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Four stages of a scientific discipline; four types of scientist

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In this article I propose the classification of the evolutionary stages that a scientific discipline evolves through and the type of scientists that are the most productive at each stage. I believe that each scientific discipline evolves sequentially through four stages. Scientists at stage one introduce new objects and phenomena as subject matter for a new scientific discipline. To do this they have to introduce a new language adequately describing the subject matter. At stage two, scientists develop a toolbox of methods and techniques for the new discipline. Owing to this advancement in methodology, the spectrum of objects and phenomena that fall into the realm of the new science are further understood at this stage. Most of the specific knowledge is generated at the third stage, at which the highest number of original research publications is generated. The majority of third-stage investigation is based on the initial application of new research methods to objects and/or phenomena. The purpose of the fourth stage is to maintain and pass on scientific knowledge generated during the first three stages. Groundbreaking new discoveries are not made at this stage. However, new ways to present scientific information are generated, and crucial revisions are often made of the role of the discipline within the constantly evolving scientific environment. The very nature of each stage determines the optimal psychological type and *modus operandi* of the scientist operating within it. Thus, it is not only the talent and devotion of scientists that determines whether they are capable of contributing substantially but, rather, whether they have the 'right type' of talent for the chosen scientific discipline at that time. Understanding the four different evolutionary stages of a scientific discipline might be instrumental for many scientists in optimizing their career path, in addition to being useful in assembling scientific teams, precluding conflicts and maximizing productivity. The proposed model of scientific evolution might also be instrumental for society in organizing and managing the scientific process. No public policy aimed at stimulating the scientific process can be equally beneficial for all four stages. Attempts to apply the same criteria to scientists working on scientific disciplines at different stages of their scientific evolution would be stimulating for one and detrimental for another. In addition, researchers operating at a certain stage of scientific evolution might not possess the mindset adequate to evaluate and stimulate a discipline that is at a different evolutionary stage. This could be the reason for suboptimal implementation of otherwise well-conceived scientific policies.

Four by four

In this article I propose a simplified model of the evolution of the scientific process, together with the classification of the nature of the scientists making the biggest contribution at each evolutionary stage. I believe this analysis could be instrumental for individual researchers in their career planning and for a constructive dialog between the scientific community and science policy makers.

It is my view that the history of different scientific disciplines reveals that they evolve through four important stages with an evolutionary time frame that can be as short as a lifespan or as long as centuries. Wars, political repressions, cultural superstitions, power struggles within the scientific community in addition to funding policies and pledged rewards can facilitate, slow down or discontinue progression of a given scientific discipline through its natural course. However, scientific disciplines continue to follow the same course of four evolutionary stages despite all these temporary deviations. Thus, philanthropists or dictators and the wisdom or ignorance of policymakers can change the time frame that the evolution of a scientific field will take but can't change the order of the evolutionary stages.

If we compare the work style, focus points and limitations of scientists that have contributed the most in the different research fields at each of their evolutionary stages, we can see that the evolutionary stage of science unites and/or differentiates researchers more than century, language, socioeconomic status and even the scientific field itself.

The methodology presented here complements previously existing theories of the scientific process including the theory of scientific (r)evolution proposed by Thomas Kuhn in his famous book [1] (Box 1).

The first evolutionary stage

As long as mankind has existed they have seen wet soil, tears on eyes and sponges. However, it was not until the 19th century that these phenomena first became the subject matter for a scientific discipline, specifically, the physics of capillary action. So, how do previously known phenomena become the subject matter of a new scientific field?

The scientists operating at the first evolutionary stage of a scientific discipline (actually, the scientist[s] creating

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Box 1. Kuhn's theory of scientific (r)evolution and the four-stage concept

The concept of four stages of scientific evolution and four types of scientists presented here is not the first work emphasizing and analyzing the cyclical nature of the scientific process. In his famous book [1], Thomas Kuhn listed three stages of the scientific process. At the first, pre-paradigm stage, a new paradigm appears as the most promising theory among several equally co-existing at the time. Kuhn calls the second stage 'normal science', because at this stage science progresses within the existing paradigm accumulating knowledge corresponding to the conceptual framework. The third, revolutionary stage results from a scientific crisis. At this stage, an old paradigm cannot explain some important observations and a new paradigm challenges the previous one to encompass explanations and a broader scope of known facts.

The fact that Kuhn's theory and present work postulate a different number of stages in the life cycle of a scientific discipline does not necessarily signify a contradiction. Instead, it might just emphasize the fact that Kuhn's theory is aimed at the analysis of events characteristic of a paradigm shift and does not have to distinguish stages between the 'birth' and 'death' of an idea. By contrast, the work presented here is not devoted to divulging the mechanisms of appearance and refutation of a paradigm. Instead, it is aimed at the analysis of the dynamics within one life cycle. Nevertheless, both approaches share the key underlying postulates. First, 'a new paradigm' in Kuhn's theory and 'the first stage work', as I call it here, both propose a new scientific language to describe phenomena under study. Second, both theories assume the psychology of scientists to have an important role. They also predict the inevitable clashes of different groups of scientists. Third, both theories note the cyclical nature of scientific evolution. One important difference between my four-stage scheme and Kuhn's is that the present scheme applies the four-stage pattern not only to the chronology of scientific developments but also to the psychological types of scientists. In other words, whereas Kuhn believes that the scientific community as a whole goes through different stages, and this shapes the psychology of individual researchers, I suggest that researchers have their own internal psychological inclinations that might run counter to the prevailing mode in the community. Overall, these two theories might complement each other as it is often the case with theories analyzing the same topic from different angles.

an entirely new field) introduce new subject matter into the realm of scientific analysis. To do this, they have to introduce a new 'scientific language' adequately describing the new subject matter.

For example, Isaac Newton introduced differential equations as a language describing mechanical movements. Thus, he helped create physics in its classic form. A first-stage chemist and the 'father of modern chemistry', Antoine Lavoisier, introduced quantitative chemical experiments that gave rise to chemical equations. Starting with Lavoisier, chemistry became a science studying how matter changes its state in a chemical reaction while the quantity of matter remains the same. More than that, Lavoisier formulated the theory of chemical elements as the fundamental blocks of chemical compounds and introduced chemical nomenclature. The language of chemical nomenclature and quantitative chemical reactions has made it possible for chemists to inform each other of their work, discuss the results and stipulate new questions in a manner similar to how the use of mathematical equations united physicists into one scientific community.

Interestingly, first-stage scientists are not necessarily the ones who discover new facts. Thus, Lavoisier did not discover any substances, did not enhance any method of chemical preparation and did not invent any apparatus. His work was mostly based on facts discovered by others and experimental techniques developed by others. However, these observations and methods did not become chemistry until Lavoisier revised them and created a language that brought the 'pieces of the puzzle' together. The same is also applicable to Newton.

In modern times, first-stage ideas rarely come from facts that have been known for centuries. Instead, they are based on new observations and experimental results. The most famous example is the central dogma of molecular biology stipulated in 1956 by Francis Crick [2,3]. The entire modern biology is based on the concept of DNA transcribed into RNA and RNA translated into protein. This model became the language of molecular biology. Thus, the discovery of the DNA double helix is crucial because it led to the appearance of the central dogma of molecular biology as a new framework of thinking. The double helix structure of DNA proposed by Watson and Crick and Crick's subsequent model of the DNA→RNA→protein information stream can be viewed as one field-defining first-stage work that was articulated in two mutually complementing publications. Obviously, first stagers Watson and Crick did not make the X-ray DNA images necessary for the discovery of the double helix. They were made by Maurice Wilkins and Rosalind Franklin. Neither did Crick experimentally obtain any of the facts he proudly referred to when stating 'This scheme explains the majority of the present experimental results!' [2]. The Harvard historian of physics Peter Galison argues that new (experimental) methods often develop in parallel and semi-independently from theoretical (new objects; new scientific language) advances [4].

In order for first-stage scientists to be able to create a new framework of thinking they often have to be somewhat imprecise and even somewhat inaccurate. The reason being that, at the time that they conceive a new scientific field, not all the necessary facts are known or properly comprehended. In fact, for a theory to be forward looking it intrinsically has to contain uncertainty at the moment it is conceived. However, what might be considered to be incompleteness and inaccuracy is, in reality, the formation of a first-stage hypothesis.

For example, Dmitry Mendeleyev stipulated the periodic law and created the periodic table, which is probably the greatest achievement in chemistry to date. Mendeleyev believed that listing chemical elements in line according to their atomic weight would reveal the repetitive pattern of chemical properties of these elements. However, not all the elements were known at the time. Attempts to create a periodic table were made before Mendeleyev, for example by John Newlands. The reason why these previous attempts were unsuccessful is that their authors were too bound to the known facts and restricted their work to elements already discovered. Contrary to this, Mendeleyev left empty positions in his table and hypothesized what the properties of the as yet undiscovered elements would be.

More than that, at the time that Mendeleyev conceptualized the periodic table, atomic weights for some elements were inaccurately known, or were known for an isotope different to that which would allow these elements to correspond with Mendeleyev's idea of periodicity. Still, the great chemist ignored these data and placed these elements into a table according to his theory. Because of these reasons, today it would be hard to publish the periodic table and no review committee would give it a fundable score if it were a grant proposal.

To complete the profile of first-stage scientists, we should point out that they must not be afraid to make mistakes that will be corrected at a later time point owing to methodological advancements in the field that they have created. Lavoisier, for example, mistakenly put light and caloric to his list of chemical elements along with oxygen, nitrogen, hydrogen, phosphorus, mercury, zinc and sulfur. In addition, first-stage scientists rarely focus their interests on one single field of study. Those who operate at the beginning of the scientific disciplines often contribute to different fields of science (Lavoisier, for example, was interested in and contributed to chemistry, biology, mathematics and physics). First-stage scientists later created sub-fields within the existing science and had a tendency to 'spread' their interest across different areas, sometimes very different ones. Thus, Ilya Mechnikov was interested in lactation almost as much as in immunology for which he won the Nobel Prize.

A first stager has to be able to ignore all the negative comments, even those made by most reputable colleagues. For example, Mechnikov sustained many years of ridicule from Pasteur and Behring, whom the humble Russian scientist respected very much. Mechnikov's belief that immunity cannot be limited only to chemical components secreted into the blood (antibodies) but must also involve a cellular response was foreign to Pasteur and his followers. Interestingly, in the current environment, a prolonged devotion to 'contrarian views' would probably result in a lack of funding for the scientists and departure from the field before they can prove their point.

First-stage scientists do not always possess exquisite technical skills. Their attempts to produce data or perform a calculation can often be inferior to many of their colleagues. For them, things such as philosophical, esthetic and cultural views and/or analogies with funny stories and literature are instrumental. These 'unrelated' topics are a tangible part of their day-to-day toolbox.

Ultimately, first stagers are better able to find their way to scientists capable of carrying out their work through the second evolutionary stage. Otherwise, all their ideas would be of little or no avail, or they would be forgotten and rediscovered by someone else who would then be capable of transferring the field to the second stagers. Only after the new scientific field is acknowledged might historians of science find that there was a proceeding work, which could have, but did not, influence the course of scientific events. Multiple tragic examples can be found in the history of science, such as in the Stalinist USSR and behind the 'iron curtain'. Operating under secrecy and restricted from free information exchange, Soviet scientists generated multiple scientific breakthroughs that could have substantially influenced the course of scientific development in the rest of the world. Yet, their ideas often had to be re-discovered in the West and published years before their Soviet counterparts work was retrospectively brought to light.

Second evolutionary stage

Scientists at the second evolutionary stage of a scientific discipline develop all the major techniques, enabling the language of the new science to be useful and sophisticated enough to describe a broader spectrum of phenomena.

For example, by the mid 19th century, physicists routinely found solutions to a far greater number of problems than Isaac Newton did. It was due to a progressive sequence of re-formulations and enhancements of the Newtonian apparatus by second-stage advancement, for example calculus. The two most noticeable changes were introduced by Joseph Lagrange and by William Hamilton. Both of them were great second-stage scientists.

Importantly, advancements in the research machinery often correct the range of research subject matters under the scope of a scientific discipline. For example, in 1620 one of the greatest philosophers of natural science, Francis Bacon, wrote his famous book *Novum Organum*. In this book he listed phenomena that he believed were associated with heat. In this list he put together 'warm or heated liquids' and 'strong vinegar and all acids'. This is not surprising if you think of tongue sensation as a method of defining heat. Later, the introduction of thermometers and calorimeters enabled corrections in Bacon's list.

It is the second-stage advancements that are the most cited later on. For example, in modern biology the most cited and the most often used methods are the classic paper by Ulrich Laemmli [5] describing protein electrophoresis and the paper by Stephen Altschul *et al.* [6] describing the basic local alignment search tool (BLAST) for comparing genes on a computer. The original paper on BLAST [6] was, in fact, the most highly cited paper published in the 1990s. Scientists working in diverse areas such as vaccine development and paleontology, neurology and agriculture have cited them.

The wave of second-stage mentality was reflected in the decisions of the Nobel Prize committee. At the turn of 20th century it was inconceivable for many biologists to grant a Nobel Prize for a method. They believed that the Nobel Prize should be granted for the discovery of a new fact, a theory or for a new remedy. However, as modern biology has progressed to its second evolutionary stage the legitimacy of the Nobel Prizes awarded for DNA sequencing (1980) or PCR (1993) does not cause much of a dispute.

Often, an original step in a second-stage breakthrough comes from re-application of methodology previously developed in another science to a new problem with substantial re-thinking and adjustments. Thus, Erwin Schrödinger re-applied the equation from optics (on which he worked in his younger years) to describe the space- and time-dependence of quantum mechanical systems. Interestingly, in 1945 the already famous Schrödinger wrote one of the most important books in the history of science: *What Is Life? The Physical Aspect of the Living Cell* [7]. In this book he presented in a popular manner first-stage achievements and conundrums discovered in biology within the first half of the 20th century. Schrödinger's popularity and the intellectual elegancy of the text enabled this book to stimulate many young physicists and chemists to move into biology. One of them was Francis Crick, who together with James Watson discovered the DNA double helix. In a way, the entire triumph of molecular biology was substantially facilitated by second stagers adapting the methodologies of physics, chemistry and mathematics to biological tasks.

The second stagers might not be the same people who contribute the most at the first evolutionary stage of the discipline. The main characteristics of the work of second stagers are ingenuity and inventiveness, an ability to implement ideas and a high-risk tolerance in the selection of their tasks. The first stagers might still have a certain role in validating the methodology developed by second stagers. Sometimes, they contribute to comprehending it. For example, it was Niels Bohr and Albert Einstein and not Schrödinger who interpreted the meaning of the psi-function in Schrödinger's equation. In other instances, first stagers might promote the new technology via their reputation. However, at this point the second stagers are more or less self-sufficient. They will be judged by one factor only: how much the instruments they develop will be used by a scientist at the third evolutionary stage.

Third evolutionary stage

A typical set of questions that a molecular biologist asks regarding any biological problem is 'what are the genes involved?', 'are the proteins encoded by these genes structural and do they participate in signal transduction or have enzymatic functions?', 'do these genes and proteins share resemblance with some other known ones?', and so on. Basically, these questions are the application of known research methods to new research subject matters. The stage of science dominated by this combinatorial approach is the third evolutionary stage.

It can be said that at this stage scientists re-describe their subject matter in the language developed at the second evolutionary stage and this creates new insights, new answers and new questions. For example, starting in the late 1970s biologists took a new look at what they had been studying from the perspective of genes and molecular biology. Similarly, engineers had previously redefined their knowledge in mathematical terms in the 19th and early 20th centuries.

Most of the actual data and useful knowledge is generated at the third stage. Combining research subjects and approaches, scientists discover new subjects and phenomena. In addition, they create new relatively minor but still highly useful alterations of the research methods while adapting them for new tasks.

As soon as new methodology developed at the second stage proves itself to be useful for the science it was originally designed for, it finds new applications. Thus, DNA sequencing, originally developed for biology, has become useful for archaeologists and historians, similar to how mathematical methods or isotope analysis did decades earlier. This complements and explains Galison's idea [4], demonstrating that the new methods emerge not at the moment when a field of application is ready to accept them but when the field they are coming from is at its third stage.

The most useful personal qualities of scientists at the third stage are much different from those at the first stage. At the third stage, extensive knowledge of philosophy or art is not instrumental. Contrary to the first stage, mistakes or imprecision are unforgivable. The leaders in the field tend to be the neatest, most hard working and detail oriented.

Interestingly, sometimes scientists at the third stage retrospectively assume that the logic of their predecessors was also technology driven. For example, contemporary immunologists often claim that Mechnikov discovered phagocytosis as a fundamental immunological mechanism because he was the first to see a foreign object injected into the larvae of starfish under the microscope. However, reading Mechnikov's Nobel Lecture leaves no room for this view. Mechnikov starts his lecture with the explanation that it was a major difference in view points between himself as a biologist and Louis Pasteur as a chemist that drove his research. This was a conceptual and not a technological debate.

Difficulties and unexplained phenomena revealed during the third evolutionary stage of science often give rise to the next first stage. Thus, the inability of classic mechanics to explain the photoelectric effect led to quantum mechanics. However, this rarely happens without serious clashes between new first-stage ideas and the psychological inertia of researchers operating within the old paradigm. Ironically, the new first stagers who take science out of this crisis are not necessarily those who would be successful as third-stage researchers.

More often than not, third stagers are receptive to new methods and technologies generated by second stagers but are hesitant to welcome first-stage propositions. One of the reasons is that the first-stage ideas might not be immediately applicable to solve specific problems. For example, the category theory is a crucial part of modern mathematics and one of the main languages introduced into mathematics in the 20th century. It was originally proposed by Samuel Eilenberg and Saunders Mac Lane in their seminal paper [8]. However, when they submitted their paper to one of the most prestigious mathematical journals, the paper was rejected and a reviewer was extremely angered. He could not accept the fact that these two scientists had proposed a theory that did not solve any specific problem. Luckily for the two scientists and for the field of mathematics, this paper, when later published, was annotated in the journal *Mathematical Reviews* by the famous mathematician Andre Weil who realized its great potential. It is not certain whether this work would have been noticed and ultimately influenced the future of mathematics if it had not been commented upon favorably by an admired scientist. It could be that, without this reference, the category theory would have had to be re-discovered by someone else who would also have to find a way through the negative attitude of third stagers.

Fourth evolutionary stage

How many new discoveries are made today in anatomy, electrical engineering or classic philology? Probably, it is not many. These sciences are at their fourth evolutionary stage. At the fourth stage, what used to be a research subject often turns into the application of previously generated knowledge for practical purposes, which constitutes engineering and other professional activities.

The main goals of scientists working at this stage are to carry on knowledge generated at the previous three evolutionary stages. Without their work, each generation would have to re-discover the same things again and again. In the world where science, society and technology are constantly evolving, it is crucial that fourth stagers be able to re-evaluate the role of their discipline in the general scheme of things and generate new ways to present it.

Interestingly, the fourth stagers are somewhat similar to the first stagers in writing comprehensive reviews and textbooks presenting a holistic view of their discipline. Thus, in 1789 Lavoisier wrote the first textbook on chemistry *Traité Élémentaire de Chimie* (Elementary Treatise of Chemistry). In this book he clearly presented all the new concepts and theories of chemistry that he developed and refuted the phlogiston theory that was prevalent at the time. (Phlogiston was posited to be an element that was released during combustion and was additional to the four elements of Greek antiquity: air, earth, fire and water.) The fact that this book was so well written made young chemists interested in Lavoisier's ideas (generally denied by their older peers). These young scientists became the second stagers necessary for the productive evolution of a new science.

The folklore of Saint Petersburg chemists claims that the desire to create a simple and logical system to explain to his students the multitude of facts on chemical elements was what drove the professor of Saint Petersburg Technological Institute and the University of Saint Petersburg Dmitry Mendeleyev to create the periodic Table [9].

Similar to first stagers, the fourth stagers can use a broad spectrum of cultural and philosophical views as their day-to-day instruments. Maybe this explains why many first stagers, who created subfields in their sciences in the 20th century, wrote great textbooks presenting what was created before their era. Among them are the textbook *General Chemistry* by Nobel Laureate Linus Pauling [10], *Course of Theoretical Physics* by Nobel Laureate Lev Landau [11] and *Generalized Functions 5 Volumes* by legendary mathematician Israel Gelfand [12].

However, it would be wrong to assume that fourth-stage work is only a side activity for scientists who would otherwise be doing something else. One of the most intriguing examples proving the contrary is the work of French mathematicians writing their books under the collective pseudonym, Nicolas Bourbaki. In the 1930s a group of young mathematicians sent to teach mathematics at provincial French universities found that they had no satisfactory textbooks that could present the sequence of mathematical advancements in the most rigorous, axiomatic and formalized way. They were opposed to the popular view at the time, influenced by the famous mathematician Jules-Henri Poincaré, who had advocated for free-flowing mathematical intuition as a substitution for strict and detailed mathematical proofs. Writing a sequence of books on different mathematical topics and experimenting with the way mathematical discoveries could be presented, the Bourbaki group created its own style, which influenced many mathematicians all over the world. As with any scientific attempt, the Bourbaki approach was not universally beneficial to all the fields of mathematics. However, it is Bourbaki's texts in the field of mathematics Lie theory that are the most used to date and have made the Lie theory more instrumental for many mathematicians [13].

Collaboration of the first and the fourth stagers could be extremely instrumental. First stagers always possess a very clear understanding of the facts and concepts, but often are not following the latest developments and might not be up to date. Thus, in his famous book, *The Double Helix* [14], James Watson wrote that Francis Crick did not remember structural formulas of nucleotides when he met with Chargaff. In addition, first stagers might not have good memory. By contrast, fourth stagers not only are good in understanding the facts but also are well informed and remember great amounts of necessary and useful up-to-date information. Collaboration between first and fourth stagers is prone to some conflicts because fourth stagers might not accept that they are not idea generators. However, with some delicacy and pragmatism these two types of scientists could be productive working together, especially for the first-stage ideas emerging in the well-developed third-stage environment.

Fourth stagers also have a role, and are necessary contributors, during the third evolutionary stage of science. They are the ones who write holistic comprehensive reviews that re-evaluate on-going developments, in addition to coordinating and helping to focus future research. Without their input, the explosion of new data generated at the third stage would be chaotic. This is why it is not surprising, for example, that, along with journals publishing predominantly third-stage papers (e.g. *Nature Genetics* or *Nature Immunology*), Nature now has an array of complementary review journals. Interestingly, it is just by coincidence that the same person can combine talents of a second or third and a fourth stager. Thus, it is questionable whether the commonly accepted practice of invited reviews written only by the most acknowledged scientists famous for their inventions or discoveries is the best tactic possible. For example, a famous creator and editor of the journal *Cell*, Benjamin Lewin, has contributed enormously to the progress of molecular and cell biology just by his talent as a fourth stager, without spending any time in the laboratory.

Implications

If my observations and conclusions are correct, then the optimal style of scientific work depends on the evolutionary stage of a scientific discipline and does not depend on free will of an individual scientist and even a scientific community. Ignoring this fact could lead to personal tragedies especially in countries in which a high school graduate immediately has to choose a university course and a future career.

For example, an eighteen year old who applies to the program in biophysics today because he is fascinated with the way of thinking of Pasteur, Mechnikov or Bohr might be much less successful as a graduate student or a post-doc (and not as happy a person) than a well-organized person who works long hours and who does not read the writings of these great scientists in all their depth but, rather, just focuses on exam preparation. For the same reason, a student who loves Watson's book *The Double Helix* [14] might not be the most successful in molecular biology today and might be better off choosing instead something such as cognitive science, which is currently at the first and second stages of development. Also, high student scores reflecting a student's ability to appreciate knowledge and techniques of a certain stage of science might not be a good predictive indicator of how productive he would be solving conundrums of another scientific stage. Therefore, I hope this work would find its application for career planning and human resources in science.

Importantly, I do not imply that scientists operating at one evolutionary stage are more or less talented than their colleagues studying a science at another stage of its evolutionary development. I believe that a different set of talents is needed to practice science at its different evolutionary stages as much as a different set of physical or artistic talents are needed for different sports or fields of art.

Of course, the same person might work in more than one field and/or one evolutionary stage of science. For example, the founder of genetics, Gregor Mendel, is one of the best examples of a first-stage scientist. However, he had only three papers in biology compared with a multitude in astronomy. In the latter field, he was a third-stage researcher. Another example is Gaspard Monge. He has almost single-handedly created descriptive geometry and brought it from the first to third stage of evolutionary development. However, this is rather the exception than the rule.

Acknowledging four mutually complementing types of scientific talents might be instrumental for building, managing and preventing or resolving conflicts within scientific teams. An ideal biotech company or an academic department would consist of a mix of first, second, third and fourth stagers. It is possible, for example, that some members would combine second- and third-stage talents and others third- and fourth-stage talents. Human resource departments and/or supervisors have to be aware of the differences between the first and the third stagers. Acknowledging these differences would be beneficial for overcoming all the inevitable confrontations. Tensions between a first and a fourth stager might occur owing to their deceiving similarity. A culture must be in place to assure that those who generate ideas are not any more or less appreciated than those who can incorporate them into the overall scientific scheme. Of course, the relative role of the scientists at four different stages will change as a project progresses. This also has to be anticipated and managed to avoid conflicts and disappointments.

Understanding the four evolutionary stages of a scientific discipline could also be instrumental for grant writing and review processes. Imagine a first-stage-minded biochemist proposing an out-of-the-ordinary first-stage idea. He is extremely intelligent, and his thinking is ground breaking. In addition, he might be privileged to have a few friends sharing the same merits. What should this young professor do before he submits a grant on his novel idea? Should he ask his first-stage-minded friends to read it and provide him with their feedback? Unfortunately, restricting his potential pre-reviewers to first stagers only would be a mistake regardless of how talented and professionally advanced they are. For example, biochemistry today is a third-stage science. The vast majority of biochemists are third stagers with all the third-stagers' mentality. Therefore, the probability that the grant will be reviewed by first stagers only is minimal, and the third-stagers view the world and process the information in a somewhat different way. They might be convinced or excited by a different set of supporting statements. Therefore, by testing his grant on first or second stagers only and optimizing the grant to their views, this researcher has set himself up for probable failure. Considering this fact, it would be a better strategy to ask some third stagers to also read the proposal and then adjust the document to make it a better proposition to them (even if it contradicts the instincts of the author).

Today, the National Institutes of Health (NIH) might be one of the most efficient governmental agencies if we assume that its overall goal is to select and further support the best third-stage research. The set of grant review criteria, the grant review process and the workflow stimulates third-stage molecular biologists to perform to the best of their ability. However, the logic of the previous example also raises the question: how effective would a scientific policy be if it is aimed to enhance first-stage activity in some subfield when most of the review committee constitutes third stagers? Would it not imply that without special techniques, which are not practiced today (at least in the USA), any congressional decisions to allocate a budget for breakthrough first-stage research would, in the end, just result in an additional budget for the third-stage work? Does the current situation in biomedical grant funding, for example, create a situation when all truly new ideas have a better chance to find their way through private investors or in countries other than the USA, for example. And, if it is so, what should the Congress do to break the vicious cycle?

I realize that, although it is easy to adequately evaluate third-stage research, it is more difficult to do so with second-stage research and is extremely challenging with first-stage work. The lack of methods to evaluate first-stage work that review committees are experiencing today will probably remain a problem for some time to come. However, the approach I propose in this paper could be useful both for the first stagers in the way they present their ideas and for the reviewers.

Application of the proposed scheme of scientific evolution to the detailed analysis and re-evaluation of science policies, building and maintaining research teams and individual career planning might be among the most fruitful utilizations of this work. However, if we apply the classification proposed in this article to itself, we could define the approach of four stages of scientific development and four types of scientists as a first-stage research. Hopefully, the second stagers will develop an apparatus of in-depth analysis of science based on the proposed idea; the third stagers will apply this apparatus to the benefits of many and they will be assisted by the fourth stagers necessary to integrate this work into a general infrastructure of knowledge and culture.

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Research Focus

The complex dance of the molecular chaperone Hsp90

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Hsp90 chaperone function requires traversal of a nucleotide-dependent conformational cycle, but the slow and variable rate of Hsp90-mediated ATP hydrolysis is difficult to envision as a determinant of conformational change. A recent study solves this dilemma by showing that Hsp90 samples multiple conformational states in the absence of nucleotides, which serve to influence, but not direct, the cycle. The conformational program of Hsp90 is conserved from bacteria to humans, although the population dynamics are species specific.

The biomedical importance of Hsp90

Although many proteins require the assistance of molecular chaperones to fold properly, the clientele of one such chaperone, heat shock protein 90 (Hsp90), seems to be restricted. Nonetheless, >200 clients of Hsp90 have been identified to date (www.picard.ch/downloads/Hsp90interactors.pdf), and many of these proteins regulate important signaling nodes that integrate diverse environmental inputs and propagate downstream signaling cascades [1–3]. Although not essential in bacteria, Hsp90 is conserved in all eukaryotes in which it seems to have attained a crucial role in maintaining both cellular and organismal viability. Moreover, Hsp90 seems to have been co-opted by cancer cells to enable them to survive both hostile environments within the host (e.g. hypoxia, oxidative stress and chemotherapeutic insult) and a high degree of chronic genetic instability [4,5]. In addition, many viruses seem to require the host Hsp90 chaperone machinery for their successful propagation [6]. It is not surprising, therefore, that Hsp90 has become a popular molecular target for drug development, and several small molecule Hsp90 inhibitors are undergoing various stages of clinical evaluation [7,8].

The Hsp90 chaperone cycle requires conformational flexibility

In light of the burgeoning interest in the possible clinical benefit of Hsp90 inhibitors, many laboratories have been intensively exploring how the protein functions. Most chaperones rely on conformational flexibility for their activity, and Hsp90 is no exception. Although the overall structures of bacterial Hsp90 (HtpG) and eukaryotic Hsp90 proteins are highly similar, only the eukaryotic proteins are known to interact with a large number of co-chaperones that stabilize various Hsp90 conformational states and participate in Hsp90-dependent client protein binding, folding and maturation. Unlike HtpG, eukaryotic Hsp90s also contain an unstructured flexible region of variable length (which is species dependent) that links the nucleotide-binding (and drug-binding) N-domain with the middle (M)-domain, which comprises part of the active site of the 'split' ATPase of the chaperone and provides docking sites for client proteins and various co-chaperones. Both bacterial and eukaryotic Hsp90 proteins exist as constitutive dimers through the interaction of the C-domain of each protomer. By contrast, the N-domains transiently dimerize in a highly regulated, ATP-dependent manner involving large movements of both the N- and M- domains of each protomer. Based on available data, the structures of the individual N-, M- and C-domains remain well preserved despite the large conformational rearrangements undergone by the Hsp90 dimer, suggesting that the conformational flexibility of Hsp90 results from displacement of the domains with respect to each other. In support of this hypothesis, studies on small-molecule inhibitor binding to the N-domain nucleotide pocket have

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