Speaker: Prof. Richard Marais

CRUK Manchester Institute - Manchester - UK

April 27th 2017 – at 13:00 pm

Title

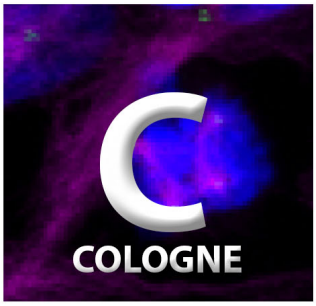
'Understanding melanoma biology from initiation to precision medicine'

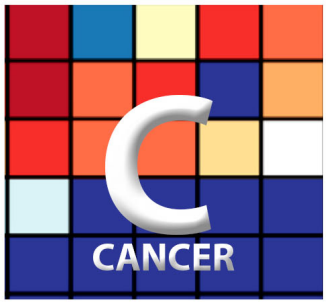
Venue

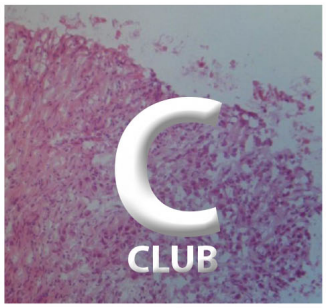
Mediathek – ZMMK – Gebäude 66
Robert-Koch-Str. 21

Abstract

Melanoma is the most deadly form of skin cancer. It is linked to exposure to ultraviolet radiation (UVR). Genome sequencing approaches do provide insight into the genomic landscape of melanoma, revealing the various subtypes defined by their driver oncogenes and chromosomal aberrations. Intriguing, these various genomic subtypes are linked body site and presumed cumulative exposure to UVR. The protein kinase BRAF is mutated in about half of cutaneous melanomas, and its upstream activator NRAS is mutated in another 20% of cases, but we still do not understand how different oncogenes interact with UVR to drive melanomagenesis. We have developed mouse models that allow us to interrogate the interaction of different oncogenes with UVR and find that UVR accelerates both BRAF and NRAS-driven melanoma, but there are clear differences in the amount of exposure required and the number cooperating oncogenes that can cooperate with these different oncogenes. These studies are beginning to reveal how UVR interacts with distinct oncogenes to drive this deadly disease.







Critically, drugs that inhibit BRAF or MEK (downstream of BRAF), increase progression free and overall survival in BRAF mutant melanoma patients, but most patients eventually develop resistance to these kinase inhibitors and so second line treatments are needed. Moreover, BRAF drugs are ineffective in NRAS mutant melanomas, and MEK drugs are only weakly effective. In parallel to targeted agents in melanoma, drugs that activate the immune system to attack the tumours have shown impressive outcomes in melanoma patients, and in some cases have even led to cures. However, we still do not know how to stratify patients for immunotherapies, and early cases of resistance to immunotherapies are starting to emerge.

Thus, while new treatment approaches have bought about a paradigm shift in the clinical management of melanoma in the last decade, the majority of patients with metastatic melanoma still die of their disease. We have therefore been investigating the possibility of developing precision medicine approaches for melanoma patients. We use next generation sequencing to reveal the genomic landscape of the tumours and use that information to develop hypothesis-driven treatment approaches for individual patients. Where possible, we validate these treatments in patient-derived xenografts (PDX). We have also developed circulating tumour cell derived xenografts (CDX) to study late-stage disease. Finally, we use cell-free tumour DNA (ctDNA) from the blood to monitor patient responses to treatments and monitor the emergence of resistance, and are currently implementing clinical trials in which ctDNA is used to guide treatment decisions.