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A quantitative key-opinion-leader analysis of innovation barriers in probiotic research and development: Valorisation and improving the tech transfer cycle

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ABSTRACT

The field of probiotics has great innovative potential, addressing several unmet medical needs. However, despite mounting evidence and opportunities in the field, relatively few strains are commercially available and probiotics are seldom in routine use in clinical practice. Innovation in the field of probiotics seems hampered. Using the barrier approach, this study identified the main barriers in the probiotic innovation process, as experienced by key-opinion-leaders (KOLs). These innovation barriers are visualised and their underlying causes revealed by means of qualitative root cause analysis. The root causes were placed in an academic-industrial valorisation cycle. Furthermore, a quantitative ranking of the barriers was used to demonstrate their relative importance. This study demonstrates that the probiotic research cycle is faulty due to specific barriers and bypasses, and that innovation is hampered in all domains of the valorisation cycle. Eleven main barriers were identified, with "difficulty in demonstrating clinical efficacy" being the most significant inhibiting factor. Other barriers could be classified as fundamental research barriers, clinical research barriers, financial barriers, regulatory barriers, collaboration barriers, marketing barriers and product barriers. Using this barrier approach, inhibiting factors are identified which allows subsequent action to be taken to re-establish the natural cycle of innovation.

1. Introduction

Due to advances in the NIH Human Microbiome Project, there is an increased understanding in how the microbiome affects human health, and in specific the association between dysbiosis and disease. Modulation of gut dysbiosis by probiotics seems promising. Probiotics are defined as 'live microorganisms that, when administered in adequate amounts, confer a health benefit on the host' [1]. Currently, there is an increasing scientific as well as a commercial interest in probiotics. The word "probiotics" alone gave >12,000 hits on PubMed (including MEDLINE), of which 766 are published in this year (July 2015). As for the commercial interest, the global probiotic market is estimated at $15 billion dollar [2], with an estimated annual growth of 7% [3].

There are indications that probiotics can be beneficial in a wide range of clinical conditions as well as for maintaining health [4]. There is consensus that probiotics in general can enhance colonization resistance, produce acid and short-chain fatty acids, regulate the intestinal transit, normalize the perturbed microbiota, increase turnover of enterocytes and exclude pathogens by competition; whereas neurological, endocrine and immunological effects can be observed in specific strains [1]. Specific probiotic strains already demonstrated a strong positive outcome in literature for certain clinical conditions [5]. This concerns diarrhoea such as antibiotic-associated diarrhoea (AAD) and infectious diarrhoea, inflammatory bowel disease (IBD; prevention and remission of pouchitis and remission maintenance of ulcerative colitis; UC) and prevention and treatment of allergy [5]. When focusing on specific target populations, evidence for probiotics in infants is strongest for necrotizing enterocolitis (NEC). In children, evidence is best substantiated for acute infectious diarrhoea, AAD and lactose maldigestion. The same holds true for AAD and maldigestion in adults and elderly, in addition to pouchitis [4]. Other potential targets for probiotics, which have

Abbreviations: AAD, antibiotic-associated diarrhoea; AD, atopic dermatitis; CMC, chemistry; CT, clinical trial; EFSA, European food safety authority; GIT, gastrointestinal tract; GRAS, generally recognized as safe; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IND, investigational new drug; KOL, key-opinion-leader; MD, medical doctor; NEC, necrotizing enterocolitis; QPS, qualified presumption of safety; R&D, research & development; UC, ulcerative colitis.

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shown effect to some degree are colic, irritable bowel syndrome (IBS) symptoms, common infectious diseases, atopic dermatitis (AD), growth parameters of malnourished children, UC, travellers' diarrhoea and vaginal infections [4].

Innovation is essential in a highly complex and dynamic environment such as the health industry [6]. Innovation can be defined as "the intentional introduction and application within a role, group, or organization, of ideas, processes, products or procedures, new to the relevant unit of adoption, designed to significantly benefit the individual, the group, or wider society" [7,8]. Especially in the probiotic industry, there is great innovative potential, since probiotics may address several unmet medical needs for which alternative therapies are lacking. For instance, a reduction in the duration of diarrhoea (by approximately one day [9]) or the prevention of NEC in preterm low-birth-weight infants can be achieved by probiotic administration [10].

Despite piling evidence and opportunities in the field of probiotics, relatively few strains are commercially available and probiotics are seldom in routine use in clinical practice. The European Food Safety Authority (EFSA) has rejected all health claims on the benefits of probiotic bacteria, even claims supported by solid scientific evidence [11]. In addition, the label "probiotics" by itself is no longer allowed by EFSA on products containing probiotic strains [12]. Whether these rejections are valid or not, innovation in the field of probiotics seems significantly hampered.

One way to approach innovation deficiencies is by focusing on the main barriers in the innovation process. By understanding the nature, origin and relative importance of innovation barriers, deeper insight is gained in the impact of the barrier on the innovation process. The understanding of barriers can aid in the process of overcoming them and thereby encourage an environment that supports innovation [13]. Using the barrier approach, inhibiting factors and their effects can be identified and subsequently action can be taken to eliminate them, re-establishing the natural cycle of innovation [14,15].

Barriers are factors that negatively influence the innovation process, and prevent commercial utilization of the innovation [13]. A differentiation can be made between external and internal barriers. External barriers include e.g., lack of fundamental knowledge, finance, customer demands and regulation. Internal barriers include for instance a lack of internal funds, technical expertise and human related barriers [14]. As external and internal barriers can be applicable cross-industry, both are taken into account in this study.

It is essential to identify the point of impact of barriers in the innovation process and to analyse their effects or consequences. The Valorization & Technology Transfer Cycle by Pronker (2013) provides a more holistic overview of the innovation process [16]. Adapted to this research, the Valorization Cycle is subdivided into four segments (Fig. 1). The first segment is fundamental (curiosity-driven) research, where an idea is realized into a patent or publication through empirical evaluation. After realization of an idea, there is a transition into the clinical and business development segment. Successfully going through the steps of proof-of-concept, evaluation (clinical, legislature and quality) and industrial upscaling will lead to market introduction and customer feedback. In the final segment of society the unmet need articulation takes place which feeds back into research. All steps in the Valorization Cycle are important for the innovation process and barriers might act on one or more points in the Valorization Cycle [16].

1.1. Research objective

To our best knowledge, there is no literature on innovation and potential barriers in the field of probiotics. This research aims to identify the main barriers, as experienced by KOLs in the probiotic innovation process, and visualize these innovation barriers and their underlying causes by means of qualitative root cause analysis.

Although the Valorization Cycle offers a clear guideline for linking unmet needs to the academic response repertoire and into prototyping for the market, further granularity is needed to plot individual barriers in such a way that defined actions and priorities become visible. For this reason we extended the Valorisation & Technology Transfer Cycle (Fig. 2) which was developed for vaccine

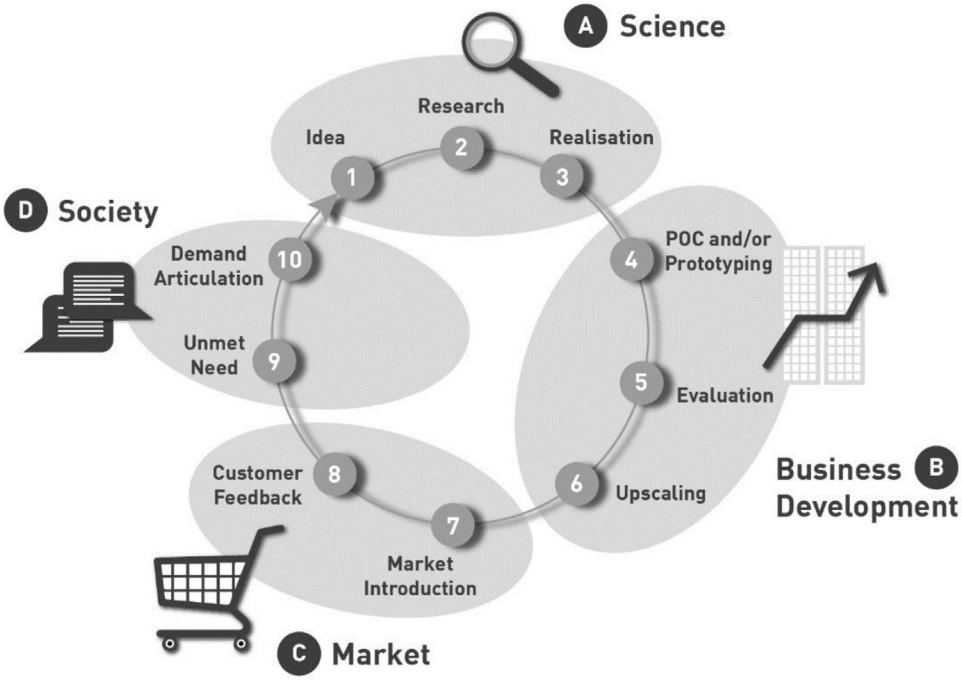

Fig. 1. The Valorisation Cycle showing the academic, industrial, market and societal domains where barriers in technology transfer may occur, adapted from Claassen [17].