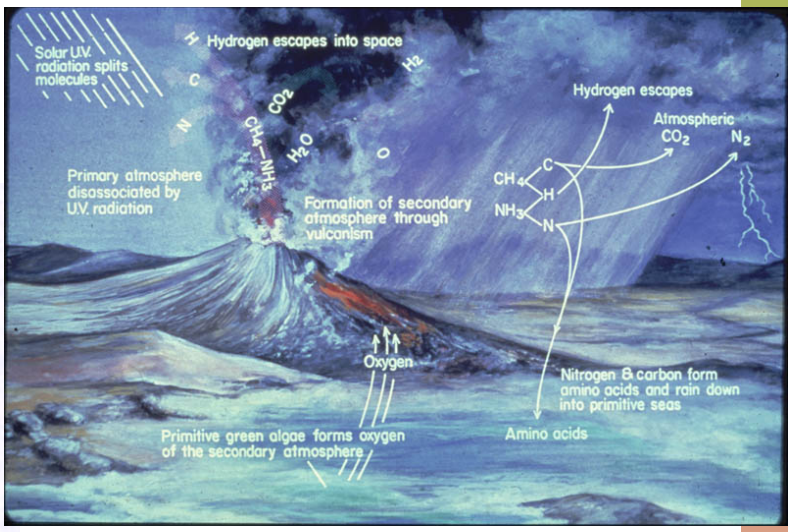
https://industrialoxygengasplant.wordpress.com/

Significance of Oxygen





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http://earth.usc.edu/~stott/Catalina/Earlyatmosphere.html

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Significance of Oxygen

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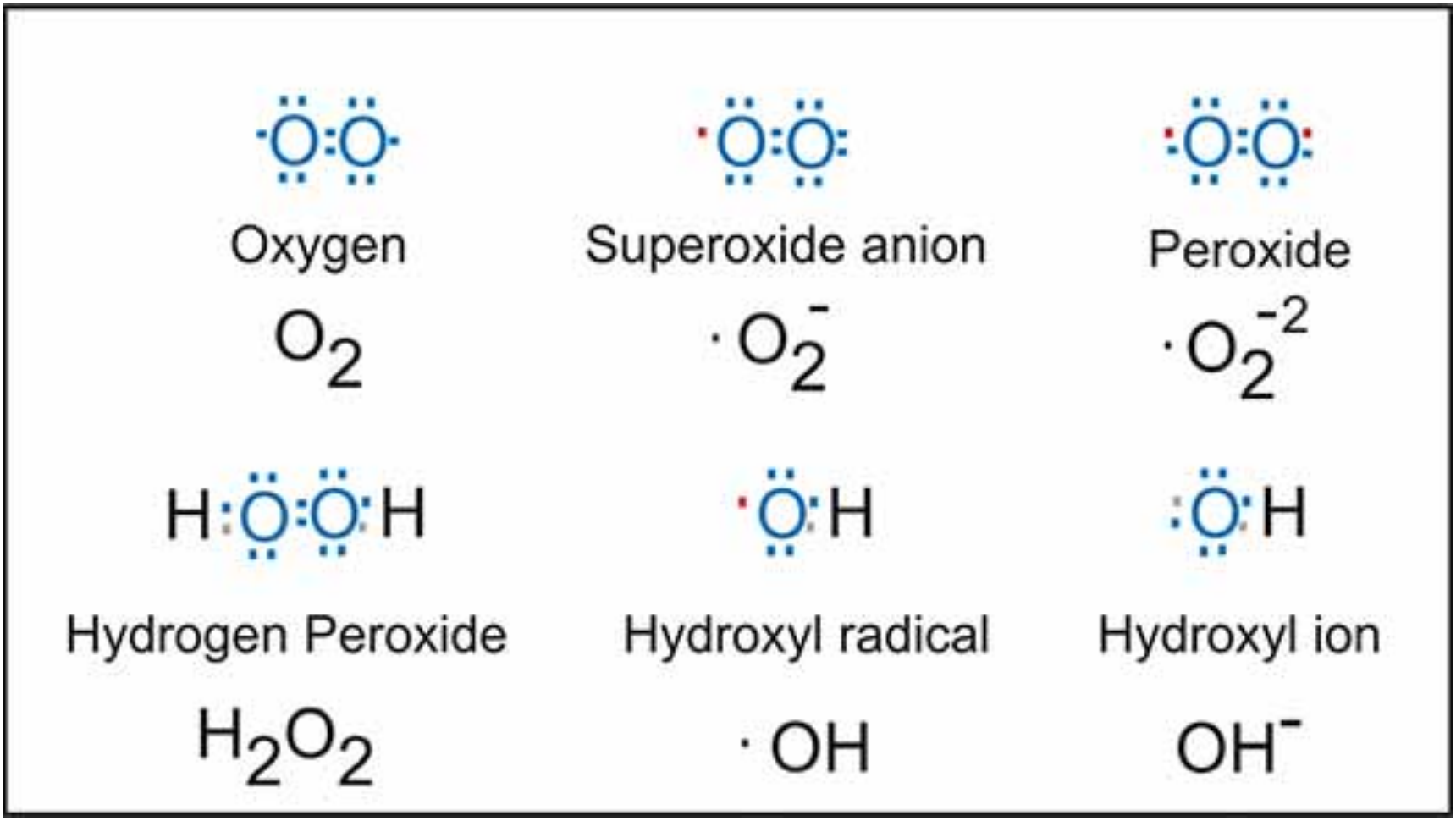
http://www.evoanth.net/2013/11/21/did-neanderthals-and-humans-interbreed/

Reactive Oxygen Species (ROS)



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http://www.biotek.com/resources/articles/reactive-oxygen-species.html

Antioxidant Defense System

Enzymatic System :

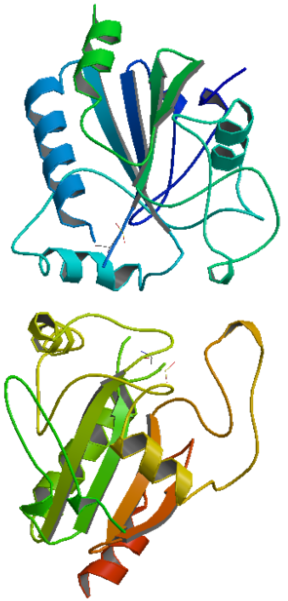
Superoxide Dismutase, Catalases,
Glutathion Peroxidases, Quinone reductases …

Molecular Reductants :

Ascorbate, Vitamin E, Carotenoids …

Genetic System :

Antioxidant Response Element (ARE)
– Mediated Gene Expression



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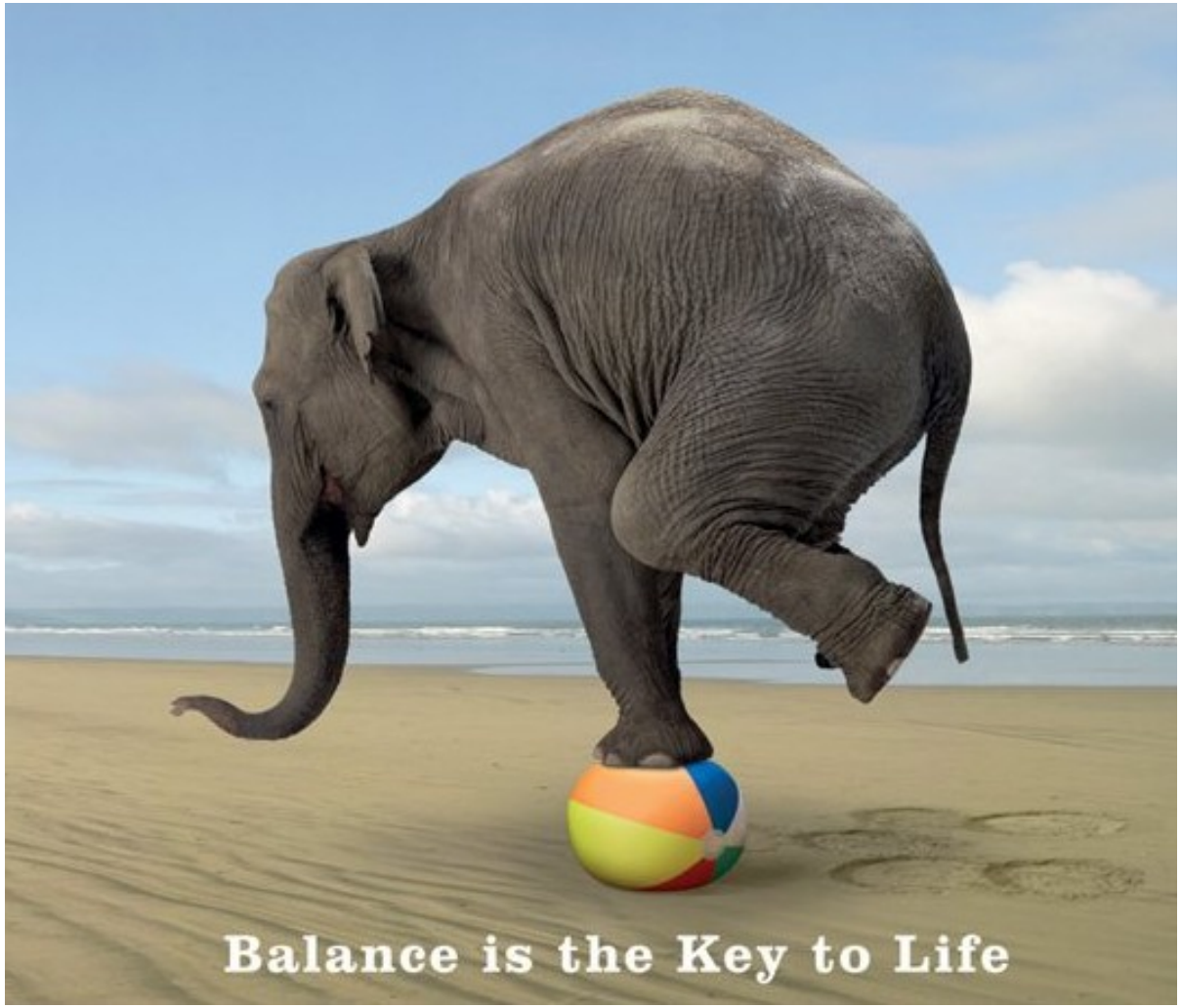
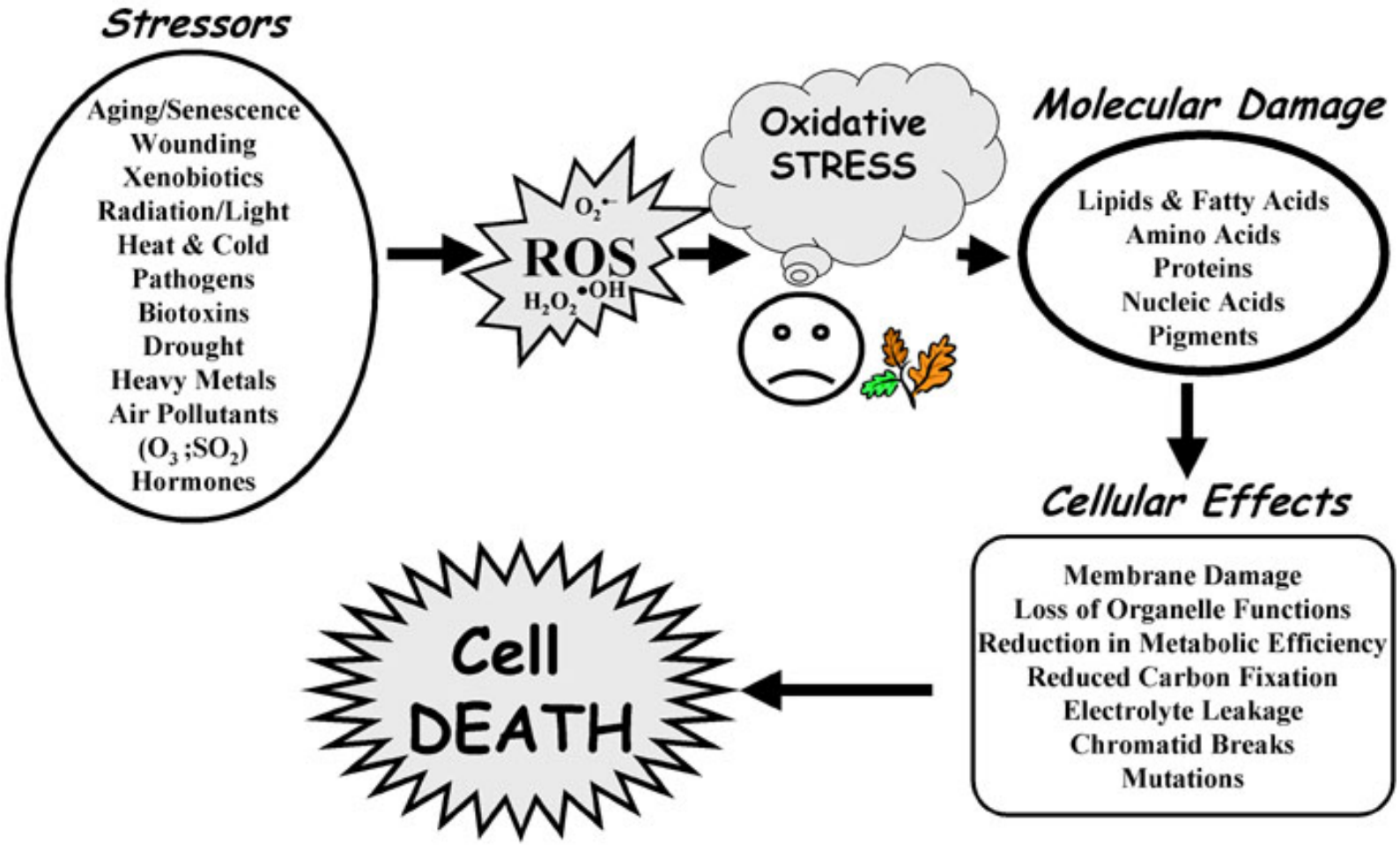
Balance



http://www.andersonpc.com/lifes-delicate-balance/balance-is-the-key-to-life-balancing-elephant-poster/#prettyPhoto

Deleterious Cellular Effects of ROS



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Journal of Medical and Biological Research, 38 (7): 995, 2005.

Diseases Associated with ROS

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http://www.neurogenol.co.uk/oxidativestress.html

Chocolate Principle

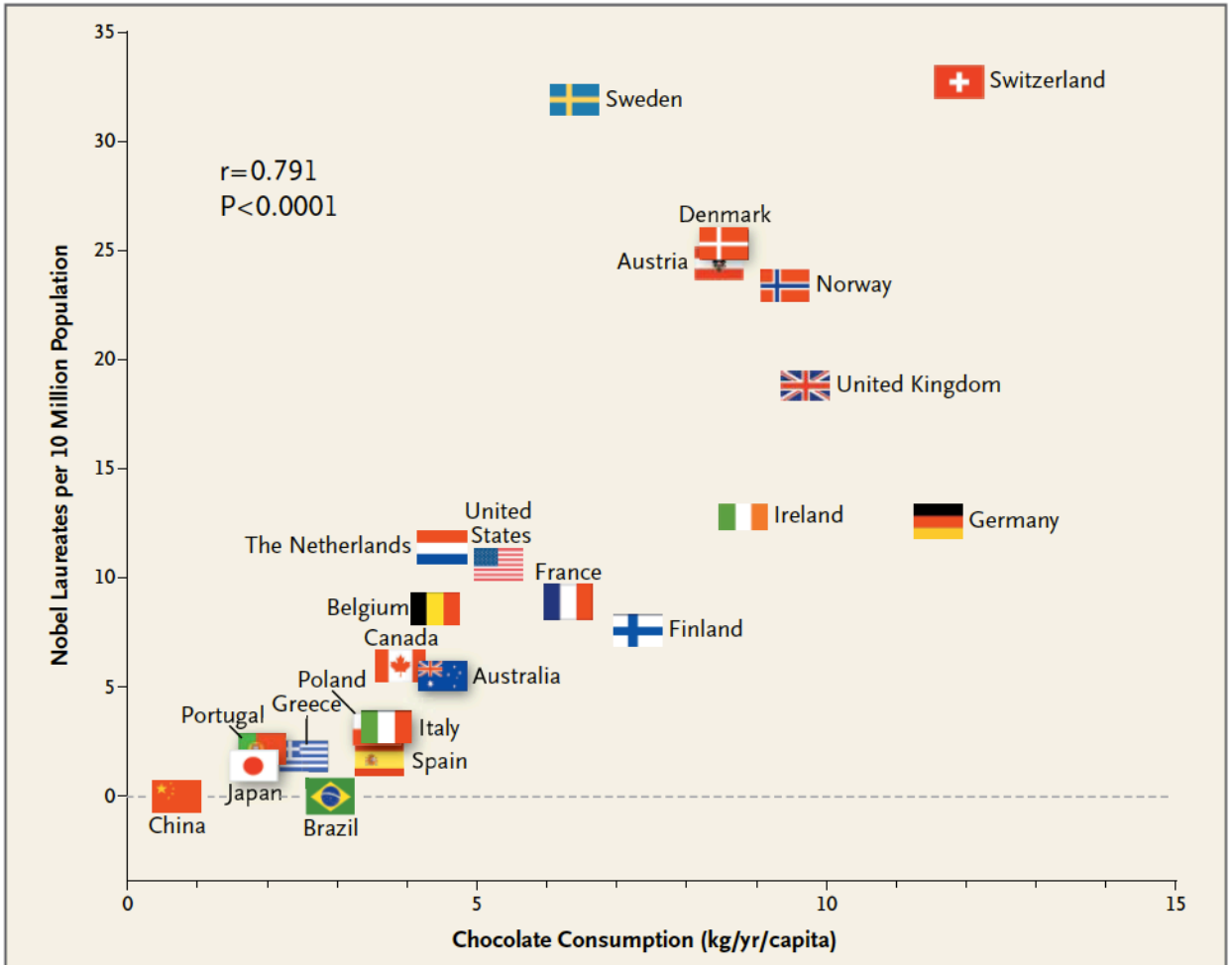

Figure 1. Correlation between Countries' Annual Per Capita Chocolate Consumption and the Number of Nobel Laureates per 10 Million Population.

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New Engl. J. Med. F. H. Messerli 1562–1564; 2012
Nature B. A. Golomb 499, 409; 2013

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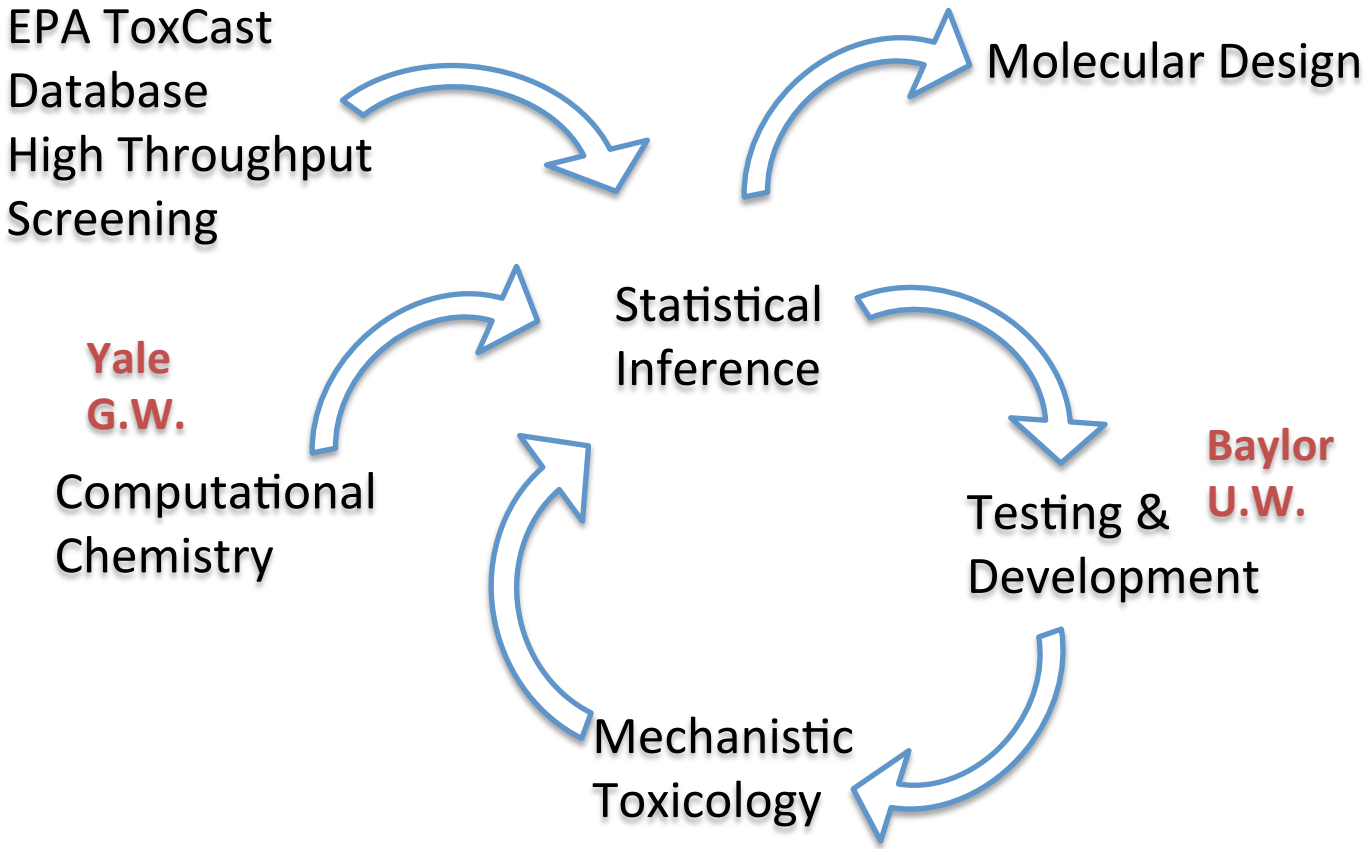
Molecular Design Against Oxidative Stress



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Strategy

"We can't solve problems by using the same kind of thinking we used when we created them"

--- Albert Einstein

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