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BIO/TECHNOLOGY PRODUCTION CONFERENCE

HOST SYSTEM POINTERS

NEW YORK—For expressing recombinant proteins, the choice of a host system used to be easy: It was *Escherichia coli* or nothing. But now there are alternatives—including yeast, filamentous fungi, insect cells, and mammalian cells. With so many choices, it is crucial for a company to select the best system for producing quantities of its favorite recombinant protein(s). And there is no "host of hosts." Not only does every protein have its own unique properties, but so does every host/vector system. And a system that works well in one lab may behave differently in another.

Developing a viable production system can be a painstaking job. In fact, as Cetus' (Emeryville, CA) Leo Lin pointed out at the *Bio/Technology* Conference on Production Systems here in May, it is just this sort of long-term project that can provide a research scientist with job security.

Nonetheless, there are some general "rules of thumb" to selecting an appropriate host, summarized at the meeting by Chris Simonsen (Invitron, Redwood City, CA). Bacteria may not secrete well (although the Gram-positives are better than the Gram-negatives, according to Lin), but they *can* express at high levels. By comparison, mammalian cells are fairly limited in their ability to express recombinant proteins, but they have no trouble secreting what they make.

Part of the trick in coaxing cells to secrete lies in the choosing of the signal peptide. And, since there are almost no cross-species signal peptides, says Lin, it is necessary to generate a library for each host. Herbert L. Heyneker (Genencor, South San Francisco, CA) suggested that the reason it is not (yet) possible to achieve the same high levels of heterologous as homologous gene expression in the filamentous fungus *Aspergillus niger* is because the signal peptide does not dock properly on the signal recognition sequence.

Once the molecular and biochemical principles of secretion are better understood, some of the difficulties in designing production host systems should disappear. One principle that is already clear, according to Lin, is that the primary sequence of a protein has something to do with the secretion mechanism.

And the fact that several strains of bacteria, of yeast, *and* of fungi are all capable of secreting chymosin (also known as rennin, an aspartyl protease used in cheese making; see table) again supports the view that a protein's primary sequence plays a role in secretion—promoters, terminators, and signal sequences aside.

—**Jennifer Van Brunt**

Comparison of Prokaryotic and Eukaryotic Expression Systems

DESIRED Characteristics	EXPRESSION SYSTEM Bacteria	Yeast	Mammalian
Rapid cell growth	+++	+++	−−−
Low cost of growth media	+++	+++	−
High expression	+++	++	+
Secretion	−−−	+−	+++
Protein folding	−−	+−	+++
Disulfide bond formation	−−	+−	+++
Glycosylation			
Simple	−−−	+++	+++
Complex	−−−	−−−	+++
High purification yields	−−	−	+++

Microbial Expression Systems for Chymosin

BACTERIA	Escherichia coli	intracellular secreted	Univ. of Tokyo Genentech Codon Celltech
	Bacillus subtilis	intracellular secreted	Genentech
	Streptococcus cremoris	secreted	NIZO
YEAST	Saccharomyces cerevisiae	secreted	Genentech/Genencor Celltech Collaborative Research
	Kluyveromyces lactis	secreted	Gist Brocades
	Yarrowia lipolytica	secreted	Pfizer
FUNGI	Aspergillus spp.	secreted	Genencor Zymogenetics Allelix
	Trichoderma reesei	secreted	Genencor