S38-3 Discovery of peptide-mimetic, water-soluble antagonists for integrin $\alpha_v\beta_3$ and $\alpha_{IIb}\beta_3$

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To improve the treatment for acute ischemic diseases, a drug which possesses both suppressive activity against the reperfusion injury and antithrombotic activity would be important. Leukocytes play important role for reperfusion injury. Therefore, dual antagonism of integrin $\alpha_v\beta_3$ (participating in the adhesion and migration of leukocytes) and integrin $\alpha_{IIb}\beta_3$ (participating in platelet aggregation) are likely to be of therapeutic value in the treatment of acute ischemic diseases. Both receptors, $\alpha_v\beta_3$ and $\alpha_{IIb}\beta_3$, bind their ligand proteins, including vitronectin and fibrinogen, through recognition of the tripeptide RGD sequence. In addition, RGD-containing cyclic peptides have been reported to vary the $\alpha_v\beta_3/\alpha_{IIb}\beta_3$ selectivity depending on their conformation. Paying attention to these lines of information, we generated a peptide-mimetics focused on rigid conformation as an $\alpha_v\beta_3/\alpha_{IIb}\beta_3$ dual antagonist. In addition, control of the $\alpha_v\beta_3/\alpha_{IIb}\beta_3$ selectivity was also achieved by changing the spacial location of each pharmacofore derived from RGD side chains. By structural development of the lead compound, drug candidates with improved activities and aqueous solubility were discovered. In the course of structural development, we focused on the symmetry and planarity of the molecules to improve the aqueous solubility. Suppression of reperfusion injury by integrin $\alpha_v\beta_3/\alpha_{IIb}\beta_3$ antagonists was first reported by the use of our compounds. MediciNova, Inc. is preparing a clinical trial of our candidate in US and Canada. Process chemistry of the candidate will be also presented in the symposium.