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Novel immunotherapies for metastatic melanoma
– from mouse models towards clinical trials

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, Göteborg, 10 januari 2020, klockan 09:00

av Elin Forsberg

Fakultetsopponent: Professor Magnus Essand
Uppsala Universitet, Sverige

Avhandlingen baseras på följande delarbeten

I. Henrik Jespersen*, Mattias F Lindberg*, Marco Donia, **Elin MV Söderberg**, Rikke Andersen, Ulrich Keller, Lars Ny, Inge Marie Svane, Lisa M Nilsson and Jonas A Nilsson. *Equal contribution.
Clinical responses to adoptive T-cell transfer can be modeled in an autologous immune-humanized mouse model.
Nature communications, 2017, 8 (1), 707

II. **Elin MV Forsberg***, Mattias F Lindberg*, Henrik Jespersen, Samuel Alsén, Roger Olofsson Bagge, Marco Donia, Inge Marie Svane, Ola Nilsson, Lars Ny, Lisa M Nilsson and Jonas A. Nilsson.
*Equal contribution.
HER2 CAR-T cells eradicate uveal melanoma and T cell therapy-resistant human melanoma in interleukin-2 (IL-2) transgenic NOD/SCID IL-2 receptor knockout mice.
Cancer research, 2019, 79 (5), 899-904

III. **Elin MV Forsberg**, Samuel Alsén, Larissa Rizzo, Henrik Jespersen, Roger Olofsson Bagge, Marco Donia, Inge Marie Svane, Anders Lindahl, Lars Ny, Lisa M Nilsson and Jonas A Nilsson.
Chimeric antigen receptor expressing tumor infiltrating lymphocytes can eradicate immunotherapy resistant melanoma.
Manuscript

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR KLINISKA VETENSKAPER

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Novel immunotherapies for metastatic melanoma
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Abstract

Immunotherapies including checkpoint blockade and adoptive T cell transfer (ACT) show great promise for the treatment of melanoma, with long-term effects in some patients. However, around half of the patients with metastatic malignant melanoma will not be cured with available therapies today, and these patients require other treatment strategies. For metastatic uveal melanoma (a rare melanoma of the eye), available immunotherapies are less effective, and there is currently no approved therapy for these patients.

To be able to study immunotherapies in mice, we in Paper I developed an immune-humanized mouse model called patient-derived xenograft (PDX) version 2 (PDXv2). In this model, tumor cells and tumor infiltrating lymphocytes (TILs) from the same patient were grafted in IL-2 transgenic NOD/SCID IL2 receptor gamma knockout (NOG) mice, and we found that responses in the mouse model correlated to responses in the corresponding patients in a clinical trial of ACT.

So far, no chimeric antigen receptor T cell (CAR-T) therapy is approved for use in solid tumors. In Paper II we tested the potential for CAR-T therapy in melanoma. First, we used TCGA to determine the expression in melanoma biopsies of targets for commercially available CAR-T cells. We found that HER2 is expressed in both cutaneous and uveal melanoma biopsies. HER2 CAR-T cells were then used to treat skin melanoma and uveal melanoma patient-derived xenografts in the PDXv2 mouse model resulting in curative responses, even in models resistant to TIL therapy. However, CAR-T cells were only effective in IL-2 transgenic mice and not in regular NOG mice.

In order to facilitate translation of the findings from Paper II into a treatment strategy for patients with melanoma, we developed CAR-expressing autologous TILs (called CAR-TILs). In Paper III, we demonstrate that this strategy could overcome resistance to treatment with autologous TILs in melanoma. Current CAR-T therapies use blood-derived T cells as a substrate for CAR-T cell production. We hypothesized that by using TILs instead, we might facilitate homing to the tumor and potentially also utilize the fact that some TILs can recognize melanoma antigens, enabling a dual targeting of CAR-TILs. We also developed an automated production protocol for TILs and CAR-TILs utilizing a bioreactor, enabling safe and less variable production of the drug product.

Keywords: Metastatic melanoma, uveal melanoma, patient-derived xenograft, immune-humanized mouse model, immunotherapy, adoptive T cell therapy, tumor-infiltrating lymphocytes, chimeric antigen receptor T (CAR-T) cells

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