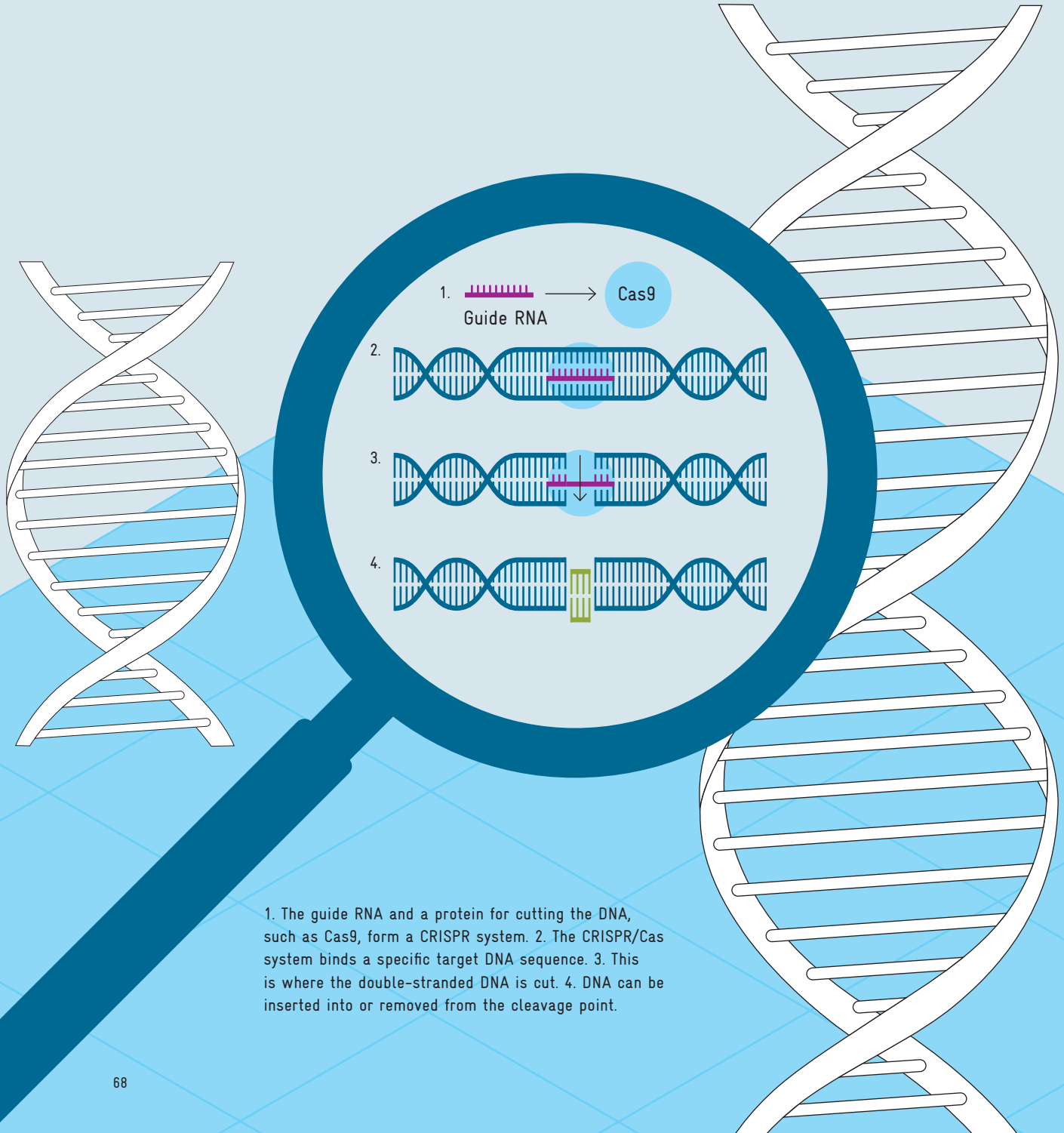
B 3 Gene Editing and CRISPR/Cas

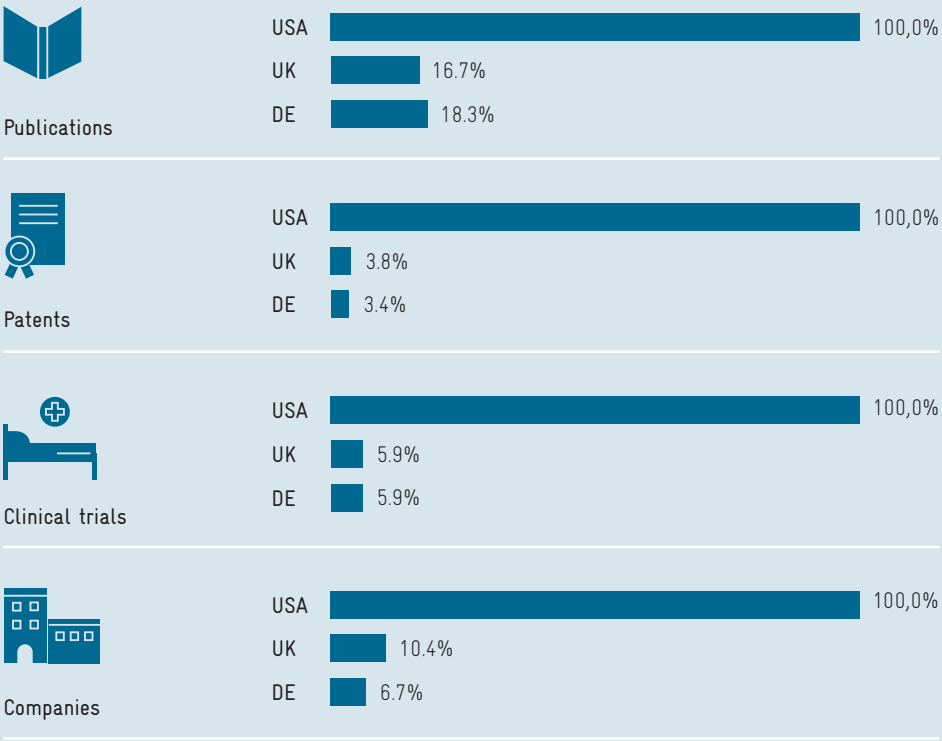
Download data

CRISPR/Cas is a gene editing tool that can be used, among other things, to find new therapeutic approaches and to decipher the causes of diseases. Experts attribute great potential to CRISPR/Cas because it simplifies gene editing and thus enormously expands the circle of researchers as well as the fields of application.

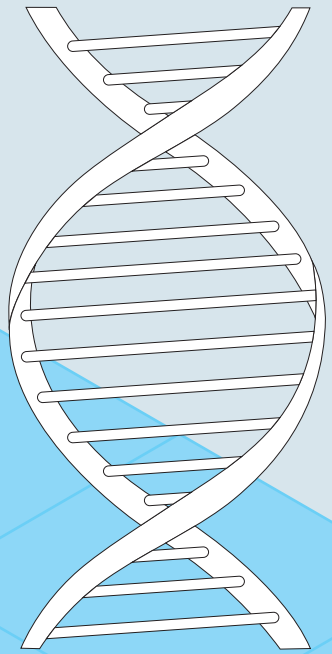


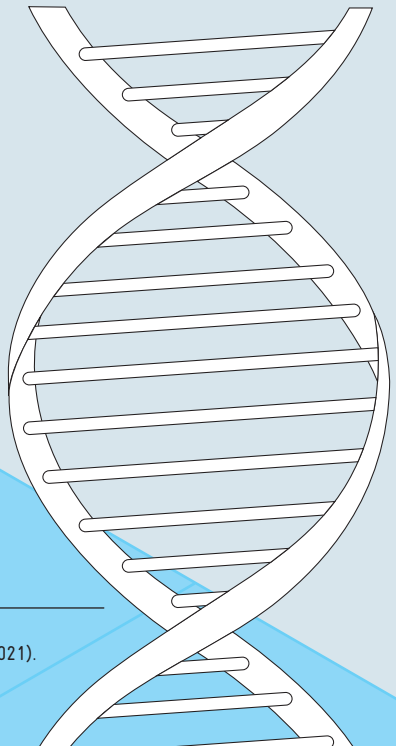
1. The guide RNA and a protein for cutting the DNA, such as Cas9, form a CRISPR system. 2. The CRISPR/Cas system binds a specific target DNA sequence. 3. This is where the double-stranded DNA is cut. 4. DNA can be inserted into or removed from the cleavage point.

CRISPR/Cas-related research and innovation activities in the fields of health and medicine as well as technical improvements in Germany and the United Kingdom relative to those in the USA 2012–2019



Germany is comparatively well positioned in CRISPR/Cas research in the fields of health and medicine as well as technical improvements. However, there is still untapped potential in Germany regarding CRISPR/Cas inventions, their use for patients and commercialization by companies.





Source: Illustration of how CRISPR/Cas works: Fröndhoff et al. (2019).
CRISPR/Cas research and development activities: Zyontz and Pomeroy-Carter (2021).

B 3 Gene Editing and CRISPR/Cas

The CRISPR/Cas gene scissors are a tool for gene editing that can be used, among other things, to find new therapeutic approaches,[232] to decipher the causes of diseases,[233] to develop genetic testing[234] and to conduct basic medical research[235] (cf. boxes B 3-1 and B 3-2).

In addition to the use of CRISPR/Cas for medical purposes (red biotechnology), CRISPR/Cas is also used in agriculture (green biotechnology) and in industrial applications (white biotechnology), for example, to produce genetically modified enzymes, cells, or microorganisms.[236] In some cases, there is enormous potential for value creation in these fields.[237] This chapter focuses on the use of CRISPR/Cas for medical purposes.

CRISPR/Cas can be used to alter, switch off and switch on genes.[238] This opens new possibilities for treating hereditary diseases. At least 3 percent of the world's population is affected by a hereditary disease caused by the error of a single gene. Correcting this faulty gene could cure the disease.[239]

Researchers attribute great potential to CRISPR/Cas because it simplifies gene editing and thus enormously expands the circle of researchers as well as the fields of application. This has in recent years

Box B 3-1

CRISPR/Cas

CRISPR/Cas was discovered as part of the adaptive bacterial immune system.[240] When this immune system detects an infection by viruses, it cuts the deoxyribonucleic acid (DNA) of the viruses to render them harmless. The excised parts of the viral DNA are then inserted into the DNA of the bacterium. Within the DNA of the bacterium, the parts of the viral DNA are located between flanking constant regions of the bacterial DNA. The alternation of repetitive flanking DNA sequences and variable DNA sequences in the DNA of bacteria was given the name CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats[241]). These CRISPR sequences in turn help the bacterium's immune system to recognize, cut and render the viral DNA harmless the next time it invades. The ability to cut DNA is used for gene editing.

To cut DNA, a CRISPR system needs two components: a guide ribonucleic acid (guide RNA) and a protein that cuts the DNA.[242] The most commonly used protein is the Cas9 protein from the scarlet fever pathogen (Streptococcus pyogenes) – spCas9. However, it can happen that the DNA is not only cut at the intended position. In this case, one speaks of so-called off-target effects. In the worst case, these can result in degeneration of the affected cell and thus the formation of a tumour.[243] Reducing off-target effects is a key subject of current research.

led to a strong increase in R&D activities related to CRISPR/Cas. Most current development work on medical applications of CRISPR/Cas is considered ethically unobjectionable.[244]

Researchers in Germany are actively involved in the further development of CRISPR/Cas. Although Germany plays a significant role in CRISPR/Cas research measured in terms of the number of publications in scientific journals, ranking third in a country comparison, it lags far behind the USA and China. In addition, weaknesses in the translation of research results into application are becoming apparent in Germany.

B 3-1 The CRISPR/Cas Gene Scissors as a New Tool for Medicine

Genetic material has a significant influence on the structure and functioning of organisms. An alteration in the genetic material can therefore result in an alteration in the structure or functioning of organisms. In humans, such alterations occur naturally through reproduction and mutation. These alterations can have positive or negative effects or can remain inconsequential. The negative effects include a variety of hereditary diseases.

One field of application for CRISPR/Cas is the cure of such hereditary diseases through the targeted modification of the genetic material. In the case of applications on humans, a distinction is made between applications in which the resulting genetic alteration is passed on (germ-line therapy,[245] cf. box B 3-13) and applications in which the change is passed on, i.e., which only affect the individual being treated (somatic-cell gene therapy).[246] CRISPR/Cas is not the first tool to be used for gene editing (cf. box B 3-2). However, it has key advantages over other gene editing tools. CRISPR/Cas is much easier to use than previous gene editing tools, while still offering high precision and effectiveness. High precision means that components of the genetic material can be cut precisely and unwanted alterations in the genetic material at other locations, so-called off-target effects, can be better addressed. In addition, it is easier to achieve high efficiency with CRISPR/Cas than with other gene editing tools. This means that it is easier to develop a suitable CRISPR/Cas tool that can successfully make the intended alteration to the genome in a large proportion of target cells. In addition, CRISPR/Cas is easier to adapt to new applications than was the case with previous gene editing tools.[247]

These advantages over earlier methods have led to CRISPR/Cas already being widely used in basic research. The principles of Open Science, too, have favoured the further dissemination of CRISPR/Cas (cf. box B 3-3). Due to its advantages over previous gene editing methods, CRISPR/Cas has the potential to contribute to new therapeutic approaches (cf. box B 3-2).

However, to make these individual and targeted new therapeutic approaches available to patients in Germany, the necessary expertise for the development and application of these treatments must be available in Germany. This requires the capacity and mechanisms to transfer research results into applications, thereby also opening new potential for value creation for companies.[248]

B 3-2 Germany's Performance Level in an International Comparison

Germany's performance in the further development and application of CRISPR/Cas can be measured by looking at various indicators. These include indicators regarding scientific publications, patent applications, number of companies and clinical trials. The following paragraphs focus on data relating to the application of CRISPR/Cas in the field of medicine and health[249] as well as data on technical improvements of CRISPR/Cas[250] that aim at the further development of CRISPR/Cas in general and are therefore not assigned to a specific field of application.

Box B 3-2

Discovery of CRISPR/Cas and Applications in Medical Research

The first targeted alterations to the existing genetic material of organisms with a cell nucleus, which includes humans, occurred in 1979 in yeasts. Later, better tools for gene editing were developed with zinc finger nucleases and so-called transcription activator-like effector nucleases (TALENs).

The fact that CRISPR/Cas9 can be used as an easily programmable tool to cut any DNA sequence was demonstrated in 2012 by a research group led by Jennifer Doudna and Emmanuelle Charpentier,[251] who received the 2020 Nobel Prize in Chemistry for their discovery. Shortly after the discovery, research groups led by Feng Zhang and George Church showed that CRISPR/Cas9 works not only in bacteria but also on animal cells, where it can cut genomic DNA.[252]

The development of CRISPR/Cas as a tool that can alter, switch off or switch on genes has made editing of genetic information present in cells accessible to a larger group of scientists. CRISPR/Cas now makes it possible for virtually any molecular biology laboratory to specifically alter genes in almost any cell. Thus, work steps that were previously impossible for most researchers became routine tasks. In addition to basic medical research, CRISPR/Cas is also used to develop new treatments for curing diseases.

Genetic diseases are often caused by the mutation of a single gene. Approximately 250 million people worldwide are affected by such a monogenic disease.[253] Examples of diseases triggered by a single faulty gene are beta-thalassaemia and sickle cell anaemia,[254] which are associated with anaemia, Leber congenital amaurosis,[255] which leads to blindness, and Huntington's disease,[256] which is associated with symptoms such as muscle atrophy and dementia and leads to premature death.[257] CRISPR/Cas-based treatments are already being tested in clinical trials for some of these diseases.

In addition to treating hereditary diseases, CRISPR/Cas can also be used to treat infectious diseases such as chronic diseases caused by the human immunodeficiency virus (HIV). The aim of the treatment is to make the cells of the immune system resistant to the pathogen by specifically inactivating certain genes.[258]

In addition, immune cell treatments against cancer are to be made more effective in the future with CRISPR/Cas by editing the immune system's cancer-fighting cells in such a way that they become resistant to the immune-inhibiting effect of the tumour cells.[259]

Good Position Regarding Number of Publications

Publications can be used as an indicator for research in the field of CRISPR/Cas. The analysis below considers scientific publications as from July 2012, the time of the landmark CRISPR/Cas publication by Doudna and Charpentier.[260] The period under consideration ends at the end of December 2019. Publications on CRISPR/Cas can be assigned to the fields of health and medicine, technical improvements, agriculture, and industrial applications.[261] Of the total of 11,552 publications recorded, 5,585 belong to the field of health and medicine, 4,719 to the field of technical improvements, 962 to the field of agriculture and 286 to the field of industrial applications.[262] The following evaluation relates to the fields of health and medicine as well as technical improvements.

The number of publications per year has risen sharply since 2012 (cf. figure B 3-4).[263] In a comparison between countries, the USA has the highest number of publications in the fields of health and medicine as well as technical improvements with 5,151 publications, followed by China (2,402), Germany (944), Japan (877) and the UK (860) (cf. figure B 3-5). With 3,003 publications in these fields, the European Union (EU) has more publications than China, but fewer than the USA. In recent years, however, China has been able to narrow the gap to

Box B 3-3

Significance of Open Science for CRISPR/Cas Research

Since the discovery of CRISPR/Cas as a gene-editing tool in 2012, over 11,000 scientific papers have been published on the subject (by December 2019) and over 4,000 patent families have been filed (by December 2018).[264]

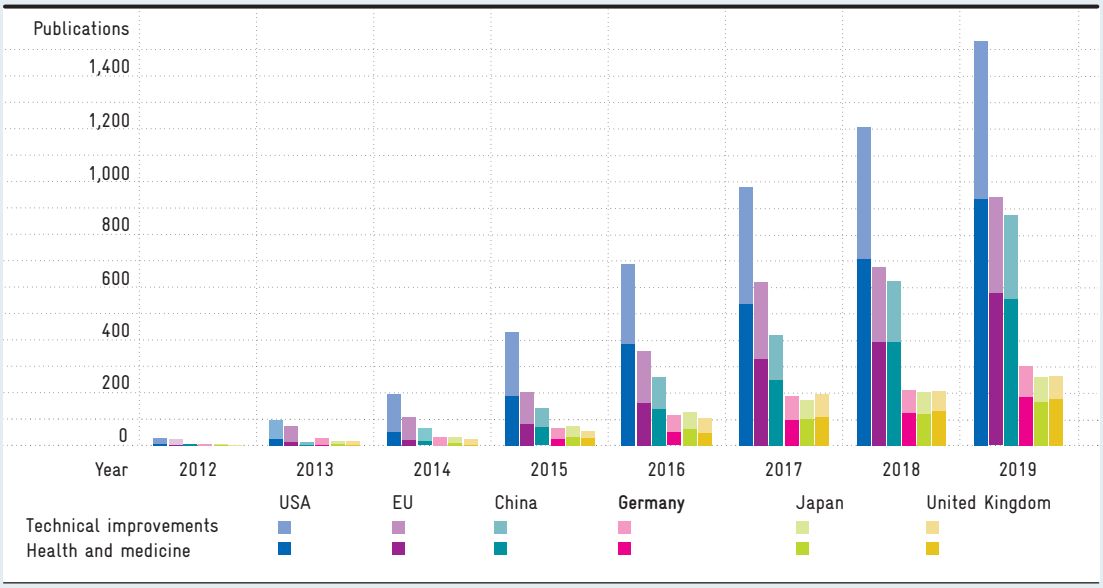
An important factor in the dissemination of CRISPR/Cas among researchers are services such as those provided by the non-profit company Addgene.[265] As a repository, Addgene collects, shares and stores plasmids (small DNA molecules) that can be used by scientists for, inter alia, CRISPR research. This allows researchers to build directly on the work of other research groups without having to duplicate their efforts. Researchers use repositories such as Addgene to deposit plasmids so that they can access their efficient, global delivery process when they request plasmids. This saves time and money. In addition, the deposit of plasmids increases the visibility of scientists, which can result in increased citations of their publications.[266]

In addition, the rapid development of research on CRISPR/Cas is also due to the fact that the Broad Institute,[267] which holds the rights to Feng Zhang's basic CRISPR patent, licenses the technology free of charge for scientific research. However, commercial use is paralyzed by an ongoing patent dispute and the uncertainties that accompany it.[268]

Fig. B 3-4

Download data

Number of CRISPR/Cas publications of selected countries and regions in the fields of health and medicine as well as technical improvements Q3 2012–2019



Source: Own representation based on Zyontz and Pomeroy-Carter (2021).

the EU. The share of publications by researchers in Germany in the fields of health and medicine and technical improvements in all publications in these fields is 9.2 percent.

Researchers in the countries and regions considered are active both in the field of health and medicine and in the field of technical improvements. In the first years of research after the discovery of CRISPR/Cas as a tool for gene editing, a large proportion of publications were about technical improvements. Over time, the share of publications in the field of health and medicine has increased in all countries and regions considered (cf. figure B 3-4).

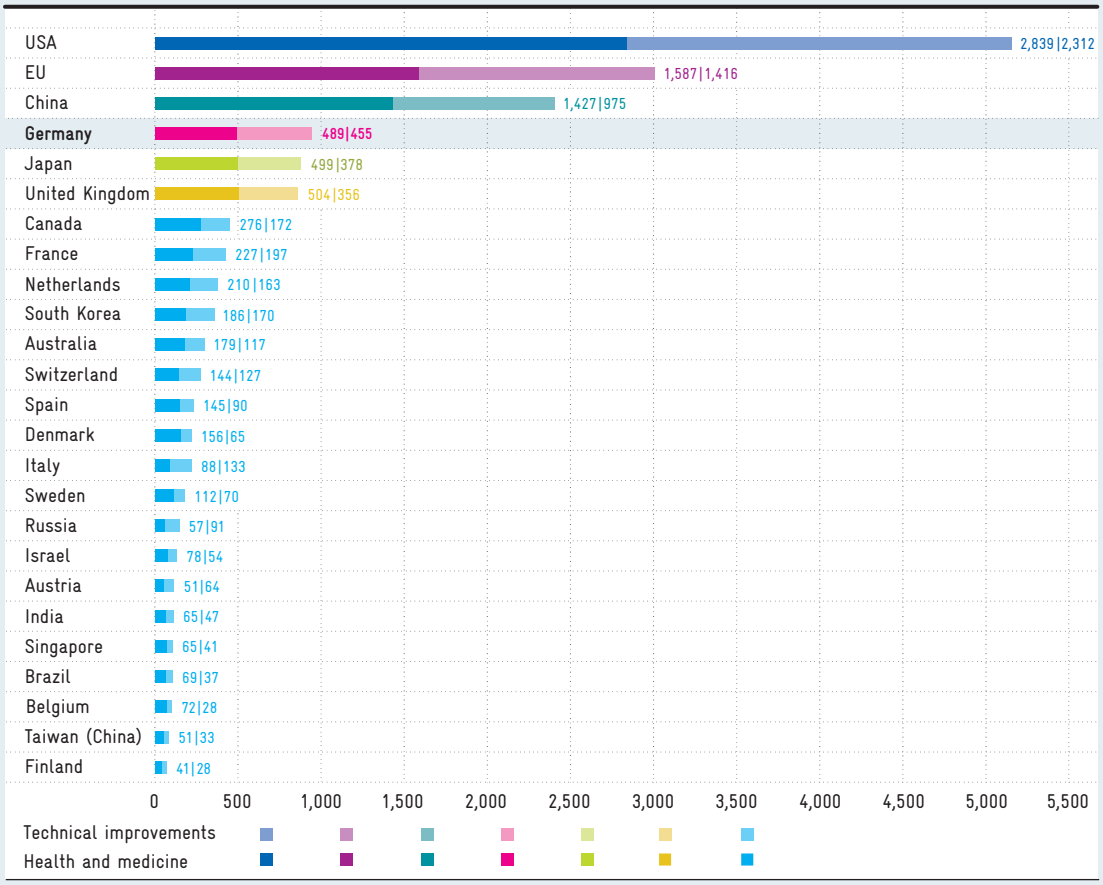
The total number of publications in highly cited scientific journals can be used as an indicator of the quality of the research work. Here, the USA ranks first with 2,283 of these top-class publications, followed by China (587), the UK (377), Germany (369)[269] and Japan (219). The EU accounts for 1,146 top-class publications.

Looking at the percentage of publications by researchers at German institutions published in highly cited journals (cf. figure B 3-6),[270] Germany, with 39.1 percent of publications, is only in the crowded midfield and just above the EU average of 38.2 percent. Switzerland, Austria, and the Netherlands have the largest percentages of publications in highly cited journals. It moreover becomes apparent that despite the large number of Chinese publications, only a relatively small proportion (24.4 percent) appear in high-ranking journals. Researchers in Japan, too, publish comparatively little in highly cited journals, at 25.0 percent of publications.

Fig. B 3-5

Download data

Number of CRISPR/Cas publications by top 25 countries and regions in the fields of health and medicine as well as technical improvements Q3 2012–2019

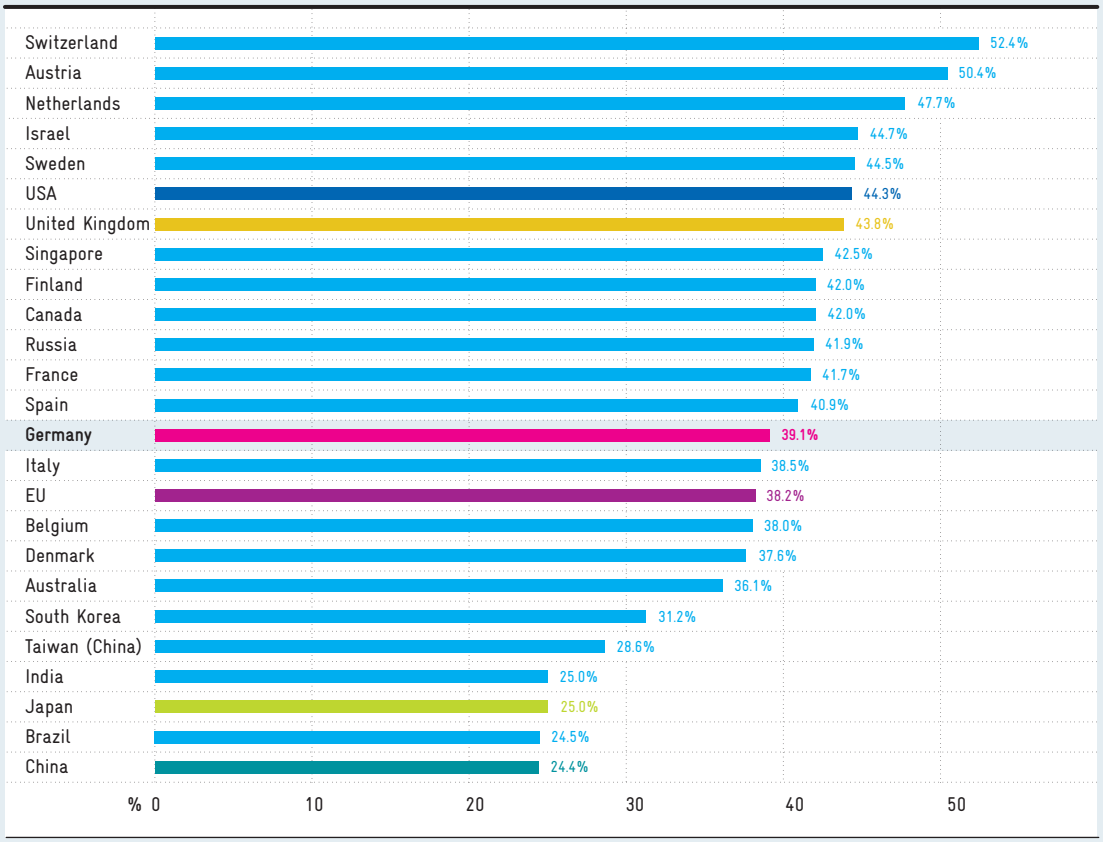


Source: Own representation based on Zyontz and Pomeroy-Carter (2021).

Fig. B 3-6

Download data

Share of CRISPR/Cas publications by top 25 countries and regions in the fields of health and medicine as well as technical improvements in highly cited scientific journals Q3 2012–2019



The publications from the fields of health and medicine as well as technical improvements are summarized in this representation.
Source: Own representation based on Zyontz and Pomeroy-Carter (2021).

Patent Backlog

By the end of 2018, patents had been filed in a total of 3,652 CRISPR/Cas patent families.[271] Of these, 1,192 patent families were in the field of health and medicine, 1,800 in the field of technical improvements, 536 in the field of agriculture, and 124 in the field of industrial applications. Some of these patent families are assigned to a year prior to 2012, the year of the first publication on CRISPR/Cas as a gene editing tool. These are patents that have been applied for before the first scientific publication to obtain patent protection. In addition, patent families are assigned to the earliest year of the patents they contain. This may result in CRISPR/Cas patent families being assigned to a year prior to 2012, as important preliminary work was patented at that time.

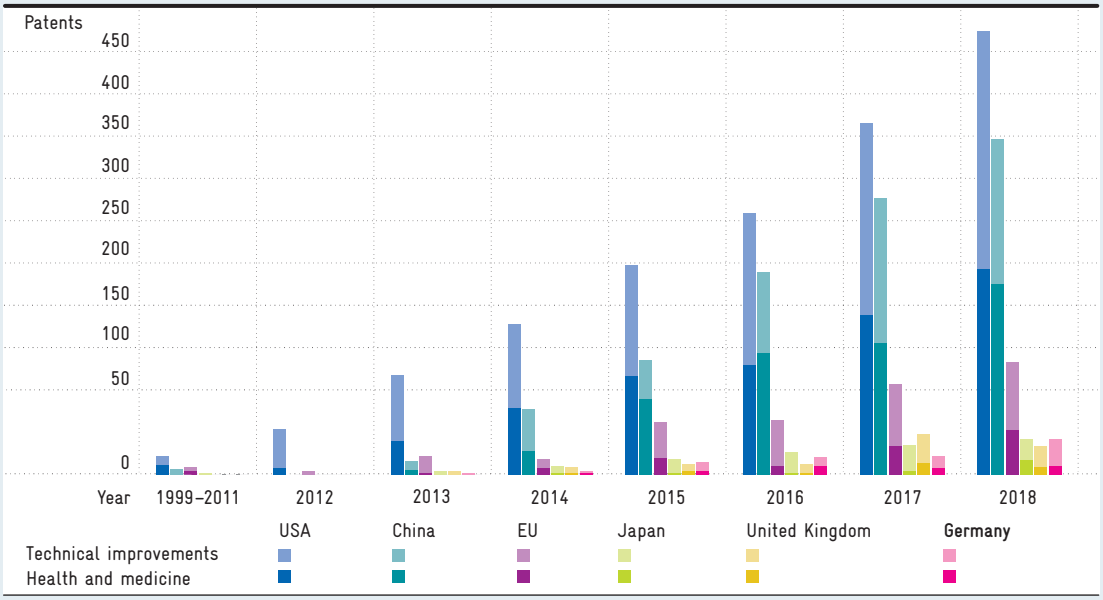
The number of CRISPR/Cas patent families in the fields of health and medicine as well as technical improvements has increased sharply after 2012 in the countries and regions considered (cf. figure B 3-7).[272] The percentage relating to technical improvements is significantly higher than that relating to the field of health and medicine. In comparison to CRISPR/Cas publications, however, the EU falls far behind the USA and China when it comes to CRISPR/Cas patent families.

Germany occupies a significantly weaker position regarding CRISPR/Cas patent families than regarding CRISPR/Cas publications. While researchers in Germany account for 9.2 percent of all publications in the fields of health and medicine as well as technical improvements, the share of patent families by inventors in Germany in the

Fig. B 3-7

Download data

Number of CRISPR/Cas patent families of selected countries and regions in the fields of health and medicine as well as technical improvements 1999–2018

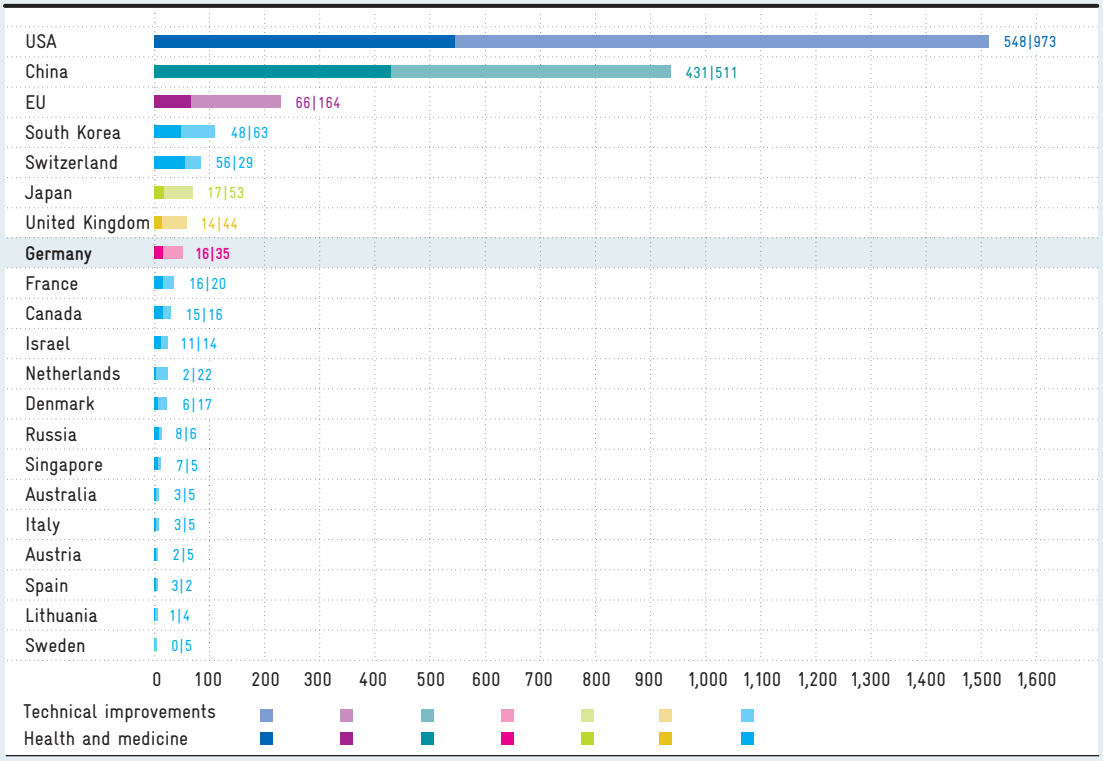


Source: Own representation based on Zyontz and Pomeroy-Carter (2021).

Fig. B 3-8

Download data

Number of CRISPR/Cas patent families by top 20 countries and EU in the fields of health and medicine as well as technical improvements 1999–2018

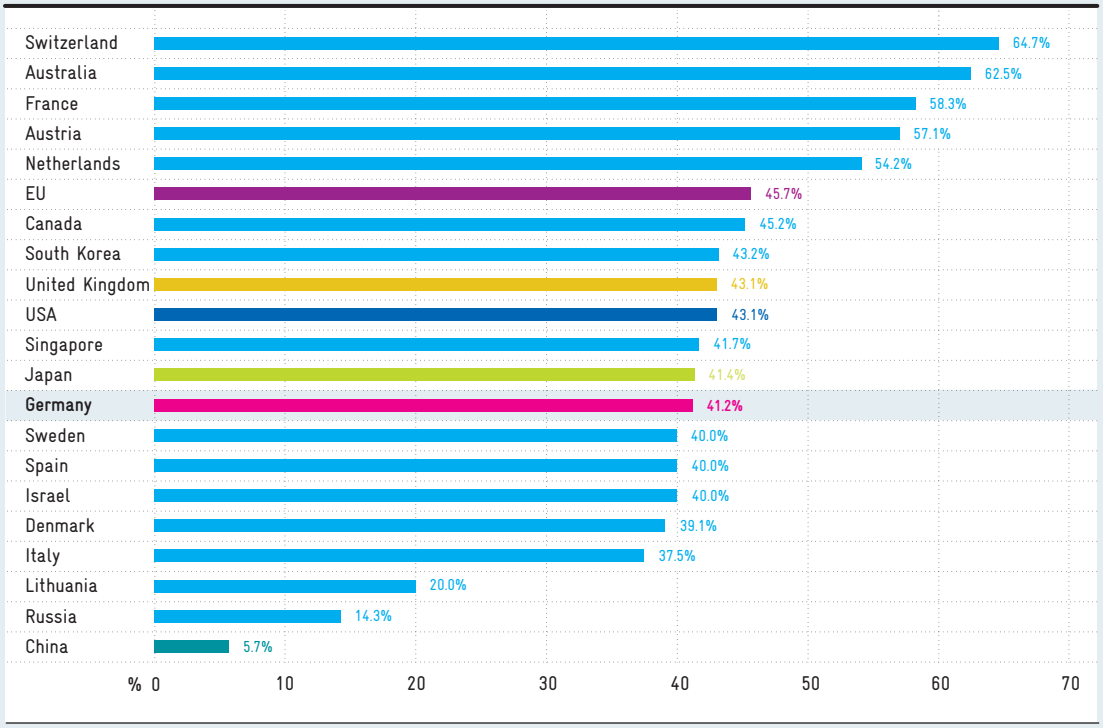


The representation considers countries with a total of at least five patent families in the fields of health and medicine as well as technical improvements.
Source: Own representation based on Zyontz and Pomeroy-Carter (2021).

Fig. B 3-9

Download data

Share of CRISPR/Cas patent families filed in at least three jurisdictions in the fields of health and medicine as well as technical improvements for selected countries and regions 1999–2018



The representation considers countries with a total of at least five patent families in the fields of health and medicine as well as technical improvements. The patent families from the fields of health and medicine as well as technical improvements are summarized in this representation. Large CRISPR/Cas patent families are those that are filed in at least three jurisdictions.

Source: Own representation based on Zyontz and Pomeroy-Carter (2021).

period under review (1999 to 2018) is only 1.7 percent of the corresponding worldwide CRISPR/Cas patent families.[273] Furthermore, although the UK, Japan, Switzerland and South Korea have fewer publications than Germany,[274] inventors in these countries file more patents than those in Germany (see figure B 3-8).

The number of jurisdictions in which a patent is filed can be used as a measure of the quality of patents. Inventors in Switzerland filed 64.7 percent of patent families in at least three jurisdictions (cf. figure B 3-9). This puts Switzerland well above the EU average of 45.7 percent, the UK and the USA with 43.1 percent each, Japan with 41.4 percent and Germany with 41.2 percent. Inventors from China filed only 5.7 percent of patent families in three or more jurisdictions.

Small Number of German CRISPR/Cas Companies

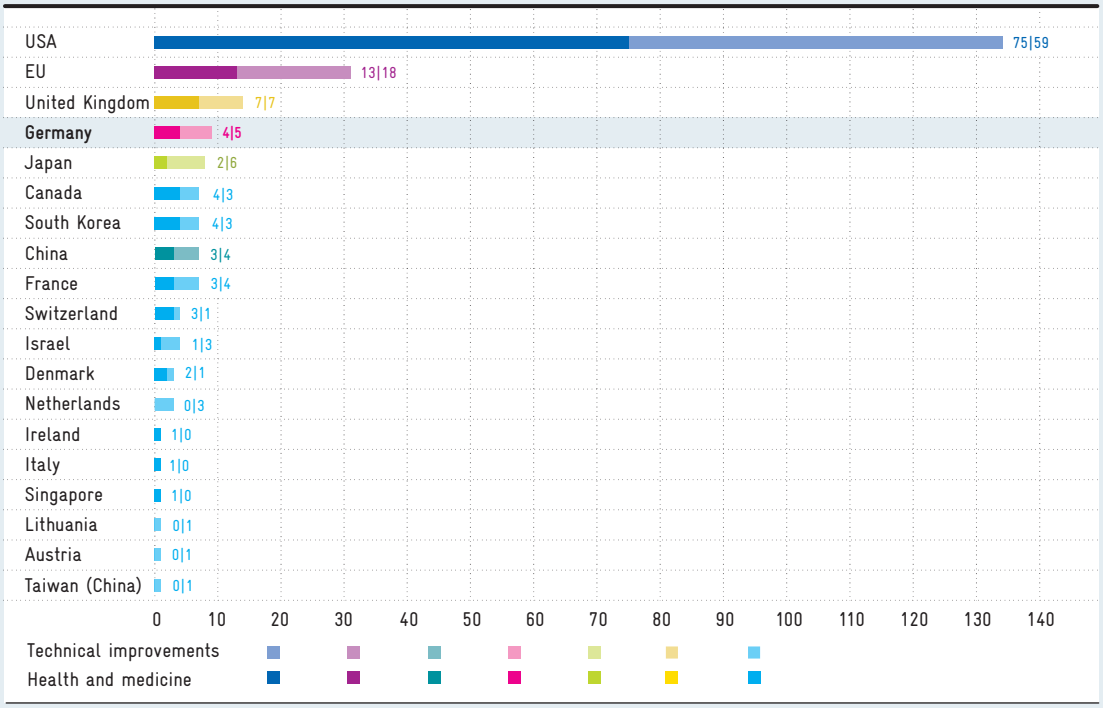
Companies commercializing CRISPR/Cas were identified by way of patent applications and company websites.[275] The basis for analysis are those companies for which further information is available in addition to their CRISPR/Cas patents.[276] For the second quarter of 2020, 278 CRISPR/Cas companies can thus be identified, some of which are active in several fields.[277] Most of these companies are active in the field of health and medicine (111 companies), followed by the fields of technical improvements (102 companies), research services (101 companies), agriculture (42 companies) and industrial applications (22 companies).[278]

By far the most CRISPR/Cas companies that can be assigned to the fields of health and medicine as well as

Fig. B 3-10

Download data

Number of CRISPR/Cas companies in the fields of health and medicine as well as technical improvements for selected countries and regions Q2 2020

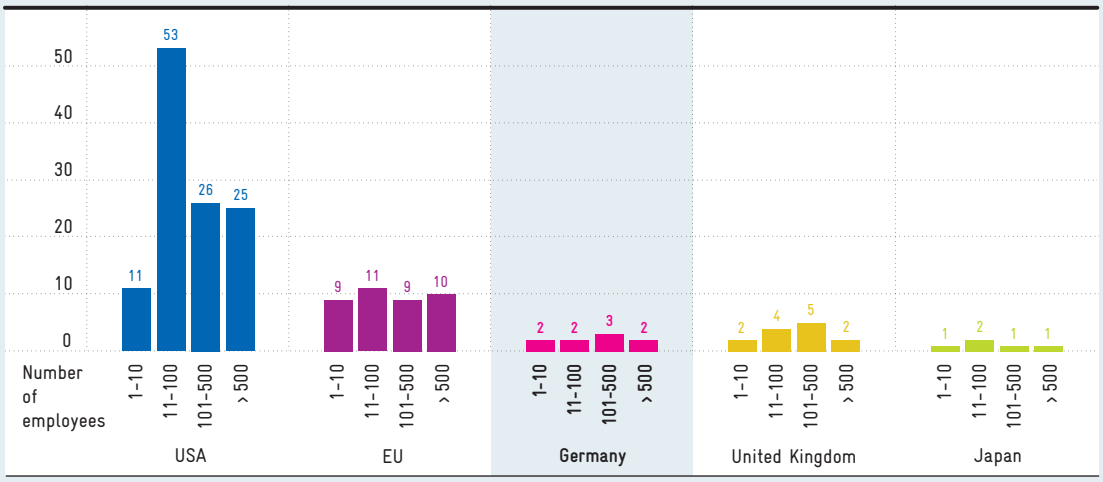


Source: Own representation based on Zyontz and Pomeroy-Carter (2021).

Fig. B 3-11

Download data

Number of CRISPR/Cas companies in the fields of health and medicine as well as technical improvements by number of employees for selected countries and regions Q2 2020



Companies from the fields of health and medicine as well as technical improvements are summarized in this representation.
Source: Own representation based on Zyontz and Pomeroy-Carter (2021).

technical improvements can be found in the USA with 134 companies. 14 such companies are in the UK and nine in Germany (cf. figure B 3-10).

In the comparison by countries, the characteristics of the companies working with CRISPR/Cas differ as well. The percentage of companies with over 100 employees is higher in Germany, at five out of nine, than in the USA, where this applies to 51 out of 115 companies (cf. figure B 3-11).[279] At the same time, the percentage of CRISPR/Cas start-ups founded from 2010 onwards is significantly higher in the USA, with 77 out of 124 companies, than in Germany, with one out of eight companies.[280] Despite the low number of observations for German companies, there are indications that CRISPR/Cas technology is being commercialized more by young companies in the USA than is the case in Germany.[281]

Need to Catch Up with Clinical Trials

In the field of health and medicine, clinical trials play a key role in the translation of research results into application. They are used, among other things, to ensure that treatments and drugs are safe and effective.

Clinical trials using CRISPR/Cas have been conducted since 2015. In most registered[282] clinical trials (32 out of 48 trials worldwide), cells modified with CRISPR/Cas have therapeutic purposes. In eight studies, CRISPR/Cas is used to create cell lines, in six studies it is used for genome sequencing and two studies are review papers.

Most registered clinical trials are conducted in China (27) and the USA (17) (cf. figure B 3-12). In Germany, only one clinical trial using CRISPR/Cas is registered.[283] In Switzerland, five clinical trials are registered, all of which go back to CRISPR Therapeutics, a company founded by Emmanuelle Charpentier.

Mixed Picture Regarding Germany's Performance

Germany ranks third behind the USA and China in CRISPR/Cas research in the fields of health and medicine and technical improvements, measured by the number of publications. However, Germany falls behind in an international comparison when key performance indicators in the application and commercialization of this technology are considered. In terms of inventions, measured by the number of patents, Germany ranks behind South Korea, Switzerland, Japan and the UK, whose researchers, however, have fewer publications than researchers in Germany.

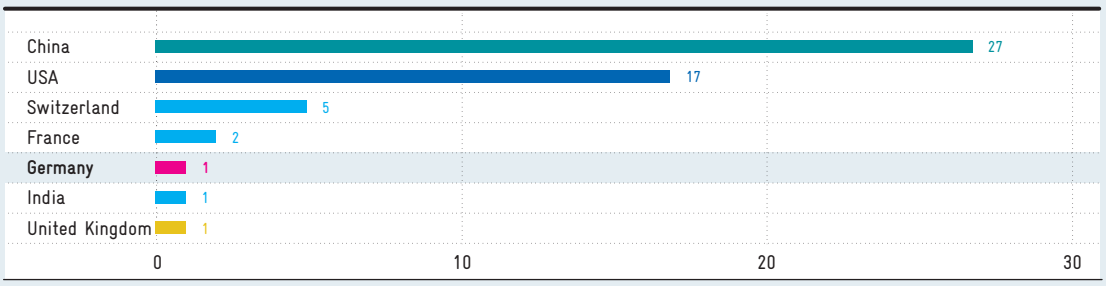
There are fewer CRISPR/Cas companies in Germany than in the UK and significantly fewer than in the USA. It also shows that commercialization in Germany tends to be driven by larger and older companies, while in the USA it is driven more by young companies. Clinical trials are necessary to make CRISPR/Cas available to patients in the form of treatments. Yet, the number of clinical trials in Germany lags significantly behind its comparatively good research position.

The analysis suggests that there is still untapped potential in Germany regarding CRISPR/Cas inventions and their use for patients and commercialization by companies.

Number of registered clinical trials using CRISPR/Cas by countries

Fig. B 3-12

Download data



Source: Own representation based on Zyontz and Pomeroy-Carter (2021).

B 3-3 Legal and Financial Framework Conditions

An international comparative study conducted on behalf of the Commission of Experts analyses the regulation of gene editing in selected countries in the fields of somatic-cell gene therapy and germ-line gene therapy with a view to its impact on R&I. The comparison looks at countries that play a leading role worldwide in the fields of genetic engineering and gene editing.[284] These countries are in intense competition with each other, particularly in basic and preclinical research and in the production of advanced therapy medicinal products,[285] which also include gene therapy medicinal products.[286] Regulatory framework conditions are of fundamental importance for R&I activities and can therefore influence competitiveness either positively or negatively.[287]

The section below first describes the legal framework governing basic medical research and preclinical research in Germany. This is followed by investigation of the regulatory framework and its interpretation regarding the clinical testing of therapeutics for somatic-cell gene therapies.[288] Subsequently, the non-legal framework conditions, in particular the financial and institutional conditions for clinical trials in the field of medical biotechnology are discussed.

Complex Research Application Processes

Basic medical research and preclinical research are prerequisites for understanding the effects of medical processes and developing new drugs.

In Germany, basic medical research and preclinical research on somatic-cell gene therapy are mainly regulated by the Genetic Engineering Act (Gentechnikgesetz, GenTG).[289] Laboratories and genetic engineering facilities in which medical research with genetically modified organisms (GMOs) is carried out must be reported by researchers and registered and approved by the competent authorities in the respective Länder.[290]

To ensure safety in basic medical research and preclinical research with GMOs, the reporting, registration, and approval procedures are associated with high content requirements. However, some researchers in Germany complain that, despite decades of experience and the means of digitalization, these procedures result in a bureaucratic burden that is disproportionate to the risk.[291] Furthermore, the enforcement of genetic engineering law in Germany seems to have recently become rather more restrictive again, probably depending on the respective Land. In addition, there is not always a uniform practice of law enforcement regarding genetic engineering law throughout Germany.[292]

The bureaucratic and regulatory hurdles mentioned here affect not only somatic-cell gene therapy, but all basic medical research and preclinical research. From the scientific point of view, animal welfare regulation has the greatest negative impact on research and development. Many scientists complain about excessive regulation and see their research significantly impaired as a result. This ultimately leads to Germany losing its appeal as a location for basic medical research and preclinical research.

To reduce the administrative burden on researchers, genetic engineering work with certain types of GMOs could by ordinance be fully or partially exempted from GenTG regulations and application procedures could be bundled. To improve the framework conditions in basic research and preclinical research, efforts could also be made to harmonize the requirements of the authorities at Länder level across the country.[293]

High Administrative Hurdles for Clinical Studies

Clinical trials are needed to ensure the safety and efficacy of therapeutics and to translate research results into application. In Germany, these are subject to approval for all types of therapeutics, i.e., also for therapeutics for somatic-cell gene therapy, and are regulated by pharmaceutical and (bio)medical law. Both pharmaceutical law and (bio)medical law are determined to a considerable extent by laws at the level of the European Union.[294]

The regulation of clinical trials in Germany, as in France, the UK, and Switzerland, is based on double preventive control.[295] Thus, on the one hand, the performance of clinical trials in Germany requires prior official approval by the Paul-Ehrlich-Institute (PEI), which certifies the safety of the clinical trial. On the other hand, the approving assessment of the institute's responsible internal ethics committee is required, which confirms the ethical justifiability of the risks of the clinical trial. The paragraphs

below first look at the requirements of the approval procedures at the PEI and the ethics committees. This is followed by a discussion of the procedural deadlines.

To obtain approval for a clinical trial, researchers must submit a corresponding application to the PEI. The documents to be submitted include, among other things, information on the subject and objectives of the clinical trials, the trial protocol, and results of preclinical studies. In addition, an official manufacturing authorization is required for the investigational medicinal products used in the clinical trials. This must be proven by compliance with good manufacturing practice (GMP) and is granted by the responsible authority at Länder level.[296]

The concrete application of compliance with the European GMP standard for the granting of manufacturing authorization for investigational medicinal products is in some cases interpreted differently within EU Member States.[297] According to researchers, the implementation and interpretation of the regulations is stricter in Germany than in other EU Member States. In the UK, for example, which at the time of the study was no longer a member of the EU but for which EU law continued to apply for the time being, compliance with a pre-GMP standard is sufficient for the granting of a manufacturing authorization.[298] In contrast, investigational medicinal products in Germany must fully comply with the GMP standard from the start.[299]

A prerequisite for approval by the responsible ethics committee to conduct clinical trials is the positive assessment of the submitted documents. These include an assessment of the foreseeable risks and disadvantages of the clinical trials as well as weighing them against the expected benefit for the patient.[300] However, the assessment is as yet not carried out based on uniform federal criteria but is left to the discretion of the respective ethics committee responsible. The same applies to multi-centre clinical trials,[301] where the ethics committee at the location of the project leader assesses the ethical acceptability of the clinical trial. This ultimately leads to different assessments of the ethical acceptability of clinical trials by the ethics committees.

In addition, approval procedures differ in their design in the countries considered here. While clinical trials in Germany require regulatory approval, in Japan they only need to be registered with the Pharmaceuticals and Medical Devices Agency.[306] In contrast to Germany, where the procedural deadlines for the approval and release of clinical trials are 90 days, in Japan and the USA approval is deemed granted after a 30-day period.[307]

In recent years, a large increase in R&D activities has been observed in the field of medicinal products for innovative treatments.[308] In view of this development, it can be assumed that, in addition to an increase

Box B 3-13

Regulation of Embryo Research and Germ-line Gene Therapy

Embryo research, i.e., research on embryos for the purpose of gaining scientific knowledge, is permitted, except for Germany, in all countries considered in the international comparative study under certain, usually extremely strict, conditions. In the countries under consideration, surplus so-called in vitro fertilization embryos produced by artificial insemination may be used for high-level research purposes and cultivated up to a maximum of the 14th day of their development. In the UK, embryos created specifically for research purposes may also be used for research.[302]

Germ-line gene therapy, i.e., the genetic modification of embryos for therapeutic purposes, on the other hand, is prohibited in practically all countries. In its statement on interventions in the human germ line published in 2019, the German Ethics Council (Deutscher Ethikrat) takes the position that no categorical inviolability of the human germ line results from the ethical analysis.[303] At the same time, however, it currently judges germ line interventions to be ethically irresponsible due to their incalculable risks and calls for a worldwide moratorium on use, in line with the WHO, among others.[304] In order to create a better information basis and to raise awareness on the subject of germ line gene therapy in particular and gene editing in general, the German Ethics Council also recommends a wide-ranging social discourse.[305]

in informal requests for advice, there soon will also be a considerable increase in formal approval procedures.[309]

Aside from huge administrative requirements, researchers in Germany are confronted with strict interpretation of the legal regulations in the approval of clinical trials, for instance, regarding manufacturing authorization. In addition, applicants must contact several authorities at federal and Länder level. Particularly in the case of multi-centre studies, Länder-specific contract models with differing content might apply, which may lead to considerable delays in the approval procedures. In addition, the localized presence of the ethics committees at universities and research institutions means that there is no evaluation based on uniform standards.

Simplification of the approval procedure,[310] the nationwide harmonization of contracts for multi-centre studies and a less restrictive interpretation of regulations could help to improve Germany's clinical trials position in international competition. To be able to process all approval procedures on time also in the future, consideration should moreover be given to expanding staff capacities at the competent approval authorities.

Lack of Translation Funding

Making the findings from medical research available to patients quickly and effectively is of great social and economic interest. Clinical trials are of key importance in translating findings from basic medical research into application and are also evidence of the innovative power of clinical research.[311]

Medical research goes hand in hand with long development and innovation cycles (cf. figure B 3-14), which is why long-term and continuous funding is needed. In particular, clinical trials are very costly. Clinical trials can be differentiated between industry-funded commercial trials and publicly funded non-commercial trials (investigator-initiated trials). While industry-funded trials are primarily associated with a commercial interest and aim to develop drugs, publicly funded trials are science-driven and often deal with open complex questions of medical care.[312] A subcategory of publicly funded trials are the so-called treatment optimization trials, which examine whether an already approved drug can possibly be used to treat other diseases.[313] In this context, the findings obtained from science-driven studies and treatment optimization studies can make an important contribution to increasing the effectiveness and quality of patient care and are thus of great importance for patient welfare.[314]

The financing of science-driven clinical trials and treatment optimization trials without a direct commercialization interest, where the expenditure often amounts to tens of millions, is a considerable problem.[315] Consequently, many fundamental questions of medical care, especially in highly innovative fields such as somatic-cell gene therapy, cannot be transferred to clinical trials.[316] Higher financial and personnel capacities of university hospitals and an improved infrastructure could remedy this situation.

Regarding industry-funded studies, experts complain that the supply of venture capital and other sources of funding for clinical trials in the field of medical biotechnology is extremely low in Germany. This is due in particular to the long investment phases in drug development, which are associated with a high level of risk.[317] For example, due to a lack of financial resources, potential drug candidates from research can often not be developed to proof of concept in phase II, in which the safety and efficacy of the drug are evaluated in clinical trials. Experts also point to considerable financing problems in the transition from phase II to phase III, in which the new drugs are tested on several hundred patients (cf. figure B 3-14).

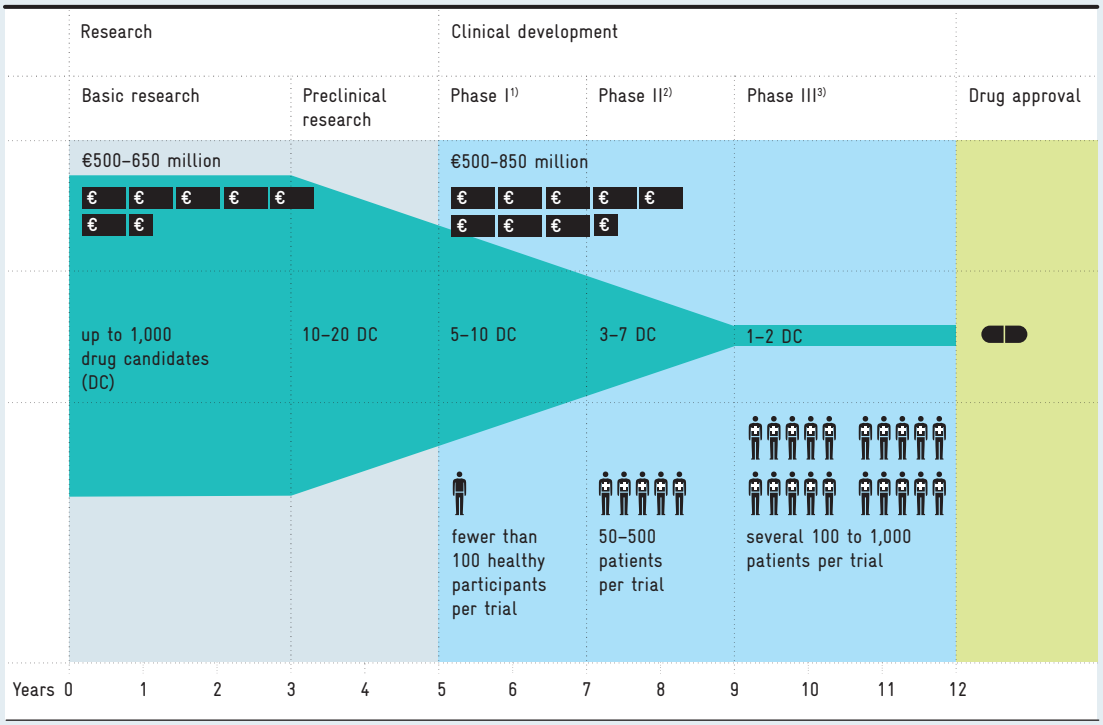
The lack of an end-to-end funding chain from public research funding to seed funding to growth funding makes it difficult to translate research results into commercial implementation and application. Against this background, the Commission of Experts welcomes initiatives such as the recently announced support programme for the development of drugs and other therapeutics against COVID-19, initially endowed with €50 million, which aims to support clinical development in phases I and II.

To improve the financing of commercial clinical trials, especially in the final phases of drug development, and to promote translation, private capital needs to be mobilized. Adequate (tax) incentives for investors could be created for this purpose. In addition, the

From basic research to drug

Fig. B 3-14

Download data



1) Phase I: Safety and tolerability tests of potential active substances.
2) Phase II: Proof of efficacy and tests for side effects.
3) Phase III: Confirm efficacy and test for interaction with other drugs.
Source: Representation based on Schüler (2016).

Future Fund (Zukunftsfonds) set up by the Federal Government can contribute to improving the financial framework conditions.[318]

In addition to financial framework conditions, there are other catalysts that are conducive to translation. For example, the 'GO-Bio initial' support measure of the Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung, BMBF), which was introduced in 2019, aims to support the identification and development of early research approaches in the life sciences with recognizable innovation potential.[319] To better prepare researchers for knowledge transfer, the programme also integrates complementary support measures such as start-up talks. The aim of the programme is to further develop the research approaches to the extent that a continuation in other support programmes, such as EXIST Research Transfer, is made possible and the translation of research results into application succeeds.[320] Equally promising are approaches such as Stanford ChEM-H,[321] where researchers from different disciplines cooperate with clinicians to quickly produce innovations in medicine.

A prerequisite for the success of such programmes is to make the performance of clinical trials attractive for physicians.[322] This can be achieved, among other things, by firmly incorporating research hours as well as through suitable organizational structures. These should allow for an appropriate ratio between research and care, thereby allowing for exchange between researchers.[323]

Some experts also advocate the creation of a centre that would network research stakeholders from different locations.[324] An institution like the Catapult programme in the UK would be conceivable. This programme

pools know-how on application and approval issues, provides start-ups and small genetic engineering companies with expertise on setting up businesses, and is a central platform for financing needs and investment opportunities.[325]

B 3–4 Recommendations for Action

The CRISPR/Cas gene scissors are a tool for gene editing that gives new impetus to basic medical research and enables new therapeutic approaches for many diseases. The targeted alteration of genetic information enables the direct elimination of the causes of hereditary diseases. The field of somatic-cell gene therapy in particular offers significant potential and is associated with high patient benefit and economic value creation potential. To leverage the potential associated with CRISPR/Cas, further major advances are needed both in research and in the translation of research results into application. The Commission of Experts therefore recommends the following measures:

Accelerate Approval Procedures

- For projects ranging from basic and applied research to human application in clinical trials, approval procedures – always under the maxim of maintaining safety and ethical justifiability – must be designed in such a way that the administrative burden for researchers is reduced.
- To ensure that approval procedures can continue to be completed as quickly as possible, staffing levels within the approval authorities must be adjusted at an early stage to reflect the expected increase in approval procedures.
- Moreover, the bundling of related applications and approval procedures should be made possible. In addition, efforts should be made to harmonize approval procedures across the Länder.

Consolidate Cutting-edge CRISPR/Cas Research

- To consolidate cutting-edge research in the field of CRISPR/Cas, several lighthouse projects at internationally competitive German locations should be expanded or newly created. In these lighthouse projects, the translation of scientific results into medical application should be given high priority.

Support Translation of Scientific Findings

- In particular, interdisciplinary collaborations and working groups should be initiated and promoted that support translation and generate innovations through early interaction between research and clinical practice.
- For advising researchers and networking with various stakeholder groups, the establishment of a German Gene Therapy Centre should be discussed, which can assume the role of a competence centre for translation of basic research and preclinical research into clinical application.
- Clinical trials are a prerequisite for the translation of research results into application. The feasibility of clinical trials should therefore be improved by means of more favourable framework conditions, such as faster, more efficient, and less detailed approval procedures. In addition, the attractiveness of participating in clinical trials should be increased for physicians.
- Programmes such as ‘GO-Bio initial’, which start at an early stage of the R&D process and aim at the seamless and professionalized translation of ideas into application, should be continued and provided with sufficient financial resources.

Improve Framework Conditions for Venture Capital Provision

- The long research and development cycles in medical biotechnology go hand in hand with enormous financing requirements and high risk. The Commission of Experts once again urges that the framework conditions for the provision of private venture and growth capital be improved. In this context, it welcomes the establishment of the Future Fund, which is intended to support both pioneering technologies, especially in the field of biotechnology, and large funding rounds for start-ups and their scaling, and calls for its rapid implementation.

Promote Social Discourse

- The Commission of Experts considers it important to regularly inform society about the potentials and risks associated with CRISPR/Cas and to continue the associated social discourse.

Expand Open Science

– The principle of Open Science made knowledge in the field of CRISPR/Cas transparent and accessible at an early stage, thus accelerating both the dissemination of scientific knowledge and its further development, as well as supporting excellence in scientific work. The possibilities and instruments of Open Science throughout the research process should therefore be further developed and supported.