Teacher Resource for:
SLC24A5, a Putative Cation Exchanger, Affects Pigmentation in Zebrafish and Humans.

Table of Contents:

GENERAL USE OF *Science* in the Classroom

Student Learning Goals:

"One fundamental goal for K-12 science education is a scientifically literate person who can understand the nature of scientific knowledge."[1]

The U.S. National Academy of Sciences defines science as: "Any new finding requires independent testing before it is accepted as scientific knowledge; a scientist is therefore required to honestly and openly report results so that they can readily be repeated, challenged, and built upon by other scientists. Proceeding in this way over centuries, the community effort that we call science has developed an increasingly accurate understanding of how the world works. To do so, it has had to reject all dogmatic claims based on authority, insisting instead that there be reproducible evidence for any scientific claim."

An important student learning goal, central to any understanding of "the nature of scientific knowledge," is to give each student an appreciation of how science is done.

This includes knowing why:

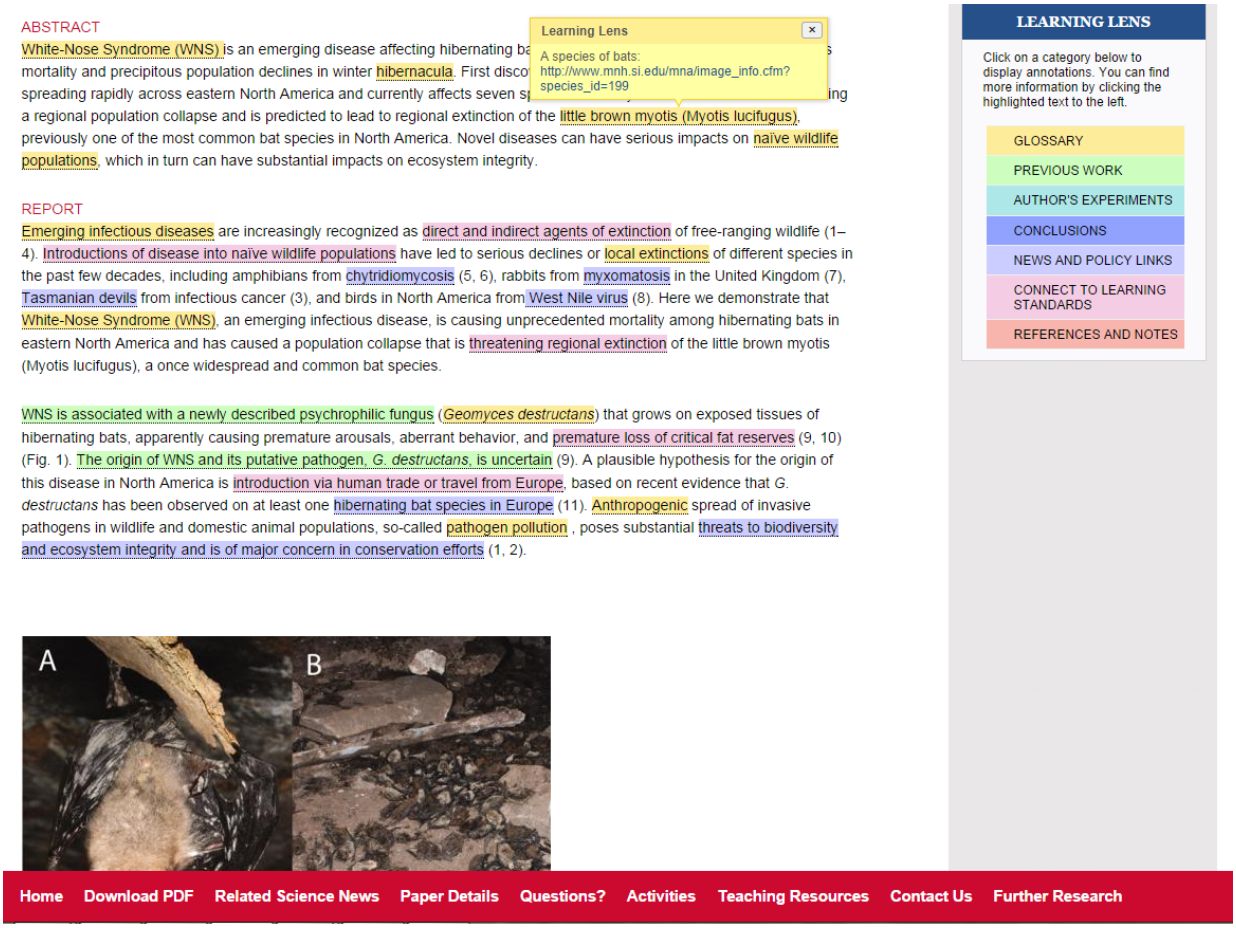
- Scientists must be independent thinkers, who are free to dissent from what the majority believes.
- Science can deal only with issues for which testable evidence can be obtained.
- All scientific understandings are built on previous work
- It is to be expected that one scientist's conclusions will sometimes contradict the conclusions of other scientists.
- Science is a never-ending venture, as the results from one study always lead to more questions to investigate.

[1] *A Framework for K-12 Science Education*, National Research Council, 2012

Using This Resource

Learning Lens:

The Learning Lens tool can be found on the right sidebar of each resource and is the source of annotations. Click on the headings to highlight portions of the text of the corresponding research article. A subsequent click on the highlighted text will produce a text box containing more information about that particular piece of text. Below is an example of the Glossary function of the Learning Lens.



An example of the resource with the Glossary, Previous Work, Author's Experiments, News and Policy Links, and References and Notes tools turned on. The Glossary tool is in use.

Learning Notes:

Learning Notes accompany each figure and are designed to help students deconstruct the methods and data analysis contained within each figure.

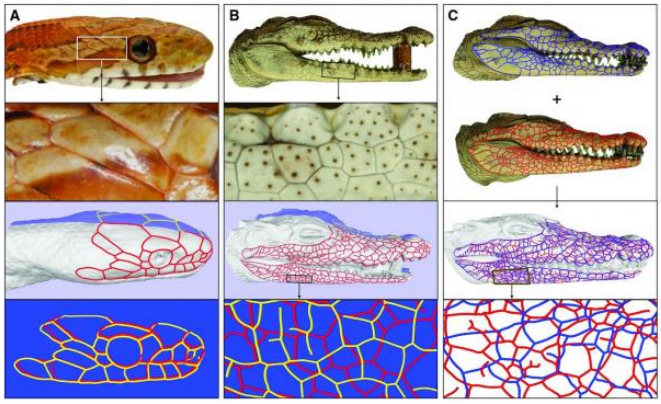


Fig. 1. Spatial distribution of head scales. (A) Head scales in most snakes (here, a corn snake) are polygons (two upper panels) with stereotyped spatial distribution (two lower panels): left (yellow) and right (red) scale edges overlap when reflected across the sagittal plane (blue). (B) Polygonal head scales in crocodiles have a largely random spatial distribution without symmetrical correspondence between left and right. (C) Head scales from different individuals have different distributions of scales' sizes and localizations (blue and red edges from top and bottom crocodiles, respectively).

Method: 3D geometry and color-texture reconstruction | Panel A | Panel B | Panel C

The authors took 120 color pictures of each animal to create detailed, three-dimensional models of reptile heads. Watch this video in which the authors further explain their modeling methods:

http://www.sciencemag.org/content/suppl/2012/11/29/science.1226265.DC1/1...

LEARNING LENS

Click on a category below to display annotations. You can find more information by clicking the highlighted text to the left.

- GLOSSARY
- PREVIOUS WORK
- AUTHOR'S EXPERIMENTS
- CONCLUSIONS
- NEWS AND POLICY LINKS
- CONNECT TO LEARNING STANDARDS
- REFERENCES AND NOTES

References:

The Reference section of each resource is annotated with a short statement about how or why each reference relates to the current research study.

6. L. Lewejohann, B. Zipser, N. Sachser, "Personality" in laboratory mice used for biomedical research: A way of understanding variability? Dev. Psychobiol. 53, 624 (2011).
7. G. Kempermann, The neurogenic reserve hypothesis: What is adult hippocampal neurogenesis good for? Trends Neurosci. 31, 163 (2008).
8. Lewejohann et al., Behavioral phenotyping of a murine model of Alzheimer's disease in a seminaturalistic environment using RFID tracking. Behav. Res. Methods 41, 850 (2009).
9. B. Steineret al., Differential regulation of gliogenesis in the context of adult hippocampal neurogenesis in mice. Glia 46, 41 (2004).
10. Garthe, J. Behr, G. Kempermann, Ad… flexible use of spatially precise learning strategies. PLoS ONE 4, e54…
11. G. Kempermann, New neurons for 'su… 27 (2012).
12. G. Kempermannet al., Why and how … brain plasticity. Front Neurosci 4, 189 (2010).
13. K. Fabelet al., Additive effects of physical exercise and environmental enrichment on adult hippocampal neurogenesis in mice. Front. Neurosci. 3, 50 (2009).
14. Amrein, H. P. Lipp, Adult hippocampal neurogenesis of mammals: Evolution and life history. Biol. Lett. 5, 141 (2009).
15. G. Kempermann, Why new neurons? Possible functions for adult hippocampal neurogenesis. J. Neurosci. 22, 635 (2002).
16. C. Crabbe, D. Wahlsten, B. C. Dudek, Genetics of mouse behavior: Interactions with laboratory environment. Science 284, 1670 (1999).
17. Lewejohann et al., Environmental bias? Effects of housing conditions, laboratory environment and experimenter on behavioral tests. Genes Brain Behav. 5, 64 (2006).
18. D. W. Bailey, How pure are inbred strains of mice? Immunol. Today 3, 210 (1982).
19. R. Lathe, The individuality of mice. Genes Brain Behav. 3, 317 (2004).
20. C. Julieret al., Minisatellite linkage maps in the mouse by cross-hybridization with human probes containing tandem repeats. Proc. Natl. Acad. Sci. U.S.A. 87, 4585 (1990).
21. R. P. Talenset al., Epigenetic variation during the adult lifespan: Cross-sectional and longitudinal data on monozygotic twin pairs. Aging Cell 11, 694 (2012).
22. P. B. Baltes, J. R. Nesselroade, S. W. Cornelius, Multivariate antecedents of structural change in development: A simulation of cumulative environmental patterns. Multivariate Behav. Res. 13, 127 (1978).
23. M.E. Raijmakers, P. C. Molenaar, Modeling developmental transitions in adaptive resonance theory. Dev. Sci. 7, 149 (2004).
24. K. Friston, M. Breakspear, G. Deco, Perception and self-organized instability. Front. Comput. Neurosci. 6, 44 (2012).
25. Van de Weerd et al., Effects of environmental enrichment for mice: Variation in experimental results. J. Appl. Anim. Welf. Sci. 5, 87 (2002).
26. D. P. Wolferet al., Laboratory animal welfare: Cage enrichment and mouse behaviour. Nature 432, 821 (2004).
27. K. Lewin, Dynamic Theory of Personality (McGraw-Hill, New York, 1935).
28. K. L. Jang, R. R. McCrae, A. Angleitner, R. Riemann, W. J. Livesley, Heritability of facet-level traits in a cross-cultural twin

Learning Lens

This paper showed that while both physical activity, like running, and living in an enriched environment can result in the generation of new hippocampal neurons in mice, a combination of the two activities leads to even greater rates of neurogenesis.

LEARNING LENS

Click on a category below to display annotations. You can find more information by clicking the highlighted text to the left.

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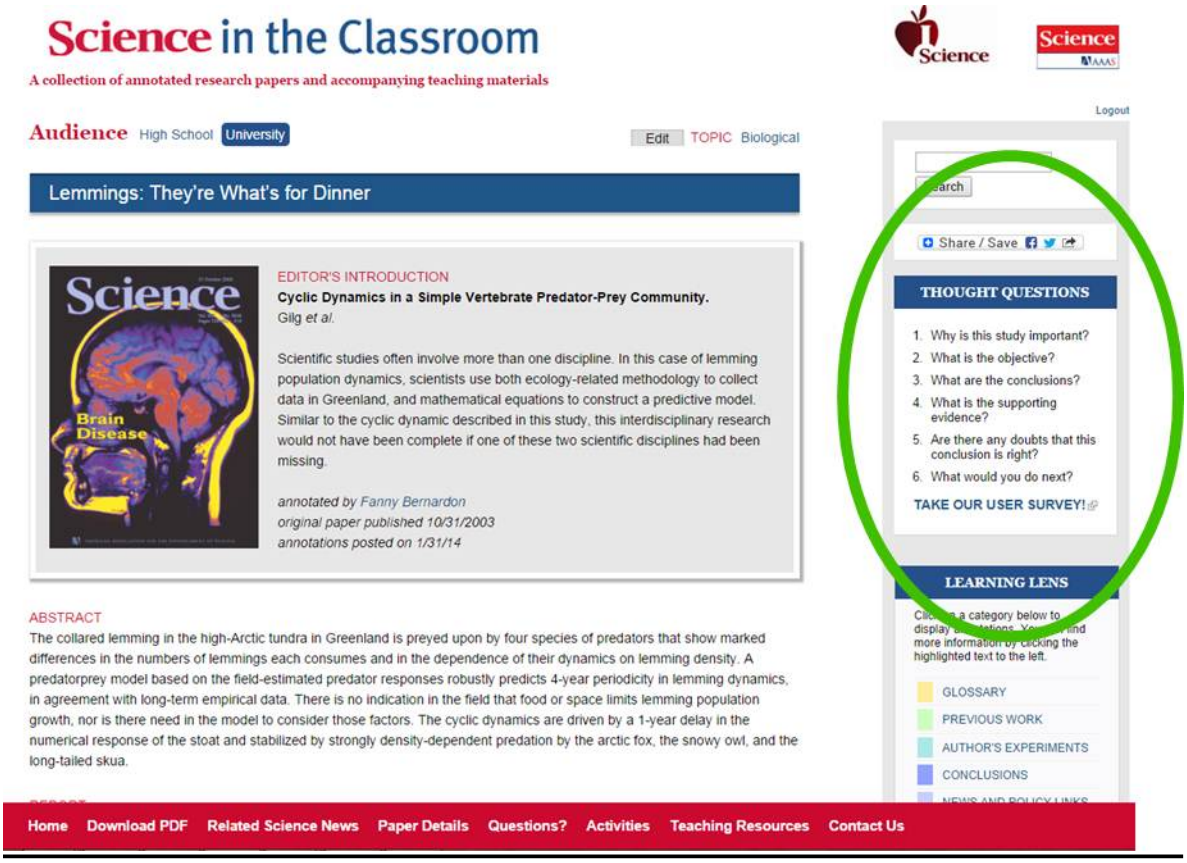
Thought Questions

Thought Questions are located above the Learning Lens in the right sidebar of each resource. These questions were written to be universal and applicable to any primary research paper. Thought questions do not have a single answer, or a correct answer for that matter, and can be used to stimulate discussion among students.



Suggestions for Classroom Use:

In addition to the thought questions discussed above, other resources are provided for use in the classroom. These can be found toward the end of the teacher guides associated with each specific article and include:

1. Discussion questions specific to the article, related to the standards, and/or associated with the figures.
2. Activities tied to the articles.

Some ways to use the Science in the Classroom articles:

1. Assign to student groups to read and discuss during class.
2. Assign small sections of the article to student groups to read and discuss during class, with the expectation that they will present or use jigsaw to teach the entire class what is in their part of the article.
3. Assign to individual students to complete during class or as homework.
4. Assign reading as an extra credit project.

Some ideas for interactive student engagement after reading the article:

1. Students write answers to discussion questions (for example, those linked to the standards or those linked to the diagrams).
2. Go over the abstract, as well as information about the purpose and structure of an abstract, and have students write their own abstracts for the articles in language that could be understood by their peers.
3. Have students edit the article, or parts of the article, to a simpler reading level.
4. Have students, alone or in small groups, use the annotated list of references to explain how the scientists who wrote this article built on the published work of at least one independent group of scientists in making their discoveries. In the process, did they produce data that supports the findings of the earlier publication that they have cited in the text? In what way does this article support the statement that scientific knowledge is built up as a “community effort”?
5. Use the article and discussion questions linked to the standards and the diagrams for a teacher-led classroom discussion. The discussion can focus on the nature of science and scientific research, as well as on the science in the article itself.
6. Have students give a classroom presentation about the article, parts of the article, or their answers to discussion questions.

ARTICLE-SPECIFIC MATERIALS

Content Overview of Research Article

Connections to the nature of science

This article illustrates how scientists can use human cell lines to study important molecular pathways. Cell culture works very well for studying the basics of proteins and genes. They're also small and inexpensive, and they divide rapidly, helping generate data quickly. But when scientists want to investigate cancer at a tissue or organism level, they need to use a more complex, expensive, and time-consuming model, such as the mouse.

The importance of this scientific research

Mutations in *p53* are very common in cancer cells. This paper was one of several in the 1980s and 1990s that illustrated its crucial role and explained why the loss of *p53* is so problematic for the cell. It also contributed to our understanding of the cell cycle and its checkpoints.

The actual science involved

The authors used several cell lines (both normal and cancerous) to investigate the checkpoint functions of *p53* and *p21*. They used homologous recombination to disrupt these genes and observe how the altered cells respond to DNA damage.

Topics covered

- Cell cycle regulation and cell division
- DNA damage
- Cancer cells

Why this research is important

Prior to this paper, p53 and p21 were known to function at the G_1-S checkpoint, but their roles at the G_2-M checkpoint, if any, were unclear. This paper showed that these proteins are required for sustaining arrest at the G_2-M checkpoint following DNA damage.

Methods used in the research

- Fluorescence microscopy
- Flow cytometry
- Western blotting
- Southern blotting
- γ irradiation

Conclusions

The p53 and p21 proteins play a crucial role at the G_2-M checkpoint of the cell cycle, preventing cells with DNA damage from entering mitosis.

Areas of further study

p53 has been the subject of a great deal of research for decades, and we now know that it plays a critical role in regulating the cell cycle and is often mutated in tumor cells. Because many "broad spectrum" chemotherapeutic drugs either induce DNA damage in cancer cell or disrupt

their cell cycle, understanding how *p53* and other genes regulate these pathways gives us a better chance of developing successful, targeted treatments. Efforts to specifically target mutant *p53* in cancer treatment are ongoing.

Discussion Questions

1. Figure 5, panels A and B show cells with defective p21 going through mitosis in the absence (A) or presence (B) of DNA damage. What would you expect these two panels to look like if normal cells were used instead?

   A: *Panel A should look roughly the same, because the absence of p21 doesn't have much of an effect on nondamaged cells. However, in panel B, a normal cell subjected to radiation should arrest prior to entering mitosis. Therefore, if you observed the normal cell over the same time period, it would not begin to divide until after the cell recovered.*

2. Vincristine is a drug used in chemotherapy to treat cancer. It functions similarly to nocodazole. Why do you think this could be an effective cancer treatment? Check the annotations to remind yourself what nocodazole does.

   A: *Vincristine and nocodazole prevent microtubules from growing, thereby keeping a cell from dividing. Prolonged exposure to these drugs will kill cells. Because only dividing cells are affected by these drugs, they preferentially kill cancer cells, whereas normal cells are relatively unharmed.*

3. Many of our genes have important functions in different signaling pathways. In the cell cycle, for example, some genes drive the cell cycle forward (called oncogenes), whereas others slow it down (called tumor suppressors). The two forces keep each other in check.
   Now, imagine a cell divides in the presence of DNA damage and the chromosomes don't separate properly, leaving the daughter cells with unequal amounts of DNA. Why is it problematic for a daughter cell to receive extra copies (or no copies) of a single chromosome?

   A: *If an extra copy of an oncogene or a missing copy of a tumor suppressor gene upsets that balance, the daughter cell might divide inappropriately, leading to cancer.*

4. *p53* is sometimes called "the guardian of the genome," and many cancer cells harbor mutations in this gene. Why do you think this is the case? You can also use this interactive to help you answer this question: http://www.hhmi.org/biointeractive/eukaryotic-cell-cycle-and-cancer (Click on "Cell Cycle Regulators" in the center and then click on the stop sign at the G1 and G2 checkpoint.)

   A: *The p53 protein (encoded by the p53 gene) plays a critical role at cell cycle checkpoints, as demonstrated in this paper. We know a little more about how p53 functions today. The protein is activated by DNA damage, and binds to the promoters of specific target genes. These target genes are often involved in regulating cell cycle progression or DNA repair. When p53 binds to the promoters of these genes, their expression increases, allowing the cell to pause and fix the damage. If the damage is too overwhelming, p53 can also induce programmed cell death (apoptosis). This is a last resort for the cell because it will die, but it*

prevents the development of cancer, which could potentially kill the organism. So, in many ways, p53 protects the genome and ensures the cell recovers from damage. When it is mutated or deleted, the checkpoints that prevent a cell from becoming cancerous are no longer in place.

Multimedia Resources from HHMI's BioInteractive (www.BioInteractive.org)

Lectures

Cancer as a Genetic Disease, Charles Sawyers, MD, 2013 Holiday Lectures on Science (http://www.hhmi.org/biointeractive/cancer-genetic-disease). Understanding that cancer is caused by mutations in genes that regulate cell proliferation has led to the development of targeted drug therapies.

From Cancer Genomics to Cancer Drugs, Charles Sawyers, MD, 2013 Holiday Lectures on Science (http://www.hhmi.org/biointeractive/cancer-genomics-cancer-drugs). Genetic data from a large number of tumor types reveal commonly mutated genes and uncover connections between different types of cancer.

Research Mechanics: Putting the Brakes on Cancer, Bert Vogelstein, MD, 2003 Holiday Lectures on Science (www.hhmi.org/biointeractive/research-mechanics-putting-brakes-cancer). Although there are numerous kinds of cancer, all stem from alterations that allow cell division to outstrip cell demise.

Chaos to Cure: Bringing Basic Research to Patients, Bert Vogelstein, MD, 2003 Holiday Lectures on Science (http://www.hhmi.org/biointeractive/chaos-cure-bringing-basic-research-patients). The identification of hundreds of genes involved in the formation and spread of cancer is leading to promising new methods for diagnosis, prevention, and treatment.

Videos

Cancer as a Genetic Disease: Video Highlights, Charles Sawyers, MD, 2013 Holiday Lectures on Science (http://www.hhmi.org/biointeractive/cancer-genetic-disease-video-highlights).

Animations

p53 (http://www.hhmi.org/biointeractive/p53). A 3D animation showing the molecule p53 binds to DNA and initiates the transcription of mRNA.

Damage to DNA Leads to Mutation (http://www.hhmi.org/biointeractive/damage-dna-leads-mutation). Reactive molecules, such as free radicals, and solar ultraviolet radiation can lead to mutations in DNA. Most mutations are corrected, but in rare cases mutations can accumulate and cause diseases such as cancer.

Mismatch Repair (http://www.hhmi.org/biointeractive/mismatch-repair). During DNA replication mistakes can occur as DNA polymerase copies the two strands. The wrong nucleotide can be incorporated into one of the strands causing a mismatch. Fortunately cells have repair mechanisms.

Cancer and Cell Fate in the Intestinal Epithelium (http://www.hhmi.org/biointeractive/cancer-and-cell-fate-intestinal-epithelium). Disrupting the normal processes of differentiation and maturation of the intestinal epithelial cells can lead to cancer.

Classroom Activities

Cancer Discovery Activities (http://www.hhmi.org/biointeractive/cancer-discovery-activities). In Activity 1, students identify the locations on chromosomes of genes involved in cancer, using a set of 139 "Cancer Gene Cards" and associated posters. In Activity 2, students explore the genetic basis of cancer by examining cards that list genetic mutations found in the DNA of actual cancer patients.

Interactive Tutorials ("Click and Learns")

Cell Cycle and Cancer (http://www.hhmi.org/biointeractive/eukaryotic-cell-cycle-and-cancer). Explore the phases, checkpoints, and protein regulators of the cell cycle and find out how mutated versions of these proteins can lead to the development of cancer.

Teacher Guides

Gene Expression (http://www.hhmi.org/biointeractive/teacher-guide-gene-expression). This curriculum guide assists in filtering through the available resources from BioInteractive and HHMI on topics related to gene expression, including RNA structure and function, transcription, RNA processing, translation, and post-translational events.

DNA (http://www.hhmi.org/biointeractive/teacher-guide-dna). This curriculum guide assists in filtering through the available resources from BioInteractive and HHMI on topics related to DNA, including DNA structure and function, DNA replication, damage to DNA, and eukaryotic chromosomal structure.

Image of the Week

Cancer Evolution (https://www.hhmi.org/biointeractive/cancer-evolution). A computer simulation of cancer growth, in which cell colors correspond to different mutations, reveals that a tumor mass is a mixture of genetically similar cells.

Synchronized Division (http://www.hhmi.org/biointeractive/synchronized-division). The early embryonic cells of the sand dollar are caught in the act of synchronized cell division.

Collections

Biology of Cells (http://www.hhmi.org/biointeractive/biology-cells). Resources for teaching cell biology, including short films, animations, Click & Learn interactives, and posters.

DNA (http://www.hhmi.org/biointeractive/dna-collection). A variety of engaging animations, lecture clips, virtual labs, and other classroom resources teach key concepts related to DNA's structure and function.

Genetics (http://www.hhmi.org/biointeractive/genetics). Resources for teaching genetics, including short films, animations, Click & Learn interactives, and classroom activities.

Chemistry of Life http://www.hhmi.org/biointeractive/chemistry-life Resources related to chemistry, biochemistry, and biological macromolecules such as DNA, RNA, proteins, carbohydrates, and lipids.