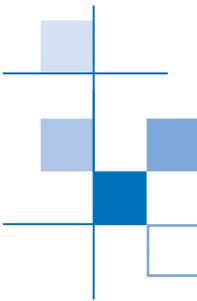
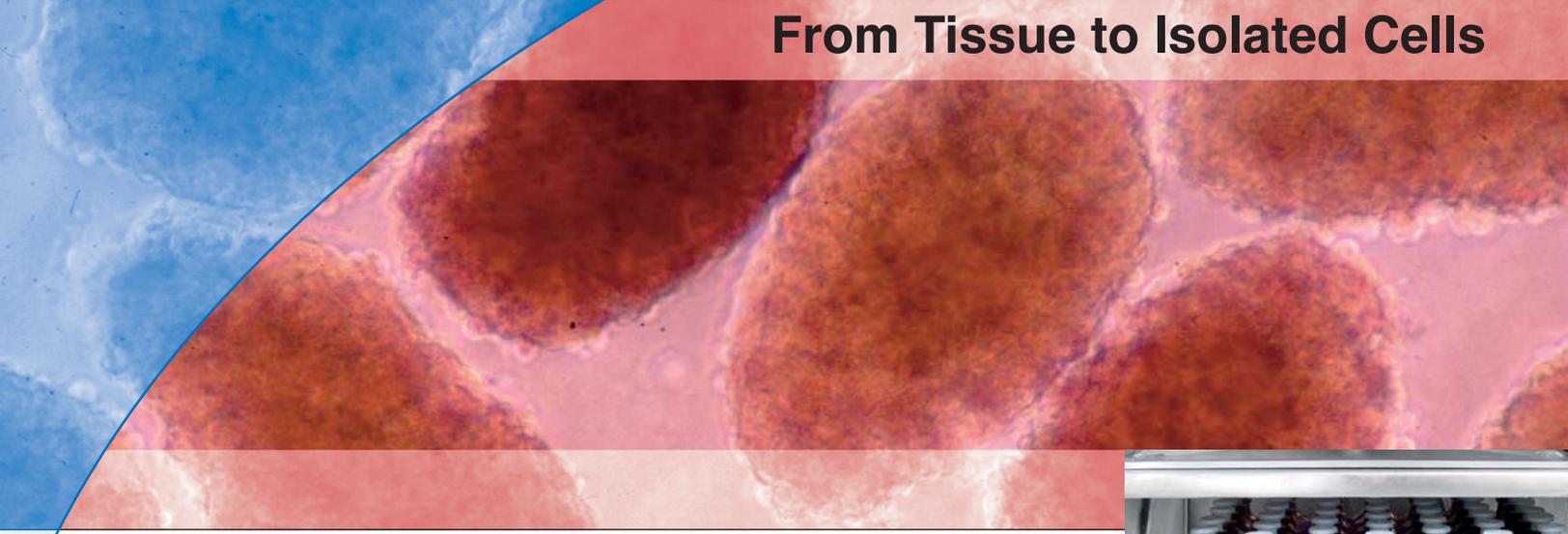




Collagenase NB

From Tissue to Isolated Cells



SERVA
Electrophoresis



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Published by:

SERVA Electrophoresis GmbH
Carl-Benz-Straße 7
D-69115 Heidelberg

www.serva.de
collagenase@serva.de

Editorial Responsibility:

Dr. Olaf Friedrich
Dr. Silke Hüttler
Dr. Manfred Kurfürst
Dr. Nicole Rämisch-Günther

Design and Typesetting:

acrobat ADVERTISING, Hamburg

Photographs:

Dr. Kirsten Bender,
Ruhr-Universität Bochum

Dr. Thierry Berney, Dr. Pascal Bucher,
Hôpitaux Universitaires de Genève

Dr. Heide and Dr. Daniel Brandhorst,
Uppsala University Hospital

Dr. Reinhard Bretzel,
Justus-Liebig-Universität Gießen

Dr. Olaf Friedrich,
Nordmark, Uetersen

Dr. Sarah Cross, Dr. Stephen Hughes,
University of Oxford

innovacell biotechnologie GmbH,
Innsbruck

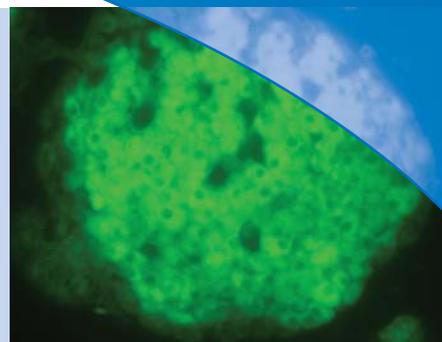
Gerd Pilz,
Fotodesign, Berlin

Dr. Nicole Rämisch-Günther,
SERVA, Uetersen

TETEC Tissue Engineering Technologies AG,
Reutlingen

Dr. Ulrike Vettel,
Fraunhofer IGB, Stuttgart

Kersten Weichbrodt,
München



Collagenases – For Tissue Dissociation

Special, defined cell types can be isolated from different human or animal tissues.

Collagenase-mediated tissue dissociation is a crucial step in cell isolation procedures influencing yield, viability and functioning of cells.

Viability and function of isolated cells are essential for their use in

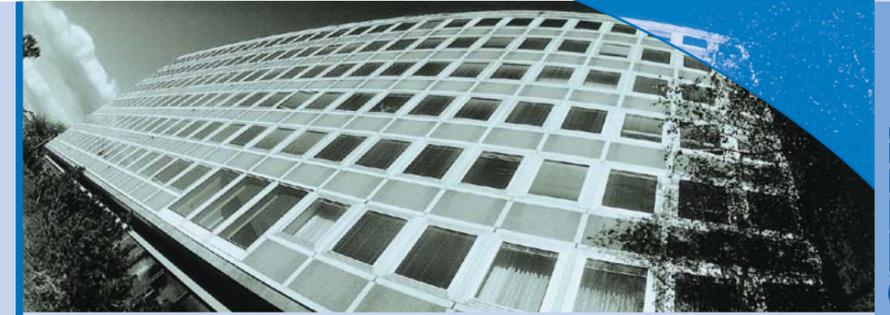
- transplantation, e.g. in diabetes therapy
- tissue engineering and transplantation, e.g. cartilage transplants
- pharmacological test systems for development of new drugs
- broad range of research purposes, e.g. physiological test systems and stem cell differentiation

SERVA collagenases are designed for different fields of application.

Superb quality and performance are assured by

- stringent quality control
- optimized purification steps
- accurate analysis of proteolytic enzyme activities
- in-process controls
- manufacture according to cGMP (current Good Manufacturing Practice) guidelines





SERVA and Nordmark ...

SERVA – High quality products to “serve” Life Sciences

Founded in 1953, SERVA was started as a supplier to the biochemistry research market. The product program has always focussed on fine biochemicals, electrophoresis products, and reagents used in bioseparation and life sciences.

In particular collagenases for tissue dissociation have been offered in the SERVA catalog for many years.

SERVA will continue to focus on the development and marketing of specialty products. Our mission is to adapt promptly to the changing needs of scientists and to provide innovative, value-added reagents to our customers.

To date, SERVA Electrophoresis GmbH is an independent company located in Heidelberg, Germany, one of the most important centers for biotechnology in the country. Known as a leading supplier to the life sciences research market for 50 years, we are committed to offer outstanding services and premium quality, backed by solid scientific and technical expertise.



... Customer Service and Qualified Production

Nordmark – The world’s largest manufacturer of Collagenases

Nordmark Arzneimittel GmbH & Co. KG, situated in Uetersen, Germany, can look back on a long tradition of manufacturing medicinal products and active pharmaceutical ingredients. Since foundation of the company in 1927, the company has been manufacturing medicinal products of biological origin at this site.

Since 1995 collagenase has been manufactured as an active pharmaceutical ingredient for a drug that is used in wound treatment. The sterile active substance is produced by biotechnological methods that comply with quality standards according to international cGMP guidelines.

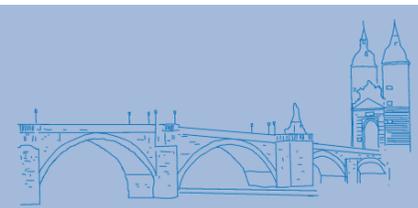
All **Collagenase NB** qualities offered by SERVA are manufactured at the pharmaceutical plant of Nordmark.

SERVA and Nordmark – A Successful Alliance

In 2002, SERVA and Nordmark formed an alliance in the manufacturing and distribution of collagenase enzymes.

Nordmark, as the world’s largest manufacturer of collagenases, and SERVA, as reputed supplier of biochemical reagents, combine their efforts to become the leading provider of collagenases for various applications.

Unique customer service backed by scientific collaborations and a global distribution network will assist our customers located world-wide to utilize **Collagenase NB** products in the field of tissue dissociation.





Activity of Collagenases

Collagen is the most abundant protein of vertebrates and occurs in virtually every tissue. Collagen proteins building collagen fibrils are the main components of the supporting matrix of connective tissue, bones, cartilage, teeth and extracellular matrices of skin and blood vessels.

Collagenases are proteolytic enzymes that are able to cleave peptide bonds in the triple helical collagen molecule.

Besides the mammalian and amphibian tissue collagenases, the collagenases expressed by the bacterium *Clostridium histolyticum* are of special interest and have been the subject of investigations for more than 40 years.

Clostridium histolyticum is known to produce a mixture of collagenases (formerly clostridiopeptidase A) which are able to digest the triple helical collagen molecule *in situ*.

The individual collagenases are divided into class I and class II collagenases based on their activities towards the synthetic peptide 2-furan-acryloyl-L-leucyl-glycyl-L-prolyl-L-alanine (FALGPA).

Both collagenases, class I and class II, act on triple helical type I, II, III and IV collagens, but in slightly different modes of action.



Besides clinical treatment of necrotic tissue, the enzymes are a valuable tool in tissue dissociation for the preparation of viable cell cultures for metabolic studies, transplantation or tissue engineering.

Collagenase is especially suitable for tissue dissociation when tissues are too fibrous or too sensitive to allow the use of trypsin, because trypsin is known to be ineffective on fibrous material, and to damage sensitive cells.

For efficient tissue dissociation the presence of both collagenase classes I and II is necessary.

Dissociation is usually achieved either by perfusing or distending whole organs, or by incubating smaller pieces of tissue with enzyme solution. Collagenase has been successfully used in the isolation of a broad variety of cell types from many different species.

SERVA **Collagenase NB** preparations include the range from standard collagenases, containing balanced amounts of other proteolytic activities, to highly purified collagenases. Therefore, **Collagenase NB** qualities are particularly suitable for various cell isolation applications.

Collagenases from *Clostridium histolyticum*:

Collagenases class I:

Collagenase isomers α , β , γ with different C-terminal processing; mode of action on collagen molecules characterized by initial cleavage of loci near the ends of triple helical domains of collagen; low activity towards synthetic peptide substrates (PZ peptide according to Wunsch, FALGPA peptide according to Bond)

Collagenases class II:

Collagenase isomers δ , ϵ , ζ with different C-terminal processing; mode of action characterized by initial cleavage in the interior of triple helical domains of collagen molecules; high activity towards synthetic peptide substrates (PZ peptide according to Wunsch, FALGPA peptide according to Bond)





From Cells to a Pharmaceutical Sterile Product

As the world's largest manufacturer of collagenase, Nordmark operates a production plant that is dedicated to the production of this enzyme.

The aseptic manufacturing process for collagenase consists of three steps:

1. fermentation
2. purification
3. aseptic lyophilization of the sterile filtered collagenase with subsequent grinding

All production steps are performed in accordance with international cGMP (current Good Manufacturing Practice) guidelines.

Collagenase is produced in a bioreactor by a special, carefully selected, not genetically modified strain of *Clostridium histolyticum*. During fermentation, collagenases are released in high concentrations into the culture medium. After the cells have been separated, the enzymatic solution is concentrated by means of ultrafiltration.

The enzyme concentrate is further purified and subsequently lyophilized and ground under aseptic conditions.

In order to meet the high pharmaceutical standards required for aseptic production, collagenase is manufactured in clean rooms that have been qualified specifically for this purpose and that are subject to extremely stringent microbiological environmental monitoring.

The TSE safety (transmissible spongiform encephalopathy) of the fermentation product has been certified by the European Authorities, EDQM.

The collagenase produced by Nordmark received international regulatory approval for the use as an active pharmaceutical ingredient in a sterile medicinal ointment, Iruxol, indicated in the debridement of necrotizing wounds¹.

... And to Collagenases for Tissue Dissociation

SERVA **Collagenase NB 4, NB 4G, NB 5 and NB 6** are manufactured based on the pharmaceutical drug product.

The natural collagenase-producing strain of *Clostridium histolyticum* has been carefully selected for the production of large amounts of collagenases and balanced amounts of other proteolytic activities.

The collagenase product is non-toxic complying with the Test of Abnormal Toxicity according to the European Pharmacopoeia. The carefully developed and aseptically operated production process as well as the high quality of raw materials guarantee a final product with low bacterial endotoxin levels.

These characteristics are essential for activity and safety in pharmaceutical as well as in tissue dissociation applications.

SERVA **Collagenase NB 4 Standard Grade** is a collagenase quality containing balanced amounts of other proteolytic enzymes like clostripain, trypsin-like proteolytic activities and neutral protease.

World-wide unique, SERVA provides this grade in pharmaceutical sterile quality, **Collagenase NB 5 Sterile Grade**, as well as in cGMP quality, **Collagenase NB 6 GMP Grade**. Both qualities are especially interesting to tissue engineering and transplantation applications, where sterile products according to the European Pharmacopoeia are required and/or cGMP requirements have to be met.

For **Collagenase NB 6 GMP Grade** Nordmark, as pharmaceutical manufacturer, provides a specific Certificate of Analysis, issued for the end-user. Further cGMP documents for filing to authorities are available.

Due to its composition **Collagenase NB 4G** is optimized for special cell types and is tested for performance in cell isolation.



¹Smith+Nephew Ltd. owns the exclusive right to market those products.





Highly Purified Collagenases

For special tissue dissociation applications, SERVA provides highly purified **Collagenase NB 1 Premium Grade**, **Collagenase NB 8 Broad Range** and **Neutral Protease NB**.

Purification is carried out by a series of chromatographic steps in production facilities dedicated to **Collagenase NB** purification following a patented process.

As to pharmaceutical manufacturing standards the purification process is carefully controlled guaranteeing reliable lot-to-lot consistency of the products.

Collagenase in cell isolation applications for human transplantation is regarded to be a critical raw material. Therefore **Collagenase NB 1 GMP Grade** and **Neutral Protease NB GMP Grade** are produced in compliance with the EU-Guide to current Good Manufacturing Practice „cGMP for active pharmaceutical ingredients“.

Dedicated facilities for the production of **Collagenase NB 1 GMP Grade** and **Neutral Protease NB GMP Grade** are equipped with a chromatography system and a lyophilization station in a clean room environment which is in full compliance with international cGMP guidelines.

The highly purified **Collagenase NB 1 Premium Grade** and **GMP Grade** are highly active and defined products designed to isolate especially sensitive cells like human pancreatic islets. Both collagenases, class I and class II, are present in a certain ratio range.

Collagenase NB 1 Premium Grade and **GMP Grade** are largely free of bacterial endotoxins. Neutral protease and other proteolytic enzymes are reduced to very low levels in this highly purified collagenase quality.

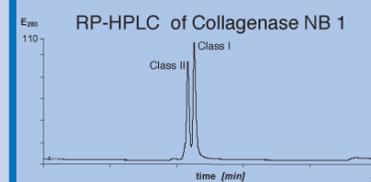
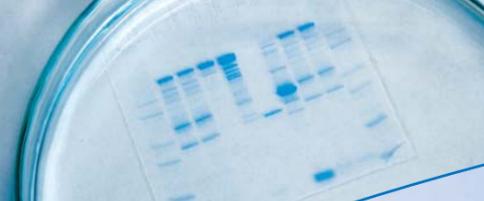
Thereby

- degradation of collagenase during storage by neutral protease is significantly reduced
- damage of cells during tissue dissociation by other proteases is avoided

In tissue dissociation, however, certain amounts of neutral protease are essential. SERVA **Neutral Protease NB** and **GMP Grade** from *Clostridium histolyticum*, chromatographically purified, are provided separately for individual dosage in the dissociation solution. The dosage depends on type and condition of the tissue and can be varied individually to achieve optimal isolation results. Moreover, separation of both products ensures high stability of the enzymes.

Collagenase NB 8 Broad Range is characterized by an increased amount of collagenase activity, reduced content of neutral protease and low levels of trypsin-like or clostripain enzyme activities. The application field is the isolation of sensitive cells as well as organ dissociation of mammals, where an enriched collagenase activity is necessary.





Controlled Quality

Analysis

State-of-the-art protein analysis techniques allow us to gain detailed insights into the composition and characteristics of our collagenase preparations.

Bioassays described in the literature as well as SDS-PAGE analysis methods have been established and validated in accordance with international ICH (International Conference on Harmonization) guidelines.

Routine analytical tests are carried out to monitor enzymatic activities of collagenases and other proteolytic enzymes in analytical laboratories for natural substances.

High-performance liquid chromatography (HPLC) technology combined with mass spectroscopic methods (MALDI) enable us to assign the activities to the appropriate molecular masses. Especially adapted protocols allow a clear characterization of individual enzymes.

Stability Testing

Storage stability testing is carried out in climatic chambers in accordance with international ICH guidelines.

Long-term storage stability is tested by monitoring enzyme activities, enzyme degradation by SDS-PAGE or HPLC, as well as microbiological contamination.

Short-term accelerated stress conditions, including elevated temperatures and humidity, are evaluated to assure product stability under conditions which might occur during transportation.

Safety

The strain of *Clostridium histolyticum* has been carefully selected to produce a pharmaceutical drug that complies with safety standards for medicinal products. The collagenase products produced by this strain are non-toxic complying with the requirements of the Test of Abnormal Toxicity (European Pharmacopoeia), which is carried out for each production batch. Moreover the absence of *Clostridia* in **Collagenase NB** qualities is tested routinely.

The TSE safety of the fermentation product is certified by a TSE-CEP which was granted by the European Directorate for the Quality of Medicines (EDQM) and by supplier's certificate of origin. **Collagenase NB** and **Neutral Protease NB** do not contain and are not derived from specified

animal risk material as defined in Commission Decision 97/534/EC.

Viral safety of **Collagenase NB** qualities is ensured by selection of raw materials and by autoclaving steps during production. Nordmark has shown the effectiveness of this step in a successful viral safety study.

The production of collagenase is carried out by qualified staff using validated and calibrated equipment in especially designed production facilities meeting cGMP guidelines in order to assure consistently high quality and safety.

Good Manufacturing Practice

Working in a cGMP environment implies strict control of process and raw materials as well as batch traceability.

Reference Collagenases are provided by SERVA

- for standard controls by SDS-PAGE analysis, carried out by the customer's QC lab upon receipt of **GMP Grade Collagenases**, in accordance with cGMP guidelines
- for tests to determine the enzyme activity

Unit definitions:

Collagenase:

PZ or Wünsch:

1 U according to Wünsch catalyzes the hydrolysis of 1 μmol 4-phenylazobenzoyloxy-carbonyl-L-prolyl-L-leucyl-glycyl-L-prolyl-D-arginine per minute at 25 °C, pH 7.1.

FALGPA:

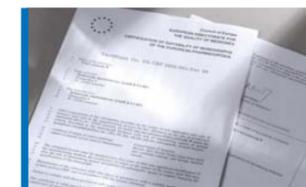
1 U is defined as the hydrolysis of 1 μmol of 2-furan-acryloyl-L-leucyl-glycyl-L-prolyl-L-alanine (FALGPA) per minute at 25 °C, pH 7.5.

Mandl or CDU:

1 U liberates 1 μmol amino acid (expressed as L-leucine equivalents) from collagen per 5 hours at 37 °C, pH 7.5.

Clostridiopeptidase A or HP:

1 U catalyzes the hydrolysis of 1 μmol N-carbobenzoyloxy-glycyl-L-prolyl-glycyl-glycyl-L-prolyl-L-alanine per minute at 37 °C.



Unit definitions:

Clostripain:

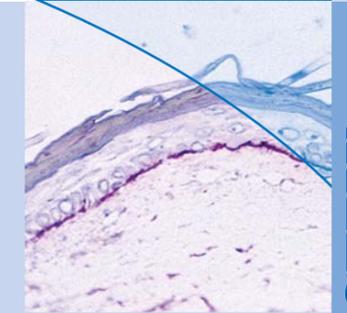
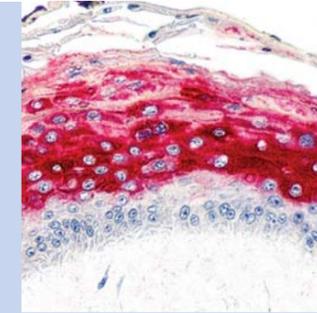
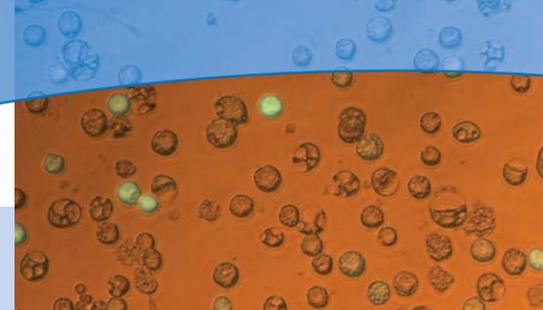
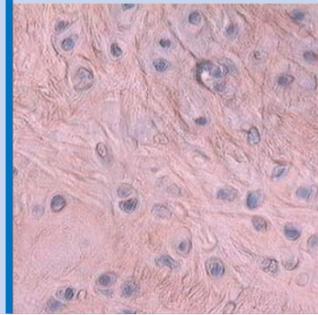
1 U hydrolyzes 1 μmol N-benzoyl-L-arginine ethyl ester (BAEE) per minute at 25 °C, pH 7.8, after activation with 1 mM calcium acetate and 2.5 mM dithiothreitol.

Trypsin-like proteases:

1 U catalyzes the hydrolysis of 1 μmol BAEE per minute at 25 °C, pH 8.0.

Endotoxin:

According to Ph. Eur.; 1 Endotoxin Unit is equal to 1 International Unit of a WHO approved reference standard Endotoxin (RSE).



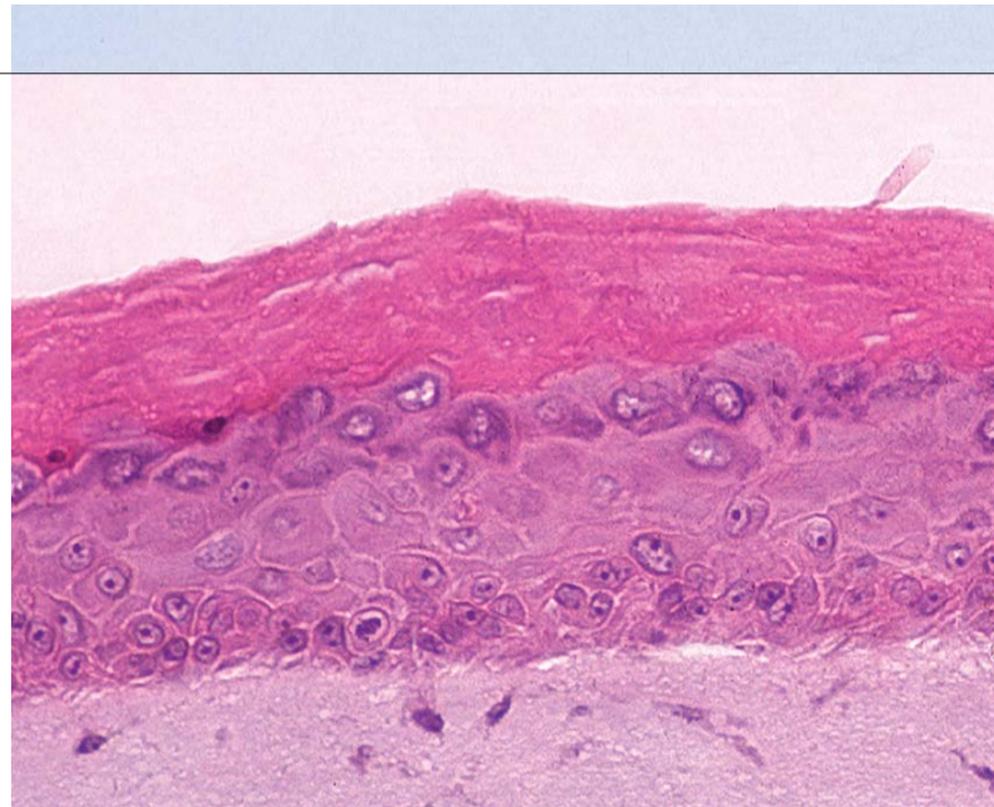
From Tissue to Isolated Cells

The isolation of intact, well defined cells from the complex tissue network without damaging the cells is a great challenge. Collagenase plays a key role in this process and influences yield, viability and functioning of the isolated cells.

SERVA collagenases have been successfully used in the isolation of a broad variety of cell types. In cooperation with research and transplantation centers, protocols for the isolation of different cell types were developed to allow best results. Using our especially designed **Collagenase NB** qualities an optimal yield of isolated, viable cells can be achieved.

Neutral protease is an essential additive for isolations with highly purified collagenase. SERVA **Neutral Protease NB** is provided separately allowing flexible dosage individually adapted to the tissue state and cell sensitivity.

Cell isolations for human transplantation and tissue engineering purposes require cGMP production standards. SERVA **Collagenase NB** and **Neutral Protease NB GMP Grade** qualities are produced and certified in accordance with cGMP guidelines and therefore are suitable for such applications.



Research Studies and Pharmacological Test Systems

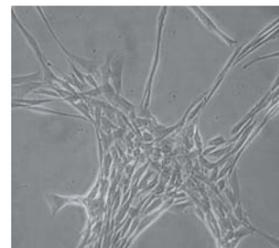
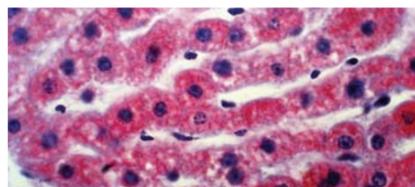
Isolated cells as well as *in vitro* cultivated tissues are performed for physiological, metabolic and functional studies or for drug testing in pharmacological test systems, e.g.:

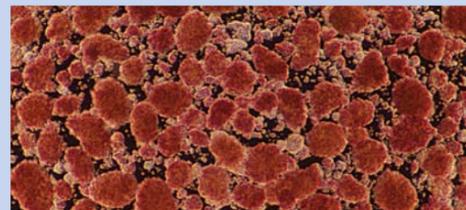
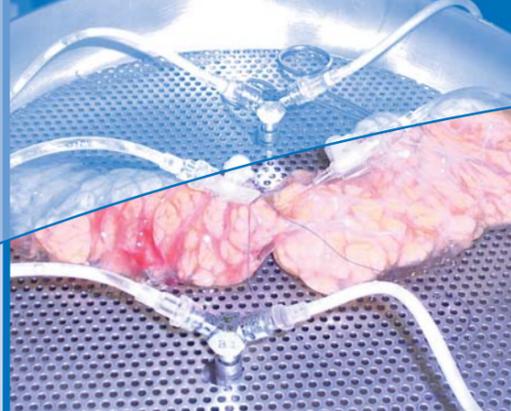
- Hepatocytes
- Fibroblasts
- Keratinocytes
- Chondrocytes
- Cardiomyocytes
- Oocytes
- Nerve cells
- Stem cells

Tissue Engineering for Transplantation

Isolation of several cell types is carried out to obtain cells or *in vitro* cultured tissues for transplantation:

- Hepatocytes are isolated and transplanted to cure chronic liver diseases or to substitute liver function after acute organ failure
- Chondrocytes are isolated and cultivated to replace damaged cartilage
- Dermal fibroblasts and keratinocytes are isolated to build up three-dimensional skin transplants to treat burning injuries, diabetic or other ulcers
- Tumor cells from various tissues are isolated and fused with dendritic cells for tumor immunotherapy
- Adipose-derived stem cells are isolated to generate functional cells and tissue





Isolation of Pancreatic Islets

Transplantation of pancreatic islets of Langerhans is a promising viable treatment option for patients with type-1 diabetes.

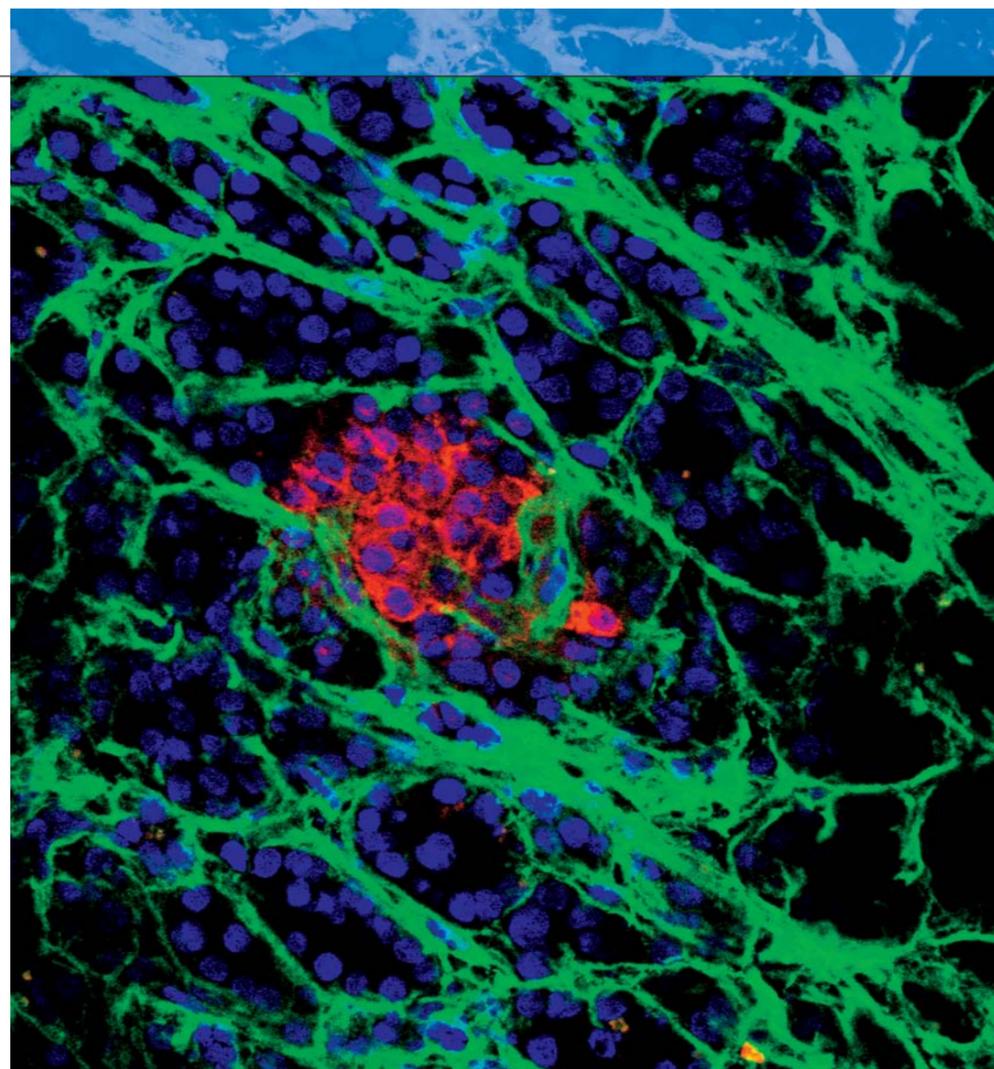
Also patients who had to have pancreatic surgery, including complete removal of the pancreas due to chronic inflammation, are transplant candidates.

Transplantation of islets may restore some of the functions of the removed organ.

A number of diabetic patients who had received injections of isolated islets into the liver were insulin-independent for several years.

Human islets for transplantation are isolated from donor pancreases with greatly varying qualities. Since availability of donor organs is limited, high yields of isolated islets per organ are required. Thus, isolation protocols and enzyme solutions have to be optimized and tailored to the individual organ quality.

Collagenase, combined with a crucial amount of neutral protease, is the enzyme composition of choice to dissociate the supporting matrix of the pancreas. High yields of islets and especially viable, functional islet cell aggregates will be achieved.



Islet stained in red, surrounded by SERVA Collagenase NB stained green bound to collagen; University of Oxford.

The isolation procedure consists of several critical steps. After preparation and cleaning of the donor pancreas, the organ is perfused with the enzyme solution. Directly after tissue dissociation, the islets are purified from the exocrine tissue. After a short recovery time in cell culture, the islets are transplanted into the liver of patients, where the islets resume their normal function.

SERVA **Collagenase NB 1** in combination with SERVA **Neutral Protease NB** is especially designed for this application. It has been demonstrated that best results with respect to digestion efficiency, islet yields, cell viability and *in vitro* function are achieved with a **Neutral Protease NB** dosage, individually adapted to the state of the donor organ.

As collagenase is regarded to be a critical raw material in islet isolation for subsequent transplantation into humans, **Collagenase NB 1 GMP Grade** and **Neutral Protease NB GMP Grade** produced in compliance with the EU-Guide to current Good Manufacturing Practice „cGMP for active pharmaceutical ingredients“ are available.

The production of these GMP Grade products fulfills the requirements of the TSE guidelines according to the European Pharmacopoeia.

For details see references:

- Brandhorst D. et al; Transplant Proc., 37(1), 241-242 (2005)
- Bucher P. et al; Transplantation, 79(1), 91-97 (2005)



SERVA Collagenase Qualities – Ordering Information

Collagenase	Properties	Application	Cat.-No.	Pack Size
Collagenase NB 1 Premium Grade from <i>C. histolyticum</i>	<ul style="list-style-type: none"> Chromatographically highly purified Contains class I and class II collagenases PZ activity* ≥ 3.00 U/mg lyophilisate Largely free of clostripain, trypsin-like activities and neutral protease Endotoxins ≤ 10.0 EU/ mg lyophilisate 	<ul style="list-style-type: none"> Isolation of pancreatic islets Use in combination with Neutral Protease NB Collagen characterization 	17455.03	≥ 2000 PZ U/Vial
Collagenase NB 1 GMP Grade from <i>C. histolyticum</i>	<ul style="list-style-type: none"> Enzymatic properties see Collagenase NB 1 Premium Grade Manufactured according to international cGMP guidelines 	<ul style="list-style-type: none"> Isolation of pancreatic islets for transplantation into humans Use in combination with Neutral Protease NB GMP Grade 	17452.01	≥ 2000 PZ U/Vial
Collagenase NB 4 Standard Grade from <i>C. histolyticum</i>	<ul style="list-style-type: none"> Contains class I and class II collagenases and a balanced ratio of proteolytic activities PZ activity* ≥ 0.1 U/mg lyophilisate 	<ul style="list-style-type: none"> Isolation of various cell types including hepatocytes, cardiomyocytes, pancreatic islets, neuronal and endothelial cells, chondrocytes, tumor cells, fibroblasts, adipocytes, muscle and epithelial cells, stem cells, gangliocytes, periodontal cells and oocytes 	17454.02 17454.01	500 mg 1 g
Collagenase NB 4G Proved Grade from <i>C. histolyticum</i>	<ul style="list-style-type: none"> Contains class I and class II collagenases as well as a balanced mix of neutral protease, clostripain and trypsin-like activities PZ activity* ≥ 0.18 U/mg lyophilisate Function tested for cell isolation 	<ul style="list-style-type: none"> Isolation of various cell types – especially adipocytes, fibroblasts, hepatocytes, chondrocytes, stem cells and frog oocytes 	17465.01 17465.02	500 mg 1 g
Collagenase NB 5 Sterile Grade from <i>C. histolyticum</i>	<ul style="list-style-type: none"> Enzymatic properties see Collagenase NB 4 Aseptic production according to European requirements for medicinal products (Pharm. Eur.) 	<ul style="list-style-type: none"> Application fields see Collagenase NB 4 Sterile and thus ready to use 	17459.03	1 g
Collagenase NB 6 GMP Grade from <i>C. histolyticum</i>	<ul style="list-style-type: none"> Enzymatic properties see Collagenase NB 4 Aseptic production according to European requirements for medicinal products (Pharm. Eur.) Manufactured according to international cGMP guidelines 	<ul style="list-style-type: none"> Application fields see Collagenase NB 4 Production of cells as well as tissue engineering for transplantation into humans 	17458.03	1 g
Collagenase NB 8 Broad Range from <i>C. histolyticum</i>	<ul style="list-style-type: none"> Contains class I and class II collagenases, and reduced levels of clostripain, trypsin-like activities and neutral protease PZ activity* ≥ 0.9 U/mg lyophilisate Endotoxins ≤ 100 EU/ mg lyophilisate 	<ul style="list-style-type: none"> Isolation of e.g. cardiomyocytes, hepatocytes, pancreatic islets, chondrocytes, tumor and thyroid cells 	17456.01 17456.02	250 mg 1 g
Collagenase N Reference Content from <i>C. histolyticum</i>	<ul style="list-style-type: none"> Contains class I and class II collagenases and other proteolytic enzymes Collagenase activity is regularly reevaluated 	<ul style="list-style-type: none"> Reference substance for enzyme activity determination 	17463.01	≥ 50 mg
Collagenase N Reference Identity from <i>C. histolyticum</i>	<ul style="list-style-type: none"> Contains class I and class II collagenases and other proteolytic enzymes 	<ul style="list-style-type: none"> Reference substance for SDS-PAGE analysis, performed for incoming goods inspection according to cGMP 	17464.01	≥ 50 mg
Neutral Protease NB from <i>C. histolyticum</i>	<ul style="list-style-type: none"> Chromatographically purified neutral protease Activity (DMC assay) ≥ 0.50 U/mg lyophilisate 	<ul style="list-style-type: none"> Tissue dissociation Cell isolation in combination with Collagenase NB 	30301.11 30301.12	50 DMC U/Vial 100 DMC U/Vial
Neutral Protease NB GMP Grade from <i>C. histolyticum</i>	<ul style="list-style-type: none"> Enzymatic properties see Neutral Protease NB Manufactured according to international cGMP guidelines 	<ul style="list-style-type: none"> Tissue dissociation Cell isolation in combination with Collagenase NB GMP Grades for transplantation into humans 	30303.01	≥ 100 DMC U/Vial
Anti-Collagenase (<i>C. histolyticum</i>) polyclonal antibody from sheep	<ul style="list-style-type: none"> Specificity against collagenases from <i>C. histolyticum</i> IgG fraction purified by Protein G affinity chromatography 	<ul style="list-style-type: none"> Use in ELISA and Western Blot experiments Immunostaining of tissue Analysis of residual collagenase impurities in cell preparations 	58050.01	100 μ g

*PZ activity according to Wünsch, measured at 25 °C

SERVA Collagenases are not intended for use in humans. Responsibility for use of these enzymes in clinical applications and the methods to isolate, purify, cultivate and transplant cells lies solely with the providing physician/researcher and the responsible Ethics Committee.

SERVA
Electrophoresis

SERVA Electrophoresis GmbH
Carl-Benz-Str. 7
D-69115 Heidelberg
www.serva.de

 **Nordmark**

Nordmark Arzneimittel GmbH & Co. KG
Pinnauallee 4
D-25436 Uetersen
www.nordmark-pharma.de

