Smoking was an exclusion criterion for controls, whereas 4 of the 21 cases were regular smokers of 2 to 10 cigarettes per day. Mean urinary excretion rates of 8-iso-$PGF_{2\alpha}$ were similar in the 4 smokers (404 pg/mg of creatinine) and in the 21 cases considered as a whole (482 pg/mg of creatinine). Urine albumin excretion rates were not tested. There was only a small glucose variability between each day (day 1 mean amplitude of glycemic excursions [MAGE], 74 mg/dL; day 2 MAGE, 76 mg/dL), and MAGE values on day 1 and day 2 were highly correlated ($r=0.87$; $P<.001$).

Finally, conflicting observations in the study by O'Byrne et al[4] could have resulted from the use of different methods in different groups of patients at different ages: enzyme immunoassay in our study (21 patients with type 2 diabetes; mean age of 64 years) vs stable isotope dilution mass spectrometry assay in O'Byrne et al (13 patients with type 1 diabetes; mean age of 36 years).

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Financial Disclosures: None reported.

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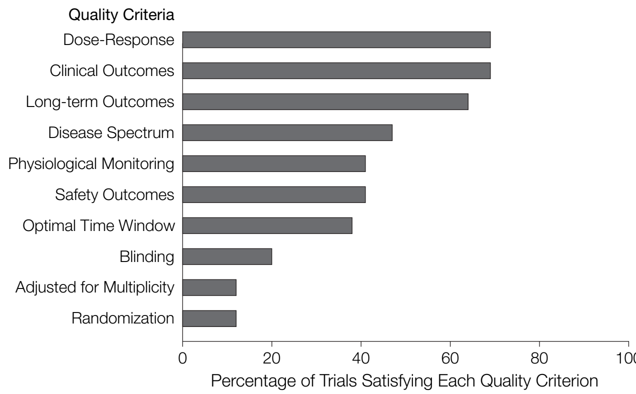
RESEARCH LETTER

Translation of Research Evidence From Animals to Humans

To the Editor: Most medical therapies in use today were initially developed and tested in animals,[1] yet animal experiments often fail to replicate when tested in rigorous human trials.[2,3] We conducted a systematic review to determine how often highly cited animal studies translate into successful human research.

Figure 1. Methodological Quality of Animal Trials (n=76)



Methods. The 7 leading scientific journals by citation impact factor (Journal Citation Reports, Thomson Scientific, Philadelphia, Pa, 2004) that regularly publish original animal studies were searched: *Science*, *Nature*, *Cell*, *Nature Medicine, Nature Genetics, Nature Immunology,* and *Nature Biotechnology*. Articles with more than 500 citations were retrieved under the assumption that such prominent findings would more likely be tested in subsequent human trials.[4] A total of 2000 articles published between 1980 and 2000 were screened, reflecting advances in molecular biology and recombinant genetics. Articles were included if they investigated a preventive or therapeutic intervention in an in vivo animal model. When there were multiple animal studies of the same intervention, the most cited study was retained. Power calculations ($\alpha=0.05$, $\beta=0.05$) estimated that 49 articles were needed to exclude a translation rate below 5%.

For each included study, a literature search identified human studies that translated the animal evidence. Successful translation was defined as replication in a randomized trial yielding results that were statistically positive according to primary outcome. Interventions and diseases analogous to those studied in the animal study were allowed.

MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, the National Institutes of Health Clinical Trials Database, BIOSIS Previews, and the International Pharmaceutical Abstracts Database were searched from their inception through May 2006. Bibliographies of topic-specific review articles were manually searched for additional studies and experts were contacted if the search was negative.

The quality of the studies was assessed based on adapted standards for the conduct of animal research (**Figure 1**).[5] Good quality was defined as a global methodology score of 50% or higher. Multivariable logistic regression was used to assess predictors of translation. The Pearson correlation test was used to determine if methodological quality of ani-

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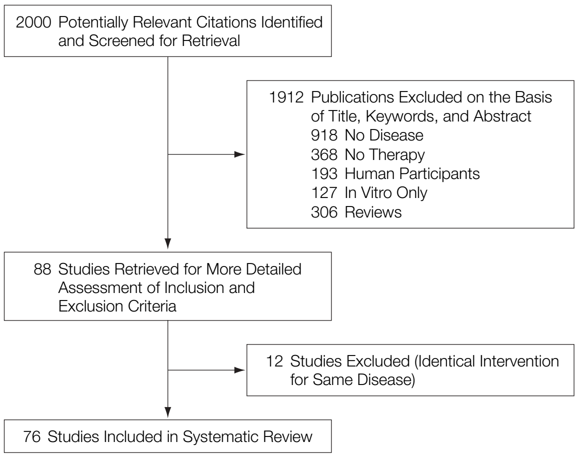
Figure 2. Search Flow and Article Retrieval



mal studies improved over time. Significance level was set at 2-sided $P<.05$. Analyses were conducted using SAS version 9.0 (SAS Institute Inc, Cary, NC).

Results. Seventy-six animal studies fulfilling inclusion criteria were identified (**FIGURE 2**; details of studies available in online eTable, available at http://www.jama.com). No animal study was negative. The median citation count was 889 (range, 639-2233). The median publication year was 1992, yielding a median of 14 years for potential translation. Of the animal studies, 37 (49%) were rated as having good methodological quality. Most studies included dose-response gradients, clinically relevant outcomes, and long-term end points (Figure 1). Few studies included random allocation of animals, adjustment for multiple hypothesis testing, or blinded assessment of outcomes. Methodological quality did not improve during the study interval ($r=-0.08$, $P=.47$).

Of the animal studies, 28 (37%; 95% confidence interval [CI], 26%-48%) were replicated in human randomized trials, 14 (18%) were contradicted by randomized trials, and 34 (45%) remain untested. Median time to replication was 7 years (range, 1-15 years). Global methodology score did not predict translation in unadjusted analyses (odds ratio [OR], 1.28 per 10% higher score; 95% CI, 0.97-1.69) or in analyses adjusted for citation rate and length of time available for human replication (OR, 1.27; 95% CI, 0.96-1.69). Animal studies incorporating dose-response gradients were more likely to translate to humans (OR, 3.3; 95% CI, 1.1-10.1). Other quality criteria, type of therapy, type of disease, species, journal, citation rate, length of follow-up, and year of publication did not predict subsequent translation. Eight replicated interventions were subsequently approved for use in patients.

Comment. Only about a third of highly cited animal research translated at the level of human randomized trials. This rate of translation is lower than the recently estimated 44% replication rate for highly cited human studies.[4] Limitations of this review include a focus on highly cited animal studies published in leading journals, which by their positive and highly visible nature may have been more likely to translate than less frequently cited research. In addition, this study had limited power to discern individual predictors of translation.

Nevertheless, we believe these findings have important implications. First, patients and physicians should remain cautious about extrapolating the findings of prominent animal research to the care of human disease. Second, major opportunities for improving study design and methodological quality are available for preclinical research. Finally, poor replication of even high-quality animal studies should be expected by those who conduct clinical research.

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Author Contributions: Dr Hackam had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Hackam, Redelmeier.
Acquisition of data: Hackam.
Analysis and interpretation of data: Hackam, Redelmeier.
Drafting of the manuscript: Hackam, Redelmeier.
Critical revision of the manuscript for important intellectual content: Hackam, Redelmeier.
Statistical analysis: Hackam, Redelmeier.
Obtained funding: Redelmeier.
Administrative, technical, or material support: Redelmeier.
Study supervision: Redelmeier.
Literature retrieval: Hackam.
Financial Disclosures: None reported.
Funding/Support: Dr Hackam was supported by a Canadian Institutes of Health Research Fellowship Award, the Chisholm Memorial Fellowship, and the Clinician-Scientist Training Program of the University of Toronto. Dr Redelmeier was supported by the Canada Research Chair in Medical Decision Sciences, the Error Management Unit of Sunnybrook Health Sciences Centre, the National Institutes of Health Resuscitation Outcomes Consortium, and the Canadian Institutes of Health Research.
Role of the Sponsors: The funding sources had no role in the design and conduct of the study; in the collection, management, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.
Additional Information: The eTable is available at http://www.jama.com.
Acknowledgment: We are grateful to Mark Crowther, MD, MSc, Gideon Koren, MD, Philippe Poussier, MD, Joel Ray, MD, MSc, William Sibbald, MD, MBA, and Matthew Stanbrook, MD, PhD, for comments on a previous draft of the manuscript. No individual received compensation for their assistance.

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eTable. Details of Animal Studies

Source	Journal	No. of Citations	Intervention	Disease
Pelleymounter et al, 1995	*Science*	2233	Leptin	Obesity
Beutler et al, 1985	*Science*	1958	TNF Ab	Sepsis
O'Reilly et al, 1997	*Cell*	1792	Endostatin	Malignancy
O'Reilly et al, 1994	*Cell*	1784	Angiostatin	Malignancy
Kim et al, 1993	*Nature*	1626	VEGF Ab	Malignancy
Trauth et al, 1989	*Science*	1440	Anti-APO-1 Ab	Malignancy
Groux et al, 1997	*Nature*	1390	$CD4^+$ T-cell clones	Inflammatory bowel disease
Simon et al, 1984	*Science*	1388	2-amino-7-phosphonoheptanoic acid	Cerebral ischemia
Ulmer et al, 1993	*Science*	1358	DNA vaccine	Influenza
Oshima et al, 1996	*Cell*	1264	MF-tricyclic	Colorectal polyposis
Kuchroo et al, 1995	*Cell*	1259	B7-1 and B7-2 Ab	EAE
Culver et al, 1992	*Science*	1254	Retroviral vector with thymidine kinase	Malignancy
Brooks et al, 1994	*Cell*	1248	Integrin α(v)β3 antagonist	Malignancy
Brooks et al, 1994	*Science*	1202	Integrin α(v)β3 Ab	Malignancy
Hotamisligil et al, 1993	*Science*	1187	TNF-α receptor IgG chimera	Insulin resistance
Simonet et al, 1997	*Cell*	1180	Osteoprotegerin	Bone-resorptive diseases
Okamura et al, 1995	*Nature*	1138	Anti-IL-18 Ab	Sepsis
Sakurai et al, 1998	*Cell*	1106	Orexin-A and -B	Feeding behavior
Cuttitta et al, 1985	*Nature*	1101	Bombesin-like peptide Ab	Malignancy
Hunkeler et al, 1981	*Nature*	1076	Flumazenil	Decreased arousal
Rosenberg et al, 1986	*Science*	1070	Adoptive immunotherapy	Malignancy
Asahara et al, 1997	*Science*	1058	Endothelial cell progenitors	Tissue ischemia
Jang et al, 1997	*Science*	1050	Resveratrol	Malignancy
Chen et al, 1994	*Science*	1040	Oral tolerance/T-cell clones	EAE
Pfeffer et al, 1993	*Cell*	1025	TNF receptor gene targeting	Sepsis
Powell et al, 1989	*Science*	1006	Cilazapril	Postangioplasty restenosis
Sheardown et al, 1990	*Science*	1004	NBQX	Cerebral ischemia
Kestler et al, 1991	*Cell*	1002	Nef gene deletion	AIDS
Koch et al, 1992	*Science*	984	IL-8 Ab/antisense	Neovascularization
Townsend and Allison, 1993	*Science*	975	Costimulatory ligand B7	Malignancy
Acha-Orbea et al, 1988	*Cell*	963	Anti-Vβ8 Ab	EAE
Fearon et al, 1990	*Cell*	944	IL-2 gene therapy	Malignancy
Schinkel et al, 1994	*Cell*	943	P-glycoprotein gene targeting	Drug resistance
Ferrari et al, 1998	*Science*	934	Bone marrow transplantation	Muscular dystrophies
Druker et al, 1996	*Nat Med*	927	Imatinib	Malignancy
Uehata et al, 1997	*Nature*	922	Y-27632	Hypertension
Huang et al, 1994	*Science*	914	Neuronal nitric oxide synthase disruption	Acute ischemic stroke
Cobbold et al, 1984	*Nature*	899	IgG2b Ab	Graft rejection
Lenschow et al, 1992	*Science*	879	CD28 and B7 targeting	Graft rejection
Schenk et al, 1999	*Nature*	867	Amyloid-β immunization	Alzheimer disease
Molkentin et al, 1998	*Cell*	866	Cyclosporine A	Left ventricular hypertrophy
Bellgrau et al, 1995	*Nature*	855	CD95 ligand	Graft rejection
Chen et al, 1992	*Cell*	848	B7-mediated gene therapy	Malignancy
Millauer et al, 1994	*Nature*	848	Flk-1/VEGF receptor–directed therapy	Malignancy
Ingber et al, 1990	*Nature*	842	AGM-1470	Malignancy
Border et al, 1990	*Nature*	841	TGF β-1 Ab	Glomerulonephritis
MacMicking et al, 1995	*Cell*	825	iNOS targeting	Sepsis
Jilka et al, 1992	*Science*	810	IL-6 Ab	Bone-resorptive disease
Faden et al, 1989	*Science*	808	N-methyl-D-aspartate antagonists	Traumatic brain injury
Rosenfeld et al, 1992	*Cell*	807	CFTR gene therapy	Cystic fibrosis
Fan et al, 1997	*Nature*	804	MTII, NDP-MSH	Obesity/hyperphagia
Lagasse et al, 2000	*Nat Med*	803	Hematopoietic stem cells	Tyrosinemia type I

(continued)

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eTable. Details of Animal Studies (cont)

Source	Journal	No. of Citations	Intervention	Disease
Ferns et al, 1991	*Science*	781	Platelet-derived growth factor Ab	Postangioplasty restenosis
Bergman et al, 1990	*Science*	771	Subthalamic nucleus–directed therapy	Parkinsonism
Huang et al, 1988	*Science*	769	Retinoblastoma gene therapy	Malignancy
Mosier et al, 1988	*Nature*	764	Leukocyte transfer	SCID
Schnell and Schwab, 1990	*Nature*	758	IN-1 Ab	Spinal cord injury
Wegner et al, 1990	*Science*	757	ICAM-1 Ab	Asthma
Tepper et al, 1989	*Cell*	756	IL-4 gene therapy	Malignancy
Bischoff et al, 1996	*Science*	755	Adenovirus mutant	Malignancy
Walczak et al, 1999	*Nat Med*	745	TRAIL	Malignancy
Larsen et al, 1996	*Nature*	741	CD40 and CD28 targeting	Graft rejection
Gussoni et al, 1999	*Nature*	738	Hematopoietic or myologic stem cells	Muscular dystrophy
Mayordomo et al, 1995	*Nat Med*	728	Tumor peptide-pulsed dendritic cells	Malignancy
Li et al, 1995	*Cell*	721	IL-1b–converting enzyme gene targeting	Sepsis
Kromer, 1987	*Science*	711	Nerve growth factor	Acute brain injury
Isobe et al, 1992	*Science*	695	ICAM-1 and LFA-1 Ab	Graft rejection
Brownlee et al, 1986	*Science*	687	Aminoguanidine	Diabetic vasculopathy
Henderson et al, 1994	*Science*	678	Glial cell line–derived neurotrophic factor	Motor neuronopathy
Yednock et al, 1992	*Nature*	669	Integrin α-4-β-1 Ab	EAE
Trujillo and Akil, 1991	*Science*	668	NMDA receptor antagonist	Opiate-related disorders
Ohlsson et al, 1990	*Nature*	667	IL-1 receptor antagonist	Sepsis
Border et al, 1992	*Nature*	665	Decorin	Glomerulonephritis
Sendtner et al, 1990	*Nature*	663	Ciliary neurotrophic factor	Motor neuronopathy
Weisman et al, 1990	*Science*	641	Soluble hcr type-1	Ischemia reperfusion injury
Mustoe et al, 1987	*Science*	639	TGF-β	Wound healing

Abbreviations: Ab, antibody; CFTR, cystic fibrosis transmembrane conductance regulator; EAE, experimental autoimmune encephalomyelitis; hcr, human-complement receptor; ICAM-1, intercellular adhesion molecule-1; IgG, immunoglobulin G; IL, interleukin; iNOS, inducible nitric oxide synthase; LFA-1, leukocyte function-associated antigen-1; NBQX, 2,3-Dihydroxy-6-nitro-7-sulfamoyl-benzo(F)quinoxaline; NMDA, N-Methyl-D-Aspartate; SCID, severe combined immunodeficiency; TGF, transforming growth factor; TNF, tumor necrosis factor; TRAIL, tumor necrosis factor related apoptosis-inducing ligand; VEGF, vascular endothelial growth factor.

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