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Capturing new BIA 10-2474 molecular data in the IUPHAR/BPS Guide to PHARMACOLOGY

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Introduction: In January 2916 a Phase I trial of BIA 10-2474 in France caused the death of one patient and the hospitalisation of others. Given the seriousness of this event it becomes crucial to collate and track both old and new molecular pharmacological data appearing in the peer reviewed literature and patents to facilitate mechanistic insights. The IUPHAR/BPS Guide to PHARMACOGY (GtoPdb) serves as an expert-curated nexus of exactly this kind of information [1]. We had already curated entries for FAAH inhibitors (target id 1400) and BIA 10-2474 (ligand id 9001). This presentation describes our work on updating related entries up to August 2017.

Methods: We explored PubMed and PubMed Central for papers related to 10-2474, FAAH inhibition and putative off-targets. The majority of publications were opinion and/or recommendation papers so it was necessary to triage these to find new molecular data. We combed through to find quantitative in vitro verified interactions [2]. These were curated into new entries in release 2017.5. Any additional data published in the next four months that passes our quality threshold will be updated for release 2017.6 and included in this presentation.

Results: 16 PubMed entries retrieving with "BIA 10-2474" included a detailed secondary clinical report from consultants for the French authorities (PMID 27806235). By adding PMC full-text papers not picked up by PubMed indexing we triaged 20 papers. Two contain experimental data and two are off-target modelling studies. The key paper in this set (PMID 28596366) included activity-based protein profiling to detect off-target proteins We have consequently expanded FAAH inhibitors to 17, including 10-2474 metabolites from posters presented at BPS Pharmacology 2016.

Conclusion: In the 18 months since the 10-2474 event we could find only one paper to curate new quantitative molecular interaction data from. This slow response of the pharmacology community in generating data that could contribute to our molecular toxicological understanding is cause for concern (although compound availability may have been a limiting factor). We are aware of at least one other molecular paper in preparation. We will thus continue to expand our relationship capture as, a global resource in this domain, including data-supported off targets and active metabolites as part of the push towards a mechanistic understanding of the tragedy and future avoidance.

References:

[1] Southan et al. (2016). Nucl. Acids Res. 44 (Database Issue): D1054-68.
[2] https://cdsouthan.blogspot.se/2016/01/molecular-details-related-to-bia-10-2474.html