MoDRN: Rational Design and Development of the Next Generation Chemicals

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

Linkages are complex

Seeking guidelines for safer chemicals.

Physicochemical Properties and Toxicity

- Electronic Charge
- Solubility
- Volatility
- Molecular Weight & Size
- Carcinogenicity
- Acute toxicity
- Subchronic & chronic toxicity
- Aquatic toxicity
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.
Molecular Design Research Network (MoDRN)

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

Biology
Engineering

Computational Chemistry
Toxicology

RESEARCH
EDUCATION
OUTREACH
Framework Structure

Chemical Selection → Computational Modeling
  electronic & thermodynamic parameters → Experimental Toxicty Assays
  *in vivo & in vitro for OS* → Model Development
  and Further Refinement → Industrial Partnerships

Education, Outreach
Oxidative Stress: What is it?
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Disruption of the balance between prooxidants and antioxidants that leads to potential damage.

http://www.redoxbalance.com/
Oxidative Stress: Why do we care

Oxygen: Life dependent substance

https://industrialoxygenasplanto.wordpress.com/
Significance of Oxygen

http://earth.usc.edu/~stott/Catalina/Earlyatmosphere.html
Reactive Oxygen Species (ROS)

- Oxygen: $O_2$
- Superoxide anion: $\cdot O_2^-$
- Peroxide: $\cdot O_2^{-2}$
- Hydrogen Peroxide: $H_2O_2$
- Hydroxyl radical: $\cdot OH$
- Hydroxyl ion: $OH^-$

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
Balance is the Key to Life

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

Stressors
- Aging/Senescence
- Wounding
- Xenobiotics
- Radiation/Light
- Heat & Cold
- Pathogens
- Biotoxins
- Drought
- Heavy Metals
- Air Pollutants
  - (O₃;SO₂)
- Hormones

Oxidative STRESS

ROS

Molecular Damage
- Lipids & Fatty Acids
- Amino Acids
- Proteins
- Nucleic Acids
- Pigments

Cellular Effects
- Membrane Damage
- Loss of Organelle Functions
- Reduction in Metabolic Efficiency
- Reduced Carbon Fixation
- Electrolyte Leakage
- Chromatid Breaks
- Mutations

Cell DEATH
Diseases Associated with ROS

- Heart Disease, Blood Pressure Hypertension, Ischemia
- Skin ageing, Psoriasis Sunburn, Dermatitis, Melanoma
- Macular Degeneration Retina Degeneration Cataracts
- Heart
- Macular Degeneration Retina Degeneration Cataracts
- Eyes
- Heart Disease, Blood Pressure Hypertension, Ischemia
- Kidney Disease Nephritis
- Kidney
- Multi Organ
- Diabetes, Ageing CFS, ME
- Atherosclerosis, Blood Flow, Clots Hypertension
- Blood
- Joints
- Arthritis, Rheumatoid Osteo, Psoriasis
- Skin
- Skin ageing, Psoriasis Sunburn, Dermatitis, Melanoma
- Immune
- Inflammations Auto Immune Disorders Lupus, MS, Cancers
- Free Radical Damage Oxidative Stress
- Brain
- Alzheimer's, Parkinson ADHD, Autism, Migraine Stroke, Cancer, Trauma
- Lung
- Asthma, Allergies Cancer, ARDS

http://www.neurogenol.co.uk/oxidativestress.html
Figure 1. Correlation between Countries’ Annual Per Capita Chocolate Consumption and the Number of Nobel Laureates per 10 Million Population.
Molecular Design Against Oxidative Stress

- EPA ToxCast Database
- High Throughput Screening
- Computational Chemistry
- Statistical Inference
- Mechanistic Toxicology
- Testing & Development
- Molecular Design

Institutions:
- Yale
- G.W.
- Baylor
- U.W.
- Yale

MoDRN
Molecular Design Research Network
“We can’t solve problems by using the same kind of thinking we used when we created them”

--- Albert Einstein
http://modrn.yale.edu

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