ed may be due to a variety of mechanisms, not just inhibition of angiogenesis.

Given the fact that antiangiogenic drugs are mainly used in combination with chemotherapy, an obvious question is whether relapses observed in patients who are treated with a targeted drug such as bevacizumab with chemotherapy occur mainly as a consequence of development of resistance to the targeted antiangiogenic drug in a manner similar to that described by Casanovas et al., or alternatively, to the chemotherapy component of the regimen. If it is the former, the need for discontinuation of the antiangiogenic drug therapy is obvious, along with its possible replacement by another drug that has a good chance of showing resurrecting efficacy. If it is the latter, continued use of the original antiangiogenic drug and a change in chemotherapy would be called for. Considering the therapeutic consequences of making the right (or wrong) decision, as well as the enormous economic implications, given the huge cost of many new anti-cancer drugs, distinguishing between the two will obviously assume an obvious degree of future importance. Viewed from this perspective, the results of Casanovas et al., and also of Mizukami et al. (2005) firmly establish the multiplicity of compensatory angiogenic pathways available to cancer cells as a likely cause of resistance to specific targeted antiangiogenic drugs, and suggest potential strategies to delay such resistance, thus facilitating not only their intrinsic antiangiogenic properties, but their chemosensitizing effects as well.

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A mouse model for studying therapy-induced cancers

As more pediatric cancer patients survive for longer periods following treatment with cytotoxic agents, therapy-induced second malignant neoplasms (SMNs) have become a major concern. In this issue of *Cancer Cell*, Chao et al. report that mice carrying a mutation in *Nf1*, the gene responsible for neurofibromatosis type 1, treated with radiation and/or cyclophosphamide, developed tumors similar to human SMNs at a significantly higher rate than did wild-type controls treated similarly. This model provides efficient and rational means for testing procedures and agents that could inform clinicians regarding second cancer risks associated with treatment and, perhaps, reducing them.

This issue of *Cancer Cell* carries a report of experiments with a mouse model of the most common hereditary condition facing the pediatric oncologist, neurofibromatosis type 1 (NF1) (Chao et al., 2005). Shannon and colleagues used adolescent and young adult mice that carry a mutation in *Nf1*, the gene responsible for NF1, to study cancer resulting from the effects of cytotoxic therapy in genetically susceptible individuals. Mice heterozygous for that mutation developed second malignant neoplasms (SMNs) with or without the administration of radiation (RAD) and/or chemotherapy with an alkylating agent (cyclophosphamide [CY]) at a significantly higher rate than wild-type controls who were similarly treated (51/81 compared to 17/100).

It was inevitable that I would be excited about this report, since the interaction of therapy and genetic predisposition in the etiology of SMNs has preoccupied me during the past 30 years of my work with survivors of childhood cancer. During the decade of the 1970s, as it became evident that children with cancer would be able to survive for many years after receiving treatment, concerns began to be expressed regarding the long-term effects of the RAD and chemotherapy responsible for cure. With colleagues at the National Cancer Institute and three major pediatric oncology centers, I embarked on a study of late effects, especially SMNs, in survivors of childhood cancers.

Our report published in 1985 on the spectrum of 308 SMNs in 292 childhood cancer survivors seen at 13 institutions in the United States, Canada, and Europe noted that 68% had developed in a tissue that had been exposed to RAD, that bone and soft tissue sarcomas were the most

Table 1. Dominantly inherited cancer syndromes and associated neoplasms

Syndrome	Primary tumor	Secondary/associated neoplasms	Gene
Genetic retinoblastoma	retinoblastoma	sarcomas, pineoblastoma, melanoma	*RB1*
Li-Fraumeni	sarcomas, breast	adrenocortical, brain tumors, leukemia	*p53*
Neurofibromatosis type 1	neurofibromas	neurofibrosarcoma, AML, JMML, glioma	*NF1*
Neurofibromatosis type 2	vestibular schwannomas	meningiomas, astrocytomas, ependymomas	*NF2*
Tuberous sclerosis	renal	brain tumors	*TSC1,2*
von Hippel-Lindau	renal	brain tumors, pheochromocytoma	*VHL*
Nevoid basal cell carcinoma (Gorlin syndrome)	basal cell carcinoma	medulloblastoma	*PTCH*
Familial adenomatous polyposis	colorectal	colon, hepatoblastoma, thyroid, desmoid	*APC*
Hereditary nonpolyposis colorectal cancer	colorectal	endometrial, ovarian, gastric, pancreatic	*MSH2/MLH1*
Familial breast cancer 1	breast	ovarian	*BRCA1*
Familial breast cancer 2	breast	pancreatic, ovarian	*BRCA2*

AML, acute myelogenous leukemia; JMML, juvenile myelomonocytic leukemia.

frequent, and that 52 of 67 bone tumors and 43 of 59 soft tissue sarcomas occurred in tissues exposed to RAD (Meadows et al., 1985). Since then, there have been numerous reports attesting to the role of therapy, notably RAD and some chemotherapeutic agents, in the etiology of SMNs in both children and adults, and we have learned much (Meadows, 2001; Rheingold et al., 2005). We know that RAD is the most common etiological factor in SMNs, that there is a dose response for tumors of bone and soft tissues (Tucker et al., 1987a), that young age and lower doses of RAD increase the risk of thyroid cancer (Sigurdson et al., 2005), that breast cancer continues to increase for years in young women who have been treated with RAD for Hodgkin's disease (Bhatia et al., 2003; Travis et al., 2003), and that certain alkylating agents and topoisomerase 2 inhibitors, depending on dose and schedule, are associated with secondary leukemias (Bhatia et al., 1999; Felix, 1999).

There were some children in that earlier cohort who developed SMNs because they were obviously predisposed: children with the hereditary form of retinoblastoma and children with NF1. Although these conditions remain the most common syndromes among children who develop SMNs after childhood cancer treatment and have been the most widely studied, other, less common genetic conditions associated with cancer, whose genes have been cloned, might also serve as models for mechanisms of transformation (Table 1).

In the hereditary form of retinoblastoma, marked by a constitutional mutation in *RB1*, an increased risk for SMNs imposed by RAD has been well documented (Wong et al., 1997). However, there have not yet been data demonstrating an unequivocally increased risk following RAD in humans with NF1. The results of these experiments in this animal model may provide sufficient evidence to convince any remaining skeptics.

Since the tumors that NF1 children develop either spontaneously or following therapy are similar to those in the *Nf1* mice, these mice provide a faithful model in which to study the induction of neoplasms in individuals treated for cancer. The model closely resembles the human experience, since related neural crest tumors, soft tissue sarcomas, and a special form of myeloid leukemia are seen in both cases. Furthermore, the induction of secondary tumors by RAD and/or an alkylating agent, even in individuals not known to be genetically predisposed, also parallels the human experience. In addition, the mechanism of solid tumor formation is also similar to that seen in humans, LOH of a tumor suppressor. As in humans, the myeloid neoplasms do not appear to use this mechanism but may result from translocation and oncogene activation. NF1 patients spontaneously develop myeloid neoplasms similar to those in *Nf1* mice treated with RAD alone. That fewer leukemias are seen in RAD/CY-treated mice parallels the finding that leukemia as an SMN was not associated with therapeutic RAD in children, since children are rarely treated with RAD alone (Tucker et al., 1987b).

Nf1 mice in these experiments also developed neural crest and myeloid tumors without treatment, but more solid tumors after RAD/CY and RAD alone than controls similarly treated. An unexpected finding was the development of four breast cancers in the RAD/CY-treated group of susceptible mice. Breast cancer, the hallmark of the Li-Fraumeni syndrome, is associated with mutations in *TP53*, and with sarcomas in young family members. While these individuals are also known to develop multiple neoplasms, the role of therapy in accelerating their production is not yet clear (Malkin et al., 1990). Gorlin syndrome, a condition in which basal cell carcinomas occur at an earlier than expected age, is similar to NF1 in providing an example of the interaction of genes and environment; RAD accelerates the development of basal cell carcinomas in the field of RAD for medulloblastoma, an embryonal neoplasm that occurs in children with the syndrome (Evans et al., 1991).

Pediatric oncologists are also familiar with the exaggerated effects of RAD in ataxia telangiectasia (ATM), a recessive condition characterized by failure to repair DNA. It has been proposed that heterozygotes, who constitute as many as 1% of the population, might be more likely than others to develop SMNs following RAD; evidence for this mechanism in women who develop breast cancer following chest irradiation is still being explored.

In addition to providing an intellectually satisfying model for the study of the tumors that result from genetic predisposition and therapy, numerous questions regarding SMNs in children, discussed by the authors, might be addressed using *Nf1* mice without having to wait years for the answers. For example, are there other drugs or combinations that either increase the incidence of SMNs or provide protection from the effects of RAD or chemotherapy, and how do these maneuvers alter the latent period between exposure and SMNs? In the case of RAD, could the well-known direct dose rate effect of RAD upon mutation

be employed to reduce SMNs by using the same dose at lower dose rates?

This research encourages us to believe that the great progress in curing children with cancer and improving the quality of their survival will continue so long as pediatric oncologists, including Dr. Shannon, ponder a child's full life span.

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