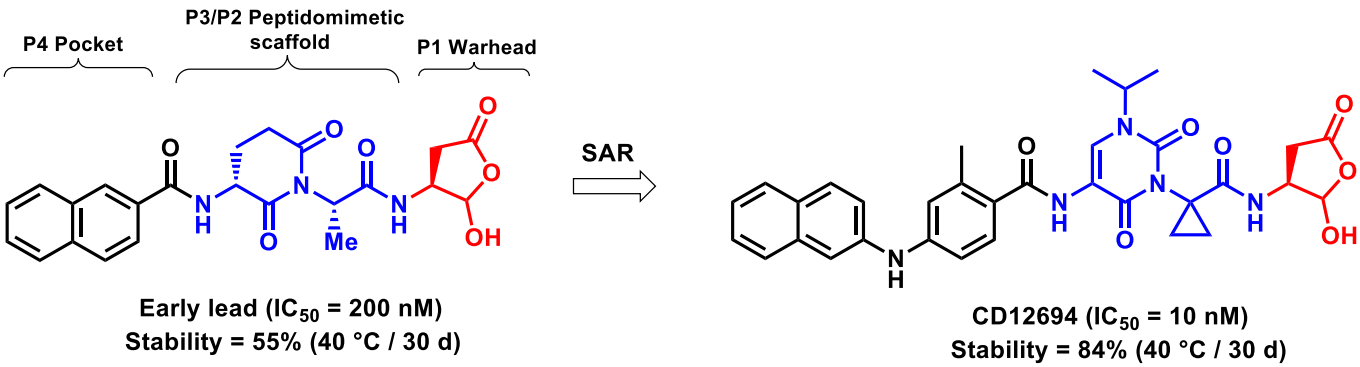
Design and synthesis of novel peptidomimetic Caspase I inhibitors as a novel topical treatment for acne

Craig Harris, Jean-François Fournier, Laurence Clary, Sandrine Chambon, Sandrine Talano, Laurence Dumais, Corinne Millois, Romain Pierre

Nestlé Skin Health, Entre deux Villes 12, 1814 La Tour-de-Peilz, Switzerland
craig.harris@galderma.com



Caspases are a family of protease enzymes called Cysteine Aspartic Proteinases. There are 12 known Caspases in humans. Caspases 1, 4, 5, 11 and 12 are all inflammatory caspases and 2, 3, 6, 7, 8, 9 and 10 are all associated with apoptosis.[1] Caspase-1, is the principal enzyme responsible for cleavage and activation of pro-Interleukin-1β (pro-IL-1β) to its active form IL-1β, which in turn is involved in the pathogenesis of several inflammatory disorders including acne vulgaris.[2]

In a recent study, we reported a comparison of lesional versus non-lesional biopsies of patients with inflammatory acne and through transcriptomic and proteomic studies, we showed a strong induction of IL-1β mRNA and IL-1β protein in lesional biopisies.[3] Consequently, the treatment of inflammatory acne with a topical agent targeting Caspase I presented an exciting opportunity for the treatment of moderate to severe acne. This presentation will focus on the design and synthesis of a novel class of peptidomimetic inhibitors for topical application.[4]

[1] a) MacKenzie, S. H.; Schipper, J. L.; Clark, A. C. *Curr Opin Drug Discov Devel.* **2010**, *13*, 568–576; b) Poreba, M.; Strozyk, A.; Salvesen, G. S.; Drag, M. *Cold Spring Harb. Perspect. Biol.* **2013**, 1-20.
[2] Contassot, E.; French, L. E. *J. Investig. Dermatol.* **2014**, *134*, 310–313.
[3] Kelhälä, H-L.; Palatsi, R.; Fyhrquist, N.; Lehtimäki, S.; Väyrynen, J. P.; Kallioinen, M.; Kubin, M. E.; Greco, D.; Tasanen, K.; Alenius, H.; Bertino, B.; Carlavan, I.; Mehul, B.; Déret, S.; Reiniche, P.; Martel, P.; Marty, C.; Blume-Peytavi, U.; Voegel, J. J.; Lauerma, A. *PLOS One* **2014**, *9*, 1 -18.
[4] a) Brethon, A.; Bouix-Peter, C.; Clary, L.; Fournier, J-F. Harris, C. S.; Lardy, C. Roche, D.; Rodeschini, V.; Talano, S. *Tetrahedron Lett.* **2016**, *57*, 5924-5927; b) Boiteau, J-G.; Bouix-Peter, C.; Chambon, S.; Clary, L.; Daver, S.; Dumais, L.; Fournier, J-F.; Harris, C. S.; Mebrouk, K.; Millois, C. *Tetrahedron Lett.*, **2016,** *57*, 2367-2371; c) Brethon , A. ; Chantalat, L. ; Christin, O. ; Clary, L. ; Fournier, J-F.; Gastreich, M.; Harris, C. S.; Isabetd, T.; Pascau, J. ; Thoreau, E. ; Roche, D. ; Rodeschini, V. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 5373-5377; d) Fournier, J-F.; Clary, L et al. *J. Med. Chem.* **2018**, *61*, 4030–4051; e) Chambon, S.; Talano, S.; Millois, C.; Dumais, L.; Pierre, R.; Ghilini, A-L.; Reverse, K.; Mouis, G.; El-Bazbouz, G.; Brethon, A.; Rodeschini, V.; Roche, D.; Clary, L.; Fournier, J-F.; Bouix-Peter, C.; Hennequin, L. F.; Harris C. S. *Tetrahedron*, **2018**, *74*, *accepted*.