Ronald James Christie et al., Immunome Res 2016, 12:2(Suppl)
http://dx.doi.org/10.4172/1745-7580.C1.005

Stabilization of cysteine-linked antibody drug conjugates with N-aryl maleimides

Ronald James Christie[1], **Ryan Fleming**[1], **Binyam Bezabeh**[1], **Rob Woods**[1], **Shenlan Mao**[1], **Jay Harper**[1], **Augustine Joseph**[2], **Qianli Wang**[2], **Ze-Qi Xu**[2], **Herren Wu**[1], **Changshou Gao**[1] and **Nazzareno Dimasi**[1]
[1]MedImmune, USA
[2]SynChem Inc., USA

Maleimides are often used to link drugs to cysteine thiols for production of antibody-drug conjugates (ADCs). However, ADCs formed with traditional N-alkyl maleimides have variable stability in the bloodstream leading to loss of drug and decreased therapeutic activity. Loss of payload occurs via a retro-Michael reaction that regenerates the maleimide group, which can then react with other thiol species that serve as an off-target sink for liberated ADC drugs. Here, a maleimide based strategy to produce stable ADCs while also maintaining efficient thiol reactivity is presented. The current approach aimed to accelerate thiosuccinimide hydrolysis after thiol-maleimide conjugation to produce a stable thioether bond. The rate of conjugate stabilization (i.e., thiosuccinimide hydrolysis) was measured directly on antibodies using mass spectrometry by observing the addition of water (18 amu) to the antibody conjugate. Conjugate stability was confirmed in both thiol-containing buffer and mouse serum at 37°C over a period of 7 days. An ADC prepared with monomethyl-auristatin-E (MMAE) comprising stable maleimide chemistry maintained potency towards cultured cancer cells following serum incubation whereas an ADC prepared with MMAE linked through a traditional N-alkyl maleimide lost potency over time. This approach could also be applied to other drug delivery or diagnostic technologies such as polymer conjugates, targeted nanoparticles and biosensors where stable thiol conjugates are critical for performance.

Biography

Ronald James Christie has received his PhD in Chemistry from Colorado State University in 2006 and completed Post-doctorate at the University of Tokyo. He has published more than 25 articles in scientific journals on topics including; drug delivery, materials science and bioconjugation. He is currently a Scientist at MedImmune, working to develop antibody-drug conjugate therapeutics.

christier@MedImmune.com

Notes: