Combining Diagnostics and Research in an Academic Laboratory

Grit Waitz[1] Stefan Handtke[2] Carlo Zaninetti[2] Linda Schönborn[2] Thomas Thiele[1,2]

[1] Institut für Transfusionsmedizin, Universitätsmedizin Rostock, Rostock, Germany
[2] Institut für Transfusionsmedizin, Universitätsmedizin Greifswald, Greifswald, Germany

Address for correspondence Prof. Dr. med. Thomas Thiele, Institut für Transfusionsmedizin, Universitätsmedizin Greifswald, 17487 Greifswald, Germany (e-mail: thomas.thiele@med.uni-greifswald.de).

Hamostaseologie 2025;45:63–69.

Abstract

Combining diagnostics and research in academic laboratories faces challenges and bears great opportunities. In this short review, we describe the objectives of diagnostic and research laboratories dealing with thrombosis and hemostasis questions. We give an overview of specific goals for diagnostic and research laboratories and explain the synergies and tasks which need to be managed in an interdisciplinary team.

Keywords

- laboratory
- research
- diagnostics
- thrombosis and hemostasis

Introduction

Thrombosis and hemostasis laboratories in an academic environment face several challenges. First, they need to perform the highest standard routine diagnostics and should be capable to serve as a reference center for methodological expertise, patient counseling, and expert opinion in the field of hemostasis. Second, these laboratories should ideally design, establish, and improve diagnostic tests and methodologies and develop research projects going beyond the scope of routine testing. The results of this research may have a direct impact on patient care when new methods translate into new routine diagnostics. Third, in an academic environment, education and training play a prominent role. This applies to students in the park of life sciences, physicians, scientists, laboratory technicians, and staff. Finally, each approach will need to be efficient and cost-effective.

Combining the resources of a diagnostic and a research laboratory is also an opportunity. Often, problem-oriented focused research strategies using synergies between clinical and research laboratories have helped to discover novel pathological mechanisms and to develop new therapeutic strategies.[1] There are numerous examples where this has been achieved in clinical laboratories, clinics, and research institutions within the GTH community. One example is the establishment of the first guideline for the diagnosis and management of vaccine-induced immune thrombocytopenia and thrombosis.[2] Research promotes quality and innovation in the routine laboratory, and vice versa, because encountering routine questions can give new impulses and ideas to scientists. This short review gives an overview of the differences between routine and diagnostic laboratories and describes the challenges and the opportunities of managing an interdisciplinary laboratory for routine diagnostics and research in thrombosis and hemostasis.

Goals and Features of a Diagnostic Laboratory

Diagnostic laboratories provide laboratory tests to diagnose and manage diseases. The obtained results in many aspects directly interfere with patient treatment, e.g., by establishing the correct diagnosis, by defining or staging certain disease conditions, or by monitoring or controlling medical treatments.

Diagnostic laboratories incorporate national and international quality management systems (QMSs) to fulfill criteria for internal and external quality control needs. These laboratories seek a highly standardized workup to achieve timely, most accurate, reproducible, and reliable test results. Many routine assays are performed on automated laboratory platforms and the throughput of patient samples is usually

received
October 21, 2024
accepted after revision
November 27, 2024

Georg Thieme Verlag KG,
Oswald-Hesse-Straße 50,
70469 Stuttgart, Germany

DOI https://doi.org/10.1055/a-2491-3668.
ISSN 0720-9355.

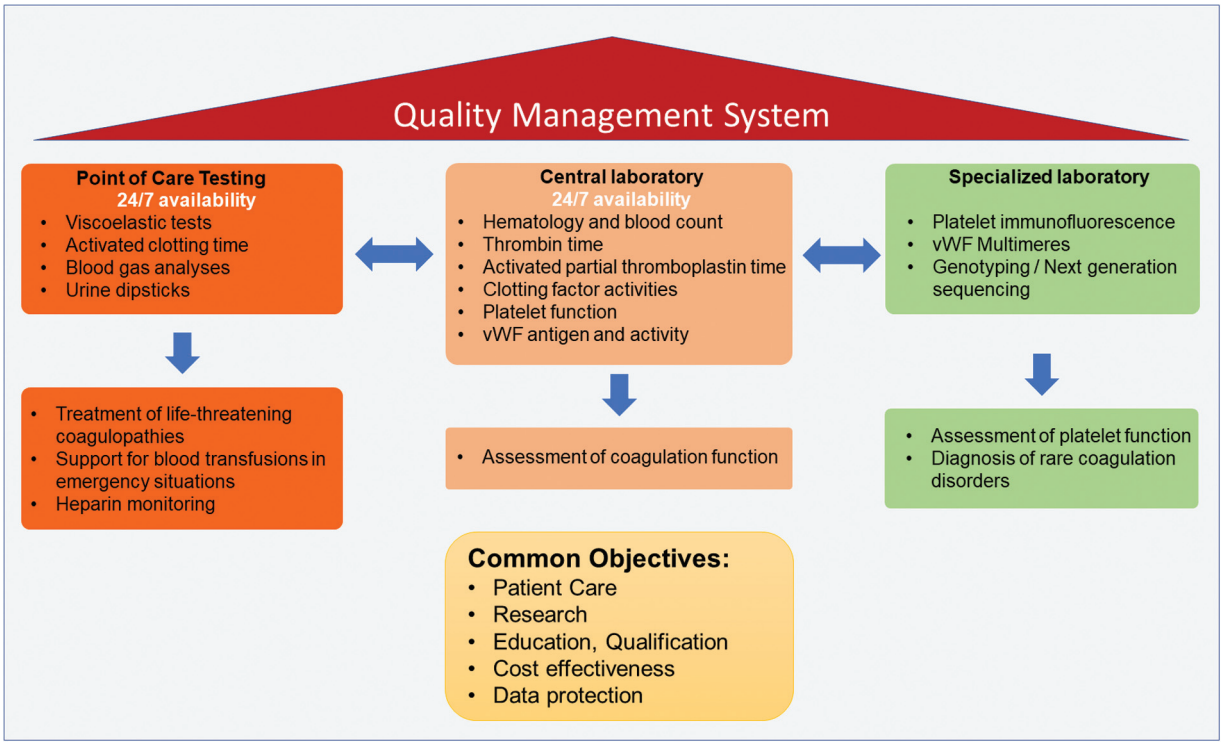

Fig. 1 Example of a diagnostic laboratory network for thrombosis and hemostasis.

increased. Furthermore, some laboratory tests must be kept available 24 hours 7 days a week for emergency testing.

There is a plethora of diagnostic tests performed in the field of thrombosis and hemostasis, which are often not completely run in one particular laboratory, but rather in several different locations in academia, including point-of-care diagnostics, tests performed in central laboratories, and those requiring special laboratories (►Fig. 1).

Specialized hemostasis laboratories perform assays to diagnose, classify, or manage rare diseases. These laboratories have the same requirements for standardization but require highly experienced staff and often sophisticated types of analyses. For many years, such laboratories have been established in academic environments. However, there is a continuous development of laboratory tests making even exceedingly specialized tests available on standardized automated platforms. For example, next-generation sequencing analyses requiring a remarkable amount of hardware and software and expertise for data analyses will foreseeably become routine for some hemostasis laboratories outside of academia because miniaturized hardware and standardized algorithms for analysis will be created.[3,4]

The International Society on Thrombosis and Haemostasis has developed a core curriculum of competencies of a thrombosis and hemostasis laboratory, which includes the performance and management of specialized tests for thrombotic and bleeding disorders, e.g., tests for thrombotic microangiopathies and platelet function tests, respectively. It provides a foundation for the development and enhancement of education and quality management of the laboratory irrespective of the jurisdictions.[5] Many efforts are taken to keep the high level of standardization and to optimize processes for better adherence to quality standards and cost effectiveness. Expenditures for laboratory services are further increasing due to expensive innovations. This makes it more important to pool resources, promote networking, and establish sustainable processes.

The high level of technical expertise, 24/7 availability, and the ability to take care of patients with severe and complex diseases require extraordinary demands on the personnel, who must be reliable and resilient to work in shifts. Staff shortages will become and are already an issue in some academic centers, putting pressure on academic institutions to educate and train the next generations of academic laboratory staff.

Goals and Features of a Research Laboratory

Academic research laboratories for thrombosis and hemostasis usually focus on their specialized research topics at universities or other public-funded institutions. The aim is to perform high-quality, internationally competitive, and in many cases interdisciplinary research. New insights into basic research, but also the development of new therapeutic approaches leading to scientific publications, patents, or clinical studies, are results of flourishing research.

A research laboratory creates and implements experimental designs and innovative methods. Investigators may apply less standardized and even unconventional approaches to address new scientific questions. The equipment is also important. Often, a wider range of instruments is needed to establish new methods. However, the ever-increasing costs of research platforms and devices force us to concentrate on capacities and to collaborate with other laboratories and/or

core facilities. The latter provides technical equipment and expertise of highly trained staff.

The core of a successful research laboratory is highly qualified personnel, including academic and technical staff. Recruiting talented scientists and experienced technicians is a prerequisite for a successful research laboratory.[6] Teamwork is most important, resulting in shared responsibilities and resources, accelerated exchange of knowledge, and experience. Developing a positive laboratory culture is thereby mandatory bringing together international scientists with different backgrounds and personalities in an open environment. Good communication in a research laboratory directly improves research outcomes.[7] It is known that diversity promotes excellence and innovation in biomedical sciences, too.[8,9] Exchange and utilization of complementary skill sets therefore broaden the scope of a research laboratory and can trigger new collaborations.

Scientific education and training are also a major task in academia, offering the opportunity to perform bachelor's and master's theses as well as MD or PhD theses. Moreover, research education allows keeping up with new methodologies and promoting exchange between researchers. This also includes active participation in scientific meetings and congresses, admitting the presentation of results and discussing them. Mentorship for students and younger scientists providing guidance for laboratory work as well as for scientific writing is crucial for career accomplishments.

Running a scientific laboratory also requires the continuous release of publications and grant applications for funding. Research is usually expensive with costs for equipment provision and maintenance, consumables, and salaries. The design of a project and the assessment of costs and search for funding sources are closely related.[10] Thus, the existence of a research laboratory often depends on regular and adequate external funding.

Regulatory Requirements

Today, a routine diagnostic laboratory is established in an exceedingly regulated environment, which requires a professional QMS and a high degree of documentation. In Germany, laboratories need to comply with the nationwide guideline of the German Medical Association for quality assurance of clinical laboratory testing, the European regulation on in vitro diagnostics, and several other international standards including risk standards. An overview is given in ►Table 1. The QMS structures and describes premises, personnel, and methodological requirements necessary for a diagnostic laboratory. It regulates the handling of patient samples including shipment and storage, standard operational procedures, education, training, and professional requirements of personnel, including physicians, scientists, and technical staff. Diagnostic laboratories have to undergo audits by governmental authorities or accreditation institutions, requiring additional efforts for preparing these meetings. However, despite all these regulatory efforts for diagnostic laboratories, even quality-labeled commercial reagents may contain faulty lots which may result in false-negative results.[11] This can ultimately be uncovered by a combined research and routine laboratory.

The high degree of standardization and quality management has direct research implications because clinical trials involving diagnostic laboratory tests usually engage quality-managed laboratories. Moreover, regulatory requirements are also relevant for research laboratories, especially for studies involving humans or animals. Here, European regulations as well as national laws apply for conducting clinical trials on pharmaceutical products for human use and on medical devices. Animal trials are regulated by the German animal protection law. Adherence to scientific and ethical standards, e.g., the Good Clinical Practice guideline or the Declaration of Helsinki, is mandatory for funding agencies. Thus, quality management requirements as well as general data protection regulations apply also for research laboratories to ensure transparency and the quality of research results.

Synergies between Diagnostic and Research Laboratories

Synergies arise when academic research and diagnostic laboratories achieve a combined spin that is larger than the sum of the individual effects. The top common goals are to exchange knowledge and expertise and to share common equipment and infrastructures. A priori, academic environments are in the position to provide a common ground to achieve these goals (►Fig. 2). A combined academic diagnostic and research laboratory provides an information hub for scientists and laboratory specialists, students and graduates, apprentices, and technicians. Sharing infrastructures and equipment helps to optimize the use of expensive devices, and may even economize energy and other resources.

However, there are additional advantages. First, a diagnostic laboratory with a certain expertise can have a supraregional outreach and may thus be able to gather samples from a large proportion of patients both nationally and internationally. This may first create a cost-efficient way to offer special diagnostic tests for rare diseases, thereof diagnostic work-up would otherwise remain challenging, as the personnel and infrastructure are optimally utilized. Second, it provides the opportunity to oversee the dynamic of an otherwise orphan disease from a national and even international perspective. Research-wise, a larger number of incoming samples is also beneficial because a reasonable power and representativity of laboratory studies can easier be accomplished. A good example to illustrate this is reference laboratories for rare infections or tumor diseases. We exemplify how diagnostics and research can be synergistically managed in our specialized platelet laboratory representative for the field of thrombosis and hemostasis (►Figs. 3 and 4).

Challenges

There are certain challenges for diagnostic and research laboratories. Shortage of qualified personnel is a growing problem.[12,13] This applies to physicians and scientific and technical staff and requires continued and increased efforts for personnel recruitment, education, and management.

Table 1 Regulations for medical and research laboratories active in Germany (nonexhaustive list)

	Regulation/law	Scope	Aim
Diagnostic laboratory	Guideline of the German Medical Association for quality assurance of clinical laboratory testing (Rili-BÄK)	Nationwide guideline for medical laboratories in Germany	To provide a basis for quality assurance systems of clinical laboratories in Germany, with specifications for carrying out laboratory tests
	ISO 15189	International standard for medical laboratories	To specify the quality management system including competence requirements for medical laboratories and basis for accreditations
	Regulation (EU) 2017/746 on in vitro diagnostic medical devices (IVDR)	European regulation on in vitro diagnostic medical devices	To regulate the market for in-vitro diagnostics in the EU and to cover their entire life cycle, from development and monitoring through to use; to define safety and performance requirements, and basis for laboratory developed tests
	ISO/IEC 17025	International guideline for testing and calibration laboratories (including medical laboratories)	To provide specific requirements for competence (applies directly to organizations that produce testing and calibration results)
	ISO 9001	International standard for quality management systems	To define minimum requirements for quality management systems
	ISO 22367	International risk standard for medical laboratories	To specify a process to identify and manage the risks for patients, laboratory workers, and service providers that are associated with medical laboratory examinations
	General Data Protection Regulation (DSGVO)	European guideline for data protection	To regulate processing and protection of personal data
Research laboratory	Declaration of Helsinki	International statement of the World Medical Association	To provide a statement of ethical principles for medical research involving human participants
	Good clinical practice	International ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects	To facilitate the mutual acceptance of clinical data by regulatory authorities for clinical trials with pharmaceutical products
	Clinical trials regulation 536/2014	European regulation	To act as clinical trial regulations for pharmaceutical products
	German Pharmaceutical Act (Arzneimittelgesetz – AMG)	National regulation in Germany	To act as clinical trial regulations for pharmaceutical products
	Medical Device Regulation 2017/745	European regulation	To act as medical device regulation
	Medizinprodukterecht-Durchführungsgesetz	National regulation in Germany	To act as medical device regulation
	Animal protection laws	National- and EU laws and international standards	To protect animals used in research projects
	Good scientific practice	Codex that applies to research work, adopted by many funding institutions	To provide standards to avoid manipulation, misconduct, and misuse of research data

Abbreviation: EU, European Union.

Whereas scientific staff is often employed for time-limited projects, staff recruited for routine diagnostics must often work in shifts during day and night times. This, however, can create unwanted competition between the diagnostic and the research part. Solutions are often individualized and tailored for qualified personnel. Furthermore, the growing body of regulatory requirements seizes capacities of the employed staff and reduces time for research, fund raising, and process optimization. Finally, academia is per se a competitive context and thrombosis and hemostasis

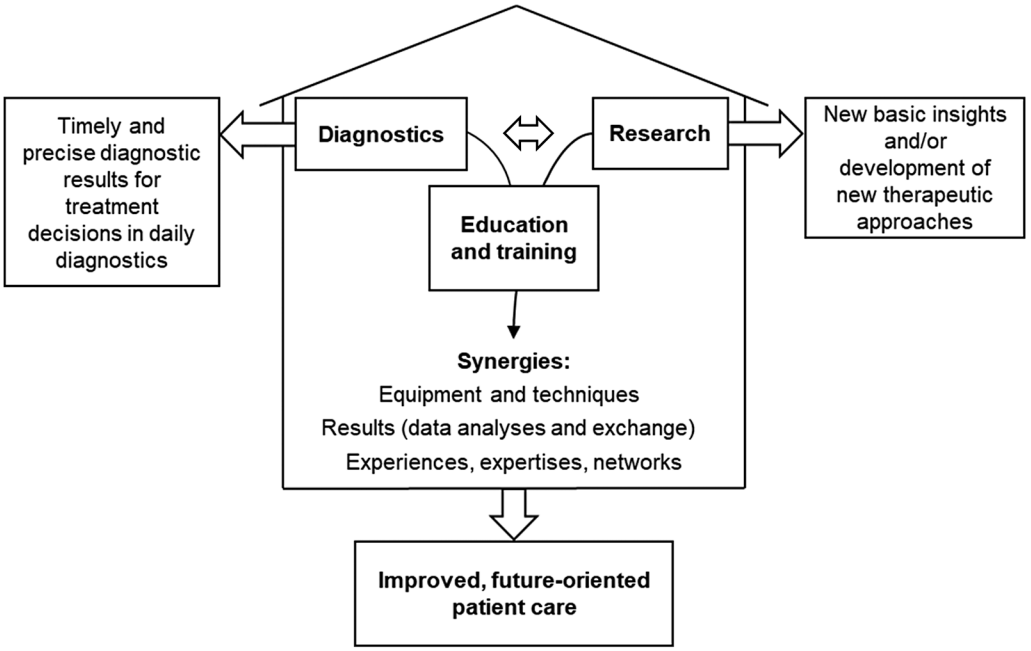

Fig. 2 Scheme of synergies between a diagnostic and a research laboratory in an academic environment.

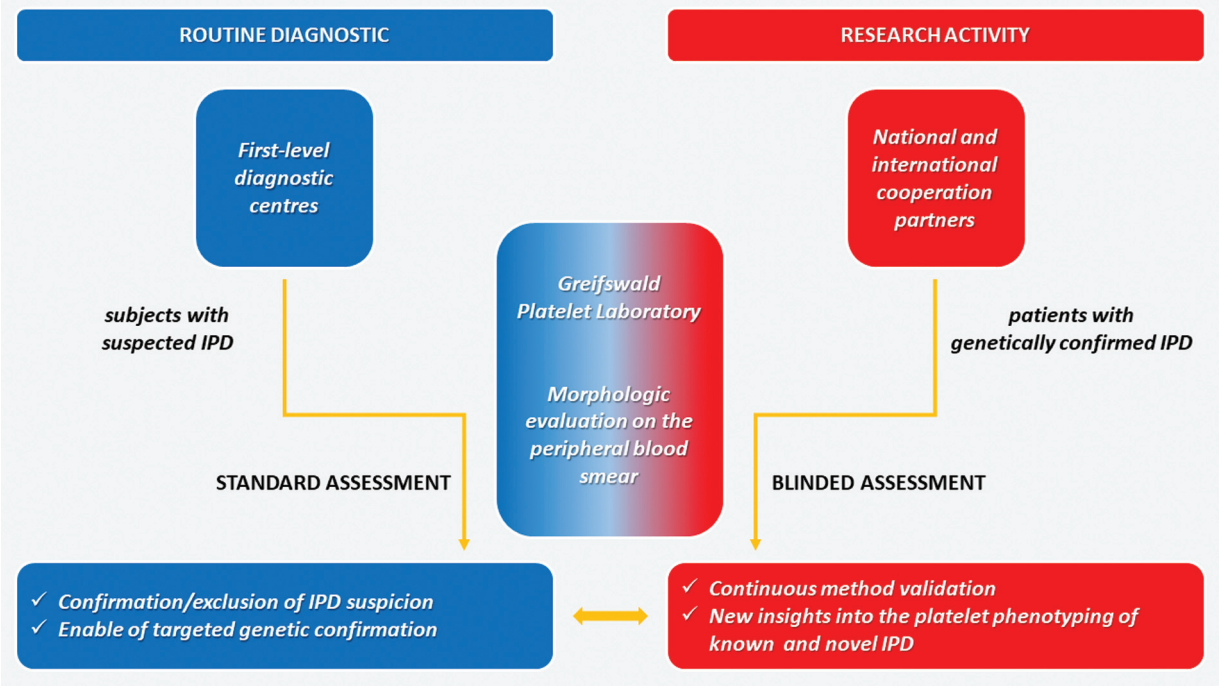

Fig. 3 Integration of diagnostic and research approaches for inherited platelet disorders (IPDs) testing by immunofluorescence microcopy in the Greifswald Platelet Laboratory. Our group has established a method for phenotyping platelets on the peripheral blood smears by combining light- and immunofluorescence microscopy.[17] The principle is to label with primary and secondary antibody platelet markers belonging to different structures (α or dense granules, cytoskeletal apparatus, surface receptors). The method has been validated as sensitive and specific for nine IPDs,[18] for which typical changes of platelet structures can be detected.[19] We introduced this investigation in our routine diagnostic activity as a screening tool for IPD. Yearly, we investigate blood smears from around 300 patients, who are referred to our laboratory by first-level diagnostic centers from Germany and beyond. Upon integration with clinical and anamnestic data, we possibly confirm the IPD suspicion and often suggest a targeted genetic confirmation of one or more IPD genes. In parallel, we regularly perform a blinded investigation of patients who had previously received a diagnostic confirmation of IPD by molecular testing. This enables: (1) a continuous validation of the method and (2) a further, multidisciplinary investigation of the phenotypic aspects of IPD. Through this integration of diagnostic and investigation approaches, we significantly contributed over the last 5 years to unravel pathogenic and clinical aspects of diverse known and newly identified forms of these rare disorders.[19–24]

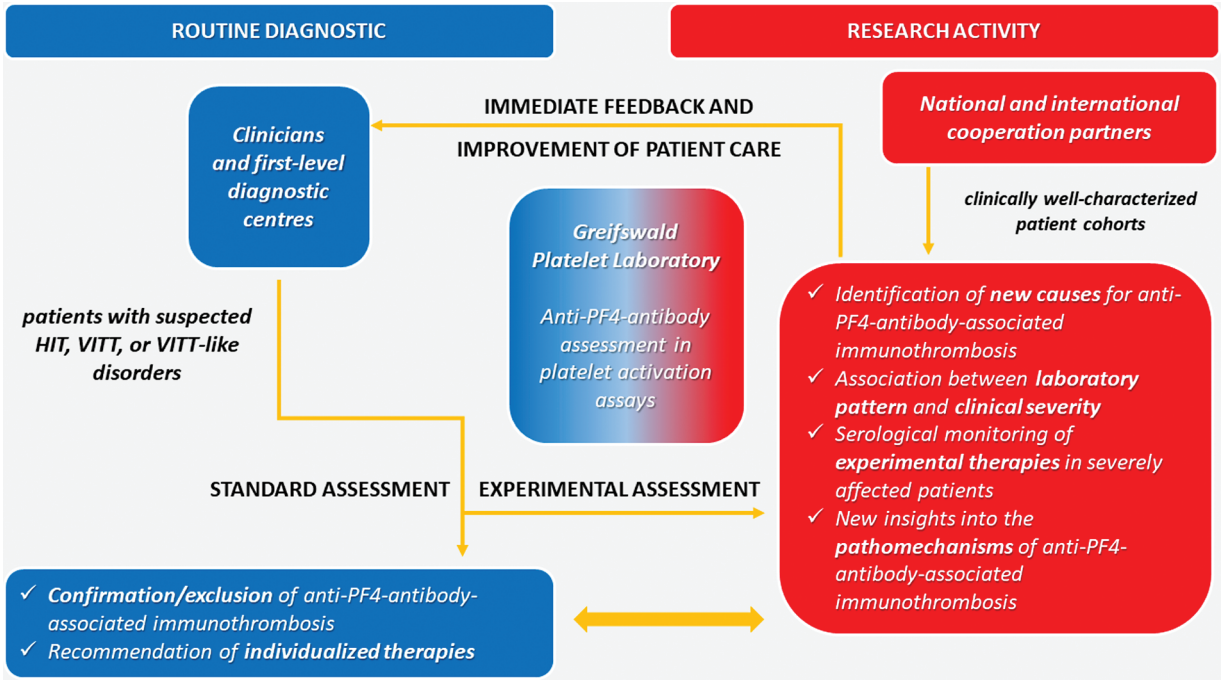

Fig. 4 Integration of diagnostic and research approaches testing for antiplatelet factor 4 (PF4)-antibody-associated immunothrombosis by platelet activation assays in the Greifswald Platelet Laboratory. The Greifswald Platelet Laboratory is a reference laboratory for the diagnostics of heparin-induced thrombocytopenia (HIT). We confirm or exclude anti-PF4-antibody-associated immunothrombosis by enzyme-linked immunosorbent assays and specialized platelet activation assays. When in 2021 the first patient samples of patients with thrombocytopenia and life-threatening thrombosis after COVID-19 vaccination were referred to the Greifswald Platelet Laboratory, the usual HIT tests did not recognize these patients. However, the already established link between routine and research laboratories and the immediate assessment of these patient samples in an experimental, newly developed PF4-enhanced platelet activation assay (PIPA) were the key, that these patients could be rapidly identified and vaccine-induced immune thrombocytopenia and thrombosis (VITT) was recognized as a new cause for anti-PF4-antibody-associated immunothrombosis.[25,26] The PIPA test was immediately incorporated into routine diagnostics and now serves as our gold standard for identifying VITT patients. Then, 2 years later the first patients with a VITT-like clinical and serological pattern but without heparin or vaccine exposure were identified. At that time, these patients were extremely rare; however, by receiving samples from all over the world, we were able to see the bigger picture and identify viral infections as an additional cause of anti-PF4-antibody-associated immunothrombosis.[27] The experimental assessment of patient samples originally sent for routine diagnostics was key to investigate new pathomechanisms of VITT and VITT-like disorders in recent years.[28,29] This in turn has therapeutic implications, which are of direct benefit for the concerned patients. An example is one of the first documented patients severely affected by chronic autoimmune VITT, who was successfully treated with ibrutinib.[30]
COVID-19, coronavirus disease 2019; PF4, platelet factor 4.

laboratories have to compete with other players in research and clinics over resources and space. It requires clever networking and qualified management to succeed in the race within each faculty. However, it is undoubtedly an advantage to be firmly grounded on a research and a diagnostic field in this arena.

A common task for the future of diagnostic and research laboratories is to deal with approaches of artificial intelligence, which will revolutionize the field of laboratory medicine,[14] research,[15] and thrombosis and hemostasis.[16] Here, new processes will have to be implemented and the research and diagnostic parts of a combined laboratory will inevitably learn from one another.

Last but not least, threats for a successful synergism may include different organizational structures within the academic environment leading to a different work focus. Pressure for rationalization and cost dumping as well as the profit-oriented structure of diagnostic laboratories on the one hand and the constant dependency of research laboratories on external funding on the other hand may also be factors that can jeopardize cooperation.

Conclusion

Integrating research and diagnostics in thrombosis and hemostasis laboratories holds many opportunities for creating new developments and driving progress in the field. It also provides a platform to design strategies addressing common and specific challenges in both areas. Communication, networking, education, research, and diagnostic skills are relevant key factors for success. Collaboration instead of competition is probably a “must” for the future, ideally in a way that all partners can profit mutually from each other. On the other hand, working in a productive team is satisfying, exciting, and makes a lot of fun! These perspectives will stay most important for attracting new generations for a position in academic laboratories and to cope with the upcoming challenges.

Conflicts of Interest

T.T. reports grants from Deutsche Forschungsgemeinschaft during the conduct of the study (Grant TH 2320/3–1); personal fees and other from Bristol Myers Squibb;

personal fees and other from Pfizer; personal fees from Bayer; personal fees and other from Chugai Pharma; other from Novo Nordisk; personal fees from Novartis; other from Daiichi Sankyo; other from Leo Pharma, outside the submitted work. L.S. reports personal fees from GTH e.V. and Baxter, and grants from Deutsche Forschungsgemeinschaft (SCHO 2052/1–1), she was supported within the Gerhard-Domagk Research Program by the Universitätsmedizin Greifswald and by the American Society of Hematology with a Global Research Award. The other coauthors have nothing to disclose.

References

1 Lämmle B. Clinical problem solving and using new paths in the laboratory: learning from case studies. Hamostaseologie 2020;40 (04):414–419
2 Oldenburg J, Klamroth R, Langer F, et al. Diagnosis and management of vaccine-related thrombosis following AstraZeneca COVID-19 vaccination: guidance statement from the GTH. Hamostaseologie 2021;41(03):184–189
3 Hu T, Chitnis N, Monos D, Dinh A. Next-generation sequencing technologies: an overview. Hum Immunol 2021;82(11):801–811
4 Kumar KR, Cowley MJ, Davis RL. Next-generation sequencing and emerging technologies. Semin Thromb Hemost 2019;45(07): 661–673
5 Moffat KA, Kiencke V, Blanco AN, et al. International Society on Thrombosis and Haemostasis core curriculum project: core competencies in laboratory thrombosis and hemostasis. J Thromb Haemost 2019;17(11):1848–1859
6 Bradke F, Maartens A, Teichmann SA. Key attributes of successful research institutes. PLoS Biol 2023;21(09):e3002267
7 Liston A, Lesage S. Starting your independent research laboratory. Stroke 2021;52(08):e520–e522
8 Swartz TH, Palermo AS, Masur SK, Aberg JA. The science and value of diversity: closing the gaps in our understanding of inclusion and diversity. J Infect Dis 2019;220(220, Suppl 2):S33–S41
9 Science benefits from diversity. Nature 2018;558(7708):5
10 Mackway-Jones K. Seeking funding for research. Emerg Med J 2003;20(04):359–361
11 Schneiter S, Colucci G, Sulzer I, Barizzi G, Lämmle B, Alberio L. Variability of anti-PF4/heparin antibody results obtained by the rapid testing system ID-H/PF4-PaGIA. J Thromb Haemost 2009;7 (10):1649–1655
12 Dignos PN, Khan A, Gardiner-Davis M, et al. Hidden and understaffed: exploring Canadian medical laboratory technologists' pandemic stressors and lessons learned. Healthcare (Basel) 2023;11(20):2736
13 Sexton JB, Adair KC, Proulx J, et al. Emotional exhaustion among US health care workers before and during the COVID-19 pandemic, 2019-2021. JAMA Netw Open 2022;5(09):e2232748
14 Rabbani N, Kim GYE, Suarez CJ, Chen JH. Applications of machine learning in routine laboratory medicine: current state and future directions. Clin Biochem 2022;103:1–7
15 Link KG, Stobb MT, Monroe DM, et al. Computationally driven discovery in coagulation. Arterioscler Thromb Vasc Biol 2021;41 (01):79–86
16 Chiasakul T, Lam BD, McNichol M, et al. Artificial intelligence in the prediction of venous thromboembolism: a systematic review and pooled analysis. Eur J Haematol 2023;111(06):951–962
17 Greinacher A, Pecci A, Kunishima S, et al. Diagnosis of inherited platelet disorders on a blood smear: a tool to facilitate worldwide diagnosis of platelet disorders. J Thromb Haemost 2017;15(07): 1511–1521
18 Palma-Barqueros V, Revilla N, Sánchez A, et al. Inherited platelet disorders: an updated overview. Int J Mol Sci 2021;22(09):4521
19 Zaninetti C, Leinøe E, Lozano ML, et al. Validation of immunofluorescence analysis of blood smears in patients with inherited platelet disorders. J Thromb Haemost 2023;21(04):1010–1019
20 Brøns N, Zaninetti C, Ostrowski SR, et al. A novel homozygous *GFI1B* variant in 2 sisters with thrombocytopenia and severe bleeding tendency. Platelets 2021;32(05):701–704
21 Palma-Barqueros V, Bastida JM, López Andreo MJ, et al; Grupo Español de Alteraciones Plaquetarias Congénitas (GEAPC) Spanish Society of Thrombosis and Haemostasis (SETH) Platelet transcriptome analysis in patients with germline RUNX1 mutations. J Thromb Haemost 2023;21(05):1352–1365
22 Palma-Barqueros V, Revilla N, Zaninetti C, et al. Src-related thrombocytopenia: a fine line between a megakaryocyte dysfunction and an immune-mediated disease. Blood Adv 2022;6(17): 5244–5255
23 Zaninetti C, Baschin M, Vater L, et al. Platelet expression of the transcription factor ETV6 associates with ETV6-related thrombocytopenia and can be detected by immunofluorescence on the blood film. Br J Haematol 2024;204(02):710–714
24 Zaninetti C, Rivera J, Vater L, et al. Aggregates of nonmuscular myosin IIA in erythrocytes associate with GATA1- and GFI1B-related thrombocytopenia. J Thromb Haemost 2024;22(04): 1179–1186
25 Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination. N Engl J Med 2021;384(22):2092–2101
26 Thiele T, Weisser K, Schönborn L, et al. Laboratory confirmed vaccine-induced immune thrombotic thrombocytopenia: retrospective analysis of reported cases after vaccination with ChAdOx-1 nCoV-19 in Germany. Lancet Reg Health Eur 2022; 12:100270
27 Schönborn L, Esteban O, Wesche J, et al. Anti-PF4 immunothrombosis without proximate heparin or adenovirus vector vaccine exposure. Blood 2023;142(26):2305–2314
28 Greinacher A, Selleng K, Palankar R, et al. Insights in ChAdOx1 nCoV-19 vaccine-induced immune thrombotic thrombocytopenia. Blood 2021;138(22):2256–2268
29 Wang JJ, Schönborn L, Warkentin TE, et al. Antibody fingerprints linking adenoviral anti-PF4 disorders. N Engl J Med 2024;390(19): 1827–1829
30 Lindhoff-Last E, Schönborn L, Zaninetti C, Warkentin TE, Greinacher A. Rescue therapy in chronic prothrombotic autoimmune anti-PF4 disorder. N Engl J Med 2023;389(14):1339–1341