


Dual switches ignite tumour-specific mRNA therapeutics

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A two-step boost with tumour-specific lipids and untranslated regions ensures safe, precise and effective mRNA expression.

Immunotherapy has revolutionized oncology, yet its efficacy is tempered by safety concerns. A key challenge is to confine immune activation to tumours, as off-target activity in normal tissues can provoke immune-related adverse events (irAEs). Messenger RNA (mRNA) therapeutics offer exceptional versatility, but conventional lipid nanoparticles (LNPs) preferentially accumulate in the liver, posing challenges for oncology applications¹. Now, writing in *Nature Nanotechnology*, Dong et al.² describe a tumour-tailored mRNA platform named TITUR, which introduces two complementary safeguards – tumour-specific ionizable lipids (TIs) and mRNA modified with tumour-specific untranslated regions (TURs) – to achieve selective expression in malignant cells while sparing healthy tissues (Fig. 1). This double-boost design enables the

safe induction of immunogenic cell death and enhances the efficacy of immune checkpoint blockade in otherwise resistant tumour models.

LNPs have already been optimized to deliver mRNA to various organs and tissues, including the liver, lung, spleen and bone marrow^{3,4}. These successes reflect how lipid chemistry can be tuned to influence biodistribution and uptake. Yet when applied to tumours, the success achieved in organ-specific targeting cannot be reproduced. Tumour heterogeneity and poor vascularization hinder efficient mRNA–LNP delivery and expression in malignant cells⁵. A further concern is that anti-cancer proteins encoded by therapeutic mRNAs are usually highly potent, and their expression outside tumours can cause severe systemic cytokine release or hepatotoxicity^{6,7}. Achieving selective tumour expression is therefore a fundamental bottleneck for advancing mRNA-based cancer therapeutics.

To address this challenge, Dong and colleagues implemented a two-layer safeguard system. The first safeguard is chemical: a library of TIs was synthesized and screened across cancer cells and primary

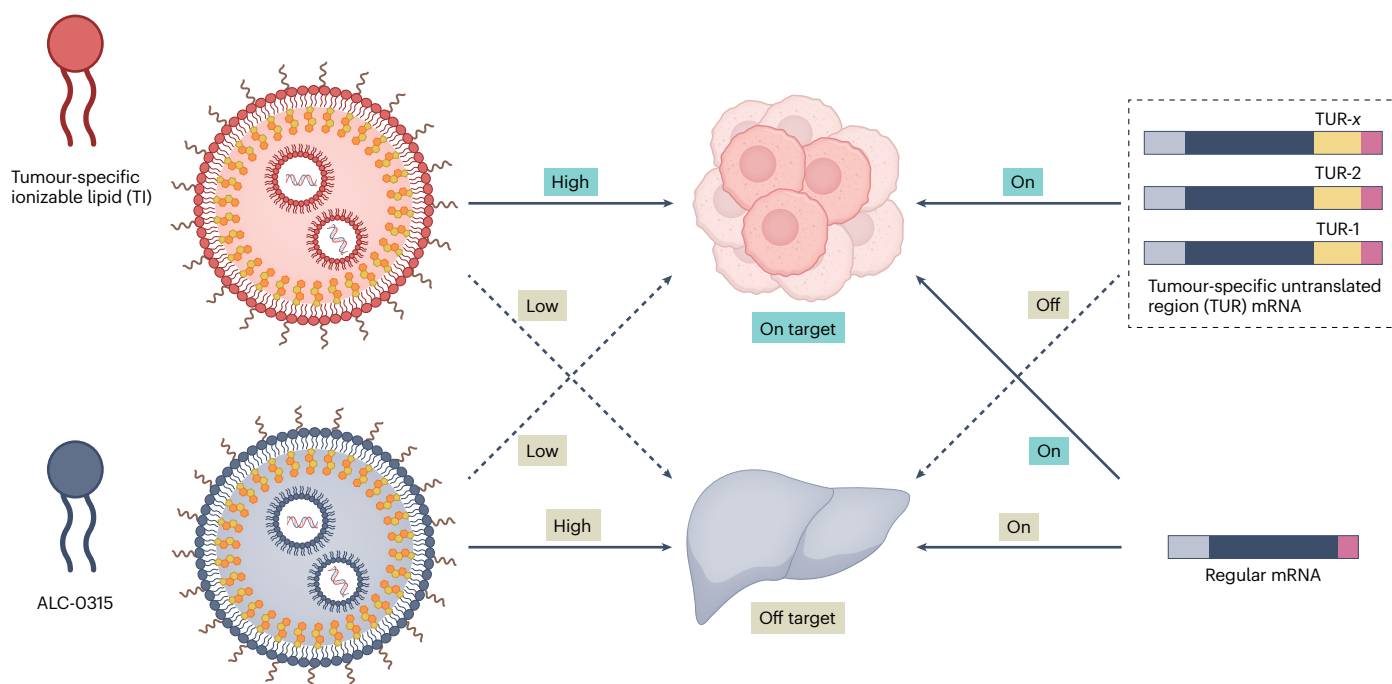


Fig. 1 | Dual switches ignite tumour-specific mRNA therapeutics. The TITUR platform employs two safeguards to achieve selective mRNA expression in tumours. Left: tumour-specific ionizable lipids (TIs) with optimized pK_a values are newly designed carriers that preferentially promote endosomal escape and subsequent mRNA expression in tumour cells. By contrast, conventional lipids such as ALC-0315, the benchmark ionizable lipid used in the Pfizer–BioNTech COVID-19 mRNA vaccine, primarily direct expression to the liver. Right: tumour-

specific untranslated regions (TURs) are incorporated into the mRNA sequence to exploit differences in microRNA profiles. In healthy tissues, abundant microRNAs bind TUR motifs and silence translation, whereas in tumours, the absence of these microRNAs permits robust protein production. Together, these dual switches confine protein expression to malignant cells, enabling potent immune activation within tumours while minimizing systemic toxicity.

hepatocytes. Ionizable lipids are the critical component of LNPs that enable endosomal escape once particles are internalized. By adjusting head group chemistry and hydrophobic tails, the authors identified TIs that favoured escape in the acidic endosomes of tumour cells while being relatively inactive in hepatocytes. This ‘outer switch’ biases mRNA delivery toward malignant cells, reducing off-target exposure in the liver. The second safeguard lies in the RNA itself. TITUR further incorporates TURs into the mRNA, which are short sequences recognized by microRNAs. MicroRNAs act as natural post-transcriptional silencers by binding complementary motifs in target transcripts. Importantly, their expression patterns differ between normal tissues and tumours. By embedding motifs recognized by microRNAs abundant in healthy organs but scarce in cancer, TUR ensures that any transcript reaching non-malignant cells will be degraded or silenced. In tumour cells lacking those microRNAs, the mRNAs are translated efficiently. This ‘inner switch’ provides an additional layer of protection by restricting expression to malignant tissue. Together, the dual safeguards substantially improve the precision of mRNA-based cancer therapy.

To demonstrate the platform, the authors selected a particularly stringent therapeutic payload: delivery of mRNA encoding the necroptosis effector mixed lineage kinase domain-like pseudokinase (MLKL). Necroptosis is a form of inflammatory cell death distinct from apoptosis. Unlike apoptosis, which is often immunologically silent, necroptosis causes the release of damage-associated molecular patterns such as ATP, HMGB1 and calreticulin. These signals alert dendritic cells, prime T cell responses, trigger strong immune activation and can convert immunologically ‘cold’ tumours into ‘hot’ ones. Yet the same potency also makes necroptosis dangerous: if triggered in normal organs, it can provoke inflammatory cascades, systemic cytokine release and multi-organ irAEs. TITUR therefore provides an ideal safeguard framework for such powerful payloads. In mouse models of melanoma and triple-negative breast cancer, TITUR-mediated MLKL expression induced robust necroptosis selectively within tumours, promoted infiltration of dendritic cells and T lymphocytes, and sensitized tumours to anti-PD-1 checkpoint blockade. Strikingly, tumours resistant to immunotherapy were converted into responsive ones, with suppression of both primary and metastatic growth. Treated animals also exhibited protection against tumour rechallenge, mimicking the effect of an in situ cancer vaccine. Equally important, systemic toxicity was minimal. Unlike conventional LNPs, TITUR did not cause

weight loss, liver damage or systemic inflammation, underscoring the importance of dual safeguards.

These findings highlight not only efficacy but also the modularity of the platform. The TI lipids can be tailored to different tumour types, while the TUR motifs can be adapted to microRNA signatures characteristic of specific cancers. This suggests that TITUR could, in principle, be applied beyond necroptosis to other therapeutic proteins, including cytokines, genome editors, or tumour suppressors. However, challenges remain. Lipid performance varied across cancer models, implying that tumour-specific screening will be required to identify optimal formulations for each indication. Likewise, microRNA expression displays marked heterogeneity, not only between patients but also within individual tumour types⁸, raising the possibility that TURs may need to be customized for clinical translation.

Despite these obstacles, TITUR represents a conceptual advance for precision mRNA therapeutics. By integrating safeguards at both the nanoparticle and payload levels, Dong and colleagues demonstrate that it is possible to confine potent immune activation to tumours while minimizing systemic risk. This dual-switch strategy establishes a blueprint for next-generation mRNA LNPs, moving beyond liver tropism and opening the way to safe and effective cancer immunotherapy.

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Published online: 12 November 2025

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Competing interests

The authors declare no competing interests.