Research & Development

The Evolving Scientific Paradigm for Evaluating Reduced Risk Products

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British American Tobacco

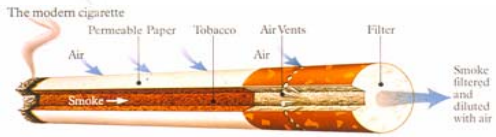
Building the foundation for evaluating PRRPs

PRRP - A product likely to reduce risks of disease based on "predictive" tests

Must demonstrate relevance for disease endpoints. But historic toxicological models cannot do this alone

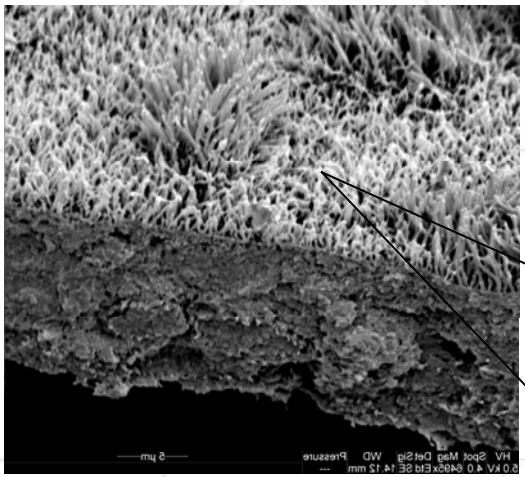
An integrated approach to predicting risk:

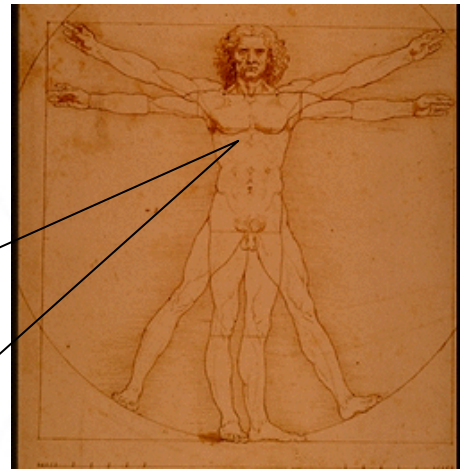
Cancer
Chronic obstructive pulmonary disease (COPD)
Cardiovascular disease

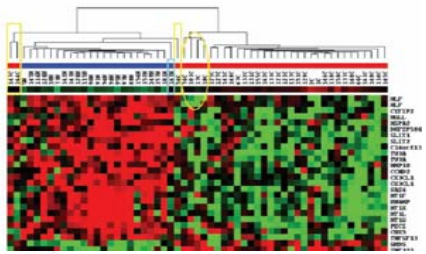


Product

***In vitro* models** | **Animal models** | **Humans**







- **Biomarkers of exposure**
- **Biomarkers of Harm**
- **Genomics**

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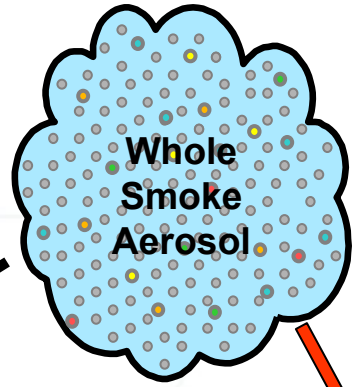
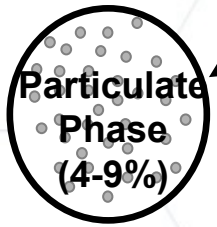
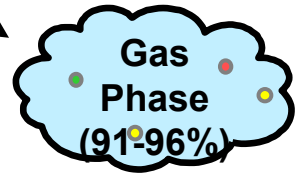
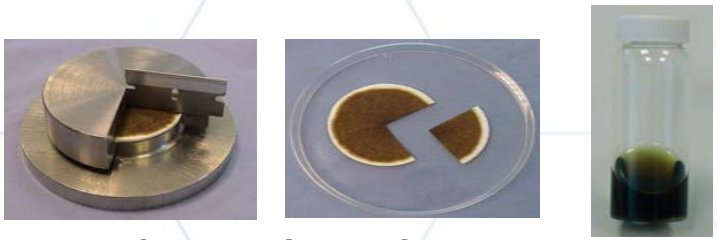
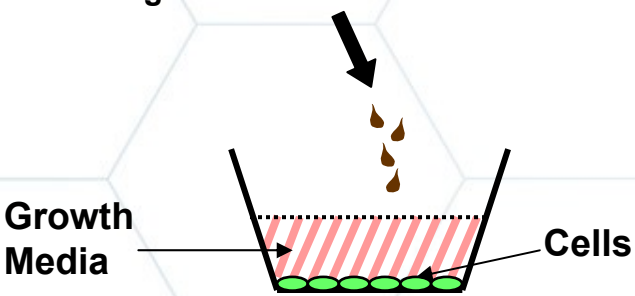
New technologies for *in vitro* testing: Whole Smoke



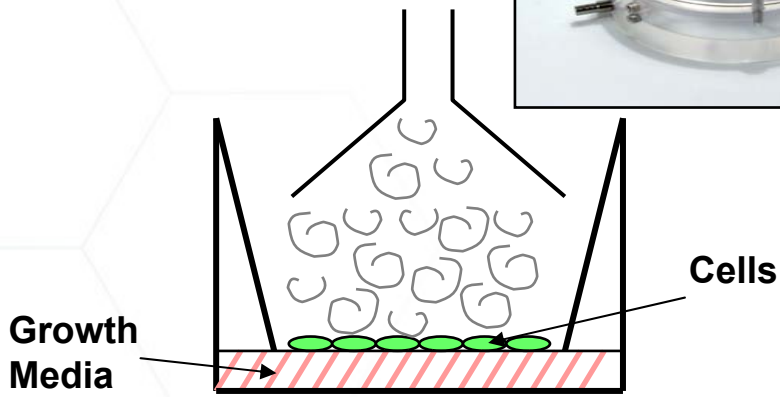






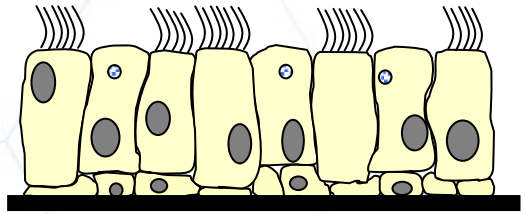


Submerged Cell Culture

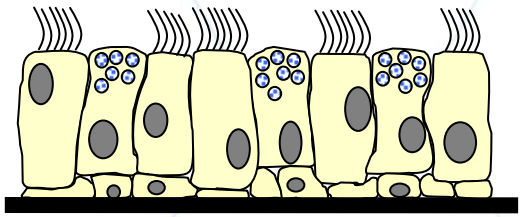


Cell Culture At The Air/Liquid Interface

BAT *in vitro* model of COPD



Airway epithelium

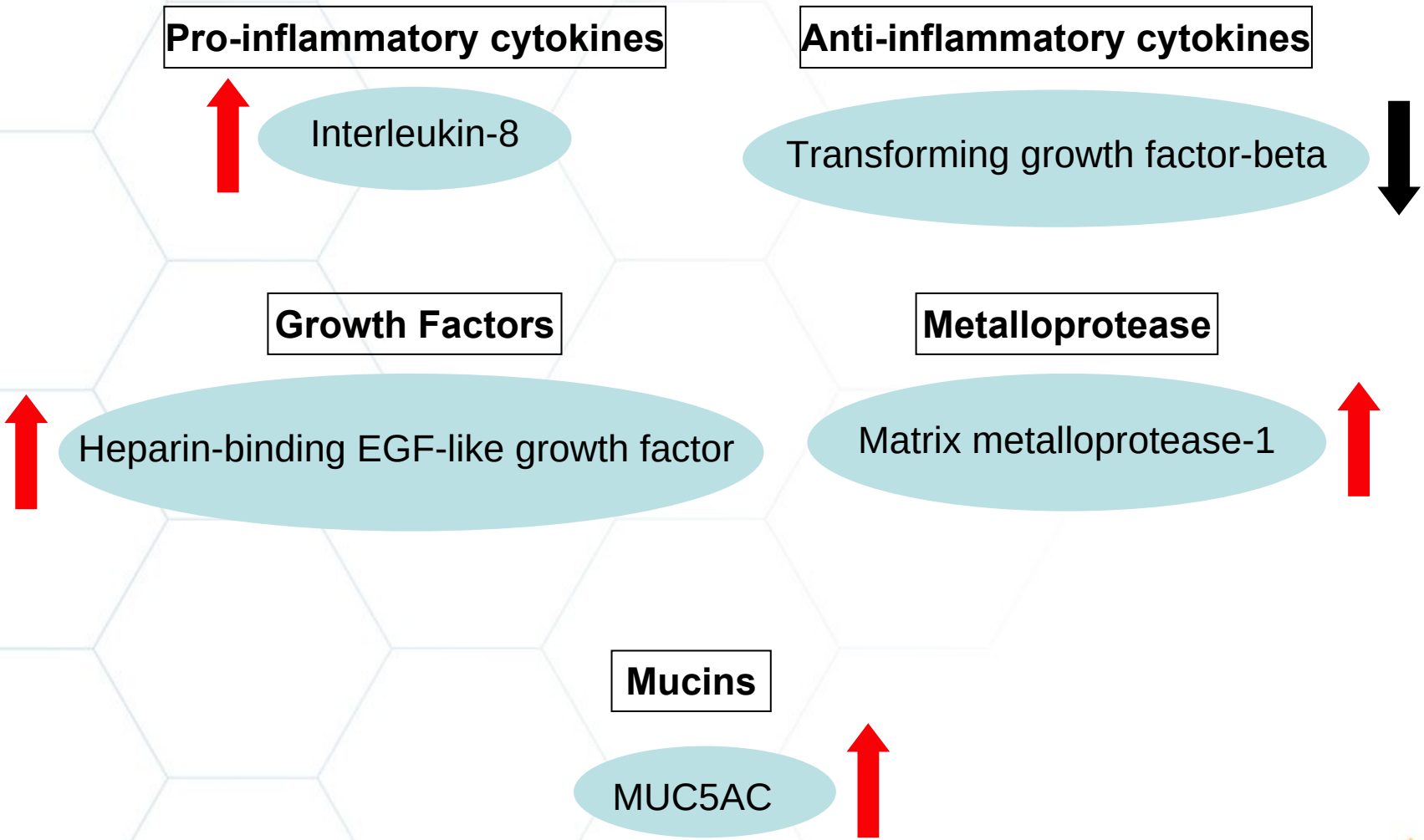


Pro-inflammatory cytokines

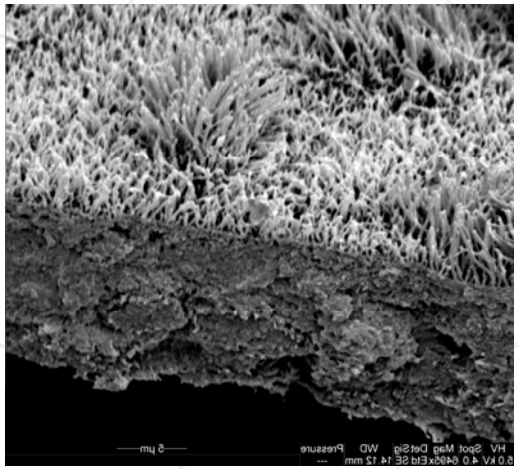
Growth factors

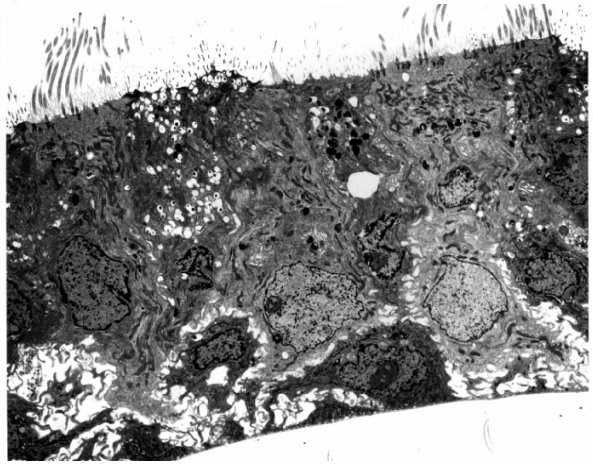
Goblet cells & Mucins

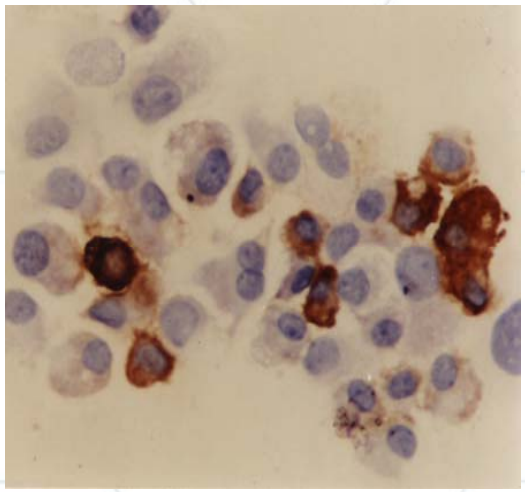
BAT *in vitro* model of COPD - gene expression mirroring changes in man

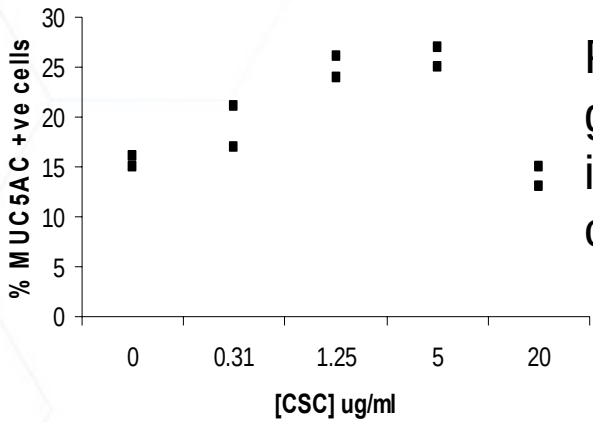


Airway structural changes *In vitro* Goblet Cell Proliferation giving a multi faceted model









Percent goblet cell in the culture

Biomarkers of Harm

- We must have a way of demonstrating reduced risk.
  - Epidemiology (Long disease latency e.g. Cancer, CVD and COPD)
  - Biomarkers of harm are short-term measures reflecting long-term outcomes of disease

We are creating a Biomarker of Harm database

- **Review of literature**
  - Database of over 100 potential Biomarkers to date
  - 10 have been short-listed for an initial pilot study

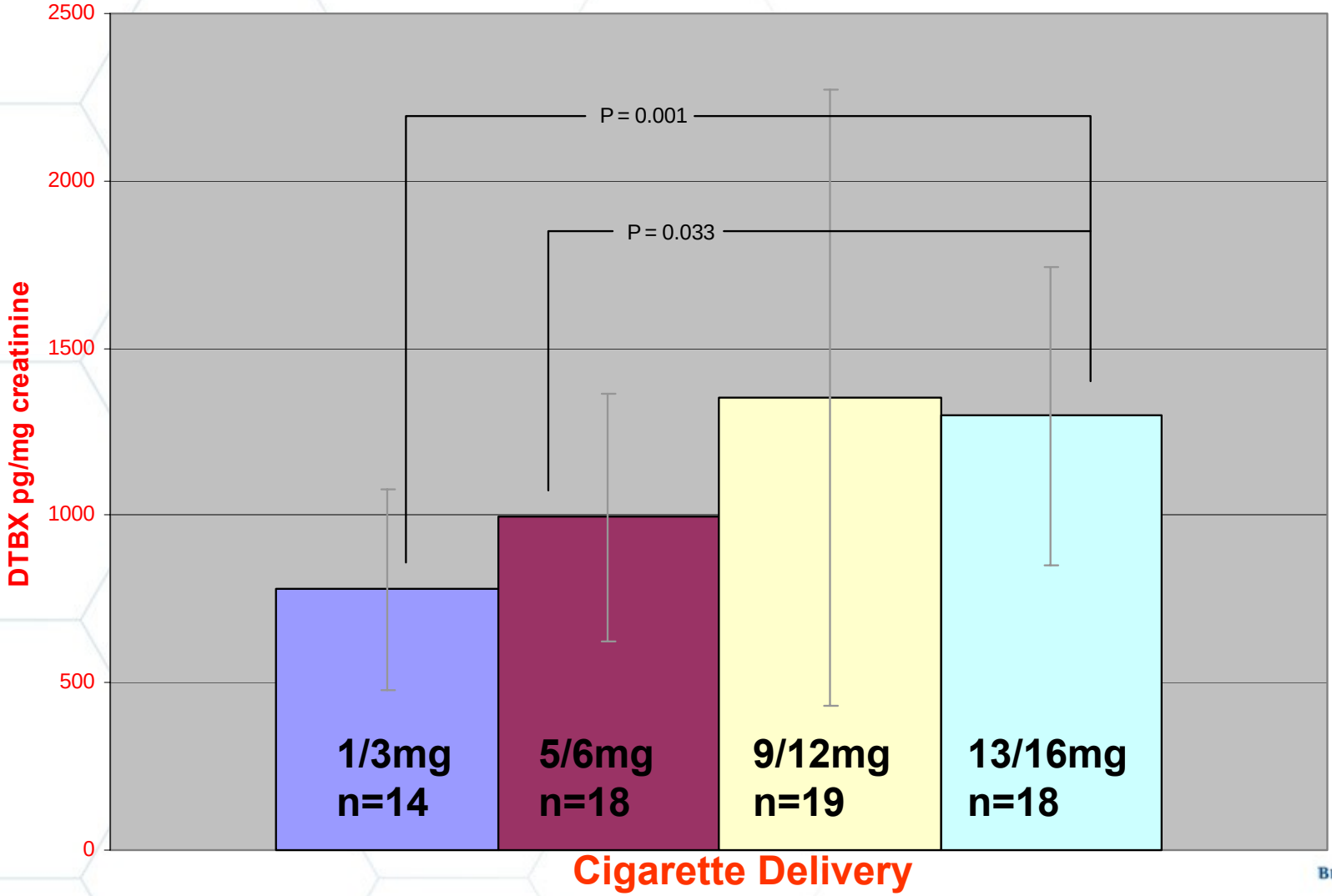
1. *Is it associated with CVD, Cancer or COPD?*
2. *Can we see differences between different levels of smoking (e.g. Heavy v's light smokers)?*
3. *Is it a short-term or a long-term biomarker?*
4. *Is there a viable technique for its detection and has it been validated?*
5. *How well accepted is this biomarker (e.g is it recommended by external body)?*
6. *Does it require an in-patient or out-patient study and what is being sampled?*

Short-listed Biomarkers

Biomarker	Sample	Disease
8-epi-$PGF_{2\alpha}$ (F2-isoprostane)	Urine	CVD
Nitrate and Nitrite	Blood	CVD
11-Dehydrothromboxane B2	Urine	CVD
Leukotriene B4	Serum	CVD
Interleukin 6	Blood	CVD
Cardiac troponin	Blood	CVD
Leukotriene B4	Breath Condensate	COPD
Desmosine/isodesmosine	BALF & Urine	COPD
DNA damage (Comet assay)	Buccal Cells	Cancer
Oxidised DNA repair	Urine	Cancer

11-Dehydrothromboxane B2

Cardiovascular disease



Biomarker Validation study

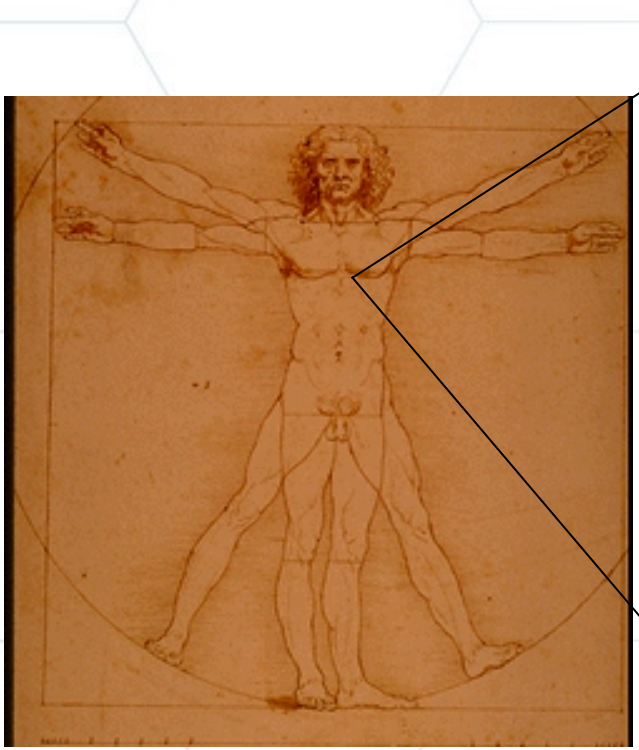
- **Combination of both epidemiology and Biomarker studies**
  - Cross Sectional Studies
  - Retrospective Case –control studies
  - Prospective Studies

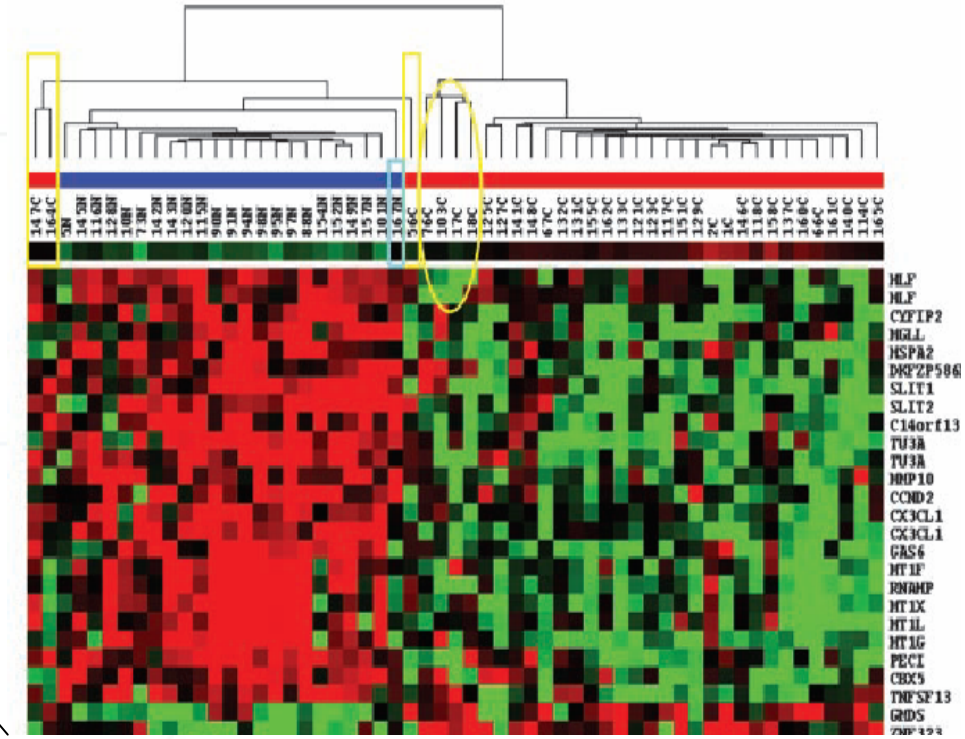
Harnessing the power of genomics

An integrated approach :

- Used to investigate which smoke constituents may be associated with the disease processes
- Provides a potential ling between the *in vitro* and *in vivo* approach
- Develop a toxicogenomic profile
  - Build toxicological & Biomarker models

Gene expression is different in the lungs of smokers compared to non-smokers





Spira *et al., PNAS* 101, 10143-8, 2004

Putting it all together to predict how product modifications might reduce disease

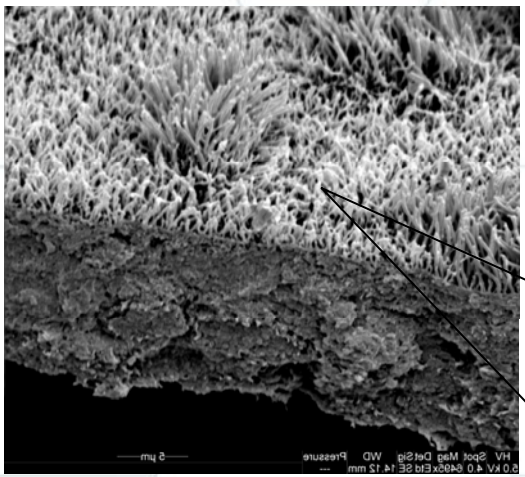
- Cancer
- Chronic obstructive pulmonary disease (COPD)
- Cardiovascular disease

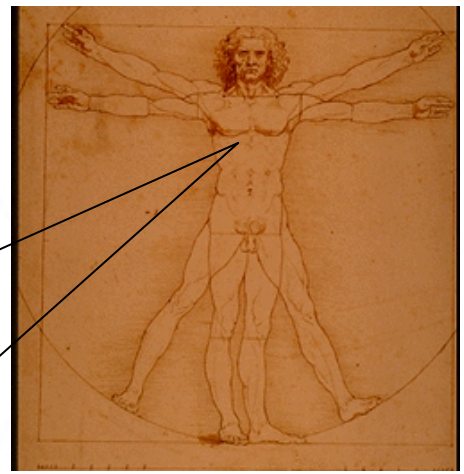
Product

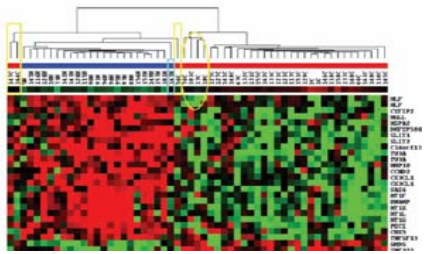
***In vitro* models**

Animal models

Humans







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