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Alternative splicing in acute leukemia-relevance in treatment response

Wojtuszkiewicz, A.M.

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CHAPTER

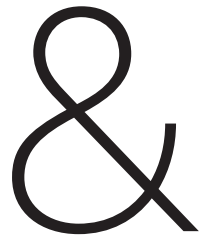
Curriculum vitae

Publications

Awards/nominations

Conference presentations

Acknowledgements/Dankwoord/Podziękowania



CURRICULUM VITAE

Anna Wojtuszkiewicz was born on February 1st 1985 in Wrocław, Poland. In 2004 she graduated from secondary school nr. VII in Wrocław where she followed a biology and chemistry oriented program. In 2009 she received a Master's degree in Biology with specialization in Microbiology at University of Wrocław in Poland. The research for her Master's thesis was conducted within the Department of Genetics and focused on identification of genes associated with ketoconazole resistance in pathogenic strains of *Candida krusei*. During the Master training she performed her primary internship at the Department of Experimental Oncology of Polish Academy of Science, where she was involved in cytotoxicity screening for novel anti-tumor agents. Her secondary internship took place at the Department of Molecular Genetics of Biomolecular Sciences and Biotechnology Institute, Rijksuniversiteit Groningen, for which she received the support of the Erasmus LPP scholarship program. During this five month internship she conducted research into the mode of action of NisB - an enzyme catalyzing metabolic conversion of an antibiotic nisin in *Lactococcus lactis*. In November 2010 she started her PhD research at the Department of Pediatric Oncology/Hematology of the VU University Medical Center (Cancer Center Amsterdam). The research within this collaborative project was conducted under the supervision of prof. dr. Gert-Jan Kaspers (Dept. of Pediatric Oncology/Hematology, VUmc), prof. dr. Yehuda Assaraf (Dept. of Biology, Technion), prof. dr. S. Zweegman (Dept of Hematology), dr. Jacqueline Cloos (Dept. of Pediatric Oncology/Hematology and Dept. of Hematology, VUmc) and dr. Gerrit Jansen (Dept. of Rheumatology). The studies were partly performed at Fred Wyzkowski Cancer Research Laboratory of Technion-Israel Institute of Technology in Haifa, Israel during a five month internship supported by the René Vogels Stipendium. The results of the research performed during that time are described in this dissertation. Currently Anna is working as a post-doc on a KIKA project focused on the role of splicing in drug resistance of acute leukemia.

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PUBLICATIONS

Wojtuszkiewicz A, Barcelos A, Dubbleman B, de Abreu R, Brouwer C, Bökkerink JP, de Haas V, de Groot-Kruseman H, Jansen G, Kaspers GJL, Cloos J, Peters GJ. Assessment of mercaptopurine (6MP) metabolites and 6MP metabolic key-enzymes in childhood acute lymphoblastic leukemia. *NNNA*. **2014**;33:422-433.

Wojtuszkiewicz A, Assaraf YG, Maas MJ, Kaspers GJL, Jansen G, Cloos J. Pre-mRNA splicing in cancer: the relevance in oncogenesis, treatment and drug resistance. *Expert Opin Drug Metab Toxicol* **2015**;11:673–689

Wojtuszkiewicz A, Peters GJ, van Woerden NL, Dubbelman B, Escherich G, Schmiegelow K, Sonneveld E, Pieters R, van de Ven PM, Jansen G, Assaraf YG, Kaspers GJL, Cloos J. Methotrexate resistance in relation to treatment outcome in childhood acute lymphoblastic leukemia. *J Hematol Oncol*. **2015**;8:61

Wojtuszkiewicz A, Raz S, Stark M, Assaraf YG, Jansen G, Peters GJ, Sonneveld E, Kaspers GJL, Cloos J. Folylpolyglutamate synthetase splicing alterations in acute lymphoblastic leukemia are provoked by methotrexate and other chemotherapeutics and mediate chemoresistance. *Int J Cancer*. **2016**;138:1645-1656

Wojtuszkiewicz A, Schuurhuis GJ, Kessler FL, Piersma SR, Knol JC, Pham TV, Jansen G, Musters RJ, van Meerloo J, Assaraf YG, Kaspers GJL, Zweegman S, Cloos J, Jimenez CR. Exosomes secreted by apoptosis-resistant acute myeloid leukemia (AML) blasts harbor regulatory network proteins potentially involved in antagonism of apoptosis. *Mol Cell Proteomics*. **2016**;15:1281-1298

Wojtuszkiewicz A, Assaraf YG, Hoekstra M, Sciarrillo R, Jansen G, Peters GJ, Pieters R, Sonneveld E, Kaspers GJL, Cloos J. The relation of aberrant folylpolyglutamate synthetase splicing with *ex vivo* methotrexate resistance and clinical outcome in childhood acute lymphoblastic leukemia. *Haematologica*. **2016**;101:e291-294.

Sciarrillo R, **Wojtuszkiewicz A**, Kooi IE, Gómez VE, Jansen G, Kaspers GJL, Cloos J, Giovannetti E. Using RNA-seq to detect novel splice variants related to drug resistance in *in vitro* cancer models. *JoVE*. **2016**; In press

Wojtuszkiewicz A, Sciarrillo R, Assaraf YG, Kessler FL, Koide K, Bressin RK, Basu U, Jansen G, Kaspers GJL, Cloos J. A novel SF3b inhibitor - Meayamycin B potently inhibits growth of acute leukemia cells (Manuscript in preparation)

AWARDS/NOMINATIONS

Wojtuszkiewicz A, awarded the **Scholar-in-Training Award** for attendance to the AACR Annual Meeting 2016, April 16-20, 2016, New Orleans, LA, USA

Wojtuszkiewicz A, nominated (within top 5 candidates) for **Tom Voûte Young Investigators Award**, Amsterdam, 2015

Wojtuszkiewicz A, awarded the **Scholar-in-Training Award** for attendance to the AACR Annual Meeting 2015, April 18-22, 2015, Philadelphia, PA, USA

Wojtuszkiewicz A, awarded the **Scholar-in-Training Award** for attendance to the AACR Annual Meeting 2014, April 5-9, 2014, San Diego, CA, USA

Wojtuszkiewicz A, awarded the **PUMPA Travel Grant for Young Investigators** for attendance to the 15th International Symposium on Purine and Pyrimidine Metabolism in Man, June 9-13, 2013, Madrid, Spain

Wojtuszkiewicz A, awarded the **René Vogels Stipendium** for an internship to the Technion-Israel Institute of Technology in Haifa, Israel, 2012

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CONFERENCE PRESENTATIONS

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Wojtuszkiewicz A, Assaraf YG, Hoekstra M, Sciarrillo R, Jansen G, Peters GJ, Sonneveld E, Kaspers GJL, Cloos J. The relevance of aberrant FPGS splicing for *ex vivo* MTX resistance and clinical outcome in childhood acute lymphoblastic leukemia. Selected as **Poster presentation** at the 10th Biennial Childhood Leukemia Symposium (CLS), April 25-26, 2016, Athens, Greece

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Wojtuszkiewicz A, Sciarrillo R, Jansen G, Assaraf YG, Koide K, Bressin RK, Basu U, Sonneveld E, Giovannetti E, Peters GJ, Kaspers GJL, Cloos J. Spliceosome inhibition as a novel therapeutic option in acute leukemia. Selected as **Oral presentation** at the American Association for Cancer Research (AACR) Annual Meeting 2016, April 16-20, 2016, New Orleans, LA, USA.

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Wojtuszkiewicz A, Assaraf YG, Hoekstra M, Sciarrillo R, Jansen G, Peters GJ, Sonneveld E, Kaspers GJL, Cloos J. The relevance of aberrant FPGS splicing for *ex vivo* MTX resistance and clinical outcome in childhood acute lymphoblastic leukemia. Selected as **Oral presentation** at the 10th Dutch Hematology Congress, January 20-22, 2016, Papendal, The Netherlands.

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Wojtuszkiewicz A, Assaraf YG, Hoekstra M, Jansen G, Peters GJ, Sonneveld E, Kaspers GJL, Cloos J. The relevance of aberrant FPGS splicing for *ex vivo* MTX resistance and clinical outcome in childhood acute lymphoblastic leukemia. Selected as **Poster presentation** at the American Association for Cancer Research (AACR) Annual Meeting 2015, April 18-22, 2015, Philadelphia, USA.

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Wojtuszkiewicz A, Assaraf YG, Ramakers-van Woerden NL, Dubbelman B, Rots MG, Escherich G, Schmiegelow K, Sonneveld E, Pieters R, van de Ven PM, Jansen G, Peters GJ, Kaspers GJL, Cloos J. Methotrexate resistance in relation to treatment outcome in childhood acute lymphoblastic leukemia. Selected as **Poster presentation** at the American Association for Cancer Research (AACR) Annual Meeting 2015, April 18-22, 2015, Philadelphia, USA.

Wojtuszkiewicz A, Assaraf YG, Jansen G, Koide K, Bressin RK, Basu U, Sonneveld E, Giovannetti E, Kaspers GJL, Cloos J. Spliceosome inhibitor Meayamycin B as a novel potential chemotherapeutic agent in ALL and AML. Selected as **Poster presentation** at the 56th American Society of Hematology (ASH) Annual Meeting, December 6-9, 2014, San Francisco, CA, USA.

Wojtuszkiewicz A, Raz S, Assaraf YG, Stark M, Koide K, Sonneveld E, Peters GJ, Jansen G, Kaspers GJL, Cloos J. Impaired FPGS splicing as an emerging determinant of MTX resistance in ALL. Selected as **Poster presentation** at the 9th Biennial Childhood Leukemia Symposium (CLS), April 28-29, 2014, Prague, Czech Republic.

Wojtuszkiewicz A, Schuurhuis GJ, Kessler FL, Piersma SR, Knol JC, Pham TV, Jansen G, Assaraf YG, Kaspers GJL, Zweegman S, Cloos J, Jimenez CR. Transfer of regulatory protein networks via extracellular vesicles as a candidate mechanism of apoptosis-resistance in acute myeloid leukemia. Selected as **Oral presentation** at the American Association for Cancer Research (AACR) Annual Meeting 2014, April 5-9, 2014, San Diego, CA, USA.

Wojtuszkiewicz A, Schuurhuis GJ, Kessler FL, Piersma SR, Knol JC, Pham TV, Jansen G, Assaraf YG, Kaspers GJL, Zweegman S, Cloos J, Jimenez CR. Transfer of regulatory protein networks via extracellular vesicles as a candidate mechanism of apoptosis-resistance in acute myeloid leukemia. Selected as **Oral presentation** at 8th Dutch Hematology Congress, January 22-24, 2014, Papendal, The Netherlands.

Wojtuszkiewicz A, Barcelos A, Dubbleman B, de Abreu R, Brouwer C, Bökkerink JP, de Haas V, de Groot H, Giovannetti E, Jansen G, Kaspers GJL, Peters GJ, Cloos J. 6-MP Metabolites and 6-MP Metabolic Key-enzymes as Predictive Factors on Childhood Acute Lymphoblastic Leukaemia (ALL). Selected as **Oral presentation** at the 15th International Symposium on Purine and Pyrimidine Metabolism in Man, June 9-13, 2013, Madrid, Spain

Wojtuszkiewicz A, Raz S, Assaraf YG, Stark M, Sonneveld E, Peters GJ, Jansen G, Kaspers GJL, Cloos J. Alterations in FPGS splicing as a plausible underlying basis of MTX resistance in ALL. Selected as **Oral presentation** at the American Association for Cancer Research (AACR) Annual Meeting 2013, April 6-10, 2013, Washington, DC., USA.

Wojtuszkiewicz A, Jansen G, Assaraf YG, Stark M, Peters GJ, Kaspers GJL, Cloos J. The relevance of alterations in FPGS splicing in MTX resistance of acute lymphoblastic leukemia. Selected as **Oral presentation** at 7th Dutch Hematology Congress, January 23-25, 2013, Papendal, The Netherlands.

Wojtuszkiewicz A, Jansen G, Assaraf YG, Stark M, Peters GJ, Kaspers GJL, Cloos J. Folylpolyglutamate synthetase splicing alterations in childhood acute lymphoblastic leukemia: implications for MTX-therapy efficacy. Selected as **Poster presentation** at the 17th Congress of European Hematology Association, June 14-17, 2012 in Amsterdam, The Netherlands

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I wish to thank my thesis committee members: **Tanja de Gruijl, Frank van Leeuwen, Robert de Jonge, Ruud Brakenhoff, Jacques Neefjes** and **Peter Hoogerbrugge** for devoting your valuable time to dive into my thesis and provide feedback. Thank you for agreeing to become my opposition and I am looking forward to our discussion during my defense.

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 i smoczyco! Moja paranimfo ;) Tyle fantastycznych wspólnych czasów za nami, począwszy od
 dziesięciogodzinnych izolacji DNA, jałowienia etanolu i przygotowywania odczynników Wojtuchala
 u doktora Skały, po niezliczone zdarzenia z udziałem świecących kostek, książek i przewysokich
 obcasów. Dziękuję, że zdecydowałaś się wyruszyć ze mną w tę roczną przygodę w Amsterdamie,
 która otworzyła przede mną tyle drzwi. Wiem, że dla Ciebie był to czas jednocześnie szczęśliwy
 jak i trudny, ze względu na rozłąkę z Maciejem. Wiedz, że bez Ciebie i tego w pewnym sensie
 przejściowego dla nas obu etapu najprawdopodobniej by mnie tu w ogóle nie było. Za to, twoje
 wsparcie i za naszą przyjaźń będę zawsze wdzięczna! Koniec końców dziękuję za twą pomoc w
 zamknięciu okresu mojego doktoratu. **Caro**, you wonderful, unique weido!! ☺ I am so glad you
 were placed at a desk next to me and I got to know your strange and curious mind. I had (and still
 have) so much fun with you both at work and outside of it. I love discussing science and all kinds of
 other wonders of this world (i.e. what strange things NASA does with their millions of dollars-worth
 of equipment :P) with you! Running into the streets in PJs in the middle of the night was somewhat
 unconventional holiday experience but I hope I can be your fire alarm again in the future (or maybe
 better not :P). Thank you for helping me with the arrangements for this occasion and I wish I could
 also have you with me on that podium during defense.

I saved my dearest and most important people in the world for the end – my beloved family and best friends. Kochani przyjaciele, którzy zaczęliście kroczyć obok mnie na różnych etapach życia – **Dyniu, Gwiazdeczko, Dorot, Molka, Quaczor, Agus i Martyn!** Nie ma nic fantastyczniejszego niż wspólne dzielenie życia. Z niektórymi z was jestem w nieprzerwanie częstym kontakcie, z innymi kontaktujemy się nieco mniej regularnie, ale wszyscy jesteście dla mnie bardzo ważni i niezastąpieni! Wasza obecność w moim życiu była dla mnie wsparciem w różnych trudnych momentach mojego doktoratu. **Dyniaszko** moja najukochańsza, odnalezienie tak bliskiej przyjaciółki w obrębie własnej rodziny jest bezcenne. Jestem bardzo wdzięczna za twoje nieustające wsparcie i zawsze pozytywnie nastawioną do świata Dyniowatość. Dziękuję, za wiele wspólnych przygód w dzieciństwie aż po dorosłość i wiem, że zawsze mogę na Ciebie liczyć (Ty na mnie też!). Już nie mogę się doczekać Twojej własnej obrony, przyszła pani współ-doktor Dyniu oraz naszych wspólnych wieczorów na ganku z kawą czy herbatą! ☺ **Dorot**, moja odwieczna przyjaciółko, na prawdę nie pamiętam czasów, w których Cię nie było. Nasze wspólne dzieciństwo i dorastanie, przeplecione oceanem przygód wiele mnie nauczyło. Zawsze byliśmy bardzo kreatywne. Dziękuję za Twoje wsparcie w potrzebie i cierpliwość, kiedy ich potrzebowałam. Ania ma wspaniały wzór do naśladowania! Uważaj tylko na to okno.. ;) **Molka**, Martyna, dzięki za wiele niezapomnianych wspólnych czasów, wypełnionych jeździectwem, pisaniem dziwnych historii, które potem się ziszczają (jak nasze tegoroczne spotkanie w Londynie), muzyką, filmami, wiszeniem na telefonie czy śpiewaniem Placebo o 46 w nocy. Dziękuję, że nauczyłaś mnie gwizdać i pluć i że zawsze wystawała nam słoma z butów. ;) Jak się niedawno okazało, do dziś stanowimy trzepnięty duet i ciekawa jestem jak to się będzie prezentowało jak będziemy miały po 60 lat. :P **Quaczor**, dzięki za lata przyjaźni i choć ostatnimi czasy trochę nam się kontakt rozluźnił, to mam nadzieję, że uda nam się nadrobić. Dzięki za wsparcie jakie mi okazałeś, za wspólne łożenie po górach i za picie wina przez Skype! ☺ Choć życie odwołało Twoje i Ani odwiedziny u nas, mam nadzieję, że następnym razem się uda. Moc uścisków i wiele szczęścia dla was obojga! **Agus**, mój prosiaczku kochany! Dziękuję za two wsparcie, zwłaszcza w trudnych chwilach. Jesteś otwarta, przebojowa i niesamowicie ciepła i zawsze potrafiłaś mnie tym podnieść na duchu. Uwielbiam nasze przedziwne i ponadczasowe poczucie humoru i mam nadzieję, że zostaniemy w przyjaźni aż do końca! **Martyn**, dziękuję, że byłaś tak nieocenionym kompanem w czasie studiów, za nasze nocne zakuwanie na parazyty i za to nieszczęsne sprawko z mikrobow :P Z czasem stało się to jeszcze bardziej zabawne :P Zawsze mogłam liczyć na Twoje wysłuchanie i wsparcie. Mam nadzieję, że jeszcze wiele wspólnych doświadczeń przed nami!

Ik wil de hele familie van Bo bedanken: **Hugo, Tilly, Sylvia, Babs, Hellen, Jesse, Kelly** en **Bruno**, jullie waren vanaf het begin vriendelijk en ondersteunend. Ik vind jullie onzettende leuke mensen, die elkaar heel veel helpen en steunen. Ik denk dat het heel bijzonder is!

Kochane **Kruczaki**, ciociu, wujku i Romku dziękuję, że zdecydowaliście się na przebycie tak dalekiej drogi żeby towarzyszyć mi w tym dniu! Po rodzicach i Marcinie jesteście zdecydowanie najbliższą mi rodziną i choć widzujemy się rzadko, gościecie często w moich myślach i za każdym razem kiedy spotykamy się na Święta, czuję się jakbyśmy się widzieli wczoraj. Oby nasze tradycje nigdy nie umarły! **Brat**, wyrosłeś na fantastycznego człowieka! Bardzo lubię Twój indywidualizm i czarne poczucie humoru. ;) Od małego mogłam na Ciebie liczyć i jest tak i po dzień dzisiejszy. Dzięki za mnóstwo wspólnych fajnych czasów w dzieciństwie, włącznie z budowaniem przedszkola biedronek,

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1 graniem w ufo, mortal kombat i budowanie statków z klocków plastikowych i drewnianych! No i oczywiście za udział w naszej ostatniej konspiracji przeciwko rodzicom! ;)

2 Kochani rodzice, tyle wam zawdzięczam, że nawet nie wiem od czego zacząć. Daliście mi życie i piękne dzieciństwo. Dziękuję za wasze wielkie serca, pełne bezwarunkowej miłości i za genialne poczucie humoru! Wyposażyliście mnie w samodzielność i rządę przygód, przez co wyfrunęłam w świat z odrzutowym impetem ;) Wiedza, otwartość umysłu i wolność wyboru zawsze były wysoko na liście cenionych przez was wartości i tego też się od was nauczyłam. Moja, silna, przekorna, bystra **mamusiu**. Tak, tak wszystkie te cechy, na dobre i na złe, odziedziczyłam po Tobie ;) Dzięki Tobie potrafię zawsze myśleć samodzielnie i powiedzieć moim przełożonym prosto w twarz, że się myślę. Twoja autorytatywna, odpowiedzialna i oparta na wiedzy postawa zawodowa do dziś jest dla mnie przykładem. Twoja otwartość na nowe przeróżniste teorie na temat rzeczywistości przypomina mi, że obok mojej krytyczności muszę również zawsze zachowywać otwarty umysł. Dziękuję, że zawsze służyłaś mi radą i wsparciem kiedy Cię potrzebowałam. **Tatusiu**, dziękuję Ci za wszystkie pasje którymi mnie zaraziłeś! Nauczyłeś mnie z odwagą podbijać świat, rozwijać swoje zainteresowania i zawsze próbować nowych rzeczy, nawet jeśli na początku nie są łatwe. Zawsze stawałeś w obronie słabszych ludzi i zwierząt, z czego do tej pory biorę przykład. Niezachwianie wierzyłeś we mnie i wspierałeś mnie w tym wyzwaniu, jakim był mój doktorat. Będzie mi szalenie brakowało naszych wspólnych rozmów, górskich wędrówek, jazdy na nartach, pieczenia pierniczek i ubierania choinki. Wszystkie nasze wspólne chwile na zawsze będą bezpieczne w moim sercu!

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& **Bo**, my schatje, despite my threats I will not embarrass you here too much ;) You are such a wonderful person and, as you dreamed, a true rock star scientist. ☺ I love our inside jokes and habits and all kinds of weird adventures we experience together. Even though you always deny this serious stuff (next to your weakness towards a certain song that I am not allowed to mention here), you are bright, very carrying and responsible (sometimes more than me ;)). Thank you for standing by me every day in so many ways. For your patience and always bringing me chocolate and veggie burrito when I'm down or just grumpy. ☺ For all the music, delicious cuisine and nerdy interests you share with me. I love talking about science and exploring the enigma of the mystical with you! Without your support, I would be lost. Ik houd super veel van je! I can't wait for our new housey and growing old together, traveling and playing Mario and other stuff. ☺ Oh, and you are the prettiest man in the whole wide lab! ☺

