Scientific Discoveries Enabled by New Approach Methodologies (NAMs)

Overview

New approach methodologies (NAMs) encompass non-animal, often human-relevant tools such as in vitro systems, organoids, organs-on-chips, high-throughput assays, and in silico or AI-based models for toxicology and drug development. These methods have moved beyond mere method development and have contributed to concrete scientific discoveries about mechanisms of toxicity, disease biology, and drug efficacy.[1][2][3]

The sections below summarize selected, well-documented discoveries where NAMs were central to generating new biological or safety insights, rather than simply reproducing known animal results.

Representative discoveries

1. AI-based repurposing of baricitinib for COVID-19

An AI-driven in silico NAM was used to mine large pharmacology and omics datasets to identify existing drugs that might block SARS-CoV-2 infection and the associated inflammatory response. This approach highlighted the JAK inhibitor baricitinib—originally approved for rheumatoid arthritis—as a candidate COVID-19 therapy by predicting its ability to interfere with viral entry and cytokine signalling pathways. Subsequent clinical studies confirmed that baricitinib reduced mortality and improved outcomes in hospitalized COVID-19 patients when added to standard care, validating the predictive power of the NAM-based drug-repurposing workflow.[4]

2. Discovery of differential cardiotoxicity of next-generation nicotine products

Human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) have been developed as a NAM for cardiac safety assessment, replacing primary animal cardiomyocytes. Using a standardized high-content assay and prediction model (Cardio quickPredict), investigators exposed hiPSC-CMs to smoke or aerosol from combustible cigarettes, heated tobacco products (HTPs), and electronic vaping products (EVPs). They discovered that combustible cigarette smoke had the highest cardiotoxic potential, HTP aerosols showed cardiotoxicity but only at roughly ten-fold higher concentrations than smoke, and the tested EVP aerosols showed no cardiotoxic potential even at the highest exposure level. This provided new quantitative evidence that different nicotine product types have distinct cardiotoxicity profiles, obtained entirely from a human-cell-based NAM.[5][6][7][8]

3. Identification of metabolites as mechanistic cardiotoxicity biomarkers

The same hiPSC-CM platform identified four small-molecule metabolites—lactic acid, arachidonic acid, thymidine, and 2′-deoxycytidine—whose concentration changes robustly predicted cardiotoxic outcomes in vitro. These metabolites now function as mechanistic biomarkers in the Cardio quickPredict assay, linking exposure to early biochemical events that precede overt cell death or functional failure. This biomarker discovery relied on non-animal, human-cell-based NAMs and has informed mechanistic understanding of smoking-related cardiotoxicity.[7][5]

4. Mechanistic mapping of seizure liability using AOP-linked in vitro screens

A government–industry collaboration integrated adverse outcome pathway (AOP) information with drug discovery data to map mechanisms leading to drug-induced seizures. By combining AOP key events with pharmacological target data, researchers identified 27 biological target families linked to seizure mechanisms and developed over 100 in vitro assay endpoints covering 26 of these families. This

NAM-based network of assays enabled systematic, mechanism-focused screening of candidate compounds for seizure liability early in development, revealing previously under-appreciated target families that can contribute to pro-convulsant risk.[9][10]

5. Skin sensitization hazard and potency prediction using defined NAM approaches

The OECD's first "Defined Approaches" guideline (TG 497) combined multiple NAMs—peptide reactivity assays (DPRA), keratinocyte activation (KeratinoSens), dendritic-cell activation (h-CLAT), and in silico models—into integrated testing strategies for skin sensitization. Case studies used these integrated NAMs to correctly classify skin sensitization hazard and potency for chemicals, including some not previously tested in animals, with performance equal to or better than traditional mouse assays. Later work showed that substituting alternative NAMs such as U-SENS into these defined approaches maintained or improved predictive capacity for human hazard categories, further demonstrating that mechanistically anchored NAM batteries can discover sensitization potential across new chemical space.[11][12][13][14][15]

6. Extending NAMs to complex mixtures and pesticide formulations

Follow-on studies applied NAM-based defined approaches, originally developed for individual substances, to more complex test items such as pesticide formulations. These investigations demonstrated that panels of in chemico and in vitro assays, together with in silico tools, could identify and rank the skin sensitization potential of formulations, revealing cases where mixture effects changed hazard relative to individual ingredients. This represented a scientific advance in understanding how combined exposures behave and showed that NAMs can address mixture toxicology questions traditionally considered to require animal studies.[16][15]

7. Organoid-based NAMs elucidating organ-specific toxicity pathways

Three-dimensional human organoids—miniaturized, self-organizing tissue models—have been established as NAMs that more faithfully recapitulate organ architecture and function than 2D cell lines. In liver and intestinal organoid systems, researchers have mapped how specific drugs and chemicals disrupt key cellular processes and tissue organization, providing experimental evidence for key events in adverse outcome pathways (AOPs) for steatosis, cholestasis, and other toxicities. These studies revealed mechanistic links between molecular initiating events (such as receptor activation or transporter inhibition) and downstream tissue-level damage, generating new knowledge about human-relevant toxicity mechanisms.[17][3][1]

8. Lung-on-a-chip discovery of antiviral efficacy and off-target effects

Human lung-on-a-chip systems recreate key aspects of the lung microenvironment, including an air–liquid interface, epithelial and endothelial layers, immune interactions, and breathing-like mechanical stretch. A recent study used an Emulate Bio lung chip to test RNA-based antiviral therapies for influenza, showing that these candidates significantly reduced viral replication and dampened inflammatory responses while exhibiting minimal off-target toxicity in the human-relevant microtissue. This organ-on-chip NAM provided new evidence about antiviral efficacy and safety under physiologically relevant conditions that are difficult to capture in traditional static cultures or animal models.[18][19][20]

9. Lung-on-a-chip and microfluidic NAMs for tumor biology and drug resistance

Microfluidic lung-on-a-chip platforms have been used to model lung cancer microenvironments, enabling high-throughput screening of chemotherapeutic drugs and nanomedicine formulations under dynamic flow. These systems have allowed investigators to observe phenomena such as label-free real-time classification of tumor cells at throughputs of around 10,000 cells per second and to track the

emergence of drug-resistant subpopulations carrying EGFR T790M mutations relevant to non-small-cell lung cancer. Such studies constitute genuine discoveries about tumor heterogeneity and resistance dynamics obtained using chip-based NAMs rather than animal xenografts.[21][22][18]

10. Integrated hiPSC-CM plus in silico platforms improving arrhythmia risk prediction

New NAM platforms now integrate hiPSC-derived cardiomyocyte assays with detailed in silico electrophysiology models inspired by the Comprehensive In Vitro Proarrhythmia Assay (CiPA) initiative. By combining a small set of in vitro measurements on hiPSC-CMs with mechanistic computer models, one such platform was able to reproduce clinical manifestations of pro- and anti-arrhythmic effects for drugs like lidocaine and other antiarrhythmics more accurately than legacy QT-interval-based metrics. This constitutes a methodological and scientific discovery: that a specific combination of human-cell NAMs and mechanistic modeling better reflects true human arrhythmia risk than older animal-centric paradigms.[23]

11. Multi-omics NAMs revealing novel toxicity pathways and biomarkers

Integrative NAMs that combine genomics, transcriptomics, proteomics, and metabolomics have revealed previously unrecognized pathways and biomarker signatures associated with chemical toxicity. Reviews of precision toxicology highlight case studies where omics-based NAMs uncovered novel oxidative stress, mitochondrial dysfunction, and immune-modulating pathways that traditional apical endpoints could not resolve, as well as omics signatures that distinguish adaptive from adverse responses. These findings have reshaped mechanistic understanding of how particular classes of chemicals exert toxicity and have generated candidate biomarkers for early, non-invasive detection of adverse effects.[2][24]

12. Curated AOP–gene annotations enabling new mechanistic insights

The adverse outcome pathway (AOP) framework describes toxicity mechanisms as linked key events from molecular initiating events to organism-level outcomes and directly guides the design and interpretation of NAMs. A recent large-scale curation project systematically linked human-relevant AOP key events to specific genes and biological systems, creating a bridge between AOPs and toxicogenomic data. This curated annotation resource allows researchers to embed AOP knowledge into the analysis of omics data generated by NAMs, facilitating discovery of new mechanistic relationships and strengthening the interpretation of complex in vitro results.[25][10]

Cross-cutting observations

Across these case studies, several themes emerge:

- **Human-relevance and mechanistic depth**: NAMs frequently provide human-specific mechanistic insights—such as metabolite biomarkers, seizure-linked target families, or AOP key events—that were previously unknown or only weakly inferred from animal data.[24][1][9]
- **Earlier detection of risk and efficacy**: Integrating NAMs into preclinical pipelines has enabled earlier identification of seizure liability, cardiotoxicity, sensitization potential, and antiviral efficacy, reducing late-stage failures and unnecessary animal use.[13][1][4][9]
- **Enabling new questions**: High-throughput chip platforms, omics-driven analyses, and integrated computational models allow investigators to ask questions—such as real-time tumor cell classification or mixture-specific effects—that were impractical or impossible with traditional tests.[3][21][18]

Taken together, these examples show that NAMs are already contributing to valid, peer-reviewed scientific discoveries across toxicology, pharmacology, and disease biology, rather than serving only as ethical substitutes for established animal tests.[1][2][3]

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