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# Pharmaceutical Analysis and the Growing Disciplines

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Pharmaceutical analysis is an important step not only for 'Drug Development' but also 'Diagnosis' that involves evaluating the human tissues for imbalanced or undesired bio-chemicals. The word 'Pharmaceutical' is derived from a Greek word pharmakon meaning 'drug', 'medicine' or 'remedy'.

Search of drug to find cure is as old as the disease itself. Advent of microscope that led to the identification of micro-organisms and germ theory of Louis Pasteur in eighteenth century accelerated the research and development to find remedies for various human inflictions. Germ theory for the first time postulated that various human diseases are caused by specific micro-organisms. This theory evolved, outmoded contemporary theories related to human diseases and gained global acceptance in the middle of 1800. Since then it remains a guiding theory that presides over the practice of modern medicine. Pasteur's remarkable contribution as a Physicist, a Chemist as well as a Biologist and Micro-biologist makes him father of the new ways of drug development. His work in stereochemistry, fermentation, silkworm disease, pasteurization and vaccination is path breaking.

Pasteur's germ theory also encouraged studies related to micro-organisms, their penetration, interaction and impact on human tissues besides garnering interest in their respective life cycles. This led to the development of materials and methods for growing these micro-organisms in sufficient quantities in lab for related R & D, giving classic directions to contemporary science; one using benign micro-organisms for expressing desired bio-chemicals by controlling their expression machinery and the other studying new molecular entities to kill the pathogens. The former approach gave birth to two new disciplines 'Genetics' and 'Molecular Biology' while latter led to the development of different classes of antibiotics including penicillin.

This remained the trend for few decades and the time witnessed the development of different classes of antibiotics and recombinant proteins. Control over bacterial expression also boosted the research on filtration and purification methods. New membranes were designed and novel downstream processing techniques were developed. An accidental exposure to an attenuated form of chicken cholera causing micro-organism that provided protection led to the first vaccine discovery yet again by Pasteur. Vaccination and inquisitiveness to understand underlying innate mechanisms in the host that defend and fight against virulent, invading microbes led to the evolution of 'Immunology', another research area. Availability of biological proteins through recombinant mode on the other hand boosted the research in 'Crystallography and Structural Biology'. Success in acquiring genetic control for expressing desired proteins through prokaryotes unintentionally enforced genes as prime controller and navigator of life forms.

Growing micro-organisms in petri-plates thus, became a tradition that was eventually followed for growing plant and animal cells as well. Attempts to grow these cells in vitro using nutrient medium mostly by adopting the methods of bacterial research gradually took the ground. Similar to bacteria, surface adherence is considered important for animal cell culture. All this progress boosted the practice of in vitro assays for pharmaceutical analysis in new drug development making cell culture an indispensible analytical tool. Huge data is generated with various parameters describing the pharmaceutical response of new drug entities through in vitro cell culture methodologies. Some drugs and many new areas and disciplines like Combinatorial chemistry, High throughput screening, Proteomics and Metabolomics have evolved during the journey.

Now after over a century another accidental discovery by growing animal cells in hydrogels has revealed a missing dimension in the flat bottom cell culture outcome [1]. A major disclosure suggestive of equal importance of both physical and chemical environment in the normal growth and behavior of cells demands serious alterations in the practices of pharmaceutical analysis. Reports that show survival of cells in three dimensions versus two dimensions (3D vs. 2D) when exposed to killer drugs demonstrate better resilience by the same cells when in 3D environment [2]. It suddenly drew attention to the immediate micro-environment and extracellular matrix (ECM) around the cells as key instructive agents controlling the genes to express in a specified manner. The implication of this is huge especially on eukaryotic cell culture. For the first time, internal factors or inheritance (aka genes) were no more protagonists but supporting actors. External environmental factors like temperature, pH, toxins and extracellular matrix gained equal importance in interpretation of functional outcome of cells and organisms.

Importance of "ECM over Gene" as functional controller of cells in eukaryotes versus prokaryotes is reasonable looking at their relative functional complexity. Prokaryotes generally enjoy a stand-alone identity or at the most remain member of a string or circular colony, whereas eukaryotic cells need to co-ordinate and remain connected to the neighboring cells to sustain their functional identity.

This grasp brought a setback shaking our confidence in analytical data accumulated through previous practices and calls for alternative tools to simulate the conditions cells are normally exposed in vivo. Quality and extent of control that a 3D environment could provide to the growing cells has opened up new possibilities. Opportunities are in sight to design and engineer artificial micro-tissues that may imitate their functional counterparts in vivo. Functionally viable 3D cell culture models can be used for in vitro pharmaceutical analyses and also for replacing the non/mal-functioning tissues in vivo [3]. Key differentiator at the moment among 3D systems seems to be the involvement of external scaffold although 3D construct of cells can be made with or without scaffold (spheroid formation in droplets vs.

porous microcarrier). Earlier involvement of extracellular matrix based scaffold is likely to have better outcome due to cell-cell and cell-ECM based junctions [4].

We need to understand the dynamics of a cell with its 3D environment and how it influences differentiation, the fourth dimension of the growing cell. Appropriate combination of stem cell and customized scaffold for their controlled differentiation can thus provide a pharmaceutical tool that never existed before. Comprehension of cell vs. ECM is bringing a technology evolution and is contributing to the fast emerging area of Tissue engineering and Regenerative medicine [5]. Hence, organ-on-chip is envisaged to be the new model for pharmaceutical testing, which is expected to minimize late stage drug failures [6].

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