Using plant molecular farming to increase regional biomanufacturing capacity across the globe for fast, resilient and cost-efficient medicine supply

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Abstract

The COVID-19 pandemic was a wake-up call to improve our ability to counter novel infectious diseases and to handle global crises. Strengthening international cooperation and diversifying production capacity into manufacturing technologies that are less dependent on specialized staff skills, expensive infrastructure and access to costly licences can improve regional independence from global supply chains. Plant Molecular Farming (PMF) - the manufacturing of pharmaceuticals and diagnostics in plants - is one such diversifying option. PMF enables fast product development within weeks, is highly scalable to millions of doses, flexible and versatile, making the system attractive for emergency response applications. Investing in this technology is an investment in an emancipated and fair healthcare and supply infrastructure across the globe.

Outline of empirical facts and issues

Many pharmaceutical products are protein-based, for example subunit vaccines and antibodies for cancer therapy [1]. Most of these proteins are produced in bioreactor-based processes (i.e. microbial or mammalian cells) with the majority of the capacity installed in Europe (47 facilities, ~7500 m3, 47% global capacity) and North America (31 facilities, ~5400 m3, 34% global capacity) [1]. In contrast, the available capacity in Australia-Pacific, Africa and Middle-East is minute (9 facilities, ~700 m3, 4% global capacity).

As an alternative to bioreactor-based systems, plants can produce even the most complex proteins (e.g. fusion proteins etc.) in a functional and biologically active form [2]. Plant-derived products include monoclonal antibodies, vaccines, enzymes and enzyme scavengers, as well as decoy receptors. There is an increasing number of commercial developments in the production of plant-derived biologics, both for communicable and non-communicable diseases details are listed in [3]. The specific advantages of plant-derived products for the prevention and control of infectious diseases have been reflected in the time after COVID [4]. Unintended immunogenicity of plant-derived proteins due to differences in glycosylation are not considered an issue based on several clinical tests and the fact that plants providing a humanized glycosylation have been developed [5]. A current limitation however is the often-low product accumulation of <1 g kg-1 wet plant biomass [6]. This can be addressed through rational protein engineering, optimization of the genetic elements like promoters and host plant engineering [7].

Although mostly using closed systems such as vertical units, PMF technologies can rely on agri- or horticultural practices and infrastructure to a large extent [8] rendering the upstream process (i.e. the plant cultivation) highly scalable and economically reasonable [9]. Various pilot scale and commercial facilities exist to demonstrate the functionality and viability of the approach [8, 10–12]. These are located, for example, in Canada, Germany, South Africa, Thailand, the United Kingdom and the USA. Challenges in terms of downstream processing (i.e. product extraction and purification) can be resolved with technologies established for food processing [13] and to a large fraction by using the same equipment as conventional bioprocesses (e.g. chromatography) in the pharmaceutical industry [14]. A typical team to operate a PMF process will therefore include a small number of biotechnologists/-engineers as well as several gardeners or farmers. Whereas the latter is a hurdle for existing pharmaceutical companies because their employees typically do not cover the latter skill set, this can facilitate capacity building in rural regions where large fraction of the population is often active in the agri- or horticultural sector and thus familiar with the necessary techniques. To our knowledge, such activities have not been initiated for plant molecular farming yet.

The production costs associated with PMF can be very low (~1 € kg-1 biomass) because agricultural practices and simple fertilizer instead of complex cell culture media (costs >100 € L-1) and bioreactors can be used [15]. Downstream costs are similar to existing bioprocesses [16]. Competitiveness of PMF products with conventional counterparts has previously been shown for antibodies and difficult-to-produce proteins [17, 18] (Figure 1).

The legal situation has several aspects. On one hand, initial patents covering high-performance promoters (to achieve high product yield) have expired or are about to expire shortly, providing substantial freedom to operate without the need for costly licences [19]. Even if several genetic engineering tools are still patent-protected, the conventional methods like restriction enzyme-based cloning suffice for screening and the generation of transgenic plants [20]. Along that line, open-innovation and technology transfer projects have been initiated to exploit the technology where it has a substantial leverage (i.e. provides access to high quality medicines at low cost in LMICs) [10].

On the other hand, many countries in North America and the European Union have established a legal framework for the assessment and approval of PMF products for pharmaceutical applications in the 2010s, which provides the necessary legal reliability for any commercial activities. In contrast, countries in the global South (e.g. Brazil, South Africa, Thailand) have substantial potential for building PMF capacity, yet in part lack regulatory harmonization with major pharmaceutical markets.

Importantly, PMF does not rely on open-field cultivation, which may compete with food and feed production. Instead, simple yet efficient vertical farming concepts can be exploited that facilitate local production even in arid zones. In fact, such zones often bolster vertical farming as sunlight and thus energy is available at large. Because vertical farms are a closed system, water consumption is minimal and fertilizers can easily be recycled. Lastly, any residual biomass can be subjected to thermal (e.g. biogas) or material recycling (e.g. insulation materials) [21].

Currently, a major hurdle to the implementation in biopharmaceutical industry and in the context of emergency responses is the lack of a combination of existing agricultural, horticultural and pharmaceutical infrastructure and expertise, which differs substantially from that established in pharmaceutical companies, that is: such companies typically do not have plant cultivation facilities and the corresponding staff.

Large research initiatives within the EU Horizon program (PharmaPlanta, Pharma-Factory, etc) have contributed significantly to the development of the technology and have always included strong international collaboration networks consisting of SMEs and research partners from the global South. We suggest to strengthen and expand the network of academic institutions and (partially locally funded) companies where the former can provide the relevant knowledge and technology whereas the latter are responsible for de-centralized capacity building. Through such public-private partnerships, economically disadvantaged countries, especially low- and middle-income countries (LMICs) can gain access to biopharmaceutical manufacturing capacity for emergency response activities.

Policy recommendations

We recommend to initiate a set of equal partnership networks between academic institutions and companies active in PMF or those wishing to participate in the topic to:

- **i)** build regional, qualified production capacity for PMF (i.e. plant cultivation facilities, downstream equipment) especially in LMICs where access to high-quality medicines and vaccines is urgently needed
- **ii)** set up global training networks (which can contain regional branches to accommodate specific needs) to educate a new generation of skilled people who can operate the PMF production facilities
- **iii)** establish global standards for PMF (e.g. modular production systems, compatible expression vectors)

In terms of the latter, flexible regulations as implemented in the USA could be used as a template for regulatory standards.

In terms of the manufacturing technology itself, funding a global workgroup to establish standards would be a very useful and rewarding activity. Here, stakeholders from both hemispheres including the PMF hubs in Brazil, Europe, Japan, North America, South Africa, South Korea and Thailand, could establish a common ground as it has been done in the last decades for conventional manufacturing systems by the pharmaceutical industry.

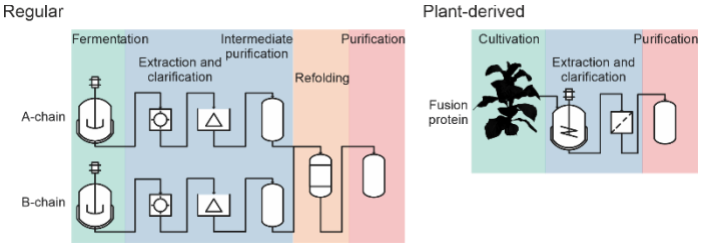
Specifically, existing small-scale facilities, start-up companies or academic institutions, especially in the global south, can be used as nuclei to establish regional PMF hubs that form a global network of distributed production capacity. For example, lively PMF communities and hubs exist in Cuba, South Africa and Thailand. It will be important to facilitate a technology transfer and open innovation collaboration among these hubs as well as the established PMF development and manufacturing sites in the Northern hemisphere. Specifically, bioprocess engineering and modelling tools can be exchanged and improved.

The important role of international cooperation for jointly developing plant-based biomanufacturing infra-

structure, closely accompanied by collaborations for education and training of skilled people, has been emphasized during the Science Summit at UNGA77 and at the Africa-Europe Science and Innovation Forum 2023. The current initiatives and networks include, for example, the European Plant Science Organisation (EPSO), providing monthly seminars (e.g. on process development and product approval, scheduled for June 2024; https://epsoweb.org/events/) or the satellite meetings and workshops hosted by the International Society for Plant Molecular Farming (ISPMF; https://www.ispmf.org/events). Providing these and similar organizations with mid to long term funding (e.g. to be used as travel bursaries for attendees from LMICs) can help to develop them in a sustainable way.

Overall, the potential of PMF has already been recognized in a Science Session on Pandemic Preparedness at UNGA78. PMF has been recommended as an additional biomanufacturing approach for reducing global inequalities in the accessibility and affordability of medicines and for improving regional independence from global supply chains, in particular in LMICs.

Figure 1. Comparison of conventional, bioreactor-based recombinant protein manufacturing (left panel) and plant-based production of a difficult-to-produce protein. Modified from [17] with permission.



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