Stien De Coninck

Publications

TET2 is a tumor suppressor in the pre-leukemic phase of T-cell acute lymphoblastic leukemia
De Coninck Stien *et al.* Under revision

Targeting hyperactive platelet-derived growth factor receptor-β signaling in T-cell acute lymphoblastic leukemia and lymphoma
De Coninck Stien *et al.* Haematologica, 2023

ZEB2 in T-cells and T-ALL
De Coninck *et al.* Advances in Biological Regulation, 2019

Additional co-author publications can be viewed on ORCID 0000-0003-0777-8205

Curriculum Vitae

2019-2024	PhD Researcher, Department of Biomolecular Medicine, Lab of Normal and Malignant Hematopoiesis, Ghent University
2017-2019	Specialized Master of Science: Experimental Biomedical Research, Université de Fribourg
2015-2017	Master of Science: Bioscience Engineering, KULeuven

GHENT UNIVERSITY

FACULTY OF MEDICINE AND HEALTH SCIENCES

Examination committee

Prof. Dr. Katleen De Preter
Department of Biomolecular Medicine, Lab of Translational Oncogenomics and Bio-informatics, Ghent University

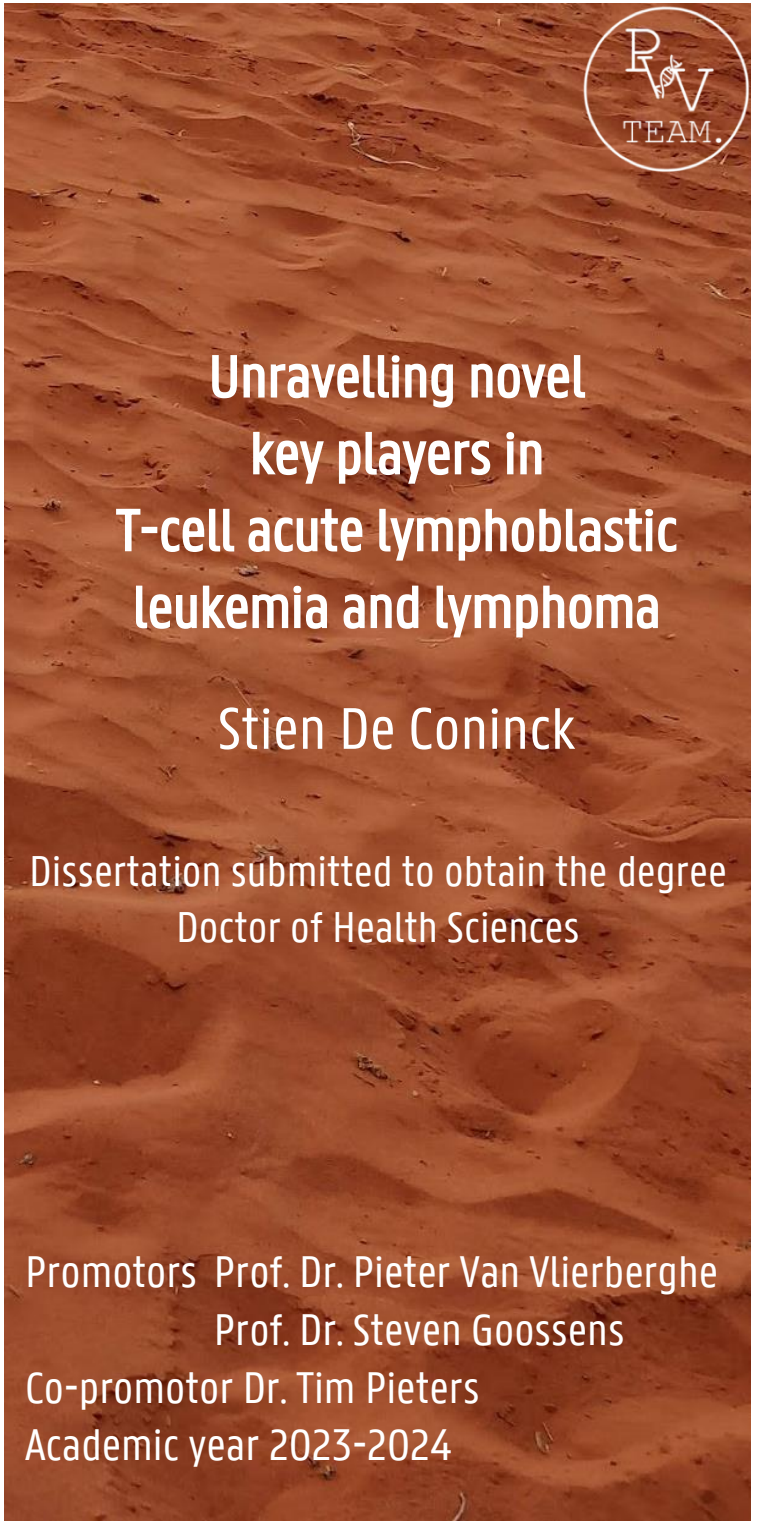
Dr. Camille Lobry
Institut de Recherche Saint-Louis, Genetic and Epigenetic control of Normal and Malignant Hematopoiesis, Université Paris Cité

Dr. Igor Fijalkowski
Department of Biomolecular Medicine, Lab for Leukemia Therapy Resistance, Ghent University

Prof. Dr. Kaat Durinck
Department of Biomolecular Medicine, Pediatric Precision Oncology Lab, Ghent University

Dr. Maaike Van Trimpont
Department of Diagnostic Sciences, Unit for Translational Research in Oncology, Ghent University

Dr. Marlies Vanden Bempt
Department of Human Genetics, Laboratory for the Molecular Biology of Leukemia, KU Leuven



Unravelling novel key players in T-cell acute lymphoblastic leukemia and lymphoma

Stien De Coninck

Dissertation submitted to obtain the degree Doctor of Health Sciences

Promotors Prof. Dr. Pieter Van Vlierberghe
Prof. Dr. Steven Goossens
Co-promotor Dr. Tim Pieters
Academic year 2023-2024

Leukemia

Leukemia is a type of cancer where the blood-forming cells in the bone marrow grow in an uncontrolled manner. This uncontrolled growth results in a rapid production of abnormal white blood cells, taking over the body's ability to produce healthy blood cells. This can impair the body's ability to fight infections and may cause symptoms such as fever, weakness and fatigue.

A specific type of leukemia is **T-cell acute lymphoblastic leukemia (T-ALL)**. T-cells are a type of white blood cells that helps the body fight infections. Acute means that this cancer progresses quickly and requires immediate treatment. This type of leukemia affects the lymphatic system which serves as a defense network against infections and diseases. T-ALL is diagnosed if more than 25% of the bone marrow is invaded by T-cell lymphoblasts. If this is less than 25%, the cancer is defined as **T-cell lymphoblastic lymphoma** (**T-LBL**).

Treatment for T-ALL/T-LBL patients involves chemotherapy to eradicate the abnormal white blood cells. Over time, researchers have made great progress in treating these patients, leading to improved outcomes for patients, especially children diagnosed with these diseases.

However, patients that relapse have a very low chance of survival and current chemotherapy treatments often cause harmful side-effects, even on the long term. Therefore, our lab tries to better understand what specifically causes T-ALL/T-LBL and how we can eradicate the cancer cell more specifically so normal tissue is not harmed.

PDGFRB

In the first part of my research, we identified a new fusiongene in a T-LBL patient. This means that this patient had two different parts of genes fused to each other that normally not lie next to each other on our DNA. The first part of this novel fusiongene is MYH9, important for cells to adhere and move, the second part is the platelet derived growth factor receptor beta (**PDGFRB**), a receptor on the cell membrane which is necessary during the formation of all our blood cells. Our experiments demonstrated that this fusiongene is the cause of T-LBL formation in this patient.

This raised the question: do other T-ALL/T-LBL patients also have similar properties? That's why we looked at how frequently present PDGFRB is in other T-ALL patients and indeed, we identified two subpopulations of T-ALL patients that had high PDGFRB levels. Since this seemed to be a more common feature in T-ALL, we looked for a specific drug that could eradicate the leukemia cells that have high expression of this receptor. Finally, we ended up with the drug CP-673451 which is very specific to inhibit the function of PDGFRB. We tested this drug on cells with the MYH9-PDGFRB fusion gene and cells with active PDGFRB and found that indeed our drug could kill these cells specifically. In a final experiment, we tested if this drug could also work in mice that had leukemia with high and active PDGFRB. We observed that mice treated with CP-673451 had less leukemia cells in the blood and bone marrow compared to mice that did not receive treatment.

So we can conclude that if T-ALL/T-LBL patients have high and active PDGFRB, treating them with CP-673451 could really increase their chances of survival.

TET2

Leukemia can be caused by specific overexpression of a protein (=oncogene), but also decreased protein expression can be an initiating step during leukemia development, in this case we're talking about a tumor suppressor. Based on two different mouse models that spontaneously develop T-ALL, we suggest a tumor suppressor role for the ten eleven translocation (**TET2**) protein during the early steps of T-ALL formation.

TET2 is an important protein during the regulation of DNA methylation. This means that certain groups (methyl, CH_3) can bind to our DNA which will make it no longer possible of translating this DNA to proteins. TET2 is specifically involved in the process of removing this methyl groups from the DNA. Our results indicate that if TET2 protein levels drop below a certain level in T-cells, these cells are more vulnerable to develop into leukemic cells.

Access to my thesis

Supported by

CRIG

Kom op tegen Kanker

fwo

CENTRUM MEDISCHE GENETICA GENT