Leibniz Gemeinschaft

Der Senat

9. Juli 2019

Stellungnahme zum Deutschen Rheuma-Forschungszentrum Berlin (DRFZ)

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Vorbemerkung

Die Einrichtungen der Forschung und der wissenschaftlichen Infrastruktur, die sich in der Leibniz-Gemeinschaft zusammengeschlossen haben, werden von Bund und Ländern wegen ihrer überregionalen Bedeutung und eines gesamtstaatlichen wissenschaftspolitischen Interesses gemeinsam gefördert. Turnusmäßig, spätestens alle sieben Jahre, überprüfen Bund und Länder, ob die Voraussetzungen für die gemeinsame Förderung einer Leibniz-Einrichtung noch erfüllt sind.[1]

Die wesentliche Grundlage für die Überprüfung in der Gemeinsamen Wissenschaftskonferenz ist regelmäßig eine unabhängige Evaluierung durch den Senat der Leibniz-Gemeinschaft. Die Stellungnahmen des Senats bereitet der Senatsausschuss Evaluierung vor. Für die Bewertung einer Einrichtung setzt der Ausschuss Bewertungsgruppen mit unabhängigen, fachlich einschlägigen Sachverständigen ein.

Vor diesem Hintergrund besuchte eine Bewertungsgruppe am 11. und 12. Oktober 2018 das DRFZ in Berlin. Ihr stand eine vom DRFZ erstellte Evaluierungsunterlage zur Verfügung. Die wesentlichen Aussagen dieser Unterlage sind in der Darstellung (Anlage A dieser Stellungnahme) zusammengefasst. Die Bewertungsgruppe erstellte im Anschluss an den Besuch den Bewertungsbericht (Anlage B). Das DRFZ nahm dazu Stellung (Anlage C). Der Senat der Leibniz-Gemeinschaft verabschiedete am 9. Juli 2019 auf dieser Grundlage die vorliegende Stellungnahme. Der Senat dankt den Mitgliedern der Bewertungsgruppe und des Senatsausschusses Evaluierung für ihre Arbeit.

1. Beurteilung und Empfehlungen

Der Senat schließt sich den Beurteilungen und Empfehlungen der Bewertungsgruppe an.

Das Deutsche Rheumaforschungszentrum Berlin (DRFZ) erforscht die Ursachen und den Verlauf rheumatischer Erkrankungen. Dabei werden zum einen im Rahmen von biomedizinischen Arbeiten die Rheuma verursachenden molekularen Mechanismen untersucht, um Ansätze für eine Behandlung zu finden. Zum anderen werden im Rahmen von epidemiologischen Arbeiten Risikofaktoren und Langzeitauswirkungen rheumatischer Erkrankungen sowie die Angemessenheit der Versorgung analysiert, um die klinische Entscheidungsfindung und die Versorgungsplanung zu optimieren.

Die **Forschungsergebnisse** des DRFZ sind von sehr hoher Qualität. Dies schlägt sich u. a. in einer sehr guten Publikationsleistung nieder. Es wird regelmäßig in hochrangigen Zeitschriften publiziert. Auch die Drittmitteleinnahmen sind beeindruckend hoch. Sie betrugen 2017 40 % des Gesamtbudgets. Dabei war das DRFZ in äußerst kompetitiven Verfahren erfolgreich. Unter anderem wurden vier ERC Grants eingeworben.

Dem DRFZ gelingt es sehr gut, seine Forschungsergebnisse in die **Anwendung** zu überführen. So werden die epidemiologischen Forschungsergebnisse im wissenschaftlichen und klinischen Bereich weltweit nachgefragt und tragen zur Verbesserung der Versorgung von Rheumapatientinnen und -patienten bei. Die Translation der grundlagenorientierten biomedizinischen Forschungsergebnisse erfolgt im Wesentlichen über die sogenannten

[1] Ausführungsvereinbarung zum GWK-Abkommen über die gemeinsame Förderung der Mitgliedseinrichtungen der Wissenschaftsgemeinschaft Gottfried Wilhelm Leibniz e. V.

Liaison-Gruppen. Diese werden in unterschiedlichem Umfang von klinischen Partnern (meistens der Charité – Universitätsmedizin Berlin) und dem DRFZ gemeinsam finanziert und ermöglichen eine enge Verzahnung von Grundlagenforschung und Anwendung. Jedoch ist derzeit nicht klar zu erkennen, wie hoch der jeweilige Finanzierungsanteil ist und nach welchen Kriterien er festgelegt wird. Der Senat erwartet, dass das DRFZ dies künftig darlegt (s. auch Abschnitt 2 dieser Stellungnahme).

Das DRFZ wurde 2009 in die gemeinsame Bund-Länder-Förderung aufgenommen. Im Anschluss an die letzte Evaluierung beschlossen Bund und Länder eine dauerhafte Erhöhung der institutionellen Förderung in Höhe von ca. 2 Mio. €, die sich somit seit 2009 mehr als verdoppelt hat (9,9 M€ im Jahr 2017). Mit den zusätzlichen Mitteln sah das DRFZ vor, die beiden bereits existierenden Programmbereiche auszubauen sowie einen neuen dritten Programmbereich einzurichten. Die Leistungen in den **drei Programmbereichen** werden wie folgt bewertet:

Von den vier Gruppen im Programmbereich „Epidemiologie und Versorgungsforschung" werden zwei als „exzellent", eine als „sehr gut bis exzellent" und eine als „gut bis sehr gut" bewertet. Die Leistungen des Programmbereichs konnten seit der letzten Evaluierung signifikant verbessert werden.

Von den 20 Gruppen im Programmbereich „Pathophysiologie Rheumatischer Erkrankungen" werden fünf als „exzellent", fünf als „sehr gut bis exzellent", drei als „sehr gut", sechs als „gut bis sehr gut" und eine als „gut" bewertet. Die Bandbreite der verfolgten Themen wurde seit der letzten Evaluierung deutlich erweitert. Dabei wurden verstärkt Arbeiten aufgenommen, die sich auf allgemeinere immunologische Fragestellungen beziehen und nicht immer einen direkten Bezug zur Rheumaforschung erkennen lassen.

Ein weiteres neues Forschungsthema wird in dem 2015 neu eingerichteten Programmbereich „Regenerative Rheumatologie" verfolgt. Die zwei bisher eingerichteten Gruppen werden als „gut bis sehr gut" bewertet. Damit bleiben die Arbeiten hinter dem zurück, was bei der letzten Evaluierung erwartet worden war. Leitung und Gremien des DRFZ sollten die geplante weitere Ausgestaltung des Programmbereichs kritisch überprüfen.

Das DRFZ steht vor einer tiefgreifenden **personellen Umbruchphase**. Sowohl der Wissenschaftliche Direktor als auch seine Stellvertreterin werden in den Ruhestand eintreten, nachdem sie das DRFZ über 20 Jahre sehr erfolgreich geleitet haben. Zur Vorbereitung der für 2019 (stellvertretende Direktorin) und 2021 (Direktor) zu erwartenden personellen Wechsel hat der Stiftungsrat vor zwei Jahren eine „Zukunftskommission" eingerichtet. Parallel zu den Wechseln am DRFZ stehen auch an der Charité im Bereich der Rheumatologie ruhestandsbedingte Wechsel auf der Leitungsebene an. Es wird sehr wichtig sein, die verschiedenen anstehenden Berufungen gut aufeinander abzustimmen. Die strategischen Leitlinien für die Besetzungen sollten die Verantwortlichen unter Einbeziehung der Ergebnisse dieser Evaluierung festlegen.

Es wird maßgeblich eine **Aufgabe der neuen Leitung** des DRFZ sein, das wissenschaftliche Profil des DRFZ wieder stärker auf Arbeiten zu fokussieren, die von besonderer Relevanz für rheumatische Erkrankungen sind (z. B. rheumatoide Arthritis, Spondylarthrose,

Bindegewebskrankheiten oder Vaskulitis). Das vom DRFZ vorgelegte Konzept zum Ausbau der Arbeiten auf dem Gebiet der personalisierten Medizin ist im Grundsatz zu begrüßen, jedoch konnten die vorgestellten Pläne für einen Sondertatbestand zum jetzigen Zeitpunkt nicht überzeugen. Der neuen Leitung bleibt es unbenommen, ein unter Berücksichtigung der Empfehlungen im Bewertungsbericht überarbeitetes Konzept auf dem dafür vorgesehenen Verfahrensweg vorzulegen.

Die enge **Kooperation** mit der Charité ist außergewöhnlich intensiv und fruchtbar. Die Zusammenarbeit bezieht sich auf derzeit sieben gemeinsame Berufungen, elf Liaison-Gruppen, vier gemeinsam betriebene Labore sowie zahlreiche drittmittelgeförderte Projekte. Unter anderem wurde 2016 mit dem Max-Planck-Institut für Infektionsbiologie ein Leibniz-WissenschaftsCampus eingerichtet. Der Senat erwartet, dass das DRFZ künftig seine Mitgliedschaft in der Leibniz-Gemeinschaft in seinem Namen Ausdruck verleiht. Das DRFZ kooperiert mit verschiedenen nationalen und internationalen Partnern, überwiegend im Rahmen von drittmittelgeförderten Verbundprojekten. Das Institut sollte es sich zum Ziel setzen, noch häufiger selbst überregionale Verbünde zu initiieren und anzuführen.

Der **Anteil von Wissenschaftlerinnen** ist mit 54 % am DRFZ insgesamt erfreulich hoch. Auf Leitungsebene sollte das DRFZ langfristig anstreben, die bereits gute Quote weiter zu erhöhen. Derzeit werden von den insgesamt 26 bewerteten Gruppen zehn (38 %) von Wissenschaftlerinnen geleitet.

Die Förderung des **wissenschaftlichen Nachwuchses** ist insgesamt hervorragend. Die Betreuung der Doktoranden ist über verschiedene strukturierte Programme sinnvoll organisiert. Auch dem bereits promovierten Personal stehen angemessene Möglichkeiten zur Weiterqualifizierung zur Verfügung.

Bei der **Übernahme der Leitung** einer DRFZ-Gruppe bzw. Liaison-Gruppe durch erfolgreiche Nachwuchswissenschaftlerinnen oder -wissenschaftler fällt auf, dass diese vergleichsweise häufig bereits vorher am DRFZ tätig waren. Sowohl im Hinblick auf deren wissenschaftliche Selbständigkeit als auch die wissenschaftliche Dynamik am Institut sollte das DRFZ häufiger Wechsel in externe Führungspositionen fördern bzw. die Besetzung von Gruppenleitungen mit Personen von außerhalb erreichen. Der Senat empfiehlt ferner, die Aufgaben und außerdem auch die Laufzeit von „Senior Groups“ (derzeit zwei) am DRFZ klarer zu definieren.

Das DRFZ erfüllt die Anforderungen, die an eine Einrichtung von überregionaler Bedeutung und gesamtstaatlichem wissenschaftspolitischem Interesse zu stellen sind. Es zählt auf seinen Arbeitsgebieten zu den international führenden Einrichtungen. Das DRFZ bündelt Kompetenzen und Technologien im Bereich der Rheumaforschung in einem Maße, wie es an einer Hochschule nicht möglich ist. Dies gilt insbesondere auch für die wichtigen langfristigen epidemiologischen Aufgaben, die das DRFZ wahrnimmt. Eine Eingliederung des DRFZ in eine Hochschule wird daher nicht empfohlen.

2. Zur Stellungnahme des DRFZ

Der Senat begrüßt, dass die Leitung des DRFZ auf der Grundlage der Empfehlungen des Bewertungsberichtes seine Leistungen zukünftig weiter verbessern möchte. Die Leitung

vertieft in ihrer Stellungnahme zudem drei Aspekte des Bewertungsberichtes. Der Senat hält dazu folgendes fest:

i) Struktur der Liaison-Gruppen: Die nun von der Leitung des DRFZ eingeführte formale Unterscheidung der Liaison-Gruppen nach Typ 1 (Finanzierung überwiegend durch DRFZ) und Typ 2 (Finanzierung überwiegend durch Partnereinrichtung) bietet eine gute Grundlage, um bei der nächsten Evaluierung die im Bewertungsbericht und dieser Stellungnahme erbetenen Angaben dazu vorzulegen, welche Mittel jeweils das DRFZ und welche die Partnereinrichtung bereitstellen. Die weiteren vorgelegten Informationen waren der Bewertungsgruppe bekannt und wurden berücksichtigt.

ii) Wissenschaftlicher Fokus des DRFZ: Die Bewertungsgruppe hatte empfohlen, die Arbeiten am DRFZ künftig wieder stärker auf Arbeiten zu fokussieren, die von besonderer Relevanz für rheumatische Erkrankungen sind. Die Leitung des DRFZ erläutert, dass aus ihrer Sicht die Arbeiten des DRFZ ausreichend fokussiert sind. Der Senat schließt sich der Bewertungsgruppe an und unterstreicht die Bedeutung eines klaren thematischen Profils für ein Leibniz-Institut, in diesem Fall einer nachvollziehbareren Ausrichtung auf entzündlich rheumatische Erkrankungen.

iii) Personalentwicklung und Förderung des wissenschaftlichen Nachwuchses: Der Senat schließt sich der Einschätzung der Bewertungsgruppe an, dass Wechsel jüngerer Wissenschaftlerinnen und Wissenschaftler vom DRFZ an andere Institutionen und von anderen Einrichtungen an das DRFZ stärker gefördert werden sollten. Die Hinweise des DRFZ zu den Personalveränderungen in den vergangenen Jahren waren der Bewertungsgruppe bekannt und entkräften die Einschätzung der Bewertungsgruppe nicht. Der Senat schließt sich auch der Empfehlung an, die Aufgaben von „Senior-Gruppen“ klarer zu definieren, insbesondere auch im Bereich des *Mentorings*.

Neben der Leitung des DRFZ hat auch der Stiftungsrat des DRFZ eine Stellungnahme zum Bewertungsbericht vorgelegt. Er geht darin auf zwei weitere Aspekte ein. Der Senat hält dazu folgendes fest:

i) Der Stiftungsrat des DRFZ informiert darüber, dass die anstehenden Besetzungen an der Charité und dem DRFZ wie empfohlen eng miteinander abgestimmt werden sollen. Der Senat begrüßt dies.

ii) Der Hinweis des Stiftungsrats, dass zusätzliche Mittel („Sondertatbestand“) der institutionellen Förderung die anstehenden Berufungen erleichtern würden, berührt die Kritik der Bewertungsgruppe an der vorgelegten Planung nicht.

3. Förderempfehlung

Der Senat der Leibniz-Gemeinschaft empfiehlt Bund und Ländern, das DRFZ als Einrichtung der Forschung und der wissenschaftlichen Infrastruktur auf der Grundlage der Ausführungsvereinbarung WGL weiter zu fördern.

21 September 2018

Annex A: Status report

German Rheumatism Research Centre, Berlin (DRFZ)

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1. Structure, Tasks and Institutional Environment

Legal form and funding

The German Rheumatism Research Centre Berlin (DRFZ) was founded in 1988 by the *State of Berlin* and the *Immanuel Krankenhaus GmbH* as a Foundation of the Civil Law (*Stiftung des Bürgerlichen Rechts*). Since 2009 and after a positive evaluation by the German Council of Science and Humanities (*Wissenschaftsrat*) the DRFZ is a member of the Leibniz Association and as such jointly funded by the Federal Government of Germany and the State Governments. The last evaluation by the Senate of the Leibniz Association took place in 2012 (on-site visit in 2011).

The DRFZ is located on the Campus Mitte of the *Charité – Universitätsmedizin Berlin,* sharing a building with the Max Planck Institute for Infection Biology. The Charité is the joint medical faculty of the *Humboldt Universität Berlin* and the *Freie Universität Berlin*. It consists of more than 100 clinics and institutes located at four different sites (campi). The Charité has two clinics working in the field of rheumatology, one of them located next to the DRFZ on the Campus Mitte. The connection to the Charité is of critical importance for the DRFZ, enabling the intended close interaction between experimental research, clinical expertise, epidemiology and patient care.

Responsible department at state level: The Governing Mayor of Berlin, Senate Chancellery – Higher Education and Research

Responsible department at federal level: Federal Ministry of Education and Research (BMBF)

Organisation of DRFZ

The organisational chart of the DRFZ is shown in appendix 1. The sovereign body of the DRFZ is the Board of Trustees. It meets at least once a year and controls the executive leadership of the DRFZ. The board has four permanent members: a representative of the Senate of Berlin, a representative of the Federal Ministry of Education and Research, a representative of the *Immanuel Krankenhaus GmbH Berlin* and a representative of the Charité. Furthermore, there are up to seven additional members, appointed by the Federal State of Berlin (4 years per term, 3 terms maximum).

The Board of Directors consists of the Scientific Director and the Administrative Director. Both are appointed by the Board of Trustees. The Board of Directors is responsible for the implementation of the scientific portfolio and the management of the DRFZ. Decisions on all matters of fundamental importance require consent of the Board of Trustees. The DRFZ has deputies to the Scientific Director and Administrative Director.

The Scientific Advisory Board (SAB) advises the Board of Trustees and the Board of Directors regarding scientific issues. Members of the SAB are up to seven international experts in rheumatology, appointed by the Board of Trustees for four years (two terms maximum).

Mission

The main purpose of the DRFZ is stated in the bylaws as follows: "*The purpose of the foundation is to promote science and research. In order to achieve this aim, the foundation should*

strive for excellence in basic research in areas of particular relevance to rheumatic diseases, and thereby contribute to clarifying the causes and conditions of rheumatic diseases. The aims are to develop effective treatment methods and preventive health care, provide training and further education in these areas, nurture national and international links through constant contact with national and international rheumatic diseases research centres and special clinics for rheumatic diseases."

Research structure

Science at the DRFZ is organised in three programme areas, which comprise 12 genuine DRFZ research groups (financed by the DRFZ) and 14 liaison research groups. In these liaison research groups physician scientists and biomedical scientists of partner institutions perform research at the DRFZ. They are co-financed to varying degrees by the partner institution and the DRFZ. The DRFZ provides these groups with lab space and access to the infrastructure and technology platforms of the DRFZ. The liaison groups balance the consumables used in the DRFZ every year. Of the 14 Liaison groups, 11 link the DRFZ with the Charité. Below, the basic structure of the three programme areas is described. It is detailed out in chapter 3.

Programme Area "Pathophysiology of Rheumatic Inflammation"

This area focuses on the identification, understanding and targeting of the cells driving chronic inflammation. It consists of

- 8 DRFZ research groups, thereof 1 supported by the Dr. Rolf M. Schwiete Foundation,
- 12 liaison research groups, thereof 9 with the Charité, and 1 each with the Robert Koch-Institut (RKI), the Berlin-Brandenburg Center of Regenerative Therapies (BCRT) and the *Freie Universität Berlin, department of veterinary medicine,* respectively.

Programme Area "Epidemiology of Rheumatic Diseases"

This area investigates determinants of the prognosis and outcome of rheumatic diseases using large epidemiologic cohorts. The programme area consists of

- 3 DRFZ research groups,
- 1 liaison research group with the Charité.

Programme Area "Regenerative Rheumatology"

This area was established in 2015. It investigates the biology of chondrocytes in osteoarthritis. The area consists of

- 1 DRFZ research group,
- 1 liaison research group with the Charité, supported by the Willy Robert Pitzer Foundation.

Technology Platforms and Shared Resource Laboratories (SRL)

The DRFZ operates the technology platform "Immune Monitoring" and, in collaboration with the Charité and other partners, 4 Shared Resource Laboratories (SRL) for the cytometric, microscopic and molecular analyses of individual immune cells, the cells of their

environment and their interactions. The SRL offer advanced technologies and ensure their standardized and quality controlled use in research.

National and international scientific environment

In Germany, several medical faculties at universities have clinics or departments performing rheumatology research, e. g. Berlin, Bochum, Dresden, Düsseldorf, Erlangen-Nürnberg, Frankfurt, Freiburg, Gießen, Hannover, Heidelberg, Jena, Kiel, Leipzig, Lübeck, Regensburg, Würzburg, München and Münster. Besides Berlin, the universities of Bochum, Düsseldorf, Erlangen-Nürnberg, Kiel, Lübeck, Hannover, Gießen-Bad Nauheim and Freiburg have Chairs of Rheumatology. According to the DRFZ, rheumatology research in Germany is highly cooperative and integrative, and the DRFZ is an integral part of it. This is documented, for example, by several Collaborative Research Centres (CRC) funded by the German Science Foundation (DFG), in which the DRFZ participates. In addition, there are several research networks funded by the BMBF. In 1999, the Competence Network Rheumatology of the BMBF had been established. Among the speakers and members have been and still are leading scientists of the DRFZ. The competence network became part of the German Society for Rheumatology and has since catalysed a number of other BMBF-funded research networks.

In Europe, according to the DRFZ the leading institutions in rheumatology research are the Karolinska Institute (Stockholm, Sweden), the University of Leiden (Netherlands), the Kennedy Institute in Oxford, the Arthritis Research Centre for Epidemiology in Manchester, the Arthritis Research Center - Leeds Musculoskeletal Biomedical Research Centre, the University of Glasgow (all United Kingdom), and the Department of Rheumatology of the University of Vienna (Austria). The DRFZ is collaborating with these institutes, e. g. in research networks funded by the European Commission in the frame of the Innovative Medicines Initiatives (IMI) programme (see chapter 4).

In addition, leading scientists of the DRFZ are involved in the European League Against Rheumatism (EULAR), which is a non-governmental organisation which represents the people with arthritis/rheumatism, health professionals and scientific societies of rheumatology of all the European nations. EULAR has currently certified 31 European institutions as EULAR Centres of Excellence. Together with the Charité, the DRFZ is certified as such a EULAR Centre of Excellence until 2021.

Outside of Europe, according to the DRFZ there are quite a few prominent research groups in rheumatology in the USA, Canada, Japan and China. Individual collaborations involve the University of Atlanta, the Columbia University, New York, the Lomonossov University, Moscow, and Chiba University, Chiba, Japan.

National interest and justification for funding as a non-university institution

According to the DRFZ, Rheumatic and musculoskeletal diseases (RMDs) are a major national (and international) challenge. RMDs affect a significant proportion of the adult population, and their relevance is increasing in the aging population of Germany and Europe. They are major causes of chronic pain, disability, and loss of quality of life, increase the risk of other chronic diseases and can lead to premature death. Inflammatory rheumatic

diseases affect around 2 % of the adult population. Novel, expensive treatments are major cost drivers in the German health insurances.

In view of the DRFZ, a comprehensive research on rheumatic diseases requires an interdisciplinary approach, a substantial format and a long-term commitment beyond the scope of a university. The independency of the DRFZ and its recognition as a neutral, national institution are important prerequisites for the great willingness of the cooperation partners to disclose their clinical data for research. As a Leibniz institute, the DRFZ provides the structure that is crucial for the establishment and maintenance of long-term research approaches. Furthermore, the flexible budget allows for the rapid acquisition of state-of-the-art technologies, especially in multiparametric cytometry and intravital microscopy.

2. General concept and profile

Embedded into the clinical environment of the Charité - Universitätsmedizin Berlin the DRFZ generates data on risk factors, outcomes and health care of persons with rheumatic diseases in order to inform clinical and political decision making. It performs basic biomedical research aiming at the development of innovative, curative therapeutic strategies, and operates technology platforms for molecular single cell analyses of the cells causing rheumatic disease.

Results

Research

The work and results of the different research groups are presented in chapter 3.

Between 2015 and 2017 the DRFZ published 587 articles (originals and reviews) in peer-reviewed journals and 56 articles in other journals (see appendix 2). Since the last evaluation the number of peer reviewed original scientific publications per year has remained relatively constant, varying between 134 and 167. In addition, between 36 and 48 review articles were published each year.

More than 70 % of the publications include co-authors of the Charité. In almost 50 % of the publications, DRFZ scientists are first or last author, i.e. main contributors. In 2017, nearly 50 % of the scientific publications of the DRFZ were published as “Golden” Open Access articles, i.e. with immediate, subscription-independent public access.

Scientific services and infrastructure tasks

Primarily a scientific research institute, the DRFZ also provides scientific services and infrastructure in the area of its main expertise, single cell analyses. The Shared Resource Laboratories (SRL, see chapter 3) are also accessible for external scientists. Rules for registration, reservation, responsibilities and reimbursement have been worked out and user guidance is provided. In addition, the DRFZ has coordinated and consented the “Guidelines for the use of flow cytometry and cell sorting in immunological studies”, the first international guidelines on this technology, published in 2017. For intravital microscopy, the DRFZ has organised a “Joint Intravital Microscopy Network” with start-up funding by

the DFG from 2012 to 2016, for dedicated project supervision from cell imaging to cell tracking in living organisms. For Mass cytometry, the DRFZ has organized the first German network on this technology. As a non-profit organisation, services offered by the DRFZ cover costs but do not generate a profit.

Scientific advisory service

In the area of epidemiology, the DRFZ regularly provides information on treatment prevalence, outcomes, current treatment strategies and the individual and socioeconomic impact of rheumatic diseases in children and adults. The DRFZ annually contributes to the Federal Health Reporting, and gives advice to the German Society for Rheumatology (DGRh), the Deutsche Rheuma-Liga e.V., and the Robert Koch-Institut. The DRFZ informs upon request the federal government, the German parliament, political parties, health insurances and physician organisations. On the European level, the DRFZ represents Germany in the EULAR standing committee on epidemiology and pharmacovigilance of RMDs at EMA.

The experimental biomedical expertise of the DRFZ is consulting the German Ministry of Research and Education, EULAR and the European Commission, as well as pharmaceutical industry, the latter in the frame of the IMI programme (see above).

Knowledge and technology transfer

The DRFZ aims at rapid transfer of diagnostic and therapeutic concepts resulting from its research into clinical application. This is supported by an open access publication strategy and a corresponding data management strategy. To ensure appropriate transfer and to protect the DRFZ and its cooperation partners, selected research results are patented by the DRFZ. By June 2018, the DRFZ held 4 granted patents and had filed another 8 patent applications (see appendix 2). All of them are based on the research of Programme Area "Pathophysiology of Chronic Inflammation". The original inventors participate according to the legal regulations for employees in Germany. They also have the option to exploit their results in spin-off companies on a contractual basis with the DRFZ.

Academic events and public relations

Between 2015 and 2017, 27 conferences and events were organized by employees of the DRFZ. Moreover, DRFZ scientists were involved in the organisation of large annual conferences, in particular the EULAR Congress and the European Congress of Immunology. The DRFZ also takes responsibility in the education of graduate students and postdocs beyond the local scale, organizing "Schools" on a national and international level, e. g. the Leibniz Summer School on Chronic Inflammation.

The DRFZ considers itself to be highly relevant to inform the public on the challenges rheumatic diseases pose for the individual and for the society, and to communicate DRFZ research results. A DRFZ Public Relations Service has been established since 2005.

Appropriateness of facilities, equipment and staffing

After joining the Leibniz Association the institutional core funding of the DRFZ increased from 4 M€ in 2008 to 5.8 M€ in 2011. After the positive assessment of an *Extraordinary Item of Expenditure* in the evaluation 2011 and its materialization in 2017, the funding increased from 7.3 M€ in 2016 to 9.6 M€ in 2017 (see appendix 3). The liaison research groups are financed to varying degrees by the institutional funding of the DRFZ, by funding from Charité or other partner institutions, respectively, and by grants.

Third-party funding of the genuine DRFZ groups increased from 5.7 M€ in 2011 to 6.5 M€ in 2017. In relation to the total budget, third-party funding decreased from 50 % (2011) to 40 % (2017). Between 2015 and 2017 the DRFZ groups received third-party funds amounting to almost 20 M€ in total. 6.4 M€ were obtained from the Federal and State governments, 5 M€ from the German Research Council (DFG), 4.2 M€ from industry, 1.8 M€ from foundations, 1.5 M€ from the EU and 1 M€ from the Leibniz Association. Further, substantial third-party funds were raised by the liaison groups. They are administered by the Charité or other partner institutions (4.7 M€ in 2017).

The main research building of the DRFZ is shared with the Max Planck Institute for Infection Biology (MPIIB). In addition to the space jointly used it provides about 2000 square meter (m^2) laboratory space and office space for the DRFZ. The part of the building in which the DRFZ is located had been financed separately by the State of Berlin, in exchange for the right of permanent use by the State of Berlin until 2107. This right is contractually fixed and registered in the Berlin Mitte Land Register (Grundbuch). The DRFZ also has about 500 m^2 of office space in a building of the Charité, just opposite of the main building, which is home of the research area “Epidemiology of Rheumatic Diseases”. As of June 2018, the DRFZ houses 127 mouse strains. The total capacity is 740 cages in the building shared with the MPIIB, and about 2300 cages in a breeding facility located in Berlin Marienfelde at the *Bundesanstalt für Risikobewertung* (BfR).

The view of the DRFZ is that present space is insufficient and additional space will be required in the future. Moreover, the Max Planck Society has announced to close the entire research building in 2024 for several years for an extensive refurbishing, although this has not been detailed out yet. Nevertheless, a decent accommodation of the DRFZ has to be secured for the future. According to the DRFZ, to continue the cooperation with the Charité, the DRFZ in any case has to be located in the immediate vicinity of the Charité Campus Mitte. In accordance with a recommendation of the last evaluation, future accommodation of the DRFZ should also provide extended animal housing facilities for the DRFZ.

The technology platforms are described in chapter 3. This technological expertise allows the DRFZ to pursue its research strategy aiming at the identification of the cells driving rheumatic diseases. Service units like the Animal Facility, the Central Laboratory and the IT-Service provide the logistic support for research at the DRFZ. The budget for investments in large equipment has increased from 781 T€ in 2011 to 1.73 M€ in 2018.

Development of the institution since the last evaluation

Since 2011, the research strategy of the DRFZ has remained by and large the same, while the profile of the DRFZ and its programme areas have changed significantly.

In the programme area "Pathophysiology of Rheumatic Inflammation", 8 research groups were terminated and 10 new groups were established between 2011 and 2018. This major turnover created opportunities to set up research on innate immune cells, epigenetic imprinting and microbiota in inflammation. Since 2016, the Leibniz ScienceCampus Chronic Inflammation (funded with 1.2 M€ until 2020) provides an additional platform for research, comparing and translating concepts of pathogenesis and therapy between rheumatology, gastroenterology, nephrology, dermatology and neurology. Partners are the Charité and the Max Planck Institute for Infection Biology. Between 2011 and 2018, four DRFZ scientists were awarded ERC grants. The ERC Advanced Grant of DRFZ's Scientific Director ran from 2011 to 2016. The ERC Consolidator Grant of one group started in 2015 and is continued at his new institute after he accepted a professorship there. In 2018, two ERC Starting Grants were acquired by DRFZ liaison research group leaders.

In the programme area "Epidemiology of Rheumatic Diseases" the treatment and disease registers have been continuously extended, now covering the diseases rheumatoid arthritis, axial spondyloarthritis and psoriasis arthritis, juvenile idiopathic arthritis and pregnancy in rheumatic diseases. Currently, the programme area has established nine different registers and cohort studies. Increasingly, the groups in the programme area have been working together in the analysis of scientific questions across the different cohorts. Research with claims data has been newly developed, combining administrative data with patient-reported outcomes in order to investigate health care, use of resources and burden of disease on the population level. Since the groups in the programme area are comparably large, deputy group leaders have been appointed. Following a recommendation from the last evaluation, the programme area epidemiology acquired third-party funding to set up research on health economy, taking advantage of the large data sets available in this programme area.

In 2015, the programme area "Regenerative Rheumatology" has been added to the portfolio of the DRFZ. It currently consists of two research groups. The liaison research group "Pitzer Laboratory for Osteoarthritis Research" was established in 2015 with support of the Willy Robert Pitzer Foundation. It investigates cellular and molecular mechanisms leading to osteoarthritis and aims to achieve biological regeneration of articular cartilage in affected joints. In 2016, the research group "Therapeutic Gene Regulation" joined the programme area. This group screens for therapeutic targets by next generation sequencing and develops oligonucleotide-based therapeutic strategies to control gene expression, e. g. in chondrocytes.

Strategic work planning for the next few years

New scientific leaders

The scientific leaders of the DRFZ and of the Charité clinic for rheumatology will retire in the years 2019 to 2022:

- The Scientific Director of the DRFZ, head of programme area "Pathophysiology of Rheumatic Inflammation" and interim head of programme area "Regenerative Rheumatology" has reached the official retirement age in March 2018. His appointment has

been prolonged until March 2021 by the Board of Trustees. Until then the Board of Trustees shall identify and appoint a successor.

- The Deputy to the Scientific Director and head of the programme area "Epidemiology of Rheumatic Diseases" will reach the official retirement age in September 2018. Her appointment has been prolonged until September 2019. An international expert meeting on the future of epidemiology, setting up the process of recruiting a successor, has been held in June 2018 in Berlin.
- The head of the Charité liaison group "Autoimmunology" and coordinator of autologous stem cell transplantations and plasma cell therapies has reached the official retirement age in January 2018. From 2019 to 2021, he will be appointed as a senior research group leader to the DRFZ. For the continuation and expansion of the investigator-driven clinical trial programmes in autologous stem cell transplantation and plasma cell therapies, the DRFZ is applying for additional funds to establish a new translational group (see below).
- The Director of the CharitéCentrum Internal Medicine and Dermatology, Medical Department, Division of Rheumatology and Clinical Immunology, will reach the official retirement age in February 2019. His appointment can be prolonged by the Charité ultimately until March 2022. Appointment of his successor is part of a larger endeavour of the Charité, which also has to replace other leading clinicians in the field of inflammatory diseases and immunologists at about the same time.

To prepare the transition of the DRFZ into new leadership, i.e. the appointment of a new Scientific Director and a new Head of the programme area epidemiology, the Board of Trustees of the DRFZ has formed a "Committee for the Future of the DRFZ" (Zukunftskommission) in 2017. The three members of the Committee are the Director of the Department of Medicine at *Medizinische Hochschule Hannover* and Chair of the Board of Trustees, the President of the German Academy of Sciences Leopoldina, and the former President of the division of mathematics and natural sciences of the Austrian Academy of Sciences. In view of the DRFZ, the harmonization of the changes in leadership at the DRFZ and at the Charité will be one of the great challenges in the years to come**.**

Expansion into the field of "Personalised Medicine for Musculoskeletal and Chronic Inflammatory Diseases"

The DRFZ follows a personalised approach to the understanding, diagnosis and treatment of rheumatic diseases. This approach takes into account that individual cell types capable of driving rheumatic diseases contribute to pathogenesis in the individual patient to varying degrees. Thus, one has to target those, and only those cells contributing to the disease in that individual patient.

This approach has been implemented at the DRFZ over the past years largely with the support of temporary third-party funding. To continue and consolidate this approach, the DRFZ applies for additional funds (Minor Extraordinary Item of Expenditure of a Scientific-Strategic Nature), to finance 8 research groups from core funding. The costs total approx. 3.95 M€ per year, comprising 1.97 M€ for personnel and 1.98 M€ for consumables, devices and IT. DRFZ will contribute 300 T€ from its own budget, leaving 3.65 M€ per year

that will be needed in addition, starting in 2021. The following 8 research groups will be established:

In the programme area "Pathophysiology of Rheumatic Inflammation"

Research group "Plasma Cell Therapies" (new)

To translate concepts of plasma cell therapies into the clinic and *vice versa*, to learn from these experimental therapies, a translational group shall be established. DRFZ applies for

- 251.000 € for personnel: 1 Physician/Clinician Scientist (TVÄ3), 1 postdoc (TVÖD 13), 1 PhD student (TVÖD 13/65%).
- 290.500 € for consumables, devices and IT.

Research group "Big Data and Single Cell Bioinformatics" (new)

The DRFZ has a traditional expertise in complex multiparametric cytometry and its integration with transcriptomics. To extract the information of these "big data" analyses, expanding them for data on microbiomes and transcriptomes of (many) single cells, as well as for complex clinical data from the cohorts of programme area epidemiology, the DRFZ applies for

- 166.000 € for personnel: 1 Technical Head (TVöD 12), 1 postdoc (TVÖD 13).
- 104.500 € for consumables, devices and IT.

Research group "Modelling of Complex Biological Systems" (consolidation and expansion)

The group will develop and apply advanced mathematical modeling to guide experimental strategies at the DRFZ. The group has been started from 2018 to 2020 with a grant from the Leibniz Competitive Funding (see research group "Systems Biology of Inflammation" in chapter 3). The additional funds will allow to continue it beyond 2020. DRFZ applies for

- 190.000 € for personnel: 1 scientist (TVöD 14), 2 PhD students TVÖD (13/65%),
- 80.500 € for consumables, devices and IT.

Research group "Cell-based Biobank" (consolidation and expansion) together with programme area "Epidemiology of Rheumatic Diseases"

Financed largely by third-party funding, a small biobank has been established to preserve cells of patients for cytometric and cell-type-specific transcriptome and epigenome analyses (see SRL Mass Cytometry Core Facility in chapter 3). The DRFZ now plans to extend it to include more materials from the epidemiological cohorts. For the consolidation and expansion of the biobank, the DRFZ applies for

- 90.000 € for personnel: 1 scientist (TVöD 13).
- 776.000 € for consumables, devices and IT.

In the programme area "Epidemiology of Rheumatic Diseases"

Research group "Digital Epidemiology" (new)

In response to the chances and challenges of digitalization in medicine and to capture digital health data from physicians and patients, all studies will switch to fully IT-based platforms. The group will develop and apply advanced statistical methods to cope with Big Data as well as observational cohort data. The DRFZ applies for

- 610.000 € for personnel: 1 senior statistician (TVöD 14), 1 senior epidemiologist/physician (TVöD 14/TVÄ 2), 1 health scientist/physician/epidemiologist, 1 informatician/data scientist, 1 statistician/mathematician (TVöD 13 each), 1 IT programmer (TVöD 12), 2 data bank managers (TVöD 9b).
- 147.000 € for consumables, devices and IT.

Research group "Health Economy" (consolidation and expansion)

Following a recommendation from the last evaluation, health economy has recently been implemented in the research group "Health Services Research and Early Cohorts" to analyse the long-term costs of different treatment strategies including personalized approaches (see chapter 3). For the continuation and expansion of this work DRFZ applies for

- 231.000 T€ for personnel: 1 senior scientist (TVöD 14), 1 statistician (TVöD 13), 1 data bank manager (TVöD 9b).
- 39.500 € for consumables, devices and IT.

In the programme area "Regenerative Rheumatology"

Research group "Connective Tissue and Interfaces" (new)

This group is aiming at a molecular understanding of the organisation of tissues to develop therapies for the precise regeneration of destroyed tissues. DRFZ applies for

- 216.000 € for personnel: 1 scientist (TVöD 14), 1 postdoc (TVöD 13), 1 PhD student (TVÖD 13/65%).
- 271.000 € for consumables, devices and IT.

Research group "Therapeutic Oligonucleotides" (consolidation and expansion)

This group has been recently established and is currently supported by the European Regional Development Fund Operational Programme (see DRFZ Group "Therapeutic Gene Regulation" in chapter 3). The group develops technologies for selective manipulation of gene expression in those cells which promote degeneration, or which can be switched on to regenerate tissues. For its continuation and the envisaged expansion DRFZ applies for

- 216.000 € for personnel: 1 scientist (TVöD 14), 1 postdoc (TVöD 13), 1 PhD student TVÖD 13/65%).
- 271.000 € for consumables, devices and IT.

3. Subdivisions of the DRFZ

Programme Area "Pathophysiology of Rheumatic Inflammation"

(Personnel as of 31.12.2017: 34 FTE research and scientific services, 18 FTE doctoral candidates, 26 FTE service staff)

The programme area analyses the development and persistence of chronic rheumatic inflammation with the aim to develop strategies for the induction of therapy-free remission. The key questions since 2011 have been:

- Which cells drive chronic (rheumatic) inflammation and how do they do this?
- How can we selectively eliminate these pathogenic cells?
- How is physiological tolerance regenerated?

Between 2015 and 2017 the programme area published 470 peer reviewed articles. In the same period, the programme area received third-party funds amounting to approx. 15 M€ administered at the DRFZ. 5.9 M€ were obtained from the DFG, 3.6 M€ from the Federal and State governments, 1.8 M€ from the EU and 1.2 M€ from the Leibniz-Association.

DRFZ Research Groups

Research Group "Cell Biology", since 1996

(6 scientists, 7 PhD students)

The group works on a molecular understanding of how experienced immune cells are imprinted and maintained over time, aiming at molecular targets for the selective ablation of pathogenic immune cells, in particular those driving chronic rheumatic inflammation. The group has developed the concept of resting memory plasma cells and memory T and B lymphocytes in niches of the bone marrow organised by mesenchymal stromal cells, a concept explaining the refraction of experienced immune cells to conventional immunosuppressive therapies. For pathogenic T cells, the group has identified a series of molecular adaptations to their history of repeated restimulation, which (a) allow to identify pathogenic Th cells driving chronic inflammation, and (b) are novel, selective targets for the induction of therapy-free remission of inflammatory diseases.

Between 2015 and 2017 the group published 54 peer reviewed original articles. In the same period, the group received third-party funds amounting to approx. 5.5 M€. 1.4 M€ were obtained from the DFG, 1.1 M€ from the European Research Council, and 1 M€ within the competitive procedure of the Leibniz-Association. The work has been supported by an ERC Advanced Grant from 2011 to 2016.

Research Group "Signal Transduction", since 2000

(1 scientist, 2 PhD students, 1 MD student)

The group investigates molecular mechanisms of lymphocyte activation and activation-induced cell fate decisions to understand the role of T cells in chronic inflammatory diseases. They use biochemical, cytometric and systems biological approaches to this end. These different global approaches to understand imprinting and function of activated T

lymphocytes aim at the unbiased generation of novel hypotheses on how pharmacological interference could prevent chronic inflammation or switch it off again.

Between 2015 and 2017 the group published 6 peer reviewed original articles. In the same period, the group received third-party funds amounting to approx. 880 T€. 650 T€ were obtained from the Federal and State governments, and 230 T€ from the DFG.

Research Group "Microbiota and Inflammation", since 2017

(4 scientists, 1 technical assistant)

The group started in 2017 as a spin-off of the research group "Cell Biology". It is dedicated to analyse the impact of distinct microbiota on the immune system with respect to protecting, or inducing and driving chronic inflammation in intestinal and rheumatic diseases. The group has also developed a novel method for the cytometric assessment of microbiota heterogeneity: High-Resolution Microbiota Cytometry. Recently, they have identified a defined species of microbiotic bacteria capable to induce expression of the cytokine TGF-ß in T cells of the gut, thus enhancing IgA expression and presumably protecting from colitogenic and arthritogenic inflammation.

In 2017 the group published 4 peer reviewed original articles. In the same year, the group received third-party funds amounting to approx. 1 M€, mainly obtained from the Dr. Rolf M. Schwiete Foundation, 820 T€) and the Federal and State government (100 T€).

Research Group "Osteoimmunology", since 2012

(2 scientists, 3 PhD students)

The group focuses on memory T cells and plasma cells residing in the bone marrow. The aim is to prevent the establishment of and to ablate established pathogenic memory T cells, refractory to conventional therapies, from the bone marrow. Presumably, these cells are one of the critical roadblocks to the regeneration of tolerance in chronic inflammatory diseases. The group has identified the precursors of resident memory Th cells, the receptors required for their homing into the bone marrow and their persistence there. They also have recently identified a target for the selective ablation of IgG-secreting memory plasma cells from the bone marrow.

Between 2015 and 2017 the group published 8 peer reviewed original articles. In the same period, the group received third-party funds amounting to approx. 530 T€. 230 T€ were obtained from the DFG and 170 T€ within the competitive procedure of the Leibniz-Association and 110 T€ from Chiba University, Japan.

Research Group "Humoral Immune Regulation", since 2015

(1 scientist)

The group investigates the structure/function relationship of the Fcμ receptor. The aim is to identify therapeutic options to ameliorate antibody-mediated rheumatic diseases. The group showed that the Fcμ receptor apparently supports the survival of B cells. Understanding the mode of action of the FcμR may point to therapeutic options to ameliorate antibody-mediated rheumatic diseases.

Between 2015 and 2017 the group published 3 peer reviewed original articles. In the same period, the group received no third-party funds.

Research Group “Chronic Inflammation”, since 2016

(1 scientist, 1 PhD student)

The group is dissecting interactions of microbiota and the immune system in the development of chronic rheumatic diseases. As a first step, the group has analysed the specificities of IgA secreting plasma cells of the lamina propria. The group has generated a set of microbiota-specific IgA antibodies, which are specific for distinct bacteria of the microbiota. These monoclonal IgA antibodies (1) are now used to expand the range of parameters of high-resolution microbiota cytometry and isolate the target bacteria for functional and molecular studies, and (2) for selective experimental and therapeutic targeting of individual arthritogenic bacterial taxonomic units of the microbiota, e. g. Lachnospiraceae.

Between 2016 and 2017 the group published 7 peer reviewed original articles. In the same period, the group did not have any third-party funds of its own. Since 2018, it receives third-party funds from the DFG (SFB 421, 42 T €).

Research Group “Lymphocyte Development“, since 2017

(3 scientists)

The group is investigating hematopoietic stem and progenitor cells in fetal liver and bone marrow, with the aim to understand immune cells “in context”, their regulation by cells of their environment, in particular mesenchymal stromal cells, and the signals controlling their localisation, quiescence, activation, and imprinting. The group has developed a synthetic niche for B lymphocyte precursors, generated B cell lines, dissected the heterogeneity of long-term repopulating stem cells and generated stable lines of long-term proliferating common lymphoid progenitors. Finally, the group has shown that quiescent hematopoietic stem and progenitor cells can harbour M. tuberculosis. This finding is not only of utmost relevance to understand latent tuberculosis, but also for rheumatoid arthritis, where reactivation of latent M. tuberculosis is observed after therapeutic blockade of TNFα.

In 2017 the group published 3 peer reviewed original articles. In the same year, the group received no third-party funds.

Research Group “Systems Biology of Inflammation“, since 2018

(1 scientist)

The group started in January 2018. As a theoretical biophysicist, the group leader aims at developing and applying advanced mathematical modeling and data analysis techniques to guide experimentation on chronic inflammation. Within the Leibniz competition funding programme, funding line "Best Minds", the DRFZ has raised third-party funds to recruit the group leader and establish this research group at the DRFZ (funding 2018 - 2020). To continue this line of research the DRFZ applies for additional funds (see chapter 2).

Liaison Groups

Liaison Research Group "Autoimmunology", since 1997

(8 scientists, 3 PhD students, 3 MD students, 1 technical assistant)

The group is defining and translating the DRFZ concept of "pathogenic, imprinted immune cells as a roadblock to tolerance induction", in particular pathogenic memory plasma cells, into experimental clinical trials for the treatment of patients with inflammatory rheumatic diseases and other chronic inflammatory, antibody-mediated "plasma cell" diseases. By showing that the immunological memory is eliminated by immunoablation, followed by autologous hematopoietic stem cell transplantation, in patients with severe autoimmune diseases, the group provided proof-of-principle evidence that it is indeed memory cells which drive the inflammation in the chronic phase. They defined the critical role of memory plasma cells secreting pathogenic antibodies, which are refractory to conventional therapies. Based on this and in collaboration with external partners, the group introduced the proteasome inhibitor bortezomib for the treatment of refractory autoimmune diseases with pathogenic autoantibodies. In a completely novel experimental approach, the group has now developed an affinity matrix technology for antigen-specific plasma cell depletion, with the perspective of selective ablation of autoantigen-specific plasma cells.

Between 2015 and 2017 the group published 25 peer reviewed original articles. In the same period, the group received third-party funds amounting to approx. 1.2 M€. 690 T€ were obtained from the DFG, 230 T € were obtained from the European Commission/EU and 250 T€ from industry.

Liaison Research Group "Glucocorticoids and Bioenergetics", since 2004

(4 scientists, 4 PhD students, 5 MD students, 2 technical assistants)

The group analyses the cellular bioenergetic adaptation mechanisms of an inflamed restrictive microenvironment. With increasing knowledge on cellular adaptation mechanisms under physiological and pathophysiological conditions (e. g. hypoxia in inflamed tissues), treatment strategies can be improved and adverse effects may be reduced or avoided. The group has shown that the degree of hypoxia influences immune cells in different ways. With respect to the analysis of oxygen availability and metabolism of immune cells driving chronic inflammation, this group is an essential element of the strategic aim of the DRFZ to understand the lifestyle of the pathogenic immune cells representing roadblocks to tolerance induction, and to target them selectively.

Between 2015 and 2017 the group published 37 peer reviewed original articles. In the same period, the group received third-party funds amounting to approx. 1.6 M€, mainly obtained from industry (760 T€) and the Federal and State governments (740 T€).

Liaison Research Group "B cell Memory", since 2004

(3 scientists, 3 PhD students, 4 MD students)

The group focuses on basic principles of the induction and maintenance of human memory B cells and plasma cells. The aim of the group is to understand the differential processes that lead to the induction and maintenance of protective versus autoreactive

immunoglobulins. Research topics include: 1) the basic mechanisms in the induction and maintenance of protective, antigen-specific memory B cells upon primary and secondary vaccination, 2) the maintenance of distinct memory plasma cell subsets in human bone marrow and secondary lymphoid organs, and 3) the specific functions of memory B cells in autoimmune disorders, such as rheumatoid arthritis, primary Sjögren´s syndrome and Systemic Lupus Erythematosus (SLE).

Between 2015 and 2017, the group published 29 peer reviewed original articles. In the same period, the group received third-party funds amounting to approx. 2.8 M€. 1.6 M€ were obtained from industry, 500 T€ from the DFG 450 T€ from foundations and 110 T € from the European Commission/EU.

Liaison Research Group "Allergology", since 2004

(7 scientist, 5 PhD students, 4 MD students)

The group links the CharitéCenter for Internal Medicine and Dermatology to the DRFZ. It investigates antibody class switching, expression of regulatory cytokines and the effects of vitamins A and D on B cells. They have originally described that Vitamin D3 induces regulatory B cells and the ability of activated B cells to convert provitamin D3 into active vitamin D3 (calcitriol), thus allowing the use of the pharmacologically by far superior 25-hydroxyvitamin D3 for the regulation of immune reactions. This is currently in clinical trial. The group provides continuity of the research line of the DRFZ on regulatory B cells, in particular focusing on human B cells.

Between 2015 and 2017 the group published 47 peer reviewed original articles. In the same period, the group received third-party funds amounting to approx. 2.5 M€, mainly obtained from industry (1.7 M€) and the DFG (800 T€).

Liaison Research Group "Immunodynamics", since 2008

(5 scientists, 3 PhD students, 2 MD students, 2 technical assistants)

The group works to understand the immune reactions inducing and maintaining chronic rheumatic inflammation "in context", using intravital-microscopy in the living tissue of viable animals, and the multi-epitope ligand cartography (MELC) technology to define cell-cell interactions histologically, in the bone marrow, the gut and in inflamed tissue. The aim is to dissect how the interaction of cells in the tissue affects chronic inflammation in rheumatic diseases. One focus of the group is the biology of long lived plasma cells. The group has originally identified bone marrow stromal cells acting as stable components of these niches. The group could show that plasma cells in the small intestine can also become long-lived, and that the microenvironment of the gut provides similar survival signals to them as the bone marrow.

Between 2015 and 2017 the group published 20 peer reviewed original articles. In the same period, the group received third-party funds amounting to approx. 690 T€, which were obtained from the DFG.

Liaison Research Group "Innate Immunity", since 2009

(2 scientists, 4 PhD students, 1 technical assistant)

The head of the group had been a DRFZ group leader until 2017. Since 2017, she holds a Heisenberg Professorship and her group continues as a liaison research group with the Charité. The main research focus is to define the innate modules and triggers of innate lymphoid cells (ILCs) and T cells, which initiate and maintain inflammation in a T cell receptor (TCR)-independent fashion and to understand whether distinct inflammatory programs can be imprinted in ILCs to promote rheumatic diseases, and make them "roadblocks" to tolerance induction and relevant targets of therapy. The group has identified such innate sensors as key check-points to modulate inflammation.

Between 2015 and 2017 the group published 12 peer reviewed original articles. In the same period, the group received third-party funds amounting to approx. 1 M€, which were obtained almost entirely from the DFG (920 T€).

Liaison Research Group "Chronic Immune Reactions", since 2009

(1 scientist, 4 PhD students, 1 MD student)

The group analyses follicular T cells (Tfh) cells and their interaction with B lymphocytes, a key event in the generation of imprinted pathogenic lymphocytes, in particular in the lung, which probably can decisively contribute to the onset of rheumatic inflammation. Andreas Hutloff originally discovered the "inducible costimulator" (ICOS) of T cells, and could show, together with Thomas Dörner, that ICOS is critical for the development of rheumatic inflammation. He has then shown that ICOS controls the differentiation of Tfh cells and their ability to activate B cells. The potential of ICOS as therapeutic target in rheumatic diseases will now be explored in preclinical models.

Between 2015 and 2017 the group published 9 peer reviewed original articles. In the same period, the group received third-party funds amounting to approx. 220 T€, which were obtained from the DFG (100 T€) and foundations (120 T€).

Liaison Research Group "Biophysical Analytics", since 2010

(2 scientists, 2 PhD students, 1 MD students, 1 technical assistant)

The former DRFZ research group became a liaison group in 2018, when the group leader accepted a joint professorship (Berlin model) at the faculty for veterinary medicine of the Free University (FU) Berlin. The group has developed decisive hard- and software tools for the intravital microscopy technology platform, allowing deeper penetration, higher resolution and more parameters, and FLIM and FRET technologies for the direct, intervention-free observation of NAD(P)H and Ca^{2+}, i.e. the direct observation of cellular activation and oxidative stress. For continued intravital-microscopy over extended time periods, i.e. weeks to months, the group has developed unique microendoscopic devices. These technologies are now used to obtain a detailed topographic and dynamic view of cellular interactions in chronic inflammation.

Between 2015 and 2017 the group published 15 peer reviewed original articles. In the same period, the group received third-party funds amounting to approx. 1.2 M€, which were obtained almost entirely from the DFG.

Liaison Research Group "Developmental and Mucosal Immunology", since 2017

(5 scientists, 6 PhD students, 1 technical assistant)

The group started in 2017 and focuses on a molecular understanding of how components of the innate immune system promote tissue homeostasis, and how microbiota control inflammatory processes. The work will be based on previous work of the group leader on innate lymphocytes and their precursors.

In 2017 the group published 2 peer reviewed original articles. In the year, the group received third-party funds amounting to approx. 1.3 M€. 640 T€ were obtained by the DFG, 300 T€ were obtained from foundations and 350 T€ from the European Research Council.

Liaison Research Group "Immuno-Epigenetics", since 2017

(1 scientist, 1 PhD student, 2 MD students)

The group leader has been a member of the DRFZ research group "Experimental Rheumatology" since 2012. She has coordinated the contribution of the DRFZ to the BMBF-funded German Epigenome Research Programme (DEEP; 2012-2017). In this consortium, research groups of the DRFZ used their expertise in the isolation of defined populations of T lymphocytes to provide pure populations of T cells representing different differentiation lines and stages, from different organs, of healthy donors and patients with chronic inflammatory diseases. In 2017, she accepted a position as junior research group leader at the Berlin-Brandenburg Center for Regenerative Therapies (BCRT) and since then continues her research at the DRFZ as a liaison group leader. The aim of the research is to (a) develop functionally-relevant epigenetic biomarkers defining the heritage of T cells involved in chronic inflammation and immunological memory, and (b) explore options for therapeutic intervention (epigenetic editing).

In 2017 the group published 2 peer reviewed original articles. Since 2018, the group is funded by a Leibniz grant, funding line "Cooperative Excellence", and a DFG grant. In 2018, the group leader has been awarded an ERC Starting Grant.

Liaison Research Group "Macrophages in Chronic Inflammation", since 2017

(1 scientist, 1 technical assistant)

The group leader has been recruited from the Clinic for Rheumatology of the Freiburg University Medical Center in late 2017. Based on her previous work on the role of DNA damage and macrophages in granuloma formation and in autoimmune inflammation, she will continue to analyse these aspects in chronic inflammatory rheumatic diseases and add aspects of pathogenic "imprinting" or "training" of macrophages, innate lymphocytes and their precursors.

In 2017 the group published 1 peer reviewed original article. In the same year, the group received no third-party funds. In 2018, the group leader has been awarded an ERC Starting Grant.

Liaison Research Group "Inflammatory Mechanisms", since 2017

(1 scientist, 1 PhD student)

The group aims to uncover pathways involved in the induction and regulation of tissue-resident T cells by the gastrointestinal microbiome of patients. The work is building upon previous research of the group leader, in which he has shown that gut microbiota induce local and systemic CD4 T cell responses in healthy individuals. These responses are altered in inflammatory bowel diseases, and here the group focuses on the cytokine oncostatin M.

In 2017, there were no publications and no third-party funds. In 2018, the group leader has been awarded a Lichtenberg Professorship.

Programme Area "Epidemiology of Rheumatic Diseases"

(14 FTE research and scientific services, 1 FTE doctoral candidates, 27 FTE service staff)

The programme area has the overarching task to investigate clinically significant questions in rheumatic and musculoskeletal diseases (RMDs) using epidemiological methods. Currently, the programme area leads nine different registers and cohort studies. The two national databases for adults and children, running for more than 20 years, have given annually updated information on the quality and development of health care of patients treated in rheumatology. The large disease and treatment registers (RABBIT, RABBIT-SpA, Rhekiss and JuMBO, see below) as well as the inception cohorts (ICON, CAPEA, and GESPIC) have given data that have found their way into clinical practice. Key research questions of the programme area are

- Which biological, clinical and environmental factors contribute to disease occurrence and progression?
- How safe and effective are new therapies in children and adults in the long run?
- What is the need for care and the quality of care in persons with RMDs?

Between 2015 and 2017 the programme area published 134 peer reviewed articles. In the same period, the programme area received third-party funds amounting to approx. 7.8 M€ administered at the DRFZ. 4 M€ were obtained from industry and 1.9 M€ from the Federal and State governments.

Research Groups

Research Group "Health Services Research and Early Cohorts", since 1991

(5 scientists, 4 data managers/programmers/assistant students)

The group provides the rheumatology community with information concerning the development and adequacy of health care of patients with RMDs in Germany. Using dis-ease-

specific cohorts, biological, clinical and social risk factors for disease progression and outcome are investigated. This research has implications for health care planning and identifies gaps in health care as well as problems that persons with RMDs face in daily life. The results are fed into the work of the German Society for Rheumatology (DGRh), the Arthritis Centres, the German League against Rheumatism as well as individual rheumatologic sites who use the data for quality assessment.

With the National database of the German Collaborative Arthritis Centres, treatment and outcomes of inflammatory rheumatic diseases have been observed since 1993. Every year, physician- and patient-reported data of around 17.000 persons treated by rheumatologists have been systematically collected and analysed.

Over the years, the group has substantiated how new therapeutic options and closer cooperation between medical disciplines are reflected in a better clinical outcome of patients. Health care provision outside of rheumatology has been investigated based upon nation-wide claims data (BARMER health insurance) which were combined with patient-reported outcomes. Large surveys including a total of 20.000 members of the insurance with diagnoses of rheumatoid arthritis, spondyloarthritis, or osteoarthritis of hip and knee were performed.

Disease-specific cohorts of patients have identified risk factors of poor outcomes such as incident co-morbidity, early retirement, disease progression and insufficient response to therapy.

Following a recommendation from the last evaluation, health economy was recently implemented. Taking advantage of the existing cohorts, the financial consequences of new treatment options and strategies were analysed.

Between 2015 and 2017 the group published 53 peer reviewed original articles. In the same period, the group received third-party funds amounting to approx. 3.3 M€, mainly obtained from industry (2.6 M€) and the Federal and State governments (730 T€).

Research Group “Health Services Research and Paediatric Rheumatology”, since 2009

(7 scientists, 2 PhD students, 9 MD students, 6 data managers/programmers/assistant students)

The group describes and evaluates the health care situation of children, adolescents and young adults with inflammatory rheumatic diseases. Special attention is paid to the most common paediatric rheumatic disease, juvenile idiopathic arthritis (JIA). Research is based on three large nationwide cohort studies: I) the national database of children and adolescents with rheumatic diseases, II) the inception cohort study of newly diagnosed patients with JIA (ICON) and III) the biologic register for young adults with JIA called JuMBO. Main research questions are i) How do children and adolescents with rheumatic diseases present today and what are the long-term outcomes in different subgroups? ii) What determines the progression of rheumatic diseases with onset in childhood? iii) How are children and adolescents with JIA treated nowadays, and how safe are novel treatment options in the long term?

The group substantiated considerable improvements in clinical and patient-reported outcomes of JIA over time, and a quality of life close to that of the general population. Data entry in the national paediatric database has been switched to a web-based platform (KRhOKo) which can also be used for comparative effectiveness analyses of clinical routine data, a new research field in paediatric rheumatology.

In close cooperation with the German League against Rheumatism, practice tools and information material for young people with RMDs and physicians were developed and evaluated, as were interventions (e. g. transition camps), with the aim to improve the transition from paediatric to adult rheumatology.

Between 2015 and 2017 the group published 44 peer reviewed original articles. In the same period, the group received third-party funds amounting to approx. 2.3 M€. 1.1 M€ were obtained from the Federal and State governments, 720 T€ from industry and 210 T€ from foundations (Rheumastiftung).

DRFZ Research Group "Pharmacoepidemiology", since 2010

(7 scientists, 1 MD student, 13 data managers/programmers/assistant students)

The group investigates the safety and effectiveness of new therapies after licensing. At approval of treatments, the knowledge on their (long-term) safety and effectiveness is limited due to the selection of patients enrolled in randomized controlled trials (RCTs), the relatively small sample sizes and the short duration of RCTs. The group developed several long-term cohort studies, so-called "registers". One of the largest biologics registers worldwide is RABBIT which has enrolled more than 17.000 patients so far. The overarching aim is to provide clinicians with reliable data on the risks of specific treatments in different groups of patients in order to tailor treatment to the features of individual patients. Overall, the results from RABBIT underline the importance of tight control of disease activity. Uncontrolled high disease activity was shown to be a major driver of myocardial infarction, stroke, congestive heart failure, and mortality. A calculator for the risk of serious infections under different treatments has been developed and provided on the internet.

Between 2015 and 2017 the group published 14 peer reviewed original articles. In the same period, the group received third-party funds amounting to approx. 2.2 M€ and were obtained from industry (2.1 M€) and foundations (100 T€).

Liaison Group

Liaison Research Group "Spondyloarthritides", since 2016

(8 scientists, 3 MD students, 5 technical assistants)

In continuation of the work of a Charité liaison group headed by Prof. Joachim Sieper that ended in 2016, the group is focusing on epidemiology of spondyloarthritis (SpA) as well as on improving diagnosis and therapy of the disease. In basic research work, the group focuses on mechanisms of inflammation and bone formation in spondyloarthritis.

The group has a focus on early diagnosis of axSpA. A referral network with primary care physicians and orthopaedic surgeons for the early recognition of patients at high risk of

axSpA has been established. A self-referral program (bechterew-check.de) has been developed and evaluated as a part of the OptiRef project. A nation-wide study to identify the optimal referred strategy (the MASTER study) was conducted. The group initiated the development of the international recommendation for early recognition of axSpA under the auspices of the Assessment of Spondyloarthritis International Society (ASAS).

The GESPIC cohort, observing > 700 patients with early axial spondyloarthritis (axSpA) since 2000, provided information on the natural course of axSpA at the early stage including progression of structural damage in the sacroiliac joints and in the spine. As a part of BMBF supported networks ArthroMark and ANCYLOSS / METARTHROS, the group identified a number of biomarkers predicting radiographic spinal progression in axSpA.

The group continues a considerable large part of the work of the former group of Joachim Listing on clinical trials. Several first-in-indication, proof-of-concept clinical trials and clinically relevant strategy trials in axSpA have been jointly performed.

Between 2016 and 2017 the group published 14 peer reviewed original articles. The former group of Joachim Listing published additional 10 original articles. In the same period, the group received third-party funds amounting to approx. 2.2 M€. 1.3 M€ were obtained from the Federal and State governments, 700 T€ from industry and 160 T€ from the DFG.

Programme Area "Regenerative Rheumatology"

(7 FTE research and scientific services, 2 FTE doctoral candidates, 2 FTE service staff)

In 2015 the new programme area "Regenerative Rheumatology" has been established. It focuses on chondrocyte biology and bone remodelling in the context of osteoarthritis. The aim is the development of therapeutic strategies that stop progression of disease and promote the regeneration of articular cartilage tissue. The following key questions are addressed:

- Which processes lead to the hypertrophy of chondrocytes and cartilage destruction in osteoarthritis?
- What is the heterogeneity of chondrocytes in healthy versus diseased areas of articular cartilage?
- How can we interfere with chondrocyte remodelling during osteoarthritis to promote cartilage regeneration?

Between 2015 and 2017 the programme area published 25 peer reviewed articles. In the same period, the programme area received third-party funds amounting to approx. 1 M€ administered at the DRFZ (800 T€ from foundations, 200 T€ from the Federal and State governments).

Research Group

DRFZ Research Group "Therapeutic Gene Regulation", since 2016

(4 scientists, 1 PhD student)

The group leader had been a postdoc in the DRFZ research group "Cell Biology". He had established research on small non-coding RNAs and therapeutic oligonucleotides at the

DRFZ, before being appointed as a group leader in 2016. The goal of the newly established group is to identify and to therapeutically target genes and non-coding RNAs which are involved in the pathogenesis of inflammatory rheumatic diseases and osteoarthritis (OA). In particular, oligonucleotides are developed for the therapeutic regulation of transcriptional programmes in defined target cells *in vivo*. In collaboration with the Radbruch group, the group could identify and selectively ablate pathogenic Th cells in a murine model system of chronic inflammation, by systemic application of miR148a antagomirs.

Since 2016, the group implemented Next Generation Sequencing (NGS) and single cell RNA sequencing (RNASeq) at the DRFZ in order to investigate the heterogeneity of murine and human chondrocytes in the context of OA, but also as a cutting-edge technology platform for the DRFZ. The group is supported until 2019 by the European Regional Development Fund Operational Programme. For its consolidation and continuation the DRFZ applies for additional funding (see chapter 2).

Between 2016 and 2017 the group published 7 peer reviewed original articles. In the same period, the group received third-party funds amounting to approx. 220 T€ from the EU (EFRE).

Liaison Group

Liaison Group "Pitzer Laboratory of Osteoarthritis Research", since 2015

(5 scientists, 8 PhD students, 5 technical assistants)

The group analyses chondrocyte biology in healthy and osteoarthritic cartilage, aiming at the identification of degenerative and regenerative molecular switches to prevent or stop degeneration of cartilage and to regenerate destroyed cartilage. Combining laser microdissection technology for the isolation of individual cells from defined areas of cartilage and bone with single-cell sequencing, the group has identified candidate genes involved in the control of angiogenesis and bone development. They also identified receptors of chondrocytes regulating their production and degradation of extracellular matrix.

Between 2015 and 2017 the group published 16 peer reviewed original articles. In the same period, the group received third-party funds amounting to approx. 2.0 M€. 970 T€ were obtained from foundations (Willy Robert Pitzer Foundation), 420 T€ from the DFG and 210 from the Federal and State governments.

Technology Platform and Shared Resource Laboratories (SRL)

The DRFZ runs the technology platform "Immune Monitoring" and, in collaboration with the Charité and other partners, 4 Shared Resource Laboratories (SRL).

Technology platform "Immune Monitoring"

(3 scientists, 1 PhD students, 2 MD students, 1 technical assistant)

The research focus is the identification of new molecular and cellular biomarkers or biosignatures, which can be used for patient, disease-risk and therapy stratification in terms of the concept of personalized precision medicine. The group has established multiparametric cytometry-based staining-panels for flow cytometry and mass cytometry (CyTOF),

allowing a detailed phenotyping of blood leukocytes and their isolation for molecular and functional characterisation. In addition, the unit develops SOPs and reagents that allow its integration for immunophenotyping into clinical studies. The group is involved in several clinical studies monitoring rheumatoid arthritis (RA), ankylosing spondylitis (AS), systemic lupus erythematosus (SLE) and inflammatory bowel disease (IBD) patients under various immunosuppressive therapies. So far, they have successfully defined cytometric biosignatures predicting the response of patients with Ankylosing Spondylitis to TNF-inhibitors.

Between 2015 and 2017 the group published 17 peer reviewed original articles. In the same period, the group received third-party funds amounting to approx. 1.4 M€. 610 T€ were obtained from the Federal and State governments, 580 T€ from the European Union/European pharmaceutical industry (IMI project) and 250 T€ from the DFG.

SRL “Mass Cytometry Core Facility” (MCCF)

(3 scientists, 1 PhD students, 2 technical assistants)

Established in 2015, this SRL provides mass cytometry technology, i.e. the ability to quantify of up to 50 different parameters (proteins) per cell simultaneously, using isotope-labelled antibodies. The group has been the first internationally to develop a certified mass cytometry staining panel (OMIP) at all. This one for patients with inflammatory diseases. In 2017, the group has established the DFG-funded network German Mass Cytometry Network (GerMaNet), bundling the expertise of the mass cytometry facilities in Germany. An important prerequisite for single cell technologies, the group has established a small cell-based biobank at the DRFZ. This biobank is storing patient-derived materials in a way allowing cytometric and molecular single cell analyses later on, thus adapting biobanking to state-of-the-art technologies. The DRFZ plans to upscale this biobank and asks for additional funding to do this (see chapter 2).

Between 2015 and 2017 the group published 7 peer reviewed original articles. In the same period, the group received third-party funds amounting to approx. 170 T€, which were obtained entirely from the DFG.

SRL “Flow Cytometry Core Facility” (FCCF)

The SRL develops and provides cutting-edge fluorescence-based flow cytometric and cell sorting technologies. In cooperation with the Berlin-based instrument developer APE GmbH, a new multispectral flow cytometer has been developed, with significantly enhanced sensitivity, and a novel LED based calibration tool (quantiFlash™), facilitating calibration of flow cytometers and significantly improving reproducibility. This project has been supported by the European Regional Development Fund (ERDF/EFRE). A further milestone in quality control of these technologies is the first development and coordination by this group of international consensus guidelines for the use of cytometry in immunology, published in 2017 in the European Journal of Immunology.

SRL “Regine-von-Ramin Laboratory for Molecular Rheumatology”

The SRL was established in 2004, enabled by the bequest of the late Regine von Ramin, a patient suffering from Rheumatoid Arthritis, and by support by the State of Berlin. Initially, it provided chip-based genome-wide gene expression technology (Affymetrix). In 2016, a Next Generation Sequencing (NGS) technology platform has been established, allowing unbiased transcriptome analyses with high sensitivity. In 2017, the DropSeq technology has been added, for the determination of the transcriptomes of single cells.

SRL Core Facility for Innovative Imaging and Microscopy Approaches (CINIMA)

The SRL develops and provides cutting-edge technologies for intravital microscopy and histology, the later by multi-epitope-ligand cartography. Results of this laboratory are described in the groups “Immunodynamics” and “Biophysical Analytics” (see above).

4. Collaboration and networking

Collaboration with the Charité – Universitätsmedizin Berlin

The Charité is the joint medical faculty of both the Humboldt Universität zu Berlin (HU Berlin) and the Freie Universität Berlin (FU Berlin). The connection of the DRFZ to the Charité, in particular its clinics for rheumatology, is of special importance for the research strategy of the DRFZ, allowing interaction between experimental research, clinical expertise, epidemiology and patient care. Main pillars of the cooperation between Charité and DRFZ are:

- 7 jointly appointed Professors:
    - 4 group leaders in the programme area “Pathophysiology of Rheumatic Inflammation”: research group “Cell Biology” and liaison groups “Autoimmunology”, “Immunodynamics” and “Innate Immunity”.
    - 2 group leaders in the programme area “Epidemiology of Rheumatic Diseases”: research groups “Health Services Research and Early Cohorts” and “Health Services Research and Paediatric Rheumatology”.
    - 1 group leader in programme area “Regenerative Rheumatology”: liaison group “Pitzer Laboratory of Osteoarthritis Research”.
- 11 Charité liaison research groups. In addition to the above mentioned 4 jointly appointed liaison group leaders, the following 6 liaison group leaders hold a professorship at the Charité (but are not jointly appointed):
    - 5 liaison group leaders in programme area Pathophysiology of Rheumatic Inflammation: “Glucocorticoids and Bioenergetics”, “B cell Memory”, “Developmental and Mucosal Immunology”, “Allergology” and “Inflammatory Mechanisms”.
    - 1 liaison group leader in programme area Epidemiology of Rheumatic Diseases: “Spondyloarthritides”.
- 4 Shared Resource Laboratories (see chapter 3).

- The Cluster of Excellence NeuroCure funded within the Excellence Initiative of the DFG, as well as 2 Collaborative Research Centers (CRC), 2 Transregio-CRCs and 3 Priority Programmes funded by the DFG.
- The Leibniz ScienceCampus "Chronic Inflammation" (see below).
- The Leibniz Graduate School on Rheumatology and the Leibniz Graduate School on Chronic Inflammation at the DRFZ are approved programmes for the education of PhDs and MD/PhDs at the Charité (see chapter 5).

The Leibniz ScienceCampus programme is a competitive funding line of the Leibniz Association to intensify the interaction of Leibniz institutes with universities. Together with the Charité and the Max Planck Institute (MPIIB) for Infection Biology, the DRFZ established the Leibniz ScienceCampus "Chronic Inflammation" in 2016 (first funding period until 2020 with 1.2 M€). The concept of the campus is the comparative analysis of inflammatory rheumatic diseases, chronic inflammatory diseases of the gastrointestinal system, the skin, and neuroinflammation. Several measures were initiated, e. g. a Postdoc college, a graduate school and a consultation hour (Entzündungssprechstunde) for patients. A coordinating, central W3 Professorship "Immunology of Inflammation" is currently installed.

Collaboration with other national universities and institutions

In addition to collaborations with the HU and FU Berlin, the DRFZ also collaborates with the Technische Universität Berlin (TU Berlin), the Beuth Hochschule für Technik Berlin and the University of Potsdam, in joint scientific projects, student education and teaching. One senior scientist of the DRFZ holds a joint professorship at the faculty for veterinary medicine of the FU Berlin (liaison group "Biophysical analytics"), and one senior scientist holds an extraordinary professorship at the University of Potsdam (research group "Signal transduction").

The DRFZ shares a research building and cooperates with the Max Planck Institute (MPI) for Infection Biology. Principle investigators and doctoral students are integrated into the Graduate School International Max Planck Research School for Infectious Diseases and Immunology. The DRFZ is linked to the Robert Koch-Institute (RKI) by the liaison group "Chronic Immune Reactions".

In Germany, the DRFZ collaborates with various universities and extramural research institutes. These collaborations mostly fall within the framework of research networks funded e. g. by the DFG or Federal and State governments, especially the Federal Ministry of Education and Research (BMBF).

Within the Leibniz Association the DRFZ is involved in two Leibniz Research Alliances: Bioactive Compounds and Biotechnology (19 Leibniz Institutes) and Healthy Ageing (21 Leibniz Institutes). The DRFZ itself has initiated the Leibniz Research Network "Immune-mediated diseases", to orchestrate activities of Leibniz institutes in the field of immune-mediated diseases. The DRFZ has recently started a collaboration with the Leibniz Institute for Prevention Research and Epidemiology (BIPS) in the analyses of primary and secondary data on pharmacovigilance held by both institutes.

Collaboration with international institutions

The DRFZ holds various contractual international cooperations with university and non-university partners. Furthermore, the DRFZ is involved in international collaboration projects and networks funded by the European Commission or the European Research Council. Two ERC Grants were awarded to group leaders of the DRFZ between 2011 – 2017 (Advanced Grant in 2011; Consolidator Grant in 2015). In 2018, two female group leaders were awarded ERC Starting Grants. The DRFZ has been and is part of several Innovative Medicines Initiatives (IMI) consortia focussing on rheumatic diseases, of the European Union. The DRFZ has been part of two Marie Curie Innovative Training Networks.

Other collaborations and networks

DRFZ scientists are engaged and take leadership responsibilities in scientific societies, especially in the fields of rheumatology, immunology and flow cytometry. These include the German Societies for Rheumatology, Immunology and Cytometry, the Society for Pediatric Rheumatology, the European League against Rheumatism, the International Society for the Advancement of Cytometry and the European Federation of Immunological Societies.

The DRFZ cooperates with partners from biotech and pharma industry and with private foundations in pursuit of the non-profit aims of the DRFZ. The DRFZ has received unconditional third-party funding from industrial partners, in particular in the framework of the European networks designed to team up industry, extramural and academic research. As a non-profit foundation under German civil law, the DRFZ does not engage in commercial activities. The DRFZ has also not been engaged in any public-private partnership in the strict sense. However, research at the DRFZ has been decisively supported by three private foundations, since 2015: the Rheumastiftung, the Willy Robert Pitzer Foundation and the Dr. Rolf M. Schwiete Foundation. Each of them has allowed to establish excellent research groups on cutting-edge topics.

5. Staff development and promotion of junior researchers

Staff development and personnel structure

On 31st of December 2017, DRFZ had a total of 212 employees under contract. Among them were 57 scientists, 33 PhD graduate students, 9 MD graduate students, and 32 service positions (mostly laboratory technicians, see appendix 4). Another 95 scientists and graduate students, financed by the Charité or other partner institutions, work in the liaison research groups at the DRFZ, on a “visiting scientist” (*Hospitant*) contractual basis.

Approximately 18 % of the DRFZ-scientists are tenured. The DRFZ understands itself as a training centre and springboard for a career in biomedical science. Research group leaders are appointed initially for a period of 5 (3+2) years. Tenure is dependent on an excellent track record, a scientific focus fitting to the strategic long term aims of the DRFZ, positive external evaluation, and approval by the Board of Trustees. Through tenure commitments, the DRFZ has enabled the establishment of professorships at academic partner institutions, in particular the Charité. Regarding the service positions (technology platforms

and infrastructure), tenured positions are used to provide continuity of expertise and continued quality control.

The DRFZ has implemented a number of qualification opportunities for its employees working in science, science support or administration. Participation is supported through time-off and, upon agreement, financial support. The DRFZ adheres to the career guidelines and to the standards for the recruitment for scientific leadership positions of the Leibniz Association.

Promotion of gender equality

The research-oriented equal opportunity standards of the DFG are applied by the DRFZ. 61% of all DRFZ employees, and 54% of the scientists are female. Of 12 DRFZ group leaders, 4 are female (33%). Of 14 liaison group leaders, 6 are female (43%). Of 18 postdocs employed at the DRFZ, 10 are female (56%), and of 33 graduate students, 21 are female (64%).

In 2016, the DRFZ received the Total E-Quality award, for the third time. A positive work-life balance is supported by flexible working hours and virtual desktops for home office working options.

Promotion of junior researchers

By 31st of December 2017, 33 PhD graduate students and 9 MD graduate students were employed at the DRFZ. 12 of the PhD students were financed by DRFZ core funding, 21 by third-party funding. An additional 29 PhD and 20 MD students were externally financed, i.e. students payed by externally administered funds of the liaison groups. 6 PhD students and 7 MD students received stipends.

Within the last three years, 48 graduate students graduated as PhD or equivalent and 14 graduate students as an MD. The average duration to complete a PhD (MD) has been 4.2 (3.5) years, in the years 2011 to 2017.

Education of DRFZ graduate students is structured in the frame of several graduate schools. Since 2014, following a recommendation of the previous evaluation, the DRFZ has established its own graduate programmes. Academic partners are the HU Berlin, FU Berlin, TU Berlin, the Charité and the University of Potsdam. Between 2014 and 2017 the DRFZ has established the Leibniz Graduate School of Rheumatology, designed for 6 PhD- and 6 MD-doctoral students, and financed through Leibniz competitive funding. In 2017 the DRFZ has established the Leibniz Graduate School on Chronic Inflammation, financed by the Leibniz Science Campus. Both schools are organized under the umbrella of the “Interdisciplinary Center of Infection Biology and Immunity” (ZIBI) Graduate School Berlin of the HU and FU of Berlin. ZIBI is one of the most superordinate graduate schools of Berlin, comprising several graduate programmes in the area of immunology, infection and inflammation. Apart from the DRFZ graduate programmes, currently the International Max Planck Research School for Infectious Diseases and Immunology (IMPRS-IDI), the DFG Research Training Group 2046 "Parasite Infections: From Experimental Models to Natural Systems" and DRFZ´s two graduate programmes are integrated in the ZIBI.

As of 31st of December 2017, 18 postdocs were employed at the DRFZ, 5 of them financed by DRFZ core funding, 13 by third-party funding. 2 DRFZ postdocs receive stipends. In addition, 22 postdocs of the liaison groups, financed externally, are working at the DRFZ.

In 2017, the DRFZ has established the Leibniz-College on Chronic Inflammation, which is open to all postdocs working at the DRFZ. It provides a platform for the structured mentoring and promotion of young scientists at the postdoctoral level. Since 2011, 10 physician and medical scientists working at the DRFZ have achieved habilitation, the German qualification to become a member of academic faculties, and 15 junior scientists have been appointed to senior academic positions.

Vocational training for non-academic staff

Since 2009, the DRFZ offers two training positions for animal caretakers. 3 persons successfully completed the training in the last years, all of them hold a position at the DRFZ. Since September 2017, a new trainee is working at the DRFZ.

6. Quality assurance

Internal quality management

The Guidelines for Good Scientific Practice (GSP), introduced by the DRFZ in 2011, and in accordance with the guidelines of the German Research Council (DFG), have been updated in 2018, now also integrating recommendations for GSP-guidelines of the Leibniz Association. Since 2011, the DRFZ has appointed an ombudsperson, whose tasks are described in detail in the guidelines.

Apart from the framework provided by the guidelines, good scientific practice at the DRFZ is ensured by several additional measures. Lab records are kept on paginated hardcover books and filed at the central office. The DRFZ is currently preparing the switch to electronic lab records. Lab managers ensure the quality of experimental logistics. Standard Operating Procedures (SOPs) have been developed for the most error prone research technologies. Internationally consented guidelines for the use of cytometry have been developed and published. It is planned to extend this approach to other cutting-edge technologies. Special training is provided to users of the Shared Resource Laboratories and the animal facility. A data safety concept has been implemented.

The DRFZ does not use performance-based bonus funds (Leistungsorientierte Mittelvergabe, LOM), since its research is financed to a large extent by grant funding anyway, and core funding is limited. Core funding is used to provide the infrastructure of the DRFZ (Housekeeping, Administration, Central Facilities) and a basic budget for each research group, usually comprising the group leader's position, a position for a graduate student, consumables and travel expenses for the two of them. Start-up funding of new research groups from core funding provides a second position for a graduate student for up to 3 years, and some new equipment for the group. Core funding is also used to bridge gaps in third-party funding, to finish experiments beyond third-party funding, so that the results can be published, for investment into expensive technology of shared resource labs, and finally to promote open access publishing.

In 2016, the DRFZ implemented guidelines for the application to third-party funding. Applications now have to be approved by the directors to ensure that the research funded externally complies with the strategic aims and the resources of the DRFZ.

All experimentation involving the use of animals is applied for and has to be approved by the *Landesamt for Gesundheit und Soziales (LaGeSo)*. DRFZ has implemented several measures to ensure animal welfare. All experimentation involving human material is based on consent, and approved by the ethical board of the Charité.

Quality management by the Scientific Advisory Board

The Scientific Advisory Board (SAB, see chapter 1 for its members), reviews research at the DRFZ on an annual basis. The SAB informs the Board of Trustees on scientific progress at the DRFZ, and recommends measures to develop it further. The SAB discusses science at the DRFZ with the leadership, the group leaders and the scientists. In 2015, the SAB has audited the DRFZ, according to the guidelines of the Leibniz Association. During this audit, all research groups have been evaluated, as well as the institute as a whole.

Implementation of recommendations from the last external evaluation

DRFZ responded to the recommendations made by the Senate of the Leibniz Association in the last evaluation (highlighted here in italics, see also Statement of the Senate of the Leibniz Association from 18 July 2012) as follows:

*1. The concept of **Liaison groups** works excellent, as can be seen in the manifold joint projects and publications. The concept should be further expanded, as intended by the institute.*

In 2011, 10 Liaison groups worked at the DRFZ. This has been expanded to 14 in 2018. Establishment of 1 more Liaison group with the TU Berlin is in progress. The DRFZ considers it important to have a certain balanced relation between the number of Liaison groups and genuine DRFZ research groups (see chapter 2).

*2. **Biobank materials** should be systematically preserved for all study cohorts of programme area Epidemiology in the future.*

Wherever financially and logistically possible, and scientifically reasonable, the DRFZ collects biomaterial from the epidemiologic cohorts. According to DRFZ, there are no generic funds available for large scale collection and storage of biomaterial. A small cell-based biobank has been established to support the quest for cytometric and molecular biomarkers and biosignatures, and make the biobanks useful for advanced molecular analyses. The DRFZ applies for additional funds to scale up this cell-based biobank (see chapter 3).

*3. The programme area Epidemiology needs to be stabilised with institutional funding, as the **proportion of third-party funding in programme area Epidemiology** with more than 90 % is too high. Although this high rate reflects a high level of performance, it also means that important long-term tasks are currently being financed with third-party funds for a limited period of time. The planned consolidation of two leading positions in programme area Epidemiology, which are currently being financed by third-party funds, is highly appreciated. It is also necessary to secure long-term financing for on-going tasks in*

the areas of cohort maintenance, statistics, biometric counselling and study design as well as in cell sorting and cytometry. These measures will also help to facilitate a systematic and long-term interlinking of the content of programme areas Pathophysiology of Rheumatic Diseases and Epidemiology. The stabilisation of the core funding should also make it possible to focus the portfolio of external funding under programme area Epidemiology more strongly on ***competitively allocated external funding*** *for research funding.*

In 2016 and 2017, a significant stabilisation could be achieved due to an increase of the core funding. The programme area "Epidemiology of Rheumatic Diseases" has been supported with additional 242 T EUR, including three permanent positions and an increase in funds for consumables and IT equipment. In 2017, the core-funding (including share of the institute's basic costs) of the program area was 1.2 M€ and the third-party funding was 3 M€, corresponding to 71.4 % third-party money of the total budget.

In view of the DRFZ the specific funding concept for longitudinal studies developed by the programme area with long-term commitments from various stakeholders is not feasible with funding agencies such as BMBF, DFG or EU alone due to the limited time frames of these funding programmes. Thus, other funders, e. g. industry consortia, have to take over after an initial funding period, as was the case with DRFZ's national databases for adults and children with RMDs. In addition to the long-term commitments for the epidemiologic cohorts, competitively allocated external funding has been raised for research with shorter time horizons (see chapter 3).

4. ***Planned Programme Area III ("Regenerative Rheumatology")****: The focus is on degenerative – not regenerative - processes in the joint. The name should be reconsidered. However, the concept is conclusive and makes sense. The development of such a programme area is an important complementation to the research programme with great potential. The responsible persons of the DRFZ have recognized this potential, and the evaluation group appreciates the efforts for a strategic advancement of the institute in this direction.*

According to DRFZ, the focus lies on understanding degenerative processes and mechanisms in joints but with the aim to develop regenerative therapies. Thus, the name of the programme area has not been changed.

5. The allocated funding can be used in the fiscal year and beyond. Hence, the management principles should be amended by the funding provider in order to allow for ***more flexible implementation of the staffing plan****.*

New management principles have been implemented. The programme budget (Programmbudget) ensures flexibility in personnel and consumable issues. The staff appointment scheme (Stellenplan) is binding only for the positions of the DRFZ directors and for professorships.

6. ***Space for offices and laboratories*** *is insufficient. The areas used for keeping experimental animals in the immediate vicinity of the DRFZ at the Charité are not sufficient to meet the demand, and the rented area in Marienfelde - only suitable as a temporary solution anyway - cannot be maintained due to reasons, which are not the responsibility of the DRFZ.*

There is an urgent need for a considerable expansion of the area close to the institute for laboratory animal husbandry which can be used on the long run.

The spatial situation has not changed since 2011. The DRFZ is discussing the situation with the Charité and the State of Berlin, especially with regards to the plans of the Max Planck Society to refurbish the joint building (see chapter 2).

Appendix 1

Organisational Chart

Appendix 2

Publications and patents

Type of publication	2015	2016	2017
Monographs	1	0	2
Individual contributions to edited volumes	7	5	6
Articles (originals and reviews) in peer-reviewed journals	201	215	171
Articles in other journals	18	22	16
Working and discussion papers	0	0	0
Editorship of edited volumes	1	0	3

Industrial property rights	Granted	Registered
Patents	4	8
Other industrial property rights	0	0
Exploitation rights / licences (number)	0	

Appendix 3 Revenue and Expenditure

Revenue		2015			2016			2017[1]		
		K€	% [2]	% [3]	K€	% [2]	% [3]	K€	% [2]	% [3]
Total revenue (sum of I., II. and III.; excluding DFG fees)		16.048			16.087			16.192		
I.	**Revenue (sum of I.1., I.2. and I.3)**	16.042	100 %		15.891	100 %		16.117	100 %	
1.	INSTITUTIONAL FUNDING (EXCLUDING CONSTRUCTION PROJECTS AND ACQUISITION OF PROPERTY)	9.148	57%		9.460	60%		9.613	60%	
1.1	Institutional funding (excluding construction projects and acquisition of property) by Federal and *Länder* governments according to AV-WGL	9.361			9688			9.892		
1.2	Institutional funding (excluding construction projects and acquisition of property) not received in accordance with AV-WGL	0			0			0		
2.	REVENUE FROM PROJECT GRANTS	6.894	43%	100 %	6.431	40%	100 %	6.504	40%	100 %
2.1	DFG	2.049		30%	1.718		27%	1.338		21%
2.2	Leibniz Association (competitive procedure)	424		6%	355		6%	221		3%
2.3	Federal, *Länder* governments	2.122		31%	1.642		26%	1.614		25%
2.4	EU	869		13%	556		9%	48		1%
2.5	Industry *(if applicable, break down by source)*	1.160		17%	1.440		22%	1.641		25%
2.6	Foundations *(if applicable, break down by source)*	173		3%	424		7%	1.248		19%
2.7	*If applicable: other sponsors (break down by source)*	97		1%	296		5%	394		6%
3.	REVENUE FROM SERVICES	0	0%		0	0%		0	0%	
3.1	Revenue from commissioned work	0			0			0		
3.2	Revenue from publications	0			0			0		
3.3	Revenue from exploitation of intellectual property for which the institution holds industrial property rights (patents, utility models etc.)	0			0			0		
3.4	Revenue from exploitation of intellectual property without industrial property rights	0			0			0		
3.5	*Revenue from other services, if applicable; please specify*	0			0			0		
II.	**Miscellaneous revenue** (e. g. membership fees, donations, rental income, funds drawn from reserves)	6			196			75		
III.	**Revenue for construction projects** (institutional funding by Federal and *Länder* governments, EU structural funds, etc.)	0			0			0		

Expenditures		K€	K€	K€
Expenditures (excluding DFG fees)		16.017	15.997	16.152
1.	Personnel	9.185	8.899	8.862
2.	Material expenses	2.737	2.737	2.876
2.1	*Proportion of these expenditures used for registering industrial property rights (patents, utility models etc.)*	37	39	69
3.	Equipment investments	1.644	1.548	1.546
4.	Construction projects, acquisition of property	0	0	0
5.	Other operating expenses (if applicable, please be specific)	2.371	2.741	2.686
6.	Other	80	72	112

DFG fees (if paid for the institution – 2.5% of revenue from institutional funding)	228	236	239

Appendix 4

Staff

(Basic financing and third-party funding / proportion of women (as of: 31.12.2017)

	Full time equivalents		Employees		Female employees	
	Total	on third party funding	Total	on temporary contracts	Total	on temporary contracts
	Number	Percent	Number	Percent	Number	Percent
Research and scientific services	75,8	54,45	98	82,66	53	90,57
Professors / Direct. (C4, W3)	3	0	3	0	1	0
Professors / Direct. (C3, W2)	2	0	2	0	1	0
Academic staff in executive positions (E15)	3	0	3	33,34	2	0
Junior research group leaders / junior professors/ post-doctoral fellows (E14)	2	50	2	100	0	0
Scientists in non-executive positions (E13, E14)	41,09	57,02	51	82,36	27	85,19
Scientists in non-executive positions (E11)	1	0	1	100	0	0
Doctoral candidates (E13)	21,45	64	33	100	21	100
Guest Scientists	2,26	11,37	3	100	1	100
Service positions	63,43	44,94	75			
Laboratory (E9 to E12)	14	53	17			
Laboratory (E5 to E8)	0,5	100	1			
Animal care (E13)	2	0	3			
Animal care (E5 to E8)	8	0	9			
Animal care (E1 to E4)	0,88	0	2			
Store/Reception desk (E5 to E8)	2	0	2			
Library (E9 to E12)	1	0	1			
Information technology - IT (E9 to E12)	3,25	0	4			
Scientific coordination (E14)	1,75	0	2			
Scientific coordination (E13)	2,88	69,57	3			
Assistants directors office (E9-E12)	3	0	3			
Data manager/programmer/assistant student (E9-E13)	19,79	84,84	23			
Lab kitchen (E1-E4)	2,5	0	3			
Other personnel epidemiology (E9-E13)	1,88	53,43	2			
Administration	10,33	13,12	13			
Head of the administration	1	0	1			
Internal administration (financial administration, personnel etc.) (E9 to E12)	6,25	8	7			
Internal administration (financial administration, personnel etc.) (E5 to E8)	3,08	27,17	5			
Student assistants	8,45	91,14	24			
Trainees	2	0	2			
Scholarship recipients at the institution	7	100	7		4	
Doctoral candidates	5	100	5		4	
Post-doctoral researchers	2	100	2		0	

25 January 2019

Annex B: Evaluation Report

German Rheumatism Research Centre, Berlin (DRFZ)

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Appendix:
Members of review board

1. Summary and main recommendations

The German Rheumatism Research Centre Berlin (DRFZ) successfully investigates the causes, course and treatment of rheumatic diseases. To this end, DRFZ pursues two research directions: on the one hand, it studies the molecular mechanisms causing rheumatic diseases in the context of biomedical research in order to find approaches to therapy; on the other, it analyses the risk factors and long-term effects of rheumatic diseases as well as the appropriateness of treatment in the context of epidemiological studies in order to optimise clinical decision-making and treatment planning.

DRFZ became eligible for funding by the Federal Government and the *Länder* in the framework of the Leibniz Association on 1 January 2009. Since then, its institutional funding has more than doubled. It increased from €4 m in 2008 to €9.9 m in 2017. On the basis of the extensive increases in institutional funding, the Scientific Director, who has been working at DRFZ since 1996, and the Deputy to the Scientific Director, who has been working there since 1991, have successfully continued to develop DRFZ.

DRFZ's publication record is very good, both in terms of quantity and quality. Research results are regularly published in high-ranking journals. The high quality of its research performance is also reflected in the impressive size of its third-party income which accounted for 40 percent of the overall budget in 2017. Particular mention should be made of the four ERC Grants that DRFZ staff were able to acquire. DRFZ is, furthermore, involved in many DFG-funded collaborative projects.

Regarding the transfer of research results into clinical applications the central elements are the liaison groups. They are co-financed to varying degrees by clinical partners (usually Charité) and DRFZ, and facilitate the close interlocking of fundamental research and clinical translation. Furthermore, DRFZ holds important epidemiological data, which are in demand amongst researchers, clinicians and patients worldwide, and which help to improve the care of patients with rheumatic diseases.

DRFZ's activities are divided into three programme areas: "Pathophysiology of Rheumatic Inflammation" comprises 20 groups. The eight DRFZ groups are predominantly rated as "good to very good" (one as "excellent", two as "very good", four as "good to very good" and one as "good"). The 12 liaison groups are predominantly rated as "very good to excellent" (four as "excellent", five as "very good to excellent", one as "very good", and two as "good to very good"). The thematic focus of research has been extended in recent years, partly to embrace also topics that no longer have a direct relationship to the treatment of rheumatic diseases.

"Epidemiology of Rheumatic Diseases" comprises four groups, which are, however, relatively large. The three DRFZ groups are rated as "excellent" in two cases and as "very good to excellent" in the other. The liaison group is rated as "good to very good".

The new programme area of "Regenerative Rheumatology", which arose from the existing programme area of "Pathophysiology of Rheumatic Inflammation" in 2015, only comprises two groups at present. Both the DRFZ group and the liaison group are rated as "good to very good". Overall, the performance of the new programme area has not achieved expectations, as voiced at the last evaluation.

DRFZ is about to embark on a period of fundamental change in personnel. Both the Scientific Director and the Deputy to the Scientific Director reached the official retirement age in 2018. It is welcomed that the Board of Trustees decided to extend both appointments until March 2021 (Scientific Director) and September 2019 (Deputy to the Scientific Director) as well as to establish a "Committee for the Future of the DRFZ" in 2017 to prepare for the change in personnel at the institute. At the same time as the changes taking place at DRFZ, its primary collaborative partner, Charité, will also experience retirement-related changes at the leadership level. This refers, in particular, to the head of the Department of Rheumatology and Clinical Immunology, which is partner in seven liaison groups. He will retire in March 2022 at the latest. In addition, the head of the important Charité liaison group on "Autoimmunology" will also retire. It will be extremely important to carefully coordinate the various forthcoming appointments of researchers at DRFZ and Charité.

Special consideration should be given to the following main recommendations in the evaluation report (highlighted in **bold face** in the text):

Strategic work planning for the next few years (Chapter 2)

1. Supported by the "Committee for the Future of the DRFZ" and considering the results of this evaluation report the Board of Trustees should develop clear strategic guidelines for the appointments of DRFZ's new Scientific Directors and, in doing so, the institute's future scientific orientation. It could be advantageous, to first appoint the new Scientific Director and then afterwards the new Deputy.
2. It will then essentially be a task for the new leadership to focus DRFZ's scientific profile more clearly. The institute should concentrate more of its efforts on work that is of particular relevance to rheumatic diseases (e. g. rheumatoid arthritis, spondyloarthropathies, connective tissue diseases and vasculitides), as stated in its statutes. In the course of growth over recent years, the breadth of topics pursued at DRFZ has expanded significantly. Research in the programme area of "Pathophysiology of Rheumatic Inflammation", in particular, partly addresses more general immunological topics that are not always directly related to rheumatic diseases research. Moreover, in 2015, a new programme area arose from the existing programme area of "Regenerative Rheumatology", which addresses an additional new research topic. So far, its performance has not come up to the expectations, as addressed at the last evaluation. It should be examined to what extent it is worthwhile to continue expanding this programme area.
3. Taking account of these recommendations, the new leadership should revisit the concept presented by DRFZ to develop work in the field of personalised medicine. The idea is fundamentally good but, at present, the plans presented are not convincing. The institute envisaged using a further increase in institutional funding (Extraordinary Item of Expenditure) totalling €3.65 m (plus the institute's own contribution of €300 k) to establish four new groups and extend four existing groups as of 2021. However, DRFZ's new leadership will have the opportunity to re-apply for an extraordinary item of expenditure on the basis of a new concept and the recommendation of the Scientific Advisory Board.

Appropriateness of facilities, equipment, and staffing (Chapter 2)

4. Institutional funding is not only used to finance the DRFZ groups but also to part-finance the liaison groups. In addition, the latter receive funding from the respective partner institutions. The liaison groups' mixed financing should be presented more transparently. It remained unclear why some liaison groups do not receive any funding from DRFZ whilst others receive very high sums. Moreover, no information was presented on the amount of the respective partner institutions' funding contributions.

Collaboration and networking (Chapter 4)

5. All in all, DRFZ cooperates with various national and international partners, largely in the context of the multiple third-party funded collaborative projects in which it is involved. DRFZ should aim to initiate and lead more supra-regional alliances itself.

Staff development and promotion of junior researchers (Chapter 5)

6. DRFZ should strive to appoint more external scientists to leadership positions at the institute. Many of the groups established in recent years are headed by individuals who were already employed at DRFZ. DRFZ should also aim to ensure that more junior scientists subsequently find external positions. It is important to achieve a higher degree of changes. This stimulates the scientific independency of junior researchers and leads to a higher diversity of approaches, fostering innovative ideas.
7. DRFZ should define the duties of senior scientists at DRFZ more clearly, particularly with regard to mentoring junior researchers, e. g. with a specified mentoring programme.
8. At 54 percent, the proportion of female scientists is, in general, pleasingly high. At the level of group leaders, however, DRFZ should strive to increase the proportion of female scientists. Of the 12 DRFZ group leaders, four are female (33%); of the 14 liaison group leaders, six are female (43%).

2. General concept and profile

Results

Research

DRFZ's publication record is very good, both in terms of quantity and quality. Research results are regularly published in high-ranking journals, whereby DRFZ scientists are often not just involved in the publications but make significant contributions to them. This is evidenced by the fact that DRFZ scientists are cited as the first or last author in nearly half the publications.

It is welcomed that DRFZ makes nearly half its scientific publications available as Golden Open Access articles, i.e., with immediate, subscription-independent public access. This facilitates the speedy translation of research results into clinical applications (see below). Furthermore, DRFZ regularly publishes review articles highlighting recent advances in rheumatological research that address both the community of practicing rheumatologists

and the community of patients. For certain selected research results, moreover, DRFZ has also registered patents.

Translation of research results into clinical applications

Employing various tools, DRFZ convincingly translates its research results into clinical applications. A central element of this process are the liaison groups which are almost exclusively located in the "Pathophysiology of Chronic Inflammation" programme area. These groups involve scientists from clinical partners and they are co-financed to varying degrees. Of the 14 liaison groups, 11 link DRFZ with Charité. The concept of liaison groups has proven its worth and is a hallmark of DRFZ.

The programme area of "Epidemiology of Rheumatic Diseases" is responsible for various registers and cohort studies on the basis of which extremely important data and decision-making tools are elaborated that are in demand worldwide. They address the risks of specific treatments in different groups of patients in order to tailor treatment to the features of individual patients. In this context, the translation of results is not only promoted by publications but also by DRFZ's very good integration in international rheumatological associations and networks, making the programme area a flagship of German rheumatology.

A further aspect of transfer activities is DRFZ's participation in the Innovative Medicines Initiative (IMI). IMI is a partnership between the European Union and the European pharmaceutical industry. It facilitates collaboration in research to advance the development of, and accelerate patient access to, personalised medicines, especially in areas of unmet medical need.

Scientific advisory service

DRFZ provides diverse advisory services for various health policy actors, health insurances and physicians' organisations. It contributes to the annual Federal Health Reporting and advises the German Society for Rheumatology (DGRh), the Deutsche Rheuma-Liga e.V., and the Robert Koch Institute. At European level, DRFZ's advice is sought by the European League Against Rheumatism (EULAR) and the European Commission as well as the pharmaceutical industry, the latter in the context of the IMI programme (see above).

Scientific infrastructure tasks

Providing scientific services is not one of DRFZ's core tasks. However, the institute's technology platforms (see Chapter 3) are also available to external researchers. Rules for registration, reservation, responsibilities and reimbursement have been drawn up and user guidance is provided.

Development since the last evaluation

Following a positive evaluation by the German Council of Science and Humanities in 2003, DRFZ has been funded jointly by the Federation and the *Länder* as a member of the Leibniz Association since 1 January 2009. Since then, its institutional funding has more than

doubled. When it joined the Leibniz Association, funding initially increased from €4 m in 2008 to €5.8 m in 2011. Implementing a recommendation of the Leibniz Association Senate made at the last evaluation in 2012, DRFZ received additional financial support (Extraordinary Item of Expenditure), which raised its institutional funding from €7.3 m in 2014 to €9.4 m in 2015. Approx. half of this additional funding was granted in order to consolidate the two existing, long-term programme areas. The other half was earmarked for developing the new programme area of "Regenerative Rheumatology" (see below for information on the three programme areas). In 2017, DRFZ's institutional funding finally amounted to €9.9 m.

On the basis of these extensive increases in institutional funding, the Scientific Director, who has been working at DRFZ since 1996, and the Deputy to the Scientific Director, who has been working there since 1991, have successfully continued to develop DRFZ. In the following, general assessments of the three programme areas are presented.

Programme Area "Pathophysiology of Rheumatic Inflammation"

DRFZ's largest programme area that is headed by the Scientific Director comprises 20 groups. The eight DRFZ groups are predominantly rated as "good to very good" (one as "excellent", two as "very good", four as "good to very good" and one as "good"). The 12 liaison groups are predominantly rated as "very good to excellent" (four as "excellent", five as "very good to excellent", one as "very good", and two as "good to very good").

Since the last evaluation, eight groups have been wound up and ten new ones established. In the process, the thematic focus of research has been significantly expanded. The very good work on the identification and understanding of the cells that drive chronic rheumatic diseases still constitutes the primary focus. In addition, successful research is now also conducted on the fundamental mechanisms of the immune system, such as on innate immune cells, epigenetic imprinting and microbiota in inflammation, whereby some groups now pursue research questions which are not directly related to the treatment of rheumatic diseases.

Programme Area "Epidemiology of Rheumatic Diseases"

This programme area comprises four groups. The three DRFZ groups have managed to substantially improve the very good performance that was attested at the last evaluation. They are rated as "excellent" in two cases and as "very good to excellent" in the other. With their research results based on longitudinal cohort studies, the groups make important contributions to improving the care of patients with rheumatic diseases. They are highly visible internationally and their results are of great relevance to researchers, clinicians and patients. The liaison group is rated as "good to very good".

Programme Area "Regenerative Rheumatology"

This programme area has been under construction since 2015 when DRFZ was granted additional funds (Extraordinary Item of Expenditure) for this purpose. It is under the temporary leadership of the Scientific Director and is based on work conducted in the "Pathophysiology of Rheumatic Inflammation" programme area. Although supported by a

large third party grant, DRFZ has, however, not been able to fully implement the plans presented at the last evaluation. A joint professorial appointment with Charité, advertised in 2011, has not yet been made. To date, only one liaison group, financed by a foundation, and one DRFZ group, financed through the European Regional Development Fund (EFRE) have been established (in 2015 and 2016 respectively).

The research conducted in this programme area aims to regenerate articular cartilage in joints damaged by arthritis. Both group leaders previously did very successful work on T cells in the "Pathophysiology of Rheumatic Inflammation" programme area. So far, they have not been able to achieve the same high level with their new research topics as they did previously. Both groups are rated as "good to very good". Overall, the performance of the new programme area has not come up to the expectations voiced at the last evaluation.

Strategic work planning for the next few years

DRFZ is about to embark on a period of fundamental change in personnel. Both the Scientific Director and the Deputy to the Scientific Director reached the official retirement age in 2018. It is welcomed that the Board of Trustees decided to extend both appointments until March 2021 and September 2019 respectively as well as to establish a "Committee for the Future of the DRFZ" in 2017 to prepare for the change in personnel. The three members of the Committee are the Director of the Department of Medicine at Hannover Medical School and Chair of the Board of Trustees, the President of the German National Academy of Sciences Leopoldina and the former President of the Division of Mathematics and Natural Sciences of the Austrian Academy of Sciences.

At the same time as the changes taking place at DRFZ, its primary collaborative partner, Charité, will also experience retirement-related changes at leadership level. This refers, in particular, to the head of the Department of Rheumatology and Clinical Immunology, which is partner in seven liaison groups. He will retire in March 2022 at the latest. In addition, the head of the important Charité liaison group on "Autoimmunology" will also retire. It will be extremely important to carefully coordinate the various forthcoming appointments of researchers at DRFZ and Charité. It would, therefore, be ideal if the committees responsible for making the appointments at Charité could include a representative of DRFZ.

Supported by the "Committee for the Future of the DRFZ" and considering the results of this evaluation report the Board of Trustees should develop clear strategic guidelines for the appointments of DRFZ's new Scientific Directors and, in doing so, the institute's future scientific orientation. It could be advantageous, to first appoint the new Scientific Director and then afterwards the new Deputy.

It will then essentially be a task for the new leadership to focus DRFZ's scientific profile more clearly. The institute should concentrate more of its efforts on work that is of particular relevance to rheumatic diseases (e. g. rheumatoid arthritis, spondyloarthropathies, connective tissue diseases and vasculitides), as stated in its statutes. In the course of growth over recent years, the breadth of topics pursued at DRFZ has expanded significantly. Research in the programme area of "Pathophysiology of Rheumatic Inflammation", in particular, partly addresses more

general immunological topics that are not always directly related to rheumatic diseases research. Moreover, in 2015, a new programme area arose from the existing programme area of "Regenerative Rheumatology", which addresses an additional new research topic. So far, its performance has not come up to the expectations, as addressed at the last evaluation. It should be examined to what extent it is worthwhile to continue expanding this programme area.

Taking account of these recommendations, the new leadership should revisit the concept presented by DRFZ to develop work in the field of personalised medicine. The idea is fundamentally good but, at present, the plans presented are not convincing. The institute envisaged using a further increase in institutional funding (Extraordinary Item of Expenditure) totalling €3.65 m (plus the institute's own contribution of €300 k) to establish four new groups and extend four existing groups as of 2021. However, DRFZ's new leadership will have the opportunity to re-apply for an extraordinary item of expenditure on the basis of a new concept and the recommendation of the Scientific Advisory Board.

Appropriateness of facilities, equipment, and staffing

The amount of support provided by the Federation and the *Länder* in the form of institutional funding is sufficient to fulfil DRFZ's portfolio of activities. In 2017, institutional funding totalled €9.9 m.

Institutional funding is not only used to finance the DRFZ groups but also to part-finance the liaison groups. In addition, the latter receive funding from the respective partner institutions. The liaison groups' mixed financing should be presented more transparently. It remained unclear why some liaison groups do not receive any funding from DRFZ whilst others receive very high sums. Moreover, no information was presented on the amount of the respective partner institutions' funding contributions.

Third-party income is very high. In 2017, it accounted for 40 percent of the entire budget. The third-party funding portfolio is extremely diverse and includes grants that have been acquired under competitive conditions. Particular mention should be made of the fact that DRFZ staff have managed to acquire four ERC Grants (Advanced Grant in 2011, Consolidator Grant in 2015 and two Starting Grants in 2018). DRFZ is, furthermore, involved in many DFG-funded collaborative projects. Other important third-party sources, especially in the field of epidemiological research, include the Federal and *Länder* governments as well as industry. In addition, substantial funding was raised from foundations and in the Leibniz Association's Competition as well as by the liaison groups which are administered by the partner institutions.

DRFZ's facilities are currently fit for purpose. The close proximity to Charité is of essential importance to the institute as a whole. Together with the Max Planck Institute for Infection Biology, it is located in a building on the Charité Campus, which belongs to the Max Planck Society (MPG); part of the building has been contractually leased to DRFZ for 99 years. Apart from the MPG building, a small section of staff is housed in a neighbouring building

belonging to Charité. Should it become necessary for DRFZ to move, another new location in direct proximity to Charité should be found.

For DRFZ's research it is very important to have space for laboratory animal husbandry. Of the capacity reserved for DRFZ use in the MPG building, 740 cages are available. Contrary to expectations at the last evaluation, DRFZ can still lease additional space (2,300 cages) from the German Federal Institute for Risk Assessment (BfR) in Berlin Marienfelde. Current needs are therefore being met.

3. Subdivisions of DRFZ

Programme Area "Pathophysiology of Rheumatic Inflammation"

DRFZ Research Groups

Research Group "Cell Biology", since 1996

(6 scientists, 7 PhD students)

This extremely successful group is headed by the Director of DRFZ and constitutes the core of the programme area. It has developed the concept of resting memory plasma cells and memory T and B lymphocytes in niches of the bone marrow organised by mesenchymal stromal cells. This concept explains the resistance of experienced immune cells to conventional immunosuppressive therapies. The group's outstanding research is documented by an impressive publication record. Third-party funding income is also very high. From 2011 to 2016, research was supported, amongst others, by an ERC Advanced Grant acquired by the head of the group. Beyond this, the group is also very active and widely visible at international level. Based on its research results, the group devises innovative therapies to selectively switch off pathogenic memory cells and thus erase the memory for rheumatic inflammation. In this context, there is close cooperation with the "Autoimmunology" and "Therapeutic Gene Regulation" groups. The group's results are also the point of departure for the research conducted by other, newly-established groups.

The group is rated as "excellent".

Research Group "Signal Transduction", since 2000

(1 scientist, 2 PhD students, 1 MD student)

This group works on molecular mechanisms of lymphocyte activation and pharmacological interference, employing innovative cytometric techniques as well as system biology and bioinformatics approaches. One of the group's results that deserves special mention is a novel technique for multiparametric visualisation of T cell subset compositions. The individual projects are interesting and fit well with DRFZ's focus. The group should, however, more clearly define the overarching scientific issue it wants to address with the technologies it has developed.

The group is rated as "good to very good".

Research Group "Microbiota and Inflammation", since 2017

(4 scientists, 1 technical assistant)

Funded by the Schwiete Foundation this group was set up in 2017 as a spin-off from DRFZ's "Cell Biology" group. It conducts successful research at the intersection of microbiota and the immune system. Its aim is to identify pro- and anti-inflammatory bacteria and to unravel their mode-of-action on the single cell level. Several very good publications have already been compiled. Furthermore, the group uses and develops innovative cytometric techniques for the single cell analysis and isolation of intestinal microbiota. The head of the group is also head of the Flow Cytometry Core Facility. Special mention should be given to a newly-developed method for the cytometric assessment of microbiota heterogeneity (High-Resolution Microbiota Cytometry). This technology opens up outstanding opportunities for the group to further its investigations. Looking to the future, the group should elaborate a strategy for translating its results into clinical applications.

The group is rated as "very good".

Research Group "Osteoimmunology", since 2012

(2 scientists, 3 PhD students)

This group focuses on memory T and plasma cells residing in the bone marrow. The aim of this interesting research is to prevent the establishment of and to ablate established pathogenic memory T cells, refractory to conventional therapies, from the bone marrow. The group's results have flowed into some good publications. In order to improve the group's performance, it should be examined to what extent approaches taken from matrix biology could be integrated into its work. Collaboration with the "Regenerative Rheumatology" programme area would also suggest itself.

The group is rated as "good".

Research Group "Humoral Immune Regulation", since 2015

(1 scientist)

This very small group investigates the structure/function relationship of the Fcμ receptor with the aim of identifying therapeutic options to ameliorate antibody-mediated rheumatic diseases. The group leader is a professor at the University of Alabama at Birmingham and a senior scientist at DRFZ. The research results are interesting and are published appropriately. The work complements other DRFZ groups very well and thus fits convincingly into DRFZ's overall strategy.

The group is rated as "good to very good".

Research Group "Chronic Inflammation", since 2016

(1 scientist, 1 PhD student)

This small group investigates interactions of microbiota and the immune system in the development of chronic rheumatic diseases. The head of the group has been at DRFZ since

2009. Prior to establishing his own group, he was involved in some very high-ranking publications produced by a group that has since been wound up due to retirement. The new group should, however, now develop its own scientific profile which should also mean that the members of the group feature more often as first or last authors in publications. Cooperation with the "Developmental and Mucosal Immunology" liaison group, for example, that was set up in 2017, could generate interesting ideas. It is very pleasing that, since 2018, the group has been involved in a DFG Collaborative Research Centre through which it has acquired the first third-party funding of its own.

The group is rated as "good to very good".

Research Group "Lymphocyte Development", since 2017

(3 scientists)

This newly-established group is headed by an extremely eminent senior scientist who was previously employed by the Max Planck Institute for Infection Biology. The aim of the group is to identify genetic controls of physiological immune reactions and of pathophysiological functions in autoimmunity. Some interesting results have already been published. No third-party funding has been raised so far, but the group is involved in a project starting in 2019 that was acquired through the Leibniz Competition.

The group is rated as "good to very good".

Research Group "Systems Biology of Inflammation", since 2018

(1 scientist)

This new, still small group started in January 2018. Through the Leibniz Competition, (funding line: Best Minds), DRFZ raised third-party funds to recruit the group leader and establish this group at the institute (funding: 2018-2020). The group fits excellently into DRFZ's overall strategy. As a theoretical biophysicist, the group leader aims to develop and apply advanced mathematical modelling and data analysis techniques to understand cell-cell interactions and to guide experimentation at DRFZ. The expected results would not only be of extreme importance to rheumatology research.

The group is rated as "very good".

Liaison Groups

Liaison Research Group "Autoimmunology", since 1997

(8 scientists, 3 PhD students, 3 MD students, 1 technical assistant)

This large group has been working for many years on the therapeutic targeting of pathogenic memory plasma cells. The group is important to DRFZ because it translates fundamental research findings, also from other groups, into experimental clinical trials for the treatment of patients with chronic inflammatory diseases. Given the forthcoming retirement of the head of the group, it has continued to pursue the approaches it was using at the time of the last evaluation and has not embarked on any fundamentally new research work. In a study of patients with SLE, the effectiveness of the proteasome inhibitor bortezomib was demonstrated. Building on this, the group developed a new

approach which is now supposed to be tested on autoimmune mouse models. It is, however, difficult to assess whether and how this approach could be translated into clinical practice.

The group is rated as "good to very good".

Liaison Research Group "Glucocorticoids and Bioenergetics", since 2004

(4 scientists, 4 PhD students, 5 MD students, 2 technical assistants)

This group works very successfully on how immune cells adapt to hostile conditions of inflammation, i.e. the low oxygen concentrations (hypoxia) and the lack of nutrients. It is impressive the way the group manages to interlace very good fundamental research and results with outstanding clinical applications. Its publication record is very good both with regard to clinical and also pre-clinical results, and its third-party income is high. Internationally, it is one of the most recognised groups at DRFZ.

The group is rated as "very good to excellent".

Liaison Research Group "B cell Memory", since 2004

(3 scientists, 3 PhD students, 4 MD students)

This group conducts successful research on the basic principles of the induction and maintenance of human memory B cells and plasma cells. In recent years, it has continuously produced new findings which form the basis for developing therapeutic ways to overcome the post-activated B cell status in autoimmune inflammatory diseases. Just like the previous group, it manages extraordinarily well to connect its fundamental research with clinical applications. Its publication record is very good and its third-party income remarkably high. Internationally, it is one of the leading groups in its field. Furthermore, given its thematic focus, it is of major importance to DRFZ's future development.

The group is rated as "very good to excellent".

Liaison Research Group "Allergology", since 2004

(7 scientists, 5 PhD students, 4 MD students)

This group links the Charité Center for Internal Medicine and Dermatology with DRFZ. It investigates antibody class switching, expression of regulatory cytokines and the effects of vitamins A and D on B cells. The research topic is very interesting but at present does not demonstrate a direct link to rheumatology issues. The group produces convincing research results in its field that are reflected in a good publication record overall and high third-party income.

The group is rated as "good to very good".

Liaison Research Group "Immunodynamics", since 2008

(5 scientists, 3 PhD students, 2 MD students, 2 technical assistants)

With multi-epitope ligand cartography (MELC) this group has developed a unique tool for the multiparametric analysis of cells. In combination with cutting-edge intravital-microscopy in the living tissue of viable animals, the group is able to define cell-cell interactions histologically in the bone marrow, the gut and in inflamed tissue. The group is a world leader in research on how plasma cells survive in tissue niches. Its excellent findings have been appropriately published. The results contribute significantly to a better understanding of immune reactions inducing and maintaining chronic rheumatic inflammation "in context". In the field of technology development, the group cooperates very closely with the "Biophysical Analytics" group (see below). Both group leaders also head DRFZ's Core Facility for Advanced Microscopy.

The group is rated as "excellent".

Liaison Research Group "Innate Immunity", since 2009

(2 scientists, 4 PhD students, 1 technical assistant)

This group has made excellent, crucial contributions to the study of innate sensors and signals driving the activation and differentiation of innate lymphoid cells. The head of the group was a DRFZ group leader until 2017 and now holds a Heisenberg Professorship. Her group continues as a liaison group with Charité. The group's results are outstanding in every respect and enjoy an international reputation. This is evidenced by the fact that the extremely successful head of the group is highly sought-after by other distinguished research institutions.

The group is rated as "excellent".

Liaison Research Group "Chronic Immune Reactions", since 2009

(1 scientist, 4 PhD students, 1 MD student)

This group does successful research on the important field of T follicular helper cells and their interaction with B lymphocytes. On the basis of very good research, a clinical study on the treatment of Sjögren's syndrome is currently being conducted. The convincing results are highly relevant, and the group fits very well into DRFZ's overall strategy.

The group is rated as "very good".

Liaison Research Group "Biophysical Analytics", since 2010

(2 scientists, 2 PhD students, 1 MD students, 1 technical assistant)

This group has developed innovative hard- and software tools for intravital multiphoton microscopy. By combining this unprecedented technology with clinical application tools, mouse model findings can be transferred to clinical practice in a unique way. These excellent results are reflected in appropriate publications and high third-party income. The group cooperates closely with other DRFZ groups, especially the "Immunodynamics" group (see above), in the framework of the Core Facility for Advanced Microscopy.

The group is rated as “excellent”.

Liaison Research Group “Developmental and Mucosal Immunology”, since 2017

(5 scientists, 6 PhD students, 1 technical assistant)

The excellent work of this group is based on the group leader’s earlier results on innate lymphocytes and their precursors at Johannes Gutenberg University Mainz, which were achieved with the support of an ERC Starting Grant for the period 2013 to 2018. The new group very successfully works on a molecular understanding of how components of the innate immune system promote tissue homeostasis and how microbiota control inflammatory processes. The overall publication record is excellent and third-party income is high. The group constitutes the core of DRFZ’s research on the relationship between microbiota and inflammatory diseases. It manages to combine excellent fundamental research with innovative clinical applications.

The group is rated as “excellent”.

Liaison Research Group “Immuno-Epigenetics”, since 2017

(1 scientist, 1 PhD student, 2 MD students)

This group successfully explores options to change the epigenetic structure of the genome as a novel therapeutic strategy for inflammatory rheumatic diseases. The group leader has been a member of the DRFZ “Experimental Rheumatology” group since 2012. In 2017, she accepted a position as a junior research group leader at the Berlin-Brandenburg Center for Regenerative Therapies (BCRT) and, since then, has continued her excellent research at DRFZ as a liaison group leader. Shortly after being set up, the group already raised impressive third-party funding. Apart from DFG and Leibniz Association funding, the group leader managed to acquire an ERC Starting Grant in 2018. Furthermore, initial results have already been published very well. The group should tackle the issue of how their innovative procedures could be translated into clinical practice at an early stage.

The group is rated as “very good to excellent”.

Liaison Research Group “Macrophages in Chronic Inflammation”, since 2017

(1 scientist, 1 technical assistant)

Until 2017, the head of this group conducted extremely successful research on the role of DNA damage and macrophages in granuloma formation and in autoimmune inflammation at Freiburg University Medical Center. This newly-established group continues to analyse these aspects in chronic inflammatory rheumatic diseases, also embracing aspects of pathogenic “imprinting” or “training” of macrophages, innate lymphocytes and their precursors. As a certified rheumatologist, the group leader runs a lupus clinic for outpatients at Charité, thus ensuring a direct connection to clinical practice. Research results are excellent and of major importance to the personalised therapy of rheumatic diseases. The group is very successful at raising third-party funding. In addition to DFG funding, the group leader acquired an ERC Starting Grant in 2018.

The group is rated as “very good to excellent”.

Research Group "Inflammatory Mechanisms", since 2017

(1 scientist, 1 PhD student)

This group very successfully investigates the dialogue between microbiota and the immune system in the intestinal mucosa in both health and disease. The work builds on the group leader's excellent previous research at the University of Oxford. Research results are very impressive and have been published in high-ranking journals. Third-party income is high. In 2018, the group leader was awarded a Lichtenberg Professorship funded by the Volkswagen Foundation. Moreover, the group is involved in a DFG-funded Collaborative Research Centre.

The group is rated as "very good to excellent".

Programme Area "Epidemiology of Rheumatic Diseases"

Research Groups

Research Group "Health Services Research and Early Cohorts", since 1991

(5 scientists, 4 data managers/programmers/assistant students)

This extremely successful group provides the rheumatology community with important information on the development and adequacy of health care for patients with RMDs in Germany. The results are fed into the work of the German Society for Rheumatology (DGRh), the Arthritis Centres, the German League Against Rheumatism as well as individual rheumatology sites which use the data for quality assessment. The most important basis for this work is the National Database of the German Collaborative Arthritis Centres (NDB) which has been in operation since 1993. In this extremely important annual study, physician- and patient-reported data from approx. 17,000 individuals treated by rheumatologists are systematically collected and analysed. Alongside other cohort studies, the group has also conducted very convincing work on the analysis of claims data. Furthermore, in response to a recommendation issued at the last evaluation, health economy was recently introduced, as well. The group's research results are excellent in every respect. Internationally, it is one of the most recognised groups at DRFZ. Its publication record is excellent and third-party income is very high.

The group is rated as "excellent".

Research Group "Health Services Research and Paediatric Rheumatology", since 2009

(7 scientists, 2 PhD students, 9 MD students, 6 data managers/programmers/assistant students)

This group very successfully analyses the health care situation of children, adolescents and young adults with inflammatory rheumatic diseases. Special attention is paid to juvenile idiopathic arthritis (JIA). The group's extremely convincing research is based on three important, large, nationwide cohort studies: i) the national database of children and adolescents with rheumatic diseases, which records more than 14,000 cases, ii) the BMBF-funded inception cohort study of newly diagnosed patients with JIA (ICON), involving the long-term observation of 950 patients and approx. 500 healthy peers, and iii) the biologics register for young adults with JIA (JuMBO) that currently has more than 1,400

participants. Since the last evaluation, the group has managed to improve its performance significantly. It is now very successful at exploiting the potential of these outstanding databases for research projects, which is reflected in appropriate publications. Third-party income is also very high.

The group is rated as "very good to excellent".

DRFZ Research Group "Pharmacoepidemiology", since 2010

(7 scientists, 1 MD student, 13 data managers/programmers/assistant students)

This group carries out extremely important research on the safety and effectiveness of new therapies after licensing. It has developed excellent long-term cohort studies as the basis for its work. The biologics register RABBIT is of major importance. Over a period of five to ten years since 2001, it has regularly enrolled more than 17,000 patients with rheumatoid arthritis at 300 institutions in the whole of Germany. RABBIT is one of the world's largest biologics registers and cooperates closely with other European registers. Based on its data, the group conducts excellent research, which provides clinicians with reliable data on the risks of specific treatments in different groups of patients. By introducing the pregnancy register, Rhekiss, in 2015, research was convincingly extended to study the course of pregnancy in all inflammatory rheumatic diseases. The web-based disease register, RABBIT-SpA that was started in 2017 and observes patients receiving new therapies for axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA), is also a convincing addition to existing work. The group's performance is excellent in every respect and has been very well received internationally.

The group is rated as "excellent".

Liaison Group

Liaison Research Group "Spondyloarthritides", since 2016

(8 scientists, 3 MD students, 5 technical assistants)

When the very successful head of this group retired in 2016, this liaison group, which had existed at DRFZ for many years, was transferred under new leadership from the "Pathophysiology of Rheumatic Inflammation" programme area to the "Epidemiology of Rheumatic Diseases" programme area, and now continues its work there. This is meaningful because, in addition to basic research work on mechanisms of inflammation and bone formation in spondyloarthritis (SpA), it focuses in particular on the epidemiology of SpA. Launched in 2000, the basis for its work is the GESPIC cohort, which observes more than 700 patients with early axial spondyloarthritis. It is welcomed that the group is also continuing the work conducted by a second group, which was wound up due to retirement, relating to clinical trials, thus implementing a recommendation made at the last evaluation. In addition, the group should now, however, propose more of its own topics and, through them, achieve greater visibility.

The group is rated as "good to very good".

Programme Area "Regenerative Rheumatology"

Research Group

DRFZ Research Group "Therapeutic Gene Regulation", since 2016

(4 scientists, 1 PhD student)

The leader of this group became a scientist in the DRFZ "Cell Biology" group in 2007 and successfully worked on small non-coding RNAs and therapeutic oligonucleotides. He is also one of the heads of the "Regine-von-Ramin Laboratory for Molecular Rheumatology" (see below). The new group that was established in 2016 is supported until 2019 by the European Regional Development Fund Operational Programme. It pursues two goals: i) Based on the group leader's earlier activities, it works on pathogenic lymphocytes in patients with inflammatory rheumatic diseases in cooperation with the "Cell Biology" group. It has already produced some very good results in this area. ii) In cooperation with the "Pitzer Laboratory of Osteoarthritis Research" (see below), research is conducted on hypertrophic chondrocytes in patients with osteoarthritis; so far, however, no notable results have been published in this field. Moreover, there is no direct connection between these activities and the work on cartilage tissue regeneration envisaged in the programme area.

The group is rated as "good to very good".

Liaison Group

Liaison Group "Pitzer Laboratory of Osteoarthritis Research", since 2015

(5 scientists, 8 PhD students, 5 technical assistants)

Until 2015, the eminent, experienced leader of this group headed DRFZ's long-term research group on "Experimental Immunology" in the "Pathophysiology of Rheumatic Inflammation" programme area, conducting extremely successful research on T cell immunology. The new group now set up under his leadership will initially be financed for five years by the Willy Robert Pitzer Foundation. The group's cogent idea is now to apply their expertise in T cell populations and their programmability to chondrocytes. Their aim is to re-programme the cells that cause arthritis so that they sustainably build regenerated cartilage. In order to achieve this highly ambitious goal, the group should complement its own existing expertise on T cells with expertise on osteoarthritis. So far, the group's publication record and third-party income have not reached the levels achieved by the group leader's previous group.

The group is rated as "good to very good".

Technology Platform and Shared Resource Laboratories (SRL)

DRFZ operates the "Immune Monitoring" technology platform and, in collaboration with Charité and other partners, the four Shared Resource Laboratories (SRL): "Mass Cytometry Core Facility", "Flow Cytometry Core Facility", "Regine-von-Ramin Laboratory for Molecular Rheumatology" and the "Core Facility for Innovative Imaging and Microscopy Approaches". These five units furnish all the groups at DRFZ with important, innovative technologies. Many of the units are headed by DRFZ group leaders and are

closely integrated in the respective groups. The units do not pursue their own recognisable research strategy but do contribute to the groups' publications.

4. Collaboration and networking

Collaboration with Charité – Universitätsmedizin Berlin

Cooperation with Charité – the joint medical faculty of both Humboldt Universität zu Berlin (HU Berlin) and Freie Universität Berlin (FU Berlin) – is exceptionally intensive and perfectly facilitates the dovetailing of fundamental research and clinical applications. Seven DRFZ group leaders hold jointly-appointed professorships at Charité. Furthermore, a total of 11 liaison groups, which are co-financed to varying degrees by Charité and DRFZ, work at DRFZ. Six liaison group leaders hold professorships at Charité (but are not jointly appointed). In addition, four Shared Resource Laboratories (see Chapter 3) are operated jointly.

DRFZ and Charité cooperate with other partners in numerous third-party funded alliances, including several DFG-funded projects. Moreover, it is very much welcomed that, in 2016, the Leibniz ScienceCampus "Chronic Inflammation" was established together with Charité and the Max Planck Institute for Infection Biology (€1.2 m for initial funding period until 2020). The concept of the campus is to conduct a comparative analysis of inflammatory rheumatic diseases, chronic inflammatory diseases of the gastrointestinal system, the skin, and neuroinflammation. A coordinating, central W3 Professorship in "Immunology of Inflammation" has been instituted. The campus also includes measures for promoting junior researchers (see Chapter 5).

Collaboration with other national universities and institutions

Apart from HU Berlin and FU Berlin, collaboration in the region also involves Technische Universität Berlin (TU Berlin), the Beuth Hochschule für Technik Berlin and the University of Potsdam. One DRFZ scientist holds a joint professorship at FU Berlin and one scientist holds an extraordinary professorship at the University of Potsdam. DRFZ is also linked to the Robert Koch Institute (RKI) by the "Chronic Immune Reactions" liaison group.

Within the Leibniz Association, DRFZ is involved in the two Leibniz Research Alliances, "Bioactive Compounds and Biotechnology" and "Healthy Ageing". DRFZ also initiated the Leibniz Research Network "Immune-mediated diseases". It cooperates, furthermore, with partners from the biotech and pharma industries as well as with private foundations.

International collaborations and networks

At international level, DRFZ is also very well connected. The institute is involved in international collaborative projects and networks funded by the European Commission or the European Research Council. It is part of several of the European Union's Innovative Medicines Initiatives (IMI) consortia, focusing on rheumatic diseases.

DRFZ scientists are active in scientific societies, including the German Societies for Rheumatology, Immunology and Cytometry, the Society for Paediatric Rheumatology, the

European League against Rheumatism, the International Society for the Advancement of Cytometry and the European Federation of Immunological Societies.

All in all, DRFZ cooperates with various national and international partners, largely in the context of the multiple third-party funded collaborative projects in which it is involved. DRFZ should aim to initiate and lead more supra-regional alliances itself.

5. Staff development and promotion of junior researchers

Staff development and personnel structure

DRFZ's personnel structure is appropriate to fulfil its mission. On 31 December 2017, DRFZ employed 212 staff, including 57 scientists, 33 PhD graduate students, 9 MD graduate students and 32 service positions (mostly laboratory technicians). Another 95 scientists and graduate students work at DRFZ in the liaison groups and are financed by Charité or other partner institutions. All members of staff are offered suitable opportunities to enhance their professional qualifications at DRFZ.

The strategy for appointing and, if appropriate, tenuring group leader positions is coherent. Positions are always advertised internationally and initially filled for five years. The Board of Trustees decides whether they should become permanent. **DRFZ should,** however, **strive to appoint more external scientists to leadership positions at the institute. Many of the groups established in recent years are headed by individuals who were already employed at DRFZ. It is important to achieve a higher degree of changes. This stimulates the scientific independency of junior researchers and leads to a higher diversity of approaches, fostering innovative ideas.**

DRFZ should also aim to ensure that more junior scientists subsequently find external positions. Since 2011, 14 of DRFZ's junior scientists have assumed leading academic positions, three of them outside of Berlin and one at Charité. Ten scientists continued to work at DRFZ, two of whom had previously turned down external offers.

Currently, two groups in the "Pathophysiology of Rheumatic Inflammation" programme area are headed by senior scientists. In this way, DRFZ enables distinguished scientists to continue working after official retirement age, thus retaining unique expertise at the institute. **DRFZ should,** however, **define the duties of senior scientists at DRFZ more clearly, particularly with regard to mentoring junior researchers, e. g. with a specified mentoring programme.**

Promotion of gender equality

At 54 percent, the proportion of female scientists is, in general, pleasingly high. Particularly at the level of junior researchers, the percentage of women is high. Of the 18 postdocs employed at DRFZ, ten are female (56%), and of the 33 graduate students, 21 are female (64%). **At the level of group leaders, however, DRFZ should strive to increase the proportion of female scientists. Of the 12 DRFZ group leaders, four are female (33%); of the 14 liaison group leaders, six are female (43%).**

With regard to the reconciliation of family life and work, DRFZ offers various measures, such as flexible working hours and virtual desktops for home office working options. In 2016, DRFZ received the Total E-Quality award for the third time.

Promotion of junior researchers

In general, the promotion of junior researchers is excellent. DRFZ trains a large number of PhD and MD students. On 31 December 2017, 68 PhD graduate students and 36 MD students were employed at DRFZ, financed either by core funding, the institute's third-party funding, the external funds of liaison group partners or stipends. Between 2015 and 2017, 48 graduate students acquired a PhD or equivalent and 14 graduate students an MD. The average time spent completing a PhD (MD) is 4.2 (3.5) years. Even though theses durations are common in the fields covered by DRFZ, it would be welcomed, if DRFZ could shorten these periods somewhat.

PhD und MD students are mentored in many differently-structured programmes. In accordance with a recommendation issued at the previous evaluation, DRFZ has established its own graduate programmes. Between 2014 and 2017, it set up the Leibniz Graduate School of Rheumatology, financed through the Leibniz Competition. In 2017, it launched the Leibniz Graduate School on Chronic Inflammation, financed through the Leibniz Science Campus (see Chapter 4). Both schools are organised under the umbrella of the "Interdisciplinary Center of Infection Biology and Immunity" (ZIBI), a Graduate School Berlin operated by HU and FU Berlin. Junior researchers from DRFZ are also integrated in various graduate programmes run by the local universities or in third-party financed networks like the Integrated Research Training Group run by the DFG-funded Collaborative Research Centre, "B cells and beyond". Various programmes offer a raft of further training measures. DRFZ should bear in mind that all PhD and MD students should be sufficiently informed about the opportunities to acquire qualifications at the beginning of their employment, irrespective of which group they work in.

Postdocs also benefit from appropriate opportunities to expand their qualifications. As of 31 December 2017, 32 postdocs were employed at DRFZ, financed either by core funding, the institute's third-party funding, the external funds of liaison group partners or stipends. It is welcomed that, since the introduction of the Post Doc College in 2017, a structured programme has been established to promote and mentor postdocs. It is financed as part of the Leibniz ScienceCampus "Chronic Inflammation" (see Chapter 5) and is open to all postdocs working at DRFZ. Since 2011, ten scientists at the institute have completed their habilitations.

Vocational training for non-academic staff

It is welcomed that DRFZ offers two training positions for animal caretakers. Three trainees have successfully completed the training in recent years; all of them now hold positions at DRFZ.

6. Quality assurance

Internal quality management

DRFZ is efficiently managed by the Scientific Director, the Deputy to the Scientific Director and the Administrative Director. Financial control is based on the programme budget, employing cost and performance accounting.

The basic budget for each DRFZ group usually comprises the group leader's position, a position for a graduate student, consumables and travel expenses for each of them. Additional funding has to be raised through third-party applications. Against this backdrop, it is logical that DRFZ does not award performance-based funds

DRFZ operates an appropriate system of internal quality assurance. The institute implements the Leibniz Association's recommendations on safeguarding good scientific practice and has an ombudsperson. Moreover, a data safety concept has been established. Lab managers ensure the quality of experimental logistics. DRFZ has implemented several measures to ensure animal welfare. All experimentation involving the use of animals has to be approved by the *Landesamt for Gesundheit und Soziales (LaGeSo)*. All experimentation involving human material is based on consent and approved by Charité's Ethics Committee.

Quality management by the Scientific Advisory Board

The Scientific Advisory Board constructively supports the institute. It meets once a year. In 2015, it presented the audit report which all Leibniz institutes are expected to produce between evaluations. In accordance with the guidelines on the "Organisation and Duties of Scientific Advisory Boards at Leibniz Institutes", the next audit report should contain assessments of the individual groups at DRFZ.

Implementation of recommendations from the last external evaluation

In the following, reference is made to the recommendations issued by the Senate of the Leibniz Association at the last evaluation (highlighted here in *italics*, see also Statement of the Senate of the Leibniz Association of 18 July 2012):

1. The concept of Liaison groups works excellent, as can be seen in the manifold joint projects and publications. The concept should be further expanded, as intended by the institute.

DRFZ has increased the number of liaison groups appropriately from 10 in 2011 to 14 in 2018.

2. Biobank materials should be systematically preserved for all study cohorts of programme area Epidemiology in the future.

As far as possible, DRFZ has taken appropriate account of this.

3. The programme area Epidemiology needs to be stabilised with institutional funding, as the proportion of third-party funding in programme area Epidemiology with more than 90 % is too high. Although this high rate reflects a high level of performance, it also means that important long-term tasks are currently being financed with third-party funds for a

limited period of time. The planned consolidation of two leading positions in programme area Epidemiology, which are currently being financed by third-party funds, is highly appreciated. It is also necessary to secure long-term financing for on-going tasks in the areas of cohort maintenance, statistics, biometric counselling and study design as well as in cell sorting and cytometry. These measures will also help to facilitate a systematic and long-term interlinking of the content of programme areas Pathophysiology of Rheumatic Diseases and Epidemiology. The stabilisation of the core funding should also make it possible to focus the portfolio of external funding under programme area Epidemiology more strongly on competitively allocated external funding for research funding.

DRFZ has increased financial provisions in both the "Pathophysiology of Rheumatic Inflammation" programme area and the "Epidemiology of Rheumatic Diseases" programme area. The third-party funding portfolio in the "Epidemiology of Rheumatic Diseases" programme area is appropriate.

4. Planned programme area III ("Regenerative Rheumatology"): The focus is on degenerative – not regenerative - processes in the joint. The name should be reconsidered. However, the concept is conclusive and makes sense. The development of such a programme area is an important complementation to the research programme with great potential. The responsible persons of the DRFZ have recognized this potential, and the evaluation group appreciates the efforts for a strategic advancement of the institute in this direction.

The development of the "Regenerative Rheumatology" programme area could not be implemented as foreseen by DRFZ and supported by the Review Board at the last evaluation (see Chapter 3).

5. The allocated funding can be used in the fiscal year and beyond. Hence, the management principles should be amended by the funding provider in order to allow for more flexible implementation of the staffing plan.

New management principles have been implemented.

6. Space for offices and laboratories is insufficient. The areas used for keeping experimental animals in the immediate vicinity of the DRFZ at the Charité are not sufficient to meet the demand, and the rented area in Marienfelde - only suitable as a temporary solution anyway - cannot be maintained due to reasons, which are not the responsibility of the DRFZ. There is an urgent need for a considerable expansion of the area close to the institute for laboratory animal husbandry which can be used on the long run.

Currently, facilities are sufficient. Contrary to expectations at the last evaluation, DRFZ was able to continue leasing space in Marienfelde (see Chapter 2) for laboratory animal husbandry.

Appendix

1. Review Board

Chair (Member of the Leibniz Senate Evaluation Committee)

Ulf **Müller-Ladner**	Medical Director of Department for Rheumatology and Clinical Immunology, Campus Kerckhoff of the Justus-Liebig University Giessen, Bad Nauheim

Deputy Chair (Member of the Leibniz Senate Evaluation Committee)

Annette G. **Beck-Sickinger**	Institute for Biochemistry, University of Leipzig

Reviewers

Thomas **Brocker**	Institute for Immunology, Ludwig-Maximilians-Universität München
Oliver **Distler**	Department of Rheumatology, University Hospital Zurich
William **Dixon**	Arthritis Research UK Centre for Epidemiology, Chair in Digital Epidemiology, The University of Manchester
Eva **Herrmann**	Institute of Biostatistics and Mathematical Modeling, University Hospital Frankfurt
Hans-Gustaf **Ljunggren**	Center for Infectious Medicine, Department of Medicine, Karolinska Institutet, Stockholm
Thomas **Pap**	Institute of Musculoskeletal Medicine, University Hospital Munster
Rosalind **Ramsey-Goldman**	Northwestern University, Feinberg School of Medicine, Chicago
Thomas **Schwarz**	Hospital for Dermatology, Allergology und Venerology, University Hospital Schleswig-Holstein
Viktor **Tybulewicz**	Immune Cell Biology Laboratory and Down Syndrome Laboratory, The Francis Crick Institute, London
Karl **Wegscheider**	Institute of Medical Biometry and Epidemiology, Medical Center Hamburg-Eppendorf
Cornelia **Weyand**	Professor of Medicine – Immunology and Rheumatology, Stanford University

Representative of the Federal Government

Roland **Krüppel**	Federal Ministry of Education and Research, Bonn

Representative of the Länder *Governments (Member of the Leibniz Senate Evaluation Committee)*

Woldemar **Venohr**	Ministry of Education, Science and Culture of Mecklenburg-Vorpommern

27 February 2019

Annex C: Statement of the Institution on the Evaluation Report

German Rheumatism Research Centre, Berlin (DRFZ)

The DRFZ is pleased to learn that the quality of its research has been appreciated by the evaluation board, rating 7 out of 26 research groups as "excellent" and 6 as "very good to excellent". Likewise, the DRFZ appreciates the recommendations of the evaluation board, which will help to improve the future performance of the DRFZ. Below, the DRFZ comments on several points that may require clarification.

Structure of Liaison Research Groups: The DRFZ apologizes for the remaining confusion in understanding how these groups are organized and financed. In principle, there are two kinds of liaison groups at the DRFZ. **"Liaison groups type 1"** are genuine and tenured **research groups of the DRFZ**, which are linked to academia, (a) to interlace academia and DRFZ, (b) to generate academic reputation for the group leader, and (c) to qualify them for grant programs targeted to academic applicants. These liaison groups are mostly financed by the DRFZ, the group leader is appointed to a W2S or W3S professorship according to the "Berliner Modell" of the Leibniz Association, i.e. their position and salary as a group leader at the DRFZ is used to reimburse the academic partner. It is not a new position, but the conversion of a preexisting, tenured DRFZ position into a professorship according to the "Berliner Modell". Such appointments are the ultimate promotion for a scientist at the DRFZ. The partner, Charité, Free University, or Robert-Koch Institute, contributes limited lab space and access to infrastructure. The appointment procedure follows the rules of the academic partner, the position is publicly announced, an appointment committee is formed jointly with the academic partner, the DRFZ group leader has to compete with external candidates, is externally evaluated, and the appointment is based on consent at several academic levels, the board of trustees of the DRFZ, and finally the Senator for Science of the State of Berlin. These are the liaison groups **Hauser, Hutloff, Niesner** and **Romagnani,** three of which were rated as "excellent" by the evaluation board. In a certain sense also the groups of **Minden, Radbruch, and Zink**, two of which were rated as excellent, although those have no space at the Charité, and thus are still listed as DRFZ groups in this evaluation, following the classification of DRFZ groups by the DFG. **"Liaison groups type 2"** are **research groups of the Charité**, which are linked to the DRFZ. The group leaders are financed by the Charité, the DRFZ provides lab space and access to the infrastructure, but no further financial support. These are the liaison research groups **Buttgereit, Diefenbach, Dörner, Hegazy, Hiepe, Löhning, Poddubnyy, Polansky-Biskup, Triantafyllopoulous,** and **Worm**. Here an exception from the rule is Falk **Hiepe**, since his professorship at the Charité is financed by the DRFZ, based on a 1996 contract between Charité and DRFZ, to support the close interaction between the clinic for rheumatology (Burmester) and the DRFZ.

Scientific focus of the DRFZ: The DRFZ considers its research portfolio in the experimental area as coherent and very focused on rheumatic diseases, as postulated by the statutes of the institute, and detailed out in the submitted report of the institute. In summary, research aims at identifying, exploring and targeting the cellular players which

drive chronic rheumatic diseases. From this research, original therapeutic concepts for the treatment of rheumatic diseases have been developed at the DRFZ in the last years, targeting pathogenic plasma cells (Ann Rheum Dis. 2015, 74(7):1474-8), regulatory T cells (Ann Rheum Dis. 2015, 74(4):791-2.), advanced proinflammatory effector T cells (J Autoimmun. 2018,89:41-52), and TNF-expressing myeloid cells (Proc Natl Acad Sci USA. 2016,113(11):3006-11), as selectively as possible. Two of these have already been tested clinically and proven their value for refractory patients.

Since research at the DRFZ is financed to considerable degree by competitive grants, the DRFZ has established procedures to ensure that this research complements the research strategy of the institute and addresses rheumatic diseases.

The DRFZ had originally planned to establish the **program area "Regenerative rheumatology"**, by appointing an external new group leader and head of this program area. After extensive headhunting and a public announcement of the joint professorship with the Charité, the position was offered sequentially to two candidates, who both finally turned the offer down, after extensive negotiations. Consequently, with support of the Pitzer foundation for 5 years, a new liaison research group with the Charité has been established three years ago (see below), headed by an eminent cell biologist and immunologist, who decided to shift the focus of his work on the most prevalent rheumatic disease, **Osteoarthritis**. This group, core of a new, to be expanded, the third research area at the DRFZ, has since its **start in 2016** extremely fast established the relevant technologies to analyse in molecular detail the biology of chondrocytes in an unprecedented way. First results are prepared for publication. This research group will be externally evaluated in 2020, and continued pending the result of the evaluation, using resources of the DRFZ. A second research group was established then in this program area, to provide novel technologies for the therapeutic targeting of chondrocytes. The envisaged further expansion of this research area with two more research groups is currently stalled due to the neglected support by the Evaluation Board of the minor item of expenditure proposal of the DRFZ.

The **program area "Epidemiology"** is undisputedly exclusively working on the epidemiology of rheumatic diseases.

The **program area "Pathophysiology of rheumatic inflammation"**, comprising 8 genuine DRFZ groups and 12 liaison research groups, is focusing on the identification of cells and bacteria that cause and drive rheumatic inflammation. In particular those that confer non-responsiveness of patients to available therapies of today (refractory patients), a medical need increasingly recognized internationally in rheumatology. **The research strategy is based on the clinical observation that a "reset" of the immune system** by Autologous Stem Cell Transplantation **regenerates tolerance** in more than

70% of **refractory patients** with inflammatory rheumatic diseases, i.e. that it is imprinted cells of the immune system, driving chronic inflammation, which are "roadblocks" to the regeneration of tolerance in these patients, i.e. the induction of therapy-free remission. It is now the strategy of the DRFZ to identify, explore and target those imprinted "roadblock" cells, for a selective reset of tolerance, preserving immune protection. A hallmark of DRFZ research in this area is the discovery of memory plasma cells secreting pathogenic autoantibodies, and refractory to conventional therapies. This DRFZ concept has been successfully translated into a novel therapy, using bortezomib (Velcade) to break the refraction of patients with **Systemic Lupus Erythematosus**, a prevalent inflammatory rheumatic disease. The DRFZ research groups Dörner, Hauser, Hiepe, Radbruch and Tokoyoda continue to focus on a molecular understanding of the lifestyle of pathogenic memory plasma cells, with the aim to develop novel therapies for the selective ablation of pathogenic plasma cells, and the prevention of their regeneration. This will be relevant for ACPA-positive **Rheumatoid Arthritis**, Systemic Lupus Erythematosus, **Vasculitides** and all other rheumatic diseases with involvement of refractory pathogenic antibodies. The first-at-all therapeutic concept for the selective ablation of plasma cells according to the specificity of the antibodies they secrete, i.e. for the selective depletion of pathogenic plasma cells, has recently been developed at the DRFZ. A second key suspect for the drive of rheumatic inflammation is the Th lymphocyte, which controls immune reactions in general, and in particular chronic ones. The DRFZ research groups Baumgrass, Buttgereit, Hutloff, Löhning, Mashreghi, Polansky-Biskup, Radbruch and Tokoyoda have in the past and continue to focus on the molecular characterization of the biology of T cells possibly involved in the control of rheumatic inflammation. Molecular markers like ICOS, Twist1, MicroRNA148a, detected by those groups, have been identified originally at the DRFZ as key to understand their lifestyle, and their refraction to conventional therapy, in Th lymphocytes isolated from patients with **Rheumatoid Arthritis**, **Reactive Arthritis**, **Psoriasis Arthritis** and **Juvenile Idiopathic Arthritis**. Preliminary evidence suggest that their selective ablation may be another way to break refraction in rheumatic inflammation, and to regenerate immunological tolerance. A new, explorative research focus at the DRFZ is the interest in cells of the innate immune system as drivers of rheumatic inflammation and potential "roadblocks to induction of immunological tolerance". This interest is based on recent discoveries of innate lymphocytes as prominent tissue-resident players in the coordination of inflammation, with a memory like adaptive lymphocytes, a key discovery recently made at the DRFZ (Romagnani). Likewise, the new concept of "Trained Immunity" has demonstrated memory-like properties of myeloid cells, which at the DRFZ are investigated by the Triantafyllopoulou group, supported by an ERC grant. The recently discovered **memory of innate immune cells** (trained immunity), and their prominent role in orchestrating inflammation, predicts that in rheumatic inflammation, they will be another reason for refraction to conventional therapies, and **a roadblock for induction of immunological tolerance in inflammatory rheumatic diseases**. New therapies targeting those pathogenic cells will best be based on a detailed molecular understanding of their lifestyle. This is addressed by the research groups Diefenbach, Romagnani and Triantafyllopoulou. The fourth focus

of DRFZ research in chronic rheumatic inflammation is actually not really new. Since its beginning in 1989, the DRFZ had a strong interest in **Spondyloarthropathies**, in particular Reactive Arthritis, a disease caused by bacteria like **Chlamydia, Shigella or Yersinia**. For many years in collaboration with the first liaison research group ever with the Charité, headed by Joachim Sieper, now continued with his successor Denis Poddubnyy, DRFZ research has aimed at understanding how mucosal infection with these bacteria leads to chronic rheumatic inflammation? While this question is still not answered, the DRFZ has now put it into the larger context of how commensal bacteria of the microbiota and pathogens may act to prevent or induce rheumatic inflammation. A fundamental proof-of-concept had been the demonstration of Ivanov and collegues in 2010 (Immunity 32(6):815-27), that in a murine model of arthritis the development of arthritis is dependent on **segmented filamentous bacteria**, which instructed the host´s immune system to generate, via Th17 cells, refractory pathogenic memory plasma cells, secreting the autoantibodies causing the chronic progressive arthritis. In human patients, distinct bacteria of the microbiota, like Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans and Prevotella copri are also most likely involved in the generation of pathogenic antibodies to citrullinated peptides (ACPA) in patients with **Rheumatoid Arthritis** (discussed in detail in: Curr Opin Rheumatol. 30(4):403-409). The research groups Chang, Diefenbach, Hegazy, and Kruglov address the connectivity between chronic inflammation of the gut and the joints, with the aim to identify bacteria protective and predisposing to rheumatic inflammation in human patients, and the therapeutic vision to correct predisposing microbiota. The DRFZ here has developed the internationally unique tool of **high-resolution microbiota cytometry**, allowing to address the diversity of microbiota in an unprecedented way, and to isolate any microbiota species for analysis and therapeutic use, which so far had not been possible.

In summary, as stated in its statutes, the DRFZ performs research focused on rheumatic diseases in all its program areas, targeting identified drivers of the diseases, and exploring the potential of novel players, e.g. innate lymphocytes, and environmental cues, e.g. microbiota, in the experimental program areas. The research rationale of the DRFZ is translated into other chronic inflammatory diseases in the frame of the LeibnizScienceCampus “Chronic inflammation”, established in 2017, together with the Charité. It has become an integral part of rheumatology research strategies at the European level in the frame of European Innovative Medicine Initiatives AUTOCURE, BT-CURE, RT-CURE.

Staff development and promotion of young scientists: The DRFZ fully concurs with the notion that a well tuned balance between change and tradition is key to an innovative research environment. It is the continued ambition of the DRFZ to achieve this balance. In summary, **6 out of 8 new research groups established since 2011 reflect new recruits** (Diefenbach, Kubagawa, Melchers, Poddubbny, Thurley, Triantaphylopoulous), 2 Charité groups headed by former DRFZ scientists (Hegazy, Polansky-Biskup) became

liaison groups (type 2), and 1 DRFZ scientist (Kruglov) was promoted to leadership of an established DRFZ group (succession Nedospasov). **5 DRFZ scientists accepted offers of external professorships** (Bacher, Fillatreau, Hoyer, Riemekasten, Scheffold) and left the DRFZ. Two more are pending. Of the 11 genuine DRFZ group leaders (Baumgrass, Chang, Kruglov, Kubagawa, Melchers, Minden, Radbruch, Strangfeld, Tokoyoda, Thurley, Zink) and the 4 liaison group type 1 leaders (Hauser, Hutloff, Niesner, Romagnani), i.e. DRFZ group leaders with an academic liaison, those in whose recruitment the DRFZ had a say, **7 out of these 15 group leaders are female (47%)**, perfectly matching the proportion of female scientists at the DRFZ (54%). It should be noted that all 3 DRFZ group leaders promoted by the DRFZ to academic liaison were female.

In more detail, the assessment of the Evaluation Board (page 4, line 13ff: "Many of the groups established in recent years are headed by individuals who were already employed at DRFZ. "), that the DRFZ often had appointed internal candidates to leadership positions of newly established groups, probably refers to the conversion of genuine and tenured DRFZ research groups into **liaison research groups of type 1** (see above), i.e. promoting them and linking them to academia. This concerns the appointments of Chang (in progress), Hauser, Minden, Niesner and Romagnani, all of which **were not newly established groups**. The DRFZ apologizes for the confusion generated by a less than perfect explanation of these appointments from its side.

Apart from those five promotions, the DRFZ has only established **three new groups** since 2011, and all of these were **headed by new recruits**. Two of these are senior research groups, "Lymphocyte development" (Melchers) in 2018, and "Humoral Immunregulation" (Kubagawa) in 2015. Both senior scientists were recruited externally. Fritz Melchers has in the meantime been honoured by a Leibniz Chair by the Board of the Leibniz Association in 2018. The third new research group leader is Dr. Kevin Thurley, a new recruit from the University of Berkeley, without any former connectivity to the DRFZ. He was appointed as leader of the new research group "Systems Biology of Inflammation". His appointment in 2018 has been enabled with support of Leibniz competitive funding (SAW), funding line "Best heads". A fourth appointment of a new group leader was made in 2017, to secure continuation of the established and successful research on lymphotoxins and TNF at the DRFZ. Here, Dr. Andrey Kruglov was appointed, in a competitive procedure, following the public announcement of the position. He had qualified himself with an outstanding publication (Science 342(6163):1243-6).

Five new liason groups of type 2, i.e. genuine Charité research groups affiliated to the DRFZ, have been appointed since 2012. Of these 5 groups, 3 (Diefenbach, Poddubnyy, Triantaphylopoulous) do not have any previous connection to the DRFZ, while 2 group leaders, who had graduated at the DRFZ (Hegazy, Polansky-Biskup) had been appointed as liaison group type 2 leaders, after extensive external Postdoc periods in Oxford and at

the Leibniz institute in Borstel, respectively, and an appointment to positions at the Charité, by the Charité. Of these 5 groups, 2 have now acquired ERC starting grants (Triantaphyllopoulous, Polansky-Biskup), and one (Hegazy) has been awarded a Lichtenberg professorship, confirming the quality of these recruits.

With respect to the promotion of junior scientists of the DRFZ to external positions (page 4, line 15ff: „DRFZ should also aim to ensure that more junior scientists subsequently find external positions.“) the DRFZ considers **11 offers of external academic leadership to DRFZ scientists** (Petra Bacher: W2-professorship at the University of Kiel, Simon Fillatreau: full professorship at the University of Paris Descartes, Anja Hauser: W3 professorship at the University of Magdeburg, Bimba Hoyer: W3 professorship at the University of Kiel, Andrey Kruglov: Junior group leader at the Fritz Lippman Institute in Jena, Max Löhning: W3 professorship at the University of Greifswald, Raluca Niesner: W2 professorship at the Technical University of Braunschweig, Julia Polansky-Biskup: W2 professorship at the University of Kiel, Gabriela Riemekasten: W3 professorship at the University of Lübeck, Chiara Romagnani: W3 professorship at the University of Tübingen, Alexander Scheffold. W3 professorship at the University of Kiel) between 2012 and 2018 as quite successful and a reflection of its mentoring and quality control.

Mentoring of junior scientists by all senior scientists is occurring constantly on an informal basis, concerning project planning, problem solving, paper and grant writing, career advancement and, in case of young group leaders, interaction with graduate students and postdocs. In particular, the weekly, topic-oriented, project-accompanying, group-overarching scientific discussion clubs are central to the mentoring of young scientists at the institute.

Statement by the Board of Trustees

The Board of Trustees of the DRFZ is since the last year already heavily involved in managing the fundamental change in personnel. It has extended the appointments of the scientific director and the deputy scientific director.

In addition it has formed the "Committee for the future of the DRFZ" which has developed strategic guidelines for these important appointments (see below). For finding a successor for the deputy director (epidemiology) a search committee (Berufungs-kommission) has now been formed under the leadership of the Charité. The advertisements will be published soon.

Regarding the strategic guidelines for appointment of a new scientific DRFZ director the Board of Trustees has joined forces and coordinated with the committee "Immunofuture" at the Charité. Here the search of names for the head of Department of Rheumatology and Clinical Immunology as well as for three other chairs at the Charité has been started in a coordinated transparent fashion. Both institutions have decided to search in this context also for the successor of the scientific director DRFZ to really find the best match between the primary collaborative partners.

Within that strategy the proposed names for each of these posts will be discussed in this "Immunofuture" committee, furthermore sent to an international board and taking their advice in to then come to a selective symposium for potential candidates about in the middle of 2019. This will all happen before these positions are officially advertised to really quickly and efficiently recruit the best people for these chairs.

The Board of Trustees would appreciate very much if according to the evaluation the Leibniz Senate could vote already for the applied extraordinary items of expenditure for new groups and extension of four existing groups as of 2021, since these extraordinary items of expenditure could make both of the DRFZ positions (scientific director and deputy scientific director) really attractive since these applications were based on recommendations of the Scientific Advisory Board and the Board of Trustees of the DRFZ.