

Discovery Biology Services

Discovery Biology at WuXi AppTec offers high quality service by working on all aspects on major drug target families, from assay development/transfer, compound management/screening, protein science and structure biology, to biomarker and PK/PD studies, in order to support integrated drug discovery programs. We are fully committed to become the best biology service provider in China.

Our Service

We are committed to provide top-quality data, fast turnaround (1-7 days), and overall value to our customers. We are technology/platform driven and target family focused, working on building up the Centers of Excellence for GPCRs, enzymes, ion channels, and anti-viral programs. In addition, we offer biomarker services to customers for both preclinical and clinical support.

Our People

We currently have a team of 12 returnees from Western countries and over 100 domestically trained talents, with >15% PhD and >70% MS. A comprehensive curriculum provides our staff with various levels of trainings. Through our service since early 2008, we have earned a proven track record of delivery, with many awards from our customers.



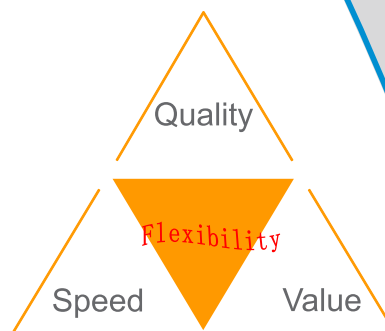
For more information on WuXi AppTec's services please contact:

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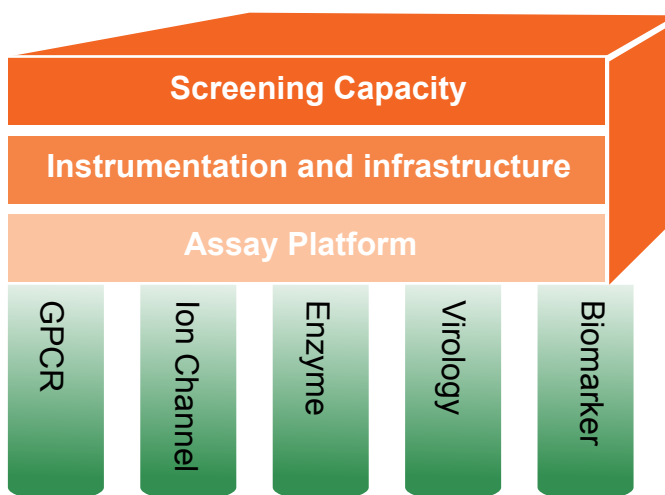


Our Tools and Facility

We have made more than ten million dollars of investment, on state-of-art readers (many of them first-in-China or only-unit-in-China), multiple liquid handlers, and facility renovation. Our capability has largely rivaled that of our Western country customers, ensuring a seamless assay development and assay transfer procedure. Our capacity has enabled us to cover multiple projects to multiple customers in parallel.



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Building up WuXi's Centers of Excellence for Major Drug Targets

GPCR

- Binding and functional assay of GPCR
 - Binding assay
 - Filtration 96-well assay
 - SPA 96-well assay
 - Functional assay
 - cAMP assay: RIA or ELISA: 96-well format
 - Ca²⁺ influx assay: 96 or 384-well format
 - GTPγS: 96-well assay
 - PathHunter eXpress β-Arrestin GPCR assay
 - Other commercial GPCR assay platforms
 - GPCR Profiling Services
 - Over 40 GPCRs expressing stable lines available
 - Cell line generation for customer's targets-of-interest and screening follow-up
 - Filtration binding assays and SPA assays
 - Ca²⁺ influx assay in FLIPR^{TETRA} and Hamamatsu FDSS7000



Enzyme

- Enzymatic assays for kinases, proteases, isomerases and polymerases etc.
- All major kinase assay technologies to support client routine screening for SAR studies
 - IC50, Km, MOA etc.
 - Substrates: proteins, lipids, carbohydrates etc.
 - Support client special requests
 - SAR driver for integrated services
- Kinase profiling platform using Z'-LYTE format.
 - Over 30 kinases established, will reach 100 in the near future
 - With gene-to-assay capability for customer's

specific needs

- Fast turnaround
- Other formats are available

Ion Channel

- Binding and functional assays for both voltage- and ligand-gated ion channels
 - IonWorks-Quattro with up to 3,000 data points per day
 - QPatch-HTX with up to 1,500 data points per day
 - Conventional patch-clamp for gold-standard studies for lead compounds
 - Conventional recording for brain slice
 - Radioligand binding assays for ion channels:
- MOA studies for lead compounds
- Cardiac Safety Services
 - hERG channel screening
 - Nav1.5, Cav2.1 and KCNQ1/mink

Anti-Viral Platform

- Targeting HCV, influenza, RSV, and HIV
- Multiple cell-based anti-viral assays including plaque reduction, CPE, pseudo viruses, and replicon
- Cell line development and screening
- In vitro viral enzyme assay development and screening
- Genetic & resistance analyses; chimeric virus construction; MOA
- Custom production of purified virus stock and viral target proteins
- Newly renovated BioSafety Level 2 facilities for anti-viral projects



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Hit Finding

“Smart, Quality and Fast”

WuXi's Smart Hit Finding provides high-quality starting point for integrated drug discovery. We take advantage of our experience in assay development and execution, the world-class instrumentation and WuXi's chemical screening library, in addition to our expertise in informatics, in order to ensure high-quality and fast-turnaround, including quick transition into the subsequent hit-to-lead and lead-optimization process with our integrated service capability.

High/Medium-throughput screening

High-content screening

Fragment-based screening



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High/Medium-throughput screening

- Dedicated and experience team for assay development on all families of drug targets
- World-class readers and robotics
- WuXi's screening library and/or customer provided compounds
- Top-standard informatic and data tools
- Capability and experience in hit triaging and follow-up

High-content screening

- Cell Health Profiling
- Cancer Study
- GPCR Study
- Translocation
- General assays

Fragment-based screening

- WuXi's designed unique fragment library
- Crystal structure based screening
 - Selected compound soaking
 - Computational modeling

Behind our Hit Finding

- Advanced informatic tools for vast data process
- Fully integrated and automated plate assembler
 - POD810 (Labcyte): with 2.5nl tip-less liquid transfer capability and 100,000 wells/day capacity
 - Multiple liquid handlers with maximum versatility
- World-class hit finding platforms
 - FLIPRTETRA and FDSS7000
 - IonWorks Quattro™
 - Envision (multiple units)
 - ArrayScan
 - MSD Platform
 - Top Counts
- WuXi's screening library
 - Over 170,000 compounds with diverse chemical space
 - Over 3,000 compounds based on WuXi's unique templates
 - Rule-of-five property compliant
 - Fast expanding with continuous novel designs

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Biomarker

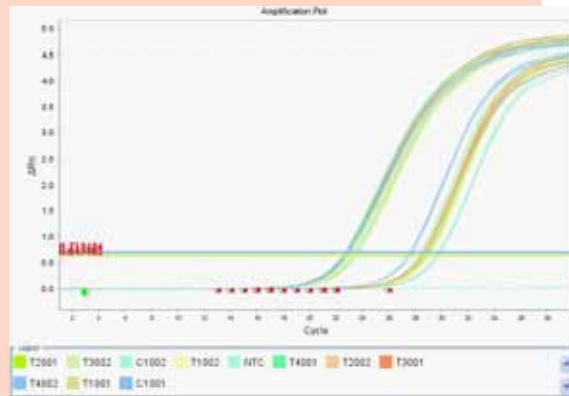
Protein/antibody-based assays:

- Luminex and MSD
- Western blot (quantitative and qualitative)
- Immunohistochemistry (IHC), Tissue microarrays
- Mass spectrometry (LC-MS, LC-MS-MS)

DNA/RNA-based assays:

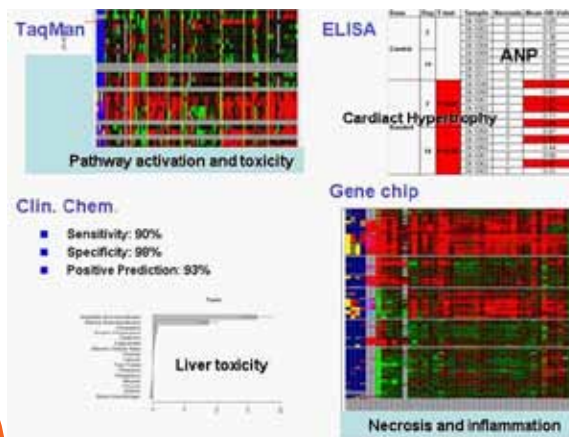
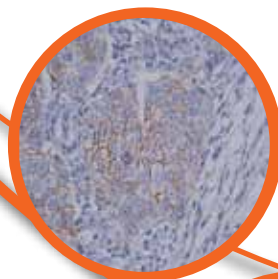
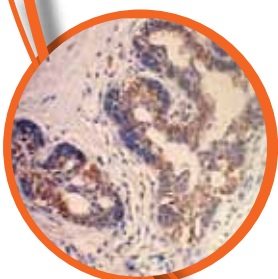
- TaqMan or qPCR
- DNA Sequencing (collaboration with outside partners)
- SNP analysis (collaboration with outside partners)
- Genotyping (collaboration with outside partners)
- qPCR- Copy Number Variation Studies, genetic stability testing

Cytometry: FACS (BD FACSCalibur)



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GPCR

Ion Channel

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- **Stable Cell Line Generation**
 Stable cell line expressing GPCR
 Stable cell line co-expressing GPCR and desired G-protein

- **Binding Assay**
 Assay format:
 - Filtration 96-well assay
 - SPA 96-well assay
 Type of assay:
 - Saturation binding assay: Kd determination
 - Competitive binding assay: IC50/Ki determination
 - Ligand on/off-rate assay

- **Functional Assay**
 Readers:
 - FLIPR^{TETRA}
 - FDSS7000
 Assay format:
 - cAMP assay: RIA or ELISA
 - Ca²⁺ influx assay
 - GTPγS
 - PathHunter eXpress β-arrestin GPCR assay
 - Other commercial GPCR assay platforms

- Type of assay
 - Activation: EC50 determination
 - Inhibition: EC50/IC50 determination; pA2 determination

- **GPCR Profiling Services**
 30 GPCRs expressing stable lines available
 40 more are under construction
 Cell line generation for customer's targets-of-interest and screening follow-up

- **Ion Channel Drug Discovery Services**
 Compounds screening

- Electrophysiology assays
 - IonWorks-Quattro
 - QPatch-HTX
 - Conventional patch-clamp
 - Conventional patch-clamp for brain slice recording

- Ion flux assays and membrane potential assays.
- Radioligand binding assays

MOA studies for lead compounds

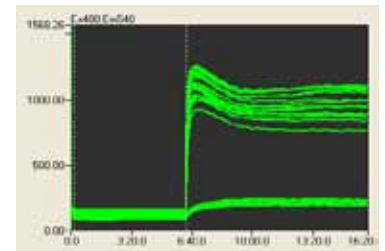
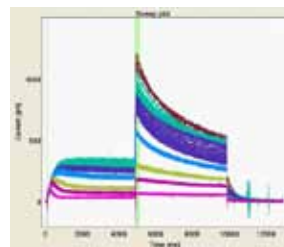
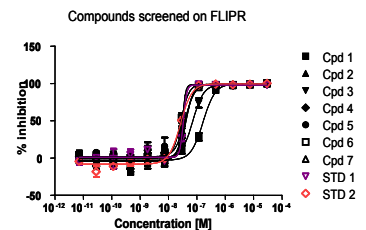
- Conventional patch-clamp studies in cell and tissue level, including stable cell lines, stem cells, native cells (dissociated DRG cells, primary cultured hippocampal neurons, dissociated aortic myocytes, etc), and brain slices.

- **Cardiac Safety Services**

hERG channel screening

Other cardiac safety channel screening

- hNav1.5 and hKCNQ1 channel screening on electrophysiology platforms



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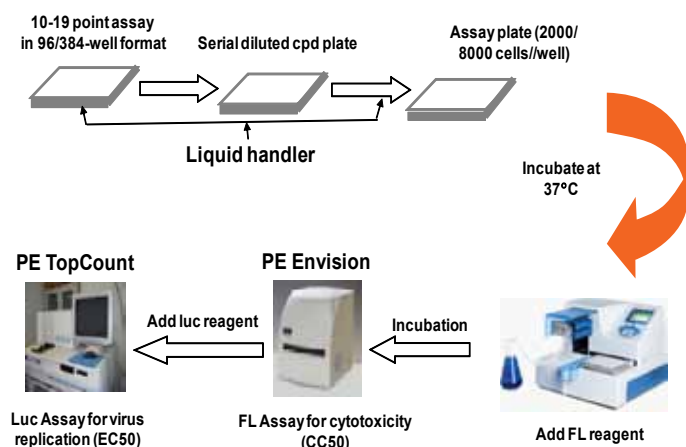
Virology

Virology Platform

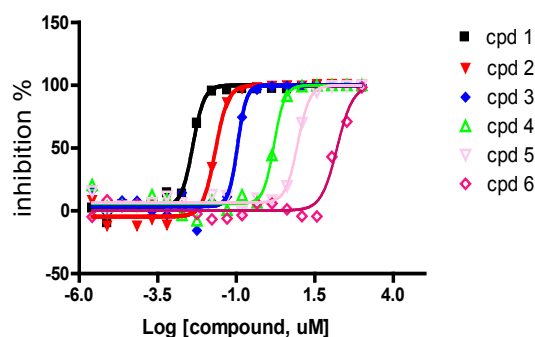
- Ongoing medchem programs targeting HCV, influenza, RSV, and HIV
- Multiple cell-based anti-viral assays including plaque reduction, CPE, pseudo viruses, and replicon
- Cell line development and screening
- In vitro viral enzyme assay development and screening
- Genetic & resistance analyses; chimeric virus construction; MOA
- Custom production of purified virus stock and viral target proteins
- Strong and experienced research team awarded by clients
- Newly renovated P2 facilities for anti-viral projects

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A Typical Antiviral Screening Procedure



Inhibition of compounds on HCV replication in host cells

HCV and HBV Clinical Virology Platform

- Viral genome quantification by COBAS® AmpliPrep/ COBAS® TaqMan®
- Genotyping
- Phenotyping



Anti-infective Platform

- Experienced in drug discovery for major bacterial and fungal pathogens
- Currently working on 2 anti-infective projects
- Determination of MIC against normal and drug-resistant bacteria/Fungi
- MOA analysis for novel agents
- Highly experienced leadership with a strong research team



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Protein Sciences

WuXi is committed to provide biomedical and drug discovery community with its unparalleled protein and structural biology expertise to shorten the path to new drugs.

Expression System

- E.Coli
- Insect cells
- Yeast
- Mammalian cells
- Cell-free

Novel/finicky Purification Methods Development

- Combine Modes of Chromatography
 - Affinity, Ion Exchange, Size Exclusion, Hydrophobic Interaction etc.
- Target to achieve protein purity >95%

Purification Capacity

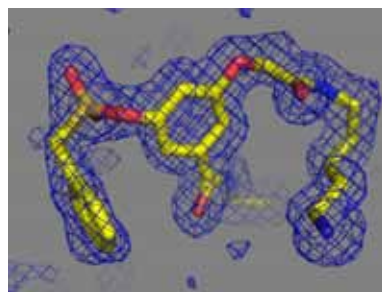
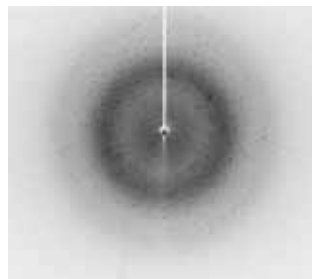
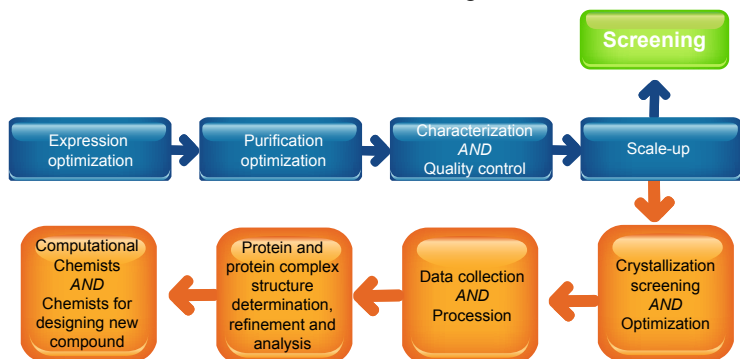
- Up to 500mg protein in a reasonable timeline

Quality Control Service

- SDS-PAGE /IEF
- Western Blotting or amino acid sequencing
- HPLC
- Mass spec
- Dynamic light scattering
- Circular Dichroism (CD) spectroscopy
- Biochemical assay
- Endotoxin control

Selected Instruments for Structural Biology

- Clonpix for stable clone generation
- Mosquito nano-liter robot
- 7 AKTAs (including Pilot, Explorer, Purifier and Xpress)
- Wave Bioreactors (5 L and 25 L)
- 2.5L/10L Sartorius 50L SUB High Clone



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Off the Shelf Crystal Service

- hPARP1, GSK3 b, hCLK2, BACE, HCV protease, NS5A, NS5B, HIV integrase...

Structure Service

- Crystallization screening
 - crystallization solution screening kits
 - +4°C Cold room
 - Mosquito nano-liter robot
- Data collection
 - Access to Shanghai Synchrotron Radiation Facility (SSRF) beam line
 - Collaboration with Shanghai Institute of Biochemistry and Cell Biology
- Structural determination and refinement
 - Determine the crystal structure with MR, MIR, SIR and MAD method
 - Model building with Coot, DS and Afitt program package
 - Refine the crystal structure with Programs CCP4, CNS

Fragment Based Drug Design Service

- Obtain the crystal of apo protein for FBDD screening
- An unique compound data base for more than 170,000 compounds
- Design the high potent ligand based on the weak binding inhibitors

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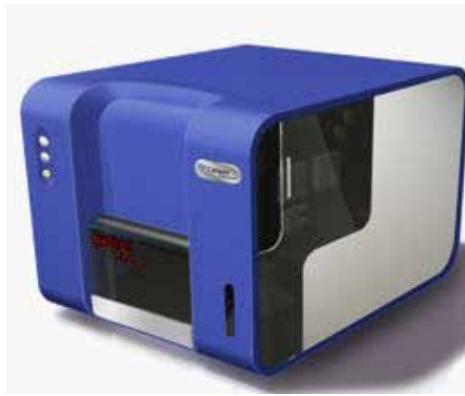
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Enzymology

- Capability to develop or transfer various enzymatic assays such as kinases, proteases, isomerase and polymerases etc..
- Capability of all major kinase assay technologies to support client routine screening for SAR studies.
 - IC50, Km, MOA etc.
 - Substrates: proteins, lipids, carbohydrates etc.
 - Support client special requests
- Ongoing build up and expansion of kinase profiling platform using Z-LYTE format. First batch of panel will include 20 – 50 kinases.



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Example of Kinase Assay Platforms

- Kinase Glo - measuring ATP depletion
- ADP-Glo, NADH absorbance, Adapta-measuring ADP product
- TR-FRET, AlphaScreen, ELISA, IMAP, microfluidic system with fluoro-substrates, filter binding, FlashPlate, SPA- measuring phosphorylated product

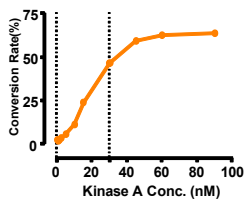
Example of Some Kinases Validated

Abl kinase (h)	CHK1 (h)	FGFR1 kinase (h)	JNK1 (h)	MINK (h)	PKA (h)
AurA/Aur2 kinase (h)	CK1alpha (h)	GSK3beta (h)	KDR kinase (h) (VEGFR2)	MST4 kinase (h)	Src kinase (h)
CaMK2alpha (h)	DYRK3 (h)	HGK (h) (MAP4K4)	Lck kinase (h)	p38alpha kinase (h)	TAOK2 (TAO1) (h)
CDK2 (h) (cycA)	EphA2 kinase (h)	JAK2 (h)	MAPKAPK2 (h)	PDK1 (h)	TNIK (h)

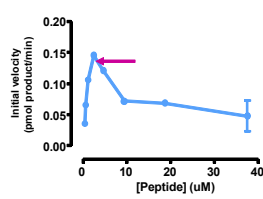
Study case 1: Mobility Shift Assay Development

- Assay Setup and Optimization

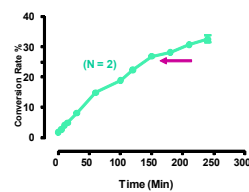
Enzyme titration



Substrate titration

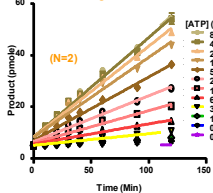


Assay Time course

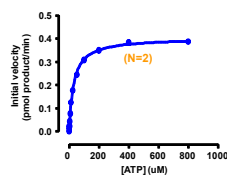


- ATP Km Determination

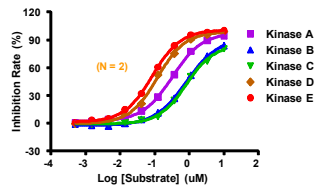
Reaction Progress Curves



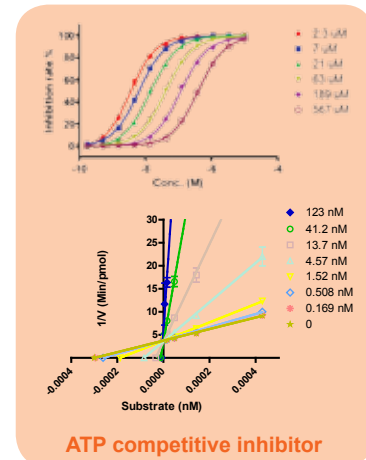
Kinase A ATP Km (Velocity vs. Substrate)



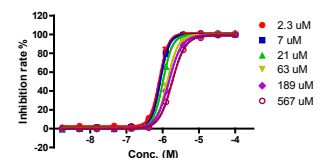
- IC50 Tests of Reference Compounds



Study Case 2: MOA Studies to Determine ATP Competitiveness of Kinase Inhibitors



ATP competitive inhibitor



Non-competitive inhibitor

WuXi's ATP Km and IC50s are consistent with the data measured by the clients

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Molecular and Cell Biology Service

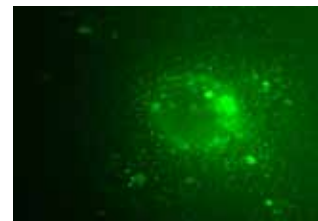
- Gene cloning and expression vector construction
- Mutagenesis
- Cell line generation for bioassay
- Cell line generation for therapeutic protein production
- Product analysis using HPLC, SDS-PAGE, Mass Spec
- Cell line characterization at cellular and molecular level
- Cell line sterility testing
- Gene expression detection at RNA level
- Gene expression detection at protein level (ELISA or western blot) in tissues or cells
- Flow cytometry based cellular marker assay
- Cell proliferation, cytotoxicity testing
- Non-GLP cell banking

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Bioprocess Development

- Supporting cell line generation by testing top-candidate-clones in bioreactors
- Supporting cell line generation by producing small amounts of reference material in bioreactors for product characterization
- Post to parental cell banking, testing the cell growth characteristics, investigating metabolite profiles, and evaluating product quality
- Performing basal medium comparisons
- Performing feed medium and feeding strategy optimization, aimed at high volumetric yield and high quality
- Performing spent medium tests, including amino acid analysis by HPLC, and metabolite analysis by Nova Profile Flex
- Other state-of-art instruments and equipments (*see below*) for process optimization and scale up, with the ultimate goal of obtaining high product yield, high quality, and high degree of process transferability.



Biologics Capability

- Providing reagent-grade antibody using immunization/hybridoma technique
- Providing reagent-grade antibody using cell culture technology, with both transient and stable expression systems
- We have integrated upstream, downstream and analytical competences and instrumentation as the basic components of our biologics capability
- Larger biologics capacity and capability is under progress



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