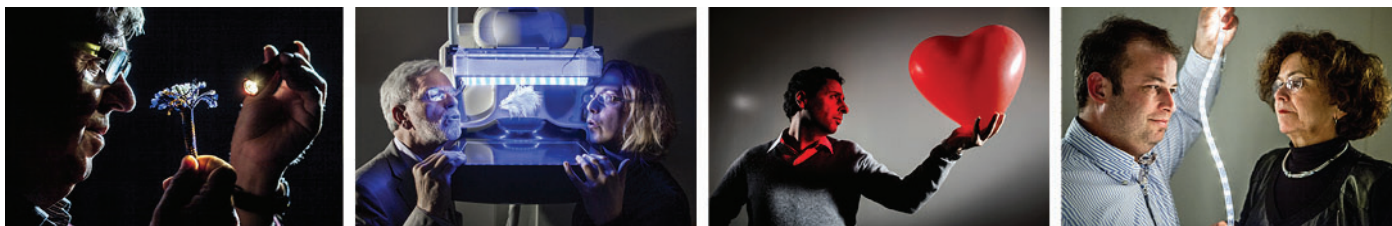


Collaboration & Licensing Opportunity



Combination therapy of ALK-positive neoplasia with an ALK-inhibitor and TRAIL

- Allows improved outcomes for high-risk, ALK-mutated neuroblastoma
- Potential for combination therapy of other ALK-mutated tumors

neuroblastoma, ALK-inhibitor, TRAIL, mesenchymal cells, combination therapy

2019

Background

Neuroblastoma is an aggressive childhood tumor, accounting for 15% of cancer deaths in children. Most high stage neuroblastoma go in complete clinical remission by chemotherapy, but ultimately relapse as therapy-resistant lethal disease. The reason why is unsolved. We have recently published that most neuroblastoma tumors consist of two tumor cell types. The predominant type is called ADRN, for adrenergic, while a minority of cells has the MES phenotype, for mesenchymal. MES cells are relatively resistant to chemotherapy in vitro. After chemotherapy, MES cells accumulate in tumors, suggesting selection of this cell type by therapy. We hypothesized that MES-type cells survive therapy and are responsible for relapse development later on. To improve outcomes for neuroblastoma patients, it will be important to develop therapies that kill both ADRN cells as well as MES cells.

The Technology

We detected that MES cells specifically express CASP8, a marker of the extrinsic apoptosis route. ADRN-type cells did not express CASP8. The extrinsic apoptosis route can be activated by external stimuli. Of a series of such known stimuli, TRAIL came out as a highly efficient and specific drug to kill MES-type cells. TRAIL is a human protein that is produced by certain cell types and that has been studied for over 20 years, also as anti-cancer drug.

To test TRAIL in vivo, we generated mouse xenograft models of human neuroblastoma cells. We equipped a MES-type neuroblastoma cell line with an inducible TRAIL transgene. Induction of TRAIL (TNF-related apoptosis-inducing ligand) efficiently killed the neuroblastoma cells in vitro. Xenografts of this cell line in mice formed tumors predominantly consisting of MES-type cells. After induction of TRAIL expression, these tumors disappeared during the full course of TRAIL induction (6 weeks), proving that TRAIL efficiently kills MES cells in vivo.

We next tested the potential of combination therapy of TRAIL (anti-MES) and an ALK inhibitor (anti-ADRN) in a neuroblastoma cell line with an ALK mutation. This cell line forms in mice tumors predominantly consisting of ADRN cells with a minority of MES cells, as is representative for most neuroblastoma tumors in patients. The xenograft tumors were treated with 1) TRAIL only, 2) the ALK inhibitor lorlatinib only or 3) the combination. Tumors rapidly grew in untreated control mice. TRAIL-only treatment did not inhibit tumor growth. Lorlatinib-only treatment induced almost complete tumor regression, which lasted during treatment (6 weeks), after which relapses emerged. This is in accordance with published literature. When TRAIL was added to the lorlatinib treatment, relapses were delayed for >2 weeks. These data indicate that TRAIL improves outcome when combined with an ADRN-specific drug.

Applications

1. Treatment with ALK inhibitors such as lorlatinib has reached the clinic for lung cancer (NSCLC) and is in development for neuroblastoma. Combining an ALK-inhibitor with TRAIL could lead to increased efficacy in delaying, preventing or treating disease recurrence.
2. Several newer generation TRAIL inhibitors are in development for liquid and solid tumours. Neuroblastoma could be an attractive new indication.

R&D Status

The fundamental principle that TRAIL kills MES cells but not ADRN cells has been sufficiently shown and validated in vitro. Furthermore, the complementary drug sensitivity of these cell-types has been proven in vivo by xenograft studies of human neuroblastoma, in which addition of TRAIL to ALK inhibitor treatment delayed relapse and prolonged survival. We are looking for an industrial partner with either an ALK-inhibitor or TRAIL in clinical development that is interested in further co-development of this combination therapy.

Intellectual Property

A patent application covering the combination therapy of an ALK-inhibitor with TRAIL has been filed in March 2019.

Inventors

Lead inventor is Prof. Rogier Versteeg, Department of Oncogenomics of the Amsterdam University Medical Center, location AMC, in Amsterdam, The Netherlands. The main focus of his research concerns the molecular biology and genetic defects of several pediatric tumors (neuroblastoma, medulloblastoma and rhabdomyosarcoma). Secondly, he studies the overall organization of gene expression of the human genome. Both research lines are supported by a strong bioinformatics and systems biology approach. Other inventors are Ellen Westerhout and Mohamed Hamdi, both from the same Department at the Amsterdam UMC.

Key Publications

The work on which this invention is based has recently been submitted for publication. It was also covered in a plenary session presentation during the AACR 2019 conference.

Further reading: van Groningen T et al, Neuroblastoma is composed of two super-enhancer-associated differentiation states. NAT GENET 2017;49 (8):1261-1266 [PubMed]