PostGenetics - Genetics beyond Genes formally abandons "Junk" DNA for the PostModern era

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The term 'Genetics' was not coined until 1905 *(G1)*, but the pre-classical era of Genetics began with Mendel 40 years earlier (1865, *G2*). The age of classical genetics in the first half of the 20th Century yielded to the Modern era of molecular genetics by discovery of the structure of DNA (1953, *G3*). Then followed two decades of intensified focus on protein coding DNA.

The term "Junk" DNA, originally coined by Ohno (1972,*G4*) to describe repetitive satellite DNA elements, became a generic term for non-protein coding DNA. With coding regions appearing to occupy <5% of the human genome, the majority 95+% of "Junk" DNA was largely ignored as unpromising terrain for inquiry. The discovery that extensive tracts of non-coding DNA divide the protein-coding sequences of eukaryotic genes into modules saw introns added to the catalogue of "Junk" DNA *(G5)*. For the last quarter of the 20th century, the dismissive epithet "Junk" stifled research that might have revealed, much earlier, the true nature of the genome's apparent "Sahara". While a geno-centric period of the genome has been highly fruitful, science historians a century hence may marvel that so much was achieved in ignorance of the "Junk DNA", beyond genes *(WR),* preserved in large chunks through the emergence of species *(WR6,10,11).*

With completion of the Human Genome Project, first announced in 2000, "Junk" DNA was found to comprise 98.7% of the sequenced genome, with only an estimated 26,000-30,000 genes comprising the 1.3% protein coding sequence. The Human Genome Project failed to meet the expectations of those who sought a genic explanation of genetic risk to many common diseases. Recent large-scale promoter analyses *(G6)* and comparative genomic studies of human, chimpanzee, and mouse genomes *(WR9,G7)* have revealed similar proportions of non-protein coding "Junk" DNA to protein coding exons. The Chimpanzee Genome Project revealed that the differences between humans and their closest higher primate relative reside largely in non-coding DNA, not in genes. Epigenetic factors governing chromatin structure *(G8)* and the emerging role of non-coding RNAs in human diseases *(G9,10)* contributed to Science concluding on 11 August, 2006 that "by the time of an updated edition of 'The Biology of Cancer, 'the concept of Junk DNA may have been abandoned altogether' *(G11).*

Indeed, it was. We established the International PostGenetics Society (IPGS) in 2005, a century after Bateson coined the term Genetics, to give priority by an International Organization to inquiry beyond protein-coding genes, by formally abandoning "Junk DNA". At our European Inaugural Conference October 2006, *(BP),* IPGS asserted that Genetics had moved beyond Genes, opening the gateway towards unravelling diseases beyond the gene definition as priority by funding agencies and other organizations. This paradigm shift affects information technology, nanotechnology *(W7)* and above all "PostGenetic Medicine" – vital for a vast segment of humanity. The IPGS proposes a transdisciplinary effort, with policies suitable to accelerating awareness and understanding the pathogenesis of non-coding DNA diseases. The territory of PostGenetics is inclusive of all DNA sequence since evolutionary processes are no respecter of whether RNA coding is a functional event in itself or proceeds to protein synthesis.

IPGS, with 44 Founders[1], and members from 33 countries, have expertise in the wide range of disciplines encompassed by PostGenetics (including information science, nanotechnology, agriculture, as well as biogenetics). In particular, for PostGenetic Medicine IPGS advocates substantial increases in funding and focused resources R&D of non-coding DNA, because of the potentially enormous health, social and economic benefits, with new technologies emerging from it. IPGS with its conferences *(BP)* and proceedings *(PR),* serves governments and the private sector by offering their expertise to formulate policies *(PR6,7).*

The IPGS originator[2] and several Founders have successfully implemented an earlier paradigm shift that provides a precedent for the transformation of Modern genetics to PostGenetics, beyond genes *(G12).* From the mindset of "Artificial Intelligence (AI)", without mathematical understanding of Central Nervous system function, they promoted the required inversion of priorities. This created the field of "Neuronal Networks" (NN, *G12)* with its priority aim of first explaining brain function, and next to policies leading to applications *(G13).*

Similarly, from the mindset of gene-based genetics, understanding of the human and other genomes was assumed to be possible dismissing most of the DNA. With this axiom becoming dogma, as a first priority, the IPGS proposes to launch a "PostGenetics Study Program" and the emergence of "PostGenetics Centers" to implement programs specified by policies.

The scientific reward of putting first priority on the overwhelming majority of the DNA will be a more complete understanding of the genome that will benefit millions worldwide. PostGene discovery must be ramped up to study diseases associated with non-coding DNA, and develop and develop novel diagnostic tools and therapies. Until now, protein-based Nanotechnology (*G15*) and next-generation information-technology have lacked the comprehensive view of the genome required to develop a solid theoretical and mathematical basis for new technologies. Both should benefit from the quantum increase in information yield that the post-genetics era promises.

Geographical trends in PostGenetics are characteristic to paradigm-shifts. Advocacy for "non-coding DNA" originated in Australia *(G16,17),* but is now a global movement. Many lesser endowed regions and countries are leapfrogging directly into the PostModern continuation of Genetics. This is analogous to developing nations skipping landline telephones by entering the "cellular" digital age. The IPGS, established in the USA, involves countries with widely different dynamics, e.g. China, Croatia, Estonia, Hungary, India, Israel, Mali, Singapore. Paradoxically, for countries with greater momentum it is relatively more difficult to accommodate a paradigm-shift, while frugal agility is actually helpful. For instance, Hungary intensified micro-RNA studies in melanoma *(PB6,PR13,G18)*, and identified Fractal sequence patterns in asthma susceptibility regions *(PR5).* Croatia, while not yet a member of the European Union (EU), has its National Genomic Program integrated with the EU PostGenetics Program *(BP3).* The USA and other established gene-focused countries might be influenced by non-scientific issues, including belief systems. IPGS will resolutely focus on high-quality science, capable of experimentally verifying or refuting its hypotheses concerning non-protein coding DNA *(WR7).*

Policy for PostGenetics Study Programs. The fields of expertise of the IGPS founders [1] reflect the interdisciplinary nature of the paradigm shift, and its potential to provide new and fundamental insights in Genomics, Medicine, Mathematical- and Information Science and Technology, Agriculture and Nanotechnology. For example, one enigma in Genomics is "complexity" *(G19).* RIKEN's initiative to functionally annotate mouse cDNAs shows complexity can be reduced by systematically identifying and characterizing coding and non-coding gene products *(G20).* At the European IPGS Inaugural, one presentation, "DNA-crossing loops" described how intergenic or non-coding DNA added a twist to current approaches to understanding complexity *(BP7,PR4).* Beneath the description of "complexity" lies the question of the intrinsic mathematical language of DNA. This question

attracted IPGS Founders[1] with expertise in neural networks, machine learning, information theory, and computer sciences, to interpret how scale-free, self-similar structures of DNA embody instructions. Computational approaches are yielding "IT tools". For instance, application of the "FractoGene" algorithm was developed to explore the causal connection between genome fractality and that of the mechanisms of biogenesis *(WR7).* Recent work suggests short, repetitive sequences may provide insights into the mathematical characteristics of "compositional patterning" of DNA *(21).* The review *(WR7)* is also relevant to a role for non-protein-coding DNA in protein-based Nanotechnology. Nano-engineering of new materials *(G15)* requires that even the simplest DNA contain a small percent of non-coding DNA with embedded fractal elements capable of driving recursive, iterative processes *(BP1).*

Policy towards PostGenetics Medicine. Increasing evidence for diseases originating in non-protein coding DNA *(G10)* requires an urgent PostGenetics Study Program, leading to substantial increase in organizational and funding support for R&D in the field *(PR6,7).* Government initiatives already launched permit, albeit not mandate, "going beyond genes" e.g. ENCODE *(G22),* but programs shall focus more than encyclopedic knowledge, also on algorithmic understanding. The IPGS has proposed USA and Asia-Pacific Inaugurals to generate scientific, political and community awareness of the potential of PostGenetics research to throw new light on common and rare "non-coding DNA" diseases. Powerful tools gene discovery and analysis developed over the past 35 years have transformed medicine; post-genetics now promises to give the revolution new impetus.

Below, "intramural" efforts by IPGS Founders[1] provide illustrative approaches towards PostGenetics Medicine.

Alzheimer's and Parkinson's diseases (AD, PD), two leading neurological disorders, may have a PostGenetics component *(PR1,PR9,G23,24,G42).* While malfunctions of the beta-Amyloid precursor, presenilin-1 and -2 genes, and the presence of epsilon4 allele of apolipoprotein E, are known risk factors for susceptibility to AD, not all studies support gene associations with AD *(G25)*. Reports do not fully support involvement of the coding portions of the K-variant of BChE and the coding ChAT *(G26).* In PD, the dinucleotide repeat sequence of the SNCA promoter was associated with susceptibility *(G42)* as found in a fractal structure *(PR9).*

Psoriasis, Asthma, MHC/HLA. The inadequacy of the gene paradigm is most evident in the Major Histocompatibility Complex and its association with allergy and autoimmunity *(BP2,G24,27).* MHC comprises 220+ genes with so far about 100 human diseases associated with the MHC/HLA complex. For all, with one possible exception (celiac disease), the mechanisms underlying the associations remain unknown. Intensifying search for only coding sequencing may be insufficient, if not misguided. A new emerging paradigm is that non-coding sequences and "Junk DNA" through regulating higher order DNA structure (e.g., fractal structures) contributes together with HLA gene polymorphisms in regulatory T cell (Tregs, CD4+CD25+FoxP3+) function in allergy and autoimmunity *(BP4,PR2,PR5 G24).*

Epigenetics and HIV/AIDS/NeuroAIDS. Reviews *(PR1,G23)* point to a promoter binding of cytokine genes by transcriptional repressors as instances of non-coding involvement in immunogene function *(G28)*. Other biological molecules might bind to chromatin elements, influencing function by altering structure. Insertions by viruses including retroposons may disrupt genomic sequences, chromatin integrity, and brain function.

Muscular Dystrophy. *(BP5,PR3)*. Sequence analysis of dysferlin cDNA identified a heterozygous substitution C to T at position 5302 of DYSF, which resulted in an amino acid change Arg to Trp at position 1768 of DSYF highly conserved protein sequence. In the homozygous form, mutation has been reported to cause Miyoshi myopathy, an allelic variant of LGMD2B. The presence of the pathogenic mutation in only one allele of the cDNA of the dysferlin gene, and the absence of the dysferlin in the skeletal muscle, directs attention to the role of non-coding DNA**.**

Non-coding DNA/RNA in Cancer. *(BP6,G18)*. Non-coding RNA has made an appearance as a critical factor in cancer initiation and progression *(G29,30)*. Three key areas are emerging: (1) The role of non-coding (nc)RNAs (ranging from microRNAs of 21-25 bp to small RNAs of 100-200 bp to large RNAs of 10,000 bp or more), involved in RNA interference, gene co-suppression, gene silencing, imprinting, and DNA methylation *(G31,32)*. (2) Mutations and rearrangements in non-coding mitochondrial DNA such the mtDNA D loop are found in some carcinomas that may regulate apoptosis susceptibility *(G33,34)*. (3) Polymorphisms in non-coding regions sometimes far upstream of exons that regulate gene expression and translational initiation *(G35,36)*. An increasing number studies are showing deregulation of microRNAs in cancer associated with loss of suppressor gene function or gain of oncogene function that are associated with patient prognosis *(G37,38)*. In addition, non-coding RNAs have been shown to contribute to embryonic and tissue stem cell fate *(G39,40)*, and we predict that they will also be found to regulate the fate of tumor stem cells or "tumor-initiating cells" in cancer.

Time to Act. The burgeoning evidence for non-coding DNA/RNA governing growth and differentiation clearly indicates that it is time for the USA and associated world agencies to develop focused PostGenetics R&D policies, such as the IPGS-proposed "PostGenetics Study Program", Journal and Conferences, to propel the former field of "Junk DNA" into a new functional realm, coordinating individuals, organizations and disease awareness advocacy groups. This PostModern expansion of Modern Genetics will accelerate understanding of human diseases and benefit the world.

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