Institution: University of Kent and University of Greenwich

Unit of Assessment: 3 Allied Health Professions, Dentistry, Nursing and Pharmacy.

Title of case study: The Guide to Receptors and Channels: a key tool in the maintenance and development of Pharmacology.

1. Summary of the impact (indicative maximum 100 words)

The **Guide to Receptors and Channels** has contributed to the development and maintenance of the intellectual infrastructure of pharmacology. The key tools it provides have influenced appropriate identification of lead drug targets and how best to study them and, as a result, it has received endorsement and financial support from the Pharmaceutical Industry. It is used widely as a teaching aid for undergraduates and research postgraduates and provides the general public with accurate information on prescription drug action. It led to the formation of the Guide to Pharmacology website in collaboration with the International Union of Basic and Clinical Pharmacology.

2. Underpinning research (indicative maximum 500 words)

The **Guide to Receptors and Channels** (**GRAC**) (3.1 – 3.3) was written by Professor Alistair Mathie together with Professor John Peters, University of Dundee and Dr Stephen Alexander, University of Nottingham. Each of the authors specialised in different areas of **GRAC** but all contributed to the total publication and were listed in alphabetical order, to signify equal contribution.

The great proliferation of drug targets in recent years drove the need to provide a logically organised synopsis of the nomenclature and pharmacology of these targets. This was the main goal behind **GRAC**. **GRAC** provides an authoritative but user friendly publication which allows a rapid overview of the key properties of a wide range of established or potential pharmacological targets. As a "*major research database"* and, therefore, a work of research scholarship (Ref 02.2011, Annex C, Definitions of research and impact for the REF), **GRAC** has contributed to the "*development and maintenance of the intellectual infrastructure"* of the field of pharmacology.

The information in **GRAC** is provided in such a way that a newcomer to a particular target group can identify the main elements "at a glance". Targets were selected for inclusion where there was sufficient pharmacological knowledge to allow clear definition or where, in the view of the authors, there was clear interest in the molecular class from the pharmacological community. Each entry was presented, wherever possible, on a single page to allow easy access and rapid oversight. One priority of **GRAC** was to present pharmacological agents which were the most selective and which were available for use either by donation or from commercial sources. **GRAC** grouped pharmacological targets into seven sections based on their similarities of structure and function: G protein coupled receptors, ligand-gated ion channels, ion channels, catalytic receptors, nuclear receptors, transporters and enzymes. In the latest edition (2011), information was provided on the properties of over 1800 established or potential individual drug targets, the key licensed medicines and experimental drugs that act on them and recommended reading lists for newcomers to each field.

The authors of the guide compiled each of the individual records, taking advice from many consultants and experts in the field. With each record, an indication was given of the status of the nomenclature as proposed by NC-IUPHAR, the nomenclature committee of the International Union of Basic and Clinical Pharmacology. Where this guidance was lacking, advice from several prominent independent experts was obtained to provide an authoritative consensus. Mathie contributed to all sections of **GRAC** but provided particular specialist input to the sections on G protein coupled receptors, ligand gated ion channels, ion channels and transporters based on his own research contributions to these fields including publications from Kent (e.g. 3.4 – 3.6) and his

links to the Pharmaceutical Industry through his Royal Society Industry Fellowship (2009-2013).

GRAC was first published in 2004 with new editions in 2006 (revised 2007), 2008, 2009 and 2011. Mathie was employed by Imperial College London in 2004, but arrived in Kent in 2007. In 2007, the revised 2nd edition of **GRAC** consisted of 100 distinct target groups on 180 pages. By comparison, the 5th edition in 2011 consisted of 166 distinct target groups (90 of them (54%) completely new compared with 2007) on 324 pages, including 50 new transporter targets. In addition, every single target page existing in 2007 was revised and updated in subsequent editions to reflect developments in the field. In October 2013, Scopus showed that the 2008 edition had been cited 516 times, the 2009 edition 423 times and the 2011 edition 425 times.

3. References to the research (indicative maximum of six references)

3.1) Alexander SPH, **Mathie A***, Peters JA (2008). Guide to Receptors and Channels (GRAC), 3rd Edition. *Br J Pharmacol* 153 (Suppl. 2): S1-S209. *joint corresponding author

3.2) Alexander SPH, **Mathie A***, Peters JA (2009). Guide to Receptors and Channels (GRAC), 4th edn. *Br J Pharmacol* 158 (Suppl. 1): S1-S254. *joint corresponding author

3.3) Alexander SPH, **Mathie A***, Peters JA (2011). Guide to Receptors and Channels (GRAC), 5th edn. *Br J Pharmacol* 164 (Suppl. 1): S1-S324 *joint corresponding author

3.4) **Mathie A**, **Veale EL** (2007). Therapeutic potential of neuronal two pore domain potassium channel modulators. *Curr Opin Invest Drugs* 8: 555-562
(Comprehensive study of the therapeutic potential of targeting a particular ion channel family)

3.5) Clarke CE, **Veale EL**, Wyse K, Vandenberg JI, **Mathie A** (2008). The M1P1 loop of TASK3 K2P channels apposes the selectivity filter and influences channel function. *J Biol Chem* 283: 16985-16992. (Fundamental research detailing influence of structure on ion channel function and regulation).

3.6) **Mathie A** (2010). Ion channels as novel therapeutic targets in the treatment of pain. *J Pharm Pharmacol* 62: 1089-1095 (Comprehensive study of potential future ion channel targets for the treatment of pain).

Authors who were based at MSOP at time of publication are in bold.

Related Grants held at MSOP:

Mathie A. The role of 2 pore domain potassium channels in primary sensory neurons. Royal Society Industry Fellowship £158,697 (2010).

Mathie A. The structural mechanism of K2P channel gating. BBSRC Industrial Partnership Award. £200,253 (2011).

4. Details of the impact (indicative maximum 750 words)

GRAC leads to impact in a number of different ways. As a consequence of its huge academic impact, exemplified by the number of citations it receives (over 1,350 since 2008, see also above), **GRAC** has impacted on educational practices for both research students and undergraduates in the UK and abroad, research in the pharmaceutical industry, the public understanding of drugs and in health and welfare. The production and publication of **GRAC** was supported by the British Pharmacological Society and by regular awards from the pharmaceutical industry, particularly

Pfizer (5.1) indicative of the importance pharmaceutical companies placed on its role in helping to appropriately identify potential lead drug targets. In its early incarnations, the emphasis was on producing a ring-bound printed copy for heavy-duty daily use in teaching laboratories and in academic and industrial laboratories. Since this format was offered free to all members of BPS and all subscribers to the British Journal of Pharmacology, it was expensive to produce. The Head of the Research Enabling Group at Pfizer states that **GRAC** is *"an important laboratory resource*" which is *"in constant use"* and has *"greatly influenced the direction of [their] work by helping [them] to appropriately identify potential new drug targets and determine the best pharmacological tools available to study them"* (5.2). Despite this emphasis on the printed copy, even in 2008, the website containing the pdf file received 182,000 hits from academic and industrial scientists across the world (5.1). More recently, the routine use of tablet and mobile electronic devices has emphasised the importance of establishing a user friendly on-line platform for **GRAC** (not simply provision of the pdf file) to extend its reach and significance. This has led to the development of guidetopharmacology.org (below, see also 5.3).

In December 2008, in recognition of the impact of **GRAC**, particularly as a resource in higher education, Alexander, Mathie and Peters were awarded the prestigious Rang Prize of the British Pharmacological Society (5.4). The award committee considered that **GRAC** was *"both a research tool and a teaching tool, and that it has made an important contribution to the maintenance and development of pharmacology as a discipline"* (5.4). In 2009, as retiring editor of the British Journal of Pharmacology, Rang stated *"another ongoing success is the **Guide to Receptors and Channels (GRAC)** a much valued and regularly updated compendium…….which brings so much credit to the Journal"* (5.5).

Also in 2009, in recognition of the importance of **GRAC**, all three authors were invited to become members of the nomenclature committee (NC) of IUPHAR. As part of its mission, NC-IUPHAR has the role of issuing authoritative guidelines for receptor and ion channel classification and maintaining a website with data on all known receptor systems freely available to all scientists and the general public anywhere in the world. Discussions between NC-IUPHAR and other organisations led to the creation of the Guide to Pharmacology (guidetopharmacology.org, 5.3) perhaps the biggest single impact arising from **GRAC**.

GuidetoPharmacology.org was launched in October 2011 and announced in a variety of media outlets including the front page of Pharmacology International (5.3). It is built on collaboration between the British Pharmacological Society and IUPHAR and is intended as a "one-stop-shop" source of quantitative information on drug targets and the prescription medicines and experimental drugs that act on them. It is targeted at both researchers and students in pharmacology and drug discovery (both in academia and Industry) and also aims to provide the general public with accurate information on the basic science underlying drug action (5.6). It provides a single entry point to the online version of **GRAC** and the related IUPHAR database. Because of its importance, it is supported financially by the British Pharmacological Society, the American Society for Pharmacology and Experimental Therapeutics, IUPHAR and a large number of pharmaceutical companies (Servier, Pfizer, Astra Zeneca, GlaxoSmithKline, Lunbeck, Merck, Abbott, Discoverx and Actelion, 5.7). Thus *Industry has invested in research and development*.

The development and curation of the Guide to Pharmacology is carried out by the IUPHAR database team led by Professor Tony Harmar. This team and NC-IUPHAR have recently received support from a Biomedical Resource Grant from the Wellcome Trust (2012-2015) "Guidetopharmacology.org – a peer reviewed online resource giving information on drugs and their targets" (£552,750). This award is allowing the resource to expand **GRAC** to provide quantitative data on all of the targets of human prescription medicines, enhance information on the therapeutic uses of drugs in the resource and allow rigorous curation of the structure and nomenclature of the chemical substances in the resource (5.8, 5.9).

Although only launched in late 2011, the guidetopharmacology already receives hits of around 130,000 per annum from both academia and industry in 166 countries (5.10) and it has already extended the use of **GRAC** as a higher education tool in a large number of HEIs worldwide. For

example, the University of Edinburgh now arranges demonstration workshops and practical tasks around guidetopharmacology to facilitate access to the information in **GRAC** for 4th year Pharmacology students (5.10), thus *educational practices have changed outside of the submitting unit*.

In summary, **GRAC** is a key tool in the maintenance and development of Pharmacology, leading to Industry investing in research and development and altering education practices in HEIs.

5. Sources to corroborate the impact (indicative maximum of 10 references)

5.1) British Pharmacological Society annual review of 2008, p5.
"The BJP published its GRAC supplement (Guide to Receptors and Channels), which received 182,420 web hits."

5.2) Letter of support, Dr Anne Phelan, Executive Director and Head of Research Enabling Group, Pfizer Neusentis.
GRAC is *"an important laboratory resource*" which is *"in constant use"* and has *"greatly influenced the direction of (their) work by helping (them) to appropriately identify potential new drug targets and determine the best pharmacological tools available to study them"*.

5.3) *Pharmacology International* (2011) vol 76 p1-2.
"Two page editorial describing the launch of the Guide to Pharmacology"

5.4) *Pharmacology Matters* (2008) vol 1 issue 2, p16-17
"Report on award of Rang Prize to Alexander, Mathie and Peters"

5.5) Rang & McGrath (2009) *Br J Pharmacol*, 156 p1-3
"Editorial describing importance of GRAC to Br J Pharmacol"

5.6) Alexander et al (2011), *Br J Pharmacol* 164 p1749-1750
"Launch of GuidetoPharmacology.org"

5.7) www.guidetopharmacology.org.sponsors.jsp
"Industrial sponsors of GuidetoPharmacology.org"
Servier, Pfizer, Astra Zeneca, GlaxoSmithKline, Lunbeck, Merck, Abbott, Discoverx and Actelion

5.8) *Pharmacology International* (2012) vol 79 p4-5.
"Aims of GuidetoPharmacology.org"

5.9) Alexander et al (2012), *Br J Pharmacol* 167 p697-698
"Aims of GuidetoPharmacology.org"

5.10) NC-IUPHAR database report October 2012 p3.
"Web hits and impact of GuidetoPharmacology.org in Education"