

Alternative Species and Toxicogenomics

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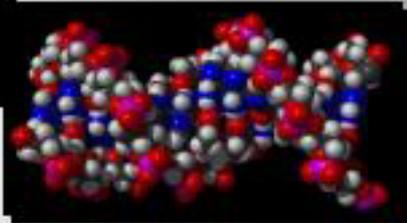
DNA Sequence vs. Gene Function

- Large Search Space for Genes: Mega-bases of Variable Sequences
- Introns, Exons, and “Junk” DNA
- Poor Correlation Between DNA & Proteins
- Post-Transcriptional and -Translational Modifications
- Protein-Protein Interactions
- Metabonomics

Understanding Gene Function



Geneticist



Computer Scientist

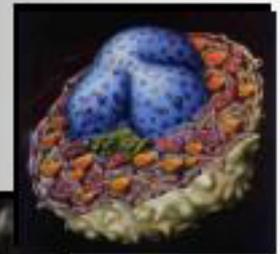


Biochemist

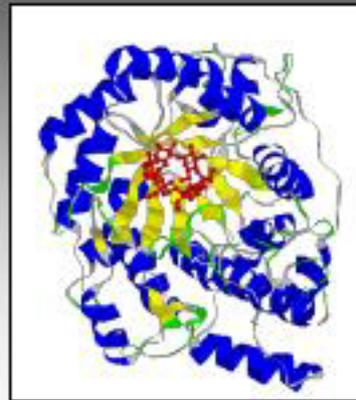
Gene Function



Physiologist



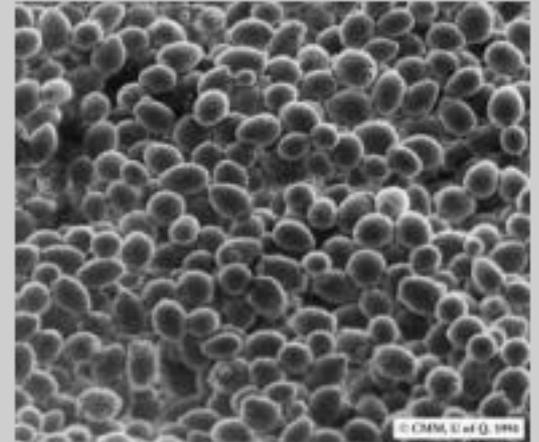
Cell Biologist



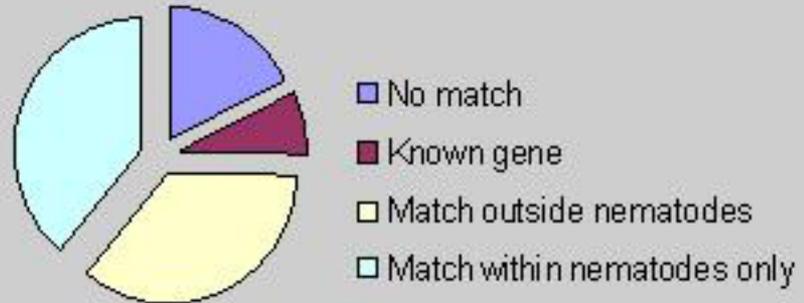
Structural Biologist

Genes in Eukaryotes

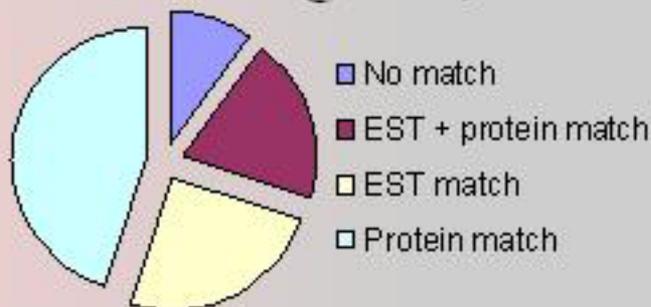
Saccharomyces cerevisiae, 1996



Caenorhabditis elegans, 1998



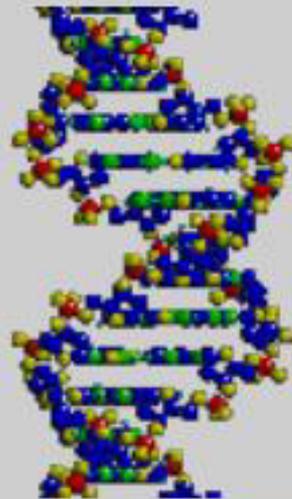
Drosophila melanogaster, 2000



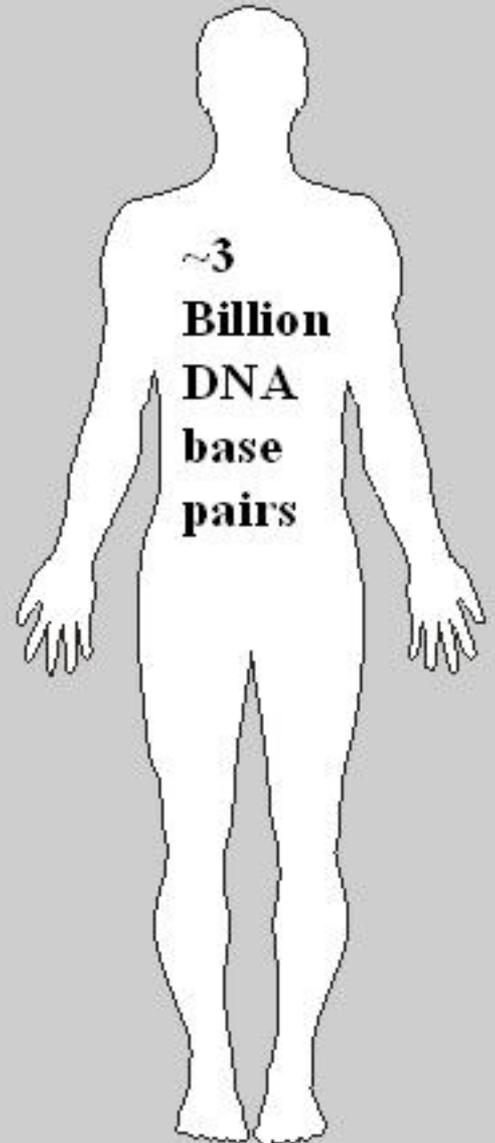
Deciphering the Genome

~35,000 genes

**~400 Million DNA
base pairs**



**~3
Billion
DNA
base
pairs**



**~1.7 Billion DNA
base pairs**



**~3 Billion DNA
base pairs**

Advantages of Using Fish in Genomic Investigations

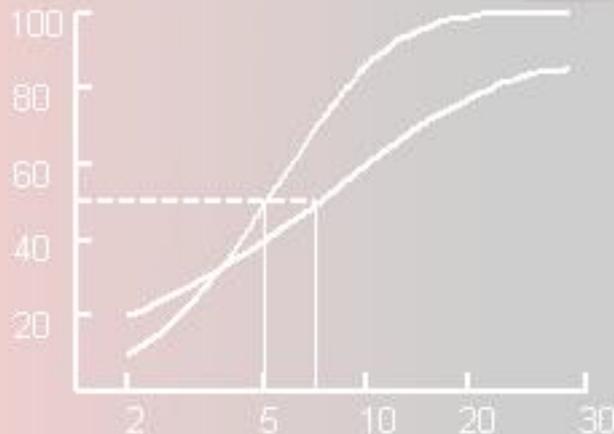
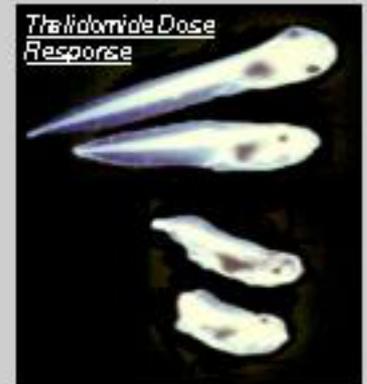
- Number of Genes in Fish \approx Mammal
- Number of Base Pairs in Fish $<$ Mammal
 - Intron sizes in Fish are greatly reduced
 - Intergenic distances in Fish are smaller
 - Very little repetitive DNA in Fish
- Highly conserved gene functions
 - Homology permits ID through hybridization & database comparisons
- DNA structures similar to human: splices falling in identical places
- Large number of *in vivo* data points/experiment (low cost replication)

What are Alternative Species?

2 years and
> \$350,000



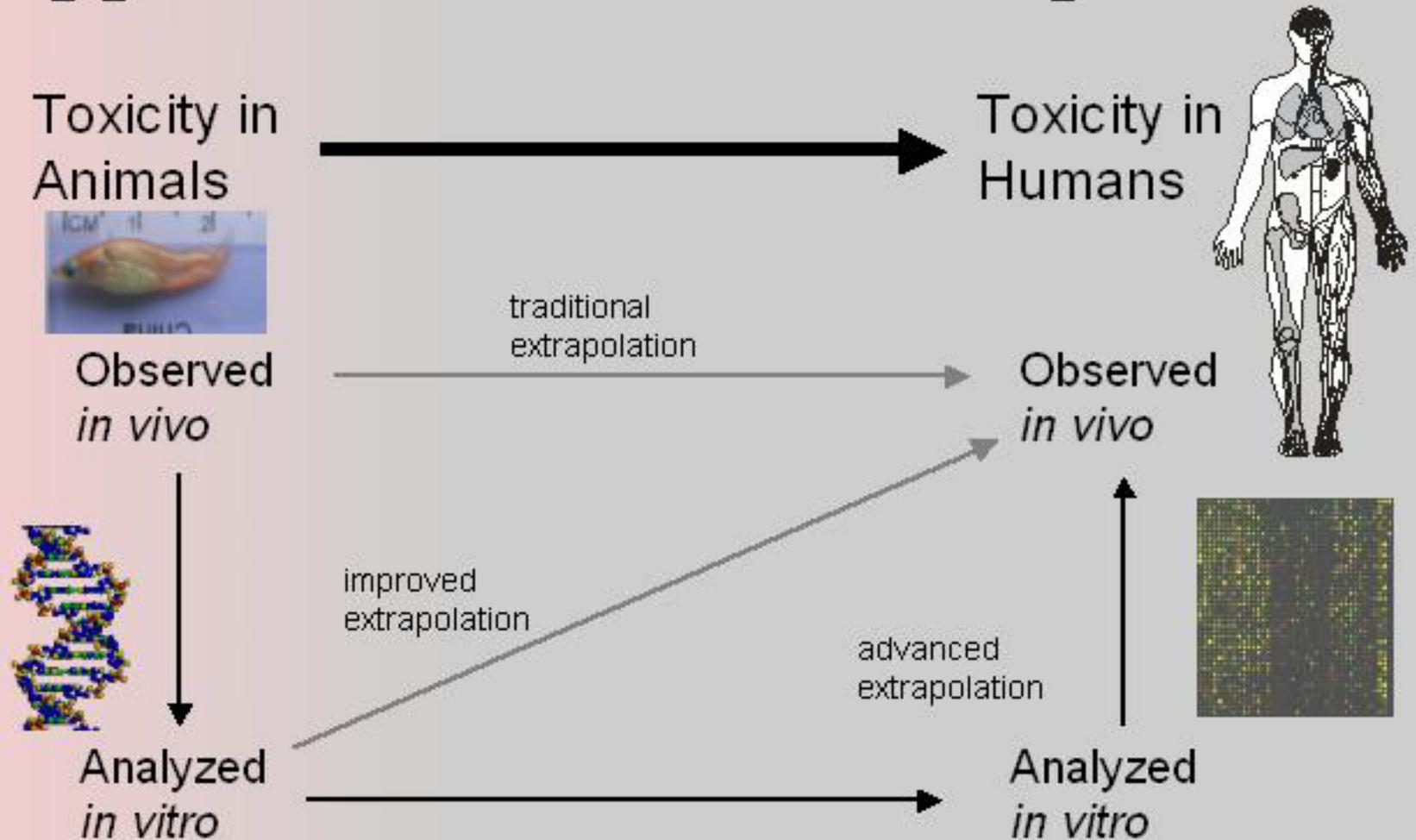
96-hours and
~\$2,000



Advantages

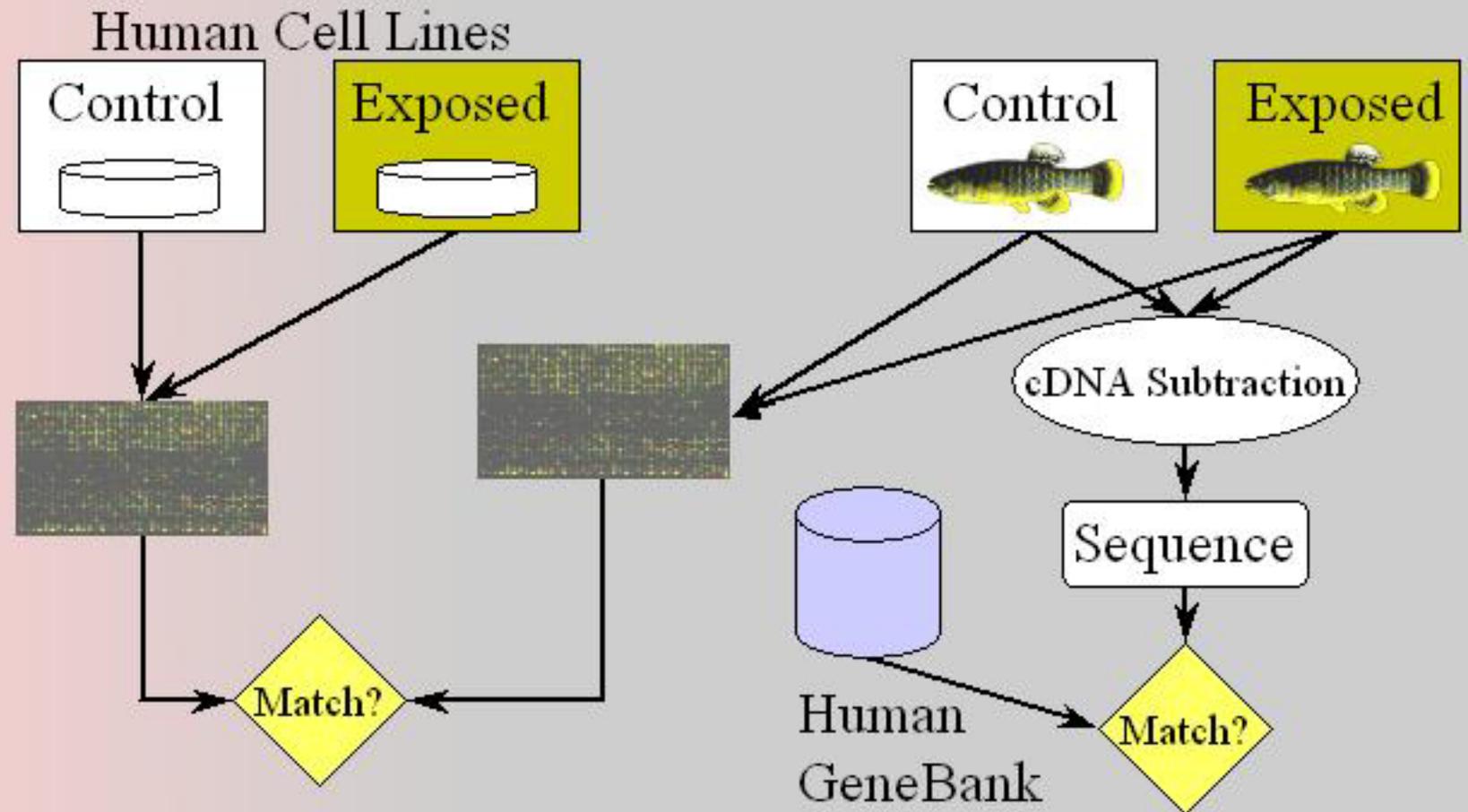
- Low Cost Bioassays
- Fast Turnaround Toxicity Testing
- Reduces the Use of Mammals

Application: Alternative Species



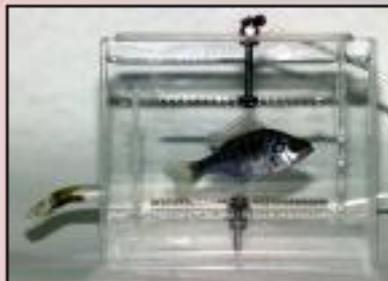
NEW: Gene Regulation & Protein Profile

Application: Gene Discovery and Function as Related to Toxicity



Application: Biomonitoring

- Biological Indicators of Exposure and Effect in Sentinel Species and Environmental Sentinel Biomonitors (*in situ*)
- Discover Potential Biomarkers of Exposure, Effect, and Susceptibility



USACEHR Plans for Genomics

- Develop High Throughput, Low-Cost, Mechanistically-Based Bioassays
- Identify and Validate Biomarkers of Exposure, Effect, and Susceptibility
- Toxicity Profiling Based on Microarray Technology & Alternative Species/Models
- Accelerate Discovery of Candidate Genes and Proteins Related to Toxicity
- Investigate Diapause Factors in Simple Species (Metabolic Downregulation)