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INTRODUCTION

GPCRs account for the major proportion of drug targets but still suffer from lack of adequate technologies for the study of challenging members such as orphans or for the detection of allosteric modulators, a new class of ligands with unprecedented opportunities. **DTect-All™** is a unique and proprietary technology allowing the identification of ligands interacting specifically with the 7-TM part of GPCRs. This technology, validated with the three GPCR families, is well suited for difficult targets thanks to a unique **collection of fluorescent probes**. Unlike standard HTS technologies, DTect-All™ allows identification of Silent Allosteric Modulators (**SAMs**), a new class of compounds giving access to a broader chemical space for GPCR modulator discovery. This poster presents key aspects of **DTect-All™** technology that represent a **alternative and complementary** approach for the study of difficult GPCR members.

1. GPCRs

- 50% of current marketed drugs with more than \$30B in annual sales
- ~950 GPCRs in the human genome, ~350 being therapeutic targets:



- GPCRs targeted by marketed drugs (50)
- Orphan GPCRs (~150)
- Insufficiently explored GPCRs (~150)

- Lack of technologies to study **orphans** or **challenging GPCRs** (peptide, lipide ...)
- Lack of technologies to explore **new chemical spaces** (linked to the use of assays originally developed for orthosteric ligand identification)
- Lack of technologies to selectively identify **allosteric modulators (AM)**, new class of ligands presenting numerous advantages over orthosteric ligands

2. Classical HTS technologies

Radioactive Ligand Binding

- + on-target
- radioactivity
- not suited for AM
- requires known ligand

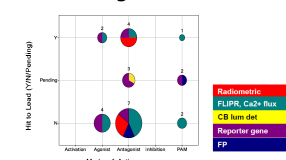
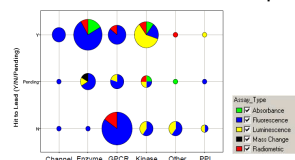
G-protein function & 2nd messenger generation

- + suited for AM
- false positive ++
- HTS with single paradigm

GPCR Downstream Signaling / HCS

- + high sensitivity
- false positive +++
- data analysis (HCS)

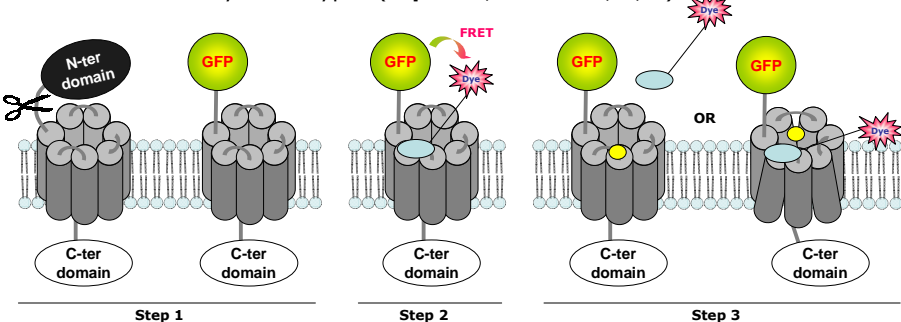
- >50% of GPCR HTS campaigns fails to give tractable hits



Rodriguez DJ and Zawadzke L. (Pfizer) Retrospective analysis of HTS assays used & success considerations. Poster, ELRIG, Liverpool, September 2009.

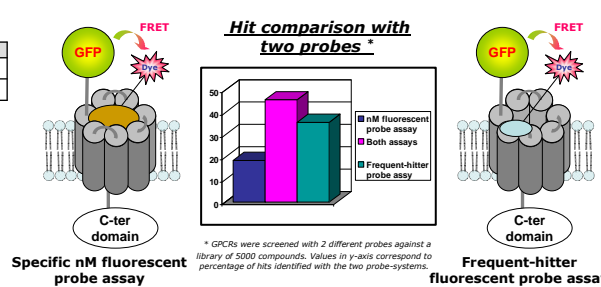
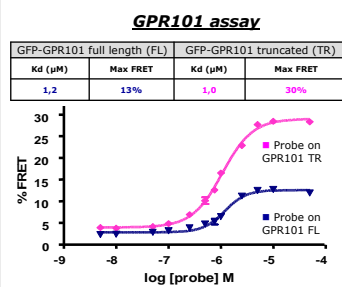
3. DTect-All™

- **DTect-All™**: proprietary FRET-based binding assay used for primary screening
- **Higher versatility**: - hits can either competitively displace the probe - or allosterically distance GFP and the dye
- Double labeling for on-target screen: reduce number of **false positives**
- Well adapted for AM identification and orphans GPCRs
- Validated for every GPCR types (**orphans**, families A, B, C)



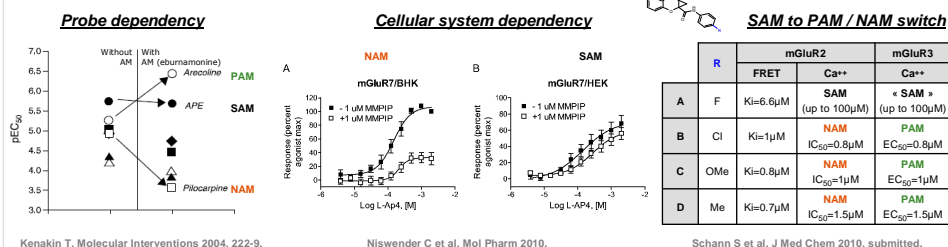
4. Frequent-hitter probe collection

- Represents one of the **competitive advantages** of our technology
- Unique proprietary collection of 5000 non-selective fluorescent compounds
- Successfully used for every GPCR family (A, B and C) and **orphans**
- Designed from **GPCR frequent-hitters** identified in screening campaigns
- Continuously enriched
- **Higher sensitivity** over nM fluorescent-assay



5. Silent Allosteric Modulators

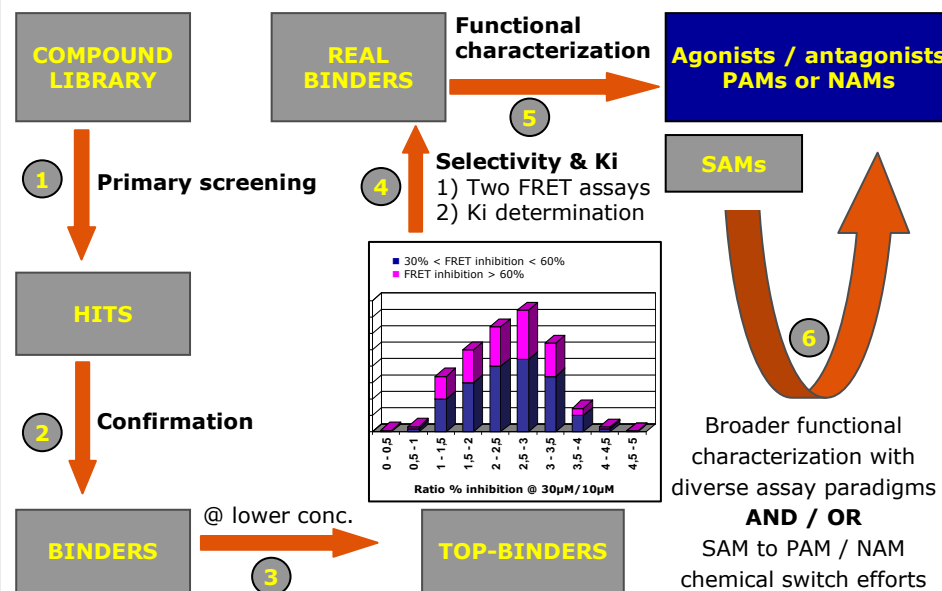
- DTect-All™ enables detection of orthosteric ligands and allosteric modulators that can either be positive (PAMs), negative (NAMs) or **silent (SAMs)**
- SAMs are binders devoid of activity **in a specific functional test**
- SAMs can be **false negatives in standard functional assays** but can turn to be PAMs or NAMs under different assay conditions
- SAMs are very close to PAMs or NAMs: **source for new chemical diversity**
- At Domain, identified SAMs are further modified by **medicinal chemistry** to switch them into PAMs or NAMs



7. DTect-All™ Positioning

- **Unique** platform to work with challenging GPCRs (orphans ...)
 - ✓ Portfolio of assays developed for CNS / metabolic / oncology GPCRs
- **Alternative** platform to reconsider a specific target
 - ✓ Contract research to develop assays and rescreen your library on your GPCR of interest
- **Complementary** platform to optimize chances of success
 - ✓ Collaborative efforts with partner to screen a GPCR with multiple approaches

6. Screening process



CONCLUSION

DTect-All™ is a unique technology platform for the screening of **challenging GPCRs**. It can be used to **reconsider a receptor** that fails to deliver tractable hits upon standard HTS technologies or in combination with those technologies to increase chances of success.

DTect-All™ is available for the Pharma and Biotech Industry under fee-for-service or collaborative partnerships.