# Novel inhibitors that targets BRAF dimers for cancer therapy

**LEAD INVENTOR:** Evripidis Gavathiotis.

THERAPEUTIC

## BACKGROUND/UNMET NEED

RAS → (B)RAF → MEK → ERK signaling pathway is involved in growth and survival. Mutations in the BRAF gene are associated with many cancers, most commonly skin cancer (melanoma). Current FDA approved treatments (inhibitors) target oncogenic BRAF protein monomers. Melanoma patients can become resistant to these current FDA approved inhibitors due to its failure to bind BRAF dimers. Targeting oncogenic BRAF dimers have been the focus of recent clinical trials of new drugs but with little success. There is a need to discover new effective inhibitors of BRAF dimers, which can dramatically increase the prognosis of more than 500,000 Americans estimated to be affected with BRAF related cancers.

## SOLUTION

Dr. Gavathiotis and colleagues, with their expertise in structure-based drug design, were able to identify a unique inhibitor binding site on the BRAF dimer that was exploited for drug development. Specifically, the team found that an existing FDA-approved drug, Ponatinib, serves as an effective oncogenic BRAF dimer inhibitor. Ponatinib treatment was shown to significantly inhibit tumor growth in melanoma cell culture. The research team was able to solve the co-crystal structure of Ponatinib bound to BRAF, a key step in resolving and unmasking the unique inhibitor binding site. Given these structural insights, the team further developed a library of Ponatinib-hybrid inhibitors (PHIs) and lead optimized a molecule called PHI1. PHI1 was shown to successfully inhibit the ERK pathway in a melanoma cell line (Figure 1a). This is a first in class, allosteric inhibitor for BRAF dimers, demonstrating highly selective binding, and potentially reducing off target effects and reducing toxicity. This technology provides the discovery framework for potent and selective inhibitors, such as PHI1, to give rise to the next generation of BRAF inhibitors.

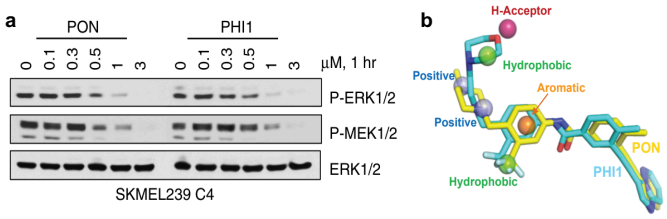


Figure: (a) Melanoma SKMEL239-C4 cell lines were treated with increasing concentrations of Ponatinib (PON) or PHI1 for 1 h. Whole-cell lysate were assayed by western blot with the indicated antibodies to assess ERK-pathway inhibition. (b) The 3D pharmacophore model hypothesis includes seven potential criteria (six spheres) superimposed to Ponatinib (PON) and PHI1 (in sticks) in their bound conformation to BRAFV600E that was used for screening candidate Ponatinib-hybrid inhibitors (PHIs).

## APPLICATIONS

- Treatment for melanoma
- Potential treatment for other BRAF-related cancers: leukemia, lung cancer, thyroid cancer
- Treatment for subset of cancer patients resistant to existing FDA-approved BRAF inhibitors

## ADVANTAGES

- First allosteric inhibiter for BRAF dimer
- Potentially reduced off target effects due to higher specificity of novel molecules.
- Overcomes resistance issues with current FDA inhibitors of BRAF

## STAGE OF DEVELOPMENT

- Preclinical stage
- Proof of concept studies completed
- Lead optimized and identified more potent inhibitors than PH1

## RELEVANT LITERATURE

- Cotto-Rios et al., Nature Comm (2020)

## INTELLECTUAL PROPERTY

Issued US Patents:

- PCT/US20/19695

## Office of Biotechnology and Business Development

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