to RAF inhibitors; thus, it will be worthwhile to examine changes in Axl expression in cell line–based models of resistance to RAF inhibitors, as well as in samples from relapsed patients. In summary, Gas6–Axl signaling may be a signaling “axis of evil” in melanoma, and it should be investigated further as a “druggable” pathway.

CONFLICT OF INTEREST
The author states no conflict of interest.

REFERENCES


Infantile Hemangioma Research: Looking Backward and Forward
Ilona J. Frieden1

This is a remarkable time to be a student of infantile hemangiomas (IHs). IH is a common tumor, estimated to occur in approximately 4% of infants. Studied for many decades, the acquisition of knowledge and pace of IH research are accelerating. The article by Greenberger et al. in this issue is a welcome addition to the literature. It examines rapamycin as a possible treatment for IH that could potentially be curative because suppression of self-renewal of stem cells might deplete hemangiomas of the stem cells from which they originate. However, before we get too enthusiastic about using rapamycin for IHs, it is important to reflect on lessons learned from previous hemangioma therapies.

Infantile hemangioma research in the 20th century
Although there was evidence as far back as the late 1930s that infantile hemangioma (IH) involuted spontaneously, studies describing the natural history of IHs published in the 1960s more clearly delineated the

characteristic natural history of rapid growth followed by gradual involution. X-irradiation therapy, an effective treatment for hemangiomas, was used widely from 1930 to 1950 (Mulliken and Young, 1988). Starting in the 1950s, prominent physicians—among them the founders of the subspecialty of pediatric dermatology, Alvin Jacobs and Sidney Hurwitz—decried the use of X-irradiation and attempts at preemptive surgical removal, advocating a hands-off approach. Why, after all, would you treat something that would go away on its own? This was sage advice, but it had its limitations. Although most hemangiomas involute without leaving major sequelae, a significant minority are problematic.

An important therapeutic breakthrough came in the mid-1960s, when systemic corticosteroids were found to be an effective treatment. Despite their many potential side effects, prednisolone and other corticosteroids became a mainstay of treatment for those hemangiomas severe enough to require systemic therapy. Treatment of IH caused medical morbidities (e.g., amblyopia or airway disease) was clearly necessary. Less clear, however, was the approach for hemangiomas that are not medically endangering but are arguably life-altering—leaving scarring or permanent distortion of important anatomic structures of the face, such as the nose and lips.

In 1982, Mulliken and Glowacki proposed a biologic classification of vascular birthmarks into “hemangiomas” and “vascular malformations.” This was a major conceptual breakthrough that helped to clearly delineate IHs as an entity distinct from other vascular birthmarks (particularly venous malformation, with which it was often lumped, under the diagnosis of “cavernous hemangioma”) (Mulliken and Glowacki, 1982). Like many other important ideas, this one seems obvious in retrospect. At the time, however, nosologic confusion was a major obstacle to understanding the biology of IH; this confusion hampered efforts to define optimal treatments. A chronic lack of funding also hindered research. Without funding from the National Institutes

www.jidonline.org 2345
of Health or pharmaceutical interest, research continued to consist mainly of case reports and small case series.

By the late 1980s and early 1990s, multidisciplinary vascular anomalies centers were being established both in the United States and internationally. These centers began to concentrate referral patients and increase collective expertise concerning hemangiomas as well as other vascular anomalies. Interested physicians and scientists began to hold informal workshops, and in 1992, the International Society for the Study of Vascular Anomalies was established. Other developments that spurred interest in hemangiomas included the trend toward increasing patient self-advocacy, which led many parents of infants with IHs to question the standard advice “not to worry” and instead look for other answers. Patient-support organizations were formed.

Advances in laser therapy, particularly the pulsed dye laser (PDL), which became commercially available in 1989, added another potential treatment for IHs. This advance, in turn, led many physicians to reconsider whether there might be better therapies (including PDL) to treat hemangiomas. In 1991, Ezekowitz et al. reported the use of interferon (IFN)-α as a novel hemangioma therapy; in 1992 they published a case series of 20 patients, most of whom had failed systemic corticosteroid therapy. Recognition of the need for better therapies is attestable to by more than a dozen articles published within five years after the initial reports of IFN therapy (Ezekowitz et al., 1992). Unfortunately, another lesson was learned from the IFN experience: in the late 1990s, severe neurotoxicity was recognized as a side effect, occurring in up to 20% of patients.

IH research in the 21st century

The pace of hemangioma research has increased significantly in the 21st century (Figure 1). In January 2000, North et al. published their seminal observation that, unlike other vascular tumors or vascular malformations, IHs stain with the immunohistochemical marker Glut-1 (North et al., 2000). This and the many observations that followed revolutionized the way we think about hemangiomas. We now know that IH is not a tumor of ordinary cutaneous blood vessels that have “run amok” but, rather, a growth with a unique vascular phenotype. The demonstration of the remarkable similarities between IH and placental blood vessels led several investigators to look more closely at the cells of origin of IH. We now recognize that IH may be not solely a disorder of angiogenesis (i.e., the sprouting of vessels from existing ones) but in fact due—at least in part—to a disorder of vasculogenesis (i.e., de novo formation of new blood vessels from circulating stem cells) (Boscolo and Bischoff, 2009; Dadras et al., 2004). The progenitor cells of IH have many pluripotent qualities, with features of myeloid, monocytic, endothelial, and even neural crest differentiation (Itinteang et al., 2010; Kleinman et al., 2007). Therefore, IHs may represent a growth of primitive mesenchymal cells in a state of arrested development. Attempts to characterize the nature of the progenitor cells of hemangiomas continue. The development of sustainable in vitro and ex vivo models was another major step. In 2000, Tan et al. reported such a model, with tissue explants of IH embedded in fibrin gel (Tan et al., 2000). In 2008, Khan et al. reported the creation of a sustainable ex vivo model in nude mice. In this model, used in the current study, isolation of multipotential stem cells from surgically removed IH tissue gave rise to hemangioma-like lesions, retaining phenotype and eventually involuting with decreased blood vessels and increased adipocytes, mimicking the natural history of IHs (Khan et al., 2008).

Over the past decade, many studies have increased our understanding of the clinical characteristics of IHs. We now know that hemangiomas are not randomly distributed. We have also moved beyond the traditional morphologic descriptions of IH as superficial, deep, and mixed to recognize two other important patterns of hemangiomas: those that are spatially confined, or “localized,” and those with a territorial distribution, or “segmental” (Chiller et al., 2002; Waner et al., 2003). The patterns of segmental hemangiomas of the face were found to correspond to embryologic prominences (such as the maxillary and mandibular placodes) that arise early in embryologic development (Hagstrom et al., 2006b; Waner et al., 2003). Like their smaller, more localized counterparts, segmental IHs have all the immunohistochemical and molecular features of other IHs, including rapid growth and spontaneous involution, but the recognition of these patterns of distribution.
and the increased appreciation that IHs can have associated structural malformations (e.g., PHACE syndrome) provided further clues that segmental IHs arise via an early error in embryologic development that is permissive for hemangioma progenitor cell growth.

A study of early hemangioma growth by the Hemangioma Investigator Group (HIG) added yet another clue to the developmental nature of hemangiomas. Both localized and segmental hemangiomas, rather than having a lateral growth phase (as one might expect from a conventional tumor), “mark out their territory” and grow volumetrically (Chang et al., 2008). Other HIG studies have helped to identify the clinical characteristics that best predict the greatest risk for complications. A prospective cohort study of more than 1,000 infants demonstrated that segmental hemangiomas have a higher risk of complications, need for treatment, and associated structural anomalies (Haggstrom et al., 2006a). Current HIG studies include the creation of a disease-severity score and the creation of an instrument for measuring the impact on parental quality of life.

This history would not be complete without mention of one of the most remarkable recent developments: the serendipitous observation that propranolol is an effective treatment for IHs. In the three years since June 2008 when Leauté-Labreze et al. first reported their findings in a letter to the New England Journal of Medicine, more than 140 articles regarding β-blocker therapy for IHs have been published, nearly all reporting positive results (Leauté-Labreze et al., 2008). Other β-blockers, such as acetebutolol and nadolol, may also be effective, and preliminary reports of a topical β-blocker, timolol, suggest that it may be helpful for smaller, more superficial hemangiomas. Experience thus far with propranolol for IHs again points to caution when treating young infants with hemangiomas—one might have expected bradycardia or hypotension as possible side effects, but, instead, hypoglycemia has emerged as a rare but potentially serious side effect.

**Future therapies**

Greenberger and colleagues’ study (2011, this issue) regarding the effects of rapamycin on an in vitro model of IH is a welcome step in this journey. Rapamycin appears to target HemSC via a mechanism distinct from corticosteroids, suggesting that the drugs used together (perhaps at lower doses) could enhance their effects. Interestingly, this report does not mention whether propranolol or other β-blockers have similar effects—something that would be of great interest because propranolol is becoming a first-line therapy in many centers. The finding of a loss of stem cell properties should be of particular interest because such an effect might conceivably offer a cure without the rebound growth that can be a problem, for a significant minority of patients, in both steroid and β-blocker use. The target of rapamycin (mTOR) is a kinase of the phosphoinositide 3-kinase signaling pathway. It is one of the most important intracellular mediators of the activity of growth factor receptors, including vascular endothelial growth factor (VEGF). Although preliminary evidence suggests that rapamycin, given systemically or applied topically, is beneficial under other conditions with vascular overgrowth (such as angiofibromas in tuberous sclerosis), its activity would not necessarily be anticipated in IH. In addition to its possible therapeutic implications, the finding of its effects in a laboratory model of IH should certainly be taken as a clue to looking closely at its effects on VEGF and VEGF receptors, which have already been shown to play a role in hemangioma growth (Jinnin et al., 2008).

The idea of yet another drug that might be useful in treating IHs is exciting, but the history of unanticipated problems with previous hemangioma therapies makes it important to inject a cautionary note. We have known for decades that not all hemangiomas need treatment; enthusiasm for a new therapy should never let us lose sight of this important fact. Given the tremendous heterogeneity in size, location, and growth potential, the development of validated disease-severity scores should help to ensure that we compare hemangiomas of similar severity rather than lumping together disparate IHs. Equally important is the recognition that the target population for hemangioma therapy is infants who both are undergoing rapid somatic growth and have rapidly maturing organs—in particular, the central nervous system. Infants may thus be particularly vulnerable to side effects that are either unanticipated (e.g., spastic diplegia with IFN) or rare in older patients (e.g., hypoglycemia with propranolol). Rapamycin (sirolimus), a calcineurin inhibitor, has many potential side effects and has boxed warnings regarding risk of immunosuppression and risk of developing lymphoma and other malignancies. Experience regarding its toxicities in infants is limited (Blatt et al., 2010). It is generally not used in combination with corticosteroids because of the potential for additive immunosuppressive effects. Do these concerns mean we should not consider rapamycin a potential treatment? Not necessarily—but we should hold ourselves to a higher standard than in decades past and study this and future hemangioma therapies in an evidence-based manner.
A recent Cochrane analysis highlights the deficiencies of previous hemangioma treatment. More than four decades after corticosteroids were found to be effective in treating IHs and two decades after the introduction of PDL for IHs, the authors of this meta-analysis were able to find only four randomized controlled trials (RCTs), involving only 271 patients, to analyze (Leonardi-Bee et al., 2011). They found insufficient evidence to support existing interventions, such as corticosteroids and laser, and concluded that there is “a need for further high-quality RCTs to validate the findings from these studies, and RCTs to assess the effect of other treatments, in particular relating to propranolol.” Fortunately, at least 10 treatment studies for IH are currently listed at ClinicalTrials.gov, including a large international RCT comparing propranolol and placebo, and it is hoped that more will follow. We owe it to infants with IHs and the scientific community to study this disease and its potential therapies rigorously.

CONFLICT OF INTEREST
The author has consulted for Pierre-Fabre Dermatology.

ACKNOWLEDGMENTS
The author thanks Toni Martin, Thea Mauro, and Jack Resneck Jr. for critical review of the manuscript; Gail Sorrough for assistance in PubMed searches; and Chris Walker for editorial assistance.

REFERENCES
Dadras SS, North PE, Bertocini J et al. (2004) Infantile hemangiomas are arrested in an early developmental vascular differentiation state. Mod Pathol 17:1068–79