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Mini Review

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Microbial Cell Therapeutics

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Abstract

Some of the microbial groups can be helpful as symbiotic involvement in several biological processes. Recent active research reveals the development of microbial cells, secretome and their products to treat diseases and for enhancement of human well-being. The advancement in technological tools of microbiology, engineering and molecular biology have paved the way to use living microbial cells as therapeutics. In this review, we covered the various view-points on development of these microbial cells as therapeutics in terms of clinical, effective drug-delivery vehicle, manufacturing, translational and regulatory aspects.

Keywords: Microbial Therapeutics; Drug-Delivery Vehicle; Manufacturing Advantages

Introduction

Unlocking the therapeutics potential of microbial cell therapy has created excitement among clinicians and health care professionals for new developments towards translational research. The diverse, microbial ecosystem community of species in the gut results in proper function and resistance to disease. On the other hand, low species ecosystem leads to functional disability and disease susceptibility and thus bringing the imbalance in the gut microbial system. This dysbiosis reduces intestinal permeability in chronic liver diseases compared to controls [1]. The intestinal microbiota transplant (IMT) has shown reduction in the inflammation without immunosuppression in ulcerative colitis [2]. The microbial ecosystem therapy (MET) re-introduces the suitable microbiota balance to resume functionality. The MET utilizes the entire microbial community to maintain or restore the health. On the other hand, there are several emerging organizations focusing on small molecule drugs that interact or alter host microbiome as targeted microbiome therapeutics [3].

Drug Delivery Vehicle

The conventional drug delivery system is prone to result in cytotoxicity, adverse drug reaction and microbial resistance. Therapeutic microbes like Lactococcus Lactis can be used as drug delivery vehicle because they have prolific characteristics like proliferation, auto-therapeutic production, delivery at targeted site, penetration into tumor cells, and enhancement of immunity. The engineered recombinant L. lactis cells are under investigation of phase-1 clinical trials for auto-immune diseases including IBD [4]. Further, endogenous CRISPR-Cas systems (gene editing tools) enables the genetically un-manageable species *L. crispatus* for mucosal vaccine delivery, probiotic enhancement and are amicable for bio-therapeutic engineering [5].

Anti-cancerous agent

Most bacterial toxins destroy tumors and interfere or alter cellular and differentiation process [6]. The natural non-pathogenic bacterial species or their toxins serve as a potential anti-tumor agents. Diptheria toxin (DT) and pseudomonas exotoxins inhibit protein synthesis and some of these toxins attach specifically to cancer cells, thereby eliciting immune reactions. Various types of DT are under investigations to target cancer cells [7].

Simple scalable manufacturing process

Microbial therapeutics is evolving as a cost-effective tools in therapeutics. The well evolved technologies of bio-pharmaceuticals

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can be easily adopted for the growth in the production as well as quality related translations [8]. The microbial therapeutic manufacturing process is already available as scalable bioprocess technologies, starting from microbial cell sourcing to finished products (Table 1). The microbial cell storage can be cryopreserved or lyophilized [9] and this enables to laydown cost effective master or working cell bank system as well as finished cell product delivery to end-user. These microbial therapeutics can overcome some of the critical process challenges of current human cell therapy. (Eg. costlier cold chain management as it includes bi-directional liquid nitrogen based dry-shipper); whereas the microbial cell therapeutic banks generation is simpler and cost effective and scalable process. Overall, microbial therapeutics will make affordable, reachable and user friendly process and product.

SL	Steps/Process elements	Microbial cell therapeutics (MCT)	Human cell therapeutics (HCT)
1	Cell sourcing	Simple, feasible, screenable, advanced strain selection strategies	Complex, exists ethical concerns, Cell selection and screening technologies are in the nascent stage of development.
2	Isolation	Validated procedures exists	Limited isolation procedures and requires optimization to get enriched purified population of cells
3	Cell banking	Master cell bank (MCB), Working cell bank (WCB) can be maintained in glycerol stocks at -70^{0}C	Liquid nitrogen storage like Dewar are needed for storage of MCB and WCB
4	Stability	Available validated stability programme and can be easily adoptable	Requires extensive stability studies and standardization of cryopreservation media
5	Scalability	Available extensive scale-up technologies ranging from stirred tank bioreactor to single use bioreactor upto 100L. Suspended cultures can be easily harvested as well.	Available scale-out technologies and are limited to cell factories or cell stacks. Most of HCT are adherent cultures and requires cell detachment steps like Trypsinization etc.
6	Cell growth media	Cost-effective media and high density culturing are emerging to maximise productivity	Complex media and contributes around 60-65% of overall cost of production process.
7	Upstream and bioprocess technologies	Most of the microbial culture are feasible to adopt biophrma's upstream and bioprocess technologies to control the growth and monitor major physiological parameters like pH, and partial dissolved oxygen (DO).	Research is "ON" for controllable, measurable bioprocess techniques during scalability and growth of cells.
8	Cold chain management studies	MCT can be easily shipped through 2 to 8^{0}C or through dry ice; Frozen in vials.	Mostly HCT can be frozen in cryobags and preferable shipping methodologies involves dry-shipper and it is a directional transport system involving dual cost of Capex of dry shipper, transportation cost; intermediate liquid nitrogen addition to dry-shipper during long duration shipping.
9	Pre-infusion activity	MCT can be frozen as DMSO free and as glycerol stocks for most cell types. Hence require minimal or no to less pre-infusion or transplantation activity.	Most of the HCT cryopreservation media involves DMSO based medium, which requires pre-infusion processing area like aseptic or LAFU or biological safety cabinet, centrifuge and cell counting machine at each clinical trial site or hospital; dilution are re-adjusted to desired therapeutic dose and involves more manual processing and interferences.
10	Regulations	MCT of upstream and bioprocess of critical to quality parameters are measurable or quantifiable; Typical bio-pharma procedures are easily applicable, which leads to generation of master validation dossier; governing regulatory friendly process	Newly evolving regulation- Ethical concerns are to be integrated in streamlining the regulatory procedures.

Table 1: Critical and differential technical, process and regulatory parameters between microbial cell therapeutics and human cell therapeutics.

Harness effective translational towards commercialization

Facility design and approval for microbial cell therapeutics manufacturing, are important aspects to reduce the cost pressure, time to market and regulatory surprise adornment policy. The layout and facility of microbial therapeutics would be similar to traditional biopharma. On the other hand, cell therapy guidelines are available to ensure the optimal manufacturing infrastructure [10]. Hence the road-map for facility design and approvals may not be a major hurdle for clinical or commercial translations.

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Adoptable regulatory compliances

There is no ethical concerns on usage of microbes as therapeutics compared human cell therapeutics [11]. Moreover, the most of the measurable process or quality parameters for manufacturing process, in-process quality controls, cell harvesting, storage, transportation and specification for release criteria can be easily adopted from microbial fermentation or bioprocess of bio-pharma industries. These measurable and scalable process variables enhance the solid foundation for master validation record as one of the critical regulatory dossier, which will help in surging towards fast-track regulatory clearances.

Figure 1: Outlook of microbial cell therapeutics. Central green circle represents new evolving and innovative field of microbial cell therapeutics and their sub-divisions in outer circles. Core advantage of MCT are adoptability, scalability and reachability are representing at each corner of triangle.

Conclusion

Microbial therapeutics offers clinical treatment strategies through the secretion of therapeutic biomolecules as well as delivering the selected microbial strain or as microbiota compositions (Figure.1). Primary safety requirements need to be demonstrated in major pre-clinical trials involving two species. Although, the efficacy and formulation of microbial therapeutics like drug-secreting microbes or microbiome-modulating bacteria is quite new area and requires extensive studies to address the deliverable challenges. Relevant understanding and addressing the above two challenges opens ups an unprecedented road-map of translational ability in scalability, cost-effectives, reachability having minimal or less manufacturing, technical and regulatory challenges, which enhances the market traction towards commercialisation.

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