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Tapping untapped: Exploring Role of ALDH in Pharmacogenetic and Toxicogenetic Studies

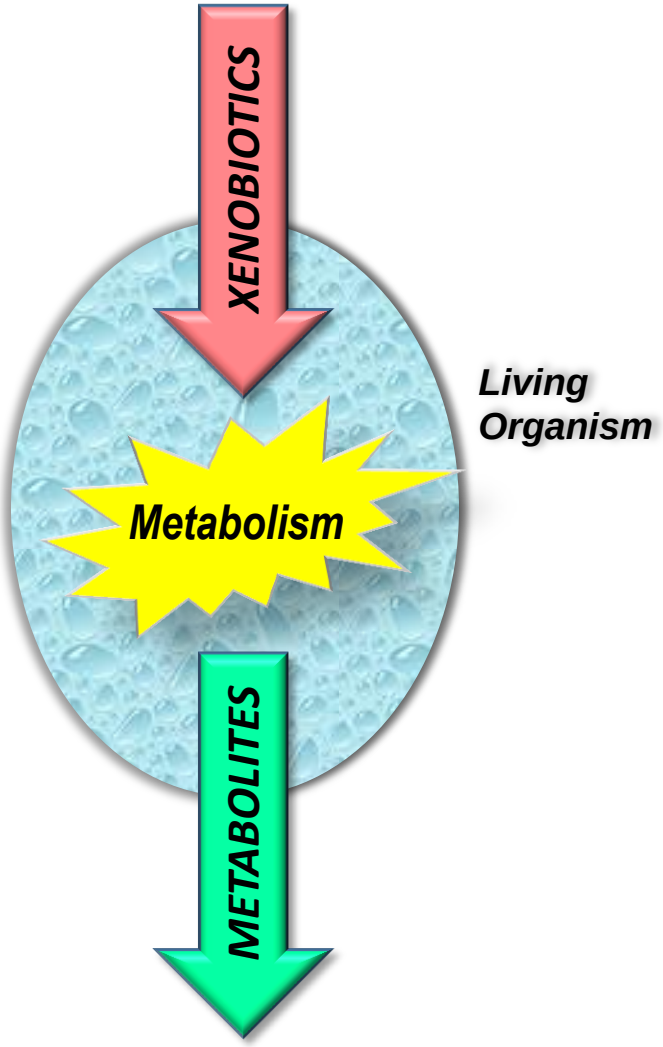
Nasir Ali Afsar
MBBS, M.Phil, Ph.D

Department of Pharmacology,
Jinnah Medical & Dental College, Karachi, Pakistan;
College of Medicine, Alfaisal University, Riyadh, Saudi Arabia.

Xenobiotic Metabolism

Food, Pollutants, Drugs

Phases I, II, III



Xenobiotic Metabolism

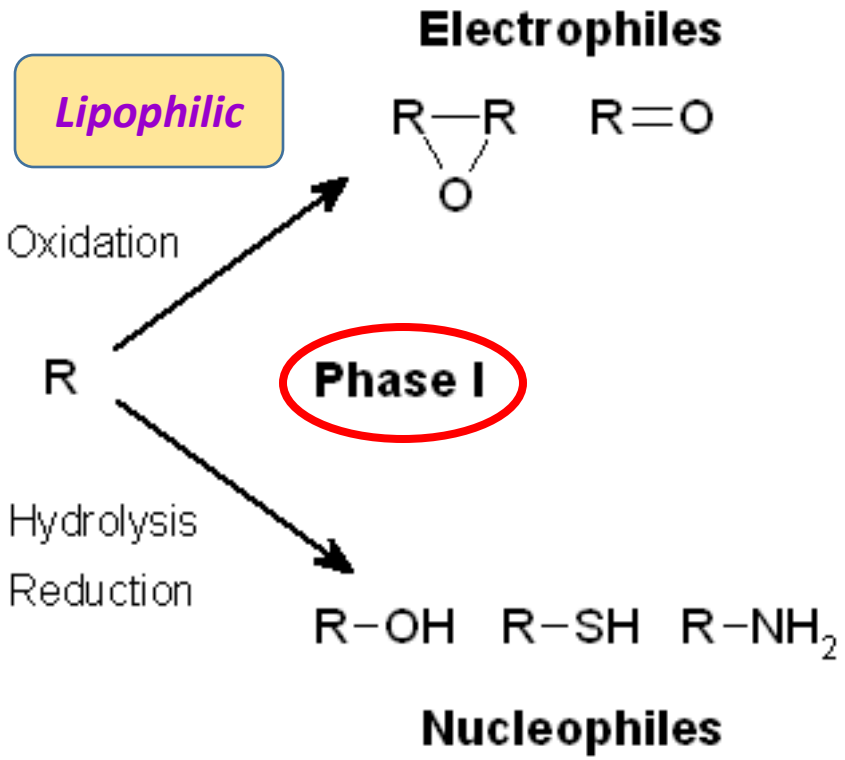
- Non-specific defence against xenobiotics – maximize polarity with minimal intervention.
- Phase-I, non-synthetic
  - Includes: Oxidation, reduction, hydrolysis
  - Important Enzyme Systems:
    - Monooxygenase Systems:
      - Cytochrome P450 (CYP) or mixed function oxidases
      - Flavin-containing monooxygenases
    - Monoamine oxidases
    - Alcohol/ Aldehyde Dehydrogenases

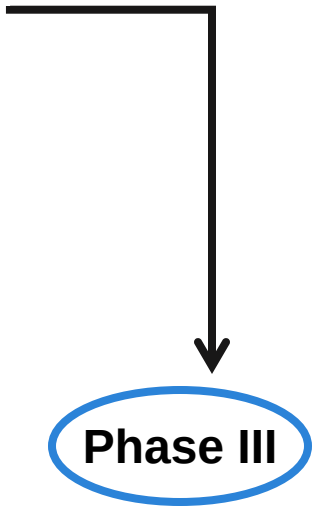
Xenobiotic Metabolism

- Phase-II, synthetic
  - Glucuronidation, sulfation, glutathionation, acetylation etc.

- Phase-III (according to some resources)
  - Efflux transporters, such as ATP Binding Cassette (ABC) Transporters. ABCB1, ABCC2 etc.

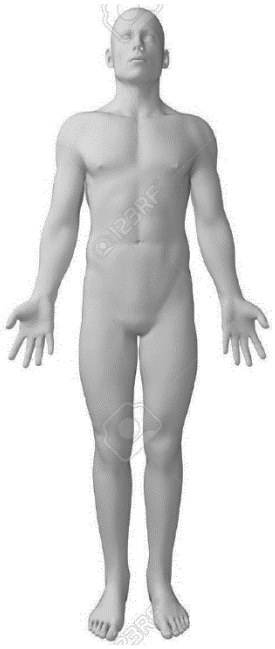
Xenobiotic Metabolism





We know the Sensory and Motor Homunculi.

Sensory Cortical Homunculus, as mapped in brain



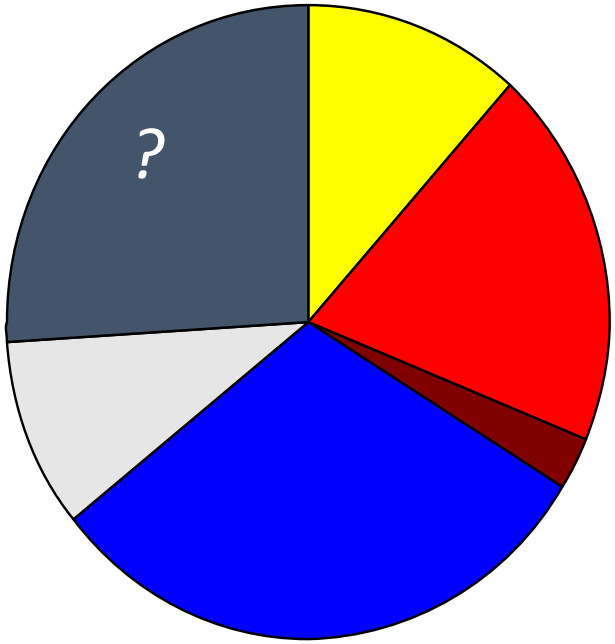
Human body or 'homunculus', as we see it !

Motor Cortical Homunculus, as mapped in brain

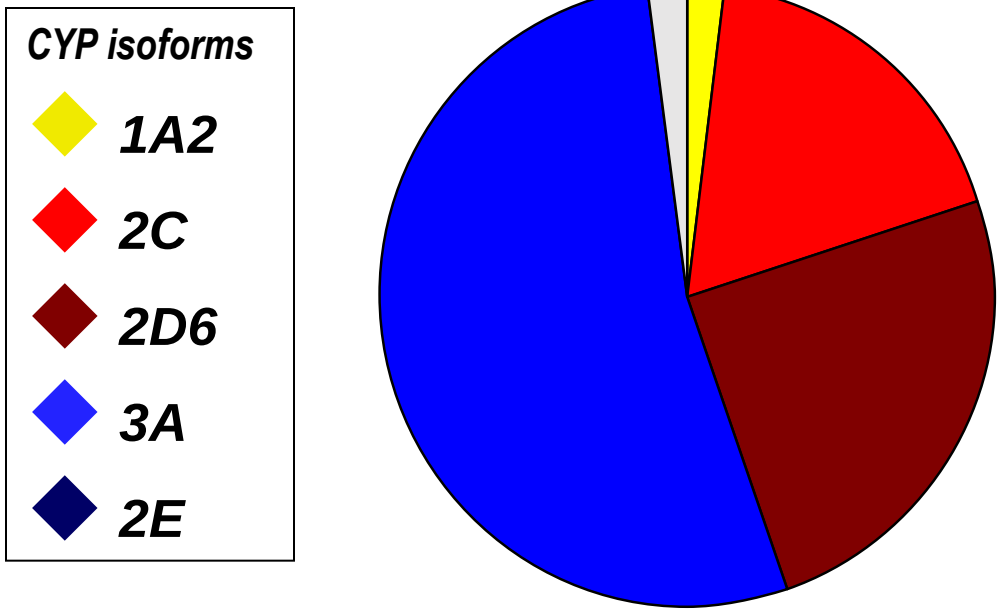
How should the "Metabolic Homunculus" appear?

Metabolic 'Homunculus'

Relative Quantities of P450s in Liver

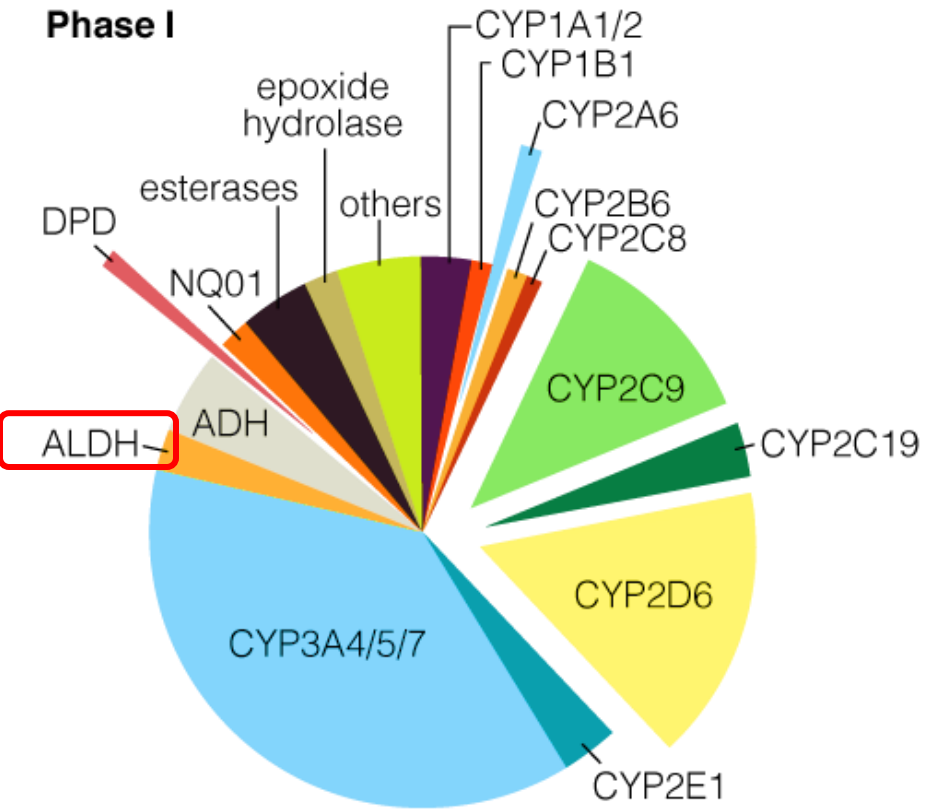


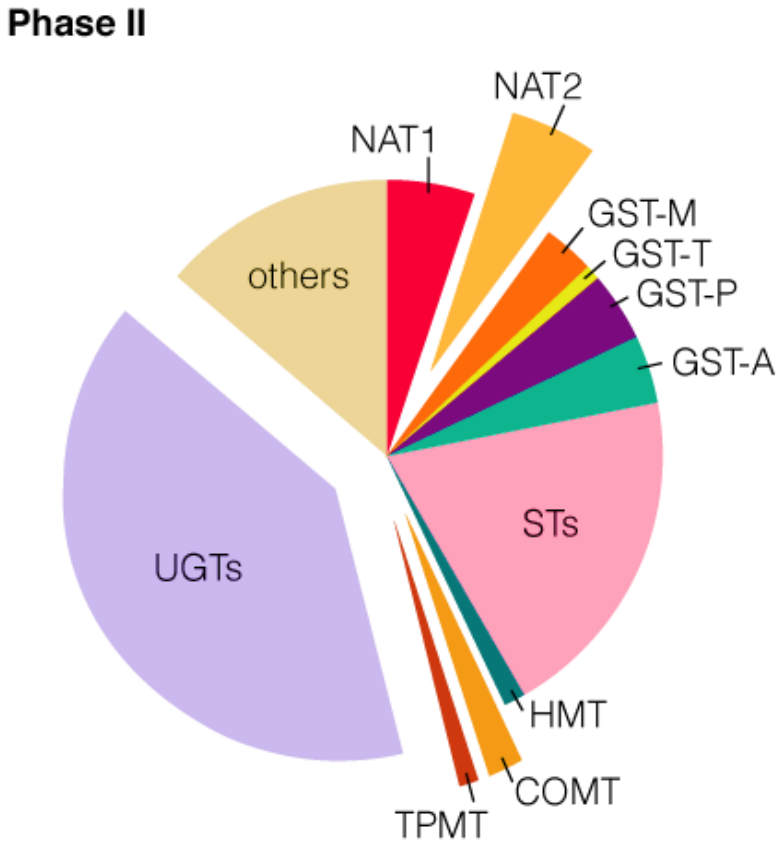
Relative Contribution of P450s in Drug Metabolism



Shimada T et al. J Pharmacol Exp Ther 1994;270(1):414.

Relative importance of CYP450 isoforms in drug metabolism





Phase-I Reactions:
Oxidation, Reduction, Hydroxylation, Hydrolysis

Phase-II Reactions:
Acetylation, Glutathionation, Sulfation, Methylation, Glucuronidation etc.

Evans WE and Relling MV (1999) Pharmacogenomics: Translating functional genomics into rational therapeutics. Science **286**; 487-491

Aldehyde Dehydrogenases

- Many isoenzymes – our focus is **ALDH3A1**
- Broad spectrum of biological activities
  - Biosynthesis of retinoic acid
  - Metabolic and Detoxification functions:
    - Aldehyde metabolism, e.g. Benzaldehyde
    - Alcohol (acetaldehyde) metabolism
    - Ester hydrolysis
    - Metabolism of lipid peroxidation and reduction of oxidative stress
    - Prevention of UV light induced damage to cornea
    - Metabolism of GABA and some amino acids
    - Clearance of certain anticancer drugs

Our previous reports…

- Certain genotypes increase cyclophosphamide clearance (CYP2C19/ ALDH3A1) and predispose to neutropenia (GSTA1) in breast cancer patients

(***Afsar NA et al. Eur J Clin Pharmacol, 2012).***

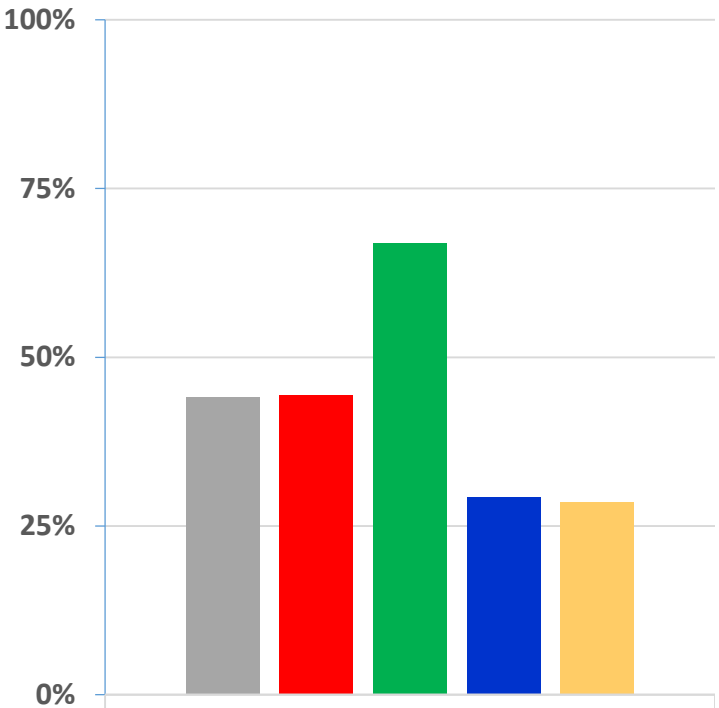
- Prevalence frequencies of some alleles (CYP2C19, ALDH3A1, ABCB1, ABCC2) among breast cancer patients showed differences when compared with HapMap database

(***Afsar NA et al. Basic Clin Pharmacol Toxicol, 2010).***

Current study

- To estimate genotype profile among **healthy** adults (Karachiites; n=155; both genders).
  - Phase-I metabolism (CYP1A1 *2A/*3, CYP1A1*2C, CYP2B6*4, CYP2B6*6, CYP2C9*2, CYP2C19*2, CYP2C19*17, CYP2D6*4, CYP2D6*10, CYP3A4*22, CYP3A5*3),
  - Phase-II metabolism (ALDH3A1, GSTA1 -69, GSTM1)
  - Efflux transporters (ABCB1 1236, ABCB1 2677, ABCB1 3435, ABCC2 -24, ABCC2 3972, ABCC2 1249)
- Techniques: Saliva samples; PCR followed by RFLP or PSQ

Variant Allele Frequencies (%) – ALDH3A1 (985 C>G)



	ALDH3A1
AFR	44.1%
CHIN	44.4%
KHI	66.9%
CAUC	29.2%
HISP	28.6%

Data (variant allele frequency) compared with major ethnic groups in HapMap.

The genotype data of **KHI** samples is given below:

Genotype	% Frequency	95% C.I.
C/C	8.1	3.7 - 12.5
C/G	50.0	41.9 - 58.1
G/G	41.9	33.9 - 49.8

Important functions

- ALDH3A1
  - determines plasma clearance of cyclophsphomide and ifosfamide by shunting to inactive metabolite pathway (Afsar et al. 2012 EJCP)
  - helps generate NO from organic nitrates (Lin et al. 2013 Nitric Oxide)

Important functions

- ALDH3A1
  - has shown association with prostate and breast cancers (Yan et al. 2014, Br J Ca)
  - protects against UV-induced corneal damage (Chen et al. 2013, P Ret Eye Res)
  - maintains visual clarity along with ALDH1 (Lassen et al. 2007, J Biol Chem)

Important functions

- ALDH3A1
  - helps synthesize CoQ and protects against mitochondrial dysfunction (Stefely et al. 2016 Nat Biotech)
  - protects cells against 4-HNE, a toxic product of lipid peroxidation (Black et al. 2012 Free Rad Bio Med)
  - protects oral and respiratory tract mucosa from food, air pollutant and smoking-induced damage (Giebułtowicz et al., 2010 Acta Biochim Pol. ; Jang et al. 2014, Free Rad Bio Med)

Potential adverse consequences of loss of ALDH3A1 function – future research potential

Increased likelihood of

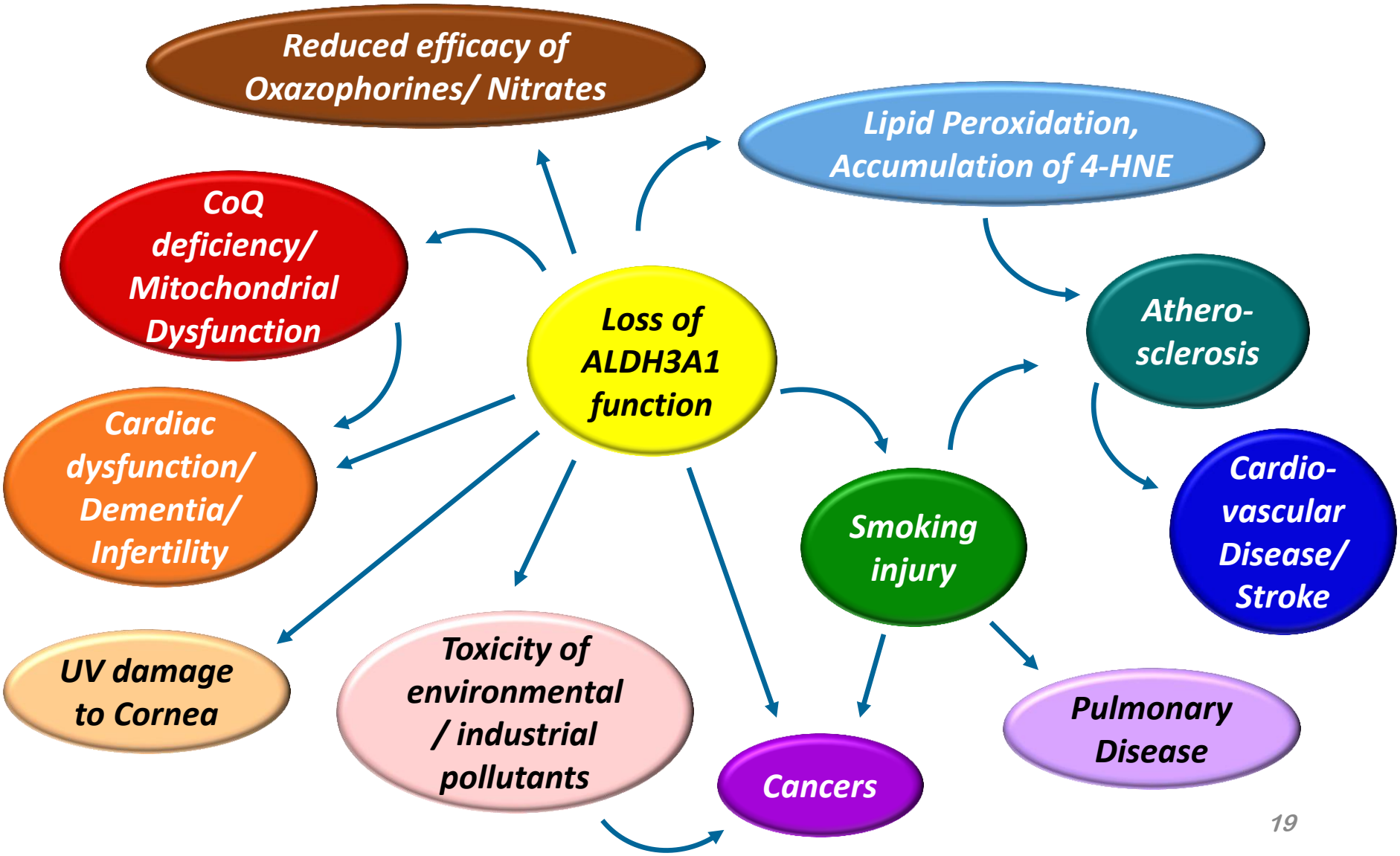
- Oxidative stress especially due to lipid peroxidation – and its consequences – aging, cancers, CVS disorders etc.
- Development of atherosclerosis – CVS disorders
- Damage from aldehydes and electrophiles in food and polluted environment – aging, degeneration, cancers
- Damage to oral, pharyngeal, laryngeal and respiratory tract mucosa by tobacco smoking – numerous consequences

Potential adverse consequences of loss of ALDH3A1 function – future research potential

Increased likelihood of

- Development of cancers and their metastasis
- Mitochondrial dysfunction leading to a number of degenerative and chronic effects
- Infertility – sperm motility problems
- Visual impairment due to UV radiation
- Suboptimal efficacy of organic nitrates

Summary


Reduced efficacy of Oxazophorines/ Nitrates
Lipid Peroxidation, Accumulation of 4-HNE
CoQ deficiency/ Mitochondrial Dysfunction
Loss of ALDH3A1 function
Athero-sclerosis
Cardiac dysfunction/ Dementia/ Infertility
Smoking injury
Cardio-vascular Disease/ Stroke
UV damage to Cornea
Toxicity of environmental / industrial pollutants
Cancers
Pulmonary Disease

Thank You

Our Team:

- Dr. Nasir Ali Afsar [1,2]
- Professor HR Ahmad [1]
- Dr. Muhammad Kashif Nisar [1]
- Ms. Britta Schwarten [3]
- Professor Ingolf Cascorbi [3]

For any querries, please write to:
nafsar@alfaisal.edu

1. Alfaisal University, Riyadh, Saudi Arabia
2. Jinnah Medical & Dental College, Karachi, Pakistan
3. Universitätsklinikum Schleswig-Holstein, Christian-Albrechts University, Kiel, Germany