1990: • Idea of **MARS®** (Molecular Adsorbents Recirculating System) formed at the Meeting "Artificial Liver Support" in Celle, Germany by Students and Mentors of Rostock

1991: • **MARS®** therapy: First patient filed by J. Stange and W. Ramlow

1992: • Jan Stange receives Grant for Artificial Liver (2 Mio DM by BMBF) and founds group with Steffen Mitzner in Rostock

1993: • Continuation in part patent filed by J. Stange, Steffen Mitzner and W. Ramlow
• 1st **MARS®**-treatment at the Department of Internal Medicine, University of Rostock

1997: • Foundation of Society for Extracorporeal Detoxification (VED) e.V.
• Establishment of Biopure Medizinprodukte GmbH & TERAKLIN GmbH
• National Champion „Biopure GmbH" - Entrepreneurs Competition „Start Up 1997"

1999: • Biopure Medizinprodukte GmbH & TERAKLIN GmbH merge to TERAKLIN AG
• 1st **MARS®** monitor with standardized sets for the MARS© therapy
• 1st **MARS®**-treatment at the Department of Internal Medicine, University of Rostock
• 1st International Symposium on Albumin Dialysis (ISAD) in Rostock

2000: • 40 centers used a **MARS®** therapy
• Dr. Jan Stange moved to the United States; attended to multicenter study with 70 patients

2001: • Nomination of **MARS®** therapy for German Future Prize

2002: • TERAKLIN AG: approvals in India, Australia, South Korea and Taiwan
• TERAKLIN AG: application for approval of **MARS®** in the USA at the Food and Drug Administration (FDA) at the end of the year

15th October **2003:** • **MARS®** in ordinance on case payments for 2004 - catalog, D

2004: • **MARS®** in catalogs of the defined benefit hospital financing system, Austria
• Establishment of Albutec GmbH
• 09/2004 Acquisition of TERAKLIN AG by Gambro

2005: • **MARS®** approval in the USA

2007: • Establishment of ARTCLINE GmbH

12th March **2008:** • Foundation of competence network „CEOS" - Center for Extracorporeal Organ Support, Rostock

2011: • Foundation of Fraunhofer Group „EXIM" - Extracorporeal Immunomodulation

2012: • Conception growth core „Support Center for Organ & Recovery" in Rostock

2013: • 13th ISAD as part of European Society for Artificial Organs (ESAO) - Congress in Rostock

The History of MARS®

Chronicle Kidney dialysis

1748 • Discovery of renal replacement therapy by Jean Antoine Nollet
1802 • Discovery of hydro diffusion by Georg Friedrich Parrot
1812 • Discovery of membrane diffusion by Nicolaus Wolfgang Fischer
1854 • Epochal discovery of colloids and dialysis by Thomas Graham
1924 • 1st dialysis with semipermeable membrane by Georg Haas in Germany
1943 • Breakthrough at artificial kidney (plow kidney) by Dutchman Willem Kolff
1946 • Development of Alwall dialyzer by Nils Alwall
1948 • Skaggs and Leonards developed the first slabs dialyzer
1950 • 1st clinically effective dialysis in Germany by Carl Moeller
1960 • 1st long-term patient with chronic renal failure receives hemodialysis
1963 • Nurol Kimkanon developed artificial kidney in the GDR (East Germany)
1966 • 1st home dialysis in Germany

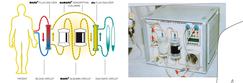
Molecular Adsorbents Recirculating System

MARS®-Therapie

The **MARS®** therapy has caused a revolution in the field of liver therapy. The blood detoxification process helps to clean the liver outside the body. With this method water-soluble and water-insoluble protein-bound liver toxins are removed from the patient's blood.

The procedure of the **MARS®** system is similar to the kidney dialysis and uses a toxin removing substance called albumin. Albumin is a human plasma protein and acts as a natural detergent drawing toxins away from the blood.

The liver dialysis **MARS®** has the potential to save the life of patients with threatening liver diseases by the detoxification of the liver.



The use of the MARS® therapy

Acute liver failure
- caused by acute viral infection, poisoning (caused by alcohol, drugs or mushrooms),
- identification: life-threatening complications (hepatic encephalopathy, jaundice, renal failure, multi-organ failure)

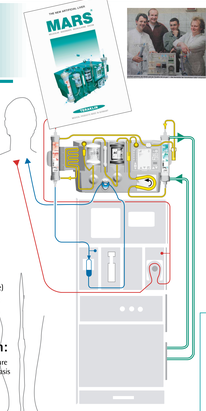
After liver transplant surgery: transplant liver failure or severe graft dysfunction

MARS© therapy has a positive effect on:

- survival rate/ - time
- hemodynamics
- hepatic function
- renal function
- hepatic encephalopathy
- intracranial pressure
- jaundice / cholestasis

Pathologies:

- Autoimmune hepatitis
- Primary biliary cirrhosis (PBC)
- Primary sclerosing cholangitis (PSC)
- Hemochromatosis
- Alpha-1- antitrypsin deficiency
- Budd-Chiari Syndrome
- Hepatocellular carcinoma (HCC)



The procedure of the MARS®-therapy

The **MARS®** system removes protein-bound and water-soluble toxins with albumin dialysis. Transport proteins with free binding sites lure behind the **MARS®**-membrane and remove the toxins from the blood. Toxin-removing material as the human serum albumin (HSA) is used. It is obtained industrially from the donor's blood. Molecules that bind to the albumin membrane are then removed by passing through a charcoal column and an anion exchange, before being reintroduced into the circuit. Both water-soluble toxins and strongly albumin-bound toxins are removed by this process.

By the **MARS®** therapy water-soluble and albumin-bound substances such as bile acids, bilirubin, fatty acids, ammonia, urea, and copper are removed.

MARS® and expenses

2004 Inclusion of **MARS®** in the OPS 301-catalog (code 8-858.0)
2004 Inclusion of **MARS®** in the DRG accounting system with additional fees ZE32
from 2005 DRG-accounting system with additional fees 2005–10 to 2012 DRG-accounting system with additional fees PA 20012-10

Forum Leberdialyse (FLD) e.V. - was founded in 1997 as an association for extracorporeal detoxification (VED) e.V.

1999 Organization and execution – 1st International Symposium on Albumin Dialysis (ISAD)
2001 Execution of the first seminar on albumin dialysis in Northern Germany
2002 Participation: 10th Day of Action against addictive dangers in Rostock
2003 Renaming to FORUM LIVER DIALYSIS (FLD) e.V.
2004 Nomination project „Olympia at the Schwanenteich" for the 1st German Prevention Award by the Federal Ministry of Health and Social Security
2006 Execution of the course „Hepatitis B + C" as part of the 7th German Liver Congress in Warnemünde
2008 Foundation of the Center for Extracorporeal Organ Support (CEOS); 12 March 2008 in Rostock
2010 Kick Off Project „Health Net-MV"
2011 Foundation of the Fraunhofer Group „Extracorporeal Immunomodulation" (EXIM)
2012 Development of the concept "Wachstumskern „ - Center for Organ & Recovery Support"
2012 13th ISAD as part of the European Society for Artificial Organs (E.S.A.O) – Congress in Rostock

sponsored by the Ministry of Education and Research, the state of Mecklenburg-Western Pomerania and the University of Rostock

Executive Board: Prof. Dr. Steffen Mitzner (Chairman)

Cases of patients treated with MARS© therapy

ACUTE DECOMPENSATION OF CHRONIC LIVER DISEASE

Dagmar Heinicke, 40 years, first MARS® patient, jaundice
- admission to the Department of Internal Medicine Rostock; falls into a coma
- cause: chronic hepatitis C with acute decompensation of liver function
- **after the second day of the MARS® treatment:** patient wakes up from coma
- discharge from hospital after several **MARS®** treatments (preparation Ltx)

MULTIORGAN FAILURE

- 8-year-old girl with no anamnesis - admission to the Department of Cardiology
- diagnosis: myocarditis, consequence: cardiac arrhythmia + cardiac arrest with the consequence of cardiogenic shock and multi-organ failure
- failure of kidney, liver and respiratory system
- reveal succeeds, but the status of organ function is critical
- **use of 3 MARS® treatments:** improvement of organ functions within 3 days + prevention from endogenous toxicopathy
- discharge from hospital in a healthy condition after 6 weeks

ACUTE LIVER FAILURE

- 30-year-old man with chronic schizophrenia: after taking 40 gram of paracetamol -> admission to hospital
- early signs of kidney failure + slight confusion, delivery in kidney station
- signs of serious liver damage, patient is unconscious
- full screen: liver failure
- **use of 5 MARS® treatments:** improvement of clinical biochemical parameters
- discharge from hospital in a healthy condition after 26 days

Awards

The **MARS®** therapy has been honored with 17 national and international awards (list: extract on awards).

As part of **MARS®** external funding investments of 10 million euros as well as industrial investments of 30 million euros were acquired.

- **1991: Promotion of MARS® in the programme „Promoting Junior Biotechnology Groups in East Germany"**, DM 2 million, 5 years
- **January 1994: Dr. Jan Stange – research grant by the Sandoz Foundation in the amount of DM 10,000**
- **National Prize Winner „Biopure GmbH" at the Founders Competition „Start Up 1997"** on behalf of the business consultancy McKinsey, the savings banks and the magazine „Stern" (under the patronage of Federal President Roman Herzog) prize money: **DM 100,000 to Aldinger, Gericke, Stange & Mitzner**
- **28 August 1998: Honor of the winners of the Entrepreneurs Competition „Start Up 1997" in the Baroque Hall Rostock**
- **2000: TERAKLIN AG: German Business Award in the amount of DM 50,000**
- **2001 Nomination of the MARS® therapy** for the **German Future Prize** (under the patronage of Federal President Johannes Rau)

MARS® – number of cases

By **2012** the number of **treated patients** increased to more than **12,000** with more than **67,000 individual treatments** in nearly **450 centers in 30 countries**. This includes more than **450 children** who were treated with **MARS®**.