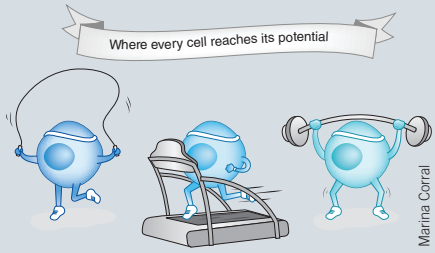
In vitro niches

Attempts to replicate the stem cell microenvironment in the culture dish continue.

Stem cells of many different types occupy special environments within the body—so-called niches—that are important for maintaining their function. Interactions with niche components are critical for stem cells to self-renew and differentiate into multiple cell types. There is tremendous interest in understanding stem cell–niche interactions; one direction of these research efforts is the recreation of the niche *in vitro*.

Building a stem cell niche *in vitro* serves at least two purposes. First, it may permit better culture and expansion of otherwise hard-to-culture stem cells. Second, it provides researchers the opportunity to study the interaction of stem cells with their niche and to model disease states that result when these interactions are aberrant.

One relatively simple and well-used approach toward building an *in vitro* niche involves coculture with stromal cells or other cells found near the stem cells *in vivo*.



Marina Corral

The right microenvironment is key for stem cell potential.

Indeed, this approach continues to be used and refined for many cell types. For instance, Shinohara and colleagues recently reported that coculture with testis cells (presumed Sertoli cells) from infertile mice could support culture of mouse spermatogonial stem cells for several months (*Cell Stem Cell* **11**, 567–578, 2012). In separate work, Shusta, Palecek and colleagues used a different coculture approach to generate organ-specific human endothelial cells. They codifferentiated human pluripotent stem cells along both the neural and endothelial lineages, thus creating an *in vitro* environment that mimicked the embryonic brain and functioned as a niche in which blood-brain–barrier endothelial cells could be generated (*Nat. Biotechnol.* **30**, 783–791, 2012)

Fully replicating a complex and dynamic system like the stem cell niche is not trivial, however. The details will vary for different stem cell types, but the many components of a niche typically include soluble and attached signaling molecules, cell-cell interactions, cell–extracellular matrix interactions, mechanical forces in three dimensions and systemically regulated small molecules such as metabolites and oxygen.

Building a niche *in vitro* therefore requires not only an understanding of the biology—still incomplete for most stem cell types—but also the ability to implement the desired three-dimensional architectures, with appropriate physicochemical and biological properties (or a functional surrogate). Materials science expertise is a critical part of this endeavor. As advances in both the stem cell and the materials fields continue to accrue, they will bring a more complete reconstruction of *in vitro* stem cell niches within closer reach. **Natalie de Souza**

Volumetric imaging in a snapshot

Microscopes that render tissue-volume images from single snapshots are making their way into biology.

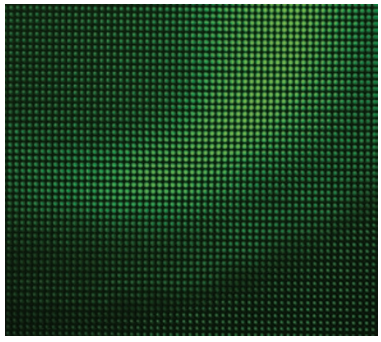
Three-dimensional (3D) fluorescence images of biological samples are normally assembled from a focal stack of 2D images acquired from multiple planes in a sequential manner, such as in confocal or light-sheet microscopy. This process is time consuming and might not be ideally suited to record certain types of fast biological events or light-sensitive samples. Moreover, these techniques often require complicated microscopy setups.

Scanless volumetric imaging approaches instead record an entire 3D focal stack from a single snapshot of the camera. Conventional epifluorescence microscopes can be turned into fast volumetric imaging devices in a seemingly uncomplicated manner.

One such approach that was introduced years ago is the light-field microscope, developed by Levoy and his collaborators at Stanford (http://graphics.stanford.edu/projects/lfmicroscope/). A light-field microscope can be built by inserting a microlens array between the main lens and the sensor plane of a conventional optical microscope. Rays that would normally come to a focus in the intermediate plane instead pass through the microlenses and are recorded separately at a light-field plane, where different points in the specimen are recorded in different images. With the aid of deconvolution algorithms, this imaging setup produces perspective flyarounds and 3D volumes from each photograph. Although diffraction forces a trade-off between axial and lateral resolution, the resulting 3D videos contain enough information to allow, for example, scanless imaging of genetically encoded calcium indicators across the entire brain of a larval zebrafish.

Microlens arrays can be introduced into the illuminating path of the microscope as well, offering easy ways of generating 3D illumination patterns.

Another approach for scanless volumetric imaging is reported in this issue by Abrahamsson, Dahan and their colleagues. The researchers adapted multifocus fluorescence microscopy methods to collect all the focal stacks simultaneously on a single camera. The microscopy setup relies on the use of diffractive grating to form aberration-corrected, multifocus-shifted images of the specimen (*Nat. Methods* **10**, 60–63, 2013). It achieves resolutions equal to that of a wide-field microscope with about half of its light sensitivity and can be applied for fast acquisition of 3D data at the level of single molecules and small organisms.



R. Portugues

A portion of the entire light-field image of a zebrafish eye as seen before image reconstruction.

Both the light-field and multifocus microscopes are promising methodologies that could make fast volumetric imaging accessible to many. **Erika Pastrana**

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