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216-11: Specific Detection of BRAF Mutations

- ✓ **More effective Pyrosequencing assay**
- ✓ **At least 31 mutation variants detectable in one-run-assay**
- ✓ **Fewer false wild-type**
- ✓ **Prone for automatic high-throughput analysis**

The Technology

The present new detection technology overcomes restrictions of commercially available approach by using a unique algorithm for the specific detection of *BRAF* mutations within exon 15 in "one run" assay.

Commercially available pyrosequencing approach for *BRAF* status detection (therascreen® *BRAF* Pyro® Kit) is designed to analyze complementary strand of DNA starting directly at codon V600. Unfortunately, due to sequencing primer's mismatching, any mutant down-stream from codon V600 will be identified as a false wild type. Both V600K and V600R mutants could be interpreted as a false V600E mutation at mutant-to-wild-type ratio equal to 25% or less. Additionally, V600E-2 – the second variant of V600E (TG>AA) mutation – is not detectable by this assay.

Background

Mutations in certain genes are associated with disease, e.g. cancer. Identification of mutations present in cancer cells is of outmost diagnostic value, since such knowledge allows prognosis to be adjusted and suitable therapy measures to be determined. Mutations of the *braf* gene are found in the majority of cutaneous malignant melanomas and metastatic melanoma as well as in papillary thyroid carcinoma (40–70%), pleomorphic xanthoastrocytomas (60–70%), and Langerhans cell histiocytosis (50–60%). BRAF mutations are also frequently observed in various other cancers, in particular borderline ovarian cancer (30%), ganglioglioma (20%), colorectal carcinoma (5–10%), and pilocytic astrocytoma (5–10%). About 85% of the *BRAF* mutations in melanoma are V600E substitutions, which can be treated with recently-FDA-proved vemurafenib, BRAF inhibitor, representing great progress in metastatic melanoma therapy. In case of variant mutations beyond V600E/K/D, the direct sequencing is required. However, direct sequencing has limited detection level (down to 20% or not detectable, if a strong background of normal tissue is present in the sample).

Advantages

- ✓ standardized procedure
- ✓ more mutation variants detectable in one run
- ✓ more specific companion diagnostic
- ✓ suitable for automatic high-throughput analysis

Commercial Opportunity

- ✓ technology for TaqMan-based qPCR (fewer mutation variants detectable in one assay, mutations are not distinguished between each other, individual assay is required for specific mutations), sequence-based detection
- ✓ companion diagnostic kit (fewer mutation variants)

Intellectual Property

Patent application EP 12 153 477.0

Reference

1. Skorokhod, A. et al. Universal BRAF State Detection by Pyrosequencing-based Assay U-BRAF^{V600} (in preparation).

2. Forbes, S. A. et al. *Curr. Protoc. Hum. Genet.* Chapter 10, Unit 11.1-26 (2008)

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