Rational Therapy for Breast Cancer: Individualized Treatment for Difficult-to-Treat Breast Cancer Subtypes

From 2011-01-01 to 2018-06-30, closed project | RATHER Website

**Objective**

Cancer genotyping has identified a number of correlations between mutations in specific genes and responses to targeted anti-cancer drugs, with many mutations occurring in kinases or downstream signaling components. While there are several ongoing large-scale genome re-sequencing studies for the major cancer types, there is no systematic effort to investigate kinase mutations in distinct biological subtypes of these cancers. Here, we will explore the rate of activation of all kinases (the “kinome”) in two poor-prognosis subtypes of breast cancer for which there are currently no targeted therapies available, namely “triple negative” (TN) breast tumors lacking the estrogen-, progesterone- and HER2 receptors, constituting 15% of breast cancers, and invasive lobular carcinomas (ILC) of the breast, which represent 10% of breast tumors. Thus, we lack effective targeted therapies for one quarter of all breast cancer patients. In this project, we will identify and validate novel kinase targets for therapy for these TN and ILC subtypes. Kinase targets will be identified via a 5-pronged approach: i) direct re-sequencing of the kinome of 150 TN and 150 ILC tumors, ii) determination of abundance and activation status of kinases in these tumors by reverse phase protein array and tissue microarray technologies, iii) determination of copy number variation by SNP arrays, and iv) mRNA quantitation of the kinome using DNA microarrays and v) RNA sequencing to provide complementary information such as evidence of alternative splicing, translocations and RNA editing within the expressed kinome. Potential kinase targets for therapy will be validated in preclinical models using RNA interference. Finally, we will perform a phase I/II clinical trial to test the efficacy of a selective PI3K inhibitor in breast cancer. The project will deliver proof-of-concept for novel therapeutic interventions, together with matched molecular diagnostic approaches for patient stratification, for up to 25% of breast cancer patients.

**Related information**

- Precision diagnosis and treatment for difficult to treat cancers
- Final Report Summary - RATHER (Rational Therapy for Breast Cancer: Individualized Treatment for Difficult-to-Treat Breast Cancer Subtypes)
- Periodic Report Summary - RATHER (Rational therapy for breast cancer: individualised treatment for difficult-to-treat breast cancer subtypes)
- Periodic Report Summary 2 - RATHER (Rational Therapy for Breast Cancer: Individualized Treatment for Difficult-to-Treat Breast Cancer Subtypes)
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Individualised Treatment for Difficult-to-Treat Breast Cancer Subtypes
Periodic Report Summary 3 - RATHER (Rational Therapy for Breast Cancer: Individualized Treatment for Difficult-to-Treat Breast Cancer Subtypes)
Periodic Report Summary 4 - RATHER (Rational Therapy for Breast Cancer: Individualized Treatment for Difficult-to-Treat Breast Cancer Subtypes)

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Subjects
Medical biotechnology - Medicine and Health

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