Commentary

Consilience and unity in ocular anterior segment research

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Abstract

In his beautiful book, Consilience: The Unity of Knowledge, the eminent biologist Edward O Wilson, advocates the need for integration and reconciliation across the sciences. He defines consilience as “literally a ‘jumping together’ of knowledge with a linking of facts ... to create a common groundwork of explanation”. It is the premise of this paper that as much as basic biomedical research is in need of data generation using the latest available techniques– unifying available knowledge is just as critical. This involves the necessity to resolve contradictory findings, reduce silos, and acknowledge complexity. We take the cornea and the lens as case studies of our premise. Specifically, in this perspective, we discuss the conflicting and fragmented information on protein aggregation, oxidative damage, and fibrosis. These are fields of study that are integrally tied to anterior segment research. Our goal is to highlight the vital need for Wilson’s consilience and unity of knowledge which in turn should lead to enhanced rigor and reproducibility, and most importantly, to greater understanding and not simply knowing.

KEYWORDS: anterior segment; ocular surface; cornea; lens; cataract; posterior capsular opacification; protein aggregation; oxidative damage; antioxidants; fibrosis; wound healing; consilience

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INTRODUCTION

In July 1844, 35-year-old Charles Darwin finished the first report of his new theory: evolution by natural selection. As narrated by Darwin’s great-great-grandson, the author Randal Keynes in his book, Darwin: His Daughter and Human Evolution, Charles next relayed to his wife Emma, “I write this in case of my sudden death as my most solemn and last request, that you will devote £400 to (the essay’s) publication”. Mrs. Darwin read the 230-page essay carefully. She was supportive but skeptical. She hit at the heart of the theory by questioning how it could explain a structure as complex as the eye. Finding his explanation unconvincing, Charles Darwin set aside his essay and went on to study his barnacles, until 14y later, when Alfred Wallace’s letter and manuscript arrived, jolting Darwin to write his book, On the Origin of Species. But even then, Charles could not really answer Emma’s question. Charles wrote in his book, “To suppose that the eye with all its inimitable contrivances … could have been formed by natural selection, seems, I freely confess, absurd in the highest degree”. Over a 150y later, the awe and the beauty of the eye have not diminished.

Whether you are looking for complexity or for simplicity, the eye has it. If you are into complexity, take the retina: five types of neurons, multiple subtypes of support cells, blood vessels, immune cells, and that is just at the anatomical level. But if you are into simplicity, take the lens: two types of cells—epithelial cells at the front and fiber cells in the rest. No nerves, no blood vessels, not even nuclei in most cells. Even organelles like ribosomes in the core lens fiber cells which may scatter light—gone. This means no translation and not even transcription. What could be simpler than that? Yet this simple structure is responsible for the number 1 cause of blindness worldwide[1-2]. Globally, there are approximately 20 million people who are bilaterally blind because of cataract. Even if we look at just the United States, over 24 million Americans are affected by cataract, and given an aging population, the numbers are expected to rise significantly (https://bit.ly/46NhV2C). Millions of surgeries are performed each year with considerable cost. And it gets worse. Cataract has a twin—presbyopia which is the loss of accommodative ability. And just like a cloudy lens is no good; a lens that cannot focus is no good either. Presbyopia is essentially universal. Practically every US adult over the age of 50 has it[3-4].
A core mission of the National Eye Institute (NEI), a component of the U.S. National Institutes of Health (NIH), is to “understand the eye and visual system”. Related to this mission, the NEI has the long-standing Cornea Program as well as Lens and Cataract Program. The aim of the former program is to support research projects directed at understanding the normal and diseased cornea (e.g., keratoconus and Fuchs’ endothelial dystrophy) as well as tear-secreting glands and their dysfunction (e.g., dry eye disease). The aim of the latter program is to support research directed at understanding normal and diseased ocular lens (especially cataract and presbyopia). This understanding is essential to be able to reduce the burden of visual disorders in the United States and worldwide. Over the years, these NEI programs have supported many research projects which can be searched via the publicly accessible RePORTER database going all the way to 1985: https://reporter.nih.gov/advanced-search.

A large number of ideas have been proposed to understand biology and disease of the anterior segment. Figure 1 lists a subset of these terms directed at funded lens and cataract projects. This list can easily be doubled. Each entry addresses a relatively-isolated part of the lens biology and pathobiology puzzle. The usual formula is: The key to lens function is understanding_and you fill in the blank. Be it aquaporins, connexins, crystallins, etc. It has been proposed. Now we can take essentially any of these stories to illustrate a key barrier in translating basic findings to clinical insights but let us take these three: protein aggregation/oxysterols, oxidative damage/antioxidants, and fibrosis/wound healing. It is critical to emphasize that these are just illustrative examples and are not unique. We can take many others. It is also critical to emphasize that the barriers we describe not only affect lens and cornea research areas but other fields of inquiry too. Relating to the anterior segment and beyond. Relating to the eye and beyond. Replace our three stories with research topics X, Y, or Z and you are likely to reach similar conclusions. The need for consilience is broad.

PROTEIN AGGREGATION AND OXYSТЕROLS
Let us take the story of oxysterols and reversing cataract. A
few years ago, two reports came out: the first in Nature titled, “Lanosterol reverses protein aggregation in cataracts”\cite{5}. A couple of months later, the second report came out in Science titled, “Pharmacological chaperone for alpha-crystallin partially restores transparency in cataract models”\cite{6}. Using Mendelian genetics (reverse approach) in the Nature work and high-throughput screening (forward approach) in the Science work, both papers hit upon an oxysterol, lanosterol in the Nature paper and a lanosterol-like molecule in the Science paper, as being able to reverse cataract in vivo. What is lanosterol? As the name implies, it is a sterol that is a key metabolite in the synthesis of cholesterol, and sterols are known to modulate membrane lipid domains in the lens\cite{7}.

These findings were really exciting because as the accompanying news and views essays made clear–this insight presented a way to chemically “dissolve” cataract\cite{5}. No surgery needed, no intraocular lenses, and no risk of secondary cataract. Beyond the clear clinical significance and the wide-utility of such intervention, there were lots of other reasons to be excited about such discovery. Most importantly, there is biological plausibility. Alpha crystallins are small heat shock proteins that act as chaperones and prevent proteins from forming light-diffracting aggregates. During aging, this chaperone function is overwhelmed, thereby allowing light-scattering protein aggregates to form which in turn results in cataract. Moreover, human subjects with a homozygous mutation in the lanosterol synthase gene have congenital cataract\cite{5}. It also turns out that a lanosterol-analogue docks nicely into a groove formed at the alpha-crystallin-A and alpha-crystallin-B dimer interface which stabilizes the native state\cite{5}. Also critically, the nice overlap between the two sets of findings, obtained independently, means there is impressive reproducibility of the conclusions. In sum, the studies had high clinical relevance, wide-utility, biological plausibility, and independent confirmation. No wonder it was called a “new dawn for cataracts”\cite{99}.

Unfortunately, a subsequent report found neither lanosterol reported in the Nature paper nor the other oxysterol reported in the Science paper successfully reversed protein aggregation\cite{10}. This report came on the heels of another paper that reported similar failure of oxysterol (lanosterol solution) to restore lens clarity from cataract\cite{11}. It is worthwhile to note these are just two publications that overcame the difficulty of publishing negative findings. One can only guess if other groups encountered the same outcome but did not report their findings in the published literature.

So, what is going on? Could it be that the original two reports were just a flash in the pan? Perhaps the new era of cataract treatment is just the same as the old? Not so fast. Because following the two reports of negative findings, there were at least eight publications, representing six new research teams, with positive findings consistent with the original Nature and Science papers\cite{12-19}. The dilemma is that the groups are using essentially different models. Indeed, a crowded set of model systems are involved in these published reports including human lenses\cite{10-11}, human lens progenitor cells\cite{5}, human induced pluripotent stem cells (iPSC)-derived lentoid bodies\cite{11}, zebrafish\cite{17}, mouse\cite{18,19}, Sprague Dawley rat\cite{10}, Shumiya cataract rat (SCR)\cite{12}, selenite-induced cataract rat\cite{14}, rabbit\cite{15}, dog\cite{5}, and cynomolgus monkey\cite{16}, not to mention in vitro\cite{13}, and in silico\cite{8,10} approaches. Needless to say, these are confusing sets of results. To quote the author Tom Peters, “If you’re not confused, you’re not paying attention”.

Of course the issue is not about this mouse, rat, or model system. It is about us. It is about answering the important clinical question: Can we have a “nonsurgical treatment for cataract” in the form of an oxysterol? The answer is: Maybe, maybe not. We do not know for sure. And beyond the lens, protein aggregation is known to play a role in some corneal dystrophies such as the link between transforming growth factor-β-induced protein (TGFB1p), an extracellular matrix protein that is the second most abundant protein in the corneal stroma, and granular corneal dystrophy (GCD)\cite{20}. This kind of situation of seemingly oppositional reports in the literature that are not reconciled into a cohesive whole may present a significant barrier to move findings from the lab to the clinic.

**OXIDATIVE DAMAGE AND ANTI-OXIDANTS**

The barrier is not limited to oxysterols and cataract nor the broader topic of protein aggregation in disease (whether in the anterior segment, the rest of the eye, or the rest of the body). The use of antioxidants to mitigate oxidative damage is another example where there is high clinical significance, broad-utility, biological plausibility, and independent confirmation, yet many questions remain unanswered. The idea of oxidative damage leading to disease is so attractive and powerful that it has been put forward to explain a wide range of diseases throughout the body, including eye diseases beyond cataract and Fuchs endothelial corneal dystrophy. The concept looks great and explains all sorts of observations. Environmental insults (e.g., smoking, pollutants, UV radiation, etc.) generate highly reactive species that damage cellular proteins, lipids and DNA which in turn lead to homeostatic dysregulation and ultimately to a disease state once the normal protective and cellular repair mechanisms are overwhelmed. Indeed, several cellular defense mechanisms are known to be involved, including superoxide dismutase, catalase, thioredoxin, peroxiredoxin, glutathione peroxidase, and glutathione S-transferase. Moreover, aging, the defining feature of age-related cataract (ARC), age-related macular degeneration (AMD), and age-related changes to the corneal surface\cite{21}, can be subsumed under the theme of
oxidative damage/stress. Fundamentally, the paradigm suggests an unmistakable way to treat the resulting disease, namely, either reduce the oxidative stress or increase the antioxidant mechanisms. A beautiful cause-effect link with a clear linear relationship. A sharp dichotomy. A balance between oxidants and reductants. In a way, it can be thought of as a central dogma of age-related disease research. So, what is the issue? Take a look at this headline: “The Myth of Antioxidants” by Moyer[22]. The author tells us that, “The oxidative damage, or free radical, theory of aging can be traced back to Denham Harman, who found his true calling in December 1945, thanks to the Ladies’ Home Journal”. Moyer concludes, “aging is far more intricate and complex than Harman imagined it to be nearly 60 years ago”. This is even more so a decade after Moyer’s 2013 article. Here is another headline: “The Science Myths That Will Not Die”[23]. The article quotes the Canadian biologist Siegfried Hekimi, that it is “one of the few scientific theories to have reached the public: gravity, relativity and that free radicals cause ageing, so one needs to have antioxidants”. Yet, the British biologist David Gems concludes, “There’s a question mark about whether really the whole thing (molecular damage causing ageing) should be checked out”.

Could it be that antioxidants are more effective when we focus on the eye? Let us take a look. A Cochrane review looked at a popular antioxidant—N-acetylcarnosine or NAC—and concluded that, “There is currently no convincing evidence that NAC reverses cataract, nor prevents progression of cataract”[24]. Maybe that is just for one specific antioxidant? Let us look more broadly. Another Cochrane review focused on the evidence for antioxidant vitamin supplementation (beta-carotene, vitamin C and vitamin E) for prevention or slowing of cataract and found no evidence of benefit[25]. In fact, the authors concluded, “We do not recommend any further studies to examine the role of antioxidants against ARC”[25]. Results from other more-recent clinical trials seemingly lend further support to these conclusions. For example, a report from the Antioxidants for the Prevention of Cataracts study found “no difference in the risk of cataract extraction between the antioxidant vitamin group (vitamins A, C, and E) and the placebo group”[26].

Here is another example. Resveratrol, a polyphenol enriched in grapes, is also thought to counteract oxidative stress. In fact, besides its purported antioxidant ability, it has been proposed to have anti-angiogenic, anti-inflammatory, anti-platelet, anti-proliferative and a Janus-faced pro-proliferative ability[27]. Published literature reports evidence of resveratrol efficacy in various ocular models, including a selenium-induced cataract mouse model[28-29], a streptozotocin-induced diabetic cataract rat model[30-31]; a naphthalene-induced cataract rat model[32]; in high glucose-induced oxidative damage in human lens epithelial cells[33], and in a human lens capsular bag model[34]. Yet the same literature currently reports zero publications for actual resveratrol efficacy against ARC in humans. Admittedly, this does not preclude that future clinical trials may yet show resveratrol efficacy. In fact, Clinicaltrials.gov shows 205 hits for resveratrol. But as things currently stand, MIT researcher Leonard Guarente’s quip comes to mind, “Resveratrol is very, very good (at activating SIRT1 and extending lifespan) if you’re a mouse” (https://bit.ly/46vaKwh).

The challenge of course is broader than NAC, resveratrol or vitamins. There is a zoo of so-called phytochemicals—both flavonoids and non-flavonoids; carotenoids and xanthophylls and other agents with promise, plausibility, and publications and yet a lot of varying views on their efficacy not to mention effectiveness[35-36]. And this is before we take into account the complexity that arises from systems biology and the various omics approaches used to do read outs of cell and tissue function and dysfunction[37]. In sum, there is a cataract of information and fragmentation. We have a lot of information on anterior segment biology but a lot less understanding of anterior segment biology.

FIBROSIS AND WOUND HEALING

The idea of too much of this process or factor, too little of that is rather entrenched in multiple areas of investigation. Take the concept of fibrosis. Just like oxidative stress is thought to result from an overload of the natural cellular repairs mechanism, fibrosis is thought to result from an overload of the tissue’s wound healing ability. But rather than subcellular damage seen in oxidative stress, fibrosis involves excessive accumulation of extracellular matrix components that results in a fibrotic scar. This is another example where there is high clinical significance, broad-utility, and biological plausibility. Yet questions remain.

Liver, heart, kidney, lung, and eye can all be affected by fibrosis. Let us take the anterior segment of the eye. We will start with the lens. Posterior capsular opacification (PCO) is an unfortunate and fairly common side effect of cataract surgery. PCO is thought to result from residual epithelial lens cells after capsulorhexis that proliferate, migrate to the posterior capsule and differentiate. These cells then clump and obstruct the light on its way to the posterior segment of the eye. The paradigm that gained the most traction to explain this pathologic process is the so-called epithelial-mesenchymal transition (EMT). Lots of work has gone into the molecular dissection of this pathway involving many proposed transcription factors and effectors. Multiple signaling pathways were also suggested with the transforming growth factor beta (TGFβ) in particular repeatedly implicated in PCO pathogenesis[38-42]. The attractiveness of the paradigm of EMT involvement in PCO goes beyond the identification of plausible transcription

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factors, effectors and signaling pathways. An intriguing and attractive idea is the potential role of TGFβ pathway in the so-called regenerative repair versus fibrotic repair[43]. Yet while the link between TGF and PCO was recognized over 3 decades ago[44-46], as of now, there are no approved drugs against PCO whether targeting the TGF/smad pathway or another. This is despite many promising reports. Here are 30 examples[47-76]. In fact, a recent *Nature* paper observed, “Approved antifibrotics have proven modest in efficacy”[77]. This is for all tissues and not just the anterior segment.

Let us now take a closer look at the cornea. Here the canvas is more vivid, yet interestingly, the dominant EMT and TGFβ paradigms seen in PCO of the lens are crowded out by a wider array of potential players in corneal wound healing. Figure 2 shows the results of an Embase search we performed to illustrate this richness. Importantly, this is not an exhaustive list. We simply pick 30 representative examples—3 for each year of the last decade[78-107]. We limited ourselves to corneal epithelial wound healing while setting aside corneal neovascularization and endothelial pathology, and we focused on small molecule or protein candidates while setting aside gene or cell-based therapies. We can easily compile numerous candidates proposed to be involved in corneal wound healing. One sees a labyrinth of potential hits and an abundance of proposals. Yet underneath this web of ideas, as with the PCO situation, again there is no clear synthesis. We find ourselves with an assortment of potential leads but little consilience. The classic Buddhist parable of the elephant comes to mind. A group of blindfolded fellows is told about something called an elephant, but none aware of its shape or form. One touches the trunk and thinks it must be a snake. Another touches the tail and is confident it must be a rope. And it goes. Leg being mistaken for a tree trunk, ear mistaken for a fan, tusk mistaken for a spear. Each confident they have the solution to the puzzle. Yet each focusing on only a piece of the puzzle while having little awareness of how the other pieces may fit together into

<table>
<thead>
<tr>
<th>Year</th>
<th>Candidate</th>
<th>Species</th>
<th>Model</th>
<th>Reference</th>
</tr>
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<tbody>
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<td>rat</td>
<td>corneal abrasion explant</td>
<td>[Yabuta et al 2014]</td>
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<td>mouse</td>
<td>in vivo</td>
<td>[Yang et al 2014]</td>
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<td>Vitreoctin</td>
<td>human</td>
<td>ex vivo</td>
<td>[Chow and Gerdano 2014]</td>
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<td>MCEC and HEC</td>
<td>[Huang et al 2015]</td>
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<td>human</td>
<td>in vivo</td>
<td>[Lin and Gong 2015]</td>
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<td>Somatostatin</td>
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<td>alka-li induced burn</td>
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<td>eye-on-a-chip device</td>
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<td>BMP3</td>
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<td>2023</td>
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<td>in vivo</td>
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<td>Dexamethasone</td>
<td>rabbit</td>
<td>vescinant (SM)-induced injury</td>
<td>[Mishra et al 2023]</td>
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</table>

Figure 2 Representative examples of candidate effectors involved in corneal wound healing.
a cohesive whole. Now this is just a parable of course. The worry, however, is that we may be seeing hints of it in the different approaches that arise in anterior segment research. So perhaps it is time to unify the clues and put the elephant together.

**CONCLUSION**

George Orwell tells us that, “To see what is in front of one’s nose requires a constant struggle”. The fragmentation in knowledge is not limited to aggregation, oxidative damage or fibrosis. These are just illustrative examples. The issue certainly transcends the anterior segment with multiple domains and research areas that are beckoning to be further developed and untangled. This fragmentation is a challenge although it is also an opportunity. But how can we reconcile discrepant reports and chaotic models of disease and more meaningfully position basic science findings to better inform translational research and ultimately better patient care?

The challenges are formidable. Peer reviewers for many granting agencies and foundations tend to favor relatively safe projects supported with an abundance of preliminary data acting essentially as a promissory note for future publication(s). The expedient measure of success is the output in terms of publications. There is little recognition that perhaps some outcomes can be essentially immeasurable, at least in real time or in short term. Thus, a project whose team worked really hard and imaginatively but came up with negative findings is not viewed as a successful project and its continuation is in serious question. It is as if the underlying biological complexity that a lab happens to encounter becomes a problem for the lab and principal investigator rather than being a problem for the field. Ironically, such expediency seems to be in the expense of longer-term, higher-risk but higher-reward and broader investment. This can lead to fragmentary information; “splitting rather than lumping”; silos; and a false sense of order and simplicity to whatever biological pathway under discussion. Arrows giving a clear sense of direction. Labels giving a sense of conciseness and precision.

One is reminded of Lewis Carroll’s Through the Looking Glass (“When I use a word,” Humpty Dumpty said, “it means just what I choose it to mean—neither more nor less”).

The goal to simplify complex biological processes is certainly understandable. But it comes at a price of giving the illusion of knowing more than we actually do. Important caveats vanishing. Incongruent details fading. Contrary to myth, we tend to assume our ability to hold in our heads the cumulative knowledge we read in the past, when in fact we are unlikely to recall even a fraction of it. Just because such material is accessible via PubMed or an Embase search, does not mean we have incorporated it into our mental models of whatever biological mechanism that happens to be under consideration. Not that everyone is affected to the same degree. But there is an illusion of mastery. Take the jargon commonly used to report on this biological process or that. “TGFβ pathway”, “PCO”, “PTMs”(post-translational modifications), “oxidative damage”, “epigenetic”, “fibrotic”, “anti-inflammatory”, “pro-inflammatory”, “neuroprotective”, and many others. Each designation clearly carrying some meaning at its core yet in reality obscuring a lot of assumptions. The proverbial advice to making profit is an apt analogy: “Buy low; Sell high”. Works great on paper yet one belatedly comes to find out that >80 different molecules as its only source of energy be it an amino acid, a sugar, or a fatty acid. The cell is robust and this robustness can frustrate the typical reductionist approaches of one gene at-a-time or one protein at-a-time or one molecule at-a-time.

Let us also recognize the importance of negative data despite the disincentives to share and publish such outcomes. Equally important is the need to acknowledge potentially conflicting data. Such discordance in findings does not necessarily mean that one set of findings is correct while the other false. Rather, it could be a result of the underlying biological complexity. Perhaps it is a reflection in the differences of the models used, definitions of a disease (e.g., “dry-eye”), biological readouts, “biomarkers” used, endpoints, or a myriad of other known and unknown factors. Here are a couple of recent cautionary tales. A comprehensive review of 162 published biomarkers for major mental disorders found that only 2 estimates met a priori defined criteria for convincing evidence, leading the authors to conclude, “This literature is fraught with several biases and is underpowered”[110]. While in another “reproducibility trial”, 246 biologists analyzed the same datasets and got widely divergent results (https://go.nature.com/3lfVFyU). Add to that, typical pathway figures/cartoons in the various published reviews which tend to give a false sense of order and simplicity to whatever biological pathway under discussion. Arrows giving a clear sense of direction. Labels giving a sense of conciseness and precision.

To illustrate his point about robustness, Wagner writes that even an organism as simple as an *E. coli* can use
in actuality this “insight/precision” is obscuring almost as much as it is informing. It seems to explain, and to a certain degree it does, but not nearly to the level at face value. And it is with many of our cherished buzzwords and lingo. As the American writer Walter Lippmann noted, we are all captives of the pictures in our heads, and we treat “these pictures as if they were the reality”. The author Derek Leebaert was even more astute when he wrote, “We live in a world to be labelled not understood.” There is a false sense of familiarity: if we label something, somehow, we understand it. But the comprehension is not merely labeling. Knowledge is not synonymous with understanding. Admittedly, the two are easy to confuse. It is a subtle trap to fall into, like the fellows examining the elephant each becoming attached to their assumptions and explanations. This is where consilience comes in. Perhaps there could be incentives to motivate people to work together to resolve these seemingly discrepant reports and observations. To bridge the gulf between plausible explanations and real explanations. This is not about your typical “hypothesis-driven” projects. Those are here to stay. More data generation projects will always be needed. But instead of each project or team pushing their own model or favorite hypothesis in relative isolation—a “consilience-driven” project may be warranted. Perhaps even a hypothesis-free project. Minimal prior assumptions. All that is needed is a child-like sense of wonder. Darwin’s bulldog, Thomas Huxley said it best, when he wrote, “Sit down before fact like a little child, and be prepared to give up every preconceived notion, follow humbly wherever and to whatever abyss Nature leads or you shall learn nothing”. Certainly, rigor and reproducibility are necessary and need to be enhanced. But more than that. It is about consilience. It is about dealing with the information overload and reducing complexity, resolving contradictory findings, reducing fragmentation, and reducing silos of basic versus clinical research. It is about understanding and not simply knowing. It is about Wilson’s Unity of Knowledge. Perhaps we can start with the Unity of Anterior Segment. The Darwins would likely approve. Afterall, unity of type (descent with modification), was at the center of Charles’s thesis to Emma.

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