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Emerging Modalities

Laying the Groundwork
for Clinical and
Regulatory Success

by Lior Shaltiel and Tina Rogers

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Emerging biopharmaceuticals are transforming how sponsors approach early development activities, not least because such drugs exhibit distinctive pharmacological behaviors. This eBook takes stock of modalities on the cusp of clinical breakthroughs, focusing on what manufacturing and analytical technologies developers will need in place to ensure that candidates are safe and efficacious.

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Exosomes

Establishing a New Modality in Regenerative Medicine and Aesthetics

Lior Shaltiel

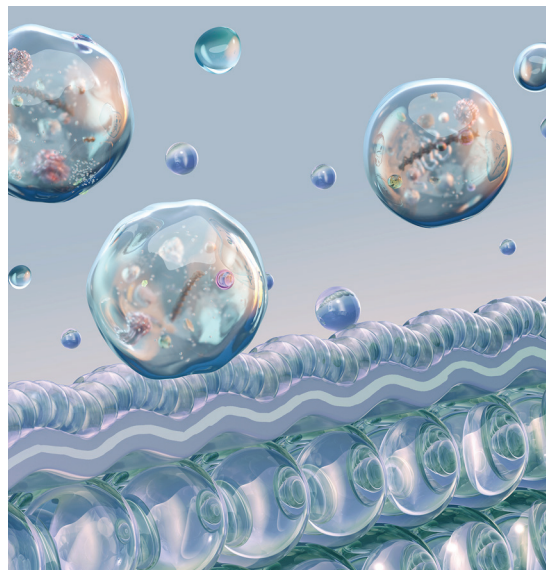
Exosomes are nanoscale extracellular vesicles (EVs) secreted by nearly all mammalian cells. Originally believed to be cellular debris, they are now understood to be sophisticated messengers carrying proteins, lipids, and nucleic acids that mediate intercellular communication. Their role in immune modulation, tissue repair, and signaling has made them attractive candidates for regenerative-medicine applications and as a drug-delivery system.

In therapeutic contexts, exosomes have regenerated tissue in models of spinal-cord injury, traumatic brain injury, and optic-nerve degeneration (1–3). In aesthetic medicine, exosomes have been marketed as injectable or topical products for skin rejuvenation, wound healing, and hair regrowth. The attraction lies in their potential to provide true biological repair. Unlike dermal fillers or laser-resurfacing procedures, exosomes can activate intrinsic repair pathways in skin and hair follicles. That capability could create a paradigm shift in aesthetic medicine. However, rapid growth in the exosomes market has outpaced regulatory oversight, leading to a patchwork of quality and safety practices. Recent regulatory interventions now provide a roadmap for how exosomes can mature into a credible modality for both medical and aesthetic applications.

A REGULATORY INFLECTION POINT IN AESTHETICS

The US Food and Drug Administration (FDA) began scrutinizing exosome products for aesthetic applications in 2019, issuing warning letters to clinics that market unapproved injectables (4). Those communications have made clear that exosomes, like stem-cell products, are considered to be biological products and thus are subject to regulation for agents that are administered directly into a person's body (whether dermally or parenterally). Despite those warnings, the aesthetics sector continued to use exosomes broadly while patient demand was strong and oversight remained fragmented. That mismatch between demand and regulation created an environment in which products varied dramatically in quality, with some being poorly characterized or derived from unvalidated sources.

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Artist rendering of nucleotide-loaded exosomes outside of a target cell

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State-level action was the next milestone. Florida (5) and Utah (6) have passed legislation permitting use of exosomes for wound healing, joint repair, and other regenerative indications. Those laws now require that exosome products meet minimum quality standards and that providers understand their products' regulatory status. The significance of such steps cannot be overstated: Aesthetic medicine is the first field in which exosomes are receiving structured oversight. That establishes an important precedent that is likely to expand globally over time.

WHY AESTHETICS COMES FIRST

The business model for aesthetic medicine represents a unique combination of high demand, rapid adoption, and comparatively low regulatory barriers. Patients seek treatments that improve appearance and quality of life, and clinics are motivated to adopt innovations that differentiate their offerings. Exosomes fit patient demand perfectly: They are minimally invasive, biologically inspired, and seem to promise outcomes beyond what traditional modalities can deliver.

Compared with therapeutics, aesthetic applications do not require long efficacy trials, which means that product adoption occurs faster. In aesthetic applications, safety typically is demonstrated through short-term dermatologic evaluations, patch or irritation testing, and clinical observation in human volunteers. Efficacy is measured using visible or imaging-based endpoints, such as improvements in skin texture, elasticity, or hydration, assessed over several weeks to months.

By contrast, therapeutic exosome programs must establish both mechanistic efficacy – e.g., by demonstrating tissue regeneration or neuroprotection in validated animal models – and clinical efficacy through controlled human studies with quantifiable endpoints, such as motor-recovery scales and functional-imaging outcomes. Early studies are supported by longitudinal follow-up to monitor treatment durability, immune response, and safety over time. As the exosomes field matures, convergence between therapeutic and aesthetic regulatory expectations is likely, particularly regarding chemistry, manufacturing, and controls (CMC) standards and evidence of biological activity.

That factor also explains why regulators have focused first on aesthetics. When unregulated products enter consumer markets quickly, the risks of harm, exploitation, and inconsistent results increase. As a result, aesthetic medicine has become the proving ground where exosome standards are being defined. The lessons learned there ultimately will apply to therapeutics.

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Aesthetic medicine has become the **PROVING GROUND** where exosome standards are being defined. The lessons learned there ultimately will apply to therapeutics.

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The evolution of exosome regulation is being shaped by the interplay between the therapeutic and aesthetic-medicine domains. Therapeutic development will follow stringent regulatory pathways comparable with those applied to protein biologics and cell/gene therapies. For clinical use, exosomes must be produced under full good manufacturing practice (GMP) conditions, with detailed CMC documentation submitted as part of an investigational new drug (IND) submission or clinical-trial application (CTA). Filings require comprehensive preclinical safety packages, including good laboratory practice (GLP)-compliant toxicology, biodistribution, and immunogenicity studies, along with validated stability and potency assays to ensure consistency across batches.

By contrast, aesthetic exosome formulations — specifically, those intended for topical cosmetic procedures — often fall under less restrictive frameworks, including those for medical devices, cosmetic treatments, or combination-product categories. Such pathways emphasize manufacturing quality, sterility, and safety verification but do not require multiphase efficacy trials prior to market entry. As a result, aesthetic applications of exosomes have advanced to market more rapidly than therapeutic ones have. However, achieving clinically meaningful regenerative outcomes in areas such as wound healing, tissue repair, and longevity is expected to require exosomes derived from human mesenchymal stem cells (MSCs), which have been studied clinically and are shown to promote angiogenesis, modulate inflammation, and stimulate tissue regeneration in multiple preclinical models (7).

LESSONS FROM THERAPEUTIC PROGRAMS

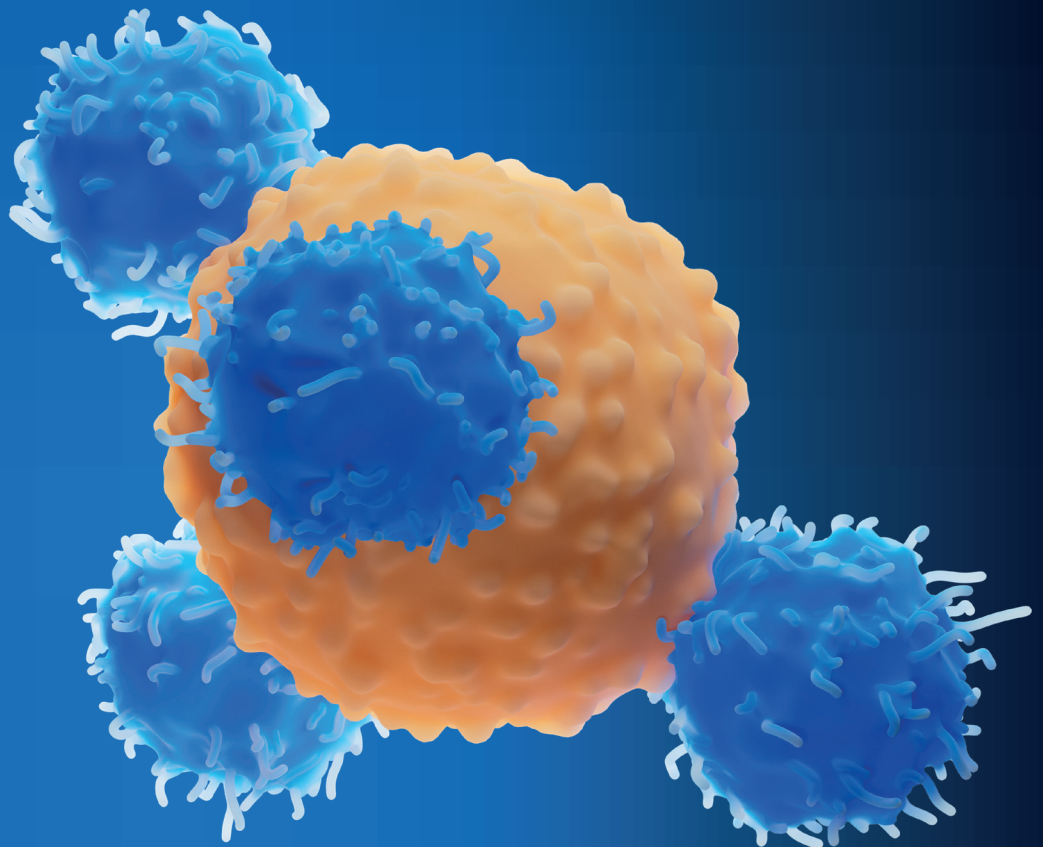
NurExone Biologic is developing the ExoTherapy platform, which uses exosomes as nanocarriers for site-specific drug delivery. Our lead candidate, the ExoPTEN nanodrug, comprises exosomes loaded with small interfering RNA (siRNA) to inhibit phosphatase and tensin homolog (PTEN), a key blocker of neural repair for CNS injury (8).

Recognizing the importance of a reliable production source from the outset, our initial strategy was to secure a master cell bank (MCB) of MSCs derived from human bone-marrow (hBM). Such material offers a sustainable, cost-effective, and unique supply of exosome-producing cells, ensuring consistency and scalability for manufacturing. The MCB will provide a foundation for US-based GMP-compliant manufacturing through Exo-Top, our fully owned US subsidiary. The site will produce exosomes both for the advancement of our therapeutic pipeline and as a reliable business-to-business (B2B) supply of GMP-grade exosomes.

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Our therapeutic programs provide valuable insights into what high-quality exosome science looks like. In spinal-cord injury models, the ExoPTEN candidate restored motor function, as validated by a CatWalk XT gait-analysis system (Noldus) for quantitative assessment of footfalls and locomotion in rats and mice (9). Such tools reduce measurement subjectivity during preclinical evaluation and provide regulators with reproducible endpoints. In optic-nerve–crush models simulating glaucoma, the ExoPTEN candidate preserved retinal ganglion cells and restored electrophysiological activity (10). Optical coherence tomography (OCT) imaging and retinal flat-mounts provided multiple independent lines of evidence.

For aesthetics, analogous methods can – and should – be applied. Instead of electrophysiology, developers can use skin biopsies, collagen deposition assays, and histology. Instead of gait analysis, digital imaging of hair density or wound closure can provide objective measures. The underlying principle should be the same: Functional assays must confirm that exosome products achieve the biological effect claimed.

Moreover, bioanalysis can serve as a critical bridge between exosome identity and clinical function. Such evaluation enables developers to link molecular signatures – e.g., RNA cargo, protein markers, and lipid composition – with biological outcomes observed in vivo. Thus, for the exosome field, safety and potency should not be established through particle counts alone. Instead, multiparametric analytics paired with functional assays must demonstrate that exosome preparations consistently drive tissue repair.

Such an approach is relevant to aesthetics as well. Patients and practitioners expect visible results such as improved skin quality, scar reduction, and hair restoration. Bioanalysis can help identify the molecular signals most closely associated with those regenerative effects, including growth factors, angiogenic proteins, and wound-healing microRNAs. Then, functional assays of keratinocyte migration or fibroblast proliferation can confirm that those molecular signatures translate into regenerative outcomes.

In my company's case, bioanalytical profiling has shown high enrichment of RNA and protein signatures associated with wound healing and tissue regeneration (11). Those findings align with functional data from preclinical models, in which exosomes demonstrated enhanced repair activity. Together, those results illustrate how bioanalysis not only strengthens the therapeutic case, but also provides a pathway for translating exosome science into the medical-aesthetics space. By defining and validating regenerative signals, bioanalysis enables development of GMP-

Those results illustrate how bioanalysis not only strengthens the therapeutic case, but also provides a **PATHWAY** for translating exosome science into the medical-aesthetics space.

grade exosomes that meet both regulatory standards and patient expectations.

MARKET OPPORTUNITY AND PATIENT IMPACT

The global aesthetic-medicine market was valued at more than US\$80 billion in 2023 and is forecasted to surpass \$140 billion by 2030 (12). Within that market, regenerative aesthetics is one of the fastest growing subsegments. Demand spans different genders and age groups, with particularly strong uptake among Millennial and Gen-Z populations, who tend to value preventive and regenerative treatments over surgical interventions.

The patient impact of exosome products will be substantial. Scarring, alopecia, photoaging, and other such conditions can diminish self-esteem, confidence, and mental health. By offering regenerative repair, exosomes could provide meaningful quality-of-life improvements. However, when unregulated products cause harm or simply fail to deliver results, they damage both patients and the credibility of the field. Establishing GMP-grade, analytically validated products ensures that the promise of exosomes translates into consistent benefits.

IMPLICATIONS FOR THE AESTHETIC INDUSTRY

The aesthetic-medicine industry has reached a turning point. Clinics face a choice between continuing with unregulated, potentially risky exosome products or adopting GMP-grade, validated alternatives. The former choice carries legal and reputational risks, whereas the latter offers credibility and consumer trust. Market leaders will emerge from those companies that choose compliance and scientific rigor. For practitioners, sourcing GMP-grade products provides protection and aligns with the evolving legal landscape in regenerative medicine. For patients, credible sourcing promotes safety and predictable outcomes. For developers, it opens doors to partnerships with reputable clinics, insurers, and possibly even crossover into therapeutic collaborations. The alignment of science, safety, and market demand will create a rare opportunity for companies positioned at the forefront of the transition to validated approaches.

A TURNING POINT

The next five years will be decisive for exosome aesthetics in the United States. We can expect more states to adopt laws like those of Florida and Utah, followed by harmonization at the federal level. The hope is that consumer education campaigns will highlight the importance of GMP-grade sourcing, while professional societies publish guidance for clinicians. Internationally, Europe and Asia

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The alignment of science, safety, and market demand will create a **RARE OPPORTUNITY** for companies positioned at the forefront of the transition to validated approaches.

will follow suit with North America, mirroring trends already seen in stem-cell and protein-biologics regulation.

At the same time, analytics will advance. Artificial intelligence (AI) might help to identify biomarkers that predict regenerative potency. Automation should streamline GMP workflows, driving down costs and making exosomes accessible to broad patient populations. Aesthetic exosomes are likely to be the first such products to achieve widespread adoption, creating the frameworks that therapeutic exosomes will follow later.

Exosomes are redefining the possibilities of regenerative medicine and aesthetics. The shift from unregulated marketing to GMP compliance marks a pivotal moment for the field. This transition is not a barrier, but rather an opportunity: It allows companies to establish themselves as leaders in safety, quality, and innovation. The Exo-Top Inc. initiative exemplifies that approach, bringing therapeutic rigor to aesthetic applications and positioning exosomes as credible, science-driven products.

Aesthetic medicine is likely to be the first domain in which exosomes achieve mainstream adoption. The regulatory frameworks established in that segment will elevate aesthetic uses while laying a foundation for therapeutic applications in neurology, ophthalmology, and beyond. The challenge ahead is clear: to prove quality, efficacy, and reproducibility. The rewards are equally clear: to promote confidence, safety, and regenerative outcomes for millions of patients.

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Integrative Approaches to Toxicology for Emerging Modalities

Tina Rogers

The rapid advancement of novel therapeutic modalities — including antibody–drug conjugates (ADCs), antisense oligonucleotides (ASOs), peptide–drug conjugates (PDCs), and others — is reshaping the contours of drug development.

Each new modality introduces distinct pharmacological behaviors, mechanisms of action (MoAs), and safety considerations that do not fit neatly into traditional toxicology paradigms.

Although foundational toxicology approaches remain essential, they now must be integrated with modality-specific strategies to ensure a complete and accurate safety profile. The evolving therapeutic landscape calls for a harmonized approach that combines *in vitro*, *in vivo*, and computational models with emerging analytical tools, enabling both scientific rigor and regulatory alignment.

WHY MODALITY-SPECIFIC TOXICOLOGY IS ESSENTIAL

Historically, drug-safety assessment has relied on paradigms designed around small molecules or conventional protein biologics. Such frameworks have provided reliable tools for assessing systemic exposure, organ toxicity, and pharmacokinetics (PK), including repeat-dose toxicology studies, clinical pathology and histopathology, and noncompartmental PK analysis. However, the emergence of novel modalities is challenging conventional assumptions. As drug constructs become more complex and mechanistically targeted, their interactions with biological systems often diverge from known patterns.

Consider ADCs, which combine the targeting precision of monoclonal antibodies (mAbs) with the potency of cytotoxic small molecules that were designed to target tumors. An ADC's safety profile is driven primarily by target specificity, linker stability, payload potency, drug:antibody ratio (DAR), and incidence of bystander effects, as well as PK. By contrast, ASOs are small, synthetic strands of nucleic acid that are designed to modulate gene expression (1). Their safety profiles are shaped less by traditional metabolism and more by sequence-specific

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Organ-on-chip microfluidic devices and other new-approach methodologies quickly are becoming essential tools in biopharmaceutical toxicology testing.

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hybridization, tissue accumulation, and immunostimulatory potential (2). Such nuances require different approaches to nonclinical study design to ensure accurate and thorough toxicity assessment.

Risk assessment must evolve beyond a one-size-fits-all model. Tailored toxicology programs informed by mechanism and platform behavior are becoming the new standard. Such programs demand revamped methodologies and new approaches to interpreting data in regulatory and translational contexts.

CORE CHALLENGES IN EVALUATING NEXT-GENERATION MODALITIES

Emerging modalities introduce nuanced risks that conventional assays do not capture adequately. Each class presents new factors that span PK, off-target effects, immunogenicity, and tissue biodistribution.

A primary concern for **ADCs** is variability in DARs. Such variability has significant bearing on drug efficacy, safety, and PK. A DAR value determines how much drug can be delivered, how long the ADC will circulate in a patient's body, and how safely it can be administered. The goal is not to achieve the highest DAR, but rather to use a DAR that balances efficacy, PK, and safety. Hydrophobic-interaction chromatography (HIC), liquid chromatography with mass spectrometry (LC-MS)-based intact and subunit analyses, ligand-binding assays (LBAs), hybrid LBA-LC-MS approaches, and other advanced bioanalytical methods can quantify free drug, conjugated payloads, and antibodies to characterize an ADC's PK profile.

Analytical characterization of **ASOs** is complicated by low circulating concentrations, extensive tissue binding, and the presence of chain-shortened metabolites, which confound accurate quantification and PK interpretation. Accumulation in specific tissues, particularly in the liver and kidneys, requires targeted biomarker monitoring to detect early signs of toxicity (hepatotoxicity and nephrotoxicity, respectively). Moreover, depending on their chemical backbones, ASOs can elicit innate immune responses, posing risks for systemic inflammation or complement activation.

Many **peptide-based therapies** are highly susceptible to rapid enzymatic degradation, resulting in short half-lives and limited bioavailability. Thus, frequent and complex dosing often become necessary. In such cases, understanding a drug's PK to pharmacodynamics (PD) relationship becomes crucial for striking a balance between efficacy and safety.

Targeted protein degraders (TPDs) are designed to eliminate disease-causing proteins by catalyzing destruction of

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intracellular proteins through the ubiquitin-proteasome system. Such agents fall into three main classes: proteolysis-targeting chimeras (PROTACs) (3), “molecular glues” (4), and lysosome-based degraders that target “undruggable” proteins (5). Consequently, conventional plasma PK is necessary but insufficient, and robust PD biomarkers must demonstrate target degradation and PK-PD response.

Generally, therapies based on **mRNA** are well tolerated, but in a toxicological sense, they are limited primarily by a potential for innate immune activation and lipid nanoparticle (LNP)-related toxicity. Regulators generally expect full immunotoxicity assessment, careful dose selection, robust control of mRNA and LNP components, and long-term follow up for chronic indications. Understanding both the duration of effect and systemic reactivity is critical.

The distinctive and inherent challenges of each modality reinforce a need for integrated, customized toxicology strategies that combine traditional safety paradigms with new technologies and mechanistic insight. Tailoring assessments to characterize modality-specific risks can help program sponsors to reduce late-stage failures, enhance translational relevance, and ensure patient safety from the earliest development stages.

INTEGRATED TOXICOLOGY APPROACHES

The safety demands of emerging modalities require adaptive and integrative toxicology methods. Meeting that need begins with embedding safety assessments earlier in product development than has been customary, using predictive tools to guide candidate selection and study design.

Safety pharmacology and genetic toxicology remain cornerstones, but a proactive, modality-tailored, and integrative approach can improve program progress. For example, early genotoxicity screening using next-generation sequencing can help flag off-target effects for ASOs or mRNA therapies before they enter costly in vivo studies. Similarly, safety pharmacology evaluations for cardiovascular and central nervous system (CNS) effects might require adjusted endpoints to reflect modality-specific risks detected at early stages of drug development.

A multimodal toolkit is crucial. LBAs, LC-MS techniques, and high-sensitivity flow cytometry now can work in tandem to monitor drug levels, active metabolites, and PD biomarkers. For example, in ADC development, LC with tandem MS (LC-MS/MS) can distinguish between intact conjugates and free payload, whereas flow cytometry can track PD biomarkers in TPD studies.

New-approach methodologies (NAMs) can enhance translational relevance further. Such tools reduce reliance on animal models,

The distinctive and inherent challenges of each modality reinforce a need for

INTEGRATED, CUSTOMIZED

toxicology strategies that combine traditional safety paradigms with new technologies and mechanistic insight.

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support 3R (replacement, reduction, and refinement) initiatives, and offer high-resolution insights into tissue-specific responses.

Example NAMs include

- cytotoxicity panels — e.g., using HepG2 immortalized human hepatoblastoma cells or hepatocytes from human induced pluripotent stem cells (hiPSCs)
- human ether-a-go-go-related gene (hERG) patch-clamp assays (automated)
- tests using hiPSC-derived cardiomyocytes
- assays with three-dimensional (3D) liver spheroids/organoids
- in chemico bacterial reverse-mutation assays (also called *Ames assays*)
- in vitro micronucleus (MNvit) assays
- lung-on-chip models
- gut-organoid testing
- zebrafish-embryo assays.

INTEGRATION IN PRACTICE

NAMs already are being translated into real-world drug-development scenarios. For ADCs, precision quantification of DAR and free payloads has become a gating factor for investigational new drug (IND) submissions. Developers are integrating LC-MS/MS and LBA platforms to assess PK, linker stability, and degradation kinetics. In ASO development, monitoring liver and kidney biomarkers — e.g., alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood-urea nitrogen (BUN), and serum creatinine — is now standard in early safety studies. Biomarker trends, paired with PK and antidrug antibody (ADA) data, inform dose selection and long-term risk mitigation.

Peptides, with their short half-lives, require chemical stabilization and targeted delivery strategies to enhance efficacy. Those considerations are paired with early immunogenicity testing to anticipate immune responses before clinical evaluation. Demonstrating TPD efficacy entails quantification of target degradation. Validated flow-cytometry methods enable detection of key biomarkers such as Aiolos and Ikaros transcription factors, supporting PD modeling and safety correlation.

STRATEGIC CONSIDERATIONS FOR PROGRAM SPONSORS

In the evolving context of drug development, sponsors must rethink how and when they approach toxicology. Engaging with

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regulators early is vital. Novel modalities might not fit into existing frameworks, requiring sponsors to justify study designs, species selection, and biomarker strategies case by case.

Species selection is particularly critical for ASOs and peptides, for which pharmacological activity and tissue distribution can differ significantly between humans and nonhuman animals. Choosing the right animal species can reduce translation gaps and enhance predictive accuracy.

Cross-functional collaboration is key, as well. Toxicologists, drug metabolism (DM) and PK scientists, and regulatory-affairs teams must work closely to align on study goals, data interpretation, and regulatory messaging. For example, a company's preclinical team must be connected to its regulatory team not merely at the start of a program, but also throughout the process to enable tight planning and rapid subject recruitment.

Timing matters. Integrating toxicology insights early in an IND-enabling process informs candidate advancement and optimizes resources. Proactive sponsors are more likely than reactive organizations to navigate regulatory complexity and head off late-stage surprises. For example, early alignment between toxicology and DMPK teams on tissue-distribution data could prompt inclusion of kidney-injury biomarkers in repeat-dose studies, enabling potential liabilities to be identified and contextualized before IND submission rather than triggering additional studies in response to regulatory questions.

NAVIGATING A DIVERSE THERAPEUTIC LANDSCAPE

As the therapeutic landscape diversifies, so too must the strategies used to assess drug safety. For emerging modalities, integrative toxicology approaches that combine traditional rigor with innovative methodologies are no longer optional. By adopting adaptive, fit-for-purpose strategies, sponsors can navigate complexity, meet regulatory expectations, and bring transformative therapies to patients safely and efficiently.

Toxicology is expected to become increasingly data-driven and mechanistically informed. As regulators encourage use of NAMs and forward-thinking, technology-based models, the field will shift toward earlier, more predictive safety assessments. Regulatory guidance will evolve in parallel, clarifying frameworks for novel modalities and setting benchmarks for biomarker qualification, in silico models, and translational endpoints. Sponsors that stay ahead of such shifts — e.g., by investing in cross-disciplinary collaboration, early regulatory engagement, and robust modality-specific program designs — will be best positioned to accelerate

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As regulators encourage use of new-approach methodologies and forward-thinking, technology-based models, the field will shift toward **EARLIER, MORE PREDICTIVE** safety assessments.

development while maintaining scientific integrity and patient safety.

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