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REVIEW ARTICLE

A review of in vivo animal studies in retinal prosthesis research

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Abstract
Background The development of a functional retinal prosthesis for acquired blindness is a great challenge. Rapid progress in the field over the last 15 years would not have been possible without extensive animal experimentation pertaining to device design and fabrication, biocompatibility, stimulation parameters and functional responses. This paper presents an overview of in vivo animal research related to retinal prosthetics, and aims to summarize the relevant studies.
Methods A Pubmed search of the English language literature was performed. The key search terms were: retinal implant, retinal prosthesis, artificial vision, rat, rabbit, cat, dog, sheep, pig, minipig. In addition a manual search was performed based on references quoted in the articles retrieved through Pubmed.
Results We identified 50 articles relevant to in vivo animal experimentation directly related to the development of a retinal implant. The highest number of publications related to the cat (n=18).
Conclusion The contribution of animal models to the development of retinal prosthetic devices has been enormous, and has led to human feasibility studies. Grey areas remain regarding long-term tissue-implant interactions, biomaterials, prosthesis design and neural adaptation. Animals will continue to play a key role in this rapidly evolving field.

Keywords Retinal implant · Retinal prosthesis · Artificial vision · Animal · Surgery · Blindness

Introduction

The development of a retinal prosthesis in order to restore functional vision to blind patients is a huge challenge. Multidisciplinary research involving engineers, neuroscientists, cellular biologists and ophthalmologists has led to pilot human implantations of both epi- and subretinal devices. The paradigm for this work was established over 15 years ago by Humayun et al., whose fundamental work showed that in retinitis pigmentosa (RP) and in age-related macular degeneration (ARMD) up to 80% of bipolar cells and up to 30% of ganglion cells survived [44, 54, 55, 97, 108]. These findings underlie the rationale for attempts to stimulate surviving retinal cells in order to restore some functional vision, using an electrical stimulation device [17, 31, 45, 46, 88, 89, 124].

Other approaches for advanced retinal degeneration which remain experimental at the present time include retinal pigment epithelial (RPE) transplantation [10, 63, 64, 85, 104] and photoreceptor (PR) transplantation [7, 14, 37, 65, 109]. Gene therapy is extremely promising; however, its potential in advanced retinal dystrophy is currently unknown [1, 8, 15, 47, 77, 83, 110, 111, 115, 118, 123].

Retinal prostheses are devices which receive and process external visual stimuli and then excite the diseased retina with these stimuli in order to elicit a functionally effective visual response. Such devices can be implanted on the

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epiretinal surface or between the RPE and the retina (i.e. subretinally) [17, 31, 45, 46, 51, 88, 89, 124]. Stimulations can also be delivered transchoroidally [72, 73]. A few reports have been published on pilot implantations in humans [20, 46, 88, 89, 119, 122].

It is still unclear to what degree a prosthetic device will ultimately be able to provide more than basic functional visual improvement to blind or poorly-sighted subjects. Many unanswered questions remain in the fields of implant design, biomaterials, electrode fabrication, packaging, surgical techniques, long-term effects and efficacy. The degenerating retina undergoes extensive and complex remodelling [67]. The consequences and implications of these processes on cell-electrode interactions, and therefore on electrically generated visual percepts, remain poorly understood. Animal models provide unique opportunities for progress in these fields. This paper discusses the animal models used in retinal prosthesis research, based on a literature review of published papers in English.

Material and methods

A Pubmed search of the English-language literature was performed. The key search terms were: retinal implant, retinal prosthesis, artificial vision, rat, rabbit, cat, dog, sheep, pig, minipig. In addition, a manual search was performed based on referenced articles quoted in the articles. Ex vivo studies (for example eye cup preparations) and early acute retinal stimulation studies were not considered for this review.

Results

We found 50 articles in the literature relevant to in vivo animal experimentation in relation to the development of a retinal prosthesis. The species involved include rats (n=6) [26, 29, 76, 80, 81, 96], rabbits (n=14) [33, 36, 42, 72, 73, 90, 94, 95, 102, 103, 105, 106, 116, 121], cats (n=18) [18, 19, 21–23, 30, 32, 43, 78, 79, 82, 93, 98, 99, 101, 114, 117, 120], dogs (n=4) [16, 39, 40, 66], sheep (n=1) [51] and pigs/minipigs (n=9) [34, 42, 49, 59, 69, 91, 92, 100, 102]. Two papers [16, 26] which involved three animal species do not figure in Table 2 due to lack of space, but are discussed in the review.

Table 1 summarizes the main anatomical characteristics of these animals

Table 2 lists the species and studies (including study design) in which they were used.

Rat

The rat is a popular small mammal model of RP, with three common strains: Royal College of Surgeons (RCS), P23H and S334ter transgenic lines. The etiology and clinical course of photoreceptor degeneration differ between these lines [28, 60]. Despite the widespread use of this animal model in non-surgical treatment strategies of RP and AMD and despite its low cost and easy availability, its use in prosthetic vision research has been limited to six studies with subretinal implants. These studies assessed long-term safety and efficacy of retinal stimulation [96], local tissue reactions to the implant and surgical procedure [76, 80, 81], and characteristics of electrically induced retinal damage [26], as well as the ability to record activation of the retinotectal pathway [29]. Results of these studies are summarized in Table 2.

Although the rat eye provides a biological environment broadly comparable to that of patients with inherited photoreceptor dystrophies, it obviously differs considerably from the human eye in terms of size and structure (Table 1). Although it has the basic features of all mammalian eyes, its axial length is roughly three times shorter than in humans, and the lens is proportionately much larger. The inner retinal blood supply is holangiotic, i.e. supplied by the central or cilioretinal arteries, as in most mammals. There is no fovea. Given the size of the rat globe and lens, an ‘ab interno’ approach to the subretinal space via a retinotomy and a vitrectomy procedure is not possible. For that reason, ‘ab externo’ approaches to the subretinal space have been used [29, 76, 78, 80, 81, 96]. Implantation is performed by transclerally injecting either basic salt solution (BSS) or a viscoelastic (e.g. hyaluronic acid, Healon®) under the retina. This procedure is performed ‘blind’, and insertion into the subretinal space cannot be controlled peroperatively.

The rat is a useful model for implant research with regard to histology, biocompatibility and impedance studies. More complex studies are limited by the small eye size.

Rabbit

The rabbit is an excellent model for wound-healing studies. The conjunctiva shows an aggressive wound-healing response, and as a result the rabbit has been used extensively in glaucoma research [2, 27, 38, 50, 52, 53, 57, 70, 107]. It is also an established model in proliferative vitreoretinopathy research [13, 24, 25, 27, 48, 52, 53, 62, 86, 112]. It is relatively cheap and easily available.

The rabbit globe is significantly smaller than in humans, and there is no macula as such but an *area centralis* with ‘visual streaks’ [56]. Furthermore, there is no dual retinal circulation, and it is therefore the only model in retinal prosthetics research with a merangiotic retinal circulation.

Preliminary studies have indicated that the rabbit visual system can be activated by subretinal [17], epiretinal [71] and episcleral [105, 106] electrical stimulation. These paradigms have been explored by several research teams

Table 1 Ocular characteristics of animal models in retinal prosthesis research: comparison with the human eye*

	Rat	Rabbit	Cat	Dog	Sheep	Domestic pig/minipig	Human
Globe length (AP axis) mm	6.29	7	21.3	21.73	26.85	24	24.15
Lens volume cm3	0.14	0.2	0.5	0.5	0.9–1.2	0.46–0.8	0.163 -0.244
Lens in % of eyeball volume	27.5	6.7	10	9.8	7.5	8.1	2.5–3.8
RPE	70% binucleate cells	85% binucleate cells	HMNC	HMNC	HMNC	HMNC	HMNC
Tapetum/cell layers	+	+	+/35 layers	+/15 layers	+/acellular	none	none
Retinal vasculature	holangiotic	merangiotic	holangiotic	holangiotic	holangiotic	holangiotic	holangiotic
Area centralis	+	+	+	+	+	+	macula/fovea
Cones (% of receptors overall)	0.85%-3%	higher cone/rod ratio than in humans	4%	5%	no published data found	12.5%	5.7%
Cone distribution across the retina	93% COS-1 cones 7% COS-2 cones	peak density at mid-visual streak, higher density in ventral than dorsal retina	horizontal region of higher density, peak density the area centralis (horizontally elongated oval region, 3–4 mm dorsolateral to the optic disc), decreasing smoothly to the ora serrata	peak density at the area centralis (horizontally elongated oval region, 3–4 mm dorsolateral to the optic disc)	no published data found	high cone density across the retina covering the optic disc and horizontal meridian (higher peaks in temporal retina near optic disc and in nasal retina 5–7 mm from optic disc)	highest density at the fovea, decreasing to the ora serrata
Dystrophic strains/models	P23H, S334ter, RCS	albino (with secondary RGC loss), pharmacotoxic models (sodium iodate, monoiodoacetic acid)	AR slow cone-rod dystrophy CEP290	rod-cone dystrophy-RCD1, progressive retinal atrophy RPE65	no	rhodopsin transgenic pig	RP genotypes

adRP: autosomal dominant RP; HMNC: hexagonal mononuclear cells; n/a: not available RCS: Royal College of Surgeons

*adapted from:

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Martin CL, Andersen BG (1981) Ocular Anatomy. In: Gelatt KN (ed) Veterinary Ophthalmology. Lea and Febiger, Philadelphia, p 22

Mutti OD, Zadnik K, Murphy CJ (1998) The effect of continuous light on refractive error and the ocular components of the rat. Exp Eye Res 67:631–636

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Szel A, Rohlich P (1992) Two cone types of rat retina detected by anti-visual pigment antibodies. Exp Eye Res 55:47–52

Ts'o M O M (1967) The retinal pigment epithelium 1. Comparative histology. Arch Ophthalmol 78:641

La Vail MM (1976) Survival of some photoreceptor cells in albino rats following long-term exposure to continuous light. Invest Ophthalmol Vis Sci 15:64–70

Table 2 Overview of publications on retinal implant research using animal models

		Palanker et al. 2004	Pardue et al. 2005	Pardue et al. 2005	De Marco et al. 2007	Salzmann et al. 2006	Walter et al. 1999	Schwahn et al. 2001	Hämmerle et al. 2002	Gekeler 2004	Rizzo et al. 2004	Sakaguchi et al. 2004	Nakauchi et al. 2005
Animal model	Rat	■	■	■	■	■							
	Rabbit						■	■	■	■	■	■	■
	Cat												
	Dog												
	Sheep												
	Minipig												
	Pig												
N (eyes)		5	22	26	19	26	10	10	n/a	10	43	5	6
Implant type	Epiretinal						▲				▲		
	Subretinal	▲	▲	▲	▲	▲		▲	▲	▲		▲	
	suprachoroidal												▲
	Episcleral												
Lens	lens-sparing	●	●	●	●	●	●	●	●	●	●	●	●
	Lensectomy												
	phacoemulsification												
Vitrectomy mode	no vitrectomy	◙	◙	◙	◙	◙		◙	◙	◙	◙	◙	◙
	pars plana vitrectomy						◙						
	trans-corneal vitrectomy												
Implantation mode	trans-scleral/trans-choroidal	♦	♦	♦	♦	♦		♦	♦	♦		♦	♦
	ab interno (with vitrectomy)						♦				♦		
	trans-corneal												
Research aims	Surgical safety/ feasability					▶	▶			▶		▶	▶
	biocompatibility						▶	▶					▶
	threshold current									▶	▶	▶	▶
	electrically evoked cortical recording				▶		▶	▶		▶	▶	▶	▶
	ERG recording		▶	▶			▶				▶		
	impedance measurements					▶							
	Optical imaging of visual cortex												
	estimation of perceptual resolution												
	OCT and/or FA					▶		▶					
	histology immunochemistry	▶	▶	▶		▶	▶	▶	▶	▶		▶	▶
	thermal effects of IR irradiation												
Follow up (fu) in months		5–9d	4,5	1,5	3	2	6	no fu	<14	no fu	no fu	no fu	no fu

d: days, ERG: electro-retinogram, FA: fluorescein angiography, h: hours, IR: infrared, n/a: not available, OCT: optical coherence tomography

		Yamauchi et al. 2005	Shah et al. 2006	Gerding et al. 2007	Sailer et al. 2007	Nakauchi et al. 2007	Siu & Morley 2008	Siu & Morley 2008	Völker et al. 2004	Eckhorn et al. 2006	Walter et al. 2005	Chowdhury et al. 2005	Chowdhury et al. 2005
Animal model	Rat												
	Rabbit	■	■	■	■	■	■	■					
	Cat								■	■	■	■	■
	Dog												
	Sheep												
	Minipig												
	Pig												
N (eyes)		9	13	2	18	18	4	4	3	13	3	9	6
Implant type	Epiretinal		▲	▲						▲	▲		
	Subretinal	▲			▲				▲	▲			
	suprachoroidal	▲				▲							
	Episcleral						▲	▲				▲	▲
Lens	lens-sparing	●	●		●	●	●	●	●	●		●	●
	Lensectomy									●			
	phacoemulsification			●							●		
Vitrectomy mode	no vitrectomy		◙		◙	◙	◙	◙				◙	◙
	pars plana vitrectomy	◙		◙					◙	◙			
	trans-corneal vitrectomy									◙	◙		
Implantation mode	trans-scleral/trans-choroidal	♦			♦	♦	♦	♦				♦	♦
	ab interno (with vitrectomy)		♦	♦					♦	♦			
	trans-corneal										♦		
Research aims	Surgical safety/ feasability			▶			▶				▶	▶	▶
	biocompatibility			▶					▶				
	threshold current	▶	▶			▶							
	electrically evoked cortical recording	▶	▶				▶	▶				▶	▶
	ERG recording	▶	▶				▶			▶			
	impedance measurements												
	Optical imaging of visual cortex									▶	▶		
	estimation of perceptual resolution									▶			
	OCT and/or FA					▶			▶				
	histology	▶		▶	▶	▶	▶						
	immunochemistry			▶									
	thermal effects of IR irradiation				▶								
Follow up (fu) in months		no fu	n/a	6–9	no fu	no fu	7d	no fu	0–15	n/a	no fu	no fu	no fu

Table 2 (continued)

		Chowdhury et al. 2005	Chow et al. 2001	Chow et al. 2002	Pardue et al. 2001	Pardue et al. 2001	Pardue et al. 2006	Wilms & Eckhorn 2005	Eger et al. 2005	Schanze et al. 2002	Schanze et al. 2003	Sachs et al. 2005	Schanze et al. 2007	Hesse et al. 2000	Majjii et al. 1999
Animal model	Rat														
	Rabbit														
	Cat	■	■	■	■	■	■	■	■	■	■	■	■	■	
	Dog														■
	Sheep														
	Minipig														
	Pig														
N (eyes)		3	19	n/a	21	9	3	4	5	7	3	3	3	4	4
Implant type	Epiretinal							▲	▲	▲	▲		▲	▲	▲
	Subretinal suprachoroidal		▲	▲	▲	▲	▲					▲			
	Episcleral	▲													
Lens	lens-sparing	●	●	●	●	●	●	●	●	●	●	●			●
	Lensectomy phacoemulsification									●			●	●	
Vitrectomy mode	no vitrectomy	◙						◙	◙	◙	◙				
	pars plana vitrectomy		◙	◙	◙	◙	◙					◙			◙
	trans-corneal vitrectomy									◙			◙	◙	
Implantation mode	trans-scleral/trans-choroidal	♦						♦	♦	♦	♦				
	ab interno (with vitrectomy)		♦	♦	♦	♦	♦					♦			♦
	trans-corneal									♦			♦	♦	
Research aims	Surgical safety/ feasability	▶	▶									▶			
	biocompatibility threshold current		▶	▶		▶	▶						▶		▶
	electrically evoked cortical recording	▶			▶				▶	▶	▶	▶	▶	▶	▶
	ERG recording		▶	▶	▶		▶	▶							▶
	impedance measurements														
	Optical imaging of visual cortex														
	estimation of perceptual resolution								▶	▶	▶				
	OCT and/or FA														▶
	histology					▶	▶								▶
	immunochemistry					▶	▶								
	thermal effects of IR irradiation														
Follow up (fu) in months		no fu	10–27	<12	n/a	6–11	36–60	no fu	no fu	no fu	no fu	12h	3	0.5	2–6

		Güven et al. 2005	Güven et al. 2006	Kerdraon et al. 2002	Schwahn et al. 2001	Hämmerle et al. 2002	Laube et al. 2003	Sachs et al. 2005	Montezuma et al. 2006	Schanze et al. 2006	Sachs et al. 2005	Gekeler et al. 2007	Johnson et al. 2007
Animal model	Rat												
	Rabbit												
	Cat												
	Dog	■	■										
	Sheep			■									
	Minipig				■	■	■	■	■				
	Pig									■	■	■	■
N (eyes)		5	4	1	6	n/a	3	5	28	8	8	11	n/a
Implant type	Epiretinal	▲	▲	▲			▲						▲
	Subretinal				▲	▲		▲	▲	▲		▲	
	suprachoroidal												
	Episcleral												
Lens	lens-sparing	●	●		●	●	●	●	●	●			
	Lensectomy phacoemulsification			●						●	●	●	●
Vitrectomy mode	no vitrectomy												
	pars plana vitrectomy	◙	◙	◙	◙	◙	◙	◙	◙	◙	◙	◙	◙
	trans-corneal vitrectomy												
Implantation mode	trans-scleral/trans-choroidal									♦	♦	♦	
	ab interno (with vitrectomy)	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦		♦
	trans-corneal												
Research aims	Surgical safety/ feasability			▶						▶	▶	▶	
	biocompatibility	▶	▶		▶	▶			▶				
	threshold current						▶			▶	▶		
	electrically evoked cortical recording				▶		▶	▶		▶	▶		
	ERG recording	▶	▶						▶				
	impedance measurements												▶
	Optical imaging of visual cortex												
	estimation of perceptual resolution												
	OCT and/or FA	▶	▶		▶							▶	▶
	histology	▶			▶	▶			▶			▶	
	immunochemistry				▶								
	thermal effects of IR irradiation												
Follow up (fu) in months		6–13	2–6	no fu	<14	<14	<18	no fu	3	10h	10h	1	no fu

in order to test/record surgical feasibility of retinal implants [33, 36, 72, 116], their long-term biocompatibility [36, 42, 72, 102, 116], electrically evoked cortical potentials (EEP) [33, 73, 90, 95, 121, 105, 106], depth of retinal neuronal activation [103], and the effect of infrared irradiation on an implanted infrared receiver [94]. Morley and co-workers performed episcleral stimulation on two models of retinal degeneration in the rabbit: the albino rabbit with retinal ganglion cell (RGC) deficits[106], and the pharmacotoxic model of selective RPE and photoreceptor degeneration secondary to systemic administration of sodium iodate (NaIO3) or monoiodoacetic acid [105]. These studies are summarized in Table 2.

Cat

Feline and human eyes are almost comparable with regard to size. The feline eye is slightly smaller and, possessing both a retinal and a choroidal circulation, is closer to the human than to the rabbit eye.

Pars plana vitrectomy is more difficult in the cat than in humans because of the large anterior segment and deep orbit. The lens volume makes up 10% of the total volume of the globe—compared to 2.5–3.8% in humans. Whereas an anterior transcorneal approach has been used by some, others have opted for a temporal approach, performing a lateral canthotomy [93] or removing the frontal process of the zygomatic bone, allowing access to the temporal sclera [18].

Whereas in the human eye vitrectomy and instrumental manipulation can be safely performed through the pars plana, the same approach in the cat is likely to cause severe bleeding or retinal detachment when instruments are inserted through sclerotomies. As a result, corneal access sites have been advocated [117]. Lensectomy and subsequent air injection into the anterior chamber have been reported to provide excellent visualisation of the posterior segment and to allow a more anterior access for instrument insertion through the corneal incisions [43]. Because of the high reflectivity of the tapetum lucidum no endoillumination is necessary, making two-port vitrectomy possible [114]. It may not be necessary to perform the hazardous step of posterior hyaloid face detachment in order to obtain a posterior vitreous detachment [114]. As in the rat, subretinal viscoelastics have been used to obtain a subretinal bleb through which to insert an implant [114]. Epiretinal device fixation using a retinal tack is thought to be unsafe in the cat, given the marked thinning of the posterior sclera [43].

Notwithstanding the particularly hazardous features of vitreoretinal surgery in the cat, it has been the most commonly used animal model in the development of visual prosthesis so far. We identified 18 studies. The cat model has been used to test the feasibility [18, 21–23, 93, 117], biocompatibility [18, 19, 79, 82, 101, 114] and functioning of specific devices or electrodes [18, 19, 21–23, 30, 32, 43, 78, 82, 93, 98, 99, 101, 117, 120]. Because of the well-established cortical recording techniques and the good understanding of the feline visual system, this model has been largely used in testing cortical representation of electrical retinal stimulation with cortical electrode recordings [18, 19, 21–23, 30, 32, 43, 58, 79, 82, 93, 98, 99, 114, 117, 120, 101](Table 2).

The Abyssinian cat has a very high prevalence of a slow rod-cone dystrophy, akin to Leber's congenital amaurosis. The mutation has recently been identified [68]. These cats, however, are not readily available commercially.

Dogs' and cats' eyes are very similar in structure, size, lens size, presence of a tapetum, holangiotic retinal circulation, and distinct, characterized retinal dystrophies (see Table 1). Retinal dystrophy in the Irish setter (RCD1 mutation) has been studied for over 20 years [3–5, 12, 87]. Retinal stimulation studies have been successfully conducted with this model [16, 39, 40, 66]. The Briard beagle carries a well-characterized retinal dystrophy [6, 113]. These dogs were famously used in the first effective viral transfection gene therapy trial for blindness [1]. Dogs are expensive to house, in particular because the retinal degeneration takes several months to develop (in RCD1 dogs, the ERG extinguishes at approximately 18 weeks) [66]. We found three canine studies in which implant-biocompatibility and biostability [39, 40, 66] and one study in which electrically elicited responses (EERs) produced by epiretinal stimulation [16] were examined.

Sheep

The ovine eye shows important differences relative to the human eye: it is approximately 30% larger and photoreceptor populations and distribution are different; there is a retinal tapetum; iris muscle orientation, ciliary body and muscle location differ from the human eye. There is no anterior ciliary artery communication with the major arterial circle of the iris [75]. We found only one study using the ovine model in retinal implant research [51] (see Table 2). The use of the sheep was justified on the grounds that the ovine ocular dimensions are larger than in humans, and that notwithstanding these differences there are many similarities between the sheep and the human eye.

Pig/minipig

A strain of transgenic pig with a rhodopsin mutation has been described and studied [61, 84], but is not commercially available.

The porcine ocular structure is close to that of humans, especially with regard to size, cone distribution and retinal

layers, with an area centralis comparable to the human macula [61]. The retinal circulation is holangiotic; this is relevant in post-implantation vascularization studies. Several anatomical differences to the human do exist: medially, there is a cartilaginous nictitating membrane which can be bothersome during and after surgery. This membrane is present in other animals such as the cat, but it is less developed. In addition to the six extraocular muscles similar to those in the human, pigs also have a powerful muscle surrounding the optic nerve and the blood vessels (m. retractor bulbi), which tends to retract the globe into the orbit, making surgical access difficult. For adequate access, it is thus necessary to paralyze the extraocular muscles peroperatively (curarisation); this may prove hazardous, especially as some strains of minipig do not respond well to general anesthesia. Other features include a vigorous inflammatory response to intraocular surgery—particularly involving the crystalline lens—and diffuse choroidal bleeding, which can be unstoppable [34].

Compared to smaller mammals, housing and breeding costs are significant. Furthermore, as Schanze and colleagues point out, there is much less accumulated knowledge about the visual system of pigs relative to that of cats [100]. Notwithstanding these limitations, minipigs and pigs have featured extensively in prosthesis research. Published studies include feasibility/safety of implant procedures [34, 92], control of retinal-implant contact using impedance measurements [49], long-term biocompatibility [42, 59, 69, 102], physiological effects of the implants using epidural recordings of evoked cortical potentials [59, 91, 92, 100, 102] and behavioural reactions to electrical stimulation [34].

Discussion

Given the uncertainty of long-term implant behaviour with regard to electronics, packaging, biotolerance, stimulation parameters and functional outcomes, further studies are evidently necessary.

A number of groups world-wide are developing and testing epi- and subretinal implants in humans. The most advanced project is the Argus I (Second Sight, Sylmar, CA, USA) 16-electrode epiretinal implant feasibility study [45], which demonstrated an effective camera system for image acquisition, wireless transmission to ocular components, array-retina stimulation and documented functional improvements, notably with regard to mobility, over a 3-year period in six subjects. A follow-up study with a 60-electrode (Argus II) device is currently underway world-wide. There are no published reports to date of other successful, long-term implantations.

It is still unclear, though, which approach (epiretinal, subretinal, episcleral or transchoroidal) will ultimately provide the best functional outcomes. In view of the invasive and complex surgery required, potential risks to the eye and unclear long-term effects, investigators wishing to implant experimental devices in humans face hard questions from their local institutional ethics committees, as well as from their medical device accreditation authorities.

With the exception of one historic pilot study on acute electrical stimulation [74] we found no published papers on retinal implants in non-human primates. In vivo pilot studies in primates with so-called ‘minimally invasive’ trans-scleral spike electrodes have indeed been reported in meetings , but no peer-reviewed articles on this subject have been published [35]. At this stage, there is no evidence that primates can provide better data than cats, rabbits dogs or pigs in retinal implant development. Given the traumatic nature of these experiments, and the scope for further experimentation in lower-order mammals, we believe primate studies are ethically questionable at the present time. This contrasts with pilot experiments using electrode array stimulation of the visual cortex [11], in which the psychophysical capabilities of the primates are essential.

Reports from feasibility studies in humans from the Doheny group with the Second Sight Argus I 16-electrode epiretinal implant [119, 122] have shown that it is safe, in certain circumstances, to make the leap to human implantation. However, the fact remains that new devices mandate extensive pre-clinical investigation. There are cogent theoretical reasons for advocating subretinal placement, however challenging this proves to be in practice. Animal experimentation in this field remains inescapable, notwithstanding the major limitations of psychophysical testing in animals. In addition, as highlighted by Hafezi et al. in an historical review on animal models for retinal degenerations and dystrophies, there are few ‘non-mouse’ models for retinal degeneration [41].

Not all studies mentioned above fit the categorization by species. For example, Chen et al. [16] studied electrically evoked potentials in mice, dogs and humans following epiretinal stimulation. Although rare, multi-species studies are useful as they provide information on how various models respond to broadly similar stimuli.

Although animal electrophysiological test protocols are well established [18, 19, 21–23, 30, 32, 34, 43, 58, 59, 79, 82, 91–93, 98–100, 102, 114, 117, 120], such testing in lower-order mammals is very difficult. In vivo electrical stimulations in the rat at both corneal and RGC levels were successfully reported by Baig-Silva et al. [9], highlighting wide variations in thresholds and charge densities between acute and chronic stimulation experiments.

Small mammals such as the rat are cheap and easy to obtain. Rat strains with RP-like retinal degenerations are commercially available, but their usefulness in prosthesis development is limited by anatomical constraints. Larger

mammals provide a closer model to the human eye, but there are no commercially available RP-like models. Compromises are therefore inevitable. Due to the close similarities between human and porcine eyes in terms of functional anatomy, and given considerations of cost and availability, the pig/minipig appears to be a useful model in retinal implant research.

In conclusion, animal models are essential in the ongoing development of retinal prosthetics. Since psychophysical testing is paramount in assessing the functional effects of an implanted device, feasibility studies in humans are admissible once the functionality of a new design has been established in an animal model. The use of primates does not appear justified at the present time.

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