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Getting Started With Cytos™

What to know when considering a CRISPR or drug screen with Cytos



Cytos™ Getting Started Guide
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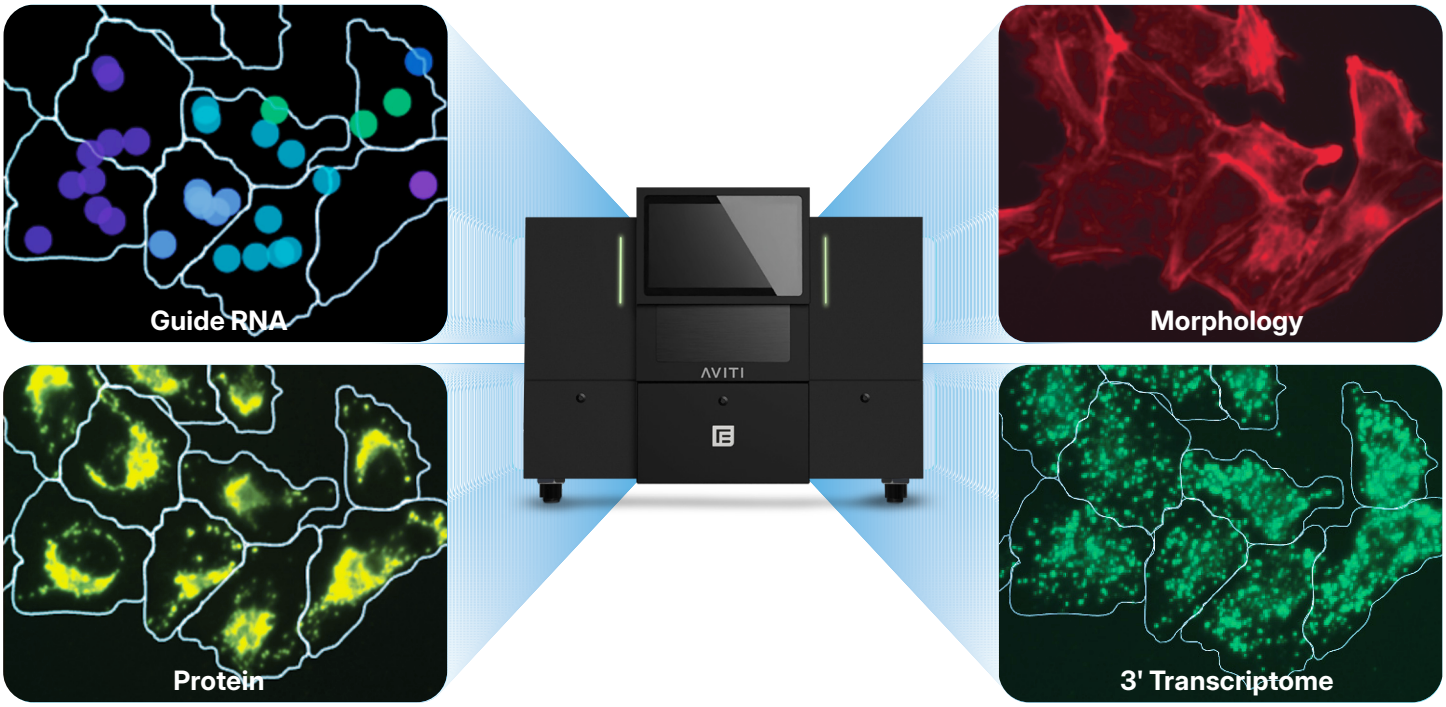
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Planning your Cytos multiomic cell screening experiment

CRISPR and drug screens are effective at identifying hits—a compound dose that cause cell death or a gene knockout that results in morphological differences. Traditionally, understanding how and why that result occurs usually means designing follow-up experiments: imaging, transcriptomics, or protein detection, each run separately, on a different sample, and analyzed independently.

Cytos integrates those measurements into a single screen, linking every readout to the perturbation behind it. In a single run on AVITI24™, Cytos captures morphology, protein, 3′ transcriptome, and guide RNA with subcellular precision.

This guide is for researchers evaluating Cytos for CRISPR screening, drug screening, or both. It explains how the workflow and chemistry work, what to think about when you're designing a screen, and what data and analysis tools you can expect.



- **Guide DNA: 10s – 10,000s** gRNAs
- **Protein: Up to 20** proteins
- **Morphology: 100+** features/target
- **3' Transcriptome: Up to 2,500** transcript counts/cell*

* Untreated HeLa cells; results may vary

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What you can study with Cytos

Cytos is built for screens where identifying a hit is the starting point. The use cases below are common reasons researchers choose it.



CRISPR screening

- **Target discovery:** Which genes drive a disease-relevant phenotype?
- **Target confirmation:** Does a candidate gene behave as expected across molecular and cellular readouts?
- **Mechanism of action:** How does a genetic perturbation reshape cellular pathways?
- **Genotype-to-phenotype linkage:** What effect does a variant have on the cell?
- **Cell state:** Which genes shape a cell's identity, activation, or stress response?
- **Resistance mapping:** Which vulnerabilities could prevent or overcome resistance?



Drug screening

- **Hit confirmation:** Is a phenotype real before you move into lead optimization?
- **Mechanism of action:** How does a compound's morphological and molecular profile compare with known mechanisms?
- **On- and off-target activity:** Is the effect coming from the intended target or from nonspecific stress?
- **Toxicity characterization:** How do toxicity signatures change across doses, timepoints, and cell states?
- **Lead optimization:** Which compound series should advance based on potency, selectivity, and phenotype?
- **Heterogeneous responses:** Are there rare responders or cell-state-specific effects?

Which cell types and samples can I use with Cytos?

Cytos currently performs best with immortalized human cell lines, including widely used lines such as HeLa, U2OS, and A549. Both adherent and suspension cells are supported. A typical run uses roughly 300,000 adherent cells or up to 1 million suspension cells, though the right number depends on your cell type and experimental design.

Other sample types, such as mouse and rat cells, primary cells, and iPSC-derived lines, can work on Cytos but typically need additional optimization. Organoids, tissue-derived samples, cells not growing in a monolayer, and single nuclei are not currently supported.

We're actively evaluating new cell types, and the range of supported samples will continue to grow. If you're planning to work with a cell type outside the validated set, we recommend an optimization run before your full experiment. A field application scientist can share the latest performance data and help you plan it.

Learn more about compatible cell types in our support hub.

What is the workflow?

Get started with Cytos by designing your CRISPR or drug screen, including controls. Use our customer designer to design custom RT and sequencing primers, and choose custom antibodies. From there, optimize cell seeding and design your run in ElemBio™ Cloud.

Running Cytos on AVITI24 is simple. Treat your cells or introduce your guide library, culture cells directly on Cytos slides, fix, and load. Cellular morphology, protein, transcriptome, and guide sequencing are captured directly on the instrument with no additional hands-on time.

Analysis starts automatically with ElemBio Catalyst™. It handles routine workflows, including transcriptome processing and alignment. Every readout comes together with CytoCanvas™ visualization and AI-tooling for downstream analysis.

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1 **Design & Optimize**



Design primers, optimize cell seeding, and layout your experimental conditions.

2 **Sample prep**



Cell and fix adherent and suspension cells.

3 **Imaging & sequencing**



Morphology, protein, transcriptome, and guide assignment captured in one run

4 **Secondary analysis**



ElemBio Catalyst handles transcriptome processing

5 **Visualization & tertiary analysis**



Dynamically visualize cells and simplify analysis with agentic skills

What readouts can I measure?

Cytos is available in three configurations based on your experimental application and desired readouts.

- **Optical pooled screening (OPS):** Guide RNA and morphology, with optional protein detection.
- **3′ Transcriptome:** Morphology, 3′ transcriptome, and optional protein detection.
- **Multimodal pooled screening (MPS):** Guide RNA, morphology, and 3′ transcriptome, with optional protein detection.

Configuration	Protein (up to 20-plex)	Cell paint (membrane, nucleus, actin, mitochondria)	3' transcriptome (poly-A-based)	Guide RNA (10s–10,000s)
Optical Pooled Screening	√	√		√
3' Transcriptome	√	√	√	
Multimodal Pooled Screening	√	√	√	√

You choose the readouts that fit your needs by selecting an application. Measuring several modalities in the same cell saves the time and cost of running separate assays, and it makes it possible to connect a phenotype directly to the pathway or protein changes behind it.

How does my existing screen design fit into the workflow?



CRISPR screens:

The most important factors when considering whether your existing CRISPR screen design is compatible with Cytos are:

1. Guide RNA expression: For optimal results, guide libraries should be highly expressed.
2. Reporter cell lines expressing fluorescent proteins: Fluorescent reporters can interfere with the imaging-based readouts and are not recommended for any Cytos runs. Learn more about the impact of fluroescent reporters.

Cytos supports up to 50 bp of sequencing, and our custom workflow designer provides automated primer design based on your existing scaffold sequence and all guide assignments are handled automatically onboard.

For more guidance on CRISPR screening with Cytos, refer to our CRISPR screening guidance.



Drug screens:

The main consideration when planning a drug screening experiment is optimizing the dose of any compounds or treatments. If the treatment kills most of the cells, the assay can fail. Running an IC50 beforehand helps you choose doses that produce the desired response while maintaining enough cells for analysis. Consider suitable timepoints for your experiment. For example, phosphorylated protein responses may show up in less than 30 minutes while seeing a change in morphology may require longer time points.

Reach out to our support team to discuss your specific project and screening needs.

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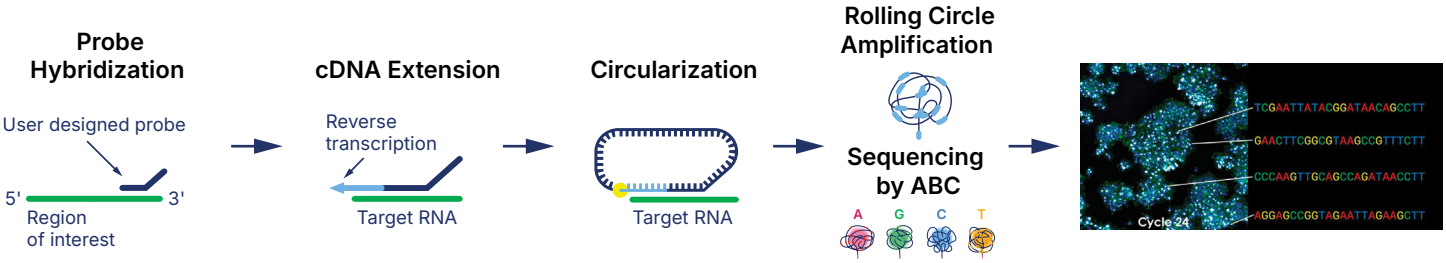
What chemistry powers Cytos?

Cytos uses two chemistries, depending on the readout—imaging for morphology and protein detection, and Direct In Sample Sequencing for RNA detection. Each modality is processed in one or more batches to avoid optical crowding for sensitive and simultaneous detection.

Direct In Sample Sequencing (DISS)

For 3' trancriptome and targeted gRNA detection, Cytos uses Direct In Sample Sequencing. Instead of extracting nucleic acids, building libraries, and performing downstream sequencing, the entire sequencing workflow happens directly inside the biological sample, preserving spatial context from start to finish.

At a high level, the chemistry begins with probe hybridization, cDNA extension, circularization, and sequencing with our Avidite Base Chemistry™. The core concept is straightforward: Cytos generates true sequencing reads directly at the site of the underlying biology. These steps together constitute PCR-free amplification of the target sequence, avoiding the pitfalls of PCR amplification.



All modalities are measured at subcellular resolution. While 3′ transcriptome is measured in a single cell, because it is captured optically, the number of transcripts detected per cell is limited by cell size. To build a full expression profile, counts are pseudobulked, or aggregated across cells grouped by morphology, protein, or guide identity. Expressed transcript space is typically saturated within a few hundred aggregated cells, achievable given run throughput.

See an example of this in a bioRxiv preprint.

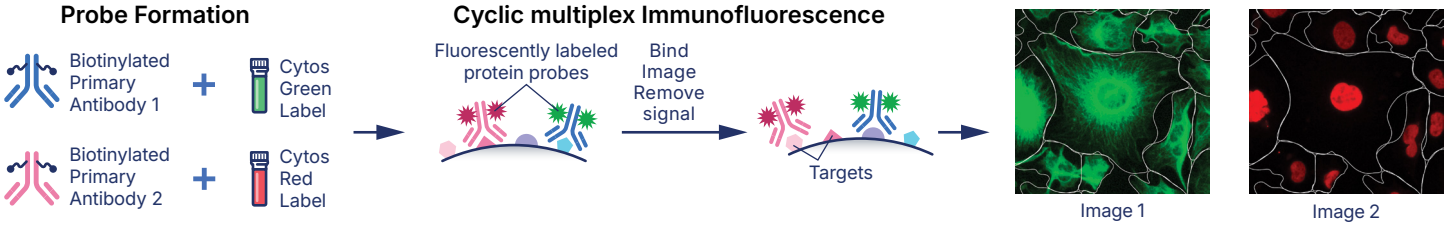
Fluorescence-based imaging chemistry for morphology and protein detection

Our imaging chemistry combines antibody and dye-based fluorescent labeling to capture rich cellular information in a single workflow.

Cell Paint labels key morphology markers—cell membrane, nucleus, mitochondria, and actin—enabling precise cell segmentation and detailed morphological feature extraction. An alternative morphology panel and/or custom antibodies can be used to add additional morphology markers. These can be used for re-segmentation, if needed.

Protein Detection uses immunofluorescence with Element-provided probes (antibody + dye label) or user-provided antibodies (combined with Element-provided dye labels to make the detection reagent) to quantify protein targets directly at the single-cell level.

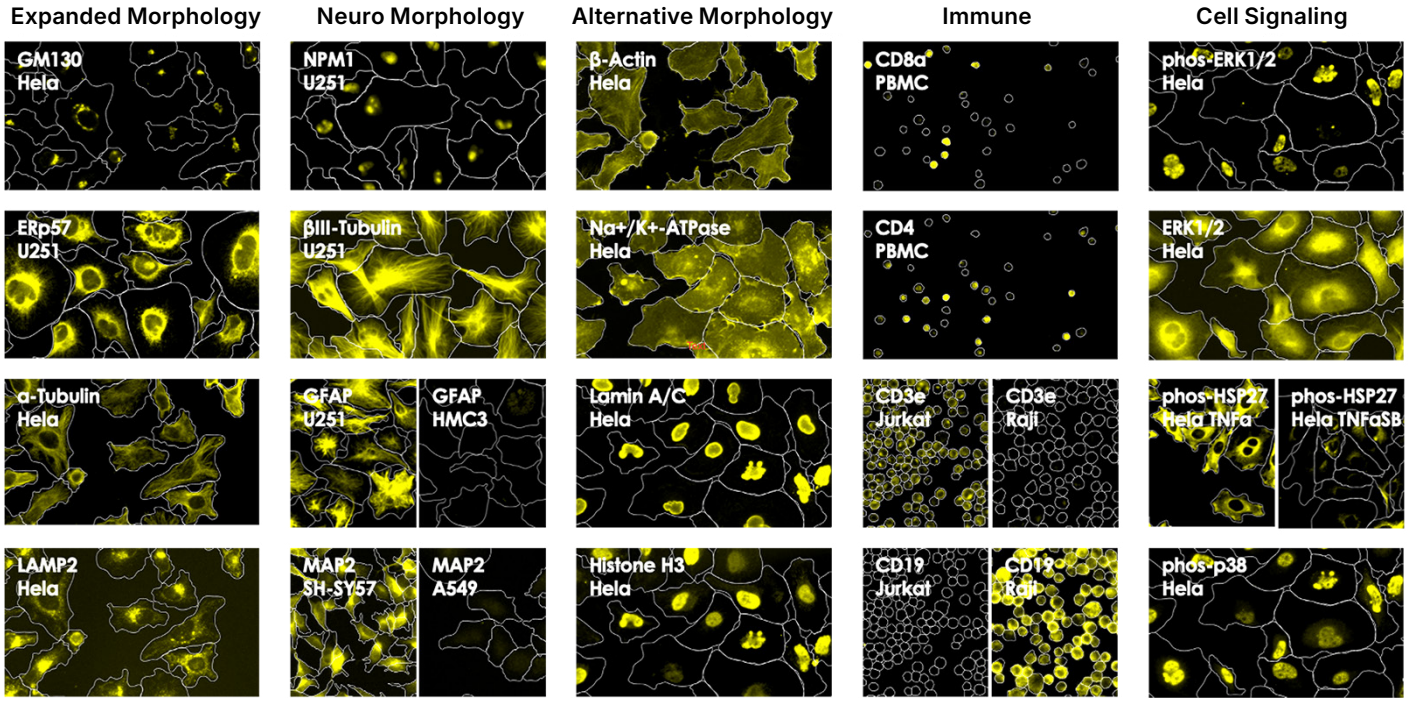
Immunofluorescence imaging chemistry enables high sensitivity with subcellular localization, a high dynamic range to detect proteins of varying expression levels, and low off-target binding. Learn more about Cytos protein detection.



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What protein and morphology markers can I use?

Cytos offers fixed, validated protein panels that can be combined to fit your experiment, along with support for custom antibodies. Learn more about our available panels in our protein catalog.



For additional protein or morphology markers, the user provides a biotinylated antibody and orders a dye label kit from Element. We recommend using monoclonal antibodies that have been validated in IF/IHC applications. Element's preferred antibody vendor, ABclonal, can assist with custom reagents, and our field application scientists can help you choose antibodies for use on Cytos.

How should I think about controls and replicates?

Tips for planning a CRISPR screen:

- Always include a non-targeting control and a guide against a gene with no expected effect in your system.
- When estimating how many cells you need per condition, start with a pilot experiment or approximate ~50% guide assignment as a starting point. See our CRISPR screening guidance for additional considerations.
- Up to ~80,000 guides can be assigned automatically onboard.

Tips for planning a drug screen:

- Randomize replicates and controls across the slide wherever possible, including across doses and time points.
- Because all wells on a slide are fixed at the same time, time-course experiments should be set up in reverse, with the longest treatments started first, so every condition reaches its endpoint at fixation.

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What data will I get and how do I analyze it?

Each run produces a Spatial Data Object (SDO), a standard format supported by the scverse ecosystem. At its center is an AnnData table, a cell-by-feature matrix in which each row is a single cell. Each cell row includes aligned 3′ counts, more than 100 CellProfiler metrics for each morphology and protein target, guide RNA counts, and associated metadata. Raw data is also provided for those who want to reprocess data or perform manual alignment.

The SDO also contains the underlying images, segmentation masks, and subcellular molecule locations in X-Y coordinates. Because every measurement comes from the same cell, readouts can be compared directly without matching data across experiments.

How analysis works:

Primary analysis runs onboard AVITI24. It performs segmentation, feature extraction via CellProfiler, protein intensity measurement, and guide alignment and assignment for CRISPR screening runs. A comprehensive QC report is ready to review as soon as the run is complete.

Secondary analysis happens automatically in ElemBio Catalyst™. 3′ transcriptome alignment runs through a Catalyst-supported Nextflow pipeline, and an editable default analysis package handles basic filtering and normalization. Re-segmentation is also available in Catalyst.

Results can be visualized in CytoCanvas. We also offer a bring-your-own-agent model to make analyzing Cytos data easy. Element provides AI analysis skills that can be loaded into the AI provider of your choice (with plugins for Claude and Cursor) for fast, reproducible analysis. For those using ElemBio Cloud and Catalyst, we also offer dynamic self-scaling sandbox compute to aid in your agentic analysis.

Questions about your screen?

Our team can help you work through cell type compatibility, screen design, and panel selection before you commit to an experiment. Reach out to us at: elementbiosciences.com/contact

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Element Biosciences

Telephone: 619.353.0300
Email: info@elembio.com