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Advances in Pharmacology and Clinical Trials

Review Article

**Received Date:** May 23, 2016
**Published Date:** June 14, 2016

# Bottleneck towards the Practice of Multi-/ Interdisciplinary Nature of Systems Pharmacology and Systems Medicine: Experience from India

**Durjoy Majumder*[1,2], Asesh Banerjee[1,3], Dibyendu Kumar Ray[1,4], Tarun Kanti Naskar[1,5], Ishita Chatterjee[1,6], Abhik Mukherjee[1,7], Subhabrata Dutta[1,8], Ranjan Kumar Gupta[1,9], Suryasarathi Barat[1,10]**

[1]Society for Systems Biology & Translational Research, India

[2]Department of Physiology, West Bengal State University, India

[3]Department of Laboratory Medicine, All Asia Medical Institute, India

[4]Department of Neurosurgery, Bangur Institute of Neurosciences, India

[5]Department of Mechanical Engineering, Jadavpur University, India

[6]Department of Applied Psychology, University of Calcutta, India

[7]Department of Computer Science & Technology, Indian Institute Engineering Science & Technology, India

[8]Calcutta Institute of Engineering and Management, India

[9]Department of Management, West Bengal State University, India

[10]Department of Information Technology, Focus R&D Pvt. Ltd., India

*__Corresponding Author:__ Durjoy Majumder PhD, West Bengal State University, India, email: durjoy@rocketmail.com

## Abstract

Presently medicine and clinical practices are viewed with systems approach. This makes a paradigm shift in the academic pursuits of the subject pharmacology, hence pharmacology with systems based approach is known as Systems Pharmacology. If Systems Pharmacology can be practiced in a proper manner it would modify the future medicine and health care system. Since towards its accomplishment, it requires multidisciplinary and/or interdisciplinary framework and however, several policy related problems may hamper its development. Some of the problems exist globally while some others are mainly India specific. Currently, India is considered to be the superpower among the south Asian countries and therefore, it may be the representative of the developing countries. Hence, development of the subject in Indian perspective is vital in the management of different diseases in the global context as well. Here we discuss the problems that confront the development and growth of the subject in India and propose some methods that may come out as solutions. Apparently it seems that the major bottlenecks are mistrust, issue of nepotism and bias in the academic pursuit, but the inner reasons are the fund crunch, problem in recruitment policy, ignorance regarding the global trend of science and its implementation in policy.

**Keywords:** Systems Biology; Systems Medicine; Systems Pharmacology; Science in India; Science policy; Teaching

## Introduction

In the post genomic era, evidence based clinical practise becomes questionable and hence suggested for systems level understanding and its clinical translation [1, 2]. To tackle the large variability of diseases in human cases, it becomes primordial necessity to address the pharmacological principles with the light of systems based approaches [3]. Systems based approaches has different facets - epigenomics and signal cascade to network biology, intercellular communication and inter-tissue to inter-organ interactions. This development of knowledge helps in appreciation of overall pharmacological action of a drug within a system, which ultimately leads towards clinical translation and has been initiated to find out resolutions in different health related issues in human [4-15]. After applying it to the clinical arena at the individual level, it gives a feedback to the developed knowledge and thereby either appreciates or criticizes the existing knowledge. Further, it may hints towards the lacunae present within the existing knowledge and provides the necessary clues for its modifications [16, 17]. This overall venture turns out the Systems Biology to Systems Medicine.

Henceforth, the approach for implementing systems medicine in reality, a multi-/interdisciplinary (**MDID**) framework is utmost necessity and has been suggested by several experts of the field since the beginning of this decade [18]. India is currently being considered as the south Asian superpower in science. Recently several developmental aspects in different facets of science including biomedical science of India were discussed in one of the leading journal in science; however, health aspects that require MDID nature was out of focus [19, 20]. To achieve the goal of systems medicine, several policy related problems persist in the scientific and academic arena that hamper its practise towards reality and some of the issues to the problem are addressed recently [21].

## MDID Programs – Global & Indian Perspective

Academic and research programs involving MDID is still a global problem in scientific endeavour; however, in the western world this issue is being addressed and separate establishments have been created [22, 23]. However, in India, yet there is no palpable initiative for development of such separate establishment particularly in the field of biomedical science. So far the accepted and pursuable MDID programs are collaboration between/within the same faculty structure, for example, a research activity between biochemistry, pharmacology and gynecology; but inter-faculty collaboration for example, pharmacology and control engineering is seldom understandable and encouraged [24].

Exercising of academic program of MDID nature is almost difficult in Indian context as most of the Indian universities do not have all the faculty structures. Broadly, Indian academic pursuits are exercised under the umbrella of Basic Science, Engineering and Medicine. Former two are within the arena of Ministry of Human Resource & Development whereas Medicine is under the Ministry of Health & Family Welfare. So, different faculty structures are under different administrative control. Hence, development of collaboration and implementation of MDID program in biomedical science especially for Systems Pharmacology/Systems Medicine is difficult. Moreover, different faculty structure has different objectivity and mind set - basic science is to pursuit academic excellence through laboratory based research, medical faculty emphases on the primary health care and the focus of engineering faculty is on the development of skilled man-power for industry. Due to administrative discrepancies, discipline based mind-set makes the concerned experts to be confined within their own domain; they neither share their professional problem with other discipline nor devote any time to understand problems of other discipline. So one discipline do not approach other to get a solve from other discipline. This makes a gap in sharing of knowledge. In India, a majority of the biomedical programs are exercised as biology program under the purview of basic science and majority of the Indian universities' teaching programs are not coupled with research or vice-versa in general academia [25]. In most of the engineering and medical institutions research is also far away and the observation of Prof. John F. Davis in the year of 1969 is still remains true to this date [26]. Contrary to several other established disciplines like biophysics or biochemistry, Systems Pharmacology and Systems Medicine is not a hybrid science and to appreciate its vastness it needs a mature mind.

## Research Programs in Systems Pharmacology

Since a particular academic department is irrelevant for investigating any MDID problem, and due to absence of MDID department; cross-enrolment of a student for an interdisciplinary program is difficult in some universities [27]. Sometimes students have hesitation to join such program, due to persuasion of mandatory PhD course work as recently required by the UGC regulation. In majority of the PhD course work selected topics are generally chosen from the single discipline; hence if the enrolled student is from other discipline may not get interest on several topics and feels unnecessary to his own research problem. Due to financial and budgetary constraints majority of the cases it is not possible to float a wide variety of course topics.

Research output with MDID nature may sometimes be published in an unrelated journals and majority of such research journals are newly developed and obviously has low impact factor and citation index score in comparison to conventional subject specific journals. Undoubtedly, in general survey based work in biomedical science gets more citation. This makes a very prominent bottleneck as it reduces the chance of getting a job and/or research grant. Generally a home department in India, evaluates one's performance on the basis of mere impact factor publication and even though are appreciated sometimes but refused to accept the person for faculty position as he may not be able to teach the basic courses of the department [27]. Even in some cases applications are turned down by the clerical screening and do not reach to the experts. It is of common experience that experts from general academia of biomedical sciences and medicine do appreciate the product based development and are unable to appreciate the development of analytical methods, computational tools and statistical methodologies which are important precursors for novel products.

Several aspects in the field of biology, conventional mathematics and approach of Physics cannot be applied and possibly in the field of medicine this is more pronounced [28]. Long histories of human disease cases constitute the domain knowledge for a specific human disease. For an understanding and tackling of human disease cases, such knowledge becomes the major pillar of Systems Pharmacology and/or Medicine. Contrary to physical sciences, there is a limitation of direct data capture in discreet time points in live animals and humans. To surpass this limitation, logic based multi-scale modelling approach and Artificial Intelligence based computer programs and algorithm are important in the arena of Systems Biology in general [29-31]. However, in Indian context, a good number of physics or mathematics trained persons are unable to appreciate the computational programs and algorithm. In general academia, majority of the academicians are unaware about the peer review evaluation system of engineering conferences [32]. Though recently this can be appreciated by implementation of PBAS (Performance Based Appraisal System) in university sector [33], but there is no clear cut policy in different academic research institutes. Contrarily, engineering community does not appreciate the hardship of data capturing methodology with live animal and human patients.

## Teaching Programs – Scope & Limitations

Teaching in general academia and engineering are mostly confined within the four walls of classroom. All problems are addressed within the scope of lab based environment and are reluctant to teach the real life problems. Most of the cases translational research is considered as product based development [21]. Though the subject Biomedical Engineering (BME) has a more close alliance with Systems Biology including Systems Pharmacology and in India several universities have BME program; however, perspective and inclination of the subject in India are quite different [34]. Similar observation was noted by Professor John F. Davis in 1969 while development of BME program in India and he criticized the basic tendency for the development of BME programs [26]. Yet as of now, instead of application of engineering approach to solve the biomedical problems, emphasis is put only on prosthesis and instrumentation. Possibly this is the reason why majority of BME programs are confined within Engineering faculty structure. On the other hand, most of medical faculty structure, emphasis is put to the primary health care management system and hence, are far away to integrate research in health care; as a result all local (including health care) problems are addressed and tackled with the solution of global problem [35]. The meaning of research in medical faculty remains confined with the population based survey works – mainly with the epidemiology or clinical trials of drug; and individual patient is neglected. In engineering and biological departments of general academia there is no scope to implement such observation based approach. This makes a major hindrance in implementation of qualitative and symptomatic understanding of disease cases. As a result, application of Systems Pharmacology/Medicine is unappreciated.

To maintain the paraphernalia in academics, conducting of teaching programs on Systems Pharmacology or Systems Medicine is more difficult in existing academic departments. In almost all Indian universities, syllabus is needed to be routed through a board consisting of some senior teachers of the concerned discipline; however, for a newer course with MDID nature there is availability of few experts in a near-by region who have exposure or prior research experience to MDID framing. Moreover, majority of the senior teachers do not have exposure or prior research experience with MDID framing. As a result, some senior teachers from the concerned discipline are chosen and if some terminology is known to them, they suggest inclusion of topics within that particular course. Inclusion of those topics makes the course redundant to rest of the course and as a result, basic objectivity and philosophy for the development of that course is lost and ultimately whole course becomes conventional due to unnecessary increase in volume. Though there is no legal bar for inviting experts from other regions, but in that case budget becomes the major constraint.

Another important aspect is the moderation process in the examination system. Generally questions are moderated (modification, corrections etc.) by some outside teacher for a particular university system; and in that case, sometimes such outside teacher makes a modification of the question in a manner that basic essence and philosophy of the original question is lost. All such schemes are exercised to avoid nepotism and bias in the educational process. However, the inherent reason is the budgetary constraint and academic departments in majority of the Indian universities are run by a modest number of teachers, sometimes not more than five faculty members. Even in some universities, there is norm to select only persons who are at rank of Professor as Ph.D. thesis examiners. Such norms also make it difficult to find out a Ph.D. thesis examiners for a research program with MDID nature especially in the field of Systems Pharmacology and Systems Medicine, as in India there is almost no expert available especially at the rank of Professor in the field.

## Research Grant

Though MDID research activity in health sector is formally being encouraged as evident by call for proposals by different granting agencies; but sanctioning scheme is far from reality. Basic tenets of MDID activity require a group of people with different skill sets but with the same mind set towards a definite problem [23]. But experts expect different skill sets to the same person. It is more ironic that they expect prior experience to that particular project proposal. It is really ironic that project grant is not sanctioned, but experience is sought. This could only possibly if one follows the "following science" scheme, as with some particular skill sets even with MDID nature; out of the box science is not possible. Generally research proposal with MDID nature requires much more money compared to uni-directed field and hence it is quite impossible to get such project by a junior investigator, as granting agencies also require previous experience of project handling. Another prominent bottleneck is that one cannot apply for grant until and unless he hold a prior faculty position (substantive position means employee with some retirement benefit – it is to be noted here that in India there is no social security for her citizen). This is in contrast of the western world where one gets a faculty position after getting a project grant. Even in the recruitment policy, experience is counted as time spent in a substantive position. However, in a substantive position exposure to MDID is never possible.

So far in the 12$^{th}$ Five Year Plan, Indian Planning Commission placed a report on "Synthetic and Systems Biology Resource Network (SSBRN)", in that 44 pages report, there is only 3 lines is mentioned on Systems Pharmacology and Systems Medicine. Not only that much emphasis is on the product based application of synthetic biology, which is basically extrapolation of biotechnology application with mathematical framework. There is almost no emphasis on the concept based development in the area of biomedical and health science. Most interesting fact is that there is no mention about any policy to access human patients and disease dynamics and there is no separate budget on Systems Pharmacology and Systems Medicine. Whatever disease related mentions are mostly lab based science exercise and the identified groups of the task force has no prior research experience in the area of health [36].

## Recruitment Policy

To avoid "complacency and nepotism" in recruitment policy, it now becomes a general trend that a candidate is not selected for a faculty position to his or her parent institution from where he is graduated. This is an unspoken norm followed in the recruitment policy in the national level institutions in India. Such norm if implemented to all sphere of science, then undoubtedly brings variation in academic culture in different academic institutions [37]. However, such policy is detrimental for pursuing implementation science. As implementation science require much more money compared to basic science, not only that science especially Systems Pharmacology and Systems Medicine require direct dealing with patients. So such policy do not bring any fruitful result in health sector, as a young investigator never get much grant money and a lot of his effort and many potential and viable years of his/her carrier will lost to develop infrastructure and collaborations. It is to be noted here that Systems Pharmacology and Systems Medicine requires collaborations with experts from diversified field but with same passion [21]. It is commonly seen in India that a lot of costly instruments are underutilized after a student left an institute; while in his present working institute his research is suffered due to lack of basic infrastructure. So in the field of implementation research especially in the field of health sector, such unspoken policy makes a huge wastage of public money and mis-utlisation of Indian talents. Generalization of this policy is good for technique and/or laboratory based science exercise where there is no need for direct patients involvement and development of concept that require domain knowledge through MDID framework.

## Appeciation in Science Policy

Team science with MDID is now become a trend for big science. However, there are no norms to decide the leader of the project. Generally a senior scientist becomes the leader, and all other recruited personnel from diversified discipline are acted as co-investigators [38]. But for the Systems Pharmacology and Systems Medicine such approach may not be fruitful and if several senior scientists are required, then there is a question who would be the leader. A norm is implemented in the PBAS scoring by UGC to assign the scientific contribution in a paper, where 1st author and communicating author will get 70% score while rest other get 30%. This may cause another hindrance to conduct research with MDID framework, especially in the area of Systems Pharmacology and Systems Medicine, as research in this area needs a full time dedication and each one's contribution is important. So such scheme raises unnecessary psychological turmoil within the colleagues. To circumvent this scientific society structure is the ideal solution; however, there is almost no scope to submit research proposals to different granting agencies by a scientific society. This is another bottleneck in this area. The reason of following such scheme is due to – 1) so far no big research project is being conducted in India, 2) most of the existing science and academic policy makers do not have exposure to MDID framework and if have, are trained in abroad and hence, little experience of pursuing research conduction in India.

Basic tenets of scientific approach lie in the approach of extrapolation of adopted technique to other domain area. Systems pharmacology and systems medicine is a field where not only technical/computational skills are needed, but also it is heavily dependent on disease specific domain knowledge. Even one cannot appreciate a computer program or model until and unless he has some research experience with the particular disease. This is why it is truly a MDID field. Blind application of experimental techniques of science which is mostly adopted in test tube based and/or fragmented knowledge generation may be integrated to sum up to a fruitful result; however, it imposes a huge cost. Conventionally evidence based practice if adopted for the field of systems pharmacology and systems medicine it would impose an unnecessary burden and possibly, developing countries cannot bear such research cost. However, if it can be applied conceptually and rationally, then patients of the developing countries will be most benefited [39, 40]. Conventionally understanding of translational research is directed not only towards product development but it has a problem of one way direction i.e., lab to clinic. The reverse direction i.e., needed modification is needed to be included. India is a huge country and contrary to western world, a lot of patients are willing to share their personal disease data for the advancement of science [41, 42]. However there is no platform where they can share it. Society for Systems Biology & Translational Research (www.ssbtr.net), a cluster of experts with multidisciplinary background and are dedicated organization took an initiative to address the above issues for developing countries.

## Conclusion

Apparently it is seen that major bottleneck is mistrust, question of nepotism and bias, but the deeper cause is the fund crunch, ignorance about the global trend of academia, recruitment policy and overall the science policies in health sectors. Change in policy for biomedical science is utmost needed for development of the subject of Systems Pharmacology and Systems Medicine in developing countries. Following policy if adopted may provide a better solution for the disease suffered people –

1. A separate council is needed to be formed for implementation and/or translational aspect of biomedical sciences.
2. Development of separate institutes is needed. If not possible then a separate section has to be developed within the existing hospital set up, but with absolute freedom and should not be intermingle with the administrative control of the existing institutes.
3. A separate MS-MD program on Systems Pharmacology and/or Systems Medicine is needed to be started.
4. Submission of research proposals should be opened for wider applicants from the society and should not be confined within university or national level institute faculties.
5. Scientific societies should be encouraged for conducting research.
6. In different cases research proposals are turned down with some vague comment "we have received

some interesting proposals, so your proposal is not considered". Hence, a good review comments should be returned to the research proposal submitting applicant.

7. During assessment of research proposals and/or recruitment, priority should be given to the work done of the applicants' own country, not with foreign collaboration.
8. Research achievement should give priority over experience in the recruitment policy.
9. All types of job experiences including fellowship, industry experience etc starting from pre-doctoral state is needed to be considered as experience instead of substantive position or post-doctoral experience.
10. For faculty positions, persons with research experience with direct human disease cases in a MDID framework are needed to be considered.
11. During recruitment, experts should be selected in a manner who has a true MDID exposure not mere from a single discipline exposure. Curriculum vitae of the experts need to be available to the applicants before interview, because it would help the candidate to judge the specific experts background and hence answering his/her questions during the interview process. A video recording should be mandatory for interview process.
12. Research achievement should be assessed on basis of implementation or its scope or strategy for human disease cases specially in Indian context, not mere on the basis of impact factor or citation index.

## Acknowledgement

This is the output of discussion since the inception of the Society for Systems Biology & Translational Research (SSBTR) and continued in subsequent meetings of SSBTR.

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