

# Hedgehogs, humans and high-school science

The benefits of involving high-school students in university research

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The 'Lisbon strategy', adopted by the member states of the European Union (EU) in 2000, aims to make Europe the most dynamic and competitive knowledge-based economy in the world by 2010. The overall aim is to increase the levels of investment that member states put into scientific research up to and beyond 3% of their Gross Domestic Product. Although this aim will certainly not be met in the expected timeframe, it is noble and important nonetheless.

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However, even if the members of the EU increase investment into research, it will be in vain if they do not also work to increase the number of researchers. Indeed, the current number of researchers per 100,000 citizens in the EU is considerably lower than the figure for the USA or Japan. As scientists, we have virtually no possibility to influence how much money our governments spend on research and development, but we can have a much more active role in making science a more attractive career option for young people—notably high-school students.

Various projects and initiatives in EU countries and the USA have sought to achieve this aim by forging closer links

between schools and universities or research institutes. Here, we describe the Cus-Mi-Bio (Centre University School of Milan for Bioscience Education; [www.cusmibio.unimi.it](http://www.cusmibio.unimi.it)) project that was developed at the University of Milano, Italy. The project's aim is to raise the levels of interest and enthusiasm of high-school students for the life sciences, and hopefully to attract some of them to a career in science.

There are various negative perceptions of science that need to be overcome when persuading students that it is a worthy career choice. Many high-school students still believe that studying the natural sciences is a hard choice compared, for example, to economics or the social sciences, and that science does not offer a rewarding career path. At least in Italy, such perceptions and their consequences are well founded: the number of students graduating in mathematics, physics and chemistry is often insufficient to meet the economy's demands, fellowships for PhD students are not sufficient to make a living, and career options are often not linked to scientific merits. Nonetheless, it is still important to invest in the future of the research enterprise by motivating young people, and to identify those with enough enthusiasm and curiosity to embark on a scientific career. Such an investment into young people will also benefit universities by attracting motivated and gifted students, and by making their transition from high school more conscious.

In Italy, the current high-school biology curriculum is out-dated, but we suspect that it might be the same in other European countries. The main problems for both teachers and students are old text books, insufficient time to cover important topics, a lack of practical experiments and not enough interest from students who often perceive biology to be a 'soft science'. Teachers therefore need to regularly update their knowledge and skills, and to learn new methods with which to engage their students. This requires new, discovery-based curricula that act to make science more appealing for students.

Establishing functional and synergistic links between the high-school education system—students and their teachers—and research universities is one way to do this. Of course, students need a basic knowledge of mathematics, physics, chemistry and biology, but, to capture their interest and curiosity, it is also important to expose them to cutting-edge research and to give them the opportunity to experience the excitement of working in a research laboratory. This, in turn, implies that the scientific curricula in high schools must not be limited to teaching the history of science, describing the organs of our bodies or just learning the Linnaean classification system, but must embrace more practical courses.

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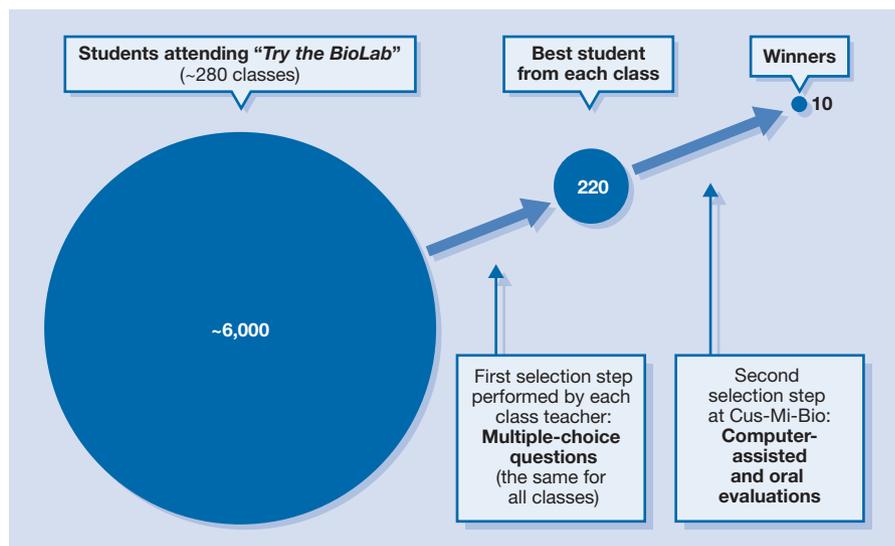
The three main players—high-school students, science teachers and researchers—must learn to interact with each other to forge links between schools and universities. Researchers are able to identify the most interesting and promising research topics, but they have limited amounts of time in which to teach and instruct high-school students; this task is better fulfilled by the teachers, who are an equally integral part of the entire project. Their close cooperation eventually generates a virtuous circle: researchers and teachers identify and propose scientific topics that can be discussed in the classrooms and that lead to related experiments; together they develop the theoretical and practical activities that stimulate the curiosity of students, who will, in turn, urge their teachers to acquire additional knowledge.

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Such a scheme should avoid an elite-focused approach that would select only the best students for participation in research experience. The scheme must include students of all levels to identify those most interested in research. This first phase must then be complemented by a second phase focused on the most gifted and enthusiastic students.

Since 2004, Cus-Mi-Bio has tried to bring this scenario to life. Cus-Mi-Bio is located on the University of Milano’s campus and includes a fully equipped molecular biology laboratory and bioinformatics facilities to host 70 students at individual workstations. Clearly, only a limited number of high schools have the facilities to carry out research activities themselves, even in Milano, the capital of the most economically developed region in Italy. The Cus-Mi-Bio laboratories are therefore an integral part of the Lombardy school system—indeed, the University of Milano and the Lombardy Education Office jointly finance the laboratory’s activities.

Cus-Mi-Bio initiatives are so far limited to the biosciences. Nonetheless, they are well-timed because the past decade has seen



**Fig 1** | Selection steps in the ‘A week as a researcher’ contest limited to talented high-school students attending BioLab activities. Numbers refer to the 2006–2007 selection.

many new advances in this field and the birth of new integrated disciplines such as bioinformatics, computational biology, imaging and systems biology. Therefore, the education system must be able to train a new generation of scientists and researchers capable of using the new tools efficiently and correctly.

At present, Cus-Mi-Bio has two high-school teachers working full-time, together with about two-dozen University of Milano scientists and professors from academic faculties as diverse as medicine, molecular biology, agriculture, pharmacology and veterinary sciences. In addition, several PhD students and post-docs act as tutors during the experimental work in the laboratory: their presence strongly facilitates productive interactions and dialogue with high-school students and helps to break down the ‘teacher–student’ barrier.

Cus-Mi-Bio also organizes specific courses and meetings on the frontiers of modern biology for high-school teachers to provide them with up-to-date scientific knowledge. So far, more than 300 teachers have taken part in these initiatives and these working groups also produce handbooks, experiments, and ‘tools and tips’ that teachers can use in their classes.

The main activity organized by Cus-Mi-Bio for high-school students is the so-called ‘Try the BioLab’. Every school day, one or two classes perform experiments in the two Cus-Mi-Bio laboratories on topics drawn from the fields of

genetics or biotechnology. These experiments include: DNA fingerprinting, identification of genetically modified organisms, cloning, genetic diseases, model systems in biology, gene hunting, and many more.

‘Try the BioLab’ is open to all high-school students and, so far, more than 11,000 students have attended at least one of these courses during the past three years. The most motivated and skilled students then participate in a competition that selects 10–15 of them to attend a ‘week as a researcher’ in a national or international research laboratory at the end of the school year (Fig 1). This contest selects talented students and helps to maintain contact with them.

Cus-Mi-Bio also launched a new initiative at the end of 2006 called, ‘Wannabe a researcher: attend a top science project’. This programme aims to combine professional research with research-based undergraduate education and is limited to the 10 winners of the contest and 30 other students who are close runners in the contest. The aim is to develop further their predisposition for science and research by having them contribute to a research project throughout the entire school year, in part at Cus-Mi-Bio and in part on their own computers at home.

The 2006–2007 project was called ‘Following the footsteps of evolution, looking for new genes’, and was based on a bioinformatics analysis of

**Sidebar A** | Participants in the ‘Wannabe a researcher?’ programme by Cus-Mi-Bio

The high-school ‘Wannabe a researcher?’ students attending the 2007 project were: Gangai Alessandra (Liceo Volta, Milano); Carlini Valentina, Ferrante Giulia, Fortunato Federica, Magni Martina, Massari Lucia (Liceo Donatelli-Pascal, Milano); Andreosso Ivan (Liceo Vittorio Veneto, Milano); Caspani Anna, Citterio Simone, Lippi Laura, Rabboni Francesca, Rossini Giulia, Sala Giulia, Saturno Elisa (Liceo Don Gnocchi, Carate Brianza, Milano); Brambilla Marta, Moretti Luca, Poletti Davide (Liceo Banfi, Vimercate, Milano); Erasmi Fulvia (Liceo Vico, Corsico, Milano); Branca Luca, Brindisi Pietro, Sutura Samuele (Istituto Tecnico Agrario Mendel-Villa Cortese, Legnano, Milano); Cappelletti Alessandro, Greco Benedetta (Liceo Novello, Codogno, Lodi); Airaghi Giulia, Bizzarro Francesca, Borroni Manuel, Gilli Marta, Lucchetti Michele, Montanari Maria Giulia, Pescatori Claudia, Restelli Enrico (Liceo Legnani, Saronno, Varese); Mason Emanuele, Mucchetti Federico, Poggi Nicolò, Scorti Andrea (Liceo Tosi, Busto Arsizio, Varese); Castelli Matteo (Liceo Volta, Como); Brusa Filippo, Msiyah Fatim Zuhra (Istituto Tecnico-Industriale Tessile Carcano, Como).

the human genome with the aim of discovering new genes. Bioinformatics and molecular evolution are rarely taught in high-school curricula and the project was therefore exciting for both the students and their teachers. In fact, genomic browsers and bioinformatics tools allow the observation—even in an abstract representation—of genes and gene transcription, and thus provide an extremely powerful tool to teach the basics of modern molecular biology. While we familiarized the students with the bioinformatics tools they were going to use, we also brushed up their knowledge of molecular biology and told them about the latest discoveries in the field.

The students in the ‘Wannabe a researcher’ programme (Sidebar A) were presented with the basic concepts of gene expression (i.e. transcription, splicing and translation), but instead of looking at schematic drawings on a blackboard, they had direct access to genomic data and annotations through the UCSC (<http://genome.ucsc.edu>) and ENSEMBL ([www.ensembl.org](http://www.ensembl.org)) genomic browsers. The UCSC browser was used because it offers basic and intuitive tools to perform simple ‘experiments’ without the need to delve into bioinformatics or statistical details. Also, it is possible to hide confusing annotations in the browser and leave only the relevant information on the screen.

The students could observe gene structure, transcription and splicing by looking at the annotations of genes—that is, images that show the alignment of transcripts to the genomic sequence, and the way they are split into exons and introns. These provide an immediate view of alternative splicing mechanisms to produce different mRNAs. In our classes, we used the human sonic hedgehog homologue (*SHH*) gene.

It immediately catches the students’ attention owing to its name and to the fact that, by clicking around and browsing through the annotations, they can discover the picture of the cartoon character after which it was named. Although the gene has a simple structure of three exons, it summarizes almost every aspect of alternative transcription and splicing—alternative transcription initiation and termination, cassette exons, retained introns, and alternative 5’- and 3’-ends—all of which are easily visible by aligning different mRNAs to the genome.

Another typical exercise consisted of providing students with one or more transcript sequences and asking them questions such as: where is the gene that produced the sequence(s) located in the genome and on which strand, and which alternative splicing events, if any, can you find? The experiment can be replayed by using protein sequences and asking the students to locate the gene that encodes for a given amino-acid sequence or, alternatively, to predict the amino-acid sequence of a mRNA sequence—thus making them more familiar with 5’- and 3’-untranslated regions, amino-acid codons, and start and stop codons.

An additional advantage of these activities is that transcript and protein alignments against the genome do not always give unique results—that is, significant sequence similarities can be found in other genomic regions. For example, by aligning the SHH RefSeq protein against the human genome, three results are obtained that can be interpreted as: the human genome contains one region that encodes for the SHH protein, but two more regions seem to encode for an amino-acid sequence that is similar to SHH. Even more interesting is that the other two

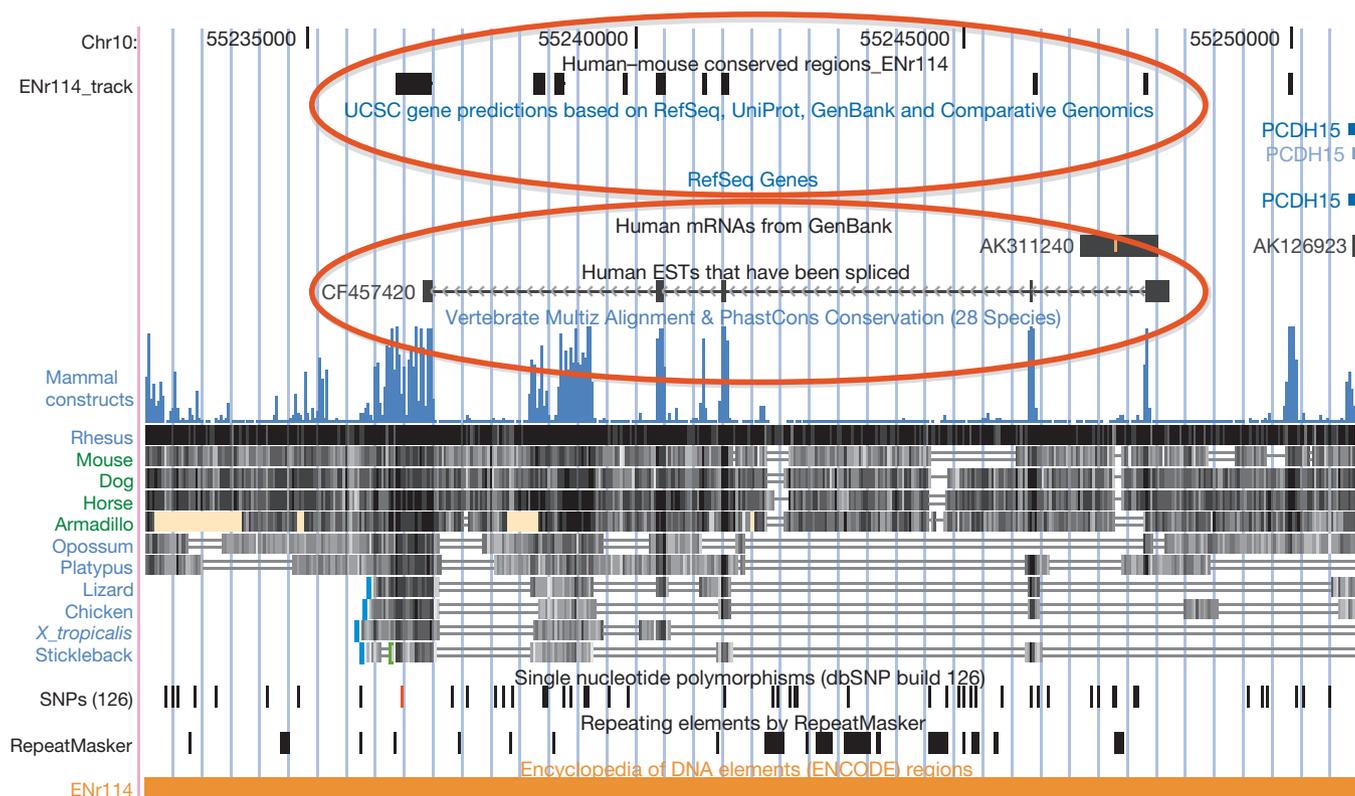
results correspond to regions where exons of two other genes are wittily annotated as ‘two more hedgehogs’.

At this point, we asked the students to align the human SHH protein against the mouse genome. Again, they obtained different ‘hits’ and discovered three regions—corresponding to genes annotated on the mouse genome—which encode amino-acid sequences similar to human SHH. By repeating the same exercise with *Drosophila*, the students were again able to find a single region located within an annotated exon. At this point, we asked the students to speculate why there are similar gene sequences in different species. They were then able to continue the searches alone—repeating the same steps with different human proteins and/or with different species—in order to answer questions such as: how many hedgehogs does it take to make a pufferfish? The fact that exercises of this kind only require a computer with internet access makes them an endless source of possible home projects.

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Once the students had discovered these genomic similarities, we asked them why a fly has a gene that can also be found in humans, and why the human genome has multiple copies of a gene. This automatically required us to explain concepts such as homology, orthology, paralogy and synteny, as well as evolutionary mechanisms, including genome rearrangements and duplications. Every concept is easily visible within the genome browser—for example, by examining alignments and conservation between genomes. Bioinformatics provides teachers with endless opportunities to teach modern biology—for example, a microRNA sequence mapped onto the genome might lead to a discussion of RNA interference.

Furthermore, genomics also gives rise to interesting questions: how many genes does it take to make a human? Why do humans, mice and all mammals have virtually the ‘same’ genes—that is, why can their proteins be mapped easily onto each other’s genomes? Why do plants usually



**Fig 2** | A putative 'new gene' discovered by one of the students attending the programme. EST, expressed sequence tags; SNP, single nucleotide polymorphism.

have more genes than mammals, and why is it that the number of genes in a simple organism, such as *Caenorhabditis elegans*, compared with that in a complex organism, such as *Homo sapiens*, is not that different? These questions, in turn, help us to introduce the latest discoveries in molecular biology, such as the concept of alternative splicing, gene expression modulation or genetic diseases caused by 'errors' in these mechanisms.

Once this crash-course in modern molecular biology and evolution was completed, our students finally started their real research project: to find out whether a likely protein-coding gene could actually be 'missing' in the sense that it might not be annotated in the available RefSeq gene annotations of the human genome. The students were split into small groups and each group was assigned a different part of the human genome. In particular, the task was to assess whether a pre-selected region of the human genome based

on the ENCODE project ([www.genome.gov](http://www.genome.gov)) could contain a new protein-encoding gene—or at least a new exon. Although the ENCODE regions are now thoroughly analysed, the students were able to identify at least three possible new protein-encoding genes (Fig 2), and a large number of new as-yet-unannotated exons.

Overall, our experience with the Cus-Mi-Bio students shows that sequencing projects and bioinformatics are not only great tools for research, but also for teaching the concepts that underlie molecular biology and evolution. Regardless of the tools used and the examples chosen, we think that letting students 'discover' things—rather than just learning about them—can greatly improve their understanding of the basic concepts of biology. For example, we did not present evolution as dogma, but rather let our students investigate and discover several 'footprints' of evolution. We believe that getting such first-hand experience of evolution and molecular biology is extremely important, especially when discoveries from the life sciences often

stir public debate and controversy. Today's students are the voters and decision-makers of tomorrow, and it is essential that we give them the best possible means to form their own opinions and ideas.

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