Drug discovery research in India

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Modern drug discovery and the role of Indian researchers have stimulated or inspired several authoritative and informative articles[1–9] and surely demand more attention. On 1 January 2015, Nitya Anand (former Director, CSIR-Central Drug Research Institute (CDRI), Lucknow, and one revered in Indian pharma affairs), completed his eventful 90th year. To commemorate this event, a one-day symposium on 'Drug Discovery in India: Past, Present and Future' was organized at CSIR-CDRI, Lucknow. This prompted us to carry out a retrospective assessment of the status of new drug discovery research in India with special attention to the role of Government research institutions.

New drug discovery and development in India had taken roots soon after its independence. With the setting up of chemistry and pharmacology-oriented laboratories, namely CDRI; National Chemical Laboratory, Pune (only for process); Regional Research Laboratory (now renamed as Indian Institute of Integrative Medicine), Jammu and Indian Institute of Chemical Technology, Hyderabad (more for process), under the Council of Scientific and Industrial Research (CSIR), a strong foundation was laid to assist and support Indian pharma efforts.

Urea-Stibamine was the first modern drug discovered in India by U. N. Brahmachari in 1922 for leishmaniasis, and was inspired by the successful use of arsenicals for syphilis by Ehrilch in Germany[10]. Post-independence, the setting up of CDRI and other CSIR laboratories led to the spread of the culture of drug discovery research in India when several multi-national pharma giants also established their R&D centres. Table 1 summarizes the Indian efforts.

In addition, there are several drugs which have been approved by Drug Controller General of India (DCGI), but

Table 1. Drugs discovered and marketed in India

Drug	Discoverer	Use	Marketed by	Year of approval
Sintamil	Ciba-Giegy Research Centre, Mumbai	Anti-depressant	Novartis, Mumbai	1976
Satraindizole	Ciba-Giegy Research Centre, Mumbai	Anti-protozoal	Alkem Laboratories, Mumbai	1980
Guglip (phytopharmaceutical)	CDRI, Lucknow	Hypolipedimic	CIPLA, Mumbai	1988
Centchroman (Ormeloxifene)	CDRI, Lucknow	Contraceptive, dysfunctional uterine bleeding (DUB), emergency contraception	Hindustan Latex Ltd, Thiruvananthapuram Torrent Pharmaceuticals Ltd, Ahmedabad	1989 1990
Bacosides (phytopharmaceutical)	CDRI, Lucknow	Memory enhancer	Nivaran Herbals, Chennai	1997
Arteether	CDRI, Lucknow	Anti-malarial	Themis Medicare, Mumbai	1997
Risorine	IIM, Jammu	Anti-tubercular	Cadila Pharma, Ahmedabad	2009
Synriam	Ranbaxy Laboratories Ltd, New Delhi	Anti-malarial	Ranbaxy Laboratories Ltd, New Delhi	2011
Lipaglyn™ (Saroglitazar)	Zydus Cadila, Ahmedabad	Diabetic dyslipidemia or hypertriglyceridemia	Zydus Cadila, Ahmedabad	2014

Table 2. Drugs discovered but not marketed in India

Drug	Discoverer	Use	Licensed to	Year of approval
Centiminazone	CDRI, Lucknow	Anti-thyroid	Unichem Laboratories, Mumbai	1972
Nonaperone	Ciba-Giegy Research Centre, Mumbai	Anti-psychotic	Novartis, Mumbai	1980
Amoscanate	Ciba-Giegy Research Centre, Mumbai	Anti-parasitic	Novartis, Mumbai	1980
Enfenamic acid	Regional Research Laboratory (now IICT), Hyderabad	Anti-inflammatory	–	1982
Cent-bucridine	CDRI, Lucknow	Local anaesthatic	Themis Medicare, Mumbai	1987
Cent-butindole	CDRI, Lucknow	Neurolaptic	Themis Medicare, Mumbai	1987
Chandonium iodide	CDRI, Lucknow, and Panjab University, Chandigarh	Neuro-muscular blocker	CIPLA, Mumbai	1994
Cent-propazine	CDRI, Lucknow	Anti-depressant	Themis Medicare, Mumbai	1996
Bulaquin	CDRI, Lucknow	Anti-malarial	Nicholas Piramal, Mumbai	1996

Table 3. Compounds of Indian companies at different stages of development

Compound	Therapeutic area	Status
Dr Reddy's		
DRF 2593	Metabolic disorders	Ongoing; phase III
Several compounds	Respiratory disorders	Ongoing; phase I
DRL 17822	Metabolic disorders/cardiovascular disorders	Ongoing; phase I
Ranbaxy		
Unnamed	Respiratory problems	Ongoing; completed phase I in collaboration with GSK and received related milestone payment from the company
Glenmark		
GRC 10693	Naturopathic pain, osteoarthritis and other types of agonist inflammatory pain	Ongoing; entered phase II trials
GRC 8200 (Melogliptin)	Diabetes type-2	Ongoing; entered phase III
GRC 3886 (Oglemilast)	COPD, asthma	Ongoing; phase II completed
GRC 4039 (Revamilast)	Rheumatoid arthritis, multiple sclerosis and other inflammatory disorders	Ongoing; entered phase II
GBR 500*	Multiple sclerosis and inflammatory disorders	Ongoing; phase I
GRC 15300	Osteoarthritis pain, naturopathic pain, skin disorders	Ongoing; phase I
GBR 600*	Anti-platelet, adjunct to PCI/acute coronary syndrome	Ongoing; completed preclinical trials
Crofelemer	Anti-diarrhoeal	Successfully completed phase III. In-licensed from Napo Pharmaceuticals, USA (now registered in India)
Biocon		
PEG-GCSF*	Oncology	Ongoing; pre-clinical
Bmab 100*	Oncology	Ongoing; pre
Bmab 200*	Oncology	Ongoing; pre
BVX-20*	Oncology	Ongoing; pre
IN 105 (Oral Insulin)*	Diabetes	Ongoing; phase III
T1h*	Inflammation	Ongoing; phase II
BIOMAb EGFR (Glioma, NSCLC)*	Oncology	Ongoing; phase III
Wockhardt		
WCK 771	Anti-infective	Ongoing; phase II
WCK 2349	Anti-infective	Ongoing; phase I
Piramal Healthcare		
P 276	Oncology (head and neck cancer)	Ongoing; entered phase II. Trials are going on in India, USA and Australia
P 276 combination with Gemcitabine	Oncology (pancreatic cancer)	Ongoing; phase I
P 276 combination with radiation	Oncology (head and neck cancer)	Ongoing; phase I
P 1446	Oncology	Ongoing; phase I in India and Canada
NPB-001-05-Bcr-Abl	Oncology (chronic myeloid leukaemia)	Ongoing; phase II
P 13 Kinase	Oncology	Ongoing; lead selection
Microbial leads	Oncology	Ongoing; lead selection
Target X – Merck	Oncology	Ongoing; lead selection
Target Y – Merck	Oncology	Ongoing; lead selection
NPS 31807-TNFa	Inflammation (rheumatoid arthritis)	Ongoing; phase II completed
P 979-TNFa	Inflammation	Ongoing; preclinical
P 3914	Inflammation	Ongoing; preclinical
IL 6	Inflammation	Ongoing; lead selection
TNFa	Inflammation	Ongoing; lead selection
P 1736 – non PPARy	Diabetes and metabolic disorders	Ongoing; phase I
P 1201 – Lilly	Diabetes and metabolic disorders	Ongoing; phase I
P 2202 – Lilly	Diabetes and metabolic disorders	Ongoing; phase I
DGAT1	Diabetes and metabolic disorders	Ongoing; lead selection
NPH30907# – dermatophytes	Anti-infective	Ongoing; phase I completed
PP 9706642# – anti-HSV2	Anti-infective	Ongoing; preclinical
PM 181104 – MRSA/VRE	Anti-infective	Ongoing; toxicity studies
Lupin		
LL 2011#	Anti-migraine (Amigra)	Ongoing; phase III
LL 4218	Anti-psoriasis (Desoside-P)	Ongoing; phase II
LL 3858/4858#	TB (sudoterb)	Ongoing; phase I
LL 3348	Anti-psoriasis (herbal desoris)	Ongoing; phase II
Unnamed	Diabetes type-2	Ongoing; preclinical
Unnamed	Rheumatoid arthritis	Ongoing; preclinical
Torrent Pharmaceuticals		
Unnamed	Diabetic heart failure	Ongoing; completed phase I

Source: Joseph, R. K., The R&D scenario in Indian pharmaceutical industry – December 2011, RIS-Research and Information System for Developing Countries; http://www.ris.org.in, http://www.newasiaforum.org

*Biologics; #These molecules are phyto-pharmaceuticals (origin from plants).

Table 4. Candidate molecules under various stages of development at CDRI, Lucknow

Molecule	Indication	Stage of development
97-78	Anti-malarial	Phase-I
99-373	Anti-osteoporotic	Phase-I
80-574 + Atorvastatin	Dyslipedimic	Phase-II
S007-867	Anti-platelet	Preclinical
S007-1500	Oral rapid fracture healing	Preclinical
914/K058	Osteogenic	Preclinical
S007-1261	Anti-diabetic	Preclinical
S007-1235	Anti-cancer	Preclinical

were not commercialized due to several factors (Table 2).

It is pertinent to mention here that Ormeloxiphene from CDRI was licensed to Zymo Genetics, Seattle, USA, for use as anti-oestporotic agent, but was dropped later due to adverse reaction in phase I. However, the same is being investigated for various types of cancer[11].

Eighties onwards, several Indian pharma companies also ventured in new drug discovery research and their intensive focused efforts have primarily been responsible for energizing this sector. This has paid good dividents and several new drug candidates are in various stages of development (Table 3).

The effective output of Indian pharma industry can be termed significant, notwithstanding the fact that several of these have been the outcome of active collaborative efforts with multinational pharma majors. However, the recent launch of Syniram (anti-malarial) by Ranbaxy and Saroglitazar (ZYH1, diabetic dyslipidemia) by Zydus Cadila marks a new chapter in Indian drug discovery research. The last two decades also witnessed the emergence of several contract research organizations who made their mark in designing molecules against specific targets using current drug discovery tools. To name a few, Aurigene Discovery Technologies, Bengaluru; Invictus Oncology, Delhi; Jubliant Biosys, Bengaluru; Syngene, Gurgaon; Advinus Therapeutics, Pune and Orchid Research Laboratories, Chennai have proved their capabilities in discovering several bioactive molecules under contract with multinationals where the bio-evaluation, IPR and subsequent works remain in the domain of the multinationals. In the recent past some of the biotech-driven start-ups, like Curadev, Connexios, Suven, etc. focusing on drug discovery against molecular targets have proved to be extremely successful and have licensed out their molecules[12].

The apparent proficiency of select pharma companies in generating new chemical entities (NCEs) albeit under contract can lead to the opinion that in the global business it is enough to be a player but not imperative to have a drug totally developed in India. This view is unwise as long-term interest of the country can only be best protected if we master the whole process of drug discovery and development. It brings us back to the question as to why public-sector laboratories like CDRI, which have done commendable work in the early post-independence era, have failed to keep pace in the last few decade (Table 4).

Drug discovery is a process where effective interactions among several competent researchers come to fruition under an effective team leader; it also requires adequate funds. The lack of success of public sector can be ascribed to: (i) lack of dynamic leadership capable of managing different disciplinary inputs; (ii) inertia in effective adaptation of modern drug discovery tools; (iii) dilution of the focus on drug research due to faulty performance evaluation parameters of the team members; (iv) lack of structured crosstalk with pharma industry, and (v) lack of adequate financial support. Organic chemistry capabilities have traditionally been strong in India and have driven the growth of the pharma generic sector. Biological disciplines in the country have a limited effective skill talent pool and public sector has been tardy in keeping up with the emerging techniques. The early success of laboratories like CDRI was based on their ability to synergize their strength in chemistry by developing a range of whole-animal (phenotypic) assay systems. However, their inability to strengthen modern biology to keep pace with the increasing use of target-specific (genotypic) assays, has slowed in later years their active drug leads. Public sector laboratories like CDRI were slow in anticipating the impact of new biology in drug discovery research and did not make commensurate, timely and adequate investments in strengthening modern biology, thus affecting the drug discovery programme. Efforts to correct this deficiency were effectively taken up by mid-90s.

The apparent present progress of Indian pharma companies is driven by their ability to attract researchers trained in modern biological tools and their optimal utilization. The new drug discovery area is fraught with hazards as is evident by cessation of Piramal efforts, and closing down of New Drug Discovery & Research (NDDR) in Ranbaxy, thus bringing the spotlight on Dr Reddy's Laboratories, Lupin Pharmaceuticals, Zydus Cadila and Glenmark Pharmaceuticals for future discoveries.

The apparent large bioactive leads generated by several Indian pharma companies under contract research for multinationals showcases our traditional strength in chemistry, but also poses a question as to why champions from business/pharma firms in India are reluctant to take leadership to successfully see through these discoveries to their logical end. This also puts in perspective the low lead molecule to NCE conversion within public sector laboratories. While the inflow of well-educated manpower is largely dependent on both the horizontal and vertical academic outflows from our universities and is subject to larger initiatives by the Government, in the short term, incorporation of the following remedial measures to augment capabilities of academia and Government laboratories may prove to be helpful:

1. Giving emphasis, due recognition and incentives to researches to forge

teams in drug discovery and development area.
2. Re-emphasizing phenotypic assays.
3. Augmenting post-discovery regulatory process.
4. Reviving natural products chemistry research in the country to harness our vast ethno-pharmacological potential.
5. Identification of biological researchers with core competence to identify new drug targets and to work on mode of action of the identified NCEs.
6. Setting up mechanisms at the National level for an early recognition/ evaluation of the commercial and intellectual potential of a new lead, for clinical trials, and to liaison with pharma business.

Drug research will flourish in India only when both academia and industry forge a mutually rewarding partnership, no single sector can shoulder the whole burden. We should not consider the new drug discovery research in India as an activity which can be deferred till our pharma industry can be financially strong enough to foot the bill for developing new drugs for national and international introductions. There is also a need to promote structured interactions between academia and pharma sector. Biological research in the West has been driven primarily by financial support to universities and national laboratories, and we need to reflect upon this.

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