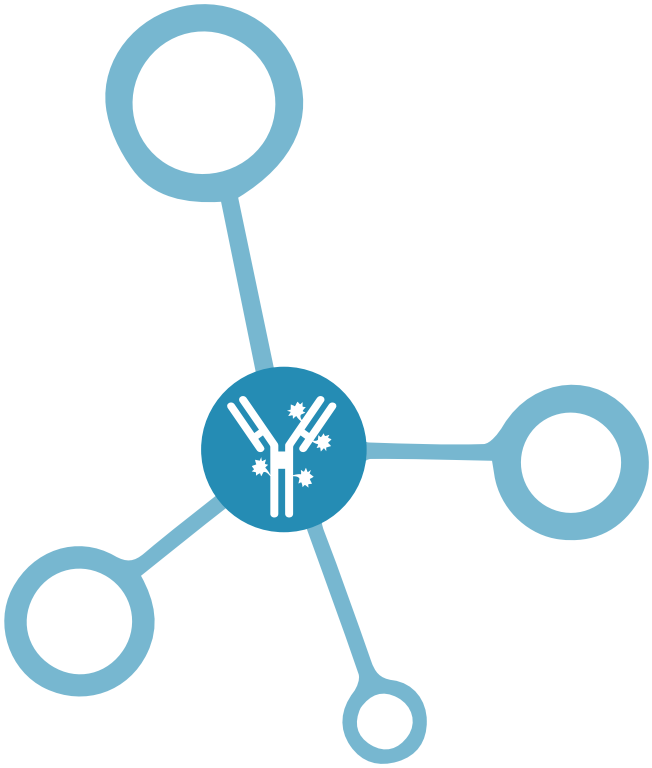
NEWSLETTER III | Mar| 2021

SIMICA

THERAPEUTIC SITE-SELECTIVE PROTEIN-MODIFICATION CHEMISTRIES

OVERVIEW OF THE PROJECT

The SIMICA Project intends to place the Instituto de Medicina Molecular João Lobo Antunes within the core of a European network of laboratories that seeks to produce cutting-edge research in the field of site-selective protein modification.



Did you know that:

Novel aqueous chemistries for the selective modification of proteins have been described in recent years and chemical protein modification has become a key instrument in chemical biology (Nat. Rev. Chem. 2019, 3, 147). It is commonly agreed that these tools will provide major insight into basic biology and enable the development of novel protein conjugates to study their intrinsic properties in cells and in vivo.

Labelling proteins through natural amino acidsf

There are currently four ADCs approved for use by the FDA, Brentuximab vedotin (Adcetris®), Trastuzumab emtansine (Kadcyla®), Inotuzumab Ozogamicin (Besponsa®), and Gemtuzumab Ozogamicin (Mylotarg®). From these, Kadcyla®, Besponsa® and Mylotarg® are constructed via modifying the antibody's surface accessible lysine residues. However, lysine residues are abundant in proteins resulting in highly heterogeneous conjugates. Cysteine modification has gained popularity in recent years due to the high nucleophilicity and low natural abundance in naturally occurring proteins.Typically, maleimides have been used extensively for cysteine modification as they react rapidly and selectively with thiols. However, it also undergoes deconjugation through a retro-Michael pathway, leading to loss of cargo and reduction in efficacy (Figure 1)(Chemistry 2019, 25, 43). Alternative methods have been developed to circumvent this problem of instability inherent in maleimide-cysteine conjugation. One interesting strategy is the use of "self-hydrolysing maleimide" reagents. These compounds undergo rapid hydrolysis to the corresponding succinamic acid, resulting in more effective/stable bioconjugates.

CYSTEINE BIOCONJUGATION

Meet the SIMICA

Dr Nikolaus Krall has experience in the development and commercialisation of companion diagnostic assays, including selection of biomarkers. His work has been within the domain of assay development of SMEs over the past 15 years. His sought-after expertise in taking products from the stage of laboratory development to market will be an asset also for iMM to see the prospective of the hurdles that ADCs need to overcome before it can reach the clinic.

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N-aryl maleimides with electro-drawing groups appeared as novel Michael acceptors capable of yielding more stable thiol-based bioconjugates (Figure 1)(Bioconjug Chem 2015, 26,145). Similarly, beta amino maleimides were found to accelerate the rate of thiosuccinimide hydrolysis in bioconjugates (Figure 1)(Nat Biotechnol 2014, 32). Alternatively, we have employed distinct thiol reactive groups, such as carbonyl acrylates that after rapid bioconjugation form an opened succinamic moiety that is resistant to deconjugation (Figure 1)(Nat. Commun 2016, 7, 13128).

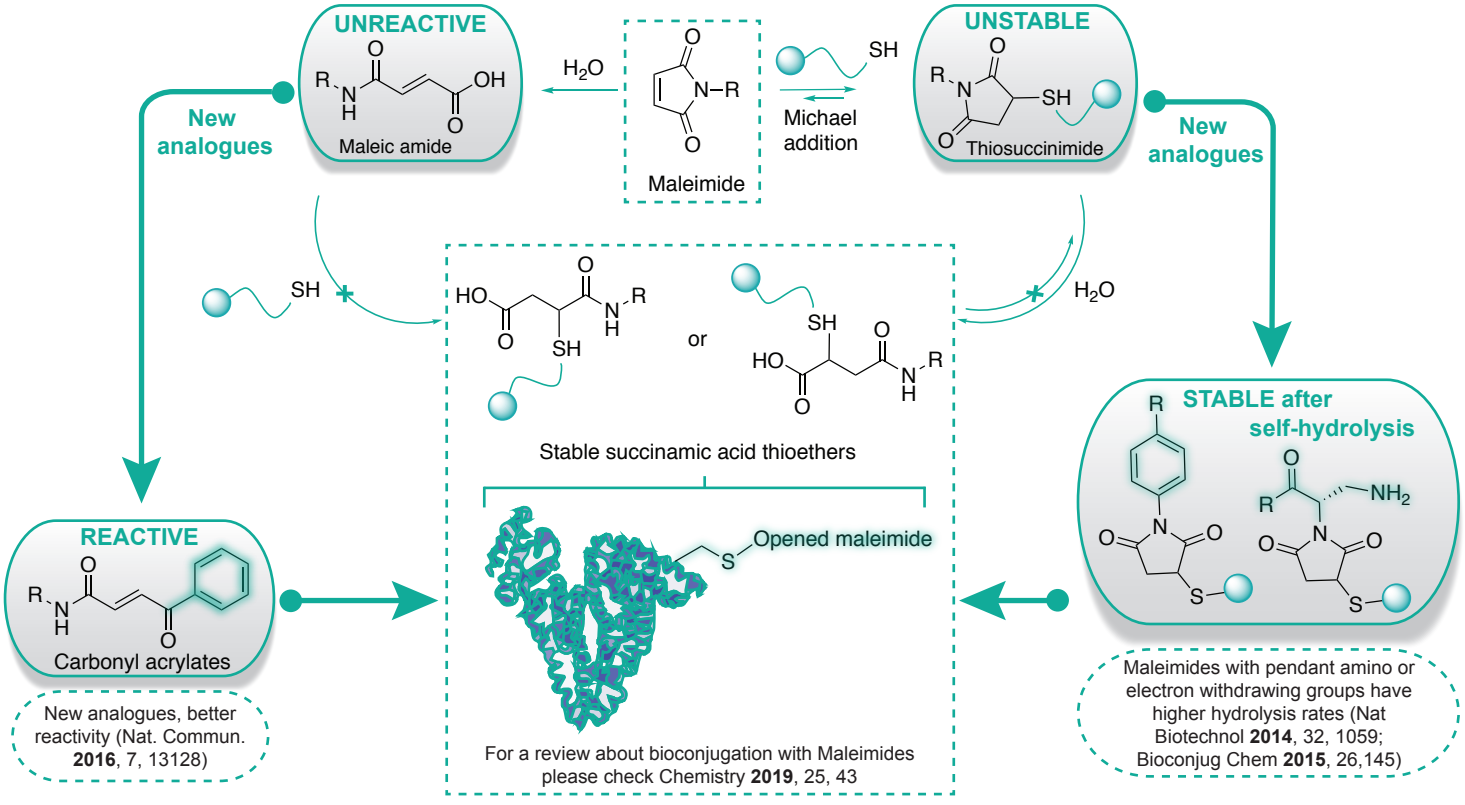

Figure 1: Strategies for more stable thiosuccinimide conjugates.