• Inhibiting protein-protein interactions with small molecules
• From Aspirin to Cox-2 inhibitors and beyond
Integrins
Inhibiting Protein-Protein Interactions
What Brings Cells Together?
Integrins are Transmembrane Proteins
Integrins are Heterodimeric Proteins
Ligand: Integrin Interactions - Fn
Integrins are Holding Our Tissues Together
Integrins in Coagulation: Platelet Aggregation

- Platelet Aggregation
  - Integrin αIIbβ3
  - Integrin α2β1

Diagram showing the process of platelet aggregation and coagulation, including subendothelium, endothelial cell, NO, Prostaglandin, ADP, AMP, Thrombin, and Prothrombinase complex involving TXA2, procoagulant activity, fibrinogen, and fibronectin.
Integrin Mediated “Final Common Pathway” for Platelet Aggregation
Integrins in Angiogenesis
Integrins in Immune Response

Immune synapse:

Activation and transmigration of leukocytes:

Leukocyte function-associated antigen (LFA-1, αLβ2, and CD11a/CD18) and very late antigen (VLA-4, α4β1, and CD49d/CD29)
Structure of Integrin
Conformational Change – Caught on Camera!
a Bent form with closed headpiece  
b Extended form with closed headpiece  
c Extended form with open headpiece bound by cRGD

a Closed headpiece  
b Open headpiece stabilized by bound fibrinogen  
c Open headpiece stabilized by α/β I-like competitive antagonist
Conformational Change Occurs in Cells – as Well!

The diagram illustrates a conformational change induced by activation. The text and diagram together suggest a study or research focused on cellular conformational changes. The specific details of the diagram, including labels and annotations, point towards a scientific context, possibly involving protein interactions or signal transduction processes in cells. The mention of "Activation: Affinity Change" and "FRET" (Förster Resonance Energy Transfer) indicates a focus on molecular interactions and their role in cellular processes. The text "Conformational Change Occurs in Cells – as Well!" sets a tone of discovery or new insights into cellular biology.

For more detailed analysis, one might look into the scientific literature to understand the specific biological processes or mechanisms being discussed, such as receptor-ligand interactions, protein-protein interactions, or changes in protein structure that affect function within cells.
αIIbβ3 α/β I-like Competitive Antagonists
Platelet Aggregation Inhibitors

Disintegrins from snake venom!
αvβ3  α/β I-like Competitive Antagonists
Angiogenesis Inhibitors
$\alpha 4 \beta 1$ $\alpha/\beta$ I-like Competitive Antagonists
Autoimmune Diseases
$\alpha_4$-Antibodies and Antagonists are Active in Animal Models of Inflammation

- Airway inflammation.
  - Antigen sensitized / airways hyperresponsiveness (mice, rats, guinea pigs, and sheep)
- Other models of inflammatory disease.
  - EAE (rats, mice, and guinea pigs)
  - chronic colitis (cotton top tamarins)
  - adjuvant arthritis (rats)
  - atherosclerotic plaque formation (mice)
  - adoptive transfer model of diabetes (NOD mice)
  - restenosis (rabbits)
  - acute cardiac graft rejection (rats)
Merck Medicinal Chemistry Lead Generation

Sequence for VLA-4 Binding on VCAM-1 and Fibronectin

CD-loop of VCAM-1

- QIDSP-

Type III CS-1 domain of FN

- ILDVP-

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Initiated a focused screening effort on carboxylic acid containing compounds.
Lead Discovery from Combinatorial Library

C-000,013
Capped dipeptide
combinatorial library

IC$_{50}$ = 58 nM

"Outsourced"
Medicinal Chemistry

- Solid phase synthesis
- Capped dipeptides
- Single compounds
Overlay of L-808116 with the CD loop of VCAM-1
Potential Therapeutic Targets for VLA-4 Antagonists

- Multiple Sclerosis
- Inflammatory bowel disease
  - Crohn’s disease, ulcerative colitis
- Rheumatoid arthritis
- Chronic obstructive pulmonary disease (COPD)
- Asthma
- Atherosclerosis
- Diabetic retinopathy

Orphan Diseases
- Sickle cell anemia
- Mobilization of CD34+ stem cells (cancer)
- Uveitis (ocular inflammation)
Potential Liabilities of VLA-4 Antagonists

Developmental Toxicity

α₄ or VCAM-1 KO’s are embryo-fetal lethal.
   Failure of chorio-allantoic fusion and epi-myocardial fusion.
   Heterozygous α₄⁻/⁺ embryos - normal development.
   Conditional KO – normal development.

Hematology

Administration of anti-α₄ prenatally resulted in fetal anemia.
   Lymphocytosis observed in animals and humans.
   Neonatal lymphopoiesis.
   Hematopoietic progenitor cells.

Infection

   Increased susceptibility to respiratory infection.
\( \alpha L \beta 2 \) Integrin – Immune Response
$\alpha L\beta 2$ $\alpha I$ Allosteric Antagonist
Autoimmune Diseases
αLβ2  α/β I-like Allosteric Antagonist
I-like Allosteric Antagonist vs. Competitive $\alpha_4$ Antagonist