Editorial

DOI: 10.5582/bst.2026.01089

Revisiting long-standing biological questions through evolving technologies

John J. Rossi*

Center for RNA Biology & Therapeutics, Beckman Research Institute of City of Hope, Duarte, CA, USA.

SUMMARY: Advances in biological sciences and technology have continuously reshaped the questions that researchers are able to address. Over the past several decades, developments in DNA sequencing, mass spectrometry, genome analysis, and omics technologies have transformed not only biomedical research itself, but also the interpretation of observations that previously remained unresolved because of technical limitations. This Editorial reflects on how evolving technologies allow long-standing scientific questions to be revisited across generations of research. Two examples illustrate this process. One concerns the structural re-analysis of a *Streptomyces* lectin first studied in the 1970s, whose molecular features could only later be clarified through advances in mass spectrometry and expanding genetic databases. The second involves a recent transcriptomic re-examination of ethanol-associated lifespan responses in *Caenorhabditis elegans*, where modern RNA-seq approaches provided pathway-level insights that were not technically accessible in earlier studies. Together, these examples highlight that scientific progress often emerges not only from asking new questions, but also from revisiting unresolved observations using new technologies and perspectives.

Keywords: transcriptomics, omics technologies, scientific continuity, biological discovery, RNA sequencing

Recent advances in biological sciences and technology have profoundly influenced biomedical research and the way scientific questions are approached. During the 1970s, when many current senior investigators began their scientific training, technologies in protein chemistry and molecular biology were undergoing rapid development. These methodological advances fundamentally changed what could be experimentally examined and interpreted.

Among the most influential developments was the establishment of amino acid and DNA sequencing technologies. Frederick Sanger first determined the amino acid sequence of insulin, representing a landmark achievement in protein chemistry (*1,2*). Sanger and his colleagues introduced the "dideoxy" chain-termination method for sequencing DNA molecules in 1977, also known as "Sanger Sequencing" (*3*). Though the first DNA sequencing method was introduced by Maxam and Gilbert, which was quickly followed by the more facile Sanger method. This Sanger sequencing was the most widely used form of sequencing for over 40 years, a technology that became the foundation of molecular biology for several decades. These advances enabled increasingly detailed analyses of genomes, gene expression, and cellular regulation, ultimately leading to contemporary genomics and transcriptomics.

The continuing expansion of genetic databases, combined with improvements in sequencing platforms, mass spectrometry, and computational biology, has accelerated biological research since the early 2000s. Modern omics technologies now allow comprehensive analyses of molecular networks, signaling pathways, and dynamic cellular responses at levels that were previously impossible to achieve. As a result, observations that once remained descriptive or mechanistically unresolved can now be revisited using broader and more integrated analytical approaches. Developments of major concepts and technologies in biology are summarized in Table 1.

One example of this process involves earlier work by Dr. Fujita-Yamaguchi on a lectin isolated from *Streptomyces* (*4*). During her doctoral studies in the 1970s at the University of Tokyo, she attempted to determine the primary structure of this lectin protein; however, the available technologies at the time were insufficient to resolve highly similar repetitive domains within the molecule (*5*). After achieving her most important early work of purifying the human insulin receptor (*6*) and conducting research in the insulin and IGF-I signaling field as a PI at Beckman Research Institute of City of Hope (COH) and Tokai University,

Table 1. Developments of concepts & technologies in respective fields of biology

	19th century	Early 20th century	1950's	1960's	1970's	1980's	1990's	2000-
Classical genetics Biochemistry	Mendel, Darwin	Metabolic pathways Enzymes	DNA as genetic material					
Modern genetics		Phage, virus, Drosophila as models	'53: Double-helix model for DNA '57:Central dogma of biology	Discovery of codons & roles of RNAs	DNA sequencing methods	Genome analysis	Genetic databases expansion	**Omics technologies:** Genomics: Transcriptomics: Proteomics: Metabolomics
Protein structure/ function		Isolation of abundant proteins by chromatography X-ray crystal structures of proteins, and other biological molecules	'53: Primary structure of insulin NMR	Affinity chromatography Purification of low expression proteins	Protein data bank expansion	Mass spectrometry Signaling pathway analyses Immunoblots Fluorescent probes Confocal microscopy	LC-MS/MS for protein sequencing	Epigenomics: Spatial Omics: Single-cell Analysis Full genome sequences of organisms CRISPR/Cas9 technology
Genetic engineering Gene manipulation				Restriction enzymes Plasmids	Genetic engineering **'78:Humulin*,** the first biosynthetic human insulin product	Genetic testing for SNPs by PCR **Humanized antibodies**** Antibody therapeutics	Production of a variety of biomedicines	

***In 1978,** scientists at City of Hope and Genentech developed a method for producing biosynthetic human insulin (BHI) using recombinant DNA technology (*10*). Eli Lilly & Co. signed an agreement with Genentech to use the rDNA method to make human insulin commercially available. ****In 1984,** Riggs and Cabilly at City of Hope and Herbert Heyneker and his group at Genentech were able to describe and patent the method for making humanized monoclonal antibodies starting from mouse monoclonal antibodies (*11*).

she returned to COH in 2014 and collaborated with Dr. Markus Kalkum to restart her graduate work, which was never completed. After advances in mass spectrometry and expansion of genetic databases, the lectin structure could finally be clarified through collaborative work at City of Hope (*5,7,8*). These later studies demonstrated how technological progress enabled re-analysis of a biological problem that had remained unresolved for many years.

A similar perspective can be applied to another study presented in this issue of *BioScience Trends* (*9*): "Gene expression profiling of the L4-stage nematode *Caenorhabditis elegans* following ethanol exposure" by Miyazawa *et al*. This research originated from earlier investigations initiated more than two decades ago at Tokai University, where the effects of ethanol exposure on *C. elegans* lifespan were examined using conventional experimental approaches. Although lifespan-associated phenotypes were reproducibly observed, mechanistic analyses at that time were necessarily limited to selected candidate pathways and could not comprehensively evaluate global transcriptional responses.

In the present study, the authors revisited this long-standing experimental framework using time-resolved RNA-seq analysis. Rather than establishing definitive causal mechanisms, the study provides transcriptomic and pathway-level perspectives on stress-response programs and longevity-associated pathways potentially linked to ethanol exposure in *C. elegans*. The observed patterns, including changes in detoxification-related pathways and stress-response signaling, illustrate how modern transcriptomic approaches can provide broader biological context for previously observed phenotypes.

Importantly, the value of such studies may extend beyond the specific biological phenomenon itself. They also demonstrate how scientific observations that once exceeded available technical capabilities can acquire new meaning when revisited through evolving methodologies. In many cases, scientific progress arises not only from generating entirely new questions, but also from returning to unresolved observations with new tools, analytical frameworks, and perspectives.

In this sense, technological advancement does not merely accelerate science; it also allows unfinished scientific questions to be revisited across generations of research.

Funding: None.

Conflict of Interest: The author has no conflicts of interest to disclose.

References

1. Sanger F, Tuppy H. The amino-acid sequence in the phenylalanyl chain of insulin. 2. The investigation of peptides from enzymic hydrolysates. Biochem J. 1951; 49:481-490.
2. Sanger F, Thompson EO. The amino-acid sequence in the glycyl chain of insulin. Biochem J. 1952; 52:iii.
3. Sanger F, Nicklen S, Coulson AR. DNA sequencing with chain-terminating inhibitors. Proc Natl Acad Sci U S A. 1977; 74:5463-5467.
4. Fujita Y, Oishi K, Suzuki K, Imahori K. Purification and properties of an anti-B hemagglutinin produced by Streptomyces sp. Biochemistry. 1975; 14:4465-4470.
5. Fujita-Yamaguchi Y, Bagramyan K, Yamaguchi Y, Ikeda A, Dohmae N, Hong TB, Kalkum M. Mass spectrometric revival of an l-rhamnose- and d-galactose-specific lectin from a lost strain of Streptomyces. J Biol Chem. 2018; 293:368-378.
6. Fujita-Yamaguchi Y, Choi S, Sakamoto Y, Itakura K. Purification of insulin receptor with full binding activity. J Biol Chem. 1983; 258:5045-5049.
7. Fujita-Yamaguchi Y, Muramatsu H, Tapia A, Bagramyan K, Desai M, Takehana Y, Igarashi M, Yamaguchi Y, Kalkum M. Proteolytic Processing, Maturation, and Unique Synteny of the Streptomyces Hemagglutinin SHA. Microbiol Spectr. 2021; 9:e0076621.
8. Quijano JC, Natsuyama H, Tapia A, Bagramyan K, Ortiz JA, Mares J, Kalkum M, Fujita-Yamaguchi Y, Ku HT. A lectin produced by a Streptomyces species targets mammalian pancreatic acinar cells in mice and humans. Sci Rep. 2025; 15:2782.
9. Miyazawa M, Ouyang C, Sezaki M, Yasuda K, Ishii N, Fujita-Yamaguchi Y. Gene expression profiling of the L4-stage nematode Caenorhabditis elegans following ethanol exposure. Biosci Trends. 2026; 20:450-460.
10. Goeddel DV, Kleid DG, Bolivar F, Heyneker HL, Yansura DG, Crea R, Hirose T, Kraszewski A, Itakura K, Riggs AD. Expression in Escherichia coli of chemically synthesized genes for human insulin. Proc Natl Acad Sci U S A. 1979; 76:106-110.
11. Cabilly S, Riggs AD, Pande H, Shively JE, Holmes WE, Rey M, Perry LJ, Wetzel R, Heyneker HL. Generation of antibody activity from immunoglobulin polypeptide chains produced in Escherichia coli. Proc Natl Acad Sci U S A. 1984; 81:3273-3277.

Received April 4, 2026; Accepted May 14, 2026.

**Address correspondence to:*
John J. Rossi, Center for RNA Biology & Therapeutics, Beckman Research Institute of City of Hope, Duarte, CA, USA.
E-mail: jrossi@coh.org

Released online in J-STAGE as advance publication June 2, 2026.