VEGF receptor-1 or VEGF receptor-2 signaling, suggests a functional role for PDGF-B in this thalidomide-stimulated reduction in angiogenesis. However, it cannot be ruled out that this correction may be mediated via the c-Kit or Abl kinases, which are also inhibited by imatinib and might also have an impact on angiogenesis. Nevertheless, transgenic mice harboring a mutant, inactive *Pdgfb* gene did not show increased retinal pericyte coverage in response to thalidomide treatment. These findings support the notion that PDGF-β released from endothelial cells in response to thalidomide acts on surrounding pericytes and their precursors to stimulate vessel maturation, endothelial cell–pericyte connectivity and the resultant vascular quiescence (**Fig. 1**).

The study by Lebrin *et al.*[4] sheds light on another mode of thalidomide action on the vascular system by demonstrating that the drug attenuates angiogenesis by bypassing the need for the endoglin–Alk-1 pathway in vessel stabilization. Targeting angiogenesis via this mechanism might prove effective in the treatment of HHT.

Despite these exciting findings, thalidomide should still be used with extreme caution in humans, not only because of the drug's potent teratogenic effects within the dose range administered in the current study but also because fairly small differences in doses seem to result in dramatic differences in vascular outcomes both *in vitro* and in mice[4]. Moreover, many antiangiogenesis agents, including bevacizumab and thalidomide, have been associated with an increased risk of thrombosis in some patients. It is also likely that each patient will show distinct angiogenic responses to thalidomide treatment because of innate genetic variation among individuals. Certainly, in different mouse strains, genetic modifiers have been shown to influence growth factor–induced corneal angiogenesis[10], vascular development in *Tgfb1*$^{-/-}$ embryos[11] and the severity of vascular lesions in mature *Eng*$^{+/-}$ mice[12]. Most pertinent to this discussion, Robert d'Amato and his colleagues have shown that there are large strain differences in response to thalidomide-mediated inhibition of angiogenesis[13].

Although thalidomide might not ultimately be the drug of choice for the treatment of HHT or other conditions, the value of probing deeper into its molecular mechanisms of action cannot be understated. Knowing how drugs like thalidomide work will help inform decisions about other therapies. For example, the angiogenesis inhibitor sunitinib should be avoided for vascular normalization in HHT, as it targets both VEGF and PDGF-B signaling. With the development of numerous new 'smart' drugs that inhibit specific signaling pathways, clinicians possess a panoply of tools with which to treat patients.

Drug selection should be made in an educated fashion. Understanding the molecular pathways that regulate both cell-autonomous and cell-to-cell cross-talk mechanisms of vascular stabilization should lead to new therapeutic combinations that may have fewer adverse side effects than bevacizumab or thalidomide.

COMPETING FINANCIAL INTERESTS
The author declares no competing financial interests.

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Thalidomide's early effects

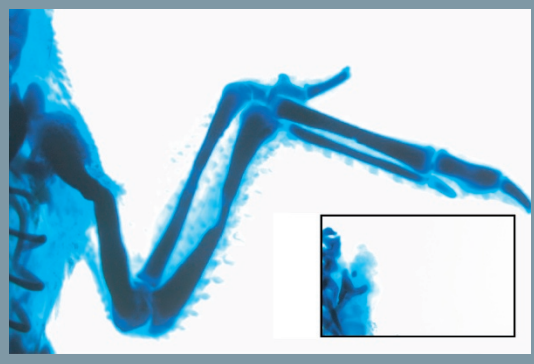
Thalidomide is not a drug that that impinges on just one biological pathway. That complexity could explain its multifaceted effects—from its ability to induce vascular remodeling in the adult, as outlined by Lebrin *et al.* in this issue (pages 420–428), to its devastating effects on the developing embryo and fetus.

It's been almost 50 years since the drug was pulled from the market for causing birth defects, but only now are researchers beginning to understand the basis for its teratogenicity. In a recent study, Takumi Ito *et al.* (*Science* **327**, 1345–1350, 2010) unravel how thalidomide might cause limb deformities during embryonic development, suggesting that it acts in this context by binding a ubiquitin ligase complex.

Using beads coated with a thalidomide derivative, the authors fished out the protein cereblon from cell lysates as a direct thalidomide target. This protein, the researchers found, is a component of a ubiquitin ligase complex. The binding of thalidomide to cereblon inhibited the activity of this complex.

In zebrafish, the authors showed that this binding is required for thalidomide to disrupt embryonic development. Knockdown of the zebrafish homolog of cereblon resulted in developmental defects similar to those caused by thalidomide treatment, and overexpression of a mutant version of cereblon, unable to bind thalidomide but still functionally active, rescued the developmental defects caused by thalidomide treatment.

The researchers observed similar mechanistic effects of thalidomide in chick embryos. Moreover, thalidomide's binding to cereblon suppressed expression of chick genes encoding two growth factors important for limb patterning, *Fgf8* and *Fgf10*—although exactly how is unclear.



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A normally-developing chick limb, and a limb exposed to thalidomide (inset).

Thalidomide may also act through other mechanisms to disrupt limb development, such as through hindering angiogenesis, as previously reported (*Proc. Natl. Acad. Sci. USA* **106**, 8573–8578, 2009). An understanding of how thalidomide acts may spur the development of derivatives that lack teratogenicity but retain therapeutic effects. —***Michael Basson***