Following the identification of the endocannabinoid anandamide (AEA) in 1992, a significant effort has been made to elucidate its possible role (1). One key conclusion to date has been that the enzyme FAAH is important in controlling the level of endocannabinoids including not only AEA, but also linoleoyl ethanolamide (LEA), N-palmitoylethanol amine (PEA), Oleoylethanolamide (OEA) and Stearoylethanolamide (SEA). Given also the hypotheses that modulating these messengers may have benefit in certain disease states (2), a number of drug discovery and development programmes have been initiated to evaluate FAAH inhibitors, together with CB1 antagonists and agonists in various indications (3). This presentation will review the clinical data for the FAAH inhibitor, PF04457845(4) and the conclusions of an integrated systems pharmacology model evaluation of FAAH as a target for pain, drawing on physiologically based pharmacokinetic and systems biology approaches. The systems pharmacology model integrated physiological compartments, the available data on the disposition of AEA, PEA, OEA and LEA, the kinetics of the enzymes controlling endocannabinoid substrate production and degradation, the PF-04457845 pharmacokinetics, pharmacodynamics and pharmacology and the CB1 receptor binding kinetics (5),(6). Using this approach it was concluded that AEA is subject to an alternative clearance process that limits the AEA increase following FAAH inhibition. On the basis of our data and the available literature we speculate that this process is due to the enzyme N-acylethanolamine hydrolysing acid amidase (NAAA). The existence of this alternative clearance process calls into question whether FAAH inhibition alone can produce sufficient increases in AEA levels to express meaningful pharmacological activation of CB1 receptors, unless accumulation in the receptor compartment would occur through a currently unknown mechanism. At present, however, quantitative methods to demonstrate AEA target engagement and pharmacological effect, the so called 'three Pillars of survival' (7), are lacking. In conclusion, the integrated systems modelling carried out prior to clinical trials, identified clear gaps in our understanding and highlighted key risks. Overall, on the basis of the model predictions we hypothesise that FAAH inhibition on its own may not provide enough ‘horsepower’ to be of clinical utility in the treatment of pain. In the context of this conclusion, the value of this modelling exercise will be discussed in detail, together with the recommendations for knowledge and methods that need to be improved to enable any further optimal clinical evaluation of the endocannabinoid system. These include; focussing on experimentally determining the origin and parameters for the additional AEA clearance process, evaluating the pros and cons of FAAH inhibitors versus CB1 agonists for a given indication, developing a robust method to demonstrate CB1 receptor occupancy in man and carrying out more detailed study to quantify the impact of CB1 occupancy on an outcome of interest. This example highlights the prospective value of integrated modelling and simulation for the selection of target and design of clinical studies (8); the requirements for more general application to other indications will also be discussed.

References

1. Pál Pacher, Sándor Bátkai and George Kunos (2006). Pharmacol Rev. 58(3): 389-462.
2. Bari M, Battista N, Fezza F, Gasperi V, Maccarrone M (2006). Mini Rev Med Chem. 6(3): 257-268.
3. Lambert DM, Fowler CJ (2005). J Med Chem. 48(16): 5059–5087
4. Li GL, Winter H, Arends R, Jay GW, Le V, Young T, Huggins JP (2011). Br J Clin Pharmacol. Nov 2. doi: 10.1111/j.1365-2125.2011.04137.
5. Metelkin E, Bagrova N., Demin O., Benson N. PAGE 20 (2011) Abstr 2260 [www.page-meeting.org/?abstract=2260].
6. Tian X, Guo J, Yao F, Yang DP, Makriyannis A (2005). J Biol Chem. 280(33): 29788-29795.
7. Morgan P, Van Der Graaf PH, Arrowsmith J, Feltner DE, Drummond KS, Wegner CD, Street SD Drug Discov Today. 2011 Dec 29. [Epub ahead of print]
8. Van Der Graaf PH, Benson N (2010). Pharm Res. 28(7): 1460-1464