nature genetics

High-input biology

A student of biology, considering a problem to solve, will examine the range of experimental approaches available, fundamental biological interest, application to health and wealth and chances of success or failure. But how often will she think of the research field biologically? For example, is the research in the lag phase of its growth curve, or spinning off labs and subdisciplines in a phase of exponential productivity? Some lines of research literally spawn ideas. In others, a small number of high-priority problems are intensively nurtured.

The enduring mystery of the Fanconi anemia pathway is a marvel of "high-input biology," reapplying a term coined by Sydney Brenner at a recent HUGO human genome meeting. During a period that includes explosions of research activity on DNA repair and replication, cell cycle control, apoptosis and tumor suppressor genes, the community of Fanconi anemia researchers has remained relatively compact and has contributed a steady stream of distinctively large insights into the pathway, as indicated by the 20 related papers published over 13 years in *Nature Genetics* (http://www.connotea.org/tag/Fanconi). The field has neither exploded nor extinguished because Fanconi anemia is simultaneously a tough and a scientifically rewarding problem. The student of biology can learn from these dedicated researchers with every advantage integrative genetics has to offer, consistently at the limits of what the method can deliver.

Fanconi anemia research has advantages of intellectual location, unpicking a devastating human disease that promises clues to carcinogenesis in unaffected people as well as fundamental insights into mechanisms of DNA repair. It uses the tools and strategies developed in a paradigm shared with other DNA repair syndromes (xeroderma pigmentosum, ataxia telangiectasia, Werner progeria and Bloom and Cockayne syndromes). There is smooth reduction in explaining phenotypes from organism to organ to cell to molecule. Cellular phenotypes can be studied and used for selection without the difficulties associated with studying specialized cells *in vivo*. Fanconi anemia research has benefited from the intersection of many disciplines since Craig Strathdee, Manuel Buchwald and colleagues first cloned a locus underlying Fanconi anemia by functional complementation of mutant cells with a *FANCC* cDNA (*Nature* **356**, 763–767; 1992).

And yet the researchers face unusual difficulties. Strathdee and Buchwald and colleagues also found, by functional complementation through cell fusion, that there were multiple loci underlying Fanconi anemia (*Nat. Genet.* **1**, 196–198; 1992). Fanconi anemia–associated proteins cooperate and act as a complex, and in this respect, Fanconi anemia poses a more difficult problem than single-gene repair defects in Bloom syndrome, ataxia telangiectasia and xeroderma pigmentosum. Linkage methods for positional cloning have been frustrated by the genetic heterogeneity of the few rare cases available worldwide. The pathway is instructive for the rest of monogenic genetics, being moderately connected and of intermediate complexity. It is unlikely to involve the level of intricacy of a ribosome or the degree of redundancy of the nuclear pore.

The interacting components of the Fanconi anemia core complex share a mutant phenotype, but until recently, it has not been possible to identify distinctive properties of the components to illuminate the pathway. That is why it is so exciting to find ligase, and now helicase and translocase, activities through which the Fanconi anemia pathway can be linked together by familiar molecules and into related pathways. In this issue, Marieke Levitus, Quinten Waisfisz and colleagues (page 934) and Orna Levran and colleagues (page 931) identified pathogenic mutations in *FANCJ* and show that it encodes the BRIP1 helicase, a BRCA1-interacting protein, which Wendy Bridge and colleagues (page 953) show functions independently of BRCA1 in the Fanconi anemia pathway. Also in this issue, Amom Ruhikanta Meetei and colleagues (page 958) found that the product of the gene mutated in a new Fanconi anemia complementation group (*FANCM*) participates in the Fanconi anemia core complex and can translocate along DNA.

Because this field is still coherent enough to be followed in its entirety, its main questions have been clearly posed and thoroughly argued. Alan D'Andrea, in his address last year to the 16th Scientific Symposium of the Fanconi Anemia Research Fund (http://www.fanconi.org), discussed arguments about the structure of the pathway, the model (presented by Larry Thompson, News and Views on page 921) of the way in which the complex senses DNA damage and the role of Fanconi anemia–associated proteins in normal development. Many of the problems he listed concern the importance of the pathway to cancer in the general population. For example, it is not known whether heterozygotes with respect to Fanconi anemia–associated mutations are cancer-prone or whether loss of heterozygosity occurs. Perhaps polymorphic Fanconi anemia variants will be found in cancer-prone individuals without Fanconi anemia.

The disease points the way to both prospects and obstacles to translational medicine. In tumors arising from defects in other pathways, sporadic somatic disruption of the Fanconi anemia pathway may occur and predict sensitivity to cisplatin therapy. But affected individuals face challenges in their bone marrow transplants and cancer therapies, because the disorder results in hypersensitivity to cytokines and to DNA crosslinking agents. D'Andrea acknowledged the advantage the researchers have in standing at the intersection of many fields, and he emphasized their responsibility to their research partners, the families with Fanconi anemia. ■