Ben-Gurion University of the Negev
The Jacques Loeb Centre
For the History and Philosophy
of the Life Sciences
Prof. Ute Deichmann, Director

From gene to genome as an integrated system. Scientific, historical, and philosophical perspectives

Ben-Gurion University of the Negev, 24-25 November 2014

Abstracts

Ramon Birnbaum, Ben-Gurion University of the Negev

Genomic view of gene regulatory elements and their role in human disease

As less than 2% of our genome codes for proteins, the majority of our genome (>98%) encompasses important sequences that function as gene regulatory elements, instructing genes when, where and at what levels to turn ON or OFF. Increasing evidences suggest that non-coding variation is a significant risk factor for human disease, but how these variants contribute to the phenotype remain elusive. In my talk, I will focus on distal transcription enhancers that promote gene expression, enabling spatiotemporal control of genetic programs such as those required in developmental processes. I will describe how to identify and functionally characterize enhancers and I will describe several examples of how mutations in these elements have been found to cause human disease. As the sequencing technologies tremendously improved, our ability to identify disease-associated mutations in these regulatory elements is rapidly increasing. Thus, deciphering the regulatory code is necessary to accelerate our basic knowledge about the human genome and diseases.

Eric Davidson, Caltech

Evolutionary perspectives on developmental gene regulatory network structure/function: the causal bases of phylogeny, of body plan stasis, and of innovation in deep time

Evolution of the animal body plan is the outcome of change in the encoded genomic regulatory program for development. Major features of Phanerozoic animal evolution relate directly to developmental GRN hierarchy. In this Chapter, we consider rapid and continuously adaptive changes occurring at the species level, in terms of regulation of effector gene expression at the periphery of developmental GRNs. Developmental processes responsible for the generation of definitive characters of the body plan shared amongst all members of given phyla or classes occur at upper levels of GRN hierarchy. We discuss regulatory mechanisms accounting for the evolutionary stasis of such developmental characters. Evolutionary mechanisms operating at different levels of GRN hierarchy are fundamentally distinct, ranging from cis-regulatory adaptation at individual genes to co-optive redeployment of whole regulatory circuits. Conservation of regulatory circuitry within GRN hierarchy leads to an explanation for the nested organization of shared character sets underlying animal phylogeny.

Eric Davidson, Caltech

Formalizing the genomic logic of spatial gene regulation in development

Developmental process operates as an automaton in which the inputs that control each successive step are the outputs of the prior steps. We show that if knowledge of the regulatory molecular biology of a developmental process is sufficiently complete, this essential property of state progression in life can be captured in a Boolean automaton model. The consequence is the demonstration that genomically encoded logic processing causes development. Recently such analysis has been extended to almost the whole of an embryo, diminishing to insignificance the external inputs, and providing a direct path to abstract visualization of the organism as an entirely self-sufficient mechanism that operates by processing internally generated regulatory information.

Ute Deichmann, Ben-Gurion University of the Negev

Chromatin - Its history, the seminal researchers and their philosophy

The concept of chromatin as a complex of nucleic acid and proteins in the cell nucleus was developed by cytologists and biochemists in the late 19th century. It was the starting point for biochemical research on DNA and nuclear proteins. The interest in chromatin declined rapidly at the beginning of the 20th century. Only decades later, a new focus on chromatin emerged, which was not only related to its structure, but also to its function in gene regulatory processes in the development of higher organisms. I will highlight the major milestones in chromatin research, analyze its decline and reappearance, and introduce the major investigators and their scientific and philosophical context.

Nir Friedman, Weizmann Institute of Science

Acquired immunity for all: somatic processes allow individuals to learn from their own immune experience

All living organisms possess immune mechanisms that provide protection against parasites, and maintain the integrity of the organism. The current paradigm, which is based primarily on the vertebrate immune system, divides immunity into two arms or sub-systems: innate immunity and acquired immunity. It has been assumed that the innate sub-system is evolutionarily more ancient, whereas acquired immunity has been seen as an evolutionary innovation that is restricted to vertebrates. However, similar to vertebrates, invertebrates, and plants are also exposed to continuous assault from various parasites, and they too must heal wounds and manage symbiotic relationships in a multi-organismal ecosystem. Recent findings have provided evidence for the existence of non-vertebrate acquired immunity. We survey these findings and propose that all living organisms must express both innate and acquired immunity.

We suggest new definitions of innate and acquired immunity, based on whether immune recognition molecules are encoded in the inherited genome or are generated through somatic processes. Specific examples for somatic mechanisms that generate diverse repertoires of acquired immune recognition will be presented, including our high-throughput analysis of T cell receptor repertoires and their organization.

We reason that both forms of immunity are similarly ancient, and have co-evolved in response to lifestyle, cost-benefit tradeoffs and symbiosis versus parasitism. However, different species have evolved different immune solutions that are not necessarily genetically related, but serve a similar general function allowing individuals to learn from their own immune experience; survival of species is contingent on the acquired immune experience of its individuals.

Myles Jackson, NYU-Gallatin
Reining in the biotech sector? Gene patenting and personal genomic companies

Two decisions last year, one by the Supreme Court of the United States (SCOTUS) and the other by the Food and Drug Administration (FDA), might signal the end of the honeymoon between the federal government and the biotech sector. In June 2013 SCOTUS ruled unanimously that genes merely isolated and excised from the genome were no longer patent-eligible. The decision was the culmination of a four-year lawsuit brought against Myriad Genetics, the owner of the patents for the so-called breast cancer genes (BRAC1 and 2), by those women who received false negative reports from the Utah-based firm, the American Civil Liberties Union (ACLU), and the Public Patent Foundation (PubPat). How will it affect research on future discoveries of genes relevant to human diseases as well as the tests for such diseases? Some fear that it will it have a negative impact on patenting products of nature in general. In late November 2013 the FDA sent a cease-and-deceased letter to the personal genomics company 23andMe demanding that the firm stop offering medical information based on genomic information until it had sound scientific evidence to support such claims. Two weeks later the company discontinued providing medical information with their DNA test. How had personal genomic companies played a role in patients taking charge of their own health care? How does the phrase "Be your own expert" actually play into the hands of private companies? Do we need to be concerned with the increasing privatization of biomedical knowledge and research?

Lucie Laplane, Institut de Cancérologie Gustave Roussy, Villejuif
History and philosophy of stem cell biology: state or entity?

What is a stem cell? Stem cells are usually defined by their ability to self-renew and to differentiate, and they are classically represented at the apex of an irreversible process of differentiation. This presentation will focus on three major events in the history of stem cell biology: cloning, induced pluripotent stem cells (iPSC), and the controversial stimulus-triggered acquisition of pluripotency (STAP). All these events contradict the classical representation of stem cells by suggesting that differentiation is a reversible process, and therefore, that non-stem cells can become stem cells. First, I will present these three technologies, which all imply gene expression modifications. Second, I will highlight the consequences they have for the question of the stem cell identity. Finally, I will discuss the existence of a stemness signature, i.e. of a specific set of over-expressed genes that would be common to all stem cells.

Florian Maderspacher, Current Biology Cell Press/Elsevier
Victory over the genes: The rise and rise of epigenetics in scientific and public discourse

Although coined by C.H. Waddington more than 70 years ago, the term "epigenetics" has become widely used only in the past two decades. While epigenetics is being constantly redefined, it has become fashionable predominantly in two main contexts: in gene regulation, where it refers to stable state changes independent of DNA sequence and in evolution, where the focus is on induced, stable phenotypic changes without a change in genotype. Moreover, epigenetics and associated concepts have gained striking popularity with the public. Here, after some historical background, I explore how and why epigenetics has become so popular both in science and the wider public. I also ask whether the hype is truly justified.

Hanah Margalit, Hebrew University of Jerusalem

Integration of post-transcriptional regulation by non-coding RNAs in the cellular networks

Until recently, our view of gene expression regulation was dominated by transcription factors and transcription regulation. This has dramatically changed with the discovery of a whole new world of non-coding RNAs (ncRNAs), regulating gene expression post-transcriptionally by binding to mRNA molecules, affecting their stability and/or translation. While regulation by ncRNAs was shown to be widespread in both pro- and eukaryotes, a full understanding of the principles and properties of this regulation, as well as its local and global effects in cellular regulatory networks, is still lacking. In my talk I will describe our studies of the dynamic properties of post-transcriptional regulation by ncRNAs, its integration with transcription regulation to form complex regulatory circuits with designed functionality, and the information flow it underlies in the cellular networks through cascades of targets co-regulated by a common ncRNA and ncRNAs with shared targets.

Michel Morange, Ecole Normale Supérieure

Gene complexes: the search for a link between genome structure and genome function

In 1934, in his Nobel lecture, Thomas Morgan emphasized the dispersion of genes on the chromosomes, independently of their functions and roles in development. Exceptions were nonetheless rapidly discovered with the existence of pseudoalleles, the occurence of gene duplication and the existence of gene complexes. In this communication, I will discuss the ambiguous role that these observations played in the emergence of research on genomes. Some of these complexes became famous, such as the homeotic gene complex and the HLA omplex. Others disappeared such as the T-complex. Although some of them played a major role in the description of distant regulatory elements (enhancers), the "raison d'être" of the persistence of these complexes is far from being obvious.

Hugues Roest Crollius, Ecole Normale Supérieure

Ancestral genomes as a means to integrate evolution into modern biology

In their seminal 1965 article that laid key foundations for phylogenetics (Zuckerkandl and Pauling 1965), Emile Zuckerkandl and Linus Pauling asked where the greatest amount of information on the past history of living systems could be found and extracted. The answer that they put forward was that genes, as "sense-carrying" molecules, would be the most favourable repositories of "historical documents" that we could mine for such information.
Fifty years later, the entire genomes of several thousands species have been sequenced and annotated. Comparative genomics has emerged as a new discipline, equipped with sophisticated software and formidable computer capabilities, providing some of the most powerful strategies to predict the position of functional regions among the vast expanses of seemingly "neutral" chromosomal DNA.

The proposal put forward by Pauling and Zuckerkandl holds its promises, since phylogenetic principles represent the conceptual and statistical framework in which comparative genomics delivers its most rigorous results. Yet, our understanding of evolutionary changes in genomes remains limited because almost all analyses are performed by comparing the genomes of living organisms. One may argue that while this is the only strategy available, it may not be the best strategy. Indeed, evolutionary processes occurred in a chronological manner, and a much more logical approach would be to consider successive ancestral genomes, for example vertebrate to amniote to mammal to primate to human, and to compare them at every step of evolution to identify novelties and losses, up to the extant version.

I will describe current efforts that try to solve this problem by reconstructing ancestral genomic information on a systematic basis. Given the abundance of extant genomic information, bioinformatics inferences of the ancestral genome sequences and structures are now possible, with varying degrees of resolution and quality. Just like archaeological artefacts allow us to reconstruct a global understanding of past civilisations, conceptually similar signatures of past events buried in genomes can be integrated to build an increasingly clearer picture of extremely old genomic structures and events. This new framework may then be exploited to introduce a Historical dimension to our approaches aimed at solving problems in Biology.

Zuckerkandl E, Pauling L. 1965. Molecules as documents of evolutionary history. *J Theoret Biol* 8: 357-366.

Ellen Rothenberg, Caltech

Genomic compositions of cellular identity in the immune system

Immune cells are derived from blood-forming stem cells in a process that continues throughout most of life. The stem cells need to be programmed both for ability to self-renew, remaining undifferentiated, and for the ability to generate at least 10-12 different types of differentiated progeny through divergent pathways of development. The gene networks leading to each of these differentiated cell fates, including immune cells, therefore have some special properties.

First, these gene networks must be capable of variable timing – while some immune cells develop immediately in the fetus, many other later cohorts of immune cells will not develop until months or years after the animal (or human) is born. Second, because a single stem cell has to be able to give rise to so many types of descendants whenever it differentiates, the pathways that lead to each of these descendants necessarily have an intimate family relationship. This family relationship is reflected in the fact that certain transcription factors (gene regulatory proteins) play key, shared roles in more than one distinct blood cell differentiation program, where they achieve different effects by working with different transcription-factor partners in each program. It is not surprising that hematopoietic (blood-forming) cell development is an area of development that is highly susceptible to variation during evolution.

This talk will focus on the earliest steps by which T cells of the immune system acquire their identity and become distinct from multipotent progenitor cells. This process depends on two context-dependent transcription factors, GATA-3 and PU.1, which work in intersecting ways to initiate the T-cell program, but have quite different roles when they work in programs to generate other cell types. Although these factors can act as antagonists, they can also collaborate in this early process. We will discuss how these factors find their target genes in the genome, how their activities are shaped by external signaling to the cells, and how their expression and activities become constrained, both by each other and by the results of their own actions. A crucial feature is the importance of the overall regulatory state, signaling environment, and developmental history in order to predict the range of actions that these ‘‘master regulators’’ can actually undertake.

Diethard Tautz, Max Planck Inst. For Evolutionary Biology

From Genes to Shape - approaching the genetic basis of complex traits involved in cranial morphology

Our understanding of genetics is anchored in the Mendelian Laws that describe the inheritance of traits caused by single genes. However, most traits of adult organisms are influenced by more than one gene. They are called "complex traits" with a "polygenic basis". The first attempts to grasp the inheritance laws for complex traits date back into the early last century, but it seems

fair to say that we have still not made much progress. Now, where we have access to all genes in genomes, we still struggle to find out how they work together to produce a complex trait. There are two major competing models, one which assumes a few major loci plus many minor ones, the other assumes an "infinite" number of minor loci interacting with each other. It is even not yet clear whether there is a predominant additive action of these loci, or whether epistatic interactions driven by different allelic combinations of loci play a major role as well. It will be one of the largest challenges of genetics in the coming decades to understand the genetic basis of complex traits. We have started to analyze the genetics of cranial shape in mice as a model trait with special relevance in evolution, since cranial shape changes are a major factor for ecological specialization of mammals. I will report on aspects of our work, with a special emphasis on unravelling the genetic architecture of complex traits.

The Jacques Loeb Centre for the History and Philosophy of the Life Sciences,
Ben-Gurion University of the Negev, P.O.Box 653, Beer Sheva 84105, Israel.
Building 39, room -112, phone +972-8-6472258, jloebcentre@bgu.ac.il, http://in.bgu.ac.il/en/loeb