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The arsenic in mice as experimental model for risk modifiers.

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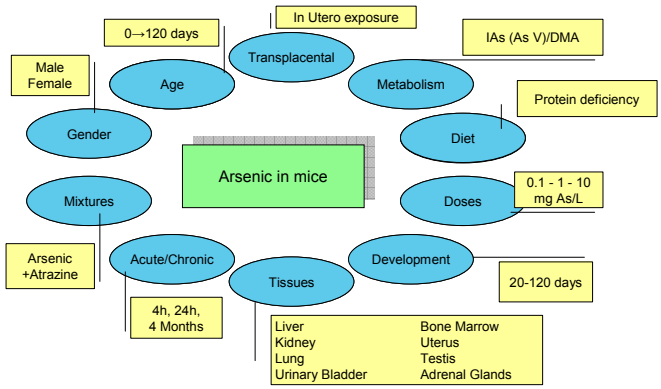
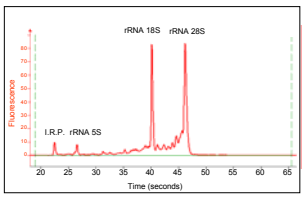
Arsenic Model

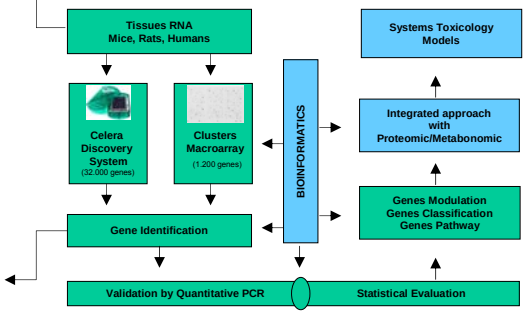


Experimental Design

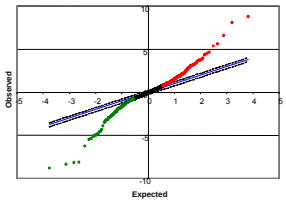
- Exposure:
  - From "in utero" to adult age (up to 4 months)
  - Arsenate/other chemicals in drinking water
  - Doses: 0.1 - 1 - 10 mg As/L
  - Diet: variable proteins content
- Tissues
  - RNA extraction and characterization
- Hybridization
  - Macroarray: Mouse Cancer 1.2 and Toxicology 1.2 clusters (Atlas™, Clontech, U.S.A) using [^{33}P]-αdATP (1.185 genes)
  - Microarray: Mouse Applied Biosystems Expression Array System using a chemiluminescence chemistry (32.000 genes).
- Quantitative Real-Time PCR
  - TaqMan Gene Expression Assays (Applied Biosystems) for validating microarray results.
- Data analyses

RNA Agilent Electropherogram

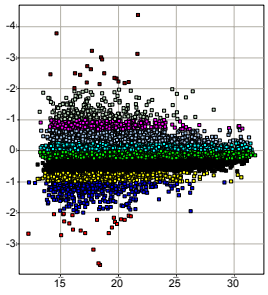




SAM Plot



Differential Expression on 32.000 genes
Fold Change vs Signal

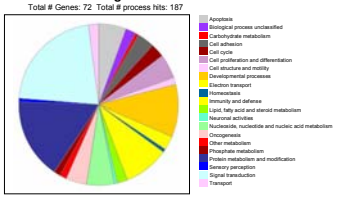


•Flags < 5000 in all arrays
•S/N > 3 in both arrays

16452 detectable probes

FC<4xdown
4xdown <FC<2xdown
2xdown <FC<1.6xdown
1.6xdown <FC<1.2xdown
1.2xdown <FC<Unchanged
Unchanged <FC<1.2xup
1.2xup <FC<1.6xup
1.6xup <FC<2xup
2xup <FC<4xup
FC>4xup

PANTHER Biological Process
Total # Genes: 72 Total # process hits: 187



Metabolism	IAs/DMA: specific tissues response for chemical species (i.g. gene modulation in lungs by DMA)
Diet	The modulation of gene expression in different tissues was not only depending on the exposure to arsenate but mainly regulated by the level of proteins in the diet.
Doses	Apparently low doses are more efficient than higher doses in modulating gene expression in tissues of mice chronically exposed to arsenate.
Tissues	Only few genes commonly modulated in different tissues.
Acute/Chronic	4-24 hours/4 months: in the liver, at 4 months only up modulated genes, few in common with 24 hours.
Mixtures	The co-exposure to atrazine and arsenate significantly modulates the transcriptional activation of genes in bone marrow cells differently than arsenate or atrazine administered alone.
Gender	The molecular mechanisms triggered by arsenic in tissues are totally different in males and females.

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