

## **EXAMPLE ABSTRACT: BASIC SCIENCE**

Species-specific differences in cerebellar cannabinoid 1 (CB<sub>1</sub>) receptor function

### **Introduction/Background & aims**

We have recently identified species-specific effects of cannabis extracts which suggested differential CB<sub>1</sub> expression and functional receptor activation by  $\Delta^9$ -tetrahydrocannabinol (THC) [1]. Here, we extend these data on CB<sub>1</sub> receptor function in cerebellar membranes from different species.

### **Method/Summary of work**

[<sup>3</sup>H]-SR1416717A (a CB<sub>1</sub> receptor antagonist) saturation binding and THC (a CB<sub>1</sub> receptor partial agonist)-stimulated [<sup>35</sup>S]-GTP $\gamma$ S binding assays were performed in cerebellar membrane preparations from mouse, rat, chicken, dog and human tissue. Assays were conducted in triplicate and 5 separate assays performed in each case. Analyses of saturation binding data were conducted by non-linear regression and fitted to a one-binding site model to determine maximal number of binding sites B<sub>max</sub> and the equilibrium dissociation constant K<sub>D</sub>. GTP $\gamma$ S binding data were analysed using a sigmoidal concentration-response model to determine EC<sub>50</sub> and maximum response (E<sub>max</sub>). Statistical significance was determined using an ANOVA followed by a Tukey's post hoc test on raw data.

### **Results/Discussion**

In saturation binding studies, a significant reduction in B<sub>max</sub> was seen in human (P<0.05 vs mouse and rat) and dog (P<0.05 vs mouse) cerebella membranes (Table 1); there were no significant changes in K<sub>D</sub> between species. THC-stimulated GTP $\gamma$ S binding showed significant differences in E<sub>max</sub> elicited by CB<sub>1</sub> receptor activation (Table 1) with a rank order of chicken = rat = dog > mouse = human (P<0.05 for all members of each group) was seen; there were no significant changes in EC<sub>50</sub> between species.

**Table 1. Cerebellar CB<sub>1</sub> receptor binding data for different species**

	Saturation binding		GTP $\gamma$ S binding	
	B <sub>max</sub> (pmol mg <sup>-1</sup> )	K <sub>D</sub> (nM)	EC <sub>50</sub> (nM)	E <sub>max</sub> (%)
Chicken (n= 5)	1.44 ± 0.2	1.57 ± 0.7	107 ± 10	33.9 ± 1.8
Rat (n=5)	1.80 ± 0.4	1.06 ± 0.1	92 ± 30	33.6 ± 2.5
Mouse (n=5)	2.40 ± 0.4	2.30 ± 0.6	138 ± 49	12.0 ± 1.8 <sup>ψ</sup>
Dog (n=5)	0.80 ± 0.2*	0.54 ± 0.2	170 ± 59	27.4 ± 1.8

Human (n=5)	0.46 ± 0.1* <sup>δ</sup>	2.07 ± 0.3	25 ± 9.9	11.3 ± 2.4 <sup>ψ</sup>
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\* p<0.05 vs mouse; <sup>δ</sup> p<0.05 vs rat; <sup>ψ</sup> p<0.05 vs each of chicken, rat and dog

### **Conclusion(s)**

We identify significant species-selective differences in CB<sub>1</sub> expression and functional receptor activation. Overall, human had a lower CB<sub>1</sub> receptor activity profile which confirm that THC effects in animal tissue models may be poorly predicted of those on human CB<sub>1</sub> receptor-mediated processes.

### **Reference(s)**

[1] Whalley BJ, Lin H, Bell L, Hill T, Patel A, Gray RA, Roberts CE, Devinsky O, Bazetot M, Williams CM, Stephens, GJ (2018) Species-specific susceptibility to cannabis-induced convulsions. Br J Pharmacol Epub ahead of print Feb 19.

## **EXAMPLE ABSTRACT: CLINICAL**

Surrogates in trials supporting European marketing authorisations of medicines for amyloidosis, cystic fibrosis, hepatitis C, and idiopathic pulmonary fibrosis.

### **Introduction/Background & aims**

Pivotal clinical trials supporting authorisation of new medicines may use surrogate endpoints to demonstrate efficacy [1]. In such cases, the surrogate should reliably predict the intended clinical outcome. We examined medicines that received standard or accelerated approvals in Europe between January 2011 and December 2018 to determine if this was the case for conditions where there were few existing effective therapies, amyloidosis, cystic fibrosis, hepatitis C, and idiopathic pulmonary fibrosis.

### **Method/Summary of work**

We used European public assessment reports (EPARs) to establish the primary endpoint of pivotal trials for products meeting the inclusion criteria. We categorised endpoints as clinical, surrogate, or both, according to the EPAR description. For surrogates, we conducted literature searches for studies confirming the surrogate validity as predictive of the intended clinical outcome and used published tools to assess validity [2,3].

### **Results/Discussion**

Twenty-five products met the inclusion criteria. Five products were withdrawn from the market and were not assessed. Of the remaining 20 products, 3 were indicated for amyloidosis, 7 for cystic fibrosis, 8 for chronic hepatitis C and 2 for idiopathic pulmonary fibrosis. 8 products received accelerated approvals (N=8; 40%). Surrogate primary endpoints were reported in the pivotal trials supporting all 20 products and were the sole endpoints supporting authorisations of all 20 products (N=20; 100%).

Based on the literature searches and applying the surrogate validity assessment tools, all surrogate endpoints were classed as non-validated.

### **Conclusion(s)**

For the indications studied, non-validated surrogate endpoints were commonly used to support marketing authorisations but the EPARs examined gave little information on the reliability of the surrogates to predict intended clinical outcomes. As non-validated surrogates may not accurately predict the effect of treatment on clinical outcomes, it is crucial that patients and clinicians are aware of the nature of evidence supporting authorisations so that they may make informed choices about treatment. Products that received standard, non-accelerated approvals should be based on comprehensive evidence of safety and efficacy.

### **Reference(s)**

[1] Grimes DA, Schulz KF. Surrogate end points in clinical research: hazardous to your health. *Obstet Gynecol.* 2005;105(5 Pt 1):1114-1118. doi:10.1097/01.AOG.0000157445.67309.19

[2] Fleming, T.R. and Powers, J.H. (2012), Biomarkers and surrogate endpoints in clinical trials. *Statist. Med.*, 31: 2973-2984. doi:10.1002/sim.5403

[3] Ciani O, Buyse M, Drummond M, Rasi G, Saad ED, Taylor RD. Time to Review the Role of Surrogate End Points in Health Policy: State of the Art and the Way Forward. *Value Health* 2017;20(3):487–495. pmid:28292495

## **EXAMPLE ABSTRACT: EDUCATION**

The UK's first undergraduate degree in clinical pharmacology

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### **Introduction/Background & aims**

The UK faces a shortage of skilled clinical pharmacologists [1]. The Clinical Pharmacology Skills Alliance identified driving awareness of clinical pharmacology in the potential talent pool and delivering high quality training as two key priorities in addressing this gap [2]. In response to this, St George's, University of London has launched the UK's first undergraduate BSc in Clinical Pharmacology. The course aim is to produce graduates ready for work or further study in drug development and research.

### **Method/Summary of work**

The course launched in September 2019, with a first cohort of 58 students; all of whom started within a year of completing A Levels (or equivalent). The curriculum is designed to teach modules in science, pharmacokinetics, pharmacodynamics, drug development, healthcare, and data and statistics simultaneously in integrated learning weeks. Novel learning methods designed to support development of synoptic understanding are shown in Table 1.

Different teaching methods, including clinical trials and laboratory skills, data handling, workshops and discussions and small group sessions are used to develop 'work-ready' skills including practical competence, communication and professional skills such as team working and personal management. These have been translated into novel online learning resources to ensure that the work-ready component of the course was not disrupted by the COVID-19 pandemic.

Table 1. Examples of novel learning approaches taken in the first year of our Clinical Pharmacology BSc

<b>Synoptic learning methods</b>	<b>Description</b>
Drug Based Learning (DBL)	Weekly small group sessions where students work collaboratively, using learning from the previous week to investigate scenarios and solve dilemmas
Hub tutorials	Weekly small group sessions where students give presentations, debate topics and appraise papers. Students sit weekly in course assessments in order to track their progress and identify areas for improvement
Dragon's Den	Students work in groups to research a drug and analyse simulated data from a clinical trial. They give podium and poster presentations to

representatives from the university and pharmaceutical industry and receive feedback
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**Results/Discussion**

Student feedback indicates that they are managing and appreciate the synoptic approach and feel that they are developing work ready skills that will assist with their careers (Table 2). This has been facilitated by a strong collaboration between pharmacologists and clinical pharmacologists in the core course team and support from industry colleagues in course design.

Table 2. Student feedback

<b>Students who agree with the following statements</b>	
My course has provided me with opportunities to bring information and ideas together from different topics	<b>98%</b>
My course has provided me with opportunities to apply what I have learnt	<b>98%</b>
The skills I have developed during my time in Higher Education will be useful in my career	<b>90%</b>
Overall, I am satisfied with the quality of the course	<b>100%</b>
<b>Free text comments</b>	
There is a variety of activities within the course that help up to consolidate our learning. Especially the clinical skills which is a personal favourite of mine	
Course leaders are amazing and very helpful. I really like the effort put in to give us the best possible skills	
Dragons Den was definitely a good way to convert theory into practise	
I have really enjoyed the variety of learning and topics we have each week. [The] highlight of my time in the course has been Dragon's Den as it was such a great change of pace from lectures.	
I really like the concept of having hub [tutorials] and DBL. It really helps me understand the topics more.	
The course professors have helped a major amount to help me understand the content further	

## **Conclusion(s)**

Students do enrol in an undergraduate degree in clinical pharmacology. They can cope with and thrive in a course designed to develop work ready skills and a synoptic understanding of the discipline of clinical pharmacology alongside more traditional acquisition of knowledge. As the course develops, we will discover whether this increases the pipeline of graduates into clinical pharmacology and whether our graduates are truly 'work ready'!

## **Reference(s)**

[1] The Association of the British Pharmaceutical Industry. *Bridging The Skills Gap In The Biopharmaceutical Industry: Maintaining The UK'S Leading Position In Life Sciences*. Available at: <https://www.abpi.org.uk/publications/bridging-the-skills-gap-in-the-biopharmaceutical-industry-jan-2019/>. Published 1st Jan 2019. Accessed 4th September 2020.

[2] <https://www.bps.ac.uk/news-events/news/articles/2017/clinical-pharmacology-skills-alliance-launched-to>