

Quantitative proteomic analysis of integrin adhesion complex dynamics



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Overview

Introduction

- Integrins as adhesion receptors
- Challenges in the field

Isolation of adhesion complexes

- Methodology
- Global analysis and candidate discovery

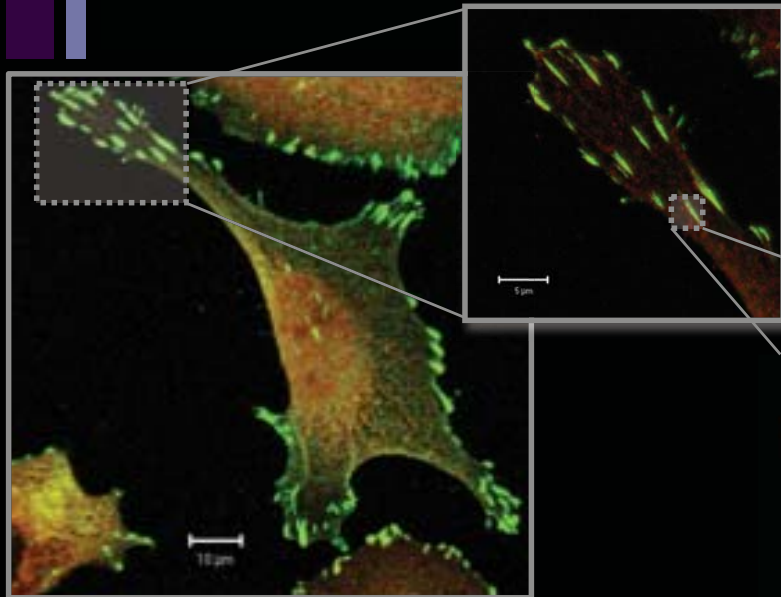
Current challenge

- Analysis of adhesion complex assembly

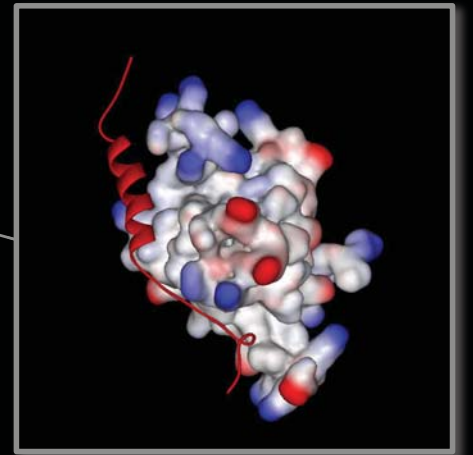
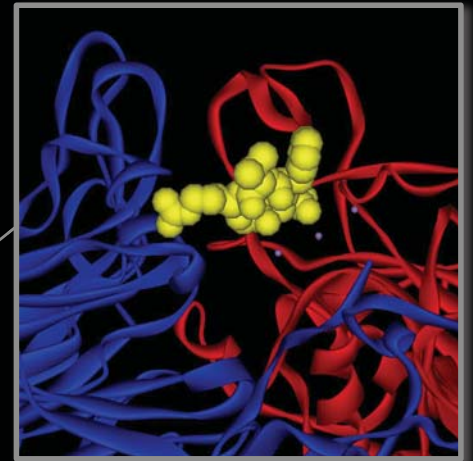
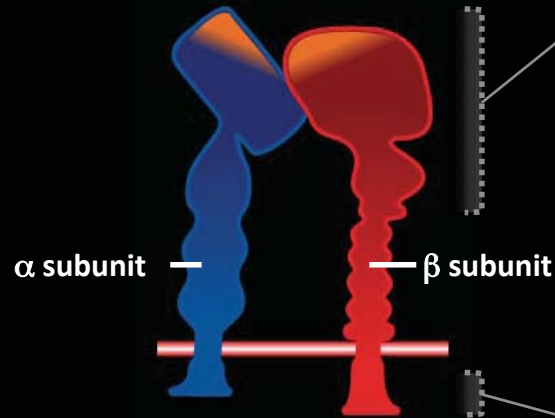
Ongoing work

- Activation state-dependent signalling

Integrins as adhesion receptors

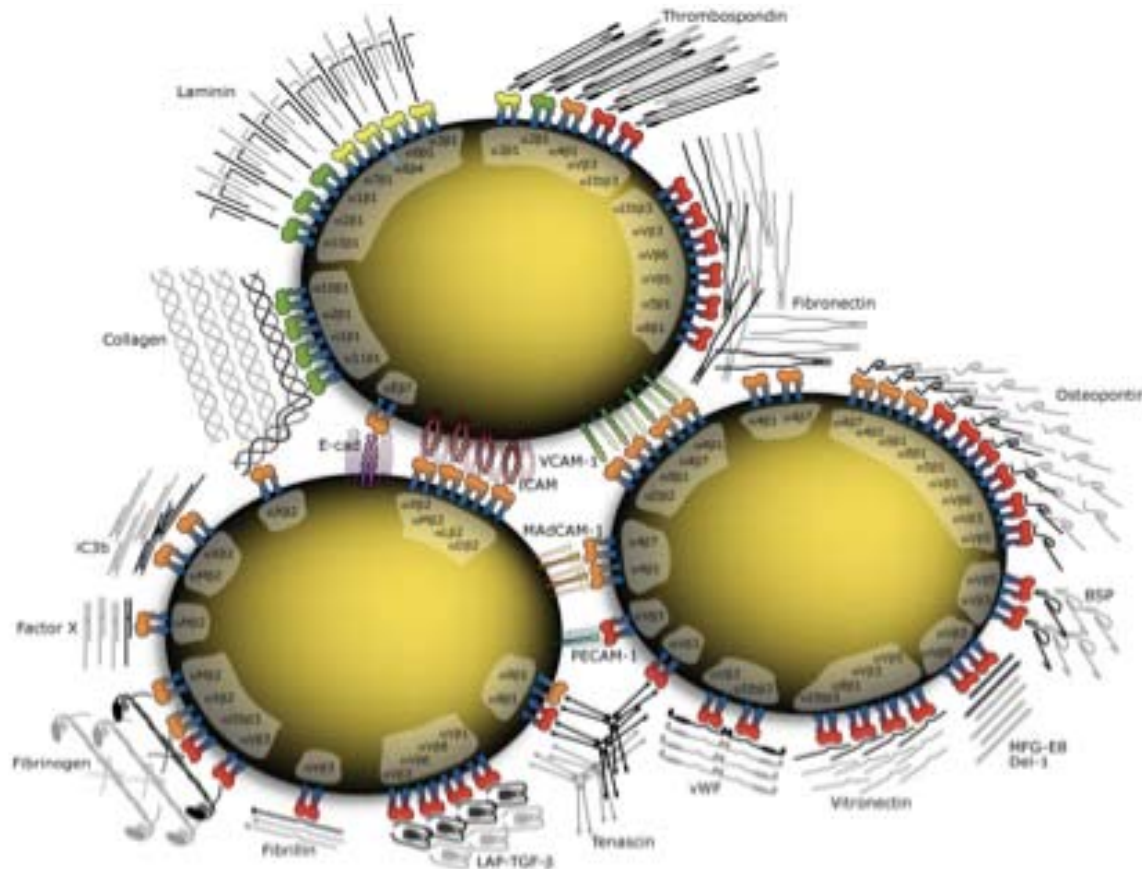


Mark Morgan



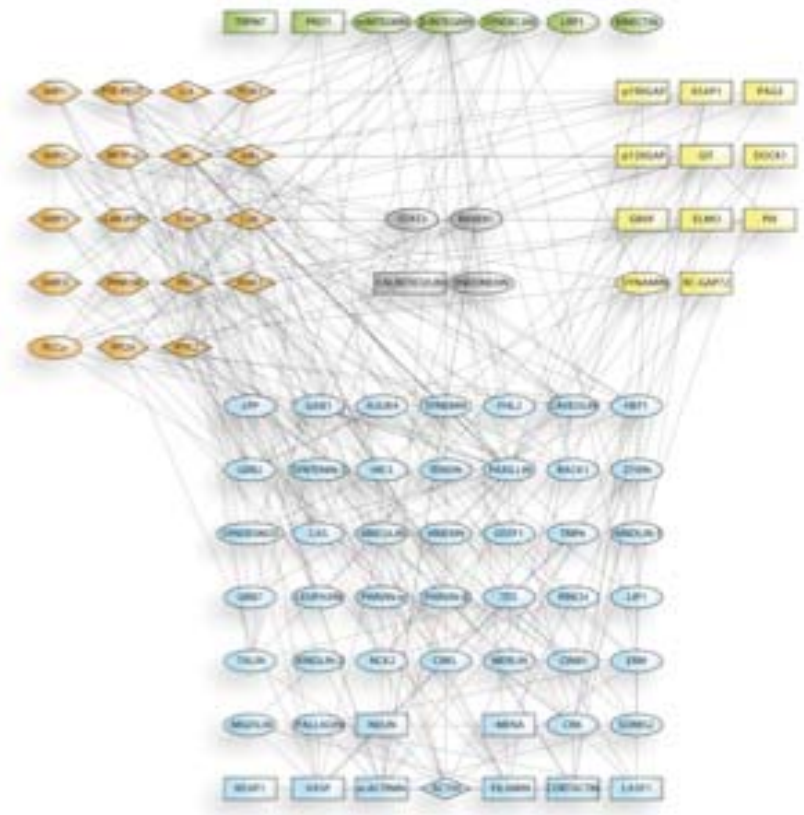
Challenges in the field

Integrin ligands



Humphries, Byron & Humphries (2006) *J. Cell Sci.* 119: 3901–3903

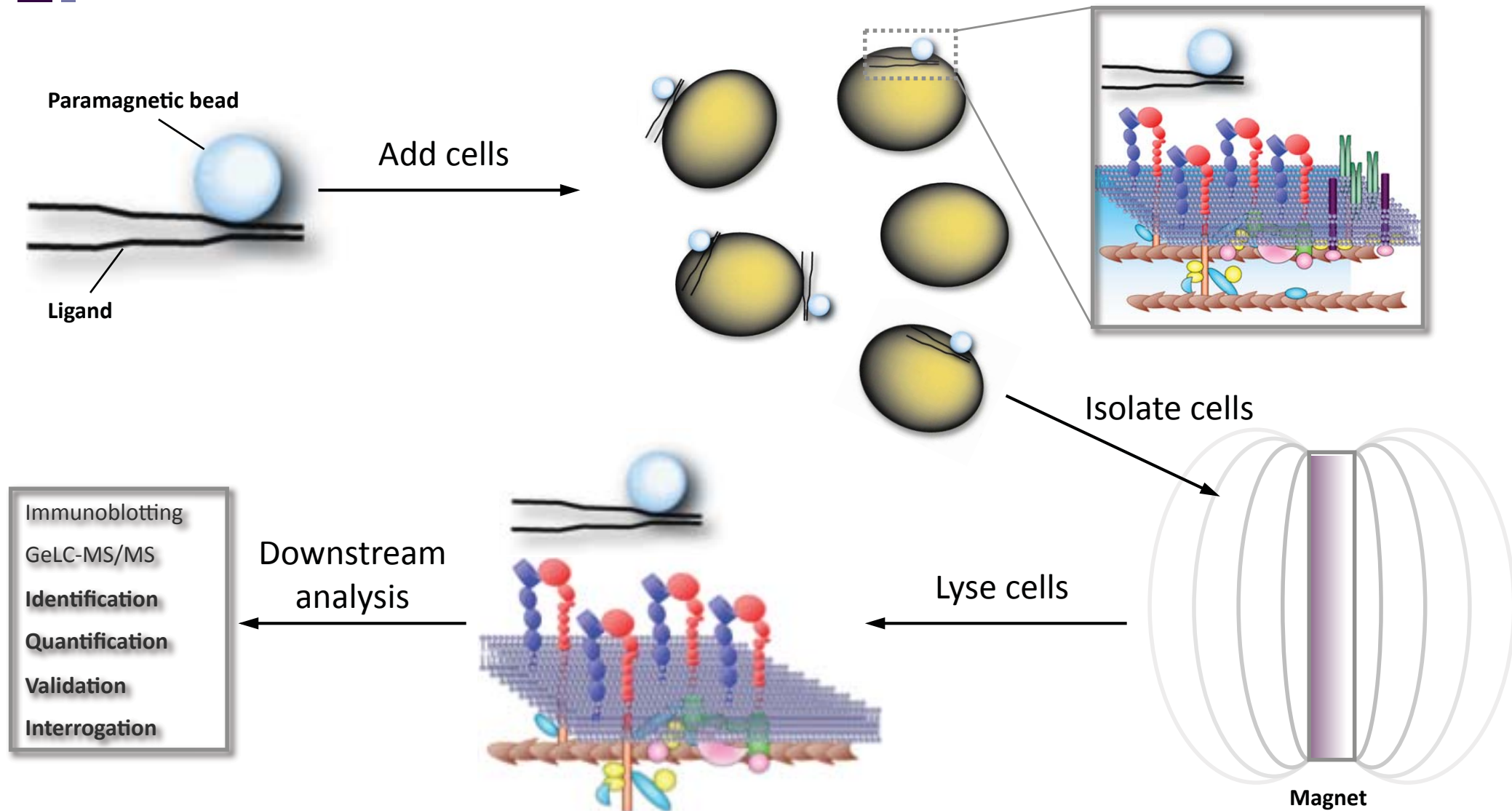
Integrin-associated proteins



Zaidel-Bar et al. (2007) *Nat. Cell Biol.* 9: 858–867

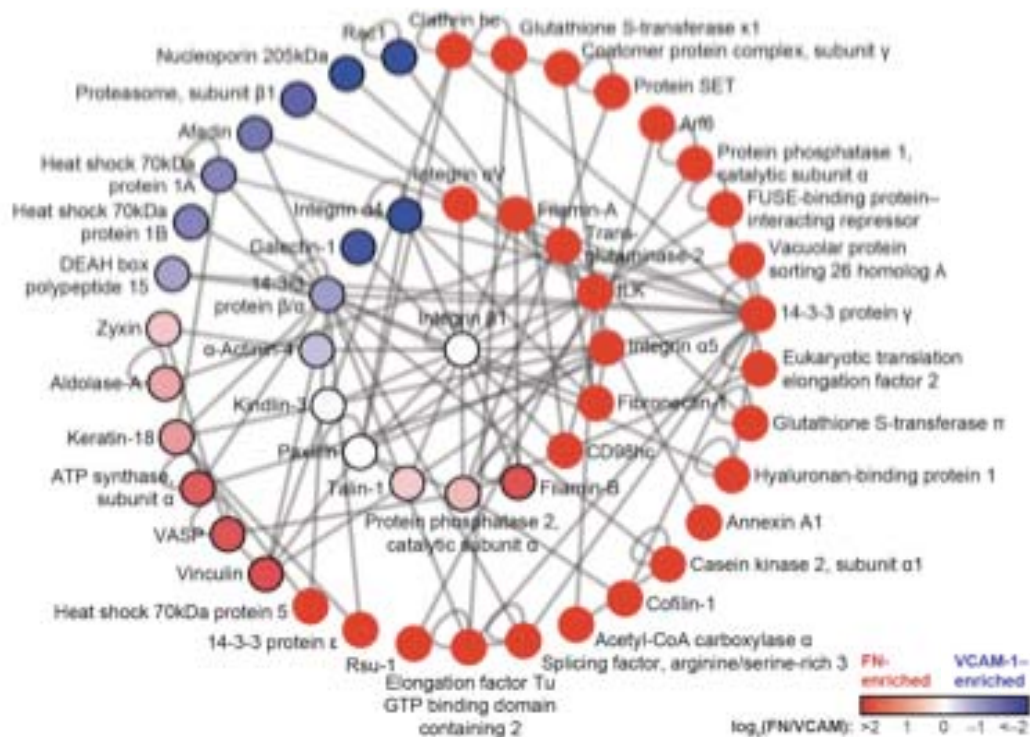
- Cell-type specificity
- Ligand specificity
- Stoichiometry
- Spatiotemporal dynamics
- Network modularity
- Network regulation

Isolation of integrin adhesion complexes

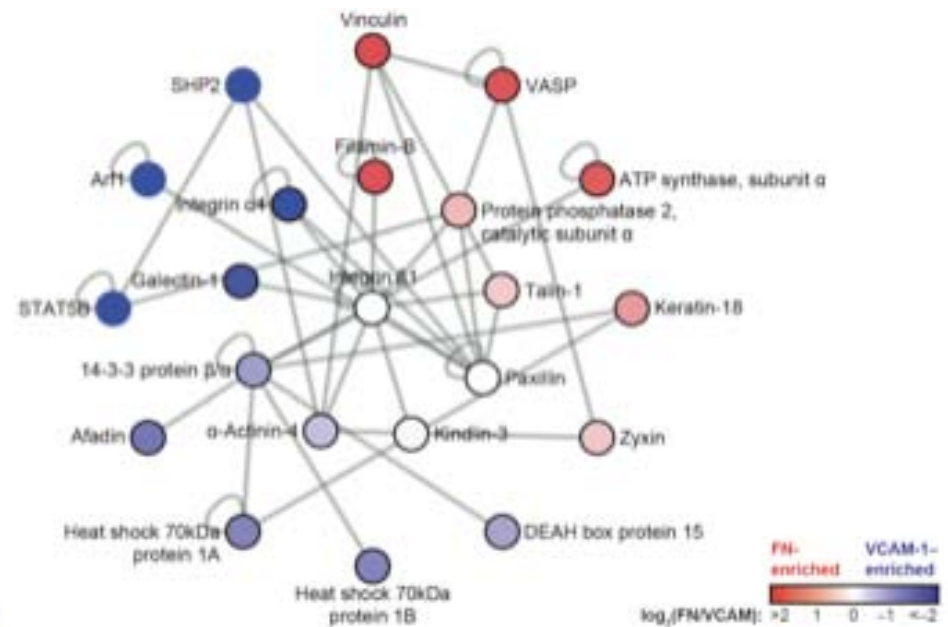


Ligand-induced interaction networks

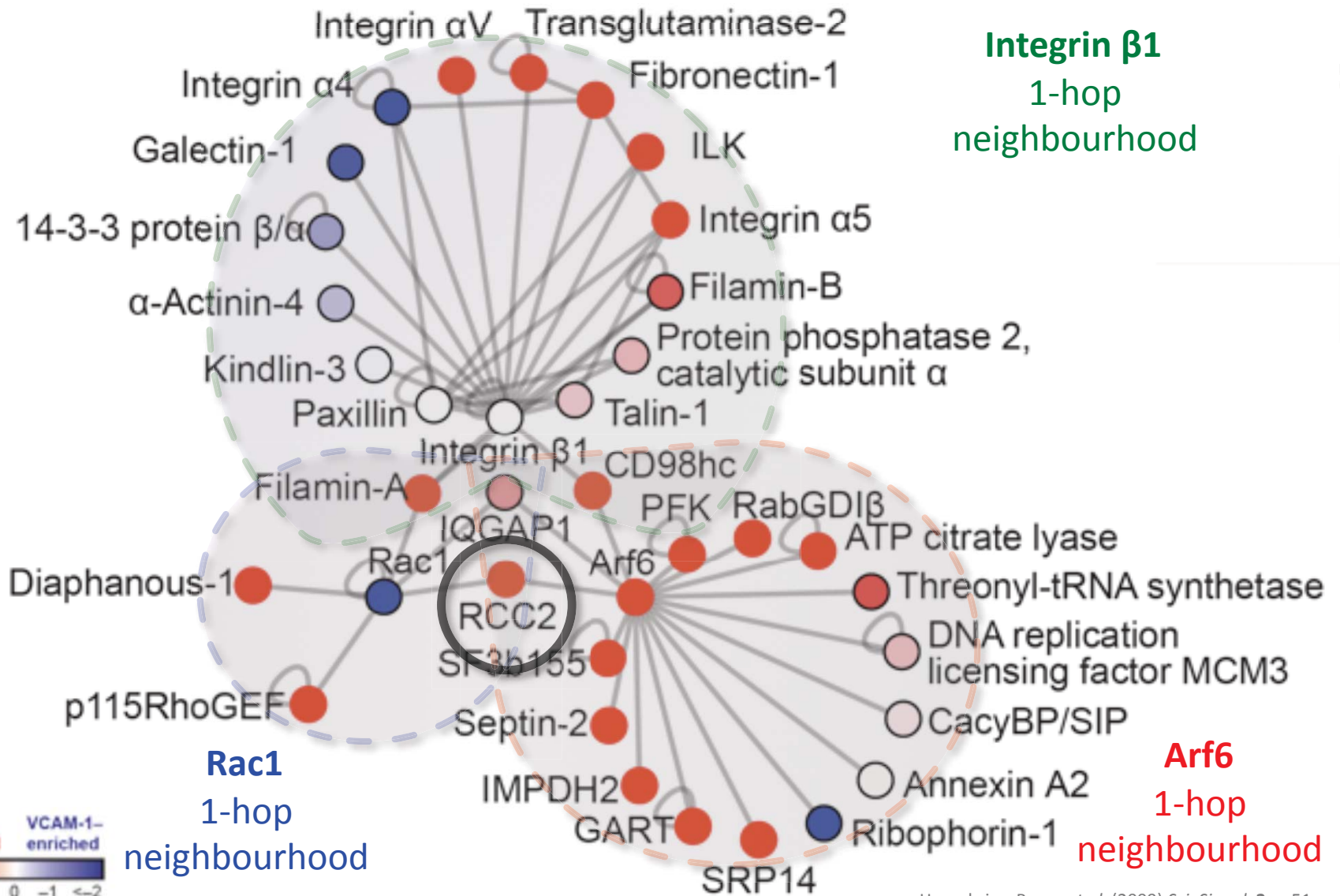
Fibronectin-induced network



VCAM-1-induced network

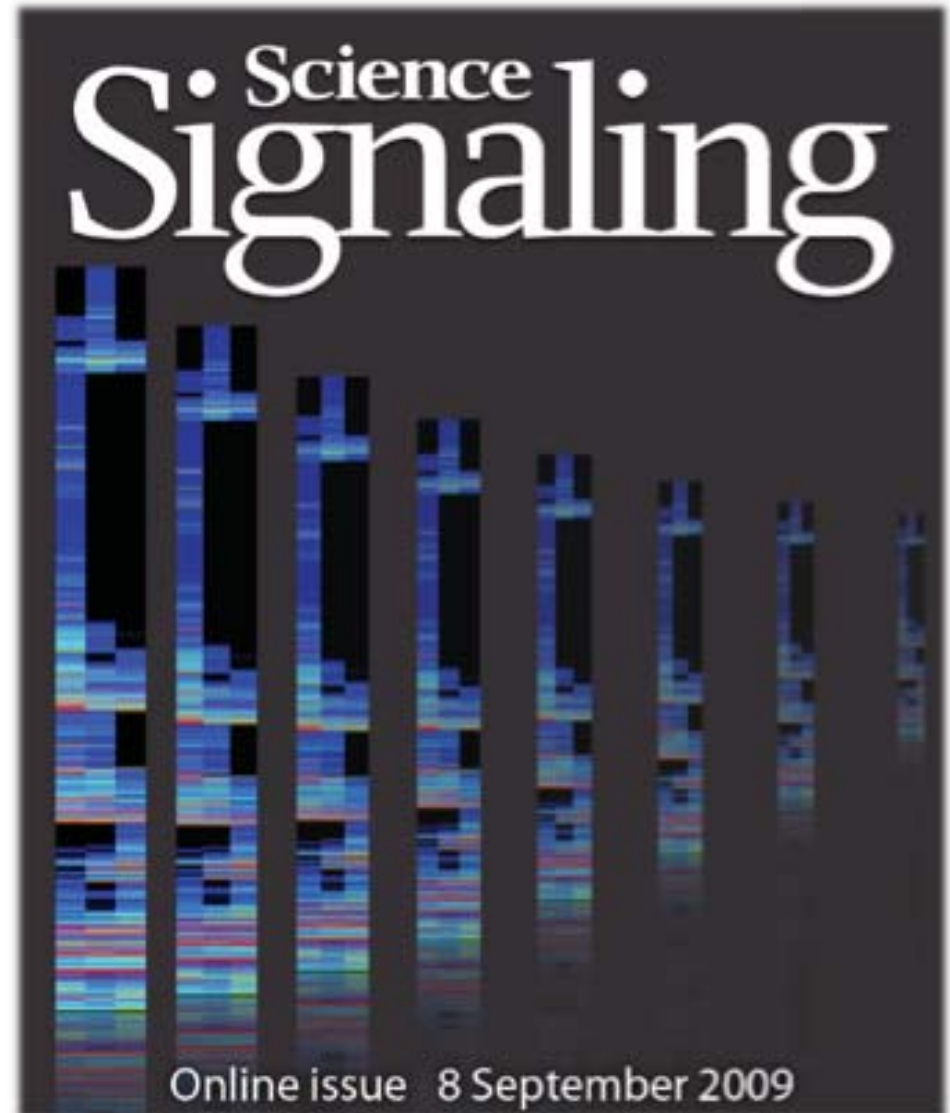
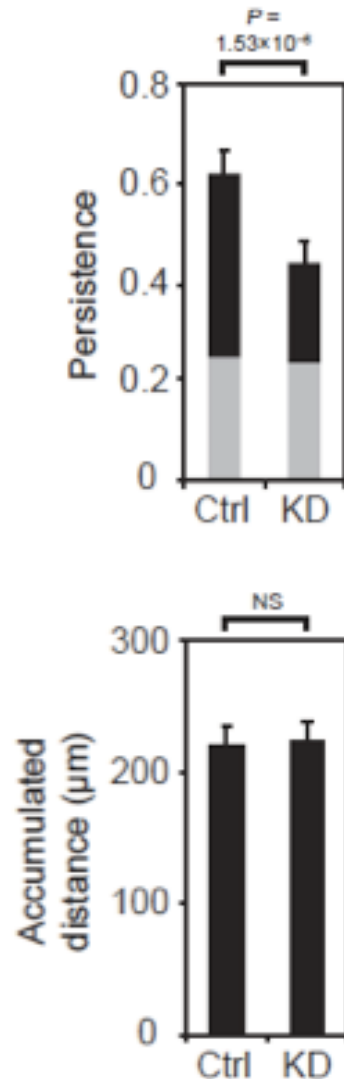


Links to GTPase signalling modules



Humphries, Byron *et al.* (2009) *Sci. Signal.* 2: ra51

RCC2 modulates directional cell migration



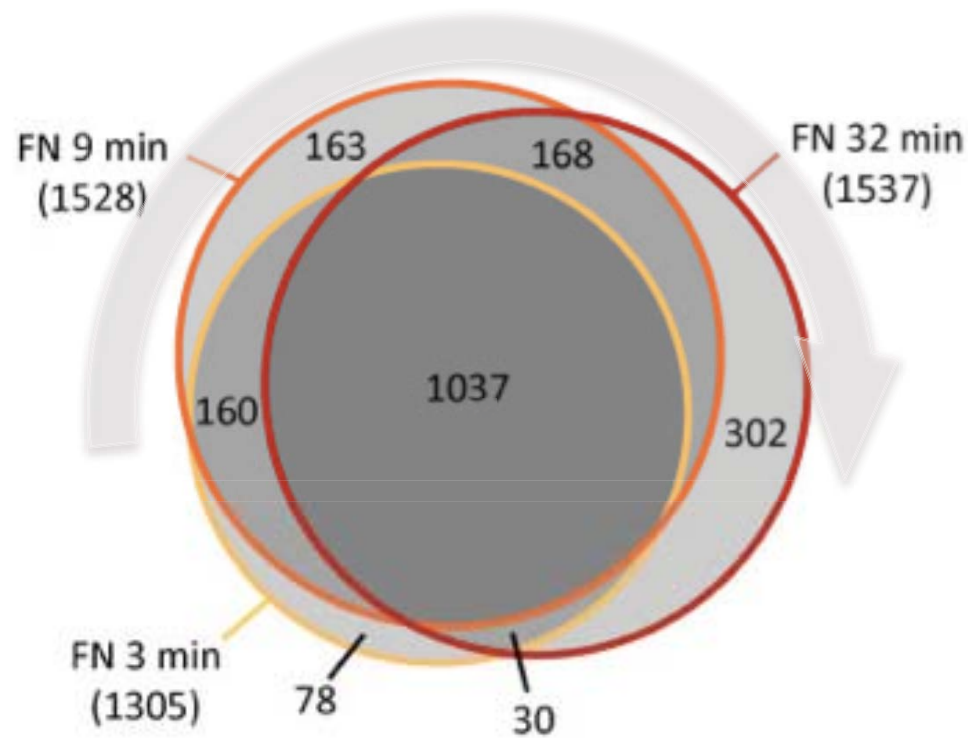
Humphries, Byron *et al.* (2009) *Sci. Signal.* 2: ra51



Current challenge

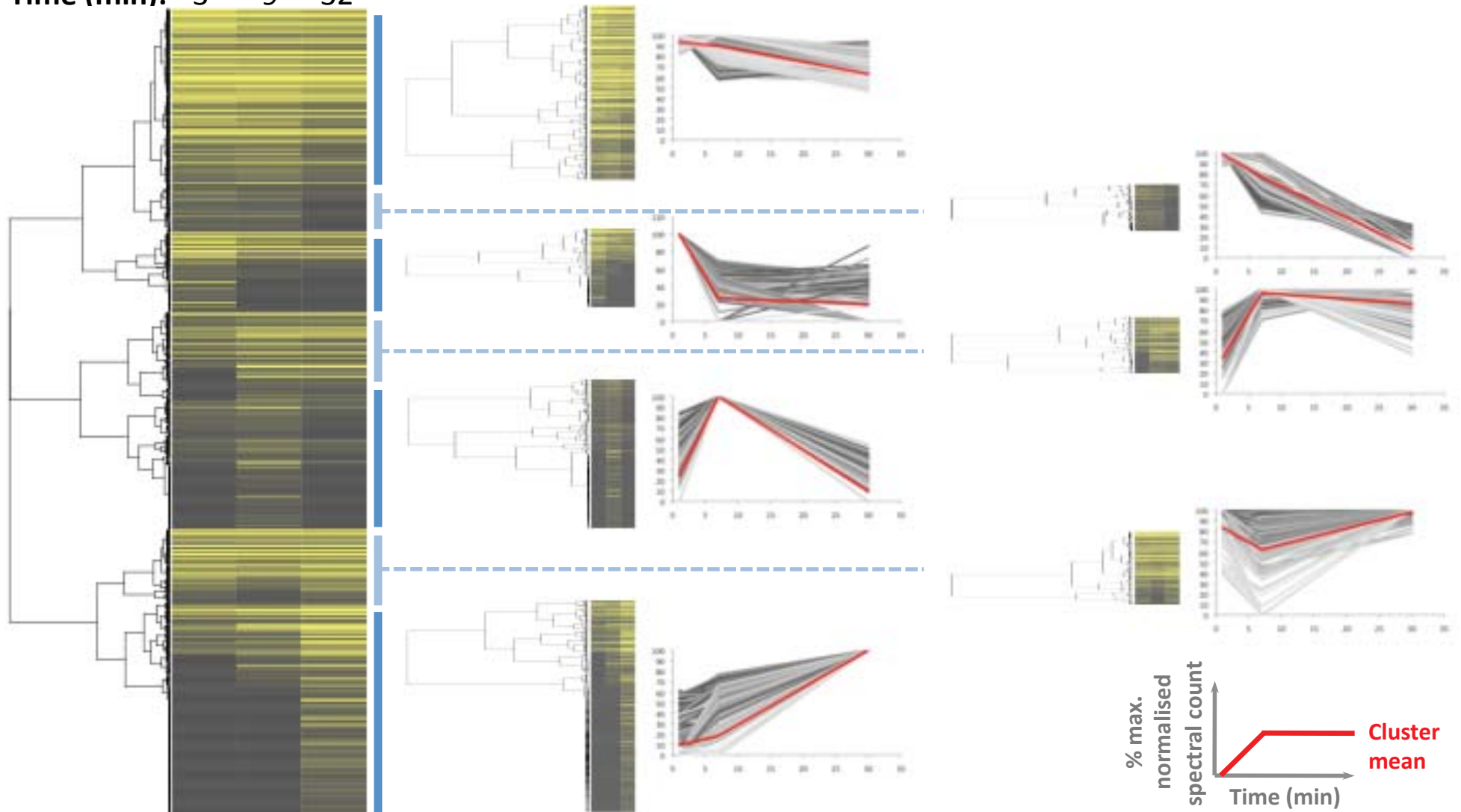
Dynamics of adhesion complex assembly

Adhesion complex assembly



Adhesion complex assembly profiles

Time (min): 3 9 32

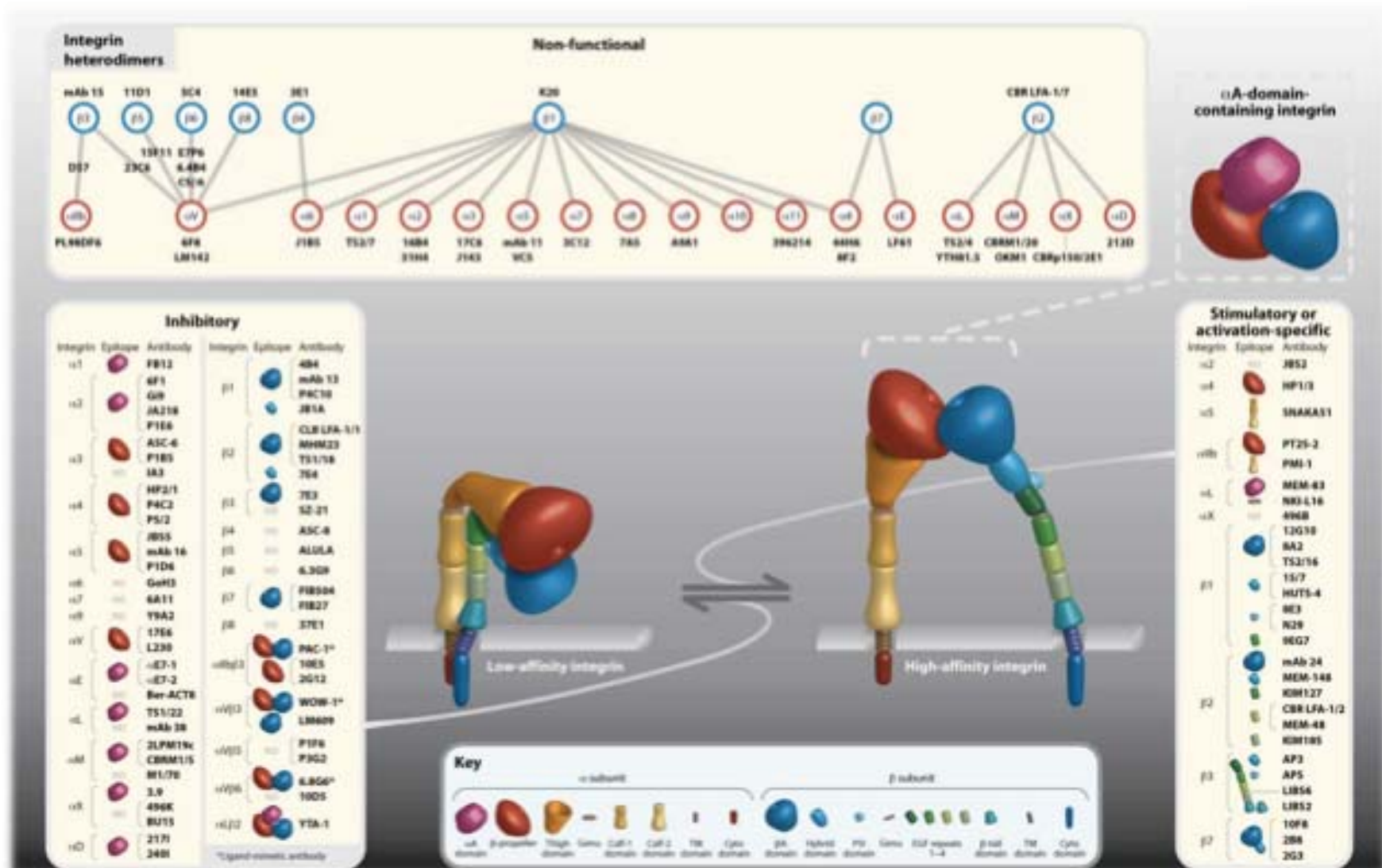




Ongoing work

Activation state-dependent signalling

Activation state-dependent antibodies



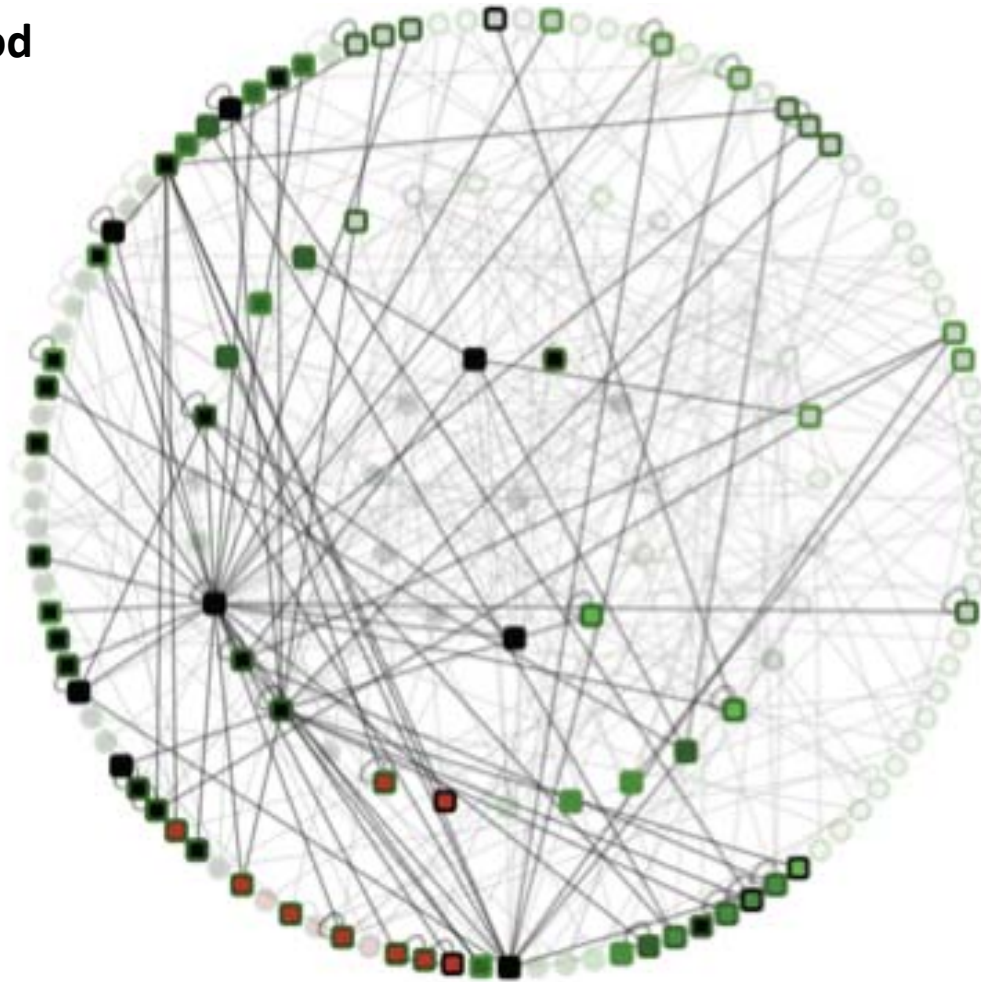
Byron et al. (2009) *J. Cell Sci.* 122: 4009–4011

Activation state-dependent networks

Integrin $\beta 1$

3-hop neighbourhood

- active integrin



Summary

Methodology

- Isolation of specific integrin-associated protein complexes
- Order of magnitude more complex than previously thought

Ligand-specific adhesion complexes

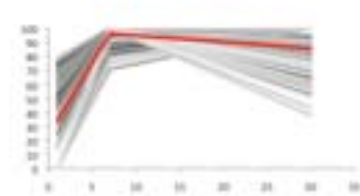
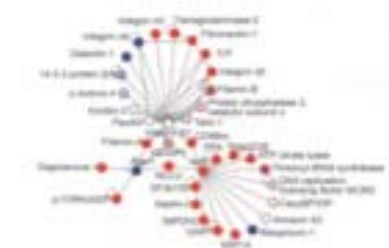
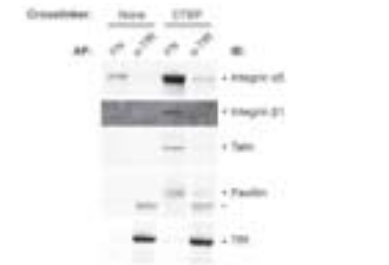
- Surprising variation in scale and composition
- Discovery of a novel regulator of integrin signalling

Adhesion complex assembly

- Complexes form within 3 min of ligand induction
- Core complex matures with distinct temporal profiles

Activation state-dependent signalling

- Antibody-mediated activation appears to mimic early phase of ligand-induced activation



Acknowledgements

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Jane Kott



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of Manchester

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