Heart-shaped clones
progenitors. Rather, growth is oriented in a pattern specific for each area of the heart, and that pattern reflects the final shape of its region. For instance, in the outflow tract of the heart, which is a tubular region, the clones grew longitudinally along the long axis. In contrast, in the rounded ventricle, the clones were oriented like the spokes of an umbrella.

A computer simulation revealed that similar clone shapes could be formed by simply restricting the plane of cell division. Thus, as long as daughter cells continue to divide along the original mitotic orientation, outside signaling among cardiac cells may not be necessary to attain the clonal shapes seen in vivo. It remains to be determined how each region of cells chooses its mitotic plane.

Other mammalian organs, such as the brain or kidney, may also be shaped by oriented cell division. Cruder shapes might be formed by variances in proliferation rates, but the group suggests that fine shaping is more easily accomplished by oriented cell division.

Membrane fusion SNAREs an inhibitor
SNARE specificity forms two mutually exclusive systems in the Golgi—one enriched at the cis and one at the trans face of the Golgi. The concentration of cis t-SNAREs at the cis face of the Golgi, where trans t-SNAREs are scarce, helps prevent vesicles bearing trans v-SNAREs from fusing there and vice versa. But even an imperfect distribution of t-SNAREs may be offset by inhibitory SNAREs (i-SNAREs), based on the new results.

The authors found that some trans-Golgi SNAREs inhibit fusion reactions by cis-Golgi SNAREs and vice versa. At least some of these iSNAREs block fusion by substituting for one of the SNARE subunits of the fusion-competent complex. Most SNARE combinations that will not cause fusion do not form a complex. However, a few nonfusogenic complexes have been seen to form in vitro. Varlamov et al. suggest that these unusual complexes are insurance against unwanted fusion events.

To test their theory, the group recreated the SNARE composition of the Golgi compartments in vitro using liposomes and yeast versions of mammalian SNAREs at concentrations mimicking those seen in vivo. Vesicles containing either cis- or trans-Golgi SNAREs accurately fused with the cis- or trans-Golgi liposomes, respectively. But if the authors removed i-SNAREs from the recreated Golgi, vesicle targeting was less faithful, and the likelihood that vesicles with a cis v-SNARE would fuse with trans-Golgi liposomes increased from 3% to 40%. The group expects that i-SNAREs also work elsewhere, such as at the ER or the plasma membrane, to direct trafficking.
Awakening heterochromatin

Sites in the human genome once thought to be inert structural material are brought to life in response to stress, according to results from Jolly et al. (page 25).

These inactive DNA stretches are binding sites for HSF1, a transcription factor that activates individual heat shock genes and accumulates in nuclear granules after heat shock. These granules were, like HSF1, expected to activate heat shock genes. So their recent localization to heterochromatic satellite III regions, which do not contain the major heat shock genes, was surprising. Jolly now shows that the stress granules activate transcription even in these repeat sequences.

Malaria protease takes an indirect route

The bug that causes malaria feeds by gobbling up chunks of hemoglobin from the red blood cells it resides in. On page 47, Klemba et al. show how the parasite brings together this food source with its own enzymes that will degrade it. The results offer insight into how to treat this deadly disease.

The parasite breaks down hemoglobin for nutrients in its specialized organelle called the food vacuole, using proteases such as plasmpisin II (PM II). Hemoglobin gets to the food vacuole in vesicles that pinch off from cytostomes—openings through the parasite plasma membrane that lead to the blood cell cytoplasm. But how the endogenous protease reaches the food vacuole to meet its substrate had not been defined, leading some researchers to wonder whether a direct targeting pathway exists from the ER to the food vacuole. The new results suggest this is not the case.

Instead, the group sees that an inactive precursor form of the protease hitches a ride with hemoglobin in cytostome-derived vesicles. GFP fusions of the PM II precursor were seen to be secreted from the ER to cytostomes. From there, the fusions traveled in vesicles shared by hemoglobin to the food vacuole, where the precursor was processed to its active form.

It is not clear whether PM II is sent directly to cytostomes or simply diffuses laterally once at the plasma membrane. If the former is true, a cytostome-targeted trafficking pathway might be a pathogen-specific target for drug treatments.

Calcium pumps need a chaperone

ER chaperones need calcium to help them in their folding duties. Work on page 35 by Li and Camacho shows that some chaperones take a proactive stance on Ca$^{2+}$ levels by regulating an ER Ca$^{2+}$ pump.

Calcium must be pumped into the ER from the cytoplasm to maintain high levels for Ca$^{2+}$-needy chaperones. This function is performed in many cells by the SERCA 2b pump. The authors show that some chaperones, in addition to helping newly synthesized proteins fold correctly, also inform SERCA 2b of the ER Ca$^{2+}$ status. And what they have to say can alter pump activity.

High Ca$^{2+}$ levels lowered pump activity by promoting an interaction between SERCA 2b and the chaperone Erp57, which catalyzed disulfide bridge formation in the luminal portion of SERCA 2b. But the SERCA–Erp57 interaction was lost at lower ER Ca$^{2+}$ concentrations.

This reduced the disulfide bridge and converted the pump into its most active form. The ER is naturally an oxidizing environment, suggesting that a reductase may act on SERCA 2b unless Erp57 gets in the way.

Another chaperone, calreticulin (CRT), was needed for the Erp57–SERCA 2b interaction. CRT binds to both ERp57 and SERCA 2b, and SERCA 2b mutants that did not bind to CRT were not inhibited by Erp57. Thus, it is possible that CRT may be the actual calcium sensor—bringing Erp57 to SERCA only when Ca$^{2+}$ levels are high enough and removing Erp57 when Ca$^{2+}$ levels are lowered so that the stores are rapidly refilled.