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Current Concerns on the Validity of *in vitro* Models that use Transformed Neoplastic Cells in Pharmacology and Toxicology

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In vitro studies in experimental biology are specified by use of constituents of an organism outside the organism. In contrast, *in vivo* studies are conducted inside the living organisms in normal, intact state, while *ex vivo* studies are conducted on functional organs that have been removed from the intact organism. *in vitro* works are conducted on various parts of the isolated cells that are derived freshly from organs or from culture of cells or tissues (Gad, 2000).

Living organisms are made up of numerous cells, genes, molecules, proteins and enzymes that need work together to produce energy and remove waste materials. To do this, several hormones and transmitters interact with each other inside the living organism (Freshney, 2005; Masters, 2000).

In the last decade, animal cell culture has become a commonly used method in various divisions of medical and life sciences such as cell and molecular biology, biotechnology, tissue engineering, pharmacology and toxicology. It needs precise control of physicochemical surroundings such as pH, temperature, osmotic pressure and level of oxygen and carbon dioxide and also physiological conditions. Although, cell lines are homogeneous and can be readily characterized to be easily scaled up in an economic manner, but, microenvironment, cell-cell and cell-matrix interactions, motility and polarity, proliferation, differentiation, cell signaling and energy metabolism in normal cells in tissue are different than those of cultured cells. For instance, *in vitro* metabolism of energy takes place by glycolysis rather than citric acid cycle. In addition, cultured cells lack the heterogeneity and three-dimensional architecture that found *in vivo*. Notably, many hormonal and nutritional stimuli are absent *in vitro*. Although primary normal cell culture is preferred but due to their limited life span, transformed cell lines are produced and used in most of cases. The transformed and neoplastic cells are anchorage-independent and unlike normal cells, they can produce constant cell lines to be passaged and used several times with low mortality. Continuous cell lines are usually smaller, less adherent, more rounded and have a higher ratio of nucleus to cytoplasm. Furthermore, they have an extra growth rate, reduced serum dependence, increased efficiency to cloning, increased heteroploidy and aneuploidy and an increased tumorigenicity. Interestingly, these transformed cells overgrow in culture medium and show no contact inhibition after reaching each other. Naturally, the biological systems are mainly dynamic and not static and the extracellular fluids containing many hormonal and nutritional stimuli continuously pass beside of the cells and are in close contact with them. On the other hand, in the body, a xenobiotic usually undergoes metabolism by liver enzymes while the metabolic systems are absent in cultured cells, although hepatic enzymes extract can be added *in vitro* but it cannot play the real exact role of metabolism that occur inside organism. Although, histotypic and organotypic cultures mimic *in vivo* three-dimensional architecture and environment of the cells but some metabolic systems are still absent in these cultures (Freshney, 2005; Masters, 2000). Polar xenobiotics and their metabolites are continuously excreted in urine or stool by the body but this is absent in artificial *in vitro* conditions (Klaassen, 2008). Therefore, the results obtained by cultured cells specially those obtained by transformed and neoplastic cells logically seem invalid and subject to high mistake. This means that extrapolating of *in vitro* findings to whole intact organism can sometimes be very challenging. Therefore, investigators doing *in vitro* works must be careful to avoid over-interpretation of their results, which can sometimes lead to erroneous conclusions about organismal and systems biology. For example, efficacy of an antibiotic can be proved by prevention of microbe

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replication in a cell culture but before any use of this compound in the human, a series of *in vivo* trials must be done. Therefore, it is so often to see inefficacy of candidate drugs *in vivo* while they have been effective *in vitro* because of parameters such as delivery of the drug to the affected tissues or the metabolism, or toxicity towards essential parts of the organism that were not examined *in vitro*. In addition, cancer cells and their derived cell lines overexpress p-glycoprotein (multidrug resistance protein) which results in enhanced resistance to anticancer drugs (Breier *et al*., 2005). Moreover, it has been shown that various cancer cell lines in culture produce more reactive oxygen species (Matsubara *et al*., 1994). Thus, antioxidants may show different effects on cancer cell lines (or even primary cancer cell cultures) in comparison to primary normal cell cultures.

Thus, for efficacy and safety evaluation of drugs, poisons or chemicals, a method based on an approved animal model and in the second level of importance, an approved primary normal cell culture is strictly recommended. This so important task should be paid proper attention to completely fulfill the objectives and avoid mistakes. Although, the advocators of animal protection laws increasingly suggest restriction of the use of laboratory animals and propose *in vitro* methods for risk assessment and safety evaluation, but to make a certain decision on the effects of a test compound, use of *in vivo* models before going forward to humans is an inevitable step.

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