Universität Basel

Research Project

Hunting for natural products targeting aberrant proliferative signaling in melanoma

Third-party funded project

Project title Hunting for natural products targeting aberrant proliferative signaling in melanoma
Principal Investigator(s) Hamburger, Matthias ;
Co-Investigator(s) Garo, Eliane ;
Project Members Hell, Tanja ;
Organisation / Research unit
Departement Pharmazeutische Wissenschaften / Pharmazeutische Biologie (Hamburger)
Department
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The incidence of melanoma, the most fatal dermatological cancer, is rising. In >50% of malignant melanomas, the BRAF V600E mutation is present, leading to aberrant MAPK signaling and uncontrolled proliferation. Contemporary genomic approaches now have identified additional oncogenic mutations that also impinge on MAPK/PI3K signaling. This has led to the new paradigm of targeted therapy, in which drugs that specifically inhibit aberrant oncogenic signaling components have been designed. A prime example is Vemurafenib, a specific inhibitor of the V600E mutated form of B-Raf. Despite spectacular initial results and low patient toxicity, vemurafenib resistance inevitably occurs on a time scale of months, precluding a long term benefit for the patient. This involves both mechanisms of non-genetic resistance, that can occur on time scales as fast as hours, and involves rewiring of signaling network feedback structures, as well as genetic resistance, which involves of acquisition secondary mutations that hardwire drug resistance. Both mechanisms contribute to re-activation of MAPK/PI3K signaling, and aberrant proliferation. The complex pathological signaling network states, as well as the large number of mutations within the MAPK/PI3K network, found in different patients, requires a larger arsenal of targeted drugs, with different modes of action, that could be used in combination therapies to efficiently block the development of cancer drug resistance.

In this proposal, we take an alternative strategy to identify novel compounds for targeted therapy. First, our approach explores the unique chemical diversity of natural products (NPs) libraries. Second, we will use assays that interrogate pathological MAPK/PI3K signaling directly within primary cultures of patient melanoma cells that harbor different primary, or drug-induced secondary mutations. Thus, this takes into account pathological signaling network feedback structures that originate from non-genetic resistance, or from different, melanoma-relevant, oncogenic mutations that now can be diagnosed using personalized medicine approaches. Unlike classically used cell free-based screening assays which do not take into account intact signaling networks, our approach has the potential to identify compounds with novel mechanisms of action that might specifically targeting pathological signaling network vulnerabilities.

Our pipeline involves state-of-the-art image-based high content screening using robust, economical assays that measure aberrant MAPK/PI3K signaling directly in melanoma patient cells. This is coupled with a powerful analytical chemistry pipeline that can rapidly prioritize NPs of interest using only minute amounts of plant/fungi crude extracts. This unique combination has the power of realizing the full promise of NP drug screening, and will identify NPs that inhibit different melanoma-relevant pathological signaling states which are not addressed by the current drugs. The project will identify novel scaffolds for medicinal chemistry efforts towards new drugs to treat melanoma using single/combination therapies.

Finally, we also propose to use our imaging technologies for characterization of known drugs and newly identified compounds to assess dynamic signaling responses at the single cell level. This will provide key insights about signaling robustness and heterogeneity that might feed in the process of drug resistance, and might enable to identify potent combination therapies that efficiently shut down pathological signaling states.

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