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Novel biotechnological approaches to produce biological compounds: challenges and opportunities for science communication

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Novel biotechnological approaches such as Metabolic Engineering (ME) and New Plant Breeding Techniques (NPBTs) are currently being developed to produce biological compounds for food and non-food products. NPBTs span a range of methods for in vivo production in crops, some of which are classified as GMOs while others aren't. Deploying such techniques will not only provide new opportunities for industry, but also challenges with respect to the regulatory environment. Similarly, the process of communicating these new techniques and their products to stakeholders and consumers will not be without its own challenges. We argue that scientists should engage more with non-scientists, either directly or through collaborators. These engagements should not only be about the science, we suggest, but also explicitly deal with real world ramifications, such as economic, environmental and social issues.

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Introduction

Biological compounds are molecules originally produced by living organisms, ranging from microbes, to plants and animals. They can be used as food additives (such as colorants and flavors), nutraceuticals (such as dietary supplements and functional foods), as well as pharmaceuticals (such as anti-inflammatory and anti-microbial compounds). Because of the combined effects of population growth, aging, climate change, natural disasters, and so on. The current agricultural capacity can hardly meet the growing demand for food and non-food products produced in traditional cultivation, and certainly not in a sustainable manner [1].

The first generation of genetic engineering (GE1.0) techniques (mainly by the use of recombinant DNA technology) have already been applied to engineer biosynthetic pathways in microbes and plants to produce for example Vitamin C [2], vanillin [3], or monoclonal antibodies-specific to Ebola [4••]. In terms of public perception it was shown that using GE1.0 to produce biological products for pharmaceuticals did not lead to very critical views or resistance [5–8]. However, when GE1.0 technology was used to produce food and feed or food additives, especially in Europe, these products were always controversial in public debate. Concerns raised impinged not only on technical issues (such as safety to humans, animals and the environment), but also covered ethics, patents, politics, transparency, and so on [9].

So while (bio)technological improvements in the production of biological compounds for food and non-food purposes are necessitated by global trends, there are many countries around the world where the public is rather critical towards biotechnological innovations, especially when it comes to food. How can this puzzle be solved in a democratic way?

One possible solution is to leave the partly stigmatized first generation of genetic engineering techniques and products behind and concentrate on the next generation that is GE2.0. This second generation represents ongoing improvements in the field of synthetic biology [10•]. Among them, metabolic engineering (ME) on microbial production systems and new plant breeding techniques (NPBTs) to develop new plant varieties are commonly applied to produce bioactive compounds for food and non-food purposes. ME (re)designs-specific biosynthetic pathways in new host cells in order to improve the production by broadening the substrate range and increasing yield and productivity. While ME has been available for several years [11], current synergies from systems and synthetic biology, as well as bioinformatics, have recently increased its potential [12,13]. For example, ME has been applied to enable *Escherichia coli* to produce polyphenol compounds that are normally only produced in plants such as berries and that can be used as food colorants or as candidates for anti-inflammatory, antioxidant, or antibiotic drugs [14••].

In most cases, NPBTs differ from the processes that generate genetically modified organisms (GMOs). The differences is significant, in fact, some of the plants

produced with NPBT are not legally classified as GMOs at all. At least eight NPBTs have been evaluated by the European Food Safety Authority (EFSA) [15,16]: Zn-finger nuclease (ZFN), oligonucleotide directed mutagenesis, cisgenesis and intragenesis, RNA-dependent DNA methylation, grafting, reverse breeding, agro-infiltration, and synthetic genomics. In addition, the rapid development of the gene (genome) editing tools such as Transcription Activator-Like Effector Nuclease (TALEN) and Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-Cas9, contributed significantly to the inventory list of NPBTs [17,18]. A handful of plants have been modified by NPBTs and made it to the market, such as CRISPR edited anti-browning mushrooms and soybeans with drought and salt tolerance [19•]. Furthermore, NPBTs can be used to convert plants into cell factories to produce bioactive compounds, for example, the newly granted European H2020 projects NEWCOTIANA (https://newcotiana.org) and CHIC (http://chicproject.eu) use NPBTs to convert tobacco and chicory to produce bioactive compounds for pharmaceuticals, cosmetics, and dietary fibre.

Apart from the technical feasibility and economic potential of these bioprocesses, the cultural aspects and other societal issues have to be taken into account. The stakeholders involved in GE2.0 are more diverse than in GE1.0. On top of industry, academia, and regulatory authorities, other stakeholders play decisive roles: consumer groups, small growers or indigenous resource suppliers, environmental/health advocacy groups, and so on.

With more stakeholders involved, (science) communication between them and with the public becomes more important. Based on past experiences with public perception of emerging technologies, it is apparent that comprehensive science communication is important for the responsible development and deployment of these techniques, as described in the responsible research and innovation (RRI) framework [10•,20••,21]. GE2.0 faces challenges as well as opportunities for science communication, while balancing the competing interests of different stakeholders.

Challenges for communicating ME and NPBT

Because of the sometimes counterintuitive regulations of biotech products, which are sometimes regulated by the product itself, sometimes by the process used to make it, or a combination of both [22], communication about these products/processes is not straightforward. Up to date, for biological compounds produced by ME, the regulation is relatively clear: they are regulated based on product category [23]. Take for example vanillin produced by ME yeast when using sugar as starting material. If the vanillin is used as food additive, the labelling of the compound is 'natural aroma' although it doesn't stem from the real vanilla plant, because it was not chemically synthesized [3,24,25]. For biological compounds produced by NPBTs, there are only a few governmental decisions regarding whether a product produced by NPBTs should or should not be declared a GMO (for more detail, see Table 1) [19•,26,27•,28]. The de-regulation on editing plants with CRISPR announced by the US Department of Agriculture in March 28th, 2018 have paved a way to market the products produced by NPBTs, or more specific, CRISPR edited plants for food and non-food applications (e.g. mushroom, maize and soybean) [19•]. The European Court of Justice (ECJ) went the other direction and classified CRISPR edited plants as GMOs [29], a decision that puzzled many plant scientists in Europe and led many to question the reasoning of this decision. Such ruling might hinder the NBPTs in Europe from research to investigation, while at the same time the proper enforcement of such ruling is in question [30]. There are two examples summing up very well the communication challenges in ME and NPBT: while vanillin produced by engineered yeast for food products is supposed to be 'natural', a plant with a single base modification in the genome that could have occurred naturally, is classified as a GMO.

Opportunities for science communication

The biggest communication opportunities with respect to ME and NPBTs arise when the technology can be deployed for the betterment of humankind and the planet, as defined by the United Nations sustainable development goals (UN-SDGs) [31]. While the first generation of GM-crops, for example, where hardly designed with sustainability goals in mind, a more responsible approach to innovation can hopefully steer ME and NPBTs in this, right, direction.

Examples that show this include: the successful production of semi-synthetic artemisinin (acid) serving as an alternative stable supply for anti-malaria drugs [32]; or current attempts to produce polyphenol compounds, known for their positive effects on health and longevity and normally found in berries, in cell factories, thus saving arable land [33]; or NPBTs that repurpose non-food plants like tobacco to produce cosmetics and pharmaceuticals. Communicating this potential may provide scientists a window of opportunity to restart a conversation with the public and all relevant stakeholders [31].

Engaging in a two-way communication

The real world success of novel techniques depends very much on the particular cultural, social and economic context and can be heavily influenced by public opinion [20••]. While scientists (and European regulators) tend to highlight mostly the techniques themselves, consumers are more interested in the final product [34•]. While the biological compounds for food and non-food applications produced via biosynthesis processes are available, it is