Exploiting serendipity for the discovery of new antimelanoma targets and scaffolds

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Despite dramatic improvement in the knowledge on resistant forms of melanoma over the last two decades, its treatment is still a challenge. Thus, efficient treatments, especially relying on innovative mode of action, are needed to overcome these resistance phenomena and propose new treatment options to patients in therapeutic failure. We used cellular phenotypic screenings of rationally focused libraries to generate new active *hits*. Optimization by structure−activity and structure-pharmacological properties relationships provided us *lead* compounds, that have been used in target identification studies. This led to the validation of an anti-melanoma protein target: GRP78, the master regulator of ER Stress response. Other targets are under investigation like the oncogene MELK. Besides, during *hit-to-lead* optimizations, several active scaffolds were discovered.