Scanning Life's Matrix: Genes, Proteins, and Small Molecules
2002 Holiday Lectures on Science
Chapter List

Lecture One
Reading Genes and Genomes
Eric S. Lander, Ph.D.

Lecture Two
Probing Genes and Genomes
Stuart L. Schreiber, Ph.D.

1. Start of Lecture Two
2. Introduction by HHMI President Dr. Thomas Cech
3. Introductory interview with Dr. Stuart Schreiber
4. If you want to understand life's processes, perturb them
5. Proteins serve as the key mechanical components of life's processes
6. Perturbing life's processes: The genetic approach
7. Perturbing life's processes: The chemical genetic approach
8. What are small molecules?
9. Demonstration: Use of molecular models in chemistry
10. Animation: How does a small molecule modulate a protein?
11. Animation: How does a small molecule activate a protein?
12. Video: Using small molecules to study the cleavage furrow of cell division
13. Video: Furrowstatin can freeze the dynamic process of cell division
14. Video: Furrowstatin perturbation is reversible
15. Animation: Furrowstatin works by binding to nonmuscle myosin II
16. Using the arrested furrow to study cell division
17. Chemical genetics lets us study dynamic processes
18. Q&A: Does furrowstatin inhibit furrow formation or furrow function?
19. Q&A: Are small molecules useful for treating disease?
20. Q&A: How do you figure out which small molecule to use?
21. Q&A: Can you define again what small molecules are?
22. Where do these small molecules come from?
23. Rapamycin, a small molecule from nature
24. Small molecules from laboratory synthesis
25. Target-oriented synthesis and its limitations
26. Introduction to diversity-oriented synthesis (DOS)
27. DOS process 1: Split to many tubes and attach to plastic beads
28. DOS process 2: Perform first reaction and split again
29. DOS process 3: Perform second reaction and further reactions
30. Animation: DOS matrix
31. Recent advances allow one person to make 88,400 new compounds
32. How do we discover which small molecules are useful?
33. Animation: Screening small molecules with a protein
34. Two screening methods for identifying small-molecule function
35. Q&A: Do you accidentally make unexpected molecules?
36. Q&A: Wouldn't sorting through molecules of DOS take a long time?
37. Q&A: Where did you get the idea to use chemistry in biology?
38. Q&A: Wouldn't rapamycin's immunosuppression cause other diseases?
39. Q&A: Could more than one small molecule interact with the protein of interest?
40. Closing remarks by HHMI Vice President Dr. Thomas Cech

Lecture Three
Human Genomics: A New Guide for Medicine
Eric S. Lander, Ph.D.

1. Start of Lecture Three
2. Introduction by HHMI Vice President Dr. Peter Bruns
3. Introductory interview with Dr. Eric Lander
4. Observing what nature has already perturbed
5. How similar are the two copies of your DNA?
6. How similar is DNA from two people?
7. Human origins and why we have little genetic variation
8. Tracing human migrations by looking at genetic variation
9. What differences do genetic variations make?
10. Single nucleotide polymorphism (SNP) can affect Alzheimer disease
11. Other examples of variations affecting diseases
12. Some mutations can protect against AIDS
13. Cataloging all human variations
14. Filling in life's matrix: Genes phenotypes, and SNPs
15. Examples of genetic bases of human phenotypic variation
16. Can "Olympic gold medalist" be a phenotype with a genetic basis?
17. Q&A: Are mutation rates different in different species?
18. Q&A: Has the mutation rate increased with a larger human population?
19. Q&A: Would alcohol digestion problems affect alcoholism?
20. Measuring variations in the levels of all RNA expressions
21. Can differences in leukemias be detected by microscopy?
22. The discovery of two kinds of leukemia: AML and ALL
23. Limitations of conventional methods for diagnosing leukemia
24. How to make a DNA microarray
25. Using microarrays to detect the activities of all the genes in a tumor
26. Using microarrays to differentiate AML and ALL
27. Using computers to sort RNA expression data
28. Discovering a novel type of leukemia
29. Building taxonomies for tumors and other biological functions
30. Q&A: How accessible is microarray technology to doctors?
31. Q&A: Are some mutations inherently bad and selected against?
32. Q&A: Wouldn't DNA variation confound the microarray detector mechanism?
33. Q&A: Are DNA microchips reusable?
34. Closing remarks by HHMI Vice President Dr. Peter Bruns

Lecture Four
Chemical Genomics: New Tools for Medicine
Stuart L. Schreiber, Ph.D.

1. Start of Lecture Four
2. Introduction by Grants Program Director Dr. Dennis Liu
3. Introductory interview with Dr. Stuart Schreiber
4. Chemical genetics used to explore many biological questions
5. Using genomics to investigate glucose sensing and type II diabetes
6. Concept of networks of proteins
7. Two networks are involved in the glucose-sensing system
8. Protein-to-protein interactions in the two networks
9. Network-to-network interactions at the node protein
10. problems in the glucose-sending system can cause type II diabetes
11. Rapamycin can induce type II diabetes
12. Finding new small-molecule probes with a small-molecule microarray
13. Animation: Small-molecule microarray
14. Limitations of the small-molecule microarray
15. Overview of the cell-based screening method
16. Using rapamycin-treated “diabetic” cells to find new small-molecule probes
17. Animation: Cell-based screening finds small-molecule inhibitor of rapamycin (SMIR)
18. Q&A: How do you know SMIR isn’t directly affecting rapamycin?
19. Q&A: Does SMIR counteract the immunosuppressive effect of rapamycin?
20. Q&A: How can you find a common adhesive for all small molecules?
21. Q&A: Could you circumvent genetic defects by using small molecules?
22. Importance of information science and GenBank
23. Overview of the ChamBank project
24. How ChemBank works: Furrowstatin as an example
25. How ChemBank may help explain SMIR’s action
26. Like genomics, ChemBank shows the importance of global measurements
27. Concept of chemical space: Measuring small-molecule diversity
28. How diverse were the molecules synthesized by DOS in Lecture Two?
29. Computation could guide synthesis to evenly distribute molecules in chemical space
30. Could distinct regions of chemical space affect specific biological functions?
31. Concept of biology space: The blood-brain barrier as an example
32. Animation: Future research may link chemical space and biology space
33. Q&A: How long would it take to describe biology space?
34. Q&A: How are scientists sorting out different proteins?
35. Q&A: How widespread is ChemBank right now?
36. Q&A: Does rapamycin affect everyone’s cells in the same manner?
37. Closing remarks by HHMI President Dr. Thomas Cech