Addendum: A History of Annual Reports in Medicinal Chemistry Volumes 1-49

HISTORY OF ANNUAL REPORTS IN MEDICINAL CHEMISTRY: HIGHLIGHTS FOR 3 BLOCKBUSTER DRUGS

1. Cimetidine (Annual Reports in Medicinal Chemistry Volumes 10, 14 and 16). The first blockbuster drug of the modern era, cimetidine (Tagamet®) became so when its sales exceeded $1 billion in 1986.1 Cimetidine (Figure 1) was discovered by Nobel Laureate Sir James Black and a team of medicinal chemists including C. Robin Ganellin,2 John C. Emmett and Graham J. Durant.3 Black was intrigued by the possibility of selective inhibition of one of the 2 known histamine receptors, and presented the idea to his managers at ICI, who directed him to focus on developing a “me-too” β-blocker. He was recruited to Smith, Kline and French as Director of Pharmacology by research director Edward Paget in 1963, and in 1964 was allowed to work on discovering H2-histamine receptor antagonists. Although Black predicted he would produce a suitable H2-receptor antagonist by Christmas of 1964, the complexity of the project delayed that finding until 1970, when the first H2-antagonist, burimamide, 1, was developed. Following successful animal testing, the group proposed to test burimamide (2, Figure 1) in medical student volunteers, but opted instead to test it on themselves to avoid a delay by the ethics committee. Thus Ganellin and Duncan were the first human subjects to receive burimamide, which reduced gastric acid dramatically, but was later found to cause agranulocytosis. Additional work by Ganellin and Durant resulted in the drug cimetidine, 2, which was 10 times as potent as 1. Cimetidine and related H2-antagonists were first discussed in Annual Reports in 1975,4 and again in 1979.5 Sir James Black shared the 1988 Nobel Prize in Medicine for his “discoveries of important principles for drug treatment” (along with ACSMEDI Hall of Fame members Gertrude Elion2 and George Hitchings2). Ranitidine (3, Figure 1), developed by Allen and Hanburys Ltd. (part of the Glaxo organization) followed in 1977, and was reviewed in Annual Reports by Jim Bristol in 1981.6

2. Atorvastatin (Annual Reports in Medicinal Chemistry Volumes 24, 34 and 39). The first of the HMG-CoA reductase inhibitors, now known as statins, were isolated in 1976. A British group headed by A.G. Brown isolated and characterized an antifungal metabolite from Penicillium brevicompactum, which they named compactin.7 Because the Brown group was only interested in the antifungal properties of the compound, they missed the fact that it was a potential antihyperlipidemic agent. In the same year, Akira Endo and his coworkers isolated the same compound, which they called mevastatin (4, Figure 2), from Penicillium citrinum, and characterized it as an inhibitor of HMG-CoA reductase, the rate-limiting enzyme in the biosynthesis of cholesterol.8 Endo hypothesized that plasma cholesterol could be lowered more effectively by inhibition of HMG-CoA reductase in the liver than by restricting absorption from the diet. He screened more than 6,000 microbes between 1974 and 1976 before identifying MK-236B (mevastatin) from Penicillium citrinum, and characterized it as an inhibitor of HMG-CoA reductase. The compound was isolated by solvent extraction, chromatography and recrystallization.5 Subsequently, Alfred Alberts of Merck, Sharp and Dohme Research Laboratories isolated mevinolin (5, aka lovastatin, Figure 2) from Aspergillus terreus. Lovastatin was FDA approved
as Mevacor® in 1987, and became the first statin to be marketed.

By 1994, there were already several statins on the market, including Mevacor® (lovastatin), Zocor (simvastatin)®, Pravachol (pravastatin)® and Lescol (fluvastatin)®. In the early 1990s, Ron Cresswell, the Chairman of Pharmaceutical Research at Warner-Lambert/Parke Davis, chose to focus the company’s limited resources on a few promising molecules, including atorvastatin (Figure 2, which was by now known as Lipitor®), a compound synthesized by Bruce Roth in 1985. The decision to develop atorvastatin was controversial, since it was generally viewed as a “me-too” drug. Senior management at Warner-Lambert were ultimately persuaded to fund the initial round of human trials, even though marketers projected that sales of Lipitor would likely not exceed $300 million annually. Initial trials were conducted in employee volunteers, and atorvastatin was shown to outperform all other statins as a cholesterol-lowering agent. The success of these early trials led Warner-Lambert to seek a partnership to address constrained sales and marketing resources. Warner-Lambert narrowed the choices to Hoffmann-LaRoche and Pfizer. Ironically, Pfizer was chosen for the partnership because they made a better offer, and were not viewed as a hostile acquirer. Lipitor was FDA approved and went on sale in 1997, the same year that the FDA first allowed drug advertising to target consumers. The fact that it was priced below the other statins, combined with an unprecedented marketing campaign, made Lipitor the top-selling statin within 3 years, and led to $125 billion in sales between 1997 and 2012. In November of 1999, Pfizer announced an unsolicited $80 billion stock offer for Warner-Lambert, the largest hostile takeover offer in the history of the industry.

The statins have appeared in several volumes of Annual Reports in Medicinal Chemistry. They first appeared in a chapter on hypercholesterolemia in Volume 24 (1989) that discussed the LDL-lowering effects of mevastatin and lovastatin. They were covered as an emerging therapy for atherosclerosis in Volume 34 (1999), at a time when statins were continuing to be developed. The pleiotropic effects of the statins were discussed in Volume 39.

3. Clopidogrel (Annual Reports in Medicinal Chemistry Volumes 34, 40 and 49). Clopidogrel (9, Figure 3) is an example of a drug that would likely not be discovered or developed today, in that it requires metabolism by cytochrome P450 for activity (i.e. it is a prodrug, and thus would not be picked up in a high-throughput screen). In addition, clopidogrel is a covalent drug, which was a neglected area in drug discovery until recently. In addition, the identification of new medical entities by random screening in multiple assays is no longer practiced in the pharmaceutical industry today. The discovery of clopidogrel was initiated in 1972, when Dr. Fernand Eloy at Sanofi started a project to identify anti-inflammatory agents related to the thienopyridine analogue tinoridine (7, Figure 3). Eloy assigned the project to Jean-Paul Maffrand, who had considerable experience in thienopyridine chemistry, and he and his group synthesized a variety of new molecules that were screened in a wide array of biological assay systems. None of these analogues had any anti-inflammatory activity, but unexpectedly, several of them had antiplatelet effects. The most active of these, ticlopidine 8, was developed, and it was marketed as Ticlid® in France in 1978. At that time, Ticlid® was only indicated for use in preventing platelets from adhering to artificial surfaces when blood was re-circulated during cardiac surgery. Subsequent large-scale clinical trials demonstrated that ticlopidine had benefits in patients at risk for thrombosis, and the drug was eventually marketed in the US in 1991. Ticlid® was found to produce hematological disorders in some patients during the first 3 months of therapy, and thus patients had to be clinically monitored. In
the search for a backup compound at Sanofi, Maffrand and his group synthesized more than a thousand analogues of 8, but only the last one made was superior to the parent. This compound was designated PCR4099, and was found to be a racemic mixture; the S-isomer of the pair was developed, and became clopidogrel, 9. It was later discovered that 9 required metabolic activation by cytochrome P450, as shown in Figure 3.18 Clopidogrel 9 is rapidly metabolized by CYP2C19 to the corresponding thiophen-2-ol 10, which possesses a tautomeric form 11. Ring opening of 11 then affords the active metabolite 12.19 Metabolite 12 binds irreversibly to the ADP receptor P2Y12, which plays a central role in platelet aggregation, thus producing an inhibition of platelet aggregation. Despite all of the modern technologies developed for drug discovery, it is clear that serendipity can still play a role – because clopidogrel is inactive in vitro, its activity would never have been noticed using today’s standard drug discovery protocols. Plavix® was marketed in the US through a partnership between Sanofi and Bristol-Myers Squibb, and became the second-best selling blockbuster drug in history, with annual sales of more than $9 billion during peak years. Patent protection for Plavix® expired in 2012.

Other approaches to antiplatelet therapy have been reviewed in Annual Reports Volume 35,20 and recent progress in the development of P2Y12 receptor antagonists are covered in Volume 49.21 An excellent review of other drugs that require activation by cytochrome P450 also appears in Volume 49.22

References

2. Denotes a member of the ACS Division of Medicinal Chemistry Hall of Fame.


