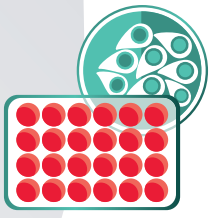
Drug discovery using QPI technology

The search for new therapies to treat widespread diseases such as cancer, neurodegeneration, and infections remains one of the main focuses of biomedical research today. In drug development, typically two main approaches are followed: target-based and phenotypic screening. **Target-based drug discovery** is characterized by screening compounds against a known molecular target. **Phenotypic drug discovery** involves observation of phenotype changes (e.g., cell morphology, viability, or behavior) without prior knowledge of the molecular target. Subsequent target deconvolution is used to identify the compound's mechanism of action. Target-based drug discovery belongs to the dominant approaches in academia and the pharmaceutical industry. However, with advances in technology such as machine learning (ML) in high-content imaging screening, Phenotypic drug discovery has seen a resurgence [1]. The Q-Phase microscope enables early detection of unbiased phenotypic changes, researchers can monitor drug effects on cell behavior in real time and without the need for fluorescent labels. These changes can be detected using the quantitative phase imaging (QPI) technique. Additionally, Q-Phase generates robust datasets well-suited for high-content screening, utilizing advanced ML analysis.

Phenotypic drug discovery workflow example

Experiment design



- therapeutic compounds
- different cell lines

Phenotypic screening

- label-free imaging
- fluorescent detection
- measurement of morphological parameters

Multiparametric data analysis

- feature extraction
- image analysis
- ML analysis

Mechanism of action profiling

- understanding the biological mechanism
- identifying molecular target

Terminology

Quantitative phase imaging	QPI is an advanced, label-free microscopy technique for imaging cells by measuring the optical phase shift of light as it passes through transparent cells.
High-content screening	High-content screening (HCS) is an automated, image-based method that combines microscopy with quantitative analysis to extract multiparametric data from cells. It enables detailed phenotypic profiling for drug discovery.
Circularity	Circularity measures how close a cell's shape is to a perfect circle and can reflect biological processes such as cell death, division, and migration. A value of 1.0 indicates a perfect circle.
Cell dry mass	Cell dry mass [pg] refers to everything inside a cell except water. It consists mainly of proteins, lipids, and other biomolecules. It is often reported as cell dry mass density, which represents the amount of dry mass per unit area in the image plane and is measured in picograms per square micrometer [pg/μm^2].

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Drug discovery

Phenotypic analysis of cisplatin response

Time-dependent morphological changes

In phenotypic drug discovery, it is important to understand how drugs affect cell morphology. Measuring morphological changes in different cell lines can reveal how various treatments influence cellular behavior. PC-3 prostate cancer cells were exposed to increasing concentrations of the chemotherapy agent cisplatin (cisPt 0, 12.5, 25, 50, 100, and 200 µM) to demonstrate the efficacy of QPI in drug discovery. By using QPI, we monitored changes in a label-free morphological parameter – cell dry mass.

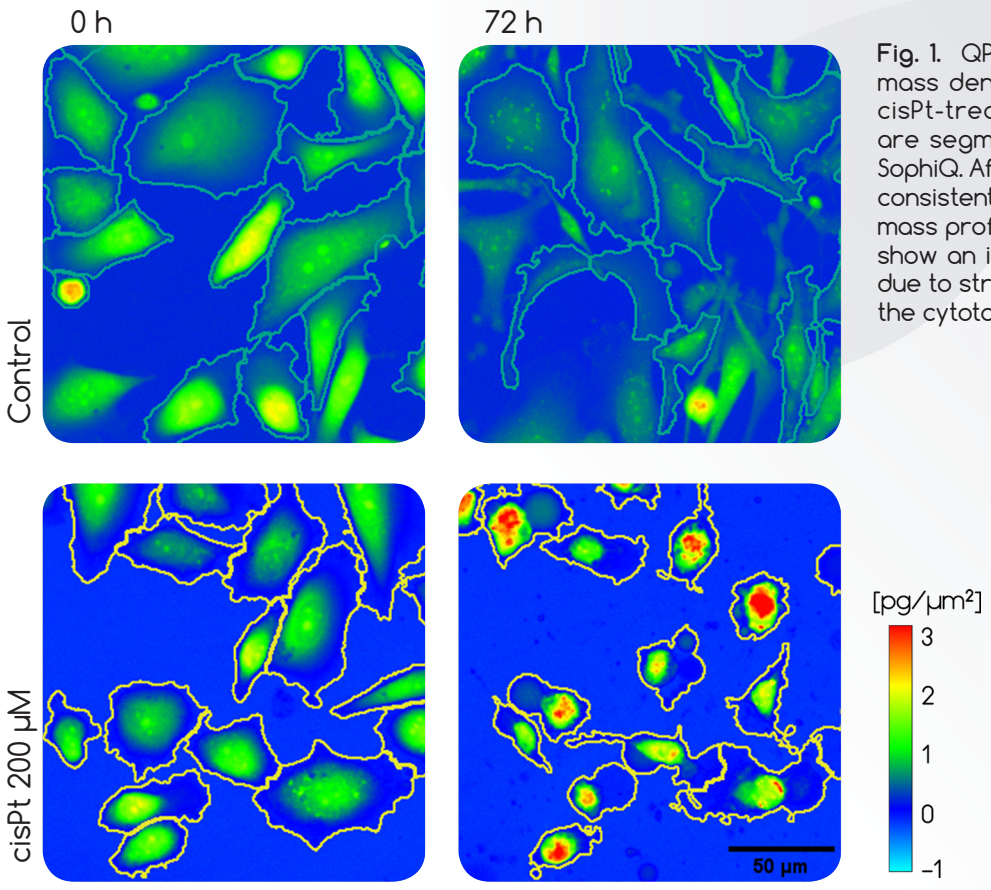
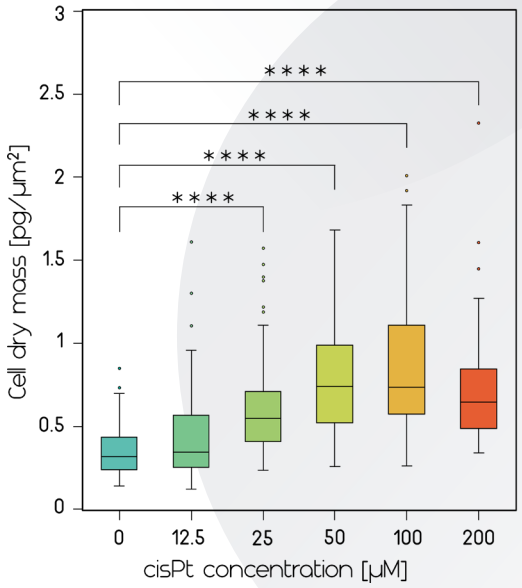


Fig. 1. QPI label-free images of cell dry mass density distribution in control and cisPt-treated (200 µM) PC-3 cells. Cells are segmented by the Telight software, SophiQ. After 72 hours, control cells display consistent morphology with stable cell dry mass profile. In contrast, the treated cells show an increase in their dry mass (red) due to structural condensation caused by the cytotoxic effect of cisPt.

Cell dry mass quantification

Fig. 2. Cell dry mass quantified using Q-Phase for each cisPt concentration after 72 hours. Boxes and error bars represent interquartile range and 95% percentile. Outliers are shown as individual dots. Statistical significance was evaluated using Kruskal-Wallis test (****, $p < 0.0001$), $n \geq 70$.



Q-Phase benefits

- monitoring subtle changes in cells
- quantitative multiparametric analysis
- studying drug responses in various cell types
- designing custom experimental set-ups

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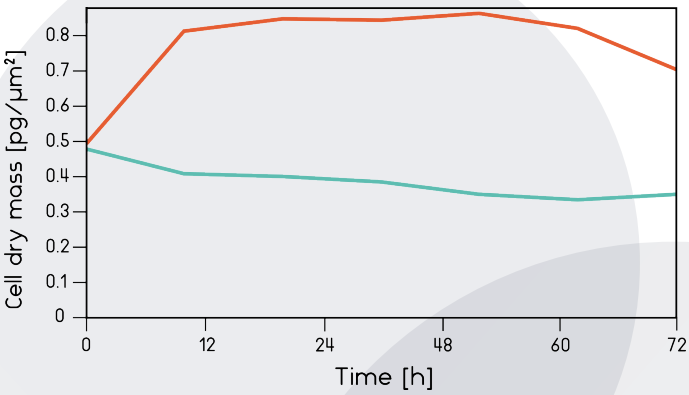

Fig. 3. Time graph of cell dry mass changes directly measured by Telight software, SophiQ, over 72 hours. CisPt (200 µM) treated PC-3 cells show an increase in density within the first 12 hours, indicating cellular condensation associated with cell death. In contrast, the cell dry mass of control cells remains relatively stable, reflecting normal proliferation.

Why is it important to quantify cell dry mass?

- Dry mass can change before the cell even shows visible signs of dying or adapting.
- If a drug just stops cell growth (cytostatic effect), the dry mass might remain stable.
- A change in dry mass can signal shifts in metabolism, helping researchers understand how a drug engages with the cell's inner economy.

From morphology changes to revealing drug mechanism

Comparing drug effects across prostate cancer cell lines

The authors of this study [2] present a promising approach that helps understand the correlation between the cell structure, cell mechanics, and function. Researchers studied the effect of anti-cancer treatments - docetaxel, cisPt, and long-term zinc supplementation on prostate-derived cell lines: PNT1A (healthy cells), 22Rv1 (primary tumor cells), PC-3 (metastatic cells). The study also shows how measuring key features like cell dry mass, shape (circularity), and how fast cells move (migration speed) with Q-Phase can give meaningful insight into biological mechanisms.

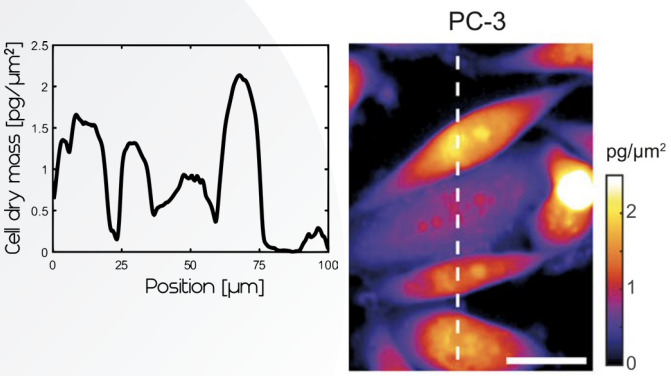

Fig. 4. QPI image of PC-3 cell of cell dry mass density (right) with their profile (left) in the corresponding cutting point (white line). Original graph and image from [2].

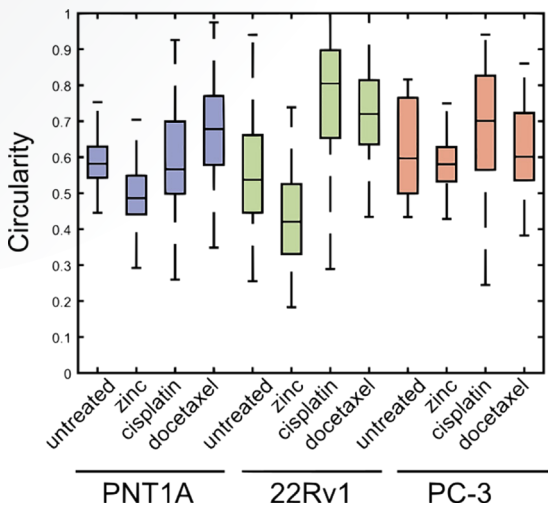

Fig. 5. Quantitative analysis of cell circularity measured by Q-Phase, following 24 hour treatment. Original graph from [2].

Summary

QPI, together with other microscopy methods (atomic force microscopy, confocal microscopy, etc.), provides a comprehensive approach for exploring how cell structure relates to biomechanical properties. The analysis revealed an association between higher cell dry mass, circularity, and increased cell stiffness measured by AFM, particularly in prostate cancer cells treated with cisplatin and docetaxel. Measuring these key features helped the researchers conclude the presumed effect of cisPt on the cytoskeleton, including its role in reducing metastatic potential.

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Linking morphological changes to Mechanism of Action

In this study [3], researchers used QPI to investigate the effects of novel anticancer agents - pentamethinium salts (PMSs). The compounds reduced cancer cell motility and growth rate, along with alterations in cell shape and dry mass, which serve as early indicators of cytotoxic effects after treatment. These findings were associated with PMSs accumulating in mitochondria and inhibiting dihydroorotate dehydrogenase (DHODH), an enzyme essential for pyrimidine biosynthesis. QPI allowed the authors non-invasive, real-time monitoring of changes in cell dynamics.

	Mass [pg/µm²]	Area [µm²]	Speed [µm/h]	Growth rate [pg/h]	Perimeter [µm]	Circularity [%]
control 1	473	912	181*	136	138	63
PMS 1	560	850	27	3	122	72
control 2	460	702	77	53	118	66
PMS 2	544	675	17	-1	106	74

Fig. 6. The PC-3 cell line measured parameters before and after treatment with PMS 1 and PMS 2. All values were automatically calculated using the Telight software, SophiQ. Original table from [3].

Why to use Q-Phase in drug discovery projects?

- QPI provides **real-time, label-free analysis** of living cells under drug treatment.
- It quantifies subtle **biophysical changes** like dry mass and cell growth which can be subsequently analyzed in our **SophiQ software**.
- QPI delivers **high-quality, artifact-free data** ideal for multiparametric analysis
- It enables automated screening with **reproducible, quantitative outputs** ideal for research replication.

Conclusion

Q-Phase is a cutting-edge light microscope based on QPI technology that provides precise visualization of cells and their dynamics without the need for fluorescent markers. In an analytical workflow, QPI is often used as a complementary imaging technique alongside methods such as confocal microscopy, atomic force microscopy, or biochemical assays. Unlike these methods, QPI is completely non-invasive, allowing long-term observation of cells without damaging or affecting them. This enables the observation of actual biological changes caused solely by the tested drug. This makes Q-Phase an ideal tool for the early stages of phenotypic drug discovery. Furthermore, by detecting dose-dependent morphological responses in cells, Q-Phase can be used in preclinical testing on patient-derived cells to support personalized medicine.

References

1. Krentzel, D., Shorte, S. L. & Zimmer, C. Deep learning in image-based phenotypic drug discovery. Trends Cell Biol. 33, 538–554 (2023).
2. Raudenska, M. et al. Cisplatin enhances cell stiffness and decreases invasiveness rate in prostate cancer cells by actin accumulation. Sci. Rep. 9, 1660 (2019).
3. Fialova, J. L. et al. Pentamethinium salts suppress key metastatic processes by regulating mitochondrial function and inhibiting dihydroorotate dehydrogenase respiration. Biomed. Pharmacother. 154, 113582 (2022).

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