

FROM PROTEINS TO DRUGS

Rational Design and Combinatorial Approaches for the Development of Selective Integrin Antagonists

Several different integrin subtypes recognize the small peptide sequence such as the tripeptide RGD or LDT in different proteins of the extracellular matrix. Our first goal was the discrimination between the RGD recognizing integrins, such as $\alpha_v\beta_3$ (vitronectin receptor) and $\alpha_{IIb}\beta_3$ (fibrinogen receptor). This was achieved using constrained cyclic peptide libraries ("spatial screening") which exhibited high selectivity for α_v when a kinked structure about Gly is provided whereas the platelet receptor $\alpha_{IIb}\beta_3$ recognizes an extended peptide backbone. As $\alpha_v\beta_3$ is important in cancer metastasis, derivatives of the highly α_v selective cyclic pentapeptide c(RGDfV) have been developed for various functions, such as:

- a drug candidate against neoangiogenesis, now in clinical phase II as an anti-cancer drug developed by Merck KGaA, Darmstadt
- a surface coating agent to stimulate cell attachment of osteoblasts on PMMA implant material (already successful for *in-vivo* experiments), and
- a tumor targeting radio tracer for visualizing metastasis

These peptidic structures were used to derive non-peptidic selective and highly active peptidomimetics by rational-combinatorial approaches. Meanwhile also selectivity for the β subtypes $\alpha_v\beta_3$, $\alpha_v\beta_5$ and $\alpha_v\beta_6$ has been achieved. A similar approach was used for $\alpha_4\beta_7$ integrin which gave highly selective and active compounds as possible drug candidates for the treatment of colitis. From extensive molecular dynamics calculations a new mechanism of signal transduction through the membrane is presented.

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Date: Thurs, Oct 17, 2002

Venue: SR 4, Blk S2

Time: 3 - 4pm

Host: A/P Kini RM

All are welcome