

Molecular Genetics in the post-genomic era 2023/24

Mondays 12.15-14.00, Katzir room, Green building 010

Teacher: Martin Kupiec

Pre-requisite: Intro to Genetics 0455-2526 (passed the Exam)

Course's aim: The course's aims are: a) To get to know the new technologies developed and the way questions can be asked once genomic sequences are available. b) To learn how to read scientific papers in a critical way. c) To learn how to present papers and how to discuss them. d) To enjoy Science. **Science is fun!**

Course format: Every week two-three students (depending on the number of participants) will each give (independently) a talk 20 min long (using Powerpoint). The talk will describe one paper from the provided list (in **YELLOW**). Each presenter is expected to read **a few additional papers** to become familiar with the subject presented. The papers are available in pdf format at the course site in Moodle. **All students in the audience must read the paper assigned for each week and are expected to participate in an active discussion following each presentation (ACTIVE participation gets graded).**

Grades will be based on 1) Active participation in discussions (20%); 2) Quality of presentation (80%).

Note: On each subject, **two-three papers** are to be read by all the class. Additional papers on the subject may appear, and I recommend that you read as many as possible (the presenter HAS to read them).

- **16.10.23 Introduction, Orientation: MARTIN**
- What is Systems Biology? How did genome sequencing change the way we ask questions? And MOST IMPORTANTLY: How does this course work?
- **23.10.23 DNA Microarrays, the Revolution MARTIN**

1) Giaever et al. (2002) Functional profiling of the *Saccharomyces cerevisiae* genome. Nature **418**:387-391.

AND

2) Hughes TR, et al. (2000) Functional discovery via a compendium of expression profiles. Cell **102**:109-26.

- **30.10.23 Stress and Drugs:** Things you can do if you have a collection of ALL the possible knockouts in an organism.

3) Gasch AP *et al.* (2000). Genomic expression programs in the response of yeast cells to environmental changes. *Mol Biol Cell*. **11**:4241-4257.

3b. Causton HC *et al.* (2001). Remodeling of yeast genome expression in response to environmental changes. *Mol Biol Cell*. **12**:323-337.

AND

4) Hillenmeyer ME *et al.* (2008) The chemical genomic portrait of yeast: uncovering a phenotype for all genes. *Science* **320**: 362-365

See also:

4b. Perlstein *et al.* (2007) Genetic basis of individual differences in the response to small-molecule drugs in yeast. *Nature Genetics* **39**: 496 - 502

- **6.11.23 Large scale protein interaction studies:** Trying to catch ALL the possible physical interactions among proteins

Yeast two hybrid:

5. Uetz P, *et al.* (2000) A comprehensive analysis of protein-protein interactions in *Saccharomyces cerevisiae*. *Nature* **403**:623-627.

See also

5b. Ito T *et al.* (2001) A comprehensive two-hybrid analysis to explore the yeast protein interactome. *Proc Natl Acad Sci U S A*. **98**:4569-4574.

AND

Complex hunting:

6. Gavin AC, *et al.* (2006) Proteome survey reveals modularity of the yeast cell machinery. *Nature*. **440**:631-636.

6b. Krogan NJ *et al.* (2006) Global landscape of protein complexes in the yeast *Saccharomyces cerevisiae*. *Nature* **440**:637-643.

- **13.11.23 Genetic circuits:** What is the logic of life?

ChIP-exo and ChIP-chip (Location analysis).

7. Harbison *et al.* (2004) Transcriptional regulatory code of a eukaryotic genome. *Nature* **431**: 99-104

7b. Rhee, HS and BF Pugh (2011) Comprehensive genome-wide protein-DNA interactions detected at single-nucleotide resolution. *Cell* **147**: 1408–1419.

AND

Network motifs

8. Milo R, Shen-Orr S, Itzkovitz S, Kashtan N, Chklovskii D, Alon U (2002). Network motifs: simple building blocks of complex networks. *Science* **298**: 824-827.

See also

8b. Alon U (2007) Network motifs: theory and experimental approaches. *Nature Reviews Genetics* **8**: 450-461

- **20.11.23 Genomics and Cancer:** How to use new technologies in cancer detection and treatment

Diagnostics and Prognosis

9. Garber, ME (2001) Diversity of gene expression in adenocarcinoma of the lung. *Proc Natl Acad Sci U S A.* **98**: 13784–13789.

9b. Lu et al. (2006) A gene expression signature predicts survival of patients with stage I non-small cell lung cancer. *PLoS Med.* **3**:e467

AND

Cancer signatures:

10. Bild AH et al. (2006) Oncogenic pathway signatures in human cancers as a guide to targeted therapies. *Nature* **439**:353-357.

See also:

10b. Liu et al. (2006) A genome-wide screen reveals functional gene clusters in the cancer genome and identifies EphA2 as a mitogen in glioblastoma. *Cancer Res.* **66**:10815-10823.

- **27.11.23 Large scale genetic interaction mapping:** Trying to catch ALL the possible genetic interactions among genes

Synthetic lethality:

11. Tong AH et al. Global mapping of the yeast genetic interaction network. *Science* **303**:808-813 (2004).

See also

11b. Costanzo et al. A global genetic interaction network maps a wiring diagram of cellular function. (2016). *Science* **353**:1381.

AND

Synthetic fitness analysis:

12. St. Onge et al. Systematic pathway analysis using high-resolution fitness profiling of combinatorial gene deletions. *Nat Gen* 2007 **39**: 199-206.

12b. Collins et al. (2007) Functional dissection of protein complexes involved in yeast chromosome biology using a genetic interaction map. *Nature* **446**:806-810.

4.12.23 More about the meaning of Genetic interactions:

What is a suppressor?

13. van Leeuwen et al. (2016) Exploring genetic suppression interactions on a global scale. *Science* **354**: 599.

13b Liu, G. et al. Gene Essentiality Is a Quantitative Property Linked to Cellular Evolvability. *Cell* **163**:1388-99.

AND

Using transposons to define functions of genes

14. Michel, AH et al. (2017). Functional mapping of yeast genomes by saturated transposition *Elife*. 6. pii: e23570. doi: 10.7554/eLife.23570.

See also:

14b. Ben-Shitrit, T., Yosef, N., Shemesh, K., Sharan, R., Ruppin, E., and M. Kupiec (2012) Systematic identification of gene annotation errors in the widely used yeast mutation collections. *Nature Methods* **9**: 373-378.

- **11.12.23 Ribosome profiling:** A novel methodology to measure protein levels

15. Ingolia NT, Ghaemmaghami S, Newman JR, Weissman JS. (2009) Genome-Wide Analysis In Vivo of Translation with Nucleotide Resolution Using Ribosome Profiling. *Science* **324**:218-223.

See also:

15b. Mills Ingolia (2016) Dynamic Regulation of a Ribosome Rescue Pathway in Erythroid Cells and Platelets. *Cell Reports* **17**:1–10.

AND

16. Cheng et al. (2018) Pervasive, Coordinated Protein-Level Changes Driven by Transcript Isoform Switching during Meiosis. *Cell* **172**: 910–923.

See also:

16b. Scheckel et al. (2020) Ribosomal profiling during prion disease uncovers progressive translational derangement in glia but not in neurons. *eLife* **9**:e62911. DOI: <https://doi.org/10.7554/eLife.62911>.

16c. Wu et al. (2020) Ribosome Collisions Trigger General Stress Responses to Regulate Cell Fate. *Cell* **182**:404–416.

- **18.12.23** Hi-C: mapping the 3D configuration of the genome:

17. Rao, S.S., Huntley M.H., Durand N.C., Stamenova E.K., Bochkov I.D., Robinson J.T., Sanborn A.L.5, Machol I., Omer A.D., Lander E.S., Aiden E.L (2015) A 3D Map of the Human Genome at Kilobase Resolution Reveals Principles of Chromatin Looping. *Cell* **159**:1665-1680.

See also:

17b. Lieberman-Aiden E, et al. (2009). Comprehensive mapping of long-range interactions reveals folding principles of the human genome. *Science* **326**:289-293.

AND

18. Lupian˜ez et al. (2015) Disruptions of Topological Chromatin Domains Cause Pathogenic Rewiring of Gene-Enhancer Interactions. *Cell* **161**: 1012–1025.

18b. Costantino L, Hsieh TS, Lamothe R, Darzacq X, Koshland D. (2020) Cohesin residency determines chromatin loop patterns. *Elife*. 2020 Nov 10;9:e59889. doi: 10.7554/eLife.59889. PMID: 33170773

See also:

18c. Umut Eser et al. (2017) Form and function of topologically associating genomic domains in budding yeast. *Proc Natl Acad Sci U S A*. **114**:E8801. doi: 10.1073/pnas.1716156114.

OUT OF PROGRAM: A fantastic review by Tom Misteli about EVERYTHING. Misteli, Tom (2020) Genome: Principles of Genome Architecture and Function. *Cell* **183**:28-45. doi: 10.1016/j.cell.2020.09.014.

- **25.12.23** Humanizing yeasts: Using yeast knowledge to study human disease

19. Outerio and Lindquist, 2003. Yeast Cells Provide Insight into Alpha-Synuclein Biology and Pathobiology (Parkinson). *Science* **302**: 1772-1775.

19b. Sun et al. (2016). An extended set of yeast-based functional assays accurately identifies human disease mutations. *Genome Res*. **26**: 670-680.

AND

20. Srivas et al (2016) A Network of Conserved Synthetic Lethal Interactions for Exploration of Precision Cancer Therapy. *Molecular Cell* **63**: 514–525.

See also:

20b. Kramer et al. (2017) Active Interaction Mapping Reveals the Hierarchical Organization of Autophagy. *Molecular Cell* **65**: 1–14.

- **1.1.24** **New Genome wide screens:** in mammalian cells

CRSPR/CAS screens

21. Wang et al. (2014) Genetic Screens in Human Cells Using the CRISPR-Cas9 System. *Science* **343**: 80-84.

See also:

21b. Shalem et al. Genome-Scale CRISPR-Cas9 Knockout Screening in Human Cells (2014). *Science* **343**: 84-87.

AND

22. Harel, I., Benayoun, B.A., Machado, B. , Singh, P.P., Hu, C.K., Pech,C.F., Valenzano, D.R., Zhang, E., Sharp,S.C., Artandi, S.E., and Anne Brunet (2015)] A platform for rapid exploration of aging and diseases in a naturally short-lived vertebrate. *Cell* **160**: 1013–1026.

22b. Olivieri et al. (2020) A Genetic Map of the Response to DNA Damage in Human Cells. *Cell* **182**: 1–16.

- **8.1.24** **Combining heterogeneous data and analyzing epigenetic memory:**

Compendium of heterogeneous data: How to get the most of it by using ALL available information.

23. Tanay, A. et al. (2005) Integrative analysis of genome-wide experiments in the context of a large high-throughput data compendium. *Mol. Sys. Biol.* doi:10.1038/msb4100005

See also:

23b. Lamb, J. et al. The Connectivity Map: Using Gene-Expression Signatures to Connect Small Molecules, Genes, and Disease. *Science* **313**: 1929 (2006)

AND

Epigenetic memory

24. Bheda et al. (2020) Single-Cell Tracing Dissects Regulation of Maintenance and Inheritance of Transcriptional Reinduction Memory. *Molecular Cell* **78**: 1–11.

24b. Brickner et al. (2016) Subnuclear positioning and interchromosomal clustering of the GAL1-10 locus are controlled by separable, interdependent mechanisms. *Mol Biol Cell*. **27**:2980-2993.