and the erythropoietin receptor, two members of the hematopoietin/cytokine receptor family (*12–15*). These observations are likely to explain the excessive erythropoiesis and the leukocyte hyperactivity seen in the *motheaten* mice.

One of the most surprising aspects of the emerging inhibitory role of PTP1C is that it contrasts with evidence for a positive signaling role of the highly related PTP1D tyrosine phosphatase (also called Syp, SH-PTP2, and PTP2C). PTP1D also contains two SH2 domains and a phosphatase domain, but in contrast to the restricted hematopoietic distribution of PTP1C, PTP1D is widely expressed. A number of lines of evidence indicate that PTP1D has a positive role in signaling induced by transmembrane tyrosine kinase receptors such as the platelet-derived growth factor receptor. PTP1D plays a positive role by acting as an adaptor that can bind to autophosphorylated receptors via its SH2 domains, become tyrosine phosphorylated by these receptors, and then serve as a binding site for the Grb-2–SOS complex that activates Ras (*16, 17*). The result is that PTP1D plays a positive role in receptor activation of Ras. It seems likely that the phosphatase activity of PTP1D also contributes to receptor signaling, as suggested by the inhibitory effects of overexpressing a catalytically inactive mutant of PTP1D (*18*) and by microinjection experiments (*19*). Interestingly, the *Drosophila melanogaster corkscrew* gene product has the same overall structure as PTP1C and PTP1D, but clearly has closer sequence similarity to PTP1D. Functionally, the *corkscrew* product also is more like PTP1D, as genetic experiments indicate that it acts positively downstream of the *Torso* receptor tyrosine kinase to specify terminal structures of the fly embryo (*20*). It is not known whether this developmental function of *corkscrew* requires tyrosine phosphatase activity or whether it uses the adaptor function. In any case, it is clear that the SH2-containing protein tyrosine phosphatases are critical, both positively and negatively, in regulating signaling by receptors that use tyrosine phosphorylation to mediate their intracellular effects.

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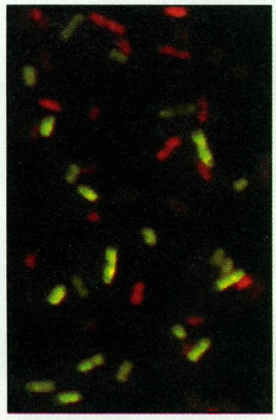
Green Fluorescent Pets

Douglas C. Youvan

Fifteen years ago, when the genes for the photosynthetic light-harvesting proteins were found, my colleagues in molecular biology asked the following question: Why can't we use these proteins as in vivo fluorescent tags, and wouldn't that be a lot better than attaching β-galactosidase to proteins and having to supply substrate for visualization? The answer was straightforward: Sure, but the light-harvesting proteins need associated pigments for their signal. You'll also have to express and regulate 20 other genes for pigment biosynthesis!



MARY YANG, KAIROS

From a crayon box of *Escherichia coli* to...

Green fluorescent protein (GFP) (*1*) gets around this problem by autocatalytically forming a fluorescent pigment from natural amino acids present in the nascent protein. GFP works across the phyla—from glowing tobacco mosaic virus with GFP-infected leaves to lighted sensory neurons in worms (*2*). To these add fluorescent zebrafish eyes, flies, yeast, and yes, possibly people—if engraftment with GFP-tagged stem cells in bone marrow becomes possible.

GFP engineering is rapidly creating a crayon box of different colors, from wild-type green to blue emitters and red-shifted excitation derivatives. Fluorescence resonant energy transfer (FRET) experiments on GFP-tagged proteins to measure distances between proteins are right around the corner. Protein-protein interactions are already assessed with GFP in the yeast two-hybrid system. But, by using different colored GFP derivatives there is the possibility of performing FRET in single cells to visualize the interaction of tagged proteins. Add to this the tools of fluorescence-activated cell sorting and confocal microscopy, and one has the makings of a methodology on par with the polymerase chain reaction.

The real fun will start in the near future when methodologies begin to collide.

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CURTIS HOLT, SCRIPPS

...tobacco mosaic virus–infected leaves.

FRET-GFP technology might be brought together with combinatorial chemistry and screening technologies with high throughput. With the help of specifically engineered cell types, this could lead to a massively parallel strategy for finding new drugs. Hundreds of thousands of chemicals could be screened, with each cell behaving as a separate instrument.

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