Development and application of a patient-derived xenograft platform to test anti-cancer agents

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska Akademin, Göteborgs Universitet kommer att offentligen försvaras i Arvid Carlsson, Academicum, Medicinaregatan 3, den 26. Maj 2017, klockan 9.00

av Berglind Ósk Einarsdóttir

Fakultetsopponent:

Professor Richard Marais

University of Manchester, United Kingdom

Avhandlingen baseras på följande delarbeten

I. **Melanoma patient-derived xenografts accurately model the disease and develop fast enough to guide treatment decisions**
Berglind O. Einarsdottir, Roger Olofsson Bagge, Joydeep Bhadury, Henrik Jespersen, Jan Mattsson, Lisa M. Nilsson, Katarina Truvé, Marcele Dávila López, Peter Naredi, Ola Nilsson, Ulrika Stierner, Lars Ny and Jonas A. Nilsson.
Oncotarget 2014; 30;5(20):9609-18.

II. **Hypoxia-regulated gene expression explains differences between melanoma cell line-derived xenografts and patient-derived xenografts**
Joydeep Bhadury, Berglind O. Einarsdottir, Agnieszka Podraza, Roger Olofsson Bagge, Ulrika Stierner, Lars Ny, Marcela Dávila López and Jonas A. Nilsson**.**
Oncotarget. 2016 Apr 26;7(17):23801-11

III. **TH1579 (Karonudib) inhibits MTH1 and microtubule dynamics and has broad anti-melanoma effects in patient-derived xenografts**
Berglind O. Einarsdottir, Joakim Karlsson#, Elin MV Söderberg#, Mattias F. Lindberg, Lydia C. Green, Elisa Funck-Brentano, Roger Olofsson Bagge, Henrik Jespersen, Annika Thorsell, Carina Sihlbom, Louise Carstam, Martin Scobie, Tobias Koolmeister, Olof Wallner, Ulrika Stierner, Ulrika Warpman Berglund, Lars Ny, Lisa M. Nilsson, Erik Larsson, Thomas Helleday and Jonas A. Nilsson. #Equal contribution**.** *Manuscript*

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Development and application of a patient-derived xenograft platform to test anti-cancer agents

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Abstract

Malignant melanoma is the most aggressive form of skin cancer and incidence rates are on the rise. Despite recent improvements in treatment options, the disease still remains lethal. Which calls for expedited solutions. In this thesis I will discuss three studies, which have not only contributed new knowledge to the research community but also led to development of tools used in cancer research.

In the first paper we developed a platform of patient-derived xenografts (PDXes) from metastatic melanoma patients. We show that PDXes can accurately predict clinical treatment responses and that the xenografts can be established in time to benefit the patients. Thus, the platform can be used for multiple pre-clinical and clinical purposes.

In the second paper we compared the transcriptome of cell line-derived xenografts (CDXes) and PDXes. The initial aim was to investigate if CDXes would be transcriptionally similar to PDXes and could therefore be used as *in vitro* surrogates for the PDXes. Instead, we identified a significant transcriptional difference between CDXes and PDXes, mainly explained by the pseudo hypoxia experienced by the cell lines once they are transplanted to the physiological environment.

In the third study, we ran a pre-clinical trial in malignant melanoma PDX mouse models with the aim of identifying a predictive biomarker of the MTH1 inhibitor, Karonudib. By comparing the genomic and transcriptomic profiles of the responding and non-responding PDXes we identified that Karonudib has cytotoxic effect independent of those profiles. Also, we discovered that Karonudib causes cytotoxic effect beyond MTH1 inhibition.

Taken together, our data shows that PDX models predict clinical responses and can be used to test drugs pre-clinically, and argues that pre-clinical testing in PDX models is superior to cell line based drug testing.

Keywords: Malignant melanoma, patient-derived xenografts, MTH1, Karonudib, pre-clinical research.

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