pitulated in cultured leukemia cell lines. They interpret this to mean that such pharmacologic interactions must be studied *in vivo*, in the setting of a clinical trial. This may be the case, but it is also possible that the result reflects analysis of only a limited number of cell lines. If such discrepancies hold up upon further analysis, however, they would add to mounting evidence highlighting the differences between cancer cell lines and the primary tumors from which they are derived.

The results of Cheok *et al*. indicate that a molecular signature of combination therapy exists, and suggest that systematic approaches to searching for such synergistic drug combinations might be feasible. Concerns over cell lines notwithstanding, one could imagine screening combinations of compounds for molecular synergy, thereby identifying combinations whose components were previously unsuspected.

The challenge, of course, will be to relate such *in vitro* molecular synergy to clinical synergy *in vivo*. Although such clinical studies would not be trivial, the past 25 years' experience in childhood ALL combination therapy is a case in point that the optimization of combinations based solely on clinical empiricism is excruciatingly slow. Certainly there is room for improvement with molecular approaches to the problem.

What is the future of combination therapy for cancer? One could argue that as mechanisms of cancer pathogenesis are elucidated, molecularly-targeted single agent therapy could gain a strong foothold in the clinic. It is more likely, however, that combination approaches will remain critical—either simultaneous targeting of a single pathway so as to avoid drug resistance, or the targeting of two or more different pathways, each of which is essential for tumor cell survival.

Early clinical experience with the tyrosine kinase inhibitor imatinib (Gleevec), targeting the *BCR-ABL* tyrosine kinase oncogene in chronic myeloid leukemia, indicates that such monotherapy can foster the emergence of drug-resistant clones[4]. Thus, the task at hand is to determine how best to combine imatinib with other agents in order to avoid such resistance. It seems likely that other kinase inhibitors will also require combination approaches to effect long-term cures.

The study by Cheok *et al*. provides another piece of compelling evidence that the era of performing clinical trials without molecular studies is coming to an end. Sophisticated molecular surveillance is becoming increasingly embedded in clinical trial design in an effort to shorten the time and lessen the cost of clinical trials. It is now clear that the collection of such genomic information as part of clinical trials is feasible; the extent to which this information will be truly useful is less certain.

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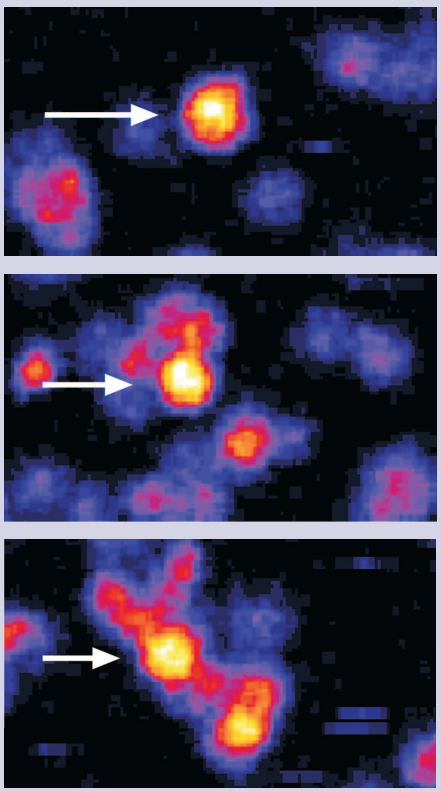

Platelet attraction

Thrombus formation begins when a few platelets settle down onto a sticky surface, such as collagens exposed during injury, or atherosclerotic plaques. The anchored platelets recruit other platelets through integrins and other adhesive proteins, forming a tight, clingy mass. This recruitment process depends on calcium oscillations that propagate from platelet to platelet, report W. Nesbitt *et al.* in the 31 March *Journal of Cell Biology*.

In the top panel, a calcium spike surges through a platelet after exposure to von Willebrand factor, a sticky protein on the surface of platelets (high calcium levels are white, medium are red and low are blue). Such calcium spikes have been observed before in platelets settling down onto substrates in vessel walls. The bottom two panels illustrate the new findings: a new platelet, swept along as if in a vessel, contacts the anchored platelet at the peak of its calcium flux. This anchors the platelet and initiates a new calcium flux. Nesbitt *et al.* could induce such platelet attraction simply by activating calcium fluxes within individual platelets using a caged calcium chelator, triggered by exposure to ultraviolet light.

The investigators found that propagating the calcium spikes between platelets required $\alpha_{IIb}\beta_3$ integrin, a target of anti-clotting drugs. Also necessary was ADP, and an ADP receptor that may indirectly regulate calcium flux from internal stores. The authors suggest that integrin binding prompts calcium signaling, which in turn activates integrin and prompts ADP release. Calcium fluxes keep platelets sticky even under conditions of high shear flow, which occurs in the microcirculation and at sites of artery narrowing.

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