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The marmoset monkey: a multi-purpose preclinical and translational model of human biology and disease

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Nonhuman primates are important models in preclinical research enabling understanding of pathogenic mechanisms in human disease that readily translates into therapy development. Safety and efficacy testing of biologicals, such as antibodies, soluble receptors, cytokines, often preclude use of lower species, e.g. when drugs fail to bind targets. These issues explain increasing interest in nonhuman primates (NHPs) as preclinical disease models, despite costs and ethical limitations.

The aim of this feature article is to highlight the common marmoset monkey as a useful model in biomedical and preclinical translational research. We cite published studies as well as unpublished information presented at the 1st Workshop of the International Marmoset Research Group (IMRG), held on June 20-21, 2011 at the German Primate Center in Göttingen, Germany.

Marmosets as experimental model of human biology and disease

The common marmoset (*Callithrix jacchus*) is a small-bodied New World monkey (Fig.1a) widely used in studies ranging from toxicology, neurological and autoimmune diseases, and reproductive biology to stem cell biology and transgenics. Marmoset colonies are outbred, but differences exist in terms of genetic heterogeneity compared to humans. As an example, the major histocompatibility complex genomic region, which encodes central regulatory molecules of immune responses is much more polymorphic in humans and Old World monkeys than in common marmosets [1]. Laboratory-housed colonies are often kept under conventional conditions that expose monkeys to naturally occurring pathogens that shape their immune system. As a consequence, marmoset disease models are appropriately complex and their use requires in-depth knowledge of the animals' biology and optimal laboratory management. There is already a vast body of knowledge on the marmoset as model of human disease (e.g. [2-4]) and on biotechnical aspects [5,6]. To be of use for the biomedical research community, this information needs to be readily accessible. This is task

of the new International Marmoset Research Group, which aims to integrate existing activities of regional marmoset research groups, e.g., *MaRGA* (Americas), *EMRG* (Europe) and a newly established *JMRS* (Japanese Marmoset Research Society) harmonizing activities in Asia.

The reproducibility and quality of marmoset-based data critically depend on high quality housing and management that minimize stress and refined protocols for health surveillance and veterinary care [6,6a]. It is thus essential that data on foraging and nutrition, natural behavior and sociobiology, collected in the marmoset's natural habitat the coastal forests of northeastern Brazil, continue to be translated into laboratory practice [7].

Marmosets in preclinical pharmacology and toxicology

Traditionally, the most frequently used NHP species for preclinical *in vivo* pharmacology, safety studies and toxicology assessment has been the cynomolgus monkey (*Macaca fascicularis*, 80%), the marmoset (15%) and the rhesus monkey (*Macaca mulatta*; 5%) (G. Weinbauer, Covance Laboratories GmbH, Germany, personal communication). The main reason for the current preference of the large-sized cynomolgus monkey (± 3 kg) is the abundant background data that can be used as a reference repository. In several disease areas, however, including immune-mediated disorders [8], available models in macaques are suboptimal as they show poor resemblance with the corresponding disease in humans.

Despite more limited usage, marmosets provide highly attractive models due to their small size (± 400 g), requiring limited amounts of test compounds; high tractability, less frequent need to sedate for handling; and the use of bone marrow chimeric twins in therapy trials [2,3]. For example, using serum monoamine levels as biomarkers, Pryce and coworkers demonstrated that the variability between fraternal siblings is much lower than between siblings of different births, complementing similar data on immune profiles [9]. This is crucial information for the design of marmoset drug studies, especially since twin monkeys can be used for both preclinical toxicity and efficacy assessment [10-12].

Marmosets in molecular biology

The sequencing and annotation of the human genome is an essential step towards a better understanding of the genetic basis of human disease. The subsequent translation of genetic into functional information is a major challenge for the future. Much groundbreaking work is already done in mice that transgenetically express human genes. However, a human gene placed in a mouse cell may behave differently than in a human cell and the marmoset can be of use here.

The analysis of the marmoset genome approaches its completion (http://may2010.archive.ensembl.org/Callithrix_jacchus/Info/Index). It will soon be possible to search for the orthologues of disease-associated human genes and disable them with siRNA, for example. Gene expression profiles of marmosets can be examined with already available technology, such as the EUMAMA microarray [13].

Sasaki and co-workers have shown that generation of transgenic marmosets is technically feasible [14] (Fig.1b). Although many ethical issues need to be solved before this technology can be generally applied, it is clear that the basis for an important contribution of transgenic marmosets to functional analysis of the human genome has been laid.

Marmosets in immunology and immunopathology

Most preclinical immunology research is based on a limited selection of specific pathogen free (SPF) bred mouse and rat strains. The clean housing environment changes the maturity of the rodent immune system. Together with fundamental differences between the rodent and human immune systems, this causes a broader response to immunomodulatory therapies than observed in nonhuman primates and humans [15]. In many respects, the marmoset and human immune systems are more similar [16]. Longitudinal analysis of experimental autoimmune disease models shows that in the course of the disease the biodistribution of activated immune cells changes between the lymphoid compartments and blood. This implies that reduced activity of a cell population of interest does not imply its suppression or elimination necessarily; it can also have disappeared from detection. In mouse immunology, spleen cells are commonly used, whereas in human immunology blood cells are used. In the marmoset both compartments are accessible, enabling better translation of data from rodent disease models to patients. Adaptation and improvements of analytical methods (e.g. Meso Scale Discovery®, Luminex®) can compensate for the limited available blood volume, being – depending on the national regulations for animal welfare – 1 to 2 ml per week for an adult marmoset.

The main role of the marmoset in preclinical immunology is in immunotoxicology [17], in the modeling of two important autoimmune-mediated inflammatory disorders, such as rheumatoid arthritis [18] and multiple sclerosis [19], and in airway hypersensitivity disorders [20]. The respective experimental autoimmune disease models, collagen-induced arthritis (CIA) and experimental autoimmune encephalomyelitis (EAE), offer distinct advantages compared to the corresponding models in macaques, which are usually more acute and severely destructive. Research into the marmoset EAE model has provided new insights into the effect of environmental pathogens, such as herpes viruses, on the immune mechanisms that initiate and perpetuate inflammation and injury of the central nervous system [21]. This creates an essentially different situation from rodent EAE models, and a vital alternative for the treatment of multiple sclerosis.

Marmosets in neuroscience

The evolutionary proximity of marmosets and humans is reflected by their comparable brain morphology, making the marmoset a potentially useful model for neuroscience and neuropathology research. The growing importance of marmosets for research in neuroscience and related fields is demonstrated by the increasing number of brain atlases based on histology and magnetic resonance imaging (MRI; for example [22,23]) that enable positron emission tomography (PET) to associate drug-induced changes in behavior with anatomically specific alterations in cerebral glucose metabolism [23a].

In neuropathology, flagship models have been developed of neuroinflammation, being the already discussed EAE model for MS, and neurodegeneration, being the unilateral lesion model of the nigrostriatal bundle with the neurotoxin 6-OHDA [24] (Fig.2) and the more advanced MPTP-induced model of idiopathic Parkinsonism [25,26]. All marmoset models are valid for their human counterparts as they develop the full spectrum of symptoms of Parkinsonism. However, a shortcoming of these models is that, aggregates of misfolded α -synuclein (Lewy bodies), are not formed. This is not trivial as these can induce similar patterns of microglia activation and neurodegeneration, as observed for β -amyloid in Alzheimer's disease [27]. This discrepancy could be overcome by inducing nigrostriatal α -synucleinopathy using viral vector-mediated overexpression of human α -synuclein [28]. In a preliminary report Alzheimer's disease-like pathology such as extracellular A β -plaques and even some intracellular A β -staining localized mainly in the cortex was reported for a 23 year old male marmoset ([29], and own unpublished data).

The costs of marmosets and ethical constraints stimulate the development of techniques for longitudinal analysis of neurological functions, aiming at collecting more data from a limited number of healthy and diseased marmosets. These comprise various *in vivo* imaging techniques - such as SPECT imaging [30], near infrared imaging (C. Dullin, University Medicine, Göttingen, pers. communication) and nuclear magnetic resonance based techniques, such as MRI, fMRI and MR spectroscopy [30-32] (see also Fig.2) – and telemetry as well as behavioral and (neuro)physiological tests [33,34].

Marmosets as models to study cognitive behavior

Several studies indicated that marmosets, in addition to macaques, can be the species of choice to investigate the impact of e.g. environmental manipulations, drugs and lesions on cognitive function, using tasks similar to those deployed in the study of human cognition and diagnosis of neuropsychiatric disorders.

Marmosets are sensitive to changes in their environment. Conducting behavioral experiments in the home cage is advantageous in avoiding the stress of handling, to save the time it takes to move the animal to a new experimental room, and to save space. In addition, home-cage testing allows for measurement of day-to-day changes in the cognitive abilities of several animals simultaneously. In this sense, a simple and convenient testing apparatus, such as a detour reaching task or a staircase test apparatus, is advantageous for assessing the marmoset's cognitive functions.

The most popular system for a computer-based home-cage testing has been the Monkey CANTAB (Cambridge Cognition, and later Lafayette Instrument), which was developed in the 1980s and has been frequently used on non-human primates [33]. Recently, a convenient PC-based apparatus was developed for marmosets [36]. Using this set-up in the home cage, it is possible to measure cognitive abilities from many marmosets simultaneously without any additional space/room for the experiments.

Marmoset as models to study sleep behavior and circadian rhythm

In common with man, the marmoset exhibits sleep cycles with stages alternating between non-REM (deep sleep and light sleep) and pREM sleep throughout the night. As strictly day-active animals, marmosets are ideally suited for sleep studies [35, 37]. Advanced telemetric systems for registration of EEG and EMG such as the NeuroLogger® (Newbehavior, Zurich, Switzerland) in combination with telemetric methods for acquisition of core body temperature and activity (Remo 200; Remo Technologies Ltd., Salisbury, UK) enable collection of biobehavioral data from freely moving and group-housed animals [38].

Marmosets as models for human obesity

Marmosets provide models for both spontaneous [38] and experimentally-induced obesity (virus-induced: [39]; fetal glucocorticoid hyperexposure: [40] adult high calorie diet [41]). Such models can manifest hypertriglyceridemia and hyperglycemia [38] and illustrate how the shorter lifespan of the marmoset is particularly useful in rapidly determining the contribution of abnormal fetal metabolic environments to adult metabolic disease.

The body weight of captive marmosets has risen about 10% per decade in the last 20 years, comparable to trends in other laboratory mammals, possibly due to improved veterinary care, husbandry, understanding of nutritional requirements and environmental enrichment [42]. These demographic data underline the importance of contemporary controls in all obesity research-related experiments. In the past, marmosets have not been well utilized in obesity research partly because 85% comparability of insulin amino acid sequence between marmosets and Old World primates, together with a reduced affinity of marmoset insulin for available anti-insulin antibodies [43,44], delayed development of a validated assay for circulating insulin [4]. With an improved method for determining pancreatic insulin dysfunction in marmosets, and the recent finding that marmoset pancreatic islets more closely resemble human islets [45] than those of Old World macaques [46], the use of marmosets in designing novel therapeutic solutions to obesity is set to increase.

In this regard, new understanding of obesity development in female mouse knockout/knock-in models, and its dependence on diminished function of non-classical estrogen receptor (ER)-alpha [47], may suggest the marmoset as a particularly appropriate preclinical model. Of relevance is the marmoset's naturally diminished signaling via ER-alpha due to intracellular inhibitory binding proteins for both ER-alpha and estrogen response elements on DNA [48]. Each provides clear potential by which manipulation of ER signaling may provide understanding of functional mechanism that is not possible in Old World monkeys.

Marmosets as model of infectious disease

The possibility to use marmosets as a model for human infectious disease has been extensively explored [3]. However, in the preclinical research of major infectious diseases, such as AIDS, malaria, tuberculosis, Old World monkeys have been the preferred species. For some infections, though, including hepatitis C, the marmoset seems to be the only easily accessible model [49].

Understanding marmoset reproductive biology yields novel models for human health

Laboratory marmosets are usually bred when housed as a male-female pair or in families or groups of unrelated animals with a breeding dominant male and female [50,51]. Behavioral and physiological mechanisms otherwise prevent reproduction, constraining females to a greater degree than males [52]. Accommodating such reproductive traits in the laboratory has truly enabled biomedical use of marmosets in translational research. Recent examples include integrating microPET brain imaging and brain region-specific gene array studies with reproductive behavioral and neuroendocrine testing to unravel female sexual dysfunction [51a], as well as transgenic marmoset offspring [14] that promise genetically manipulated monkeys and more reliable translation to therapeutics in humans than mouse genetic models.

Common marmosets were the first monkeys from which primate embryonic stem (ES) cells [53] were derived, enabling the first derivation of ES cells from humans [54]. This stem cell heritage provided the needed foundation for inducible pluripotent stem cells that can be reliably manipulated into expressing specific phenotypic characteristics [55,56] and promise autologous stem cell therapies for replacement organs and tissues for humans.

Development of transgenic marmosets and marmoset stem cells has benefitted from recent revelations concerning marmoset reproductive physiology and a key difference to Old World primates, including humans. In marmosets, chorionic gonadotropin (CG) in addition to placental expression and maintenance of pregnancy [48], is also expressed by pituitary gonadotropins [59,60]. Episodic release of CG from the marmoset pituitary regulates ovarian follicle growth, triggers ovulation and supports corpus luteum function in females [59], and in males regulates testicular testosterone production in support of spermatogenesis [61]. In Old World primates and humans, however, pituitary luteinizing hormone (LH) supports ovarian and testicular function, while CG expression is relegated to the placenta for pregnancy recognition [48]. Understanding this reproductive difference was key to refining gonadotropin-stimulated oocyte retrieval [57,58], 58a] that unlocked progression towards multiple transgenic disease-related phenotypes [14].

Concluding remarks

The common marmoset is a small-bodied, multi-purpose nonhuman model that can be used to study many aspects of human biology and disease. Attractive aspects of marmosets for drug development are i) small size, requiring small amounts of test compound for preclinical toxicology and efficacy studies in one species, and ii) chimeric twinning enabling matched-control studies and efficient production of transgenic individuals.

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Figure 1: A marmoset with germ-line expression of green fluorescent protein (GFP). The high reproduction rate and the relatively short time to sexual maturity makes the marmoset suitable for transgenic modification. Proof of principle was demonstrated by the germ-line expression of GFP [12]. The pictures show a normally developed transgenic marmoset (a) with expression of GFP in the skin (b). The pictures were a kind gift of Dr. Erika Sasaki, Central Institute for Experimental Animals, Kawasaki, Kanagawa, Japan.

Figure 2: Combined MRI and SPECT image of a marmoset monkey brain.

A marmoset was unilaterally lesioned with 6-hydroxy dopamine in 2003. Eight years later the depicted scans were made. The yellow/red colors indicate high density of dopamine transporters in the basal ganglia visualized with the ligand [I-123]FP-CIT. a) Coronal section; b) Transverse section; c) Sagittal section. Pictures were kindly provided by Dr. Enrique Garea-Rodríguez and Dr. Gunther Helms, Göttingen, Germany.