

Kinobeads™ Technology

What is Kinobeads™?

Cellzome's technology, *Kinobeads™*, can quantitatively measure the extent that compounds or drugs interact with kinases within cells and tissues.

Kinobeads™ is a kinase-binding matrix that can be used to measure the potency of compounds for ~300 different kinases. The technology is so effective that compounds can be uniquely "finger-printed" for their kinase interactions. The resulting information can not only demonstrate a compound's mode of action and the diseases it might be used against, but also point to potential side effects.

Kinobeads™ can replace or complement the current established methods for screening and selectivity profiling of kinase inhibitors to overcome some of the challenges in kinase drug discovery.

Why the interest in kinases?

A kinase is an enzyme that transfers phosphate groups to specific target molecules (e.g. other proteins, lipids or sugars) in a process called phosphorylation. Phosphorylation of a protein can activate or inhibit its function.

Protein kinases are key molecular switches in cellular signaling events, which regulate fundamental functions, e.g. cell growth and division. Because of their central role in many diseases, like cancer or inflammation, kinases are attractive targets for drug discovery.

Kinases in drug discovery

About 30% of all discovery and development spending (approx. \$20bn) currently focuses on kinases, especially in oncology, inflammation and metabolic diseases.

Despite this, only 9 small molecule kinase inhibitors have so far reached the market, the most well-known being Gleevec®, for chronic myeloid leukemia.

How does Kinobeads™ work?

• Capturing a sub-proteome of drug targets

The *Kinobeads™* Matrix binds more than 1,000 different proteins, primarily kinases but also other enzymes that can bind to ATP or other nucleotides (e.g. helicases or phosphodiesterases).

With mass spectrometry, the level of the different kinases isolated by *Kinobeads™* from any cell or tissue type can be precisely monitored.

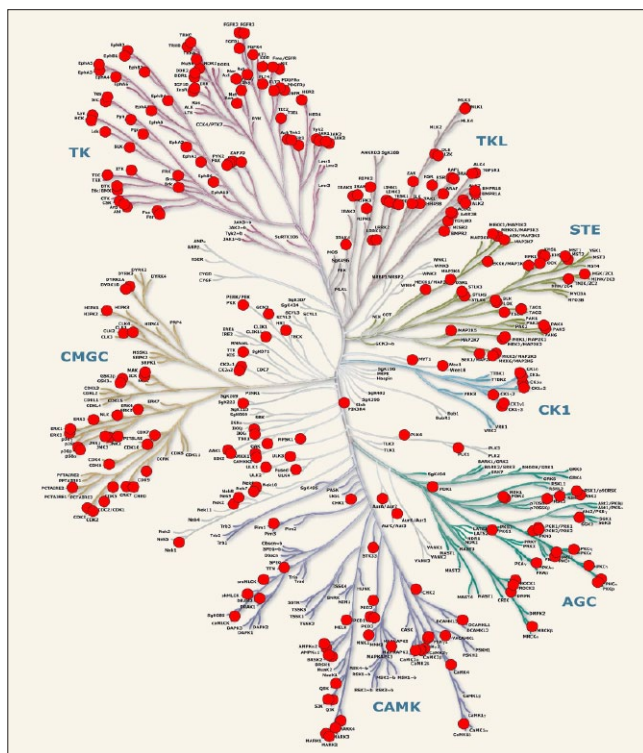
• Measuring the effect of compounds

A compound or drug added to a cell or tissue contents before *Kinobeads™* will compete for binding of the kinases. This competition is quantified with mass spectrometry and a full quantitative target profile can be determined from a single tissue sample.

What are the advantages over other techniques?

Kinobeads™ shows the effect of compounds or drugs on native kinases, as they are present in cells or tissues - a much

more relevant approach to drug discovery. There is no labelling or use of artificially produced (recombinant) proteins required. This allows discovering drugs for kinases where it is difficult to make a recombinant kinase.



A diagram of the kinome – the part of the genome coding for kinases. The bullets show the kinases captured by Kinobeads™. Kinase tree adapted with permission from Cell Signaling Inc.

Cellzome and Kinobeads™

Kinobeads™ drives Cellzome's proprietary drug discovery projects:

• Target and biomarker discovery

The kinases in different tissues (e.g. from disease state vs. healthy tissue) can be analysed by *Kinobeads™*/mass spectrometry and their activation status can be compared. Kinases which are only present or only activated in a disease state are good biomarker and/or target candidates.

• Screening

We screen compound libraries of about 40,000 compounds against kinase targets, which are otherwise difficult to screen. The kinases are targeted in their natural environment, in their right activation state and with their right protein partners. We can screen several kinases in one experiment.

• Selectivity profiling

One of the big hurdles in kinase drug discovery is the lack of selectivity of drug candidates, which may cause side effects. With *Kinobeads™*, our leads and drug candidates are tested against all the kinases in a tissue or cell type in one experiment. In this way we can identify whether a drug candidate also inhibits unwanted kinases and should be further optimized rather than progressed.



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