Phosphoprotein patterns predict trametinib responsiveness and

optimal trametinib sensitisation strategies in melanoma

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**Multiplex phosphoproteomic profiling predicts trametinib responsiveness and optimal trametinib sensitization strategies in melanoma**

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Abstract

Malignant melanoma is a highly aggressive form of skin cancer responsible for the majority of skin cancer- related deaths.

Recent insight into the heterogeneous nature of melanoma suggests more personalised treatments may be necessary to

overcome drug resistance and improve patient care. To this end, reliable molecular signatures that can accurately predict

treatment responsiveness need to be identiﬁed. In this study , we applied multiplex phosphoproteomic proﬁling across a panel

of 24 melanoma cell lines with different disease-relevant mutations, to predict responsiveness to MEK inhibitor trametinib.

Supported by multivariate statistical analysis and multidimensional pattern recognition algorithms, the responsiveness of

individual cell lines to tram etinib could be predicted with high accuracy (83% correct predictions), independent of mutation

status. We also successfully employed this approach to case speciﬁcally predict whether indi vidual melanoma cell lines

could be sensitised to trametinib. Our predictions identiﬁed that combining MEK inhibition with selective targeting of c-JUN

and/or FAK, using siRNA-based depletion or pharmacological inhibitors, sensitised resistant cell lines and signiﬁcantly

enhanced treatment efﬁcacy. Our study indicates that multiplex proteomic analyses coupled with pattern recognition

approaches could assist in person alising trametinib-based treatment decisions in the future.

ABSTRACT

Malignant melanoma is a highly aggressive form of skin cancer responsible for the majority of skin cancer- related deaths. Recent insight into the heterogeneous nature of melanoma suggests more personalized treatments may be necessary to overcome drug resistance and improve patient care. To this end, reliable molecular signatures that can accurately predict treatment responsiveness need to be identiﬁed. In this study, using a custom-developed phosphoprotein 11-plex panel (ProtATonce Ltd), we performed phosphoproteomic proﬁling across a panel of 24 melanoma cell lines with different disease-relevant mutations, in order to predict responsiveness to the MEK inhibitor trametinib. Supported by multivariate statistical analysis and multidimensional pattern recognition algorithms, the responsiveness of individual cell lines to trametinib could be predicted with high accuracy (83% correct predictions), independent of mutation status. We also successfully employed this approach to case speciﬁcally predict whether individual melanoma cell lines could be sensitized to trametinib. Our predictions identiﬁed that combining MEK inhibition with selective targeting of c-JUN and/or FAK, using siRNA-based depletion or pharmacological inhibitors, sensitized resistant cell lines and signiﬁcantly enhanced treatment efﬁcacy. Our study indicates that multiplex proteomic analyses coupled with pattern recognition approaches could assist in personalizing trametinib-based treatment decisions in the future.