In vivo RNAi screening for novel therapeutic cancer targets

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Melanoma is the most aggressive type of skin cancer and its incidence is steadily increasing. Melanomas tend to spread rapidly, which is associated with a grim prognosis. Until recently, most advanced stage melanomas were refractory to the available therapeutic options, but there are recent developments offering better perspectives. For example, new therapeutic approaches have become available, which target genetic vulnerabilities within the melanomas. A primary example of such a dependency is the common $BRAFV^{600E}$ mutation, which is essential for proliferation and survival of melanoma cells. In the clinic, the mutant BRAF oncogene product can be targeted by specific inhibitors, including vemurafenib, which cause unprecedented melanoma regression. However, relapse eventually occurs around six months due to a variety of resistance mechanisms, both MAP kinase-dependent and -independent. Therefore, in spite of these new perspectives, there is a dire need to identify additional targets amenable to therapeutic intervention, to be used in combination with vemurafenib or other specific inhibitors to overcome or prevent drug resistance and achieve more durable responses. To achieve this, we set out to identify melanoma factors that are required for proliferation and survival specifically in an *in vivo* setting. Thus, we performed negative selection RNAi screens parallel *in vitro* and *in vivo* and focused on the hits that were preferentially depleted in tumors relative to the corresponding cells in culture. The results from these screens will be discussed.

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EDUCATIONS/TRAINING

1982-1988	Master's in Medical Biology, VU University Amsterdam
1988-1994	Graduate Research (Ph.D.) at Leiden University, Division of Molecular Carcinogenesis. Thesis advisor: Prof. A.J. van der Eb
1994-1995	First Postdoctoral Training, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA, Division of Neoplastic Disease Mechanisms, Laboratory of Dr. M.E. Ewen (Division head: Prof. D.M. Livingston)
1995-2000	Second Postdoctoral Training, Netherlands Cancer Institute, Amsterdam, Division of Molecular Carcinogenesis, Laboratory of Prof. R. Bernards (Division head)

POSITIONS

2000-2002	Research Associate, Netherlands Cancer Institute
2002-2005	Assistant Professor ('AvL Fellow'), Netherlands Cancer Institute
2005-2008	Associate Professor and permanent staff member, Netherlands Cancer Institute
2008-	Affiliate Professor of Functional Oncogenomics, VU University Medical Center (VUmc), Amsterdam
2012-	Head, Division of Molecular Oncology, Netherlands Cancer Institute
2012-	Chair of the Scientific Faculty Council, Netherlands Cancer Institute

HONORS & AWARDS

2005	Elected EMBO Young Investigator (YIP)
2006	VICI Award (Netherlands Organisation for Scientific Research (NWO))
2007	Society for Melanoma Research (SMR) Jr. Researcher Award 2007
2008	Elected EMBO Member
2009	Queen Wilhelmina Award by the Netherlands Cancer Society (KWF;€ 2,000,000) awarded by Queen Beatrix of the Netherlands

RECENT PUBLICATIONS

1. Kaplon J, Zheng L, Meissl K, Chaneton B, Selivanov V, MacKay G, van der Burg S, Verdegaal E, Cascante M, Shlomi T, Gottlieb E and Peeper DS. A critical role for the mitochondrial gatekeeper pyruvate dehydrogenase in oncogene-induced senescence. ***Nature*** 498: 109-112, 2013.
2. Desmet CJ, Gallenne T, Prieur A, Reyal F, Wittner BS, Geiger TR, Smit MA, Visser NL, Laoukili J, Iskit S, Rodenko B, Evers B, Horlings H, Ajouaou A, Zevenhoven J, van Vliet M, Ramaswamy S, Wessels LFA and Peeper DS. Identification of a pharmacologically tractable Fra-1/ADORA2B axis promoting breast cancer metastasis. ***PNAS*** Published online before print March 12, 2013.
3. Vredeveld LCW, Possik PA, Smit MA, Meissl K, Michaloglou C, Horlings HM, Ajouaou A, Kortman PC, Dankort D, McMahon M, Mooi WJ and Peeper DS. Abrogation of BRAFV600E-induced senescence by PI3K pathway activation contributes to melanomagenesis. ***Genes Dev*** 26: 1055-1069, 2012.
4. Hömig-Hölzel C, van Doorn R, Vogel C, Germann M, Cecchini MG, Verdegaal E, and Peeper DS. Antagonistic TSC22D1 variants control BRAF(E600)-induced senescence. ***EMBO J*** 30: 1753-1765, 2011.
5. Kuilman T, Michaloglou C, Mooi WJ and Peeper DS. The essence of senescence. ***Genes Dev*** 24: 2463-2479, 2010.
6. Smit MA, Geiger TR, Song J-Y, Gitelman I and Peeper DS. A Twist-Snail axis critical for TrkB-1 induced EMT-like transformation, anoikis resistance and metastasis. ***Mol Cell Biol*** 29: 3722-3737, 2009.
7. Kuilman T, Michaloglou C, Vredeveld LCW, Douma S, van Doorn R, Desmet CJ, Aarden LA, Mooi WJ and Peeper DS. Oncogene-induced senescence relayed by an interleukin-dependent inflammatory network. ***Cell*** 133: 1019-1031, 2008.
8. Michaloglou C, Vredeveld LCW, Soengas MS, Denoyelle C, Kuilman T, van der Horst CMAM, Majoor DM, Shay JW, Mooi WJ and Peeper DS. BRAFE600-associated senescence-like cell cycle arrest of human nevi. ***Nature*** 436: 720-724, 2005.
9. Douma S, Van Laar T, Zevenhoven J, Meuwissen R, Van Garderen E, Peeper DS Suppression of anoikis and induction of metastasis by the neurotrophic receptor TrkB. ***Nature*** 430: 1034-1039, 2004.