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Making a difference

"Serendipity favors the prepared mind." *- Louis Pasteur*

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Abstract

This is a personal account of one academic scientist who founded two biotechnology companies. Both companies were initially incubated within the walls of the university under a creative student incubator program whereby biology students could pursue their graduate academic degrees while gaining valuable biotechnology experiences. After the companies transitioned out of the university environment, the professor and his students pursued diagnostic and therapeutic drug development resulting in the completion of several clinical trials. The value of international scientific collaborations with colleagues at the University of Padova (Italy) is also described.

Key words*:* biotechnology; incubator; drug development; clinical trials; sphingolipids.

The value of ideas

What are ideas? Descartes said, "I think, therefore I am." That is true. It is also true that ideas can spawn spiritual development, if you sit in Zen meditation, for example. I would like to argue here something on a more mundane level. I find that there is great value in conceptualizing an invention, a nifty way of testing a physical concept, a notion of how muscles work, or a new insight on how to treat cancer. These more pedestrian thoughts are what I dealt with every day of my professional career. Added value came from teaching where I had the privilege of imparting some of these ideas to inquisitive minds and encouraging students to think critically about the physical world.

University life

Shortly after I was hired into the Department of Biology at San Diego State University (SDSU) in 1977, the department adopted a concept called the "Teacher-Scholar Model." The model embraced the idea that the teachers of modern science should also be active scientists because of the rapidly changing nature of the discipline. I loved teaching and never tired of that activity. I taught human physiology for pre-medical and graduate students for more than twenty years. I also taught basic biology, cell and molecular biology and various graduate seminar courses. I enjoyed teaching non-biology majors about physiology and started a course on the biology of sex. I also taught my international security course for many years. After my retirement in 2008 and well into 2014, I guest-lectured in a bioethics course. This was a course required to be conducted by any university receiving grant funds from the National Institutes of Health (NIH). In my presentations, I instructed the students in the responsibility of a scientist not only in engaging in ethical conduct, but on their responsibly speaking out on public policy issues. I was not advocating that they take any partisan position. Rather, I suggested that their special knowledge of science should be used to educate the public and our elected representatives on critical societal issues that affect human health and the environment. I argued it was their obligation to do so.

My university was living in the shadow of the University of California, San Diego (UCSD) which is to this day a premiere research institution. At SDSU, we attempted to distinguish ourselves from UCSD by balancing excellence in teaching with excellence in research. The model we created gave undergraduates, persons of color and Masters-level students opportunities to conduct laboratory and field research with SDSU professors. The Master of Science program (MS) became a very valued degree with a great reputation state-wide. Our MS graduates were sought after by governmental agencies and the emerging biotechnology and pharmaceutical industry. Most of our MS theses were as robust as a Ph.D. thesis. We instituted a Joint Doctoral (JD) Program in Molecular Biology with our UCSD colleagues. It was an excellent program where students would take courses at UCSD but perform their research with SDSU faculty. Thesis committees would include faculty from both schools. Students who started in the MS program often transitioned into the JD program if their interests and aptitude were demonstrated. When first hired, I was one of the few research-active faculties in the Biology Department's area

of cell and molecular biology. Along with some colleagues in the Chemistry Department, we formed hiring committees and modernized the life sciences area of the College of Sciences. I served as chair of many hiring committees and made sure we brought in new faculty who would embrace the Teacher-Scholar model. SDSU soon became the flagship of the California State University (CSU) System. Because of those efforts, our department was not only ranked at the top of the CSU but also ranked in the upper half of the UC campuses. We were aware of the highly competitive academic culture of the UC campuses and local institutions like Scripps Research Institute and the Salk Institute. We tried with some success to pool our resources, cooperate, and collaborate in forming an academic environment where synergy and efficiency were created. An added benefit was that we very much liked each other. Some of my best friends are my former SDSU colleagues. For example, a small group of us commonly ate lunch together. We called ourselves the Lunch Bunch and we ate and socialized together for more than 30 years. Jerry Johnson, Sandy Bernstein, Terry Frey, and Gary Sumnicht are those dear friends. To me, they were brothers more than colleagues. I live in Oregon now, but when I get back to San Diego, we get the Lunch Bunch together for old-time's sake. Others of us skied and vacationed together and we had many parties where students, staff, and faculty mingled. It pleases me to declare my affection and deep admiration for many other SDSU colleagues.

The College of Sciences was very progressive in promoting minority access to careers in science. Under the leadership of Dean Don Short, along with Paul Paolini and others created fourteen programs to promote under-represented persons of color in pursuing careers in science and medicine which were designed to mitigate educational inequities in minority communities. I was involved with several of these programs and sponsored many minority students in my lab. I mentored minority students toward careers in biomedical research though the Minority Biomedical Research Support (MBRS) and the Maximizing Access to Research Careers (MARC) programs.

We founded the SDSU Molecular Biology Institute and the SDSU Heart Institute. We instituted a master's degree in molecular biology which is a highly-regarded degrees by the local academic and biotechnology entities in the greater San Diego area.

SDSU also created a robust pre-profession health advising center that groomed students for successful entry into top medical, dental, and veterinary schools. At one point, the center boasted an 86% success rate in getting our graduates into top medical schools like Harvard. Provost

Nancy Marlin promoted international programs where all departments and colleges were incentivized to send students abroad for valuable international experiences. For several years, I directed the College of Sciences international programs on Nancy's behalf. Nancy and her husband Fred Kolkhorst remain best of friends to this day. We vacation together almost every year in the Dolomites, Italy, and I speak with Fred by phone almost every week.

Padova, Italy

International travel and collaborative research with colleagues from foreign institutions is now considered routine and modern. It is common to see papers co-authored by collaborators from many institutions across the globe. In 1984, I took my first sabbatical leave in Italy. I chose Italy because I wanted to collaborate with Giovanni Salviati who published a paper that caught my attention. I believed we were thinking along the same lines on a topic. Giovanni was a professor at the prestigious University of Padova in Padua, Italy. I became a visiting professor there and started a collaboration that ended with Giovanni's untimely death twenty years later.

Founded in 1222, *il Bo*, as it is affectionately called, boasts that it is the oldest medical school in the world and the second oldest university (after Bologna). The first woman to ever have graduated from a university received her medical degree from the Bo, Elena Piscopia Cornaro. She was the daughter of the Doge of Venice who retired in Padova. In the foyer of the old university, there is a statue celebrating her accomplishment. Padova was and still is also very progressive in other ways. In contrast to most other European universities, Jews could study at the *Bo*. As a result, Jews from all over Europe came to the university to study medicine. Between 1517 and 1721, 229 Jews graduated in medicine.

Galileo Galilei taught mathematics and astronomy from 1592-1610. Galileo's research in astronomy began in Padova. He designed his first telescope using lenses made for him by the famous glass-blowers of Murano near Venice. If you visit *il Bo*, you can see Galileo's lectern which is preserved in the hall where students defend their theses. Before leaving the university, Galileo announced the first of his discoveries in astronomy. Before leaving the University of Padova to take a position in the de Medici court in Florence as court mathematician and philosopher, Galileo announced the first of his discoveries in astronomy using his telescopic observations in the form of a publication entitled, *Sidereus Nuncius* (*The Starry Messenger*, published in March of 1610). While most of Galileo's work was published in Italian, *Sidereus*

Nuncius was published in Latin by the printer, Thomas Baglioni. *Sidereus* sold all printed 550 copies and was an instant success and made Galileo the most famous scientist in Europe at the time. *Sidereus Nuncius* supported the Copernican heliocentric system and began Galileo's conflict with the Catholic Church–a controversy, named "The Galileo Affair." He also pioneered the teaching of experimental science at *il Bo* and greatly influenced scientific thought and modern science. From all over Europe, renowned scientists like William Harvey flocked to Padova to work there with other thought-leaders. On occasion, I have been privileged to present my own scientific work in *il Bo* surrounded by the family crests of great scientists who worked there.

Years later, after two successful sabbaticals and numerous visits, I learned that one of my ancestors, Moshe **(**Moisè**)** Sabbadini (1575-1640), was a leader in the Jewish community of Padova during the same period that Galileo was teaching there at the university (1592-1610). The *Bo* is close to the Ghetto of Padova and I imagined that Moshe Sabbadini and Professor Galileo had a glass of wine together on occasion. I wonder what they may have discussed.

The disciplines of anatomy and surgery were born in Padova and the use of the first of its kind anatomical theater was instrumental for its development. The concentric layers of observation gallery allowed medical students and visiting scientists to view the dissections of human cadavers that were placed on a central platform. The purposeful absence of windows prevented religious inquisitors from seeing that human bodies were being dissected. In those days, it was against Papal Law to conduct vivisection on corpses with two exceptions, criminals executed for capital crimes and professors. Professors could donate their bodies to science after death. The dedication of one's body or body parts to science began with this practice in Padova. There is a room to the side of the anatomical theater where one can see the bronze busts of those professors who donated. Since there were not enough legitimate cadavers to satisfy the need, other cadavers were used in violation of the law. If the Catholic inquisitors were to raid the anatomical theater, a trick was devised whereby the dissection table would be flipped so that the human cadaver would conveniently drop below into the Piovego River. A dead goat was positioned on the underside of the rotatable table so that it would appear to be the object of the anatomy lesson. Ingeniously, the anatomical theatre was purposely constructed above the river so that the evidence could easily be dispatched.

In 1984, I was one of the first visiting professors to have taken a sabbatical in the Department of Pathology of the medical school. With the help of Giovanni and Anna Salviati, we rented a flat in town. Our daughter Amy, then 7-years-old, was enrolled in a neighborhood school. She did not speak Italian but soon became fluent and spoke with a Veneto accent. Amy's initial resistance to living in Italy was soon overcome. She was the center of attention at school. All the kids wanted to touch her and be her friend. More importantly, we arrived in February which is the season of *Carnavale* which is the celebration leading up to Lent. There were continuous parties at school with special cakes and pastries and all the kids wore costumes. We bought Amy a *principessa* costume - she relished playing the part of a medieval princess. Our son Scott celebrated his first birthday in Padova. Gail would take the kids to the *centro* to shop. They became known by the locals as *I Tre Biondi*, the 3 blond ones. Every time we go to Padova (which is almost every year), we stop by the local cheese shop to pay our respects to Roberto Carpanese, the owner of *Casa del Parmigiano*. If he is not busy, we go out for a coffee together. Cheese is important to me. My great friends, Giovanni Salviati and Romeo Betto, introduced us to Italian cheese and the proper wine for pairing to various cheeses. My favorite cheese became Carnia stravecchio. It is difficult to find even in Padova. Invariably Robert Carpanese carried it. To this day, I bring some home to share with my lovely granddaughter, Hannah, who considers Carnia to be her favorite cheese. Giovanni and Romeo taught us many epicurean ways. Our son, Scott, was greatly influenced by them and made a career of winemaking because of that guidance. Scott is now the head winemaker in a boutique winery in Oregon. Our family's sacraments have become Carnia paired with Amarone wine. Now that Giovanni is gone, Romeo and I often raise a glass of Amarone in his honor. Giovanni, Romeo, and I were like brothers. We called ourselves "The Three Amigos." (Figure 1)

The friendship between Romeo and me has greatly deepened since Giovanni's passing. We see each other at least once a year, usually in Padova. To say that our families are very close does not do justice to the affection that binds us. (Figure 2)

In March of 2018, a great friend and colleague, Ugo Carraro, organized a scientific meeting, *The 2018 Padua Muscle Days*, commemorating the life and scientific accomplishments of Giovanni Salviati. Giovanni's wife, Anna, and their adult children, Leonardo and Alessandro, were invited to hear testimonies by Giovanni's friends and colleagues. I was asked to give a keynote speech and chair a scientific session in Padova at the *Accademia Galileiana di Scienze, Lettere e Arti*. It

was to be the last scientific presentation of my career, and I was pleased to speak, not about my scientific accomplishments, but about those of someone whom I deeply loved and respected. [1-4] Over the years, many of our great Italian friends visited us in San Diego. Some took sabbatical leaves in my lab. Ernesto Damiani, Romeo Betto, and Sergio Salvatori were among the visiting scientists. One great friend and professor of pharmacology at Padova, Sisto Luciani, visited me in San Diego and proposed including San Diego State University in a novel program he initiated, an international doctorate degree. I became a faculty member of this international doctorate program and hosted one of the first students, Barbara Visentin. Barbara defended her thesis work in the *Bo* in the room adjacent to where Galileo taught. She presented work that she performed in my lab. I wish I could have been there. Barbara eventually came back to San Diego and worked in my lab as a postdoctoral fellow. Barbara ended up becoming a Senior Scientist in a company I founded, Lpath, Inc. and now works in the San Diego biotechnology community. She also has become a U.S. citizen.

Biotechnology years

I founded two biotechnology companies in San Diego from work that I began while a professor at SDSU. It was several years between my first discovery and when I first founded Medlyte Diagnostics/Lpath Therapeutics in 1997 and then co-founded Mpex/Vaxiion in 2000. Lpath went public in 2005 and was NASDAQ (National Association of Securities Dealers Automated Quotation)-listed in 2012, raised $70 million (4 PIPEs; 2 register directs; 1 public offering; $12 million in NIH and other grants). We received equity investments from Johnson & Johnson Development Corporation as well as Biogen-Idec and partnerships with Merck-Serono and Pfizer. We conducted 6 clinical trials, two of which were Phase 2 therapeutic trials. The company was sold to Apollo Endosurgery in 2016 and its technology was subsequently licensed from Apollo to Resolute Pharma, Inc. in 2018. The Chief Executive Officer (CEO) of RPT is Dan Chambers, the former patent attorney for Medlyte/Lpath. Several of Lpath's research-use-only products are currently sold by Echelon Biosciences. Vaxiion Therapeutics remains a privately-held company currently under the leadership of Matt Giacalone, one of my former students who got his Ph.D./MBA at SDSU under the joint doctoral program between SDSU and UCSD. Vaxiion remains in operation as a pre-clinical research and development company based

in San Diego. Vaxiion was originally funded by private equity, $6 million from Western States Investment Group (WSIG) plus $4 million in non-dilutive funds.

Along the way we published scores of scientific papers in cancer,[5-9] traumatic brain injury,[10,11] cardiac and skeletal muscle disorders,[12-20] and vaccine research.[21-23] I am the major inventor on 36 issued U.S. patents and many other patents in international jurisdictions. I have presented our work at many international scientific meetings and have been invited to speak at such illustrious academic institutions and even unusual venues such as the US Patent and Trademark Office (USPTO). I have made countless presentations to pharmaceutical and biotechnology companies, investment bankers and venture capitalists. I wore suits and ties - strange attire for a guy who exclusively wore blue jeans up to that point.

What follows is a somewhat detailed and partially technical description of how the two companies came into being and some of their triumphs and disappointments along the way.

Aha!

The first "*eureka*!" moment that led me on the path of entrepreneurship occurred in Padova in 1990 while collaborating with Giovanni Salviati, Alessandra Teresi, and Romeo Betto during my second sabbatical. It was a serendipitous discovery that led me into the field of bioactive lipids.[8] Bioactive lipids are lipid molecules that have signaling functions in that they usually act on extracellular receptors or ion channels to alter the activity of the target cell. Prior to the 1990's the only molecules thought to have signaling properties were proteins such as cytokines, hormones and growth factors. They generally exerted their actions as ligands by binding to and activating specific receptors on the extracellular membranes of target cells. If one could neutralize that ligand-receptor interaction, cancer cells would not be as aggressive as they otherwise would be.[2-3] Or the heart would not create as much pressure in patients with septic shock.[12]

We now know that bioactive signaling lipids can be dysregulated in diseases and disorders much like certain growth factors and other proteins are upregulated or deficient. Therefore, bioactive lipids can be biomarkers as well as targets for drug discovery. As it turned out, both bioactive lipids we worked on at Medlyte/Lpath served as biomarkers and drug targets.[16]

Long before Medlyte/Lpath was formed, I had been working on calcium channels that controlled the contraction cycles of cardiac and skeletal muscle. This interest started during my Ph.D. work

with Ron Baskin and continued through my postdoctoral work with Giuseppe Inesi.[24-25] I theorized that the deficiencies in dystrophic muscle and dysfunctional heart could be due to alterations in the internal flux of calcium. Calcium is stored inside muscle and heart cells in an internal membrane structure known as the sarcoplasmic reticulum (SR). Another membrane system, the transverse tubules (TT), form a junction with the SR and stimulates the SR to open a calcium channel, the ryanodine receptor (RyR). Calcium then flows out of the SR sacs and causes the contractile proteins to do their work in producing force. I went to Padova to study how the RyR was regulated, *i.e.*, how it opens and closes. I theorized that an enzyme called protein kinase C (PKC) phosphorylated the RyR to modulate calcium flux. I was wrong about the role of PKC but in proving the hypothesis wrong, we discovered something potentially important.

At that time, there were no established inhibitors of PKC making it difficult to use a pharmacological approach in studying PKC's role. Fortunately, I found a paper written by Yusef Hannun showing that a naturally-occurring sphingolipid called sphingosine (SPH) inhibited PKC: I bought some from Sigma Chemical Co., put it in my suitcase and took it to Padova. Alessandra Teresi was a student in Giovanni's laboratory. She had isolated SR vesicles and set up an experiment to test calcium flux. In a control experiment, she added SPH to the isolated SR membranes and it completely blocked calcium release from the RyR calcium channel. Since it did not matter whether ATP was in the mixture, it demonstrated the SPH had a direct effect on the channel independent of PKC or any other kinase. We published our initial work on sphingolipids in 1991 and 1992.[8]

When I got back to my laboratory in San Diego, I searched the literature for sphingolipids like sphingosine and sphingosine-1-phosphate (S1P). Before 1992, only 6 papers were published on S1P (4 in mammalian cells, 2 with slime molds). In 1991, Sarah Spiegel published a paper showing that S1P promoted cell proliferation. However, Yasuyuki Igarashi published a paper showing the opposite effect. Also, no receptors for any bioactive lipids, including sphingolipids, had yet been discovered. It would take 6 more years for that to happen.

Subsequently, we made measurements of sphingolipids and embarked on a series of studies suggesting that heart cells produced sphingolipids in response to various types of cardiac stress.[9] We published work demonstrating that during experimental heart failure, the protein growth factor, TNFα, could stimulate sphingolipid production.[12] The resulting increase in sphingolipids

could block the calcium channels and produce a negative inotropic effect (*i.e.*, a weaker strength of contraction).

I also hypothesized that sphingolipids such as sphingosine or S1P could be biomarkers for the ischemic heart (*i.e.*, lack of blood to the heart).[16] I theorized that one could make antibodies to these bioactive lipids and the antibodies could be used in an *in vitro* diagnostic test for cardiac ischemia. As of this writing, there continues to be no biomarker for ischemia. There are several biomarkers for myocardial infarction (*i.e.*, MI or heart attack) where heart cells die and release specific cardiac enzymes into the blood. There are several FDA-approved *in vitro* diagnostic tests for infarction but none so far for cardiac ischemia. Most angina pectoris (*i.e.*, chest pain) is due to non-MI ischemia. This type of ischemia is called Acute Coronary Syndrome (ACS). Consequently, there would be an unmet need if one had a marker for ACS and a test kit where cardiac ischemia could be distinguished from myocardial infarction.

As required by my contract with SDSU, I disclosed my invention to the university. At that time, there was no technology transfer office at SDSU or at any CSU campus. At SDSU, Larry Feinberg oversaw tech transfer and intellectual property development. Feinberg was the Dean of the Graduate Division. I told Feinberg that I wanted to file a patent on my invention. According to my contract, the university would own all intellectual property rights and I would be the inventor. Since the university would own the invention, SDSU would be required to pay patent attorney fees and filing fees with the US Patent and Trademark Office. In the end, the university did not want to invest in the patent and it sat on my invention for nearly 4 years.

Meanwhile, I was moving ahead with work on bioactive lipids and the field was developing. I filed other disclosures and the university did nothing regarding patent prosecution. My contract did not have a performance clause in it requiring them to give the intellectual property rights back to me. However, in 1995, I asked anyway and Larry Feinberg re-assigned all rights back to me.

Subsequently, I took $7,000 of my own money, hired a patent attorney, Ned Israelson, and filed my first provisional patent in 1997.

In those days, there were very few biotechnology and medical device companies in the San Diego area. However, there were a small number of *in vitro* diagnostic development companies. One of my former Ph.D. students, Brad Cunningham, was, in fact, working with one, Wynteck Diagnostics. I called Brad and asked his advice. Under a Confidential Disclosure Agreement

(CDA), I met with Brad and disclosed to him my invention and asked him what I should do. He recommended that I make a presentation of the invention to his boss, Chris Fan, which I eventually did. A few days after giving my pitch to Chris Fan, I received a call from Brad to say that Fan liked it and wanted to buy the patent for $400-500K. Wow!

I was thinking that I could do a lot of research with that sum of money. I was not thinking of profiting personally from the deal. After two days, Brad called to increase to $600K and then 2 days later to $800K. Now, I was over my head and needed expert advice.

The only other scientist that I knew who had become an entrepreneur was Dr. Robert Engler. Bob had started a company called Collateral Therapeutics. I knew Bob from his UCSD and VA Hospital days where he was the first scientist to propose that heart cells die by a process known as apoptosis. I knew about apoptosis and programmed cell death from work I did as a visiting professor at the University of Western Australia working with Arun Dharmarajan. Consequently, Bob and I had much in common.

Bob and Kirk Hammond at UCSD were working on another hot topic, angiogenesis. Angiogenesis is the production of new blood vessels under the influence of certain growth factors like bFGF. Collateral Therapeutics was developing a way to increase blood vessel formation in the heart through bFGF gene therapy. A co-Founder and corporate attorney for Collateral was Craig Andrews.

I met with Bob Engler and disclosed to him my invention and told him that Chris Fan had offered me a lot of money for the patent. Bob advised me to “surround yourself with people who are smarter than you are” and that I should be willing to share equity with others. Bob suggested I meet with Craig Andrews and he set us up with a meeting. Craig was working for the law firm Brobeck, Phleger & Harrison that specialized in the emerging biotechnology industry.

Craig explained to me the various options I had available to me. He explained who venture capitalists (VCs) were and how they operated, how money is raised through VCs vs. Angel Investors and partnerships or license agreements with the pharmaceutical industry. Craig also explained how one started a company and why one would go that route rather than selling or licensing the technology to another entity. He basically asked me if I wanted to continue working in the area myself and if I wanted to usher the technology forward. If so, then I should start a company. At SDSU no one in the biological sciences had started a company and no technology

transfer office had yet been established. After pondering my options for a few days, I put myself in Craig's hands.

I formed a company in September of 1997 and initially held 100% of the equity (*i.e.*, the shares). Craig did not charge me for filing the paperwork with the State of Delaware to form the company we called Medlyte Diagnostics, Inc. The agreement was that I would square it with him when we raised money for my company. As a prerequisite for raising money, I needed a business plan. Craig suggested I get help from two investment bankers he knew, Roy Lessard and Mason Fleming. They had an office next door to that of Sol Price, the entrepreneur who started Price Club/Costco and Fed Mart. As part of the business plan, I had to come up with a cogent path towards a value creation point. In scientific terms that meant obtaining proof-of-concept (POC) data from a clinical trial and developing the test kit.

The investors preferred the diagnostic opportunity because the path to value creation is shorter than in therapeutic drug discovery and is less costly getting to market. A bit later in 2000, I filed patent applications on targeting bioactive lipids with anti-sphingolipid antibodies for therapeutic applications in cancer, angiogenesis, and inflammation.

In 1998, I had no experience with cardiac diagnostics. Luckily, one of my former students, Wyatt Smith, was working as a physician at the Naval Medical Center of San Diego. I told Wyatt what I was up to and he introduced me to a cardiologist named Jeff Carstens. Wyatt, Jeff, Brad, and I started regular meetings at cocktail hour at the Hilton Hotel in Mission Valley and mapped out a clinical design to test sphingolipids as biomarkers for the cardiac ischemic event, Acute Coronary Syndrome (ACS).

Wyatt and Jeff argued that there was no biomarker, cardiac scan, EKG signature or other test for ACS, we could use the extent of coronary artery stenosis (blockage or occlusion) as an indication of ischemia. Jeff was an interventional cardiologist who performed angiograms and balloon angioplasty with stenting to remove blockage of the coronary arteries revealed by angiography. Jeff devised a scoring system for evaluating the over-all stenosis which we called Coronary Artery Disease or CAD score. Meanwhile, the business plan called for Medlyte to develop a rapid, point-of-care (POC) *in vitro* diagnostic (IVD) kit with Brad's help.

With a business plan in hand and with Roy Lessard's help, I made presentations to several venture capitalists, including Drew Senyei of Enterprise Partners and Scott Pancoast of Western States Investment Group (WSIG). I received offers from both but chose WSIG as Enterprise

Partners wanted 90% of the company's equity**.** In February of 1998, we closed the first round of financing by WSIG et al $1.2 million. I came to understand later that the VCs were impressed not only by the science but also by the fact that I had put up my own money to file the patent application. Also, they were impressed to learn that I had not accepted cold cash from Chris Fan of Wynteck Diagnostics. Those activities signaled to the investors that I had faith in the technology.

Wyatt, Jeff, and Brad asked if they could be given founders shares along with Craig to whom I had already pledged. The equity split became: Roger Sabbadini 800,000 shares, Wyatt Smith, and Jeff Carstens each 200k, Brad Cunningham with 100k and Craig Andrews/ Brobeck got 200k.

Next, we had to form a board of directors. Craig suggested bringing in as chair of the board someone with great experience in the medical device arena, John Lyon. John Lyon was CEO of a local public company, Vista Medical Technologies. Scott Pancoast, Craig Andrews, Roger Sabbadini and John Lyon were the initial members of the board. Not long after, we got an equity investment from Johnson & Johnson Development Corporation (JJDC) and Cousins came on the board representing JJDC. We had board meetings at my home, after which we would play poker and smoke cigars. Biogen-Idec later came in with an investment but did not take a board seat. The board had a quasi-managerial role. I was president of the company and the board oversaw all important business decisions. I had weekly discussions with John Lyon who taught me volumes about starting and running an early-stage company. Most importantly, John was there for me when times were tough. He taught me never to give up and I will forever be in his debt for his wisdom. John and I became great friends and remain so to this day. John and Christine bought a second home near our house in Bend, Oregon. We see each other often and enjoy mountain biking together and play poker at times. We both like various Campari cocktails.

SDSU Incubator

I did not want to give up my academic position at SDSU. The problem became how could I have one foot in academia and the other foot in biotech? I came up with a great solution by turning my laboratory into a biotechnology incubator where SDSU graduate students could be trained for top positions in the emerging biotech sector. It became a win-win for all parties, Roger Sabbadini, the company, the university, and the students. I was grateful for the free education I had received

from the State of California and I wanted to give back. I was also grateful that the public gave me a job as a professor.

Faculty and administration at SDSU recognized the value of what I called “academic diversity” where such pursuits gave strength to a truly modern university that recognized and encouraged entrepreneurship. Such academic diversity required that my first responsibility was to the university and to the public that supported SDSU. I could not have developed the incubator without the leadership and help of Don Short, Dean of Sciences, Sandy Bernstein, Chair of the Biology Department at the time and Sally Roush who was vice president (VP) of Business and Finance. Most helpful was Joe Vasquez who was the university’s attorney and business manager. Joe wrote up the contract and made sure that the university and its students profited from the enterprise.

According to my university contract, I could devote 20% of my time in the pursuit of other activities. Faculty in engineering and computer science had long taken advantage of this and had rich experiences serving as consultants for industry. Those experiences allowed consulting faculty to better serve their students. Consequently, Medlyte (and later, Lpath) hired me as a consultant. Even though I was President of the company, I was a consultant on the books. Another premise was that potential conflicts of interest needed to be disclosed up-front: and, that there was a clear distinction between my academic and industry duties, all of which would be spelled out in an agreement between the company and the university. Above all, the incubator had to avoid any appearance that the State of California was subsidizing a for-profit enterprise. I proposed that the company rent my academic laboratory space and make use of university facilities at fees above market. I proposed that 100% of research activities performed in that space be devoted to incubator activities for companies.

Regarding facilities fees, my department was thrilled. Suddenly, the chair and the business manager had a discretionary fund. In the face of shrinking budgets and the resulting reductions in operating expense allocations, the Biology Department had the extra source of income to maintain essential programs. Substantially more money came through the company to the university when I started buying back my time. This was called “release time.” Faculty could reduce their teaching loads if grants would reimburse the university for some percentage of the faculty’s salary. Since fully-tenured professors were more expensive than part-time lecturers in terms of salary, the department could hire two lecturers for the price of one faculty stipend. In

periods of shrinking OE budgets, buying release time for me was yet another windfall for the department.

On grants, I was no longer to write for federal grants through the university. All grants like the NIH Small Business Innovative Research (NIH/SBIR) grants would be submitted from the company and money would flow to the university via the student incubator agreement. I did not realize this at the time, but the NIH/SBIR program was to become a windfall for me. While the chances of landing an academic NIH/RO1 grant was 20%, I was nearly 100% successful in getting SBIR grants and obtained over $10 million of these funds, much of which supported student research.

Because of company funds flowing into the university, I was able to fully-support many MS and Ph.D. students such as Neil Berkley, Matt Giacalone, Amy Cavalli, Nobuku Nakajima, Trevor Page, John Vekich, Joe Ligutti, Nicole O'Brien, Nicole Gellings and Barbara Visentin. We also made it possible for the students to become staff scientists in my companies. One of our star employees was an undergraduate in my academic lab, Kelli Moreno. Kelli progressed from lab assistant at SDSU to Senior Scientist in the company.

Hiring former SDSU students was a win-win for both the company and the students. The company was pleased to have a fully-trained researcher on day-one and the former student was afforded the opportunity of continuing his/her work beyond the degree. Students were also given stock options in the company during his/her tenure as a graduate student. One student, Neil Berkeley, became co-Founder of Mpex/Vaxiion, a company we spun out of Lpath. Another former student, Matt Giacalone, is now President and CEO of Vaxiion.

It is important to note that all my former students continue to hold valued positions in the biotech/pharma industry. Several of my students simultaneously enrolled in the MBA program and received both science and business degrees making them marketable in the biotech and pharma industries. John Vekich, Matt Giacalone, Trevor Page and Neil Berkeley are among those.

Importantly, there were no restrictions on publishing their thesis work because I put all graduate students on projects for which the intellectual property had already been filed with the USPTO. Their work represented "reduction to practice" at best which carries no IP rights. Other IP rights were clearly defined so that any further inventions by me were conceived on company time and did not belong to the university.

The student incubator was a big win for both the students and the university because our joint doctoral and our master's programs had limited resources which would restrict the number of students our department could enroll in the program. With our incubator, the department could increase the total number of graduate student numbers at no cost to the State of California. It was a win for the students not only because they had a position that otherwise would not have been available to them but they also did not have to teach to support themselves. Through the incubator, the company gave them a free ride. My last student, Nicole Gellings, received her Ph.D. at an estimated cost of $300k, all of which was borne by the company. In addition to Nicole's stipend of $35k per year, the company paid for all her research expenses, travel to scientific meetings and all publication costs.

In the end, three companies were incubated under such an agreement, Medlyte/Lpath, Mpex and Vaxiion. Without any *quid pro quo* and after the student incubator agreement had been executed, SDSU was given stock in all three companies. The stock was held in an endowment that Gail and I created. We stipulated that the endowment was to be used to promote graduate student research in the Biology Department.

The MIRF trial

Between 1998-2000, Medlyte worked towards the milestone of proving that sphingolipids were biomarkers for obstructive coronary artery disease as an indirect measure of the ischemia of Acute Coronary Syndrome. In 2000 the MIRF (myocardial ischemia risk factor) trial was completed on time and under budget. We consented 308 consecutive patients and demonstrated that serum S1P was more predictive of CAD than the traditional risk factors (age, sex, family history of CAD, diabetes mellitus, hypertension, and lipid profile). Our results were published in the American Heart Journal.[16]

Meanwhile, I had filed a patent claiming that neutralizing serum sphingolipids like S1P could be an effective treatment for disease. To my pleasure, Roy Cousins of Johnson & Johnson influenced the board to widen the scope of the company's R&D focus to include therapeutics.

Antibodies to Lipid Targets

Our original business plan called for the development of a proprietary test kit to measure sphingolipids like S1P in blood. The kit would require the development of antibodies to the

sphingolipid analytes as key components of a rapid, POC IVD. Thus, the generation of anti-sphingolipid antibodies was a second milestone that would trigger more investment and continued R&D. The patent that I filed in 2000 claimed that these antibodies could be potential drugs in treating diseases where sphingolipids were up-regulated. The dysregulated lipids would then be neutralized by the antibodies.

Two of the company's Key Opinion Leaders (KOLs), Gordon Mills and Bill Garland, told the board that it was *not* possible to make antibodies against lipids. They had previously formed a company, Atairgin, that tried and failed to make antibodies against lysophosphatidic acid (LPA) for the purpose of developing a diagnostic assay for LPA. Some of my academic colleagues who were immunologists argued that our lipid targets were not antigenic enough to elicit antibody production in mice. I thought they were wrong and I would prove it to them.

The pressure was on me and the team to make antibodies to S1P. Ultimately, we were successful in making monoclonal antibodies (mAbs) to S1P. Those antibodies were humanized and evaluated in Phase 1 and Phase 2 clinical trials as therapeutic agents in the treatment of cancer and age-related macular degeneration. We also developed anti-LPA antibodies that were tested successfully in a Phase 1 clinical trial just prior to the sale of the company. The non-human, murine-based mAbs are reagents that form the basis of test kits to measure S1P and LPA in blood and as naked antibodies for *in vitro* and *in vivo* animal studies. They are currently being sold by Echelon Biosciences for research-use-only studies. Before the company was sold, we made our antibodies available free-of-charge to at least 100 academic scientists world-wide through Material Transfer Agreements (MTAs). Those antibodies proved to be very valuable reagents used in many scientific publications.

Before we were successful, we had many failures. I hired Bob Klepper to make mAbs by immunizing mice. Bob had great experience in making mAbs for other companies but was initially unsuccessful in doing so with our project. He made a presentation to the board declaring that Gordon Mills and Bill Garland were correct in their assertion that antibodies to bioactive lipids could not be made. The board's response was that we were to let Bob Klepper go and that I would wind things down with the last $150k left in the bank. There were no hard feelings because 90% of early-stage biotech companies fail, and all understood that our venture was high-risk, high-return. The board said it is better to fail early before too much money is invested.

There I was, with no employees, no more money and one graduate student, Nicole O'Brien, who was writing up her thesis work. The only board member who did not give up on me was John Lyon, chair of the board. One day we had fish and chips and a craft beer in Encinitas to drown our sorrows. John's response to my whining about the impending failure of the company was, "Never give up." I did not. Nicole and I were the only ones left in a near-empty laboratory. We brainstormed and came up with an idea as to what the problem had been. It was an "Aha!" moment. Let me backtrack a little! Key to making antibodies against S1P was to present the antibody in a way such that the functional end of the lipid was the antigen.[26] Being a lysolipid, S1P has a head region that is charged and a long hydrocarbon tail that is hydrophobic – like a lollipop. The charged or polar end is the functional end of the amphipathic molecule followed by an uncharged hydrocarbon tail. For successful immunization, we needed to make an analog of S1P. This idea came from discussions I had with Joe Witztum of our Scientific Advisory board. It required the synthesis of an organic derivative of S1P that had a reactive group such as a thiol (SH group) tagged on the end of the hydrocarbon chain. The SH tag on the end would be cross-linked to a carrier protein and this complex would be the antigen for immunizing mice. A few mice in the colony responded but we could not make good mAbs. It turned out that this half of the process had been working fine. Most the mice responded well to our antigen but we just did not know it. Nicole and I were brainstorming in the lab one day and Nicole asked how sure I was in having a robust way of detecting antibody responses in mouse serum. This insightful question suggested that maybe our assay was not detecting serum responses. Wow!! That was the "Aha!" moment. We had been using conventional thinking in the ELISA plate assay that is commonly used for detecting antibodies in the serum against protein targets/antigens, not lipids. It then occurred to me that we were washing out all the natural S1P in the mouse serum and it was not sticking to the plate that had the serum-containing antibodies that we laid down first. I had the idea that we should use the thiolated-S1P as the capture reagent of the ELISA plates, that is, lay down the thiolated S1P first and then run the mouse serum-containing-antibody over the plate. In other words, we needed to completely re-engineer the ELISA assay with lipid-protein interactions in mind rather than protein-protein interactions of conventional assays. The problem was that all the mice in our colony had been sacrificed by Bob Klepper and the team. On a whim, I called Manoj Sharma who was a scientist at Strategic BioSolutions which we had hired some time earlier to immunize mice. I was hoping that he had not sacrificed all the mice used in his

immunizations. The next day, he called me back to tell me that his technicians had killed all the mice except one. Bingo!!! Manoj sent me a serum sample from that mouse and we used the new ELISA assay on the serum. Luckily, the mouse showed a response. I went back to the board and told them of the result and the thinking behind it. Our investors infused more cash into the company and we were back in business. Manoj felt bad and offered to do 5 new mice at his expense. All responded with the re-engineered ELISA. WSIG infused more money and we went on to a very successful 40-animal project and chose clone #306D326.26 in early 2004. This hybridoma strain expressed an excellent, highly-specific and high-affinity mAb which we called *sphingomab* or LT1002.

Lpath grows up

We went on to create great monoclonal antibodies using our newly-engineered ELISA. At this point, we were poised to grow and become a *bona fide* biotechnology company that had both diagnostic and therapeutic R&D programs. We could also envision generating many antibody products directed against the thousands of potential bioactive lipids that possibly existed. Our next target would be LPA, the lysophospholipid against which our KOLs had told us it was impossible to make antibodies (by the way, we were successful in that effort – see below).

At long last, we had a very good murine antibody to S1P in hand. We filed patent applications that covered both diagnostic and therapeutic applications for that antibody and any antibody variant, including a putative humanized mAb which we contemplated making as a next step towards a clinical trial.

We also believed that we had invented a platform technology which we called Immune Y-2, where we could make mAbs directed against many other bioactive lipid targets. One of our Scientific Advisory Board members, Ed Dennis of UCSD, had organized a consortium of universities whose mission was to map the lipidome and identify bioactive and other lipids. The human genome and proteome had been mapped. Ed Dennis argued that the lipidome could be much larger and could comprise 500,000 lipids, 1-2,000 of which could be bioactive lipids and good targets for drug discovery. The problem was that extracellular receptors for almost all those putative bioactive lipids had not yet been discovered. An additional problem with lipid targets, unlike protein targets that commonly have a single gene and resulting enzyme responsible for the target's biosynthesis, is that lipids have complex biosynthetic pathways. LPA for example, has 5

independent routes of synthesis. Our idea was to target the lipid itself and not the enzymes that made the lipids target nor the receptors on which the bioactive lipid acted. I proposed that we could develop antibodies against those lipids and use those antibodies as reagents to demonstrate potential physiological roles of the target lipids in animal and other studies. After the target was validated in this way, the antibodies would be developed into drug products. That was the platform.

Accordingly, we changed our name from Medlyte Diagnostics to Lpath Therapeutics in 2004 (and then shortened it to Lpath, Inc.). Lpath stood for **L**ipid **path**ways to reflect that we were a platform company. Further, we were no longer a virtual company and, consequently, needed to build a management team and a R&D group. We moved out of SDSU and rented space in the Sorrento Valley area of San Diego where many biotech companies were clustered.

Bill Garland came on as VP of Development and we hired Scott Pancoast as President and CEO. (Figure 3) I became the Chief Scientific Officer. Gary Atkinson was the Chief Financial Officer and Cole Workman was Controller. We also hired Geneviève Hanson as VP of Research (and then MaryAnn Campbell to replace Geneviève soon thereafter) and we built out the research team such that we had approximately 25 employees. (Figure 4)

We hired many former SDSU students according to our custom (Figure 5) but branched out to hire some truly excellent scientists like Jon Wojciak, Rosalia Matteo, Johnathan Fleming, Cindy Dickerson, and Bill Schetowsky. Angela Gentile came over from Mpex to join us. Angela was one of the best scientists who had come out of SDSU and we were fortunate that she joined us. The mission of the research team was to develop the anti-bioactive lipid platform and to perform sophisticated experiments designed to humanize our antibodies.

The humanization of antibodies for therapeutic use such as for the treatment of cancer and inflammatory disease was pioneered by Sir Gregory P. Winter who received the Nobel Prize in Chemistry in 2018. Winter shared the Prize with Francis H. Arnold (for directed evolution of proteins) and George C. Smith (for phage display techniques used to screen engineered proteins). Humanization is a process whereby the specific regions of the murine antibodies that specifically recognize the target are identified. The complementarity determining regions (CDRs) of the murine monoclonal antibodies are in the variable domains of an antibody. During the process of humanization, one clones out the CDRs (3 different ones on each arm of the antibody) and then grafts them onto a human antibody framework (the Fab region). This is done to make a human-

like antibody that is not rejected by the drug recipient's immune system. The process is more complicated than I have just described. Our company needed expertise in antibody engineering and we hired people with that knowledge. At the time we started this process, there were only a handful of companies, Genzyme, Abbott, Biogen-Idec, and Genentech, which were marketing humanized antibody drugs but this was the fastest growing segment of the therapeutic market. Now, there are over 60 humanized or fully-human antibody drugs. All the marketed antibody drugs are directed against protein targets, not lipids.

Lpath becomes a public company

Scott Pancoast's mission was to take the company public, which he did in 2005 with very little help from investment bankers or institutional venture capitalists. It was quite an accomplishment. We were introduced to Marvin Hausman and Jay Eddington who had purchased a defunct company that was public but never had got off the ground. The business model of Neighborhood Connections was to repair phone booths. Rather than create an initial public offering (IPO), Scott performed a reverse merger into the shell company and that is how we instantaneously became a public company. We were initially traded over the counter (OTC) and, eventually in 2012, Lpath became listed on NASDAQ.

Shortly after going public in 2005, Scott, Marv and I went on what they call "the road show." Marv had connections with high-net-worth individuals and investment bankers. I was the science guy and founder and Scott became the CEO. We made presentations to investors from New York to Beverly Hills to Hong Kong, Paris, and Switzerland.

This was a new, exciting, and strange environment for me, schmoozing with ultra-rich people, staying in first-class hotels, and doing business over dinner in the finest restaurants. Venues included after-hours private parties at the Smithsonian Museum of Natural History, the Monterey Aquarium, the Museum of Flight, and the Locanda Cipriani restaurant in Torcello, Venice.

On one memorable occasion in Paris, we enjoyed a private dinner after hours at the Palace of Versailles. The investment banking group Rodman & Renshaw put on an annual investment conference. In May 2005, the Techvest Global Healthcare Conference was held in Paris at the historic, luxury Intercontinental Hotel. The conference brought investors together with emerging growth companies in the biotech and healthcare industry like Lpath Therapeutics. This conference was like the JP Morgan Healthcare Conference held every year in San Francisco, an

investor meeting that Lpath also started attending. At the Paris meeting, Marv scheduled meetings for Scott and me at various hotel suites. Typically, I would make a scientific presentation, followed by Scott and Marvin's presentation of the investment opportunity. Networking would continue in the evenings at dinners and parties. One such dinner was held at the famous cabaret, *Le Lido de Paris*. on the Champs-Elysees. R&R had rented the entire nightclub for our group where they served dinner while we watched the dance review that featured beautiful, partially-clad women.

The most impressive evening was one in which R&R bused us to the Palace of Versailles for a private after-hours dinner party. The evening began with a Champagne cocktail party on the veranda overlooking the famous gardens. We were entertained by 17th Century minstrels dressed in period costumes. Then, the Sun King (Louis XIV) and Maria Theresa made a grand entrance arriving in a horse-drawn carriage. They greeted their guests. We then took a private tour of the palace followed by a sit-down dinner in the 390ft Hall of Battles. We sat at a very long dining table where each person's place-setting had gold-embossed, personalized menus. We were served by waiters in period costumes and entertained by minstrels.

Milestones

In 2007 US patent no. 7,169,390 was issued from the USPTO. The patent was entitled, "Compositions and Methods for the Treatment and Prevention of Cancer, Angiogenesis, and Inflammation".

We humanized the murine anti-S1P mAb, *sphingomab*, so that it could be administered intravenously to cancer and other patients. Bill Garland and Amy Cavalli became our drug development team and began studies to test the safety and pharmacodynamics of the humanized antibody, we called *sonepcizumab*.

We pursued the platform and developed great antibodies to our second lipid target, LPA.[27] Then, we ran into a problem. The half-life of *sonepcizumab* in pharmacodynamics studies was shorter than expected for an antibody when administered intravenously. It was not a catastrophe for the program, but we needed to hedge our bets with a clinical program that did not depend on a long half-life for the drug substance.

Ocular Focus

Bill Garland suggested that we pursue ocular disease where the antibody could be administered intravitreally in the back of the eye rather than systemically, thus avoiding the short half-life issue.

We had demonstrated in our pre-clinical studies that *sphingomab* was an anti-angiogenic agent. I had written a patent application claiming that anti-S1P antibodies could be anti-cancer agents by, in part, eliminating the blood supply of a very needy cancerous tumor. Bill Garland argued that wet age-related macular degeneration (AMD) is a disease of inappropriate angiogenesis and that our antibodies could work in the eye. Importantly, our patents covered inappropriate angiogenesis. We wrote additional patent applications calling out AMD as a disease target (US patent, No. 8,444,970, is entitled, "Compositions and Methods for the Treatment and Prevention of Ocular Conditions" was issued in 2013). Meanwhile, we embarked on a series of pre-clinical studies designed to test our antibodies in animal models of AMD.

We engaged an ocular consultant, Glen Stoller. Glen was a retinal ophthalmologist living in Long Island. Glen helped design the animal studies that would form pre-clinical pharmacology POC for an ocular program while Bill and Amy pursued GLP toxicology and other studies. The research team pursued chemistry, manufacturing, and control (CMC) work with the help of outside consultants.

Partnerships with pharma on clinical trials

In 2008, I retired from my tenured position at SDSU to dedicate full energy to Lpath. I continued writing SBIR grants and landed two very big ones ($2M each) in cancer and AMD. The NIH asked me to serve on several review panels for the SBIR program and Lpath became a poster child for the NIH/SBIR National Cancer Institute.

In 2008, Lpath formed a collaboration agreement with Merck-Serono on the cancer project which we called ASONEP. Merck infused $17 million into the clinical program that resulted in a Phase 1 clinical safety study where we consented all-comers with solid tumors who had failed at least three prior treatments. The study was completed in 2010. We demonstrated an excellent safety profile in cancer patients given a single dose of ASONEP (the systemic formulation of *sonepcizumab*). The problem was that there were no responses to drug treatment. This was not unexpected since these patients only received a single dose and they were very beat up physiologically after several prior treatments. They were end-stage cancer patients.

The most significant problem was that the engineered antibody had as short a half-life in humans as it did in monkeys. Merck-Serono discontinued their support for the collaboration because of the short half-life issue and because of negative findings in some of their pre-clinical studies. Lpath hired two new people with advanced credentials. Gary Woodnut was hired as Sr. VP of Research and Dario Paggiarino, M.D. came in as Ex. VP of Clinical Development. Dario had recently left Pfizer when it closed its ocular division and decided to continue in ophthalmics only in collaboration with biotech.

On the ocular front, Lee Hsu, VP of Business Development for Lpath worked a partnership with Pfizer on the ocular opportunity. The agreement was consummated in 2010. Pfizer had a strong interest in competing with Genentech that had the only marketed treatment for wet-AMD. Genentech marketed two drugs, both of which were antibodies that targeted an angiogenic growth factor called VEGF, Avastin and Lucentis. Lucentis was the ocular drug and AVASTIN was for systemic delivery. A few years later a third anti-VEGF, Eylea, came on the market and started taking market share from Lucentis in the wet-AMD space.

In collaboration with Lpath, Pfizer funded two clinical trials for iSONEP (the ocular formulation of *sonepcizumab*). One was a Phase 1 safety study in wet-AMD patients and then followed by the NEXUS study which was a large multi-centered randomized trial testing iSONEP in wet-AMD patients who had not responded well to any anti-VEGF treatment (i.e., sub-responders). Although the Phase 1 trial was designed to test safety and tolerability as all Phase 1 studies are required to, several of the Phase 1 AMD patients showed remarkable responses to a single intravitreal dose of our antibody.

This led Pfizer to put up $27 million for the POC Phase 2 NEXUS study.

The first patient was dosed in May of 2013. A total of 126 patients completed the study consisting of 4 randomized and blinded groups: *sonepcizumab* 4.0 mg alone, *sonepcizumab* 0.5 mg plus anti-VEGF, *sonepcizumab* 4.0 mg plus anti-VEGF and anti-VEGF alone. Patients were treated at day 0, 30, 60 and 90 and they were evaluated for best-corrected visual acuity (BCVA) at day 0, 30, 60 and 90 and at day 120. Fluorescein angiograms and total lesion area measurements were also performed as anatomical read-outs. The official study ended at day 120 at which point the data were analyzed by an independent contract research organization (CRO). Patients were evaluated up to 9 months but those longer-term read-outs were not official end-points prescribed by the clinical trial protocol. Unfortunately, there was no effect of iSONEP in

any of the above group's responses to the anti-VEGF treatment groups or iSONEP in combination with anti-VEGF. In other words, this trial failed to meet its end-point. However, post-hoc analysis showed that a small number of patients showed marked improvement at 9 months past the time point at which official data was analyzed. Pfizer did not care.
The collaboration was over and no follow-up trial was contemplated.
Near that same time, we got results from the small cancer trial with ASONEP. It also failed to meet the pre-established end-point. Our clinical development team in collaboration with Dr. Rupal Bhatt of Harvard Medical School and Deaconess Hospital conducted a 40-patient study. The study consented patients with clear cell metastatic renal cell carcinoma (mRCC) who had failed 1-5 prior therapies. Although the study did not achieve its primary endpoint based on the 2-month progression-free survival (PFS), a median overall survival (OS) of 21.7 months was observed. Four patients (10%) demonstrated a partial response, with a median duration of response of 5.9 months. Three patients experienced PFS of >24 months. All patients had failed prior therapies and their tumors were progressing prior to ASONEP therapy. Overall, 32% of patients responded in some way. Pfizer required 50% and the trial was considered a failure and no follow-up trials were considered for the sub-group who demonstrated some measure of response.

Cancer patient visits Lpath

One of the 3 patients who experienced PFS of >24 months asked the head clinical investigator of the study if he could visit Lpath to thank the scientists. The FDA and the independent ethics committee agreed to the visit but only if the identity of the patient was kept confidential. Dario invited patient JC to Lpath. Dario organized a reception for him in our conference room. Scientists do not generally get to see the real people who are being treated with the drugs that the scientists may have discovered so this was a big event for us. JC expressed his heart-felt appreciation to us for extending his life. He was given the death sentence by his oncologist because he had failed all other treatments and his disease was progressing. Dario asked me if I wanted to say something as inventor of the drug. I thanked JC for coming and then I introduced the research team. I asked each of our scientists to explain, in lay terms, what each of them had contributed to the drug discovery. This was a great moment for me and for the team. At that moment, we felt that we had made a difference in one man's life.

After the visit, I thought to myself, “what is the life of one person worth?” I was not referring to monetary terms.

It was certainly worth all the blood, sweat and tears we all gave to Lpath.

In that moment, I did not regret all the sacrifices I had made or the disappointments I had suffered.

List of abbreviations

ACS, Acute Coronary Syndrome

AMD, age-related macular degeneration

CAD, Coronary Artery Disease

CDA, confidential disclosure agreement

CDRs, complementarity determining regions

CEO, Chief Executive Officer

CMC: chemistry, manufacturing, and control

CSU, California State University

IVD, in vitro diagnostic

JD, Joint Doctoral

JJDC, Johnson & Johnson Development Corporation

KOLs, Key Opinion Leaders

LPA, lysophosphatidic acid

Lpath, Lipid pathways

mAbs, monoclonal antibodies

MARC, Maximizing Access to Research Careers

MBA, Master of Business Administration

MBRS, Minority Biomedical Research Support

MI, myocardial infarction

MIRF, myocardial ischemia risk factor

MS, Master of Science

NASDAQ, National Association of Securities Dealers Automated Quotation

NIH/SBIR, NIH Small Business Innovative Research

NIH, National Institutes of Health

PKC, protein kinase C
POC, proof-of-concept
RyR, ryanodine receptor
S1P, sphingosine-1-phosphate
SDSU, San Diego State University
SPH, sphingosine
SR, sarcoplasmic reticulum
TT, transverse tubules
UCSD, University of California, San Diego
UKN, unknown
USPTO, US Patent and Trademark Office
VCs, venture capitalists
VP, vice president
WSIG, Western States Investment Group

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Figure 1. The Three Amigos.

Figure 2. Dear friends and collaborators Romeo Betto and Daniela Danieli-Betto (alias in many publications Danieli D.).

Figure 3. Lpath management team.

Figure 4. Lpath team.

Figure 5. Students.

Table 1. Key international collaborators and influential academics.

Salviati Giovanni, Italy
Bernardi Paolo, Italy
Betto Romeo, Italy
Carraro Ugo, Italy
Ceoldo Stefania, Italy
Crack Peter, Australia
Cuvillier Oliver, France
Dalla Libera Luciano, Italy
Damiani Ernesto, Italy
Danieli-Betto Daniela, Italy
Daugherty Wayne, USA
Furlan Sandra, Italy
Luciani Sisto, Italy
Malavaud Bernard, France
Margreth Alfredo, Italy
Megias Alicia, Spain
Megighian Aram, Italy Morganti-Kossmann, Australia
Pasteur Louis
Pebay Alice, Australia
Presotto Cristina, Italy
Salvatori Sergio, Italy
Sandri Marco, Italy
Svenssson Camilla I., Sweeden
Teresi Alessandra, Italy
Tobaldin Antonio, Italy
Vescovo Giorgio, Italy
Volpe Pompeo, Italy

Table 2. United States collaborators and influential academics.

Andrews Craig, USA
Archibald J. David, USA
Barlow Steve, USA
Baskin Ron, USA
Bernstein Sanford, USA
Calcutt Nigel, USA
Castens Jeff, USA
Castro Ernesto,
Chatterjee Subroto, USA
Cohen Joel, USA
Craig Rian, USA
Dahms Steve, USA
Deamer David, USA
Deamer David, USA
Dettbarn Christine, USA
Dickerson Cindy, USA
Drake Richard, USA
Engler Robert, USA
Frey Terry, USA
Glembotski Chris, USA
Kolkhorst Fred, USA
Lebherz Herbert, USA
Long Joseph, USA
Marlin Nancy, USA
Matteo Rosalia, USA
McDonald Whitney, USA
McDonough Patrick, USA
Millican Blake, USA
Mills Gordon, USA
Morris Andrew, USA
Murphy Alexander, USA
Palade Phil, USA
Paolini Paul, USA
Peethambaran Arun, USA
Quintana P.J.E., USA
Sabbadini Roger, USA
Salvemini Daniela, USA
Scales Don, USA
Shestowsky Bill, USA
Shestowsky Wm., USA

Grant Maria, USA
Greb G. Allen, USA
Gupta Dipak, USA
Harris Greg, USA
Harris Neil, USA
Heller-Brown Joan, USA
Hiraiwa Masao, USA
Huxford Thomas, USA
Inesi Giuseppe, USA
Inesi Giuseppe, USA
Johns David, USA
Johnson Gerald, USA
Klepper Robert, USA
Short Don, USA
Sibbald Brad,
Spiegel Sarah, USA
Stoller Glenn, USA
Sweedler Alan, USA
Tsuji Shingo, USA
Wilson Barry, USA
Wilson Barry, USA
Witztum Joeseph, USA
Wojciak John, USA
Yeomans David, USA
Zyskind Judith, USA

Table 3. Students who worked in the Sabbadini laboratory.

Acord Elizabeth, USA
Alcantar Eddie, USA
Bell Jason, USA
Berkley Neil, USA
Brewer Steve, USA
Brooker Madeline, USA
Pat Castillo, USA
Cavalli Amy, USA
Chambers Amy, USA
Chittenden Kelli, USA
Collvmore Angela,USA
Comstock Kevyn, USA
Cormier Robert, USA
Cota Daniel, USA
Cote Lynn, USA
Craig Rian, USA
Cunnigham H. Brad, USA
Do Catherine, USA
Domingo Ron, USA
Elmore Joanne, USA
Fleming Johnathan, USA
Fraser Ellen, USA
Gastoo Ernesto, USA
Krown Kevin, USA
Larsen Catherina, USA
Leake Dennis, USA
Ligutti Joseph, USA
Louis John, USA
Mallari April, USA
Markus Neil, USA
Montinez Tom, USA
Moreno Kelly, USA
Moulton Garner, USA
Moulton Michael, USA
Nakajima Nobuko, USA
Nguyen Cuong, USA
Nixon Cecilia, USA
Norton Kurt, USA
O'Brien Nicole, USA
Okamoto Vincent, USA
Page Trevor, USA
Pedraza Melinda, USA
Pillai Sabitha, USA
Priest Anne, USA
Renken Christian, USA
Royce Adam, USA

Gellings Nicole, USA
Gentile Angela, USA
Giacalone Matt, USA
Grossman Mike, USA
Guintivano Albert, USA
Gutierrez Alessandra, USA
Gutierrez Veronica, USA
Guo Maria, USA
Jachec Chris, USA
Jenkins Gary, USA
Hamidy Wali, USA
Harrelson Sam, USA
Hart Mary, USA
Higdon Alyssa, USA
Higgins Carmen, USA
Ho Piter,USA
Kang Jaw-Jou, USA
Karg David, USA
Kawakami Jan, USA
Kennedy Carol Lynn
Korf Ashley, USA
Rought Steffney, USA
Runte Eric, USA
Shatkin Stacy, USA
Short Christy, USA
Sibbald Brad, USA
Slavin Nicole, USA
Smith Wyatt, USA
Sumnicht Gary, USA
Swaney Jamie, USA
Tarantini Niki, USA
Thompson Aurora, USA
Tsow David, USA
Tsu Leo , USA
Twamley Austin, USA
Vekich John, USA
Visentin Barbara, USA
Watkins Amanda, USA
Webster Robert, USA
Welch Jessica, USA
Winters Monica, USA
Yazaki Paul, USA

Table 4. Other United States influential people from the business sector.

Andrews Craig, USA	Garland Bil, USA	Paggiarino Dario, USA
Atkinson Gary, USA	Gerhard Bill, USA	Pancoast Scott, USA
Bernstein Laurel, USA	Hsu Lee, USA	Rought Sally, USA
Chambers Daniel, USA	Lessard Roy, USA	Swortwood Donald, USA
Flemming Mason, USA	Lyon John, USA	Vasquez Joseph, USA