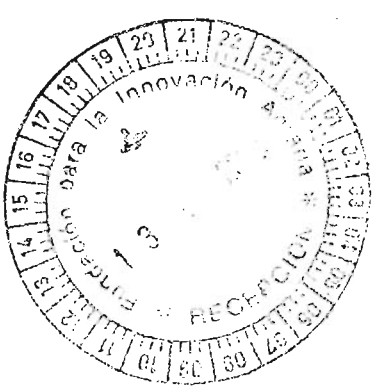
INFORME TÉCNICO

FERIA BIOTECHNICA HANNOVER 2003

Fundación para la Innovación Agraria
Cámara de Comercio Chileno-Alemana

Lina Razeto Olivares
Noviembre 2003



GOBIERNO DE CHILE
FUNDACIÓN PARA LA
INNOVACIÓN AGRARIA

CONTENIDO DEL INFORME TÉCNICO

PROGRAMA DE FORMACIÓN PARA LA INNOVACIÓN AGRARIA

1. Antecedentes Generales de la Propuesta

Nombre: Participación en la delegación chilena que asistió a la Feria Biotecnológica de Hannover.

Código:

Nombre Postulante Individual: Lina Razeto Olivares

Lugar de Formación (País, Región, Ciudad, Localidad): Alemania, ciudades de Berlin (Potsdam), Hannover y Marburg.

Fecha de realización: Lunes 6 a Viernes 10 de octubre 2003

Objetivos de su participación en la actividad:
El objetivo general de mi participación fue obtener conocimientos acerca de innovaciones en biotecnología, especialmente aquellas aplicables en el sector agroindustrial y conocer el estado del arte de la biotecnología en Alemania.

Como objetivos específicos se planteó adquirir conocimientos en los siguientes ámbitos:

- Aplicaciones de la biotecnología en la producción de alimentos
- Nuevas tecnologías en el área medioambiental
- Estructuración de las políticas del gobierno alemán para fomentar el desarrollo de la industria e investigaciones biotecnológicas.

Como objetivo adicional se presentó la búsqueda de proveedores de enzimas.

2. Antecedentes Generales:

Biotechnica se ha erigido como una de las ferias más importantes que se realizan a nivel mundial en el ámbito de la Biotecnología. Por otro lado Alemania se configura hoy y se proyecta hacia el futuro como el país de la Unión Europea con más adelantos en el campo de la Biotecnología, sea a nivel de investigación como a nivel de sus aplicaciones empresariales. Es por ello que además de visitar la Feria se concertaron reuniones con actores relevantes dentro del mismo ámbito de la Biotecnología Alemana

Las primeras actividades que se realizaron fueron en Potsdam – Rehbrücke, donde se visitaron el Instituto Alemán de Nutrición Humana y el Instituto de Investigación del Trigo, donde además asistimos a una conferencia de la empresa Biopract. Desde mi punto de vista fue la visita más interesante del viaje, pues estaba dirigida a mis áreas objetivo.

El Instituto Alemán de Nutrición Humana tiene la misión de mejorar la salud humana a través de investigación básica y clínica en el campo de la nutrición, en particular los dos puntos esenciales son:

- Estudiar el mecanismo de pato fisiologías causadas por desórdenes nutricionales, en especial el síndrome metabólico y el cáncer.
- Determinar nuevos enfoques y definir una base científica para recomendaciones nutricionales.

Este instituto fue fundado en 1992 por el Ministerio de Ciencias, Investigación y Cultura de Brandenburg como una institución independiente con financiamiento compartido (privado y público) y su presupuesto anual es de 9.8 millones de euros. Consta de 8 departamentos y 2 grupos de investigación.

El Instituto de Investigación del Trigo realiza investigación con aplicaciones industriales, por lo que está muy ligado a la empresa privada. Su presupuesto anual es de 5 millones de euros y su financiamiento es compartido (3% Ministerio de Agricultura, 50% privado, 47% licitaciones públicas o proyectos concursables). Este instituto tiene competencia y experiencia en procesamiento de alimentos, agricultura y biotecnología; su misión es la de investigar y desarrollar tecnología de innovación transferible y aplicable a la producción. Por ejemplo, en este instituto se desarrollan tecnologías para elaboración de productos de panificación, productos dietéticos para ciertas enfermedades, uso de cereales para materiales técnicos, uso de algas para alimentación, cosmética o biorremediación. Además funciona como laboratorio acreditado de certificación de productos y procesos para empresas.

BIOPRACT es una empresa privada cuyas esferas principales son el desarrollo de producción de enzimas y servicios medioambientales. Las enzimas industriales son desarrolladas en laboratorios microbiológicos especializados según la necesidad de la empresa solicitante, siendo las principales especies las lipasas, celulasas y fitasas. En cuanto a sus servicios medioambientales desarrollan procedimientos para la limpieza o descontaminación de ciertos medios. Principalmente mediante Biolift y Estimulación Biológica.

La presentación de estas tres entidades nos dio a conocer el estado del arte de una de las principales regiones de Alemania, Potsdam/Berlín, en cuanto a biotecnología. Sin duda la información que se nos entregó y la posibilidad de ver in situ el trabajo de los profesionales dedicados a este tema nos dan una perspectiva diferente para afrontar los desafíos empresariales e institucionales en cuanto al desarrollo de proyectos biotecnológicos en Chile. Estas visitas nos permitieron entrever la sinergia positiva que surge de la relación entre la

investigación y la empresa en Alemania sumadas al apoyo del Gobierno, pero sin duda también nos enfrentó a una realidad nacional muy lejana a la europea, cuya brecha debemos acortar.

La siguiente actividad fue la visita a la 13ª Feria Biotecnológica de Hannover, BIOTECHNICA 2003. Con cerca de 200 expositores dirigí mi atención hacia aquellos que guardaban relación con mis objetivos.
Presentaré a continuación la información de los stands que más me interesaron:

Institute of Microbiology, Technical University Braunschweig. Es un importante Instituto Tecnológico alemán, de carácter interdisciplinario, de nivel internacional y con altos estándares científicos. Exponía Técnicas Biológicas para el Medioambiente, como la biorremediación.
Nadicom, empresa relativamente nueva, fundada a comienzos del 2002 por el Instituto Max Planck para Microbiología Terrestre, en Marburg. Su principal servicio es detectar e identificar microorganismos usando métodos de biología molecular. Además realizan investigación, desarrollo y producción en temas como eco fisiología de muestras medioambientales, modificación de cultivos de hongos o bacterias para optimizar ciertas transformaciones bioquímicas, caracterización de genes en microorganismos, etc. También se dedican a la educación, ofreciendo seminarios dirigidos a personal de laboratorios y a estudiantes universitarios, y a consultorías en el campo de la microbiología
Chia Meei Health Biotechnology, es una compañía de Taiwán especializada en la producción de varios tipos de purés de frutas y vegetales, concentrados e ingredientes para alimentos funcionales, como por ejemplo extractos botánicos estandarizados, extractos de hierbas, de frutas y vegetales, series biocelulosas, etc. Lo interesante de esta empresa es que potencia industrialmente tradiciones orientales en cuanto a alimentación preventiva promoviéndolas a niveles internacionales.
Westfalia Separator Engineering, empresa alemana de gran importancia a nivel internacional, la cual provee maquinarias e instalaciones de automatización para las empresas. El Gerente de Westfalia Chile S.A. es el actual asesor técnico del proyecto FONTEC que lleva a cabo la empresa en que trabajo, Agroindustrial Razeto Ltda.
Porto Conte Ricerche, es un polo italiano de biotecnología asociado a la agroindustria y al medioambiente. Actualmente desarrollan investigación en temas tales como estudio de sustancias naturales con efectos antioxidantes y antimutágenos en alimentos; innovaciones en productos enológicos, olivícolas, lácteos, entre otros.

Durante nuestra participación en la feria asistimos a una exposición dictada por un miembro del Ministerio Federal de Educación e Investigación sobre el programa nacional de biotecnología. Se nos entregó información acerca de la organización, financiamiento y los principales focos de trabajo en biotecnología.

Asistí también a un work shop dedicado a la "Biotecnología como Negocio" donde se relacionaba la biotecnología con la empresa privada, cuáles eran las principales dificultades y fortalezas, y cómo potenciar esta unión. Estaba enfocado exclusivamente a la farmacología.

Finalmente se realizó una visita al Instituto Max Planck para Microbiología Terrestre, fundado en 1991 para promover la investigación en el área de microbiología de hábitat terrestres. Aquí se estudia bioquímica, biogeoquímica, eco fisiología, interacciones simbióticas y mecanismos de regulación genética de microorganismos para abono. Asistimos a una exposición sobre el

trabajo realizado por el Departamento de Interacciones de Organismos, relacionado con la fitopatología molecular, con especial énfasis en el *Ustílago Maydis*.

3. Itinerario Realizado:

Fecha	Actividad	Objetivo	Lugar
6/10/03	Visita al Instituto Alemán de Nutrición Humana	Conocer investigaciones biotecnológicas aplicadas a la nutrición	Potsdam
6/10/03	Visita al Instituto de Investigación del Trigo	Conocer aplicaciones e investigaciones biotecnológicas industriales del trigo	Potsdam
7-9/10/03	Visita a Biotechnica 2003	Conocer el estado del arte de la biotecnología a nivel internacional y realizar contactos	Hannover
8/10/03	Charla Organización de la Feria Biotechnica	Recavar información respecto de cómo participar en la Feria Biotechnica	Hannover
8/10/03	Charla con Ministerio Federal de Educación e Investigación	Informar respecto de las políticas del Gobierno Alemán hacia la biotecnología y cómo ésta se organiza en el país.	Hannover
9/10/03	Presentación Biocon Valley MVP	Informar sobre la organización de Empresa e Institutos de Investigación relacionados con biotecnología en la región de Mecklenburg-Vorpommern	Hannover
10/10/03	Visita Max Planck Instituto para Microbiología Terrestre	Conocer el funcionamiento de este prestigioso instituto alemán de investigación y los trabajos que actualmente realiza.	Marburg

4. Resultados Obtenidos:

Los resultados obtenidos se vinculan a la adquisición de conocimientos específicos en diferentes áreas de la Biotecnología y su situación coyuntural, principalmente en Alemania. Algunos de los conocimientos adquiridos se ordenan en este informe en tres secciones:

- La Biotecnología en Alemania
- Nutrición y Salud.
- Área Medioambiental

LA BIOTECNOLOGÍA EN ALEMANIA

El Ministerio Federal de Educación e Investigación de Alemania financia la biotecnología y la ingeniería genética como la clave tecnológica para futuras innovaciones y, por lo tanto, esencial para el futuro desarrollo científico y tecnológico. Su uso potencial juega un importante rol en la ciencia y en la industria. Las posibilidades de usar la biotecnología en el área de la medicina humana y veterinaria, agricultura y nutrición así como también en medioambiente son extremadamente diversas y nos acercan a nuevas soluciones a los problemas.
La biotecnología es una tecnología genérica. Su uso comercial se manifiesta en los variados métodos en la mayoría de las áreas de la industria que están ligadas a la ciencia. Esta contribuye a:

- Mantener y aumentar estándares internacionales de ciencia e investigación
- Crear nuevos y permanentes puestos de trabajo y reemplazar los trabajos tradicionales por aquellos con orientaciones modernas
- Mantener un mejoramiento de la competitividad alemana como industria e investigación.

El Ministerio Federal de Educación e Investigación, el año 2001, abrió un nuevo programa promoviendo la industria biotecnológica y la ingeniería genética para los siguientes 5 años. En la próxima década, se predice que la biotecnología se transformará en la más importante área de la ciencia como puerta hacia nuevos conocimientos e introducción de innovaciones en medicina, farmacología e industria biotecnológica, agricultura así como en el sector alimenticio y en protección al medioambiente. Durante estos 5 años se entregarán 800 millones de euros para financiar este programa biotecnológico.
Este programa está destinado a contribuir en forma importante a resolver los actuales problemas en salud humana, protección al medioambiente y creación de trabajos altamente calificados. El Gobierno Federal apoya las estrategias de desarrollo de la biotecnología, encomendando el uso responsable del potencial para la innovación, tomando como lema "Investigación para la gente".
Un resumen de las actividades clasificadas por las distintas áreas financiadas por el Ministerio Federal desde el año 2001 se entregará a continuación:

Bases de Conocimientos: campo de la investigación en el cual se espera obtener un conocimiento importante y nuevas aplicaciones en la ciencia viva y en otras ciencias relacionadas.

- **Análisis del Genoma en el Sistema Biológico en la Planta – GABI**: Investigación dentro del genoma de la planta modelo *Arabidopsis thaliana* así como también en la cebada; análisis de secciones seleccionadas del genoma de otras plantas importantes. Implementación de la información genética obtenida en investigación aplicada hacia otros objetivos, caracterización de la red de acción de importantes plantas funcionales.

- **Neurobiología**: Investigación fundamental del desarrollo de nuevos productos farmacéuticos, investigación dentro del modo de las funciones neuronales sobre la autoorganización de estructuras cognitivas. Futuros centros competentes para la biología basada en la exploración del procesamiento de la información cerebral mediante neuro informática así como también un acercamiento metódico de la asistencia computacional de la investigación cerebral.
- **Competencia según BioFuture**: La posibilidad que jóvenes investigadores nacionales o extranjeros que tengan una experiencia considerable en investigación para trabajar con grupos propios en investigaciones innovadoras dentro de las ciencias biológicas. El objetivo es financiar una carrera científica top o un prometedor empresario, fortaleciendo a Alemania como un país para la investigación biotecnológica.

Comercialización: Medidas estructurales que consideran la investigación y la colaboración de instituciones de cooperación de la industria y la ciencia.

- BioChance: Énfasis en el auspicio del desarrollo del know-how en jóvenes compañías de biotecnología con el objetivo de posicionarlos en forma segura y efectiva en el mercado.
- BioProfile: Desarrollo de perfiles expertos y competitivos internacionalmente, dentro de las regiones biotecnológicas. En conjunto con BioChance, BioProfile constituye un fondo que apunta a mejorar la comercialización de la biotecnología alemana.
- Bioproducción Sustentable: Explotación de la producción de organismos biológicos con potencial para nuevos y económicos recursos, ahorro energético y disminución de desechos industriales en procesos de producción. Financiamiento de la aplicación, especialmente en las áreas de la química, farmacéutica, alimentos y bebidas, papel y celulosa e industrias textiles y del cuero.
- Nutrición, Alimentos y Salud: Desarrollo de nuevos tipos de alimentos activos funcionales en proyectos piloto, que apuntan a la prevención de enfermedades ampliamente propagadas, como el cáncer y desórdenes cardiovasculares. Poniendo en marcha redes multidisciplinarias de investigación hacia la acción preventiva de alimentos o elementos particulares de los alimentos exhibiendo su acción preventiva.

Tecnologías Plataforma: Métodos y procesos biotecnológicos innovadores que comprenden diversas aplicaciones y que atraviesan numerosos campos de investigación, desarrollo y aplicación.

- Red de Investigación del Genoma Nacional: Con esta Red, Alemania se sitúa a la cabeza en Europa en cuanto a financiamiento público en análisis funcional sistemático de genes e implementación de resultados de investigación en la lucha contra enfermedades frecuentes, en particular en desórdenes cardiovasculares, enfermedades del sistema nervioso, enfermedades medioambientales e infecciosas y quemaduras.
- Nuevos procedimientos para el Análisis del *Proteoma* Funcional: Investigación acerca de cómo operan los genes y las proteínas y sus códigos basados en las investigaciones del genoma. Visualización del actual campo de la proteína y la explicación de las funciones biológicas de las proteínas dentro de una célula, un órgano o un organismo. Contribuciones significativas hacia el desarrollo de la "farmacéutica hecha a la medida".

- Ingeniería en Tejido: Cultivo y propagación de células o tejidos en "tubos de ensayo". Con lo que respecta al sector clínico, la más importante aplicación es el cultivo de tejidos naturales como la piel y los cartílagos tomados de células de los propios pacientes involucrados. El objetivo es el reemplazo de partes o funciones orgánicas defectuosas.
- Nanobiotecnología: investigación y desarrollo de sistemas en relación con escalas nano en al menos una dimensión, como por ejemplo no mayores que unos pocos millonésimos de milímetro. Desarrollo de materiales con propiedades con sorprendentes propiedades así como también tecnologías completamente nuevas.
- Bioinformática: Procesamiento y evaluación de datos obtenidos de análisis biológico moleculares para mejorar el progreso en otras disciplinas biotecnológicas. Financiar la unión de proyectos para el desarrollo de la eficiencia de herramientas bioinformáticas así como el entrenamiento de actuales y futuras generaciones de científicos.
- Diagnósticos TSE: Proyectos de investigación para verificar *Transmissible Spongiform Encephalopathies*. (TSE; enfermedades como las cerebrales); incluyendo BSE (aplicada en bovinos). Financiando también estos campos económicamente significativos se apunta particularmente al diagnóstico de las enfermedades TSE (desarrollando exámenes en organismos vivos).
- Biología de los Sistemas: Combinación de conceptos que contienen biología, ciencia computacional y ciencias sistémicas; modelación y simulación de procesos biológicos o de una célula completa, también en diseño de experimentaciones conducidas sobre células virtuales. Como resultado de las aplicaciones de los métodos de la biología de sistemas se esperarán adquirir decisivos conocimientos concernientes al desarrollo de medicamentos.

Convenios Gubernamentales: Tratos para posibles riesgos y consecuencias de las aplicaciones de biotecnologías nuevas. Además se incluye la búsqueda de sustitutos para experimentos con animales, que mantengan calidad en la investigación

- Investigación y monitoreo de la Seguridad Biológica: Predicciones de las consecuencias de los comportamientos del crecimiento en un medio natural de plantas genéticamente modificadas. Financiamiento de investigación segura y desarrollo de métodos para el monitoreo del proceso completo de cultivo. Consideración de las objeciones científicamente fundadas que provienen de la tecnología genética ecológica dirigidas al debate público.
- Biodiversidad: Desarrollo del Ministerio Federal de Educación e Investigación, en conjunto con otros Ministerios para mantener la biodiversidad como un importante principio de vida. Implementación de un compromiso atado legalmente, incluyendo aquellos temas ligados a la diversidad biológica ya legislados por la convención de la ONU. Investigaciones dentro de la diversidad genética dentro de los objetivos del programa biotecnológico.
- Métodos Alternativos para la Experimentación con Animales: Otras investigaciones dentro de las tendencias positivas hacia la reducción del número de experimentos con animales realizados en Alemania (los cuales disminuyeron desde 1991 a 1999 en 33.8%). Mejor orientación hacia métodos modernos como biología molecular y bioinformática en la búsqueda de otras alternativas a la experimentación animal, incluyendo aquella realizada in vitro.

Cooperación Internacional: El Ministerio de Educación e Investigación financia el desarrollo biotecnológico dentro de las ciencias e industrias en China, Indonesia, Israel, Rusia, Vietnam y Australia entre otros países, mediante cooperación internacional.

NUTRICIÓN Y SALUD

En países industrializados un creciente número de personas está sufriendo por las llamadas 'enfermedades causadas por la civilización moderna', como enfermedades cardiovasculares, alergias, cáncer y diabetes tipo II. Ellas empeoran considerablemente la calidad de vida de las personas afectadas y son una carga para la sociedad debido a la necesidad de solicitar licencias médicas y la utilización de medicinas y recursos.

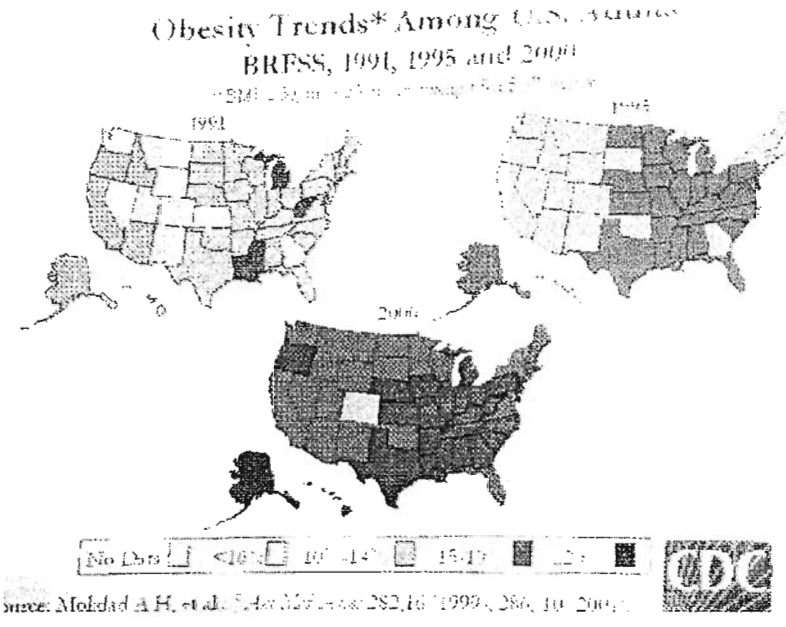


Foto nº 1

Hay una estrecha relación entre estas enfermedades y la dieta. Con el financiamiento del foco 'redes de investigación molecular nutricional: alimentos para proteger la salud de las personas - prevención de enfermedades a través de nutrición' desde el año 2000, el Ministerio Federal de Educación e Investigación está proveyendo un nuevo soporte en esta área con el objetivo de crear programas de investigación en Biotecnología y Salud. El objetivo es investigar en detalle exactamente qué efectos tienen los alimentos en las enfermedades y dilucidar acciones para prevenirlas.

Contaminantes y aditivos son a menudo considerados como la causa de enfermedades nutricionales. Sin embargo desde un punto de vista dietético esto es sólo una consideración secundaria. Hay una relación directa entre una dieta incorrecta (exceso de grasas, alcohol, bajo en fibra, etc.) y enfermedades metabólicas y cardiovasculares y cáncer. Algunos cuadros clínicos pueden prevenirse mediante una nutrición apropiada. En este contexto alimentos funcionales están siendo introducidos en forma creciente en el mercado.

El conocimiento de la interacción molecular y funcional entre alimentos y/o componentes de los alimentos y enfermedades incluyendo los efectos de largo plazo de nutrición y dieta son prerrequisito para una intervención nutricional.

Estos logros requieren de una estrecha cooperación entre nutricionistas, físicos, biólogos, químicos y técnicos en alimentos. En el pasado esta cooperación interdisciplinaria era muy pequeña en Alemania, tanto en el ámbito industrial como en universidades y centros de investigación.

Medidas estructurales y de calificación sirven para dar consolidación a estos centros. Entre las medidas se incluye la puesta en marcha de una cátedra para investigación nutricional

molecular o medicina nutricional así como la formación de un proyecto grupal, el cual continuaría su trabajo más allá del período subsidiado por el Gobierno.
Actualmente las áreas de investigación desarrolladas en Alemania con respecto a este tema son:

Alimento grasos y Variabilidad en el Metabolismo Genético, regulación, función y componentes alimenticios funcionales:

El sobrepeso está ampliamente propagado por todo el occidente. En efecto, uno de cada tres alemanes sufre de este problema, que además gatilla numerosas enfermedades como el síndrome metabólico, la diabetes o la arteriosclerosis, por ejemplo. La relación que existe entre el sobrepeso y el síndrome metabólico está ya determinada por estudios epidemiológicos, lo importante ahora es realizar investigaciones detalladas en los factores que son verdaderamente complejos y que conducen a esta propagada enfermedad.
La intención de las actuales redes de investigación en Alemania es explicar detalladamente la relación entre el consumo de grasas, lipólisis, metabolismo de lípidos y el síndrome metabólico. También es necesaria la investigación de los genes involucrados en el metabolismo de lípidos. El objetivo es desarrollar estrategias preventivas y terapéuticas para reducir o retardar la absorción de los ácidos grasos desde el intestino.

Cómo afectan en la Arteriosclerosis los Aminoácidos, péptidos y proteínas biológicamente activos, además de los fosfolípidos como agentes nutritivos:

La Arteriosclerosis en humanos está influenciada por la dieta, entre otros factores. Los metabolismos de lípidos y proteínas juegan un importante rol, así como también la predisposición genética. En particular la influencia de los genes y su interacción con la dieta no se ha determinado todavía.
El objetivo de las redes de investigación en Alemania es el de explicar las interacciones moleculares y funcionales y desde ahí mostrar nuevas opciones para la prevención de la arteriosclerosis a través de la dieta y la nutrición. Dentro de los objetivos de este proyecto está identificar, entre otros, factores como los componentes de los alimentos que pueden ser absorbidos por el intestino y el desarrollo de su acción protectiva contra la aterosclerosis. De acuerdo con recientes estudios, elevadas concentraciones en la sangre de sulfuros que contienen amino ácidos aumenta la posibilidad de gatillar la arteriosclerosis. La causa es a menudo la deficiencia de vitamina B6, B12 y ácido fólico, cuyos efectos tienen relativamente altas posibilidades de ser revertidos con el consumo de estas sustancias

Foto n° 2

El rol de los componentes de los alimentos en la génesis de enfermedades intestinales y las opciones de prevención no obstante la dieta y nutrición:

Existe una relación entre nutrición y enfermedades intestinales. De acuerdo a estudios realizados, una dieta elevada en calorías y baja en fibras, que contenga una elevada proporción de carne promueve la aparición de neoplasmas al colon. Por otro lado, a ciertos componentes de los alimentos y plantas se les atribuye una función preventiva. Los estudios relacionados con mecanismos moleculares como base de la acción preventiva del cáncer no han sido ampliamente estudiados.
Dentro del trabajo en materia de nutrición, la intención es investigar la interacción entre los componentes de los alimentos y las enfermedades intestinales. Esto incluye el estudio de los efectos que producen seleccionados componentes, desde jugo de frutas y carbohidratos modificados en las células, tanto en hombres como en animales. El resultado debería ser útil para desarrollar nuevos procesos de producción de jugos de fruta y alimentos funcionales en general, entre otros importantes usos.

Chip Adipositas:
Es un proyecto que se lleva a cabo con la supervisión del BioProfile "Nutrigenomic Research Berlin – Brandemburg" por la empresa biotécnica Scienon en cooperación con la Universidad de Humboldt, en Berlín y el Instituto para la Tecnología Biomédica. Con este proyecto se pretende explorar la conexión entre el aspecto genético – molecular y la obesidad y las enfermedades que esta causa, como la alta presión y la diabetes, siendo esta conexión aún muy poco estudiada. Con el soporte financiero del Ministerio Federal de Educación e Investigación, los genes relevantes para la adiposidad son identificados en estudios sobre animales y personas, combinados con un chip de ensayo, que se prueba para su viabilidad en el desarrollo de futuros diagnósticos y potenciales terapias. Los modelos sobre animales se llevan a cabo con diferentes grupos de ratas y debería conducir al entendimiento del rol específico que juegan los genes en la determinación de porqué algunos animales engordan con una dieta rica en grasas y otros no.

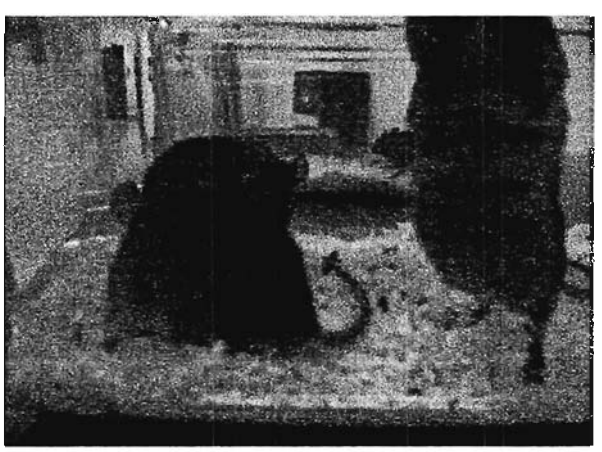


Foto n° 3

Los datos recogidos del análisis biológico de las muestras y la evaluación del peso, presión sanguínea y pulso a distintos tiempos de los ratones en estudio, convergen en una plataforma para el diagnóstico de la adiposidad sobre una base tecnológica usada para el desarrollo de Biochips como herramientas de diagnóstico. Esta base de datos, las estaciones de hibridación, los escáner y la evaluación de los software desarrollados durante el proyecto harán posible la aplicación de estas herramientas no sólo en el ámbito de la investigación, sino también en diagnósticos de seres humanos.
Con la ayuda de los descubrimientos obtenidos durante el proyecto sobre conexiones entre genotipo , nutrición y adiposidad , se pretende desarrollar herramientas y sistemas de ensayo viables para determinar sistemáticamente las

efectos biológicos de ciertos factores, como nutrientes, aditivos de los alimentos y sustancias farmacéuticas sobre personas con propensión genética pueden ser determinados perfectamente. Además entregan las bases biotecnológicas para desarrollar terapias de tratamiento contra la obesidad. Eventualmente, los entes involucrados en esta investigación, esperan crear un "freno contra el apetito", con nuevos agentes activos para el control del consumo de alimentos basado en anticuerpos, lo que posee un enorme potencial de comercialización.

ÁREA MEDIOAMBIENTAL

Principios Ecológicos de Biorremediación in Situ

La técnica para el tratamiento del medioambiente que me pareció más interesante fue la Biorremediación in Situ, investigada por el Instituto de Investigación del Trigo, realizada por la empresa Biopract (Potsdam), e investigada también por Institute of Microbiology, Technical University Braunschweig.

La biorremediación se ocupa de la utilización de medios biológicos, tales como enzimas y bacterias, para producir rupturas o cambios moleculares de tóxicos, contaminantes y sustancias de importancia ambiental en suelos, agua y aire, generando compuestos de menos o ningún impacto ambiental. Estas degradaciones o cambios ocurren normalmente en la naturaleza, sin embargo, las velocidades de tales cambios es baja.

El biotipo natural de los microorganismos presentes en la tierra o en aguas superficiales en la mayoría de los casos se encuentra en un estado de adormecimiento vegetativo o latencia, en el cual el crecimiento esta detenido o es muy lento. La razón es una concentración extremadamente baja de nutrientes, sólo del orden de 10 μg/l, en su hábitat natural, lo cual es cerca de 1 millón de veces menor que un medio de nutrientes típico de laboratorio. El estado de adormecimiento se alcanza en el ecosistema luego de un período de inanición durante el cual mueren la mayoría de las bacterias quedando sólo entre un 1 y 0.1 % vivas.

El adormecimiento vegetativo es la fuente de la diversidad microbiana en terrenos. Un gramo de esta tierra debe contener entre 1.000 y 10.000 individuos de especies particulares de bacterias en estado de latencia, y producir una cantidad total de células entre 10^7 y 10^8, cada una de estas especies bacterianas tiene su propio proceso metabólico específico. Luego, la tierra contiene un bioecosistema de microbios latente, de una considerable diversidad y potencial para degradar una amplio rango de componentes.

La manera en que se comporta un sitio contaminado, corresponde al proceso de descarga de un acumulador eléctrico. Un sitio contaminado es algo así como una "batería ecológica" en el cual el individuo, células conectadas en serie (Substancias E2 $\Rightarrow$ Aceptor de electrones $\Rightarrow$ Agente oxidante) se debilitan y se descargan (reducción química). La actividad metabólica está virtualmente detenida, esto no se debe a que se han alcanzado los límites de la habilidad degradativa microbiana, ni a la existencia de deficiencias microbianas, sino que se debe a que los sitios del "acumulador ecológico" han disminuido y se han descargado bajo condiciones donde nutrientes contaminantes han sobrecargado la tierra.

El principio ecológico de la biorremediación deriva del entendimiento de la persistencia de un contaminante: el acumulador ecológico, con sus células individuales, necesita recargarse y los aceptores de electrones que están agotados necesitan regenerarse. Medidas que apuntan en este sentido ponen fin al estado de adormecimiento vegetativo y a la inactividad metabólica y a la persistencia de los contaminantes químicos.

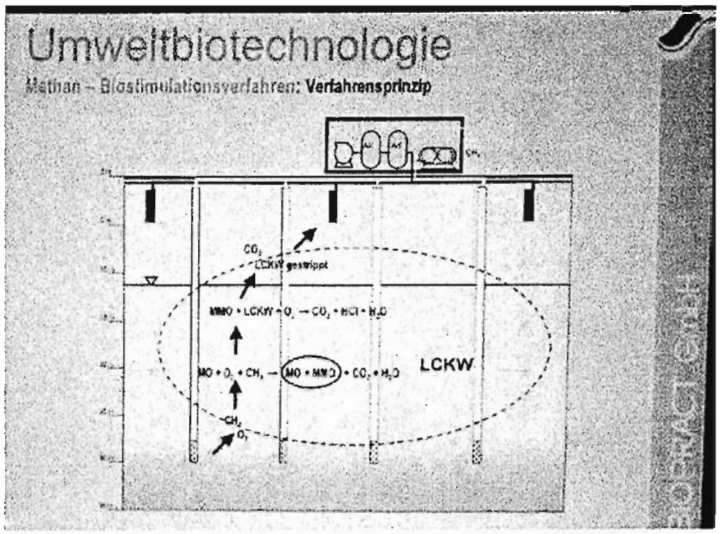


Foto n° 4

Se ilustra el proceso microbiano individual involucrado en la recarga de una batería ecológica. Los aceptores de electrones, como carbonato, sulfato, Hierro (III), Manganeso (IV) y nitrato, son regenerados y su estado reducido por la acción microbiana. Se introduce oxígeno atmosférico y los electrones aceptores, esenciales para la biorremediación, son reconstruidos a través de la oxidación. Los electrones aceptores, habiendo sido consumidos por el proceso reductor durante el establecimiento del contaminante, son ahora objeto de regeneración vía oxidación.

Las medidas técnicas utilizadas en biorremediación tienen el propósito de inducir esta oxidación y eventualmente restaurar el sitio a su carga natural y a su estado descontaminado.

5. Aplicabilidad:

La Comisión para el Desarrollo de la Biotecnología, representada por el Subsecretario de Economía, Álvaro Díaz, el Premio Nacional de Ciencias, Jorge Allende, y el director ejecutivo de la CONAMA, Gianni López desarrollaron un informe que contiene las bases de una política nacional de biotecnología.

De acuerdo a información extraída de la página web del Ministerio de Economía, la Comisión arribó a tres grandes conclusiones. Primero, que la biotecnología es una herramienta crucial para aumentar la competitividad y sustentabilidad de la economía, así como para mejorar la calidad de vida de la población chilena. Segundo, que en el transcurso de los próximos diez años, Chile puede constituirse en un referente mundial en áreas específicas de la biotecnología, particularmente aquellas relacionadas con recursos naturales. Y tercero, que para maximizar los beneficios de la biotecnología y gestionar adecuadamente sus riesgos, se requiere de un marco regulatorio eficaz y transparente, construido sobre la base de instituciones públicas fuertes y confiables, así como de una ciudadanía bien informada y con oportunidades de participación.

La Comisión considera que a pesar de los esfuerzos realizados, Chile aún no cuenta con una política clara respecto de la biotecnología, lo que constituye un obstáculo para su desarrollo. Para situar a la biotecnología como nueva herramienta de competitividad y bienestar, se requiere de una política de Estado, que impulse un esfuerzo estratégico y persistente en el tiempo. Para ello la Comisión propuso 30 iniciativas de acción en los siguientes ámbitos: fomento de la innovación empresarial; desarrollo de capacidades científico-tecnológicas; formación de recursos humanos; desarrollo de un marco regulatorio eficaz, y participación pública y transparencia.

Con la realización de esta propuesta, las políticas de gobierno en cuanto a biotecnología se acercarán a las actuales políticas alemanas en el tema, pero sin duda existe un gran retraso en el proceso que actualmente vive nuestro país comparado con lo que se viene desarrollando en Alemania desde hace algunos años. El gran retraso lo podemos constatar al comparar las inversiones totales en investigación entre Chile (0,6% del PIB) y países industrializados (entre 2 y 3 %).

De acuerdo al informe realizado por la Comisión de Desarrollo de Biotecnología, el fomento estatal en el área de la biotecnología se realiza esencialmente a través de los fondos de fomento tecnológicos: FONTEC y FDI de CORFO; FONDEF y FONDECYT de CONICYT; FIA y Fondo para el Mejoramiento del Patrimonio Sanitario (SAG) del Ministerio de Agricultura; Iniciativa Científica Milenio, del Ministerio de Planificación y Cooperación. Estos instrumentos operan a través de líneas de financiamiento que aplican criterios generales y horizontales de asignación de recursos.

La I+D y la innovación en biotecnología con frecuencia requiere tipos de apoyos que no responden adecuadamente a los criterios generales de los fondos tecnológicos, por lo que demandan una adecuación de las líneas de financiamiento disponibles en estos fondos, de manera que se adapten a las especificidades de la biotecnología especialmente respecto de los plazos de ejecución y montos necesarios para el desarrollo de los proyectos. Este tipo de proyectos debe contemplar además, la formulación cuidadosa de planes de negocios, la formación de redes en el ámbito de la investigación y la transferencia de los productos generados. Otro aspecto que debe ser considerado en forma especial en el financiamiento de proyectos biotecnológicos es lo relativo a equipamiento. La investigación en biotecnología requiere instrumental sofisticado que debe ser actualizado periódicamente de acuerdo al desarrollo de la ciencia. Es por lo tanto necesario establecer algún mecanismo de

financiamiento para la adquisición de equipamiento avanzado estableciendo un programa de asignación que permita racionalizar su uso.
En la Tabla 1 se detalla la asignación de recursos para proyectos de I+D en biotecnología entre los años 1991 y 2001, por fondo:

TABLA 1. Asignación de recursos para proyectos de I+D en biotecnología por fondo, 1991 – 2001

AÑO	1991-1997		1997-1999		2000-2001	
Fondo Tecnológico	Proyectos	Monto US$ Mill.	Proyectos	Monto US$ Mill.	Proyectos	Monto US$ Mill.
FONTEC	23	1,25	34	3,3	12	0,59
FDI	n.i.	n.i.	5	2,8	8	1,9
FONDEF	49	30	24	9,2	18	4,4
FONDECYT	116	5,5	61	7,0	23	1,36
FIA	n.i.	n.i.	6	0.8	22	3,4
SAG	n.i.	n.i.	3	0,3	5	1,7
TOTAL	188	36,75	133	23,4	88	13,35
Prom. anual 26,9		5,25	44,3	7,8	44,0	6,68

Fuente: Informe de la Comisión para el Desarrollo de la Biotecnología

La gran parte del fomento estatal se concentra en las universidades e institutos tecnológicos. Sólo entre un 15 a 20 % de los recursos financieros fueron entregados para el fomento de actividades de I+D de empresas, mostrando el bajo interés de éstas por integrar la investigación y desarrollo a sus actividades.

En Alemania se encuentran claramente detallados las áreas de investigación y desarrollo que se están fomentando y están siendo financiadas por el gobierno, una de ellas, la comercialización, que busca la cooperación entre centros de investigación y la empresa privada, potencia entre otros el estudio de "Nutrición, Alimentos y Salud: Desarrollo de nuevos tipos de alimentos activos funcionales en proyectos piloto, que apuntan a la prevención de enfermedades ampliamente propagadas, como el cáncer y desórdenes cardiovasculares. Poniendo en marcha redes multidisciplinarias de investigación hacia la acción preventiva de alimentos o elementos particulares de los alimentos exhibiendo su acción preventiva".
Este sector de la investigación representa una oportunidad de negocios biotecnológicos de mediano y largo plazo en un sector productivo estratégico de la economía nacional, como lo es el agroindustrial que estaría dirigido a mejorar la calidad de alimentación humana, pero también dentro del sector acuícola, pues uno de los principales desafíos futuros que se ha identificado en biotecnología es la producción de alimentos para estas especies. Todo esto conlleva a estudios prospectivos de amplia participación, estudios que aún no han sido abarcados con la dedicación que requiere.
En este sentido, Agroindustrial Razeto Ltda. trabaja en la producción de aceites vegetales con características funcionales. Demostrado por científicos internacionales, el aceite extra virgen de oliva es altamente beneficioso para la salud, en esta misma línea nos encontramos desarrollando el aceite extra virgen de palta, con características muy similares al de oliva. Nuestro objetivo es seguir en esta línea de producción de alimentos funcionales e innovar en este tema utilizando otros productos. Para el desarrollo de nuevos productos es necesario el apoyo financiero de gobierno, pues la investigación representa un riesgo económico elevado para la empresa privada.

En cuanto al tema medioambiental, actualmente en Chile, según el informe citado anteriormente, las aplicaciones biotecnológicas de remediación están en estado embrionario, pero se espera una rápida expansión en respuesta a las crecientes exigencias en esta materia. Para tener una idea de los proyectos y sus respectivas aplicaciones en la Tabla 2 se muestra un listado de éstos, así como también la fuente de financiamiento.

Tabla 2 Proyectos ejecutados en biotecnología ambiental: 1996 - 2002

	FONDECYT	**FONDEF**
AGUA		
Eliminación de materia carbonácea	8	5
Eliminación de nutrientes (N, P)	3	0
Eliminación de compuestos tóxicos y recalcitrantes (sistemas combinados)	10	0
Digestión de lodos (aerobio, anaerobio)	2	0
SUELO		
Biorremedicación de sitios contaminados (fenoles clorados, PCP; PAH, entre otros)	3	3
Biolixiviación	4	2
AIRE		
Remoción de compuestos volátiles (olores, mercaptanos, compuestos sulfurados)	1	0

Fuente: Informe de la Comisión para el Desarrollo de la Biotecnología

Pocas empresas han utilizado biotecnología para resolver problemas ambientales en Chile. El sector productivo que ha dado las primeras señales en incorporar la biorremediación de suelos, es el petroquímico. Con el propósito de aprovechar las posibilidades que abre la biotecnología en este campo es conveniente que las empresas chilenas cuenten con información relativa a las técnicas disponibles de biorremediación y así poder considerarlas en sus programas de producción limpia.

La biorremediación podría ser fundamental para tratamientos de residuos en la minería, refinería, industria química en general, accidentes químicos, y para la descontaminación de fondos marinos y búsqueda de soluciones para el problema de las toxinas marinas en moluscos.

GOBIERNO DE CHILE
FUNDACIÓN PARA LA INNOVACIÓN AGRARIA

6. Contactos Establecidos:

Institución/Empresa	Persona de Contacto Cargo/Actividad	Fono/Fax	Dirección	E-mail
German Instiute of Human Nutrition	Dr. Ilka Grötzinger	49(0)33200-88444	Arthur-Scheunert-Allee 114-116 14558 Bergholz-Rehbrücke	
Instituto de Investigación del Trigo	Dr. Ralph Thomann Chemist, section manager	49(0)33200-89201	Arthur-Scheunert-Allee 40/41, D-14558 Bergholz-Rehbrücke	R_thomann@ igv-gmbh.de
BioPract	Dr. Matthias Gerhardt Managing Director	49(0)3063926205	Rudower Caussee 29 Eingang Kekuléstr. 7, 12489 Berlin	sales@biopract.de
Ministerio Federal de Educación e Investigación	Dr. Hans-Michael Biehl			
Biocon Valley	Dr. Heinrich Cuypers SeniorProject Manager	49(0)3834515108	Walther-Rathenau-Straβe 49a D-17489 Greifswald	Hc@bcv.org
Institute of Microbiology, Technical University Braunschweig	Prof. Dr. Hans Helmut Hanert	49(0)5313915803	Spielmannstraβe 7 D-38106 Braunschweig	h.hanert@tu-bs.de
Nadicom	Dr. Bernhard Nüβlein Managing Director	49(0)6421-13175	Pflanzgarten 10 35043 Marburg	nuesslein@nadicom.com
Instituto Italiano para el Comercio Exterior	Michael Berz Trade Analyst	49(0)3088 44 0323	Schlüterstr. 39 D-10629, Berlin	michael.berz @berlino.ice.it
Deutsche Messe AG Hannover	Andreas Grüber Project Manager	49(511) 89-32118	Messegelände D-30521 Hannover	andreas.gruber@messe.de

7. Detección de nuevas oportunidades y aspectos que quedan por abordar:

La actividad realizada nos dio una apertura de miras hacia lo que países industrializados están desarrollando en materia de biotecnología, nos permitió también detectar nuevas oportunidades hacia nuevas técnicas. Considero que para la aplicación de estas nuevas tecnologías, así como también para innovar e investigar en materia biotecnológica estas actividades son indispensables, pues entregan muchas herramientas para lograr los objetivos. La investigación, así como la innovación deben ir de la mano de un proceso de aprendizaje continuo, no sólo para seguir las últimas tendencias internacionales, sino también para ser en algún modo precursores de los cambios.

Creo que una de las principales debilidades que existen en Chile en materia de investigación e innovación es la falta de colaboración entre centros de formación (universidades en general) o centros de investigación y empresa privada. Es por eso que presento en este informe el ejemplo de Alemania, en donde actualmente se están formando compañías jóvenes al alero de estos centros de estudios, contando así con un gran respaldo para posicionarse de la mejor manera en el mercado.

8. Resultados adicionales:

La identificación de oportunidades tiene como consecuencia un estudio de factibilidad para integrar alguna de ellas dentro de mi empresa, por lo que no se descarta la posibilidad de la realización de un nuevo proyecto de innovación.

Por otro lado, el grupo que participó en esta actividad, proveniente de distintas regiones del país y dedicados a diversas áreas de la biotecnología, se relacionó en un ambiente de cooperación y compañerismo, por lo que se generaron lazos importantes dentro de los participantes. Esto permite abrir la posibilidad a la realización de trabajos en conjunto y multidisciplinarios.

9. Material Recopilado:

Tipo de Material	Nº	Caracterización (título)
Foto	1	"Evolución de la obesidad en USA" Presentación Instituto de Nutrición Humana
Foto	2	Alimentos Funcionales, Instituto de Inv. Del Trigo
Foto	3	Proyecto Adipositas Chip, Neutrogenomic
Foto	4	"Biorremediación" Presentación BioPract
Boletín Informativo		Ministerio Federal de Educación e Investigación
Artículo		Remediation of Cantaminated Sites in Situ
Artículo		Scienion
Folleto		Chia Meei Health Biotechnology
CD		BioCon Valley
Folleto		Nadicom

GOBIERNO DE CHILE
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10. Aspectos Administrativos

10.1. Organización previa a la actividad de formación

a. Apoyo de la Entidad a cargo de la organización del viaje (Camchal)

X bueno _____ regular _____ malo

Se entregó el itinerario detallado de las actividades a realizar. Se proporcionó traductor durante la mayoría de las actividades. La mayoría de las actividades se realizaron puntualmente y cumplieron con las expectativas.

b. Información recibida durante la actividad de formación

X amplia y detallada _____ aceptable _____ deficiente

c. Trámites de viaje (visa, pasajes, otros)

X bueno _____ regular _____ malo

d. Recomendaciones:

10.2. Organización durante la actividad (indicar con cruces)

Ítem	Bueno	Regular	Malo
Recepción en país o región de destino	X		
Transporte aeropuerto/hotel y viceversa	X		
Reserva en hoteles	X		
Cumplimiento del programa y horarios	X		

11. Conclusiones Finales:

La participación en esta gira biotecnológica fue de gran importancia para mi desarrollo profesional, lo que se verá reflejado directamente en el trabajo que realizo dentro de la empresa Agroindustrial Razeto Ltda.

Respecto al cumplimiento de los objetivos planteados creo que la participación en Biotechnica me permitió estar al tanto de innovaciones en las áreas de mi interés y con esto identificar oportunidades para el desarrollo de nuevos productos. Por otro lado, la visita a los distintos centros de investigación superó ampliamente mis expectativas, pues tuvimos la oportunidad de ver in situ cómo desarrollan la investigación en Alemania y cuáles son los temas que se están estudiando.

Por otro lado los profesionales que integramos esta delegación actuamos con un gran espíritu de cooperación, complementando nuestros conocimientos para un mejor entendimiento de lo que se nos iba presentando. Esto habla muy bien de la calidad humana de los participantes, así como también de la persona de CAMCHAL que nos acompañaba como guía, Antje Wandelt Gerente Marketing Ferias, pues hubo siempre una excelente disposición a ofrecer y dar apoyo, una actitud grupal muy positiva y en general se generó un grato ambiente de compañerismo. En particular, debo destacar la gestión de la Gerente Marketing Ferias de CAMCHAL pues el itinerario se cumplió sin mayores contratiempos ni modificaciones.

Después de mi participación en esta gira, creo estar en grado de poder compartir los conocimientos adquiridos para de alguna forma poder aportar al desarrollo de la investigación biotecnológica en Chile, tanto a nivel académico como industrial. Al mismo tiempo creo tener la necesidad y el deber de seguir creciendo en estos temas, y continuar mi proceso de aprendizaje y actualización hacia nuevas tecnologías. Es esta mi motivación para participar en estas actividades y valoro profundamente que existan estas instancias, vale decir estos fondos concursables del FIA o de otras instituciones, que promuevan y a la vez auspicien a profesionales en su proceso de desarrollo profesional con miras hacia el desarrollo del país.

13 de noviembre de 2003

Lina Razeto Olivares

INFO BIOTECHNOLOGIE

bmb+f
Bundesministerium für Bildung und Forschung

Pte
Projektträger des BMBF und BMWi
Forschungszentrum Jülich GmbH

BioFuture

Initial Aid for Young Scientists

BMBF's young scientist teams competition meets with great response at home and abroad

With BioFuture the Federal Government supports excellent young scientists in the field of the life sciences. The competition addresses participants up to 39 years of age at home and abroad who are already experienced in research. Prize winners of BioFuture are given the opportunity to work on innovative, basic research oriented approaches in the biosciences in Germany for five years in their own team independently of given structures.

Support thus paves the way for young researchers into a scientific top career or a promising business foundation. The young scientist teams competition of the German Federal Ministry of Education and Research aims at binding scientific top know-how in Germany, counteracting the drain of knowledge and winning back qualified researchers after their stay abroad.

Since its start in April 1998, BioFuture has met with great response at home and abroad. Within a period of three years, in four application rounds comprising roughly 900 applications, scientists who had been working abroad at the time of filing their application. 68 scientists from abroad also applied for support.

The project outlines were selected by a jury of interdisciplinary composition. Up to the present, 38 teams of young scientists have been recommended for support, of which 32 have already taken up work*.

With supporting funds of DM three million on average over a period of five years, the prize winners of the selection rounds can set up a research team of up to seven staff members.

The call for proposals was started in 1998 under the BMBF Framework Programme "Biotechnology 2000" and has been continued since 2001 within the follow-on Framework Programme "Biotechnological Research and Technology". BioFuture has since established itself as a recognized instrument of support for young scientists. Funds totalling DM 150 million are provided for this purpose by the Federal Government. The competition will be continued in 2002 with a further round of calls for proposals.

* as of May 2001 when the awards were granted to the winners of the fourth

The Winners of the BMBF-Contest Bioregio

Winner	Institution	Topic
Dr. Frank Bier	Fraunhofer Institute for Biomedical Engineering IBMT, Bergholz-Rehbrücke	Biomolecular nanostructuring of surfaces by nucleic acids
Dr. Dolores Cahill	Max Planck Institute of Molecular Genetics, Berlin	3D protein and antibody chips
Dr. Frank Caruso	Max Planck Institute of Colloid and Interface Research, Golm	Nanofabrication of novel biofunctional materials and bioencapsulation
Dr. Roland Eils	University of Heidelberg	Development of bioinformatic techniques for a disease-specific mutation analysis and functional genome analysis by means of DNA chip technology and the multicolour fluorescent labelling technique
Dr. Christian Freund	Free University of Berlin	Structure-function relation of important T-cell proteins and the design of agonists and antagonists of the immune response mediated by T-cells
Dr. Stanislav Gorb	Max Planck Institute of Developmental Biology, Tübingen	Design and biomechanics of biological friction surfaces for biomimetics
Dr. Heidi Hahn	University of Technology, Munich	Patched-signal transduction path in tumour formation and therapy
Dr. Stephan Hahn	University Medical Hospital, Bochum (Langendreer)	Functional genomics and proteomics on the tumour suppressor gene DPC4/Smad4
Dr. Stefan Hesse	Free University of Berlin	Development of a computer-aided walking trainer to assist in restoring the standing and walking abilities of patients with CNS lesions
Dr. Andres Jäschke	Free University of Berlin	Application of ribozymes in drug synthesis
Dr. Ute Krämer	Max Planck Institute of Molecular Plant Physiology, Golm	Hyperacculumation of heavy metals in plants: from molecular analysis to the creation of transgenetic model plants as a contribution to a technology for remediating soils contaminated with heavy metals
Dr. Markus Lappe	University of Bochum	Theoretical and cognitive neuroscience
Dr. Andreas Lendlein	German Wool Research Institute at the University of Aachen	Tailor-made, intelligent polymer systems for application in minimally invasive medicine
Dr. Frauke Melchior	Max Planck Institute of Biochemistry, Martinsried	SUMO-1 and the transportation of proteins into the cell core
Dr. Markus Sauer	University of Heidelberg	Handling, detection and analysis of individual biomolecules with pulsed diode lasers and multiplex dyes
Dr. Thomas Schmidt	University of Kiel	Plant centromeres-molecular isolation and application for the development of artificial plant chromosomes
Dr. Evelin Schröck	Institute of Molecular Biotechnology, Jena	Identification of basic cellular mechanisms of tumour-specific chromosomal translocations
[illegible]	Max Planck Institute for Marine	Structural, biochemical and molecular genetic elucidation of the biomi-

Dr. Cornelius Schwarz	University of Tübingen	Interaction of cerebral cortex and cerebellum in learning and performing motor and cognitive skills
Dr. Andreas Schwienhorst	University of Göttingen	New drugs and biocatalysts through evolutive biotechnology in microstructures
Dr. Petra Schwille	Max Planck Institute for Biophysical Chemistry, Göttingen	Fluorescence spectroscopy single-molecule analysis methods in biophysics and evolutive biotechnology based on nanotechnology
Dr. Claus Seidel	University of Göttingen	Multidimensional singlemolecule fluorescence spectroscopy of biomolecules: screening methods and time-resolved investigation of biological processes
Dr. Horst Simon	University of Heidelberg	Basic molecular principles for developing nerve cells of relevance to Parkinson's disease
Dr. Torsten Stachelhaus	University of Marburg	Efficient design and combinatory biosynthesis of peptide antibiotics
Dr. Roland Heinz Strauß	University of Würzburg	Elucidation of the higher-level control of running behaviour by the insect brain using methods of Drosophila neurogenetics
Dr. Michael Stürzl	GSF-Research Centre for Environment and Health, Neuherberg	Molecular action mechanism of a new intracellular regulator for endothelium cell proliferation: prospects for the diagnosis and therapy of malignant diseases
Dr. Heinrich Terlau	Max Planck Institute for Experimental Medicine, Göttingen	Identification and characterization of the specific action of toxins from marine cone shells
Dr. Thomas Tuschl	Max Planck Institute for Biophysical Chemistry in Göttingen	Function and evolution of RNA-processing ribonucleoprotein complexes
Dr. Uwe Vinkemeier	Free University of Berlin	Basic molecular principles of cellular signal processing
Dr. Henning Walczak	German Cancer Research Centre, Heidelberg	Identification and preclinical evaluation of new members of apoptose-modulating protein families
Dr. Erich Wanker	Max Planck Institute for Molecular Genetics, Berlin	Inhibition of amyloid formation in Huntington's disease and other neurodegenerative diseases
Dr. Matthias Wilm	European Molecularbiology Laboratory (EMBL), Heidelberg	Systematic approach towards efficiently elucidating the function of individual proteins

4. Selection Round 2001

Dr. Jutta Eichler	German Research Center for Biotechnology, Braunschweig	Synthetic mimicry of conformationally defined bindingsites through scaffolded peptides and peptide libraries
Dr. Albert Jeltsch	University of Giessen	Development of programmable DNA methyltransferases for applications in biotechnology and molecular medicine
Dr. Christoph Klein	University of Munich	Organisation and function of genomes of single micrometastatic tumour cells: a novel approach for the study of human cancer evolution and progression
Dr. Fritz-Olaf Lehmann	University of Würzburg	An integrated approach towards the mechanisms, efficiency and evolution of unsteady aerodynamic performance in flying animals and its application to microrobotic air vehicles
Dr. Helle Ulrich	Max Planck Institute for Terrestrial Microbiology, Marburg	The role of the ubiquitin system in postreplicative DNA-repair
Dr. Jean-Nicolas Volff	University of Würzburg	Positional cloning of the sex-determining gene in the platyfish Xiphophorus

Bundesministerium für Bildung und Forschung

BIOTECHNOLOGY

Projektträger des BMBF und BMWi
Forschungszentrum Jülich GmbH

Bioinformatics

From the „Code of Life" to the Virtual Cell

BMBF sponsors six bioinformatics technology centres of competence / Contribution towards rapid training of bioinformation science specialists

What means Bioinformatics?
Bioinformation science or Bioinformatics combines molecular biology, biochemistry and genomics with computer science, on the one hand, and with computer linguistics, on the other. It is playing an ever-increasing role in the areas of biology, above all, also in the economically significant areas of medicine, pharmacognosy, and agriculture as well as in environmentally compatible industrial production. It is only after the implementation of computer-aided methods, that it has become possible to create mathematical models in the life sciences and to use these for computation purposes. The importance of computer science for biology is comparable to that of mathematics as an indispensable tool for physics.

The German Federal Ministry of Education and Research (BMBF) has been funding this new branch of science with its „Training and Technology Initiative Bioinformatics" of 22.September 2000. In addition to funding research, the intention has been to make a contribution towards the training of up and coming scientists as, in the meanwhile, bioinformation scientistshave become specialists much in demand in both research and in industry.

Genes and the flood of data
With the completion of the sequencing of the human genome in 2000, the general public became more greatly aware of bioinformation science. At this point in time at the latest, it became apparent that the „decoding" of human genes was not only a successful accomplishment of the molecular biologists and their automated laboratory technologies. The determination of the sequence of all three thousand million „letters of life"- the nucleotide building blocks adenine (A), cytosine (C), guanine (G) and thymine (T) of human DNA - was, rather, also an impressive achievement of bioinformation scientists and their computers.

In the meanwhile, researchers have begun working on the solution to an incomparably more difficult task - the reading and understanding of this text, or„structure of life", i.e., the

The decoding of the hereditarymaterial, DNA, and other progress made by modern molecular biology is inconceivable without information technology (IT). At the same time, with the aid of bioinformatics, it is becoming increasing possible to transfer investigation from the laboratory over to the computer.

actual decoding of the content and function of the genetic code.
The essential thing now is to find out which sequence of letters generate a meaningful content, in particular, whether they represent genes and what function these have. Only with the help of bioinformation tools can the explosion-like increase in the amount of data arising from this be stored, processed and interrelated.

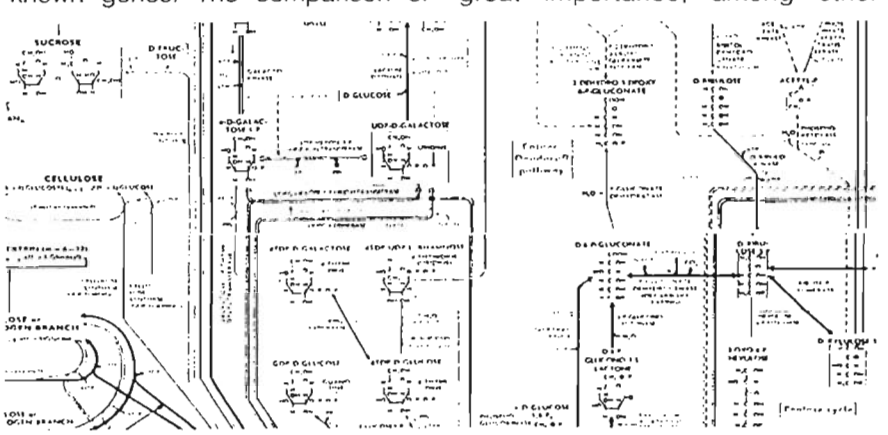
Tasks of bioinformatics

The tasks of bioinformatics are continuously expanding. Some of the fundamental objectives are described below.

Functional analysis or "functional annotation". Proteins as building blocks of all forms of life are generally complex protein molecules of enormous diversity. In the human body alone, there are an estimated one million different proteins. They comprise amino acids, the sequence of which are coded in DNA. Not all segments of the genes, however, have a coding function. The first step following sequencing is thus functional analysis or „functional annotation". This involves searching for those sections on the DNA that represent genes and investigates what function they have. Facilitative for functional analysis is the fact that in numerous organisms there are many similar and often already known genes. The comparison of newly discovered sequences with those already known and stored in databases often leads to the rapid identification of unknown genes (see „Protein search in databases" p.3).

Prediction of protein structure. When a coded section has been found on the DNA, interest focuses on a prognosis of the structure and function of the protein the DNA section concerned is responsible for „manufacturing". The properties of the protein are not only determined by the chemical, but also by the three-dimensional structure of the molecule - in particular, the nature of its folding. Just what role the spatial structure plays is made clear by the BSE "pathogen", which differs from the normal harmless prion proteins only with respect to folding. To enable any predictions on the protein properties, among other techniques, IT methods are implemented, which can calculate the 3-D structure of a protein from the sequence of its amino acids.

Protein docking. In this context, molecular biologists have been devoting especial attention to the question of whether and which molecules bind to (dock onto) specific domains of individual proteins and form a stable complex (protein docking). The discovery of molecules that bind to such targets is of great importance, among other areas, for pharmaceutical research since these molecules represent potential active substances. Genetic and geometric algorithms as well as other IT tools, for example, are being implemented for such investigations.



Circuit diagram of life: This section of metabolic processes with the proteins and other molecules involved looks like a complicated circuit diagram. The computer-aided rendition of the metabolic processes occurring within organisms is one of the applications of bioinformatics.

For investigations into so-called protein dokking different IT methods are implemented. This means that medicament development can be visualised on the screen, for example: A new pharmaceutical substance (yellow) must match a specific protein (white-red-blue) in the organism like a key fitting into a lock.

Rendition of the metabolic processes. Another application of bioinformation science is the computer-aided analysis and rendition of the complicated metabolic processes in living organisms. For an abstract visualisation of a metabolic process and the proteins as well as other molecules involved, methods of pattern identification, similarity searches in databases and functional analysis are implemented. The figure on the left shows a minute section of such a schematic metabolic diagram.

The virtual cell

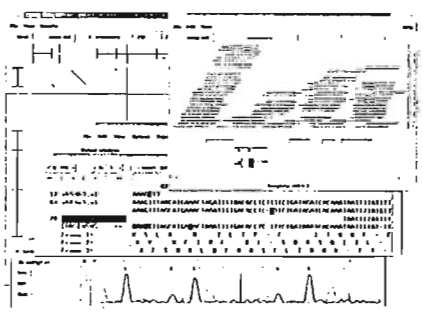
With ever more refined methods, bioinformation science is becoming increasingly capable of providing independent answers to questions arising in the field of molecular biology by developing models of biological systems to compute data instead of experimenting in the laboratory. The vision of the bioinformation scientist is the realisation of the „virtual cell" - the simulation of the many complex biochemical cellular processes in the computer, which can

thus be investigated more or less „*in silico*" („in silicon"), in this way creating completely new approaches towards the prediction and use of customised biological systems.

Analysis of 3D-models of molecules.

Centres of competence and training. To fund the development of the new key discipline and to promote the training of the bioinformation scientists, in such high demand, six centres of competence have come into existence within the scope of the funding activities of the BMBF „Training and Technology Initiative Bioinformatics" in Berlin, Braunschweig, Gatersleben/Halle, Jena, Cologne and Munich (see p.4).

It is the task of these centres of competence, in interdisciplinary teams from universities, industry and non-university-affiliated research institutes, to develop innovative tools for application in all fields of the life sciences, especially concerning the amount of data arising as a result of genome research. A further objective of these centres is the creation of common bioinformation standards. It is intended that all data which have proved to be necessary to understand the function of individual genes should be generated, acquired, analysed and rendered comparable, if possible, for all the genes within an organism. The bioinformation scientific research on the interpretation and integration of these data must thus cover the entire section of the DNA sequence of the genome, including the phenotype of the organism, from purely fundamental research up to application, e.g., in the field of medicine. A further major task of the centres of competence comprises the training of qualified bioinformation scientists. In collaboration with the German federal states and universities, they should conceive extension and training courses and realise these within the scope of joint projects.



Special computer programs such as GAP4 from the „Staden Genome Analysis Package" were developed to search for and identify genes using comparative gene analysis.

Protein search in databases

In the meanwhile, there is so much molecular biological information stored electronically, that the analysis of an unknown protein structure always starts out initially within a database. This involves comparing the section (in general a gene) of the DNA, which codes for the protein being searched for, with already known sequences in the database. This is also where the structure of the proteins encoded by the known sequences is stored. Furthermore, those molecules of interest can be searched for which dock onto the protein. In this context, powerful software has already been developed and tested within the scope of BMBF-funded joint projects. The program FlexX (Targid, Association) is currently the only one of its kind worldwide enabling screening of entire active substance databases. (In the Internet: http://cartan.gmd.de/flexx)

In the meanwhile, there are over one hundred diverse molecular biology databases. One problem, apart from the large number, is their heterogeneity. To at least create a common internet portal for the bioinformation resources developed in Germany, the BMBF is funding the Helmholtz Network for Bioinformatics (HNB). Within the scope of this network, the partners involved link together the software they have developed and network them with internationally available software. In addition, (HNB in the Internet: www.hnbioinfo.de).

Within the scope of an BMBF-funded Eureka-project, LION Bioscience AG is following a different route to remedy the deficiency of standardisation in publications within the field of molecular biology. This company has developed a text mining system that is capable of extracting specific data from original publications. This is also intended to function even when the texts have not been written in a standardised, but in a „natural form". Such a system puts very high demands on computer linguistics.

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Munich

GSF – National Research Center for Environment and Health, Neuherberg; Ludwig Maximilian University of Munich (LMU); University of Technology, Munich; University of Erlangen; Biomax Informatics AG; Genomatix GmbH; Molecular Networks GmbH

Bioinformation on the functional analysis of mammalian genomes:

- Methods of genome analysis
- Structuring of databases, analysis of complex data sets ("data mining") and visualisation
- Methods of experimental functional analysis of data generated on the industrial scale (high throughput techniques)

Gatersleben/Halle

Institute for Plant Genetics and Crop Plant Research IPK Gatersleben; Martin Luther University Halle-Wittenberg, Institute of Plant Biochemistry IPB, Halle (Saale); Konrad Zuse Zentrum für Informationstechnik Berlin (ZIB); Kelmann Gesellschaft für GenInformation mbH

Bioinformation tools for the analysis of phytobiological data:

- Plant Data Warehouse for cultivated plant data
- Analysis and modelling of metabolic and regulatory networks
- Methods for the automatic recognition of spatial-temporal development patterns
- Methods of data analysis

Berlin

MPI for Molecular Genetics; Humboldt-Universität zu Berlin; Freie Universität (FU) Berlin; Technische Fachhochschule Berlin University of Applied Sciences; Konrad Zuse Zentrum für Informationstechnik Berlin (ZIB); Callisto Gen AG

combination of genome and medical research by means of bioinformation research tools:

- Database and knowledge management technology
- Sequence annotation
- Prediction of the structure and function of gene products
- Modelling of cellular and pathological processes

(Internet: www.zib.de/bcbnet)

Jena

Friedrich Schiller University Jena; Fachhochschule Jena; The Hans-Knöll-Institut for Natural Products Research HKI; Institute of Molecular Biotechnology (IMB); MPI of Chemical Ecology; Clondiag Chip Technologies GmbH; BioControl Jena GmbH; EnTec Endocrinological Technology GmbH; Jena Drug Discovery GmbH

New bioinformation tools with respect to molecular communication processes in normal and pathological cell states:

- Analysis of gene and protein expression data
- Investigations on regulation processes
- Prediction of protein structures and binding properties of potential active substances
- Comparative genome analysis to identify regulatory DNA elements and virulence genes

(Internet: www.imb-jena.de/jcb)

Braunschweig

German Research Centre for Biotechnology (GBF), Braunschweig; BIOBASE GmbH; TU Braunschweig; FH Braunschweig/Wolfenbüttel University of Applied Sciences

Intergenomics – genom-coded processes involved in infection mechanisms:

- The concept comprises six steps from the setting up the databases to the modelling of intercellular interactions

Cologne

University of Cologne in co-operation with Science Factory; INFAI GmbH; Grünenthal GmbH; Bayer AG; A&M Laboratory for Analytics; Evotec GmbH; Dr. Jung Laboratory GmbH; MEMOREC-Stoffel; Phytowelt GmbH

Molecular networks in organisms:

- Methods for the parallel analysis of genome, transcriptome, proteome, structural, functional and metabolome data to simulate biological processes
- Integration of bioinformation science and genetics
- Methods for developing medicaments

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VDI Technologiezentrum
Physikalische Technologien

Nanobiotechnology

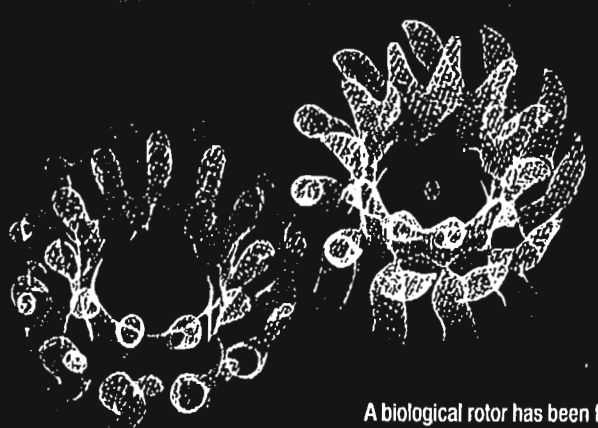
When Molecules Become Tools

BMBF is supporting the investigation and utilization of biological phenomena at the molecular and atomic level

Biotechnology and nanotechnology are amongst the most promising technologies of the 21st century. Nanobiotechnology has emerged at their interface. It represents a new quality of key technology. The dynamics to be expected in this field can be compared to the vehement developments in microelectronics.

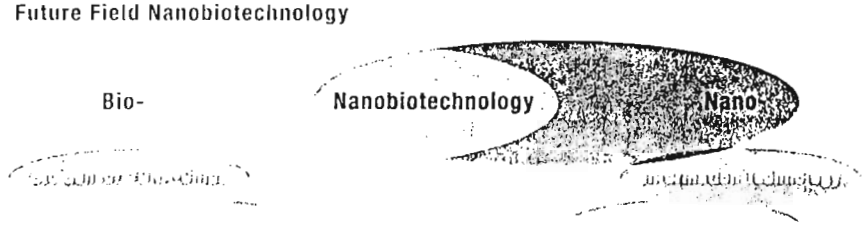
Focus: objects on the nanoscale

The Federal Ministry of Education and Research (BMBF) launched the „Nanobiotechnology" funding activity as a part of its biotechnology framework programme in April 2000. Funds of about DM 100 million have been earmarked for this topic up to the year 2006. The nanobiotechnology funding activity gives Germany a good chance of being among the leading nations in this field, flanking the US an Japan. In addition to a fundamental understanding of the functional units of biological cells, nanobiotechnology is dealing with the functional units of animate nature. Generated in a controlled manner and appropriately ordered, their frequently unique properties should give rise to novel technical systems. The principal targets of this new scientific discipline are biological and biomimetic objects on the nanoscale, i.e. with dimensions of a few millionths of a millimetre. Nanobiotechnology consequently deals with individual biomolecules or groups of molecules.

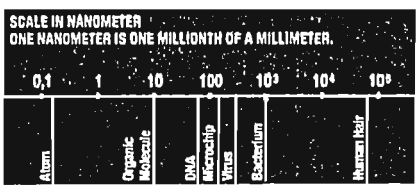


A biological rotor has been found in *Ilyobacter tartaricus* whose three-dimensional structural model can be seen here. This tiny biological rotor is a part of the machinery that ensures the energy supply to the cell. It is composed of eleven identical protein subunits. Each subunit consists of two transmembrane (α-helices, which form an inner and an outer ring in the membrane. A view of the periplasma is shown (in green, the region adjacent to the cell wall) and also of the cytoplasma (in red, the plasma enclosed by the cell membrane). The diameter of the ring is about five nanometres. (Max Planck Institute of Biophysics, Frankfurt am Main, Structural Biology, Janet Vonck, Tassilo Krug v. Nidda, Werner Kühlbrandt; ETH Swiss Federal Institute of Technology, Zürich, Peter Dimroth).

Future Field Nanobiotechnology



The main topics of the new support programme include the therapeutic and diagnostic application of nanoparticles as well as the use of nanostructure technology as a key to ultrasmall devices for pharmaceutical research and medical diagnostic methods. On the other hand, the first biomolecules are already being applied in electronic components and alternative data memory systems.



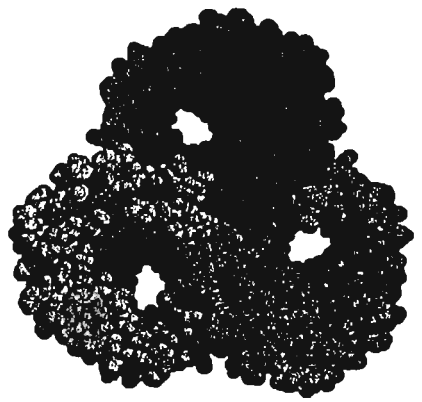
Joint Initiative

The novel approaches required at the interface of physics, biology, chemistry and the engineering sciences should lead to a broad industrial exploitation of the findings. Nanobiotechnology is being promoted by the BMBF in a joint initiative „Physical Research" and „Biological Research".

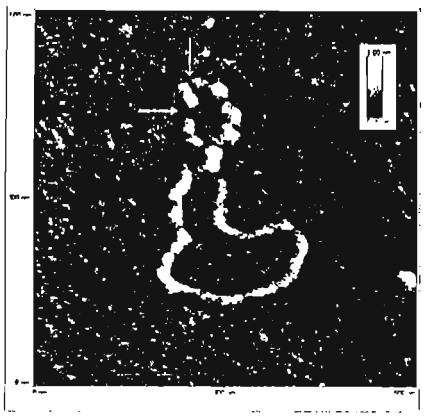
Specifically, the „Nanobiotechnology" funding activity offers special support for the following research and development projects:

- nanobiological analysis and characterization processes
- nanotechnological harnessing of biological adaptation, repair and self-organizing capabilities
- nanomanipulation techniques for biological/biochemical objects
- nanoreaction techniques
- molecular engineering technology

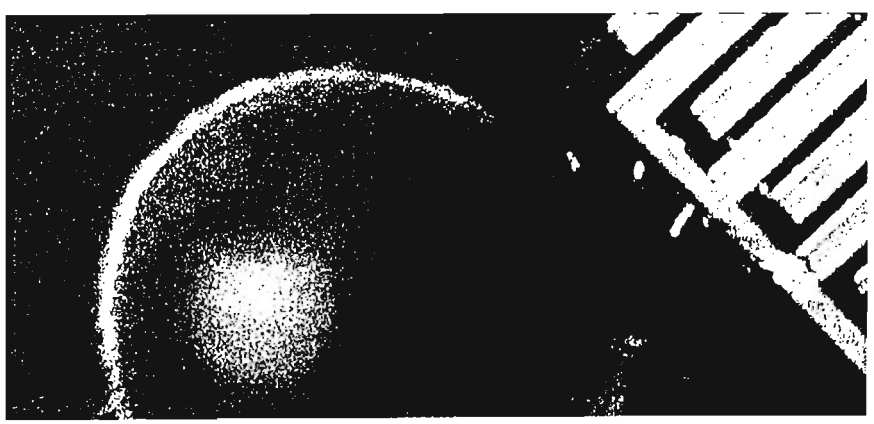
In this context, the BMBF has realized that funding of these topics should be accompanied with projects considering ethical, legal and social aspects at an early stage.



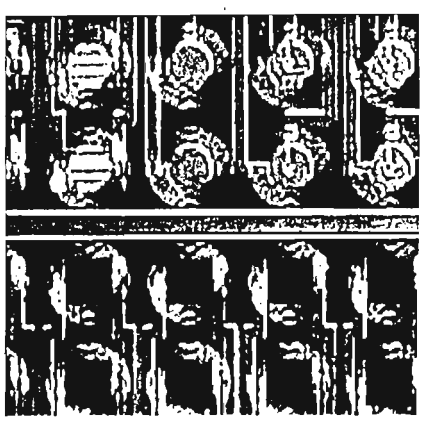
Gram-negative bacteria make their cell membrane permeable by using porins - special proteins of the bacterial cell wall. However, they are permeable to molecules of a certain size and with distinct properties. This feature can be used to produce novel nanofilters. Such filters can even distinguish between very similar molecules - for example different types of sugar. The figure shows a computer model of a PhoE Trimer of *Escherichia coli*. A pore has an aperture of about 0.7 x 1.1 nm.



With the aid of the new AFM (Atomic Force Microscopy) technique, it is possible to map the surface structures of biological materials with almost atomic resolution. This technique can be used to map individual DNA double strands. The photograph taken by Prof. Dr. Norbert Hampp's working group (University of Marburg, Department of Chemistry) shows a non-contact AFM picture of single pUC18 plasmid DNA after being cut twice (arrow). This DNA can also be manipulated with the aid of AFM. Thus, Researchers have a powerful tool for observing and processing biological macromolecules in the nanometre range.



The array technique opens up attractive possibilities for DNA and protein chips operating completely electronically. Such biochips can be used as part of a so-called „lab on a chip" and as complete microanalysis systems.

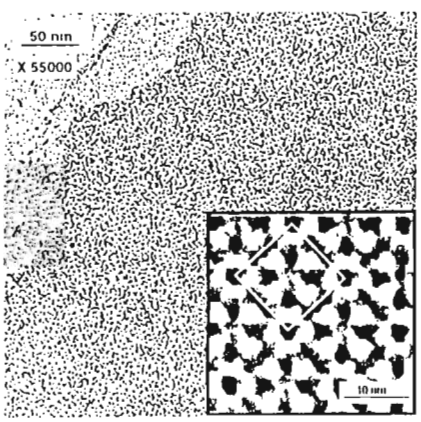


Examples of applications from nanobiotechnology

Biobased Technology

New high-tech materials for the future of computer engineering or medicine will require a technological understanding of surface structures just a few nanometres in width. It will probably no longer be possible to use conventional, generally complex production processes such as the fabrication of microelectronic components. For this purpose it may, in contrast, nanoscale structures are produced naturally with the aid of relatively simple and sustainable techniques based on the principles of self-assembly.

Nanobiotechnology makes use of such „smart" structures of biomolecules - as can be found, for example, on the surface of bacteria - functioning as a template. Highly selective filters, catalysts, materials for biobased electronic circuitry etc. can be produced by depositing metals or other substances. The templates can selectively be modified in nanodimensions by means of genetic methods. This is an enormous advantage to adapt the natural template to technical requirements.

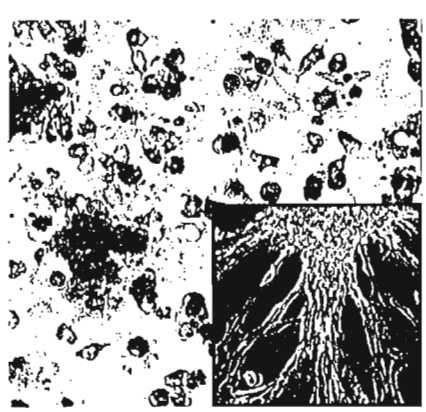


Transmission electron microscope pictures of platinum clusters (larger photograph) synthesized on bacterial envelope proteins (S-layers) via biomolecular templating. The average cluster size is about 2 nm. The arrangement of the clusters strictly follows the symmetry of the underlying protein template (small picture). The clusters preferentially grow in the pores of the protein matrix. (Dresden University of Technology, Institute of Materials Science, Prof. Dr. Wolfgang Pompe and co-workers)

Nanoparticles as tools in medicine

It has proved difficult to channel pharmaceuticals into the brain. A type of cell barrier protects the brain from pathogens and many harmful molecules. This blood-brain barrier also denies access to many therapeutic substances. Studies have shown that nanoparticles (diameter between 10 and 1000 nm) with distinct surface properties can overcome this barrier. At the University of Frankfurt am Main, a team headed by Prof. Dr. Jörg Kreuter is successfully working on transfering substances into the brain with the aid of microscopically small plastic spheres.

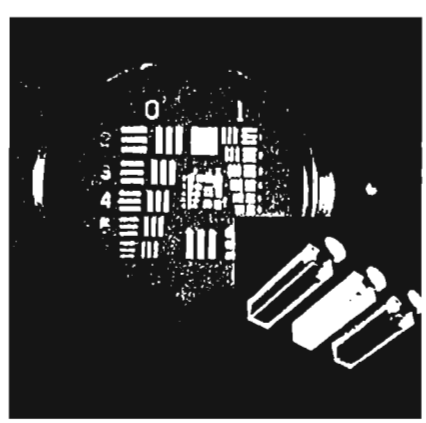
Magnetic nanoparticles could also be of use in combating cancer, as shown by the so-called magnetic liquid hyperthermia developed by Dr. Andreas Jordan and co-workers at the Charite Hospital in Berlin: Firstly, iron oxide particles are selectively transported into the carcinoma. Then, an alternating magnetic field heats the nanoparticles and thus the cancer cells, which are killed by overheating. The particles are produced for instance by the Leibniz Institute for New Materials in Saarbrücken (INM). Prof. Dr. Helmut Schmidt and colleagues from INM attempt to modify the surface of the nanoparticles according to the requirements of the Berlin group so that the particles can be delivered to the blood stream. Above all, only cancer cells incorporate the particles, so that healthy cells are unaffected.



Cells of a malignant brain tumour (glioblastoma) without (small picture) and after the uptake of nanoparticles (brown specks, diameter about 13 nm).

Protein design for optical information processing

Bacteriorhodopsin originates from so-called halobacteria using this protein to convert light energy into other suitable forms of energy. Bacteriorhodopsin changes colour from purple to yellow when it is irradiated by light. The photochromic properties can selectively be modified and stabilised with the aid of genetic techniques. This entails it is interesting as a high-performance material for optical media, especially for holographic pattern recognition and interferometry. Many other applications are also possible. For example, biofilms coated with the protein can be produced thus creating optical data memory systems with extremely high capacities. In the past few years, the necessary biotechnological tools have been established so that bacteriorhodopsin can be technologically exploited. Research is currently undertaken on integrating the new material into optical systems ready for application.



Small photograph: Bacteriorhodopsin changes colour from purple to yellow when it is irradiated by light. The greater picture shows a test pattern on a bacteriorhodopsin display. The biodisplay was developed by Prof. Norbert Hampp's working group (University of Marburg, Department of Chemistry).

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BIOTECHNOLOGY

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Tissue Engineering

Spare Parts for Humans

BMBF is funding research into technologies concerned with the reconstruction of damaged biological tissues and organs.

Several years ago the culturing and multiplication of living cells derived from humans (and animals) in the laboratory outside the organism was still inconceivable. Today a young branch of biotechnological research - tissue engineering – is very much involved with this procedure.

The first applications are already to be found in clinical practice. By using new cell culturing techniques and other innovative technologies implemented in tissue engineering, patients can be treated with new biologically „manufactured" body's own (autologous) cells. After their *in vitro* multiplication outside the organism, they can be applied after reimplantation, for example, for the regeneration of damaged tissue (see also p. 3). For other purposes – the reconstruction of a damaged external ear, for example – using appropriate measures, the cells are afforded the necessary functional stability. To achieve this, the cells are cultured on a three-dimensional carrier (matrix) made of a biologically compatible material.

The first major successes were achieved

With the aid of new cell culturing techniques researchers working at Biotissue Technologies AG in Freiburg have cultured this finger joint from autologous cells of a patient. The starting material comprises cells taken from the pelvic bone and cartilage cells from the ribs. They are induced to proliferate in the laboratory and in

This auricular cartilage transplant was grown from human cells. Photo: Status after 7 days' *in vitro* culturing (Universitätsklinikum Benjamin Franklin, HNO-Klinik and AG Tissue Engineering, Charité, both Berlin, Germany).

with the generation of larger cell aggregates as well as „spare parts" for damaged blood vessels, parts of the heart, joints and even nerves. However, there is still a long way to go until entire organs can be manufactured in the laboratory.

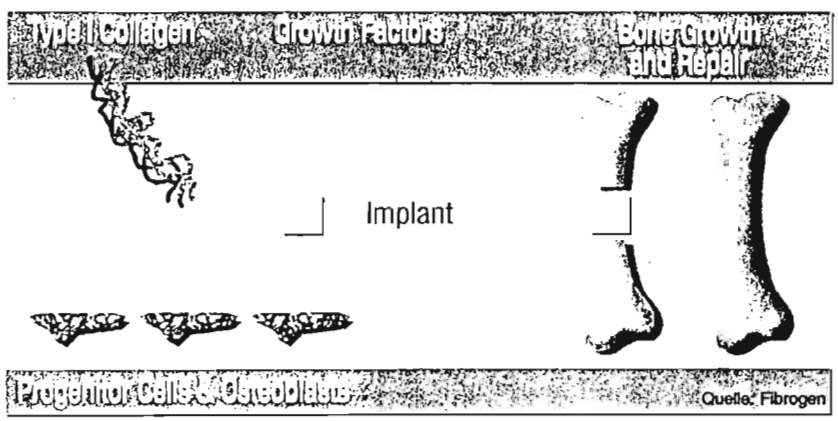
Furthermore, active substances for pharmaceutical products can be tested on tissue aggregates and organ substitutes grown *in vitro*. The results from these tests have the advantage that they are directly transferable to humans. One desirable „side effect" of such tests is the reduction in the number of animal experiments.

Tissue engineering is based on the interdisciplinary collaboration of scientists from the fields of biology, chemistry, physics, material sciences, appliance and process engineering, informatics as well as medicine. As a result of the cooperation between this large number of scientific disciplines, on the one hand, and the task of investigating further into the interaction of the structure and function of organic cellular tissue – in addition to the practical applications. On the other, considerable knowledge is expected to be gained in the field of the life sciences.

The driving force behind the rapid development of tissue engineering is, above all, however, the constantly increasing demand for replacement tissues and organs. Numerous research groups have become established in this area over the last few years, German scientists playing a significant role here in Europe.

To implement the extensive knowledge gained within this field in practice, with its funding activity „Tissue Engineering" (First announcement of 13.1.2000), the Bundesministerium für Bildung und Forschung (BMBF – Federal Ministry of Education and Research) promotes industrial research and precompetitive development projects. Funding is conducted as a joint initiative with the Health Research Program of the BMBF.

Financial aid is given in particular to promote work contributing to the production of biological material for tissue reconstruction and hybrid replacement tissue at the three levels of the molecule, cells and tissues and/or organs. Projects relating to human embryonal stem cells research are excluded.



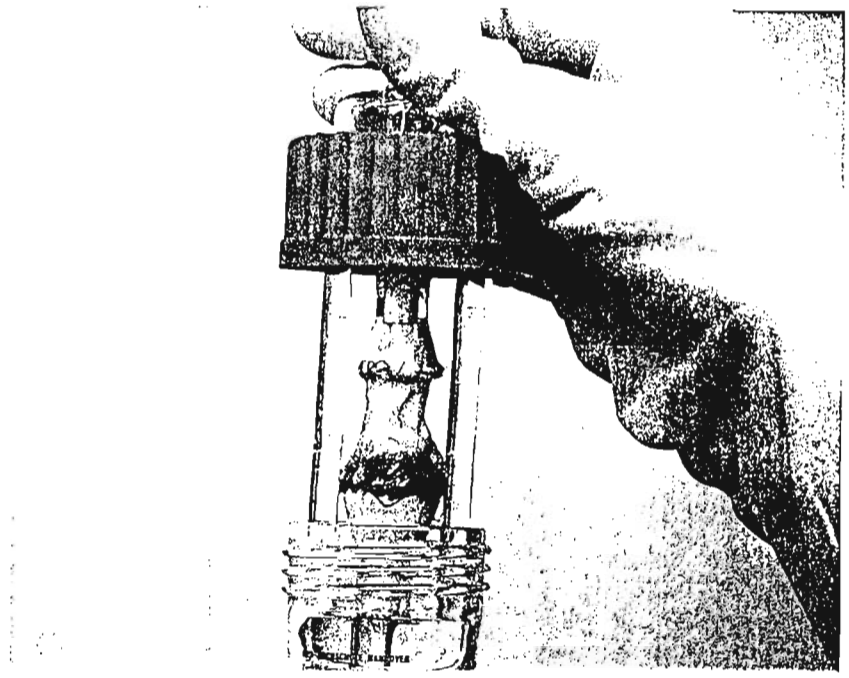
To repair bone, precursor cells and bone cells are applied to a three-dimensional carrier matrix (for example, collagen or a biodegradable polymer) and stimulated to form a new piece of bone.

Tissue Engineering: Examples of Use

Heart valves from autologous tissue

The BMBF has been sponsoring research into replacement heart valves manufactured biosynthetically since 1998. Among other companies, coworkers at Bionicor GmbH in Hechingen near Tübingen have been involved in this research. As starting material, they have been using porcine heart valves. Like their human counterparts, these comprise heart cells grown on a supporting collagen matrix. Colonisation by human heart cells in a bioreactor (photo) follows removal of the porcine heart cells.

What is special about the worldwide, patented procedure is the transformation of animal collagen into the human form? In this way, a biological heart valve is created from the patient's own tissue, which can be transplanted without any problems, caused by the bodys immun response. After manufacturing a large number of such valves, clinical studies are planned for the not too distant future.



Porcine heart valve in the bioreactor.

New cartilage for joints

One of the already established applications of tissue engineering is the growth of chrondrocyte (cartilage cell) transplants for the treatment of the knee joint: Healthy chondrocytes are removed from the patient, cultured in autologous serum in the laboratory and allowed to proliferate over a period of four weeks, after which the cells are transplanted into the knee joint, where they begin to form new load-bearing cartilage.

Since 1997 it has been possible to treat over 800 patients successfully with such transplants manufactured by co.don AG in Teltow near Berlin. This company belongs amongst the leading concerns for the regeneration of cartilaginous, osseus and intervertebral disk tissue. Their research into the growth of cartilage and bone has been sponsored by the BMBF for many years.

Production of biological „spare parts" in a clean-room.

Bundesministerium
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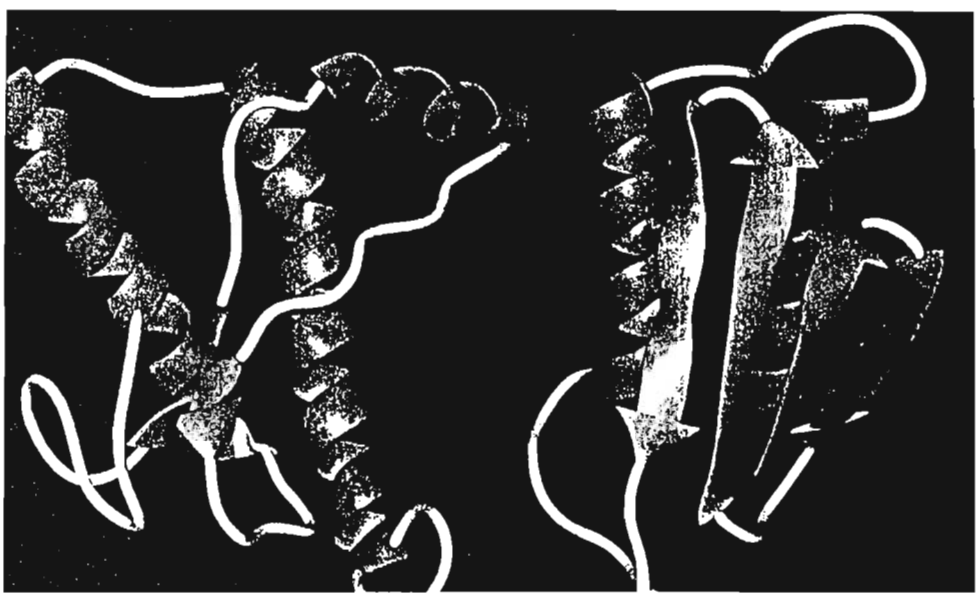
Forschungszentrum Jülich GmbH

TSE-Diagnostics

Prions: The Spongiformous Damage of the Brain

The search for an innovative diagnostic tool for Transmissible Spongiform Encephalopathies (TSEs) is being funded by BMBF



The appearance of „mad cow disease", BSE (*Bovine Spongiform Encephalopathy*), in Germany since the end of the year 2000 demanded the development and establishment of new diagnostic procedures for TSEs (*Transmissible Spongiform Encephalopathies*) in humans and in animals.

TSEs cause an increasing loss of function of the brain which results in initial clinical symptoms as behavioural and motor disturbances which always lead to death in the longer run. To date, neither any form of therapy nor a vaccination against TSE is available. Apart from humans and cattle TSEs have also been observed in numerous other species. Known for the longest period of time is scrapie in sheep, which was already reported in 1732 (for more see Box p.2).

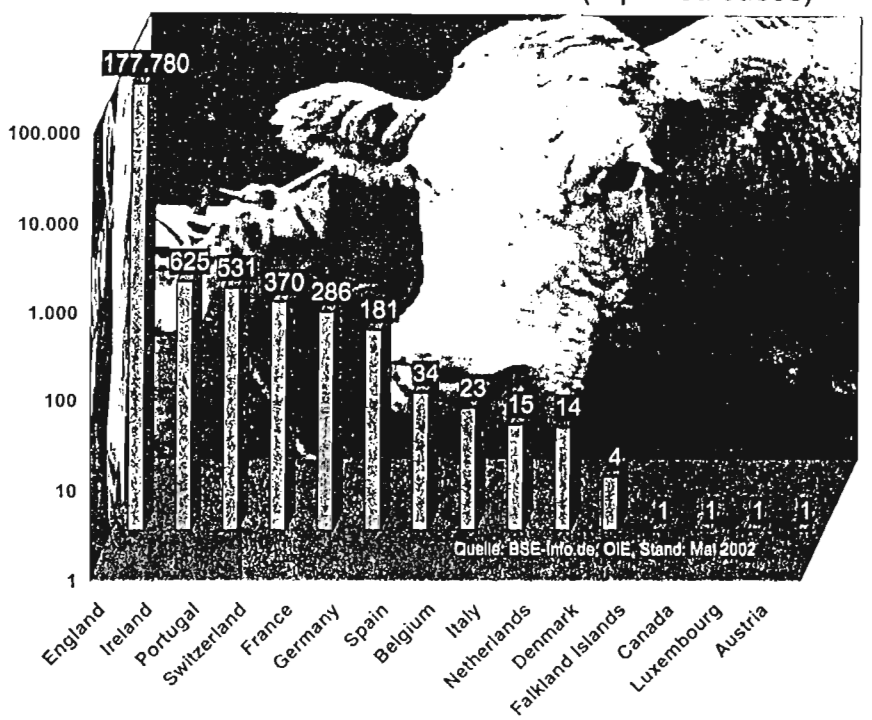
So far, BSE has caused considerable damage in agriculture and in the meat industry throughout central Europe.

It is even more worrying that a new variant of the human Creutzfeldt-Jakob Disease (vCJD) might be caused by infection due to the consumption of BSE-contaminated meat.

According to the current state of knowledge, TSE pathogens belong to a new class of pathogens – pathologically misfolded proteins. Prions represent the pathogenic form (PrP^{Sc}, Sc for scrapie) of a healthy, cellular protein (PrP^{C}, c for „cellular"). The pathological prion protein does not differ chemically from the normal form. However, the three-dimensional folding of the macromolecules differs

Two computer-based models of prion proteins that are completely identical in their chemical composition. The lethal difference is caused by the spatial folding of the molecules. Cellular prion proteins (PrP^{C}) are proteins formed in the plasma of the brain cells. On the left, the healthy, normal form, on the right, the infected, TSE-triggering variant is depicted. Prions represent a class of pathogens that contain no genome.

Worldwide distribution of BSE (reported cases)



which is accompanied by a considerable difference in physical and biochemical properties: In the healthy organism, the protein exists as a single molecule, bound to the surface of the cells. The pathogenic variant forms large, insoluble aggregates that are extremely stable: Only concentrated acids or bases and chlorine-containing solutions are capable of reliably inactivating prions, Conventional disinfectants, on the other hand, are rather ineffective.

Up to now, the unambiguous identification of TSE diseases has only been possible after death and requires the sampling of brain and/or spinal marrow tissue. In these samples the concentration of prions is sufficient to be detected by standard procedures giving the disease its name („spongiform").

Prophylaxis, foodstuff and drug safety require new and more sensitive detection methods than the quick test used up until now. They should enable a reliable diagnosis of TSE in humans and animals at an early stage of infection. Above all, the tests must be feasible for living organisms and use readily accessible tissues or body fluids. Thus, within the scope of the BMBF funding activity „TSE diagnostics" and the German Federal Government's framework programme biotechnology, innovative approaches are being demanded. Special attention is being paid to procedures that enable reliable, highly sensitive and economical assays. At the same time, they should

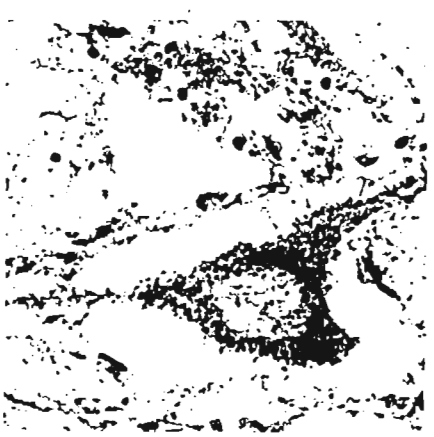
Transmissible Spongiform Encephalopathies (TSEs)

Transmissible Spongiform Encephalopathies (TSEs) include transmissible, sponge-like changes of the brain in humans and animals. In general, they are neurodegenerative diseases, characterised by a long incubation period (many years up to decades), necrosis of nerve cells and a massive degradation forming sponge-like structures within the brain.

The disease causes the stepwise loss of brain function, which, in addition to initial behavioural and motor disturbances, always leads to death. To date, there is neither any form of therapy nor vaccination against TSE available.

Apart from BSE in cattle and scrapie (the oldest known TSE) in sheep and goats, four other TSEs in mammals are reported so far : the Chronic Wasting Disease of certain species of American deer (CWD), Transmissible Encephalopathy in mink (TME), Feline Spongiform Encephalopathy in cats (FSE) and spongiform encephalopathy in antelopes.

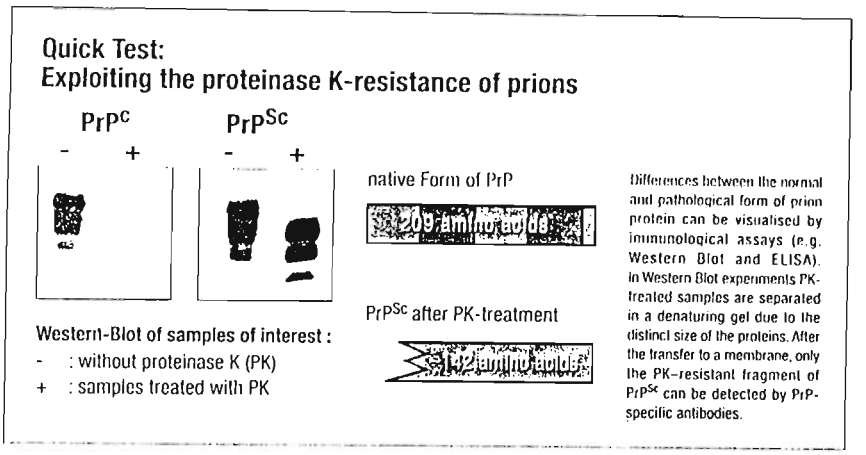
In humans different TSEs like the Creutzfeldt-Jakob Disease (CJD), the Gerstmann-Sträussler-Scheinker Syndrome (GSS), the Fatal Familial Insomnia (FFI) and Kuru are described.



Examples of diagnostic assays for TSE

Quick Test

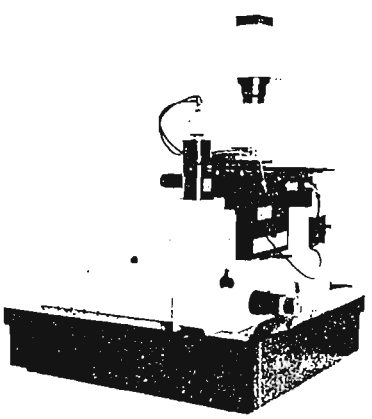
The quick test is the most common detection assay employed today. To determine whether pathological prion proteins (PrP^{Sc}) are present or not, the resistance of PrP^{Sc} towards the protein digesting enzyme „proteinase K" is exploited. Extracts taken from the brain tissue of animals are submitted to proteinase K treatment. The normal form, PrP^{C}, is completely digested, whereas due to its great stability, the pathogenic form resides as a shortened molecule with a smaller number of amino acids. The proteinase-resistant form can then be immunologically detected with PrP-specific antibodies. The huge disadvantage of the quick test is the restriction on material derived from dead animals/organisms.



Single-molecule testing

To conduct a test on living organisms, prions have to be detected in body fluids such as blood, urine or spinal fluid. Because the concentration of prions in these fluids is very low, the test must be highly sensitive.

A promising technology considering the problem of low prion protein concentrations in living organisms is provided by the so-called multimode fluorescence spectrometer (Evotec Analytical Systems GmbH), which allows the detection of single molecules. A TSE test using this technique exploits the property of the prions to form large, stable aggregates. Special PrP molecules with a dye attached can bind to the aggregats labelling the prions. Thus, allowing the subsequent detection by fluorescence spectroscopy FCS is possible .



Cell cultures

Still considered as the gold standard with regard to the available TSE assays is the infection study in animals. The effect observed here is based on the infectivity of the sample in question. Disadvantages of this test are the long incubation times as well as ethical aspects of the animal experiment.

Exploiting the pathogenic property of prions for a test is highly specific, yet only possible in living systems. An alternative to animal experiments might be provided by the development of susceptible cell cultures, allowing the propagation and generation of new infectious prions *in vitro*. Such a test is based on the biological properties of the prions. The *in vitro* growth would be highly specific and could be validated by a quick test or some other detection method.

So far, animal experiments are considered as the gold standard with regard to infection studies. But *in vitro* systems may provide suitable alternatives in the future.

BMBF funding activity TSE-diagnostics

Projektträger des BMBF und BMWi
Forschungszentrum Jülich GmbH

The aim of the BMBF funding activity „TSE-diagnostics" is the development of new and highly sensitive detection methods that provide a reliable diagnosis in humans and in animals at an early a phase of infection.The assay should be applicable to living organisms and should only require readily accessible tissue or body fluids.

Funding will address the following thematic priorities:

- Investigation of the properties of the TSE pathogen, allowing the development of new testing procedures,
- pathogen classification and differentiation,
- establishing transgenic model systems,
- application of proteomics to identify TSE-specific markers and their exploitation to develop immunological tests,
- biophysical and biosensoric detection methods,
- validation of tests.

The ongoing research projects include optical detection methods, which exploit the structural properties of the pathogen, in particular, the ability to form aggregates. Other projects aim at the diagnosis of human Creutzfeldt-Jakob disease, immunological diagnostic methods as well as the standardisation of new testing procedures. Furthermore, projects for establishing cell cultures as test systems, to diagnose TSE in deer and red deer as well as the evaluation of decontamination procedures are considered.

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Funding activities on the Internet:
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Framework programme Biotechnology:
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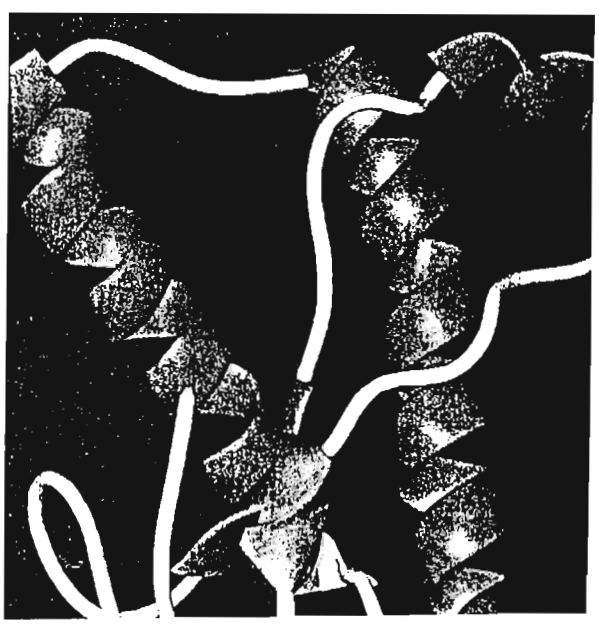

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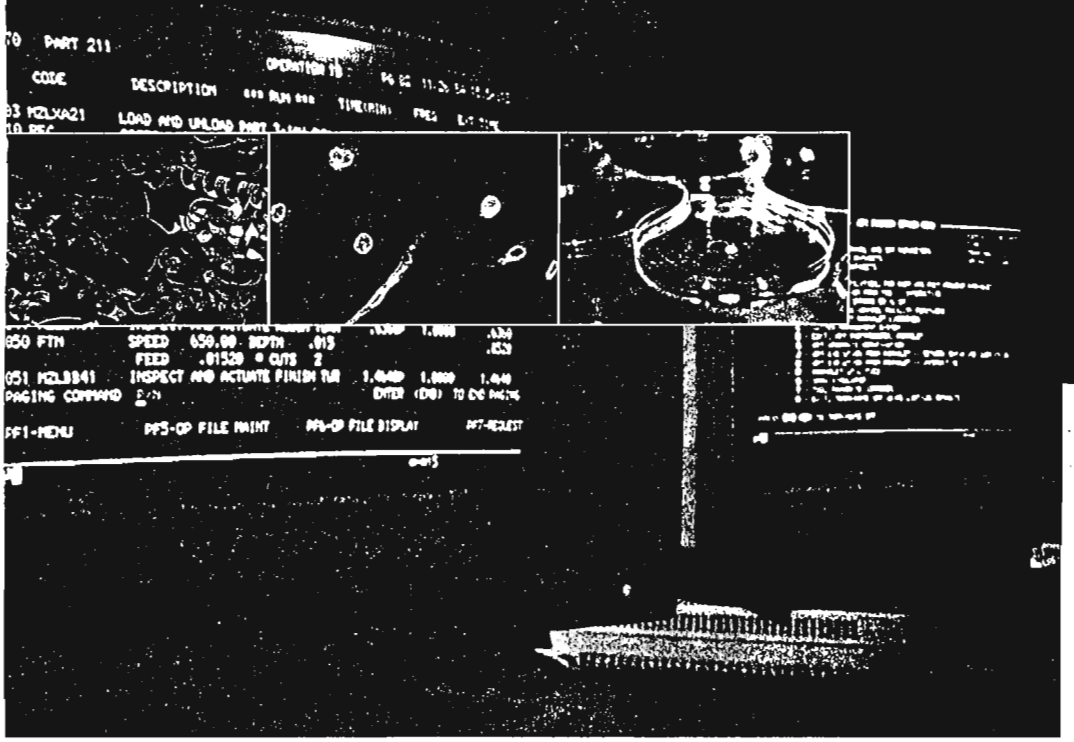
Systems of life – systems biology

An insight into life

BMBF funding priority on the development of reality-based models of life processes



A reality-based computer model of a biological functional unit – for example a cell – is the aim of many researchers. It offers the unique opportunity to gain a better understanding of complex life processes. On the basis of the system's behaviour, hypotheses can be derived from the model and tested in experiments for their validity. In this way it will be possible to generale new knowledge on the causes and effects of diseases.
External influences on the system (e.g. the impact of toxic substances) can initially be studied in the model and then simulated in an experiment. This would help to reduce the number of expensive toxicological studies. However, it will be necessary to first develop the scientific basis for such a

The desire to understand the molecular basis of life is not new; it can be traced back at least to the first half of the 20th century. It summarises the study and influencing of life at the molecular level and the resulting benefit for biology and medicine. This alone is not sufficient to the interactions between the cellular compounds. This is the long term object of the new discipline of systems biology. Decades of research work using methods of traditional biochemistry and molecular biology have led to the identification of genes and proteins and to

The Funding Priority "Systems biology"

Within the framework of the funding priority "Systems of life – systems biology", the BMBF is planning to set up an interdisciplinary competence network linking the biosciences with the systems and engineering sciences, computer science and mathematics under the umbrella of systems biology.

The network of competence consists of the three modules of methods development, modelling and cell biology, which must all be closely interlinked.

The individual research activities will be supported in the form of collaborative projects or as individual projects within the framework of the planned platforms "cell biology" and "modelling/bioinformatics". A coordinator at the DECHEMA Gesellschaft für Chemische Technik und Biotechnologie e.V. will assist with the coordination and integration of all the research activities within the framework of the competence network.

The competence network will focus on the development of standardised methods, tools and cell material in order to generate comparable data right from the beginning of the funding measure. These data, saved in a joint database serve as a basis for the development of a virtual model of the hepatic cell.

Systems biology will be funded over several funding periods. To establish a national network of competence, three collaborative projects and six individual projects linked with the platforms were selected for the first funding period. After two years an evaluation step of the competence network will help to decide on the further development of the network. The aim is to incorporate the national funding programme into international systems biology activities.

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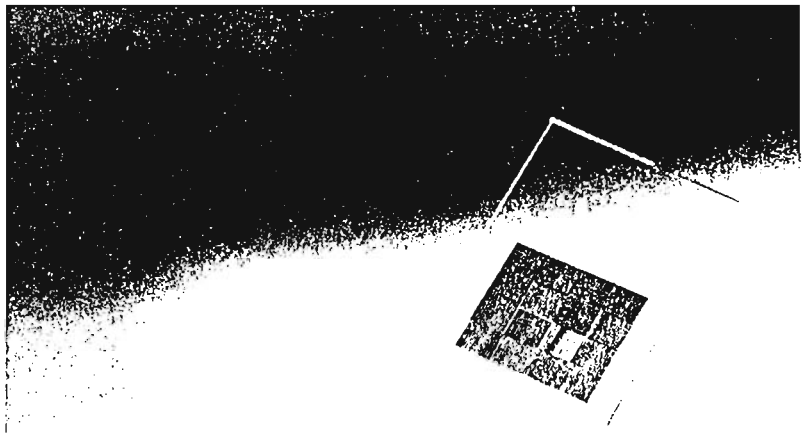
National Genome Research Network NGFN

Genome Research Contributes to Fight Major Widespread Diseases

The German Federal Ministry of Education and Research is Funding the Systematic Functional Analysis of Genes as a Contribution to Prevention and Treatment of Major Widespread Diseases



Over the last few years, genome research has achieved considerable success, leading to new molecular methods, which today can be implemented on a routine basis in medical research. As a result of decoding the human genome, pathogenetic research can now be conducted more effectively. Although great improvements in modern medicine could be achieved, about two thirds of all diseases still can only be treated on the level of symptoms and remain causative incurable. Therefore it is essential to gain further insights into the molecular and genetic causes of diseases.

By establishing the National Genome Research Network (NGFN) the German Government is taking up the new and promising possibilities of combating diseases. Funding started in 2001 for an initial period of three years with a total sum of 180 million €, center of attention being major widespread diseases. Due to their frequent incidence and high mortality rates as well as due to the burden they represent to the health care system and therefore to the national

chers with different backgrounds is required: molecular geneticists, clinicians from disease areas, specialists from the area of bioinformatics, protein researchers as well as biostatisticians, they all have to contribute their specific knowledge in joint projects. The NGFN is thus organized in a cooperative network.

Specific methods such as DNA Chip Technology help scientists to identify genes that effect diseases such as cancer or hypertension. In the NGFN experts of various areas of research work together. The collective results of molecular biologists, clinicians, geneticists and bioinformation scientists make up the basis of significant progress in the prevention and

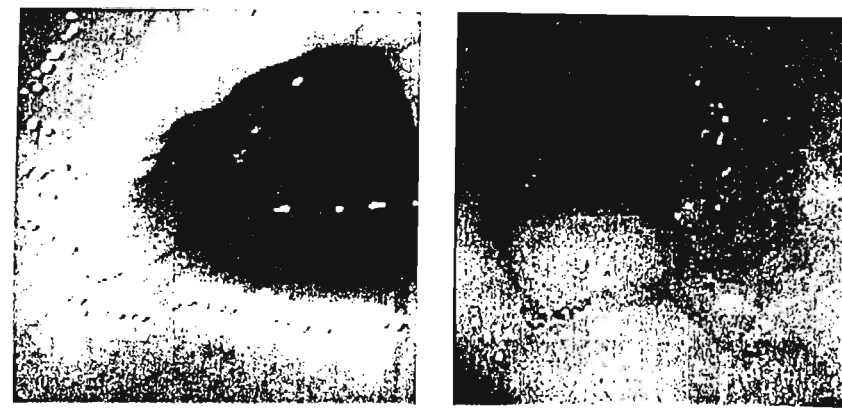
assistance in clinical research, use of common infrastructure as well as an organized exchange of materials and experience.

By identifying disease-relevant genes and analyzing their function, it is possible to understand the causes of diseases. As a result, chances increase of finding new approaches for diagnostic and therapeutic procedures and of developing new active substances for treatment. In addition to the benefit for patients, the success of the research conducted by the NGFN may also substantially influence national economic prospect. The international competition in the field of genome research is considerable and therefore a rapid transfer of results from research to commercial exploitation is a main concern of the NGFN. This is taken into account by the participation of various biotechnology companies in the NGFN as well as by providing an efficient system of propriety right protection and technology transfer.

Thus, the funding initiative NGFN is an important investment for the future, which will strengthen the German position in an internationally highly competitive field, including competition for future markets and jobs, in particular compared to the leading industrial nations in this field: USA, Japan and Great Britain.

Disease-Oriented Genome Networks

Diseases due to Environmental Factors



Morbus Crohn is a chronic inflammatory bowel disease resulting from an overreaction of the body's immune system. The cause of the disease is still unknown. Right: Bowel of a Morbus Crohn patient, left: Healthy bowel.

Berlin, Kiel, München

Research areas: Chronic inflammatory bowel diseases; atopic dermatitis (inherited chronic inflammation of the skin); allergen induced sensitisation and respiratory inflammation; psoriasis; sarcoidosis (chronic granulomatous disorder potentially affecting most organs).

Cancer

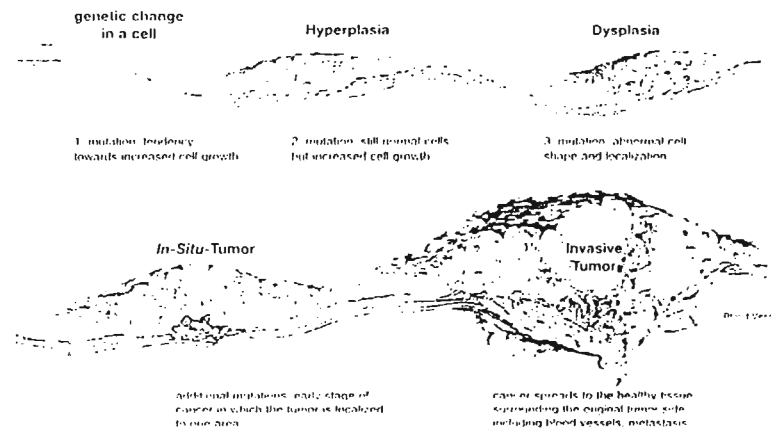
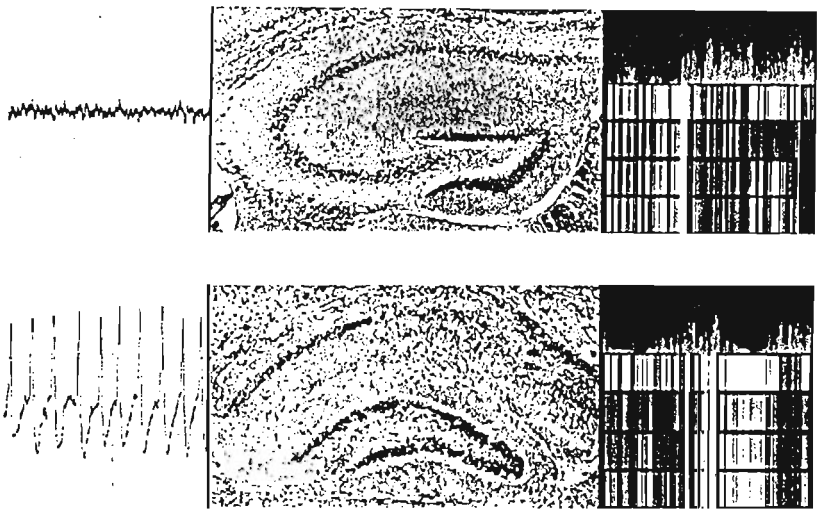


Figure: Development of a malignant tumor.

Berlin, Erlangen, Essen, Frankfurt, München

Research areas: Identification of candidate genes for tumorgenesis; cancer classification; bioinformatic analysis of clinical and genetic data for more precise diagnoses and predictions of cancerous disease outcome; design of new experimental strategies. Analysis of the biology of various tumors, especially breast cancer, malignant lymphomas, large bowel malignancies, brain tumors, colorectal cancer and acute leukaemias

Diseases of the Nervous System



Reaction of the brain to epileptic seizures. This convulsion affliction is accompanied by changes in the electroencephalogram (left-hand column), nerve cell damage (middle column) and errors in the genetic program of brain cells (right-hand column). Top: healthy, bottom: diseased brain. The coloured patterns on the right (profiles of gene-expression) shows results from a so-called gene chip analysis

Bonn, Hamburg, Heidelberg, Marburg, München

Research areas: Functional genomics of neurological and psychiatric diseases, such as neurodegenerative disorders, e.g. Alzheimer, epilepsy, stroke and Parkinson's disease; furthermore schizophrenia and affective disorders, addiction, migraine, mental retardation, susceptibility to underweight and obesity and prion diseases.

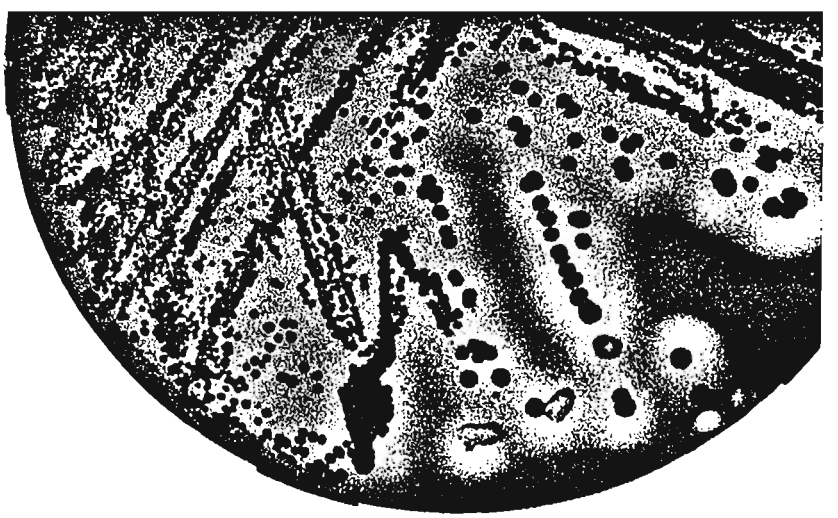
Cardiovascular Diseases

„Calcified" coronary vessel. Arteriosclerosis is a frequent cause of myocardial infarction, a secondary disease of hypertension.

Berlin, Göttingen, Lübeck, München

Research areas: Hypertension and hypertensive end-organ damage; genetic susceptibility to cardiac arrhythmias; causes and mechanisms of contractile

Infection and Inflammation



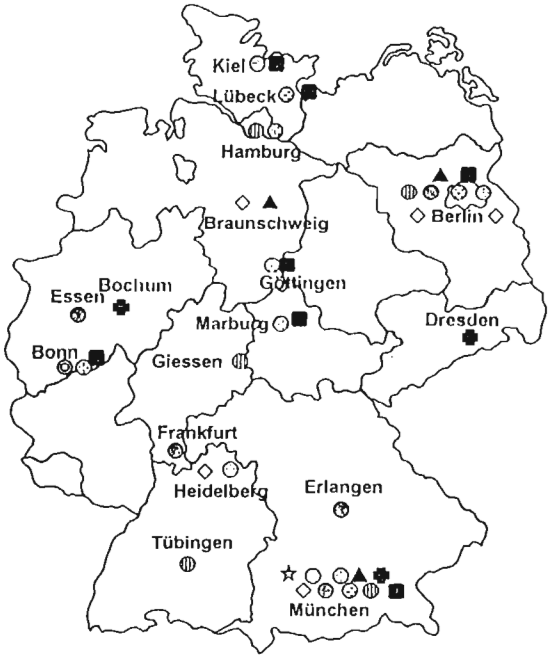
Sepsis inducing pathogen Staphylococcus aureus. Severe septicaemia (blood poisoning) and septic shock are the main causes of death in the non cardiological intensive care units worldwide.

Berlin, Giessen, Hamburg, München, Tübingen

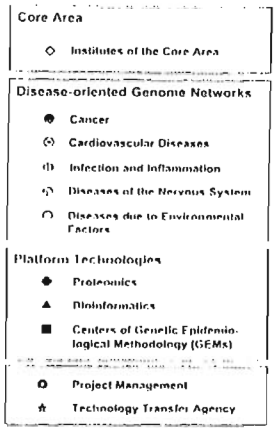
Research areas: Chronic inflammatory diseases and autoimmune phenomena (e.g. rheumatoid arthritis or systemic lupus erythematosus); problems resulting from host-bacterium interactions (e.g. sepsis and pulmonary

Organisation and Locations

Locations of the institutions



National Genome Research Network



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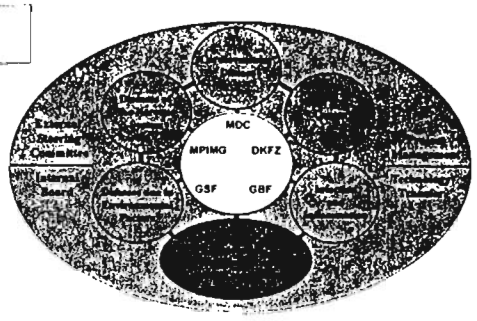

Clinical research is mainly conducted by university institutions. The five disease-oriented genome networks (red) relate to the areas cardiovascular diseases, cancer, diseases of the nervous system, diseases due to environmental factors as well as infection and inflammation.

The disease-oriented research groups cooperate closely with the scientists working in the core area (yellow) and the platform technologies bioinformatics, proteomics and the centers of genetic epidemiological methods (GEM, blue). Main research areas in the core area are: Genomic evolution and sequencing, gene expression analysis, phenotyping, genotyping, bioinformatics, protein re-

The research groups working in the core area and the platform technologies are predominately located in non-university-affiliated research institutions.

Two committees guarantee the successful implementation of the goals of the NGFN: The „Internal Board" (Project Committee) of the NGFN and the external Steering Committee.

The NGFN bureau for Project Management and the NGFN Technology Transfer Agency are located in Bonn and München, respectively.

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für Bildung
und Forschung

New efficient methods for functional proteome analysis

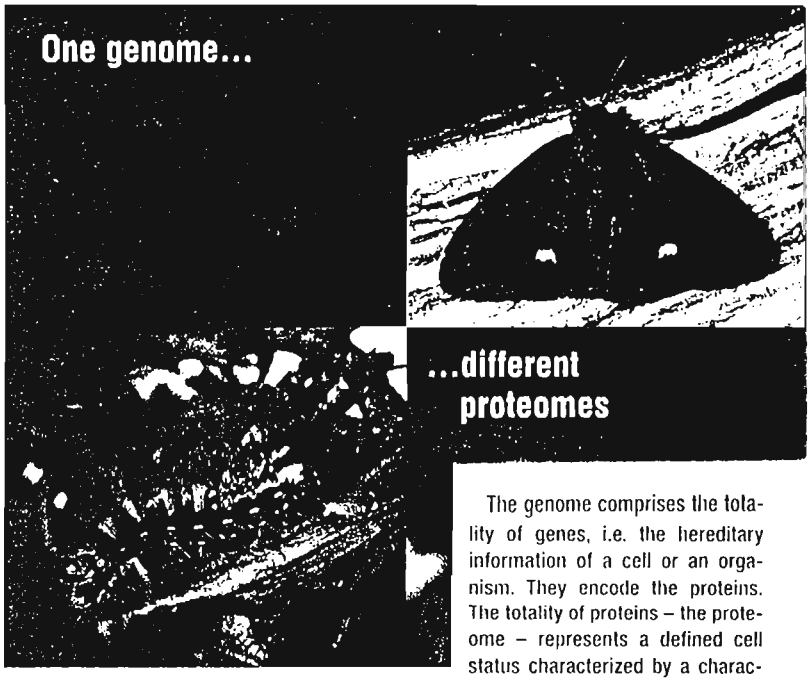
No life without proteins

Elucidation of protein functions reveals the secrets of life

Deciphering the genetic code of humans has been one of the greatest achievements of biosciences. But this success has also led to the sobering finding that the genetic code alone does not provide sufficient information on the structure and function of proteins. However, protein molecules are necessary for all important activities of living systems! Thus, for example, the process of seeing – starting from the crystalline substance of the eye lens through signal transfer up to imaging in the brain – is a complex interaction of proteins, whose operation and regulation are not understood from the genetic data alone.

Insights into the complex processes of a biological system are only obtained by exploring the proteome – the totality of all proteins of a cell or an organism at a defined cell status.

A gene can produce many different proteins which, depending on the location of action, perform different functions. The slightest modifications of the protein structure can disturb its function and interactions and thus lead to diseases.



Understanding the complexity of proteins and their functions is therefore a great challenge for life sciences in the coming years. The causes of disease can be identified and new forms of therapy derived by exploring these correlations. However, because of its complexity proteome research requires the application of innovative methods and high throughput technology.

The genome comprises the totality of genes, i.e. the hereditary information of a cell or an organism. They encode the proteins. The totality of proteins – the proteome – represents a defined cell status characterized by a characteristic mixture of proteins at a defined point in time. This mixture changes constantly in the course of the cell cycle or the life of an organism. An example is caterpillar and butterfly, which exhibit different proteomes while having the same genome.

Nature has found ways to make many proteins from relatively few genes. The human genome consists of roughly 40,000 genes – not many more than present in the plant Arabidopsis. However, in human cells, in principle, up to 400,000 different proteins can be

Cont. from P. 1

This is where the Federal Government started out with its call for "New efficient methods for functional proteome analysis" of June 2000. This call for proposals focused on technological development as a basis for creating an active and internationally competitive proteome scene in Germany. In the first funding period extending over five years, 75 million Euros have been appropriated for this purpose.

In the meantime, the pharmaceutical and diagnostics companies' interest in proteome research has also risen worldwide. Many diseases are caused by misdirected or failed protein functions – for instance, diabetes in the case of insulin protein deficiency. Such proteins are declared to become therapeutical targets. Applied for the establishment of *test systems, they enable the development of* entirely novel, tailor-made pharmaceuticals with enhanced effect.

A sales increase from currently US $ 1.5 billion to US $ 3-10 billion is expected for the global proteomics market by 2010. This should have positive effects on the labour market, especially for small and medium-sized enterprises.

In the meantime, an international run on the scientific exploitation of proteome research has begun; the USA, for example, will fund ten proteome centres with US $ 150 million in the next seven years. The Chinese government will provide US $ 200 million for the international human liver proteome project.

Not least due to the BMBF's early technology funding and the start-up activities in proteo- [illegible] achieved an inter-

Technology development in proteome research

From sample preparation through molecule separation up to the analysis techniques – without efficient automation and without support by bioinformatics, the demands made on proteome analysis cannot be satisfied. Protein chips will also gain enormous significance in the future.

The efficiency in elucidating the function of the proteins is essentially determined by the methods available. Good progress has been achieved in recent years. Three examples are presented in the following text.

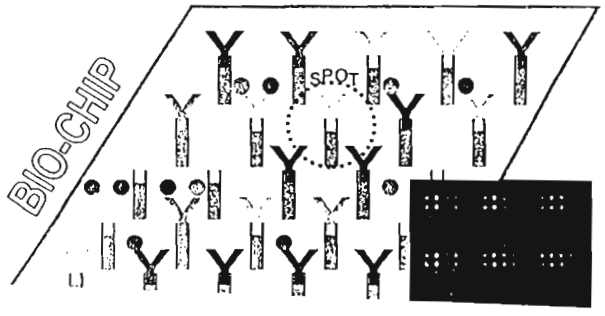
Fast protein chips

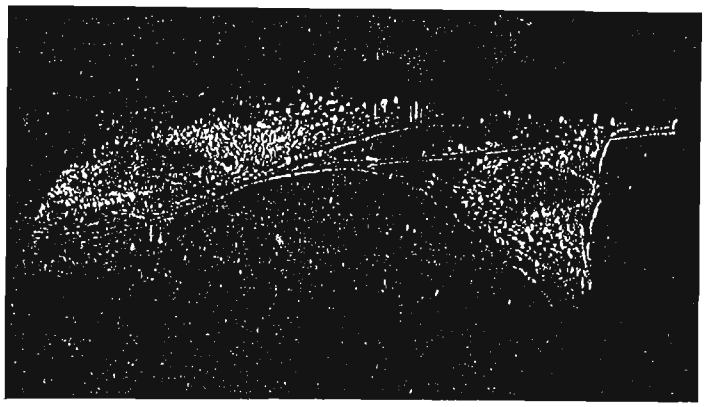
In biochips, innumerable probe molecules are fixed on a glass slide, a few square centimetres in size, e.g. gene fragments (DNA chips), defined proteins or known antibodies (protein chips).

These probe molecules can entrap and retain matching bond partners from a sample (e.g. blood serum) according to the lock-and-key principle. The molecules of the test substance are labelled with a fluorescent dye. The probe molecules which have bound a partner are revealed through this fluorescence labelling.

In this way, for example, protein markers in blood serum can be detected and a disease diagnosed on a patient.

Several thousand analyses are simultaneously possible with one chip. The successful DNA chips have already proved efficient in the automated analysis of hereditary material or in medical analysis. The protein chips attain ever increasing significance for proteome research.





Proteins become visible

The exact localization of a protein inside a cell, i.e. the detection of its location of action, provides important information for functional analysis. For this purpose, special "traitors" were created, such as the green-fluorescent protein (GFP). It can be coupled to another protein and reveals the latter's location by glowing. This made it possible to observe proteins in living cells for the first time.
Another technique, the multi-epitope-ligand mapping technology (MELK), combines the possibility of a selective labelling of the proteins searched for with electronic imaging. In this way, a spatial still picture of a cell's proteome state can be obtained. The picture shows a map of two cells of the same type generated by the MELK technology. The individual colours clearly distinguish the differently labelled protein clusters inside the cells, which are thus recognized to be in different functional states.

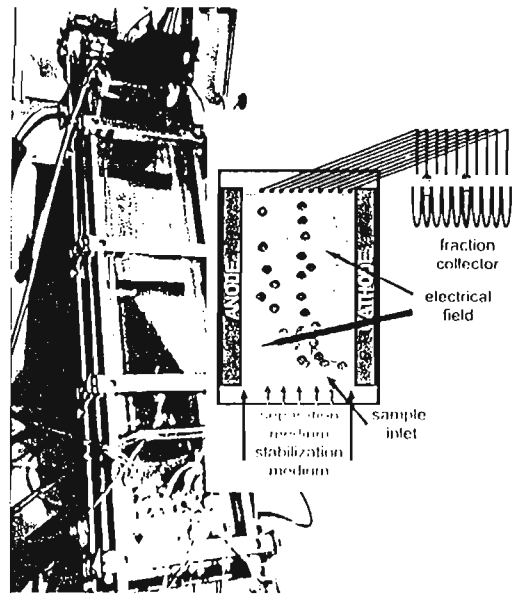
Continuation from P. 2

Besides research funding the transfer of know-how to industry and the economic exploitation of results are important to secure an adequate global market share for Germany.
The "Deutsche Gesellschaft für Proteomforschung (DGPF – German Society for Proteome Research)", to which a large number of companies are affiliated, supports proteome research activities in Germany.
At the international level, national and regional proteome initiatives are combined in a global organization – the Human Proteome Organization (HUPO). It pursues the goal of advancing knowledge about the human proteome. Germany has taken the lead in two of the five HUPO projects under way.

FFE: free flow – more possibilities

Indispensable for the researchers is the possibility of separating a protein mix into its constituents. Great progress has been achieved by free-flow electrophoresis (FFE). This method is characterized by the fact that, in contrast to "classical" 2-D gel electrophoresis, the separation process takes place in a free-flowing medium and the molecules are no longer embedded in a relatively solid gel matrix. It has thus been possible to further increase the sensitivity. By means of FFE, moreover, particles can be identified which have not been separable in the past. In combination with other proteomic techniques, it is thus possible to obtain more information from complex biological samples.
The applicability of FFE for the analysis of different cell organelles and membrane proteins is currently being investigated within the framework of funding established collaborative projects of partners from science and industry.

FFE permits the separation of different protein molecules. In order to do so, the protein mix is passed in a uniform liquid flow through a chamber with an electric field generated by two electrodes (anode and cathode). Depending on their charge, the individual proteins are differently deflected and thus separated. The illustration and photograph show the separation chamber, the heart of a modern FFE apparatus.



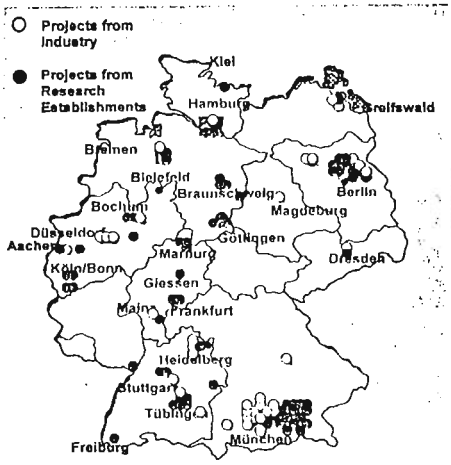
BMBF – Funding of Proteomics

Facts and Figures

On June, 15th 2000, the German Federal Ministry of Education and Research (BMBF) established the guidelines for the funding priority "New efficient methods for functional proteome analysis". An expert panel selected the 28 most innovative project ideas from 136 proposals submitted.

A total of 117 single beneficiary projects from science and industry are involved in this research programme. Total costs are in the range of 100 million Euros. The BMBF funding is around 75 percent; the remainder is financed by industry.

Proteom Research in Germany



The research programme incorporates universities, non-university institutions as well as small and medium-sized industrial enterprises (SMEs) from all over Germany. Particular efforts are concentrated in Bavaria, North Rhine-Westphalia and Berlin. These regions have the highest density of companies

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Funding activities on the Internet:
http://www.fz-juelich.de/ptj
http://www.proteomicsnetwork.de

Framework Programme Biotechnology:
http://www.bmbf.de/pub/rahmenprogramm_biotechnologie.pdf

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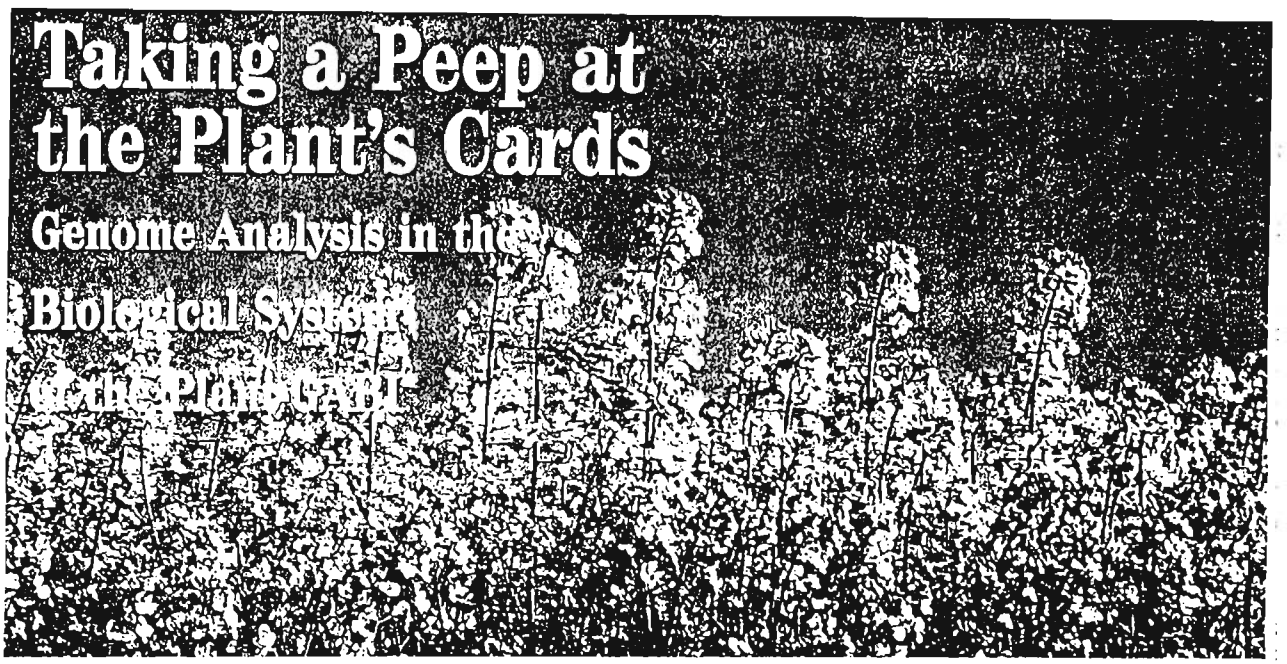
Taking a Peep at the Plant's Cards

Genome Analysis in the Biological System of the Plant - GABI



The rapidly growing resources of molecular biological research have made genetic engineering one of the key technologies for the coming century. An important field of application for this technology is plant breeding and plant biotechnology with the opportunity of improving the food supply and of producing interesting raw materials for chemical processes. The international competition to elucidate the function of economically relevant plant genomes, patenting the results and thus establishing market positions for new plant varieties with tailor-made properties is already underway with considerable public and private investment in research.

In order to more intensively exploit the chances arising from this development for Germany and to make a contribution towards securing the competitiveness of German industry, after extensive discussions and in cooperation with representatives from science and industry, the BMBF has launched the initiative "Genome Analysis in the Biological System of the Plant - GABI".

With the initiative, the BMBF is pursuing funding, economic and scientific goals for the successful further development of plant genome research in Germany, for which tailormade instruments have been developed and applied.

• A prerequisite for effective plant genome research in Germany is the creation and expansion of a comprehensive network of expertise with a critical mass of know-how, staff and technical equipment. To this end, the available expertise must be coordinated and reinforced across the boundaries of the different scientific disciplines. This involves contributions from plant breeders, botanists, molecular biologists and geneticists. Furthermore, bioinformatics specialists are, however, also indispensable in modern plant genome research to provide the tools for recording and evaluating the enormous volumes of data arising; moreover, biochemists, chemists and engineers are required to develop automated and miniaturized instruments and methods (e.g. DNA chips). Special services required by a number of working groups are concentrated in resource centres in order to ensure the maximum level of rationalization and standardization of methods and experimental boundary conditions.

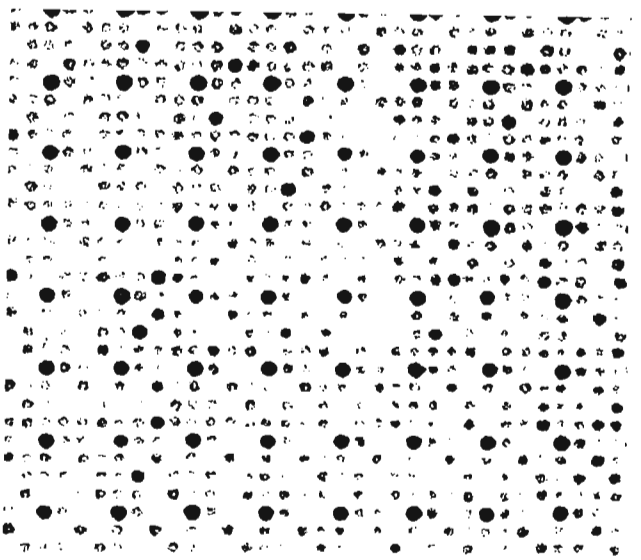
• A decisive task within the network of expertise is not only to make the necessary tools and methods generally available, but also to adapt them to the special needs of plant genome research and to further develop them. To this end, there is a need for research in all the above-mentioned disciplines. In order to ensure that the tasks are formulated as examples and to guarantee the greatest possible comparability of results in the exchange of information, the research work is restricted to two model plants:

- Mousecar cress *(Arabidopsis thaliana)* represents the large group of dicotyledonous plants. Since it has a comparatively small genome for a plant it has already been established as a model plant for research purposes so that extensive findings are available. Moreover, Arabidopsis is relatively closely related to oilseed rape thus enabling results to be transferred between the two plants.

- Barley is a representative of the monocotyledenous plants, which also include all other cereals. It is very widespread above all in Germany (in addition to wheat) and therefore also of considerable interest to breeders.

• The third central concern of GABI, in addition to the establishment of a network of expertise and basic methodological and functional research on model plants, is to extend cooperation between industry and science and to expand existing contacts. Newly obtained findings on the plant genomes, their structure, function and expression should be directly reflected in the work of plant breeders and manufacturing industry. Commercial enterprises therefore have the opportunity of jointly implementing projects with research institutions concerning those plants which are characteristic of Central European agriculture and are of economic significance, and which, moreover, function as a model for research into important issues:

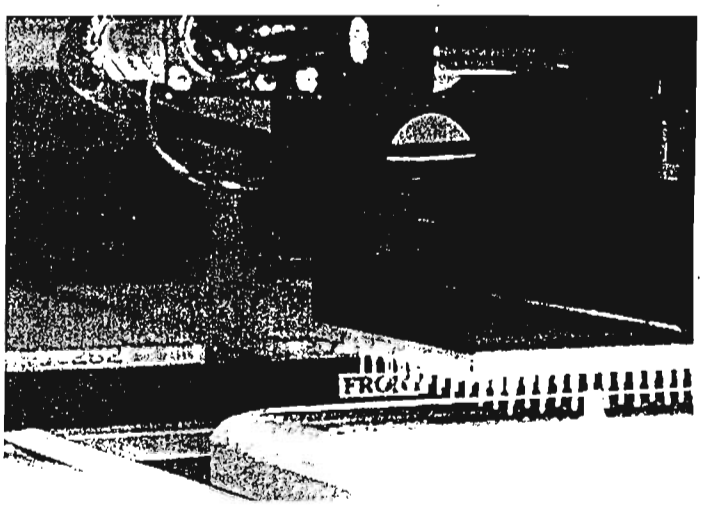
- Oilseed rape is the most significant oil plant in our latitudes and is also relatively closely related to Arabidopsis. It is therefore particularly suitable for verifying the transferability of the results obtained with the model plant Arabidopsis.



High-Density-Arrays

Arabidopsis thaliana

Maize



- As a significant fodder crop, maize is adapted to warmer climates. It is therefore especially suitable as a model for investigating cold tolerance phenomena.

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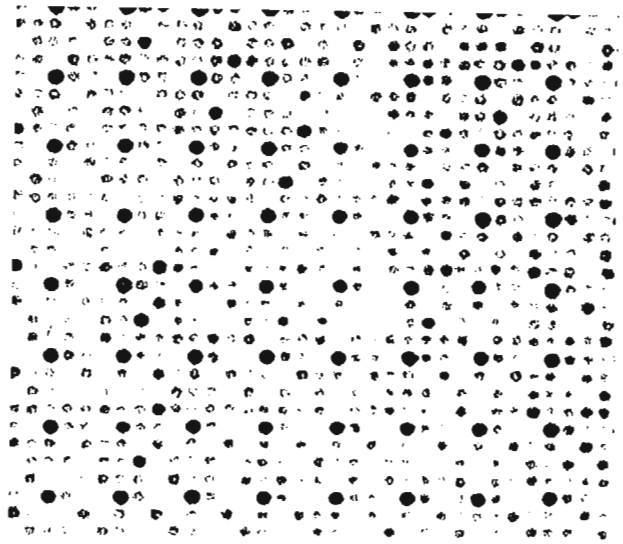
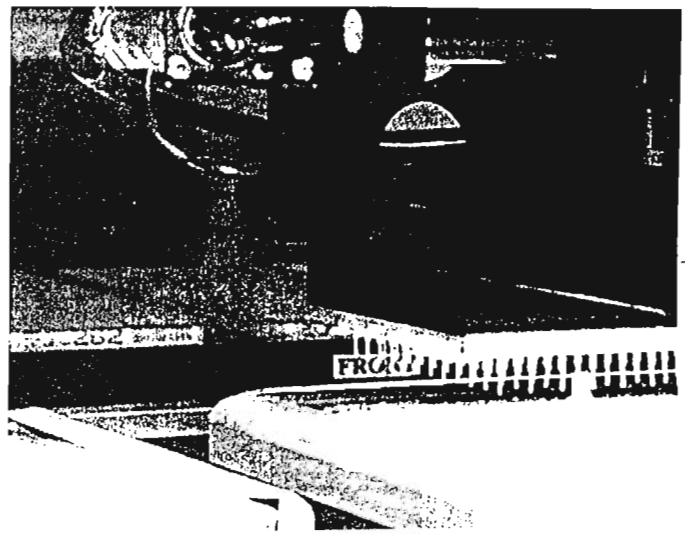
- Sugar beet is the most important tuber-forming plant in



High-Density-Arrays

Arabidopsis thaliana

Maize



- The working groups themselves have elected some of their number to form a scientific coordinating committee which ensures continuous harmonization and a continual exchange of information between the regular status seminars and thus contributes towards vitalizing the planned network of expertise.

- A quite essential prerequisite for the success of GABI and the competitiveness of German industry is protecting research findings in the form of protective rights and patents. BMBF recognized deficiencies concerning this aspect of German research funding several years ago and has already launched a corresponding patent initiative. With respect to GABI, decisive support is provided by the WPG through the establishment of a patent and licensing agency for GABI (PLA).The PLA is a core element of the technology transfer model tailored to the largely medium-sized enterprises in the plant breeding sector. Its mission is to ensure, by advisory services and active participation, comprehensive proprietary protection for research findings and the efficient conversion of research results into innovative technologies, products and services and thus to contribute to improving the competitiveness of German industry.

In a first tranche at the beginning of the year 2000, projects were approved concerning the above-mentioned topics which will be supported by the BMBF with a total of about DM 70 million. Further calls for proposals are planned, for which an overall financial volume of approximately DM 30 million per year is earmarked.

Further information on GABI can be obtained:
- at GABI's website (http://www.mips.biochem.mpg.de/proj/gabi/),
- at the project management's website (http://www.fz-juelich.de/beo),

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"BioMonitor" support programme in existence since 1997 was concluded by the BMBF in 1999 with the aim of replacing it by calls for proposals on biological safety research. The first call for proposals, "*Safety Research and Monitoring*" was published in the Federal Gazette in April 2000.

The aim of the new concept is to support safety research accompanying field tests with genetically modified plants and to develop methods for monitoring cultivation. This thus exclusively relates to the field of "*green genetic engineering*". On the basis of the new support concept, research projects are being funded on the following priority topics.

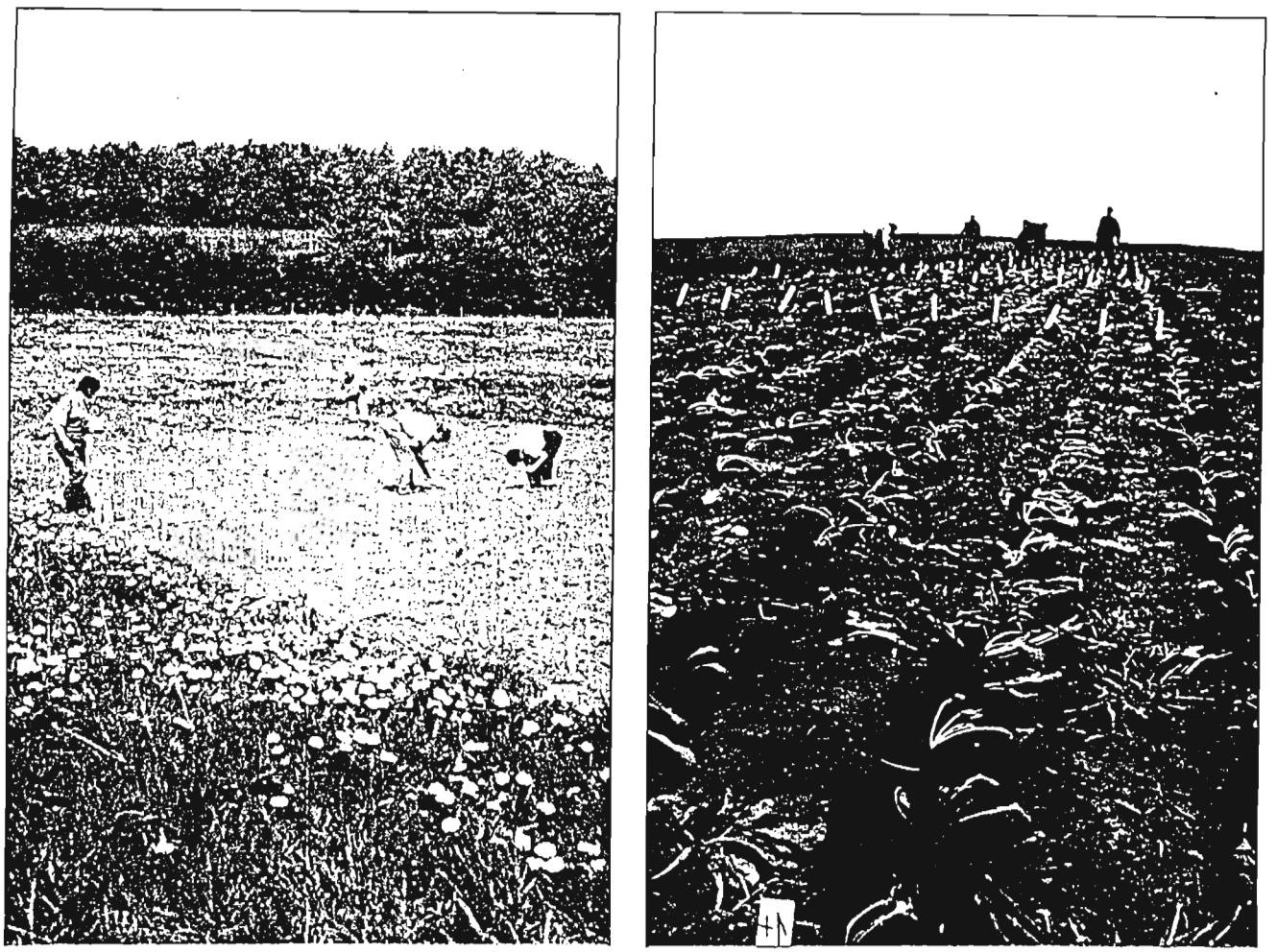
The priority topic "*Research Approaches for Safety Research Accompanying Environmental Releases*" is intended to investigate scientific issues accompanying field experiments with genetically modified plants which are of interest in connection with the genetic modifications or the specific crop species.

With respect to genetic modifications, work involves, amongst other aspects, developing strategies to make an active contribution to the safety of genetically modified plants. This can be achieved, for example, by delimiting the gene sequence to be transferred as closely as possible or by developing methods for restricting the dispersion capacity of genetically modified plants. There is a need for research concerning the development and standardization of procedures for identifying genes transferred by genetic engineering. Above all, there is an urgent need for detection procedures permitting large scale tests to monitor the behaviour of these genes and their fate in the environment. Furthermore, it is also planned to support research approaches concerning crop-specific issues. The research concepts will concern plants released in Germany or expected to be cultivated here. This includes oilseed rape, sugar beets, potatoes, maize, cereals and woody plants (timber, fruit plants, ornamental shrubs, and vines). In order to ensure that the support is specifically targeted at current research needs, concrete issues are formulated in the support concept to which funding is oriented. In many cases, an objective assessment of the impacts of genetically modified plants requires a comparison with conventionally bred plants and conventional methods. The research projects should therefore, whenever possible or relevant, include a comparison of genetically modified plants with nongenetically modified plants and with traditional agricultural techniques.

The development of genetically modified plants has now

Release experiment with genetically modified oil seed rape. In a research project the impact of wild bees on the transfer of pollen has been studied.

Photos: BBA Kleinmachnow



For example, extensive research has been performed at the Chair of Ecology at Aachen University of Technology since 1992 on the environmental release of genetically modified sugar beet with a genetically engineered resistance to the virus disease rhizomania. Photos: RWTH Aachen

progressed to such an extent that transgenic plants are expected to become commercially available in the near future and wide-scale cultivation in Europe is to be expected. With respect to this development, projects will be supported in the research priority "*Development of Methods for Cultivation Monitoring*" which will define proposals for optimum structures and models for establishing a monitoring network after genetically modified plants have become commercially available. Moreover, the needs and the possibilities will be assessed for developing central data documentation continuously recording results of experiments and studies with genetically modified plants.

The results of biological safety research represent an important basis for the activities of licensing and executive authorities and are of great significance for an appropriate and balanced public discussion on the topic of "green genetic engineering". The new support concept therefore envisages funding for a project on "*Communication Management in Biological Safety Research*", whose task involves communicating present and future results of biological safety research in the field of "green genetic engineering" to politicians, public officials and the general public, and to ensure the transparency and accessibility of data and information in this field. The tasks of this project also include support for the project coordinators of the research projects funded in summarizing and evaluating research findings and in organizing conferences and workshops. In doing so, the Federal Government hopes to make a contribution to the rapid implementation of research findings in political practice, to the transparency of findings for the general public and to objectifying the public debate in this field.

Examples from previous support:

Within the framework of research support for biological safety research in the field of "green genetic engineering", which has been in existence since 1987, work has been performed on issues including the ecological impacts of genetically modified sugar beet, potatoes, oilseed rape, maize and aspens in greenhouse and field experiments.

For example, extensive research has been performed at the Chair of Ecology at Aachen University of Technology since 1992 on the environmental release of genetically modified sugar beet with a genetically engineered resistance to the virus disease rhizomania. All previous studies within the framework of the support measure have indicated that no risks emanate from cultivating the genetically modified plants.

In a collaborative research project between the University of Rostock, the University of Oldenburg, the Federal Biological Research Centre for Agriculture and Forestry, Braunschweig, and the Federal Centre for Breeding Research on Cultivated Plants, Quedlinburg, studies have been performed on the ecological impacts of transgenic potato plants which produce the antibacterial active ingredient T4-lysozyme as a protection, in particular, against potato soft rot. To date, no negative impacts on the bacterial populations associated with the potato plants living in the soil have been identified in the field from the lysozyme produced in the plants and released in small quantities into the soil.

The only release experiment with genetically modified microorganisms to date in Germany was performed within the framework of a collaborative research project supervised by the University Bielefeld in 1995 and 1997 at two release sites in the north and south of Germany. The luminescent gene from a glow-worm was inserted by genetic engineering into the bacteria (Sinorhizobium meliloti) in order to label them and make them easy to identify. Previous longterm studies on the fate and ecological impacts of the bacteria lead one to assume that the impacts of relaese of genetically modified bacteria on other soil microorganisms can be regarded as slight. Nor was it possible to detect any transfer of the luminescent gene to other soil bacteria.

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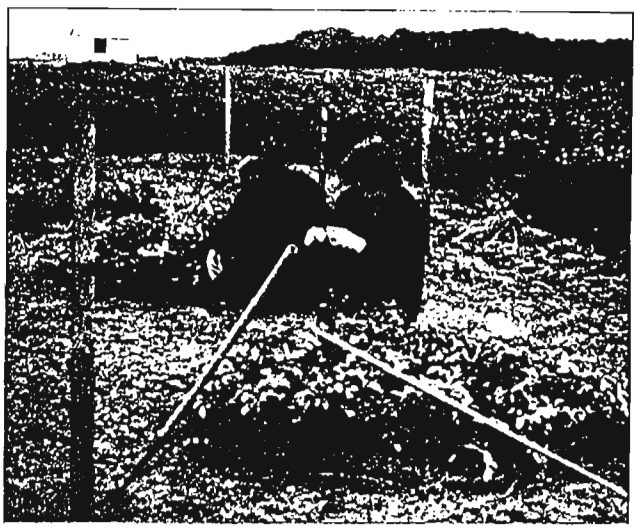

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Photo: University Rostock

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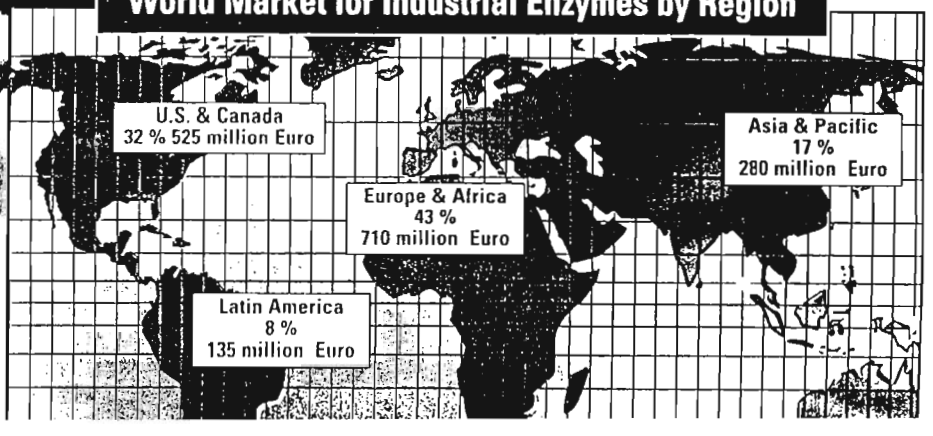
High-Tech Biology in the Service of Sustainable BioProduction

BMBF programme supports environmentally friendly biological technologies

The reorientation of the current economic system towards a sustainable approach is one of the central challenges of the 21st Century. This involves the long-term protection of the natural environment - air, water, land - on which the life of present and future generations depends. The development and implementation of a national sustainability strategy is a central goal of the German Federal Government.

As here at SunGene in Gatersleben (Saxony-Anhalt), researchers of the BASF Plant Science Division are working worldwide on making plants more resistant to cold and drought, achieving greater contents of oils, proteins and carbohydrates, or increasing the content of substances such as vitamins and healthy fatty acids.

World Market for Industrial Enzymes by Region



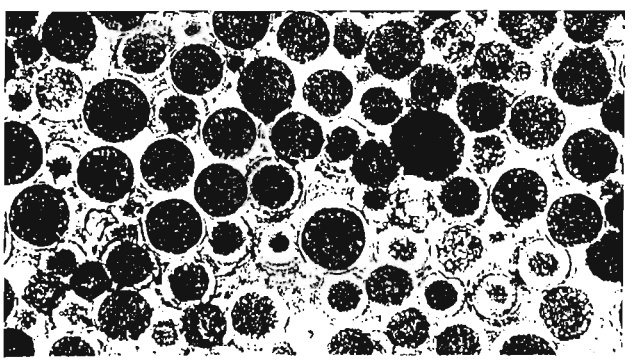
Modern biotechnological techniques can make an important contribution to achieving this goal. A separate chapter was therefore devoted to biotechnology in the Agenda 21 of the United Nations Conference and Development (UNCED) signed by more than 170 states in Rio de Janeiro in 1992.

In comparison to conventional chemical processes, biotechnological techniques offer a number of advantages:

- mild reaction conditions in an aqueous environment at room temperature,
- avoiding by-products and waste products as far as possible,
- high efficiency ensuring high yields with given amounts of raw material,
- production-integrated closed loops using biological residues and waste materials as raw material for making products.

Moreover, new products made possible only by modern biotechnological methods are increasingly entering the market. They include, for example, numerous new therapeutic agents on the basis of recombinant proteins.

The investigation and application of modern biotechnology is one of the reasons why site-specific aspects are taking on global significance. For many companies, the availability and application of biotechnological know-how will - in the foreseeable future - develop into a key competence in national and international competition.



The microalga Haematococcus pluvialis under the microscope. Under conditions of mass production and in a completely carbon-dioxide-neutral manner, alga can be used to produce valuable substances for the chemical, pharmaceutical and food industry, including vitamins and dyes, amino acids and antibiotics.

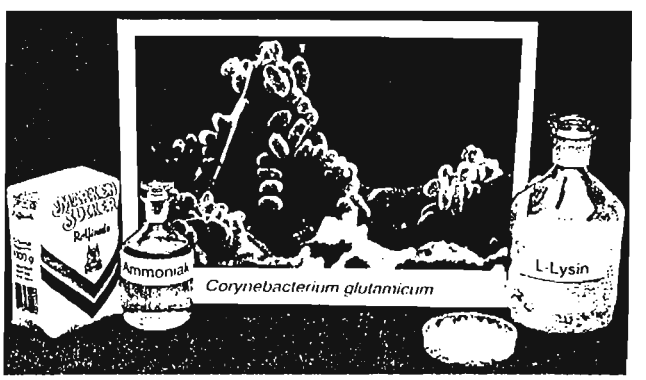
The amino acid L-lysine can be produced with the aid of genetically modified strains of Corynebacterium glutamicum using glucose and ammonia as the carbon and nitrogen sources, respectively. Sufficient quantities of this amino acid are necessary for growth and the functioning of the immune system, especially in the case of children. The rapidly growing soil bacterium Corynebacterium glutamicum was discovered in Japan in the fifties as a natural producer of glutamic acid. It is now used industrially to produce this and other amino acids.

Scientists are continually developing new methods of producing industrially interesting enzymes. These are biocatalysts which in nature ensure smooth functioning of the metabolism in the cell.

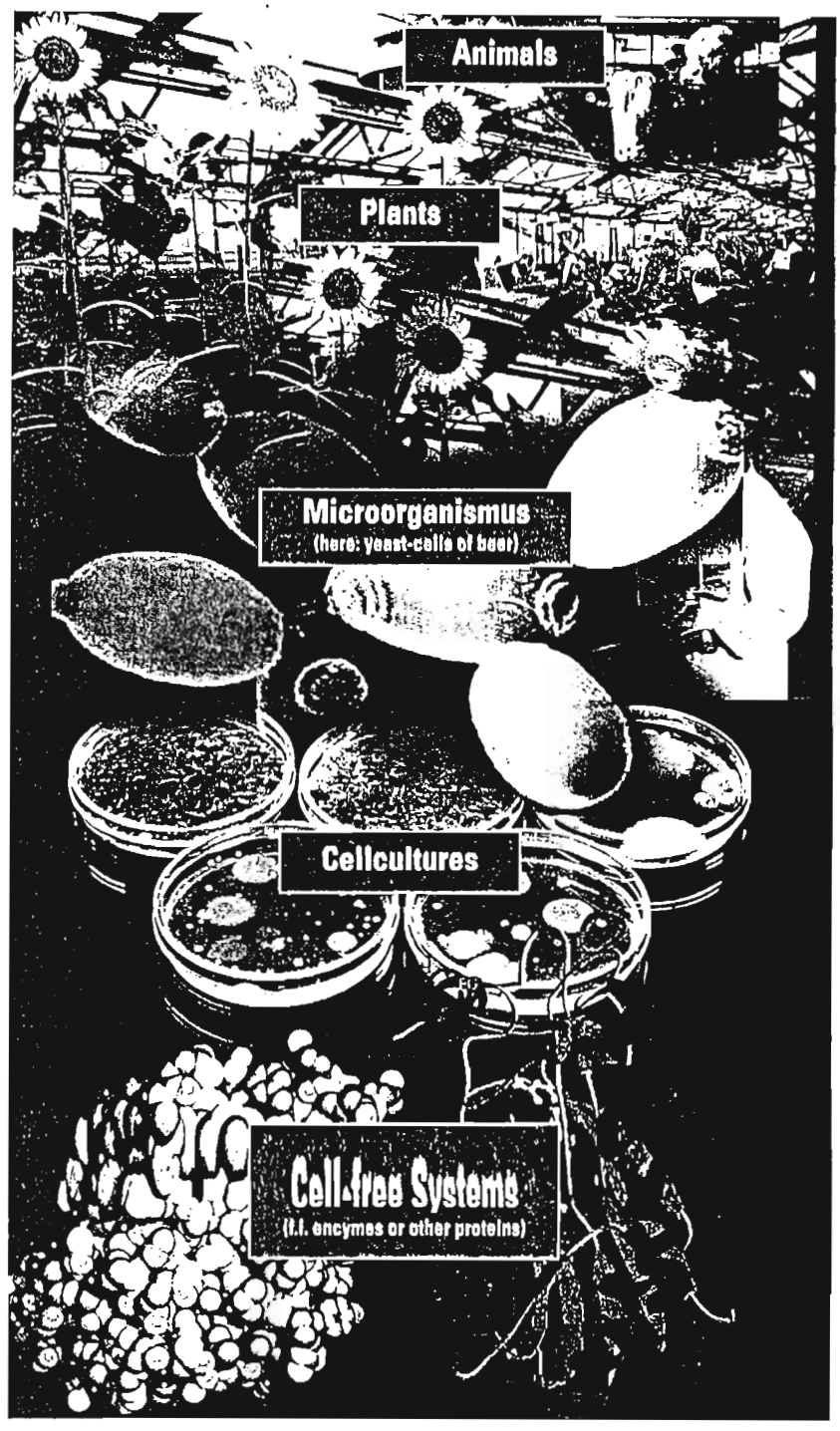
New Funding Programme

The "Sustainable BioProduction" funding programme of the Federal Ministry of Education and Research (BMBF) will enable companies, in particular small and medium-sized enterprises, to participate in advanced developments and to contribute towards securing the future competitiveness of German industry. This programme is specifically addressed to the sectors of chemistry and pharmaceuticals, food and beverages, paper and pulp, as well as textiles and leather.

The aim of the support programme is to convert biotechnological know-how into new environmentally acceptable and resource-conserving production methods, products and relevant services.



Biotechnological Production and Transformation Systems



It will be possible to utilize biological processes under industrial conditions with the aid of innovative biotechnological approaches such as the modelling of metabolic pathways, evolutive enzyme design, metabolic flux analyses and modern biochemical engineering approaches. Isolated biocatalysts (enzymes), cell cultures, microorganisms and higher organisms can, for example, be taken into consideration as biological production or transformation systems.

New Prospects

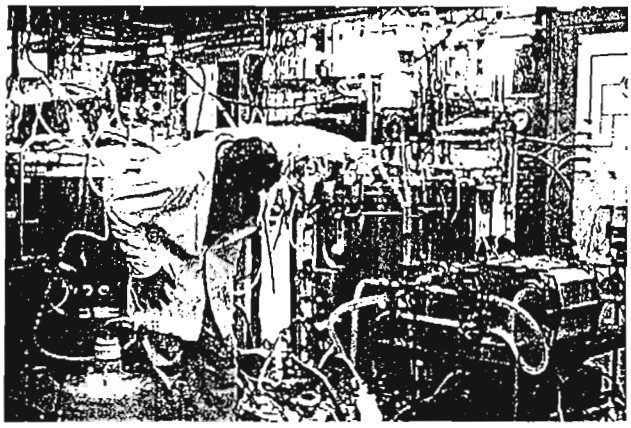
The enormous scientific progress made in the life sciences in the past few years, especially by genome research, is opening up completely new prospects for industrial application of biotechnological methods. Innovative approaches, such as the modelling of metabolic pathways, evolutive enzyme design, metabolic flux analyses and new biochemical engineering appro-

Objectives

The BMBF intends to support projects with the following objectives:

1. Replacement of existing, conventional industrial methods by environmentally friendly biotech processes, for example in

- the production of industrial foodstock chemicals

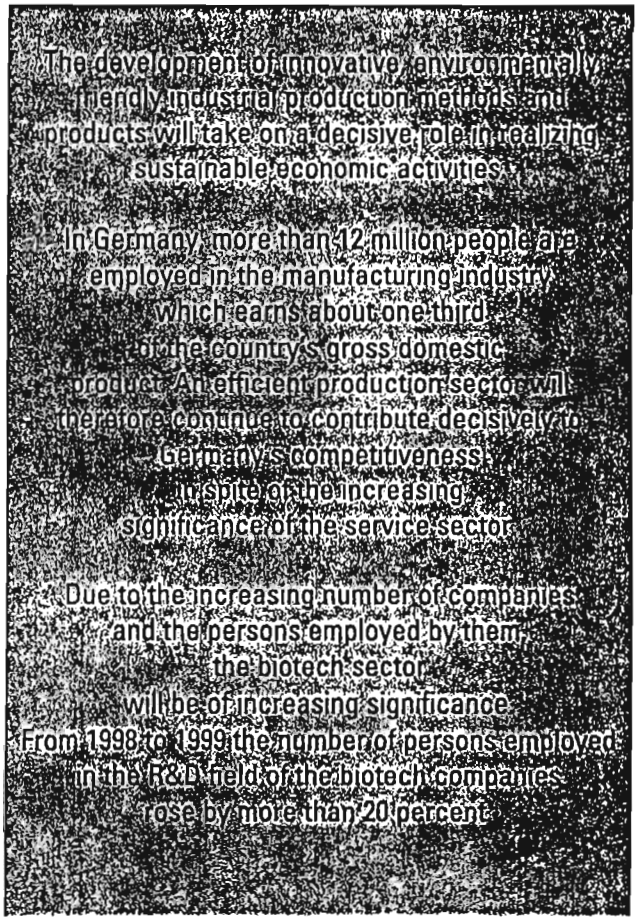


Bioreactor for growing cell cultures. (The photograph shows a 3500-l reactor in the pilot-scale bioengineering facility of the National Research Centre for Biotechnology in Braunschweig.)

2. Development of efficient, environmentally friendly and resource-conserving methods for the production of new active ingredients, materials and products, for example, of

- proteins and nucleic acids for therapeutic applications, vaccines and antibiotics,
- environmentally compatible high-tech biomaterials,
- textiles and foodstuffs with new properties.

Accompanying studies in close cooperation with the companies supported will increase knowledge on the conditions for sustainable bioproduction. These studies should also accelerate the development of a set of instruments applicable in practice for assessing sustainable biotechnological approaches for industry and society. The analysis of material flows will play a decisive role here.



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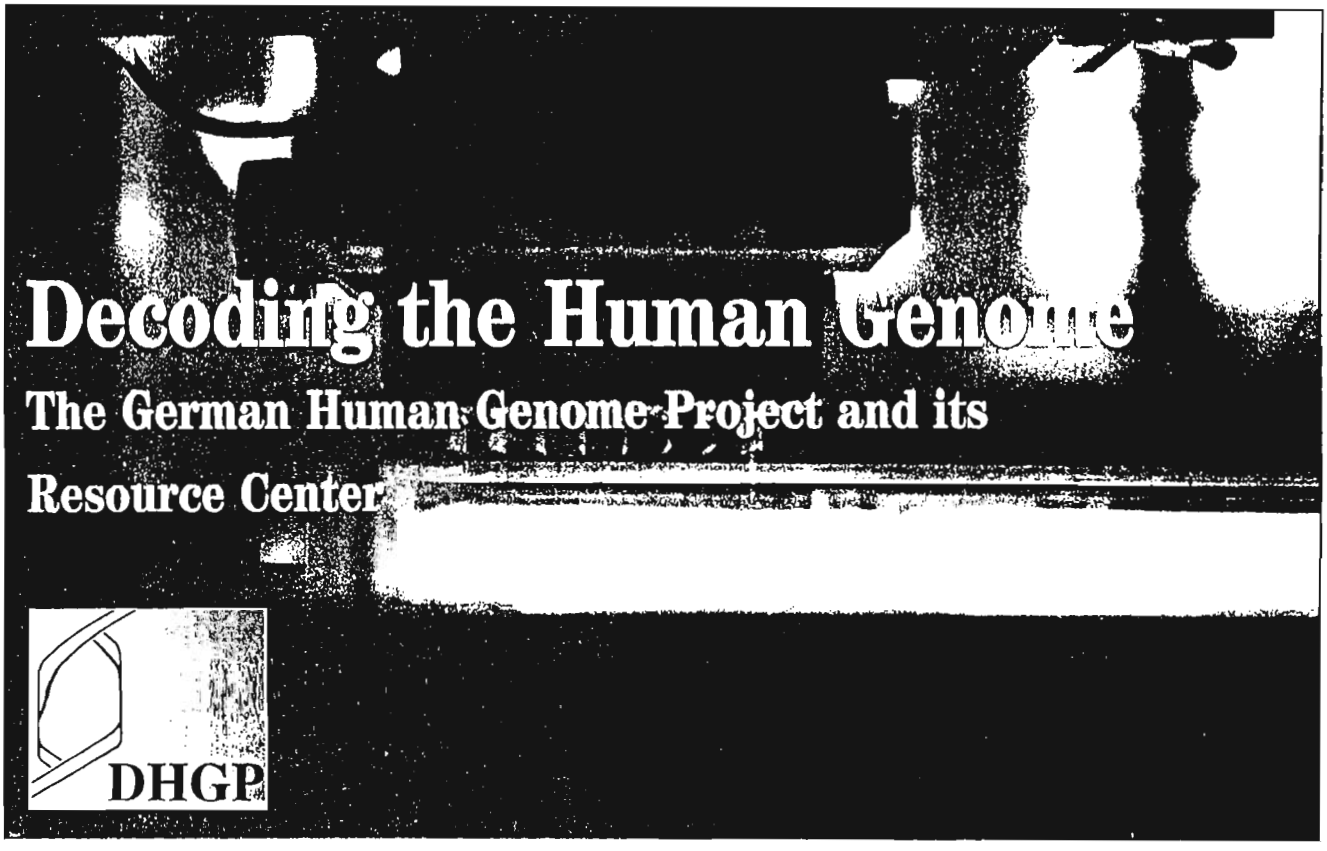
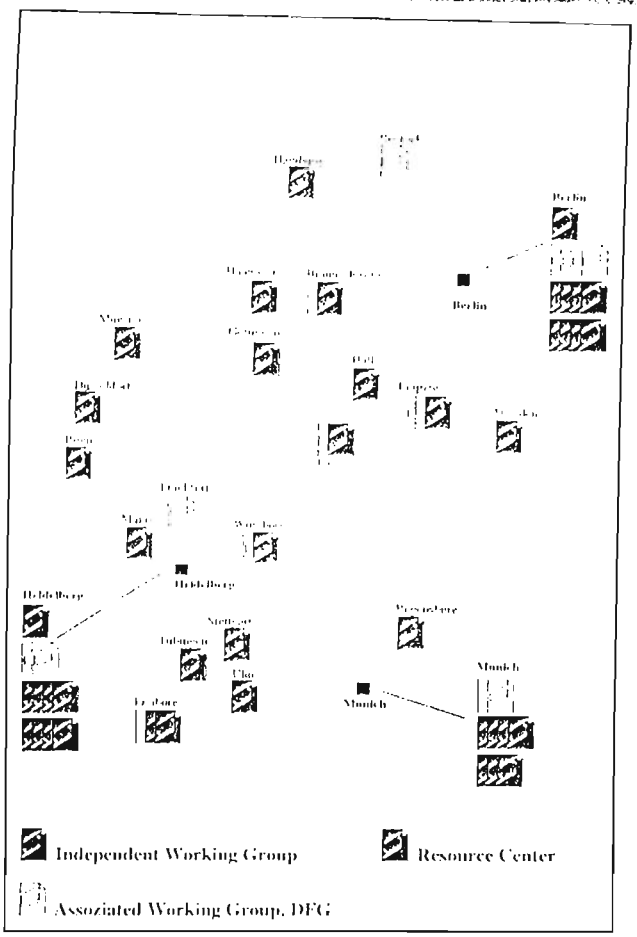


Research activities relating to the decoding of the human genome have become an increasingly importend for the development of advanced diagnostic and therapeutic methods as well as with for the creation of new pharmaceutical products.

The aim of the Human Genome Project is the determination of the complete nucleotide sequence of human DNA with its 3 billion modules as well as the identification of the all genes constituting the basic set of inherited "instructions" for the development and functioning of a human being.

This comprehensive analysis of the human genome will diseases. In June 1995, Germany joined the global efforts of this large-scale project started in 1990. Integrated in the internationally coordinated scheme, scientists of the German Human Genome Project (DHGP) have contributed significantly to the characterization and functional analysis of the human genome. In cooperation the two central infrastructure facilities, Resource Center (RZPD) and Patent and Licensing Agency (PLA), the 42 research projects currently realized are the core of the DHGP, which is funded by the Federal Ministry of Education and Research (bmb+f) with approx. DM 44 mill. per year. In addition



Geographical distibution of the DHGP research projects

cellular and physiological relevance of gene products in model organisms such as mouse, rat and zebrafish as well as on the sequencing of the human genome and the relatedtechnological development. DHGP research teams have substantially contributed to the sequencing of chromosomes X, 7, 11, and 21, and also to the development of advanced methods of automating routine processes .

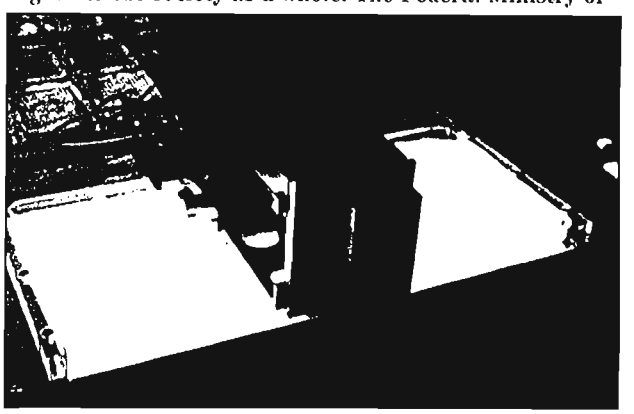
A Japanese-German cooperation has yielded the complete sequence of chromosome 21 being published in March 2000. Further chromosomes will follow soon. A provisional "working draft" of the total human genome will be produced by early summer of 2000.

The projects of DHGP's second phase started in 2000, are clearly more targeted towards applied research projects. In particular, the interaction of genes and their products as well as studies with regard to different pre-dispositions to delicate health and the varying effectiveness of drugs due to genetic differences are moving in the center of attention. Right from the beginning, the DHGP has attached great importance to economic exploitation of the research findings. The pharmaceutical industry as well as start-up enterprises have been integrated in the project by the "Verein zur Förderung der Humangenomforschung e.V." in terms of structural background and financial situation. The protection of the results in terms of intellectual property and their exploitation is carried out directly via DHGP's Patent and Licensing Agency. The successes of this alliance is efficient:

- 20 technology and process patents as well as 280 patents for genes have been either issued or applied for.
- Genome research under DHGP has led to 9 business start-ups in Germany having created 200 qualified jobs – and the situation is taking an upward trend.

However rapid development within genome research however also implies far-reaching social issues. Many of the new possibilities gained by the discoveries and technologi

cal advances achieved require a careful regulation with regard to the society as a whole. The Federal Ministry of



Picking robot transfering DNA clones from culture plates into storage boxes

Education and Research therefore suggest conferences and research projects relating for the ethical issues of genome research (currently 8 projects are being with the total amount of 3 DM mill). The results from these projects will help to establish supporting measures covering genetic diagnosis and advice in the frame of regular medical care as well as in terms of the relevant jurisdiction to be adjusted accordingly.

The Resource Center

Corresponding with the start of the German Human Genome Project, in 1995 the Resource Center as its central infrastructural unit, was founded. In this facility the source material for carrying out genome research is generated and provided to interested research teams. In addition, its Primary Database where all data produced by the DHGP projects are stored, is open to the public and thus serves as a platform for the interchange of results.

The generation of material and the collection of data lead to valuable synergy effects whicht are of great advantage to the different research projects.

Furthermore, the Resource Center develops effective methods and technologies in order to support research activities in the field of molecular biology. In this connection, the Resource Center assists above all the DHGP research teams, but also provides its services for scientists of academic facilities and industrial enterprises worldwide.

The application of highly advanced automation technologies facilitates the generation of products at an industrial level as well as the realization of larg-scale projects (see table 1).

Most of the material generated at the Resource Center is based on gene libraries (fragments/clones of the genetic information systematically put into archives) that have been either produced on the spot or imported by other research teams. In total, approx. 16 million clones of more than 25 different organisms, stored in 136 genomic and 194 cDNA libraries (genetic information transmitted through the design of the proteins) , are available. By

Key data of the Resource Center

Contacts

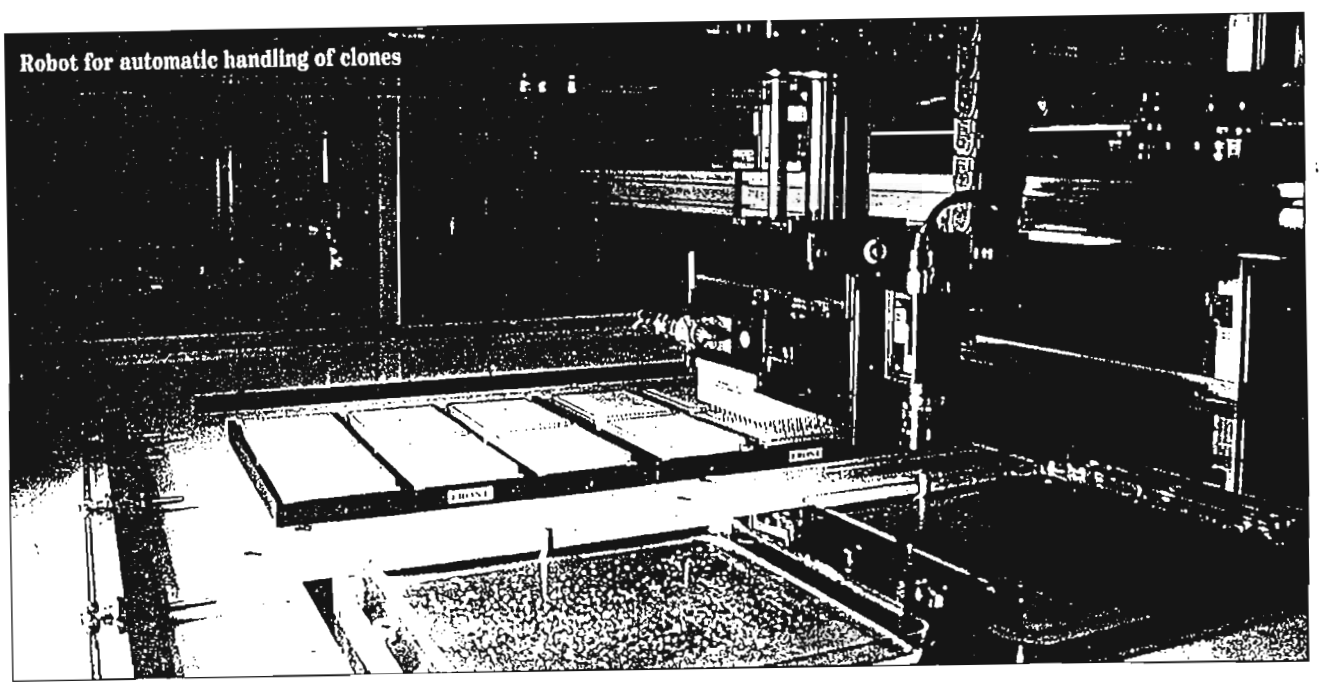
registered customers	6.000
registered institutions	1.450
international	ca. 50 %

Database

sequences	1.800.000
generated by DHGP	41.000
results of hybridisation	25.000
in situ images	500

Distributed products since set-up

distributed filters	50.000
distributed DNA pools	84.000
distributed clones	130.000



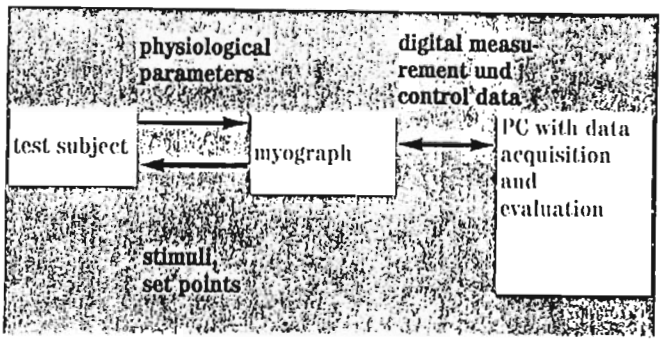
Robot for automatic handling of clones

pharmacopoeias thus saving about 20 000 guinea pigs and mice per year.

In close cooperation with other partners, Heraeus Instruments GmbH (Osterode branch) succeeded in completely replacing the in vivo production of monoclonal antibodies in mice by *in vitro* production in a bioreactor. This bioreactor, known affectionately to the scientists as the "glass mouse", has already replaced the living mouse as a medium for the production of antibodies for many years.

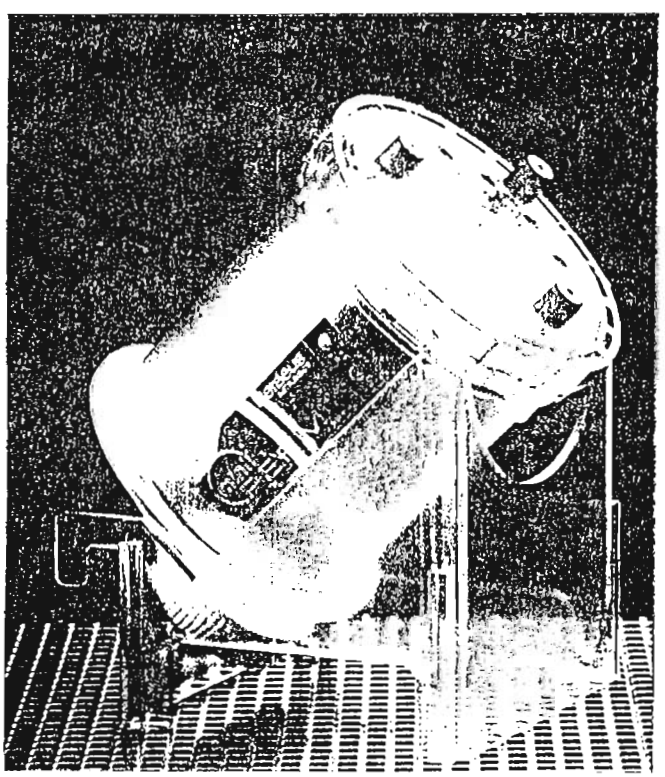
In a project by Wolfgang Kuck Medizin-Elektronik, a myograph system was developed to replace the "classical frog experiments" in practical physiology courses. The instrument permits students to perform all experiments in the nerve/muscles field on themselves without pain, damage or invasive operations. The electronic measuring technique applied is better able to record undistorted contraction sequences than the systems previously used for studies on frog muscles. The results achieved with the myograph are not only a replacement for experiments with isolated frog muscles, but they are also much more extensive and serve to reinforce the course content.

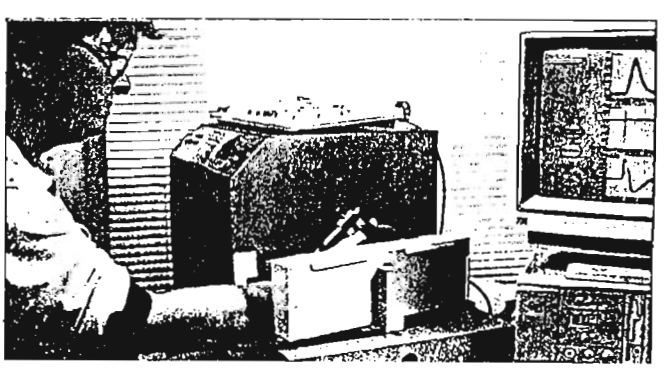
The project leaders of the working groups involved at Kuck Medizin-Elektronik GmbH and the University of Frankfurt were awarded the Felix Wankel Animal Wellfare Research Prize for this development in December 1997.



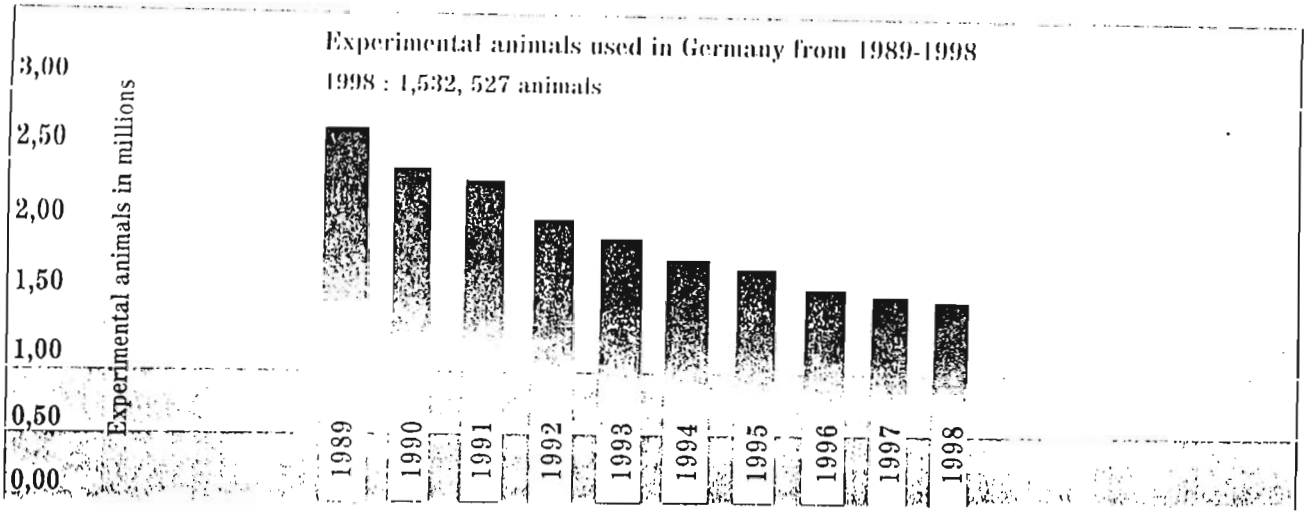
Myograph system

"Glass mouse"





The myograph developed by Kuck Medizin-Elektronik GmbH and the University of Frankfurt with support from the BMBF enables students in practical physiology courses to perform all experiments concerning muscles and nerves physiology painlessly on themselves by means of a computer-controlled measuring and recording system (MYOLogos).
(Photograph: Kuck Medizin-Elektronik GmbH)



Number of Animal Experiments in Germany 1989-1998

The number of animal experiments in Germany has been reduced by about 40 % from 1989 to 1998 (see fig.).

Development of the Research Priority

From 1980 to 1999, a total of 226 research projects were supported in the framework of this support measure and funds of DM 143 million expended. At present, DM 9.5 million is made available annually by the BMBF for this research priority alone (see fig.).

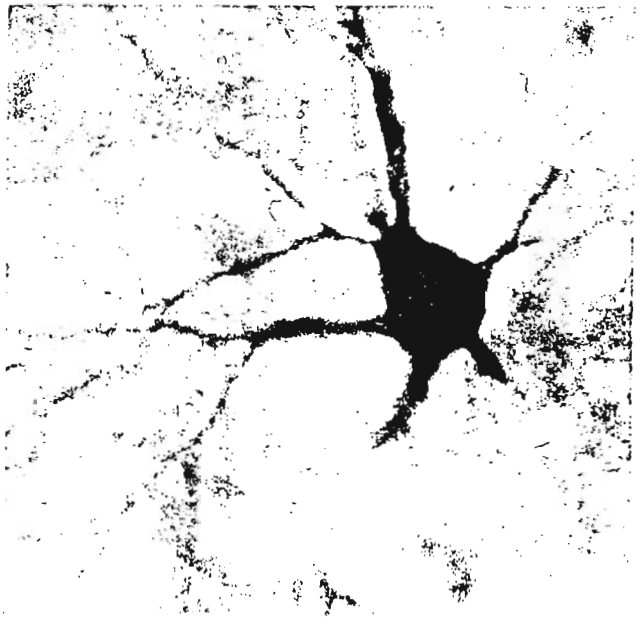
Outlook

The aim of the research priority on "Methods Replacing Animal Experiments" is to support sustainably the development discussed above and thus to contribute to a further reduction of animal experiments in research and development in Germany.

Neuronal Cell Culture

The figure shows a labelled neuron from a rat brain. Visualization was performed with an antibody isolated from the yolk of eggs from immunized chickens. The antibody is directed against cholecystokinin (CCK-8). These methods are alternatives in the sense of the 3-R concept (replacement, reduction, refinement). The studies were undertaken by Dr. R. Schade in cooperation with Prof. Hörtnagl and collagues.

Photograph: Medical Faculty (Charité), Institute of Pharmacology and Toxicology, Berlin



Supplementary Information

1. Animal Protection Report 1999: "Report on the Status of the Development of Animal Protection", German Bundestag, 14th Parliamentary Term, printed paper 14/600 (in German)
2. Announcement of the support guidelines "Methods Replacing Animal Experiments" in the "Biotechnology 2000 programme of the Federal Government of 17 June 1998, Federal Gazette no. 117, p. 9051

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Re example 3: Heraeus Instruments GmbH, Zweigniederlassung Osterode, Am Kalkberg, 37520 Osterode

Re example 4: Fa. Kuck Medizin-Elektronik GmbH, Schönfeldstraße 15, 83022 Rosenheim

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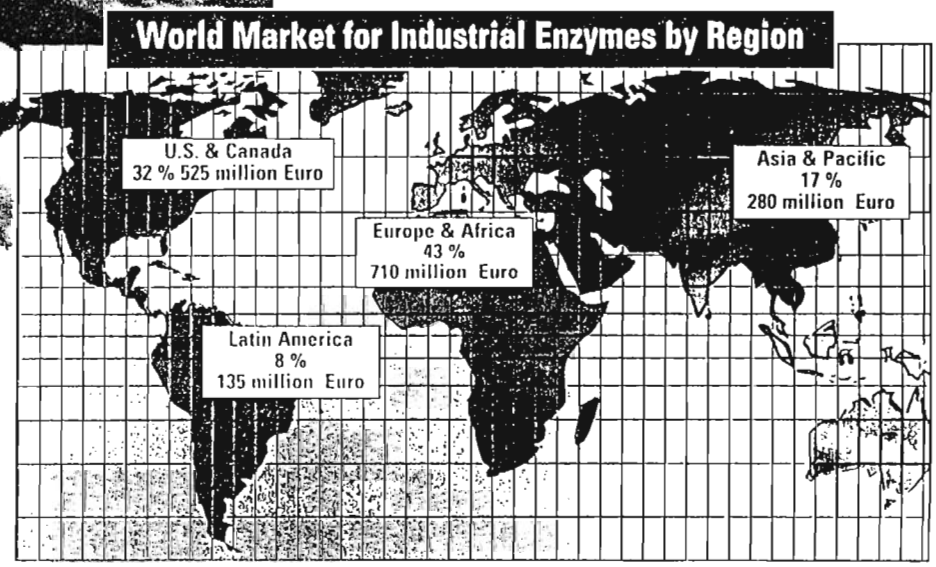
As here at SunGene in Gatersleben (Saxony-Anhalt), researchers of the BASF Plant Science Division are working worldwide on making plants more resistant to cold and drought, achieving greater contents of oils, proteins and carbohydrates, or increasing the content of substances such as vitamins and healthy fatty acids

High-Tech Biology in the Service of Sustainable BioProduction

BMBF programme supports environmentally friendly biological technologies

The reorientation of the current economic system towards a sustainable approach is one of the central challenges of the 21st Century. This involves the long-term protection of the natural environment - air, water, land - on which the life of present and future generations depends. The development and implementation of a national sustainability strategy is a central goal of the German Federal Government.



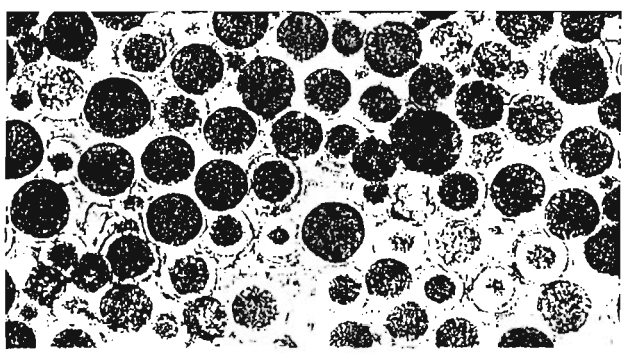
Modern biotechnological techniques can make an important contribution to achieving this goal. A separate chapter was therefore devoted to biotechnology in the Agenda 21 of the United Nations Conference and Development (UNCED) signed by more than 170 states in Rio de Janeiro in 1992.

In comparison to conventional chemical processes, biotechnological techniques offer a number of advantages:

- mild reaction conditions in an aqueous environment at room temperature,
- avoiding by-products and waste products as far as possible,
- high efficiency ensuring high yields with given amounts of raw material,
- production-integrated closed loops using biological residues and waste materials as raw material for making products.

Moreover, new products made possible only by modern biotechnological methods are increasingly entering the market. They include, for example, numerous new therapeutic agents on the basis of recombinant proteins.

The investigation and application of modern biotechnology is one of the reasons why site-specific aspects are taking on global significance. For many companies, the availability and application of biotechnological know-how will - in the foreseeable future - develop into a key competence in national and international competition.



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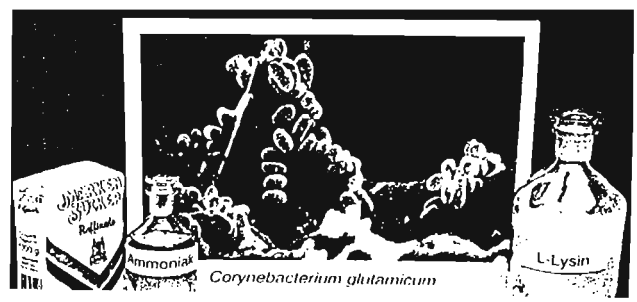

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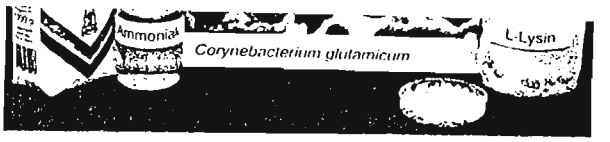
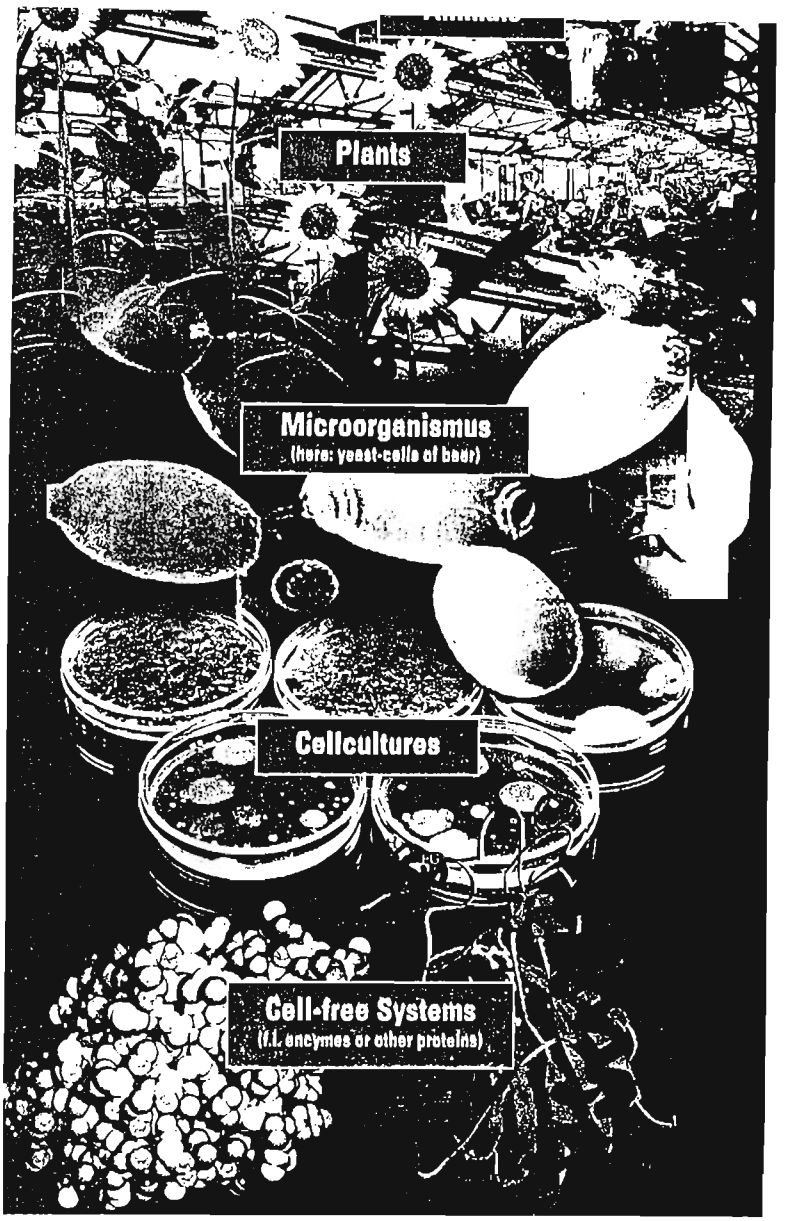


Production and Transformation Systems



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New Prospects

The enormous scientific progress made in the life sciences in the past few years, especially by genome research, is opening up completely new prospects for industrial application of biotechnological methods. Innovative approaches, such as the modelling of metabolic pathways, evolutive enzyme design, metabolic flux analyses and new biochemical engineering approaches will be technically harnessed in interdisciplinary working groups from science and industry and realized in practice on the basis of concrete examples under economically competitive conditions.

Objectives

The BMBF intends to support projects with the following objectives:

1. Replacement of existing, conventional industrial methods by environmentally friendly biotech processes, for example in
   - the production of industrial feedstock chemicals and fine chemicals, polymers and biocatalysts,
   - the treatment of cellulose fibres, removal of printing in the paper industry,
   - the surface modification of textile fibres.

Analytical services

Ecophysiological Examination

To properly understand microbial processes in environmenta samples, it is often necessary to analyze the biogeochemica transformations which occur. With our experience in basic scientific research and analysis of biochemical parameters, Nadicom is also ir this area a reliable partner.

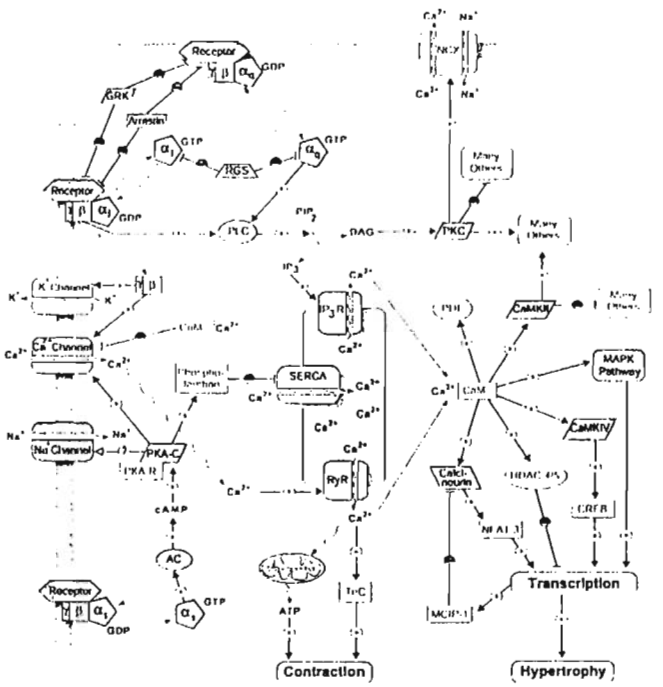
We offer the following analytical methods:

- Gas Chromatography:
  - Detection of principle atmospheric gases (N_2, O_2, CO_2) and trace gases (including CH_4, CO, H_2, N_2O, NO_x)
  - Analysis of organic acids

- HPLC:
  - Analysis of organic acids
  - Cation and anion analysis
  - Protein analysis (alternatively we also offer MALDI-TOF analysis)

- Isotopic analysis:
  - Use of stable isotopes and radioactive isotopes to examine biogeochemical pathways
  - Detection of stable isotopes and radioisotopes by GC, HPLC und IR-GCMS

- Fermentation measurement according to DIN 38414 with a Eudiometer



The computerization of metabolic pathways (here a section of the pathway of calcium) is the aim of systems biologists.

and/or the function of these molecular components of a biological system. This is true at the level of genes and the corresponding proteins, which, as so-called players of the cells, are responsible for nearly all life processes. This knowledge in particular is an essential key to the understanding of the basis of life. The focus is on two questions: How do the innumerable, individual components of the cell of an organism interact, and what controls their interaction?

To interpret the existing data, one will have to proceed from the analysis of individual components of biological systems to a holistic systems understanding. A prerequisite for this provides the interdisciplinary cooperation of many research disciplines (including biology, chemistry, medicine, computer science, mathematics, systems and engineering sciences). The single steps range from understanding the interaction of molecular cell components to an understanding of biological processes and their regulation and control to the systematic influencing of defined processes.

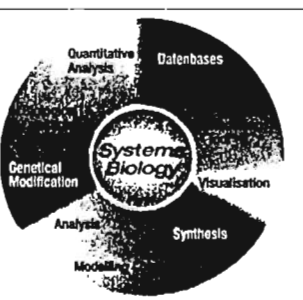
For this purpose, experimental, quantitative data is collected in order to develop reality-based models of physiological processes of biological systems and to simulate these in the computer, i.e. *in silico*.

The possibility of modelling and/or simulating life processes on the computer promises interesting applications in research and industry. Computer experiments on "virtual cells" could lead to new knowledge quickly and inexpensively. Medical drugs could be developed faster and at a lower cost. In addition, the number of animal experiments could be reduced drastically as side effects could be predicted with the aid of the virtual model.

A call for proposals for the new funding priority "Systems of life – systems biology" was therefore made in December 2001 under the programme of the Federal Government "Biotechnology – using and shaping its opportunities". For the first funding period, € 50 million are to be made available over a period of five years.

WHAT IS SYSTEMS BIOLOGY? (DEFINITION)

Systems biology characterises a holistic approach, that aims to study biological processes at the systems level. To achieve this goal, it is necessary to analyse the complicated networks that produce the complex functionality. The step from the qualitative, descriptive approach to quantitative biology is to be taken in this way. Mathematical modelling is an essential tool for a theory-based approach, and the different levels of understanding of the biological system can only be linked successfully by means of interdisciplinary cooperation between all branches of the natural sciences.



Remediation of contaminated sites

without the need to remove superstructures

Harborth, Peter; Kucklick, Martin and Hanert, Hans Helmut

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A. Ecological principles of in situ bioremediation

Principles

In their natural biotopes in "soil" and "ground water", microorganisms are in an almost permanent state of vegetative dormancy, in which growth is either at a complete stand still or is very slow indeed (see Fig. left). The reason is the extremely low nutrient concentration - often only around 10 µg/l - found in their natural habitat, which is about one million times lower than in a typical laboratory nutrient medium (E_1 in Fig. left, electron donor) with a nutrient concentration of approximately 20,000,000 µg/l. A state of dormancy is reached in the ecosystem following a period of starvation during which most of the bacteria die, leaving only 1 to 0.1‰ of the bacteria still viable (Fig. centre left shows a section of the death phase).

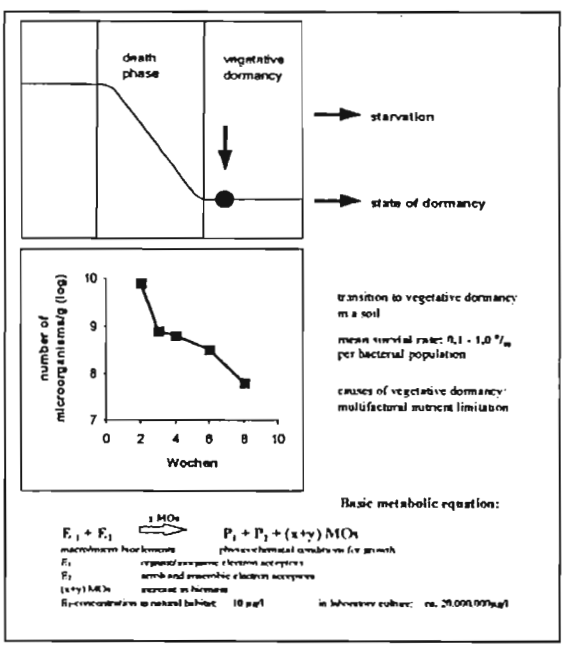
Vegetative dormancy is the source of microbial diversity in natural soils. Since one gram of soil is known to contain between 1000 and 10000 individuals of a particular species of bacteria in a state of dormancy, and to produce a total cell count of between 10^7 and 10^8, it can be deduced that the same amount of soil is home to between 1000 and 10000 different species of bacteria, each with its own specific metabolic potential. Thus, soil contains a latent microbial biocoenosis of considerable diversity and potential for degrading a wide range of compounds by way of a kind of microbial "division of labour".

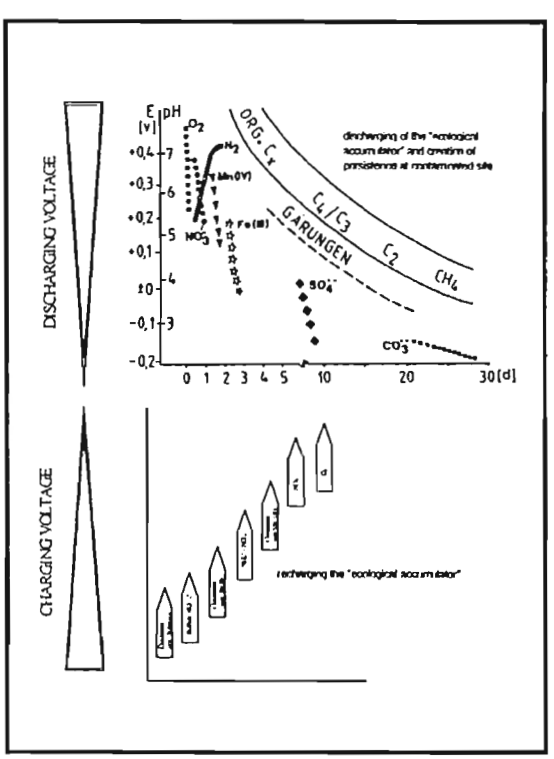
The way persistency of a contaminated site arises corresponds to the discharge process of an electric accumulator. A contaminated site is a kind of "ecological battery" in which the individual, serially connected cells (E_2 substances ≙ electron acceptors ≙ oxidation agent) havebeen run down and discharged (chemically reduced) (Fig. top right). Metabolic activity is virtually at a stand still, not because the limits of microbial degradation ability have been reached, or because of deficiencies in the microbial biocoenosis, but because the site's
"ecological accumulator" has run down and discharged under conditions where the contaminating nutrients have overloaded the soil.

The principle of ecological bioremediation is derived from this basic ecological understanding of contaminant persistence: the ecological accumulator, with its individual cells, needs to be recharged, the exhausted electron acceptors regenerated. Measures that do this put an end to vegetative dormancy and the metabolic standstill, and to the persistence of the contaminating chemicals.

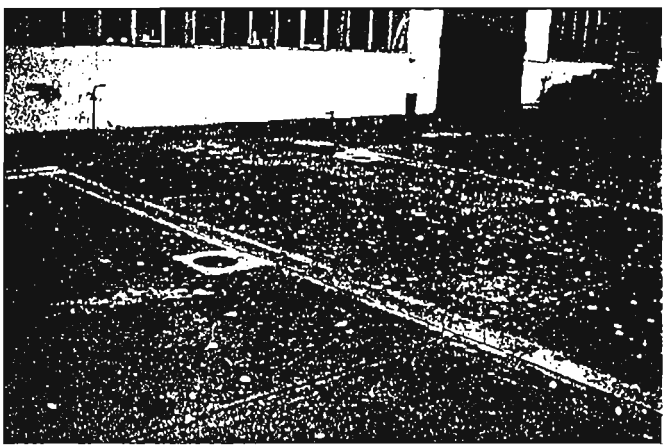
In the top right of the figure the individual microbial processes involved in recharging the ecological battery are illustrated. The electron acceptors, carbonate, sulphate, Iron(III), Manganese(IV) and Nitrate are regenerated from their reduced states by microbial action. Atmospheric oxygen is introduced and the electron acceptors essential for bioremediation are oxidatively reconstituted. The electron acceptors, having been consumed through reductive processes during the establishment of contaminant persistency, are now subjected to oxidative regeneration.

The technical measures employed in bioremediation have the purpose of inducing these oxidative processes and eventually restoring the site to its naturally charged and uncontaminated state.



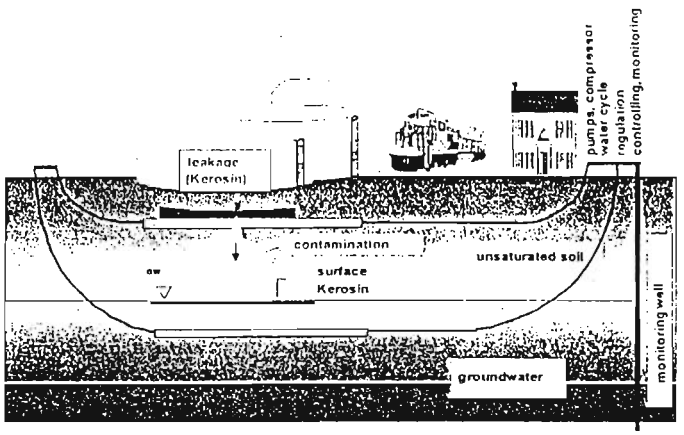


Three innovative methods of in situ bioremediation (recharging the ecological accumulator)



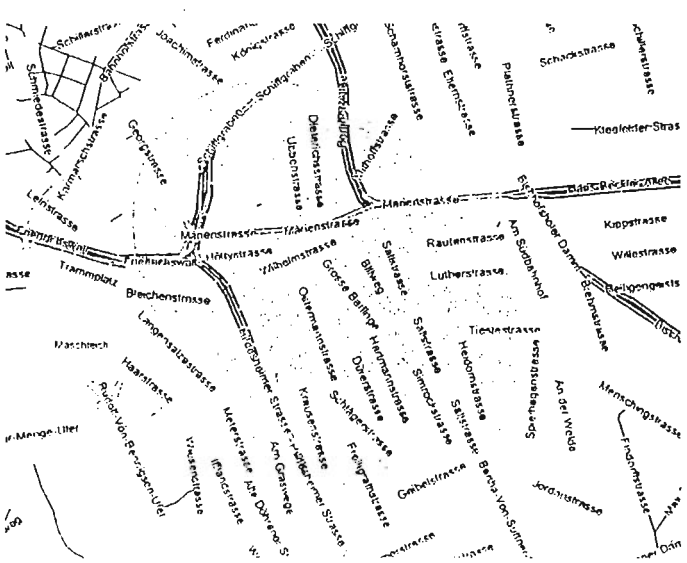
1. Circular horizontal slow sand filter (CHS)

This method creates a closed circuit of slowly flowing ground water between a central extraction well and five peripheral injection wells with a radius of up to 10 m. The amount of injected water is adjusted so as not to cause the ground water to rise by more than a few centimetres (<10 cm), thus leaving the natural ground water level virtually unaltered. The water extracted from the central well is not decontaminated above ground. Instead it has electron acceptors added to it before being reinjected through the peripheral wells. The illustration on the left of the figure shows a special instance of this method at the site of a chemical plant (CHC/BTEX contamination). The extraction wells, injection wells and supply conduits are laid underground and form a closed circuit. The chemical plant can remain fully operational during the course of remediation.



2. Circular vertical slow sand filter (sandwich method)

This method involves the in situ treatment of contaminated soil in the saturated and unsaturated zones between two filter levels located one above the other. Structures and operations on the contaminated site can remain in place and are unaffected during the course of remediation. Treatment involves the alternating injection and extraction of air and passing nutrient solution for the microbial biocoenosis between the two filter levels (Fig. centre left). In this way biodegradation of the contaminants can be activated without destroying soil structure. This method imitates the natural flow of materials with the same vertical seepage that resulted in the initial contamination. Compared with the bio-venting method for the unsaturated soil zone (vertical infiltration and extraction wells, horizontal subterranean infiltration facilitates the supply of nutrients for the site biocoenosis over a horizontally extensive area



3. Laminar drift slow sand filter (FRAM method)

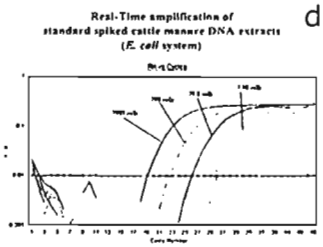
This method, which is suitable for the decontamination of very extensive or built-up areas, particularly in cities, does not involve setting up subterranean circulation and on-site decontamination plants. No pipes are laid and no contaminated ground water is extracted. The biocoenosis of the contaminated soil is supplied with the necessary nutrients by the natural flow of ground water in the aquifer (moving at the rate of 30 - 100 m/a) and by transversal diffusion. Nutrients are injected into the aquifer upstream from the contamination. At parallel point lying across the direction of ground-water flow injection wells are through which the nutrients are injected in such a fashion that in a set amount of time the whole contaminated area is adequately supplied through ground water drift. We also refer to this as the FRAM method, since it corresponds to the way the Norwegian, Fridjof Nansen, allowed his research ship FRAM, to drift in the pack ice of the Arctic Ocean last century.

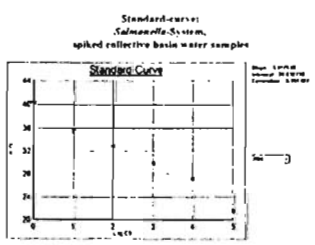
Detection of potentially pathogenic microorganisms

Quantitative real-time-PCR is the best method for the rapid detection of potentially pathogenic microorganisms. By using DNA oligonucleotide primer/probe combinations which are developed to specifically target particular pathogens, Nadicom is able to detect the following microbial groups in water samples:

- *Bacillus cereus* Group (contains *Bacillus anthracis*, *B. cereus*, *B. thuringiensis*, *B. mycoides)*
- Thermophilic *Campylobacter* species: *Campylobacter jejuni*, *C. upsaliensis*, *C. coli*, *C. lari*
- *Escherichia coli*, *Salmonella* spp., *Yersinia enterocolitica*
- *Enterococcus faecalis*, *Enterococcus faecium*
- *Clostridium perfringens*
- *Cryptosporidium parvum*

Compared to classical cultivation methods, which usually require many days, the methods used by Nadicom are much more time-effective. The customer can obtain results within 6 hours of sample receipt by Nadicom. The analysis report details whether or not the target organism(s) was detected in a sample, and if so, the size of the population(s) in the sample.





The method is sensitive enough that a single cell can be detected in a sample. The method can also detect microorganisms that are no longer active, but may already have produced toxins

Besides the microorganisms listed above, Nadicom can also develop detection systems for further microorganisms, depending upon the wishes and interests of the customer.

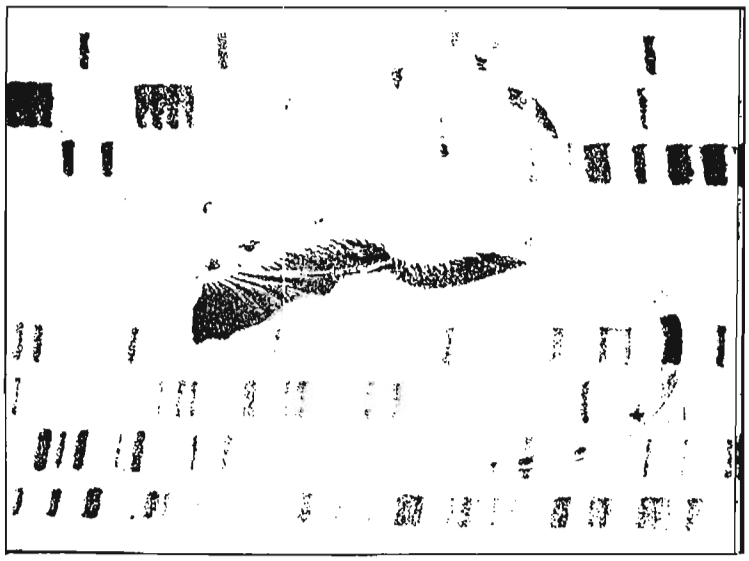
INFO
BIOTECHNOLOGIE

bmb+f
Bundesministerium für Bildung und Forschung

BEO
Projektträger Biologie, Energie, Umwelt des BMBF und des BMWi
Forschungszentrum Jülich GmbH

Mice, Rats and Other Animals

BMBF Support for the Development of New Methods Replacing Animal Experiments



Research work with the aim of replacing, reducing and refining animal experiments has been supported by the BMBF 1980. From 1980 to 1999, 226 projects were performed within the framework of the research priority on "Methods Replacing Animal Experiments" on almost all topics of relevance in this field with participation by institutes from industry, universities and other research establishments. A total of DM 143 million had been spent on this priority up to the end of 1999. Relative to the financial volume, this research priority is therefore probably the most significant government funding worldwide on developing alternatives to animal experiments.

The funding priority does not, however, only support research projects (currently on the basis of the support guideline of 17.06.1998) aiming at a complete replacement of certain animal experiments -which is after all probably only possible in a few cases - but rather all projects leading to a reduction in the number of experimental animals or a decrease in stress for the experimental animals used. Preference is given to application-oriented projects with the goal of developing or validating alternative methods to stressful animal experiments or of replacing animal experiments requiring particularly large numbers of animals.

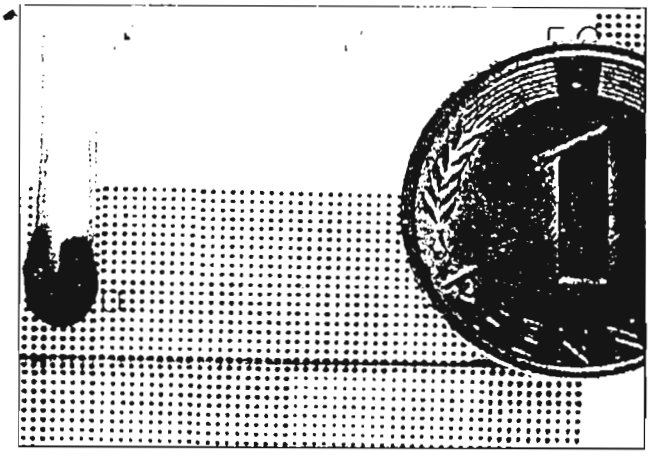
This will be illustrated by four examples:
An interlaboratory comparison coordinated by the Federal Institute for Health Protection of Consumers and Veterinary Medicine validated the so-called ATC method for determinating the acute oral toxicity of chemicals as a replacement for the LD50 test. The ATC method reduces the number of experimental animals in comparison to the LD50 test by an average of about 70 %. The new testing method was officially recognized by the OECD and the EU in 1996 and can now be used worldwide.
From 1993-1995, a research project was performed at the Pau-Ehrlich-Institute in Langen concerning a "Study on the Informativeness of the Pharmacopoeia Regulation on Testing for Anomalous Toxicity of Vaccines". The results of this project let to the regulation being deleted in numerous

means of robots, the clones arebeing implanted in high density into certain carriers. The so-called arrays generated by this process facilitate a cost-effective and rapid search for new genes as well as an extended analysis of genes already known.

At present, the Resource Center holds (worldwide) the most comprehensive non-redundant collection of genes of man (71,000 clones), mouse (25,441 clones) and rat (28,896 clones) worldwide.

The known genes of one organism have been compiled into so-called Unigene Sets, i.e. one array contains all human genes that are known. One possible application for such Unigene Sets is the comparison of active and non-active genes in sound and in tumor tissue. From these observations, conclusions can be drawn on the mechanisms leading to the emergence of tumors.

In addition, the Resource Center carries out specific tasks with regard to arrangement and resorting of gene libraries as well as to the generation of high-density arrays.



High-Density-Arrays on glas slides (density: 500 dots/ cm^2

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The Model System

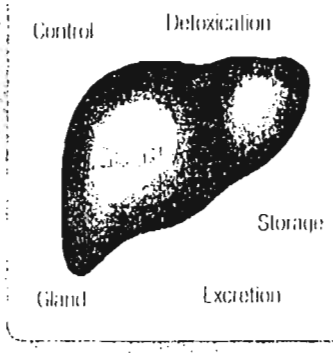
Interesting hepatocytes

The model system of the BMBF's funding activity on systems biology is the human hepatocyte. This model was selected with regard to its central function in higher organisms.

The liver is a highly complicated "biochemical factory" which synthesizes, converts or breaks down more than 10,000 substances a day. This includes numerous processes related to the utilization of food as well as other essential metabolic functions.

The liver supplies the organism with necessary substances such as proteins, carbohydrates and fats, which are absorbed from food.

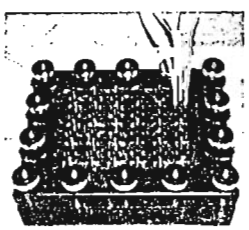
The hepatocytes are largely responsible for the many different metabolic pathways and their control. They make up about 90 per cent of the liver mass. They were chosen as the model system because of their various vital functions and their manifold potential applications in medicine, pharmaceutical research and other areas.



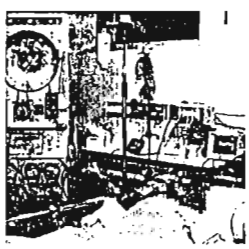
The liver fulfils many essential functions. As a storage organ, it accumulates reserves of important substances. From the organism it eliminates toxic substances and pathogens ingested, for example, with food and converts them into harmless substances. As a gland producing nearly one litre of bile per day, the liver supports the digestive process. Many metabolic waste products are released into the intestine and eliminated together with the bile while numerous fat-soluble substances are made water-soluble in the liver through chemical conversion processes finally released with the urine. An important property of the liver is its regenerative ability which is essential for natural healing processes as well as for organ and tissue engineering.

Range of Application

Drug Screening



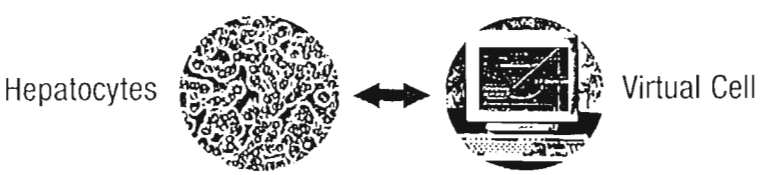
Toxicity Analysis



Therapy of Liver

Alternatives to Animal Experiments

Pharmaceutics



Experiments can be simulated and hypotheses developed and tested for their accuracy in biological experiments with the aid of mathematical models. As a result the discovery and development of active agents could be speeded up and at the same time costs could be reduced. Furthermore, toxicological test series could be simulated and as a result the number of animal tests reduced.

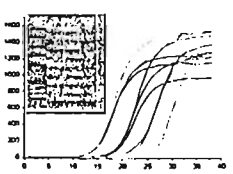
The application potential of the chosen model system of the hepatic cell underlines its economic and social significance for Germany. Other countries (USA, Japan) have launched systems biology research initiatives focussing on the bacterium *Escherichia coli*, on yeast, on *Drosophila*, on *Caenorhabditis elegans* and on cardiac muscle cells or b lymphocytes.

Identification of Microorganisms

Quantitative analysis of microorganisms in mixed cultures

For the quantitative analysis of microorganisms Nadicom recommends molecular biological methods, in particular fluorescence in situ hybridization (FISH) and quantitative real-time-PCR.

In FISH, oligonucleotide probes labeled with a fluorescent dye are employed. These probes can be designed to specifically target individual species, so that an exact estimate of the population sizes of particular microbial species can be made in a sample containing diverse species.
The analysis involves fixation of the sample, hybridization with the fluorescent probes, and examination by epifluorescence microscopy, all of which are performed in Nadicom laboratories.
The customer receives a report which includes the results of the population counts and (on request) photographic documentation of the analysis.



Quantitative real-time-PCR allows a rapid and sensitive quantitative assessment of microbial populations. It is based on the PCR reaction, but the examination of product does not follow qualitatively by standard gel electrophoresis, but rather though a measurement of the kinetics of the PCR reaction which is facilitated by the use of oligonucleotide probes labeled with fluorescent dyes. Like FISH, this method allows the quantification of individual species in a sample containing diverse microorganisms.
One useful application of this method is quantitative detection of pathogenic organisms in liquid and solid samples. Its primary advantage over cultivation-dependent methods is the speed of analysis. A result is obtainable within 6 hours of sample receipt in the laboratory. The Nadicom Databank also allows specific primer systems to be designed for most microorganisms.
With this method the customer avoids potentially costly delays between sampling and obtaining results.

Identification of microorganisms

DNA fingerprints

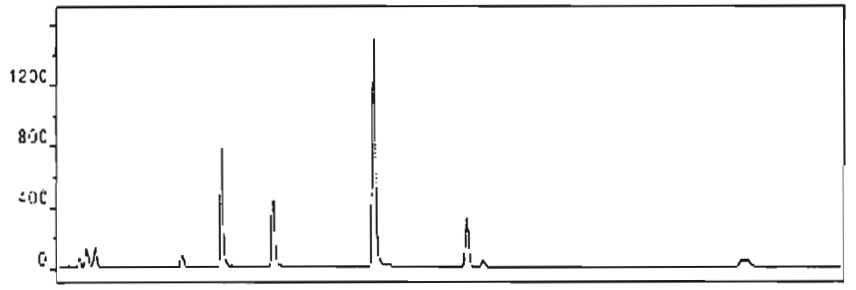
DNA fingerprinting is the molecular characterization of complex samples. The fingerprint of a sample is a pattern composed of individual units specific to each of the microorganisms present in the sample. Nadicom uses various fingerprinting methods for the following technical and scientific purposes:

- Documentation of shifts in the composition of microbial communities
- Testing culture purity
- Verification of strains used in economic ventures
- Characterization of bacterial cell banks

The following fingerprinting methods are used:

- RAPD-PCR (Random Amplified Polymorphic DNA)
- RFLP (Restriction Fragment Length Polymorphism)
- T-RFLP (Terminal Restriction Fragment Length Polymorphism)

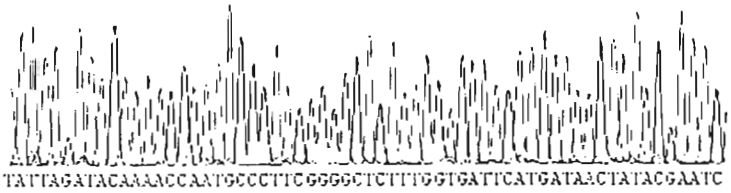
These methods are used by Nadicom for the quality control of pure cultures.
They are also used to determine if two organisms that are identical based on biochemical and physiological tests are also phylogenetically identical.



Identification of Microorganisms

Qualitative Identification of Microorganisms in mixed cultures

To identify and characterize in the shortest possible time the microorganisms present in complex environmental samples, Nadicom employs molecular biological methods. These rapid methods are based on state-of-the-art genetic technology and have widely replaced classical methods of microbial community analysis based on cultivation.
Nadicom performs polymerase chain reaction (PCR) -based methods on DNA extracted from a sample. The PCR reaction is performed with standard primers, or with primers developed specifically by Nadicom to target a desired microorganism. Then the PCR products are cloned and DNA from the clones is sequenced.



The DNA sequence data obtained is analyzed against the Nadicom-Databank, and when desired a phylogenetic tree is constructed showing the taxonomic position of the microorganisms detected.

The customer receives an analysis report which includes the sequence data and the phylogenetic tree. When desired the results are presented in a publication-quality format.

Animal models to be carried out with different groups of rats allow first studies, for instance on

why some animals become fat on a diet high in fats and others do not, and what role certain genes play in this determination.

The data collected from analyzing biological samples and evaluating body and organ weights, blood pressure and pulse rate at various times, flow into a diagnostic adiposity platform on the basis of which SCIENION technology is used to develop diagnostic tools in the form of biochips. Databases, hybridization stations, scanners and evaluation software worked out in the alliance project will make it possible to apply these tools not only in research, but also in human diagnostics.

"With the help of the findings about the connections between genotype, nutrition and adiposity obtained during the project, we intend to develop suitable tools and test systems in order to track down systematically the causes of obesity and their connections with resulting illnesses," explains SCIENION's CEO. "With this knowledge, the biological effects of such factors as nutrients, food additives and pharmacological substances on people with a genetic predilection can be tested more accurately. It also brings us a great deal closer to developing new biotechnology-based therapies for the treatment of obesity." Eventually the partners in this collaborative effort hope to create an "appetite brake," new active agents for the control of food intake on the basis of antibodies – a lifestyle medication with gigantic market potential.

Brief Company Portrait:

SCIENION AG *(www.scienion.de, located in Berlin-Adlershof, started as a spin-off of the Max Planck Institute for Molecular Genetics in April 2001. Its product portfolio ranges from customer-specific DNA arrays for functional genome research on microorganisms, through the ready-to-use sciTRACER Inflammation 400, the CardioVascular 700 DNA microarrays for human genome research, and ready-to-spot oligo sets (MALDI-TOF-MS quality certified), all to way to protein microarrays. With the benchtop sciFLEXARRAYER Piezo-Spotter and incubation systems for biochips, SCIENION customers have access to high-quality instruments from Adlershof as well. SCIENION AG is supported by a pool of investors consisting of the 3i Group, PEPPERMINT. Financial Partners and IBB Beteiligungsgesellschaft. Chairmen of the board are Dr. Holger Eickhoff and Dr. Alan Bullock.*

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公司簡介

Company Profile

位於台灣的佳美健康生技是佳美集團成員之一；主要致力於植物萃取、微生物酸酵等機能性素材的研究開發與製造。目前主要產品為：去醣基大豆異黃酮、生物纖維、去苦味茶多酚、植物萃取物等。

Chia Mei Health Biotechnology in Taiwan, a spin-off company from Chia Mei Group, is devoted on the R&D and production for phytochemical ingredients and fermentation products by application of advanced biotechnology. Our product lines at the present are : **Soy Isoflavone Aglycone, Biocellulose, Debittered Tea Polyphenol and Botanical Extracts.**

佳美集團

Chia Mei Group

佳美集團創立於西元1968年，致力於研發與製造各種果蔬原汁濃縮汁，以及機能性食品原料。產品行銷台灣、中國大陸、韓國、日本、歐盟、美國等20餘國。總公司設於台灣，並同時在其他亞洲各國(包括中國大陸、越南、印尼、菲律賓、新加坡等)有19個生產工廠與事業單位。

Chia Mei Group is founded in 1968 and specializing in the production of various kinds of fruit and vegetable puree, concentrate and functional food ingredients. Chia Mei's business extends over 20 countries worldwide, including Taiwan, China, Korea, Japan, European Community and United States. Our head office is located in Taiwan and with 19 branch factories and offices in the Asia Pacific countries, including China, Vietnam, Indonesia, Philippine and Singapore etc.

我們的品質認證(通過年度)

Our Quality Assurance (Year of Recognition)

- JAS日本農林標準(Japanese Agriculture Standard)平成4年10月13日, Oct 13, 1992
- CAS中華農業標準(Chinese Agricultural Standard)認證編號 No:0308
- HACCP危害分析與重要管制點系統(Hazard Analysis and Critical Control Point)
  認證編號 No:3700-02-0142
- ISO9001:2000國際標準組織(International Organization for Standardization)
  認證編號 No:3700/200214096
- CNLA:ISO/IEC 17025中華民國實驗室認證體系(Chinese National Laboratory Accreditation)
  認證編號 No:0929

JAS(1992) CAS(1994) ISO 9001:2000(2002) HACCP(2002) CNLA:ISO/IEC 17025 (2003)

JAS CAS CQC CQC CNLA

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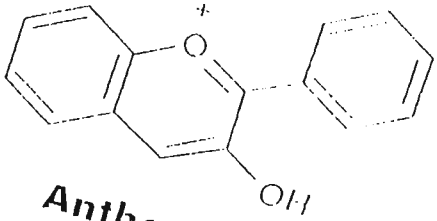
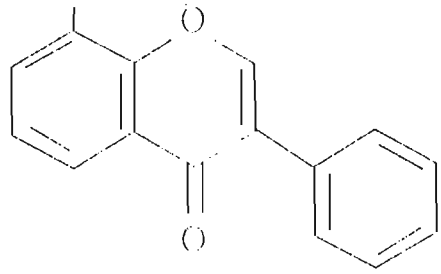
佳美健康生技

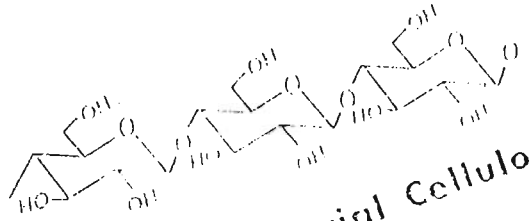
Chia Meei Health Biotechnology



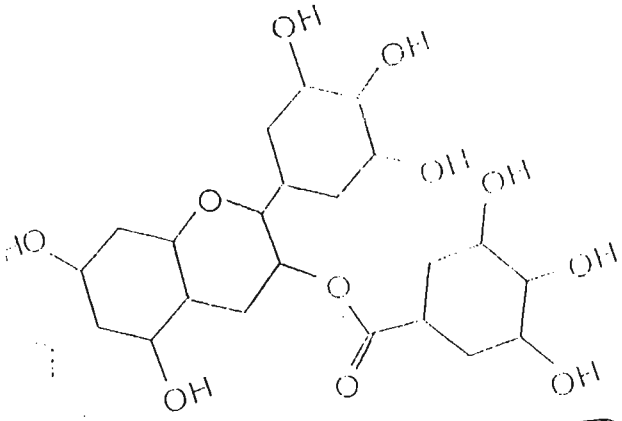
Anthocyanidin



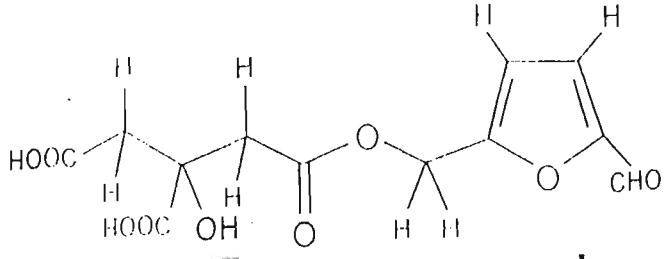
Isoflavones Aglycone



Bacterial Cellulose



Epigallocatechin Gallate



Mumefural

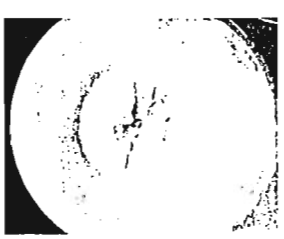
CHIA MEEI GROUP

Identification of Microorganisms

Prokaryotic pure cultures

To precisely identify Bacteria and Archaea, Nadicom uses 16S rRNA as a specific phylogenetic marker. DNA is extracted from cultures and the 16S rRNA gene sequenced. The identification is then carried out by comparative sequence analysis to the Nadicom Databank, which contains more than 20 000 sequences.
For more specific identification of particular functional microbial groups, Nadicom employs PCR primers targeting particular function-specific genes, and applies comparative sequence analysis to extensive databanks of these genes.
The customer receives a complete analysis report which contains the nucleotide sequence data determined for the culture, a phylogenetic tree showing the position of the culture relative to other prokaryotes, and (on request) a list of the ten most closely related organisms.

Fungal pure cultures



For fungal identification Nadicom sequences the ribosomal 18S rRNA gene. Comparative sequence analysis is performed against the Nadicom Databank.
For closer identification, the ITS- (intergenic transcribed spacer region) and the IGS- (intergenic spacer region) are analyzed. The morphology and developmental stage of the fungus are also described.
The customer receives a complete analysis report which contains the nucleotide sequence data, a phylogenetic tree, and (on request) a list of the ten most closely related organisms. The report also includes a complete summary of the characterization of the fungus, highlighting any special or unusual properties determined.

PRESS RELEASE

"Why Do We Have Such (Over-) Large Appetites?": SCIENION AG and Partners Aspire to Appetite Brake

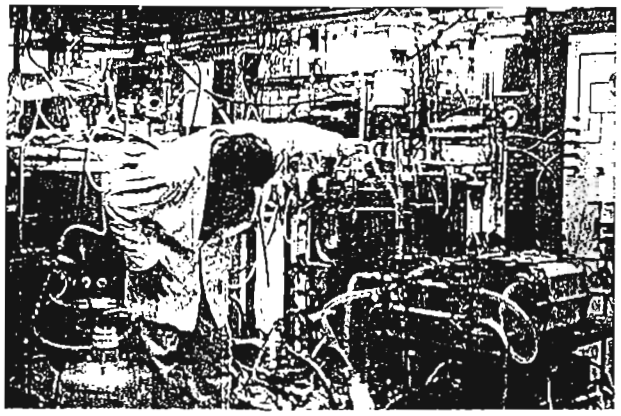
Biotech company from Berlin developing adiposity chip/Nutrigenome Research project alliance analysing genetic factors of obesity

***Berlin/Hannover, 7 October 2003.*- A constant increase in excess weight and obesity (adiposity) in the populations of industrial nations has been observed for years. In Germany, one of every two adults is already overweight; of these, nearly every fifth is very fat or even obese – and the trend is on the rise. What's also alarming: the number of overweight children has multiplied in recent years. An increase in body fat also means an increase in patients with high blood pressure, diabetes, cardiac-circulatory disorders, and even cancers. The yearly costs of adiposity to the economy are estimated in the billions. Studies have shown that in addition to unhealthy nutrition by individuals, a high proportion of the affected is presumably genetically predisposed for adiposity. In a project alliance funded by the federal ministry for education and research (BMBF), "Nutrigenome Research Berlin-Brandenburg," experts from SCIENION AG, the renowned Charité Hospital and the Fraunhofer Institute are getting to the bottom of the molecular-genetic causes of obesity with the goal of developing an antibody-based therapeutic regimen.**

"At this time there is no procedure applied in the world with which the complex processes of adiposity can be identified, characterized and monitored on the molecular level," SCIENION chairman Dr. Holger Eickhoff outlines the task of the alliance project. "Each of the partners involved is contributing his long years of expertise to use microarrays in the identification and analysis of genetically conditioned factors of obesity, and then to develop an antibody-based therapy, a natural appetite inhibitor." Clinical research and new platform, information and detection technologies come together in the alliance project, consisting of SCIENION AG of Berlin, a complex supplier of biochip products, hardware and services, the Franz Volhard Clinic of the Charité hospital, represented by Dr. Stefan Engeli, and the Fraunhofer Institute for Biomedical Technology, represented by Dr. Frank Bier.

The "adiposity chip," part of the BioProfile emphasis of the Nutrigenome Research Berlin-Brandenburg, is intended to explore the at yet little understood molecular-genetic connections between obesity and the illnesse that accompany it, such as high blood pressure and diabetes. With the financial support of the BMBF, genes relevant for adiposity are identified in animal and human studies, combined on a test chip, and tested for their suitability in the development of future diagnostic and therapeutic potential.

was founded in 2001 and has become since then a leading
or microarray related products in central europe. SCIENION is a
om the MPI for Molecular Genetics in Berlin. Our mission is to
ur collaborators to quickly identify the functions of genes for
gical and biomedical research area. SCIENION has established
g microarray technology platform, which is applicable to DNA,
Antibodies and Cells. SCIENION believes that there will be a
us need to speed up biological processes as the community,
/ in clinical environments, moves from the identification of the
understanding and quantitating its function.

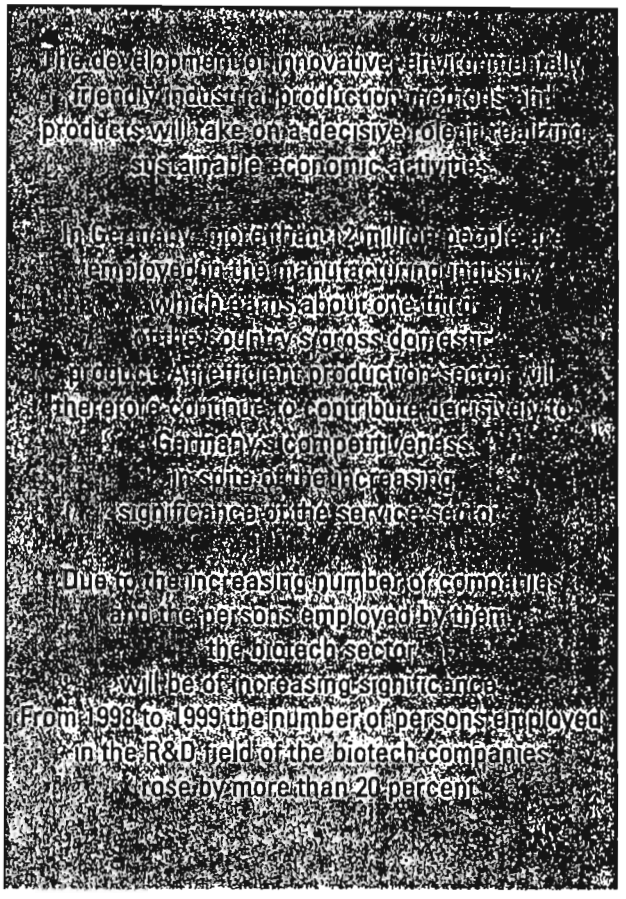


Bioreactor for growing cell cultures. (The photograph shows a 3500-l reactor in the pilot-scale bioengineering facility of the National Research Centre for Biotechnology in Braunschweig.)

2. Development of efficient, environmentally friendly and resource-conserving methods for the production of new active ingredients, materials and products, for example, of

- proteins and nucleic acids for therapeutic applications, vaccines and antibiotics,
- environmentally compatible high-tech biomaterials,
- textiles and foodstuffs with new properties.

Accompanying studies in close cooperation with the companies supported will increase knowledge on the conditions for sustainable bioproduction. These studies should also accelerate the development of a set of instruments applicable in practice for assessing sustainable biotechnological approaches for industry and society. The analysis of material flows will play a decisive role here.



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Analytical services

Ecophysiological Examination

To properly understand microbial processes in environmental samples, it is often necessary to analyze the biogeochemical transformations which occur. With our experience in basic scientific research and analysis of biochemical parameters, Nadicom is also in this area a reliable partner.

We offer the following analytical methods:

- Gas Chromatography:
  - Detection of principle atmospheric gases (N_2, O_2, CO_2) and trace gases (including CH_4, CO, H_2, N_2O, NO_x)
  - Analysis of organic acids

- HPLC:
  - Analysis of organic acids
  - Cation and anion analysis
  - Protein analysis (alternatively we also offer MALDI-TOF analysis)

- Isotopic analysis:
  - Use of stable isotopes and radioactive isotopes to examine biogeochemical pathways
  - Detection of stable isotopes and radioisotopes by GC, HPLC und IR-GCMS

- Fermentation measurement according to DIN 38414 with an Eudiometer