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CORRESPONDENCE

Epilogue to the Gerald Maggiora *Festschrift*: a tribute to an exemplary mentor, colleague, collaborator, and innovator

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Abstract

In May 2022, *JCAMD* published a Special Issue in honor of Gerald (Gerry) Maggiora, whose scientific leadership over many decades advanced the fields of computational chemistry and chemoinformatics for drug discovery. Along the way, he has impacted many researchers in both academia and the pharmaceutical industry. In this Epilogue, we explain the origins of the *Festschrift* and present a series of first-hand vignettes, in approximate chronological sequence, that together paint a picture of this remarkable man. Whether they highlight Gerry's endless curiosity about molecular life sciences or his willingness to challenge conventional wisdom or his generous support of junior colleagues and peers, these colleagues and collaborators are united in their appreciation of his positive influence. These tributes also reflect key trends and themes during the evolution of modern drug discovery, seen through the lens of people who worked with a visionary leader. Junior scientists will find an inspiring roadmap for creative collegiality and collaboration.

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"If your actions inspire others to dream more, learn more, do more and become more, you are a leader"—Dolly Parton, 1997 [1]

A Trek to the Sonoran Desert: Origins of the Gerald Maggiora Special Issue

Veerabahu Shanmugasundaram, Jürgen Bajorath

What catalysed a group of individuals to travel long hours from Basel (Switzerland), Barcelona (Spain), Mexico City (Mexico), and from various corners of the USA—Arizona, California, Connecticut, Kansas, Massachusetts, Michigan, New Jersey, and New York—to trek to the Sonoran Desert near Tucson, Arizona, in late February 2019?

No, it was not the beautiful scenic vistas of Sabino Canyon in the Santa Catalina Mountains, neither was it the long stalactites underground in Kartchner Caverns. Nor was it the sunny weather and sandy wilderness of this region. In fact, prior to their journey, these individuals were cautioned by several well-meaning Tucson residents to stay away from the mad crowds gathering during the Tucson Gem and Mineral Show held at the same time and because it was going to be unusually cold that particular weekend—well, it might even snow! And yes, they were right, it certainly did snow that weekend in the Sonoran Desert.

And it was only partly the Mini-Symposium, "Drug Discovery—Current Trends and Future Prospects," that we had organized at the University of Arizona, Tucson. Rather, to this group of self-professed and dedicated "Maggiora Mentees," this was an opportunity to bask and recharge themselves in the aura of their mentor—Gerry Maggiora—(Fig. 1) to celebrate his 80th birthday and give salute to decades of impressive science (Fig. 2).

Gerry was a full professor at the University of Kansas, in Lawrence, before he was recruited by the Upjohn Company to lead their Computer-Aided Drug Design (CADD) Group. Later he transitioned from Pharmacia back to the University of Arizona, Tucson, to pursue his academic interests. One of the unusual legacies of Gerry's career in the pharmaceutical industry is the impressive number of scientists and researchers working in the CADD field whom he has mentored and/or collaborated with. Many of these individuals work or have worked in the biotech/pharmaceutical industry and in universities or research institutions around the world and are thought leaders in their own right.

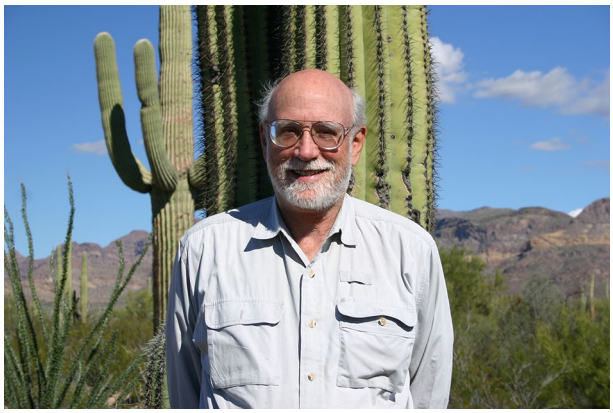

Fig. 1 Gerald (Gerry) M. Maggiora, in the Sonoran Desert outside Tucson, AZ, circa 2006

This type of positive impact and influence Gerry has had on the next scientific generations while in the industry is far from being the norm and, unfortunately, is not often witnessed anymore. Perhaps his unparalleled creative approaches in research, his ability to provoke thinking towards off-the-beaten paths, his work ethic, inexhaustible drive and positive energy, or his joie de vivre attracted many of us. Whatever it was—and still is—we needed a bolus of it, and we came to bottle it up and take it back home to imbue, replant, or clone it. Gerry has always been – and will always remain—a true student of the scientific method, a pioneer, positive role model, teacher, advisor, consultant, and a great friend to many of us.

Needless to say, it was just a matter of time until our collective affections, so beautifully reinforced during the Sonoran Desert trek, would translate into another manifestation of Gerry's legacy. Terry Stouch, who was present at this gathering, felt that spark and was inspired to initiate a Journal of Computer-Aided Molecular Design (*JCAMD*) *Festschrift* for CADD thought leaders in the field. Terry knew he could call upon Jürgen Bajorath, who was feeling guilty about being unable to travel from Germany (due to mandatory commitments at the University of Bonn at the very same time), to join the endeavor.

These efforts resulted in an avantgarde Gerald Maggiora Special Issue of *JCAMD* in May 2022 (Volume 36, Issue 5), which was planned and initiated by Terry Stouch, Jürgen Bajorath, and Veerabahu (Veer) Shanmugasundaram and published with Jürgen acting as a Guest Editor. This Special Issue is equally relevant for CADD aficionados and

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Fig. 2 Attendees at the "Drug Discovery—Current Trends and Future Prospects" Mini-Symposium, February, 2019, Tucson, AZ
Back row (L to R): Veerabahu Shanmugasundaram, Ashwini Shanmugasundaram, Jeff Howe, Christian Parker, Mark Johnson, Karina Martinez-Mayorga, Mic Lajiness, Herschel Weintraub, Joe Moon, John Van Drie, Ludwig Weimann, Terry Peppard, Pat Walters, Andrea Walters, Michele Maggiora, Norma Durazo, Alice Bodnar, Paul Bodnar, Nathalie Meurice
Front row (L to R): Wendy Cornell, Andrea Miller, Susan Maggiora, Gerry Maggiora, Jane Peppard, José Medina-Franco

Gerry's followers and will hopefully trigger further scientific discourse that will bloom every year like the cactus flowers in the Sonoran Desert.

The research papers and a personal reflection ("The Power of a Mentor") by Michael (Mic) Lajiness in the *Festschrift* are complemented by this multi-author tribute, which was conceptualized and spearheaded by Veer. We wish to thank all the authors who contributed to the Special Issue and this multi-author epilogue to celebrate Gerry, his scientific careers, and his impact on us and the field. Our special thanks are due to Linda L. Restifo who substantially contributed to and shaped the epilogue.

Reflections about Gerry Maggiora

Ralph (Chris) Christoffersen

In the fall of 1966, I took my first real job and arrived at the University of Kansas (KU) as an Assistant Professor of Chemistry, and proceeded to set up a research group using computational chemistry and ab initio quantum mechanics to study chemistry problems. Shortly after arrival I was able to recruit my first postdoc—Gerry Maggiora. Gerry had just finished his PhD in biophysics and drove with his wife Linda from San Francisco to Lawrence, Kansas, to help me start the research group. It must have been quite a shock to move from the San Francisco area to Lawrence, Kansas, but Gerry jumped right in and got to work.

We were a bit of an "odd couple", since I had worked on ab initio computational studies of very small molecules (H^{3+}), and Gerry had quite different interests in theoretical problems in biochemistry. In addition, we were surrounded by a very collaborative group of faculty members in Chemistry, Biochemistry and Medicinal Chemistry who kept telling us how quantum mechanics ought to be able to make a significant contribution to problems of interest to them. So, the earliest days of my career were filled with conversations with Gerry how we might develop a meaningful research program. After a long series of conversations, we decided that we would try to do something unheard of in the quantum mechanics field at that time; we decided to apply ab initio quantum mechanics and computational chemistry to large molecules, including those of pharmaceutical interest.

The approach used Gaussian basis functions, since we knew that all of the integrals could be solved, and formulated a Hartree–Fock computational approach to determining wave functions and energetics for medium-sized organic molecules. We located some of the Gaussian orbitals in bonding regions of the molecule, since our interest was in chemical bonds and not nuclear energies, and called the approach "Ab Initio Studies of Large Molecules Using Molecular Fragments." We soon added the use of multiple configurations to the studies so that we could estimate correlation effects as well. Not surprisingly, we used a huge amount of computer time, and quickly became the largest computer users on the campus.

The results were quite encouraging, and I wound up publishing more than 100 peer reviewed papers, many of them having Gerry as a co-lead author. We thought of these studies as creating a new field of research, that evolved into Quantitative Structure–Activity Relationship (QSAR) modeling and other related studies on large molecules that have had a significant impact in both chemistry and pharmaceutical research.

Along the way, Gerry's talents and insights did not go unnoticed. In a most unusual move for a post-doc, Gerry was appointed to the KU faculty as a tenure-track member and went on to have a very distinguished academic career at KU. His ability to create new theoretical approaches to biology and biochemistry problems were very valuable and unusual assets and put him in demand from both students and faculty.

By 1983 my interests had taken me to the Upjohn Company in Kalamazoo, Michigan, and I took the opportunity to recruit Gerry to come to Upjohn to be a colleague once again and form the Computational Chemistry Group. This was a new endeavor for both Upjohn and the pharmaceutical community, intended to show how computational chemistry was relevant to drug design in a commercial setting.

Gerry has since returned to the academic world, where he is continuing to produce new and innovative approaches to solving chemistry and biological problems using theoretical and computational techniques. He has been a terrific friend and colleague over more than 50 years, and it is a real pleasure to honor his work.

The 1986 Michigan 500. A recollection

James D. Petke

My association with Gerry Maggiora goes back a long way, beginning in 1976, when I joined the research group co-directed by Gerry and Ralph Christoffersen in the chemistry department at the University of Kansas. We were using quantum mechanical methods to calculate visible and ultraviolet absorption spectra of photosynthetically important molecules, such as chlorophylls, under a grant from what is now the U. S. Department of Energy. Later in 1985, I joined the CADD research group at The Upjohn Company in Kalamazoo, Michigan. Gerry was the director of the unit.

As I got to know Gerry, one thing that I noticed was that he knew a lot about many branches of science. As a true biophysical chemist, he had a strong background in such fields as chemistry, biochemistry, molecular biology, quantum chemistry, and biophysics. His store of knowledge covered the molecular and biomolecular worlds.

Gerry was also always very interested in everything new, ideas or experiences, within science or otherwise. In this connection, sometime in early 1986, I proposed that we attend an automobile race at the Michigan International Speedway (MIS) later in the year. He agreed, and I opened an account at the Speedway and purchased a few tickets.

For fans of motor racing (I count myself among them), living in Southern Michigan is advantageous because you are a reasonable distance from MIS. The track is a 2.0-mile D-shaped oval with long, sweeping, steeply banked turns. It is known for its high speeds and wide roadway, 72 feet, which gives a driver ample space in which to maneuver.

The event that we would be attending was the 1986 Michigan 500, a 500-mile race for Indy cars. In 1986, the race was one in a series of seventeen races sanctioned by Championship Auto Racing Teams, Inc. (CART), a corporation which organized the race series (the "CART series") and formulated the rules. The flagship event in the CART series was the famous Indianapolis 500-mile race (the Indy 500). The name "Indy car" was a generic name used to identify the type of car that ran in the Indy 500 and all other CART series events.

Indy cars are pure single-seater racing cars with exposed wheels and suspension components, and a rear-mounted engine. In 1986, they were powered by a 2.65-L turbocharged V-8 engine which produced approximately 800 horsepower using methanol fuel. Indy cars in 1986 were extremely fast because of two basic features, a powerful engine and aerodynamic downforce. It stands to reason that if you install an 800-horsepower engine in a 1500-pound car, it will be intrinsically fast. The phenomenon of aerodynamic downforce is less obvious but not difficult to understand. In simple terms, the underside if an Indy car consisted of a set of venturi tunnels, integrated with the car's floor, and when the car was in motion, air flowing through the tunnels generated a region of low pressure under the car. Consequently, the car was pressed down into the track by the higher ambient pressure above the car. It's the reverse of what happens when an aircraft is lifted by an airfoil shaped to produce low pressure on the topside of the wing. Additional downforce was obtained from inverted airfoils attached to the front and rear of the car, such that at speeds above 180 miles per hour, the amount downforce was enormous. On a track such as MIS, this allowed a driver to negotiate the high-banked turns at or near maximum speed.

On August 2, 1986, Gerry and I, along with several others whose identities I do not specifically recall, set out for MIS by car. Conditions for the race were forecast to be ideal, with essentially no chance of rain, and news from the track suggested that the race might be run at record speed. During qualifying runs, the day before, Rick Mears, one of the best Indy car drivers and a master of the high-speed oval, won the pole position with a lap turned at an average speed of 223.401 miles per hour, the fastest lap ever turned on a closed track.

Our 90-mile trip, taken mostly on Interstate 94, was uneventful until near the end, when we ran into a bottleneck in the village of Brooklyn, Michigan, approximately four miles north of the track. Traffic came to a halt, and we inched along, wondering if we would get to the track in time for the start of the race. Once we reached the center of Brooklyn, we discovered the root of the problem: there was a traffic light that was set to give preference to cross traffic, not to

the heavy traffic running south though the village on the way to the track. Only 5 or 6 southbound cars at a time were getting through. Apparently, someone in a position of authority in Brooklyn did not like racing fans and had devised a scheme to spoil their day. With time running out, we finally left Brooklyn behind, drove to the track, parked the car in an off-site lot, and walked the final half-mile to the track. We reached our seats no more than five minutes before the command to start engines was given. (Note: Later, I learned that this "Brooklyn problem" had been going on ever since MIS was opened in 1968. Apparently, Brooklyn officials believed that they should be compensated by the track for the inconvenience caused by the presence of large crowds on race weekends. Track owners were never receptive to this idea, and because the track was located entirely within Lenawee County, while Brooklyn was located in Jackson County, the issue was never resolved by political means.)

The standard procedure for starting an Indy car race is as follows. Before the race actually starts, there are two warmup laps. The first, run behind a pace car, is run at a slow speed, perhaps 80 miles per hour. Subsequently, the pace car will leave the track and the second warmup lap is run at a faster speed which is set by the driver who is starting in the pole position. The cars will line up in rows of three on the backstretch and then will wait for the driver starting from the pole position to accelerate. Usually, that point will be somewhere in the final turn. Finally, as the cars approach the starting line, the green flag will be waved.

Our seats in the center grandstand gave us an excellent view of the section of the track that included both the final turn and the starting line. I explained the starting procedure to Gerry and told him to watch the final turn and to keep his eyes on the cars until they passed by. The start of an Indy car race is one of the most hair-raising spectacles in sports, but sometimes it can be chaotic.

Rick Mears began accelerating at full throttle halfway around the final turn, and the field of 28 cars shot forward like rockets as methanol was burned in the engines, producing massive amounts of pure classical kinetic energy. The starter waved the green flag and Mears took the lead followed by a cluster of three or four other cars. But the yellow caution flag was displayed on the third lap when a car grazed the outside wall. (When a race is run under yellow flag conditions, the pace car is sent out and the cars follow it in single file at greatly reduced speed. Each driver is allowed to catch up to the car in front of him, but no passing is permitted.). It was a minor incident, and after the track was checked for debris, the racing continued. Mears continued to lead while the field gradually spread out, but by lap 12, an enormous black cloud had settled directly over the track. Rain was inevitable and moments later, on lap 18, the race was halted (red-flagged) as the skies opened up and completely flooded the track. We, and tens of thousands of other spectators, were totally drenched well before we were able to take shelter under the center grandstand. It would clearly be a while before the cars would return to complete the final 232 laps of the 250-lap race.

We waited for 90 min while the track was dried with jet driers and other equipment. When the race was restarted, the drivers were confronted with a different track surface, one that had been washed and cooled by the earlier rain. These changes in track condition may have been partially responsible for an outbreak of five crashes which occurred between lap 47 and lap 126. Most of these incidents were minor, resulting only in damaged cars, but one was serious enough to send the driver, Randy Lanier, to the hospital with a broken leg.

As the second half of the race began on lap 126, Rick Mears was in the lead. He had run in the top three positions during most of the race, but now faced a serious challenge from two other drivers, Bobby Rahal and Michael Andretti. Mears led until lap 137, when he pulled into the pits with a vibration in his car. He continued, but would drop out later, on lap 181, with engine failure. As the race went on, the pace picked up, as Rahal and Andretti continued to battle and exchange positions. But then, when Andretti's engine failed on lap 196 and when Rahal made a pit stop, another driver inherited the lead.

That driver was Johnny Rutherford, who had started back in the field in fourteenth place. Rutherford had been driving Indy cars since 1962 and in his prime, had been a star of Indy car racing, a three-time winner of the Indianapolis 500. But now in the latter part of his career, he was driving for a team with limited resources. The team had given Rutherford a fast car, but not quite as fast as those driven by Mears, Andretti, Rahal, and others. Wisely, Rutherford had relied on his experience and had driven a smart tactical race in which he had conserved his engine, avoided trouble, and steadily moved through the field as others fell by the wayside. It was still possible for Rahal to catch him, but when Rahal's engine expired on lap 219, Rutherford appeared to have a clear path to victory. However, in this crazy race, there would still be more action to come.

On lap 235, 15 laps from the finish, only eight cars were still running. Rutherford held the lead, and the only other car on the lead lap was driven by Josele Garza, a young Mexican driver who was trying to make a name for himself in Indy car racing. Garza was almost a full lap behind Rutherford, while the other cars were several laps behind. The race proceeded normally until lap 239, when a car suddenly lost power and was rammed by another car following closely behind. The yellow flag was displayed, and the pace car was driven out onto the track. Now, Garza would have a chance.

The remaining cars closed up behind the pace car with Rutherford in position 1 followed by two cars that were several laps behind, then Garza in position 4, less than 100

yards behind Rutherford. When the race was restarted on lap 247, Garza immediately passed the two cars in front of him, but he had nothing for Rutherford, who pushed his car to its limit. After qualifying for the race with a lap of 212 miles per hour, Rutherford drove the final 4 laps at 217 miles per hour and beat Garza to the finish line by 1.82 s.

Our trip home was less stressful than our drive to the track; we simply went where the deputy sheriffs and state police told us to go and eventually made it back onto I-94. During the following week, we all agreed that we had had an interesting time and decided to make our visit to the Michigan 500 an annual event. But there was one issue, the "Brooklyn problem", that needed to be addressed. Thus, armed with a pile of county maps, I returned to MIS in October, drove around for a couple of hours, and mapped out a "secret route" to the track. After that, we never were caught in a traffic jam and never had to drive through Brooklyn again.

The Upjohn Company

W. Jeffrey Howe

My time with Gerry goes back to the mid-1980's when the (then) Upjohn Company formed a new CADD group, moving computational-minded drug discovery scientists from other groups in the company into a single, focused unit. Our expertise covered a broad range of science, but it was all aimed at applying computational methods to the design and discovery of new molecules. Gerry was hired from the University of Kansas to lead the group and to expand it in size, breadth of technology expertise, and reach—into the Upjohn discovery process. During the next decade and a half, Gerry did all of that and more. He was a well-regarded scientist in his own right already, but soon showed his additional colors as mentor, collaborator (internally and externally), and one who could walk a fine line in industry between the hands-on application of CADD methods to ongoing drug discovery projects, and the more academically oriented innovation in areas where there was not yet any therapeutic application target. Gerry was always generous with his time, collaborated scientifically with many scientists in the group leading to numerous publications, and furthered his own research interests as well. I think that's the definition of leadership in science, and I count my time working with Gerry as some of the most productive and enjoyable years of my career. The special issue of *JCAMD* (May 2022) is a well-deserved honor for his contributions to our disciplines across the full academia/industry spectrum.

Our first meeting

Mark Johnson

It was with some apprehension that I met Gerry. Our CADD unit had been organized under the leadership of Jeff Howe, a computational organic chemist, and under the auspices of Udo Axen, a medicinal organic chemist. Jeff had spearheaded the development of Cousin, our well-received database system for structural querying our screening data. Udo, with whom I met monthly, felt that statistical and pattern recognition approaches were needed in drug discovery. Both were instrumental in my being transferred from the preclinical statistical unit to the new CADD unit. Barely a year had passed when Udo left to organize an Upjohn drug discovery branch in Japan. Ralph Christoffersen, a quantum chemist, took over Udo's responsibilities.

The administrative changes that were underway were personally concerning. Back when Ralph was a consultant for the quantum and physical chemists at Upjohn, he had been asked to meet with me to get his take on a 2-dimensional approach for studying structure–activity relationships that I was developing. The conversation was enjoyable and enlightening, but not particularly encouraging. Consequently, when he took over the administrative reins of our unit, I wanted to know how he viewed the role of QSAR in drug design. That he wasn't really sure there was "such a beast" didn't bode well for my CADD future.

His first order of business was to hire a competent director to free up Jeff's time to develop a user-friendly molecular modeling program. After getting our suggestions, he took them to Gerry Maggiora, his long-time friend and collaborator at the University of Kansas. On his return, he said Gerry might be interested in the position and would be interviewing for the job.

When Gerry stepped into my office, I was concerned that he too might not appreciate my statistical interest in QSAR. Gerry's friendly manner and interest in new ideas quickly silenced that concern. When I sketched out some of my notions of molecular similarity, he wanted to know more and get involved. He suggested we organize an American Chemical Society (ACS) mini-symposium on different similarity concepts arising in CADD. The success of the mini-symposium led to our coediting the book, Concepts and Applications of Molecular Similarity. It was the beginning of a long and enjoyable collaborative relationship with Gerry that I and, fortunately for me, Ralph and so many others have experienced.

Not all who wander are lost

Dimitris Agrafiotis

I first met Gerry Maggiora in the early 1990's during a visit to the Upjohn Company at Kalamazoo, at the onset of my own professional career. That visit left an indelible impression on me and profoundly influenced my own development as an industrial researcher. It was there that I first saw a research setting where academic rigor, innovation and a practical mindset came together to form a powerful and highly effective team.

Gerry's contributions to the field of chemical informatics have been significant, numerous, and remarkably varied. His major strength stems from his unparalleled ability to take ideas originating from seemingly unrelated disciplines, synthesize them, and apply them successfully to important problems in his own field. For a researcher who spent most of his time in the industry, his publication record is nothing short of impressive. He is the author of nearly 150 scientific papers, and the co-editor (with Mark Johnson) of the book "Concepts and Applications of Molecular Similarity" published in 1990 by John Wiley & Sons, which has become one of the true "classics" in the field. His articles are well thought out, stimulating and clearly written. Apart from his pioneering work on molecular similarity and diversity, where he was the first to introduce the concept of asymmetry in quantifying the similarity between two molecules in order to alleviate the size dependency that plagues conventional similarity metrics, he is particularly well known for introducing fuzzy and rough set theory in chemistry, exploring the potential of neural networks in predicting chemical reactivity, demonstrating the utility of rule-based systems in helping medicinal chemists make more effective decisions based on both quantitative and qualitative data, and for numerous other contributions in the areas of structure–activity correlation, directed and focused screening, chemotype classification, and information theory.

It was his deep expertise in this latter field, and in mathematical chemistry in general, that prompted me to solicit his input on my first manuscript as an independent author dealing with the use of information theory for quantifying molecular diversity. His commentary was insightful and thought provoking, just like all our scientific exchanges in the years that followed.

Having found the optimum balance between the theoretically interesting and the practically useful, Gerry has been able to conduct his research in a rigorously academic manner despite the pressures of his industrial environment. It is also indicative of his personality and attitude towards science that despite the comfort of his industrial position he has played a very active role in the promotion of chemical information science across the world. In addition to his prolific publication record, Gerry has served on several editorial and scientific advisory boards and grant review committees, organized numerous symposia and conferences, lectured extensively in national and international fora, and mentored numerous students and colleagues, many of whom left their own lasting impact in the field.

Gerry is a person of the highest moral character and integrity, who is widely admired for both his intellectual and human qualities. He is a kind, sophisticated and articulate individual, who is always willing to help those who seek his sage counsel. He is an eminent scholar and a visionary leader, whose inter-disciplinary research has helped shape the field of chemical informatics and turn it into a truly integrative discipline standing on the crossroads of chemistry, biology and computer science.

True leaders are judged by the number of people they inspire and want to follow on their footsteps. I know many individuals inspired by Gerry, and I am most certainly one of them.

Working with Gerry Maggiora

Pil Lee

Gerry was the one who hired me for my first industry position in computational chemistry at the Upjohn Company (later Upjohn and Pharmacia, then Pharmacia, eventually Pfizer). He was interested in solvent effects in drug discovery which was and still is an important area of science. He is warm with a big Santa Claus-like smile, genuinely interested in science, curious about new ideas, a good listener, always thinking out loud. I remember he was always talking to somebody in the hallways or in his office. People were constantly seeking him out for his advice, discussions about projects, and for collaboration. That trend has continued to follow him by looking at the sheer number of his collaborators to this day.

One memorable project I have done with Gerry is the "Calculation of the Relative Binding Affinity of Chemically Diverse HIV-2 Protease Inhibitors" using the software DelPhi developed in Barry Honig's lab at Columbia University. With the X-ray structures solved by Keith Watenpaugh at Upjohn, we had reasonable rank ordering of the compounds. Besides the internal study report, the work was presented at the ACS national meeting and was very well received. I regret that I did not pursue the publication of the work.

Forever young

Jürgen Bajorath

I met Gerry for the first time in the early 1990s on the Hawaiian Islands at the Pacific Symposium on Biocomputing. It was exciting since some of his work was already well known to me at that time. The encounter left a mark. Maybe it was the combination of the science we discussed that evening, Gerry's genuine friendliness, and his interest in what I was doing, maybe it was more than that – the first time we met still seems like yesterday to me. Although we did not work together for some years to come, we have stayed in touch ever since. As I proceeded along my scientific path, increasingly concentrating on SAR analysis and computational methods for medicinal chemistry, we became closer, shared work on molecular similarity, activity landscapes and cliffs, collaborated in various ways, and started publishing together. I will never forget Gerry's excitement and personal encouragement while developing new methodological concepts for SAR analysis and visualization. Among other episodes, I vividly recall an out-of-the-blue note from him saying how happy he was to see this area of research flourish and further expand and to be a part of it. Gerry is gracious and inspirational. Whenever we had an opportunity to meet over the years, at the ACS or elsewhere, it was a joy for me, beyond science and papers we shared; a special kind of friendship I cherish.

Gerry has been staying forever young in science. His pioneering efforts have helped to shape our field and continue to be well recognized. His scientific curiosity and interests are genuine and refreshing, his creativity and scientific rigor have set standards. To this date, one of his most characteristic traits is his unselfish encouragement and unconditional support of young scientists deserving it. Gerry's magic spell results at least in part from a unique combination of scientific dedication and excellence, benevolent appreciation of contributions from others, and his endearing personality. To me he is as much a mentor as he is a friend. Together with Arnold T. (Arnie) Hagler, the late Anton J. (Tony) Hopfinger, and Peter Willet (in alphabetical order), Gerry is one of few individuals who have influenced me most along the way – and I am very grateful for this. Scientifically, Gerry has remained closest to me.

I truly regret having missed a memorable gathering of Gerry's inner scientific circle in Tucson (Fig. 2) in honor of his 80th birthday in 2019 (it was beyond my control). However, just about a month later I had the fortunate opportunity to get together with Gerry and his late wife Susan at an ACS banquet in New Orleans. This evening will remain among my fondest memories, just as much as our very first encounter way back when on paradise islands.

Industry-University strategic alliance

Leslie A. Kuhn

I've known Gerry Maggiora since the mid-90's, when I became a professor at Michigan State University (MSU). Gerry was Director of CADD working on HIV-1 protease inhibitor discovery in nearby Kalamazoo at what was then Upjohn and soon became Pharmacia & Upjohn, then Pfizer. I found Gerry to be an exceptionally enthusiastic colleague, at the center of a world-class group of researchers. Without my really realizing it, Gerry took me under his wing. He was interested in my group's work, and he also knew I was somewhat on my own as the university's first computational structural biologist. Gerry is a leader in developing and applying new methodology to active drug discovery projects and he knows everyone, everywhere. Gerry led the Pfizer sites in using our water-mediated ligand binding prediction software, Consolv, and our flexible ligand screening and docking software, SLIDE. His group gave us very useful feedback, eventually leading to a Strategic Alliance between my group and Pfizer Global R&D, with Lakshmi Narasimhan, Barry Finzel, Brajesh Rai, and Jeff Howe. Gerry became an External Advisory Board member for the Center for Biological Modeling and the Quantitative Biology and Modeling Initiative at MSU. He was active in advancing our programs and presenting at our conferences as well as engaging young scientists in the Gordon Conferences he led in QSAR and drug design. When Gerry moved to the University of Arizona, we stayed in touch and continued to exchange visits. I've found Gerry to be an extraordinarily influential, steadfast colleague and role model. Not only has he developed cutting-edge methodology, but he just as actively and enthusiastically supports new work by others. Gerry has built a world of friends and colleagues that is extremely amiable, open-minded, mutually supportive and progressive, and it just keeps going! Younger scientists' lives and careers have been transformed by him. So, when I think of Gerry Maggiora, I think of smiles and hugs as well as the great scientific enterprise he has built!

Crossing boundaries across the years

Jay T. Goodwin

My collaborations with Gerry might best be considered as having taken place across three key timeframes in the life of the Upjohn Company. In the mid-1990s I joined the Drug Absorption and Transport group, a discovery interface unit within the larger Development organization at Upjohn. This group, led by Phil Burton, Tom Raub, and Norman Ho, had

built an industry-wide reputation for cutting edge research into the pharmaceutic and biophysical determinants of small molecule therapeutic delivery. Much of this work derived from innovations in the group around novel in vitro cell monolayer models of intestinal and blood–brain barriers, in response to trends away from more expensive, time-consuming, and lower-throughput in vivo animal studies. Phil, Norman and colleagues had begun Caco-2-based assessments of transcellular and paracellular transport of small peptides as model systems for assessing physicochemical determinants of permeability; my first project was to expand this dataset across a range of both lipophilic and hydrogen-bonding potentials. As this work proceeded, it was clear that this study would offer up the quality of measured data ideal for structure-based computational models – and such models were in vogue in the pharma industry, in large part due to the contemporary trends of protein target-based high-throughput screening and combinatorial chemistry driving larger rates of pharmacological hit identification and needs for selecting viable lead candidates from those hits. Gerry, as the director of the CADD unit at Upjohn at this time, and a well-respected member of the broader computational chemistry research community, recognized the opportunity for a cross-divisional collaboration that could be effective both in developing such models, and in providing an example of the value inherent in a more integrative and holistic approach to discovery science at the company. Working closely with Boryeu Mao, and with Gerry's blessing, we published this work, and more importantly, helped establish the precedent for such collaborations, forming the foundation for more expansive efforts to follow.

The next timeframe of note really reflects the dynamic (frenetic?) period of pharma mergers and acquisitions that were taking place in the mid-90 s through the early 2000s; Upjohn was no exception to those events. As a result of several of these in relatively rapid succession, we had expanded our discovery science footprint both domestically (in Skokie, Illinois, and St. Louis, Missouri, through the merger with Searle) and internationally (in Nerviano, Italy, and Uppsala, Sweden, through the merger with Pharmacia), finding common cause with colleagues looking to develop, characterize, and implement computational approaches for predicting ADME (absorption, distribution, metabolism, and excretion) properties in service of accelerating selection and design of high-quality lead candidates. We launched the globally networked Computational Biopharmaceutics group as a result, and I recall fondly many discussions with Gerry around the challenges and opportunities for such efforts to have a positive and fruitful impact on the therapeutic discovery process, including how to exercise caution when some models caught fire in the broader discovery community, in particular the sometimes naïve application of Lipinski's Rules of 5. These were originally a mnemonic device that Chris Lipinski had extracted from examination of orally administered drug candidates that were easier or more challenging to formulate and correlating those challenges with simple descriptive metrics such as molecular weight, calculated lipophilicity, and hydrogen-bond numbers. These discussions informed our publication in 2004 urging caution in application of such simplified rules to selecting lead candidates and showed up later in Gerry's 2012 manuscript proposing softening or 'fuzzification' of such rules when used in drug discovery. This was a particularly poignant idea that we knocked around for a while, and one that manifested more clearly in the timeframe that followed.

Of course, the merger and acquisition trends of that period were not without their victims, and the original Upjohn research site eventually succumbed following the 2003 merger with Pfizer—this was what one might call the post-shutdown timeframe. Along with the diaspora of scientific expertise—some to Pfizer, many others to different destinations or retirement, and Gerry back to academic scholarship in Arizona—several of us chose to 'stick around' Kalamazoo (as the marketing phrase used by the local economic development group). Phil Burton and I, along with several other ex-Upjohn/Pharmacia colleagues, launched ADMETRx, a contract research organization leveraging expertise from drug metabolism, high-throughput screening, and in vitro ADME to provide high-quality preclinical biopharmaceutical data in service of pharma drug discovery. We were very fortunate to have Gerry join our Scientific Advisory Board, and in that role, Gerry worked very closely with us on developing a concept that had its origins in our earlier work on the 'fuzzification' of categorization methods such as the Rules of 5. We had begun our work back in the early '90s on developing mechanistically relevant in vitro transport models as part of a trend towards deconvoluting the complexity and opacity of in vivo bioavailability studies, and had now come full circle, recognizing the need to reintegrate the outputs from these distinct property assessments (permeability, solubility, protein binding, metabolic susceptibility, and so on) into holistic and comprehensive models to inform the various decisions made in advancing from hit identification, to lead optimization, and eventually to clinical candidate selection. Gerry had been ruminating on these issues, of incorporating multiple determinants into the discovery decision-making process, and this dovetailed directly into our work on understanding the potential trade-offs in these determinants when selecting viable drug candidates—for instance, where intestinal solubility and permeability can compensate for each other manifesting in viable absorption characteristics. This led us to implementing a multi-criteria decision-making platform, aspects of which were described in Gerry's 2012 paper [2]. This approach had the potential advantage of capturing the 'corporate' knowledge of discovery and development scientists, yielding greater

clarity around decision-making to advance hits to leads, and eventual lead candidates, in a testable manner with greater objectivity, by reflecting the trade-offs among critical determinants that must be accommodated to find viable therapeutics to be brought forward in service of human and animal health. Although our company was not able to implement this platform more broadly due to the impacts of the 2008 financial crisis on our business, Gerry has clearly made good use of these concepts, expanding them with the use of rough set theory and applying them to other drug discovery decision making settings.

Each of these examples describe at a high level some of the professional and intellectual interactions I've had with Gerry, but to really understand their value it is vital to recognize the remarkable combination of characteristics of the person. Gerry is at once a scholar, an artist (with words and ideas if not manifesting in other ways), an aesthete, a gentleman of impeccable intellectual curiosity and taste, and generous to his colleagues across all of these identities. Rarely a day passes when some interaction I've had with Gerry doesn't inform my thinking and actions, and I consider myself fortunate to have had the chance to work so closely with him, across so many distinct venues, over the past 25 years. Truly a pleasure and an honor.

QSAR Gordon Research Conference

M. Katharine Holloway

I first met Gerry Maggiora when he was quietly interviewing to head up the Merck modeling group in Pennsylvania back in the late 1980s. The local head of chemistry at that time, Paul Anderson, was hot to bring him in house. Unfortunately, Gerry decided to stay put at Upjohn in Kalamazoo, MI. Definitely our loss!

But my fondest memories of Gerry are from the QSAR (now CADD) Gordon conference. I was elected to serve as his vice chair (program organizer) for the 1999 meeting. I had not previously organized a meeting program of this size and importance, so I leaned heavily on Gerry for suggestions and guidance. He was a pleasure to work with and never failed to give me sound advice. It was especially stressful as the conference was on probation that year based on low numbers of completed end-of-meeting surveys and some less than stellar comments at the previous meetings. So, we really had to deliver a good program and a stimulating environment between sessions. I will always remember Gerry standing outside the poster venue smoking a cigar and breathing a sigh of relief after the last session on Thursday night when our job was completed. And successfully, as the conference has gone on to become consistently oversubscribed. Gerry also brought to that 1999 meeting a post-doc, Veer Shanmugasundaram, who later went on to chair the conference himself.

Industrial post-doc: a local conformation change that led to global motions

Veer Shanmugaundaram

A phone call by John Van Drie catalysed it all. The department of medicinal chemistry at the State University of New York at Buffalo used to organize an annual summer symposium where researchers from universities, industry and national labs were invited to participate. Great opportunity for graduate students to listen, learn and network. Among others, this is where I heard Sir Derek Barton give his lecture on the principles of conformational analysis, Suvit Thaisrivongs present Upjohn's tipranivir HIV-1 protease structure-based drug design story, Chris Lipinski present his Rules of 5, Bob Gadwood present the Pharmacia & Upjohn's linezolid story, Mark Murcko present his Bemis-Murcko scaffold analysis and John Van Drie present the DANTE pharmacophore methodology. When I was close to graduation, I wrote to a few individuals with whom I had interacted with at these symposia, seeking career advice and soliciting their input. John called me back, spoke to me at length and encouraged me to consider post-doctoral studies in the industry.

That call would lead me to apply for a post-doc opening in the CADD group at Pharmacia & Upjohn in Kalamazoo. And in Gerry, I found a mentor for life who would change my world. The next few years in Kalamazoo were the foundational years of my scientific training—first as a post-doc, later as a colleague and to this day as a "Maggiora Mentee." What began initially as long lectures on chemistry spaces, molecular similarities, nearest-neighbor searches, BCUT metrics, diversity analysis, turned to compound acquisition strategies for Pharmacia & Upjohn, promiscuity analyses, activity landscapes, SAR visualization and analysis, high-throughput screening (HTS), hit-to-lead discovery, fuzzy and rough set theories and all concepts related to cheminformatics. We would go on to publish several book chapters on molecular similarities and diversity analysis. Mic Lajiness and Gerry would not only collaborate on scientific experiments but also conduct social experiments at Pharmacia to illustrate human biases – a classic publication is the paper in Journal of Medicinal Chemistry (J. Med. Chem.) titled Assessment of the Consistency of Medicinal Chemists in Reviewing Sets of Compounds [3].

I still fondly recall my first ACS meeting & presentation in San Francisco, where we gave a 2-part presentation: Gerry on theory of chemistry spaces and I on applications of chemistry spaces for diversity analysis and compound acquisition.

Then it was at the ACS Meeting in Chicago, where I gave a talk on activity landscapes, where I would meet Jürgen Bajorath. Little did I know then that introduction would lead to future collaborations with Jürgen and form another seminal mentor/mentee relationship. I recall my first corporate flight from Kalamazoo, Michigan to Santa Fe, New Mexico—for a collaboration with BioReason on using phylogenetic-like trees for HTS analysis and knowledge discovery. I found myself on dinner invitations with various consultants, collaborators, seminar speakers who would regularly drop by Kalamazoo, MI (to name a few—Bob Pearlman, Bill Jorgensen, Brian Shoichet, Frank Burden, Subash Basak).

My first QSAR Gordon Conference was in Tilton, NH, in 1999, a conference that regularly brings together who's who in the field. Gerry was the Chair of that conference and Kate Holloway (Merck) was the Program Chair. Another introduction that would lead to several ACS divisional activities in my future as Kate would pull me into the ACS COMP Executive Committee. Twenty years later I would go on to Chair the 2019 CADD Gordon Conference in Mount Snow, Vermont. Gerry and I have organized various scientific conferences; some that stand out in my mind include the ACS Herman Skolnik Award symposium in Philadelphia, PA, the Applications of Information Theory in Chemistry in San Diego and the 80th birthday celebration symposium in Tucson, AZ (Fig. 2).

When Jeff Howe (another mentor who would transform my career trajectory) recruited me to join the CADD group and provided me the opportunity to work on a hot project at that time—beta-secretase (BACE, perhaps still a hot topic to this day)—I would continue to leverage Gerry's vast knowledge and experience. Richer conversations around BACE, aspartyl proteases, virtual screening, directed screening vs. screen them all approaches, CNS permeability, blood–brain barriers and ADME properties would follow. These would lead to another J. Med. Chem. publication on hit-directed nearest-neighbor searching [4].

Gerry is always ahead of the scientific community in his thinking. We continue to have conversations on the limitations of a reductionistic approach to drug discovery, pathway and network-based approaches, scientific strategy in industry, business decisions, investments in science, university-industry relationships, health care and the current curriculum in universities. His perspective on world events, living and leading through change, aging gracefully—in essence how to live one's life—will influence my own thinking. To this day, Gerry is always just a call away to share in my successes and to provide encouragement and perspective when I need that and all it takes is an hour on the phone with him to recharge my batteries.

My industrial post-doc tenure with Gerry Maggiora would become that pivotal local conformational change which would set off global motions in my scientific career (a reference borrowed and attributed to a Ken Dill lecture). Gerry's approach to science, decision making, collaborations, people, mentorship, work ethic and his joie de vivre has had a significant and profound impact on my perspective and my life, and I consider myself extremely blessed to have experienced that.

Not Y2K!

Thompson (Tom) N. Doman

As 1999 ended, something happened that would have a big effect on me, and it wasn't Y2K. Pharmacia & Upjohn (P&U) merged with my company, Monsanto, to form Pharmacia. This introduced me to the excellent computational chemistry group of the former Upjohn in Kalamazoo and one of its pillars, Gerry Maggiora. Gerry was stepping out of the group leader position into a research fellow role during that time. In the ensuing 3 years in which Pharmacia existed prior to the Pfizer purchase, I made the drive from Chicago to Kalamazoo 13 times. The only formal project I remember having with Kalamazoo staff was an effort to harmonize the P & U and Monsanto rules for preferred screening collection molecules, with the late and brilliant medicinal chemist Gordon Bundy. But 13 visits? Why?! Gerry inhabited a fishbowl office without any external windows, which a procession of likewise fun and stimulating colleagues would pass by and drop in to talk about a project or just an idea with him. Imagine perpetual office hours with your favorite professor. Gerry was instantly recognizable in a crowd: the hats, the footwear, the laid-back vibe of a 60's hippie looking for (scientific) revolution, a commanding figure; very tall, consummately kind and friendly, bearded, he seemed to have stepped out of an L. L. Bean catalog.

I was drawn to Kalamazoo for the extremely stimulating discussions with Gerry and colleagues like Veer Shanmugasundaram, Mark Johnson, Mic Lajiness and others, usually in the fishbowl. The famed author and monk Thomas Merton wrote of his Columbia University professor Mark Van Doren: "Mark would come into the room and, without any fuss, would start talking about whatever was to be talked about. Most of the time he asked questions. His questions were very good, and if you tried to answer them intelligently, you found yourself saying excellent things that you did not know you knew, and that you had not, in fact, known before"[5]. Reading this passage many years ago, I instantly thought of Gerry.

Unfortunately, the details of those long-ago discussions are mostly lost to time. Only sketchy phrases stick in my head. I recall Gerry talking often of "fuzzy sets" and "rough sets." Though somehow, if given enough time, I think we'd have done some amazing things.

But one wonderful gold nugget emerged from a strip-mining of my files for information for this tribute. I discovered 4 sheets of used paper which I had fished out of my recycling bin in late 2004 to jot down some notes from a phone call I was having with Gerry. One sheet of paper had some arcane documentation on software I had written. Another had verbiage from the website of a hotel. The other two sheets were drafts of a recommendation letter I had written for a summer intern.

But on the reverse side—oh goodness! The notes from my call with Gerry. All stuff from him. Paraphrasing the journalist H. L. Mencken of the Baltimore Sun [sic]: "Nobody ever went broke underestimating the intelligence of the American people"[6]. A reference to the war film "The Battle of Algiers" and a notation of parallels with the Vietnam and Iraq wars. I can remember Gerry talking about how the French lost the hearts & minds of the Algerian people. None of this I had ever heard of before. There is mention of Zbigniew Brzezinski but no details. To me he was only a government official with a colorful name from an administration I could not place. Also, that Gerry re-read "1984" and saw parallels to that time around language, the "New Speak" in the novel. Gerry noted that at the time he no longer heard the word "prisoner", the term was "detainee." "Terrorists" had become "insurgents." He asked with mock confusion "What ARE weapons of mass destruction?" I jotted down "Wag the Dog," the Dustin Hoffman film that Gerry interleaved into the conversation. And this goes on and on across the 4 pages of "trash" paper I recycled. Neal Postman, John Kerry, The Apprentice (The Apprentice? Did Gerry have some premonition of what the future held for that series' presenter?). The word "rapacity" is there. I have never used that word and don't exactly know what it means. You have to consult the 1913 Webster's Dictionary to find the definition: "extreme gluttony." I have notes about books with titles like "Sore Winners" and "The Winner-Take-All Society," the latter with the notation "too scholarly." If Gerry says it's too scholarly, I ain't touching it. "War Is a Force that Gives Us Meaning." The bottom of the 3rd page mentions the World War I "Christmas Truce." Gerry asks, "Have we really progressed?" Below that is the verbiage "molecular dynamics—fix potential functions; still not good; sample others." And below that "collateral damage," the euphemism used by Timothy McVeigh. The final page bears the heading "HR systems" and the notes: "promote competition/foster a more political atmosphere/promote short-term thinking/discourage creativity." Whew! All this on four pieces of trash. A conversation with Gerry was always highly literate, fascinating, and mind-expanding.

Boy, do I miss those heady days in the early 2000's and those trips to Kalamazoo. I have been a computational scientist in the pharmaceutical industry for just shy of 30 years. There have been highs and lows, many stimulating colleagues, lots of near-misses and a few big successes along with copious amounts of failure. Trying to discover drugs is just like that. But among those glittering diamonds in the recollection of my career, that time with Gerry and the other colleagues in Kalamazoo stands out for me. A mental game I play sometimes is to imagine I can clone myself and make arbitrary numbers of copies who can go out in the world and do interesting things. Ostensibly I do this to see if I am missing any latent possibilities I might still be able to accomplish, but in reality these are often fanciful and totally unrealistic: Broadway dancer, baseball star, stand-up comedian, that sort of thing. But one of the happiest thoughts is to send out one of these clones to be a postdoc in Gerry's lab. It's as close to scientific nirvana as I can imagine. Thank you, Gerry!

NIH panels

W. Patrick (Pat) Walters

I first met Gerry Maggiora when we were both on a panel reviewing NIH grants sometime in the early 2000s. Having learned a lot of what I know about molecular similarity from the book "Concepts and Applications of Molecular Similarity" that Gerry edited with Mark Johnson, I was somewhat intimidated. However, upon meeting Gerry in person, I quickly realized what a warm, enthusiastic, welcoming individual he is. I still have fond memories of riding back with Gerry on the Washington, DC, Metro and talking about our shared love for Tucson, Arizona, where I went to graduate school, and he is a professor. Sadly, Gerry didn't arrive at the University of Arizona until several years after I had graduated. I wish I would have had the opportunity to interact with him as a student.

I've always been impressed by the elegance and practicality of Gerry's work. His focus has never been purely on computation, but on how computation can be used to influence the design of new molecules. His early work on activity cliffs set the stage for the ways that SAR is analyzed on drug discovery programs today. One of my favorite papers from Gerry is his 2004 publication in J. Med. Chem. entitled "Assessment of the Consistency of Medicinal Chemists in Reviewing Sets of Compounds". In that paper, Gerry, Mic Lajiness, and Veer Shanmugasundaram took a systematic look at a practice that many of us were engaged in at the time. In order to select a set of compounds from a real or

virtual screen, we would print out molecules on sheets of paper and ask chemists to circle the ones they considered worthy of synthesis or purchase. As Gerry and his team showed, the results were not consistent between chemists. The concept of "molecular beauty" is subjective and tends to be shaped by a particular individual's good or bad experiences.

In addition to reading Gerry's papers, I've had the pleasure of interacting with numerous individuals he had mentored over the years. I am constantly impressed by the affection that all of these people have for Gerry. In many ways, Gerry has been a role model for those working in both academia and in industry. I'm proud to have been able to participate in the symposium honoring Gerry's 80th birthday and am thrilled to be able to contribute to this article.

9/11

Suzanne Schreyer

I first met Gerry when he was already on his third? fourth? regeneration in his career. I was a new callow Ph.D. looking for that elusive first job and wondering what my career path would be. Gerry literally plucked me from my academia post-doc and brought me over into industry. I recall that he called me quite late at night the first time we chatted, and it was the most fun and stress-free interview I have ever had. Even on the phone, I could feel his energy and enthusiasm.

Well, Gerry offered me the position in the CADD group at Pharmacia, and so I made the trip over to Michigan to meet the group and have them meet me. That first physical meeting was rather an inauspicious beginning, since I was on-site to meet Gerry and his team—on September 11, 2001.

Despite that start, over the next year and half, it was an absolute pleasure to soak up the knowledge and ideas from Gerry. He was passionate about his science, full of creative ideas and despite already being a leader in the field—always looking to learn. A true scholar—and they are very rare to find. It was a privilege to work for him.

Unfortunately, Pharmacia was bought, and the site dispersed, so Gerry went to Arizona and the rest of us scattered to various positions in industry. However, the knowledge and passion for science that he inspired has stayed with me throughout my subsequent career. In fact, it is amazing that it has been 20 years! Still feels like just yesterday when we would be sitting in his office, writing equations on his board and running through various ideas and scenarios.

It was an absolute pleasure to have him as a mentor, and I consider myself lucky to have Gerry as an inspiration in my early career stage. If I could inspire just a bit of the enthusiasm he brings to the field to those I work with—it will be a fitting tribute to an amazing mentor and scholar.

My beginning with Gerry

José Medina-Franco

I was very fortunate to work under the supervision of Prof. Gerald Maggiora at the University of Arizona in the College of Pharmacy. My first contact with him was by email on November 16th, 2004. (I keep his first email response to an inquiry I wrote him to join his group.) I joined his research group in February 2005, first doing a three-month research visit and in August 2005 as a postdoctoral fellow, right after I got my Ph.D. in Chemistry from the National Autonomous University of Mexico (UNAM, for its name in Spanish). At the time, the BIO5 Institute building of the University of Arizona was being built (all in Gerry's group signed the last beam of the building!). In August 2007, I finished the postdoctoral fellowship to join the Torrey Pines Institute for Molecular Studies (TPIMS), opening a new site in Port St. Lucie, Florida. I remembered very well the day when Gerry came into the office after returning from an invited lecture he had at TPMS in San Diego and told me: "Jose, I have a new project for you." The project was related to do a visual representation of the chemical space of combinatorial libraries. I was starting and trying to understand the concept of chemical space. At that time, I had no idea that the new project would become my first contact and then my first job as an independent researcher at TPIMS, whose position Gerry encouraged me to take and supported my application.

The continued learning

It would take several pages to try to summarize the many things I have learned from Gerry. Herein, I would like to summarize key concepts and the way to see, approach, and tackle research problems. While at the University of Arizona, I participated in several studies related to the basics of chemoinformatics, rough set theory, chemical space, and activity landscape modeling. We also worked on molecular scaffold analysis and performed structure–activity relationships using several methods. Anecdotally, one of the first days I joined his group Gerry handed me a print copy and asked me to read a close-to-final version of his seminal paper "On Outliers and Activity Cliffs-Why QSAR Often Disappoints," later published in 2006 in the Journal of Chemical Information and Modeling [7]. I did not know that that paper (currently with more than 460 citations and more than 5,450 views) would become the foundation of activity landscape modeling and research on activity cliffs. Activity landscape modeling is a research topic that I liked a lot and still continue working on.

Gerry also constantly advised me to look at the data differently, using different perspectives. "Interrogate the data,"

as he used to say, from different angles and get the most of it. Stay open to new points of view and borrow concepts from various disciplines. Phrases such as "eat with your data, sleep with your data" encourage us to think and go as deep as possible into analyzing a research problem to get meaningful information using a broad array of computational tools. Gerry encouraged us to pay close attention to molecule representation and bear in mind that "representation, representation, representation" are the three most essential aspects of chemoinformatics. I liked that he allowed us to explore new avenues to address a problem and provide guidance to be critical and practical. He also guided us by giving insights to assess if a further analysis or approach was useful beyond an academic or intellectual exercise. His rigorous manner of addressing a problem and then writing the papers was always inspiring. This has been a continued lesson for me over the years.

In addition, Gerry gave me several practical suggestions for my career that I still try to practice. For instance, keep a journal with new studies that came to mind and revisit that "project book." He used to say: "write it down because you may need it that later." I remember Gerry's advice every time I look at the "project book" he advised me to start.

Going places: scientific conferences and meetings

Gerry was also supportive of attending local, national, and international meetings that gave his research team significant exposure to the area by meeting face-to-face with many other scientists that I had known from their publications and scientific interactions with Gerry. Among the several conferences, one of the most memorable for me was in August 2008, the ACS meeting in Philadelphia, PA, where Gerry got the Herman Skolnik Award. It was a significant event and memory. Being a witness of the world-class recognition of Gerry's legacy was a tremendous honor. I was very excited to witness that occasion and had the opportunity to meet personally so many other researchers, colleagues, and Gerry's friends. I appreciate that Gerry was always inclusive of his research team and invited us to be part of the discussions, work, and social meetings that continued to be learning, fun, and new experiences.

Food for thought

Every morning Gerry stopped by the office where I was working on his way to get coffee at a nearby coffee place. During the short walk to and from the cafeteria, Gerry used to tell us what he read the previous afternoon or share his thoughts and new insights he got into the projects or bring up a new idea for us to think about. There were few but rich minutes of conversation; for me, they were daily lectures and "food for thought," as he used to say (those short but rich talks were like an "intellectual breakfast" that help us to grow). Similarly, after having lunch with the group, Gerry shared his thoughts, ideas, or past experiences in the industry.

A continued interaction

The end of the postdoctoral fellowship was followed by continued interaction with Gerry by email, meetings, and get-togethers that have lasted to the present day. He generously continued sharing his ideas, thoughts, suggesting books and papers to read, study-specific concepts. Since then, we have had the opportunity to write joint papers where I continue learning from him.

An extraordinary human being

Besides being an incredible mentor and scientist, I regard Gerry as an extraordinary *human being*. Comprehensive, patient, inclusive, a true leader by example with great power to inspire others to keep searching, keep wondering and studying, looking for new ways, and staying open to revisit and revive previous concepts.

Love is the answer to "the question"

During a get-together celebrating Gerry's 80th birthday, someone at the gathering (Fig. 2) asked the question: "What is Gerry's secret to bringing together people, literally from around the USA and the world, to come and join him in this celebration?" I think that the answer to that question is "love": Gerry's love for science, genuine devotion to his family, friends, co-workers, students. Love, and passion for continued searching, studying, addressing unanswered or partially answered questions; love for giving and sharing his knowledge, his friendship.

I cannot thank Gerry enough for all he has done for science and the profound and positive influence he has had on so many lives, including mine. Thank you so very much, Gerry, for being a friend, my mentor for life.

Beyond formal appointment

Karina Martinez-Mayorga

The people that cross paths impact our careers and life. I came to know Gerry through José Medina in 2005; we both were postdoctoral fellows at the University of Arizona. While I was at Dr. Michael Brown's lab (where I learned to love G-protein coupled receptors), he was at Gerry´s lab, and we enjoyed discussing the new areas and concepts we were learning. To date, I continue to learn from both

(academically and beyond). I remember practicing an oral presentation on scaffold analysis, cyclic systems, and molecular similarity. Later on, I incorporated those concepts and ways of thinking into my own research. With time, I realized how important it is to be open to different approaches for solving problems, maintaining essential characteristics to describe the object of study, and "ignoring" non-relevant ones. This leads to Gerry´s emphasis on molecular representation and how engaging with the data and looking at it from different perspectives helps uncover how to represent and analyze it, ultimately making sense of it and generating knowledge. These ideas are general and are applied within and beyond drug discovery. Having a background in food chemistry, I got interested in the application of chemoinformatics in food-related databases. Together with José and Gerry, we suggested this area as Foodinformatics, described in a book of the same name. We and others continue to work on this topic.

Even though I did not have a formal appointment with Gerry, his knowledge and passion for science have certainly permeated and enriched my career and that of my students. My interaction with Gerry has helped me know new topics and new people, ask new things, and look and engage in things with different perspectives. Thank you, Gerry, for sharing your knowledge and for pushing others with your example. Science should always be seen with the smile and enjoyment that you maintain.

Beyond single targets

Linda L. Restifo

I met Gerry in 2006. More specifically, I sought him out because I needed his expertise. My research group was about to embark on a drug screen using a unique cell-based assay—with a genetic twist—that we had developed using primary cultured neurons from the brains of mutant fruit flies. Anticipating the imminent arrival of my NIH award notice, I had a growing awareness of how little I knew about drug discovery. I'm a biologist who took required chemistry and biochemistry courses, but then forgot much of that material decades ago. Moreover, my immediate environment was a University of Arizona basic science department which, at the time, had little or no enthusiasm for applied research. I had attended workshops and conferences to learn the basics about the drug-discovery-and-development pipeline and was intrigued by lead optimization. One day, Dr. Martha Narro, a former protein chemist who developed our NeuronMetrics™ software for quantifying neuronal morphology, described a seminar on activity cliffs that Gerry had presented. Fascinating – but might activity cliffs derail our repurposing screen of a mere thousand or so known compounds? And could I even trust the claim by the company from which we bought the drug library that the compounds were "chemically diverse"? I had a big spreadsheet with names and chemical formulas, but no idea how to use the structures to compare them.

I believe it was Dr. Laurence Hurley, professor of medicinal chemistry and then Associate Director of the BIO5 Interdisciplinary Research Institute, who introduced me to Gerry. That led quickly to Gerry bringing his then-postdoc, Dr. José Medina-Franco, into the conversation. They patiently explained different aspects of molecular structure and the use of principal component analysis for mapping compounds in chemical space, a concept that was completely new to me. Indeed, when Gerry and José analysed the 1040 structures that comprised the drug library, the compounds proved to be quite a diverse set. Meanwhile, my lab team was busy with our phenotype-based screen which, for several reasons, was entirely manual; even semi-automated NeuronMetrics™ software was not used in the primary screen. The strategy was to directly observe neurons growing in culture under the influence of drugs at different concentrations. In retrospect, if we had automated the screen, we would have missed important cellular effects, especially drug toxicity with morphological manifestations–such as that caused by the statins.

From discussions with representatives of biotech companies or scientists who had recently left industry to work in academia, I knew that our screening approach ran counter to prevailing trends. First and foremost, we didn't know what molecular target(s) might be relevant. In fact, I thought it was premature to speculate about targets as we screened for drugs that altered the aberrant morphology of fascin-deficient neurons. But, to my frustration, most current or former industry scientists with whom I spoke at the time wanted to know about "the target." Gerry, in contrast, understood my perspective that, given the biological complexity of the system, other than fascin per se, we really could not guess the targets, let alone choose the best one. Second, our screen was bi-directional; we were simultaneously looking for compounds that could rescue neuronal morphology (specifically neurite trajectory) as well as for those that made it worse. Indeed, we did identify hits of both types. However, this confused endless grant reviewers, as if we couldn't make up our minds – *what were we interested in, brain development or tumor metastasis?* Gerry understood that the fascin bioassay addressed both.

At the end of the screen, there we were, with ~ 80 hits roughly split between the two groups. Naively, I had imagined they would tell a story, pointing to a signalling pathway or a pharmacological mechanism. The hits were scattered throughout the 3-dimensional 'cloud' of the whole library, and the groups with opposite effects were intermingled. Once again, Gerry and José (then at Torrey Pines Institute in Florida) helped us make sense of the structures, this time

by pointing out the value of the inactive relatives of the hits. Indeed, they were able to develop half a dozen SAR hypotheses. I am very proud of the paper we ultimately published together in 2013 [8].

Later when I moved to the medical school, Gerry attended our weekly group meetings, adding priceless insights and asking questions that went beyond our usual topics. He also sat in on my graduate-level human genetic disease course, serving as an informal consultant, especially when the class discussed the challenges of preclinical drug discovery and therapeutic clinical trials. Looking back, I realize that we have an unfinished project or two. I hope we can re-activate those in the coming years.

Concluding remarks

Linda L. Restifo, Jürgen Bajorath

Each contribution in this collection was independently written, from a very personal perspective, as an homage to Gerry—as a scientist, mentor, and friend. If viewed altogether, however, the collection becomes more than the sum of its parts. It also mirrors the evolution of science at the interface between academia and the pharmaceutical industry over many years, paying tribute to its diversity and uniqueness. As such, the contributions in honor of Gerry provide a valuable resource, notably for students and young investigators in academia or industry interested in better understanding the roots of some of the research we carry out today. Nobody will be happier about this than Gerry himself.

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