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PRESS RELEASE

# Introducing the biology of the future

## *Researchers at Cellzome AG and EMBL publish a record-breaking analysis of a cell's proteome*

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**Functional organization of the yeast proteome by systematic analysis of protein complexes**

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# PRESS RELEASE

# Introducing the biology of the future

## *Researchers at Cellzome AG and EMBL publish a record-breaking analysis of a cell's proteome*

(Heidelberg) Scientists are calling it "biology of the next generation," and a major step towards transforming information from genome projects into applications such as the discovery of new drugs. Today researchers from Heidelberg have announced the completion of a large-scale study of the "molecular machines" formed by nearly two thousand proteins in a living cell.

In a paper published in the current edition of *Nature*, a team of scientists from the biotechnology start-up company Cellzome and the European Molecular Biology Laboratory (EMBL) describe the discovery of over a hundred new protein machines, ranging in size from two to eighty-three molecules, in baker's yeast.

"Most things that happen in cells are directed by the activity of protein complexes," says Giulio Superti-Furga, scientific director of Cellzome and head of a research group at EMBL. Cellzome is housed in the new International Technology Transfer Center on EMBL's Heidelberg campus. "These 'molecular machines' play crucial roles in diseases as well as the everyday life of the cell." By analyzing the DNA sequences of human and other cells, genome projects have provided the complete instruction book by which cells create proteins. But this information doesn't tell when and where molecules will become active in cells, or how they will combine into machines – any more than a list of the contents of a huge kitchen would explain how to cook or how to create a menu. The next task for biology is to decode the "proteome", understanding the functions of molecules and charting their interactions, and Anne-Claude Gavin, Giulio Superti-Furga and their colleagues have now made a major step towards this goal.

Although researchers have known that proteins frequently carry out their tasks in large complexes, technical limitations have made it hard to capture and analyze them. But two years ago an EMBL team headed by Bertrand Séraphin developed a new method of teasing proteins attached to entire, intact machines out of living cells. Peer Bork and colleagues at EMBL identified proteins that could be used as "bait" to fish for the complexes using this technique. Combined with parallel improvements in another technology called mass spectrometry, pushed by Matthias Wilm and his group at EMBL, researchers suddenly had an efficient way to take apart such machines and identify the individual proteins that compose them.

Gitte Neubauer, Scientific Director for Mass Spectrometry and Bioinformatics, says that the project was an enormous logistical challenge, particularly from the point of view of mass spectrometry. "It was necessary to analyze more than 20,000 protein samples, ultimately lead-

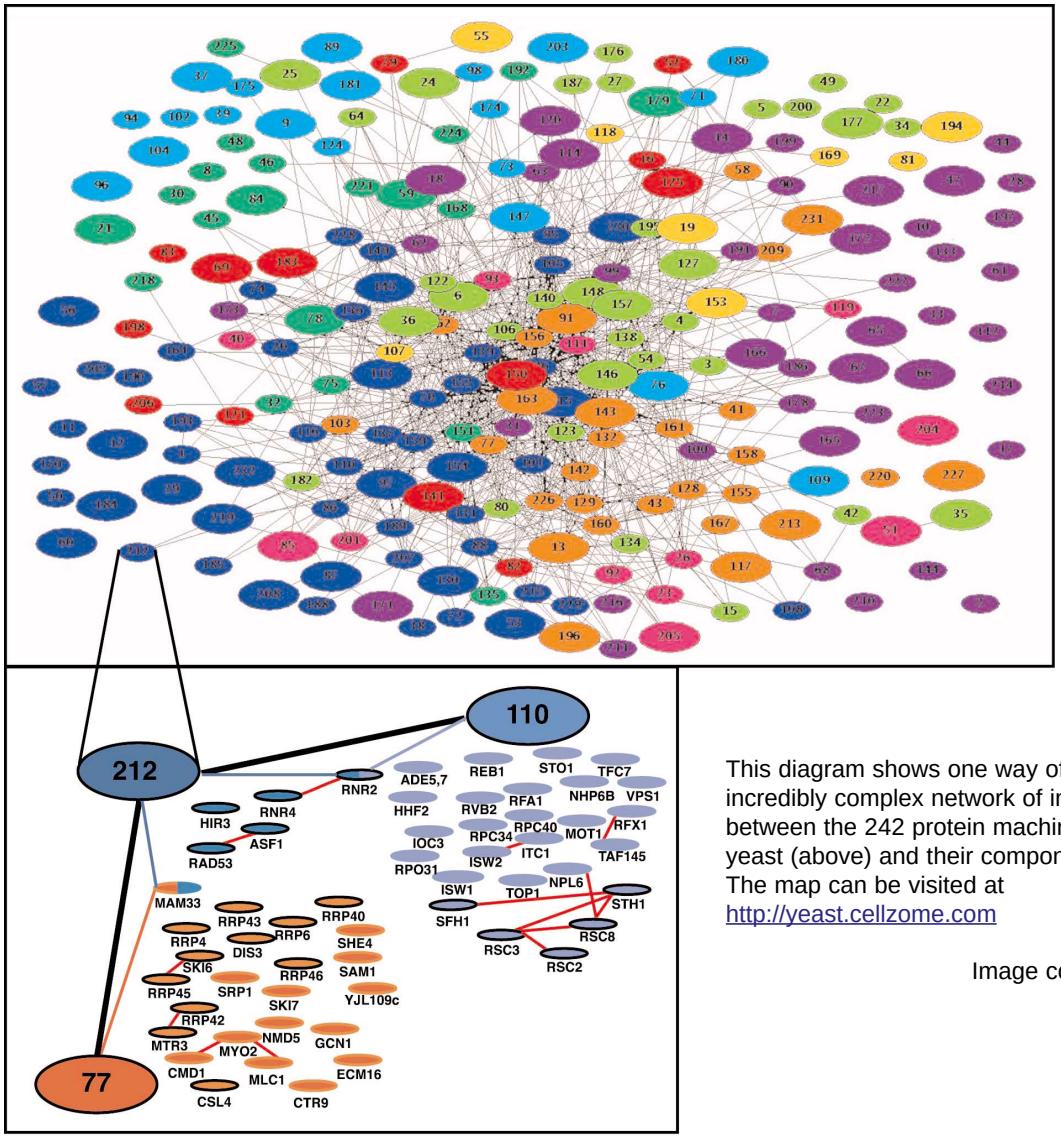

Giulio Superti-Furga, Anne-Claude Gavin,
and Gitte Neubauer of CellZome
photo by Marietta Schupp, EMBL

ing to the identification of 17,000 proteins. While at the beginning this was a slow process – the analysis of the very first complex took a whole week! – towards the end we were routinely analyzing between 1000 to 1500 protein samples in that same amount of time. To our knowledge this is the largest screen that has ever been done using mass spectrometry to dissect protein complexes."

Many of the 17,000 proteins were the same, and often tmachines turned up more than once in slightly different forms, requiring an intensive bioinformatics effort to sort everything out. The researchers had to build customized databases and special imaging software to display the networks of protein interactions. The result is an entirely new catalogue of the enormously complex relationships between over 1,400 yeast proteins – about a third of the genome. The researchers discovered 232 multi-protein machines, 134 of which were totally new. They also found new components lurking in nearly all of the other 98 complexes that had already been described. They discovered that small machines could be integrated into different types of much larger complexes to perform particular tasks, before being dismantled again.

The analysis yielded a number of surprises. Researchers still don't know the functions of a large number of yeast proteins; many of these turned up in molecular machines, which gives a good idea of what jobs the molecules perform in cells. Secondly, dozens of different complexes used many of the same components, which means that many proteins seem to have more functions than scientists have suspected. "And something very interesting happens when you plot all of these machines onto a single map," Superti-Furga says. "There are many ways to depict the networks. You can link complexes by their components, or by their known cellular functions. You obtain a picture of a higher level of organization than we have ever been able to see before. It's somewhat like looking at a French *pointiliste* picture. If you stand too close, because of the technique they used in painting, all you see are single colored dots. As you move away, you begin to see a coherent image."

Researchers know that the list is far from being complete. The group still has to look at the other two-thirds of the yeast genome. "And we were looking at a generic sort of yeast cell; as the cell goes through particular parts of its life-cycle, or experiences dramatic environmental changes, it undoubtedly makes use of different machines," Superti-Furga says. "Additionally, some machines are probably put together and taken apart so quickly that they may be hard to capture with the present methods."




This diagram shows one way of visualizing the incredibly complex network of interactions between the 242 protein machines found in yeast (above) and their components (below). The map can be visited at http://yeast.cellzome.com



This initial project focuses on proteins which have close relatives in human cells – there are many such molecules, because yeast and humans belong to the same major evolutionary branch. “We found that yeast and human cells share a very high number of similar machines, composed of related proteins,” Superti-Furga says. “This means that while single molecules have changed significantly through mutations over the course of evolution, the cells of new species continue to build the same types of machines, using the altered components.” Thus the study should help researchers identify the components of similar machines in human cells, which scientists regard as a key step in developing new “post-genomic” types of medicine.

The map of the machines, their components, and their very complex interconnections can be found at the Cellzome website, under the address http://yeast.cellzome.com.

- Russ Hodge

## Notes for editors:

**About Cellzome**
Cellzome AG, with laboratories and operations in Heidelberg, Germany and Elstree, just north of London, UK is a biopharmaceutical company that uses its proprietary functional proteomics technology for target discovery, validation, and drug development. The Company was founded in May 2000 with a team of scientists from the European Molecular Biology Laboratory (EMBL), including pioneers in the fields of protein mass spectrometry, bioinformatics, structural biology and signal transduction. The company currently has 105 employees. Learn more at www.cellzome.com.

**About EMBL**
The European Molecular Biology Laboratory is a basic research institute funded by public research monies from 16 member states, including most of the EU, Switzerland and Israel. Research at EMBL is conducted by approximately 80 independent groups covering the spectrum of molecular biology. The Laboratory has five units: the main Laboratory in Heidelberg, Outstations in Hinxton (the European Bioinformatics Institute), Grenoble, Hamburg, and an external research programme in Mouse Biology in Monterotondo near Rome. The cornerstones of EMBL's mission are: to perform basic research in molecular biology, to train scientists, students and visitors at all levels, to offer vital services to scientists in the member states, and to develop new instruments and methods in the life sciences. The Laboratory also sponsors an active Science and Society programme, Visitors from the press are welcome. For more information see the EMBL website at:

http://www.embl-heidelberg.de

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