

Fragment screening of GPCRs using Grating Coupled Interferometry (GCI) technology

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Industry

Biologics, Pharmaceuticals,
Small molecules

Use case

Evotec uses GCI with WAVESystem (a Creoptix technology) for fragment screening of GPCRs

Challenge

Studying binding affinity and interaction kinetics of membrane proteins despite intrinsic protein instability

Solution

The WAVESystem, a Creoptix GCI Technology, with waveRAPID

Results

With WAVESystem, Evotec was able to develop a pipeline to study membrane proteins with a focus on G protein-coupled receptors (GPCRs) as a target class. The assay setup they developed allowed the hit screening of a library of 5,500 fragment-like compounds against multiple targets in just three weeks.

A reliable solution for unstable proteins

Recently, Evotec successfully harnessed Grating Coupled Interferometry (GCI) technology for fragment screening against G protein-coupled receptors (GPCRs). As Dr. Edoardo Fabini, Principal Scientist at Evotec, explains:

“The key aspect of GPCRs is their low surface activity, as they are very unstable once they are removed from their natural membrane environment.” As a result, “having a fast and sensitive technology like GCI opens up new possibilities when it comes to quantifying low-signal, weak binding events with confidence.”

In a [recent webinar](#) hosted by Malvern Panalytical, Dr. Fabini walked attendees through the challenges that come with studying GPCRs, and the solutions provided by the WAVESystem, which is engineered around our proprietary GCI technology.



Maintaining surface activity

When removed from their native environment, GPCRs deteriorate quickly.

The WAVEsystem and waveRAPID provide a double improvement. Firstly, assays can be rapidly optimized to select the optimal protein construct. Taking advantage of all four sensor surfaces, testing a series of constructs against control compounds allows the experimentalist to identify the optimal constructs and conditions that have the highest chances of producing a robust screening assay to pursue further with structural studies. This can be done in hours rather than days with waveRAPID. Researchers can screen more analytes using waveRAPID compared to traditional biosensor-based methods – as a result the membrane protein sensor surface will have less time to lose surface activity.

“When you work with challenging targets such as membrane proteins, having the right construct for downstream studies is key to success. Using waveRAPID technology, protein material recovered during small-scale expression and purification can be readily immobilized on the sensor surface. Functionality can be quickly probed to identify constructs that provide high quality results and are worth pursuing for mid/large-scale production.”

Working with crude samples

The non-clog WAVEchip vastly reduces the time spent on protein purification and can even remove this step altogether.

“Not being afraid of clogging the IFC* allows us to reduce purification steps and get material quickly to binding studies, which can greatly help maintain higher protein functionality” as stated by Dr. Fabini.

The WAVEchip integrates all the instrument's microfluidics - which add to the instrument's preciseness and allows the use of a very small quantity of fluid - into a disposable cartridge rather than the device core. It also places large bore standard valves downstream to the instrument instead of having the microvalves near the chip. This minimizes the risks of clogs, allowing less purified samples to be analyzed with peace of mind, and preventing instrument downtime for unclogging.

“Previously, our workflow used to involve many steps that took time away from analyzing fragment interactions.” Dr. Fabini concludes “By greatly reducing the time spent on purification, the WAVEsystem allows us to spend more time doing what's the most important for our research.”

The innovative design of our patented WAVEchips supports crude samples, pathogenic samples, harsh solvents, and large particles up to 1,000 nm, normally only achieved with plate-based assays. As Dr. Fabini states:

“Being able to perform harsh cleaning often, without risking damaging/altering the IFC*, helps us to have a sharp system with the highest sensitivity when it matters. There are no issues with quickly switching between different biological system from one day to the next.”

Reliable measurements even with low surface stability

Traditional biosensor-based methods can struggle to detect weak fragment interactions with GPCRs; furthermore, the GPCR biosensor can even lose activity over time. This is particularly troublesome given the intrinsic instability of GPCRs. As noted by Dr. Fabini,

“Having a fast and sensitive technology like GCI opens up new possibilities when it comes to quantifying with confidence low-signal, weak binding events.”

GCI boasts extremely high sensitivity compared to traditional biosensor-based methods. Our Wavechips with parallel flow channels enable ultra-fast transition times. Furthermore, it provides reliable determination of off-rates up to 10 s⁻¹, and superior signal-to-noise ratios (0.01 pg/mm² at 1 Hz).

As a result, even weak interactions with low biosensor surface activity can be detected. This is further enhanced by the WAVEsystem's speed, as the shorter experiment time entails a lower loss of membrane protein activity.

Limit non-specific binding interactions

Non-specific binding (NSB), where an analyte binds to an unintended location such as the detergent or micelles, can result in complexities during data interpretation. The lipophilicity of GPCRs mean they tend to clump into micelles, leading to NSB. However, by performing very fast measurements, waveRAPID ensures a short contact time between the analyte and surface, thereby limiting the potential for non-specific binding.

“Keeping injections length as short as possible allows less time for secondary interactions to build up and give more relevance to the primary “high affinity” interaction. We like to be able to cleanly detect the unbinding process of the ligand-target complex and use the kinetic component to infer complex stability even with a single concentration.”

Surpass these challenges with ease

The WAVEsystem's WAVEcontrol software provides superior and simplified data analysis for a wide range of sample types and sizes. The software helps you move seamlessly from sample to data in a simple step-by-step process, generating outputs at the touch of a button. Every step, from assay setup to data evaluation and report writing is simplified with an intuitive design that mirrors the way you work.

Meanwhile, through the Direct Kinetics 1-click evaluation tool, you can obtain automated calculations of your kinetic parameters with mathematically sound error analysis. Hundreds of interactions are automatically analyzed in 3-5 minutes. Direct Kinetics thus enables quick decision-making, fewer errors, increased ease of use, and ensures reproducible data.

Overall, the WAVEsystem can transform workflows, turning projects that would take weeks into processes that take days.

Dr. Fabini was able to “hit screen a library of 5,500 fragments against six targets in just three weeks”.

“Thanks to the WAVEsystem’s speed and flexibility, Evotec can conduct screenings quickly, and for a broad variety of applications.”

About Evotec

Evotec is a life science company that is committed to advancing drug discovery and development through its collaborations with biotech, pharma, academia, and government agencies. Its focus is on data-driven precision medicine and early disease relevance, and its integrated platforms provide partners with access to the most comprehensive drug discovery engines.

Want to learn more?

- Watch our webinar “[Fragment screening of GPCRs using Grating Coupled Interferometry \(GCI\) technology](#)”
- Read the poster: “[Fragment screening of G protein-coupled receptors using Grating-Coupled Interferometry \(GCI\) technology](#)”
- Download our technical note “[Quick characterization of binding onto unpurified GPCRs](#)”

* Editor's note, IFC means Integrated micro-Fluidics Cartridges (IFC).

About Malvern Panalytical

Malvern Panalytical is a global leader in the analytics of material and life sciences. We unleash the power of small things to make big things happen for our customers.

Our vision is to make the world cleaner, healthier, and more productive.

We partner with our customers to make their solutions possible through the power of precision measurements, our expertise, trusted data, and insights.

Our people are partners in discovery. We collaborate with our customers and with each other to discover new possibilities and achieve breakthroughs.

Our culture is a healthy, high-performance culture shaped by our values: Own it, Aim High and Be True.

We're committed to Net Zero in our own operations by 2030 and in our total value chain by 2040.

With over 2300 employees across the globe, we are part of Spectris plc, the world-leading precision measurement group.

Malvern Panalytical. We're big on small™

Service & Support

Malvern Panalytical provides the global training, service and support you need to continuously drive your analytical processes at the highest level. We help you increase the return on your investment, and ensure that as your analytical requirements grow, we're there to support you.

Our worldwide team of specialists adds value to your business processes by ensuring applications expertise, rapid response, and maximum instrument uptime.

- Proactive local and remote support
- Full and flexible range of service agreements
- Compliance and validation support
- Onsite or classroom-based training courses
- e-Learning training courses and web seminars
- Digital services, including MyStore and My Customer Support Portal
- Sample analysis, method development, and applications consultancy



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