Supplementary Material

Catechol O-methyltransferase as a target in translational and clinical research: a personal reflection on a real pioneer trail

A successful pharmaceutical creation is the product of sustained teamwork, optimism and serendipity, the portion sizes of which may vary. The catecholamine-Omethyltransferase (COMT) inhibitor entacapone and the triple-product combination of entacapone plus levodopa and carbidopa are no exceptions to this broad principle. As some of those who had the great good fortune to play central roles in the discovery and development of the first commercialised COMT inhibitor, it is our pleasure to recount as part of this anniversary review some of the backstory associated with this success.

The past, it has been said, is a foreign country where people do things differently [1]. Compared with 2024 that is undoubtedly true of the 1980s, where the story of our translational project begins. In those times, drawings for publications were created using pencils and stencils by lead investigators who had no pretensions to artistic talent and no access to computer graphics packages – or indeed to computers. PUBMED did not exist nor did the internet more generally and neither in any meaningful sense did email or mobile phones. Protocols for pivotal clinical trials could be (and were) delivered in 20 typed pages. Regulatory limitations on both pre-clinical and clinical studies were exiguous to an extent the modern perspective might struggle to comprehend.

Whether consequentially or paradoxically it was a golden age of pharmacological innovation (as, for example, the emergence of beta-blockers) and one that encouraged our hopes that there was room for further new discoveries, specifically in the area of COMT inhibition. It was in this context of modest material resources but great optimism and limited oversight that one of us (PTM) was engaged in 1982 as head of the then tiny pharmacology department of Orion Pharma, a middlesized Finnish pharma company, and given a single task summarised in delightfully simple terms: develop an original drug. We were helped on our way with a small funding, agreed upon on 30 November 1982, and then largely left alone to get on with it. Thus, we started with scanty though high-quality human resources and very

little money: but we had ideas, energy and resourcefulness – and were still young enough to think that those things would suffice!

What happened next is set out in greater detail in the main body of this review. Suffice it to say here that – 40 years on – our journey continues, having along the way generated hundreds of publications and dozens of PhD theses. It's been a wonderful career of scientific research and of learning, and interactions (some fraternal, others competitive) with commercial rivals – and in the course of it we discharged the original task assigned to us, identifying through our own resources a wholly new pharmaceutical agent that has been brought to market and used to the advantage of hundreds of thousands of patients with Parkinson's disease.

The broad sweep of this recollection contains more events than we can summarise in any detail. Two episodes, however, merit a special place in the record. First, some of us Finnish pioneers made trips to the USA in the early 1980s to explore the potential of COMT inhibitors with experts. In particular, we met with Cyrus R. Creveling at the US National Institutes of Health in Bethesda, Maryland. Cyrus (Bob) was a pioneer of COMT research and his positive opinion about our ideas was a source of great encouragement. In 1986 we met several other COMT scientists, notably Ronald (Ron) T. Borchardt in Lawrence, Kansas [2]. He had tried himself to develop COMT-inhibiting compounds but none of his candidates had been adequately effective. He too was wonderfully encouraging and supplied us with several of his publications that we had not previously discovered. In Buffalo, New York, we met Jerome A. Roth, who had made remarkable progress in defining the different roles of soluble- and membrane-bound-COMT. His studies were done using human brain samples, a phenomenon in itself.

The second episode of note took place at the 6th International Catecholamine Symposium, held in Jerusalem in June 1987, where we presented a series of posters setting out our concept and summarising our progress to date. There we encountered researchers from another Pharma company (a big one, for a change) who were also active in COMT inhibitor research: both groups were astonished to find out that the other existed. It emerged that we had both discovered independently that nitrocatechol was the critical structure for effective and selective COMT inhibition. Despite that obvious overlap, both companies were able to get solid patents for their respective

compounds. This meeting motivated the competing group to publish their existing results and to accelerate their project, disclosing their lead molecule, tolcapone. Clinical evidence was collected very speedily and they may have been drawing ahead of us at that juncture, but the adverse liver effects identified with tolcapone brought us back into contention.

Readers who noted that, at the start of this reminiscence, we described entacapone as our “first commercialised COMT inhibitor” would be right to think that is not necessarily the same thing as our “first COMT inhibitor”. That distinction belongs to nitecapone, the eventual fate of which is a cautionary tale about the vagaries of drug development.

In the late 1980s, nitecapone (otherwise known as OR-462) was our lead compound for an anti-Parkinson’s therapy. Phase I studies were initiated in 1987 and we had high expectations for the molecule in that indication. Fate, however, decreed otherwise. Further pre-clinical appraisals revealed a less favourable balance to the risk–benefit calculus and nitecapone is today memorialised to the world in a two-line Wikipedia obituary that notes simply: “It was patented as an anti-parkinson medication but was never marketed.” Quite so.

The loss of nitecapone set back the Orion Pharma COMT inhibitor programme. Starting again with entacapone meant several years elapsed while all the pre-clinical toxicology studies and Phase I investigations were repeated before we could move on to Phase II & III clinical trials. That’s not infrequently how it goes in pharmaceutical research, but in our case the adventure ended well enough. And, as the rest of this review illustrates, we learned such a lot along the way – even if we have not yet compassed the full extent of the significance of COMT inhibition as a therapeutic instrument, or its possible limitations or hazards.

References

1. Hartley LP. *The Go-Between*. Hamish Hamilton. London, 1953.

2. Schowen KB, Schowen RL, Borchardt SE, et al. A Tribute to Ronald T. Borchardt: Teacher, Mentor, Scientist, Colleague, Leader, Friend, and Family Man. J Pharm Sci. 2016 Feb;105(2):370-385. doi: 10.1002/jps.24687.