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LIFE SCIENCE

DIAMONDS IN THE ROUGH

There is a perception that medical advances are mostly made incrementally through years of toil in laboratories and clinics with only occasional breakthroughs changing care dramatically. Nothing reinforces that impression more than the recent striking success of mRNA vaccines in preventing COVID-19 infection after many years of proof-of-concept work perfecting the pieces that have come together for this very timely breakthrough.

But there are many striking examples of both medical breakthroughs that went unnoticed and supposed breakthroughs that were not so. Nothing illustrates the former as well as the story of the Greek physician, John Lykoudis, who developed a treatment for gastric ulcers that proved decades ahead of its time. Gastric ulcers were long believed to be caused by stress, diet and lifestyle, and adjustments to these as well as prescription anti-acid treatments and occasional surgery, were the mainstays of therapeutic intervention well into the 1990s. Dr. Lykoudis successfully treated his own gastroenteritis with antibiotics in 1958 and received a Greek patent in 1960. His attempts to publish his findings in *JAMA* were rejected and he was fined 4,000 drachmas by the Athens Medical Association Disciplinary Committee in 1968 for treating his peptic ulcer disease patients with antibiotics, though he cured an estimated 30,000 of them. He was shunned by the medical establishment of his time, or at best, considered an eccentric provincial physician, and died in 1980, just short of his vindication. This came more than two decades after his breakthrough. Barry Marshall and J. Robin Warren demonstrated that *Heliobacter pylori* caused gastric ulcers and could be cured by antibiotics. It took another

PACYLEX:

TARGETING MYRISTOYLATION TO SELECTIVELY KILL CANCER.

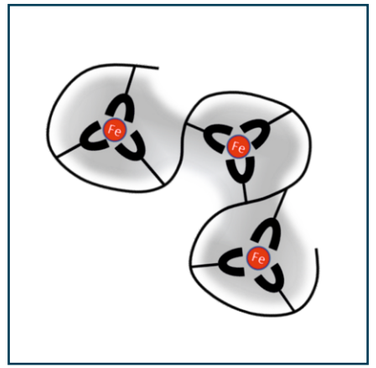
decade from their first publication of their findings in 1984 in *The Lancet* to the general acceptance by the NIH in 1994 that evidence supported *H. pylori* as the cause of peptic ulcer disease. They were eventually lauded with the 2005 Nobel Prize in Medicine.

The irreproducibility of marquee work. About a decade ago, several pharmaceutical companies went public with their stunningly low success rates for reproducing research published in top journals from reputable labs often in marquee institutions. In a 2011 paper titled, “Believe it or not,” scientists at Bayer Healthcare analyzed 67 in-house projects that attempted to validate new potential targets of interest for drug development. Only in ~20–25% of the projects were the relevant published data completely in line with their in-house attempts to reproduce them.

In 2012, the Amgen head of translational research, C. Glenn Begley, published in the journal Nature their results of a decade of attempts to reproduce marquee findings in global cancer research. They identified 53 “landmark” publications - papers in top journals, from reputable labs – and tried to double-check the findings before advancing them into drug development. 47 of the 53 could not be replicated. Amgen went the extra mile when findings could not initially be reproduced; the original authors were contacted to discuss the discrepant findings, reagents were exchanged and experiments repeated under the authors' direction, sometimes in the laboratory of the original investigator.

The prestige of a journal proved no guarantee that the research would be reproducible. In studies for which findings could be reproduced, authors had paid close attention to controls, reagents, investigator bias and describing the complete data set. For results that could not be reproduced, data were not routinely analyzed by blinded investigators and frequently presented the results of only one experiment, such as a single Western-blot analysis. These less rigorous practices lead to the potential for confirmation bias to influence interpretation of the results, and the peer review system has historically been influenced by institution and individual reputations more than the data. In my own conversation with Dr. Begley, he indicated that the 6 studies they could reproduce all came from second tier labs; they had a greater burden to prove beyond a shadow of a doubt that they were right.

Life science diamonds in the rough. Those second tier labs whose breakthroughs had to be impeccably researched to publish in top tier journals are a great example of what I call “life science diamonds in the rough”. These are innovations in medicine that arise outside the mainstream of scientific dogma, beyond the hallowed halls of marquee institutions, in offices and labs of researchers or practitioners not labeled “key opinion leaders”. These are people looking to solve a medical problem, unburdened by the need to confirm “what we already know”. This freedom leads to many blind alleys but occasionally to a genuine breakthrough.



Breakthroughs from unexpected quarters are generally greeted skeptically. Even though they eventually were awarded the Nobel Prize in 2005, when Marshall and Warren initially submitted in 1983 their findings that a spiral bacteria was associated with gastritis (gastric


Luc G. Berthiaume
Founder & CSO
Pacylex

ulcers) to the Gastroenterological Society of Australia, the reviewers turned their paper down, rating it in the bottom 10% of those they received that year. Their positions at the Royal Perth Hospital did not place them in the elite. The next year they were successful in publishing their findings in *Lancet,* and after Barry Marshall fulfilled Koch's postulates on himself, in the *Medical Journal of Australia.* But it still took until 1994 for their results to be mainstreamed and NIH to recommend antibiotics be used for treatment.

The challenges of physicians and researchers like John Lykoudis, Barry Marshall and Robert Warren are experienced by thousands of others who struggle to bring their innovations and discoveries to light, both through publication in widely recognized scientific journals, but more importantly, to actual development as products. For nearly 14 years, I have been helping to create and support biotech startups with genuine breakthrough products.

How do I help them? I am anchored in one of the premier biotech hubs, the San Francisco Bay area, minutes from Stanford where I am a SPARK mentor for the Medical School, and only 2 exits from the legendary Bay Area Venture Capital address of Sand Hill Road. After 15 years of experience in public companies developing drugs, writing business plans for new products and curating portfolios, I help Life Science Diamonds in the Rough define their product and profile, plan its development, tell the story to investors and build the team to execute. Two perfect examples of Life Science Diamonds in the Rough are Pacylex Pharmaceuticals and Chelation Partners, two companies I am currently leading. Located in Edmonton Alberta and Halifax Nova Scotia respectively, these companies are far from the epicenters of Biotech.

Pacylex Pharmaceuticals

Pacylex is developing a new first-in-class therapeutic to hit a new target in cancer. Dr. Luc Berthiaume, a professor at the University of Alberta, discovered a connection between a biological process called myristoylation and certain cancers, particularly blood cancers, like leukemia, lymphoma and myeloma. He found that a drug that suppresses the process of myristoylation had a disproportionate impact on leukemia, lymphoma and myeloma cell lines, killing them at drug concentrations that spared normal cells. He and his colleagues also discovered that one of the two enzymes involved in human myristoylation, N-myristoyltransferase 2 (NMT2), was epigenetically suppressed in many cancer cell lines. Epigenetic suppression is often a hallmark of a tumor suppressor.

Myristoylation is a biological process of adding a small fourteen carbon fatty acid to the amino-terminus of roughly six hundred proteins in the body that are responsible for controlling normal growth and metabolism. The myristoylation process is critical for certain regulatory complexes involved in certain cancers, like the B cell receptor complex, which is involved in modifying proliferation and pro-survival signaling in lymphoma through Bruton Tyrosine Kinase (BTK), an important cancer signaling molecule which is a target for a class of very successful cancer compounds called BTK inhibitors. In 2012, Dr. Berthiaume and his colleagues Dr. John Mackey, an oncologist with substantial clinical trial experience in hematologic cancers, leukemias, lymphomas and myelomas, and Ryan Heit, who had worked in Dr. Berthiaume's lab and went on to earn an MBA, co-founded Pacylex. In 2015, they licensed a family of NMT inhibiting molecules from the University of Dundee that suppressed the process of myristoylation, including the drug they found to be effective in laboratory studies.

Pacylex subsequently contracted with research labs to test PCLX-001, their lead drug candidate, in mouse models with transplanted tumor tissue. PCLX-001 inhibited tumor growth and at the highest dose, completely regressed or eliminated lymphoma and leukemia tumors in most animals with as few as five once-a-day doses of the drug. It even completely regressed tumors grown from a patient whose cancer was resistant to the multidrug chemotherapy treatments typically given to patients with his form of lymphoma. Though the patient who donated the tumor tissue died, the mice showed PCLX-001 was just as effective on this “drug resistant” tumor as on any other. It worked in animal models of Diffuse Large B-cell Lymphoma, Burkitt's Lymphoma, and Acute Myeloid Leukemia. But it also worked in some models of solid tumor cancers like breast cancer and certain lung cancers.

New target and first in class is a double edged sword. Efforts to publish these results in high impact factor journals were stymied by the requests of editors and reviewers for more and more experiments. Without peer reviewed validation, venture investors were reluctant to consider a new target and therapy, especially without toxicology or human data. Though a first mover in this space, moving from research to development, often referred to as crossing the valley of death because so many innovations die before completing this transition, was a huge challenge.

Luc Berthiaume, CSO, John Mackey, CMO and Erwan Beauchamp, Dir. Discovery Biology of Pacylex at the World's Longest Baseball game cancer fundraiser.

PACYLEX

ACCELERATING THE PACE OF CANCER CARE

Fortunately for Pacylex, local Edmonton pride and philanthropy stepped in. The founders provided the initial seed money for the company and the Alberta Cancer Foundation provided key grant support for research. The next wave of funding required to complete the product manufacturing scale up and toxicology testing essential for entering clinical trials came from local cancer philanthropists and investors. The Cure Cancer Foundation took a keen interest in this research because it represented a genuine local treatment breakthrough arising from the Dr. Berthiaume's research at the University of Alberta and they made the PCLX-001 project the beneficiary of its World's Longest Baseball Game in the summer of 2019. Their World's Longest Hockey Game likewise benefited the program in February of 2021 when it raised a record amount of cancer funding. Several donors to the Cure Cancer Foundation took a further interest in investing in Pacylex and in February of 2020, closed a SEED financing round of $5M CAD. This funding allowed the company to bridge the valley of death and it is now poised to start clinical trials.

Suddenly the world changes. The pandemic struck right after the SEED financing closed. Drug substance manufacturing in India was slowed by their lockdowns but other progress accelerated. Despite the challenges, the company is on the verge of finally breaking out because of four developments in late 2020. After years of efforts and many rounds of revisions addressing reviewers' and editors' questions and requests for additional experiments and comprehensive data sets, a response perhaps to the previous failures of journals to adequately validate breakthrough discoveries, the lymphoma research of Dr. Berthiaume and his colleagues was finally published in *Nature Communications*. Fierce Biotech did a profile of the drug candidate, PCLX-001, on the day the Nature Communications paper was published. Less than 3 months later, the breast cancer proof of concept evidence was also published in Breast Cancer Research and Treatment. Suddenly the scientific, peer reviewed validation which had been so elusive, was established. Between those two publication dates, two venture funds, Sofinnova Partners and Brandon Capital broke the ice on venture investment in this target by making a SEED investment in a competing company in the UK called Myrix Pharma that had just been established. In addition, the progress in 2020 has the company on the verge of initiating the first clinical trial, having completed GLP toxicology studies and filed a CTA in January of 2021. Clinical dosing is expected to commence in the spring of 2021. Lastly, comparisons to dasatinib and ibrutinib, two extraordinarily successful cancer drugs Sprycel and Imbruvica respectively, revealed that PCLX-001 is ~10-times as potent as these two drugs in vitro, and PCLX-001 could be the logical successor to this important cancer drug class known as BTK inhibitors. That positioning has opened investors' eyes to the market potential and a Series A fundraise is now underway with a much stronger prospect for success.

Chelation Partners

Chelation Partners is a Nova Scotia company co-founded by Dr. Bruce Holbein, who invented a non-toxic, iron-binding copolymer for use as a potent, broad-spectrum, antimicrobial agent active even against drug resistant organisms. Dr. Holbein and his colleagues characterized this polymer in 21 published peer-reviewed studies, many conducted in collaboration with leading labs in Canada.

The polymer exploits the absolute requirement of pathogens for iron in order to grow and reproduce. Although it scavenges the iron required for infections, it is completely non-toxic to normal human cells. Because of its unique mechanism of action, it is immune to the development of microbial resistance. When I described this to Barry Marshall, yes the Nobel Prize winner mentioned before, he responded: “Sounds interesting…we do need anti infectives which are non toxic but attack a fundamental metabolic process of bacteria.”

Despite this impressive collection of published research, the company struggled to secure enough funding to bridge that same valley of death Pacylex has nearly crossed. Small grants and modest investment, mostly in the form of loans, much of it from James Drage who found and supported the company after almost losing his teenage daughter to a drug resistant infection, kept Chelation afloat. But it didn't enable it to transition into clinical development because it was never enough to conduct the manufacturing scale up and non-clinical studies necessary to become a clinical stage product. Large investors reacted poorly to the novelty of the mechanism of action because “chelation” defines a narrow market of three FDA approved drugs for a very limited set of iron overload conditions, and also a host of less mainstream medical practices with other compounds without adequate clinical evidence of effectiveness. Chelation therapy has not been a therapeutic approach applied clinically to infectious disease.

The most recent disappointment was when the company tried to offer its therapeutic in response to COVID-19. Although there was research evidence that chelation may help treat viral disease, and plenty of published evidence suggesting it would lower the bioburden of secondary infections and moderate the septic shock killing patients, there was no interest in this polymer as a potential therapeutic for COVID-19 because it was still too early in development.

After clearing the books of some prior debt obligations affecting the Company's investability, Mr. Drage brought me in to help reorganize the company's effort and recruit a new team and independent Board members who would guide the company forward into clinical development.

Iron sequestration is also effective against cancer, sepsis, and inflammatory disorders, and this water-soluble polymer is ideal for many different routes of administration. In animal studies it has been delivered orally, topically, to the eyes, ears, peritoneum, and intravenously. It is a platform technology and needed an identity untethered from the baggage of chelation and a team deeply experienced in developing therapeutics. The company agreed to focus on the biology and dysregulation of iron, the common thread weaving through all these conditions.

What emerged is a company with a strong US-based development team and Board, and an incredible pipeline of product for major unmet medical needs like sepsis, antimicrobial resistant infections, cholera, and cancer. And with that team and pipeline came interest from DARPA for solving sepsis, a contract with NIAID to help with preclinical work, and a Series A financing, currently in progress, to supplement the non-dilutive government support and initiate safety studies in normal volunteers and IND enabling studies for a Phase 2 program in sepsis and drug resistant infections.

Storytime

Recently I was discussing one of my companies with the business development representative from a large pharma and she said, “it's time for storytime”. I said, “what's that”? She said it was the list of questions they ask to gather the key information they need for candidates for business deals. Polishing a diamond enough to be worthy of storytime is what every breakthrough needs friends to help it do, because it is never lonelier than when you are first and outside the comfortable cocoon of the status quo, especially if everyone else thinks you are nuts.