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Serendipity Engineering with Photonics: Harnessing the Unexpected in Biology and Medicine

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ABSTRACT: Serendipity has long shaped transformative scientific discoveries, from penicillin and microwave oven to cosmic microwave background. These advances were not accidents but arose when prepared minds encountered unexpected phenomena in environments that enabled recognition and follow-up. In today's research climate, which often emphasizes narrowly defined goals and short-term deliverables, the role of serendipity is undervalued and frequently left to chance. This review introduces the concept of serendipity engineering: the intentional design of technologies, analytical frameworks, and research cultures that enhance the probability of meaningful chance discoveries. We outline four core principles — (i) expanding the observable space with advanced measurement tools, (ii) preserving anomalies through unbiased data stewardship, (iii) applying analytical methods that surface rare or emergent patterns, and (iv) fostering openness to unexpected results. Emphasis is placed on applications in biology and medicine empowered by advanced photonics and electromagnetism, where system complexity and disease heterogeneity make serendipitous findings particularly impactful. We propose a roadmap for embedding serendipity as a strategic component of 21st-century science, transforming it from a passive hope into an active driver of discovery.

1. INTRODUCTION

Scientific history is replete with discoveries that were not the intended outcome of an experiment but rather the result of unanticipated observations interpreted by prepared and curious minds [1–3]. From Alexander Fleming's chance observation of mold inhibiting bacterial growth, leading to penicillin (1945 Nobel Prize in Physiology or Medicine) [4], to Arno Penzias and Robert Wilson's detection of the cosmic microwave background while attempting to eliminate persistent "noise" from a radio antenna (1978 Nobel Prize in Physics) [5], such breakthroughs demonstrate that chance, coupled with scientific preparedness, can yield transformative advances [6]. Other well-known examples include the discovery of pulsars by Jocelyn Bell Burnell while scrutinizing chart-recorder anomalies (1974 Nobel Prize in Physics) [7], and the invention of the microwave oven after Percy Spencer noticed a candy bar melting in his pocket during radar testing [8] — reminders that serendipity is not confined to a particular discipline or era. More recently, Emmanuelle Charpentier's identification of the CRISPR-Cas9 genome editing system began with unexpected findings on the role of a small RNA (tracrRNA) in *Streptococcus pyogenes*, which turned out to be essential for CRISPR function (2020 Nobel Prize in Chemistry) [9, 10]. One could add Wilhelm Röntgen's observation of X-rays through an unknown fluorescence near a cathode-ray tube (1901 Nobel Prize in Physics) [11];

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Hideki Shirakawa's accidental synthesis of conducting polymers after the addition of excess catalyst (2000 Nobel Prize in Chemistry) [12]; Roy Plunkett's inadvertent creation of polytetrafluoroethylene (Teflon) while experimenting with refrigerants [13]; and Koichi Tanaka's discovery of soft laser desorption while analyzing biomolecules with a mixture of ultrafine metal powder and laser irradiation, which later revolutionized mass spectrometry (2002 Nobel Prize in Chemistry) [14]. In each case, the enabling ingredients were similar: instrumentation that surfaced an irregularity, an observer who recognized its potential significance, and an environment that allowed further probing rather than premature dismissal.

These episodes are not rare curiosities to be celebrated only in hindsight; they illustrate a general engine of progress — the power of the unexpected. Empirical studies suggest that exposure to novelty and atypical combinations is associated with higher-impact scientific outputs, often reflected in citation profiles and breakthrough recognition [3]. Likewise, several documented serendipitous innovations exhibit a "low-cost, high-value" profile, delivering outsized economic returns and shorter development trajectories than those planned [15]. Yet contemporary research ecosystems, which are hypothesis-based, goal-oriented, risk-averse, and metrics-driven, tend to treat serendipity as an unreliable byproduct rather than a cultivable principle [16]. Hypercompetitive funding and evaluation regimes that reward short-term deliverables, narrowly scoped testable hypotheses, and predictable outputs bias investigators toward exploitation over exploration, optimizing for incremental gains at the expense of surprise [17, 18]. Tight scoping, aggressive milestones, and incentives for "clean" narratives can suppress the reporting of anomalies, discourage follow-ups on odd results, and reduce the likelihood that weak signals are recorded, shared, or reanalyzed. The result is a culture in which the very observations that could seed new fields are filtered out as noise.

In this article, we advocate a deliberate and systematic approach to fostering serendipity — *serendipity engineering* — with particular emphasis on biology and medicine, where the complexity of living systems and the unpredictability of disease processes and treatment responses make unexpected findings especially consequential. By serendipity engineering we mean the intentional design of research environments, measurement technologies, analytical frameworks, and cultural practices that increase the likelihood of capturing data with meaningful anomalies and transforming them into unanticipated discoveries. Although the timing and nature of such events cannot be predicted, we can create the physical, intellectual, and institutional conditions that make them more probable (Figure 1) by: (i) expanding the observable space with advanced tools that capture biological phenomena across multiple dimensions and scales with fine resolutions; (ii) retaining, rather than discarding, anomalies through metadata recording, unbiased data storage, and reanalysis pipelines; (iii) establishing analytical strategies that surface rare cell states, emergent biomarkers, or unexpected therapeutic responses; and (iv) cultivating cognitive, social, and institutional openness to results that deviate from established models. Importantly, this vision resonates with the emerging paradigm of "AI for science" [19–21], in which machine intelligence not only analyzes complex datasets but also proposes experiments, guides closed-loop investigations, and accelerates the recognition-to-response cycle that underlies serendipitous discovery. Conceived this way, serendipity engineering functions less as a single method than as an operating system for discovery in the life sciences, enabling researchers to detect, preserve, and pursue the unforeseen in ways that can transform both basic biology and clinical practice.

2. PRINCIPLES AND PRACTICES OF SERENDIPITY ENGINEERING

Central to this approach is the development of platform technologies that increase the dimensionality (e.g., space, time, phase, and molecular specificity), the scale (e.g., spatial, temporal, and intensity ranges) and the granularity (e.g., spatial, temporal, and intensity resolutions) of observation (Table 1, top left part of Figure 2), enabling scientists to detect phenomena that traditional tools would miss. Advanced imaging systems that transcend two-dimensional snapshots in limited fields of view, such as gigapixel microscopy for whole-tissue mapping at subcellular resolution [22], quantitative phase imaging for label-free nanoscale dynamics [23], light-sheet and lattice light-sheet methods for low-phototoxicity volumetric imaging in vivo [24], and ultrafast modalities for capturing micro- to nanosecond events [25], allow researchers to visualize large-scale, functional, and volumetric data from complex, dynamic systems. These capabilities enable, for example, tracking immune cell-pathogen interactions in real time, mapping neural signaling across entire brain circuits, and observing the spatiotemporal progression of metastatic cancer in living organisms.

Beyond imaging, high-throughput microfluidic and lab-on-a-particle platforms capable of probing millions of single cells, interacting cell pairs, or extracellular vesicles under precisely controlled conditions have revealed transcriptionally-defined cell types, stochastic gene-expression bursts, phenotypic switching in bacterial populations, and rare circulating tumor cell (CTC) clusters — events invisible in ensemble measurements [26, 27] (Table 1, top right part of Figure 2). Droplet microfluidics has enabled directed-evolution experiments by screening billions of enzyme variants for improved catalytic activity [28, 29], while inertial and acoustofluidic devices isolate scarce cell types, microbial aggregates, or subcellular structures from complex matrices [30, 31]. Nanovials, crescent-shaped microparticles that act as suspended wells for individual cells, allow probing of thousands of cells, their associated secretions, and underlying gene expression. Such an approach linking secretion with single-cell sequencing (SEC-seq) has uncovered an unexpected lack of correlation between mRNA levels and protein secretion [32]. In parallel, wearable and implantable electronics, such as wearable biosensors, in vivo nanobiointerfaces, and multiplexed electrophysiological arrays, expand the range of physical and chemical signals that can be monitored continuously and noninvasively, turning daily life and naturalistic behavior into experimental contexts [33–39] (Table 1, bottom left part of Figure 2). Coupled with single-molecule sensing, automation, closed-loop experimentation, and "AI for science" approaches

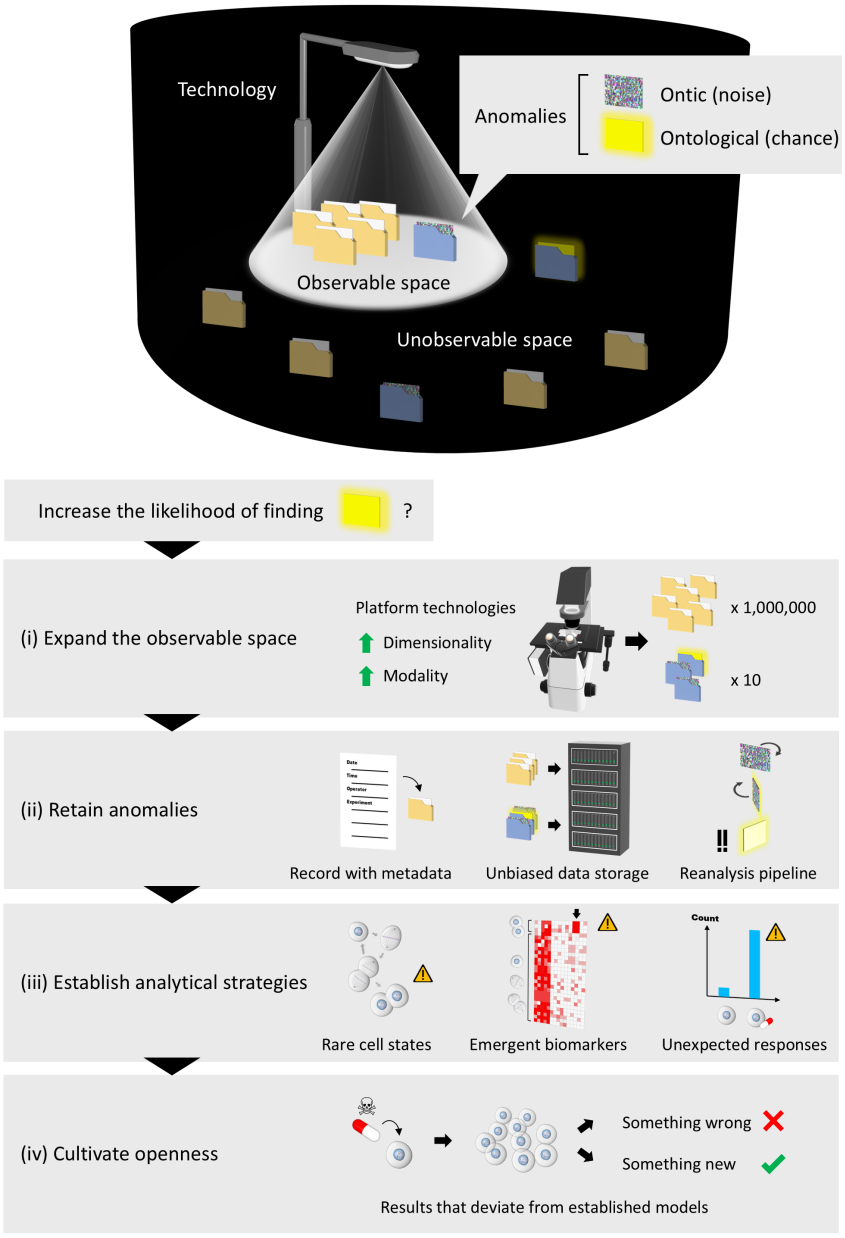

FIGURE 1. Framework for increasing the likelihood of serendipitous discovery. To capture unexpected anomalies within normality and reframe them as ontological chances, shifting conditions of intelligibility, rather than dismissing them as mere ontic noise, a productive framework entails: (i) expanding the observable space with advanced tools that capture biological phenomena across various scales; (ii) retaining rather than discarding anomalies through metadata recording, unbiased data storage, and reanalysis pipelines; (iii) adopting analytical strategies that surface rare cell states, emergent biomarkers, or unexpected therapeutic responses; and (iv) cultivating openness to results that deviate from established models.

including robotic protocols, adaptive experiment design, Bayesian optimization, and active learning, these systems not only broaden what can be measured but also iteratively steer measurements toward informative surprises [1, 19, 40, 41].

Equally important are advances in data and analysis (Table 1, bottom right part of Figure 2). Modern discovery platforms generate high-dimensional, longitudinal datasets whose volume and complexity can overwhelm ad-hoc analysis. Multi-dimensional data integration, such as correlation analysis, probabilistic modeling, and deep learning, connects data with varying dimensionality, scale, and granularity via their intrinsic relationships to create synergy [42–46]. AI and machine learning methods, such as unsupervised anomaly detection, representation learning, causal discovery, graph analysis, and generative modeling, transform such datasets into fertile ground for unexpected findings by highlighting subtle patterns, rare outliers, or emergent behaviors that may lead to new hypotheses [47]. To realize this potential, data must be embedded in provenance-aware data architectures that preserve raw signals, intermediate outputs, and analytic decisions. They should also support versioned reanalysis and ensure that negative or ambiguous results are retained rather than discarded. Practices such as outlier logging, "weirdness dashboards", and scheduled re-mining of archives with improved algorithms help ensure that what ap-

TABLE 1. Summary of key technologies and their serendipity-enabling capabilities.

Category	Key technology	Serendipity-enabling capability	Reference
Imaging	Gigapixel microscopy	Map whole tissues at subcellular resolution	22
	Quantitative phase imaging	Detect nanoscale dynamics without labeling	23
	Lattice light-sheet imaging	Image 3D structures in vivo with low phototoxicity	24
	Ultrafast imaging	Capture micro-nanosecond events	25
Microfluidics	Lab-on-a-particle technology	Probe millions of interacting cell pairs or extracellular vesicles	32
	Droplet microfluidics	Probe millions of single cells	28, 29
	Inertial and acoustic microfluidics	Isolate scarce cell types, microbial aggregates, or subcellular structures from complex matrices	30, 31
Wearable & implantable electronics	Wearable biosensing	Monitor physical and chemical signals from the human body continuously and noninvasively	33-36
	Multiplexed electrophysiological arrays		37
	In vivo nanobiointerfaces		38-39
Artificial intelligence	Multidimensional data integration	Connect data with varying dimensionality, scale, and granularity	42-46
	Unsupervised anomaly detection	Highlight subtle patterns, rare outliers, or emergent behaviors	47
	Representation learning		
	Generative modelling		

pears to be noise today can become a signal tomorrow [47]. Importantly, open-ended exploration should be coupled to confirmatory follow-up, including pre-registered replication, orthogonal assays, and blinded validation, to distinguish genuine discoveries from artifacts and guard against p-hacking or data dredging [1].

3. EXEMPLARS OF SERENDIPITY ENGINEERING IN BIOLOGY AND MEDICINE

Examples of successful serendipity engineering are emerging across disciplines (Figure 3). In cell biology, single-molecule localization methods (e.g., STORM/PALM) have uncovered previously unknown nanoscale architectures in the cytoskeleton and revealed how membrane proteins organize within intact cells [48, 49]. In microbiology, image-activated cell sorting has surfaced rare microbial phenotypes with complex morphologies that elude conventional flow cytometry [50, 51], while diffraction-phase microscopy has captured dynamic transitions during bacterial division and antibiotic stress responses [52]. In neuroscience, large-scale gigapixel or light-sheet imaging now maps connectivity across entire brain regions while preserving synapse-level detail, revealing unexpected long-range projections and rare structural motifs [53, 54]. In cancer biology, optical-resolution photoacoustic microscopy has visualized microvascular remodeling and hypoxia-driven angiogenesis in vivo [55]; fluorescence-lifetime imaging flow cytometry has uncovered rare tumor subpopulations and tracked drug-induced nuclear dynamics at scale [56–58]; and inertial microfluidics has enabled isolation of rare CTCs, bacterial aggregates, and activated and highly deformable leukocyte populations from blood for early cancer and sepsis detection [31]. In hematology, massive image-based single-cell profiling has shown that circulating platelet aggregates possess diagnostic and prognostic value in cardiovascular disease and COVID-19, revealing disease-specific aggregate signatures invisible in bulk assays [59, 60]. In physiology, multimodal wearable biosensors provide continuous, noninvasive monitoring of metabolites, electrolytes, and stress biomarkers in sweat or interstitial fluid, disclosing transient physiological states previously unmeasurable outside clinical settings [36, 61]. In clinical oncology, digital breast tomosynthesis has unexpectedly improved early breast cancer detection by providing 3D information and unveiling lesions obscured in conventional mammography [62], while low-dose computed tomography has surprisingly revealed sub-centimeter lung nodules associated with reduced cancer mortality in high-risk populations [63]. Across these domains, platform technologies designed for breadth, resolution, adaptability, and reanalysis have expanded the observable landscape, enabling detection of rare, transient, or complex phenomena that legacy tools would have missed or filtered out.

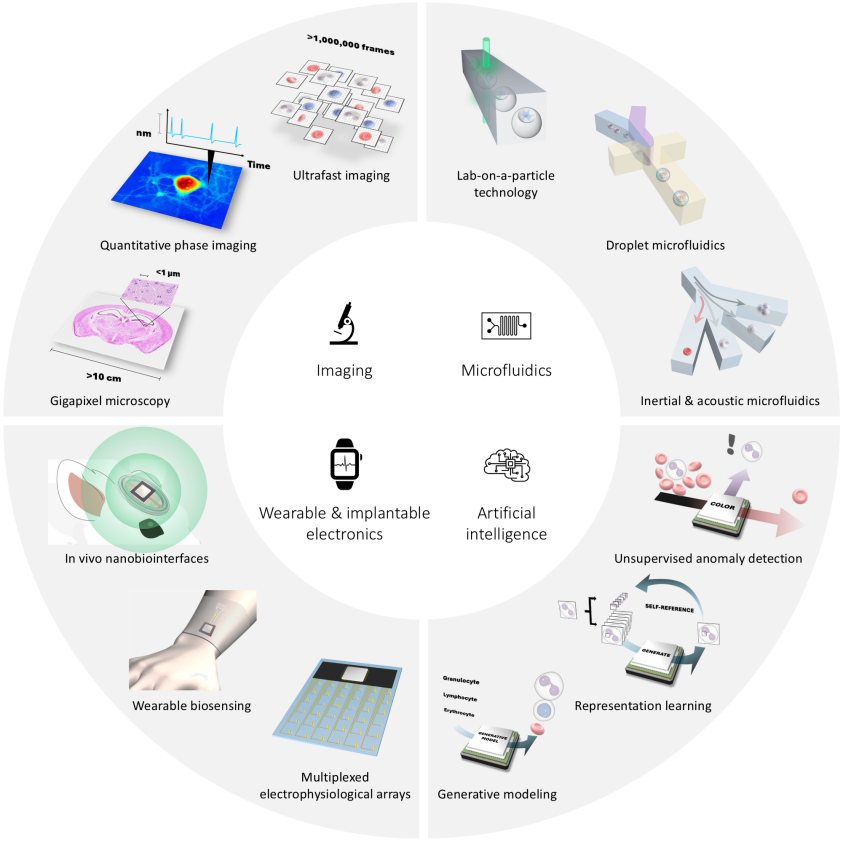

FIGURE 2. Representative technologies that expand the dimensionality (e.g., space, time, phase, and molecular specificity), the scale (e.g., spatial, temporal, and intensity ranges), and the granularity (e.g., spatial, temporal, and intensity resolutions) of observation. Imaging: gigapixel microscopy, quantitative phase imaging, ultrafast modalities. Microfluidics: high-throughput, droplet-based, inertial, and acoustofluidic systems. Wearable and implantable electronics, such as wearable biosensors, in vivo nanobiointerfaces, and multiplexed electrophysiological arrays. Artificial intelligence: anomaly detection, representation learning, generative modeling. Together, these technologies broaden the landscape of observable biological phenomena and increase the chance of detecting the unexpected.

4. TOWARD SYSTEMIC CHANGE: POLICY, EDUCATION, AND INSTITUTIONAL DESIGN

To translate these individual successes into systemic change, broader shifts are required at the levels of research policy, education, and institutional design (Figure 4) [16, 18, 64]. Funding mechanisms should support open-ended research enabled by broadly applicable technologies including shared instruments, cross-disciplinary cores, and community datasets rather than exclusively outcome-driven projects [65, 66]. Calls can explicitly allocate space for exploratory aims, staged validation, and archiving/anomaly pipelines. Institutions can lower barriers to interdisciplinary collaboration through co-appointed faculty lines, shared graduate programs, and incentive structures that reward tool building and cross-field impact [67, 68]. Education and mentoring should cultivate intellectual humility, epistemic curiosity, and the capacity to pivot in response to unexpected findings; practical training can include modules on anomaly detection, data stewardship, and experimental design for exploration [69, 70]. Culturally, labs can normalize "odd result seminars," near-miss reports, and internal registries of unexplained observations with time-stamped metadata and hypotheses-to-watch lists [70].

At the same time, we need both quantitative and qualitative frameworks to assess the serendipity potential of tools, workflows, and organizations. A provisional "serendipity index" (Figure 4) might combine (i) exposure (dimensionality, coverage, and duty cycle of measurement), (ii) retention (fraction of raw data archived, richness of metadata, frequency of reanalysis), (iii) recognition (algorithmic sensitivity to outliers, diversity of expert review), and (iv) response (time from anomaly to validated result, availability of orthogonal assays) [3, 71]. While a one-for-all metric may not be feasible for diverse research areas and topics, this index should aim to evaluate the degree of extension achieved by a proposed platform technology or methodology — a contrastive metric that highlights how much more likely it becomes to detect rare, transient, or meaningful anomalies. Bibliometric signals (e.g., cross-field citation bursts), laboratory-level process metrics, and case-study audits could help prioritize investments [71]. Complementary policies such as credit for negative and exploratory results, repositories for "failed" experiments, reproducibility incentives, and open hardware/standards would further reinforce the ecosystem [1, 72]. Ethical guidelines should emphasize privacy-preserving analytics for human data, safeguards against over-interpretation, and transparent reporting of exploratory versus confirmatory phases.

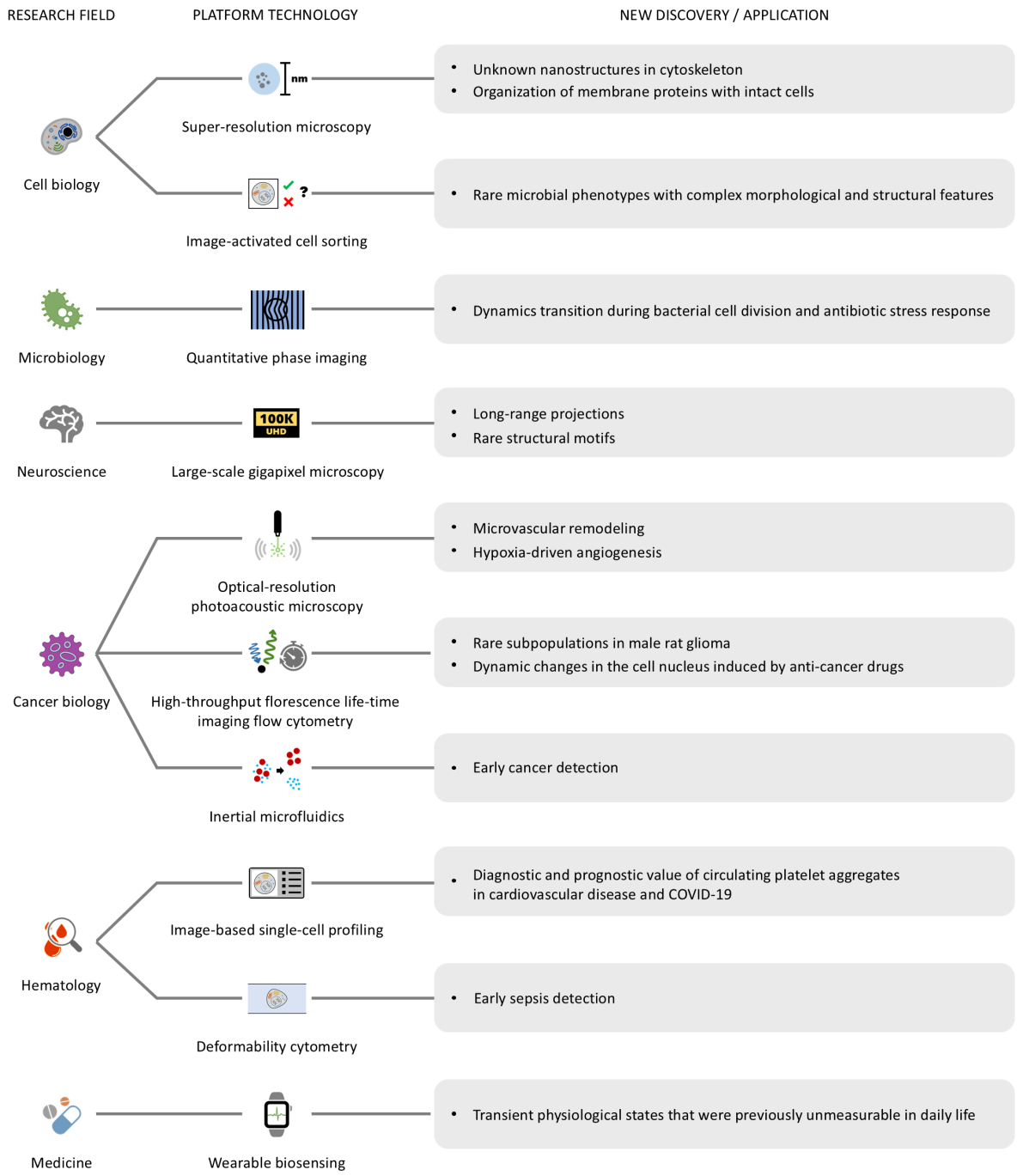

FIGURE 3. Exemplars of serendipity engineering across disciplines. Illustrative cases where platform technologies revealed unexpected biological insights. Cell biology: super-resolution microscopy uncovered nanoscale cytoskeletal structures. Microbiology: image-activated cell sorting identified rare microbial phenotypes. Neuroscience: gigapixel and light-sheet imaging revealed unrecognized structures. Cancer biology: photoacoustic microscopy and fluorescence lifetime imaging flow cytometry uncovered intricate tumor microenvironments and rare subpopulations. Hematology: image-based profiling revealed disease-specific platelet aggregates. Medicine and physiology: wearable biosensors captured transient physiological states.

While cultivating serendipity offers considerable promise, its risks must be carefully managed. Serendipitous insights often arise from reanalyzing or integrating heterogeneous datasets that may contain sensitive personal or biomedical information. An emphasis on the unexpected can also encourage overinterpretation of anomalies or divert resources from rigorously validated research programs. Moreover, AI systems trained on unbalanced or incomplete datasets may inadvertently amplify inequities, influencing which deviations become detectable or prioritized in the first place. Institutions may further face challenges in evaluating success for initiatives defined by uncertainty rather than predefined outcomes. Mitigating these risks requires grounding serendipity-oriented research in strong methodology, transparency, and reproducibility. Data privacy

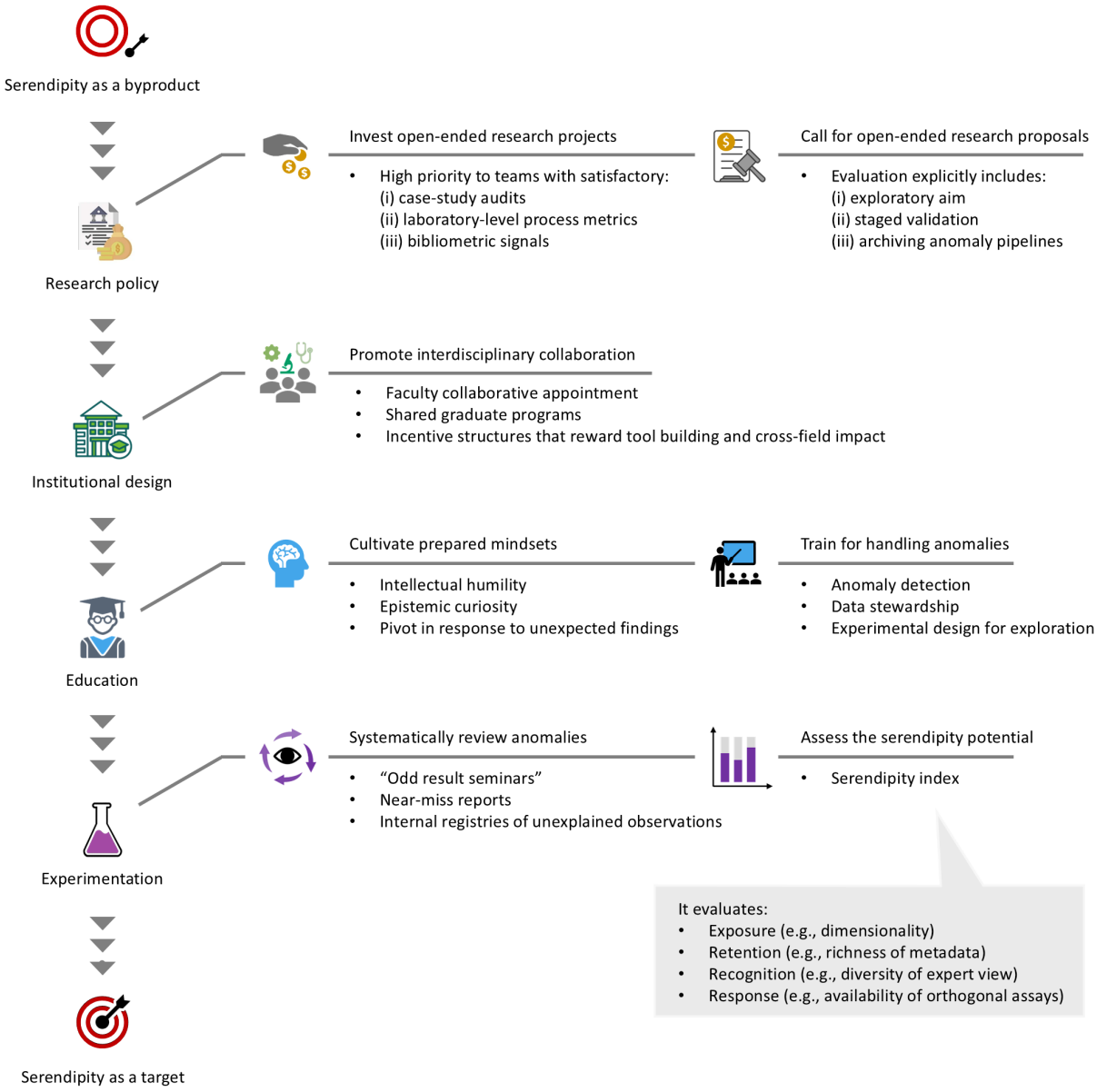

FIGURE 4. Broad shifts required at the level of research policy, education, and institutional design. Serendipity can be transformed from a byproduct of science into a deliberate target by embedding it into policy, institutional design, education, and laboratory practices. Key elements include open-ended funding programs, interdisciplinary collaboration, cultivation of prepared mindsets, anomaly-handling training, and systematic review of unexpected results. The proposed "serendipity index" evaluates exposure, retention, recognition, and response to quantify serendipity potential.

protections, including de-identification, consent clarity, and secure data governance, are essential to prevent misuse and maintain public trust. Cross-disciplinary review and mentorship can help distinguish meaningful signals from artifacts. Complementary practices, such as maintaining balanced portfolios that include both exploratory and hypothesis-driven studies, will help ensure that the pursuit of discovery remains both innovative and reliable.

5. CONCLUSIONS

More than 150 years ago, Louis Pasteur reminded us that "*dans les champs de l'observation, le hasard ne favorise que les esprits prepares* (in the field of observation, chance favors only the prepared mind)." In today's biological and medical sciences, marked by increasing complexity, interdisciplinarity, and long experimental cycles, it is unrealistic to be prepared for every eventuality. What we can do, however, is intentionally design our research environments and practices to remain receptive to the unexpected. Serendipity engineering does not replace the rigor of hypothesis-driven science; rather, it complements it by embedding discovery under uncertainty as a deliberate principle. By expanding the scope of what we can observe, preserving anomalies, applying analytical methods attuned to novelty, and nurturing a culture that values curiosity-driven follow-up, we can transform serendipity from a passive hope into an active strategy. To realize this paradigm shift, researchers must consciously build serendipity-enabling habits into their research practice, funders must stay open to invest in exploratory and high-variance research, and institutions

must reward intellectual risk-taking and open collaboration. As many disciplines approach diminishing returns from targeted innovation, the greatest breakthroughs of the 21st century may well emerge from this deliberate readiness to recognize and act upon the unforeseen. Serendipity, often dismissed as mere luck, should instead be regarded as a strategic asset — one that can be systematically cultivated to drive the next wave of transformative advances in science and medicine.

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