

models use endogenous mouse tumors that also express the antigens of interest. Even in these models, however, it may not be possible to exactly test the intended product, but rather a model product that incorporates the mouse homolog of the target antigen.

In both animal studies and clinical trials, the candidate tumor vaccine must generate effective responses to self or modified self antigens as rapidly as possible, and do so in a tumor-bearing host, in order to be effective. These are formidable challenges to vaccine-platform technologies that were initially developed with infectious disease in mind, where the antigens are foreign and immunization occurs before exposure to the pathogen.

Despite these challenges, significant progress is being made, reflected in a number of recent successful phase 1 and 2 clinical trials. For the most part, these approaches use cells as sources of antigen, delivered either directly as tumor cells, as heat shock proteins extracted from tumor cells or as dendritic cells loaded with tumor antigens. The vaccines often are combined with administration of cytokines, most frequently granulocyte-macrophage colony-

stimulating factor (GM-CSF)³⁻⁸. The vaccines themselves are challenging, although not impossible, to mass-produce.

The clinical results are very important because they help define the attributes of a successful cancer vaccine platform: colocalization of antigens and costimulatory molecules, efficient antigen presentation, local or systemic delivery of cytokines as adjuvants and inclusion of multiple antigens if possible. Building on this success, a vaccine based on plasmid DNA formulated in poly(lactide coglycolide) microparticles has shown promise against premalignant lesions induced by human papilloma virus⁹.

The study by Padua *et al.* represents an advance on several fronts². Human acute PML is associated with chromosomal translocations involving retinoic acid receptor- α (RAR- α)¹⁰, activating the PML-RAR- α oncoprotein. PML accounts for about 10% of all acute myelogenous leukemias, which strike about 14,000 individuals per year in the US.

Padua *et al.* studied spontaneous leukemias arising in transgenic mice expressing the rearranged human receptor gene. These tumors have the advantages of

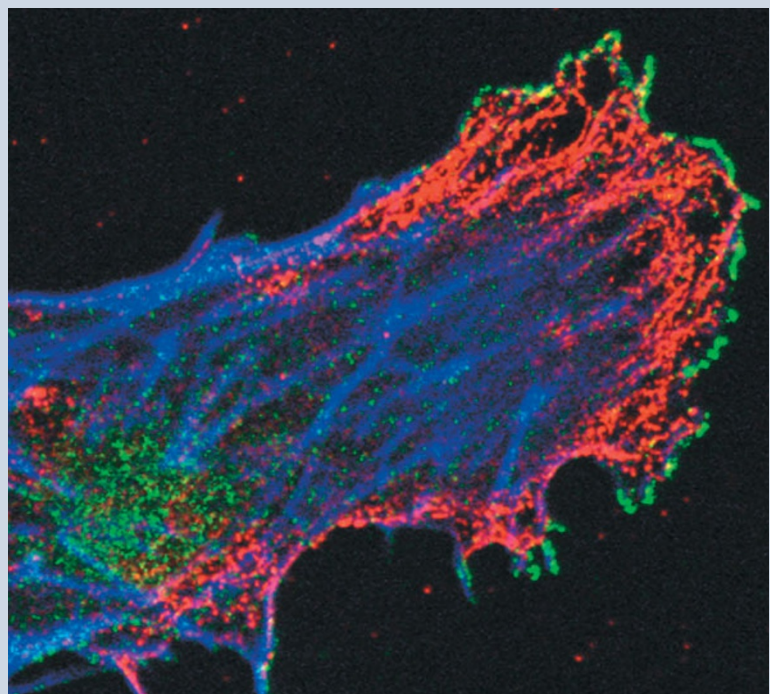
a well-characterized transforming mutation that also provides a cell-surface target for an immune response, and are transplantable into the parental mouse strain. In addition, the leukemias retain the ability to signal through the transgenic receptor and are susceptible to ATRA. This compound is used to treat leukemias because it induces granulocytic differentiation and eventual death of the leukemia cells. ATRA is more effective in immune-competent mice than in immune deficient ones, suggesting a role for acquired immune responses induced during chemotherapy¹¹.

Padua *et al.* began their studies with the observation that mice immunized with the transgenic leukemia cells survived best if they had formed antibodies to the PML-RAR- α receptor. The authors reasoned that a vaccine might further promote survival, so they generated an effective DNA vaccine by fusing PML-RAR- α to fragment C of tetanus toxin. The latter is a potent stimulus of CD4⁺ T-cell responses in mice, and in this case increased the potency of the DNA vaccine. ATRA or the DNA vaccine alone both improved the survival of mice that had been injected with the leukemia cells. But given together, the combination

Tinged migration

Cell migration enables essential processes such as wound healing, but also gives legs to cells during metastasis. In the October *Developmental Cell*, Shiro Suetsugu *et al.* take a close look at how cells move. Shown is a migrating mouse fibroblast induced to migrate with platelet-derived growth factor. The cell is stained for actin (blue), matrix metalloproteinase-2 (MMP-2; red) and WASP family verprolin-homologous protein-2 (WAVE-2; green). During migration, MMP-2 and other proteases degrade the extracellular matrix, breaking the way for the leading edge of the cell. At this leading edge, WAVE proteins activate the Arp-2/3 complex, which nucleates actin and causes rapid polymerization. These processes precede lamellipodium extension and attachment to the substratum, which create a scaffold for the next step of leading-edge extension. The investigators found that WAVE-2 is essential for leading-edge extension and directed migration. Another protein, WAVE-1, colocalizes with MMP-2 and is essential for MMP-dependent migration in the extracellular matrix. The researchers are now investigating the role of WAVE proteins in metastasis.

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