Severe Chronic Neutropenia International Registry (SCNIR)
March 2018

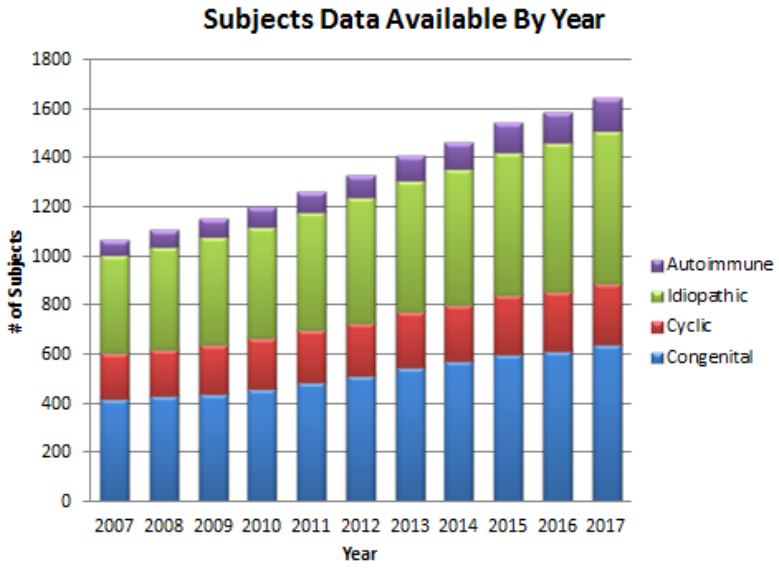
Introduction:

The SCNIR (the Registry) opened in 1994. The original goal was to collect data on the safety of long-term administration of G-CSF (Neupogen) to adults and children with severe chronic neutropenia (SCN) for reports to the Food and Drug Administration (FDA) and European Medicines Agency (EMA). Over time, the SCNIR has become an invaluable resource for understanding the genetic and molecular basis for chronic neutropenia and the outcomes of long term treatment of neutropenia with Neupogen/G-CSF and other therapies.

Patients:

There are currently 1647 subjects enrolled through the Seattle SCNIR office. Figure 1 shows the distribution by diagnostic category: congenital, cyclic, idiopathic and autoimmune neutropenia for SCNIR/Seattle:

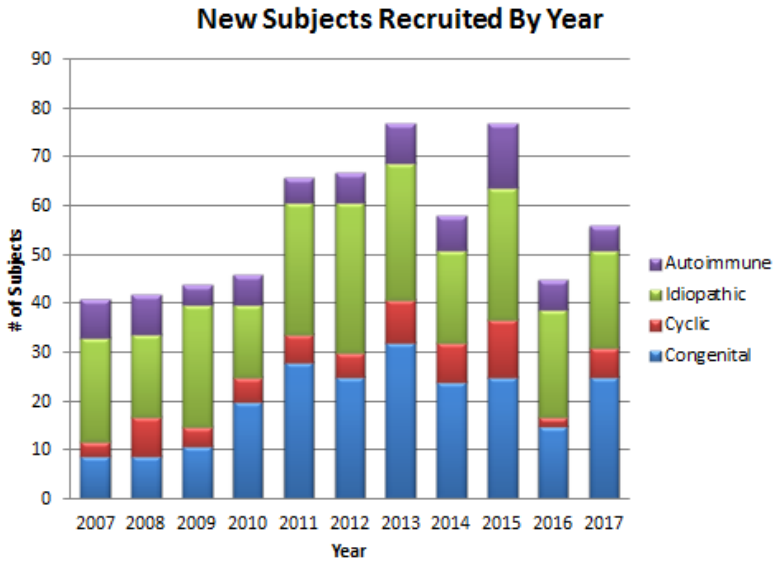
Figure 1



New Enrollees:

Figure 2 shows the number of new subjects enrolled by the SCNIR/Seattle for the years 2007 through 2017. The range is 41 to 77 subjects, mean 56 subjects.

Figure 2



Publications:

This list includes papers, chapters, editorials, commentaries and abstracts published from the SCNIR and its Advisory Board for the period 2014 to the present.

Research Reports

2014

1. Myers KC, Bolyard AA, Otto B, Wong TE, Jones AT, Harris RE, Davies SM, Dale DC, Shimamura A. Variable clinical presentation of Shwachman-Diamond syndrome: update from the North American Shwachman-Diamond Syndrome Registry. J Pediatr. 2014;164:866-70. PMCID: PMC4077327
2. Dale DC, Mackey M. Understanding, treating and avoiding hematological disease: better medicine through mathematics? Bull Math Biol. 2014;76(9):2091-121. PMCID: PMC4362913
3. Wilson DB, Link DC, Mason PJ, Bessler M. Inherited bone marrow failure syndromes in adolescents and young adults. Ann Med. 2014;46:353-63. PMCID: PMC4426964
4. Day RB, Link DC. Megakaryocytes in the hematopoietic stem cell niche. Nat Med. 2014;20:1233-4. PMID: 25375920
5. Alter BP. Inside Blood: Pearson syndrome in a Diamond-Blackfan anemia cohort. Blood. 2014;124:312-13. PMCID: PMC4102705
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8. Shaver A, Walkovich K, Boxer L. Chronic neutropenia. Hematology. 2014;19:431-432. PMID: 25155521
9. Zeidler C, Grote UA, Nickel A, Brand B, Carlsson G, Cortesão E, Dufour C, Duhem C, Notheis G, Papadaki HA, Tamary H, Tjønnfjord GE, Tucci F, Van Droogenbroeck J, Vermylen C, Voglova J, Xicoy B, Welte K. Outcome and management of pregnancies in severe chronic neutropenia patients by the European Branch of the Severe Chronic Neutropenia International Registry. Haematologica. 2014;99(8):1395-402. PMCID: PMC4116840
10. Desplantes C, Fremond ML, Beaupain B, Harousseau JL, Buzyn A, Pellier I, Roques G, Morville P, Paillard C, Bruneau J, Pinson L, Jeziorski E, Vannier JP, Picard C, Bellanger F, Romero N, de Pontual L, Lapillonne H, Lutz P, Chantelot CB, Donadieu J. Clinical spectrum and long-term follow-up of 14 cases with G6PC3 mutations from the French Severe Congenital Neutropenia Registry. Orphanet J Rare Dis. 2014;9:183. PMCID: PMC4279596

2015

1. Boxer LA, Bolyard AA, Kelley ML, Marrero TM, Phan L, Bond, JA, Alter BP, Bonilla MA, Link D, Newburger PE, Rosenberg PS, Dale DC. Use of granulocyte colony-stimulating factor during pregnancy in women with chronic neutropenia. Obstet Gynecol. 2015;125:197-203. PMCID: PMC4286310
2. Makaryan V, Zeidler C, Bolyard AA, Skokowa J, Rodger E, Kelley ML, Boxer LA, Bonilla MA, Newburger PE, Shimamura A, Zhu B, Rosenberg PS, Link DC, Welte K, Dale DC. The diversity of mutations and clinical outcomes for *ELANE* associated neutropenia. Curr Op Hematol. 2015;22:3-11. PMCID: PMC4380169
3. Klimiankou M, Klimenkova O, Uenalan M, Zeidler A, Mellor-Heineke S, Kandabarau S, Skokowa J, Zeidler C,

Welte K. GM-CSF stimulates granulopoiesis in a congenital neutropenia patient with loss-of-function biallelic heterozygous CSF3R mutations. Blood. 2015;126:1865-67 PMID: 26324699

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6. Alter BP, Giri N, Savage SA, Rosenberg PS. Telomere length in inherited bone marrow failure syndromes. Haematologica. 2015;100:49-54. PMCID: PMC4281312
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9. Fioredda F, Iacobelli S, van Biezen A, Gaspar B, Ancliff P, Donadieu J, Aljurf M, Peters C, Calvillo M, Matthes-Martin S, Morreale G, van 't Veer-Tazelaar N, de Wreede L, Al Seraihy A, Yesilipek A, Fischer A, Bierings M, Ozturk G, Smith O, Veys P, Ljungman P, Peffault de Latour R, Sánchez de Toledo Codina J, Or R, Ganser A, Afanasyev B, Wynn R, Kalwak K, Marsh J, Dufour C; Severe Aplastic Anemia the Inborn Error, and the Pediatric Disease Working Parties of the European Society for Blood and Bone Marrow Transplantation (EBMT) and Stem Cell Transplant for Immunodeficiencies in Europe (SCETIDE). Stem cell transplantation in severe congenital neutropenia: an analysis from the European Society for Blood and Marrow Transplantation. Blood. 2015;126:1885-1892. PMID: 26185129

2016

1. Nustede R, Klimiankou M, Klimenkova O, Kuznetsova I, Zeidler C, Welte K, Skokowa J. ELANE mutant-specific activation of different UPR pathways in congenital neutropenia. Br J Haematol. 2016;172(2):219-227. PMID: 26567890
2. Rosenthal EA, Makaryan V, Burt AA, Crosslin DR, Kim DS, Smith JD, Nickerson DA, Reiner AP, Rich SS, Jackson RD, Ganesh SK, Polfus L, Qi L, Dale DC, UW Center for Mendelian Genomics, Jarvik GP, on behalf of the NHLBI GO Exome Sequencing Project. Association between absolute neutrophil count and variation at *TCIRG1:* the NHLBI Exome Sequencing Project. Genet Epidemiol. 2016;40(6):470-4. PMC5079157

2017

1. Provencher Langlois G, Potts J, Leber B, Dale DC, Arnold D, Mackey MC. A case report of cyclic thrombocytopenia with statistically significant neutrophil oscillations. J Hematol Oncol. (submitted)
2. Steward CG, Groves SJ, Spence CT, Maisenbacher MK, Versluys B, Newbury-Ecob R, Ozsahin H, Hamilton L, Damin MK, Bowen VM, McCurdy KR, Apostu R, Mackey MC, Bolyard AA, Dale DC. Barth syndrome: an under-recognized cause of chronic neutropenia which may be intermittent, persistent or cyclical in nature. Orphanet J Rare Dis. 2017 (submitted)
3. Dale DC, Bolyard AAB. An update on the diagnosis and treatment of chronic idiopathic neutropenia. Curr Opin Hematol. 2017;24:46-53. PMCID: PMC5380401
4. Makaryan V, Kelley MK, Fletcher B, Bolyard AA, Aprikyan A, Dale, DC. Elastase inhibitors as potential

therapies for *ELANE*-associated neutropenia. J Leukoc Biol. 2017;102(4):1143-1151. PMCID: PMC5597518

5. Dale DC. How I manage children with neutropenia. Br J Haematol. 2017;178(3):351-363. PMID: 28419427
6. Skokowa J, Dale DC, Touw IP, Zeidler C, Welte K. Severe congenital neutropenias: genotypical and phenotypical heterogeneity. Nat Rev Dis Primers. 2017;3:17032. PMCID: PMC5821468
7. Provencher Langlois G, Arnold DM, Potts J, Leber B, Dale DC, Mackey MC. A case report of cyclic thrombocytopenia with statistically significant neutrophil oscillations. J Hematol Oncol. (submitted)
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2018

9. Xia J, Miller C, Baty J, Ramesh A, Jotte MRM, Fulton RS, Vogel TP, Cooper MA, Walkovich KJ, Makaryan V, Bolyard AA, Dinauer MC, Wilson DB, Vlachos A, Myers KC, Rothbaum RJ, Bertuch AA, Dale DC, Shimamura A, Boxer LA, Link DC. Somatic mutations and clonal hematopoiesis in congenital neutropenia. Blood. 2018;131(4):408-416. PMID: 29092827

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1. Dale DC, Welte K. Neutropenia and Neutrophilia. In: Kaushansky K, Lichtman M, Prchal J, Levi MM, Press O, Burns LJ, Caligiuri M, eds. Williams Hematology. 9th ed. New York, NY: McGraw-Hill; 2015;chpt 65.
2. Dale DC. Neutropenia. In: Encyclopedia of Life Sciences. Chichester, England: John Wiley & Sons, Ltd.; Oct 15 2015. Available at: http://www.els.net [doi: 10.1002/9780470015902.a0002179.pub3]
3. Boxer, LA. Neutropenia. In: Bope ET, Kellerman RD, eds. Conn's Current Therapy. Waltham, MA: Elsevier; 2014:833-38.
4. Bessler M, Mason PJ, Link DC, Wilson DB. Inherited Bone Marrow Failure Syndromes. In: Orkin SH, Nathan DG, Ginsburg D, Look AT, Fisher DE, Lux S, eds. Nathan and Oski's Hematology and Oncology of Infancy and Childhood. 8th ed. Philadelphia: Elsevier Saunders; 2015:182-253.
5. Walkovich K, Newburger PE. Leukopenia. In: Kliegman RM, Stanton BF, St. Geme III JW, Schor NF, Berman RE, eds. Nelson Textbook of Pediatrics. 20th ed. Philadelphia: Elsevier; 2015:1047-1053.
6. Dale DC. How I diagnose and treat neutropenia. Curr Op Hematol. 2016;23:1-4 PMCID: PMC4668211
7. Dale DC, Welte K. Neutropenia and Neutrophilia. In: Kaushansky K, Lichtman MA, Prchal JT, Levi MM, Press OW, Burns LJ, Caligiuri M, eds. Williams Hematology. 9th ed. New York, NY: McGraw-Hill; 2016:991-1004.
8. Dale DC. Neutropenia. In: Encyclopedia of Life Sciences. Chichester, England: John Wiley & Sons, Ltd.; Oct 15 2015. Available at: http://www.els.net/WileyCDA/ElsArticle/refId-a0002179.html

EDITORIALS, COMMENTARIES AND LETTERS

1. Dale DC. Intersections of hematology, immunology, dermatology and infectious diseases. Curr Op Hematol. 2015;22:1-2. (Editorial) PMID: 25469835
2. Dale DC. Editorial for myeloid biology 2017. Curr Opin Hematol. 2017;24:1-2. (Editorial). PMID: 7820737
3. Dale DC. Editorial: myeloid biology issue 2018. Curr Opin Hematol. 2018;25:1-2 (Editorial). PMID: 29049086

ABSTRACTS:

1. Myers K, Bolyard AA, Wong T, Biggins C, Moore J, Loveless S, Mount L, Harris R, Davies S, Keel S, Dale D, Shimamura A. The North American Shwachman-Diamond syndrome registry: 5 years of follow-up. (American Society of Pediatric Hematology/Oncology [ASPHO] Annual Meeting Abstracts). Pediatr Blood Cancer. 2015;S26:#4020

2. Myers KC, Bolyard AA, Leung J, Moore J, Loveless S, Mount L, Harris RE, Davies SM, Keel S, Dale DC, Shimamura A. North American Shwachman-Diamond Syndrome Registry: Genetically undefined Shwachman-Diamond Syndrome. (ASH Annual Meeting Abstracts). Blood. 2015;126:3614.

3. Steward CG, Groves SJ, Taylor C, Maisenbacher MK, Versluys B, Newbury-Ecob R, Ozsahin H, Hamilton L, Damin MK, Bowen VM, McCurdy KR, Mackey MC, Bolyard AA, Dale DC. Barth Syndrome: an under-recognized cause of chronic neutropenia. (ASH Annual Meeting Abstracts). Blood. 2015;126:2195.

4. Dale DC, Bolyard AA, Kelley ML, Makaryan V, Bonilla MA, Boxer LA, Mellor-Heineke S, Welte KH, Newburger PE, Zeidler C. Long term outcomes for patients with cyclic neutropenia on treatment with granulocyte colony-stimulating factor (G-CSF). (ASH Annual Meeting Abstracts). Blood. 2015;126:996.

5. Dobbins NJ, Bolyard AA, Chang RT, Self J, Provencher Langlois G, Mackey MC, Dale DC. Application of spectral density/periodogram analysis to serial neutrophil counts to diagnose cyclic neutropenia. (ASH Annual Meeting Abstracts). Blood. 2015;126:4608

6. Boxer LA, Bolyard AA, Marrero TM, Tran EL, Bonilla MA, Newburger PE, Dale DC. Is there a role for anti-neutrophil antibody testing in predicting spontaneous resolution of neutropenia in young children? (ASH Annual Meeting Abstracts). Blood. 2015;126:2211

7. Olga Klimenkova, Maksim Klimiankou, Lothar Kanz, Cornelia Zeidler, Karl Welte, Julia Skokowa. Differential expression of neutrophil granule protein genes in bone marrow myeloid cells at the peak and nadir of neutrophil counts in cyclic neutropenia. (ASH Annual Meeting Abstracts). Blood. 2015;126:2194

8. Cornelia Zeidler, Sabine Mellor-Heineke, Maksim Klimiankou, Julia Skokowa, Karl Welte. First case of leukemia in a child suffering from cyclic neutropenia with ELANE mutation. (ASH Annual Meeting Abstracts). Blood. 2015;126:997

9. Maksim Klimiankou, Olga Klimenkova, Lothar Kanz, Cornelia Zeidler, Karl Welte, Julia Skokowa. Time course of acquisition of a *CSF3R* mutation and subsequent development of AML in a patient with cyclic neutropenia. Blood. 2015;126:885

10. Loghmani-Khouzani H, Klimiankou M, Kandabarau S, Zeidler C, Welte K, Skokowa J. Homozygous mutations in phrf1 and pparg in a patient with congenital neutropenia and profound monocytosis: understanding the pathway beyond monocyte versus granulocyte cell-fate choice. Blood. 2015;216:648

11. Steward, CG, Groves SJ, Bolyard AA, Dale, DC. Incidence, characteristics and management of neutropenia in Barth syndrome. Barth Syndrome Foundation Meeting Abstracts, July 2016

12. Dale D, Bolyard AA, Kelley M, Makaryan V, Boxer L, Bonilla MA, Cavieres M, Tan P, Firkin F. *ELANE* mutation C223ter predisposes patients with severe congenital neutropenia to acute myeloid leukemia. (European Hematology Association [EHA] Meeting Abstracts). Haematologica. 2016;101(s1): 679,Abstract PB1661

13. Myers KC, Bolyard AA, Leung J, Moore J, Loveless S, Mount L, Harris RE, Davies SM, Keel S, Dale DC, Shimamura A. North American Shwachman-Diamond syndrome registry: genetically undefined Shwachman-Diamond syndrome. 8th International Congress on Shwachman-Diamond Syndrome Abstracts, April 2016

14. Duncavage E, Qualls D, Cottrell C, Heusel J, Corliss M, Pfeifer J, Dale D, Link D. Exome sequencing based diagnostics for severe congenital neutropenia. (Association of Molecular Pathology [AMP] 2016 Annual Meeting). J. Mol Diagn. 2016;18:962, abstract H45

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16. Makaryan V, Fletcher B, Kelley ML, Bolyard AA, Duncavage E, Qualls D, Link DC, Dale DC. TCIRG1 mutations as a cause for chronic neutropenia. (ASH Annual Meeting Abstracts). Blood. 2016; 128:2511

17. Makaryan V, Kelley ML, Fletcher B, Dale DC. The effects of the neutrophil elastase inhibitors MK0339 and sivelestat on the survival, proliferation and maturation of iPSC and HL60 cells expressing mutant neutrophil elastase. (ASH Annual Meeting Abstracts). Blood. 2016;128:406

18. Dale DC, Makaryan V, Kelley ML, Bolyard AA, Boxer L, Newburger P, Bonilla MA, Klimiankou M, Skokowa J, Zeidler C, Welte K. Termination and frameshift mutations in *ELANE* are associated with adverse outcomes in patients with severe chronic neutropenia. (ASH Annual Meeting Abstracts). Blood. 2016;128:1326

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20. Xia J, Shimamura A, Myers KC, Boxer LA, Dale DC, Ramesh A, Jotte M, Link DC. Mutation burden in hematopoietic stem cells is not increased in congenital neutropenia. (ASH Annual Meeting Abstracts). Blood. 2016;128:405

21. Myers KC, Nelson A, Sheehan B, Malsch M, Furutani E, Gloude N, Sandella R, Levesque A, Towers G, Bolyard AA, Moore J, Loveless S, Butts A, Davies SM, Keel S, Hanna R, Fleming M, Lorsbach R, Dale DC, Shimamura A. Germline and somatic genetic characterization of Shwachman-Diamond syndrome. (American Society of Pediatric Hematology/Oncology [ASPHO] Annual Meeting Abstracts). Pediatr Blood Cancer. 2017: 64(S1):206

22. Dale DC, Bolyard AA, Leung J, Tran E, Marrero T, Newburger P. Cyclic neutropenia congenital and idiopathic neutropenia. (ASH Annual Meeting Abstracts). Blood. 2017; 130:2275

23. Dale DC, Bolyard AA, Marrero T, Weinstein D, Zeidler C, Welte K. Long-term outcomes for G-CSF treatment of patients with glycogen-storage disease type 1b. (ASH Annual Meeting Abstracts). Blood. 2017; 130:996

24. Makaryan V, Fletcher B, Kelley ML, Dale DC. The effect of the MK-0339 neutrophil elastase inhibitor on proliferation and maturation of iPSC derived from the patients with *ELANE, TCIRG1* and *CXCR4* associated neutropenia. (ASH Annual Meeting Abstracts). Blood. 2017;130:545

25. Dale DC, Bolyard AA, Dick E, Kelley ML, Makaryan V, Johnson R, Gan L, Parasuraman S. X4P-001: a novel molecularly-targeted oral therapy for WHIM syndrome. (ASH Annual Meeting Abstracts). Blood 2017; 130:995