

NIEHS Metabolic Profiling
May 15, 2003
Research Triangle Park, NC

Metabolic Profiling: An FDA Perspective

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for

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Some general issues

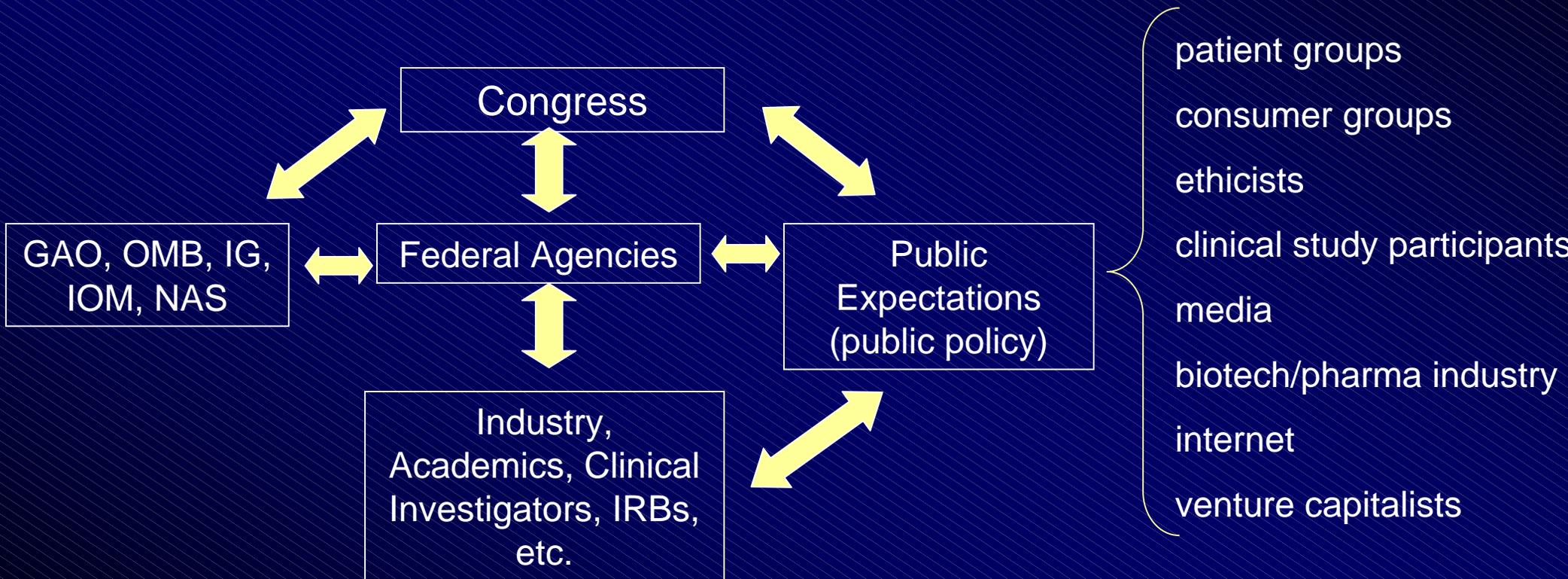
- The biotechnology revolution has greatly expanded our knowledge of cell and tissue biochemistry and function
- It is creating innovative products and therapies
 - Evaluation requires non-traditional approaches
- And providing opportunities for improved safety evaluation
- These changes may revolutionize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

The Key Questions

Are we prepared for the challenges?

Will we capitalize on the opportunities?

Regulatory and Public Policy



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

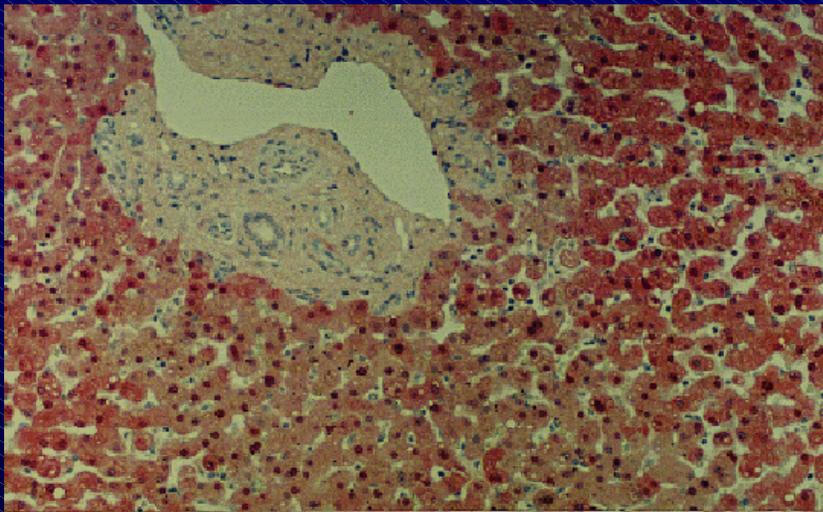
Biomarkers can be integrated with other technical advances

- “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

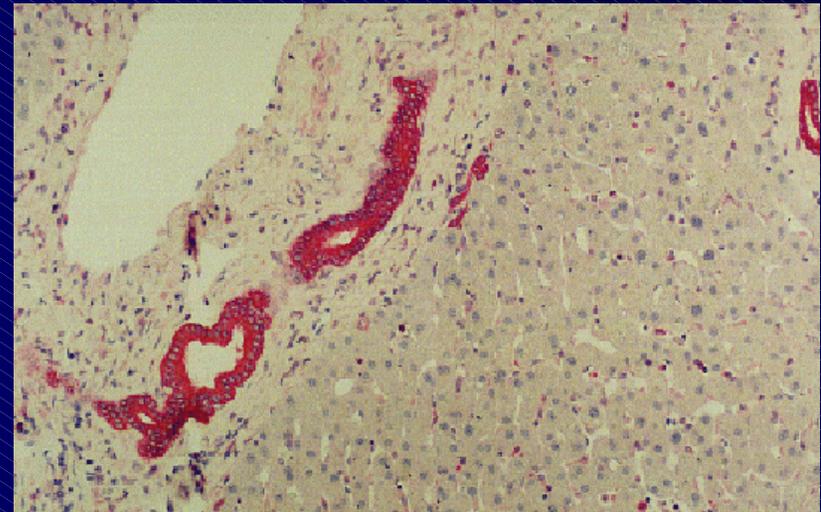
Biomarkers of cell and tissue integrity: a "ripe" opportunity

- ▶ 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



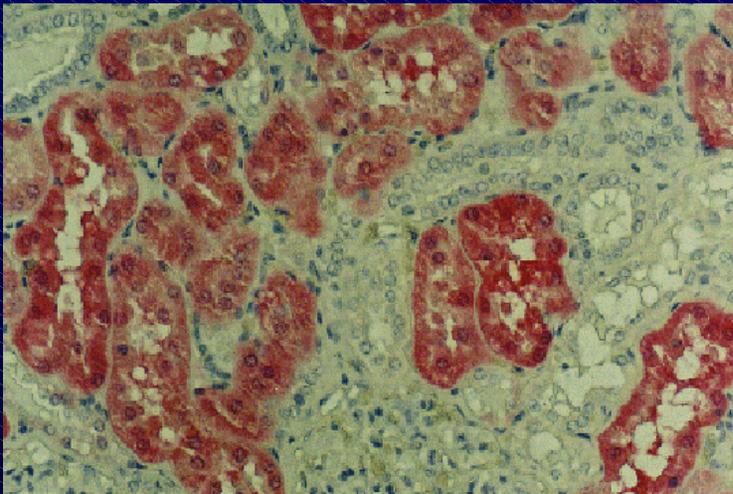
α GST in Hepatocytes



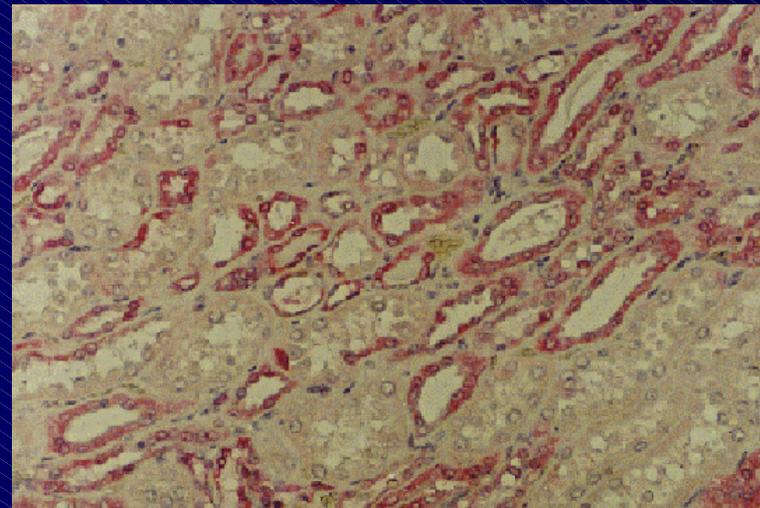
π GST in Bile Duct Epithelium

(Courtesy of Biotrin International)

Immunohistochemical Localisation of GST Isoforms In The Human Kidney



α GST in Proximal Tubules

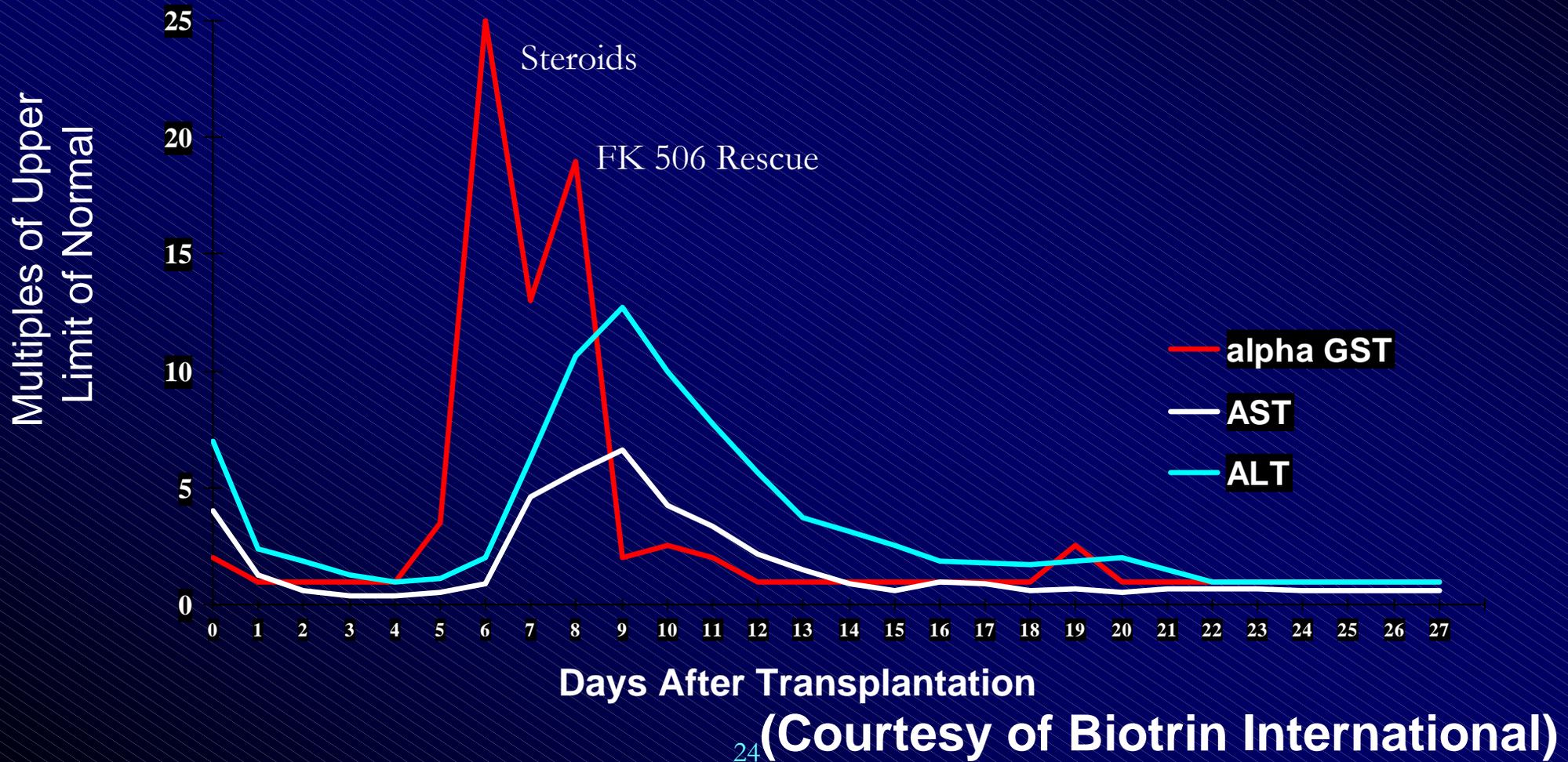


π GST in Distal Tubules

(Courtesy of Biotrin International)

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

Alpha GST Levels During Acute Steroid-Resistant Rejection



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