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Bench to bedside: Still a pipedream?

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The proteomics approach has taken centre stage in biology research. However, scientists are yet to fully explore its clinical relevance. Every proteomics researcher is confronted with the question – can proteomics deliver the expected promises? The answer isn't very encouraging right now – not because of the lack of potential or efforts, but perhaps because of the complexity of proteomics science.

Heterogeneity in disease phenotypes poses a big challenge and the application of proteomics techniques to individual samples is not yet robust or cost effective. While these are issues for proteomics researchers everywhere, Indian scientists face additional challenges that need particular attention.

What's ailing translation?

Among the two million proteoforms in the human proteome, one or more represent a specific disease condition. These disease specific proteoforms could be used in many ways. They could help predict, prevent and better manage diseases. Indian researchers are pursuing the discovery and functional evaluation of the protein biomarkers vigorously and with considerable success. However, the clinical validation phase is yet to take off in India.

There is a great need for knowledge exchange between the scientist and the clinician so that each understands mutual strengths and needs. The clinical queries of relevance can then be addressed with appropriate technologies and specimen cohorts so that the journey from the bench to bedside becomes more achievable.

Most hospitals do not have an institutionalised clinical record management system, nor is there a system at the national level to accommodate these important aspects of translation, including patient follow-ups. Further, there is need to catalogue protein biomarkers and their variants for diseases prevalent in the country and use them intelligently to apply for specific clinical questions. In the present scenario, most proteomic studies are in the domain of cancer biomarkers, neglecting metabolic disorders and other diseases. For example, the recognition of other glycated proteins in addition to haemoglobin can be important for clinical applications. Similarly, the detection of protein variants in cardiovascular disorders can be interesting to pursue.

Publishing discoveries or filing patents is not adequate. Engaging industry for licencing discoveries and an active effort for product development is required with greater intensity. However, the current environment in India is not very conducive for strong large-scale interactions between academia and industry for translation of technologies and concepts. Companies, especially multinationals, are also bound to their headquarters for R&D. The lukewarm interest shown by industry partners in taking discoveries to the clinic is a big limitation for translation.

Suboptimal infrastructure, lack of financial support and trained manpower to handle data in an integrated manner are some other limiting factors.

The sporadic progress in translational proteomics research in India can also, in part, be attributed to the reluctance of young investigators in taking up this field of research. Established senior investigators are slow to appreciate the advantages of omics platforms in general and proteomics in particular and venture into these new technologies. Rapid changes in instrumentation platforms and the prohibitive costs for front line equipment prevents less-endowed labs and educational institutions from undertaking this area of research.

There are also challenges on the technology front. Advances in quantitative proteomics have made it possible to pinpoint even minor differences in the protein levels between normal and pathological samples[1]. However, more innovative methods to mark even structural differences in proteins introduced by mutations or structural variations induced by post-translational modifications or protein truncation that are associated with pathologies would be useful and an important value addition.

The road ahead

Not many studies in India have addressed the clinical course of diseases or defined the source material for targeted proteomic inquiries. They have focussed on differential expression of proteins between normal and diseased samples. Some questions begging primary attention pertain to clinical subtypes, sub-sites, subcellular number of samples, when to use tissue or body fluids, time and mode of collection, storage, transport, likely concentration of the marker, pre-fractionation of the protein mixture and technology platform to be used.

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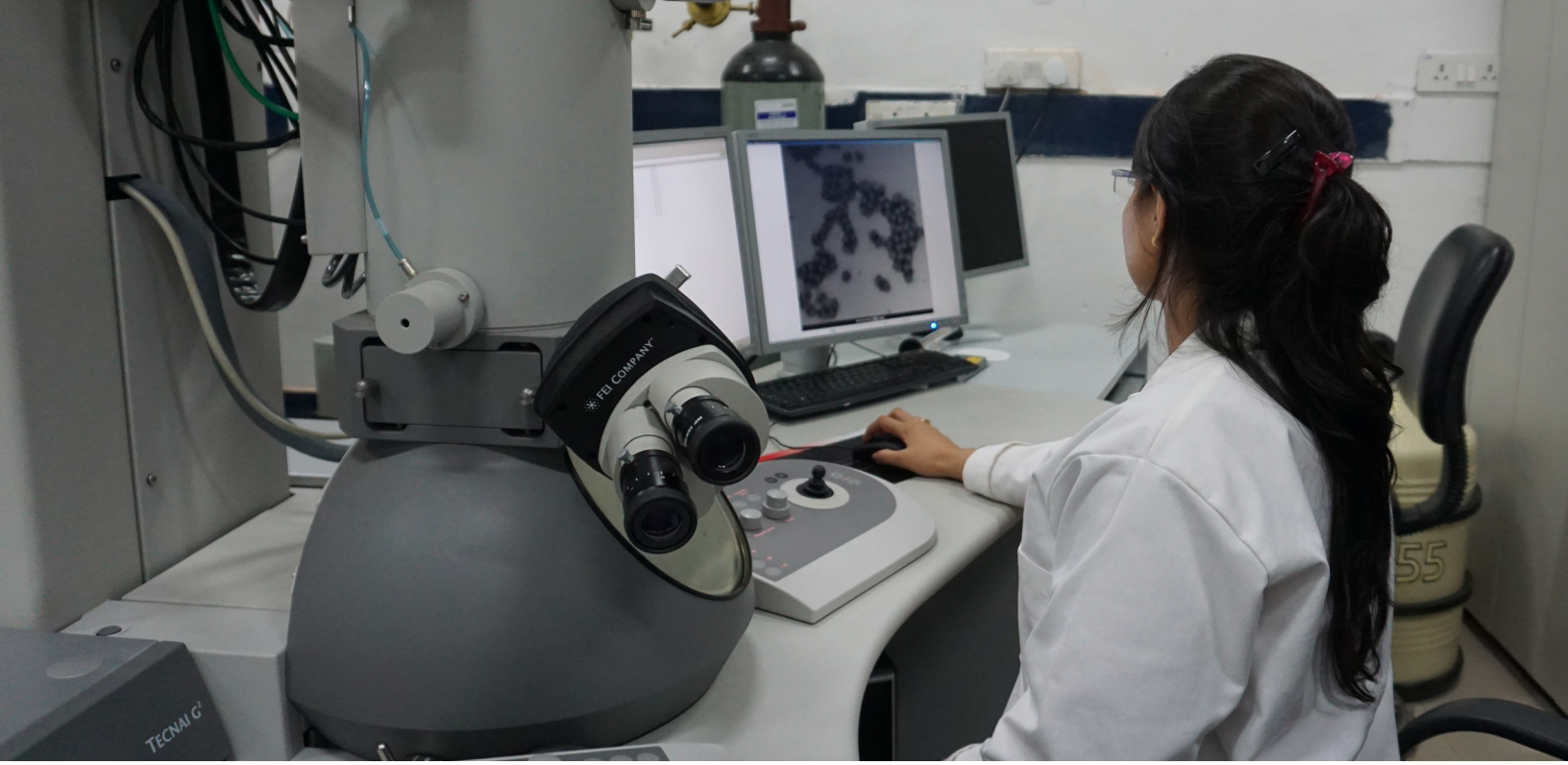

At this important crossroad in proteomics research, scientists must go beyond generic research and utilise discovery data to address unmet clinical needs. It is essential to move beyond studies of protein expression and define the intended use of such data in clinics. Focusing on specific areas such as cancers and infectious diseases prevalent in the country would be of utmost importance. Study designs should direct specific /discrete action to identify markers for risk assessment, early detection, diagnosis, prognosis, prediction or potential targets for therapy so that the outcome of the investigations have clinical relevance.

Organised tissue repositories and hospital information systems for clinical data are the primary need for translation. Only then, the biomarkers emerging from discovery research can be taken forward for multi-centre validation in larger cohorts. These issues are now receiving some attention and need more intense effort.

For clinical applications, body fluid proteomics occupies a key position. To overcome the limitations of the present techniques[2, 3] to achieve the depth of the proteome in body fluids or to detect protein variants associated with clinical conditions, researchers need simple technologies which can be tailored for on-line pre-fractionation or identification of the variants based on specific recognition sites like reporter amino acids. The immobilised metal-ion affinity (IMA) concept, based on the recognition of accessible histidine residues on a protein by divalent transition metal ions, has excellent potential for the simple detection of variants[4]. Such newer approaches may be explored. Finally, special attention for the development of user friendly, point-of-care devices is particularly important in the Indian system, given large number of centres with limited technical expertise.

India with its diverse demography is a great resource of clinical material. With scientific expertise, optimal funding and increased communication between the scientist and the clinician, India can contribute effectively to the bench to bedside translation. CME programmes, workshops and free interactions between the two groups is the way to develop an integrated discipline. While this might take some time, the volume of omics information publicly available today has opened the door to an era of integrative and hypothesis-driven science, connecting with even metabolomics in the downstream. The largest international proteomics forum, the Human Proteome Organization (HUPO), has taken up several proteomics initiatives with implicit translation goals[5]. However, exploration of human biology is an integral element that cannot be side-lined. So, it is imperative to continue scientific efforts in acquiring new methods and trends while simultaneously pursuing improvements in clinical paradigms to enable more effective fusion of the two segments. There are some publications from Indian groups now which show the promise of translation both in thinking and in effect[6, 7].

India needs to strengthen the public-private-partnership (PPP) model for the industry partners to shape and develop technologies with government funding. Research-oriented hospitals, who could join hands in clinical proteomics, should be encouraged by government agencies. It is time that funding agencies considered proteomics as truly translational just like genomics. Establishment of tripartite partnerships involving clinicians, academia and industry will be the way forward for clinical proteomics in India so that the bench to bedside dream moves from being a pipedream to a reality.

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