Ideazione di un progetto di ricerca

Recessione, le accuse della Ue
Banche e consumi: tutti i rischi

Pil, l'Istat conferma: -0,2%. Dombrovskis: pesa l'incertezza sulla linea economica del governo

Alberto D'Argenio

l impatto dell'incertezza delle politiche economiche sulla fiducia delle imprese e sulle condizioni finanziarie sta diventando rapidamente visibile. Così Dombrovskis, Vicepresidente della Commissione Ue, commenta con *Repubblica* la recessione tecnica italiana certificata dall'Istat.

pagina 2

servizi di **GRECO, LOPAPA, PETRINI PULEDDA e RUFFOLO,** *pagine 2, 3 e 4*
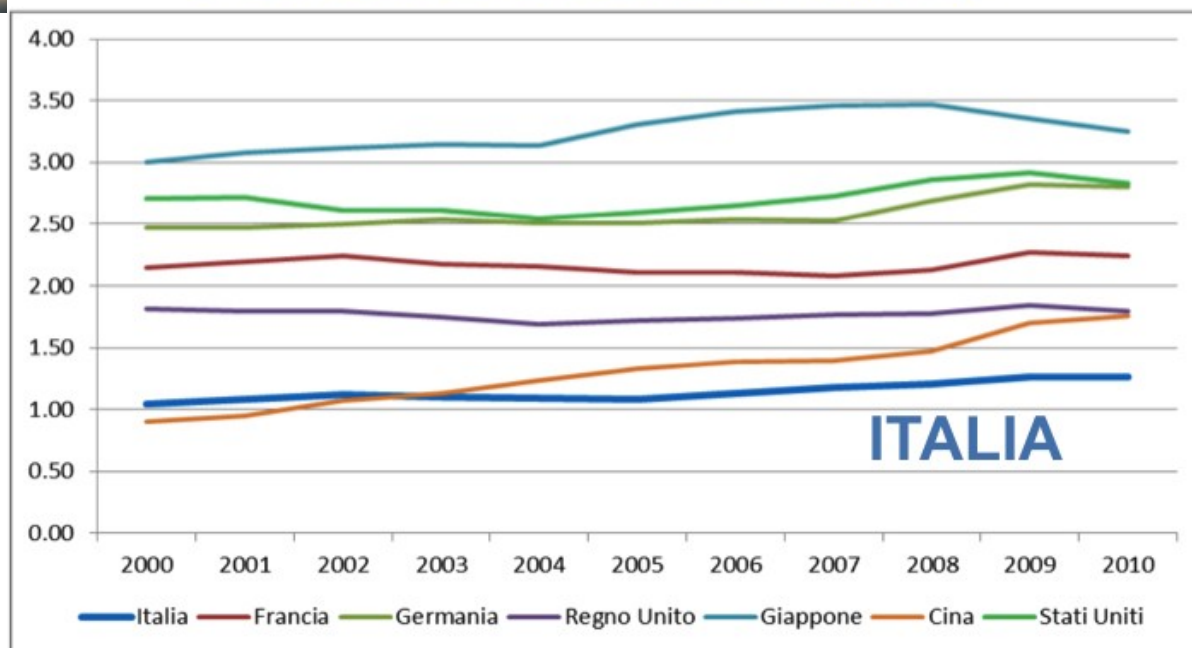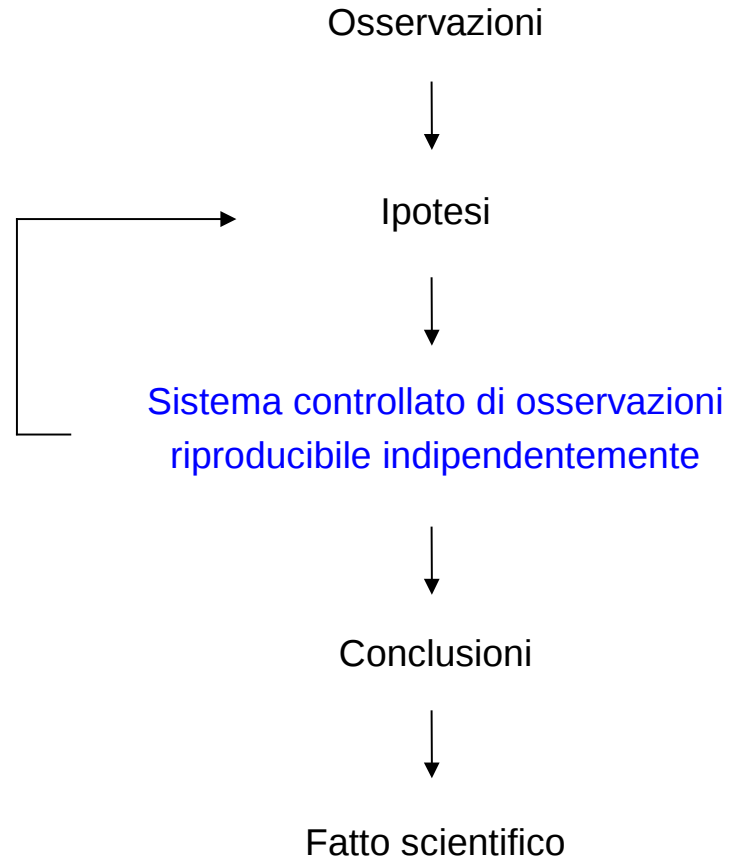
SPESA IN RICERCA E SVILUPPO (% PIL)

Figura 2.5 Spesa totale in R&S in rapporto al PIL, 2000-2010. Fonte: OCSE, Main Science and Technology Indicators

Il "metodo scientifico"

Osservazioni

↓

Ipotesi

↓

Sistema controllato di osservazioni
riproducibile indipendentemente

↓

Conclusioni

↓

Fatto scientifico

Ricerca guidata da ipotesi

Ricerca guidata da domande (esplorazione)

Sviluppo di metodi o strumenti

Misurazioni

Philosophies of Funding

Maureen A. O'Malley,[1,*] Kevin C. Elliott,[2] Chris Haufe,[3] and Richard M. Burian[4,*]
[1]Egenis, University of Exeter, Exeter EX4 4PJ, UK
[2]Department of Philosophy, University of South Carolina, Columbia, SC 29208, USA
[3]Department of Philosophy, University of Chicago, Chicago, IL 60637, USA
[4]Department of Philosophy, Virginia Tech, Blacksburg, VA 24061, USA
*Correspondence: m.a.o'malley@exeter.ac.uk (M.A.O.), rmburian@vt.edu (R.M.B.)
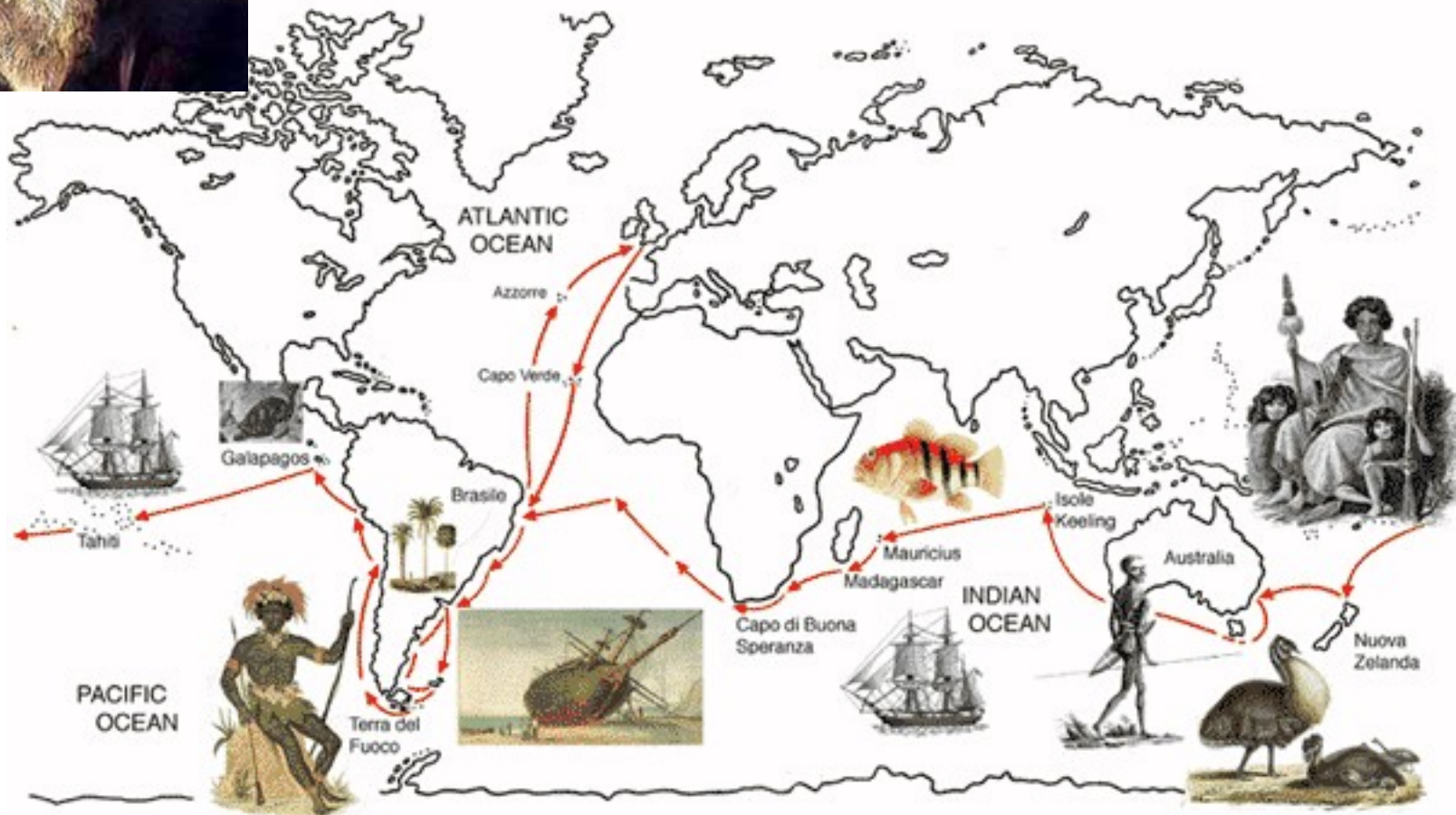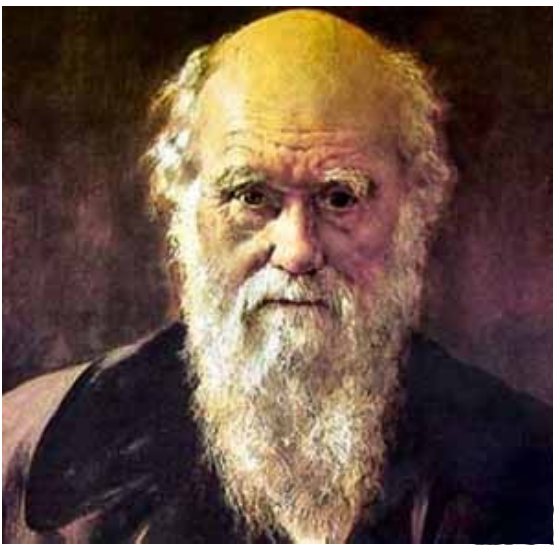DOI 10.1016/j.cell.2009.08.008

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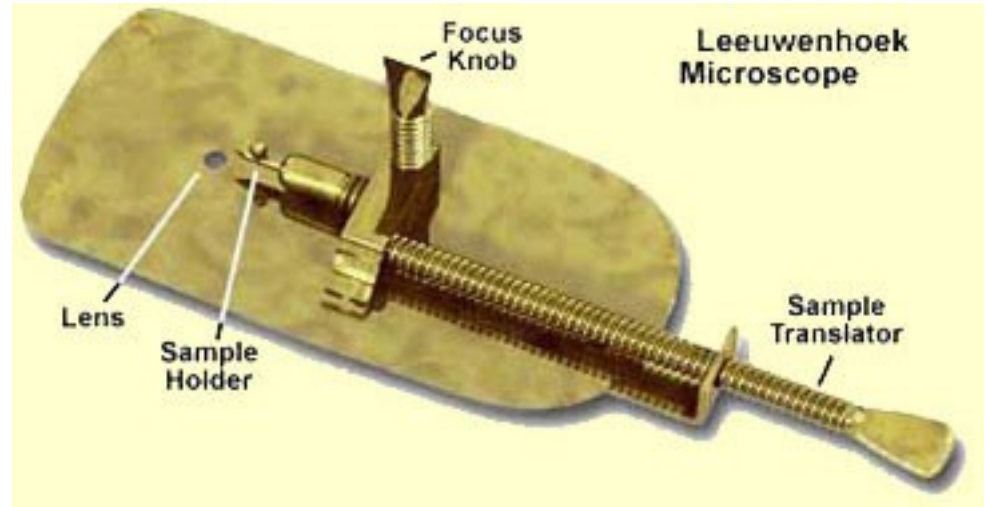
Philosophy is often regarded as abstract and irrelevant to practical concerns. Yet, when it comes to decisions about funding science, philosophical conceptions
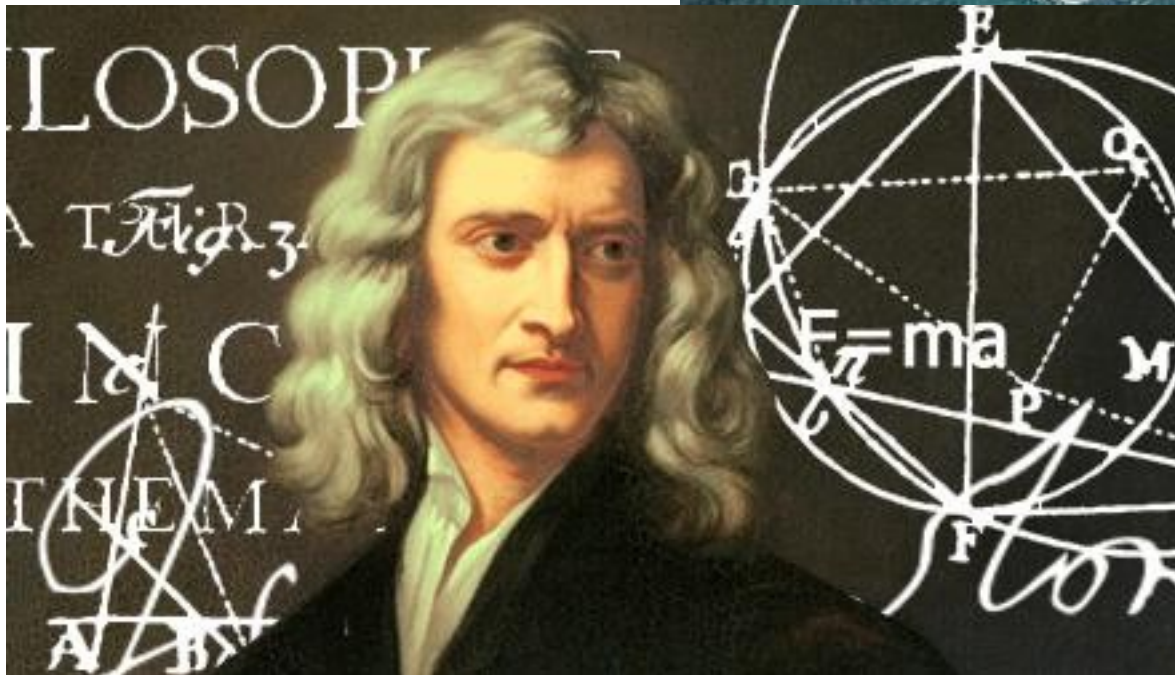
the most crucial arenas in which this widening of perspective must occur is in the funding of science. Although we believe that inspiration, effort, commu-

A Broad Account of Scientific Practice
It is standard for scientists, philosophers, and other commentators on sci-

ATLANTIC
OCEAN

Azzorre

Capo Verde

Galapagos

Brasile

Tahiti

PACIFIC
OCEAN

Terra del
Fuoco

Capo di Buona
Speranza

Mauricius

Madagascar

INDIAN
OCEAN

Isole
Keeling

Australia

Nuova
Zelanda

Focus Knob

Leeuwenhoek Microscope

Lens

Sample Holder

Sample Translator

16

Dal bando AIRC 2019

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

...

•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;

...

•descriptive epidemiology studies [misurazione];

...

Studi osservazionali e sperimentali

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
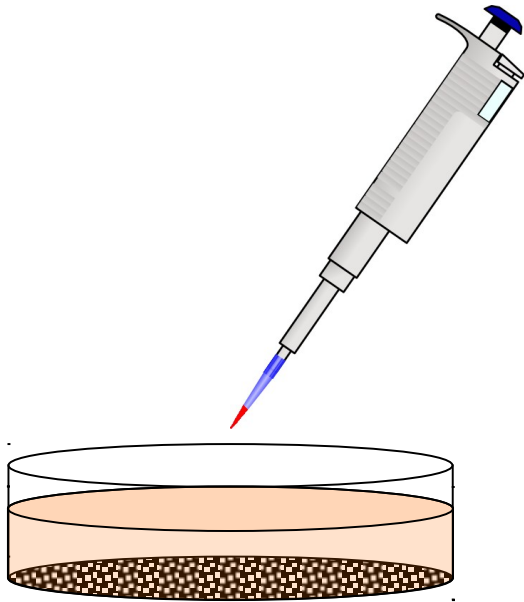

L'epidemiologia non può fornire dimostrazioni;
ciò non toglie che dia indicazioni importantissime

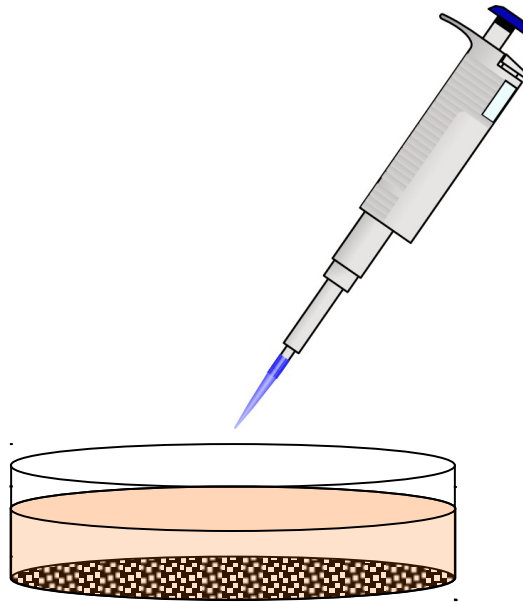Nessun grado di correlazione fra due fenomeni può fornire dimostrazione di un rapporto di causa ed effetto
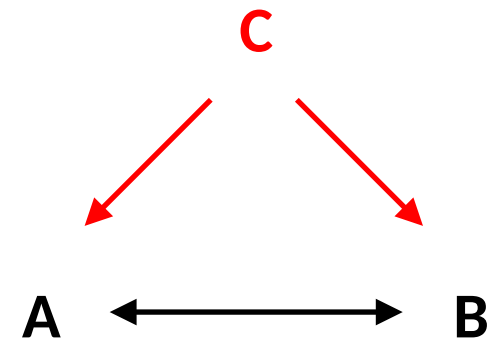
C

A ⟷ B

Isolamento della variabile allo studio

X   Variabile indipendente
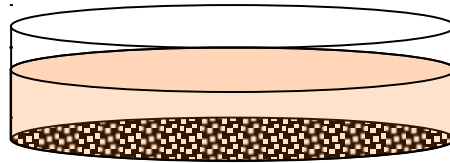
A   B   C   A   B   C

Isolamento della variabile allo studio
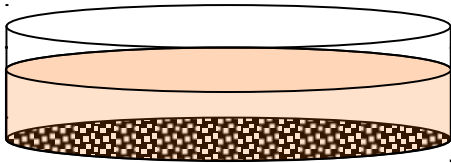
X — Variabile indipendente

A **B** C   A B C — 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

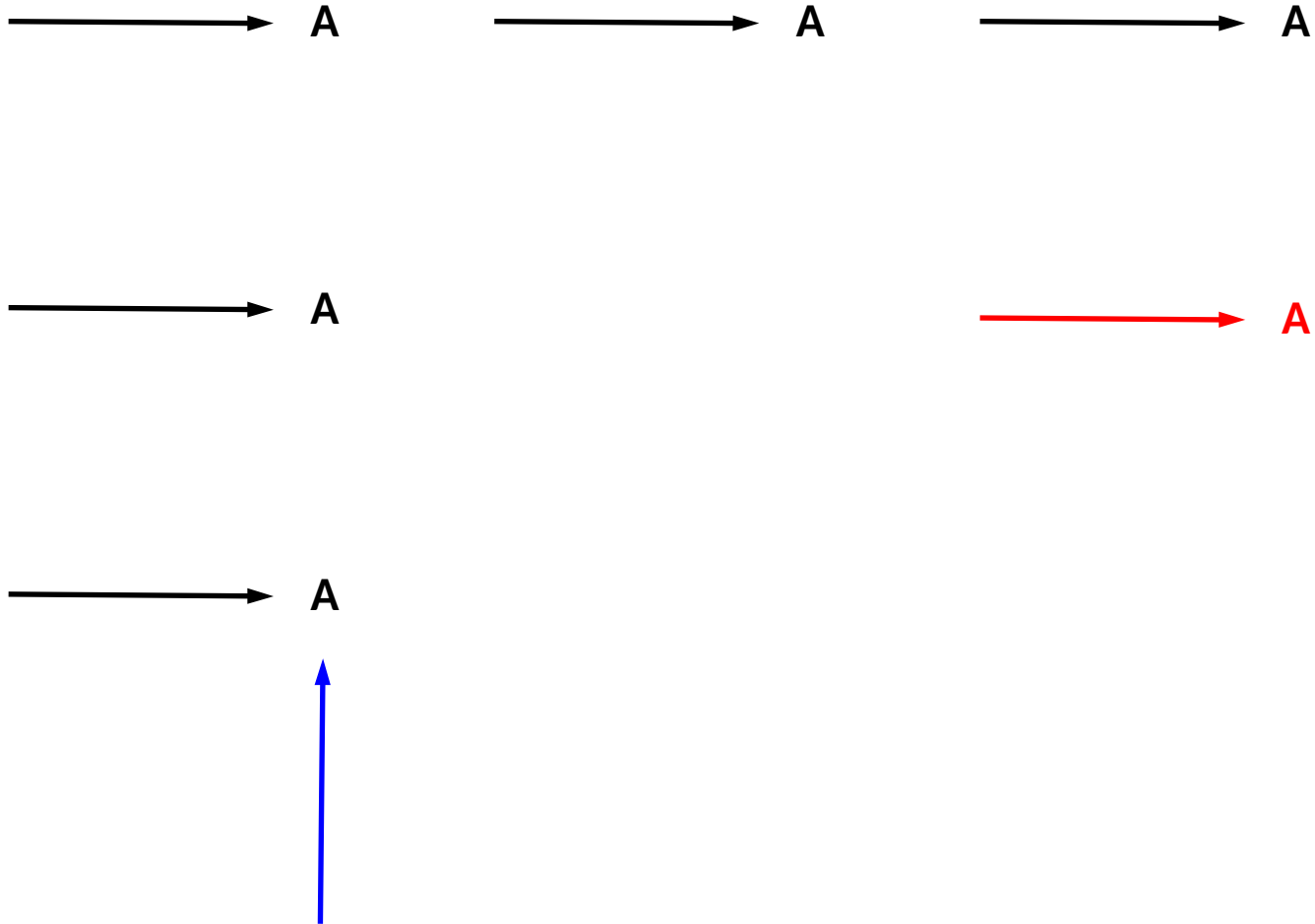Somministrazione di terapia
sostitutiva a 10.000 donne

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
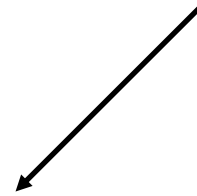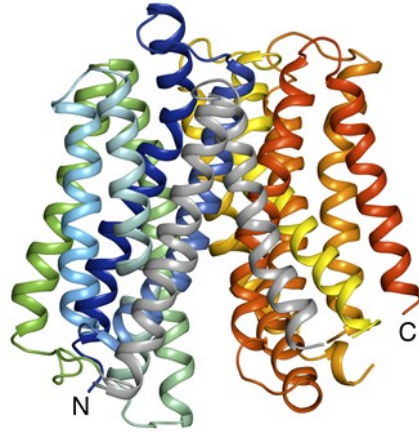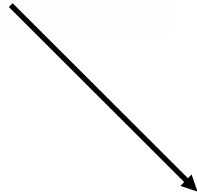
9 x 16 = 144   9 x 16 = 144   9 x 16 = 144

9 x 16 = 144   9 x 16 = 144

9 x 16 = 144   144 : 9 = 16

36 : 0,25 = 144
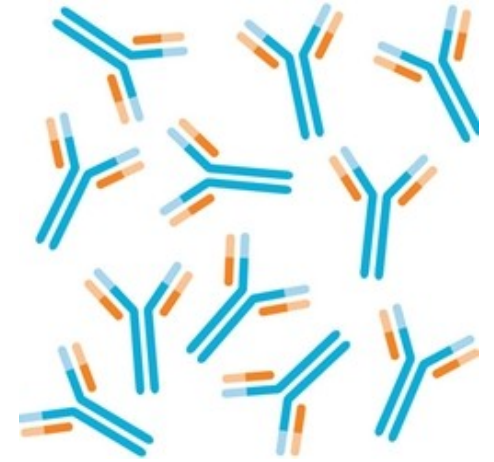
Il processo di ideazione

Domanda

Approccio sperimentale

Progettazione degli esperimenti

Esecuzione degli esperimenti

Interpretazione dei risultati

Porsi domande importanti

Identificare un gap conoscitivo

Focalizzare la domanda

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

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?
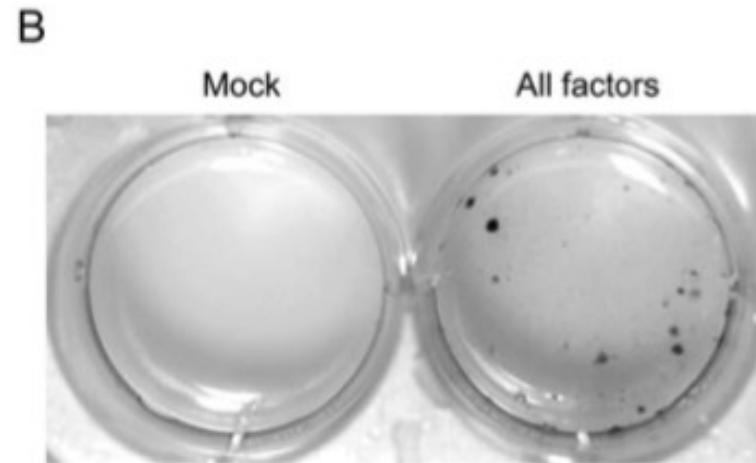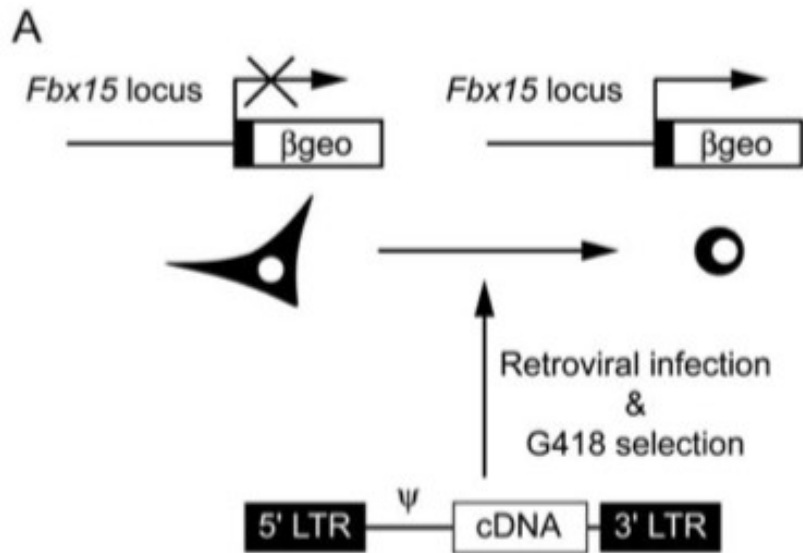
Clonal Integration of a Polyomavirus in Human Merkel Cell Carcinoma

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

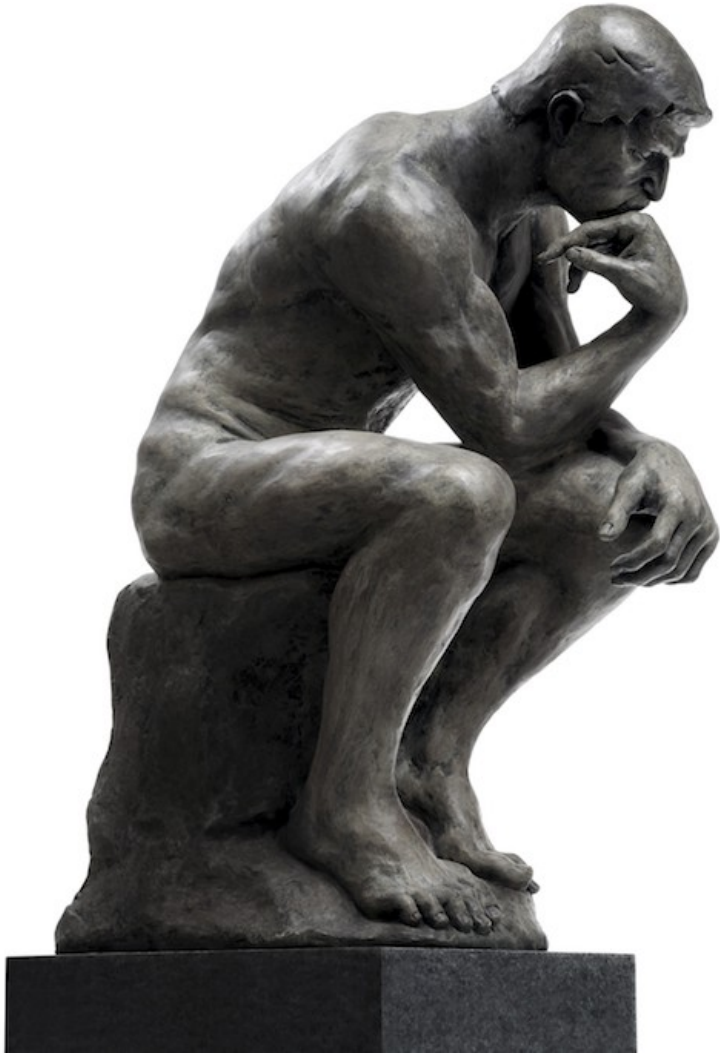# Seguire la naturale evoluzione del proprio filone di ricerca
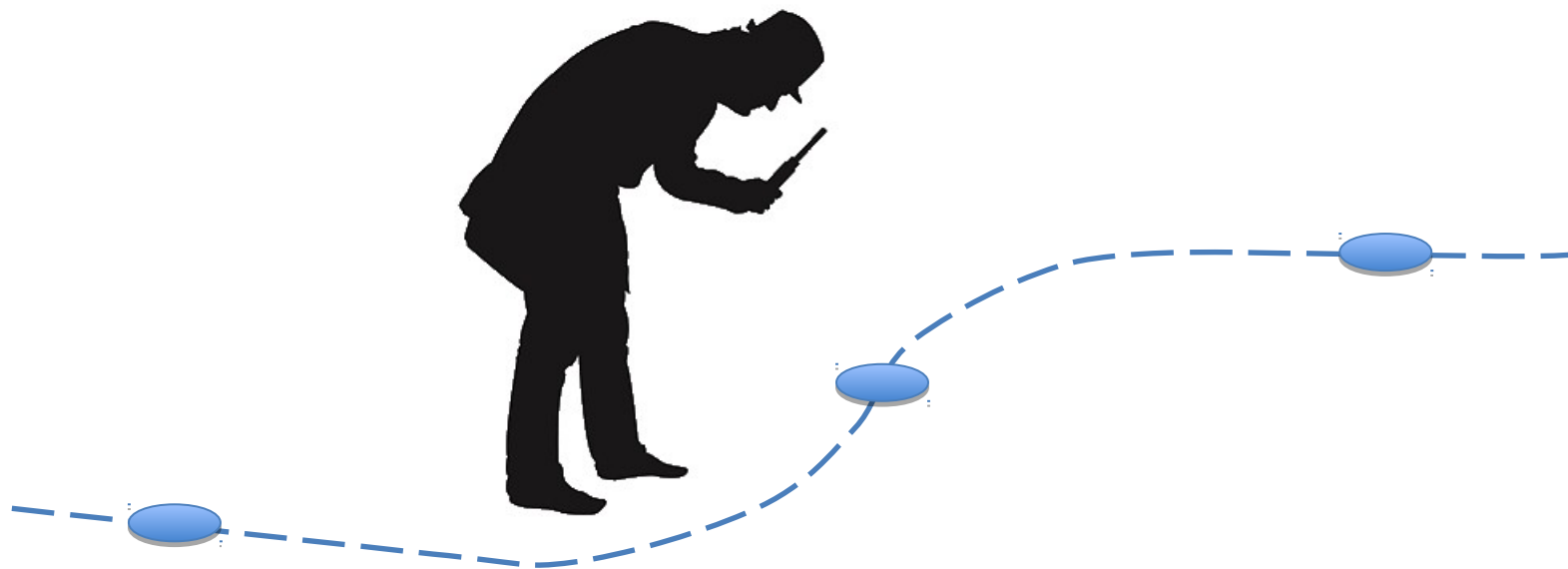
chromatin starfish

🔍

All   Images   Videos   Shopping   News   More   Settings   Tools

About 41,900 results (0.33 seconds)

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**.
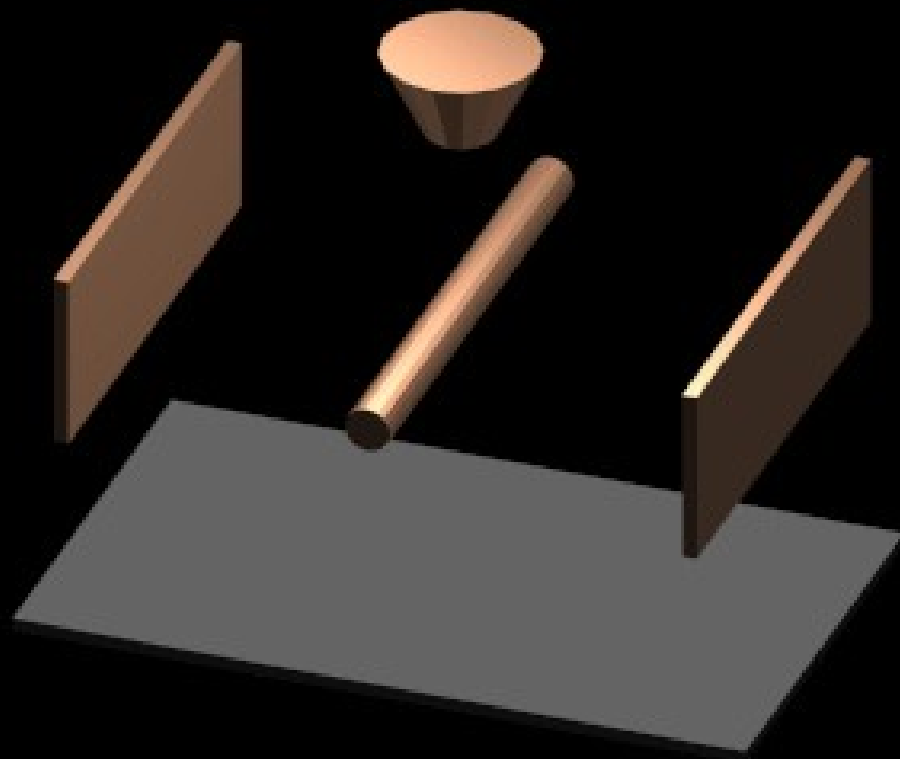
Esperimenti "quick and dirty"

E' molto importante individuare le possibilità di fallimento di un obiettivo e prevedere strategie di recupero o alternative

Potenziale problema	Strategia alternativa
L'ipotesi proposta potrebbe rivelarsi falsa	Sarà verificata l'ipotesi alternativa...
La trasfezione potrebbe avere una bassa efficienza	Verrà utilizzato un lentivirus
Il saggio potrebbe non essere abbastanza sensibile	Adotteremo il seguente metodo...
Il numero di pazienti potrebbe essere insufficiente	Sarà utilizzato materiale di archivio

Controlli positivi e negativi

-                                    +

X   Y
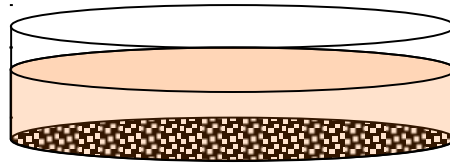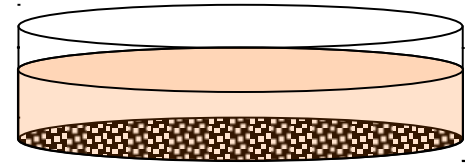
A **B** C   A B C   **A** **B** **C**

I controlli positivi:

1.verificano il buon funzionamento tecnico dell'esperimento

2.convalidano i risultati negativi

I controlli negativi:

1.verificano la specificità dei risultati

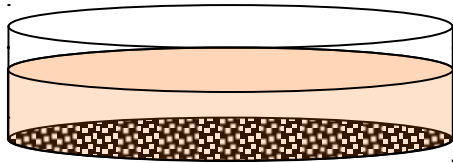2.forniscono una misura del segnale nello stato basale e dell'eventuale rumore di fondo nelle osservazioni quantitative

Domanda

Approccio sperimentale

Progettazione degli esperimenti

Esecuzione degli esperimenti
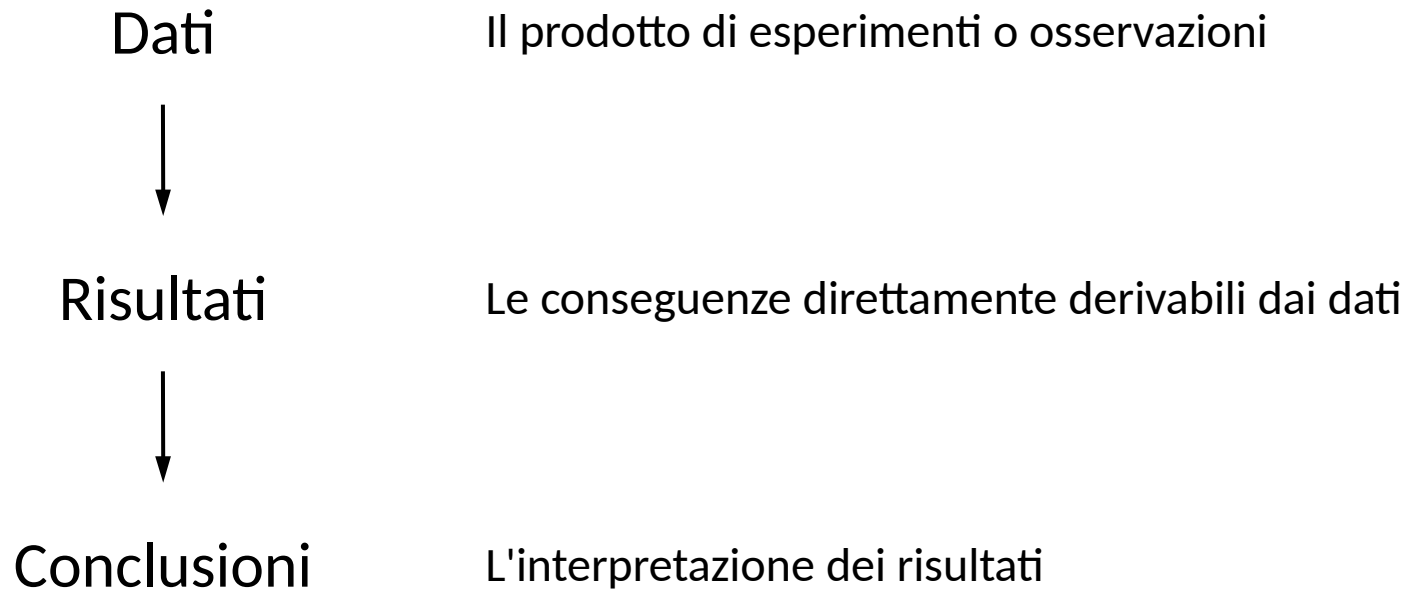
Interpretazione dei risultati

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

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

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.
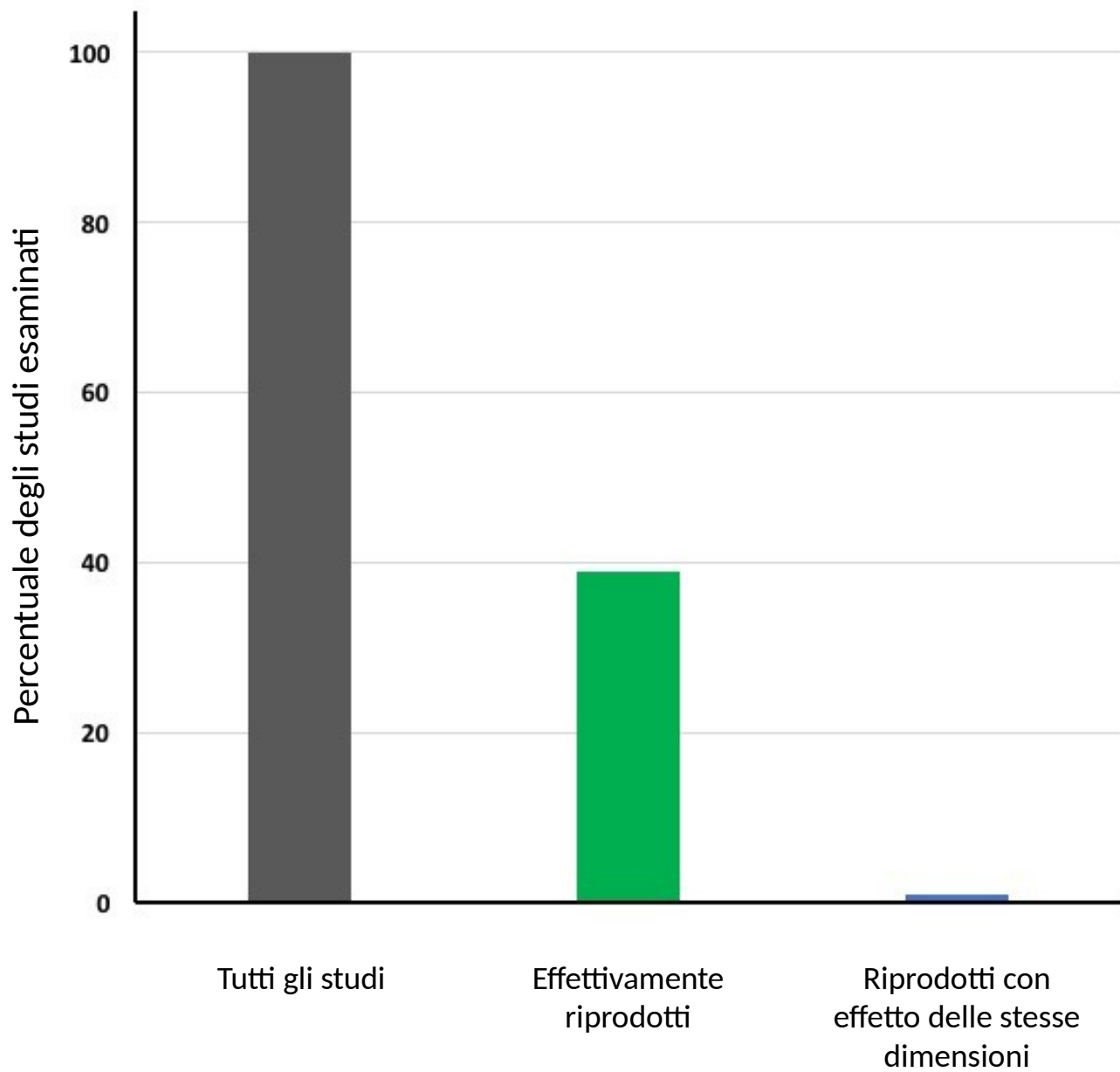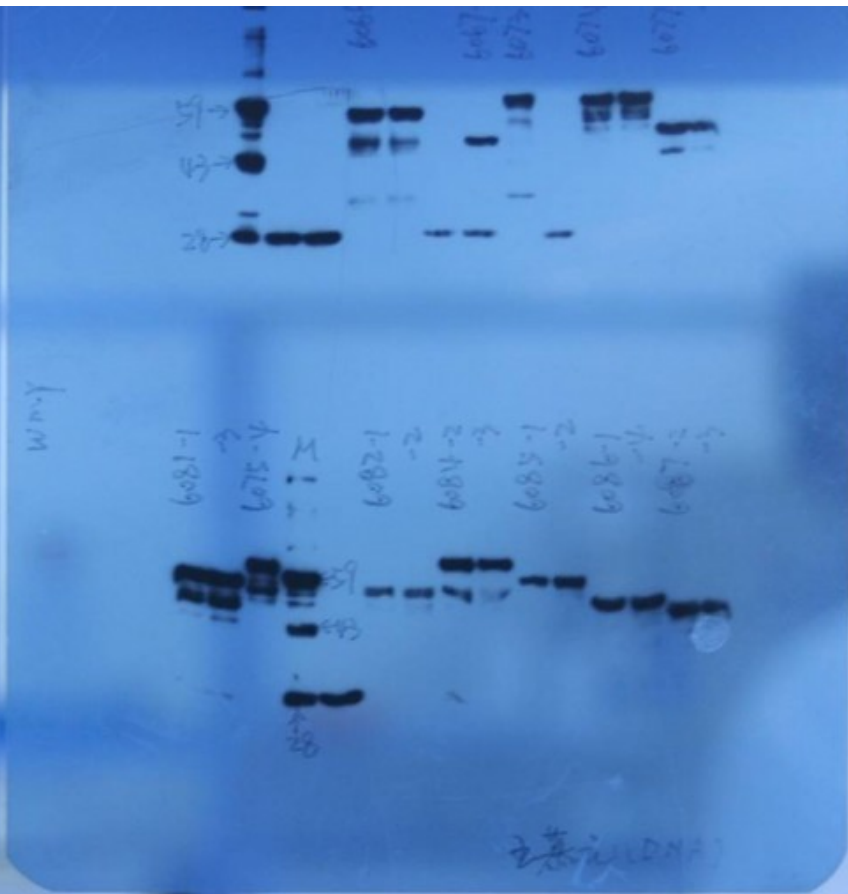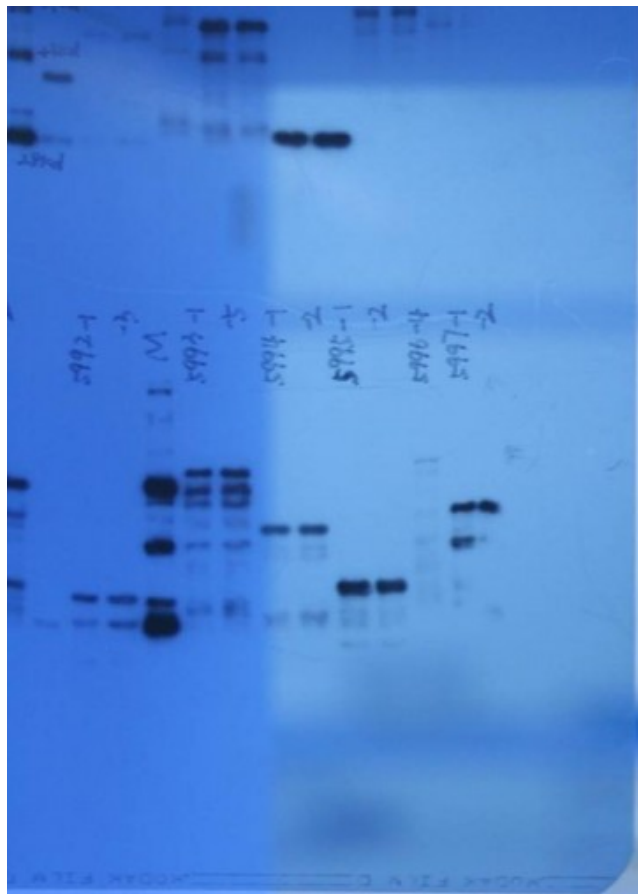
Statistica

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

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

Statistica

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

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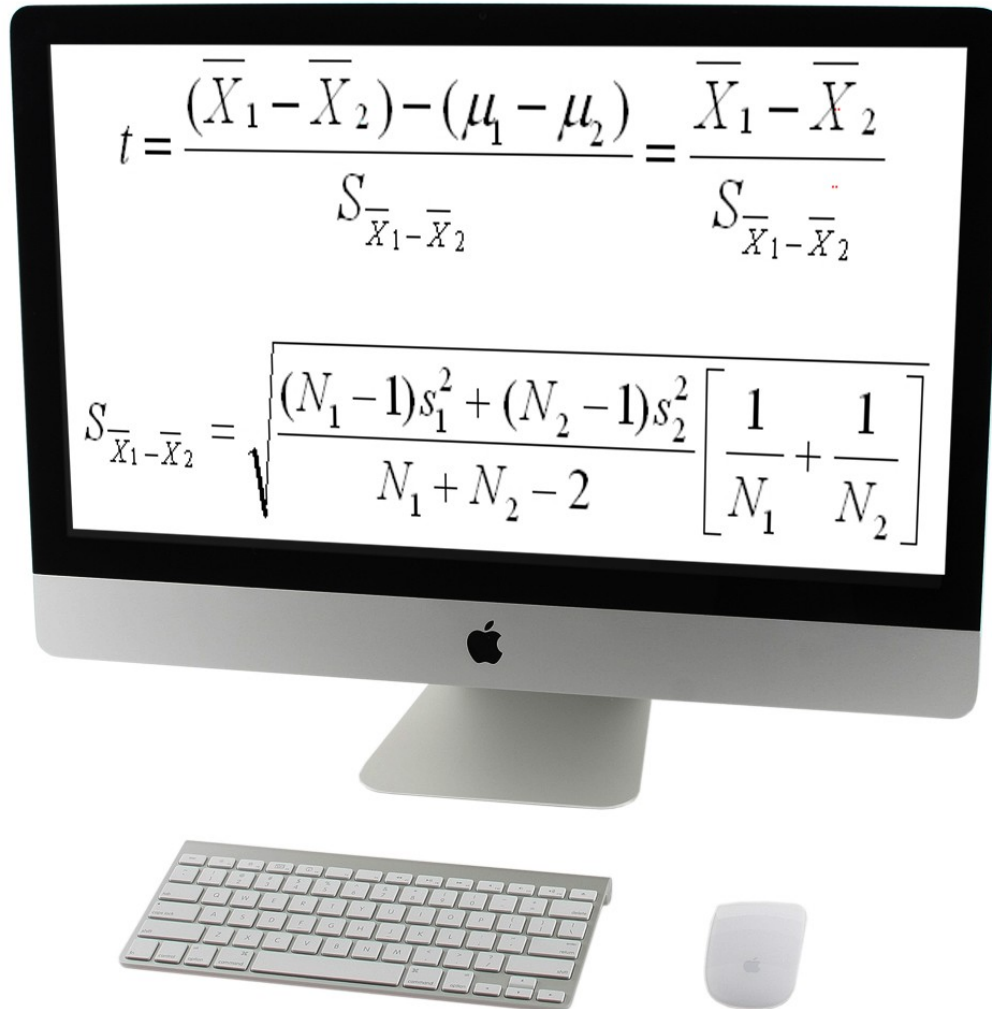
Riepilogo

- Chiarirsi il tipo di approccio: verifica di ipotesi, esplorazione, sviluppo di metodi o strumenti, misurazioni

- Elaborare un disegno sperimentale rigoroso

- Prevedere ridondanza di evidenza, quando possibile e opportuno

- Identificare un gap conoscitivo e/o seguire il proprio filone di ricerca

- Focalizzare la domanda

- Disporre di dati preliminari

- Utilizzare approcci quantitativi, statistici