Discovery Biology Services

One-Stop Solution for Drug Discovery

- **Antibody Engineering**
- *In vitro* **Pharmacology**
- *In vivo* **Pharmacology**

GenScript
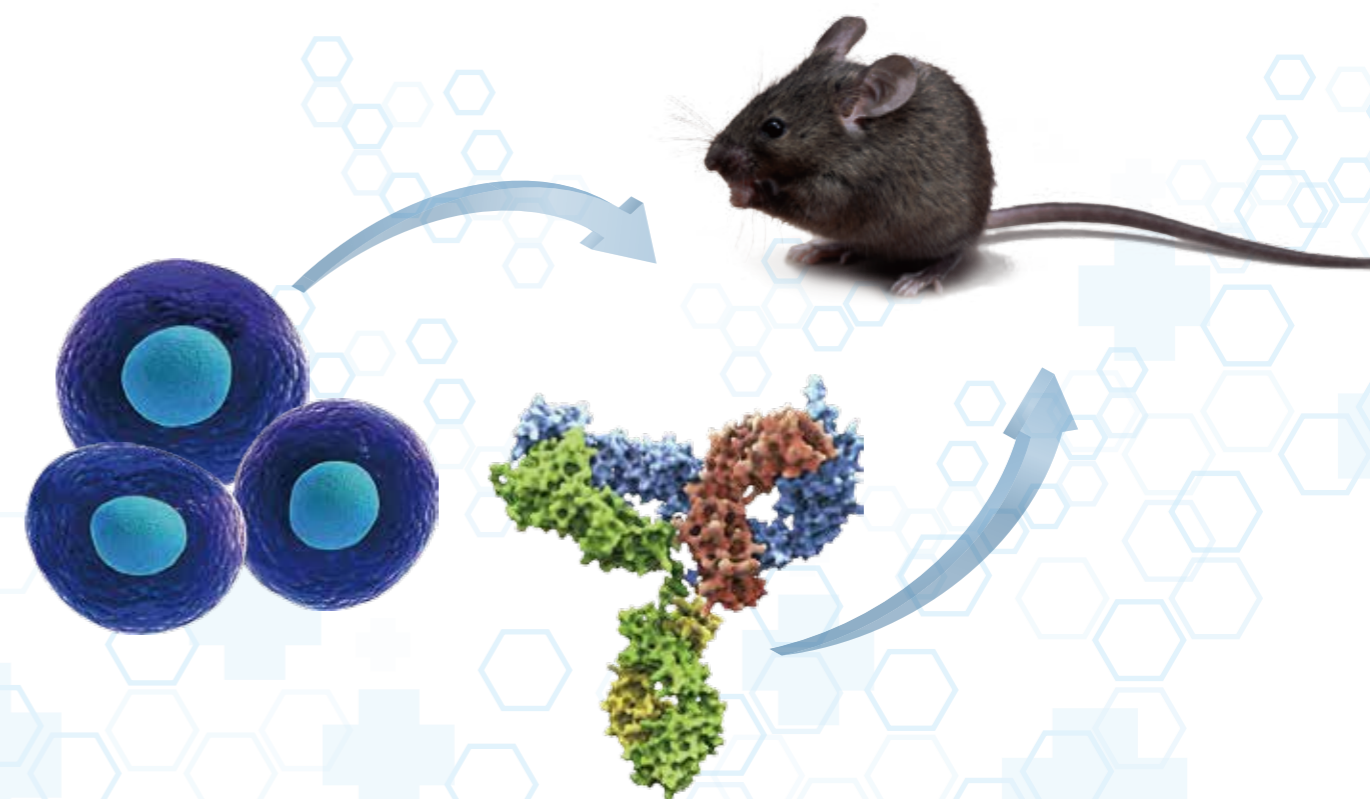Make Research Easy

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GenScript
Make Research Easy

SFD150723

Who we are:

GenScript is a leading provider of drug discovery and preclinical study services. Founded in 2002, the company has grown to a workforce of over 1,400 worldwide. With its state-of-the-art technology platforms, GenScript has established its reputation as a trusted partner for one-stop discovery biology services.

Headquarters in New Jersey, USA

Office in Tokyo

Office in the Netherlands

Office in Nanjing, China

> 40,000 customers in > 80 countries

What we do:

GenScript offers full drug discovery capability, including specialty services such as single domain (camelid) antibody generation and engineering, genome editing with CRISPR technology, recombinant stable cell lines with CellPower™ lentiviral platform, and over 70 *in vivo* disease models covering oncology, inflammation, fibrosis, allergy and metabolic diseases.

What we deliver:

A comprehensive discovery biology platform, with quality, speed, communication, and cost-efficiency set as its core values. GenScript is your ideal partner in drug discovery!

Flexibility in working with GenScript

GenScript is a one-stop solution for discovery research. Starting from molecular biology all the way to animal studies, working with GenScript can save significant time and cost compared to working with multiple CROs. Working with a single trusted CRO ensures data integrity and project confidentiality. Below are the different ways we can work together.

Individual services

GenScript's individual services provide clients with cost efficiency, turnaround time and quality

Gene Synthesis   Peptide Synthesis   Protein Production   Antibody Generation   Discovery Biology

Project-based

Simply provide us with the name of the target, and we can provide an antibody lead

FTE model
Production scientists and project managers will be fully dedicated to your projects, ensuring seamless communication between your internal R&D and GenScript

Fee-for-service model
Our project management team will provide timely project status updates as well as teleconferences at key milestones

Antibody Engineering
From target sequence to novel antibody lead, including sdAbs

Pages 3-4

In vitro Pharmacology
Knock-out, knock-in or overexpression cell lines and assay development

Pages 5-6

In vivo Pharmacology
Validated fibrotic disease and tumor models

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Research News and Service Index

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Antibody Engineering Services

Antibody drug discovery can now be as seamless as providing a Genbank accession number of the target antigen to receiving an optimized lead antibody, tailored to your specifications. As a one-stop antibody discovery CRO, we take care of your needs, starting from gene synthesis all the way to testing antibody candidates *in vivo*. In addition to drug discovery with conventional antibodies, we are also the only CRO offering a fully custom camelid single domain antibody (sdAb) service.

Camelid single domain antibodies (sdAbs)

- Expedited lead optimization, with multi-targeting potential. Excellent physical and thermostability properties leads to economy in production
- GenScript has over 5 years of experience with a track record of success

Advantages of sdAbs over conventional antibodies

- Small, only one heavy chain variable domain (V_HH) ~ 13 kDa
- Monomeric V_HH subunit required for antigen binding
- Highly amenable to downstream engineering
- Maintains stability and potency at extreme pH and temperatures
- Can be manufactured in yeast or other microbial systems

V_HH

Single domain antibody (sdAb)

Heavy chain antibody (HCAb)

Conventional IgG
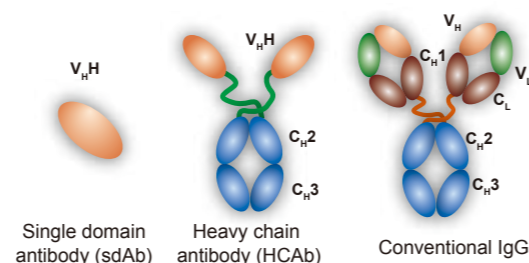
Applications for sdAbs

- Next-generation novel therapeutic against cancer, inflammation, infectious diseases, metabolic diseases and neurological disorders
- High stability and affinity make sdAbs ideal biosensors for diagnostic applications
- Demonstrated as an excellent crystallization chaperone, especially for membrane proteins and receptors

Custom immunization strategies to ensure success

| Method	Best for
DNA / whole cell / lipoparticles	Targeting membrane proteins and conformational epitopes
Peptides	Epitopes that are defined
Proteins	Targeting soluble proteins and extra cellular domain (ECD) of membrane proteins
Combination	Increasing the probability of success with difficult targets

Gene sequence of target

Provide GenScript with the name of the target, or provide the gene sequence and we deliver a therapeutic antibody lead
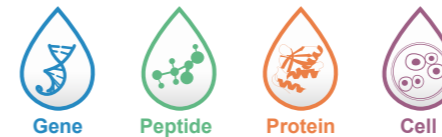
Antigen design and selection

Gene · Peptide · Protein · Cell

GenScript provides high-quality starting materials for antibody generation

Generation of antibody
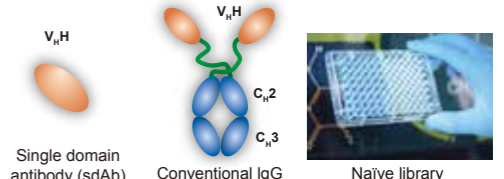
Single domain antibody (sdAb) · Conventional IgG · Naïve library

Choose from camelid, mouse and rabbit monoclonal or naïve library

Screening for hits

Ligand-mAb Analyte-antigen protein

| K_a (1/Ms)	K_d (1/s)	K_D (M)
1.80E+05	2.56E-04	1.42E-09
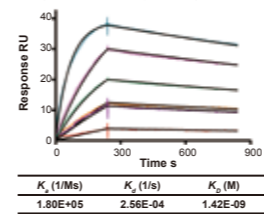
ADCC & CDC

GenScript provides phage display screening, biophysical antibody-ligand interactions and functional *in vitro* screening, including ADCC&CDC and immune-checkpoint assays

Antibody sequencing

Over 1,500 antibodies sequenced with 100% success

Reports include annotation and alignment sequences. Fast 10-day turnaround time

Optimization of leads
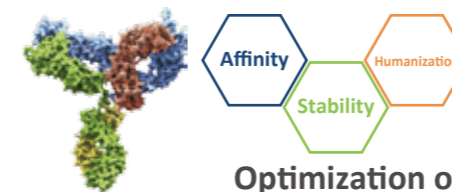
Affinity · Humanization · Stability

Our affinity maturation achieves results while ensuring stability. Our humanization method guarantees an affinity equal or better than that of the parental antibody. We also optimize antibodies for pH sensitivity, serum half-life, thermostability and expression

In vivo testing of leads

AUC:MIC · C_{max}:MIC · Time>MIC · MIC
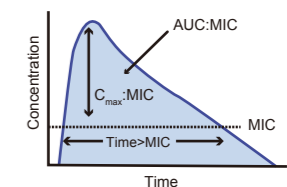
Syngeneic tumor models to evaluate efficacy of immunotherapies in immuno-competent mice. PK and biomarker studies to guide optimization

Therapeutic antibody lead

Our scientists and project managers will provide regular updates during the process. All deliverables and a detailed final report will be provided at the conclusion of the project

In vitro Pharmacology Services

With hundreds of stable cell lines succesfully delivered to customers, our scientists are highly experienced in working with difficult cell lines and optimizing target expression. With CRISPR/Cas9 genome editing technology, we deliver cell lines with gene knock-out or targeted insertion.
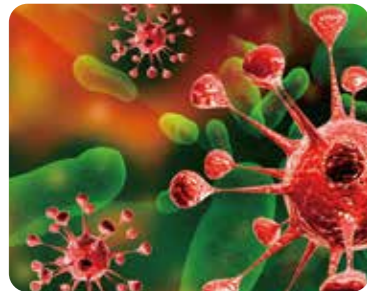
Stable cell lines for assay development

- Delivered over 700 stable cell lines for assays
- Collection of over 160 GPCR and ion channel cell lines for purchase, also available as membrane preps
- CellPower™ platform using lentiviral transduction for difficult-to-transfect cells and low-expression genes
- Non-lentiviral based stable cell line service with stability testing also available

GenCRISPR™ Genome editing

- Expertise with viral-, lipid- or nucleofection-based knock-out or knock-in
- CRISPR gRNA design using GenScript's proprietary bioinformatics tool, freely available
- One-stop provider for CRISPR-based services, from gRNA design to target sequence-validated cell line

Highlights for CRISPR/Cas9 technology:

- Simpler and more efficient than TALEN- or zinc finger nuclease (ZFN)-based gene editing methods
- Applicable for knock-out, knock-in or targeted mutations in host genome
- Revolutionizing biomedical research

Stable cell lines for antibody and protein production

- Bioproduction grade cell line with stability screening
- Gram-level production of antibodies
- Cell banking available for stable cell lines

Legal Statement of GenCRISPR Services and Products:

1) GenCRISPR™ services and products are covered under US 8,697,359, US 8,771,945, US 8,795,965, US 8,865,406, US 8,871,445, US 8,889,356, US 8,889,418, US 8,895,308, US 8,906,616 and foreign equivalents and licensed from Broad Institute, Inc. Cambridge, Massachusetts.

2) The products and the reagents generated from these services shall be used as tools for research purpose only, and exclude (a) any clinical use, (b) direct human, veterinary, livestock or agricultural use, (c) therapeutic or diagnostic use for humans or animals.

3) The use of the products and the reagents generated from GenCRISPR services are under the Limited License.

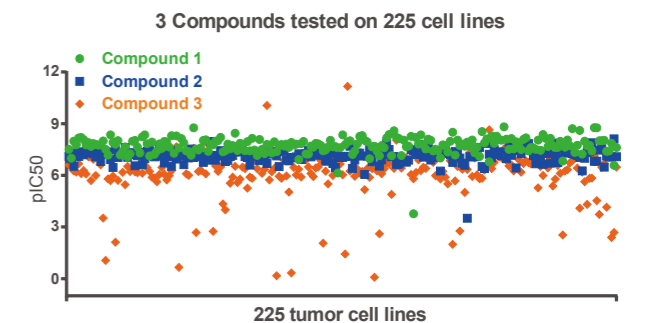## Cell-based Assays

GPCR and Ion Channel Screens

- 160+ GPCR and ion channel stable cell lines, ready for screens and available for purchase
- Ready-to-run radiometric and fluorescence-based assays with validated controls
- Electrophysiology expertise and equipment to perform manual and automated patch clamp ion channel screens

Melatonin on MT1 target
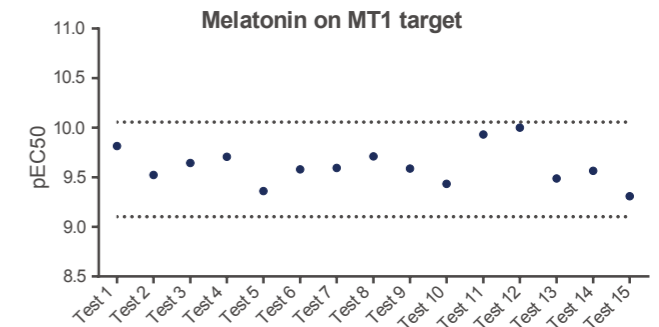
MT1 GPCR assay detecting intracellular calcium mobilization in CHO-K1/MT1/Gα15 cells. An example of data reproducibility over 15 tests

Tumor cell line profiling

- Oncoprofiler - Choose from over 200 cancer cell lines to profile for apoptosis and growth
- Xenoprofiler - Choose from over 40 cancer cell lines validated in *in vivo* xenograft models

3 Compounds tested on 225 cell lines

Dose response IC50 of three compounds against 225 different tumor cell lines. Luminescence-based proliferation assay was used to profile compound effect.

ADCC & CDC assays

- Endpoint-based assay for antibody therapeutics
- Recombinant NK-92 cell line as effector improves reproducibility over PBMC-derived effector cells

Herceptin Mediated ADCC Lysis of SK-BR-3 Cells
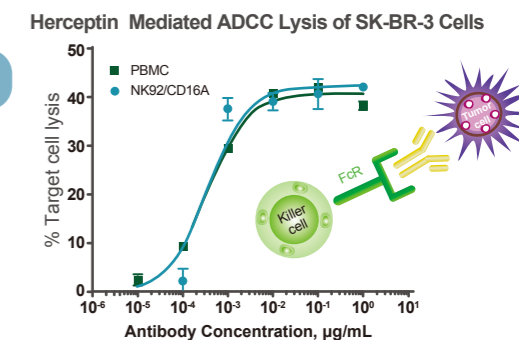
Immune-checkpoint assays

- Validated with an approved anti-PD-1 antibody therapeutic
- Expertise in developing stable cell lines overexpressing immune-checkpoint proteins
- Available as a mixed lymphocyte reaction with CD4+ T cells and dendritic cells
- Additional immune-checkpoint protein assays coming soon!

Mixed Lymphocyte Reaction
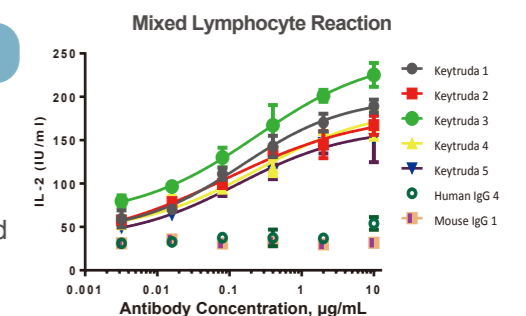
Reproducibility of mixed lymphocyte reaction. The EC50 curve of five independent screens with Keytruda® is shown. Human IgG4 and mouse IgG1 are used as a negative controls

Fibrotic Disease Models

GenScript is one of the few CRO's that offer fibrotic disease models. With over 5 years experience in developing hepatic, renal and pulmonary fibrotic disease models, we have validated the models using clinical grade reference compounds as controls. Histological and biochemical measurements are included in our assessment of therapeutic efficacy.

Liver fibrosis models

- GenScript offers carbon tetrachloride (CCl_4)-induced and bile duct ligation (BDL)-induced liver fibrosis models. Below is an example of a mouse CCl_4-induced liver fibrosis model, validated with reference drug, Pirfenidone

Olive oil   CCl₄   CCl₄+PFD
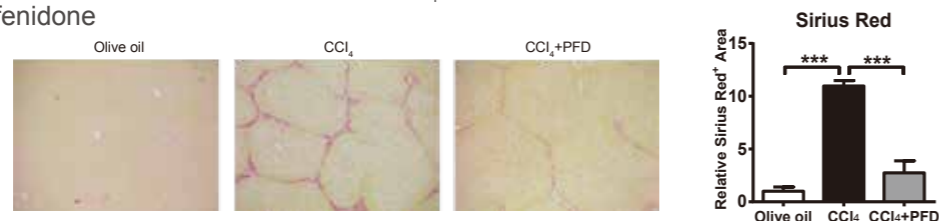
Sirius Red

Fibrotic (CCl_4-induced) liver tissue exhibits a significant increase in collagen deposits as detected by Sirius red staining, compared with non-fibrotic (olive oil) and pirfenidone–treated (CCl_4+PFD).

Kidney fibrosis models

- Unilateral ureteral obstruction (UUO)-induced kidney fibrosis model in rat and mouse mimics chronic renal damage and fibrosis in human kidneys. Below is an example of a rat UUO-induced model, validated with reference drug, Pirfenidone

Sham   UUO   UUO+PFD

Sirius Red

Pirfenidone at 500 mg/kg ameliorates renal interstitial fibrosis induced by UUO in a rat model, as shown by Sirius red staining of connective tissue in renal interstitium.

Additional fibrotic disease models

- GenScript also offers bleomycin-induced lung fibrosis model, which produces lung injury and inflammation hallmarked by high deposits of fibrous tissue in the lung
- Validation of new models under development

Bronchoalveolar Lavage   Lung weight/Body weight   HE   Masson's Trichrome
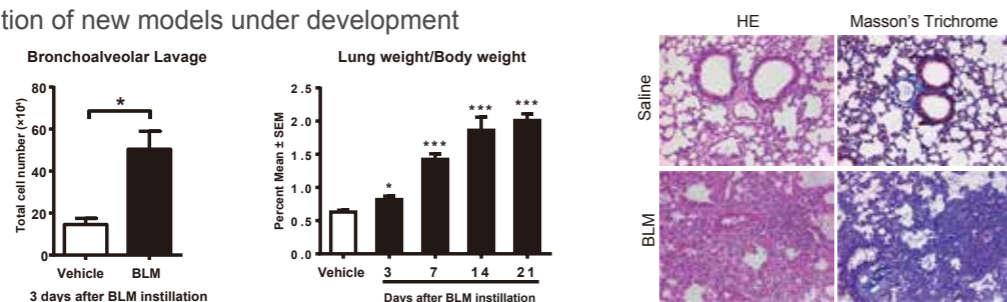
Bleomycin (BLM) instillation of lung induces fibrotic tissue deposits after 21 days, as shown by histological staining.

Oncology models

As part of GenScript's commitment to oncology preclinical research, we offer validated models for drug efficacy evaluation, including syngeneic tumor models for the study of cancer immunotherapeutics. Our orthotopic model platform takes advantage of GenScript's cell line engineering capabilities to develop luciferase-labeled tumor cells and uses bioluminescence imaging to analyze tumor growth.

Subcutaneous Xenograft

- Cost-effective for rapid screening of lead efficacy
- Over 70 validated models available
- Histological and biomarker endpoints

Tumors isolated from SC xenograft models of small-cell lung carcinoma (SHP-77). Top row from vehicle treated animals, bottom row from Irinotecan treated animals.

Syngeneic Tumors

- Reliable models for studying immune-checkpoint modulators
- Bioluminescent imaging for enhanced analysis of tumor size and metastasis, using luciferase-labeled tumor cell lines

Monotherapy and combination therapy with PD-1 and CTLA-4 antibodies in MC38 tumor model
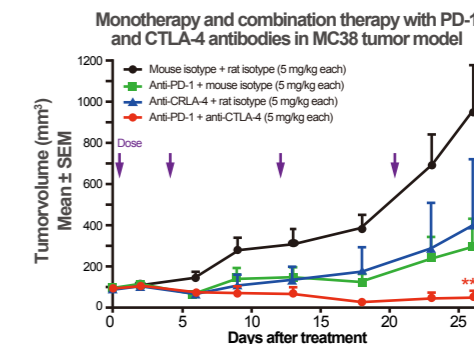
Tumor growth curve of MC38 s.c. xenograft model treated with anti-PD-1 antibody, anti-CTLA-4 antibody or the combination.

Orthotopic Tumors

- Determine drug efficacy in tumors implanted at the orthotopic sites, to mimic primary tumor microenvironment
- Bioluminescent imaging provides accurate analysis of tumor growth and metastasis
- Over 20 validated models available
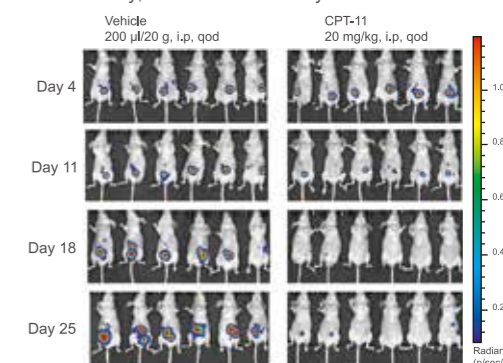
Bioluminescence imaging and validation of colorectal cancer orthotopic model. Model developed with luciferase labeled HT-29 cells.

Patient Derived (PDX) Tumors

- Over 250 PDX models available
- Over 120 primary tumor cell lines available
- Genetic annotation with whole exome sequencing and RNAseq available for select models
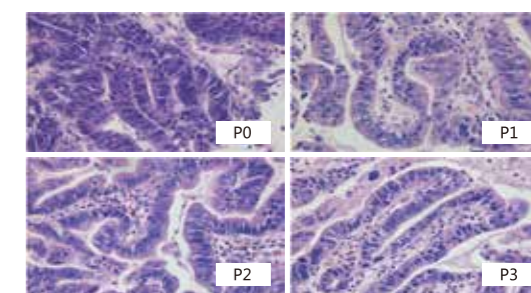
PDX model of gastric cancer. Tumors from sequential passages showed identical histopathological characteristics

Keeping up with the latest research trends is critical to drug discovery. GenScript provides our customers with new and exciting findings through our email blasts and news pages. Below are a sample of some of the topics covered.

Immune-checkpoint therapeutics
Can targeting two proteins synergize efficacy?
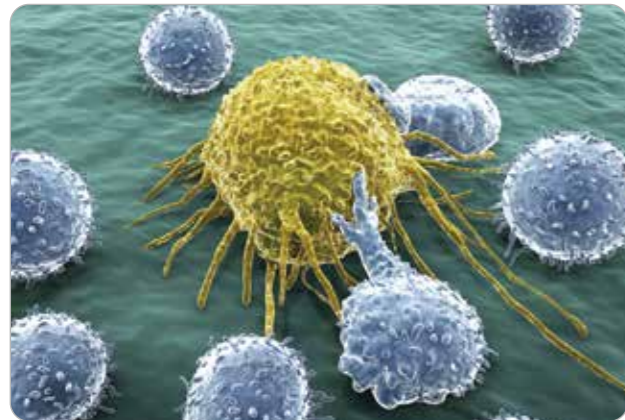
Drug resistance in cancer
Can GWAS studies uncover additional targets?

CRISPR/Cas9
Will CRISPR translate into the clinic?

Orphan drug development
Which drugs did the FDA approve?

Check our discovery biology news page for the latest updates:
http://www.genscript.com/discoveryBiology_news.html

Antibody engineering

Service	Description	URL
Camelid single-domain antibody (sdAbs)	• A promising platform for next-generation and multi-targeting antibodies	http://www.genscript.com/camelid_single_domain_antibody.html http://www.genscript.com/single-domain-antibody-resource.html
Antibody sequencing	• Leader and variable domain sequencing • Antibody coding sequence sub-cloned into plasmid	http://www.genscript.com/mAb_sequencing.html
Biomolecular interaction analysis	• Surface plasmon resonance-based detection with BIAcore T200	http://www.genscript.com/biomolecular_interaction_analysis_services.html
Affinity maturation	• Greater than 10-fold affinity improvement over parental antibody • Guaranteed protein stability	http://www.genscript.com/Antibody_Affinity_Maturation.html
Humanization	• Proprietary framework assembly platform with FASEBA screening • Affinity guaranteed to be equal or greater than parental antibody	http://www.genscript.com/Antibody_Humanization.html

In vitro pharmacology

Service	Description	URL
CellPower™ stable cell lines for assay development	• Delivered over 700 stable cell lines • Lentiviral-based cell line development	http://www.genscript.com/guaranteed-stable-cell-line.html
GenCRISPR™ genome editing cell line service	• CRISPR/Cas9-based service to generate knock-out and knock-in cell lines	http://www.genscript.com/CRISPR_genomic_editing_order.html
Stable cell lines for antibody and protein production	• Bioproduction grade cell line with stability screening	http://www.genscript.com/production-stable-cell-lines.html
GPCR and ion channel screens	• Over 160 GPCR and ion channel stable cell lines ready for screens • Manual and automated patch clamp	http://www.genscript.com/gpcr_assay_services.html http://www.genscript.com/ion_channel_assay_services.html
Tumor Cell line profiling	• Screen against over 200 cancer cell lines, proliferation and apoptosis assays	http://www.genscript.com/tumor-cell-line-profiling.html
ADCC & CDC assays	• Measure antibody efficacy with a biologically-relevant assay	http://www.genscript.com/ADCC_and_CDC_assay_services.html

In vivo pharmacology

Service	Description	URL
Fibrotic disease models	• Hepatic, renal and pulmonary models available with reference drugs	http://www.genscript.com/fibrotic-disease-models.html
Subcutaneous tumor models	• Cost effective animal model for screening lead compounds	http://www.genscript.com/animal_model_services_subcutaneous_xenograft.html
Syngeneic tumor models	• Study immuno-oncology therapeutics in an immunocompetent mouse model	http://www.genscript.com/animal_model_services_syngeneic.html
Orthotopic tumor models	• Study drug efficacy in primary tumor environment	http://www.genscript.com/animal_model_services_orthotopic_tumor.html
Patient-derived (PDX) tumor models	• Provides relevance for drug evaluation	http://www.genscript.com/Patient_derived_human_primary_tumor_models.html