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Ex Vivo Drug Evaluation Using Human Ocular Cells: A Contribution to Drug Discovery

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The field of therapeutics is fundamentally and heavily dependent on drug discovery. The record number of new agents being developed probably conceals how ardent the task is [1]. Drug discovery is indeed a long, costly, and high-risk process that takes over 10-15 years with an average cost of over $1-2 billion for a new drug to be approved for clinical use [2]. What is astonishing is the failure rate of candidate drugs. By most accounts over 90% of drug candidates fail to be approved for clinical use. Lack of clinical efficacy and poor drug-like properties along with unmanageable toxicity are among the frequent reasons for their failure. The transition between basic and clinical science, known colloquially and the "valley of death", is where most promising discoveries meet their demise [3]. Multiple efforts have been made to overcome this difficult situation that adversely affects modern therapeutics [2].

Working on the discovery of drugs for ocular diseases Master et al have recently developed a novel approach based on ex-vivo culturing of ocular surface cells [4,5]. This method, when fully developed and validated, could accelerate drug discovery by effectively screening candidate agents at the early stages of this long process [6]. Indeed, as aptly noted, the success of clinical drug development will be determined by best drug candidate selection [1]. Below, we provide the main points of this promising method and discuss its potential in the context of ocular therapeutics.

Historically, because of their practicality, immortalized cell lines have been the preferred option to initially assess agent efficacy and safety. However, their limited predictive value has been a critical disadvantage [7,8]. A major reason for this limitation is the significant changes that cells undergo during their transformation to cell lines, which is further compounded by successive cell divisions. The method of Master et al, however, seems to have overcome this limitation [11].

The eye is perhaps the best suited organ for the development of an ex vivo short-term cell culture in which cells maintain the main attributes they had in-situ. The cells of the ocular surface are easily accessible by impression cytology and are involved in a significant number of ocular diseases, adequately representing, therefore, a therapeutic target tissue.

Impression cytology is a minimally invasive method that transfers cells from the upper layers of the ocular surface (mainly interpalpebral conjunctiva) by applying on it a membrane either directly or using a specialized instrument [9,10]. The several reported permutations of impression cytology share one drawback: the proportion of cells adhering to (and recovered from) the membrane can vary widely. This problem has, however, been resolved by the same team whose modification of impression cytology made cell retention and recovery quantitative [11].

Using this improved impression cytology method, Master et al harvested conjunctival cells and grew them on mixed cellulose ester membrane filters (MCFs). Remarkably, 100% of human and animal conjunctival cells that were cultured on these filters ex-vivo were viable at 24 h, while nearly half of them were viable at 72 h. The experimental usefulness of their method was suggested by the observation that in human cells, out of 84 genes involved in ocular inflammation ex-vivo culturing maintained intact the expression of two thirds of these genes [6]. Thus, the response of these cells to a drug could be considered, at least preliminarily, highly informative.

In a limited assessment of this notion, human and rabbit conjunctival cells cultured ex vivo were treated with phosphosulindac, a small molecule under development for the treatment of dry eye disease [4]. As a readout they used the expression of CXCL10, a cytokine participating in the pathogenesis of dry eye disease [12]. Phosphosulindac suppressed its expression by 32% and 70%, respectively.

These findings indicate that human and animal conjunctival cells cultured ex vivo as reported maintain their biological integrity, and their response to biological and pharmacological agents could guide preclinical ocular drug development, abbreviating a laborious, lengthy, and expensive process. Additional applications of this method to mechanistic studies have been envisioned and are entirely plausible.

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