Drug Development Perspectives: From New NSAIDs to Novel Prostacyclins

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The development of new medicines is a high risk and hugely expensive business. If successful, the reward can be substantial, both in terms of finance but more importantly, this complex scientific endeavour can lead to major benefit for healthcare in our society. Having worked earlier in the Pharmaceutical Industry for some 20 years, my involvement in a great number of projects has always been rewarding, even if some projects never came to fruition to yield a novel drug. Joining the-then private company, the Wellcome Research Laboratories in Beckenham, Kent, UK, I was immediately involved in projects encompassing both the gastro-intestinal tract and the cardiovascular system.

One such project focussed on the development of novel anti-inflammatory agents, a topic which our leader, the Nobel Laureate, Sir John Vane had an on-going interest having earlier discovered the link between aspirin, inflammation, and the lipid mediators, prostaglandins. As the major side-effects of non-steroidal anti-inflammatory agents (NSAIDs) are gastro-intestinal injury and ulceration, we were keen to avoid such actions. A lead series of non-acidic compounds, exemplified by BW755C, was shown to exert powerful anti-inflammatory activity, but did not damage the stomach as it selectivity inhibited pro-inflammatory prostanoids yet did not affect the protective gastric mucosal prostanoids. Some 10 years later, others identified that there were indeed two classes of the synthesizing enzyme, cyclo-oxygenase (COX), explaining the tissue-selective inhibition. These GI-safe COX-2 inhibitors were rapidly developed by Searle (celecoxib) and by Merck (rofecoxib, Vioxx®), though following post-marketing reports of serious cardiovascular side-effects, Vioxx® was taken off the market. However, important development lessons have been learnt by the industry, and we now know that such adverse cardiovascular events are shared by all NSAIDs to varying extents, such information being currently highly important to the prescribing of NSAIDs to susceptible patient cohorts such as the elderly.

Prostacyclin mimetics are currently widely used to successfully treat severe pulmonary arterial hypertension (PAH), a highly proliferative, vascular remodelling and often fatal disease. Prostacyclin (or PGI_2) itself was discovered at Wellcome by our team led by John Vane and Salvador Moncada. The first use of prostacyclin for the successful treatment of PAH was reported in the early 1980's, while the synthetic formulation of prostacyclin, epoprostenol (Flolan®) was launched in 1995. Very soon after the discovery of prostacyclin in 1976, our search for a suitable synthetic stable analogue which would have a more beneficial pharmacological and pharmacokinetic profile was initiated. This detailed project resulted after 5 years and 1,000 compounds in the choice of a tricyclic analogue, BW15AU for further pre-clinical development. After the closure and take-over of Wellcome by Glaxo, the compound was acquired by a then small start-up US company, United Therapeutics, renamed treprostinil and very rapidly developed for PAH, being approved within 5 years by the FDA for this disease. Various formulations of treprostinil for use by other routes including inhalation and oral forms, have now become available for the treatment of serious PAH over the past 15 years since its approval, to great clinical and commercial success.

We have focussed in the past 5 years on the mechanisms underlying the pharmacological efficacy of the prostacyclins. This work had identified the multiple prostanoid receptors that can be activated by treprostinil and we have studied the distinct differences in the receptor activating profile of the different prostacyclins[1]. We have now shown the broad beneficial profile of treprostinil on prostanoid receptors promoting key pharmacological actions including vascular relaxation and anti-proliferative properties in the pulmonary arterial vasculature, which underlies its therapeutic value in PAH.

1. Whittle B.J., A.M. Silverstein, D.M. Mottola, and L.H. Clapp. **2012**. Binding and activity of the prostacyclin receptor (IP) agonists, treprostinil and iloprost, at human prostanoid receptors: treprostinil is a potent DP_1 and EP_2 agonist. *Biochem. Pharmacol.* 84:68-75.