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Selective inhibition of matrix metalloprotease-3 and hyaluronidase by hyaluronic acid alkylamide derivatives for the intra-articular treatment of osteoarthritis

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Osteoarthritis (OA) is a disease resulting in most cases in the degeneration of articular cartilage. The process of OA development involves inflammation in the early stage of the disease and many mediators, which regulate the expression of several inflammatory proteins and induce the activation of cartilage-degrading enzymes. While the pathway that results in cartilage breakdown is still unclear, there is strong evidence that hyaluronidases (specifically Hyal-2) and metalloproteases (e.g., MMP13 and MMP3) are relevant for the degradation of the ECM. In this study, hyaluronic acid (HA) alkylamides (HYADDs) were selected as the strongest MMP and hyaluronidase inhibitors among a number of glycosaminoglycans which are currently used as viscosupplements, including natural and chemically cross-linked HAs. The role of the alkyl moiety was investigated using HA derivatives with varying alkyl chain lengths and degrees of modification. *In vitro* and ex vivo studies in synovial fluid from OA patients confirmed the marked inhibition potency of HYADD4 on hyaluronidase (100-fold higher compared to fully sulfate HA). HYADD4 was then screened against 10 different human MMPs *in vitro*, and the results were validated ex vivo in human synovial fluid (SF). HYADD4 showed the highest inhibition potency against MMP13 and MMP3 (competitive inhibition with Ki in the μmolar range), and no activity against ADAMTS4, elastase and GAPDH (control). Molecular modeling and molecular dynamics studies suggested that HYADD4 may behave as a competitive inhibitor vs. MMP3 (Figure 1A) because of its ability to interact with collagen-binding groove and to participate in the coordination of the catalytic zinc ion. Moreover, C16 alkyl chain may bind effectively to S1' additional pocket, increasing the affinity of HYADD4. A pilot clinical trial focusing on the inhibition of SF MMP3 by Hymovis® (HYADD4) in OA patients is ongoing in order to confirm the *in vitro* and in silico results.

Biography

Cristian Guarise is a Senior Researcher at Fidia Farmaceutici Spa, Italy. His main activity includes "Multi-step synthesis of modified natural polymers for application in the field of Osteoarthritis, Wound Healing, Ophthalmic Surgery and Aesthetic Medicine. From 2008-2011, he was a QC Analytical Chemist at Fidia Farmaceutici Spa, Italy. He completed his Master's degree in Pharma-Biotechnology in 2004 at University of Padua and PhD in Molecular Chemistry at the same university in 2008. His research project entitled "Rapid synthesis and screening of hetero-functionalized catalysts".

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