The Institute for the Study of Non–Model Organisms and other fantasies

William Sullivan
Department of Molecular, Cell and Developmental Biology, University of California, Santa Cruz, Santa Cruz, CA 95064

ABSTRACT **In his classic novel *Invisible Cities*, Italo Calvino describes a series of fantastic imagined cities that fulfill core human needs that remain unmet in ordinary cities. In light of the recent founding of a number of high-profile biomedical institutes, Calvino's descriptions encourage us to consider the unmet needs of the biomedical community and imagine unorthodox institutes designed to fulfill these needs.**

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In his novel *Invisible Cities*, Italo Calvino recounts conversations between the explorer Marco Polo and the Mongol emperor Kublai Khan. The young Polo describes to the aging Khan a series of imaginary cities he has come across in his travels. The cities are fantastic: Eutropia is a city in which the citizens change jobs every few years—the trash collector becomes the mayor, and the mayor becomes the gardener. In the city of Armilla, only pipes and plumbing are left glistening in the sunlight and spouting beautiful fountains. Euphemia is a city where memories and emotions rather than carpets and kitchenware are traded in the main plaza. As the novel progresses, it becomes clear that many of these imaginary cities fulfill core human needs that remain unmet in ordinary cities.

Marco Polo had a keen interest in science and technology and achieved instant fame by returning from his travels with such marvels as gunpowder, paper money, and the compass. Perhaps in the evenings when Kublai Khan tired of Polo's descriptions of imagined cities, they discussed science, and the emperor may have asked Polo to describe the science academies and institutes he had come across in his travels. If so, would they have matched the fantastic nature of the cities in which they resided? And would they have filled unmet needs of the scientists of that time?

I bring this up because the past few decades have been witness to the formation and maturation of a number of extraordinary biomedical institutes. Because of their success, many are household names (at least in households with scientists). Like cities, each has a distinctive style, personality, and mission: the Howard Hughes Medical Institute (HHMI) "empowers exceptional scientists and students to pursue fundamental questions about living systems"; Scripps is devoted to "pursuit of fundamental scientific advances through interdisciplinary programs"; Stowers was formed "to make a significant contribution to humanity through medical research by expanding our understanding of the secrets of life, and by improving life's quality through innovative approaches to the causes, treatment and prevention of diseases"; and the mission of the Broad is to "act nimbly, work boldly, share openly and reach globally."

All of these new institutes have been tremendously successful, recruiting top-notch investigators and providing them with resources and rich environments to tackle key biomedical questions. While the investigators at these institutes are clearly innovative and imaginative, they share, of necessity, many core similarities in questions addressed and approaches taken, because they have the common goal of addressing fundamental outstanding issues in biology. A researcher at any one of these institutes would quickly feel at home if transplanted to another.

Given the abundance and similar goals of these institutes, the question arises as to whether there is a need for additional institutes. Reading *Invisible Cities* makes one wonder about the unmet needs of biomedical scientists and whether we might imagine institutes to meet these unfulfilled needs. Below, I attempt to describe examples of such imaginary institutes. Just as the oddball museums devoted to topics such as sewage, torture, and broken relationships fill key gaps left by the Smithsonian and Field museums, I envision the institutes described below as filling key gaps left by HHMI and others.

INSTITUTE FOR THE STUDY OF NON–MODEL ORGANISMS

It is estimated that the planet is host to 8 to 10 million species of plants and animals with approximately 1.5 million currently documented in the Catalogue of Life. Yet much of our current knowledge

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Address correspondence to: William Sullivan (sullivan@biology.ucsc.edu).

Abbreviations used: CRISPR, clustered, regularly interspaced short palindromic repeats; HHMI, Howard Hughes Medical Institute; MTOC, microtubule-organizing center; RNAi, RNA interference.

of biochemical, molecular genetic, and cellular processes relies on studies of fewer than a dozen model organisms. It is a safe bet that a majority of the findings and data from the institutes mentioned earlier are derived from work on these organisms (humans included). Without question, the sharp focus on a handful of model organisms has paid off and, in large measure, has led many observers to proclaim this to be the century of the life sciences. The downside, of course, is that we know very little about the biology of the vast majority of organisms with which we share the planet.

Our current situation is much like the produce department of a U.S. chain grocery store. Approximately 20–30 fruits and vegetables account for the majority of all purchases at U.S. grocery stores. These can be grown inexpensively and in abundance, handle the rigors of transport, have a long shelf life, and often taste very good. However, spend a few hours in Bangkok and it becomes clear there is a bounty of insanely delicious fruits and vegetables that never make it into the food bins of chain grocery stores. For example, there are more than 100 varieties of mangoes, each with a distinctive taste and texture. Yet our grocery stores, for sound economic reasons, only stock one or two varieties. It should be pointed out that grocery stores are beginning to respond to these yearnings, and their shelves now include exotics such as rambutan and lychee.

It is clear that molecular and cellular biologists are experiencing similar yearnings, wanting to taste the scientific delights of non–model organisms. Bob Goldstein, a well-established *Caenorhabditis elegans* investigator at the University of North Carolina–Chapel Hill, has invited tardigrades (water bears) into his lab (Gabriel *et al.,* 2007). Like *Drosophila* and *C. elegans*, tardigrades are multicellular organisms that molt, undergo complex development, and have a complex nervous system. Tardigrades have fascinated biologists for centuries, because they are indestructible: they survive years of dehydration, high pressure, freezing, and even the punishing environment of outer space. The Goldstein lab is applying its *C. elegans* chops toward understanding the development and biology of these creatures. Similarly, the Marshall lab at the University of California–San Francisco has begun studying *Stentor*, a single-celled organism with a length of 1 mm (Slabodnick and Marshall, 2014). This Boeing 747 of the cellular world has a complex body plan, sophisticated behavior, and a memory. It can be sliced and diced, with the fragments behaving like the chopped brooms in the *Sorcerer's Apprentice*: each piece regenerates to become a new intact cell. Marshall's group is studying *Stentor* to understand the mechanisms regulating cell and organ size. In my lab, we have focused on the order Hymenoptera (ants, wasps, and bees) to understand the mysteries of virgin birth (Ferree *et al.*, 2006). Females in this order are capable of parthenogenesis, and when one cracks open their oocytes, the images are so bizarre one might as well be looking at the cell biology of an organism from Mars. Each oocyte nucleus buds off hundreds of satellite nuclei that contain core centrosome components rather than chromosomes. On egg laying, these blossom into hundreds of functional centrosomes, each with its own microtubule-organizing center (MTOC).

These are only a few of the countless examples of organisms with fascinating biology that have been largely overlooked by the molecular and cell biologists. With the advent of RNA interference (RNAi); clustered, regularly interspaced short palindromic repeats (CRISPR) tools; advanced imaging technologies; and a battery of fluorescent reagents, the timing is perfect for labs to adopt new non–model organisms. Unfortunately, it is very difficult for a lab to obtain the funding required to launch into the molecular or cell biology of a new organism.

A new Institute for the Study of Non–Model Organisms would help fill this void. Instead of yet another artist's rendition of the double helix, the institute's lobby would be filled with terraria, cages, and ponds stocked with exotic creatures, the centerpiece being a large aquarium containing hundreds of *Elysia chlorotica*, a stunning green sea slug that feeds on algae and absorbs chloroplasts into its cells, with the chloroplasts remaining functional and the slug becoming photosynthetic. The institute would include a full-time staff of investigators and would host visiting researchers. In addition to state-of-the-art core microscopy, mass spectrometry, and sequencing facilities, there would be a team of experts to help with cultivation and propagation of the unusual organisms being studied. An entire wing of the institute would be devoted to organisms and ideas that once enjoyed popularity but have fallen out of favor (e.g., *Sciara coprophia*, a fungal gnat harboring disposable chromosomes). This wing would include a beautiful library and a team of scholars to read classic texts and manuscripts by the likes of Thomas Morgan, Ernst Haeckel, E. B. Wilson, and Theodor Boveri. Once a month, these scholars would host a seminar in which they would present highlights of the texts to the institute. A second wing, sponsored by Carolina Biological Supply, would be devoted to the study of the wonderful organisms sold to high school biology classes: *Euglena*, centipedes, tarantulas, sow bugs, and many others. Another wing would be devoted to organisms that exhibit unusual forms of reproduction. For example, there are a number of unisexual hybrid fish species (Lampert and Schartl, 2008). During meiosis, the hybrid eliminates all the chromosomes derived from one of the parental species (that is, if A and B refer to the chromosomes from each parental species, A/B hybrids produce only A gametes and mate with B males to produce only A/B progeny). One can imagine that there would be interesting unexpected molecular and cellular processes underlying this unusual form of reproduction.

INSTITUTE FOR THE ADOPTION OF ORPHANED GENES

Advances in sequencing technology have provided complete genome sequences for dozens of organisms. This has resulted in an extensive "parts list" and given rise to the emerging fields of systems and synthetic biology, as well as the promise of bioengineers crafting designer organisms. However, even though many of these organisms were sequenced more than a decade ago, we still know little about the placement and function of a large fraction of these parts. Imagine having a parts list for a motorcycle in which half of the pieces just have an identification number assigned to them with no description or picture to hint at their function or how they fit into the whole. Engineers relying on this list would be forced to build new motorcycles based only the well-characterized parts, a vehicle I certainly would not want to ride down the freeway.

Writing a decade after the sequencing of the human genome, Edwards and colleagues stated, "Yet more than 75% of the protein research still focuses on 10% of proteins that were known before the genome was mapped …" (Edwards *et al.,* 2011). They also found that, in spite of the fact that the human genome contains approximately 500 kinases, 65% of the papers published in 2009 focused on the same 50 kinases studied in the 1990s. I imagine other investigators have shared our experience, in which genome-wide genetic screens yield lists peppered with uncharacterized genes. Some of these will have hints of a domain (Leucine Zipper, PDZ, SH3, etc.), and, like a child peering through the torn wrapping of a birthday present, we vainly try to guess at their function.

While there are many reasons for our collective reluctance to pursue these orphaned genetic elements, lack of funding probably ranks at the top of the list.

Thus there is a great need for an institute devoted entirely to the study of uncharacterized genes. SWAT-like teams of investigators at the institute would be tasked with rapidly characterizing these genes. A battery of reagents, including antibodies, green fluorescent protein constructs, mutants, RNAi and CRISPR constructs, and purified proteins, would be developed for this work. Once every year, the results of their efforts would be published in *PLoS Neglected Genes*.

In the entrance hall of this well-funded institute would be a Rube Goldberg exhibit, the kind you see at airports, consisting of ramps, tubes, levels, pulleys, paddles, and springs that transport ping-pong balls. Once a year, on April 14th (the declared date of completion of sequencing the human genome), all 365 researchers would gather around the exhibit for the "Selection Ceremony." Each would grab a ball as it bounces off a small trampoline. These balls would have the gene identification numbers of 365 randomly selected, uncharacterized genes. The researchers' task is clear: they have a year to characterize their assigned genes.

INSTITUTE FOR THE ADVANCEMENT OF ODD RESULTS

Spend any amount of time at the bench and strange unanticipated results crop up: non-Mendelian outcomes in a crossing scheme, an unexpected band on a gel, or an unusual fluorescent image. In fact, breakthroughs often originate through follow-up on unexpected results. Perhaps the most famous example is Morgan's discovery of the white-eyed fruit fly. His capture and breeding of this oddity led to proof of the chromosome theory of inheritance, the discovery of sex linkage, and the founding of a new field of science: genetics.

All too often, however, our response to a surprising result is to mention it to a colleague over lunch or at a meeting, but, unfortunately, the pressures of productivity and funding demand we ignore them and move on. For example, while I was teaching an undergraduate genetics lab, my students made an interesting chance discovery. The class was using a *Drosophila* line in which a cell cycle kinase was inappropriately expressed in the fly eye, producing a dominant abnormal rough-eye phenotype. If this line was outcrossed to *Drosophila* directly taken from the wild, the phenotype was suppressed, yet no suppression occurred when it was crossed to wild-type lab strains of *Drosophila*. Somehow, genomes of *Drosophila* from nature but not from the lab were able to shut down (or compensate) for the misexpressed kinase. I have often thought about following this up but have yet to put flies to pad. An informal survey of my colleagues revealed that each of them had encountered multiple examples of interesting puzzling observations that have been left by the wayside.

Launching an Institute for the Advancement of Odd Results would provide a means to follow up on interesting serendipitous findings. Researchers could send very brief descriptions of their findings to the institute. A selection committee composed of biomedical scientists, psychics, and clairvoyants would make a best guess on whether a particular odd finding was worth pursuing. The researcher who submitted the project would serve as an advisor, while the institute would supply two years' worth of resources, personnel, and reagents to carry out the initial studies.

The entrance to this institute would be a visual celebration of the odd and unusual. Eclectic museums throughout the world would be tapped to loan their displays. The grand opening would include collections of barbed wire, human hair, and UFO debris.

Clearly, my list of imagined institutes is incomplete, and others might have different priorities. Colleagues have suggested establishing institutes for Unorthodox Collaborations, Frugal Science, and Experimental Conferences, as well as the Think-Tank for Theoretical Genetic Screens. Where would these institutes be located? My preference would be the city of Andria. Marco Polo describes its citizens as self-confident and prudent, because "any change in Andria involves some novelty (change) in the stars" and "every innovation in the city influences the sky's pattern, before taking any decision, they calculate the risks and advantages for themselves and for the city and for all worlds."

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