

Image courtesy of the National Institutes of Health (NIH)

Scanning electron micrograph of an apoptotic HeLa cell

Cell spotting – let’s fight cancer together!

“Tell me and I forget, teach me and I may remember, involve me and I learn,” Benjamin Franklin once said. Make that quote yours and involve your students in a real cancer-research project that will teach them more than just genetics and cell death.

By **António J Monteiro, Cândida G Silva and José C Villar**

Efficient cancer drugs need to selectively destroy tumour

cells without harming healthy cells. Existing chemotherapy treatments have failed to reach that ideal level of selectivity, but many research teams continue to look for compounds that



BACKGROUND

HeLa cells

HeLa cells are a special human cell line. They originate from a woman called Henrietta Lacks, who died from cervical cancer in 1951. Her doctor took some cells from her tumour and managed to grow them in a culture medium, developing the first human cell line. HeLa cells are the most widely used human cells in biology labs across the world.

could become the effective and side-effect-free drugs of tomorrow.

The search for suitable compounds is performed primarily by robotic systems that quickly test and identify millions of candidate chemical compounds: they put cancer cells together with potential drugs and observe whether the cells die or survive. Such experiments generate thousands or even millions of cell images that then need to be analysed according to several parameters – such as the cell's status, the release of cellular content, the distribution of the mitochondria, or the shape of the nucleus – and classified to determine the cell's response to each potential drug. The ideal solution to treat this huge amount of data would be to use computers. However, they are not good enough to recognise patterns: nothing beats the human eye for that task (Lostal et al, 2013a; 2013b)!

That is where you and your class step in. Researchers need help from as many volunteers as possible to support them with image analysis and to identify potential new drugs against cancer as rapidly as possible. Your students will learn about cell death by helping scientists to characterise

the response of HeLa cells to different chemical compounds.

The Cell Spotting project

The Cell Spotting team is testing more than 14 000 chemical compounds in HeLa cells and observing their reaction using advanced optical microscopy techniques. HeLa cell cultures are being photographed every half hour in three different channels: normal light, blue and green fluorescence (Lostal et al, 2013a; 2013b). The normal light reveals the global shape of the cell membranes; the blue fluorescent channel is specifically for the observation of the cell nuclei (they are dyed with the fluorochrome Hoechst 33342, which emits blue light when bound to DNA); and the green light is for the observation of the cells' mitochondria (which are dyed with the fluorochrome Mitotracker). By combining data acquired from the three channels, the scientists can generate images that contain detailed information about these three elements of the cells' structure and also videos that show cell movements, division and death over time. More than 4000 images are taken per day and about 14 112 images are produced in a single experiment.



- ✓ Biology
- ✓ Technology
- ✓ Ages 14–18

This article describes a student-centred activity that introduces the concept of efficient cancer drugs and how different compounds are tested to see if they are effective in killing cancer cells. Students are then led through an exercise in which they learn about HeLa cells and how these are cultured with isolated compounds to test the effect of that compound on cancer cells. They also learn about cell apoptosis and cell necrosis through visual examples.

Students are then introduced to the Cell Spotting research project, which allows participants to analyse cells and contribute to the project by uploading their analyses.

Each step of the project is supported by clear instructions and explanatory notes to help students use their knowledge and contribute to the project.

Dr Shaista Shirazi, UK

REVIEW

Biology

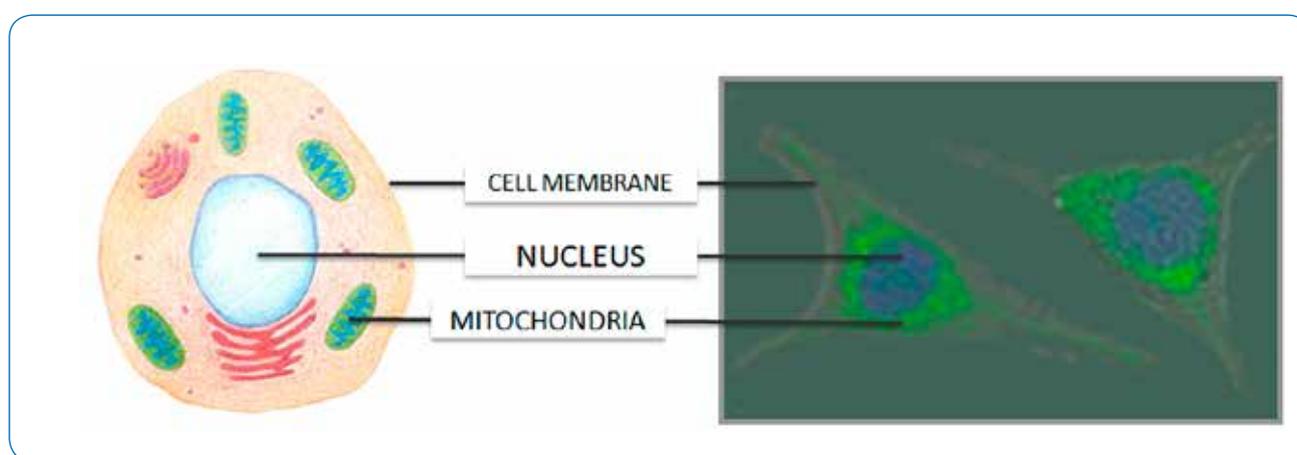


Image courtesy of SOCIENTIZE

Figure 1. Comparison of an animal cell representation with a HeLa cell image

Spot cells and help fight cancer from your classroom

This activity is designed to be implemented in biology courses for students aged between 14 and 18 years old, however you can also adapt it for other groups. It explores themes such as cell division, cell death, genetic regulation, cancer and biotechnology.

The activity is divided into two parts:

- A) Explore the Cell Spotting research project and understand its context, and
- B) Play with the Cell Spotting application.

Materials

The resources available for this activity are:

- a video^{w1} that puts the Cell Spotting research project into context
- a didactic unit^{w2} that provides a potential lesson plan and activities to do with students
- a teacher's package^{w3} that contains a detailed document about the research, a PowerPoint presentation and three short clips about HeLa cells.

Procedure

A) Explore the Cell Spotting research project and understand its context.

In the first part of the activity, students should use enquiry-based thinking to learn about the research project and its methodology.

- 1) Watch the video^{w1} 'Socientize: Cell Images Experiment' to place the activity into the right context.
- 2) Go through the didactic unit^{w2} and find the answers to the following questions:
 - a) What is José Villar doing in his research?
 - b) What type of cells is he using?
 - c) What methodology is he using to observe the cells?
 - d) What results can he expect from different chemical compounds?
 - e) What type of cell death does José Villar want to induce in cells? Why?

At this stage, it may be useful to build a simple diagram like the one shown in figure 2:

- 3) Show your students how to differentiate between apoptosis and

necrosis and to identify healthy HeLa cells from dying cells:

- a) Ask your students to analyse figure 5 from the didactic unit and to build a table similar to table 1 to summarise the main morphological differences between the two types of death: cell volume differences, nucleus condensation and final reaction.
- b) Watch the three short clips showing HeLa cells in different states (healthy, in apoptosis, in necrosis) from the teacher's package. Ask students to identify which cell state is represented in each short clip based on the morphological differences.

Now your students are ready to help José identify HeLa cell images!

B) Play with the Cell Spotting application.

The Cell Spotting application^{w4} allows you and your students to analyse HeLa cell images and send your analysis to the research team. The application interface is very intuitive, user-friendly and self-contained, so everybody can easily access and

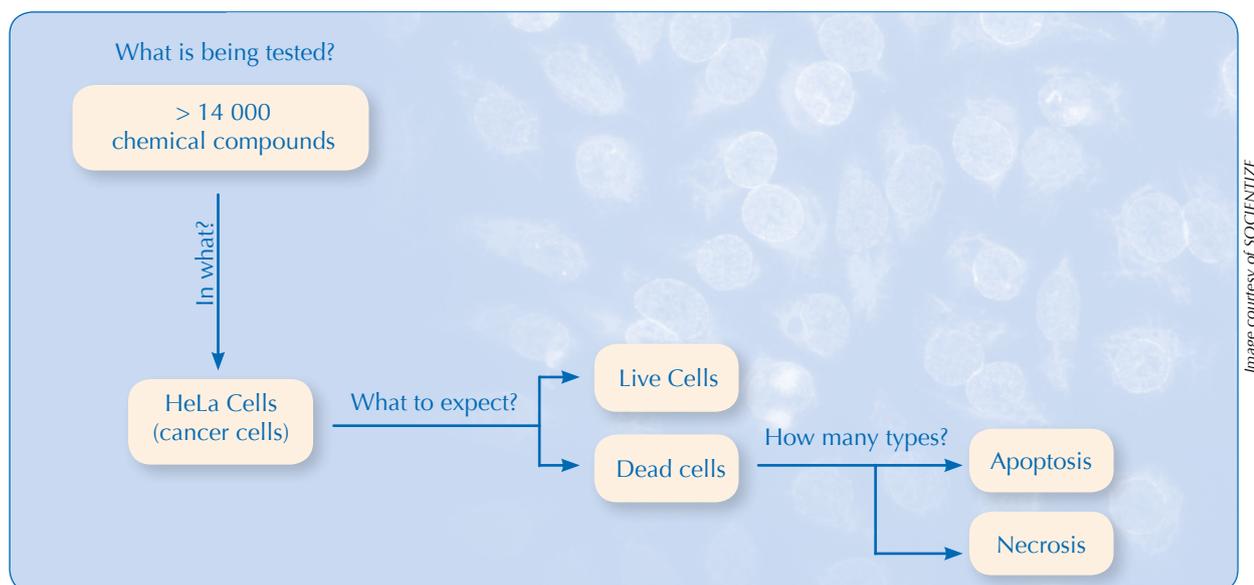


Figure 2. Example of a diagram to explore the Cell Spotting experiment

Image courtesy of SOCIENTIZE

	Apoptosis	Necrosis
Cell volume	Decrease	Increase
Cell nucleus	Fragmentation after condensation	Volume increase
Content release	No (formation of apoptotic bodies)	Yes
Inflammatory response	No	Yes

Table 1. Example of a table summarising the main morphological differences between apoptosis and necrosis

contribute. When you access the application for the first time, we recommend that you follow the tutorial that explains its structure, objectives and resources. This will ensure that you have all the necessary details before you log in and start spotting and tagging cells with specific stamps.

To complete each task, you need to analyse the same image according to four parameters:

- Current cell status (dead or alive)
- Cell content release (whether the cell releases material or not)
- Mitochondria distribution (whether the mitochondria are clustered or scattered inside the cell)
- Other remarks (e.g. multinucleated cell, abnormal sized cells and nuclei)

- 1) Ask your students to log in the application and register so their contributions do not remain anonymous.
- 2) Explore the application with your students and define exactly what they should do. If you have a projector, this can easily be achieved by doing a cell image analysis together while projecting it on a wall.

In a nutshell, the application includes:

- the blue bar (see A on the image) on the top, which summarises what you need to do and the resources to achieve that task, including:

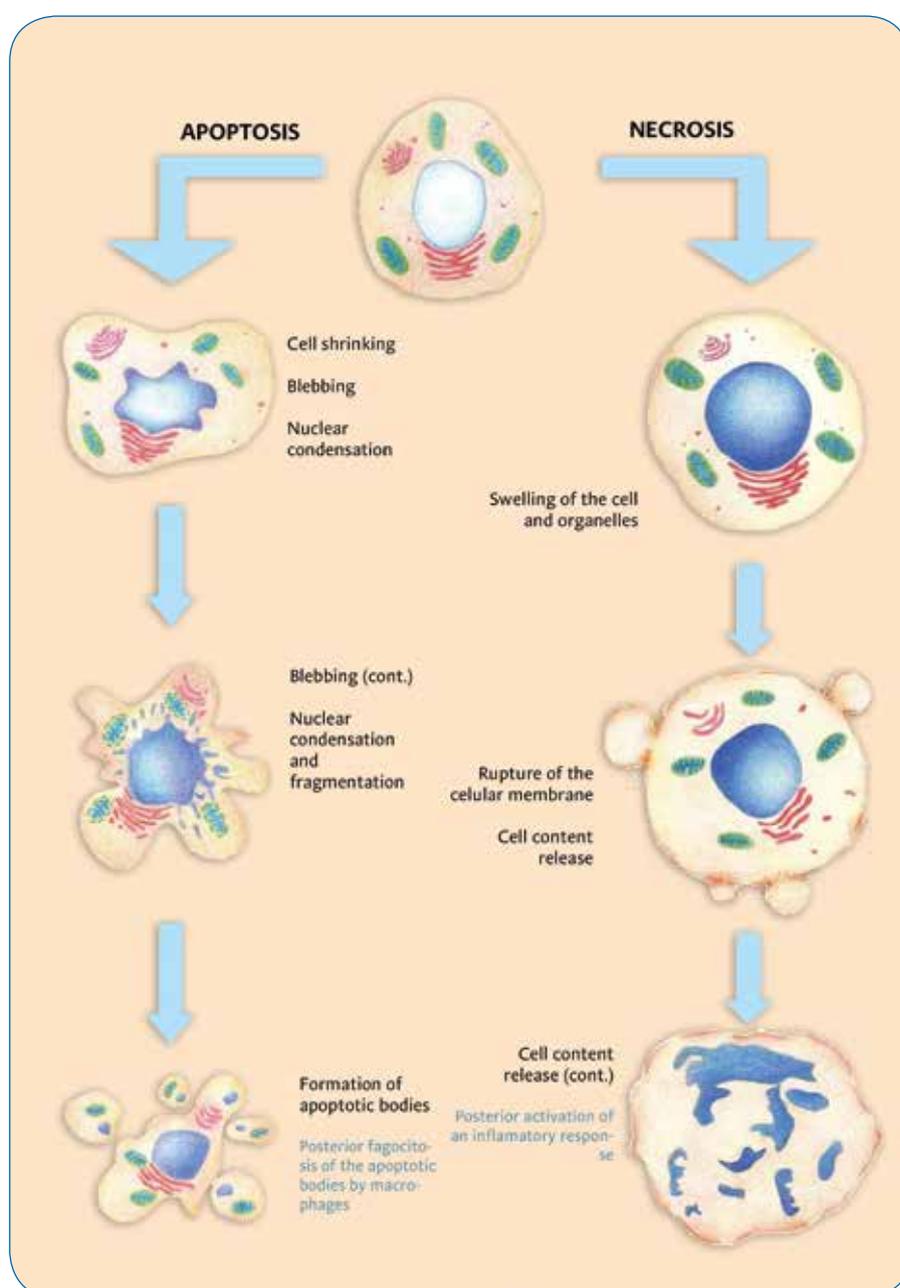
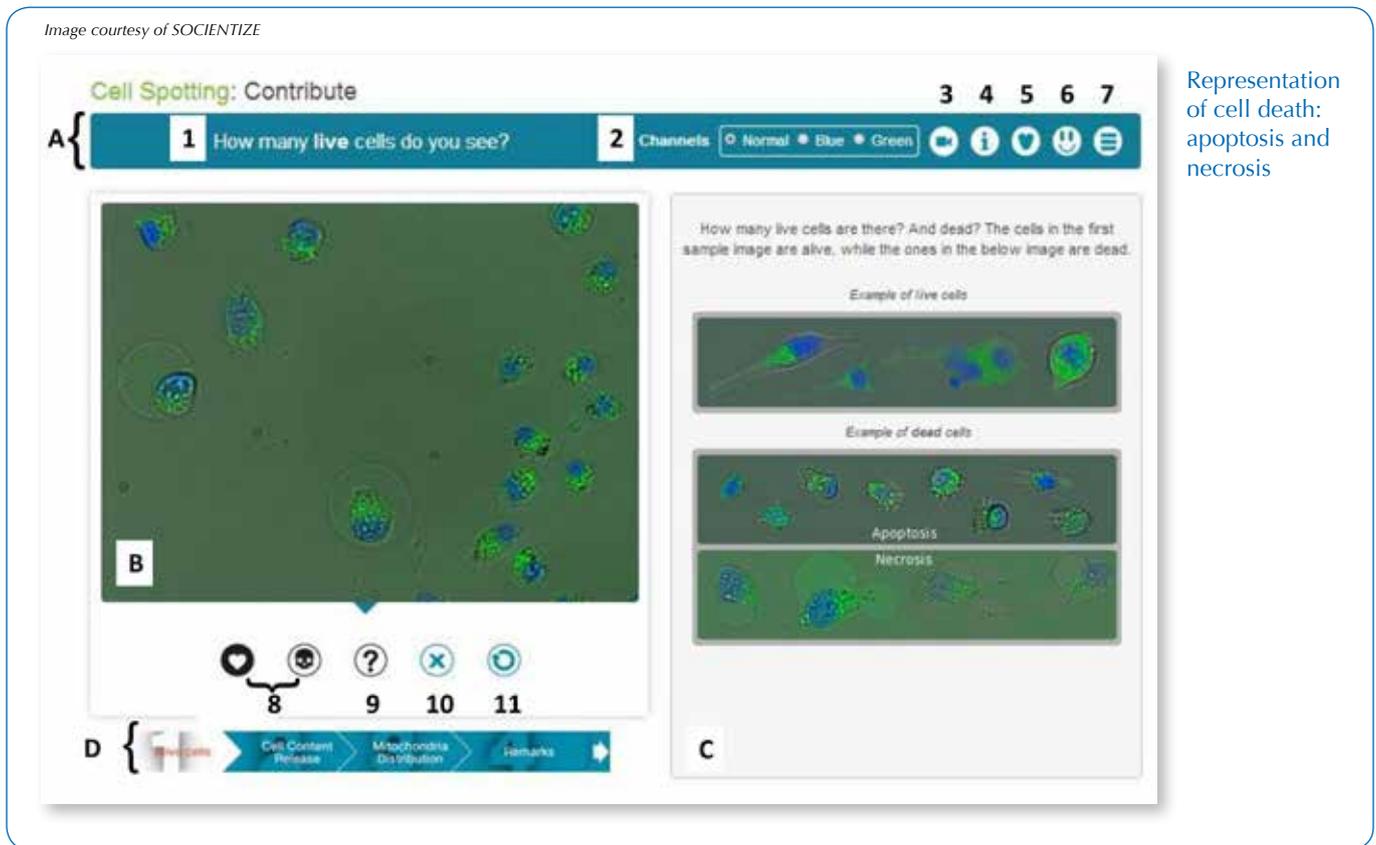


Image courtesy of Juliana Bortolero

Figure 3. Representation of cell death: apoptosis and necrosis

Image courtesy of SOCIENTIZE



Representation of cell death: apoptosis and necrosis

Figure 4. Cell Spotting application

- the specific question that you need to answer
- the three different light channels that you can use to visualise specific details on the image: blue to visualise the nucleus; green to view mitochondria; and normal, which is a result of the blue, green and bright white field images merged
- the video from which each image was extracted
- additional information on each step
- access to Vish, the Virtual Science Hub, an educational platform where you can virtually visit the lab where Cell Spotting takes place
- a feedback survey
- a direct link to the didactic unit

The image awaiting analysis is in box B (in figure 4). Below it you can find the various stamps to tag the cells and identify their state (see point 8 on Fig. 4). You can also remove the tags individually (see point 10 on Fig. 4) or start over (see point 11 on Fig. 4). If you are not sure how to classify the cells, you can use a specific tag with a question mark (see point 9 on Fig. 4). Box C provides you with a set of examples of the patterns that need to be identified.

Finally, below the image for analysis, you will find a progress bar with the four parameters that you need to complete for each task (see box D in figure 4). Every time you finish analysing a parameter, you must click on the arrow to the right of the progress bar so you can move to the next parameter. When the four parameters have been analysed, an icon will appear so you

can finish the task. After that, a new image will automatically appear and you can start the analysis all over.

NOTE: A guide to get started with Cell Spotting is available in the teacher's package. The analysis is very simple and your students will probably do it easily.

3) Let your students play with the programme and contribute freely. Let them know that they can also log in from home.

References

- Lostal E, Serrano F, Carrodegua JA, Martínez P, Sanz F, Val C (2013a) Cell Images Analysis as a Case of Citizen Science for Advanced Education: Laboratory and School, Back and Forth. In *Proceedings of the 7th International Technology, Education and Development Conference (INTED 2013)* pp 2489–2496. Valencia, Spain: IATED
- Lostal E, Serrano F, Carrodegua JA, Martínez P, Sanz F, Val C (2013b) A case of Citizen Science for Cell Biology Images Analysis. In *Proceedings of the XXXIII Congresso da Sociedade Brasileira de Computação (CSBC 2013)* pp 1855–1862. Maceió, Brazil: CSBC

Web references

- w1 – Watch the ‘Socientize: Cell Images Experiment’ video on Ibercivis Ciencia’s YouTube channel:
- in English: <http://youtu.be/XXegth8CmM4>
- in Portuguese: <http://youtu.be/OGTITEp-ybI>

w2 – Download the didactic unit for the Cell Spotting activity:

- in English: www.ibercivis.net/?p=6985

- in Spanish: www.ibercivis.net/?p=6987

- in Portuguese: www.ibercivis.net/?p=6989

w3 – The teachers’ package for the Cell Spotting activity contains a detailed document about the research, the Cell Spotting guide, a version of the didactic unit with solutions, and three short videos of different health states of Hela cells. You can download it here:

- in English: http://bit.do/ibercivis_teacherspackage

- in Portuguese: www.ibercivis.net/?p=6993

w4 – To access the Cell Spotting application and start playing, visit the Socientize website: <https://pybossa.socientize.eu/pybossa/app/cellspotting/>

Resources

Find out more about the EU-funded project Socientize from its official website: www.socientize.eu. You will also find other citizen science projects that you can get involved in.

To keep track of citizen science projects promoted by Socientize, consult the official website of the Ibercivis project: www.ibercivis.com

For another cancer-related teaching activity, see:

Communication and Public Engagement team (2010) Can you spot a cancer mutation? *Science in School* **16**: 39–44. www.scienceinschool.org/2010/issue16/cancer

Students working on a class assignment in the computer lab



Image courtesy of Michael Surran/Flickr

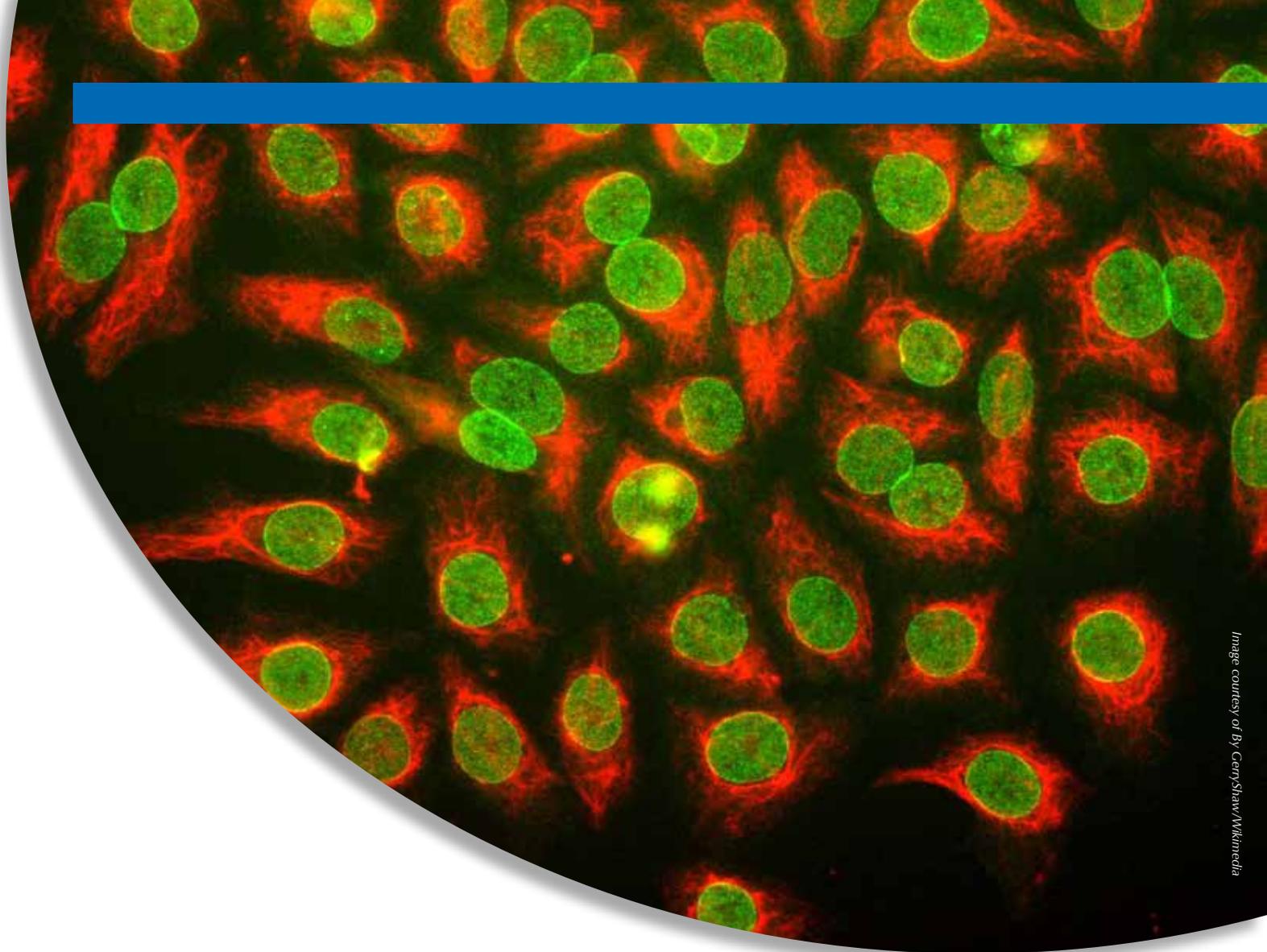


Image courtesy of By: Gernyshaw/Wikimedia

António Monteiro is a biologist with an MSc in biology and geology teaching. He is actively involved in the citizen science FP7 project 'Socientize – Society as e-Infrastructure through technology, innovation and creativity'. He has worked for the Science Museum of the University of Coimbra in Portugal since 2009 as an exhibition guide and education developer of science activities, mainly for the Researchers Night. He is also involved in promoting the museum via social media.

Cândida G Silva holds a degree in mathematics and computer sciences and a PhD in chemoinformatics. During the past four years, she has been an active collaborator of two citizen science and volunteer computing projects: ibercivis.net and

socientize.eu. Her current scientific interests focus on machine learning, data mining, drug discovery, citizen science, e-science, volunteer computing and data warehousing.

José Carrodegua Villar, PhD, is a researcher at the Institute for Bio-computation and Physics of Complex Systems (BIFI) at the University of Zaragoza in Spain. He leads a research group focused on the study of apoptosis in cancer, the immune system, nervous system and other systems. He is also the principal researcher of the Cell Spotting experiment and is actively involved with citizen science projects and activities at Socientize and Ibercivis.

This is an activity proposed by Socientize, a project funded by the European Union Seventh Framework Programme under contract RI-312902.



HeLa cells grown in tissue culture. Red: cytoskeleton; green: nucleus