Journal of **BIOLOGICAL RESEARCHES**
ISSN: 08526834 | E-ISSN:2337-389X
Volume 22| No. 2| June | 2017

Opinion

Molecular biology education in Indonesia - suggestions for improvement

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Abstract

Education in molecular biology is considered difficult because it is complex and requires a lot of basic knowledge. Focused on basic science facts, it is usually taught with little connection to everyday life. A second problem is that the topic is rather abstract and results are only indirectly observed: we know that DNA is a double helix - but nobody has seen it directly. In contrast to subjects in the humanities and social sciences, molecular biology is a handy-craft where sophisticated theory and practical lab-work go hand in hand. Molecular biology is not so much a specific sub-discipline of biosciences but rather a huge tool box which is indispensable for all other fields of biology. It is therefore absolutely required for all biologists to know the basics and the potential of molecular biology in their specific field of interest. We present some thoughts how to make the theory more attractive, how to combine learning, training and teaching of theory and practice, how to stimulate independent, critical thinking in students and finally, how to identify and support excellent students who should advance science in the next generation. Last not least, we emphasize the necessity to expand information and teaching of molecular biology to the public.

Keywords: Education, fake news, public understanding of science, scientific literacy, teaching

Received: 27 February 2017 Revised: 04 May 2017 Accepted: 12 May 2017

Biosciences are Underestimated

In contrast to mathematics, physics and chemistry, biology is frequently considered "soft science" with watching birds and looking at flowers. It is rarely seen, that modern biosciences are an interdisciplinary approach of all natural sciences plus engineering to address essential questions in medicine, pharmacy, agriculture, animal breeding, food production and food processing, material science, environmental science, ecology, biodiversity, neuroscience etc. All these applications require sophisticated instruments from high-tech imaging devices to high-throughput sequencers and elaborate informatics. Most importantly, applications require extensive basic research to provide the appropriate knowledge and tools. It has become impossible for a biologist, to be expert in all sub disciplines. However, all biologists share the interest in life science and a basic understanding of the other sub disciplines is required. This makes bioscience probably the most demanding subject.

With a little bit of irony one may suggest to new students to rather study mathematics if he or she wants a simple discipline. In mathematics they can concentrate on one subject and do not have to learn so much about physics, chemistry, informatics, engineering and biology.

Molecular Biology as a Key Element in Biosciences

Molecular Biology has become an indispensable accumulation of methods on which all sub disciplines of biology depend. Biodiversity research requires bar coding and deep sequencing, biochemistry requires expression of recombinant proteins, human genetics requires mutation analysis etc. And all require model systems to establish, test and evaluate new molecular methods.

In contrast to e.g. physiology, ecology, biochemistry etc., molecular biology is rather a technical discipline that provides a toolbox. More than other bio scientists, molecular biologists have to think and to work interdisciplinary. To explain this challenge should be one of the first crucial lectures for new students.

The European and the Indonesian Teaching Approach

Indonesia is a large and diverse country. To our knowledge, a comprehensive study on teaching methods has not been carried out so far. The following statement is therefore based only on personal experience in various schools and universities on the main islands.

In Indonesia, a lot of teaching is done "front-to-back". Students mostly memorize, questions are answered in chorus because there appears to be only one possible answer. Questions are usually "what is …?" i.e. asking for a definition, rarely the question is "what if …?" asking for solving a problem using the previously learned facts. Understanding in context and questioning the teaching contents is mostly unknown. This is good for the basic concepts of molecular biology where facts have to be learned, but it leaves out an essential idea of science: concepts are subject to change and only valid until new research introduces extensions or alterations of the current models. It should be kept in mind that the "Central Dogma" of molecular biology had several extensions that were not anticipated before! For example, before the discovery of reverse transcriptase, the flow of information was strictly unidirectional from DNA to RNA - never reverse! Students need knowledge of the (current) facts of biology - but they also have to apply these facts, they have to raise doubts, to ask questions, to challenge the models. Somewhat simplified: Indonesian students learn

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facts but they lack the competence to work with these facts and to challenge them. The Ministry of National Education distinguished between "creating knowledge" and "Re-configuration of knowledge" which comes close to the simplified statement above (1, https://www.researchgate.net/profile/Hugo_Verheul/publication/226294879_Higher_Education_Reform_in_Indonesia/links/542a898e0cf27e39fa8ea6f4.pdf).

In Europe, the emphasis is on "competence", the ability to learn if required and the competence to understand biological concepts (not the actual understanding of the concepts!). Essentially, Europe is moving towards competence without knowledge of facts. All competence to discuss and compare and evaluate is, however, quite useless, when the knowledge of facts to be discussed, to be compared and to be evaluated is not sufficiently available.

Both approaches are insufficient: we need very good knowledge of the (current) facts and at the same time the competence to ask critical questions. One does not work without the other.

In both regions, the principles of basic science are usually not taught in a context to understand why science is important. There are three main reasons for the importance of biosciences: First and easiest is to explain the impact of science on everyday life. Insulin, chymosine, blood clotting factors, lactase etc. are convincing examples for the benefits of gene technology. Food supply has become significantly better over the last 40 years due to genetics in plant and animal breeding. Health has improved by vaccinations etc.

The second reason is that the understanding of molecular biology, without the aim of a specific application, is the most important prerequisite for applications. Without the investigation of bacterial defence systems (restriction enzymes), no applications like e.g. insulin would have been possible. Research on restriction enzymes was not done to make cloning possible but gene technology emerged from the discovery of restriction enzymes! Interestingly, the new gene technology (CRISPR/Cas9) also emerged from basic research on bacterial defence systems (Jinek et *al*., 2012).

A third, reason for doing science is the human interest to understand the environment and the world as a whole. This is more or less a philosophical reason and not always easily transferred to young students. It may, however, encourage students to be curious.

All over the world, there is an intrinsic interest in nature and in asking questions about nature at a very young age. However, this becomes weaker when students grow up. At this point, role models become very important. A scientist appears not to be a fascinating role model, but mostly because students do not know many scientists who are enthusiastic about their occupation. It is a valuable experience to meet a scientist from outside the own school or university and hear about his or her research and why they love to do it. It is not even necessary to invite a famous first-class researcher. A "normal" scientist who can explain in an interesting way why a certain project interests him or her is even more realistic and convincing. He or she may serve as a role model and at least some students may "catch fire" and understand the enthusiasm.

Combinatorial Thinking/Transfer

The complexity of molecular biology makes it impossible for a single person to know all details. This is not only an immense challenge but also demonstrates the beauty of the bio-molecular world and emphasizes the necessity of an interdisciplinary, collaborative approach. Basic concepts like replication, transcription, translation should be taught as single, separate topics to obtain a step by step basic understanding. But then the "transfer thinking" should come in very soon and give the first lessons in competence to connect different topics. For example, when explaining PCR, it is worth to go back to replication and ask the question what the similarities and the differences are. Why do we not need helicases in PCR? Why is it better to use DNA than RNA primers? These first examples train students in "connective thinking". The concept of replication is applied but there are (logical!) variations.

"Connective thinking" should also be part of exams - especially to identify "hidden talents" among the students who are able to combine knowledge and may come up with innovative ideas.

Connections to other sub disciplines of biology are essential for molecular biology and should always be emphasized. How does *Thermococcus aquaticus* maintain double stranded DNA far above the melting temperature? Why does *Deinococcus radiodurans* survive doses of radiation that are lethal to other organisms? How are huge specific DNA sequences elements eliminated from the macronuclear genome of hypotrichous ciliates? These questions apply basic knowledge in molecular biology on general biological problems. They are somehow out of the context expected by the students and require to view biology as a complex system with many different aspects. The answers by students may not always be correct in respect to the actual facts but they may still show basic understanding and suggest solutions that could, in theory, be right.

Example for transfer and "out-of-context" question:
To determine biodiversity in a volcanic hot spring, water samples are taken and spread on an LB agar plate at room temperature. Individual colonies are examined by PCR using rDNA primers. After sequencing the results are compared to a microorganism data base to identify the isolated microorganisms.

The question seems to aim at PCR and sequence comparison. However, the mistake is in the cultivation procedure. Bioscience is not one dimensional - many things have to be taken into consideration when planning an experiment. Everything in this statement is right. Except that microorganisms from a hot spring are very unlikely to grow on LB plates at room temperature and that, in any case, most microorganisms cannot be cultivated in the laboratory at all

Once the answer is known, it appears very simple and obvious. The experience "why did I not come to this simple solution?" will leave a mark in the students' memories.

The next step is to stimulate students to come up with rational questions. For the example above, this would not be "why did I not find the solution?" but rather "why did I not even ask this question?". This can be trained in seminars, where papers are presented and discussed. Students have to prepare at least one question on the content of the paper and the question, not the answer is graded.

Hands-on Training and Independent Experimentation

Lab courses for students are usually well prepared and the experiments "give good results". This is a serious misconception. An experiment asks a question where there may be an expected result, but essentially the result is not known! What is mostly done in student courses, are reproductions of established experiments and this should be clearly distinguished from real experiments. In research, most initial experiments "fail" i.e. they do not give the expected answer, the method has to be adjusted, the question has to be reformulated or the entire hypothesis has to be changed. "Bad results" may lead us to new mechanisms and new theories. Research requires to "invent" experimental conditions and it requires to think: was the hypothesis wrong or was the experimental set-up not appropriate? At least in part, this concept can be taught in courses e.g.by running a gradient PCR to determine the optimal temperature or by running parallel PCRs with different Mg^{2+} concentrations.

Reproduction of established experiments is good and necessary in student courses. In many cases, however, a second misconception is propagated: all ingredients, buffers, chemicals etc. are readily set up and have been tested. In a real experiment, this is usually not the case (Fig. 1).

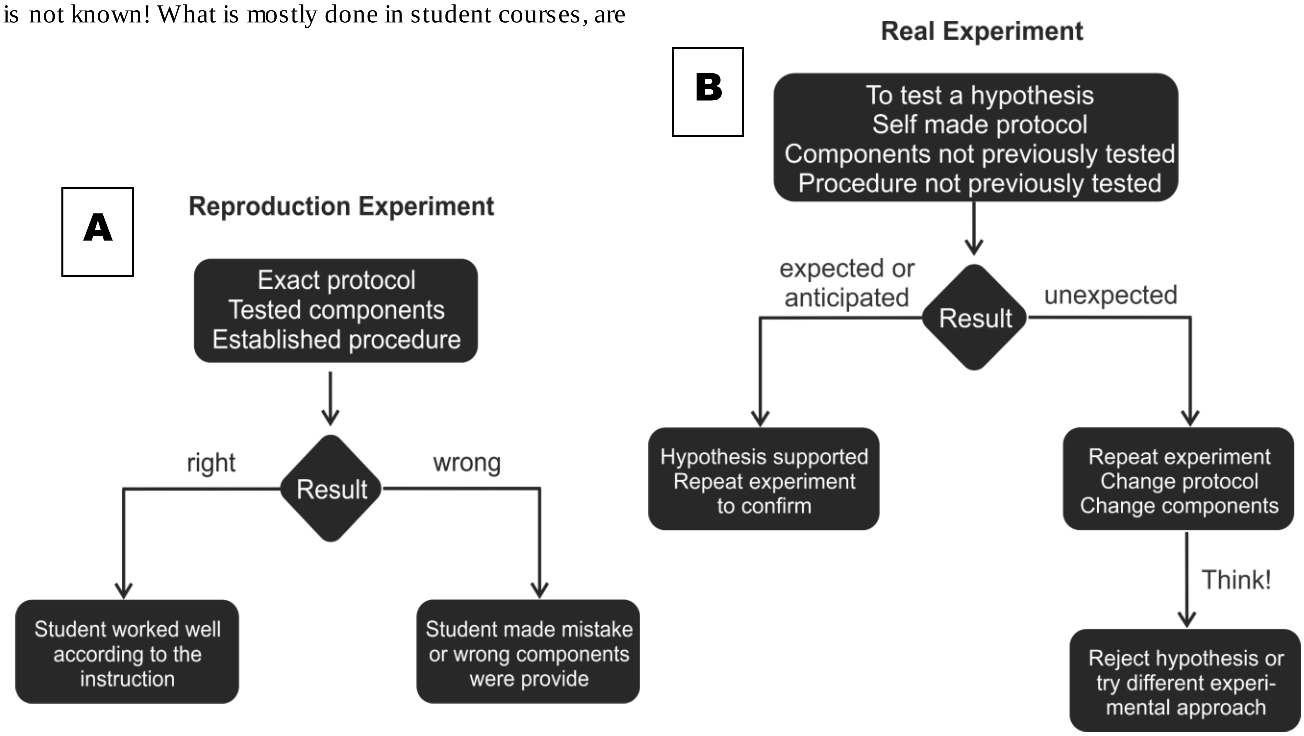

Figure 1. Experiments in student courses are usually reproduction experiments (a) to learn and get first experience with a method. It has to be explained very carefully that a real scientific experiment (b) is very different. A reproduction experiment only gets close to a "real" experiment, when the "wrong" results are obtained. If there is time in a student course to do trouble shooting, then the work becomes similar to a "real" experiment.

Demonstration experiments, where a lecturer performs an experiment and the students observe, may be quite entertaining. In terms of learning and combining theory and practice, they are not useful.

In regular undergraduate courses, learning-by-doing is difficult to establish. In Europe as well as in Indonesia there is insufficient investment in equipment, materials and especially in good tutors and lecturers. Universities are out-put oriented: the quantity of graduates counts, not the quality. A cruel, but realistic view: many students graduate in biology but never have the intention to work in this field. They have no serious interest in the subject. In experimental sciences, especially in biosciences, this is very expensive. Students do not only sit in lectures and seminars, they have to do lab work and use costly instruments as well as costly materials. In addition, less motivated students require more attention and supervision by tutors and lecturers. Consequently, this results in neglecting motivated students because they will "somehow" manage the course by themselves.

The (not ideal!) solution is to select the best students and specifically support them. The concept of Science Bridge (www.sciencebridge.net), now also established in Indonesia(https://sciencebridgeindonesia.wordpress.com/) does exactly that. Set up as a school and public laboratory, undergraduate and graduate students take over extracurricular responsibility to develop experiments and make them as simple as possible. However, the work is not simple at all. To adjust a genetic fingerprint or the expression of a recombinant protein for the high school or public level, requires detailed knowledge and understanding of the experiment. The tasks of the students include the adjustment of parameters, trouble shooting and even the "invention" of simple equipment. In addition, students learn the compilation of appropriate teaching material and science communication – a very important skill to make science transparent for the public (see below). Science Bridge activities are demanding and time consuming - this selects for motivated students who are willing to take a deeper look into science. At least in Germany the success is quite convincing: far above average, Science Bridge students receive prestigious stipends and become excellent teachers and researchers.

Science is like cooking: you can heat up an instant meal to fill your stomach or you can make experiments with lots of fine ingredients and specific ways of cooking, frying, baking, and simmering to get something new and fantastic! Not every student will become a four-star chef, but those who have the potential should be supported as much as possible.

Hands-on experience is the most important part of life science training. Understanding theory is absolutely required, but without lab work, theory is an empty shell!

Critical Reading of the Literature

More than in Europe, there is a strong belief in Indonesia that everything that is printed is true. The concept that scientific theories should always be challenged is not very well understood. Similarly, students (and many researchers!) are not really aware that the (preliminary!) answer to a scientific question immediately gives rise to the next question. Science is never complete!

The validity of methods and data as well as the validity of conclusions from experiments has to be challenged. This requires an understanding of methods, statistics, controls and data interpretation. There are several ways to teach these skills. The easiest way is to give examples for misinterpretation, e.g. the difference between correlation and causality.

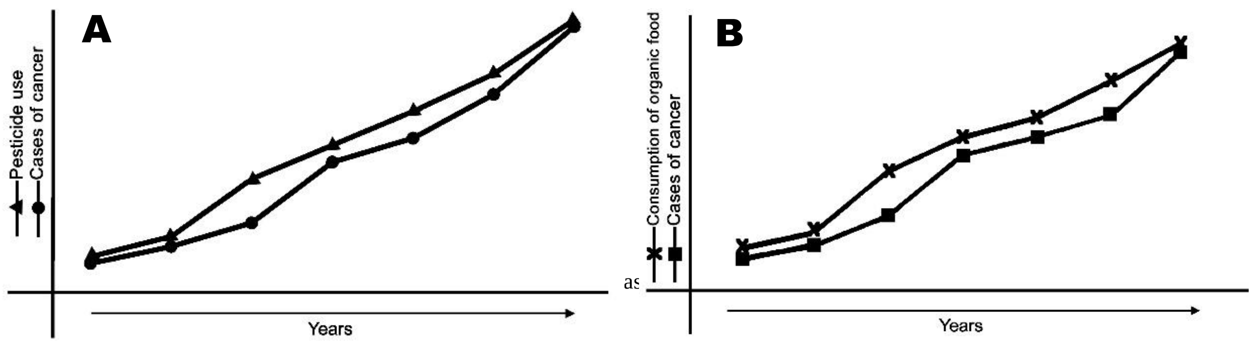

Figure 2. Graphs showing correlation between two variables. (a): application of pesticides in agriculture over a number of years is compared to observed cases of cancer. (b): in this graph the consumption of organic food is compared to observed cases of cancer. Both graphs are roughly redrawn from actual data. When shown alone, the left graph is mostly interpreted by students as a causal relationship between cancer and the use of pesticides. In contrast, there are immediate doubts about the right graph because it does not meet the expectations.

Intuitively, the first correlation (Fig. 2a) is considered causal while immediate doubts come up with the second graph (Fig. 2b). Both are correlations and may or may not give a clue to causal relationships. Based on correlations, a hypothesis can be developed and may be accepted or rejected by experiments.

The second approach, which is quite laborious, would be to write up a fictitious research paper with hidden mistakes (e.g. lack of controls, wrong statistics, wrong conclusions) and let the students find the mistakes.

Another, rather demanding task for students could be to examine papers that have been retracted for scientific reasons and let the students discuss why the science in these papers is not sound. Retracted papers can be found at http://retractionwatch.com/. One infamous example is the "Seralini Affair" (Seralini et al., 2014) https://en.wikipedia.org/wiki/S%C3%A9ralini_affair, page last modified on 2 February 2017, at 07:20). There are many publications and blogs discussing this paper and it is an excellent source for dissecting dubious science, biased data interpretation and inconsistent conclusions.

Science is moving fast and it is difficult to keep updated, even in a small specialized field. For textbooks in molecular biology, new editions are released about every five years. For lectures and seminars, at least some scientific literature not older than one year should be presented.

Reasonable Research Projects

The frequent misconception that research questions can be answered by simply "cooking" according to an established "recipe", often results in projects that are more difficult to carry out than initially anticipated. In theory, cloning a gene and expressing the protein in *E. coli* is simple routine – but only in a laboratory where this is done every day. Some DNA fragments "do not like" to be cloned, some *E. coli* strains "refuse" to take up a certain plasmid and some gene fusions are only functional with a C-terminal, but not with an N-terminal tag. Many of these problems are rapidly solved in a laboratory where five PhD students work with similar methods – and when they talk to each other! If not enough critical mass is available in one group, joint lab meetings with other groups are helpful for more rapid success. Joint lab meetings are also essential to teach an aspect of science which is neglected in Indonesia: collaboration! Most scientific papers in Europe and the US have many authors from different groups. Essentially, only collaborative projects with the combination of different expertise, have a chance to be published in a high ranking journal. Students and young scientists have to learn early on that collaborations increase their own knowledge and significantly advance their chances for a scientific career. What are reasonable research projects, starting out with a student project (see below), a BSc thesis and continuing with a MSc and PhD thesis

1. Is there a new question that has not yet been answered by others?
2. Are there (internationally) competitors who are addressing the same question and may be further advanced and have more scientific power?
3. Are the required methods available and established in the lab (to establish a new method may easily take half a year - even if it works routinely in a different lab!)
4. Is sufficient funding available to purchase the required chemicals and materials?
5. Are there contacts to other laboratories that may provide support or advice?
6. Last not least: has the literature been carefully screened for previous work on the question and for methods that may be useful?

If there are doubts on any of these questions, the project should be reconsidered!

The same questions have to be asked for student projects like e.g. the iGEM competition. It is brave to try and compete on the very high level of iGEM, but the chances for Indonesian students are miniscule. Opportunities are rather found outside the mainstream in smaller competitions and in scientific niches where competition is not as strong. It is even more demanding to define such projects that have a realistic chance to be successful. Most of all, good guidance by an experienced lecturer/researcher is required to maintain motivation and to avoid that such projects run into a frustrating dead end.

How to Achieve a Better Understanding of Bioscience?

To understand biosciences, we have to start out with simple things. One way could be to discuss with students what the outcome of a course should be, how to learn different topics and how to connect them. It would be interesting to do this discussion before and after the course to make students and lecturers aware of a change in perspective without and with basic knowledge. For first and second year students, more experienced, advanced students should serve as tutors, answer questions and provide examples from their own research projects. When tutors are carefully trained by the lecturers, they can more easily transfer knowledge and the enthusiasm for science -this includes frustration when an experiment failed as well as euphoria when an experiment was successful!

Tutors as well as lecturers can make mistakes. Mistakes are even found in textbooks (Fig. 3). It is very important that mistakes are admitted, correted and, if necessary discussed - this stimulates the attention of students and their critical learning.

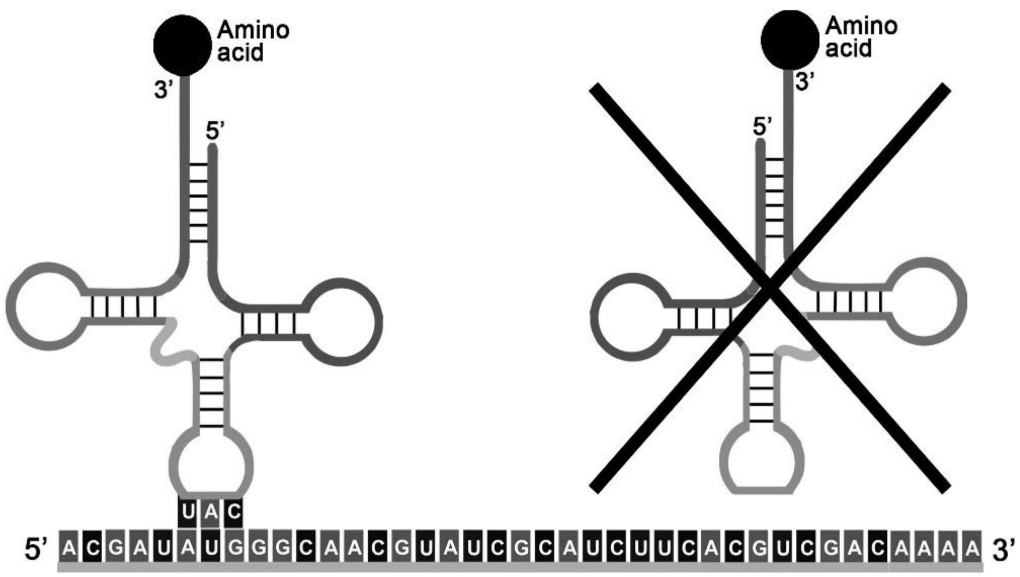

Figure 3. An mRNA is mostly depicted from left to right in 5' to 3' direction. Obviously, tRNAs have to be in the opposite orientation when they form hydrogen bonds to the mRNA codons (left). In graphs, the orientation of tRNAs is symbolised by the amino acid attached to the 3'-end. It is not so rare that textbooks show the wrong orientation (right). Especially good students who carefully read the material, will get confused if they do not have an experienced tutor they can ask and a lecturer who encourages them to ask.

Teaching may actually contain deliberate mistakes - with the subsequent question “what was wrong in the last five minutes?”. BioMedCentral has a series “What is wrong with this picture?” (https://www.biomedcentral.com/collections/wiwwtp). Examples from there can be taken e.g. for exams.

Science is everyday life. Unfortunately, students separate strictly between learning and “normal” life and most lecturers do not refer to current discussions and problems concerning biosciences. It is frustrating to see that in a class of 150 biology students at most 10 know when the Nobel Prize was awarded to a biologist. Lecturers do not discuss the pros and cons of the Nagoya Protocol and its impact on biodiversity research. Recently, a space mission returned and showed that algae and tardigrades (water-bears) survive the extreme conditions (temperature, radiation, vacuum) in space. Chicken flu and Zika, gene drive to eliminate malaria and dengue, the use of natural pesticides, invasive species that challenge ecosystems – almost every day a current topic from the news can be integrated into a lecture to demonstrate that the teaching contents are of general interest. There are many sites in social media that deal with current advances in molecular biology. “Belajar Biologi Moleculer” is an example for an Indonesian Facebook site where students, but also some faculty post recent papers. The newly established Facebook site “Science Bridge Indonesia” (bilingual) is similar but also reaches out to high school students. It is not always easy to initiate a discussion on these site but the statistics show that students read the page.

It is also essential to appeal to the responsibility of the students: they have the privilege to learn all these topics and they have the duty to explain to those who have not learned it. Students are the bioscience experts of the future - who else could it be?

Public Understanding of Science

In Europe, especially in Germany, the appreciation of science is deteriorating. This is exemplified by the political decision to ban all gene technology from agriculture. This was done despite of 25 years of state funded safety research with the conclusion that there was no additional risk in genetically modified plants. The legislation was explicitly not justified by scientific reasons but by a “feeling” in the population. Similarly, the campaign, especially in the US, against vaccination is dangerously successful. Science no longer counts. Public opinion is ruled by “fake news” and “alternative news”. These terms have become popular since the Trump presidency in the US, but the strategy of biased information has been successfully used in Europe for many years, leading to a continuous distrust in science. Bioscience has failed to explain its mission and its intentions to the public.

Indonesia can learn from this failure. The public interest in bioscience is still low, but it is high time that scientists improve their teaching at the universities, that they go out and explain science at the high schools and that they also approach the public to lay a foundation for science appreciation. Public understanding of science will determine the future of science and the advancement of Indonesia and the rest of the world! High schools are the source for future students and support by the public will improve the chances for funding and for a better quality of science for the benefit of the country.

The future of bioscience is probably in Asia. Indonesia has to act very soon in order not to be left behind competing nations like Malaysia, Vietnam and most of all China.

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