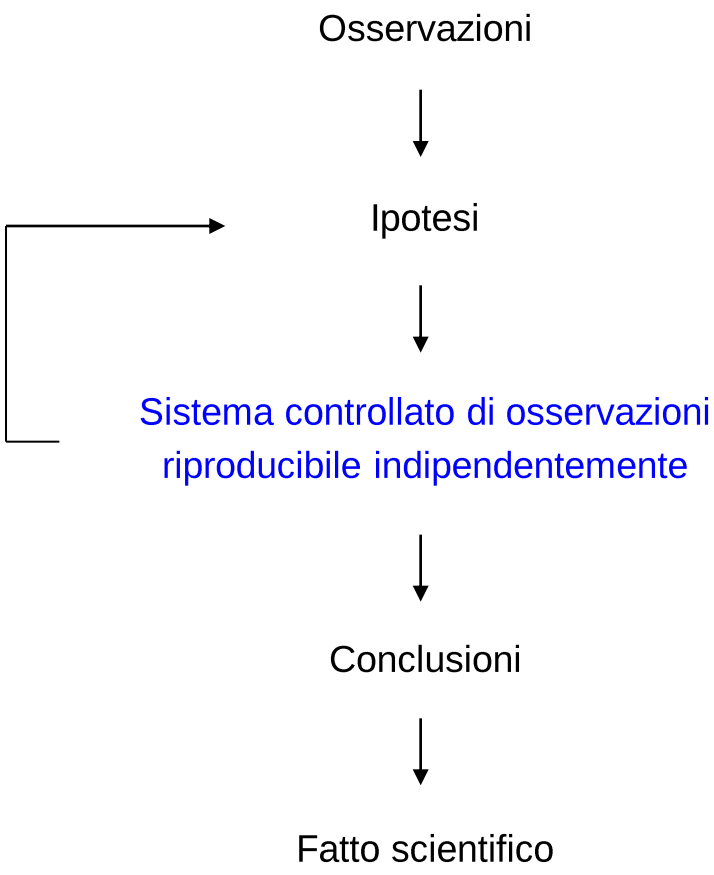
Ideazione di un progetto di ricerca

Il "metodo scientifico"



Ricerca guidata da ipotesi

Ricerca guidata da domande (esplorazione)

Sviluppo di metodi o strumenti

Misurazioni

Dal bando AIRC 2017

The following kinds of proposals will receive **low priority and have marginal chances of being funded:**

- studies that are essentially confirmatory in nature or represent marginal "variations-on-the-theme" of well-established concepts in cancer research;
- studies contemplating descriptive screenings of molecules and/or phenotypes without mechanistic insights and/or elements of innovative discovery [esplorazione]. These include purely descriptive microarray and proteomic profiling studies that are not associated with a strong strategy for clinical application, or the generation of chemical compounds without validating their anti-tumor activities in pharmacological and biological studies;
- generation of reagents and/or optimization of technologies [sviluppo di metodi o strumenti], or creation of services/technological facilities in the absence of a coherent and innovative research plan;
- chemical and/or viral carcinogenesis studies not embodied in the framework of mechanistic studies;
- requests for on-going routine collection of current statistics, such as cancer registry;
- descriptive epidemiology studies [misurazione];
- ...

Leading Edge
Commentary

Cell

Philosophies of Funding

Maureen A. O'Malley,[1,*] Kevin C. Elliott,[2] Chris Haufe,[3] and Richard M. Burian[4,*]
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[3]Department of Philosophy, University of Chicago, Chicago, IL 60637, USA
[4]Department of Philosophy, Virginia Tech, Blacksburg, VA 24061, USA
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DOI 10.1016/j.cell.2009.08.008

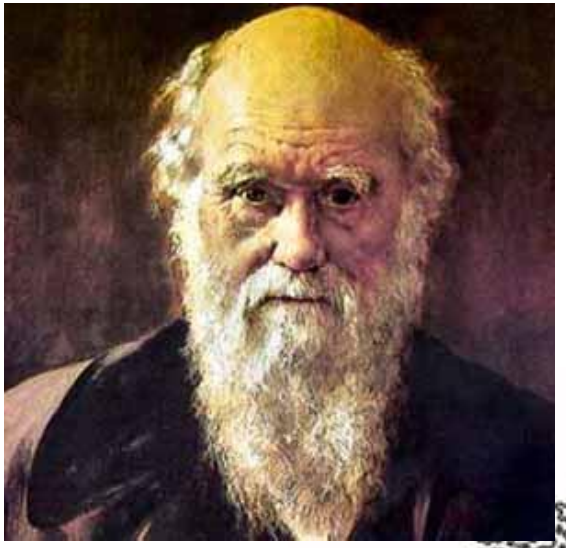
Successful scientific practice encompasses broader and more varied modes of investigation than can be captured by focusing on hypothesis-driven research. We examine the emphases that major US and UK funding agencies place on particular modes of research practice and suggest that funding agency guidelines should be informed by a more dynamic and multidimensional account of scientific practice.

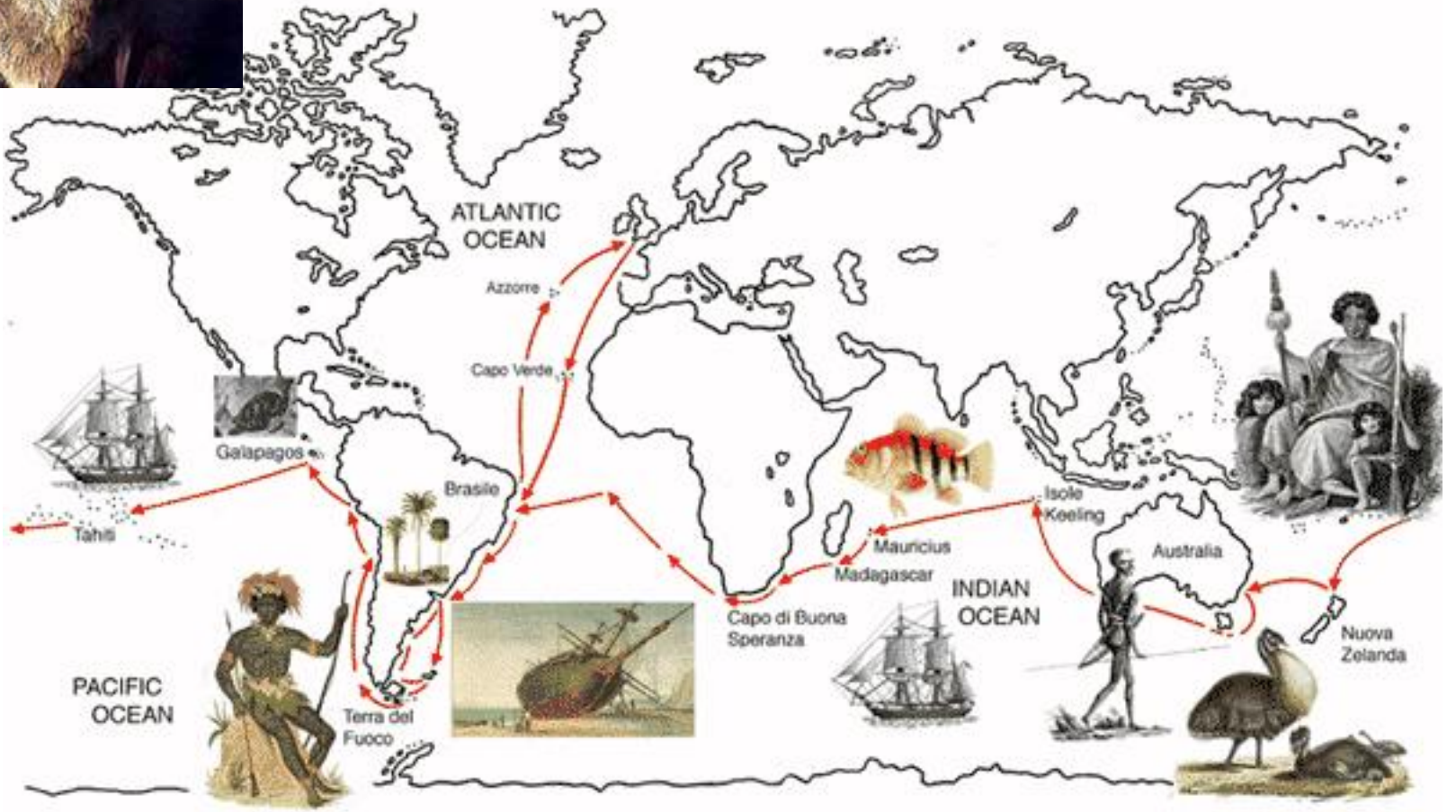
Philosophy is often regarded as abstract and irrelevant to practical concerns. Yet, when it comes to decisions about funding science, philosophical conceptions the most crucial arenas in which this widening of perspective must occur is in the funding of science. Although we believe that inspiration, effort, commu-

A Broad Account of Scientific Practice

It is standard for scientists, philosophers, and other commentators on sci-

Cell 138:611-615, 2009

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Azzorre
Capo Verde
Galapagos
Tahiti
Brasile
Terra del Fuoco
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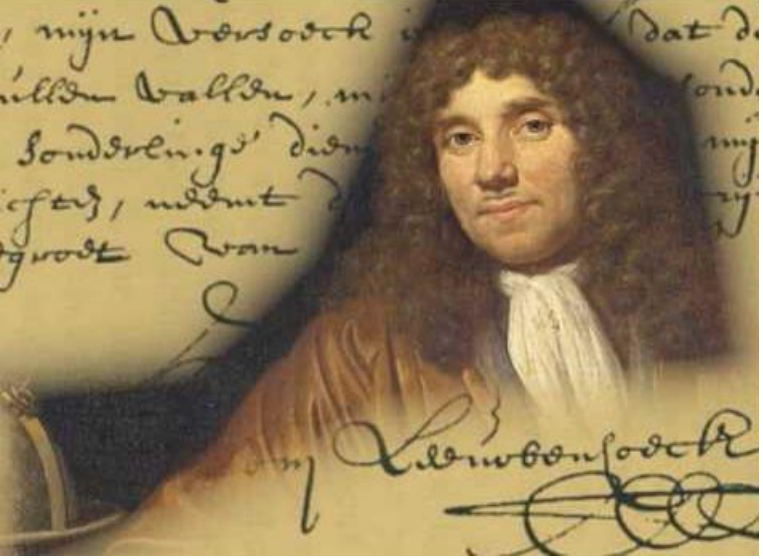
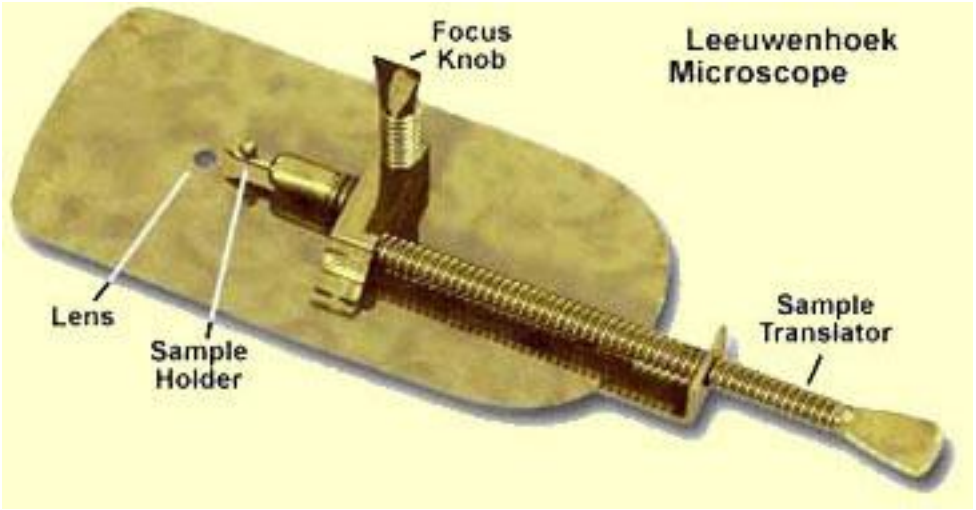
Capo di Buona Speranza
Madagascar
Mauricius
INDIAN OCEAN
Isole Keeling
Australia
Nuova Zelanda




Focus
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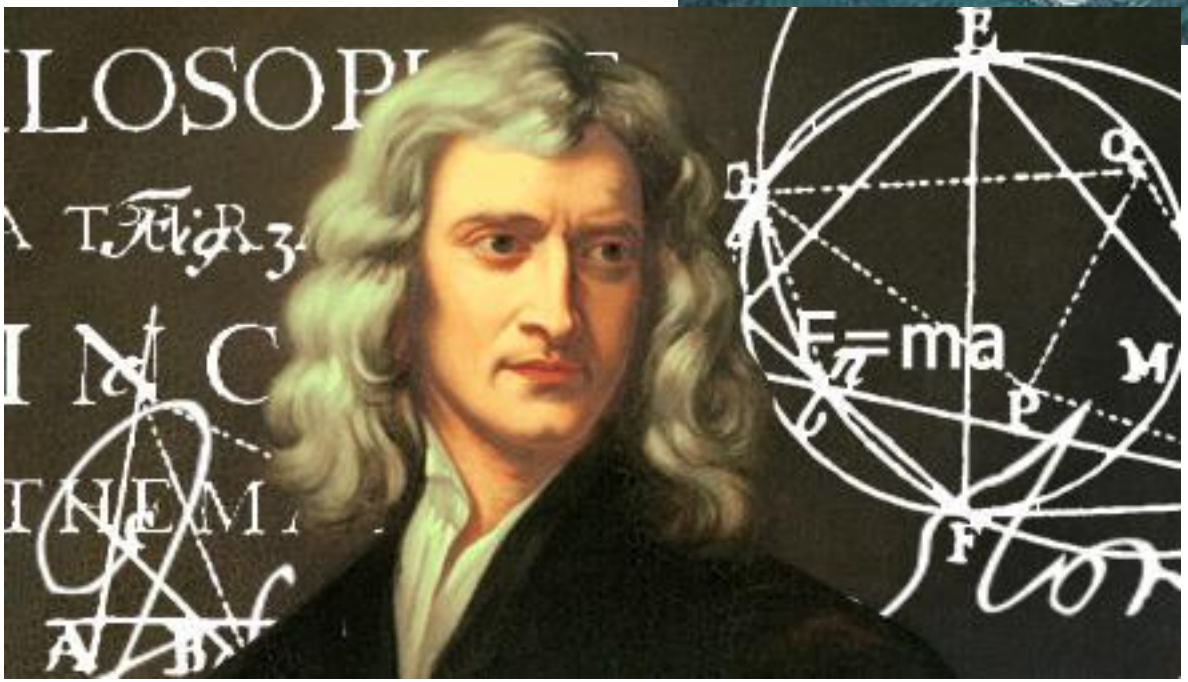
Microscope
Lens
Sample
Holder
Sample
Translator


16


F = ma

Studi osservazionali e sperimentali

[CANCER RESEARCH 33, 1485–1496, June 1973]

Possible Etiologies of Cancer of the Cervix Other Than Herpesvirus[1]

E. Russell Alexander

Department of Epidemiology and International Health, School of Public Health and Community Medicine, University of Washington, Seattle, Washington 98195

Summary

Various hypotheses concerning both infectious and noninfectious causes have been proposed for the etiology of cervical cancer. The evidence for noninfectious agents and for infectious agents other than herpesvirus is reviewed here. Although some carcinogenic potential for smegma may be inferred from experimental studies, epidemiological studies do not indicate a significant role for either smegma or circumcision in human cervical cancer. Coppelson and colleagues have developed a hypothesis to explain the importance of early coitus in cervical cancer, proposing that sperm is the nucleic acid vector and the potential mutagen for tissues undergoing active metaplasia. The most attractive aspect of this hypothesis is the suggestion that any sperm may be a potential mutagen, not because of some special intrinsic property but because of a particular susceptibility of the target tissue at certain times.

Six infectious agents have an established association with cervical cancer. The association with *Trichomonas*, syphilis, and gonococcal infections in all probability merely reflects the fact that these infections are strongly associated with promiscuity. The correlation of mycoplasmal infection with mild cervical dysplasia, as well as with promiscuity, calls for more serious consideration of this infection, but there is no consistent association between mycoplasmal infection and cervical cancer. Chlamydial infections may be important because of their chronicity, their association with chronic inflammatory disease, and their venereal mode of transmission. Cytomegalovirus infections may be implicated upon similar grounds. This virus is known to be associated with chronic inflammatory disease, but evidence for a venereal mode of transmission and for male genital infection is less convincing. Whatever the evidence for the association of these agents with cervical cancer, none appears to be so likely a candidate for its cause as herpesvirus type 2.

However, future analytic studies should include examination of male partners and the study of semen for infectivity and such studies should be designed to test multifactorial hypotheses. Too often our hypotheses are single-agent oriented; the design and analysis of studies should both be structured to study multiple possibilities.

Any consideration of etiological hypotheses for cervical cancer must begin with consideration of the epidemiological characteristics of that disease. These characteristics, which have been summarized by Rotkin (44), are now universally accepted, since there is remarkable uniformity among studies of diverse populations done at different times (Table 1). Thus, at highest risk of cervical cancer are women who have had 1st coitus at an early age (43), have had multiple sex partners, are sexually promiscuous (50), and are of lower socioeconomic status (28). Any hypothesis must also account for those women at lowest risk, in particular the celibate (14), and to a lesser degree the nulliparous and Jewish women (50). There are many further refinements which might be made to a list of positive and negative risk factors, such as early marriage, early pregnancy, multiple marriages, and multiple pregnancies (55), some of which appear more important in some studies than in others, but the most important variables are generally accepted to be the 1st ones stated.

Smegma and Circumcision

The remarkable difference in risk of cervical cancer between Jewish and non-Jewish women, and the undeniable decreased risk of penile carcinoma in Jewish men, resulted in a series of studies designed to test the hypothesis that circumcision was the key factor in decreased risks and furthermore that smegma was the culprit, either as a carcinogen itself or as a vehicle for an infectious agent which was carcinogenic.

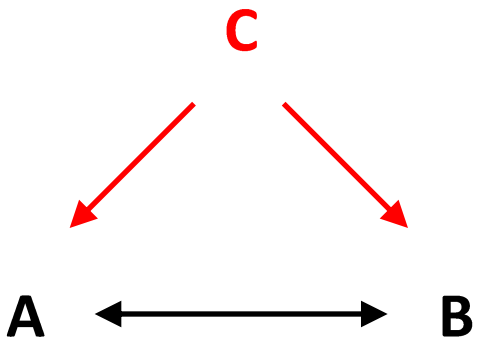
Rotkin has already reviewed the series of studies that showed that not only were women surprisingly ignorant of the circumcision status of their sexual partners (27) but that there was, in fact, no relationship between cancer of the cervix and the circumcision status of the husband, when that status was objectively measured (1). The same conclusion was reached in a recent study by Terris *et al* (49), which also showed that there was no association between accumulation of smegma and cancer in sexual partners, even though accumulation of smegma was correlated with degree of circumcision. Comparisons in other circumcized populations, such as Moslems, have been contradictory, perhaps because of problems with assessment of disease. Despite negative epidemiological evidence of association between smegma and cervical cancer, there have been attempts to examine the biological basis for such a hypothesis. One approach tested the carcinogenic potential of smegma experimentally in an animal model; another looked for infectious agents in this material.

The experimental animal models have yielded variable results. Initial experiments by Fishman *et al.* (11) and later

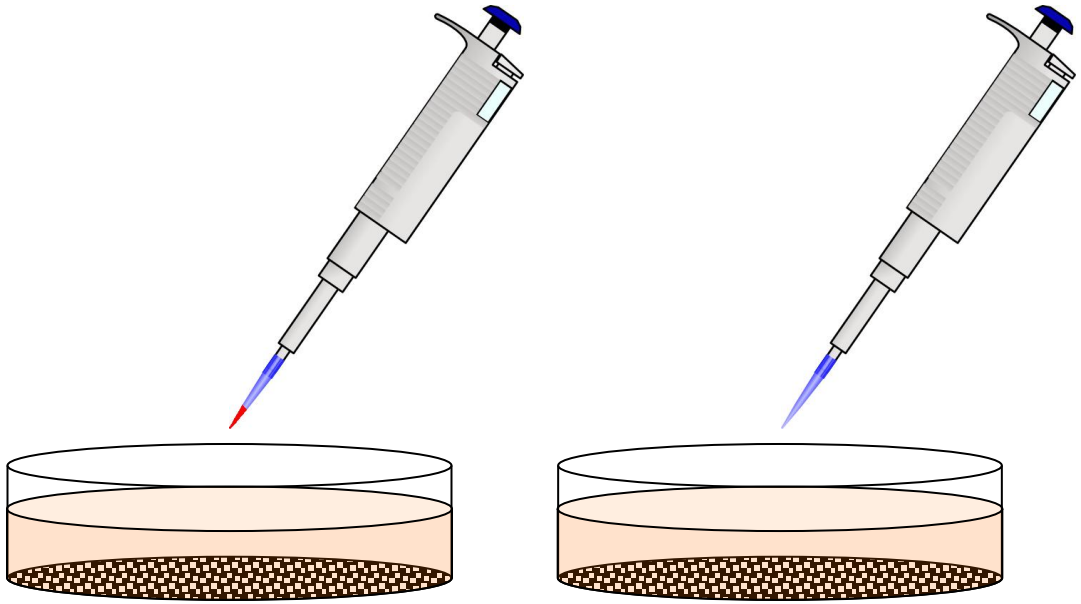
[1] Presented at The American Cancer Society Conference on Herpesvirus and Cervical Cancer, December 8 to 10, 1972, Key Biscayne, Fla. This work was supported by USPHS Grant ROI CA 11703.

L'epidemiologia non può fornire dimostrazioni;
ciò non toglie che dia indicazioni importantissime

Nessun grado di correlazione fra due fenomeni può fornire dimostrazione di un rapporto di causa ed effetto



Isolamento della variabile allo studio

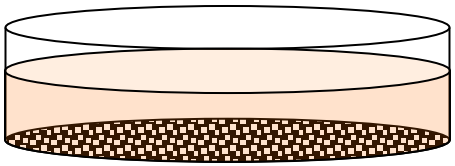


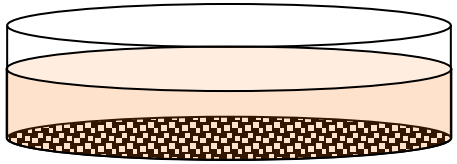
X

Variabile indipendente

A B C D E **A B C D E**

Isolamento della variabile allo studio





X

A **B** C **D** E

A B C D E

Variabile indipendente

Variabili dipendenti

La terapia ormonale sostitutiva previene le malattie cardiache in menopausa?

10.000 donne in terapia sostitutiva

10.000 donne di controllo

Minore incidenza di malattie cardiache

Randomizzazione

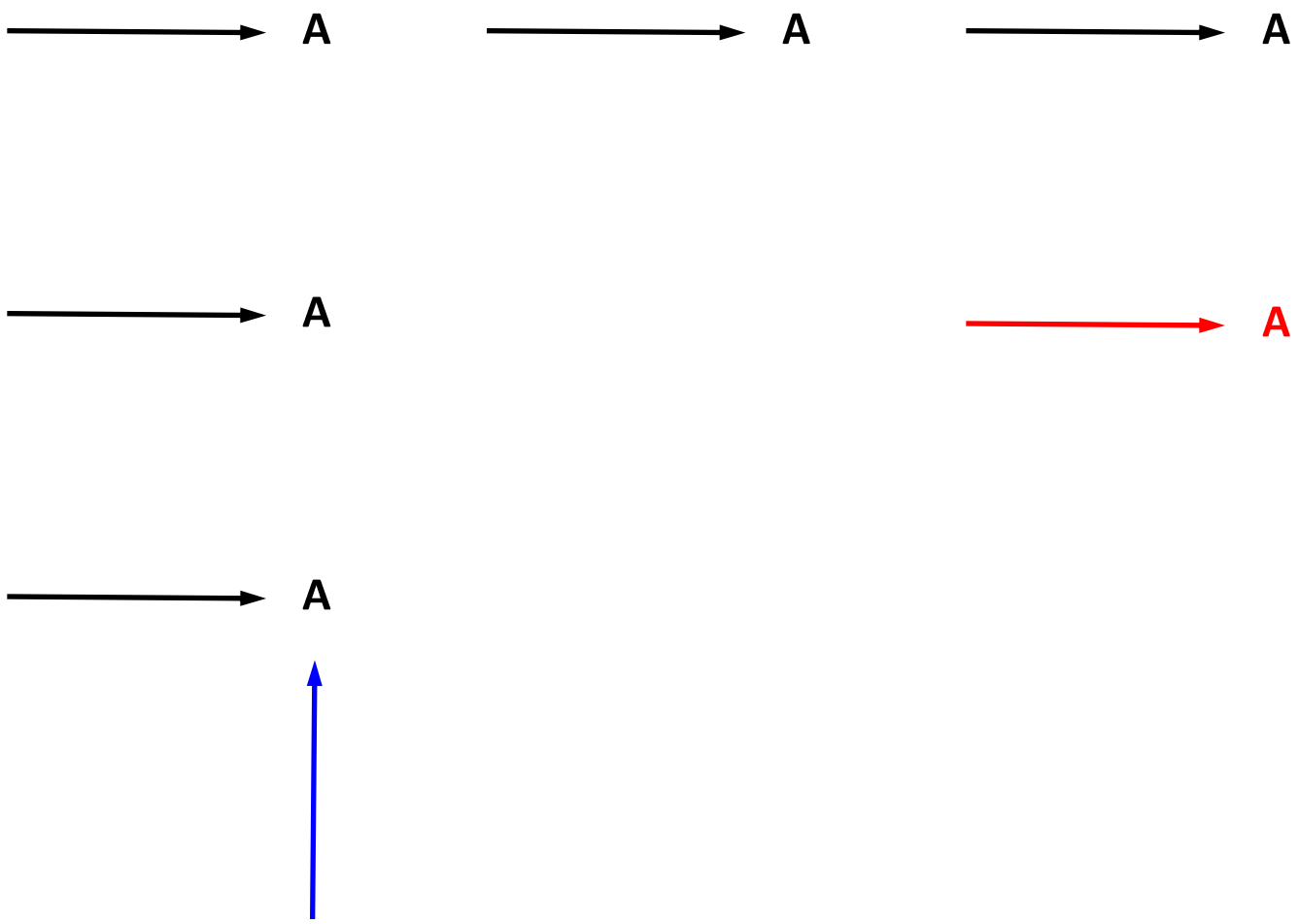
Somministrazione di terapia sostitutiva a 10.000 donne

Placebo a 10.000 donne di controllo

Aumentata incidenza di malattie cardiache

Ridondanza di evidenza

Verificare un risultato o una conclusione





Problema: un cestino contiene 9 mele. Abbiamo 16 cestini. Quante mele in tutto?

Il peso complessivo delle mele è di 36 kg, le mele pesano in media 0,25 kg

9 x 16 = 144

9 x 16 = 144

9 x 16 = 144

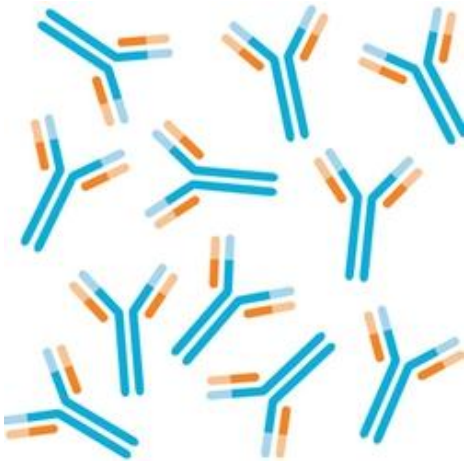
9 x 16 = 144

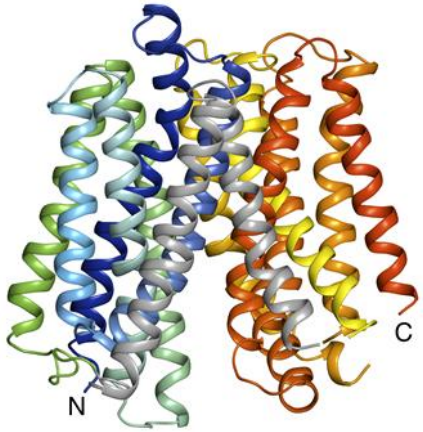
9 x 16 = 144

9 x 16 = 144

144 : 9 = 16

36 : 0,25 = 144




N
C

Nature 508:215-221, 2014

ARTICLE

doi:10.1038/nature13181

MTH1 inhibition eradicates cancer by preventing sanitation of the dNTP pool

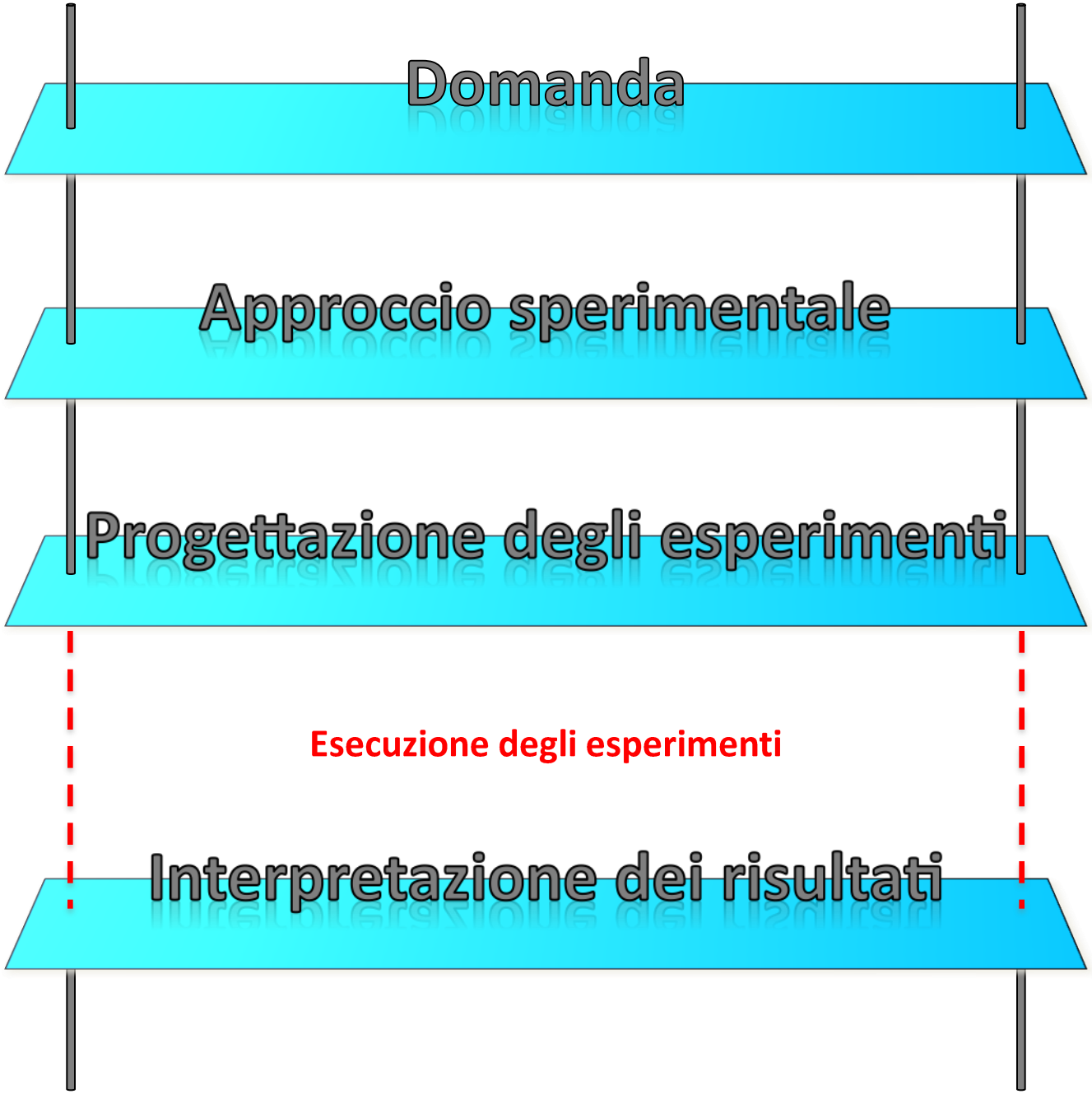
Nature 508:222-227, 2014

ARTICLE

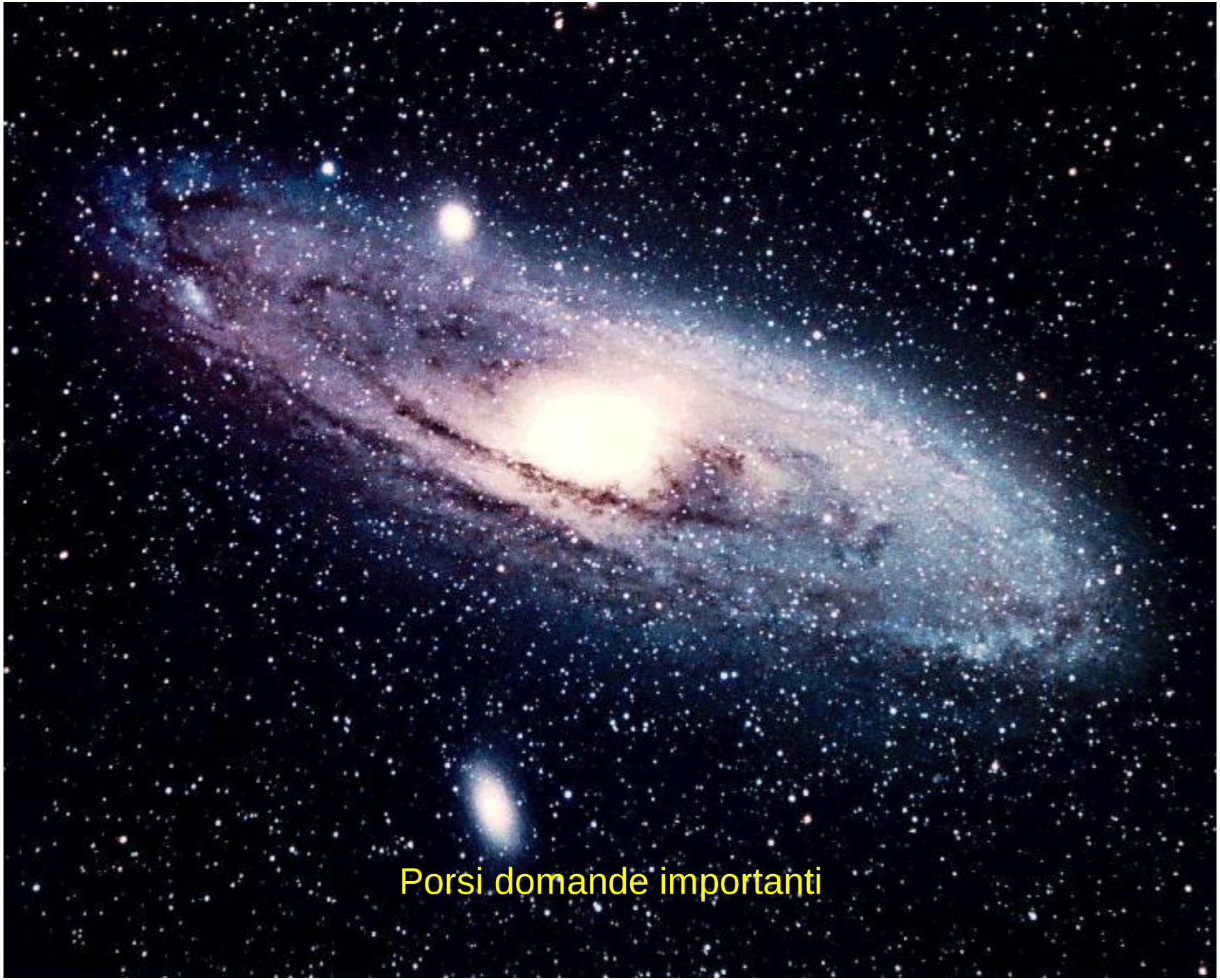
doi:10.1038/nature13194

Stereospecific targeting of MTH1 by (*S*)-crizotinib as an anticancer strategy

Il processo di ideazione


Domanda
Approccio sperimentale
Progettazione degli esperimenti
Esecuzione degli esperimenti
Interpretazione dei risultati


Domanda
Approccio sperimentale
Progettazione degli esperimenti
Esecuzione degli esperimenti
Interpretazione dei risultati


Porsi domande importanti

Focalizzare la domanda

Definire chiaramente il problema aiuta molto a trovare un modo per risolverlo

Cell

Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors

Kazutoshi Takahashi[1] and Shinya Yamanaka[1,2,*]
[1]Department of Stem Cell Biology, Institute for Frontier Medical Sciences, Kyoto University, Kyoto 606-8507, Japan
[2]CREST, Japan Science and Technology Agency, Kawaguchi 332-0012, Japan
*Contact: yamanaka@frontier.kyoto-u.ac.jp
DOI 10.1016/j.cell.2006.07.024

SUMMARY

Differentiated cells can be reprogrammed to an embryonic-like state by transfer of nuclear contents into oocytes or by fusion with embryonic stem (ES) cells. Little is known about factors that induce this reprogramming. Here, we demonstrate induction of pluripotent stem cells from mouse embryonic or adult fibroblasts by introducing four factors, Oct3/4, Sox2, c-Myc, and Klf4, under ES cell culture conditions. Unexpectedly, Nanog was dispensable. These cells, which we designated iPS (induced pluripotent stem) cells, exhibit the morphology and growth properties of ES cells and express ES cell marker genes. Subcutaneous transplantation of iPS cells into nude mice resulted in tumors containing a variety of tissues from all three germ layers. Following injection into blastocysts, iPS cells contributed to mouse embryonic development. These data demonstrate that pluripotent stem cells can be directly generated from fibroblast cultures by the addition of only a few defined factors.

INTRODUCTION

Embryonic stem (ES) cells, which are derived from the inner cell mass of mammalian blastocysts, have the ability to grow indefinitely while maintaining pluripotency and the ability to differentiate into cells of all three germ layers (Evans and Kaufman, 1981; Martin, 1981). Human ES cells might be used to treat a host of diseases, such as Parkinson's disease, spinal cord injury, and diabetes (Thomson et al., 1998). However, there are ethical difficulties regarding the use of human embryos, as well as the problem of tissue rejection following transplantation in patients. One way to circumvent these issues is the generation of pluripotent cells directly from the patients' own cells.

Somatic cells can be reprogrammed by transferring their nuclear contents into oocytes (Wilmut et al., 1997) or by fusion with ES cells (Cowan et al., 2005; Tada et al., 2001), indicating that unfertilized eggs and ES cells contain factors that can confer totipotency or pluripotency to somatic cells. We hypothesized that the factors that play important roles in the maintenance of ES cell identity also play pivotal roles in the induction of pluripotency in somatic cells.

Several transcription factors, including Oct3/4 (Nichols et al., 1998; Niwa et al., 2000), Sox2 (Avilion et al., 2003), and Nanog (Chambers et al., 2003; Mitsui et al., 2003), function in the maintenance of pluripotency in both early embryos and ES cells. Several genes that are frequently upregulated in tumors, such as *Stat3* (Matsuda et al., 1999; Niwa et al., 1998), *E-Ras* (Takahashi et al., 2003), c-*myc* (Cartwright et al., 2005), *Klf4* (Li et al., 2005), and β-*catenin* (Kielman et al., 2002; Sato et al., 2004), have been shown to contribute to the long-term maintenance of the ES cell phenotype and the rapid proliferation of ES cells in culture. In addition, we have identified several other genes that are specifically expressed in ES cells (Maruyama et al., 2005; Mitsui et al., 2003).

In this study, we examined whether these factors could induce pluripotency in somatic cells. By combining four selected factors, we were able to generate pluripotent cells, which we call induced pluripotent stem (iPS) cells, directly from mouse embryonic or adult fibroblast cultures.

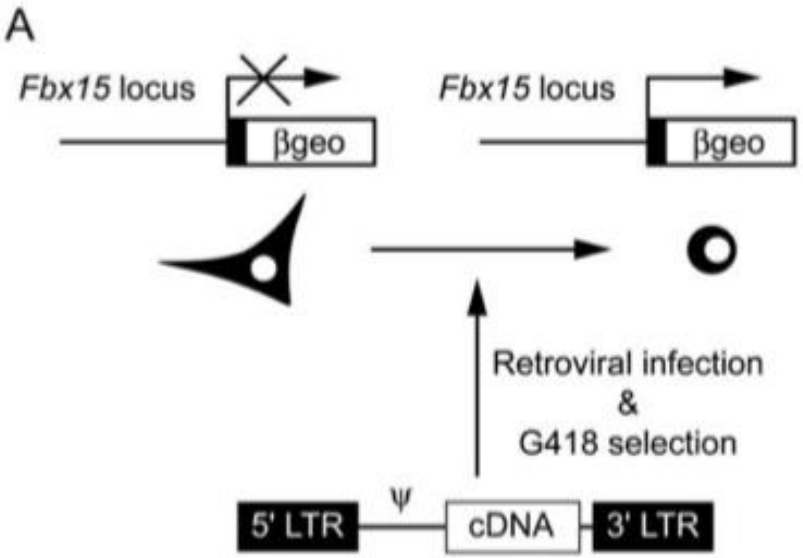
RESULTS

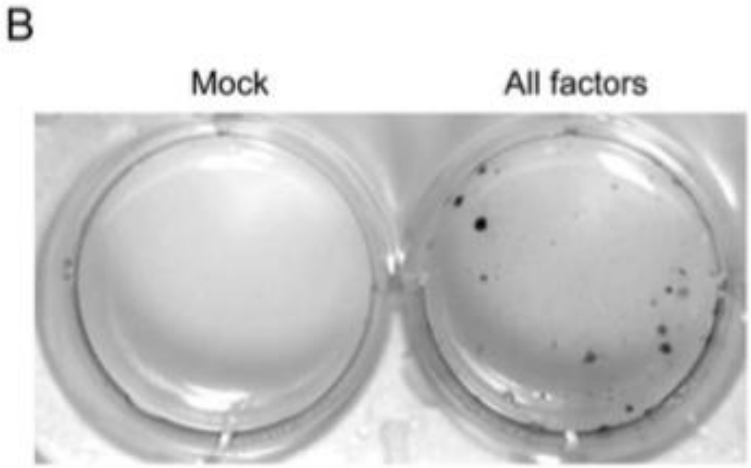
We selected 24 genes as candidates for factors that induce pluripotency in somatic cells, based on our hypothesis that such factors also play pivotal roles in the maintenance of ES cell identity (see Table S1 in the Supplemental Data available with this article online). For β-catenin, c-Myc, and Stat3, we used active forms, S33Y-β-catenin (Sadot et al., 2002), T58A-c-Myc (Chang et al., 2000), and Stat3-C (Bromberg et al., 1999), respectively. Because of the reported negative effect of Grb2 on pluripotency (Burdon et al., 1999; Cheng et al., 1998), we included its dominant-negative mutant Grb2ΔSH2 (Miyamoto et al., 2004) as 1 of the 24 candidates.

E' possibile convertire cellule somatiche in cellule staminali?

I fattori di trascrizione possono effettuare questa conversione?

Specifici fattori di trascrizione possono effettuare la conversione?

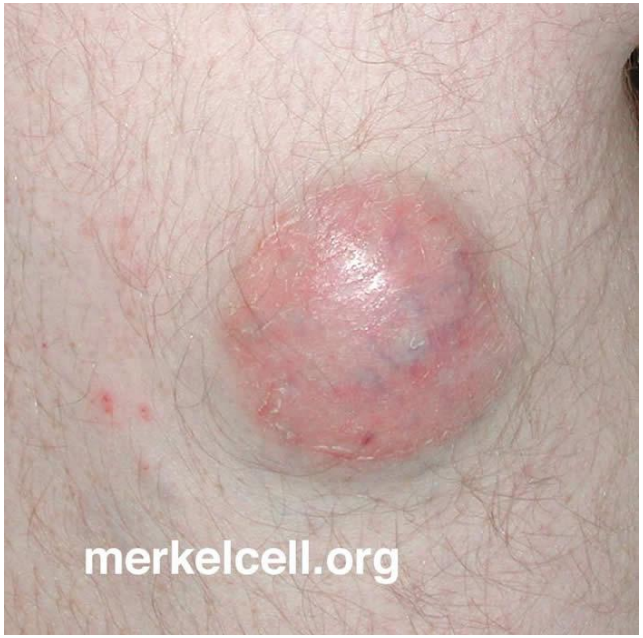


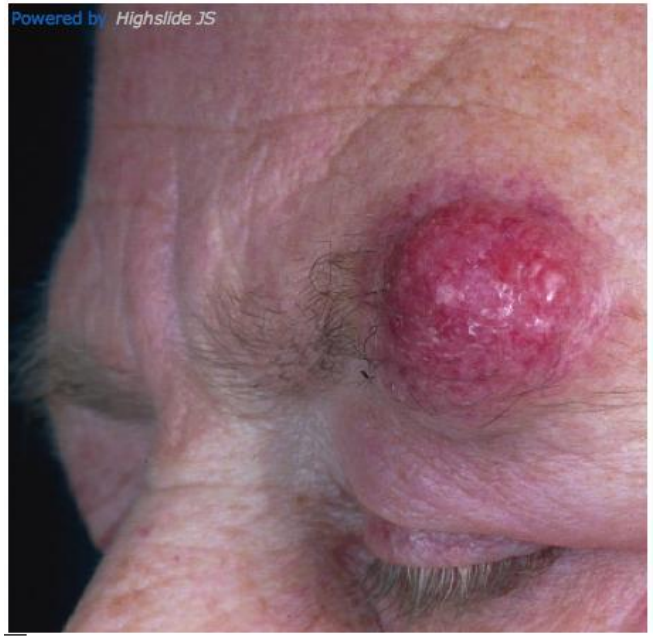


Science 2008;319:1096-1100

Clonal Integration of a Polyomavirus in Human Merkel Cell Carcinoma

Huichen Feng, Masahiro Shuda, Yuan Chang,* Patrick S. Moore*

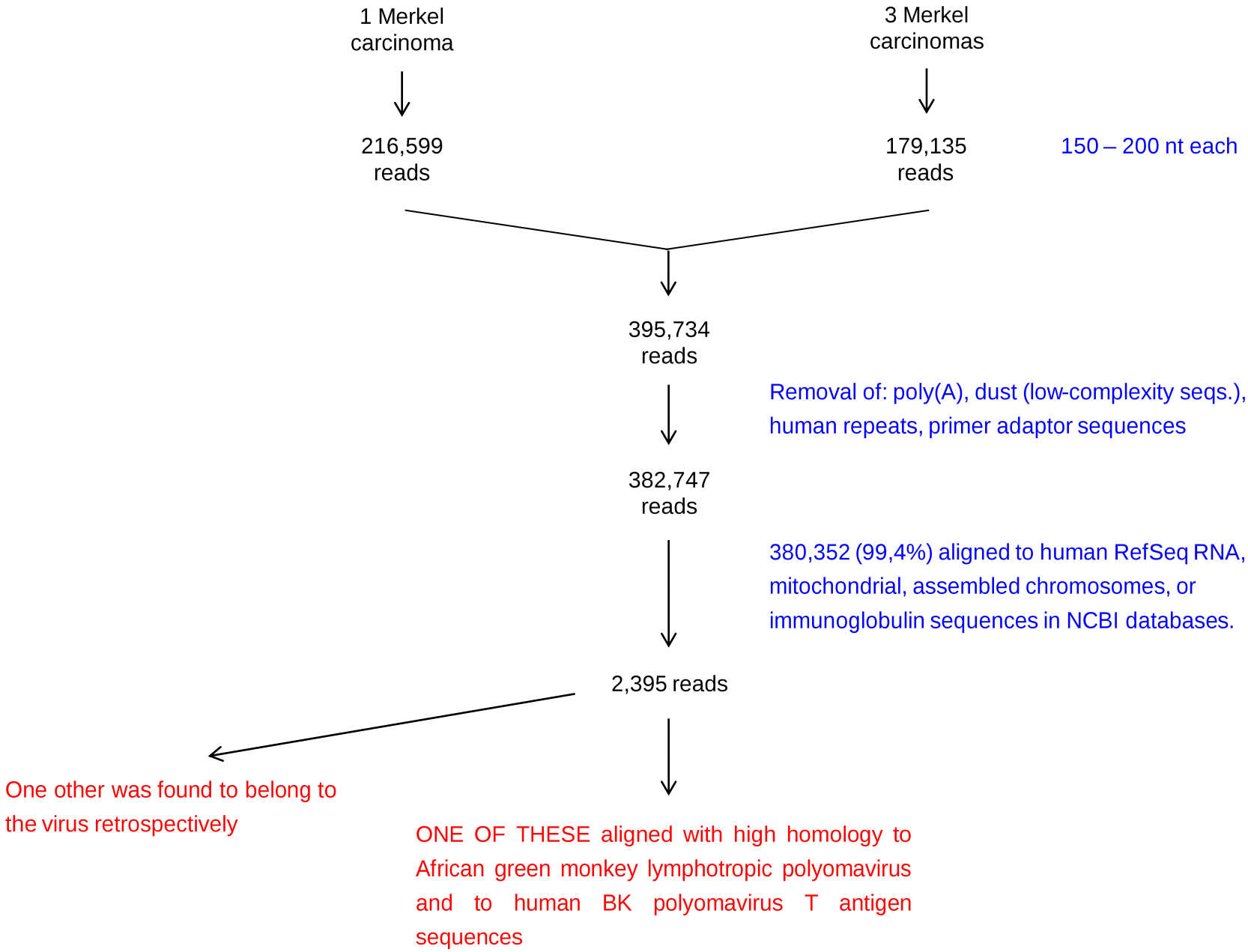




Esiste una causa microbiologica per il carcinoma a cellule di Merkel?

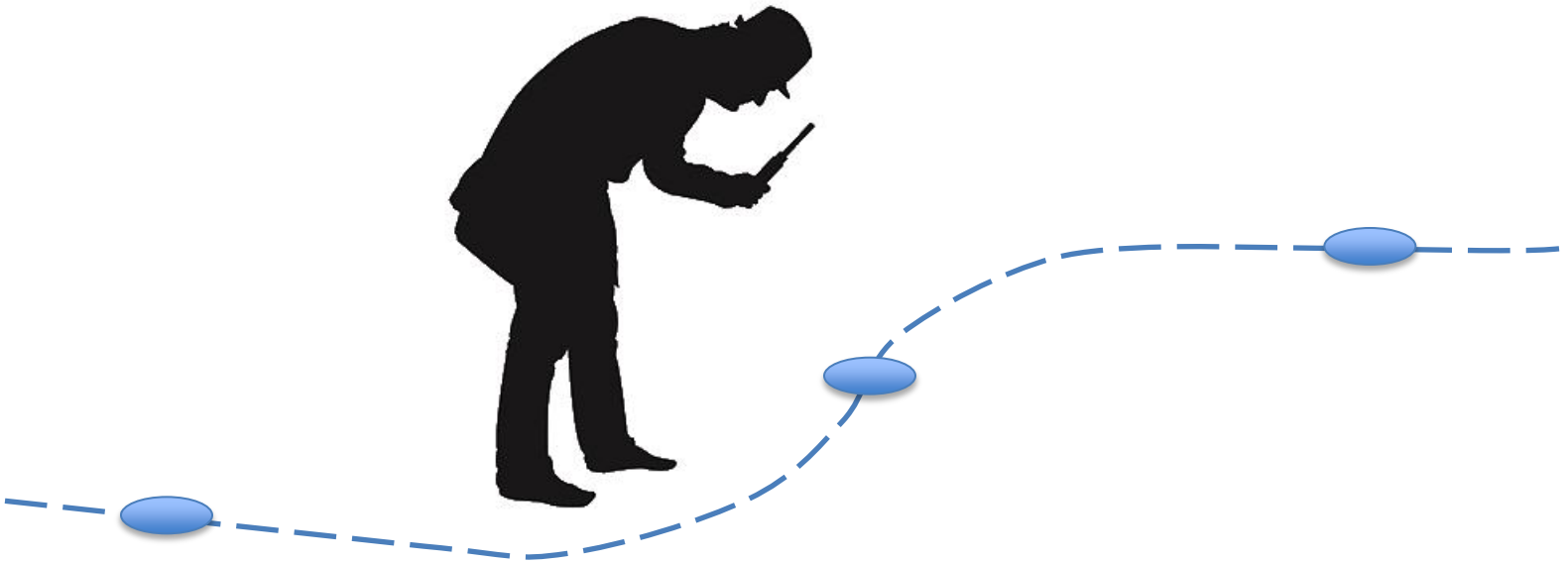
Esiste *un virus* che causi il carcinoma a cellule di Merkel?

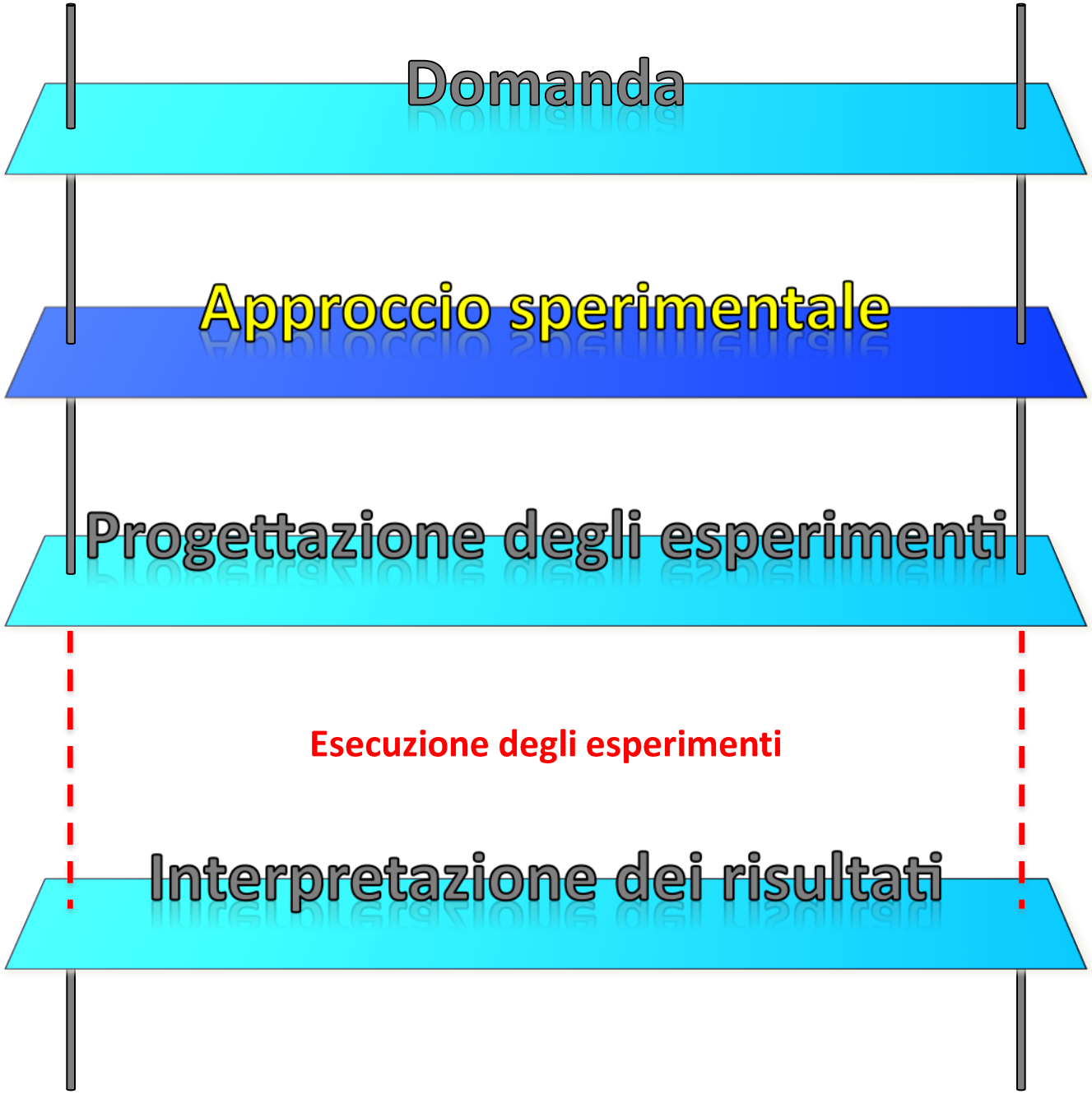
E' possibile trovare nel tumore *tracce genetiche* di un ipotetico agente causale?


1 Merkel carcinoma
3 Merkel carcinomas
216,599 reads
179,135 reads
150 – 200 nt each
395,734 reads
Removal of: poly(A), dust (low-complexity seqs.), human repeats, primer adaptor sequences
382,747 reads
380,352 (99,4%) aligned to human RefSeq RNA, mitochondrial, assembled chromosomes, or immunoglobulin sequences in NCBI databases.
2,395 reads
One other was found to belong to the virus retrospectively
ONE OF THESE aligned with high homology to African green monkey lymphotropic polyomavirus and to human BK polyomavirus T antigen sequences

Identificare un gap conoscitivo

Seguire la naturale evoluzione del proprio filone di ricerca

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Approccio sperimentale
Progettazione degli esperimenti
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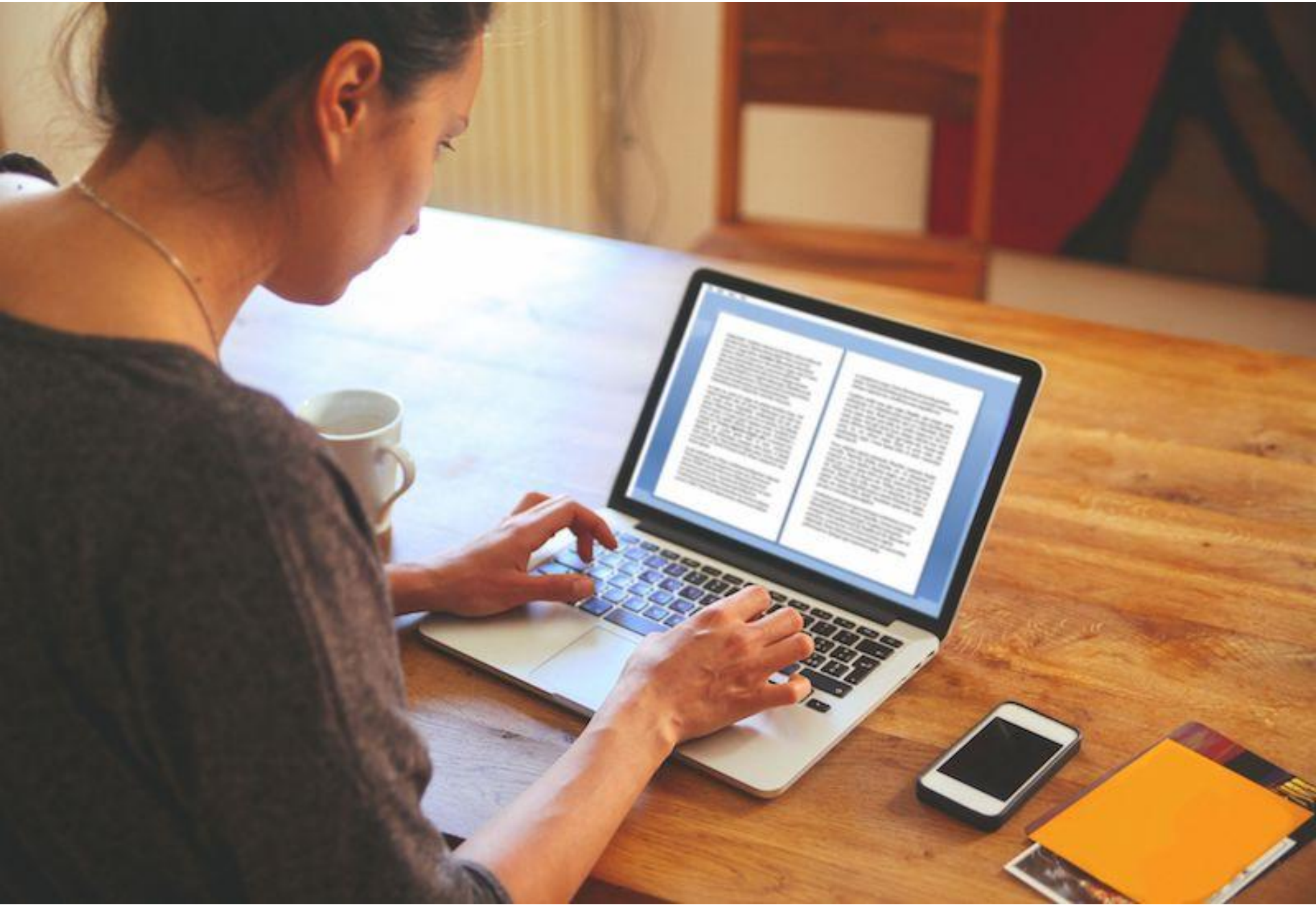
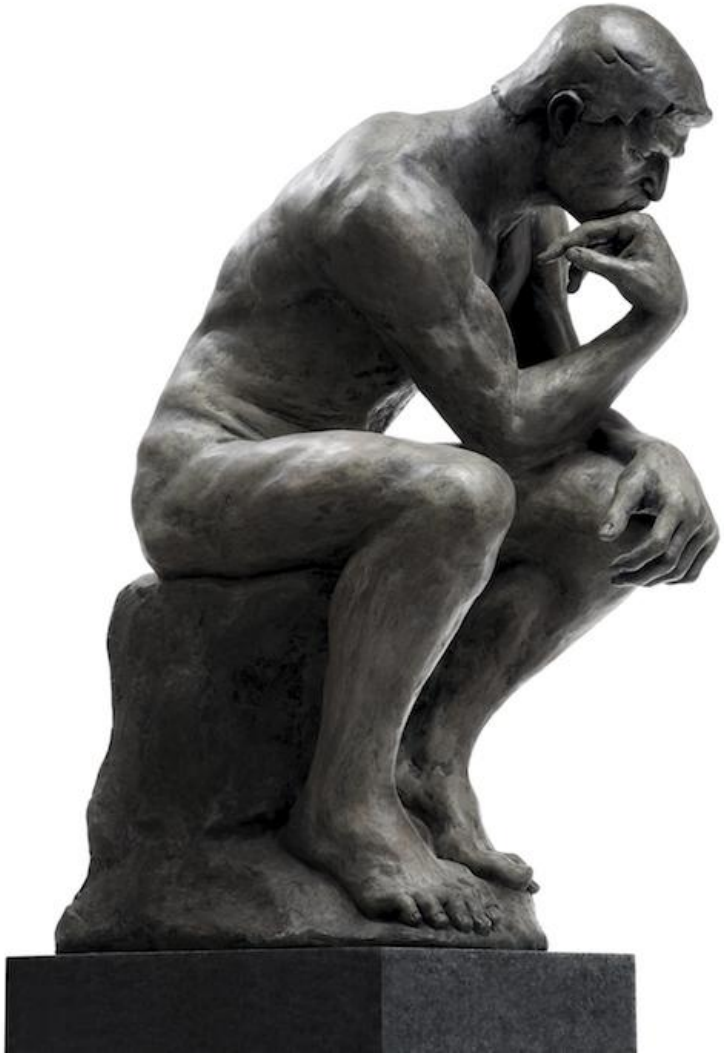
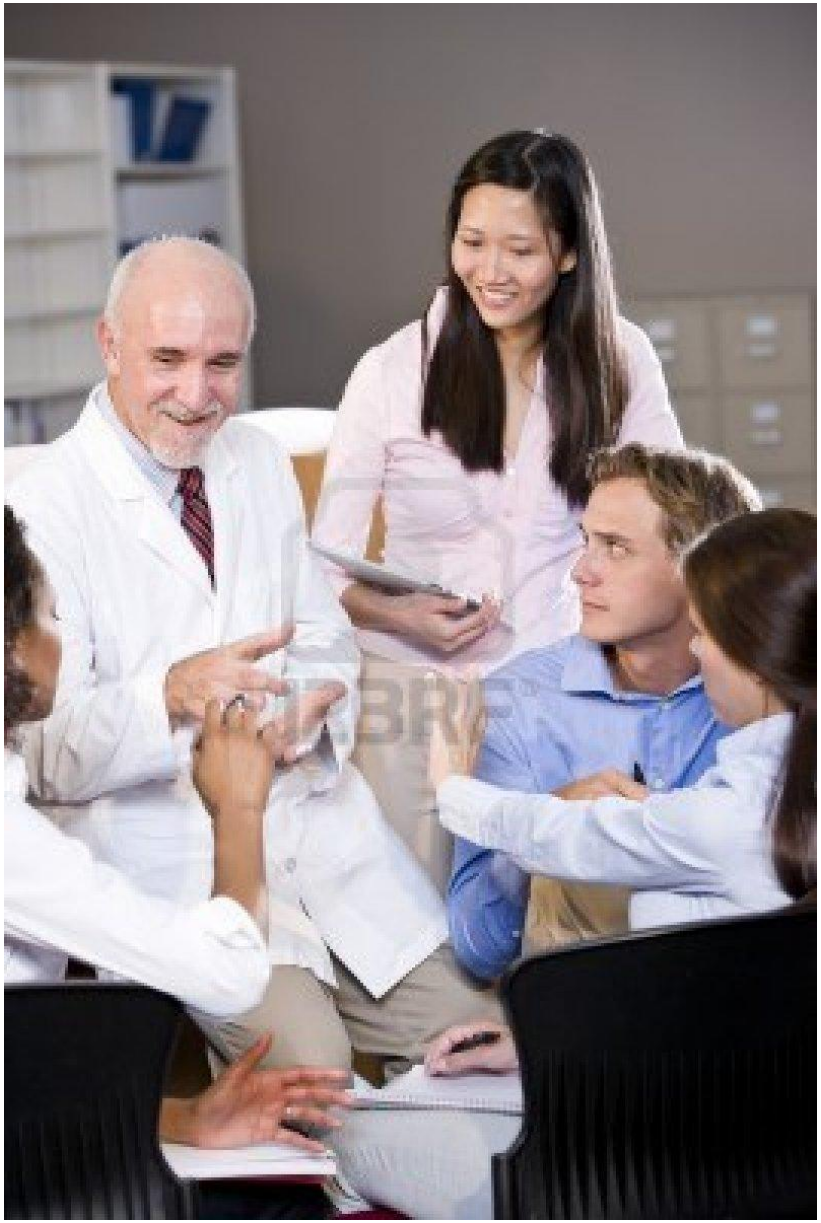
Interpretazione dei risultati







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chromatin starfish

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Nucleosomal structure of sea urchin and starfish sperm chromatin ...

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC327216/

by IA Zalenskaya - 1981 - Cited by 66 - Related articles

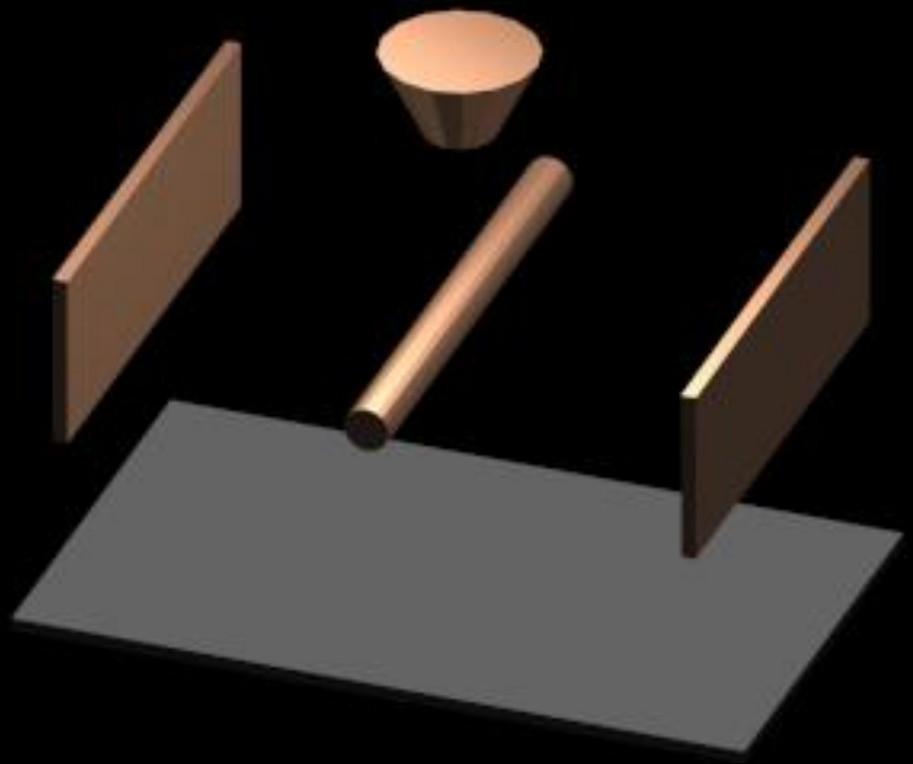
Comparison has been made between sea urchin and **starfish** sperm **chromatin**. The only protein by which chromatins from these sources differ significantly is histone H2B. Sea urchin sperm H2B is known to contain an elongated N-terminal region enriched in Arg. Analysis of the micrococcal nuclease digests of sea urchin ...

Nucleosomal structure of sea urchin and starfish sperm chromatin ...

https://www.ncbi.nlm.nih.gov/pubmed/7220345

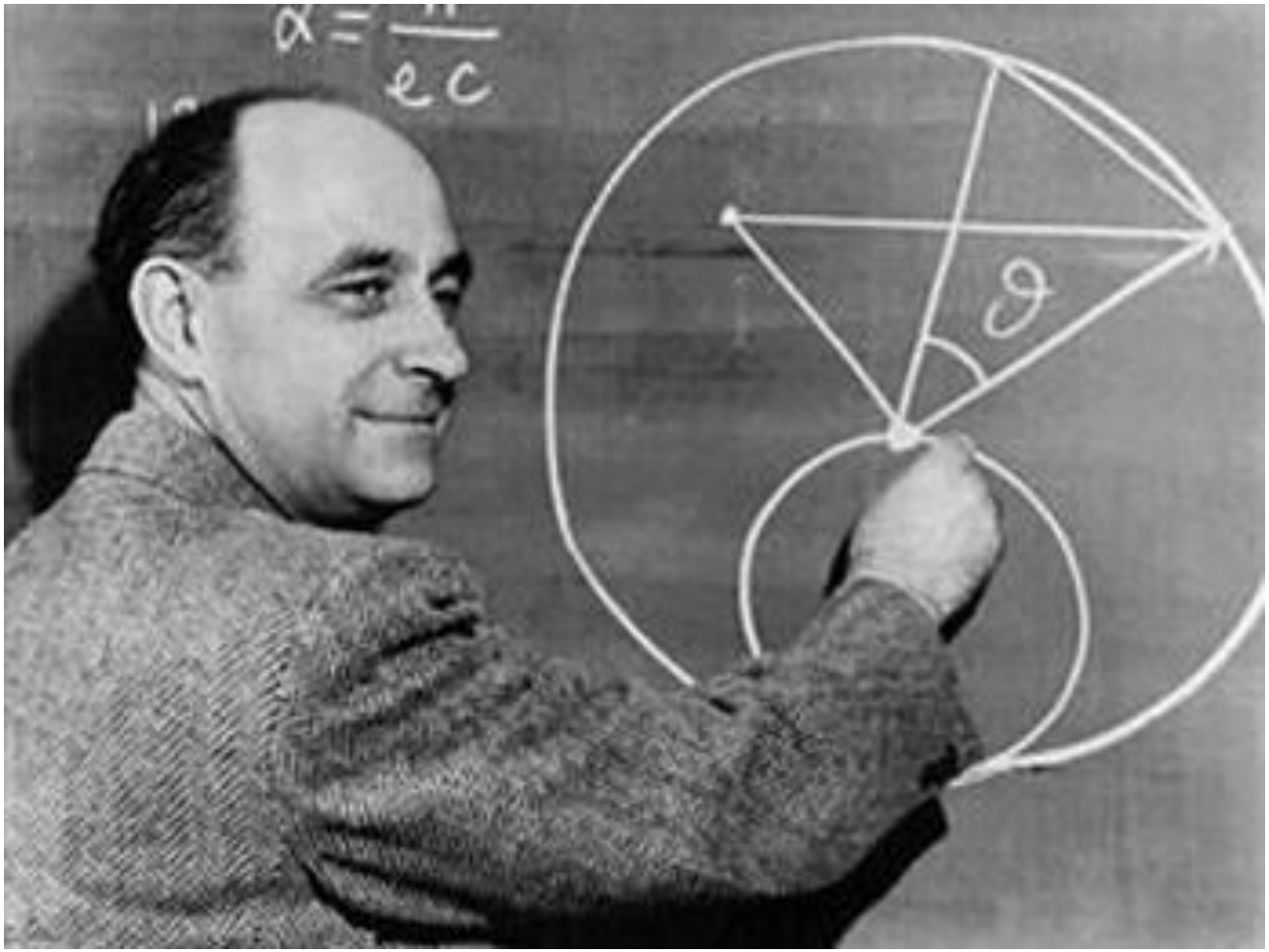
by IA Zalenskaya - 1981 - Cited by 66 - Related articles

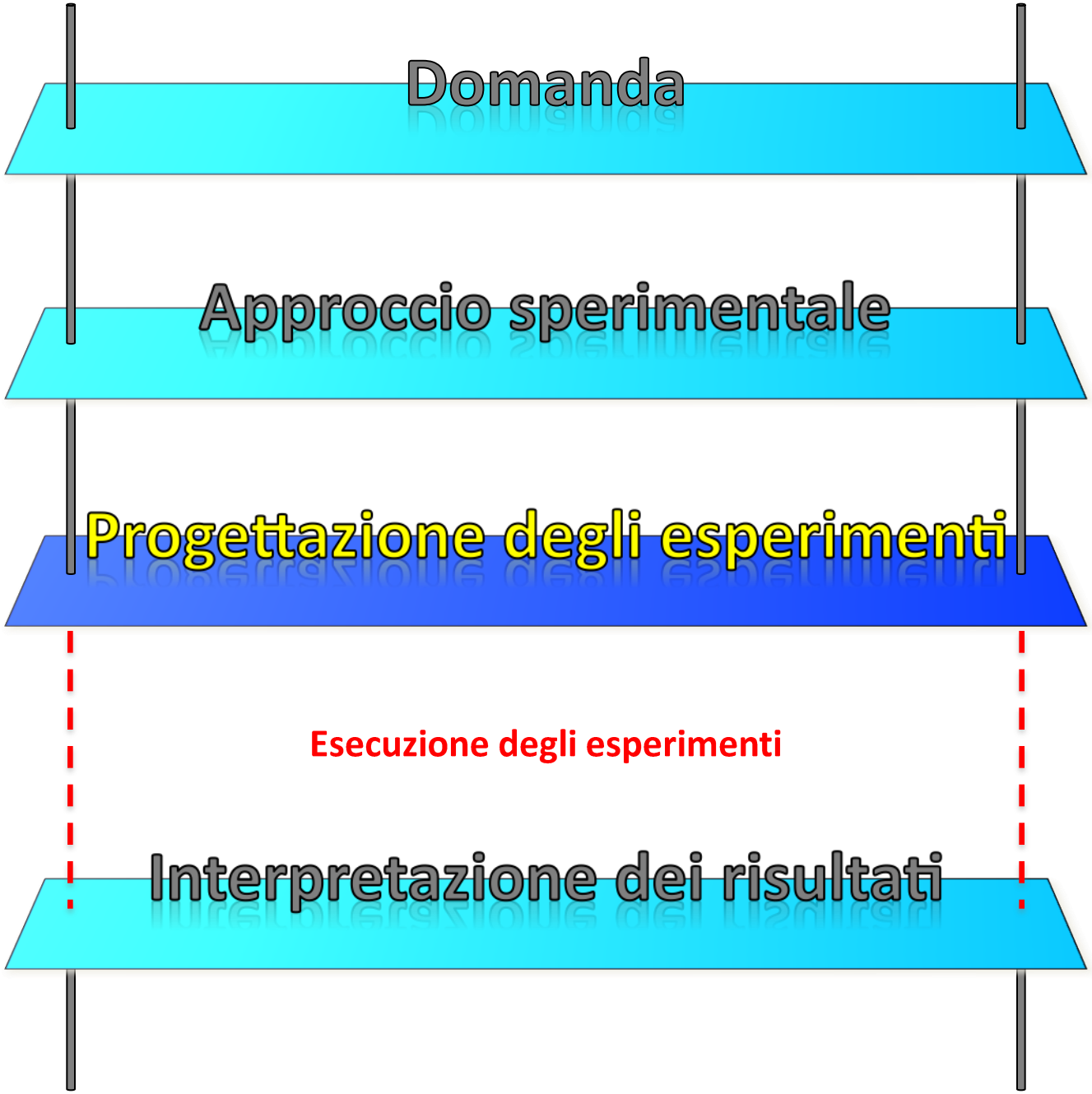
Nucleic Acids Res. 1981 Feb 11;9(3):473-87. Nucleosomal structure of sea urchin and **starfish** sperm **chromatin**. Histone H2B is possibly involved in determining the length of linker DNA. Zalenskaya IA, Pospelov VA, Zalensky AO, Vorob'ev VI. Comparison has been made between sea urchin and **starfish** sperm **chromatin**.



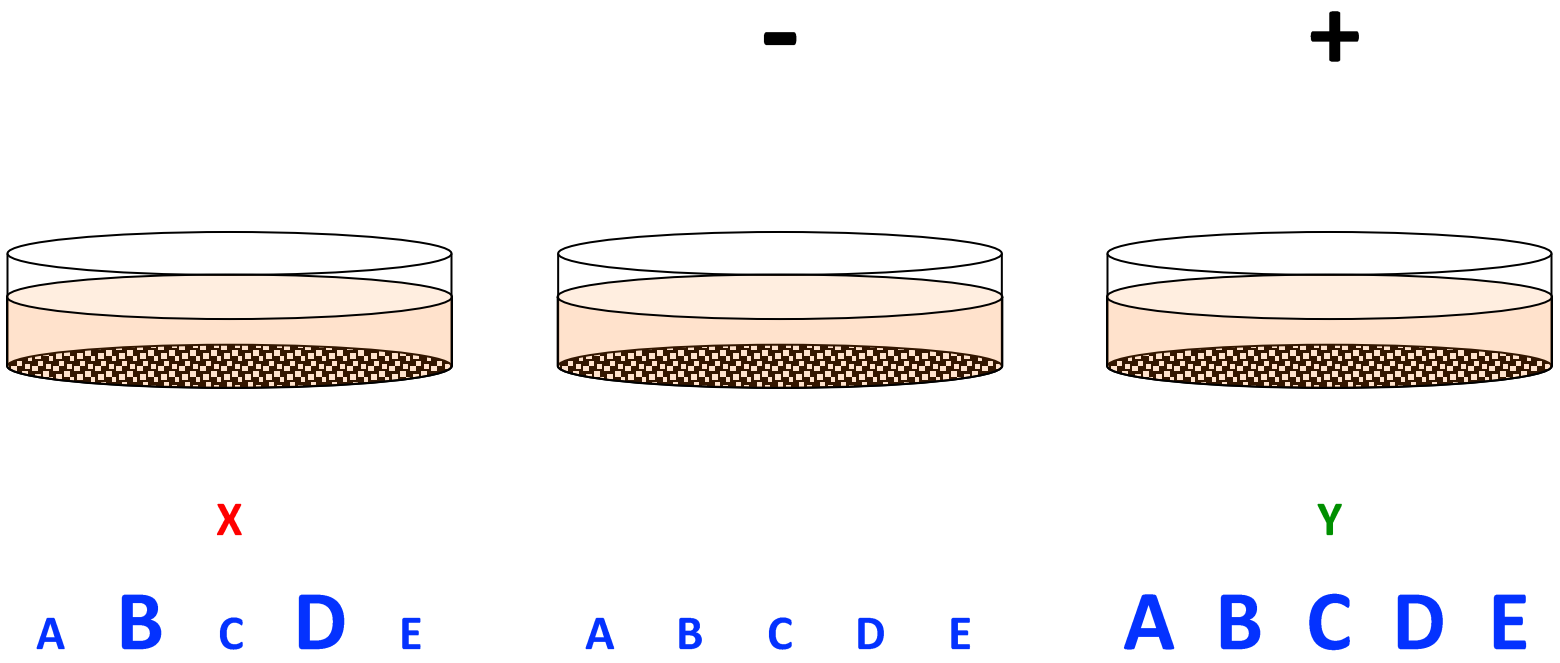
Esperimenti “quick and dirty”

Problemi di Fermi




Domanda
Approccio sperimentale
Progettazione degli esperimenti
Esecuzione degli esperimenti
Interpretazione dei risultati

Isolamento della variabile allo studio

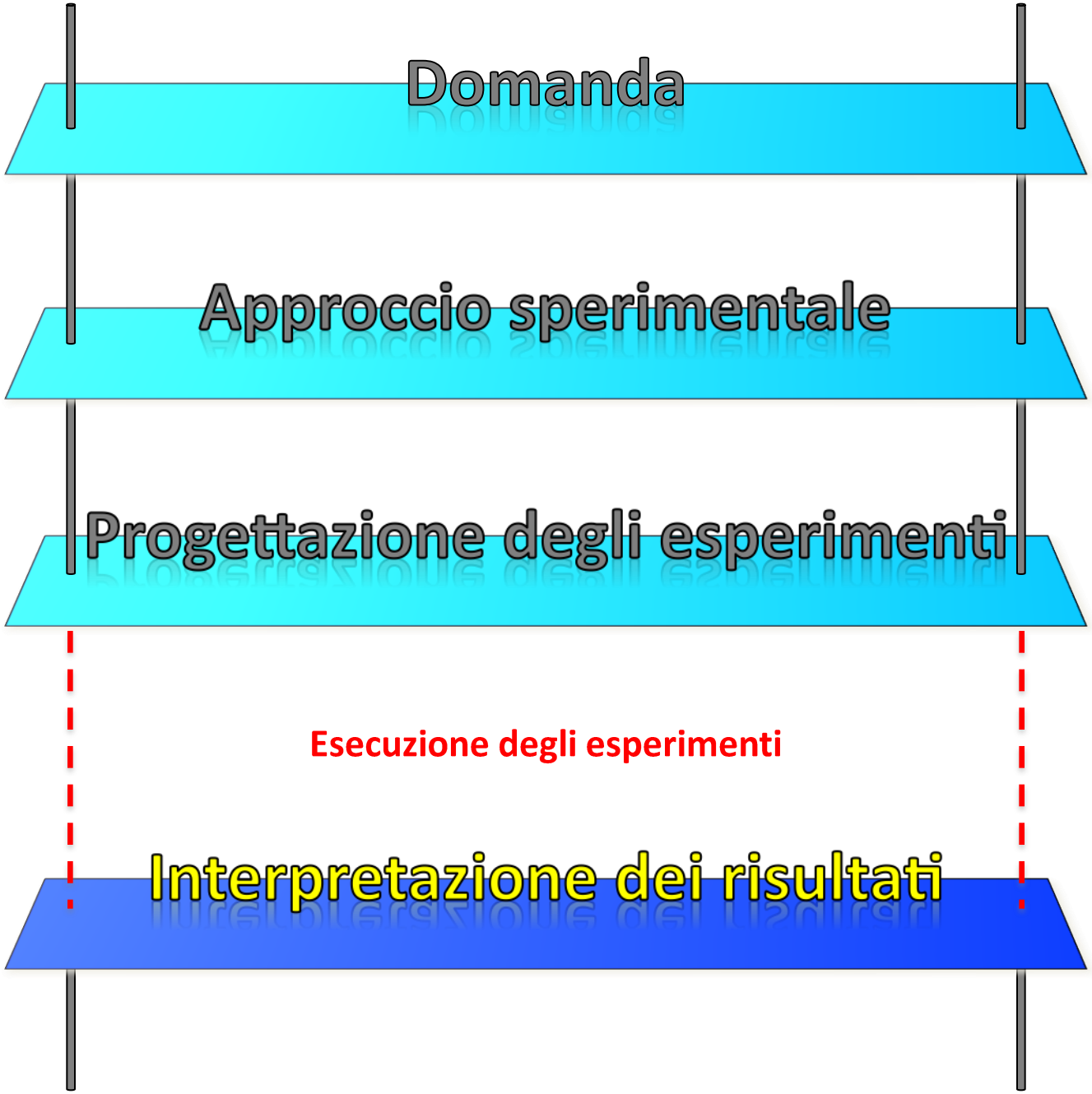


Il controllo positivo:

1. verifica il buon funzionamento dell'esperimento
2. convalida i risultati negativi

Il controllo negativo:

1. verifica la dei risultati
2. fornisce una misura dell'eventuale segnale di fondo nelle osservazioni quantitative


Domanda
Approccio sperimentale
Progettazione degli esperimenti
Esecuzione degli esperimenti
Interpretazione dei risultati

Dati	Il prodotto di esperimenti o osservazioni
↓	
Risultati	Le conseguenze direttamente derivabili dai dati
↓	
Conclusioni	L'interpretazione dei risultati

Nelle conclusioni bisogna necessariamente generalizzare i risultati, ma non c'è una regola per farlo: la generalizzazione si basa sulle conoscenze e sull'esperienza dello scienziato

In quanto interpretazioni, le conclusioni non sono mai univoche

La dimensione quantitativa

Open access, freely available online

Essay

Why Most Published Research Findings Are False

John P. A. Ioannidis

Summary

There is increasing concern that most current published research findings are false. The probability that a research claim is true may depend on study power and bias, the number of other studies on the same question, and, importantly, the ratio of true to no relationships among the relationships probed in each scientific field. In this framework, a research finding is less likely to be true when the studies conducted in a field are smaller; when effect sizes are smaller; when there is a greater number and lesser preselection of tested relationships; where there is greater flexibility in designs, definitions, outcomes, and analytical modes; when there is greater financial and other interest and prejudice; and when more teams are involved in a scientific field in chase of statistical significance. Simulations show that for most study designs and settings, it is more likely for a research claim to be false than true. Moreover, for many current scientific fields, claimed research findings may often be simply accurate measures of the prevailing bias. In this essay, I discuss the implications of these problems for the conduct and interpretation of research.

RESEARCH ARTICLE

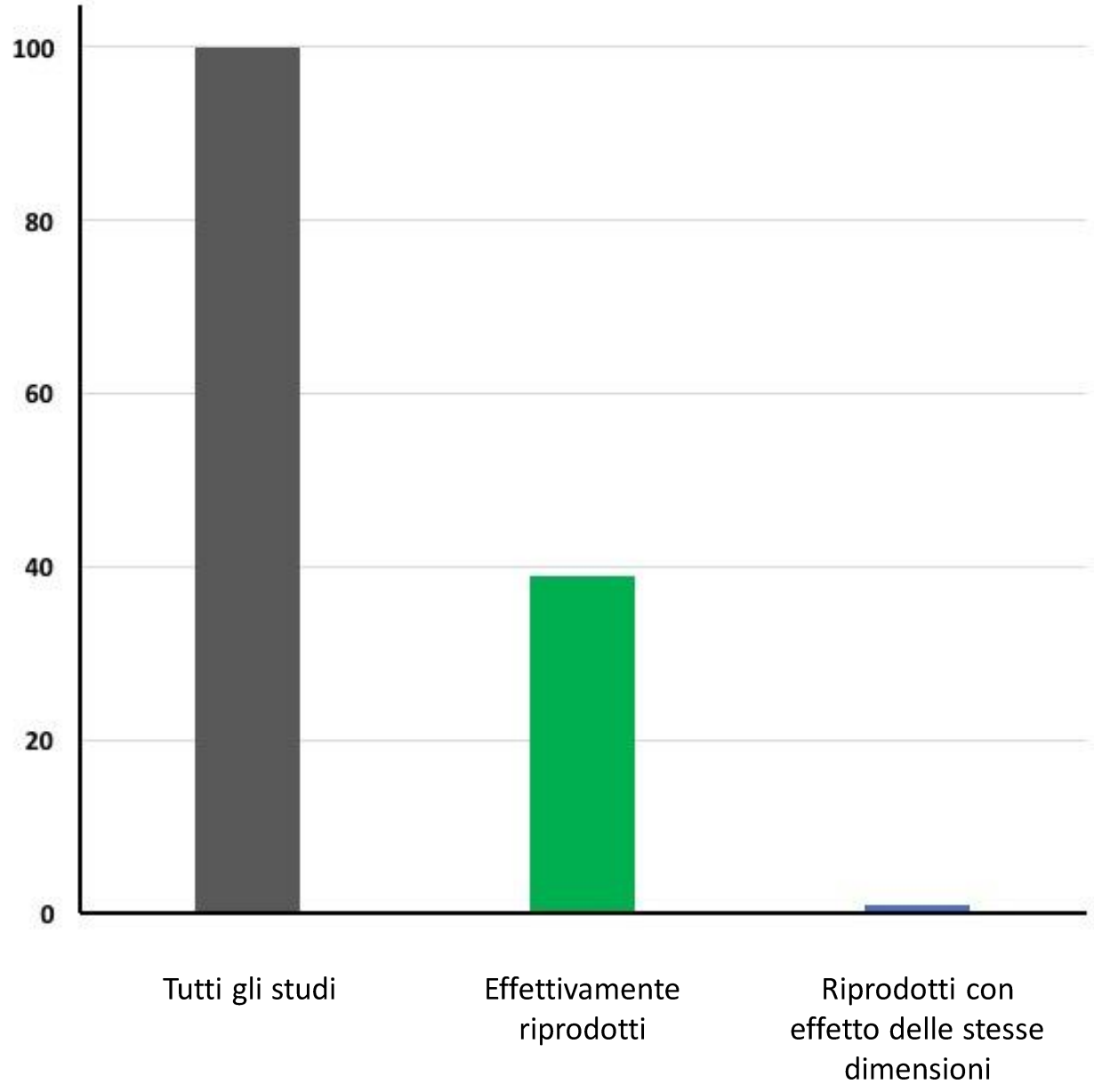
Science 349:aac4716, 2015

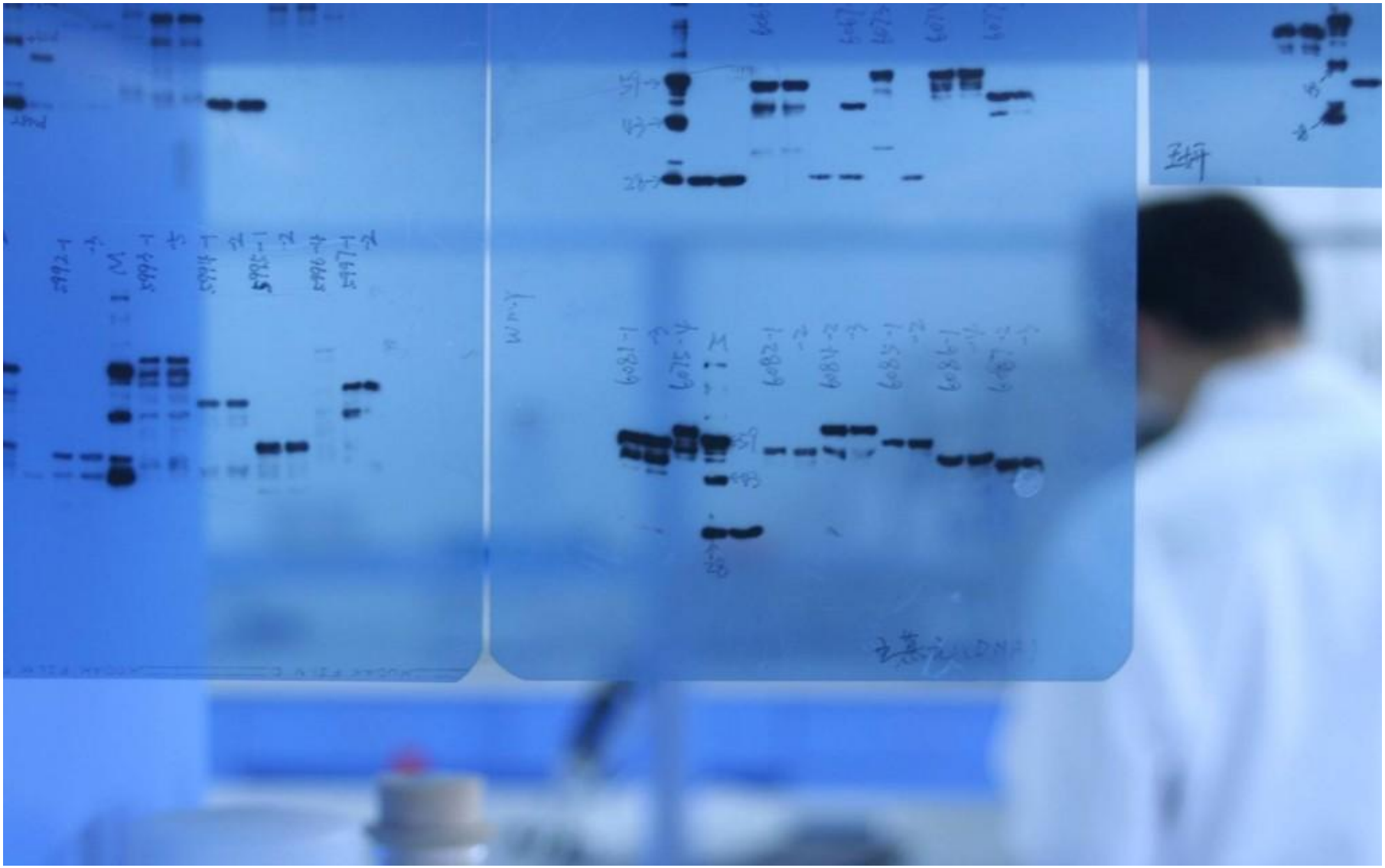
PSYCHOLOGY

Estimating the reproducibility of psychological science

Open Science Collaboration*†

Reproducibility is a defining feature of science, but the extent to which it characterizes current research is unknown. We conducted replications of 100 experimental and correlational studies published in three psychology journals using high-powered designs and original materials when available. Replication effects were half the magnitude of original effects, representing a substantial decline. Ninety-seven percent of original studies had statistically significant results. Thirty-six percent of replications had statistically significant results; 47% of original effect sizes were in the 95% confidence interval of the replication effect size; 39% of effects were subjectively rated to have replicated the original result; and if no bias in original results is assumed, combining original and replication results left 68% with statistically significant effects. Correlational tests suggest that replication success was better predicted by the strength of original evidence than by characteristics of the original and replication teams.


100
80
60
40
20
0
Tutti gli studi
Effettivamente riprodotti
Riprodotti con effetto delle stesse dimensioni

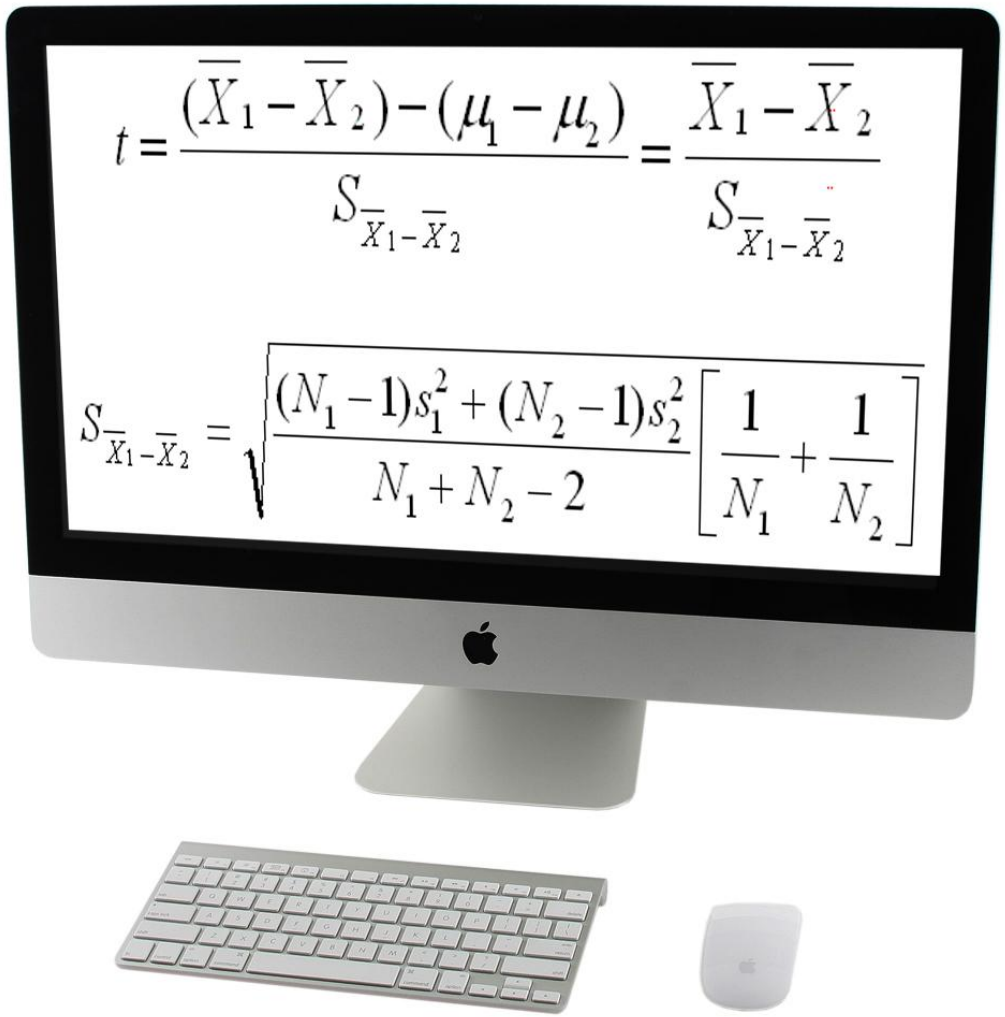


Statistica

$$t = \frac{(\overline{X}_1 - \overline{X}_2) - (\mu_1 - \mu_2)}{S_{\overline{X}_1 - \overline{X}_2}} = \frac{\overline{X}_1 - \overline{X}_2}{S_{\overline{X}_1 - \overline{X}_2}}$$

$$S_{\overline{X}_1 - \overline{X}_2} = \sqrt{\frac{(N_1 - 1)s_1^2 + (N_2 - 1)s_2^2}{N_1 + N_2 - 2}\left[\frac{1}{N_1} + \frac{1}{N_2}\right]}$$

Statistica

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