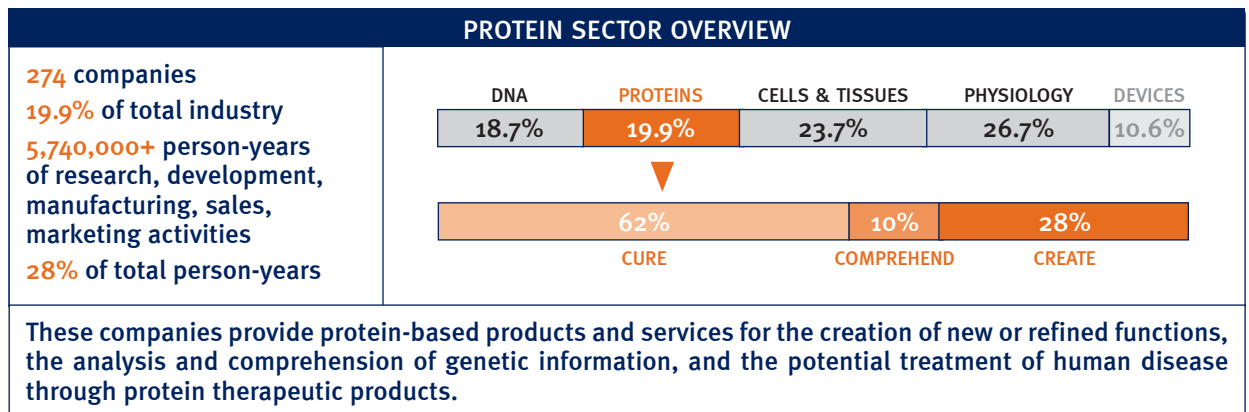


PROTEINS

Proteins are the “Swiss Army knives” of biology: they are used as structural supports, act as devices to accelerate chemical reactions, and manage information within physiological systems.

Proteins are fundamental to life because they are the structural units from which our cells, organs, and tissues are constructed. Proteins also serve a variety of nonstructural roles, including functioning as catalysts of chemical reactions (where proteins act as enzymes), regulating chemical processes in the body (where proteins act as hormones) and strengthening the immune system (where proteins act as antibodies). These versatile molecules are made of long chains of smaller chemical units called amino acids. The number and type of amino acids along the protein chain determine the size, shape, and function of proteins. In the past 20 years, the development of techniques to control the structure and function of proteins has led to the emergence of a growing protein-based market sector within the biotechnology industry.



Scientific Overview

STRUCTURE OF PROTEINS

Proteins are built from a pool of 20 common amino acids, which are stable chemical structures.

From the pool of 20 amino acids, a typical cell creates approximately 15,000 different proteins at any given time, with 2,000 of these proteins found in abundance (that is, with more than 50,000 copies of a specific protein present in a given cell). Different proteins exhibit a wide range of polymer lengths, from a few dozen amino acids (a small protein) to approximately 1,000 amino acids (a large protein).

FUNCTION OF PROTEINS

Proteins serve a wide range of functions in the body and play varied roles as structural agents, enzymes, regulators, and antibodies.

Proteins as Structural Agents

Often proteins have a structural role, providing mechanical integrity to a cell. The internal architecture of a cell is typically based upon a dense network of protein filaments, called the cytoskeleton. On a larger scale, muscle contraction depends on the action of assemblages of proteins such as actin and myosin. On a macro scale, collagen is a type of protein that is found in all multicellular animals and is present in hair, bone, skin, and most tissues. It is a very abundant protein, making up about 25 percent of the total protein found in the human body. Proteins are the basic structural unit of all living beings.

Additional mechanical roles for proteins include their use as storage vehicles and in the transport of molecules from one location to another. In terms of storage, proteins often bind to small molecules to protect and control their presence in the cell. For example, within red blood cells hemoglobin is a protein that binds to oxygen and supports the breathing processes. In terms of transport, proteins help move around other cellular components ranging from electrons to ions to other large proteins. For example, neurotransmitter receptors are complexes of proteins that control the migration of ions across nerve cells and support the control of nerve impulses.

Proteins as Enzymes

When proteins function as enzymes, they serve as biological catalysts in chemical processes, increasing the rate of a specific chemical reaction by a million-fold or more without being used up in the reaction itself. Enzymes are involved in virtually every aspect of biological function, including DNA replication, DNA transcription, and RNA translation, as well as food digestion, the creation of chemical energy, the development of an embryo, and the functioning of the brain. Further, the non-protein components of cells are often synthesized and controlled by enzymes.

Proteins as Regulators

Proteins can regulate chemical processes at several different spatial scales. On the spatial scale of DNA molecules, proteins can function as regulators of transcription and translation, impacting the construction and modulation of genetically encoded molecules such as RNA and other proteins. Proteins serving these roles are often called transcription or translation factors. These factors coordinate cellular activity so that the appropriate gene products are synthesized in the right place and at the right time, in the appropriate amount for a specific context. The essence of genetic regulation is the often-subtle control of this coordination so that materials are not wasted in the cell, but rather, built “just in time,” permitting efficient cellular function.

On a larger spatial scale, proteins can control and coordinate chemical processes occurring between cells, tissues, and organs in different parts of the body, and protein-based hormones are often carried in the bloodstream from one part of the body to another to act as long-distance chemical messengers. Proteins can also serve as the receptors for hormones.

Proteins as Antibodies

The immune system of humans depends on the production of antibodies to defend against foreign invaders such as bacteria and viruses. Protein-based antibodies bind to specific foreign substances (antigens) to render them biologically inactive and therefore harmless to the body. Each antibody can bind only to a specific antigen.

Given this wide range of functions, how are proteins made in the cell in such a precise and controlled fashion?

CREATION OF PROTEINS

DNA is used as a template to develop an intermediate form of information, termed RNA, which bridges the gap between genetic information and protein synthesis. The two main steps in the process are transcription and translation.

In the previous chapter on DNA, we described the “central dogma”—the flow of genetic information (see page 22). This section describes the process in greater technical detail. Understanding this process is important because many biotech applications interfere with or amplify it to produce a specific result.

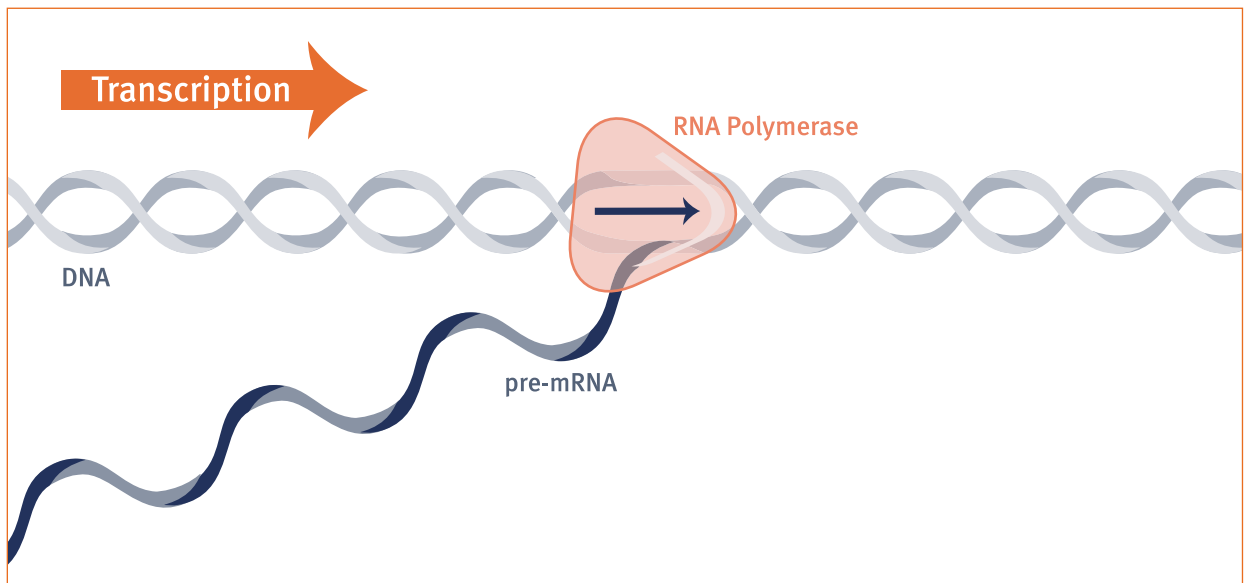
Transcription

The first step, copying the DNA information into RNA, is called transcription. During transcription, specific DNA sequences are copied into RNA sequences by the enzyme RNA polymerase.

The selection of which DNA sequences to transcribe is carried out by a combination of regulatory proteins, called transcription factors, that bind to DNA, and short DNA sequences, called promoters, which regulate the expression of nearby genes.

A set of three enzymes, called RNA polymerases (I, II, and III), bind to the transcription factors and open the DNA double helix. As the RNA

AN OVERVIEW OF TRANSCRIPTION



polymerase complex proceeds down one strand, it assembles chemical units into a strand of RNA. Each chemical unit of RNA is attached to the growing RNA strand following the rules of base pairing already described for DNA.

Why is RNA formed as an intermediate step in the creation of proteins from DNA? RNA is used as a working copy, and is modified as proteins are created and ultimately destroyed by the cell. If this were done to the parental DNA strand, precious and unique genetic information would be forever lost, so the RNA intermediate permits a “transient” library of genetic information to form when needed by the cell. RNA is inherently unstable, and quickly degrades in many environments. As such, it is rarely used as the basis for biotechnology products.

From Transcription to Translation: RNA Processing

After transcription and before translation, the RNA transcripts are processed to produce mature messenger RNA (mRNA). Processing the RNA transcript includes the following steps: 1) RNA transcripts are cut into appropriate size classes; 2) they are folded into specific shapes; 3) the transcripts are chemically modified at both ends of each molecule; 4) non-coding sequences (introns) are spliced from the interior of the transcripts; and 5) transcripts migrate from the cell nucleus to the cytoplasm. This complex, multi-step processing permits fine control and tight coordination of the expression of specific genes.

Splicing

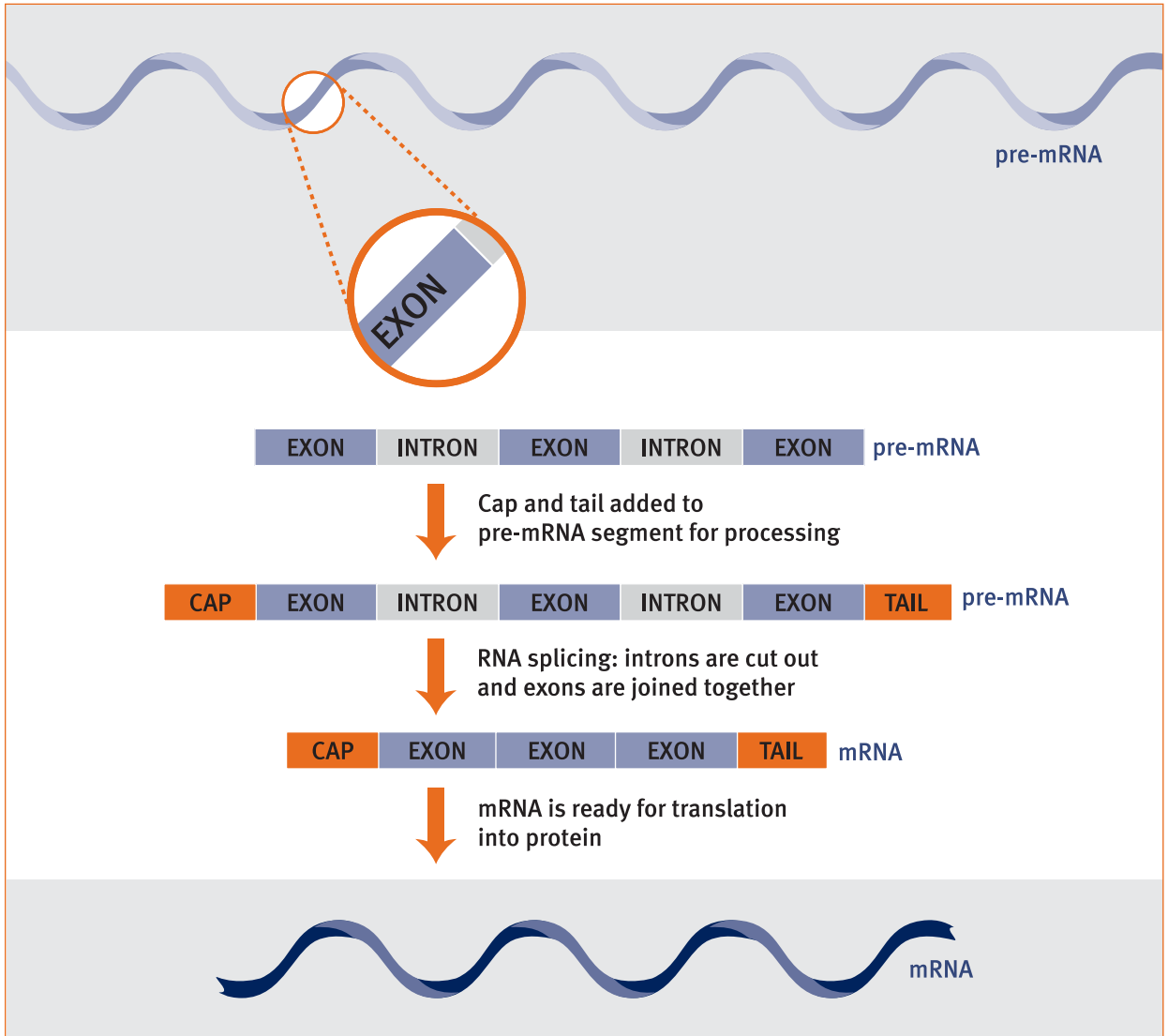
Splicing RNA transcripts involves precisely excising introns, non-coding RNA sequences, from exons in the RNA strand. Removing introns and joining together exons results in the final RNA transcript sequence.

Why is this process occurring in the cell? Splicing provides a mechanism for producing a wide variety of proteins from a small number of genes. One of the most dramatic examples is the “DSCAM” gene, which codes for 108 exons, providing the capacity to produce 38,016 unique RNA transcripts, each of which might be needed in a different place in the cell at a different time, for a unique biological purpose. Thus, while there is a one-to-one correspondence between DNA and RNA sequences, there is a many-to-one relationship between RNA and protein molecules. This many-to-one relationship will be critical in the studies and analyses of the total protein set in a cell, a field of research called “proteomics,” described later in this section.

Translation

Translation is the process of converting an RNA sequence into an amino acid strand comprising a protein. In this process, RNA molecules are translated by large, complex molecules called ribosomes. Translation occurs in three stages: initiation, elongation, and termination.

RNA PROCESSING



Initiation

The initiation of transcription requires a mechanism to ensure the initiation of every messenger RNA at the same site on that RNA; cells resolve this by having the ribosomes begin the translation process at a specific “start” codon (AUG) on the RNA sequence. The messenger RNA (mRNA), the mature product of transcription and splicing, carries the code for the insertion of amino acids. Protein synthesis occurs by reading the RNA message sequence three bases at a time, along consecutive codons, with no commas, and with no overlaps.

Elongation

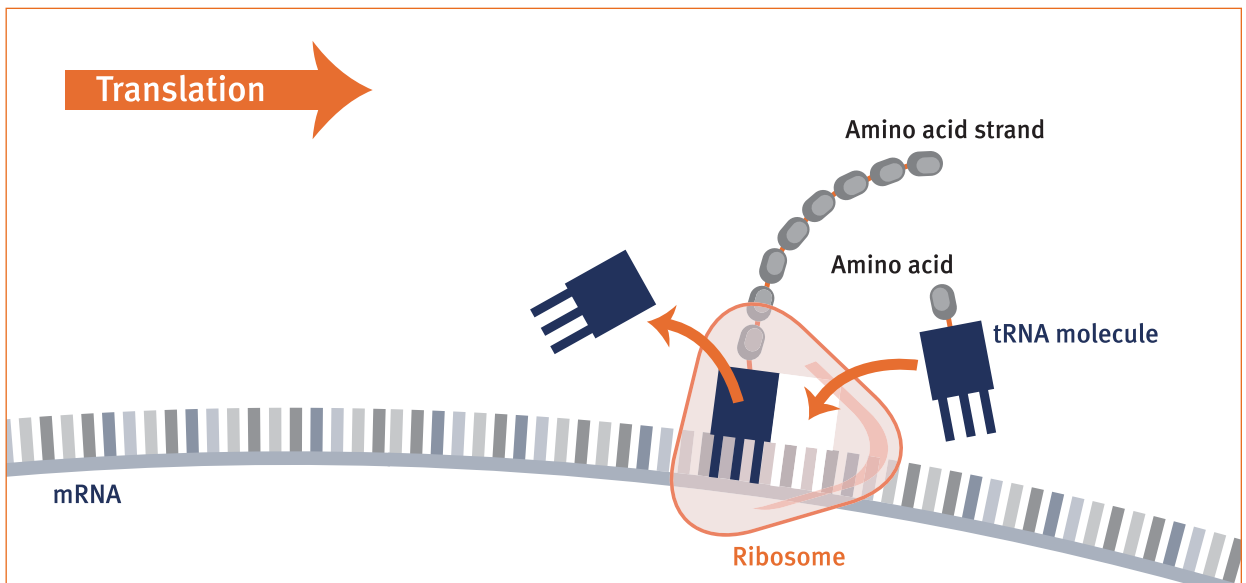
A set of 20 unique transfer RNA (tRNA) molecules carry out the translation or RNA sequences to amino acid strands. There is a tRNA for each of the 20 common amino acids. Each of the tRNA molecules recognizes a specific RNA sequence on one end of the molecule and binds to a specific amino acid on the other end of the same molecule.

From a free-floating pool of tRNA molecules, specific tRNA molecules are attracted to a specific RNA sequence through their specific affinities. This also brings the appropriate amino acids in close proximity to one another and in the correct order. Ribosomes are the site of the catalytic activity that is responsible for forming the peptide bond during protein synthesis. A strong and stable chemical bond is formed between adjacent amino acids held by tRNA molecules, after which the tRNA molecules fall away from the growing amino acid strand.

ERYTHROMYCIN & ZITHROMAX

The commonly prescribed antibiotics Erythromycin and Zithromax are examples of drug products in which the design leverages a knowledge of elongation. Many antibiotics interfere with the translation process, stopping protein synthesis, and crippling the physiology of the bacterial cell.

AN OVERVIEW OF TRANSLATION



Termination

To avoid having an RNA sequence produce an endless amino acid strand, a termination process must be present to indicate when and where translation is to cease. When the ribosome encounters any of a set of three synonymous “stop” codons (UAA, UGA, UAG), the ribosome falls off the RNA strand, and the completed amino acid sequence is free to be processed into a mature protein.

Once proteins have been synthesized in the cell, what is responsible for the inherent complexity of protein behavior? Protein modification, folding, traffic, and degradation all change the structure and function of proteins and prepare the proteins for specific tasks in the cell.

FINE-TUNING OF PROTEINS

Proteins are fine-tuned for specific uses by adding new structures to their surfaces, and are often cut into smaller pieces as they are properly shaped and transported to their sites of use. By changing the sizes, shapes, and surfaces of proteins, they can be targeted for highly specific uses in the cell.

Protein Modification

To aid in targeting the proteins towards highly specific functions in the cells, newly synthesized proteins are often modified after translation is completed. Cleavage is one of several fates of newly synthesized polypeptides, and the nascent protein may be cleaved either at an end or internally to form a mature protein.

Another common post-translation modification is the addition of other chemical groups to specific amino acids within the protein. A wide variety of chemical modifications may occur. Since only specific amino acids in certain proteins become modified, each modification system must have a mechanism for recognizing and distinguishing the target amino acids. None of these modifications is mutually exclusive; indeed, they often occur concurrently and are typically carried out in a specific dependency.

Protein Folding

As a protein is processed into its final, mature form, it is folded into its active three-dimensional shape. Proteins are initially linear polymers composed of a sequence of amino acids; these amino acid sequences can

IBM / BLUE GENE

Since the amino acid sequences of proteins are encoded by DNA, a linear substrate of genetic information, it should be possible to predict the three-dimensional structure of a protein from its linear gene sequence. The development of an encompassing framework for this predictive calculation, known to biologists as the “protein folding problem,” has eluded scientists for almost 50 years. IBM is currently building the biggest supercomputer in the world (termed “Blue Gene”) to attempt to solve this fundamental issue in modern biology.

“Blue Gene” was designed as a \$100 million exploratory research initiative to build a supercomputer 500 times more powerful than what are currently the world’s fastest computers. The computer is designed to perform more than one quadrillion operations per second (one petaflop). This level of performance will provide the computer with 1,000 times more power than the “Deep Blue” machine that beat world chess champion Garry Kasparov in 1997, and will be about one million times more powerful than the fastest desktop computers. Why all the computer power? Because tracking the time- and distance-dependent motions of all the atoms in all the amino acids of a folding protein requires an enormous number of calculations.

be very diverse. The three-dimensional structures of proteins are therefore also extremely diverse, and range from completely fibrous to highly globular. Two fundamental shapes are often found within proteins: alpha-helices and beta-pleated sheets. A single protein may contain several helices and sheets within a single amino acid strand, and several proteins may aggregate together into a supra-molecular complex, providing for very fine control over the ultimate shape and size of a protein complex.

Protein structures can be determined to an atomic level by X-ray diffraction studies of crystallized proteins, and more recently by nuclear magnetic resonance (NMR) spectroscopy of proteins in solution. However there are many proteins whose structures cannot yet be determined.

Protein Traffic

Proteins are not uniformly distributed within cells; instead, they are localized in any of several different compartments within the cells, where each compartment has its own localized protein complement.

In bacteria and other simple cells, these compartments include the outer membrane, the periplasmic space, the inner membrane, the cytosol and the extracellular space. In human cells, there are many more compartments and several organelles. An organelle is a discrete body found in the cytoplasm of a cell, defined by a surrounding membrane, and performing a specific function. The organelles in a human cell include: the mitochondria, the endoplasmic reticulum, the Golgi apparatus, the plasma membrane, secretory granules, lysosomes, and nuclei. Each of these is discussed in the next chapter on cells and tissues.

In contrast, there is only a small set of protein synthesis sites in the cell: the cytoplasm, the endoplasmic reticulum, the chloroplast stroma (in plants), and the mitochondrial matrix. Thus, for most proteins, the endpoints of localization differ from their site of synthesis. Correct localization requires complex direction of signals and cellular machinery. In the absence of such a signal, a protein is directed to its “default” target.

Protein Degradation

The ultimate fate of most proteins is destruction. One common mechanism for protein destruction is via proteasomes, hollow cylinders in which proteins are recognized by specific chemical tags (such as “Ubiquitin”) that lead to degradation by specific protein destruction mechanisms. Proteins can also destroy themselves, in which case they are said to be autolytic. Proteins are destroyed so that appropriate, transient concentrations and locations of proteins can be maintained as a cell ages,

changes its physiological status, or develops into another cell type. In all these cases, the constant presence of a protein under all conditions and contexts would decrease the adaptability of the cell to sudden perturbations, developmental plans, or metabolic changes.

When a protein is destroyed, the amino acids that made up the protein are broken down into monomers (single molecules that can combine with others to form a polymer) by a class of enzymes called “proteases.” These amino acid monomers are then freely available to be taken up into newly synthesized proteins. Thus protein destruction provides both a coordination mechanism for dynamic cellular machinery and a recycling process for the amino acid components of a protein strand.

CURE

The ability to control the transcription of DNA into RNA and the translation of RNA into protein has led to new products to treat infectious diseases and to prevent certain genetically based diseases.

The companies engaged in this medicinal sector of the biotech industry produce products to treat a wide variety of infectious diseases, including antibiotics, therapeutic antibodies, growth factors, and proteins derived from microbes, plants, and animals. Indeed, the first protein-based biotechnology drug product to reach the market was insulin, which, when produced in 1982, heralded a new era in the treatment of diabetes.

Drugs that are composed of proteins are called “protein therapeutics.” Recombinant technology provides an alternative source for producing protein therapeutics. Recombinant proteins are produced by creating a template for the genetic information that codes for the expression of the protein of interest, introducing the engineered gene into a living cell, and growing the cells to produce and harvest the specific protein. Most recombinant therapeutic protein products are expressed in cell cultures such as bacteria, yeast, and insect cells, or in mammalian cells or transgenic animals such as mice. Therapeutic proteins are typically made in a cell fermentation process, in which the proteins are excreted from cells into a surrounding growth medium, from which they are then purified. Modern growth media are well-defined products manufactured on an industrial scale.

COMPREHEND

Proteomics is the study of proteins as they change their structure, function, location, and utility in an organism adapting to new environmental or physiological conditions. Through studying the patterns of these changes, diseases can be better diagnosed and eventually cured.

The capacity to detect proteins and track their structures, functions, and movements within cells has led to the creation of a protein-based analytical sector of the biotechnology industry focused on understanding the functions and misfunctions of proteins that maintain health or trigger disease. These companies produce a substantial range of products and services to analyze proteins and protein chemistry, including the development, manufacturing, and marketing of products related to RNA probes, transcription systems, and large-scale protein analyses (“proteomics”).

Industry Overview

ELI LILLY

Indianapolis, IN
www.lilly.com

Founded:	1876
Employees:	41,100
Public	LLY
Annual Revenue: (2001)	\$11,542.5 million

Eli Lilly, a publicly traded pharmaceutical company, was founded more than 125 years ago and currently employs more than 41,000 people worldwide. Lilly made the most significant breakthrough in diabetes care since the 1920s with its 1982 introduction of Humulin®, a protein-based insulin identical to that produced by the human body. Humulin was the world’s first human-health-care product created using recombinant DNA technology. Lilly later applied this technology to the introduction of Humatrope®, a new therapy for growth hormone deficiency in children.

PROTEIN: CURE

170 companies
12.4% of total industry
414,000+ person-years of research

The “Protein: Cure” sector focuses on tools for the development of protein-centered therapeutic products.

CIPHERGEN

Fremont, CA
www.ciphergen.com

Founded: 1993
Employees: 229
Public: CIPH
Annual Revenue: (2001) \$19 million

Ciphergen Biosystems was founded in 1993 in the emerging market of protein-based biology research. The company develops, manufactures, and sells ProteinChip Systems and related products that discover, characterize, and test proteins from biological samples.

SURROMED

Mountain View, CA
www.surromed.com

Founded: 1997
Employees: 77
Privately held: —

SurroMed is engaged in large-scale phenotyping activities, which involve quantifying the molecular components of complex organisms in order to understand interactions between genetic and environmental factors in diseases. By capturing and analyzing enormous amounts of clinical and biological information in a massively parallel fashion to identify useful biological markers, SurroMed plans to enable the precise diagnosis and effective treatment of disease.

PROTEIN: COMPREHEND

≥8 companies
2% of total industry
46,000+ person-years of research

Companies in the “Protein: Comprehend: sector provide tools for the analysis of protein structure, function, and interaction in the cell.

The “proteome” of an organism comprises the complete set of proteins encoded in its genome. This word is misleading, however, in that, unlike genome sequencing, there is no single description of the set of proteins found in a cell. Rather, the concentrations, locations, structures, and functions of proteins change as cellular conditions change, even within a single cell. Proteins are synthesized at different times, modified in different ways after translation, and degraded at different rates, depending upon the cell type, the developmental stage of the cell or the current physiological status of the cell.

Proteomics provides a framework to systematically analyze the dynamic and transient inventory of proteins functioning in specific cells under specific conditions. In addition, this typically large-scale effort often maps out the interactions of proteins with one another and seeks to determine their sub-cellular locations, concentrations, and biochemical activities. There are two main strategies for proteomics: expression proteomics and functional proteomics.

Expression Proteomics

Expression proteomics focuses on the relative analyses of proteins detected when comparing tissues. For example, one might analyze the concentration of a protein found in a certain muscle and compare that level to the same protein found in skin. In this manner, clues can be derived which suggest or implicate certain proteins in the natural functioning of particular tissues and organs. Further extending the example above, if a protein was found at moderately high concentrations in muscles but at extremely low concentrations in skin, it suggests that the protein may have a more important structural role in muscle relative to skin. Importance, however, is hard to gauge by relative concentration alone, and many more experiments must be carried out to prove or disprove such a hypothesis.

Functional Proteomics

Functional proteomics focuses on how certain proteins interact with other proteins as well as additional components in the cell in order to determine proper protein function. This branch of proteomics is inherently complex, in that potential interactions of many billions of proteins with one another (in all possible combinations) provides an upper boundary on the potential complexity of the system. In practice, analyses typically focus on only a small set of proteins implicated in particular pathways, often in disease states such as cancer. By focusing on a specific pathway or set of pathways, researchers can integrate proteomic information with genetic,

physiological, and clinical data, all of which may be relevant in the study of a disease or the analysis of a potential therapy for that disease. The integration of this data is high-dimensional, mathematically sophisticated, and requires interdisciplinary teamwork.

CREATE

Harnessing the intentional production of proteins within cells has led to the design of new protein-based products to mass produce, highly purify, and proactively manipulate proteins. These include the development, manufacturing, and marketing of products and services related to amino acid production, enzyme growth, peptide synthesis and separation, and protein purification.

Protein Synthesis and Purification

There are several highly refined methods that separate proteins according to distinct chemical and physical properties such as their size, shape, and electrical charge. Proteins can be purified by sequentially applying methods that separate a desired protein from all others based upon its uniquely differentiated combination of chemical and physical behavior. Before purifying a protein it is important to develop a strategy based upon how much protein is needed, how pure it needs to be, and whether the purified protein needs to be in its natural shape and/or behave with its normal function. Examples of protein-based products range from proteases used for laundry detergents to insulin used to control the symptoms of type I diabetes.

Molecular Breeding

Based on the original DNA-centered PCR technique, an enormously powerful tool called “molecular breeding” was developed in the 1990s by Pim Stemmer and colleagues. A typical protein is a linear chain of several hundred amino acids (length, N), and there are 20 possible amino acids at each position in the chain. Thus the “sequence space” of possible proteins is enormous (20^N). In the four billion years that life has existed on earth, nature has had a chance to explore only a small fraction of the possible structures. Instead, natural evolution has selected specific proteins that are structurally and functionally optimized for their particular environmental niche, so that they are well adapted to specific selective pressures. This is called “local optimization.”

MAXYGEN	
Redwood City, CA www.maxygen.com	
Founded:	1997
Employees:	308
Public:	MAXY
Annual Revenue: (2001)	\$30.5 million
Maxygen is developing directed molecular evolution technology. This technology consists of recombination and screening technologies to optimize genes and proteins in a two-step process that mimics the natural events of evolution. The company is currently working on more than 40 different potential products spanning the areas of protein pharmaceuticals, protective and therapeutic vaccines, chemicals, and agriculture.	

PROTEIN: CREATE
170 companies 12.4% of total industry 414,000+ person-years of research
Companies in the “Protein: Create” sector develop tools and services for the creation of intentionally engineered protein and peptide products: amino acid production, peptide synthesis, protein and enzyme production, protein engineering, separation, and purification.

Molecular breeding is a form of “directed evolution,” in which the structure and function of a protein is (more) globally optimized in a laboratory. In this process, the coding of DNA sequences for related, similar proteins are pooled together and the mixture is exposed to restriction enzymes, which cut the sequences at similar locations, creating a pool of structural “modules.” This mixture is then exposed to ligase enzymes to paste together the individual modules, now in different orders and unique combinations, and PCR is used to amplify the recombinant structures so that they can be studied further. This forced genetic recombination mimics the process that occurs during sexual recombination, namely the mixing of genes from both parents. Indeed, this technique has also been referred to as “sexual PCR” to reflect the powerful genetic recombination process occurring in the test tube.

Once amplified, the DNA can be expressed in a controlled manner to the corresponding protein function to be studied. Through functional analyses of the corresponding protein, it’s possible to find improved function from the pool of recombinant structure. Often a specific protein function can be improved several hundred-fold, and occasionally, several thousand-fold, after just a few days of laboratory work. In this manner, the genetic effects of several hundred generations (and several thousand years) of reproductive cycles can be mimicked in a test tube in just a few days.

VALUATION OF BIOTECHNOLOGY PRODUCTS

When the biotech industry began in the 1970s, only 15 or so proteins were considered as potential products. Many industry observers thought that once these proteins had been purified and produced in large quantities, the biotech industry would no longer expand. Today, there are more than 2,200 products in development, and many of these are either protein-based or depend upon proteins for their proper functioning. Some of these potential products are inherently more valuable than others. For example, some protein therapeutics do not work as well as anticipated, often due to unexpected interactions with other proteins or other molecules in a diseased cell. There are many risks and uncertainties associated with product development, and the cost of research is high.

Given the complexity of both an individual protein’s function and the relatively long durations and high uncertainties associated with the overall product development process, how can one effectively value such products and the companies that produce them?

There are several techniques used to estimate the value of biotechnology products in development, including comparable analyses, discounted cash flow-based estimates, and real options. Often these approaches are carried out in parallel for a comprehensive valuation.

Comparable analyses assess the value of a particular product or company based upon its relative similarity to other products or companies. For similar products or similar companies, transactions that require the determination of value can be used as benchmarks for the value of the product or company for which a value is sought. For example, if a product were licensed from one company to another, and the terms of the licensing agreement are known, then the value associated with the licensed product can be used as a benchmark. Similarly, if a company developing a single product were acquired by another company, the acquisition price associated with the transaction can be used as a valuation benchmark. Alternatively, if the comparable company is publicly traded, its market capitalization (total shares outstanding times price per share) can be used as a valuation benchmark. There are no perfect benchmarks, and often several comparables are used in the same valuation to determine a reasonable range of potential value.

Another approach to valuation is based upon a discounted cash flow analysis (DCF). One DCF approach is to value a biotechnology company by discounting expected cash flows to the company (“cash flow to the firm”), that is, the residual cash flows after meeting all operating expenses and taxes, but prior to debt payments, at the weighted average cost of capital (the average cost of the different components of financing used by the company, weighted by their market value proportions). This approach is typically used to value biotechnology companies with products that are either on the market or near to being fully commercialized, since companies that have only an early-stage product (i.e., far from being available on the market) would not be expected to have product-sales based revenues. Often the time scale for the cash flow analyses is the “next three years,” since a longer time frame provides a less predictive framework in an inherently dynamic industry such as biotechnology.

A real options valuation is based upon several assumptions: 1) the market will have uncertainties, reflected by volatilities, e.g. changes in market size, market share, and product price; 2) information is revealed over time as uncertainties are resolved; and 3) better, more valuable decisions can be made with better information. In this approach, the traditionally implicit value of both flexibility and learning are explicitly taken into account. In particular, by considering both risk adjustment and the flexibility of strategic options, a real-options-based valuation can more often effectively estimate value. In contrast, DCF valuations do not take the flexibility and potential complexity of a strategic path into account; calculations depend only on endpoints.

Real options frameworks recognize (for example) that as time progresses, and costs become sunk, the value associated with the right to build operating capacity and expand R&D or manufacturing activities can increase. Thus a “call” option, the right to buy at a fixed price at a fixed time, can be valuable if value accrues with time. Conversely, if progress to a fully operating state is slower than expected, a “put” option, the right to sell at a fixed price at a fixed time, can limit a loss and protect cash. In the context of a biotechnology company, the research stage provides an option to bring a therapeutic product to market, and the price of the option is the investment cost associated with that research. The underlying asset would be the expected net present value of the future earnings, and the strike price for the option would include the sales, marketing, and distribution expenses associated with the entry of that product onto the market.

