

**Editorial****Tribute to Promethean thinker — *in memory of Susumu Ohno*****Sergei N. Rodin, Editor\*****Arthur D. Riggs, Co-Editor-in-Chief**

Susumu Ohno occupies a special place even among the most inventive and original thinkers of the 20th century biology. On February 1st 2008, he would be 80 years old; it is precisely on this day that Dr. Ohno's colleagues and friends gathered to pay tribute to his genius and numerous achievements. Dr. Ohno's career is virtually inseparable from the Beckman Research Institute of the City of Hope (Duarte, California); thus, it seems fitting that the tribute was realized as the special Beckman symposium entitled *Emergence of the genetic code, genomes and epigenomes (in memory of Susumu Ohno)*.

In this time of ever-more-overspecialized researchers, Susumu Ohno was a remarkable exception. The range of his professional curiosity knew no limits. It has been said about Mikhail Lomonosov, the de facto father of modern Russian science, "... he [Lomonosov] was a founder of our first University

...to be more precise, he WAS our first University" (Alexander Pushkin). Dr. Ohno was just like that, a true renaissance (or age of enlightenment) man, a man of encyclopedic interests and knowledge.

This said, he was also a man of focus, rigour and parsimony. Susumu Ohno was partial to the idea, put forward by the contemporary philosophers and historians of natural sciences (see, for example, Prigogine, I., Stengers, I., 1984. *Order Out of Chaos*. Bantam Books, New York, 349 pp) that the most powerful discoveries are the "set-back" ones, *i.e.* the discoveries that effectively ban, or inhibit, the concepts that appeared to be well-established, unshakeable, and "self-evident" before. For example, in physics, any conceptual revolution (or paradigm shift) has always been directly linked to a new ban / inhibition of some sort (*e.g.*, the second law of thermodynamics, inability to transmit information faster than the speed of light,



Dr. Susumu Ohno

uncertainty principle, *etc.*). In context of scientific research such bans are in fact very productive, for they "cut off" the nonsensical potential research venues, thus allowing us to concentrate our time, energy and resources along the "allowed" research directions. Susumu Ohno felt very strongly that theoretical biology, being much "younger" than theoretical physics, has not yet developed such a well-defined, powerful and logical "immune system", able to rapidly and painlessly separate research wheat from research chaff.

Susumu Ohno, D.V.M., Ph.D., came to United States from Japan as a postdoctoral fellow, and soon emerged as a scientist with international reputation and influence. The scope of his research interests was vast. His first project (while still in graduate school) was related to immunology, and he never lost interest in this subject, culminating in his work on the evolution of the immune system. At the City of Hope, his early work on using cytology techniques led to increased interest in chromosomes and, subsequently, to the first major milestone of his illustrious career --- discovery of X chromosome inactivation (1959). This discovery was a harbinger of the exciting (and currently flourishing) research area of epigenetics and epigenomics.

Reflection on chromosome and genome size evolution led, in 1971, to the publication of Susumu Ohno's seminal monograph (and arguably his greatest achievement, at least from the possibly biased viewpoint of this evolutionary geneticist) entitled *Evolution by Gene Duplication*. Thirty-six (and counting) years later, in our "post-modern" epoch of successfully realized human (and other species) genome projects, it is virtually impossible to find a research paper on the evolution of multigene systems and whole genomes that does *not* reference the above classic.

Another fundamental aspect of evolution that fascinated Dr. Ohno (fitting his interest in aforementioned "set-back" discoveries) was the "hindsight evolution" principle --- the natural selection is strictly a tactical, "here-and-now", force. As such, it never works in advance, never knows of any long-term strategy and has no foresight to meet the future demands. In this regard, the numerous origin(s)-associated paradoxes of the "chicken-or-egg" variety particularly intrigued him. The absurdity of the "evolutionary foresight" was always obvious to Susumu Ohno, whatever biological system of increasing complexity and uncertain origins would capture his mind and imagination at the time -- from the tRNA cloverleaf as the genetic code adaptor to the enzyme that detoxifies atropine in the wild rabbit of Spain (*Oryctolagus cuniculus*) to the incredible complexity of the ribosome to the self-nonsel self discrimination in the immune system.

In Greek mythology vernacular, which Dr. Ohno liked to use, evolution works as Epimethius (who has hindsight only) rather than his brother Prometheus

(endowed with foresight). However, if we consider evolution of knowledge, it appears that Susumu Ohno *himself* belonged to that rare group of thinkers whose Promethean ideas not only fail to fade out but, on the contrary, tend to shine even brighter with progression of time, as if he did indeed possess the foreknowledge of the future challenges of science. The X chromosome inactivation, the leading role of gene duplications in evolution of novelties and the intriguing repetitive pattern in gene sequences likely preserved since primordial RNA life are but three examples of Dr. Ohno's incredible foresight that immediately occur to any theoretical geneticist. There are more.

During the last 10-15 years of his career, having made significant contributions to such diverse fields as genetic predisposition to cancer, self-nonsel self discrimination by the immune system, *etc.*, Susumu Ohno's primary interests shifted towards understanding the origins of the genetic code and translation machinery. As a part of that research, he found many singular internal periodicity patterns in various genetic sequences, and somehow even managed to translate them into the musical notation. In his opinion, the beauty of these basic repeating motifs might have reflected the primary modules of emerging bilingual (built of nucleic acids and proteins) life. Thanks to the genius and whimsy of Susumu Ohno, today we can enjoy this ancient beauty not only by observing it in sequences but even by actually *listening* to it!

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During the morning session of the Beckman symposium, three of the presenters, namely Ernest Beutler (Scripps Institute, La Jolla, USA), Bruce Cattanach (Mammalian Genetics Unit, MRC, Harwell, UK) and Melvin Cohn (Salk Institute, La Jolla, USA) reflected, among other things, on the aforementioned "foresight" of Dr. Ohno's many and diverse contributions.

Dr. Beutler's talk centered on the phenomenon of G6PD inactivation, in historical context. G6PD inactivation is a phenomenon of major public health importance, and thus its molecular and, eventually, epidemiological understanding was absolutely crucial. And it was Dr. Ohno's X-inactivation work that both contributed to, and benefited from, that understanding. Now we, of course, know the trait is X-linked, and only one X-chromosome remains active. We owe that knowledge to the early-60s Beutler-Ohno collaboration.

Dr. Cattanach's talk unfolded a fascinating story of how we arrived from the early hints and puzzles to the modern, comprehensive (but still evolving) understanding of the mechanisms and consequences of imprinting. One of the milestones along this journey was the seminal 1962 work by Ohno and Cattanach

in which they demonstrated a cytological proof of X-inactivation hypothesis in mouse.

In his presentation, Dr. Cohn concentrated on the conceptual and mechanistic logic of the immune system, and how it must have been necessarily shaped by the evolutionary pressures and considerations. More quantitatively-minded members of the audience especially enjoyed his description of the immune response simulator, a sophisticated computational modeling software package developed and maintained by Dr. Cohn's group.

In the afternoon session of the symposium, the discussion was continued by Paul Schimmel (Scripps Institute, La Jolla, USA), Sergei Rodin (Beckman Research Institute, City of Hope, Duarte, USA), Takashi Gojobori (Center for Information Biology National Institute of Genetics, Mishima, Japan) and Kenneth Wolfe (Trinity College, Dublin, Ireland).

In his talk, Dr. Schimmel explored an intriguing connection between, on one hand, origins of the genetic code, its possible precursor in the acceptor stem of tRNA and translation machinery and, on the other hand, certain human diseases --- the somewhat unexpected link being provided by the aminoacyl tRNA synthetases. The latter, in addition to their protein synthesis responsibilities, are also procytotoxins, thus being of potential importance in angiogenesis.

Dr. Rodin continued the aminoacyl tRNA synthetases theme, touching upon the genetic code, two classes of synthetases and primordial complementarity-based link between the acceptor and anticodon domains of tRNA molecule. Vestiges of this link can still be detected in extant synthetases and tRNAs. Dr. Rodin combined the above into a theory of genetic code origin, with roots in the mid-90s Rodin-Ohno's hypotheses of the dual complementarity and the concerted origin of two synthetase classes from sense-antisense strands of same ancient gene.

Dr. Gojobori reflected on both his personal memories of Dr. Ohno, and on modern interpretation of some of the Dr. Ohno's evolutionary ideas in light of the massive amounts of genomic sequences available for analysis today. Specifically, he concentrated on the genomic evolution of neural genes, presenting massive composite phylogenetic trees thereof. This was of a special interest to the phylogenetic analysis / bioinformatics researchers in the audience.

Last but most certainly not least, Dr. Wolfe talked about eukaryotic genomic evolution and polyploidy. Until

recently, the latter, including full genome duplications, was considered to be an important factor in plant evolution, but recent evidence suggests (in a full accord with Ohno's ideas) that it might be a relatively common phenomenon throughout eukaryotic kingdom in its entirety. Dr. Wolfe ended the afternoon session on a somewhat lighter tone, noting that some first and foreign-language editions of *Evolution by Gene Duplication* nowadays fetch more than 500 Euro on eBay.

In summary, a beautiful day and gathering in memory of Susumu Ohno, enjoyed by all. We would like to extend our special acknowledgements and gratitude to the Beckman Research Institute of the City of Hope, for sponsoring and organizing the event; to the speakers, who graciously found time in their busy schedules to join us in this celebration; and to Midori Ohno, for providing many pictures and materials.

## **Appendix:**

### **Emergence of the genetic code, genomes and epigenomes**

--- in memory of Susumu Ohno ---

(Beckman Research Institute of the City of Hope, Duarte, CA, USA; February 1, 2008)

#### **Morning session**

Arthur D. Riggs: 10 min

Ernest Beutler (*Scripps Institute, La Jolla, USA*)

#### **G6PD Deficiency**

Bruce Cattanach (*Mammalian Genetics Unit, MRC, Harwell, UK*)

#### **Events leading to the discovery of imprinting**

Melvin Cohn (*Salk Institute, La Jolla, USA*)

#### **The logic of immune behavior**

Paul Schimmel (*Scripps Institute, La Jolla, USA*)

#### **Genetic Code Development and Connection to Disease**

Sergei Rodin (*BRI COH, Duarte, USA*)

#### **One ancestor for two codes**

Takashi Gojobori (*Center for Information Biology National Institute of Genetics, Mishima, Japan*)

#### **Genomic evolution of neural genes in light of Ohno's view of biological order and disorder**

Kenneth Wolfe (*Trinity College, Dublin, Ireland*)

#### **The impact of polyploidy on eukaryotic genome evolution**

(\**Theoretical Biology, Beckman Research Institute of the City of Hope; 1500 E. Duarte Road, Duarte, CA 91010-3000, USA. e-mail: srodin@coh.org*)