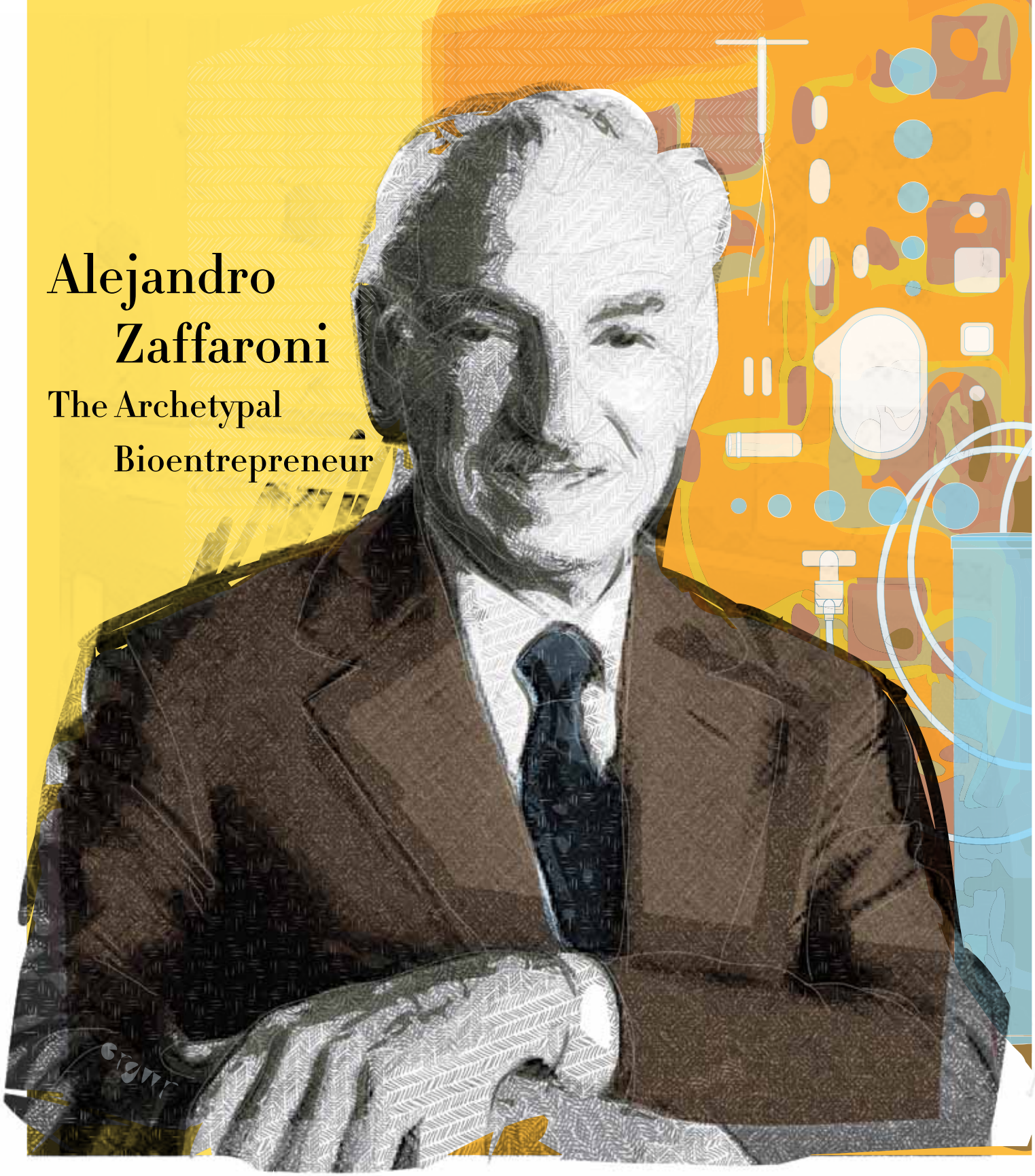
LSF Magazine

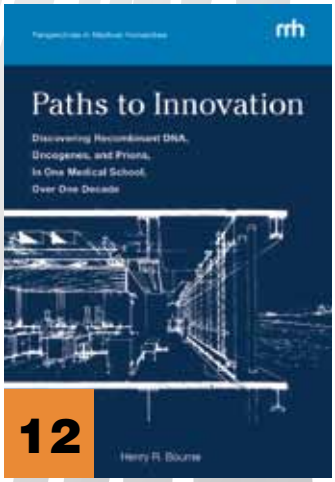
Fall 2012

Telling the Story of Biotechnology



Alejandro Zaffaroni

The Archetypal Bioentrepreneur



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From the president and CEO

Heather Erickson

It is with much excitement that I join the Life Sciences Foundation (LSF) and the enthusiastic community that has contributed to its formation.

Since inception, LSF has been dedicated to capturing the history, preserving the heritage, and sharing the stories of biotechnology. In coming months, we will develop detailed plans for deploying LSF's rich collection of historical information to educate and inspire future innovators, engage the general public, and provide lay audiences with a sound appreciation of the life sciences and biotechnology. LSF aims to be the leading steward of life sciences and biotechnology heritage – we are both an independent, scholarly resource and a trusted translator of biotech's extraordinary stories.

LSF's creation is timely. Two refrains have emerged from my meetings with members of the biotech community. First, the founding generation is passing; there exists an urgent need to collect, preserve, and share their stories and wisdom. Secondly, life science professionals recognize a pressing need for informed, measured dialogues about the evolution and implications of the collective enterprise.

LSF will be focusing its near term activities on capturing founders' stories and shaping a definitive account of the industry's formation, and developing a robust, segmented communication plan to ensure that LSF's outreach efforts connect effectively with targeted audiences.

With a rich and growing collection of historical materials, LSF is poised to become an invaluable resource both within and beyond the biotech community. The achievements we have the honor of recording are truly inspiring. I invite you to learn more and to help enrich our collective history.

From the editor

Mark Jones

J.P. Morgan once said, "A man always has two reasons for what he does – a good one, and the real one." Morgan claimed to know too much, for personal motives are necessarily matters of speculation, not fact, but the saying has resonance. Experience teaches that motives are mixed, complex, densely-layered, often conflicted, occasionally confused.

The stories in this issue of LSF Magazine contain accounts of moral ambiguity in the life sciences and biotechnology. A father wants to save his children from a fatal genetic disorder, a cancer survivor wants to empower patients and reform cancer research and care, scientists and entrepreneurs want the freedom to discover and create. If these are real reasons, are they also good ones? The answers aren't always clear. The people in these stories sometimes find themselves at odds with the status quo, the 'establishment,' or 'the way things are.'

This is why justifications – Morgan's good reasons – are of special interest and utility to historians, even if they fail reliably to correspond with actual motives. Justifications represent the concrete values and expectations of organizations, institutions, and communities. Individuals are obliged either to honor them or change them if they can.

What ought to count as good can always be debated, but for practical historical understandings of why things happen as they do, good reasons almost always explain more than real ones.

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LSF News

Heather Erickson Named President and CEO of LSF

Heather R. Erickson became President and Chief Executive Officer of the Life Sciences Foundation (LSF) in July following the retirement of founder Arnold Thackray. Thackray was instrumental to LSF's founding and early successes. He will continue to serve the Foundation and the biotech community as a consultant on matters of history and scholarship. Before joining LSF, Erickson excelled in effecting organizational growth, most recently at the New-York based MedTech Association- a non-profit trade association serving the entire bioscience and medical technology community. Her tenure saw four founding companies blossom to nearly 100 organizations representing more than 68,000 employees across the state.

Meet the Newest Members of the LSF Board of Directors

LSF is pleased to welcome **Brook Byers**, **Carl Feldbaum**, **Frederick Frank**, and **Ivor Royston** to the Foundation's Board of Directors. They join G. Steven Burrill, Dennis Gillings, John Lechleiter, Phillip Sharp (academic advisor), and Henri Termeer. The Board of Directors will work closely with LSF's President and CEO to guide the organization. LSF is grateful for the interest and support of biotech's foremost pioneers. We appreciate their invigorating enthusiasm, contributions, and service.

LSF Welcomes Sally Smith Hughes and Rachel King to the Board of Advisors

Sally Smith Hughes, Ph.D., is an Academic Specialist in History of Science at the Regional Oral History Office of The Bancroft Library on the campus of the University of California, Berkeley. She has created an extensive collection of in-depth oral histories on bioscience, biomedicine, and biotechnology. She recently published *Genentech: The Beginnings of Biotechnology* (University of Chicago Press, 2011), the definitive historical account of the formation of the world' first molecular biotechnology company. She is also the author of *The Virus: A History of the Concept* (Heinemann, 1977).
Rachel King is one of the top women in the biotech industry. She began her career at ALZA Corporation, and later served in a series of leadership roles at Genetic Therapy, Inc. (GTI) from its start-up phase, successfully gathering $38 million from an A-list group of venture companies. She is the founder and current CEO of GlycoMimetics of Gaithersburg, MD. The company develops medicinal compounds that mimic the structure and biological activity of carbohydrates. Glycomimetics has a lead drug in Phase II trials as a treatment for vaso-occlusive crises in sickle cell disease. King serves on the boards of MDBio, the Biotechnology Industry Organization (BIO), and the Dean's Council of the Harvard School of Public Health, among others.

LSF Board members making news

Henri Termeer was honored with a Lifetime Achievement Award during the RARE Tribute to Champions of Hope' Gala and Rare and Genetic Disease Patient Advocacy Summit on September 27 in Newport Beach, CA. **William Bowes** has joined the Multiple Myeloma Research Foundation's (MMRF) Board of Directors. A non-profit established in 1998, MMRF has since raised over $200 million dollars to research a cure for multiple myeloma, a cancer with one of the lowest five-year survival rates. MMRF is hailed for its fiscal responsibility and is the top private funder of multiple myeloma research in the world.

Join LSF in San Diego on November 7th

The Life Sciences Foundation and the Giesel Library at the University of California, San Diego are proud to present a first of its kind event in La Jolla on November 7: **What's Past is Prologue: Creating the Life Sciences Industry in San Diego**. Jim Blair, Kevin Kinsella, and Tim Wollaeger, legendary venture capitalists and creators of such high-profile companies as Dura Pharmaceuticals, Vertex Pharmaceuticals, and Pyxis, will reflect on their roles in the formation of San Diego's world-class cluster of biotechnology firms. They will discuss valuable lessons learned and share thoughts about current conditions and future prospects for commercial biotech ventures. Hybritech found Ivor Royston will moderate the one-hour discussion. For more on the event, go to **www.lifesciencesfoundation.org/sandiego**

Innovation Night at the La Jolla Playhouse

Join On Dec. 5th, LSF will travel to San Diego for an evening of arts and sciences. **Innovation Night** brings together leaders in the life sciences and technology for an evening of networking and to celebrate creativity and innovation. The La Jolla Playhouse will present the world premiere of the musical Yoshimi Battles the Pink Robot directed by Tony Award-winner Des McAnuff. We hope to see you there!

A Great Friend Departs

The life sciences and the biopharmaceutical industry lost a loyal and powerful friend and guardian when Arlen Specter, former Senator from Pennsylvania died on Sunday, October 14, 2012, at his home in Philadelphia. He was 82. Specter had announced in August that he was battling non-Hodgkin's lymphoma.

Vice-President Joseph Biden spoke at a funeral service held at Har Zion Temple in the Philadelphia suburb of Narberth, where hundreds gathered to say goodbye: "I've never seen as much undaunted courage as Arlen had — both physically and politically. He believed he could change the world, if he just worked hard enough at it."

Specter served in the Senate for thirty years. He lost his seat in 2010, after crossing party lines to ensure that the stimulus package passed by Congress in 2009 would apportion $10 billion to sustain biomedical research at the National Institutes of Health.

BIOCOM Annual Dinner

John Crowley, CEO and President of Amicus Therapeutics, is the guest speaker for the **BIOCOM Annual Dinner** on November 15 in San Diego. He defied conventional wisdom and great odds, and risked his family's future to pursue a cure for his children's life threatening disease. See pg 16 for his inspiring story. **biocom.org**

LSF Oral History Program

Robert F. Johnston

Oral histories are narrative accounts of events and historical processes as told from the point of view of eyewitnesses and participants. They preserve the experiences, recollections, and testimonies of history-makers.

LSF is assembling a virtual archive of oral histories from biotech pioneers, accounts yet to be heard by scholars, journalists, and the general public. We announce a new addition to the collection, a conversation with entrepreneur Robert F. Johnston. With candor and wit, Johnston paints a vivid picture of ups and downs in biotech finance during the industry's early days.

After earning a bachelor's degree in economics from Princeton and an MBA from New York University, Robert F. Johnston began a career in investment banking at F. S. Smithers in 1960. He moved on to Smith Barney, before establishing his own investment company, Johnston Associates, in 1968.

Johnston kept an eye on developments in the life sciences, and in 1977, placed an unusual ad in Science, surely the first of its kind: "Wanted, president of a new company creating products utilizing recombinant DNA techniques." The company did not yet exist.

The ad was answered by J. Leslie Glick, a PhD biologist who had experience running a cell culture company in Buffalo, New York called Associated Biomedics Systems (ABS). Glick and Johnston each contributed $1,500 to the new venture, and incorporated Genex in July of 1977. Glick was to run the company as CEO; Johnston's role was, as he puts it, "dialing for dollars." Genex was the third biotechnology company to appear on the scene, following Cetus and Genentech. Over the next four years, it grew to be the largest.

Johnston and Glick recruited highly-regarded biologists to the company's scientific advisory board (SAB), including molecular biologist Richard J. Roberts of Cold Spring Harbor Laboratory, who had recently established that genes can be 'split.' He later shared a Nobel Prize for the discovery with Phillip Sharp of MIT. The SAB suggested an unexploited niche: using recombinant DNA techniques to improve the manufacture of specialty chemicals, amino acids, vitamins, enzymes, and hormones for industrial use. Johnston began to investigate funding opportunities in the area:

> I sent out letters out to a lot of companies, including Koppers, a large Pittsburgh-based manufacturer of chemicals and carbon materials. One day, the Vice-Chairman and the head of R&D showed up unexpectedly at Genex. I was there with Les, a secretary, and one of the scientists. That was it, but they were interested and put up $3 million. They were trying to skip three generations of technology. They were creosoting railroad ties. Compared to a company like Dow, they weren't even on the playing field, but they were gentlemen, and great people to work with.

When Genex was ready to make a public offering in 1982, Wall Street was still generally unfamiliar with edgy biotech financing:

> We did our initial public offering with First Boston. At that time, they knew virtually nothing about biotechnology. It was interesting. First Boston had big institutional clients, and we were a tiny biotech company. One of the analysts said in the due diligence meeting, 'Bob, look at these numbers – this says you're going to run out of money in 60 days.' I said, 'Yes, that's why we're doing the financing.'

In 1980, Johnston established Cytogen, an early monoclonal antibody firm, in Princeton. Investors were already clamoring for opportunities in biotechnology. Raising money had become relatively easy. By then," says Johnston, "everyone thought I was a genius. Even my wife thought so for a while!" Cytogen intended to work in oncology:

An established record of achievements as a scholar and researcher coupled with broad understanding of both the biological sciences and administrative concerns are the primary qualifications.

Submit curriculum vitae to:

Provost David C. Knapp
Chairman of the Search Committee
300 Day Hall
Cornell University
Ithaca, New York 14853

Cornell University is an Affirmative Action Employer.

ENTREPRENEUR

Wanted, the president for a new company creating products utilizing recombinant DNA techniques: prefer background in this technology and in business. Contact **Robert Johnston at 609-924-3131 or Johnston Associates, Pretty Brook Road, Princeton, N.J. 08540.**

EPIDEMIOLOGIST

To develop a research program to investigate the health and disease effects of environmental pollution with initial emphasis on air pollution. Strong background in biology, physical sciences, and air pollution research desirable. Send résumé and references to: **LAWRENCE BERKELEY LABORATORY, Employment Office, One Cyclotron Road, Building 90, Room 3024, Berkeley, Calif. 94720.** *An Equal Opportunity and Affirmative Action Employer.*

8 APRIL 1977

mit credentials including a statement of
terest to: **Dr. Fuad S. Farah, Chief**
Dermatology, Department of Medicine, U
cal Center, 750 East Adams Street, Sy
York 13210.

FACULTY POSITION

Applications are invited for a faculty ap
the Department of Medical Microbiolog
Medicine, effective 1 July 1978. Such a
are usually made as assistant professor.
crobiology, virology, or immunology to
graduate students. Research should be
biochemical or genetic level. Postdoc
ence in microbiology and biochemistry
ferred. *Applications from all qualifie*
elcome. Women and minorities encou
Send curriculum vitae and four lette
mendation to: **Dr. Paul Sypherd, Departm**
cal Microbiology, University of California
lege of Medicine, Irvine, Calif. 92717, bef
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GENETICISTS

The Laboratory of Genetics, Univer
consin-Madison, expects to make two
pointments in 1977–78 or 1978–79 at the a
fessor level. Applications in plant cell cu
cytogenetics, clinical genetics, *Drosoph*
and developmental genetics are especi
but all areas will be considered. Appli
send a curriculum vitae, publication list,
research and teaching interests, and t
three references. Send applications t
Crow, Chairman, Genetics Building,
Wisconsin, Madison, Wis. 53706.

1977 ad placed in *Science* by Robert F. Johnston

We had the first patents for attaching radioisotopes to the constant region of the antibody. The antibodies were delivery vehicles for radioisotopes. We used non-lethal isotopes for imaging purposes. We injected the antibodies, which targeted the tumor, lit it up, and enabled us to make radiographic images of its location. Then we attached a more lethal isotope to kill the tumor. We conducted tests with mice. We injected tumor cells and they developed big lumps. We injected antibodies and radioisotopes, and that would shrink the tumors. We put before and after pictures of the mice in the prospectus. The SEC didn't like that. They thought the pictures were too promotional, and made us remove them. As it turned out, it was not the best science. It was too early. Ron Cape, the Cetus CEO, once said to me, 'If mice could pay, we would all be in great shape.'

The Cytogen story incorporated a plot element shared by a host of industry period pieces – the cliffhanger financial crisis episode in which there isn't enough money in the bank to meet payroll. Johnston describes how it felt:

We were on a family trip in Scotland, and I got a phone call from the CFO who told me we couldn't meet payroll in three weeks. The venture capitalists at Charles River said they would put up the money, but they wanted an option on half of my shares at my cost. I owned about 30% of the company. I said, 'That's an expensive deal.' We had planned to do a public offering at twelve dollars a share. In the original financing, my cost on shares had been fifteen cents. It was pretty painful. I remember walking on the beach at Inverness with my wife, and saying, 'I didn't sleep last night. I don't think I'm going to sleep tonight; we should go home and address this problem.' I went to the bank. I got a second mortgage on my house. I said, 'OK, I'll put up my share, three hundred thousand dollars, and everybody else puts up their pro rata. We passed the hat and made payroll.

Cytogen recovered, made an IPO in 1986, and remained an independent, publicly-traded company until acquired by EUSA Pharma in 2008. Johnston went on to found several other public companies, including Sepracor, i-STAT, Ecogen, Vela, and Envirogen. He was also involved in the formation of private firms, such as Biocyte, ExSar, Immunicon, Praelux (originally SEQ), Sonomed, and Targent.

Johnston currently lives with his wife, Lynn, in Hanover, New Hampshire. The Johnstons are involved in education reform. In 1992, they established a private foundation called Educational Ventures, to fund solutions for systemic problems. Robert serves on the Board of Directors at the Center for Education Reform (CER), an advocate for charter schools, and on the advisory for the Molecular Biology at Princeton University.

To see Robert F. Johnston's oral history in its entirety visit LSF online at **biotechhistory**.org

Advisory Board Spotlight

William H. Rastetter

Commonplace propositions: science and art are distinct spheres of culture and modes of experience. One is systematic and analytical, the other expressive and undisciplined. One embodies reason, the other emotion.

The assumptions are familiar; the contrasts are false. Science and art have much in common. Both are modes of representing and ordering. Both are methodical and conservative, on the one hand, but inherently innovative on the other. Both involve discovery and invention, and both demand originality. Science and art spring from the same impulses, the same well of human creativity.

It should be no surprise to find individuals who display interests and talents in both art and science. LSF Advisory Board member William H. Rastetter is such a person. Surprised?

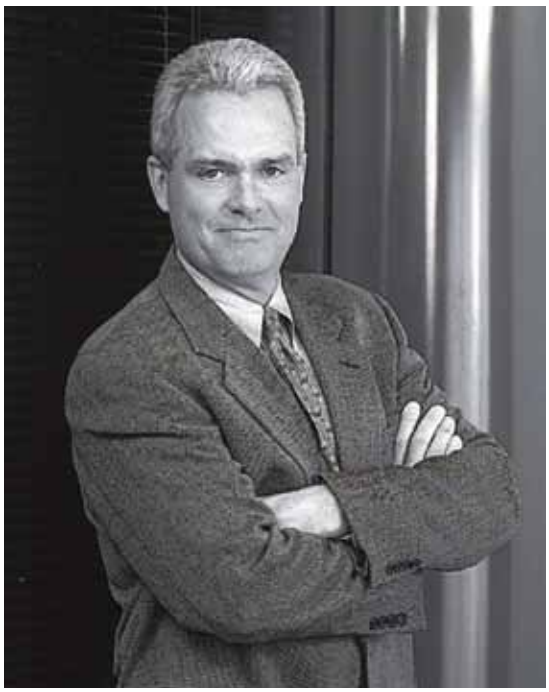
Bill Rastetter has demonstrated talents in a number of fields. In 1975, he earned a PhD in organic chemistry from Harvard University, and became a member of the faculty at MIT. In 1982, he moved to Genentech to establish a protein engineering group. It was a unique opportunity. At the time, Genentech was one of the few organizations in the world capable of undertaking such a project.

In 1984, Bill made a career transition from science to business. He was appointed Genentech's Director of Corporate Ventures. In 1986, Rastetter accepted an invitation to become the first (and only) CEO of Idec Pharmaceuticals. At Idec, he directed the development of Rituxan®, the first FDA-approved monoclonal antibody treatment for cancer. Rituxan became a mega-blockbuster product, and today remains the world's top-selling cancer drug. When Idec merged with Biogen in 2003, Rastetter served the combined entity as Executive Chairman.

In 2006, Rastetter joined Venrock Associates as a partner, and embarked on a third career, in finance. He currently serves as Chairman at four biotechnology companies – Fate Therapeutics, Illumina, Neurocrine Biosciences, and Receptos.

Lately, Bill has returned to an old avocation and taken up a fourth serious line – photography. He began taking photographs at age eleven while living in Costa Rica, the son of a US diplomat. At sixteen, he took a part-time job with the US Information Agency, working on black & white publicity shots of JFK in a US Embassy darkroom, in connection with the President's visit to Latin America in March 1963.

Today, Rastetter owns a state-of-the-art sixty megapixel Hasselblad digital SLR camera, but favors old-fashioned techniques: "I like to shoot on film," he explains, "with a custom handmade large format 4x5 view camera. I process prints in a commercial scale black & white darkroom. It's more challenging than the newer technologies that allow you to make and correct all kinds of mistakes." Rastetter's works have been put on exhibition in several shows in San Diego County. Please enjoy the images.



Photographer Bill Rastetter, former Executive Chairman of Biogen Idec

Scripps Pier Kelp
Walkers Waves

Scripps Pier
From Below

From the artist:

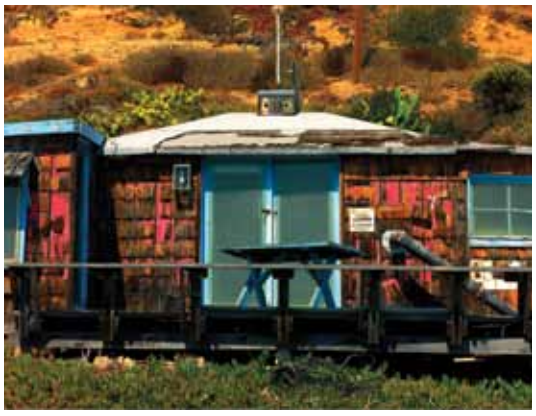
The pier shot is a time exposure taken at 8:30 p.m., hence the tranquil water. I think of the pier as providing a nexus between our footing on land and the horizon and beyond. In this sense, the pier (and the photograph by extension) might represent our science and its connection between the known and the distant realities known only as we reach out to new horizons.

Only through the science of the camera was the horizon visible — it was pitch black to the human eye. And the elements of the pier naturally frame and reveal the objective, the distant horizon; the elements of our science, too, must frame and reveal all new knowledge.

Succulent House

"The most beautiful experience we can have is the mysterious – the fundamental emotion which stands at the cradle of true art and true science."

"After a certain high level of technical skill is achieved, science and art tend to coalesce in esthetics, plasticity, and form. The greatest scientists are always artists as well."



Picnic Table House

Quotes by Albert Einstein

Gems from the Archives

The British failure to patent hybridoma technology

In August of 1975, German cell biologist Georges Köhler and Argentine biochemist César Milstein announced the invention of hybridoma technology in *Nature*. The experiments were performed in Milstein's Cambridge laboratory, which was funded by the British Medical Research Council. Köhler was visiting the lab, conducting post-doctoral research on antibody genetics. In the course of this work, he and Milstein stumbled on a cell fusion technique that enabled, for the first time, the continuous and copious production of specific immunoglobulins against distinct antigens of interest – monoclonal antibodies. They famously concluded the paper by stating that the invention "could be valuable for medical and industrial use."

Milstein was philosophically opposed to patenting scientific discoveries. He believed that privatization could hinder scientific progress by prohibiting or discouraging researchers from pursuing promising lines of inquiry. He was a pragmatist, however, and allowed that "patents are perhaps necessary for the development of products that will ultimately benefit society." Milstein approached the MRC to recommend a patent filing. After a cursory review, the agency judged that the invention did not merit the expense.

The MRC evidently did not recognize the significance of the invention. American entrepreneurs at companies such as Hybritech and Centocor rushed in to seize opportunities created by the MRC's inaction. The British have been sore about it ever since. A sympathetic American commentator has said: "Anonymous administrators responsible for such decisions should be publicly exposed for their bad judgment and incompetence. Perhaps the time has come to restore the stockades and gallows at Tyburn as a way of reintroducing accountability." The MRC's decision not to patent hybridoma technology turned out to be a gaffe of titanic proportions, and a major blow to British biotechnology.

Historians at the Life Sciences Foundation are currently locating and rescuing materials of historical interest (papers, correspondence, photographs, and so on) to be made available to scholars, educators, journalists, and the general public in a digital archive.

If you have documentary materials to donate, please contact gavin@biotechhistory.org.

Above: Milstein and Köhler receive the Nobel Prize in Physiology or Medicine, 1984
Opposite: Letter from consultant to MRC advising against patenting hybridoma technology

NRDC

National Research Development Corporation
PO box 236 Kingsgate House 66/74 Victoria Street London SW1 E 6SL
Telephone 01-828 3400 Telegrams Nardec London SW1 Telex 23580

Your ref /

Our ref EJT/AED

7th October 1976.

Mr. L.D. Hamlyn,
Medical Research Council,
20 Park Crescent,
London, W1N 4AL.

Dear Jimmy,

Continuous Cultures of Fused Cells

We have now had an opportunity to study the paper by Kohler and Milstein to which you referred in your letter of 24th September addressed to Ron Homer.

Although the authors suggest that the cultures which they have developed, or rather similar cultures, could be valuable for medical and industrial use, I think this statement should be taken as a matter of long term potential rather than immediate application. It is certainly difficult for us to identify any immediate practical applications which could be pursued as a commercial venture, even assuming that publication had not already occurred. I would add that the general field of genetic engineering is a particularly difficult area from the patent point of view and it is not immediately obvious what patentable features are at present disclosed in the Nature paper.

In summary, therefore, unless further work indicates a diagnostic application or industrial end product which we can protect, despite the disclosure in the Nature paper, we would not suggest taking any further action ourselves.

Kind regards,

Yours sincerely,

Eric.

E. [redacted]
Biosciences Group

Biotech Bookshelf

Henry Bourne

Henry Bourne. (2011). ***Paths to Innovation: Discovering Recombinant DNA, Oncogenes, and Prions, in One Medical School, Over One Decade.*** **Berkeley: University of California Press.**

Why UCSF?

The University of California at San Francisco (UCSF) is a world-class clinical and medical research institution. In 2012, *U.S. News and World Report* ranked the school #1 in the nation in primary care and #5 in biomedical research.

In the 1970s and early 1980s, UCSF was the site of remarkable technological breakthroughs and Nobel Prize-winning discoveries. Faculty members, postdocs, and visitors became central figures in the emergence of the biotechnology industry – the names include Herb Boyer, David Gelfand, Howard Goodman, Herb Heyneker, Ed Penhoet, Bill Rutter, Peter Seeburg, Axel Ullrich, and Pablo Valenzuela. UCSF became a special place during an extraordinary period in the history of science.

The flurry of productivity was unexpected. Until the 1960s, UCSF had the reputation of a provincial medical school, a teaching institution. The campus sponsored little research. When physician Richard Havel interviewed for a faculty position in 1955, he expressed concerns about the paucity of scientific resources. In response, his campus tour guide, UCSF biochemist Izzy Edelman, quipped: "Look at it this way, Dick. You've got nowhere to go but up!"

What accounts for UCSF's astonishing metamorphosis? Henry Bourne's recent book, *Paths to Innovation* tells the story, and reflects on the ways in which creativity and innovation can be fostered (or hindered). The book draws on a rich collection of documentary materials – oral histories, scientific literatures, university archives, and the author's own direct personal experience. Bourne is a physician and cell biologist who joined the UCSF faculty in 1969. He ran a laboratory at the institution until his retirement in 2007.

In 2009, Bourne published a personal memoir of his scientific career, *Ambition and Delight: A Life in Experimental Biology*. In *Paths to Innovation*, he describes the institutional milieu within which he worked, and which also happened to be immensely consequential in the development of the life sciences in the late twentieth century.

The Great Transformation at UCSF

Founded in 1873 as the Medical Department of the University of California, UCSF moved to its Parnassus Avenue site on the slopes of Mt. Sutro in 1898. The loss of buildings in the 1906 earthquake led to a space crunch. Instructors in the basic sciences (physiology anatomy, and pathology) were transferred to the university's main campus in Berkeley. Clinical medicine remained in San Francisco. The rupture wasn't mended until 1958 when the science departments returned to Parnassus.

A qualitative shift in UCSF's research programs began to take shape in the late 1950s and early 1960s under the leadership of four individuals: Edelman and Havel (who had signed on despite the scientific deprivation), and physicians Julius H. Comroe and Lloyd 'Holly' Smith. All four became well-known, highly-regarded investigators. They overcame the institution's chronic administrative lethargy and managed to recruit a number of top-notch scientists.

A key turning point was the arrival of biochemist William J. Rutter. In the 1960s, the UCSF Department of Biochemistry was undistinguished. Smith and Edelman led the search for a new chairman, a time-consuming process that included many failures and false starts. Ultimately, they resorted to a "painstakingly deliberate campaign" to recruit Rutter, then Professor of Biochemistry at the University of Washington. Rutter had turned down the posi-

William J. Rutter

tion in 1965 without even visiting the campus. Three years later, Smith and Edelman made another attempt to entice him.

Edelman invited Rutter to his home, and introduced him to another candidate who had also turned down the position, NIH scientist Gordon Tompkins. "I decided," Edelman later explained, "to let them recruit each other. I plied them with coffee and cake, and the three of us started talking. Pretty soon, they started talking to each other, and within two hours they sold each other on the idea of coming together."

Rutter assumed the Chair in Biochemistry in 1968. He changed the name of the department to Biochemistry and Biophysics, and set out to establish a leading center of molecular biology. Tompkins joined the following year as Vice-Chairman, and helped Rutter add eleven new faculty members by 1973. The unit's former inertia was swept away. "Cleaning up was a big problem," Rutter says, "and there were rough edges in that, but I had to get it done.

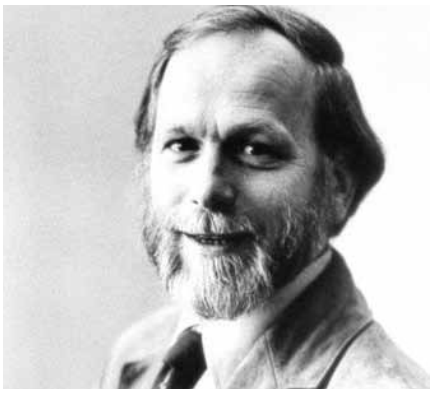
Since the inception of molecular biology in the 1930s, most fundamental questions in the field had been asked (and many had been answered) in studies of prokaryotes — relatively simple (and mostly) single-celled organisms. Bacteriophage and *E. coli* were the principal experimental models. In the 1960s, molecular biologists began examining processes of cellular differentiation and morphogenesis in higher organisms, eukaryotes. Many of Rutter's new hires worked in eukaryotic biology, in specialities with potential bearing on medicine. Collectively, they moved UCSF onto the disciplinary cutting edge.

The charismatic Tompkins passed away tragically in 1975. His loss was a big blow, but Rutter continued to elevate the department. During Rutter's tenure as Chair, which lasted until 1982, additions to the department included Bruce Alberts, John Baxter, Roger Cooke, Harvey Eisen, Bob Fletterick, Howard Goodman, Christine Guthrie, Regis Kelly, Marc Kirschner, David Martin, Patrick O'Farrell, Louis Reichardt, Jim Spudich, Bob Stroud, John Watson, and Keith Yamamoto. All went on to fashion distinguished careers. The vitality of the group attracted top faculty from neighboring departments as well. Numerous cross-disciplinary research projects ensued.

According to Bourne, UCSF's ascent was due in no small measure to Rutter's skill in judging scientific talent and identifying in individuals – Tomkins and Alberts, notably – qualities of intellectual and organizational leadership that complimented his own. By recruiting the right people and deploying them in the right combinations, Rutter created a department that was at once both highly competitive and highly collaborative, and, as a result, extraordinarily productive.

"Wild Cards"

Much of *Paths to Innovation* is devoted to discussions of what Bourne calls "wild cards"— young UCSF researchers who had not established records of distinction prior to joining the university, did not receive star treatment, and were mostly overlooked in the early stages of their careers, but went on to make major scientific discoveries and substantial contributions to UCSF's rise to



'Wild cards' clockwise from top left: Herb Boyer, Stanley Prusiner, Harold Varmus, Michael Bishop

prominence. Bourne contends that UCSF's emergent culture of innovation enabled their achievements.

Herb Boyer was the first "wild card." Boyer joined the UCSF Department of Microbiology in 1966, fresh from a postdoc at Yale University, where he had searched in vain for enzymes presumed to be responsible for the phenomenon of plasmid restriction in *E. coli*. His early investigations in the area did not set the scientific world afire.

In negotiations concerning the position at UCSF, Boyer had been promised a new laboratory, but on arrival he was directed to three tiny rooms in an antiquated facility short of essential pieces of equipment. He felt slighted and unappreciated. In addition, he perceived a lack of scientific collegiality, disliked teaching biology to medical students, and grew frustrated with the slow progress of his research. Discouraged, he began looking for a new job.

Before Boyer could arrange an exit, however, his circumstances and outlook began to improve. Virologist Michael Bishop, Bourne's second "wild card," left the NIH to join the UCSF Department of Microbiology in 1968. He provided Boyer with good company and intellectual stimulation. Rutter arrived the same year, commenced his transformative work, and UCSF became, from Boyer's perspective, "a much different place."

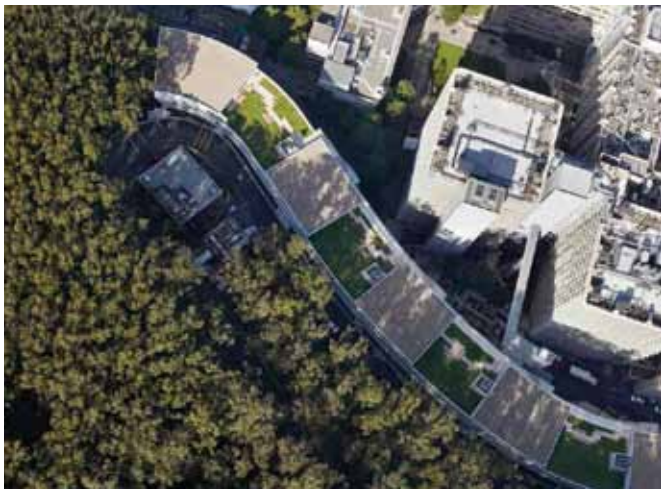
Fortune smiled in 1970 – a graduate student in Boyer's lab, Robert Yoshimori, purified the restriction endonuclease *Eco*R1. The discovery put Boyer on an experimental path leading to the invention of recombinant DNA technology in 1973. Over the next several years, UCSF laboratories directed by Boyer, Rutter, and Howard Goodman employed the tool to accelerate progress in molecular genetics and cell biology, and to establish the technical foundations of a new life sciences industry.

In 1969, Harold Varmus, a third "wild card," joined Bishop's lab as a postdoc. He and Bishop worked with the Rous sarcoma virus (RSV), a retrovirus with a known cancer-causing gene (an 'oncogene'), to identify the first of a class of genes that control cell growth and division. Using a radioactive nucleic acid probe specific to part of the RSV genome containing the viral oncogene, they discovered oncogene-like materials (proto-oncogenes) in normal cells. They proposed that disturbances of these genes, through mutation or over-expression, could make cells cancerous.

Earlier theories held that oncogenes were viral in origin. Varmus and Bishop's experiment showed that RSV had acquired its oncogene from previous host cells – an origins story that was subsequently found to be true for many retroviral oncogenes. The discovery of proto-oncogenes revolutionized both the study of cell growth factors and the conceptual foundations of cancer research and anticancer pharmacology. The achievement was recognized with a Nobel Prize in 1989.

The wildest of UCSF's "cards," as Bourne tells the story, was Stanley Prusiner. Prusiner came to the university in 1969 for a medical internship. He was brash and combative, but plainly talented. In 1972, Holly Smith scribbled on his residency application, "Prickly, but worth it." As a resident, Prusiner became fascinated by the case of a patient suffering from Creutzfeldt-Jakob disease (CJD), a brain-wasting condition said to be caused by a 'slow virus.' He decided to take up the study of CJD and other transmissible spongiform encephalopathies (TSEs).

UCSF hired him in 1974 as an Assistant Professor of Neurology. Prusiner pressed ahead with his research on TSEs. He ignited



Aerial view of UCSF, Parnassus Heights campus

The Rutter Center, UCSF Mission Bay

a controversy in 1982 when he claimed, in an article published in Science, and in the absence of clinching empirical evidence, that scrapie, a TSE found in sheep, was caused by a protein, which he called a "prion" (a proteinaceous infectious particle). The idea was greeted with skepticism, and even ridicule, but Prusiner clung to it tenaciously for years. Experimental findings confirmed his predictions in the early 1990s. Prusiner was awarded a Nobel Prize in 1997.

Bourne suggests that Prusiner's "quirky, difficult personality drove every step of his discovery," but the book doesn't present individual character or action as a free-standing explanation. One of the keys, from Bourne's point of view, is that Prusiner was allowed at UCSF to pursue an unorthodox and frequently disparaged line of inquiry. "Crucially," Bourne observes, "no one dictated to Prusiner what research he should do, or how he should do it."

Lessons

What factors allowed scientific creativity to flourish at UCSF? What enabled so many discoveries in such a short period of time? In the 1970s, UCSF did not have sparkling labs, a roster of eminent, award-winning scientists, or long tradition of scientific excellence. It did, however, provide young researchers with the latitude to pursue unorthodox ideas and risky programs of research

Those in charge had the good sense to let talented people do their thing in an environment that valued imagination, creativity, collaboration, competition, and ambition – all of it unfettered. Can the formula be bottled?

Bourne, the scientist, is wont to encapsulate history lessons in the form of testable hypotheses. He proposes, for example, that "competition and cooperation are often both essential for creative innovation, but collaboration may thrive best under conditions that mitigate overt competition between the collaborators." Elsewhere, however, he observes that processes of discovery are diverse, and outcomes often unexpected. "Consequently," he says, "conditions and policies conducive to discovery must…change, often quite rapidly."

To conclude the book, Bourne considers broad institutional obstacles to sustained innovation. He believes that 'big science,' scarce funding, and declining opportunities for independent work now pressure young scientists to adopt conservative research agendas. As an antidote, he promotes the construction of "innovation incubators" within research universities. The territory is unexplored, so Bourne advises small-scale experimentation. He insists that commitments to such projects must be maintained over many years.

At a book release event at UCSF in December 2011, Bourne summed up his message: "I want everyone to realize what a delicate and chancy thing science is, and that it has to be fostered." Intellectual freedom is essential ingredient. The researchers who revitalized UCSF and reshaped biology in the 1970s did not join the university because it was a leading academic center. "It absolutely was not," Bourne states," but it was a place where they were free to do what they wanted to do without interference."

BIOTECH BE

WE PLAN, GOD LAUGHS

The son of a New Jersey police officer who died on duty when he was seven years old, John Crowley graduated from the Harvard Business School in 1997 and prepared to move his young family – wife Aileen, two-year old son, John, and one-year old daughter, Megan – from the East Coast to Walnut Creek, California. He was set to begin a promising career in management consulting with the highly-regarded San Francisco firm, Marakon Associates. Financial security was on the horizon. Aileen was expecting the couple's third child. Life was good, the future seemed bright. "We were on top of the world," says Crowley.

Suddenly, the world came apart. At fifteen months, Megan had not taken her first steps (although she otherwise appeared normal and healthy). In March 1998, a week after Aileen gave birth to a second son, Patrick, a series of tests led to a rare diagnosis – Megan had Pompe disease. Neither John nor Aileen had ever heard of it. Doctors informed them that their daughter would become progressively weaker. Her heart would begin to fail. She would struggle to breathe, and probably not live beyond five years of age. There was no treatment. The Crowleys were instructed to go home and prepare for the inevitable.

There was a 25 percent chance that Patrick was also afflicted. Pompe – named for the Dutch pathologist who first characterized the illness in 1932 – is a genetic disease that occurs when a child receives a defective copy of a recessive gene from both parents. The gene implicated in Pompe disease codes for an enzyme called acid alpha-glucosidase (GAA). GAA plays a critical role in the conversion of glycogen to energy. Mutations in the gene reduce the molecule's biological efficacy, resulting in an enzyme deficiency. In the absence of sufficient functional GAA, glycogen accumulates in cells. Lysosomes – cytoplasmic organelles that break down cellular waste and debris – are overwhelmed. Cells become clogged; organ

The story of John Crowley's heroic efforts to save his children from a rare, fatal illness has been the subject of a front-page article in the Wall Street Journal, a book by journalist Geeta Anand, and a Hollywood movie starring Harrison Ford. There was no treatment for the disease. Crowley embarked on a quest to find one. He soon found himself running a startup biotechnology company – quite unexpectedly, because he had no prior experience in the field.

As the company struggled to develop a medicine, Crowley's children grew weaker. On more than one occasion, desperation led him to push envelopes in science and business development. His personal and professional stakes in the work did not always coexist harmoniously. Examining Crowley's unusual predicament yields insights into the practical moral foundations of biotechnology as a scientific, commercial, and human enterprise.

ENEFICENCE

function declines; muscles atrophy. Patients become immobile. Eventually, they die.

For John and Aileen, the diagnosis was shattering. The couple's dreams were wiped out in an instant, replaced by anxiety and dread. They put off testing Patrick for a time, since he appeared robust. They felt ill-prepared at that moment to face more devastating news. When John Crowley looks back on this period of his life, he reflects on an old Yiddish proverb: "We plan, God laughs."

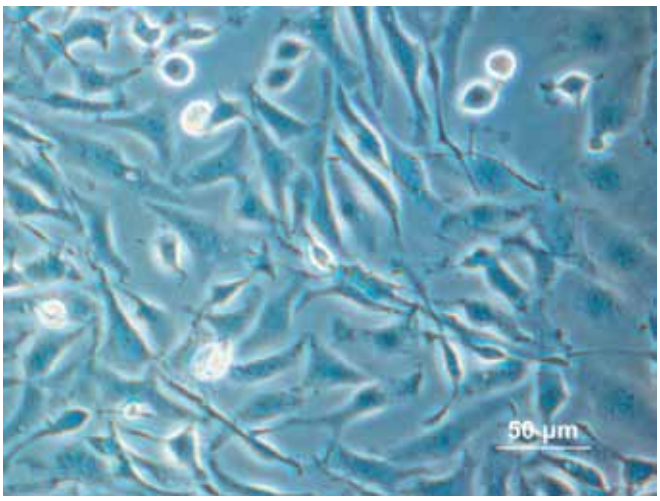
TAKING ACTION

John found that passive acceptance of his daughter's plight was impossible. Compelled to act, he went online to educate himself about Pompe disease and the current state of biomedical research on the condition. He discovered a small, dispersed, and underfunded community of physicians and endocrinologists working to improve care for patients with Pompe and other rare lysosomal storage disorders (LSDs). He also found a ray of hope.

Crowley learned of two research groups that were planning clinical trials of experimental enzyme replacement therapies (ERTs). Geneticist Yuan-Tsong Chen of Duke University was making recombinant GAA in Chinese hamster ovary (CHO) cells, with assistance from a Taiwanese company called Synpac. In Manhasset, New York, on Long Island, Pompe expert Dr. Alfred Slonim was working with a Dutch company called Pharming that had bred thousands of transgenic rabbits carrying the gene for human GAA. Pharming scientists were purifying a supply of the enzyme from rabbit milk.

The Crowleys returned to New Jersey, where John and Aileen had both grown up, to be closer to top medical specialists, and to the couple's support network of friends and family. John resigned from Marakon Associates and accepted a position in sales and marketing at Bristol-Myers Squibb in Princeton. It was nearby, the pay

Left: Yuan-Tsong Chen, Duke University
Below: Chinese hamster ovary (CHO) cells



was good, the health insurance was excellent, and the regular hours enabled him to devote considerable time and energy to pursuing a cure for Megan.

As the Crowleys adapted to their new reality, the burden of Pompe on the family grew heavier – test results showed that Patrick, too, had the disease. John hit on the idea of starting a private foundation to raise money for research. He established the Children's Pompe Foundation and sought funds to support a clinical trial in which his children could be enrolled. He worked with the Muscular Dystrophy Association to increase awareness of the disease among philanthropists, and over the next two years, collected more than $1 million to support the work of Chen, Slonim, and others.

In November 1998, Crowley attended a medical conference on Pompe at the National Institutes of Health in Bethesda, Maryland. He listened to Dr. William Canfield of the University of Oklahoma Health Sciences Center describe preliminary efforts to develop a chemically modified version of GAA that would significantly increase uptake of the enzyme by affected cells. Canfield claimed that the Duke and Pharming enzymes were inferior and would have to be administered at very high doses in order to achieve therapeutic effects.

The claim was disconcerting because Crowley knew the Duke and Pharming teams were struggling to deliver enough GAA for clinical trials. Chen's group had lost a batch of precious enzyme when its CHO cells became contaminated by a virus, and the Pharming team had reported disappointing yields from the rabbit milk purification method. If the supply problems weren't solved, the first trials would enroll only infants because clinical efficacy could be established with less enzyme. The Crowley children might not qualify to receive the treatment.

NOVAZYME

A year passed. The Duke and Pharming programs stalled. Megan and Patrick grew progressively weaker. Both needed ventilators to help them breathe. Crowley was tired of waiting. In January 2000, he contacted Canfield, who had resigned his position at the University of Oklahoma to start a private firm called Targeted Therapies. The company, located in Oklahoma City, was grossly undercapitalized. Crowley offered to help raise the first $250,000 in capital for the business.

Canfield needed an experienced CEO to raise money. Crowley helped him conduct a search, in vain. They couldn't find a suitable candidate willing to move to Oklahoma. Acutely aware of the ticking clock, Crowley nominated himself for the job. Given the lack of alternatives, Canfield took the proposal seriously.

Aileen was taken aback by it. John was doing well at BMS, and earning an annual salary of over $100,000 . His position provided the family with a measure of security and – importantly – health insurance. On the other hand, jumping to Canfield's startup was a way for John to become directly involved in finding a cure for Megan and Patrick, and others like them. Aileen didn't stand in his way. "We were so desperate to take control of the situation," says John, "that we were willing to do almost anything to drive toward

Genzyme Headquarters, Cambridge, MA

a treatment for our kids."

The family remained in New Jersey; John commuted to Oklahoma City as needed. He and Canfield courted angel investors, and collected a total of $1.2 million. Then Canfield persuaded a Pennsylvania-based biologics company called Neose Technologies that his chemistry could improve replacement therapies for a wide range of enzyme deficiency disorders. Neose agreed to partner on the Pompe project, and put in another $500,000. The Neose commitment was an important validation of Canfield's science. Suddenly, venture capitalists were willing to invest. Crowley changed the name of the company to Novazyme, and sold portions of it to Perseus-Soros, Catalyst, and HealthCare Ventures. Novazyme closed its Series A financing round with over $8 million in the bank.

The fundraising went well, but Crowley's lack of experience soon became an issue. A few executive miscalculations prompted members of the Novazyme board of directors to question whether they had the right CEO in place. They were concerned that Crowley's desire to obtain a medicine for his children at any cost was encouraging recklessness, and impairing his judgment regarding the best interests of the company and investors. At one point, an overenthusiastic spin on preliminary data from a less than rigorous experiment prompted a board member to question seriously whether the enterprise was even legitimate. John acknowledges mistakes, but believes that his passion and sense of urgency were essential ingredients in the company's success: "If I had done things the conventional way at Novazyme, I don't think we would have moved as quickly as we did."

By mid-2001, Novazyme had grown impressively. The payroll had expanded from a handful of employees to over a hundred. Canfield had completed animal studies of the modified enzyme, and the company had built a small pilot manufacturing plant in anticipation of a clinical trial in human beings. The next infusion of venture capital, however, was tied to a benchmark – a treatment in the clinic by September. Crowley knew the timetable was nearly impossible to meet.

In order to move forward, the small firm needed to tackle a series of daunting technical and organizational challenges with which it had no prior experience. Novazyme would have to design and conduct a Phase III clinical trial that would deliver unequivocal evidence of the safety and efficacy of the company's medicine to the FDA. If successful, the firm would need to begin manufacturing substantial quantities of the product – again according to stringent regulatory standards – and to distribute it to physicians treating Pompe patients all around the world.

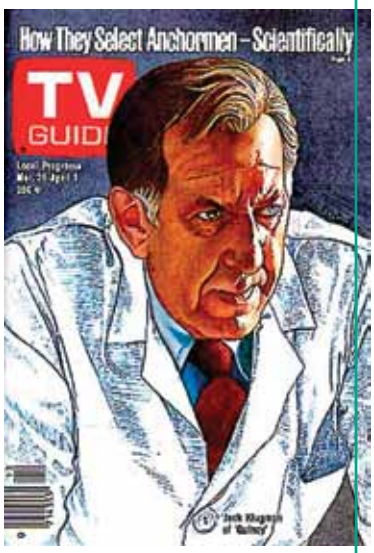
Given the magnitude and complexity of the looming tasks, Crowley was reluctant to take them on without assistance. He concluded that the best way to deliver appropriate returns to investors, guarantee survival of the GAA research program, and speed the production of an ERT for Pompe patients, including his own children, was to solicit aid from a larger corporate partner. He sent out invitations to an open house.

Two big biotech companies stopped in to visit. Genentech in South San Francisco, California proposed a partnership to help bring Canfield's enzyme to market, an arrangement in which Novazyme would retain substantial control of the project. Boston-based Genzyme was also interested. Making orphan drugs for lysosomal storage disorders had become the company's biggest business. By 2001, Genzyme had marketed two highly successful treatments for Gaucher disease, completed a Phase III study of an ERT for Fabry disease, and set its sights on Pompe. Genzyme wanted to discuss a full acquisition of Novazyme.

The choice between Genentech and Genzyme was difficult, and later became the subject of a Harvard Business School case study ("Novazyme: A Father's Love"). Crowley reasoned that Novazyme's Pompe program would be one among many projects at Genentech, and could get lost in the shuffle. At Genzyme, in contrast, it would likely become a top priority. Genzyme had already made a serious investment in the area – it had taken over Pharming's assets and purchased rights to Chen's enzyme from Duke University. It had also initiated its own internal research program. Crowley imagined that work on a treatment for Pompe disease "would keep the Genzyme board up at night knowing that it had to succeed."

He saw that pricing Novazyme would likely become a major

Abbey Meyers and NORD



Abbey Meyers played an important role in the passage of the Orphan Drug Act. Her son suffered from Tourette's syndrome. His treatment included 'off-label' prescriptions for a drug that was found in post-market studies to be ineffective for its intended use. Johnson & Johnson discontinued the product, arguing that there were too few Tourette's patients to make it economically viable. Meyers organized a grassroots campaign that persuaded company executives to reverse their decision. She then formed the National Organization of Rare Disorders (NORD) which pressured Congress for legislation.

When an episode of the popular NBC drama, 'Quincy, MD,' featured a character with Tourette's who was unable to get treatment, thousands of letters poured in to Meyers' organization. The next season, NBC broadcast an episode of the show entitled 'Give Me Your Weak' that again put NORD's message in front of millions of primetime television viewers. The impact was such that the star of the show, Jack Klugman, was invited to make a statement before Congress in support of orphan drug legislation. Public awareness of rare genetic diseases was heightened, and the nation made a commitment to help.

obstacle. Investors were encouraged by the firm's performance. They hoped to compete with Genzyme, not join it. Moving a product into clinical testing would set the stage for a lucrative public offering. Crowley needed to secure a valuation on the order of that potential return. He was not optimistic, but managed to negotiate a deal in which the Bostonians gave up $137.5 million, with additional payments contingent on the future performance of Canfield's technology.

It was enough. Novazyme became a wholly-owned subsidiary of Genzyme, and Crowley became a Senior Vice-President with responsibility for Genzyme's Pompe program – the largest and most expensive R&D project in the company's history. Crowley had put together a wonderfully cohesive organization at Novazyme by stressing patient advocacy as a core element of the company's mission. Genzyme CEO Henri Termeer wanted to encourage the same spirit in Genzyme's Pompe work. He later told the Wall Street Journal, "I wanted John to come in here, make a lot of noise, shake every corner of the company, and get things moving."

THE MOTHER OF ALL EXPERIMENTS

Genzyme was prepared to spend unprecedented sums on Pompe, but it could not afford to take four independent research programs forward. From the enzymes under development at Duke, Pharming, Novazyme, and Genzyme, the company needed to select one on which to concentrate its efforts. Crowley drew up a plan to conduct a rigorous test in mice in 2002. The trial was so important that it became known in Genzyme lore as the "Mother of All Experiments." Managing the competition between the project teams required a good deal of diplomatic skill.

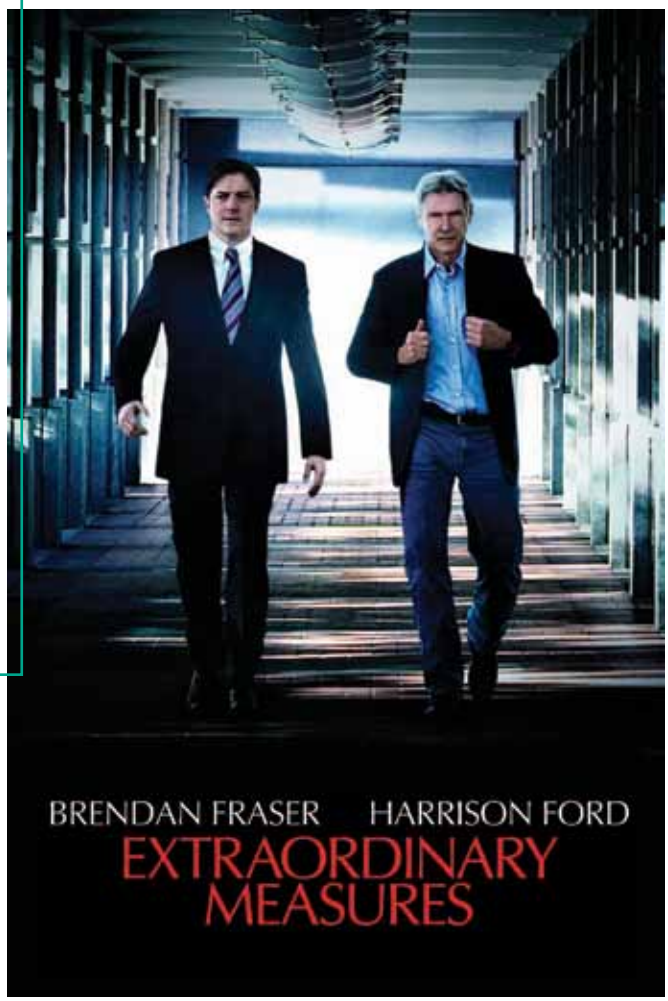
Each of the four therapies was at a different stage of development. Canfield's modified enzyme was promising, but less advanced, and still not ready for a trial with human beings. It was a longshot. The process was blinded. Enzyme supplies were color-coded and stripped of all other identifiers. Only two people at Genzyme knew which was which. The result was a virtual tie between two of the candidates. The final selection was based on manufacturing yield because very high doses were required to produce therapeutic effects – twentyfold higher than replacement therapies for other LSDs. The ultimate winner of the contest was an enzyme that had been developed in-house at Genzyme with a high-producing CHO cell line.

The next step was a global clinical trial, a colossal undertaking. As the experimental therapy moved closer to the medical marketplace, Crowley entered what he calls the most difficult period of his career. Scaling up enzyme production remained difficult. There was not enough GAA to conduct a meaningful clinical trial with older children or adults. The trial was designed for infants and children up to three years old. Megan and Patrick did not qualify. John Crowley was shipping medicine to patients all over the world, but time was running out for his own children. Doctors estimated that they had less than a year to live.

Genzyme's physicians sought a scientific rationale for treating Megan and Patrick. A sibling trial was proposed, a comparative study of the same therapy administered to patients carrying the

Extraordinary Measures

In 2003, the Wall Street Journal published an article on the Crowley family saga. So many readers were touched that the author, Geeta Anand, expanded the story into a full-length book. In August 2006, HarperCollins published **The Cure: How a Father Raised $100 Million – and Bucked the Medical Establishment – in a Quest to Save His Children**. Hollywood soon came calling. Harrison Ford expressed interest in adapting a movie screenplay. The end result was **Extraordinary Measures**, released in 2010, with the marketing tag-line, 'Don't hope for a miracle. Make one.' Details of the story were altered for dramatic effect, but according to Crowley, the film "captured the emotion in everything the family lived through."



same mutations in the GAA gene, but presenting with different clinical manifestations. Megan was stronger than Patrick. A study of how each responded to the drug could provide the company and regulators with important information regarding how to prescribe and administer it. Genzyme approached the Children's Hospital of Philadelphia about serving as a trial site. The institution was uncomfortable with the appearance of enrollment bias and declined.

The Crowleys were crushed by the news. John cast about for an alternative means of getting medicine to his children. He dreamed one night of simply taking enzyme from the company to treat Megan and Patrick himself. He knew better than to do that, but then, without consulting his colleagues, arranged for a sibling trial to be conducted at the University of Florida. Company officials were incensed by the maverick gambit, and problems in the trial design forced them to cancel it. CEO Henri Termeer commented, "You can't blame the guy for trying, but in the end, we had the systems in place to rein him in."

Genzyme made another attempt to set up a sibling trial, this time at St. Peter's University Hospital in New Brunswick, New Jersey. Crowley resigned from Genzyme in order to eliminate any potential conflict of interest. The protocol was approved. In January of 2003, John pressed a button at St. Peter's to begin the infusion therapy for Megan and Patrick. The Genzyme ERT saved their lives.

Today, Megan and Patrick are both in public high school in Princeton, NJ, a sophomore and freshman, respectively. Their muscles remain weak and they are still dependent on ventilators, wheelchairs, back-up batteries, and nurses, but they are stable and healthier. Their hearts, once dangerously enlarged, have returned to normal size. In April 2006, the FDA concluded its review of clinical evidence on the safety and efficacy of Genzye's enzyme replacement therapy for Pompe disease, and approved sales of the product under the trade name Myozyme®. When Megan Crowley was diagnosed with Pompe disease in 1998, her parents were told, 'There is no treatment.' Now, thanks in part to John Crowley's determined efforts, many families dealing with diagnoses of rare genetic disorders are told, 'Here is what we have for you…'

AMICUS THERAPEUTICS

Crowley's short but pressurized stints at Novazyme and Genzyme supplied him with valuable experience as a biotech executive. He felt equipped to do more in the field. For a time, he worked in the Princeton office of the venture capital firm, Domain Associates, evaluating life science investment opportunities. He also remained active in rare disease advocacy. In the summer of 2004, Crowley was offered the CEO post at Amicus Therapeutics, a newly-seeded startup that planned to develop 'next-generation' therapies for

The Amicus Therapeutics team
Opposite: The Crowleys (from left) Megan, John, John Jr., Aileen, and Patrick, on vacation in Vail, CO, 2012

LSDs. He declined, but agreed to serve on the company's board of directors.

Amicus was operating in an incubator space in New Jersey with a handful of employees. The firm made steady progress in animal studies over the course of the year. By December 2004, Crowley was ready to join. He had become convinced that the company's technology represented the next best chance to improve health and quality of life for patients with Pompe disease and other rare disorders. Myozyme was a life-saving therapy, but not a perfect drug, and not a cure. Amicus had a chance to elevate the field once more. Its R&D teams were working to extend pioneering research conducted by company co-founders Robert J. Desnick and Jian-Qiang Fan, geneticists and leading authorities on LSDs at New York University's Mount Sinai School of Medicine.

In many LSDs, the central problem is the manufacture of misfolded, dysfunctional enzymes. Amicus is developing orally-administered small molecule 'chaperones' that target, bind, and stabilize misshapen proteins, and facilitate proper folding. The goal is to restore rather than substitute, in order to circumvent delivery and immunogenicity problems that continue to plague many ERTs. Chaperone molecules can be employed in conjunction with ERTs, but also as independent monotherapies. Amicus and development partner GlaxoSmithKline are currently testing a chaperone for Fabry disease (migalastat HCl) as a monotherapy in a pivotal Phase III clinical trial. Preliminary results are expected later this year. A chaperone-ERT combination product for Pompe disease is in Phase II testing, and the company is investigating applications for Gaucher and other orphan diseases as well.

Crowley's work at Amicus is no longer driven by the desperation and intense emotion that motivated his entry into the field at Novazyme and his direction of the Pompe disease program at Genzyme. He remains unapologetic, however, about occasionally subordinating objectivity to passion and sentiment in organizational leadership and strategic decision-making. To recreate the patient-centered culture that he established at Novazyme, Crowley supplements standard mission statement ideals (teamwork, communication, and excellence, for example -- organizational habits or characteristics that contribute directly to the efficient execution of operational objectives) with others that are unique to Amicus. In the articulation of core values for Amicus, he unabashedly affirms compassion and humanitarian service, virtues not routinely viewed as assets in the competitive worlds of science and business, and sometimes regarded as liabilities.

In practice, Amicus works closely with patients and rare disease advocacy organizations. The company disseminates information on disease management, treatment options, access to experimental therapies, and clinical trial enrollments. It connects patients and families with support services and resources that can help them interact productively with medical professionals, negotiate insurance and reimbursement mazes, and effectively manage various daily coping challenges. The company is also engaged in broader forms of outreach including public education, public policy formation, and community-building among rare disease advocacy groups. In organizing these various functions, Amicus draws on the practical wisdom of its chief executive, the father of two children suffering from a severely disabling lysosomal storage disorder.

THE ORPHAN DRUG ACT

The conflicts of interest and commitment that Crowley wrestles with in his professional life are reproduced on broader scales in political frictions and moral dilemmas that rare diseases generate in society at large. Drug development is an enormously expensive undertaking. In economic terms, attending to the medical needs of small patient populations is wasteful and unsustainable. In moral terms, from a purely utilitarian point of view, it is unfair and unjust.

To allocate scarce healthcare resources for the treatment of rare diseases is to resolve – provisionally – essential tensions between equality, justice, and individual rights as social values. It favors rights. Individuals, organizations, and states treat rare diseases

despite the high cost because failing to do so would constitute abandonment. The story of the Crowley family has moved mass audiences because it resonates with a broadly shared and deeply ingrained sentiment – abandonment is tragic and ethically unsettling.

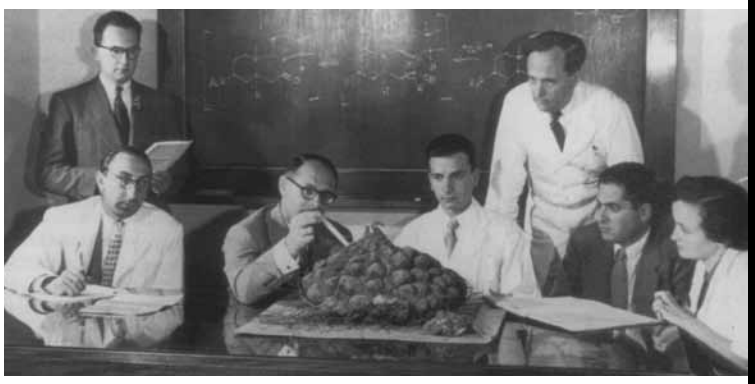
The commitment of the American people to beneficence, charity, and medical rights was expressed materially in the Orphan Drug Act (ODA) of 1983. The ODA apportions grants to support research on new treatments for rare ailments and tax credits for offset the costs of clinical testing. Manufacturers of orphan drugs do not have to pay FDA user fees, and orphan products are usually given expedited reviews; regulatory delays have been minimized. The clinching incentive furnished by the Act is the provision of seven years of exclusive marketing rights to manufacturers of orphan drugs. Without the ODA, it would be economically infeasible for biotech and pharmaceutical companies to develop new treatments for rare diseases. Thanks to this piece of legislation, there are more than 350 FDA-approved orphan drugs on the market in the United States, products that ease pain and suffering and frequently save lives in previously neglected patient populations.

John Crowley has been a vocal champion and defender of the ODA. In 2010, he testified on behalf of the Biotechnology Industry Organization (BIO) before the Senate Committee on Health, Education, Labor and Pensions. He reminded the august body that the Orphan Drug Act has effectively stimulated innovative R&D projects, improved the lives of millions of patients and families, and helped to launch a new industry. Crowley went on argue that if these benefits are to be maintained in increasingly challenging economic conditions, and in the era of genomics – in which the identification of 'ultra-rare' diseases will almost certainly accelerate – the incentives offered by the Orphan Drug Act need to be updated. Our beneficence will be tested again. **Ø**

Alejandro Zaffaroni's remarkable career in science and business spanned six decades. He was an early contributor to the technical and commercial success of Syntex, which became, in the 1960s, the first new entrant to the North American pharmaceutical industry since the turn of the twentieth century. He participated in the invention of more than a hundred innovative processes and devices that improved drug discovery, drug delivery, and methods of biochemical analysis. He established and directed nine pioneering biomedical startup companies – the last at the age of eighty-three. He mentored scores of scientists and executives, and served as an advisor to dozens of entrepreneurial life science firms. Through all of it, Zaffaroni exerted a powerful influence on the development of the biotechnology industry in the San Francisco Bay Area. Here, we present the first part of his story…

Alejandro Zaffaroni

The Archetypal Bioentrepreneur



Syntex press conference to announce the synthesis of cortisone, 1951. George Rosenkranz, center

Early Years

Alejandro Zaffaroni was born on February 27, 1923 in Montevideo, Uruguay. From an early age, he was drawn to science and medicine. He studied a pre-med curriculum at the University of Montevideo, became fascinated by biochemistry, and decided to make a career in the field. Advanced training was not available in Uruguay, so he applied to PhD programs abroad. He received letters of acceptance from the Harvard University and Rochester University. In July of 1945, as World War II was winding down, Zaffaroni hitched a ride on a US military cargo vessel bound for New York City.

His entrepreneurial bent was already evident. On arriving in the United States, Zaffaroni went directly to Harvard, where he learned that graduate research projects were selected by advising professors. He didn't like the idea. He traveled on to Rochester. He found that the department chair at Rochester, Walter Ray Bloor, encouraged students to pursue independent research. Bloor also promised lab space. That suited the young scientist: "The notion that I could be my own master and have my own place where I could close the door and work in my own little kingdom was extraordinary. I was thrilled and accepted the Rochester offer immediately."

Zaffaroni chose to investigate corticosteroids, regulatory hormones produced by the adrenal cortex. The first molecules in the class had been identified a decade earlier by several American research groups. As the 1940s drew to a close, biochemists had begun exploring possible medical applications. The chemical structures of several corticosteroids had been identified, but there were no analytical techniques for identifying and measuring those secreted into the bloodstream. Developing this capability promised to enhance understandings of the roles played by corticosteroids in metabolic regulation. Zaffaroni took up the problem as his thesis topic.

He came across a scientific paper by British researchers Archer J.P. Martin and Richard L.M. Synge that described the use of partition chromatography to separate and analyze closely-related, water-soluble proteins and protein hormones by weight. It was an important invention – Martin and Synge were awarded a Nobel

THE HISTORY OF CORTISONE

Cortisone was first isolated in the 1930s, from the adrenal glands of cattle. During World War II, the US government contracted Merck & Co. to synthesize and manufacture it. Director of Research Lewis Sarett called the hormone Compound E, and worked out a partial synthesis. Yields were low. In 1948, Mayo Clinic rheumatologist Phil Hench requested Compound E to treat a woman with severe rheumatoid arthritis. Sarett sent Merck's last gram. The result was miraculous. After only a few days, the previously bedridden patient could move about, and even dance. Hench persuaded Merck officials to supply more of the steroid. The drug had a similar therapeutic effect on other patients. Hench published his findings in 1949, and the following year shared a Nobel Prize with Edward C. Kendall and Tadeus Reichstein, the chemists responsible (independently) for isolating the hormone.

Pharmaceutical companies raced to develop a more efficient method of production. Chemists at Syntex made a breakthrough in 1950. They synthesized cortisone from a plant source, diosgenin, derived from an inedible Mexican yam, rather than expensive animal extracts. At the time, Alejandro Zaffaroni served the company as a consultant: "The experience convinced me that first-rate research in steroids was possible south of the border." The Upjohn Company of Kalamazoo, Michigan soon developed an even better method of enzymatic synthesis via microbial fermentation. Upjohn became the leading manufacturer of cortisone, but the company's success was a boon to Syntex as well. The Upjohn process began with the oxygenation of progesterone, also derived from disogenin. Large quantities progesterone were required. Only Syntex could provide it.

In the end, cortisone's status as a wonder drug was undermined by its side effects, including edema and hypertension, but its remarkable therapeutic properties stimulated the formation of steroid research programs all over the world in both academia and industry.

Top:
Carl Djerassi
Above:
George Rosenkranz

THE ORIGINS OF SYNTEX

Syntex (a combination of synthesis and Mexico) was founded in 1944, in Mexico City, by two chemists, American Russell Marker and German Federico Lehmann, and Hungarian lawyer Emeric Somlo. The company was based on Marker's research on the Mexican yam (*Dioscorea mexicana*), known colloquially as *cabeza de negro.* After working out a method – known as the 'Marker degradation' – for synthesizing mammalian sex hormones from plant steroids, Marker had learned that the yams contained high concentrations of diosgenin. He went to Mexico and collected enough diosgenin to synthesize two kilograms of progesterone, a hormone that regulates pregnancy. Two kilograms was then half of the world's total supply. Marker approached Solmo, who owned a Mexican company called Laboratorios Hormona. The pair decided to start Syntex.

The founders soon fell out, and Marker left. Searching for another technical director, Solmo found George Rosenkranz, a Hungarian chemist who had fled the Nazi invasion of his homeland and spent the war years working as a refugee in Cuba. Rosenkranz was recruited to reconstruct and improve Marker's chemistry. American chemist Carl Djerassi joined in 1949, and Zaffaroni two years later. In 1951, Syntex switched to collecting the dioscorea species *barbasco*, which contained even greater amounts of diosgenin. This allowed the company to build a thriving business that supplied large quantities of progesterone to American pharmaceutical companies. Together, Rosenkranz, Djerassi, and Zaffaroni – known as the 'three musketeers' – built Syntex into a world-class center of industrial chemical research.

Prize for it in 1952. Zaffaroni modified the method for use with insoluble lipids, including steroid hormones. The 'Zaffaroni system,' became an essential analytical tool in steroid synthesis. It was the only reliable method of identifying and characterizing steroid hormones with high degrees of specificity. Zaffaroni gained a bit of visibility and acclaim when the Upjohn Company used his invention to manufacture the new steroid wonder drug, cortisone.

Syntex

On completing his PhD in 1949, Zaffaroni accepted a two-year fellowship at the National Institutes of Health (NIH), where he carried on work in steroid biosynthesis. Afterwards, he received multiple job offers, including an invitation to join the one of the world's top steroid labs at the Sloan-Kettering Institute. He was also offered a full professorship at the University of Utah, an assistant professorship at Harvard, and positions at several major pharmaceutical firms. Zaffaroni elected instead to join a little-known Mexican chemical company called Syntex SA. He went to Syntex for the same reason he had chosen Rochester over Harvard – the company offered scientific freedom, a stimulating and open-ended research agenda, and opportunities to innovate.

Zaffaroni had been introduced to Syntex's chief chemist, George Rosenkranz, at the Laurentian Hormone Conference in New Hampshire, in 1950, while at NIH. The pair had struck up a friendship. Zaffaroni became a consultant to the company. In July 1951, he signed on as Associate Director of Biochemical Research, and moved to Mexico City. He intended to use his paper chromatography system to work on cortisone analogs and related compounds.

Syntex's main lines of business were dependent on the extraction of disogenin, a phytoestrogen, from Mexican yams. The

From the 1963 Syntex Annual Report- at the Palo Alto building site

substance served as the starting raw material for the synthesis of steroid hormones. The yams came from the state of Veracruz. Zaffaroni observed that the quality was highly variable. The peasant farmers who dug up the tubers frequently left them out in the elements or in storage for extended periods before transporting them. The roots often arrived in Mexico City partially dried out or partially putrefied. Yields of diosgenin were inconsistent and unpredictable. "It wasn't really a good deal for anyone," Zaffaroni said later. "The *campesinos* weren't paid much, and we were buying a rotten product."

Zaffaroni volunteered to improve the collection process himself. He traveled to rural Veracruz to set up a small shop for the preliminary treatment of fresh root supplies. He established a relationship with Don Emilio Fortanet, an old man who ran a yam collecting business. Fortanet agreed to help Syntex procure a better product, but he didn't want to work at the beck and call of big shots in Mexico City. He agreed to set up a processing plant so long as he did business exclusively with Zaffaroni, whom he trusted.

Zaffaroni found the experience exhilarating, even though the accommodations were spartan and the climate was disagreeable: "The three-room 'hotel' in the jungle was often flooded by rainwater, in which case we wore high rubber boots to wade through two or three feet of rainwater in the lobby. We tried to sleep in our clothes on cots, but the place was hot and humid and insects of all sizes kept us awake—huge, heavy beetles and mosquitoes that buzzed around the room all night. In desperation, I would turn on the fan to get rid of the bugs, but the fan was so loud I could only stand it for a short time before turning it off. That was how the night passed: on and off, on and off."

Despite the hardships, Zaffaroni standardized the operation, increased the workers' pay, and made the extraction process more efficient— the plant processed four hundred tons of plant material per month. "Although I didn't realize it at the time," Zaffaroni reflected, "the experience of organizing the root collection and improving our production was the start of my learning to be a manager and entrepreneur as well as a scientist."

In 1956, Solmo sold Syntex to New York financier Charles Allen. Allen promoted Rosenkranz and Zaffaroni to executive management positions. The reorganization provided a tremendous opportunity. Rosenkranz and Zaffaroni saw an opening to transform Syntex from a bulk supplier of steroids into a full-fledged pharmaceutical company. The company had assembled a supremely talented team of scientists that included Bert Bowers, Carlos Casas-Campillo, Carl Djerassi, Luis Miramontes, Howard Ringold, and John Zderic. Syntex was ready to take on the world.

The company's move into pharmaceuticals was realized through the development of a topical corticosteroid called Synalar®. Company chemists synthesized the compound in 1958. Its anti-inflammatory properties made it ideal for treating psoriasis, an autoimmune disorder of the skin. One of the company's academic advisors, dermatologist Judson Schultz, of the University of Southern California, wanted to improve the absorption of the steroid by psoriatic lesions. He had the idea to cover the applied compound with Saran Wrap™ in order to make the drug more effective. The contraption worked.

The low-tech 'occlusive' method proved its mettle in clinical trials, and enabled the company to dominate the market for topically applied anti-inflammatories. Each tube of the cream came with a miniaturized container of Saran Wrap. "I have no doubt," Zaffaroni has said, "that Syntex's success as a pharmaceutical company was due to Synalar. Synalar made Syntex a highly profitable company and showed that we could successfully develop and market a drug."

From the 1965 Syntex Annual Report- lobby of the Palo Alto administration building

Syntex Laboratories, Palo Alto, California

Rosenkranz and Zaffaroni realized that if Syntex was to become a competitive pharmaceutical company with staying power, it would need to establish a foothold in the US market. A plan was devised to establish a pharmaceutical subsidiary north of the border. A large chunk of Syntex's research operation would relocate so the company's laboratory and clinical studies would qualify for review by the FDA.

Instead of setting up shop in New Jersey, where many major pharmaceutical companies were located, Rosenkranz and Zaffaroni, at the urging of Carl Djerassi, decided to settle in the Stanford Research Park in Palo Alto, California. There, the firm could take advantage of proximity to Stanford University's impressive roster of world-class biologists and biochemists. Djerassi had recently left the company to accept a faculty position at the school, and with support from Syntex, had set up the Institute for Molecular Biology on Porter Drive.

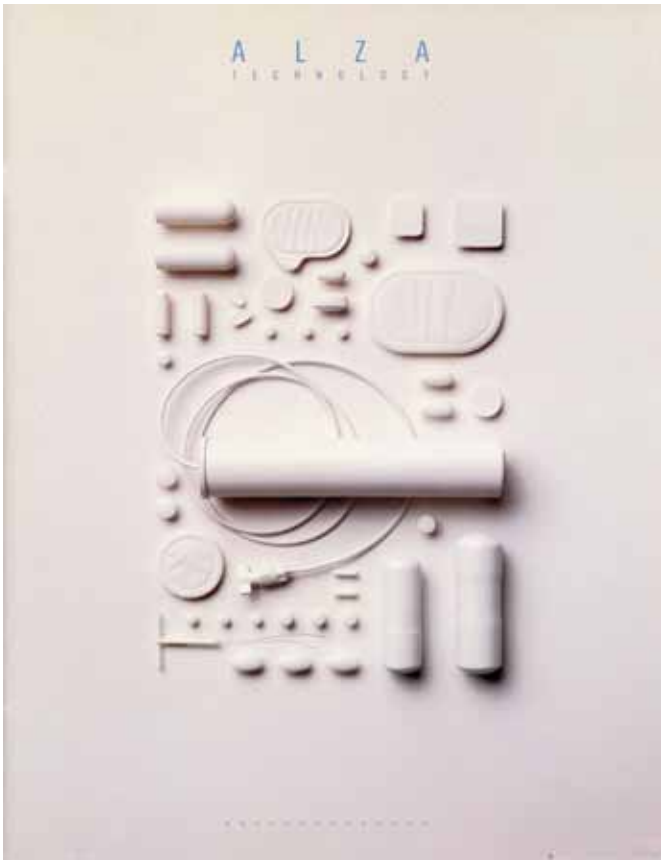
Zaffaroni was appointed President of the new subsidiary. He moved to Palo Alto in 1962 to begin setting up the operation. He directed construction of a new facility in the research park, overseeing every detail of the design. He insisted on the highest architectural standards, and a physical layout that encouraged collegiality. He incorporated an area for temporary art exhibitions and other public events. He was adamant that the building needed to be impressive: "I wanted the world at large to see that we weren't some fly-by-night operation, but a high-quality American company, here for the long term and part of the community." Syntex researchers moved into the new research center in 1964.

The culture of the enterprise reflected the spirit of its leader – experiment and innovation were encouraged in both science and management. Zaffaroni introduced the idea of free-standing research institutes as part of his vision for the company's maturation: "We would grow, I hoped, not by expansion, the way most American corporations did, but in a much stronger and more creative, even biological way, the way cells themselves grow: we would grow by division." The institutes gave researchers a great deal of freedom and autonomy within clearly delimited areas of responsibility.

The direction of research was largely decentralized, but the company remained intensely focused on steroid research. Synalar was by far the company's leading revenue generator. An oral contraceptive became a second highly profitable product. Syntex was already well-known for its role in the development of the birth control pill. George Rosenkranz, Carl Djerassi, and Luis Miramontes had synthesized and patented the key active ingredient, norethindrone, in 1951, but Syntex had no plans at that time to market a contraceptive. Djerassi has said, "Not in our wildest dreams did we imagine it." Although convulsive change was on the way, Western culture in the early 1950s was simply not yet prepared for a birth control pill. G.D. Searle introduced the first oral contraceptive, Enovid®, in 1960. Syntex followed in 1964 with a safer, more effective product, called Norinyl®.

To wring value from the many additional lines of research generated by Syntex's creative scientists, Zaffaroni favored the creation of spin-off companies. Syva Corporation was an important joint venture between Syntex and Varian Associates, one of Silicon Valley's first high tech companies, the first tenant in the Stanford Research Park, and a pioneer in the development of nuclear magnetic resonance (NMR) imaging. The subsidiary, established in 1966, eventually became a diversified diagnostics and instrumentation company. Zaffaroni also pushed for the creation of a satellite com-

Left: Zaffaroni with Martin Gerstel
Below: ALZA product brochure



pany focused on pest control using an insect-molting hormone, ecdysone. That project became Zoecon, a company led by Carl Djerassi until it was taken over by Occidental Petroleum in 1978.

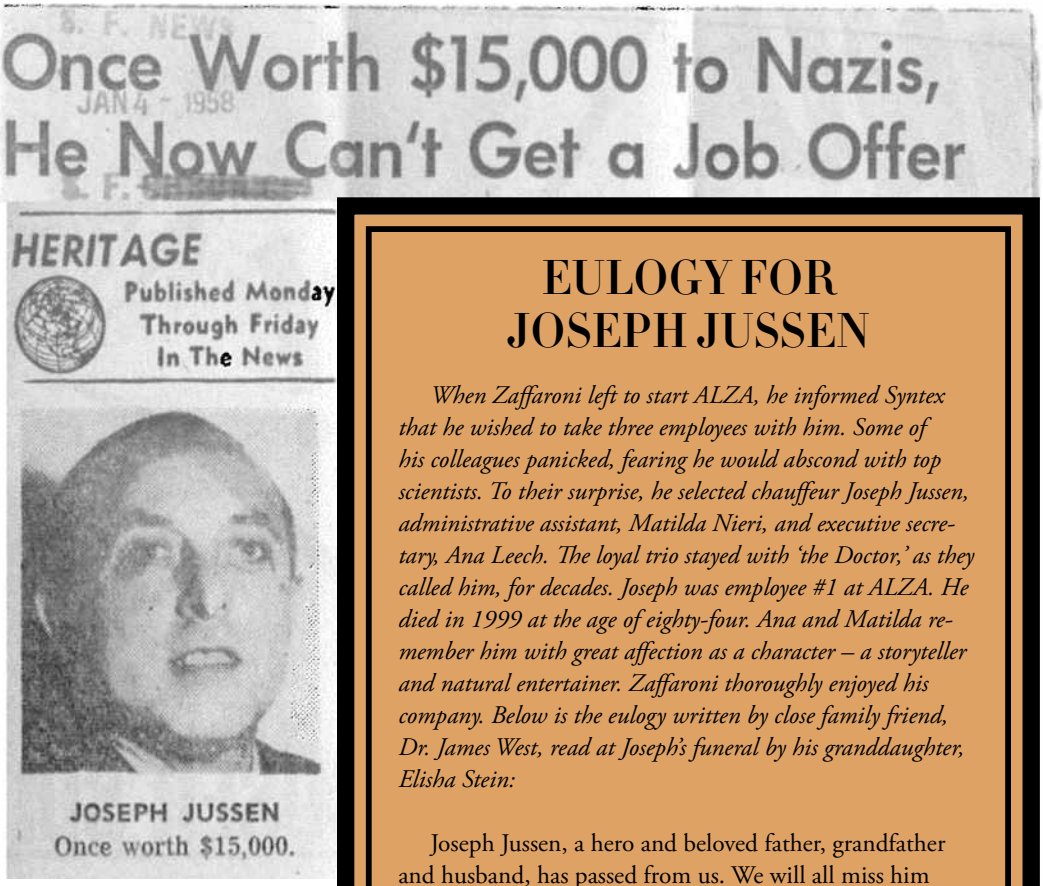
Eventually, Syntex's innovative spirit was stifled by its own spectacular growth. The company's great value made the board of directors wary of taking risks. Some members preferred a conventional growth by acquisition strategy to Zaffaroni's free-wheeling research-driven approach. By the late 1960s, Zaffaroni wanted Syntex to explore new drug delivery technologies, which he believed could dramatically improve the safety and efficacy of existing pharmaceutical products, but he could not persuade the company to invest. It was time for Zaffaroni to leave: "Most large industrial enterprises are not responsive to innovation, and I suspected that Syntex was turning into that type of company."

ALZA

In 1968, with blessings from his friends, George Rosenkranz and Charlie Allen, Zaffaroni founded a new company called ALZA to develop innovative methods of drug delivery. Initially, the firm was bankrolled with $3 million of Zaffaroni's own money, proceeds from sales of Syntex stock: "I wanted to put my head on the platter," he said, "to put everything on the line and pursue the concept of drug delivery until we absolutely made it work or went under trying."

Zaffaroni was certain that the time was ripe. "Centuries had passed," he later wrote, "without significant changes in drug delivery; pills, tablets, inhalations, ointments, powders, and solutions were all in use before 1800. Capsules were developed around 1840, injections around 1850, and intravenous drug administration sometime during World War I. In the 1960s, when I was thinking about all of this, most drugs were still given in the form of one pill several times a day, a practice that struck me as illogical at best, and potentially quite harmful."

Traditional means of administering drugs, such as pills or injections, are problematic in a number of ways. They put drugs rapidly into the bloodstream at uncontrolled rates. Active ingredients are often wastefully metabolized, and frequently produce distressing or harmful side-effects. The therapeutic benefits of the drug quickly subside; more pills or injections are required, and another round of side-effects ensues. Improving drug delivery systems, Zaffaroni believed, would have great commercial appeal.


S. F. NEWS
JAN 4 - 1958
Once Worth $15,000 to Nazis, He Now Can't Get a Job Offer
HERITAGE
Published Monday Through Friday In The News
JOSEPH JUSSEN
Once worth $15,000.

To organize and run the business, he hired twenty-six year-old Martin Gerstel fresh out of the Stanford School of Business. Gerstel had recently appeared on the cover of *Business Week* magazine, and in an article profiling the nation's top business schools and business students. He became ALZA's Treasurer and Vice-President of Finance. He quickly adapted to Zaffaroni's unique style of business and management. "I learned," says Gerstel, "that if you wanted him to do something, the best thing to do was to say to him, 'This hasn't been done before.'"

Zaffaroni set about hiring the best people he could find. He brought in an extraordinary team of engineers, biologists and chemists, and promoted a collaborative culture based on "freedom and resources to make the most of collective talents." He encouraged interdisciplinary approaches to product development. He also sought to "stimulate ALZA employees to a high sense of personal contribution and accomplishment by placing great emphasis on opportunities for the individual's creativity and self-realization in his or her professional work."

ALZA became a public company in 1969, the first US company without revenues to do so. Then, through a series of creative private and public financings, substantial funds were raised for the support of the company's product development projects. Over the next several years, ALZA's development teams invented a series

EULOGY FOR JOSEPH JUSSEN

When Zaffaroni left to start ALZA, he informed Syntex that he wished to take three employees with him. Some of his colleagues panicked, fearing he would abscond with top scientists. To their surprise, he selected chauffeur Joseph Jussen, administrative assistant, Matilda Nieri, and executive secretary, Ana Leech. The loyal trio stayed with 'the Doctor,' as they called him, for decades. Joseph was employee #1 at ALZA. He died in 1999 at the age of eighty-four. Ana and Matilda remember him with great affection as a character – a storyteller and natural entertainer. Zaffaroni thoroughly enjoyed his company. Below is the eulogy written by close family friend, Dr. James West, read at Joseph's funeral by his granddaughter, Elisha Stein:

Joseph Jussen, a hero and beloved father, grandfather and husband, has passed from us. We will all miss him dearly. Joseph was a passionate man, with a giant heart and an incredible love for life. The memory of Joseph's many acts of kindness, and the joy and laughter he brought to friends and strangers alike, will last long after his passing. Always willing to share what he had with others and to play the part of the fool, he touched the hearts of so many people and spread joy wherever he went. Who could ever forget the sight of Joseph dancing the Hula, dressed in his grass skirt, outrageous wig, and coconut shell bra?

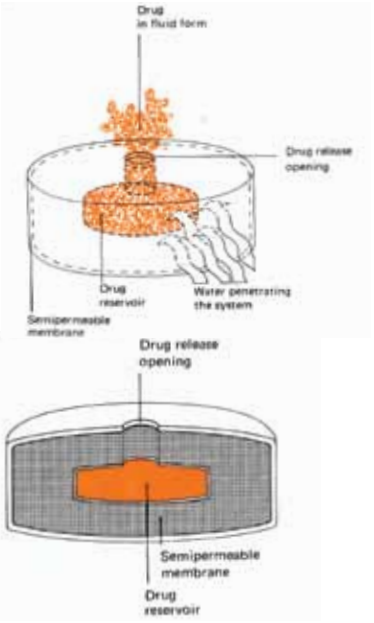
Joseph meant different things to different people. To the Jews he smuggled across the borders of Holland, he was their personal savior and hero. To many villagers of Indonesia, he was the kind soldier who brought food for their hungry children. To his family, he was a wonderful husband, father, grandfather and friend. To others, he was the life of the party, entertaining all with his jokes, wild antics, warm hugs and beautiful accordion music.

The youngest of 13 children, Joseph was orphaned when his parents died in the bombing of Holland at the end of WWI. Raised by his sister, Anna, Joseph grew up fast, tough and street smart. During WWII, Joseph worked for the Dutch Underground. He saved many Jewish lives by helping them cross the borders under the cloak of darkness. Joseph was eventually captured by Nazi soldiers while attempting to smuggle a truckload of provisions for the resistance. He was tortured for weeks, but refused to release the names of his accomplices, claiming that he operated alone. Honored and respected for his courage under torture, Joseph's friends devised a bold scheme for his escape.

continued next page...

THE OROS SYSTEM

The OROS® Push-Pull Osmotic Pump system allowed for the time-controlled release of a drug in pill form. OROS stands for 'oral-osmotic' (osmosis refers to the movement of solvent molecules across permeable membranes). ALZA scientists John Urquhart and Felix Theeuwes designed a pill composed of a semi-permeable lipid membrane surrounding an osmotic drug-containing core. A laser was used to create a tiny hole in the membrane. When the pill reached the gastrointestinal tract, water seeped through the membrane, gradually dissolving the drug. The added water pressure pushed the drug solution through the tiny hole in the membrane for release into the bloodstream. The result was a constant-flow delivery that increased therapeutic efficacy while minimizing side effects.



of improved drug delivery technologies. In 1974, the FDA approved the Ocusert® system, a time-released ocular insert to treat glaucoma. Previously, patients had to use eye drops multiple times a day, leaving them with hours of headaches and blurry vision. The Ocusert system delivered low, steady doses of pilocarpine, a compound that reduces intraocular pressure. The Ocusert system was followed by Progestarset, an intrauterine time-release contraceptive device, the OROS pill delivery system, and transdermal patches for motion sickness and smoking cessation, among many others.

Drug companies were not terribly interested in any of it. They remained locked into the chemical paradigm of pharmaceutical development: drugs are improved by moving molecules around. Even if the new technologies worked well, the big companies were in no hurry to implement them. They had few incentives to move so long as their competitors remained similarly complacent. Improving drug delivery remained a mostly foreign concept. According to Zaffaroni, Martin Gerstel once told a pharmaceutical executive that ALZA was in the drug delivery business; the executive inquired about the company's fleet of trucks.

ALZA's chemistries and engineering designs were immaculate, but the company's technical achievements did not translate into immediate commercial successes. Ocusert failed to live up

...EULOGY, continued from previous page

On the day of his scheduled execution, Dutch resistance fighters, dressed in Nazi uniforms and speaking perfect German, marched through the local prison, to Joseph's cell, demanding to escort the prisoner to the firing squad. Upon reaching the yard, they boosted Joseph over the prison walls to a waiting car. His picture was posted all over the area with a large reward offered for information leading to his capture.

With the end of the war in Europe, Joseph joined the Dutch Marines. He was sent to Indonesia. Indonesia brought Joseph a life-long love affair with both the tropics and his future wife, Jackie. Always with an eye for beautiful women, he passed Jackie on his motorcycle while she was walking along the roadside. Quickly turning around, he offered her a ride. Jackie turned down the offer, claiming that she was waiting for a ride from a friend and had to return to tend to her six children. Joseph passed by a couple times more (he sure could be persistent!), before giving up. As fate would have it, a party brought them together a few weeks later. Much to Jackie's embarrassment, he asked her "How are your six children?" Her friends exclaimed, "Why, Jackie has no children!" And so began their life together.

The flamboyant Dutch marine showered her with gifts and expensive clothing. Jackie wondered at how a simple soldier could afford such luxuries. With a shake of the head and a finger raised to his lip, Joseph answered with his classic "Never ask!"

When the Dutch departed from Indonesia, Jackie and Joseph settled in Holland, where their Daughter, Josie, was born. Seeking to provide a better life for his family, Joseph came to America. Hungry and destitute, Joseph was on his last legs and ready to concede defeat when he told his story to a passerby. This man turned out to be a reporter, who published an article about Joseph in the *San Francisco Chronicle*. Once again, Joseph was saved in the nick of time! On the day before his return flight to Holland, Mr. Stevens, a retired stockbroker, drove up in a Cadillac and offered Joseph a job. Weeks later, he sent Joseph back to Holland to return with his wife and daughter. Their second daughter, Linda, was born a few years later.

After Mr. Steven's death, and a few odd jobs, Joseph had the great fortune to find a job working for Dr. Alex Zaffaroni, then president of Syntex Corporation. The rest is ALZA history. Many, many times I have heard Joseph say, "Never in the whole world was there as good a boss as Dr. Zaffaroni."

We are grateful for the time Joseph was able to spend with his daughters, Josie and Linda and his grandchildren, Joshua and Elisha. Joseph, we miss you so much! We love you Joseph. We will always remember your favorite saying, "Make you happy!"

Dynapol CEO
Steve Goldby

DYNAPOL: REGULATORY TROUBLE

Just as R&D programs at Syntex had done, ALZA's scientists and engineers generated more good ideas than they could properly develop in-house. In 1972, Zaffaroni created Dynapol (dynamic polymers) in order to spin out a promising technology. He appointed ALZA patent attorney Steve Goldby as CEO. The company aimed to make food additives with improved safety profiles. Dynapol scientists attached large polymer molecules to artificial colors, sweeteners, and preservatives in order to prevent absorption through the walls of the gastrointestinal tract. Early on, the company's main project was the invention of safe artificial sweetener. Cyclamates had been introduced as chemical sugar substitutes in 1958, but were banned by the FDA in 1969, when high doses in animal testing were found to produce a range of ill effects. Then, in the early 1970s, animal studies indicated that saccharin, a coal tar derivative that had been on the market for decades, was carcinogenic in rats. In 1973, the FDA required warning labels for saccharin, but did not impose a ban. Dynapol was largely dependent on a contract with the DeKalb Company. When saccharin was spared the regulatory death penalty, Dekalb elected to discontinue funding for Dynapol's work on a safer but more expensive sugar substitute. The young company carried on for a decade, but was caught in further regulatory snares, and never managed to gain momentum. Eventually, it went into liquidation.

to expectations as a revenue generator. It was an era before the widespread use of contact lenses. Older patients were generally leery about placing a small patch directly on the eyeball, and few ophthalmologists were willing to take the time to educate and encourage their patients to do so, especially when Merck had just released a once-a-day eye drop for glaucoma, Timoptic®.

It seemed as if the device was ill-fated from the start. Gerstel remembers receiving a phone call informing him that the plane carrying the first shipment had slid off the runway into San Francisco Bay. "That was not a good omen," he says. Progestasert was also star-crossed. It chances in the marketplace were seriously harmed by litigation and publicity surrounding the Dalkon Shield®, another intrauterine device introduced in 1970 by the A.H. Robins Company. The Dalkon Shield was linked to severe pelvic inflammation and many deaths. Progestasert was perfectly safe – it possessed an admirable safety record – but consumers were spooked.

The commercial failure of these technological achievements weighed heavily on Zaffaroni. "It was hard to accept the fact that such well-conceived programs could fail, and that even if our work was the best in the world, there was no guarantee of success. The repercussions of those failures for both ALZA, and me personally, were devastating and demoralizing. I felt that my idea of creating a full-fledged pharmaceutical company with its own sales force had failed. Our sales force had nothing to sell, and we were headed for bankruptcy."

By 1976, ALZA was on the brink. The firm was forced to lay off 200 employees, a third of its workforce. To keep the company afloat, ALZA executives knocked on the doors of multiple pharmaceutical, chemical, and oil companies in search of corporate partners – to no avail. Finally, the company negotiated a massive recapitalization with Ciba-Geigy in 1977, ceding full control to the European pharmaceutical firm in the process. "It was a difficult time for me," recalls Zaffaroni. "I had left one big company, only to find myself working for an even bigger, more bureaucratic one."

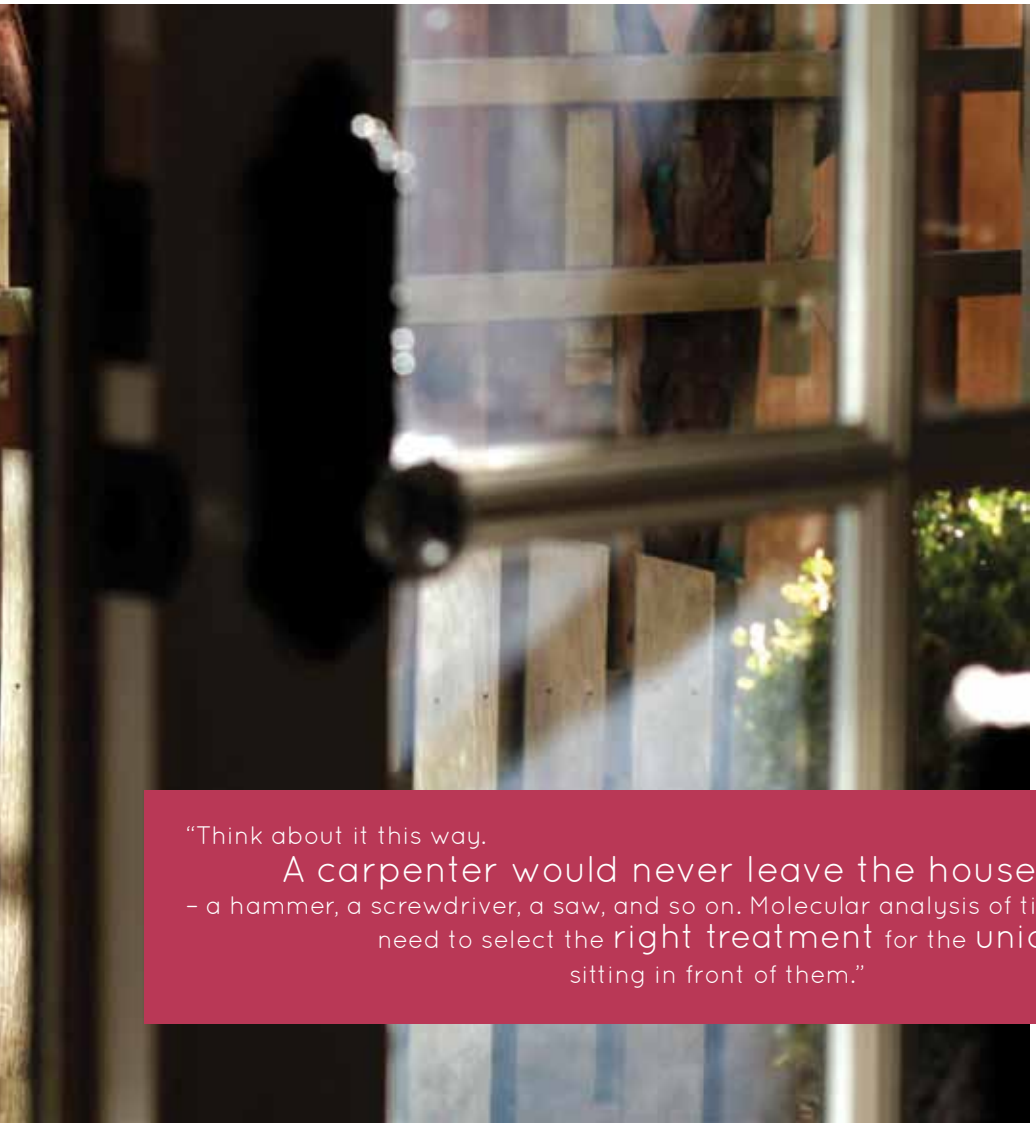
Entrepreneurship and innovation entail serious risks. Scientific and technological masterpieces do not automatically translate into commercial success. The company managed to survive, but at the cost of its autonomy. For Zaffaroni, the episode was a crushing disappointment and a turning point.

Stayed tuned for part II in the next issue. **Ø**

Storming the Silos

In Part I, we recounted how former oil executive Bonnie J. Addario survived lung cancer and embraced a new calling: patient activism. She started the Bonnie J. Addario Lung Cancer Foundation (BJALCF) with two goals: 1) to raise public awareness about the relative neglect of lung cancer in biomedical research, and 2) to help lung cancer patients navigate effectively through the healthcare system toward the best available care.

Addario soon realized the necessity of a third goal: to enlist the aid of physicians and biomedical scientists in the reorganization of cancer research. In November 2007, she convened the first annual BJALCF Lung Cancer Summit in San Francisco, and posed a simple question to an audience of prominent oncologists: "If money were no object, what would you do to increase lung cancer survival rates?"



"Think about it this way.
A carpenter would never leave the house without a full toolbox
– a hammer, a screwdriver, a saw, and so on. Molecular analysis of tissues is the tool that oncologists need to select the right treatment for the unique patients sitting in front of them."

Tissue is the issue

Dr. Harvey Pass, Director of the NYU Division of Thoracic Oncology, stood to respond: "We need a bio-repository operated by an honest broker, and collaborative agreements to ensure that institutions donate tissues." The fight against cancer in the emerging era of genomics and personalized medicine depends crucially on the identification of tumor biomarkers – mutated genes or molecules associated with the development of specific types of malignancies. Biopsied tissues are basic raw materials that researchers need to develop improved diagnostic tests and targeted therapies. As Bonnie puts it, sample collection is "a search for gold."

The value of biomarkers in the development of diagnostic tests and therapies has been amply demonstrated. In the case of lung cancer, for example, a genetic test is now available to detect a specific mutation in the gene that codes for a protein called epidermal growth factor receptor (EGFR). The mutation causes overexpression of the protein, which leads to aggressive forms of lung cancer (and colorectal, ovarian, and pancreatic cancers as well), tumors that readily metastasize and are resistant to standard chemotherapies. For lung cancer patients who carry the mutation, the best available drug is Genentech's Tarceva®. Tarceva targets EGFR and inhibits its biological action.

"Think about it this way," says Bonnie. "A carpenter would never leave the house without a full toolbox – a hammer, a screwdriver, a saw, and so on. Molecular analysis of tissues is the tool that oncologists need to select the right treatment for the unique patients sitting in front of them."

Oncologists have long collected and analyzed tissue samples in order to characterize, predict, and monitor the progression of tumors. It was never common, however, to share samples broadly. With limited tools and techniques for the investigation of cancer genetics and scarce understanding of the heterogeneity of cancer as disease category, demand was limited. Specimens were regularly discarded after testing. Now, however, genomics technologies permit far greater differentiation in tumor typing. Demand for specimens is growing. Comprehensive identification of mutations and gene expression patterns implicated in oncogenesis will require genomic analysis of large sets of tissue samples.

Group shot from the
ALCMI summit, 2009

Boom and bust

In the early 1990s, there were great expectations among genome scientists, entrepreneurs, investors, and drug companies that the identification of genetic markers would streamline drug discovery and development and form the basis of a new sector of the pharmaceutical industry. A large cohort of companies appeared, ready to implement genomics technologies in drug target screening, identification, and validation, but the data licensing business model adopted by most firms proved unsustainable.

Information alone doesn't make a drug. Drug design involves making safe and effective interventions in strictly regulated and finely tuned biochemical signaling pathways nested in highly complex biological systems. A lot can go wrong. Even if a pharmaceutical company possesses a promising target, there is no guarantee that it will be able to develop an efficacious drug. Most attempts fail. If all goes well in the laboratory and clinical testing – a very rare course of events – then one might expect a drug in perhaps ten years at a cost of half a billion dollars.

Given the length, expense, and uncertainty of the drug development process, pharmaceutical companies questioned the value of biomarkers. What is a fair price? Eventually, the answer became clear: not enough in many cases to support the commercialization of biomarkers as a main line of business. After pharmaceutical houses had made a first pass and selected priority drug development targets, demand for biomarkers slackened. Firms licensing gene sequences struggled to remain profitable. Many genomics companies elected to divert resources to the downstream development of diagnostic products or drugs. Oncologists had anticipated an avalanche of cancer biomarker data, but only a trickle arrived.

Academic labs carried on the study of cancer genomics, but with fewer resources, and in a mostly uncoordinated manner. The advent of genomics has increased demand for tissue specimens by several orders of magnitude, yet competition in science has continued to put pressure on academic laboratories to generate data and publications independently rather than cooperatively. There have been few concerted efforts to pool genomics data in cancer research. There is no central repository.

When Bonnie Addario surveyed the institutional landscape, she saw a case market failure. She was enthusiastic about the promise of genomics for the development of individualized treatments and improved outcomes for lung cancer patients, but frustrated by the organizational and economic impediments to translation of biomedical advances from 'bench to bedside.' Attendees at the BJALCF Lung Cancer Summit agreed that patients would benefit from changes in the way cancer biomarker data are generated and disseminated.

Storming the silos

After the meeting, Bonnie assembled a team to organize the proposed clearinghouse. Joining her as president of the Addario Lung Cancer Medical Institute (ALCMI – pronounced 'alchemy') were Steven Young, former Executive Director of the Multiple Myeloma Research Consortium, and a core group of leading oncologists, thoracic surgeons, and laboratory scientists – Harvey Pass from NYU Langone Medical Center, David Carbone of the Vanderbilt University Medical Center, David Gandara, from University of California-Davis School of Medicine, David Jablons, from the University of California, San Francisco, Pasi Jänne from Harvard Medical School and the Dana Farber Cancer Institute,

Making it global: Institutions participating in ALCMI (clockwise from top) University of Torino in Turin, Institut Gustave Roussy in Vellejuif, France, Hospital Duran i Reynals, a site of the Catalan Institute of Oncology; center, tissue samples

Ite Laird-Offringa of the University of Southern California, Rafael Rosell from the Catalan Institute of Oncology in Spain and Giorgio Scagliotti from the University of Torino.

"These were really the top guys in the business," says Young, who was appointed President of the organization. As the only non-scientist on the board, Bonnie represented the patient perspective. "I insisted that she have veto power," says Young, "to make sure that our mission wasn't hijacked." Addario was gearing up to wage "a battle against the status quo." She had selected a board that she believed was willing to reform established institutional processes in biomedical research.

The group formulated goals, established ground rules, and developed a unique operational model. ALCMI was established to break down barriers. Bonnie intended the group to serve as a virtual mediator that would 1) establish connections and facilitate communication between 'research silos' (academic and industrial laboratories reluctant to collaborate and share information); 2) link and standardize existing biobanks in a cooperative network; and 3) provide an information technology infrastructure for the broad and efficient dispersion of data across the institutional topography of the global cancer research establishment.

The initial goal, agreed upon at the first meeting of the ALCMI board, was to affect the clinical management of lung cancer in a significant way within three years. The timetable was ambitious. It reflected Bonnie's "no-nonsense" business approach to leading the consortium. The cancer survivor and former oil company executive had little patience with the established conventions of academic life. "A lot of people were doing good things in cancer research," she says, "but didn't fully understand the need to shake up the academic system. We're running ALCMI as a business. We don't sit around and create ideas and not implement them. We make sure they happen and we measure what we're doing. We operate using business principles."

Fourteen academic universities and community hospitals have joined formally as collaborators. In the United States, participating institutions include the Dana Farber Cancer Institute in Boston, the Hoag Memorial Hospital Presbyterian in Newport Beach, California, the Lahey Clinic in Burlington, Massachusetts, New York University, the University of California, Davis, the University of California, San Francisco, the University of Southern California in Los Angeles, Alta Bates Summit Medical Center in Oakland, Palo Alto Medical Foundation in Palo Alto, Vanderbilt University in Nashville, Tennessee, and Memorial Cancer Institute in Hollywood, Florida. Abroad, ALCMI enrolled programs at the Catalan

> "Is it good for the patient? If yes, we do it. If no, we don't."

Institute of Oncology in Barcelona, Spain, the Institut Gustave Roussy in Villejuif, France, and the University of Torino in Turin, Italy. Four additional medical centers in the U.S. have been invited to join ALCMI, bringing the total number of community hospitals to eight— ALCMI is unique in engaging community-based clinicians and community hospitals in translational research.

Despite the urgency of her mission, Bonnie understood that laboratory research moves forward according to its own timetable. Advancing basic science takes time, money, and luck. Breakthroughs can't be predicted. They can't be planned. Bonnie

ALCMI summit in 2009
Top: David Gandara, Roy Herbst, Ite Laird-Offringa
Bottom: Jack West, Harvey Pass, Tony Addario

believed, however, that promising findings too often circulate for extended periods through restricted academic channels in which interests in publication and tenure take precedence over the translation of research to medical applications. Bonnie and company planned to operate differently. Steven Young says, "ALCMI is not a private playground for scientists in the consortium. We stated that clearly to our academic partners. We said, 'We're not trying to continue what you normally do. We're creating this resource so that scientists around the world can access it.'"

As new member organizations joined and coordination challenges arose, ALCMI evolved into a contractual consortium. In order to gain access to the organization's bio-repository resources, participating institutions must agree to adhere to non-negotiable policies on control of data and intellectual properties, tissue collection and usage, and revenue sharing. These contractual agreements obviate the need to negotiate separate deals with multiple technology transfer offices. They streamline the process of involving new institutional participants and contributors. The goal is effective collaboration with far less red tape. Through the contract system, ALCMI has been able to re-route flows of information in academic collaborations – investigators and research institutions have evidently recognized the sense and value in ALCMI's innovative methods.

ALCMI is not the only non-profit organization working to share tissue samples and disseminate biomarker data, but similar groups are few in number. According to Steven Young, "there are only three or four of these around the world. It takes a lot of nerve and a lot of money." ALCMI is currently the only group dedicated exclusively to the acceleration of lung cancer research.

Remove the bricks, remove the mortar, disseminate the research

Two years ago, ALCMI expanded its bold experiment to include the analysis of tissue and plasma samples. The organization initiated the CASTLE Network Study (Collaborative Advanced Stage Tissue Lung Cancer Network), a networked research project that performs laboratory testing on tumor specimens donated by lung cancer patients. The structure is simple. Late-stage cancer patients provide tissue and blood samples at one of seven participating institutions nationwide. Clinicians perform molecular tests to identify biomarkers that might provide clues about the future behavior of the cancer. The samples remain in the bio-repository as a resource for researchers worldwide; test results are sent to the patient's doctor to help determine the best course of treatment.

The CASTLE study is the beginning of a move toward improved, personalized treatment plans for lung cancer patients. Participating physician and ALCMI board member David Carbone explains that information provided by the institute "enables physicians to make informed decisions on best available treatments – it often allows them to make earlier therapeutic interventions and to prescribe highly effective, targeted drugs rather than non-specific and toxic chemotherapies." CASTLE study findings also help researchers identify new biomarkers and learn more about the genetic preconditions, cascading biochemical pathways, and cellular dysfunctions that characterize cancers in lung tissues.

CollabRx: The internet's answer to cancer

If every cancer patient had Bonnie looking after them, none would need additional help to navigate effectively in the healthcare system. But as Steven Young laments, "There are very few Bonnies." There is, however, CollabRx, a Bay Area information technology company involved in the design of web-based tools to guide cancer patients to the best treatments and clinical trials. CollabRx's Targeted Therapy Finder can't replicate Bonnie's firecracker personality, but it can lead patients to a personalized treatment plan in just a few clicks.

Marty Tenenbaum, co-founder and chairman of CollabRx, has a story much like Bonnie Addario's. When diagnosed with metatistic melanoma, he consulted several oncologists. Each recommended a different treatment. None could tell him which would work best. Dismayed, Tenenbaum drew on his background in computer science to develop a solution — fellow patient advocates describe him as a "very inventive and creative guy." Tenenbaum founded a private company called CollabRx in 2008. The company developed an online tool and information repository for lung, melanoma, and colorectal cancer patients seeking personalized treatment recommendations. To access the information, patients on the CollabRx site use a 'Targeted Therapy Finder' application to respond to four questions about their cancer (stage, histological information, metastatic sites, and molecular information). Almost immediately, they receive a personalized report detailing next steps, best health-sustaining practices, and recommended clinical trials and drugs. CollabRx has put three 'Targeted Therapy Finder' applications online for lung, melanoma, and colorectal cancer patients. More are scheduled to appear shortly.

Research is moving ahead. In April 2011, Biodesix, a molecular diagnostics company located in Broomfield, Colorado, a Denver suburb, began testing tissue samples collected from late-stage cancer patients enrolled in the CASTLE study with a serum proteomics test called VeriStrat®. In January 2012, researchers at the University of California, San Francisco (UCSF), with support provided by the BJALCF, developed a similar molecular test in hopes of accurately predicting the future behavior of lung tumors.

Parallel drug testing projects are underway with support from the BJALCF. In 2010, Dr. David Gandara, a member of ALCMI's Scientific Board, and a special advisor for experimental therapeutics at the University of California, Davis (UCD) Cancer Center, began collaborating with Jackson Laboratory-West and the National Cancer Institute Center for Advanced Preclinical Research to test the effects of varied drug regimens against specific tumors. Malignant cells from lung cancer patients receiving treatment at UCD have been engrafted onto multiple mouse models and tested serially for positive responses to newly-developed anti-cancer therapies. The goal, Gandara says, is to identify the specific lung cancer mutations that are most common, and most treatable: "There are at least 150 different types of lung cancer, so every patient a physician sees is going to be a little different. We need to find, say, the five or six characteristics that are shared by all the cancers – the most common mechanisms. That's where we should focus treatment."

The BJALCF began funding Gandara's research in 2010. A recent progress report revealed that mice engrafted with variations of the EGFR mutant tumor model showed virtually complete reductions in tumor size when treated with afatinib, a drug being tested by Boehringer Ingelheim for patients with EGFR mutation positive non-small cell lung cancer (NSCLC), in combination with cetuximab (Erbitux®), a monoclonal antibody marketed by Bristol-Myers Squibb and Eli Lilly and Company that targets EGFR receptors. Clinical trials of the experimental combination therapy in human beings are underway, after the encouraging preliminary results in animal testing.

Developing alternative treatment options also requires enrolling more patients in clinical trials. Pharmaceutical companies often struggle with recruitment. Fewer than 5 percent of lung cancer patients participate in tests of experimental therapies. As a former patient, Bonnie understands their reluctance: "Most people think of clinical trials as a last resort. They think it signals the end of the road." For many people with cancer, entering a clinical trial marks

"Patients have earned a spot at the table. They should not be patronized."

ALCMI President Steven Young

Bonnie J. Addario

a passage in status, from patient receiving care to doomed guinea pig. She has firsthand experience with the phenomenon. When her cousin was diagnosed with pancreatic cancer, the doctor recommended a clinical trial. At her cousin's next appointment, a trial representative walked into the physician's office wearing a suit and carrying a briefcase full of enrollment paperwork detailing risks. The reaction from Bonnie's cousin was immediate and powerful: "No way."

Bonnie is mobilizing the BJALCF to develop more effective enrollment techniques: "I tell patients that at one point, Tarceva was in a trial, and that the people who took it lived longer. We can get patients into clinical trials, but we need to educate them. We have to explain what trials are all about, and tell how genomics is enabling the invention of better medicines." Her message is that clinical trials give patients the best chance for survival. As Steven Young indicates, the BJALCF's patient recruitment effort is an important piece of the virtual network: "BJALCF can get access to the patients, ALCMI has access to the scientists, and we have established an infrastructure to support the research. Our contracts, our data systems, our processes for doing correlative science studies are changing lung cancer research and care."

"Our purpose is to move the needle on the survival of this disease."

"Patients must be a big part of the solution, and they want to be."

Lung cancer education

In 2012, the BJALCF and ALCMI have launched further initiatives to inform and empower patients and enlist the aid of healthcare professionals. Working collaboratively with GE Healthcare Oncology Solutions, BJALCF is developing the Patient 360 program. A pilot version has been introduced at El Camino Hospital in Mountain View, California, under the direction of Dr. Shane Dormady. The BJALCF is also compiling a "360 Degree Patient Handbook" for patients, their families, and health care providers. The handbook is a goldmine of information covering all aspects of the lung cancer experience including diagnosis, cancer staging, targeted treatments, and clinical trials. Bonnie recalls her own firsthand introduction to the world of oncology: "Everyone kept saying that cancer is a journey, but no one could provide me with a roadmap. This handbook is the culmination of years of research, conversations with lung cancer experts and patients, and my personal experience." A free iPhone app will alert patients of new discoveries and breakthroughs in lung cancer research.

Bonnie insists that the best patient advocates are educated patients themselves. The BJALCF is working hard to encourage and enable informed, proactive participation by patients and families in cancer care: "We want to teach the patient what to ask for from the very beginning of the long hard road on which they will travel. When the doctor says, 'You have a metastasis to the brain, you need radiation,' they will have the background knowledge to reply, 'Well, are we considering whole brain radiation, gamma knife, or cyber knife procedures?' They will be able to personalize their treatment and demand a seat at the table."

Before patients demand a seat at the table, they are offered a space on a couch at the BJALCF Lung Cancer Living Room support group. The Living Room is an open forum for patients and their families to voice questions and concerns, share lessons learned, and hear from experts in the field of lung cancer research and medicine. Recently, Living Room conversations debuted on the worldwide web. "We are now live streaming into patient's homes," Bonnie reports. "It's open to anyone who wants to dial in, and that includes the pharmaceutical industry. We are not restricting access. We are not keeping anyone out."

These patient-focused programs are part of a larger campaign by the BJALCF and ALCMI to reshape the institutional foundations of cancer care. Efforts to create more knowledgeable, more responsive, and better equipped community hospitals are another important part of the process. Seventy to eighty percent of all

A "Google map for health"

To achieve their goals, patient activists need the support of the biomedical establishment. They need well-placed allies to speak out, apply pressure, and implement change. Recently, movements for change initiated by patient groups attracted the attention and support of two key movers and shakers: Dr. Francis Collins, Director of the National Institutes of Health (NIH), and Dr. Susan Desmond-Hellmann, Chancellor of the University of California, San Francisco.

In November 2011, the National Academy of Sciences, published a report compiled at the request of Dr. Collins. Entitled "Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease," the report called for the creation of virtual institutions to collect and link patient data with emerging biomedical research. The hope is that information pooling will generate a kind of "Google map for health," and guide doctors, patients, and biomedical scientists together to better understandings of health and illness and more effective disease treatment options.

Desmond-Hellmann spoke out to endorse the initiative. The goal of a 'knowledge network,' she wrote, would be "the marriage of molecular research and clinical data at the point of care, as opposed to research information continuing to reside primarily in research labs or publications." Translational research is too often stalled or derailed. Desmond-Hellmann bemoans the fact that "a decade after completion of the human genome sequence, too little clinical benefit has been realized. Why, given the explosion of scientific knowledge in the last decade, haven't we seen greater gains in health outcomes?"

Public education and participation in biomedical research are crucial to improving the situation. Desmond-Hellmann calls for a "new social contract" between informed patients and the various organizations and institutions charged with advancing science and extending the practical reach of contemporary biomedicine. "It is patients," says Desmond-Hellmann, "who uniquely understand the potential value of arrangements in which they both contribute personal clinical data and benefit from knowledge gained through collaboration."

cancer patients are treated at community hospitals, but molecular testing is far from a widespread or standard procedure, and many patients do not learn about the latest treatment options. "Patients are getting the same old, same old," says Bonnie. "Whatever the oncologist was giving them before, that's what they're kept on." BJALCF is spearheading a community hospital referral program. The program is designed to provide community hospitals with incentives to improve, to acquire the tools and forms of expertise required to diagnose and treat cancers based on the results of personalized molecular testing. And if superior resources or specialists are to be found elsewhere, the BJALCF will refer patients out to complete their treatment at different hospitals.

"The tissue under the microscope"

Bonnie J. Addario has extended patient activism to the formation of a virtual research network that links cancer patients, oncologists, biomedical researchers, and pharmaceutical companies in order to realize the potential of cancer genomics and personalized medicine. She is attempting to tear down institutional walls and push scientific and medical experts to work smarter and more cooperatively in order to save more lives. Her message to researchers, physicians, and industry leaders is that their work is profoundly important to cancer patients and their friends and families – never forget it! The tissue under the microscope, she reminds them, came from a human being who desires to live: "When you go back to your labs, remember that you're not just looking at cancer cells. You're looking at a patient. This person has given you their tissues, their cells, to help you advance lung cancer care."

"We're in the phase now," says Bonnie, "where we have identified a genetic mutation or bio-marker for something like thirty or forty percent of lung cancers. Many of them we can treat." The mission shared by the BJALCF and ALCMI is to identify the other sixty percent and make sure that patients know about it. Bonnie sums up the project: "We partner and collaborate with academic institutions, pharma corporations, and biotech firms. We take our most prized possessions and share them in order to speed the delivery of life-saving medical products to patients. We have to do it."

Reflecting on her life and luck, Bonnie says, "When I became President of Olympian Oil, someone said to me, 'You're really lucky.' I thought, 'Me? Lucky?' But then I realized I was lucky. I loved what I did every day. But I also realized that I hadn't been called to do it. I didn't know what I was meant to do, but I knew my job at Olympian wasn't it. Now I know. This is it. What more can we do, what better footprint can we leave, than to say 'I saved a life?' Even if it's just one, that's pretty good." **Ø**

Photo Finish

The First Four

When Alejandro Zaffaroni (*center*) left Syntex to start ALZA, he announced that he would take three employees with him. Some of his colleagues panicked, fearing he would abscond with top scientists. To their surprise, he selected chauffeur Joseph Jussen (*opposite*), administrative assistant, Matilda Nieri (*right*), and executive secretary, Ana Leech (*left*).

LSF Publishes Book Honoring Biotech Leaders

LSF has published a highly-illustrated coffee table book honoring outstanding individuals, companies, and scientific achievements that have been inducted into the Biotech Hall of Fame at the annual Laguna Biotech Meeting. The meeting is co-sponsored by Kleiner Perkins Caufield & Byers and Burrill & Company. The book was commissioned to mark the 25th anniversary of the Biotech Meeting, an invitation-only retreat for biotech CEOs. Distribution has been limited to meeting participants and Biotech Hall of Fame award winners. LSF is currently working on a comprehensive scholarly history of the origins of commercial biotechnology, scheduled for publication in 2014.

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