Biosketch

Solomon Iyasu, MD, MPH is the Director of the Office of Pharmacovigilance and Epidemiology, Office of Surveillance and Evaluation, Center for Drug Evaluation and Research, US Food and Drug Administration (FDA) with expertise in medical epidemiology, postmarket medical product safety assessment and regulation of medical products. Dr. Iyasu has been with FDA since 2002 and has worked in pediatric drug development and safety evaluation, post market passive and active medical product safety surveillance systems, development and application of pharmacopidemiology safety studies and building regulatory drug safety research programs. Prior to FDA, he worked at the Centers for Disease Control and Prevention conducting perinatal and pediatric epidemiology studies to evaluate pregnancy and infant outcomes. Dr. Iyasu has published several scientific research papers and book chapters pertaining to medical product safety, regulatory policy and public health. Dr. Iyasu is trained in medicine, epidemiology and completed a residency in Preventive Medicine.

Abstract: none
On February 25, 2000, Arthur Karmen, Director of the Clinical Laboratories at the Hospital of the Albert Einstein College of Medicine, in Bronx, New York, the well-known clinical chemist and a pioneer in the use of chromatography for the analysis of biologically important substances, celebrated his seventieth birthday.

Arthur Karmen was born and studied in New York City, receiving his M.D. degree in 1954 from New York University. After a two-year residency in internal medicine at Bellevue Hospital, in New York City, he joined the research staff of the National Heart Institute, National Institutes of Health (N.I.H.), in Bethesda MD, where he worked for seven years, first in the Laboratory of Metabolism and then in the Laboratory of Technical Development. From 1963 to 1968 he was associated with the Division of Nuclear Medicine at Johns Hopkins University, in Baltimore MD. Since 1968 he has been a clinical pathologist and Director of Laboratories, first at New York University Medical Center and from 1971 on, at Albert Einstein College of Medicine. Since 1973 he has also served as the Chairman of the Department of Laboratory Medicine of the University.

Dr. Karmen’s probably most important contribution to clinical diagnostics originated in 1952, while still a medical student, working on a summer project: he demonstrated using paper chromatography the presence of elevated levels of glutamic oxaloacetic transaminase and glutamic pyruvic transaminase (aspartate and alanine aminotransferases) in patients immediately after an acute myocardial infarction. Subsequently he developed a spectroscopic assay for their measurement in serum which essentially is still used universally for diagnostic testing today. All those millions who suffered a heart attack can ultimately thank Dr. Karmen for the early diagnosis of their illness.

In gas chromatography Dr. Karmen pioneered in the development of several ionization detectors such as the radiofrequency glow discharge detector; non-radioactive, self-sustained electric discharge argon and helium ionization detectors; and most importantly, the alkali-flame thermionic detector selective for halogen- and phosphorus-containing organic compounds. He was also instrumental in the development of a series of methods for measuring radioisotopes in chromatographic effluents.

As the head of large clinical laboratories Dr. Karmen had been active in solving the problems associated with providing large numbers of assays to an extended medical community and improving the reliability of the various methods used for the testing of biological samples.

For his achievements in chromatography and in biochemical investigations Dr. Karmen received the Alfred Sloan Award for Cancer Research (1957), the Van Slyke Award of the New York Metropolitan Section of the American Association of Clinical Chemists (AACC) (1979), the M. S. Tswett Medal of the International Symposium on Advances in Chromatography (1981) and the 19th Annual AACC Award for Outstanding Contributions to Clinical Chemistry (1991).

By gifts, interests and innovative contributions, Dr. Karmen is genuinely a Renaissance man physician, chemist, physicist and instrument maker. His strength in being able to deal with a wide variety of subjects stems from his exceptional knowledge of basic sciences. This foundation, his vast and solid understanding of fundamental scientific principles, allows him to develop and build new approaches in various fields of science. He is also a very resourceful colleague who does his best in helping his junior associates in their own scientific endeavors. In addition, he is a good and caring teacher, regularly organizing summer student programs, and has always been personally involved in the students’ assignments and projects. And last, but not least, he is a friend on whom one can rely, a most colorful person and a wonderful entertainer.
In the name of his many friends, of the editors and publishers of Chromatographia and of the chromatographic community at large, we extend our heartfelt congratulations to Professor Arthur Karmen on the occasion of his seventieth birthday, wishing him many more productive years and further enjoyment of life.

Abstract: Rapid Spectrophotometric Assay of Serum Transaminases

Biochemists AE Braunstein, P P Cohen, and J Awapara in the 1940s discovered and measured enzymes that converted amino acids to keto acids when reacted with keto glutarate, and found enzyme activities in many tissues such as heart and skeletal muscle, liver, kidney, and others. When tissues were injured by chemicals, hypoxia, or other processes, enzymes were released from tissue cells into the circulation and their activity could be detected in plasma or serum. In 1952-3 clinical cardiologist John S Ladue and research cardiologist Felix Wroblewski recruited a NYU medical student, Arthur Karmen, to measure serum activity of aspartate transaminase as an indicator (now would be called biomarker) of acute myocardial infarction. Karmen first used the tedious process of quantitative paper chromatography to measure serum oxalacetate produced from aspartic acid, then developed the rapid, five-minute assay of “SGOT” activity, with ideas of Severo Ochoa using the coupled reaction of reducing oxaloacetate to malate with added malate dehydrogenase and reduced diphosphopyridine nucleotide (DPNH, now called nicotinamide adenine dinucleotide, reduced, NADH) to “pull” the reversible transamination reaction to rapid completion. The results were published in the Journal of Clinical Investigation in January 1955, although a shorter announcement appeared in Science in September 1954.
Biosketch

I am currently the Director of the Department of Transfusion Medicine and Hematology at the Ospedale Alessandro Manzoni, Lecco, in Italy.

I received my medical degree from the University of Milan, in 1991. In 1992 I obtained a research fellowship in the Transfusion Research Laboratory at the University of California, San Francisco, USA, where I carried out studies on the complications of blood transfusion. From 1993 to 2003 I was responsible of the Laboratory of Virology and the Viral Hepatitis Out-Patient Clinic at the Blood Transfusion and Transplantation Immunology Center – Ospedale Maggiore, Milano, Italy.

During the past ten years, I had quite an intense experience as member of the governing board of scientific associations. In 2010, I was appointed Scientific Committee member of the European Association for the Study of the Liver (EASL) and became member of the Board of Directors of the Italian Foundation for Research in Hepatology (FIRE). These mandates ended in 2013. From February 2007 to February 2010 I served as Secretary General of the Scientific Board of the Italian Association for the Study of the Liver (AISF). Since 2011 I have been a member of the Steering Committee of the Italian Society of Transfusion Medicine and Immunoematology (SIMTI), and my mandate will end at the end of 2014.

My main scientific interests focus on the epidemiology, diagnosis and treatment of viral hepatitis and chronic liver disease, as well as on different aspects of blood transfusion safety and efficacy. I have published numerous scientific papers on these topics, and served on several related committees, advisory boards, and editorial boards of medical journals.

Abstract: What’s Normal?

It is generally agreed that the traditional approach of defining universal normal limits of laboratory values, valid for all patients and in all clinical situations, should be abandoned.

The concentration of liver enzymes is expressed as a quantitative variable, and therefore the concept of different cutoff values corresponding to different levels of sensitivity and specificity seems more appropriate than the generic concept of normality, which depends from a dichotomous definition. In this regard, the advantages of a continuous rather than a dichotomous approach are well documented in the clinical as well as in the research setting. Analytical methods and the criteria for the choice of reference populations need to be consistent. Until approximately a decade ago, definitions applied for ‘normal’ ranges of serum ALT were highly variable. For example, the upper limit of normal (ULN) ranged between 30 and 72 U/L in a number of studies on hepatitis C. This variability depended from several factors, but primarily from the choice of the reference population. ULNs were defined prior
to introduction of identification of some common liver diseases, including hepatitis C and non-alcoholic fatty liver disease. Given the frequency of these conditions, mostly without obvious symptoms, the reference population included people with mild–moderate chronic liver disease. In fact the distribution of ALT values in the general population was skewed, the degree of skew being influenced by factors including gender, ethnicity and metabolic factors.

Several approaches have been undertaken to define normal ALT. These include the identification of low-risk reference populations, mortality studies whereby the relative risk of mortality from liver disease was assessed as a function of ALT, and response studies based on data collected in patients cured from liver disease. All three approaches suggested that the reasonable cut off values for the evaluation of patients with suspected liver disease are around 20 U/L in women and 30 U/L in men.

Several factors, however, still need to be addressed. Methodological variability, related to the introduction of new assays based on different reaction conditions, have an impact on the definition of reference values. Furthermore, the effectiveness of diagnostic-therapeutic strategies based on different cut values can only be assessed by large randomized and/or surveillance studies. Such studies are mostly lacking in the field of liver disease, including drug induced liver injury.
Biosketch

Dr. Dufour is Consultant, Pathology and Hepatology, at Veterans Affairs Medical Center, Washington DC, and Emeritus Professor of Pathology, George Washington University. He has published over 200 articles, abstracts, and book chapters, mostly in the areas of laboratory testing for liver disease and endocrine disorders. He was lead author on the National Academy of Clinical Biochemistry/AASLD Guidelines for Use of Laboratory Tests in Diagnosis and Monitoring of Liver Disease.

Abstract: Down with the Tower of Babel

Alanine Aminotransferase (ALT) is the most widely used marker for recognition of hepatocellular damage. Liver injury is usually recognized by intermittent or persistent elevation in ALT activity above the upper reference limit (upper limit or normal, ULN). This presentation will review briefly the theory of population-based reference intervals, the methods used to establish them, and data on currently used and likely appropriate values of ALT for excluding liver disease. For a number of parameters, including weight, blood pressure, and markers of carbohydrate and lipid metabolism, population-based reference limits have been found inappropriate markers of disease risk. The presentation will conclude with a summary of published data on whether health-based ALT reference limits may be of benefit in evaluating presence of or monitoring the course of liver disease.
Nira Pollock, M.D., Ph.D., D(ABMM)  
Associate Medical Director, Infectious Diseases Diagnostic Laboratory, Boston Children’s Hospital  
Division of Infectious Diseases, Beth Israel Deaconess Medical Center  
Assistant Professor of Medicine, Harvard Medical School

Biosketch

Dr. Pollock is currently the Associate Medical Director of the Infectious Diseases Diagnostic Laboratory at Boston Children's Hospital and a member of the Infectious Diseases Division at Beth Israel Deaconess Medical Center, both affiliated with Harvard Medical School. Dr. Pollock's training includes an MD/PhD from UCSF, residency in internal medicine at Brigham and Women's Hospital in Boston, infectious diseases and clinical microbiology fellowships at Beth Israel Deaconess Medical Center in Boston, and a Master's of Medical Sciences (MMSc) from Harvard Medical School. Dr. Pollock has an active research program focused on the development and evaluation of novel diagnostic tests for infectious diseases and related applications, particularly those meant for use at the point-of-care. She has collaborated since 2009 with Diagnostics For All (a non-profit company in Boston, MA) and George Whitesides' group (Harvard Chemistry Department) to develop and validate a paper-based point-of-care fingerstick transaminase test.

Abstract

A paper-based test for rapid visual measurement of alanine aminotransferase (ALT) in fingerstick and venipuncture samples

Nira Pollock, MD, PhD (Boston Children’s Hospital/Beth Israel Deaconess Medical Center) and Diagnostics For All (Boston, MA)

We have developed a paper-based, multiplexed, microfluidic assay to visually measure alanine aminotransferase (ALT) in a fingerstick sample, generating rapid, semi-quantitative results. Early pre-clinical testing on clinical serum and whole blood specimens demonstrated that the paper-based device could yield accurate visual measurements with >90% accuracy (Pollock and Rolland, Science Translational Medicine 2012) and was therefore ready for field testing. Thereafter, the first fingerstick evaluation of the test was performed in 600 HIV-infected persons receiving care in a busy HIV clinic in Vietnam, considered an ideal target setting for application of this test. That evaluation study (Pollock et al, PLoSOne 2013) demonstrated that the device operation and reading process were both feasible and extremely reproducible in this target setting, but highlighted the need for further device optimization to reduce hemolysis rates and improve the accuracy of the device. The device subsequently underwent extensive optimization and recalibration against an automated reference standard, Abaxis Piccolo Xpress.
We have recently completed a validation study of the optimized ALT test as performed in ambulatory outpatients with liver disease or on hepatotoxic medications, each of whom required ALT monitoring as part of routine care. The goals of this study were to evaluate the performance of the optimized paper-based test for measurement of ALT levels in both fingerstick blood and venipuncture serum for patients with a range of baseline ALT levels, as compared to results of testing the serum on two FDA-approved automated platforms in wide clinical use (Abaxis Piccolo and Roche/Hitachi). As a result, we were able to evaluate the impact of sample type on results of the paper test, as well as to compare performance of the paper test to that of each automated platform. We also assessed the potential utility of cell-phone cameras to allow remote interpretation of the paper test results.
Leonard B. Seeff, M.D.
Consultant
Einstein Healthcare Network
mahler68@hotmail.com

Biosketch

A graduate in 1961 of the University of the Witwatersrand Medical School, Johannesburg, South Africa, Dr. Seeff came to the United States in 1964 to work with Dr. Hyman J Zimmerman, then Chief of Medicine at Mt Sinai Hospital, Chicago, Ill. A year later, he moved with Dr. Zimmerman to the VA Medical Center in Washington DC to complete training in general medicine and a fellowship in GI/Hepatology. Thereafter, he initiated and coordinated 4 large-scale VA cooperative studies on post-transfusion hepatitis B and C funded by the VA, NIAID, NHLBI, and NCI. He moved to the VA Medical Center in Boston in 1968, returning to the Washington VA Medical Center in 1971 as Assistant Chief of Medicine for 8 years. He was appointed Chief of Gastroenterology and Hepatology in 1979 and Co-Director of the VA Medical Center-Georgetown University-NIH Gastroenterology & Hepatology Training Program. He continued research in viral hepatitis B and C, focusing on the natural history of the two viral diseases. In 1984, he was appointed Professor of Medicine at Georgetown University School of Medicine. In 1998, he joined NIDDK, NIH as Senior Scientist for Hepatitis Research where he helped develop and oversee several NIDDK-funded multicenter studies such as the HALT-C Trial and the Drug-Induced Liver Injury Network (DILIN), as well as organize a number of meetings and Workshops (Consensus Development Conferences on Hepatitis C, Drug-Induced Liver Injury, Complementary and Alternative Medicine and Liver Disease, Liver Cancer, HCV and the Kidney, HCV in Prisons, etc.). In 2009, he retired from the NIH but then joined the Food & Drug Administration (FDA) as a consultant in Hepatology. He is a long-time member of the American Association for the Study of Liver Disease (AASLD) where he served as Councilor-at-Large from 1997-2000 and where he has served on several committees. He is the senior author of the AASLD guidelines for the treatment of hepatitis C as well as other guidelines. His primary research interests are viral hepatitis and drug-induced liver injury. He has received a number of awards and has published over 160 articles and over 50 chapters.

Abstract: What Should Be the Baseline and Trigger ALT Values For Potential Drug-Induced Liver Injury?

Definitive drug-specific biomarkers of impending drug-induced liver injury (dili) remain elusive, so consideration for possible developing dili continues to depend on identifying rising levels of serum enzymes, particularly ALT, that develop within 6 to 9 months of beginning drug treatment. However, the ALT as a trigger of concern for dili has both shortcomings and uncertainties. First, an elevated ALT level is a non-specific marker of liver (and sometimes muscle) injury, requiring that all other causes of liver injury be eliminated before considering dili as the source. Second, there is no consensus agreement on the level of increase of ALT that should spark concern for possible impending dili, as well as the baseline (comparator) value against which the elevation should be measured. Third, recent therapeutic advances have introduced drugs for persons with chronic liver disease, largely chronic hepatitis C, who present with persistently elevated ALT levels, the very marker used to identify dili. To circumvent these limitations, the compromise is to develop practical criteria that can hopefully be generally accepted. The first issue is what the baseline, comparator ALT level should be; baseline testing may reveal a “normal” value, although there is debate regarding what that value actually is,
or it may be abnormal from the start. To deal with both of these problems, a better approach is to use each subjects’ own ALT value as the comparator value, obtained at the outset if the subject is HCV-negative, or if HCV-infected and antiviral treatment is begun, after the initially-abnormal ALT value reaches the nadir normal value following treatment. Thereafter, the suggested ALT trigger for possible dili should be 3X the comparator if <100 U/L but 2X if 100 IU/L or more. Further details will be presented.
Biosketch

Ted Guo, Ph.D., is a statistical reviewer and researcher at the Office of Biostatistics under Center for Drug Evaluation and Research (CDER) of the FDA. He was educated in Tong-Ji University in Shanghai, PRC, and graduated with a BS and MS majoring in mathematics and statistics in 1982 and 1985, respectively. He received a Ph.D. degree in 1991 from the Medical College of Virginia, Virginia Commonwealth University. His recent focus is the development of a software solution for the evaluation of drug-induced liver injury named eDISH. He is creating a software tool for the evaluation of adverse events reported to FDA’s AERS database using the Likelihood Ratio Test (joint with Ram Tiwari, Ph.D.) named LRT.

Abstract: Development of eDISH 2

In evaluation of drug-induced liver injury, it is crucial to get the data input right, get the thought process right, and get the right tool that implements the thought process. The tool, eDISH was thus created and continues to evolve to meet the real life challenges and demands. John Senior and Ted Guo at the FDA collaborate using combined knowledge in medicine, statistics and computer in the development of eDISH.
Dr. Chalasani currently serves as David W. Crabb Professor of Medicine and Cellular & Integrative Physiology at Indiana University School of Medicine and is the Director of its Division of Gastroenterology and Hepatology. He completed his medical education in India and subsequently completed internal medicine residency and gastroenterology and hepatology subspecialty training at Emory University in Atlanta. Two broad themes to his research focus are nonalcoholic fatty liver disease and idiosyncratic drug induced liver injury and he has made several important contributions to both of these areas. He is the Associate Editor for Gastroenterology and he has previously served or currently serving on the editorial board of many journals including *Gastroenterology, Hepatology, Clinical Gastroenterology and Hepatology, American Journal of Medicine, Journal of Clinical Gastroenterology, and Nature Reviews Gastroenterology & Hepatology*. He has been funded by the National Institutes of Health since 1998 for conducting investigations related to liver disease. He has published over 170 original publications, 20 textbook chapters and 19 editorials and commentaries. He was the lead author for the multisociety practice guideline on the diagnosis and management of nonalcoholic fatty liver disease published simultaneously in multiple GI journals in June 2012. He was the lead author for the American College of Gastroenterology Practice Guideline for the diagnosis and management of drug induced liver injury which was published in June 2014.

**Abstract: The American College of Gastroenterology (ACG) Practice Guideline for the Diagnosis and Management of Idiosyncratic DILI**

The American College of Gastroenterology (ACG) commissioned a working group led by Dr Chalasani to develop a practice guideline for the diagnosis and management of idiosyncratic DILI by the clinical practitioners. This working group consisted of Drs. Chalasani, Hayashi, Bonkovsky, Navarro, Lee, and Fontana, all members of the Drug Induced Liver Injury Network. Drs. Paul Watkins and Neil Kaplowitz were invited to be part of this working group but due to time and effort conflicts they were unable to participate in the working group. The ACG uses GRADE system (Grading of Recommendations, Assessment, Development and Evaluation) for assigning strength and quality of evidence for each recommendation made. Strength of recommendation is either “strong” or “conditional” whereas the quality of evidence is categorized into “high”, “moderate”, “low”, or “very low”. The practice guideline has a total of 13 recommendations that cover (a) work up of a suspected hepatocellular, mixed, or cholestatic DILI; (b) when to consider a liver biopsy; (c) rechallenge/reexposure; (d) management including prompt withdrawal and specific treatment; (e) DILI due to herbal and dietary supplements; and (f) DILI in individuals with chronic liver disease. The practice guideline discusses about biochemistry monitoring in patients with chronic liver disease when they receive a potentially hepatotoxic agent. While majority of the recommendations received a “strong recommendation”, there were some that received “conditional
recommendation”. Not unexpectedly, however, the quality of evidence to large part ranged between “very low” and “low”.

Reference

Patrick Kirby, PhD  
Toxicologist  
Department of Drug Safety  
Takeda Pharmaceuticals

Biosketch

Patrick Kirby is a toxicologist at Takeda Pharmaceuticals in the department of drug safety. He is responsible for biomarker activities at Takeda Boston. He is also active in the Predictive Safety Testing Consortium (PSTC) and is the co-chair of the PSTC Hepatotoxicity working group. He received his PhD in genetics from La Trobe University in Victoria, Australia and completed his post-doctoral training in gene therapy at Stanford University.


Kirkby1, Schomaker4, Lawrence3, King2, Sauer2, Cisnierz2, Marcinak1, Gao1, Robinson-Gravatt4, Kullak-Ublick5, Joos6, Knorpp6, Göpfert6

1Takeda, 2C-Path, 3Amgen, 4Pfizer, 5Novartis, 6Natural and Medical Sciences Institute

In collaboration with the Safer and Faster Evidence-based Translation Consortium (SAFE-T) the Predictive Safety Testing Consortium (PSTC) characterized normal reference ranges for 12 liver biomarkers in 81 healthy volunteers (HV). The data generated within this study will be used by PSTC and SAFE-T as part of their Drug Induced Liver Injury (DILI) biomarker qualification process. Subjects were recruited at the Jasper clinic in Kalamazoo, MI. There were 40 males and 41 females with 41 subjects in the 20-39 yr range and 40 patients in the 40-70 yr range. The population was 84% white and 16% non-white. The mean BMI was 27 with 69% of the population overweight/obese by CDC criteria. Plasma and serum samples were collected over 21 days on days 1, 6 (±1), and 20 (±1). There were 263 samples for quantitative biomarker measurement with twelve technically validated immuno-(10) and colorimetric (2) assays generated by SAFE-T and affiliates. Arginase-1, LECT2, MCSF1R, prothrombin, paraoxonase-1, caspase-cleaved keratin18, full length keratin18, α-fetoprotein, osteopontin and GSTα were measured by immunoassay. GLDH and SDH were measured by colorimetric assay. The intra- and inter- subject variability was investigated using 3 serial samples over a 21-day course. 95th percentile was obtained as upper bound for normal range for all 12 liver safety markers, and the mean value was also obtained for all but K18. K18 had 93% of the samples below lower limit of quantification of the assay. The 95th percentile upper bound are as follows: arginase-1 (19.5 ng/ml), LECT2 (448 ng/ml), MCSF1R (571.6 ng/ml), prothrombin (86.3 µg/ml), paraoxonase-1 (690.8 ng/ml), caspase-cleaved keratin18 (260.2 U/L), full length keratin18 (122.8 U/L), α-fetoprotein (1.97 ng/ml), osteopontin (10.3 ng/ml), GSTα (60 ng/ml), GLDH (7.2 U/L) and SDH (7.7 U/L). Stratification factors such as gender, age or BMI did not demonstrate differences in reference ranges.
Biosketch

Lana joined the Office of Surveillance and Epidemiology (OSE) as the Associate Director for Executive Operations and Strategic Planning in August 2009. Her staff is responsible for long-range strategic planning, quality development and best-practice implementation as well as developing and implementing Office-wide training.

Prior to this position in OSE, Lana was the Director of the Quality Management Staff (QMS) in the Office of Executive Programs (OEP). Lana joined QMS in November 2000. The QMS was responsible for conducting quality assurance audits, as well as developing a quality system for the Center. She served as Acting Director from March 2002 until her selection as Director in February 2003.

Lana received her Masters degree in Public Health from the Uniformed Services University of the Health Sciences in 1993 (through an FDA-sponsored program). In 1998 she completed a year-long Excellence in Government Fellows Program with the Council for Excellence in Government (CEG).

In 2006, Lana was selected as a National Examiner for the Malcolm Baldrige National Quality Program administered by the National Institute of Standards and Technology, and completed three years as an examiner for the program. This opportunity afforded her the ability to bring additional insight about best practice in performance excellence back to the Agency.

Lana started her career with the FDA in September 1990. She served as a Project Manager for 6 years in the Division of Metabolic and Endocrine Products (DMEP) prior to being named as the Chief, Project Management Staff in the Division of Reproductive Products (DRUP). She was then named the Associate Director in DRUP, in which she served as a policy expert regarding FDAMA and PDUFA.

Abstract: Drugs, Chemicals, Hepatotoxins: Is it the Substance or the Person?

For many years, drug-induced liver injury (DILI) was the number one reason that drugs were either not approved and/or were removed from the market.

Unfortunately, there are many misconceptions about how DILI can be detected, how it is diagnosed, and how the findings are communicated. To date, for example, there is no consensus on the nomenclature nor how to assess causality. This discussion will center on some of these common misconceptions and fundamental questions that we still need to address.
Biosketch

John Senior, a native of Philadelphia (17 July 1927), attended the Central High School of Philadelphia (B.A., 1945), studied chemical engineering at Drexel University (1948), physics at the Pennsylvania State University (B.S., 1950), and medicine at the University of Pennsylvania (M.D., 1954). After internship and medical residency (1954-7), he was a clinical fellow in gastroenterology (1957-9), all at the Hospital of the University of Pennsylvania. He then was a National Institutes of Health Special Research Fellow at Harvard University and Massachusetts General Hospital (1959-62), where he worked out mechanisms of intestinal absorption of fats across the small intestinal epithelial cells into lymph and blood in the rat and man.

Returning to Penn, he established a Gastrointestinal Research Laboratory at the Philadelphia General Hospital (PGH), and worked on detection of viral hepatitis after transfusion of blood (“serum hepatitis”). PGH was the first hospital in the world to screen donor blood for a marker (“Australia antigen”) of hepatitis B and to exclude positive units from use, leading to the reduction of post-transfusion hepatitis incidence there by 65%. He worked closely with the discoverer of that antigen, Baruch Blumberg, who was awarded the Nobel Prize in Medicine or Physiology in 1976 for discovery of the hepatitis B virus.

Senior was elected to the Council of the American Association for Study of Liver Diseases in 1969, was its 25th President in 1973-4, and served on its Governing Board until 1979. He investigated use of computer simulation of patients for testing candidates for certification of medical competence by the American Board of Internal Medicine and National Board of Medical Examiners (part-time at the Presbyterian Hospital). He returned to Penn at Graduate Hospital, in 1974 to direct its Clinical Research Center, then opened a special treatment unit for serious medical complications of alcoholism in 1975 for over 3500 patients referred from Philadelphia and six surrounding counties in Pennsylvania and New Jersey from 1974-9.

He worked in pharmaceutical research and development, at Squibb as Director of Regulatory Projects (1979-81), then at Sterling-Winthrop Research Institute as Vice President for Worldwide Clinical Affairs (1981-4). He was an independent consultant (1984-95) to pharmaceutical companies in Europe, Japan, and North America for design and optimization for approvability of clinical trial data and new drug applications.

In June 1995 he joined the Center for Drug Evaluation and Research, Food and Drug Administration (FDA) as a medical reviewer for gastrointestinal drugs. In January 2000 became Senior Scientific Advisor to the Office of Drug Safety, consulting on drug-related liver problems to reviewing divisions and conducting research on detecting and attributing causality for idiosyncratic drug-induced liver injury. In July 2003 he was named Associate Director for Science, Office of Surveillance and Epidemiology in 2005, and serves as principal consultant in hepatology at the Agency, focusing on preventing serious drug-induced liver injury.
He has been married to the former Sara Elizabeth Spedden (CW’52) of East Falls, Philadelphia PA since 27 December 1952; they have three grown children, six grandchildren, and two great-grandchildren. He is a retired Rear Admiral, Medical Corps, United States Naval Reserve, after serving 39 years (1945-84).

Abstract: Ideas build on ideas; do we do it right? RefsCitedLinks

Humans uniquely have progressed by verbal and written communication, and it is assumed that writing is more carefully thought out than is speech. Published articles, chapters, and other writings usually are subjected to varying degrees of editorial and peer review and critique, revisions often required, so that the “literature” acquires substantial credibility. Is it well deserved? Do writers accurately understand, capture and build upon what others have written? Did those writers express well what they intended to write? Errors in the understanding or interpretation of writing create problems. Can we do it better?

I was asked last year to prepare a chapter on the current state of understanding about drug-induced liver injury (DILI) for a book on various adverse, unintended, off-target effects of drugs, and obtained agreement that the chapter would be made available at no cost in the public domain. This little exercise is an experiment to examine if one writer (me) who cited 52 other writers and groups did in fact understand those he cited, or not. If so, then fine; but if not, what can both learn from each other? To test the question, I obtained pdf copies of the references cited, sending out to the authors cited both what I wrote and what they wrote, asking if I rightly caught the meaning of what they wrote and built upon it correctly. Some of those authors are here with us today, and many have responded. Let’s look at the findings (see slide set).
Abstract: Assessing Liver Toxicity of Cancer Treatment Using the CTCAE

Common Terminology Criteria for Adverse Events (CTCAE) was developed in 1983 by the Cancer Therapy Evaluation Program to aid in the recognition and grading of adverse effects of chemotherapy in its sponsored cancer therapy trials. Since then, there have been 3 revisions to the CTCAE to accommodate new classes of agents with new adverse events as well as changes in diagnosis and treatment of adverse events. Currently, there is a revision under way. CTCAE v5 will include new terms, more granular grading if needed, editorial changes and navigational and “consider” notes. The capture of liver damage from a pharmaceutical agent has been difficult. The use of liver function tests is the standard for warning of liver damage from treatment. The difficulty is that the values of these tests have not always corresponded well with clinical status. Also, as some patients will have elevated levels in baseline, the change and not the absolute value may be a more significant hint of activity. The grading of liver dysfunction under CTCAE has been a challenge as the laboratory changes have not always corresponded with the clinical picture. CTCAE captures both the laboratory changes as well as clinical status. The value of the CTCAE terms and grading would be discussed.
Biosketch

Karen A. Hicks, M.D. is a senior medical officer in the Division of Cardiovascular and Renal Products at the Food and Drug Administration (Center for Drug Evaluation and Research). She has over 11 years of experience in regulatory review of multiple products for the treatment of acute coronary syndrome, stent thrombosis, hypertension, and chronic kidney disease. She has also reviewed drug-device combinations for the treatment of coronary and peripheral arterial disease. Dr. Hicks received her undergraduate degree from Duke University, Master of Science degree from Georgetown University, and MD degree from the Georgetown School of Medicine. She completed her internship and residency in Internal Medicine and fellowship in Cardiovascular Disease at Walter Reed Army Medical Center. She completed her Interventional Cardiology training at The Johns Hopkins Hospital and subsequently was Director of the Cardiac Catheterization Laboratory at Madigan Army Medical Center. She is board certified in Cardiovascular Disease and Interventional Cardiology. She remains clinically active at Walter Reed National Military Medical Center. On behalf of the FDA, Dr. Hicks is a frequent speaker on regulatory policy at national and international meetings. She leads two large multi-stakeholder Initiatives to Standardize Data Collection for Cardiovascular Trials. In addition to chairing the Writing Committee for the 2014 American College of Cardiology (ACC)/American Heart Association (AHA) Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials, Dr. Hicks has participated in other ACC/AHA writing committees. Her interests include interventional cardiology, definition and harmonization of cardiovascular endpoints, clinical trial design, and cardiovascular risk factor modification.

Abstract: Transaminase Elevations in the Treatment of Heart Failure

There is a mutual relationship between the heart and the liver. Hepato-cardiac diseases can be classified into 3 categories as follows: 1) Heart diseases affecting the liver; 2) Liver diseases affecting the heart; and 3) Conditions affecting the heart and the liver.

Acute heart failure can lead to acute liver injury, also known as acute ischemic hepatitis. Chronic heart failure can lead to chronic congestive hepatopathy and the development of a “nutmeg liver” characterized by deep red-brown spots in the centrilobular areas of the liver due to necrosis. Liver dysfunction improves with the treatment of the underlying heart failure.

There are 3 major mechanisms of acute liver injury: 1) Hypotension; 2) Hypoxemia; and 3) Increased metabolic demand. Profound hypotension due to acute cardiopulmonary collapse can occur in the setting of acute myocardial infarction (AMI), heart failure (HF), pulmonary embolus, or a sustained arrhythmia. HF accounts for most cases of acute liver injury. Hypoxemia, in the absence of hypotension, can occur in the setting of respiratory failure or obstructive sleep apnea and can also result in acute liver injury. Lastly, toxic/septic shock increases metabolic demand and can precipitate acute liver injury.
In heart failure when hepatic flow is decreased, the liver attempts to protect itself by increasing oxygen extraction. However, in some cases the initial insult overwhelms the ability of the liver to compensate and hepatocellular injury ensues.

Patients with acute liver injury may be asymptomatic or may experience nonspecific symptoms such as nausea/vomiting, anorexia, malaise, right-upper quadrant pain, jaundice, oliguria, and flapping tremors. Laboratory evaluation typically shows sharp increases in serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), total bilirubin (TB), alkaline phosphatase (ALP), lactic dehydrogenase (LDH), and prothrombin time (PT). These laboratory abnormalities peak 1-3 days after the initial insult and normalize in 5 to 10 days. Occasionally, these laboratory abnormalities may be accompanied by renal impairment. An ALT/LDH ratio < 1.5 is more typical of acute liver injury than viral hepatitis or drug-induced liver injury (DILI). Pathophysiologically, acute liver injury is characterized by centrilobular necrosis of zone 3 hepatocytes. Acute liver injury due to acute heart failure is usually benign and self-limited.

Chronic heart failure may result from a number of conditions such as
1) Ischemic/nonischemic cardiomyopathies; 2) Pulmonary arterial hypertension; 3) Valvular heart disease (e.g., mitral stenosis, tricuspid regurgitation); 4) Constrictive pericarditis; and 5) Congenital heart disease, including postoperative consequences from the Fontan procedure. All of these conditions can lead to right ventricular dysfunction and increased venous pressure. Symptoms of chronic liver injury may include 1) mild, dull right upper quadrant pain; 2) hepatomegaly; 3) peripheral edema; and 4) ascites. Jaundice is uncommon. Laboratory evaluation typically shows increases in AST, ALT, LDH, gamma glutamyl transferase (GGT), and ALP that are 2-3x the upper limit of normal (ULN). TB is also increased but rarely exceeds 3 mg/dL. Serum albumin is usually low. Pathophysiologically, chronic liver injury is characterized by an alternating pattern of hemorrhage and necrosis in zone 3 and normal or slightly steatotic areas in zones 1 and 2. Although chronic liver injury due to chronic heart failure can improve with treatment of the underlying heart failure, in most cases, chronic heart failure has a slowly progressive course.

Given the transaminase abnormalities that are typically observed with acute and chronic heart failure, it can be challenging to assess the potential for a drug product to cause DILI. DILI involves hepatocellular injury, as indicated by rises in aminotransferases (AT) from the injured liver cells. Severe DILI occurs only when the hepatocellular injury is substantial enough to decrease the liver’s ability to clear bilirubin or to synthesize prothrombin and other coagulation factors. With severe DILI, ALT and AST typically exceed 3x ULN and TB exceeds 2x ULN in the setting of a normal ALP. There should be no other reasons to explain the combination of increased AT and TB (e.g., hepatitis, preexisting or acute liver disease, another drug capable of causing the observed injury, PK interactions).

In general, the drugs that have caused severe DILI in humans did not show clear hepatotoxicity nonclinically nor toxicity that was clearly dose-related. Acetaminophen, however, is a clear exception to these findings. Sometimes, severe DILI can occur as a result of an idiosyncratic reaction (e.g., bromfenac, troglitzaone, ximelagatran). When evaluating potential DILI in clinical trials, there is typically a control group, and it is helpful to determine whether there is an excess of AT elevations to > 3x ULN, 5x ULN, 10x ULN, or 20x ULN in the study drug treatment group compared to the control group.

In summary,
1. There is a mutual relationship between the heart and the liver.
2. Acute heart failure can lead to acute liver injury (acute ischemic hepatitis).
3. Chronic heart failure can lead to chronic liver injury (chronic congestive hepatopathy).
4. Treat the underlying heart failure.
5. In the setting of heart failure, it can be challenging to assess whether a drug product can cause drug-induced liver injury.
Biosketch

Wendy Carter is a senior medical officer in the Division of Antiviral Products at the Food and Drug Administration with over 8 years of experience in regulatory review of multiple products for treatment of HIV, hepatitis C and B, influenza and emerging infectious diseases. She completed her Internal Medicine training at Philadelphia College of Osteopathic Medicine and her Infectious Diseases training at University of South Florida. She is board certified in Internal Medicine and Infectious Diseases. Prior to joining FDA, she was in private practice in Infectious Diseases in St. Petersburg, Florida. She also currently volunteers as an attending for the hepatitis C clinic at the Baltimore VA Medical Center.

Abstract

Evaluation of drug-induced liver injury (DILI) in patients with underlying liver disease can be challenging because a precise definition of DILI and guidance for identification and management in this population are lacking. Recently FDA has encountered several examples of potential DILI in patients enrolled in trials evaluating investigational agents for chronic hepatitis C infection. Underlying infection with chronic hepatitis C can make evaluation of changes in liver biochemistries and potential DILI more difficult to ascertain during a drug-development program. The potential of an investigational drug to cause DILI in patients with chronic hepatitis C requires thorough evaluation. Multiple factors are considered during the evaluation for DILI including the overall trend in liver biochemistries, concomitant medications, underlying co-morbidities, host factors and characteristics of the investigational drug. Lack of consensus regarding criteria for stopping investigational drugs versus requiring additional or more frequent monitoring poses additional challenges. Examples of potential DILI will be presented to illustrate the challenges of evaluating the potential for DILI during a development program for an investigational drug to treat chronic hepatitis C.
Biosketch

Willis C. Maddrey, MD, is Professor of Internal Medicine and Assistant to the President at The University of Texas Southwestern Medical Center at Dallas. Dr. Maddrey graduated from Wake Forest University summa cum laude in 1960. Dr. Maddrey received his medical degree from The Johns Hopkins University School of Medicine in 1964 and completed his residency on the Osler Medical Service of The Johns Hopkins Hospital. He was Chief Medical Resident in 1969. Additional postgraduate work included a fellowship in liver disease with Dr. Gerald Klatskin at Yale University School of Medicine.

From 1970 to 1981, Dr. Maddrey directed the liver unit at The Johns Hopkins University School of Medicine and during this time he served as Assistant Dean for Postdoctoral Programs and Faculty Development (1975-1979) and subsequently was Professor of Medicine and Associate Physician in Chief (1979-1982). From 1982 to 1990, he was Magee Professor and Chairman of the Department of Medicine at Jefferson Medical College.

Dr. Maddrey is a member of many societies and was President of the American Association for the Study of Liver Diseases in 1981. He is a Master of the American College of Physicians and served as its President in 1992-93. He is also a Fellow of the Royal College of Physicians of London, the Royal College of Physicians of Glasgow, and the Royal Australasian College of Physicians and Surgeons. He is a member of the American Society for Clinical Investigation and the American Gastroenterological Association.

Dr. Maddrey was awarded the George Stuart Outstanding Teacher Award at The Johns Hopkins University School of Medicine and the Christian R. and Mary F. Lindback Award for distinguished
teaching in the clinical sciences at Jefferson Medical College in 1986. He received the Distinguished Service Citation from Wake Forest University in 1991. In 1998 he was awarded the Distinguished Educator Award by the American Gastroenterological Association. He was named the Adelyn and Edmund M. Hoffman Distinguished Chair in Medical Science at UT Southwestern which he holds in addition to the Arnold N. and Carol S. Ablon Professorship in Biomedical Science. He was awarded the Distinguished Service Award of the American Association for the Study of Liver Diseases in 2000 and was elected to membership in the Johns Hopkins Society of Scholars in 1994. He was awarded the Distinguished Alumnus Award by the Johns Hopkins University School of Medicine in 2008.

Dr. Maddrey has published extensively in the areas of drug-induced liver disease, alcohol-induced liver disease, liver transplantation, chronic viral hepatitis, and primary biliary cirrhosis. He has edited or co-edited ten books including *Transplantation of the Liver* and *Schiff's Diseases of the Liver*. 
Biosketch

Dr. Robert Temple was recently appointed Deputy Center Director for Clinical Science of FDA’s Center for Drug Evaluation and Research and is also Acting Director of the Office of Drug Evaluation I (ODE-I). He has served in this capacity since the office’s establishment in 1995. Dr. Temple received his medical degree from the New York University School of Medicine in 1967. In 1972 he joined CDER as a review Medical Officer in the Division of Metabolic and Endocrine Drug Products. He later moved into the position of Director of the Division of Cardio-Renal Drug Products. In his current position, Dr. Temple oversees ODE-I which is responsible for the regulation of cardio-renal, neuropharmacologic, and psychopharmacologic drug products. Dr. Temple has a long-standing interest in the design and conduct of clinical trials and has written extensively on this subject, especially on choice of control group in clinical trials, evaluation of active control trials, trials to evaluate dose-response, and trials using “enrichment” designs.

Abstract: None
Biosketch

Dr. Uetrecht is Professor of Pharmacy and Medicine and the Canada Research Chair in Adverse Drug Reactions. He received his Ph.D. in organic chemistry at Cornell University in 1972, M.D. at Ohio State University in 1975 and did his internal medical residency at the University of Kansas Medical Center from 1975-1978. He completed his clinical pharmacology fellowship in 1981 at Vanderbilt University and then joined the faculty. He moved to the University of Toronto in 1985 and was the associate dean of pharmacy from 1994 to 1998. His research is focused on the mechanisms of idiosyncratic drug reactions.

Abstract: Navigating immunologic responses to drugs and biologics to predict clinical outcomes

It is generally accepted that most types of idiosyncratic drug reactions (IDRs) are immune-mediated. In contrast, the role of the immune system in idiosyncratic DILI (IDILI) has been more controversial. However, the evidence for an immune mechanism of IDILI is growing and includes HLA associations, histological features, anti-drug antibodies, and positive lymphocyte transformation tests. There is also a lot of circumstantial evidence that most IDILI is caused by chemically reactive metabolites of drugs, and the fact that liver is the major site of drug metabolism is presumably why it is a common target for IDRs. However, not all drugs that form reactive metabolites are associated with a high risk of IDILI. This raises the question as to how reactive metabolites induce an immune response that in some patients leads to serious IDILI. A major impediment to answering this question has been the lack of animal models that could be used to rigorously test mechanistic hypotheses. However, after many failed attempts to develop animal models by trying to stimulate an immune response, we were finally able to produce IDILI models with characteristics similar to IDILI in humans by inhibition of immune tolerance. That observation alone provides an important clue to the mechanism of IDILI. We also have a good animal model of nevirapine-induced skin rash in which we were able to demonstrate that the rash is caused by an immune response to a reactive benzylic sulfate metabolite formed in the skin. It is known that animals deficient in components of the inflammasome are resistant to contact hypersensitivity, and the mechanism of nevirapine-induced skin rash is similar to contact hypersensitivity. We used an in vitro assay with THP-1 cells to compare the ability of drugs to activate inflammasomes and found that those associated with a high risk of IDRs activated inflammasomes while very similar drugs that were not associated with a high IDR risk did not. However, this only works if the drug has intrinsic chemical reactivity or is metabolized to a reactive metabolite by THP-1 cells, and these cells have very little P450. Therefore, it is not useful for the study of drugs that require P450 bioactivation, and detecting inflammasome activation in vivo in the liver is a greater challenge. Under various stimuli the liver releases microvesicles. Given the right stimulus these particles contain molecules such as HMGB-1 and ATP, which are very potent activators of inflammasomes, and macrophages, which are the major cell type that have high inflammasome activity are likely to phagocytize such structures and become activated. Therefore we are trying to test the hypothesis that treatment of animals with drugs that cause IDRs results in the release of microvesicles that can activate inflammasomes. Such an assay has the potential to be a biomarker of IDR risk. Although most people that take a drug that can cause an IDR do not have an obvious immune response, it is clear that some, if not most, do have an immune response that can be detected by flow cytometry. This provides another possible biomarker to predict IDR risk. There has been a large
increase in the development of biological drugs. It is not surprising that agents used to block immune tolerance can cause IDR\(s\). In addition, given our animal models, they are likely to also lead to drug interactions and increase the risk of IDR\(s\) to other drugs. What is more surprising is that drugs such as infliximab whose therapeutic mechanism is to suppress inflammation can also cause autoimmune hepatitis. At present the major treatment of IDILI is supportive; however, if these IDR\(s\) are immune mediated, and the injury continues after the drug has been discontinued, this provides a window during which IDILI could be effectively treated. In our animal model of IDILI, depletion of CD8 T cells prevented the injury. Although clinical trials would be challenging, if it were possible to effectively treat serious IDILI it would be a major breakthrough.
Biosketch

Albert J. Czaja, MD is professor emeritus of medicine at the Mayo Clinic College of Medicine, Rochester, Minnesota. He graduated from Dartmouth College in 1965, and Harvard Medical School in 1968. He was trained in internal medicine at the Philadelphia General Hospital, University of Pennsylvania Division, from 1968-1972, served in the military at the US Army Institute of Surgical Research from 1972-1975, and completed his training at the Mayo Clinic under the mentorship of W.H.J. Summerskill, MD from 1975-1977. He joined the Mayo Clinic Division of Gastroenterology and Hepatology in 1977, and he was appointed professor of medicine in 1986. His research has focused on autoimmune hepatitis, and he has contributed to the understanding of its diagnosis, treatment, prognosis, genetic predispositions, pathogenic mechanisms, and consequences. Dr. Czaja received the Fiterman Award for Distinguished Clinical Investigation in Hepatology by the AGA in 1997; the Henry S. Plummer Distinguished Physician Award by the Mayo Clinic Department of Medicine in 2006; the Distinguished Clinician Award of the AGA in 2007; and the Distinguished Clinician Educator Award of the AASLD in 2008. Dr. Czaja was a founding member of the International Autoimmune Hepatitis Group, and he has published over 500 articles, abstracts and book chapters.

Abstract: Autoimmune Hepatitis-Transitioning From Idiopathic To Explainable

Autoimmune hepatitis is a self-perpetuating inflammatory liver disease of unknown cause that is characterized by autoantibodies, hypergammaglobulinemia, and interface hepatitis on histological examination. The codified criteria for its diagnosis require the exclusion of acute and chronic liver diseases that may resemble it, including viral, drug, hereditary, and metabolic diseases. Multiple viruses (hepatitis A virus), drugs (minocycline, nitrofurantoin), nutritional supplements (black cohosh), and environmental toxins (trichloroethylene) can produce serological and histological changes that indicate immune reactivity, but all triggering agents have typically been unable to induce a self-sustaining disease. Self-perpetuation distinguishes idiopathic autoimmune hepatitis from other etiologically-defined liver diseases with a similar phenotype, and the factors that sustain it may include genetic predispositions and dysfunctional homeostatic mechanisms that are maintained by self-amplification loops. DRB1*0301 and DRB1*0401 are the susceptibility alleles for autoimmune hepatitis in white North American and northern European patients, and they each encode an antigen binding groove on class II molecules of the major histocompatibility complex (MHC). The six amino acid sequence, LLEQKR, is the common sequence encoded by each susceptibility allele between positions 67-72 on the DRβ polypeptide chain, and susceptibility to autoimmune hepatitis is most strongly associated with a leucine (K) at position 71. The susceptibility alleles in Mexicans, Japanese and mainland Chinese are DRB1*0404 and DRB1*0405, which encode the same amino acid sequence with the exception of an arginine (R) for a leucine (L) at DRβ71. In South America, the principal susceptibility allele is DRB1*1301, which encodes a different motif (ILEDER) between positions DRβ67-72. These findings suggest that the predisposition for autoimmune hepatitis is strongly influenced by the antigen-presenting class II MHC molecules and that an understanding of the full peptide binding repertoire of the class II MHC molecules and the complementary specificities of the receptors of the T and B effector cells would allow characterization of the triggering antigen. Other disease non-specific genetic
polymorphisms outside the MHC have been proposed to influence susceptibility and phenotype, but only a variant of the SH2B3 gene (rs3184504*A) has been found to have a genome-wide association with autoimmune hepatitis (P=7.7 x 10^-8) in Dutch and German patients. SH2B3 regulates T cell activation, and rs3184504*A has been described in diverse autoimmune diseases, including PBC and PSC.

The cell mediators of tissue-specific autoimmune diseases are the cells that comprise the innate (dendritic cells, natural killer cells, macrophages) and adaptive (Th1, Th2, Th3, NKT and gamma delta T cells) immune responses. Both immune responses have been implicated in autoimmune hepatitis, and they probably contribute by secreting pro- and anti-inflammatory cytokines, altering the expansion and function of regulatory T cells, and influencing the apoptosis of effector cells, hepatocytes and hepatic stellate cells. Regulatory T cells are the key modulators of the immune responses, and reversible deficiencies in number and function have been described that may perpetuate the disease. Discrepancies between studies must be resolved before the role of regulatory T cells can be fully understood and targeted for therapy. Autoimmune hepatitis is becoming explainable, but it is still not explained. Genetic associations that differ between ethnic groups and between different ages within the same ethnic group and geographic region suggest that the antigenic exposures can vary in different regions and at different stages of life. Multiple similar antigens can be presented by the same MHC molecules; and the sensitized effector cells may generate a promiscuous immune response against homologous epitopes within and outside the liver. Molecular mimicry and epitope spread may also sustain and extend the immune response. The explanation of autoimmune hepatitis will require a firm understanding of the factors that perpetuate it and ultimately the antigens that trigger it. This understanding may lead to highly individualized therapies that increase antigenic tolerance and restore immunological homeostasis.
Abstract
Autoimmune DILI – recognition and management

Drug-induced immune-mediated liver injury is an adverse response against hepatic proteins leading to a syndrome of drug-induced autoimmune hepatitis (DIAIH). DIAH has been well documented associated with the use of several drugs such as nitrofurantoin, minocycline, methyldopa, hydralazine and infliximab. It is clinically important to identify drugs as potential triggers of self-perpetuating autoimmune liver disease. In many cases the liver injury can resolve with cessation of the implicated agent. The frequency of DIAH among patients with classical features of autoimmune hepatitis (AIH), with autoantibodies, and/or hypergammaglobulinemia and histological features of AIH has been reported to occur in 9-17% of patients, based on retrospective studies. In a recent study approximately 9% of patients with drug-induced liver injury (DILI) were diagnosed with DIAH. DILI associated with infliximab is frequent, developing in 1 out of 120 patients treated with the drug, in whom approximately 50% have DIAH but most do not require long-term immunosuppression. The risk of DILI associated with infliximab has been shown to less with concomitant therapy of methotrexate. Interestingly, follow-up of unselected patients with DILI has been shown to increase the risk of AIH development with time and a second episode of DILI more likely to be associated with features of AIH. Autoimmune, clinical and histological features are similar in patients with DIAH and classical AIH, although cirrhosis is rarely observed at presentation among the DIAH patients, whereas cirrhosis can be present in classical AIH at diagnosis in at least 20% of patients. In a patient with a high clinical suspicion of DILI with positive autoantibodies and/or with the syndrome of DIAH, immunosuppression is indicated if aminotransferases remain elevated despite discontinuation of the suspected drug. Discontinuation of immunosuppression in patients with DIAH when attempted is usually successful and immunosuppression is rarely required long-term in these patients.
Abstract: Why drug-associated immune organ injuries are important

In the large spectrum of immune-mediated adverse events, drug-induced autoimmunity, in some cases manifesting as autoimmune hepatitis (AIH), is gaining increased attention by regulatory scientists. It is notable that close to 100 agents are associated with known risk for drug-induced lupus (DIL) and in some instances AIH. These reactions which are marked by the presence of characteristic sets of autoantibodies and often arise during prolonged chronic treatment, have been tied to potentially life-threatening outcomes. There are also expanding numbers of prescriptions of biological
agents as well as cell-cycle checkpoint inhibitors for use in the treatment of malignancies which are tied to serious autoimmune reactions. All of these treatment-related risks present a number of key challenges to clinicians and regulators. First, despite common mechanisms and/or markers of autoimmunity, there is inter-individual variation in which organs are injured due to exposure to a number of these agents. Second, there is a yet an undefined role of genetic susceptibility in AIH. Third, the development of reliable predictors or markers of such individual susceptibilities will be an important milestone in the future. However, although different sets and types of serum autoantibodies directed against distinct cellular and extracellular antigens often correspond to serological signatures of DIL induced by particular drugs, their titers vary considerably and do not typically correlate with clinical levels of autoimmunity. Finally, because DIL and drug-induced AIH (DIAIH) typically often develop insidiously after prolonged treatment (> 2 months to several years), recognition of these entities by clinicians and regulatory scientists is often challenging. It is worth noting that the RUCAM scoring criteria do not accurately correspond to the typical temporal course of these reactions before and after drug withdrawal, and their characteristic systemic manifestations, response to steroid treatment, presence of certain risk factors and appearance of serum autoantibodies, when considering the development and application of an algorithmic scoring system of causal association of DIAIH in clinical practice.
David Berman MD, PhD  
Vice President, Head of the Immuno-Oncology Exploratory Development Team  
Bristol-Myers Squibb  
david.berman@bms.com  

Biosketch

David joined Bristol-Myers Squibb (BMS) in 2005 where he contributed to the early phase ipilimumab clinical and translational studies. He has continued to work in immuno-oncology over the past 10 years including as the global clinical leads for elotuzumab and ipilimumab. David is currently the Head of the Immuno-oncology Exploratory Development Team with responsibility for developing the internal, early stage immuno-oncology portfolio of drugs.

Prior to joining BMS, David was an attending in the Laboratory of Pathology at the National Cancer Institute where he conducted translational research in signal transduction and immunotherapy. David received a B.S. from MIT and M.D., Ph.D. from the University of Texas Southwestern Medical School. He completed a residency in anatomic pathology at the National Cancer Institute and a fellowship at the Johns Hopkins Hospital.

Abstract: Immune-mediated toxicity from immuno-oncology therapies

Immuno-oncology (I-O), the use of immunotherapy to treat cancer, is an emerging treatment modality. The goal of I-O therapy is to activate the immune system to attack cancer cells. There are a broad range of I-O therapies in clinical development, including those that target T cells, NK cells and antigen presenting cells. I-O therapies targeting T cell inhibitor receptors, referred to as ‘checkpoints’, are the most advanced and include inhibitors of PD-1 and CTLA4.

Activation of the immune system by inhibitors of these T cell checkpoints may lead to immune-mediated toxicity, which may be serious and potentially fatal. Immune mediated toxicity from ipilimumab, an inhibitor of CTLA-4, has been reported in a variety of organs including the skin, GI system, liver, endocrine system among other organs. While the exact mechanisms of toxicity have not yet been elucidated, translational studies have begun to characterize the type of inflammatory damage and compare the pathophysiology with other immune mediated diseases such as auto-immunity and graft-vs.-host disease. Further exploration of immune mediated toxicity from I-O therapies will continue to increase in importance as these therapies become integrated into cancer clinical practice.
Biosketch

Dr. Regev received his B.Sc. and M.D. degrees from the Hebrew University in Jerusalem, Israel. He completed residency in Medicine and fellowship in Gastroenterology at Rabin Medical Center and Tel Aviv University, where he continued working as attending physician and Associate Chief of Medicine. He subsequently completed clinical fellowship in Hepatology and Transplant Hepatology at the Division of Hepatology of the University of Miami, and Jackson Memorial Hospital in Miami, Florida. After his fellowship he continued working in the Division of Hepatology as full time faculty and subsequently Associate Professor of Medicine and Director of the Hepatology Fellowship Program until 2007. Dr. Regev has conducted numerous clinical trials in the field of viral hepatitis and liver transplantation. He was the principal investigator of a number of NIH funded clinical trials and has served as principal investigator on several investigator initiated and industry supported clinical trials in the area of viral hepatitis and liver transplantation. He is the author of numerous publications in major medical Journals including *American Journal of Gastroenterology, Clinical Gastroenterology and Hepatology, Journal of Hepatology, Liver Transplantation, Gut, Transplantation, Proceedings in Transplantation, and Digestive Diseases and Sciences*. He authored several chapters in major medical textbooks including *Schiff's Diseases of the Liver, The Clinician’s Guide to Liver Disease, Viral Hepatitis, Requisites in Gastroenterology and Advances in Internal Medicine*. Dr. Regev received Teaching and Research Awards at the University of Miami as well as Tel Aviv University. He served as an active member of the *Training and Clinical Policy Committee* of the American Association for the Study of Liver Diseases. In January 2007 Dr. Regev joined Eli-Lilly in a Hepatology Consulting position and as Chair of the Liver and GI Safety Committee in the Global Patients Safety organization. He is currently an adjunct Associate Professor of Medicine at the Division of Gastroenterology and Hepatology of Indiana University, and he heads the Safety Advisory Hub at Eli Lilly and Company.

Abstract: Dose-Dependent Hypersensitivity-Type DILI: A Case Series

The mechanisms underlying idiosyncratic DILI are still a matter of debate, and immune mediated mechanisms are still not completely understood. This case series describes 6 patients (4 females, 2 males, age 32-59) who presented with acute hepatocellular liver injury with hypersensitivity features during a Phase I clinical trial with a novel anti-inflammatory drug. The patients presented 16-34 days (mean 22 days) after starting the drug, with clinical features that included epigastric pain, fatigue, nausea, low-grade fever, rash, and in two cases urticaria. ALT levels were elevated >3X ULN in all 6 cases, and were ≥15X ULN in 4, and ≥45X ULN in one. ALP and total bilirubin did not exceed 1.5X ULN. Five of the 6 patients had eosinophilia of >10%, and in 2 patients eosinophil count was > 20%. Two patients required hospitalization, underwent liver biopsies, and were treated by local hepatologists with N-acetylcysteine. Liver histology showed marked zone 3 necrosis with numerous portal and lobular eosinophils and no evidence of fibrosis. Patients who were receiving higher doses of the drug were significantly more likely to develop DILI and had more severe injury. The highest dose was associated with a DILI incidence of more than 55%.

Although presence of hypersensitivity features in DILI suggests immunologic idiosyncrasy, it now seems likely that at least in some cases the primary abnormality may be related to generation of highly reactive metabolites. The cases
described herein showed strong dose-relationship and hypersensitivity features. The suspected mechanism and role of immune-mediated injury in these cases will be discussed.
Biosketch

Dr. Paul B. Watkins is director of the Hamner-University of North Carolina Institute for Drug Safety Sciences. He is also Professor of Medicine, Pharmacy and Public Health at the University of North Carolina, Chapel Hill. Dr. Watkins is a trained clinical hepatologist and also an accomplished basic and translational investigator in the fields of drug metabolism and hepatotoxicity. He is one of the most frequently cited authors in the field of pharmacology according to www.ISIhighlycited.com. He is the recipient of numerous honors and awards including the Therapeutic Frontiers Award from the American College of Pharmacy election to the Association of American Physicians (AAP), the Agilent Therapeutic Frontiers Award, and he will receive the Rawls-Palmer Award for Innovation in Medicine at the 2015 annual meeting of the American Society for Clinical Pharmacology and Therapeutics. He serves as the chair of both the Steering and Genetics Committees for the U.S. Drug-Induced Liver Injury Network (DILIN) (U01DK065201). He is also an advisor for the large research projects involving drug-induced liver injury (SAFE-T and MIP-DILI) sponsored by the European Innovative Medicine Initiative (IMI). Dr. Watkins consults widely with industry and regulatory agencies concerning liver safety.

Abstract: none
A. Personal Statement

As a physician scientist, the focus of my research is to understand and modulate mechanisms by which innate immunity contributes to inflammation and tissue injury in the liver. My independent research career of 23 years has contributed to the understanding of cellular and molecular mechanisms of liver inflammation in alcoholic and non-alcoholic liver diseases and hepatitis C virus infection. I am a nationally and internationally recognized expert in the field of innate immunity and the role of pattern recognition receptors, exogenous and endogenous danger signals in alcohol-induced tissue injury. I pioneered discoveries on alcohol-induced activation of the inflammasome complex by alcohol use that is a common molecular target of tissue damage in the brain and the liver. In this application I aim to bring my expertise in molecular regulation of inflammation to advance understanding and identify potential therapeutic targets in alcohol-induced neuroinflammation. Most recently, we discovered the critical role of micro-RNAs in alcohol-induced tissue inflammation in the brain and identified novel mechanistic roles for miRNA-155 in alcohol-induced macrophage activation. My expertise in innate immunity, signaling and alcohol-induced tissue injury has been recognized nationally and internationally as reflected by numerous invitations to conferences and prestigious institutions as invited speaker and/or advisory board member. I had the honor to give the State of the-Art lecture at DDW 2009 and the Zimmerman lecture at AASLD in 2010 on innate immunity in liver disease and the keynote lecture at the Shanghai Transplantation Immunology meeting on miRNA regulation in liver disease. Most recently, I was invited to serve on the External Scientific Board of the NIH Extracellular RNA Communication Program. I also served as Associate Editor of Hepatology and currently as Field Editor of Alcoholism, Clinical & Experimental Research. I am member of the Scientific Program Committee of the Research Society on Alcoholism and President-Elect of the American Association for Studies in Liver Disease (AASLD) in 2014.

B. Positions and Honors

Postdoctoral Training
1985 Postdoctoral Research Fellow, Health Institute, University of Innsbruck, Austria
1986 Postdoctoral Research Fellow, Dept of Infectious Dis., Univ. Hospital, Leiden, The Netherlands
1986-1988 Research Associate, Dept of Surgery and Mol Gen & Microbiol, UMass Medical School, USA

Licensure and Certification
1993-1995 ECFMG Certificate, USMLE Parts I, II and III
1996 Massachusetts Medical License
1997 Diplomate, American Board of Internal Medicine
2001, 2013 Diplomate, American Board of Subspecialty Medicine, Gastroenterology

Academic Appointments
1993-1995 Research Associate Professor, Dept of Surgery, and Immunology and Virology Program, Graduate School of Biomedical Sciences, UMass Medical School, Worcester, MA
1993-2002 Associate Professor of Medical Sciences, Graduate School of Biomedical Sciences, Immunology/Virology Program, UMass Medical Center, Worcester, MA
2002-Pres. Professor of Medicine, Dept of Medicine, (2006-Tenure) UMass Med School, Worcester, MA
2008-Pres. Associate Dean for Clinical and Translational Sciences, UMass Med School, Worcester, MA
2009-Pres. Director, MD/PhD Program, UMass Medical School, Worcester, MA
2010-Pres Vice Chair for Research, Department of Medicine, UMMS, Worcester, MA

Professional Societies/Committee Appointments
1990-Pres. Society for Leukocyte Biology; Research Society on Alcoholism
1991-Pres. Int’l Society for Biomedical Research on Alcoholism; American Association of Immunologists
1994-Pres. American College of Physicians
1998-Pres. American Association for Study of Liver Disease; American Gastroenterological Association
2000-Pres. Clinical Immunology Society; Int’l Endotoxin Society, Int’l Cytokine Society
2001-2009 AASLD, Chair, Basic Research Committee (2006-2009); NIH Liaison Committee (2009-2010)
2009-2013 Member, National Advisory Council on Alcohol Abuse and Alcoholism
2010-2016 Councilor, AASLD (President - 2015)

Editorial Boards
1993 Review Board member, Immunology and Infectious Diseases
2004-Pres. Reviewing Editor, Alcoholism: Clinical and Experimental Research
2006-2011 Associate Editor, Hepatology

Scientific Review Groups (NIH)
Chair (ad hoc)
2000 Special Emphasis Panel; Lung Biology and Pathology Study Section, CSA, NIH
2008-2009 Chair, ZAA1 BB (02) Study Section
Permanent Member
1992-Pres. Site visit team member; General Clinical Research Center Committee, NIH, Alcohol Center Grants Review Committee NIAAA; Alcohol Center Grants Final Review Committee, NIAAA/NIH, Member, Special Review Committee, NIAAA/NIH, AIDS and Related Research, IRG, NIH, Special Emphasis Panels, NIAAA; ALTOX-4 IRG, NIAAA, NIH; Special Emphasis Panel; Lung Biology and Pathology Study Section, CSA, NIH, AA-1 Subcommittee; XNDA, HBPP, IHD
1994-1995 Immunology and AIDS, Alcohol Biomedical Research Review Subcommittee Member
2005-2009 Hepatobiliary Pathophysiology Study Section (HBPP) Member

Awards and Honors:
2004 Diploma of Honorary Membership and “Geza Hetenyi” Award, Hungarian Society of Gastroenterology
2005 Doctor Honoris Causa, Semmelweis University, Budapest, Hungary
2006-Present Advisory Board, Yale Liver Center
2007 National Commission for Digestive Diseases, Advisory Board Member
2008 Dean’s Special Lecture, Georgetown University, Washington, DC
2009 State-of-the-Art Lecture, DDW
2009, 2012 External Advisory Board Member, NIAAA, NIH
2009 “Women in Science and Health Achievement Award” Univ of Massachusetts Medical School
2009-2010 Fellow, Hedwig van Ameringen Executive Leadership in Academic Medicine (ELAM) Program
2009 Kelsey Family Named Professor, Div Gastro and Hepatology, Mayo Clinic, Rochester, MN
2010 Edward Moore Lectureship, Virginia Commonwealth University, Richmond, VA
2010-2013 Member, National Advisory Board, National Institute for Alcoholism and Alcohol Abuse
2010-2013 Member, Biomedical Advisory Council, American Beverage Medical Research Foundation
2010-2014 Councilor, AASLD (President 2015)
2010 Zimmerman Lecture, The Liver Meeting, AASLD
2013 Elected Member, Hungarian Academy of Sciences, Budapest, Hungary
2013 Lean Schiff Lecture, Univ of Cincinnati, Cincinnati, OH
2013-2018 External Scientific Board of the NIH Extracellular RNA Communication Program

Recent Presentations (partial list)
2010 Invited Speaker, Rockefeller University, Study of Hepatitis C Seminar Series, New York, NY
2011 Invited Speaker, 8th APASL Single Topic conference
2012 Invited Speaker, Immunology of Liver Disease, EASL Monothematic Conference, Birmingham
2012 Invited Speaker, ISBRA 16th Alcohol World Congress, Sapporo, Japan
2012 Invited Speaker, Congree of the European Federation of Internalt Medicine, Madrid, Spain
2012 Invited Speaker, Society of Leukocyte Biology, Maui, HI
2012 Invited Speaker, AASLD, The Liver Meeting, Boston, MA
2013 Keynote Speaker, Hepatology – Gastroenterology and Immunology Course, Santiago, Chile
2013 Invited Speaker, International Society for the Study of Xenobiotics, Boston, MA
2013 Invited Speaker, International Society for Extracellular Vesicles, Boston, MA
2013 Invited Speaker, International Liver Congress of EASL, Amsterdam
2013 Invited Speaker, 2nd Alcohol and Cancer Conference Breckenridge, CO
2013 Keynote Speaker, ESBRA, Warsaw, Poland
2013 Keynote Speaker, International Viral Hepatitis Symposium, Melbourne, Australia
2013 Invited Speaker, NIDDK, NIH, Bethesda, MD

C. Selected Peer-reviewed Publications (from a total of 158)


D. Research Support

Ongoing Research Support

**ACTIVE**

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<tr>
<th>Grant Number</th>
<th>Principal Investigator</th>
<th>Title</th>
<th>Status</th>
<th>Start Date</th>
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<tr>
<td>1R01AA020744-03</td>
<td>Szabo</td>
<td>Micro RNA’s in Alcohol Liver Disease</td>
<td>Investigates the role of miR-155 in development of inflammation in alcoholic liver disease in mice.</td>
<td>09/10/11-6/30/16</td>
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<td>Szabo</td>
<td>Micro RNA’s in Alcohol Liver Disease</td>
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<td>5R01AA011576-14</td>
<td>Szabo</td>
<td>Alcohol and Monocyte Signaling</td>
<td>The overall goal of this research proposal is to define molecular mechanisms that regulate the “switch from the acute, anti-inflammatory to the “chronic,” pro-inflammatory effects of alcohol.</td>
<td>4/1/13-31/3/14</td>
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<td>NCE $337,824</td>
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<td>5R01AA017729-05</td>
<td>Szabo</td>
<td>TLR4 Signaling in Alcoholic Liver Disease</td>
<td>This application further investigates that the absence of TLR4, but not of the MyD88 adaptor, protects mice from alcoholic liver disease.</td>
<td>08/20/09-07/31/14</td>
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<td>5R37AA014372-11</td>
<td>Szabo</td>
<td>HCV, Alcohol and Host Defense</td>
<td>This project investigates pathogenic interactions between HCV and alcohol use or co-activation of cells of the innate immune system.</td>
<td>09/15/03-08/31/18</td>
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<td>1U01AA021902-02</td>
<td>Szabo</td>
<td>Novel Therapies in Alcoholic Hepatitis-Admin Core</td>
<td>The goals are to: 1) direct the administrative core and act as Chair of the Executive and Steering Committees; 2) integrate various administrative functions of the project to meet needs; 3) oversee all components with the help of the Steering Committee and guide all projects to meet the overall goals of the consortium.</td>
<td>09/15/12-6/30/2017</td>
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<td>1U01AA021907-02</td>
<td>Szabo</td>
<td>Novel Therapies in Alcoholic Hepatitis-Translational Component</td>
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The goal of this component is to test novel therapeutic approaches and reveal new biomarkers in alcoholic hepatitis.

Novel Therapies in Alcoholic Hepatitis-UMMS Clinical Trial
The major goals are to: 1) develop innovative non-invasive biomarkers based for ALD; 2) develop genetic signatures that predict sensitivity of patients to individual and/or combined therapies; 3) develop lead therapeutics for treating patients with AH.

NIH 1 T32 GM107000-01 (Szabo) 7/1/13-6/30/18 0.12 Calendar
NIH/NIGMS $134,784
Medical Scientist Training at UMMS
PENDING
None.

COMPLETED
5R01DK075635-04 (Szabo) 03/01/08-02/28/13 0.24 calendar
NIH/NIDDK No cost extension
Toll Like Receptor – Mediated Pathways in Liver Injury
This project investigates the mechanisms of TLR9 plus TLR2 stimulation in induction of liver granulomas and sensitization to LPS-induced liver injury.
OVERLAP
No scientific or commitment overlap.

Abstract: MicroRNA-122 - uses and applications

MicroRNAs (miRNAs) are short (18-25 nucleotides) noncoding RNA molecules that bind to and degrade a specific set of target mRNAs. miRNAs have been extensively studied for their role in post-transcriptional gene regulation as tumor suppressors, biomarkers, and essential components in normal cellular development. MicroRNA-122 comprises nearly 70% of all hepatic small RNAs where it regulates pathways in hepatocyte differentiation, apoptosis, metabolism, stress response and carcinogenesis. Several studies have demonstrated that in different liver diseases serum miR-122 levels are increased and correlate with increases in serum transaminases. In APAP toxicity miR-122 can be detected in the serum earlier, and at lower doses of APAP, compared with serum alanine aminotransferase (ALT) activity indicating its potential as a serum marker of liver injury. Another major role of miR-122 is in hepatitis C virus infection where the host miR-122 is used by HCV for its advantage in replication. New lessons were learned from therapeutic approaches with the locked nucleic acid-miR-122 inhibitor, miravirsen, that showed efficacy in reducing serum HCV viral levels without significant side effects or toxicity in humans. The absence or inhibition of miR-122 in the liver in animal models resulted in accelerated development of hepatocellular cancer and liver inflammation. miR-122 in hepatocytes targets cholesterol metabolism. Steatosis, a key component of non-alcoholic fatty liver disease, is regulated by hypoxia-inducible factor-1α (HIF-1α). In methionine-choline-deficient (MCD)-induced steatohepatitis miR-122 levels were significantly decreased in livers and/or isolated hepatocytes compared to methionine-choline-supplemented (MCS) controls. The maximum reduction in miR-122 occurred at the fibrosis stage (8 weeks of MCD diet). Increased NF-κB activation was found in MCD diet-fed mice and MAP3K3 regulated the NF-κB DNA binding in naive hepatocytes. HIF-1α mRNA and DNA binding and expression of the HIF-1α target gene, profibrotic lysyl oxidase, was increased in advanced steatohepatitis (8 weeks). In addition, there was an increase in vimentin and Sirius red staining (liver fibrosis) at 8 weeks of MCD diet. Using miR-122 overexpression and inhibition approaches, we confirmed that HIF-1α, vimentin and MAP3K3 are novel miR-122 targets in hepatocytes. We found transcriptional repression of miR-122 in NASH snf decreased liver miR-122 was associated with elevated circulating mir-122. These data suggest that decreased liver miR-122 contributes to upregulation of modulators of tissue remodelling (HIF-1α, vimentin and MAP3K3) and might play a role in NASH-induced liver fibrosis.
Biosketch

I am currently Medical Director of Liver Transplantation at the University of North Carolina but was trained in several places before arriving here. I got my bachelors in microbiology at UCLA and medical degree at the University of California, San Diego. I completed my gastroenterology fellowship at the University of California, Davis Medical Center. Thereafter I left California holding several clinical and academic positions as well as doing graduate work. I spent 2 years at the NIH completing a clinical research fellowship in the Liver Disease Section of the NIDDK in Bethesda, Maryland. After that I was on faculty at Loma Linda University in California. I then volunteered for the U.S. Air Force Medical Corp and was stationed outside Tokyo, Japan for 3 years before being transferred to Lackland Air Force Base, San Antonio, Texas. I entered as a Major and was honorably discharged at the rank of Lieutenant Colonel. While in the Air Force, I was on faculty with the Air Force’s Gastroenterology Division and did clinical research in liver disease. After leaving the Air Force, I completed a liver transplant fellowship at the University of Colorado in Denver and then a Masters in Public Health at Saint Louis University, St. Louis, Missouri. While getting my Masters, I was on faculty at Saint Louis University as a transplant hepatologist. Now at University of North Carolina, I am currently involved in clinical research regarding transplant outcomes, hepatocellular carcinoma screening, cirrhosis management and drug induced liver injury.

Selected References:


**Abstract: DILIN Experience with Hy’s Law in Patients with Existing Liver Disease**

Patients in a clinical trial who develop drug related increases in serum aminotransferases > 3x upper limit of normal [ULN] and serum bilirubin >2x ULN (without significant alkaline phosphatase elevation) are termed “Hy’s Law Cases”. It is often assumed that the risk of liver failure postmarketing will be roughly 10% of the incidence of Hy’s Law Cases in the clinical trials. However, data supporting this extrapolation of risk has come from observations in patients without pre-existing liver disease. There is increasing interest in developing medications targeting patients with viral hepatitis, non-alcoholic fatty liver disease and other chronic liver disorders. Predicting post-marketing risk of liver failure from the incidence of Hy’s Law Cases has not been determined in these patient populations. The challenge of assessing hepatotoxicity signal in these groups remains two-fold: (1) baseline liver biochemistries will often be elevated challenging Hy’s Law’s use of ULN cut-offs and (2) the tolerance of liver injury will likely be lower or at least highly dependent on level of existing liver fibrosis or dysfunction. Statistical remodeling on baseline liver biochemistries2 may help in addressing the first issue. However, DILIN data supports concerns for the second. Pre-existing liver disease and meeting Hy’s Law at presentation were both more common in those dying or requiring a liver transplant at 6 months follow-up (24% vs. 11%, p < 0.01 and 46% vs. 26%, p < 0.01, respectively).3 Other preliminary data from the DILIN suggests that mortality was significantly higher amongst those with existing liver disease.4 Of the 88 patients with existing liver disease in the DILIN 32% met Hy’s Law at presentation, while a similar 29% of the 894 patients without existing liver disease met Hy’s Law. Analysis of how well Hy’s Law predicts severe liver injury in each group is ongoing.


4. Chalasani, N. for the DILIN. Personal communication.
Biosketch

Tom earned his PharmD degree from the University of North Carolina in 2001 after majoring in chemistry as an undergraduate, and received his PhD in Pharmaceutical Sciences and Pharmacogenomics from the University of California San Francisco in 2007, where he studied the functional consequences of genetic variation in membrane transporter genes under the direction of Kathleen Giacomini. He then completed a postdoctoral fellowship under the mentorship of David Goldstein at Duke University Medical Center (DUMC), and became one of the founding faculty members of the Duke Center for Human Genome Variation in 2010. He is currently an assistant professor in the Division of Pharmacotherapy and Experimental Therapeutics, the Center for Pharmacogenomics and Individualized Therapy, and the UNC Hamner Institute for Drug Safety Sciences. Tom’s research is focused on genome-wide genotyping and sequencing approaches to the study of infectious disease (primarily hepatitis B and hepatitis C viruses), and rare drug toxicities such as drug-induced liver injury and drug-induced arrhythmias, among other traits. Tom serves as an executive member of the NIDDK Drug-Induced Liver Injury Network Genetics Committee and on the Scientific Management Committee of the International Serious Adverse Events Consortium (iSAEC).

Selected publications:


**Abstract: Update on Genetic Susceptibility to Drug-Induced Liver Injury**

Advances in genomic technology over the past several years have contributed to an unprecedented rate of progress in our understanding of the genetic basis of human disease. The application of these technologies to pharmacogenomics studies has lagged behind their use in the study of human disease risk, with perhaps the primary reason for this being the limited availability of large, well-phenotyped patient cohorts. This difficulty is felt particularly keenly in the arena of rare drug toxicities such as drug-induced liver injury (DILI), as the low event rates mean that tremendous effort is required to assemble large enough patient cohorts to perform meaningful genomic analyses. Efforts over the past decade, involving large national and international collaborations with the goal of studying patients with rare severe drug toxicities, have remedied this problem in several key areas, especially for DILI. A recent genome-wide association study performed as a joint analysis of data generated by the Drug Induced Liver Injury Network (DILIN) and the International Serious Adverse Events Consortium (iSAEC) has revealed a number of novel genetic risk factors for DILI, including specific rare HLA types not previously associated with DILI, as well as novel genetic risk variants outside of the HLA region. While these discoveries are likely not specific enough to aid significantly in clinical decision making, they may provide novel diagnostic tests for DILI, and help in developing our understanding of the mechanisms underlying individual susceptibility to DILI. Through continuing collaborative efforts among these groups and others, it is hoped that identification and validation of genetic variants with potential for prediction of DILI will be achieved in the near future.
Biosketch

Dr. Merrie Mosedale is a member of Dr. Paul Watkins' lab at the Hamner-UNC Institute for Drug Safety Sciences. Through partnerships with pharmaceutical companies and academic scientists, she is exploring novel \textit{in vitro} and \textit{in vivo} approaches to understand and predict adverse drug reactions in humans. Currently, Dr. Mosedale is researching the use of genetically diverse mouse populations to effectively model the liver injury liability for drugs where traditional nonclinical models have failed. She is also interested in combining translational pharmacogenomics with a systems biology approach to identify genes and pathways that underlie drug toxicity susceptibility. Findings from her research highlight the potential for population-based approaches to improve human risk assessment in drug-safety testing as well as to provide mechanistic insights into drug toxicity. She has been recognized for her work by the Society of Toxicology and the American Society for Pharmacology and Experimental Therapeutics. Prior to joining The Hamner Institutes, Dr. Mosedale received her B.S. from Duke University and her Ph.D. from the University of California, San Diego.

Abstract: Personalized DILI Risk Management – The Tolvaptan Initiative

Merrie Mosedale$^1$, William J. Brock$^2$, Sharin Roth$^2$, J. Scott Eaddy$^1$, Tim Wiltshire$^3$, O. Joseph Trask Jr.$^1$, Robert W. Corty$^3$, Yuying Xie$^3$, William Valdar$^3$, and Paul B. Watkins$^{1,3}$

$^1$The Hamner-UNC Institute for Drug Safety Sciences, RTP, NC; $^2$Otsuka PDC, Rockville, MD; $^3$The University of North Carolina at Chapel Hill, Chapel Hill, NC

The vasopressin receptor 2 antagonist tolvaptan is a promising candidate for the treatment of Autosomal Dominant Polycystic Kidney Disease (ADPKD). FDA approval has not yet been received, however, in part due to drug-induced liver injury (DILI) associated with tolvaptan use in a small fraction of ADPKD patients. The goal of this research initiative is to develop a personalized medicine approach to manage the risk of DILI in tolvaptan treated patients through the identification of genetic and non-genetic risk factors for tolvaptan-induced liver injury. A second objective is to provide a mechanistic understanding of the tolvaptan toxicity in order to further direct discovery efforts and to provide biological plausibility for empirically derived biomarkers. This talk will highlight recent findings from the tolvaptan research initiative, including 1) the identification of genetic risk factors associated with susceptibility to tolvaptan DILI using a new mouse genetic resource, the Collaborative Cross and 2) identification of stress response pathways initiated in primary human hepatocytes exposed to tolvaptan. These findings will now guide a targeted, hypothesis-based approach to biomarker discovery in the DNA and sequential samples of plasma and urine that were collected and archived from clinical trials.
Biosketch

Dr Dan Antoine is currently a Wellcome Trust funded research fellow at the MRC Centre for Drug Safety Science (CDSS) and lecturer in Molecular and Clinical Pharmacology at the University of Liverpool, UK. Dr Antoine completed his PhD in 2009 in Pharmacology. Prior to his PhD, Dr Antoine completed his B.Sc (Hons) in Biochemistry (first class) and worked in research posts within Molecular Toxicology at AstraZeneca. He undertook postdoctoral training at the CDSS with Prof BK Park and Prof M Pirmohamed as well as Royal Society International Travelling Fellowships at the Harvard Medical School, USA, with Prof JV Bonventre and at the Karolinska Institute, Sweden, with Prof U Andersson. Dr Antoine is currently the coordinator of the safety biomarker research group at the CDSS, Liverpool, UK. His research is mainly focused on the understanding of fundamental mechanisms related to adverse drug reactions and the prediction of drug-induced liver injury (DILI) through the development of translational biomarkers. He is a member of the DILI project team for the SAFE-T (Safer And Evidence based Translation) IMI consortium to develop and qualify safety biomarkers. He also sits on the British Toxicology Society’s (BTS) Education, Training and Early Career Toxicologists Sub-Committee and is the co-chair of the British Pharmacological Society (BPS) Toxicology Affinity Group. In 2014, Dr Antoine was elected to serve as a Councillor for the International Union of Basic and Clinical Pharmacology (IUPHAR) Drug Metabolism and Drug Transport Section Executive Board. In 2013, Dr Antoine received the British Toxicology Society’s Early Career Investigator Award and the Bain Memorial Travel Fellowship from the BPS in 2014. He is also an active member of the Society of Toxicology’s (SOT), European Association for the Study of the Liver (EASL), American Association for the Study of Liver Disease (AASLD) and the International Society for Xenobiotics (ISSX) as well as an editorial board member for the journals *Pharmacology Research & Perspectives* and *Biomarkers*. Dr Antoine’s academic research is currently funded by grants awarded from the European Commission, Medical Research Council, Wellcome Trust, The Royal Society and the pharmaceutical industry.

Abstract: HMGB1 variants determine if DILI is benign or dangerous

The prediction of clinical DILI remains difficult, particularly in cases characterized by marked inter-individual variation. A lack of sensitivity, specificity and an indirect mechanistic basis of currently used biomarkers of hepatic injury remains a factor for the delayed identification of DILI. Elevations in ALT activity can occur frequently in clinical trials that do not lead to serious DILI. Therefore, there is a need to identify and develop biomarkers that can distinguish between benign or serious liver injury in man and experimental models in the assessment of DILI risk that can be used to support ‘Hy’s law’. High Mobility Group Box-1 (HMGB1) is a chromatin binding protein that sits at the intersection between sterile and infectious immunity. HMGB1 is released passively by dying cells and acts as DAMP (Damage Associated Molecular Pattern) that connects cell death with the activation of the immune response by targeting Toll-like receptors (TLR), CXCR4 and the receptor for advanced glycation end products (RAGE) to promote cytokine production and chemotaxis. Activated immune cells also secrete HMGB1, a process that requires acetylation of HMGB1. We have previously shown that the acetylated version of HMGB1 represents a circulating biomarker that is highly associated with prognosis during clinical acetaminophen overdose [1, 2]. Our laboratory has
discovered that HMGB1 inflammatory function is highly dependent upon and is regulated by post-translational redox modifications of three key cysteine residues (C23, 45 and 106) [3]. Three key HMGB1 isoforms exist with mutually exclusive functions in the form of disulfide-HMGB1 (cytokine inducing via TLR4-MD2 binding), fully reduced-HMGB1 (chemotaxis via CXC4-CXCL12 binding) and sulfonyl-HMGB1 (immunological inert). Our hypothesis is that HMGB1 signalling is critical to drive the pathogenic process of DILI, that redox isoforms of HMGB1 contribute to this process and can be used as informative mechanism-based DILI biomarkers. Here we report that a novel conditional hepatocyte knock-out mouse for HMGB1 shows reduced liver injury (ALT, histology) and inflammatory cell infiltration compared to wild type mice when treated with acetaminophen [4], thus confirming the critical role played by HMGB1 in experimental DILI. In patients with serious liver injury following acetaminophen overdose, all functional HMGB1 redox-dependent isoforms can be identified in serum. Absolute quantification of each isoform demonstrates that the disulfide and fully reduced redox isoforms are elevated in patients that die/require a liver transplant. Moreover, in healthy volunteers that develop transient increases in ALT activity with therapeutic acetaminophen or heparin treatment, the only observed HMGB1 isoform released by these dying cells is the sulphonyl or immunologically inert isoform. These data are also supported by preclinical studies of acetaminophen overdose were the circulating HMGB1 profile can be modulated experimentally. These data suggest that redox-dependent and functionally relevant HMGB1 isoforms show characteristic signatures associated with outcome and can distinguish between benign or serious liver injury in man and experimental models.

These observations form part of a collaboration between the MRC Centre for Drug Safety Science (UK) and the Hamner Institute for Drug Safety Science (USA).

Biosketch

Brett Howell is a Co-Project Lead for the DILI-sim modeling team and a Lead Scientist and Manager at the Hamner Institutes. Dr. Howell’s research experience has focused on the use of mathematical modeling techniques to solve interesting biological problems. He has published in a variety of areas including the use of physiological modeling to optimize drug overdose treatment, the use of liposomes to test chemicals for ocular toxicity without animals, basic principles associated with lipid-membrane interactions, and most recently, modeling of drug-induced liver injury. Dr. Howell, along with Dr. Scott Siler, leads the modeling effort for the DILI-sim Initiative and acts as a technical contributor. The DILI-sim Initiative is a pre-competitive partnership between The Hamner and a diverse set of stakeholders to develop a computational model that will predict whether new drug candidates will cause drug-induced liver injury (DILI) in patients. The goals of the Initiative are to improve patient safety, reduce the need for animal testing, and reduce the costs and time necessary to develop new drugs. Dr. Howell holds Bachelors of Science degrees in chemical engineering and textile engineering from North Carolina State University and a Ph.D. in chemical engineering from the University of Florida.

Abstract: Interpreting Elevations in Serum Cytokeratin 18 and Alanine Aminotransferase With a Mechanistic Model of DILI - A Case Study Involving a Novel Drug Candidate

A novel compound (Compound X) was associated with dose dependent elevations in serum ALT in phase I clinical studies. Using data obtained from in vitro and cellular systems, a systems toxicology model of DILI (DILIsym®) suggested oxidative stress as the primary mechanism for the liver effects, and that both apoptosis and necrosis of hepatocytes was likely to be involved. This was confirmed by measurement of cytokeratin 18 and its caspase cleaved fragment (cK18) in archived serum samples. It was also noted that cK18 was more sensitive to the liver effects than ALT, suggesting this assay may have a future role in risk management of DILI. While regulatory guidelines indirectly suggest that a 3-fold elevation of ALT signals clinically important DILI, there is no similar guideline for cK18. We developed a model for cK18 in DILIsym® and explored the predicted relationships among cK18, ALT, and extent of hepatocellular death for a variety of injury dynamics, as well as for the potential DILI caused by Compound X. The model predicts that a 3-fold increase in serum ALT and a 1.5-fold increase in cK18 are indicative of similar amounts of hepatocyte death via necrosis and apoptosis, respectively. This is true regardless of whether the liver injury is sudden (acute) or more prolonged. DILIsym® also predicted an optimal dosing and monitoring regimen to maximize liver safety of compound X. The project highlights the value of mechanistic modeling in the interpretation of novel biomarkers and optimization of clinical protocols.
Minjun Chen, PhD  
Principal Investigator  
National Center for Toxicological Research, FDA  
Minjun.chen@fda.hhs.gov

Biosketch

Dr. Minjun Chen received his Ph.D. in 2003 from Zhejiang University. Immediately, after receiving the Ph.D. degree, he worked as an Assistant Professor at the School of Pharmacy at Shanghai Jiaotong University in China, and was promoted to Associate Professor in 2005. Dr. Chen came to the United States in 2006 as a postdoctoral fellow jointly with the FDA’s National Center for Toxicological Research and University of Medicine and Dentistry of New Jersey. In 2008 he was promoted to a FDA Staff Fellow at the National Center for Toxicological Research. Now, Dr. Chen is a principal investigator of the National Center for Toxicological Research, working on bioinformatics and drug-induced liver injury. Dr. Chen has been the author or co-author of over 50 peer-reviewed research articles and 3 book chapters with an H-index of 23. He is the receipt of the FDA Scientific Achievement Award for Outstanding Junior Investigator in 2012 and the NCTR Scientific Achievement Award for Excellence in Analytical Science in 2014.

Abstract: What drug properties predict DILI?

Drug-induced liver injury (DILI) is considered to depend both on properties of the drugs themselves and on host idiosyncratic susceptibility factors. Some drugs in a class are more dangerous than others; some patients are more susceptible than most others to hepatotoxicity from the same dose of the same drug. Recent advances in the field have disclosed that daily dose and lipophilicity, namely ‘rule-of-two’, are strongly associated with serious DILI potential. We are working to develop a Liver Toxicity Knowledge Base (LTKB) that focuses on collecting data on drug properties, and aims to develop predictive concepts for assessing DILI risk in humans. We will discuss some rules derived from drug physiochemical and toxicological properties that may influence their significant association with causing DILI. We further found that formation of reactive metabolites can further improve the DILI prediction of the ‘rule-of-two’. We also found that formation of reactive metabolites is a useful predictor of drug reactions with rash, eosinophilia and systemic symptoms. After confirmation and validation, these DILI predictive rules may support decision-making in drug development or regulatory processes to reduce potential DILI liability.
Biosketch (Gerbes)

Alexander Gerbes obtained his MD degree following study at Univ. of Munich, UCSF at San Francisco and the Royal Hallamshire Hospital, Sheffield, UK from the Ludwig-Maximilians-University Munich in 1981. He began his professional career as staff physician at the Dept. of Medicine, Univ. of Munich where he was appointed as assistant professor in 1990. Following a research stay at Univ. of Montreal, Canada 1991-1992 he was granted lifetime full professorship (C3) at the Dept. of Medicine, Univ. of Munich in 1995. In 2001 he was appointed as deputy chief of the Dept. of Medicine 2 of the Munich university hospital where he founded the Liver Center Munich in 2008. Currently he is acting chief of the Dept. of Gastroenterology and Hepatology at the Munich university hospital and is medical director of the Munich liver transplantation program.

From the start of his academic career Alexander Gerbes has focused his research on pathophysiology, diagnosis and treatment of liver diseases with emphasis on complications of cirrhosis. He established the DFG research group 440 “Prevention of ischemia-reperfusion injury” and was head of this joint research initiative 2001 – 2008. In recent years he has had an increasing interesting in acute liver injury and in DILI and since 2009 has served on the scientific committee of the CLIF consortium of the EASL. Together with Dr. Andreas Benesic he developed MetaHeps, a novel technology for diagnosis of DILI in individual patients. This research has been supported by grants from exist technology transfer (2012) and the m4 award for research innovation in personalized medicine (2014), respectively.

Alexander Gerbes has been honored with the GASL award of the German Association for the Study of the Liver and the Rudolf-Pichlmayr award of the German Transplant Society. Since 2010 he has served as deputy editor of GUT, a leading journal of gastroenterology and hepatology (2013 impact factor 13,3). He has co-authored over 200 articles in acknowledged journals including N Engl J Med, Lancet, Gastroenterology, Gut, Hepatology and J Hepatol with a lifetime citation of 44 (Hirsch Index).

Biosketch (Benesic)

Following his study of medicine at the Julius-Maximilians-University of Wuerzburg and a training visit at the Royal North Shore Hospital, University of Sydney, Australia, Andreas Benesic obtained his MD degree in 2003. He worked as staff physician at the Dept. of Medicine, Univ. of Wuerzburg in the Dept. of Infectiology and Hepatology. From 2004 to 2006 he held a post doc position at the Institute of Physiology supported by a DFG grant. In 2006 he joined the group of Professor Alexander L. Gerbes at the University of Munich. Since then he has been leading research projects on drug-induced liver injury. He is a member of the Munich liver transplantation program.

From the beginning of his academic career Andreas Benesic has focused his research on pathophysiology and toxicology of food contaminants and drugs, starting with research on nephrotoxicity of the food contaminant ochratoxin A. He performed research on side-effects of HAART in HIV-patients. Afterwards he investigated mechanisms of ifosfamide nephrotoxicity in human primary proximal tubule cells after obtaining personal funding by
Andreas Benesic is member of the editorial board of GUT. He has co-authored several articles on in vitro toxicology and drug side effects.

Abstract: Transforming monocytes into hepatocyte surrogates

Background: Drug-induced liver injury (DILI) is the major cause for acute liver failure in developed countries and accounts for a significant number of drug withdrawals, restrictions of use and clinical trial terminations. A large number of drugs have been shown to cause idiosyncratic DILI (iDILI), typically occurring with low incidence (e.g. 1:10.000), without clear dose-dependency and with very variable latency to onset. According to current concepts an individual’s susceptibility to iDILI by a given drug seems to be influenced by individual hepatic drug metabolism in combination with immune mechanisms. Since there are no in vitro or animal models that reproducibly model iDILI, investigations of the underlying mechanisms remain very challenging.

Aim: Monocytes seem to play a role in modulation of drug hepatotoxicity (1) and might also be partially capable to obtain hepatocyte characteristics (2). We have developed a method to generate hepatocyte like cells from peripheral monocytes (MH) that exhibit several hepatocyte characteristics (3). In order to investigate if MH cells could be useful for the diagnosis of iDILI, we performed a pilot study with MH cells derived from patients with iDILI and patients with other causes of acute liver injury, respectively.

Methods: Monocyte-derived hepatocyte-like (MH) cells were generated after gradient centrifugation and adherence separation as followed by cultivation in media containing Adenosine, IL-3, M-CSF, deoxycholate, caffeine and EGF, FGF-4, Glucagon, Insulin and Heparin, respectively (3). Gene expression analysis and CYP450 activities and induction were compared to primary human hepatocytes from the same donor. Patient data and blood samples were collected prospectively from patients presenting at the Liver Center Munich®, LMU university hospital with acute liver injury and intake of at least one drug with DILI concern. Acute liver injury was defined according to (4) as ALT≥5xULN or AP≥2xULN or ALT≥3 and Bilirubin≥2xULN without history of liver disease or cirrhosis. RUCAM score (5) was used for clinical DILI probability. Typical drug signatures to additionally assess iDILI causality were obtained using the LiverTox website (6) or case reports from literature. For individual toxicity testing MH cells were incubated with the respective drugs. Toxicity was determined by release of LDH, calculated as LDH-activity supernatant / (LDH activity lysate+ LDH-activity supernatant) and complete lysis by detergent was set as 100% toxicity. Results were normalized to 2XSD of the vehicle controls for each test as an experimentally determined upper limit.

Results: Gene expression of ADME-genes in MH cells approximated the expression patterns in primary human hepatocytes from the same donor. Activities and induction of CYP450 in primary human hepatocytes were reflected by MH cells from the same donors.

In order to investigate whether MH cells generated from patients with iDILI can reflect individual drug toxicity, samples of 11 patients with unequivocal iDILI and 12 patients with undoubtedly other causes of liver injury were used. RUCAM was ≥6 in all iDILI cases whereas 2 non DILI cases were false positive. MH cell toxicity ≥2 identified 10 of the 11 iDILI cases and classified all 12 non DILI cases correctly.

As yet 54 cases have been investigated (31 iDILI, 23 non-DILI) and the results seem to corroborate the finding that increased in vitro toxicity in MH cells is found in patients with iDILI. Interestingly, MH cell toxicity seemed to identify the causative drug in polymedicated patients with iDILI. The specificity of the test was investigated using MH cells derived from 81 healthy donors and no toxicity of the drugs implicated in the iDILI cases could be observed.
Conclusions: MH cells represent monocyte derived cells with several hepatocyte functions. The results from the ongoing study suggest that MH cells could be a promising novel tool to confirm or exclude the diagnosis of iDILI in individual patients. MH cells might help with the identification of the causative agent in polymedication. Research to further characterize MH cells using omics-technologies is ongoing. We plan investigations in a greater patient cohort.

References: