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Autologous Peripheral Blood Stem Cells Expansion: A Clinical Scale Micro-Fluidic Strategy

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Peripheral Blood Stem Cells (PBSCs) are present in the circulation; they can be mobilize into the peripheral blood and collected with ease to treat many hematological disorders [1]. These qualities have since enthralled scientist around the world to conduct research and clinical trials on the potentials of PBSC to repopulate the hematopoietic system. Granulocyte colony stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) have been commonly used to mobilize PBSCs [2,3]. Despite their wide adoption for mobilizing PBSCs, some patient even after several collections will not achieve therapeutic dose [4]. Even those with potential to respond well to mobilization may be discouraged to proceed after analyzing the pre and post apheresis cost implication [5]. To address these challenges, laboratorians have long sort for ways to expand PBSC *ex-vivo* but their efforts had been confined to fetal bovine serum (FBS) and serum free culture media until recently [6]. Some clinical trials using PBSC expanded *ex-vivo* in FBS, serum free media and human serum have already been done using different cytokine combination, concentration and different mode of culture [7,8]. Outcome from such trials have been largely controversial owing to the heterogeneous nature of the studies [6]. Most of the studies have been criticized for using feeder cell, animal proteins or microbial agents that might contaminate these cells while current evidence suggests that serum free media are unable to support expansion for multiple passages, a step necessary for the repopulation of the hematopoietic system [9]. Attention is being shifted to human serum particularly autologous serum to avoid ethical and safety concerns. An example of trials using autologous serum was reported by Brugger et al, in 10 patients with solid tumor. They expanded autologous PBSC in-vitro using SCF, IL-1b, IL-3, IL-6, EPO, RPMI 1640 and 2% autologous plasma for 12 days. 6 of the 10 patients transfused solely with these expanded cells engrafted and recovery was rapid but not different from the control [10]. In another study, cytokine curtail prepared with SCF, IL-1b, IL-3, IL-6, EPO in autologous serum, CD34-selected cells expanded after they were cryopreserved but the recovery was not sustained [11].

Recent studies are now indicating that cells cultured in autologous serum expanded better than those cultured in fetal calf serum and serum free media [12].

With the potential of PBSC *ex-vivo* expansion in autologous serum being better understood by the day, a clinical scale micro-fluidic strategy system should be considered. The culture environment may be constructed inside an incubator like body that is connected to an external valve controlling the flow of pressurized air to a reservoir containing the curtail media outside the incubator like body. The pressure component should be design to force the curtail media into a micro-valve pneumatic connections which will supply the media through a tubing into the culture flask positioned inside the incubator like body. Once the dose volume of the curtail media per pump is known, the precise flow rate may be established by defining the number of pumps per time unit. A spectrophotometer like light should be made to pass through the culture flask at a fixed time to generate information regarding the accumulation of inhibitory factors and current nutrient profile in the culture environment. Light from a CO_2 and O_2 sensor inside the incubator like body should be directed to a PH meter to take measurement of the pH in the environment. A laser light should also be positioned inside to take measurement of the temperature simultaneously. The light signal from the spectrophotometer should also be able to control the external valve to pump or halt the supply of nutrient depending on the concentration of the inhibitory factors detected or nutrient available. The system should have a time lapse monitoring device fixed inside the incubator to provide a real time picture of the cultured cells while a tube is also positioned inside the culture flask and directed outside the incubator so that occasionally a small volume of the cultured cell is aspirated into a plate for automated immune-staining within the plate.

If clinical trials are conducted in a system like this and are properly harmonized and restricted to autologous serum, a better understanding of *ex-vivo* expansion of PBSCs for clinical application could be achieved.

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