SystemsX.ch
The Swiss Initiative in Systems Biology

Newsletter #13
September 6th 2007

«Tout Science» at the Kick-off of SystemsX.ch at Bellevue in Berne

From today seven Swiss universities engage themselves in SystemsX.ch and strive for a world wide pole position in Systems Biology. At the same time, the first call for proposals was issued. Teams have time to apply until January 1st, 2008.

Ralph Eichler, President of ETH Zurich since September 1st, is signing the contract. *Photo Andrea Kaufmann*

Bern. AK/VDM. SystemsX.ch is officially launched. Hence, the Swiss Initiative in Systems Biology became a truly national endeavour this afternoon, when Charles Kleiber, State Secretary for Education and Research and SNSF-Director Daniel Höchli attended the signing of the SystemsX.ch Partnership Agreement by the Presidents and Rectors of seven Swiss universities. The contract was elaborated with all involved partners, ETH Zurich, EPF Lausanne and the Universities of Basel, Berne, Geneva, Lausanne and Zurich.

Since the kick-off event took place just before a meeting of the Rectors' Conference of the Swiss Universities (CRUS) in Bern, Rectors from universities which are not SystemsX.ch partner were present as well. University of Fribourg expressed strong interests to become a SystemsX.ch partner soon.

What's new in SystemsX.ch?

SystemsX.ch functions as a simple partnership and will merge the strengths of two existing cooperation efforts. In the lémanique area, the biomedical and genomics research (Universities of Lausanne

und Geneva and EPF Lausanne) recently bundled into a Swiss genomics initiative, and in the German speaking part of Switzerland, ETH Zürich and the Universities in Zürich and Basel had built up the Systems Biology initiative SystemsX.

The Federal Council proposed in his message about Education, Research and Innovation 2008-2011 to support Systems Biology in Switzerland and to fund SystemsX.ch with CHF 100 Mio for four years, starting January 1, 2008. However, the Message is subject to approval by the parliament in October 2007.

The State Secretariat for Education and Research (SBF/SER) will coordinate the flow of money from the Swiss University Conference (SUK/CUS) and the ETH-Board, which are responsible for the cantonal Universities and the Swiss Federal Institutes, respectively.

Swiss National Science Foundation SNSF was given a mandate by the SBF/SER for scientific quality assessment and monitoring of SystemsX.ch projects. Project funding follows the approval by the SNSF. SystemsX.ch contributes up to 50% of the funding of the projects, 50% shall be provided by Universities in kind or in cash.

Call for proposal

With the official launching of SystemsX.ch today, the first call for proposals is published. SystemsX.ch will support so called large integrated research projects that implement all aspects of Systems Biology. Researchers can submit proposals for Research, Technology and Development Projects (RTD), Interdisciplinary Pilot Projects (IPP) and Interdisciplinary Ph.D. Projects (IPhD). Please find more information on the application procedure and forms on the website.

How the review works

An international, interdisciplinary review panel (see table) of the Swiss National Science Foundation (SNSF) will evaluate submitted proposals for RTD and IPhD Projects. Inter-disciplinary Pilot Projects (IPP) are regarded to be seed and high-risk projects. IPPs are evaluated by the Scientific Executive Board (SEB) of SystemsX.ch.

Charles Kleiber at the SystemsX.ch Kick-off Meeting. *Photo Kaufmann*

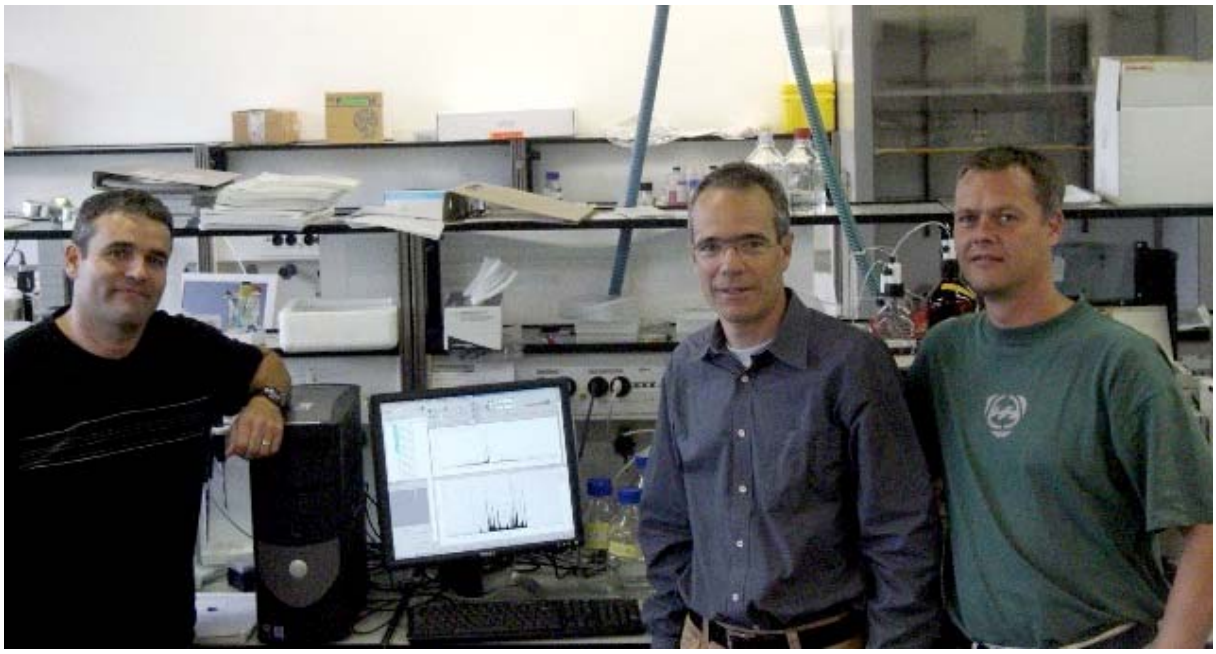
Reviewing and monitoring of proposals and projects will be done by the SNSF which will stay in close contact with the SEB. The SEB can submit SystemsX.ch initiated projects, such as technology infrastructure projects that are critical to the success of the whole initiative. These SystemsX.ch-initiated proposals will also be evaluated by the SNSF. For each project, the decision will be taken on a case-by-case basis, regarding exclusively added value to Systems Biology and scientific quality. Further details on the selection criteria are found on the webpage.

The International Review Panel for SystemsX.ch

Name	Affiliation
Schwarzenbach René P.,*Chair*	Swiss National Science Foundation (Division IV)
Butcher Eugene	Stanford University
Cassman Marvin	University of California, San Francisco
Chiu Wah	Baylor College of Medicine Houston
Eckmann Jean-Pierre	Swiss National Science Foundation (Division II)
Folkers Gerd	Swiss National Science Foundation (Division IV
Grütter Markus Gerhard	Swiss National Science Foundation (Division III)
Leibler Stanislas	The Rockefeller University
Leumann Christian	Swiss National Science Foundation (Division II)
Meyer Tobias	Stanford University
Peitsch Manuel	Swiss National Science Foundation (Division III)
Quake Stephen	Stanford University
Rine Jasper	University of California, Berkeley
Shraiman Boris	University of California, Santa Barbara
Silver Pamela	Harvard Medical School
Stark Jaroslaw	Imperial College London

The Art of Filing a Proteome

The listing of the proteins is just the first step towards the development of a revolutionary technology to analyze proteomes efficiently. The Scientists of the Center for Model Organism Proteomes are convinced that serious Systems Biology starts here.



Christian Ahrens, Konrad Basler and Erich Brunner, the core team of the Center for Model Organism Proteomes.

Zurich. The life of a cell can be likened to a symphony. The reading of the score alone won't tell you exactly how the orchestra will sound, even if it is noted how many violins and trumpets are present. When you hear the concert, you cannot be sure that the conductor and the musicians follow the notes accurately. So, to really understand what goes on in the concert hall, you need to be able both to read the notes, and listen precisely.

From Thomas Müller (Text and Photo)

In a similar sense, knowing the genes of a cell or an organism does not tell you exactly how the proteins in the cell actually behave. You can't even be sure, that it will be possible to predict all the proteins that will be found in a certain cell type at any given time. A snap shot of this orchestration of protein activity is called proteome, derived from the words PROTEin and genOME. The cataloguing of all the proteins present in three widely used model organisms is the goal of the SystemsX.ch «Center for Model Organism Proteomes», C-MOP.

The task appears to be huge, and it is. While the genome is fixed for its lifetime, the proteome is in constant flux – as with the sound of an orchestra. Some proteins, like instruments, appear regularly and perform the motif. Others contribute only occasionally, but are nonetheless essential for the overall performance. The analogy breaks down however, when it comes to scope. While a large orchestra has some dozens of instruments, the number of active proteins in a cell runs into the thousands.

But what is the deeper biological motivation for filing all the proteins of – let's say – *Drosophila melanogaster*? «The catalogue by itself is not the end of the play, but the beginning of doing Systems Biology seriously», explains Konrad Basler, Professor of Molecular Biology at University of Zurich and Director of the C-MOP. Quantification is one of the highly praised cornerstones of Systems Biology, but the efficient acquisition of accurate and comprehensive quantitative protein datasets is yet to be solved. C-MOP is working to overcome this challenge.

It has been possible for some time now to measure the expression level of all messenger RNAs in a cell, the so-called transcriptome, using microarray technology. Christian Ahrens, bioinformatician, and one of the coordinators of C-MOP says: «Our aim is to provide an analogous technology for the measurement of protein levels».

A Two-Step Strategy

«Technologically this is a daunting task», says Erich Brunner, the second C-MOP coordinator who explores the *Drosophila* proteome. «Despite technological advances, no proteome has yet been comprehensively analyzed and the effort required to do so is enormous and can take months or perhaps years to complete». The C-MOP team tackles this issue with a two-step strategy, in close collaboration with Ruedi Aebersold and Ernst Hafen, professors at the ETH Institute of Molecular Systems Biology who launched the C-MOP initiative.

The first step, relies on an initial investment into a «discovery phase» in which, all proteins of an organism are mapped out by high throughput sequencing. The resulting «proteome catalogue» contains the information about where a protein is expressed and which part of a protein can be observed by a mass spectrometer. In the second step (the scoring phase) proteins are no longer randomly sequenced but selectively identified via a specific protein signature, a so-called proteotypic peptide (PTP), that was determined in the discovery phase: For every protein in the proteome catalogue there are peptides which are unique (i.e. proteotypic) and thus contain sufficient information to identify and quantify this protein in any experiment. Since only this little and pre-defined piece of information is needed to detect and quantify any protein, the group envisages, with this targeted approach, to be able to record a proteome that is relevant for a biological system in a very short time.

Besides the *Drosophila* proteome, C-MOP is annotating the proteomes of *Arabidopsis thaliana* worked on by the groups of Ueli Grossniklaus (Institute of Plant Biology, UZH) and Wilhelm Gruissem (Institute of Plant Sciences, ETH) as well as the nematode *Caenorhabditis elegans* by the lab of Michael Hengartner (Institute of Molecular Biology, UZH). The first comprehensive *Drosophila* catalog has been published this year in Nature Biotechnology, and the proteome catalogues of *Caenorhabditis elegans* and *Arabidopsis* are about to be released soon.

The Gauging of the Gene Models

The huge discovery step is comparable with the genome projects of the nineties. While the biological insight stemming directly from the genomes was relatively meagre, the functional genomics technology emerging from the genome projects advanced the understanding of a wide range of basic biological processes, and, for example, identified a wealth of disease-specific biomarkers (see «Looking into the Mirror of Health» in SystemsX Newsletter #12). Similar to the genome projects, technology developments are important to shorten the discovery phase. An iterative proteome mapping strategy developed by Christian Ahrens that significantly speeds up the discovery phase, is already applied by all C-MOP research groups (see table).

One of the immediate applications of the list of expressed proteins identified in the discovery phase is the validation of the

Center for Model Organism Proteomes (C-MOP) at a glance	
Head:	Prof. Konrad Basler, University of Zurich
Coordinators:	Dr. Erich Brunner, Dr. Christian Ahrens
Collaborating Institutions:	Institute of Molecular Systems Biology, ETH Zürich; Functional Genomics Center (FGCZ), University and ETH Zürich; Center for Information Sciences and Databases (CISD); Institute for Systems Biology (ISB), Seattle USA.
Number of Research Groups:	4
Number of People at C-MOP:	22

gene models predicted by the genome projects. «Sometimes we find proteins for which we can't find the gene models, in other cases we do not find the proteins belonging to a predicted gene», explains Konrad Basler. «But, because we measure the real thing, the proteins, it will be possible with our technology to gauge the accuracy of these gene models». This is one example of how the desired interplay between theory and experimentation will work in Systems Biology.

Welcome to the Proteom Age

Basler, Brunner and Ahrens are convinced of the huge potential of the technology developed by C-MOP, but bemoan the scarcity of funding. One explanation, also within SystemsX.ch, might be that the group failed to stress enough that the listing of the proteins is just the first step towards the development of a revolutionary technology to analyze proteomes efficiently. In fact, the quantitative proteomics datasets generated by this technology are an important pre-requisite for any proteomics-based Systems Biology approach.

Basler is convinced that it was a mistake of Switzerland's scientific community not to enter the genomics stage in the nineties, when the relevant technologies were being developed, but waited until the technologies were available off the shelf. «This meant that a lot of know-how had to be bought and imported first, setting back Switzerland's biological research.»

With the technologies that are being developed at C-MOP in close collaboration with Ruedi Aebersold, Basler, Brunner and Ahrens are convinced that Switzerland will be able to propel itself to the front in the proteome age.

Organism	Number of genes	Number of distinct proteins	Already detected genemodels: number and %
Drosophila	13'972	16'743	9'510 (68,9 %)
C. elegans	19'735	22'269	10'631 (53.9%)
Arabidopsis	26'751	29'075	14'128 (52.8%)

The table shows the progress of the protein listing in the three model organisms of C-MOP.

Franziska Biellmann enforces SysX.ch-Office

Zurich. VDM. With the publication of the call for SystemsX.ch proposals, the work load in the management office, which is already high, will increase. SEB approved one position, which was advertised in August. We are happy to inform you that Franziska Biellmann will start her new job with the All-SystemsX.ch-Day on September 17. Franziska Biellmann is about to finish her PhD studies on glycosyltransferases in the mouse model at the Institute for Physiology at the University of Zurich. She did her Masters degree in Biotechnology/Biomedical Sciences at the University of Heidelberg (D) and completed her Bachelor studies (Microbiology) in Athens, GA USA. Although she is originally Swiss, Franziska grew up in USA and is therefore bilingual. We look forward to welcoming her in the SystemsX.ch community.

Push for Synthetic Biology in UK

Swindon. thm. The British Biotechnology and Biological Sciences Research Council (BBSRC) and the Engineering and Physical Sciences Research Council (EPSRC) are issuing a joint call for proposals for Networks in Synthetic Biology. Other partners are the Arts and Humanities Research Council (AHRC) and the Economic and Social Research Council (ESRC).

Up to £950K is available for the call, subject to the scope of the proposals received. The Research Councils anticipate funding six to eight networks, subject to quality of the proposals received. BBSRC contacted SystemsX.ch for collaboration between the two bodies.

More information here

Roadmap to European Systems Biology

Strasbourg. thm. The European Science Foundation in Strassbourg has developed a roadmap to invest in Systems Biology. The aim is to initiate, coordinate and fund a single Grand Action on Systems Biology (GRASB), which should become the world's largest and most effective single Systems Biology programme. GRASB should build on the major Systems Biology already in place in Europe and achieve breakthroughs in biomedical, pharmaceutical and biotechnological research. The programme is supposed to be developed by summer 2008, the activities are planned to be coordinated by a European Systems Biology Office (ESBO). The plan builds on the work of the ESF Advisory committee on Systems Biology. Ruedi Aebersold from the Institute of Molecular Biology of ETH Zurich is a member of the committee. Further planned activities of GRASP are a massive technology development initiative for Systems Biology, a setting up of European Reference Laboratories and multi-disciplinary teaching programmes.

More information here.

Upcoming Events

Date	Location	Topic
September 10-12 2007	The New Forest, UK	Seventh International Conference on Modelling in Medicine and Biology
September 13-14 2007	Buxton, Derbyshire, UK	17th New Phytologist Symposium Systems Biology and the Biology of Systems: how, if at all, are they related?
September 9-12 2007	Stuttgart, Germany	2nd Conference Foundations of Systems Biology in Engineering (FOSBE 2007)
September 17-18 2007	EPF Lausanne	All-SystemsX.ch-Day
September 19 2007	ETH Hönggerberg	Conference of the Swiss Biochemical Society 2007
October 1-6, 2007	Long Beach, California	International Conference on Systems Biology (ICSB-2007)
October 11-13 2007	Jeju-do, Korea	Frontiers in the Convergence of Bioscience and Information Technologies (FBIT 2007)
November 14-16 2007	Montreux, Switzerland	Trends and Visions in MicroNano Technologies for Biosciences
November 24-29 2007	Sant Feliu de Guixols, Spain	European Conference on Synthetic Biology (ECSB)
November 26-28 2007	Zurich/Basel	Scientific Advisory Board Meeting
January 4-8 2008	Big Island, Hawaii	From Molecules to Cells to Organisms Pacific Symposium on Biocomputing conference
February 6-7, 2008	EPF Lausanne	Biology meets Engineering - Union of the Swiss Societies for Experimental Biology (USGEB 2008)

Recent Publications from SystemsX Scientists

Publications from SystemsX Projects, which have been released since Newsletter 12.

Department of Biosystems Science and Engineering of ETH Zurich

Osteopenia, decreased bone formation and impaired osteoblast development in Sox4 heterozygous mice.
Nissen-Meyer LS, Gautvik KM.et al.
J Cell Sci. 2007; 120(Pt 16): 2785-95.

Polycomb/Trithorax response elements and epigenetic memory of cell identity.
Ringrose L, Paro R.
Development. 2007; 134(2):223-32.

Genetic progression and the waiting time to cancer.
Beerenwinkel N., Nowak M. et al.
Submitted 25. July 2007.
[arXiv]

Viral population estimation using pyrosequencing.
Eriksson N., Beerenwinkel N. et al.
Submitted 1 July 2007.
[arXiv]

Predicting HIV co-receptor usage based on genetic and clinical covariates.
Beerenwinkel N., P. Richard Harrigan R. et al.
Antiviral Therapy, in press.

Conjunctive Bayesian networks.
Niko Beerenwinkel, Eriksson N. and Bernd Sturmfels B..
2007. Bernoulli, in press.
[arXiv]

Analysis of epistatic interactions and fitness landscapes using a new geometric approach. Beerenwinkel N., Richard E. Lenski et al.
BMC Evolutionary Biology, 7:60, 2007.
[BMC]

Improved prediction of response to antiretroviral combination therapy using the genetic barrier to drug resistance.
Altmann A., Lengauer T. et al.
Antiviral Therapy, 12(2):169-178, 2007.
PDF

Application of oncogenetic trees mixtures as a biostatistical model of the clonal cytogenetic evolution of meningiomas.
Ketter R., Rahnenführer J. et al.
International Journal of Cancer, 121(7):1473-80, 2007.

Mutagenetic tree Fisher kernel improves prediction of HIV drug resistance from viral genotype.
Sing, T. and Beerenwinkel N.
In: B. Schölkopf, J. Platt, and T. Hoffman, eds. Advances in Neural Information Processing Systems 19, pages 1297-1304, MIT Press, Cambridge, MA, 2007.
[NIPS Proceedings]

A mutagenetic tree hidden Markov model for longitudinal clonal HIV sequence data.
Beerenwinkel N. and Drton M.
Biostatistics, 8(1): 53-71, 2007.
[PubMed]

Epidemiology of primary drug resistance in chronically HIV-infected patients in Nordrhein-Westfalen, Germany, 2001-2005.
Oette M, Häussinger D. et al.
Dtsch Med Wochenschr 132(18): 977-82, 2007.
[PubMed]

Competence Center for Systems Physiology and Metabolic Diseases

High sensitivity detection of plasma proteins by multiple reaction monitoring of N-glycosites;
J. Stahl-Zeng, Domon B. et al.
Molecular and Cellular Proteomics, 2007, in press.

Ensemble modeling for analysis of cell signaling dynamics.
L. Kuepfer, J. Stelling et al.
Nature Biotechnology, 25, Number 9, 2007.

Systematic evaluation of objective functions for predicting intracellular fluxes in Escherichia coli.
R. Schuetz, L. Kuepfer, and U. Sauer.
Molecular Systems Biology, 3:119, 2007.

The VHL tumor suppressor: riding tandem with GSK3beta in primary cilium maintenance.
Thoma CR, Frew IJ, Krek W.
Cell Cycle. 2007: 6(15): 1809-13.

pVHL and GSK3beta are components of a primary cilium-maintenance signalling network.
Thoma CR, Krek W. et al.
Nat Cell Biol. 2007; 9(5):588-95.

Institute of Molecular Systems Biology

An integrated mass spectrometric and computational framework for the analysis of protein interaction networks.
Rinner, O., Aebersold, et al.
R.Nat. Biotechnol., 2007: 25, 345-352.

SuperHirn – a novel tool for high resolution LC-MS based peptide/protein profiling.
Mueller L.N., Müller M. et al.
Submitted (2007).

Efficient classification of complete parameter regions based on semidefinite programming.
Kuepfer L, Sauer U, Parrilo PA.
BMC Bioinformatics. 2007; 15;8(1):12

Getting closer to the whole picture.
U. Sauer, M. Heinemann, N. Zamboni.
Science, 2007: 316: 550-551.

The standard protein mix database: A diverse data set to assist in the production of improved peptide and protein identification software tools.
Klimek J, Martin DB. et al.
J Proteome Res, 2007.

Activator-Mediated Recruitment of the MLL2 Methyltransferase Complex to the beta-Globin Locus.
Demers C, Brand M. et al.
Mol Cell., 2007.

Advances in proteomic workflows for systems biology.
Malmstrom J, Lee H, Aebersold R.
Curr Opin Biotechnol., 2007.

The minimum information about a proteomics experiment (MIAPE).
Taylor CF, Hermjakob H. et al.
Nat Biotechnol., 2007.

High sensitivity detection of plasma proteins by multiple reaction monitoring of N-glycosites.
Stahl-Zeng Domon B., et al.
Mol Cell Proteomics, 2007.

An essential switch in subunit composition of a chromatin remodeling complex during neural development.
Lessard J, Crabtree GR. et al.
Neuron., 2007: 19;55(2): 201-15.

SPARC from olfactory ensheathing cells stimulates Schwann cells to promote neurite outgrowth and enhances spinal cord repair.
Au E, Roskams AJ. et al.
J Neurosci., 2007; 4; 27(27): 7208-21.

Analysis of protein complexes using mass spectrometry.
Gingras AC, Aebersold R., et al.
Nat Rev Mol Cell Biol., 2007; 8(8): 645-654.

Isolation of N-linked glycopeptides from plasma.
Zhou Y, Aebersold R, Zhang H.
Anal Chem. 2007; 79(15): 5826-37.

Quantitative Proteomics Analysis Reveals That Proteins Differentially Expressed in Chronic Pancreatitis Are Also Frequently Involved in Pancreatic Cancer.
Chen R, Bronner MP. et al.
Mol Cell Proteomics., 2007; 6(8):1331-1342.

Center for Cellular Imaging and Nanoanalytics

Function and molecular architecture of the Yersinia injectisome tip complex.
Broz P, Cornelis GR. et al.
Mol Microbiol. 2007; 65(5):1311-20.

Reprint of "Cell-free production of G protein-coupled receptors for functional and structural studies" Klammt C., Bernhard F. et al.
[J. Struct. Biol. 158 (2007) 482-493].
J Struct Biol. 2007; 159(2): 194-205.

3rd International conference on structure, dynamics and function of proteins in biological membranes.
Engel A, Winkler FK.
J Struct Biol. 2007; 159(2):165.

Anakinra in Patients with Treatment-Resistant Adult-Onset Still's Disease: Four Case Reports with Serial Cytokine Measurements and a Review of the Literature.
Kotter I, Kanz L. et al.
Semin Arthritis Rheum. 2007.

The supramolecular assemblies of voltage-dependent anion channels in the native membrane.
Hoogenboom BW, Fotiadis D. et al.
J Mol Biol. 2007; 6; 370(2): 246-55.

YscU recognizes translocators as export substrates of the Yersinia injectisome.
Sorg I, Cornelis GR. et al.
EMBO J. 2007; 20; 26(12):3015-24.

Center for Model Organism Proteomes

The Decapentaplegic morphogen gradient: from pattern formation to growth regulation.
Affolter M, Basler K.
Nat Rev Genet. 2007; 8(9): 663-74.

An optimized transgenesis system for Drosophila using germ-line-specific phiC31 integrases.
Bischof J, Basler K. et al.
Proc Natl Acad Sci U S A. 2007; 27; 104(9):3312-7.

Helping Wingless take flight: how WNT proteins are secreted.
Hausmann G, Banziger C, Basler K.
Nat Rev Mol Cell Biol. 2007; 8(4): 331-6.

Model for the regulation of size in the wing imaginal disc of Drosophila.
Aegerter-Wilmsen T, Aegerter CM, Hafen E, Basler K.
Mech Dev. 2007; 124(4): 318-26.

Center for Systems Biology of Biomembranes

Involvement of a Golgi-resident GPI-anchored protein in maintenance of the Golgi structure.
Li X, Kaloyanova D, Helms JB. et al.
Mol Biol Cell. 2007; 18(4):1261-71.

Editorial overview.
Small PL, van der Goot G.
Curr Opin Microbiol. 2007; 10(1):1-3.

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