with free excess to treadmill exercise. The drug industry should pay more attention to this probable scenario.

Moreover, these notions are not restricted to CNS drug development. For example, short-term treadmill exercise training of rats was shown to improve myocardial tolerance to ischemia–reperfusion injury[8] and diaphragm antioxidant capacity[9]. Another striking example is given by a recent study in which rats were maintained for 12 weeks in specially designed raised cages that required them to rise to erect bipedal stance to eat and drink. These rats had significantly increased muscle and cortical bone mass in their tibias compared with control rats housed in standard laboratory cages[10].

The immune system is also more active in exercised rats compared with docile animals: voluntary exercise on running wheels for 5 weeks dramatically augmented *in vivo* natural killer cell toxicity[11]. Numerous studies demonstrate that exercised rodents are generally healthier, which is not surprising given the obvious advantages of physical activity in humans, and in view of the high similarity between the mouse and the human genomes[12].

Conclusions

The above examples illustrate that regular voluntary physical activity can alter various aspects of mouse and rat physiology that could be relevant for drug development. Clearly, more attention should be paid to such effects in the context of the quest for new drug targets. This cautionary note might be in particular valid for CNS drug development, but could also concern immune-related drug targets. Hippocrates, the founder of scientific medicine, wrote some 2400 years ago:

> Of all the causes which render the life of man short and miserable, none have greater influence than the lack of proper exercise.

The drug industry should take notice that this in all probability is also true for laboratory rodents, our distant mammal relatives.

Box 1. The outstanding questions

- How similar are mice and humans in their need for regular physical activity?
- To what extent is CNS gene expression modified in docile mice or rats compared with physically active laboratory rodents?
- Are changes in gene expression in active animals transient or long-lasting, and how do they affect the suitability of these animals to model human diseases?
- Could favorable CNS drug targets be missed by the routine use of inactive laboratory rodents?
- Will voluntary physical exercise allow laboratory rodents to be better animal models for human neurological and psychiatric diseases?
- Should running wheels be implemented in standard laboratory protocols for laboratory rodents in drug development research? What other measures could be applied to ensure that they are allowed the best levels of physical activity for serving as human disease models?

References

1 Malakoff, D. (2000) Animal research. Activists win big on rodent, bird rules. *Science* 289, 377

2 Ferry, J. (1999) New calls made for changes in research on animals. *Lancet* 354, 1978

3 Eilam, R. *et al.* (1999) Locomotor activity causes a rapid up-regulation of vasoactive intestinal peptide in the rat hippocampus. *Hippocampus* 9, 534–541

4 O'Neal, H.A. *et al.* (2001) Prepro-galanin messenger RNA levels are increased in rat locus coeruleus after treadmill exercise training. *Neurosci. Lett.* 299, 69–72

5 Russo-Neustadt, A.A. *et al.* (2000) Physical activity and antidepressant treatment potentiate the expression of specific brain-derived neurotrophic factor transcripts in the rat hippocampus. *Neuroscience* 101, 305–312

6 van Praag, H. *et al.* (1999) Running enhances neurogenesis, learning, and long-term potentiation in mice. *Proc. Natl. Acad. Sci. U. S. A.* 96, 13427–13431

7 Anderson, B.J. *et al.* (2000) Exercise influences spatial learning in the radial arm maze. *Physiol. Behav.* 70, 425–429

8 Powers, S.K. *et al.* (1998) Exercise training improves myocardial tolerance to *in vivo* ischemia–reperfusion in the rat. *Am. J. Physiol.* 275, R1468–R1477

9 Vincent, H.K. *et al.* (2000) Short-term exercise training improves diaphragm antioxidant capacity and endurance. *Eur. J. Appl. Physiol.* 81, 67–74

10 Yao, W. *et al.* (2000) Making rats rise to erect bipedal stance for feeding partially prevented orchidectomy-induced bone loss and added bone to intact rats. *J. Bone Miner. Res.* 15, 1158–1168

11 Jonsdottir, I.H. *et al.* (2000) Enhancement of natural immunity seen after voluntary exercise in rats. Role of central opioid receptors. *Life Sci.* 66, 1231–1239

12 Gurwitz, D. (2000) Physical activity: good for your health, very good for your gene expression. *Clin. Genet.* 57, 249–251

David Gurwitz
National Laboratory for the Genetics of Israeli Populations
Sackler Faculty of Medicine
Tel Aviv University
Tel Aviv 69978, Israel
e-mail: gurwitz@post.tau.ac.il

Gene therapy: will it deliver for RA? ▼

Rheumatoid arthritis (RA) is a debilitating disease associated with increased mortality. Chemically derived drugs are still considered as the primary treatment of RA. However, these treatments are only partially effective in controlling the progression of the disease and are associated with several side effects.

In the past decade, the results of biomedical research have increased our knowledge regarding the pathological processes that take place in rheumatoid joints, in particular, the role of cytokines. These findings led to the use of tumor

  PII: S1359-6446(01)01750-0

necrosis factor inhibitors, which can be considered as a major breakthrough in the treatment of RA[1,2]. Interleukin-1 (IL-1) also plays a major role in the pathogenesis of RA and its natural inhibitor, the IL-1-receptor antagonist (IL-1Ra), ameliorates the course of the disease in several experimental models of arthritis. The administration of IL-1Ra is associated with significant improvement in disease activity and a reduction in the frequency and severity of radiological signs of joint damage[3,4]. However, the systemic administration of biological agents has important limitations primarily due to their high cost to produce.

The local delivery of cytokines or other mediators by gene therapy can overcome some of the limitations associated with the systemic administration of biological agents. Therapeutic products can be synthesized in disease tissues in high quantities and consumed locally, thus having only limited effects systematically. In a recent issue of *Drug Discovery Today*, Ghivizzani *et al.* provided an excellent overview of the different approaches to direct local gene delivery[5]. Previously, this group has published several studies in which *in vitro* transduced synovial fibroblasts were transplanted into the joints to produce cytokines or soluble receptors. Using this *ex vivo* gene therapy strategy, the authors successfully treated several experimental models of arthritis. In addition, they conducted the first clinical trial in patients with RA[6].

Clinical relevance

What should we expect of gene therapy to consider this approach as clinically relevant for the treatment of RA? It should provide a high level of expression of the transgene in disease tissues and this production should be long-lasting. In addition, the procedure should be easy, widely available and safe. Another problem is that RA is, by definition, a polyarticular disease. Hence, it will be important to obtain the expression of therapeutic genes in several joints. Unfortunately, as mentioned by the authors, most of these issues are not resolved yet.

The paper is divided into two parts in which they reviewed in detail the advantages and limitations of virally mediated and non-virally mediated methods of local gene delivery. Vectors derived from viruses have several limitations such as immunogenicity, which leads to short-term expression by adenoviral vectors, and lack of effective infection by retroviral vectors, which only infect dividing cells. Some of these problems can be overcome using other vectors such as the lentiviral vector, which can infect non-dividing cells. However, the potential risk of insertional mutations due to integration of additional virus sequences into the host genome is a concern. Non-viral gene therapy is another interesting approach. The authors presented some of their studies on different DNA formulation. Unfortunately, their results show that the expression of the transgene was also very short. The levels of IL-1Ra were elevated only 24 h after the injection and were undetectable after 48 h. In addition, the occurrence of an inflammatory reaction following the injection of DNA is another potential concern.

Conclusion

In conclusion, the local delivery of therapeutic genes in disease tissues is very attractive and has numerous advantages over classic drug therapy. However, as mentioned by the authors, a considerable quantity of work remains to be performed before gene therapy moves from the bench into the clinic for the treatment of RA.

References

1 Elliott, M.J. *et al.* (1994) Repeated therapy with monoclonal antibody to tumour necrosis factor α (cA2) in patients with rheumatoid arthritis. *Lancet* 344, 1125–1127

2 Maini, R.N. *et al.* (1998) Therapeutic efficacy of multiple intravenous infusions of tumor necrosis α monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum.* 41, 1552–1563

3 Bresnihan, B. *et al.* (1998) Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. *Arthritis Rheum.* 41, 2196–2204

4 Jiang, Y. *et al.* (2000) A multicenter, double-blind, dose-randing, randomized, placebo-controlled study of recombinant human interleukin-1 receptor antagonist in patients with rheumatoid arthritis. *Arthritis Rheum.* 43, 1001–1009

5 Ghivizzani, S.C. *et al.* (2001) Direct gene delivery strategies for the treatment of rheumatoid arthritis. *Drug Discov. Today* 6, 259–267

6 Ghivizzani, S.C. *et al.* (1997) Gene therapy for arthritis – treatment of the first three patients. *Arthritis Rheum.* 40, S223

Cem Gabay
Division of Rheumatology
Department of Internal Medicine
University Hospital of Geneva
26 Avenue Beau-Sejour
1211 Geneva 14
Switzerland

Wither solid-phase chemistry? – Reply ▲

Initial letter: Terrett, N. (2001) *Drug Discovery Today* 6, 16

Response from Mark Bradley

What is the balance between solid- and solution-phase chemistry? This is hard to judge with so many different philosophies and approaches, but I do not think it is as stark as Nick Terrett portrays. For example, a recent review by Roland Dolle[1] actually showed that, although solution methods accounted for 50% of total libraries produced and reported in 1996, this was a peak, and solution-phase synthesis of libraries has since fallen to 33% in 1997 and 1998 and to just 20% in 1999. Another example of the continued power of solid-phase chemistry is the runaway success of Irori (almost an industry standard now) and the recent advent

 PII: S1359-6446(01)01748-2