ization; when added to cartilage, it induces breakdown of the matrix material. This suggests that the β form is involved in the joint erosion associated with rheumatoid arthritis. The IL-1α molecule, on the other hand, exhibits homology with fibroblast growth factor—which aids in wound healing and also stimulates fibrosis—and with a murine IL-1 cloned by Steven Mizel (Pennsylvania State University, University Park), Peter Lomedico (Hoffmann–La Roche, Nutley, NJ), and their associates.

The α and β forms share characteristics as well. Gillis has shown that both stimulate lymphocytes, apparently through the same receptor. He has been able to identify and quantitate these receptors for a number of cell types. The receptor density falls in the range of hundreds to thousands per cell, somewhat on the low side for a typical polypeptide hormone. Characterization of these receptors will allow the creation of therapeutic agents—IL-1 antagonists—which can block receptor function.

Nabil Hanna, director of immunology at Smith Kline & French Laboratories (Philadelphia, PA), says that his group has also identified a multi-gene IL-1 family in the human system. They have found two products which can be separated by physicochemical means. The two components have different isoelectric points and do not cross-react. Unlike Immunex's α and β molecules, however, those isolated at Smith Kline & French seem so far to be functionally identical. The two subtypes may instead be elicited by different stimuli, react with different receptors, or have different affinities for the same receptor.

Peter Lomedico, director of the department of molecular genetics at Hoffmann–La Roche, has studied the murine IL-1 system extensively. In this system there seems to be only one IL-1 gene. Lomedico and associates have cloned and expressed the gene in *Escherichia coli*; it codes for a 270-amino-acid precursor polypeptide. This precursor is secreted by macrophages and then enzymatically processed to the final form. Differential processing results in a heterogeneous population of molecules with ragged amino termini; they all, however, contain the IL-1 sequence at the carboxy terminus. Lomedico has recently cloned the human homolog of the mouse protein, and he finds it significantly different from homologs reported by other groups. This again supports the theory that the human interleukin-1 gene family contains two members, if not more.

—Jennifer Van Brunt

MEETING REPORT

PROTEIN STRUCTURE AND DESIGN

KEYSTONE, Colo.—Organizers report that the Genex-UCLA Symposium (held here in April) drew more interest than any program in the series' history. Designing a new protein demands constructive interplay of amino acid analysis, sequence determination, chemical modification, peptide synthesis, and information on structural aspects such as folding patterns. Thus, as Yale's Fred Richards noted, it is optimistic to expect a single site-directed mutagenesis to produce a specific desired transformation in a protein. Still, symposium speakers attested to the technique's power to illuminate vital areas.

Structure-function relationships. Joe Kraut (University of California, San Diego) has used oligonucleotide-directed, site-specific mutagenesis to modify the *Escherichia coli* dihydrofolate reductase (DHFR) enzyme. A mutation at amino acid position 39 (Pro 39 to Cys 39) did not affect the activity of the reduced enzyme. The oxidized mutant was also as active as the wild type, but was much more stable (as measured by unfolding in guanidinium chloride) than either the wild type or the reduced mutant. A mutation at position 27 (Asp 27 to Asn 27), however, had severe effects, reducing the enzyme's activity to only 0.1 percent of wild type. This underlines the importance of this amino acid in catalytic events, where it is thought to act as a proton transfer group.

Substrate specificity. William Rutter (University of California, San Francisco) reported that replacing glycines with alanines in the active site of trypsin (positions 216 and 226) enhances its specificity for arginine and lysine (see also *Science* **228:**291, 1985). A mutation in trypsin at position 102—from Asp to Asn—does not affect the Michaelis constant but does lower the enzyme's rate of catalysis for peptide substrates and raises it for ester substrates.

Conformational stability. Chris Matthews (Pennsylvania State University, College Park) has introduced mutations in DHFR at positions 28 and 139 to study protein unfolding rates. He finds that a mutation from Leu 28 to Arg 28 slows the rate of unfolding, whereas a mutation from Glu 139 to Lys 139 increases the unfolding rate. The rate of unfolding seems to depend on salt bridges: the formation of a salt bridge slows unfolding, while decreased bridge stability speeds unfolding.

DNA binding proteins. Robin Wharton (Harvard University) replaced the putative DNA-binding α_3 portion of the λ434 repressor protein with that of the P22 repressor protein. The protein encoded by the resulting gene—named 434R (α_3P22R)—bound to P22 operators *in vivo* and *in vitro*. This suggests the existence of separate recognition regions in the protein; replacing them changes the recognition specificity. Carl Pabo (Johns Hopkins University) has also studied the λ434 repressor protein. He introduced Tyr to Cys mutations at either position 85 or 88: the latter mutation resulted in stable disulfide-linked dimers. Binding of this dimer to the O_RI operator site on the DNA was ten-fold tighter than that of the wild type. The Cys 85 mutant, although it does not form a stable dimer, can be forced into the disulfide form. In this configuration, binding to the helix was ten-fold looser.

Model peptides. If the biological and physical properties of a peptide are dependent on the secondary structural features of a particular region, it should be possible to design a system having minimal homology to the natural peptide but still able to form a similar secondary structure. Emil Kaiser (Rockefeller University) has synthesized model peptides mimicking the effects of calcitonin, apolipoprotein B, and mellitin I. Mellitin I is a red-cell-lysing peptide with 26 amino acid residues. Residues 1–20 constitute an amphiphilic helix; residues 21–24 (Lys-Arg-Lys-Arg) are the recognition site. Kaiser synthesized a model peptide in which he retained the recognition site but changed the amino acids in the helix region. The modified region, only slightly homologous to native mellitin I, retained a similar secondary structure. This model peptide lysed red cells even more efficiently than the natural molecule. These results suggest that structural and recognition features are more important for biological activity than conservation of amino acid residues.

Thermostability. David Hirsch (Synergen, Boulder, CO) described a method for making a thermostable kanamycin nucleotidyl transferase by transferring the gene from a mesophilic microorganism to a thermophile (*Bacillus stearothermophilus*) and expressing it. The mutant enzyme was isolated on a kanamycin affinity column. The wild type and mutant enzymes had the same Michaelis constant and rate of catalysis.

—from S. Subramanian