Institution: University of Aberdeen

Unit of Assessment: 5 - Biological Sciences

Title of case study: From melatonin receptors to Valdoxan - a novel and effective therapeutic anti-depressant drug

1. Summary of the impact

Original basic research on melatonin receptors undertaken at the Rowett Institute, University of Aberdeen, and funded by the Scottish Government, provided the opportunity for Servier pharmaceuticals to develop a new line of therapeutics for depression.

The company exploited Rowett know-how and invested in new research to develop a new line of compounds and to understand their structure-function relationships. This work enabled the development of melatonin analogues for clinical trials and ultimately led to the development of melatonin compounds for treatment of circadian related disorders.

One (S20098) was identified as having positive effects for disrupted circadian rhythms and beneficial outcomes for patients with depression. S20098 (also known as Agomelatine) was launched after EU authorization in 2009 as a novel anti-depressant drug called **Valdoxan®**. Today Valdoxan is an award winning anti-depressant drug recognised for its novel mechanism of action and few side effects. Valdoxan is the only anti-depressant drug to be brought to the market in the last 10 years. In summary, supported by *investment from industry* research *undertaken at the University of Aberdeen* contributed to the development of a novel antidepressant drug that provides *a new clinical intervention* with advantages over previously available antidepressants that will make a *significant impact on the health and well-being* of those afflicted by depression.

2. Underpinning research

In a research programme funded by the Scottish Government, undertaken at the Rowett Research Institute, University of Aberdeen, Professor Peter Morgan and Dr Lynda Williams (senior research scientist) identified the pars tuberalis of the ovine pituitary gland as site of a high-density melatonin receptor expression. This discovery was important for two reasons. 1) It allowed Professor Morgan and Dr Perry Barrett (senior research scientist) to develop a novel cell-based bioassay system to characterise the molecular pharmacology of melatonin receptors for the first time and, 2) it provided an important source of RNA for subsequent cloning of the ovine melatonin receptor [1]. As a result of this new knowledge and know-how, the French Pharmaceutical company Servier approached the Morgan/Barrett group directly to enter into a Strategic Alliance to develop novel analogues targeted towards the melatonin receptor. The Strategic Alliance was composed of three parts: 1) use of the novel bioassay to screen potential analogues of the melatonin receptor for bioactivity as agonists and antagonists; 2) cloning and use of recombinant melatonin receptors in pharmacological and bioactivity assays and 3) extending understanding of the structure-function relationship of the melatonin and its analogues with the melatonin receptors. The research and development involving pharmacological profiling of Servier synthesised compounds undertaken in Aberdeen facilitated the development of Valdoxan through the use of primary expressing endogenous melatonin receptors or heterologous cell cultures expressing cloned and engineered melatonin receptors.

The work, which contributed to the development of Valdoxan, was carried out between 1993 and 2004, and also involved collaboration with Professor Donny Strosberg, an expert in G-protein coupled receptors at the Institut Cochin, Paris. The collaboration between the Morgan/Barrett lab in Aberdeen and the Strosberg lab in Paris led to the cloning and use of recombinant ovine and human melatonin receptors as tools to characterise the signal transduction pathways utilised by melatonin receptors. It also led to the functional characterisation of novel melatonin analogues, designed and synthesised by Servier chemists. For this work, primary cell cultures of ovine pituitary (expressing native melatonin receptors) and cell lines stably-transfected to express recombinant melatonin receptors were used interchangeably to determine drug actions and

efficacies. Luciferase-reporter assays in engineered HEK-293 cells expressing melatonin receptor subtypes [2] were used to establish the pharmacology and efficacy of a selection of candidate Servier compounds based on a napthalenic core with a range of substitutions [3]. Importantly site directed mutagenesis studies established which amino acids within the transmembrane domains of the melatonin receptor were important for binding and biological function. Additionally studies using chimaeras of the melatonin receptor with the closely related but non-melatonin binding orphan receptor (GPR50) [4,5,6] showed that there was little or not cross-reactivity between GPR50 and the melatonin receptor for the compound subsequently selected for clinical trials. Together the studies performed at Aberdeen (in collaboration with Strosberg in Paris) provided essential information, based on ligand affinity, selectivity and efficacy at the melatonin receptor, for the selection of the two compounds taken forward for clinical development. These were the agonist S20098 (also known as Agomelatine) and the antagonist S20153. These compounds were selected for toxicology testing and clinical trials. S20098 was approved as a **new anti-depressant product, which was commercialised** in the European Union in 2009.

3. References to the research

All Aberdeen based research in the following publications was funded by the core research grant to the Rowett from the Scottish Government and the Strategic Alliance partnership funded by Servier pharmaceuticals:-

[1] Barrett P, Conway S, Jockers R, Strosberg AD, Guardiola-Lemaitre B, Delagrange P, Morgan PJ. (1997). Cloning and functional analysis of a polymorphic variant of the ovine Mel1a melatonin receptor. *Biochemica et Biophysica Acta* 1356:299-307. *This paper describes the cloning of the ovine (MT1) melatonin receptor used as the first tool for melatonin analogue drug screening and identified first of polymorphisms of the receptor with implications for structure-function relationships in the MT1 receptor.* Cited 57 times

[2] Conway S, Canning SJ, Howell HE, Mowat ES, Barrett P, Drew JE, Delagrange P, Lesieur D, Morgan PJ (2000). Characterisation of human melatonin mt(1) and MT(2) receptors by CRE-luciferase reporter assay. *Eur J Pharmacol* 390:15-24. *This paper describes the development of a CRE-luciferase reporter assay for high throughput screening used in the development of Servier compounds for agonist or antagonistic properties. Cited 41 times*

[3] Leclerc V, Fourmaintraux E, Depreux P, Lesieur D, Morgan P, Howell HE, Renard P, Caignard DH, Pfeiffer B, Delagrange P, Guardiola-Lemaitre B, Andrieux J (1998). Synthesis and structure-activity relationships of novel naphthalenic and bioisosteric related amidic derivatives as melatonin receptor ligands. *Bioorg Med Chem* 6:1875-1887. *One of several publications detailing the synthesis of melatonin receptor ligands in the development of potential therapeutic compounds to target the melatonin receptor. Cited 28 times*

[4] Conway S, Canning SJ, Barrett P, Guardiola-Lemaitre B, Delagrange P, Morgan PJ (1997). The roles of valine 208 and histidine 211 in ligand binding and receptor function of the ovine Mel1a beta melatonin receptor. *Biochem Biophys Res Commun* 239:418-423. *This paper identifies two essential amino acids in the binding pocket of the melatonin MT1 receptor that is important to binding of melatonin and the melatonin receptor agonist Valdoxan*. *Cited 47 times*

[5] Conway S, Mowat ES, Drew JE, Barrett P, Delagrange P, Morgan PJ (2001). Serine residues 110 and 114 are required for agonist binding but not antagonist binding to the melatonin MT(1) receptor. *Biochem Biophys Res Commun* 282:1229-1236. *This paper identifies two amino acid residues in transmembrane domain 3 of the melatonin receptor important for binding Servier developed agonists, but not an identified antagonist of the melatonin receptor, implicating a deeper binding pocket for agonist binding. Cited 25 times*

[6] Conway S, Drew JE, Mowat ES, Barrett P, Delagrange P, Morgan PJ (2000). Chimeric melatonin mt1 and melatonin-related receptors. Identification of domains and residues participating in ligand binding and receptor activation of the melatonin mt1 receptor. *J Biol Chem* 275:20602-20609. *Melatonin receptor with transmembrane domains substituted with from a closely related but non-melatonin binding receptor identified a glycine residue in transmembrane domain 6 as an important part of the binding pocket accommodating for the accommodation of the 5 methoxy group of melatonin and Servier developed agonists. Cited 38 times*

4. Details of the impact

The World Health Organisation estimates that depression affects about 121 million people and is a leading cause of disability worldwide. A variety of pharmacological agents are available on prescription to reverse clinical symptoms of depression, improving mood and health. However, these often have side effects of varying severity including drowsiness, sleep disorder, nausea and in older patients, increased risk of bone loss and fracture as a result of a fall. Abrupt termination of medication with these anti-depressants can cause serious withdrawal symptoms.

Disruption of circadian rhythms has been linked to endocrine and physiological abnormalities and associated with depression. Consequently the circadian system is a target for therapeutic intervention in the treatment of depression. Melatonin is the key chronobiological hormone which entrains the circadian system to the 24h light:dark cycle, through melatonin receptors which express the brain's biological clock. Disruption of the natural 24h rhythm of melatonin production by the pineal gland leads to sleep disorders and associated consequences, which can include depression.

An important element of drug development is the acquisition of as much detailed information as possible on potential therapeutic compounds. This is critical to enable informed decisions to be taken on whether development of lead compounds should proceed in to clinical trial, given the huge costs associated with clinical trial stages of development and the need to provide detailed supporting information to regulatory authorities. The Aberdeen research provided important information on the selectivity and efficacy of Servier's novel melatonin analogues at the melatonin receptor, using both native and heterologous receptor expression systems. In turn this research contributed to the development of the drug Valdoxan.

Valdoxan is a novel anti-depressant developed by the French pharmaceutical company Servier, based on the melatoninergic system. In humans and animal models the drug has been shown to have positive outcomes for disrupted circadian rhythms including by inducing phase advanced sleep and body temperature decline, but the major beneficial effect was found to be for the symptoms of depression.

The action of Valdoxan is through high affinity agonist activity at melatonin receptors MT1 and MT2 and an approximately 3 orders of magnitude antagonist activity at the 5HT2c receptor. Valdoxan was developed with the aid of strategic research funding provided by Servier to the Morgan/Barrett laboratories to understand the mode of action of melatonin and related compounds. Valdoxan was licensed for use in the European Union in 2009. Valdoxan is a highly valued alternative to other anti-depressants, being very well tolerated with few side effects. It is the only anti-depressant drug to be brought to the market in the last 10 years and no other compound with a similar activity has been registered, making Valdoxan unique among the pharmaceuticals available to treat depression. Valdoxan is registered in 74 countries with 3 million depressed patients having received or receiving treatment with Valdoxan. The award of the 2012 Italian Prix Gailen Innovative product award, a prestigious prize in the field of biomedical and pharmacological therapy which is assessed by a prominent panel of clinicians, toxicologists, pharmacologists and pharmacists acknowledges Valdoxan as an innovative anti-depressant therapeutic [e].

In summary, with the aid of investment from industry, research undertaken at Aberdeen University contributed to the development of a novel antidepressant drug that provides a new clinical intervention without side effects experienced with previously available antidepressants that will make a significant impact on the health and well-being of those afflicted by depression. The investment in research and development funded by Servier into the Morgan/Barrett lab continued

for over 10 years and involved extensive interaction and collaboration. This required regular reports and project meetings (2-3 per year) between Servier and the Morgan/Barrett team.

Claimed impact as defined by REF guidance: *A new product has been commercialised,* which has efficacy to improve *public health and well-being involving a new process* (a new paradigm for the treatment of depression).

5. Sources to corroborate the impact

[a] Directeur Scientifique, Servier, France
Servier Lead Scientist for the project on the development of melatonin-related therapeutic compounds.

[b] **Information on Valdoxan including pharmacological properties:-**
http://www.servier.co.uk/pdfs/Valdoxan_SPC.pdf and
http://www.medicographia.com/2011/10/valdoxan-a-novel-treatment-for-depressive-episodes-with-a-distinctive-profile-of-antidepressant-efficacy/
The above URLs provide information on the pharmacological properties and mechanism of Valdoxan action. The second URL also provides some information on the absence of adverse side effects and positive effect on emotion and well-being derived from clinical trial.

[c] European medicine agency public assessment report summary for Valdoxan.
Valdoxin pharmacology -
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000915/human_med_001123.jsp&mid=WC0b01ac058001d124
This URL provides a link to the European Medicines Agency providing further details on the use, mechanism of action, clinical trials, risks and a summary of the Committee for Medicinal Products for Human use of the European Medicines Agency for Valdoxan. This summarises the efficacy in preventing relapse in outpatients with Major Depressive Disorder.

[d] http://www.medicalnewstoday.com/releases/85521.php
Summarises the efficacy in preventing relapse in outpatients with Major Depressive Disorder

[e] http://www.servier.com/content/valdoxan®-agomelatine-award-italian-prix-galien-2012
Announcement of the Prix Galien award