



The European Molecular Biology Laboratory

**Europe's flagship
laboratory for the life
sciences**

How is biological matter organized ?



- ❑ Proteins inside cells:
up to 300-400 grams per liter
- ❑ Proteomes occupy ~40% of the
total cell volume
- ❑ Compartmentalization

Marsh et al. (2001). Proc. Natl Acad. Sci. USA 98.

Pancreatic beta-cells

Free ribosomes, orange

ER, yellow

Microtubules and mitochondria, green

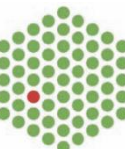
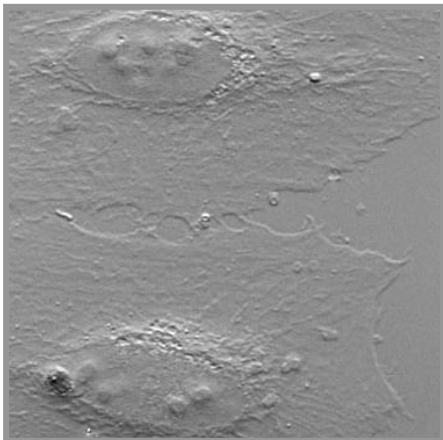
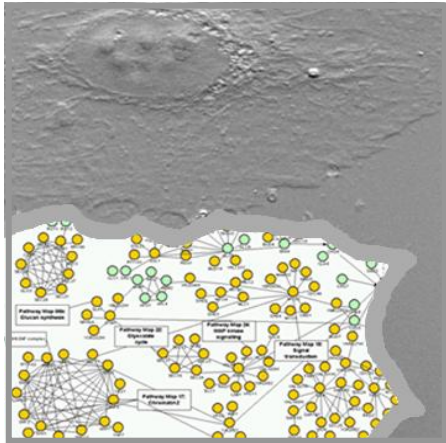
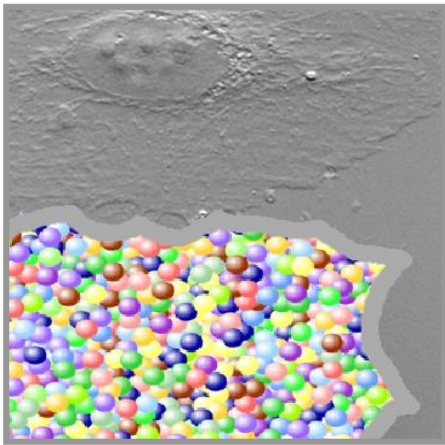
Clathrin-negative vesicles, white;

Clathrin-positive vesicles and compartments, red



Molecular Organization of the Cell

- ❑ Genomes, proteomes, -omes elucidated in their components
- ❑ Underlying functional organization remains largely unknown
- ❑ Cellular function is the result of the coordinated action of proteins acting in complexes, pathways and/or networks
- ❑ Functional organization essential to understand disease and drug action

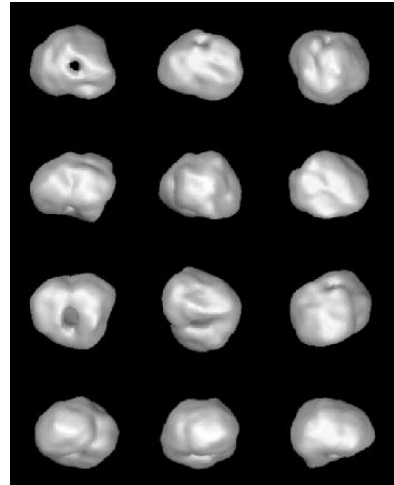
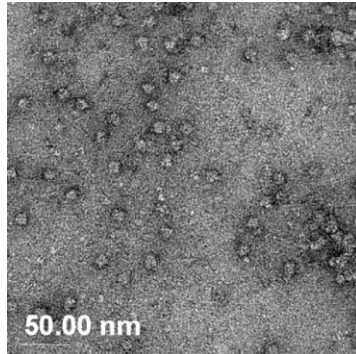
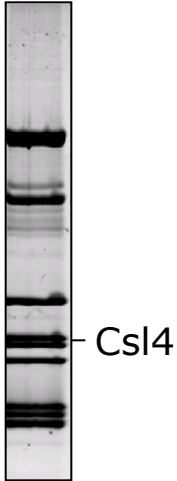


Protein Complexes - Molecular Machines

EM picture

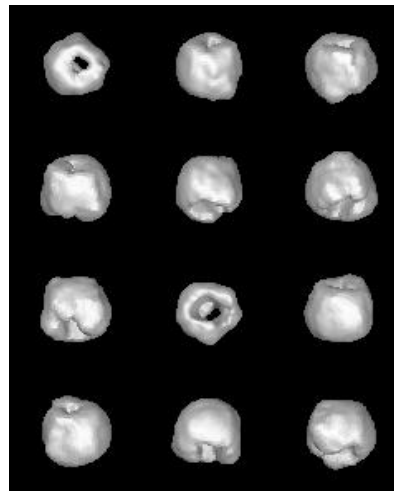
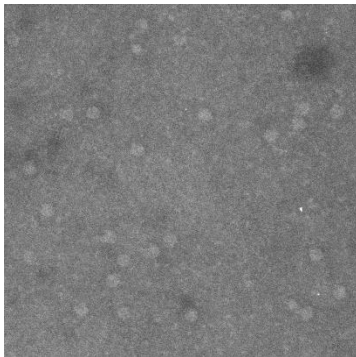
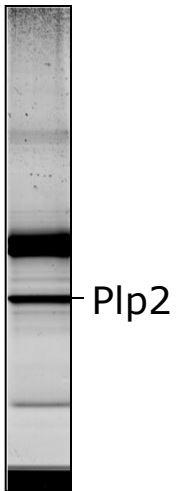
3D reconstruction

TAP purification



The exosome complex

- 3' to 5' exoribonuclease



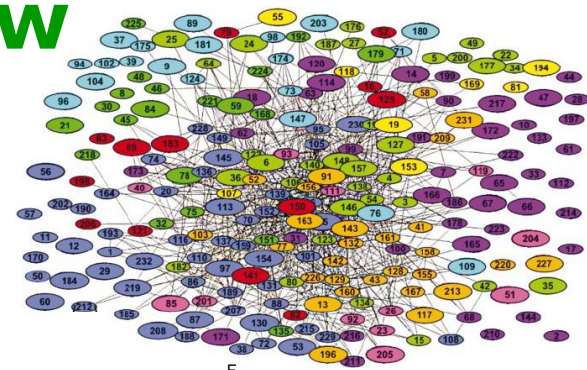
The CCT complex

- Protein chaperon complex
- Delivering $G\beta\gamma$ to the plasma membrane

Research Interests - Overview

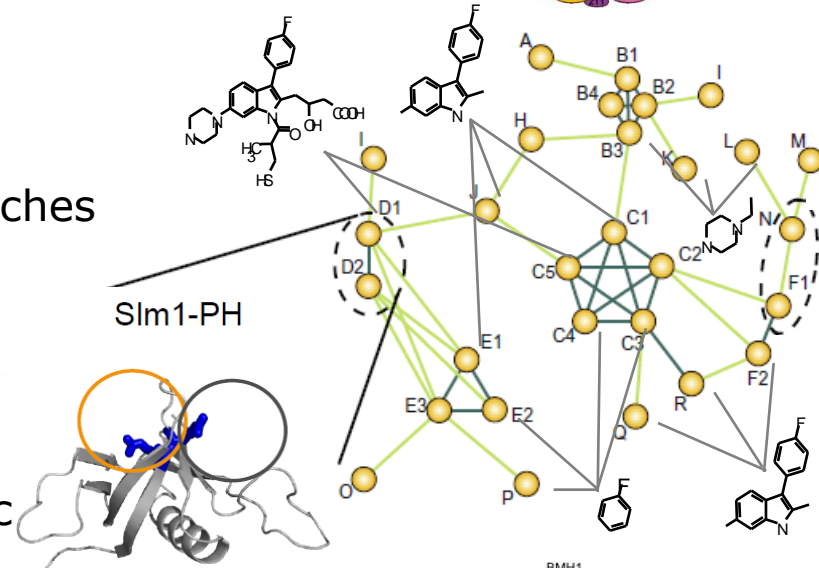
Biological Networks - Systematic charting

- Characterization of protein complexes - Protein-protein, protein-metabolites, ...
- (Bio)chemical, MS
- Model organism: *Saccharomyces cerevisiae*



Large-scale Biochemistry - New approaches

- Microfluidic microsystems, metabolite arrays
- Affinity-based methods/MS

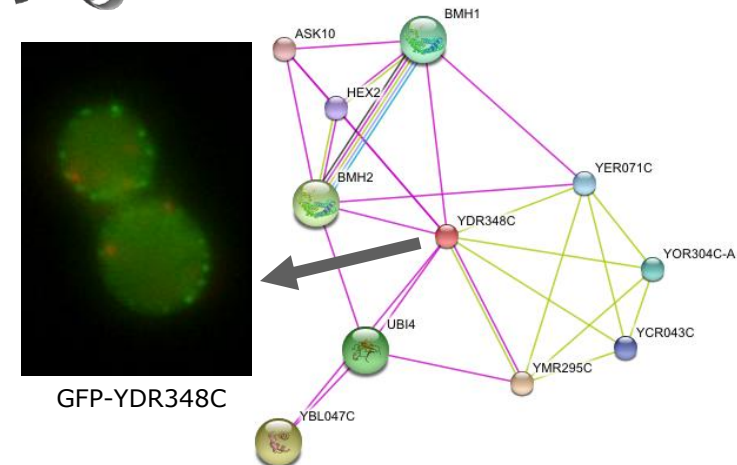


Interaction Code - Structural, mechanistic

- Towards an atomic resolution of a cell

Networks in Health & Disease

- Human pathogens: *Mycoplasma pneumoniae*
- Ageing in human stem cells and age-associated disorders



Molecular Anatomy of a Human Pathogen, *M. pneumoniae*

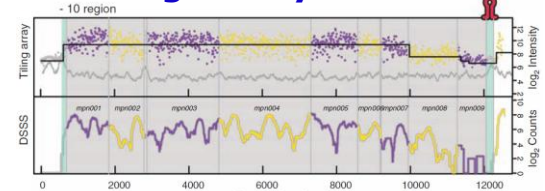
Collaboration: Peer Bork, Bettina Böttcher, Achilleas Frangakis, Robert Russell, Luis Serrano

- ❑ *M. pneumoniae* a minimal human pathogen
 - Atypical pneumonia; 20% of all lung infections
- ❑ Minimal cell concept
 - Among the smallest self replicating genome (691 ORFs)
 - Two putative Ser/Thr protein kinases
 - One protein phosphatase
 - Five transporters

Systematic charting of biological networks

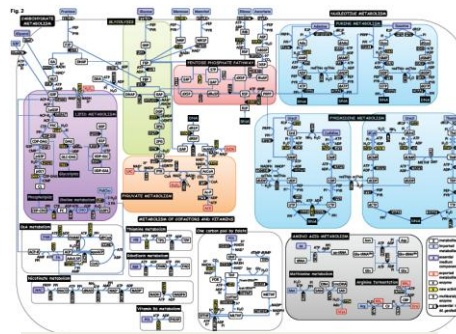
- ❑ Frequent non-coding RNAs (~13% of all transcripts)
- ❑ Operons can be divided into smaller transcriptional units; many alternative transcripts.
- ❑ Multifunctionality: proteome organization and metabolism
- ❑ Phosphorylation & K-acetylation form interconnected networks
- ❑ Optimized for host adaptation and not for growth

Gene regulatory networks



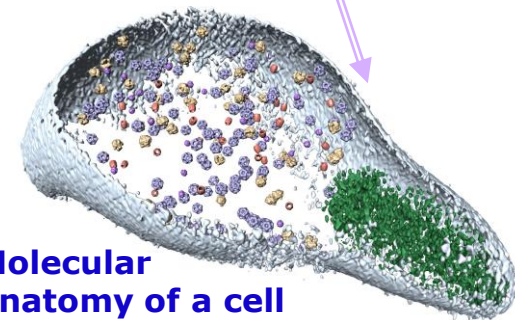
Güell *et al.* (2009) *Science* **326**,1268
Yus *et al.* (2012) *Mol. Syst. Biol.* **8**, 585

Metabolic networks

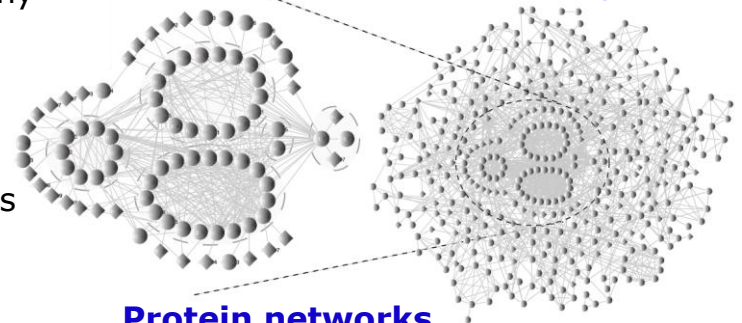


Yus *et al.* (2009) *Science* **326**,1263

Molecular anatomy of a cell



Kühner, van Noort *et al.* (2009) *Science* **326**,1235



Protein networks

Maier *et al.* (2011) *Mol. Syst. Biol.* **7**,511; van Noort *et al.* (2012) *Mol. Syst. Biol.* **8**,571
Minguez *et al.* (2012) *Mol. Syst. Biol.* **8**,599

Proteome Organization in a Genome-Reduced Bacterium

Genome-wide analysis of soluble protein complexes (TAP-MS)

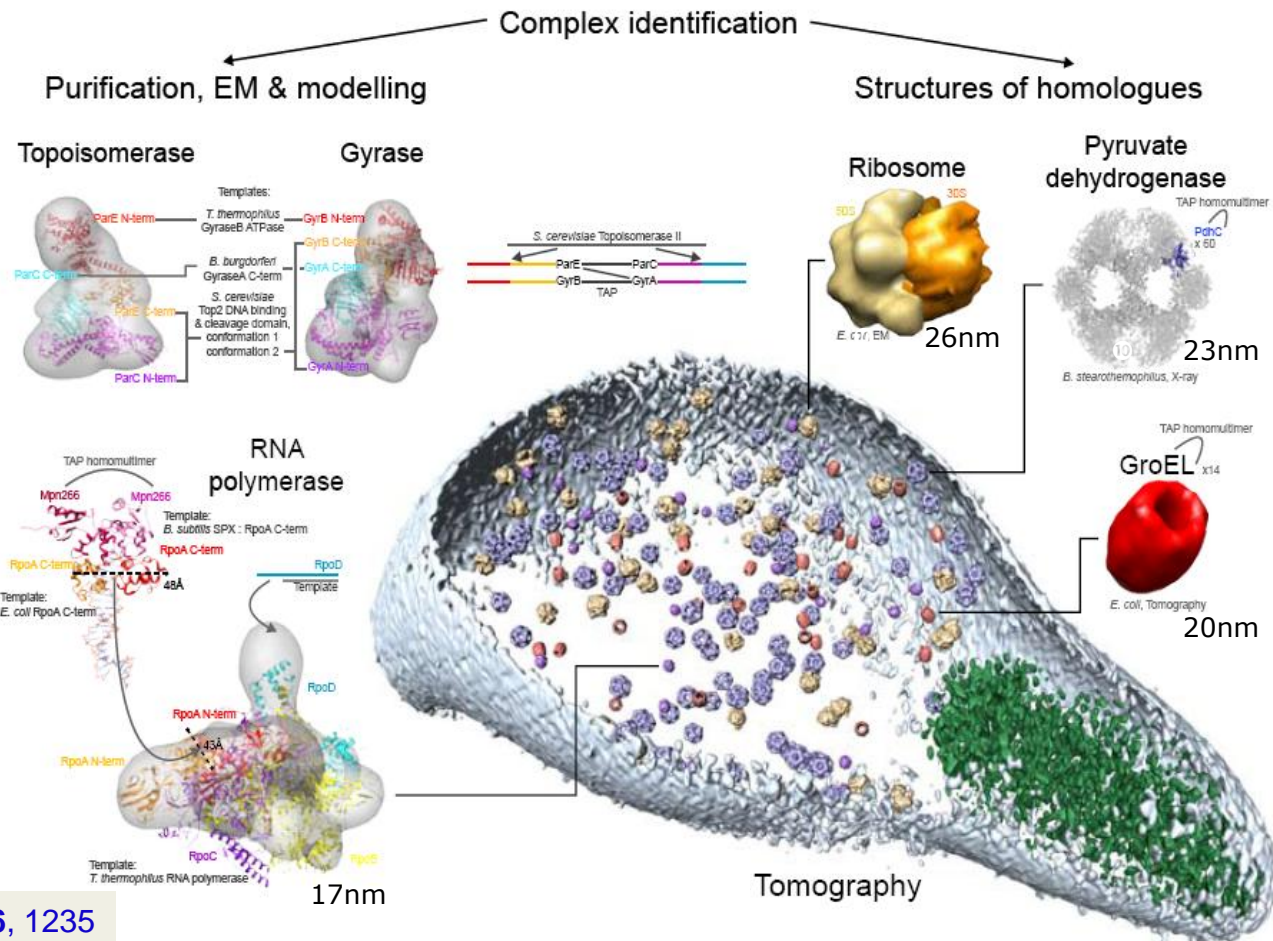
- 116 heteromeric, 62 homomeric complexes
- 90% of analyzed proteins were part of protein complexes

Protein structure available for ~3/4 of all ORFs (484)

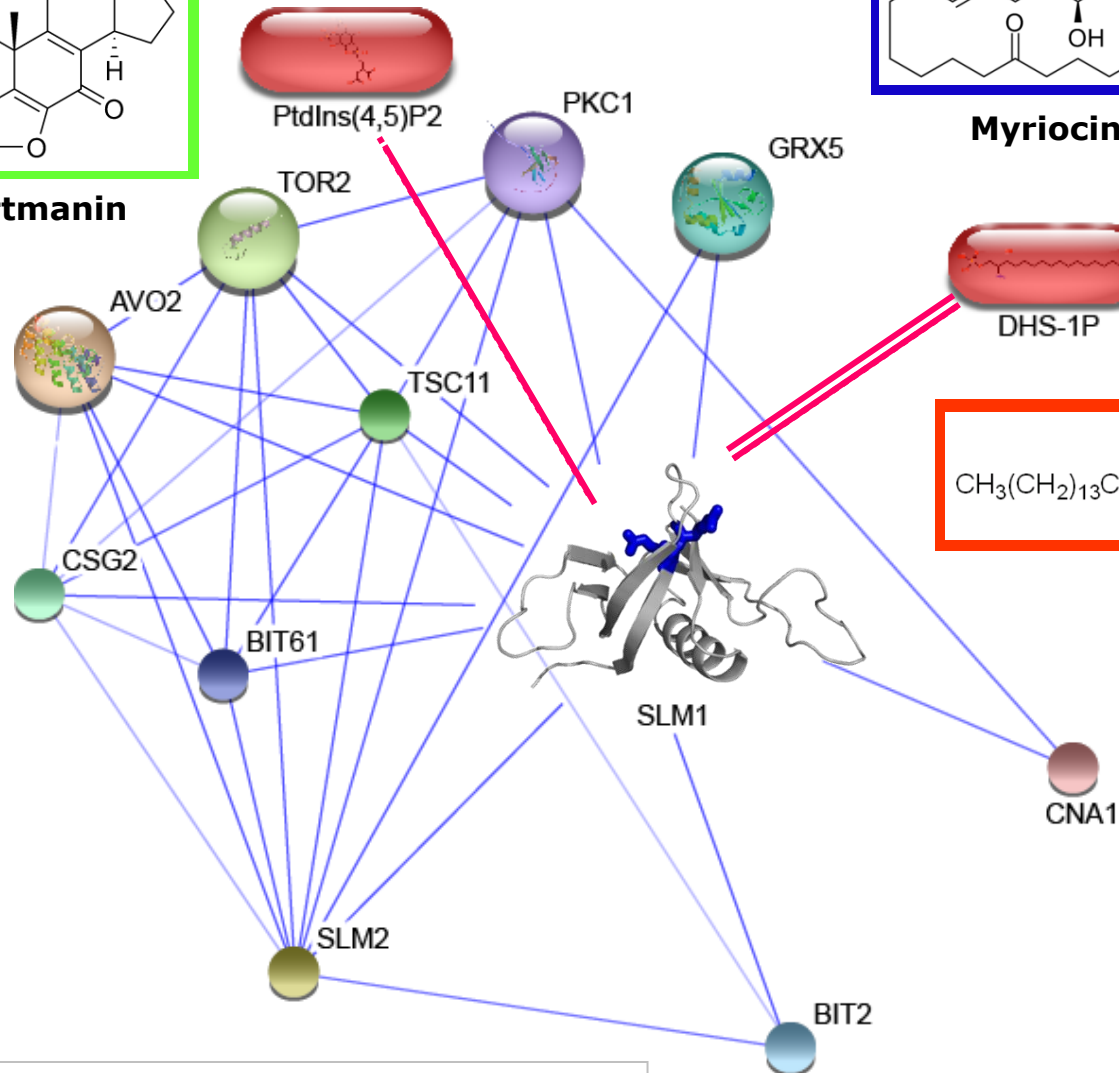
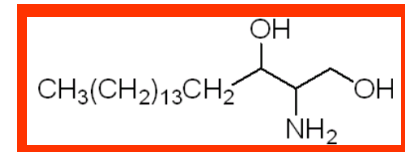
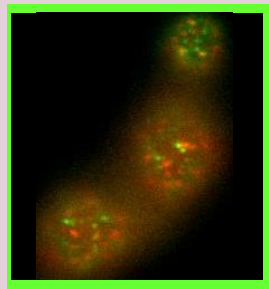
- Binary interactions 153
- Heteromeric complexes 29
- Homomeric complexes 57

Structural validation for novel components

Towards a molecular anatomy of a cell



Phenotypic recording: GFP-Slm1 dynamics



Collaboration: M. Kaksonen, EMBL-HD