IN HONOR OF ROBERT BITTMAN

1942-2014

Overview by Gabor Tigyi, Julie Saba, Nigel J. Pyne, Richard N. Kolesnick, Gilbert Arthur, Elina Ikonen, Antonio Gomez-Munoz, and Walter Shaw

With the passing of Dr. Robert Bittman the lipid science community has lost one of its leading organic chemists. He set new standards in the synthesis of bioactive lipids and their analogs and has done it with ingenuity and elegance. His synthetic schemes benefited basic researchers and industrial chemists alike. Those of us who collaborated with him were beneficiaries of unique reagents, which provided new tools that led to many discoveries.

Dr. Bittman was a gifted student who distinguished himself at an early age by graduating from high school at the age of 16. He finished his undergraduate studies as a chemistry major at Queens College of the City University of New York, the same university that he joined the faculty of seven years later. He obtained his PhD in chemistry at University of California, Berkeley under the mentorship of Andrew Streitwieser in 1965. The same year, he was accepted to the laboratory of Nobel Laureate Manfred Eigen at the Max Planck Institute for Physical Chemistry in Göttingen, Germany. He remained a favorite and respected fellow of Prof. Eigen and they kept in touch throughout Bob’s career. In 1966, he joined the faculty of CUNY and rose through the ranks to become Distinguished Professor of Chemistry and Biochemistry of Queens College and the Graduate Center of CUNY in 1988. He was an MERIT awardee of the National Heart Lung and Blood Institute from 1986. He dedicated a lot of his time to provide novel reagents to lipid biochemists and chemists in federal research programs. Bob served on numerous NIH Study Sections, including the Biophysical Chemistry Study Section for two periods, the Panel on Minority Biomedical Research Support, the Panel on the National Cooperative Drug Discovery Group, and on a Program Project Review Panel.

Bittman’s synthetic schemes benefited basic researchers and industrial chemists alike. Those of us who collaborated with him were beneficiaries of unique reagents, which provided new tools
that led to many discoveries. Bittman synthesized analogs of phospholipids such as lysophosphatidic acid, phosphatidylinositol, sphingosine 1-phosphate, phosphatidylcholine, and sphingomyelin; antitumor ether lipids such as ET-18-OCH3; immunostimulatory lipids such as -galactosylceramide; immunosuppressive lipids such as FTY720; photoactivatable cholesterol and phospholipids; cell trafficking lipid tools such as BODIPY-cholesterol and BODIPY-lactosylceramide, and chemopreventive sphingadienes. He was the first to prepare cell-permeable ceramide analogs in 1992 giving ceramide research a huge impetus. He developed many new methods for the enantioselective synthesis of sphingosine, ceramide, and phospholipids. With these new reagents he probed the roles of sphingolipids in the fusion of alpha viruses with cholesterol-containing viruses; sterol side chain structure and sphingomyelin structure in lipid raft formation; and the effects of ceramide structure on ceramide’s dipole potential in monolayers. He published 321 peer-reviewed papers with several more under preparation posthumously by his coworkers and collaborators. Dr Bittman has contributed 64 book chapters; many of them were published in the Organic Reactions, series by Wiley and Sons. He has 19 US patents granted or pending.

Dr. Bittman’s research has made a fundamental impact on lipid research in the United States and worldwide. He presented plenary lectures at many international conferences from Finland to Japan. Dr. Bittman was an outstanding teacher and mentor. He has trained over 20 post-doctoral and 23 graduate students, all of whom have moved on to important positions in lipid science. Dr. Bittman for many years has taught a course in Membrane Lipid Biochemistry at the City University of New York that featured leading investigators in the lipid field from the USA. This course was a favorite among the graduate students, and for those of us invited as visiting professors it was an honor we were much looking forward to. He served as member and later as Chairman of the Biophysics Section of the New York Academy of Sciences. Dr Bittman was elected Vice President of the Queens College Chapter of Phi Beta Kappa. Dr. Bittman has served on the editorial board of the Journal of Lipid Research, Subcellular Biochemistry, Chemistry and Physics of Lipids, Journal of Liposome Research. He was Secretary and Co-Secretary Organic Reactions since 1968 to the end of his life. He was honored with the Avanti Award of the American Society of Biochemistry and Molecular Biology in 2003 and as a Fellow of the AAAS in 2004.
Dr. Bittman was an avid tennis player and a fan of the performing arts. He would never miss the US Open Championship and had an exquisite understanding of the game and the players. He was happy to tell me that he tries to make it to the tennis court as often as he can while receiving chemo- and radiation therapy. Because of his exceptional determination, will power and of the love of his work, he continued his research until the very end without letting anybody know about his terminal disease. With the passing of Dr. Bittman, the field has lost an exceptional investigator, a scholar, and to those of us who knew him a dear friend.

PERSONAL TRIBUTES

*Gilbert Arthur*

As a relatively new assistant professor at the University of Manitoba scouting around for a project completely different from anything I had done to date, I stumbled on the Antitumor Ether Lipids and Bob Bittman in 1992. Bob had synthesized a number of compounds that I was sure would be invaluable to the research I wanted to pursue and after quickly realizing the futility of attempting to synthesize them myself, I decided to write to Bob and request some of his compounds. The letter was written with the expectation that there would be no response. After all, would a Distinguished Professor at Queens College, CUNY, even have the time to respond to an assistant professor at the University of Manitoba with no track record in the field? To my surprise and delight Bob responded almost immediately. He promptly sent the compounds and we have been collaborating ever since. Together we have published at least 23 papers, a book chapter and have 3 joint patents. He has been a co-investigator on several of my grants. It is not an exaggeration to say that I owe my career to Bob. I consider him a very good friend and looked forward to my trips to New York every 2 years to participate in his Membrane Lipid Biochemistry course. Bob and Marlene always warmly welcomed me into their home and were very generous with their time and hospitality. Bob spent the weekends showing me around NYC and always had something new planned for each stay. I always left for Winnipeg loaded down
with new compounds and full of enthusiasm after our chats and in great anticipation of the results we would get with the new compounds. I feel very privileged to have met and known such a great scientist and an even greater human being. Bob will always have a special place in my heart and I will miss him dearly.

Antonio Gomez-Munoz

My first interaction with Bob dates back to 1993 when I was a postdoc at the University of Alberta in Edmonton (Canada). At that time I became interested in ceramide 1-phosphate, a phosphosphingolipid that had been observed by Rich Kolesnick in human leukemia cells a couple of years before. This molecule was not commercially available at the time, so I needed someone who could be capable of synthesizing it for me. I was fortunate to have heard of a highly reputed organic chemist in the States who might give us a hand on this endeavor, and there was Bob Bittman! So we contacted Bob and he became even more enthusiastic than I on the project. Upon speaking with him, I could feel his energy and enthusiasm through my skin. Not only he provided me with the compound, but he taught me excellent organic chemistry and gave me suggestions that turned out to be crucial for my studies. Our first joint publication came in 1995 when I was back in Spain. We now have a total of six publications together on caged ceramide 1-phosphate, plus three others that are in preparation. Paradoxically, Bob and I did not meet personally until 2012, but I can say that we have kept a long-lasting friendship via e-mail and phone discussions from the very beginning. In the spring of 2012 Bob landed in Bilbao with the only purpose of meeting up (at last!) and chatting about our future work. He was accompanied by his wife Marlene, and we had a great time touring around town and discussing exciting and provocative research plans. We met a couple of more times in New York in the last two years to plan on future work. As time goes by, I realize how much I have learned from Bob, and how important he has been for my scientific career. Bob was an international authority in organic chemistry and a rigorous and committed scientist, but above all he was a caring person and a good friend. I will miss him, and my heart will always keep a place for him.

Richard Kolesnick
I had the privilege of publishing four papers with Bob between 1991 and 1996. Around 1989, I realized that I needed a short-chain ceramide to add to cells to study signal transduction, and called Norm Radin. Norm said that he thought he might have some C8:0 ceramide buried in a freezer from the 1970’s that he’d try to find. Indeed he found a vial, and it worked beautifully in a set of studies looking at EGF receptor phosphorylation in collaboration with Tzipora Goldkorn and John Mendelsohn. It was at this time that I found Bob Bittman, who I came to regard as a national treasure. I needed additional sphingolipids to study structure function relationships for our newly-identified ceramide-activated protein kinase. Amazingly, there was this chemist at Queens College of CUNY, right over the 59th Street Bridge, who was primarily a lipid chemist, and not just any lipids, but he specialized in sphingolipids, lipids without a cause.

As far as I am concerned, Bob Bittman was the number one go-to-guy when you wanted a sphingolipid synthesized, bar none. A short telephone call request to Bob was never a short call. After Bob would let you to explain your needs for a few minutes, he would have ten additional ideas as to how to generate new analogs that you never could have conceived of, that would further advance your idea. After his 45-minute tutorial on the structure of sphingolipids and their organic synthesis that was mostly fascinating, you realized that you really didn’t know as much about your field as you thought, and you were thankful. Further, Bob did not seem to have the words, “no” or “can’t” in his vocabulary. He would say, let me go into the lab and see what I can whip up. About six weeks later, you would get a call where he’d state that he’d made the analog you wanted, a couple of the ones that you’d discussed, and a few more that he thought of in between. His lab was a veritable sphingolipid candy store, and you were always dazzled. Bob was a gem and will be greatly missed by those of us who had a chance to see him sparkle.

_Nigel Pyne_

I was introduced to Bob by Gabor Tigyi in the form of a small tube containing a chemical compound he had made when I visited Gabor in his laboratory in 2009. Little did I know it then, but this small tube of material, which was put in my suitcase on my homeward journey, would lead to an enriching collaboration and friendship with Bob. We ended up publishing 16 papers together with Sue Pyne that allowed us to interrogate sphingosine 1-phosphate biology. Sadly, I
only wish we had more time together. For me, the papers we published are a lasting memory of Bob’s genius in chemical design and eye to spot a complex biological problem that required solving. This is actually of very rare attribute; to be able to discard the periphery and to go straight to the central question. Bob was rather good at spotting these central questions, primarily because his mind was one that was unburdened and constantly searching for biology problems to solve with his compounds. His publication record is a testament to how good he was at that. In fact, his chemical synthesis of discriminatory tools, based on rather complex and challenging organic chemistry has really helped biologists decipher lipid biology. He was a trailblazer in this regard and many people benefited enormously from Bob’s vocation. Bob’s attention to detail was a distinguishing feature that I think set him apart from other scientists; of course his abilities in chemistry were spotted early in his career, with him working with the best. This included the Nobel Laureate Manfred Eigen at the Max Planck Institute in Gottingen, Germany. Bob made a very significant contribution to enzyme kinetics at that time using stop-flow kinetics, which was very cutting edge at that time. He was fortunate in his life to have worked at a time in biochemistry that was still in the golden age and to have made a substantial contribution to it. His attention to detail was also a godsend to proofing manuscripts. Although I have to say we always sent manuscripts to him with some apprehension; knowing they would come back with large numbers of mistakes corrected, he was really a line-editors dream (but probably making them largely redundant) with all typos spotted and grammar, punctuation and spaces corrected. This just goes to show that he had a good education in English and is a real testament to his teachers. He was always patient in allowing you to pick up the chemistry and I think this really demonstrated his capacity to teach well. I was fortunate to teach in one of his courses in 2011 at CUNY and I could really see the high regard and respect his students had for him. And of course he has mentored many students and post-docs coming through his lab, something which I think they will regard with fondness in the future. To me Bob was a New Yorker; tough, fair and always friendly with a lot of warmth. He could have worked anywhere in the world as he was truly distinguished in his field, but I think he was honest to his roots and that was New York, where he had the support of Marlene and family. There were no airs or graces with Bob, just honesty and hard work; that’s what you see from him and his scientific papers. I was fortunate to know him and to have some legacy with him with our work together,
but this will not replace the friendship. I and Sue will miss him very much, but, to use tennis parlance, at least he played a love game in life.

Julie Saba

I met Bob in 2005 at an ASBMB meeting, after having known him through his published work for many years. I remember being struck with an immediate affinity for the man who within minutes of our introduction began postulating structures and chemical hypotheses while leaning casually over the banister in the fifth floor hallway and looking out into the empty space of the gallery as though he could see the chemical structures floating there. As we chatted during that first encounter, Bob’s scientific brilliance, curiosity, determination, and utter unpretentiousness impressed me deeply. These are the characteristics that have continued to make it such a pleasure and an honor to collaborate with him as I have done for the past decade. Our collaboration has resulted in six publications and three manuscripts in preparation. However, even more than the publications, the bounty of collaborating with Bob lies in what he has taught me about chemistry in particular, and about how to approach scientific problems in general. His insight and contributions to the field are seminal and unique. He has generated compound standards, fluorescently labeled molecular tools, reactive intermediates and potential therapeutic and nutraceutical agents. Such tools are never made available through commercial venues until someone with Bob’s ingenuity develops the methods to synthesize them, leading the way for others. Without these precious reagents, my laboratory would never have been able to investigate the influence of lipids and the enzymes that modify them on complex processes such as cancer, inflammation, and the integrity of DNA. While the names of the many structures Bob has synthesized would bore all but the geekiest of us, the insights that were made possible by Bob’s ingenious contributions to the projects of so many of our colleagues are relevant to everyone who eats food, breathes and burns oxygen and whose bodies are susceptible to the ruthless ravages of human disease. I know that I speak for the entire field in saying that Bob was not just a colleague. He was dear to us, and he will be deeply missed.

Walt Shaw

I have known Bob since the early 70's and during this time I have seen him work his synthetic “sorcery” with organic molecules to produce numerous compounds that were thought to be beyond our field’s current synthetic capabilities. His knowledge of biochemistry, biophysics and biology led him to produce reagents that expanded biochemical, biophysical and biological
understanding of lipids. A great example of these molecules is his fluorescent cholesterol derivative that is routinely used to study the interaction of cholesterol in biological membranes. Of course, his work with sphingolipids is legendary. Bob’s personal interactions with his colleagues exemplified a kind and generous personality. Bob visited Avanti several years ago when he was the plenary speaker at the Southeastern Regional Lipid Conference. During his visit he readily shared from his vast knowledge of synthetic wiles, and I was fortunate to have had the opportunity to gain some small insight into his passion for the synthesis of lipid molecules. Being honored as the 2003 recipient of the ASBMB Avanti Award in Lipids demonstrated his tremendous impact on lipid research and the respect which he has garnered over the years from his colleagues. Our field has lost a great chemist, but more importantly, the World has lost a truly great man.

Elina Ikonen

How many times have you sent an email to a stranger and hoped for a reply – in vain? I sent an email to a complete stranger almost 10 years ago and was not expecting any response. This time I was completely wrong. I had hit a gold mine! This gold mine was Bob Bittman. My question was whether he might be willing to share one of the fluorescent lipid derivatives he had recently synthesized, BODIPY-cholesterol, with us. Not only did he reply promptly but more positively than I ever expected. This was the beginning of an active collaboration that, among other things, defined this compound as being suitable for assessing the behavior of cholesterol in cell membranes.

Bob has synthesized several lipid analogs for my lab based on our naïve inquiries of whether this or that compound could be synthesized. Rather than being frustrated or bored about our inquiries, he always took them seriously and went through the trouble of explaining why some of our suggestions may or may not be feasible. We all hear buzzwords about crossing borders, doing multidisciplinary science etc. but in reality what this entails is a person – a person like Bob: a top-notch expert in his area with a curious, humble attitude towards other areas of science. A highly gifted, generous person. And a disciplined collaborator who actually keeps his promises. Like Bob always did. Well, with the exception that he often did more than promised.
I only met Bob once. But I know him much, much better than what one would assume based on this. Bob and I obtained a jubileum grant from the Finnish Medical Foundation Duodecim for 2011-2012, and in the ensuing meeting, I had the pleasure of hosting Bob and Marlene in Helsinki. I cherish wonderful memories of this visit. It also brought Bob to life to my daughters, who had gotten used to mommy discussing/emailing with Bob in the evenings (7 h time difference between Helsinki and New York). But that this person, a Distinguished American Professor, actually showed up, in the flesh, with his lively wonderful wife in Helsinki was astonishing.

We have so far published seven papers together with Bob. One of the latest ones was chosen as the best biomedical paper of the year in Finland (Kanerva et al. Dev Cell 2013). The novel cholesterol analog synthesized by Bob was instrumental for this study. We are continuing on a number of additional tracks with yet other compounds from Bob and novel assays based on using these probes in live-cell imaging. Bob’s legacy will keep on living.

Gabor Tigyi

I was introduced to Bob by Fred Snyder in 1995 at a conference in Taos. As a young assistant professor, I was looking for a collaborator who could help us develop inhibitors of the different lysophosphatidic acid receptors. Bob needed no convincing to realize the enormous potential of harnessing the LPA system, and we began a life-long collaboration that grew into a friendship. We coauthored 17 papers over the years. He was as much a sculptor of organic molecules as he was of sentences, who would not tolerate the smallest ambiguity in his manuscripts. Bob created many reagents for the LPA and sphingolipid field that are in use by investigators around the world. Our professional interactions expanded into a friendship between our families and children. We have stayed at each other’s houses for visits. We were more frequent visitors to the Bittman household. During these visits we enjoyed the hospitality of Bob and Marlene. They helped plan our visits with what shows, exhibits to visit and what restaurants to eat at. My wife and I always felt a close friendship with Bob and Marlene. They were exceptional folks who always rose from the worst challenges of life. Their house burned down while they were at the movies on a Friday evening just to arrive to see that there was nothing left. Bob was deeply
saddened by the loss of the family dog, a golden retriever. One of the first things they have replaced was the dog, a golden doodle named Charlie. Bob was always a very disciplined and proper gentleman, except when dealing with Charlie, when he was the dog’s best pal. It was on a Sunday evening shortly after 9 pm when the phone rang and the caller ID showed Bob’s name. I thought he misdialed; I could not imagine what he wanted to talk about at this time of the day. He broke the news that he has cancer and it is one of the worse kinds. He was calm and told me about his plan how to fight the disease against all odds. My wife and I were completely shocked and stayed up that night unable to cope with the prospect of losing Bob. He survived the diagnosis by many-many more months than projected. In a way, it was his triumph over an unbeatable disease.