At the start of our research programme that lead to amlodipine, a once-daily calcium antagonist for the treatment of angina and hypertension, there were over 90 published patents around the parent dihydropyridine ring system which posed a significant challenge for innovative drug design. Moreover, all agents of the class suffered poor pharmacokinetics, and there were no clues on how these might be improved. However, rational medicinal chemistry led to a novel series of dihydropyridines with potent calcium antagonist activity that displayed high, and uniform bioavailability, and long plasma half-lives. After extensive pharmacological profiling, UK 48,340 (amlodipine) was selected for clinical development and subsequently received worldwide approval as Norvasc™ for the treatment of hypertension and angina. Norvasc™ became the world’s leading antihypertensive agent and the fourth best selling drug, with some billions patient days of therapy achieved since launch.

Sildenafil, the first oral treatment for male erectile dysfunction, was the result of a research programme to block the action of PDE 5 and increase tissue levels of cGMP, even though the endogenous ligand that stimulated guanylate cyclase was unknown at the time. Starting from zaprinast, a weak and non-selective PDE 5 inhibitor, computer modelling guided rational medicinal chemistry to achieve significant increases in potency and selectivity within a novel series of pyrazolopyrimidines. Optimisation of SARs and pharmacokinetics led to UK 92,480 (sildenafil) that was essentially devoid of cardiovascular activity in clinical trials. However, the emerging role of nitric oxide and cGMP in controlling blood flow in the penis suggested that sildenafil would have a beneficial effect on erectile dysfunction. This hypothesis was confirmed by extensive clinical trials in nearly 5000 patients and sildenafil was approved by the FDA in March 1998 for male erectile dysfunction. Viagra™ is now one of the most widely prescribed medicines, and has been used by 100s of millions of patients throughout the World.

These research programmes will be discussed from a personal perspective that will highlight the importance of multidisciplinary project teams, challenges that arose during discovery and development and factors that influenced key decisions.