Opinion

Shifting the therapeutic paradigm in medicine from post mutational (& pathological) intervention to preemption – a synopsis of the 'nuts and bolts'

Abstract

Contemporary Paradigms in Medicine while having positive dimensions do make an insidious impact on Humans as well as on Healthcare and Socioeconomics. To meet these challenges it is necessary to restructure the fundamental paradigm of Medicine from therapeutic intervention that is exclusively post-mutational (pathological) to one that includes a long term strategy permitting ***Preemption in Real Time***. ***Preemption*** can eventually be accomplished by melding historical methods and principles of Evolutionary Genetics, specifically ***Interspecific Hybridizations***, with the efficiency and resolving power of contemporary methods. The strategy in this undertaking is a ***Combinatorial Approach*** which melds two lynchpin but broadly overlapping phases under an operational umbrella for a multiplicity of parallel and multi- directional approaches. This is accompanied by ***Real Time*** (continuous and simultaneous entry) recording of emerging data and results into appropriate pre-allocated categories in Super - computers.

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Introduction

The first broad ***Discovery Phase*** draws on the Evolutionary Genetics of Speciation (EVS) known to elevate the frequency of genetic lesions in ***Interspecific (or Hybrid) Genomes*** that have direct mechanistic and physiological relevance. Its principle is based on Darwinian Natural Variation (DNV) in the Genetic regulation of ***coevolved*** Genes maintaining and repairing the Genome and inserting lesions when they fail (refs therein).[1–6] It is irreplaceable by any of the contemporary methods. These ***Interspecific Genomes*** e.g. of mice are the only comprehensive source of relevant mechanisms, molecules and Genetic Networks inserting lesions into the Genome collectively constituting the ***Mutome*** (refs therein).[1–7] The second but overlapping and broad ***Analytical Phase*** applies contemporary methods including OMICs, Imaging, Optonics, Photonics, and Biosensors, Single Cell/ Molecule and Atomic scale Analyses, Communications via Nanobots Radio waves, Cyborg assembly and analyses by Super-computing followed by reverse flow of corrective commands to cells (refs therein).[6,7] The ***Analytical Phase*** is obligatorily informed by the nature of results emerging from the ***Discovery Phase*** with both consisting of broadly multi-phasic progressions and course corrections in parallel. For example results from ***Interspecific*** mice and their DNAs from the initial ***Discovery phase*** are entered into tiered arrays of computers or Super-computers while the ***Analytical Phase*** is being initiated. The ***Combinatorial Approach*** comprising of both (***Discovery*** and ***Analytical Phases***) will culminate in the ***Systematization, Surveillance and Control of Networks*** (molecules and mechanisms) ***of Genes Regulating and Maintaining Mammalian Genome Biology in Real Time*** and eventually enabling the ***Preemption*** of thousands of Human Genetic Disease Lesions (refs therein).[6,7] A broad schematic diagram or a flow chart could be:

(1) preparative ***Organizational Phase*** <-> -> (2) initiation of parallel and multidirectional ***Discovery Phase*** (mice) <-> -> (3) Super-computation <-> -> (4) overlapping, progression into, parallel and multidirectional ***Analytical Phase*** <-> -> (5) Super-computation <-> -> (6) ***Operational Phase*** in mice (7) translation of results and systems to humans <-> -> (8) Super-computation <-> -> (9) ***Operational Phase*** in humans <-> -> (10) ***Preemption*** of Genetic Disease Lesions

The scale, nature and dynamics of the working hypothesis of the ***Combinatorial Approach*** are mirrored in other similar undertakings in the Life and Physical Sciences. The principles of relatively unknown input components, processed by unknown processes and yielding unknown output products resolved by computational or Super-computational analyses are shared with comparable endeavors in the Life and Physical Sciences. These include next generation sequencing (NGS), mapping of Connectomes, discovery of Sub-atomic Particles in Particle Accelerators (e.g. the Large Hadron Collider), mapping of Tectonic Plate movements or Weather Patterns and Exploration of Space. While the technical, conceptual, scientific, ethical and economic challenges are daunting, they are not insurmountable. It is the Culture of Science as defined by Dr. Albert Einstein and reflected in the resistance to the work of Dr. Barbara McClintock, Dr. Robert Oppenheimer and Dr. Andrei Sakharov that remains the single most significant barrier to initiating this endeavor (references therein).[7–10] Based on projections of Economic and Health Budgets ***Preemption*** ameliorates hundreds of trillions of dollars per annum while representing the only ***'real cure'*** for intractable and dehumanizing diseases! While the technical, conceptual, scientific, ethical and economic challenges are daunting, they are not insurmountable. Very simply put these results cannot by definition ever emerge if this undertaking were not initiated. We address challenges to the ***Combinatorial Approach*** by reviewing select segments of the Classical and Contemporary literature that are directly relevant to the undertaking and then presenting an approach in the eBooks (ref 6 – 7 accepted).[6,7]

Synopsis

More than 13,700 genetic diseases are entered into the database represented in MIM and OMIM.[12,13] More recently based on re-purposing of health insurance data on 560 diseases it is projected that 65% of all diseases either have a genetic (40%) or a genetic and

environmental (25%) basis.[14] The projected Economic costs of only 5 of these diseases over a 20 year period from 2010 – 2030 range from $47.3 to $63 trillion.[15,16]

The etiology of these diseases are sharply demarcated by the sequential events preceding and following the insertion of Genetic Lesions (mutations) into the Genome. These genetic lesions, their pre - mutational components and complexes constitute the human ***Mutome***. Current paradigms in Medicine are confined to post – mutational therapeutic intervention which is often too late for extracting positive outcomes in refractory diseases e.g. some cancers and neurodegenerative disease(s). However, Genetic Lesions and the ***Mutome*** can be ***Preempted*** by establishing a system of ***Surveillance*** and ***Control*** of networks of ***Genes*** maintaining the human ***Genome*** in ***Real Time.*** Components of networks of Genes maintaining Chromosome (Genome) Biology and Genome Biology are evolutionarily conserved, from bacteria to humans and include protective genetic systems specifically designed to restrict (exclude) interspecific DNA from cross-contaminating genomes. However, as predicted by Darwinian Natural Variation (DNV), they display differences in structural and functional characteristics that can be genotypic and phenotypic. In interspecific genomes including between 2 species of mice which populate ***Natural Hybrid Zones (NHZ)*****,** DNV likely induces the well-established spectrum of Genetic Lesions at high frequencies (up to 10^6x > Neutral Mutation Frequency (NMF) (ref therein).[1–7] The lesions are of a broad spectrum and representative of most or all human genetic disease lesions (ref therein).[1–7] They can therefore be identified by non-selective '***Panning***'. They define the ***Spectrum of High Frequency Serendipitous Subversions of Chromosome* (*Genome*) *Biology* (*SHFSSCB*)**. Due to DNV of networks of Genes ***NHZ-SHFSSCB*** ostensibly uncouples or induces failure of ***co-evolved*** regulator (or structural) genes from regulated (maintained) sequences or loci and so this approach is necessarily relevant, representative and comprehensive for the ***Discovery Phase*** of mechanisms revealing the ***Mutome*** (ref therein).[1–7]

Of importance for '***Panning***' as well as for mechanistic relevance they are inserted by failures of Genes in ***coevolved*** sequences that are resident at their native loci as well as with Genome coverage ranging from 10^4 to 2.5 x 10^5 orders of magnitude per nucleotide (based on clines of 1 of 6 known ***NHZ***) (ref therein).[1–7] The estimated global population size of interspecific mice in ***NHZ*** as well as their molecular, cellular and genomic components including cellular chimerism ensures saturation of the ***Mutome*** content with a minimum genome coverage of 10^4x orders of magnitude per nucleotide per ***NHZ*** (ref therein).[1–7] Subversion or failure of endogenous and ***coevolved*** regulator and regulated Genes for maintenance of the Genome is a key difference between ***NHZ-SHFSSCB*** and contemporary methods such as *CRISPR/Cas9-Pam* which involve exogenous bacterial enzymes (ref therein).[1–7]

The resultant ***Mutome*** is subsequently screened by non-selective and low resolution '***Panning***' of the coincidental mutagenesis of contiguously encoded genes or sequences. These include documented traits of known susceptibility to underlying mechanisms of dys-functional Chromosome Biology revealed by e.g. visual inspection of coat colors, sex, anemia, either hybrid vigor or inviability, sterility and indicators of other parasitic infection and pathological symptoms (ref therein).[1–7] This in principle is similar to the application of single nucleotide polymorhisms (SNPs) underlying discovery of interactions of unlinked Genomic loci in specifying traits by Genome Wide Association Studies (GWAS) (ref therein).[1–7] Unlike contemporary methods involving mutagenesis, selection and screening, detection of products generated by ***NHZ-SHFSSCB*** by non-selective '***Panning***' reveals mechanisms that are relevant to assembling the ***Mutome*** and insertion of Genetic Disease Lesions. Although contemporary methods such as *CRISPR/Cas9-Pam* are of higher efficiency, resolution, power and broader applicability, which may be useful in the subsequent ***Analytical Phase***, they cannot recapitulate mechanisms for generating and processing the ***Mutome*** into lesions. Genetic Lesions inserted by ***NHZ-SHFSSCB*** are both revelatory as well as being a source of causal pre-mutational molecules, genes, networks, physico-chemical-biological forces and mechanisms assembling the ***Mutome*** (ref therein).[1–7]

NHZ-SHFSSCB mechanisms as well as the ***Mutome*** can be further characterized by the power, precision and resolution of an array of contemporary ***Physico-Chemical-Biological-Methods* (*PCBM*).** The specific choices of ***PCBM*** or methods are of necessity informed and directed by emerging results such as the nature of lesions, genes, loci, mechanisms and ***Physico-Chemical-Biological*** forces inserting a specific Genetic Lesion. A sampling of specific choices of ***PCBM*** include the array of OMICs, Mass Spectra, Optonics, Photonics, (MSOT/FMT/Optogenetics, Nanoscale Ultraviolet (UV) epifluorescence, Infrared (IR) autoemission analyses, atomic scale AFM/laser or atomic tweezers) and High Content Analyses (ref therein).[1–7] These ***PCBM*** are facilitated or sequentially followed by a combination of communications as well as analytical power of Radio Waves, Fiber-optics, Nanobots, derivation of Cyborg mice, ***Bioinformatics* and *Super Computational Analyses (BSCA)*** (**references therein**).[1-7] A reverse flow of commands from ***BSCA*** as well as ***PCBM*** analyses of products of ***NHZ-SHFSSCB,*** will transform ***Surveillance* and *Control of murine Chromosome* and *Genome Biology*** into ***Real Time Operations (RTO)*** (ref therein).[1–7] This now constitutes the fully operational ***NHZ-SHFSSCB-PCBM-BSCA-RTO*** in mice abbreviated to the ***Combinatorial Approach*** in mice (ref therein).[1–7]

Application of selected methods of ***PCBM*** e.g. Synteny, HapMaps, Comparative Sequencing, GWAS and Functional Genomics will ***transduce*** data, results and applications from mice to humans. As threshold(s) of data, methods, results and concepts that are already extant, either coalesce with or reinforce newly attained versions in humans, all phases of the ***Combinatorial Approach*** will become fully operational in humans as ***Real Time Operations.*** Eventually permitting the capability for ***Preemption*** of the human ***Mutome*** and so the various disease states it induces (ref therein).[1–7] This now constitutes the fully operational ***NHZ-SHFSSCB-PCBM-BSCA-RTO*** in mice abbreviated to the ***Combinatorial Approach*** in humans (ref therein).[1–7] Very simply put, as is the case with all major endeavors, these results cannot by definition ever emerge if this undertaking were not initiated.

Current therapeutic methods, such as *CRISPR*/Cas9-Pam, Immuno-therapy and induced Pluripotent Stem Cells (iPSCs) are all necessary as efficient but transitional methods (ref therein).[1–7] Each has its operational limitations (ref 1 – 7 therein). They are all ***inappropriate*** for long term therapeutic projections required for enunciating Health and Economic Policy (ref therein).[1–7] These contemporary methods are neither ***Preemptive***, nor universally applicable to all forms of genetic disease lesions and their respective pathology(s), nor relevant to the etiology of the disease ***Mutome*** (ref therein).[1–7] They are

often ineffective while confining Medicine to the paradigm of post mutational therapeutic intervention (ref therein).[1–7]

Despite largely superficial assertions of its infeasibility, rigorous analyses of the ***Combinatorial Approach*** drives home an obvious transformative impact on the current paradigm in Medicine with all its consequent Socioeconomic dimensions. This includes relieving untenable human and economic costs, rendering the ***Combinatorial Approach*** not only cost effective but also indispensable! Although the technical, scientific, conceptual, economic and ethical challenges faced by this ***Combinatorial Approach*** are daunting they are far from insurmountable. The principal barrier to instituting the ***Combinatorial Approach*** remains those of ***Scientific Culture*** as defined by Dr. Albert Einstein and reflected in the resistance to the work of Dr. Barbara McClintock, Dr. Robert Oppenheimer and Dr. Andrei Sakharov (ref therein).[8–11] Some of its many components follow.

(i)lack of exposure of significant sections of the contemporary Scientific community to the relevant classical literature documenting Evolutionary Genetics of Speciation inducing dysfunctional regulation of Chromosome/Genome biology in Interspecific genomes so as to generate components of ***Mutomes*** which are processed into Genetic Lesions; (ii) the absence of the necessary communication between Scientists of distinct backgrounds (e.g. Evolutionary Geneticists, Chromosome/Genome/Physico-Chemical/Computational Biologists and Mouse/Human Geneticists or Developmental Biologists) leading to the absence of synthesis, integration, coordination and development of requisite technologies and concepts required for ***Preemption*** of the ***Mutome*****,** (iii) confusion of technical and scientific requirements for the ***Discovery Phase*** e.g. the ***Mutome*** with those required for the ***Analytical Phase*** e.g. mapping and sequencing a Genetic Lesion or elucidating steps causing the resultant pathological condition; (iv) which has led to contemporary conditions in science lacking the necessary flexibility and indiscriminately imposing, artificial, arbitrary requirements of precision, depth, focus, stringency, immediacy, proximity and unconditional relationships between Genetic Lesion and clinical pathology (e.g. Hypothesis Driven requisites excluding the serendipity that yielded many discoveries including Penicillin); (v) only one illustrative example is that of cells harboring ***Driver Mutations*** causing cancer remaining quiescent for indeterminate periods and for unknown reasons before growing into a full blown tumors; these results lead to the confused perceptions of ***Driver Mutations*** being irrelevant for cancer as opposed to being their fulfilling some necessary but insufficient requirement; (vi) the mis-perception within the scientific community that the minimal thresholds of methods, technology and concepts required to even initiate the ***Combinatorial Approach*** are currently lacking or absent; (vii) counter-productive Socioeconomic and Sociopolitical competition among scientists precluding the collaboration necessary for implementing undertakings such as the ***Combinatorial Approach*** or for that matter progress in any field; (viii) additional examples follow in the eBook review that is submitted (ref therein).[6,7]

Summary

The prohibitive costs of ignoring issues addressed by this ***Combinatorial Approach*** for preempting the insertion of Genetic Disease Lesions and consequently, perpetuating the current paradigm of post mutational (pathological) state of therapeutic intervention are sketched.[3–6,8–11,12–17]

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Conflicts of interest

Author declares that there are no conflicts of interest.

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