"Science is the basis for a better future and the bedrock of a knowledge-based society and a healthy economy". Máire Geoghegan-Quinn, European commissioner for research, Innovation and Science.

RRiGEM: Responsible Research and innovation and how it affects iGEM

1. Introduction. Responsible Research and Innovation: reinventing the rules.

The beginning: without research and innovation no science is possible.

Science is the set of knowledge systematically structured. This knowledge is obtained through the observation of regular patterns, from which questions are generated and hypotheses are constructed in order to deduce principles and general laws.

Science and technology are based on research and innovation, especially new emerging branches of science as synthetic biology, genomics or nanotechnologies. But, what do we understand by "research" and "innovation"?

Research is defined as a systematic investigation to establish facts in order to reach new conclusions. Research must be systematic and follow a series of steps and a rigid standard protocol. These rules are broadly similar but may vary slightly between the different fields of science. Scientific research must thus be organized and undergo planning, including performing literature reviews of past research and evaluating what questions need to be answered. Any type of 'real' research, whether scientific, economic or historical, requires some kind of interpretation and an opinion from the researcher. This opinion is the underlying principle, or question, that establishes the nature and type of experiment.

Innovation is a superior process or product, often the effective commercialization of an invention. It is based in the process of introducing new things and making changes in anything established to obtain solutions that meet new requirements. Innovation differs from invention in that innovation refers to the use of a better and, as a result, novel idea or method, whereas invention refers more directly to the creation of the idea or method itself. But also innovation differs from improvement in that innovation refers to the notion of doing something different rather than doing the same thing better.

From science to RRI.

Innovations are global in reach and potential. They are the source of considerable competitive advantages. The challenge of RRI is achieving a balance between innovation and growth with the need for effective, safe and appropriate products.

Responsible Research and Innovation means that societal actors work together during the whole research and innovation process in order to better align both the process and its outcomes with the values, needs and expectations for (in our case, European) society. RRI is an

ambitious challenge for the creation of a Research and Innovation policy driven by the needs of society and engaging all societal actors via inclusive participatory approaches. The Responsible Research and Innovation framework consists of 6 key pillars [1]:

- Engagement. One of the ideas encouraged by the concept RRI, even it can seem utopian and overoptimistic, is the mutual learning to develop joint solutions to societal problems.

- Gender Equity. Developed countries seem to have overcome gender differences; nevertheless research institutions need to keep a modern structure, particularly regarding their human resources management.

- Science education. To make change happen, education for future researchers is necessary; this might be achieved by launching creativity and encouraging children and youth towards maths, science and technology and, of course, creativity.

- Open Access. In order to be responsible, research and innovation must be both transparent and accessible for everybody. Nowadays scientific results are becoming underdeveloped due to the difficulty to access many publications and data due to their non-free online access.

- Ethics. Society is based on shared values, and that's why research and innovation must respect fundamental rights and legal aspects and display the highest ethical standards. However we all should try to discover if these standards suppose an advance or, if instead of that, they draw out high quality results.

- Governance. Policymakers have the responsibility to prevent harmful or unethical developments in research and innovation.

As a result of the European Commission for Research and Innovation, we get through [2] an understandable and accessible definition of "Responsible Research and Innovation" that allows a first approach of the public society to the meaning before initiating a deeper point of view:

"A transparent, interactive process by which societal actors and innovators become mutually responsive to each other with a view to the (ethical) acceptability, sustainability and societal desirability of the innovation process and its marketable products (in order to allow a proper embedding of scientific and technological advances in our society)". [3]

But, **how can RRI be applied?**

After this overview on the meaning of the term "Responsible Research and Innovation", some examples are usually cited [4] in order to achieve a better comprehension level:

- Research focus on social benefit. The Netherlands organization for health research and development created a long-term investment fund to encourage the launching of interdisciplinary projects that involve diverse fields as ethics, social science, law, economics, applied science and engineering.
- The NanoKommission forum. In order to contribute to the High-Tech Strategy, Germany established this Nanotechnologies forum, which main aim was to develop working and organizing recommendations for contributing to sustainable development by reducing negative impacts of new creations on the environment, on human health and on our limited resources.
- The UK EPSRC Nanomedicine public dialogue. Based on that report, the UK initiated a campaign to promote the searching of grand challenges trying to raise awareness and prioritize about the important role nanotech has on healthcare.
- The European Code of Conduct for Responsible Nanosciences and Nanotechnologies Research. In this guide, developed by the European Commission, a set of principles that should underpin research activities, interaction amongst key stakeholders and "good governance" for the responsible development of nanotechnologies are established.
- A new "Hippocratic Oath" for Scientists. The responsibilities of individual scientists have been discussed at various times by a large number of individuals and institutions. This concept of a statement of principles for individual scientist

But now we address some inevitable questions, when and why does the concept of RRI appear?

When did the concept appear?

The term "Responsible Research and Innovation" has increased its relevance during the last two years, in particular within the European Commission's Science in Society program, in the context of the Horizon 2020 Strategy, which aims are to strengthen the Union's excellence in research, to face global challenges jointly and to support the Union's external policies. [4]

Nevertheless, the term RRI sprang forth a decade ago (Hellstrom 2003; Guston 2004; Owen et al. 2009a; Owen and Goldberg 2010; von Schomberg 2011a,b; Lee 2012; Armstrong et al. 2012).

As an example of the strength of the RRI in the 2020 Horizon strategy, EC Deputy Head of Cabinet Waldemar Kutt gave a speech at the Euroscience Open Forum meeting, held last year in Dublin, which was entitled 'Can Responsible Research and Innovation expedite Europe's economic renewal?' During his presentation, Mr Kutt stressed the importance of economic growth, jobs and economic governance.[5]

Why RRI?

Experience has demonstrated that in every field of life people can always improve what is supposed *a priori* "un-improvable". In the frame of RRI, society can prove that we have all learnt the lessons of the past and use them to understand present challenges and prepare the ones to come. Some of the factors that lead to the growing interest in Responsible Research and Innovation are:

- To stimulate the employment of new technologies for social benefit. We should understand that these new technologies appear to face significant and urgent problems. Technologies are not useful *per se*, they are only useful if they are used in a useful way.
- To abstain from losing out technological advances. For example, the complete prohibition of genetically modified organisms has precluded people and environment from their patent benefits. Is this the example we want to follow with other emergent technologies?
- To forestall catastrophes as it could be the liberation of non-blessing genetically modified crops that could oust local farming.
- The dread among negative consequences. Evidence how difficult is to anticipate adverse results, manage them and change course when obstacles arise. [6]
- The loss of trust of societal actors among science and technology. RRI pretends the creation of a shared understanding of the correct behavior of the governments, or in other words, to involve all groups in thinking through the choices and the decisions that are made.
- Globalization and the need of race. Life is continually changing, and progress must be unstoppable, but it depends on individuals' wrong choices. RRI aims not to be an obstruction to innovation but an incentive for success; a responsible, sustainable and social success.

2. *A hierarchical analysis of the situation: Do we all follow the standard regulation? State of the art and working methodology.*

State of the art: RRI in Synthetic Biology and in the iGEM competition.

In order to understand the present situation of RRI in Synthetic Biology we have taken as our main reference the report by Conor M. Douglas [8] about ruling SynBio for recovering new health frontiers.

As commented above, the term RRI first appeared in 2003 with the passing of the US "21st Century Nanotechnology Research and Development Act". In a first step RRI pretended to identify and approach uncertainties and risks that appear when novel areas of research start their development, and this is the case of Synthetic Biology.

Synthetic Biology is characterized by its potential "usability"; nevertheless, it does not supplant classical techniques for preventing and treating illnesses and it can be best understood as a supporting framework of tools and techniques that can offer potentially outstanding contributions. For example, SynBio can be used to develop a new version of the antimalarial compound artemisinin, such as the famous achievement by Jay Keasling's lab [9]; it can also turn out to be a successful approach to develop novel and low-cost diagnostics and biosensors by engineering biological systems; it can be applied to produce and deliver antigens as oral ingested vaccines; or it can pave the way towards an innovative strategy to engineer safer, stronger and more nutritious crops [8].

Nevertheless, all the advantages that can be offered by this scientific discipline seem to disrupt established boundaries between scientific professionals and society governants. In order to understand what SynBio can offer to society and the way it can do it, it is necessary take into account a variety of forms through which it is organized, practiced and steered.

Douglas (2013) recently set out the discussion of the role of non-professional SynBio practitioners and global governance in shaping and governing SynBio. An example used by Zhang is the iGEM competition, in which, as she says, hundreds of student teams from all over the world come together to display their SynBio projects made up of BioBricks freely available from an open-source Registry of Standard Biological Parts. The "get and give" philosophy that characterizes this competition "is seen to have significantly promoted open-access culture", and by integrating "human-practices" they try to do an overview of social issues concerning biosafety, biosecurity, IP regimes and ethics. This is one of reasons why iGEM competition has provided such an important advance for the global development and governance of SynBio.

A relatively similar case is the Do-It-Yourself Biology (DIYbio) community, in which a "heterogeneous collection of students interested amateurs and/or "off-dutty" researchers constitute an open science and technology movement that aims to provide an increasing number of people the necessary skills to engineer biology, based on "de-skilling" approaches of SynBio"[8].

Even if both of these community movements are still developing, everything points out that they hold the potential to create and encourage more inclusive forms of governance that may offer novel ways to match SynBio to global needs. All this is in concordance to what we mentioned in the introduction: one of the aims of RRI is the need to incorporate societal skateholders in an interactive process with innovators.

Let's see now what iGEM can offer to RRI.

Going deeper into the iGEM contest we wanted to enhance how different teams from all over the world during this almost 10 years of competition have dealt with the six fundamental keys of RRI:

- Engagement. We think there is no doubt in this point: we, young students are struggling against time to achieve our research goals. Goals that in most of the cases are really ambitious, maybe so difficult to achieve that only young and mad minds dare to deal with them…

- Gender Equity. One of the characteristics that enhance iGEM is that it is fully integrated by heterogeneous student teams coming from different countries overcoming gender differences.

- Science education. What can be more educative than being stimulated to create your own project? The power of being free to take control of your ideas and develop them, that is science education and that is iGEM, a competition in which team work, understanding, sacrifice and, after that, satisfaction are a key "Standard Part".

- Open Access. This has been developed above, thanks to the Registry of Standard Biological Parts, iGEM is characterized by its capacity to provide all the information of every year projects to who needs it. However, there is still some controversy on the future status and owning of the Registry.

- Ethics. Every team taking part in this SynBio contest has the responsibility to complete general safety forms, in which they (we) accept to assume the reponsability of the work and the BioBricks involved in the project. Beyond that, most of the teams develop extra work, for example, arranging meetings in schools or cultural centers to try to bring science closer to society and trying to be assume a humble role in society.

- Governance. Maybe this issue is less obvious in iGEM. But if we consider that in, let's say, two decades, some of the current igemites may have responsabilities as biotechnology/SynBio researchers, stakeholders and policymakers, the impact of the competition on governance may not be negligible at all.

Reached this point, the relationship between RRI and iGEM is evident, but has any team specifically worked on it? The answer is no: nobody has specifically done the reflection we are actually doing with this report.

We have checked the work of the all past iGEM teams in their Human Practices projects and we have only found flashes of understanding, that is the reason why our team has faced this challenge with such enthusiasm and keenness.

In 2011, KU Leuven team did an important advance through what we would now call "Responsible Research and Innovation". They developed a complete work around self-governance and governance over SynBio and iGEM teams. They remarked the debate in which synthetic biology is involved with society and found it difficult to raise the awareness of those people who can only see the negative part of SynBio. (To know more, see: http://2011.igem.org/Team:KULeuven/Law&Patents)

Also that year, Paris Saclay team worked on the concept of "Open Source", and they organized debates to explain what it is. One can consider this as a first step to discuss one the fundamental pillars of RRI: open access. In science it should be similar, research processes carry risks as well as benefits. (To know more: http://2013.igem.org/Team:Paris_Saclay/Press)

RRI in Valencia Biocampus iGEM project: objectives and methodology.

Since our 2013 project started, Valencia Biocampus team decided to study the meaning of the term "Responsible Research and Innovation". After providing a general viewpoint, we broke up each important fundamental concept, we determined to go one step further: we were going to integrate into the whole project what RRI meant for us.

We committed to apply "Responsible Research and Innovation" from the first day of work to the last, so that, we would be able to show everyone the clarity and openness that characterizes what we have done.

What we pretended with this was to set in placxe an self-critical approach towards our own work. For example, we recorded at least once a week during all the summer a laboratory diary in which not only magnificent results were shown, but we did also show with humility our not achieved goals, failures and mistakes.

- **iGEM News**

Everyday our team members brought up to date the dry and wetlab work in the notebook wiki page in order to keep everyone informed and let anyone interest follow our project, step by step. Not satisfied with this, we filmed each important lab-event, as for example, when we obtained cells transformed with one of our BioBricks. In these videos we also explained why some experiments were difficult to perform and their progress day by day, which we think stands out the transparency that characterizes the different tasks we have performed.

- **Biosafety**

Safety issues are –or should be- one of the most important parts in each project. In order to improve the environmental and public protection, the organization has developed for the first time in the history of the competition a three level review process. (To know more see: http://2013.igem.org/Safety).

Valencia Biocampus team, concerned with that, completed the iGEM 2013 Basic Safety Form and submitted it to the iGEM European Biosafety Committee, but also, answered the four

questions that formed the biosafety part during previous editions, because we believe that those questions were also informative.

- **Ten tales on Synthetic Biology.**

We also consider part of this transparency work the book imagined by all us (ten students) and written and illustrated by three of us: "Ten tales on Synthetic Biology", in which five of our students, randomly chosen, gave a negative and catastrophic point of view of how the world could become if SynBio would be used maliciously; whereas the remaining five were assigned an optimistic -almost utopic- point of view. What we wanted to show with this is that, like everything in life, Synthetic Biology has its benefits but also its limitations, but these limits do not have to assume something negative, but on the contrary, are limits that through responsible research and innovation could become profits. This book is an exercise of self-criticism and –we hope- humility. There are no true conclusions there; only ten fiction visions, half of them positive and half negative, like a RRI version of "Dr Jeckyll and Mister Hyde".

But, how are research topics chosen?

In addition to a RRI approach on our Project, we wanted to find out how research topics are chosen by professional researcher. In order to do so, we performed an on-line inquiry to scientific "actors" from all around the world that are engaged in research in different branches of science. In these e-mails, sent to virtually hundreds of "corresponding authors", we asked a single, and simple question:

- Factors determining the choice of a new research topic. Pick from 1 to 6 the following factors, with 1 being the highest priority and 6 the lower mark.

Budget	
Scientific and personal curricular benefits it can bring	
Contribution to unscientific society	
Contribution to scientific society	
Environmental implications	
Interest or personal experience in the subject	

3. Results.

As commented above, thinking in science and thinking in what we believe it should be, we realized a really hard transparency work.

In addition to our wiki, we created a YouTube Channel, in which you will be able to see what we have done:

http://www.youtube.com/channel/UCvnn8shHH64omOF17Ei4H7w

To complete our safety work, we filled out, in addition to the Basic Safety Form, a second Biosafety Form in which we explain why one of our parts coming from *Xenorhabdus nematophila* is not dangerous for public safety.

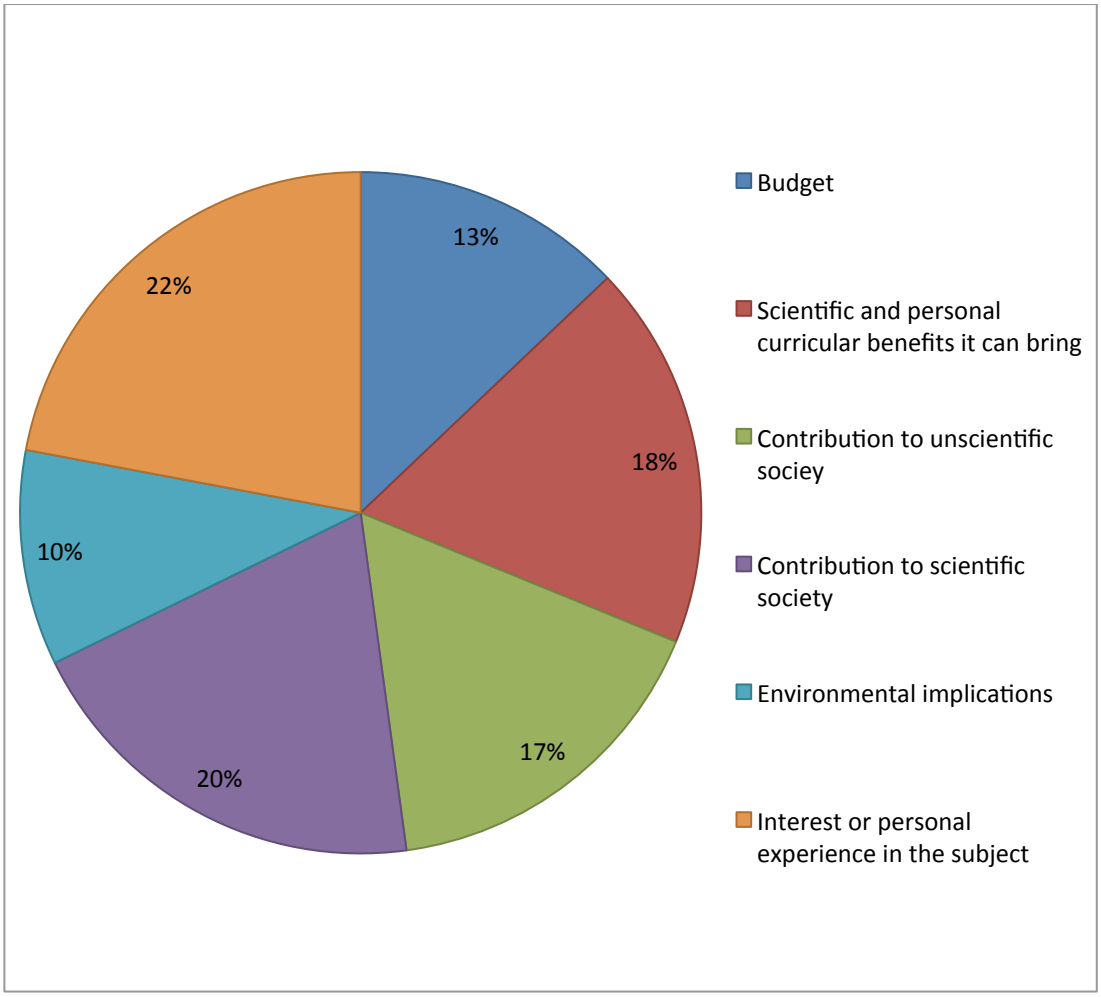
http://2013.igem.org/Team:Valencia_Biocampus/Safety

We are also glad to introduce our book "Ten Tales on Synthetic Biology" to society. Even if radical points of view may not correspond to a realistic view, we wanted to force us to keep on that opposite positions, and force ourselves to imagine five positive and optimistic stories about the benefits that SynBio can offer to society and five negative ones that contemplate that everything misused can be dangerous to society and environment. The tales were written by Samuel Miravet with the collaboration of Jessica de Loma and A. Corman illustrated the tales with drawings like these ones:

We contacted two important players in the Synthetic Biology debate: Robert Carlson, a synthetic biologist known for his book “Biology is Technology”; and Kathy Jo Wetter, a member of the ECT group, critical with the (mis)use of new technologies. We were very happy when they both agreed to write a preface for the optimistic and pessimistic parts of the book, respectively. Kathy Jo, for example, stated on our book “ I found the description of your initiative extremely interesting and creative. It's a great way for students to think about broader implications of technology in practice and about how technology assessment can move beyond a narrow consideration of health and safety risks.”

When we described our idea in the section above, we compared it with “Dr. Jeckyll and Mister Hyde”, a black-and-white vision on synthetic biology. In an exercise of humility, we only wrote what me imagined. Conclusions, not unlike R .L. Stevenson masterpiece, should be drawn by you, dear reader.

Beyond our project, we contacted hundreds of researchers worldwide with a survey on the main factor driving their research efforts. And these are the results obtained from the survey:



From the graphic we can deduce that:

- All factors have similar importance (10-22%) as “research boosters”
- The budget and the environmental implications are the options less appreciated when starting a research project.
- The possibility to contribute to scientific society is more important for researchers that the contribution to unscientific one.

4. General –and short- conclusions.

After considering all the advantages that RRI can provide to SynBio and vice versa, we have achieved the following conclusion. Science needs people in the same way in which people and societal actors need science. SynBio is a promising emerging branch of science in which different ethical, political and economical aspects should be taken into account to allow innovation without risks, trying to minimize negative consequences to overcome the loss of trust among science and technology. We should learn from past negative experiences, such as the GMOs (a commercial success and a disastrous in public image) and prepare better the way for SynBio for it to be what RRI wants any technology to be: a useful tool to improve our lives.

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