Giuseppe Roberto Burgio
(Palermo 30/04/1919)
(Pavia 08/03/2015)

American Journal of Medical Genetics 100:255–256 (2001)

Ann Allergy Asthma Immunol 117 (2016) 1–8

Giants in Allergy-Immunology

Joseph A. Bellanti, MD,

Encomium

Professor G. Roberto Burgio: A Man for all Seasons

Joseph A. Bellanti*

Department of Pediatrics and Microbiology-Immunology, International Center for Interdisciplinary Studies of Immunology, Georgetown University Medical Center, Washington, DC

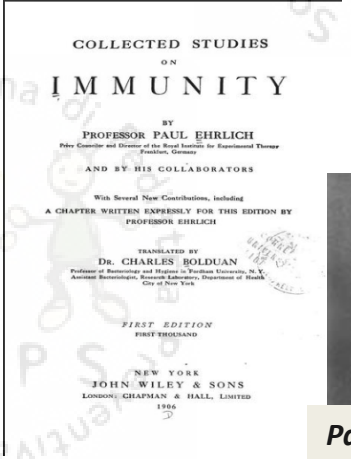
At the invitation of Professor Opitz, I am both deeply honored and privileged to present this encomium to Professor G. Roberto Burgio, an internationally renowned clinician-investigator, educator, author, mentor, colleague, and friend, and above all, "a man for all seasons." His "Living History Biography: Practicing a Culture of Pediatric Immunogenetics," which appears within the pages of this issue, is an instructive and fascinating tribute to a great man and his many important contributions over a lifetime of dedicated study and service to medicine and to humankind.

How did this tribute come about? Who is this man? What is his place in the history of genetics? Why is it important to include his biography in this journal?

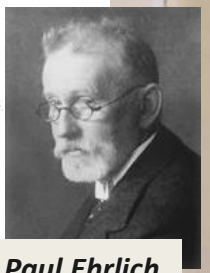
After meeting Professor Burgio and knowing of his many contributions in the fields of gonadal dysgenesis and sex differentiation, chromosomal aberrations, and immunogenetics, Professor Opitz recognized the importance of sharing the contributions of this great man with the readership of this journal.

cum laude from the University of Palermo School of Medicine, he was drawn to pediatrics, undoubtedly because of his love of children as well as the myriad of hematologic disorders and infectious diseases prevalent at that time in that place. He received his pediatric training at the Children's Hospital in Palermo where he attained the rank of Assistant Professor of Pediatrics and University Lecturer (libero docente). Under the tutelage of his chief-of-service, Professor Gerbasi, he conducted studies elucidating the role of vitamin B-12 deficiency in the pathogenesis of infant megaloblastic anemia (Gerbasi anemia), the role of vitamin K malabsorption in neonatal purpura, and studies of kwashiorkor and the immunologic sequelae of a wide variety of infectious diseases. These early studies impressed this young clinician investigator of the importance of the immunogenetic controls that were being exerted on the host in response to environmental and infectious disease stimuli.

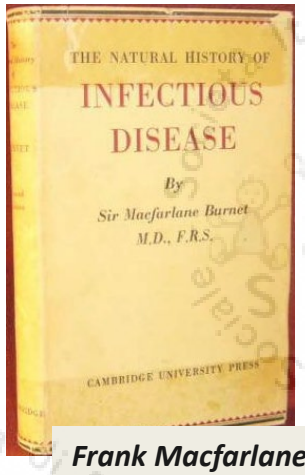
Destined for a brilliant career in academic pediatrics,



1

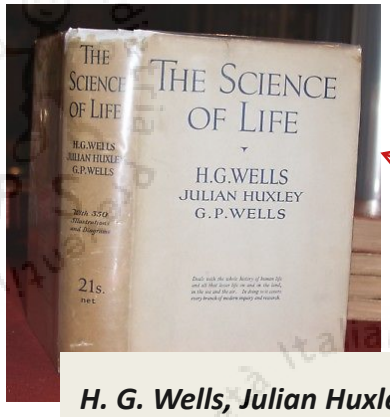


Paul Ehrlich



2

Frank Macfarlane Burnet



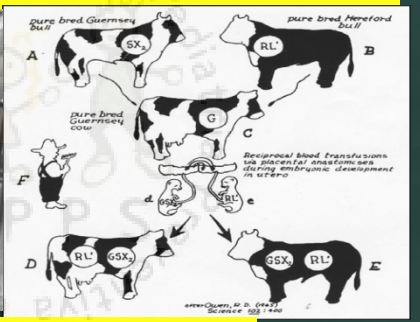
***H. G. Wells, Julian Huxley , G. P. Wells*,**

Springer Verlag (1987)

Immunology of the Neonate

3

Owen, R. D. 1945. ***Immunogenetic consequences of vascular anastomoses between bovine twins.*** Science 102: 400–401.→ ***Microchimerism***



Ray David Owen (30 10 1915 – 21 09 2014)

Burgio, G.

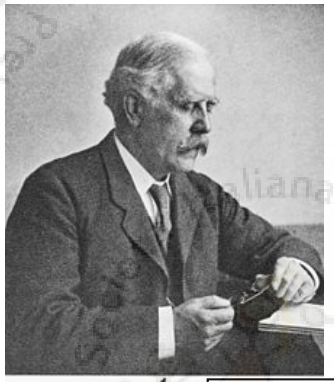
Peter Medawar

(28 02 ***1915*** *– 2 10 1987)*

La «***tolleranza immunologica acquisita***» dimostrò che le **risposte immunitarie** contro un insieme definito di agenti possono essere **abolite, o almeno attenuate**, usando un approccio biologico…

Acta Biotheretica **38**: 143–159, 1990.

THE "BIOLOGICAL EGO". FROM GARROD'S *"CHEMICAL INDIVIDUALITY"* TO BURNET'S *"SELF"*



G. Roberto Burgio
Paediatric Department, University of Pavia, Italy

"Man knows himself only inasmuch as he knows the world: he perceives the world only in himself and himself only in the world" (J.W.v.Goethe)

*L'uomo conosce **se stesso** solo nella misura in cui conosce il **mondo**; conosce il **mondo** solo attraverso **se stesso** ed è consapevole di **se stesso** solo attraverso il **mondo** (J. W. v. Goethe)*

Starting from the conceptual premises of Garrod, who as long ago as 1902 spoke of "chemical individuality", and of Burnet (1949), who recognized as *self* one's own molecular antigenic structures (as opposed to the antigenic "alien": the *non-self*), the discovery and understanding of HLA antigens and of their extraordinarily individual and differentiated polymorphisms have gained universal recognition. Transplant medicine has now dramatically stressed, within man's knowledge of himself, the characteristic of his "biological uniqueness". Today man, having become aware of being a biological antigenic-molecular individuality which is unique and different from that of all of his fellow men (except for monozygotic twins), can therefore easily consider himself a true "biological Ego".

Burgio, G.R. (1984). Die biologische Individualität. Zur Begriffsbestimmung des biologischen Ich.- Med. Welt 35: 1150.

Eur J Pediatr (1999) 158: 769–775

REVIEW

A. Martini · G. R. Burgio

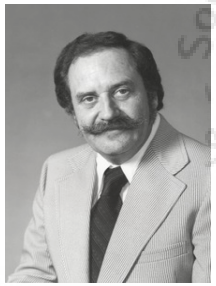
Tolerance and auto-immunity: 50 years after Burnet

Abstract Fifty years ago Sir F. Macfarlane Burnet published his first fundamental contribution to the theory of immune tolerance he perfected 10 years later. Since then an impressive amount of new information on the function of the immune system has been gathered. As any original meaningful theory, Burnet's hypothesis on the development of immune tolerance has undergone extensive modifications to take into account all these new findings. An improved understanding of the mechanisms of tolerance has led to new possibilities for the treatment of auto-immune diseases.

Conclusion All new information in the field of immune function is rooted in Burnet's contribution which set the stage for the development of modern immunology.

Key words Immune tolerance · Auto-immunity

Abbreviations *APC* antigen presenting cell · *HLA* human leucocyte antigen *IFN* interferon · *IL* interleukin · *MHC* major histocompatibility complex · *TCR* T-cell receptor · *Th* T helper · *TNF* tumour necrosis factor



ELSEVIER

EXPERIMENTAL HEMATOLOGY

Experimental Hematology 28 (2000) 479–489

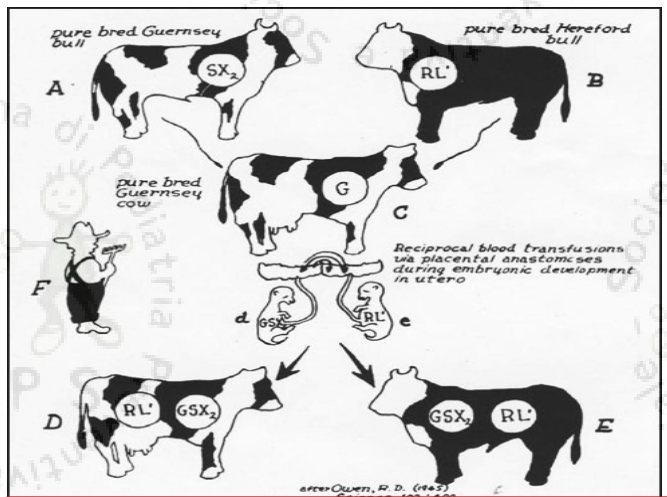
Tolerance and hematopoietic stem cell transplantation 50 years after Burnet's theory

Franco Locatelli[a], Damiano Rondelli[b], and G. Roberto Burgio[a]

[a]*Department of Pediatrics, University of Pavia, IRCCS Policlinico San Matteo, Pavia, and*
[b]*Institute of Hematology and Medical Oncology "Seragnoli," University of Bologna, Bologna, Italy*

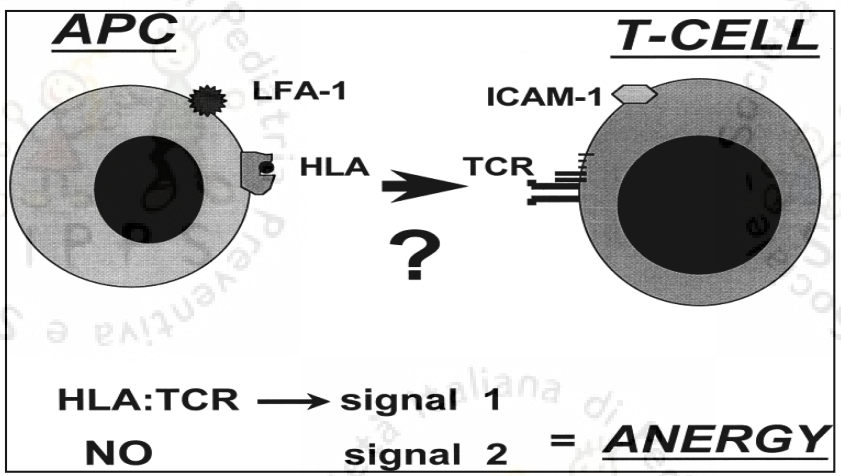
(Received 22 September 1999; revised 26 January 2000; accepted 27 January 2000)

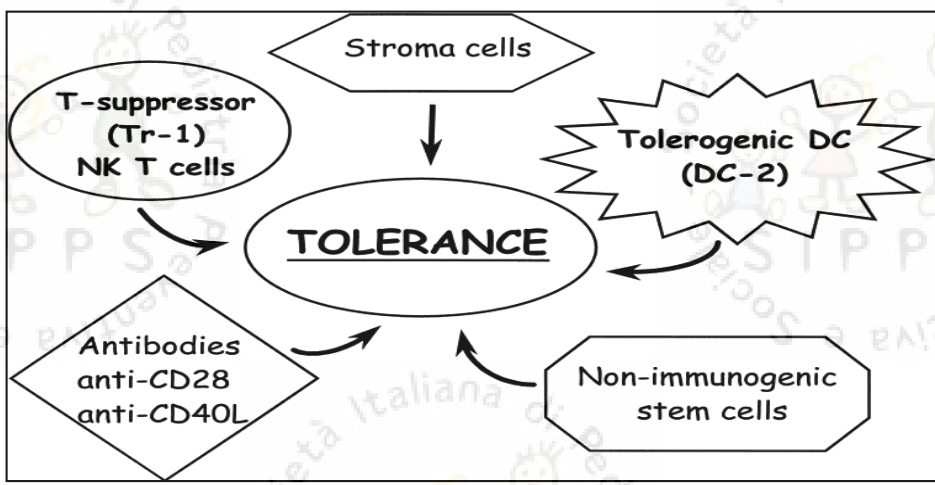
Objective. **In 1949, the original formulation of Burnet's theory on the mechanisms responsible for the capacity of the immune system to discriminate between foreign antigens (i.e., the "non-self") and the cells of its own body (i.e., the "self") was published. Since then, further refinements and reconsiderations of the basic concepts underlying the achievement of a state of tolerance toward a certain antigen have been reported. Here, we attempt to analyze critically new clinical and experimental strategies aimed at inducing alloantigen-specific unresponsiveness.**



RAY OWEN (**immunologic tolerance due to exchange of blood cells *in utero***)
Science, 102 (1945), p. 400

Induction of antigen-specific unresponsiveness through **blockade of costimulatory molecules**





Department of ethics

Lancet 2003; 361: 250–52

Ethical reappraisal of 15 years of cord-blood transplantation

Giuseppe Roberto Burgio, Eliane Gluckman, Franco Locatelli

Since the first successful use of cord blood as source of haemopoietic stem cells for transplantation in 1988, more than 2000 patients with malignant or non-malignant disorders have been treated with this procedure. Collection and storage of cord blood has prompted ethical considerations, mainly dealing with the issues of autonomy in making decisions about donation of cord blood, and of privacy and confidentiality in the tests required before use of placental cells for transplantation. The ethical implications of possible storage of cord-blood cells for autologous use has also been discussed. Preimplantation selection of HLA-matched embryos to obtain a donor of cells for cord-blood transplantation of a sibling with a life-threatening disease has raised the issue of the extent to which this approach complies with the principles of bioethics.

Potential advantages of transplantation of umbilical cord blood haemopoietic stem cells compared with bone marrow transplantation

For the donor

Easy and safe collection, without the risks associated with general anaesthesia (needed for marrow harvesting)

Lower risk of psychological disorders

For the recipient

Prompt availability

No risk of donor refusal

No donor attrition

Reduced risk of acute and chronic graft versus host disease

Possibility of transplantation with one or two donors with different HLA antigens

Low risk of viral contamination (eg, human cytomegalovirus, Epstein Barr virus)

Biological individuality and the new frontiers of immunological tolerance in hematopoietic stem cell transplantation

Giuseppe Roberto Burgio,[1] Marco Zecca,[2] Patrizia Comoli,[2,3] Rita Maccario[2,3]

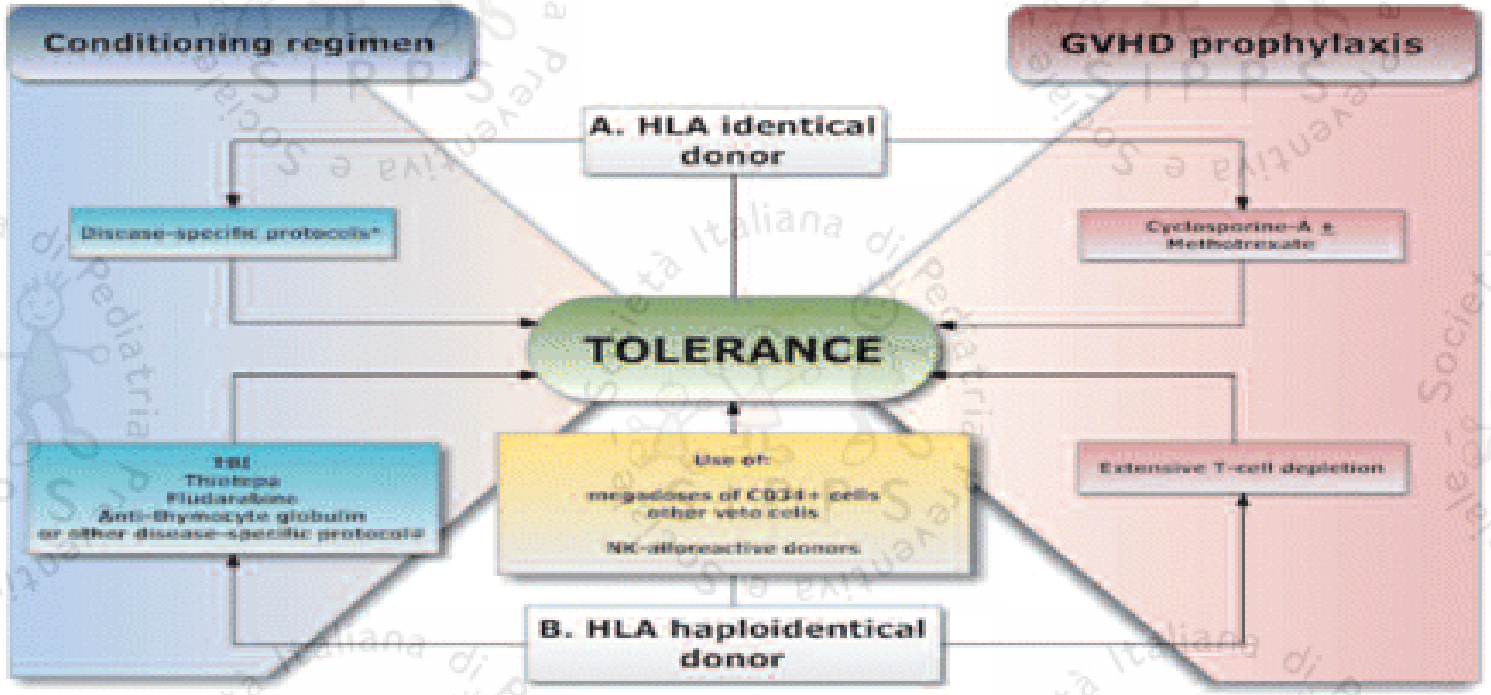
[1]Professor Emeritus University of Pavia, [2]Pediatric Hematology-Oncology and [3]Research Laboratories Fondazione IRCCS Policlinico San Matteo, Pavia, Italy.
E-mail: r.maccario@smatteo.pv.it doi:10.3324/haematol.2010.027078

Haematologica. 2010 Sep;95(9):1447-51

Hematopoietic stem cell donors: rethinking traditional choices

From the time of the first successful experiences of allogeneic bone marrow transplantation,[1,2] and during the long previous history of failure,[3] it became clear that HLA-identity/compatibility between donor and recipient was an essential condition for the success of the transplant. Such compatibility is constantly found in h
(who also have identical minor histoc
gens) and statistically in 25% of sibling

patibility was a necessary condition for the desired creation of a "biological chimera"; but transplant tolerance had to be promoted by lowering the recipient's immune response to prevent rejection, at least unless the patient was not seriously immunocompromised as, for example, in some cases of severe combined immunodeficiency. In particular, the use of total body irradiation since 1959, of



Conceiving a hematopoietic stem cell donor: twenty-five years after our decision to save a child

Giuseppe Roberto Burgio,[1] Luigi Nespoli,[2] Rita Maccario,[3] Annapia Verri,[4] Patrizia Comoli,[3] Marco Zecca[3]

[1]Professor Emeritus University of Pavia; [2]Department of Experimental Medicine, University of Insubria, Varese; [3]Pediatric Hematology-Oncology and Research Laboratories Fondazione IRCCS Policlinico San Matteo, Pavia; [4]IRCCS National Neurological Institute C Mondino Foundation, Pavia, Italy

E-mail: m.zecca@smatteo.pv.it *doi:10.3324/haematol.2011.060004*

Haematologica. 2012 Apr;97(4):479-81

To conceive a child to save a child

Planning the birth of a baby who could be a hematopoietic stem cell (HSC) donor for an older brother or sister affected by a pathology which can be treated by sibling HLA-compatible HSC transplant represents an "extreme remedy" as opposed to an "extreme evil".[1] We first faced this problem 25 years ago when the question was whether it was ethically acceptable to conceive one baby to "save" another. In October 1984, a couple was informed that their only daughter, who at the time was four years old, had been diagnosed with Ph+ chronic myeloid leukemia. They asked if it were possible to treat their daughter by bone marrow transplant. They had considered trying to conceive another child, hoping that this new baby would be HLA-compatible with the sister. We replied that this which was practically unprecedented.[2] Details were made available in the literature together with some anecdotal observations and personal comments.[12] In the meantime, our case was being reported in all the most important European newspapers and magazines. In any case, our refusal to go along with the parents decision, besides heralding a death (the choice and the experience of death for such a refusal have also been reported[12]), would have seemed like putting their intentions on trial, with the view of rather than not to treat the sick child but more as insisting on treating her at all costs. In fact, our experience[2] was immediately discussed with great authority in the philosophical literature in the United States,[10] and only 28 months later the experience was reprogrammed and repeated. In April 1990, a new "programmed" baby was

ANNO XI - Numero 3 - 2016
ISSN 1970-8165

SOCIETÀ ITALIANA DI PEDIATRIA PREVENTIVA E SOCIALE

PEDIATRIA PREVENTIVA & SOCIALE

ORGANO UFFICIALE DELLA SOCIETÀ ITALIANA DI PEDIATRIA PREVENTIVA E SOCIALE

I venticinque pediatri, decorati con la Medaglia d'oro della Sanità, hanno scritto la storia della Repubblica

Studio realizzato in occasione del LXX anniversario della fondazione della Repubblica italiana

Farnetani I.

The saviour sibling

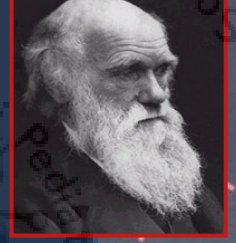

Daily Mail
NEWSPAPER OF THE YEAR
HOLBY CITY GIRL DIES
Exclusive: Mother who gave birth to Britain's first designer baby to try to save his sick brother attacks her 'heartless' critics
YES, I'D DO IT ALL OVER AGAIN

In the spotlight: A British mother defends her decision to select a baby that is a potential stem-cell donor to its sick brother under full media glare and a growing debate about how such developments should be regulated.

La Medaglia al trionfo della vita

Un altro decorato, Giuseppe Roberto Burgio, direttore della Clinica pediatrica dell'Università di Pavia, è stato colui che ha promosso la Trapiantologia in Italia.

Il 3 aprile 1987 fu effettuato con successo il trapianto di midollo osseo "dal fratellino programmato". In quegli anni fece scalpore la storia di una bimba di sei anni malata di leucemia mieloide cronica che non poteva disporre di alcun donatore di midollo compatibile nella propria famiglia. I genitori, pur di salvarla, avevano messo al mondo un altro bambino, con la speranza che potesse donare il proprio midollo alla sorella. L'intervento ebbe successo e la bambina guarì, ma nonostante questo la scelta di Burgio di consigliare ai genitori una nuova gravidanza animò a livello nazionale un notevole dibattito, anche piuttosto acceso. Fra chi andava contro l'operato di Burgio c'era anche il Premio Nobel Rita Levi Montalcini, che riteneva non etico concepire un bambino per salvarne un altro. Fra i favorevoli, invece, Marcello Pera, che in seguito sarebbe diventato presidente del Senato della Repubblica Chiara la scelta delle Istituzioni, basta controllare alcune date: il trapianto di midollo alla bimba avvenne il 3 aprile 1987, il successivo conferimento di una Medaglia d'oro il 30 marzo 1990, quando l'allora Ministero della Sanità decorò proprio Giuseppe Roberto Burgio. Questo era un modo chiaro per dimostrare come le Istituzioni fossero a difesa della vita.



Alfred I. Tauber

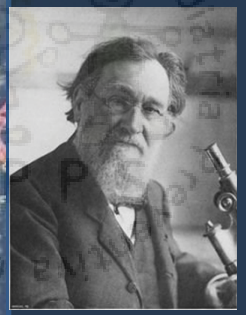
1

Hologenome

- ***Nature/Genome*(?)**
- ***Metagenome(Microbiome)***
- ***Epigenome***
- ***Nurture/Environment/Culture***

L'IMMUNOLOGIA DELL'IO

2

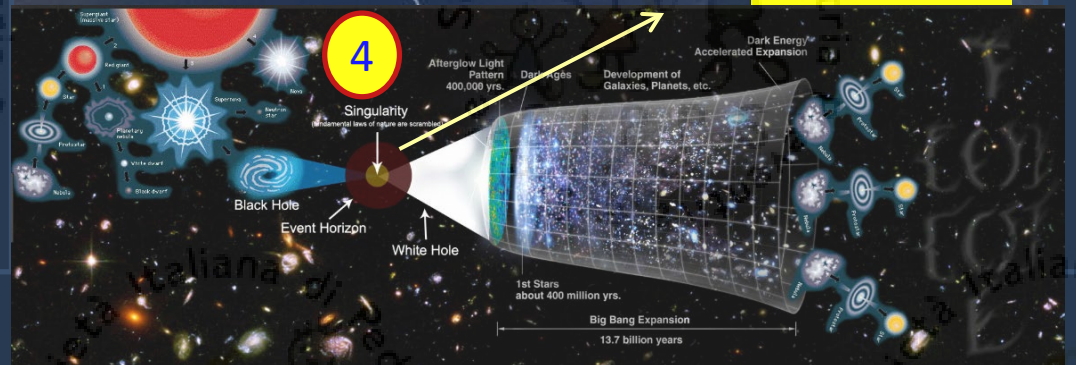


Io biologico/immunologico/neuro-psichico

*How?/Where?/**When**?*

4

Consciousness



3

Self/Not Self

Alfred I. Tauber

4

The Immune Self: Theory or Metaphor (1997)

L'immunologia dell'io

Prefazione di Gilberto Corbellini

1

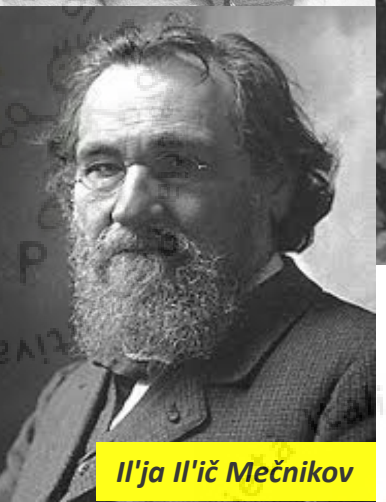
2

McGraw-Hill

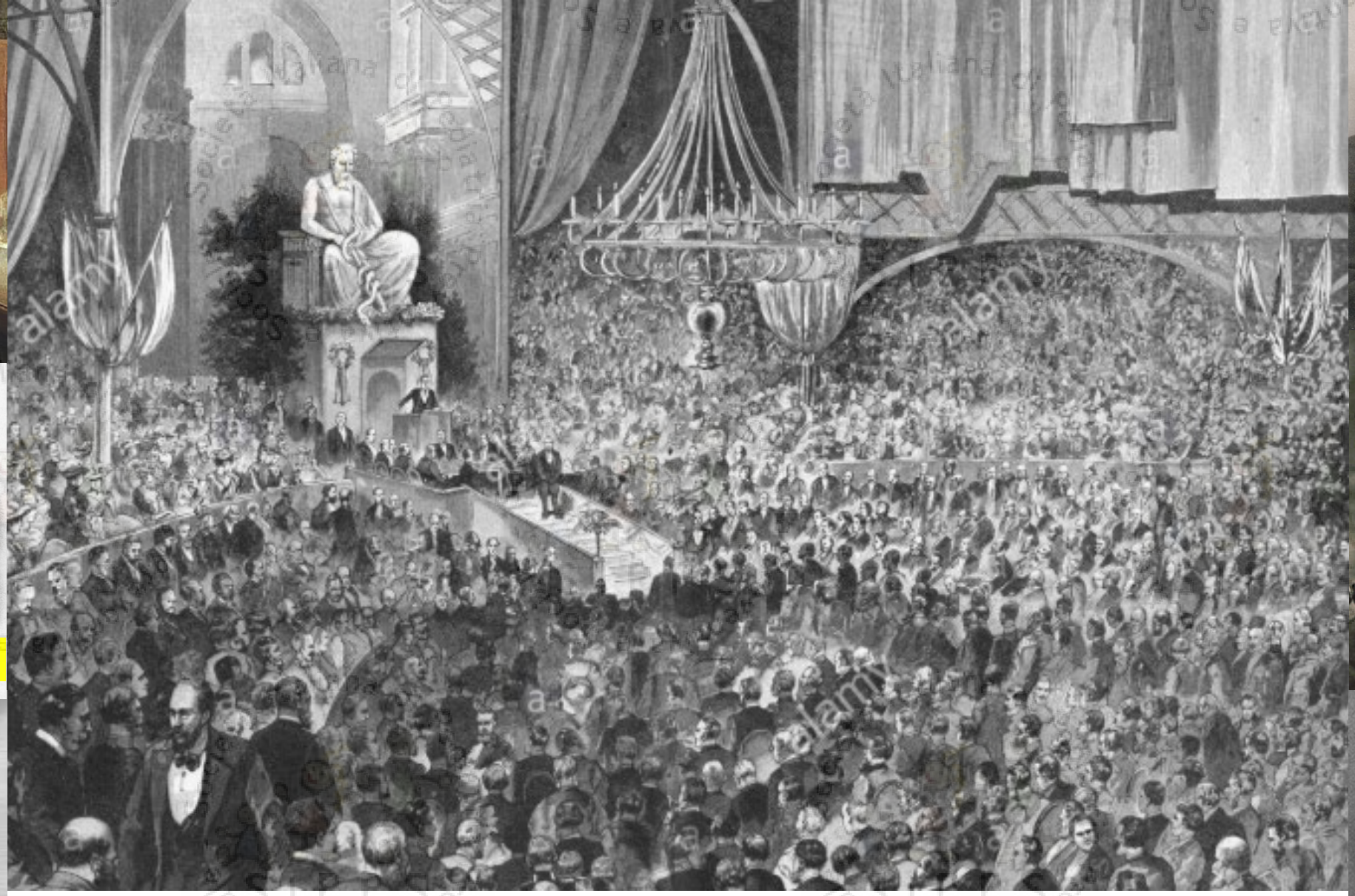
Milano New York San Francisco Washington, D.C. Auckland Bogotá
Lisbon London Madrid Mexico City Montreal New Delhi San Juan
Singapore Sydney Tokyo Toronto

Louis Pasteur

Rudolf Virchow



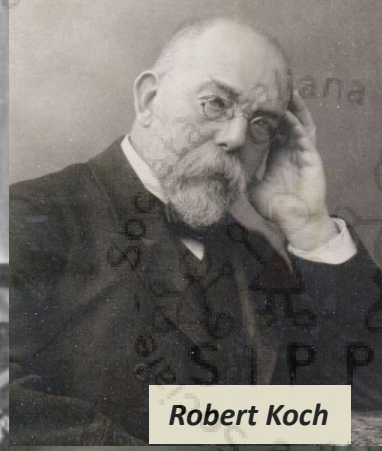
Il'ja Il'ič Mečnikov



The ceremonial opening of the Medical Congress in Berlin (1890):
7000 partecipanti (623 USA, 421 Russia, 352 GB, 171 FRA…)

Cellularisti

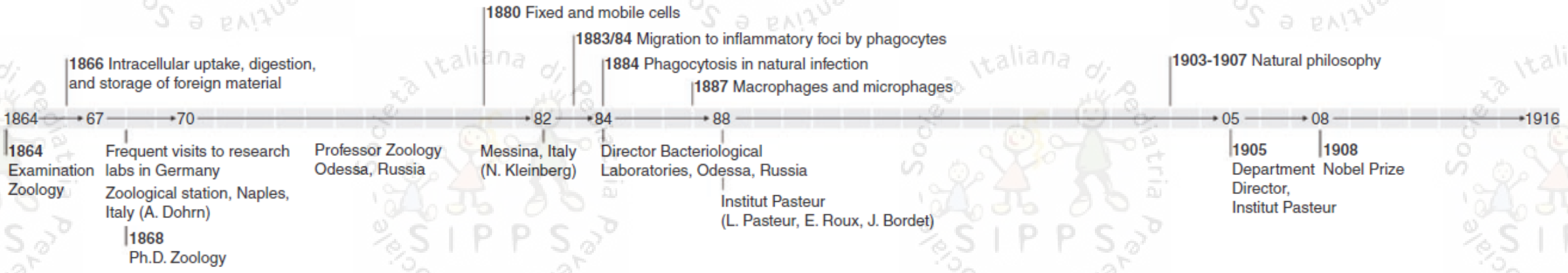
Umoralisti

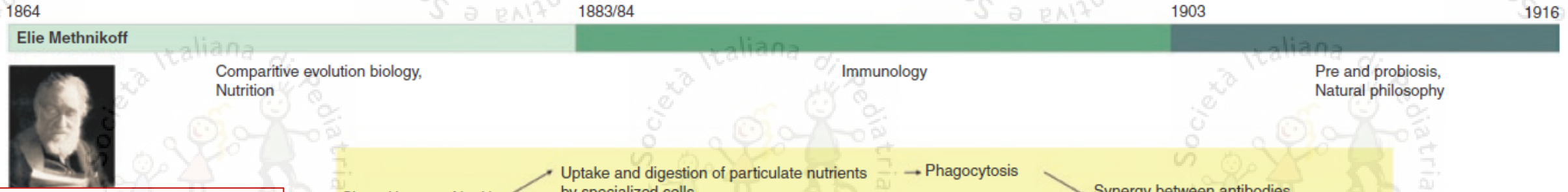


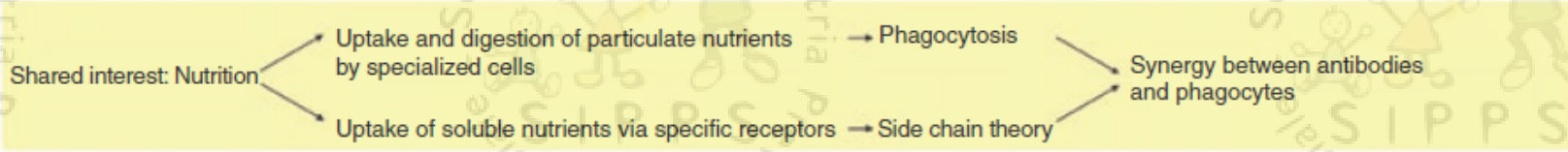
Robert Koch

Emil von Behring

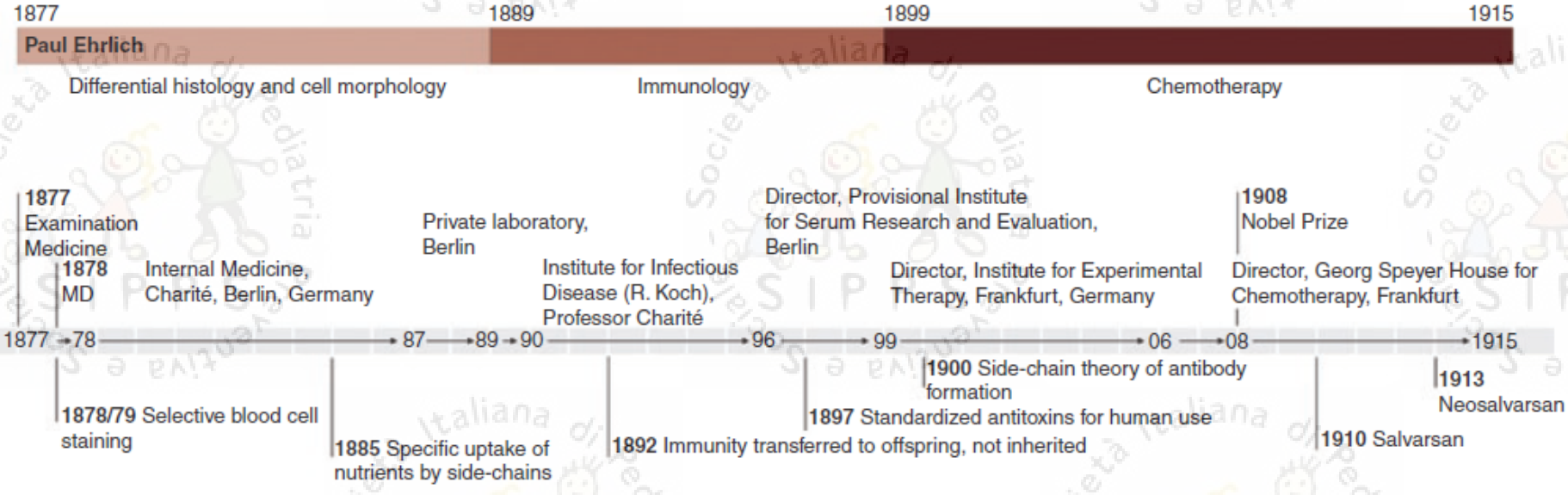
Paul Ehrlich





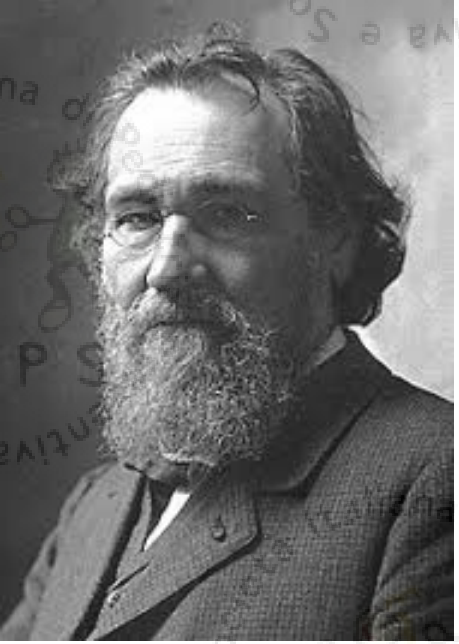


Metchnikof, aveva per primo concepito i processi immunitari come quelli in grado di "definire ontologicamente l'individuo"; la sua teoria era stata lungamente avversata, in un periodo storico dominato dal positivismo e dal riduzionismo meccanicista, in quanto sentita come ***vitalista***.



Cap 3 *UN PRIMO APPROCCIO ALL'IO BIOLOGICO*

Kaufmann SH. *Immunology's foundation: the 100-year anniversary of the nobel prize to paul ehrlich and elie metchnikoff. Nat Immunol.* (2008) 9:705–12



Per Tauber la **grande intuizione di Metchnikof** sarebbe stata, in pratica, che alcuni **processi riparativi e ricostruttivi** – in particolare l'***infiammazione*** – avrebbero, **nelle prime fasi** dell'***ontogenesi embrio-fetale*, un ruolo per così dire *creativo*,** contribuendo, appunto, alla definizione della **forma corporea**. Un ruolo-chiave in tal senso svolgerebbero, sia in ambito *ontogenetico-costruttivo*, sia in ambito *infiammatorio-difensivo*, i ***fagociti*** ..

Cap 3 *UN PRIMO APPROCCIO ALL'IO BIOLOGICO*

Kaufmann SH. *Immunology's foundation: the 100-year anniversary of the nobel prize to paul ehrlich and elie metchnikoff. Nat Immunol.* (2008) 9:705–12

*Per Metchnikof i processi immunitari sono, soprattutto, attività che **stabiliscono l'identità dell'organismo** e che svolgono **una funzione di protezione solo in conseguenza di fenomeni secondari**...*

*Solo alla metà degli anni 50 gli sviluppi della medicina e della biologia richiesero la riapertura del problema sollevato da Metchnikof. E fu allora che furono posti problemi come quelli della natura della **tolleranza** e del **trapianto**..*

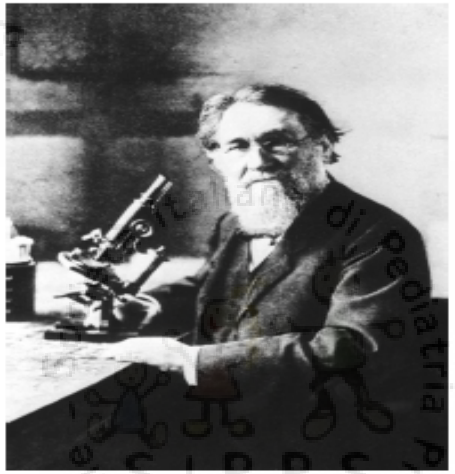
Historical Insight: During those periods when immunology was oriented toward medical or biological subjects, Darwinian concepts predominated. These included Metchnikoff's phagocytic theory and Ehrlich's receptor theory during the early years and Burnet's clonal selection theory after the 1950s. During the immunochemically oriented interim, instru[illegible] theories were not so much anti- as a-Darwinian.

Darwinism and immunology: from Metchnikoff to Burnet

Arthur M. Silverstein

Institute of the History of Medicine, Johns Hopkins School of Medicine, 1900 East Monument St., Baltimore, MD 21205, USA. (arts@jhmi.edu)

I have indeed dared to put forward a new theory of inflammation, only because I felt that I had Darwin's great conception as a solid foundation to build upon ...
Elie Metchnikoff, 1893[1]



Elie Metchnikoff. (Courtesy of the National Library of Medicine.)

Darwinian evolution is not a monolithic theory, but really a set of five subtheories, as Ernst Mayr has pointed out[2]: evolution *per se* (that is, change); common descent; gradualism; speciation; and natural selection. These are not of equal importance when we consider the influence of Darwinism on any particular scientific specialty. In the 19th century, those scientists most interested in Darwinian thought were[3]: (i) geologists, interested in the time-span of change and the gradualist contradiction of saltationist and cataclysmic theories; (ii) paleontologists, interested in the contradictions that common descent and speciation posed for essentialist and typological views of the fixity of species; and (iii) zoologists and botanists, interested in the morphological relations among taxa, usually on the higher levels of whole organisms or major systems and functions.

It is the purpose of this commentary to examine the history of Darwinian influences on immunological thought during its formative years. It may be noteworthy that the only discussion devoted broadly to this question is that of Alain Bussard's "Darwinisme et Immunologie", presented by this multitalented individual to a meeting of philosophers in 1982[8]. But those who knew him will recall that Bussard remained throughout his career an unreconstructed immunochemist, always searching for an instructionist alternative to Burnet's Darwinian clonal selection theory. He seems in this discussion to perpetuate the traditional 19th and early 20th century French distaste for Darwinism[9] and, indeed, repeats somewhat ruefully that "one of my Anglo-Saxon colleagues [noted that] there is always present in the heart of a Frenchman a slumbering Lamarckian".

The struggle for existence

Darwin's "survival of the fittest" was expressed in terms of a Malthusian contest[10] among individuals within a species, selection favoring those best able to compete. In 1882, Virchow's student Paul Grawitz advanced a theory of acquired immunity based upon the idea that disease represents an interspecies struggle between the cells of the host and the parasite[11]. He supposed that infection or active immunization would specifically "energize" host cells to battle more efficiently, a vital quality that he thought would be inherited by later generations of cells. It was Ilya Metchnikoff, with his phagocytic theory of immunity, who gave full voice to the suggestion that the critical struggle in disease is between different species; the immune response represents the principal weapon used by the host to combat the pathogenic organism actively[12].

Metchnikoff was initially critical of the Malthusian basis of

L'altro grande punto di riferimento della ricostruzione storico-filosofica di Tauber è, inevitabilmente, **Franck Macfarlane Burnet,** il virologo australiano al quale dobbiamo le teorie che rappresentano tuttora i tre capisaldi del modello immunologico dominante: la chiara definizione di un ***Self*** radicalmente contrapposto a un ***Not Self*** essenzialmente microbico e potenzialmente nemico e le teorie della ***tolleranza*** e della ***selezione clonale***. Un modello apparentemente ***forte*** che negli ultimi anni mostra alcune inattese, quanto intriganti ***debolezze.***

Cap 3 *UN PRIMO APPROCCIO ALL'IO BIOLOGICO*

Self vs. non-self immunity

https://www.khanacademy.org/science/high-school-biology/hs-human-body-systems/hs-the-immune-system/v/self-versus-non-self

Arthur M. Silverstein
Noel R. Rose

Immunol Rev. 1997 Oct;159:197-206; discussion 207-18.

Arthur M Silverstein
Johns Hopkins Medicine | JHUSOM · Institute of the History of Medicine

Con la scoperta della tolleranza.. e, in particolare, con la scoperta della restrizione HLA ..il termine "***Io immunologico***" e la frase "***discriminazione Self/Non Self***" hanno acquisito grande valore. .. Il concetto di ***Self***, sin dai tempi di *Macfarlane Burnet*, ha attivato "***ingranaggi concettuali mistici heggianti***" diventando il paradigma centrale dell'immunologia moderna .. In questo articolo, **sfidiamo alcune delle affermazioni più eclatanti sul Self immunologico**, rivedendo i meccanismi dell'evoluzione darwiniana e ricordando che .. la **risposta immunitaria non può discriminare tra (agenti) benigni e nocivi**.

On the mystique of the immunological self

Summary: Since the time of Paul Ehrlich 100 years ago, we have known that the immunological apparatus somehow inhibits most damaging autoimmune responses while permitting a response to exogenous immunogens. With the discovery of tolerance, the concept of immunological surveillance, and especially with the discovery of HLA restriction of T-cell recognition, the term "the immunological self" and the phrase "self-nonself discrimination" have gained wide currency. Immunology has been called "The Science of Self", and self-nonself discrimination has been assigned as the driving force for its complex evolution. The concept of self has thus been given such mystical trappings since the time of Macfarlane Burnet that recent workers have felt free to pronounce it the central paradigm of modern immunology, and to claim to overthrow it! In this article, we challenge some of the more egregious claims about the immunological self by recalling important historical findings, by reviewing the mechanisms of Darwinian evolution, and by remembering that the general pathology of immunogenic inflammation shows that the immune response cannot discriminate between the benign and the noxious.

Perspectives

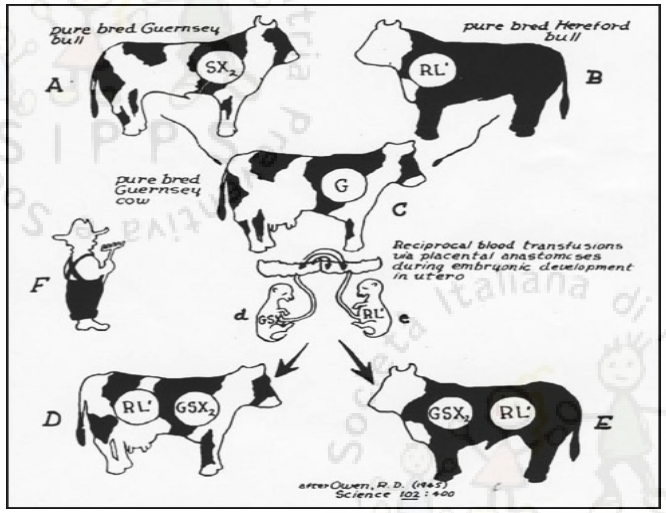
Anecdotal, Historical And Critical Commentaries on Genetics

Edited by James F. Crow and William F. Dove

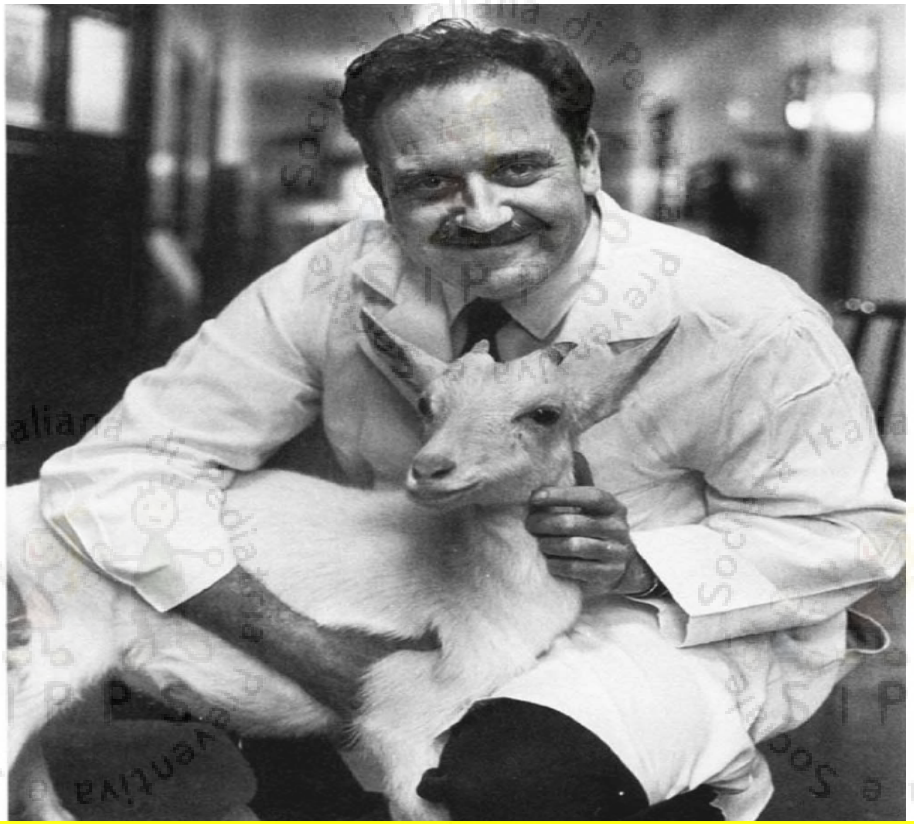
A Golden Anniversary: Cattle Twins and Immune Tolerance

James F. Crow

Genetics Department, University of Wisconsin, Madison, Wisconsin



RAY OWEN (**immunologic tolerance due to exchange of blood cells *in utero***) Science, 102 (1945), p. 400 → ***Microchimerism***



Ray David Owen (October 30, **1915** – September 21, **2014**

Le analisi di ***Owen*** rivelarono che **vitelli gemelli generati da padri diversi erano *chimerici***, ciascuno essendo dotato **anche di cellule del sangue derivate dal fratello gemello** e che i gemelli erano **immunologicamente compatibili:** furono proprio gli studi di Owen a dimostrare che il ***self*** era **appreso** dal sistema immunitario **nel corso dello sviluppo** e a consentire a ***Burnet*** e ***Medawar*** di conseguire il Premio Nobel in Fisiologia o Medicina (1960)* per la scoperta della ***tolleranza immunologica acquisita .***

Furono inoltre le scoperte di Owen ad aprire, di fatto, la strada alle ricerche sull'**induzione della tolleranza** e sull'**immunologia dei trapianti**

→ ***Microchimerism***

* In verità, in una lettera a Owen, ***Medawar*** ammise che Owen avrebbe dovuto essere incluso nel premio..
[Crow JF ***A golden anniversary: cattle twins and immune tolerance***
Genetics. 1996 Nov;144(3):855-9.

seminars in **IMMUNOLOGY**, Vol. 12, 2000: pp. 173–178
doi: 10.1006/smim.2000.0228, available online at http://www.idealibrary.com on IDEAL

There is only one immune system! The view from immunopathology

Arthur M. Silverstein[a,*] *and Noel R. Rose*[b]

The generators of B and T cell diversity produce specificities for both autochthonous and exogenous paratopes. A wide variety of positive and negative, central and peripheral mechanisms has evolved to regulate the immune response. All potential immunogens are recognized by the system using the same set of 'rules', without discrimination between 'self' and 'nonself' or between the 'toxic' and the 'benign'. In every response, whether positive or negative, the factors mobilized and the balance between protection and damage

Immunology—is it really *gnothi seavton*?[e]

As for the concept of self/nonself 'discrimination', this is a delusion. The world is not divided between the self and the not-self (foreign). The immune system does not 'know' the difference. Only obedience to the immunological rules defines what is tolerated and what is intolerable. SELF IS ONLY THAT COLLECTION OF POTENTIAL IMMUNOGENS THAT CANNOT STIMULATE A RESPONSE (or only a subliminal one) AT THAT TIME AND PLACE! This

Per quanto riguarda il concetto di **Self/Not-Self, è solo un'illusione**.
Il mondo non è diviso tra Self e Not Self (estraneo).. Il sistema immunitario **non** "conosce" la differenza.
Solo l'obbedienza alle regole immunologiche definisce ciò che è tollerato e ciò che non lo è.
IL SELF È SOLO QUELLA RACCOLTA DI IMMUNOGENI POTENZIALI CHE NON PUO 'STIMOLARE UNA RISPOSTA
(o soltanto una subliminale) IN QUELLO SPECIFICO TEMPO E LUOGO!

12-1-2012

A Symbiotic View Of Life: We Have Never Been Individuals

Scott F. Gilbert
Swarthmore College, sgilber1@swarthmore.edu

J. Sapp

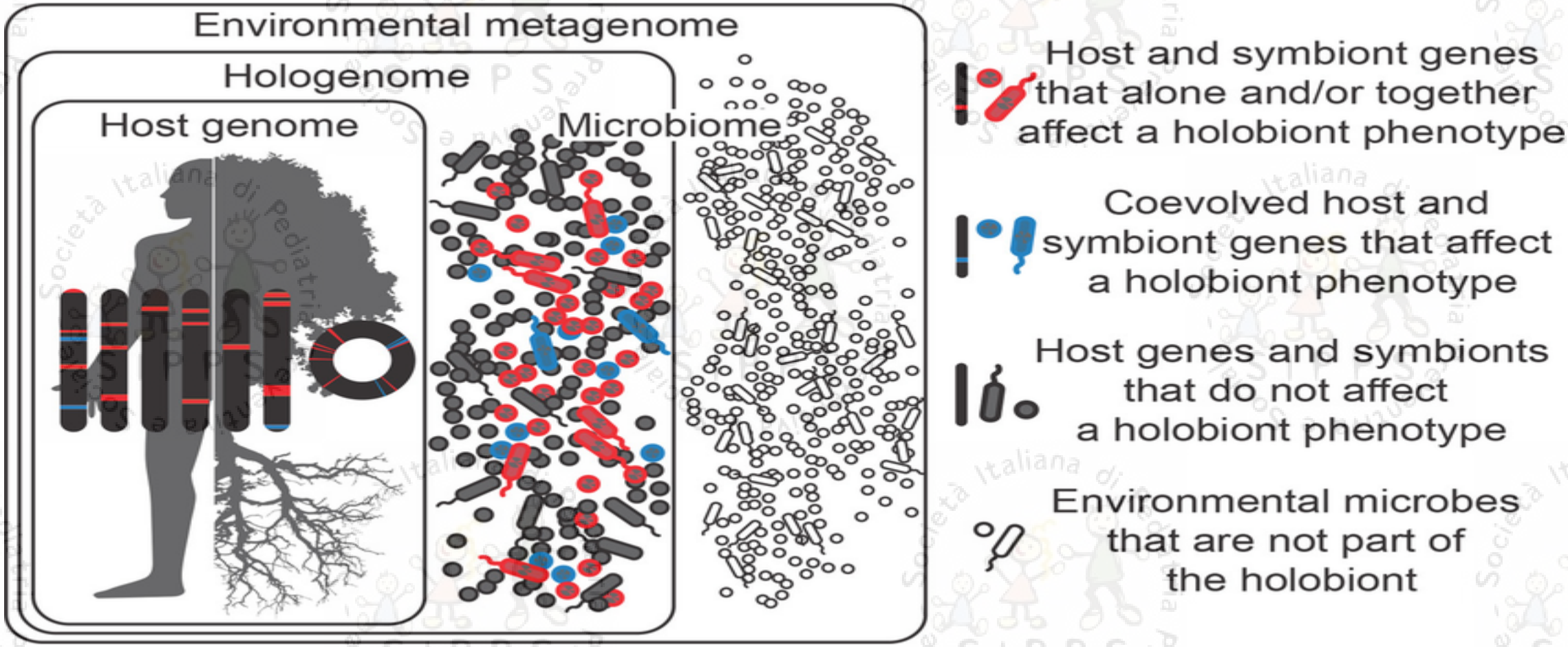
A. I. Tauber

CHICAGO JOURNALS

A Symbiotic View of Life: We Have Never Been Individuals
Author(s): Scott F. Gilbert, Jan Sapp and Alfred I. Tauber
Source: *The Quarterly Review of Biology*, Vol. 87, No. 4 (December 2012), pp. 325-341
Published by: The University of Chicago Press
Stable URL: http://www.jstor.org/stable/10.1086/668166

The notion of the "biological individual" is crucial to studies of genetics, immunology, evolution, development, anatomy, and physiology. Each of these biological subdisciplines has a specific conception of individuality, which ha
conceptual contexts for integrating newly acquired data. During t
acid analysis, especially genomic sequencing and high-throughp
challenged each of these disciplinary definitions by finding signifi
animals and plants with symbiotic microorganisms that disrupt th
heretofore had characterized the biological individual. Animals ca
individuals by anatomical or physiological criteria because a dive
both present and functional in completing metabolic pathways an
physiological functions. Similarly, these new studies have shown
development is incomplete without symbionts. Symbionts also co
of genetic inheritance, providing selectable genetic variation for n
immune system also develops, in part, in dialogue with symbionts
as a mechanism for integrating microbes into the animal-cell com
the "holobiont"-the multicellular eukaryote plus its colonies of per
critically important unit of anatomy, development, physiology, immunology, and evolution opens up new investigative avenues and conceptually challenges the ways in which the biological subdisciplines have heretofore characterized living entities.

Una **visione simbiotica della vita: non siamo mai stati individui..**
La nozione di "individuo biologico" è cruciale per gli studi **di genetica, immunologia, evoluzione, sviluppo, anatomia e fisiologia**. ..
Durante l'ultimo decennio, il sequenziamento genomico ha sfidato le varie definizioni trovando **interazioni significative in animali e piante con i microrganismi simbiotici che rompono i confini che prima avevano caratterizzato l'individuo biologico.. lo sviluppo animale è incompleto senza simbionti**…
I simbionti costituiscono una **seconda modalità di ereditarietà genetica.. il sistema immunitario si sviluppa nel dialogo con i simbionti**. **Riconoscere l'olobionte - l'eucariota multicellulare più le sue colonie di simbionti persistenti - come unità di anatomia, sviluppo, fisiologia, immunologia ed evoluzione criticamente importanti** concettualmente **sfida i modi in cui le varie discipline biologiche hanno fino ad ora caratterizzato le entità viventi.**


Environmental metagenome
Hologenome
Host genome
Microbiome
Host and symbiont genes that alone and/or together affect a holobiont phenotype
Coevolved host and symbiont genes that affect a holobiont phenotype
Host genes and symbionts that do not affect a holobiont phenotype
Environmental microbes that are not part of the holobiont

REVIEW ARTICLE

Rambam Maimonides Med J. 2019 Jan 28;10(1). doi: 10.5041/RMMJ.10359

The Hologenome Concept of Evolution: Medical Implications

Eugene Rosenberg, Ph.D.* and Ilana Zilber-Rosenberg, Ph.D.

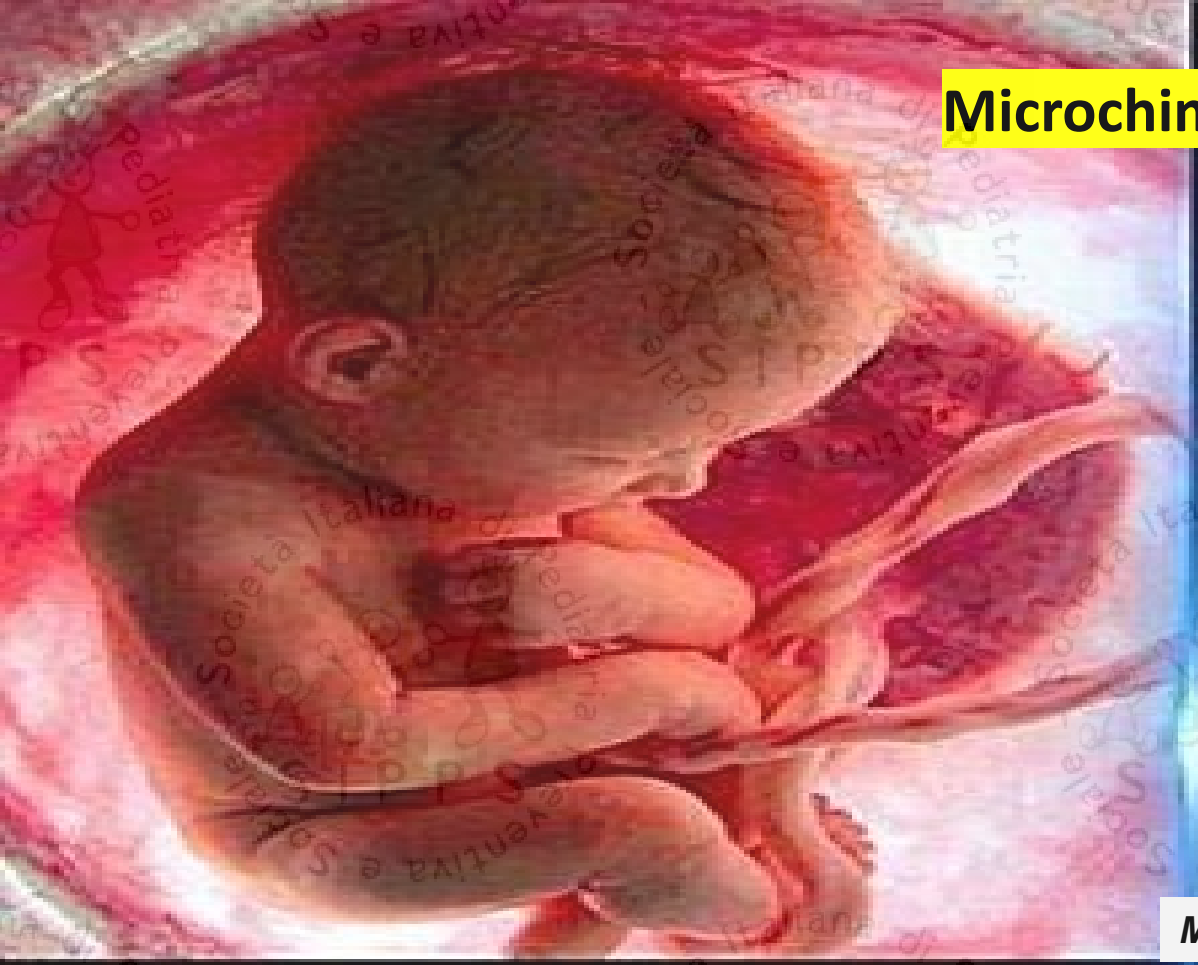
Department of Molecular Microbiology and Biotechnology, Tel Aviv University, Ramat Aviv, Israel

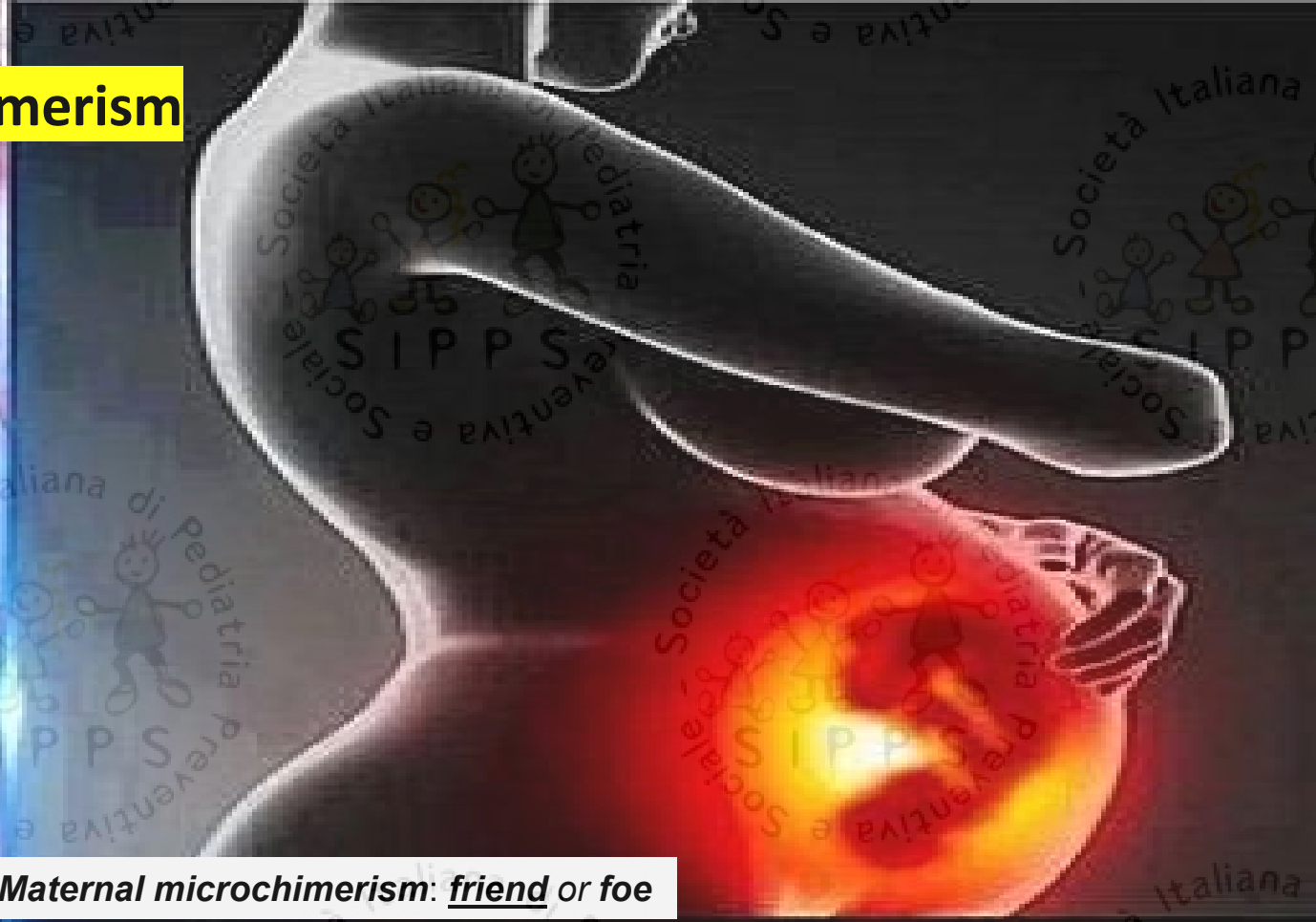
All natural animals and plants are holobionts, consisting of the host and microbiome, which is composed of abundant and diverse microorganisms. Health and disease of holobionts depend as much on interactions between host and microbiome and within the microbiome, as on interactions between organs and body parts of the host. Recent evidence indicates that a significant fraction of the microbiome is transferred by a variety of mechanisms from parent to offspring for many generations. Genetic variation in holobionts can occur in the microbiome as well as in the host genome, and it occurs more rapidly and by more mechanisms in genomes of microbiomes than in host genomes (e.g. via acquisition of novel microbes and horizontal gene transfer of microbial genes into host chromosomes). Evidence discussed in this review supports the concept that hol
in the n
obesity,
microbi

- Tutti gli animali e le piante naturali sono ***olobionti***, costituiti dall'ospite e dal ***microbiota***..
- **una frazione significativa del microbiota/microbioma viene trasferita grazie ad una varietà di meccanismi dai genitori alla prole per molte generazioni**.
- le **variazioni genetiche negli olobionti possono verificarsi... più rapidamente e con più meccanismi nei microbiomi rispetto ai genomi ospiti** (ad es. tramite acquisizione di nuovi microbi e a **trasferimento genico orizzontale di geni microbici nei cromosomi dell'ospite**)…

- sebbene i cambiamenti nel microbioma possano portare all'evoluzione dell'olobionte, possono anche portare a disbiosi e malattie (ad esempio obesità, diarrea, malattia infiammatoria intestinale e autismo)…

Microchimerism





Maternal microchimerism: ***friend*** *or* ***foe***

In the womb, the fetus receives blood proteins from his mother through the placenta which protects him against various diseases for the rest of his life.

When the mother suffers organ damage such as heart attack, the fetus sends stem cells through the placenta to repair the damaged organ.

nature REVIEWS GENETICS

Nature Reviews Genetics **18**, 128–142 (2017)

Mosaicism in health and disease – clones picking up speed

An adult human body is likely to contain as many versions of the genome as the number of somatic cells. This is a result of the fact that every cell division is coupled with risk for new mutations. The

Germline variation (GV)
- Constitutional and intergenerational; the classic type of genetic variation inherited from germ line to zygote
- Together with DNVs the most frequently studied type of genetic variation in GWAS

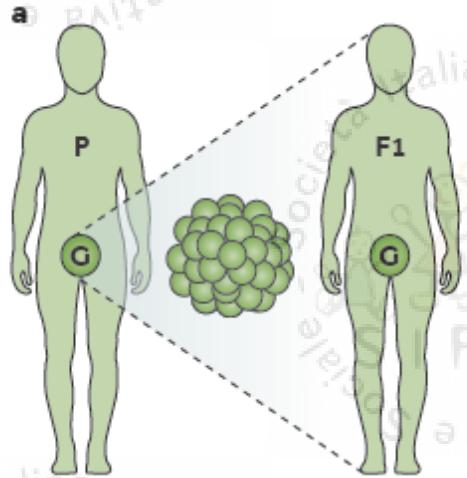
Post-zygotic variation (PZV)
- Variants arising at the first division of the zygote or later in different somatic cell lineages
- Variants arise in one soma and typically disappear from the population with the death of its carrier
- PZV is a possible driver in many disease processes but is often an ignored source of variation

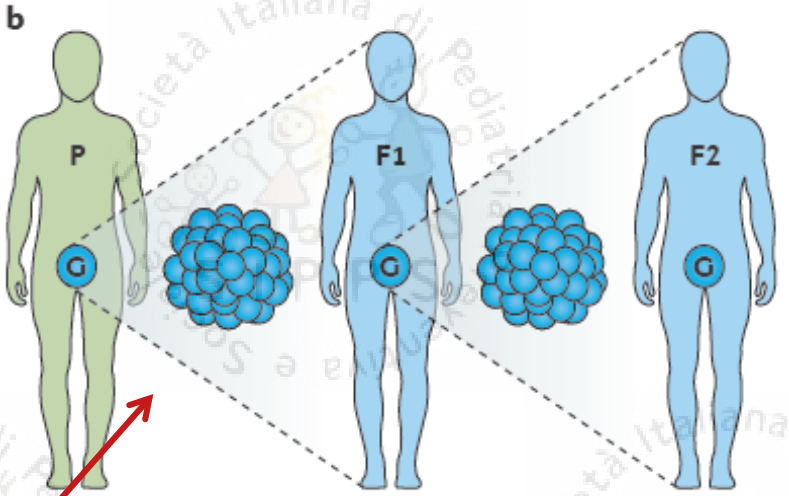
Cellular depletion (CD)
- Reduction of mosaicism by age-associated cell death

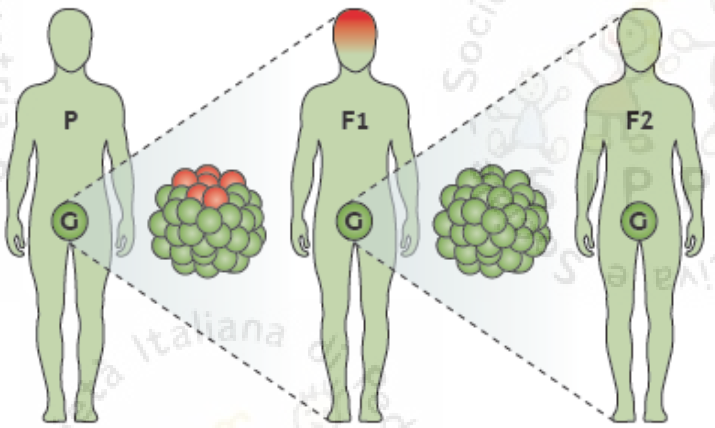
***De novo* variants (DNVs)**
- Arise in cells of the germ line in parental generation and are present in the next generation
- Also encompass variants arising by gonadal mosaicism

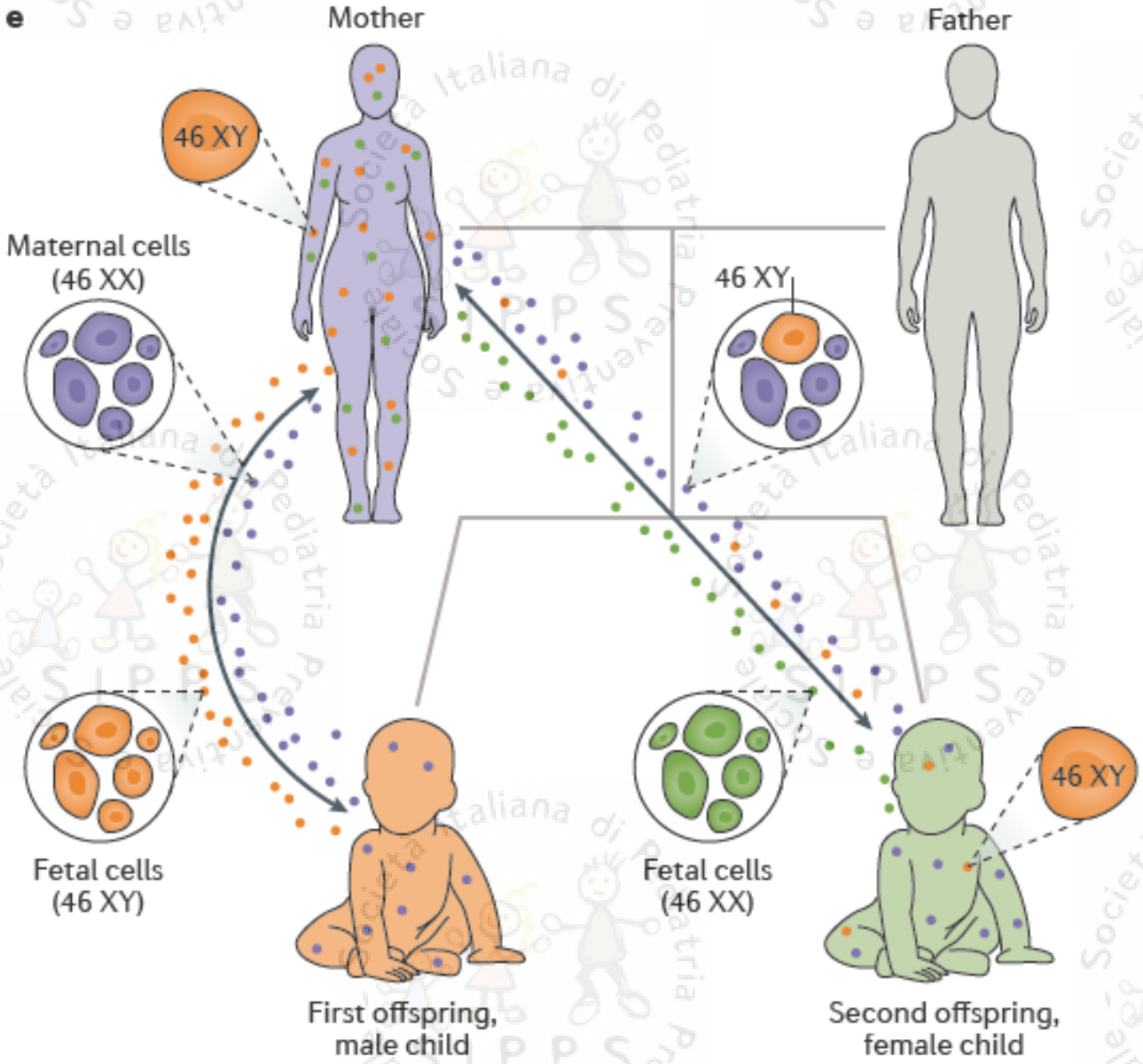
Microchimerism (MC)
- The presence of cells from another subject in the soma of a host individual

Revertant mosaicism (RM)
- Reduction of total variation of the soma by back mutations

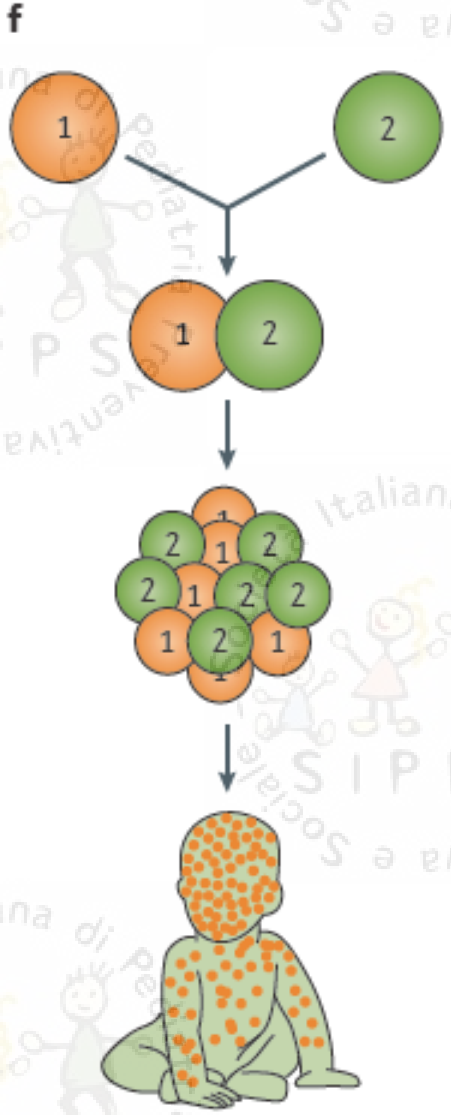




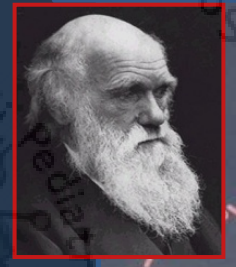




Microchimerism



Classical chimerism is a rarely observed phenomenon that occurs when **an embryo is formed from two independently conceived zygotes**. It results in a fetus with a **mixture of cells with genotypes derived from different germ cells**



Alfred I. Tauber

Nature/Genome(?)

1

Metagenome(Microbiome)

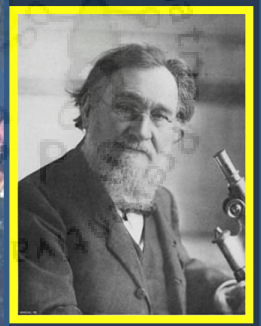
Hologenome

Epigenome

Nurture/Environment/Culture

L'IMMUNOLOGIA DELL'IO

2

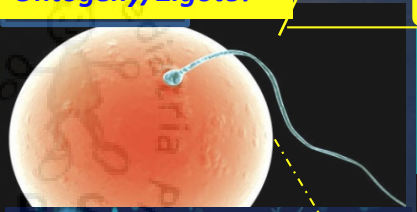


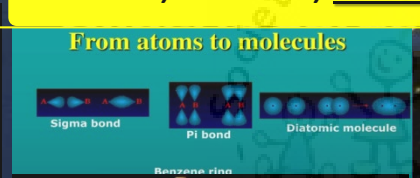
4 Io *biologico/immunologico/neuro-psichico*

4C *Ontogeny/Zigote?*

How?/Where?/***When***?

Consciousness 4A





4B

Philogeny/Viruses/Bacteria.. ***Mutants!***

Alfred I. Tauber

The Immune Self: Theory or Metaphor (1997) 4

L'immunologia dell'io

Prefazione di Gilberto Corbellini

1

2

3

Self/Not Self

Nothing in Biology Makes Sense

Except in the Light of Evolution

THEODOSIUS DOBZHANSKY

As recently as 1966, sheik Abd el Aziz bin Baz asked the king of Saudi Arabia to suppress a heresy that was spreading in his land. Wrote the sheik:

"The Holy Koran, the Prophet's teachings, the majority of Islamic scientists, and the actual facts all prove that the sun is running in its orbit . . . and that the earth is fixed and stable, spread out by God for his mankind. . . . Anyone who professed otherwise would utter a charge of falsehood toward God, the Koran, and the Prophet."

The good sheik evidently holds the Copernican theory to be a "mere theory," not a "fact." In this he is technically correct. A theory can be verified by a mass of facts, but it becomes a proven theory, not a fact. The sheik was perhaps unaware that the Space Age had begun before he asked the king to suppress the Copernican heresy. The sphericity of the earth had been seen by astronauts, and even by many earth-bound people on their television screens. Perhaps the sheik could retort that those who venture beyond the confines of God's earth suffer hallucinations, and that the earth is really flat.

Parts of the Copernican world model, such as the contention that the earth rotates around the sun, and not vice versa, have not been verified by direct observations even to the extent the sphericity of the earth has been. Yet scientists accept the model as an accurate representation of reality. Why? Because it makes sense of a multitude of facts which are otherwise meaningless or extravagant. To nonspecialists most of these facts are unfamiliar. Why then do we accept the "mere theory" that the earth is a sphere revolving around a spherical sun? Are we simply submitting to authority? Not quite: we know that those who took time to study the evidence found it convincing.

The good sheik is probably ignorant of the evidence. Even more likely, he is so hopelessly biased that no amount of evidence would impress him. Anyway, it would be sheer waste of time to attempt to convince him. The Koran and the Bible do not contradict Copernicus, nor does Copernicus contradict them. It is ludicrous to mistake the Bible and the Koran for primers of natural science. They treat of matters even more important: the meaning of man and his relations to God. They are written in poetic symbols that were understandable to people of the age when they were written, as well as to peoples of all other ages. The king of Arabia did not comply with the sheik's demand. He knew that some people fear enlightenment, because enlightenment threatens their vested interests. Education is not to be used to promote obscurantism.

The earth is not the geometric center of the universe, although it may be its spiritual center. It is a mere speck of dust in cosmic spaces. Contrary to Bishop Ussher's calculations, the world did not appear in approximately its present state in 4004 B.C. The estimates of the age of the universe given by modern cosmologists are still only rough approximations, which are revised (usually upward) as the methods of estimation are refined. Some cosmologists take the universe to be about 10 billion years old; others suppose that it may have existed, and will continue to exist, eternally. The origin of life on earth is dated tentatively between 3 and 5 billion years ago; manlike beings appeared relatively quite recently, between 2 and 4 million years ago. The estimates of the age of the earth, of the duration of the geologic and paleontologic eras, and of the antiquity of man's ancestors are now based mainly on radiometric evidence—the proportions of isotopes of certain chemical elements in rocks suitable for such studies.

One of the world's leading geneticists, Theodosius Dobzhansky is professor emeritus, Rockefeller University, and adjunct professor of genetics, University of California, Davis 95616. Born in Russia, in 1900, he is a graduate of the University of Kiev and taught (with J. Philiptschenko) at the University of Leningrad before coming to the U.S., in 1927; thereafter he taught at Columbia University and the California Institute of Technology before joining the Rockefeller faculty, in 1962. He has been president of the Genetics Society of America, the American Society of Naturalists, the Society for the Study of Evolution, the American Society of Zoologists, and the American Teilhard de Chardin Association. Among his many honors are the National Medal of Science (1964) and the Gold Medal Award for Distinguished Achievement in Science (1969). He holds 18 honorary doctorates from universities in this country and abroad. Among his well-known books are *The Biological Basis of Human Freedom* (1956) and *Mankind Evolving* (1962). The present paper was presented at the 1973 NABT convention.

1 *Diversity of Living Beings*

The diversity and the unity of life are equally striking and meaningful aspects of the living world.

2 *Unity of Life*

The unity of life is no less remarkable than its diversity. Most forms of life are similar in many respects. The universal biologic similarities are particularly striking in the biochemical dimension. From viruses to man, heredity is coded in just two, chemically related substances: DNA and RNA. The genetic code is as simple as it is universal. There are

Minimal mutational distances between human cytochrome C and the cytochrome C of other living beings are as follows:

Monkey	1	Chicken	18
Dog	13	Penguin	18
Horse	17	Turtle	19
Donkey	16	Rattlesnake	20
Pig	13	Fish (tuna)	31
Rabbit	12	Fly	33
Kangaroo	12	Moth	36
Duck	17	Mold	63
Pigeon	16	Yeast	56

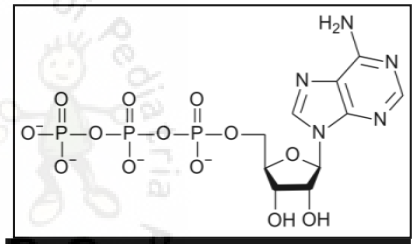
3 *Comparative Anatomy and Embryology*

The biochemical universals are the most impressive and the most recently discovered, but certainly they are not the only vestiges of creation by means of evolution. Comparative anatomy and embryology proclaim the evolutionary origins of the present inhabitants of the world. In 1555 Pierre Belon established the presence of homologous bones in the superficially very different skeletons of man and bird.

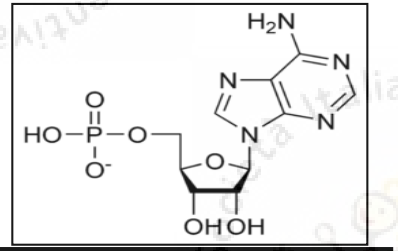
Strength and Acceptance of the Theory

Seen in the light of evolution, biology is, perhaps, intellectually the most satisfying and inspiring science. Without that light it becomes a pile of sundry facts—some of them interesting or curious but making no meaningful picture as a whole.

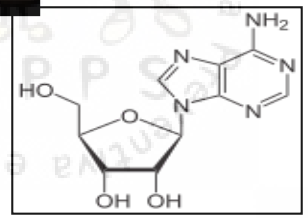
$E = Mc^2 = I$



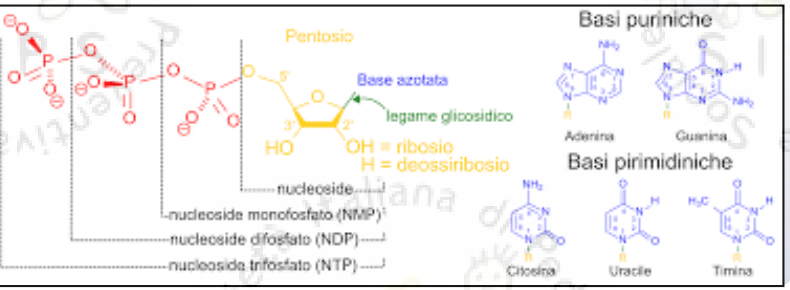
ATP - Adenosina trifosfato

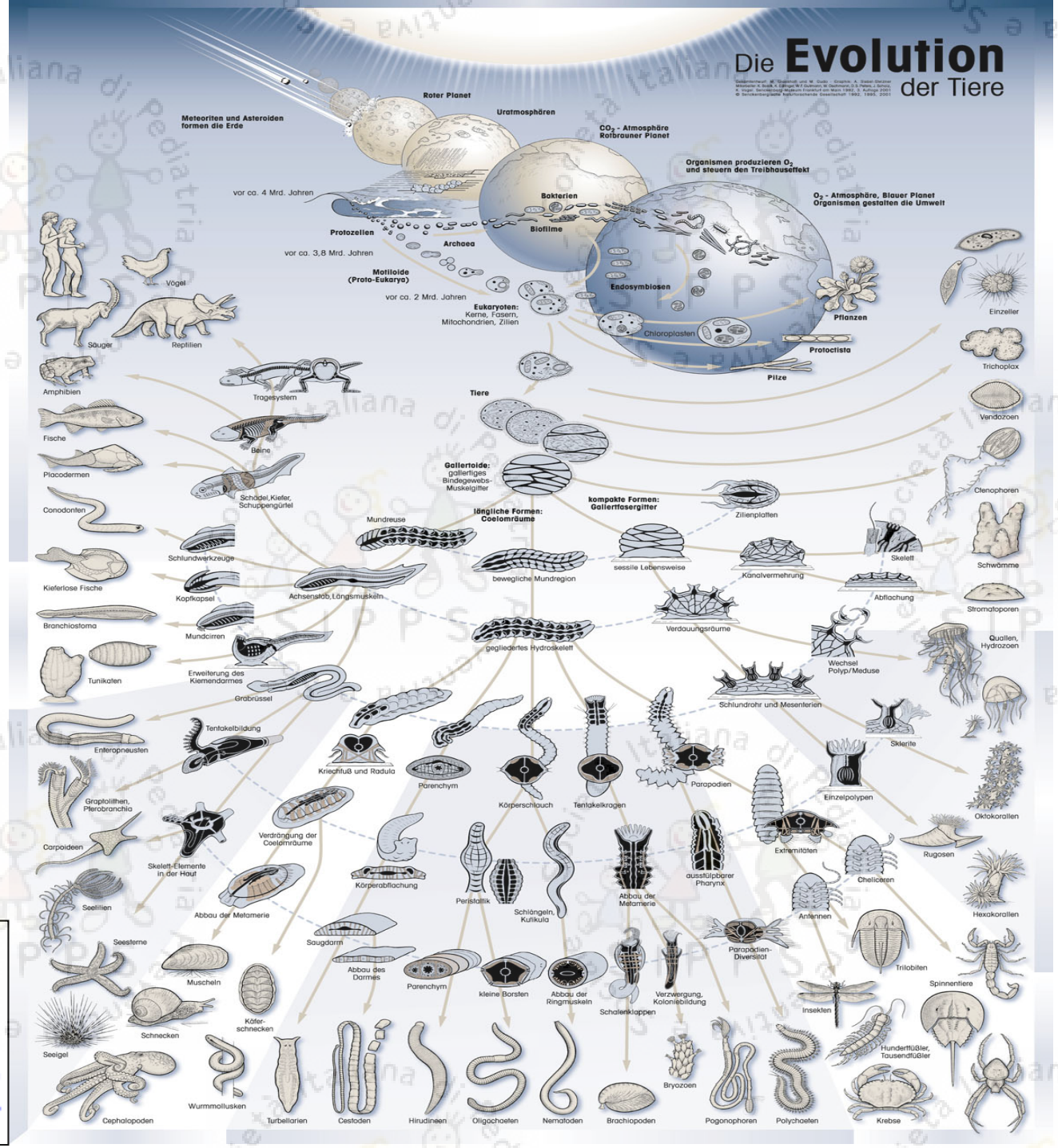


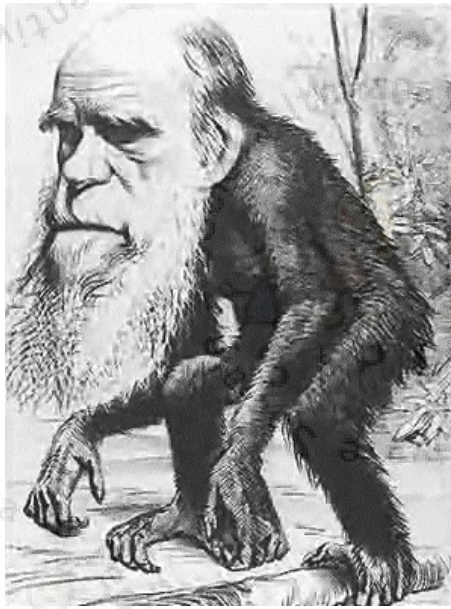
AMP - Adenosin monofosfato

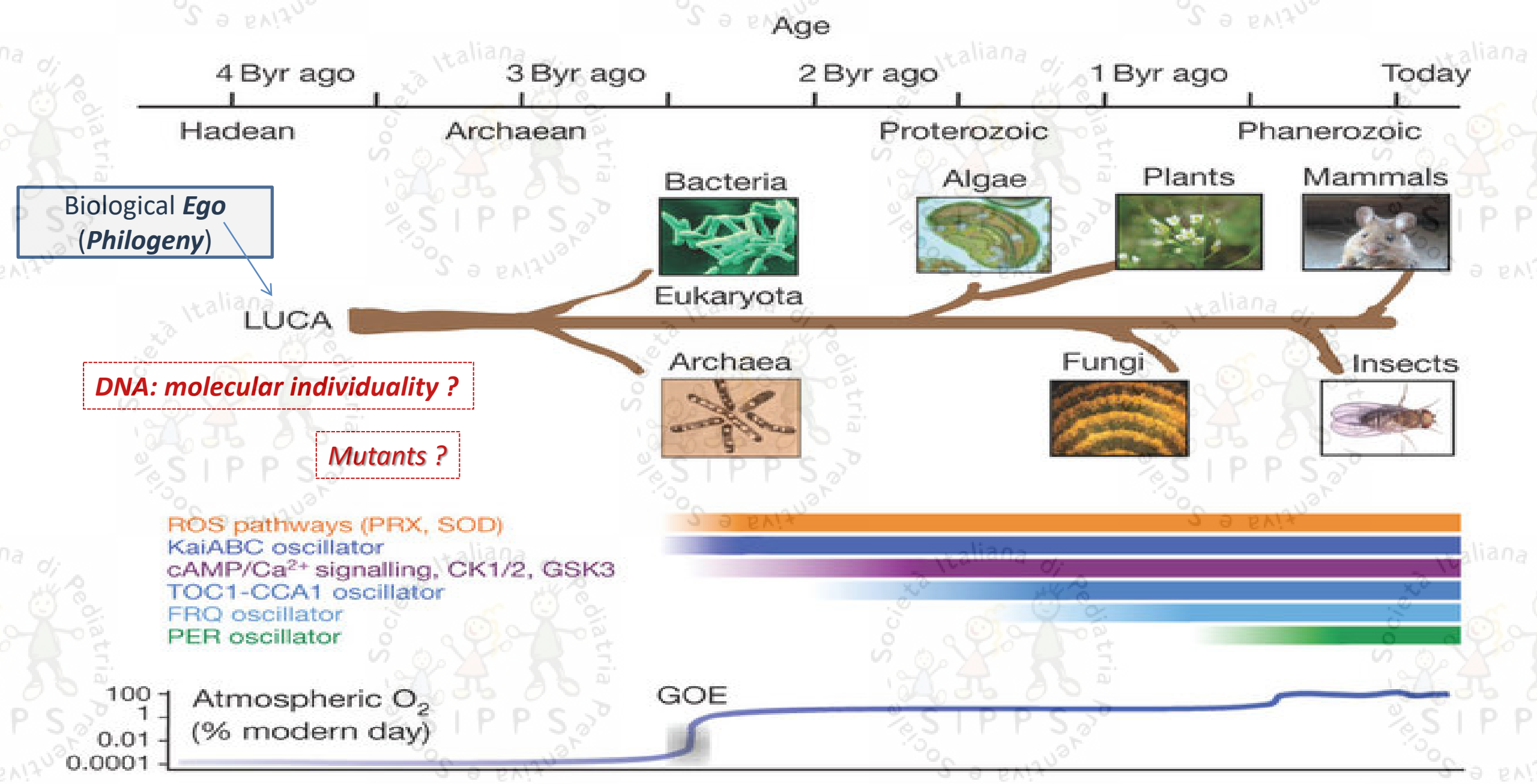


L'***adenosina*** è un nucleoside che ha un ruolo fondamentale
- sia nel **trasferimento di *Energia*** (ATP --> ADP),
- sia nella costituzione degli acidi nucleici (***Informazione***),
- sia nella **trasduzione del segnale** (cAMP = secondo messaggero)



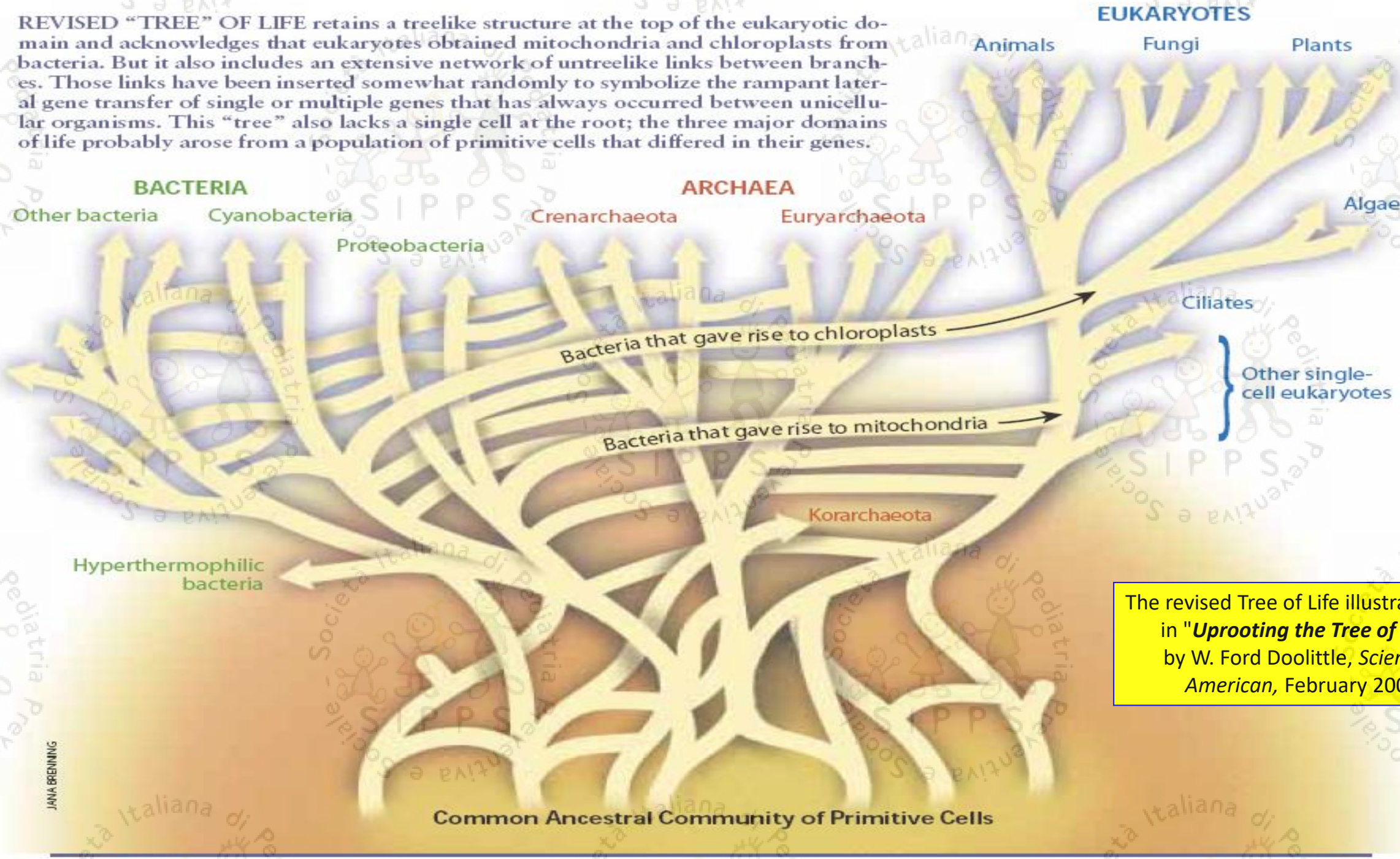




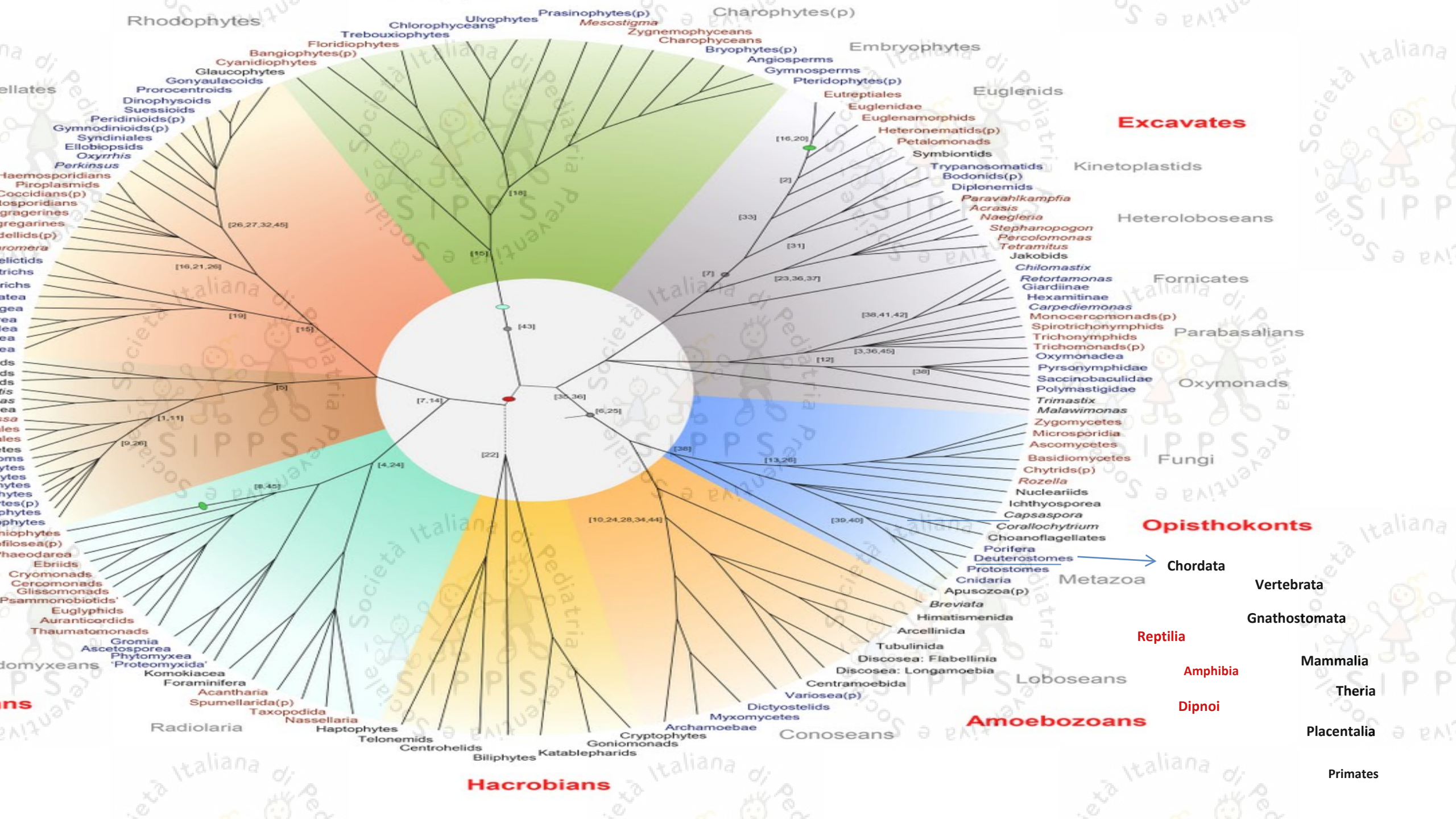


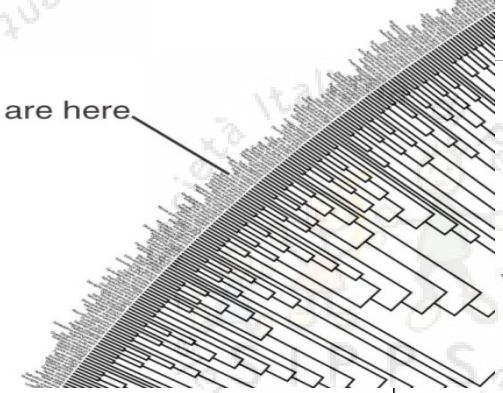
Last Universal Common (Cellular) Ancestor (LUCA)

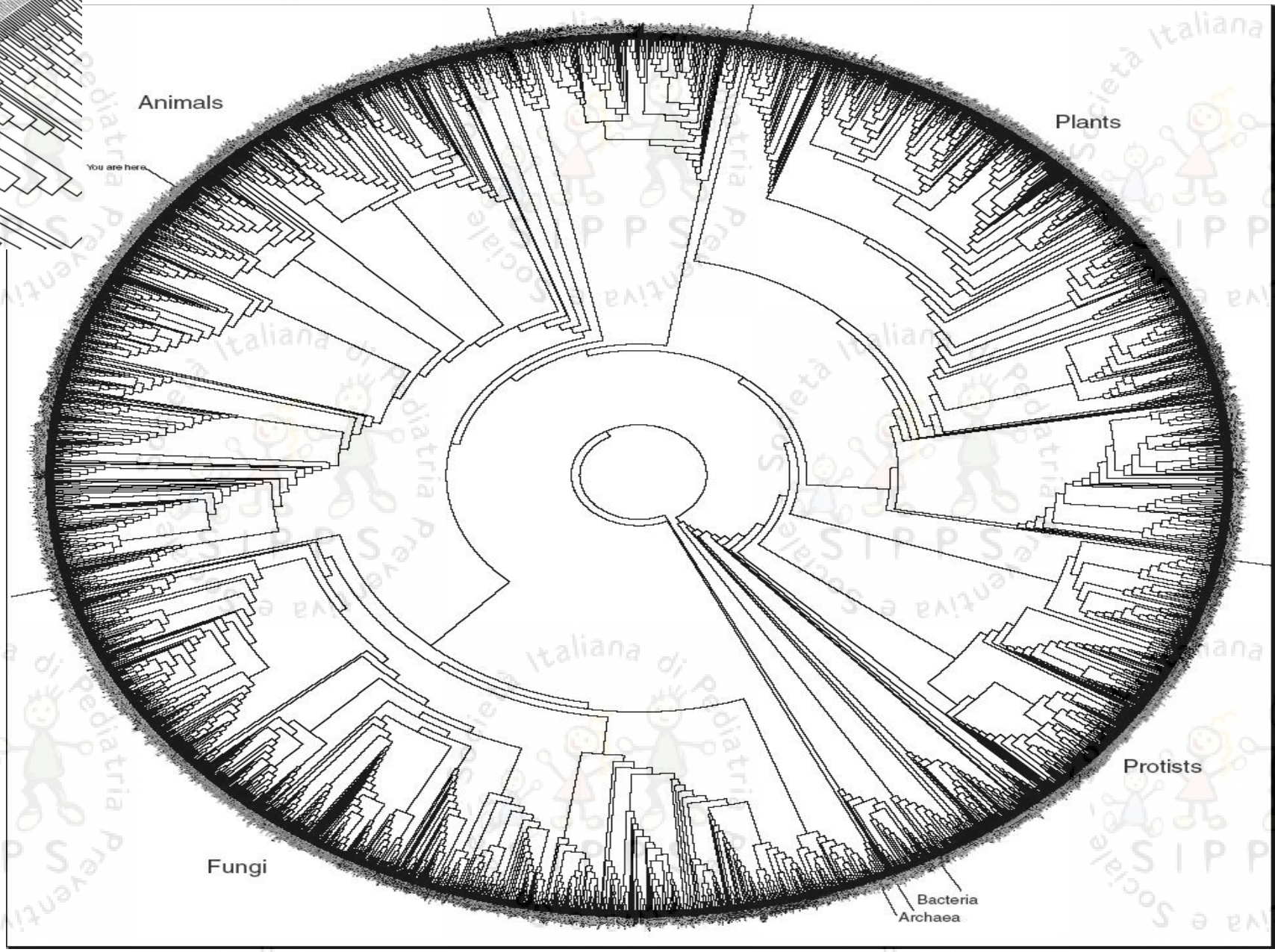
REVISED "TREE" OF LIFE retains a treelike structure at the top of the eukaryotic domain and acknowledges that eukaryotes obtained mitochondria and chloroplasts from bacteria. But it also includes an extensive network of untreelike links between branches. Those links have been inserted somewhat randomly to symbolize the rampant lateral gene transfer of single or multiple genes that has always occurred between unicellular organisms. This "tree" also lacks a single cell at the root; the three major domains of life probably arose from a population of primitive cells that differed in their genes.



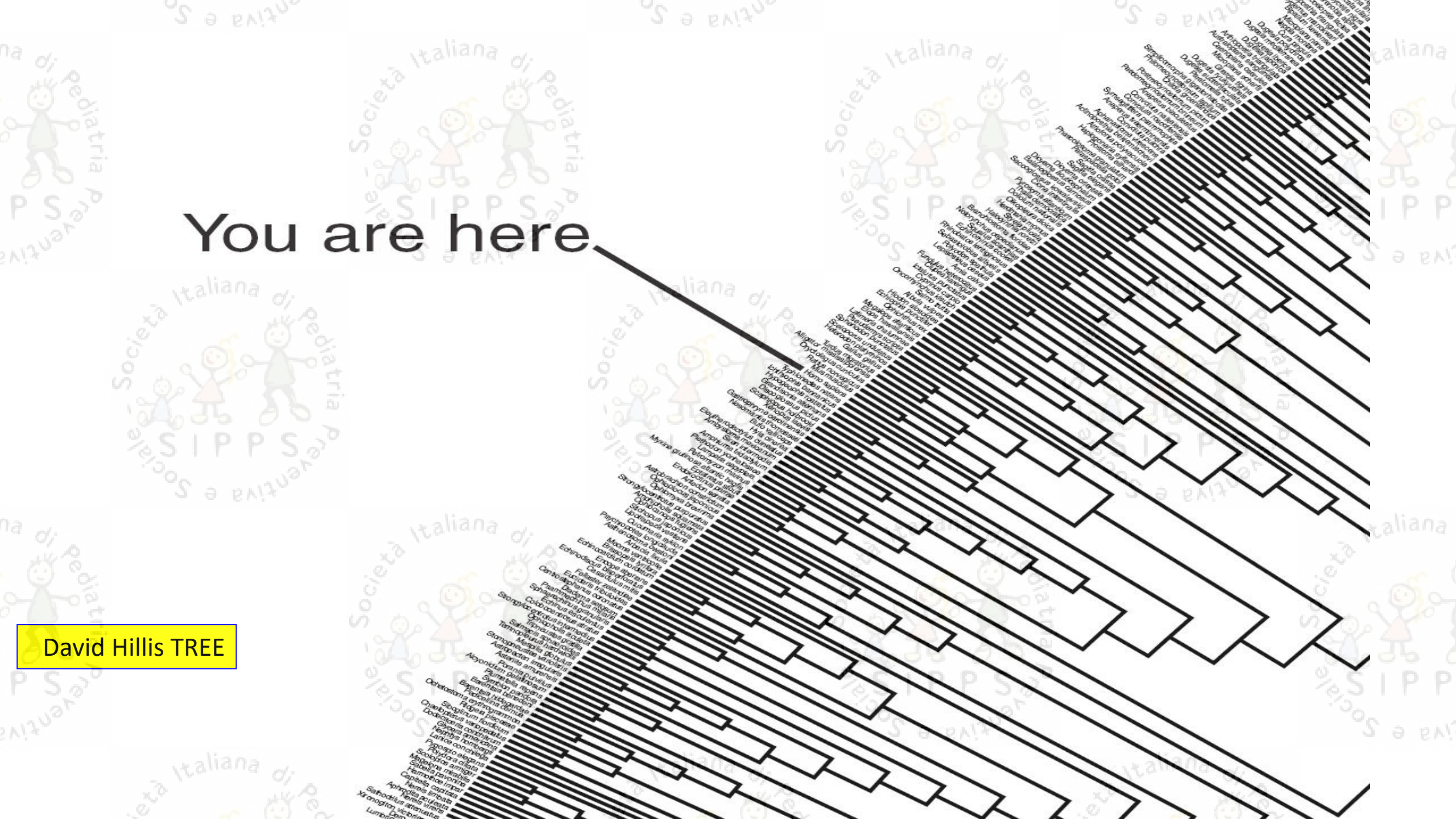
The revised Tree of Life illustrated in "***Uprooting the Tree of Life***" by W. Ford Doolittle, *Scientific American,* February 2000


Rhodophytes
Chlorophyceans
Ulvophytes
Prasinophytes(p)
Mesostigma
Charophytes(p)
Zygnemophyceans
Charophyceans
Trebouxiophytes
Floridiophytes
Bangiophytes(p)
Cyanidiophytes
Glaucophytes
Gonyaulacoids
Prorocentroids
Dinophysoids
Suessioids
Peridinioids(p)
Gymnodinioids(p)
Syndiniales
Ellobiopsids
Oxyrrhis
Perkinsus
Haemosporidians
Piroplasmids
Coccidians(p)
Embryophytes
Bryophytes(p)
Angiosperms
Gymnosperms
Pteridophytes(p)
Euglenids
Eutreptiales
Euglenidae
Euglenamorphids
Heteronematids(p)
Petalomonads
Symbiontids
Excavates
Kinetoplastids
Trypanosomatids
Bodonids(p)
Diplonemids
Paravahlkampfia
Acrasis
Naegleria
Heteroloboseans
Stephanopogon
Percolomonas
Tetramitus
Jakobids
Chilomastix
Retortamonas
Giardiinae
Fornicates
Hexamitinae
Carpediemonas
Monocercomonads(p)
Spirotrichonymphids
Trichonymphids
Trichomonads(p)
Parabasalians
Oxymonadea
Pyrsonymphidae
Saccinobaculidae
Polymastigidae
Trimastix
Malawimonas
Oxymonads
Zygomycetes
Microsporidia
Ascomycetes
Basidiomycetes
Chytrids(p)
Fungi
Rozella
Nucleariids
Ichthyosporea
Capsaspora
Corallochytrium
Choanoflagellates
Porifera
Deuterostomes
Protostomes
Cnidaria
Metazoa
Apusozoa(p)
Opisthokonts
Breviata
Himatismenida
Arcellinida
Tubulinida
Discosea: Flabellinia
Discosea: Longamoebia
Centramoebida
Loboseans
Variosea(p)
Dictyostelids
Myxomycetes
Archamoebae
Amoebozoans
Cryptophytes
Goniomonads
Katablepharids
Conoseans
Biliphytes
Centrohelids
Telonemids
Haptophytes
Nassellaria
Taxopodida
Spumellarida(p)
Acantharia
Foraminifera
Komokiacea
'Proteomyxida'
Phytomyxea
Ascetosporea
Gromia
Thaumatomonads
Auranticordids
Euglyphids
'Psammonobiotids'
Glissomonads
Cercomonads
Cryomonads
Ebriids
Haeodarea
filosea(p)
Radiolaria
Hacrobians
[16,20]
[2]
[33]
[31]
[7]
[23,36,37]
[38,41,42]
[3,36,45]
[12]
[38]
[39,40]
[13,26]
[38]
[6,25]
[35,36]
[10,24,28,34,44]
[22]
[7,14]
[4,24]
[8,45]
[9,26]
[1,11]
[5]
[19]
[15]
[16,21,26]
[26,27,32,45]
[18]
[43]
Chordata
Vertebrata
Gnathostomata
Reptilia
Mammalia
Amphibia
Theria
Dipnoi
Placentalia
Primates





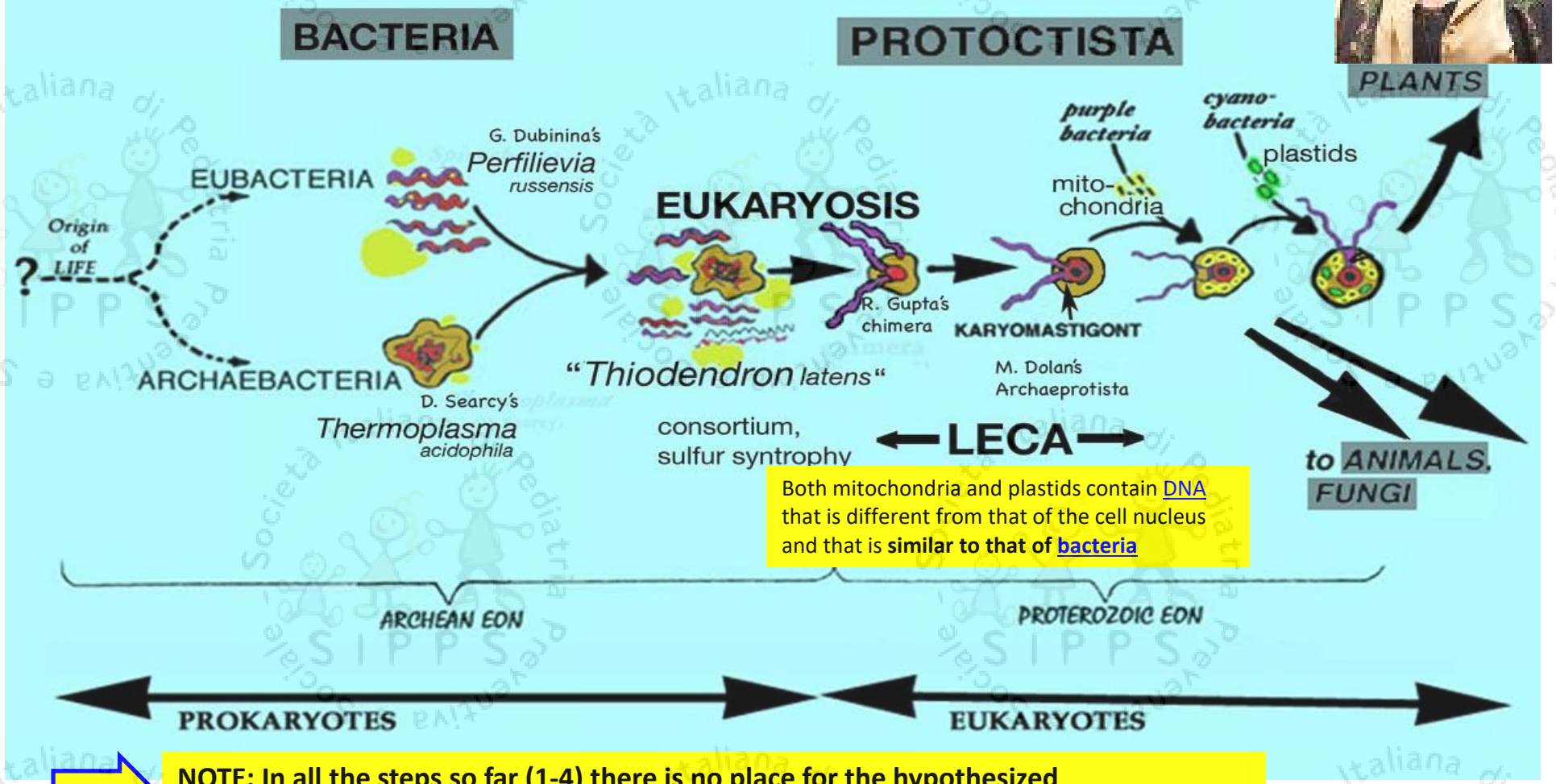
David Hillis TREE



David Hillis TREE

The incorporation of microbial symbionts, and the progressive formation of eukaryotic cells .. and then the formation of multicellular organisms, etc.

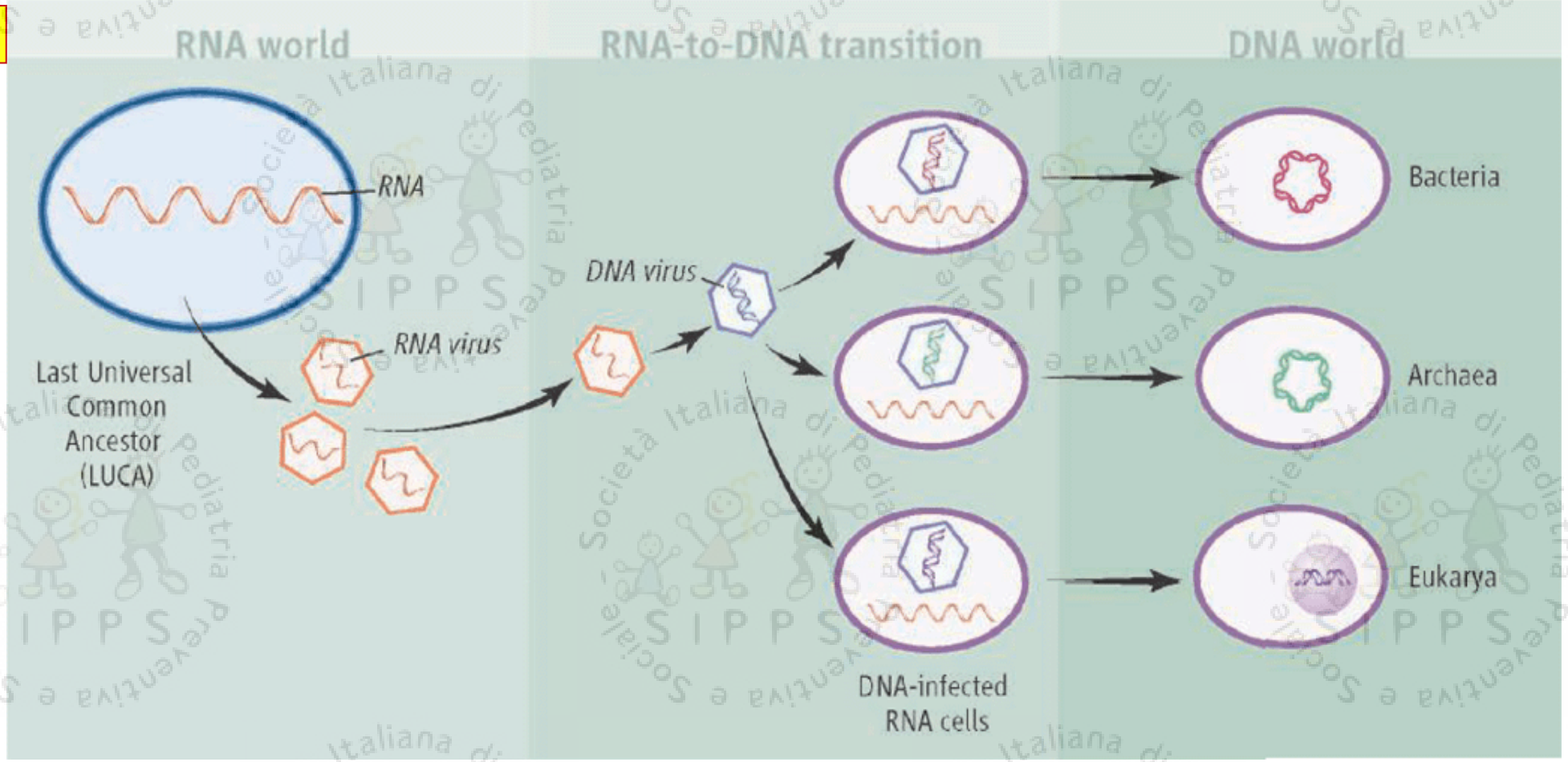
The **endosymbiotic theory** was first articulated by the Russian botanist Konstantin Mereschkowski in 1905 and substantiated with microbiological evidence by Lynn Margulis in 1967.. According to Margulis and Dorion Sagan "**Life did not take over the globe by combat, but by *networking*" (i.e., by *cooperation*).**



Both mitochondria and plastids contain DNA that is different from that of the cell nucleus and that is **similar to that of bacteria**

NOTE: In all the steps so far (1-4) there is no place for the hypothesized stochastic genetic mutations as a key driver of the process

And *Viruses*?



Forterre proposes that **all living organisms share a common ancestor that stored its genetic information in RNA. Some of its genes evolved into viruses**.
Later, **some of those viruses evolved DNA as a way to defend their genes from attack, and DNA-based viruses became incorporated into hosts**.
Host genes were then transferred onto viral chromosomes and shared. In the process, the three major domains of DNA-based life emerged

Did DNA Come From Viruses? ***SCIENCE*** *12 May 2006: vol. 312 no. 5775 870-872*

PROCEEDINGS OF THE AMERICAN PHILOSOPHICAL SOCIETY VOL. 148, NO. 3, SEPTEMBER 2004

Can Viruses Make Us Human?[1]

LUIS P. VILLARREAL
Director, Center for Virus Research
University of California at Irvine

A hugely **underrated role** is played by the **(retro)viruses** and by **HGT** (horizontal transfer) of mobile sequences: in particular **in higher organisms major acquisitions and transformations are produced by gene insertions ..**

THIS QUESTION WILL SEEM preposterous to most. Viruses are molecular genetic parasites and are mostly recognized for their ability to induce disease in their host. Their effect on host evolution has long been thought to be like that of a predator on its prey, eliminating the host with weakened defenses. How can we propose any constructive role for viruses? Many viruses, however, can infect their host in a stable and persisting manner, generally with no disease, often for the life of the host. Such viruses can bring to bear onto their host the viral seeds of genetic creation. For such persisting viruses to successfully colonize their host, they must superimpose a complex viral molecular genetic identity onto their host.

A ***key-example***: the ***placenta***. ***Syncytiotrophoblast*** being the **product of a protein encoded by a retrovirus… mammals are the "product" of the insertion** of retroviruses' in genomes of previous organisms...

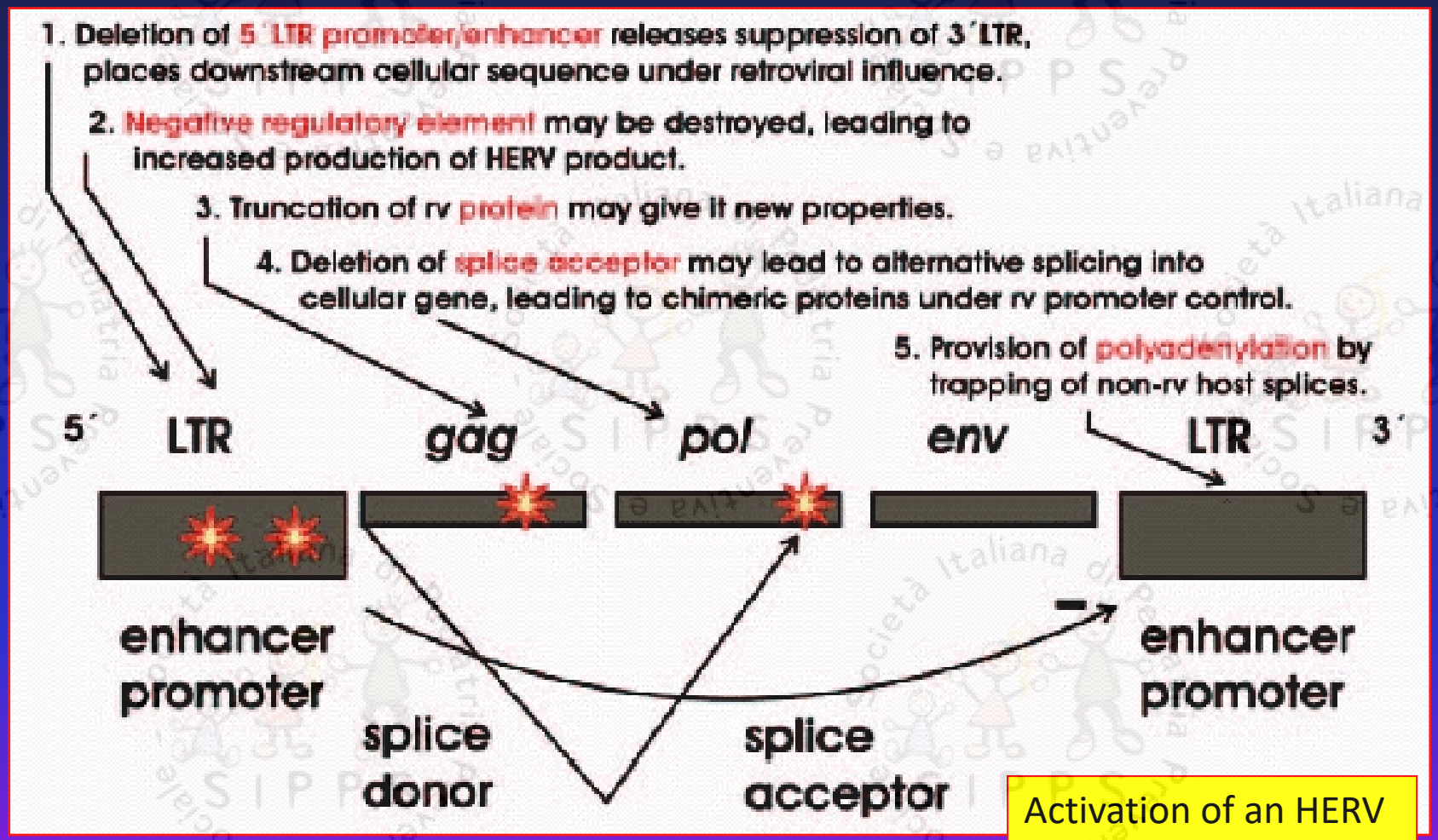
« Hotwiring the Human Genome: The Programming Language of Life | Main | MIT Scientists Mimic Plants' Energy Storage System -Discovery to Unleash Solar Revolution »

August 01, 2008

Were Ancient Viruses a Key to Human Evolution?

When the mapping of the human genome was completed in 2003, researchers discovered a shocking fact: our bodies are littered with the shards of retroviruses, fragments of the chemical code from which all genetic material is made. This discovery has created a new discipline, paleovirology, which seeks to better understand the impact of modern diseases by studying the genetic history of ancient viruses.

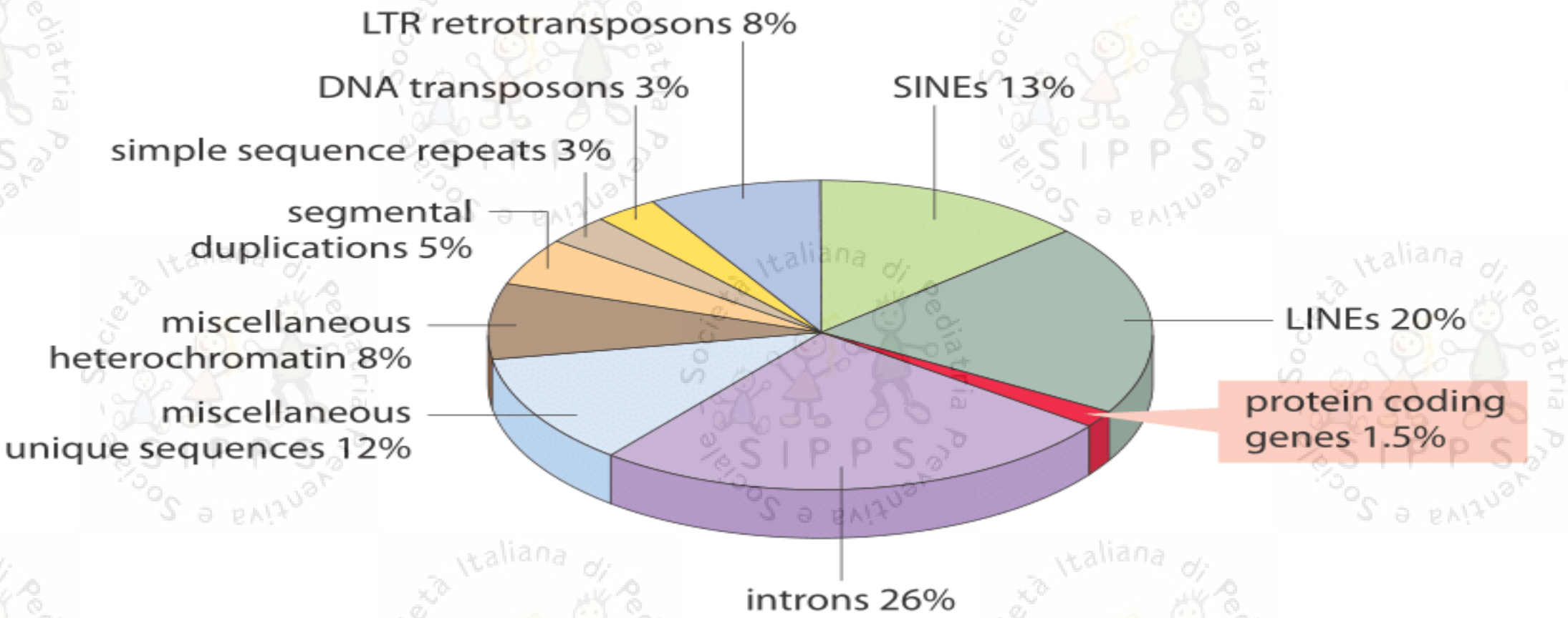
… playing a **reactive-adaptive role.. processing / engineering** the entire genome (→ Shapiro's ***Natural Genetic Engineering***)



Activation of an HERV through mutation

Retroviruses are our more intimate symbionts

main components of the human genome



About 1.5% of the genome consists of the ≈20,000 protein-coding sequences which are interspersed by the non coding introns, making up about 26%. Transposable elements are the largest fraction (40-50%) including for example long interspersed nuclear elements (LINEs), and short interspersed nuclear elements (SINEs). (adapted from T. R. Gregory Nat Rev Genet. 9:699-708, 2005 based on International Human Genome Sequencing Consortium. Initial sequencing and analysis of the human genome. Nature 409:860 2001.)

BioEssays Vol. 18 no. 9
© ICSU Press 1996 pp. 695–696 BIO1029

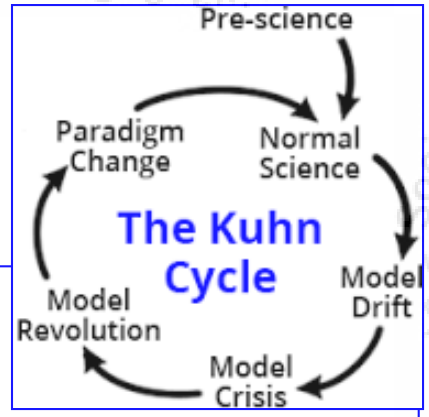
Are there 'Kuhnian' revolutions in biology?

Adam S. Wilkins

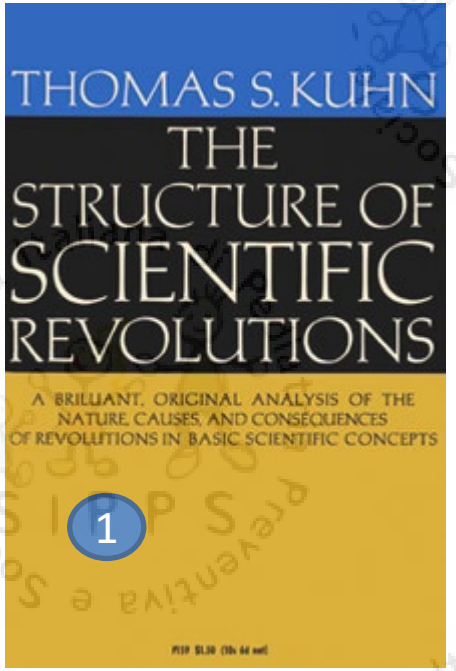
The recent death, on 17 June 1996, of the noted philosopher of science, Thomas Kuhn, at age 73, provides a suitable occasion to remember and commemorate his contributions to the philosophy of science. It also provides an appropriate moment to ask how well the Kuhnian idea of scientific revolutions, which was developed principally from study of the physical sciences, applies to biology.

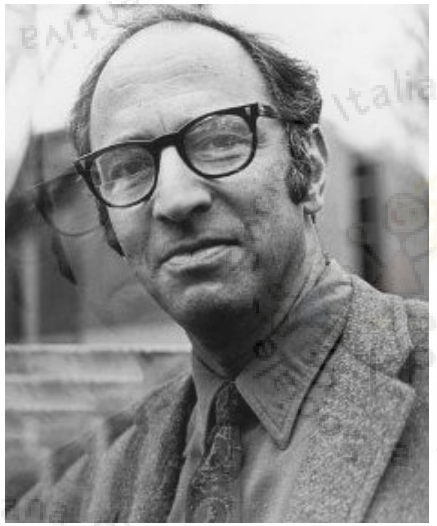
Kuhn, a professor emeritus at MIT in recent years, had written or coauthored five books and numerous scholarly articles, but he is undoubtedly best known, and will be best remembered, for *The Structure of Scientific Revolutions*[1], first published in 1962. In this seminal work, Kuhn argued persuasively against the traditional idea of 'scientific progress', the notion that scientific knowledge involves the steady growth of understanding through the application of something called 'The Scientific Method'. He argued that, in reality, science involves two distinctly different processes. For the most part, scientists work within certain conceptual frameworks or models, 'paradigms'. This work serves to embellish and strengthen the central paradigm at the heart of each field and is essentially conservative in nature. Kuhn termed such activities 'normal science'. Yet, the continued practice of normal science within a field often shows up weaknesses in the central paradigm. When these weakdigms' and the like. The notion that what scientists believe at any one time is determined in part by group consensus – in some corridors, there were mutterings that the idea involved little more than 'mob rule' in deciding scientific truth, a notion vehemently denied by Kuhn himself[3] – was unsettling. Furthermore, the neurological implications – that young brains are much more likely to generate and be receptive to major conceptual breakthroughs – though not new, could not have been comforting to those past their first youth. Nevertheless, the impact of Kuhn's idea was immediate and pervasive. It would not be inappropriate to refer to the 'Kuhnian revolution' in the philosophy of science.

The question of generality, however, still nags. In contrast to many earlier, *a priori*, philosophical theories of knowledge, Kuhn built his case from examples, in effect inductively. (Kuhn's ideas co-exist uneasily today with those of Karl Popper, an arch-foe of argument from induction; it is, in fact, impossible to be both a Kuhnian and a Popperian, at least at the same instant.) Kuhn's primary examples were all drawn from physics and chemistry – Kuhn had taken his bachelor's degree in physics – and involved some of the classic discoveries in those sciences: the Copernican, Newtonian and Einsteinian revolutions and Lavoisier's disproof of the phlogiston theory.



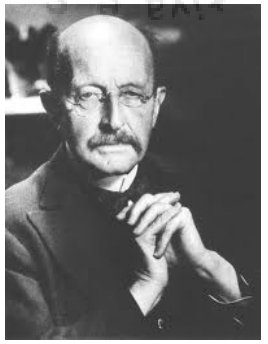
The recent **death**, on **17 June 1996**, of the noted philosopher of science, **Thomas Kuhn**, at age 73, provides a suitable occasion to remember and commemorate **his contributions to the philosophy of science.** It also provides an appropriate moment **to ask how well the Kuhnian idea of scientific revolutions, which was developed principally from study of the physical sciences, applies to biology**.



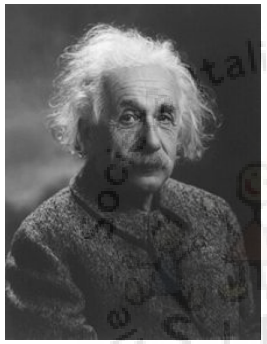


Ludwig Boltzmann

James Clerk Maxwell



Max Planck



Albert Einstein**

Louis de Broglie

E Schrödinger **

Classical physics draws a **distinction between particles and *energy***, holding that only **the latter exhibit waveform characteristics**, ***whereas quantum mechanics*** **is based on the observation that matter has both wave and particle aspects** and postulates that the state of **every subatomic particle can be described by a wave-function—a mathematical representation** used to calculate the **probability** that the particle, if measured, will be in a given location or state of motion… These **models could not easily be reconciled with the way objects are observed to behave on the macro-scale of everyday life**. The **predictions** they offered often appeared **counter-intuitive and caused much consternation among the physicists —often including their discoverers** **.

W. Heisenberg

Niels Bohr

Boltzmann had a tremendous admiration for **Darwin** and he wished **to extend Darwinism from biological to cultural evolution**. In fact **he considered biological and cultural evolution as one and the same things**. ... In short, **cultural evolution was a physical process taking place in the brain**. Boltzmann included ethics in the ideas which developed in this fashion (S.R. de Groot)

Towards a *Kuhnian Revolution* in Biology

nature biotechnology

COMMENTARY

EPIGENESIS AND COMPLEXITY

The coming Kuhnian revolution in biology

Richard C. Strohman

The Watson-Crick era, which began as a narrowly defined and proper theory and paradigm of the gene, has mistakenly evolved into a revived and thoroughly molecular form of genetic determinism.

2

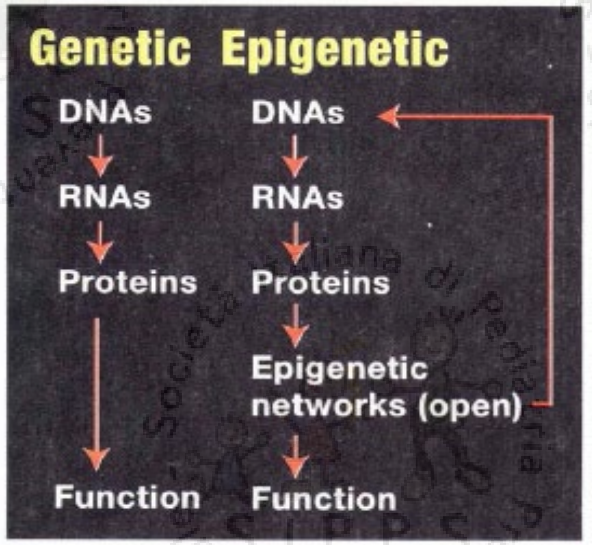


Figure 1. Genetic and epigenetic theories of information processing.

We have **wrongly extended the linear theory of the gene** to the "realm" of the gene management.. . but the **gene management is an entirely different process,** involving **interactive cellular processes that display an interactive complexity... which is epigenetic in nature**

3

1

In 1997 the well known molecular biologist **R. Strohman** attempted an oblique **attack against the *central dogma* of molecular biology**; the **deterministic, linear, uni-directional pathway from DNA to RNA to proteins to phenotype..**

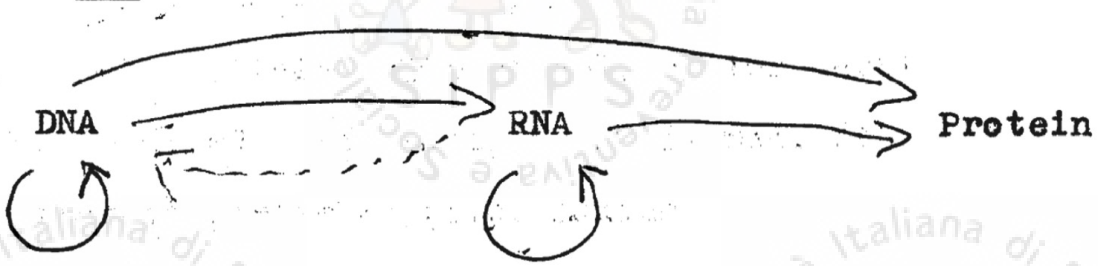
Francis Crick's statement of the central dogma, from an early draft of Crick (1958)
available at http://profiles.nlm.nih.gov/SC/B/B/F/T/_/scbbft.pdf

Ideas on Protein Synthesis (Oct. 1956)

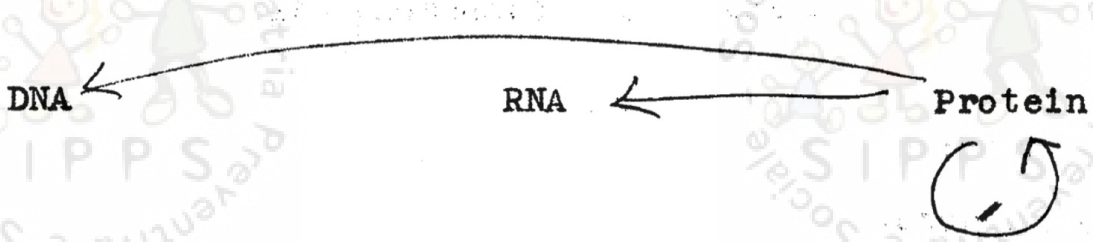
The Doctrine of the Triad.

The Central Dogma: "Once information has got into a protein it can't get out again". Information here means the sequence of the amino acid residues, or other sequences related to it.

That is, we may be able to have



but never



where the arrows show the transfer of information.

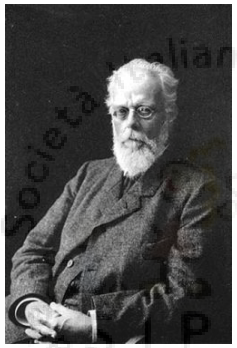
biology letters

The main *dogmas* of the twentieth century biology

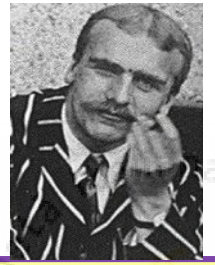
Genetic determinism

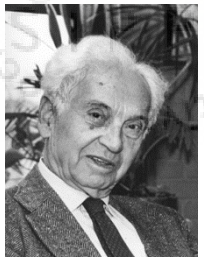
Genetic determinism is the belief that **genes** determine **morphological and behavioral traits** and do so with **little or no influence from environmental factors.**

August Weismann



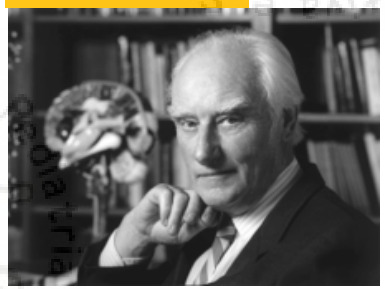
The **Weismann barrier** is the principle that **hereditary information moves only from genes to body cells**, and never in reverse. In more precise terminology **hereditary information moves only from germline cells to somatic cells** (that is, **soma to germline feedback is impossible**).

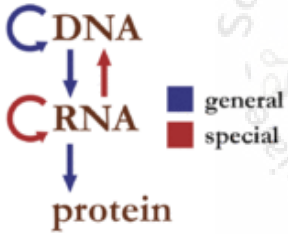


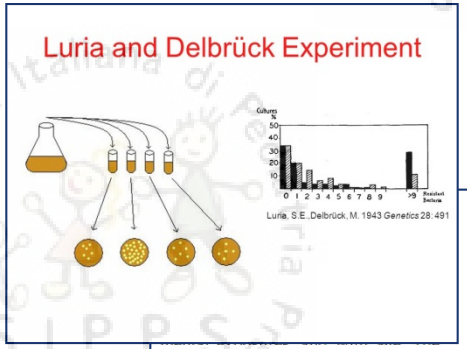

The Modern Synthesis: Following the rediscovery of Mendel's principles of genetics, several theorists such as **RA Fisher, JBS Haldane, Sewall Wright, Ernst Mayr** and **Theodosius Dobzhansky** contributed to the **synthesis of Mendel and Darwin's concept of natural selection…** The **organism** responds to a **dual causation**, one based on **laws of physics**, the other based on a **genetic program…** reflecting the **mechanics** of its constituent parts & the **phylogenetic history encoded in its genes**

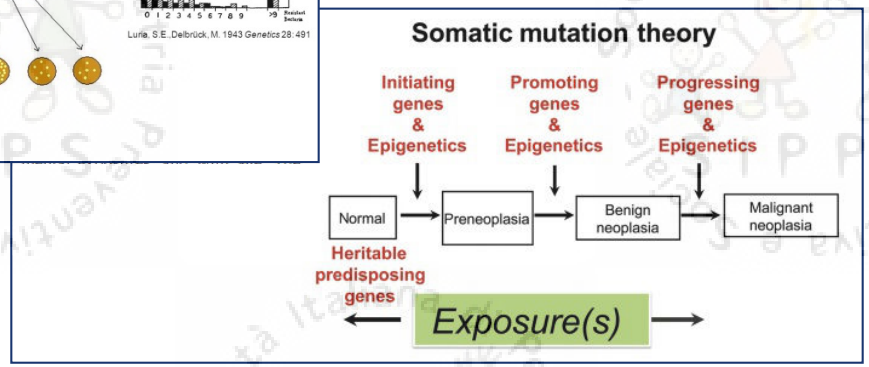
Francis Crick



The **Central Dogma of molecular biology** deals with the **detailed residue-by-residue transfer of sequential information.** It states that such **information cannot be transferred back from protein to either protein or nucleic acid.**





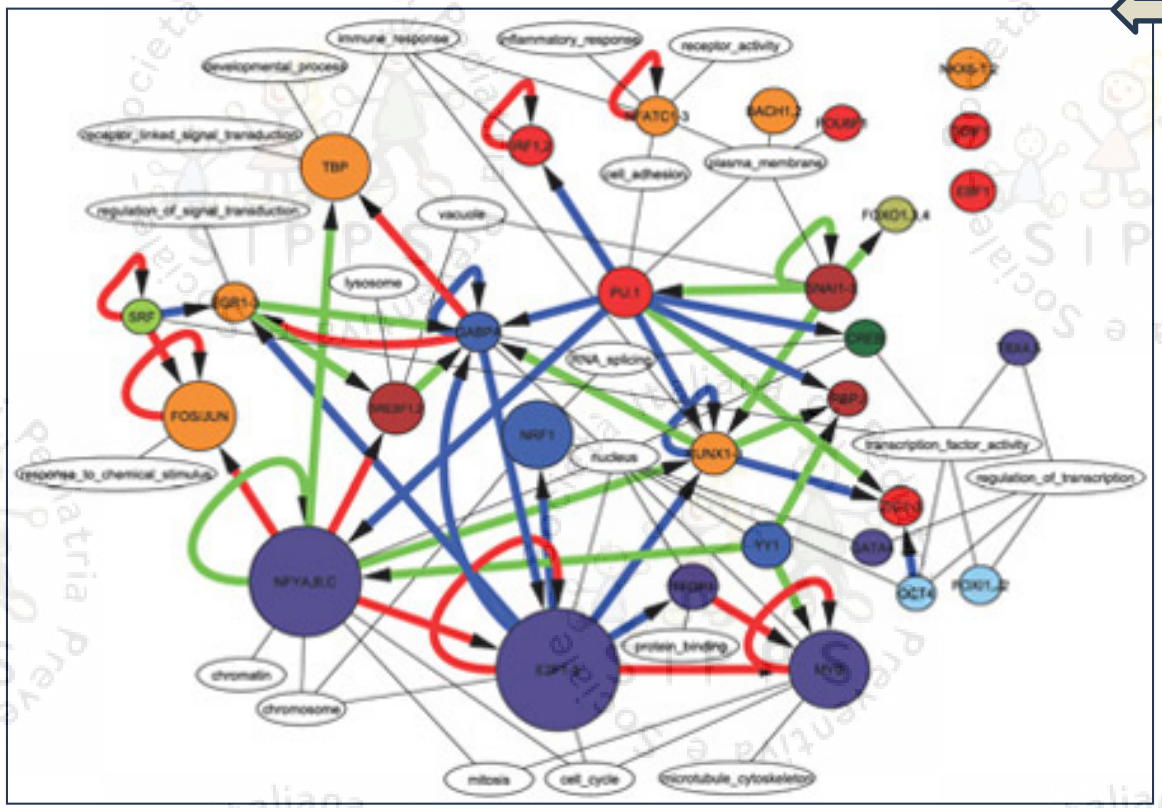


Science
AAAS

ScienceInsider
Breaking news and analysis from the world of science policy

From directing **the fate of stem cells to determining how.. we grow**, **the genes in our body act in complex networks..** the whole ***Genome*** is a Complex and **highly dynamic molecular Network** of ***interacting Genes*** and ***non-codifying sequences.***. and ***proteins***

....Genes Know How to Network…BUT…



http://news.sciencemag.org/sciencenow/2009/04/21-03.html

IN FACT Genes need to be told to switch "off" and "on":

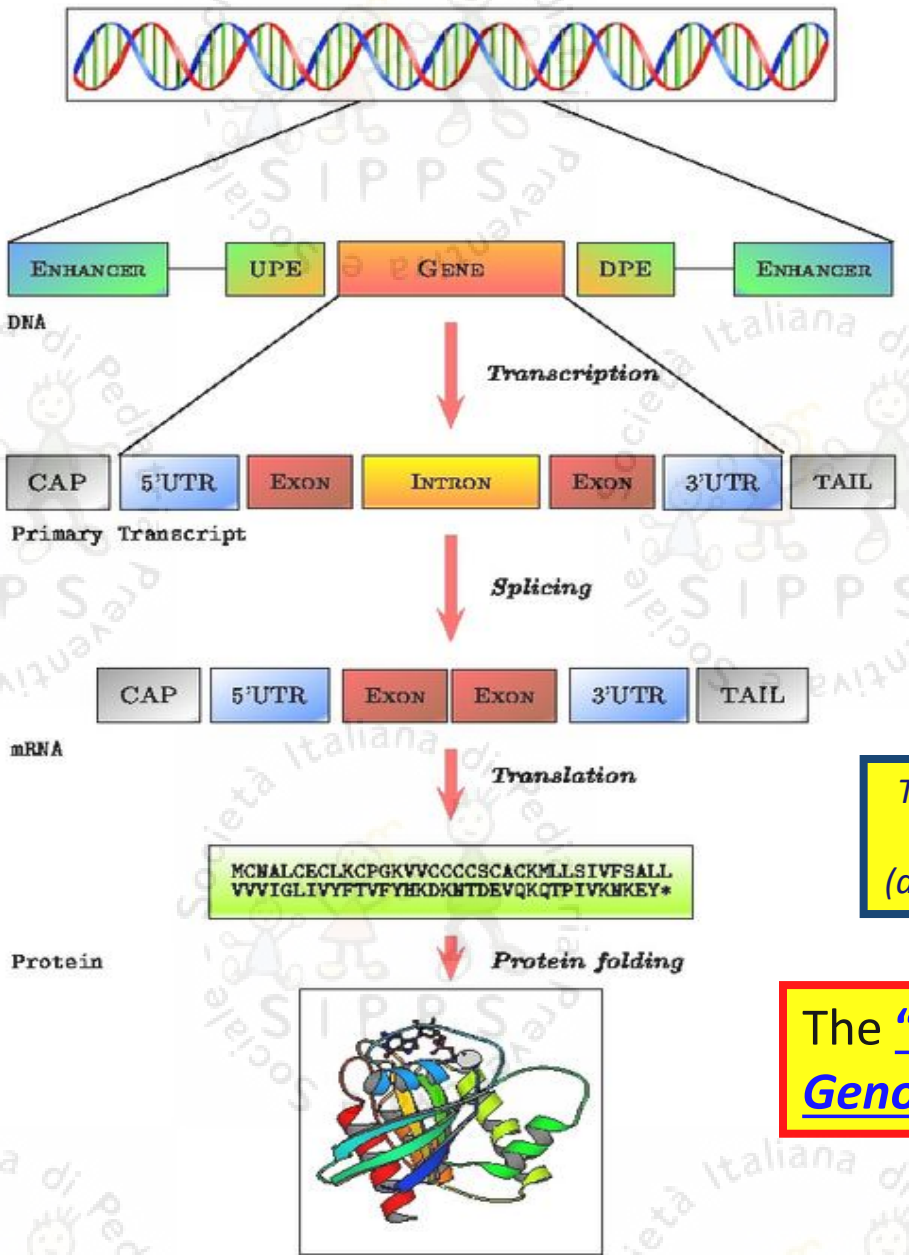
- **Genes need to be told** how much **expression (protein) is required** and where.
- **Genes need to be regulated** – this **regulation is not performed by DNA** but by many other controls arranged in a **complex network**
- DNA has been called the *Book of Life* by the *Human Genome Project* scientists, but many other biologists consider **DNA to be simply a random collection of words from which a meaningful story of life may be assembled…**
- **In order to assemble that meaningful story, a living cell uses a second informational system. (...)**

The key concept here is that these dynamic-epigenetic networks have a life of their own —they follow network-rules not specified by DNA

Strohman R. , April 2001 Beyond genetic determinism

If the **Central Dogma** of Molecular Biology depicted **one direction-flow of genetic information**……

we now know that things are quite different: **information flow is circular between genome and environment**



SYSTEMS **GENOMICS** ***(BIOLOGY)***

REVERSE TRANSCRIPTION

GRNetworks

TRANSPOSABLE ELEMENTS

NATURAL GENETIC ENGINEERING

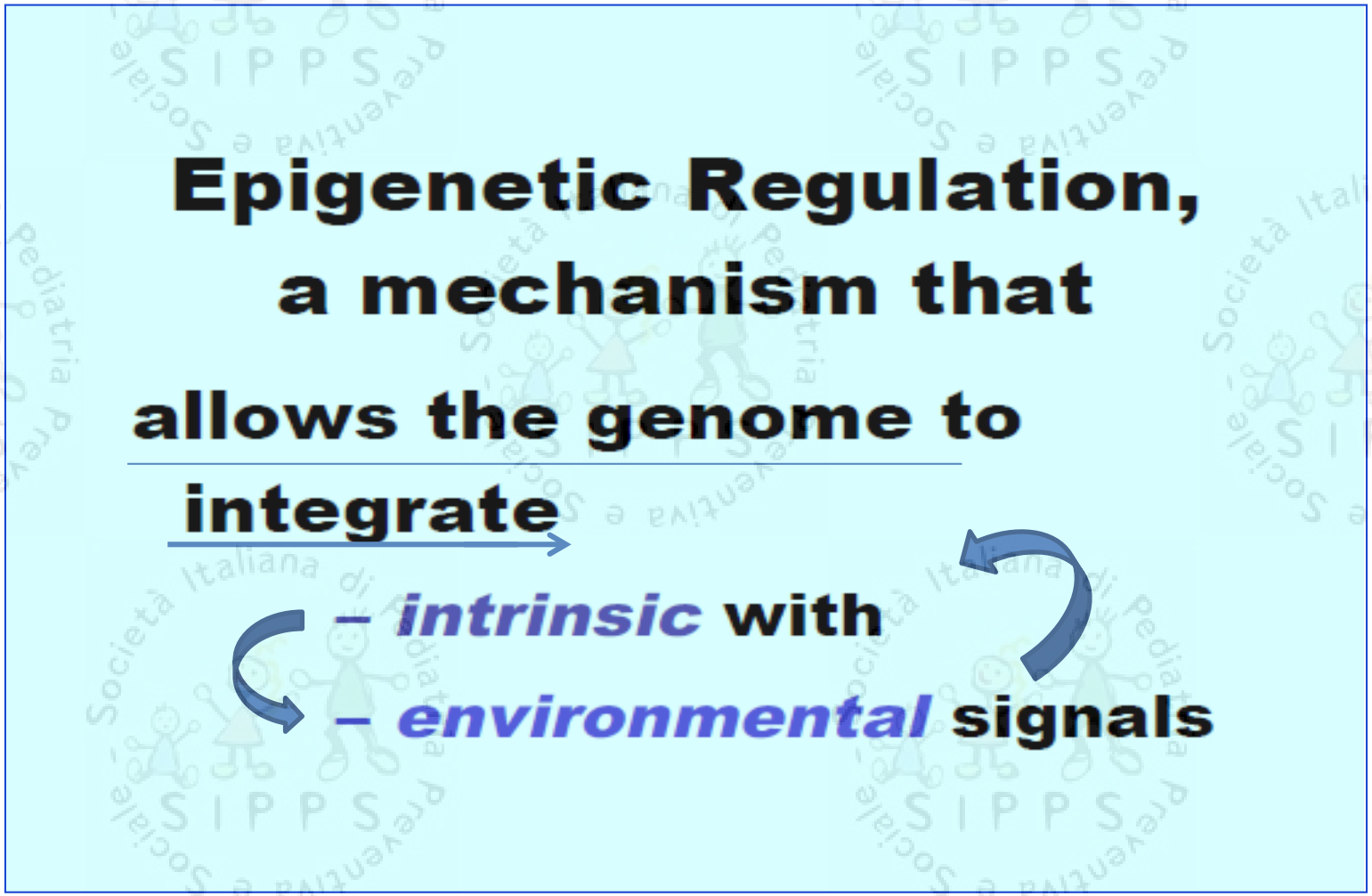
TRANSCRIPTION FACTORS (and COFACTORS)

EPIGENETIC CHANGES

The ***"Fluid Genome"***

ENVIRONMENT

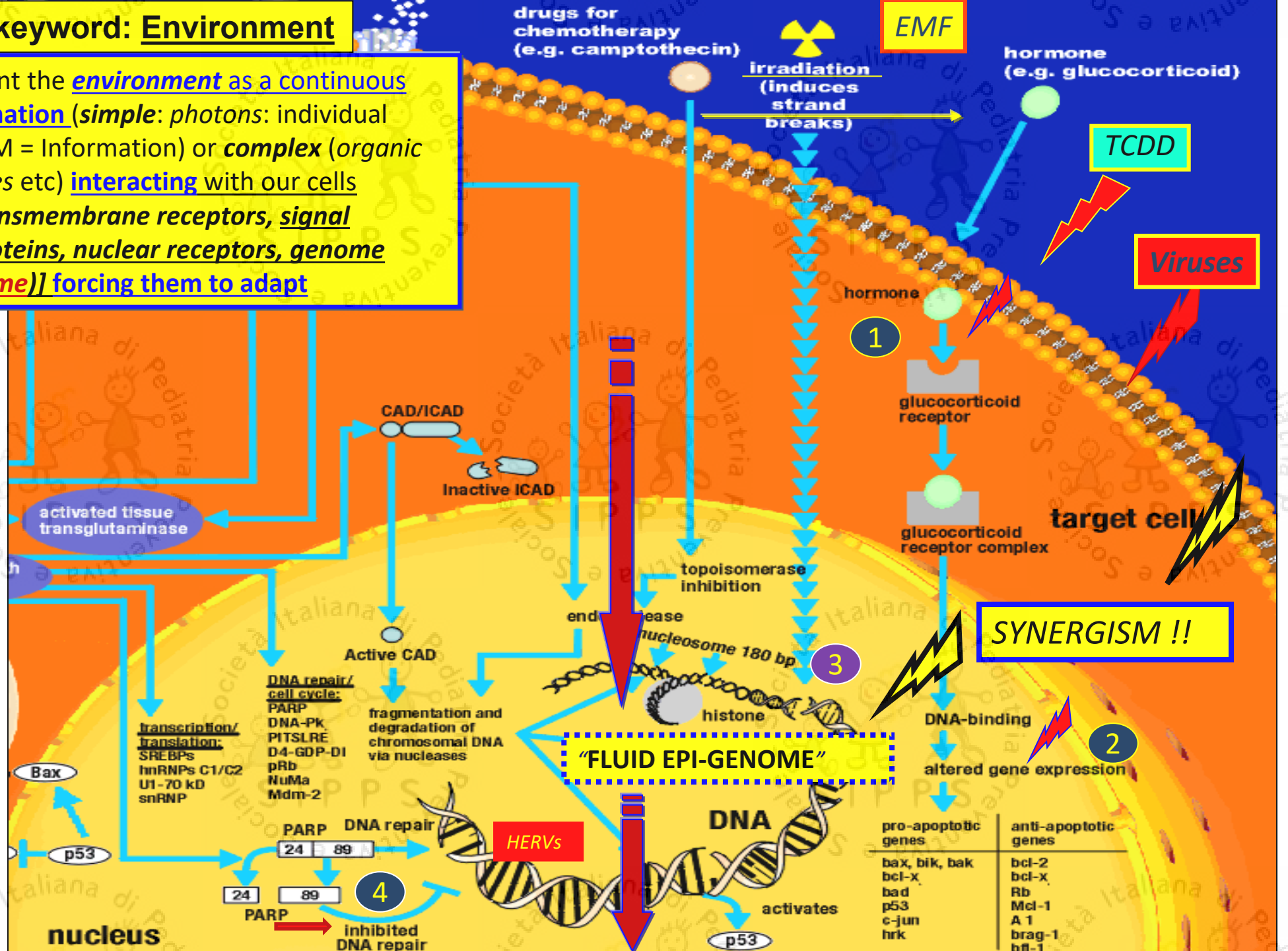
In such a **fluid and systemic model** the ***epigenome*** (also defined by some scientists as **the controlling *software*** of the genome) behaves as a sort of *compensation chamber* - the specific place where the flow of **information** that comes from outside (*environment* and *microenvironment*) meets and interacts with the **information encoded in the genes** for millions years (the ***hardware***)



Rudolf Jaenisch- Whitehead Institute and Dept. of Biology, MIT, Cambridge, MA

The **second keyword: Environment**

We may represent the ***environment*** as a continuous stream of **information** (***simple***: *photons*: individual packages of E = M = Information) or ***complex*** (*organic molecules, viruses* etc) **interacting** with our cells [***membrane /transmembrane receptors, signal transduction proteins, nuclear receptors, genome (DNA + Epigenome)]*** **forcing them to adapt**

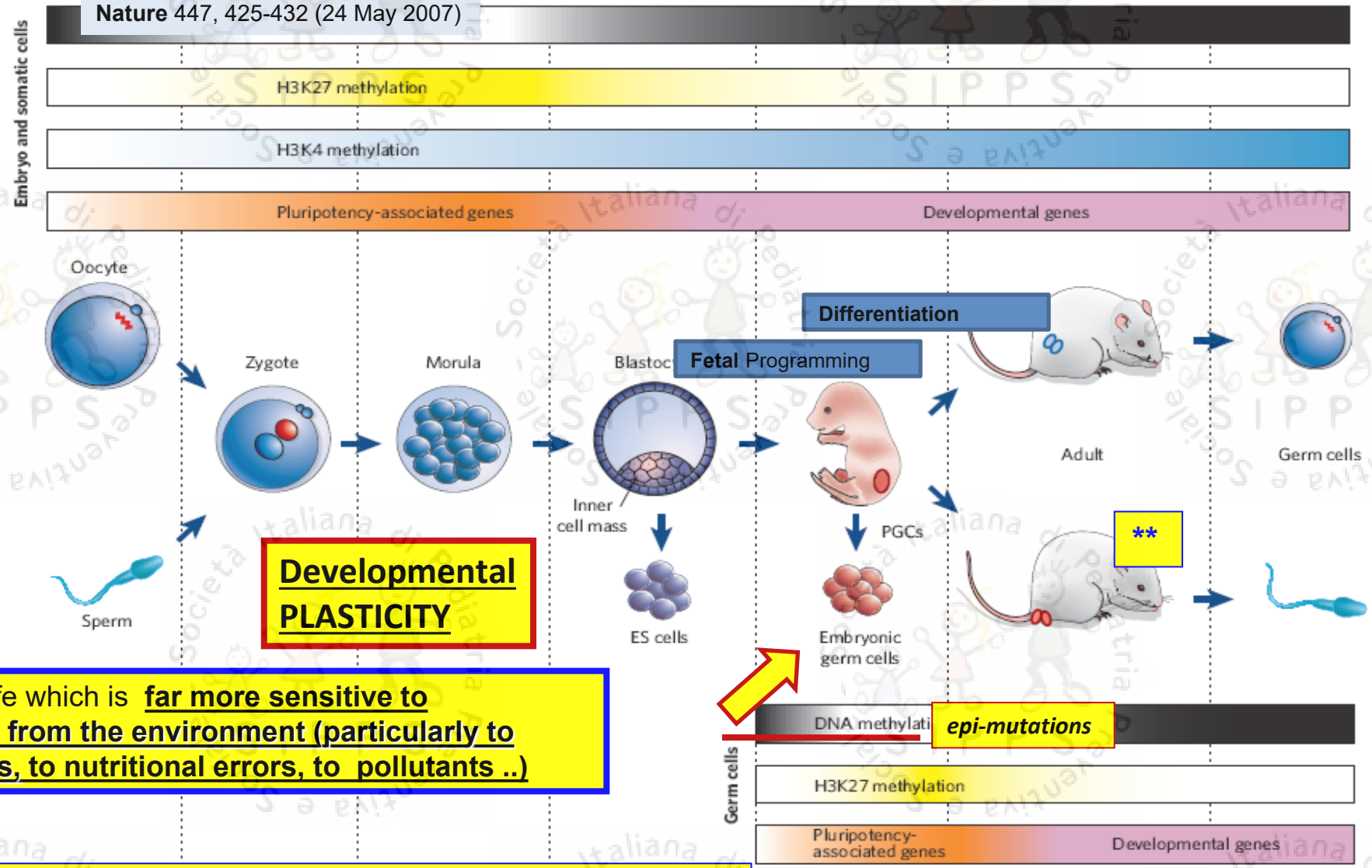


The **fourth** keyword is ***developmental plasticity***

Cellular Differentiation*: an *epigentic process

The actual genetic program of a single multicellular organism is the product of nine months of epigenetic adaptive-predictive "formatting" of trillions of cells)

Stability and flexibility of epigenetic gene regulation in mammalian development



Developmental PLASTICITY

1 → 2

Differentiation is the process through wich the organism changes **from a zygote to a complex system** of **tissues** and **200 cell types (genetically identical.. each with its own epigenetic and morpho-functional characteristics) ..**

3

This is the stage of life which is **far more sensitive to information coming from the environment (particularly to maternal-fetal stress, to nutritional errors, to pollutants ..)**

The ***brain**** is by far the ***most plastic organ*** during all (human) life

ylation. During the early development of PGCs, DNA methylation and

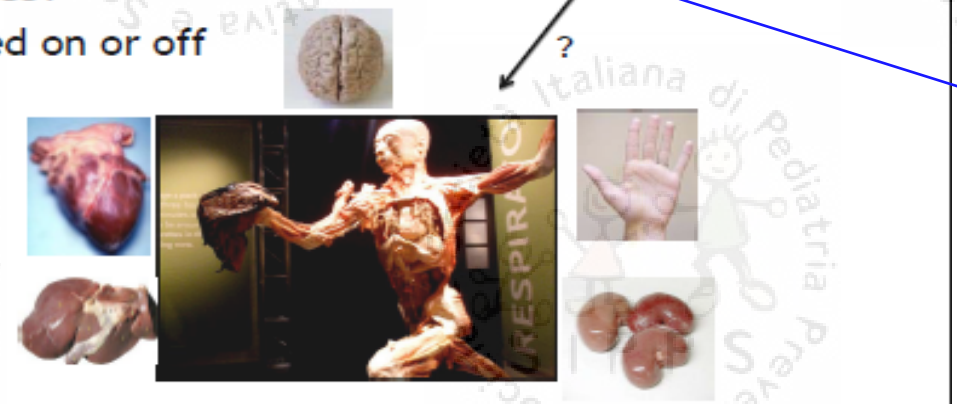
The **fourth** keyword is ***developmental plasticity***

Same DNA, Different Look

- We are made up of over 200 cell types.
- Each cell has the same DNA!
- How can they look so different?

Epigenetics!

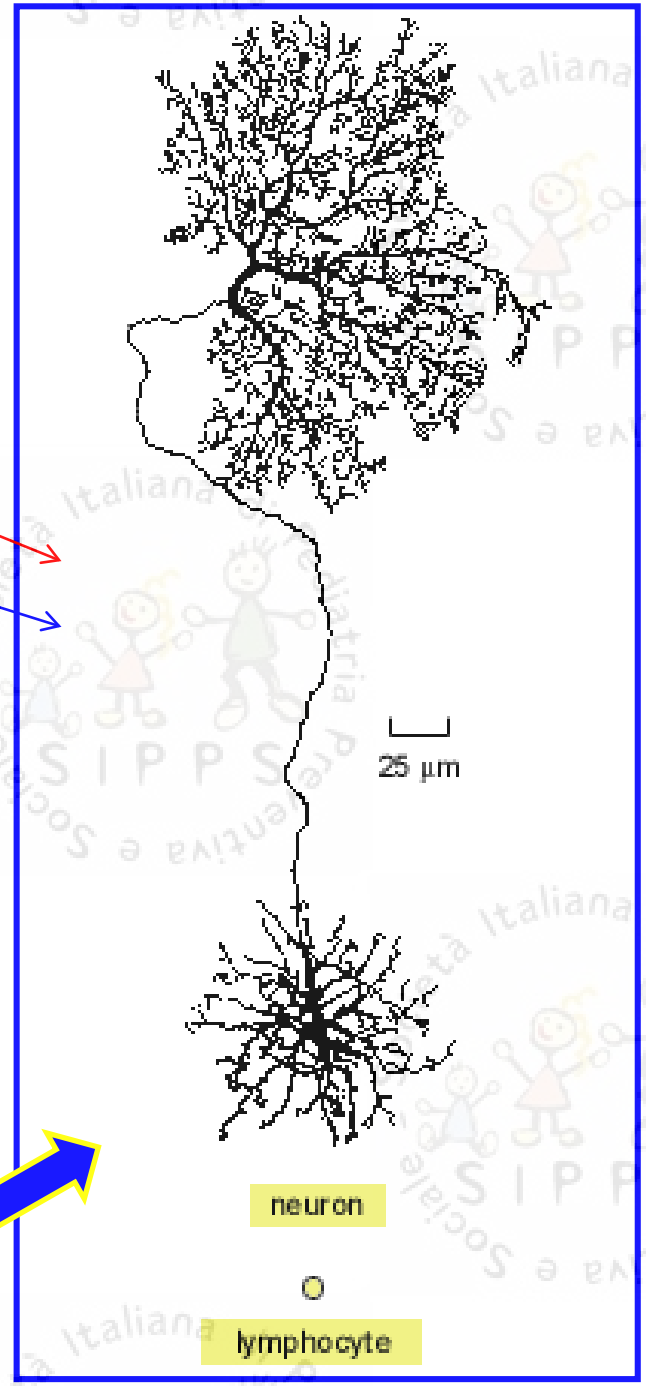
- Genes turned on or off



Wikimedia Commons, ORNL.gov, Flickr: richdelux

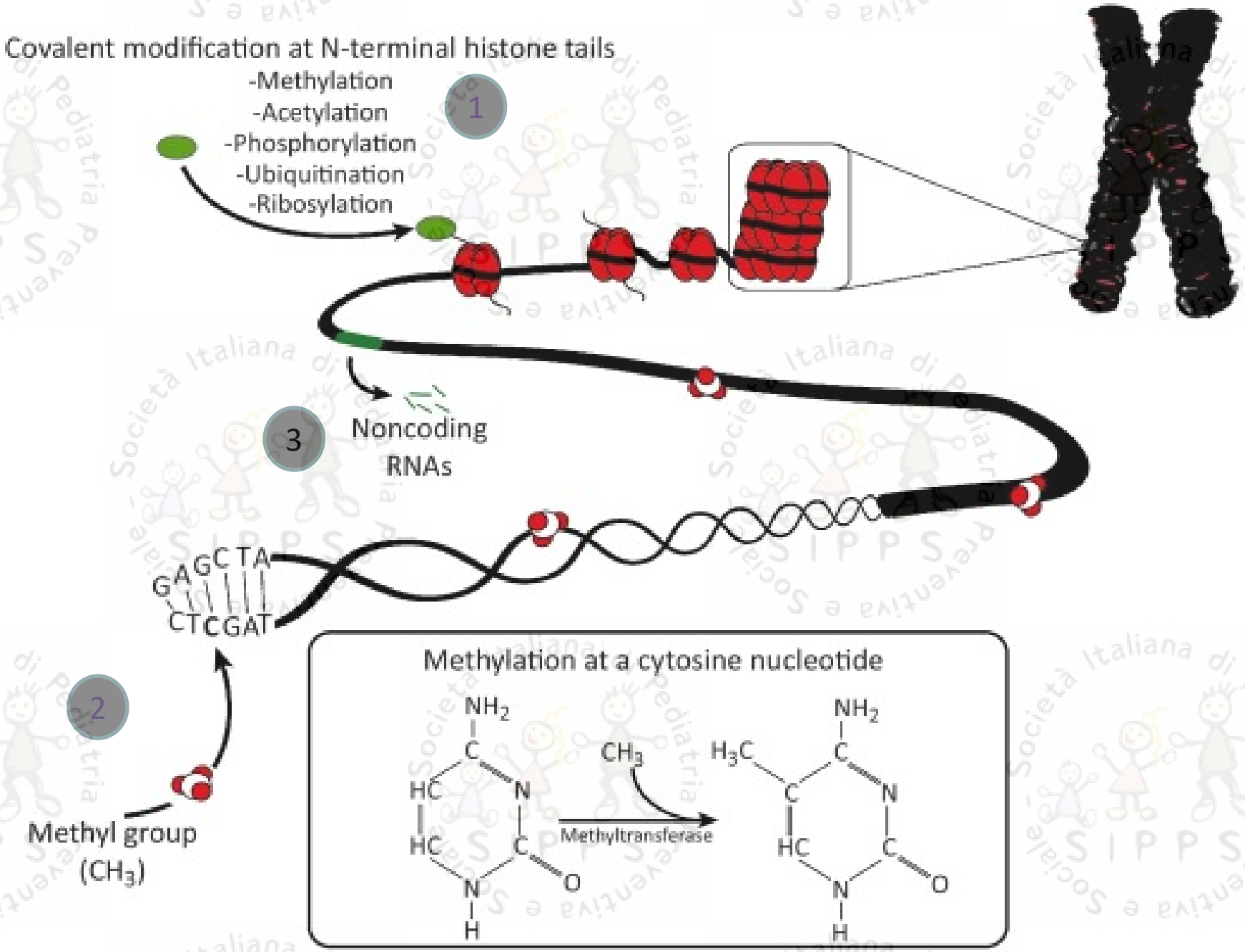
HARVARD MEDICAL SCHOOL

This image clearly shows the **"power" of the epigenome** and the **predominant role of environmental information in the phenotypic shaping of cells, tissues , organisms** .. the **huge phenotypic (morpho- functional) difference** between a *lymphocyte* and a *neuron* **is not due to DNA, which is virtually identical in the two cells** , but to the manner in which **the same genome has been utilized by the two cells**, on the basis of the **information (positional and environmental) received during the first months of life (for neuron in the first 2 years)** and **processed by the epigenetic networks**

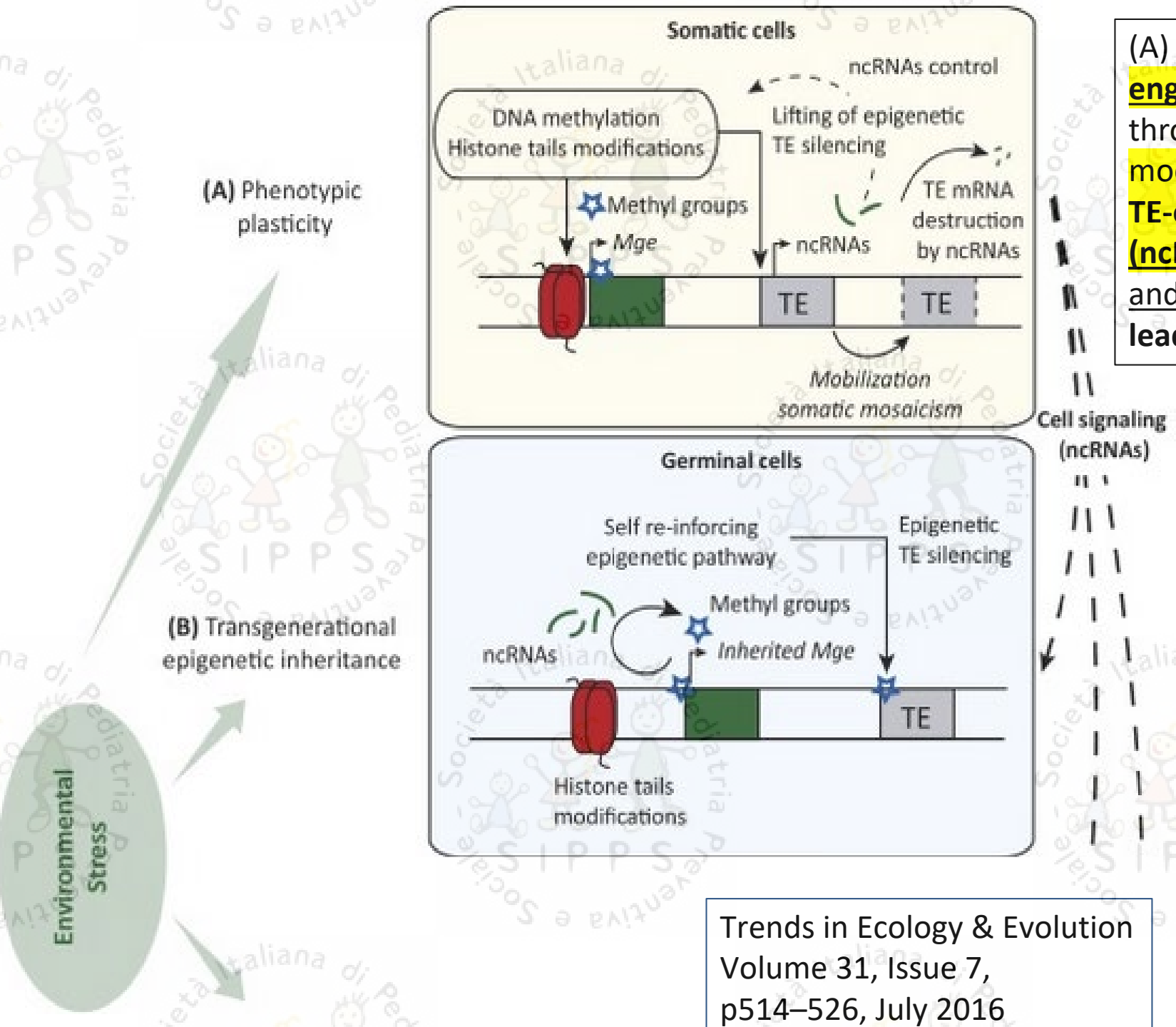


Adaptation to Global Change: A Transposable Element–Epigenetics Perspective

Trends in Ecology & Evolution
Volume 31, Issue 7,
p514–526, July 2016



Trends in Ecology & Evolution



(A) **Under stress, the activation of the TE–EC engine** in somatic cells induces **plastic responses** through: (i) DNA methylation and/or modifications of histone tails; (ii) **transcription of TE-encoded regulatory noncoding RNAs (ncRNAs)**; and (iii) lifting of epigenetic silencing and **mobilization of TEs in somatic cells, leading to somatic mosaicism.**

(B) **Stress induces epigenetic modifications in germline cells**. The resulting **phenotypes can be stabilized over generations (transgenerational epigenetic inheritance) through self-reinforcing epigenetic pathways**.

Stress perceived in somatic cells can also induce the **production of circulating ncRNAs that may modify the epigenome of remote germline cells** [dashed arrow from (A) to (B)].

Trends in Ecology & Evolution
Volume 31, Issue 7,
p514–526, July 2016

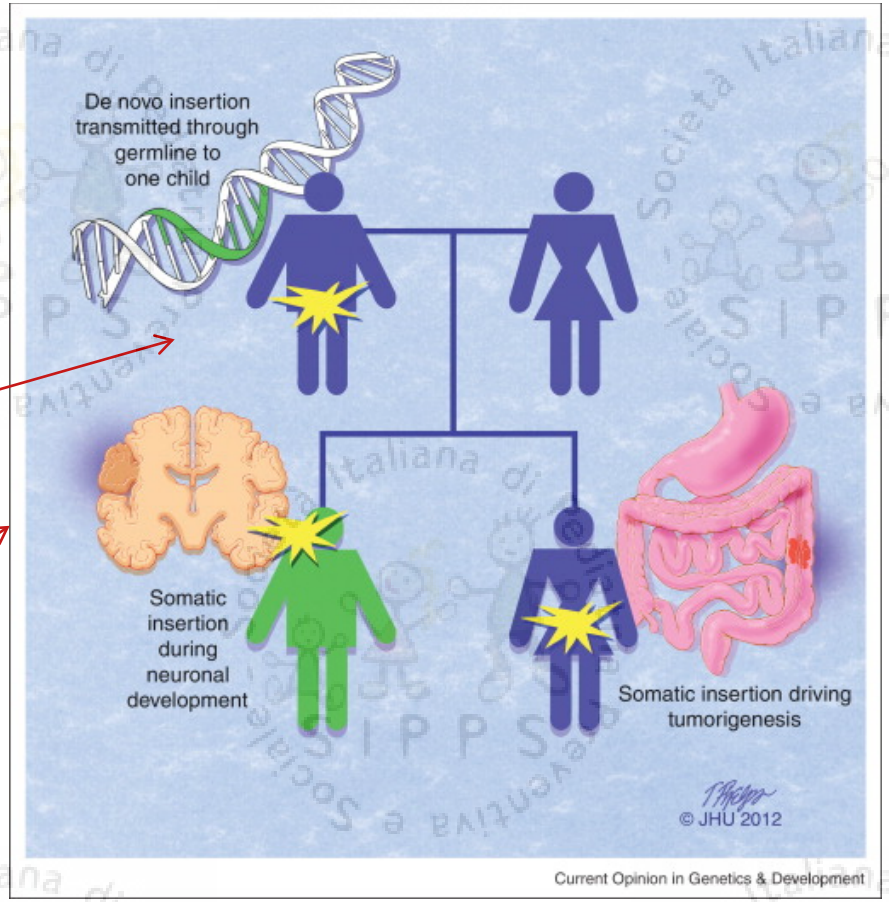
Current Opinion in Genetics & Development
Volume 23, Issue 3, June 2013, Pages 264-270

Functional impact of the human mobilome

Timothy D Babatz [1, 2], Kathleen H Burns [1, 2, 3, 4]

Three families of human retrotransposons remain active today: **LINE1, *Alu*, and SVA** elements. Since 1988, *de novo* insertions at previously recognized disease loci have been shown to generate highly penetrant alleles in Mendelian disorders. Only recently has the extent of **germline-transmitted retrotransposon insertion polymorphism (RIP)** in human populations been fully realized. Also exciting are recent studies of **somatic retrotransposition in human tissues** and reports of **tumor-specific insertions**

(Stochastic *versus* Active/Reactive or even Pro-evolutive)



Transposable elements can be seen as a natural genetic engineering system capable of acting not just on one location at a time but **on the genome as a whole** ..This dynamic view of the genome has been illustrated most impressively by *Shapiro* who stated that **the genome is composed of modular units arranged in a "Lego-like" manner that can be altered under circumstances**

ELSEVIER

Available online at www.sciencedirect.com

SCIENCE DIRECT®

Gene 345 (2005) 91–100

GENE
SECTION
EVOLUTIONARY GENOMICS

www.elsevier.com/locate/gene

Review

A 21st century view of evolution: genome system architecture, repetitive DNA, and natural genetic engineering

James A. Shapiro

Department of Biochemistry and Molecular Biology, University of Chicago, 920 E. 58th Street, Chicago, IL 60637, United States

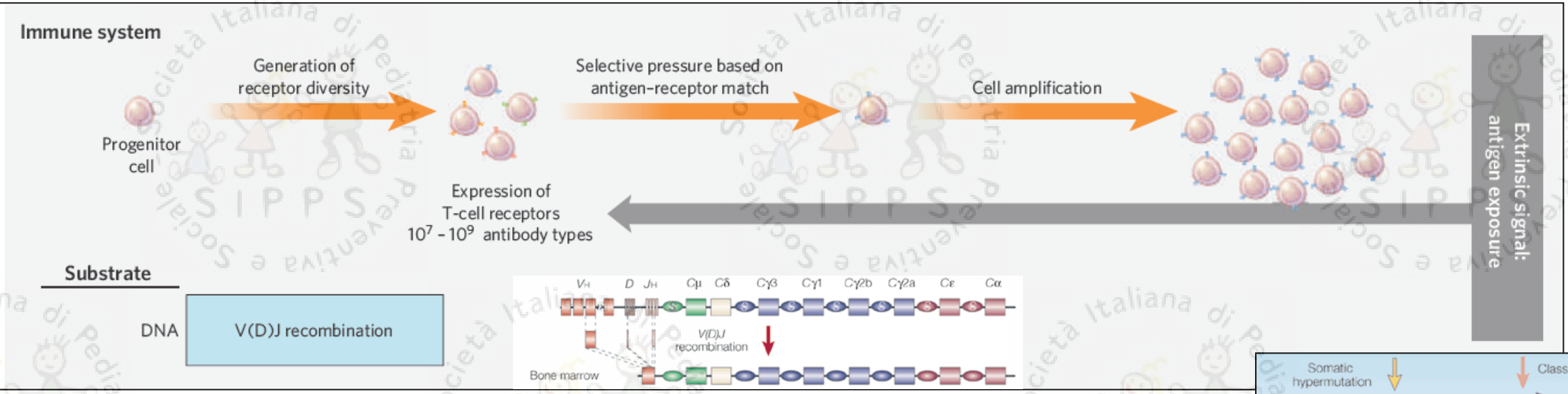
The last 50 years of molecular genetics have produced an abundance of new discoveries and data that make it useful to revisit some basic concepts and assumptions in our thinking about genomes and evolution. Chief among these observations are the complex modularity of genome organization, the biological ubiquity of mobile and repetitive DNA sequences, and the fundamental importance of DNA rearrangements in the evolution of sequenced genomes. This review will take a broad overview of these developments and suggest some new ways of thinking about genomes as sophisticated informatic storage systems and about evolution as a systems engineering process.

1 2 3 4 5

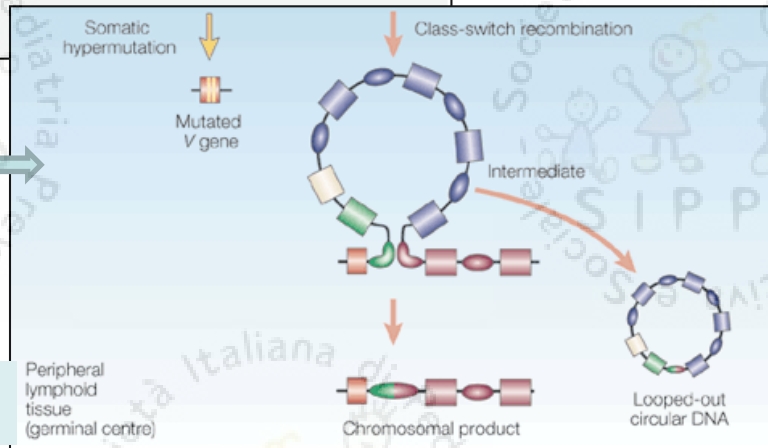
NATURE|Vol 441|29 June 2006|doi:10.1038/nature04959

Generation of neuronal variability and complexity

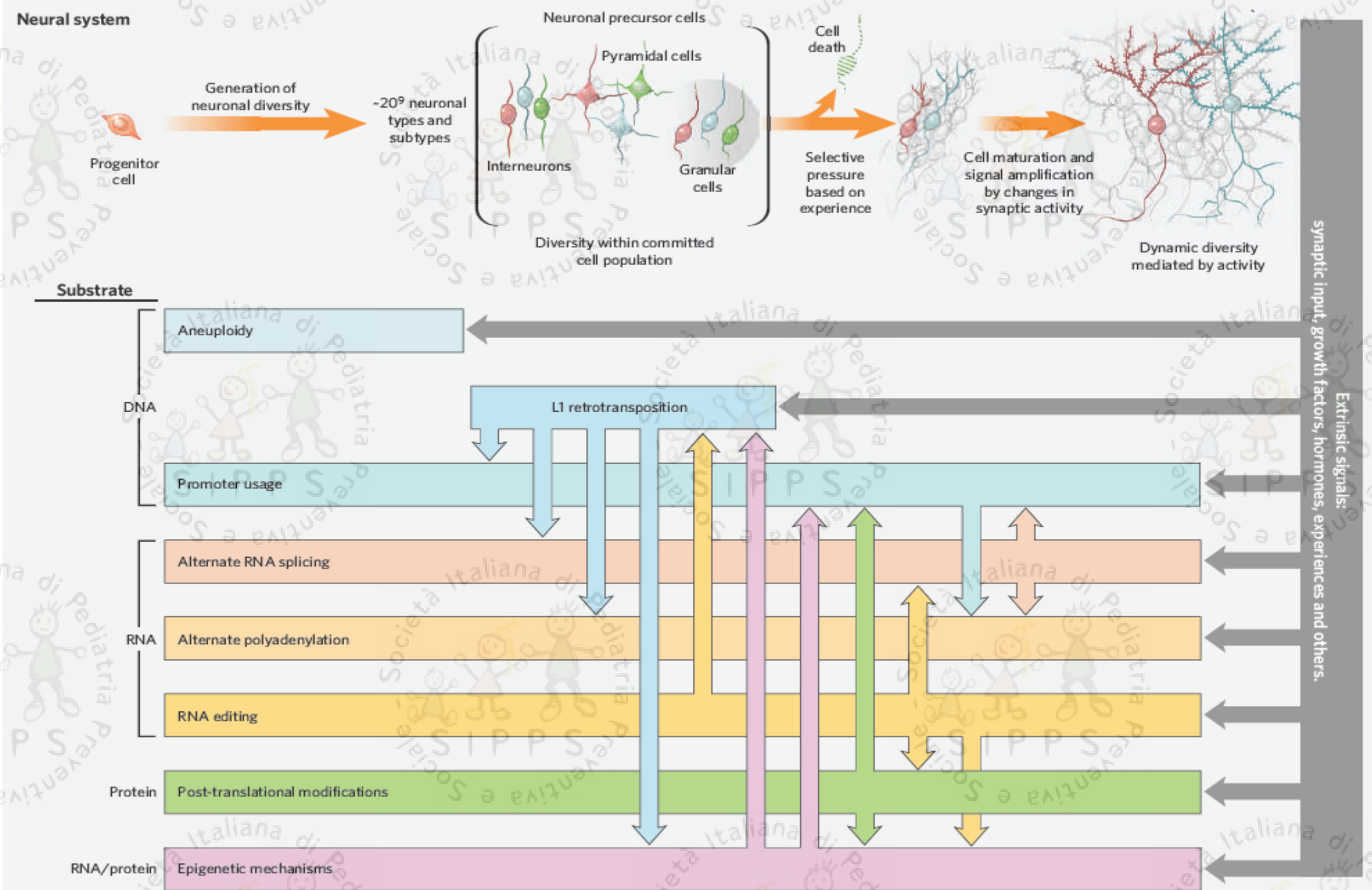
Alysson R. Muotri[1] & Fred H. Gage[1]



+ Somatic Hypermutation !



Kinoshita K., Honjo T. *Linking class-switch recombination with somatic hypermutation*
Nature Reviews Molecular Cell Biology (2001) 2, 493–503


Neural system
Neuronal precursor cells
Pyramidal cells
Cell death
Generation of neuronal diversity
~20⁹ neuronal types and subtypes
Progenitor cell
Interneurons
Granular cells
Selective pressure based on experience
Cell maturation and signal amplification by changes in synaptic activity
Diversity within committed cell population
Dynamic diversity mediated by activity
Substrate
Aneuploidy
DNA
L1 retrotransposition
Promoter usage
Alternate RNA splicing
RNA
Alternate polyadenylation
RNA editing
Protein
Post-translational modifications
RNA/protein
Epigenetic mechanisms
Extrinsic signals: synaptic input, growth factors, hormones, experiences and others.

Historical insight: The clonal selection theory of antibody formation has recently been subjected to challenge from many quarters. A review of its history and that of scientific theories in general points to the importance of distinguishing between the central hypotheses of a theory and its subsidiary implications.

The Clonal Selection Theory: what it really is and why modern challenges are misplaced

Arthur M. Silverstein

Institute of the History of Medicine, Johns Hopkins School of Medicine, 1900 East Monument St, Baltimore, MD 21205, USA. (arts@jhmi.edu)

> *Like every theoretical statement ... the 1957 theory was made in terms of contemporary knowledge ... [and is] incomplete ... [and] expressed in terms that have now become meaningless.*
>
> F. M. Burnet (1967)[1]

The Clonal Selection Theory (CST)[2] of Macfarlane Burnet and David Talmage seems to be under fire currently from several directions. Irun Cohen[3], in considering the role of autoimmunity in the economy of the body, suggested that, "Progress in immunology appears to have rendered the clonal selection paradigm incomplete, if not obsolete; true it accounts for the importance of clonal activation, but it fails to encompass, require, or explain most of the subjects being studies by immunolo- and self-nonself as challenges to the central meaning of CST. Again, in their book *The Generation of Diversity*[7], S. Podolsky and A. Tauber discuss the several challenges to Burnet's idea of self-nonself and conclude that, "Specifically, we must ponder whether CST, as constructed by Burnet, Talmage, and Lederberg [*sic*![8]] ... is now being seriously challenged". Kenneth Schaffner, in his elegant discussion of the philosophical bases of CST, *Discovery and Explanation in Biology and Medicine*, formally defines three levels of hypothesis in CST and actually assigns Burnet's tolerance hypothesis to a secondary level. But even he sometimes seems to suggest that tolerance experiments may serve as tests of CST[9].

From instruction to selection

Between 1930 and the early 1960s, the accepted explanation for the large repertoire of antibody specificities was that antigen somehow acts as a template to transfer information to the globulin-producing mechanism. This was termed an "instruction theory" and was advanced in different forms[10–12]. At a time when immunology was preoccupied with chemical approaches[13], and when little was known about how proteins are formed, these instruction theories seemed plausible. No matter that they could not explain such observations as the persistence of antibody formation, the accelerated and enhanced secondary response or what would later be termed affinity maturation.

SCIENCE sciencemag.org
2 OCTOBER 2015 • VOL 350 ISSUE 6256

NEURODEVELOPMENT

Somatic mutation in single human neurons tracks developmental and transcriptional history

Michael A. Lodato,[1]* Mollie B. Woodworth,[1]* Semin Lee,[2]* Gilad D. Evrony,[1] Bhaven K. Mehta,[1] Amir Karger,[3] Soohyun Lee,[2] Thomas W. Chittenden,[3,4]† Alissa M. D'Gama,[1] Xuyu Cai,[1]‡ Lovelace J. Luquette,[2] Eunjung Lee,[2,5] Peter J. Park,[2,5]§ Christopher A. Walsh[1]§

Neurons live for decades in a postmitotic state, their genomes susceptible to DNA damage. Here we survey the landscape of somatic single-nucleotide variants (SNVs) in the human brain. We identified thousands of somatic SNVs by single-cell sequencing of 36 neurons from the cerebral cortex of three normal individuals. Unlike germline and cancer SNVs, which are often caused by errors in DNA replication, neuronal mutations appear to reflect damage during active transcription. Somatic mutations create nested lineage trees, allowing them to be dated relative to developmental landmarks and revealing a polyclonal architecture of the human cerebral cortex. Thus, somatic mutations in the brain represent a durable and ongoing record of neuronal life history, from development through postmitotic function.

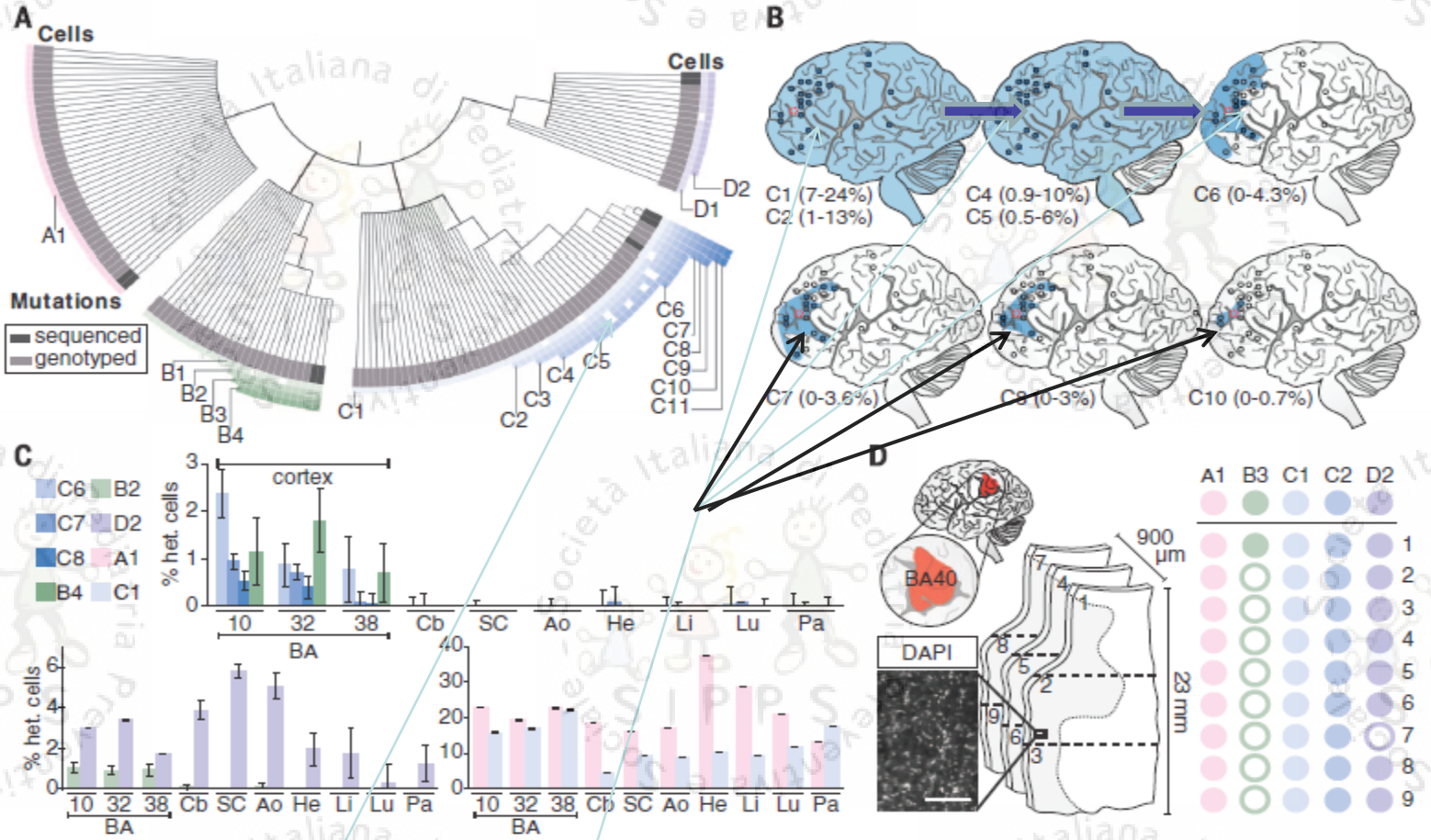


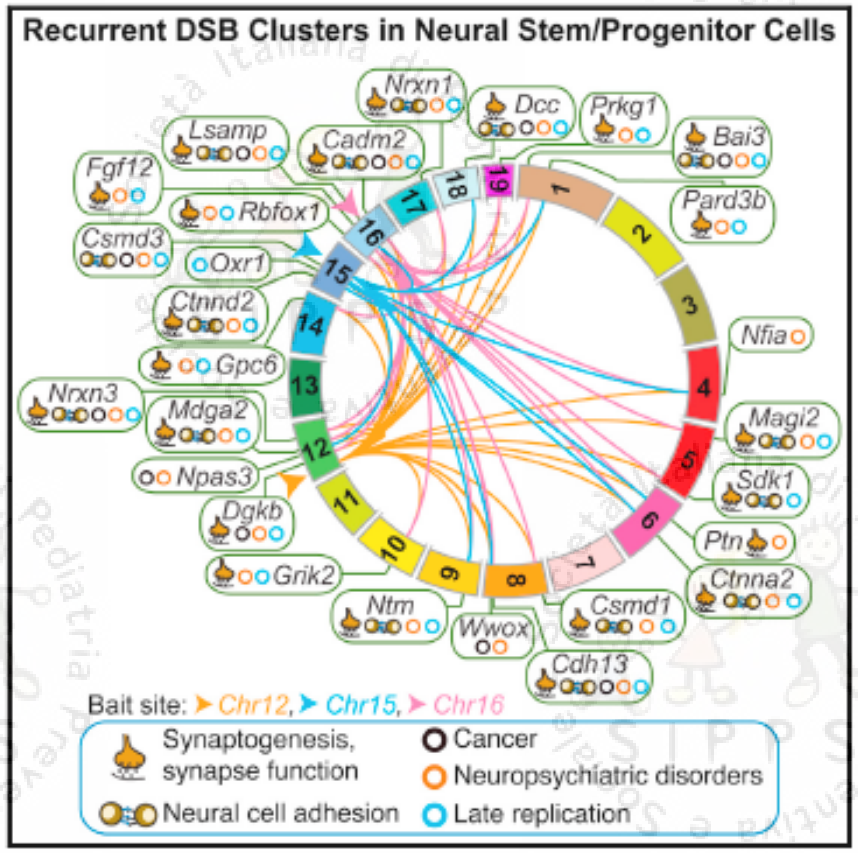
Fig. 3. Somatic mutations are shared between multiple neurons and demonstrate lineage relationships. (**A**) Lineage map of 136 human cortical neurons from brain B derived from 13 clonal somatic mutations, including SNVs, long interspersed nuclear element (LINE) insertions, and a TG-dinucleotide expansion. Neurons are placed into four distinct nested clades (pink, green, blue, purple) defined by one or more independent mutations. Cells are ordered within clades according to the presence of multiple somatic mutations. A few cells in each clade fail to manifest individual SNVs shared by other cells of the same clade (indicated by open squares), likely representing incomplete amplification (fig. S2). Dark gray boxes represent cells analyzed by WGS; light gray represents cells analyzed by Sanger-based genotyping. Genomic locations of somatic mutations are given in fig. S11. (**B**) Ultradeep sequencing of mutated loci across the cortex of brain B. Clonal SNVs from a single clade are progressively regionally restricted to frontal cortex and become progressively rarer in bulk tissue, reflecting their later origin during development and neurogenesis. Blue circle, mutation present; empty circle, mutation absent; blue shading, likely spatial distribution of mutation. Percentage range of heterozygous cells is indicated for each SNV. (**C**) Ultradeep sequencing of mutated loci across the brain and body. Some variants are brain-specific (top) and others are shared across germ layers (bottom). Samples sequenced are prefrontal cortex [Brodmann area (BA) 10/BA46], cingulate cortex (BA32/BA8), temporal cortex (BA38), cerebellum (Cb), spinal cord (SC), aorta (Ao), heart (He), liver (Li), lung (Lu), and pancreas (Pa). (**D**) Genotyping shared variants in small sections of human cortex. Left: 4′,6-diamidino-2-phenylindole (DAPI) stain of segment of representative section; scale bar, 200 µm. Center: Three consecutive 300-µm coronal sections from BA40 (red, upper left) were dissected into three axial regions each (1 to 9). Right: Genotyping results for dissected sections. Solid circles denote presence of mutation in indicated sample; open circles denote absence. Mutations with high allele fractions are present in all or virtually all regions, whereas only the least prevalent somatic variant (present in <0.5% of cells) is present in one region but not most regions.

Cell

Article

Long Neural Genes Harbor Recurrent DNA Break Clusters in Neural Stem/Progenitor Cells

Graphical Abstract



Authors

Pei-Chi Wei, Amelia N. Chang, Jennifer Kao, Zhou Du, Robin M. Meyers, Frederick W. Alt, Bjoern Schwer

Correspondence

alt@enders.tch.harvard.edu (F.W.A.), bjoern.schwer@childrens.harvard.edu (B.S.)

In Brief

Neural stem and progenitor cells undergo massive genomic alterations in a very restricted set of genes involved in synapse function and neural cell adhesion, processes that are likely to govern the special behavior of brain cells. Many of these genes have also been implicated in mental disorders.

Highlights

1) **27 Recurrent DSB clusters (RDCs)** are identified **in neural stem/progenitor cells**

2) All RDCs are within genes, most of which are long, transcribed, and late replicating

3) Most RDC genes are **involved in synapse function and/or neural cell adhesion**

4) A nucleotide-resolution view of **replication stress-associated fragile sites** is provided

Leading Edge
Previews

Cell 164, February 11, 2016 ª2016 Elsevier Inc. 593

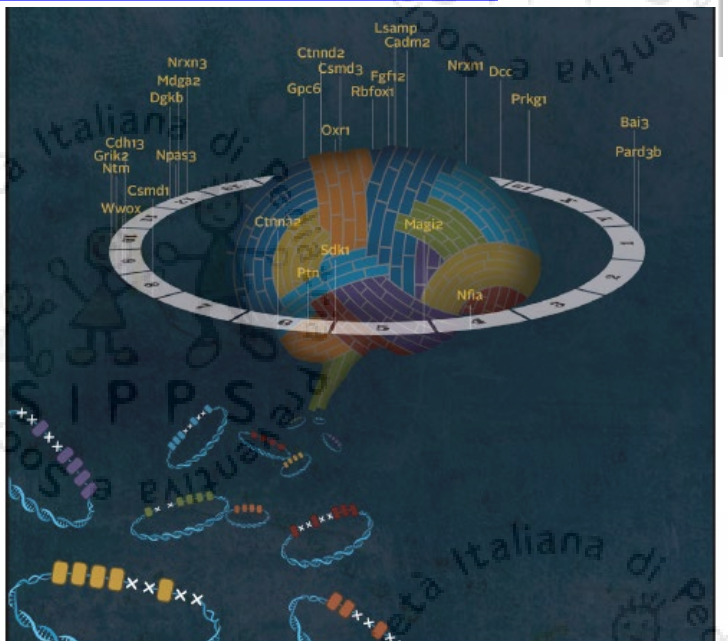
Cell

A Mechanism for Somatic Brain Mosaicism

Irving L. Weissman[1,*] and Fred H. Gage[2,*]
[1]Institute of Stem Cell Biology and Regenerative Medicine, Stanford University School of Medicine, Stanford University, Palo Alto, CA 94305, USA
[2]The Salk Institute for Biological Studies, Laboratory of Genetics, La Jolla, CA 92037, USA
*Correspondence: irv@stanford.edu (I.L.W.), gage@salk.edu (F.H.G.)
http://dx.doi.org/10.1016/j.cell.2016.01.048

Double-strand break repair is required for neural development, and brain cells contain somatic genomic variations. Now, Wei et al. demonstrate that neural stem and progenitor cells undergo very frequent DNA breaks in a very restricted set of genes involved in neural cell adhesion and synapse function.

Many of the identified genes are **expressed in NSPCs located in the brain regions responsible for higher functions such as short-term learning,** and mutations in these genes in humans are associated with (and maybe predispose to) **psychiatric and neurological disorders manifested in mind functions—autism, manic depressive and depressive disorders, schizophrenia**, and others



.. *unlike your **genome**, which is **fixed from the moment of conception*** **(…)**

your **connectome* changes throughout your life**.

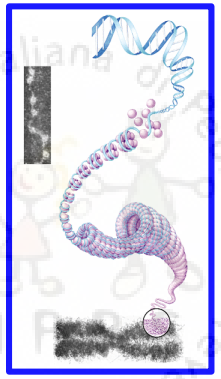
Neurons adjust…their connections (to one another) by ***strengthening*** or ***weakening*** them.

Neurons **reconnect by creating and eliminating synapses**, and **they rewire by growing and retracting branches**.

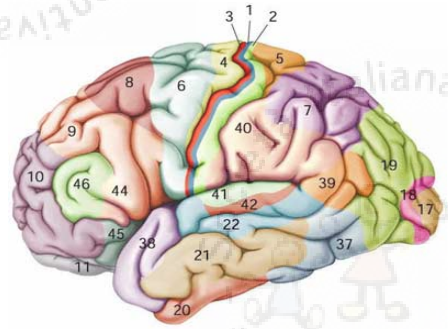
***You are more than your genes. You are your connectom* (*Sebastian Seung, MIT*).**

Seung S. ***Connectome: How the brain's wiring makes us who we are*** (2012)

Phylogeny



of 4 billion years of molecular coevolution * (in particular, our **DNA** is the **product** of this long journey) ..



We should never forget that **we are at the same time the product**

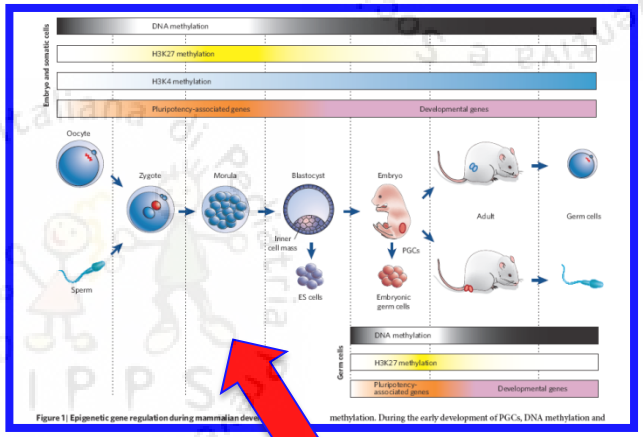
Mismatch

and of **9 months of an individual development**

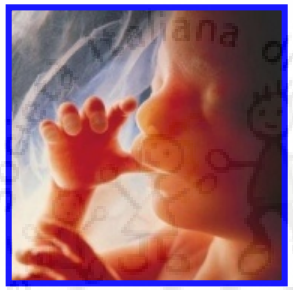
The **epigenome** being the product of nine months of ***cellular and tissue programming*** (**adaptive** to an environment that is rapidly changing)..

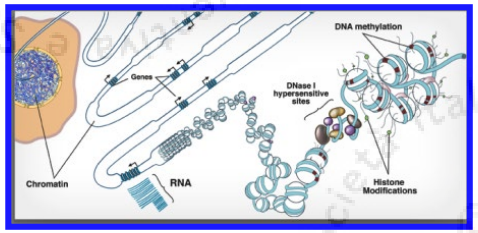
Devo-Evo

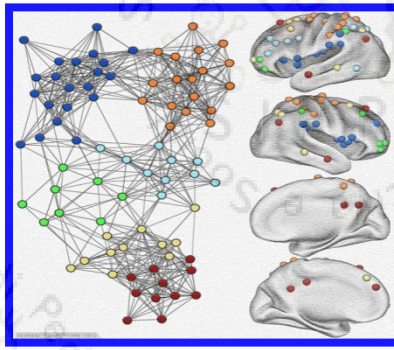
Ontogeny



Ontogeny Recapitulates (***anticipates***) ***Phylogeny***







A ***major risk***: the **EDCs** and other ***xenobiotics*** (***not*** being the product of ***molecular coevolution***) can interfere at this level, acting as ***pseudo-morphogens***

The chimpanzee DNA is for 98.77% identical to the human .

On average, a gene encoding a protein in a man differs from its chimpanzee ortholog by only two aa substitutions

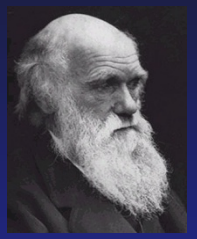
.. almost one third of human genes

has exactly the **same protein translation** as their orthologs

in chimpanzee

We are quite stable (for millions of years) both genetically and phenotypically

Species ***phylogeny***



From the Tree of the Life Website, University of Arizona

Evo

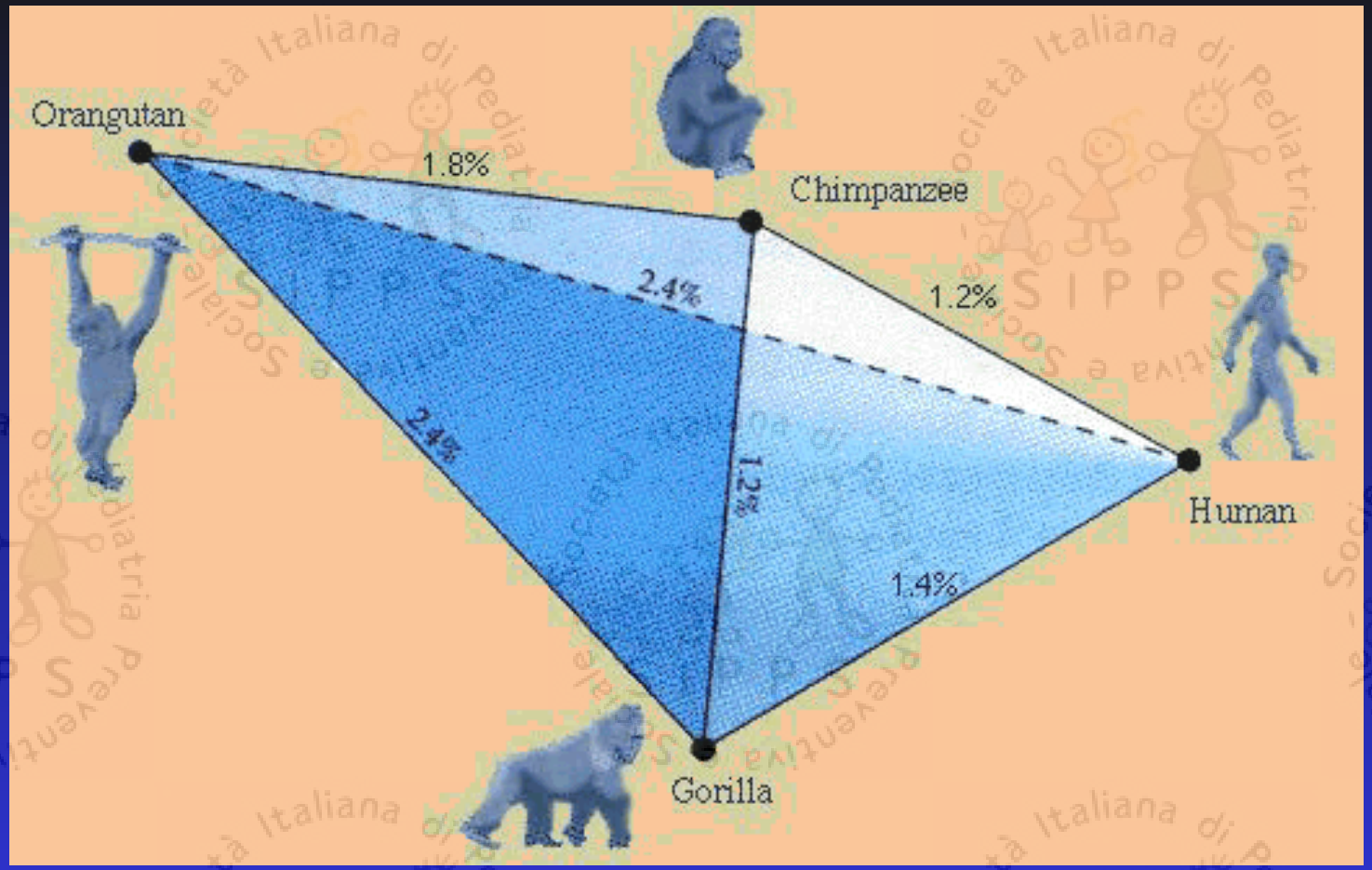
Orangutan

Gorilla

Chimpanzee

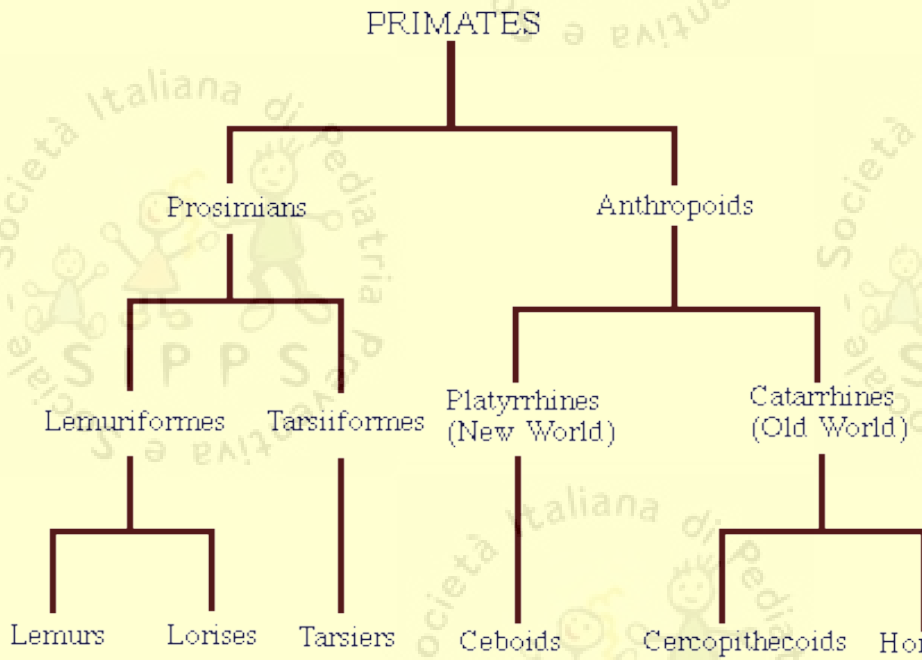
Human

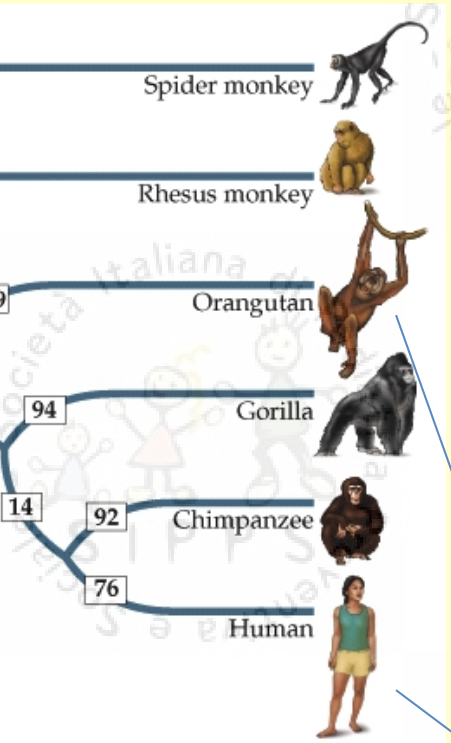
Sanger Institute

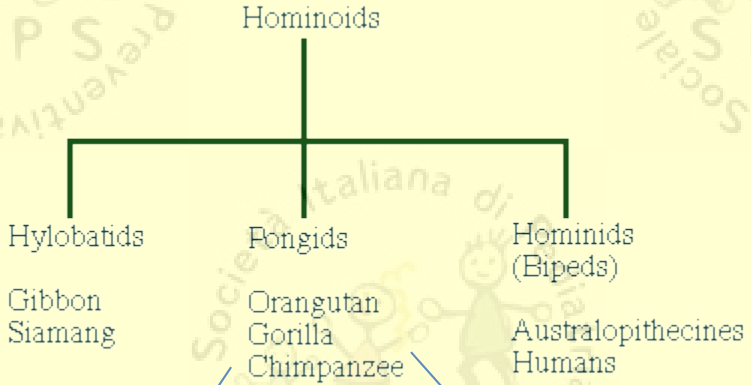


Molecular (genetic) distances between Hominoids.
Chimpanzees are actually closer to humans genetically than to Orangutans and the same genetic distance from Gorillas.

Orangutans are the most different from humans genetically yet relatively closer to Chimpanzees

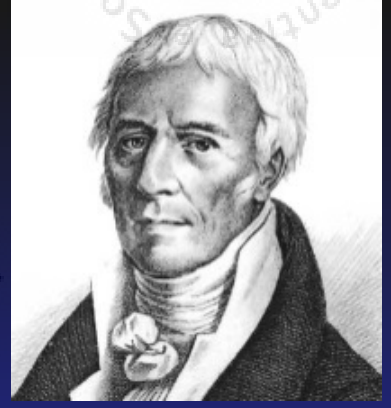




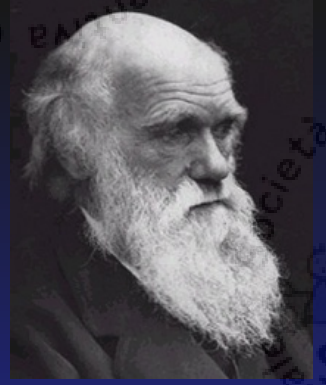


A Hominid Tree

Base-pair changes in the globin region of DNA



Chimpanzee-human divergence



Evo

Brain:
a *rapidly evolving Organ ?*

6-8 million years

The ***ancestral*** **wiring**

Hominids or hominins

The ***Individual*** wiring !!

+ Soft Wired-memory

Chimpanzees

Humans

INC DAY 2017
BRAIN & EPIGENETICS

OCT 16 2017

KEYNOTE LECTURE BY :
Edith Heard (Collège de France, Paris)
Epigenetics in development and disease : lessons from the x chromosome

INVITED SPEAKERS :
Tracy Bale (UPenn)
Bérénice Benayoun (UC Davies)
Ernesto Burgio (Brussels)
Giacomo Cavalli (Montpellier)
Johannes Gräff (Lausanne)
Claudine Junien (Paris)
Francesca Merlin (Paris)
Marc Potenza (USA)
Jonathan Weitzman (Paris)

Organizers : J. Fagard, V. Lallemand-Mezger, C. Legay, C. Meunier
In partnership with the BCPP, BME-Paris, Cogmaster and PCFA Masters

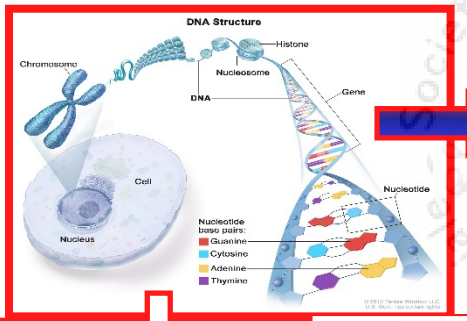
UNIVERSITÉ PARIS DESCARTES
AMPHITHÉÂTRE VULPIAN
12 RUE DE L'ECOLE DE MÉDECINE 75006 PARIS

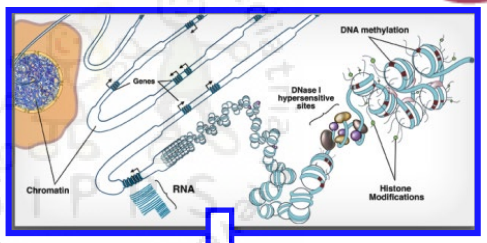
INSTITUT NEUROSCIENCES COGNITION | UNIVERSITÉ PARIS DESCARTES | USPC Université Sorbonne Paris Cité | bme paris BioMedical Engineering Master Program

Categories: EVENTS, INC MEETINGS

INC Day 2017 : Brain and Epigenetics – Oct 16th.

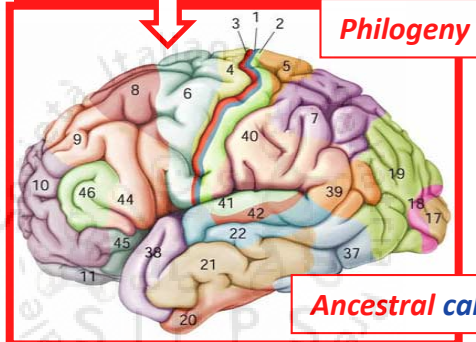
INSTITUT NEUROSCIENCES COGNITION PARIS DESCARTES



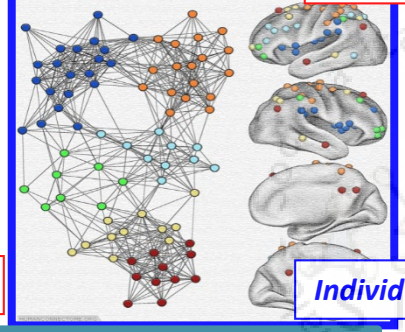


Philogeny

Ontogeny



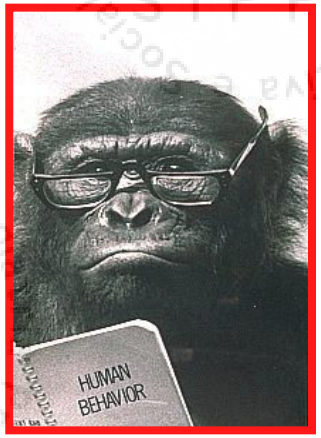
Ancestral cablage



Individual cablage

Brodmann areas

The human Connectome



(I) The building of the ***hardware*** is under ***genetic control***

(Ib) The building of the ***software*** (the ***connectome***) is ***epigenetically*** modulated

Neurodegenerative diseases

Neurodevelopmental disorders

Neuropsychiatric diseases

Brain Evolution and Neurodevelopmental Disorders

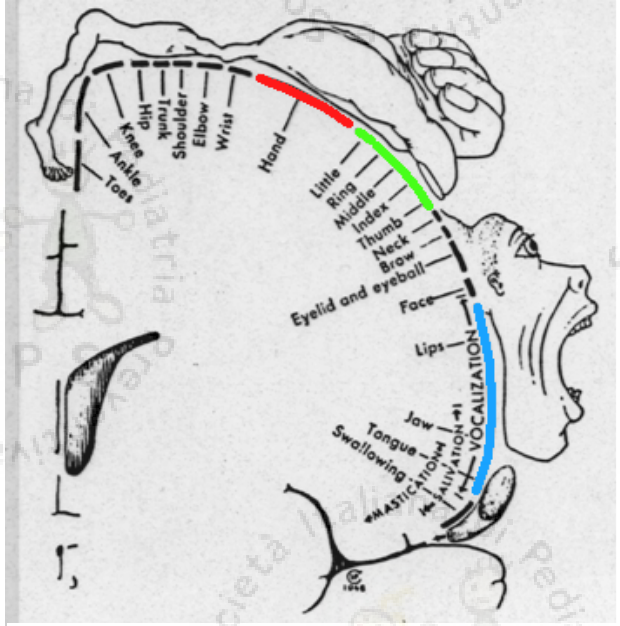
ECERI
European Cancer and Environment Research Institute

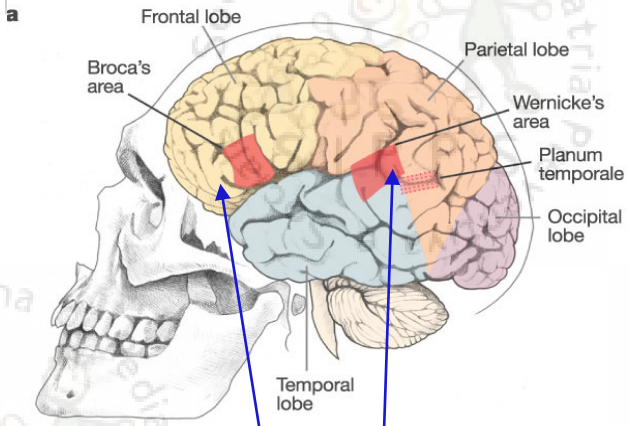
From Genetics to Epigenetics

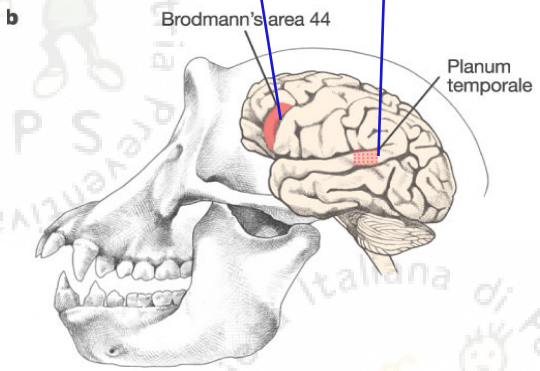
Ernesto Burgio (ECERI, Brussels, Belgium

The ***ancestral*** wiring

Le ***câblage*** ancestral





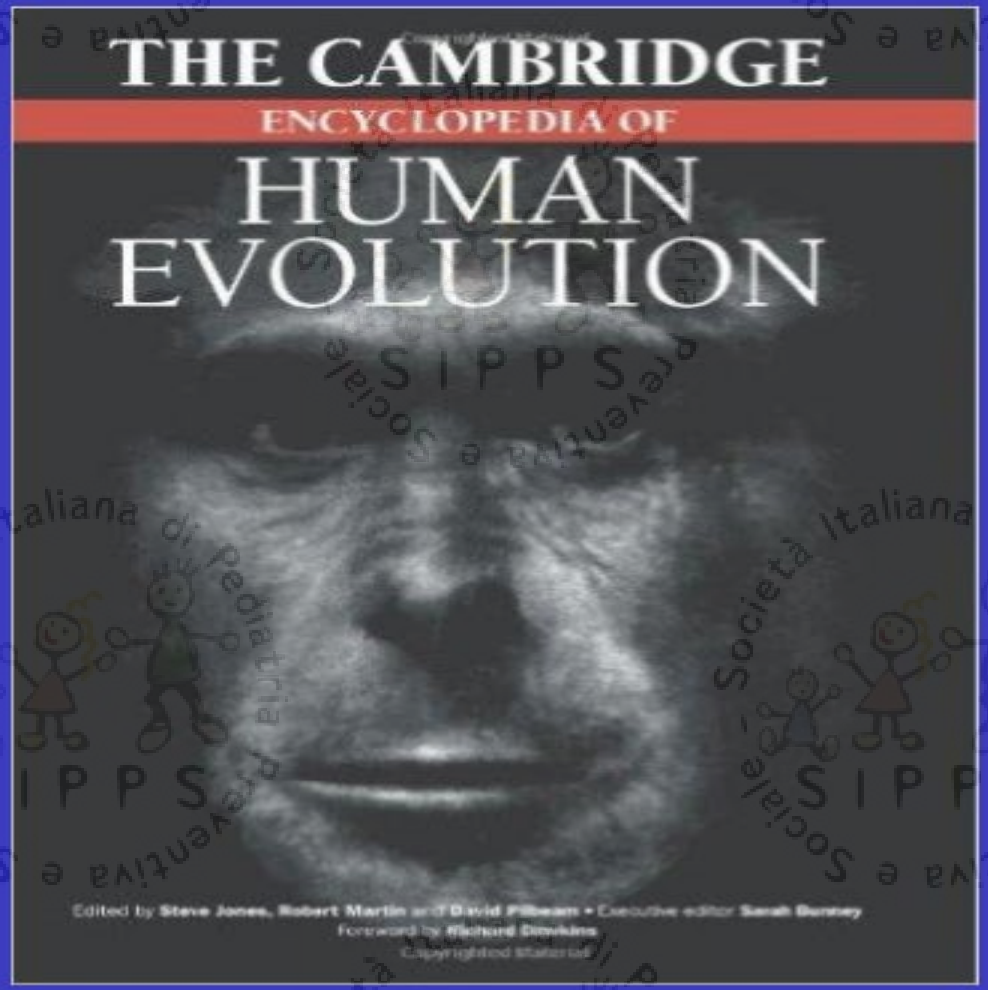


As with the **sensory cortex**, **Wilder Penfield** was responsible for **mapping the motor cortex…**
Chimps also have a motor cortex, but the **area of cortex devoted to vocal control is restricted** relative to what you see in the human animal.
Their brains are just not built for the detailed vocalizations you need to **in order to pronounce all the phonemes** that comprise linguistic verbal communication. Neurologists knew this, and **had the chimp trainers consulted a neurologist before starting, they would have saved themselves years of wasted effort**, and moved directly to the more realistic goal of seeing whether chimps could learn sign language

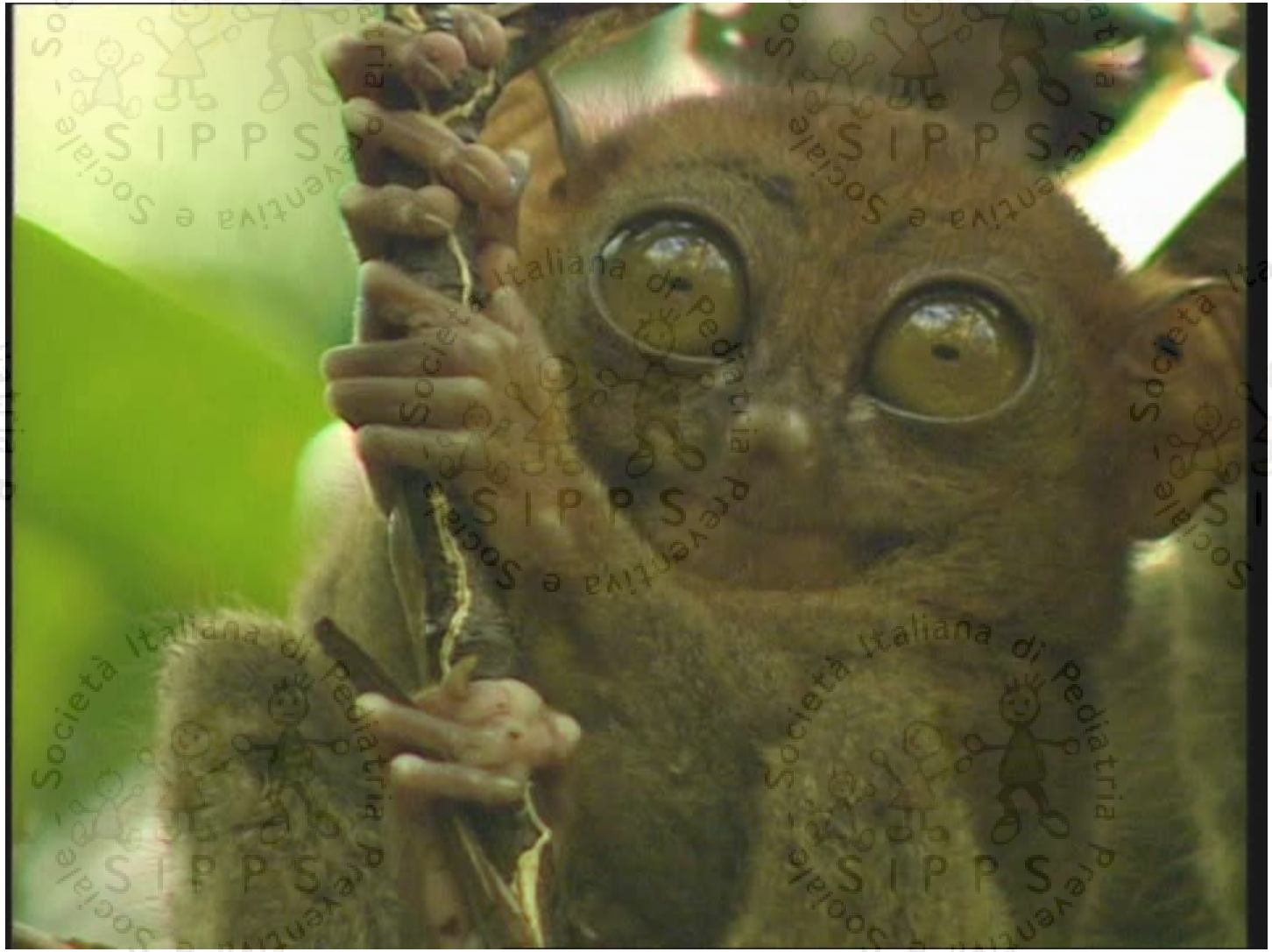
Carroll SB ***Genetics and the making of Homo sapiens*** Nature (2003) 422, 849-857

Phylogenèse des primates

The Cambridge Encyclopedia of Human Evolution (1994)



20 million years ago: **opposable thumb** and **frontal position of the eyes ..**



Tarsius tarsier (Tarsio spettro)

Mais la quadrupédie est toujours possible

National geographic

babouin

Alex Wilkinson Media

chimpanzé

gibbon

lemur

Se tenir debout est fréquent chez les primates actuels

Kevin Jenner / Howletts and Port Lympne

Gorille

hereiomania.wordpress.com

Babouin

Louise LeGresley/Getty Images

Izanbar

Gibbon

Lémurien

La locomotion en mode bipède aussi

Smithsonian magazine

Chimpanzé

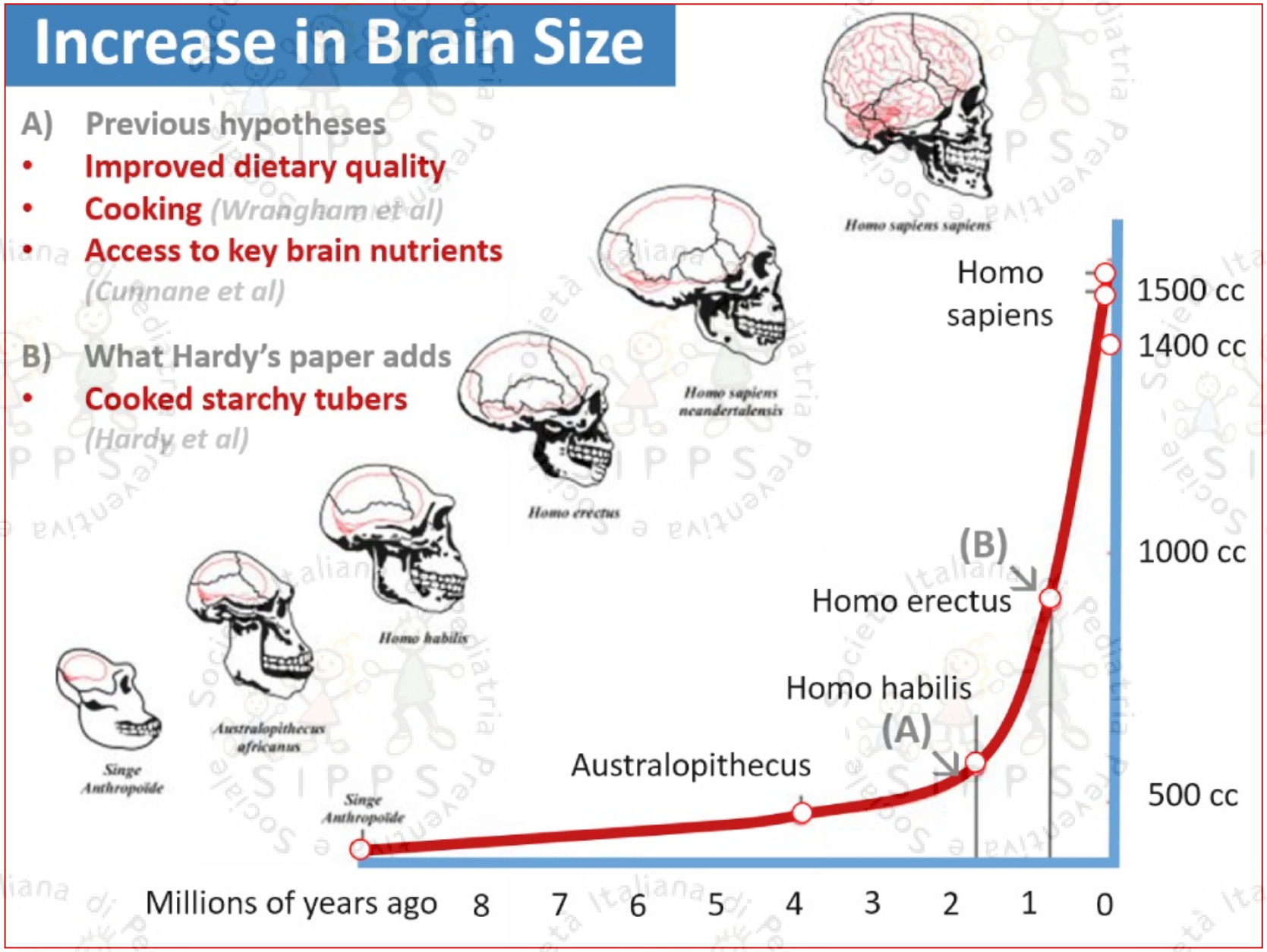
Gorille

Se tenir debout est une question d'équilibre neuro et psychomoteur

primatology.net

Smithsonian magazine

Brain Size and Intellectual Capabilities The absolute **brain size of hominids has tripled since the Pliocene** age (from an average of **450 cm³ in *Australopithecus*** to 1,345 cm³ in *H. sapiens*: Holloway, 1996)



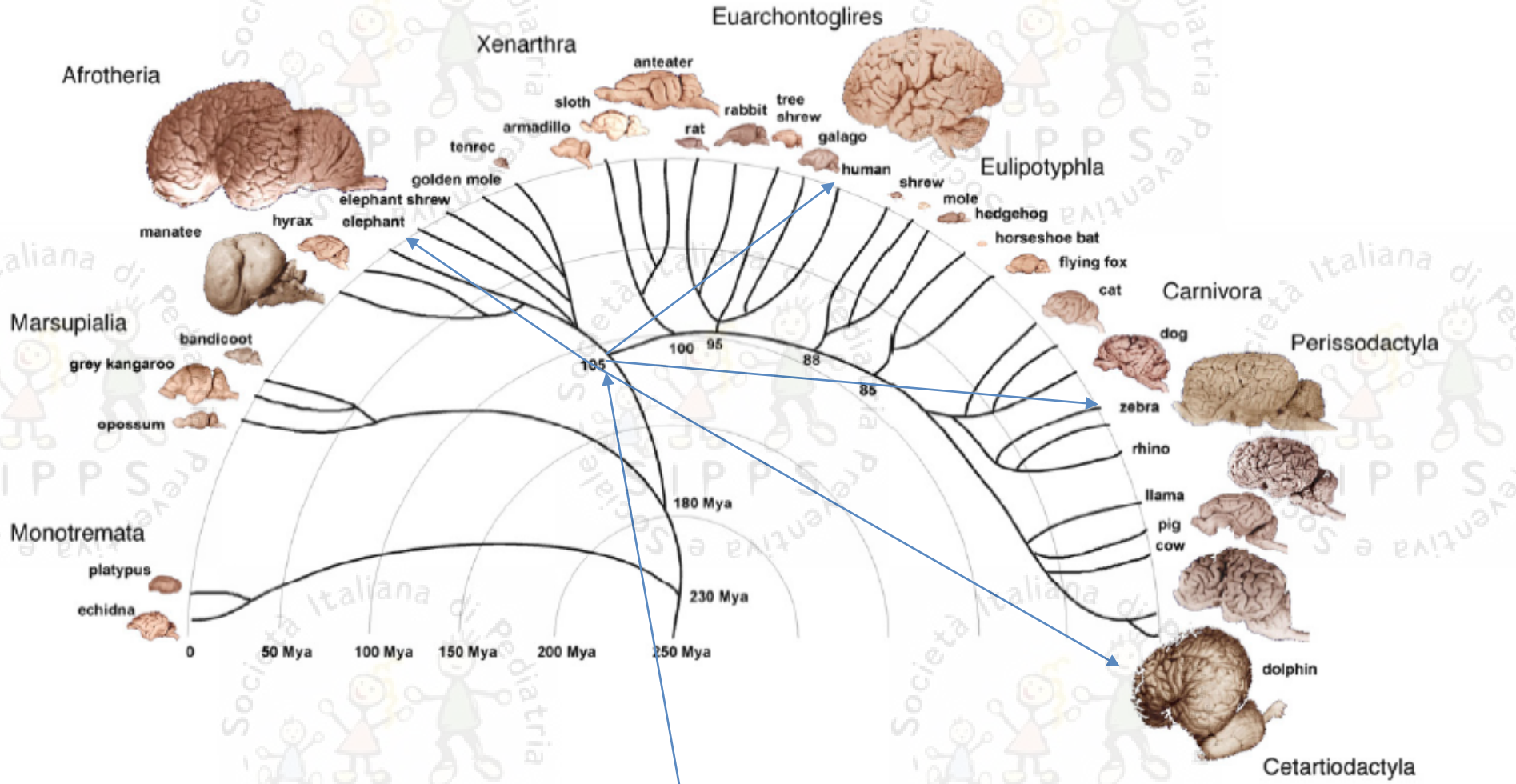
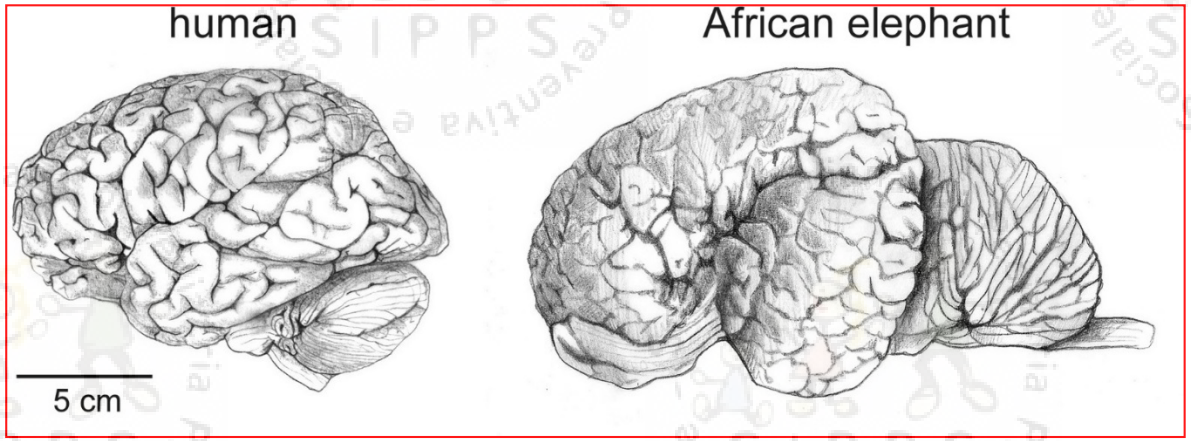
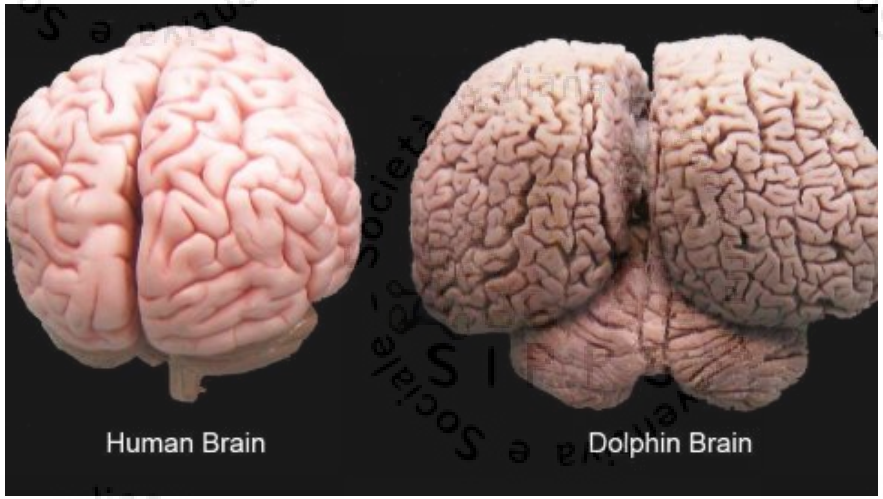


Fig. 1. Large brains appear several times in the mammalian radiation. Example species are illustrated for each major mammalian group. The mammalian radiation is based on the findings of Murphy et al. (18) and Kaas (19). Brain images are from the University of Wisconsin and Michigan State Comparative Mammalian Brain Collections (www.brainmuseum.org).

What is more important in **determining the complexity and richness of the functions** of a brain / mind?
The **mass / volume**? The **number of neurons**? The **number of connections**? The **organization of neuronal circuits**?

The human brain is not the largest.





Across species, brain size correlates with body size in a way that can be described mathematically with a power function, thus allowing **the predicted brain mass to be calculated for any species**

Absolute Brain Weight – Does it reflect intelligence?

**Capodoglio (*Physeter*

Species	Adult Brain Weight (grams)
Chimpanzee	450
Human	1,350
Bottlenosed dolphin	1,600
African elephant	6,075
Fin whale	7,200
Sperm Whale	9,200

Size of Adult Human Brain

- Range: 1000 to 2000 grams
- Average male = 1,350 g
- Average female = 1,200 g
  - Anatole France = 1,000 g (20th century poet)
  - **Albert Einstein = 1,230 g**
  - Lord Byron = 2,380 g (Romance poet)

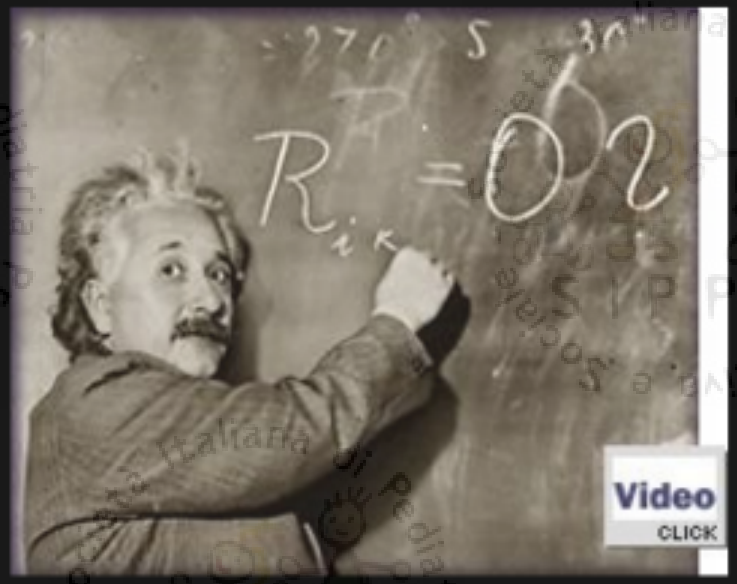
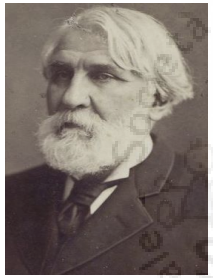


TABLE I.

Name.	Age.	Occupation.	Nationality.	Brain-weight.
Turgenev.	65	Poet and novelist.	Russian.	2012
Bouny.		Jurist.	French.	1935
Cuvier.	63	Naturalist.	German descent.	1830
Knight, E. H.	59	Mechanician.	American.	1814
(Kraus, F. X.).	42	Theologian.	German.	1800
Abercrombie.	64	Physician.	English.	1786
Butler, Benj. F.	74	Statesman.	American.	1758
Olney, Edward.	59	Mathematician.	American.	1701
Levi, Herman.	60	Composer.	German.	1690
Winchell, A.	67	Geologist.	American.	1666
Thackeray.	52	Humorist.	English.	1658
Lenz, Rudolf.		Composer.	German. ?	1636
Goodsir.	53	Anatomist.	English.	1629
Curtice.	68	Mathematician.	American.	1612
Atherton.	49	U. S. Senator.	American.	1602
Siemens.	68	Physicist.	German.	1600
Brown, George.	61	Journalist.	Canadian.	1596
Konstantinoff.	25	Author.	Bulgarian.	1595
Pepper, William.		Physician.	American.	1593
Harrison, R. A.	45	Jurist.	Canadian.	1590
Hermann, F. B. W.	73	Economist.	German.	1590
Riebeck.	61	?	German.	1580
Büchner.	51	Hygienist.	German.	1560
Bittner.	57	Playwright.	German.	1556
Lavollay.		Merchant and publicist.	French.	1550
Cope.	57	Paleontologist.	American.	1545
McKnight.	57	Physician.	American.	1545
Allen, Harrison.	56	Anatomist.	American.	1531
Simpson.	59	Physician.	English.	1531
Train, G. F.	75	Promoter.	American.	1525
Taguchi.	66	Anatomist.	Japanese.	1520
Dirichlet.	54	Mathematician.	French.	1520
De Morny.	54	Statesman.	French.	1520
Webster.	70	Statesman.	American.	1518
Lord Campbell.	82	Statesman.	English.	1517
Wright, C.	45	Philosopher.	American.	1516
Schleich.	55	Author.	German.	1503
Chalmers.	67	Theologian.	English.	1503
Mallery.	63	Ethnologist.	American.	1503
Seguin, E. C.	55	Neurologist.	French descent.	1505
Napoleon III.	65	Sovereign.	French.	1500
Fuchs.	52	Pathologist.	German.	1499
Agassiz.	66	Naturalist.	French descent.	1495
Giacomini.	58	Anatomist.	Italian.	1495
De Morgan.	73	Mathematician.	English.	1494
Gauss.	78	Mathematician.	German.	1492
Letourneau.	71	Anthropologist.	French.	1492
(————.)	53	Statesman.	Swedish.	1489
Powell.	68	Anthropologist.	American.	1488
Pfeufer.	63	Physician.	German.	1488
Wuelfert.	63	Jurist.	German.	1485
Broca.	56	Anthropologist.	French.	1484
Mortillet.	77	Anthropologist.	French.	1480
Aylett.	58	Physician.	American.	1474

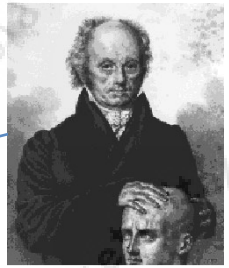
TABLE I.—*Continued.*

Name.	Age.	Occupation.	Nationality.	Brain-weight.
Lord Jeffrey.	76	Jurist.	English.	1471
Asseline.	49	Journalist.	French.	1468
Skobeleff.	39	General.	Russian.	1457
Bischoff, C. H. E.	79	Physician.	German.	1452
Gylden.	55	Astronomer.	Swedish.	1452
Kobell.	79	Geologist.	German.	1445
Mihalkovicz.	55	Biologist.	Hungarian.	1440
Dupuytren.	58	Surgeon.	French.	1437
Siljeström.	76	Physicist.	Swedish.	1422
Rice, A. T.	35	Diplomat and editor.	American.	1418
Oliver.	65	Mathematician.	American.	1418
Meyr, M.	61	Philosopher.	German.	1415
Leidy, Philip.	53	Physician.	American.	1415
Nussbaum.	61	Surgeon.	German.	1410
Grote.	75	Historian.	English.	1410
Huber.	49	Author.	German.	1409
Pond, J. B.	65	Soldier and lecture-manager.	American.	1407
Babbage.	79	Mathematician.	English.	1403
Assézat.	45	Journalist.	French.	1403
Kupffer.	73	Anatomist.	German.	1400
Bertillon.	62	Anthropologist.	French.	1398
Goltz.	68	Physiologist.	German.	1395
Coudereau.	50	Physician.	French.	1390
Whewell.	72	Philosopher.	English.	1389
Wistar, Isaac J.	78	General.	American.	1389
Wilson.	61	U. S. Vice-president.	American.	1389
Szilagyi.	61	Statesman.	Hungarian.	1380
Rüdinger.	64	Anatomist.	German.	1380
Schmid.	65	Author.	German.	1374
Hovelacque.	52	Statesman.	French.	1373
Bischoff, T. L. W.	76	Anatomist.	German.	1370
Cheve.		?	French.	1365
Gross, S. D.		Physician.	American.	1361
Hermann, C. F.	51	Philologist.	German.	1358
Liebig.	70	Chemist.	German.	1352
Schlagintweit.	51 ?	Naturalist.	German.	1352
Fallmerayer.	71	Historian.	German.	1349
Bennett.	63	Physician.	English.	1332
Pettenkofer.	82	Pathologist.	German.	1320
Senzel.	50	Sculptor.	French.	1312
Zeyer.	56	Architect.	German.	1320
Kolar.	84	Dramatist.	Bohemian.	1300
Grant, R. E.	80	Astronomer.	English.	1290
Whitman.	72	Poet.	American.	1282 ?
Cory.	55	Physician.	English.	1276
Guardia.	67	?	Spanish.	1272
Seguin, Edouard.	68	Psychiatrist.	French.	1257
Tiedemann.	79	Anatomist.	German.	1254
Lasaulx.	57	Philologist.	German.	1250
Laborde.	73	Physiologist.	French.	1234
Buhl.	64	Anatomist.	German.	1229
Hausmann.	71	Naturalist.	German.	1226
Ferris.	89	Jurist.	American.	1225
Gall.	70	Phrenologist and anatomist.	German.	1198



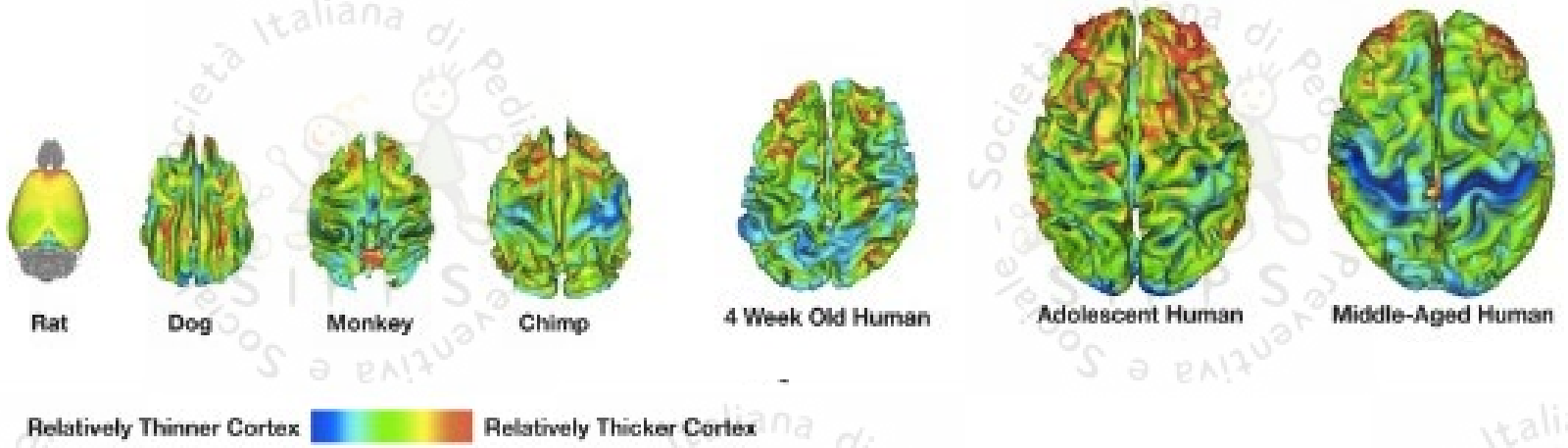
Ivan Turgenev 2012 gr

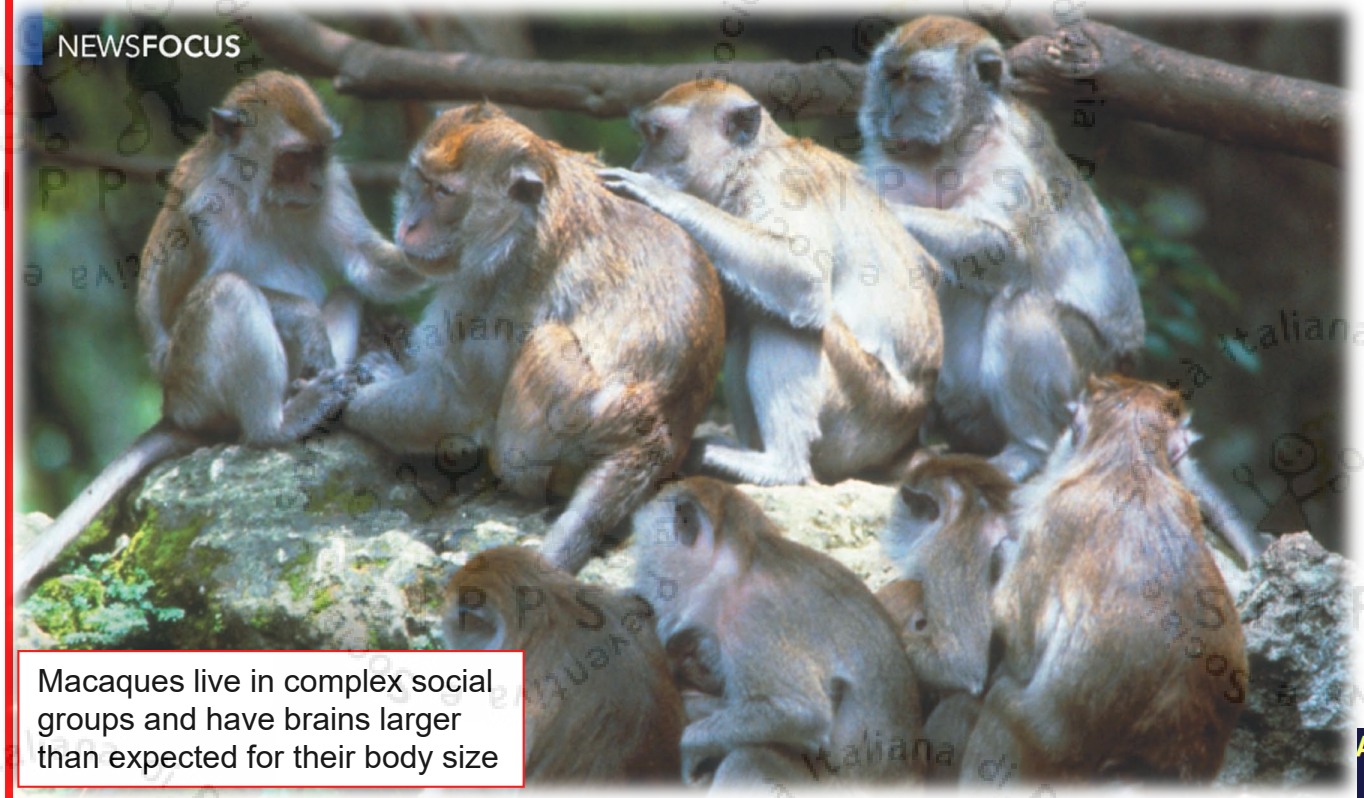
Interestingly, the smallest brain was that of Franz **Joseph Gall** (1758–1828) the father of ***phrenology***



Anatole France 1100 gr.

Table I from [Spitzka (1907)] which includes the name, age, occupation, nationality, and brain weight of different personalities (the average adult brain today is about 1,450 grams)





Macaques live in complex social groups and have brains larger than expected for their body size

Why Are Our Brains So Big?

Science, 2012

Giovanni Biggio
Centro di Eccellenza per la "Neurobiologia delle Dipendenze", Università degli Studi di Cagliari

Adolescenza, Stili di Vita, Psicopatologia

Giovanni Biggio

Centro di Eccellenza per la "Neurobiologia delle Dipendenze",
Università degli Studi di Cagliari

Extraordinary intelligence and the care of infants

Published online before print May 23, 2016, doi: 10.1073/pnas.1506752113
PNAS May 23, 2016

Steven T. Piantadosi[a,1] and Celeste Kidd[a,1]

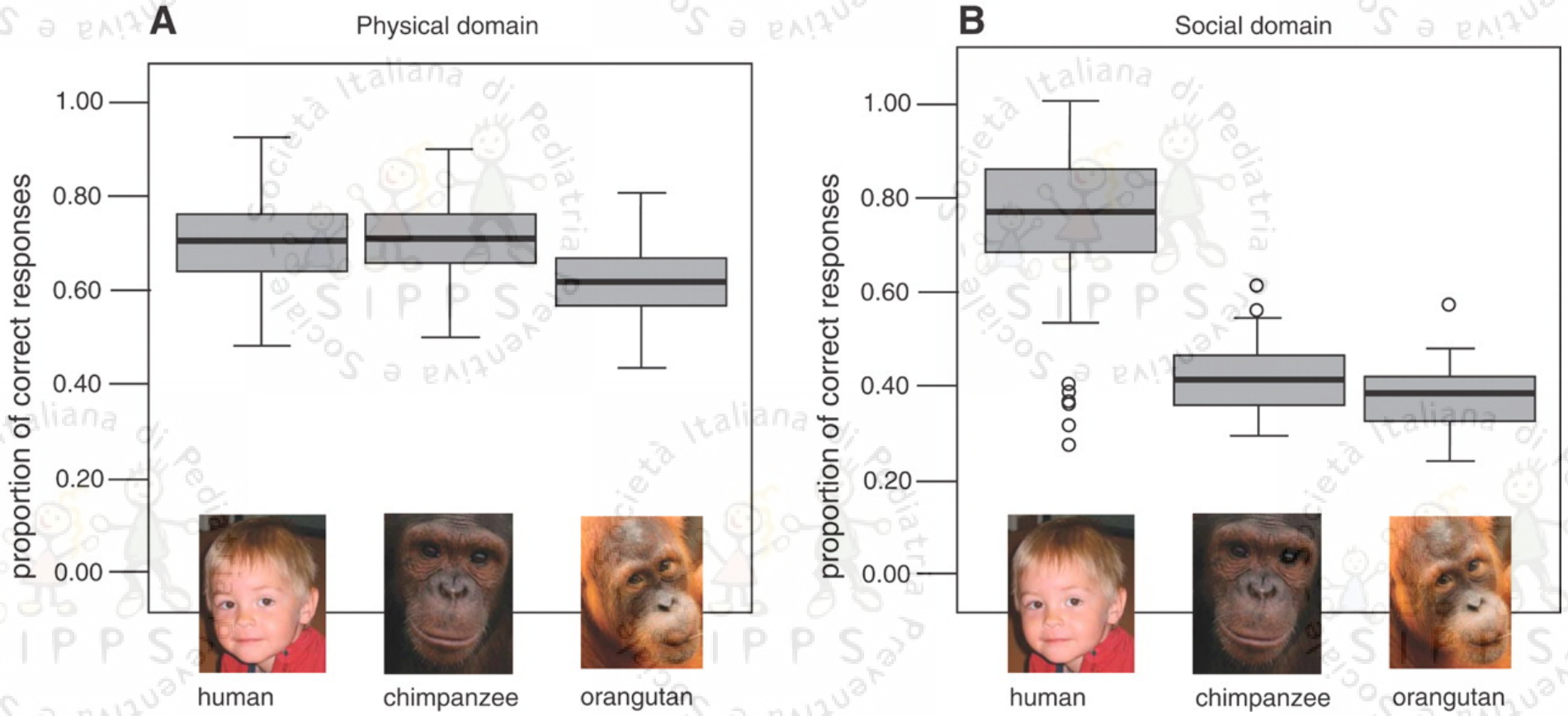
[a]Department of Brain and Cognitive Sciences, University of Rochester, Rochester, NY 14627

We present evidence that pressures for early childcare may have been one of the driving factors of human evolution. We show through an evolutionary model that runaway selection for high intelligence may occur when (*i*) altricial neonates require intelligent parents, (*ii*) intelligent parents must have large brains, and (*iii*) large brains necessitate having even more altricial offspring. We test a prediction of this account by showing across primate genera that the helplessness of infants is a particularly strong predictor of the adults' intelligence. We discuss related implications, including this account's ability to explain why human-level intelligence evolved specifically in mammals. This theory complements prior hypotheses that link human intelligence to social reasoning and reproductive pressures and explains how human intelligence may have become so distinctive compared with our closest evolutionary relatives.

"**Our theory is that there is a kind of self-reinforcing cycle where big brains lead to very premature offspring and premature offspring lead to parents having to have big brains.** What our formal modeling work shows is that those dynamics can result in **runaway pressure for extremely intelligent parents and extremely premature offspring.**"

"**Humans have a unique kind of intelligence**. We are good at social reasoning and something called ***'theory of mind'***--**the ability to anticipate the needs of others, and to recognize that those needs may not be the same as our own**.. This is especially helpful when taking care of an infant who is not able talk for a couple of years."

https://www.sciencedaily.com/releases/2016/05/160523160445.htm



In the social domain, a very different pattern emerged.
Averaging across all of the tasks in the social domain, the human children were correct on ~74% of the trials, whereas the two ape species were correct about half as often (33 to 36% of the trials). **Statistically, the humans were more skillful than either of the two ape species ($P < 0.001$ in both cases), which did not differ from one another.**


Who is really
nurturing who?

Sex differences in the structural connectome of the human brain

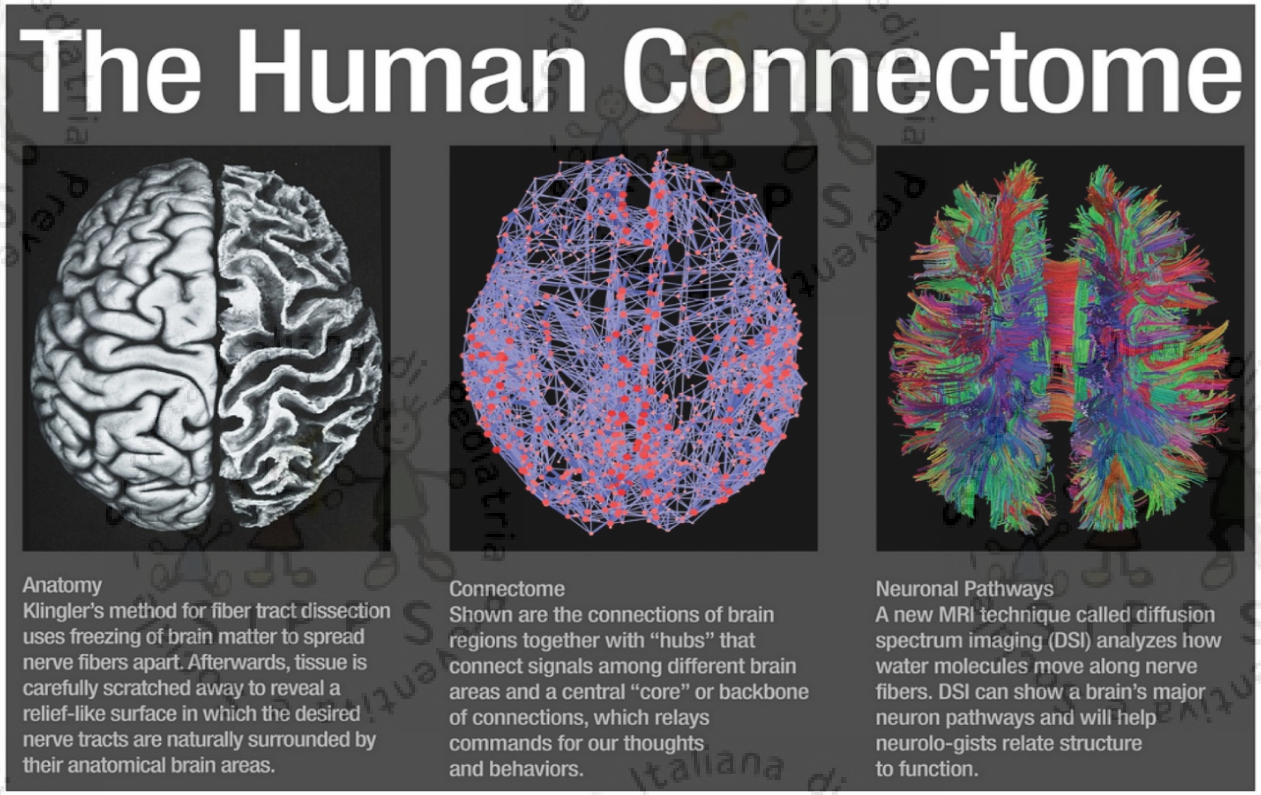
Madhura Ingalhalikar[a,1], Alex Smith[a,1], Drew Parker[a], Theodore D. Satterthwaite[b], Mark A. Elliott[c], Kosha Ruparel[b], Hakon Hakonarson[d], Raquel E. Gur[b], Ruben C. Gur[b], and Ragini Verma[a,2]

Sex differences in human behavior show adaptive complementarity: Males have better motor and spatial abilities, whereas females have superior memory and social cognition skills. Studies also show sex differences in human brains but do not explain this complementarity. In this work, we modeled the structural connectome using diffusion tensor imaging in a sample of 949 youths (aged 8–22 y, 428 males and 521 females) and discovered unique sex differences in brain connectivity during the course of development. Connection-wise statistical analysis, as well as analysis of regional and global network measures, presented a comprehensive description of network characteristics. In all supratentorial regions, males had greater within-hemispheric connectivity, as well as enhanced modularity and transitivity, whereas between-hemispheric connectivity and cross-module participation predominated in females. However, this effect was reversed in the cerebellar connections. Analysis of these changes developmentally demonstrated differences in trajectory between males and females mainly in adolescence and in adulthood. Overall, the results suggest that male brains are structured to facilitate connectivity between perception and coordinated action, whereas female brains are designed to facilitate communication between analytical and intuitive processing modes.

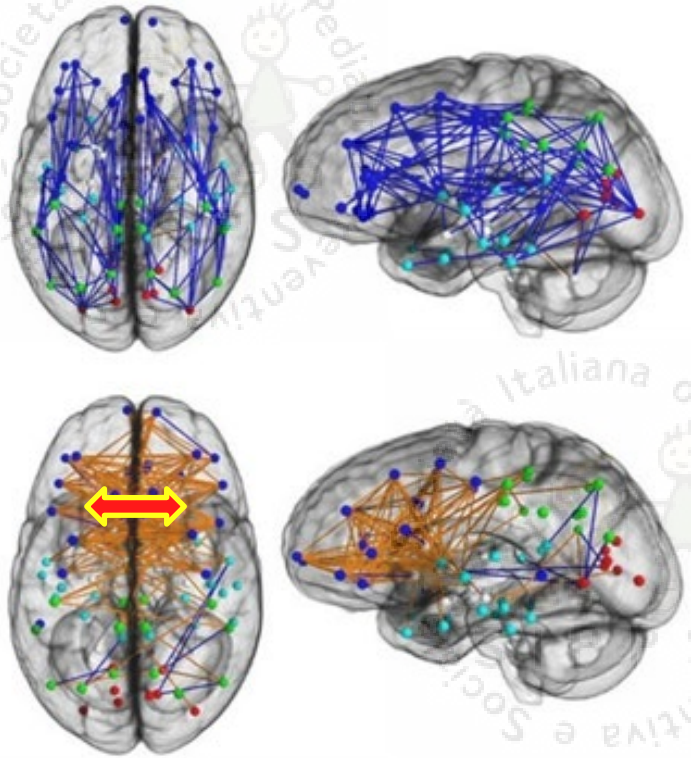
Sex differences are of high scientific and societal interes
because of their **prominence in behavior of humans and nonhuman species**. This work is highly significant because it studies **a very large population of 949 youths** (8–22 y, 428 males and 521 females) **using the diffusion-based structural connectome of the brain, identifying novel sex differences**. The results establish that **male brains are optimized for intrahemispheric** and **female brains for interhemispheric communication.**

The developmental trajectories of males and females separate at a young age, demonstrating wide differences during adolescence and **adulthood**. The observations suggest that **male brains are structured to facilitate connectivity between perception and coordinated action**, whereas **female brains are designed to facilitate communication between analytical and intuitive processing modes.**

http://www.humanconnectomeproject.org/



The Human Connectome - Eugen Ludwig, Josef Klingler, Patric Hagmann & Olaf Sporns - 1956, 2008



♂

♀

Male brains during development are structured to facilitate within-lobe and within-hemisphere connectivity, with networks that are transitive, modular, and **discrete** whereas **female brains have greater interhemispheric connectivity and greater cross-hemispheric participation.**

♂

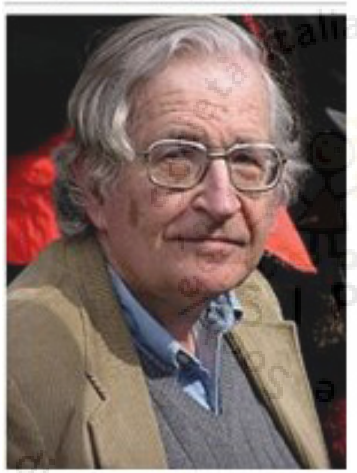
♀

Le ***connectome*** est un **plan complet des *connexions neuronales*** dans un cerveau

Innate linguistic knowledge

One of the most important of Chomsky's ideas is that most of this knowledge is innate, with the result **that a baby can have a large body of prior knowledge about the structure of language in general**, and **needs only actually *learn* the idiosyncratic features of the language(s) it is exposed to.**

Chomsky was not the first person to suggest that **all languages had certain fundamental things in common** (he quotes philosophers writing several centuries ago who had the same basic idea), **but he helped to make the innateness theory respectable after a period dominated by more behaviorist** attitudes towards language



Universal Grammar

- Innate linguistic knowledge which consists of a set of principles common to all languages

Neural language networks at birth

Daniela Perani[a,b,c,1], Maria C. Saccuman[a], Paola Scifo[b,c], Alfred Anwander[d], Danilo Spada[a], Cristina Baldoli[b,e], Antonella Poloniato[f], Gabriele Lohmann[g], and Angela D. Friederici[h,1]

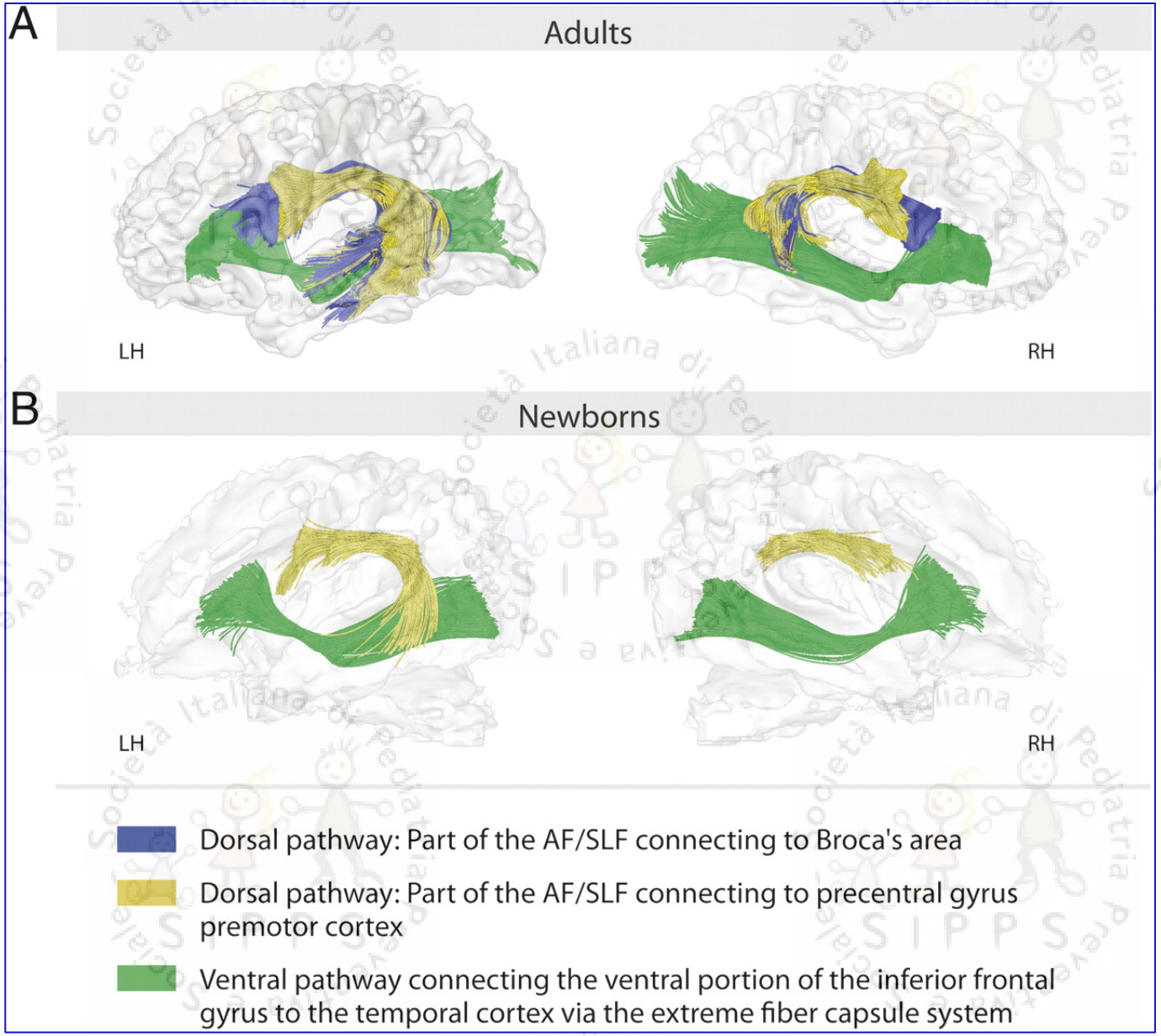
The ability to learn language is a human trait. In adults and children, brain imaging studies have shown that auditory language activates a bilateral frontotemporal network with a left hemispheric dominance. It is an open question whether these activati the complete neural basis for language present at b demonstrate that in 2-d-old infants, the language-r substrate is fully active in both hemispheres with a p in the right auditory cortex. Functional and structural within this neural network, however, are immature connectivities only between the two hemispheres, co the adult pattern of prevalent intrahemispheric Thus, although the brain responds to spoken lang at birth, thereby providing a strong biological bas language, progressive maturation of intrahemisphe connectivity is yet to be established with language ex brain develops.

16056–16061 | PNAS | September 20, 2011 | vol. 108 | no. 38

The ability to learn language is a human trait. In adults and children, **brain imaging studies have shown that auditory language activates a bilateral frontotemporal network with a left hemispheric dominance**

Here we demonstrate that **in 2-d-old infants, the language-related neural substrate is fully active in both hemispheres with a preponderance in the right auditory cortex**. **Functional and structural connectivities within this neural network, however, are immature, with strong connectivities only between the two hemispheres, contrasting with the adult pattern of prevalent intrahemispheric connectivities**. Thus, **although the brain responds to spoken language already at birth, thereby providing a strong biological basis to acquire language, progressive maturation of intrahemispheric functional connectivity is yet to be established with language exposure as the brain develops**

Structural connectivity results.

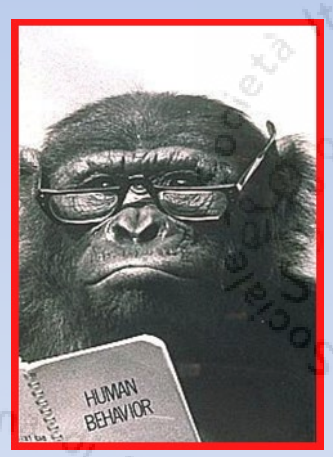


Daniela Perani et al. PNAS 2011;108:16056-16061

PNAS

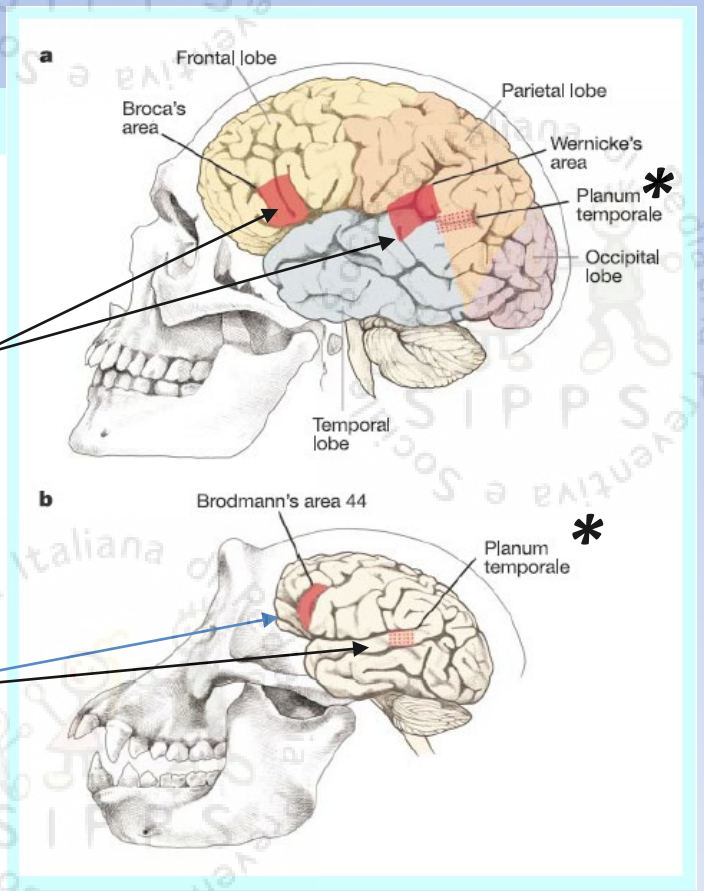
Questo è probabilmente l'esempio più chiaro e significativo della preponderanza e soprattutto della **maggior rapidità e potenza, in ambito evolutivo, dei meccanismi istruttivo-costruttivi (lamarckiani) rispetto a quelli selettivi (darwiniani).**

Possiamo dire che **il linguaggio è stato il più potente induttore/catalizzatore dei processi evolutivi che trasformano il *connettoma*-base dei primati antropomorfi nel connettoma specifico di *homo sapiens sapiens***.



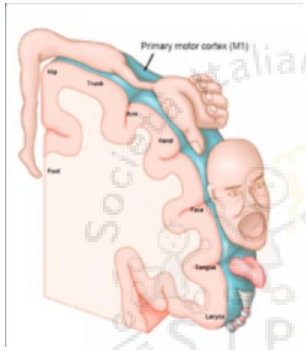
Selected traits that distinguish humans from other apes[5–7]

- Body shape and thorax
- Cranial properties (brain case and face)
- Relative brain size
- Relative limb length
- Long ontogeny and lifespan
- Small canine teeth
- Skull balanced upright on vertebral column
- Reduced hair cover
- Elongated thumb and shortened fingers
- Dimensions of the pelvis
- Presence of a chin
- S-shaped spine
- Language
- Advanced tool making
- Brain topology

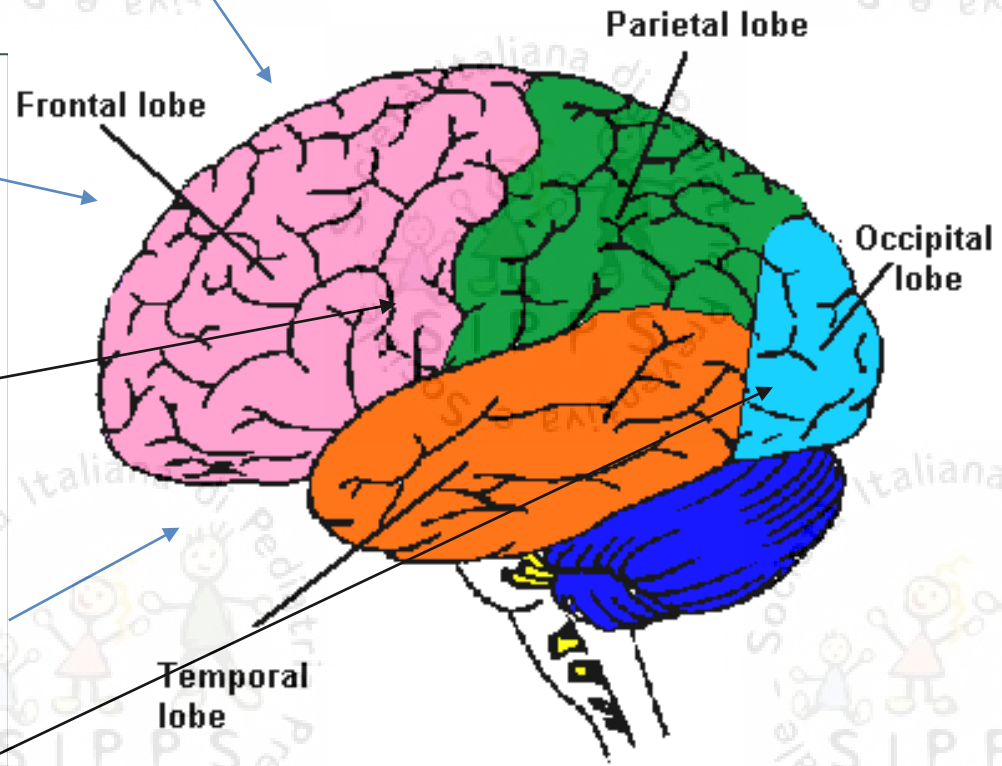


Carroll (2003) *Nature* **422**, 849-857

Ma potremmo anche estendere il modello istruttivo costruttivo all'intero processo di formazione/costruzione delle reti neuronali e quindi della corteccia cerebrale, non solo negli ominidi, non solo nei primati, ma più in generale negli animali.



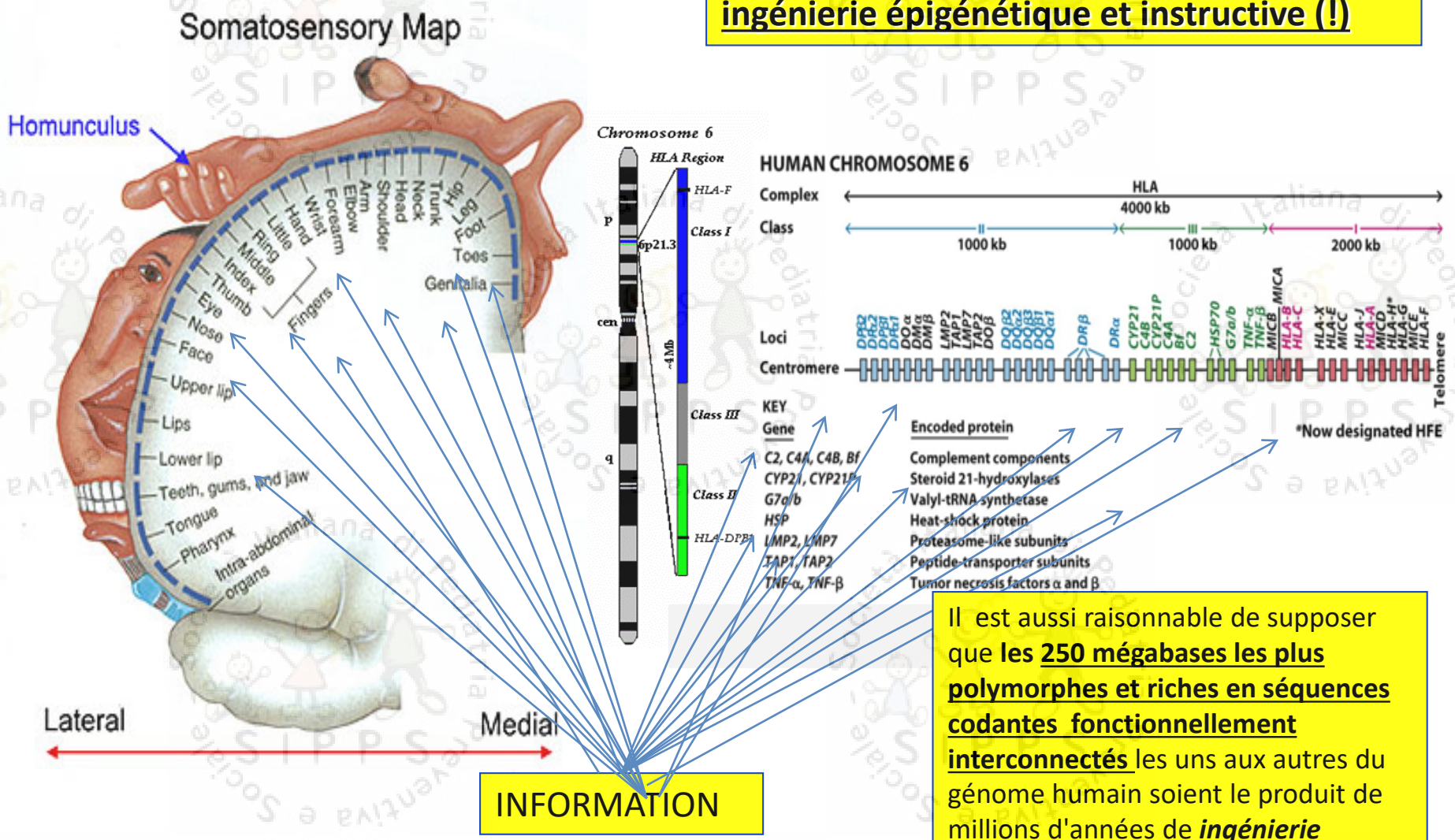
… pensiamo al modo in cui tutte le altre forme di vibrazione/campi elettromagnetici/radiazioni acustiche ecc. vengono via, via recepite, trasmesse ed elaborate da aggregati molecolari, organuli recettoriali, circuiti neuronali, aree cerebrali specifiche ..
e a tutti i segnali che dalla periferia corporea vengono via, via trasmessi verso i gangli centrali e, negli organismi superiori, verso la corteccia senso-motoria, determinandovi la formazione di un'area cerebrale specifica che rappresenta letteralmente la proiezione speculare capovolta dell'intera forma corporea, (come del resto nelle aree visive si va via, via formando l'immagine proiettiva speculare capovolta del mondo esterno



How to explain **the inverted body map in the brain (*Penfield Homunculus*) in phylogeny**

Vers un ***modèle instructif et constructif*** plutôt *qu'**(uniquement) sélectif*** dans l'évolution

Inversion du flux d'informations - également dans l'évolution – signifie reconsidérer les organismes (et les génomes) comme le produit d'une ingénierie épigénétique et instructive (!)



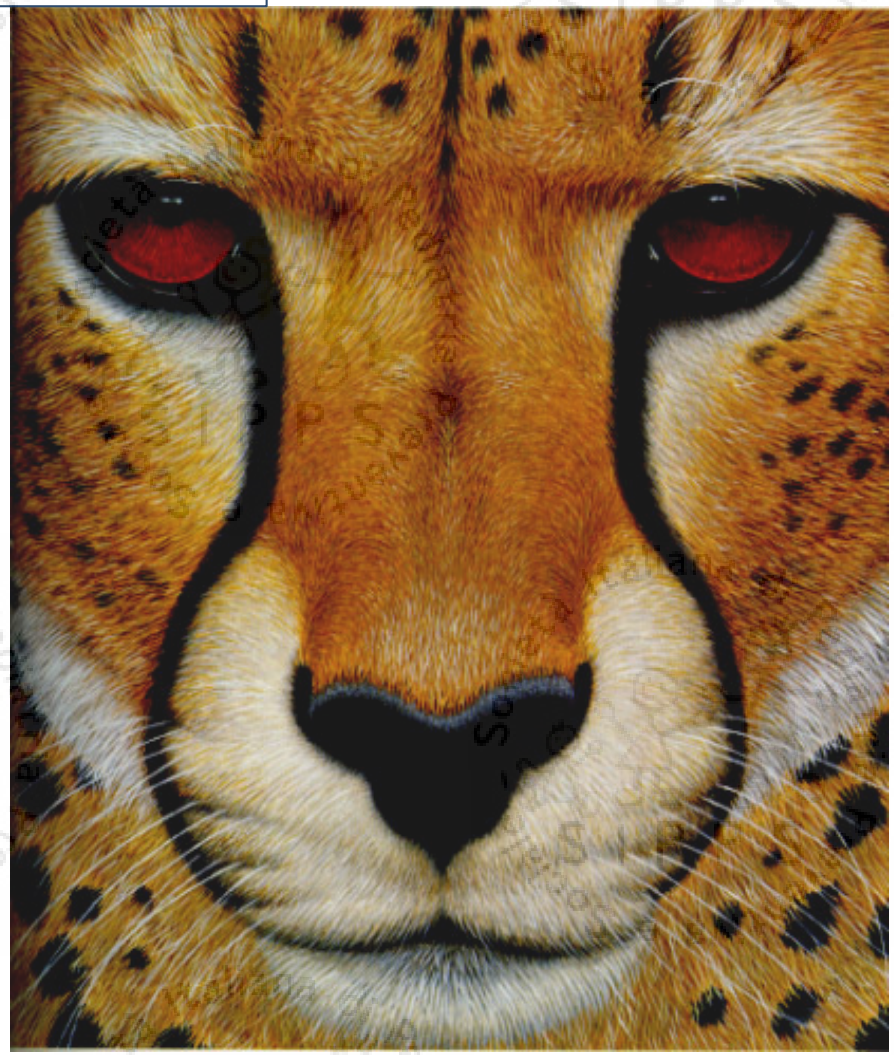
INFORMATION

Il est aussi raisonnable de supposer que **les 250 mégabases les plus polymorphes et riches en séquences codantes fonctionnellement interconnectés** les uns aux autres du génome humain soient le produit de millions d'années de ***ingénierie génétique naturelle*** (ce qui est attesté par une forte présence de HERVs)

Dawkins R, et al. ***Genomics of the major histocompatibility complex: haplotypes, duplication, retroviruses and disease*** Immunol Rev. (1999);167:275-304

INTELLIGENT DESIGN ?!

Nature



Culture

Nurture

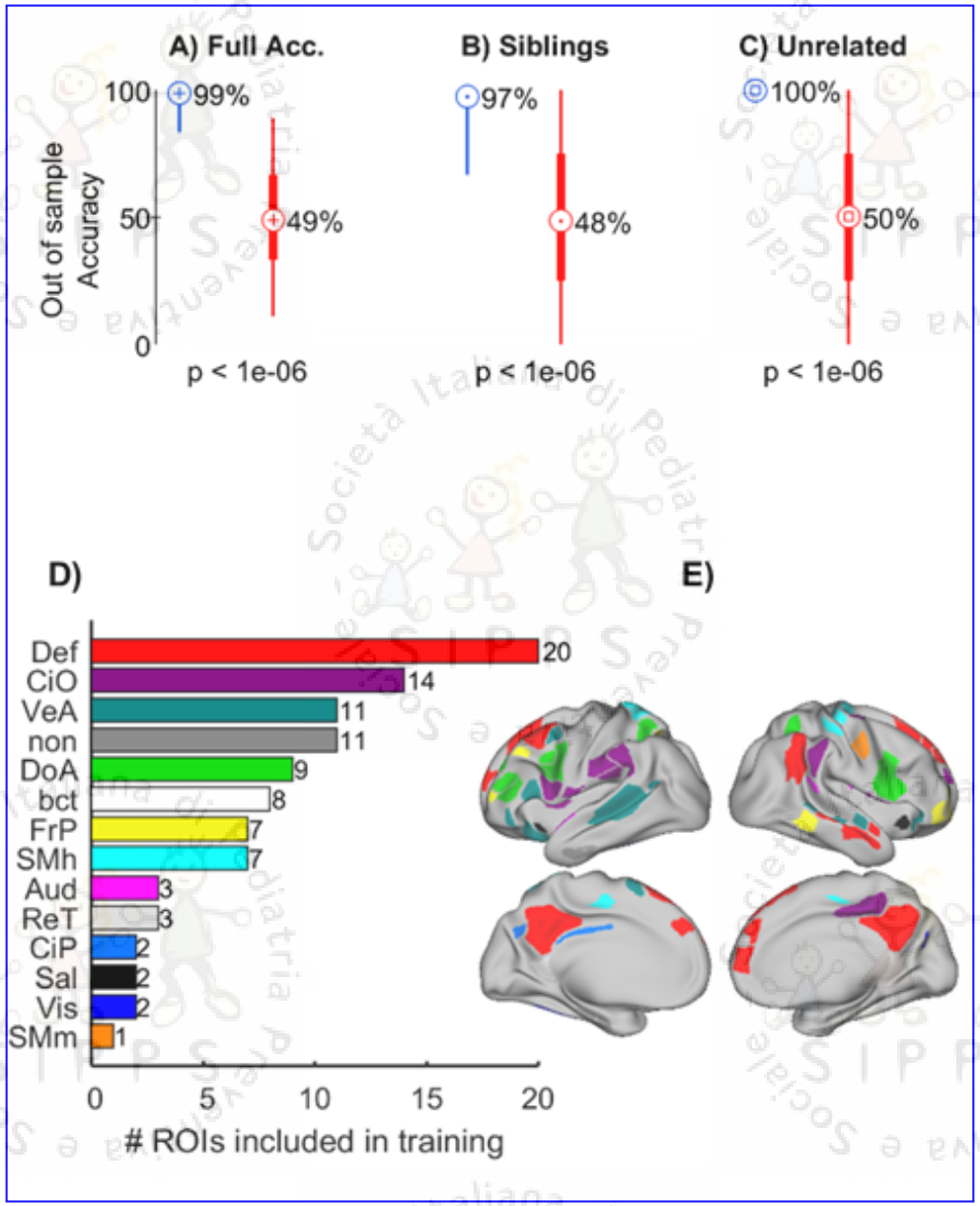
Miranda-Dominguez, O., Feczko, E., Grayson, D. S., Walum, H., Nigg, J. T., & Fair, D. A. (2017). Heritability of the human connectome: a connectotyping study. *Network Neuroscience*. Advance publication. https://doi.org/10.1162/netn_a_00029

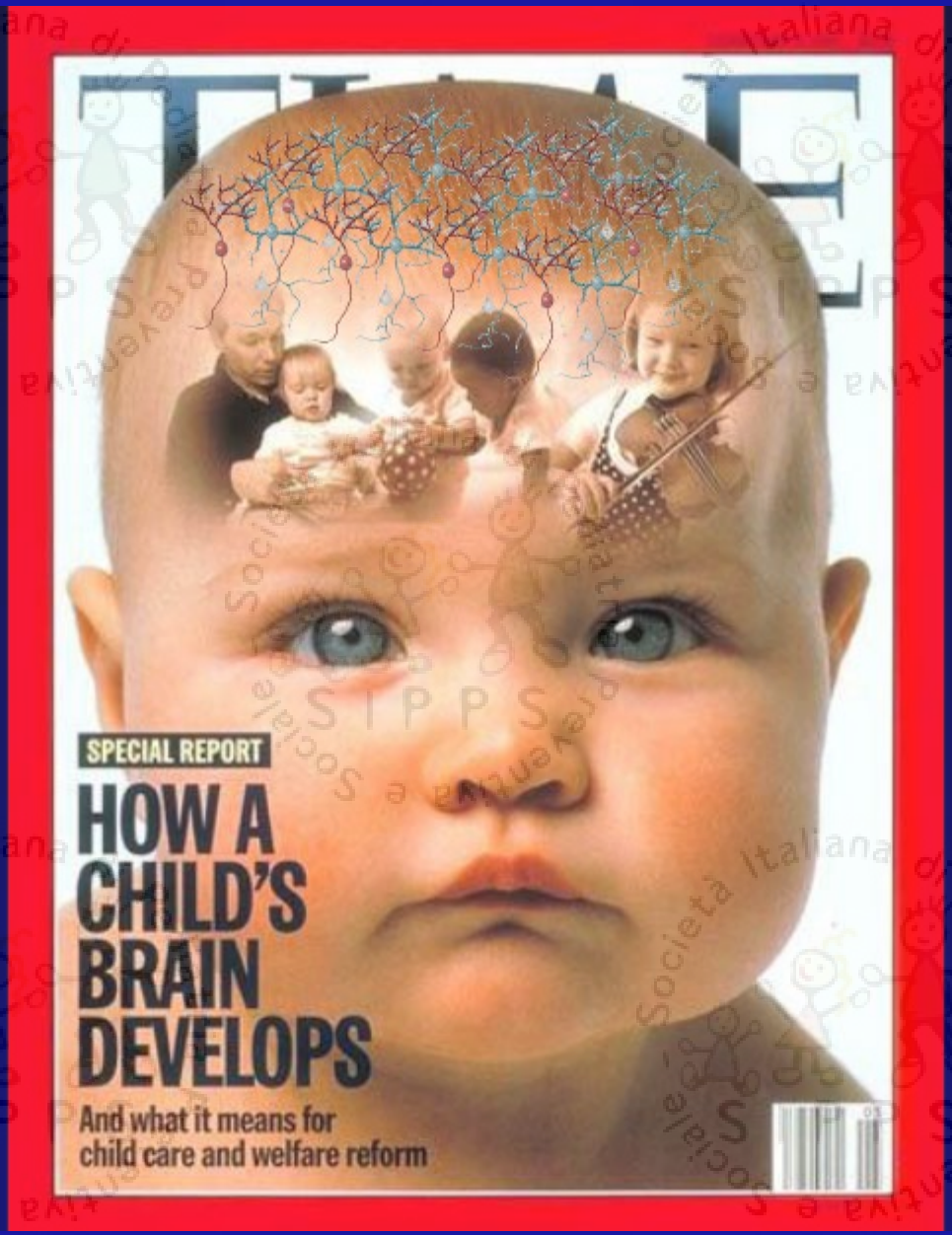
Heritability of the human connectome: a connectotyping study

First we show that **individual connectotypes** were reliably identified even several years after the initial scanning timepoint.

Familial relationships between participants, i.e. **siblings vs. unrelated**, were also accurately characterized. ***The connectotype demonstrated substantial heritability driven by high-order systems including the fronto-parietal, dorsal-attention, ventral-attention, cingulo-opercular, and default systems***.

This work suggests that **shared genetics and environment contribute towards producing complex, individualized patterns** of distributed brain activity, rather than constraining local aspects of function. These insights offer new strategies for characterizing individual aberrations in brain function and **evaluating heritability of brain networks.**





Giovanni Biggio
Centro di Eccellenza per la "Neurobiologia delle Dipendenze", Università degli Studi di Cagliari

The ***Individual*** wiring

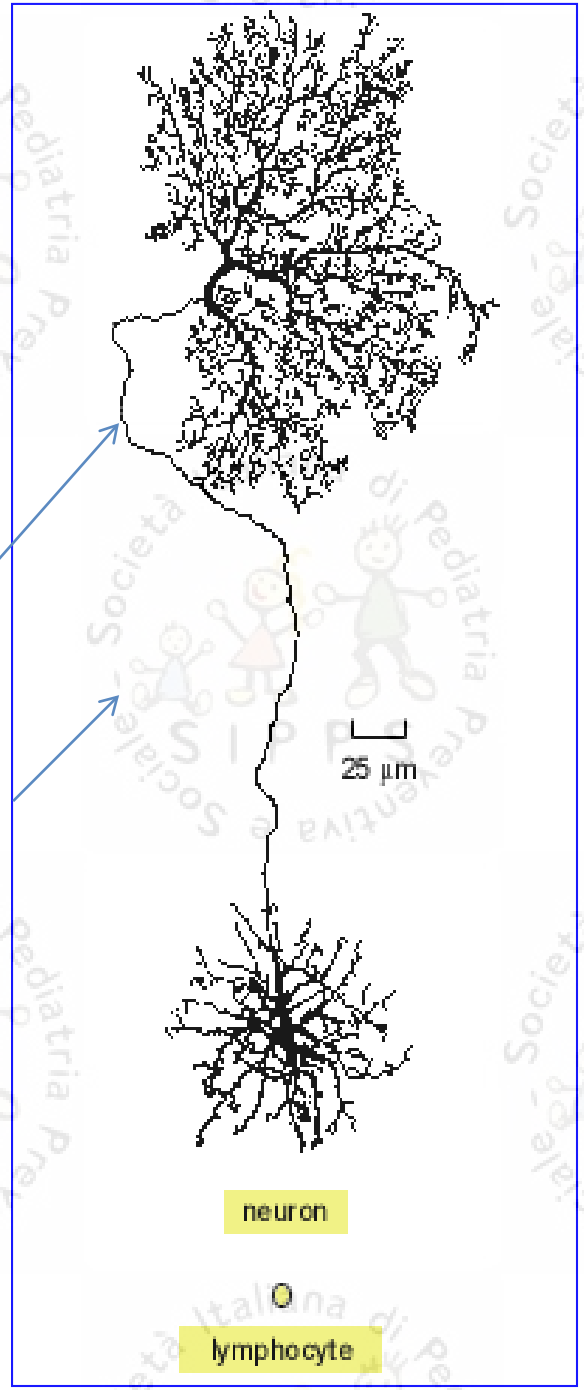
.. what really interests us here is the ***software***
(which is essentially constituted by ***neuronal circuits***
and thus by the ***synaptic connections*** **)**

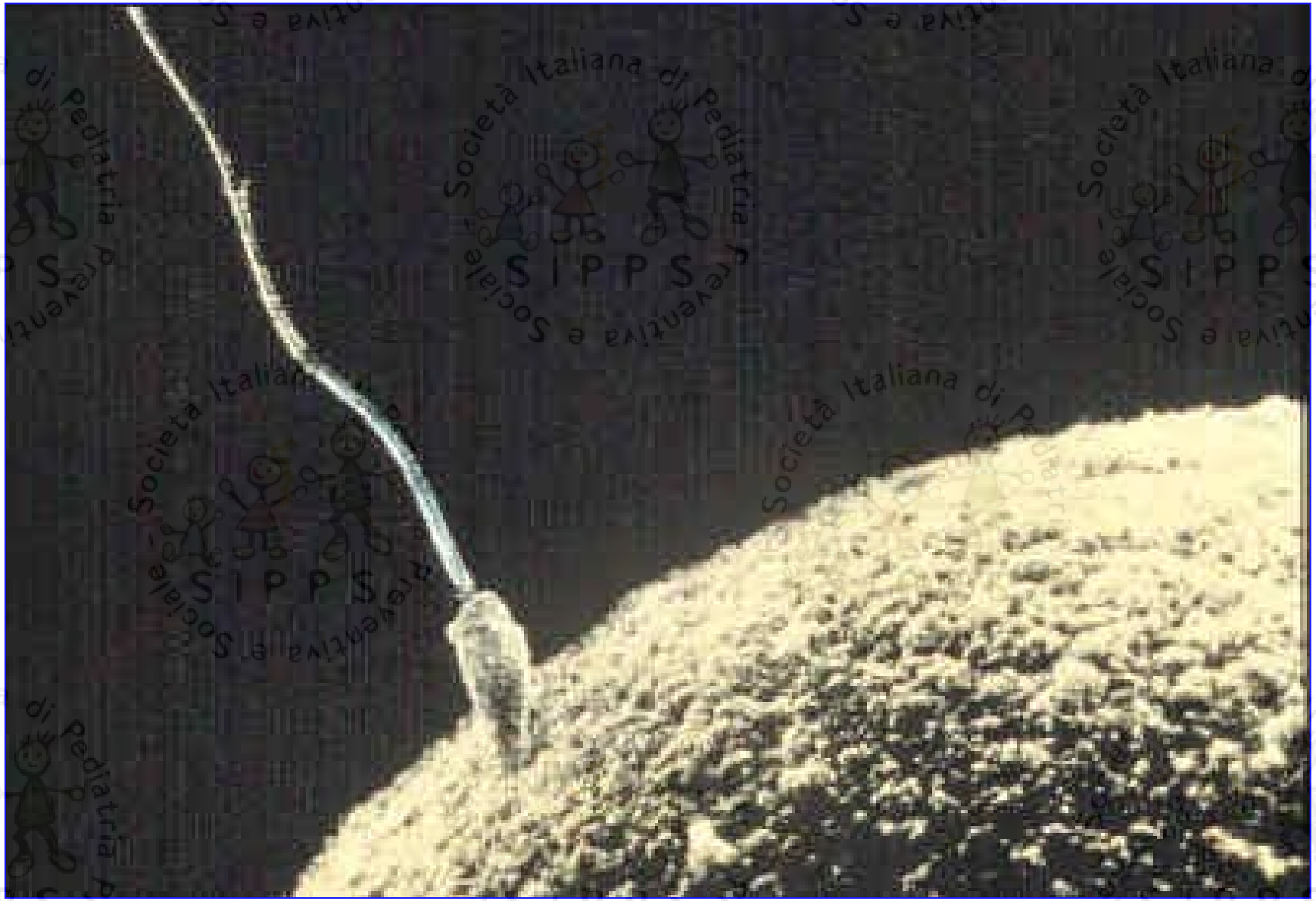
and the way in which - in the course of ***ontogenesis***, mainly
during the **fetal life*** and the **first two years of life**
(ie in the period of maximal ***developmental plasticity***)

billion of dendritic tree structures are connecting with each other in response to information coming from the environment
and **from the rest of the "network " under construction**

[what is really hard to understand is why so many scientists prefer,
even in this context , **a selective (neo-Darwinian) evolutionary model** rather than **an instructive and constructive one**
(***Lamarckian*** and Darwinian)]

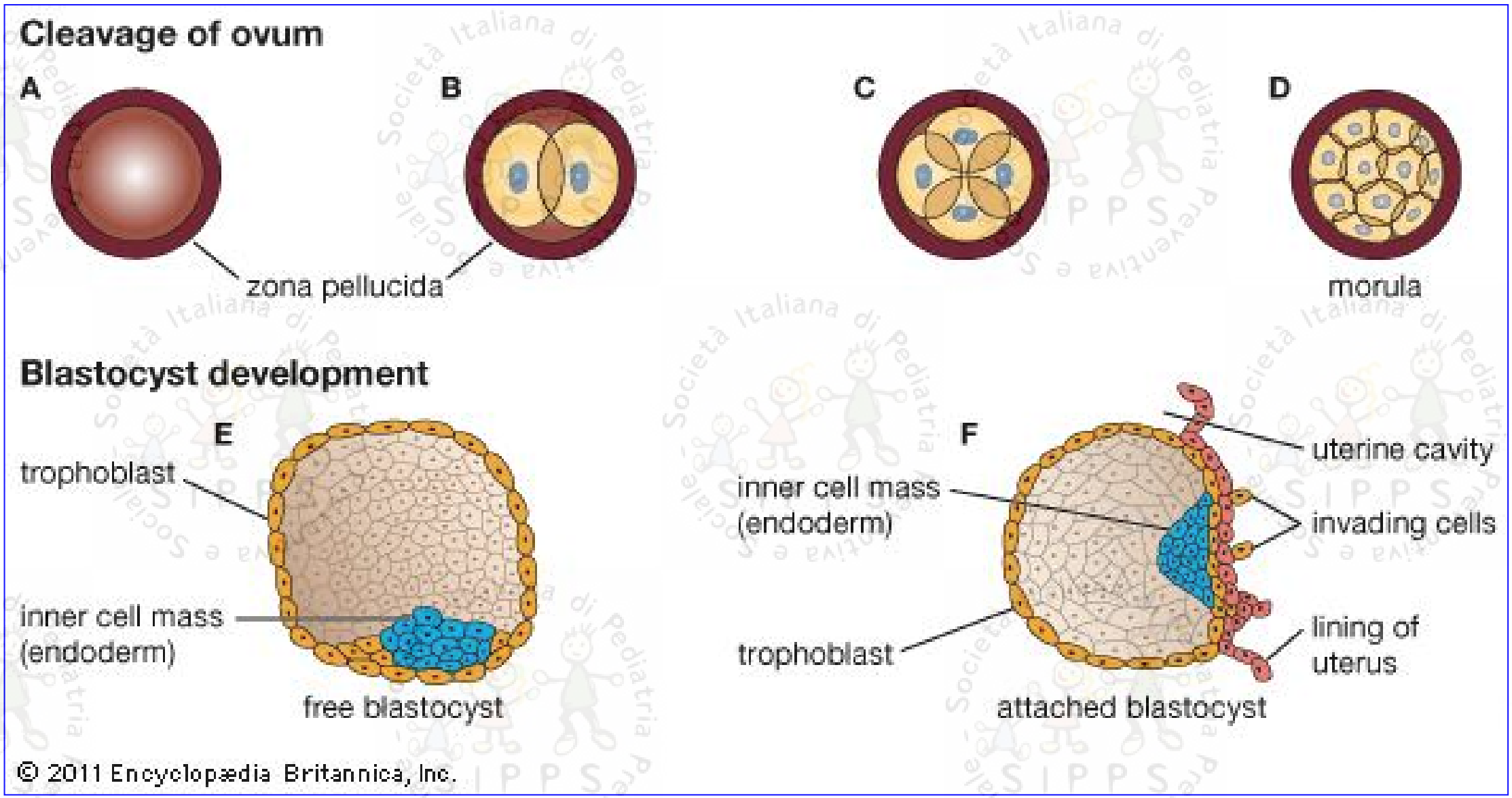
* In our species ***synaptogenesis*** begins as early as the **second month of fetal life** (in ***other mammals*** **only a few synapses are in place at birth**)



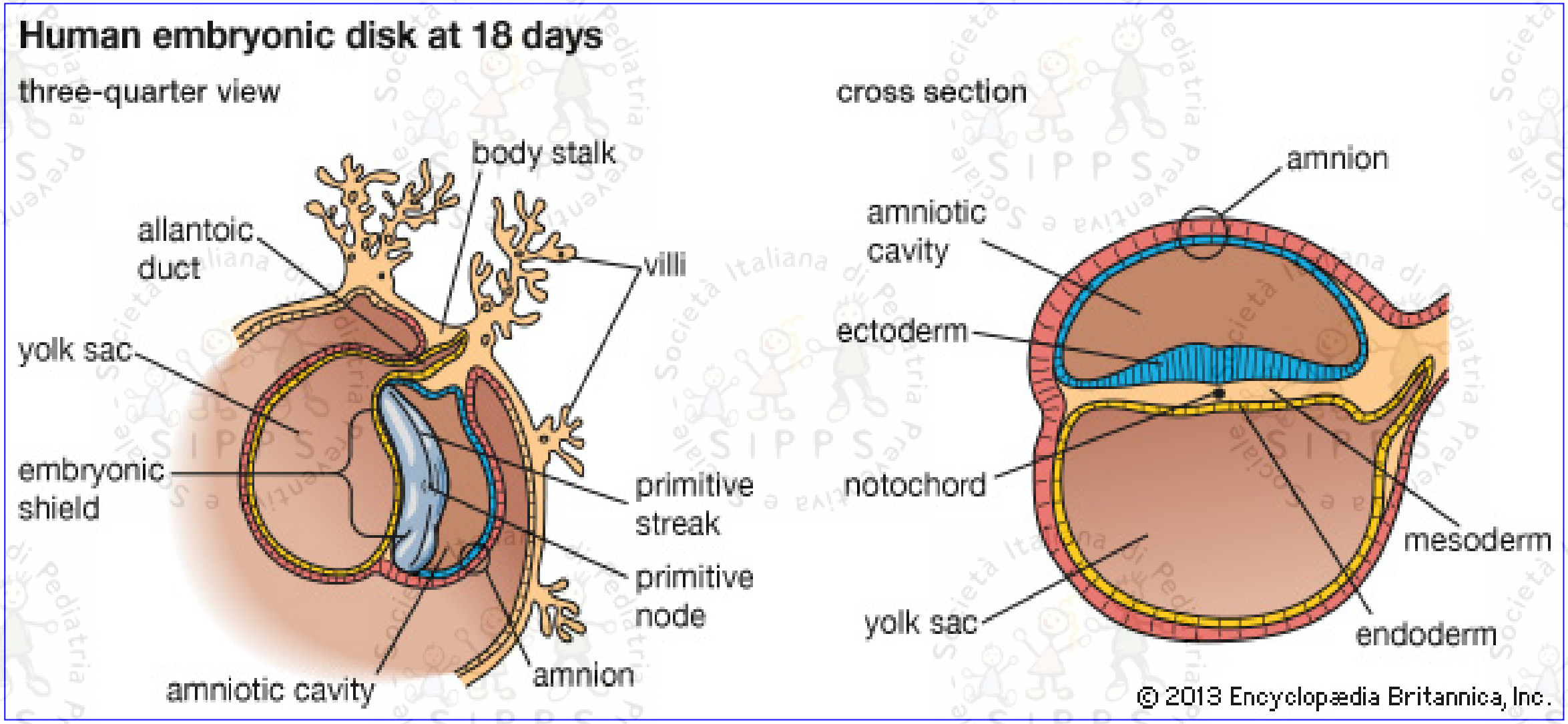


A sperm cell attempting to penetrate an egg (ovum) to fertilize it.

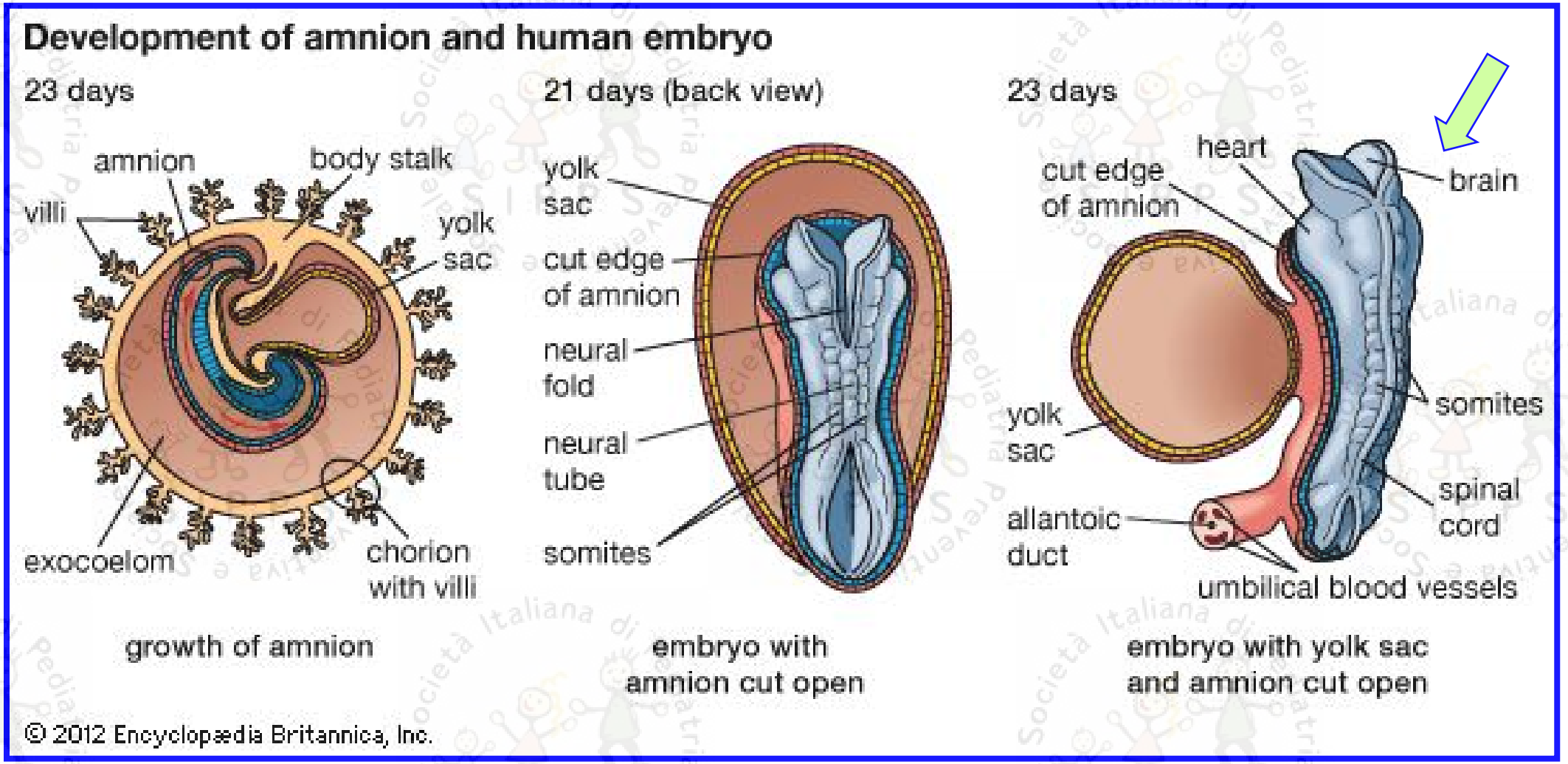
http://www.britannica.com/science/prenatal-development



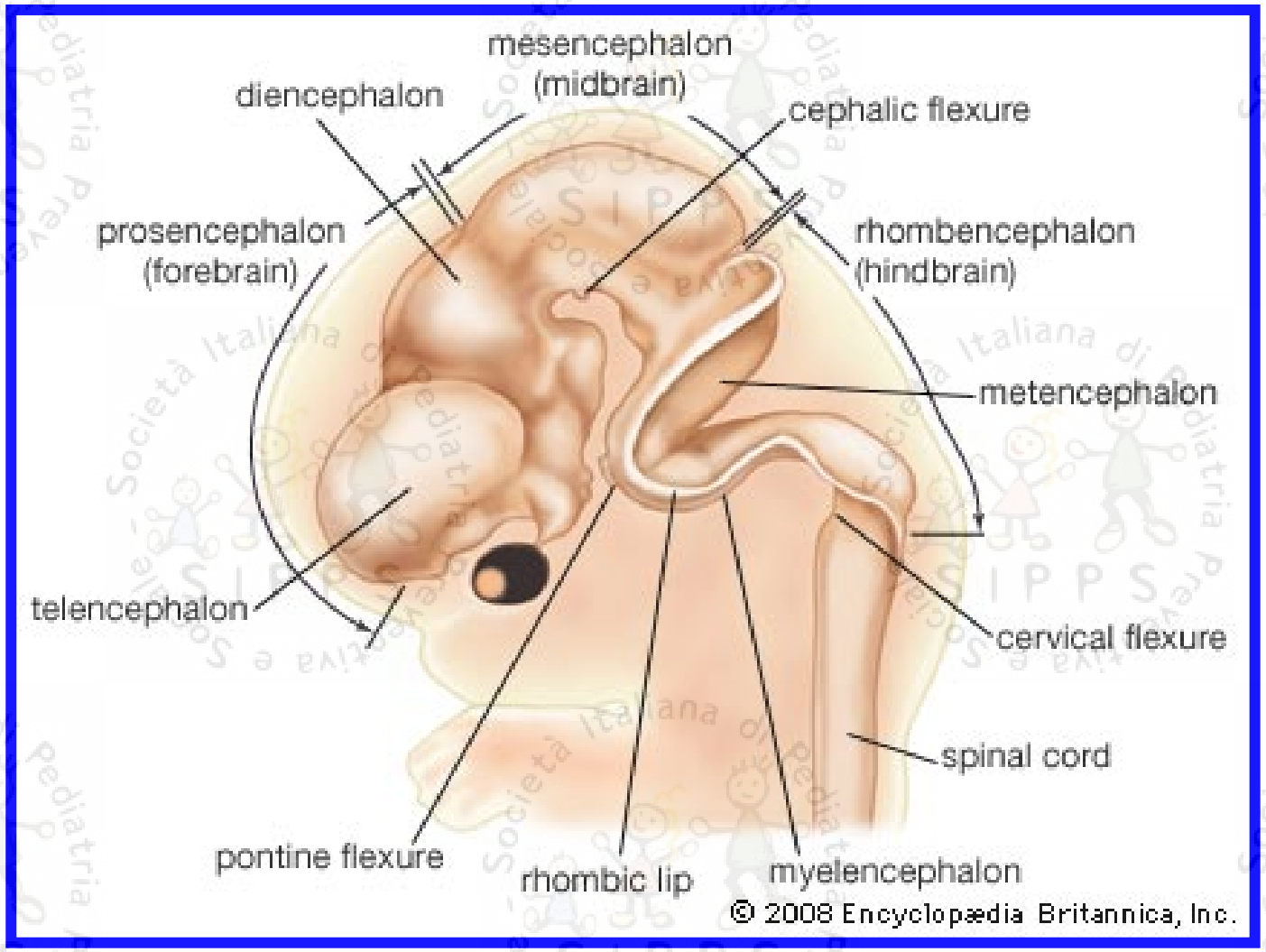
First stages of human development. (A–D) Cleavage of ovum. (E–F) Blastocyst development.



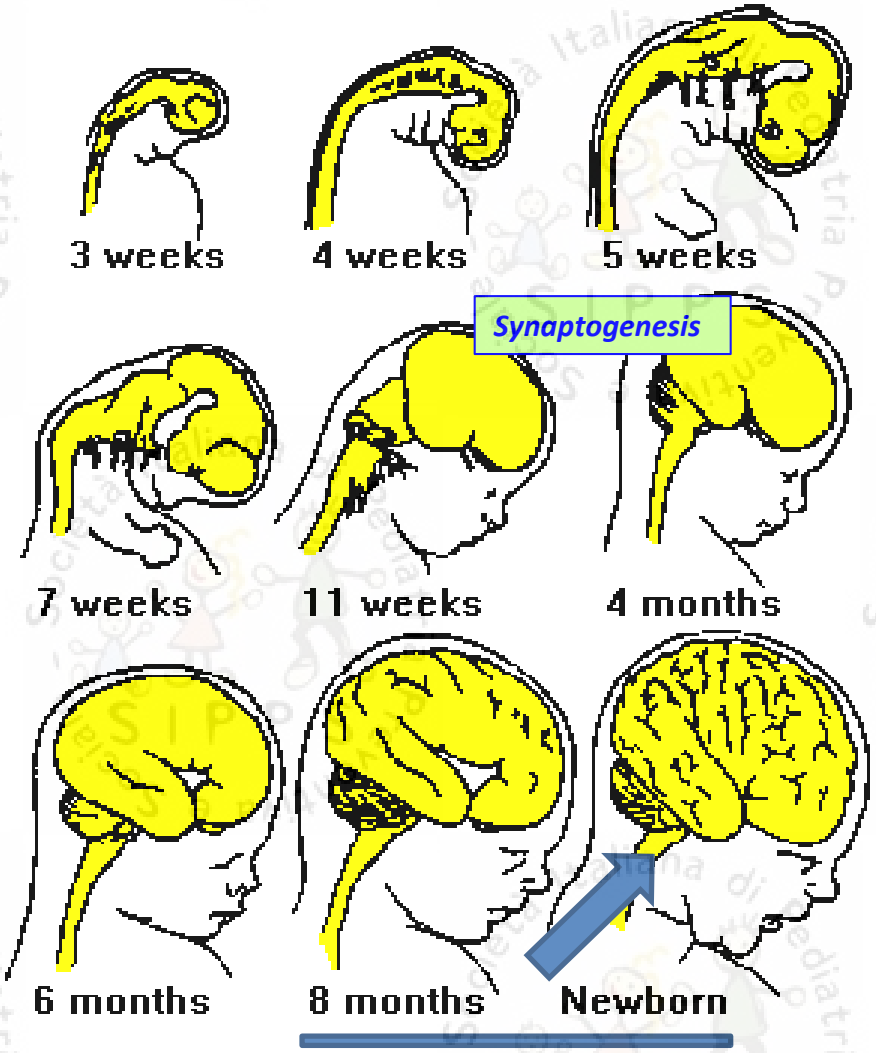
Embryo of 18 days at disk or shield stage, (Ja) three-quarter view, and (Jb) cross section



Embryo of 23 days showing (K) growth of the amnion, (L) amnion cut open, and (M) yolk sac and amnion cut open.



Profile of the **brain** of a human fetus at **10 weeks**



The brain grows at an amazing rate during development.
At times during brain development, **250,000 neurons are added every minute!**
At birth, almost all the neurons that the brain will ever have are present.

However, the brain continues to grow for many years after birth.

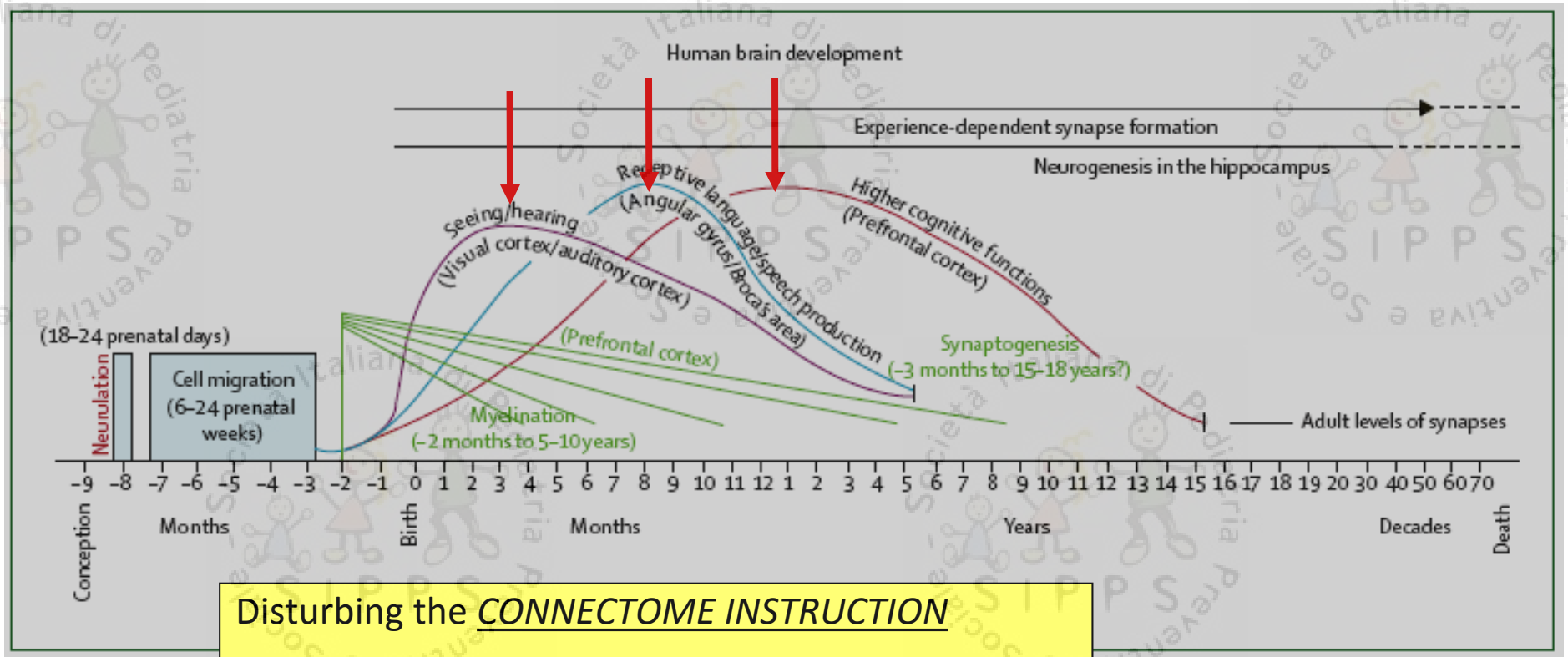
By the age of 2 years old, the brain is about **80% of the adult size**

A **stegosaurus dinosaur weighed approximately 1,600 kg but had a brain that weighed only approximately 70 grams (0.07 kg).** Therefore, **the brain was only 0.004% of its total body** weight. In contrast, an adult human weighs approximately 70 kg and has a brain that weighs approximately 1.4 kg. Therefore, **the human brain is about 2% of the total body weight**. This makes the brain to body ratio of the human **500 times greater than that of the stegosaurus**

The ***Individual*** wiring

Early critical periods in the development of SYNAPTOGENESIS and brain functions

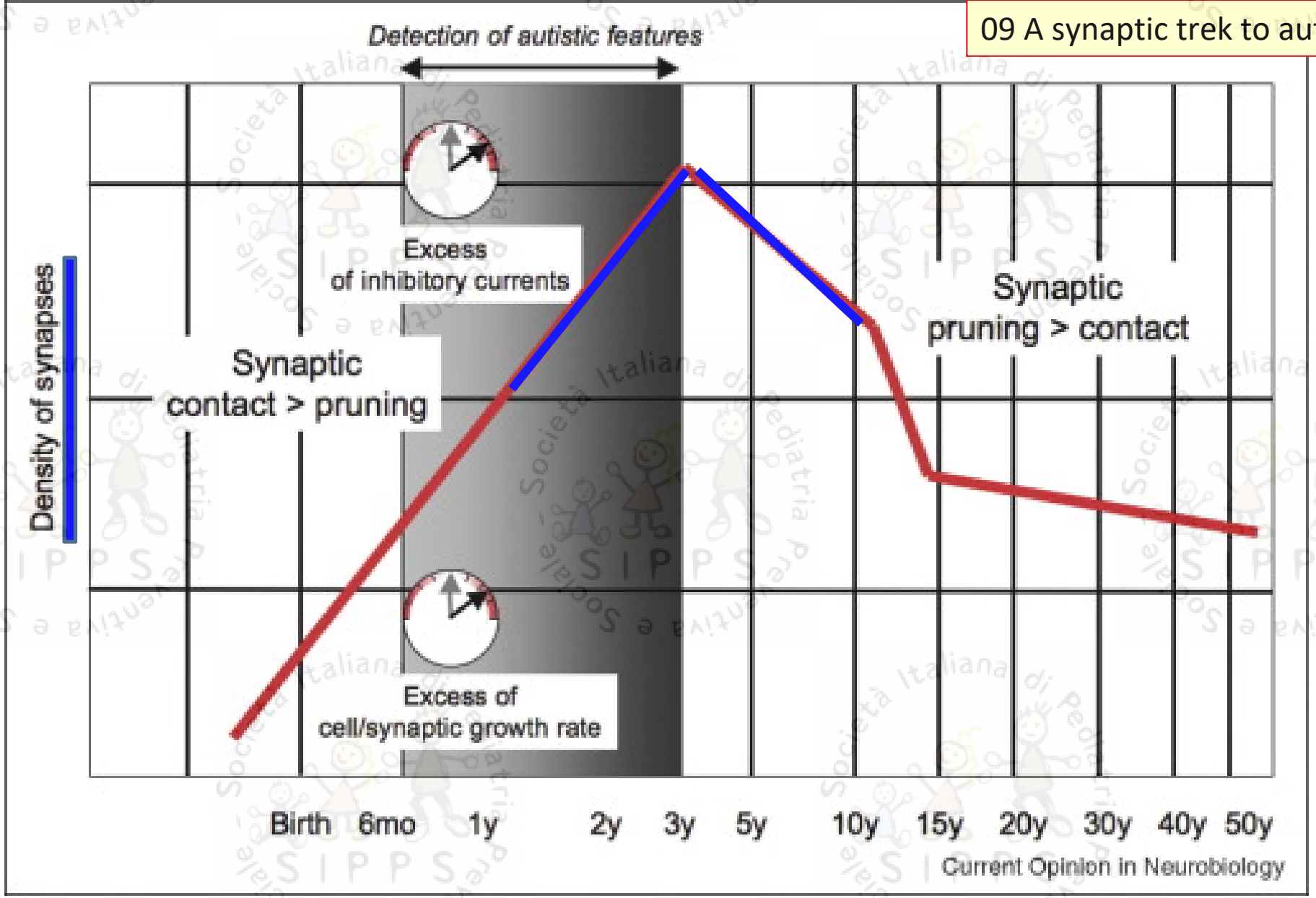
Formation of new synapses following stimulation..



Disturbing the *CONNECTOME INSTRUCTION*

Figure 1: **Human brain development**
Reproduced with permission of authors and American Psychological Association[37] (Thompson RA, Nelson CA. Developmental science and the media: early brain development. *Am Psychol* 2001; 56: 5–15).

09 A synaptic trek to autism



Schematic representation of the **different phases of synaptogenesis** in the human brain.
During the first three years of life, an excess of cell/synaptic growth rate and inhibitory currents could increase the risk of ASD.

NEUROSCIENCE

WHAT MAKES EACH BRAIN UNIQUE

How can identical twins grow up with different personalities? "Jumping genes" move around in neurons and alter the way they work

By Fred H. Gage and Alysson R. Muotri

IN BRIEF

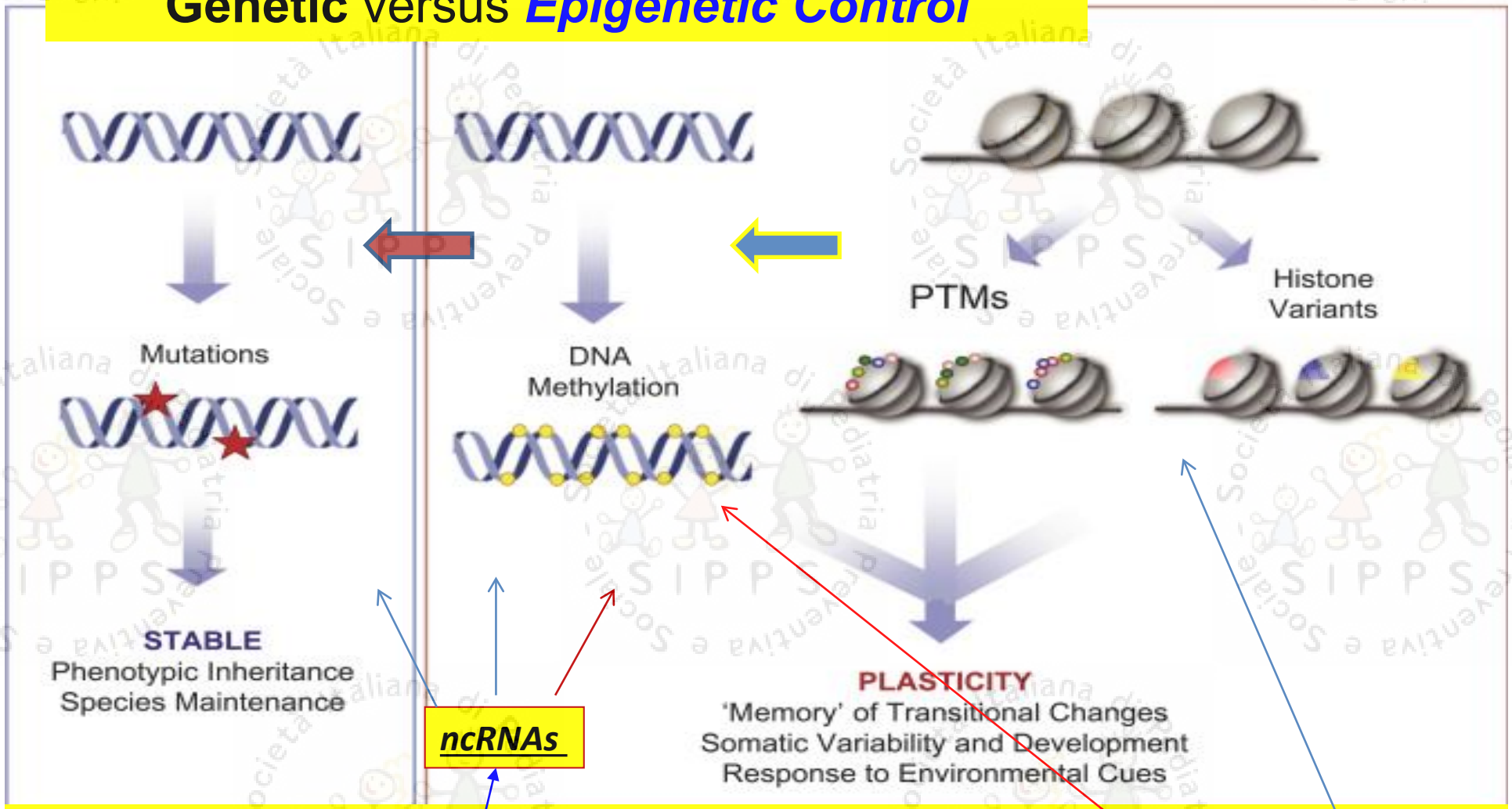
Genes we inherit and environmental factors both influence human behaviors. Scientists have recently discovered other underlying processes at work.

So-called jumping genes, segments of DNA that can copy and paste themselves into new places in the genome, can alter the activity of full-length genes. Occasionally they will turn on neighboring genes in these locations. That activity occurs more in the brain than other areas, resulting in different traits and behaviors, even in closely related individuals.

These mobile genetic elements may also turn out to play a role in people's disposition to psychiatric disorders.

Researchers are now beginning to investigate whether jumping genes help us adapt to rapidly changing environmental conditions.

Genetic versus ***Epigenetic Control***



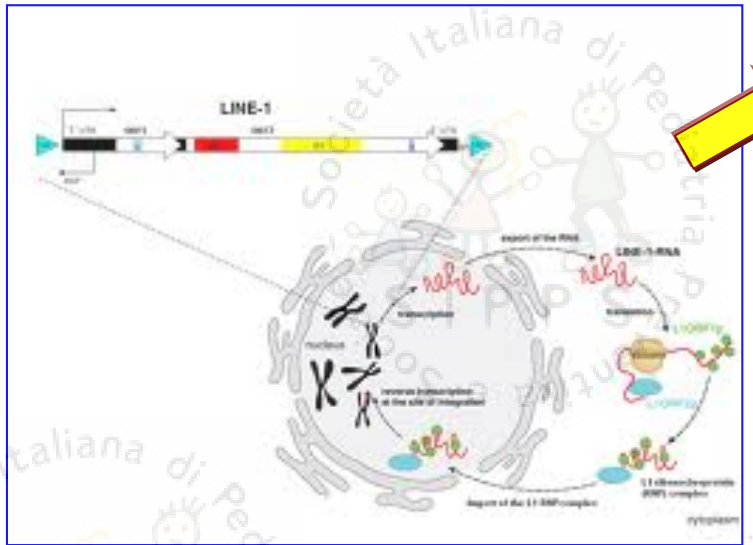
Variation in the chromatin template can be brought about ***by posttranslational modifications*** *(PTMs; colored beads)* ***added to histones***, exchange and replacement of major histones with ***specialized variants*** (colored wedges), or ***ATP-dependent nucleosome remodeling*** (not depicted), which alters histone-DNA contacts. All of these mechanisms, along with ***DNA methylation*** and potential ***interactions with noncoding RNAs*** (not depicted), likely act together to bring about the ***plasticity*** that helps to define epigenetic phenomena

However, claiming that **the genome remains fairly stable throughout life** is **not only a simplification, but a big mistake**

in fact the **genome changes constantly , not only in its *software* (the *epigenome*)** assigned to respond physiologically to ***stress*** and to ***information*** coming from outside, **but also, and with amazing frequency – mainly in the human brain - within the DNA sequence,** thanks to the continuous transfer of mobile sequences..

If we are right, and **the activity of the L1 jump really increases as the nervous system learns and adapts to the outside world** ,

this would indicate that the **individual brains and neural networks** of which they are made change and **are constantly changing at every new experience , even in genetically identical twins (which affects the assumption that identical twins are really genetically identical)**



Gage FH, Muotri AR. ***What makes each brain unique***.Sci Am. (2012);306(3):26-31

Leading Edge
Previews

Cell 164, February 11, 2016 ª2016 Elsevier Inc. 593

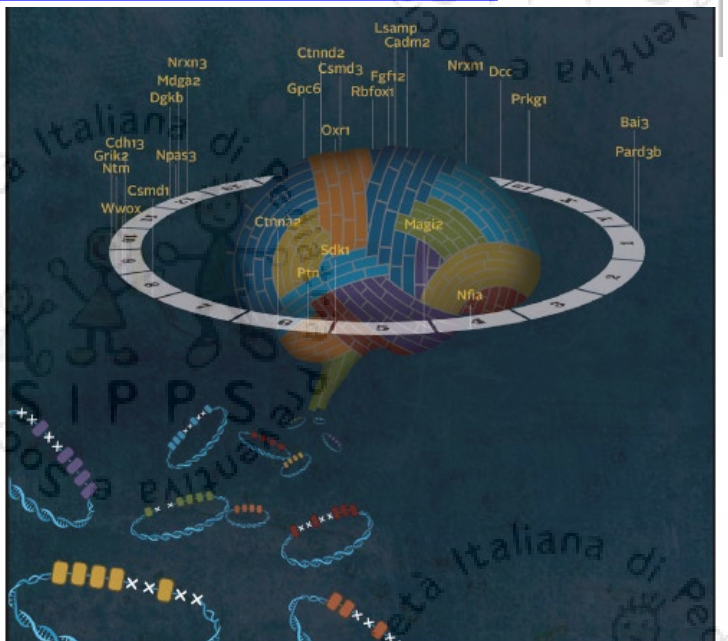
Cell

A Mechanism for Somatic Brain Mosaicism

Irving L. Weissman[1,*] and Fred H. Gage[2,*]
[1]Institute of Stem Cell Biology and Regenerative Medicine, Stanford University School of Medicine, Stanford University, Palo Alto, CA 94305, USA
[2]The Salk Institute for Biological Studies, Laboratory of Genetics, La Jolla, CA 92037, USA
*Correspondence: irv@stanford.edu (I.L.W.), gage@salk.edu (F.H.G.)
http://dx.doi.org/10.1016/j.cell.2016.01.048

Double-strand break repair is required for neural development, and brain cells contain somatic genomic variations. Now, Wei et al. demonstrate that neural stem and progenitor cells undergo very frequent DNA breaks in a very restricted set of genes involved in neural cell adhesion and synapse function.

Many of the identified genes are **expressed in NSPCs located in the brain regions responsible for higher functions such as short-term learning,** and mutations in these genes in humans are associated with (and maybe predispose to) **psychiatric and neurological disorders manifested in mind functions—autism, manic depressive and depressive disorders, schizophrenia**, and others



Università degli Studi di Padova

Dipartimento di Psicologia Generale

16 Aprile 2018
Aula I. Nievo Palazzo del Bo
Università di Padova

Science of Consciousness

con la partecipazione di FEDERICO FAGGIN

INGRESSO LIBERO
(fino a esaurimento posti)

Questo evento, promosso dal Science of Consciousness Research Group del Dipartimento di Psicologia Generale, ha lo scopo di presentare per la prima volta a studenti, colleghi e al pubblico, **lo stato dell'arte della ricerca sulla natura della coscienza**, dell'esperienza soggettiva e della sua relazione con il mondo fisico.
La scienza della coscienza è una disciplina nuova e intimamente interdisciplinare comprendente le neuroscienze, la filosofia, la psicologia, la fisica e l'antropologia, che indaga **la relazione ancora incompresa tra la mente, il cervello e la realtà fisica**.
Si affronteranno quindi temi che spaziano dalle implicazioni epistemologiche alla base della scienza della coscienza, agli aspetti psicologici e neurobiologici (Facco e Burgio) per estendersi fino alla fisica dell'infinitamente piccolo (Fracas), dell'infinitamente grande (Tormen) e all'intelligenza artificiale (Faggin).

PROGRAMMA

9.15: Presentazione a cura di ***Daniela Lucangeli***

Relazioni

9.30: **Enrico Facco**
L'enigma della Coscienza

10.30: **Ernesto Burgio**
Evoluzione e sviluppo del cervello ed emergere della coscienza

Pausa

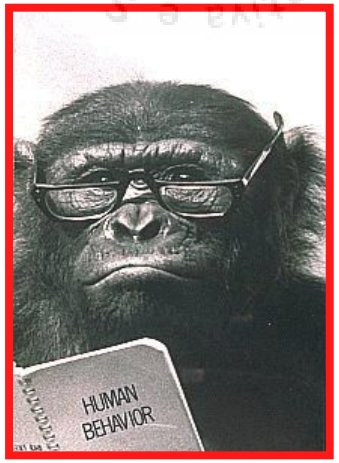
11.45: **Fabio Fracas**
Il mondo secondo la Fisica Quantistica

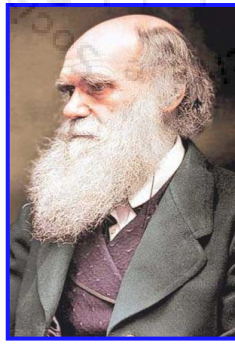
12.45: **Giuseppe Tormen**
Noi e l'infinitamente grande

Pausa

14.45: **Federico Faggin**
Robot coscienti: realtà o fantascienza?

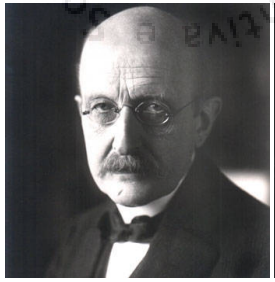
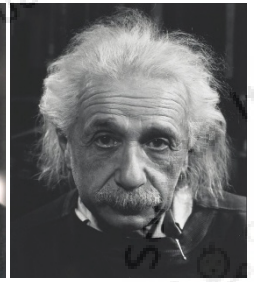
16.00: Tavola rotonda con tutti i relatori e dibattito generale

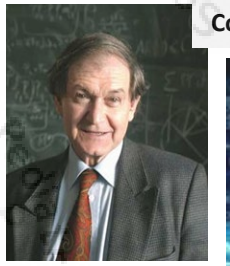


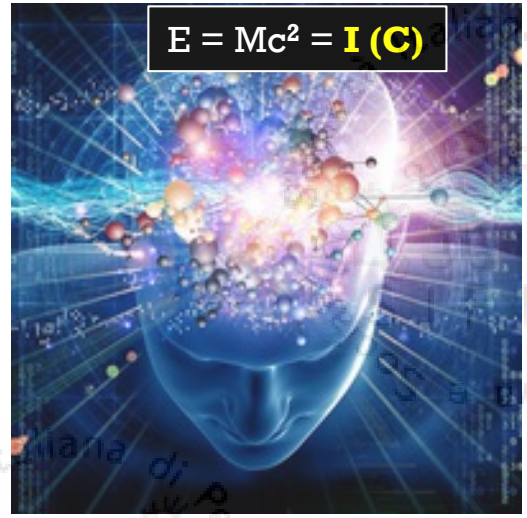


Evoluzione e Sviluppo del Cervello
e(d emergere) della Coscienza

Coscienza
Cervello — Inconscio
Reti Neurali — Mente — Psiche
Connettoma — Anima





Ernesto Burgio (ECERI, Brussels, Belgium

ECERI
European Cancer and Environment Research Institute

Nature **436**, 29 (7 July 2005) | doi:10.1038/436029a; Published online 6 July 2005

nature International weekly journal of science

Concept

The mental Universe

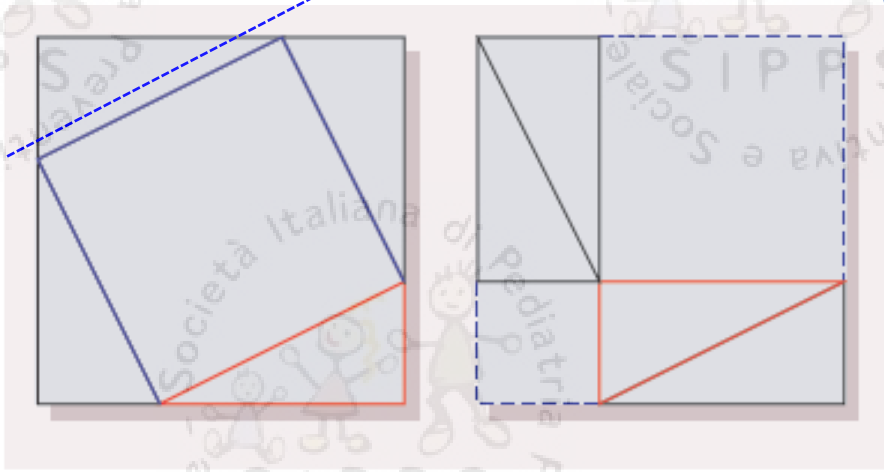
Richard Conn Henry[1]

1. Richard Conn Henry is a Professor in the Henry A. Rowland Department of Physics and Astronomy, The Johns Hopkins University, Baltimore, Maryland 21218, USA.

The only reality is mind and observations, but observations are not of things. To see the Universe as it really is, we must abandon our tendency to conceptualize observations as things.

▲ Top

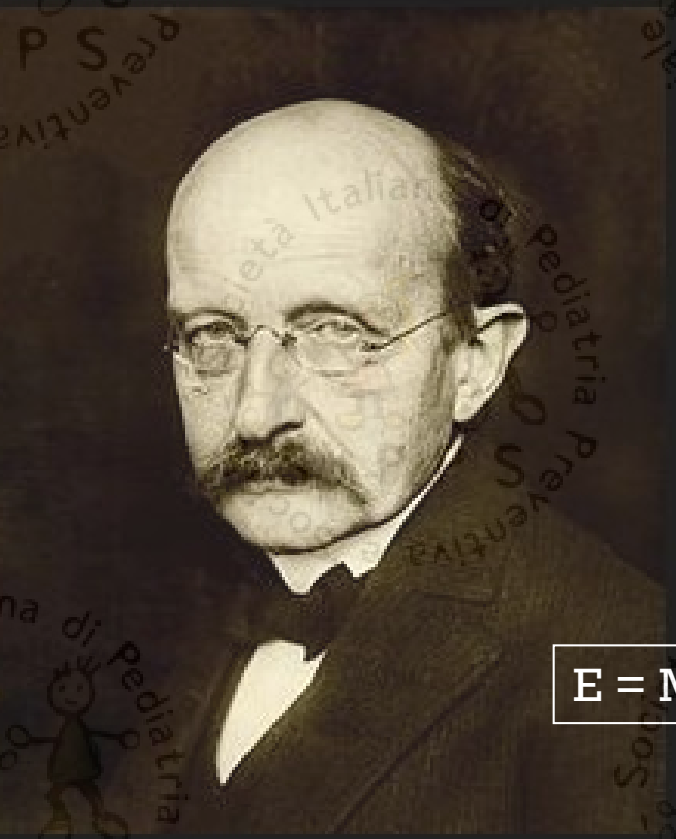
correct understanding of physics was accessible even to Pythagoras. According to Pythagoras, "number is all things", and numbers are mental, not mechanical. Likewise, Newton called light "particles", knowing the concept to be an 'effective theory' — useful, not true. As noted by Newton's biographer Richard Westfall: "The ultimate cause of atheism, Newton asserted, is 'this notion of bodies having, as it were, a complete, absolute and independent reality in themselves.'" Newton knew of Newton's rings and was untroubled by what is shallowly called 'wave/particle duality'.



Proof without words: Pythagoras explained things using numbers.

The 1925 discovery of quantum mechanics solved the problem of the Universe's nature. Bright physicists were again led to believe the unbelievable — this time, that the Universe is mental. According to Sir James Jeans: "the stream of knowledge is heading towards a non-mechanical reality; the Universe begins to look more like a great thought than like a great machine. Mind no longer appears to be an accidental intruder into the realm of matter... we ought rather hail it as the creator and governor of the realm of matter." But physicists have not yet followed Galileo's example, and convinced everyone of the wonders of quantum mechanics. As Sir Arthur Eddington explained: "It is difficult for the matter-of-fact physicist to accept the view that the substratum of everything is of mental character."

Physicists shy from the truth because the truth is so alien to everyday physics. A common way to evade the mental Universe is to invoke 'decoherence' — the notion that 'the physical environment' is sufficient to create reality, independent of the human mind. Yet the idea that any irreversible act of amplification is necessary to collapse the wave function is known to be wrong: in 'Renninger-type' experiments, the wave function is collapsed simply by your human mind seeing nothing. The Universe is entirely mental.



$E = Mc^2 = \mathbf{I}\ (\mathbf{C})$

I regard consciousness as fundamental. I regard matter as derivative from consciousness. We cannot get behind consciousness. Everything that we talk about, everything that we regard as existing, postulates consciousness.

(Max Planck)

Cosmic Evolution

From Big Bang to Humankind

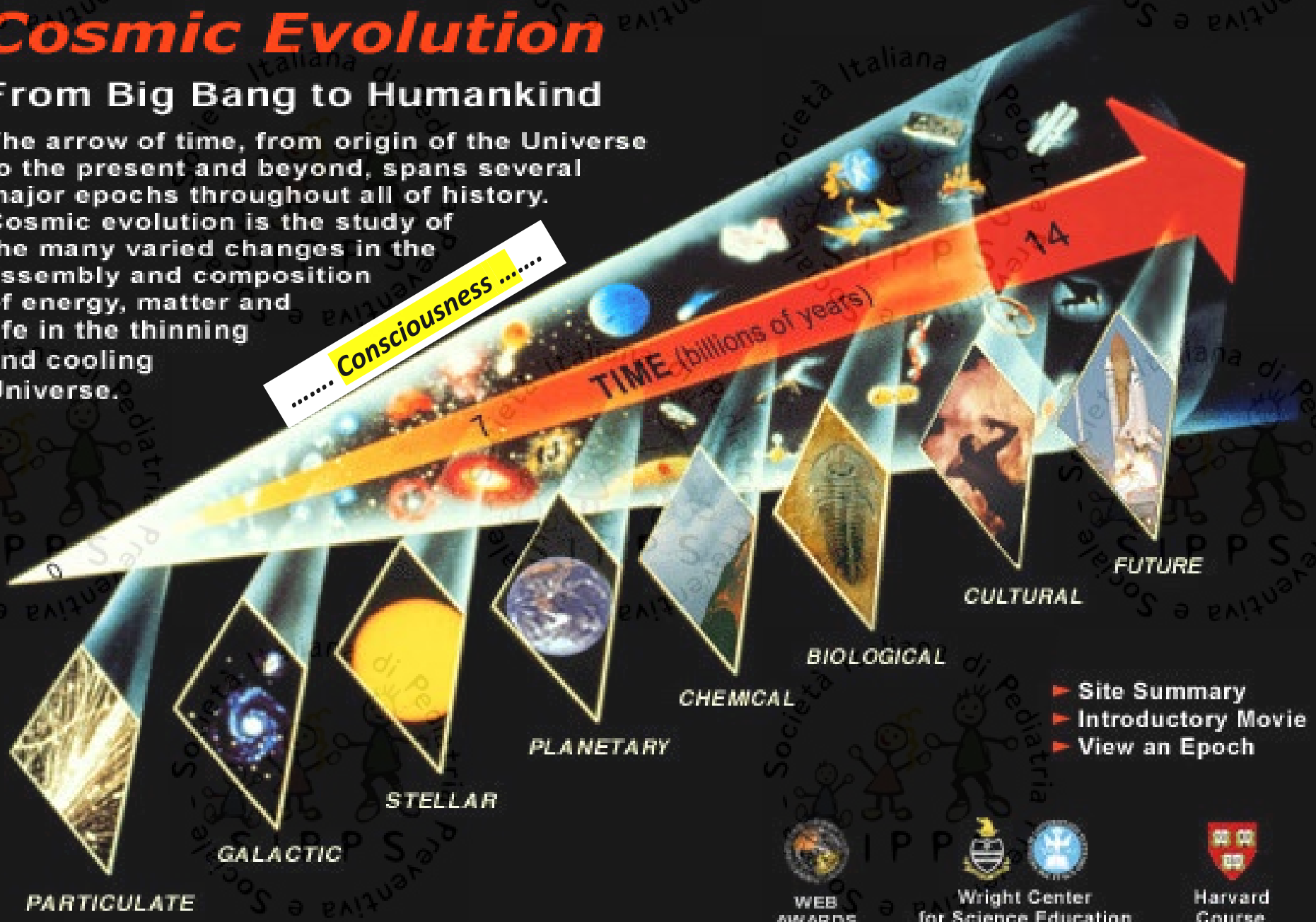
The arrow of time, from origin of the Universe to the present and beyond, spans several major epochs throughout all of history. Cosmic evolution is the study of the many varied changes in the assembly and composition of energy, matter and life in the thinning and cooling Universe.

Deep Time

when (?)

where (?)

how (?)



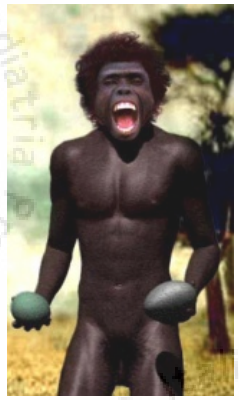
- Site Summary
- Introductory Movie
- View an Epoch

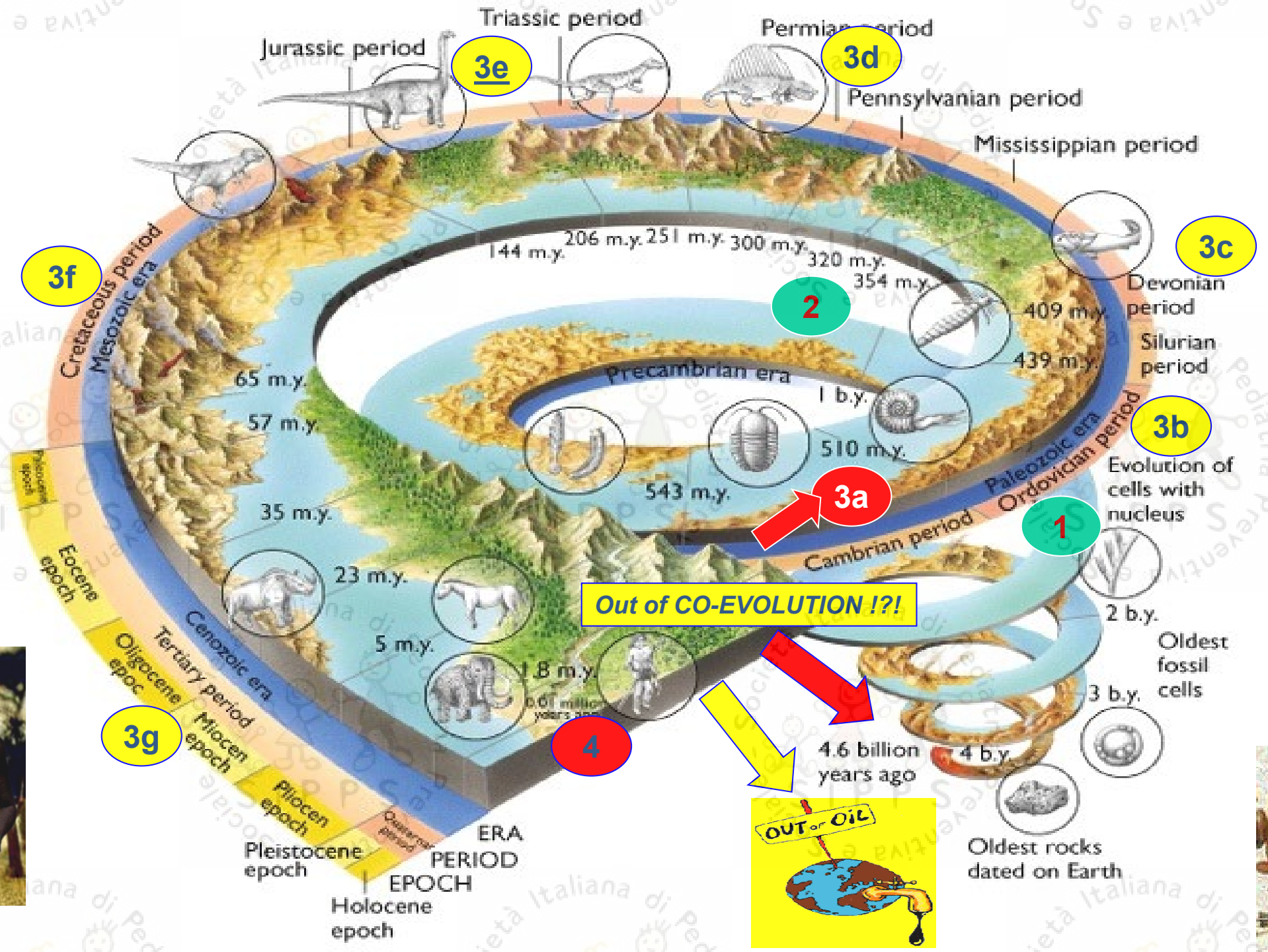
WEB AWARDS

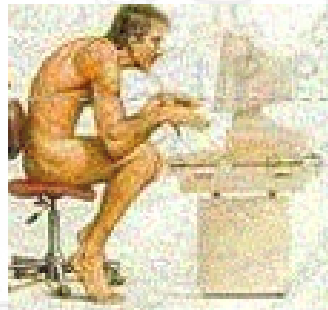
Wright Center for Science Education Tufts University

Harvard Course Syllabus

http://www.mukto-mona.com/Special_Event_/Darwin_day/




Triassic period
Jurassic period
Permian period
Pennsylvanian period
Mississippian period
Devonian period
Silurian period
Ordovician period
Cambrian period
Paleozoic era
Precambrian era
Mesozoic era
Cretaceous period
Cenozoic era
Tertiary period
Eocene epoch
Oligocene epoch
Miocen epoch
Pliocen epoch
Pleistocene epoch
Holocene epoch
ERA
PERIOD
EPOCH
144 m.y.
206 m.y.
251 m.y.
300 m.y.
320 m.y.
354 m.y.
409 m.y.
439 m.y.
510 m.y.
543 m.y.
1 b.y.
65 m.y.
57 m.y.
35 m.y.
23 m.y.
5 m.y.
1.8 m.y.
3a
3b
3c
3d
3e
3f
3g
1
2
4
Evolution of cells with nucleus
2 b.y.
Oldest fossil cells
3 b.y.
4 b.y.
4.6 billion years ago
Oldest rocks dated on Earth
Out of CO-EVOLUTION !?!
OUT OF OIL



(*OLOCENE*)

31 DICEMBRE - ULTIMO MINUTO

- ore 23,59'15" --> i **Sumeri** in Mesopotamia
- ore 23,59'43" -->Alessandro Magno - Primo "**Impero**"
- ore 23,59'46" --> **Gesù Cristo**
- ore 23,59'49" -->**Caduta Impero** Romano d'Occidente
- ore 23,59'57" --> Scoperta dell'**America**
- ore 23,59'59" --> **Rivoluzione Industriale** * e Francese Colonialismo- Guerre Mondiali- **Globalizzazione**

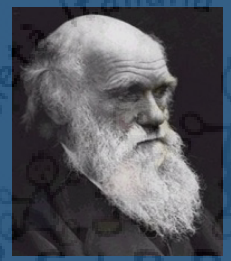
*"***Antropocene***": con la **I (Carbone/Macchine)** e soprattutto con la **II (Chimica/Petrolio) Rivoluz. Industriale** ***Homo S. Sapiens*** si è trasformato in ***potenza tellurica*** (*Stoppani1873 - Crutzen 1995*).. Con la **III (*Telematica*)** è nata una ***nuova entità***: la ***Prima Specie Globale (WWW)***

Milioni di anni

Evolution

"Ambiente"

Challenge "naturale"



I processi *filo-genetici* durano milioni di anni

1 Agenti Fisici

Xrays-EMFs

Adattamento

Co-evoluzione

Sistemi Neuro-endocrino Immunocompetente

2

Fall-Out Chimico

>100mila molecole "*nuove*" non portato di una di co-evoluzione

MHC

Danger Signals !!

Genoma

Self

Tolleranza

Antigeni

Non self

3

Agenti Biologici

virus

(*Retro-viruses*)

HERVs

Onco-géni

(Epi)-genoma

Genosfera

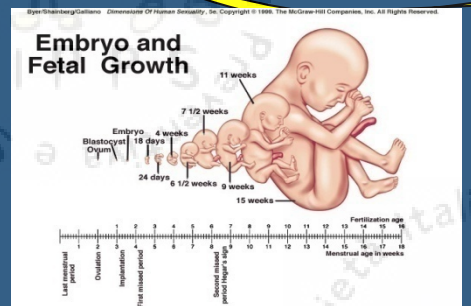
(*Retro*)*Trasposons*)

V-onc

C-onc

Fetal Programming

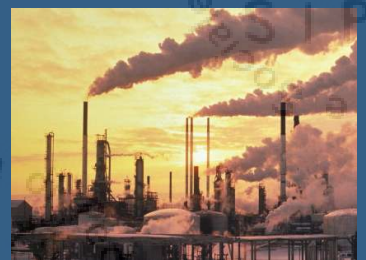
Biosfera



Devo-Evo

IXX-XX SECOLO

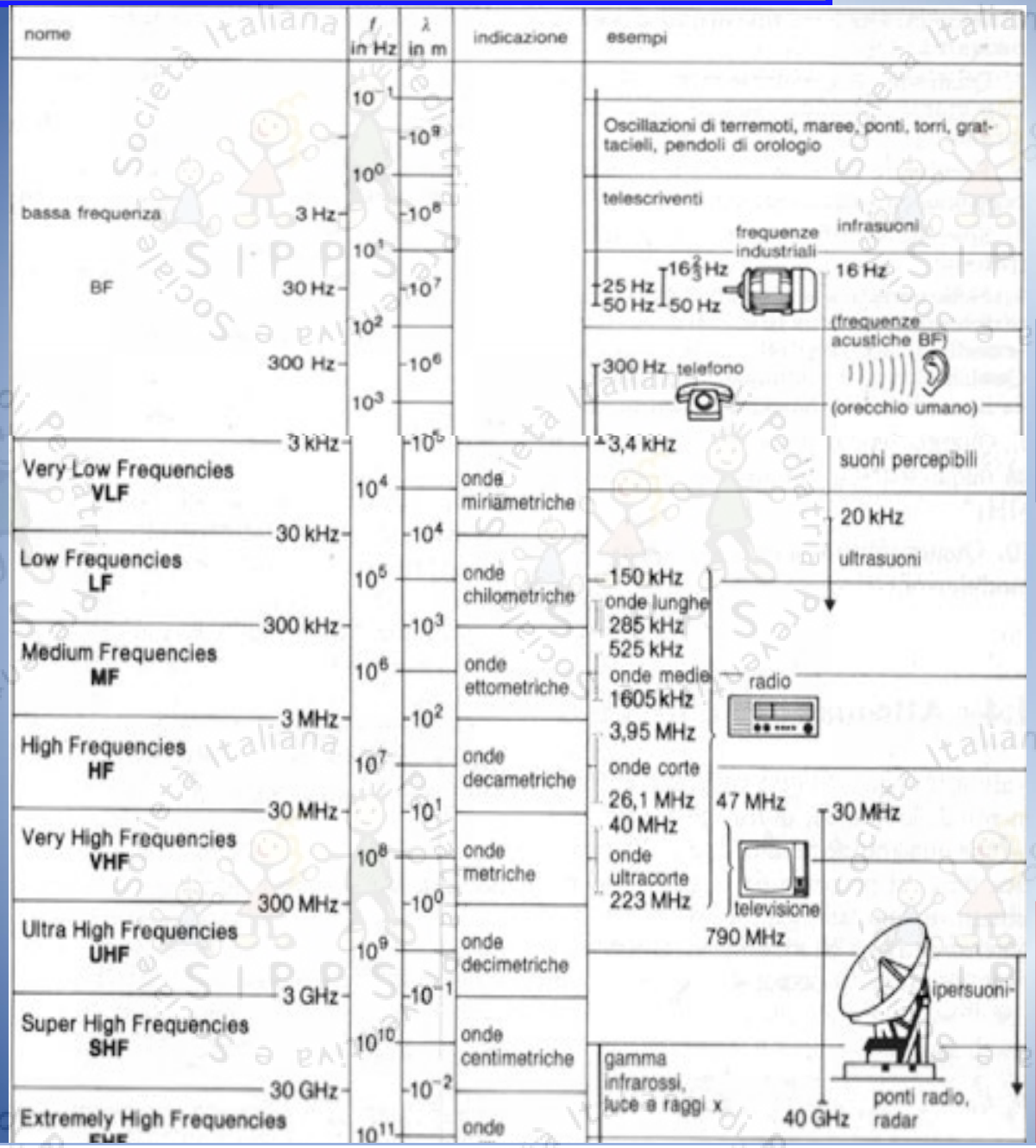
Drammatica Trasformazione Ambientale e Climatica



Lo sviluppo *onto-genetico dura 9 mesi → una vita*

Il problema dell'esposizione **collettiva** /**crescente** → limiti epidemiologia

Lezioni ed esercizi di elettronica 2
Editrice La Scuola



<u>Fino al 1930 circa, la parte dello spettro delle onde radio sopra i 30 MHz era praticamente vuota</u>: non esistevano segnali prodotti dall'uomo

Ai giorni nostri, lo spettro delle frequenze radio è estremamente sfruttato e viene per comodità **diviso in varie <u>bande di frequenza</u> <u>dai 3 kHz delle frequenze molto basse (VLF) fino ai 300 GHz delle frequenze estremamente alte (EHF).</u>**

Le bande di frequenza sono **divise in base alle caratteristiche che ne determinano l'impiego in certi settori** piuttosto che in altri.

http://www.torinoscienza.it/dossier

…. Tout ce qui n'est pas le produit de cette coevolution moleculaire peut faire des degats →DANGER SIGNAUX.. HSPs


I'M AFRAID MY BRAIN HAS LEFT FOR THE DAY
©PNTS