Abstract

During the development process of cancer drugs, costly and time-consuming animal tests should be substituted with more effective experimental methods that go beyond traditional cell culture in multi-well plates. Over the past two decades, new research areas have emerged that are heading toward experimental models that reproduce the organ-specific microenvironment in order to maintain cell differentiation and tissue-specific function. Research and industry in the field of drug development and therapeutics is not sufficiently covered by flexible platforms suitable for the use with conventional cell culture methods, despite the presence of several complex systems attempting to mimic the conditions occurring inside human organs. Additionally, it is hard to employ in situ live traditional detection methods during cell growth, which are often used in biology laboratories, including the measurement of absorbance in multi-well plates and the monitoring of physical, chemical and biological factors during cell development, or accurate in vitro tracking of early/late apoptosis and necrosis of cells, as well as physical variables like pH and O_2 content, NO_x and glucose. Additionally, the acidity of the culture medium influences the cell metabolism, gene regulation and life cycle, making in situ pH monitoring an effective tool for the development of cell cultures. As a result of studies on pH monitoring in cell cultures, systems for real-time pH monitoring, including OECTs (organic electrochemical transistors) have been developed. They are a type of biosensors widely studied in recent years, offering advantages such as excellent sensitivity, exceptional stability, and low cost. In this work, a versatile and programmable multi-well plate culture system compatible with the growth of both normal and tumorous lung cells is proposed. By periodically increasing the hydrostatic pressure inside the culture chamber, such system exposes cells to mechanical stimulation that mimics a normal breathing cycle. The controlled hydrostatic pressure increase inside the culture chamber, on the other hand, increases the partial pressure of gases in the culture chamber, particularly CO_2, which can result in the production of carbonic acid and a lowering of the pH of the culture medium once it has dissolved in the fluid used for cell growth. The development of pH-sensitive OECTs which are designed to operate directly inside the system to monitor pH variations within the culture medium during cell growth is proposed. The system discussed in this dissertation showed the feasibility of growing a cell culture inside it, and the stability of the pressure cycles set via software via a microcontroller unit. Moreover, no significant temperature perturbation induced by

the pressure cycles have been observed within the system, since this parameter could influence cell development. An array of pH-sensitive OECTs have been developed, which turned out to be suitable for working inside cell culture media, opening the path for future cell culture in situ monitoring. Despite the pH sensitivity of such devices has been demonstrated, further investigation is needed to improve OECTs performance and to make them suitable not only to detect pH, but also to open the path to the detection of key biomarkers during cell growth. Further research work should be made in the future, to integrate the programmable cell culture platform with an array of OECT-based biosensors.