CHAPTER 1

IN TRIBUTE TO JOHN C. MARTIN

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One of the jobs as Editor-in-Chief of Medicinal Chemistry Reviews is to ask prominent figures in our field to share a personal essay about how they ended up pursuing a career in chemistry/drug discovery, their most memorable experiences, and words of wisdom to share with the community. It had always been my intention to ask John C. Martin, who hired me into my first job in pharma and is someone I have always respected and admired, for a contribution. Regrettably, John died unexpectedly at age 69 in the spring of 2021.[1] This was and still is a huge loss for family, friends, colleagues, and people across the globe who benefited from his work. Although the opportunity to have John's own personal essay is no longer possible, I still wanted to capture John's unique leadership style and the impact he had on those around him. My idea was to ask people who were close to John over the years to provide a personal essay highlighting a shared experience that illustrates the kind of person and leader John was. On the advice of my Medicinal Chemistry Reviews predecessor Editor-in-Chief Manoj Desai from Gilead, I reached out to Lillian Lou, John's life partner and the head of the John C. Martin Foundation, who graciously provided me with a list of people to contact. I was delighted that so many people immediately said, "Yes, of course." What follows is a collection of short vignettes from several of John's colleagues, with the central theme being his impact on drug discovery. While each vignette is a little different in perspective and recollection, all of the essays capture aspects of John's remarkable qualities that shaped him and inspired those around him. My hope is that these stories will provide valuable insights and lessons, and bring a smile as you imagine this very down-

John C. Martin, 2019
(Scott Buschman Photography)

2022 Medicinal Chemistry Reviews, Volume 57
ISSN 2575-9175
http://dx.doi.org/10.29200/acsmedchemrev-v57.ch1

to-earth individual who ended up accomplishing so much. I would also refer readers to a number of recent articles[2] and a special issue of *Antiviral Therapy*[3] summarizing the discovery and impact of several drugs that were developed under John's leadership. The content of the present collection of vignettes is intended to be more personal and to stand in, at least in part, for the essay that John might have written himself.

Vignettes (in alphabetical order) are from:

- Norbert Bischofberger (Gilead colleague)
- Joanne Bronson (Bristol-Myers colleague)
- Erik DeClercq (Collaborator, Katholieke Universiteit Leuven)
- Manoj Desai (Gilead colleague)
- Zdeněk Havlas (Collaborator, Czech Academy of Science; Institute of Organic Chemistry and Biochemistry)
- Piet Herdewijn (Collaborator, Katholieke Universiteit Leuven)
- Mick Hitchcock (Bristol-Myers and Gilead colleague)
- Mike Jung (Gilead consultant)
- Bill Lee (Gilead colleague)
- Muz Mansuri (Bristol-Myers and Gilead colleague)
- Ernie Prisbe (Syntex and Gilead colleague)
- Raymond Schinazi (Emory University)
- Pete Schultz (Scripps Research)
- S. Swaminathan (Bristol-Myers and Gilead colleague)
- Richard Whitley (Collaborator, University of Alabama)
- Lianhong Xu (Gilead colleague)
- Taiyin Yang (Gilead colleague)

My sincere thanks to all of the contributors.

John C. Martin at Syntex, circa 1978
(Ernie Prisbe)

Norbert Bischofberger: currently CEO of Kronos Bio; colleague of JCM at Gilead Sciences 1990-2018

I met John Martin almost 40 years ago in 1983 at Syntex. I was a post-doc and he was a new employee. He came to me and inquired about how to run a singlet oxygen reaction—converting a diene to an endoperoxide. John then left Syntex to join BMS, and we both independently joined Gilead in 1990. He was my boss, and I reported directly to him for the next 27 years. John was initially in charge of R&D and assumed the CEO position in 1996. And then, coincidentally and independently, in 2018 we both felt it was time to do something new. John handed over the Gilead CEO job to someone else. I joined Kronos Bio as the CEO and President, and John joined Kronos Bio's Board of Directors.

The initial focus of Gilead was antisense oligonucleotides, a very simple and appealing concept. Any sequence of RNA can be inhibited by a complementary oligonucleotide sequence. The challenge that we encountered was that oligonucleotides, because of their multiple negative charges and large size, do not efficiently permeate across the lipid bilayer into cells. As a risk mitigation strategy, we initiated medicinal chemistry programs that resulted in the discovery of Tamiflu. We also in-licensed a portfolio of nucleoside phosphonates, which later became the cornerstone of Gilead's HIV and HBV medications.

I remember John as a scientist at heart. Decisions about what to pursue, which companies to acquire and which research projects to prioritize were always made based on science. John was also very proud that after having been CEO for more than two decades, he could still draw chemical structures of our nucleosides in development.

A strong belief of John's was making a difference for patients—those with the resources to obtain medications, but equally important, those residing in low-income countries. In the end, tens of millions of people worldwide have benefited from Gilead's medications, and today millions of people continue to take these drugs because of programs that John built. HIV used to be a certain death sentence. Today, it has been converted, for most people, into a chronic, treatable disease. An equally important part of John's legacy is the impact that Gilead made on hepatitis C. With the introduction of Gilead's antivirals, HCV is now curable, for the majority of people, with a single pill taken for 8-12 weeks.

John is not physically with us anymore, but his legacy lives on!

Joanne Bronson: currently Senior Scientific Director at Bristol-Myers Squibb; colleague of JCM at Bristol-Myers 1986-1990

I am so fortunate that John Martin was the person who hired me right out of graduate school to work at Bristol-Myers in 1986. Even though the merger with Squibb came only three years later, with John's departure not long after, the lessons I learned working with John have lasted my entire career. A few are listed here:

- Value the diverse skills and ideas of people on the team. John had high expectations and put us in situations that played to our strengths, but he didn't expect us to fit the same mold. Valuing diversity is something you hear about all the time, but John did this in a purposeful and consistent way that is rare in my experience.
- Recognize and thank people for day-to-day successes, no matter how big or small. Whether it was getting a difficult reaction to work or figuring out an unexpected result or generating encouraging data, John would regularly go out of his way to acknowledge people for what they brought to the table. Genuine positive feedback is a great motivator. It certainly worked for me.
- Think through the outcomes you want to achieve. I vividly remember having strategy sessions with John before a meeting with upper management. He would be really clear on what he wanted to achieve, but recognized that the path could take different twists and turns. It was an incredible learning experience to see his thought process as he talked through different strategies to arrive at his desired outcome. His success rate was high.
- Trust people and give them opportunities outside their comfort zone. My project when I started in John's group was on the phosphonate nucleotides (PMEA, PMEG, HPMPC, etc.) antivirals as part of the collaboration with Antonín Holý at the Czech Academy of Sciences. In 1988, John sent me to Prague to work in Professor Holý's lab for two weeks, followed by an additional week at a conference in Bechyne. I had only been at the company for two years, and choosing me to go instead of other more experienced people was a real gift. Professor Holý was a gracious host and he paired me with one of his researchers, Hana Dvorakova, who helped make the trip productive and thoroughly enjoyable. It was an eye-opening experience for many reasons, including that this was before the fall of the Berlin Wall. This is just one of many opportunities that John provided. It didn't matter where you were in the hierarchy. If John thought you were the right person, he'd tap you for an assignment and support you all the way.

John gave our small antiviral team an entrepreneurial, risk-taking culture in the midst of a large pharma company that didn't always know quite what to make of his approach. He instilled a sense of urgency, encouraged external visibility, engaged a large network of external collaborators, and inspired creative thinking. John's move to Gilead undoubtedly gave him more freedom to drive the discovery and development of critical medicines, including the ultimate success of drugs like tenofovir. I remain grateful for the opportunity I had to work with John and see him in action first-hand.

Dr. Erik De Clercq: currently Professor Emeritus, Katholieke Universiteit Leuven; collaborator with JCM/Gilead Sciences starting in mid-1980s

From the many encounters I had with Dr. John C. Martin when he was the Director of Chemistry at Bristol-Myers (BM) at the end of the 1980s, I remember a question he asked (and for which he had himself probably deciphered the answer), that is whether for the treatment of HIV infections, BM should opt for (i) a nucleoside phosphonate analog such as PMEA (adefovir) (PMPA [tenofovir] would only be discovered in 1992) or (ii) TIBO? The question came down to the choice between Antonín Holý (PMEA) and Paul Janssen (TIBO). For me, this was a delicate choice in view of my intimate relation with both Tony and Dr. Paul. I strongly defended both compounds, thereby emphasizing the merits of both approaches: (i) PMEA would have the most potent efficacy, while also yielding the greatest risk for toxicity, whereas (ii) TIBO would be softer, engendering less efficiency, but confer a higher risk for resistance development. From PMEA, tenofovir was finally developed, which was successively marketed as tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF); and TIBO gave rise to a wide variety of non-nucleoside reverse transcriptase inhibitors (NNRTIs), from which rilpivirine eventually emerged. Both compounds that I had originally recommended to John Martin in the late 1980s finally found their niche in the treatment of HIV infections when combined, together with emtricitabine (Emtriva®), in the marketed products Complera® (U.S.) and Eviplera® (E.U.).[a] The combination of TDF and TAF with emtricitabine (commercialized as Truvada® and Descovy®, respectively) has also been approved for the pre-exposure prophylaxis (PrEP) of HIV infections.[b]

a. De Clercq, E. Role of tenofovir alafenamide (TAF) in the treatment and prophylaxis of HIV and HBV infections. *Biochem. Pharmacol.* **2018**, *153*, 2-11, doi:10.1016/j.bcp.2017.11.023.
b. De Clercq, E. Tenofovir at the crossroad of the therapy and prophylaxis of HIV and HBV infections. *J. Cell. Immunol.* **2020**, *2*, 23-30.

Also in the 1980s, I had the unique opportunity to get into a lively conversation with the late Dr. Paul (Janssen) and John C. Martin at the Gordon Conference on Chemotherapy of AIDS in Oxnard, California; 14-18 March 1988. J.C. Martin was a regular participant, whereas Dr. Paul had been specifically invited by Dr. John Driscoll, Chairman of the Conference. During one of the meeting breaks John, Dr. Paul, Dr. Masanori Baba, and I got together. It was the first time (as far as I know) that Paul Janssen ever met with John Martin. I remember that Dr. Paul asked John about his ultimate goal in life. John offered that he would not mind becoming as famous as Dr. Paul in running a pharmaceutical company as successful as that created by Dr. Paul himself. Paul Janssen gave him one chance out of hundred that John would ever achieve this goal. John replied that he would settle for this 1% chance. John Martin was elected the new President of the Gordon Conferences on Chemotherapy of AIDS (following John Driscoll), and his successful presidency of Gilead Sciences followed a few years later.

Manoj Desai: currently CEO of Lilac Therapeutics; colleague of JCM at Gilead Sciences 2003-2018 (JCM retirement in 2018)

I met John for the first time during my interview in September 2003. He was an amazing leader scientist; he took risks, but he backed it up by staying supremely well informed about the data/science, which nourished a confidence in his convictions. The inherent uncertainties during drug discovery would instill purposeful ambiguity within the executive ranks, but John was far from it. John excelled at making timely calls to push the clinical candidate(s) and in-license drug candidates to rally the development organization. *John, at heart, was a chemist who was a CEO rather than a CEO who was a chemist.*

He had an encyclopedic knowledge of the nucleoside/nucleotide SAR. I would hesitate to discuss the topic, just because I was new to the field, and he was aware of many unpublished results. He was very proud of the book he edited (published in 1989): *ACS Symposium Series 401: Nucleotide Analogues as Antiviral Agents*. This was published at a time AZT was the only approved treatment (March 1987) for AIDS. He surmises:

> "... [A] number of substances described in this book have the potential to be developed as antiviral therapies. As our knowledge of the biological properties (potency, mechanism of action, toxicity, pharmacokinetic, and metabolism) of nucleotide analogues increases, the rational design of superior antiviral agents should become increasingly successful."

It took nearly fifteen years for Viread (tenofovir prodrug) to get approved, and since then, tenofovir prodrugs have been the preferred backbone for the treatment of HIV that has saved many lives across the globe.

You may suspect John would read C&E News, but he was also an avid reader of *Annual Reports in Medicinal Chemistry (ARMC)*! He proudly displayed ARMC and the Medicinal Chemistry Reviews in his office. His medicinal chemistry division membership was in disarray, so it became my responsibility to ensure he got hard copies of the volume he loved to browse. When Joanne took over the responsibility of *Editor-in-Chief* from me, he was thrilled.

Zdeněk Havlas: Vice President, Czech Academy of Sciences and Honorary Chair, Institute of Organic Chemistry and Biochemistry; worked with JCM/Gilead Sciences starting in 2002

In 2002 I replaced Professor Antonín Holý in the position of IOCB director with the duty to continue the in-licensing policy with Gilead. From the very first meeting with John, I recognized that he was a very efficient manager, an excellent chemist, and a remarkable human being. He was already a good friend of Tony Holý and Eric DeClercq, an excellent virologist from Rega Institute in Leuven, Belgium. IOCB and Rega share the licenses of antiviral compounds from which Gilead developed drugs against HIV and HBV. After few meetings with John, we became good friends too. The visits of John and the delegation from Gilead to Prague, and our visits to Gilead, were not just professional working meetings but also meetings of friends with an intensive social program (dinners, opera performances, sightseeing, etc.).

I wish to mention only a few moments from our mutual contacts. First is the signing of the Amendment No. 6, in which we (IOCB, Rega, Gilead) agreed that the distribution of anti-HIV drugs will be on a non-profit basis for developing countries. The list consisted of 68 such countries. Pharmaceutical companies often have a rather bad reputation for making huge money on account of patients. This Amendment proved that it need not always be so. Thanks to John, Gilead showed a human face.

Second, in 2004 I took John from his hotel to the airport very early in the morning. Because Tony Holý already had health problems, John asked me what we could do for him. I recommended that we support his research. John came up with the idea to extend that support and establish the IOCB-

Gilead Research Center Prague from the selected research groups of IOCB. The research orientation was not limited. During our mutual meetings (twice a year, once in Prague, once in Foster City), we would report our results, and Gilead would have priority right to license. This Center is still active today.

Drug development is rarely straightforward. Today the very successful drugs from Gilead are excellent examples, with periods of success and periods of downfall, of the personal risks taken by John and his personal investment to turn things around. When I told this story to my friend from a very popular Prague theater, he decided to write a play about the history of Gilead's drug development ("The Elegance of the Molecule," by Petr Zelenka). The main hero is, of course, John Martin, together with Eric DeClercq and Tony Holý—the Trinity that represents all the fantastic teams of Gilead, IOCB, and Rega. John came to Prague to see the premiere in 2018, and he was quite excited, even though it was played in Czech (with English subtitles). The story still fascinates the audience, and it is very difficult to get a ticket.

I hope that these three moments of John's life illustrate that John was a memorable person, influencing others, and helping millions all over the world though his successful work.

Piet Herdewijn: retired from Katholieke Universiteit Leuven; collaborator with JCM/Gilead Sciences starting in mid-1980s

The first time I met John Martin was in 1985, when we went to a reception for the inaugural lecture of Dr Paul Janssen, who had received the Francqui Chair at KULeuven. John admired Janssen for what he had achieved and understood the importance of having a strong scientific background when leading a pharma company. The second time I met John was in 1988, when he was responsible for the antiviral projects in Bristol-Myers in Connecticut. We were part of the discovery of d4T and 2-Fluoro-araddA as anti-HIV compounds. He wanted to know more about it, and invited me for a lecture. However, there were also other historical moments happening in the city at that time, and in the evening he sent us to go to watch a legendary battle between Larry Bird of the Boston Celtics and Magic Johnson of the L.A. Lakers, which I never forgot. In 1991 Magic Johnson announced that he was infected with HIV, and I suppose he benefited a lot from the later discoveries of John in the HIV field. But it showed me that John liked to relax with friends after the job, which I experienced later several times

during Gilead visits, when we met at conferences, and other occasions. Often, he suggested going for a beer to escape from the public attention and just go to chat about anything in a nearby bar.

He became CEO of Gilead in 1996. At that time, I asked John why he left science to become a business person. His answer was, "Science goes slow, and I need more action." Being an excellent scientist himself, he recognized what good and reliable results are, and he wanted to use scientific achievement to make an impact, in which he wonderfully succeeded. From that moment on, he invited me every four years to give a lecture at Gilead so that he was aware of what we were doing. During these visits, we also had small talks at his office, where he asked advice about different issues. Although John was at that moment a very respected leader of a pharma company, he still wanted to ask advice of friends he could trust before making a decision. John was always ready to help his friends. I remember when we had organized a conference and became short on budget, it only took a phone call to John, and he sponsored the meeting immediately and kept us out of trouble.

Numerous were his visits to the Rega Institute when he collaborated with Eric De Clercq on the compounds of Antonín Holý. We had frequented a lot of restaurants in the evening where John didn't talk about science or business, but about real life. He wanted to know how it was going with his friends and the people he knew. During these visits, I came to know John as a very intelligent, honest man, a sharp mind who stayed modest despite his position and with a good sense of humor. John was a man of his word. He really didn't like to be in the spotlight. The last time I saw John was in 2019, when he joined the celebration of my retirement from KULeuven. I was honored by his presence, expressing 34 years of friendship, and I will never forget the words that once he said to me a while ago: "Although we live far away from each other, you're my best friend."

Mick Hitchcock: Board of Directors at Biomea Fusion and Renogenyx; colleague of JCM at Bristol-Myers 1985-1990 and Gilead 1993-2018 (JCM retirement in 2018)

John Martin's style of leadership was memorable (but not always smooth). During the early days of Gilead commercializing HIV drugs, he knew that we were too inward-looking, mostly focused on what was happening with the science in the lab. He wanted us to get to know the customers for our products—the doctors and the patients.

During our bi-annual gatherings of the management (known as the Operating Group), he would very publicly go around the room. It did not matter if you were the head of research, or HR, or the CFO, you'd get the same question: "When was the last time you were out in the field?" And of course if the answer was positive, he would want to know which salesperson you went with and who did you see (just to make sure you had really done it). And if you hadn't been out in the field, he would take a note and want you to let him know when you had scheduled it.

Through his own visits to the field and connecting with patients and doctors, he became acutely aware of the obstacles to therapy. Initially, the issues of tolerance precluded long-term uninterrupted therapy. Then the challenges of "pill burden" made him focus on the "holy grail" of therapy: one pill, once a day. This led to Truvada through the purchase of Triangle Pharmaceuticals, and then later Atripla through the partnerships with BMS and Merck. And, of course, this led to the later single-tablet regimens that are widely used today.

This focus on patients led him to take a trip to Africa with then Secretary of the Department of Health and Human Services Tommy Thompson. Seeing the enormous impact of HIV first-hand, he knew that we had to overcome the major obstacle to therapy in the developing world—getting the price down to a level that was affordable. Other pharma companies had not managed to solve the problem. Initial efforts led to Gilead's "no-profit" pricing strategy, but this met with limited success, since we were unable to achieve the necessary manufacturing savings. The strategy to license Gilead's drugs to generic companies became the solution—non-exclusive licenses to multiple companies created competition between the manufacturers and thus brought the cost to the lowest possible amount.

Shortly after his death, I was informed that there were about 19 million patients on Gilead drugs worldwide. There are a lot of people alive today because of John Martin.

Michael Jung: Distinguished Professor of Chemistry in the Department of Chemistry and Biochemistry at the University of California at Los Angeles; consultant for Gilead starting in 1996

I first met John Martin in Syracuse in March 1985 when I visited the Bristol-Myers labs there and gave a seminar. I was invited by my former postdoc,

Muz Mansuri, who worked with John (along with Choung Kim). I was impressed by John's breadth of knowledge and his engaging personality. We renewed our relationship in June 1996 when I gave a seminar at Gilead, where John had moved in 1990 to become head of research. When I started consulting for Gilead Process in 1996 and then their Med Chem program in 1997, we had many chances to see each other again. Occasionally he'd ask for a slot so we could discuss chemistry—and the world—during one of my biannual two-day visits. And we often had dinner together and opined about the state of affairs at Gilead, in antiviral research, and just about anything else. I was convinced then, and am even more convinced now, that the huge success that Gilead has had over the years is due in large part to John and to the close scientific team he gathered around him, including Norbert Bischofberger, Choung Kim, and many others. I can remember drinking beer with him at summer parties at Gilead on Friday afternoons. And dining together at many restaurants in the area. But my fondest memory was when he agreed to participate in a half-day symposium I put together at UCLA when I won the Glenn T. Seaborg Medal in November 2016. I wanted to have the very best people who had made a difference in medicinal chemistry and medicine, in both academics and industry. The speakers were John, Paul Wender, and Peter Dervan. The night before the symposium, I hosted a dinner at the restaurant, Providence, for the speakers and their spouses and companions. It was phenomenal! John never stopped enthusing over the quality of the meal and the accompanying wines. He opened the symposium that Saturday afternoon and blew the audience away with his lecture, describing the successful "conquest" of HIV that he had led at Gilead. His talk was spectacular—thorough, but easy-going with a very smooth style, a very tough act for the rest of us to follow. At dinner that night in the Luskin Center at UCLA, I spoke and thanked each of the speakers for their contributions, both that evening and also to my career. At one point, I asked all my current and former group members in the audience to stand up and be recognized. John shouted, "What about those who want to work for Mike Jung?" And so I said, "Sure, they could stand up too." And, of course, John and his Gilead colleagues, Bill Lee and Swami Swaminathan, as well as others, all stood up. I loved him for that simple gesture, which showed respect and, especially, humor!

The last time we were together was in October 2017 when he invited me to join him and a couple of his friends, Abe Sofaer and John Cogan, for a dinner at Tamarine in Palo Alto, where the conversation ranged from

chemistry to health care to politics and beyond—quite heady stuff for an organic chemist like me. But John was voluble on all of those subjects and made many salient points.

I miss John for his intelligence, his smile, his humor and his friendship. We lost him much too early.

Bill Lee: retired from Gilead in 2021; colleague and friend of JCM at Gilead Sciences 1991-2018 (JCM retirement in 2018)

Follow the Pipes

In late 1995, Gilead filed a New Drug Application for Vistide, an IV formulation of the nucleotide analog cidofovir, for the treatment of CMV retinitis in HIV patients. This was at a time in the HIV epidemic prior to triple combination therapy where AIDS patients were facing blindness due to CMV as their immune function deteriorated. We manufactured the drug substance, cidofovir, at Raylo Chemicals, a specialty manufacturing site in Edmonton, Canada, which had deep expertise in nucleotide chemistry. Raylo did not have extensive experience in GMP manufacturing, especially for drugs that were administered by IV infusion. During the release testing of one of the registration batches of drug substance, the presence of trace amounts of mold was detected. This result triggered an extensive inspection of the facility by the FDA and, as a result, numerous 483's[a] were issued; the approval of Vistide was dependent on resolution of these issues. John Martin was head of R&D at the time and was acutely aware of how important this was for the product and for the company. John ordered a full court press to support and help Raylo resolve the 483's. As a result, Taiyin Yang, Ernie Prisbe, Ray Pritchard and myself as well as others including Susan Edl, my administrative assistant, spent much of the winter of 1996 in a very snowy, cold and dark Edmonton helping Raylo prepare for the re-inspection. During this period, John required daily updates, always challenging us to do it faster and made clear we had no budgetary restrictions with regards to transforming the site. After four months of refinishing floors, eliminating wood products, repairing roofs, rewriting SOPs, staff training and mock inspections, we thought we were ready. A week before the FDA re-inspection, John Martin and Howard Jaffe visited the site to inspect the progress. The site looked good. As we were showing John around, he asked, "Let's look at

a. A Form 483 is an inspectional observation by the FDA that relates to a quality system or facility deficiency.

the basement." Taiyin and I were stunned. Despite having practically lived at the site for the winter, we had never been to or even knew there was a basement—it was not on the site plans! The basement door was hidden in a remote part of the plant, hidden to almost everyone except John, that is. Fortunately, after descending the dreaded steps, we discovered the mystery room only required minor housekeeping. How did John know? He followed the piping in the facility and noticed it bent downward in a particular place and concluded that there must be a basement. John had the exceptional ability to look at things orthogonally, and he paid attention to detail. He applied this to every problem, whether it was the selection of a molecule for development, a clinical trial design, or a strategic commercial decision. We have all improved our game by working alongside John.

Muz Mansuri: Venture Partner at F-Prime Capital; colleague of JCM at Bristol-Myers 1985-1990 and Gilead Sciences 2010-2016

Over forty years ago, at a wedding reception in California, Tim, the groom, pointed out John Martin and told me to "watch that guy" because he was really good. Tim and John were post-docs at Syntex, a premier pharmaceutical company at the time, where John had just discovered ganciclovir. Four years later, in 1984, John became my boss at Bristol Myers Squibb (BMS). In 1990, he left BMS for Gilead. And twenty years later, I was again working with John Martin at Gilead.

John had a tremendous impact on everyone who worked with him. His mind was razor-sharp and always in overdrive. He worked very hard and assumed that everyone else did, too. He was a thorough and meticulous planner, usually several steps ahead of anyone else. Like so many of my colleagues, I trusted his plans because the mission and goals were clear and shared: how do we make a great drug and get it out to all patients in need; then, how do we go back and innovate an even better product? This singular focus remained constant over time.

Several things stand out in reflecting on what was notable and memorable about John (other than a spotless and empty desk). The first was his ability to understand and celebrate other people's achievements, big and small: getting a reaction to work, getting something to crystallize, or modifying an existing formulation. John realized that accomplishments such as these gave people a sense of belonging, movement, achievement, and engagement. It is a rare CEO who can connect with many people across the

company. At both BMS and Gilead, John could pay attention to these things and, at the same time, be thinking about some really big issues like global access to life-saving medications. He reveled in talking with scientists about their experiments and then, five minutes later, talking to a foreign dignitary about global health.

The second thing was John's openness to new ideas. Regardless of a problem's scale, he wanted ideas and insights from a wide range of people, including executives and those at the frontline of the crisis, issue, or problem at hand, from bench scientists to senior government officials. To John, the best idea was the idea that should win, and it didn't matter where the idea came from. He embraced great ideas and made things happen, whether working on phosphonate prodrugs at BMS or acquiring Triangle and Pharmasset at Gilead.

Finally, and perhaps most impressively, John didn't change much as a person, despite his great professional success, financial success, and enormous impact on the world. His love of science, his incredible work ethic, his creativity and commitment, his somewhat quirky sense of humor, his humble demeanor, and his loyalty to friends and family are the attributes that, in my mind, defined John over the nearly four decades that I knew him. In my experience, he was pretty much the same guy at the end of his career as he was at the beginning.

Ernie Prisbe: Retired; colleague of JCM at Syntex 1978-1984 and Gilead Sciences 1992-2008

I smoothed down my lab coat lapels and stepped into the room. It used to be storage space for folding chairs but now in 1978 is occupied by a brand-new Varian T60 NMR spectrometer. A friendly faced post doc was snapping his index finger against the plastic ink cartage that rode the recording arm. "I'm here to be signed off on the T60," I said. "Hi, I'm John Martin," the post doc replied without looking up. Though only a temporary employee of a few months at Syntex Research in Palo Alto, John had convinced management that chemists needed a "hands on" NMR to speed their research by circumventing the process of submitting samples to the Analytical Chemistry Department and waiting days for the results. To push through his proposal, John suggested that he could set up and maintain the machine and also train chemists on its use. I wondered why it took so long to have such a benefit and why we had to wait for a post doc to get it done.

Months passed, and a job opening in the Institute of Bio-Organic Chemistry, the department where I worked, materialized. My boss was the hiring manager and had meticulously screened more than a dozen candidates, narrowing the choice to two post docs who worked in the Institute of Organic Chemistry. It was a toss-up in his mind, so he asked for my opinion. "Without a doubt, hire John Martin," I said. "He takes initiative and gets things done. Like getting us a T60. I've never seen the likes of that before in someone fresh out of school."

And so, John Martin joined our research group. The focus at that time was on aminoglycoside antibiotics and cardiac glycosides, and John was tasked with synthesizing analogs of fortimicin, a pseudodisaccharide antibiotic. But with positive results slow in coming, it didn't take long before John wanted some changes. He had read the seminal paper of Elion and Shaeffer[a] describing acyclovir and persuaded management to shift our focus to nucleoside antiviral research.

The new focus brought fresh vigor to the group, and morale was up. John's philosophy for drug discovery was to work on a variety of molecules simultaneously, never confine yourself to one molecular genre, and to recruit whatever help necessary to maximize speed. His first target was 9-(1,3-dihydroxy-2-propoxymethyl)guanine[b] (DHPG, ganciclovir) an acyclic nucleoside that he synthesized in three months and that became an important treatment for cytomegalovirus infection. Other classes under our scrutiny were DHPG phosphates and phosphonates,[c] carbocyclic nucleosides,[d,e] 2′,3′-dideoxy nucleosides,[f] and 2′-fluoronucleosides.[g]

Regrettably, John left Syntex in the middle of 1984 to take a job as Director of Antiviral Chemistry at Bristol-Myers in Connecticut. Shortly after his departure, his DHPG patent,[h] granted in October of 1982, came under

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dispute by three different pharmaceutical companies. Each company claimed that they had synthesized DHPG before John had. Since John was gone, I was asked by Syntex's patent attorneys to look through John's notebooks and records for the first evidence of John having obtained the DHPG molecule. "Here it is," I said over my office phone, "it's an NMR that John ran himself on our T60 spectrometer." The three patent disputes were summarily vanquished.

Raymond F. Schinazi: Frances Winship Walters Professor of Pediatrics, Emory University School of Medicine; friend, collaborator, colleague of JCM through affiliations with Emory, Triangle Pharmaceuticals, Pharmasset starting in mid-1980s

A Visionary Businessman and Renaissance Scientist

I first heard of John C. Martin when he was working at Syntex under the tutelage of two remarkable organic chemists, Julien PH Verheyden and John G Moffatt (famous for the Pfitzner-Moffatt oxidation, as well as many nucleoside transformations). With Julien, he discovered ganciclovir, the first acyclic nucleoside antiviral agent primarily used to treat cytomegalovirus (CMV) infections. John quickly realized the value of acyclic nucleosides, and he closely followed the work of several of the leading nucleoside experts. Howard J. Schaeffer at SUNY at Buffalo was busy making acyclic nucleosides and then acyclovir, which became a blockbuster for Burroughs-Wellcome for herpesvirus infections, especially HSV-1 and 2. On another continent Antónin Holý in the Czech Republic was busy synthesizing some of the most exciting broad spectrum acyclic nucleoside phosphonates to date such as tenofovir, which later became popular as tenofovir disoproxil fumarate (TDF)- and tenofovir alafenamide (TAF)-containing HIV cocktails such as Atripla and Truvada. Acyclic nucleotides did not escape John's attention when he worked at Syntex and BMS and then at Gilead. BMS thought these acyclic nucleotides were too toxic, having observed crystallization of the drug in renal tubules of guinea pigs. But that did not deter John, who licensed for Gilead these acyclic nucleotides from BMS and produced Cidofovir used for CMV. This drug had issues of solubility in the kidneys, but at an ISAR 1993 meeting in Venice I suggested to Howard S. Jaffe, who led the Development organization at Gilead, to use probenecid, which can inhibit the organic anion transporter, prevent tubular uptake, and protect the kidneys. Surprisingly John supported its use, and thus the kidney issue became less of a concern. Cidofovir was Gilead's first

ever FDA drug approval, and it led to the development of the phosphate-masked acyclic nucleosides TDF and TAF that are now used for HIV and HBV infections and are components of numerous HIV cocktails, including those containing emtricitabine (FTC), originally developed in our Emory laboratories.

My wife, Nadira, is a fashionista. She is elegant and graceful. So, when John and Lily came to visit us in Los Cabos, Mexico, they often complimented my wife on her style. However, John in particular seemed to be very knowledgeable about brands, colors, and the latest trends. My wife was very surprised and when asked how he knew all that, he mentioned that he reads many fashion magazines, especially WWD (*Women's Wear Daily*). "I read the whole magazine," he said, laughing. "I love it!" My wife could not stop laughing. She got herself a WWD subscription and with every page she often thinks of John. Who knew he had such a sense of fashion?

Pete Schultz: President, The Scripps Research Institute; JCM became a Board Member of The Scripps Research Institute in 2018

John and I first met at a Yale Symposium many years ago while he was at BMS—he gave a wonderful talk on his work on nucleosides and antivirals, which formed the basis of Gilead. Many years later I was fortunate enough to convince John to join the Scripps Board as he was winding down at Gilead. He was very enthused about the model we were building at Scripps to seamlessly bridge basic biomedical research and the discovery and development of new medicines. He brought incredible insights into the challenges and opportunities we faced in developing this new model and helped pave the way with important industry and foundation collaborations, including a major collaboration with Gilead that will likely continue his impact on the treatment and prevention of HIV. As a Board member, John was short on words, always to the point, and encouraged us to do bold new initiatives. He had just agreed to be the new Chair before his passing, and we miss his presence daily.

John was one of my scientific heroes. He had a love for basic research and always wanted to hear about the newest discoveries and talk with exciting young faculty. But what made him special was the impact he had through his translation of science into important new medicines that have touched almost everyone's life. This required a unique blend of great science, world-class drug discovery and development expertise, managerial skill, and

business savvy. Very few people in the world could do what John did so successfully and with such humility.

At the same time, John's forceful personality, generosity, and strong sense of public welfare inspired Gilead to make these important medicines available at low cost to low- and middle-income countries around the world, saving countless lives. He set an example for all the life science industry to follow, one which Lily continues through the John Martin Foundation and we at Scripps continue through our partnership with the Gates Foundation.

John had a remarkable impact on the world through science. He was a terrific persona and friend, and his life is a model to inspire young scientists now and in the future.

S. Swaminathan: colleague of JCM at Bristol-Myers 1988-2001 and Gilead 2002-2018 (JCM retirement in 2018)

I met John for the first time in 1988, when I was working in Wesleyan University and John was the head of Antiviral Chemistry at Bristol Myers. My first impression from that meeting was that John, aside from being an excellent scientist, was a great communicator as well as a great listener. My subsequent conversations with him reinforced this impression and had a profound impact on my inclination to pursue my scientific career in Drug Discovery. These chats enlightened me about medicinal chemistry and its subtleties. He was thorough, concise, and precise at the same time, especially on the topic of discovery and development of nucleosides as drugs, and the complexities of phosphorylation and the lifetime of the triphosphate inside the cell. The few hours I spent with him on this topic were more educational than any long course could have been.

During this time, I also learned that to be a good modeler, one has to understand the data generated in any discovery program as well as the medicinal chemist, and then overlay the molecular recognition understanding that you gain from computational chemistry on top of it. He always used the phrase "Making a difference" as a way of describing the actions that are seemingly minor innovations, many of which then add up to become a major innovation. He was fond of saying "Keep making a difference every day, and success will come." He encouraged me to talk to a lot of his colleagues, and it became clear that he surrounded himself with a lot of bright people with passion and drive. All of this encouraged me to

join Bristol Myers. But soon after that, the company merged with Squibb, and the priorities changed. This led John to leave the company and join Gilead Sciences.

When the opportunity came to join Gilead, there was no hesitation on my part because of my confidence in John as a scientific leader. Over the many years at Gilead, he assembled an excellent scientific team that eventually led to the success we have had. He contributed a lot and enabled us to contribute in multiple ways, and it is a tribute to his leadership that many of us who joined him stayed with him for many years.

One cannot talk about John and leave out his passion for universal access to life-saving drugs. This took a lot of effort to corral multiple organizations and agencies to accomplish, and he succeeded. On a personal side, he enabled me to contribute to this effort, encouraging me to accompany the teams and help them on their multiple visits to India.

Richard J. Whitley (Distinguished Professor, University of Alabama at Birmingham; Friend and colleague since the mid-1980s; subsequent member of the Board at Gilead Sciences)

I had the privilege of knowing John Martin since the mid-1980s when we collaborated in the development of ganciclovir for the treatment of congenital cytomegalovirus infection. This was no small feat. It was at a time when the pharmaceutical industry had absolutely no interest in developing therapeutics for infections of children, let alone those that were newborns. With ganciclovir, it was well known that the drug was mutagenic, teratogenic, and carcinogenic; thus, it had liabilities that would preclude it for development in the newborn by traditional pharmaceutical companies. Nevertheless, John allowed us to develop the drug through the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. These studies provided data from Phase I, Phase IIA, and, ultimately, Phase III studies of ganciclovir for the treatment of newborn infection. The Collaborative Antiviral Study Group was able to demonstrate that ganciclovir improved hearing in afflicted newborns. Subsequently, the pro-drug of ganciclovir, namely valganciclovir, was evaluated by the Collaborative Antiviral Study Group and provided data that demonstrated both improved hearing and improved Bailey Developmental Scores. Today, valganciclovir is the only licensed drug for the treatment of the most common congenital infection in the developed world.

This was just the beginning of my relationship with John. Over the years we traveled both for business and pleasure. For business, we went to meetings in Europe as well as the United States, including those sponsored by the National Institutes of Health. For pleasure, we traveled to the Galapagos, Machu Picchu, and, of all places, Little Cumberland Island, a barrier island off the coast of Georgia. In all these circumstances, the intelligence and the caring, giving nature of John Martin was obvious.

I was fortunate enough to watch John develop global programs after I joined the Board of Gilead Sciences. Two initiatives are of special importance. These were the Access Program and contributing Gilead's patents to the WHO Patent Pool. These contributions were nothing short of remarkable. The Access Program provided drugs for the treatment of patients with HIV, HBC, and HCV in the developing world, allowing millions of individuals to be alive today.

On a personal note, I lost a very dear friend in the death of John Martin, indeed, my best friend. He is a friend whom I admired and respected. He is an individual who contributed to changing the world and making it a better place to live. We will all miss him.

Lianhong Xu: Senior Vice President, Brii Biosciences; colleague of JCM at Gilead Sciences 1998-2018 (JCM retirement in 2018)

John was an icon in the biotech and pharmaceutical industry, especially for chemists in drug discovery and development. I had heard about John and his legendary stories with Syntex, BMS, and Gilead during my early years with Abbott Labs (current AbbVie). Although I hadn't interacted with him personally, his track record and great work with drugs at Gilead, including tenofovir and oseltamivir, convinced me that Gilead was where I needed to be, so I joined the company. During my 20-year tenure at Gilead as a scientist and middle-level manager, I got to know John better as a leader. John was a visionary, and his work shaped not only Gilead, but also the whole pharmaceutical industry. It was both an honor and privilege to have had the opportunity to work with him and contribute to the development of medicines that have helped millions.

One of John's most unique qualities was his practicality. Throughout my career, I've tried to emulate him by identifying the most practical approach, from selecting targets to pursue, to identifying a lead to optimize,

to choosing a candidate for clinical study. When I was working on the pharmaco-enhancer project, there were many compounds known in literature that could be used as a lead. However, we decided to use ritonavir as the starting point since it is the most practical way, given the known clinical data collected with ritonavir and potential mechanism of action learned from the data. We were able to quickly identify deoxy-ritonavir as the lead and subsequently optimized it to successfully obtain cobicistat. Cobicistat has desirable properties of a pharmaco-enhancer, especially when compared with ritonavir, including no antiviral activity and more selective with desirable physicochemical properties allowing fixed dose co-formulation. Cobicistat enabled the once-daily dosing single tablet regimens (STRs) Stribild and Genvoya. All along, from start to finish, John's visionary idea of integrase inhibitor-based STRs and strong support of the project allowed unprecedented speed in bringing the STRs to the market to become standard-of-care at the time. Stribild is the third STR for treatment of HIV, approved six years after the first STR, Atripla, which was also brought to the market by John and his team.

While John's practicality is the most important quality that I learned from him in pursuing new drugs, I will always remember how approachable and compassionate he was. He truly embraced the open-door policy by seeking us out. During company gatherings and weekly company happy hours, John would approach employees outside of the executive team. He would blend into crowds to discuss topics covering everything from the company's mission to sports, and from project strategy to our families. I enjoyed my discussions with John during these occasions and felt I could share my perspectives more freely. When John learned in one of these gatherings that my daughter was going to college, he later made a special point to follow up and spent more than an hour talking with her to share his insights on career choices. Even though I left Gilead in 2018 to explore a startup opportunity with Brii Biosciences, John and I kept in touch. He imparted his priceless vision on startups and industry direction, which helped me a great deal in navigating the journey.

John has contributed greatly to saving millions of lives who suffered or have been afflicted with diseases including HIV, HCV, and HBV. His untimely passing is a huge loss to us, the company, the industry, and patients. His vision and contributions of bringing novel medicines to patients will be forever remembered. And certainly his compassion for those around him will be sorely missed.

Taiyin Yang: Executive Vice President, Pharmaceutical Development and Manufacturing Gilead; colleague of JCM at Gilead Sciences 1993-2018 (JCM retirement in 2018)

An innovator in the business of developing medicines for devastating diseases and averting threats to human health with a global impact, John C. Martin, Gilead's longtime former CEO, was always ahead of his time. John took the company to scale new heights leading to Tamiflu® for influenza, single-tablet regimens for HIV, broad access to antiviral medicines in developing countries, curative regimens for HCV, and expanding into cell therapy for cancer cure. John once said the real reward is the opportunity to make a difference in curing diseases and helping patients.

John led the pursuit of Tamiflu in the 1990s, partnering with Roche, to become the mainstay regimen for pandemic preparedness during the 2005 avian flu and 2009 swine flu outbreaks. More than a decade ago, John foretold that the greatest threat to human health is emerging infectious diseases and put forth his steadfast passion and commitment to combatting this threat. The world now knows such resolve in the making of remdesivir—the first antiviral for treating hospitalized COVID-19 patients. Remdesivir was approved in the U.S. a short seven months after the pandemic lockdown began in March 2020.

John recruited and always surrounded himself with diverse experts; in the early years, many were from Bristol-Myers Squibb, Genentech, and Syntex. I worked under John's leadership for a quarter century at Gilead and knew him for my entire professional life of 40 years. John's enduring advocacy for underserved patients, his laser focus on outpacing the competition, and his constant pursuit of a cure have been the beacon for driving our success. A classic example is the invention and commercial launch of Atripla® in 2006, the first complete single-tablet regimen for HIV treatment, which was propelled by a simple-yet-powerful concept of "all or nothing" coined by John. Patients fail HIV therapy if they don't take all their medications, so to have a regimen with all the drugs in one pill was revolutionary at the time. John's confidence in the pharmaceutical development and manufacturing organization at Gilead enabled this success.

John stayed true to his aspiration of curing diseases to address unmet medical needs. John made HCV research a priority to tackle the disease full-on while he directed Gilead's acquisition of Pharmasset in 2011 to launch

the era of HCV cure. In the quest for curing cancers, John oversaw Gilead's expansion into cell therapy with a defining move of acquiring Kite Pharma in 2017. In making these pivotal moves, John was indeed ahead of his time.

On a personal level, John's advice, said in simple words throughout my career, was unassuming and powerful. Check your to-do list every day; do fewer items and do them well. Stay grounded and create your own path by putting one foot in front of the other. Put in more than you had planned each day to be better prepared for the future. Apply critical decision-making and focus on what matters. In his subtle way, John led by example and influenced a generation of pharmaceutical professionals.

With deepest appreciation and admiration, thank you, John, for this rewarding journey.

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