Exploring Biodiversity: The Search for New Medicines
2009 Holiday Lectures on Science
Chapter List

Lecture One
From Venoms to Drugs
Baldomero M. Olivera, Ph.D.

1. Start of Lecture 1
2. Welcome by HHMI President Dr. Robert Tjian
3. Profile of Dr. Baldomero Olivera
4. Venomous animals
5. Venom defined
6. Diversity of venomous animals
7. Uses of venom
8. Predatory strategy spectrum
9. Demonstration: Live cone snail
10. Video: *Conus catus* strikes a fish
11. Cone snail venom system
12. Video: Philippines biodiversity
13. Geological reasons for the Philippines biodiversity
14. Phylogenetic tree of cone snails
15. Video: *Conus textile* strikes a snail
16. Video: *Conus imperialis* strikes a worm
17. Hunting specialization and phylogenetic tree
18. Demonstration: *Conus geographus* can kill you
19. Biodiversity of venomous snails
20. Q&A: Does *Conus geographus* make deadlier venom or just more?
21. Q&A: How many people are stung by cone snails?
22. Venoms as research tools
23. Chromatography helps identify venom components
24. Conus geographus has over 200 venom components
25. Venom components that paralyze mice
26. Undergraduate pioneers new assay
27. Behavioral spectrum from intracranial injection
28. Undergraduate discovery leads to new pain medication
29. Animation: Prialt blocks motor synapse in fish
30. Animation: Prialt blocks pain signaling in mice
31. Review of synapse function and Prialt action
32. Prialt-sensitive and Prialt-insensitive channels
33. Calcium channel diversity
34. 22 years from discovery to drug
35. Prialt is one of thousands of candidate drugs
36. Q&A: Would Prialt work with all human calcium channels?
37. Q&A: How many components have been tested and approved as drugs?
38. Closing remarks by HHMI President Dr. Robert Tjian

Lecture Two
Shedding Light on an Invisible World
Bonnie L. Bassler, Ph.D.

1. Start of Lecture 2
2. Welcome by HHMI Vice President Dr. Peter Bruns
3. Profile of Dr. Bonnie Bassler
4. Hidden biodiversity: the microbes
5. Family trees
6. Evolutionary trees of related organisms
7. Three main branches of life
8. Bacteria predominant on Earth
9. Bacterial cell structure
10. Bacteria traits appear simple
11. Bacteria inhabit extreme environments
12. Humans are covered in bacteria
13. You are mostly bacterial
14. Most bacteria are beneficial or neutral
15. Pathogenic bacteria
16. How can tiny bacteria affect humans?
17. A model system to study host-bacterial interaction
18. The bobtail squid and bioluminescent bacteria
19. Video: Bobtail squid swimming and burrowing
20. Bioluminescent bacteria for camouflage
21. Daily cycle of bacterial growth in squid
22. Q&A: What makes bacteria so resilient?
23. Q&A: Can the bacteria live outside the squid?
24. Q&A: How do the bacteria get into the squid?
25. Q&A: How big is the squid's light organ?
26. Q&A: Is the use of antibacterial soap detrimental?
27. Q&A: How do bacteria survive in extreme environments?
28. *Vibrio fischeri* only makes light at high cell density
29. Quorum sensing and autoinducers
30. *Vibrio harveyi* is not symbiotic
31. Demonstration: Glowing bacteria in a flask
32. Quorum sensing activates a large network of genes
33. Pathogens also use quorum sensing
34. QS allow bacteria to act collectively
35. Bacteria receive signals by membrane receptors
36. Receptors as kinases and phosphatases
37. Molecular basis of QS pathway
38. QS turns on or off a gene regulator
39. Animation: The LUX operon controls light production
40. Summary
41. Q&A: Can you add autoinducer and make the bacteria glow?
42. Q&A: Can *Vibrio fischeri* make light outside of the squid?
43. Q&A: What benefit is there to making light in the ocean?
44. Q&A: Can you make a bacteria unable to detect autoinducer?
45. Q&A: Does QS lead to specialization of bacteria?
46. Closing remarks by HHMI Vice President Dr. Peter Bruns

Lecture Three
Biodiversity at a Snail's Pace
Baldomero M. Olivera, Ph.D.

1. Start of Lecture 3
2. Welcome by HHMI Program Director Dr. Dennis Liu
3. Profile of Dr. Baldomero Olivera
4. Why are there so many venom components?
5. Video: *Conus striatus* strikes a fish
6. Venom components disable different targets
7. Each toxin blocks a different synaptic event
8. Animation: Motor cabal toxins block motor neuron synapses
9. Snails discovered multiple drug therapy
10. The motor cabal is like a poison blow-dart
11. Motor cabal takes 20-30 seconds to paralyze
12. Video: A Taser causes rigid paralysis
13. The snail's lightning-strike cabal
14. Animation: Lightning-strike cabal acts like a Taser
15. Video: *Conus bullatus* "lightning strike"
16. Multiple venom components provide speed and safety factor
17. Venom is also used for defense and competition
18. *Conus geographus* stings a man in defense
19. Venom composition and a snail's complex environment
20. Q&A: How is Prialt administered?
21. Q&A: What effects do other conotoxins have on humans?
22. Q&A: What effects do the non-predation peptides have?
23. Fish hunters not limited to hook-and-line strategy
24. Video: *Conus tulipa* hunts fish by net
25. Net hunters use nirvana cabal toxins
26. Nirvana cabal toxins may yield drugs to treat epilepsy
27. 3D structure of toxin peptides
28. Cysteine cross-links form peptide scaffolds
29. Toxins in a superfamily with similar shapes but different functions
30. Hypermutation in non-cysteine peptide sequences
31. Convergent evolution between toxin superfamilies
32. Molecular basis for venom divergence
33. Turrids are the most numerous venomous snails
34. Phylogeny of Turrids
35. Video: Deep nets to harvest Turrids
36. Generous biodiversity in a single net
37. Turrid venom is hugely diverse
38. Q&A: What about toxins that interfere with clotting?
39. Q&A: When do cone snails' prey actually die?
40. Closing by HHMI Program Director Dr. Dennis Liu

Lecture Four
Eavesdropping on Tiny Conspiracies
Bonnie L. Bassler, Ph.D.

1. Start of Lecture 4
2. Welcome by HHMI President Dr. Robert Tjian
3. Profile of Dr. Bonnie Bassler
4. Helpful and harmful bacteria use quorum sensing
5. Notorious pathogenic bacteria
6. Pathogenic strategies
7. Pathogenic strategies under QS control
8. Structures of QS signaling molecules
9. Demonstration: Models of QS molecules
10. Autoinducers allow for intra-species communication
11. The Lux signaling cascade in low cell density
12. Short RNA inhibits the cascade in low cell density
13. Signaling cascade in high cell density
14. Animation: The molecular cascade in bacterial quorum sensing
15. Small RNAs also regulate genes in higher organisms
16. Autoinducer 2 handles inter-species communication
17. Two parallel QS circuits
18. QS1 signals "self," QS2 senses "other"
19. QS1 and QS2 differentially affect gene expression
20. How antibiotics kill bacteria
21. Can QS be used to treat bacterial infections?
22. Q&A: Can pathogens sense when they are too virulent?
23. Q&A: If you inhibit QS, would bacteria grow uncontrollably?
24. Q&A: Would a QS-based treatment require a functioning immune system?
25. Q&A: Do any diseases come from inter-species QS?
26. Developing drugs for blocking either QS1 or QS2
27. Two ways to generate candidate anti-QS drugs
28. Rational design of anti-QS drug candidates
29. Screening massive chemical libraries for drug candidates
30. Video: Screening chemical libraries with robotics
31. Bioluminescence as an assay for QS block
32. Differentiating QS2 versus poison
33. First screen finds potential QS2 blockers
34. Second step screens out toxins
35. Preclinical testing of new drug candidates
36. Looking to nature for other ways to interfere with QS
37. Multicellularity, bacteria, and human cells
38. Inspired by nature and biodiversity
39. Q&A: How do bacteria attack other species's QS molecules?
40. Q&A: What are some of the side effects of antibiotics?
41. Q&A: How many bacteria constitute a quorum?
42. Q&A: Can we remove rather than block the QS signals?
43. Closing remarks by HHMI President Dr. Robert Tjian