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EDITORIAL

Special issue of *The Journal of Antibiotics* dedicated to the late Professor C Richard Hutchinson

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It is our distinct privilege as Guest Editors of this special issue of *The Journal of Antibiotics* to honor the late Professor C Richard Hutchinson with a diverse collection of Reviews, Original Research Articles and Notes on various aspects of natural product discovery, biosynthesis, engineering, and drug discovery and development, passionately contributed by many of his former students, postdoctoral fellows, collaborators, colleagues and friends. These contributions serve as a reminder of the remarkable impact that extraordinarily passionate individual can have on any chosen discipline.

C Richard 'Dick'/'Hutch' Hutchinson, PhD, Edward Leete Professor Emeritus of Medicinal Chemistry and Professor Emeritus of Bacteriology, University of Wisconsin-Madison, died on 5 January 2010 at the age of 66 after a courageous 3-month fight against cancer.[1] During a distinguished career that spanned nearly four decades at the University of Connecticut, University of Wisconsin-Madison, Kosan Biosciences and Centrose LLC, Professor Hutchinson trained many future academicians and industrial leaders, touched many lives with his wisdom, made major advances in understanding the biosynthesis of naturally occurring drugs through studies of the molecular genetics and biochemistry of antibiotics production in microorganisms, and worked tirelessly and enthusiastically through creative entrepreneurship to translate laboratory findings into clinical products.

Professor Hutchinson's early training and independent work were in chemistry, where he made many important contributions to alkaloid biosynthesis. He initially focused on the biosynthesis of plant products such as camptothecin and iridoids. Even to this day his studies on camptothecin represent most of what we know about the biosynthesis of this important clinical compound.[2–5] He extended his work into microbial natural products, beginning with macrolide brefeldin A[6–11] and polyether lasalocid A[12–16] in the late 1970s. In the early 1980s, attracted to microbial genetics, he gradually and, eventually, entirely shifted the focus of his biosynthetic work toward a genetic and biochemical approach. For the following 20 years, he studied the biosynthesis of many biomedically important polyketide natural products, heavily pioneering the field of combinatorial biosynthesis and natural product drug discovery. Professor Hutchinson was one of the world leaders who elegantly blended the art and science of chemistry, biochemistry and molecular biology to understand secondary metabolite biosynthesis in actinomycetes, and was one of the very first chemists to master and combine these fields.

Professor Hutchinson made seminal contributions to both type I and type II polyketide synthases (PKSs). For type II PKSs, he is best known for his work on the tetracenomycin (Tcm) and daunorubicin

(Dnr) biosynthesis gene clusters.[17] Legacies of his work include (i) the *tcm* and *dnr* clusters as two of the best-characterized type II PKS gene clusters to date, serving as models for aromatic polyketide biosynthesis in general;[18–21] (ii) *in vitro* reconstitution and characterization of the Tcm PKS, which opened the possibility to study the enzyme mechanism and structure of type II PKS *in vitro*;[22] and (iii) cross-talk between fatty acid biosynthesis and Tcm biosynthesis in *Streptomyces glaucescens*, which led to the identification and subsequent confirmation of the malonyl CoA:acyl carrier protein transferase as the missing link between fatty acid (primary metabolism) and polyketide biosynthesis (secondary metabolism).[23] For type I PKSs, he is best known for his work on erythromycin, tylosin and rifamycin (Rif) biosynthesis gene clusters. Highlights from his work in this field include (i) his hypothesis and demonstration by feeding experiments that type I PKS acts by a processive mechanism, which was widely considered as a milestone for macrolide biosynthesis; this conceptual advance was

critical for the subsequent discovery and characterization of the modular type I PKS;[24] (ii) the fundamental studies on erythromycin biosynthesis in *Saccharopolyspora erythraea*, which were critical to the eventual discovery of the very first modular type I PKS;[25–30] and (iii) characterization of the *rif* cluster and isolation of a family of elongating polyketide intermediates, which experimentally confirmed for the first time the processive mechanism of type I PKS.[31–33]

Professor Hutchinson was a pioneer of combinatorial biosynthesis for the structural diversity of natural products. The most notable contribution of his laboratory was the development of methodologies, strategies and concepts dictating effective combinatorial biosynthesis. Highlights from his laboratory include (i) the demonstration that the ketoacyl synthase α- and β-subunits of type II PKS both contribute to the chain length for aromatic polyketide biosynthesis;[34,35] (ii) the recognition that synthesis of aromatic polyketides bearing starter units other than acetate requires dedicated enzymes that interact with the type II PKS complex;[36,37] (iii) exploration of environmental DNAs for the production of complex natural products;[38] and (iv) the production of epirubicin, a commercially important clinical drug, by a metabolically engineered organism,[39] the only example known to date that has been practically advanced by combinatorial biosynthesis.

While his early work on brefeldin A still represents some of the best examples of fungal polyketide biosynthesis by the traditional approaches,[6–11] Professor Hutchinson returned to fungal polyketides in the 1990s, but adopting a more contemporary approach. Recognizing that fungal PKSs are mechanistically and structurally distinct from bacterial PKSs and that fungal polyketides represent a major source of clinically important natural products, he worked on lovastatin biosynthesis in *Aspergillus terreus* as a model system for polyketide biosynthesis in fungi. The cloning, sequencing and characterization of lovastatin gene cluster unveiled a novel type of PKS and set the stage for the engineering and production of novel lovastatin analogs,[40,41] a class of the most successful antihypercholesterolemic drugs on the market.

Professor Hutchinson helped to create the mold for what is now termed 'translational research'. He was integral to the operations of numerous pharmaceutical companies. After retiring from the University of Wisconsin-Madison in 2000, he joined Kosan Biosciences, Hayward, CA as a Vice President of New Technologies. He returned part-time to the University of Wisconsin-Madison in 2004 to help run the University of Wisconsin-Madison National Cooperative Drug Discovery Group. In December 2006 he left Kosan and shortly thereafter co-founded Centrose LLC, Madison, WI. Most recently, he served as the President and Chief Scientific Officer of Centrose LLC.

Professor Hutchinson was an extraordinary teacher and mentor who trained and inspired a generation of young scientists in the chemistry, biochemistry and molecular biology of secondary metabolite biosynthesis. During his tenure at the University of Connecticut (1971–1974) and University of Wisconsin-Madison (1977–2000), Professor Hutchinson trained and mentored over 100 graduate students, postdoctoral fellows and visiting scientists. Many of these people are now successful scientists at both academic and industrial institutions nationally and internationally. A symposium, titled Natural Product Biosynthesis, Engineering, and Drug Discovery, honoring Professor Hutchinson's distinguished career and featuring 11 presentations by former Hutch Lab members, on the occasion of his 65th birthday, was held in 2008. The symposium was attended by more than 150 former lab members, collaborators, colleagues and friends. All were, and continue to be, grateful beyond words to have had the opportunity to celebrate Professor Hutchinson's accomplishments and life example and to show their appreciation to his tremendous contributions to his beloved profession. The annual C Richard Hutchinson Lecture was established in 2008 at the School of Pharmacy, University of Wisconsin-Madison, ensuring that Professor Hutchinson's legacy of scientific rigor, progressivism and standard of excellence will be continued.

Finally, we would like to express our sincere gratitude and appreciation to the authors for their outstanding contributions to this special issue dedicated to Professor Hutchinson. One of us (BS) also would like to take this opportunity to pay his tribute to Professor Hutchinson for the scholarly and scientific advice and mentorship that has so profoundly impacted his career, as well as the friendship, for which he and his family are forever grateful. Professor Hutchinson will be remembered for his strength of spirit, zeal for life and new experiences, and his boundless intellectual curiosity. He has left an indelible mark, not only in our field of science, but even more so on the lives of those lucky enough to have learned from him and who considered him a friend and a role model.

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