

## EXPERIMENTAL SURGERY TO EVALUATE BIOMATERIALS

MILENA FINI, ROBERTO GIARDINO, GLANLUCA GIAVARESI  
Experimental Surgery Department-Rizzoli Orthopaedic Institute (I.O.R.), Bologna-Italy

The Department of Experimental Surgery in Rizzoli Orthopaedic Institute (I.O.R.) of Bologna was built in 1991 following strictly the EEC directives. In fact, now animal experimentation must be performed in very qualified and organised centres and a modern experimental surgery department is a complex structure that needs a pound, an operative unit and laboratories for *in vitro* and *ex vivo* studies.

From the beginning of our work we have studied induced animal models of human disease to increase knowledge of the pathogenesis and alleviation of the symptoms of disease in both human and animal. But a particular attention has always been paid to the studies of biomaterials because they are the major therapeutic revolution of this century and because surgery has always used biomaterials from its beginning.

In particular, in the following table the researches and the animal models in the field of biomaterials, are summarised.

RESEARCH	ANIMAL MODEL	STUDY AND BIOMATERIALS
PERIPHERAL NERVE REPAIR	RAT	CONDUITS MADE OF RESORBABLE MATERIALS
FRACTURE AND BONE LOSS TREATMENT	RABBIT AND SHEEP	METALLIC AND RESORBABLE MATERIALS COATED AND UNCOATED MATERIALS $\alpha$ , $\beta$ TCP, HA, BIOLOGICAL MATERIALS
ISCHEMIC/REPERFUSION DAMAGE	RABBIT AND RAT	POLYMERISED SUPEROXIDE DISMUTASE
SMALL DIAMETER VASCULAR PROSTHESIS	RABBIT AND SHEEP	SYNTHETIC AND BIOLOGIC PROSTHESIS
SORBENTS FOR BLOOD PURIFICATION	RABBIT AND PIG	CHARCOAL, RESINS, MEMBRANES
WOUND DRESSING	RAT AND RABBIT	BIOLOGIC AND SYNTHETIC DRESSINGS

Some of the mentioned *in vivo* or *ex vivo* experimental models are shown in Fig. 1, 2, 3, 4.

When a new biomaterial is developed for a specific medical field the tests to which it must be submitted are many and they can be divided in *in vitro*, *ex vivo* and *in vivo*.

*In vitro* and *ex vivo* tests with tissue culture or isolated organs and tissues must always precede the subsequent *in vivo* phases of the research.

However, sometimes they can be insufficient because they can not reflect the complicated biochemical, physiological and biological interactions of a living system.

The *in vivo* systems with the use of animals can be divided in 2 different kinds:

- *in vivo* models for general biocompatibility testing
- specific *in vivo* models.

The *IN-VIVO* MODELS FOR GENERAL BIOCOMPATIBILITY TESTING are used for safety assessment of biomaterials regarding the tissue reaction, irritation and absorption studies. As far as tissue reaction or histocompatibility is concerned, standard samples are implanted subcutaneously and in muscle of rodents. Other sites may be used in order to expose the implant material to special cells as mesenchymal cells of the peritoneal cavity where the tendency of carcinogenesis or adhesion formation can be investigated. Cornea and dura mater are other sites for special implant procedures.

Also irritation studies must be performed in this preliminary step of general biocompatibility assessment. They consist of acute and chronic systemic toxicity, allergic reaction, pyrogenicity tests and so on. Usually they are made by i.p. or i.v. injection of the extracts of the biomaterial. Animals are checked after 4, 24, 48, 72 hours and any clinical symptoms of toxicity must be evaluated. We can say that all these previously summarised tests are now quite standardised from ASTM standards and they differ regarding to the clinical applications which is proposed for the biomaterial. Animals used are usually mice, rats and rabbits.

Then, the SPECIFIC *IN VIVO* MODEL is performed and the prototype of the biomaterial with proportioned shape, dimension and use which are proposed for the patient implant must be studied. This is a very difficult step of the study because differently from the previous *in vivo* tests, in this phase standards to follow in the choice of the animal model do not exist. For example often researchers base their choice on what has been done before. Moreover a written check-list of all the logistic support necessary compared with what is available and a pilot study to assess the feasibility of the chosen option may always precede the real study.

Moreover now a law keeping to EEC directives exists in Italy with the aim to reduce animals discomfort and their irrational use (D.L. n. 116 27 Gennaio



Fig. 1 - Intraoperative picture of the positioning of a conduit in the sciatic nerve of rat in order to evaluate the peripheral nerve healing with the tubulization technique.



Fig. 2 - Positioning of a metallic material in rabbit femur for biocompatibility and biofunctionality evaluations.



Fig. 3 - The measurement of insertion and remotion torque of coated and uncoated titanium pins.



Fig. 4 - A vascular prosthesis in the carotid artery of a sheep.

1992). So the final animal model choice is very difficult and usually it represents the synthesis of all these considerations.

Unfortunately an animal species perfectly similar to human beings does not exist and although animals sometimes present different physiological and biological parameters these do not jeopardise the results of a surgical research; the importance is to know these differences and consider them in the evaluation of the final results. The concept we would like to point out is: know your animal!

So we have seen that although experimental surgery shares with other disciplines most of the problems, that concern biomedical research, it presents some particular aspects which specifically condition its development. It is sensitive to the necessity of "avant-garde" technological contributions coming from multiple sectors ranging from the chemical to the electronic industry. Because of the large variety of patient subjects, it is a wide and elective field that includes an unquantifiable series of steps and experimental models. We tried to underline some aspects such as:

- the method to follow. A correct methodology which starts with *in vitro* tests and ends with the final animal model is the only one able to give an experiment validity;
- the utility in terms of potential social benefits of a project;
- the reliability which is mainly due to the choice of the experimental model;
- the feasibility.

To sum up, apart from any emphatic attitude, experimental research on biomaterials has never been so useful as today. Unfortunately some problems still exist and in particular they are the necessity of an active collaboration among researchers of various disciplines and of a standardisation of the animal models used by the scientists.

#### REFERENCES

- *Handbook of Biomaterials Evaluation*. Andreas F. von Recum (Ed), Macmillan Publishing Company New York, 1986.
- LEMLEY, C.J., GREEN, P., LEAR, J.E. ANGELL-JAMES, *Essentials of Experimental Surgery*. Butterworths & Co London, 1990.
- BAGGI RIGGIANI, B., BRAGAGLIA, A., TALLARICO, M., FERRI, R., GIARDINO, G., GIANNINI, M., ROCCA, «Obiettivi e Documenti Veterinari», 5, 15, 1992.