REPORT ON THE IMMUNOINFORMATICS-MEXICO COURSE

April 8-10, 2019

On April 8th-10th, 2019, the *First International IUIS IMMUNOINFORMATICS Course* took place in the Center of Complexity Sciences (C3), at the National Autonomous University of Mexico (UNAM), Mexico City, organized in collaboration to the Latin American Association of Immunology, the Mexican Society of Immunology, Immunopaedia and C3 UNAM.

To prepare scientists from developing countries to the interdisciplinary Next Gen Immunology, *IUIS IMMUNOINFORMATICS* provided a general but scrupulous review of fundamental concepts on Systems Immunology and the recent advances in computational applications to complex immunobiomedical systems and a practical workshop in mathematical and informatics tools that best answer Immunology-related research questions.

The course considered three session formats: Introductory, Hans-On-Practice and Application Sessions. In addition, a module-organized online pre-course was provided to all participants and two poster sessions maximized students experience.

Participation included 36 students from 8 countries within the African Continent and Latin America, and 24 organizers and lecturers from 9 countries in Latin America, Canada, Europe, Africa and the U.S.

We were committed to promote gender equality in science and to support career development. Accordingly, 10 fellowships were granted and a special *Women in Science Award* session was conducted.

The aims of this specialized event were met, highlighting the relevance of complexity perspectives for the cutting-edge science.

PARTICIPATION

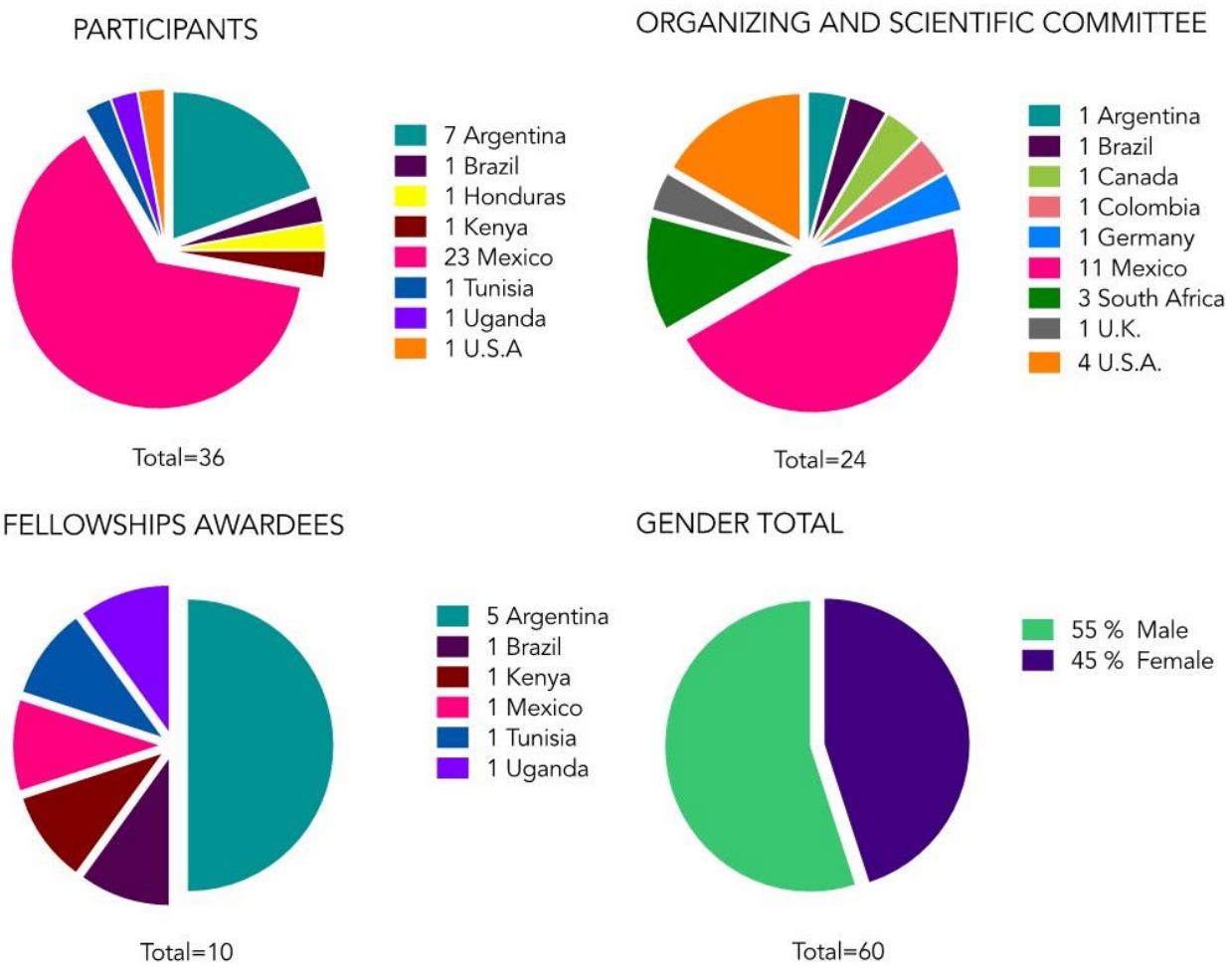
The availability for this course was limited to thirty-six participants who did undergo a selection process based on the submitted application to the website https://iuisimmunoinformat.wixsite.com/course. Moreover, to guarantee a homogeneous basic knowledge level, applicants completed two on-line pre-courses and included the approving evaluations in their submission documentation.
Participants included clinical and basic research fellows, postgraduate students, postdoctoral trainees and junior investigators, who were involved in immunological systems that may be investigated from the complexity perspective. The represented countries were Argentina, Brazil,

Honduras, Kenya, Mexico, Tunisia, Uganda and U.S.A. Moreover, 10 students from Argentina, Brazil, Kenya, Mexico, Tunisia and Uganda were awarded by the IUIS with travel fellowships. Approved participants were required to present their work in a Poster Session and International Achievement certificates were expedited.

Fifteen invited lecturers from Latin America, Europe and the U.S. were prestigious researchers with proven expertise in the fields of computational immunology, bioinformatics or artificial intelligence. Women constituted 45% of total participation and 33.3% of Faculty.

To chair the conference, Dr. Dietrich Kabelitz (Institute of Immunology, Universitätsklinikum Schleswig - Holstein Campus Kiel, Germany), Dr. Clive Gray (University of Cape town, South Africa, videoconference) and Dr. Rosana Pelayo (CIBIOR, Mexican Institute for Social Security, Puebla, Mexico), represented the IUIS Education Committee, while Dr. Leopoldo Santos-Argumedo (CINVESTAV, Mexico City, Mexico) and Rogelio Hernández-Pando (INNCMNSZ, Mexico City, Mexico), represented the Latin American Association of Immunology and the Mexican Society of Immunology (SMI), respectively.

Of note, the active work from M.Sc. Jennifer Enciso at the academic organization, from the Immunopaedia team -Bon Holtak, Cheleka Mpande, the Immunopaedia founder Clive Gray and Latin American ambassadors), from Dr. Michelle Letarte (Past-chair of EDU committee) and Dr. Olivera Finn (chair of Gender Equality and career development) was crucial.



AGENDA

A fundamental course on basic and translational knowledge of Systems Immunology and Immunoinformatics was organized with a schedule including a scientific program featuring 6 distinct educational sessions: two 1h-introductory sessions, ten 1h-application sessions, three 2h-hands-on practice sessions, two 1.5 h-poster presentation sessions, continuous academic discussion and one Gender Equality dinner session.

The opening Presidium was established by Dr. Elena Álvarez-Buylla, current Director of the National Council of Science and Technology in Mexico (CONACyT), Professors Dietrich Kabelitz and Clive Gray, Dr. Rogelio Hernández Pando and former SMI Presidents Rosana Pelayo and Leopoldo Santos Argumedo. A general message highlighted the importance of regional immunology incorporating new informatics approaches that allow a more systematic, quantitative and predictive development in biomedical sciences.

Following her inaugural address, Dr. Alvarez-Buylla opened three days of intensive work and discussion on high-level systems biology, mathematical modeling and in silico experimentation and applications for immunology. Activities on the first day focused on mathematical models, while

the second day was dedicated to bioinformatics and machine learning and the third day mainly to three-dimensional models.

Introductory sessions

The goal of introductory sessions was to look over the main concepts and fundamentals to apply throughout the course. The opening lecture on Systems Biology, Systems Immunology and Bioinformatics, provided an overview of the conducted research to understand the immune system from the perspective of systems biology, which allows us to better understand the complex dynamics of living systems. Dr. Alvarez-Buylla highlighted the relevance of systems biology not only to find patterns, but also to understand regulation and to find new prediction strategies. As an example, how a model of Boolean networks can reproduce the differentiation of CD4+ T cells and their functional plasticity. These models can be applied to multiple biological systems, such as carcinogenesis and metabolic diseases, just to mention a few examples whose applicability will be decisive for Health. If we understand the transition process from a healthy to a preclinical or disease state as a systemic and dynamic process, the minimum and necessary components to maintain the healthy status for longer may be sought. In addition, by identifying these components one can know how they interact within biological systems and lead the whole system behavior".
The second introductory topical lecture, by Dr. de Oliveira from Brazil, discussed crucial concepts to address global health needs, like reverse engineering for vaccines design. It is now possible to select immunogenic epitopes of a pathogenic microorganism by bioinformatic analysis, suitable candidates for immunization, discarding those that are not in the membrane and therefore are not accessible to protective antibodies.

Application sessions

Computer science as a working tool for biomedical and clinical immunology was addressed in 10 application lectures, some of which are detailed below:

Immune systems computational modeling, from the construction of genetic regulatory networks to virtual cultures: Luis Mendoza focused on systems biology for the integration of organization levels in the hematopoietic system and discussed three major methodologies that included Boolean networks, continuous models and virtual culturing. He showed the dynamic analysis of regulation networks of the various lineage cells of the immune response from Boolean networks, with the biological states being the attractors of a robust network that gives stability to the differentiation system. Likewise, the multi-compartmental interaction between the regulation networks can be modeled, simulating interaction processes. Importantly, these models reproduce the expression patterns found *in vivo*, and therefore can be used to perform virtual experiments that predict biological behavior and to generate new hypotheses.

Plasticity in the immune system: from model to mechanisms: Martinez analyzed the ability of CD4+ T cells to respond to environmental cues by simulating cell transitions with continuous models, showing that there are plastic cells and cell fates that do not change upon external stimulii, and suggesting the plasticity of the immune system is asymmetric

Immunomics of Infectious Diseases: Fernán Agüero is dedicated to build a complete atlas of antigen, epitopes and antibody-binding specificities for human pathogens, with emphasis in the case of Chagas Disease (Trypanosoma cruzi), endemic in Latin America. There is no vaccine against the parasite, so the development of new methodologies to improve diagnosis and treatment of the disease are needed. By Immunomics technology and microarrays of high density

peptides, one can find antigens and antibody binding sites, with the possibility of analyzing hundreds of thousands to millions of peptides in the same assay. This session allowed participants to access the databases to maximize the learning experience.

Lymphocyte Repertoire and Comparative Genomics for the Study of Immune Responses: The study of antibody repertoires requires bioinformatics techniques due to the immense amount of possibilities in a single individual and the differences from one individual to another. Here, M-Barnetche reviewed work on genomic studies to understand the diversity of immune cell receptors that recognize pathogens and their applicability to the study of health and disease, prevention and treatment. For this, lymphocytes must be considered as a dynamic population influenced by evolutionary forces such as clonal selection and genetic changes. Similar to the selection process of biological species, the repertoire should be selected depending on the environmental conditions. In this course, the adaptive immune receptor repertoire sequencing (AIRR-seq,) was discussed as a technique showing the high dimension complexity required by a bioinformatic analysis to deeply understand diversity.

B cell epitopes prediction using docking: The lecture by L. Domínguez focused on the various platforms to perform structural biology, with attention to epitopes prediction by molecular docking, due to their relevance in drug design and protein engineering. He introduced fundamental aspects of bioinformatics laboratories versus wet labs and presented his YouTube channel where tutorials explain step by step how to use some platforms so that interested students can easily approach to bioinformatics field.

Hands-on practice sessions

Certainly, practical sessions were another strength of the course, where participants performed real analyzes using different open source software. For example, docking analyzes were performed for prediction of B cell epitopes, principal component analysis for multi-dimensional data management and analysis in the Bioconductor package (http://www.bioconductor.org) that is designed to provide tools for analyzing genomic data and other big data of biological origin, and that is a free development on the programming language R.
As an example, the training on *discrete modeling strategies to simulate cell differentiation networks with microenvironment feedback*, showed how to build regulatory network models, from database curation to applications to understand the physiology of differentiation and the molecular basis of pathologies. For this, there are platforms such as the Kyoto Encyclopedia of Genes and Genomes (KEGG), a database that integrates genomic, chemical and functional information, or the MEDLINE PubMed search engine, where the information is obtained directly from the experimental reports. Automated programs like STRING, use bioinformatics methodologies and machine learning methods to analyze genes and find interaction networks between them. We worked on discrete models, where stable patterns of gene expression are associated with cell types and networks determine the transition from one stable pattern to another in cell differentiation or the emerging phenotypes resulting from temporary stimuli. Platforms like Rstudio and BoolNet were used throughout the session.

Poster presentations

The participants presented their research work in two poster sessions that were successfully conducted, encouraging the close communication between students and the Faculty throughout the course. There was a rigorous judge committee (Faculty) and 3 presented works were awarded on the basis of the immunoinformatics contents of the work, originality, design and quality of the

poster (text, graphics, models, images, etc.) and oral presentation by the author (scientific management of the topic, clarity, analysis, discussion and perspective). First place award went to "Bioinformatic study of response to targeted therapies and immunotherapies in melanoma" by Yamil Damian Mahmoud, while two participant works were awarded Second place: "Evaluation of T-cell response against predicted neoantigens for a patient treated with the CSF-470 vaccine" by Enrique Podaza and "Macrophages and Breast Cancer Interactions: A Dynamical Approach" by Ugo Avila. Of note, at the closing ceremony, they presented to the audience an executive 5 min talk on their work including a graphical abstract.

Photography: José Israel León Pedroza, MD, MSc

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Gender equality session

The special session dedicated to Gender Equality in the Nube7 at UNAM is part of a series of initiatives coordinated by the IUIS GEC and EDU Committees, ALAI and SMI, which promote gender equality by visibility of the work from women scientists and encourage their professional development. It was an activity of great importance, where the PhD student Karina Eva Canziani, from the National University of La Plata, Argentina, was awarded by the Mexican Society of Immunology (SMI) with the *Gender Equality Travel Award*, and the IUIS GEC, awarded Dr. Selene Fernández-Valverde from the National Laboratory of Genomics for Biodiversity (LANGEBIO-CINVESTAV), with the *Gender Equality Trophy* in appreciation of her brilliant work and for being an inspiration to the women immunologists around the world.

Within an emotional speech, Karina mentioned the major problems awaiting solution, such as sexual harassment and gender-based workplace harassment, as well as the prejudices that prevail in the scientific community and prevent it from achieving the desired gender equality.

She kindly asked the audience to do a simple exercise: “Close your eyes, relax and imagine. I want you to imagine someone peering into a telescope, sitting at a computer typing out a grant proposal or a future Nobel Prize winner. You can open your eyes. Did you picture a man or a woman?...the answer depends on where you live” she said.

According to UNESCO, only 30 percent of researchers around the world are women. However, it is different in Latin America, where this average increases to 44%. Indeed, in Argentina the frequencies go up to 52%. However, such general numbers hide inequalities in some disciplines such as engineering, physics and astronomy, where male participation is 64%, 75% and 61%, respectively. Additionally, women participation in administrative and leadership positions at research institutions is crucially reduced. Canziani mentioned we are making progress in gender disparities in Latin America and highlighted the different aspects we must work on, including research, public policies, incentives at all stages, safe conditions for career development and

visibility of women in science, according to analyses from Bonder and Rodriguez Hertz, two experts in this area.
The special guest of the session was Selene Fernandez-Valverde, a Mexican young investigator who has achieved an outstanding career at the intersection between bioinformatics and developmental evolutionary biology, and actively participates in different science organizations, such as More Science for Mexico, Mexico Science Clubs and Women in STEM (Science, Technology, Engineering and Mathematics): Future Leaders. In 2016, she received the L'Oreal-UNESCO Research Fellowship For Women in Science award in addition to the L'Oreal-UNESCO International Rising Talents distinction in 2018.
Fernández-Valverde emphasized the need to eradicate any trace of discrimination for the construction of equality and shared with the audience her personal experience in an area dominated by men (computational science). Gender inequality became evident during her international postgraduate studies when she experienced gender bias and started looking for facts about the status of gender discrimination in Science and found that in some places, even in high-income countries, women had to be 2.5 times more productive than men to be awarded the same grant. She mentioned a recent study finding that women with young children receive less citations and less funding than their male peers. In our culture, women are also generally expected to take on most of the burden for childcare and rearing at home. She talked about the various factors influencing the performance of both women and men in science, like cultural stereotypes, maternity/paternity and sexual harassment in the workplace, as well as the growing opportunities of psychological and/or legal support, promotion of appropriate legislation, etc.

“We are fortunate to be living in a time of change, particularly in term of gender equality. I am convinced that a more inclusive academic environment can foster innovation and growth, particularly in developing economies such as ours. As women comprise 50% of the world population, gender equality represents a great opportunity to capitalize on underused talent in the areas of STEM that can transform into knowledge to help solve the most challenging problems of our times”, Selene concluded.
Rosana Pelayo and Dieter Kabelitz confirmed the local and international commitment to promote actions that urgently guarantee equal opportunities for women and men in science. Of note, this was the third time immunologists in Mexico work in collaboration with IUIS to recognize gender equality as a way to build a better community.
Finally, on behalf of the GEC committee and its chair, Dr. Olivera Finn, they awarded Fernandez-Valverde the Gender Equity Trophy.

Immunopaedia

A pre-course module comprising thirteen sections in total was constructed and inserted into the Immunopaedia.org website https://www.immunopaedia.org.za/online-courses/iuis-courses/iuis-immunoinformatics/introduction-to-iuis-immunoinformatics/.
Prior to the meeting, students were required to complete: seven core modules of basic immunology materials (*A snapshot of the immune system, Ontogeny of the immune system, The innate immune system, Overview of T cell subsets, Thymic T cell development, B cell activation and plasma cell differentiation,* and *Antibody structure and classes*), two selected thematic sections (*Introduction to immunization strategies* and *Cancer immunotherapy*) and all four Immunoinformatics sections (*Introduction to Immunoinformatics, Omics technologies, Computational modeling, Machine learning methods*). They were also committed to complete the MCQ quiz at the end of each module and score 75% or above in total of the questions asked to be eligible for their official certificate.

Immunopaedia Ambassadors J.Enciso, J.C.Balandrán and J.L.Maravillas worked on the Immunoinformatics sections for the pre-course module, Immunopaedia report and a course video, respectively. Find below a link to the video showing the various activities during the course:

https://drive.google.com/open?id=1-mc6P_aQaFDX3HxMDTLvlmO7mGHunLog

FUNDING and SCHOLARSHIPS

The course had no registration fee. However, availability was limited to 36 participants. Fellowships covering full accommodation and travel awards were approved to 13 selected candidates: Mtimet Ghanem, Lucrece Ahovegbe, Musyoki Stanslaus, yamil Mahmoud, David Romanin, Andrea Maglioco, Lorena Juriol, Abraham Culupú, Mayela Espinoza, Karina Canziani, Babatunde Olusola, Birhanu Avelign Jemere and Henok Andualem. Unfortunately, three participants (Birhanu and Henok from Ethiopia, and Babtunde from Nigeria), had to cancel due to immigration issues, since they were not granted transit visas for Europe. As their flights had already been purchased from IUIS funds, such cancellation led to a long process of request partial refunds to the correspondent airlines. We have already achieved 40% from 2 flights and still waiting for KLM-Nigeria.

The total cost of this course was **$36,612.40 USD**. To cover it, the IUIS Education Committee contributed 12,000 EUR ($13,353.6 USD), ALAI contributed $11,629.40 USD and SMI contributed $11,629.40 USD.

IUIS funds were completely applied to international flights for most (but not all) awarded students (see enclosed Excel database), while ALAI and SMI covered hotel accommodation for students and Faculty, travel expenses for faculty and organizers, meals and coffee breaks for all attendants.
Note: If within the next few weeks the process is solved with KLM, we would be receiving around 1052 USD as reimbursement, which would be applied to awarded students Lorena Juriol´s and/or Mayela Espinosa´s flights.
In addition, we had an extraordinary contribution from the National University so facilities and operating expenses at the C3 venue were not covered by us. In addition, Laboratorios Juárez and MACROFILTER Puebla directly assumed all costs of gifts for teachers and students, recognitions and stationery, etc.

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