In Vivo
Informa Pharma Intelligence

Point Man On Protein Science

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By William Looney

IN THIS LATEST EDITION OF THE LAB LINKS series on notable figures responsible for major advances in drug discovery, *In Vivo* talks to Harvard Medical School professor and biologist Timothy Springer on his 50-year record as an academic scientist, business entrepreneur and philanthropist. His latest venture is being co-founder – and principal funder – of the independent non-profit Institute for Protein Innovation, an institution designed to fill a critical niche in open-source biomedical research.

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As an academic biochemist, Timothy Springer has authored original insights on the structure, function and interactions of biomedically important proteins: one 1990 paper, on the cell recognition molecules that drive immune response, has been cited in peer review more than 10,000 times. His work has shaped medical practice in key fields like immunology, inflammation, hematology and infectious diseases, accomplishments reflected in the clinic through at least four blockbuster drugs, all now available to patients worldwide. Though a skeptic at first, Springer has also emerged as a savvy start-up entrepreneur, earning outsize returns as a founder and investor in seven biotech companies, gains he has now applied as an advocacy philanthropist testing new business models to plug research silos, address unmet medical needs and promote the open-source dissemination of knowledge.

All told, Springer has the receptive mind of a true explorer: who else could relate the physical properties of a protein to a novel on fly-fishing and the purposeful, irresistible flow of water in a stream? Highlights of our interview follow below.

***In Vivo*:** *What initially attracted you to a career in science? Was it a book, a person – or something else?*

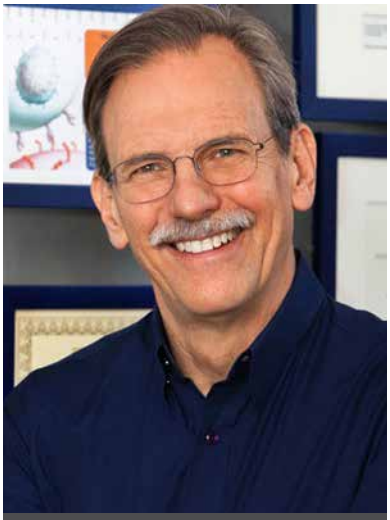
Timothy Springer: Coincidence and good fortune led me to science. My hay fever, which as a young boy required frequent trips to an allergist for "desensitization," led to my interest in immunology. Before I left home in Sacramento, CA, to begin undergraduate studies at Yale University, I was aware of the role of histamine and immunoglobulin E (IgE) in allergic reactions.

But my future as a researcher was never pre-ordained. After freshman year at Yale, I volunteered for a year in the VISTA program (the domestic version of the Peace Corps), serving as a community organizer on the Yomba Shoshone Reservation in Nevada. I then transferred to UC Berkeley, where my VISTA experience led me to anthropology, sociology and biological psychology. Along the way, I found I loved organic and physical chemistry and physics. My junior year I switched my major to biochemistry and had noted professor Dan Koshland as my advisor, who inspired in me a love for protein conformational change, which is critical to understanding all the basic biomolecular interactions in humans.

I graduated with an honors degree in biochemistry and went on to do a PhD in Molecular Biology and Biochemistry at Harvard. After a one-year NIH postdoctoral fellowship in Cambridge, England, I joined the faculty of Harvard Medical School (HMS) where I have been for 43 years. I run a lab where we investigate molecular mechanisms in fundamental areas of biology that are also clinically relevant. Molecules and mechanisms discovered in this work have opened new areas for drug discovery and extended my horizon

from academia to drug discovery and development, business, and, most recently, philanthropy.

***In Vivo*:** *Why has protein science garnered top billing in your work over the years, to the point where you have invested your own money in a new non-profit entity – the Institute for Protein Innovation (IPI) – to bring the best thinking of academia and industry forward in one place? What do these complex chains of amino acids hold for results in the clinical setting, beyond the lab?*



TIMOTHY SPRINGER

The mission of IPI is to foster protein science. We "democratize" high-throughput protein expression and antibody discovery by making antibodies available to talented researchers that are motivated by discovery – not profit. By removing the high capital cost of our platforms, which are perhaps better than any in industry, we enable the creation of new knowledge and open source reagents, as would normally be done in academia.

"Completion of the human genome, microarrays, single cell transcriptional profiling and more resulted in a tsunami wave of high-throughput tools and techniques that washed over all of biology."

I also believe that protein science is a deserving field that requires attention from the research community. During my graduate career at Harvard University in the 1970s, some lab groups worked on membrane proteins. Others worked on molecular genetics and DNA, including a fellow student and his mentor who went on to win Nobel Prizes. That division of learning in graduate school mirrors a large shift since molecular cloning came of age: away from proteins and enzymes – which comprise the machinery of life and almost all drug targets – to DNA and RNA, which provide the instructions on what to build.

Completion of the human genome, microarrays, single cell transcriptional profiling and more resulted in a tsunami wave of high-throughput tools and techniques that washed over all of biology. The result is that almost all academic biomedical researchers, and most in biopharma, are now molecular biologists and geneticists. People in this field know little about proteins.

This divide is not perpetuated by funding or academic organizations, but by expediency and professional market considerations.

Here's the cycle. DNA and RNA are much easier to work with than proteins. The research is published faster. Grants are easier to obtain. And in academia this results in prestige and more promotions.

Grants were increasingly awarded for cloning and studying recombinant proteins in transfected cells but lost for research on proteins isolated from living organisms or discarded human tissues. As a result, we now know a lot about proteins expressed or mutated in cultured cells, but little about how those proteins assemble and signal in complex tissues in living organisms.

There is real therapeutic promise here: antibodies are so specific that they can be used to discover the function of proteins in living organisms and connect that to what proteins in isolation or on living cells do in test tubes. That is why I was so excited to learn during my postdoc how to make monoclonal antibodies personally from César Milstein, whose hybridoma technology earned him the 1984 Nobel Prize for physiology or medicine.

Inspiration from César, a new way of discovering antibodies using yeast libraries rather than animal immunization, and my desire to strengthen protein science and biological and therapeutic discovery, is what led

me three years ago to tap some of the earnings from my business ventures to found, along with my young Harvard colleague Andrew Kruse, the Institute for Protein Innovation. IPI has a mission that is incredibly important and catalytic: to create open-source antibodies that are high quality and unique in the ability to recognize identical epitopes and proteins in mouse models and humans. Although HMS and Boston Children's Hospital, where we are both on the faculty, have been supportive and IPI is located in their midst, IPI is independent of them.

One goal with IPI antibodies is to understand the mechanism of action behind proteins in cells and in mice; and to quickly translate those insights into clinical results that benefit patients in multiple disease categories. And as the world mobilizes its scientific and industrial resources to fight COVID-19, new and improved antibodies are critical to eliminating the virus as a public health threat. IPI is building an arsenal of antibodies spanning the entire family of coronaviruses. If a new strain appears in humans, we'll be there with an effective option.

In Vivo*: *Does mentoring – the human element – continue to drive progress in science, particularly as competition among individual researchers escalates in an era of scarce resources, lax controls on data governance and reliance on "distance learning?" How much have earlier leaders in the field contributed to your own success?

Mentorship is one of the most important ways of ensuring great science continues to grow.

Jack Strominger, my PhD adviser at Harvard (still going strong today at age 94), taught me some invaluable lessons. Pick important problems. Be critical. You have to have skin as thick as an elephant. The list goes on to even fundamental skills such as how to write manuscripts.

César Milstein had a small lab where he worked, often by himself. He loved to discuss and argue points, and taught me – in his image – to be both a scientist and a gentleman.

The brilliant chair of pathology at HMS, Baruj Benacerraf, hired me, taught me much immunology, and reinforced working on important biological problems. Baruj did wonderful things for me, but he also tormented me. While at HMS, he won a Nobel Prize for his work at New York University (NYU) and NIH. Yet during his career at HMS his science went astray, he turned on me, and died a bitter man. I worried a tragedy was in the making the day I arrived from my postdoc, yet was helpless, because Baruj could never admit mistakes or accept scientific counsel from me.

Fred Rosen, a pioneer in the study of pediatric immunodeficiency diseases at Boston Children's Hospital, hired me as a professor and made me vice-president at the Center for Blood Research. From him I learned leadership, and by trying, how difficult it is to raise funds for philanthropy. Fred had earlier provided the patient blood sample that allowed me to discover that the first family of signaling integrins, which I had already discovered with monoclonal antibodies, were missing in patients' white blood cells that failed to leave the bloodstream at sites of infection. This discovery of what is now known as Leukocyte Adhesion Deficiency taught me that integrins were not only important in T-lymphocyte recognition of antigen-bearing cells, but also in white blood cell recognition of just where to leave blood vessels to hone in to specific sites of infection and generate effective immune responses.

What I took from all these great scientists is that mentoring builds on itself, strengthening and reinforcing an innovation ecosystem. What I learned from them has in turn helped me launch the careers of some of today's best young biologists and chemists. I take great pride in The Springer Lab's alumni network – which spans the globe, from academia to industry.

In Vivo*: *As a longtime advocate of interdisciplinary solutions to scientific challenges, are you satisfied with the current state of play among biologists, chemists, physicists and other mainstays of the drug development process? Are the academic silos that have in the past slowed the pace of medicines innovation truly gone?

To some extent, separations in academic fields have been overcome. As understanding of biological and clinical mechanisms deepens and is supported statistically with big data, interdisciplinary work and its understanding and interpretation is essential.

However, my experience of "glue" grants (large-scale collaborative projects) and similar interdisciplinary efforts is that they often miss the mark, because they require not just experts from different disciplines, but also people who are multidisciplinary themselves. I point to my own education as an undergrad at UC Berkeley, where I studied and grew to love biology, chemistry and physics along with a little bit about the brain in biological psychology. All that led to my majoring in biochemistry. I have an interdisciplinary mindset, but I prefer to see myself as simply a scientist. What does make me unusual in the fields I inhabit – selectin, integrins, TGF-β, von Willebrand factor, and parasite adhesin are the key ones – is that I use in all of them the physical concept of tensile force, or what happens when a molecule undergoes a conformational change in response to various biological factors, as an investigational marker. It's like Norman Maclean's famous novella about fly-fishing, A River Runs Through It, and how all things eventually merge into one stream – except in my case, it's the impact and outcomes of tensile force. The notion is fundamental across all of the biological systems in which these molecules operate. The physical properties and equations are very simple, yet despite my use of props and videos in talks, and my best attempts at writing, these concepts are very difficult to get across to my colleagues and even to some of my own lab members. This is where having that interdisciplinary context can help.

Experience leads me to conclude that multiple disciplines must be ingrained at an early stage of the scientists' academic journey, in university and also in high school. Failure to do so means scientists are likely to reach points in their careers where they cannot progress further, without the insights that spring from the sometime contentious interplay of different perspectives.

You have to understand what people in other fields are doing to move science to the next level. I tell all my associates not to forget that.

In Vivo*: *The past decade has seen a surge in big pharma interest in academic science – understanding what's taking place in the lab on basic research is a strategic priority, because no company can build a productive R&D platform without exposure to ideas from outside. What is your take on the current state of play in academic science? Are there cracks in the system? What do today's researchers require to be successful in the lab?

Academic science has always been a tough space in which to conduct research. You must be very strategic in identifying an important biological challenge that is both impactful and difficult to solve, but not impossible. The risk is high. I've been in situations where I took that big first step forward without knowing exactly how I would get to the final goal. And I want to prove the thesis of a paper not once but three times. The first scientific project I took on as a postdoc – and on which I wrote a successful NIH fellowship application – was founded on fraudulent research published in Nature. Luckily, I discovered this relatively quickly, after only six months of wasted effort. I rolled with the punches and switched to working with César Milstein – a momentous turning point in my career. I've never forgotten the episode, and it reinforced my rigor in using and interpreting data in my own lab and always taking a critical approach to reading scientific papers.

Academia in biomedicine is heavily influenced by grant money. Public institutions like the National Institutes of Health (NIH) and the National Science Foundation (NSF) set the world standard for sponsored research. The NIH peer review system undergirds US leadership in medical innovation. Nevertheless, grants exert strong pressure that can distort and even corrupt biomedical research. And the risk of antagonizing potential peer reviewers inhibits raising critical questions at scientific meetings.

It is much harder to obtain an NIH grant today than when I was a graduate student in the 1970s. Then,

about 30% of grant applications were funded; today, its 5% to 10%, depending on the therapeutic field. Surely this pressure for success in obtaining grants and publications, and promotions in academia, must be in part responsible for the dilemma facing pharmaceutical companies that when they try to repeat those academic research findings in publications, 70% to 90% of them cannot be reproduced.

Much of this irreproducibility stems from human frailty and hypothesis-driven research. The purpose of doing an experiment is to disprove a hypothesis. However, too many people discard experiments or data because it does not agree with their hypothesis, instead of taking the scientifically correct action and discarding the hypothesis.

One needs to be critical of oneself and also of the literature. To make new discoveries, it is sometimes important to recognize that biology might actually work a little differently than has previously been supposed.

I prefer hypothesis-free research, also known as discovery research, like determining three-dimensional structures of proteins or transcriptional profiles. Each requires obtaining very large datasets, contributes a permanent scientific record that can be mined for further insights by the scientific community for many years to come, and paints a beautiful, rich picture.

The NIH should really focus on the track record of the investigator in consistently moving a field forward and laying a solid foundation for clinical breakthroughs. Some academic research sponsors like the Howard Hughes Medical Institute rely on such criteria in funding decisions, and it works very well.

***In Vivo*:** *How did you make the transition from academic research to starting companies? Are there any lessons from your experience in scoring new technologies that can succeed commercially in the competitive market for medicines?*

Growing up I did not know anyone in business. At Berkeley and Harvard as a student and later as a faculty member, I was interested in learning and discovery. One formative experience was the loss of my military deferment while I was posted to VISTA, and in my first year at Berkeley, I was ordered to take my pre-induction physical exam. Luckily, my draft board appeal succeeded, so I was not sent to Vietnam. In the context of that era, the wide use of poisonous agents like Napalm and Agent Orange had made me very skeptical of the chemical industry and the whole US military-industrial complex. However, as a doctor's son and the beneficiary of Sudafed (pseudoephedrine) for most of my life, I did have a positive image of the pharmaceutical industry.

I went into academics thinking that I would make less money than my dad but that the freedom and fun would more than compensate. The 1980s were an incredibly heady period of discovery for me. I discovered the first cell-cell recognition molecules of the immune system: LFA-1, CD2, LFA-3, ICAM-1, ICAM-2 and ICAM-3. I discovered the first like-unlike adhesion molecule pairs in all of biology: LFA-1:ICAM-1 and CD2:LFA-3. I discovered the first family of integrins: LFA-1, Mac-1, and p150,95, highlighting their deficiency in driving inherited human disease, which provided yet more insights.

By this time, some of my lab trainees had made their way to pharma, and started funding projects in my lab. Later, I visited Biogen to forge a collaboration on cloning LFA-3. My lab found that both the LFA-1:ICAM-1 and CD2:LFA-3 pathways were required for T-cell responses, and I proposed that blocking either could prevent autoimmune disease, as indeed was subsequently demonstrated by approved medicines. Those LFA-3 discoveries ultimately resulted in one of our earliest drugs, Amevive (alefacept). Mike Dustin, a former graduate student, and I received royalties and are exceedingly proud that our work benefitted patients with psoriasis.

In 1991 my lab published another big finding about three steps, each with a large set of potential molecular interactions that were required for white blood cells to move from the bloodstream into tissues to find and fight infec-

tion and confer immunity. At least one receptor and its cognate ligand were required in each step, for a particular type of leukocyte or lymphocyte subset to leave the bloodstream in response to a particular type of inflammatory or autoimmune stimulus. Each potential cognate receptor and ligand at each step provided a target for drug discovery. The number of targets was large: selectins and their ligands; G-protein coupled-receptors and their ligands, and the integrins LFA-1, α4β1, and α4β7 and their ligands on endothelium. This "area code" model had extensive therapeutic potential because blocking either the receptor or the ligand at any one step would block emigration entirely. With alternative ligands and receptors at each step, it seemed possible to find drugs that would selectively block emigration of specific leukocyte types or emigration into different types of specific sites in the body. Because this process is critically important to the functioning of the human immune system, the scope for drug discovery was so large it could not be accomplished in my own lab.

Hence in 1992 I started a company named LeukoSite, a play on the leukocyte, a white blood cell, and "Site" to highlight the precision targeting that drove our science (*see Exhibit 1)*. I wrote a business plan, recruited venture capital investment, and established a top-notch scientific advisory board. We launched an integrin receptor drug development program which, years later, resulted in the blockbuster drug Entyvio (vedolizumab) for treatment of ulcerative colitis and Crohn's disease. Millennium Pharmaceuticals acquired LeukoSite for $635m in stock in 1999, and the following year our market cap, as 35% of Millennium, was worth $3bn. Two decades later, after Millennium's own acquisition by Takeda Pharmaceuticals in 2006, Entyvio is Takeda's top-selling drug, authorized for sale in more than 60 countries, with revenues of nearly $3bn in 2019.

After LeukoSite, I "retired" from business for eight years as my lab entered new areas of research. Then, in 2008 I entered biotech again, but this time as an investor, purchasing stakes in three start-ups, including a fortuitous $5m series A investment in the current mRNA technology leader, Moderna Therapeutics.

I met VC pioneer Amir Nashat, now managing partner at Polaris Ventures, and joined the Polaris advisory board. Amir is now a close friend and my biotech muse.

Next I co-founded a company, Scholar Rock, with a mission to develop antibodies to modulate activation of the TGF-β (transforming growth factor) family of proteins of fundamental importance in cell development and homeostasis. Scholar Rock has two ongoing clinical trials of inhibiting antibodies that target TGF-β1 in immuno-oncology and the myostatin protein associated with spinal muscular atrophy. I founded Scholar Rock with equal investments from myself and Polaris. As the Scholar Rock deal was struck flying back from a Polaris retreat, Len Zon, who runs his own stem cell and hematology lab at HMS and Boston Children's Hospital, came in as co-founder.

Polaris and I again invested equally in 2015 when I founded Morphic Therapeutic. After 35 years of working on integrins, and going deep into their structural biology, postdoctoral fellow Albert Lin and I discovered a new type of integrin inhibitor that stabilized the inactive, rather than the active conformation, allowing development of a safe and clinically useful oral drug to proceed. Morphic is developing an oral small molecule version of intravenous Entyvio in ulcerative colitis and a small molecule inhibitor of a different integrin for fibrosis. I also brought in Schrödinger, the leading computational chemistry company, essentially as a co-founder for providing advanced computational services. (*Also see "Will Advanced Technology Simulations Lead To More And Better Drugs? Start-Up Schrodinger Says It Can " - In Vivo, 19 Mar, 2018*.)

My latest project, in addition to IPI, is my role as investor, board chair and co-founder with my Harvard colleague Andrew Kruse, in Tectonic Therapeutic, which is focused on yet another class of proteins, the G-protein-coupled receptors (GPCR). GPCRs are triggers in many diseases and account for 30% of all currently approved drugs. Our goal is to tackle the most challenging receptors in the class by developing new types of biologics.

Exhibit 1:

Portfolio Of A Polymath: Tim Springer's Biopharma Business Ventures

1992

LeukoSite, Inc.
- Founder
- Board Director
- Chair of Scientific Advisory Board
- Acquired in 1999 by Millennium Pharmaceutical, now Takeda Pharmaceuticals

2008

Selecta Biosciences
- Investor (series B through IPO and latest follow-on)
- Board Director*
- Scientific Advisory Board member*

2010

Moderna Therapeutics
- Founding Investor (series A, B and C)
- Board Director
- Scientific Advisory Board member

2012

Scholar Rock
- Co-Founder
- Investor (seed and series A through IPO)
- Board Director
- Scientific Advisory Board member

2013

Editas Medicine
- Founding (series A) Investor

*currently

2014

Morphic Therapeutic
- Founder
- Founding Investor (seed and series A through IPO)
- Board Director*
- Scientific Advisory Board member*

2017

Institute for Protein Innovation
- 501(c)(3) non-profit
- Co-Founder
- Founding Philanthropist
- Executive Chair*

2019

Tectonic Therapeutic
- Co-Founder
- Founding Investor (convertible note)
- Founding Chair*

***In Vivo*:** *Your early $5m stake in the pioneering but unproven mRNA technology of an unlisted start-up, Moderna, looks unusually prescient as the now-public company's market cap has soared beyond $20bn. What factors do you look for in evaluating the merits of an investment – is there a formula or is it all about intuition?*

I attribute my success to deep knowledge and rigor. Polaris Ventures co-founder Terry McGuire says I have the founder piece, I think like an investor but I am also creative about company structure and research priorities. My foundational studies in physics, chemistry and biology; my graduate education as a recipient of research fellowships; and the accretive knowledge gained in 50 years of research with molecules, antibodies, cells in test tubes, knock-out mice, single molecules and structural biology; has given me a deep reservoir of what we call "intuition." Daniel Kahneman, in his influential book Thinking, Fast and Slow, calls it fast thinking. But I also engage in slow, deliberative thinking. My students bring up not only my attention to the big picture, but also to details. Small details can be incredibly important in science, yet such "slow thinking" also results in many dead ends. Nonetheless, I love the intricacies of even the smallest atomic structures, always enjoying myself along the way.

***In Vivo*:** *Today's watchword that seems to stimulate the interest of life sciences investors is value. As a scientist entrepreneur, do you believe that investors and inventors are on the same page in defining what value actually means?*

Early on, I believed that if a project was based on novel science and was defensible in terms of clinical need, it would be valued enough to gain financing. What I've discovered over time is more complicated. While investors always claim to be looking for the next big thing, attracting their support often requires staying close to the script that's worked for them before.

Even some of the most sophisticated VC investors think a winning model can be reproduced as if it were a formula. In contrast, the companies I have built are all very different from one another. In addition, many investors want a quick return as measured by the "internal rate of return" (IRR) and concepts like a stock's "multiple," or current price divided by earnings per share – that, to them, is the "value" that you seek to define in this question. But investing in new biology and science requires more risk and a longer wait for results. Instead of that elusive "multiple," I just invest in good science for the long-term. My favorite holding period for a stock is forever. The "promise" in a biotech is very hard to assess and the markets are often way off. It is on assigning value over the long-term where, as a scientist, I think I have an edge over the street.

IPI is an example of creating long-term value. I invite *In Vivo* readers to see IPI as a real precedent for pharma and to follow our progress going forward.

***In Vivo*:** *What do you consider to be your key and most enduring accomplishments in advancing the biology of medicine?*

My most important contributions have come from discovering new biology, which in turn has opened up new fields for drug discovery. In the late 1970s, when other colleagues wanted to discover the T cell receptor, I took the path not taken. I hypothesized there might be a unifying theme shared by cell recognition by many types of cells. In deep study, I learned of the central importance of the Mg2+ ion in killer T-cell antigen-dependent binding to target cells as well as in fibroblast adhesion to extracellular matrix. This work convinced me that cell recognition receptors other than those for antigens were required for T-cells to recognize other cells. I searched for them and discovered LFA-1, CD2, and LFA-3 in mouse and human studies in 1981-1982. This search led me at the same time to the integrins, all of which are Mg2+ ion-dependent.

As noted earlier, I not only discovered Mg2+-dependent LFA-1 binding to the intercellular adhesion molecule (ICAM – a protein essential to guiding immune response), but also Mg2+-independent CD2 binding to LFA-3. Whereas little came of drugs geared to the T-cell receptor and major histocompatibility complex protein (MHC), which were much vaunted targets of drug discovery at the time, it was efalizumab (Raptiva), tagged to LFA-1 and alefacept (Amevive), an LFA-3/Fc fusion, that ended up being FDA-approved, both in 2003 – just as I had predicted nearly three decades earlier.

These two drugs were the first-ever in a new class of therapeutics that modulated cell-recognition receptors. Why was this so important? Because not only did I discover the first cell-to-cell recognition receptors in the immune system, but these discoveries created the paradigm that cell-recognition receptors actually existed and influenced immune response. My discovery of cell-recognition receptors stimulated discovery of many more, including the checkpoint receptors CTLA-4, PD1 and PDL-1.

Academic science allowed us the freedom to explore these new avenues of therapeutic potential. The high cost of therapeutic development and the low percentage of candidates that establish efficacy and safety in large-scale Phase III clinical trials make pharmaceutical companies very conservative. As a result, there is a herd mentality to avoid risk and for all companies to move in similar directions. When LeukoSite was starting up, our VC backers required me to take monoclonal antibodies out of the business plan because of a recent antibody clinical failure. Nonetheless, we soon put them back in. Although efalizumab and alefacept were later withdrawn, their lasting importance was that they established in 2003 the proof of concept that biological drugs that bind to cell recognition molecules on white blood cells could modulate immune responses and reverse immune dysregulation that occurs in auto-immune diseases. Such precedents are very important milestones for commercial success in the pharmaceutical industry.

Efalizumab and alefacept were followed by many equally innovative FDA-approved therapeutics that tar-

geted cell recognition receptors: Tysabri (natalizumab) to integrins α4β1 and α4β7 (in 2004); Yervoy (ipilimumab) to CTLA-4 (2011); Keytruda (pembrolizumab) and Opdivo (nivolumab) to PD-1 (2014); and Entyvio (vedolizumab) to integrin α4β7 (2014); later came more antibodies to PD-1 and its ligand PDL-1. These therapeutic antibodies all block a cell recognition molecule on one cell from binding to its cognate ligand on another cell, just like efalizumab and alefacept. Tysabri and Entyvio block Mg2+-dependent integrin binding on a white blood cell to a cognate ligand on another cell, a paradigm first established in my lab with LFA-1 and ICAM-1, and in the clinic with Raptiva. Yervoy to CTLA-4 and Keytruda and Opdivo, to PD-1, also block binding of a receptor on a white blood cell to a ligand on another cell. These "checkpoint" inhibitors enhance immune response to tumor cells and have revolutionized cancer therapy.

That T-lymphocytes would have so many cell-recognition receptors – approximately 20, at present – was difficult to imagine before I began my deep dive into the research and discovered the first two such cognate receptor-ligand pairs in the early 1980s. Immunologists at the time thought that the concept of cell-recognition receptors was inconsistent with the antigen-specificity of immunity response. In a hotel bar after one of my talks, a colleague passed me a napkin inscribed with the blunt declarative "It doesn't work." Yet the field grew rapidly and my review on the cell-recognition molecules of the immune system, published in Nature in 1990, has been cited in the literature over 10,000 times.

As I look back on those discoveries in the 1980s and 1990s, I am gratified they contributed to therapies that have helped patients and saved many lives. But all of it happened so quickly there was little time to reflect. My lab discovered immune system cell-recognition receptors at the same time as we were discovering the first family of integrins – all on leukocytes, which now comprise only a single subfamily of integrins – which led in turn to the "three step" model for leukocyte exit from the bloodstream and the subsequent founding of my first company, LeukoSite Inc. The integrin receptor antagonist class of drugs alone has produced four world-class drugs:

- Raptiva, for psoriasis;
- Tysabri, for MS and Crohn's disease;
- Entyvio, for ulcerative colitis and Crohn's; and
- Xiidra, for dry eye disease.

Together these four medicine innovations posted $5bn in global sales in 2018 (*see Exhibit 2*).

In Vivo*: *At age 72, are you still optimistic about the prospect for more progress in the fight against disease, especially now that much of the 'easy work' in discovery medicine has been accomplished?

I am extremely optimistic because we now have groundbreaking platform technologies capable of delivering a wide range of advanced therapeutics to not only treat disease but to cure it. Modern genetics with rapid DNA and RNA sequencing has multiplied the number of druggable targets. Cellular and gene-based products have yielded new therapeutic modalities. Relating to my own interests, protein science and immunology have yielded new biologicals including antibodies, chimeras and ligand traps. Protein engineering, computational biology, and directed evolution are yielding new ligands that selectively bind to certain receptors, avoid others, and have improved pharmacodynamics and pharmacokinetics. Interesting work on selective tolerization to proteins, including those that are derived from bacteria, viruses, or are completely synthetic (from de novo design), will enable new therapeutic responses among patients resistant to conventional treatment.

And to your point on the "easy work," yes, most of it is done but many areas of interest still remain. For example, less than two years ago my lab published a paper on a "new" protein that associates with and is required for activation of TGF-β1 in macrophages and microglia cells. The "new" protein had previously been misassigned as having different functions and associations with other proteins. Because little work is done

Exhibit 2:

New Drugs Approved From Discovery Work Of Timothy Springer Lab And LeukoSite Inc.

Drug	FDA Approval Date	Indication	Manufacturer	Discovery Significance
Raptiva (efalizumab)	2003	psoriasis	Genentech (Roche)	Identification of LFA class of antibodies that blocked immune responses
Amevive (alefacept)	2003	psoriasis	Biogen	Identified lymphocyte function associated-3 (LFA-3) antigen and cloned it for therapeutic use with Biogen
Mozobil (plerixafor)	2008	autologous bone marrow transplantation for non-Hodgkins lymphoma or multiple myeloma	Sanofi Genzyme	Identification of ligand SDF-1 and receptor CXCR4 and mobilization of stem cells
Entyvio (vedolizumab)	2014	ulcerative colitis and Crohn's disease	Takeda	Discovery of three-step model of leukocyte diapedesis led to foundation of LeukoSite Inc. and new clinical approach to treat auto-immune disease
Campath-1 Lemtrada (alemtuzumab)	2001	B-cell chronic lymphocytic leukemia and multiple sclerosis	Sanofi Genzyme	With LeukoSite science advisory board member Dr. H. Waldmann of Oxford U. brought Campath-1 to commercialization
Velcade (bortezomib)	2003, 2008, 2014	multiple myeloma and mantle cell lymphoma	Takeda Janssen (JNJ)	Helped LeukoSite acquire ProScript Inc. and the first proteasome inhibitor for hematological cancers
Xiidra (lifitegrast)	2016	dry eye	Novartis	Identification of LFA-1 and its Intercellular adhesion molecule (ICAM) ligands

nowadays on native tissues, many protein-protein associations and functions remain unknown at the *in vivo* stage. This type of discovery can be done with antibodies and is one of our motivations for founding IPI.

***In Vivo*:** *How would you define your legacy – and given the significant financial reserves you can now command, in what way do you intend to fulfill a larger purpose in philanthropy?*

IPI is my legacy project. It encapsulates, in a practical, integrative way, all that I have accomplished in researching the functions and interactions of biomedically important proteins to create treatment advances in immunology, hematology, infectious disease and cancer.

When I talk about IPI to pharmaceutical and biotech CEOs and CSOs, I hear the same thing: it is extremely difficult to find well-trained protein scientists. They want IPI and academia to train many more. A huge shift from protein science to molecular biology and genetics, i.e. to DNA and RNA, has been underway ever since I was in graduate school. Industry researchers need help because they know that proteins pose a bigger investigatory challenge than genes. That's what the IPI intends to do, exploring and building our own antibodies to reveal disease pathways and then sharing these tools with researchers. We will make the sequences of these antibodies freely available to speed and spread research – and will also distribute these antibodies to academia, biopharma and other institutions where interest is high.

On the policy front, whereas Germany has made a conscious effort to strengthen protein science, the US has no such plan. There is currently no public funding body like NIH or a philanthropic organization that can support the unmet demand in the biomedical community for high quality, validated antibodies to detect and probe the function of the protein products encoded by the human and mouse genomes.

"The NIH should really focus on the track record of the investigator in consistently moving a field forward and laying a solid foundation for clinical breakthroughs."

Active philanthropy at IPI can fill this gap. Our technology of high-throughput recombinant proteins with native-like post-translational modifications, coupled to high-throughput screening of one of the world's largest yeast display libraries, facilitates discovery of antibodies with higher levels of specificity. Reactivity of IPI's antibodies with epitopes and proteins that are highly conserved between mouse and human is unprecedented. It enables new biological discovery and therapeutics for a wide range of diseases and pathogens.

IPI is a non-profit. The antibodies we produce – over 2,000 have been characterized to date – will encourage therapeutically useful projects that under commercial investment parameters may not have gone forward. The IPI business model is disruptive because for-profit companies that make antibodies do not disclose their sequences—they remain trade secrets.

This is why a philanthropic approach makes good sense. My vision is to expand the boundaries of protein science to provide more options for the clinic, and I am eager to find others who share this vision, particularly because running costs limit the number of receptors and ligand families to which we can make antibodies, and thus the biology that can be discovered and the number of patients that can be helped. In contrast, the platforms and robotics we have set up could be easily scaled to cover the entire set of extracellularly exposed proteins – in five years.

IPI's new executive director, Alex Burgin, who joined us from the management team at the Harvard-MIT Broad Institute last December, is pursuing more alliance and collaboration opportunities. That includes not only biotech and big pharma companies but foundations, patient groups and public entities as well. Though I've spent many years in the lab and have become financially secure as a biotech founder and investor, it is as an active philanthropist where I hope to achieve the biggest reward: seeing my childhood interest in science become, through the IPI, a permanent, living asset that improves health for all.