# Ligand Based Virtual Screening

## Introduction

Melanoma is a highly aggressive cancer type with a strong tendency to metastasize. When diagnosed at an early stage, removal of local tumours is mostly curative, however, late diagnosis of invasive or metastatic melanoma often carries a poor prognosis [1]. Melanomas originate from the malignant transformation of melanocytes, neural-crest derived cells specialized in the production of the pigment melanin, which contributes to skin and hair pigmentation and confers ultraviolet light protection [2]. Cutaneous melanoma, originated from the melanocytes at the basal layer of the epidermis, is the most common form of the disease.

The malignant transformation of melanocytes is the result of a complex interaction between both exogenous and genetic factors [1]. Ultraviolet (UV) exposure is the main risk factor of cutaneous melanoma. UV radiation, stimulates cyclic AMP production through a melanocortin-dependant mechanism, leading to increased proliferation and melanogenesis [3]. This proliferative process is regulated by BRAF, a serine-threonine kinase that triggers the MAP kinase pathway. The importance of this pathway in melanocyte growth might explain its extraordinarily high mutation frequency. Importantly, up to 70% of human melanomas harbour mutations in BRAF [3].

The most common BRAF mutation, which accounts for more than 90% malignancies involving this gene, is a substitution of glutamic acid for valine at position 600 (V600E) [3]. Mutated BRAFV600E shows approximately a 500-fold increased activity, and it induces constitutive signalling through the RAS–MEK–ERK pathway (MAP kinase signalling pathway) and nuclear factor kappa-B (NF-kB) activation [2, 4]. Through complex downstream mechanisms, BRAF activity promotes cell survival, proliferation, angiogenesis, invasion and metastasis [5].

Mutated BRAF has been observed to play an important role in malignant melanocyte transformation and is already present and in up to 80% of the benign skin lesions called naevi [2]. Moreover, mutated BRAF activity stimulates many of the hallmarks of cancer. This suggests that BRAF mutation might be a founder event in the onset of the disease and sustain its progression [2].

In view of this, we propose that BRAF inhibition would be an optimal therapeutical approach for BRAFV600E-mutated melanomas. Through the inhibition of the BRAF serine/threonine-protein kinase we would be able to stop the signalling cascade that leads to cell proliferation and survival at an upstream position. Moreover, since BRAF mutation appears at early stages of the disease, it could be an appropriate potential treatment to avoid melanoma progression.

## Methods

### Ligand Based Virtual Screening

crystal ligand (Dabrafenib, P60)