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Monash Research Leads To ACS Warning On Assay Hit Pains

Monash University says its research has led to the American Chemical Society warning of the dangers of artefacts making assay hits appear useful when they are useless.

Monash University said that 160,000-member "the world's largest scientific society [had changed its editorial policy] in a move that could save government and industry millions of dollars a year in preventing dead-end research".

The University said that research by its Prof Jonathan Baell and the University of Minnesota's Prof Michael Walters identified compounds that could create false positives, leading researchers to waste years optimizing promising-looking drug candidates that could not be developed into drugs for the targeted disease.

The original research was published in the Journal of Medicinal Chemistry in 2010 and Nature in 2014.

The American Chemical Society editorial said that "Studies that omit critical controls against experimental artefacts caused by pan-assay interference compounds may waste years of research effort as useless compounds are progressed".

"The American Chemical Society is eager to alert the scientific community to this problem and to recommend protocols that will eliminate the publication of research articles based on compounds with artificial activity," the Society said.

The editors' letter was co-written by nine editors and entitled 'The Ecstasy and Agony of Assay Interference Compounds' was published in the American Chemical Society journal 'Central Science', with the first page of the article available at: http://pubs.acs.org/doi/abs/10.1021/acscentsci.7b00069.

The 2014 Nature article, headlined 'Chemical con artists foil drug discovery' said that "naivety about promiscuous, assay-duping molecules is polluting the literature and wasting resources" and is available at: http://go.nature.com/2rWFcvx.

"Academic researchers, drawn into drug discovery without appropriate guidance, are doing muddled science," the Nature article said.

"When biologists identify a protein that contributes to disease, they hunt for chemical compounds that bind to the protein and affect its activity," the article said.

The article said that assays screen thousands of chemicals, with hits becoming tools for studying the disease and starting points for treatments.

"But many hits are artefacts, their activity does not depend on a specific, drug-like interaction between molecule and protein [while] a true drug inhibits or activates a protein by fitting into a binding site on the protein," the Nature article said.

"Artefacts have subversive reactivity that masquerades as drug-like binding and yields false signals across a variety of assays," the article said.

The article said that pan-assay interference compounds (Pains) had defined structures, covering several classes of compound, but biologists and inexperienced chemists rarely recognized them, instead the compounds were reported as having promising activity against a wide variety of proteins.

"Time and research money are consequently wasted in attempts to optimize the activity of these compounds," the article said.

"Chemists make multiple analogues of apparent hits hoping to improve the fit between protein and compound, meanwhile, true hits with real potential are neglected [and] the apparent activity of Pains is so seductive that work continues despite published reports explaining that a compound interferes with assays." the article said.

The article concluded that drug discoverers must be more vigilant.

"Molecules that show the strongest activity in screening might not be the best starting points for drugs. Pains hits should almost always be ignored. Even trained medicinal chemists have to be careful until they become experienced in screening," the article said.