# Precision oncology

- PAM-free hairpin target binding activates trans-cleavage activity of Cas12a
- Deep learning algorithms from histopathological images stratify molecular subtypes for leiomyosarcoma: a proof-and-concept diagnostic study
- Molecular Genetics of Renal Cell Carcinoma: A Narrative Review Focused on Clinical Relevance
- Design and Development of a Device (Sifilotto<sup>®</sup>) for Tumour Tracking in Cervical Cancer Patients Undergoing Robotic Arm LINAC Stereotactic Body Radiation Therapy Boost: Background to the STARBACS Study
- NCT-CXR: Enhancing Pulmonary Abnormality Segmentation on Chest X-Rays Using Improved Coordinate Geometric Transformations
- Development and In Vitro Characterization of [<sup>3</sup>H]GMC-058 as Radioligand for Imaging Parkinsonian-Related Proteinopathies
- Potential Applications of PRP-Enhanced Polybutylene Succinate Graft as Vascular Access for Chemotherapy in Oncological Patients: A Systematic Review
- Material-Driven Therapeutics: Functional Nanomaterial Design Paradigms Revolutionizing Osteosarcoma Treatment

Precision oncology is an innovative approach to cancer treatment that tailors therapies to the specific molecular and genetic characteristics of a patient's tumor.

## Key Concepts

Beyond Location-Based Treatment: Unlike traditional oncology, which classifies cancer primarily by where it occurs in the body (e.g., lung, breast, colon), precision oncology focuses on the biological drivers of the cancer, regardless of location.

Molecular Profiling: This involves sequencing the tumor’s DNA and RNA to identify specific mutations, gene fusions, amplifications, or other abnormalities.

Targeted Therapies: Based on the tumor's unique molecular profile, clinicians may use drugs that specifically target those abnormalities (e.g., EGFR inhibitors for EGFR mutations, ALK inhibitors, BRAF inhibitors, etc.).

Immunotherapy Integration: Biomarkers such as PD-L1 expression or microsatellite instability (MSI-H) can inform the use of immune checkpoint inhibitors.

Companion Diagnostics: Many therapies require FDA-approved tests to confirm the presence of a specific mutation before treatment is started.

## Clinical Applications

NGS (Next-Generation Sequencing) is a cornerstone of precision oncology.

Frequently used in lung cancer, melanoma, colorectal cancer, and increasingly in glioblastomas, sarcomas, and pediatric tumors.

Plays a major role in liquid biopsy (non-invasive testing via blood samples).

# Limitations

Not all tumors have actionable mutations.

Targeted therapies can be very expensive.

Tumor heterogeneity and resistance mechanisms can limit long-term efficacy.

# Preclinical translational research studies

Precision oncology preclinical translational research studies focus on bridging the gap between laboratory discoveries and clinical applications, aiming to develop targeted therapies that improve patient outcomes. These studies involve several key components:

### **1. Preclinical Models in Precision Oncology** - **Patient-Derived Xenografts (PDX)**: Tumors from patients implanted in immunodeficient mice to maintain the tumor's genetic and histological characteristics. - **Organoids**: 3D cultures derived from patient tumors that mimic in vivo conditions, allowing high-throughput drug screening. - **Genetically Engineered Mouse Models (GEMMs)**: Mice modified to develop tumors with specific genetic mutations seen in human cancers. - **Syngeneic Mouse Models**: Murine tumors implanted in immunocompetent mice to study interactions between cancer and the immune system.

### **2. Translational Biomarker Development** - **Genomic Profiling**: Next-generation sequencing (NGS), whole-exome sequencing, and RNA sequencing to identify mutations and gene expression changes. - **Proteomic and Metabolomic Approaches**: Mass spectrometry-based analysis to uncover protein and metabolite signatures linked to treatment responses. - **Liquid Biopsy**: Circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), and exosomes as non-invasive biomarkers for monitoring therapy response.

### **3. Drug Sensitivity and Resistance Mechanisms** - **High-Throughput Drug Screening**: Testing large panels of drugs on patient-derived models to identify effective compounds. - **CRISPR and RNAi Screening**: Genome-wide functional screening to discover resistance mechanisms and potential drug targets. - **Single-Cell Sequencing**: Unraveling intratumoral heterogeneity and identifying subpopulations that drive resistance.

### **4. Immuno-Oncology in Precision Medicine** - **Checkpoint Inhibitor Studies**: Preclinical testing of PD-1, PD-L1, and CTLA-4 inhibitors in various models. - **Chimeric Antigen Receptor (CAR) T-Cell Therapy**: Evaluating the efficacy of CAR-T cells in solid tumors. - **Tumor Microenvironment Analysis**: Investigating immune cell infiltration and stromal interactions using spatial transcriptomics and multiplex imaging.

### **5. AI and Computational Approaches in Translational Oncology** - **AI-Based Drug Discovery**: Machine learning models predicting drug-target interactions and resistance pathways. - **Multi-Omics Data Integration**: Using AI to combine genomic, transcriptomic, proteomic, and metabolomic data for personalized therapy recommendations. - **Digital Pathology**: AI-powered histopathological image analysis for tumor classification and biomarker discovery.

### **6. Translational Impact and Clinical Implications** - **Clinical Trial Design**: Incorporating preclinical findings into adaptive and basket trials for targeted therapies. - **Companion Diagnostics Development**: Validating predictive biomarkers for FDA-approved drugs. - **Real-World Data and Patient-Derived Insights**: Integrating patient outcomes into preclinical modeling for therapy refinement.

---

Peng et al. developed a fast, efficient, and complex culture system (IPTO, individualized patient tumor organoids) that accurately recapitulates the cellular and molecular pathology of human brain tumors. Patient-derived tumor explants were cultured in induced pluripotent stem cell (iPSC)-derived cerebral organoids, thus enabling the culture of a wide range of human tumors in the central nervous system (CNS), including adult, pediatric, and metastatic brain cancers. Histopathological, genomic, epigenomic, and single-cell RNA sequencing (scRNA-seq) analyses demonstrated that the IPTO model recapitulates cellular heterogeneity and molecular features of original tumors. Crucially, they showed that the IPTO model predicts patient-specific drug responses, including resistance mechanisms, in a prospective patient cohort. Collectively, the IPTO model represents a breakthrough in the preclinical modeling of human cancers, which provides a path toward precision oncology [1)].

---

Advances in whole genome sequencing have led to identification of genes involved in a variety of diseases. Moreover, biomarkers indicating severity of disease or susceptibility to treatment are increasingly being characterized. The continued identification of new genes and biomarkers specific to disease subtypes and individual patients is essential and inevitable for translation into personalized medicine, in estimating both, disease risk and response to therapy. Taking into consideration the mostly unsolved necessity of tailored therapy in oncology the innovative project MOBIT (molecular biomarkers for individualized therapy) was designed. The aims of the project are: (i) establishing integrative management of precise tumor diagnosis and therapy including systematic biobanking, novel imaging techniques, and advanced molecular analysis by collecting comprehensive tumor tissues, liquid biopsies (whole blood, serum, plasma), and urine specimens (supernatant; sediment) as well as (ii) developing personalized lung cancer diagnostics based on tumor heterogeneity and integrated genomics, transcriptomics, metabolomics, and radiomics PET/MRI analysis. It will consist of 5 work packages. In this paper the rationale of the Polish MOBIT project as well as its design is presented. (iii) The project is to draw interest in and to invite national and international, private and public, preclinical and clinical initiatives to establish individualized and precise procedures for integrating novel targeted therapies and advanced imaging techniques [2)].

---

The field of oncology is currently undergoing a paradigm shift. Advances in the understanding of tumor biology and in tumor sequencing technology have contributed to the shift towards precision medicine, the therapeutic framework of targeting the individual oncogenic changes each tumor harbors. The success of precision medicine therapies, such as targeted kinase inhibitors and immunotherapies, in other cancers have motivated studies in brain cancers. The high specificity and cost of these therapies also encourage a shift in clinical trial design away from randomized control trials towards smaller, more exclusive early phase clinical trials. While these new trials advance the clinical application of increasingly precise and individualized therapies, their design brings ethical challenges [3)].

1)

Peng T, Ma X, Hua W, Wang C, Chu Y, Sun M, Fermi V, Hamelmann S, Lindner K, Shao C, Zaman J, Tian W, Zhuo Y, Harim Y, Stöffler N, Hammann L, Xiao Q, Jin X, Warta R, Lotsch C, Zhuang X, Feng Y, Fu M, Zhang X, Zhang J, Xu H, Qiu F, Xie L, Zhang Y, Zhu W, Du Z, Salgueiro L, Schneider M, Eichhorn F, Lefevre A, Pusch S, Grinevich V, Ratliff M, Loges S, Bunse L, Sahm F, Xiang Y, Unterberg A, von Deimling A, Platten M, Herold-Mende C, Wu Y, Liu HK, Mao Y. Individualized patient tumor organoids faithfully preserve human brain tumor ecosystems and predict patient response to therapy. Cell Stem Cell. 2025 Feb 5:S1934-5909(25)00002-5. doi: 10.1016/j.stem.2025.01.002. Epub ahead of print. PMID: 39938519.

2)

Niklinski J, Kretowski A, Moniuszko M, Reszec J, Michalska-Falkowska A, Niemira M, Ciborowski M, Charkiewicz R, Jurgilewicz D, Kozlowski M, Ramlau R, Piwkowski C, Kwasniewski M, Kaczmarek M, Ciereszko A, Wasniewski T, Mroz R, Naumnik W, Sierko E, Paczkowska M, Kisluk J, Sulewska A, Cybulski A, Mariak Z, Kedra B, Szamatowicz J, Kurzawa P, Minarowski L, Charkiewicz AE, Mroczko B, Malyszko J, Manegold C, Pilz L, Allgayer H, Abba ML, Juhl H, Koch F; MOBIT Study Group. Systematic biobanking, novel imaging techniques, and advanced molecular analysis for precise tumor diagnosis and therapy: The Polish MOBIT project. Adv Med Sci. 2017 Jun 21;62(2):405-413. doi: 10.1016/j.advms.2017.05.002. [Epub ahead of print] PubMed PMID: 28646744.

3)

Gupta S, Smith TR, Broekman ML. Ethical considerations of neuro-oncology trial design in the era of precision medicine. J Neurooncol. 2017 May 29. doi: 10.1007/s11060-017-2502-0. [Epub ahead of print] Review. PubMed PMID: 28555425.