CHAPTER TWO

My Path in Seeking New Medicines

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Contents

I was born in New York City, the middle of Moses and Helen Bernstein's three sons. My father was a pharmacist, my mother a bookkeeper. Our parents were very supportive of us, asking only that we do our very best in whatever field we chose.

From an early age, science fascinated me; I got my first Gilbert chemistry set when I was still very young. In seventh grade, I learned that teachers were not infallible. My science teacher was introducing us to the concept of radioactive decay and half-lives. He drew a bar graph showing exactly half the original radioactive material remaining at the end of each half-life period, but it also seemed to indicate that, until that period expired, 100% of the original material was still there. When I raised my hand to ask whether the decay, in fact, occurred constantly over time, we ended up in an argument, followed quickly by a note home to my parents. Their advice was simple: "Yes you are right, but you shouldn't embarrass the teacher by correcting him!"

A key moment for me was during my sophomore year at the University of Rochester when I took Organic Chemistry, taught by Professor Jack Kampmeier. His passion for organic chemistry was infectious, and I caught the bug. The following summer, I won an NSF undergraduate research participation grant and chose to work with Professor Richard Schlessinger. Working with him was hard as he was very demanding. I soon learned from the local NSF program Director that he was not happy with the number of hours I was working. After investigating, the Director learned I was being productive and working about 65 h a week. He suggested that I try to work out an understanding with Professor Schlessinger, and if that did not pan out,

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he offered me a place in his lab or help in finding another spot. I succeeded with Professor Schlessinger and by the end of the summer, I was obsessed with synthesis. Over the next 2 years, I took many graduate chemistry courses, spent a summer working at Kodak in their color synthesis group, and did my senior research in the labs of Professor Andrew Kende.

By then, I knew my goal was a Ph.D. in Organic Synthesis and that I wanted to prepare biologically active molecules as potential medications. Somewhere along the line, I had read a copy of *Burger's Medicinal Chemistry* (in those days, only a single volume), and this had narrowed my focus. I was accepted at several graduate schools and, lured by the West Coast, visited both Stanford and Berkeley in the spring of my senior year. But I found that discussions with several distinguished professors, including W.S. Johnson, often ended with commentary like, "With your set of interests and having been accepted to Columbia, why aren't you going to work with Professor Stork?" Though I no longer relished living in New York City, I accepted that my immediate future might lay on the East Coast after all. Columbia it was.

My time there rapidly flew by, and working in the labs of Professor Gilbert Stork turned out to be a dream. There were many brilliant scientists in his group who had an impact on me—Paul Wender, William Greenlee, and Minoru Isobe, to name just a few. Columbia was an open environment, with students encouraged to discuss their science broadly across the chemistry department. I was impressed by this culture of openness, which I have tried to emulate ever since. Upon graduating, I did a postdoctoral fellowship with Professor Barry Trost at the University of Wisconsin. I felt that working with Professor Trost, who was then focused on developing new synthetic methodology, would help balance my training, which had thus far centered on synthetic route design and delivery of complex molecules. Little did I know that my time with Professor Trost, which resulted in a formal total synthesis of Vitamin D, would be so influenced by my prior experience.[1]

At this point, industry came calling, and I accepted an offer from ICI Pharmaceuticals in Wilmington, Delaware. It was a great opportunity in the U.S. pharmaceuticals division of one of the world's biggest chemical conglomerates. My hope was that working at ICI in a smaller group would provide some of the flexibility and entrepreneurship of a start-up or small company, with the stability of a major firm.

My first assignment was to a selective antimuscarinic program targeting asthma. Within about 6 months, we disproved some of the project's

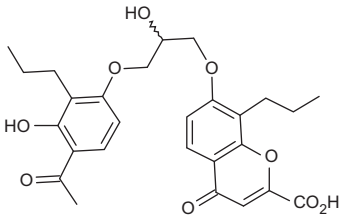
foundations, and I was asked to propose a new antiasthma target. This was a challenging assignment that required me to read the literature broadly. I offered two options. The first was blocking the leukotrienes (LT), either with an antagonist or with a biosynthesis inhibitor. The second involved antagonism of platelet-activating factor. Management chose LT antagonists and asked me to start before we actually had biologists on the team. My first task was to develop an in-house synthesis that would allow us to generate LTs in sufficient quantity and quality to use as standard agonists. As I worked on this, the management team used the promise of such a supply to lure key bioscientists to join us.

The synthesis was exceedingly difficult, time-consuming, inspiring, frustrating, and rewarding. It would have not been successful without the efforts of my colleagues Jim Maloney, Ed Vacek, and Tom Maduskuie. At times, our findings were groundbreaking, and this was a bit heady for someone so new to drug discovery. To achieve our synthetic goal, we needed to introduce prep-HPLC and spend lots of time on the department's new high-field ^{1}H NMR. Working on the leukotrienes led to interactions with leading pulmonary clinicians as we established various collaborations to study the effects of our synthetic leukotrienes in humans. After writing the chemistry portion of a Drug Master File that was submitted in support of those studies, I also had direct interaction with reviewing chemists at the FDA.

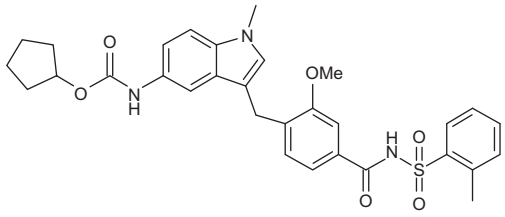
Three years into my new job, I realized that, although I was working hard, sometimes till 11:00 p.m., my expectations of recognition in a large organization were not being met. I responded by ramping up my professional activities outside work, including becoming involved with the local section of the ACS—chairing symposia, becoming an alternate councilor and joining committees. I also decided to add a hobby. After trying several, I settled on whitewater kayaking. Kayaking taught me that one has to make decisions even with imperfect data. Planning, acting, and having a back-up plan are critical when one is about to enter a set of rapids or go over a waterfall. Worse than making a "wrong" decision is to delay making one, only to be carried along out of control.

Back on the leukotriene project, I was joined in my efforts by Alvin Willard, Ying Yee, and Fred Brown. Together, we made analogs of the leukotrienes and of FPL-55712,[2] the only known antagonist. Hybridization of our output led us to a novel indole series that we focused upon as a shared effort. This was a key decision, underpinning the eventual success of our program, which we made under the guidance of Barrie Hesp. Our team did not have the experience to understand how valuable a lead the indoles

were, although we all knew that there were many competitors working on analogs of the LTs and FPL-55712. Victor Matassa joined our team to replace Alvin Willard and, shortly after that, ICI-204219 was submitted as our development candidate, zafirlukast.[3]

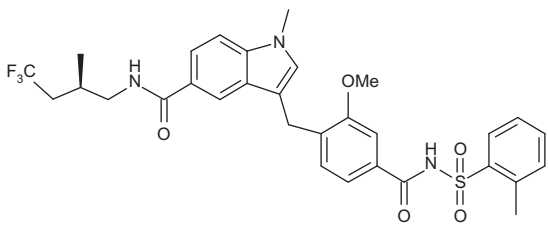


FPL-55712



ICI-20419 [zafirlukast]

It was about this time that another major change occurred in my life when I fell in love with Ala Hamilton-Day, a complex and beautiful trial attorney. We married after a whirlwind courtship and soon had two children, Sarah and Matthew. At work, I remained on the leukotriene project, and, in addition to supporting the development of zafirlukast, I also strove to deliver a back-up. The goal was driven by our desire for a compound that did not have an aryl amine substructure. We succeeded with ZD3523,[4] which was out-licensed to Mitsubishi when, ultimately, we did not need it as a replacement for zafirlukast. It had been so long since pharmaceuticals had out-licensed a compound that the finance department was unsure which group should be credited with the licensing fees, a fact I learned on receiving a letter from the head of R&D thanking me for my role in delivering an unexpected windfall to his budget. This was Zeneca R&D because ICI had just "demerged" and the pharmaceuticals group had gone to the newly created Zeneca Pharmaceuticals.



ZD-3523

With the closure of the discovery effort on leukotrienes, I chose to move to the human leukocyte elastase (HLE) inhibition project. Although it was a

very different type of biological target, a circulating enzyme rather than a membrane-bound G protein-coupled receptor, the project itself remained on familiar territory, focusing as it did on chronic obstructive pulmonary disease. While this was not asthma, it was another pulmonary disease, and I felt working on it would allow me to continue to develop my knowledge of respiratory diseases. The impetus behind my decision was that I had come to believe that one of the keys to successfully driving a small molecule drug discovery project forward was having at least one chemist on the team who understood enough about the bioassays to adequately discuss them with the lead bioscientists. Many times over my career, we have considered assays for a project that seem great in isolation but, upon detailed inspection, fall short of our needs. For example, the team might want to use qSAR to drive prediction of future results, but the test output is too removed from the quantitative interaction (e.g., binding constant or enzyme inhibition value) to be used for this purpose. Or perhaps the precision of the assay after it was "optimally" configured (to give higher output/lower cost) was not high enough to understand the pharmacology of the drug candidate.

In the HLE inhibitor project, Peter Warner had just made the breakthrough discovery of a nonpeptide backbone for such inhibitors[5] and I joined it when he returned to England. Our goal was to increase potency and deliver an easy-to-synthesize analog that was orally efficacious. During that effort, we learned important lessons about needing to understand the physical properties of drug candidates: solubility, lipophilicity, and non-specific protein binding that previously had been examined only in retrospect after compounds had become fairly advanced. Our chemistry department created its own section devoted to generating this data.

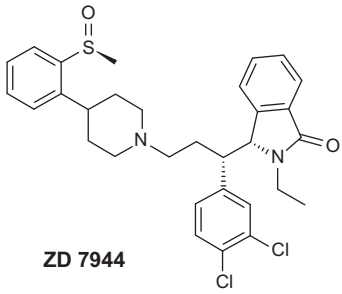
While working on this project, I had a lesson of my own in effective communication. I learned that a computational scientist was frustrated by my refusal to honor his request to prepare a phosphinamide derivative that he predicted would be an excellent compound. While researching routes to comply with his request, however, I had learned that such aryl phosphinamides were inherently unstable to disproportionation and could not be isolated. Unfortunately, he interpreted my report that I *could not* make the derivative as I *would not* make it, a fact I discovered only later. Had I offered a fuller explanation of the roadblock I encountered, I could have avoided the ensuing confusion.

In the end, in spite of significant progress on the nonpeptidic series,[6] the two development candidates that resulted from these efforts, ZD0892 and ZD8321, were both peptidic.[7] My gamble to stay in respiratory diseases

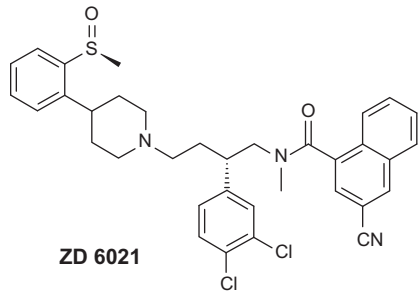
had paid off. At this point in my career, I had produced many papers, presentations, and reviews and had helped deliver development candidates opposite two targets. Internally, I received a promotion to ICI's scientific ladder; externally, I was invited to meetings of the *Collegium Internationale Allergologicum*, to join the *American Thoracic Society* and to participate in discussions defining similarities and differences between asthma and rhinitis.

My next project targeted Neurokinin antagonists for treating asthma and was well underway when I came on board. The timing of my return to an asthma project was auspicious because zafirlukast had been approved a short time before and was facing some postlaunch challenges. On a personal level, I also learned the joy that you feel when people reap the benefits of a drug you have helped develop. A kayaking friend who had asthma went on zafirlukast and sent me a personal note on how it had changed her life. She had been doing an exercise routine that respected the limits her condition placed on her. If she started her aerobic exercise without taking a β-agonist, she would need to stop after a certain time because she was out of breath. Alternately, if she took the β-agonist, she would have to stop after a different amount of time because her heart was pounding. However, after starting zafirlukast, she discovered that she did not know when to stop. Her routine had actually been disrupted because she was no longer limited by shortness of breath or a pounding heart.

On the neurokinin project, the team had already delivered ZD7944, a selective NK2 antagonist, when I joined it. Project pharmacologists had just discovered that simultaneous administration of NK2 and NK1 antagonists resulted in synergistic increases in efficacy in several disease models. Therefore, I was asked to explore the development of dual NK1/NK2 antagonists.



ZD 7944



ZD 6021

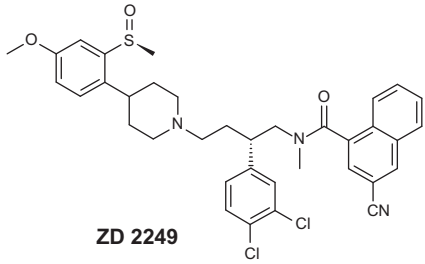
My approach was to use the newly developed technology of robotic-assisted synthesis to rapidly explore the SAR space around ZD7944 and see if we could find lead-like dual agents related to this selective NK2

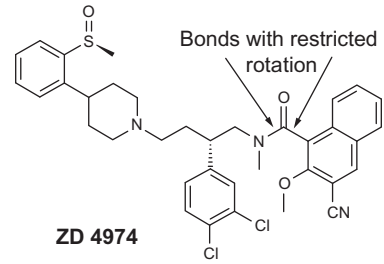
antagonist. Our robotic technology group was located in the United Kingdom, and I collaborated with them to produce hundreds of analogs for us on the >100 mg/compound scale. The U.K. team, however, did not then have automated purification and analytical instrumentation that could handle this sort of output. Luckily, we did in the United States, and by combining the strengths of both teams, we delivered several libraries. Most compounds were >95% pure; a few were lower, but none with <85% purity was submitted. In a couple of iterations, we learned that not only were dual agents possible, but we had found a compound that almost fit our criteria for a development candidate. (It fell short, however, as it was a nitro naphthalene derivative that we were sure would be Ames positive.) Upon considering replacements for NO_2 that would yield the desired profile, we decided to make the corresponding cyano-compound.

My experiences at this time reinforced my respect for the power of new technology both to deliver and to corrupt. It delivered, as we would never have progressed so far and fast without the robotic-aided synthesis. It also corrupted, since some of my colleagues could not accept that my associate and I had gone from making so many compounds to so few. We were now under "quota," and that was bad. That we had good theoretical reasons to target one difficult-to-make compound only worked in our favor after it was made and profiled well enough to be a development candidate, ZD6021.[8] How difficult efficient synthesis of the cyano-naphthoic acid proved is best exemplified by a series of papers from my process chemistry colleagues.[9]

We knew ZD6021 had two weaknesses: relatively rapid metabolism and moderate permeability. Working closely with a DMPK team led by Karin Kirkland, we chose to determine where metabolism was occurring and then prepare analogs that would specifically block that site. I believe that this was the first time in Wilmington that a medicinal chemist and a DMPK scientist had collaborated in such a way. Together, we learned that oxidative metabolism was occurring in both the naphthalene and piperidine regions of the molecule. Adding blocking groups to the aryl piperidine substituent led to improvements in clearance and afforded a dual-acting backup ZD2249.[10] Concurrently, to confirm the site of metabolism in the naphthalene, we prepared two isomeric hydroxy-substituted analogs and chose to make them via the intermediate methoxy analogs. Although the methoxy compounds had been made as intermediates, we submitted them for testing and made a surprising discovery. The 2-methoxy substituent not only decreased clearance and increased

permeability but also had a dramatic impact on receptor selectivity, converting our dual agent to a highly selective, brain-permeable NK1 antagonist.



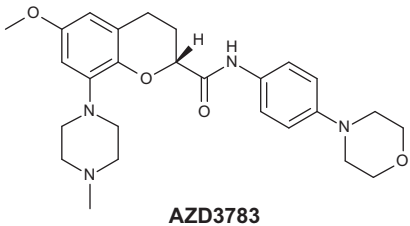


The timing of this discovery was fortuitous, since it occurred about when Astra and Zeneca merged and at a time when Pfizer and Merck had reported results with NK1 antagonists as potential central nervous system (CNS) drugs. A result of the AstraZeneca merger was that respiratory disease research stopped in Wilmington, with future research limited to CNS and pain. Our NK1-selective and improved compound was nominated as ZD4974 for development as an antidepressant.[11] Our experience with it led to our explaining NK1/NK2 selectivity via the existence of specific orientations of the aryl group and the amide linker and to discussions on the impact of atropisomers in drug development.[12]

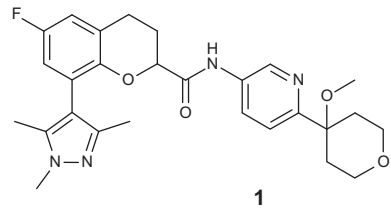
In some ways, this was the most frustrating set of projects I had worked on because the NK1, NK1/NK2, and NK2 teams nominated six compounds for development, and none of them made it to humans. All were stopped for toxicological reasons that varied between compounds. Our analysis of their structures and the toxicological data showed that the only feature all of these compounds had in common was a 3,4-dichlorophenyl-substituted methine.[13] Looking more broadly within the AstraZeneca and MDDR databases, we realized that this feature was very common in advanced candidates but at that time was found in only one marketed drug. Candidates opposite many disease targets had failed to deliver for a variety of reasons. This was our first inkling that substructures might exist that led to potent receptor interactions such that they were found in a broad array of candidates but that they were generally problematic, with rare exceptions.

Leaving neurokinins, my team and I worked for short periods on β-estrogen antagonists, γ-secretase inhibitors, NMDA antagonists, and H_3-antagonists before we settled into 5-HT_{1B} antagonists for another significant effort. The5-HT_{1B} team had already nominated two compounds for clinical development, ARA-2 and AZD1134. These had been stopped

due to toxicology findings, and our goal was discovering compounds with improved profiles. I joined the project just before Bob Jacobs, the project chemistry leader, left AstraZeneca. This was fortunate for me because I ended up taking over a very well-thought-out and advanced chemistry program. The goal was to find a compound with reduced phospholipogenic potential that also had improved DMPK (permeability and clearance) and physical (solubility) properties. Using an *in vitro* PLD screen, newly developed pharmacophore models and computer-based predictive tools to guide us, we delivered AZD3783.[14] This compound had an improved profile and progressed into clinical development. We also worked to deliver a backup to AZD3783. Unfortunately, long-term toxicology studies on AZD3783 led to the termination of its development and also caused us to reject any backup that had even a theoretical possibility of inducing phospholipidosis. By this point, I was the project leader and my chemistry team, led by David Nugiel, succeeded in preparing a proof-of-concept compound **1**.[15] This compound was the first "nonbasic" 5-HT_{1B} antagonist and, therefore, had no potential to be phospholipogenic. Regrettably, AstraZeneca was backing away from such targets, and the project closed without the opportunity to deliver a compound suitable for development.



AZD3783



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My final AstraZeneca project was developing a dual NET/DAT inhibitor as a follow-up to nomifensine, an effective antidepressant that had been pulled off the market due to idiosyncratic toxicology. Like both the 5-HT_{1B} and the H_3 programs, an increasingly important component of this drug discovery project was based on information technology. Computational chemistry played critical roles in compound design, information tracking, and data analysis validation. The last is easily overlooked due to the desire to set specific biochemical parameters as criteria for succession to candidate. The theory is that rigid criteria make it "easier" to decide whether a compound should advance. Unfortunately, the assays are not always accurate enough to give significant answers to the specific questions. In this case, the key to progress was

recognizing that the assays, as originally configured, did not provide a precise enough number for the ratio of NET and DAT activities to deliver a compound meeting the candidate drug target profile. Only after modification were they adequate for project progression. Although significant progress was made opposite this target, my site and all psychiatric research were terminated before we could deliver a clinical candidate.

After retiring, I established Pha*R*maB LLC as a platform from which to remain professionally active—as a scientific and/or editorial advisory board member, lecturer, editor, consultant, symposium organizer, and author—while also seeking to find a new balance point in life.

REFLECTIONS

I have had an extremely fortunate career as a medicinal chemist. I joined the field just as an explosion of scientific knowledge was opening up vast opportunities for drug discovery. This led to what I consider a Golden Age of drug discovery in the late 1980s and early 1990s, during which success via utilization of new technology seemed assured. Unfortunately, all good things come to an end, and I also experienced the crashing of the old Pharma model. In an attempt to meet unrealistic financial expectations, many companies focused on potential "blockbusters," merged, cut back operations, and engaged experts from outside the R&D environment to increase R&D efficiency.

As this happened, some companies forgot that key scientists are not fungible and misapplied otherwise effective tools for increasing efficiency. For example, many processes in discovery (e.g., running an assay or reporting results) may be greatly improved through the implementation of efficiency analyses; however, invention requires going outside the known. Because of this, and as reported in a *Business Week* article on 3M, some ways to improve the production process (e.g., lean-six-sigma analyses) can squelch the innovation required to invent something new.[16]

More recently, I have seen several major pharmaceutical companies take successful steps to reclaim productivity in both discovery and development. Moreover, vitality and passion essential to early drug discovery efforts are often now found in smaller organizations. For those companies, the primary focus is less on getting a compound that fits rigid criteria and a specific development model and more on determining how to successfully deliver their compound to patients.

Early in my career, there seemed to be greater openness and civility in drug discovery. Although there was competition, there was also a belief that patients would be better served with multiple drugs acting at the same target and that more than one drug could be successful. That viewpoint led to greater sharing of precompetitive information, which then helped the overall drug discovery development process. In the intervening years, an often-expressed view (in the popular press, by politicians and reimbursement agencies) is that only the first drug in a class should be reimbursed. The trope is that other compounds are just "me-too" drugs being pushed by greedy pharmaceutical companies. That there may only be one acceptable drug has led to heightened competition and less sharing of information.

It is my aspiration that the growing acceptance of personalized medicine will help to reverse this mentality. Personalized medicine recognizes that not all people with a given condition will respond identically to the same drug. As this concept gains greater acceptance, I hope that more open sharing will take place because I believe it will lead to greater overall success rates, making a genuine difference in the lives of others.

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