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Lesson

Metastatic Mastery: A Case and Game-Based Approach to Learning About Cancer Mechanisms

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Abstract

Mechanisms that contribute to the development of cancer are numerous and complicated, though most can be traced to a set of mutations in cell cycle regulatory genes that throw the process of cell division off balance. Communication of these complex mechanisms in an engaging way often presents a challenge in a large introductory course with students from varied backgrounds and at distinct knowledge levels. We present a mixed active learning approach to facilitate student understanding of how mutation-mediated disruptions in cell cycle regulation can lead to the development of lung cancer. This lesson includes a case-based scenario, a card game about cell cycle checkpoints, mutations, and disrupted mechanisms in cancer, a problem-solving worksheet about mutations, and several electronic audience response questions interspersed throughout to monitor student progress. Through assessment of student content knowledge and perceptions, we have found this lesson to be an effective, engaging, and enjoyable way for students to learn about the molecular mechanisms underlying cancer development.

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Additional author notes: †Created the card designs for the Metastatic Mastery game. ††Played a leadership role in game design and provided the name for the cancer card game.

Learning Goals

Students will:

- understand the mechanisms that lead to the development of cancer.
- recognize the impact of carcinogens in cigarette smoke on human health.
- be able to relate/make connections between cellular mechanisms and their daily life.

Learning Objectives

Students will be able to:

- to identify types of point mutations.
- explain the effects of carcinogens on DNA.
- distinguish between oncogenes and tumor-suppressor genes.
- demonstrate how a mutation in the TP53 gene affects p53 protein function, leading to the development of lung cancer.
- explain how cell cycle checkpoints are regulated.
- identify mechanisms that lead to the development of lung cancer.

INTRODUCTION

In our bodies, there is a large turnover in cells as they perform different functions, grow and divide. At the same time, we interact with the environment which affects our cells. Sometimes, the effect is harmful to cells and can lead to the development of diseases such as cancer. Medical cases provide an engaging way for students to relate complex concepts (1). Cancer develops when mutations in genes that regulate cell division accumulate over time. Deleterious mutations in these genes lead to production of dysfunctional proteins that are unable to regulate the cell cycle (2). This lesson helps students understand connections between these disruptions in the cell cycle and the development of cancer by interacting with a case study about an individual who has Stage III squamous cell carcinoma with an emphasis on mutation in the tumor suppressor gene TP53 (3,4).

The lesson presented here is unique in that it combines multiple evidence-based approaches including a case-based scenario, a card game, a problem-based worksheet about mutations, and several real-time classroom-response questions interspersed throughout as a mechanism to gauge student progress. At the core of the lesson is a card game about cell cycle checkpoints, mutations, and mechanisms that are disrupted in cancer, which reinforces these concepts in an engaging way. This provides a holistic approach to student learning as they engage with peers in collaborative teams.

Intended Audience

This lesson is designed for a large-enrollment introductory biology class for science majors. In the sequence of the course, this lesson is taught during the genetics unit after students learn about DNA replication, gene expression, and the regulation of gene expression. Although this lesson is designed for an introductory course, it could also be used in an upper division cancer biology course.

Required Learning Time

This lesson is designed to be covered in a 75-minute class session.

Prerequisite Student Knowledge

To fully engage with the material covered during this class, students should be able to describe the steps in the processes of transcription and translation. They should be able to illustrate what occurs in each cell cycle phase. They should be able to identify different types of point mutations within DNA (missense, nonsense, silent, frameshift). Completing the pre-class assignment (Supporting File S1. Metastatic Mastery – Pre-class Assignment) and reading the relevant chapter on the cell cycle and its regulation, from a standard introductory biology textbook is recommended preparation for the lesson (for example, pages 257-260, 398-399, 349 in reference 5). According to student survey responses, they find the pre-class assignment helpful in preparation for the lesson.

Prerequisite Teacher Knowledge

Instructors should possess knowledge about the cell cycle, the role of oncogenes and tumor-suppressor genes in regulating the cell cycle, the functions of p53 and its role in the development of cancer, as well as general knowledge about cancer progression and treatment options. Resources that can help are cited in this article, listed in the references section and in the presenter notes section of the in-class presentation (Supporting File S6. Metastatic Mastery – In-class Presentation), and in Table 1.

SCIENTIFIC TEACHING THEMES

Active Learning

This lesson represents a mixed active learning approach to facilitating student learning in the classroom that includes the use of multiple evidence-based strategies for a single lesson. This approach enables the use of a combination of active learning techniques to facilitate student learning based on best fit to address the learning objectives for the lesson. Mixed active learning approaches provide similar results as those obtained using a single active learning approach with respect to student performance and satisfaction (6). The use of multiple strategies to engage students can enhance the retention of complex concepts.

Our lesson includes the following active learning strategies (7):

- Electronic audience response questions. Questions that gauge student comprehension are interspersed throughout the lesson. These questions can help inform your approach to communicating the concepts.
- Problem-based learning within the context of a case. Our lesson follows the story of Gene who develops lung cancer as a consequence of chronic exposure to carcinogens in cigarette smoke. Students engage in problem-based learning activities within the framework of this story. Using the context of a case fosters student interest and helps students to make connections to their lived experiences.
- Game-based learning. Games are an engaging way to help students practice using scientific terms, make connections between concepts, and increase social interaction with peers (8). Our lesson integrates a card game (Figure 1) within the framework of a case in which students engage in problem solving with their peers.
- Collaborative learning. During the entirety of the lesson, students interact and work with other students in teams. This provides them an opportunity to gain diverse perspectives during learning activity discussions, share knowledge, and form a small community in a large-enrollment course.

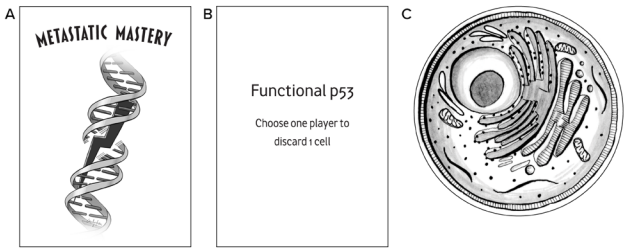

Figure 1. Card designs from the game Metastatic Mastery. The front **(A)** and back **(B)** of an Action card and **(C)** a Cell card are shown.

Assessment

When this lesson was taught by the corresponding author over multiple semesters, students were given a pre- and post-test via a classroom response system called Top Hat that contained 6 multiple-choice questions (Supporting File S7. Metastatic Mastery – Pre-Post Assessment). These questions were designed based on the learning objectives for the lesson. Students were given the pre-test before they received any instruction about topics related to the lesson. The students were given a post-test containing the same questions at the end of the class when the lesson was taught. In addition, throughout the lesson, students answered clicker questions to reinforce background knowledge, quizzed each other during the game using pre-designed Game Questions (Supporting File S4. Metastatic Mastery – Game Questions) as a self-evaluation tool, and worked through the p53 Mutation worksheet (Supporting File S5. Metastatic Mastery – p53 Mutation Worksheet) to apply their knowledge of gene expression to transcribe and translate a portion of the wild-type and mutated sequence of the TP53 gene. They then compared the resulting amino acid sequences to identify the mutation in p53 that the individual in the case study might have. All of these questions and activities helped assess their background knowledge, engage with new information that they were learning, and provided opportunities to apply that knowledge to solve problems. At the end of the class during which this lesson was taught, students were invited to complete a perceptions survey (Supporting File S8. Metastatic Mastery – Student Perceptions Survey) to share their reflections about the lesson. The survey contained Likert scale and open-ended questions to assess the effectiveness of the card game and the lesson as a whole.

Inclusive Teaching

- Students come in with different levels of background knowledge and motivations to learn. Working in teams provides them an opportunity to share their experiences and knowledge with peers.
- The mixed active learning approach used in this lesson provides diverse forms of engagement for students.
- The case narrative can facilitate connections and discussions among students who have known someone affected by cancer.
- The card game Metastatic Mastery provides an opportunity for students to engage in a way that minimizes student discomfort.
- The use of non-gendered pronouns for the central character in the case study facilitates inclusive teaching in biology.

LESSON PLAN

Pre-Class Assessment (Pre-Test)

The pre-test questions (Supporting File S7. Metastatic Mastery – Pre-Post Assessment) are asked before the students are taught the lesson. We asked the questions in class through an electronic real-time classroom response system during the week before the lesson was taught and before the pre-class assignment (Supporting File S1. Metastatic Mastery – Pre-class Assignment) was made available to students. A timeline for the lesson can be found in Table 2.

Pre-Class Student Preparation

The pre-class assignment (Supporting File S1. Metastatic Mastery – Pre-class Assignment) can be made available to students the week before teaching the lesson for them to become familiar with some terminology and basic concepts so they are prepared to engage in class. Students read the relevant information from the textbook and complete the pre-class assignment before coming to class.

Pre-Class Instructor Preparation

Student teams

Students were randomly assigned teams at the beginning of the semester. Each team consisted of five students that worked together on collaborative activities throughout the semester.

Preparation of materials

Materials to print before class for each team include: one Action Card set (Supporting File S2. Metastatic Mastery – Game Action Cards), one Cell Card set (Supporting File S3. Metastatic Mastery – Game Cell Cards), one copy of the Game Questions document (Supporting File S4. Metastatic Mastery – Game Questions), and one p53 Mutation Worksheet (Supporting File S5. Metastatic Mastery – p53 Mutation Worksheet). The first time we implemented this lesson (50 teams), Action Cards were printed and cut by the printing service on our university campus, while Cell Cards were printed by the same service, but since they did not have a circular cutter, the cutting was done manually by the instructional team [instructor and 10 undergraduate Learning Assistants (LAs)]. One set each of the Cell Cards and Action Cards were placed in a Ziploc bag for each team. Assembling the card packets is a one-time investment, as they can be reused in subsequent semesters.

In-Class Facilitation and Activities

At the beginning of class, students are introduced to the case of Gene, who has recently been diagnosed with smoking-related non-small cell lung cancer. The progression of the case study leads to students discovering the cellular pathways and molecular mechanisms that may be affected in this type of cancer. The presentation slides introduce the case, walk students through general information about lung cancer, and then lead to more specific details about the cell cycle, the TP53 gene, and the role of p53 protein in the cell cycle. There are two key points during the presentation where students are given time to either play the Metastatic Mastery card game with their team (Supporting File S2. Metastatic Mastery – Game Action Cards, Supporting File S3. Metastatic Mastery – Game Cell Cards, Supporting File S4. Metastatic Mastery – Game Questions) or work through the p53 Mutation Worksheet (Supporting File S5. Metastatic Mastery – p53 Mutation Worksheet), either individually or in teams depending on their level of familiarity with transcribing and translating given DNA sequences. Slide 15 in the PowerPoint presentation (Supporting File S6. Metastatic Mastery – In-class Presentation) contains instructions on how to play the game that the instructor can walk students through. Materials for the game are handed out by LAs immediately before the in-class time for the game or the worksheet begins. Groups consist of 4-5 students and a single LA facilitates learning and play for 3-4 groups. Teams are asked to return materials to LAs immediately after each activity ends. The game is rooted in principles of game-based learning (8).

Over several semesters of teaching this lesson, some additional fun strategy twists were added based on suggestions from students with a competitive spirit. Slide 19 provides a lead-in to the p53 Mutation Worksheet (formative assessment). The students' task is to transcribe and translate a region of the TP53 gene sequence that contains a missense mutation (G→A; Arg248→Gln248) commonly associated with non-small cell lung cancer. Teams are given sequences of wild-type and mutated TP53 gene segments to derive the respective amino acid sequences, compare them, and identify the mutation. Immediate feedback, an element of team-based learning (9) is provided when the instructor walks students through the key on Slide 20. Slide 21 provides students with more information on how the mutation affects the DNA-binding ability of p53. Since p53 is a transcription factor, this ability is crucial to initiate transcription of its target genes (10,11,12). Slide 22 makes connections back to Gene's case, summarizing the impact of the TP53 gene mutation and how this combined with additional similar mutations in other cancer-causing genes might have led to the development of lung cancer in Gene. The remaining slides provide information on lung cancer progression and a few possible strategies that can be used in the treatment of lung cancer.

Post-Class Assessment of Student Learning (Post-Test)

The post-test questions are asked in class at the end of the lesson through an online real-time classroom response system (e.g., TopHat) (Supporting File S7. Metastatic Mastery – Pre-Post Assessment). The same questions can also be asked on the subsequent exam (summative assessment) that covers this topic to assess retention of the concepts.

TEACHING DISCUSSION

This lesson is designed to primarily achieve the foundational levels of Bloom's taxonomy: Remember, Understand, and Apply (13). The lesson helps students begin to understand the different mechanisms which lead to cancer development. More importantly, it provides a comprehensive look at how environmental factors (cigarette smoke) can lead to changes in the genetic information inside cells, thereby disrupting the function of specific molecules ultimately resulting in disease through physiological changes. The mixed active learning approach used to implement evidence-based teaching strategies to enhance student learning has been very well received by students. The case study format helps students relate the content to something that they might experience in their lives. It also addresses some common misconceptions that students might have, for example, that one mutation or a mutation in one gene is always sufficient for cancer to develop. All the surveys and activities that are part of this lesson helped assess their background knowledge, engage with new information that they were learning, and provided opportunities to apply that knowledge to solve problems.

We first developed and implemented this lesson in an introductory biology course of about 220 students in the Fall of 2016. During the pilot semester, we observed student interactions as they played the Metastatic Mastery card game. We noticed that the students were more focused on the game mechanics than engaging in a discussion about the terms on the action cards that related to the topic of cell cycle and cancer. To address this issue, we developed a list of questions to go along with the game (Supporting File S4. Metastatic Mastery – Game Questions) so that as the students played the game in their teams, they would quiz each other about the terms on the cards before they could perform the action listed on the card. We provided the answer key as well, to provide immediate feedback and a low-stakes environment where students could check their answers without the pressure of being graded. This worked really well in enhancing peer learning and student discussions about relevant concepts. Interestingly, some teams added a competitive element to the game in that the player who got a question about the term on their card could avoid a non-beneficial action if they answered the question correctly or were prevented from carrying out a beneficial action if they answered incorrectly. We added this as an optional strategy in subsequent semesters.

Assessment of Student Learning

Content knowledge

Since piloting the lesson in Fall 2016, we have implemented this lesson over several semesters and consistently see improvements in the percentage of students answering correctly on most of the assessment questions after the lesson has been implemented. The Pre-Post assessment questions (Supporting File S7. Metastatic Mastery – Pre-Post Assessment) are tied to the learning objectives listed for the lesson. On an average, students perform much better on the post-assessment immediately after engaging in the lesson, and these learning gains are maintained when students are asked the same questions on the exam at the end of the module during which the lesson is taught, indicating knowledge retention. Specifically, the largest learning gains for students immediately after completing the lesson are seen on the questions that ask students to compare the impact of point mutations caused by exposure to benzopyrene, identify the type and impact of FAS receptor mutation, and identify the role of angiogenesis during metastasis. Interestingly, students do not show immediate learning gains on the questions asking them to identify the reason for p53 being a tumor suppressor protein after the lesson, but a higher percentage answered the question correctly on the exam that followed, suggesting that reviewing the information might facilitate better understanding of the role p53 plays during the cell cycle. Students are also able to develop a better understanding of p53's role as a transcription factor immediately after engaging in the lesson, although this knowledge isn't retained as well on the exam. Students completed the Pre-test earlier in the semester before they learned any genetics-related concepts. They completed the post-test after engaging with the lesson. The questions in the pre-post tests were also asked on the subsequent exam to assess learning retention.

Student perceptions/feedback

We have also collected student perceptions data about their experiences during the implementation of the lesson. A majority of students who engaged in the lesson during class completed the pre-class assignment. Also, most of the students strongly agreed or agreed that the pre-class assignment helped them prepare for the class session, that they enjoyed playing the Metastatic Mastery card game, that it helped them learn about cell cycle regulation and cancer mechanisms, and that the game should be implemented in future semesters of the course (questions in Supporting File S8. Metastatic Mastery – Student Perceptions Survey).

Qualitative comments from students were about different components of the lesson that reflect how these components worked together to enhance the learning experience. They liked having the pre-class assignment as a scaffold to prepare for in-class engagement. The mixed active learning approach allowed them to learn information and then apply it while playing the game, completing the worksheet, or answering electronic response questions. There was also a bit of self-assessment involved as the students could gauge their own progress by answering the pre-post assessment questions. Most students thought playing the game was a fun experience. Some students commented on peer learning during gameplay stating that team members were excited to explain answers to each other thereby contributing to shared understanding among team members. This led to students learning from each other. Some students enjoyed playing the game because it made discussion of a difficult topic like cancer more accessible. Others liked the real-life application aspect of the case study.

Modifications for Scale and Course Level

This lesson can easily be scaled for smaller class sizes. Upper-level cancer biology and genetics courses that contain entire modules with a focus on gene regulation and/or cancer genetics can expand this lesson to include additional smoking-related oncogenic or tumor-suppressor mutations implicated in lung or other types of cancer. Some examples can include EGFR, VEGF/VEGFR and KRAS mutations (14). There can also be increased focus on the types of treatment options available, especially novel treatments like immunotherapy or genetic therapies (15, 16). This lesson can also be taught

over two 50-minute class periods by presenting Slides 1-15 in the presentation and ending with students engaging in the card game. Slides 16-27 can be presented in the second class along with students engaging in the p53 mutation worksheet. Instructors that teach flipped courses can provide the mini-lecture part of the presentation as videos posted on the learning management system and can spend the in-person class time on solving the case through engaging in the game and mutation worksheets (more gene mutations can be added for practice). Some of the time can be devoted to minute-papers, Q&As, or team trivia to provide students an opportunity to ask questions. Lastly, this lesson can be adapted to the online environment by recording a video of the presentation interspersed with interactive questions added via tools like Panopto. Students can be directed to complete the p53 worksheet through an online assignment. The corresponding author has taught the lesson in this format when all courses were transitioned online due to the COVID-19 pandemic. Unfortunately, we have yet to work on developing an online version of the card game. Instructors can use online trivia platforms like Kahoot! to engage students in a trivia game based on the content in the Game questions document (Supporting File S4. Metastatic Mastery – Game Questions) instead.

We have thoroughly enjoyed developing and implementing this cancer lesson in our large-enrollment introductory biology course and hope that you enjoy integrating it into your courses too!

SUPPORTING MATERIALS

- Supporting File S1. Metastatic Mastery – Pre-class Assignment. This assignment is meant for students to familiarize themselves with the cell cycle, the different cell cycle checkpoints, and names of some of the proteins involved in regulating the cell cycle.
- Supporting File S2. Metastatic Mastery – Game Action Cards. This file contains a set of 49 Action cards plus two cards that have the name of the game and credits respectively. We recommend printing all the cards on cardstock paper (matte or glossy) so the sets can be used again in future semesters. This file should be printed front-to-back followed by cutting around the edge of each card to obtain 49 rectangular action cards with a design on the back.
- Supporting File S3. Metastatic Mastery – Game Cell Cards. This file contains one page with 10 cell shapes. Five copies of this page make one set of 50 cells. We recommend printing all the cards on cardstock paper (matte or glossy) so the sets can be used again in future semesters. The number of sets printed depends on the number of teams. For example, if there are 10 teams in class, the instructor prints 10 card sets (1 game set includes 49 Action cards and 50 cell cards). The instructor should print and cut all the cards ahead of time and distribute them in quart-sized Ziploc bags such that each team gets one game set. Both a Word document and a PDF are included.
- Supporting File S4. Metastatic Mastery – Game Questions. This document contains questions to be used by students while playing the Metastatic Mastery game.
- Supporting File S5. Metastatic Mastery – p53 Mutation Worksheet. The worksheet contains the solutions that the instructors can delete before printing and handing out to students or posting on the learning management system for students to complete.
- Supporting File S6. Metastatic Mastery – In-class Presentation. This PowerPoint file contains lecture slides that also contain instructions to the card game and solution to the p53 Mutation Worksheet that can be presented to students for immediate feedback.
- Supporting File S7. Metastatic Mastery – Pre-Post Assessment. This is a set of six multiple-choice questions that can be used by instructors to gather data on student learning before and after engaging in the lesson.
- Supporting File S8. Metastatic Mastery – Student Perceptions Survey. These questions can be used by instructors to gather data on student engagement with and enjoyment of the lesson.

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Table 1. Resources that instructors can use to gain conceptual knowledge for the lesson. Some of these resources can also be shared with the students.

Author/Book Name	Resource Name and URL	Resource Type
Scitable by Nature Education	Eukaryotes and The Cell Cycle	Web resource
Molecular Biology of The Cell	The Molecular Basis of Cancer-Cell Behavior	Book chapter
HHMI BioInteractive	DNA Damage and Mutations	Video resource
Scitable by Nature Education	p53: The Most Frequently Altered Gene in Human Cancers	Web resource
HHMI BioInteractive	Role of p53 in Transcription	Video resource
Molecular Biology of The Cell	Cancer Treatment: Present and Future	Book chapter

Table 2. Timeline for the Lesson.

Activity	Description	Estimated Time	Notes
Preparation for Class			
Post Pre-class assignment for students to complete before class	Post the Pre-class assignment to the learning management system (LMS) or the course website for students to complete before class.	About 5 minutes	Completing the assignment will help students become familiar with the cell cycle and some important checkpoint proteins that regulate the cell cycle. The students will also become familiar with apoptosis, cancer mechanisms, and treatment options.
Print Metastatic Mastery game card sets	1. Make one copy of the game card set (50 cells and 49 action cards) per team of 4-5 students. 2. Cut along the borders to create one stack of cells and another for action cards. 3. Place 1 game card set in a separate Ziplock bag per team.	Variable depending on the number of teams.	• Game card sets are provided in Supporting Files S2. Metastatic Mastery – Game Action Cards and S3. Metastatic Mastery – Game Cell Cards. • Printing services usually can do the cutting. This takes the most time if done by the instructor, but once the sets are made, they can be used over several semesters. Enlist a lot of help! • Ziplock bags are durable and last several semesters.
Print Metastatic Mastery game questions	Print one copy per team. You can use a copier for this too.	5-10 minutes	• Students will use these to quiz each other while playing the game. • The key is included for immediate feedback and to reduce the pressure that students might feel to have the "right" answer.
Prepare the p53 Mutation Worksheet to hand out in class	Print one copy per team. You can use a copier for this too.	5-10 minutes	• Mutation Worksheet is provided as Supporting File S5. Metastatic Mastery – p53 Mutation Worksheet. • You can provide this to every individual, or post it on the LMS for easy access, but the key is for each team to discuss and work through the questions together.
Supporting File S6 Metastatic Mastery – In-Class Presentation			
Slides 1-8	Setting up the case	8 minutes	Introduction to the learning objectives, the case and general information about carcinogens and lung cancer to capture student interest.
Slides 9-11	Information on carcinogens in cigarette smoke.	4 minutes	Attention is drawn to carcinogens that exist in cigarette smoke focusing in on Benzo(a)pyrene, its metabolite BPDE and DNA adduct formation.
Slides 11-13	Review of point mutations and connection to cell cycle regulation	5 minutes	These slides are designed to gauge student knowledge/ preparation. You can review concepts covered earlier in the module/course as needed.
Slide 15	Metastatic Mastery Game instructions	5 mins for instructions and material handout 15 mins to play the game	This slide introduces students to the game which will help them learn concepts related to the cell cycle and cancer.
Slides 16-18	Oncogenes and tumor suppressor genes, p53 and cancer	4 minutes	A few examples of genes that are commonly mutated in cancer are presented, bringing students' attention to p53, which is the focus of the case. Background on p53 function and dysfunction in lung cancer.

Activity	Description	Estimated Time	Notes
Slides 19-20	Instructions for the p53 Mutation Worksheet. Students will transcribe and translate a portion of the TP53 sequence, then compare the wildtype and mutated sequences to identify the location and type of mutation that disrupts p53 function.	About 20 minutes	Hand out the p53 Mutation Worksheet (Supporting File S5) to students to work on. Students can work on this as a team or individually depending on whether they've had prior practice transcribing and translating sequences. You can move around the classroom to help students as they work. At the end of the allotted time, walk the students through the key (Slide 20) to provide immediate feedback.
Slide 21	Impact of p53 mutation	3 minutes	This slide shows that Arg 248 is important for DNA binding and that the missense mutation to Gln disrupts this association, preventing p53 from facilitating transcription of target genes.
Slide 22	Connections to the Case (big picture)	3 minutes	This slide ties all of the cellular mechanisms back to Gene's case and summarizes the impact of the mutation in TP53 on the development of lung cancer.
Slides 23-26	Lung Cancer Progression and Treatment options	3 minutes	Overview of lung cancer progression and the treatment options that are available to patients.
Slide 27	Recap of Learning Objectives	Optional	Learning Objectives presented at the beginning of the lesson are presented again as "Can You" to remind students of their learning achievement.

* 5 minutes buffer time in case some discussions or activities run longer