TACONIC

THE CIEA NOG mouse®

A SUPER IMMUNE DEFICIENT MOUSE WITH UNPARALLELED POTENTIAL FOR ENGRAFTMENT OF HUMAN CELLS AND TISSUES

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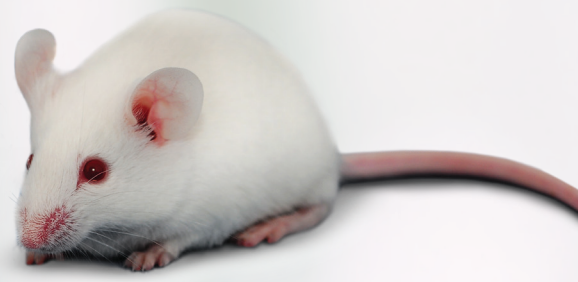
A SUPER IMMUNE DEFICIENT MOUSE WITH UNPARALLELED POTENTIAL FOR ENGRAFTMENT OF HUMAN CELLS AND TISSUES NOD.Cg-*Prkdc*^{scid} *Il2rg*^{tm1Sug}/JicTac



Compared to other immunocompromised mouse models, the CIEA NOG mouse® has a more comprehensive and severe immunodeficient phenotype, with none of the leakiness or shortened life span displayed by some other models.

Mice engrafted with human cells and tissues allow for the study of human cells under *in vivo* conditions. The CIEA NOG mouse® represents a new generation of immune deficient mice for human cell and tissue engraftment research. This severely immune compromised mouse carries the *scid* mutation and a targeted mutation of the *Il2rg* gene on the NOD/ShiJic genetic background. The functional knock out of the IL-2Rγ chain results in reduction of residual innate immunity of the NOD/ShiJic background and superior engraftment of human cells and tissues compared to any other immune deficient mouse model.

TO DISCUSS YOUR NEEDS

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CHARACTERISTICS OF THE CIEA NOG mouse®:[1,5,49,73]

- Lack of functional T, B and NK cells.
- Reduced complement activity.
- Dysfunctional macrophages and dendritic cells.
- NOD SIRP α allele promotes enhanced engraftment of human hematopoietic lineages.
- Deficiencies in immune signaling, including impaired cytokine production.
- Very low lymphoma development resulting in a lifespan of more than 1.5 years, comparable to other inbred strains.
- No T or B cell leakiness observed at 7 - 10 months of age.
- Does not develop diabetes.
- The Il2rg gene is sex-linked.
- Excellent model for a variety of xenograft and human cell engraftment studies.

HOW CAN THE CIEA NOG mouse® BE USED?

The unparalleled engraftment potential of human cells and tissues in this model offers an array of new opportunities for basic and translational research in areas such as:

- Xenotransplantation of human normal and cancer cell lines and tissues
- Reconstitution of the immune system for the study of the immune component in cancer as well as efficacy and mechanism of action studies for therapeutic antibodies
- Immunity and development of the immune system
- Hematopoiesis
- Stem cell research
- Infectious disease studies
- Safety assessment of new therapeutics
- Regeneration of damaged tissues
- Development of new human cell and tissue engrafted models

WHAT OTHER BENEFITS DOES THE CIEA NOG mouse® OFFER YOU?

- Excellent availability with local production in the US and Europe.
- No upfront fees or license agreements.
- Production at the Taconic Biosciences Restricted Flora™, Excluded Flora and Defined Flora health standards permits confidence in the health of the animals used in your studies.
- Researchers purchasing the CIEA NOG mouse® may receive technical support from the inventor of the model as well as Taconic's engraftment laboratory.

TO ORDER

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FIGURE 1: GROWTH CHART FOR CIEA NOG mouse® PRODUCED AT RESTRICTED FLORA™

This represents a sampling from Taconic US production colonies at the Restricted Flora™ health standard. Data was collected from 2012-2013 and represents 100 animals per sex. All animals were fed NIH-31M and housed at densities appropriate for their age. The range shown is +/- two standard deviations from the mean, however note the sample size is not large enough to necessarily represent a normal population.

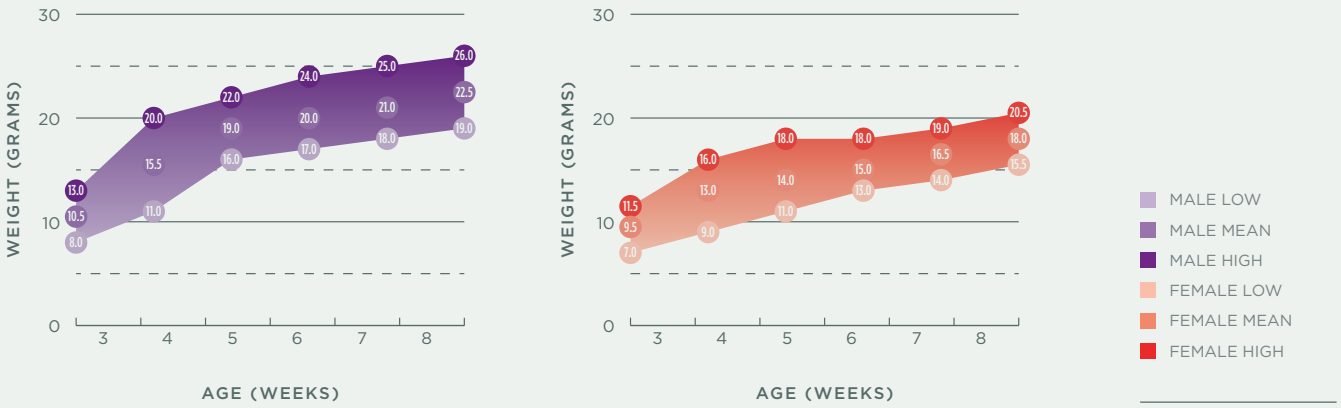


FIGURE 2: GROWTH CHART FOR CIEA NOG mouse® PRODUCED AT DEFINED FLORA

This represents a sampling from Taconic US production colonies at the Defined Flora health standard. Data was collected in 2013 and represents 25 animals per sex. All animals were fed NIH-31M and housed at densities appropriate for their age. The sample size for this study is too small for calculation of a standard deviation to be meaningful.

FIGURE 3: HEMOLYTIC COMPLEMENT ACTIVITY - NOD scid AND NOG mice

Defect of hemolytic complement activity in sera of NOD scid and NOG mice.
The CIEA NOG mouse® shows defects in complement activity.

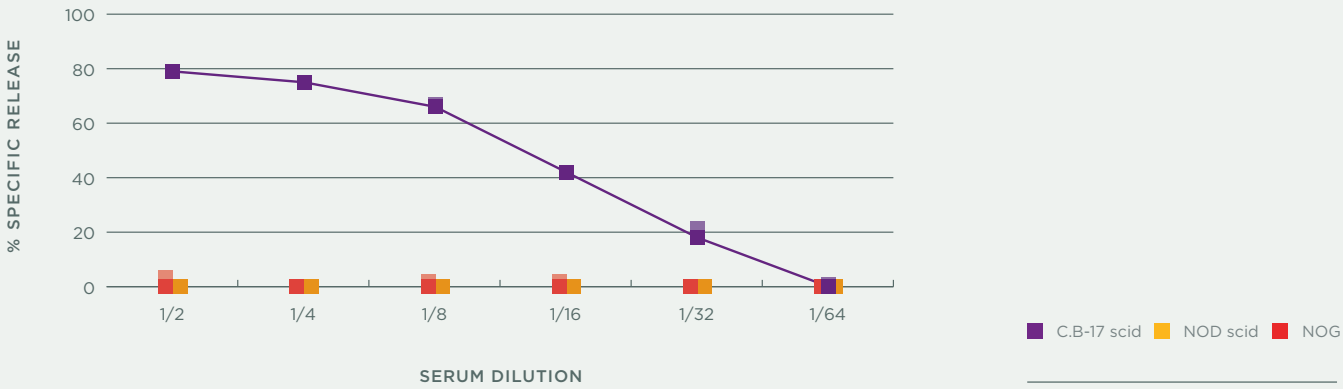
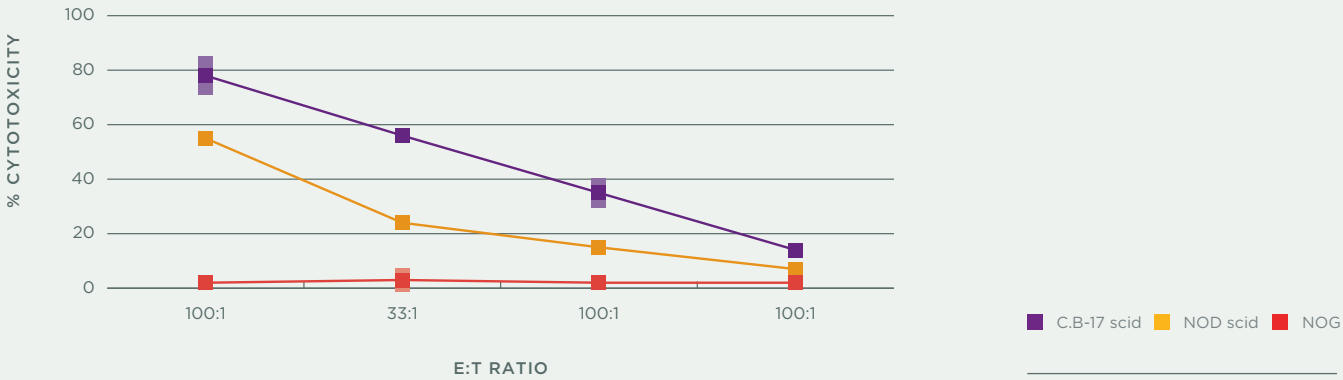


FIGURE 4: NK ACTIVITIES DEFECT - NOG mice

Defect of NK activities in spleen cells of NOG mice.
The CIEA NOG mouse® lacks NK cell activity.



APPLICATIONS OF THE CIEA NOG mouse®

CANCER XENOGRAFTS – CELL LINES AND PATIENT-DERIVED XENOGRAFTS (PDX)

The CIEA NOG mouse® excels at xenografts and has been used successfully to engraft a variety of solid and blood tumors. The CIEA NOG mouse® is a natural choice for cell lines or tissue types with poor take rates in other models and is recommended as the model of choice for use with patient-derived tumors.[47,108,110,119,121,136]

FIGURE 5: HISTOPATHOLOGICAL EVALUATION OF ESTABLISHED TUMOR LINES IN NOG MICE

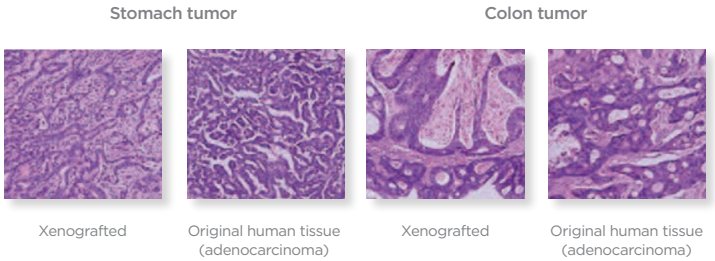


FIGURE 6: DEVELOPMENT OF PATIENT-DERIVED TUMOR LINES IN THE NOG MOUSE

Figure 5 and 6: The CIEA NOG mouse® may be used to establish patient-derived tumor models. Fresh human cancer samples were subcutaneously inoculated into the flank of NOG mice. A total of 326 tumor specimens were implanted into the mice, with *in vivo* tumor models successfully generated from 54 of the tumor samples (successfully passaged *in vivo* at least three times). Samples included tumor tissue from the original tumor site as well as metastatic sites and lymph nodes adjacent to the tumor. Histopathology of the derived *in vivo* tumor models was similar to that of the original tumor sample. Data from reference 47 and IWHM 2006 meeting (Poster 18): Chen YU et al., Tokyo, Japan, Oct 11-12, 2006.

CANCER ORIGIN	NUMBER OF IMPLANTED SAMPLES			NUMBER OF SUCCESSFUL PDX MODELS GENERATED		
	PRIMARY	METASTATIC	LYMPH NODE	PRIMARY	METASTATIC	LYMPH NODE
EPITHELIAL TISSUES						
Large intestine	48	0	14	17	0	4
Stomach	18	3	2	3	1	1
Ampulla of Vater	4	0	0	2	0	0
Uterus	10	0	1	2	0	0
Ovary	18	2	0	1	1	0
Mammary gland	57	2	13	3	0	0
Cervix	4	0	2	0	0	1
Prostate	12	0	0	0	0	0
Testis	3	0	1	0	0	0
Kidney	18	0	0	3	0	0
Bladder	7	0	0	2	0	0
Lung	2	1	3	1	0	0
Pancreas	6	0	1	1	0	1
Skin	10	0	1	0	0	0
Thyroid	7	0	1	0	0	0
Others	4	1	3	0	0	0
Primary unknown	0	7	9	0	3	1
MESENCHYMAL TISSUES						
Brain	6	0	0	1	0	0
Hematopoietic	6	0	0	0	0	0
Bone	3	0	0	0	0	0
Others	16	0	0	5	0	0
TOTALS	**259**	**16**	**51**	**41**	**5**	**8**

As a highly immunodeficient model, the NOG mouse provides the best opportunity for engraftment of primary tumor samples and exerts less selection pressure which may alter tumor composition in less immunodeficient hosts. Engraftment of primary blood cancers is a key application facilitated by the NOD strain-specific Sirpa allele.[45] Male NOG mice are generally non-aggressive and can be group-housed. Thus, either male or female NOG mice may be used for general xenograft studies.

EXAMPLES OF COMPLEX CANCER MODELS GENERATED USING THE CIEA NOG mouse®

Primary adult **T-cell leukemia-lymphoma (ATL)** cells from human patients engraft successfully in the CIEA NOG mouse® via both intraperitoneal or subcutaneous implantation, resulting in infiltration by cancer cells into various organs.[26]

Implantation of either human T-cell leukemia virus type-1 (HTLV-1)-infected cells or primary human ATL cells into the NOG results in infiltration of tumor cells into various organs in a leukemic manner within a rapid 2-3 week period,[11,26] In another report, investigators generated a HTLV-1 infected humanized NOG mouse by intra-bone marrow injection of human CD133+ stem cells.[138]

Implantation of the U266 cell line results in a reproducible **multiple myeloma** model in the CIEA NOG mouse®, but not in C.B-17 scid or NOD scid mice. This myeloma model requires only intravenous inoculation of myeloma cells into irradiated or non-irradiated adult mice,

FIGURE 7: THE NOG MOUSE HAS BEEN SHOWN TO SUCCESSFULLY ENGRAFT MANY CANCER CELL LINES

CANCER TYPE	CELL TYPE
Breast Cancer	MCF-7[25], MDA-MB-231[25,141, 144]
Esophageal cancer	KE4[116]
Cholangiocarcinoma	RBE, HuCCT1[143]
Cervical cancer	HeLa[66]
Colon cancer	COLO320DM, HCT116, HT29, LoVo, LS174T, WiDr[48]
HTLV-1 transformed T cell line	Hut-102, MT-2, MT-4, SLB-1[11]
Leukemia	ED-40515(-)[11], MT-1[11], NB4[16], TL-oml[11], TRL-01[34], OSU-CLL[137]
Lung cancer	QG56[116]
Lymphoma	BCBL-1[27], HDLM2[19], KM-H2[19], L428[19], L540[19], LM-2-JCK[56], TY-1[27], SNK6[127]
Melanoma	A375, A2058, G361, HMY-1[18]
Myeloma	KMM-1[14], U266[13,14], RPMI8226[128], NCI H929[128]
Pancreatic cancer	AsPC-1, BxPC-3, Capan-1, Capan-2, MIA PaCa-2, PL45, Panc-1[38]
Pleural mesothelioma	ACC-MESO-1[97]

FIGURE 8: THE NOG MOUSE ENGRAFTS CELL LINES OTHER MODELS CANNOT

CELL LINE	CANCER CELL TYPE	COMPARISON LINE	COMPARISON LINE TAKE RATE	NOG TAKE RATE
U266[13,14]	human multiple myeloma	C.B-17 scid	0/5	20/20
U266[13,14]	human multiple myeloma	NOD scid	0/5	20/20
A2058[18]*	human melanoma	NOD scid	0/6	6/6
A375[18]*	human melanoma	NOD scid	0/9	8/9
G361[18]*	human melanoma	NOD scid	0/6	2/6
HMY-1[18]*	human melanoma	NOD scid	0/8	2/8
AsPC-1[38]**	human pancreatic cancer	NOD scid	8/9	9/9
BxPC-3[38]**	human pancreatic cancer	NOD scid	0/8	8/8
Capan-1[38]**	human pancreatic cancer	NOD scid	0/10	9/10
MIA PaCa-2[38]**	human pancreatic cancer	NOD scid	0/10	10/10
PANC-1[38]**	human pancreatic cancer	NOD scid	0/10	8/8

* Presence of distant metastases after iv inoculation.

** Measurement of liver metastases after intrasplenic injection.

and not more difficult methods such as human fetal bone implantation or intra-osseus injection.[13]

Dissociated human **glioblastoma** cells can be implanted orthotopically in NOG mice to develop patient-specific models that recapitulate various properties of the human tumors. *In vivo* tumorigenicity correlated with clinical aggressiveness. Similarly, invasiveness, proliferation index and microvessel density of the xenograft and parental tumors were correlated. Treatment of the mouse avatars with whole brain radiation showed increased survival compared to untreated controls, and this increased survival was correlated to the progression free survival in the radiation-treated patients.[121]

The CIEA NOG mouse® also serves as a good model for the study of cancer **metastasis**. Four different **melanoma** cell lines, A2058, A375, G361 and HMY-1, all showed metastasis by 6 weeks post-iv injection in the CIEA NOG mouse®, whereas no metastasis was observed in NOD scid mice.[18] Metastatic potential of various **pancreatic cancer** cell lines have been assessed in the CIEA NOG mouse®,[38,139] with significantly more metastases seen compared to the NOD scid model.[38] The CIEA NOG mouse® also serves as a reliable liver metastasis model for **colon cancer**.[48]

In comparison to other **Hodgkin's disease** models, which either display very low engraftment rates or require conditioning such as total body irradiation or innate immunity-blocking treatments, unconditioned NOG mice efficiently engraft B-cell type Hodgkin's lymphoma cells. Tumors form within 30-60 days and retain original tumor morphology and marker expression. Depending on the route of administration, tumor cells infiltrate into regional lymph nodes or organs such as liver, lung, spleen or bone marrow.[19]

The superior engraftment ability of the CIEA NOG mouse® was demonstrated by dilution experiments. Indeed, as few as 10 implanted HeLa cells formed tumors with a 50% take rate.[66] The higher susceptibility of NOG mice to xenotransplanted tumor cells indicates this model may be superior for tumorigenicity testing conducted as part of the safety assessment of stem cell therapies and other cell transplantation treatments.[51,72]

FIGURE 9: THE CIEA NOG MOUSE® PROVIDES A TOOL TO EVALUATE METASTATIC CAPACITY OF DIFFERENT CELL LINES

Compared to the NOD scid model, the CIEA NOG mouse® had a far higher incidence of liver metastasis after intrasplenic injection of various pancreatic cancer cell lines. Liver metastases were dose dependent.[38]

CELL LINE	CELL DOSE (cells/mouse)	NUMBER OF ANIMAL WITH LIVER METASTASIS Metastasis/Total	
		NOD scid	NOG
MIA PaCa-2	$1x10^4$ $1x10^3$ $1x10^2$	0/10 (0.0%) 0/7 (0.0%) 0/6 (0.0%)	10/10 (100.0%) 5/6 (83.3%) 5/7 (71.4%)
AsPC-1	$1x10^4$ $1x10^3$ $1x10^2$	8/9 (88.9%) 2/8 (25.0%) 0/6 (0.0%)	9/9 (100.0%) 8/8 (100.0%) 4/7 (57.1%)
PANC-1	$1x10^4$ $1x10^3$ $1x10^2$	0/10 (0.0%) 0/6 (0.0%) 0/7 (0.0%)	8/8 (100.0%) 6/8 (75.0%) 3/8 (37.5%)
Capan-1	$1x10^4$ $1x10^3$ $1x10^2$	0/10 (0.0%) 0/10 (0.0%) 0/8 (0.0%)	9/10 (90.0%) 5/10 (50.0%) 0/8 (0.0%)
BxPC-3	$1x10^5$ $1x10^4$	0/8 (0.0%) 0/8 (0.0%)	8/8 (100.0%) 1/8 (12.5%)
Capan-2	$1x10^5$ $1x10^4$	0/8 (0.0%) ND	0/8 (0.0%) 0/10 (0.0%)
PL45	$1x10^5$ $1x10^4$	0/8 (0.0%) ND	0/8 (0.0%) 0/10 (0.0%)

CANCER IMMUNOTHERAPY

The CIEA NOG mouse® is an ideal choice for cancer immunotherapy experiments.[65,79,93,116,125,129] Combine tumor engraftment with human immune system engraftment or engraftment of specific human cell types such as NK or CTL cells. Various immunotherapy approaches, including passive immunotherapy (antibody drugs and ADCC effects), active immunotherapy (cancer vaccines), and other immunomodulatory therapies can be studied using the NOG mouse.

XENOTRANSPLANTATION OF NORMAL HUMAN TISSUE

The superior engraftment potential of the CIEA NOG mouse® permits transplantation and development of normal human tissue in this model. This capacity makes the CIEA NOG mouse® a promising model for use in regenerative medicine studies. For example, the CIEA NOG mouse® can serve as a model of normal human endometrium *in vivo*, offering a more relevant model system to study human menstruation and reproduction. Ovarectomized NOG mice implanted with primary human endometrial tissue and treated with sex hormones show high levels of engraftment. This model system maintains normal tissue structure and serves as a model of the human menstrual cycle.[22] Functional endometrial tissue can also be reconstituted in the CIEA NOG mouse® via implantation of singly dispersed human endometrial cells.[41]

HUMAN IMMUNE SYSTEM ENGRAFTMENT

As a super immune deficient model and a better recipient for engraftment of human cells, the CIEA NOG mouse® is the ideal model for human immune system engraftment experiments. The CIEA NOG mouse® may be engrafted with human hematopoietic stem cells (HSCs), which differentiate *in vivo* to form a functioning human immune system in a mouse. The NOG mouse readily accepts various sources of HSCs with high engraftment rates and successful differentiation into the various cells types of the immune system. Multiple HSC sources have been shown to engraft well in the CIEA NOG mouse®: [5,10] In comparison to NOD/Shi-*Prdkc*^{scid} (NOD scid) mice, NOD/Shi-*Prkdc*^{scid} mice treated with anti-asialo GM1 antibody and NOD.Cg-*Prdkc*^{scid} *B2m*^{tm1Unc}/J mice, the CIEA NOG mouse® displayed higher engraftment in peripheral circulation, spleen and bone marrow compared to all other models tested.[5]

Complex experimental systems such as human/murine hybrid fetal thymic organ culture (FTOC) are not necessary for engraftment in the CIEA NOG mouse®. HSCs can simply be injected intravenously into neonatal, weanling or adult mice, with or without prior irradiation of the host. In contrast to other models, HSCs migrate with high efficiency into the thymus and peripheral lymphoid organs of the CIEA NOG mouse®.[6]

CELL TYPE DIFFERENTIATION

Nearly all cell types of the human immune system will differentiate and develop upon engraftment of the NOG mouse with human HSCs, however the interaction between those cell types may be incomplete in some cases. Production of functionally mature human T cells is possible in the CIEA NOG mouse® after implantation of HSCs, with human T cells developing in the mouse thymus, migrating to the periphery and maturing, and demonstrating production of human cytokines as well as cytotoxic capability. These differentiated T cells display a diverse Vβ repertoire.

Immature B cells are found primarily in bone marrow, with mature B cells in the spleen. Natural killer cells are found in both bone marrow and spleen. Human IgM, IgA and IgG from mature B cells are detectable in the sera of humanized CIEA NOG mice. In comparison, engrafted NOD.Cg-*Prkdc*^{scid} *B2m*^{tm1Unc}/J mice had little to no expression of human IgM and no expression of human IgA and IgG.[9] Human mast cells of both the connective tissue- and mucosal-types also form in NOG mice after reconstitution with HSCs, with distribution similar to that in humans: in skin, lung, gastric tract, lymph nodes, spleen, and the peritoneal cavity.[15] NOG mice reconstituted with HSCs can maintain human hematopoiesis for more than one year.[40]

The BLT model, which involves surgical engraftment of autologous human liver, thymus and enriched CD34+ HSCs is a more complex model to generate, but may result in more functional and mature human cell types. Graft versus host disease (GvHD) has not been found in the CIEA NOG mouse® after reconstitution using cord blood hematopoietic stem cells, however, implantation of human peripheral blood mononuclear cells (PBMCs) can induce graft versus host disease reliably.[7,9,69]

Induce GvHD via engraftment of PBMCs in order to develop models of diseases involving dysfunctional T cells.[133] Or engraft PBMCs from patients with autoimmune diseases like lupus or Stevens-Johnson Syndrome to develop small animal models of that disease.[114]

Human cell products may be produced in human immune system engrafted NOG mice. The CIEA NOG mouse® may be reconstituted with HSCs and immunized with the peptide of interest. Hybridoma lines derived from spleen cells of immunized mice can produce a human-derived antibody against a given peptide.[30]

Reconstitution of the CIEA NOG mouse® via cell or tissue engraftment will be an important tool for infectious disease studies as well as efficacy and safety testing of biologics and vaccines. The CIEA NOG mouse® could serve as an appropriate test species for any biologic directed at a target expressed on a human cell that can be grown in or differentiated in the CIEA NOG mouse®. This may permit the reduction of primate studies in some instances.[33]

MYELOABLATION

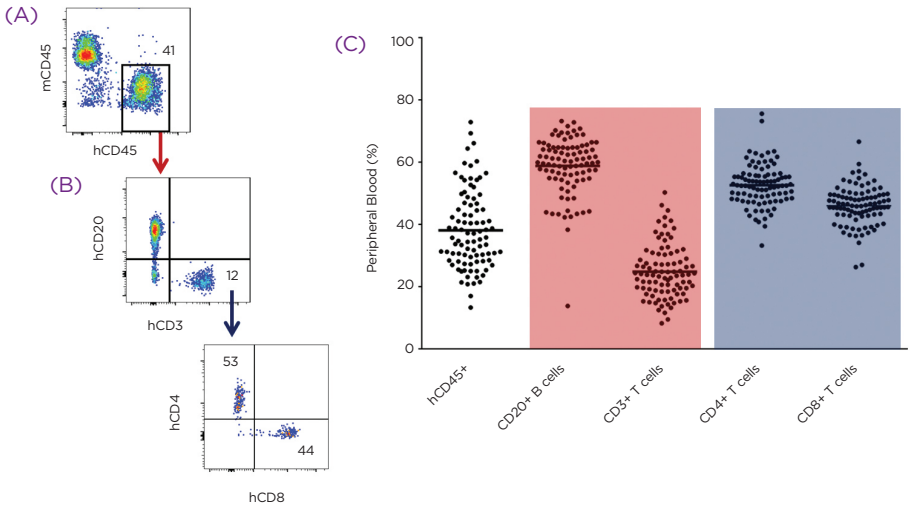
Myeloablation improves engraftment of human hematopoietic stem cells by providing a physical niche for engraftment. Myeloablation is recommended for human HSC engraftment experiments, but is not required for human PBMC engraftment. Irradiation is the most common myeloablative treatment. Use care in selecting radiation doses, as the NOG mouse (like all scid mice) is sensitive to radiation. Radiation sensitivity will vary by age and weight of the mouse. Taconic recommends users perform an irradiation dose study starting below 1 Gy to determine the most appropriate irradiation dose for your experimental setup.

Alternatives to irradiation include treatment with myeloablative drugs such as busulfan.

IMMUNE SYSTEM ENGRAFTMENT MODELS

MODEL	ENGRAFTMENT PROCEDURE	BENEFITS	LIMITATIONS	NOTES
Hematopoietic stem cells (HSCs)	Intravenous injection of CD34+ HSCs.	Good model of T cell functionality. No GvHD observed. Simple technical procedure (iv injection).	Engraftment and differentiation requires minimum of 12 weeks. Some cell types missing or in low numbers. Some cell types are not completely mature or functional.	Adults, neonates and juveniles have been used. Engraftment effciency and function are better in neonates and juveniles than in adults, and females engraft better than males. Juvenile mice are easier to source in large, consistent cohorts, so 3-4 week old females are recommended for this application.
BLT surgical model	Co-implantation of fetal liver and thymus tissue fragments under renal capsule, plus intravenous injection of CD34+ HSCs.	Human thymus provides human thymic micro-environment for maturation of T cells. Human liver provides important human cytokines for cell maturation. Better B cell function than in HSC model.	Engraftment and differentiation requires minimum of 12 weeks. Some cell types missing or in low numbers. Some cell types are not completely mature or functional. Some incidence of GvHD possible. Complex surgical procedure required.	Use of 4 week old females is recommended.
Peripheral mono-nuclear blood cells (PBMCs) or purified cell subsets	Intravenous injection of peripheral blood mononuclear cells.	Ready to use quickly. Mature and functional human cells present. Simple technical procedure (iv or other type of injection).	Usage limited to ~4-6 weeks only as GvHD will develop after engraftment of mature human T cells.	Male or female adult mice may be used.

FIGURE: 10 FLOW CYTOMETRY ANALYSIS OF HUMAN CELL LINEAGES AFTER CD34+ HSC ENGRAFTMENT IN THE NOG MOUSE

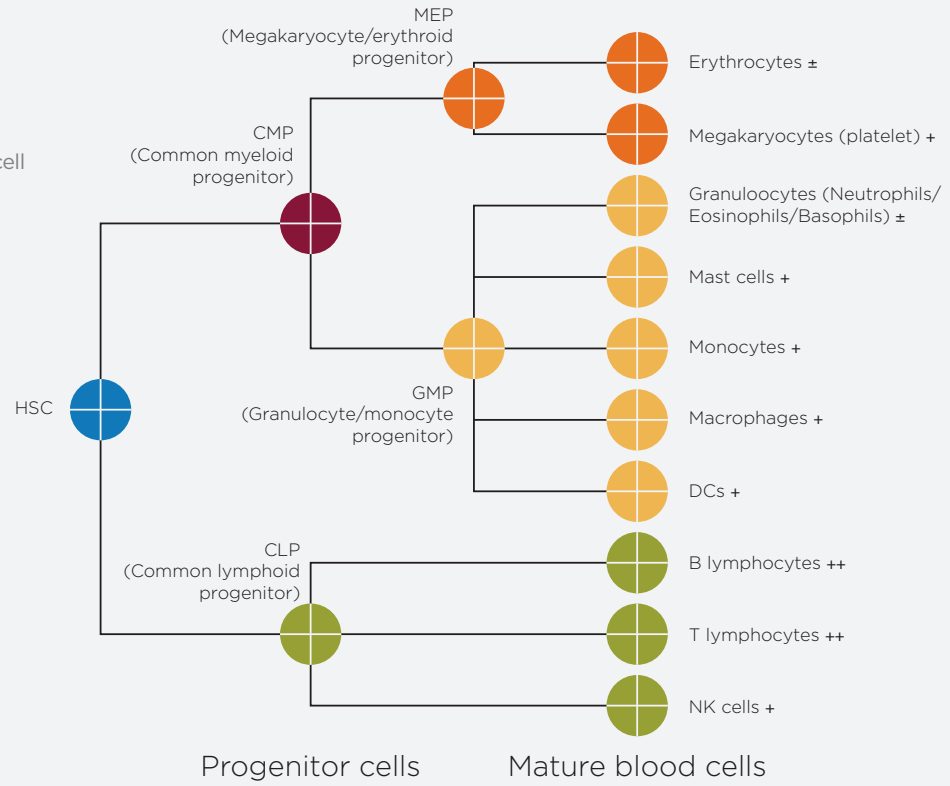


Flow cytometry analysis of human cell lineages after CD34+ HSC engraftment.

(A) Representative flow cytometry plot of the human (hCD45+) cell to mouse cell (mCD45+) ratio at 12 weeks post-engraftment. (B) Relative percentage of human cells expressing the B cell marker CD20 vs. the T cell marker CD3. (C) Consistent engraftment ratios of greater than 25% hCD45+ cells in over 80 percent of animals (n=91), with highly reproducible relative T cell and B cell enrichment levels. Each dot represents an individual mouse analyzed by flow cytometry 12 weeks post CD34+ HSC engraftment.

FIGURE 11: A SUMMARY OF HUMAN HEMATOPOIETIC CELLS DIFFERENTIATED FROM CD34+ CELLS IN NOG MICE

A summary of human hematopoietic cell types differentiated from CD34+ cord blood cells after implantation into the CIEA NOG mouse®.



++ means dominant and well-developed; + means developed;
± means no or very few cells detected.

INFECTIOUS DISEASE MODELS

HIV

The CIEA NOG mouse® serves as a unique small animal HIV model. With ongoing hematopoiesis, this model permits the study of the infectious process, as well as the study of persistent infection. When implanted with peripheral blood mononuclear cells or cord blood HSCs and infected with the R5 or X4 HIV-1 isolates, the CIEA NOG mouse® experiences a massive and systemic HIV-1 infection. In this experimental system, the mouse develops a stable and systemic infection with high viral loads and production of HIV-specific antibodies.[20,36]

Human immune system engrafted NOG mice can be used to study HIV transmission, prophylaxis, and treatment.

EPSTEIN-BARR VIRUS

NOG mice engrafted with cord blood HSCs and infected with Epstein-Barr virus (EBV) serve as a comprehensive small animal model of human EBV infection. Infection of NOG mice engrafted with human HSCs with large doses of EBV resulted in a mostly fatal lymphoproliferative disorder, similar to that seen in immunocompromised human patients. Lower doses of EBV induced a persistent, asymptomatic infection. The infected NOG mice developed an EBV-directed CD8+ T cell response and produced antibodies directed at EBV.[62] In another study, humanized NOG mice infected with EBV developed erosive arthritis.[102] An animal model of chronic active EBV infection was developed through injection of peripheral blood mononuclear cells isolated from patients with chronic EBV into NOG mice.[135]

ORIGINS OF THE CIEA NOG mouse®

The CIEA NOG mouse® was developed by Mamoru Ito of the Central Institute for Experimental Animals (CIEA) in Japan in 2000. The *Prkdc*^{scid} mutation was identified by Mel Bosma of the Fox Chase Cancer Center in a C.B-17 congenic mouse population. This mutation was backcrossed onto the NOD/ShiJic strain at CIEA for at least eight generations. The *Il2rg* targeted mutation was developed by Kazuo Sagamura of Tohoku University by targeting the gene in ES cells derived from a 129 strain. Targeted ES cells were injected into C57BL/6 blastocysts. Resultant chimeras were backcrossed onto the C57BL/6JJic background for at least eight generations. The NOG mouse was developed by back crossing the C57BL/6JJic-*Il2rg*^{tm1Sug} line to the NOD/ShiJic-*Prkdc*^{scid} line for a total of eight generations. Taconic received stock in 2006, and the line was derived through embryo transfer. The mice are maintained by breeding females homozygous for both the *Prkdc*^{scid} and *Il2rg* mutant alleles with males that are homozygous for the *Prkdc*^{scid} allele and hemizygous for the *Il2rg* mutant allele.

THE CIEA NOG mouse® PATENTS AND TRADEMARKS

The CIEA NOG mouse® is produced and distributed under license rights to the following patents and trademarks:

- Japanese Patent No. 3,753,321
- US Patent No. 7,145,055; 5,464,764; 5,487,992; 5,627,059; 5,631,153; 5,789,215; 6,204,061; 6,653,113; 6,689,610
- EP Patent No. 1,338,198
- Japanese Trademark Reg. No. 4,823,423
- US Trademark Reg. No. 3,118,040
- EU Trademark Reg. No. 3,736,758

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Purchase NOG mice

NOG mice are produced in the US and Europe. Call Taconic Customer Service today to place an order for immediate delivery. There are no upfront fees or agreements to sign.

Purchase human immune system engrafted NOG mice

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REFERENCES DESCRIBING THE CIEA NOG mouse®

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