NIEHS Metabolic Profiling
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Metabolic Profiling: An FDA Perspective

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Some general issues

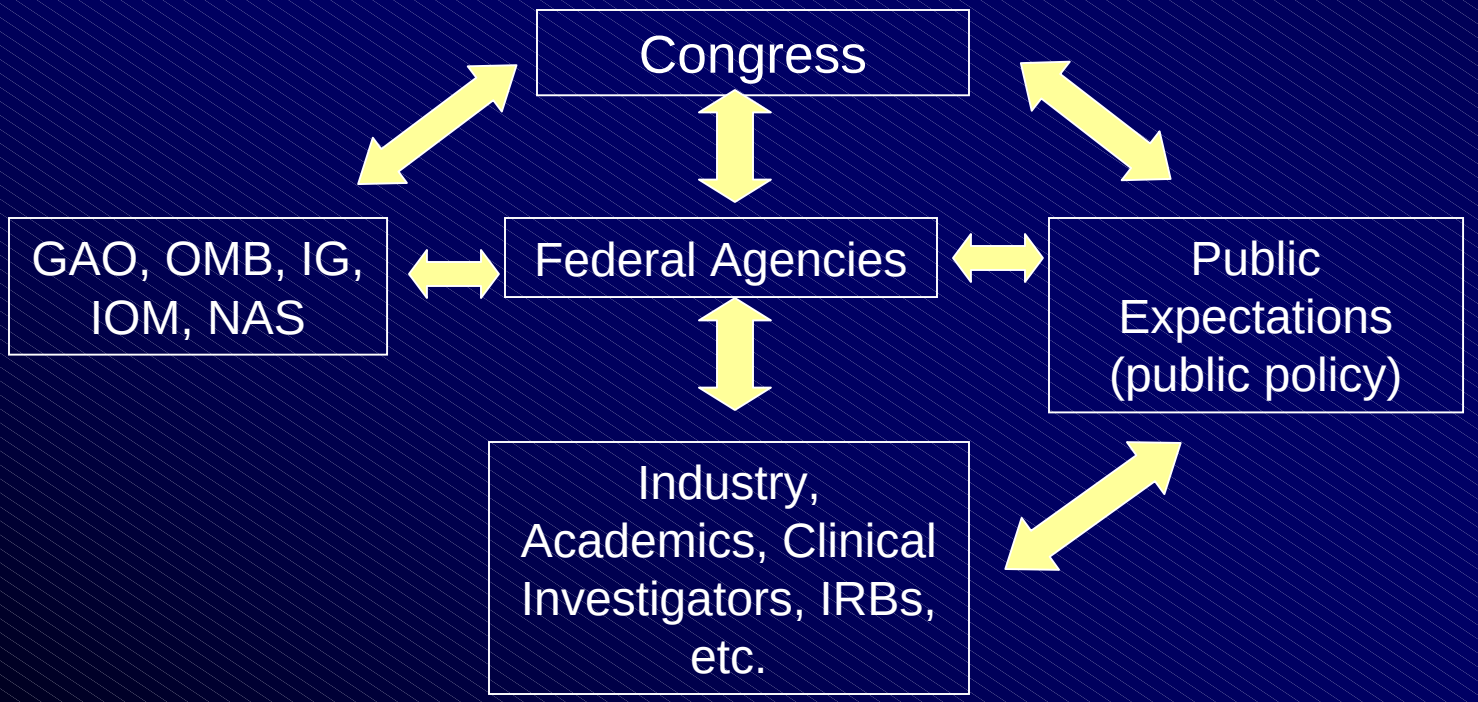
- The biotechnology revolution has greatly expanded our knowledge of cell and tissue biochemistry and function
- It is creating innovative products and therapies
  - Evaluation requires non-traditional approaches
- And providing opportunities for improved safety evaluation
- These changes may revolutionize our regulatory approaches

The Key Questions

Are we prepared for the challenges?

Will we capitalize on the opportunities?

Regulatory and Public Policy



- patient groups
- consumer groups
- ethicists
- clinical study participants
- media
- biotech/pharma industry
- internet
- venture capitalists

FDA Policies and Authorities

- Centers for:
  - Drugs
  - Food Safety & applied Nutrition
  - Devices & Radiological Health
  - Biologics
  - Veterinary Medicines
  - Toxicological Research
- Regulatory Affairs-Inspectors & Field Labs
- Metabonomics will have applications in each area, but focus may differ

Potential Impacts of Profile Information

- Pharmaceuticals-strong current focus
- Foods and Nutrition-direct relationship to metabolic endpoints
- Individualization of medications and diet
- Metabolic profile may reflect genetic characteristics, disease, probable health outcomes
  - Major opportunities for improved health
  - Major societal and ethical considerations

Public Acceptance will be a Key Factor

- Privacy issues are a major concern
  - Insurability, family & interpersonal relationships, employability can all be affected
- Benefits will be weighed against privacy issues and individual desires to know, or not know, probable health outcomes
- FDA must structure regulations and guidances that balance these factors

Industry Acceptance will Depend on Government Approaches and Public Opinion

- Industry must have clear definition of regulatory consequences of alternative development approaches
  - Their financial viability depends on it
  - FDA must provide clear guidance on regulatory applications of new scientific information
- Industry must respond to public perceptions
  - Use of their products depends on it
  - Public participation in product development depends on it

Careful attention must be given to both science and public perception

- Including terminology and language
  - "Profiling", for example, may have a negative connotation--eliciting thoughts of:
    - racial profiling
    - religious profiling
    - socioeconomic profiling
- Regulatory implementation needs to include input from all "stakeholders", including the public
  - FDA Advisory Committee system provides for this
  - The "scientific" Advisory Committees need to provide a bridge between the science, the public, and regulatory implementation

To implement new technologies effectively:

Need to move all aspects simultaneously

- Scientific
- Societal
- Legal
- Regulatory

The Role of FDA (1)

The FDA Does Not:

- regulate the practice of medicine
- direct the development of new technology
- set public policy

The Role of FDA (2)

FDA can play a major role in implementing new approaches and technologies by:

- Providing forums for discussion among government, industry, academia, and the public
- Providing clear definition of regulatory requirements, expectations, and consequences
- Providing guidances on implementation and application

A specific opportunity

- Genomics, proteomics, and metabonomics technologies have the potential to revolutionize safety assessment

They provide the potential for:

- Molecular biomarkers that link laboratory studies to human outcomes ("bridging biomarkers")
- Simultaneous measurement of entire cellular classes of molecules ("-omics" technologies)
  - Can monitor complete biochemical pathways rather than single biomarkers

Current approach to safety evaluation

Treat for various durations and measure or observe:

- Behavior/appearance/body weight
- Clinical Chemistry
- Hematology
- Histopathological alterations

Conduct special tests for:

- reproduction & development
- cancer
- mutation
- neurotoxicology, immunotoxicology
- etc.

Current practice: biomarker categories

- Cellular integrity
  (AST, ALT, AP, CPK, troponins, etc.)
- Function/homeostasis
  (BUN, creatinine, electrolytes, BSP, cell type, body & organ wts., etc.)
- Damage/stress-response
  (Morphology, cellular host defense responses, apoptosis markers)

Nonclinical Toxicological Practice

- Major Limitation: Uncertainty of quantitative extrapolation from laboratory models to the human
- Major Opportunity: Bridging biomarkers that permit monitoring of functional pathways, damage, and damage-response in both humans and laboratory models
  - *Human markers must be minimally invasive*

Opportunities for improved biomarkers

- Cellular integrity
  - Systematic i.d. of cell/tissue-specific markers
- Function/homeostasis
  - Pathway monitoring (**metabonomics**, proteomics, expression arrays)
- Damage & damage-response
  - Expression arrays & proteomics for discovery
  - Knowledge-based: apoptosis signals; cyto- and chemokines

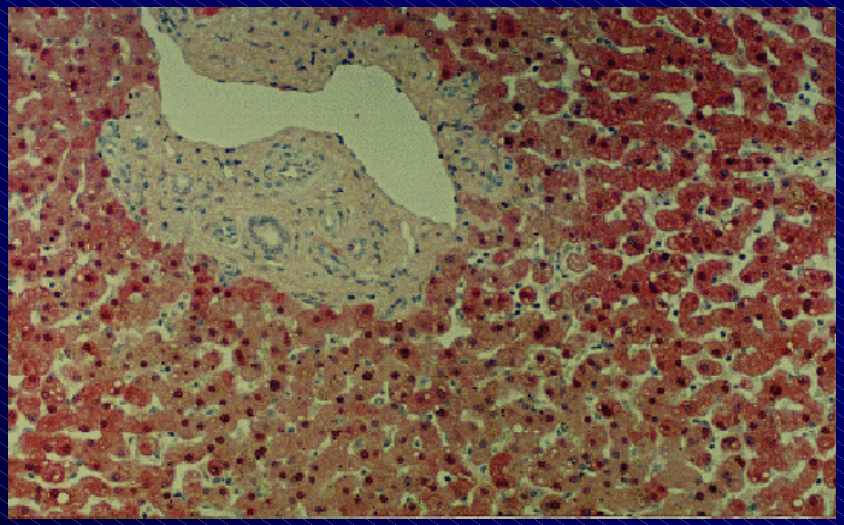
Biomarkers can be integrated with other technical advances

- "Humanized" laboratory models with human molecular targets
- Noninvasive pathology and functional monitoring *via* imaging of molecular biomarkers
- Identification of genetic variations that modify sensitivity of humans to disease and treatments

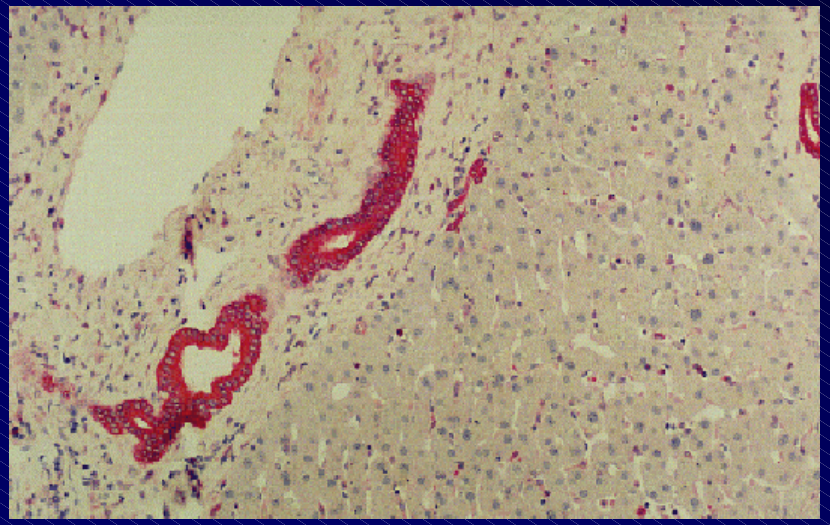
Biomarkers of cell and tissue integrity: a "ripe" opportunity

- Biomarkers of cellular integrity are an indispensable element of toxicological assessment and clinical practice
- Those markers developed in the 1950s have "stood the test of time"
- No systematic approach to identification & application of tissue-specific markers of integrity has yet been undertaken
- Proteomic, metabonomic, & other new tools provide an exciting opportunity to undertake such a systematic approach

Immunohistochemical Localisation of GST Forms in The Liver



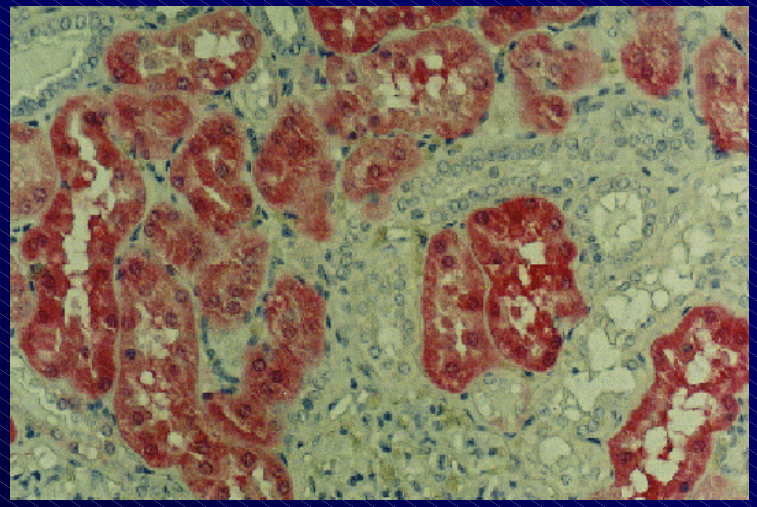
α GST in Hepatocytes



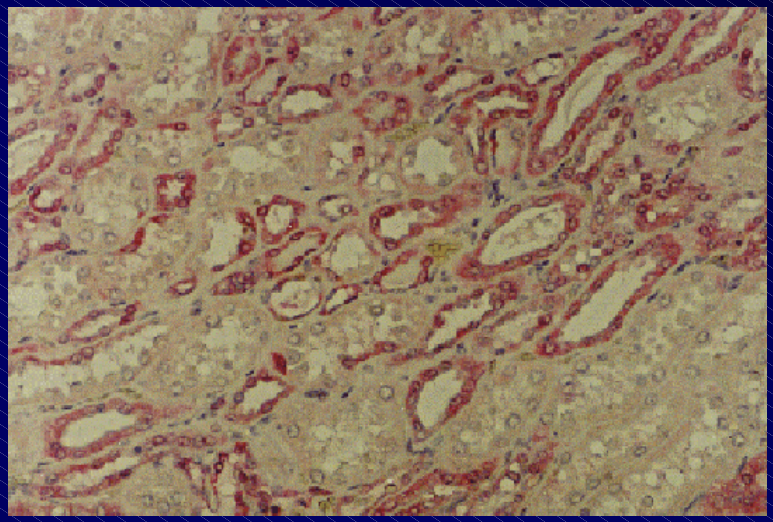
π GST in Bile Duct Epithelium

(Courtesy of Biotrin International)

Immunohistochemical Localisation of GST Isoforms In The Human Kidney



αGST in Proximal Tubules

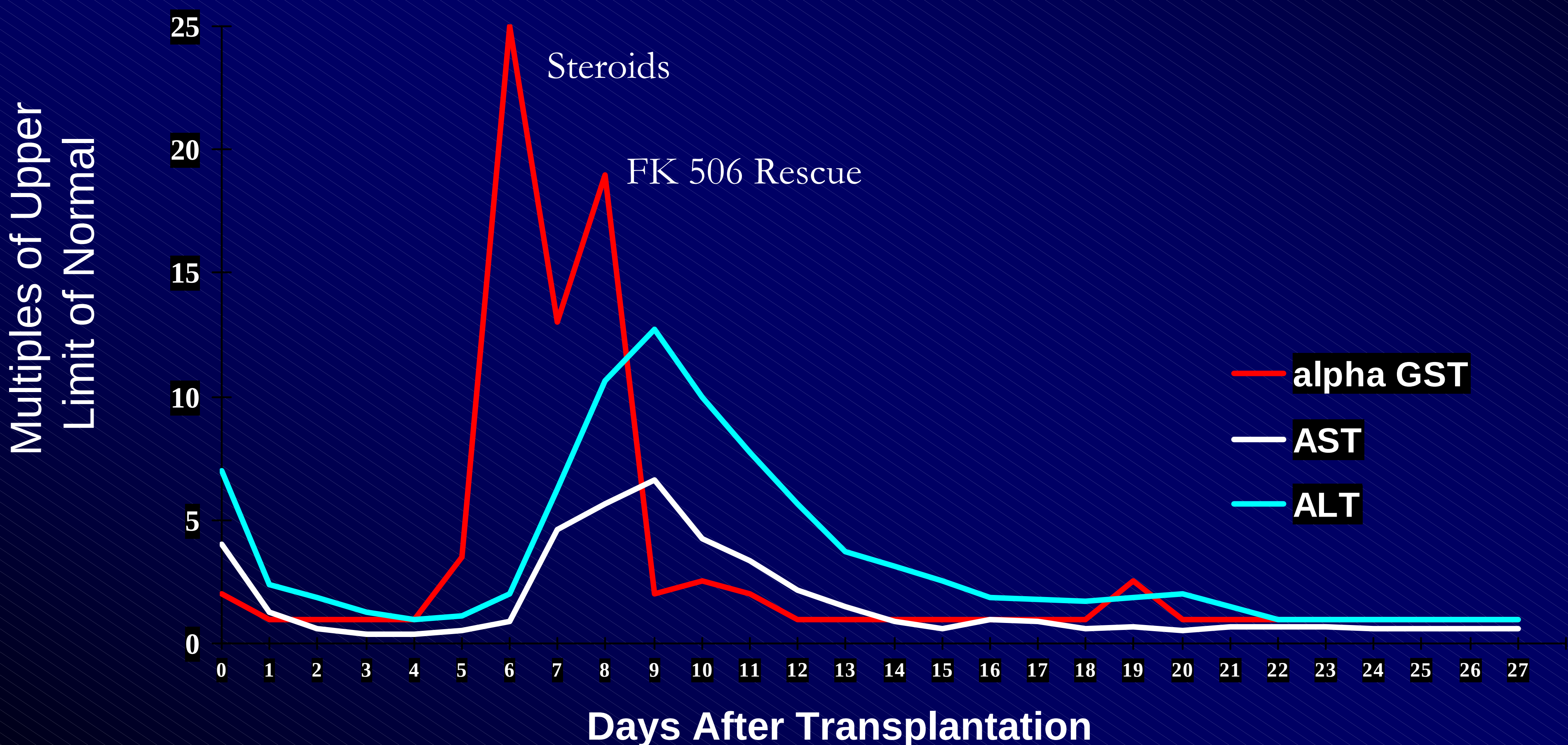


πGST in Distal Tubules

(Courtesy of Biotrin International)

- **Q:** What makes an ideal biomarker?
- ***A*:** It depends on your application.

Alpha GST Levels During Acute Steroid-Resistant Rejection



(Courtesy of Biotrin International)

Value of accessible cell- and tissue-markers of injury

- A set of markers, specific to key cell and tissue types, or characteristic of a particular mechanism of injury, could provide:
  - A minimally-invasive means to monitor cell and tissue damage in animals and in humans
  - A means to identify those tissues in which damage is occurring or has occurred
  - Information about mechanisms of injury
  - A marker of pathology that could be easily monitored as a function of time

How can we best develop and introduce new technologies?

- Through collaboration on common-interest science among FDA, industry, & public (government) and private institutions
  - CRADAs and collaborations
  - ILSI Consortia: cancer bioassays, genomics
  - JIFSAN, PQRI
- By allocating resources to foster innovation in regulatory science

Consortium approaches may be particularly useful for:

- Addressing sensitivity & specificity issues
- Quantitative correlations between biomarkers & pathology
- Comparative evaluation of biomarkers for same types of injury
- "omic" approaches to identification of appropriate markers for specific cell populations
- Validation & regulatory acceptance of suitable biomarkers

The Future

- Novel products and therapies that require specific regulatory evaluation
- "Bridging biomarkers" to monitor key damage responses in laboratory models and humans
- Reliable estimates of human risk from laboratory studies
  - Safer and better products
- Integrated studies of efficacy
- Identification of sensitive individuals
  - Protection of sub-populations at risk of adverse reactions