Agri Articles
(e-Magazine for Agricultural Articles)
Volume: 02, Issue: 01 (JAN-FEB, 2022)
Available online at http://www.agriarticles.com
©Agri Articles, ISSN: 2582-9882

Recent Advances in Synthetic Biology using Engineered Bacteria for Diagnostic and Therapeutic Applications

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Bacteria are key elements for human health. Two evidences support this notion, the existence of a stably population of microbes, termed microbiota, in healthy individuals and the number of health disorders associated to axenic (germ-free) animals (Sekirov et al., 2010).The development of efficient DNA technologies for manipulation of microbial genomes and the increasing knowledge of the molecular basis of diseases are allowing the engineering of tailored bacteria for the treatment of human disorders. Bacteria can be altered to produce a continuous and inexpensive supply of heterologous molecules of biomedical interest, such as human hormones, interleukins (ILs) and antibodies (Abs) within specific organs or tissues. The controlled in situ delivery of biologics (e.g. enzymes, cytokines, and antibodies) by engineered bacteria of our micro biome will allow the sustainable production of these complex and expensive drugs locally in the human body, overcoming many of the technical and economical barriers currently associated with the global use of these potent medicines. Engineered bacteria can be effective treatments against multiple pathologies, including autoimmune and inflammatory diseases, metabolic disorders, diabetes, obesity, infectious diseases and cancer, hence contributing to achieve the Global Sustainable Goal : ensure healthy lives and promote well-being for all at all ages.The continued development of tools for engineering more species, alongside data describing their natural physiological attributes, therefore remains an important area for research. Although the use of bacteria as therapeutics dates back more than a century, the synthetic biology are making the clinical use of genetically engineered bacteria as ‘smart’ therapeutics and diagnostics a tangible reality. Bacteria interact intimately with their niche in the human body, respond to a range of diseases and are well tuned by evolution towards detecting and producing physiological levels of biomolecules of interest. It is the combination of these features with the abilities of living systems, such as chemotaxis and biomolecule secretion, that could allow engineered bacterial systems to one day outperform traditional diagnostics and therapeutics. Applications of bacteria as engineered therapeutics have targeted diseases as disparate as diabetes mellitus, inflammatory bowel disease, HIV infection and cancer. The bacteria engineered to deliver therapies that otherwise degrade in the stomach or bloodstream, to achieve effective treatment with reduced systemic drug exposure, to activate the immune system in novel ways, including DNA-based and protein-based vaccination (Steidler et al., 1998**)**, and to record transient signals, such as reactive inflammatory metabolites, for noninvasive testing. Despite this sky is the-limit potential, the number of engineered therapeutic bacteria that are

tested in clinical trials remains limited. It is thus timely to pause and reassess whether our approaches to preclinical development are sufficient to make good on the promise of engineered bacteria. This is particularly pertinent given the speed of technological development, including an ever-increasing ability to rapidly engineer bacterial strains, which outpaces the ability to test those (Nielsen et al., 2016**)**. Therefore, it would be highly desirable to establish strategies for evaluating promising technologies for their likelihood of future success in early phases of development. The recent examples of engineered bacteria that have been preclinicallyor clinically tested and technological advances that will allow the development of more complex, safe and successful clinical applications. Presently focus on recent examples of rational gain of function genetic engineering and examples that have been tested in complex environments. To also propose areas that deserve particular attention when assessing preclinical engineered bacteria, particularly more rigorous testing and modeling of thresholds for successful therapeutic delivery and robustness of engineered functions when delivered to patients.

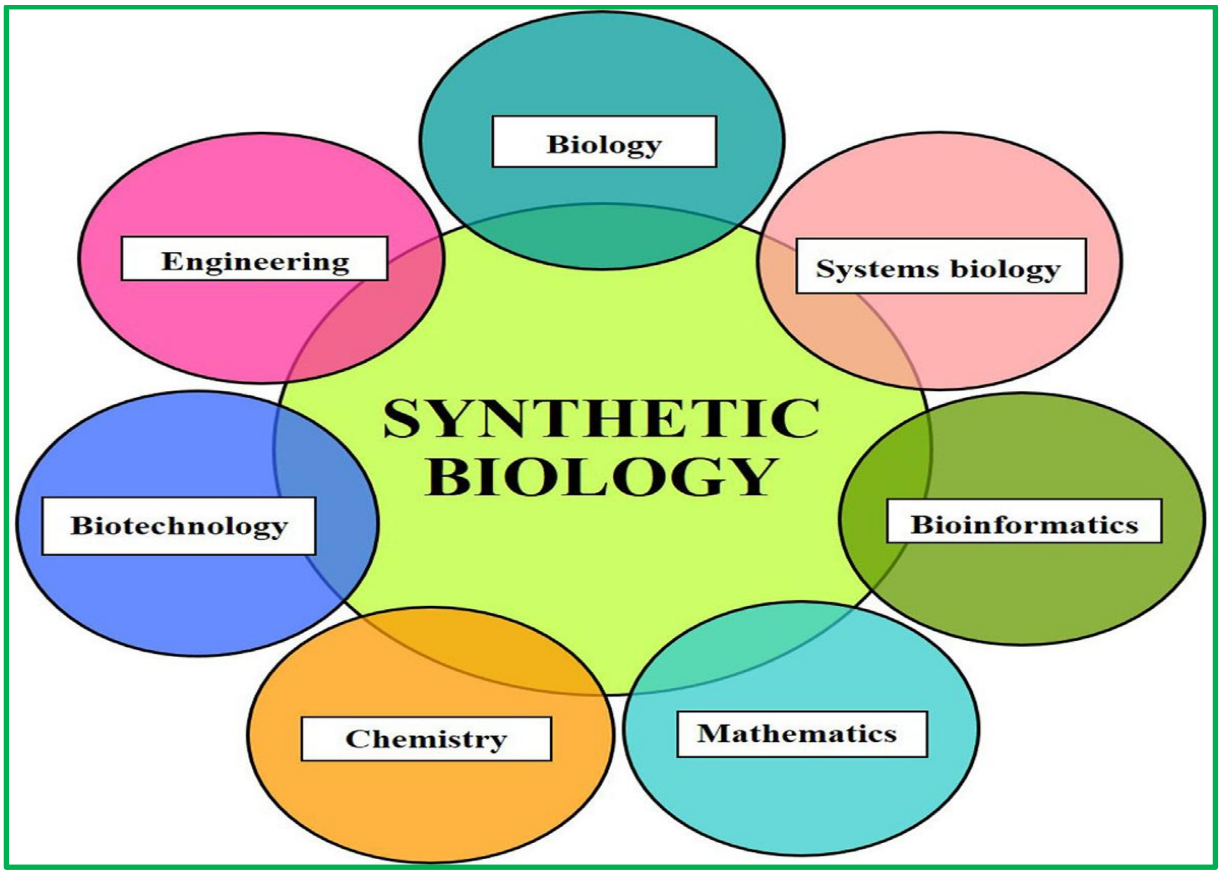

Fig. Synthetic Biology : A Multidisciplinary Approach

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