# DBP6: Integrin

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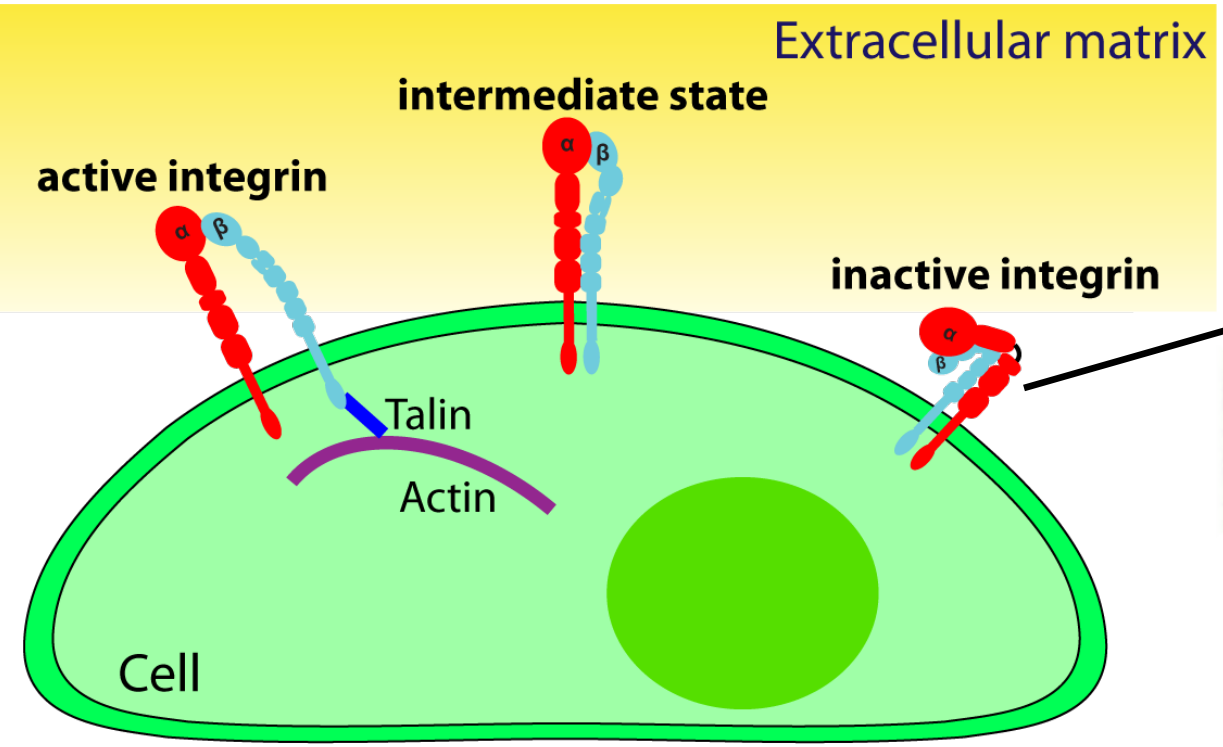
# DBP6: Integrin

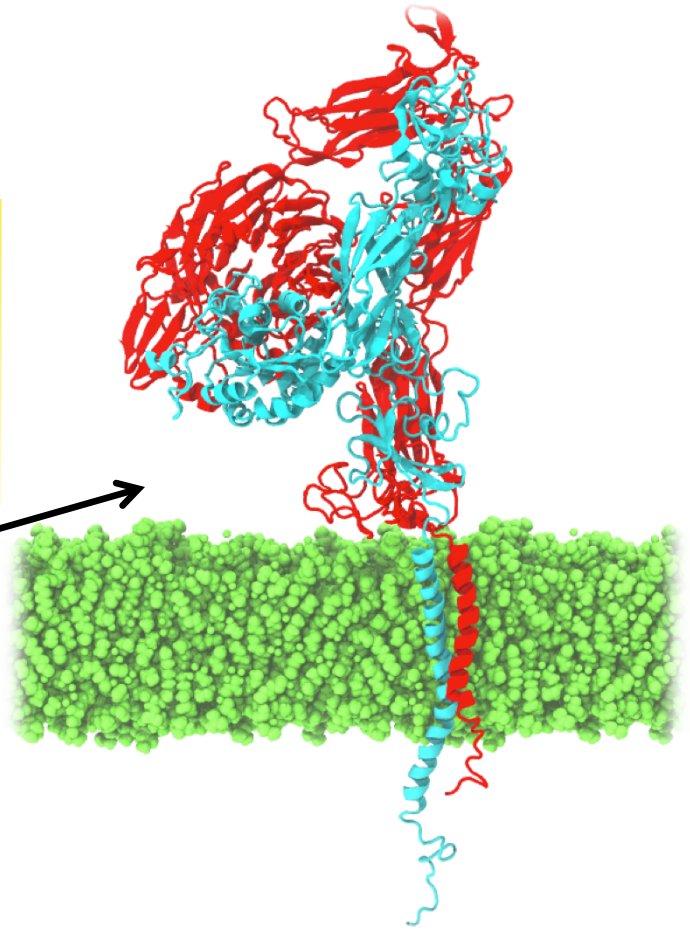
## Biomedical significance of integrins:

- A major group of adhesion **receptors** that **transmit signals bidirectionally** across the membrane.
- Involved in many biological processes, e.g., cell migration, morphogenesis and hemostasis.
- Major targets for many diseases, e.g., cancer, inflammatory disease and infection.

## Computational challenges:

- Long time scale ~100 μs, 1 M atoms.
- Large conformational changes ~200 Å.
- Accurate description of ions.

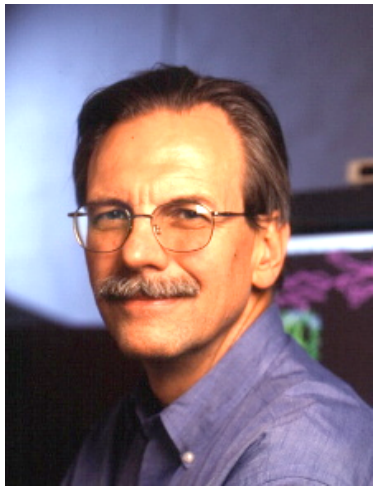


Structure of inactive integrin

# DBP Collaborators

## Crystallography

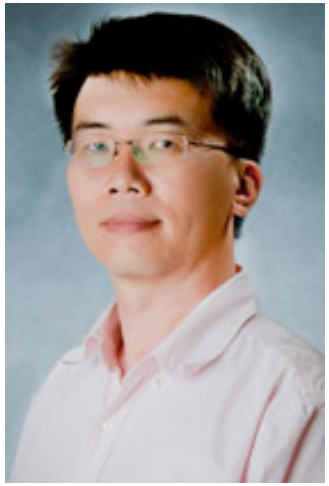


### Timothy Springer
### HHMI (Harvard)

- 30+ years in integrin field
- 100+ publications describing all aspects of integrin structure and function

Completed ectodomain structure of integrin

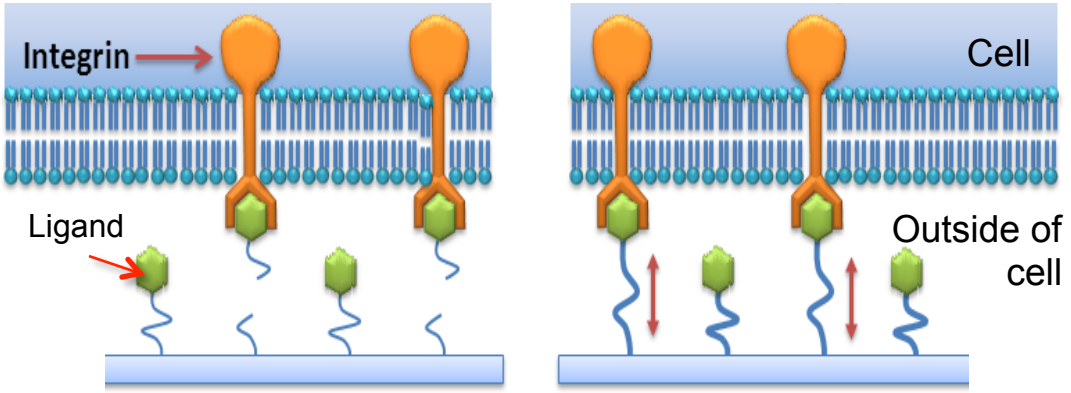
## Single-molecule experiments



### Taekjip Ha
### HHMI (UIUC)

- Expert in single-molecule biophysics
- 100+ publications

Determination of binding force between integrin and RGD ligand




<u>Weak tether</u>
Tether breaks; integrin and ligand remain bound to each other.

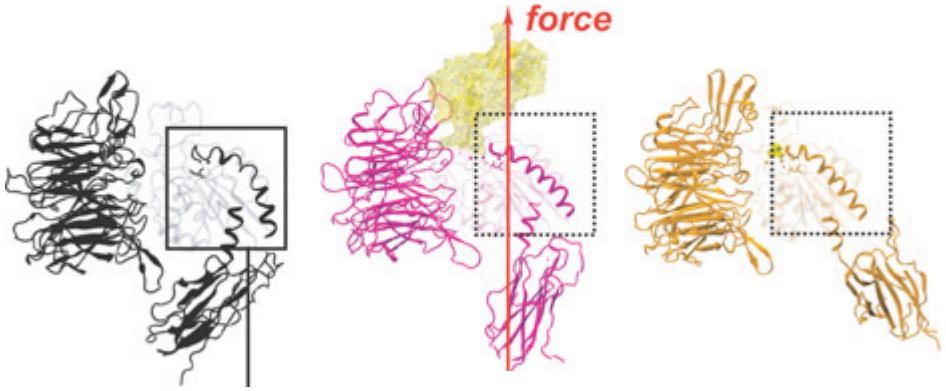
<u>Strong tether</u>
Binding between integrin and ligand breaks.

# Prior Related Work of BTRC

Integrins are mechanical proteins; the BTRC has already studied such systems:

- Integrin signaling: 5 publications
- Mechanical systems: 45 publications

Transition along the integrin hinge-opening pathway




Closed headpiece | Steered dynamics simulation | Open headpiece

Eileen Puklin-Faucher, Mu Gao, Klaus Schulten, and Viola Vogel. How the headpiece hinge angle is opened: new insights into the dynamics of integrin activation. *Journal of Cell Biology*, 175:349-360, 2006.

1. **Molecular dynamics simulations of forced unbending of integrin $a_vb_3$**. Wei Chen, Jizhong Lou, Jen Hsin, Klaus Schulten, Stephen C. Harvey, and Cheng Zhu. *PLoS Comput. Biol.*, 7(2):e1001086, 2011

2. **How the headpiece hinge angle is opened: new insights into the dynamics of integrin activation**. Eileen Puklin-Faucher, Mu Gao, Klaus Schulten, and Viola Vogel. *Journal of Cell Biology,* 175:349-360, 2006

3. **Structural insights into how the MIDAS ion stabilizes integrin binding to an RGD peptide under force**. David Craig, Mu Gao, Klaus Schulten, and Viola Vogel. *Structure,* 12:2049-2058, 2004

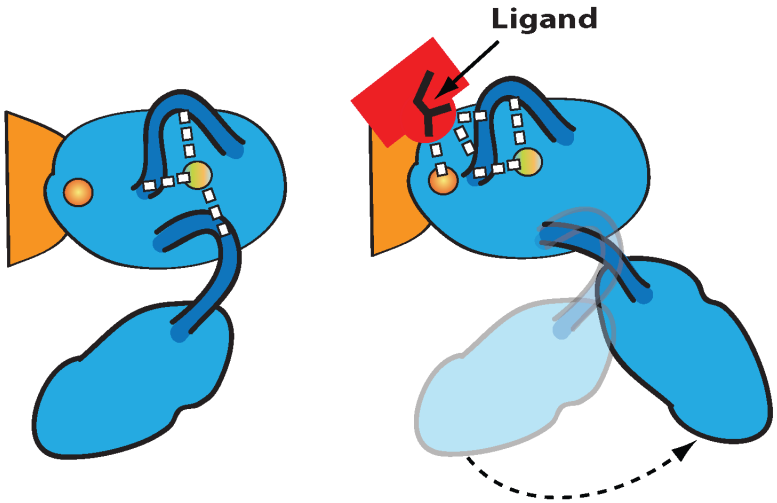
4. **Integrin activation in vivo and in silico**. Mu Gao and Klaus Schulten, *Structure,* 12:2096-2098, 2004

5. **A structural model for force regulated binding to fibronectin's RGD-synergy site**. Andre Krammer, David Craig, Wendy E. Thomas, Klaus Schulten, and Viola Vogel. *Matrix Biology,* 21:139-147, 2002

# TR&D Connections and Challenges

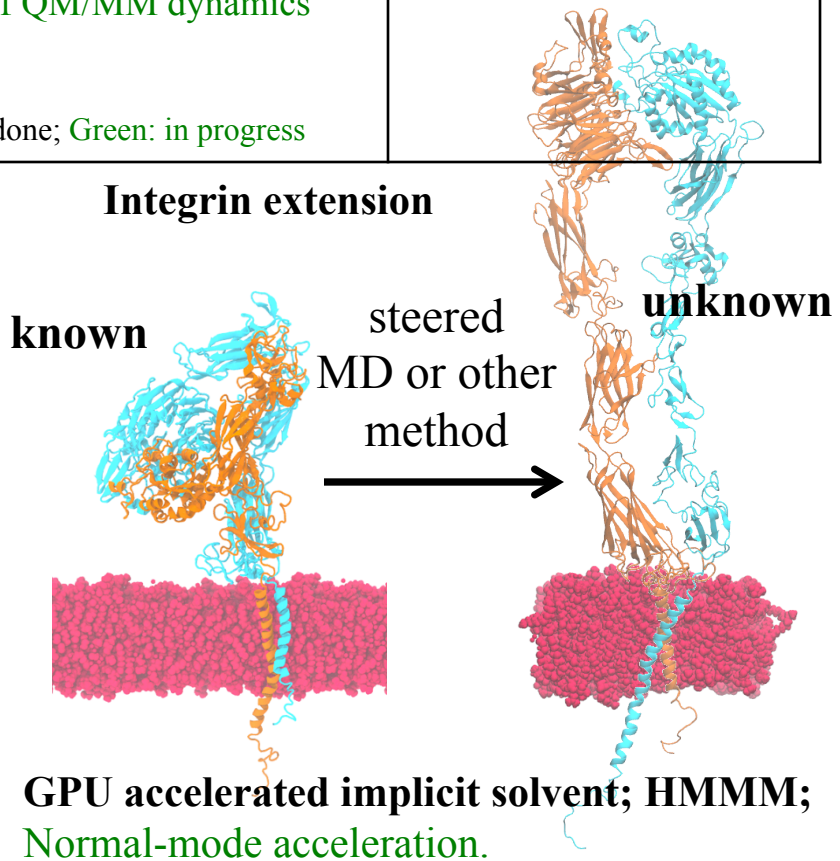
| **TR&D1** (NAMD) | **TR&D2** (VMD) | **TR&D3** (HMMM) |
|---|---|---|
| GPU accelerated implicit solvent<br>AMBER99SB-ILDN Force Field<br>QM/MM calculation<br>AMOEBA polarizability model<br>Normal-mode acceleration<br>Dynamic Importance Sampling | Improved ion placement<br>Fast analysis of long time simulation<br>Visual. of QM/MM dynamics<br><br>Black: done; Green: in progress | HMMM builder<br>Membrane builder |

**Ligand-induced headpiece opening**




**AMBER99SB-ILDN Force Field; QM/MM;**
Dynamic Importance Sampling.

**Integrin extension**




**GPU accelerated implicit solvent; HMMM;**
Normal-mode acceleration.