



Annual report 2023

Anniversary brochure

**DEUTSCHES INSTITUT FÜR
ZELL- UND GEWEBEERSATZ**

Gemeinnützige Gesellschaft mbH

30 1993
YEARS
DIZG
2023

Safety -
Made in
Germany





Contents

- Seizing new opportunities 5
- Our history..... 6
- Latest news**
 - Spongioflex® for the knee..... 8
 - The federal organ and tissue donor register 9
- Review**
 - The 30th anniversary..... 11
 - The DGV emphasizes the relevance of the DIZG's autologous cell cultures 12
 - The Shark Screw® was introduced in Germany..... 13
- Figures 2023**
 - Living and post-mortem tissue donation..... 14
 - Which tissues were donated 15
 - Helping with tissue donations 15
 - Increased delivery of allogeneic transplants 16
- Tissue donation**
 - Insights into tissue donations 17
- Manufacture**
 - How donated tissues are turned into urgently needed transplants 24
- Research and development**
 - Research: developing the new, analyzing the familiar 32
 - Versatile allografts 33
 - Scientific publications 38
 - Student projects and theses 42
- Autologous cell cultures**
 - Grafts for burns medicine and hard-to-heal wounds 44
 - Manufactured to the highest standards 45
 - The keratinocyte sheets 46
 - The keratinocyte suspension..... 47
 - The production steps of autologous cell cultures 48
 - Helping severely burned patients 50
- Quality and safety**
 - Zero infections: demonstrably safe..... 52
 - Security for clinics and doctors..... 54
 - DIZG transplants are of human origin..... 55
- The DIZG at a glance..... 56
- References 58





Take advantage of new opportunities

Dear friends of the DIZG,

Last year, the effects of the reduced tissue donations were clearly noticeable – for us and therefore also for medical users: the demand for safe allogeneic hard and soft tissues far exceeded the supply. At the beginning of 2023, we entered into a cooperation with a US-based charitable donation program to counteract this imbalance. Unfortunately, official approval has not yet been granted. In addition, we were able to gain further clinics throughout Germany as partners for endoprosthetic femoral head donations. The additional donated femoral heads will enable us to expand the production of urgently needed transplants for patient care.

AN ANNIVERSARY AND NEW TRANSPLANTS

The occasion of our internal summer party was a pleasant one: 30 years of DIZG – this milestone anniversary was celebrated on a small scale with the employees. They are the ones who are committed to improving the health of sick people every day. Since our foundation in 1993, we have been able to provide around 798,000 allogeneic bone and soft tissue transplants for medical treatment. Our non-profit-institute has long been one of the largest pharmaceutical and biotechnology-oriented non-profit organizations of its kind in Europe.

Despite the challenges in 2023,

we can continue to report positive developments. During spring, we launched the Shark Screw® in Germany. The special feature: The innovative bone screws for hand and foot surgery are colonized by the body's own cells after implantation and are then gradually converted into the patient's own bone during remodeling. This spares patients a second operation to remove the metal and the associated risks.

With Spongioflex® for the knee, we provide surgeons with a human transplant for patient care that is suitable as a meniscal replacement. It has already been used in around 100 cases. Initial results of a case report indicate rapid ingrowth of the human transplant within twelve weeks.

UNIQUE SERVICES

Our meniscus matching service was launched in the spring of last year. With this Germany-wide unique service we offer doctors the opportunity to check the availability of a suitable human meniscus for total replacement.

Recognition was awarded to our autologous cell cultures, of which we are the exclusive provider for Germany-wide and which are often the only treatment option for severely burned patients. In 2023, the Executive Board of the German Society for Burns Medicine (DGV e. V.) classified the provision of

these by the DIZG as an essential component of successful treatment for severely burned patients.

It was a year in which we entered into new collaborations to further optimize the supply of human tissues. In 2024, we will continue these efforts to gain further partners. Regardless of this, we were able to successfully collaborate with clinical partners in almost 68,000 supply cases last year. I would like to thank you and all those involved in the clinics for your cooperation.

Yours sincerely

Jürgen Ehlers
Managing Director

Our history

1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022 2023

Previous history

The DIZG originated from an initiative of doctors and scientists from Berlin's Humboldt University and the universities of Leipzig and Erlangen-Nuremberg.

1994

The DIZG becomes a member of the **EATB** (European Association of Tissue Banks) and obtains manufacturing authorization for allogeneic avital tissue transplants.

1999

The DIZG receives permission to **produce autologous cell cultures**.

2000

The **merger agreement** with BIOCON Inc. is signed. It also includes MTF, currently the largest tissue bank in the world.

2001

Relocation to the **Wuhlheide Innovation Park**. The allogeneic transplants will continue to be sterilized and aseptically processed in Leipzig.

2005

Issuance of **pharmaceutical licenses** according to § 21 AMG for all transplants of the DIZG by the PEI/BfArM

2007

September
The **new production building** in the Innovation Park is inaugurated and the Leipzig location is closed.

October
The DIZG receives the manufacturing license for allogeneic transplants for the Wuhlheide site and is the only facility in Germany to have an authorization according to § 21 AMG for the human acellular dermis.

2008

The DIZG develops the **Cell Sprayer** as the first medical product for application of keratinocytes in the treatment of second-degree burns.



2010

Final and indefinite extension of approvals for allogeneic transplants as a medicinal product

2018

25th anniversary

2020

The DIZG employs more than **100 employees**.

The **handy Cell Spray** replaces the Cell Sprayer.

2021

Authorization for **Fiberfill®**

The foundation for **Facility 2024**, our new production facility, is laid.

2022

Topping-out ceremony for the 2,526 m² Facility 2024 for human bone and soft tissue

2023

The DIZG continues to grow and employs **125 employees** (01.03.2024).

The DIZG celebrates its **30th anniversary**.

Germany-wide introduction of the **Shark Screw®**

Spongioflex® for the knee

The menisci are important for distributing joint pressure and stabilizing the knee joint. Loss of the meniscus can lead to functional limitations in the short term and to knee osteoarthritis¹ in the long term. The DIZG is pleased to provide surgeons with Spongioflex®, which is suitable as a partial meniscal replacement. Initial results of a case report indicate rapid ingrowth of the human transplant within twelve weeks.²

Once rehydrated, Spongioflex® regains its elasticity and flexibility, becoming highly stable and highly resistant to suture tears. Surgeons can easily adjust the implant size with a scalpel to ensure a precise fit.



STRUCTURE AND PROPERTIES

- > Spongioflex®, a demineralized cancellous bone, offers a unique arrangement of collagen fibers in a trabecular structure.
- > Due to its flexibility, Spongioflex® can also be used arthroscopically via suitable portals.

POSSIBLE AREAS OF APPLICATION

- > Loss of meniscal tissue
- > Arthroscopic partial meniscectomy (APM) for irreparable meniscus ruptures



Rehydrated Spongioflex® becomes very easy to insert arthroscopically..

The organ and tissue donor registry of the federal government

On March 18, 2024, the registry for organ and tissue donation declarations (organ donation registry) went online. The decision for or against organ and tissue donation can be recorded in this central electronic register – free of charge and on a voluntary basis. Even before the launch the register kept the non-profit German Society for Tissue Transplantation (DGFG) busy.

THE TRANSPLANTATION LAW HAD TO BE OPTIMIZED

Last year, the DGFG took a stand for the registry and called for a change in the law of the § 2a Transplantation Act (TPG), which the DIZG supported with a letter to the Federal Minister of Health, Karl Lauterbach.

Among other things, the following aspects were critically assessed:

- > exclusive access by authorized hospital employees,

- > no possibility of a register query outside the hospital environment,
- > narrow access mechanisms to the data of deceased persons in Section 2a § 4 TPG. These limit the important regulation for tissue donation in Section 7 TPG, which defines data processing and information obligations.

For months, the DGFG held intensive discussions with representatives of the Federal Ministry of Health (BMG), with members of the Bundestag, various specialist societies, transplantation officers and doctors.

The commitment has paid off. The BMG reports in a reaction: It is "a concern of the Federal Government that even after commissioning of the registry (...) any tissue donation can be realized, provided there is a corresponding willingness to donate." And: "In the opinion of the

BMG, there are in principle no legal reasons to prevent the appointment of external doctors employed by tissue establishments with authorization to access the register."

The lack of register access for tissue donation facilities would have additionally increased the already high workload of the person authorized to access the register within the clinic with each donation request, further limiting the number of post-mortem tissue donations and thus jeopardizing safe patient care. Thank you, DGFG!

How practical the access is, remains to be seen.



The 30th anniversary

30
1993
YEARS
DIZG
2023

DIZG and its employees celebrated its 30th anniversary in 2023 with a summer party. A small exhibition recalled the beginnings and the development of the company over the three decades. We have been producing human bone and soft tissue transplants and providing them for patient care throughout Germany since 1993. Since the company was founded, we have supplied around 798,000 allogeneic tissue transplants for medical treatments. The DIZG has long been one of the largest pharmaceutically and biotechnologically oriented nonprofit organizations in Europe. Our motivation has remained unchanged since the beginning:

We want to offer as many people as possible with severe tissue defects an improved healing perspective. For this reason, our institute promotes tissue donation and is constantly developing the diversity of transplants with its own R&D department.

The DGV emphasizes the relevance of the autologous cell cultures of the DIZG



In 2023, the board of the German Society for Burn Medicine (DGV e. V.) classified biotechnologically processed autologous keratinocytes, which the DIZG is the only institution in Germany to provide, as an essential component of successful therapy for severely burned patients. Prof. Dr. Kremer, board member of the DGV, explains their relevance.

Why are our autologous cell cultures so relevant for the treatment of severely burned patients?

There are patients with an extent of burns that cannot be covered by healthy skin alone. Those patients, whom we can't treat because of a skin deficiency, are therefore not viable. Even in these cases coverage and closure can be achieved with cultivated keratinocytes. In combination with the patient's own skin, they can also shorten the time of wound closure. This in turn reduces possible consequences such as infections and sepsis, thus ensuring the survival of our patients.

Thanks to this accelerated wound closure, autologous cell cultures improve the patient's quality of life. The faster the wound is closed, the fewer functional restrictions occur.

How important is the DIZG's service? Couldn't the autologous cell cultures be provided directly by the burn centers?

For regulatory reasons, not every center can maintain its own structure for providing autologous cell cultures. The production of autologous cell cultures must be centralized in compliance with all regulatory require-

ments. In Germany, this is currently only possible at the DIZG and therefore, it ultimately ensures the care of severely burned patients throughout Germany. We have already had to experience what it is like in Germany when the DIZG is unable to deliver: Patients either could not be treated or only from abroad using emergency permits. There is currently no legal framework for this.

The importance of autologous cell cultures is not reflected in the corresponding guideline. Instead, there is an optional recommendation in justified individual cases. Uncertainties remain regarding the indication and appropriate reimbursement. How can these be eliminated?

We are talking about two pillars here:

- > The guideline is currently being revised. The new version will be published this year. The recommendation will be more specific, although it is a recommendation based on consensus, not an evidence-based recommendation.
- > We need to create evidence to demonstrate the importance of keratinocytes. This is undisputed from my clinical experience. There are patients that we cannot treat without keratinocytes.

Our institute has been providing autologous keratinocytes for more than two decades. What does this mean for you and the centers?

For us, it is part of caring for our patients – without it, we would not be able to treat them. A trusting relationship has developed between the treating centers and keratinocytes.

This enables us to provide the right indications. The cooperation between cell culture department and patient treatment over the entire period is only possible in close coordination: a cycle begins with the biopsy of the skin cells and leads to the return and transplantation of the cultivated cells. Due to the small time window for transplantation, this process must be well coordinated at all times. This has been established with the DIZG in recent years and distinguishes the cells from a pure medical product that is available at any time. Autologous cell cultures are a complex biological system.

What else do you think is important?

There is a risk that there will be more patients with high-percentage severe surface area burns, as the experience in Ukraine shows. With regard to emergency preparedness, we should not retrospectively conclude that something has been missed. This does not only apply to Ukraine, it has become more uncertain overall. The risk of Bundeswehr deployments with many casualties seems to have increased. The necessary structures for, for example, ten severely burned patients at the same time should not be set up only then.

Prof. Dr. Kremer, thank you for the interview.

The Shark Screw® was launched in Germany



Jürgen Ehlers, Managing Director of the DIZG. Possible complications that can be triggered by metals in the body are ruled out.⁴

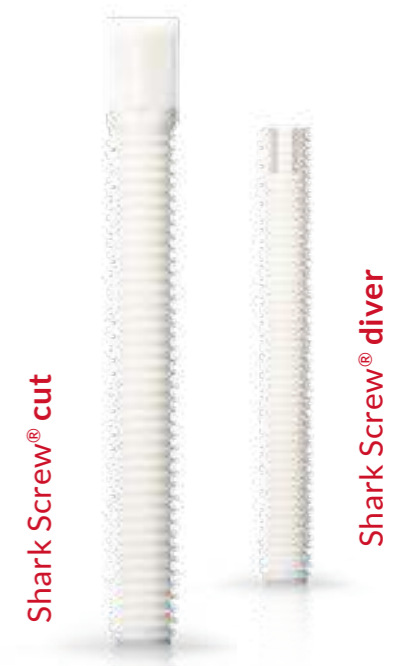
Another special feature of the Shark Screw® is its 2 % swelling within 24 hours of insertion into the recipient bone. This ensures an even more rotationally stable bony connection.⁵ In addition, the bone bridge protrudes deep into the bone – a first for many operations.

Shark Screws® provide hand and foot surgeons with a human-derived transplant that promotes a natural healing process.

In March 2023, Dr. Ali Dadashi, Surgical Practice Clinic Landshut, was the first in Germany to use the Shark Screw® for the surgical treatment of an arthrodesis in the left big toe. The innovative Shark Screws® offered by the DIZG throughout Germany are colonized by the patient's own cells after insertion. These screws then promote growth and are gradually converted into the patient's own bone through natural bone remodeling. This biological process is the key strength of the Shark Screw® transplant.

A BIOINTELLIGENT PROCESS CHARACTERIZES THE SHARK SCREW®

Screws, typically made of titanium or bone, are used to aid bone healing. But unlike metal screws, Shark Screws®, crafted from donated bone tissue, integrate seamlessly with the body's natural bone metabolism. This "biointelligent process" triggers remodeling into the patient's own bone within weeks to months. "Consequently, these screws create bone structures that can continuously adapt to mechanical stress, mimicking the body's natural bone behavior," explains



Living and post-mortem tissue donation

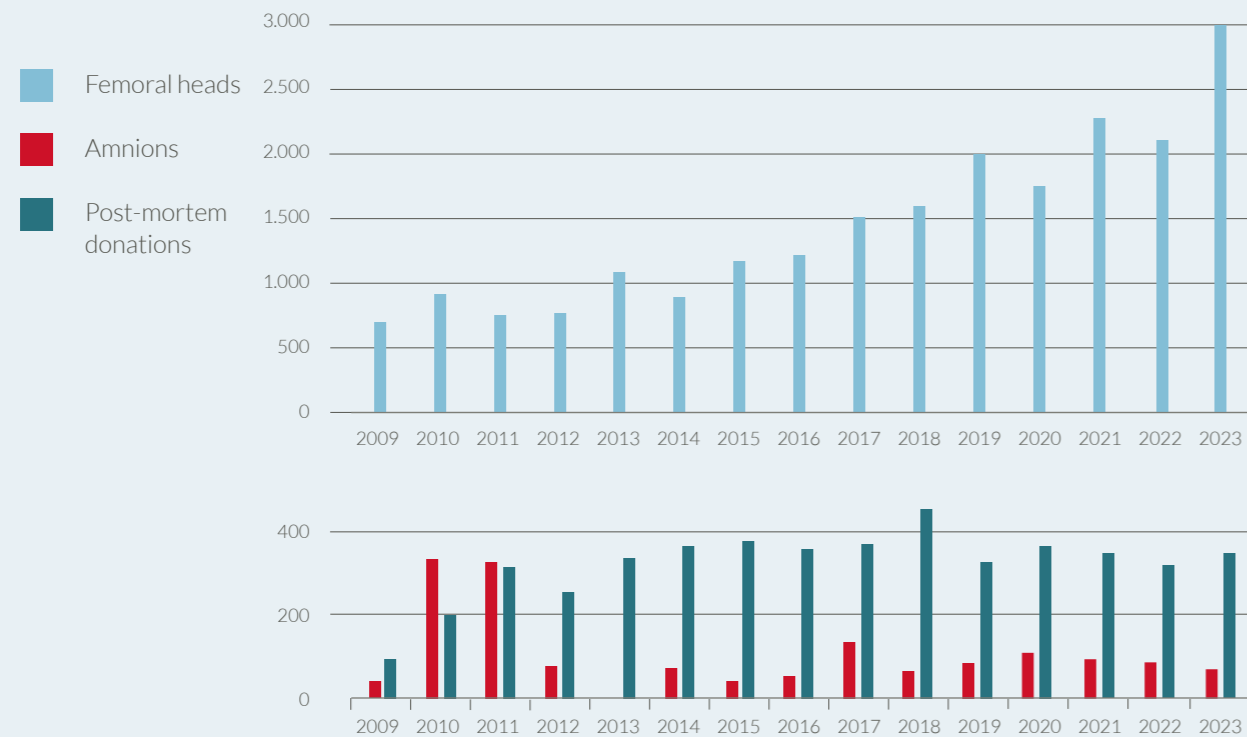
In the reporting year, **3,293** people donated tissue, which is **770** more than in the previous year. The number of post-mortem donations rose by **43** to **353** in the same period. **6,643** individual tissues were obtained from these donations.

The development is very pleasing in the number of femoral head donations received, from endoprosthesis operations: Last year, **2,932** femoral heads were donated – **746** more than in 2022.

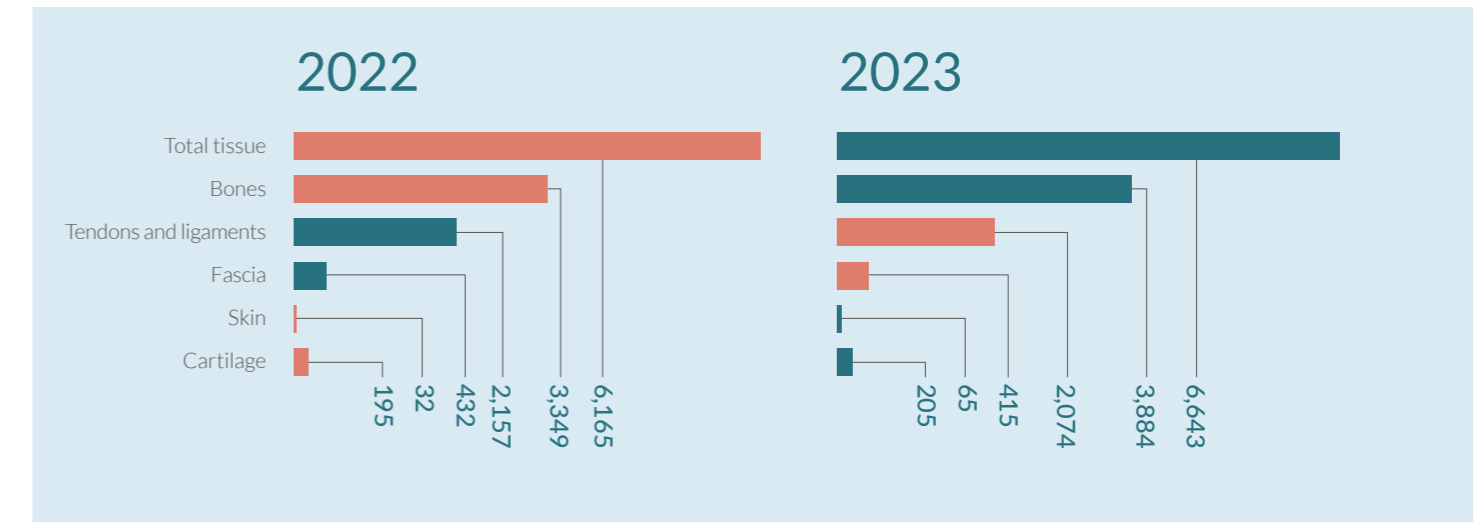
Unfortunately, there was a further decline in amnion donations. The DIZG received **67** in the year 2023, **14** fewer than in the previous year.

However, there has been an increase in bone donation, which rose from **3,349** to **3,884**.

TISSUE DONATIONS PER YEAR 2009 – 2023



Which tissues were donated



A total of **9,642** individual musculoskeletal tissues (including skin) were received in the reporting year, which were released for tissue processing in the same period.

Help with tissue donations

Anyone who makes the decision to donate tissue enables other people to improve their quality of life. The transplantation of donor tissue means the end of a period of suffering for many patients and can even prevent amputations. Surgical therapy with bone and tissue transplants allows patients to regain more mobility and thus the chance to lead a much more active life. This is exactly what the DIZG is committed to.





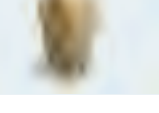


Increased delivery of allogeneic transplants

In the reporting year, 67,828 allogeneic transplants were delivered – 950 more than in 2022. The DIZG made these available to clinical facilities throughout Germany and in 27 other countries.

March was once again a very strong month in terms of sales, with 7,365 transplants provided. Ideally, this means that just as many patients could be helped.

TRANSPLANTS THAT WERE PARTICULARLY IN DEMAND IN 2023

	Description	Quantity	
1	Granulate	24,895	
2	Chips	15,639	
3	Cancellous bone blocks and wedges	8,859	
4	DBMx-press, putty	4,776	
5	Femoral heads	4,540	

These transplants are used, for example, in the fields of orthopaedics and traumatology, spinal surgery, sports medicine and oral and maxillofacial surgery.

i We are happy to support you in the supply of tissue transplants that are not available nationally on prescription from a doctor.



OVERNIGHT DELIVERY

If necessary, the DIZG delivers the transplants required for medical care overnight.



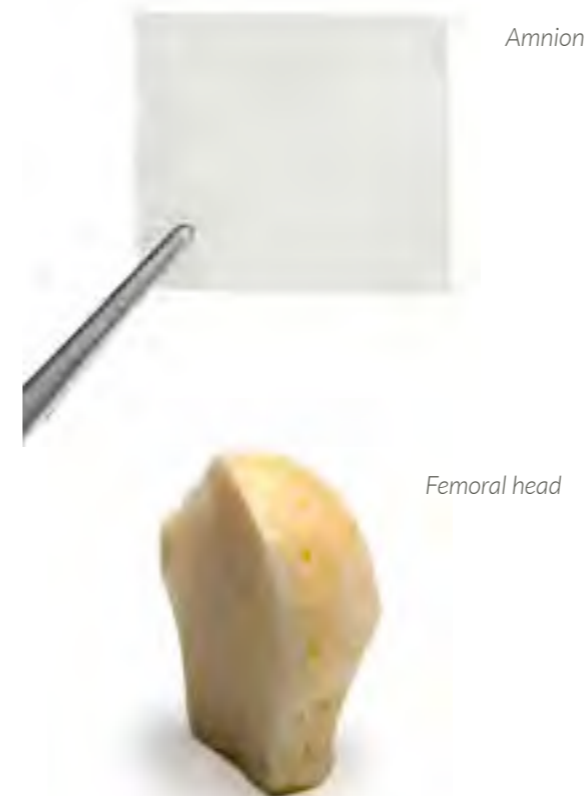
SAFELY SUPPLIED

For clinical facilities that do not have their own bone bank, we are happy to take over the complete supply of safe allogeneic tissue transplants.

Insights into tissue donation

The Tissue Donation Department plays a central role in carrying out essential tasks. Without the commitment of this team, there would be a lack of donated tissue that can be processed into human transplants for upcoming operations in various medical fields. National and international recovery programs and clinics that participate in living donation programs are therefore very important cooperation partners. The comprehensive donor screenings commissioned to external laboratories must also be coordinated.

Live versus post-mortem tissue donation



Tissue can be donated by living donors or post-mortem. Examples of living donations are

- > Amnion donations and
- > femoral head donations.

Everyone from the age of 16 can consent to tissue donation. Whether the tissue is suitable for donation must be carefully examined on a case-by-case basis. Every donation is free of charge.

i The anonymization of the donation is enshrined in law. The recipient of a tissue transplant does not know the name of the donor. The donor's relatives also do not know who receives the donated tissue.

Clinics benefit from tissue donation

The enormous demand for safe human tissue transplants exceeds the supply. They are used in all specialist disciplines, but particularly in:



Trauma surgery



Orthopaedics



Maxillary and facial surgery



Reconstructive surgery

These transplants are used in a variety of specialized areas such as endoprosthetic revision surgery, tumor surgery and burns medicine.



The more clinics participate in the donation process, the more patients can be supplied with transplants throughout Germany and Europe. To achieve this, expansion of tissue donation is necessary.

Post-mortem tissue retrieval

Post-mortem tissue donation is only possible if it corresponds to the presumed will of the deceased. The willingness to donate can be documented via the organ donor card or a patient decree. The next of kin are also contacted in order to confirm the presumed will of the deceased.

Donation programs are important

The DIZG does not have its own recovery team, but works together with partners:

- > Germany-wide,
- > Europe-wide and
- > in the USA.

The recovery programs are generally non-profit organizations that have worked hard to establish a hospital network to enable tissue donation. The Tissue Donation Department works closely with these teams. The aim is also to attract more clinics to participate in tissue recovery to increase the availability of allografts for patient care.



MTF Biologics – a reliable partner since 2000

The DIZG received more than 12 % of all tissue donations in 2023 from its non-profit US sister company MTF Biologics, currently the world's largest tissue bank.

The high availability is primarily due to the dedicated employees of the Tissue Donation department. They are driven by the knowledge that they are noticeably improving the quality of life of recipients and also helping donor families to respect the wishes of deceased relatives. They conduct outstanding work and ensure that thousands of DIZG-quality tissue transplants are available every year.



An insight into the work of the Tissue Donation Department

i Organ donors can also be tissue donors, the reverse case is rather rare. The law stipulates that organ donation always takes precedence over tissue donation. It must be documented that tissue donation does not interfere with organ donation or that the latter is not possible.



4



1



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2



3



6

- Fig. 1* The aim is to recruit further clinics for the tissue donation program.
- Fig. 2* Storage of the tissue until final release
- Fig. 3* Temperature control of incoming tissue donations
- Fig. 4, 5* Checking the plasma samples according to the four-eyes principle
- Fig. 6* The majority of incoming living donations are femoral heads.

The living femoral head donation

The femoral head is donated after medical consultation and with informed consent of the patient as part of a necessary hip joint endoprosthesis. This means that the femoral head, which would otherwise be medically disposed of, is made available. This donation is a simple way of helping other people to improve their quality of life.

ARRIVAL OF FEMORAL HEADS

The clinics send the donated femoral heads collected and frozen to tissue banks such as the DIZG. Once they arrive, the temperature is first checked.

BEFORE FURTHER PROCESSING

Only after extensive screening and the determination of donor suitability are donated femoral heads released for further processing into transplants.

THE PROCESS AT A GLANCE



1

Before collection: Legal requirements

Conclusion of a contract with the DIZG and registration of a responsible physician at the donating hospital



2

Before collection:

Training in the clinic by employees of the DIZG



3

Donor selection

Medical history in the clinic, medical assessment of donor suitability, medical consultation and informed consent



4

Removal of the femoral head

Removal as part of a planned operation using the usual surgical technique



5

Serological tests

Comprehensive screening is carried out by the DIZG. If all criteria are met, the tissue is released for further processing into a transplant.

In the donation program for 15 years

Interview with Dr. Axel Radelhof, Schön Klinik Hamburg Eilbek



Your clinic has been a partner of the DIZG in the field of endoprosthetic femoral head donation for 15 years. Why are you involved?

When I came to the Schön Klinik over 15 years ago, there was already an up-and-coming orthopaedics department. What did not exist, however, was participation in a donation program. I was familiar with the DIZG and had always been interested in revision arthroplasty. The cases thereof in particular are associated with larger bone defects that can be easily filled with transplants. However, if nobody gets involved in donation programs, there are no transplants available for patient care. So, as a young senior physician, I committed myself to participating. If not us, who else? I think it's important to get involved.

Where do you see the greatest challenges for femoral head donation in Germany?

The challenges arise from changing demographics and people's increasing life expectancy. There will be an increase in revision endoprosthetics. In general, the challenge will lie in patient care. We already need more donor tissue for the treatments than we can supply.

How high is the approval rate among patients?

All patients who are scheduled for a hip endoprosthesis and for whom there are no exclusion criteria in the medical history are informed about the possibility of donation and receive a questionnaire. Consent to donation is very high and is well over 90 % in our clinic. Patients like the fact that their removed femoral head is processed into human transplants that can help others instead of being disposed of.

What are patients' biggest concerns?

There are no concerns about the donation itself. After all, the removed femoral head would otherwise simply be disposed of medically. There are also no uncertainties among the recipients after the information session. They are aware of the exclusion criteria, the extensive screenings and that transplants no longer contain any organic material and therefore pose no risk of infection.

If you could change anything about the hip donation process, what would it be?

If I could change anything about the process, it would be mandatory participation for every clinic. This is unlikely to be enforced, even if every removed femoral head could then be processed into transplants. Over the years, the considerable amount of bureaucracy involved has become apparent. The organization in the clinic is not easy either; it can take some time for the process to settle in. Nevertheless, the personnel

deployment, the costs, the necessary laboratory tests – all combined involve less effort than running your own bone bank.

What words would you use to motivate other clinics to participate in the donation program?

Particularly at a time of maximum challenges in the treatment of elderly patients and an increased need for bone donation, participation should be a matter of course – especially as an endoprosthesis center. Despite the effort involved, it is worthwhile because sufficient donor material is then permanently available and patient care can therefore be better provided.

Dr. Radelhof, thank you for the interview.

How donated tissue becomes urgently required transplants

Within the tissue bank's three teams—preparation, aseptic processing, and labeling—donated tissues are released for processing into transplantable materials for patient care. We spent a day with our colleagues to learn more about their activities and the various steps involved. Today they'll be processing tissue for a batch of cancellous bone, among others.

The upcoming tasks and team assignments are clearly visible on the weekly schedule, while the aseptic team uses a large planning board.

PREPARATION

In hygienically monitored rooms, donated post-mortem tissue undergoes thawing in the first step using a new disinfecting process with a defined microorganism-reducing peracetic acid solution. After thawing, the cancellous tissue is cleaned, ground (Fig. 1), sawed and rinsed (Fig. 2) by a team of two to three colleagues. Tissue samples are then collected for bioburden analysis and later handed over to the Quality Control & Documentation (QCD) department. In this analysis, the number and type of microorganisms present in the donated tissue are determined after preparation and before sterilization. As in all areas of production, each process step is immediately documented in detail (Fig. 3).

At the end of preparation, the cancellous tissue is ready for sterilization or subsequent process steps. Until then, it is temporarily stored at -35 °C. However, further processing of

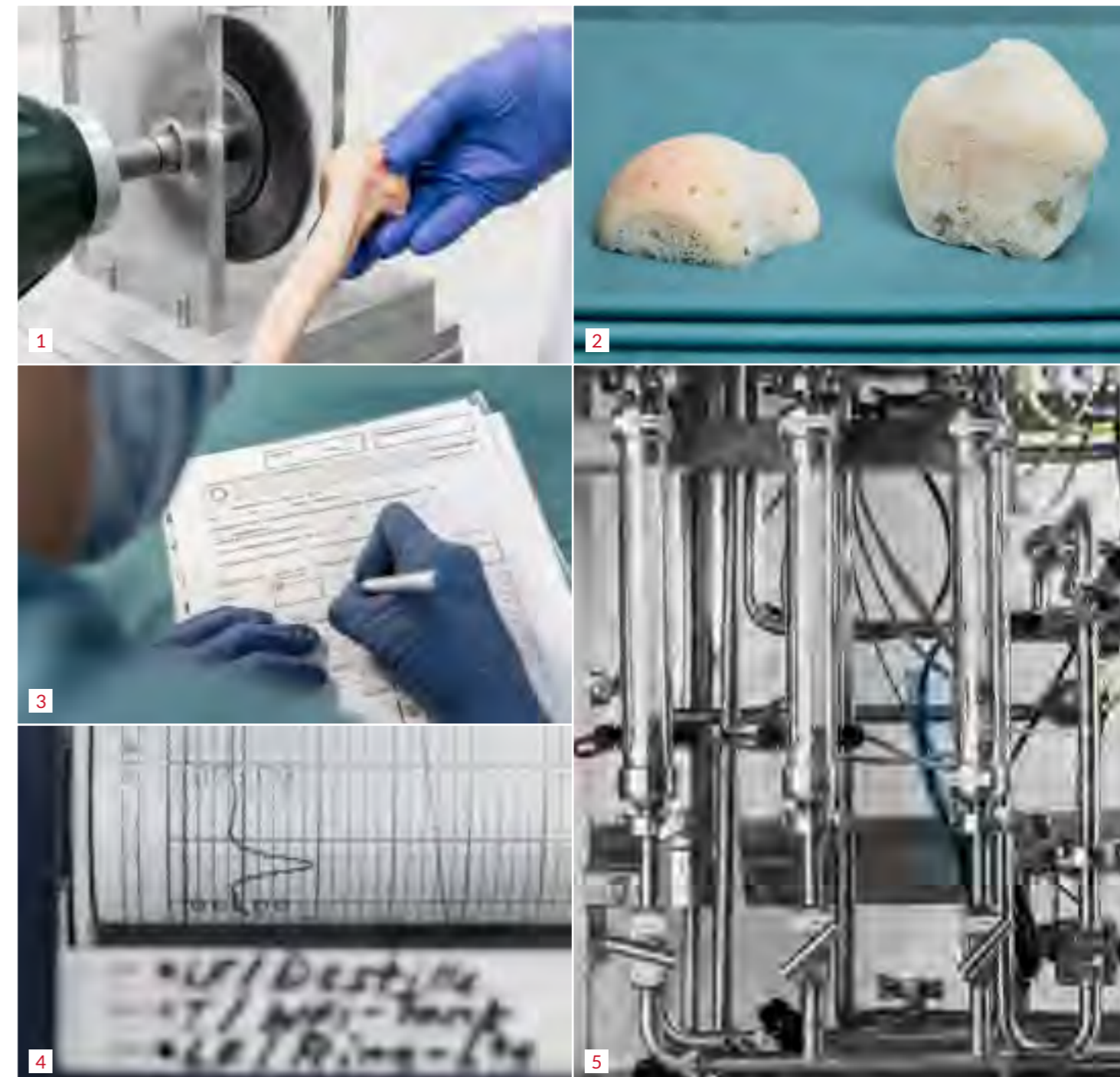
the tissue can only take place once the findings of the bioburden analysis have been confirmed and the tissues have been released for sterilization by the QCD department.

CLEAN ROOM WORK

Before entering the cleanroom, various tasks have to be completed. It is particularly important to check all systems. It must be ensured that they all function properly and that the required quality of the rooms, such as air purity, temperature and humidity, as well as the media, such as water, is guaranteed (Fig. 4 and 5).

At the same time, three other teams have registered for cleanroom work. One of them is located in the class D rooms, where they sterilize the tissue and prepare the instruments, primary packaging, labels for identifying the preparations and the devices. The other two teams will enter class B cleanrooms via a complex,

multistage induction process. These also contain the cleanroom class A zones. After sterilization, tissue may only be handled in this highest cleanroom class.





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STERILIZATION AND REPROCESSING

The team begins the work processes in the class D rooms. First, the tissue to be sterilized is placed at room temperature in sterile filtered water for injection (WFI), i.e. water of particularly pure quality, thawed according to the rules of the pharmacopoeia. During this time, the sterilization solution based on peracetic acid and ethanol is prepared (Fig. 6). The tissue is placed in a globally unique sterilization container (Fig. 7) and then covered with the sterilization solution (Fig. 8). The sterilization container is closed, moved into one of the "sterilization tunnels" and connected to the required media: Compressed air, vacuum and WFI (Fig. 9).

THE PRINCIPLE OF STERILIZATION TUNNELS

Sterilization takes place in rooms that create a connection between cleanroom class D (sterilization) and A (aseptic removal after sterilization) and are therefore called sterilization tunnels. Cleanroom class A is created and maintained in the tunnel by active ventilation with filtered air and environmental monitoring. Permanent control is carried out by a monitoring system (Fig. 10), which records all relevant values and can later print them out for each process. This data then is part of the batch documentation.

The electronically controlled sterilization process takes four hours. During this time, the D Team can take care of the other reprocessing processes: The instruments, primary packaging materials, labels and trays in which sterilized tissue is stored are cleaned and prepared for hot steam sterilization (Fig. 11 and 12).

After peracetic acid sterilization, the sterilization containers are also cleaned, steamed and checked using a filter integrity test (Fig. 13).

After the sterilization time has elapsed, the sterilization solution is drained and the tissue is rinsed with sterile-filtered WFI until less than 1 ppm peracetic acid is detected. Once the requirements for cleanroom class A in the tunnel are fulfilled, the aseptic removal of the sterilized tissue can begin. During peracetic acid sterilization, the other two cleanroom teams have already aseptically packed a batch of previously sterilized and preserved tissue.



14



15



16

ASEPTIC REMOVAL OF THE TISSUE

The aseptic removal of the sterilized cancellous bone tissue is carried out by a team of two, of which only one person has contact with the sterilized tissue. The other prepares everything necessary for the removal: This person places the trays in which the sterilized tissue is transferred in the cleanroom class A zone, opens and disinfects the window to the sterilization tunnel and unlocks and opens the lid of the sterilization container. Now, the person handling the tissue enters the A zone, puts on a new, second sterile pair of gloves, removes the sterilized tissue from the sterilization container and places this in the tray prepared by the partner (Fig. 14). Up to three sterilizations can be performed daily in parallel.

PRESERVATION OF THE TISSUE

After sterilization and aseptic removal, preservation of the tissue is the next step. For this purpose, the cancellous tissue in the trays is placed in the freeze-drying unit (Fig. 15). The tissue is then freeze-dried for two days.

PACKING OF THE SPONGIOSA TISSUE

After freeze-drying, the cancellous bone tissue from a sterilization cycle can be aseptically packaged as a single batch. This process also takes place in cleanroom class A and is again carried out by a team of two. Once again, only one person handles the already sterilized containers, instruments, labels and packaging materials.

The packaged tissue is provided with identifying labels, packed in

two sterile bags and shrink-wrapped. During the execution of the work steps, the second person documents the complete chronological sequence with all details of each packaged unit and all incidents or deviations (Fig. 16).

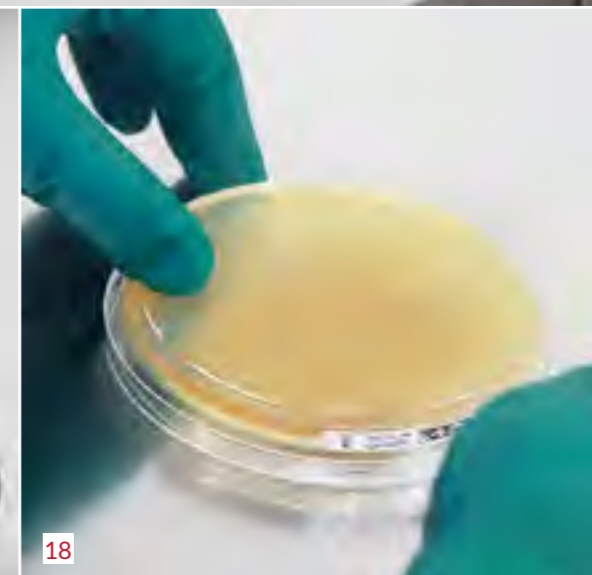
All aseptic steps are carried out under cleanroom class A conditions and are subject to comprehensive technical monitoring to ensure that the requirements for rooms, equipment and personnel are met at all times. Air velocity, particles, temperature, humidity and pressure are also continuously measured using probes (Fig. 17) and the results are documented electronically. To ensure sterility and microbiological monitoring of work surfaces and personnel, samples are taken from each batch. For microbiological air monitoring in the clean room during each sterile packaging of a batch, sedimentation plates are placed at

defined critical points (Fig. 18).

After checking for sterility, the preparations that have just been sterile-packed and the corresponding documentation for the batches must be discharged from the cleanrooms. Each batch remains in sealed boxes between the next work steps (Fig. 19 and 20).



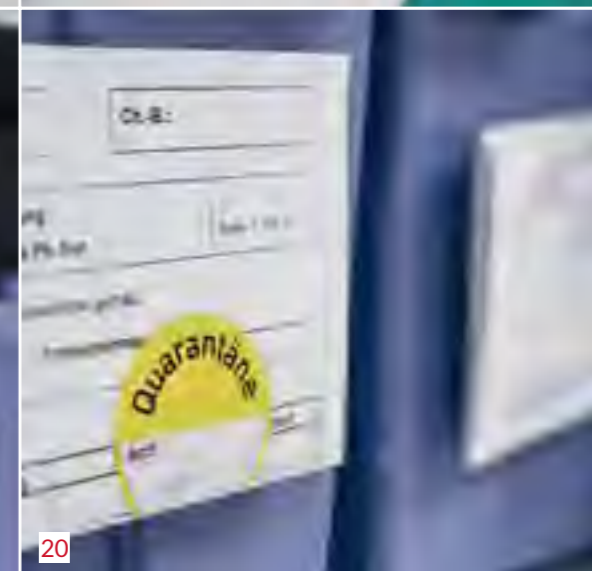
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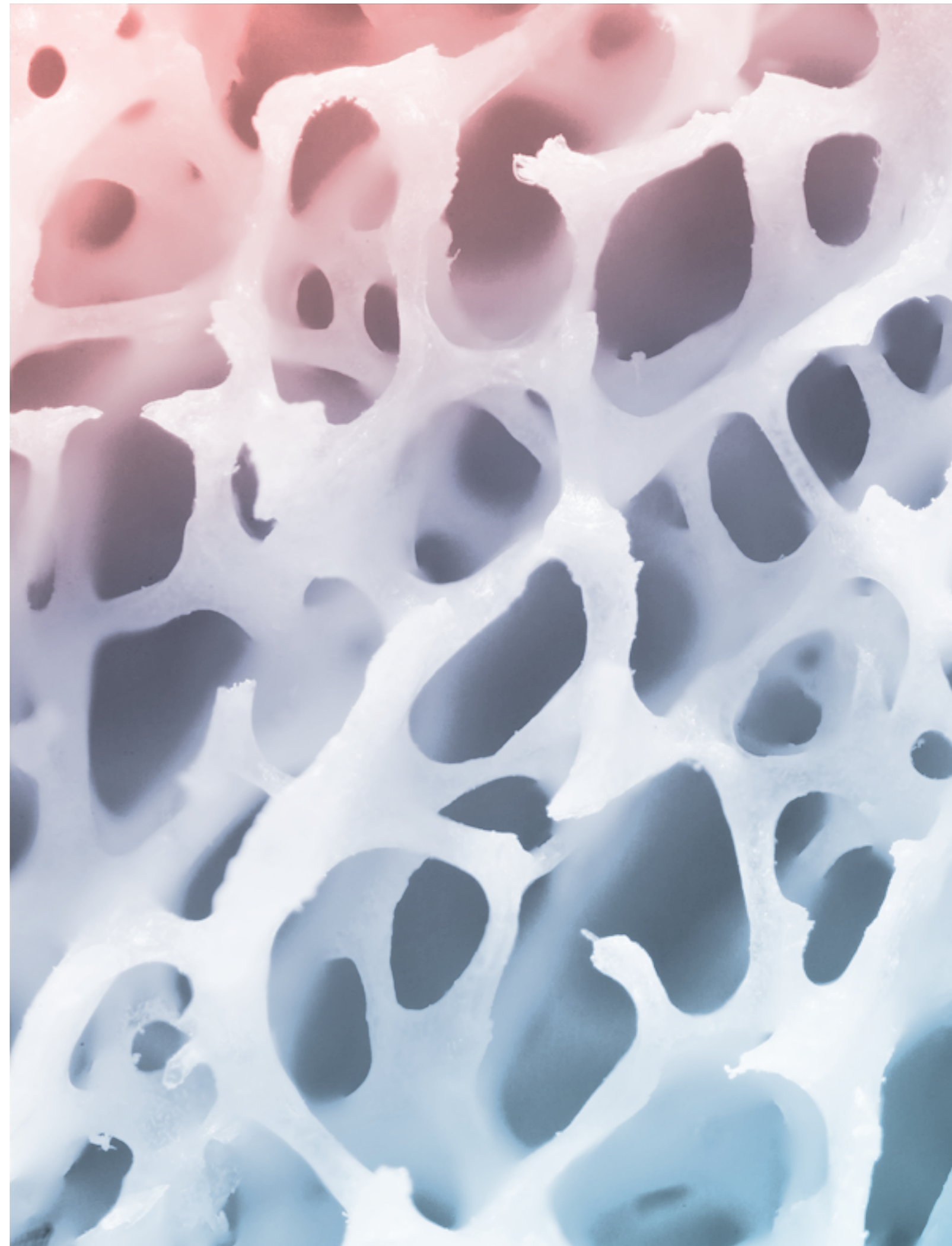
LABELING OF THE ALLOGRAFTS

The sealed crates are handed over to the labeling team, which also documents all work steps. Before the preparations can be labeled by one or two colleagues in rooms that are also hygienically monitored, work steps such as printing the labels, identifying the required User Leaflet and Summary of Product Characteristics and preparing the required folding boxes must be carried out (Fig. 21).

During the process of labeling a batch, each preparation and the corresponding label are scanned and checked: The content of the bag, i.e. the preparation, the article number and the data on the label must match. Only then can the

labels be affixed to the preparation, the folding box, the UL and SmPC and the transplant record sheet form enclosed (Fig. 22).

Labeling time depends on the batch size, typically taking around half a workday. Once labeled, the transplants remain in the labeling rooms until handover to the Quality Control Department.



Research: Developing the new, analyzing the familiar

The Research and Development (R&D) team is driven by the desire to optimize transplant properties, adapt them to constantly changing clinical requirements, identify new surgical applications for existing transplant forms and develop new transplants. The aim is to provide surgeons with the best possible access to human transplants in order to ultimately offer patients improved prospects of recovery, a more active life and a higher quality of life. Patience and persistence pay off.

The development of a transplant can take several years. It is essential not to be demotivated by setbacks during experiments. After all, not everything always goes as planned. Changing your point of view, staying interested, and asking questions, all while paying close attention to details and documenting and analyzing them, are the essence of research.

Anyone working in this field must be meticulous, self-critical and highly self-motivated. Even with

disappointing results, perseverance and the urge to discover new things, must prevail.

2023: THE PORTFOLIO CONTINUES TO GROW

The DIZG has expanded its portfolio with the introduction of the Shark Screw® in Germany and three additional Spongioflex® sizes.



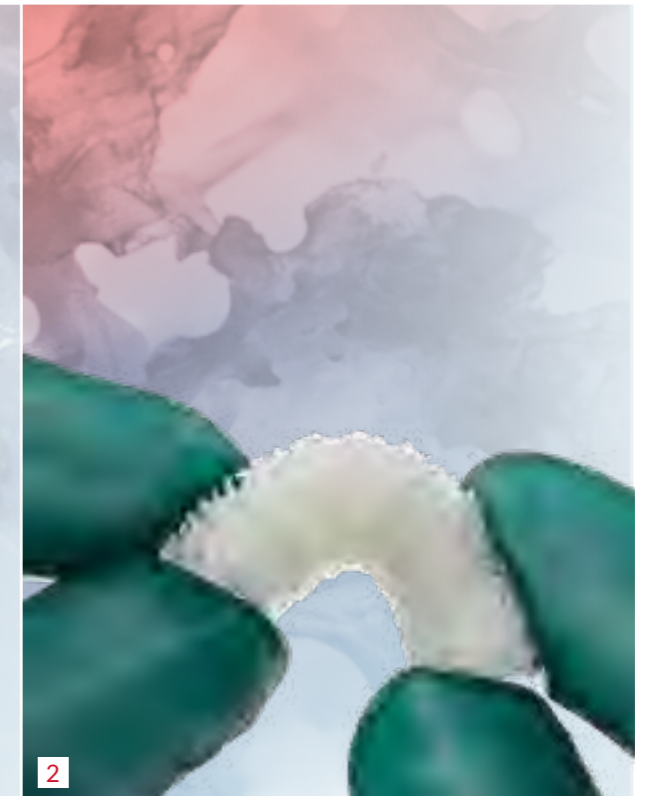
The aim is to answer questions about processes and transplants arising from production or projects as clearly as possible with the help of our own investigations and available information from others, such as scientific studies and publications.



Versatile allografts



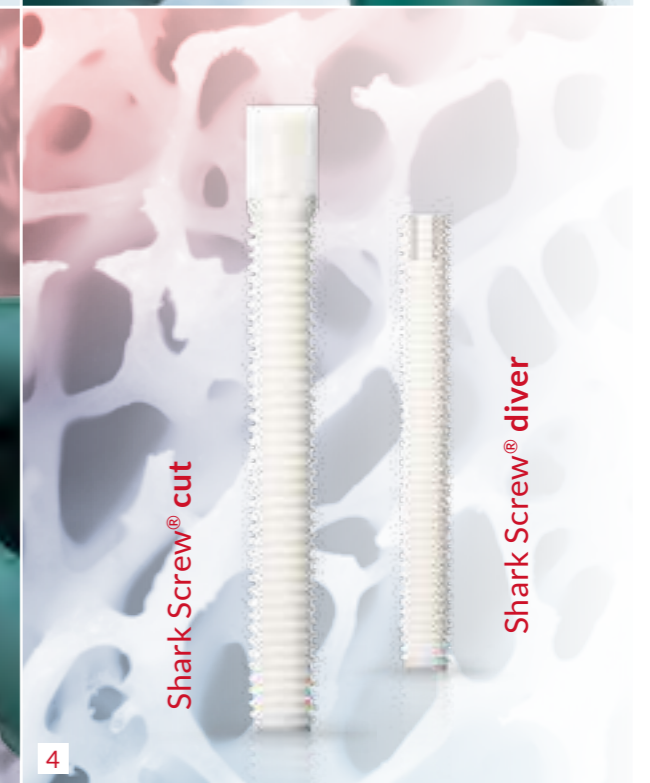
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2



3



4

Allogeneic transplants are particularly impressive and can be used in a wide range of indications, as the R&D team has shown in a joint publication with Prof. Dr. Carsten Perka, Medical Director of the Center for Musculoskeletal Surgery at the Berlin University Hospital, and Dr. Tu-Lan Vu-Han, head of the DGOU working group "Allogeneic tissue transplants".⁶

The publication shows that medical users' interest in allografts has grown due to improved manufacturing processes, increased safety and better availability. The result: demand for allografts has risen rapidly over the last ten years. Between 2008 and 2018, the use of allogeneic bone grafts in orthopaedic surgery increased by 74.1 % in Germany alone, while the use of autologous bone grafts fell by 14.3 % in the same period.⁷ In addition, in some areas, such as allogeneic meniscus transplantation, there are simply no autologous alternatives.

The wide range of applications for allogeneic transplants offers surgeons and patients a variety of treatment options. We briefly present some of these versatile allografts

1. DBM putty

DBM putty consists of the demineralized bone matrix (DBM) of human donor tissue and a biocompatible carrier substance. During production, the mineral components are first removed from cortical bone. The DBM obtained in this way is then mixed with a sodium hyaluronate solution. The sodium hyaluronate has an anti-inflammatory effect⁸, accelerates the healing process⁹ and supports vascularization.¹⁰

Possible areas of application include fractures, fracture clefts, spondylodesis, reconstruction of comminuted and splinter fractures, filling of drill canals, cysts, the treatment of cages on the spine, tumor surgery and orthodontics.

2. Spongioflex®

Spongioflex® consists of demineralised human cancellous bone tissue. Once rehydrated, the transplant regains its elasticity and flexibility, becoming highly stable and highly resistant to suture tears. Due to its flexibility, Spongioflex® can also be used arthroscopically via suitable portals.

Prof. Dr. Philipp Moroder published an arthroscopic procedure for the reconstruction of small to moderate anterior glenoid defects with demineralized cancellous bone in 2018.¹¹ Since then, he has been investigating this procedure in a prospective study using Spongioflex® with very good interim results.¹²

Three other Spongioflex® sizes are suitable as partial replacements for meniscus damage. Initial results of a case report indicate rapid ingrowth of the human transplant within twelve weeks.²

3. Fiberfill®

Fiberfill® combines demineralized bone matrix and cancellous granules, both of which are of human origin. By using the cancellous bone granules as a supplier for calcium and phosphate, the osteogenic potential of osteoblasts is higher than with demineralized granules alone.¹³ This means that the combination of DBM and cancellous bone optimizes healing.¹⁴

After rehydration, Fiberfill® is:

- > cohesive,
- > malleable and
- > adaptable to the defect situation.

In addition, this human filler and carrier graft is characterized by a very good absorption capacity and a long-lasting elution of antibiotics.¹⁵

These properties make the graft suitable for a wide range of applications in aseptic and septic bone surgery, e.g. for:

- > chronic osteomyelitis,
- > septic and aseptic pseudarthrosis,
- > the filling of cysts and
- > revision arthroplasty.

Results of animal studies show that demineralized fibers

- > heal a critical femoral defect in rats, comparable to the autologous gold standard,¹⁶
- > did not show systemic toxicity and immunogenicity in a study with rats.¹⁷

4. Shark Screw®

The human bone screw, which becomes the patient's own tissue through remodeling³, can be used in hand and foot surgery. For example in:

- > Arthrodesis^{18,19},
- > Refixation of bone fragments¹⁹,
- > Osteotomies,
- > Fractures and pseudarthroses²⁰,
- > osteochondral defects and
- > revision surgery²¹.

In addition to hand and foot surgery The Shark Screw® is used in Austria for other indications, e.g.

- > Osteotomies on the radius and ulna (ulnar advancement, sagittal ulna splitting),
- > Refixation of dissecates on humerus and radius,
- > Latarjet operations, Bankart lesions,
- > Refixation of dissecates (osteochondrosis dissecans) and
- > antegrade screw connections of cartilage-bone injuries.

The biological transformation of the Shark Screw® is its great advantage over metal screws, which may require further surgery. This is why the human bone screw is also used in pediatric surgery in Austria.

THE TRANSPLANT FORM

Obtaining information on how transplants are used is important for the DIZG. Only through this approach can we identify optimization possibilities and provide even better guidance to surgeons. A transplant information sheet is therefore enclosed with every transplant. It asks, for example, about the patient's age, gender, diagnosis, type of surgical procedure, special features during the operation and localization.

Each completed and returned form supports the DIZG's allograft register, which currently contains 62,600 verified data sets on the use of allogeneic avital hard and soft

tissue transplants and thus also enables the further and new development of human transplants. Based on the information received, trends in the use of specific transplant groups can also be identified.

Inquiries to the DIZG allograft register are free of charge. Inquiries are processed from those clinical institutions that actively contribute to further data by returning fully completed transplantation forms to the DIZG, as well as those that support nationwide care through an active tissue donation contract with the DIZG. Please send your request by e-mail to allograftregister@dizg.de.

RESEARCH

The knowledge of current publications relating to DIZG transplants and methods of analysis used plays a major role in every aspect of R&D activities. Scientific information is also crucial for German Medicines Law (AMG)-compliant approval procedures for tissue transplants. Here, existing publications must be used to argue the safety and efficacy of human tissue. With the researched studies and publications, our transplant specialists also provide doctors with the latest information in direct discussions.



Knowledge of current studies is also mandatory for own publications.

The form is titled 'Transplantationsbegleitschein (Transplantaterfassungssystem)' and is issued by the 'DEUTSCHES INSTITUT FÜR ZELL- UND GEWEBEERSATZ'. It contains various fields for data entry, including 'Datum der OP', 'Klinik', 'Fachrichtung', 'Alter des Patienten', 'Geschlecht', 'DIAGNOSE', 'ART DER OPERATION', 'ICD Codes', 'OPS Codes', 'LOKALISATION DER OP AM KÖRPER', and 'Beschreibung der Lokalisation'. It also includes a QR code and contact information for the DIZG.

Transplantation form: Each completed form is entered into the allograft register.

Scientific publications in international journals to which DIZG employees or research partners have contributed - selected examples

- 1 **Falkner F, Mayer SA, Heuer M, Brune J, Helt H, Bigdeli AK, Dimmler A, Heimel P, Thiele W, Sleeman JP, Bergmeister H, Schneider KH, Kneser U, Thomas B.** Comparison of Decellularized Human Dermal Scaffolds versus Bovine Collagen/Elastin Matrices for Engineering of Soft-Tissue Flaps. *Plastic and Reconstructive Surgery*. 2024 Jan 1;153(1):130-141.
- 2 **Bormann N, Schmock A, Hanke A, Eras V, Ahmed N, Kissner MS, Wildemann B, Brune JC.** Analysis of the Ability of Different Allografts to Act as Carrier Grafts for Local Drug Delivery. *Journal of Functional Biomaterials*. 2023 Jun 1;14(6):305.
- 3 **Söhling N, Heilani M, Fremdling C, Schaible A, Schröder K, Brune JC, Eras V, Nau C, Marzi I, Henrich D, Verboket RD.** One Stage Masquelets Technique: Evaluation of Different Forms of Membrane Filling with and without Bone Marrow Mononuclear Cells (BMC) in Large Femoral Bone Defects in Rats. *Cells*. 2023 Apr 30;12(9):1289.
- 4 **Barski D, Tsaour I, Boros M, Brune J, Otto T.** Functional Recovery after the Application of Amniotic Tissues and Methylene Blue during Radical Prostatectomy—A Pilot Study. *Biomedicine*. 2023 Aug 13;11(8):2260.
- 5 **Dabaghi M, Eras V, Kaltenhaeuser D, Ahmed N, Wildemann B.** Allografts for partial meniscus repair: an in vitro and ex vivo meniscus culture study. *Frontiers in Bioengineering and Biotechnology*. 2023 Oct 12;11:1268176.
- 6 **Behrendt S.** MRI follow up of bilateral partial meniscal substitution with a demineralized bone block. A case report. *Radiology Case Reports*. 2022 Oct 27;18(1):21-26.
- 7 **Vogt W, Borchert GH, Ahmed N, Brune JC.** Anatomical acromioclavicular joint stabilization with chemically sterilized tendon allografts: A retrospective study. *Shoulder & Elbow*. 2023 Aug;15(4):411-423.
- 8 **Ahmed N, Eras V, Pruß A, Perka C, Brune J, Vu-Han TL.** Allografts: expanding the surgeon's armamentarium. *Cell and Tissue Banking*. 2023 Mar;24(1):273-283.
- 9 **Huber T, Hofstätter SG, Fiala R, Hartenbach F, Breuer R, Rath B.** The Application of an Allogenic Bone Screw for Stabilization of a Modified Chevron Osteotomy: A Prospective Analysis. *Journal of Clinical Medicine*. 2022 Mar 3;11(5):1384.
- 10 **Pastl K, Pastl E, Flöry D, Borchert GH, Chraim M.** Arthrodesis and Defect Bridging of the Upper Ankle Joint with Allograft Bone Chips and Allograft Cortical Bone Screws (Shark Screw®) after Removal of the Salto-Prosthesis in a Multimorbidity Patient: A Case Report. *Life (Basel)*. 2022 Jul 11;12(7):1028.
- 11 **Falkner F et al.** A Comparative Study of Decellularized Human Dermal Scaffolds versus Bovine Collagen/Elastin Matrices for in vivo Engineering of Axially Vascularized Soft Tissue Flaps in Rats. 2022 (accepted, not published yet).
- 12 **Minkus M, Akgün D, Thiele K, Karpinski K, Moroder P.** Bankart-Plus zur Behandlung von Patienten mit anteriorer Schulterinstabilität und kleinen bis moderaten Glenoiddefekten. *Obere Extremität*. 2022 Oct 6;17(4):243-249.
- 13 **Beier L, Faridi A, Neumann C, Paepke S, Mau C, Keller M, Strittmatter HJ, Gerber-Schäfer C, Bauer L, Karsten MM, Kümmel S, Blohmer JU.** Human Acellular Dermal Matrix (Epiflex®) in Immediate Implant-Based Breast Reconstruction after Skin- and Nipple-Sparing Mastectomy and Treatment of Capsular Fibrosis: Results of a Multicenter, Prospective, Observational NOGGO-AWOGyn Study. *Breast Care (Basel)*. 2021 Oct;16(5):461-467.
- 14 **Blohmer JU, Beier L, Faridi A, Ankel C, Krause-Bergmann B, Paepke S, Mau C, Keller M, Strittmatter HJ, Karsten MM.** Patient-Reported Outcomes and Aesthetic Results after Immediate Breast Reconstruction Using Human Acellular Dermal Matrices: Results of a Multicenter, Prospective, Observational NOGGO-AWOGyn Study. *Breast Care (Basel)*. 2021 Aug;16(4):335-342.
- 15 **Eras V, Graffunder J, Ahmed N, Brune JC.** Influence of peracetic acid-ethanol sterilisation on the biomechanical properties of human meniscus transplants. *Journal of Experimental Orthopaedics*. 2021 Mar 5;8(1):18.
- 16 **Verboket RD, Irrle T, Busche Y, Schaible A, Schröder K, Brune JC, Marzi I, Nau C, Henrich D.** Fibrous Demineralized Bone Matrix (DBM) Improves Bone Marrow Mononuclear Cell (BMC)-Supported Bone Healing in Large Femoral Bone Defects in Rats. *Cells*. 2021 May 19;10(5):1249.
- 17 **Barski D, Gerullis H, Ecke T, Boros M, Brune J, Beutner U, Tsaour I, Ramon A, Otto T.** Application of Dried Human Amnion Graft to Improve Post-Prostatectomy Incontinence and Potency: A Randomized Exploration Study Protocol. *Advances in Therapy*. 2020 Jan;37(1):592-602.
- 18 **Söhling N, Leiblein M, Schaible A, Janko M, Schwäble J, Seidl C, Brune JC, Nau C, Marzi I, Henrich D, Verboket RD.** First Human Leucocyte Antigen (HLA) Response and Safety Evaluation of Fibrous Demineralized Bone Matrix in a Critical Size Femoral Defect Model of the Sprague-Dawley Rat. *Materials (Basel)*. 2020 Jul 13;13(14):3120.
- 19 **Verboket RD, Leiblein M, Janko M, Schaible A, Brune JC, Schröder K, Heilani M, Fremdling C, Busche Y, Irrle T, Marzi I, Nau C, Henrich D.** From two stages to one: acceleration of the induced membrane (Masquelet) technique using human acellular dermis for the treatment of non-infectious large bone defects. *European Journal of Trauma and Emergency Surgery*. 2020 Apr;46(2):317-327.
- 20 **Ackermann C, Frings J, Alm L, Frosch KH.** Arthroscopic Controlled Closed Reduction and Percutaneous Fixation of Posterolateral Tibia Plateau Impression Fractures. *Arthroscopy Techniques*. 2019 Jul 19;8(8):e867-e874.
- 21 **Anavi Lev K, Chaushu L, Schwarz F, Artzi Z.** Bone-implant-contact and new bone formation around implants placed in FDB blocks compared to placement at the adjunction of particulate FDB. *Clinical Implant Dentistry and Related Research*. 2020 Feb;22(1):21-28.
- 22 **Wagner JM, Conze N, Lewik G, Wallner C, Brune JC, Dittfeld S, Jaurich H, Becerikli M, Dadras M, Harati K, Fischer S, Lehnhardt M, Behr B.** Bone allografts combined with adipose-derived stem cells in an optimized cell/volume ratio showed enhanced osteogenesis and angiogenesis in a murine femur defect model. *Journal of Molecular Medicine (Berlin)*. 2019 Oct 1;97(10):1439-1450.
- 23 **Janko M, Sahn J, Schaible A, Brune JC, Bellen M, Schroder K, Seebach C, Marzi I, Henrich D.** Comparison of three different types of scaffolds preseeded with human bone marrow mononuclear cells on the bone healing in a femoral critical size defect model of the athymic rat. *Journal of Tissue Engineering and Regenerative Medicine*. 2018 Mar;12(3):653-666.
- 24 **Verboket R, Leiblein M, Seebach C, Nau C, Janko M, Bellen M, Böning H, Henrich D, Marzi I.** Autologous cell-based therapy for treatment of large bone defects: from bench to bedside. *European Journal of Trauma and Emergency Surgery: Official Publication of the European Trauma Society*. 2018 Oct;44(5):649-665.
- 25 **Knels R, Stüpmann K, Pruß A, Klerke J, Kardoeus J, Hiller J.** Coding of Tissue and Cell Preparations Using Eurocode. *Transfusion Medicine and Hemotherapy*. 2017 Nov;44(6):401-405.
- 26 **Paprottka FJ, Krezdorn N, Sorg H, Könniker S, Bontikous S, Robertson I, Schlett CL, Dohse NK, Hebebrand D.** Evaluation of Complication Rates after Breast Surgery Using Acellular Dermal Matrix: Median Follow-Up of Three Years. *Plastic Surgery International*. 2017;2017:1283735.
- 27 **Pruß A.** Coding of Tissue and Cell Products. *Transfusion Medicine and Hemotherapy*. 2017 Nov;44(6):382.
- 28 **Schroeter J, Schulz T, Schroeter B, Fleischhauer K, Pruß A.** Implementation of the Single European Code in a Multi-Tissue Bank. *Transfusion Medicine and Hemotherapy*. 2017 Nov;44(6):396-400.
- 29 **Vitacolonna M, Belharazem D, Hohenberger P, Roessner ED.** In-vivo quantification of the revascularization of a human acellular dermis seeded with EPCs and MSCs in co-culture with fibroblasts and pericytes in the dorsal chamber model in pre-irradiated tissue. *Cell and Tissue Banking*. 2017 Mar;18(1):27-43.
- 30 **Vitacolonna M, Doyon F, Belharazem D, Tsagogiorgas C, Hohenberger P, Roessner ED.** Transplanted fibroblasts proliferate in host bronchial tissue and enhance bronchial anastomotic healing in a rodent model. *The International Journal of Artificial Organs*. 2017 Sep 15;40(9):515-521.
- 31 **Hohenberger P, Rössner E, Nowak K.** 9.7 Tumoren der Thoraxwand. In: *Expertise Thoraxchirurgie*, edited by Müller MR, Watzka SB. Thieme Verlag 2016, 331-338.

- 32 **Smith MD, Brune JC, Petschke B, Mönig HJ, Hartmann B.** 21 Kultivierte autologe Hautzellentransplantate: Historie, Regulatoria und Praxis. In: Verbrennungschirurgie, Lenhardt M, Hartmann B, Reichert B. Springer Verlag 2016, 195-220.
- 33 **Henrich D, Verboket R, Schaible A, Konradowitz K, Oppermann E, Brune JC, Nau C, Meier S, Bonig H, Marzi I, Seebach C.** Characterization of bone marrow mononuclear cells on biomaterials for bone tissue engineering in vitro. *BioMed Research International*. 2015;2015:762407.
- 34 **Kasetty G, Kalle M, Mörgelin M, Brune JC, Schmidtchen A.** Anti-endotoxic and antibacterial effects of a dermal substitute coated with host defense peptides. *Biomaterials*. 2015;53:415-25.
- 35 **Vitacolonna M, Belharazem D, Hohenberger P, Roessner ED.** Effect of dynamic seeding methods on the distribution of fibroblasts within human acellular dermis. *Cell and Tissue Banking*. 2015 Dec;16(4):605-14.
- 36 **Vitacolonna M, Belharazem D, Maier P, Hohenberger P, Roessner ED.** In vivo Quantification of the Effects of Radiation and Presence of Hair Follicle Pores on the Proliferation of Fibroblasts in an Acellular Human Dermis in a Dorsal Skinfold Chamber: Relevance for Tissue Reconstruction following Neoadjuvant Therapy. *PLoS One*. 2015 May 8;10(5):e0125689.
- 37 **Bormann N, Schwabe P, Smith MD, Wildemann B.** Analysis of parameters influencing the release of antibiotics mixed with bone grafting material using a reliable mixing procedure. *Bone*. 2014 Feb;59:162-72.
- 38 **Roessner E, Vitacolonna M, Schulmeister A, Pilz L, Tsagogiorgas C, Brockmann M, Hohenberger P.** Human acellular dermis seeded with autologous fibroblasts enhances bronchial anastomotic healing in an irradiated rodent sleeve resection model. *Annals of Surgical Oncology*. 2013 Dec;20 Suppl 3:S709-15.
- 39 **Vitacolonna M, Belharazem D, Hohenberger P, Roessner ED.** Effect of static seeding methods on the distribution of fibroblasts within human acellular dermis. *BioMedical Engineering Online*. 2013 Jun 24;12:55.
- 40 **Brune JC, Hesselbarth U, Seifert P, Nowack D, von Versen R, Smith MD, Seifert D.** CT Lesion Model-Based Structural Allografts: Custom Fabrication and Clinical Experience. *Transfusion Medicine and Hemotherapy*. 2012 Dec;39(6):395-404.
- 41 **Roessner ED, Vitacolonna M, Hohenberger P.** Confocal laser scanning microscopy evaluation of an acellular dermis tissue transplant (Epiflex®). *PLoS One*. 2012;7(10):e45991.
- 42 **Roessner ED, Thier S, Hohenberger P, Schwarz M, Pott P, Dinter D, Smith M.** Acellular dermal matrix seeded with autologous fibroblasts improves wound breaking strength in a rodent soft tissue damage model in neoadjuvant settings. *Journal of Biomaterials Applications*. 2011 Jan;25(5):413-27.
- 43 **Roessner E, Smith MD, Petschke B, Schmidt K, Vitacolonna M, Syring C, von Versen R, Hohenberger P.** Epiflex® a new decellularised human skin tissue transplant: manufacture and properties. *Cell and Tissue Banking*. 2011 Aug;12(3):209-17.
- 44 **Karbe T, Braun C, Wulff B, Schröder AS, Püschel K, Bratzke H, Parzeller M.** Practical experience in post-mortem tissue donation in consideration of the European tissue law. *Forensic Science, Medicine, and Pathology*. 2010 Mar;6(1):3-8.
- 45 **Putzier M, Strube P, Funk JF, Gross C, Mönig HJ, Perka C, Pruß A.** Allogenic versus autologous cancellous bone in lumbar segmental spondylosis: a randomized prospective study. *European Spine Journal*. 2009 May;18(5):687-95.
- 46 **Von Versen-Höyneck F, Steinfeld AP, Becker J, Hermel M, Rath W, Hesselbarth U.** Sterilization and preservation influence the biophysical properties of human amnion grafts. *Biologicals*. 2008 Jul;36(4):248-55.
- 47 **Pruß A, von Versen R.** Einfluss europäischer Regulatoria auf Qualität, Sicherheit und Verfügbarkeit allogener Zell- und Gewebetransplantate in Deutschland [Influence of European regulations on quality, safety and availability of cell and tissue allografts in Germany]. *Handchirurgie, Mikrochirurgie, plastische Chirurgie*. 2007 Apr;39(2):81-7.
- 48 **Scheffler S, Trautmann S, Smith M, Kalus U, von Versen R, Pauli G, Pruß A.** No influence of collagenous proteins of Achilles tendon, skin and cartilage on the virus-inactivating efficacy of peracetic acid-ethanol. *Biologicals*. 2007 Oct;35(4):355-9.
- 49 **Galambos B, Csöngé L, von Versen R, Olah A, Tamas L, Zsoldos P.** Preservation of vein allograft viability during long-term storage. *European Surgical Research*. 2005 Jan-Feb;37(1):60-7.
- 50 **Scheffler SU, Scherler J, Pruß A, von Versen R, Weiler A.** Biomechanical comparison of human bone-patellar tendon-bone grafts after sterilization with peracetic acid ethanol. *Cell and Tissue Banking*. 2005;6(2):109-15.
- 51 **Von Versen-Höyneck F, Hesselbarth U, Möller DE.** Application of sterilised human amnion for reconstruction of the ocular surface. *Cell and Tissue Banking*. 2004;5(1):57-65.
- 52 **Pruß A, Göbel UB, Pauli G, Kao M, Seibold M, Mönig HJ, Hansen A, von Versen R.** Peracetic acid-ethanol treatment of allogeneic avital bone tissue transplants – a reliable sterilization method. *Annals of Transplantation*. 2003;8(2):34-42.
- 53 **Pruß A, Kao M, Gohs U, Koscielny J, von Versen R, Pauli G.** Effect of gamma irradiation on human cortical bone transplants contaminated with enveloped and non-enveloped viruses. *Biologicals*. 2002 Jun;30(2):125-33.
- 54 **Pruß A, Perka C, Degenhardt P, Maronna U, Büttner-Janitz K, Paul B, Müller K, Klumpp C, Bruck JC, von Versen R.** Clinical efficacy and compatibility of allogeneic avital tissue transplants sterilized with a peracetic acid/ethanol mixture. *Cell and Tissue Banking*. 2002;3(4):235-43.
- 55 **Von Versen-Höyneck F.** Humanes Amnion – Experimentelle Untersuchungen und klinische Erfahrungen. 1–111, Dissertation an der Medizinischen Fakultät Charité der Humboldt-Universität Berlin, 2002.
- 56 **Pruß A, Baumann B, Seibold M, Kao M, Tintelnot K, von Versen R, Radtke H, Dörner T, Pauli G, Göbel UB.** Validation of the sterilization procedure of allogeneic avital bone transplants using peracetic acid-ethanol. *Biologicals*. 2001 Jun;29(2):59-66.
- 57 **Pruß A, Hansen A, Kao M, Gürtler L, Pauli G, Benedix F, von Versen R.** Comparison of the efficacy of virus inactivation methods in allogeneic avital bone tissue transplants. *Cell and Tissue Banking*. 2001;2(4):201-15.
- 58 **Pruß A, Kao M, Kiesewetter H, von Versen R, Pauli G.** Virus safety of avital bone tissue transplants: evaluation of sterilization steps of spongiosa cuboids using a peracetic acid-methanol mixture. *Biologicals*. 1999 Sep;27(3):195-201.
- 59 **Thielicke U, Thielicke B, von Versen R, Denner K.** Klinische Studie zum Einsatz von demineralisierter Knochenmatrix (DBM) in der Chirurgischen Stomatologie [Clinical study on the application of demineralized bone matrix (DBM) in surgical orthodontics]. *Beiträge zur Orthopädie und Traumatologie*. 1990 Aug;37(8):461-5.
- 60 **Denner K, von Versen R, Freistedt B, Klein W, Dehmlow R.** Relevanz labor diagnostischer Methoden zur Bewertung der Osteoinduktivität von Knochenmatriximplantaten [Relevant laboratory diagnostic methods for the evaluation of the osteoinductivity of bone matrix implants]. *Zeitschrift für medizinische Laboratoriumsdiagnostik*. 1989;30(3):159-64.
- 61 **Von Versen R, Denner K, Freistedt B, Seht B, Matthes G.** Verfahren zur Präparation demineralisierter Knochenmatrix [A method for the preparation of demineralized bone matrix]. *Zeitschrift für medizinische Laboratoriumsdiagnostik*. 1989;30(3):154-8.
- 62 **Von Versen R, Starke R.** The peracetic acid/low pressure cold sterilization – a new method to sterilize corticocancellous bone and soft tissue. *Zeitschrift für experimentelle Chirurgie, Transplantation, und künstliche Organe*. 1989;22(1):18-21.
- 63 **Starke R, Hackensellner HA, von Versen R.** Experimentelle Untersuchungen zur Entkeimung von Transplantationsmaterial mit Peressigsäure [Experimental studies of the sterilization of transplantation material with peracetic acid]. *Zeitschrift für experimentelle Chirurgie, Transplantation, und künstliche Organe*. 1984;17(5):254-8.

Selected examples

JAHR	TITEL	NAME	ABSCHLUSS
2023	Influence of a spray application for primary human dermal fibroblasts on their behaviour in a wound healing model	Thilo Brill	Master
2023	Qualität von Röhrenknochen in Abhängigkeit der Reinigungsmethode	Hanan Kdouh	Bachelor
2023	Optimierung der Medienzusammensetzung bei der Kultivierung humaner Keratinozyten	Felix Hüttig	Bachelor
2022	Etablierung eines Verfahrens zur Trocknung von allogenen Knochenpräparaten	Dominik Lehmann	Bachelor
2022	Entwicklung eines Entfettungsprozesses für dermales Gewebe zur Herstellung humaner Allografts unter Verwendung superkritischer Fluidextraktion	Leon Unger	Master
2022	Xeno-freie Kultivierung von humanen Keratinozyten	Emily Elise Pgetz	Bachelor
2022	Bewertung von serumfreien und feederfreien Kultivierungsalternativen humaner Keratinozyten	Christina Leonie Frohn	Bachelor
2021	Etablierung von Methoden zur objektiven Zustandsbeschreibung des proliferativen Potentials von Keratinozyten in Kultur	Nora Gaertner	Bachelor
2021	Behandlung von Surrogaten und Hartgewebe mittels scCO ₂	Lennart Suckow	Praktikum
2021	Delipidierung humaner dermaler Matrices durch mechanische Verfahren – Einfluss auf die biomechanischen Eigenschaften der Matrices	Leon Schäfer	Bachelor
2021	Progenitorfrequenzanalyse in humaner Keratinozyten-Zellkultur	Henrike Keil	Master
2020	Optimierung einer Dezellularisierungsmethode für die Herstellung einer humanen azellulären dermalen Matrix	Svenja Ebeling	Bachelor
2020	Etablierung einer Holoklonfrequenzanalyse von Humanen Epidermalen Keratinozyten	Jan Renziehausen	Bachelor
2019	Optimierung der Herstellung von Amnion-Transplantaten	Ngoc Hai Chu	Bachelor
2019	Untersuchung verschiedener Einflussparameter auf die Entfettung humaner Spalthaut während der Prozessierung der hADM Epiflex®	Sarah Köhler	Projektarbeit
2019	Untersuchung der biomechanischen Eigenschaften humaner Sehnentransplantate	Kassandra Hoetzel	Bachelor
2019	Delipidierung humaner dermaler Matrices durch Triglycerid-Hydrolyse – Einfluss auf den residualen TG-Gehalt und die biomechanischen Eigenschaften der Matrices	Lena Schollmeyer	Bachelor

JAHR	TITEL	NAME	ABSCHLUSS
2018	Comparison of nozzle types used in cell spray applications	Miriam Heuer	Master
2017	Entfettung humaner Gewebetransplantate – Methodvalidierung einer enzymatischen Triglyceridbestimmung in hADM-Transplantaten als Grundlage für die Kontrolle der Restfettgehaltreduktion	Mandy Kästorf	Bachelor
2016	Entwicklung von Tests für die objektive Beurteilung biologischer und physikalischer Eigenschaften von Knochentransplantaten	Anja Hanke	Master
2016	Isolation und Nachweis von therapeutisch relevanten Proteinen aus Amnion	Sabrina Engel, geb. Pfeffer	Bachelor
2015	Optimierung von Qualitätsstandards und des Hilfsstoffes Choleratoxin in der Kultivierung von epidermalen Sheets	Emelie Maximiliane Landmann	Master
2015	Entwicklung eines Assays zur Beurteilung der Eignung von Feederzellen für die Kultur humaner Keratinozyten für Verbrennungsoffer	Constanze Dermitzel	Projektarbeit
2015	Biomechanische Beurteilung von ausgewählten Hartgewebetranplantaten. Eignung zum Einsatz beim Impaction Bone Grafting	Anne Grünberg	Projektarbeit
2015	Erfassung und Analyse von Rückmeldungen zur Anwendung von Transplantaten	Emelie Maximiliane Landmann	Projektarbeit
2014	Entwicklung eines Antikörper-Panels zur Beurteilung der Qualität humaner Keratinozytensheets	Christin Gävert	Master
2013	Prüfung der Einflüsse verschiedener Medienmengen auf das Wachstum von Keratinozyten	Jenny Hoffmann	Bachelor
2012	Isolation und Charakterisierung von Zellen aus humanem Amnion	Alexandra Wagner	Bachelor
2011	Einfluss extrakorporaler Stoßwellen auf das Proliferationsverhalten von Keratinozyten in vitro	Sandra Münch	Diplomarbeit
2005	Tissue Engineering von autologen Fibroblasten in allogenen Matrices: Untersuchungen zum Stofftransport in Weichgewebetranplantaten	Doris Kappelt	Diplomarbeit

Grafts for burns medicine and hard-to-heal wounds

Autologous cell cultures are often the only treatment option for severely burned patients.²² With these and with donated (allogeneic) skin grafts for hard-to-heal wounds, the DIZG makes a significant contribution to improving patient care.

The medical treatment of extensive burn injuries is extremely complex and requires multimodal therapy with multiple surgical interventions. In burn surgery, the use of autologous cell cultures proves to be essential in many cases. The DIZG is the only facility in Germany to provide these. We thus offer clinics and burn centers a life-saving treatment option as well as an improved chance of recovery for those patients who do not have enough healthy skin to transplant elsewhere (autografting).

We provide autologous keratinocyte transplants as sheets and as a suspension. Since June 2020, the suspension has been applied using the Cell Spray, which replaced the Cell Sprayer. The advantage: several doctors can spray at the same time.



Keratinocytes as a sheet



Keratinocytes as suspension

i In third-degree burns, it is particularly if the dermis is regenerated before autologous keratinocytes are transplanted. This can be achieved by transplanting dermis substitutes or by using keratinocytes in combination with autologous skin. The aim is to increase the elasticity of the regenerated skin and reduce scarring.



Microscopic control of cell growth

Autologous cell cultures

Manufactured under the highest requirements

The cultivation and provision of keratinocytes are subject to strict regulatory requirements. Among other things, these make it necessary for the DIZG to have a separate clean room area just for them.



Editing

i Our autologous keratinocytes are registered as orphan medicinal products for the treatment of partial-thickness and full-thickness burns (Orphan Drug; EU/3/21/2483).

The recognition by the European Commission, based on a favorable opinion from the European Medicines Agency (EMA) confirms the relevance of the life-saving therapy option that DIZG offers severely injured patients.

The production of autologous keratinocytes is a process that requires extreme care and takes time. This process already begins with the biopsy, when cells are taken from the patient. Skin sampling must be sterile and from clinically healthy areas. Suitable sites for collection include the retroauricular scalp, lower abdomen, upper and lower legs, or other intact, unburned regions.

During collection, microbiological contamination must be avoided at all costs, this could lead to possible complications and delayed delivery of the cultured keratinocytes.

The keratinocyte sheets

The autologous keratinocyte sheets fixed on a carrier dressing are suitable for the treatment of extensive skin wounds and for the care of severely burned patients. They are indicated:

- > In case of extensive burns on the body surface,
- > In case of insufficient or poorly healing skin sampling sites²³,
- > To accelerate the re-epithelialization of dermal wounds in combination with widely expanding autologous skin grafts²³.
- > In children, the use of autologous keratinocyte grafts is indicated even for smaller areas because of the often limited donor sites.²³

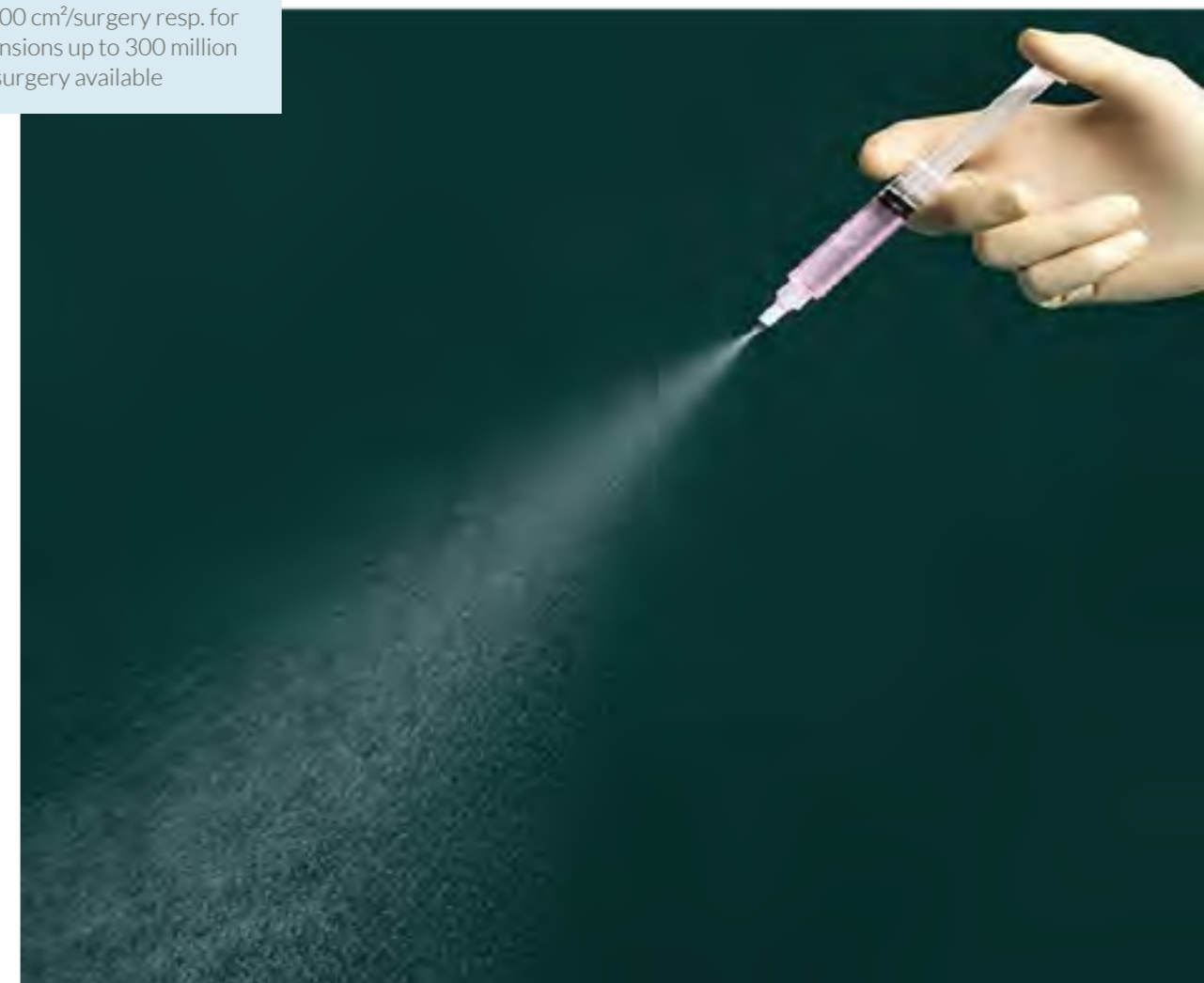


Keratinocyte sheet

The keratinocyte suspension

The ready-to-use autologous keratinocytes as a suspension are indicated for skin wounds and grade 2b burns. The treatment of burns using the Cell Spray in visible areas of the body such as the face, hands, neck and décolleté or in areas with complex topography achieves good results.²³

i Orderable area for sheets up to 4,500 cm²/surgery resp. for suspensions up to 300 million cells/surgery available



Uniform application of cultured cells with the Cell Spray

The production steps of autologous cell cultures

1. EXTRACTION/PREPARATION



Extraction kit

The DIZG extraction kit contains biopsy tubes, documents such as the consent form, the collection form and a collection guide.



Shipping of the biopsies to the DIZG

The biopsies are sent to the DIZG refrigerated (5-22 °C). Temperature control is performed when the kit is received in the DIZG.



Preparation of the biopsy specimen for cell isolation

Prior to cell isolation, biopsies are gently decontaminated by incubation in various buffer solutions.

2. PROCESSING



Processing the cells

The cells are processed in a class A clean room.



Cell reproduction

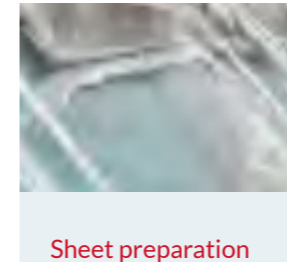
The autologous cells are incubated in previously sterilized incubators at 37 °C.



Control of culture growth

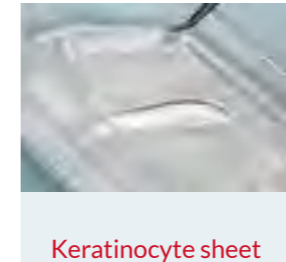
The growth and proliferation of the cells are controlled microscopically.

3. PREPARATION OF SHEETS FOR TRANSPLANTATION



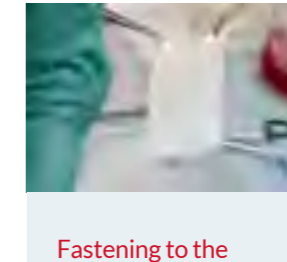
Sheet preparation

Preparation begins with culturing the cells until they form a thin membrane.



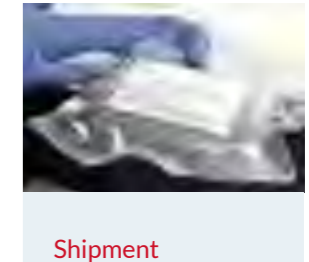
Keratinocyte sheet

It takes an average of about three weeks from sowing the cells to the formation of a firmer membrane.



Fastening to the gauze

With the enzymatic treatment of the keratinocyte sheets, the preparation begins: each sheet is dissolved and bound to a support. Afterwards, the sheets are ready for transplantation.



Shipment

A special courier is used to send the finished transplants refrigerated. These can remain in the box until transplantation.

4. PREPARATION OF THE SUSPENSION FOR TRANSPLANTATION



Time of preparation

The keratinocyte suspension can be prepared for transplantation after ten (+/- two) days.



Filling the syringes

On the day before transplantation, the cells are enzymatically treated and separated, and the concentration and viability are determined. The finished suspension is filled into the syringes.



Packing & Shipping

The finished suspension is shipped refrigerated. It can remain in the box until use.

Helping severely burned people

In 2023, **16 cases** were processed and **505 transplants** were sent. Keratinocyte sheets with a total area of **19,140 cm²** and keratinocyte suspensions with a total cell count of **1.2 billion cells** were delivered. The latter were applied using the Cell Spray, which enables easy handling.



COMPREHENSIVE SUPPORT FOR BURN CLINICS

When using autologous cell cultures, burn clinics must meet regulatory requirements. This means that each clinic must obtain its own license for the extraction and provision of biopsies for the cultivation of autologous cells in accordance with § 20b (1) or permission through a contractual relationship with a manufacturer such as the DIZG according to § 20b (2) of the German Drug Law (AMG). The DIZG assists burn clinics in obtaining this certification. The clinics benefit in particular from our many years of experience.

Zero infections

Since it was founded in 1993, the DIZG has manufactured 798,000 allogeneic tissue transplants.

Since then, no graft application has ever evidently resulted in graft-derived transmission of microbiological or viral infection. This impressively demonstrates that quality and safety are our top priority.

DIZG grafts are produced to the highest quality standards, in part under Class A cleanroom conditions. DIZG is subject to oversight by the Paul Ehrlich Institute and the LAGeSo Berlin (State Department of Health and Social Affairs) and holds approvals and authorizations according to Article 21 and 21a

AMG as well as the corresponding manufacturing authorizations according to Articles 13 and 20c AMG. A large number of laws, regulations and standards are taken into account during the manufacturing process.

Besides numerous other safety precautions, we use a validated and published inactivation procedure for viruses and microorganisms which simultaneously protects the biological integrity of the tissue.

Reviewing the donor file for donor exclusion criteria



THE FOLLOWING SAFETY STEPS ARE THE BASIS OF THIS HIGH LEVEL OF SAFETY:

1. Screening of medical history

Assessment of the medical history by clinicians in hospitals according to strict internationally standardized exclusion criteria as part of an agreed quality management system.

2. Serological screening in certified laboratories

The scope of serological screening for tissue donations performed by DIZG exceeds the requirements of EU Directive 17/2006/EC. In addition to the serological screening mandated by law, DIZG also carries out PCR tests to rule out HIV and hepatitis B and C.

In addition, after preparation/ before sterilization, a bioburden analysis is completed on the donated tissue, in which the total reproducible germs are counted. Only if the colony forming units (CFU) are below the defined limits, the bone tissues are released for further processing.

3. Validated sterilization and inactivation procedure

The validation study was conducted in collaboration with the Charité Hospital and the Robert Koch Institute. The study analyzed the efficacy of the procedure using model organisms (enveloped and non-enveloped viruses as well as bacteria and spore-forming organisms) in

accordance with European guidelines and official recommendations. The results were published.

4. Testing for sterility

Release of a manufactured batch for clinical use requires validation of batch sterility in accordance with the applicable testing requirements specified in the European Pharmacopoeia. This testing is carried out in certified laboratories.

5. Quality management

DIZG operates a quality management system in accordance with the requirements of the GMP and Best Practice regulations. Procedures for obtaining the tissue donations; transporting the tissue; producing allogeneic and autologous transplants; testing; release and delivery, as well as the process for procedural changes, are all strictly regulated and monitored. Based on the above safety levels, the competent medicinal product regulators and state health authorities have granted medicinal product licenses and authorizations according to Article 21 and 21a AMG and manufacturing authorizations according to Articles 13 and 20c.

Safety for hospitals and physicians

The Patient Rights Act passed in 2013 strengthened patients' rights. This also gave user safety a new dimension. That means: Hospitals are forced to take out adequate insurance against potential claims. Surgery is particularly affected. Errors in the storage of clinically produced femoral heads typically due to incorrect temperatures, faulty or inadequate documentation in the in-house production of femoral head transplants and the signatures

associated with the release process took on a new legal relevance with the Patient Rights Act.

As a non-profit manufacturer of medicinal products, according to Articles 20c and 13 of the German Medicinal Products Act, DIZG is subject to regulatory oversight. All DIZG tissue grafts have marketing authorizations according to Article 21 AMG or approvals according to Article 21a AMG.

Processing an order



DIZG transplants are of human origin

A SELECTION OF OUR DIZG TRANSPLANTS FROM AROUND 230 DIFFERENT PACK SIZES



Cancellous bone blocks



DBM putty



Femoral heads



Cancellous bone chips



Fascia lata



Spierings chips



Amnion



Epiflex® Human skin, acellular



Fiberfill®



Epiflex® ≥ 3 mm



Shark Screw®



Spongioflex® knee



You can find a complete overview in our transplant catalog.

The transplants approved according to § 21 AMG and those approved according to § 21a AMG are produced using a validated virus inactivation process. They have the following properties:

- > Free from preservatives and antibiotics

- > Safe due to validated sterilization process

- > free from animal-derived constituents

- > Free from thermal treatment

- > Storage of freeze-dried transplants at room temperature

The DIZG at a glance

FOUNDED

August 1993 as a non-profit GmbH company in Berlin

MANAGING DIRECTOR

Jürgen Ehlers

INSTITUTE HEADQUARTERS

Innovationspark Wuhlheide in Berlin

NUMBER OF EMPLOYEES

125 employees as of 01.03.2024

FIELDS OF ACTIVITY

The German Institute for Cell and Tissue Replacement (DIZG) is a non-profit manufacturer of allogeneic tissue transplants and autologous cell cultures. The focus is on research and development with the aim of offering people with severe tissue defects an improved prospect of recovery. DIZG graft use must always be based on the surgeon's assessment that the use of human tissue grafts is indicated for medical reasons. The variety of transplants is constantly being expanded. More than 67,000 patients a year now benefit from around 230 different types of transplant from the DIZG clean rooms.

MARKETING AUTHORIZATIONS FOR MEDICINAL PRODUCTS

Eleven marketing authorizations for medicinal products in accordance with Article 21 AMG

Musculoskeletal tissue

- > Human cortical bone, freeze-preserved, DIZG
- > Human cortical bone, lyophilized, DIZG
- > Human cancellous bone, freeze-preserved, DIZG
- > Human cancellous bone, lyophilized, DIZG
- > Human connective/tendon tissue, freeze-preserved, DIZG
- > Human fascia, lyophilized, DIZG
- > Demineralized human bone matrix, lyophilized, DIZG
- > Human cartilage, freeze-preserved, DIZG

Tissue for wound healing and soft tissue reconstruction

- > Human amniotic membrane, dried, DIZG
- > Human skin, freeze-preserved, DIZG
- > Epiflex® human acellular dermis, lyophilized, DIZG

Two medicinal product authorizations according to Article 21a AMG

Tissue preparation

- > Bone screw (Shark Screw®), freeze-dried, DIZG
- > Fiberfill® freeze-dried, DIZG

LEGAL FORM

Non-profit limited liability company [Gemeinnützige GmbH]

MANUFACTURING AUTHORIZATION

Authorization according to Articles 13 and 20c AMG for the manufacture of allogeneic tissue grafts and autologous cell cultures

CUSTOMER SERVICE

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ADDRESS

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Gemeinnützige Gesellschaft mbH
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References

1. **Jørgensen U, Sonne-Holm S, Lauridsen F, Rosenklint A.** Long-term follow-up of meniscectomy in athletes. A prospective longitudinal study. *The Journal of Bone and Joint Surgery. British Volume.* 1987 Jan;69(1):80-3.
2. **Behrendt S.** MRI follow up of bilateral partial meniscal substitution with a demineralized bone block. A case report. *Radiology Case Reports.* 2022 Oct 27;18(1):21-26.
3. **Brcic I, Pastl K, Plank H, Igrec J, Schanda JE, Pastl E, Werner M.** Incorporation of an Allogenic Cortical Bone Graft Following Arthrodesis of the First Metatarsophalangeal Joint in a Patient with Hallux Rigidus. *Life (Basel).* 2021 May 24;11(6):473.
4. **Schildhauer TA.** Metallentfernungen. *Trauma und Berufskrankheit.* 2007 Sep 9; 9(Suppl 3):S292–S296.
5. **Holzapfel G, Sommer G.** Einfluss des Gewindedetalradius auf die biomechanischen Eigenschaften von Osteosyntheseschrauben aus humaner Corticalis – Experimental- und FEM-Studie. *Technische Universität Graz.* 2012.
6. **Ahmed N, Eras V, Pruß A, Perka C, Brune J, Vu-Han TL.** Allografts: expanding the surgeon's armamentarium. *Cell and Tissue Banking.* 2023 Mar;24(1):273-283.
7. **Rupp M, Klute L, Baertl S, Walter N, Mannala GK, Frank L, Pfeifer C, Alt V, Kerschbaum M.** The clinical use of bone graft substitutes in orthopedic surgery in Germany-A 10-years survey from 2008 to 2018 of 1,090,167 surgical interventions. *Journal of Biomedical Materials Research Part B: Applied Biomaterials.* 2022 Feb;110(2):350-357.
8. **Altman R, Bedi A, Manjoo A, Niazi F, Shaw P, Mease P.** Anti-Inflammatory Effects of Intra-Articular Hyaluronic Acid: A Systematic Review. *Cartilage.* 2019 Jan;10(1):43-52.
9. **Alcântara CEP, Castro MAA, Noronha MS, Martins-Junior PA, Mendes RM, Caliarí MV, Mesquita RA, Ferreira AJ.** Hyaluronic acid accelerates bone repair in human dental sockets: a randomized triple-blind clinical trial. *Brazilian Oral Research.* 2018;32:e84.
10. **Park D, Kim Y, Kim H, Kim K, Lee YS, Choe J, Hahn JH, Lee H, Jeon J, Choi C, Kim YM, Jeoung D.** Hyaluronic acid promotes angiogenesis by inducing RHAMM-TGFβ receptor interaction via CD44-PKCδ. *Molecules and Cells.* 2012 Jun;33(6):563-74.
11. **Moroder P, Böhm E, Scheibel M.** The Arthroscopic Bankart-Plus Procedure for Treatment of Anterior Shoulder Instability With Small to Intermediate Glenoid Defects. *Arthroscopy Techniques.* 2018 Mar 19; 7(4):e379–e384.
12. **Minkus M, Akgün D, Thiele K, Karpinski K, Moroder P.** Bankart-Plus zur Behandlung von Patienten mit anteriorer Schulterinstabilität und kleinen bis moderaten Glenoiddefekten. *Obere Extremität.* 2022 Oct 6;17(4):243-249.
13. **Lafzi A, Vahabi S, Ghods S, Torshabi M.** In vitro effect of mineralized and demineralized bone allografts on proliferation and differentiation of MG-63 osteoblast-like cells. *Cell and Tissue Banking.* 2016 Mar;17(1):91-104.
14. **Babiker H, Ding M, Overgaard S.** Demineralized bone matrix and human cancellous bone enhance fixation of porous-coated titanium implants in sheep. *Journal of Tissue Engineering and Regenerative Medicine.* 2016 Mar;10(3):245-51.
15. **Bormann N, Schmock A, Hanke A, Eras V, Ahmed N, Kissner MS, Wildemann B, Brune JC.** Analysis of the Ability of Different Allografts to Act as Carrier Grafts for Local Drug Delivery. *Journal of Functional Biomaterials.* 2023 Jun 1;14(6):305.
16. **Verboket RD, Irrle T, Busche Y, Schaible A, Schröder K, Brune JC, Marzi I, Nau C, Henrich D.** Fibrous Demineralized Bone Matrix (DBM) Improves Bone Marrow Mononuclear Cell (BMC)-Supported Bone Healing in Large Femoral Bone Defects in Rats. *Cells.* 2021 May 19;10(5):1249.
17. **Söhling N, Leiblein M, Schaible A, Janko M, Schwäble J, Seidl C, Brune JC, Nau C, Marzi I, Henrich D, Verboket RD.** First Human Leucocyte Antigen (HLA) Response and Safety Evaluation of Fibrous Demineralized Bone Matrix in a Critical Size Femoral Defect Model of the Sprague-Dawley Rat. *Materials (Basel).* 2020 Jul 13;13(14):3120.
18. **Krasny C, Radda C, Polke R, Schallmayer D, Borchert GH, Albrecht C.** A human, allogeneic cortical bone screw for distal interphalangeal joint (DIP) arthrodesis: a retrospective cohort study with at least 10 months follow-up. *Archives of Orthopaedic and Trauma Surgery.* 2023 Jul;143(7):4557-4564.
19. **Pastl K, Schimetta W.** The application of an allogeneic bone screw for osteosynthesis in hand and foot surgery: a case series. *Archives of Orthopaedic and Trauma Surgery.* 2022 Oct;142(10):2567-2575.
20. **Sailer S, Lechner S, Floßmann A, Wanzel M, Habeler K, Krasny C, Borchert GH.** Treatment of scaphoid fractures and pseudarthroses with the human allogeneic cortical bone screw. A multicentric retrospective study. *Journal of Orthopaedics and Traumatology.* 2023 Feb 10;24(1):6.
21. **Pastl K, Pastl E, Flöry D, Borchert GH, Chraim M.** Arthrodesis and Defect Bridging of the Upper Ankle Joint with Allograft Bone Chips and Allograft Cortical Bone Screws (Shark Screw®) after Removal of the Salto-Prosthesis in a Multimorbidity Patient: A Case Report. *Life (Basel).* 2022 Jul 11;12(7):1028.
22. **Hartmann B, Ekkernkamp A, Johnen C, Gerlach JC, Belfekroun C, Küntscher MV.** Sprayed cultured epithelial autografts for deep dermal burns of the face and neck. *Ann Plast Surg.* 2007 Jan;58(1):70-3.
23. **Hartmann B.** Arzneimittelzulassung autologe Hautzellprodukte – Stellungnahme zum klinischen Einsatz von autologen Keratinozyten-Suspensionen sowie von Sheets von humanen Keratinozyten zur autologen Anwendung. 2021, unpublished.

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