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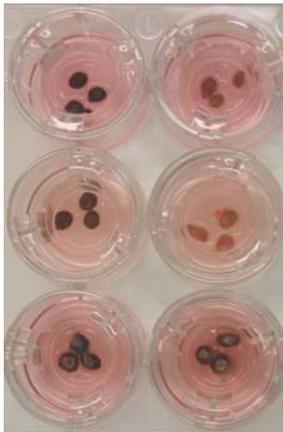
Cardinal Bernardin Cancer Center



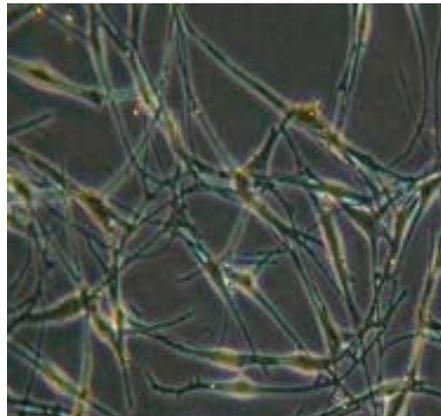
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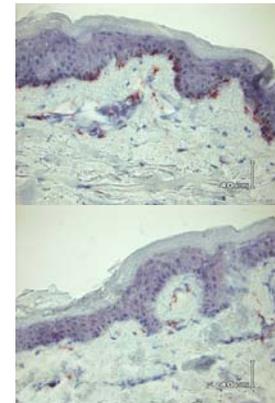
at the microscope



bleaching human skin



melanocytes in culture



loss of melanocytes in vitiligo

### Vitiligo Research Program

Research in the laboratory is focused primarily on the autoimmune response to pigment cells that contributes to the progressive loss of pigmentation in vitiligo. There is clearly a complex hereditary component to vitiligo, which predisposes certain individuals to developing the disease. Such genetic differences can affect pigment cell function either directly, or indirectly by mounting an immune response that spreads to areas of remaining pigmentation. We have shown previously, that during progressive disease the skin contains an abundance of macrophages, dendritic cells and T cells, each contributing to the development of autoimmunity. The T cells in particular help explain why melanocytes are specifically targeted in vitiligo, and this arm of the immune response is of particular interest because the same T cells are a source of superior reactivity to melanoma cells, an area which we are actively pursuing.

For progressive disease to develop, an early event causing stress to melanocytes in the skin triggers a specific response to prevent cell death. A particular set of molecules is upregulated which, once they find themselves outside the cell, serve as a warning signal to the immune system and trigger an immune response to the cells from which they are derived. For this reason, such heat shock proteins are in use as vaccine components. They are very well conserved throughout evolution, from plants to bacteria all the way to humans, which tells us they have an important role to play. The events that trigger an autoimmune response offer a potential route of intervention and this is another area of active research in the lab. Understanding the effects of stress on melanocytes has led us to focus on chemicals commonly used to bleach the skin in advanced disease. The fact that melanocytes are much more sensitive to these chemicals than surrounding cells can tell us a lot about why pigment cells become an exclusive disease target in vitiligo. The molecular structure of bleaching agents suggest that these compounds will interact with enzymes involved in pigment production, and our research in this area is set to define these processes in more detail. In summary, there is an intriguing dichotomy between the autoimmune responses that lead to progressive depigmentation in vitiligo, and less effective immune responses mounted to malignantly transformed melanocytes in melanoma. Learning from one disease we can develop strategies to treat the other.

#### Recent reviews

Le Poole IC, Luiten R.M. Autoimmune etiology of generalized vitiligo. *Curr Dir Autoimmun* 10, 227-243 (2008).

Schallreuter KU, Bahadoran P, Picardo M, Slominski A, Ellassiuty YE, Kemp EH, Giachino C, Liu JB, Luiten RM, Lambe T, Le Poole IC, Dammak I, Onay H, Zmijewski MA, Dell'Anna ML, Zeegers MP, Cornall RJ, Paus R, Ortonne JP, Westerhof W. Vitiligo pathogenesis: autoimmune disease, genetic defect, excessive reactive oxygen species, calcium imbalance, or what else? *Exp Dermatol.* 17:139-60 (2008)

Le Poole IC, Norris DA. Immune and Inflammatory Aspects: Cell-mediated immunity. In: *Handbook on vitiligo.* Taieb A, Picardo M (Eds.) Springer Verlag *In Press*

#### Scientific description

We are characterizing T cell receptors from T cells derived from perilesional vitiligo skin of high affinity towards melanosomal antigens gp100 and MART-1, to be cloned into vectors suitable for treatment in a condition where high avidity responses are more desirable, namely malignant melanoma. At the same time this characterization is important to identify target molecules and quantify the contribution of T cell mediated immune responses to depigmentation in either condition. Specific autoimmunity is ultimately triggered by environmental events that upregulate stress proteins, among which HSP70 is of particular interest for its role in activating dendritic cells through enhanced processing and presentation

of peptides chaperoned by the stress protein. As HSP70 can be secreted by live cells, stress can be considered an initiating event in vitiligo. The role of HSP70 in vitiligo is an area of active research in the lab. One of the stressful events that specifically affects melanocytes and is therefore of great interest to vitiligo development and progression, is contact with bleaching phenols. Either accidentally in the workplace, or intentionally as in depigmentation treatment, melanocytes are specifically affected by bleaching phenols. Enhancing our understanding of the depigmentation process initiated by individual bleaching phenols by defining their cytotoxic effects, the role of melanosomal enzymes and potential involvement of immune factors in the process can lead to improved applications, which may have implications for melanoma treatment as well.

#### Selected references

Le Poole IC, van den Wijngaard RMJGJ, Westerhof W, Dutrieux RP, Das PK: Presence or absence of melanocytes in vitiligo lesions: An immunohistochemical investigation. *J Invest Dermatol* 100, 816-822 (1993)

Le Poole IC, Mutis T, van den Wijngaard RMJGJ, Westerhof W, Ottenhof T, de Vries RRP, Das PK: A novel, antigen presenting function of melanocytes and its possible relation to hypopigmentary disorders. *J Immunol* 151: 7284-7292 (1993)

Le Poole IC, van den Wijngaard RMJGJ, Westerhof W, Das PK. Presence of T cells and macrophages in inflammatory vitiligo skin parallels melanocyte disappearance. *Am J Pathol* 148: 1219-1228 (1996).

Le Poole IC, van den Wijngaard RMJGJ, Westerhof W, Das PK. Tenascin is overexpressed in vitiligo lesional skin and inhibits melanocyte adhesion. *Br J Dermatol* 137: 171-178 (1997)

Le Poole IC, Yang F, Brown TL, Cornelius J, Babcock G, Das PK, Boissy RE. Altered gene expression in melanocytes exposed to 4-tertiary butyl phenol (4-TBP); upregulation of the A2B adenosine receptor. *J Invest Dermatol*, 113:725-731 (1999)

Yang F, Sarangarajan R, Le Poole IC, Medrano EE, Boissy RE. The cytotoxicity and apoptosis induced by 4-tertiary butylphenol in human are independent of tyrosinase activity. *J Invest Dermatol*, 114: 157-164 (2000)

Le Poole IC, Boissy RE, Sarangarajan R, Chen J, Forristal JJ, Sheth P, Westerhof W, Babcock G, Das PK, Saelinger CB. PIG3V, an immortalized human vitiligo cell line, expresses dilated endoplasmic reticulum. *In Vitro Cell Dev Biol Anim* 36: 309-319 (2000)

van den Wijngaard R, Wankowicz-Kalinska A, Le Poole C, Tigges B, Westerhof W, Das P. Local immune response in skin of generalized vitiligo patients. Destruction of melanocytes associated with the prominent presence of CLA+ T cells at the perilesional site. *Lab Invest* 80: 1299-1309 (2000)

van den Wijngaard RMJGJ, Aten J, Scheepmaker A, Le Poole IC, Tigges AJ, Westerhof W, Das PK. Expression and modulation of apoptosis regulatory molecules in human melanocytes: significance in vitiligo. *Br J Dermatol* 143: 573-581 (2000)

Le Poole IC, Sarangarajan R, Zhao Y, Stennett LS, Brown TL, Sheth P, Miki T, Boissy RE. 'VIT1', A novel gene associated with vitiligo. *Pigment Cell Res* 14: 475-484 (2001)

Le Poole IC, Stennett LS, Bonish BK, Dee L, Hernandez C, Robinson JK, Hann SK, Nickoloff BJ. Expansion of vitiligo lesions is associated with epidermal CDw60 expression and increased expression of HLA-DR in perilesional skin. *Br J Dermatol*, 149: 739-748 (2003)

Kroll TM, Bommasamy H, Boissy RE, Hernandez C, Nickoloff BJ, Mestril R, Le Poole IC. 4-Tertiary butyl phenol sensitizes human melanocytes to dendritic cell mediated killing: relevance to vitiligo. *J Invest Dermatol* 124: 798-806 (2005)

Hernandez C, Reddy SG, Barfuss A, Le Poole IC. Contact Leukoderma After Application of a Compounded Phenol Cream and Narrowband-UVB. *Eur J Dermatol*.18: 593-5 (2008).  
Denman CJ, McCracken J, Hariharan V, Klarquist J, Oyarbide-Valencia K, Guevara-Patiño JA, Le Poole IC. HSP70i Accelerates Depigmentation in a Mouse Model of Autoimmune Vitiligo. *J Invest Dermatol*.128: 2041-8 (2008).

Web site

*[www.meddean.luc.edu/depts/path/LePoole.htm](http://www.meddean.luc.edu/depts/path/LePoole.htm)*