Metabolomics in community-acquired pneumonia: exploring metabolomics-based biomarkers for diagnosis and treatment response monitoring of community-acquired pneumonia

Hartog, I. den

Bibliography

1. Bjarnason, A. *et al.* Incidence, etiology, and outcomes of community-acquired pneumonia: A population-based study. *Open Forum Infectious Diseases* **5** (2018).
2. Jain, S. *et al.* Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults. *New England Journal of Medicine* **373,** 415–427 (2015).
3. Prina, E., Ranzani, O. T. & Torres, A. Community-acquired pneumonia. *The Lancet* **386,** 1097–1108 (2015).
4. Kothe, H. *et al.* Outcome of community-acquired pneumonia: Influence of age, residence status and antimicrobial treatment. *European Respiratory Journal* **32,** 139–146 (2008).
5. Angus, D. C. *et al.* Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Critical care medicine* **29,** 1303–1310 (2001).
6. Wiersinga, W. J. *et al.* Dutch Guidelines on the Management of Community-Acquired Pneumonia in Adults. *SWAB* (2011).
7. Aliberti, S., Dela Cruz, C. S., Amati, F., Sotgiu, G. & Restrepo, M. I. Community-acquired pneumonia. *The Lancet* **398,** 906–919 (2021).
8. Wiersinga, W. J. *et al.* Management of Community-Acquired Pneumonia in Adults: 2016 Guideline Update From The Dutch Working Party on Antibiotic Policy (SWAB) and Dutch Association of Chest Physicians (NVALT). *The Netherlands journal of medicine* **76** (2016).
9. Lee, J. S., Giesler, D. L., Gellad, W. F. & Fine, M. J. Antibiotic Therapy for Adults Hospitalized With Community-Acquired Pneumonia: A Systematic Review. *JAMA* **315,** 593–602 (2016).
10. Avdic, E. *et al.* Impact of an Antimicrobial Stewardship Intervention on Shortening the Duration of Therapy for Community-Acquired Pneumonia. *Clinical Infectious Diseases* **54,** 1581–1587 (2012).
11. Viasus, D., Vecino-Moreno, M., De La Hoz, J. M. & Carratalà, J. Antibiotic stewardship in community-acquired pneumonia. *Expert Review of Anti-infective Therapy* **15,** 351–359 (2017).
12. Aulin, L. B. *et al.* Biomarker-Guided Individualization of Antibiotic Therapy. *Clinical Pharmacology & Therapeutics* **110,** 346–360 (2021).
13. Karakioulaki, M. & Stolz, D. Biomarkers in Pneumonia—Beyond Procalcitonin. *International Journal of Molecular Sciences* **20** (2019).

14. Kohler, I. *et al.* Integrating clinical metabolomics-based biomarker discovery and clinical pharmacology to enable precision medicine. *European Journal of Pharmaceutical Sciences* **109,** S15–S21 (2017).

15. Gao, P. & Xu, G. Mass-spectrometry-based microbial metabolomics: recent developments and applications. *Anal Bioanal Chem* **407,** 669–680 (2015).

16. Orešič, M., Vidal-Puig, A. & Hänninen, V. Metabolomic approaches to phenotype characterization and applications to complex diseases. *Expert Review of Molecular Diagnostics* **6,** 575–585 (2006).

17. Tounta, V., Liu, Y., Cheyne, A. & Larrouy-Maumus, G. Metabolomics in infectious diseases and drug discovery. *Molecular Omics* **17,** 376–393 (2021).

18. Aretz, I. & Meierhofer, D. Advantages and Pitfalls of Mass Spectrometry Based Metabolome Profiling in Systems Biology. *International Journal of Molecular Sciences* **17** (2016).

19. Bingol, K. Recent advances in targeted and untargeted metabolomics by NMR and MS/NMR methods. *High-Throughput* **7,** 9 (2018).

20. Lau, S. K. P. *et al.* Metabolomic Profiling of Plasma from Patients with Tuberculosis by Use of Untargeted Mass Spectrometry Reveals Novel Biomarkers for Diagnosis. *Journal of clinical microbiology* **53** (ed Land, G. A.) 3750–9 (2015).

21. Kauppi, A. M. *et al.* Metabolites in Blood for Prediction of Bacteremic Sepsis in the Emergency Room. *PLOS ONE* **11** (2016).

22. Banoei, M. M. *et al.* Plasma metabolomics for the diagnosis and prognosis of H1N1 influenza pneumonia. *Critical care* **21,** 97 (2017).

23. Slupsky, C. M. *et al.* Pneumococcal Pneumonia: Potential for Diagnosis through a Urinary Metabolic Profile. *Journal of Proteome Research* **8,** 5550–5558 (2009).

24. Schoeman, J. C. *et al.* Metabolic characterization of the natural progression of chronic hepatitis B. *Genome Medicine* **8,** 64 (2016).

25. Müller, D. C. *et al.* Phospholipid levels in blood during community-acquired pneumonia. *PLOS ONE* **14** (2019).

26. Chong, J., Wishart, D. S. & Xia, J. Using MetaboAnalyst 4.0 for Comprehensive and Integrative Metabolomics Data Analysis. *Current Protocols in Bioinformatics* **68** (2019).

27. Kanehisa, M. & Goto, S. *KEGG: Kyoto Encyclopedia of Genes and Genomes* 2000.

28. Szklarczyk, D. *et al.* STITCH 5: Augmenting protein-chemical interaction networks with tissue and affinity data. *Nucleic Acids Research* **44,** D380–D384 (2016).

29. Meijvis, S. C. A. *et al.* Dexamethasone and length of hospital stay in patients with community-acquired pneumonia: A randomised, double-blind, placebo-controlled trial. *The Lancet* **377,** 2023–2030 (2011).

30. Endeman, H. *et al.* Clinical features predicting failure of pathogen identification in patients with community acquired pneumonia. *Scandinavian Journal of Infectious Diseases* **40,** 715–720 (2008).

31. Wunderink, R. G. & Waterer, G. W. Community-Acquired Pneumonia. *New England Journal of Medicine* **370,** 543–551 (2014).

32. Postma, D. F. *et al.* Antibiotic Treatment Strategies for Community-Acquired Pneumonia in Adults. *New England Journal of Medicine* **372,** 1312–1323 (2015).

33. WHO. *Antimicrobial resistance: global report on surveillance* tech. rep. (2014).

34. Saleh, M. A. A., Van De Garde, E. M. W. & Van Hasselt, C. J. G. Host-response biomarkers for the diagnosis of bacterial respiratory tract infections. *Clinical Chemistry and Laboratory Medicine* **57** (2019).

35. Pearce, E. L. & Pearce, E. J. Metabolic pathways in immune cell activation and quiescence. *Immunity* **38,** 633–643 (2013).

36. Khovidhunkit, W. *et al.* Effects of infection and inflammation on lipid and lipoprotein metabolism: Mechanisms and consequences to the host. *Journal of Lipid Research* **45,** 1169–1196 (2004).

37. Zhou, A. *et al.* Metabolomics specificity of tuberculosis plasma revealed by (1)H NMR spectroscopy. *Tuberculosis* **95,** 294–302 (2015).

38. Laiakis, E. C., Morris, G. A. J., Fornace, A. J., Howie, S. R. C. & Howie, S. R. C. Metabolomic Analysis in Severe Childhood Pneumonia in The Gambia, West Africa: Findings from a Pilot Study. *PloS one* **5** (2010).

39. Antcliffe, D., Jiménez, B., Veselkov, K., Holmes, E. & Gordon, A. C. Metabolic Profiling in Patients with Pneumonia on Intensive Care. *EBioMedicine* **18,** 244–253 (2017).

40. Adamko, D. J., Saude, E., Bear, M., Regush, S. & Robinson, J. L. Urine metabolomic profiling of children with respiratory tract infections in the emergency department: a pilot study. *BMC infectious diseases* **16,** 439 (2016).

41. Varma, S. & Simon, R. Bias in error estimation when using cross-validation for model selection. *BMC Bioinformatics* **7,** 91 (2006).

42. Zou, H. & Hastie, T. Regularization and variable selection via the elastic net. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)* **67,** 301–320 (2005).

43. Statnikov, A., Tsamardinos, I., Dosbayev, Y. & Aliferis, C. F. GEMS: A system for automated cancer diagnosis and biomarker discovery from microarray gene expression data. *International Journal of Medical Informatics* **74,** 491–503 (2005).

44. Yzerman, E. P. *et al.* Sensitivity of three urinary antigen tests associated with clinical severity in a large outbreak of Legionnaires' disease in the Netherlands. *Journal of Clinical Microbiology* **40,** 3232–3236 (2002).

45. Gutierrez, F. *et al.* Evaluation of the Immunochromatographic Binax NOW Assay for Detection of Streptococcus pneumoniae Urinary Antigen in a Prospective Study of Community-Acquired Pneumonia in Spain. *Clinical Infectious Diseases* **36,** 286–292 (2003).

46. Sordé, R. *et al.* Current and potential usefulness of pneumococcal urinary antigen detection in hospitalized patients with community-acquired pneumonia to guide antimicrobial therapy. *Archives of Internal Medicine* **171,** 166–172 (2011).

47. Van Elden, L. J., Nijhuis, M., Schipper, P., Schuurman, R. & Van Loon, A. M. Simultaneous detection of influenza viruses A and B using real-time quantitative PCR. *Journal of Clinical Microbiology* **39,** 196–200 (2001).

48. Emwas, A. H. *et al.* Nmr spectroscopy for metabolomics research. *Metabolites* **9** (2019).

49. Ning, P. *et al.* Metabolic profiles in community-acquired pneumonia: developing assessment tools for disease severity. *Critical Care* **22,** 130 (2018).

50. Noga, M. J. *et al.* Metabolomics of cerebrospinal fluid reveals changes in the central nervous system metabolism in a rat model of multiple sclerosis. *Metabolomics* **8,** 253–263 (2012).

51. Torres, A. *et al.* Pneumonia. *Nature Reviews Disease Primers* **7,** 1–28 (2021).

52. Falguera, M. *et al.* Predictive factors, microbiology and outcome of patients with parapneumonic effusion. *European Respiratory Journal* **38,** 1173–1179 (2011).

53. Sureja, B. R., Govani, K. J., Sureja, J. B. & Sureja, R. B. An Assessment of Clinical Profile & Outcome in Patients with Community Acquired Pneumonia (CAP). *National Journal of Community Medicine* **12,** 221–224 (2021).

54. Kok, M., Maton, L., van der Peet, M., Hankemeier, T. & van Hasselt, J. G. Unraveling antimicrobial resistance using metabolomics. *Drug discovery today* **27,** 1774–1783 (2022).

55. Páez-Franco, J. C. *et al.* Metabolomics analysis reveals a modified amino acid metabolism that correlates with altered oxygen homeostasis in COVID-19 patients. *Scientific reports* **11,** 1–12 (2021).

56. Overmyer, K. A. *et al.* Large-Scale Multi-omic Analysis of COVID-19 Severity. *Cell Systems* **12,** 23–40 (2021).

57. Ploder, M. *et al.* Serum phenylalanine in patients post trauma and with sepsis correlate to neopterin concentrations. *Amino acids* **35,** 303–307 (2008).

58. Wang, J., Sun, Y., Teng, S. & Li, K. Prediction of sepsis mortality using metabolite biomarkers in the blood: a meta-analysis of death-related pathways and prospective validation. *BMC Medicine* **18,** 83 (2020).

59. Den Hartog, I. *et al.* Metabolomic profiling of microbial disease etiology in community-acquired pneumonia. *PloS one* **16** (2021).

60. Marcovina, S. M. *et al.* Translating the basic knowledge of mitochondrial functions to metabolic therapy: Role of L-carnitine. *Translational Research* **161** (2013).

61. Hoppel, C. *The role of carnitine in normal and altered fatty acid metabolism* 2003.

62. Langley, R. J. *et al.* Integrative "omic" analysis of experimental bacteremia identifies a metabolic signature that distinguishes human sepsis from systemic inflammatory response syndromes. *American Journal of Respiratory and Critical Care Medicine* **190,** 445–455 (2014).

63. Ayres, J. S. A metabolic handbook for the COVID-19 pandemic. *Nature Metabolism* **2,** 572–585 (2020).

64. Otsubo, C. *et al.* Long-chain Acylcarnitines Reduce Lung Function by Inhibiting Pulmonary Surfactant. *Journal of Biological Chemistry* **290,** 23897–23904 (2015).

65. Rousseau, M. *et al.* Associations Between Dietary Protein Sources, Plasma BCAA and Short-Chain Acylcarnitine Levels in Adults. *Nutrients* **11,** 173 (2019).

66. Moreno, F. A., Macey, H. & Schreiber, B. Carnitine Levels in Valproic Acid-Treated Psychiatric Patients: A Cross-Sectional Study. *The Journal of Clinical Psychiatry* **66,** 2314 (2005).

67. Mynatt, R. L. Carnitine and type 2 diabetes. *Diabetes/Metabolism Research and Reviews* **25,** S45–S49 (2009).

68. Darcy, C. J. *et al.* An observational cohort study of the kynurenine to tryptophan ratio in sepsis: association with impaired immune and microvascular function. *PloS one* **6** (2011).

69. Suzuki, Y. *et al.* Serum activity of indoleamine 2,3-dioxygenase predicts prognosis of community-acquired pneumonia. *Journal of Infection* **63** (2011).

70. Arshad, H. *et al.* Decreased plasma phospholipid concentrations and increased acid sphingomyelinase activity are accurate biomarkers for community-acquired pneumonia. *Journal of Translational Medicine* **17,** 1–18 (2019).

71. Lawler, N. G. *et al.* Systemic Perturbations in Amine and Kynurenine Metabolism Associated with Acute SARS-CoV-2 Infection and Inflammatory Cytokine Responses. *Journal of proteome research* (2021).

72. Takikawa, O. Biochemical and medical aspects of the indoleamine 2, 3-dioxygenase-initiated L-tryptophan metabolism. *Biochemical and biophysical research communications* **338,** 12–19 (2005).

73. Orabona, C., Pallotta, M. T. & Grohmann, U. Different partners, opposite outcomes: a new perspective of the immunobiology of indoleamine 2, 3-dioxygenase. *Molecular medicine* **18,** 834–842 (2012).

74. Jones, S. P. *et al.* Expression of the Kynurenine Pathway in Human Peripheral Blood Mononuclear Cells: Implications for Inflammatory and Neurodegenerative Disease. *PloS one* **10** (2015).

75. Mezrich, J. D. *et al.* An interaction between kynurenine and the aryl hydrocarbon receptor can generate regulatory T cells. *The Journal of Immunology* **185,** 3190–3198 (2010).

76. Changsirivathanathamrong, D. *et al.* Tryptophan metabolism to kynurenine is a potential novel contributor to hypotension in human sepsis. *Critical care medicine* **39,** 2678–2683 (2011).

77. Leisman, D. E., Deutschman, C. S. & Legrand, M. Facing COVID-19 in the ICU: vascular dysfunction, thrombosis, and dysregulated inflammation. *Intensive Care Medicine* **46,** 1105–1108 (2020).

78. Neurauter, G. *et al.* Chronic immune stimulation correlates with reduced phenylalanine turnover. *Current drug metabolism* **9,** 622–627 (2008).

79. Pacheco, R., Gallart, T., Lluis, C. & Franco, R. Role of glutamate on T-cell mediated immunity. *Journal of Neuroimmunology* **185,** 9–19 (2007).

80. Nassar, T. *et al.* tPA regulates pulmonary vascular activity through NMDA receptors. *American Journal of Physiology - Lung Cellular and Molecular Physiology* **301,** 307–314 (2011).

81. Collard, C. D. *et al.* Neutrophil-derived Glutamate Regulates Vascular Endothelial Barrier Function. *Journal of Biological Chemistry* **277,** 14801–14811 (2002).

82. Baker, D. A., Thomas, J., Epstein, J., Possilico, D. & Stone, M. L. The effect of prostaglandins on the multiplication and cell-to-cell spread of herpes simplex virus type 2 in vitro. *American Journal of Obstetrics and Gynecology* **144** (1982).

83. Dalli, J. *et al.* Human sepsis eicosanoid and pro-resolving lipid mediator temporal profiles: correlations with survival and clinical outcomes. *Critical care medicine* **45,** 58 (2017).

84. Bruegel, M. *et al.* Sepsis-associated changes of the arachidonic acid metabolism and their diagnostic potential in septic patients. *Critical Care Medicine* **40,** 1478–1486 (2012).

85. Schwarz, B. *et al.* Severe SARS-CoV-2 infection in humans is defined by a shift in the serum lipidome resulting in dysregulation of eicosanoid immune mediators. *Journal of immunology* **206,** 329 (2021).

86. Lundström, S. L. *et al.* Asthmatics Exhibit Altered Oxylipin Profiles Compared to Healthy Individuals after Subway Air Exposure. *PLOS ONE* **6,** e23864 (2011).

87. Balgoma, D. *et al.* Linoleic acid-derived lipid mediators increase in a female-dominated subphenotype of COPD. *European Respiratory Journal* **47,** 1645–1656 (2016).

88. Dennis, E. A. & Norris, P. C. Eicosanoid storm in infection and inflammation. *Nature Reviews Immunology* **15,** 511–523 (2015).

89. Malcher-Lopes, R., Franco, A. & Tasker, J. G. Glucocorticoids shift arachidonic acid metabolism toward endocannabinoid synthesis: A non-genomic anti-inflammatory switch. *European Journal of Pharmacology* **583,** 322–339 (2008).

90. Chen, J. S. *et al.* Nonsteroidal Anti-inflammatory Drugs Dampen the Cytokine and Antibody Response to SARS-CoV-2 Infection. *Journal of Virology* **95** (2021).

91. Nickler, M. *et al.* Systematic review regarding metabolic profiling for improved pathophysiological understanding of disease and outcome prediction in respiratory infections. *Respiratory Research* **16,** 125 (2015).

92. Hurley, B. P. & McCormick, B. A. Multiple roles of phospholipase A2 during lung infection and inflammation. *Infection and Immunity* **76,** 2259–2272 (2008).

93. Mecatti, G. C. *et al.* Lipidomic Profiling of Plasma and Erythrocytes From Septic Patients Reveals Potential Biomarker Candidates. *Biomarker insights* **13** (2018).

94. Vromman, F. & Subtil, A. Exploitation of host lipids by bacteria. *Current Opinion in Microbiology* **17,** 38–45 (2014).

95. Flieger, A. *et al.* Phospholipase A secreted by Legionella pneumophila destroys alveolar surfactant phospholipids. *FEMS Microbiology Letters* **188,** 129–133 (2000).

96. Gregoriades, A. Interaction of influenza M protein with viral lipid and phosphatidylcholine vesicles. *Journal of Virology* **36,** 470–479 (1980).

97. Kawasaki, K. & ichi Ohnishi, S. Membrane fusion of influenza virus with phosphatidylcholine liposomes containing viral receptors. *Biochemical and Biophysical Research Communications* **186,** 378–384 (1992).

98. Vijay, R. *et al.* Critical role of phospholipase A2 group IID in age-related susceptibility to severe acute respiratory syndrome–CoV infection. *The Journal of Experimental Medicine* **212,** 1851 (2015).

99. Müller, C. *et al.* Inhibition of Cytosolic Phospholipase A2α Impairs an Early Step of Coronavirus Replication in Cell Culture. *Journal of Virology* **92,** 1463–1480 (2018).

100. Houten, S. M. & Wanders, R. J. A general introduction to the biochemistry of mitochondrial fatty acid β-oxidation. *Journal of Inherited Metabolic Disease* **33,** 469–477 (2010).

101. Newsholme, P. Why Is L-Glutamine Metabolism Important to Cells of the Immune System in Health, Postinjury, Surgery or Infection? *The Journal of Nutrition* **131,** 2515–2522 (2001).

102. Lawton, K. A. *et al.* Analysis of the adult human plasma metabolome. *Pharmacogenomics* **9,** 383–397 (2008).

103. Maas, P. *et al.* The Immunometabolic Atlas: A tool for design and interpretation of metabolomics studies in immunology. *PLOS ONE* **17** (2022).

104. Battleman, D. S., Callahan, M. & Thaler, H. T. Rapid Antibiotic Delivery and Appropriate Antibiotic Selection Reduce Length of Hospital Stay of Patients With Community-Acquired Pneumonia: Link Between Quality of Care and Resource Utilization. *Archives of Internal Medicine* **162,** 682–688 (2002).

105. Marco-Ramell, A. *et al.* Evaluation and comparison of bioinformatic tools for the enrichment analysis of metabolomics data. *BMC Bioinformatics* **19,** 1 (2018).

106. Pletz, M. W. *et al.* Unmet needs in pneumonia research: a comprehensive approach by the CAPNETZ study group. *Respiratory Research* **23,** 1–15 (2022).

107. Guo, S., Mao, X. & Liang, M. The moderate predictive value of serial serum CRP and PCT levels for the prognosis of hospitalized community-acquired pneumonia. *Respiratory Research* **19,** 1–9 (2018).

108. De Jong, E. *et al.* Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: A randomised, controlled, open-label trial. *The Lancet Infectious Diseases* **16,** 819–827 (2016).

109. Seymour, C. W. *et al.* Metabolomics in pneumonia and sepsis: An analysis of the GenIMS cohort study. *Intensive Care Medicine* **39,** 1423–1434 (2013).

110. Breier, M. *et al.* Targeted metabolomics identifies reliable and stable metabolites in human serum and plasma samples. *PLoS ONE* **9** (2014).

111. Goodman, K. *et al.* Assessment of the effects of repeated freeze thawing and extended bench top processing of plasma samples using untargeted metabolomics. *Metabolomics* **17** (2021).

112. Neill, A. M. *et al.* Community acquired pneumonia: aetiology and usefulness of severity criteria on admission. *Thorax* **51,** 1010–1016 (1996).

113. Van Der Ham, T., Meulman, J. J., Van Strien, D. C. & Van Engeland, H. Empirically based subgrouping of eating disorders in adolescents: A longitudinal perspective. *British Journal of Psychiatry* **170,** 363–368 (1997).

114. Josse, J., Pagès, J. & Husson, F. Multiple imputation in principal component analysis. *Advances in Data Analysis and Classification* **5,** 231–246 (2011).

115. Parks, E. J. Effect of Dietary Carbohydrate on Triglyceride Metabolism in Humans. *The Journal of Nutrition* **131,** 2772–2774 (2001).

116. Banoei, M. M. *et al.* Plasma lipid profiling for the prognosis of 90-day mortality, in-hospital mortality, ICU admission, and severity in bacterial community-acquired pneumonia (CAP). *Critical Care* **24** (2020).

117. Colombo, S. *et al.* Phospholipidome of endothelial cells shows a different adaptation response upon oxidative, glycative and lipoxidative stress. *Scientific Reports* **8** (2018).

118. Nan, W. *et al.* Myristoyl lysophosphatidylcholine is a biomarker and potential therapeutic target for community-acquired pneumonia. *Redox Biology* **58,** 102556 (2022).

119. Wu, G. Amino acids: Metabolism, functions, and nutrition. *Amino Acids* **37,** 1–17 (2009).

120. O'Neill, L. A., Kishton, R. J. & Rathmell, J. A guide to immunometabolism for immunologists. *Nature Reviews Immunology* **16,** 553–565 (2016).

121. Cheng, S.-C. C., Joosten, L. A. B. & Netea, M. G. The interplay between central metabolism and innate immune responses. *Cytokine and Growth Factor Reviews* **25,** 707–713 (2014).

122. Ashburner, M. *et al.* Gene ontology: Tool for the unification of biology. *Nature Genetics* **25,** 25–29 (2000).

123. Gene Ontology Consortium. The Gene Ontology resource: enriching a GOld mine. *Nucleic Acids Research* **49** (2021).

124. Szklarczyk, D. *et al.* STRING v11: Protein-protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets. *Nucleic Acids Research* **47,** D607–D613 (2019).

125. Lombardot, T. *et al.* Updates in Rhea: SPARQLing biochemical reaction data. *Nucleic Acids Research* **47,** D596–D600 (2019).

126. Madeira, F. *et al.* The EMBL-EBI search and sequence analysis tools APIs in 2019. *Nucleic Acids Research* **47,** W636–W641 (2019).

127. Bateman, A. *et al.* UniProt: The universal protein knowledgebase in 2021. *Nucleic Acids Research* **49,** D480–D489 (2021).

128. Yates, A. D. *et al.* Ensembl 2020. *Nucleic Acids Research* **48,** D682–D688 (2020).

129. Ferguson, C. *et al.* Europe PMC in 2020. *Nucleic Acids Research* **49,** D1507–D1514 (2021).

130. Murphy, K. & Weaver, C. *Janeway's immunobiology* 213–252 (Garland Science, Taylor & Francis Group, LLC, 2017).

131. Garris, C. S., Blaho, V. A., Hla, T. & Han, M. H. Sphingosine-1-phosphate receptor 1 signalling in T cells: trafficking and beyond. *Immunology* **142,** 347 (2014).

132. Matloubian, M. *et al.* Lymphocyte egress from thymus and peripheral lymphoid organs is dependent on S1P receptor 1. *Nature* **427,** 355–360 (2004).

133. Liu, G. *et al.* S1P1 receptor overrides regulatory T cell-mediated immune suppression through Akt-mTOR. *Nature immunology* **10,** 769 (2009).

134. Noronha, A. *et al.* The Virtual Metabolic Human database: integrating human and gut microbiome metabolism with nutrition and disease. *Nucleic Acids Research* **47** (2019).

135. Hubler, M. J. & Kennedy, A. J. Role of lipids in the metabolism and activation of immune cells. *Journal of Nutritional Biochemistry* **34,** 1–7 (2016).

136. Lovewell, R. R., Sassetti, C. M. & VanderVen, B. C. Chewing the fat: Lipid metabolism and homeostasis during M. tuberculosis infection. *Current Opinion in Microbiology* **29,** 30–36 (2016).

137. Wang, Z. *et al.* Detection of Metabolite–Protein Interactions in Complex Biological Samples by High-Resolution Relaxometry: Toward Interactomics by NMR. *Journal of the American Chemical Society* **11** (2021).

138. Ashtiani, M. *et al.* A systematic survey of centrality measures for protein-protein interaction networks. *BMC Systems Biology* **12,** 1–17 (2018).

139. Gilbert, D. N. *et al.* Enhanced Detection of Community-Acquired Pneumonia Pathogens With the BioFire® Pneumonia FilmArray® Panel. *Diagnostic Microbiology and Infectious Disease* **99,** 115246 (2021).

140. Poole, S. *et al.* Molecular point-of-care testing for lower respiratory tract pathogens improves safe antibiotic de-escalation in patients with pneumonia in the ICU: results of a randomised controlled trial. *Journal of Infection* **85,** 625–633 (2022).

141. Sindelar, M. A., Zepeski, A. E., Lawler, B. J., Johnston, S. D. & Faine, B. A. MRSA nasal swab PCR to de-escalate antibiotics in the emergency department. *The American Journal of Emergency Medicine* **55,** 133–137 (2022).

142. Tsang, N. N. Y. *et al.* Diagnostic performance of different sampling approaches for SARS-CoV-2 RT-PCR testing: a systematic review and meta-analysis. *The Lancet Infectious Diseases* **21,** 1233–1245 (2021).

143. Bouzid, D. *et al.* Agreement of respiratory viruses' detection between nasopharyngeal swab and bronchoalveolar lavage in adults admitted for pneumonia: a retrospective study. *Clinical Microbiology and Infection* (2023).

144. Pepe, M. S. & Thompson, M. L. Combining diagnostic test results to increase accuracy. *Biostatistics* **1,** 123–140 (2000).

145. Gant, V. & Singer, M. Combining pathogen and host metagenomics for a better sepsis diagnostic. *Nature Microbiology* **7,** 1713–1714 (2022).

146. Xie, F. *et al.* Clinical metagenomics assessments improve diagnosis and outcomes in community-acquired pneumonia. *BMC Infectious Diseases* **21** (2021).

147. Brands, X. *et al.* An epigenetic and transcriptomic signature of immune tolerance in human monocytes through multi-omics integration. *Genome Medicine* **13,** 1–17 (2021).

148. Schuurman, A. R. *et al.* Integrated single-cell analysis unveils diverging immune features of covid-19, influenza, and other community-acquired pneumonia. *eLife* **10** (2021).

149. Wootton, D. G. *et al.* A longitudinal modelling study estimates acute symptoms of community acquired pneumonia recover to baseline by 10 days. *European Respiratory Journal* **49,** 1602170 (2017).

150. Cheng, J. Y. *et al.* Longitudinal associations of serum survivin with the severity and prognosis of community-acquired pneumonia patients. *Respiratory Investigation* **61,** 84–94 (2023).

151. Yao, M. X. *et al.* Cross-sectional and longitudinal associations of serum Cysteine-rich 61 with severity and prognosis among community-acquired pneumonia patients in China. *Frontiers in Medicine* **9** (2022).

152. Aimo, L. *et al.* The SwissLipids knowledgebase for lipid biology. *Bioinformatics* **31,** 2860–2866 (2015).

153. Koistinen, V. *et al.* Towards a Rosetta stone for metabolomics: recommendations to overcome inconsistent metabolite nomenclature. *Nature Metabolism* **5,** 351–354 (2023).

154. Hicks, K. G. *et al.* Protein-metabolite interactomics of carbohydrate metabolism reveal regulation of lactate dehydrogenase. *Science* **379,** 996–1003 (2023).

155. Rubio-Aliaga, I. *et al.* Metabolomics of prolonged fasting in humans reveals new catabolic markers. *Metabolomics* **7,** 375–387 (2011).

156. Krug, S. *et al.* The dynamic range of the human metabolome revealed by challenges. *The FASEB Journal* **26,** 2607–2619 (2012).

157. Morris, C. *et al.* The relationship between BMI and metabolomic profiles: a focus on amino acids. *Proceedings of the Nutrition Society* **71,** 634–638 (2012).

158. Van Der Laan, T. *et al.* High-Throughput Fractionation Coupled to Mass Spectrometry for Improved Quantitation in Metabolomics. *Analytical Chemistry* **92,** 14330–14338 (2020).

List of Abbreviations

ADP	Adenosine diphosphate
AHR	Aryl-hydrocarbon receptor
aLEA	Alpha-linolenoyl ethanolamide
AMR	Antimicrobial resistance
ANOVA	Analysis of variance
API	Application programming interface
ATP	Adenosine triphosphate
AUC	Area under the curve
BER	Balanced error rate
BH4	Tetrahydrobiopterin
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
C. burnetii	*Coxiella burnetii*
C. psittaci	*Chlamydophila psittaci*
CAP	Community-acquired pneumonia
ChEBI	Chemical Entities of Biological Interest database
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
cor	Correlation
COX	Cyclooxygenase
CRP	C-reactive protein

CURB	Confusion, uremia, respiratory rate, blood pressure
CV	Cross validation
DEA	Docosatetraenoyl ethanolamide
DGLEA	Dihomo-gamma-linolenoyl ethanolamide
EA	Ethanolamine
EBI	European Bioinformatics Institute
EM-PCA	Expectation maximization - principal component analysis
EN	Elastic net regression
FA	Fatty acids
FAIR	Findable, accessible, interoperable, reusable
FC	Fold change
FDR	False discovery rate
FN	False negative
FP	False positive
Gln	Glutamine
Glu	Glutamic acid
GO	Gene Ontology
HMDB	Human Metabolome Database
HPA axis	Hypothalamic–pituitary–adrenal axis
HSV	Herpes simplex virus
ICU	Intensive care unit
ID	Identifier
IDO	Indoleamine-2,3-dioxygenase
IMA	Immunometabolic Atlas
L. pneumophilia	*Legionella pneumophilia*
LCAC	Long-chain acylcarnitine
LOS	Length of stay
LOX	Lipoxygenase
LPC	Lysophosphatidylcholine
LPE	Lysophosphatidylethanolamine
LPI	Lysophosphatidylinositol
LPS	Lysophosphatidylserine
LR	Logistic regression
M. pneumoniae	*Mycoplasma pneumoniae*
Max	Maximum
MCAC	Medium-chain acylcarnitine
Min	Minimum
MS	Mass spectrometry
n	Number
NMDA	N-methyl-D-aspartate
NMR	Nuclear magnetic resonance
NOS	Nitric oxide synthase
NSAID	Non-steroidal anti-inflammatory drugs
p-value	Probability value
PC	Phosphatidylcholine

PCA	Principal component analysis
PCR	Polymerase chain reaction
PCT	Procalcitonin
PE	Phosphatidylethanolamine
PGE2	Prostaglandin E2
PGF2a	Prostaglandin F2 alpha
Phe	Phenylalanine
PLA2	Phospholipase A2
PMID	PubMed identifier
POEA	Palmitoleoyl ethanolamide
PSI	Pneumonia Severity Index
PUFA	Polyunsaturated fatty acids
q	P-adjusted significance
RheaDB	Rhea-Annotated reactions database
ROC	receiver operating characteristic
ROS	Reactive Oxygen Species
RR	Respiratory rate
RSV / RS virus	Respiratory syncytial virus
S. pneumoniae	*Streptococcus pneumoniae*
SCAC	Short-chain acylcarnitine
SD	Standard deviation
SDMA	Symmetric dimethylarginine
SM	Sphingomyelin
STRING	Search Tool for the Retrieval of Interacting Genes/Proteins database
S1PR	Sphingosine-1-phosphate receptor
TB	Tuberculosis
TDO	Tryptophan-2,3-dioxygenase
TG	Triglyceride
TN	True negative
TP	True positive
TriHOME	9,10,13-TriHOME
Trp	Tryptophan
TXB2	Thromboxane B2
Tyr	Tyrosine
VIP	Variable importance in prediction

List of Publications

Ilona den Hartog*, Laura B. Zwep*, Thomas Hankemeier, Jacqueline J. Meulman, Ewoudt M.W. van de Garde, J.G. Coen van Hasselt. Longitudinal metabolomic profiling of Streptococcus pneumoniae-associated community-acquired pneumonia. *Metabolomics* (2024). (* Shared first authors)

Ilona den Hartog, Naama Karu, Laura B. Zwep, G. Paul Voorn, Ewoudt M.W. van de Garde, Thomas Hankemeier, J.G.C. van Hasselt. Differential metabolic host response to pathogens associated with community-acquired pneumonia. *Metabolism Open* **18** (2023).

Pascal Maas*, Ilona den Hartog*, Alida Kindt, Sonja Boman, Thomas Hankemeier, Coen van Hasselt. The Immunometabolic Atlas: A tool for design and interpretation of metabolomics studies in immunology. *PLoS One* **17:5** (2022). (* Shared first authors)

Ilona den Hartog, Laura B. Zwep, Stefan M.T. Vestjens, Amy C. Harms, G. Paul Voorn, Dylan W. de Lange, Willem J.W. Bos, Thomas Hankemeier, Ewoudt M.W. van de Garde, J.G. Coen van Hasselt. Metabolomic profiling of microbial disease etiology in community-acquired pneumonia, *PLoS One* **16: 6** (2021).

Pichet Praveschotinunt, Noémie-Manuelle Dorval Courchesne, Ilona den Hartog, Chaochen Lu, Jessica J. Kim, Peter Q. Nguyen, Neel S. Joshi. Tracking of Engineered Bacteria In Vivo Using Nonstandard Amino Acid Incorporation. *ACS Synthetic Biology* **7:6**. (2018).

Remco Arts, Ilona den Hartog, Stefan E. Zijlema, Vito Thijssen, Stan H. E. van der Beelen, Maarten Merkx. Detection of Antibodies in Blood Plasma Using Bioluminescent Sensor Proteins and a Smartphone. *Analytical Chemistry* **88:8** (2016).

List of Affiliations

Sonja Boman
Division of Systems Pharmacology & Pharmacy, Leiden Academic Centre for Drug Research, Leiden University, Leiden, The Netherlands.

Willem J.W. Bos
Department of Internal Medicine, Leiden University Medical Center, Leiden, The Netherlands.

Ewoudt M.W. van de Garde
Division of Pharmacoepidemiology and Clinical Pharmacology, Department of Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands.
Department of Clinical Pharmacy, St. Antonius Hospital, Nieuwegein, The Netherlands.

Thomas Hankemeier
Metabolomics and Analytics Centre, Leiden Academic Centre for Drug Research, Leiden University, Leiden, The Netherlands.

Amy C. Harms
Metabolomics and Analytics Centre, Leiden Academic Centre for Drug Research, Leiden University, Leiden, The Netherlands.

J.G. Coen van Hasselt
Division of Systems Pharmacology & Pharmacy, Leiden Academic Centre for Drug Research, Leiden University, Leiden, The Netherlands.

Naama Karu
Metabolomics and Analytics Centre, Leiden Academic Centre for Drug Research, Leiden University, Leiden, The Netherlands.

Alida Kindt
Metabolomics and Analytics Centre, Leiden Academic Centre for Drug Research, Leiden University, Leiden, The Netherlands.

Dylan W. de Lange
Intensive Care, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands.
National Poison Information Center, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands.

Pascal Maas
Metabolomics and Analytics Centre, Leiden Academic Centre for Drug Research, Leiden University, Leiden, The Netherlands.

Jacqueline J. Meulman
LUXs Data Science, Leiden, The Netherlands.
Department of Statistics, Stanford University, Stanford, CA, United States.

Stefan M.T. Vestjens
Department of Medical Microbiology and Immunology, St. Antonius Hospital, Nieuwegein, The Netherlands.

G. Paul Voorn
Department of Medical Microbiology and Immunology, St. Antonius Hospital, Nieuwegein, The Netherlands.

Laura B. Zwep
Division of Systems Pharmacology & Pharmacy, Leiden Academic Centre for Drug Research, Leiden University, Leiden, The Netherlands.

Dankwoord

Dit proefschrift is het resultaat van de samenwerking tussen vele mensen. Aan de start van dit onderzoek stonden mijn promotoren en co-promotor. De metabolomics analyse van de patiëntsamples is mogelijk gemaakt door medewerkers van het St. Antonius Ziekenhuis te Nieuwegein en het Biomedical Metabolomics Facility te Leiden. Ander experimenteel werk en de data analyse is gedaan in samenwerking met studenten en medewerkers van de afdeling Systems Pharmacology & Pharmacy van het LACDR aan de Universiteit Leiden, in het bijzonder met de Van Hasselt groep. De gepubliceerde wetenschappelijke artikelen zijn tot stand gekomen in samenwerking met collega's van verschillende universiteiten en medisch centra.

Op meer informele wijze waren mijn familie, schoonfamilie en vrienden, met in het bijzonder mijn partner Stefan, zeer belangrijk bij het tot stand komen van dit proefschrift.

Curriculum Vitae

Ilona den Hartog was born in Montfoort, the Netherlands, in 1992. She attended high school at the Kalsbeek College Woerden and received her VWO diploma in 2010. She obtained her propaedeutic diploma in Human Movement Sciences at the VU Amsterdam in 2011. She received her Bachelor's and Master's degree in Biomedical Engineering at the Eindhoven University of Technology, graduating in 2017.

During her Bachelor's internship, Ilona studied the detection of antibodies in blood plasma using bioluminescent sensor proteins for point-of-care diagnostics. In her Master's, she specialized in Protein Engineering in the group of Maarten Merkx. Her thesis focused on DNA-based antibody detection using rolling circle amplification to reach single molecule sensitivity. During her Master's she visited Harvard University, Boston, USA for a four month research externship at the Wyss Institute for Biologically Inspired Engineering in the group of Neel Joshi. During her externship she worked on improving genetically engineered bacteria that incorporate non-standard amino acids in the extracellular matrix of biofilms, marking specific environments and facilitating drug targeting to disease.

In 2017, Ilona started her PhD research on metabolomics in community-acquired pneumonia at the Leiden Academic Centre for Drug Research (LACDR) under supervision of Coen van Hasselt, Thomas Hankemeier, and Ewoudt van de Garde. Since October 2022, Ilona works as a technical author at Etteplan in Amersfoort.