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The Scientific Method and Advancing Omic Technologies: Breakthroughs in Psoriatic Disease

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ABSTRACT. A morning workshop addressing the topic of "What You Always Wanted to Know About Science but Were Afraid to Ask" was held at the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) 2024 annual meeting. In brief, Profs. Stephen Pennington and Nicole Ward covered the effect of recent multiomics and artificial intelligence technologies on psoriatic disease research by introducing these revolutionary advances in the context of the traditional scientific method. The workshop presented the fundamentals of genomics, transcriptomics, proteomics, and metabolomics; the limitations and challenges of these technologies; and current methods to present and interpret big data.

Key Indexing Terms: artificial intelligence, GRAPPA, precision medicine, psoriasis, psoriatic arthritis

The scientific method: a refresher

The scientific method is a systematic approach to research and is often applied as a series of discrete steps (Table).[1] The design of the method ensures that clinical practice and medical interventions are evidence-based and a result of reproducible and rigorous research. It is vital that critical thinking is applied at each step.

Karl Popper's philosophy of science influenced the formulation of the scientific method.[2,3] His core idea required that scientific theories be falsifiable, or, in other words, the theory should comprise testable predictions—or hypotheses—able to be proven false by a single counter example. Scientific knowledge advances through cycles of proposing, testing, and either accepting or rejecting hypotheses based on experimental outcomes. This iterative process leads to robust, refined theories over time.

Making a hypothesis is fundamental to the scientific method, and a hypothesis is different from a theory.[4] A *hypothesis* is an educated guess based on observations and existing knowledge that a researcher decides to test using particular methods of study. A *theory* is an explanation of some aspect of the natural world that is well-substantiated based on a body of evidence and multiple verified hypotheses. Whereas a hypothesis is specific, testable, temporary, and refutable, a theory is broad and integrates a large body of knowledge.

Technological advances in biomedical sciences: the multiomics revolution

In recent years, a multitude of datasets have been, and are being, generated using advancing omics technologies, including genomics, epigenomics, transcriptomics, proteomics, metabolomics, clinomics, and others.[5] These technical advances require the creation of new tools and code to analyze and integrate large datasets to draw conclusions and generate new testable hypotheses. This GRAPPA workshop focused on genomics, transcriptomics, proteomics, and metabolomics.

Genomics refers to studying whole genomes (ie, complete sets of DNA) using gene sequencing and mapping through high-throughput sequence analysis. To date, genomic analyses have identified more than 80 genetic loci associated with psoriasis (PsO), including *HLA-Cw6, interleukin (IL)-12B*, *IL-23R*, and *LCE3B/3C.*[6] Some of these PsO disease susceptibility loci are shared with psoriatic arthritis (PsA).[7]

Transcriptomics uses high-throughput sequence analysis to study the complete set of RNA transcripts produced by "reading" the genome, providing insights into gene expression. Transcriptomic technologies traditionally identified mRNA transcripts, but other RNA forms, including long noncoding RNAs and micro-RNAs, can also be studied.[5] Each transcriptome is distinct to a type of cell, and transcripts can vary over time and with changing conditions. For example, lesional skin from patients with PsO exhibits elevated *IL17A* and *IL23* transcript expression compared to nonlesional skin, and effective treatment lowers expression levels of these transcripts.[8,9] Early bulk transcriptomic (RNA sequencing [RNA-seq]) studies investigated transcriptomes of whole tissues. More recently, single-cell RNA-seq (scRNA-seq) allows more specific analysis of gene expression in individual cells.[10] scRNA-seq, coupled with spatial transcriptomics and sophisticated bioinformatic analysis, gives insights into both the location and gene expression of

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Table. Steps in the scientific method.

	Step	Explanation	Example
1	Observation	Medical research often begins with an observation or a question.	Some patients respond to a treatment whereas others do not.
2	Hypothesis formation	A testable statement predicting the relationship between measurable variables, based on the initial observation.	Genetic variation affects patients' responses to a certain medication.
3	Experimentation	Methods used to test the hypothesis with the intention of disproving it. Experiments may be based in the laboratory using models of health or disease or may involve clinical trials. Experiments should be performed in exactly the same way several times to compare data across replicates.	A randomized controlled trial to test whether a new drug is effective for patients with a genetic variation.
4	Data collection and analysis	Data from experiments are collected and analyzed methodologically to determine whether the results support or refute the hypothesis. This step involves statistical analysis of repeated experiments to compare one condition to another, ensuring the findings are not due to chance.	Patient outcomes on the tested drug are analyzed together with their genetic data to determine whether the new drug is more effective for those with the specific genetic variation compared to those without.
5	Conclusion	Researchers draw conclusions based on the comprehensive data analysis. Depending upon whether the results support or refute the original hypothesis, the hypothesis may be revised or new hypotheses may be developed.	The results indicate that the new drug is significantly more effective for patients with the genetic variation than without, leading to personalized treatment recommendations.
6	Publication and peer review	Researchers submit their findings to scientific journals, where other experts in the field review the work. This peer review process is crucial for maintaining scientific integrity.	Manuscript published in scientific journal.
7	Replication and further research	Other researchers replicate the study to verify the results. Consistent findings across multiple studies strengthen the evidence and can lead to widespread changes in medical practice.	A different research group repeats the study in a different patient population.

cells in tissues and can infer cell-cell interactions. Initial reports combining scRNA-seq with spatial transcriptomics reported new cell populations (CD20+ B cells) in lesional skin that had not previously been thought to be involved in PsO. These studies also demonstrated a proinflammatory role for fibroblasts, dissected roles for different layers of the epidermis in PsO, and determined how keratinocytes within each epidermal layer communicate with immune cells to drive inflammation.[11,12]

Proteomics analyzes an entire set of proteins using liquid chromatography and mass spectrometry (MS).[13] Liquid chromatography separates proteins or peptides according to their physicochemical properties. MS characterizes molecules based on their mass to charge ratio, where the intensity of the signal (ion) reflects the quantity of the protein or peptide. Recently, cytometry by time-of-flight (CyTOF) and single-cell MS have allowed detection of protein expression changes within individual cells.[14] CyTOF has identified impaired skin trafficking of circulating regulatory T cells in PsO and phenotypic differences in circulating and synovial fluid T cells in PsA and rheumatoid arthritis.[15-17]

Metabolomics examines a complete set of metabolites to provide information about the metabolic state of an organism or a cell. Metabolites are low molecular weight biomolecules that may be metabolically active or downstream products of biological processes.[18] They can be identified and quantified using nuclear magnetic resonance as well as MS. Single-cell metabolomics combined with bioinformatic analyses have elucidated how individual cell metabolism changes in a disease state and how these changes drive cell communication resulting in inflammation or disease remission. Metabolomics has identified changes in amino acids and lipid metabolism in psoriatic disease, including dysregulated metabolism of arachidonic acid.[18]

Examples of presentation and interpretation of big data

The vast amounts of data generated through omics methods require accompanying creative and innovative analysis and presentation methods. Commonly used data presentation methods include heatmaps, uniform manifold approximation and projection (UMAP) plots, and Circos plots. Prof. Nicole Ward used examples from her GRAPPA meeting keynote lecture to explain approaches used in Ma et al's study on PsO skin using scRNA and spatial sequencing.[12]

Heatmaps present differences in gene expression across individual samples or conditions. Figure 1A illustrates a heatmap with each row representing a gene and each column representing a cell type (grouped 1-6).[12] Each cell type is represented in Figure 1B by a user-generated color code, demonstrating spatial localization of each cell type within a lesional PsO plaque. Each cell type is defined and clustered by their most highly expressed genes.

UMAP plots are also used to visualize gene expression changes identified by scRNA-seq.[19] Figure 2 shows a UMAP plot generated from scRNA-seq from healthy normal skin (NS), nonlesional PsO skin (PN), and lesional PsO skin (PP). In these plots, each point represents an individual cell, colored by cell type, and cells are placed on the map based on gene expression levels. Cells of the same type cluster together in these plots due to similar gene expression. Notably, different subsets of the same cell type localize to different areas within the plot, such as keratinocytes derived from different layers of the epidermis

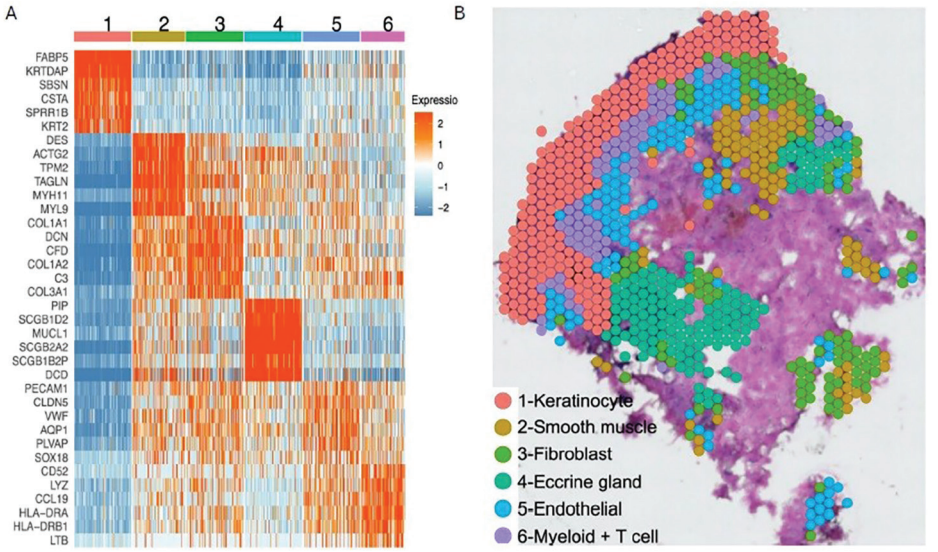

Figure 1. Heatmaps present changes in gene expression. (A) Heatmap showing the representative marker genes for each cluster in B. The color scale represents the scaled expression of each gene. (B) Spatial plot for 764 spots colored by clusters; the coordinates of the spot correspond to the location in the tissue. Figure reproduced from Ma et al[12] with Creative Commons license: https://creativecommons.org/licenses/by/4.0/

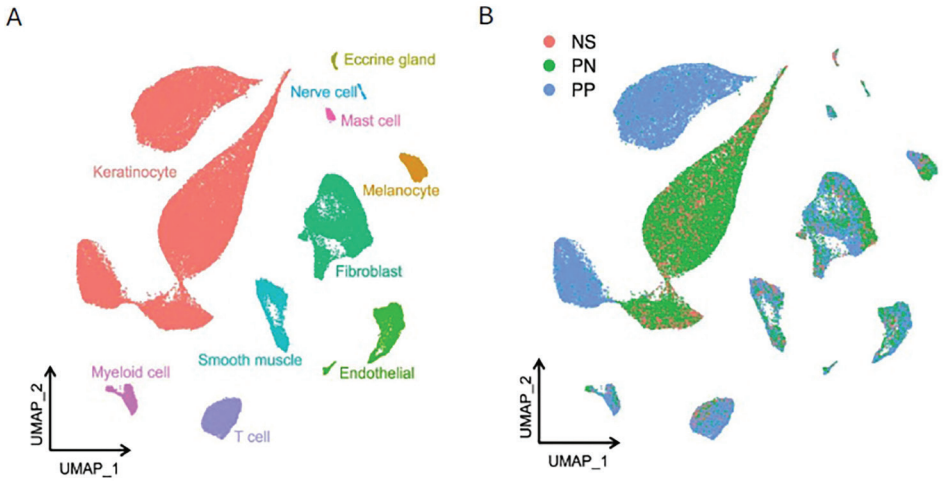

Figure 2. UMAP plots present cell populations clustered by gene expression. (A) UMAP plot showing 67,378 cells colored by cell types. (B) UMAP plot showing the cells colored by disease conditions. Figure reproduced from Ma et al[12] with Creative Commons license: https://creativecommons.org/licenses/by/4.0/. PN: nonlesional psoriasis skin; PP: lesional psoriasis skin; NS: healthy normal skin; UMAP: uniform manifold approximation and projection.

(Figure 2A). Figure 2B shows the same cell types as in Figure 2A, with individual colors representing NS, PN, and PP skin. Note the significant gene expression changes in 2 keratinocyte clusters in PP skin and in 2 different clusters in PN skin. Changes in gene expression in endothelial cells, T cells, myeloid cells, fibroblasts, and mast cells were also observed in PP skin compared to the other groups (Figure 2B).

Additional tools allow further analyses beyond upregulation or downregulation of differentially expressed genes. The gene ontology knowledge base holds information on the functions of genes and allows interpretation of enriched pathways, for example, multiple changes in transcripts related to proliferation or differentiation pathways.[20] Reactome is a comprehensive and freely available database of biological pathways.[21] New codes for large datasets can also allow inference of cell-cell interactions based on receptor-ligand pairings. For example, CellChat is an R package designed to infer, analyze, and visualize cell-cell communication derived from scRNA-seq datasets.[22] The predicted ligand-receptor interactions can be presented using Circos plots.[23] Figure 3A shows predicted ligand-receptor interactions between keratinocytes in different layers of the epidermis, with arrows marking each ligand-receptor interaction. The results of several interaction prediction analyses between different cell types can be presented using a heatmap, as in Figure 3B, which shows a higher number of ligand-receptor pairs in PP compared to NS among different cell types. Rows

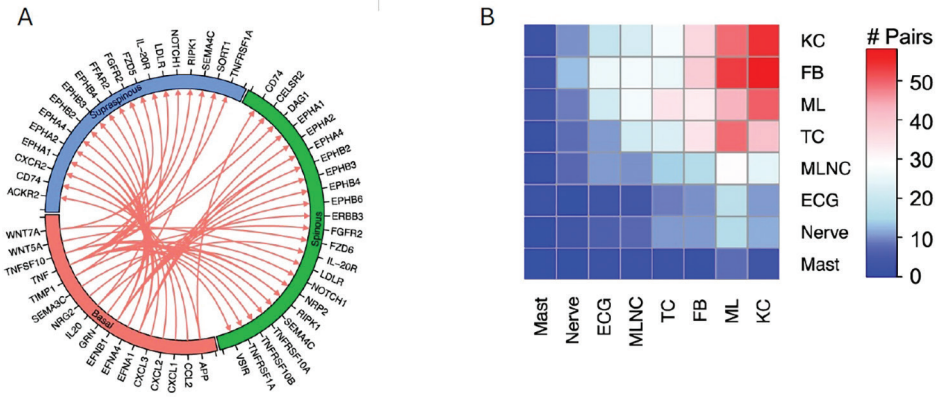

Figure 3. Circos plots present cell-cell communication by ligand-receptor pairs. (A) Circos plot showing ligand-receptor interactions, with a higher score in PP compared to NS. Ligands are expressed by basal keratinocytes, whereas receptors are expressed by other cell subtypes. (B) Heatmap showing the number of ligand-receptor pairs, with a higher score in PP compared to NS among the cell types. Each row represents ligands expressed and each column represents receptors expressed by the named cell types. The color scale represents the number of ligand-receptor pairs. Figure reproduced from Ma et al[12] with Creative Commons license: https://creativecommons.org/licenses/by/4.0/. ECG: eccrine gland cells; FB: fibroblasts; KC: keratinocytes; ML: myeloid cells; MLNC: melanocytes; NS: healthy normal skin; PP: lesional psoriasis skin; TC: T cells.

represent ligands and columns represent receptors expressed by the indicated cell types. The color scale represents the number of ligand-receptor pairs; in this example, keratinocytes and fibroblasts have the most predicted interactions. Transcriptional changes do not necessarily reflect changes in protein expression or activity, so biological relevance of transcriptomic analyses must be further validated.

Publicly available data

"Big datasets" are frequently required to be made publicly available after publication of the findings using repositories such as the gene expression omnibus (GEO) and Proteomics Identifications (PRIDE) database.[24,25] To allow data analyses by others, raw FASTQ files are uploaded along with metadata (ie, the "code break"), which provides necessary details about individual files and experimental details. Online resources like the Human Protein Atlas and Human Cell Atlas integrate data from different omics technologies.[26,27]

Limitations and challenges of big data

Although big data generation offers significant potential for uncovering new biological insights, several challenges remain, such as variable data quality and integrity and a lack of standardized data formats and protocols. Independent validation adds rigor to the scientific data but can be resource-intensive and time-consuming. Differences in data structure and format often make data from different sources difficult to integrate and compare. Still, handling large datasets to ensure that findings are reproducible and can be used by others continues to improve as journals and funding agencies implement data sharing requirements, including storage of accurately curated data together with relevant metadata. There are also legal, ethical, and social implications to data sharing, including patient and researcher consent for secondary data use, data ownership, intellectual property rights, and equitable access to resources. International collaborations add challenges due to differences in regulatory requirements. For example, GRAPPA members in large international consortia such as HIPPOCRATES (Health Initiatives in Psoriasis and Psoriatic Arthritis Consortium European States) know the challenges of implementing data sharing agreements among consortia partners and developing a platform for secure data storage and access that meets the requirements of multiple institutions worldwide.

Artificial intelligence

Artificial Intelligence (AI) allows computers to learn from data, adjust to new inputs, and perform human-like tasks.[28,29] Most examples of AI rely heavily on deep learning and natural language processing. The process begins with a foundation model, in which the model is trained by processing large amounts of raw, unstructured data to recognize patterns in the data. The model makes predictions and adjusts itself to minimize the difference between its predictions and actual data. The foundation model is tailored (tuned) to the AI application and produces outputs based on prompts. The output is continually assessed and improved.

Generative AI is AI that creates original content—such as text, images, video, audio, or software code—in response to a user's prompt or request. It offers productivity benefits and is increasingly used. By 2026, over 80% of organizations are projected to deploy generative AI applications, according to a conversation Prof. Stephen Pennington had with Microsoft Copilot in July 2024. Publishing houses have recently written guidelines on the extent of AI usage allowed when writing articles for publication, with some offering their own AI-powered writing assistance. AI can also trace plagiarism and data manipulation in published manuscripts and can be reported in online blogs such as Retraction Watch (https://retractionwatch.com/).

AI platforms are developing fast and not all are equal. Depending on the platform, the question posed and any linked

data will automatically go into the public domain, possibly reducing ability to claim intellectual property. Importantly, all AI platforms, including those used to analyze big data, are inherently based on what has already been published, some of which is known to be either incorrect or not reproducible.[30,31]

Conclusion

In summary, omics technologies and AI are revolutionizing biomedical research. They provide exciting opportunities but require adaptations and new collaborations. While learning to use these powerful tools, we should continue to apply the scientific method and critical thinking.

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COMPETING INTERESTS

NLW received research funding from Sun Pharma. The remaining authors declare no conflicts of interest relevant to this article.

ETHICS AND PATIENT CONSENT

Institutional review board approval and patient consent were not required.

PEER REVIEW

As part of the supplement series GRAPPA 2024, this report was reviewed internally and approved by the Guest Editors for integrity, accuracy, and consistency with scientific and ethical standards.

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