ISAJ
Indian Scientists Association in Japan

NEWSLETTER

Vol. 4 Issue 2 December | 2019

From the Editor's Desk

Greetings and a warm welcome on the second issue of ISAJ Newsletter for 2019! We take this opportunity to convey the seasonal greetings for coming festive season. May happiness and prosperity fill your life forever!

In this issue, we present three diverse articles. Two of them briefly summarize research work on track monitoring and anti-cancer treatment, while the third article recaps the experience of author at Gap Summit 2019 hosted at Broad Institute of MIT & Harvard, Boston.

Under the section Event Report, the author shares her experience at Gap Summit 2019. The Author was selected as one of the 100 Leaders of Tomorrow by Global Biotech Revolution (GBR) for the world-class biotechnology leadership summit. The core objectives of the summit were to (i) substantively discuss pressing challenges being faced by the bio-economy and (ii) catalyze innovations to solve these challenges.

Continuing from the previous issue, we present you another article on cancer treatment based research under the section From the Pen of Young Mind. Author has summarized her work on designing epigenetic tools which inhibits PD-L1 expression that will ultimately block the PD-1/PD-L1 axis and will reactivate killer T cells to kill cancer cells. This work could be a potential substitute for PD-1 blockade therapy, which presently costs almost USD $1M per patients.

Research Spotlight section briefly outlines the work on track profile estimation using responses of in-service trains, which could be an economical alternative to the commonly used yet expensive Track Recording Vehicle also known as Yellow Doctor for monitoring the track of bullet trains.

Next, We take pleasure in informing that our 10th ISAJ annual symposium on **"Interdisciplinary Science and Technology Innovation for Sustainable Society"** was held on **Dec 9, 2019** at **Osaka University Hall, Toyonaka Campus Osaka University Osaka**. Event commemorated the 10th anniversary of ISAJ. H.E. Mr. Sanjay Kumar Verma, Ambassador of India to Japan inaugurated the symposium and Mr. B. Shyam, Consul General of India Osaka-Kobe delivered a special lecture. Symposium was attended by approximately 60 Indian and Japanese researchers.

We hope you would find the current issue of our Newsletter interesting. We look forward to receiving your feedback. Any suggestions/ideas for improving the upcoming newsletters are also welcomed.

In This Issue

News and Notes

10th ISAJ Annual Symposium

Theme:

Interdisciplinary S&T Innovation for Sustainable Society

Date:

9th Dec. 2019 (Monday)

Venue:

Osaka University Hall, Toyonaka Campus, Osaka University

More information: http://isaj.org

Event Report

Gap Summit 2019: Global Biotech Revolution

Held on: **June 16-20, 2019**

At: **Kendall Square, Cambridge, MA**

Organized by: **Global Biotech Revolution (GBR)**

Report by: **Ankita Jain, Business Development Associate, Healios K.K.**

Key takeaways from the Gap Summit: Convergence, Consensus & Coordination.

The aim of the Gap summit is to bring together different stakeholders ranging from the academia to the industry and from NGOs to international organizations, to discuss and solve the different 'gaps' that exist in the global biotech ecosystem. Themes for this year revolved around the burning questions of the current times:

- **R&D Productivity**: How can we reduce the high failure rates in the research and development of pharmaceutical products?
- **Bench to Market:** How can we make technology transfer a more seamless process?
- **AI & Digital Health**: What would be the impact & repercussions of deep-tech penetration in biotech industry?
- **Biosecurity & Bioethics:** How can we incentivize stakeholders to actively participate in policy making globally?
- **Sustainable Healthcare Economics:** How would we be able to provide accessible & affordable healthcare with ageing population and increasing healthcare expenditure?
- **Sustainability & Agri-Tech**: with increasing population, depleting resources and climate change can biotech industry provide the solution to feeding population?
- **Global Bioeconomies:** how can we make biotechnology industry more democratized?

The 5-day long summit from 16-20th June 2019, kicked in with introductory remarks by Dr. Tedros Adhanom, Director General, World Health Organization. This was followed by Panel Discussions on each "Gap" by representatives from leading pharma companies: Novartis, Biogen, Bayer etc.; Global organizations such as World Bank, Bill & Melinda Gates Organization; Eminent academicians like Prof. Phillip Sharp, Nobel Laureate, MIT.

Apart from the opportunity to interact with the pioneers of current biotech industry, the 100 Leaders also participated in a 4-month long Bio-Innovation Competition. Under this, participants worked in teams with mentorship support, to identify key challenges in the existing gaps and propose innovative solutions. I had the opportunity to collaborate with 4 other leaders from Denmark, UK & US. Under the mentorship of experienced R&D leaders from Johnson & Johnson, we worked towards development of a digital solution for providing 1st line of screening for women fertility health. During the summit, teams pitched their ideas to leading venture capitalists & investors. A few selected teams received initial seed-funding and further mentorship to build their ideas into biotech startups post-summit. In addition, career path guidance was provided for interested leaders.

All in all, Gap Summit is an excellent opportunity for young professionals & students in the biotech industry to connect with like-minded peers globally. For example, this year's summit hosted competitively selected 100 leaders from 44 different countries. Gap summit also provides a platform to get insights into cutting edge scientific research & industry trends, growing opportunities in the field of Biotechnology & its future in next 50 years.

Biotechnology, in future, will shape every aspect of human life – not only healthcare but also domains such as energy, food-industry, biosecurity and material sciences to name a few. More interdisciplinary teams will be needed to collaborate and co-develop innovative solutions for addressing both the present and the future challenges. The need of the hour is to understand the role and responsibility of different stakeholders for developing better coordination.

Applications for Gap Summit 2020 are open, apply & be a part of Global Biotech Revolution. https://www.gapsummit.com/apply/

Ankita Jain

Email: alphaankita@gmail.com

Currently working as a Business Development Associate in a Japanese Biotechnology Company, Healios K.K. Graduated from the University of Tokyo in 2016 with a Masters in Bioengineering.

Ankita has represented both India & Japan at multiple global platforms namely, Novartis Biotechnology Leadership Summit, Rising Star: Women in Engineering Workshop, Asian Dean's Forum, Japan India Exchange Platform Program (JIEPP) Symposium, Cultural Ambassador Nikkei Inc. & others.

Ankita is passionate about Biotechnology and has core-expertise in technology assessment & tech-transfer. Her career goals include establishment of India-Japan Biotechnology tech-transfer and empowerment of women in STEM.

Combination Immunotherapy using synthetic genetic switches

Cancer is the second most leading cause of deaths worldwide. The number of new cancer cases per year is expected to rise to 23.6 million by 2030. While chemotherapy is the most preferred way of treatment to treat cancer cells, the toxic side effects and the resistance to chemotherapeutic agents warrants the need for an alternative strategy [1]. Cancer immunotherapy, the fourth pillar of cancer treatment has shown very encouraging clinical trial results for many types of cancers irrespective of their origin. The interaction of programmed cell death protein 1 (PD-1, an immune-inhibitory receptor expressed on activated T cells) and its ligand (PD-L1, expressed on cancer cells) causes T cells inhibition, thereby inhibiting the anti-tumor immunity [2]. Blocking the PD-1/PD-L1 signaling causes reactivation of T cells and enhances anti-tumor immunity. U.S. FDA has approved anti-PD-1 or anti-PD-L1 antibodies for the treatment of many different types of cancers like renal cell carcinoma, head and neck carcinoma, Hodgkin lymphoma and many more. The high cost of PD-1 blockade therapy (approx. USD $1M per patient in a year) mainly restricts its worldwide application to treat cancer considering 70% cancer patients are from developing countries. Epigenetic strategies got proclaimed to cancer immunotherapies, however, the lack of sequence specificity is a major concern. N-Methylpyrrole (P) and N-methylimidazole (I) are hairpin polyamides that selectively recognize Watson–Crick base pairs of DNA sequences located within the minor groove that modulate endogenous gene expression [3]. We have conjugated PIP with CTB (HAT activator) that switches 'ON' the selected gene [4]. We have also successfully conjugated the nitrogen mustard alkylating agent, chlorambucil (Chb) to PIPs and showed that they have a much stronger sequence-specific DNA-binding capacity and reduce target gene expression [5]. We have developed designer PIPs as a cost-effective combinatorial approach to Switch OFF and Switch ON the genes of interest that will enhance the efficacy of checkpoint blockade immunotherapy in two ways: a) Targeting cancer cells using genetic OFF Switches - Chb-PIP conjugate is expected to 'Switch OFF' the PD-L1 expression in cancer or host immune cells (macrophage, dendritic cells, myeloid cells) which could result in blockade of PD-1/PD-L1 axis and activate killer T cells, b) Targeting CD8 effector T cells using genetic ON switches - designer PIPs conjugated with the epigenetic activator CTB to target and induce the specific transcription factors for mitochondrial activation and biogenesis i.e., Tfeb that will finally upregulate PGC-1α. We synthesized Chb-PIPs that are expected to selectively switch OFF the PD-L1 gene expression (Figure 1). We found PD-L1 expression is inhibited in Chb M and Chb M' treated group compared to base compound chlorambucil (Chb) at the transcript level (Figure 2) as well as protein level (Figure 3). Next, we are screening the PIPs for upregulation of mitochondrial biogenesis mediated by PGC-1 α. Further, we will test the combinatorial effect of both PIPs on the activation of T cells *in vitro* co-culture experiment and *in vivo* tumor model. These initial findings will pave a way for the development of cost-effective PD-1 blockade therapy to benefit more cancer patients.

References:

1. Br J Cancer. 2008, 99(3): p387–391.
2. EMBO J. 1992, 11: 3887–3895.
3. Nature. 1996, 382(6591):559–561.
4. Eur. J. Med Chem. 2017, 138:320e327.
5. J Clin Invest. 2017, 127(7):2815–2828.

Madhu Malinee

Kyoto University Japan

madhu.malinee.65x@st.kyoto-u.ac.jp

Currently, a Ph.D. scholar in the 'Department of Anatomy and Developmental Biology, Graduate School of Medicine, Kyoto University. Madhu has graduated in Biochemistry from Hyderabad Central University in 2013. Her research interests includes epigenetics and cancer immunotherapy with special attention to PD-1 blockade therapy. Her specialization emphazes on employing epigenetic approach for enhancing PD-1 blockade cancer immunotherapy to rescue less sensitive patients in a very cost-effective approach.

Fig 1

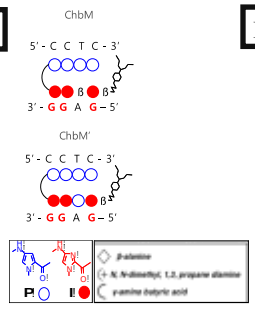

Fig 2

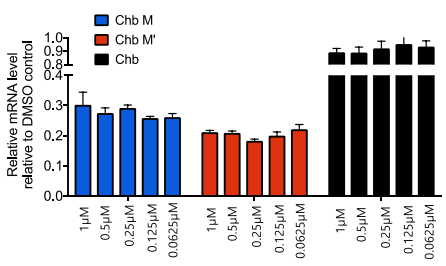

Fig 3

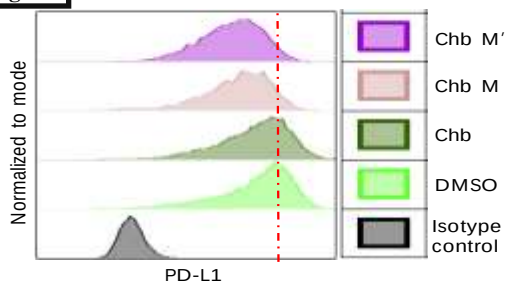

Fig.1. Designer PIPs for PD-L1 suppression- Chb M and Chb M'. Pyrrole (P) recognize A/T base while Imidazole (I) binds with G of DNA sequence.

Fig.2. PD-L1 suppression at transcript level. NCI-H460 cells were treated with the indicated concentration of Chb M, Chb M' and Chb for 72 hours, Followed by RNA harvest and qPCR analysis. GAPDH was used as control.

Fig.3. PD-L1 suppression at protein level. Representative histogram of PD-L1 for each group is shown.

Response Based Track Profile Estimation Using Observable Train Models

Dr. T. Jothi Saravanan

JSPS Postdoctoral Fellow,
Yokohama National University, Japan
tjs.sarvanan@gmail.com

Currently a JSPS Postdoctoral fellow at Institute of Advanced Sciences at Yokohama National University. He has obtained his doctorate degree from the University of Tokyo in 2018. He has graduate in Civil Engineering and obtained his Master degree in Engineering of Structures from College of Engineering Guindy, Chennai, India in 2012, and the CSIR -Structural Engineering Research Centre, Chennai, India in 2014, respectively. His graduation study is a part of Academy of Scientific & Innovative Research initiative of the Indian government.

His field of interests include: Structural Health Monitoring, Track Profile Estimation, Smart Materials and Structures, Vision based Monitoring, Wave Propagation Mechanics, Non-destructive Evaluation, Structural Dynamics, Vibration analysis and Experimental Techniques in Structural Engineering.

Local railway networks suffer from age-related deterioration and poor maintenance and it might be unable to perform adequate monitoring. It is essential to improve the comfort level and service life of local railway lines. Track profile, which directly influences the ride quality and safety of rail tracks need to be estimated for the maintenance purpose. Currently, Track Recording Vehicle (TRV) such as Doctor Yellow, a high speed test train in Japan is utilized for the track condition monitoring. But the demerits of TRV are that it is expensive and cannot be frequently used for local railway lines. It is used only once in a year for most of lines. Therefore, track profile estimation through vehicle response measurements potentially provides efficient and frequent measurements. However, the current on-board measurement system still relies on the qualitative inspection by repetitive tests. The main challenge to detect the vertical and lateral track profile and the other rail track irregularities is the unstable solution for the inverse analysis. A simpler, more robust and cost effective system for in-service train vehicle is desirable. Thus, data assimilation method is necessary for estimating the unknown inputs. For inverse analysis technique generally augmented Kalman Filter is being utilized. However, issue of un-observability need to be solved. To solve the above mentioned problem, we have developed a robust inverse analysis scheme for the track geometry estimation from local in-service train responses. The proposed algorithm is verified by measurement to be effective, resulting in the realization of the dynamic characteristics of vehicles and track irregularity estimation.

- Proposed extended Augmented State Kalman Filter (ASKF) technique to solve the Observability Rank Condition (ORC) for the state space model. Theoretically obtain the appropriate sensor types and their placements and the issue of un-observability is solved for data assimilation technique.
- Estimated both vertical and lateral railway track profile using extension of ASKF data assimilation technique for a rigid body motion train model. Practical sensors (accelerometer and gyroscope) are mounted on car body floor and bogie mass. Proposed approach is performing better for train models (4 DOF & 6 DOF)
- Performed Multi-Body Simulations (MBS) using SIMPACK to investigate the influence from different factors under various scenarios and to validate the proposed estimation algorithm. For straight track section (ideal case), it resulted in good agreement for vertical track profile estimation and can estimate only above wavelength of 8 m for lateral track profile. For curved track section (real case), it leads to good agreement for vertical track profile estimation and for lateral track profile: splined section of the track cannot be evaluated due to wheel-rail interaction problem and lateral track excitation is not influencing the dynamics of the train.
- Validated the proposed inverse analysis on experimental measurements obtained from in-service local railway line.

Smartphone Application: iDRIMS

RTRI sensor and Smartphone

Onboard data management system

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isaj@gmail.com

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Editor

Mahendra Kumar Pal, PhD

Hyogo Earthquake Research Center (E-Defense)
National Research Institute for Earth Science and Disaster Resilience (NIED)

Write @: er.mahendra.biet@gmail.com