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14. ABSTRACT

This project sought to discover new genes involved in mammary gland carcinogenesis using ENU mutagenesis. The initial approach involved screening ENU mutagenised mice for mammary tumors. Screening of 1100 mice by mammary whole mount histology identified a number of pedigrees with mammary tumours attributable to ENU-induced recessive mutation. We failed in all cases to recapitulate the original phenotype in subsequent rounds of breeding, indicating the influence of environmental mutagenic events in this initial screen. In our second attempt we are screening for reduced latency to palpable mammary tumors in response to expression of a doxycycline-inducible myc oncogene, that is produced by the loss of a second gene knocked out by random ENU mutagenesis. This screen is currently underway. A number of factors have slowed the progress of this project. Firstly the unexpected failure of the first screen forced a change in strategy. The new strategy, employing oncogene sensitization, required the import of a mouse model from the USA. Stringent animal house regulations in Sydney and Canberra forced this line to be rederived twice by embryo transplantation. The failure of the first round caused the loss of our space in the ENU facility, and new space only became available following the construction of a new ENU facility in Canberra. Despite these set backs we are continuing with the project using funds obtained from the Australian NH&MRC, and hope to discover new oncogenes cooperating with myc during carcinogenesis.

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Introduction

To date there has been no systematic search for genes controlling mammary development and carcinogenesis, and this project seeks to undertake the first such search by participation in the large scale ENU mutagenesis project currently being conducted at the John Curtin School, Australian National University (ANU), Canberra.

Body

Functional characterization of genetic loci is urgently required if the completion of the mouse genome is to be of immediate benefit. This requirement is being met in a number of ways, including a number of large scale ENU mutagenesis projects under way worldwide. Of these, just three are undertaking genome wide recessive screens. Recessive mutations, requiring the loss of function of two alleles, provide far greater insight into the genetic control of normal development and carcinogenesis than dominant, gain-of-function mutations, but require more complex breeding of pedigrees. This has been achieved at the ANU, where the established program of ENU mutagenesis has recently received significant financial support from the Australian Federal Government ($A11.5 million Major National Research Facilities Grant) and The Australian National University ($A8 million) for the construction of expanded animal handling facilities. This facility is now operational and has been further supported by an $8 million Enabling Grant from the National Health and Medical Research Council. Our participation in the application for these grants, made possible by funding from the US Army BCRP for ENU mutagenesis projects at the ANU, provided multi-Institutional support for the proposals that was crucial for their success.

We adopted this technology early in its evolution at the ANU and screened the pedigrees that were produced by the first round of mutagenesis. Screening was undertaken using whole mount histology of the 4th inguinal mammary gland. Approximately 1100 mice were analyzed, and a number of abnormalities and tumors were identified. From these 6 pedigrees were selected

for propagation. Male siblings of affected females from these 6 selected pedigrees were used to recreate the pedigrees using a 3 generation inbreeding scheme. Members of these pedigrees were tested by mammary biopsy to identify affected individuals that could then be used to establish stable breeding lines and begin the mapping crosses. As detailed in our first annual report this strategy failed as we were unable to reproduce tumors at the frequency at which they were first detected. As a result of the failure of this first attempt we lost our animal holding space within the ANU facility to competing ENU mutagenesis projects. Consequentially we were forced to wait for the construction of the new facility to continue, and in this time we investigated alternative approaches that we could take.

We believe that our failure to reproduce the tumor phenotypes detected in the original screen was due to the multiple mutations required for tumor formation. In the original screen the ENU provided a sensitizing mutation, and the environment the subsequent mutations required for tumorigenesis. By definition these subsequent hits occurred within a short time frame to allow the detection of tumors at 8 months. When we attempted to recapitulate these pedigrees we believe that although the ENU mutation was present, the other hits did not occur within the time frame allowed by the necessity to breed from affected animals.

We had expected that a single mutation provided by ENU would provide sufficient sensitization to tumor formation for success, but the experiment has shown us otherwise. This failure has led us to redesign our methodology to include a sensitizing event in the background, allowing ENU to provide a second hit. We believe that introduction of a transgenic oncogene into the background will enable ENU to provide a second hit in the carcinogenic process. We believe, based on the proven enhancement of carcinogenesis by combined oncogenes (such as myc and ras), that this approach will allow us to regenerate pedigrees with enhanced tumorigenesis due to the ENU-induced loss of tumor suppressor gene function.

In year one to two we investigated the constitutively active C3-SV40T transgenic model as a prototype transgenic model. The issue with such models was whether the pregnancy-induced decrease in tumor latency, which is seen in most mammary specific transgenic models due to the

sensitivity of the MMTV promoter to pregnancy hormones, would hamper successful breeding of our pedigrees. We examined 58 breeding pairs held at the Garvan Institute. Twelve (21%) females were unable to wean pups due to tumor burden following the first pregnancy. Of the 36 animals examined following a second pregnancy, 27 (75%) were unable to wean pups. Ethical considerations, of <10% tumor burden, generally precluded a third mating. This investigation demonstrated that constitutive transgene expression would greatly hamper the breeding of pedigrees and the mapping crosses, especially as we would expect tumor latency to decrease in the context of an ENU-induced loss of a tumor suppressor gene.

An inducible transgene system is required. Such a system was constructed in the laboratory of Dr Lewis Chodosh. It utilizes the MMTV promoter to drive the expression of the reverse tetracycline-dependent transactivator, resulting in mammary specific expression of the tet-operator controlled transgene in response to treatment with tetracyclin. This model is insensitive to the hormonal state of the animal and shows no tumorigenic activity in the absence of doxycycline . We know from our experience to date that a single ENU-induced mutation does not hamper the breeding of pedigrees, and so use of this system, where transgene activity is induced for screening, but remains off for animal propagation, offers us the best method of achieving our aims.

The transgene of choice would induce tumors with a latency of six months or more, allowing us to find animals harboring homozygous ENU induced mutations due to significantly decreased latency. The transgene should also have direct relevance to human breast cancer. Ideally, many of the tumors would regress once transgene expression was turned off. All these criteria are met by the tet-operator-myc bi-transgene model developed by the laboratory of Dr Lewis Chodosh.

We imported the two transgenic lines from the Laboratory of A/Prof Lewis Chodosh, and had them released from quarantine. The lines were rederived and placed behind the barrier of our SPF facility at the Garvan Institute. The colonies of each line were established and PCR based genotyping assays were established and verified. We commenced the three-stage intercross of

these lines to provide animals (TOM*/* MTB */ in the scheme below) suitable for breeding with ENU mutagenized animals.

The new ANU facility was completed on schedule mid in mid 2004, at which point commissioning began and it is now operational, see http://www.apf.edu.au for details. This new facility was unable to accept our animals until January 2005, and then required that they were rederived, despite their demonstrated SPF status, to comply with the instructions of their newly appointed Scientific Advisory Committee. The animals have now been rederived into the facility and our screen for mutations that enhance myc-induced oncogenesis is underway. This project will continue through 2006 with funding obtained from the Australian National Health and Medical Research Council. As a result of these delays we are a long way behind the SOW.

Although the scientific findings of this project are yet to be made, this project and our initial attempts have been viewed favorably by a number of independent grant review panels. We participated in two grants that have provided very significant funding for the construction of a new animal facility, and the banking of induced mutants. We have also obtained ongoing funding for the ENU-myc project. These grants are detailed below.

This project has great potential to discover genes that interact with myc during the carcinogenic process, and to thus provide insight into this process in human carcinogenesis.

Project outline

Abbreviations.

TOM = tet on Myc which is the myc oncogene driven by tet on promoter.

MTB = MMTV-rtTA which is the reverse tetracycline transactivator driven by mouse mammary tumour virus LTR. Mammary specific.

/ Homozygous transgenic animal

*/ Heterozygous transgenic animal

Production of animals suitable for breeding to ENU mutagenized males.

The tet inducible system is bitransgenic, requiring the intercross of the imported mice to produce animals suitable for breeding, as follows.

1.TOM*/* bred with MTB */ produces 50% TOM*/ , MTB*/

2. TOM*/ , MTB*/ bred with TOM*/* produces 25% TOM*/*, MTB*/

3. TOM*/*, MTB*/ bred with TOM*/* produces 50% TOM*/*, MTB*/ suitable for breeding with ENU mice.

Cross with ENU mice.

We will make two populations, a control population without ENU mutations to accurately establish the kinetics of tumour induction, and a test population to screen for ENU mutations which accelerate or prevent tumourigenesis in response to myc. We will test each for dominantly and recessively acting mutations

Control population

wt C57Bl6 male mated with FVB TOM*/* MTB */ female. Wt population- aim for 320 animals made from 20 pedigrees. These animals are generated first and establish the normal profile of tumour onset in response to induction of myc.

Test population

G1: G1 males produced by breeding ENU treated B6 males with normal B6 females. G1 Bl6 male mated with FVB TOM*/* MTB */ female (test group, begin 12 weeks after WT group begins). 16 animals per pedigree, 200 pedigrees.

Dominant screen

Breed and keep eight female G2 progeny that are TOM */ MTB */ =50% of females (requires average of 16 females to be bred and typed from each pedigree). All are F1 Bl6/FVB. Add doxcyclin/sucrose to drinking water at 6weeks. Observe characteristics of tumour onset in the wt population that is running 12 weeks ahead of the test group. Involves palpating mammary glands for tumours, recording onset, number, position etc.

Identify animals in the test group that show accelerated tumour onset (early tumors) or resistance to tumour onset (late or no tumours). Remove Dox from water and breed affected female with WT FVB male to begin mapping.

Recessive screen

Keep four male and four female G2 offspring from each pedigree for breeding to G3. Generate animals as above, for both wt and ENU populations but then intercross progeny to produce G3 females homozygous for mutations. An intercross of male and females that are het for both MTB and TOM results in the following animals

	wt	MTB*/	MTB*/*
wt	1/16	2/16	1/16
TOM*/	2/16	4/16	2/16
TOM*/*	1/16	2/16	1/16

So 4/16 of animals are the exact genotype but 9/16 have both TOM and MTB transgenes, but the MTB*/* animals (3/16) will be poor breeders. How tumorigenesis will be effected by dosage of TOM and MTB is unknown. The system shows titratable expression with Dox, so with luck gene dosage will not dramatically effect tumour onset. It is possible to distinguish homozygotes from hemizygotes using quantitative PCR. We will need to test this as we go in the control group. We expect that a combination of F2 FVB/Bl6 and variable gene dosage will make tumor onset more variable, but dramatic phenotypes, such as no tumors, should remain detectable. Screen and map as for the dominant screen.

REVISED SOW 2003-2005

Task 1.
Months 1 to 9.

1. Establish Tet-myc bitransgenic mice at ANU by rederivation.
2. Establish genotyping PCRs and test.

Task 2. Establish and screen 200 inbred pedigrees
Months 9 to18.

a. Mate homozygous FVB Tet-myc bitransgenic females with 200 C57Bl6 ENU mutagenised males to establish 200 pedigrees. Keep G1 males. Simultaneously mate 20 unmutagenised males to establish 20 control pedigrees.
b. Mate G1 males to homozygous Tet-myc bitransgenic females to produce G2 offspring.
c. Mate G2 females with their fathers to produce 25 G3 females per ENU or control pedigree.
d. Induce transgene expression at 9 weeks of age with doxycycline. Monitor G3 females for mammary tumors by palpitation every 10 days. Select females with tumors from the ENU group which become palpable before tumors are seen in the control group.

Task 3. Establish pedigrees from selected females.
Months 12-24

a. Stop doxycycline treatment and mate tumor bearing female with father, or brother if father fails to breed. Test progeny for accelerated tumorigenesis and breed pedigree to homozygosity. Examine tumor phenotype to prioritize pedigrees for mapping.

Task 4. Map mutations
Months 24-36.

a. Mate homozygous females to male FVB to produce F2
b. Phenotype F2 and collect DNA into affected (20 animals) and unaffected (20+ animals) pools.
c. Genotype using 100 micro satellite markers polymorphic between FVB and C57Bl6 chosen throughout the genome.
d. Identify locus and regenotype using 100 locus specific polymorphic markers.
e. Continue intercross/backcross if no informative recombinations are found.
f. Identify candidate genes at a sub 1 cM locus from the mouse genome map. Exclude those not expressed in the mammary gland. Begin sequencing of remaining candidates to identify ENU-induced mutation.

Key research accomplishments

• Screening of 1100 mutagenised mice and the identification of a number of developmental abnormalities including tumorigenesis, providing a proof of principal example that ENU mutagenesis can be used to find recessive cancer causing mutations. Correlation of developmental abnormalities, such as increased side branching, with tumor formation.

• Demonstration that uncontrolled environmental factors contributed to tumour formation in the ENU pedigrees, demonstrating the requirement for a sensitizing mutation approach to this project.

• Investigation of the C3-SV40T transgenic line as potential sensitizing mutation, and rejection based on pregnancy driven carcinogenesis. This led to the use of an inducible system.

• Import, rederivation and release from quarantine of the bi-transgenic tet inducible myc model of mammary carcinogenesis. Two mouse lines were imported. The TOM*/* line and the MTB */ line.

• Development of a quantitative PCR genotyping approach to enable homozygote transgenic animals to be distinguished from heterozygote animals.

• Export of the TOM/MTB line to Canberra and its subsequent rederivation (again) into the Australian Phenomics Facility. Release from internal quarantine.

• Intercross of the the two lines for production of TOM*/* MTB */ animals for breeding to ENU mutagenized males.

• Production of the control population beginning July 2005 and the production of the ENU mutagenized pedigrees for screening, beginning August 2005.

• Monitoring of test pedigrees from September.

Reportable outcomes

Presentations regarding this ENU mutagenesis project.

2002 Australian Health Medical Research Congress, Melbourne.
2002 Era of Hope US Army Breast Cancer Conference
2004 Victorian Breast Cancer Research Consortium Melbourne
2005 Australian Phenomics Facility Opening Symposium

Grants referring to this ENU mutagenesis project.

NHMRC Enabling Grant $1.5M over 5 years.
Title: NHMRC Australian Phenome Bank
CI: Chris Goodnow, David de Kretser, Moira O'Bryan
Assoc Investigators: Brandon Wainwright, Antony Basten, Chris Ormandy, Anthony D'Apice, Warren Alexander, Anthony Scalzo, DAvid Pass

Grant to provide banking of ENU-induced mutant mice and other induced mutants.

Commonwealth MNRF Grant $11.5 M.
Title: Australian Phenomics Facility
Participating Organisations: ANU, Dairy CRC, Monash Uni, The Garvan Institute, Institute of Molecular Bioscience

Grant to build the new ENU facility. This grant secured an additional $8M from the ANU in matched funding and further funding from the ACT Government, providing the funds for the construction of the APF. See attached .pdf brochure for a description of the facility.

NHMRC Program $5M over 5 years.
Title: Control of cell proliferation and differentiation in breast and prostate cancer
CI:Robert Sutherland, Roger Daly, Liz Musgrove, Chris Ormandy

Grant, part of which will provide continuing funding for this ENU project.

Salaried positions

Research Assistant for 4 years

Filled by 2002Simon Junankar, 2003-2004Micheal Kazlauskas, 2005Daniel Gorman.

Animal Technician s at ANU. Rotating Roster of many people.

Conclusions

So What?

If we are successful we will discover new tumor suppressor genes that are active in the mammary gland, in the case of reduced latency mutations, or genes essential for myc-induced tumourigenesis, in the case of increased latent or tumor-free pedigrees. This will have direct relevance to breast cancer, providing potential markers of prognosis and new targets for therapy.

Appendices

1. APF Brochure

THE AUSTRALIAN NATIONAL UNIVERSITY

MONASH University

The Garvan Institute of Medical Research

THE UNIVERSITY OF QUEENSLAND
AUSTRALIA
IMB Institute for Molecular Bioscience

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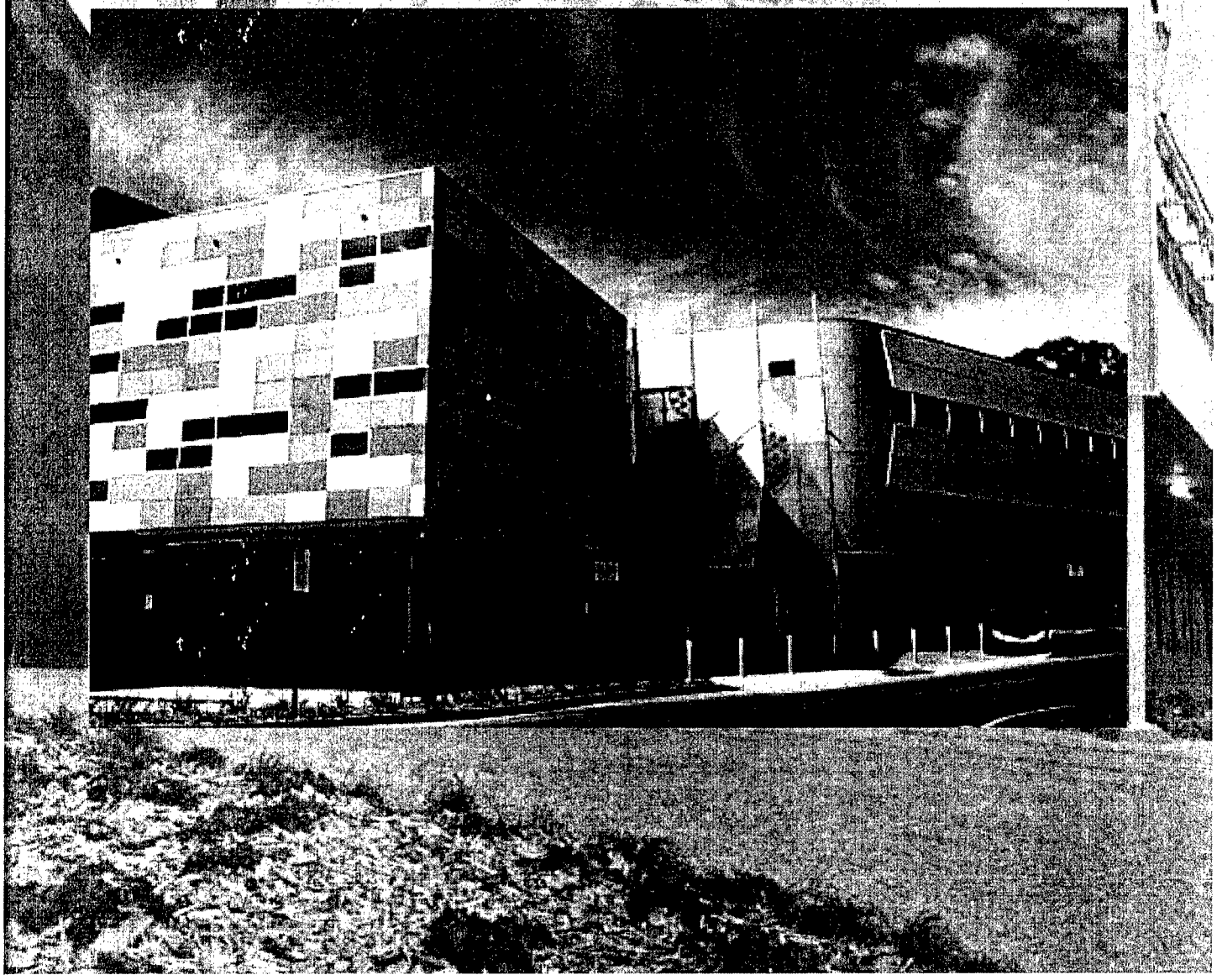

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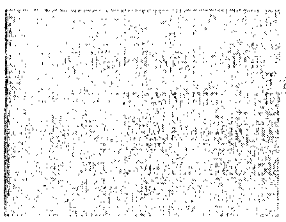

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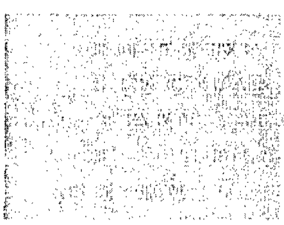

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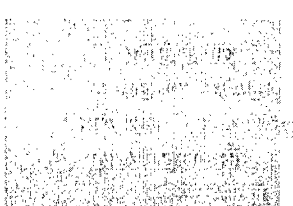

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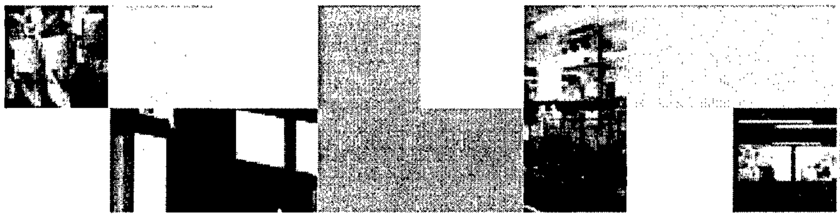

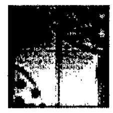

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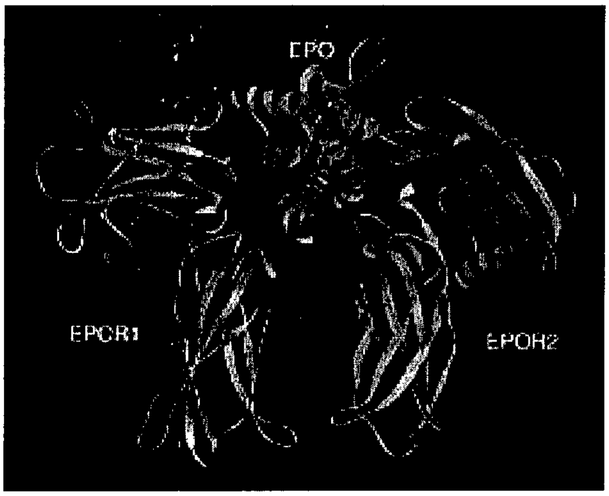

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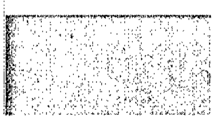

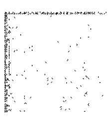

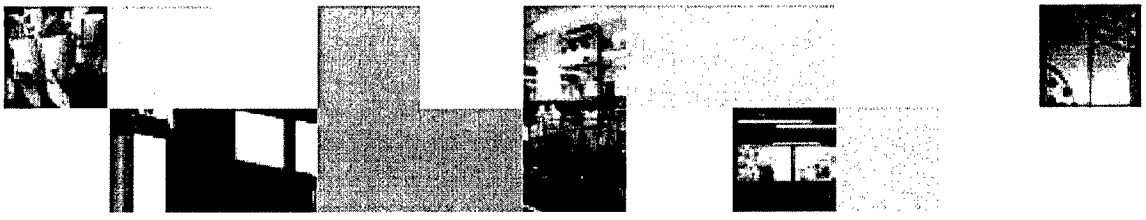

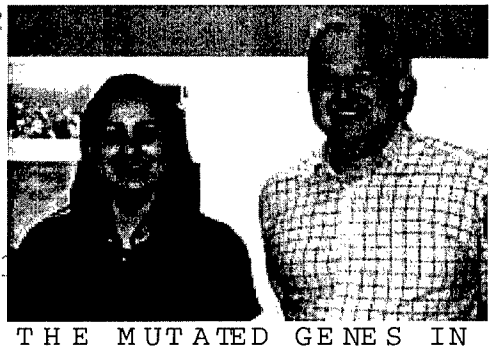

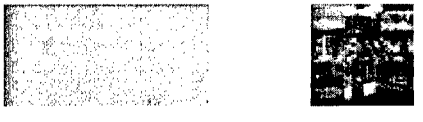

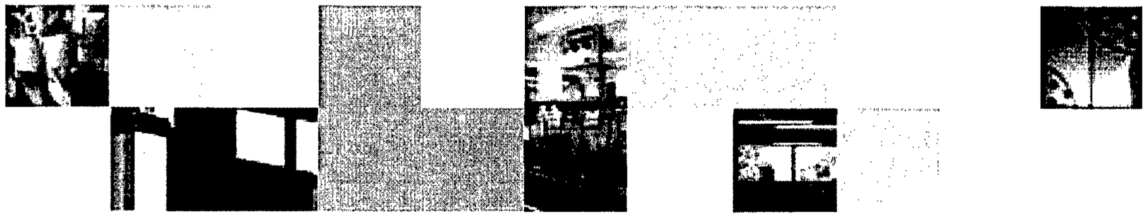

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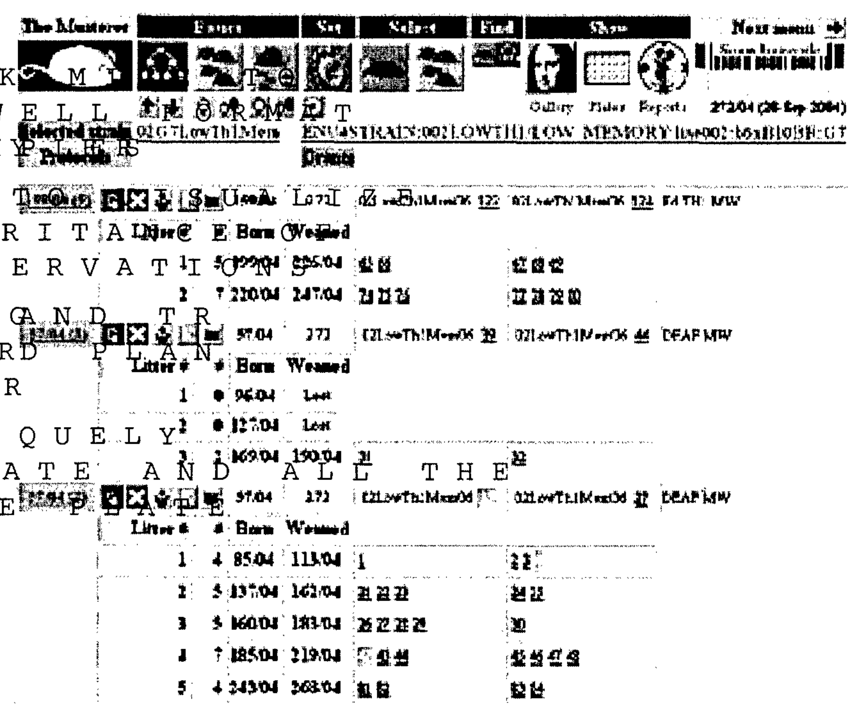

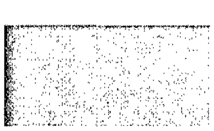

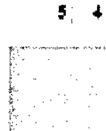

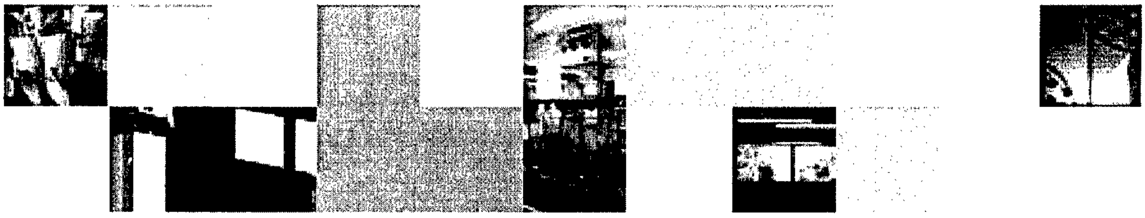

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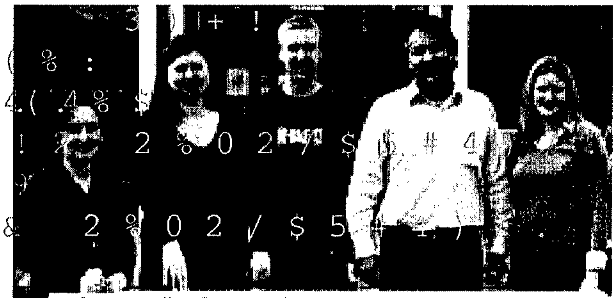

MONASH INSTITUTE
of Reproduction and Development

h #UENTRLY EWDEOINAGR TOJEPEL T RDF
TO % .5 MUTAGENIZED MICE

4HE ONGOING PHAETEROIT XTPIIOCN CAHNADR
LINKAGE OF LINES WITH MALE INFERTILITY

4HE ESTABLISHMENT OF A REPOSITORY OF A KNOCKOUT KNOCKIN TECHNOL
AND ASSOCIATED OGENOMAINODFOR. THE FREVEALDEPIC ESHRTIE S
' MALES FOR PRODUCTION OF MICE CARRYING
MODIFICATIONS IN SPENTCLYE WCE GENES #URR
CALLING THEVSER GENEHPSITORY
AND IT IS BEING ESTABLISHED AS A COLLABOR
BETWEEN THE !2 #OF #% EXCELLENCE
IN "IOTECHNOLOGY AND $EVELOPMENT - ONASH
5NIVERSITY AND THE EDENSING THE SCR

$.! OF THESE FOUNDER MICE
TO DETECT THOSE CARRYING M
OF pI ESTE BPOMRTM ESERMALES
RETRIEVOM DAO ZEFNKRH IAVE AND USE
REGENATE RTHE LINE USE PRODUCTAIRVT
TECHNOLOGIES SUCH RS 4HOVIS D ERPR
AN ACTIVE ALTERNATIVE AND

4HE ESTABLISHMENT OF AFIANH
0 HE NOME "AESERVATION OF IRN
FERTILIZATION ACYTOPLASMIC
INJECTION)#3) TECHNOLO
ESTABLISHED AT CENTURY BAENIDN
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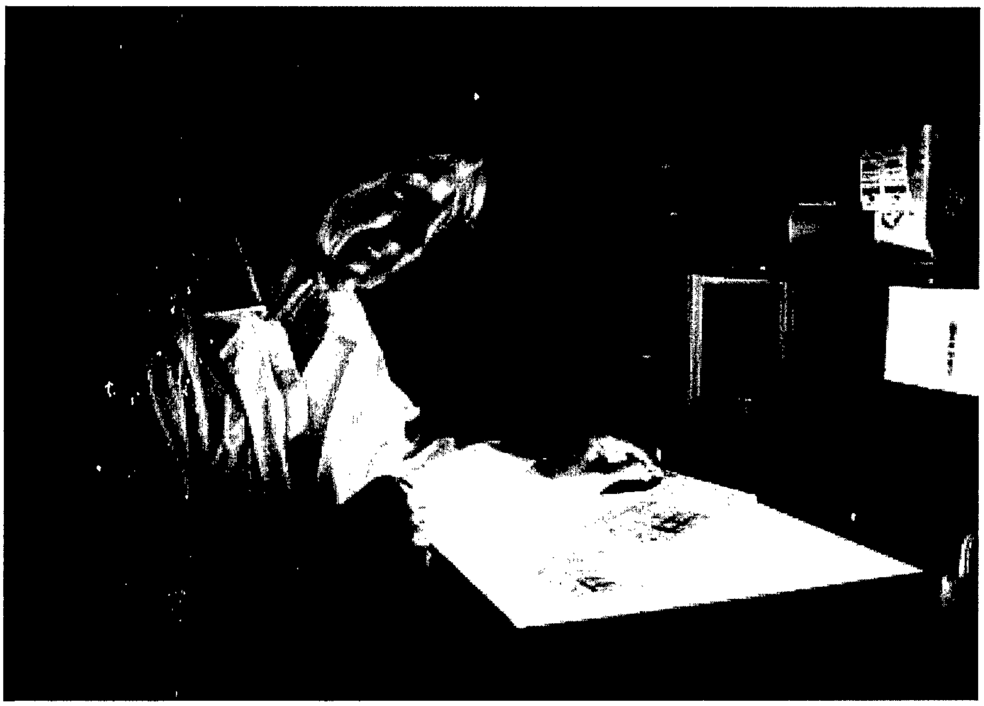

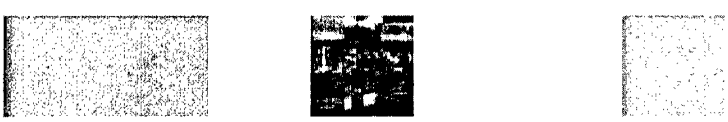

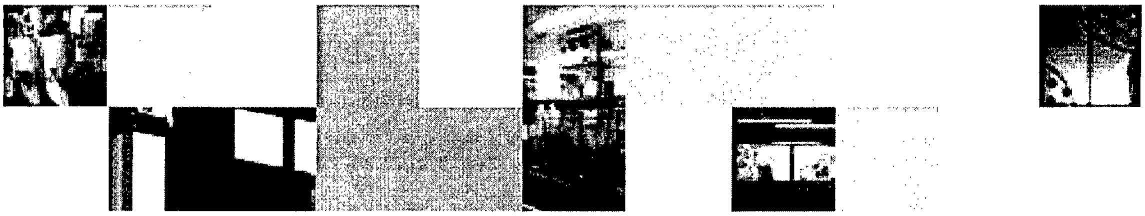

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4HE !0V&IDE S PACE EQUIPMENT AND EXPERTISE

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LOCATION AND IDENTIFY THE AFI

VARIANT MADNUS OBTAINED %F R

VARIANARIES COBRR HE R 0HENOME

4HE !0V&IDE PSR

s %XPERT ADVAIDING AIN DATA EERH EN

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DISCOVERY OF MUTATIONS

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4HE !0V&IDE SPARFACE S ECAISETRY DEFPOR

AND CRSYEROVE RSOMETR MIR FAMRONUSSE

4HIS TECHNICQIUVE NG MADNUS SHERS S HERN

DEVELOPED AT SI O)N AIS ANT 5CNIIRVAETEL

THOUSANDS INSO OF MICE WHIEDL A T

!0& FACILITY AND THEIR INFORMATION DEPOSITED ON

0HENOME "ANK

CHROMOSOMAL LINKAGE GENE IDEN

0HENOME BANK TO WINCLUDE GIRI STS

STAINS USED AMIAN GENE RESOURCE T

EXCHANGE AND EXPERTISE AND MI

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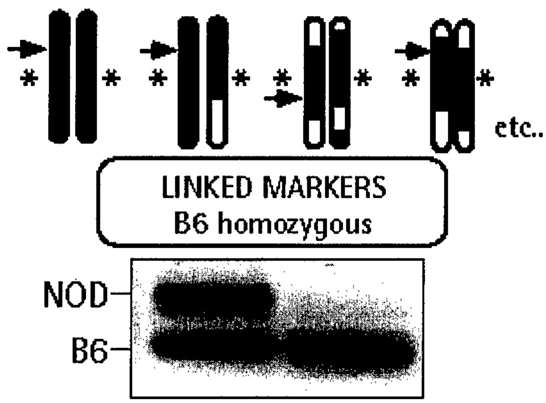


!0& USERS HAVE ACCESS TO THE DATAB

AND COLLECTIONS OF MOUSE MODI

ABTAE HEIRS HER MAINTAINING NUCLEAI

CRYOPRESERVED DEPOSITED ON

3 4 2 !) . ! 6 !) , ! ") ,) 4 9

4HE !0&S GENE FAMILY WHIC

HAVE ALREADY BEEN IDENTIFIED AND S

UNIQUE MODELS FOR VARIETY

AUTOIMMUNITY AND DEVELOP

)N ADDITION TO THE DISCOVERY AT NE

STRAINS AT AN EARLIER STAGE

LOCATION PRIMARY PHENOTYPE I

RESEARCHER CAN USE THE !0& FACILIT

BE GENES AND FUNCTIONS VIA THE AI

- OUSE STRAINS OF INTEREST WILL

THAWED FROM RESERVED SPERM BAND STRAINS AND

CARRIER GENOTYPES THAT WILL BE FERTILIZED

4HESE CAN BE SHIPPED AFTER

REQUESTED

. (-2# ! 5 3 4 2 ! ,) ! . 0 (%

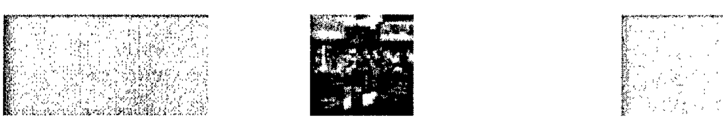
4HE 0HENOME BANK IS AN ONLI

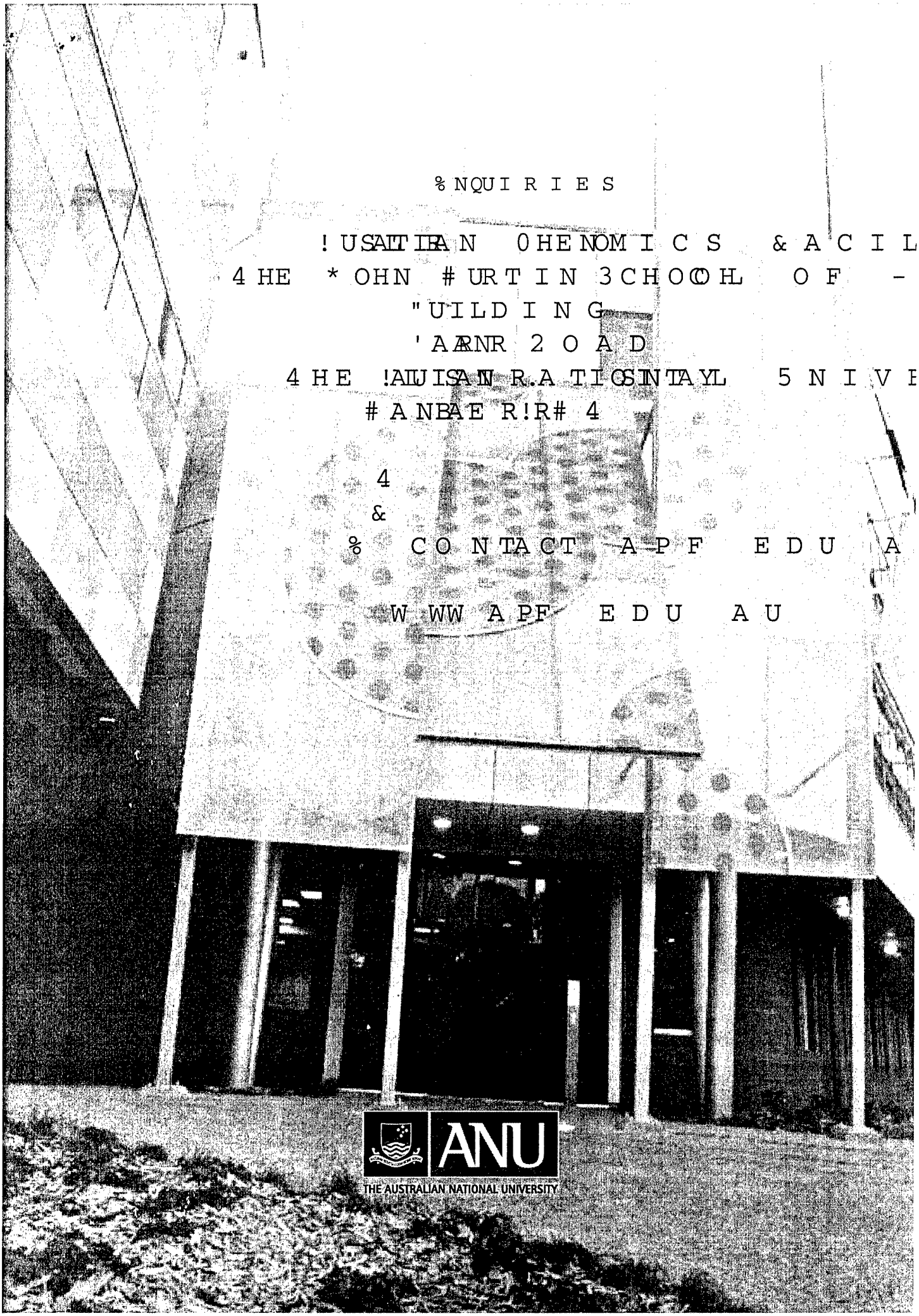
ARCHIVE OF GENETIC STRAINS OF MICE

BEING DEVELOPED STARTING AT THE !

INCLUDES AVAILABLE STRAINS WITH

DATA ON PHENOTYPE BY GENE REGISTER





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