EDITORIAL

# Lung Cancer Organoids as Avatars of Patients With Lung Cancer in the Prediction of Therapeutic Response

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Takamasa Koga et al.[1] have reported in the *Journal of Translational Oncology and Clinical Research Reports* the clinical significance of establishing lung tumor organoids accomplished through the establishment of organoid models derived from surgically resected lung cancer specimens. These organoid models hold substantial clinical use, particularly in the context of ex-vivo drug assay testing, predicting drug efficacy in patients posing complex management dilemmas. For instance, Mitsudomi et al.[1] found that the combination of trametinib plus an SOS1 inhibitor inhibited tumor growth in a patient-derived lung tumor organoid (PDLO) harboring a *KRAS G12C* mutation. Another PDLO obtained from a metastatic lung adenocarcinoma carrying the EGFR exon 20 H773delinsYNPY displayed a significant tumor growth inhibition effect with poziotinib and osimertinib at very low half-maximal inhibitory concentrations of the drugs. The patient was subsequently administered osimertinib, resulting in noteworthy radiologic regression of the lung metastatic lesion, according to the ex vivo drug assay outcomes, and a decrease of the serum carcinoembryonic antigen levels.[1]

What is an organoid? Organoids are self-organized and differentiated cell aggregates derived from stem cells and cultured three-dimensionally (3-D). Cancer cells growing in 3-D have similar characteristics as their tissue of origin. Cancer cells in 3-D cultures effectively preserve the cell-cell and cell-matrix interactions observed within the native tumor microenvironment, in contrast to cells grown in two dimensions.[2] The drug sensitivity of cancer cells in a 2D environment is different from that in cells cultured in a 3-D cell culture system.[3] Sotorasib (AMG 510) exhibits better sensitivity in spheroid growth conditions (3-D) than in monolayer (two-dimensional) conditions according to the cell viability assay in KRAS G12C lines such as NCI-H358 and MIA PaCa-2.[4] The preclinical analysis performed by the same canon group also clearly indicated that the in vitro combination drug testing in KRAS G12C cell lines with matrices of sotorasib (AMG 510) and inhibitors targeting various HER kinases—including EGFR, SHP2, PI3K, AKT, and MEK—had several degrees of synergism. Significantly, this synergistic interaction was further augmented when the experiments were conducted under spheroid growth conditions.[4]

The mechanisms of sensitivity and resistance in different lung cancer settings are typically explored using cell lines purchased from the American Type Culture Collection or from patient-derived cell lines obtained by cancer research centers. However, the establishment of patient-derived organoids (PDOs) as avatars of patients with cancer allows personalized high-throughput drug screening that, coupled with genomic analysis of the PDO, could represent unique opportunities for identifying effective cancer treatments for individual patients.[2] Contemporary advancements in organoid technology have significantly streamlined the process of establishing PDOs, paving the way for individualized treatment testing. This innovative approach not only enables the tailoring of therapeutic strategies to the unique characteristics of each patient but also provides a platform for investigating the intricate biological pathways responsible for rapid adaptive resistance. This phenomenon,

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which has been prominently observed in response to targeted therapies, can now be mechanistically dissected within the context of organoid models, offering valuable insights into the underlying molecular mechanisms.[5–7]

Organoids exhibit remarkable self-renewal and proliferative capabilities, affording them the ability to be sustained in culture over extended periods, which can, therefore, permit patient-derived avatars to be used in co-clinical studies to assess the development of rapid adaptive resistance, a phenomenon potentially triggered within as little as 48 to 72 hours after the initiation of targeted therapy. The use of organoids as patient-specific models, thus, presents an unparalleled opportunity to gain insights into the mechanisms underpinning rapid adaptive resistance.[5,7] Koga et al.[1] outline specific criteria for the successful establishment of organoids as follows: (1) formation of a 3-D structure; (2) sustained survival across a minimum of three passages; and (3) culture maintenance for a duration of at least 3 months, or alternatively, the potential for sufficient expansion to facilitate cryopreservation within 3 months. In their study, the researchers succeeded in the creation of 53 lung tumor organoids derived from a total of 79 samples sourced from 78 distinct patients. The establishment rate was lower in squamous cell lung carcinoma (48%) in comparison with non–squamous cell lung cancer types (75%). Of interest is the fact that the overall survival for patients with long-term cultured lung tumor organoids (defined as more than 10 passages) tended to be worse than other patients. The establishment was also associated with tumor size because tumors must have a maximum diameter of 8 mm or greater during the lung resection. The authors also obtained normal lung parenchyma with the aim of creating normal lung organoids for the patients. Koga et al.[1] were able to compare the genetic alterations in the lung tumor organoids and the matching parental lung tumors of the patients. No less important was the fact that the investigators were able to set up patient-derived xenografts.

Metastatic lung adenocarcinoma patients with or without driver alterations often progress and the chance to establish PDOs upfront or at clinical progression could provide valuable information for treatments that could be found fortuitously using personalized high-throughput drug screening.[2,8,9] For example, it was found that vorinostat enhanced the effects of EGFR inhibitors in patients with colorectal cancer.[2]

The molecular mechanisms underlying the action of histone deacetylase inhibitors, such as vorinostat, have been observed in breast cancer, in which they exhibit the ability to restore the expression of the leukemia inhibitor factor receptor (LIFR), among other targets.[10]

Intriguingly, loss of LIFR has been reported in KRAS-mutant NSCLC. Furthermore, LIFR plays a regulatory role in the localization of the scribble protein, which has recently been identified as undergoing subcellular misplacement after KRASG12C inhibitor therapy. This misplacement phenomenon occurs within a relatively short time frame of 48 to 72 hours postinitiation of treatment and is accompanied by an up-regulation of MRAS.[7] Intriguingly, MRAS forms a trimeric complex alongside PP1C and SHOC2, with the latter being deemed indispensable for the maintenance of 3-D cultures of lung cancer cells.[11] PDO models can also be established from pleural effusion samples; however, it is pertinent to note that, for a substantial proportion of patients with lung cancer, the acquisition of a lung tumor biopsy remains a requisite for the successful generation of PDOs. Within our institution, a well-defined PDO protocol has been formulated, strategically involving a video-assisted mini-thoracotomy procedure in the context of metastatic lung adenocarcinomas. This surgical approach ensures the procurement of adequate lung tumor tissue, thus, facilitating the subsequent establishment of PDLOs that can be subjected to various drug combinations for assessment.

The study of Mitsudomi et al. paves the way for establishing PDO protocols in patients with lung cancer, enabling PDOs to serve as avatars for drug screening that—coupled with ex-vivo preclinical assessment—could decipher canonical and noncanonical mechanisms of resistance at different time points of clinical evolution. PDO technology also requires the adequate use of personalized high-throughput drug screening and further preclinical research. PDO platforms warrant a warm reception and should be seamlessly integrated into ongoing investigation endeavors. The synergy among PDOs, genomic analysis, and liquid biopsy enhances cancer management efficacy. PDOs integrated into clinical trials could invigorate the understanding of rapid and multifarious resistance to targeted therapies and chemotherapies.

## CRediT Authorship Contribution Statement

**Rafael Rosell:** Conceptualization, Methodology, Writing.

**Carlos Pedraz-Valdunciel:** Conceptualization, Methodology, Writing - preparation.

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