ISSN: 2454-6968
RNI No. UPENG/2013/54102

Volume 7
Issue 75
October 2019

Rs. 800

BIOTECH EXPRESS

Guestorial:

UNSUNG HEROES: the rise of Shantha Biotech, talk with Prof. Ramareddy Guntaka – the scientific brain behind the unparalleled success

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VOLUME 7 ISSUE 75
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Publisher : Kamal Pratap Singh

Printed at : Monex offset, B-12 SD complex, near MMG hospital, Ghaziabad- 201005.

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Guestorial

UNSUNG HEROES: the rise of Shantha Biotech, talk with Prof. Ramareddy Guntaka – the scientific brain behind the unparalleled success

By Kamal Pratap Singh and Prof. Ramareddy V Guntaka

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In a paper ''***Globalization and Health, Biomed Central 7: 9 (2011)'' by Justin Chakma, Hassan Masum, Kumar Perampaladas, Jennifer Heys and Peter A Singer*,*** the authors interviewed Mr. Varaprasad Reddy (VR), MD, Shantha Biotechnics and more than 20 scientists and other employees. Not even once, the name of Prof. Guntaka was mentioned in this interview. Neither VR nor the scientists revealed the contribution of Guntaka, however he was Scientific Advisor of the company at that time. While casually browsing, Prof. Guntaka came across the above mentioned paper and immediately sent an email to the Principal author Dr. Peter A Singer, who in turn asked Dr. Hassan Masum to investigate. Incidentally, Guntaka happened to be in Hyderabad and so Masum called him there and spoke for about an hour, he realized the truth and replied to Dr Singer that

'Based on our conversation and prior reading, I believe that our writing on Shantha would have benefited if we had known to interview Professor Guntaka. I apologized for any incompleteness in the perspective we wrote, and assured Professor Guntaka that we would have loved to interview him had we known of his involvement. In response Dr Peter Singer said, Dear Hassan and Prof Ramareddy, This sounds just perfect. Most of all I am delighted to know about your pivotal role Prof Ramareddy. Congratulations on your contribution to saving lives through vaccines. Best wishes, Peter Singer

THE HINDU • FRIDAY, FEBRUARY 10, 2006

Biotechnology parks in 6 states by 2010: official

Geetha Reddy opens BioAsia-2006, foresees upswing in BT

BEFITTING HONOUR: *Minister for Industries J. Geetha Reddy presenting Genome Valley Excellence Award to Rama Reddy V. Guntaka of the US at BioAsia conference in Hyderabad on Thursday.* – PHOTO: SATISH H.

This was just an incident, the publishing space is full of success stories of Shantha Biotech, telling only about Varaprasad Reddy (VR), as the hero of Success. But what has not been told that he did not made this vaccine, instead he hired people, making false promises and at the end when the company was sold initially to Merieux Alliance and later to Sanofi at a valuation of USD$784 million (over Rs 3,770 crore), After the Merieux $175 million deal, the man which made this 1$ Hep B vaccine, was not given the recognition as well as the 5% for which he was assured from the very starting,

''VR always discussed about himself, he left all others in crowd, Said Prof Ramareddy V Guntaka, the man who made this most competitive and affordable vaccine for Indians. He was the Scientific Advisor of Shantha Biotechnics Pvt. Ltd., from 1993-2000 and carried out the Cloning and Expression from beginning to end. He trained scientists at Shantha Biotechnics. According to Prof Guntaka, many of these scientists did not have much knowledge in this area.

In 1990, next year after 89 Nobel Prize, the famous Journal *Nature* accepted and published a correspondence of Ramareddy Guntaka when he was called ''Antecedents of a Nobel Prize'' for his role in the discovery of Proto-oncogenes. (https://doi.org/10.1038/343302a0)

Now Prof Guntaka is working in the University of Tennessee Health Science Center as Professor in the Department of Microbiology, Immunology and Biochemistry, College of Medicine. He still works at

the bench in laboratory and trying to bring other vaccines, mainly vaccine for Hepatitis C Virus to the market at affordable cost. In fact, there is no vaccine for this silent killer virus anywhere in the world and Guntaka is approaching developing this vaccine by fusing several epitopes of the virus proteins. In the future he is also planning a similar approach to bring a vaccine for Dengue virus and other viruses.

To bring these vaccines and other high value therapeutics in to market at an affordable price, they started Sudershan Biotech Ltd. in Hyderabad. In addition to being a promoter he is the principal scientific advisor to this company.

Starting with the story(2019) of Shantha Biotech, Prof Gunataka said, there is no doubt that the founder, VR was not hardworking, he made all arrangements to build and run a company that could be valued at USD$784 million or around Rs 3,770 crore. But he did not made the Vaccine and that is where he forgot all his accomplices when the deal was done. My share in the company was 5%, which was never shared, he smiled.

At that time, Merck and GlaxoSmithKline (formerly Smith Kline Beecham) had developed recombinant vaccines in 1986, and they held a monopoly with over 90 other patents covering manufacturing processes such as isolation and purification. Over 100,000 Indians were dying every year from Hepatitis B infection. About 40 million individuals were chronically infected, and 4% of the Indian population were carriers.

In year 1993, I was contacted to be a part of Shantha, and was requested to become Scientific advisor of the company. At the time my papers were coming and I was called 'Antecedents of a Nobel Prize, and this would attracted VR toward me. So I was promised to get 5% share in the company if I would make hep b vaccine at lower cost. I joined in 1993 and soon in 1997 we launched the hep b vaccine named Shanvac.

The launch of 'Shanvac-B' (first recombinant health product in India and first cheapest drug in world for prevention of Hepatitis B) which I made for Shantha brought immense name and fame to company and like promised I was happy to become a rich scientist. Many media houses were approaching the founders and interviews were keep coming. The sad note here to make is that VR did not even once said that he is thankful to the team, he made it to look like that he did all the work. We made a big scientific team and did non-stop research to make things happen because wealth resources were exhausting very suddenly at that time.

VR hide all others' efforts very diligently, our names were not described at any place.

Slowly, VR, founder, started to take away all the things to his credit, name he already took and now he was aiming for fame too. He started to ignore calls whenever I asked him for my share, then he tried to get away of me by giving a meagre amount that was not even my salary as Scientific Advisor.

How it all started

Varaprasad Reddy came to me through his relations in USA, and one of them introduced him to me. We met and spent a day talking about it. At that time, I was also thinking of doing something for India (though I was full professor in 1986). When we talked further with three people who approached me, I accepted and agreed to help. Since we were planning of making Hep B vaccine cheap, I was excited and took it as a challenge for a scientist who recently has missed Nobel Prize because of some politics and other things. I agreed and started preparation to get this work done for my country and its people, though the impact was large which I knew at the earliest point.

Technology was the biggest hurdle

Following that discussion, we agreed to proceed, but I told them it is a new technology. We will be able to release this product not before 5 years because it was also new for me. To learn and understand one of their people came to my US lab for several months, though not that competent. So, I had to begin work on this myself with my own hands. We still have materials from this project in our lab.

BOX: Among the discovery of Hep B vaccine his other outstanding pioneer contributions are:

1. First group (with Bishop and Varmus) to show that retrovirus DNA replication occurs in the cytoplasm and then in the nucleus of infected cells.

2. First group (with Bishop and Varmus) to show accumulation of supercoiled DNA in the nuclei of retrovirus-infected cells.

3 First group (Shank, Bishop, Varmus; Taylor) to demonstrate the presence of Long Terminal Repeats (LTRs) at the ends of retroviral DNA.

4. First group (with Stehelin, Bishop, Varmus) to discover proto-oncogenes

5. First one to clone an infectious Rous sarcoma virus DNA (Walter Gilbert' group sequenced this clone)

6. First to show methylation of provirus in nonpermissive cells

7. Demonstrated formation of triplexes of Triplex-forming oligonucleotide with the collagen gene promoter (resulted in a patent assignment to Guntaka)

8. First group to sequence the Indian strain of Hepatitis C Virus

Nobody on Varaprasad side knew many of the necessary techniques, many of them didn't know much of the technologies needed, I showed them and demonstrated processes. I directed everything, we got the colonies - We had to do PCR to see what to clone first. I used to bring all the reagents with me to India from US.

I was surprised to see Shantha story described as indigenous – much was not except me, if we talk about scientific work.

When we completed the initial work in US, I took some of the purified proteins, in Missouri, an Indian-American tested that proper protein was there in the sample, I did around 10-15 experiments at that point to purify required protein.

That was a time when India did not have a special Biotechnology department, DBT was started in 1986. In India, in early days nobody was expert in recombinant DNA, nor there were regulatory details. I did my pioneering cloning work in 1983, I was cloning from 1980 onward, and even after these many discoveries I still feel hungry to make many success stories like the one Shantha Biotech has.

Solving Bankruptcy

According to reports, VR attended one conference and got an idea to manufacture affordable vaccine, though he was not a biologist. But Varaprasad persisted, and raised $1.2 M USD (7.2 Crores INR) by selling his father's properties, and was seeking investment from family and friends to make his dream come true. Unfortunately, by 1995, Shantha had exhausted its initial investment and was on the verge of bankruptcy. After the initial failure, VR tried many Indian banks and financial institutions for funding but that went all in vague until one financer agreed to pour 1.2 million USD for a 50% stake in the firm. Dr. Varaprasad found an unexpected ally in the Foreign Minister of the Sultanate of Oman, H. E. Yusuf Bin Alawi Abdullah, who wanted an affordable vaccine for his own citizenry, too.

But His Excellency Abdullah said, I won't invest any money until I meet scientist involved, he later came as foreign minister of Oman to New York, we had a meeting in Manhattan where he stayed.

In 1989, Bishop and Varmus got Nobel Prize, but there was a controversy about whether more of us should

have been included since I and another worked with them, I later wrote a letter to Nature (1990 article) that calmed down the controversy and I got credit through some news articles and papers (The discovery of Proto-oncogene by J Michael Bishop, https://doi.org/10.1096/fasebj.10.2.8641572).

His Excellency heard of some of this background, and agreed to come in and met me and was talking a lot to me as if he wanted to see if I am genuine or not. Thereafter, Shantha's project was approved and they received around 1.2 million USD in 1995.

Fight for survival

It was not easy to bring vaccine in the market, money was a factor, but we had to fight much for patents hurdles and regulatory approvals too. For example, Dr Chari Cohen sent a letter saying to stop work because of patent violation. We decided to contest that, we had a meeting in London, with His Excellency and a lawyer. After few talks, they (a corporation in Phoenix) took few royalties. Varaprasad also had difficulties with regulatory details as Biotechnology and/or Recombinant DNA Technology (RDT) was young at that time, but the vaccine was finally released and all were happy. During all these times, I stood firmly with Varaprasad and helped him to get out of any trouble.

ShanVAC B Release: Starting of exponential earning

In 1997, Shanvac-B, India's first home made recombinant product, launched at a price of about USD $1 a dose, it was upto 23 USD earlier. The vaccine was produced in *Pichia pastoris*, a yeast system different from that used by the original inventors of the vaccine.

The first year projected sales was 100,000 USD but actual sales in 1997 was 1.6 million USD. The sale was from private sector mostly as vaccine did not come under regular programs. Just after 10 years, in 2008, the sale of vaccine doses reached to 30 million and made earning of company close to 90 million USD.

I also worked to bring Shanferon (against Hepatitis B) which was also produced in *Pichia pastoris*. Shanferon, which I pushed and pushed - finally released in 2001.

In 2006 Merieux-Alliance (France) acquired a 60% stake in Shantha after the Omani investors sought an exit. In 2009, the firm was awarded a USD$340 million UNICEF contract for pentavalent vaccines, and in parallel, India adopted the vaccines for its immunization schedule at the recommendation of the WHO.

Sidetracking

In later years, Shantha people started slowly sidetracking me, since I was full time Professor in US, I could not run behind all this. They can talk whatever they want after the fact - it is all business tactics. We didn't have a dispute but I got sidelined since I had to do my teaching job at university. I got only a small amount of remuneration after sales started, less than originally understood.

It was not one or two times I tried to get my share, both scientific credit and money he promised, but he never done the deed as decided. He started to give interviews without acknowledging any scientific staff.

When the Shanvac was success, in 1999, I wanted to turn my attention to Hep C vaccine, initially Varaprasad promised me facilities, so I came on sabbatical, but he didn't give me a single penny, therefore I took materials from Deccan College, I did work on Hep C, completed in 2001 and released genome of Indian strain of Hep C virus.

Now my satisfaction with Shantha affair is kids are getting vaccinated cheaply, that was my consolation on whole episode. Varaprasad ideas were good but the more he became a capitalist, the more he became money-minded (and he made a lot of money)

Advice for future on partnerships - be less naive

People naturally want to help good cause and will skip proper agreement, now I would suggest put on paper etc. officially without considering other factors like country, origin, relationships etc.

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Editorial

General Understanding of Transdermal Drug Delivery System

By Dipanwita Bhattacharjee, Pritha Roy and Barun K. Bhattacharyya*
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Abstract

The transdermal drug delivery system (TDDS) has proved as one of the most promising method for new drug delivery system. To overcome the disadvantages associated with conventional dosage form, this area is an exciting and challenging field of pharmaceutical R & D. With transdermal drug delivery system one can deliver drugs through the skin to systemic circulation at a predetermined rate and maintain clinically effective concentration over prolonged period of time, taking advantage of passive transport method, diffusion. By the help of this advanced modern technology, through effective formulation, development and evaluation a large number of drugs can be delivered, eliminating the troubles of frequent dosing and plasma level peaks. Over the last two decades many such patches are approved worldwide. As the drug administered by TDDS bypass the gastrointestinal tract (GI) thus avoid metabolism by liver, there is lesser chances of side effects like GI irritation and liver dysfunction.

Key Words : Transdermal Drug Delivery System, Skin Permeability, Polymeric matrix , Patch

Introduction

Since the dawn of civilizations, people used to grind medicinal plants and herbs for development of formulations. Idea was to directly apply them on the wounds, bruises, and sprains to heal inflammation, itch and pain. Evidence of topical treatment at the time of 1400 BC was portrayed in Egyptian tomb paintings of an ointment workroom[1]. In China medicated plaster (more like recent medical patches) containing multiple ingredients can be traced back at around 2000 BC[2]. Almost 70 years ago reference of *Belladonna* (a local analgesic), Mustard (an effective local irritant) and Salicylic Acid (a keratolytic agent) getting used in plasters were found in USP[3].

Evidences show that in ancient India Ayurvedic formulations of Vedic period had wonderful healing capacities of nature. They also understood the physiological as well as physical benefits of nurturing touch. Sushruta Samhita Sutrathanam *(36.V.10.)* in Sushrut Samhita (200 BC) has described herbs like Haldi (*Curcuma domestica*), Vans Karpoor (*Bambusa arundinacea)*, Guduchi (*Tinospora cordifolia)*, Devadaru (*Cedrus deodara)*, Babul (*Acacia arabica)* can be effectively used in reducing swelling, pain, soreness of the fracture [4].

In Today's time, topical medications like, gels, creams, foams and ointments containing different kinds of medicines (like antibiotics, anti-bacterial, anti-inflammatory, analgesics and others) are applied directly as and where they are needed, without systemic exposure.

Transdermal Drug Delivery System

Transdermal medications are modern in approach and utilize the large expanse of skin and the underline systemic circulation to deliver the medicine to the body with advanced potential means. Since the first transdermal drug, Scopolamine, (to treat nausea in motion sickness) was approved by the US FDA in 1979 (www.accessdata.fda.gov) great strides in transdermal drug delivery have been achieved. This development of a new drug delivery system, other than topical, oral and parental route of existing drug molecule, has not only improved the drugs' safety and efficacy, but also has improved patient acceptance and therapeutic benefits to a significant level.

The skin of an adult human being covers a surface of approximately 16.1 – 21.5 sqft that receives about one third of the blood circulating in the body. The peripheral circulatory system consisting of arteries and veins are present in the arms, hands, legs and feet, chest and abdomen. TDDS (Transdermal Drug Delivery System) has been established as one of the most suitable systemic deliveries of drugs through blood vessels network under the skin. Once the medication is delivered steadily in the blood stream, it circulates and reaches the target location. The therapeutic as well as the adverse effect of the drug, on the patient, depend on the concentration of the same at the site of action. This in turn, depends on the dosage form and the absorption extent of the drug substances.

Permeation of drug molecules through the skin take place by following mechanisms[5] Fig. 1 :

- Release of drug molecule from TDDS and penetration of the molecule on the surface layer of the skin epidermis.
- Diffusion through underlying dermis a connective tissue and hypodermis.
- The molecule is then taken up by blood for systemic circulation.

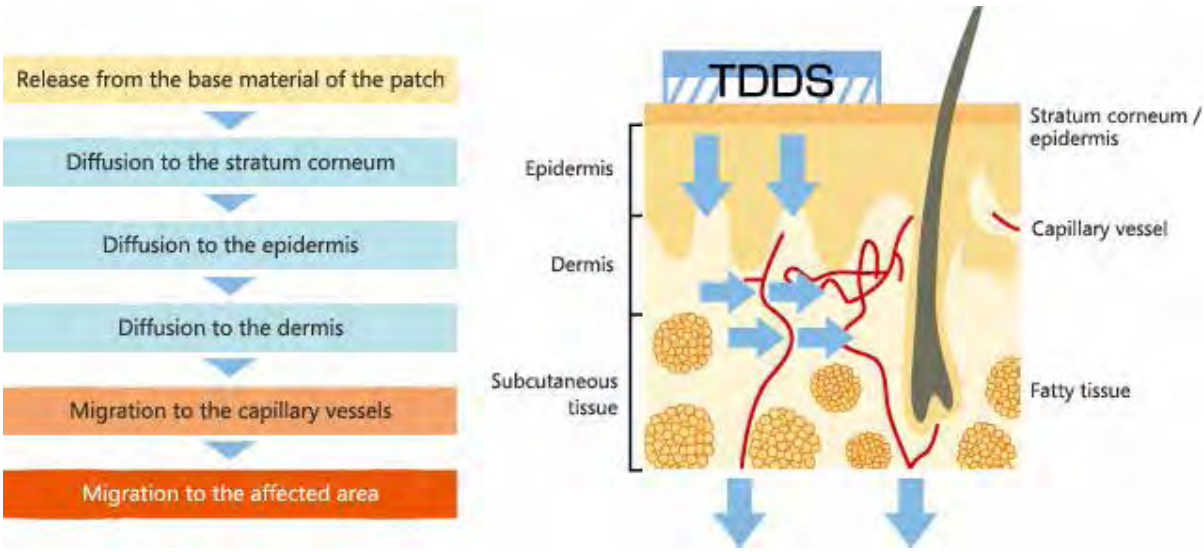

Fig 1. Transdermal mode of drug penetration[5].

Types and Components of TDDS:

It is almost four decades since the first US patents were issued to TDDS technology and today hundreds of the same being issued for the Transdermal drug delivery devices. These devices are of three types Adhesive device, Monolithic matrix device and Reservoir system. The components of these devices are [6-8]:

1. Backing layer
2. Drug reservoir
3. Release control layer
4. Adhesive and peel strip
5. Enhancers and excipients

Rationale to Develop TDDS

Development of TDDS Fig. 2 (www.pharmatutor.org) is a multidisciplinary activity. It involves, selection of suitable components (drug, excipients, enhancer, adhesive), demonstration of drug permeability through the skin, physiochemical and stability factors of the drug, patient's comfort, user friendliness and cosmetic appeal. Not to forget about the pricing and reduced skin irritation.

Following points are taken into consideration while developing TDDS system [9]:

- Molecular weight of the drugs should be less than 400 Daltons.
- Biological half life of the drugs should be short i.e. not more than 10 hours.
- Drugs should have affinity for both lipophilic and hydrophilic phases to cross the skin barrier.
- Drugs must not remain bound to skin layer.
- Properly diffusion of drugs through the matrix polymer.
- The enhancers should control skin permeability in such away that, body fluids should not be lost during, alteration of the permeability of the skin along with proper absorption of drug.
- Generally the pressure sensitive adhesive (PSA) exerts a strong holding force between skin and itself. It should be compatible to the drug biologically and physiochemically and should be easily removable from skin surface.
- The backing layer should protect the drugs from external atmosphere and it should be impermeable to drugs.
- The excipients, enhancers, matrix, adhesives should be non-toxic, non-allergic, economical and cosmetically acceptable.

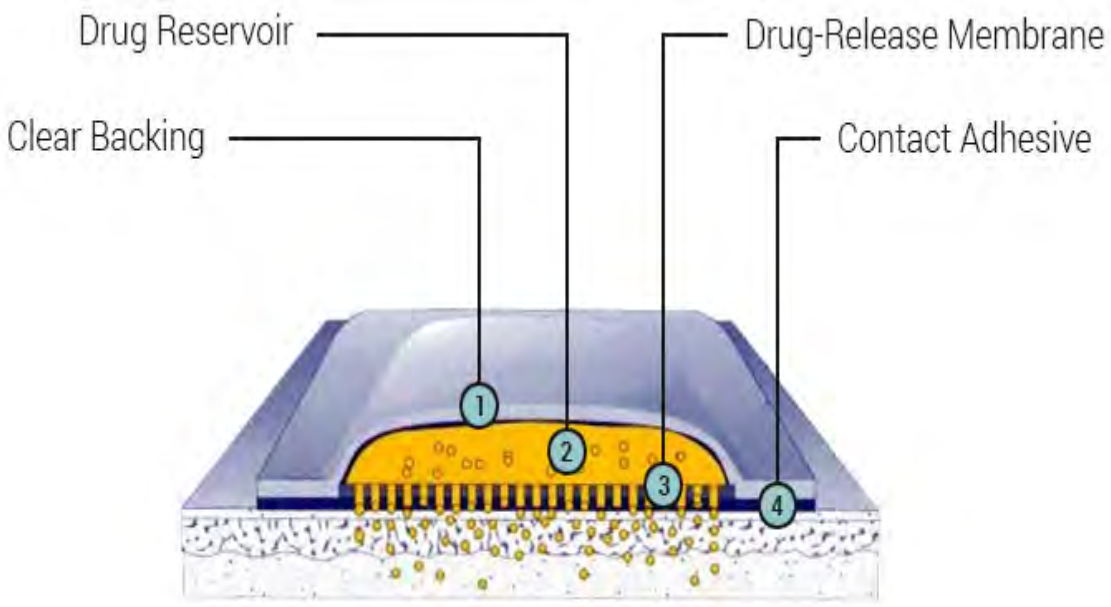

Fig 2. Major components of TDDS patch (www.pharmatutor.org).

General Instructions to Follow During TDDS Usage:

Some of the general instructions are[5]:

- The TDDS patch should be applied on clean, dry, unbroken skin devoid of lotion and moisturizer.
- The site of application of the patch recommended should be followed.
- The patch should be applied firmly at its place.
- In case of skin irritation, consult doctor immediately.
- Direct exposure to external heat source like staying out in sun, heating pad, electric blanket, hot baths etc. should be avoided.
- Keep it away from children or pets.

Polymer Matrix

Polymer matrix is the structural back bone of Transdermal Drug Delivery System which controls the release of drug from the device. These kinds of matrices are manufactured as mulilayerd polymeric laminates. A drug reservoir or drug polymer matrix is sandwitched between two polymeric layers, backed by outer impervious layer. The polymeric layer act as adhesive inside the device[10].

The following properties should be satisfied by the said polymers:

1. The molecular weight, chemical properties of the polymer molecule should be suitable for proper diffusion of the drug.
2. The polymer must be stable, non-toxic and non reactive in nature.
3. Commercially the polymer molecules should be inexpensive and easily producible.

Generally the polymers used by the industry for the manufacturing for Transdermal devices are [11]:

1. Natural polymers : Cellulose derivatives, Zein, Gelatin, Shellac, Starch, Waxes, Gums etc.
2. Synthetic elastomers : Polybutadiene, Hydrin rubber, Silicone rubber, Neoprene nitrile, Acrylonitrile, Butyl rubber.
3. Synthetic polymers : Polyvinyl alcohol, Polyvinyl chloride, Polyethylene, Polypropylene, Polyacrylate, Polyamide.

Permeation Enhancers

Enhancers are used to accelerate skin permeability by altering the skin as a barrier to the flux of a desired penetrant. A large number of investigations were carried out to establish the ability of different compounds to enhance the permeability of epidermis. These compounds are classified in the following groups [11]:

1. Solvents: Water alcohols – methanol and ethanol, alkyl methyl sulfoxides – dimethyl sulfoxide, dimethyl acetamide and dimethyl formamide, isopropyl palmitate.
2. Surfactants: These are of two types:

A. Anionic surfactants: Dioctyl sulphosuccinate, sodium lauryl sulphate, decodecyl methyl sulphoxide.
B. Nonionic surfactants: Pluronic F127, Pluronic F68.

3. Binary systems: Propylene glycol-oleic acid, 1,4-butane diol-linoleic acid.
4. Miscellaneous chemicals: Urea, N,N-dimethyl-m-toluamide, Calcium thioglycolate.

Regulatory Parameters of TDDS[12]:

- **Product quality test**

Identification of drug.
Drug content determination assay.
Impurities assay
Content uniformity test.
Moisture content of the formulated matrix.
Drug interactions studies.
Water vapour permeability evaluation.
Particle size test.
Crystal formation test.
Leak test

- **In vitro drug product performance**

In vitro drug release tests
In-vitro skin permeation studies
In-vitro adhesion studies, # Liner release test # Peel adhesion test

- **Residual drug test in TDDS after use**
- **Skin irritation studies**

Advantages of TDDS Technology

- Patches has been formulated to deliver the drug across the skin to the blood stream, in a continuous manner, to provide body wide systemic effect where pain control, addition treatment, hormonal treatment, diabetes control are required.
- Drug delivered by the TDDS does not come across with the digestive system, therefore does not have any side effects like gastric irritation and liver damage which is often associated with oral painkillers.
- TDDS route is suitable when oral application of the drug is unsuitable, as in case of patients with vomiting, mouth sores, diarrhoea, cancer and also in case of children and older persons.
- Drugs that are required at relatively constant level in blood plasma can be delivered transdermally.
- Drugs with short biological half life and drugs that are broken down by acid in stomach, not well absorbed at the intestine or extensively degraded at the digestive tract, can be delivered using TDDS.
- TDDS avoids patient inconvenience of parental administration.
- Reoccurrence of symptoms upon getting up in the morning, are results of low drug levels during the night. It can be avoided with the help of TDDS.
- Patients' do not have to remember to swallow frequent dosages.
- When formulated, the drugs in the TDDS patches used for local effects penetrate only the upper layer of skin, and do not reach the blood stream. Thus during pain management the risk of unwanted body wide side effects are significantly reduced.
- TDDS patch can be added to existing pain treatment plan and it does not interfere with systemic analgesics. For those patients, requiring several pain medications this technology is helpful.

Limitations of TDDS Technology

- It can not achieve high drug level in blood, where rapid dose is required, like acute pain.
- It can not be used if any of its component like drug, excipients, enhancers, matrices, adhesives cause common adverse effect i.e. irritant contact dermatitis
- (an inflammatory response caused by repeated or indirect exposure of skin to weak irritants) or infrequent adverse effect i.e. allergic contact dermatitis (delayed T cell mediated inflammatory response to a specific allergen)[12].
- Drug absorption is inversely proportional to molecular weight. Thus it can not be developed for a drug which has large molecular weight.
- Several biological factors like aged skin, thickness of skin, hydration of skin, temperature of the skin and environmental factors like sunlight, cold season, air pollution effect transdermal permeation of drug [5].
- Wearing too many patches can cause overdose.

Market Forecast for Global Transdermal Patches:

The global transdermal patches market is expected to grow at a CAGR of 4.85 % during the period of 2017 – 2023. The ease of administration, non invasiveness, prolong activity of the drug, less amount of drug in blood plasma may attribute to its growth rate if the major side effects of skin irritation can be overcome. Global TDDS product sales[11] by segment are discussed in Fig. 3 .

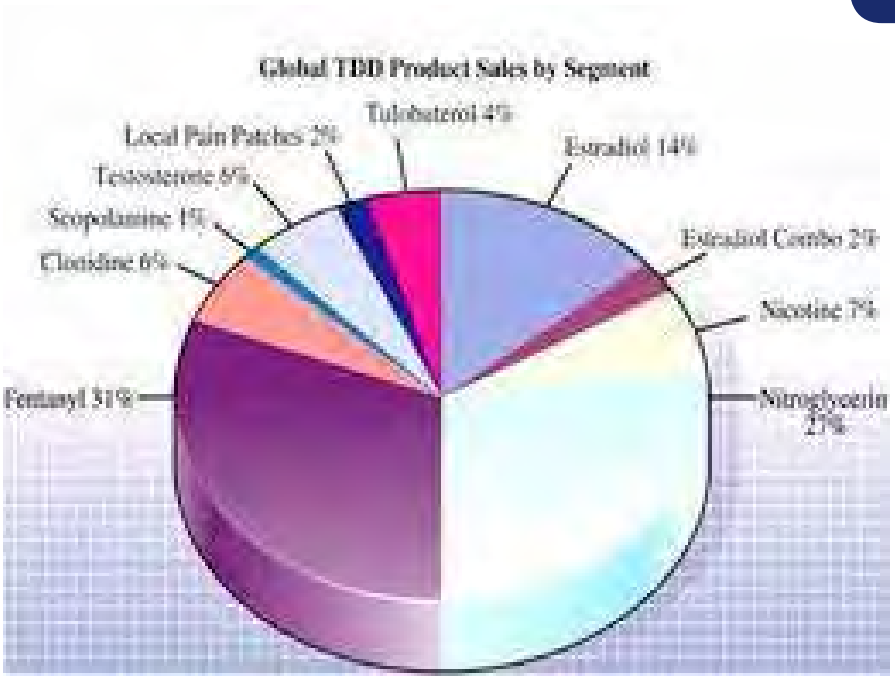

Fig 3. Global TDDS product sales by segment[11].

Key market players:
The major companies through out the world manufacturing and marketing the Transdermal drug delivery systems are Hisamitsu Pharmaceutical (Japan), Mylan (USA), UCB (Belgium), Novartis (Switzerland), Glaxo Smithkline (UK), Boehringer Ingelheim (Germany), Johnson & Johnson (USA). Table 1, summarizes some of the US FDA approved commercially available Trandermal Drug Delivery System products prescribed and available in the market[13].

Improvement of efficiency of TDDS Technology:

Empowered with our greater understanding of basic functions of skin that is to protect and containment and how to modify these properties for successful delivery of new drug molecules transdermally, the limitations of TDDS could be overcome in near future.
The points to ponder are:

- ❖ A chemical modification of physiochemical properties like lipophilicity of drug molecule can increase its permeation across skin through lipophilic epidermis[14].
- ❖ It is also observed that drug formulation with pH values between 4 and 8 close to skin surface pH 5.5 and minimizing their concentration in formulation may result in less skin irritation to tolerable limit[15].
- ❖ Solvents with acceptable safe use like isopropyl alcohol, propylene glycol, isopropyl myristate (up to 60%) should be used to formulate the TDDS[16].
- ❖ The control release system, liposome or microsphere entrapt drug in hydrogel formulation hydrates epidermis, help in penetration and sustained release of drug, avoid build up of drug concentration under the skin hence decreasing the skin irritation. Manipulating the chemical such as of skin permeation enhancers also reduce irritation of skin.

Conclusion

The increasing number of chronic diseases like AIDS, Hepatitis, Duodenal ulcer likely to support global needle-free drug delivery market and is likely to increase significantly during the year 2018-2026. The manufacturers are largely focused towards research and development, to launch better new products and also to improve existing one to uphold the growth in the TDDS industries.

Acknowledgement

Authors are thankful to the management of East India Pharmaceutical Works Limited, Kolkata for providing facilities and encouragement.

Table 1. List of US FDA approved commercially available transdermal Patches[13]

Trade name	Drug	Type	Indications	Site of application	Duration of application	FDA approval
Transderm Scop®	Scopolamine	Therapeutic	Motion sickness	Behind ear	72 h	1979
Habitrol®	Nicotine	OTC	Anti-smoking	Outer part of arm	24 h	1990
Duragesic®	Fentanyl	Therapeutic	Chronic pain	Chest, back, upper arm	72 h	1990
Nicoderm CQ®	Nicotine	OTC	Anti-smoking	Anywhere in the body other than joint	24 h	1991
Minitran®	Nitroglycerine	Therapeutic	Angina pectoris	Chest, back, upper arm, shoulder	12-14 h	1996
Exelon®	Rivastigmine	Therapeutic	Alzheimer's and Parkinson's disease	Upper/ lower back, upper arm/ chest	24 h	2007
Flector®	Diclofenac	Topical	Topical treatment of acute pain	The painful area	12 h	2007
Salonpas®	Menthol	Topical	Muscle and joint pain	The effected area	8-12 h	2008
Qutenza®	Capsaicin	Topical	Neuropathic pain	The most painful area except face and scalpe	Single 1 h application	2009
Butrans®	Buprenorphine	Therapeutic	Chronic pain	Chest, upper arm, upper back	7 days	2010
Minivelle®	Oestradiol	Therapeutic	Female hormone replacement therapy	Lower abdomen	3-4 days	2012
Zecuity®	Sumatriptan	Active	Migraine	Upper arm	4 h	2013

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Guest Article

Chitinolytic actinomycetes with plant growth potential

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Abstract

The use of chemical fertilizers to the crops is very serious issue which has adverse effects on the soil quality and also the environment. The biological approach must be used for the plant growth promotion. The actinomycetes were isolated from the rhizosphere soil samples of maize from Dhule district and College of Agriculture, Pune, India. The isolates were studied for plant growth promoting traits viz., chitinase activity, phosphate solubilisation, indole acetic acid production and antifungal activity. The effect of actinomycetes and also with addition of chitin was studied on the plant growth. The isolates showed chitinolytic activity and phosphate solubilisation. Antifungal activity was shown by two isolates against the fungal phytopathogens. The chitinolytic actinomycetes also showed increase in the growth of plants viz., maize, wheat and bajra. The study shows that actinomycetes can be used for the enhancement of growth of different plants and as strong biological control agents.

Keywords: Rhizosphere, chitinase, indole acetic acid, antifungal, biological

Introduction

The use of chemical fertilizers to increase the crop yield has adversely affected the soil quality. The biological approach is very necessary, where the plant growth promoting rhizobacteria (PGPR) promote the plant growth by several mechanisms viz., production of Indole Acetic Acid (IAA), gibberellins, cytokinins, solubilisation of minerals, siderophores, ammonia (NH_3) production, etc.

The microbes in rhizosphere help plants in growth promotion and yield. Actinomycetes are one of the major components of rhizosphere microbial populations and are useful as well as plant growth promotion[1]. Actinomycetes are gram positive, aerobic and mycelia forming bacteria, found in various habitats including sea water, fresh water, soil, marsh area etc. Actinomycetes produce secondary metabolites viz., lytic enzymes, plant growth promoting substances and antibiotics[2]. The actinomycetes, mainly those belonging to *Streptomyces* spp. form important group of soil microbes. *Streptomyces* spp. convert complex molecules to simple molecules and help in the plant growth[3,4].

The aim of the present paper was to isolate the actinomycetes from the rhizosphere soil of maize, study the plant growth promoting traits and effect of seed bacterization on the plant growth viz., maize, wheat and bajra.

Materials and Methods

Isolation of Actinomycetes From the Rhizosphere Soil of Maize

Sampling

The rhizosphere soil samples of maize were collected from different regions viz., Dhule district, and College of Agriculture, Pune, India. The plants were uprooted and soil adhering to roots was collected in the sterile bags.

Isolation, Characterisation and Identification of Actinomycetes

Soil samples (1 g) each were suspended in 9 ml sterile saline and subsequently diluted to 10^{-2}, 10^{-3}, 10^{-4} and 10^{-5}. Each dilution (0.1 ml) was spread plate on starch casein agar (SCA) plate and the plates were incubated at 28°C for six days. Typical actinomycetes colonies were randomly selected and sub cultured on SCA plates and incubated at 28°C for 48 h. Well isolated colonies of actinomycetes were plated on colloidal chitin agar plates. Plates were incubated at 28°C for six days. The morphological, physiological and biochemical characteristics of the isolates were studied and confirmed using Bergey's Manual of Determinative Bacteriology[5].

Chitinolytic Activity of the Isolates

The suspension 0.1 ml was spot inoculated on colloidal chitin agar medium and the plates were incubated at 28°C for three days. After incubation, the plates were observed for zone of clearance.

Plant Growth Promoting Traits of Chitinolytic Actinomycetes

Phosphate Solubilisation

An aliquot (5 µl) of the culture was spot inoculated on National Botanical Research Institute's Phosphate (NBRIP) agar medium[6]. The plates were incubated at 28°C for seven days and checked for the zone of clearance around the colony.

Production of IAA

The production of IAA by the actinomycetes isolates was determined by the spectrophotometric method using Salkowasky reagent[7].

Antifungal Activity

The antifungal activity of the bacterial isolates was checked by agar well diffusion method[8]. The fungal phytopathogens viz., *Aspergillus pholnicis* (MTCC 4012), *Phoma glomerata* (MTCC 2210), *Alternaria solani* (MTCC 2101), *Fusarium graminacaerum* (MTCC *1898*), *Fusarium oxysporum* (MTCC 284), *Helminthosporium* (MTCC 1899) were obtained from Microbial Type Culture Collection (MTCC). The antifungal activity was evaluated by measuring the inhibition zone diameter against the phytopathogenic fungi.

Effect of Chitinolytic Actinomycetes on the Plant Growth

Disinfection of the Seeds

Chitinolytic actinomycetes isolates were studied for their effect on the plant growth. Seeds viz., maize, wheat and bajra were selected. The seeds were disinfected with 70% ethanol for 5 min and subsequently with 0.1% (w/v) mercuric chloride ($HgCl_2$) for 1 min and washed three times with sterile distilled water.

Pot Experiment

The seeds viz., maize, wheat and bajra were bacterized with chitinolytic actinomycetes for 5 min. The plastic pots were disinfected with alcohol. The experimental design included viz., soil (180 g) + actinomycetes (2 x 10^7 cells/ml), soil (180 g) + 1 g chitin + actinomycetes (2 x 10^7 cells/ml) and soil (180 g). Four seeds each of maize, wheat and bajra were sown in the pots. After fifteen days, the effect on the plant growth over the control was studied by determining the following parameters viz. root length, shoot length, root, shoot and leaf dry weight and vigor index.

Results and Discussion

Identification and Characterisation of the Isolates

The isolates were Gram positive, oxidase negative and catalase positive, indole, methyl red, Voges Proskauer negative and citrate positive, and were found to belong to *Streptomyces* sp.

Chitinolytic Activity of the Actinomycetes

In this study, six different chitinolytic actinomycetes strains were isolated from the rhizosphere soil of maize. All the isolates showed zone size >10 mm with more chitinase activity by isolate No. 2.

There is a report on chitinolytic actinomycetes isolated from rhizopshere associated soils from Ubon Ratchathani and Srisaket province[9]. Chitinase production by the actinomycetes can be a mechanism of biocontrol[10].

Phosphate Solubilization

The isolates No. 1, 3, 5 and 6 showed phosphate solubilization activity on NBRIP agar medium (Table 1), with highest phosphate solubilization activity by isolate No. 1, followed by isolate No. 3.

The enhanced phosphate availability to different crops will represent a possible mechanism of plant growth promotion under field conditions[11]. The main mechanism involved in the solubilization of phosphorus is related to organic acids[12]. Besides the organic acids, release of protons H^+ by the external cellular surface of ATPases, the production of chelating substances or the production of organic acids can constitute alternative mechanisms for solubilization of inorganic phosphates[13].

IAA Production

The chitinolytic actinomycetes were negative for IAA production.

Antifungal Activity

The isolate No. 4 showed antifungal activity against the fungal phytopathogens *Aspergillus pholnicis*, *Alternaria solani* and *Helminthosporium*, whereas isolate No. 5 exhibited antifungal activity against all the fungal phytopathogens (Table 2). This is in conformity with the results of several studies carried out by other investigators[14].

Streptomyces lydicus WYEC108 inhibited *Pythium ultimum* and *R. solani in-vitro* by the production of antifungal metabolites[15]. Similarly, *Streptomyces* isolates showed activity against five phytopathogenic fungi, *Alternaria brassicicolla*, *Penicillium digitatum*, *Fusarium oxysporum*, *Sclerotium rolfsii* and *Penicillium* spp[16]. The antagonistic activity of *Streptomyces* to fungal pathogens is usually related to the production of antifungal compounds[17] and extracellular hydrolytic enzymes[18].

Table 2 - Activity of chitinolytic actinomycetes against the fungal phytopathogens

Fungal phytopathogens	Inhibition zone (mm) → Actinomycetes isolates ↓					
	1	2	3	4	5	6
Aspergillus phoenicis	–	–	–	10	10	–
Phoma glomerata	–	–	–	–	18	–
Alternaria solani	–	–	–	12	15	–
Fusarium gramincarum	–	–	–	–	14	–
Fusarium oxysporum	–	–	–	–	12	–
Fusarium moniliformis	–	–	–	–	18	–
Helminthosporium	–	–	–	14	5	–

-: no activity by actinomycetes against the fungal phytopathogens

Effect of Bacterization on the Plant Growth

In case of isolate No. 5, the wheat seeds showed 100% germination in soil + chitin + actinomycetes (Table 3).

Table 3 - Effect of seed bacterization on germination

Isolates No.	Seeds	Seed germination (%)		
		Soil *	Soil + Actinomycetes	Soil + chitin + Actinomycetes
4	Maize	0	75	75
	Wheat	0	100	50
	Bajra	0	100	100
5	Maize	0	75	75
	Wheat	0	75	100
	Bajra	0	75	75

*: Control

The data is average of triplicates.

In case of isolate No. 4, the root length of wheat plant was 10.5 cm in soil + actinomycetes and in combination of soil + chitin + actinomycetes it was 12.0 cm (Table 4). In case of isolate No. 5, the root length of maize and wheat plants was 9.7 and 7.6 cm respectively in combination of soil + actinomycetes and 16.0 and 10.5 cm respectively in combination of soil + chitin + actinomycetes.

Table 4 - Effect of seed bacterization on the root length

Isolate No.	Plants	Root length (cm)		
		Soil *	Soil + Actinomycetes	Soil + Chitin + Actinomycetes
4	Maize	0	16.0±1.41	14.2±16.97
	Wheat	0	10.5±4.10	12.0±1.41
	Bajra	0	6.6±0.28	4.0±2.82
5	Maize	0	9.7±7.42	16.0±1.41
	Wheat	0	7.6±6.64	10.5±2.82
	Bajra	0	6.7±2.40	6.7±1.69

*: Control

The data is average of triplicates ± SD.

In case of isolate No. 4, the shoot length of maize and bajra plant was 9.2 and 12.7 cm respectively in soil + actinomycetes and in combination of soil + chitin + actinomycetes it was 11.5 and 16.0 cm respectively (Table 5).

Table 5 - Effect of seed bacterization on the shoot length

Isolate No.	Plants	Shoot length (cm)		
		Soil *	Soil + Actinomycetes	Soil + Chitin + Actinomycetes
4	Maize	0	9.2±2.47	11.5±2.12
	Wheat	0	4.1±6.43	4.5±0.70
	Bajra	0	12.7±3.95	16.0±5.65
5	Maize	0	12.5±8.83	11.5±2.12
	Wheat	0	5.3±3.74	4.5±0.70
	Bajra	0	3.7±0.98	3.6±0.56

*: Control

The data is average of triplicates ± SD.

In case of isolate No. 4, the root dry weight of wheat plant was 19.2 mg/plant in soil + actinomycetes and 36.5 mg/plant in soil + chitin + actinomycetes (Table 6). In case of isolate No. 5, the root dry weight of wheat and bajra plants was 19.6 and 3.6 mg/plant respectively in combination of soil + actinomycetes and 21.1 and 6.9 mg/plant respectively in combination of soil + chitin + actinomycetes.

Table 6 - Effect of seed bacterization on the root dry weight

Isolate No.	Plants	Root dry weight (mg/plant)		
		Soil *	Soil + Actinomycetes	Soil + Chitin + Actinomycetes
*4	Maize	0	69.1±2.89	41.9±14.77
	Wheat	0	19.2±4.17	36.5±21.35
	Bajra	0	7.0±9.68	4.0±5.65
5	Maize	0	107.6±95.38	39.4±45.82
	Wheat	0	19.6±27.57	21.1±10.88
	Bajra	0	3.6±4.87	6.9±3.67

*: Control, The data is average of triplicates ± SD.

In case of isolate No. 5, the shoot dry weight of maize, wheat and bajra plants was 153.6, 15.5 and 0.1 mg/plant respectively in combination of soil + actinomycetes and 198.1, 18.3 and 5.8 mg/plant respectively in combination of soil + chitin + actinomycetes (Table 7).

Table 7 - Effect of seed bacterization on the shoot dry weight

Isolate No.	Plants	Shoot dry weight (mg/plant)		
		Soil *	Soil + Actinomycetes	Soil + Chitin + Actinomycetes
4	Maize	0	184.5±7.77	169.0±38.25
	Wheat	0	20.8±5.58	5.4±0.56
	Bajra	0	10.2±2.33	2.5±3.46
5	Maize	0	153.6±108.61	198.1±40.80
	Wheat	0	15.5±10.96	18.3±9.54
	Bajra	0	0.1±0.07	5.8±2.89

*: Control

The data is average of triplicates ± SD.

In case of isolate No. 5, the leaf dry weight of maize and wheat plants was 78.8 and 29.3 mg/plant respectively in soil + actinomycetes and 138.5 and 39.6 mg/plant respectively in soil + chitin + actinomycetes (Table 8).

Table 8 - Effect of seed bacterization on the leaf dry weight

Isolate No.	Plants	leaf dry weight (mg/plant)		
		Soil *	Soil + Actinomycetes	Soil + Chitin + Actinomycetes
4	Maize	0	130.6±6.57	82.1±42.77
	Wheat	0	44.1±0.56	18.0±5.44
	Bajra	0	14.1±3.11	3.7±4.94
5	Maize	0	78.8±55.72	138.5±61.94
	Wheat	0	29.3±20.71	39.6±25.24
	Bajra	0	12.9±2.68	10.0±3.95

*: Control.

The data is average of triplicates ± SD.

In case of isolates No. 4 and 5, the vigor index of maize, wheat and bajra plants was found to increase (Table 9).

There is a report on effect of plant growth promoting *Streptomyces* sp. on growth promotion and yield of chickpea (*Cicer arietinum* L.)[19]. Also, there is a report on plant growth promotion of sorghum by *Streptomyces* sp. under greenhouse and field conditions. The plant height, leaf area and weight, root length and weight, shoot weight, panicle and seed weight were increased[20].

Table 9 - Effect of seed bacterization on the vigor index

Isolate No.	Seeds	Vigor index		
		Soil *	Soil + Actinomycetes	Soil + Chitin + Actinomycetes
4	Maize	0	1890.0	1957.5
	Wheat	0	1095.0	1650.0
	Bajra	0	1447.5	1500.0
5	Maize	0	1665.0	2062.5
	Wheat	0	967.5	1500.0
	Bajra	0	780.0	772.5

*: Control

*Vigor index = (Mean root length + Mean shoot length) x % seed germination[21]

The data is average of triplicates.

Conclusion

Actinomycetes isolates study showed plant growth promoting traits viz., phosphate solubilization and chitinase activity. The actinomycetes isolated from the maize rhizosphere can be used for the enhancement of growth of different plants and as strong biological control agents. This will also minimise the use of chemical fertilizers.

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PRESS RELEASE

Winners of 2019 Nobel Prize in Physiology or Medicine

William G. Kaelin, Jr., Sir Peter J. Ratcliffe and Gregg L. Semenza.
for their discoveries of how cells sense and adapt to oxygen availability

SUMMARY

Animals need oxygen for the conversion of food into useful energy. The fundamental importance of oxygen has been understood for centuries, but how cells adapt to changes in levels of oxygen has long been unknown.

William G. Kaelin Jr., Sir Peter J. Ratcliffe and Gregg L. Semenza discovered how cells can sense and adapt to changing oxygen availability. They identified molecular machinery that regulates the activity of genes in response to varying levels of oxygen.

The seminal discoveries by this year's Nobel Laureates revealed the mechanism for one of life's most essential adaptive processes. They established the basis for our understanding of how oxygen levels affect cellular metabolism and physiological function. Their discoveries have also paved the way for promising new strategies to fight anemia, cancer and many other diseases.

Oxygen at center stage

Oxygen, with the formula O_2, makes up about one fifth of Earth's atmosphere. Oxygen is essential for animal life: it is used by the mitochondria present in virtually all animal cells in order to convert food into useful energy. Otto Warburg, the recipient of the 1931 Nobel Prize in Physiology or Medicine, revealed that this conversion is an enzymatic process.

During evolution, mechanisms developed to ensure a sufficient supply of oxygen to tissues and cells. The carotid body, adjacent to large blood vessels on both sides of the neck, contains specialized cells that sense the blood's oxygen levels. The 1938 Nobel Prize in Physiology or Medicine to Corneille Heymans awarded discoveries showing how blood oxygen sensing via the carotid body controls our respiratory rate by communicating directly with the brain.

HIF enters the scene

In addition to the carotid body-controlled rapid adaptation to low oxygen levels (*hypoxia*), there are other fundamental physiological adaptations. A key physiological response to hypoxia is the rise in levels of the hormone erythropoietin (EPO), which leads to increased production of red blood cells (erythropoiesis). The importance of hormonal control of erythropoiesis was already known at the beginning of the 20th century, but how this process was itself controlled by O_2 remained a mystery.

Gregg Semenza studied the EPO gene and how it is regulated by varying oxygen levels. By using gene-modified mice, specific DNA segments located next to the EPO gene were shown to mediate the response to hypoxia. Sir Peter Ratcliffe also studied O_2-dependent regulation of the EPO gene, and both research groups found that the oxygen sensing mechanism was present in virtually all tissues, not only in the kidney cells where EPO is normally produced. These were important findings showing that the mechanism was general and functional in many different cell types.

Semenza wished to identify the cellular components mediating this response. In cultured liver cells he discovered a protein complex that binds to the identified DNA segment in an oxygen-dependent manner. He called this complex the *hypoxia-inducible factor* (HIF) . Extensive efforts to purify the HIF complex began, and in 1995, Semenza was able to publish some of his key findings, including identification of the genes encoding HIF. HIF was found to consist of two different DNA-binding proteins, so called transcription factors, now named HIF-1α and ARNT. Now the researchers could begin solving the puzzle, allowing them to understand which additional components were involved and how the machinery works.

VHL: an unexpected partner

When oxygen levels are high, cells contain very little HIF-1α. However, when oxygen levels are low, the amount of HIF-1α increases so that it can bind to and thus regulate the EPO gene as well as other genes with HIF-binding DNA segments (Figure 1). Several research groups showed that HIF-1α, which is normally rapidly degraded, is protected from degradation in hypoxia. At normal oxygen levels, a cellular machine called the *proteasome*, recognized by the 2004 Nobel Prize in Chemistry to Aaron Ciechanover, Avram Hershko and Irwin Rose, degrades HIF-1α. Under such conditions a small peptide, *ubiquitin*, is added to the HIF-1α protein. Ubiquitin functions as a tag for proteins destined for degradation in the proteasome. How ubiquitin binds to HIF-1α in an oxygen-dependent manner remained a central question.

The answer came from an unexpected direction. At about the same time as Semenza and

Ratcliffe were exploring the regulation of the EPO gene, cancer researcher William Kaelin, Jr. was researching an inherited syndrome, von Hippel-Lindau's disease (VHL disease). This genetic disease leads to dramatically increased risk of certain cancers in families with inherited VHL mutations. Kaelin showed that the VHL gene encodes a protein that prevents the onset of cancer. Kaelin also showed that cancer cells lacking a functional VHL gene express abnormally high levels of hypoxia-regulated genes; but that when the VHL gene was reintroduced into cancer cells, normal levels were restored. This was an important clue showing that VHL was somehow involved in controlling responses to hypoxia. Additional clues came from several research groups showing that VHL is part of a complex that labels proteins with ubiquitin, marking them for degradation in the proteasome. Ratcliffe and his research group then made a key discovery: demonstrating that VHL can physically interact with HIF-1α and is required for its degradation at normal oxygen levels. This conclusively linked VHL to HIF-1α.

Oxygen sHIFts the balance

Many pieces had fallen into place, but what was still lacking was an understanding of how O_2 levels regulate the interaction between VHL and HIF-1α. The search focused on a specific portion of the HIF-1α protein known to be important for VHL-dependent degradation, and both Kaelin and Ratcliffe suspected that the key to O_2-sensing resided somewhere in this protein domain. In 2001, in two simultaneously published articles they showed that under normal oxygen levels, hydroxyl groups are added at two specific positions in HIF-1α (Figure 1). This protein modification, called *prolyl hydroxylation*, allows VHL to recognize and bind to HIF-1α and thus explained how normal oxygen levels control rapid HIF-1α degradation with the help of oxygen-sensitive enzymes (so-called *prolyl hydroxylases*). Further research by Ratcliffe and others identified the responsible prolyl hydroxylases. It was also shown that the gene activating function of HIF-1α was regulated by oxygen-dependent hydroxylation. The Nobel Laureates had now elucidated the oxygen sensing mechanism and had shown how it works.

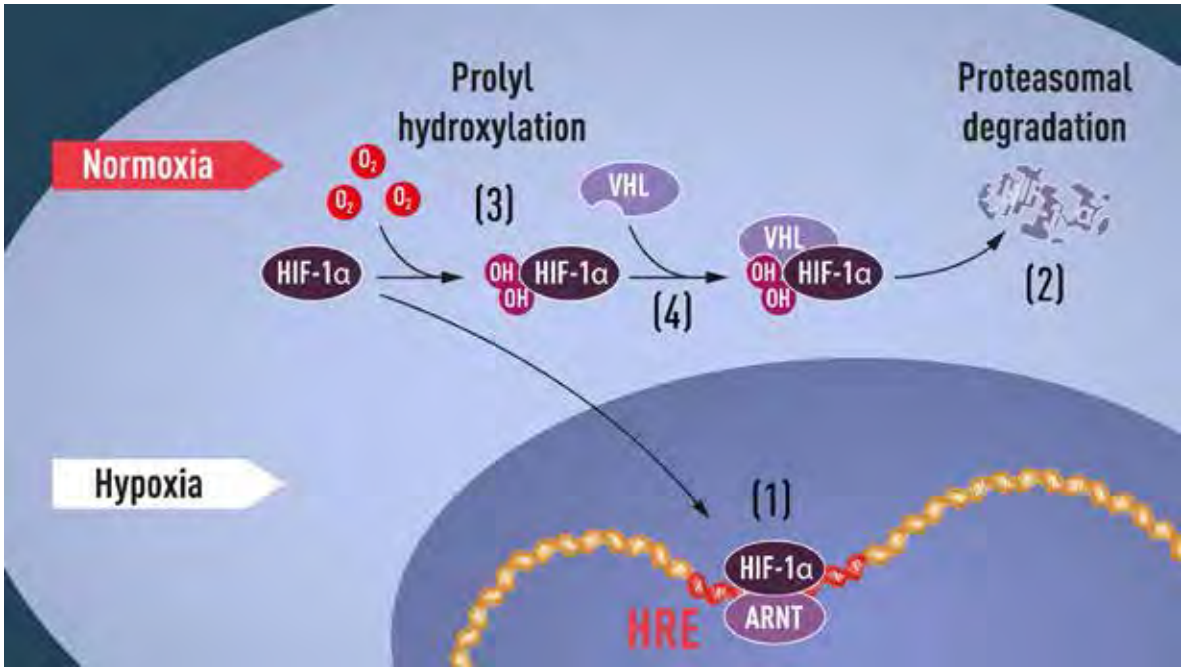

Figure 1 When oxygen levels are low (hypoxia), HIF-1α is protected from degradation and accumulates in the nucleus, where it associates with ARNT and binds to specific DNA sequences (HRE) in hypoxia-regulated genes (1). At normal oxygen levels, HIF-1α is rapidly degraded by the proteasome (2). Oxygen regulates the degradation process by the addition of hydroxyl groups (OH) to HIF-1α (3). The VHL protein can then recognize

Oxygen shapes physiology and pathology

Thanks to the groundbreaking work of these Nobel Laureates, we know much more about how different oxygen levels regulate fundamental physiological processes. Oxygen sensing allows cells to adapt their metabolism to low oxygen levels: for example, in our muscles during intense exercise. Other examples of adaptive processes controlled by oxygen sensing include the generation of new blood vessels and the production of red blood cells. Our immune system and many other physiological functions are also fine-tuned by the O_2-sensing machinery. Oxygen sensing has even been shown to be essential during fetal development for controlling normal blood vessel formation and placenta development.

Oxygen sensing is central to a large number of diseases (Figure 2). For example, patients with chronic renal failure often suffer from severe anemia due to decreased EPO expression. EPO is produced by cells in the kidney and is essential for controlling the formation of red blood cells, as explained above. Moreover, the oxygen-regulated machinery has an important role in cancer. In tumors, the oxygen-regulated machinery is utilized to stimulate blood vessel formation and reshape metabolism for effective proliferation of cancer cells. Intense ongoing efforts in academic laboratories and pharmaceutical companies are now focused on developing drugs that can interfere with different disease states by either activating, or blocking, the oxygen-sensing machinery.

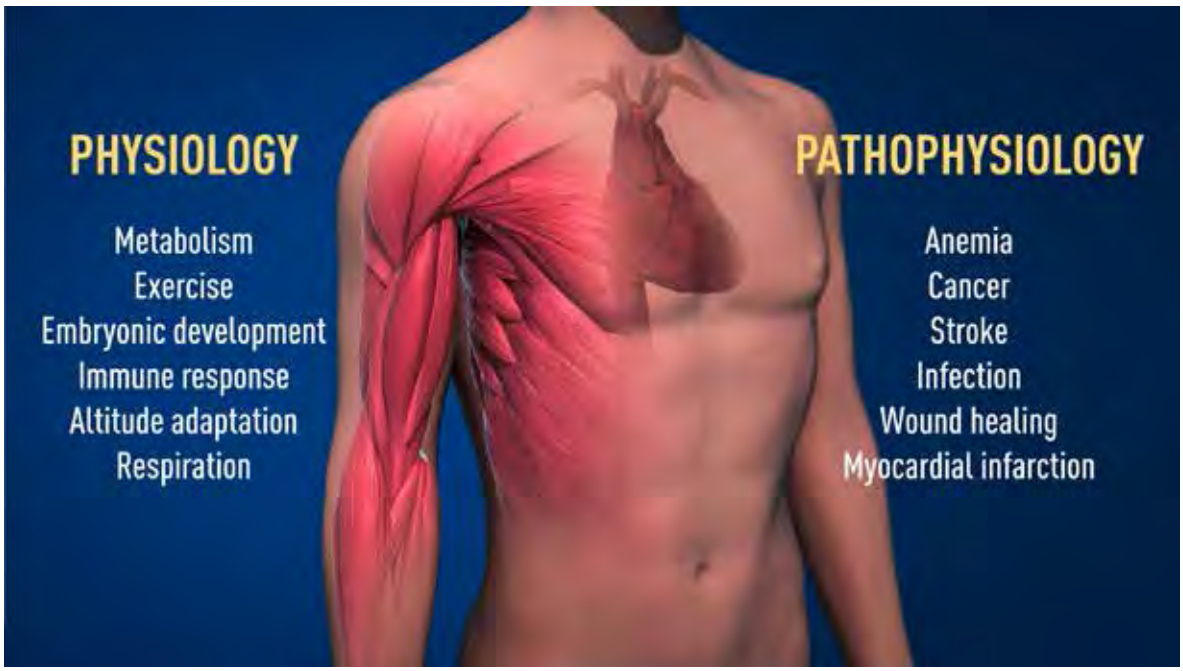

Figure 2 The awarded mechanism for oxygen sensing has fundamental importance in physiology, for example for our metabolism, immune response and ability to adapt to exercise. Many pathological processes are also affected. Intensive efforts are ongoing to develop new drugs that can either inhibit or activate the oxygen-regulated machinery for treatment of anemia, cancer and other diseases.

William G. Kaelin, Jr. was born in 1957 in New York. He obtained an M.D. from Duke University, Durham. He did his specialist training in internal medicine and oncology at Johns Hopkins University, Baltimore, and at the Dana-Farber Cancer Institute, Boston. He established his own research lab at the Dana-Farber Cancer Institute and became a full professor at Harvard Medical School in 2002. He is an Investigator of the Howard Hughes Medical Institute since 1998.

Sir Peter J. Ratcliffe was born in 1954 in Lancashire, United Kingdom. He studied medicine at Gonville and Caius College at Cambridge University and did his specialist training in nephrology at Oxford. He established an independent research group at Oxford University and became a full professor in 1996. He is the Director of Clinical Research at Francis Crick Institute, London, Director for Target Discovery Institute in Oxford and Member of the Ludwig Institute for Cancer Research.

Gregg L. Semenza was born in 1956 in New York. He obtained his B.A. in Biology from Harvard University, Boston. He received an MD/PhD degree from the University of Pennsylvania, School of Medicine, Philadelphia in 1984 and trained as a specialist in pediatrics at Duke University, Durham. He did postdoctoral training at Johns Hopkins University, Baltimore where he also established an independent research group. He became a full professor at the Johns Hopkins University in 1999 and since 2003 is the Director of the Vascular Research Program at the Johns Hopkins Institute for Cell Engineering.

The Nobel Assembly, consisting of 50 professors at Karolinska Institutet, awards the Nobel Prize in Physiology or Medicine. Its Nobel Committee evaluates the nominations. Since 1901 the Nobel Prize has been awarded to scientists who have made the most important

Key publications:

Semenza, G.L, Nejfelt, M.K., Chi, S.M. & Antonarakis, S.E. (1991). Hypoxia-inducible nuclear factors bind to an enhancer element located 3' to the human erythropoietin gene. *Proc Natl Acad Sci USA*, *88*, 5680-5684

Wang, G.L., Jiang, B.-H., Rue, E.A. & Semenza, G.L. (1995). Hypoxia-inducible factor 1 is a basic-helix-loop-helix-PAS heterodimer regulated by cellular O_2 tension. *Proc Natl Acad Sci USA, 92*, 5510-5514

Maxwell, P.H., Wiesener, M.S., Chang, G.-W., Clifford, S.C., Vaux, E.C., Cockman, M.E., Wykoff, C.C., Pugh, C.W., Maher, E.R. & Ratcliffe, P.J. (1999). The tumour suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis. *Nature, 399*, 271-275

Mircea, I., Kondo, K., Yang, H., Kim, W., Valiando, J., Ohh, M., Salic, A., Asara, J.M., Lane, W.S. & Kaelin Jr., W.G. (2001) HIFα targeted for VHL-mediated destruction by proline hydroxylation: Implications for O_2 sensing. *Science, 292*, 464-468

Jakkola, P., Mole, D.R., Tian, Y.-M., Wilson, M.I., Gielbert, J., Gaskell, S.J., von Kriegsheim, A., Heberstreit, H.F., Mukherji, M., Schofield, C.J., Maxwell, P.H., Pugh, C.W. & Ratcliffe, P.J. (2001). Targeting of HIF-α to the von Hippel-Lindau ubiquitylation complex by O_2-regulated prolyl hydroxylation. *Science, 292*, 468-472

19 - 21 December, 2019

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VENUE:
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ORGANIZERS:

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Registration opens:
September 1, 2019

Last Date for Registration:
October 10, 2019

CONTACT:
aicbc2019@gmail.com

SPEAKERS:

Sumantra Chattarji
NCBS, Bangalore

Anuradha Ratnaparkhi
ARI, Pune

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IIT Guwahati

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www.aicbc2019.org

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FORWARD

सत्यमेव जयते
Department of Biotechnology
Govt. of India

IUSSTF
Indo-US Science and Technology Forum

KHORANA Program for SCHOLARS

The Department of Biotechnology (DBT), Govt. of India, Indo-U.S. Science and Technology Forum (IUSSTF) and WINStep Forward are partnering to support the prestigious **Khorana Program for Scholars** named in honor of Dr. Har Gobind Khorana, who won the Nobel Prize in 1968 for his work at the interface of Chemistry and Biology while a member of the University of Wisconsin-Madison faculty. **The Khorana Program will provide opportunities to Indian students to undertake research at leading U.S. universities over Summer 2020 for a period of 10-12 weeks.**

The Khorana Program is envisaged to:

- Provide encouragement to young scholars to undertake R&D
- Enable students to carry out research at a premier University in the United States
- Transform research into societal benefits
- Build a seamless scientific community between India and the United States

Eligibility:

- Pre-final year students enrolled in B.Tech., M. Tech., MSc., B.E., M.E., M.S., Integrated B.S-M.S., B.Sc., B.V.Sc., M.V.Sc., B. Pharm., M. Pharm., MBBS., and Master in Medical Science and Technology (MMST) at recognized institutions of higher education in India in Biotechnology and allied areas are eligible to apply.
- First Year, Final Year and Ph.D. students are NOT eligible to apply.

Scholarship includes:

- Stipend
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- Health Insurance

For additional program information, please visit
www.iusstf.org

For program information contact:
Dr. Nishritha Bopana
Indo-U.S. Science and Technology Forum (IUSSTF)
12 Hailey Road, Fulbright House,
New Delhi - 110 001
E-mail: scholar@indousstf.org

Application Deadline : 31 October 2019

BIO-EVENTS

17th IAAM Annual Conference on "MICROBIOLOGY IN THE NEW MILLENIUM"

On November 29 & 30, 2019

MNM–2019 is an initiative to provide a common platform for researchers working in the field of microbiology to share knowledge and ideas for technological advancements. This conference will bring in experts in microbiology from both academia and industry, from India and abroad. The meeting will update current knowledge on various processes involving microorganisms and their impact on human welfare and will provide a platform for sharing and gaining insights into recent innovations in microbiology and allied fields.

The Conference includes the following thrust areas:
Role of microbes in Agriculture and Environment
Food and Industrial Microbiology
Microbiota in human health and diseases
Microbial Genomics and Computational techniques in genome analysis
Microbial Proteomics and Metabolomics
Therapeutic Microbial metabolites
Designing of newer drugs and vaccines

For further information on the conference, technical programme and registration fees, please visit the conference website at: https://www.kalasalingam.ac.in/site/iaam2019

Organizing Committee
Department of Biotechnology, School of Bio and Chemical Engineering, Kalasalingam Academy of Research and Education, Krishnankoil–626126, Virudhunagar District, Tamilnadu, India

For details, please contact
Dr. V. Deepak, Assistant Professor (+91 999 400 5974)
Dr. S. Ram Kumar Pandian, Assistant Professor (+91 900 344 0063)

Centre for Functional Genomics & Bioinformatics, TDU and Bengaluru Genomics Centre (BGC)

jointly organizing

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November 11 - 14, 2019

Last Date: 31 st October, 2019

Program Directors

Prof. Malali Gowda, TDU

Dr. Pruthvi Chakravarthi T, BGC

For Registration and Fee Details :
http://tdu.edu.in/genomics/genomics-events/

genomics@tdu.edu.in
reach@bgc-genomics.com
+91- 9972978966
+91- 8105872635

Organizing Secretaries

Ravindra Raut, TDU

Pushpendra Jat, BGC

The University of Trans-disciplinary Health Sciences and Technology (TDU)
Bengaluru

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International Society for Advancement of Cytometry (ISAC),
Trust for Education and Training in Cytometry (TETC)

27th January - 7th Febuary, 2020

VENUES

1.) CSIR-National Institute of Oceanography (CSIR-NIO), Goa
"Basics of Flow Cytometry and its Applications in Oceanography"
(27th-28th Jan, 2020)

2.) M.S. Ramaiah Medical College, Bengaluru
"Clinical Applications of Flow cytometry"
(29th- 30th Jan, 2020)

3.) Panjab University, Chandigarh
"Flow Cytometry Applications in Biomedical Research"
(2nd- 5th Feb, 2020)

4.) Eternal University, Himachal Pradesh
"Basics of Flow Cytometry and its Applications in Plant Biology"
(6th- 7th Feb, 2020)

TETC
Trust for Education and Training in Cytometry

ISAC
INTERNATIONAL SOCIETY FOR ADVANCEMENT OF CYTOMETRY

National Institute of Oceanography, Goa

RAMAIAH Medical College

Panjab University

Eternal University

Contact Details

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flowsols@gmail.com
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on

In Vitro and Cryopreservation Approaches for Conservation of Plant Genetic Resources

ICAR-National Bureau of Plant Genetic Resources
Pusa Campus, New Delhi, India

November 5-19, 2019

Application

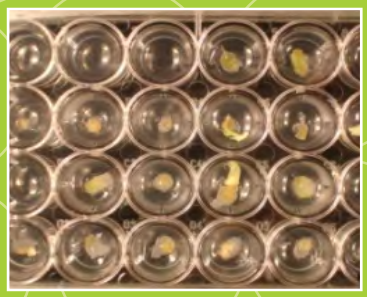
Applicants should preferably have prior experience and/or be actively working on *in vitro* conservation and cryopreservation of PGR, plant tissue culture and / or using molecular marker techniques in their research work.

The application form is attached herewith. The completed application should be sent to:

Dr Anuradha Agrawal
Officer-In-Charge, Tissue Culture and Cryopreservation Unit
ICAR – National Bureau of Plant Genetic Resources
Pusa Campus, New Delhi-110012, India
Tel: +91-11-25802786 Fax: +91-11-25842495
Email: Anuradha.Agrawal@icar.gov.in

Last date for application: June 30, 2019

Maximum number of participants: 15



For further information contact

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South and Central Asia,
Bioversity International,
Bioversity International -
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For more information, contact:

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Global Bio-India 2019
Make in India Cell, BIRAC
1st Floor, MTNL Building,
9, CGO Complex, Lodhi Road
New Delhi-110003

Dr. Manish Diwan
info@globalbioindia.com
www.globalbioindia.com

INTERNATIONAL CONFERENCE OF CARDIOVASCULAR SCIENCES-2020 (ICCS-2020)

Incorporating Annual Conferences of International Academy of Cardiovascular Sciences (IACS)-India Section & International Society of Heart Research (ISHR)-India Section

(February 21–23, 2020)

THEME

Convergence of Clinicians and Scientists for Cardiovascular Health

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DELHI PHARMACEUTICAL SCIENCES AND RESEARCH UNIVERSITY

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NOTIFICATIONS

जैव प्रौद्योगिकी विभाग
Department of Biotechnology
Ministry of Science & Technology
Government of India

EUROPEAN UNION

INDIA-EU CO-FUNDING ANNOUNCEMENT FOR PROPOSALS UNDER 'HORIZON 2020' WORK PROGRAMME: 2019-2020, ON HEALTH, BIOECONOMY, CLEAN ENERGY AND BIOTECHNOLOGY

Researchers and innovators from universities, research organisations and enterprises from India can team up with European partners in the calls for proposals published by the European Commission (EC) under its Research and Innovation programme 'Horizon 2020' (2014-2020).

Through participation in 'Horizon 2020', Indian partners can benefit from access to talent, knowledge, data and infrastructures, and connect to world-leading teams, networks, value chains and address jointly global challenges. To ensure funding for successful Indian applicants, DBT and the EC have concluded a Co-Funding Mechanism (CFM) by which DBT agrees, in pre-selected calls, and subject to specific conditions and modalities, to fund the successful Indian participants that have been selected in Horizon 2020 project(s).

On 2 July 2019, the EC published the 'Horizon 2020' updated Work programmes for 2019-2020, in which the Department of Biotechnology (DBT) has agreed to participate in 30 call topics in the areas of its mandate. See in Section 1 hereunder, the full list of topics per thematic area earmarked by DBT for co-funding. The list indicates the exact Call IDs, the opening and closing date of the call; the type of action provided and the link to the full call text as published in the Horizon 2020 Funding & Tenders Portal.

The guidelines in this notice also explain various modalities of participation that the Indian applicants have to comply with in order to be eligible for funding by DBT (see hereunder Sections 2 and 3, including Annex 1 on Administrative and Financial Considerations).

All proposals should be submitted to the Horizon 2020 Funding & Tenders Portal and to DBT, including the budget requested from DBT. In the absence of this, DBT will disqualify the Indian participants from funding (see Section 4 hereunder).

At the end of the notice, information is also provided on how to access and go about 'Horizon 2020' formalities, which Indian applicants have also to comply with (Annex 2) and on How to find partners (Annex 3).

Interested participants must also ensure complete understanding about the call text itself on the Horizon 2020 Funding & Tenders Portal for the overall conditions and modalities.

Notice

DETAILS FOR "ICMR-CNMC STS EXCELLENCE AWARD"- 2019 APPLICATIONS

The ICMR- Calcutta National Medical College (CNMC) Short Term Studentship (STS) Excellence Award was instituted by CNMC Alumni Association, Kolkata in 2015. This award is conferred upon a medical undergraduate student who has been awarded ICMR-STS (2016, 2017 & 2018) and has published a paper in an indexed journal as the first author. This award aims to encourage undergraduate medical students to take up research.

The Award carries a cash award of Rs. 25,000/- and a Certificate of Honour

Last date of submission of applications is November 30th, 2019.

Eligibility and Terms & Conditions:

1 A student pursuing MBBS or/has completed MBBS AND who has been awarded ICMR-STS successfully AND published an original article as first author in an indexed peer reviewed journal based on his STS research work will be eligible to apply for this award. The journal should be indexed in MEDLINE or Science Citation Index (SCI)/Journal Citation Reports (JCR) index Clarivate Analytics only. No other indexing will be considered.

2 The application in a given format accompanied by CV and original Publication in an indexed journal (as stated in point above) may be submitted by the student.

3 Case reports/letters to editors/papers in non-peer reviewed/non-indexed journals/review articles/chapters in books/abstracts/conference proceedings or any other reports will not be entertained for this award.

4 **STS 2016, 2017 and 2018 awarded students**, who have published their paper till November, 2019 shall be eligible to apply for ICMR-CNMC STS Excellence Award-2019.

5 The student should have followed ethical norms for conduct of research and have acknowledged STS Program of ICMR in the publication.

6 The topic for research could be any kind of biomedical and health research involving either clinical, laboratory, experimental, epidemiological, qualitative, quantitative, or community based work *etc.* carried out under ICMR-STS programme.

7 Application for the award should be sent ONLY in the specified format given below.

8 The selection will be based on scientific merit only and no other considerations will be taken into account.

How to apply:

Applicants should send their duly filled and signed application only by email to stsaward@gmail.com by 30th November 2019, with the following documents (mandatory) as email attachments. No paper/hard copies will be accepted.

Kindly send the pdf of the following:

a. Filled and duly signed in application in the given format (pdf).
b. Signed and dated CV (pdf).
c. Reprint/ Original Publication in an indexed journal (as required) (pdf).

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DEPARTMENT OF SCIENCE & TECHNOLOGY

Technology Bhavan, New Mehrauli Road,
New Delhi – 110 016

Website: http://www.online-inspire.gov.in

Call for Applications under INSPIRE Fellowship-2019

INSPIRE FELLOWSHIP FOR PURSUING DOCTORAL PROGRAMME IN SCIENCE & TECHNOLOGY

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Applications are invited from
i) INSPIRE Scholars after completion of their post-graduation degree in Science areas and
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HOW TO APPLY
Students need to apply through On-line mode only. To apply Online, please visit the website: http://www.onlineinspire.gov.in and follow the process prescribed therein. The Online application submissions will commence on 7th October, 2019 (0900 Hrs) and will be available up to 6th November 2019 (1730 Hrs).

NATIONAL INSTITUTE OF IMMUNOLOGY

(An Autonomous Research Institute of Department of Biotechnology, Govt. of India)

Career Opportunities for Scientists- Rolling Advertisement

The National Institute of Immunology, New Delhi, is a leading research Institute in India with a long-standing reputation for scientific excellence. The institute is equipped with state-of-the-art infrastructure for pursuing research in immunology and allied sciences. The Institute also imparts vigorous long-term research training leading to a Ph.D degree.

The Institute invites applications from early as well as mid-career scientists, with potential for intellectual leadership and passion for innovative research to set up independent research programmes in the areas of (but not restricted to) Immunology, Virology, Microbiology, Structural, Chemical and Molecular Biology, Immunology and Vaccines, Infectious and Autoimmune Diseases, Metabolic Disorder and Chronic diseases, Structural and Computational Biology, Genetics, Cell and Developmental Biology to address immunological problems at the expanding interface of modern biology for filling 2 positions of Staff Scientist-III and 5 positions of Staff Scientist-IV as per details given below:

Name of the post/ Number of vacancies	**Pay Level (7th CPC)**	**Qualifications and Experience**	**Upper Age Limit**	**Remarks**
Staff Scientist-III (2 Vacancies)	11	1st class M.Sc with 5 years experience or 1st class M.Tech/ MD/ MVSc/ M.Pharm/ M.Biotech with 4 years R&D experience **OR** Ph.D with 4 years postdoctoral experience in the relevant field.	40 years	1-UR 1-for Person with benchmark disability (deaf and hard of hearing)
Staff Scientist-IV (5 Vacancies)	12	1st class M.Sc with 9 years experience or Ist class M.Tech/ MD/ MVSc/ M.Pharm/ M.Biotech with 8 years R&D experience **OR** Ph.D or corresponding degree in other disciplines with original work as evidenced by patents or publications. Evidence of leadership with about 8 years of R&D experience.	50 years	2-UR 2-OBC 1-SC

NOTE: Call for applications will remain open till the vacancies are filled. The applications will be accepted throughout the year and will be scrutinized / shortlisted on quarterly basis. The last date for receipt of applications for each quarter is is March 31st, June 30th, Sept 30th, and Dec 31st.

Government of India
Ministry of Science and Technology

DEPARTMENT OF BIOTECHNOLOGY
Public Health, Food and Nutrition Division

Call for R&D Proposals on "Food fortification and newer technologies to improve bioavailability of nutrients"

Rationale: Nutritional anaemia is primarily caused due to deficiencies of micronutrients Food fortification as a strategy to address micronutrient malnutrition, has the dual advantage of being able to deliver nutrients to large segments of the population without requiring radical changes in food consumption patterns. With an aim of making food fortification more efficacious and to help to reduce the burden of micronutrient malnutrition in the country, this department **proposes to support R&D proposals in the following thrust areas of food fortification**:

1. Novel fortificants/additives that can enhance the bioavailability of fortificants.
2. Sensory, acceptability and stability studies of fortified staples in real field conditions, food interactions and methods to overcome negative nutrient-nutrient/food interactions
3. Generate data on bioavailability of bio-fortified versus fortified food.
4. Micronutrient combinations to impact anaemia, bone health, reproductive health, work productivity, immunity etc among vulnerable population groups.
5. Studies that would evaluate potential negative interactions on health in response to consumption of fortified foods.
6. Role of other micronutrient nutrients (eg, calcium, zinc, vitamins) in determining co- fortification levels with iron for staples.
7. Studies that would provide new insights, data on fortified food acceptance, consumption, enablers, deterrents from the various stake holders (farmer, miller, consumer, socio economic, behavioral and cultural interactions).

Eligibility: Applications may be submitted by public and private universities, colleges, Institutes, non-profit organizations (recognized by DSIR as a Scientific and Industrial Research Organization (SIRO)). Development of interdisciplinary collaborative research team with involvement of experts from biomedical field is encouraged.

How to apply: Applicants should submit full proposal on or before the deadline through DBT Epromis portal and submit two hard copies to **Dr. Balendra Singh,** Scientist-C, Department of Biotechnology, Block- 3, Room No. 525B, 5th floor, CGO Complex, Lodhi Road, New Delhi – 110003 and email the soft copy to email: **balendra.singh@dbt.nic.in**. The link to DBT epromis format: https://dbtepromis.nic.in/sample_forms.aspx

The deadline for submission of full proposal is 23rd November, 2019

For any queries, contact Dr. Balendra Singh, Scientist-C, Email- balendra.singh@dbt.nic.in / Dr. A.Vamsi Krishna, Scientist-E, Email- vk.addanki@nic.in

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Department of Biotechnology, Vignan's Foundation for Science, Technology and Research, (Deemed to be University)

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VIGNAN'S UNIVERSITY

Recruitment of JRF

A JRF position is available in MoEF (Ministry of Environment, Forest and Climate Change), New Delhi, supported research grant proposal entitled " Phylogenetic analysis and Barcoding of Indian Apple Snails (Ampullaridae) as a prelude to their conservation strategy" in the Department of Biotechnology, Vignan's Foundation for Science, Technology and Research (Deemed to be University), Vadlamudi 522213 A P. Candidates with M.Sc/M.Tech in Bioinformatics will be given preference. Interested candidates may submit their CV along with a note indicating their interest in doing research in Molecular Phylogeny to the email: hodbt@vignan.ac.in at the earliest. Selected candidates will be made to enroll for a Ph.D. program in the Department of Biotechnology, VFSTR.

Contact Person: Prof.S.Krupanidhi, PI, HoD, Dept of Biotech, VFSTRU

Vignan's Foundation for Science, Technology and Research (VFSTR)

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Dean – Admissions

Call for Nominations/ Applications for ICMR Awards & Prizes- 2019

The Indian Council of Medical Research (ICMR) invites Nominations/Applications from Indian scientists for ICMR Awards & Prizes for the year 2019 (list given below) in various fields of biomedical sciences. Last date of receipt of Nominations/Applications is 30th November, 2019

List of ICMR Awards/Prizes for the year 2019

Dr. B.R. Ambedkar Centenary Award for excellence in Biomedical Research (Biomedical Research)
Dr. Subhas Mukherjee Award (Assisted Reproductive Technology, Reproductive Biology & Endocrinology and Reproductive Health in General)
Basanti Devi Amir Chand Prize (Biomedical Sciences)
Shakuntala Amir Chand Prize (Clinical Research) - Age below 40 years (Number of prizes – four)
Amrut Mody Unichem Prize (Gastroenterology)
Dr. H.B. Dingley Memorial Award (Paediatrics) – Age below 40 years.
ICMR Kshanika Oration Award (Biomedical Sciences) – for Indian women scientists
ICMR Prize for Biomedical Research for Scientists belonging to underprivileged communities (Biomedical Sciences)
ICMR Prize for Biomedical Research conducted underdeveloped areas – (Biomedical Sciences)
ICMR Tilak Venkoba Rao Award (Psychological Medicine) - Age below 40 years
JALMA Trust Fund Oration Award (Leprosy and other mycobacterial diseases)
Major General Saheb Singh Sokhey Award (Communicable Diseases) – Age below 40 years
Smt. Kamal Satbir Award (Non-tuberculosis Chest Diseases, especially Respiratory Allergy and Chronic Obstructive Lung Diseases) - Age below 40 years
Dr. D.N. Prasad Memorial Oration Award (Pharmacology)
Dr. J.B. Srivastav Oration Award (Virology)
Dr. M.O.T. Iyengar Memorial Award (Malaria, Filariasis, Plague or Medical Entomology)
Dr. Prem Nath Wahi Award (Basic and/or Clinical Cytology and/or Preventive Oncology)
ICMR Chaturvedi Ghanshyam Das Jaigopal Memorial Award (Immunology)
ICMR Chaturvedi Kalawati Jaghmohan Das Memorial Award (Cardiovascular Diseases) – Preferably a medical person
ICMR Smt. Swaran Kanta Dingley Oration Award (Reproductive Biology)
ICMR-CNMC STS Excellence Award (for medical undergraduate student who has been awarded ICMR STS)

Address for correspondence:

The Director General, [Kind Attention: Dr. N. C. Jain, Scientist-G & Head, Division of Human Resource Planning and Development (HRD)], Indian Council of Medical Research, V. Ramalingaswami Bhawan, Ansari Nagar, Post Box No. – 4911, New Delhi-110029 Telephone: 011-26589258, email: drencejain@gmail.com

Indian Academy of Sciences, Bengaluru
Indian National Science Academy, New Delhi
The National Academy of Sciences, India, Prayagraj

Science Academies' Summer Research Fellowship Programme for Students and Teachers – 2020

Applications are invited from interested students and teachers from all universities and colleges affiliated to UGC/AICTE/MCI/Accredited Institutions of State Universities for these Fellowships. The application should include: (a) the application form in the prescribed format; (b) scanned copies of marks sheets from class X till the last examination; (c) a write-up (about 150–250 words) as to what the applicant wants to learn and achieve. Student applicants should provide the e-mail id of one of their teachers or HoD familiar with their work. The Academy will approach them for a recommendation letter in the prescribed format. The selected candidate should work with the assigned guide for two months any time during the calendar year, preferably during the summer.

Applications should be submitted by logging onto one of our websites (www.ias.ac.in; www.insaindia.res.in or www.nasi.org.in). The registration number assigned soon after online submission must be quoted in all future correspondence.

The last date for receipt of applications online is 30 November 2019.

Information of selection along with concurrence of the guide will be despatched around February–March 2020. The selected students/teachers will be provided appropriate round trip train fare and a monthly fellowship to meet their living expenses at the place of work.

Professor M R N Murthy Chairman, Joint Science Education Panel Indian Academy of Sciences, Bengaluru

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ISSN: 2454-6968 RNI No. UPENG/2013/54102

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