Did Experimental Biology Die? Lessons from 30 Years of p53 Research

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The recent decade has greatly challenged biological research because there has been exponential growth in the amount of information that has been accumulated and published. Now, more than ever before, piles of biological data are waiting to be sieved through robust scientific reasoning and experimentation to produce the final product of basic science: conclusions. Given this situation, biological research is becoming increasingly dependent on computers. New branches of biology have sprung up in recent years in an effort to comprehensively understand the cell and the organism as a system.

As biology becomes more and more computerized, classic molecular biology is sometimes considered old-fashioned and even obsolete. As molecular biologists we often wonder about the significance and relevance of our research. Are we in an era in which experimental biology should be abandoned and computational biology should be adopted exclusively? Have we reached the limit of what can be learned from experimental biology and should now continue to a mathematical representation of cells and organisms? Did experimental biology die?

An elegant solution to this challenge was offered by Yuri Lazebnik as he points out a basic flaw in the experimental biologist approach: The absence of a common language among biologists creates confusion and may lead to a paradox in which the more facts we know the less we understand the process we study. According to Lazebnik, similar to a radio circuit, a living cell is comprised of certain components. If these components could be properly categorized and formally described, it would be easier for us to understand living cells and even fix their malfunctions much like an engineer who can repair a radio. At the end of the day the living cell, albeit complex, obeys a set of physical rules like any other system we know. Embracing a universal language in which all the components in a given system are eventually tagged and categorized will lead to a much more thorough understanding of the cellular system as a whole, and will eventually enable us to produce precise predictions as to the behavior of the system (1).

Let us put this approach to a test. In the late 1970s several reports revealed the existence of a new protein in transformed cells (2, 3). It soon became clear that this protein was overexpressed in cancer cells at large (4, 5). The overwhelming concentrations of this protein in cancer cells, followed by the observation that it enhanced transformation in mouse cells, prompted the notion that this protein was associated with a transformed phenotype (6–8). This newly discovered protein was given the unpresumptuous name p53.

At this point, at least according to the formal description approach, after establishing the involvement of p53 in tumorigenesis the scientific community would carry on defining other essential components in the cellular puzzle. Should new evidence surface that related p53 with anticancerous traits it would clash with the formal description of p53 and therefore might be more conveniently attributed to other yet undefined cellular components. In the lack of formal description, this evidence would no doubt confuse the researchers but because they were not shackled to any rigid definitions they would more easily question the very essence of p53 function. As it happens, this was exactly the case some 20 years ago. Although p53 seemed to be associated with malignancy, clear proof of its oncogenic activity was debatable because some laboratories obtained inconsistent data (9). Moreover, some tumors seemed to lack p53 altogether (10–12). These controversial observations resulted in confusion that led scientists to question the relevance of p53 to cellular transformation. The debate peaked in a very dramatic statement published in an editorial in the journal *Nature* in 1983: "If one transformed cell type can survive without p53, how essential is it for anything?" (13).

From this bafflement the resolution arose that wild-type p53 was actually a tumor suppressor, whereas a mutant form of p53 that was often present in cancer cells seemed to facilitate transformation. Given that the mutant form is abundant in cancer cells, it was the first to be discovered and thus was misconceived as wild-type p53. Eventually this theory was confirmed by several studies showing the tumor suppressive activity of wild-type p53 (14–16). (For a detailed overview of the p53 history see ref. 17).

Another point that should be taken into account is that a protein might be involved in a variety of cellular processes. Tagging it to a certain function might limit our thought to this function only, and may result in a biased interpretation of newly discovered evidence that alludes to different functions of the protein. Once again, p53 can serve as an example. Years of research illuminated our understanding of the involvement of p53 in cancer. Unfortunately, it cast a shadow over other p53 activities that had been wrongfully neglected for years. Several discoveries gave rise to the notion that the initial role of p53 was surveillance of cell division integrity. In higher organisms, harboring somatic cells that can redivide, this surveillance received extra meaning, as p53 activity serves to prevent these cells from deviating into malignancy. This insight allows us to zoom out and grasp the function of p53, not merely as a tumor suppressor, but in a broader sense as a protein maintaining normal cell division and perhaps participating in other processes such as development and differentiation (18). Surprisingly, mice lacking p53 were born without any apparent abnormalities (19). The fact that these mice did not exhibit any developmental defects disheartened many

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researchers, and the notion that p53 was involved in development was temporarily abandoned. Nonetheless, the concept was not completely put to rest as new evidence that questioned that initial observation began to pile up. When this issue was revisited carefully, it was realized that embryos lacking p53 did exhibit some developmental defects, adult mice showed diverse disorders, and a role for p53 in differentiation was established (20–22). These discoveries would have emerged much sooner had p53 not been categorized merely as a cancer-associated protein.

Attenuating the progression of science because of cemented misconceptions is not a new phenomenon. During the 19th century, Charles Darwin presumed that evolution was an immensely slow process that probably lasted billions of years. In 1866 the physicist Sir William Kelvin estimated the earth's age, based on thermodynamic calculations, to be 100 million years, a time course far shorter than the one required for proving Darwin's theory. Only four decades later it would be arbitrated that Kelvin's calculations were incorrect due to insufficient knowledge about the earth's cooling process. Although retrospectively ill-based, the decisive opinion of an influential physicist did not halt the acceptance of the evolution theory but it most certainly hindered it. Darwin himself searched for possible "short-cuts" in his theory in order to match it to Kelvin's time frame (23).

We believe the two examples presented above reveal the Achilles' heel of the formal description approach offered by Lazebnik. The lag between data acquisition and valid scientific conclusions is addressed by Lazebnik because he claims that a living cell should be approached by a biologist similarly to an engineer approaching a radio. In other words, categorize and tag each component in the system until the entire circuit is defined. When approaching a malfunctioning radio an engineer has the privilege of knowing the identity of each component, its location, function, and connection to other components. The radio analogy emphasizes how little we know about a living cell. Because scientists did not produce the components nor do they really know what each one actually does, as we learned from p53 research—initially categorizing it as an oncogene for example might simplify the inherent complexity of a biological system—it also might simply be wrong. We argue that the absence of a common language is not a flaw as was suggested but rather an important aspect of a good and unbiased scientific approach, which if interpreted properly may lead to a better understanding of the investigated subject. Having a common language essentially means categorizing and filing a certain component or phenomenon, thus leading to stagnation in their impartial research.

Both a radio and an organism are subjected to a constant evolutionary process. There is however a fundamental difference and that is the driving force for their evolution. Advanced radios will prevail over others on the basis of their functional advantages. A new organism however is not necessarily the best model but rather the fittest. It is not uncommon to encounter an organism that has not evolved to produce the most sophisticated and advanced biological machinery but succeeded in fulfilling its ultimate goal: survival. In contrast, old technologies will be found at best at the science museum. Unlike a radio, biological components constantly evolve to take on new or extended functions that serve as a platform for adaptation and speciation. A radio designed by an engineer is as complex and as broad as its designer. We cannot afford to lower biology to our level but should strive to rise to its level. The only way to do so is to assume the role of an active observer and not a creator. Acknowledging our position is crucial for making useful and sustainable science.

Should we adopt the formal description approach? In our opinion the answer is no. We should always take into account that the definition of each component in a system might be temporal and partial and that questioning it, despite the confusion it might cause, is our scientific obligation.

Modern biology undoubtedly faces an unprecedented amount of information, which rather than promoting human knowledge might sometimes inhibit it. In agreement with Lazebnik, we claim that the current methodology implemented in experimental biology is not the sole approach that should be taken. Other methodologies deal with the complexity of biology in different manners. The systems biology approach focuses on understanding a system's structure and dynamics and may provide insights into the essential principals of a living system such as robustness and redundancy. Another approach, synthetic biology, integrates engineering and biology. It addresses biological issues by artificially generating a reproducible unit in an effort to recapitulate the living cell. This approach enables us to investigate the living cell not merely as a "black box" in which the study is conducted with only partial knowledge of the system, but rather in a regulated environment that allows us to control the layers of complexity in a given system.

Although experimental biology often lacks the ability to produce systematic and global insights as do the above mentioned approaches, it possesses a heretofore irreplaceable feature: the capacity to thoroughly characterize a biological phenomenon, a task less likely to be accomplished by the newer biological approaches. This is analogous to medical treatment in which diagnosis can be more usefully achieved through "high throughput" screening such as periodical blood tests, etc. However, when we face a crucial physiological predicament we will seek the best possible solution and that is a doctor who specializes in our problem.

So where is biology headed? The current segregation between "wet" and computer-based biology will gradually disappear. This process is already in play as numerous experimental studies utilize high throughput screening and computer models and vice versa. The new age of information will give rise to a new biologist, one who not only integrates experimental and computational biology but also grasps them as one inseparable discipline. Bioinformatic training will become as basic and as thoroughly studied as molecular biology and physiology, and no bachelor degree will be complete without it.

For us, the elaborate journey of p53 research briefly described here represents the nature of investigating a biological phenomenon. It is full of what seems at first glance to be a contradiction, encompassing misleading concepts and misinterpreted results. However, at the end of the day when examined carefully, these obstacles eventually lead to unexpected paths and intriguing discoveries.

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