

MEMORIAL RESOLUTION
ON BEHALF OF
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David Alastair Flockhart, MD, PhD was born July 22, 1952, in Edinburgh, Scotland, the eldest of five children to Pamela Ellison Flockhart (née Macartney) and the Rev. D. Ross Flockhart. His parents originally hailed from Australia and emigrated to Scotland in 1951 where Ross studied Divinity at Edinburgh University. Both parents were committed to working for social justice by serving the community and as such the family home had an open door policy. The strong current of diverse dinner table discussion and a deep concern for the wellbeing of those less fortunate was an established part of David's early years and throughout the rest of his life. David took great pride in his Scottish heritage and frequently took his three children to visit the family home in East Lothian and the tranquil Isle of Iona – where his family spent many holidays when his father served with the ecumenical Iona Community [courtesy of Carola Akindele-Obe].

As a child, Dr. Flockhart was tutored by a governess, and later attended junior school in Aberdeen. He attended George Watson's College in Edinburgh for the majority of his secondary schooling before earning his undergraduate degree in biochemistry at the University of Bristol in England in 1973 and a Ph.D. from the Welsh National Medical School, UK, in 1976.

After completing his PhD, Dr. Flockhart moved to the United States to do a postdoctoral fellowship in physiology at Vanderbilt University. Following his fellowship, he traveled to New York where he served as Visiting Assistant Professor of Cell Biology at Rockefeller University for one year before returning to Tennessee to take a position as assistant professor in the department of physiology at Vanderbilt University. At this time Dr. Flockhart developed a strong interest in translating basic findings into patient care. In pursuit of this goal he decided to study clinical medicine and enrolled in medical school at the University of Miami from 1984 to 1987. Upon graduation he moved to Washington DC and Georgetown University Medical Center where he completed a medical residency and served as Chief Medical Resident. After completing his residency in 1991, he immediately enrolled in Georgetown University's Clinical Pharmacology fellowship program. He subsequently joined the Division of Clinical Pharmacology, Department of Pharmacology at Georgetown University as a faculty member. There he gained valuable clinical pharmacology experience under the tutelage of internationally recognized scientists including Drs. Darrel Abernethy, MD, PhD, Carl Peck MD, and Raymond Woosley MD, PhD. He went on to serve as acting Chief and then the Director of the Division of Clinical Pharmacology and held the Francis Cabell Brown Professorship.

In 2001, Dr. Flockhart was recruited by Dr. D. Craig Brater to lead the Clinical Pharmacology program at the Indiana University School of Medicine (IUSM) in Indianapolis, Indiana. In addition to serving as the Chief of the Division, Dr. Flockhart held faculty appointments in the departments of Medicine, Medical and Molecular Genetics, Pharmacology and Toxicology and Obstetrics and Gynecology and he held the Edith Gladstein Chair in Cancer Epidemiology and Genetics. He was the Associate Director for

Therapeutics of the Indiana Clinical and Translational Sciences Institute (CTSI). In 2011, he founded the Indiana Institute for Personalized Medicine (IIPM) and served as its director. The IIPM is one of the nation's first such institutes focused on tailoring treatments for individual patients.

Dr. Flockhart was a board-certified clinical pharmacologist and an internist. He was a key player in activities that enhanced the field of clinical pharmacology and translational sciences and he achieved national and international prominence through his pioneering contributions that spanned the entire translational spectrum, but particularly in the areas of drug-drug interactions, pharmacogenomics and personalized medicine. His research touched nearly every aspect of medicine, from cancer to cardiology, and obstetrics to infectious disease.

His early research focused on genetic causes of drug-induced toxicity in humans, including cardiotoxicity caused by antipsychotic drugs (e.g., pimozide). His group was the first to show that pimozide is metabolized mainly by CYP3A, which allowed prediction of its drug-drug interactions (e.g., with clarithromycin, a CYP3A inhibitor). This work also identified genetic polymorphisms of CYP2D6 as the key component in interindividual variability and QTC prolongation by pimozide which led to further study and notable contributions in identifying the genetic polymorphisms of CYP2D6 early on in the 1990s.

Another major contribution made by Dr. Flockhart and his group, and one that has directly impacted countless women around the world, has been the fundamental understanding of the modulation of the beneficial and adverse effects of the anti-estrogen drug tamoxifen, a widely used therapy for breast cancer and other endocrine disorders. His group identified endoxifen, an active metabolite of tamoxifen, and showed the heavy influence of CYP2D6 polymorphisms on the concentrations of this metabolite and tamoxifen treatment outcomes. This work also identified drug interactions that may compromise the efficacy of tamoxifen. These findings formed the basis for a change in the FDA label on tamoxifen and endoxifen is currently being evaluated as a potential new breast cancer therapy. This work also led to the discovery of other active metabolites of tamoxifen that form the basis for a whole new drug development program. Specifically, a group of structures have been identified that interacts with the estrogen receptor system and with aromatase, a sentinel observation that has implications for a number of therapeutic areas in women's health.

Dr. Flockhart was a well-funded investigator, a PI of several U01s, RO1s, U54s, and T32s from the National Institutes of Health (NIH). For more than 10 years, he served as the Principal Investigator of the NIGMS Pharmacogenetics Research Network site at Indiana and as the lead investigator of the Consortium on Breast Cancer Pharmacogenomics (COBRA), an NIH-funded collaboration between the breast cancer programs at the Indiana University School of Medicine, the University of Michigan, Johns Hopkins University and Baylor College of Medicine.

Dr. Flockhart had a strong interest in advancing research in clinical pharmacology in pregnancy and pediatric populations. He co-founded PREGMED, the Indiana University Center for Pharmacogenetics and Therapeutics Research in Maternal and Child Health. This collaborative effort between obstetrics and pediatrics formed the basis for IU's NIH-funded Obstetric-Fetal Pharmacology Research Units Network (U10) grant focused on new discoveries regarding individualized pharmacotherapy in pregnancy on which Dr. Flockhart served as PI. It also led to the awarding of an NICHD Specialized Center in Research in Pediatric Developmental Pharmacology Program (U54) grant on which he served as co-PI with his former trainee, Jamie Renbarger. This award seeks to improve the treatment of children with cancer by identifying the best combinations of biomarkers to predict response to anticancer chemotherapeutic agents and the creation of new dosing algorithms to optimize the treatment of this pediatric population.

In recent years his research was directed at efforts to implement pharmacogenomics as a means of improving drug therapy for the individual patient within short time frames. As PI of the INGENIOUS U01 project, funded by the NIH and part of the IGNITE network, Dr. Flockhart collaborated with other leading researchers from around the nation to study effective application of genomics in clinical care. He quickly assumed a leadership role within IGNITE, serving as the Chairperson of the group until his passing.

Dr. Flockhart's infectious passion for discovery and patient care made him an exceptional teacher and mentor and he has trained a new generation of clinical pharmacologists. Throughout his career he actively mentored 7 medical and graduate students, 27 clinical and postdoctoral fellows and served as a primary mentor for 10 junior faculty members during the course of their career development awards (including RO1, K01, K08, K23, and K12 awards). Many of these junior faculty members have progressed from their K awards to become productive, independently-funded investigators. His mentees now hold academic and leadership position in academic medicine, pharmaceutical industry, and drug regulatory agencies in the USA and around the world.

In addition to his direct mentorship, Dr. Flockhart was exceedingly generous with his time and informally mentored graduate students, fellows and junior faculty throughout IU and beyond. He actively sought to expand the learning opportunities through NIH training grants and he served as PI on adult and pediatric training grants at IU and he developed a clinical pharmacology training program in Obstetrics and Gynecology. A critical component of the training program he developed at IU included a series of didactic lectures that was widely attended by division faculty, fellows and graduate students, as well as pharmacy residents and industry professionals, and he taught Clinical Therapeutics to fourth year medical students. Dr. Flockhart's commitment to teaching extended beyond his work at IU and included organizing and teaching the American Society for Clinical Pharmacology and Therapeutics Curriculum Review Course and lecturing in the NIH Principles of Clinical Pharmacology course. He also developed a critical tool for the rational prescription of medicines that is used by physicians, pharmacists and scientists around the globe through his website, www.drug-interactions.com. Dr. Flockhart further shared his knowledge by lecturing around the world and through his publications of more than 250 articles, reviews, and book chapters.

As a physician and scientist, Dr. Flockhart understood the importance of treating the individual patient and he is widely recognized as a pioneer in promoting personalized medicine. His highly specialized clinical practice focused on adverse drug reactions and patients traveled from around the country, and from abroad, to benefit from his expertise.

D. Flockhart was a leader in the field of clinical pharmacology. He was a member of many professional organizations and he received several of the field's most prestigious awards for his scientific contributions. These include the ASCPT Rawls Palmer Award for Progress in Medicine (2011), ACCP Nathaniel T. Kitt Award for Excellence in Research and Education (2009), William B. Abrams Lecture, FDA and ASCPT (2014), and Leon I Goldberg Memorial Lecture Lectureship Award, University of Chicago (2015). He served on NIH study sections for NIGMS, NIA, NIDA and NIMH, and completed a 5 year term as a member of the NCRR GCRC study section. In July 2010, he was appointed to the NCRR Advisory Council. In 2015, he became Chair of the National Human Genome Research Institute NIH/NHGRI IGNITE Network. He was the North American editor of British Journal of Clinical Pharmacology and he served as associate editor or editorial board member of several additional peer reviewed, prestigious pharmacology and pharmacogenomics journals.

Dr. Flockhart's work in implementation of pharmacogenomics connected him with the Personalized Medicine Coalition, an advocacy group committed to the adoption and implementation of personalized

medicine. He was elected to Personalized Medicine Coalition's Board of Directors just months before he passed away.

Dr. Flockhart formed a strong pharmacogenomics group at IUSM which broadened and deepened the opportunities for collaboration in both research and training across different basic and clinical specialties within the University and beyond. Under Dr. Flockhart's leadership, the Division of Clinical Pharmacology and the Indiana Institute for Personalized Medicine has emerged as a vibrant, multidisciplinary, and energetic group of well-funded investigators drawn from a broad range of specialties. The multidisciplinary nature of this group is a critical element within the translational research enterprise of the Indiana University medical center. The division is unique and esteemed among clinical pharmacology divisions in the US.

Dr. Flockhart made immeasurable contributions to the field of clinical pharmacology, pharmacogenomics, and personalized medicine in particular. We have lost a generous and humble man, a friend and a colleague, a great scientist, mentor, and visionary leader. He has influenced immensely the lives and careers of countless scientists and patients and he made the world a better place. We will greatly miss him and Clinical Pharmacology is considerably poorer by his passing. Our sympathies go to his children (Andrew, Julia and Peter), his siblings (Patrick, Carola and Andy and their spouses) and Tara, his former wife.

Nimita Dave, PhD
Zeruesenay Desta, PhD
Christine McDonald
Todd Skaar, PhD

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