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PMed-TRIAL PDX database: integrated multidimensional information to facilitate new drug development

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Introduction

PDX models play a crucial role in pre-clinical research for new drugs. In recent years, research based on PDX models has entered the 'Big Data Era.' On the one hand, there are numerous factors influencing drug responses, such as cancer types, genetic backgrounds, clinical treatment histories, and more. Therefore, selecting the appropriate PDX models for drug efficacy testing based on relevant information has become increasingly important. On the other hand, conducting in-depth genomic and transcriptomic analyses on PDX models allow us to gain a deeper understanding of the mechanisms of drug efficacy and drug sensitivity.

After years of effort, LIDE has successfully built and maintained over 2000 PDX models from 40 different cancer types. At the end of 2023, we launched LIDE's PMed-TRIAL PDX database website. As a comprehensive database of PDX models, it includes fundamental PDX clinical information, medication history, growth curves, and standard of care (SOC) data. It also contains whole exome sequencing data and RNA-seq data.

Cancer is a complex and heterogeneous disease characterized by tumor heterogeneity, encompassing both inter-tumor diversity (between patients) and intra-tumor variability (within a single patient), thereby complicating drug responsiveness. PDX models preserve heterogeneity of individual patients, and a robust PDX cohort is essential for accurately representing inter-tumor heterogeneity. LIDE's PDX cohorts effectively capture representative molecular subtypes across various major cancer types, highlighting their potential as a valuable resource for pre-clinical trials.

LIDE's PMed-TRIAL PDX database comes with a concise and efficient web user interface. Users can search and filter models using keywords, such as drug names, gene symbols, and other information. The website can now be accessed via the following URL (https://pmed.lidebiotech.com:8000/).

Database Content

The PMed-TRIAL database presently encompasses 1805 distinct PDX models, representing over 40 different cancer types.

Each model meticulously documents clinical background information, including patient age, gender, cancer type, clinical diagnosis, and clinical medication history. Additionally, PDX pathology is recorded, and models are categorized based on treatment status as either 'Treatment Naïve' or 'Pre-Treated'.

Multi-omics Data

More than 900 models are accompanied by Whole Exome Sequencing and Transcriptome sequencing results, which include data on mutations, copy number variation (CNVs), gene expression and gene fusions.

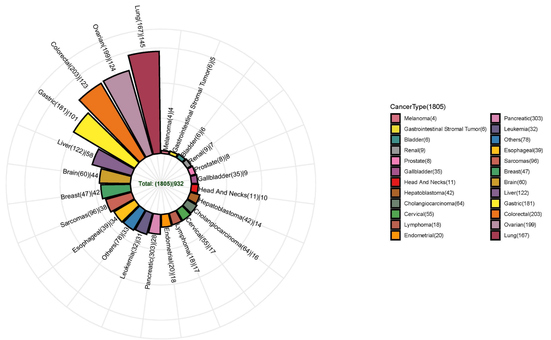


Figure 1. Statistics of Various PDX Cancer Types with Omics Results

Database Content (CONT)

Growth Curve

The growth curve depicts the rate of mouse tumor growth, accompanied by tumor volume measurements. It also captures data on the mouse strain, passage, and changes in mouse weight. Presently, the database contains records of growth curves for 1793 models.

SOC（Standard of cure）

264 models feature Standard of Care (SOC) experimental data, crucial for evaluating model drug efficacy and drug sensitivity. SOC data encompasses tumor size at various time points and details about mouse strains and passages, serving as valuable references for model selection.

IHC (Immunohistochemistry)

The database comprises IHC data for over 100 targets, across 789 different models.

Figure 2. Illustrative Example of Growth Curve, SOC Data, and IHC Analysis

Genomic Diversity is well preserved

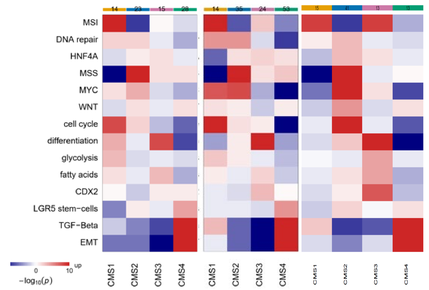


Figure 3. CMS Subtyping Categories for Colorectal Adenocarcinoma

The figure shows CMS subtyping[1] results for TCGA-COAD, TCGA-READ, and LIDE's PDX-COREAD from left to right. It can be observed that LIDE's PDX repository covers a sufficient number of samples for various subtypes.

PDX ID	Cancer type	HPV status	HPV genotype
LD1-0010-362390	Cervical cancer	positive	HPV16
LD1-0010-360655	Cervical cancer	positive	HPV16
LD1-0010-361943	Cervical cancer	positive	HPV16
LD5-2010-410946	Cervical cancer	positive	HPV16
LD1-0010-362824	Cervical cancer	positive	HPV16
LD1-0010-362343	Cervical cancer	positive	HPV16
LD1-0010-200625	Cervical cancer	positive	HPV18
LD1-0010-200615	Cervical cancer	positive	HPV33
LD5-1010-411019	Cervical cancer	positive	HPV33
LD5-0010-410648	Cervical cancer	positive	HPV33
LD5-0010-410733	Cervical cancer	positive	HPV33
LD1-0010-200614	Cervical cancer	negative	/
LD1-0010-361798	Cervical cancer	negative	/
LD2-0010-200714	Cervical cancer	negative	/
LD1-0010-362143	Cervical cancer	negative	/
LD1-0010-362783	Cervical cancer	negative	/
LD5-0010-362925	Cervical cancer	negative	/

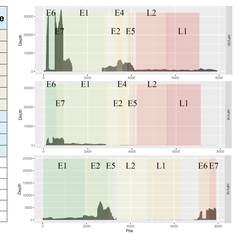


Figure 4. The HPV Status of Cervical Cancer PDX Models

In LIDE's PDX database, we detected various HPV subtypes in different Cervical Cancer models, particularly noting a significant prevalence of HPV16 and HPV33 infections. Virus sequence alignment also reveals elevated expression levels of viral genes.

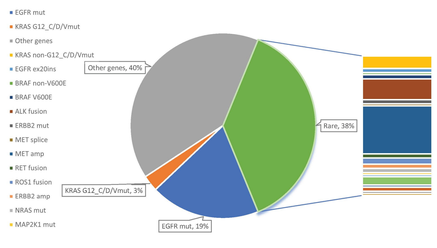


Figure 6. Mutation profiling of Non-Small Cell Lung Cancer (NSCLC) PDX Models

Referring to the literature[2], we present common EGFR and KRAS mutations, as well as relatively rare mutation spectra. It can be observed that LIDE's PDX database enriches for many models with rare mutations, such as ALK fusion and MET amplification. Additionally, our database enriches for other gene mutations mainly associated with drug-resistance, such as PIK3CA mutations, CDKN2A loss, CCND1 amplification, CDK4/6 amplification, and so on.

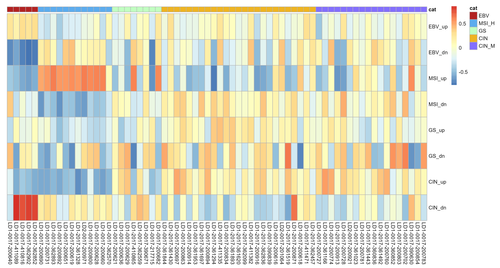


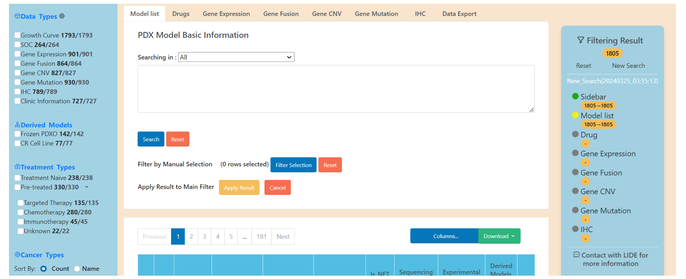
Figure 5. Subtyping for Gastric Cancer PDX models

At the DNA level, we analyzed the EBV status, MSI status[3], genomic stability (GS), and chromosomal instability (CIN)[4], dividing gastric cancer models into mainly four subtypes[5]: EBV, MSI-H, GS, and CIN. Additionally, some models tended towards CIN but lacked sufficient resolution, thus provisionally defined as CIN_M (Median). Furthermore, we demonstrated the gene expression signatures described in the literature[6], which exhibited strong correlations in EBV and MSI-H signatures, while also indicating tendencies for GS and CIN signatures.

User Interface

The PMed-TRIAL website offers a user-friendly design interface, making it easy to navigate and utilize. Here are some key features:

- **Powerful**: Users can easily search and filter PDX models based on keywords, drug names, gene expression, fusion, CNV, and mutation.
- **Flexible**: Various filtering criteria can be combined as desired. Users can specify cancer types or data types through the sidebar. Different logic can be applied between different genes and drugs. The Filtering Result panel provides real-time display of the number of models meeting the criteria.
- **Convenient**: Reset, new search, and history record functions are available. This allows users to conduct multiple searches simultaneously and switch between them conveniently.



Summary and Conclusion

The PMed-TRIAL Database undergoes continual updates and expansions to integrate additional sequencing data and various other valuable information.

1. More PDX models and additional datasets, such as growth curves, SOC data, gene sequencing data, and PDX histopathology (HE) images, will be added to the database.

2. Further uploads of bioinformatics analysis data will encompass HLA Type, Virus Status (HPV, HBV, EBV, etc.), and MSI status.

3. Development is underway for databases dedicated to CDX models, syngeneic models, and conditionally reprogrammed cell lines.

References

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