CVJ Centre for Metabolic Engineering and Synthetic Biology (CMESB)

Inspired by the life and work of Shri. C.V.Jacob, Founder, Synthite Group of Industries **CVJ Centre for Metabolic Engineering and Synthetic Biology (CMESB)** is proposed to be established at Cochin University of Science and Technology embracing the two emerging areas (Metabolic Engineering and Synthetic Biology) in support of Biotechnology Industry. It is an initiative of Synthite Group of Industries partnering with CUSAT to build a world class Institution that will be renowned for its thought leadership and innovation centered on research and education.

Metabolic engineering is the practice of optimizing genetic and regulatory processes within cells to increase the cell's production of a certain substance. These processes are chemical networks that use a series of biochemical reactions and enzymes that allow cells to convert raw materials into molecules necessary for the cell's survival. Metabolic engineering specifically seeks to mathematically model these networks, calculate a yield of useful products, and pin point parts of the network that constrain the production of these products (Yang et al., 1998). Genetic engineering techniques can then be used to modify the network in order to relieve these constraints. Once again, this modified network can be modelled to calculate the new product yield.

The ultimate goal of metabolic engineering is to be able to use these organisms to produce valuable substances on an industrial scale in a cost-effective manner. Current examples include producing beer, wine, cheese, pharmaceuticals, and other biotechnology products (Milne et al., 2020). Some of the common strategies used for metabolic engineering are (1) overexpressing the gene encoding the rate-limiting enzyme of the biosynthetic pathway, (2) blocking the competing metabolic pathways, (3) heterologous gene expression, and (4) enzyme engineering (Kulkarni, 2016).

Since cells use these metabolic networks for their survival, changes can have drastic effects on the cells' viability. Therefore, trade-offs in metabolic engineering arise between the cells ability to produce the desired substance and its natural survival needs. Therefore, instead of directly deleting and/or overexpressing the genes that encode for metabolic enzymes, the current focus is to target the regulatory networks in a cell to efficiently engineer the metabolism (Vemuri et al., 2005) (Adapted from Wikipedia).

Synthetic biology (**SynBio**) is a multidisciplinary area of research that seeks to create new biological parts, devices, and systems, or to redesign systems that are already found in nature.

It is a branch of science that encompasses a broad range of methodologies from various disciplines, such as biotechnology, genetic engineering, molecular biology, molecular engineering, systems

biology, membrane science, biophysics, chemical and biological engineering, electrical and computer engineering, control engineering and evolutionary biology.

Due to more powerful genetic engineering capabilities and decreased DNA synthesis and sequencing costs, the field of synthetic biology is rapidly growing. In 2016, more than 350 companies across 40 countries were actively engaged in synthetic biology applications; all these companies had an estimated net worth of $3.9 billion in the global market (Bueso et al., 2017) (Adapted from Wikipedia).

Objectives under the Synthite – CUSAT Partnership

1. Development of novel processes and products for the enhanced production of vital compounds of interest in support of bio-medical industry.
2. Capacity building in Metabolic Engineering and Synthetic Biology.
3. Entrepreneurship development in Metabolic Engineering and Synthetic Biology.

Road map in Institution build up

1. Constitution of a Task Force to design and build the Institution
2. Harnessing the potential of CUSAT (Intellectual and Infrastructure) to initiate the programme
3. Identification of goals – immediate, short term and long term.
4. Development of specific time bound projects using the available infrastructure with CUSAT.
5. Creation of additional space dedicated for the Institution in CUSAT campus, and selection and appointment of the required manpower in self sustained mode.

Mile stone 1. Constitution of a Task Force to design and build the Institution (proposed - To be constituted by the University)

Chairman: Prof. (Dr.) K.N. Madhusoodanan, Vice Chancellor, Cochin University of Science, and Technology, Cochin -682022

Convener: Prof. (Dr.) P.G.Sankaran, Pro - Vice Chancellor, Cochin University of Science, and Technology, Cochin - 682022.

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Members

1. Representative of Synthite Group

2. Prof. Valsamma Joseph, Director, National Centre for Aquatic Animal Health, Cochin University of Science and Technology, Cochin - 682016.

3. Dr Parvathi A., Professor and Head, Department of Biotechnology, Cochin University of Science and Technology, Cochin -682022.

4. Prof. Pawan Dhar,Jawaharlal, Nehru University, New Delhi.

5.Dr. Vijay Singh, Associate Professor & Dean (Research & Innovation), Department of Biosciences, School of Science, INDRASHIL UNIVERSITY, Rajpur, Mehsana-382740, Gujarat.

6. Prof. Sam Thomas, School of Management Studies, Director, Centre for Innovation, Technology Transfer, and Industrial Collaboration (CITTIC), Cochin University of Science and Technology, Cochin -682022.

7. Prof. N. Manoj, N., Department of Applied Chemistry,Managing Director, CUSATECH Foundation, Cochin University of Science and Technology, Cochin - 682022.

8. Prof. I.S.Bright Singh, University Emeritus Professor,National Centre for Aquatic Animal Health, Cochin University of Science and Technology, Cochin -682022.

Note: The Task Force can be empowered to constitute subcommittees and working groups at National level to address specific issues.

Mile stone 2.Harnessing the potential of CUSAT (Intellectual and Infrastructure) to initiate the programme

Two Institutions of CUSAT (National Centre for Aquatic Animal Health & Department of Biotechnology) can actively participate in the building up of CMESB at this initial stage by extending their expertise and the available infrastructure.

a) National Centre for Aquatic Animal Health

Functional Laboratories

Microbiology, Molecular Biology, Marine Drug Discovery, Bioprocess Technology, Animal Tissue Culture and Virology, Aquaculture Chemistry, Algal Biotechnology, Immunology, Histology and Histopathology, Fish Genetics and Genetic Improvement, Repository of Pathogens and parasites of Aquatic animals, Repository of Beneficial Organisms in Aquaculture, Bioinformatics Centre (BIC) supported by DBT, Sequencing Facility

Credentials in Synthetic Biology:

i) Successfully completed a project onMarine Synthetic Biology:Building National capacity and human resource in collaboration with Jawaharlal Nehru University and Pondicherry University and trained 45 graduates in biotechnology in Synthetic Biology.

ii) Ph. D. programme in progress**:** Pyocyanin as the drug of choice in aquaculture: Synthetic Biology based production, downstream process, product design and application

iii) Expertise in genome editing:Host-specific Bicistronic Vector System for CRISPR/Cas-based Genome Editing in *Danio rerio*

Projects

Optimization of Genome Editing for Loss-of-function Study in *Danio rerio* - DRG/DRF Cell Line Using RNA-guided Cas9 Nuclease.

Development of CRISPR/Cas9 Engineering Platform for Genome Editing in *Danio rerio* and Generation of mstn-Knock-out Lines

Establishment of embryonic stem (ES) cells from Orange-spotted grouper (*Epinephelus coioides*) as germline transmission platform, and strain improvement through genome editing

Genetic improvements in the giant freshwater prawn *Macrobrachium rosenbergii* and the State fish *Etroplus suratensis* for augmented production by way of forward and reverse genetic approaches

Ph. D. programme
CRISPR-Cas9-Mediated Targeted Mutagenesis and Efficient Genome Editing in Teleost Fishes.

b) Department of Biotechnology

Facilities: PCR unit-Automatic Thermocycler (Applied biosystems) Gel documentation system (Biorad), HPLC –preparative and analytical (Shimadzu), Carbon dioxide incubators,Protein gel electrophoretic systems (Amersham Pharmacia),Chromatographic columns (Amersham Pharmacia),Refrigerated Centrifuge (Heraeus),Spectrophotometer (Shimadzu 2),Fermenter 14 litre - Fully automated (Scigenics),Mini jar fermenter (Eyela Inc. Japan),Gamma Counter (ECI),Phase contrast microscope (Nikon, Japan),Inverted Phase Contrast Microscope (Olympus CK 40),Lyophilizer (Yamata Neocool, Japan),Electronic balance (Mettler), Real Time PCR-applied Biosystems), Nanospectrophotometer, Cryostat, -80˚C Deep Freezer (Thermo, Panasonic, Eppendorf), Pulse field gel electrophoresis (PFGE)-Bio-Rad, Level II-Biosafety cabinets, Walk –in –cold room, Multimode plate reader, Fluorescent cell sorter- FACs, Inverted microscope with camera attachments and other accessories, Fluorescent microscope, Plant tissue culture facility, Animal Cell Culture facility, Zebra fish facility, *C elegans* Facility, Small Animal Facility.

Credentials: Plant genome editing -Genome editing *via* gene knockdown using RNA interference in tomato for disease and pest resistance, Tissue culture facility to regenerate genetically modified plants, Anti-miRNA technology for silencing the key miRNAs regulating the metabolic pathways, Genome editing can be used to enhance, the level of antioxidant lycopene in tomato and to increase the shelf life of tomato fruits

Mile stone 3. Identification of goals – immediate, short term and long term.

Objective 1. Development of novel processes and products for the enhanced production of vital compounds of interest in support of bio-medical industry

Immediate: Identification of immediate requirements of the Synthite Group in finding solutions to the problems confronted.

Short term: Support to the research underway at National Centre for Aquatic Animal Health and Department of Biotechnology in the discipline.

Long term:

The goal of synthetic biology is to make the construction of novel biological systems into practical and useful devices.

The Indian synthetic biology market is segmented on the basis of product, technology, and applications. Based on the product, the market is segmented into enabling products, core products, and enabled products. **Core product includes synthetic genes, synthetic cells, synthetic DNA, chassis organisms and Xeno Nucleic Acid (XNA), and are expected to hold a significant share in the market owing to extensive use of core products in R&D. Based on technology, the market is segmented into, and gene synthesis & sequencing, genome engineering, bioinformatics, and others**. Based on application, the market is segmented into medical applications, industrial applications, food & agriculture, and environmental applications.

Hence the long term objective is to establish a repository of **synthetic genes, synthetic cells, synthetic DNA, chassis organisms and Xeno Nucleic Acid (XNA)** to create new inter changeable biological parts, devices, and systems, or to redesign systems that are already found in nature. The range of potential applications is vast, encompassing, but not limited to: diagnostics, therapeutics, sensors, environmental remediation, energy production, and a host of other biomolecular and chemical manufacturing outputs. Synthetic biology can also help us gain valuable insight into fundamental biological principles and improve our quantitative understanding of the living world.

Here, one can visualize a blend of metabolic engineering and synthetic biology for developing new processes and products.

On its long run **CMESB** would be in position to support the playerswhichinclude Twist Bioscience Corp., Merck KGaA, GenScript Biotech Corp., Thermo Fisher Scientific Inc., Amyris Inc., CodexisInc, and many others. These players are focusing on agreements along with new product launches for expanding their business.

Objective 2. Capacity building in Metabolic Engineering and Synthetic Biology.

Immediate: Restructuring the curricula of M.Sc in Biotechnology and M.Tech. in Marine Biotechnology having metabolic engineering and Synthetic Biology as the core components**.**

Short term: Six months skill development certificate programme in Metabolic Engineering and Synthetic Biology.

Long term: Masters programme in Systems and Synthetic Biology & Metabolic Engineering in par with the educational programmes in MIT Synthetic Biology Centre.

Objective 3. Entrepreneurship development in Metabolic Engineering and Synthetic Biology.

This must be undertaken at a long term basisconsidering the requirements of the industry to have start ups in a mission mode taking all precautionary measures for attaining success.

Mile stone 4. Development of specific time bound projects using the available infrastructure with CUSAT.

This component has to be developed by the Task Force taking in to consideration of the vision and requirements of Synthite Group as well as the National requirements. By this time CMESB must have developed functional linkages with the Industrial houses and chalked out short and long term programmes.

Mile stone: 5: Creation of additional space dedicated for the Institution in the CUSAT campus, and selection and appointment of the required manpower in self sustained mode.

Accomplishment of the four milestones shall bring out the dimensions of the physical structure to be built to accommodate theactivities ofCMESB in the long run.

Duration: Three Years

Budgetary Requirements: Rs. 20.0 Crores (Inclusive of recurring and non-recurring costs)

References

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