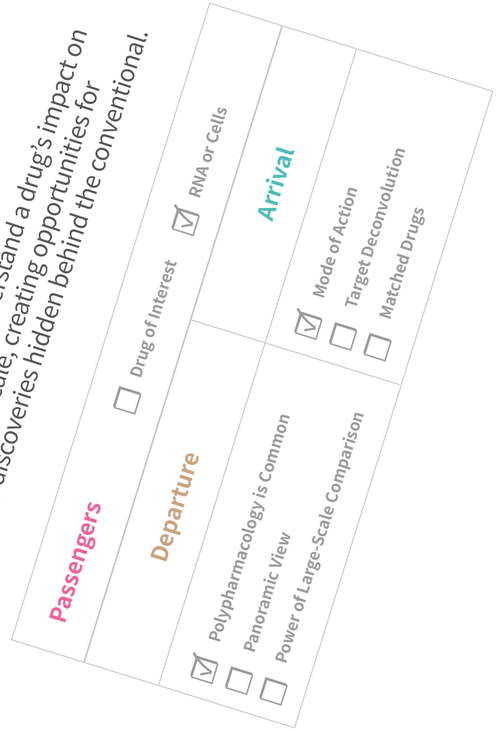
KaiPharm × "Precision Genomics" DNA LINK

Guide to Drug Development With Big Data & Expert Partners in Biology

Kmap Express™

We enable customers to understand a drug's impact on cells on a genomic scale, creating opportunities for unexpected discoveries hidden behind the conventional.



Unexpected Activity?

- Understand a drug's systematic mode of action (MoA) or disease processes/subtypes at the transcriptome level.
- Reveal secondary effects that compromise therapeutic outcome.
- Predict potential off-targets.

Insufficient Efficacy?

- Identify perturbed pathways that offset a drug's intended effect.
- Match the appropriate disease model with a patient subgroup for successful development.
- Search optimal drug pairs for effective combination therapy.

New Discovery?

- Drug repositioning for different disease models/patients.
- Discover novel indications for candidate, existing, or failed drugs as well as natural products.
- Apply a diverse range of drug modalities like small molecules, protein degraders (PROTAC and AUTOTAC), and antibodies.

"Colorful Discovery"

AI is an express aide in drug development.

For more discussions & studies, please CONTACT US.

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Passengers

Kmap Express™ "Colorful Discovery"

Disclaimers

- We claim NO intellectual property rights. Any intellectual property is owned by the customer 100%.
- Before sample preparation, it is recommended to share experimental protocols, such as cell harvesting and RNA extraction, to avoid miscommunication and ensure accurate transcriptomic profiling. Any information shared with us to support your efforts is protected by CDA.
- Drugs and biological samples (RNA, cells) must be provided within a maximum of 5 days of collection to avoid degradation or contamination.
- Identifiers (IDs) for users, project names, and samples can be no more than 30 characters in length, consisting of only English letters, numbers, or "_".

The required amount/concentration to be provided at the first consultation.

For RNA
total RNA >1 μg and a concentration between 15 and 20 ng/μl.

For Cells
>10^6 shipped in dry ice.

Departure

Polypharmacology is Common

- A drug (candidate) acts on multiple targets. Most approved drugs were developed as specific agonists or antagonists for a single target at the time of filing. However, subsequent studies have revealed that a drug has an average of about 15 experimentally validated targets.
- Similarly, a monoclonal antibody also has off-targets, causing side effects ranging from common allergic hives or itching to severe anaphylaxis shock or autoimmune disease[1] .
- A deeper understanding of the target, tissue, safety, patient, and commercial potential (5R Framework) lead to an approximately 4.75× increase in the successful completion of Phase III clinical trials in AstraZeneca[2].

1 Hansel, T., Kropshofer, H., Singer, T. et al. The safety and side effects of monoclonal antibodies. Nat Rev Drug Discov 9, 325–338 (2010). DOI: 10.1038/nrd3003
2 Morgan et al. Impact of a five-dimensional framework on R&D productivity at AstraZeneca. Nat Rev Drug Discov 17:167–181 (2018). DOI: 10.1038/nrd.2017.244

Panoramic View

- Genes are pleiotropic, having multiple functions according to cell type, developmental stage, and conditions. A single gene is frequently involved in multiple pathways, and thus, its function is most comprehensively understood in a global or genome-level context.
- Conventional *in vitro* and in vivo assays reveal a tiny fraction of a drug's activities. In contrast, genome-scale transcriptomic profiling broadens our view on drug action unbiased.
- The drug discovery process is similar to a long journey along a complex trail in a dark forest where it is easy to get lost. **KMAP Express™** is like having a map, showing you shorter and cost-/time-saving paths along your journey to successful drug discovery.

Power of Large-Scale Comparison

- Developed by **KaiPharm**, **KMAP®** is a high-quality NGS-generated full transcriptomic profiling dataset for thousands of small molecule drugs approved in the United States, the European Union, and Japan at three concentrations in two cell lines with triple replicates across all conditions.
- The transcriptomic profiles of customer's drug candidates are generated under identical conditions as those of **KMAP®** and comparatively analyzed against ~3,000 approved drugs (**KMAP®** version 2021), covering a broad range of targets and indications.
- In contrast to other assays or experimental approaches, the dimension of comparison in **KMAP Express™** is unparalleled interrogating 20,000 genes in 50,000 samples for each requested expression profile.

Arrival

Mode of Action

- *Pathways* are the standard unit of functional interpretation of Omics analysis. Major pathway databases, such as Kyoto Encyclopedia of Genes and Genomes (KEGG), Reactome, and Gene Ontology (GO), are internally curated for minimal redundancy and maximal coverage of human genes.
- Related pathways are manually grouped under a common *biological theme* (e.g. immune system, cell cycle, lipid metabolism) to enable a higher level interpretation.
- Up/downregulated *Pathways* and their corresponding genes can be inspected across samples using the web platform that is a visually informative and interactive user interface supporting instant searching, sorting, and selecting. Analytic results are conveniently presented in different formats like heatmap and plotting through our network viewer using state-of-the-art data visualization technology.

Target Deconvolution

- Unknown drug off-targets are a major cause of safety-related failure of preclinical (~75%) and clinical (~50%) trials, but are highly difficult to identify using conventional approaches.
- Potential (off-)targets of a drug (candidate) are inferred on the basis of expression similarity to drugs or compounds of known targets included in **KMAP®**.
- Multiple target prediction models are applied; and a ranked list of potential off-targets is provided based on the integrated score.

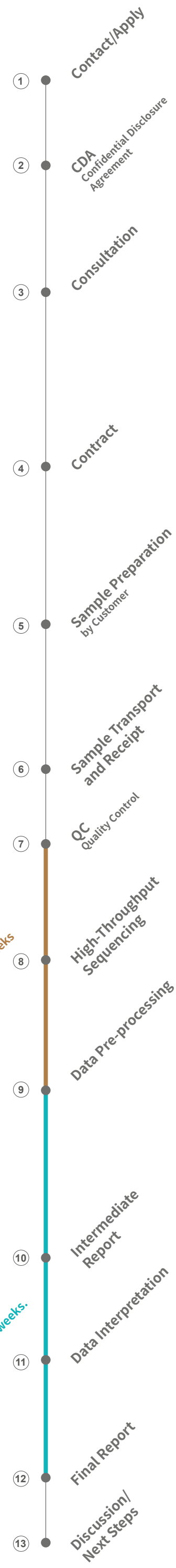
Deliverables

- High-quality RNA sequencing data (cloud storage or external hard drive available)
- Sequencing QC report
- Identification of differentially expressed genes (DEGs)
- Notation of enriched functional pathways
- Inferred drug (off-)targets
- List of drug repositioning candidates
- Results securely available online through the **KMAP Express™** web platform

Matched Drugs

- The expression profiles of disease models, whether cell, organoid, or patient, are evaluated against the extensive **KMAP®** dataset, indicating promising drug repositioning candidates. This approach has been validated by many internationally recognized peer-reviewed scientific publications[3,4,5].
- Drug repositioning candidates can be inferred in a disease subtype-specific manner.
- The customer's drugs of interest are compared against those of KMAP, and the top-ranked KMAP drugs are listed on the basis of expression similarity.

3 Kwon et al. Connectivity map-based drug repositioning of bortezomib to reverse the metastatic effect of GALNT14 in lung cancer. Oncogene 39:4567–4580 (2020). DOI: 10.1038/s41388-020-1316-2.
4 Hong et al. Large-scale pharmacogenomics based drug discovery for ITGB3 dependent chemoresistance in mesenchymal lung cancer. Mol Cancer 17:175 (2018). DOI: 10.1186/s12943-018-0924-8.
5 Kwon et al. In silico drug repositioning: from large-scale transcriptome data to therapeutics. Arch Pharm Res 42:879–889 (2019). DOI: 10.1007/s12272-019-01176-3.



Next Arrival

Side Effects

- An inference module for side effects and toxicity is under development using AI driven approaches. The module will be integrated in the next version of **KMAP Express™**.
- Hundreds of side effects may be effectively predicted to guide optimization steps (e.g. hit-to-lead and lead) in early drug discovery and development.

Matched Diseases

- We have processed thousands of expression datasets and collected hundreds of disease signatures under strict quality control and data curation standards.
- By contrast-pattern matching between the above disease signature dataset and a customer's drug signatures, we identify high-potential new indications to minimize our customer's R&D efforts.
- Candidates, lead molecules, and failed/approved drugs are all applicable to this analysis.