“Each year, ICAN Series is THE event where world-renowned cardiometabolic scientists converge to discuss ideas and forge new collaborations in a “Parisian” atmosphere over 3 days. As an original initiative, young researchers (PhD students, postdoctoral fellows & junior researchers) are also offered the unique opportunity to present short talks about their work and benefit from audience mentoring. For most of them, this marks the beginning of a long and fruitful collaboration. ICAN Series is definitely more than a simple symposium - it is a club.”

Karine Clément
Chief Executive Director

“We sought to create a one-of-a-kind event, with a top-notch scientific program and where junior researchers have the opportunity to interact with internationally acclaimed senior scientists. The selection process allowed us to reward the best scientific achievements and turn junior scientists into active members of the meeting. This edition, we gave junior investigators the chance to co-chair each session with senior experts. ICAN is championing a translational approach to research and care. We would thus like to keep this transversal mode of interaction between senior and junior researchers to facilitate and accelerate their work.”

Nourédine Farah
Executive Director

ICAN Series Vision
OVER 150 PARTICIPANTS
20 SPEAKERS
10 SHORT TALKS
14 COUNTRIES

KEY FIGURES

70% FRENCH
30% INTERNATIONALS

AUSTRIA, BELGIUM, CANADA, DENMARK, EGYPT, FRANCE, GERMANY, ISRAEL, LEBANON, NETHERLANDS, SWEDEN, SWITZERLAND, UK, USA
THE EXPERTS HAVE THE FLOOR
There are three main ethical issues surrounding genetic sequencing disease: 1) clinical utility, 2) sharing data, and 3) the type of genomic sequencing. The first is easiest to address, many different laboratories around the world have shown the clinical utility of sequencing, particularly for rare and undiagnosed disease, as well as cancer. Sequencing can actually change care outcomes and help solve misdiagnoses, and even if causes aren’t identified, there’s still comfort knowing everything possible has been done. Additionally, data may have personal utility to the patient and immediate and extended family.

The second deals with resulting data. When an entire genome is read, genetic characteristics unrelated to the focal disease may be discovered. These are known as secondary or incidental findings and may be of extreme interest. Thus at Hudson Alpha, we believe this should be a highly consultative process between patients and doctors, with the input of trained genetic counselors.

The third topic relates to whether exome sequencing or whole-genome sequencing should be offered. It’s much cheaper to sequence the coding portion of the genome, the exome, but only 1.5% of the genome is covered, compared to 98% with whole-genome. There are studies reporting that up to 80% of the coding+non-coding genome is functional at a biochemical level, but we don’t yet really know the proportion which is truly functional. Thus the easiest question to ask is: Which would YOU do for YOUR family? These points merit further discussion together to create future diagnostic possibilities for patients.
Following the sequencing of the human genome, it was initially surprising to discover that only 2-3% contained protein-coding sequences, and that more than 90% of the genome was “junk” DNA, with no function. We are studying these sequences, called RNAs, or non-coding RNAs. Many of these RNAs are transcribed, and can be classified into at least two different classes, microRNAs of around 22 nucleotides in length, and long non-coding RNAs greater than 200 nucleotides.

MicroRNAs bind to mRNA transcript targets and can either inhibit translation, or induce mRNA degradation, thus controlling gene expression. One of the cardiac-expressed microRNAs, miR-92a, has anti-angiogenic functions in endothelial cells. We developed a cardiovascular therapy based on this microRNA by generating anti-sense RNAs which specifically bind to microRNAs and inhibit their function. We demonstrated pro-angiogenic effects and enhanced vascularization after ischemia using these anti-miRs in animal models. In addition, this anti-miR prevented atherosclerotic lesion formation, and miR-92a knockout mice presented with an interesting metabolic phenotype. After validation in porcine models, we are moving towards clinical trials in humans.

Much less is known about long non-coding RNAs (IncRNAs), of which approximately 30,000 are expressed in endothelial cells. They can act as both epigenetic and splicing regulators, with multiple potential unknown functions. One such IncRNA we’ve been studying is IncRNA malat1, which regulates endothelial cell function, perhaps via epigenetic effects on cell cycle progression. One of the IncRNAs subfamilies are circular RNAs generated by back-splicing. There is evidence that these circular RNAs may be useful as potential biomarkers, as well as having potential therapeutic applications in angiogenic signaling.
Much progress has been made in understanding the genetic basis of coronary artery disease and its potential for clinical translation. Worldwide investigative networks have identified 56 loci associated with coronary disease risk. However, the majority of these loci act via unknown mechanisms. Thus understanding these mechanisms will have important implications for developing new treatments for coronary artery disease, as enormous progress has already been made in identifying novel drug targets with some of the genetic variants.

Other benefits from this large international collaboration are that we have identified many biomarkers associated with cardiovascular disease, however it’s unclear if they’re causal, or associated for other reasons. We are now able to do Mendelian randomization to distinguish those causal variants using large genetic databases arising from GWAS studies. This will aid the prioritization of those molecules vital to novel drug development.

These discoveries may have important implications for improving coronary artery disease prediction, as well as for patient stratification, or personalized medicine. The disease risk of those carrying the bottom 20% of variants is about one fifth of the risk of those who carry the top 80% of variants. Thus early identification of those at high risk of developing coronary artery disease will translate into earlier implementation of preventive measures.
Over the last ten years, we have discovered nearly 200 genetic variants associated with common phenotypes of obesity, BMI, and waist-hip ratio. However, within these genetic loci, we don’t know which genes are causal. So instead of investigating broad phenotypes, we are studying more refined phenotypes, such as fat percentage, or levels of the adiposity biomarker, leptin.

We performed genome-wide association studies (GWAS) for genes associated with fat percentage, and yielded interesting genetic variants highly relevant to the biology of obesity. The leptin GWAS highlighted six variants, one was leptin, another FTO, but the remaining four were brand new biomarkers. So by refining the phenotype, we get closer to the underlying biology.

We have also performed preliminary studies on low-frequency genetic variants which have coding or functional effects. From a huge meta-analyses of more than half a million people, we identified low-frequency variants that have big effects. For example, one rare variant was associated with body mass index. If you are one of the 1 in 10,000 people who carry this variant, you will weigh eight kilograms more than if you don’t carry it.

Using genetic studies in combination with refined phenotypes and low-frequency phenotypes, we can learn more about the biology of obesity.
Epigenetics is a novel area of genetics that promises to explain much of the missing variability in cardiometabolic traits and cardiovascular disease. We measured epigenetic DNA methylation at 470,000 CpG-rich regions across the genome in our GOLDN study cohort. The CPT1A gene, which is very important in beta-oxidation of fatty acids, was strongly associated with triglycerides, VLDL-cholesterol, other LDL particles and VLD particle sizes, as well as obesity. This finding has been replicated in many other European and US studies, including ethnic groups such as African Americans. Therefore increased methylation may be an important epigenetic biomarker resulting in reduced gene expression.

We also identified ABCG1, which is involved in sterol transport across the cell membrane. In both the GOLDN and ARIC studies, this gene was strongly predictive of BMI and waist circumference. Further work is required to better understand the functional relevance of both these genes, and how we could utilize reduced epigenetic processes to impact and prevent hypertriglyceridemia and obesity in the future.

Additionally, the relationship between the gut microbiome and epigenetics is a hot new area. We aim to study whether the gut microbiome can really predict epigenetic profiles in populations.
We focus on common human diseases such as diabetes, heart disease, and cancer, we aim to predict those individuals that will develop disease as well as develop better drugs. Much progress has been made in understanding these diseases using approaches such as genome-wide association (GWAS) studies. Results show that these diseases are actually very complex, with thousands of genetic factors. This isn’t really enough; simply knowing which genes or loci are associated with a disease doesn’t explain their exact role in the disease. Additionally, genes only account for a very small fraction of disease, partly because the environment is so important, partly because there are multiple unknown interactions.

Therefore we use experimental models such as mice to better understand disease conditions. We control the environment and the genetic background to understand and intensely characterize patterns of DNA variation, methylation differences, transcript differences, protein levels, metabolites, and even gut bacteria. We then integrate this information via genetic mapping, trait correlation, and mathematical modeling, to gain a deeper insight into the interactions between genes and the environment and how they contribute to disease.
In collaboration with ICAN, we are investigating the molecular mechanisms that give stem cells their "stemness". We’ve identified the long-sought-after novel progenitor stem cell which is present in all tissues and gives rise to blood vessels. These stem cells are also involved in the metabolic regulation of fat content, lean mass, and the overall metabolic status of the animal.

What’s particularly interesting about the genes we used to identify these cells, is that they’re mammal-specific, and have mammal-specific regulation. These genes may explain why lower vertebrates such as fish and salamanders can regenerate so well, whereas we as humans regenerate so poorly. Thus this is a perfect investigational target in understanding what underlies our weaker capacity to regenerate and recover from illness.
We’ve performed a large-scale genome-wide association study (GWAS) examining betaine metabolite levels in a cohort of heart patients from the Cleveland Clinic. Betaine is a derivative of choline, a dietary substrate found in foods like eggs, cheese and meat. We found that betaine levels were linked to certain genetic regions, one of which contains a gene involved in the urea cycle, carbamoyl-phosphate synthase 1, or CPS1. This gene is associated with betaine levels but also a variety of other metabolites involved in the degradation of choline down to the amino acid glycine. Observed genetic effects seem to be different between men and women. Therefore, CPS1 is associated with decreased betaine levels, increased glycine levels, and decreased risk of heart disease in women. So perhaps the amino acid glycine can be protective against heart disease in women.
At SciLifeLab in Stockholm, we apply affinity-based plasma proteomics to discover novel biomarkers of cardiovascular disease. We have a vast resource of antibodies covering most of the human proteome, and can use them to screen for novel biomarkers in biological fluids.

One of our major projects was to perform antibody-centric proteome-wide screening in all available cardiovascular samples. Via this screen we identified promising targets for acute coronary syndrome. Another project involved a more gene-centric approach, where >1000 candidates were screened in venous thromboembolism. We identified both first-event predictive biomarkers as well as biomarkers for acute diagnosis.

We have strategies in place to identify the potential clinical value of these markers at an early stage so that research resources are optimized.
At the European Institute for Systems Biology, we are actively changing the paradigm of current medical practices. Previously, only population averages were considered, now we have the ability to combine unlimited numbers of measurements with global genomic assessments. Due to the rising use of mobile devices, we can now capture continual lifestyle measurements, enabling greater understanding of how wellness can transition into high disease risk. We must understand these factors before disease onset, so that hospitals, research, and the pharmaceutical industry can develop improved diagnoses and treatments. In this way, we can also eventually decrease healthcare and hospitalization costs.

We are now at the turning point of this revolution, so to move forward, we have partnered with ICAN and colleagues from Lyon, Grenoble and Nantes, to create a workforce that interacts with other systems medicine centers in the USA, India, China and Europe. Using a bottom-up approach, we will investigate single individuals over time, with the goal to transform healthcare practices from reactive to anticipatory, all within the timeframe of one generation. We aim to promote healthy practices, not only to reduce the cost of maintaining wellness, but also to reduce drug development costs due to lessening impacts on the health economy.

At the heart of this approach is the empowerment of individual citizens, so they can control their own data while simultaneously protecting their privacy. We aim to integrate systems medicine with patient organizations and proactive individuals within social networks to create personalized data to predict undesirable events.

This is a huge change in how we approach health and wellness, as well as disease states and treatment methods. The creation of novel interconnection opportunities via devices and big data analytics will enable the personal follow-up of health and nutrition, the subject of this conference, as well as stress, sleep and other daily habits, including social interactions with families and communities.
At the Nestlé Institute of Health Sciences at the Lausanne Federal Institute of Technology, we believe there needs to be an integrated solution for personalized health and nutrition, at the intersection of food, pharma, and diagnostics. Thus we aim to personalize and individualize targeted nutritional approaches that can prevent disease and maintain health, particularly in mental health (such as Alzheimer’s), intestinal health (intestinal inflammatory disorders) and in metabolic health (diabetes).

While we also contribute to teaching the university, we mainly perform fundamental translational biomedical research in maintaining health to help determine “who needs what” in terms of diagnostics and nutrition. The answers depend on genetic predispositions, family history, food intake, living location, physical activity levels, work and travel habits, and every other unique personal lifestyle factor. We perform long-term detailed individual assessments on volunteers and patients to test responses to interventions, whether they be dietary or physical. These results define body resilience or the ability to restore homeostasis, and are much more informative than a single assessment visit, after done while fasting and at rest.

Our aim in performing these collaborative clinical studies, is to define which groups of individuals share enough similarities so that we can deliver an appropriate targeted solution that fits their specific needs. It’s the total opposite of a one-size-fits-all approach.
YOUNG INVESTIGATORS, ON THE STAGE
I first attended the ICAN Series in 2014 as it was directly relevant to my research. It was a very nice experience to hear world-leading researchers in such an intimate setting. Also, Paris is a lovely in December. The 2014 meeting was well organized and I learnt a lot.

Because of this good experience, I was really eager to return. I noticed that this year’s topic was Omics, one with which I’m not very familiar. As ICAN had invited world-leading researchers last year, so I was sure it would be similar this year, and that would be an excellent opportunity for me to learn more about Omics.

The ICAN Series is definitely something special. Staying at the venue generates excellent opportunities to interact with speakers outside of the conference. Everybody comes together. All the young researchers had the chance to meet senior researchers with extensive experience. Normally, when you attend large congresses, especially those on cardiology which are gigantic, you never get to meet the specialists. You can only listen to a session, then rush to another one. Here you have the time and the opportunity to meet and network.
I think this is a great opportunity for young investigators. I started my PhD at the Institute of Nutrition and Functional Foods in Quebec five months ago, so it’s an excellent time to present my project to speakers and researchers from all over the world.

It can be intimidating, but not too much because it’s such a relaxed atmosphere. It’s easy to chat to other speakers during the breaks, and it’s fascinating to learn what researchers in other countries are investigating, and to compare our results with theirs.

This meeting is fascinating as so many interesting topics were covered in only two and a half days.
I think this is a fabulously intimate meeting. There was a lot of informal interaction between more senior faculty and people like myself who are early-career investigators. Everybody has been incredibly welcoming. The quality of science is very high, they really are the rock stars of science. Jake Lusis is talking right now and I was star-struck when I first saw him.

It’s a great mix of investigators from all over the world and from different domains. So we have the microbiota, and the epigenome, and genetic variations. This meeting is an excellent microcosm of the science in this field.
This amazing meeting is really targeted towards junior researchers. I came here to learn new concepts, to keep up to date with the knowledge of the international community, and to network with researchers attending this meeting.

This meeting is unique because there is a lot of personal interaction. Last year was focused on obesity, this year it’s more about omics science, both very interesting subjects with more with this evolving research field.

I would tell all junior researchers in the field that they will find what they need at this excellent meeting, it’s also very useful for the key opinion leaders as well.
VISIT OF THE LOUVRE MUSEUM

YOUNG INVESTIGATORS SELECTED FOR SHORT TALKS ARE PRIVILEGED TO CHAT WITH SPEAKERS IN FRONT OF THE LOUVRE’S FAMOUS PAINTINGS.
AWARDS

BEST SHORT TALK : HUGOLINE DE HAAN (2000€)
BEST POSTERS : ERIN COYNE (1000€) & BRANDON KAYSER (1000€)
BEST PARTICIPATION : STELLA ASLIBEKYAN (ICAN SERIES 2016 FREE PASS)

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