

MAGNETIC SEPARATION DEVICE FOR CELL SORTING AND ANALYSIS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. provisional patent application 61/276,303, filed on Sep. 9, 2009, entitled "Magnetic separation device for cell sorting and analysis", and hereby incorporated by reference in its entirety.

GOVERNMENT SPONSORSHIP

[0002] This invention was made with Government support under contract number NCI 1U54CA119367 awarded by the National Cancer Institute. The Government has certain rights in this invention.

FIELD OF THE INVENTION

[0003] This invention relates to magnetic methods for handling biological cells.

BACKGROUND

[0004] Numerous biomedical applications require rapid and precise quantification of biological cells and/or molecules in a sample. One approach for performing such quantification is to employ magnetic probes which can bind to the species of interest and be captured by a magnet. For example, a wall of a device can contain a magnet, and species that have magnetic probes attached can be captured at the wall. However, such approaches can suffer from several shortcomings, such as large size, low capture rate, and cumbersome release methods.

[0005] For the specific case of biomolecules, a magnetic sifter approach was considered in US 2007/0181466, hereby incorporated by reference in its entirety. The magnetic sifter has pores that pass through a substrate such that a soft magnetic material is present near the pores. With this arrangement, magnetically labeled biomolecules can be captured at and released from the pores of the sifter by using an external magnetic field to alter the magnetic field produced by the soft magnetic material at the pores.

[0006] Controllably capturing and releasing biomolecules from the pores of a magnetic sifter is substantially easier than performing the same operation for biological cells, because molecules are smaller than cells and have more predictable behavior. Accordingly, it would be an advance in the art to provide capture and release of biological cells using a magnetic sifter.

SUMMARY

[0007] A magnetic sifter is adapted for manipulation of biological cells by providing a greater pore density at the edge of the sifter than at the center. Application of an external magnetic field to the sifter causes high magnetic fields and field gradients at the sifter pores. These conditions are suitable for capturing magnetically tagged or labeled cells at the sifter pores. Altering the external magnetic field can provide controlled capture and/or release of magnetically labeled cells from the sifter pores.

[0008] The purpose of having a greater pore density at the periphery of the sifter than at the center is to provide improved flow rate uniformity through the sifter. The pore arrangement

of the sifter is preferably selected such that the flow rate distribution is substantially uniform across the channel. The pore density is greater at the edge of the sifter than at the center to compensate for the effect of fluid viscosity, which ordinarily leads to a greater flow rate at the center of a channel than at the edges of a channel.

[0009] Providing enhanced flow rate uniformity through a magnetic sifter has numerous advantages, which can be better appreciated by considering some aspects of typical biomedical applications.

[0010] Isolating cells has important applications in the research, diagnosis, and treatment of many diseases, including cancer. Often the cell populations of interest are extremely rare, with clinically relevant concentrations ranging from parts per ten thousand to parts per billion. The high capture efficiency and high release efficiency of the sifter and the option for directly quantifying cell populations make the present approach ideally suited for point of care as well as laboratory cell separations.

[0011] However, most such applications rely on cell quantification, and for cell quantification it is important for the flow rate through each pore of the sifter to be substantially the same. The reason for this is that cell capture and release rates are a function of flow rate, and a non-uniform flow rate therefore leads to non-uniform capture and/or release rates at various locations on the sifter. Such non-uniformity can lead to error, if it is incorrectly assumed that these rates are uniform across the sifter, or to increased measurement complexity, if the non-uniformity is characterized and accounted for. Thus, the advantages of providing flow rate uniformity in a magnetic sifter include improved accuracy for cell quantification and/or decreased complexity of cell quantification methods/apparatus. Flow uniformity also allows titrating fractions which elute differently depending on viscous flow rate and the number of adsorbed nanoparticles per cell.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] FIGS. 1*a-b* show top and side views of a magnetic sifter according to an embodiment of the invention.

[0013] FIGS. 2*a-b* schematically show laminar flow in a tube and uniform flow in a tube having a magnetic sifter.

[0014] FIG. 3 shows a top view of an alternate embodiment of the invention.

[0015] FIG. 4 shows several possible pore shapes for magnetic sifters.

[0016] FIG. 5 shows an arrangement where a magnetic sifter is placed in a flow cell such that optical characterization of captured particles/cells can be performed.

[0017] FIG. 6 shows cascaded magnetic sifters.

[0018] FIGS. 7*a-b* show magnetic field configurations relating to magnetic sifter operation.

[0019] FIG. 8 shows a plot of measured capture efficiency vs. flow rate through a magnetic sifter.

DETAILED DESCRIPTION

[0020] In the present work, a magnetic sifter is adapted for manipulation of biological cells by providing a greater pore density at the edge of the sifter than at the center. The top and side views of FIGS. 1*a* and 1*b*, respectively, show an example, where a substrate **102** and soft magnetic layer **104** form a layered structure through which several pores pass, one of which is referenced as **108**. The side view of FIG. 1*b* is taken along line **110** on FIG. 1*a*. The pore density at a peripheral