Nutrigenomics

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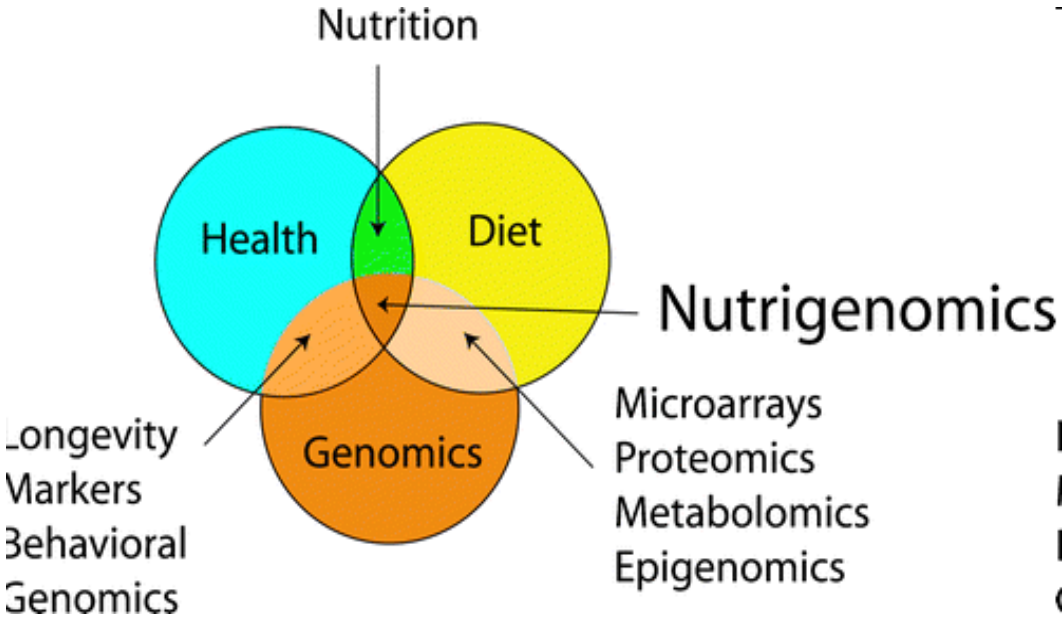
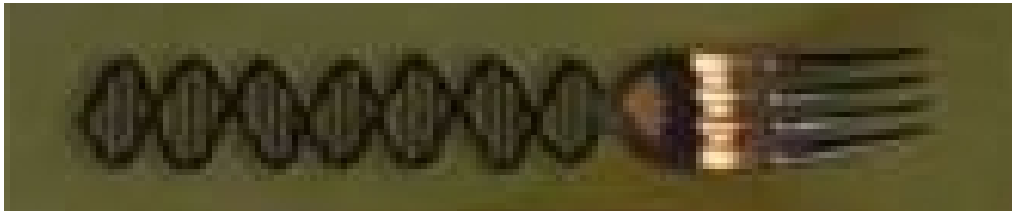
Roadmap

- What is it?
- What prompted it?
- Goals
- Tools
- Methods
- Example
- Problems
- Cartoons!

What is it?

- Using genomics tools to research effects of food on metabolism and gene expression
- Working towards understanding
  - How regulation of homeostatic control is disturbed in a diet-related disease
- Nutrigenetics – To what extent an individual's genotypes influences metabolic pathways
  - (Müller & Sander, 2003)





What prompted it?

- More information via new research procedures
  - New technology
  - New Methods (GWAS)
- Research began to indicate the importance of genetic predisposition
  - can be an important contributor to cardiovascular disease, diabetes type II, cancers
    - (Keating and Sanguinetti, 1996)
- Nutrients began to be seen as contributing factors

What are the goals?

- How nutrition influences metabolic pathways
  - Identification of transcription factors that function as nutrient sensors and the genes they target
  - Indicative biomarkers
    - Clinical diagnosis
  - Gene expression signatures
    - Clinical and research implications
- the identification of genotypes that are risk-factors for the development of diet related diseases

Table 1 | **Transcription-factor pathways mediating nutrient–gene interactions**

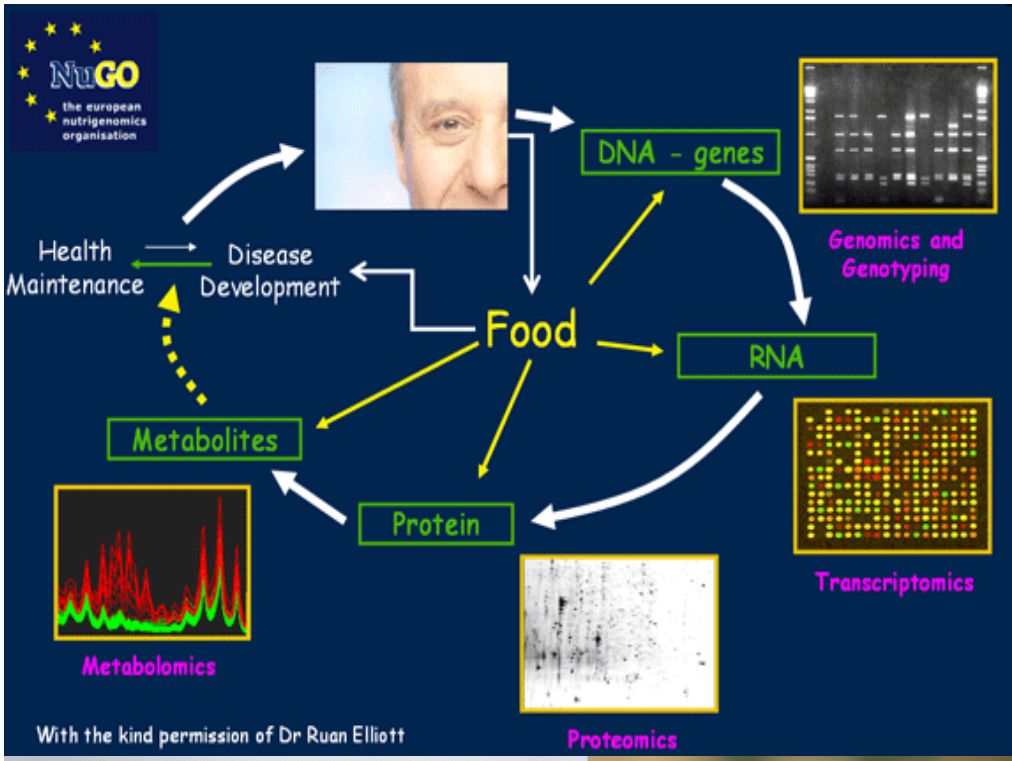
Nutrient	Compound	Transcription factor
Macronutrients		
Fats	Fatty acids	PPARs, SREBPs, LXR, HNF4, ChREBP
	Cholesterol	SREBPs, LXRs, FXR
Carbohydrates	Glucose	USFs, SREBPs, ChREBP
Proteins	Amino acids	C/EBPs
Micronutrients		
Vitamins	Vitamin A	RAR, RXR
	Vitamin D	VDR
	Vitamin E	PXR
Minerals	Calcium	Calcineurin/NF-ATs
	Iron	IRP1, IRP2
	Zinc	MTF1
Other food components		
	Flavonoids	ER, NFκB, AP1
	Xenobiotics	CAR, PXR

AP1, activating protein1; CAR, constitutively active receptor; C/EBP, CAAT/enhancer binding protein; ChREBP, carbohydrate responsive element binding protein; ER, oestrogen receptor; FXR, farnesoid X receptor; HNF, hepatocyte nuclear factor; IRP, iron regulatory protein; LXR, liver X receptor; MTF1, metal-responsive transcription factors; NFκB, nuclear factor κB; NF-AT, nuclear factor of activated T cells; PPAR, peroxisome proliferator-activated receptor; PXR, pregnane X receptor; RAR, retinoic acid receptor; RXR, retinoid X receptor; SREBP, sterol-responsive-element binding protein; USF, upstream stimulatory factor; VDR, vitamin D receptor.

Muller and Sander, 2003

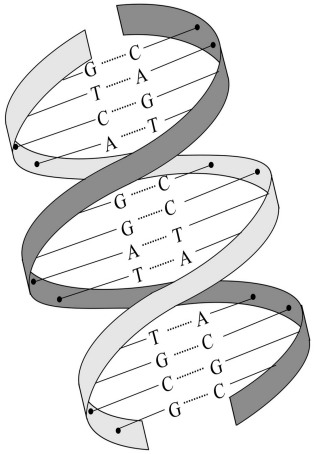
Methods

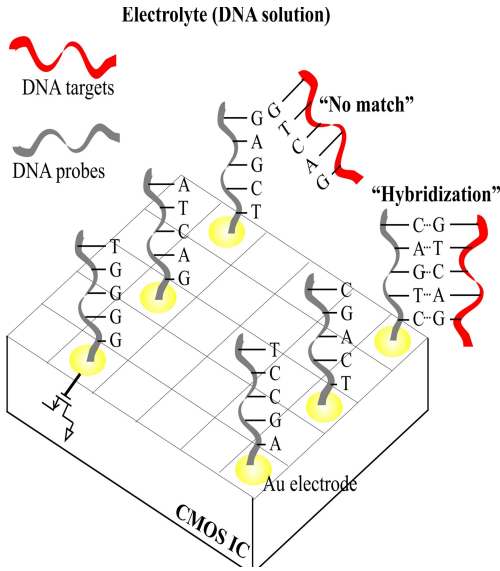
- Outlook: Systems biology
- Other fields
  - Genomics
  - Metabolomics – allows measuring of metabolites in blood or organs
  - Proteomics – study of proteins
  - Transcriptomics – study of RNA
- Model organisms
  - Drosophila
    - adipose-like tissues & lipid transport system
  - transgenic and knockout mouse models

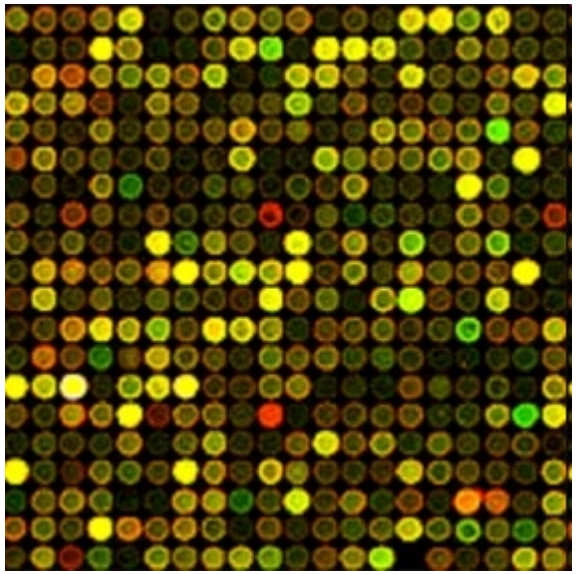


Tools

- Tools
  - DNA microarray,
    - SNP arrays
  - Gel electrophoresis
  - Mass Spectrometry
  - Proton Nuclear Magnetic Resonance
    - MRI scans

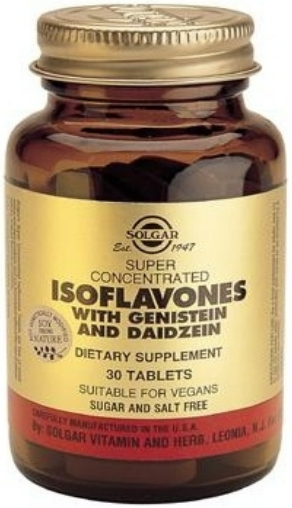


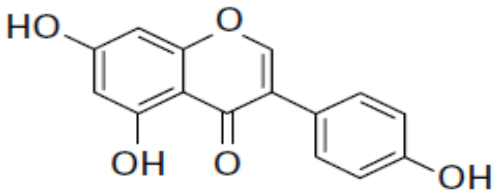




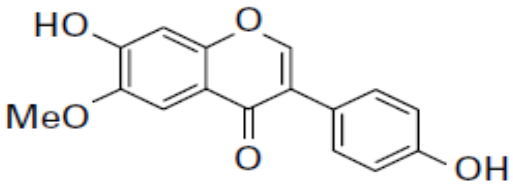
Example - Effect of Isoflavones on Breast & Prostate Cancer

- Human studies seem to indicate a correlation between soy isoflavone consumption and protection towards breast and prostate cancers
- Isoflavones – class of bioactive phytochemicals
  - potential role in the prevention of various chronic diseases
- Mechanisms
- Nutrigenetics
  - Individual variability in gut microflora composition and gene polymorphisms

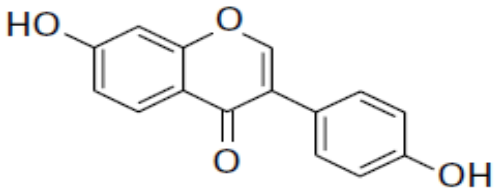




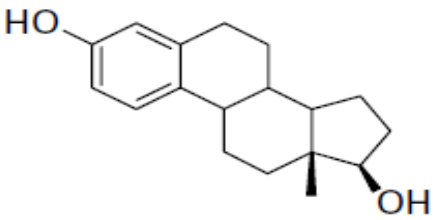
Genistein



Glycitein



Daidzein



17β-Estradiol

Isoflavones Mechanisms

- Breast Cancer - Estrogen Receptors
  - Estrogens are mediated by the binding of one of the two specific nuclear receptors which can induce gene transcription of estrogen-responsive target genes
    - ERa and ERb
  - Estrogens acting via ERa exert strong proliferation stimulatory effects; those interacting with ERb tend to reduce this stimulation.
    - More ERa during tumour progression
- Genistein correlated with downregulation of ERa and an upregulation of ERb mRNA and protein levels in breast cancer cells
  - A decrease in ERa protein expression in mammary tumours of rats after consumption of a soy extract

Isoflavones Mechanisms

- Prostate Cancer - Androgen Receptors
  - Genistein (isoflavone) exerts anti-androgenic effects and downregulates the expression and secretion of PSA
  - Numerous studies show a decrease in AR expression at mRNA and protein levels in prostate cells after exposure to isoflavone
    - Higher AR levels are correlated with higher risk or prostate cancer
  - Long-term soy protein consumption also lowered AR expression in prostate of men with high risk

Isoflavone Gene Interaction

- Known polymorphism
  - Phytoestrogen-gene interaction - CYP19 codes for the enzyme that catalyzes the irreversible conversion of androgens to estrogens.
  - 4 known haplotypes, 1 haplotype with T, 3 with C
  - The T allele of the CYP19 3'UTR T-C polymorphism is associated with higher mRNA levels and thus higher enzyme activity
    - This enzyme catalyzes androgens to become estrogen
- The TT genotype allows a specific nutrient-gene interaction which converts androgen receptors into estrogen receptors, decreasing the susceptibility to prostate cancer

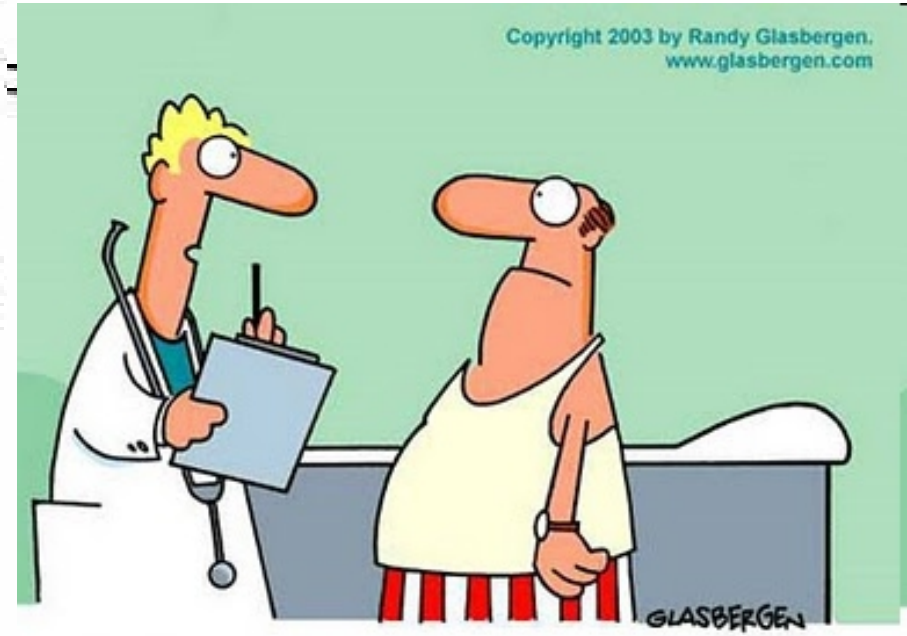
Problems and Roadblocks

- Problems with Research
  - Control of intake
    - Diets are variable
    - Animal studies are more popular
  - Bioavailability
    - Uptake usually not measured
      - Critical to food studies
  - Biomarkers
    - Can't rely on just one biomarker for a complex problem
  - Lack of knowledge of pathways
    - Lots of groundwork to be laid

- Roadblocks in advancement
  - Funding
  - Ethical Issues
    - Who will have access to this information?
      - Business v. Public Knowledge
    - "Functional Foods" efficacy?
    - What sort of behavior does this encourage?

'Four thousand packets of the new anti-obesity drug, please'

I'VE GOT THE 'FAT BASTARD' GENE



"What fits your busy schedule better, exercising one hour a day or being dead 24 hours a day?"

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