

**BIOMATERIALS:
RESEARCH DIRECTIONS FOR CSIRO**

JULY 1990

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1 INTRODUCTION

1.1 The Issues

This report addresses the scope and direction of future biomaterials research in CSIRO. It is based on an analysis of current biomaterials research and associated market opportunities.

It is framed so as to respond to five key questions.

- . should CSIRO be involved in biomaterials research?
- . what are the priority areas for research?
- . what is an appropriate balance of short and longer term research in these areas?
- . what is the preferred commercialisation strategy?
- . what are appropriate funding and administrative arrangements?

Biomaterials research shares a number of characteristics common to other research within the Division of Biomolecular Engineering and across CSIRO, namely:

it is long term in nature, although there are potential medium term spin-offs. Typically the time between initial research and commercialisation of new products is 5-10 years (including clinical trialling)

research is multi-disciplinary, requiring effective integration of physical and biological science talents. Project teams need to include scientific and engineering expertise in material design and biological impact and have effective links with clinicians

commercial success is dependent on international markets. Australia accounts for just a small proportion of the global market and would be unable to sustain a viable local industry in its own right

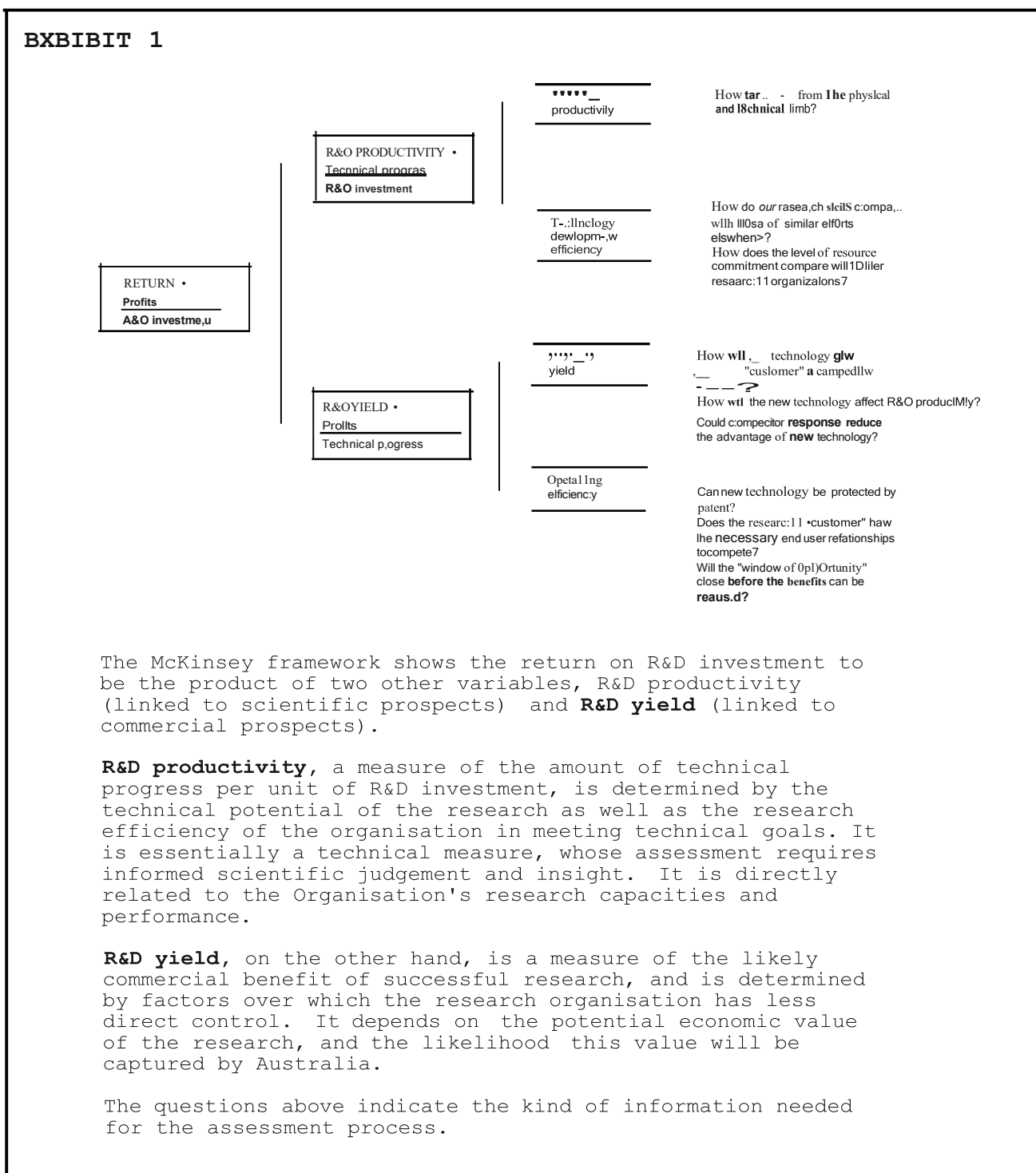
there are limited opportunities for collaboration with Australian-owned or Australian-based firms which are capable of exploiting research-based export markets.

Another characteristic, less common, is the cost and time associated with regulatory hurdles, in this case principally the US Food and Drug Administration 510K and PMA clinical test requirements.

1.2 The Approach

The Study follows the approach set out in the 1987 McKinsey and Co. report on rare earth processing and rare earth magnet production, entitled "Assessing Commercial Prospects for Research". This methodology was also employed in the IIT report "Research Opportunities in the Polymer and Plastics Industry" (1988).

A key part of the approach is the separate scientific and commercial appraisal of research activities. The framework is set out in EXHIBIT 1.



2. BIOMATERIALS MARKETS¹

2.1 Definitions²

While definitions in biomaterials research have historically been quite varied, recently an international consensus was achieved on many important terms². From this, a biomaterial is defined as "a non-viable material used in a medical device, intended to interact with biological systems.

"Biomaterials may be of three basic kinds:

Implantable materials where the function is the key point and the device is not load-bearing
 - e.g. cardiovascular, ophthalmology, soft tissue, and wound healing

Materials for short-term, extra-corporeal uses or in vitro biotechnological applications
 e.g. catheters for short term implantation, and material surfaces (membranes) for biotechnological applications

Implantable structural, load-bearing materials
 - e.g. replacement hip joints, orthopaedics generally, and dental

The biomaterials industry is heterogeneous, and has been defined¹ to include the following sub-markets:

Artificial Organs
 Biosensors
 Biotechnology
 Cardiovascular/Blood Products
 Commodity/Disposables
 Drug Delivery
 Equipment/Devices
 Maxillofacial, etc
 Ophthalmology
 Packaging
 Wound Management

These segments are listed in Appendix 1, which gives examples of products in each sub-market.

¹ The following text draws on material presented in the DITAC (1988) publication *Polymeric Biomaterials: A Perspective for Australia* and at a recent Conference ("DITAC Workshop on Material for Medical Devices-Biocompatibility", Leura, NSW, May 1989. It also draws on a 1988 US National Research Council (NRC) *Report of the Committee to Survey the Needs and Opportunities for the Biomaterials Industry* and a 1988 report *Biomaterials* from the Theta Corporation (USA).

² "Definitions in Biomaterials", in *Progress in Biomedical Engineering*, Vol.4, ed. Williams, D.F., Elsevier, 1987.

This report focuses on several of these namely:

- biotechnology
- cardiovascular
- equipment/devices
- maxillofacial
- ophthalmology
- wound management

Others are outside the direct scope of this report and are not addressed further. Overlap with biosensors research should however be noted, namely:

the development of methods for the assembly of composite biomaterials. These also apply to the assembly of the detector system of a biosensor - each requires the immobilisation, in an optimally active form, of a protein (such as an antibody or an enzyme) onto a membrane, other polymeric surfaces, metal or ceramic.

the development of protein-based ligand binding systems, to determine the specificity, affinity and "turn-off" mechanism of biosensors or to optimise the action at the biological-material interface (in both the case of biomaterial and for implantable or blood-contacting biosensors). The "custom design" of such ligand binding proteins (antibodies or enzymes) and signal transduction systems to have novel specificity and characteristics may be achieved by protein engineering, including by molecular biological techniques.

biosensors for use in medical applications, such as short or long term implants or for rapid assay of blood or other tissue fluid components, have the same requirements for biocompatible coatings as do biomaterials for cardiovascular applications.

2.2 Worldwide Demand

Biomaterials are part of the fast growing biomedical and dental products industry.

Current worldwide biomaterials sales amount to about \$13bn per year. The United States accounts for over 40% of the total market, followed by the European Community and Japan. Australia is a net importer; local production in 1988 is estimated at about \$300m, with imports of \$300m-plus and exports of about \$100m.

The size of the different segments is shown in Table 1 below.

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TABLE 1
Estimated worldwide Markets
in Selected Biomaterials

Submarket	Product	Market Size 1990 (\$m)	Growth Rate %/Year
Cardiovascular ¹	Pacemaker leads	144	5
	Vascular grafts	132	5
	Cardiac valves	162	5
Commodity/Disposables ¹	Catheters	1725	5
Drug delivery ³	Time release polymers	106	60
Equipment/Device (Extracorporeal)	Dialysers (etc)	1622	5
.Maxillofacial ¹	Dental Implants	141	10
Ophthalmology ¹	Intraocular lenses	850	6
	Contact lenses	4533	6
Orthopaedics ³	Knee/hip/others	700	5
	Bone grafting	82	20
wound Management ²	Traditional dressings	1466	-2
	Synthetic dressings	352	16
	Biological dressings	37	25
	Sutures	1018	5

Sources

- 1 Biomedical Business International (Various issues)
- 2 Wound Management Products: Markets and Technologies Arthur D Little. Substantially higher values are given in "Development of Wound Care", G L Evans, Clinica 1987.
- 3 Biomaterials Report No.743 Theta Corporation (June 1988)

A broad **overview** of all submarkets is provided in "The Clinica Fact Book", Clinica, 1988.

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2.3 Interrelationship of Biomaterials Research

Common features of biomaterials research are:

its interdisciplinary character

common market characteristics, such as producers and distributors operating in a number of submarkets (although each would have separate, specialist marketing approaches for each submarket), and

a linking research focus, notably the study and understanding of biocompatibility, i.e. the ability of a material to perform with an appropriate response in a specific application. This requires an understanding of fundamental aspects of biological tissue interactions with synthetic substances, an understanding of materials science, and an ability to control both bulk and surface properties of biomaterials.

2.4 Future Prospects

The 1988 US National Research Council report on biomaterials noted:

"Specific recommendations for future research and development include the needs for improving existing systems based on metals, polymers, and ceramics, and the expansion into new systems using combinations and composites of these existing biomaterials. Totally new biomaterials will evolve."

"There will eventually be a need for biomaterials that duplicate the physical biological properties of all native tissues in the body. The demand is currently driven by biomedical applications which are felt to be on the threshold of major advances. If one were to judge the need in relation to the most common diseases or infirmities which could benefit from advances, the priority list of opportunities could well be very different from the current ranking of demands. Chronic conditions such as urinary incontinence, atrophy of the dental alveolar ridge, soft tissues contour deformation, and replacement of tendons and joints could well rank as high or higher than the better known cardiovascular applications, which owe their primacy to the more dramatic conditions they are expected to obviate."

The 1988 DITAC report on polymeric biomaterials identified biomaterials as an area of potential Australian research and production skills, established pre-clinical testing capacities, supportive high skill surgery base, some industrial capacity and recorded export successes, e.g. bionic ear, pacemakers, and contact lenses.

Finally a survey in 1988 of 45 research areas by the Institution of Engineers identified biomedical materials and biomedical engineering as high priority in terms of potential economic importance in Australia.

3. THE BIOMATERIALS INDUSTRY IN AUSTRALIA

3.1 Local Players

Australia's biomedical research strengths are not matched by a large local export-oriented industry; the same is the case with biomaterials.

Table 2 provides a summary of the major Australian-based companies in each biomaterial market segment, with sales, R&D effort, number of employees and ownership.

The local market is rather thin in terms of Australian-owned companies. The major Australian success story has been Nucleus, parent company of Telectronics, Cochlear and Domedica, which grew to become one of Australia's leading export companies. Since being taken over by Dunlop Pacific in early 1989, Nucleus have transferred the manufacturing of cardiac pacemakers and related R&D activities to their Florida plant. At interview Nucleus pointed out that the company will continue in Australia its manufacturing and R&D activities in the new business area of implantable defibrillators. In addition the total Australian R&D budget for the company had not decreased following the takeover, and the company was very interested in biosensor and biomaterials R&D related to cardiac pacing applications such as chronically implantable sensors.

Nucleus has been a major beneficiary, through GIRD and other arrangements of past collaboration with CSIRO and has received about \$20m in R&D and export grants from the Federal government over the past ten years.

The offshore moves of Nucleus have potential relevance to other Australian companies. The recent Australian Manufacturing Council (AMC) Report *"What Part Will Manufacturing Play in Australia's Future"* observed that "the advantages of being close to major markets and leading-edge customers, of being located near to suppliers and subcontractors and the benefits of more mature venture capital markets provide powerful incentives for fast-growing firms like Nucleus to locate not only product assembly, but also marketing, R&D and Headquarters' activities in larger countries such as the USA."

Other major Australian companies are F H Fauldings Pty Ltd and Memtec Pty Ltd, each with significant export orientation. Fauldings has limited direct involvement in biomaterials, interviews having confirmed the firm's strong interest in slow release technology for drug delivery (their relatively narrow focus in this market is being addressed by a spin-off company Enterovax). Memtec primary research interests are in the membrane area; it also is involved in biosensors R&D through membership of the AMBRI consortium.

Smaller Australian companies of note include Bionova Neotechnics (recently reconstituted as Bionova International), Vaso Products and Laserex. However these have sales revenues

'IBLB 2

Details of selected Australian Based Firms Involved
in Biomaterials R&D Manufacture and Marketing

Submarket	Companies	Ownership	Products	Company Sales \$m	R&D Aust	Manuf Aust	No. Employees	Worth/Condition
Biotechnology	Memtec P/L		Research membranes	\$10.6m	Yes	Yes	138	Good
Cardiovascular	Telectronics	Pacific Dunlop	Pacemakers	\$42.8m	\$SM	Yes	420	\$27M-Good
	Johnson & Johnson	J&J (USA)	Vascular grafts	\$315m	Yes	Yes	1200	\$101M-Good
	Bio Nova International		Vascular grafts	<\$1m	Yes	Yes		
Commodity/Disposables	Terumo Aust	Terumo Corp Japan	Disposable medical supplies	\$15m	Yes	Yes	150	
Drug Delivery	ICI Aust	ICI (U:K)	Drug delivery	\$3100m	Yes	Yes		Strong
	F H Faulding		Slow release	\$461m	Yes	Yes	1000	Good
	Auspharm International		Drug delivery Wound management	\$10m	Yes	Yes	130	Good
Equipaent/ Device	Domedica	Pacific Dunlop	Renal Dialysis	\$6m		Yes	40	\$SK-Strong
	Tuta Laboratories (Aust)	otsuka Pharmaceuticals Japan	Blood bank equip	\$6m	Yes	Yes	380	\$6M
Maxillofacial etc	Cochlear	Pacific Dunlop	Bionic Ear	\$15m	<\$1M	Yes	67	\$9M-Good
	Southern Dental Industries		Dental consumables	\$10m	Yes	Yes	110	\$6M-Good
	Biodental Research		Dental composites	\$0.75m		Yes	6	Unknown
Ophthalmology	Eycon Lens Laboratories		Contact lenses	\$1m	Yes	Yes	25	Fair
Wound Management	Johnson & Johnson	J&J (USA)	Wound Management, Sutures	\$315m	Yes	Yes	1200	\$101M-Good
	Cyanamid Aust	American Cyanamid	Suture/Pharmac.	\$65m	Yes	Yes	425	\$11M-Good

Australian based firms are defined as those strategically managed within Australia; they may not be wholly Australian owned.

of less than \$2-3m and lack the resources by themselves to maintain a long and costly clinical trialling, and marketing presence in major overseas markets.

The other major Australian-based players are multinational subsidiaries such as J&J, Cyanamid and Terumo, which conduct R&D and manufacturing in Australia. (These are listed in Table 2; this also includes information on company size and employment). Except for Cyanamid and Terumo none of these presently maintains a "high-tech" biomedical manufacturing capacity in Australia.

Finally there are Australian subsidiaries of overseas companies involved in biomaterials but not conducting Australian research. These are shown in Table 3. They include companies such as Becton Dickinson, W L Gore, Smith and Nephew, and Baxter Health Care.

3.2 Timescale for Product Development

The product development stage for biomaterials is frequently prolonged because of the need for trials to demonstrate the safety and efficacy of the product. This may involve extensive animal studies, then limited clinical trials and finally large scale human trials prior to general market approval.

Since the North American market is a major part of the total market, the trials should comply with the US FDA requirements, which are frequently the most demanding.

The extent and duration of trials is dependent upon the type and applications of the device, being less demanding (and less costly) in cases where failure is not life-threatening or dangerous to the patient, e.g. in the dental submarket, or where the new device is substantially similar to existing devices. Development funding in the case where lengthy clinical testing is required represents a barrier to small scale local manufacturers, relative to low-risk devices with shorter and less costly trialling and local manufacturing opportunities.

3.3 Commercialisation Options

Biomaterials require effective international marketing in a narrow market niche. High-technology surgical products require a specialised technical sales force, quite different from over-the-counter products.

Successful marketing is the third major element of commercialisation, the others being research and trialling for regulatory approval. As noted, trialling can be long-term - up to ten years for high medical risk materials - and require sustained and significant funding.

There are cases other than Nucleus where research has been matched by early commercialisation efforts.

'IBLB 3

Details of Selected Australian subsidiaries of Overseas companies Involved
in Biomaterials But Not Active in Biomaterials R&D in Australia

Submarket	Companies	Ownership	Products	Company Sales	R&D Aust	Manuf. Aust	No. Employees	Worth/Condition
Biotechnology	Millipore Aust	Millipore (USA)	Filters/membranes	\$14m	No	Yes	70	Good
Cardiovascular	W L Gore	W L Gore (USA)	Vascular grafts		No	No		\$1.6m
	Pfizer	Pfizer Corp (USA)	Valves	\$64m	No	Yes	290	Fair
Commodity/Disposables	Baxter Healthcare	Baxter (USA)	Intravenous solutions/tubing	\$72m	No	Yes	607	Good
	William A. Cook	William A. Cook (USA)	Catheters	\$3m	No	No		
Equipment/Devices	Becton Dickinson	Becton Dickinson (USA)	Medical and lab equipment	\$25m	No	No	70	Good
Ophthalmology	Alcon Laboratories Aust	Alcon (USA)	Intraocular lenses		No	No		
	Iolab	Johnson & Johnson (USA)	Intraocular lenses		No	No		
Orthopaedic	Zimmer Aust	Zimmer Inc (USA)	Hips/knees	\$17m	No	No	42	Good
	Howmedica Aust	Pfizer (USA)	Hips/knees	\$35m	No	No	60	Good
Wound Management	Smith & Nephew	Smith & Nephew (UK)	Wound management	\$58m	No	Yes	450	Good

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BioNova pushed their Omni flow prosthesis through the regulatory hurdles in Europe. Vase Products prepared and was granted an Investigational Device Exemption from the FDA to conduct human clinical trials at the Royal North Shore Hospital and in the USA based on this exemption.

The key point is that the infrastructure exists in Australia to develop implantable biomaterials to the stage where full scale production and marketing is required. The main element missing in the blueprint for success, however, is a strong **capacity to manufacture locally and to market the device worldwide.**

These problems are common to other industries. The AMC has noted three factors that add to the difficulty of launching new technology firms and limit their ability to conduct aggressive manufacturing and export are:

the small domestic market, leading to an imperative to export very early;

the lack of strong clusters of related industries in Australia, and

problems in obtaining capital due to relative immaturity of the venture capital industry in Australia.

What is to be avoided is embarking on research whose results are transferred overseas at no or low cost, effectively a case where the Australian tax-payer is subsidising the development activities of an overseas company. A starting point is that unless there is some Australian-based fabrication (and associated exports) then the research should not be undertaken. An exception to this could be where there are substantial external benefits of the research in terms of likely indirect or longer term flow-on to Australian industry.

Other than working with a large Australian firm there appear to be several options:

(i) **Collaboration with a small Australian firm**

The problems faced by small firms have been noted above and relate principally to the funding of research and development, manufacturing scale up and market entry.

CSIRO has experienced problems in the biomaterial area with such alliances (e.g. the Wallace Agreement between the Division of Protein Chemistry, Melbourne University and Wallace) although they have enabled significant research. The long or even medium term future of these companies is uncertain.

The main advantage in collaborating with such companies is their entrepreneurial enthusiasm and focused approach to early phase R&D.

(ii) **Strategic alliance with a large Australian-based multinational subsidiary**

A strategic alliance with a major overseas firm (Table 3) is another possibility. The Factor F scheme provided a framework for collaboration between the Australian based pharmaceutical industry and research organisations, and in related fields several major collaborations have been negotiated between Australian-based pharmaceutical subsidiaries and R&D organisations.

With the ending of the Factor F Scheme, increasing attention is being given by DITAC to the use of Offset provisions for scientific and medical instruments and devices under the expanded Offsets Program effective from mid-1990. This could provide a framework for future strategic alliances with subsidiaries of large overseas companies.

(iii) **Three-way Strategic Alliance**

A further possibility is a three-way alliance between CSIRO, a small Australian owned start-up company with good potential, and a large multinational with subsidiaries in Australia. This would reduce some of the major hurdles such as product development, international regulatory approval, marketing and financing that accompany the successful commercialisation of a human biomaterial on the world market.

In any such alliance it would be up to CSIRO to negotiate an agreement that maximises the benefit to Australia of the research.

4. CSIRO BIOMATERIALS RESEARCH

Current IIT research in the biomaterials area is summarised below, based on the principal Submarket target(s), and considered, topic by topic on the following pages.

<i>Division</i>	<i>Topic</i>	<i>Section</i>	<i>Page No</i>
Biotechnology & Cardiovascular			
DBE*/DCP	Molecular design of bioactive surfaces	4.1	15
Cardiovascular			
DCP	Polymeric materials for medical implants	4.2	17
DBE*/DCP	Biomaterial coatings for small diameter vascular grafts and percutaneous implants	4.3	19
Equipment/Devices			
OAP	Ultrasonic Blood Characterisation	4.4	21
Maxillofacial, etc (Dental)			
DBE#	Collagen-based biomaterials for periodontal repair	4.5	23
Ophthalmology			
DBE#	Stabilised collagen gels for ophthalmic applications	4.6	25
Orthopaedic (and Maxillofacial: Dental)			
DAP	Improved CFRC for human Implants	4.7	26
DMST	Alloys for Medical Implants	4.8	28
DMST	Biomedical applications of Sintered Hydroxyapatite Ceramics (Also other submarkets)	4.9	29
Wound Management			
DBE#	Collagen-based biomaterials for wound management	4.10	31

<i>Div</i>	<i>Topic</i>	<i>Section</i>	<i>Page No</i>
Strategic Research Activities			
DBE#	Evaluation of biomaterial performance (for Wound Management, Dental, Cardiovascular and other sub-markets)	4.11	33
DCP/DBE*	Evaluation of biomaterial surfaces (for Cardiovascular sub-market)	4.12	35
DCP/DBE*	Studies of Cell matrix interactions (for Biotechnology, Cardiovascular and other submarkets)	4.13	36

DBE# Refers to research within project: **Structure and Function of Connective Tissue Proteins**

DBE* Refers to research within project: **Cell-Matrix Interactions and Biomaterials**

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Submarket: CARDIOVASCULAR**4.1 Molecular** Design of Bioactive Surfaces

Researchers: DCP, DBE, UNSW (Centre for Biomedical Engineering) (GIRD)

Objectives: To develop bioactive surfaces by techniques- of radiofrequency plasma treatment and subsequent chemical attachment of biologically active factors, for use in implantable devices, materials and biosensors.

Description: Surface modification techniques are being used to prepare biomaterial surfaces with superior performance, due to the combined chemical and biological characteristics of a composite plasma **skin** bioactive factor surface.

The aim is to design modified surface coatings that are not merely biologically passive, but rather are active in evoking desired biological responses (e g tissue integration of a biomaterial). It is intended to use an understanding of the biological processes at the biomaterial-tissue interface in this design process.

The project arises principally from the capabilities of the DCP in plasma modification and surface analysis, and that of the DBE in understanding cell interactions with artificial materials. Test systems for cell and tissue interactions with surfaces are in place, and will be set up for initial evaluation of haemocompatibility.

Current Status:

Evaluation of plasma modification techniques commenced at a low level in 1989. The GIRD project commenced in early 1990 and will run to 1992.

One patent application lodged in 1989 as complete specification; one provisional patent application to be lodged April 1990.

Resources:

		1990/91	1991/92
DCP	Approp	0.7 prof	0.7 prof
	GIRD	1 prof, 1 tech	1 prof, 1 tech
DBE	Approp	0.7 prof	0.7 prof
	GIRD	1 prof, 1 tech	1 prof, 1 tech

R&D

Productivity: Plasma modification methods of biomaterial development are being studied in a number of companies and research (e g vascular grafts) have recently been introduced to the market. The plasma modification technology at DCP is believed to be internationally competitive.

The plasma technology to be employed is believed to be applicable to a wide range of substrata, including polymeric (fluoropolymers and polyesters) materials and metals, ceramics. The possibilities of novel biomaterial surfaces to be made using this technology are therefore numerous, and potential applications very broad.

it could apply to the modification of existing devices to enhance performance, as well as the design of totally new devices/products

in addition it is applicable to both first-generation novel biomaterial surfaces (e g plasma- modified alone) as well as second generation novel surfaces (plasma modified then bioactive molecule coupled on).

The short term goals of the project are partly dependent upon animal implant evaluation and evaluation of haemocompatibility.

R&D Yield:

This GIRD project has as commercial collaborators Cyanamid (Australia), Telectronics Pty Ltd, and Terumo (Australia) Pty Ltd, and the biosensor consortium AMBRI (Australian Membrane and Biotechnology Research Institute).

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Submarket: CARDIOVASCULAR**4.2 Improved Polymeric Materials for Medical Implants**

Researchers: DCP in association with UNSW (Centre for Biomedical Engineering): (GIRD)

Objectives: The development of improved polyurethane elastomers for use in implantable devices.

Description: Polyurethanes have good mechanical properties which have led to their use in pacemaker leads, heart valves and catheters. Undesirable features of polyurethane biomaterials however are the toxicity of urethane monomer and failure of devices in long term implants due to biologically-induced degradation and calcification.

This project aims to provide more stable, and therefore more biocompatible polyurethane elastomers by methods of polymer synthesis, blending, and surface modification.

An additional aim is the development of accelerated test systems to screen polymers for haemocompatibility and biostability and to study polymer stability in the biological environment.

Current Status:

The GIRD project commenced in 1989 and will run to 1991.

		1989/90	1990/91
<i>Resources:</i>	DCP	2 prof, 1 tech	2 prof, 1 tech
	DCP & UNSW	4 prof, 3 tech	4 prof, 3 tech

R&D

Productivity: The project arises principally from the capability and accumulated expertise of the Division in the synthesis, surface modification and characterisation of polymers for specialty applications. Research productivity is equally dependent, however, upon the development of understanding of the biological processes involved at the biomaterials interface in the biocompatibility of the implant.

The short term goals of this project, as well as other biomaterials projects within the cardiovascular submarket, are dependent upon the ability of research collaborators to conduct animal evaluation of implants. Successful development of accelerated test systems for haemocompatibility is likely to be important in the productivity of this project.

A related need is specialized processing/fabrication equipment capable of handling small experimental quantities of material.

R&D Yield:

The present total market value of polyurethane devices for cardiovascular and extracorporeal applications is approximately \$1bn worldwide. Improved polyurethanes are sought to maintain and expand current market position. Improved polyurethanes will also make available new products and be incorporated into devices that currently use inferior materials (e.g. silicone, PVC). There are also potential benefits for chronic heart assist devices.

This GIRD project has a consortium of Medical Engineering Research Association (MERA) companies (including Cyanamid Australia, Telectronics Pty Ltd and Terumo Australia Pty Ltd) and opportunities for commercialisation of research output is therefore high.

A provisional patent application has been filed to cover 3 classes of synthetic polyurethane. Significant knowhow exists and further applications will be made when more biological test data become available.

Submarket: CARDIOVASCULAR4.3 **Biomaterial Coatings for Small Diameter vascular Grafts and Percutaneous Implants**

Researchers: DBE, DCP and UNSW (Centre for Biomedical Engineering).

Objectives: To develop prototype vascular prostheses and percutaneous access devices containing biomaterial coatings and evaluate their performance in animal trials.

Description: The two biomaterial surfaces to be evaluated arose from a previous GIRD (National Biotechnology Program) project between CSIRO (Division of Biotechnology and DCP) and Telectronics Pty Ltd.

Limited initial animal trials were conducted in 1989 in a Telectronics-funded project conducted by the Division of Biotechnology and the University of New South Wales.

The two surfaces developed during the GIRD project each show greatly enhanced capacity to support attachment and growth of fibroblasts and endothelial cells, including human artery and vein endothelial cells, when compared to unmodified fluoropolymers such as Teflon.

The research activity aims to evaluate these surfaces as modifications of devices for two applications where good polymer-cell interaction would be desirable: percutaneous access devices, where good tissue integration is needed to give effective infection; and small diameter vascular grafts to be used in conjunction with endothelial cell seeding techniques.

<i>Resources:</i>	1990/91	1991/92
DCP	0.65 prof*	0.65 prof*
SRF#	1 prof, 1 tech	1 prof, 1 tech
DBE	1.25 prof*	1.25 prof*
SRF#	3 prof, 3 tech	3 prof, 3 tech

Proposed syndicated research funding

* Supervisory staff funded by SRF

Current Status:

Following the Pacific Dunlop takeover of the Nucleus group of companies, Telectronics and CSIRO wish to recruit additional commercial partners to the project. An Expression of Interest process is being conducted (April-June 1990) and venture capital funding is being sought.

Patent applications for the two biomaterial surfaces and related methods have been lodged (complete specification in 1989). The method of manufacture of one of these surfaces is proprietary to CSIRO.

R&D

Productivity:

This project has generated two novel polymeric biomaterial surface coatings that require testing for performance in conjunction with the method of "Endothelial Cell Seeding". This method is in clinical trials at present and suitable enabling technology has been marketed in kit form by W L Gore. Endothelial cell seeding should enhance the development of small diameter vascular grafts, a market for which is large and for which there presently is no satisfactory synthetic graft.

R&D Yield:

A report on the commercial value of an investment in a project to evaluate these biomaterial surfaces in small diameter vascular grafts and in percutaneous access devices has been prepared by Invetech.

The report noted the high degree of risk inherent in this type of R & D activity, but was favourable in its assessment of the project.

SUBMARKET: EXTRACORPOREAL**4.4 Ultrasonic Blood Characterisation**

Researchers: DAP

Objectives: The development of instrumentation for characterising blood by measuring the flexibility of red blood cells.

Description: The collection, storage and transfusion of blood is an important part of medical practice. During storage, blood deteriorates through the loss of flexibility of the red blood cells, a condition that can also result from certain pathological conditions in a patient. Research at DAP has shown that it is possible to monitor the flexibility of red blood cells ultrasonically.

This project aims to further research the interaction of ultrasonic waves with blood cells to arrive at a reliable means of testing blood.

It further aims to develop the technology required to make measurements on blood quickly, conveniently and at a low cost so that the technique can be widely adopted as a recognised standard method.

Current status: Work has been progressing at a low level for three years..An injection of commercial funds will enable completion of the project within three years.

<i>Resources:</i>	Person-years	
	1989/90	1990/91
DAP Appropriation:	0.5	0.2
External		1

R&D

Productivity:

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The feasibility of the technique has already been demonstrated and the aims are believed to be achievable .

At the present time there is a world lead in this area of research but levels of resource commitment have been low. The project depends on external funding to achieve an adequate level of efficiency .

R&D Yield:

The potential Australian market for the products of this research is estimated to be \$12m per annum with the world market up to 50 times that. There is currently no similar or competitive device on the market.

Certain aspects of the technology are protected by patent and there is a significant know-how component. Customers are available for the technology who have necessary end-user relationships. There is still a wide window of opportunity.

A favourable report on the commercial value of this project has been prepared by Invetech.

Submarket: DENTAL

4.5 Collagen-based biomaterials for periodontal repair.

Researchers: DBE, University of Melbourne, Wool Technology.

Objective: To develop a collagen-based biomaterial for periodontal repair.

Description: Periodontal disease is characterised by the loss of the connective tissue attachment of teeth and by destruction of the supporting bone. Currently, progress of the disease cannot be reversed easily. The predisposition of epithelium to ingrate rapidly and prevent the regeneration of bone and connective tissue attachment is seen as the main hindrance to therapy. Implementation of a suitable barrier to control epithelial ingration provides a new approach to therapy.

Links to other

Research: Dental studies provide an ideal model for development of products for hard tissue regeneration and osseointegration. Pilot studies on a complex of collagen with a calcification inducing peptide are in progress. The membrane may have other surgical applications.

Current

Status: A collagen-based membrane barrier with good physical and mechanical properties has been developed. This material has been used successfully in animal studies for repair of periodontal degradation. Application is currently pending for clinical evaluation.

Resources:

	1990/91	1991/92
Approp		
DBE	0.5 prof	0.5 prof
DWT	0.2 prof	
External		
U Melb	0.5 prof, 0.5 tech	0.5 prof, 0.5 tech
DBE		1.5 prof, 1.0 tech

R&D

Productivity:

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it does not invoke an immunological response nor lead to proliferation of inflammatory cells, and it encourages new bone formation.

R&D Yield:

Research has previously been supported by a commercial partner (Wallace) and a new partner should now be sought.

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Submarket: OPHTHALMIC**4.6 Stabilised collagen gels for ophthalmic applications**

Researchers: DBE, Division of Wool Technology

Objectives: To develop stabilised, translucent collagen gels for ophthalmic applications

Description: This has been a very low level activity which arose from previous research in the Division of Protein Chemistry. Studies on the structure and packing of collagen in tissue (using a rat tail tendon model) conducted by the former Chief, Dr Fraser, required that a mild method of introducing specific cross-links which did not perturb the collagen packing be developed. It was later realised that the cross linking method which had been developed may be suitable for collagen gel stabilisations. Subsequent studies showed this to be the case.

Current Status:

Research to demonstrate the concept has been completed and material for a provisional patent application prepared. Studies to see whether the technology could be used to stabilise gels of the denatured form of collagen, gelatine, have now been completed, so the application should be lodged in June 1990.

<i>Resources:</i>	1990/91	1991/92
DBE	0.2 prof	0.2 prof
DWT	0.1 prof	0.1 prof

R&D

Productivity: The possible products which could emerge from the trials include, corneal shields as "dressings" after eye surgery, drug delivery systems for both clinical and veterinary use and contact lens materials. These products can be based on highly purified, non-immunogenic collagens which provide an advantage to potential competitive products.

R&D Yield: Materials suitable for testing are available and once patent protection is available, commercial support can be examined for continuing this phase of development. It is expected that funding of the additional development could be by the commercial partner, with on-going technical input from CSIRO.

Development of a "disposable, extended wear, contact lens, would probably have high economic value.

Submarket: RECONSTRUCTIVE**4.7 Improved Carbon Fibre Reinforced Carbon (CFRC) for Human Implants**

Researchers: DAP in Association with UNSW (Centre for Biomedical Engineering) and St George Hospital (**GIRD**).

Objectives: To demonstrate that the improved wear resistance characteristics of ion irradiated CFRC can lead to superior prosthetic devices.

Description: Irradiated CFRC materials offer the major advantages of iso-elasticity, improved wear resistance, enhanced robustness and potentially substantial cost savings. This project aims to demonstrate, in a series of test stages, the mechanical and biocompatibility advantages of prosthetic devices manufactured to make optimum use of these characteristics.

Current

Status: The GIRD project commenced in 1989 and will run to 1992.

		<u>Person - Years</u>		
		1989/90	1990/91	1991/92
<i>Resources:</i>	DAP	3	1.25	0.75
	UNSW	1.25	1.25	1.25
	St George Hosp.	0.25	0.25	0.25

[**R&D**
Productivity:

However, it is an area of application where we have a substantial know-how advantage over potential competitors. We believe that we are the only group currently pursuing the use of ion irradiation to improve the mechanical properties of CFRC materials. The assembled team covers the

important areas of ion beam technology, bio-engineering assessment and user (i.e. orthopaedic surgeon) assessment. It is highly likely that we will generate primary information in the field.

This is a new awareness of research which acts individually for the CSIRO and the other parts of the

R&D Yield:

The majority of implantable structural devices used in Australia are imported. Targeted prosthetic devices are primarily manufactured in Switzerland and the USA. The current world-wide market for these devices, both dental and reconstructive, is about A\$1bn, the larger part of which (80%) is in the latter category. The Australian component is about \$20m.

This GIRD project has the Sedgman Group as commercial partners. While not experienced in the field of biomaterials, this group have strong credentials for exporting new technology in cooperation with CSIRO.

Submarket: RECONSTRUCTIVE**4.8 Alloys for Medical Implants***Researchers:* **DMST***Objectives:* The development of improved alloys and associated surface treatments for medical implants.*Description:* DMST is involved with a team orthopaedic and dental surgeons in the possible formation of a joint venture company to produce within Australia surgical prostheses and other implants, initially for the local market but with a long term view to the export market, especially SE Asia.

The initial thrust of the program will be to produce an Australian hip prosthesis of superior design from currently accepted medical alloys (Co-Cr-Mo type). DMST would provide the technical infrastructure and characterisation capability for this phase of the project. The next stage of the project would be the development of improved alloys and finishing techniques and to make use of ceramic components both to reduce wear and to enhance the osseointegration of prostheses.

Current Status:

The project is essentially at the feasibility stage. While the market within Australia is more than adequate to support an Australian company, the conservative nature of the medical profession and surgeons in particular, makes it difficult to estimate the market penetration that is likely to be attainable.

A cementable hip prosthesis is being designed and reactions to this design will be sought from a wide range of orthopaedic surgeons before the future of the project is decided. Department of Veterans Affairs has indicated a positive attitude to the project and would support the application for an NPDP grant for the first phase of the project if it proceeds.

Resources: Resources for future research dependent on nature of research collaboration with Meditech, uncertain at this stage*R&D**U;i Productivity:* Competitive with other groups in the world*R&D Yield:* The market potential within Australia for hip prostheses alone is of the order of \$20m and all are currently imported. The SE Asia market is very large and unlike the general world market is expected to be very price sensitive.

SUBMARKET: RECONSTRUCTIVE/EXTRACORPOREAL**4.9 Biomedical applications of Sintered Hydroxyapatite Ceramics in Reconstructive Surgery and for Percutaneous Feed-Throughs**

Researchers: DMST, UNSW (Centre of Biomedical Engineering), University of Melbourne (Department of Otolaryngology), Telectronics.

Objectives: To develop methods to highly sinterable hydroxyapatite powders and fabrication techniques for the production of near-net shape, dense, HAP ceramic bodies.

To collaborate with various end-users in the design and construction of prototype HAP components for clinical trials.

Project

Description: Because of its bio-compatibility, $\text{Ca}_{10}(\text{OH})(\text{OH})_2$ HAP is a prime candidate for many applications where mechanical strength, wear resistance, and non-irritability are of importance. Because of its powder processing and ceramic fabrication skills, the DMST has been examining the production of relatively strong HAP pieces with near-net shapes after sintering. These components will be incorporated into more complex devices or be employed in certain surgical procedures by the collaborating partner.

Current

Status: In the past 12 months, experimental parameters have been established to produce fully (99+%) dense HAP and dense, graded HAP/whitlockite (ie, Tricalcium Phosphate) ceramic bodies. Under some conditions, a translucent form of HAP has also been obtained. Tensile strengths of sintered HAP pieces have reached 120 MPa (4-point bend method). Small ceramic pieces with intricate shapes, such as buttons, ferrules and lugs, have been fabricated.

Three bio-medical applications of these sintered HAP components are currently being examined in collaboration with outside researchers:

- i) Cochlear implants - fabrication of micro-ferrules for electrical feedthroughs between middle and inner ears.
- ii) Orthopaedic - anchors for artificial anterior cruciate ligaments (ACLs).
- iii) Soft Tissue - percutaneous input/output devices for periodontal cardiac pacemaker power supplies and for renal dialysis feedthroughs.

Resources: To date approximately 1.5 man-years ES effort have been expended by the DMST on producing HAP powders and fabrication of sintered components. Extensive use of the Division's powder processing, ceramics and physical characterisation facilities have been required. In 1990/91, the collaborators will expend at least a comparable effort.

R&D

Productivity: In view of the expertise in powder and ceramic processing within the DMST, research productivity has been high to date. When coupled to the existing achievements by our collaborators in areas such as the cochlear implant and pacemaker design, this expertise can be targeted to specific commercial goals within a relatively short period.

The ability to design, prepare and fabricate custom HAP devices, should allow several Australian bio-research programs to proceed much further than they would otherwise (e.g. that on artificial ACLs). However, in practically all cases the value of the HAP components, is minor when compared to the materials or intellectual value of the complete device or surgical procedure. Any competitive advantage we develop will depend in the total package filling a market niche or enabling new markets to develop. Numerous applications of HAP have already been commercialised or are being actively investigated throughout the world.

R&D Yield: Our research skills in powder and ceramics processing place us in a competitive position. There is ample scope for further technical development of HAP devices, when closely linked to end-use. Resource commitment is adequate if it can be maintained at current levels - any possible future increase in resources should be derived from the end-users.

Submarket: WOUND MANAGEMENT**4.10 Collagen-based biomaterials for wound management.**

Researchers: DBE, University of Melbourne.

Objective: To develop collagen-based biomaterials for wound management.

Description: Collagen is the principal protein component of all connective tissues, including skin, bone, tendon, ligament and cartilage. Because of its vital role in tissue, it has been long been seen as having the potential to provide the basis of biomaterials. To use collagen as a biomaterial, it is made soluble, purified, and reconstituted into material which retains the packing of the native structure. In this process, the immunogenicity of native collagen can be essentially eliminated.

Collagen has extremely useful biological properties which can be exploited in the development of collagen-based biomaterials. It interacts with platelets and to activate the coagulation cascade, culminating in the conversion of fibrinogen to fibrin. Also, it plays a vital role in the extracellular matrix for adhesion, organization, differentiation and growth of different cells.

The work has established technology to produce a cost effective, purified and reconstituted collagen product, which retains the essential biological properties of native collagen but is not immunogenic. Current research is developing this material in a form suitable for guided tissue regeneration in wound healing applications.

Links to other

Research: The materials which have been developed have uses in applications beyond wound management, including use as a coating to assist in tissue integration for other devices, providing synergy to other Institute projects. The technology developed has been transferred to parallel studies in dental repair.

Current status:

The technology which allows the collagen to be reconstituted in various forms, including powders, dry sponge-like sheets, wet membranes, and so forth has been established using reconstitution of enzyme solubilized and purified collagen. This material behaves like native collagen; it is effective in causing platelet aggregation, and is a suitable substratum for

cell attachment and proliferation. Tests have confirmed that the material was non-immunogenic and endotoxin free.

Resources:	1990/91	1991/92
DBE Approp	0.5 prof	0.5 prof
External		
	U Melb 0.5 prof, 0.5 tech	0.5 prof, 0.5 tech
	DBE	1.5 prof, 1.0 tech

R&D

Productivity: The increased understanding of the biology and biochemistry of collagen, has led to an enormous number of potential medical uses for collagen. A few have been developed to a commercial level so that they are widely available in a standard form with reproducible properties and performance standards. Previously, collagen has not been a cost effective material for many purposes. The novel technology, for which a patent has been awarded in Australia with applications pending overseas, has provided a cost effective means of producing medical grade collagen in a variety of formats.

This technology is highly competitive with other groups in the world. The research group has been internationally recognised for their expertise in the uses of collagen as a biomaterial.

R&D Yield:

The market potential for use of collagens in a range of wound healing applications is very high - the world market is currently estimated to be \$SOM with an annual growth rate of 25%. This project received significant funding, \$500,000, from Wallace which has allowed the development and testing of the technology. Progress has been such that it is now beyond the stage which may be suitable for GIRD support.

Submarket: STRATEGIC RESEARCH**4.11 Evaluation of biomaterial performance for wound management, dental, cardiovascular, and other submarkets**

Researchers: DBE, University of Melbourne.

Objectives: To develop a range of highly specific monoclonal antibodies to connective tissue proteins, especially the collagens, for use in immunohistological evaluation of the host response to biomaterial implants. These data will enable the development of new or enhanced products.

Description: The technology which is being developed is generic, and pre-competitive. It offers advantages to CSIRO and to Australian companies involved in the development of a broad range of biomaterial implants. Although in vitro trials and experiments are important during the initial stages of biomaterial development, potential new products still require extensive testing in animals. These tests are expensive, particularly when long-term studies are required. A method which provides an early and more accurate evaluation of performance will reduce costs and allow selection of materials for optimum performance.

Links to other

Research: The antibodies have a broad range of other applications, including use in normal histopathology, and in serum-based diagnostic screening. Support from the CSIRO/University of Melbourne Research Fund has been provided towards the cost of a pilot study on diagnostic screening. Their use in understanding collagen-antibody interactions has received support from the CSIRO/UTS Research Fund. Certain antibodies affect collagen-induced platelet adhesion and aggregation and so may provide important data on this mechanism.

Current

Status: Seed funding for this topic was provided by the MERA. The topic has recently been supported by a GIRD funding offer which is expected to commence shortly, October 1990. The range of techniques needed for the project, including antigen-directed electrofusion, a new electrophoretic assay and histological approach to screening have been established and initial antibodies obtained. Preliminary application of the antibodies to biomaterial evaluation have been successful. A model system for generating fibrous capsule is being established.

<i>Resources:</i>		1990/91	1991/92
	DBE Approp	1.8 prof, 0.5 tech	1.8 prof, 0.5 tech
	External		
	DBE	1.5 prof, 0.5 tech	1.5 prof, 0.5 tech
	UMelb	0.5 prof	0.5 prof

R&D

Productivity: The researchers have established a lead compared with other groups on the immunohistological evaluation of connective tissue proteins for implant retrieval analysis.

R&D Yield: Seed funding from MERA and GIRD support have been obtained.

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Submarket: STRATEGIC RESEARCH**4.12 Collaborative DBE-DCP evaluation of biomaterial surfaces (for cardiovascular sub-market)**

Researchers: DBE, DCP

Objectives: Evaluation of polymeric materials produced at DCP for biomaterials applications, by screening compatibility for cell attachment and growth.

Description: This has been a low key principally tactical activity, conducted by staff on appropriation funding. DBE and DCP have conducted evaluations since 1988.

Surfaces evaluated in this program during 1989 led to two patent applications and one aspect of the GIRD project "Molecular design of bioactive surfaces" (see section 4.2).

Links to other Research:

This has been an embryonic project which has nevertheless been quite profitable in tactical results. DCP has further groups of surfaces for evaluation and the extension of these studies has been proposed to permit a strategic approach. The proposed extension using chemical syntheses, blending and surface modification, has the potential to produce biomaterials that have superior performance at the blood interface. It would however require improved haemocompatibility testing to be established as a **CSIRO** effort.

<i>Resources:</i>	1989/90	1990/91
DCP	1-2	
DBE	O.Sprof, a.Stech	Limited by resources

R&D

Productivity: DCP has a capability to generate advanced polymeric material of controlled structure that are highly likely to offer improved properties at the biological interface. The synthetic and surface modification skills are competitive on an international basis.

Submarket: STRATEGIC RESEARCH**4.13 Studies of cell matrix interactions for cardiovascular, biotechnology and other submarkets***Researchers:* **DBE***Objectives:* Interaction of cells with extracellular matrix (ECM) and other signal molecules, in order to understand mechanisms of tissue structure and the maintenance of cell phenotype. The findings can then be exploited in the development of novel biomaterial surfaces for use within tissue implants as well as for in vitro biotechnological applications.*Description:* The study of the interaction of cells with extracellular matrix and trophic factors is essential to the rational design of biomaterial surfaces for applications where good tissue integration is required (e.g. some cardiovascular applications, such as endothelial cell seeding, percutaneous access devices etc.).

This project approaches the study of tissue structure by development of a panel of monoclonal antibodies raised against components of ECM. The panel of monoclonal antibodies permit the structure of the ECM to be determined and also the analysis of the role of ECM components in determining the phenotype of attached cells.

The studies are at the stage that monoclonal antibodies to adhesive glycoproteins found in both ECM and in serum have been developed and characterised.

Links to other Research:

These studies have shown that for a range of synthetic polymeric biomaterials, colonisation with tissue cells is dependent upon adsorption onto the biomaterial surface of certain adhesive glycoproteins. This finding has obvious importance for the use of polymers in biomaterial applications where attachment and growth of tissue cells (such as endothelial cells) is desired, and has led to one aspect of the "Molecular design of bioactive surfaces" project (see section 4.2).

The monoclonal antibodies developed in this project enable sensitive screening of biomaterial surfaces for adsorption and orientation of these adhesive glycoproteins,

and give the project a competitive advantage in the design of biomaterial surfaces, particularly for in vitro biotechnological applications.

Some of the monoclonal antibodies developed in this project have been licensed as research tools to Life Technologies Inc. as research reagent tools and as manufacturing tools for the preparation of cell culture components.

Resources:

	1989/90	1990/91
	2 prof, 2 tech	1 prof, 2 tech

S. FUTURE BIOMATERIALS RESEARCH

The analyses in Section 4 underscore the size and variety of biomaterials research within IIT. The current level of CSIRO research effort in this area is some 11-12 professional-scientist-years, a figure to be augmented if syndicated research funds become available.

Five questions were raised in the introduction. Each of these is addressed below.

Should CSIRO be involved in biomaterials research?

The international markets for biomaterials are large and are growing rapidly. While much of biomaterials R&D is high risk, due to long lead times and regulatory barriers, in most cases this is matched by potentially very high returns.

CSIRO, and Australia's skills in the area are well established, and in certain areas well recognised. In addition to its strong skills in biotechnology and cellular and molecular biology (in DBE), IIT is strong in skills in materials science and in polymers (both synthetic and natural) and in surface modification techniques (in DCP, DMST, DAP and DBE). Integration of materials and biological skills are essential to almost all aspects of biomaterials development.

On the other hand there are problems in capturing the benefit of successful research for Australia. There is not a well-developed commercial infrastructure in Australia able to support longer term research and trialling and to provide effective entry into international markets.

Future research projects need to be closely linked to areas where there is effective, integrated strategic research, prospects for successful commercial collaboration with a clear commercial return to this country (see previous discussion in Section 3).

What is the appropriate balance of short and longer term research?

There is not a large established biomaterials industry in Australia, which the IIT can enhance by its activities. Appropriate emphasis, with an increased priority, could be placed on those projects which may get products to market in the shorter term such that a large industry involvement in this manufacturing sector can be established. These projects could be either those which are at an advanced stage of development or those which require a shorter time to market because they are in low patent-risk categories.

At the same time a significant level of fundamental research on biomaterials is needed in order to generate intellectual property for future commercial materials and sustained returns on this research. For this, it is important that the portfolio of projects not be all "me-too" in character. Moreover, the long-term nature of biomaterials research/

development/trialling calls for substantial strategic studies in parallel with the early tactical phases, in order to reduce the risk of project failure at a later tactical stage due to inadequate studies at a basic level.

These factors - the long term nature of biomaterials research and associated commercial returns - point to a relatively high ratio of strategic:applied (tactical) research overall.

What is the preferred commercialisation strategy?

Equally the commercialisation strategy needs to be long term in nature. At present CSIRO is only in the early stage of its commercial collaborations. Indeed collaborations -most over periods of less than 5 years- have involved experience in the R&D phase rather than commercialisation.

How can CSIRO enter into arrangements that will maximise returns to Australia? Access to world markets is essential for market success in practically all biomaterials. But it has to be recognised companies will be attracted to move manufacturing and R&D closer to major markets (notably USA) - as has been the case with Nucleus/Telectronics.

Key commercialisation considerations include:

- worldwide market prospects

- early company involvement, to maximise:

- technical evaluation of products
 - assistance with project direction
 - marketplace assistance
 - financial support

- access to Government offsets and opportunities for longer term development funding

- some projects will require substantial extra years funding for continuing development, animal and clinical trialing. Government funding schemes to support this activity will maintain CSIRO equity in these projects and reduce reliance on commercial collaborators

- development of arrangements involving more than one company

- this could be via a consortia of companies to interface with strategic research, with a view to developing a long-term commitment between companies interested in the biomaterials area at the level of a strategic research program, rather than simply individual deals concerning specific projects. Alternatively strategic alliances involving smaller local companies and large (often multinational) companies equipped to address overseas markets.

- strategic employment of research funding opportunities (such as GIRD

The GIRD scheme has been successful in stimulating commercialisation of CSIRO research at an early stage, and has provided clear opportunities for developing commercial interactions with consortia of companies. Nonetheless it is important that future research not just be responsive in character, for example in relation to opportunities provided by the GIRD scheme. A better balance for example is possible than at present when, in cardiovascular and related devices, research on haemocompatibility is applicable to three existing GIRD projects, although CSIRO itself has no research effort going into the mechanisms of interactions of materials with blood.

What are the priority areas for research?

Major areas of current research are looked at first, followed by other areas of promising research.

Biotechnology/Biocompatibility:

DBE's strengths in this area, particularly in relation to the cellular and molecular biology aspects of biocompatibility, are mainly being applied to specific submarkets (as discussed below), but could provide the basis for an expanded generic research program into biocompatibility which could benefit all Divisions of the Institute. A strengthened capacity in this area would benefit the development of enhanced biomaterials in most submarkets, notably through incorporation of novel biological molecules (including growth factors) into the devices. Consideration should be given to additional resources into strategic research for this area, building on existing skills.

Cardiovascular:

Polymer modification and synthesis technologies permitting enhancement of existing devices are of high commercial interest. Modification of the surfaces may be either by chemical means or by the application of a chemical-biological composite (Section 4). The polymer technologies also have application in a range of other submarkets. An important threshold question in cardiovascular research is the need for a haemocompatibility strategic research base.* Factors such as market size and local manufacturing activity underlie the case for increased strategic research in this area. Alternatively serious consideration should be given to withdrawing from this area of research once GIRD projects expire should this not be added to the portfolio of CSIRO biomaterials research.

Maxillofacial:

Although currently a small project this is soon to move into clinical trials. Since dental products are generally considered a low risk/materials for patients, the regulatory approval periods are often shorter, allowing for the more rapid development of marketable products. The market is not monopolised by a few overseas companies, and opportunities for developing Australian products may exist.

Orthopaedic:

The expertise in ceramics may be of particular interest in this market. A wide range of opportunities exists for the manufacture of low-risk devices which could be developed in the short-term. Developments in other areas may have long-term potential for import replacement, but could be competing with a few well established companies in overseas markets.

Wound management:

In wound management, including tissue repair, the major growth markets are for synthetic and biological dressings, with further opportunities for composites with biological factors arising from biotechnology research. The strong research base for collagen which exists is particularly relevant to this market segment.

Implanting of any biomaterial devices leads to some form of **wound**. Therefore, additional strategic research into wound healing and tissue repair should lead to benefits in a broad range of submarkets. For example, development of devices incorporating growth factors will undoubtedly impact on a broad range of biomaterials used in implanted devices.

• *Low Thrombogenicity surfaces for Cardiovascular and Extracorporeal Applications*

The cardiovascular and extracorporeal submarkets are substantial in size (Table 1) and there are a number of Australian-based firms (including firms that are local manufacturers) active in these submarket areas (Table 2). To be useful in the cardiovascular and extracorporeal markets, a biomaterial needs to be poorly thrombogenic, i.e. not induce blood clotting during either acute or chronic exposure to the blood. Exactly what chemistry is desirable in order to make a biomaterial surface resistant to blood clotting is very poorly understood. The biochemical rules that govern blood-surface interfacial interactions need to be elucidated in order to provide a strategic base for the rational design of biomaterials for direct blood contact applications.

IIT has projects in collaboration with the University of New South Wales in which the effect of various changes in surface chemistry upon blood compatibility are being examined, but these projects are somewhat empirical in approach. UT does not have a commensurate, strategic research base into biomaterial-blood interfacial biochemistry, which would allow for a more rational design of biomaterial surfaces for use in direct contact with the blood. To develop such a project to analyse biomaterial: blood interactions would require a new research team, a collaborative effort between DBE and DCP and would be best conducted in collaboration with a Biomedical Engineering Department and/or Haematology Department in a major teaching hospital or appropriate research groups overseas eg in the UK. Such a new team would be able to draw upon related expertise and research tools in both the Parkville and North Ryde laboratories of DBE and chemical modification and analysis skills of the Biomaterials and Membranes groups of DCP.

Other Areas:***Drug delivery:***

Drug delivery is a major growth area (60% per annum) as many of the new biotechnological pharmaceuticals need specialised delivery systems. The polymer and biochemical approaches to this technology could be priority areas for new research.

Ophthalmology:

Opportunities in this field will probably arise from research activities in other areas of biomaterials research, and would probably need early commercial involvement.

Equipment/Devices:

Australia's expertise in scientific equipment development and manufacture provide a strong background for future development in biomaterials-related equipment and devices. These products, in some cases, may enable a short term entry into overseas markets. There is significant synergy with the development of biosensor technology as mentioned earlier in the report.

What are the appropriate funding and administrative arrangements?

During this review it became clear that there is a need to improve communication between researchers in different parts of the Institute (and elsewhere in CSIRO) working in the biomaterials area. In addition, improved coordination of business contacts maintained by separate parts of CSIRO is a priority.

Due to the broad scope of biomaterials projects being conducted in IIT unification into one interdisciplinary program would be complex and may not be the most effective means improving communication and coordination. Instead it is recommended that a technical meeting involving biomaterials researchers be organised for the purposes of:

to exchange information on present projects and objectives, technical capabilities and skills, business opportunities and plans

to identify research synergies, and methods for effective interdisciplinary contacts to best exploit CSIRO skills in the biomaterials area

to review support for individual projects (considerations as to minimum critical size are important here)

,to review needs and opportunities associated with a strengthened biocompatibility strategic research effort

to review existing and proposed strategic research in projects involving haemocompatibility (see discussion above) and decide how to proceed, noting that setting up a strategic base in this area would require substantial funding. (One option could be a collaborative research program with other Australian or overseas groups with established strategic research in mechanisms of haemocompatibility.)

to consider the potential synergy between biomaterials and biosensors technology and links with IIT work on biosensors, with a view to strengthening strategic research in areas of overlap.

Decisions on appropriate funding and administrative arrangements could then follow consideration of the outcome of this meeting by the IIT Director and Chiefs.

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APPENDIX 1

Biomaterials industry segments, with examples of products within each category:

Artificial Organs

artificial pancreas
artificial kidney - Extracorporeal membrane oxygenators

Biosensors

in vivo/in blood chemistries

Biotechnology

process/purification membranes
enzyme or cellular immobilization substrates
cell culture systems {hollow fibres, microencapsulation}
fermentation polymers {PHB}

Cardiovascular

vascular grafts
heart valves
artificial hearts

Commodity/Disposables

catheters {angioplasty}
syringes
gowns/gloves

Drug Delivery/Hybrid Artificial Organs

in vivo controlled/sustained release {ocular, uterus)
transdermal release
insulin pumps
artificial pancreas
extracorporeal therapy
synthetic oxygen carriers

Maxillofacial, Dental, Ear Nose & Throat, Cranial

artificial teeth
soft tissue
mandibular augmentation
ossicular replacement and reconstruction
intracochlear and extracochlear prostheses for the
profoundly deaf

Ophthalmology

contact lenses
intraocular lenses
artificial corneas/intraocular implants
vitreous implants
bioadhesives

Orthopaedics

- artificial joints (hip, knee)
- artificial bone (ceramic, "bioglass," hydroxyapatite)
- fixation plates/screws
- fixation cements (PMMA)
- spinal fusion
- tendon prostheses
- artificial ligaments

Packaging

- personal care/hygiene (sanitary napkins, tampons, condoms)
- diapers
- environmentally degradable polymers
- parenterals

Wound Management

- sutures
- bioadhesives
- dressings
- staples
- artificial skin
- burn dressings

From: Barenberg, S. A (1988) *J. Biomed. Materials Res.* 11(12)
1267-1291.