

izabilities for effective trapping and patterning. This prevents the guarantee of homogeneous cell populations, which can be assured only through molecular specificity.

[0206] In view of the foregoing, one embodiment according to the present disclosure is directed to the assembly of a two-dimensional tissue, as illustrated in FIGS. 41-43. In one exemplary implementation, capillary endothelial cells are considered, wherein the cells are assembled by coating magnetic beads with antibodies to PECAM and suspending the beads in solution with the dissociated endothelial cells. As shown in FIG. 41, cells that are attached to the beads can be separated and then guided into formation over a Fibronectin (FN)-coated chip surface using the microcoil array 202B of an IC chip 102. In particular, as shown in FIG. 41(a), a two-dimensional endothelial cell layer is precisely assembled using the microcoil array 200B, wherein micropatterned Fibronectin (FN) is shown with thick black lines. In FIG. 41 (b), endothelial cells occupy those regions indicated by darkened microcoils, which have non-zero DC currents thereby creating magnetic fields. Once in position, the cells are allowed to adhere and spread on the chip surface, forming a confluent monolayer of defined geometry.

[0207] Subsequently, this endothelial tissue is assembled as an “embedded tissue” within a preexisting cardiac muscle tissue. In one embodiment, two-dimensional cardiac tissues may be built by culturing neonatal rat ventricular myocytes on micropatterned Fibronectin. Dissociated cardiac myocytes are cultured in micropatterned FN lines, as shown in FIG. 42(a). The cardiac myocytes adhere to and align with the FN lines, self-assembling into a confluent, anisotropic monolayer that is capable of conducting action potential wavefronts. FIG. 42(b) shows the cardiac tissue constructs, simulating a capillary parallel (top) and perpendicular (bottom) to the cardiac fibers. FIG. 42(c) shows the spacing of focal-adhesion sized FN islands.

[0208] Using the microcoil array, capillary endothelial cells may be embedded in precise formations relative to the fiber orientation of the engineered cardiac tissue, as shown in FIG. 43. In FIGS. 43(a), capillary endothelial cells marked by magnetic beads (see FIG. 43(b)) are guided into position amongst previously cultured cardiac myocytes using the microcoil array. When in the appropriate position, they are held long enough for integrin attachment to the micropatterned FN. As shown in FIGS. 43(c) and (d), the endothelial cell binds the FN and extends lamellipodia to attach to other islands and the edges of the FN lines upon which cardiac myocytes are attached.

[0209] The small, focal adhesion-sized FN islands may not be amenable to myocyte adhesion and spreading because the spontaneous contraction of these myocytes tears them from a single, small FN island before they can sufficiently adhere. However, capillary endothelial cells bind these islands and extend lamellipodia to spread to occupy several simultaneously. Thus, regions that are micropatterned with small FN islands are capable of selectively hosting endothelial cells but not cardiac myocytes (See FIG. 42). Endothelial cells attached to magnetic beads are added one at a time by the microcoil array as shown in FIG. 43, because putting them in solution after the myocytes have adhered to the substrate may lead to mixed, uncontrolled populations along the micropatterned FN lines. The constructed endothelial embeds are allowed to spread in culture for 24 hours

or less. Immunohistochemistry may be used to mark the cells to track their growth at specific time points after the microcoil array-based construction. Specifically, the tissues may be triple-stained for sarcomeric α -actinin, PECAM, and nuclear DNA (DAPI) in order to precisely locate the demarcation line between the endothelial cells and the cardiac myocytes, as well as to check for possible migration and proliferation of the endothelial cells. In one aspect, the refined media conditions minimize endothelial cell proliferation but support endothelial cells spreading and myocyte beating.

[0210] According to the foregoing methodology, uniformity and geometric precision of the endothelial cell embed, as well as preventing the invasion of endothelial cells amongst the cardiac muscle fibers, may be accomplished. Applicants have recognized and appreciated that prepositioning of the cardiac myocytes on the micropatterned surface prior to the assembly of the endothelial cell embed is an important step in the process. In particular, cardiac myocytes require more time to attach and conform to extracellular matrix cues than other cell types. Additionally, capillary endothelial cells are quite migratory, whereas the cardiac myocytes are not. Thus, by prepositioning the cardiac myocytes, the cells of the endothelial embed may be effectively contained to their designated regions after assembly.

[0211] Conclusion

[0212] Various embodiments of a hybrid system as discussed herein incorporate elements of electromagnetics, microfluidics, semiconductor physics, lithographic techniques, high frequency (e.g., RF) electronics, analog/digital integrated circuits, feedback control and biology in a complementary system. In various exemplary implementations, such a hybrid system may be configured as a “bio-chip,” providing a versatile programmable device that can perform a wide range of biological experiments on a sub-micron scale, and thereby significantly benefit “lab-on-a-chip” development of industrial, scientific and military interests.

[0213] Having thus described several illustrative embodiments, it is to be appreciated that various alterations, modifications, and improvements will readily occur to those skilled in the art. Such alterations, modifications, and improvements are intended to be part of this disclosure, and are intended to be within the spirit and scope of this disclosure. While some examples presented herein involve specific combinations of functions or structural elements, it should be understood that those functions and elements may be combined in other ways according to the present invention to accomplish the same or different objectives. In particular, acts, elements, and features discussed in connection with one embodiment are not intended to be excluded from similar or other roles in other embodiments. Accordingly, the foregoing description and attached drawings are by way of example only, and are not intended to be limiting.

1. An apparatus, comprising:

- a plurality of CMOS fabricated field-generating components;
- a microfluidic system configured to contain a fluid in proximity to the plurality of CMOS fabricated field-generating components; and