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How the antihypertensive losartan was discovered

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Based on interviews and publications, this case study is a history of how DuPont scientists discovered losartan, the first angiotensin II receptor antagonist. Essential aspects of the story include: i) the discovery occurred at a young and inexperienced pharmaceutical business; ii) three bench scientists had recently graduated from PhD programmes and only the fourth had any industrial research experience; iii) pivotal to its success was the support and risk-taking of the highly experienced and recently hired head of pharmaceutical research; iv) a timely patent issued to Takeda Chemical Industries suggested a new line of research; v) a mistake made by an inexperienced pharmacologist yielded pivotal information; vi) the bench scientists were given the freedom to explore while being supported by research managers; vii) luck favoured the scientists in losartan's subreceptor-binding and metabolite; and viii) the marketing group insisted that losartan not be developed until Merck expressed an interest in the drug candidate. Today, losartan is a multibillion dollar drug.

Keywords: angiotensin II receptor antagonist, discovery process, risk taking

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1. Introduction

A pioneering, multibillion dollar antihypertensive drug almost came not to be. Discovered in March 1986 by scientists on their first assignments at a corporate research lab after completing their PhDs, losartan was the first in a new class of antihypertensive drugs, angiotensin II (Ang II) receptor antagonists. The company, DuPont, was also new to pharmaceuticals. Oil shocks of the 1970s and high prices for petroleum and natural gas feedstocks for its traditional chemical businesses, led senior executives to seek new businesses that would reduce dependence on these inputs and generate higher profit margins [1]. Following its long-practice of creating new businesses and growth from research in its labs, DuPont had launched efforts by 1980 to create pharmaceuticals and other life sciences businesses (Figure 1). The losartan work was among these early lab endeavours. This is its history of discovery based on oral histories of scientists and research managers, patents and publications.

Losartan's discovery came from taking risks, scientists having the freedom to explore with the unstinting support of research managers, creativity, meticulousness, trying new approaches, making assumptions in the absence of data, mistakes and luck. Inexperience and experience both proved essential; they complemented one another. In a pharmacologist's mistake, inexperience proved to be a boon. However, it needed an experienced research manager to recognise promise in the mistake's results and persuade others that the new line of research that had been opened up, needed to be pursued. However, DuPont's inexperience later proved to be a liability when it almost decided not to develop losartan. This time, it needed an experienced company, Merck, to recognise the potential of losartan, which persuaded DuPont that the drug candidate had promise and should be developed.

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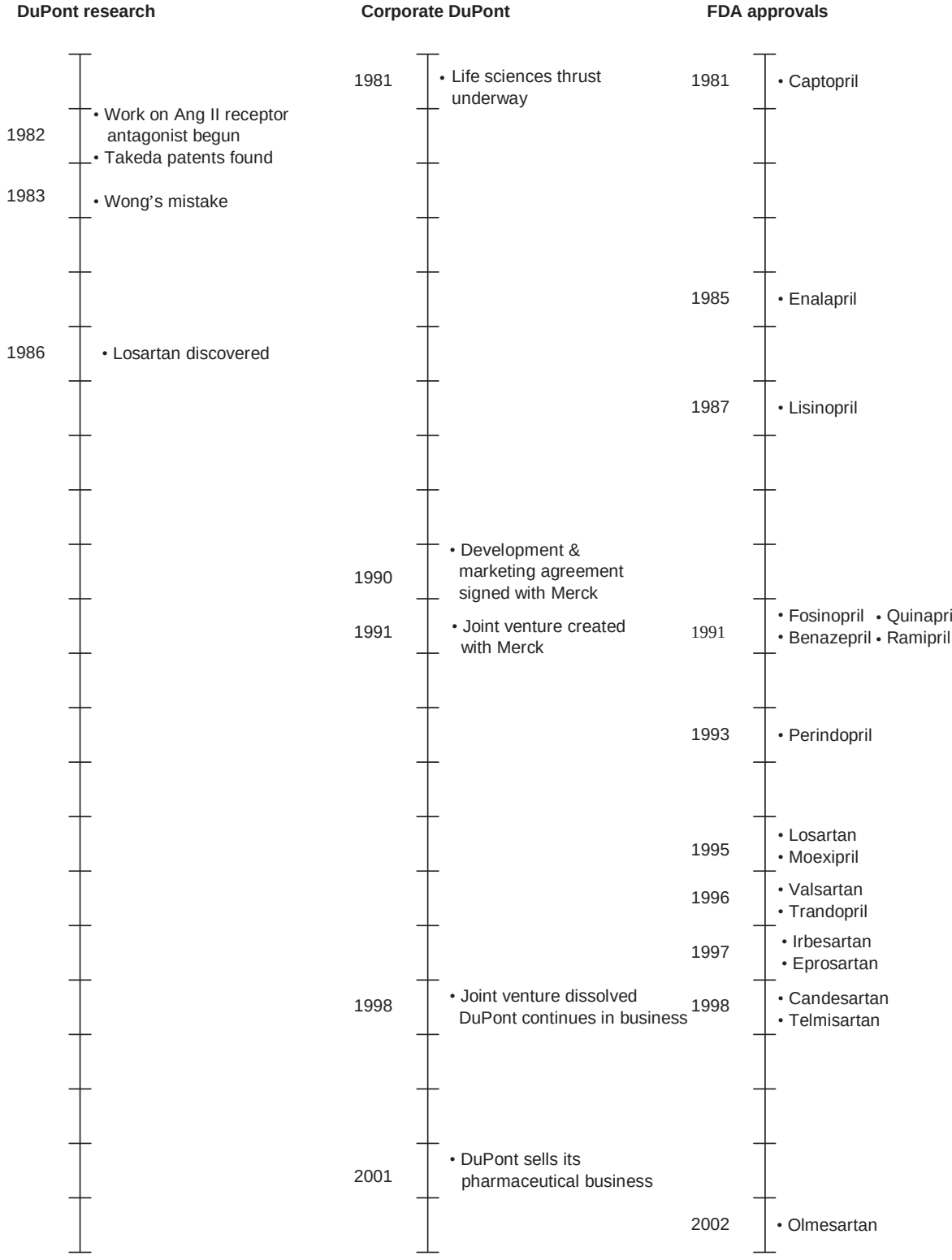

Figure 1. Timeline of key events in the discovery of losartan.

2. Research on the renin–angiotensin system in the early 1980s

Hypertension results from the high force of blood on vessel walls. The pumping of the heart sends rhythmic pulses of blood surging through blood vessels. Under normal conditions, vessels dilate and contract to accommodate the undulating flow of blood. For many reasons, vessels may lose their flexibility or muscle tissues in vessels may contract. To move the same amount of blood that is needed by the body, the heart must now pump with a greater force to overcome the higher resistance. Over time, this creates high blood pressure. Besides doing damage to the heart, hypertension can be detrimental to other organs such as the liver, kidney and brain. Consistent high blood pressure can increase the chances of heart attack, stroke, kidney diseases and eye blood vessels bursting.

The causes of hypertension are many, complex, and not entirely known, leaving room for many different approaches to targeting the disease. By the 1970s, pharmaceutical companies had begun drug discovery efforts aimed at the renin–angiotensin system (RAS), which was known to play a role in regulating blood pressure (Figure 2). However, much was still unknown in 1982 when DuPont scientists turned their attention to RAS in their quest for an antihypertensive drug.

RAS regulates blood pressure by a sequence of steps, starting with the production of the protein angiotensinogen in the liver [2]. Released into the bloodstream, it is not harmful by itself. The kidneys release the enzyme renin into the bloodstream. Renin is specific to angiotensinogen, cleaving it to form angiotensin I (Ang I), a decapeptide hormone. Subsequently, angiotensin-converting enzyme (ACE), which is nonspecific, cleaves Ang I to form Ang II, an octapeptide hormone. Ang II is active in causing high blood pressure and other physiological effects. The Ang II molecule binds to receptors on the surface of muscle cells lining blood vessels. The binding results in the contraction of the vessels and rising of blood pressure. Thus, RAS presented at least three targets for drugs to interfere with its functioning and lower blood pressure.

Drugs can be designed to inhibit the two enzymes – renin and ACE. In blocking renin, a renin inhibitor drug would prevent the cleaving of angiotensinogen and the subsequent steps that lead to hypertension. Renin was an attractive target because in being specific to angiotensinogen its physiological function was limited. A renin inhibitor drug would, thus, probably have few side effects. A few compounds that inhibited renin had been discovered by the early 1980s, but they could not be made orally active to turn into drugs. Even by mid-2006, after decades of research, no drug in this class had been launched in the market.

Targeting ACE to prevent the formation of Ang II and subsequent steps leading to hypertension had been more successful by the early 1980s. The first ACE inhibitor, captopril from Squibb, had been approved by the FDA in April 1981. It was evidence that interfering with RAS could lower blood pressure, increasing industry's interest in discovering drugs targeted at RAS, especially ACE inhibitors.

Lastly, a drug can be designed to bind with Ang II's receptors and prevent it from doing so. No Ang II receptor antagonist drugs existed until losartan was discovered. Industry attempts over many years had resulted in a few antagonists, peptide analogues of Ang II, that were active *in vitro*, but could not be made into drugs. They lacked oral absorption and had short half-lifes – some of just a few minutes. Some even showed agonistic activity.

In the early 1980s, scientists were aiming their drug discovery efforts at all three RAS targets.

3. Origins of the work

In March 1982, DuPont hired RI Taber, a scientist with nearly 20 years of research experience at the Schering Corporation, to head pharmaceutical research at DuPont. By now, the company's thrust into pharmaceuticals was well under way and a number of research programmes were in progress. On joining, Taber began reviewing them all [3].

Cardiovascular research at DuPont had been going on for many years, but the effort was small compared with those at established pharmaceutical companies. A number of compounds had been synthesised and tested, but none had made it as a drug. Taber found the scientists working on a variety of cardiovascular compounds for a number of targets. He noticed some of these were of the types that had been abandoned by others in the industry. Among vasodilators were some that were similar to minoxidil. Similar compounds had been shown to produce cardiac lesions in dogs and were no longer being pursued by others in the industry. Another discovery attempt combined different types of compounds, such as ACE inhibitors, β-blockers and vasodilators. These yielded large molecules that were not stable. Taber decided to quickly put an end to these lines of cardiovascular research. He did not think any were likely to result in a drug.

On completing his survey of all the pharmaceutical research efforts at DuPont, Taber concluded that the overall work was fragmented and spread thin. So he began by focusing efforts in a few areas that included cardiovascular, central nervous system, anti-inflammatory and a small cancer programme. He suggested setting up three targets. Taber said, '*We will go off and look for compounds for these three targets and wherever we succeed, that will be our research programme*'. AL Johnson, who headed the medicinal chemistry group in cardiovascular research, underlined the importance of such choices, '*I think one of the major problems is identifying a good area and going after it, and committing the resources to it to make sure it succeeds. The trouble with research is we can never predict (which area will turn out to be good)*'.

Of the three targets, one that Taber suggested was the Ang II receptor. Taber reasoned that instead of targeting the

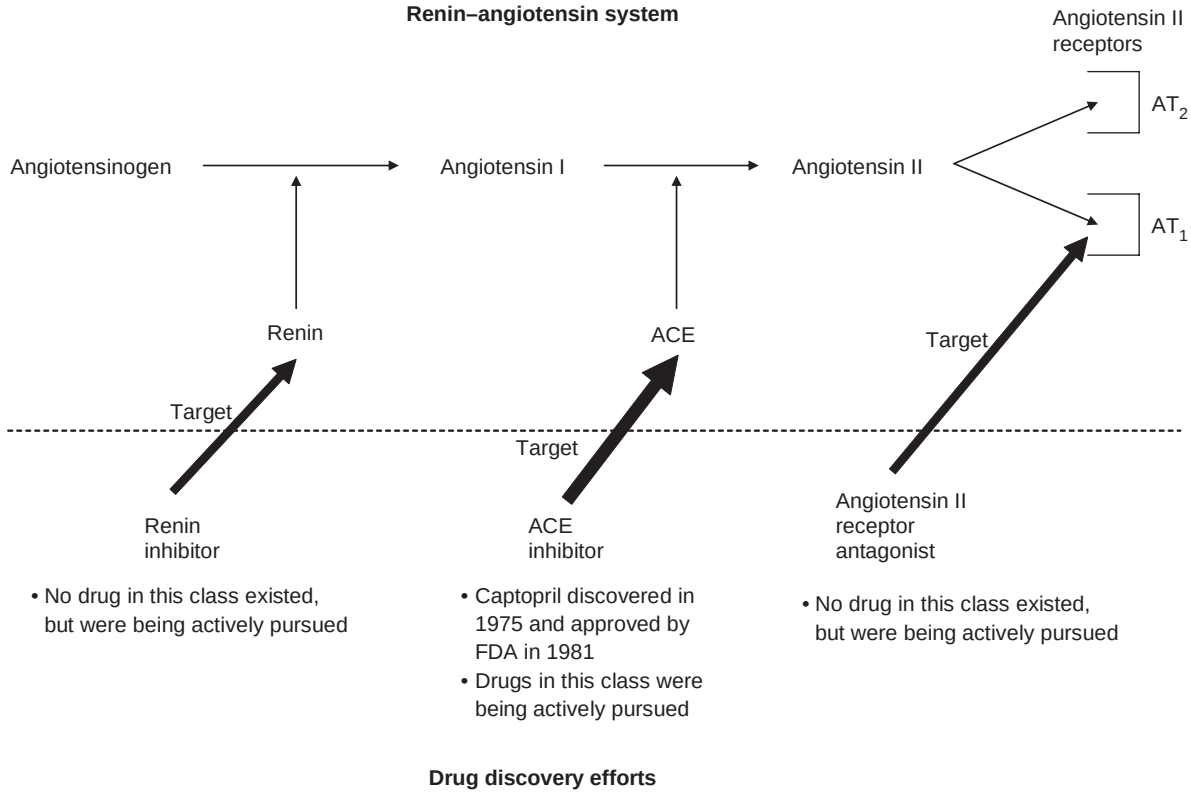

Figure 2. Drug discovery efforts aimed at the renin–angiotensin system in the early 1980s.
Angiotensin II receptor sub-types were not known in the early 1980s.
ACE: Angiotensin-converting enzyme.

enzymes in RAS, the receptor might yield something novel and beneficial. No Ang II receptor antagonist drug existed. The first in this new class of antihypertensives would have an edge in the market. With captopril already being sold and ACE inhibitors being pursued by many others, there was little point in chasing those for a small research group such as DuPont's. Moreover, Taber felt that the history of pharmaceutical research showed that a drug with a new mode of action often yielded important findings and led to unforeseeable therapeutic benefits. Why not try an alternative route to drug discovery? He argued, '*An angiotensin receptor antagonist would do everything that an ACE inhibitor would do and perhaps would not be as toxic*'. However, the DuPont scientists were not alone in their pursuit.

4. Initial work with peptides

JV Duncia, a chemist who had joined DuPont after obtaining a PhD in organic chemistry from Princeton University in 1981, was assigned to the Ang II receptor work. He chose to synthesise peptides, despite no one having had any success with this approach before. Although no peptide analogue had yet led to an Ang II receptor antagonist, the approach did not preclude the possibility. Besides, he did not have a better lead. '*There was not much out there scientifically*', noted Johnson of those days.

Duncia felt that the peptide approach at least had some advantages. There was some literature on peptide antagonist compounds. Plus, the structure of captopril had originated in peptides. Squibb scientists had taken a peptide obtained from snake venom and designed analogues of it that led, in 1975, to the discovery of the nonpeptide captopril. Peptides held the prospect of a more rational approach to drug design. Duncia reasoned that if he could find an analogue that antagonised Ang II, he would try fixing the undesirable characteristics. However, dealing with peptides was not easy. They were floppy molecules, making drug design difficult. Nonpeptides were easier to work with because they were rigid and small. They were also easier to manufacture and more effective as drugs. However, he did not have any nonpeptide leads.

Duncia began making small peptide analogues of different fragments of Ang II to see if any would bind to the receptor

and prevent Ang II from doing so [4]. The literature contained some information, but it was contradictory. He pursued a claim that a central tetrapeptide had strong binding activity. His analogues of that fragment did not exhibit any strong binding activity. Another report noted that a terminal tetrapeptide had good binding activity. Duncia created an analogue and found binding activity that was barely detectable. He synthesised analogues of other fragments, many that were two or three amino acids long, but found nothing. Eventually, after ~ 1 year and many inactive molecules later, he concluded that contrary to the assumption with which he had begun his work, analogues of small fragments of Ang II would not work. Most of Ang II was probably involved in binding, so a peptide with six to eight amino acids would most likely be necessary to attain binding activity. However, that was far too large a fragment to analogue. Duncia's peptide analogue approach had failed to produce a promising molecule.

The scientists also took another approach by setting up a receptor-binding assay to screen compounds from DuPont's chemical library. Despite screening > 10,000 compounds, they found nothing useful. About four molecules were 'barely active'. Even the hint of promise had eluded their search for an Ang II receptor antagonist. '*Finding it was like looking for a needle in a haystack*', observed Johnson. '*Back in 1982, we thought it was a formidable objective*', agreed Duncia.

5. A mistake and pivotal findings

After months of unyielding search, the scientists got their first break at the end of 1982. A routine patent search for Ang II receptor antagonists found two promising patents assigned to Takeda Chemical Industries [101,102]. The patents, issued in July and October 1982, described a family of compounds that were novel imidazole derivatives which the company claimed had '*excellent angiotensin II antagonistic activity and hypotensive activity and are useful as a hypotensive agent*' [102]. Excitingly, these were that rarity – nonpeptides.

Many other companies besides DuPont must have noticed the patents and Takeda had a head-start. Hurriedly, DJ Carini, a chemist who had just arrived at DuPont in 1982 after completing his PhD in organic chemistry from the Massachusetts Institute of Technology, was given his first assignment to synthesise the Takeda compounds so that their effects could be verified. If found promising, they would, finally, be a new line of attack. Carini synthesised compounds that seemed most promising from the family described in the patents. One was named S-8307 (Figure 3). Meanwhile, despite his lack of success, Duncia persevered with the synthesis of peptides because nothing conclusive had yet been shown about the Takeda compounds – there was no guarantee they would lead anywhere.

Two pharmacologists, AT Chiu and PC Wong, were responsible for testing the compounds. Chiu used a receptor-binding assay to first determine whether a particular compound would bind with Ang II receptors in isolated tissues. Wong then evaluated the molecule in a functional assay to check whether in binding the molecule actually antagonised. Another functional assay checked to see whether the molecule diminished the vasoconstrictor effect due only to Ang II. Other chemicals in the body also cause vascular contraction that is essential and does not result in high blood pressure. If the synthesised molecule reduced vasoconstriction due to these chemicals as well, it would not be selective in its action – undesirable in a drug. Subsequently, the molecule would be tested *in vivo* to verify whether *in vitro* effects also held in animals.

Chiu's receptor-binding assay results of the Takeda compounds synthesised by Carini caused disappointment. They were at odds with the patents' claims. S-8307 and the other molecules did bind with the Ang II receptor, but extremely weakly [5,6]. They could have been dropped for lack of promise. They were at some other companies [7]. However, instead of stopping with these results, Chiu and Wong continued onto confirming the results in functional assays and then *in vivo*. They were being thorough, but follow-on tests in the absence of anything worthwhile in the receptor-binding assay could be viewed as a waste of resources and time. However, Chiu believed that *in vitro* tests had to be correlated and verified *in vivo* because many factors could cause results to differ in these tests. The two persevered.

Wong had also joined DuPont only recently, after completing his PhD in pharmacology in 1981 from the University of Minnesota. The Ang II receptor antagonist programme was his first assignment. Accustomed to academic research in pharmacology, Wong was not used to the differences involved in industrial pharmacology. Responsible for testing the Takeda compound *in vivo*, he injected a large quantity (100 mg/kg) of it into a rat. In a human weighing 70 kg, it would amount to an intravenous dose of 7000 mg. As a comparison, losartan taken orally by a human only has 50 mg of the compound. Taber observed, '*It was like adding the animal to the drug instead of adding the drug to the animal*'.

When Wong showed others his results, the immediate reaction was of dismay at the mistake. However, Taber, himself a pharmacologist, quickly noticed, this time with amazement, that although the molecule was extremely weak, it was selective. It was evidence of the mode of action they were seeking. A drug with such selectivity would have the desired effect with probably few side effects. As the compound was extremely weak, it took a vast quantity injected directly into the rat's bloodstream to show selectivity [5,6]. The Takeda patents made no mention of selectivity, only potency that had, in any case, proved to be extremely weak. Wong also showed that S-8307 was a competitive antagonist that indeed lowered blood pressure in rats, although weakly, with the very high dosage [5,6].

Wong's mentor in graduate school had impressed upon him that selectivity was more important than potency. Focused on

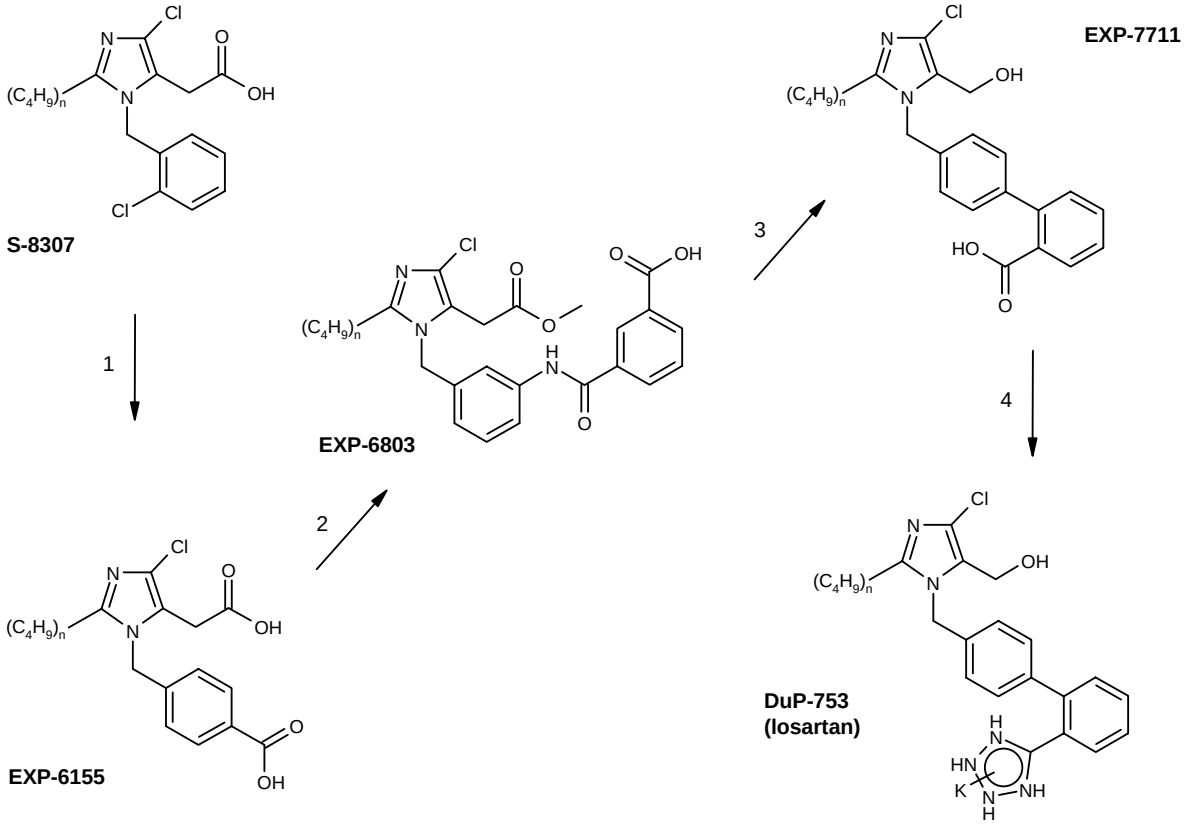

Figure 3. Important molecules in the discovery of losartan.

evaluating the former, and knowing from *in vitro* results that the compound was extremely weak, he did not think twice about the massive intravenous dose. He was unaware that such an amount was unacceptably large for drug discovery. Had he known that, he would have injected the 'right' (lower) amount. They would not have found selectivity and the Takeda compounds would have been dropped.

Through personal conversations, one of the DuPont scientists later learned that Takeda had tried unsuccessfully to increase the potency of their compounds. After a while, they gave up and turned their attention elsewhere. Given the interest in Ang II receptor antagonists, the Takeda compounds were no doubt pursued at many other companies. In conducting their tests correctly, they would not have found any results of promise. It took a mistake to discover selectivity.

Thrilled by the results, Taber suggested directing discovery efforts at the Takeda lead to design compounds that were similarly selective, but far more potent and which could be taken orally. His view was not shared by everyone. The increase in potency needed was unrealistic, they said, and they were skeptical the molecule could be made orally available. They agreed that the Takeda compounds were the first indication of a nonpeptide Ang II receptor antagonist, but argued that this was also an untested approach. Carini recalled this discussion: '*At that time it was felt that our chances of getting that kind of increase in activity were not good, and, admittedly, they probably weren't. The fact that it worked does not change the fact that the odds were against us when we started*'. However, Taber had little doubt that S-8307 was a viable lead that just had to be followed. Carini later described Taber inquiring during the debate, '*Well, do you have anything else? No? Well then, hell yes, it is a lead*'. It was 1983.

6. Nonpeptides and losartan

Carini began synthesising a series of structural variants of S-8307. Their activity, he found, was at best no better than that of S-8307. Most were inactive. Not long after, Duncia joined him, abandoning his peptide work.

Duncia began by synthesising a couple of simple analogues and then moved to computer modelling to take a more rational approach. He wanted to overlap and compare the structures of Ang II and S-8307 to see how more potent analogues could be made by better mimicking the binding portion of Ang II. The chemists now believed S-8307 was weak because it was too small compared with most of the Ang II they believed was involved in binding. The question still remained: which portion of Ang II bound and how?

Duncia found a model of Ang II's three-dimensional structure from some published spectroscopic work [8]. This model hypothesised Ang II's conformation in solution, not when it was binding to the receptor. There was no X-ray data available on the structure. However, starting with that conformation, he realised he could use modelling to hypothesise about Ang II's contact points with the receptor. Then, the structure of S-8307 could be overlapped with that of Ang II to see what modifications were necessary in S-8307. The computer modelling required making a number of assumptions that later research showed were not entirely accurate. Nonetheless, in the absence of better information, assumptions had to be made. Fortunately, modelling led to ideas that worked. The first assumption was taking the particular Ang II model as valid. There were also others in the literature and the information was not consistent. Duncia chose his model because it was based on Ang II's conformation in water. He reasoned it was closer to reality than conformations in other kinds of solution. Moreover, Ang II was floppy. Its shape in solution could be very different from its shape when binding with the receptor. '*It was a big leap of faith*', said Duncia. Next, assuming that S-8307 partially mimicked Ang II in order to overlap their structures was another such leap. Unfortunately, there was no information available on the receptor's structure.

The computer equipment needed for modelling in those days was huge, taking up an entire room. There was only one such machine at DuPont and a single individual, WC Ripka, ran it. Ripka plugged-in the structural models of the two molecules in the computer. The two structures were then overlapped with Duncia's instructions and moved around to find the right alignment. More assumptions went into this process. For example, both molecules had carboxylic acids. Duncia assumed they were congruent. He also assumed that both molecules bound in the same way with the receptor. It need not have been so. Adding to the difficulty of computer modelling was the crude technology. '*It was like a hand overlap. The computer did not do anything. We overlapped it by hand, twisting it until finally I saw the groups line up the way I wanted them to line up*', said Duncia. Overlapping suggested that S-8307 may lack a second acidic functionality compared with the Ang II computer model. Adding that would make S-8307 larger. Takeda had not patented a second functionality. If they could find an appropriate one, it would also make their molecule different and patentable. Duncia added carboxylic acid as the second functionality and created a new molecule, EXP-6155 [8]. '*The modelling was based on a lot of assumptions. And the probability of something working after all those assumptions was very small*', he noted. Potency shot up 10-fold when EXP-6155 was tested.

The improvement in potency was encouraging, but not sufficient. EXP-6155 was not orally active in rats, even in large doses. The working hypothesis remained that Ang II needed almost all of its amino acids for its activity, so EXP-6155 had to be enlarged to raise potency. They continued modifying and expanding it while retaining the carboxylic acid group Duncia had earlier added [2,8]. An appendage on the molecule, an amine, was used to 'hook on' other functional groups to enlarge the molecule. They made a large number of analogues. The effort eventually yielded EXP-6803, which showed another 10-fold boost in potency. It, too, was not orally active.

Further synthesis now proceeded based on EXP-6803 [9,10]. The chemists had been given a deadline 6 months earlier to find orally active compounds; otherwise their line of research would be terminated. It was now 1 month past the deadline, but no one had yet mentioned it. Someone surely would, soon. Despite the big advances they had made so far, without oral activity they had no drug. The molecule had to pass through cell membranes, which are greasy, to get into the bloodstream. To pass through, the molecule too had to be greasy. Carini thought that a very different molecule, structurally simpler, was required compared with the ones they had been synthesising. At the same time, it had to retain those characteristics they had found boosted potency. He hypothesised that an amide bond linking two aromatic rings on their molecule was the culprit – it was not greasy enough. Furthermore, often in turning a peptide into an orally active nonpeptide the amide groups were replaced. Thus, he began synthesising analogues of the linkage to replace the amide. He substituted various groups. They did not work. Eventually, he attached the hydroxymethyl group to the fifth position on the imidazole ring. It made the molecule greasy. The simpler structure would later shorten the synthesis work and contribute in producing a metabolite with unexpected benefits. They now had the molecule EXP-7711 that was orally active and it was able to lower blood pressure for an extended period [9,10]. However, there was no increase in potency.

The next series of molecules were modifications of EXP-7711 [2,4,9]. With oral activity attained, the aim was to continue increasing potency. EXP-7711 was still too weak to be made into a drug. Much of the effort revolved around replacing a carboxylic acid group with a variety of acidic functional groups. None were better than EXP-7711. After synthesising a number of molecules, Duncia attached an unusual acidic functional group called tetrazole that led to yet another 10-fold increase in potency. They had losartan [103]. It was March 1986.

A tetrazole is a five-membered ring where four of the five atoms are nitrogen. It is found in vinegar and some other common chemicals. Tetrazoles had been used in medicinal chemistry, but never as an acidic isostere in an approved drug. It was unusual enough that a number of people inquired what it was. Why did Duncia use the tetrazole? Calling it a miracle, he explained, '*I did not see it in the literature even though it was there, but I did not happen to come across it. I just started drawing a heterocyclic analogue of a carboxylic acid. And I drew four nitrogens and I saw, yeah, the valency is okay; you know, the number of bonds is okay; everything is satisfied. I wonder if this thing really exists? And I*

had a chemistry book that I had bought for $2 at Barnes & Noble on 18th Street and 5th Avenue in Manhattan… in the old days they used to have bins of books for a buck or two. As a graduate student I would take a bus ride (from Princeton, New Jersey) to go up there to see what books I could get for a couple of dollars. And I got this organic chemistry book written by a couple of German authors [11]*. Sure enough, in that book it gives you a recipe for making tetrazole. I go, my goodness, I got to do this. I asked Carini, Dave you have a precursor for making the tetrazole. Can I borrow some to make a tetrazole? He said, 'Sure John.' It was very kind of him to do that. And I made it*'.

Duncia continued, '*Sometimes you have to take leaps of faith. Sometimes you are not lucky, but sometimes you get that 10-fold kick in activity. And if you are very conservative and are afraid to step out, you probably won't get there*'. Adding the tetrazole resulted in the final breakthrough – losartan or DuP-753. The tetrazole improved oral absorption and increased potency. Losartan was 1000-times more potent than S-8307. Between the two molecules lay hundreds others that had to be synthesised to reach the desired levels of potency and oral activity.

7. Selling losartan within DuPont

Despite the excitement losartan generated among the scientists, it elicited little enthusiasm among the marketers in DuPont's pharmaceutical business. Taking losartan to subsequent phases of development and commercialisation proved to be a difficult sell. In late 1987, the company estimated that development would require approximately a couple of hundred million dollars and take ~ 10 years. Comparable sums would then have to be spent on marketing, distribution, and promotion. The marketers presented their report. They doubted losartan could be successful, based on the characteristics of the compound, the drugs already available, and the nature of the hypertension market. It was not worth developing and commercialising. The best move, they recommended, was to out-license losartan. It was a 'me too' compound, in being a 'modified ACE inhibitor'. With captopril selling successfully, enalapril from Merck recently approved by the FDA in 1985, and other ACE inhibitors in various stages of development, there was little to differentiate losartan. Why would anyone buy it? Losartan would need a vastly superior safety and efficacy profile that it was unlikely to have. In the 10 years that it would take to launch it, new products would continue to enter the market and generics would exist. The market would be saturated by then. Most importantly, there were no existing unmet medical and marketing needs in this therapeutic area. Not only was DuPont unlikely to earn a profit, it may not even recoup its expenditures in development and commercialisation.

The DuPont scientists and research managers disagreed vehemently. It was scientifically incorrect of the marketers to label losartan a 'modified ACE inhibitor' and a 'me too' drug. It did not inhibit an enzyme, but antagonised a receptor. Rather than being a 'me too' drug, it was a scientific breakthrough. It was the first orally active, potent, nonpeptide Ang II receptor antagonist. Although aimed at the same disease, it lowered blood pressure through an entirely new mode of action. Pharmaceutical history was full of instances where a new mode of action yielded unexpected benefits. It may not have the side effects associated with ACE inhibitors. In any case, the concerns about losartan could only be settled after some development work. As this was a new class of drugs, there did not already exist a body of necessary scientific information. Data from at least Phase I and early Phase II clinical trials were needed to draw valid conclusions. Only then should economic and market analyses be performed. It was premature to reject losartan's development and recommend its out-licensing. They were not basing the decision on appropriate data. In both scientific and marketing terms, losartan would contribute to DuPont's reputation in the pharmaceutical industry.

P Timmermans (who had been hired to head cardiovascular research) noted that none of the major drugs representing new classes in hypertension and congestive heart failure could have been 'predicted based on paperwork'. A similar analysis would have resulted in none of them ever having been developed. Taber, Timmermans, and others spent great effort in convincing those outside drug discovery at DuPont of the promise of losartan. Some initial development work was done, but it did not receive high priority. Its continued development remained clouded. Then, Merck stepped into the picture and changed it.

8. Codevelopment with Merck

With a few promising molecules in various therapeutic areas, DuPont recognised that it lacked the expertise to conduct the sophisticated clinical trials needed. The company approached Merck, for its experience and capabilities in drug development, to explore the possibility of codeveloping the drug candidates emerging from DuPont's young pharmaceutical labs. Merck saw losartan's potential. Given its well-established position in the industry, its reaction carried weight. Doubts at DuPont turned to resolve. The struggling drug candidate suddenly gained credibility and high priority.

The two companies signed an agreement to collaborate on the development and marketing of losartan, starting in January 1990. Besides development capabilities, Merck also had marketing and sales capabilities that were lacking at DuPont and invaluable in launching and establishing a drug in a new class. For Merck, with its large presence in the cardiovascular market, here was an opportunity to be part of a new class of drugs. The relationship between the two was further strengthened in January 1991 by the formation of a joint venture, the DuPont Merck Pharmaceutical Company. The discovery of a new drug led to the creation of a new company.

9. Unexpected benefits

Pharmacological studies in rats revealed that losartan created an active and potent metabolite [2,12]. Fortunately, it amplified the antagonistic effect of losartan and extended its duration. Troublingly though, animal tests showed that the metabolite's creation varied by species. It was created in rats, but not in dogs. Naturally, there were worries about its creation and effects in humans. Clinical trials revealed that losartan created a major, active metabolite in humans also. Luckily, it had beneficial effects. Working in tandem with losartan, the metabolite lowered blood pressure much further than losartan could have on its own. Together, losartan and its metabolite were 10,000-times more potent than S-8307. Whereas losartan had a half-life of 2 h, the metabolite had a half-life of 6 h. Losartan's antagonistic effects, thus, lasted much longer and the drug could be taken just once daily.

Subsequent research showed that the Ang II receptor actually consisted of two subtypes – AT_1 and AT_2 [12]. Although Ang II bound with both subreceptors, it was only the binding with AT_1 that caused vascular constriction, leading to high blood pressure. Despite Ang II also binding with AT_2, the latter played no role in hypertension. The physiological function of AT_2 would remain unclear for many years to follow [13]. Astonishingly, it emerged that losartan binds only to AT_1. The molecule was not consciously designed to do so. This binding contributed to its efficacy.

As Taber remarked, drawing on > 20 years of research and management experience in drug discovery, '*You also have to be very lucky in the field of pharmaceutical research. There are many things that can happen that are totally outside your control*'.

10. Expert opinion and conclusion

Approved by the US FDA in April 1995, losartan was launched that month as the first Ang II receptor antagonist (losartan is the generic name of the drug; Merck sells losartan under the trade names Cozaar™ and Hyzaar™, which are registered trademarks of E. I. Du Pont de Nemours and Company, Wilmington, DE; Hyzaar is a combination of losartan and a diuretic). The two companies shared the revenue. Losartan's new mode of action proved very effective and its selectivity probably resulted in its having few side effects [14]. With its potency, long duration, and mild side effects, losartan was generating > US$ 3 billion in annual sales by 2005 [201]. At the time of its launch, analysts had estimated annual sales of ~ US$ 200 million [202]. The market for antihypertensives proved larger than had originally been estimated by DuPont's pharmaceutical marketing group. By 2006, it was estimated that > 60 million people in the US suffered from high blood pressure [15]. Along with losartan, the market also sustained other drugs that operated through various modes of action to lower blood pressure.

Losartan's structure served as prototype for others in their design of new AT_1 receptor antagonist compounds, such as candesartan, irbesartan, saprisartan, tasosartan, telmisartan, valsartan and zolasartan [2,16,17]. By 2002, the FDA had approved seven AT_1 receptor antagonists and ten ACE inhibitors (Figure 1). Among those was eprosartan that also owed its origins to the Takeda patents, but was discovered independently by SmithKline Beecham using a different modelling approach [2,16].

In 1997, the American Chemical Society awarded Duncia, Carini, Wong and two scientists from Merck its Award for Team Innovation. The joint venture between the two companies was dissolved in 1998. DuPont continued alone for a while until exiting the pharmaceutical business in 2001. Merck continues to successfully sell Cozaar and Hyzaar.

Bibliography

1. HOUNSHELL DA, SMITH JK Jr: *Science and Corporate Strategy: Du Pont R&D, 1902-1980*, Cambridge University Press, New York, NY (1988).
2. WEXLER RR, GREENLEE WJ, IRVIN JD *et al.*: Nonpeptide angiotensin II receptor antagonists: The next generation in antihypertensive therapy. *J. Med. Chem.* (1996) 39:625-656.
3. BHARDWAJ G: Oral history information and quotations are from the following interviews conducted by the author: DJ Carini - June 15 (1999), June 21 (2000); JV Duncia - June 15 (1999), June 21 (2000); AL Johnson - July 21 (1999); RI Taber - July 20 (1999); PBMWM. Timmermans - July 23 (2001); July 25 (2001); RR Wexler - June 23 (1999); PC Wong - July 22 (1999); June 23 (2000).
4. DUNCIA JV, CARINI DJ, CHIU AT *et al.*: The discovery of DuP 753, a potent, orally active nonpeptide angiotensin II receptor antagonist. *Med. Res. Rev.* (1992) 12:149-191.
5. WONG PC, CHIU AT, PRICE WA *et al.*: Nonpeptide angiotensin II receptor antagonists. I. Pharmacological characterization of 2-*n*-butyl-4-chloro-1-(2-chlorobenzyl)-imidazole-5-acetic acid, sodium salt (S-8307). *J. Pharmacol. Exp. Ther.* (1988) 247:1-7.
6. CHIU AT, CARINI DJ, JOHNSON AL *et al.*: Nonpeptide angiotensin II receptor antagonists. II. Pharmacology of S-8308. *Eur. J. Pharmacol.* (1988) 157:13-21.
7. WONG PC, TIMMERMANS PB: Historical development of losartan (DuP 753) and angiotensin receptor subtypes. *Blood Press.* (1996) 5:11-14.
8. DUNCIA JV, CHIU AT, CARINI DJ *et al.*: The discovery of potent nonpeptide angiotensin II receptor antagonists: a new class of potent antihypertensives. *J. Med. Chem.* (1990) 33:1312-1329.
9. CARINI DJ, DUNCIA JV: The discovery and development of the nonpeptide angiotensin II receptor antagonists. *Adv. Med. Chem.* (1993) 2:153-195.
10. CARINI DJ, DUNCIA JV, ALDRICH PE *et al.*: Nonpeptide angiotensin II receptor antagonists: The discovery of a series of *N*-(biphenylylmethyl)imidazoles as potent, orally active antihypertensives. *J. Med. Chem.* (1991) 34:2525-2547.

11. HILGETAG G, MARTINS A: *Preparative Organic Chemistry*, John Wiley & Sons, New York (1972).
12. WONG PC, CHIU AT, DUNCIA JV *et al*.: Angiotensin II receptor antagonists and receptor subtypes. *Trends Endocrinol. Metab.* (1992) 3:211-216.
13. SICA DA: Angiotensin receptor blockers: new considerations in their mechanism of action. *J. Clin. Hypertens.* (2006) 8:381-385.
14. MAVROMOUSTAKOS T, APOSTOLOPOULOS V, MATSOUKAS J: Antihypertensive drugs that act on renin-angiotensin system with emphasis in AT_1 antagonists. *Mini Rev. Med. Chem.* (2001) 1:207-217.
15. STANDARD & POOR'S INDUSTRY SURVEYS: *Healthcare: Pharmaceuticals.* May 25 (2006).
16. TIMMERMANS PB: Angiotensin II receptor antagonists: an emerging new class of cardiovascular therapeutics. *Hypertens. Res.* (1999) 22:147-153.
17. BÜHLMAYER P: Angiotensin-II antagonists: patent activity since the discovery of DuP-753. *Curr. Opin. Thera. Patents.* (1992) 2:1693-1718.

Patents

101. TAKEDA CHEMICAL INDUSTRIES LTD: US4355040 (1982).
102. TAKEDA CHEMICAL INDUSTRIES LTD: US4340598 (1982).
103. DU POINT US: US5138069 (1992).

Websites

201. http://www.merck.com
Merck annual report (2005).
202. http://www.newyorktimes.com
Merck cleared by FDA to see new hypertension drug.

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