Protein Engineering and Biotechnology : A 360° perspective

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This article is a 'motivational piece' written to inspire students contemplating entering a career in protein biotechnology.

This article has been written to communicate the excitement and ferment in the specific area of science and technology in which I work; specifically, to convey a sense of what the field is like, i.e., what it involves and also what prospects lie ahead of a student choosing this area for a career.

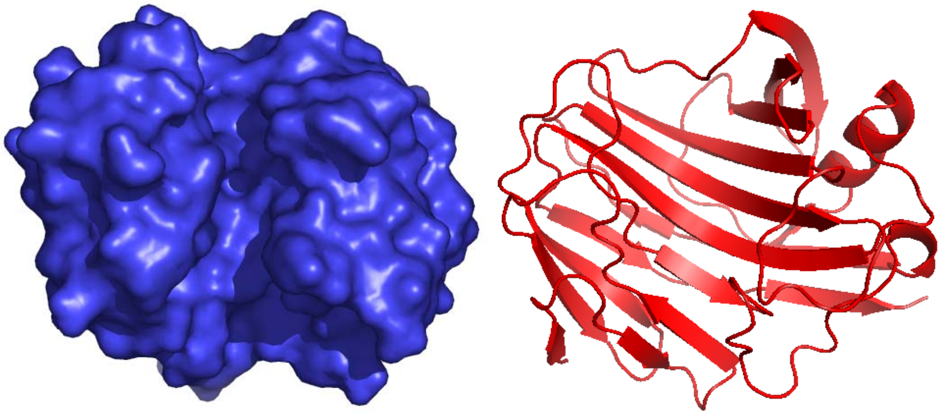
The field is variously known as ‘protein engineering’, ‘molecular genetic engineering’ or ‘protein biotechnology’. It is a sub-discipline of the much larger subject areas of molecular biology and biotechnology. Working in this area requires one to combine – either as an individual, or in collaboration with other researchers - the insights, principles and practices of fields as diverse as pharmaceutics, biophysics, biochemistry, mathematics, microbiology, immunology, computer sciences, and chemical engineering, as well as the newly emerging area of molecular medicine.

Together with areas such as bioinformatics, and proteomics, protein biotechnology has of late become a subject of intensive R&D worldwide, especially in relation to the development of (a) therapeutically important protein drugs, and (b) enzymes used in the food, textile or chemicals and drugs industries. What is perhaps most interesting about this area is that it straddles the wall traditionally separating the basic and applied sciences, offering students the opportunity to both understand how life functions at the molecular level from a physical (or material) point of view, and to apply rapidly the insights thereby gained.

Below, I have tried to paint a picture of protein biotechnology, deliberately using a rhetorical question-and-answer format intended to make the article rapidly accessible to those who wish to read it diagonally. However, the sections are also arranged in a manner suitable to conventional linear reading. To begin then…..

What are proteins ? Proteins are long chain polymers of smaller molecules called amino acids, joined together by bonds called peptide bonds (which those trained in chemistry could think of as amide bonds). These ‘polypeptide’ chains adopt compact shapes through a process called ‘folding’. To use a crude analogy, folding can be imagined to be similar to the compaction of a long string of wool into a ball. Once the long chain has adopted a ball-like (globular) structure, the detailed topographical features of its surface allow it to interact with other molecules in unique ways, and to perform unique functions within the living cell, like a miniature machine.

Protein's are thus nature's molecular machines. In the attached picture, a surface view is shown of a protein (an enzyme known as a cellulase) which sports a long groove on its surface which grips a polysaccharide (sugar) chain, known as cellulose, and breaks it into individual glucose units. In size, the cellulase spans at most 1-2 nanometers in any direction. The human body contains tens of thousands of such molecular machines with unique structures, each machine consisting of one or more different sequences of amino acids joined together into polypeptide chains that fold to perform a variety a particular task, utilizing surface features exquisitely adapted to that task.



The formation of these surface features (topography) depends critically, of course, on how the polypeptide chain itself becomes compact and adopts the basic chain organization (topology) underlying these structural features. From the representation showing the surface and the groove, it is not obvious how these structures are formed by a linear chain. So, in the figure shown alongside, the route, or trajectory traced by the folded chain within the protein molecule is shown in a cartoon ribbon-diagram representation showing how the chain is organized into regular helical and sheet like features. It is seen that the chain has a particular 'topology', or pattern of connectivity of chain sections, i.e., a particular scheme of interactions in which distant regions of the chain can lie next to each other in the structure, while nearby regions of the chain can occupy distant regions of the structure. Along with the sequences of amino acids, the topographical features as well as topological features of polypeptide chains are unique to each protein.

What are amino acids ? So, we have learnt that proteins are chains of linked amino acids, folded into specific structures. But what are amino acids ? Well these are molecules that are basically small clusters of covalently linked atoms, principally nitrogen, carbon, hydrogen, oxygen, and also occasionally sulphur. Amino acids contain both an amino group and a carboxyl group, which can be used to join them to other amino acids through amide (peptide) bonds. The formation of peptide bonds involves the release of one water molecule per bond; conversely, peptide bonds can also be chemically hydrolyzed in aqueous solutions, but this involves the use of very low pH and high temperatures. Although there are several hundred naturally-occurring substances that can be called amino acids, and a virtual infinitum of conceivable molecules that could potentially be created, and then called amino acids, there are only twenty specific amino acids that are used by nature to make proteins with. Some of these twenty are like others within the same group of twenty (i.e., they have homologs, or analogs) whereas others have no analogs of a similar nature, within this group of twenty. These twenty different amino acids have names like alanine (Ala), valine (Val), tryptophan (Trp), lysine (Lys) and cysteine (Cys). Nobody yet fully understands why there are only twenty amino acids used to create all proteins with, and why nature has chosen only these particular amino acids as building blocks for proteins.

How are proteins different from peptides and polypeptides ? Chemically, peptides, polypeptides and proteins, are very similar. They differ only in terms of the different lengths to which amino acids are joined together to form polypeptide chains. Polypeptides that range in length from 2 to 10 amino acids are simply called peptides. Chains ranging between 10 and 30, or 40, amino acids in length are called polypeptides. When chains get longer than this, they are called proteins (particularly in the folded form) although the chains themselves are still technically only polypeptide chains.

One important difference between (poly)peptides and proteins is that the synthesis of proteins within biological systems is always specified directly by information contained within the genetic material of a cell (in an entity called a ‘gene’). Polypeptides and peptides, on the other hand, can be generated both by the defined fragmentation of proteins, and by other (synthetic) means that have nothing to do with genes. Another important difference is that peptides and polypeptides do not necessarily fold to adopt unique structures by themselves, whereas this is almost always the case with proteins (although occasionally maturation of a protein's structure requires binding to a designated partner molecule).

How many amino acids make a protein chain ? Protein chains can vary greatly in length. The length can range from as few as 40 or 50 amino acids (in small proteins that work as inhibitors of enzyme reactions), to as many 10,000 amino acids (in complex molecules that are responsible e.g., for the synthesis of fatty acids). Protein chains also vary in terms of the sequence in which different amino acids from the group of twenty are strung together. Thus, often proteins performing similar biological functions are related at the level of their amino acids sequences, and also at the level of their three-dimensional globule-like structures. Proteins with no similarity of function, on the other hand, are usually quite different from each other. Further, a single protein can consist of a single folded chain, or multiple co-folded chains.

In how many ways can amino acids be strung together to generate 'proteins' ? The diversity that protein sequences can show is unimaginably large. Consider that if any of the twenty amino acids could occupy each position in a protein chain, there would be 400 (i.e., 20x20) ways of joining two amino acids drawn from the group of twenty, 8000 (20x20x20) ways of joining three amino acids, and so on. By the time we were talking of protein chains made of 70-80 amino acids, we would be talking of a total number of ways of making such chains (20^n) that would exceed the total number of physical atoms of all kinds estimated to exist in this universe of a hundred billion galaxies of a hundred billion stars each. Fortunately, for those who study proteins, nature uses only an infinitesimally small fraction of this astronomically large variety to build the proteins that are deployed in living organisms. Contrarily, we do not know if the sequences that have not yet been used by nature can also be generated in the future, i.e., whether such sequences (e.g., a random sequence put together by a classroom of scholars) might fold to perform yet unknown functions that will be useful to living organisms of the future.

What do proteins do ? In one word, everything. Proteins are both the workhorses of the cell, and its governors. They perform virtually all the functions needed to be performed within cells. Proteins are involved in the trapping and binding of small and big molecules. They are involved in the transport of substances ranging from atoms (protons) to small molecules (nitric oxide, carbon dioxide or oxygen) to large molecules (whole proteins, or assemblies of proteins) between different locations within a cell, or from the outside of a cell to its inside, or even between cells, or between different organs, within an organism. Specific proteins are involved in the synthesis of lipids, fats, sugars, nucleic acids such as DNA and RNA, amino acids, and proteins of all other kinds, not to talk of vitamins and all secondary metabolites through the performance of their varied and diverse enzymatic functions. Proteins act as the carriers of non-physical signals from the outside of a cell to its inside, as switches that turn on specific cellular characters, as skeletal material defining the shape of every living cell, as well as the shape of the body, and even as the basis of the body's defense mechanism against invading disease-causing microbes. There would be no life without proteins.

Think of the other well-known molecule in biology, DNA, which functions as the sum total of the genetic material you inherit from your parents, is the equivalent of your digital diary, or spirit. It contains all the relevant information about what you need to do, where you need to do it, when you need to do it, in what capacity, and to what extent. Once you have thought of DNA as the spirit, think of the proteins that are involved in the actual doing of these tasks as the equivalent of your body, and mind. Of course, the diary appears to run your life, but equally it appears that you have a role to play too in deciding what goes into this diary. Who is the master ? Who is the slave ? From a certain perspective, it appears that the diary is the master. From another perspective, it appears that you are. So it is - between DNA and proteins. Of course, in recent times, man has been discovering that DNA does much more than specify the production of proteins, but you have probably understood the broad picture. Proteins are important.

Let us summarize this with a little poem (in blank verse !) :

Proteins know how to (and indeed, do)
synthesize every category of biomolecule;
perform every sort of transport-, binding-,
and catalysis-related function;

Proteins define the shapes of cells,
of organs, and organisms;
they give life mobility; and defend it
against other invading forms of life.

When allowed to do their own thing,
they even know how to shape themselves
into exquisite structures,
perfectly adapted to designated tasks.

They also know how to manufacture
a molecule called DNA,
and use it as an "Erasable, Programmable,
Read-Only" device;

... One that faithfully stores, and plays back too,..
information that's comprehensive;
about how each protein would like to get made,
using which components, ...at what levels, ... where , ... and when.
Much like a digital diary.

Eveventually, of course, you can't do without the organizer.
It runs your life, tells you what to do and when,
and you are quite lost without it.
But you're comfortable enough,
to let it run your life.

You don't mind when the world thinks
that the tail wags the dog (never mind the mixed metaphors).

Which is the tail, and which the dog ?
As long as nobody figures out who really calls the shots,
what's a little devolution of control,
now and then, between workmates ?

Master and slave, whipmaster and workhorse,
DNA and proteins; now one, then the other.
O Proteins ! Versatility is thy name !

How are proteins made ? The substance known as DNA consists of genes. Genes contain information mainly about the different sequences in which amino acids need to be joined together, to make different proteins. This information is transcribed (copied) first from a piece of DNA into a molecule called a messenger RNA. Then, it is translated by objects within cells known as ribosomes. These objects appear to physically read the language written in the DNA/RNA (akin to how Braille is read by blind people) and convert this language into the language of proteins, in a step-wise manner that decodes information concerning the sequence in which amino acids need to be joined together, and then actually concomitantly perform the physical act of joining the right amino acids in the specified sequence to produce a growing polypeptide chain. Eventually, once all the requisite amino acids have been joined, the chains falls off from the ribosomes, and become compact through folding (either during, or after the synthesis) and adopt a particular three-dimensional structure, or shape. They then start functioning, either immediately, or shortly after they have been transported to a site(s) at which they need to function, either within the cell, or outside the cell, or in the bodily fluids. Genes also contain information about where, in what amount, and when, during the life of a cell, or organism, a particular protein needs to be made by the ribsome machinery.

Are protein folding and stability relevant to health and disease ? Well, a protein chain that does not adopt the particular three-dimensional structure specifically designed for it by nature automatically also fails to perform the function it is supposed to perform within the living system in which it is synthesized. Moreover, if the protein chain does not adopt its designate structure in a stable-enough manner, it stops performing its designated function sooner rather than later, even if started out life by functioning exactly as intended. The non-occurrence of correct folding can owe both to structure-destabilizing or structure-destroying amino acid changes (mutations) and also to changes in cell metabolism checkpoints. The non-performance of functions resulting from the non-occurrence of correct folding is probably, therefore, the single-most important factor contributing to non-infectious diseases in man and animal.

In addition to diseases resulting from the loss of protein functions, there are also diseases that result from the gain of new, mischievous functions. There are now nearly 30 to 35 different diseases known, mainly involving the brain and nervous system, which result from the incorrect folding, or misfolding of protein chains. Some well known examples are Alzheimer’s disease, Parkinson’s disease, mad cow disease et cetera. Thus, whether one likes the idea or not, protein folding lies at the core of all life, and also all physical health and well-being.

Do we understand how proteins fold ? In one word, and if we had to give an honest answer, the answer would be ‘No’. Some chemists who deal with small molecules and their structures are discomfited by this assertion, but I’m trying to state it like it is. The real picture is as follows (important, because one cannot engineer proteins without understanding at least some things about how they fold).

We understand some things. It is not as if we understand nothing about protein folding. In fact, we do understand a great deal already. But we do not understand enough about proteins yet to predict exactly what type of three-dimensional structure would be formed by a given protein chain of a given amino acid sequence, especially if we had never encountered a similar sequence before (with a known and already-determined structure). This is a major issue, because we have already seen how incredibly diverse protein sequences can be, and we are still discovering new sequences used by nature, practically every day.

There is a lot that we don't understand. What is most mystifying is that logic suggests that a given protein chain of a defined amino acid sequence can adopt an astromically large number of possible structures, just as we've already seen that there are an astronomically large number of conceivable amino acid sequences. Almost every chemical bond in a protein is rotatable. This causes each amino acid to become capable of adopting a few tens of structures, amounting to an infinite number of conceivable structures even for a small protein. Yet, every time a living cell produces a chain of a defined sequence, the chain ends up adopting exactly the same structure, usually on its own and without any special assistance, despite the astronomically large number of possible structures into which it could conceivably have folded.

Nature understands everything. Nature clearly knows which sequence will fold into which structure, and perform which function. It also knows how to ensure that folding occurs with high fidelity. We don't; at least not fully, or reliably, yet. But we are learning. Different protein scientists understand proteins at different levels, and to different extents, and there are wide differences in the scope and breadth of this understanding amongst the practitioners of the discipline. Thus, there are differences in the success with which protein scientists find they can manipulate proteins, often dosed with a good helping of destiny.

To conclude the discussion on this important issue, we don't fully understand how to reliably predict the effects of genetic changes on protein structure and stability, but we already have the tools with which to manipulate protein sequences, as well as the tools with which to study the effects of the changes made.

So, can proteins be engineered ? Yes. However, strictly speaking, one should say that proteins can be 'altered' through genetic engineering, although this cannot always be done with the precision that the word 'engineering' demands.

We can synthesize new genes. Man now understands enough about how genes can be changed, or altered, or totally synthesized from scratch, to alter any protein that nature produces, as well as to produce any totally new protein not produced hitherto by nature.

We can use microbes as factories. Man also now possesses the scientific understanding and the technology necessary to get bacterial, fungal, insect or mammalian cells to incorporate within their genetic material the novel genes suitably engineered by man to direct the formation of novel proteins, and then get such cells to over-produce such novel proteins in preference to the proteins needed for their own (cellular) metabolism by working as cellular 'factories'.

We can purify engineered proteins. What is more, man also knows how to purify such proteins (known as 'recombinant and engineered' proteins) from such cellular factories, to a level and a grade necessary both for their study and for their use in industry, and medicine. Therefore, some of this science and technology has come of age.

But we can't guarantee engineering success. However, protein science and engineering is still a fledgling science in which a tremendous amount remains to be done, with thought and care (as explained later in this article). Note that in the previous section we have discussed how little we know about how to predict the folding of a new, or profoundly altered, protein, even though the necessary tools with which to make such changes are fully perfected.

The tools are ready, but the understanding is half-baked. It is like an electronic engineer attacking the multi-level printed circuit boards of an electronic instrument with a multimeter, soldering gun, screwdriver, and some electronic components in hand; however, without the aid of anything even remotely like a circuit diagram, and with all the markings on the installed components wiped out beyond recognition, and some new components showing up all the time.

The effects of any changes the engineer makes will depend critically on how well he understands and analyzes electronic circuits through a combination of his logic, experience and intuition, and not simply on how efficiently he can measure voltages and currents, or how neatly he can carry out the soldering work, although these too are important. Regardless of their varying degrees of success, different engineers will all admit that they cannot fully understand how the circuit does what it does, without an explicit chart clarifying the original designer's plan.

So it is - with proteins and protein engineering, and indeed with all genetic engineering. The solace is that though the effects cannot be predicted reliably, they can be measured accurately, and used as feedback in iterative cycles of design and redesign.

To have adventured onto the sea in a raft, and returned within the hour on a favorable wind and a strong sail is enough to tell us that we can sail on the ocean (at least when the ocean wants us to sail on its surface). But woe betide any human who thinks that such an adventure amounts to a mastering of the ocean, or even of ocean travel. The sea does not reveal its secrets even to large ocean liners; indeed, it crashes the biggest of them upon icebergs and rocky crags. And yet, man's indomitable spirit can conquer some of the lay of the land. New, energetic and better-informed individuals are always needed. But more on this issue later.

Does India have groups engaged in protein engineering ? There are many research groups in the country that engage in protein engineering at different levels of complexity, both in the research institutes (e.g., IISc, NCBS, CCMB, CDFD, TIFR, IICB, CDRI, NII, IGIB, ICGEB, AIIMS, IMTECH & PGIMER) and in the departments of various universities.

At the simplest level, there is the protein engineering involving the introduction of directed amino acid changes at specific sites within the copy of a protein-specifying gene in a cell's genetic material (the genome), to examine the effect of such changes on the cell's metabolic pathways, without the researcher necessarily purifying and studying the altered protein.

A somewhat more sophisticated approach is to produce a minimally altered copy of such a protein within a cell that does not ordinarily make it, and produce it with such high purity that it becomes immediately useful, whether as a target for an experimental assay, or for a diagnostic test, or even as an injectible medicine (which, of course, requires ultra-high purity that is a tough challenge).

At an intermediate level of complexity, there is the introduction of more profound changes made through the introduction of multiple mutations, usually accompanied by a high-level purification of the altered protein, and followed by a thorough study of the protein's altered characteristics.

At even higher levels of complexity, there is the introduction of such profound changes that the protein might as well be called a new entity, followed by its small-and-large scale purification, not merely for its study and characterization but also for its testing and eventual use as a product in the textile, or chemicals, or food-processing industries, e.g., as a novel enzyme. At the highest level of all, there are the profoundly engineered, or novel, proteins that are also purified with the strictest standards, and tested and used in medical treatment as human injectibles.

Groups practicing protein engineering at all of the above levels exist in the country.

Entry into protein engineering careers : Which backgrounds are useful ?

Physics and physical chemistry : Proteins are stabilized by a bundle of different forces, and their engineering requires some understanding of these forces and how they act at short interatomic and molecular distances, in the presence and absence of solvents. Also, the structures of engineered proteins have to be determined at atomic resolution, to confirm the structural effects of the engineering. This requires the use of X-ray crystallography and sophisticated spectroscopic techniques, including multi-dimensional heteronuclear NMR, circular dichroim, fluorescence, dynamic light scattering and various forms of mass spectrometry.

Computer science and bioinformatics : Some simulations of the effects of making changes in known protein structures can be performed by computer software capable of modeling the dynamics of protein molecules in solutions, or predicting the structural effects of amino acid sequence alterations. Bioinformatics is also put to great use to cull-out information from existing databases and examine how the sequences of proteins differ amongst different living organisms, so that protein engineers can get a foretaste of which changes nature has already tried and tested, and left evidences of within the evolutionary record.

Molecular Biology and Biotechnology : The making of specific changes in genes, and the synthesis of new (or substantially altered) genes, requires knowledge and competence in the practice of all the techniques of recombinant DNA science and technology, including DNA sequencing, DNA digestion, ligation, site-specific mutagenesis, polymerase chain reaction, gene splicing et cetera.

Chemical engineering : There is usually a lot of work involving molecular separations based on the combinatorial use of chromatography and electrophoresis, to separate molecules on the basis of size, charge or specific affinity, best performed by those who have a good understanding of fundamental chemical engineering principles.

Chemistry : Protein engineering is ultimately about changing the stability, or activity, of a protein. Where activity is defined by the performance of a specific catalytic function, an understanding of chemical principles often helps in determining how protein structural alterations mediated by mutations will affect the rate, or nature, of the catalytic action of an enzyme.

Biochemistry and biophysics : Different proteins differ widely in their size, shape, charge, amino acid polarities, activities, and other functions and characteristics. Different proteins also require handling in solutions of different pH, metal, inorganic and organic composition, and ionic strength, and testing at temperatures that are uniquely suited to each protein. Biochemistry is thus the ‘base’ subject from which all protein engineering starts.

Microbiology, cell biology and plant/animal biology : Since microbes and eukaryotic cells are used as factories for the production of engineered proteins, a deep knowledge of their handling and culturing, and also their genetic traits and characteristics, is essential, as is the understanding of the anatomy and physiology of the organisms in which engineered enzymes will be used.

So, what is this new thing called proteomics ? Proteomics is a new word that mainly describes man’s effort to identify and catalog all the proteins used by different living beings. This cataloging is done by organism, by organ, tissue, cell type or intracellular location. Eventually, however, the word 'proteomics' will probably come to mean virtually all R&D work involving proteins. Some of the techniques and technologies of proteomics overlap with those of protein biotechnology; however, proteomics is like a sub-discipline of protein biotechnology, which is much larger in its breadth and coverage.

How does one plan a career in protein biotechnology ? First of all, you need to decide what drives you. Is it mainly doing good for humanity, or discovering new things.

If it is the former, you then need to figure out whether you want to merely implement things that are useful (e.g., processes, or products, developed by others), or develop them yourself.

Joining industry straightaway. If you wish to implement things, and do so rapidly, you are best off doing a B.E or a B.Tech in biotechnology and joining one of the upcoming industries. There, you will be taught the nitty-gritty of what you need to know, and how to perform it. There are now tens of companies who are already in, or are entering, protein biotechnology (virtually all the well-known pharma majors, such as Ranbaxy, Wockhardt, Reddy's Labs, Cadila, or Shasun chemicals; enzyme companies such as Biocon; contract research organizations such as Reliance Life Sciences, or Syngene; and dedicated companies such as Shanta Biotech, or Bharat Biotech). Alternatively, you might join companies involved in the trading of biotech products, and there are a number of them mushrooming in each major city.

Joining industry after suitable preparation, or working in an institute, or university. If you wish to develop new products, or processes, you need to first learn the field properly. You need to do a Ph.D. Also, if you wish to derive new insights from fundamental research, you need to do a Ph.D. In India, you can do this at the various research institutes mentioned earlier, all of which have vibrant protein engineering groups. To be paid a stipend while doing a Ph.D, you need to clear one of the national level examinations held e.g., by the CSIR, UGC, DBT, or ICMR, which guarantee you 4-5 years of stability and financial support. Alternatively, you can gain experience without necessarily working for a Ph.D, by working for a few years as a project assistant in a protein engineering group.

How well does it pay ? Today, as a starting research scholar with a fellowship doing a Ph.D, you get paid a little over Rs. 12,000/- per month (including allowances), which gets upgraded after a couple of years to Rs. 14,000/-. These amounts are slated to rise by nearly fifty percent or more in the coming year or two. If you work as a project assistant with an M.Sc., you would be earning between 7,000/- and 12,000/- depending on your experience. A postdoctoral project assistant, i.e., someone with a Ph.D in an allied field who wishes to gain experience in protein engineering would get about 12,000/- or more per month (this figure also being slated to rise by fifty percent very soon). Once you have done your Ph.D, and/or postdoctoral work, either in India, or abroad, you can get a position in an institute, university, or industry. The amount that you then get varies currently from 25,000/- per month to 70,000/- per month, depending on where you work, what experience you have, which level you join at, and other such factors. Of course, government organizations offer less salary, but more job stability, than non-governmental ones.

Where can one learn to do protein biotechnology ? Protein biotechnology is not taught at the undergraduate, or postgraduate, levels anywhere in the country. However, a basic training in biotechnology, or biochemistry, can be very useful. On the national scale, there are a very large number of different universities and institutes offering degrees in biotechnology. The oldest and most well-known of these are the ones at Madurai (MKU), Pune (PU), Baroda (MSU), Benares (BHU), and Delhi (JNU), and at some of the IITs (particularly Bombay, and Kharagpur). JNU conducts a national entrance exam for entrance to the Masters' level courses of several tens of well-known university departments. Many different universities have very respectable departments of biochemistry at which one can also gain a sound background in the science of proteins.

However, one can only really learn to do protein biotechnology during a Ph.D, and not during one's M.Sc or B.Sc. And for this, one could have taken basic training in any of the areas mentioned earlier, and not just in biotechnology or biochemistry. All the national institutes mentioned above have groups offering Ph.Ds by research; some offering their own fellowships, in addition to accepting students with national fellowships.

Attributes that help. Well, any combination of (or all of) the following would help : the right background, interest, passion, dedication, grit, intelligence, a logical mind, systematicity at work, good articulation, good writing and interpretative skills, good understanding of geometric concepts, ability to plan, organize and implement. In short, all the skills that help in any human activity are useful in R&D in protein biotechnology.

But one must have sharp reasoning, the ability to work hard, patience, passion and the ability to concentrate with a long attention span.

I wish all students who are inspired by this article, and who wish to enter the field as a consequence, the very best of luck.

Kindly note : This is an inspirational article, written to encourage people to work in science in general, and in the area of proteins, in particular. Please do not consider this to be an advertisement concerning the laboratory that I run, or an invitation to join my group. I only take the odd student now and then (about once a year; sometimes even less frequently).

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