

# KRAS PROTAC-mediated degradation and its implication in MAPK pathway activation: *SureFire® Ultra™* as a unique technology for measuring downstream effects



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## 1. Overview

The Kirsten rat sarcoma viral oncogene homologue (KRAS) is recognised as one of the hottest targets in oncology.

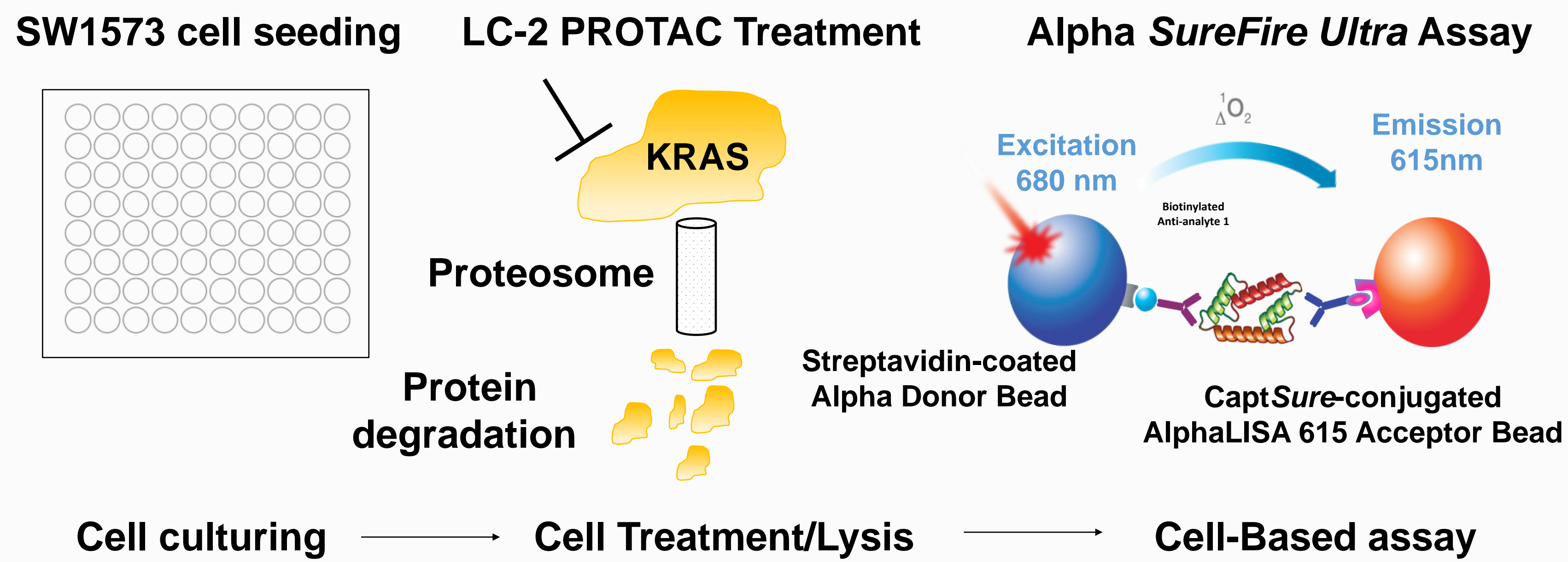
KRAS transmits signals from receptor tyrosine kinases promoting activation and subsequent phosphorylation of ERK/MAPK pathway.

The dysregulation of this activation results in hyperactivation of downstream signalling which leads to uncontrolled cell proliferation and tumour growth.

The use of PROTAC for specific KRAS degradation has become a powerful alternative to effectively diminish downstream activation effects.

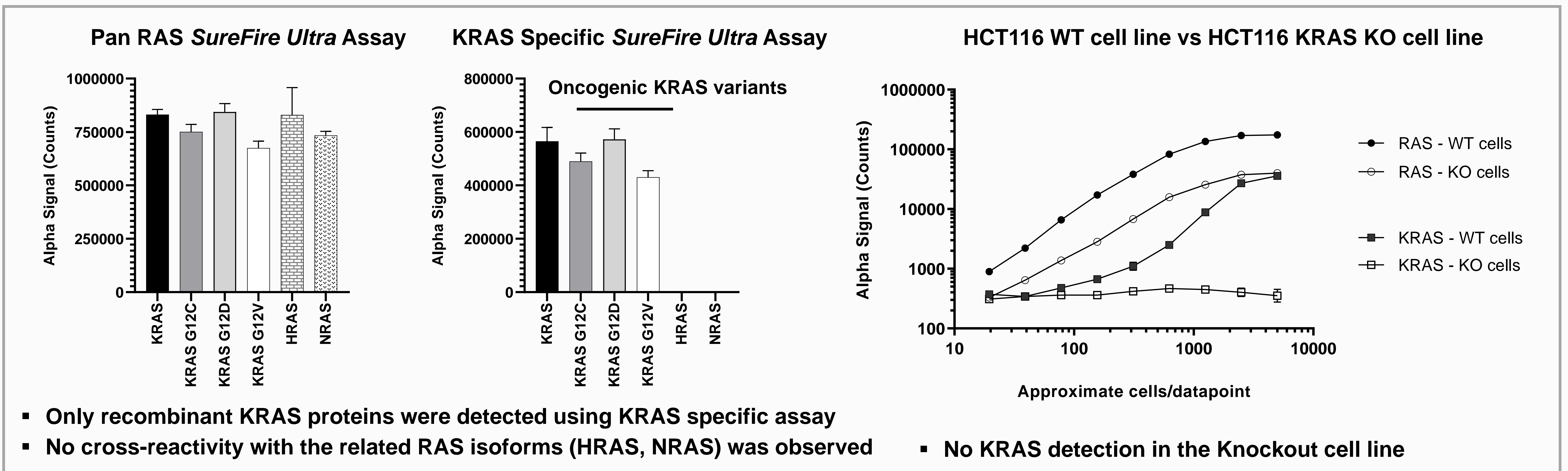
This study describes a high throughput method that specifically measures KRAS PROTAC-mediated degradation and investigate further the downstream MAPK phosphorylation effects resulting from target degradation.

## 2. Methods

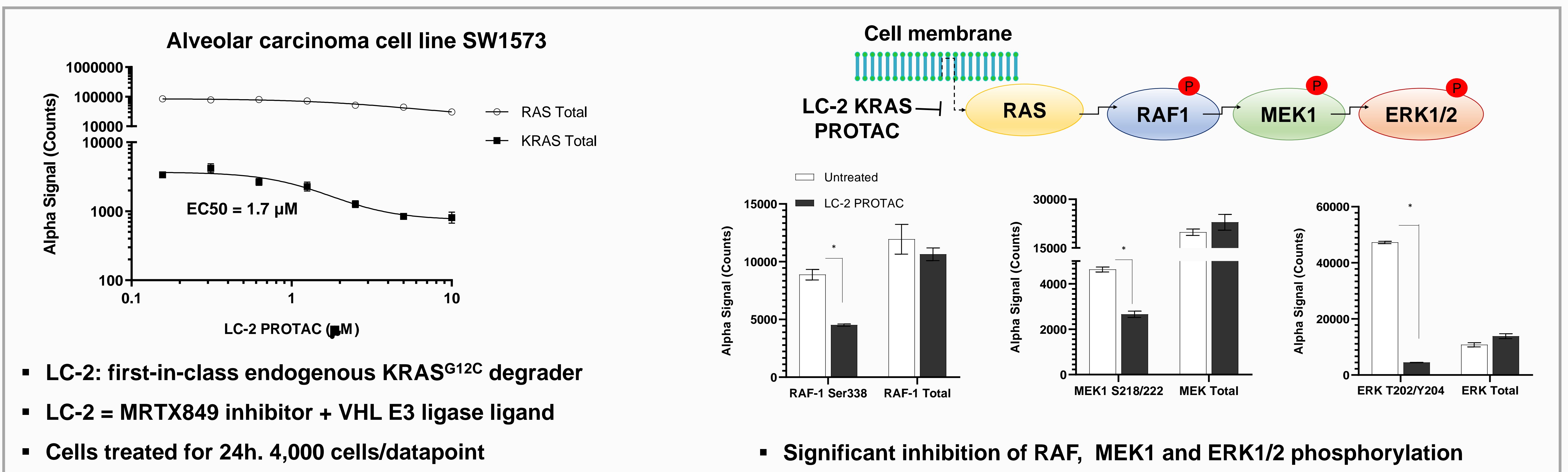


## 3. Results

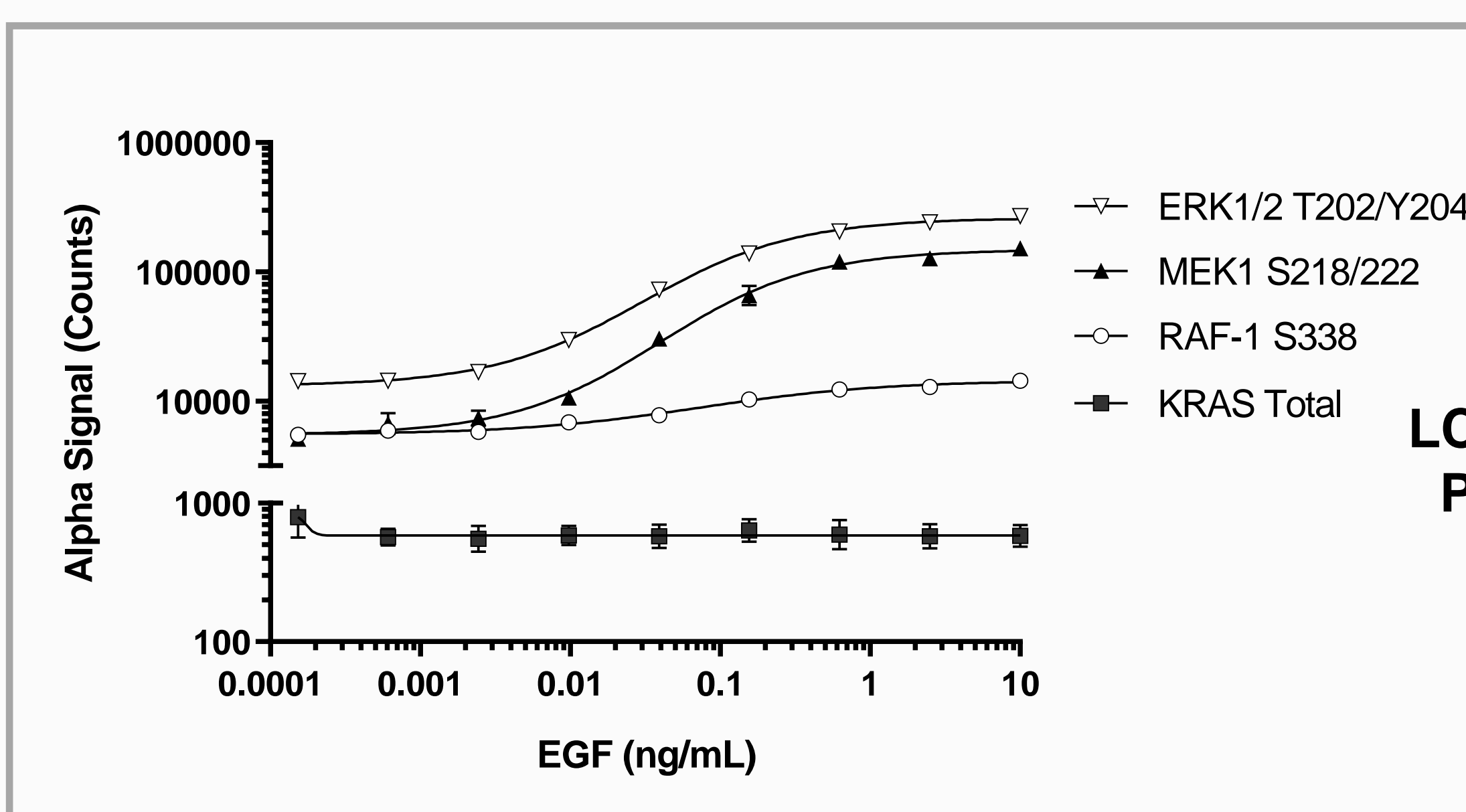
### 3.1 Development of a specific KRAS *SureFire Ultra* Assay



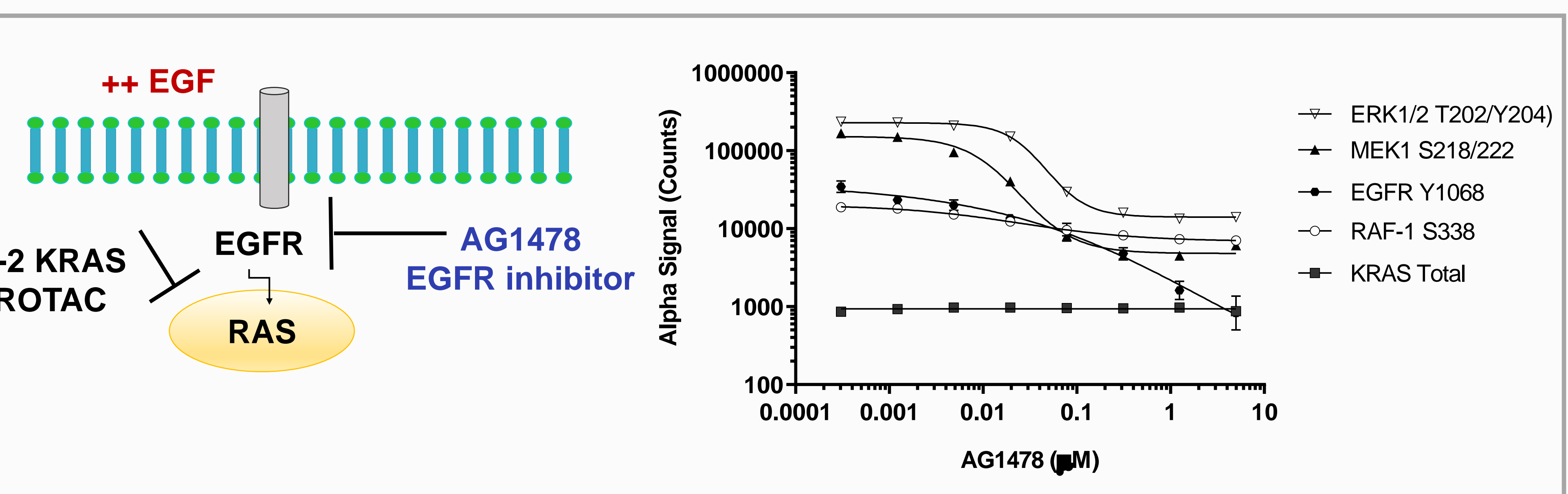
### 3.2 KRAS degradation is followed by a significant suppression of MAPK signalling pathway



### 3.3 MAPK pathway is reestablished upon EGF stimulation



### 3.4 MAPK pathway is permanently suppressed using combining therapy



## 4. Conclusions

- A robust, rapid and homogeneous cell-based assay was developed using *SureFire Ultra* technology to effectively measures endogenous KRAS in various cell systems.
- This new assay in combination with the existing kits in the *SureFire Ultra* portfolio has allowed us to investigate further the downstream MAPK associated events upon KRAS targeted degradation.
- This study highlights the effectiveness of *SureFire Ultra* technology for the validation and characterisation of high-profile targets and demonstrates the value of cascade pathway analysis.