GenScript
Make Research Easy

Bispecific Antibody: The Next Generation Therapeutics

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GenScript
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Presentation Overview

Overview of Antibody Therapeutics

Bispecific Antibody

SMAB Case Study

Summary

About GenScript

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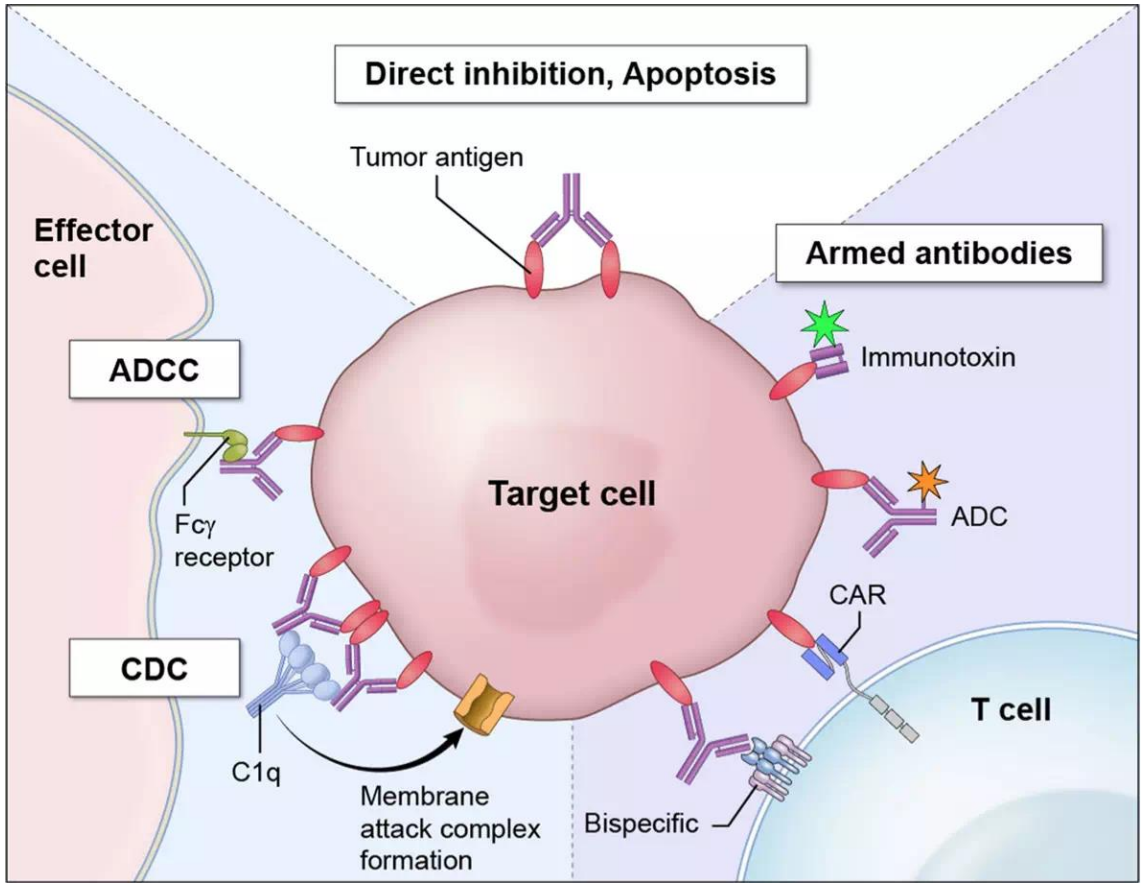
Overview of Antibody Therapeutics

Overview of Antibody-Based Cancer Therapies



Mechanism of Action

- **Direct inhibition or apoptosis**

  Herceptin

- **ADCC/CDC**

  Rituxan

- **Immune cell activation and recruitment**

  Opdivo, Keytruda, Yervoy

  Kymriah

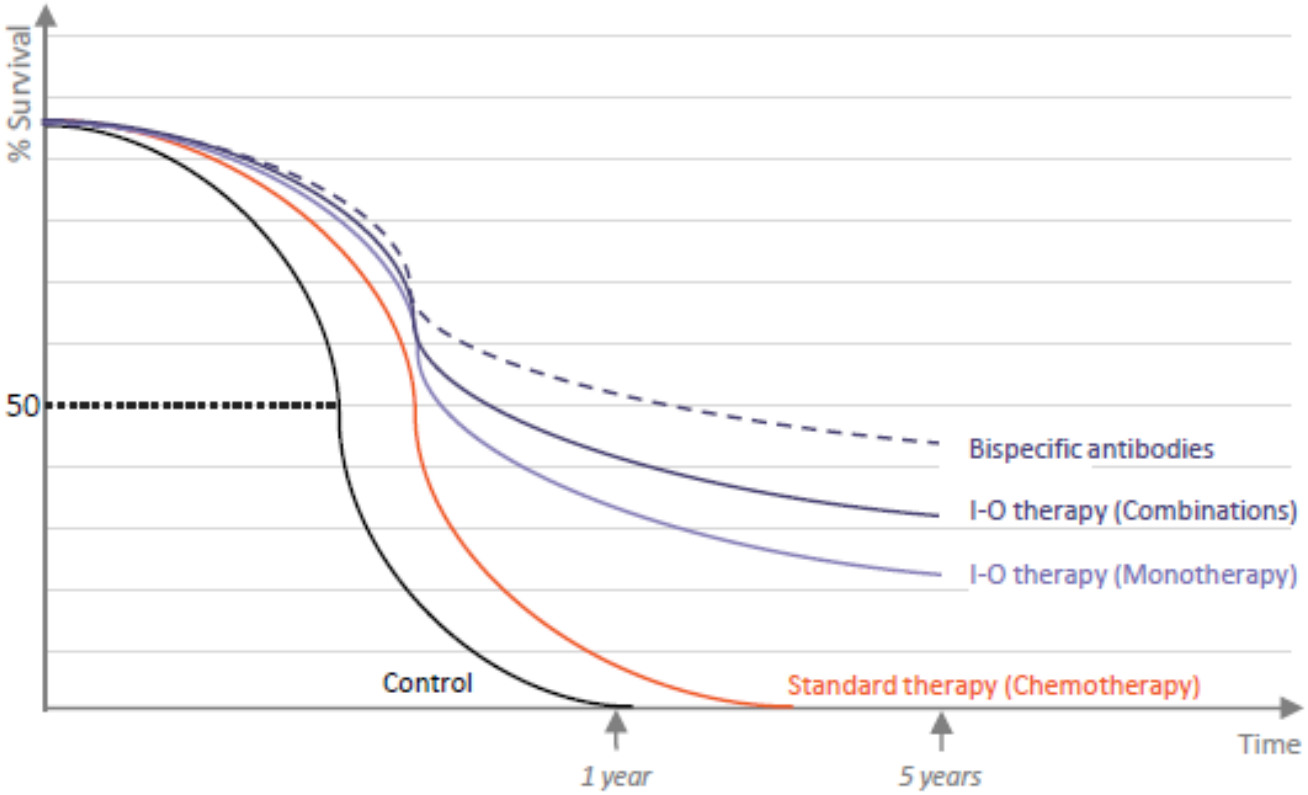
- **Cytotoxin delivery**

  Mylotarg, Adcetris, Kadcyla

2017 First-in-Class Drugs

Limitation of Monotherapy: Efficacy

Schematic Kaplan-Meier Plot for Therapeutic Survival with Various Cancer Treatments



Reproduced and adapted from:
-Chen TT. J Immunother Cancer. 2013; 1:18.
-Ribas A, et al. Clin Cancer Res. 2012; 18: 336-41
-ASCO 2015

Limitation of Combo-therapy: Safety

	Median PFS (%)	Median Duration of Response (most at >18 mos)	AE Grade 3-4 (%)
Opdivo + Yervoy	11.7	Not reached	58.5
Opdivo	6.9	31.1	20.8
Yervoy	2.9	18.2	27.7

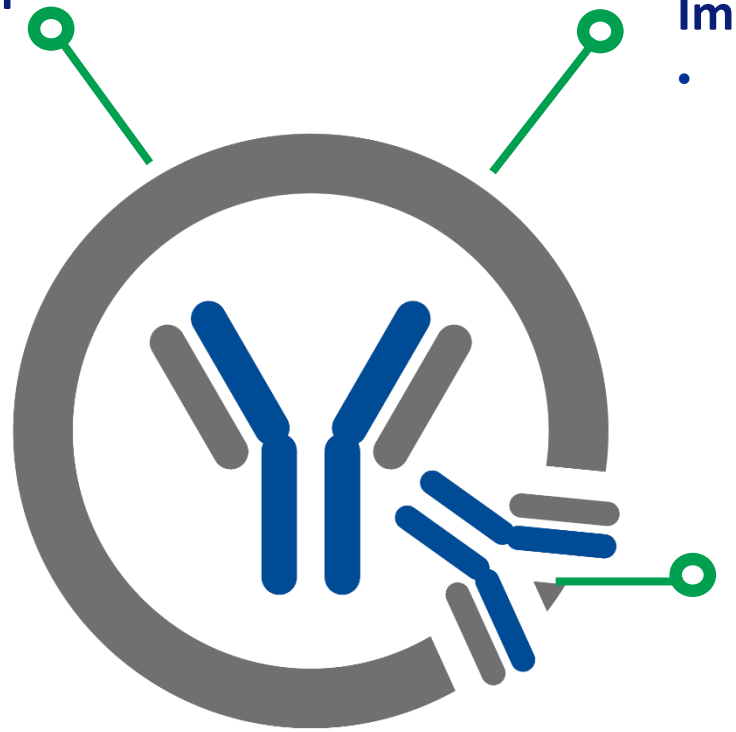
- BMS Checkmate 067 in advanced melanoma, Phase III
- 945 untreated patients
- Opdivo and Opdivo+Yervoy are superior to Yervoy alone
- Substantially more Grade 304 adverse effects with combination treatment

Larkin et al., AACR 2017

Bispecific Antibody v.s. Combo Therapy

Superior Potency through Novel *MOA*

- Redirected T cell activation & killing
- Modulation of receptor signaling
- Simultaneous targeting of multiple co-inhibitory receptors or checkpoints
- Targeting multiple epitopes on a pathogen for enhanced neutralization and/or clearance



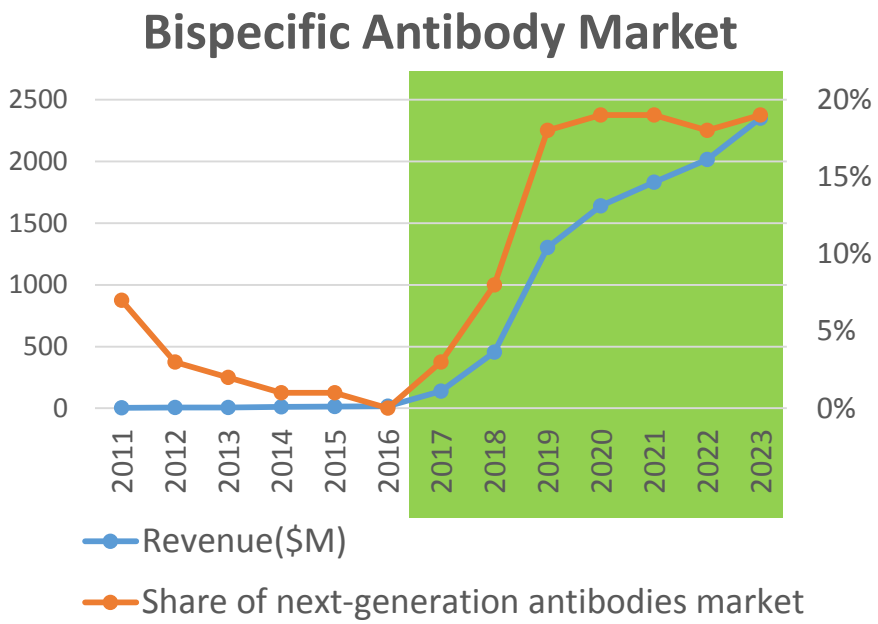
Improved *Safety*

- Low off-target binding may reduce side effects

Controlling *Price*

- Develop only 1 molecule and save half of investment in comparison with combination therapy

Impressive bsAb Market



- The bispecific antibody(bsAb) market size is estimated at ***$455M*** in 2018 and will reach ***$2023M*** in 5 years.
- 3 market drugs:
  - Catumaxomab: CD3+EpCam
  - Blimatumomab: CD3+CD19
  - Emicizumab: factor Ix+ factor X

Target Combination & MOA of bsAb

MOA	Target & Company	Company
T-cell/NK cell recruiter	CD3/CD16 + HER2/Epcam/CD20/CD19 …	Amgen/MedImmune, BI, Macrogenics, Pfizer, Roche, Janssen, etc.
Two ligand inactivation	HER3+HER2/ IGF-IR/EGFR VEGFR + Ang-2 IL17 + IL17F IL4 + IL13	BMS, Ablynx, Roche, Merck, Abbvie
Two factor dimerization	Factor XI + Factor X	Roche/Chugai
Immune checkpoints	PD-1 + CTLA-4, PD-L1 + CTLA-4	Merus
Break blood-brain barrier	BACE1+ TfR	/
Internalization	PRLR + HER2/PD-1	/

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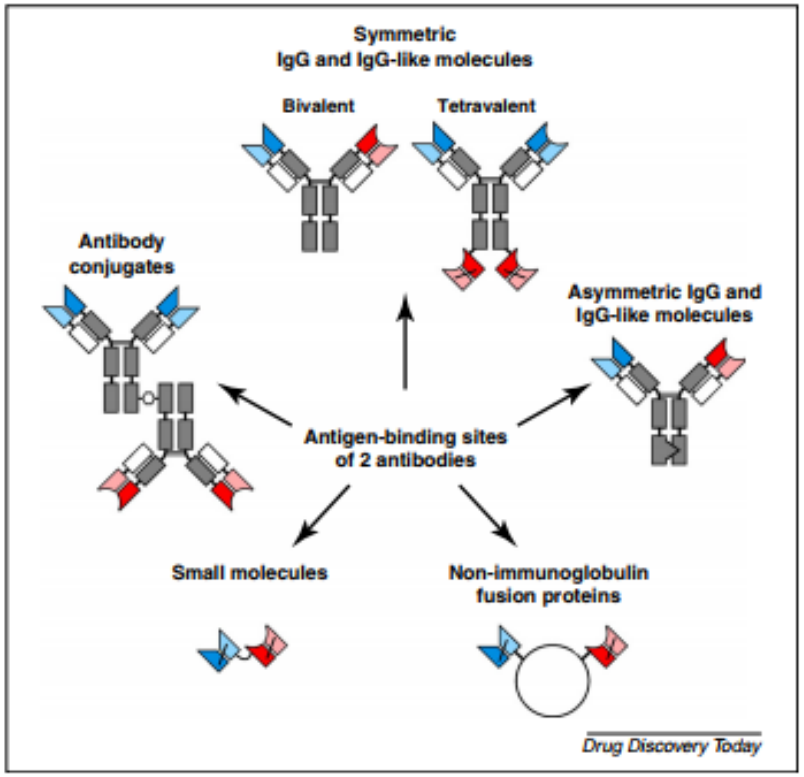
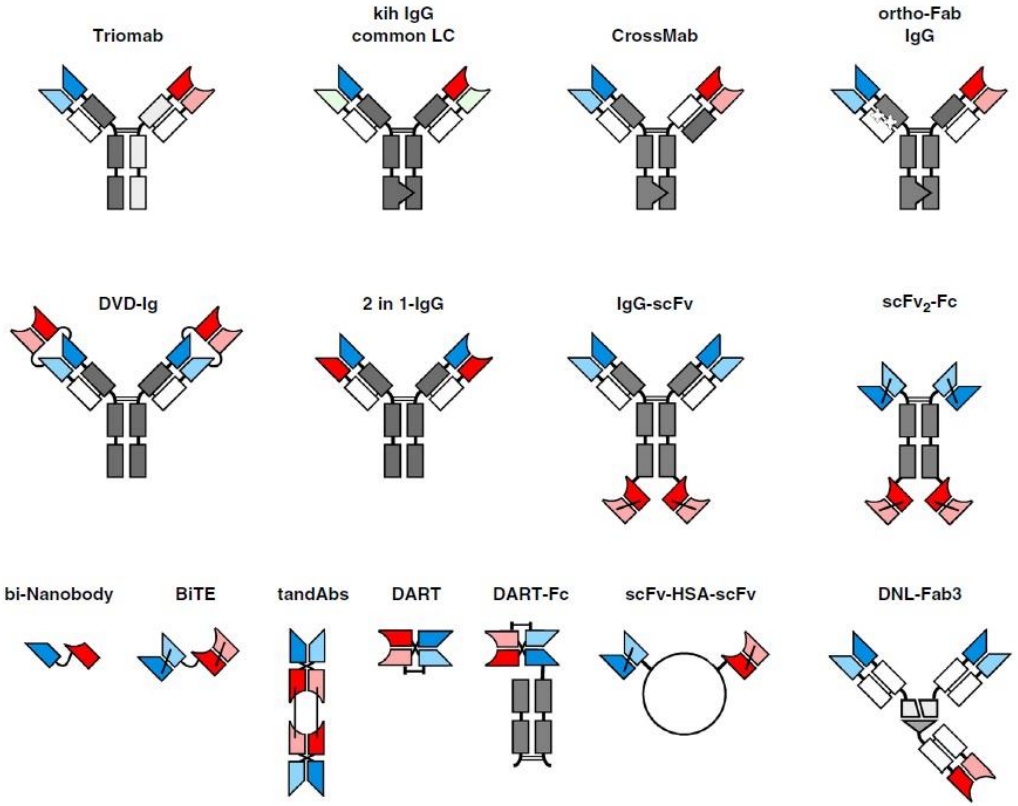
Bispecific Antibody Platforms

Strategies of Constructing bsAb

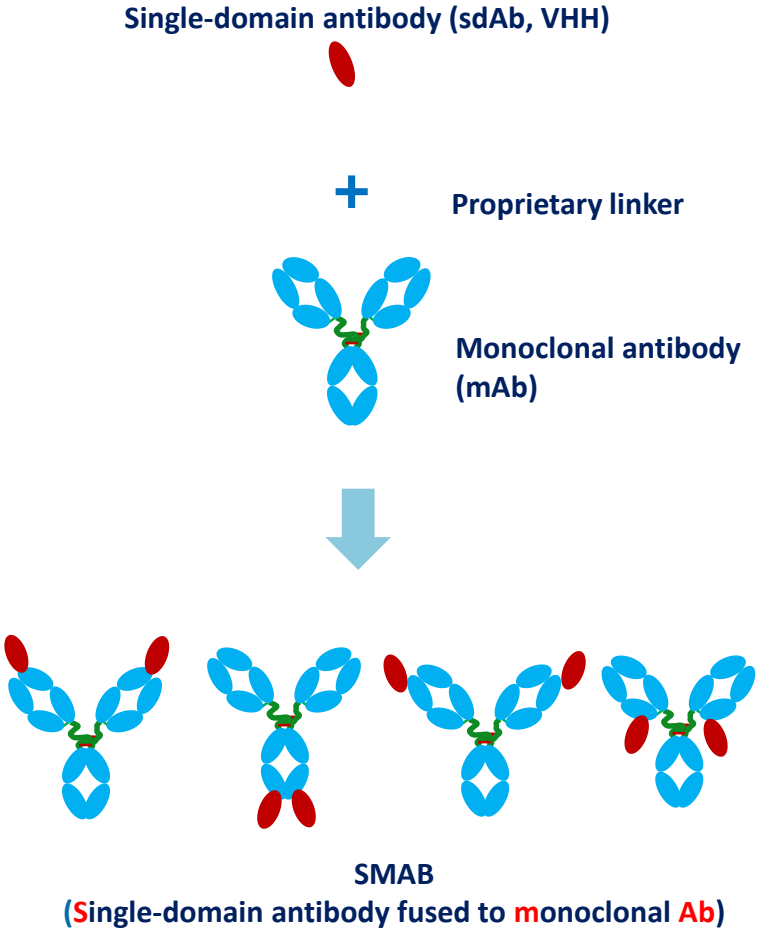




Concerns in Developing bsAb

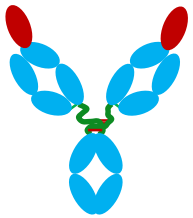
Immunogenicity	• Unnatural format
Manufacture problems	• Product instability • Low expression level • Complex purification process

SMAB - Molecular Design and Advantages

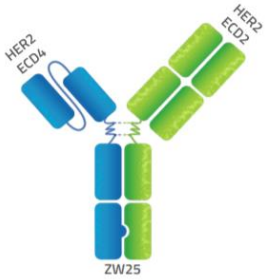


- **Symmetric structure without Fc engineering** (2 chains, intracellular assembly, no mismatch)
- **Single-step processing to yield pure product** (Protein A purification)
- **Developability comparable to conventional mAbs**
- **High yield** (same as mAb, gram level in cell line dev.)
- **High concentration formulation with desirable stability** (up to 200 mg/ml)
- **Flexible format** able to target >=2 targets/epitopes by “plug and play” fashion
- **Biosuperior** over stand-alone or combination treatment

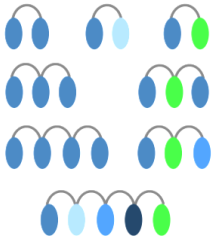
SMAB & Other Bi-specific Antibodies



GenScript SMAB

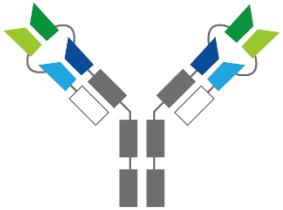


Zymeworks
Asymmetric bispecific Ab



Ablynx
Nanobody

GenMab
Duobody

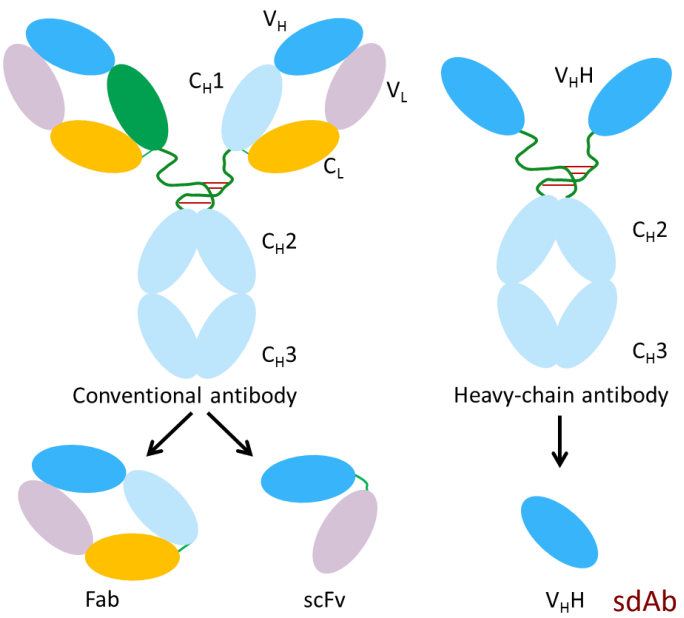


Abbvie
DVD-Ig

SMAB

- Symmetric design favoring production and stability
- Natural Fc supporting long serum half-life

Why sdAbs?



Target engagement moiety

Half-life extension moiety

2nd epitope/target engagement moiety

Small in size (~13 kDa)

- Better tissue penetration
- Affinity can reach pM range
- Ability to bind “hidden” epitopes
- Favorable biophysical properties
- Superior stability and solubility

Expressible in yeast or microbial systems

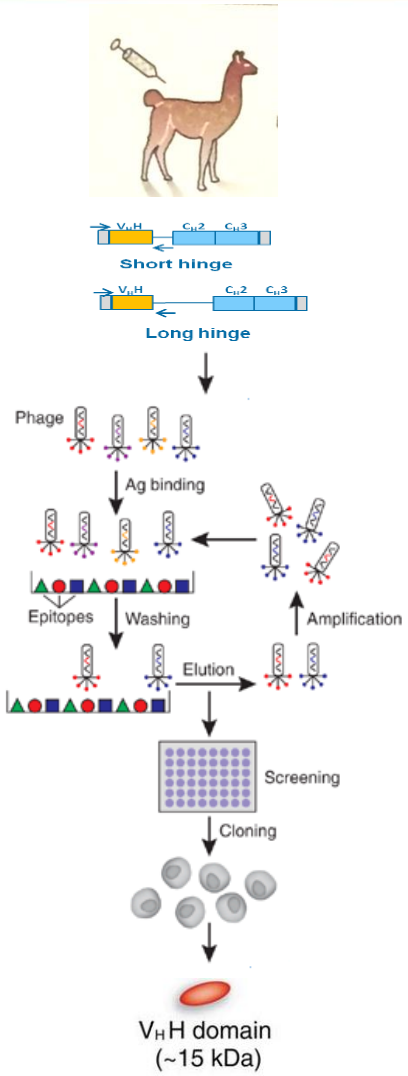
- Expressible in yeast or microbial systems
- Economy in production

Flexibility in modality design

- Straight sdAb
- Biparatopic sdAb
- Bi- or multi-specific sdAb

(GenScript SMAB Platform)

sdAb Discovery through Phage Display



Preparation of immunogen
(Provided by client or GenScript)

↓

Llama/Camel immunization
(10 weeks for llama; 8 weeks for camel)

↓

Phage display library construction
(4 weeks)

↓

Phage biopanning for 2-3 rounds
(3 weeks)

↓

FASEBA HTS to identify best binders
(4 weeks)

↓

Antibody production and
characterization (3 weeks)

Timeline~22 weeks

Technologies to Generate mAbs

Hybridoma technology

- Hybridoma with human transgenic mice/rats

  >>>> *Human antibody (Medarex, Abgenix, Regeneron, OMT, Kymab, Trianni, Harbour)*
- Hybridoma with B-cells from immunized human body

  >>>> *Human antibody*
- Hybridoma with rodent system

  >>>> *Humanized antibody*

Library technology

- Phage / Yeast / Ribosome display

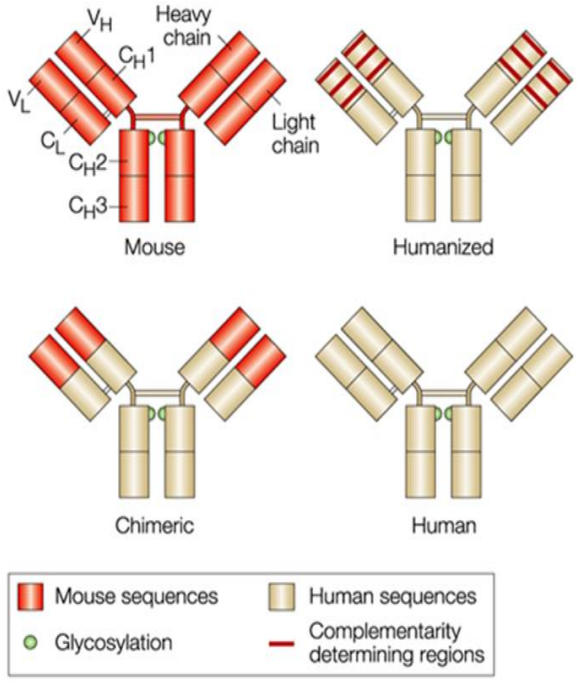
  >>>> *Human/Humanized antibody*

Other technologies (single B cell)

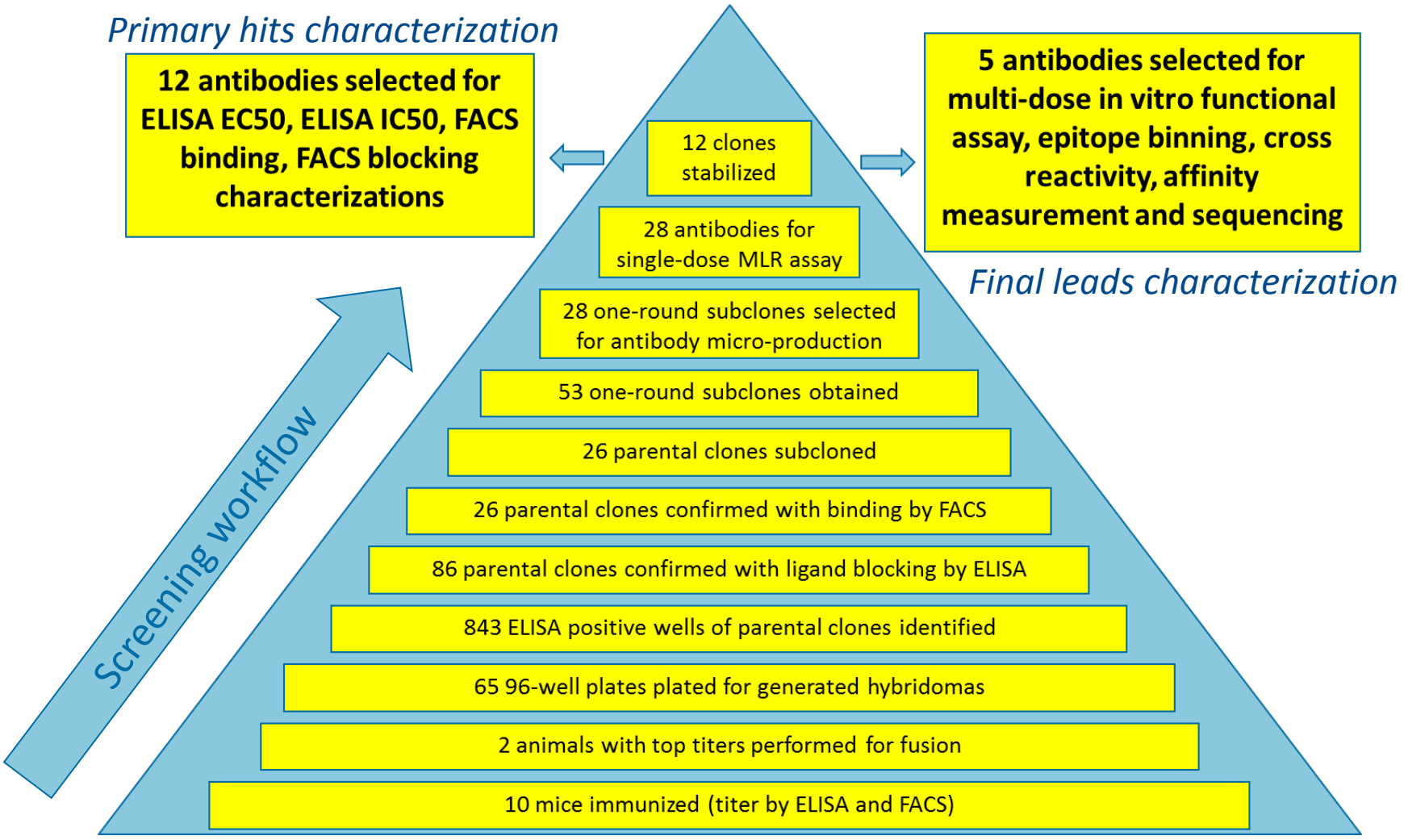
- SLAM technology

  >>>> *Humanized antibody*
- Next generation antibody sequencing

  >>>> *Human/Humanized antibody*



Hybridoma Generation



Fully Human Naïve Fab Library

Isolate PBMCs

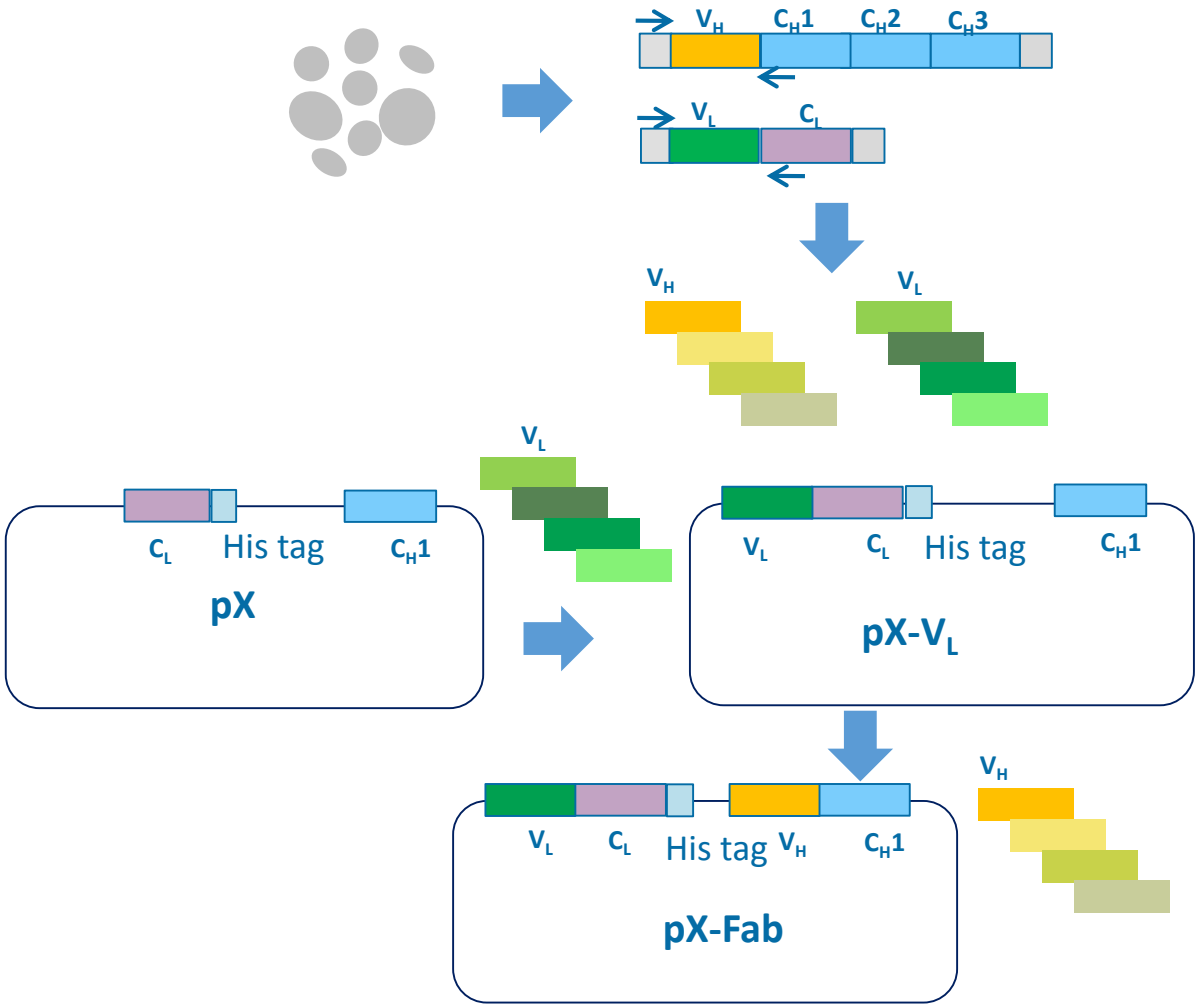
Extract total RNA, cDNA

PCR amplify of heavy and light chain variable domains

Insert light chain variable domains into phage display vector

Insert heavy chain variable domains into phage display vector

Fab Phage display library



Comparison of Ab Lead Generation Technologies

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Hybridoma

- Pros
  - Good developability
  - Usually no need for affinity maturation
  - Can apply to all targets
- Cons
  - Immune tolerance issue
  - Need humanization or license fully human platform
  - Relative slow

Phage Display

- Pros
  - Fast
  - Large library
  - No immune tolerance issue
- Cons
  - Developability issue
  - Specificity issue
  - Difficult to apply to certain targets(e.g. GPCR, ion channel)
  - Usually need affinity maturation

B cell cloning

- Pros
  - Fully human
  - Natural occurring
- Cons
  - Limited to infectious diseases
  - Application to other disease area is uncertain
  - Difficult to identify target

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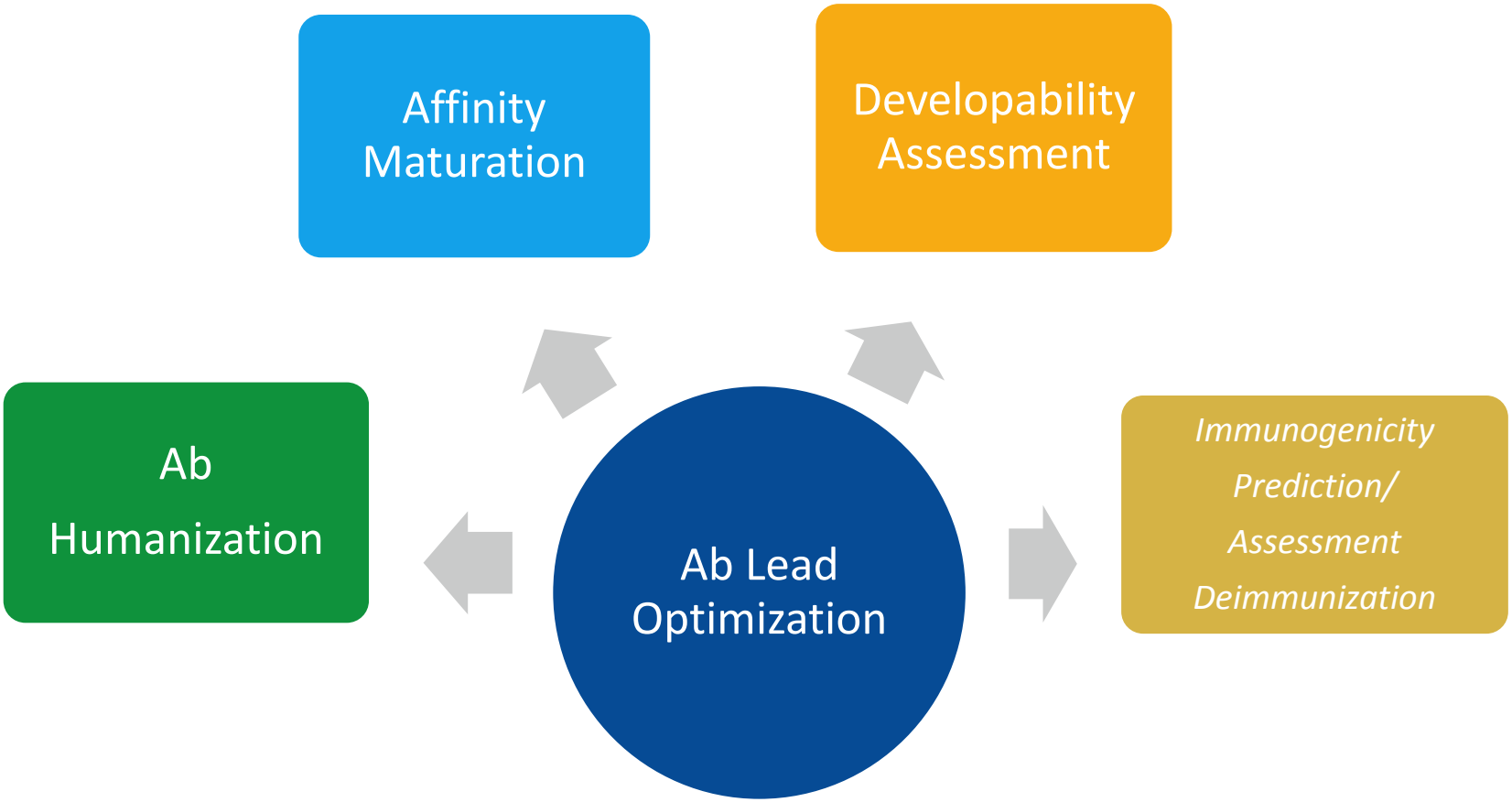
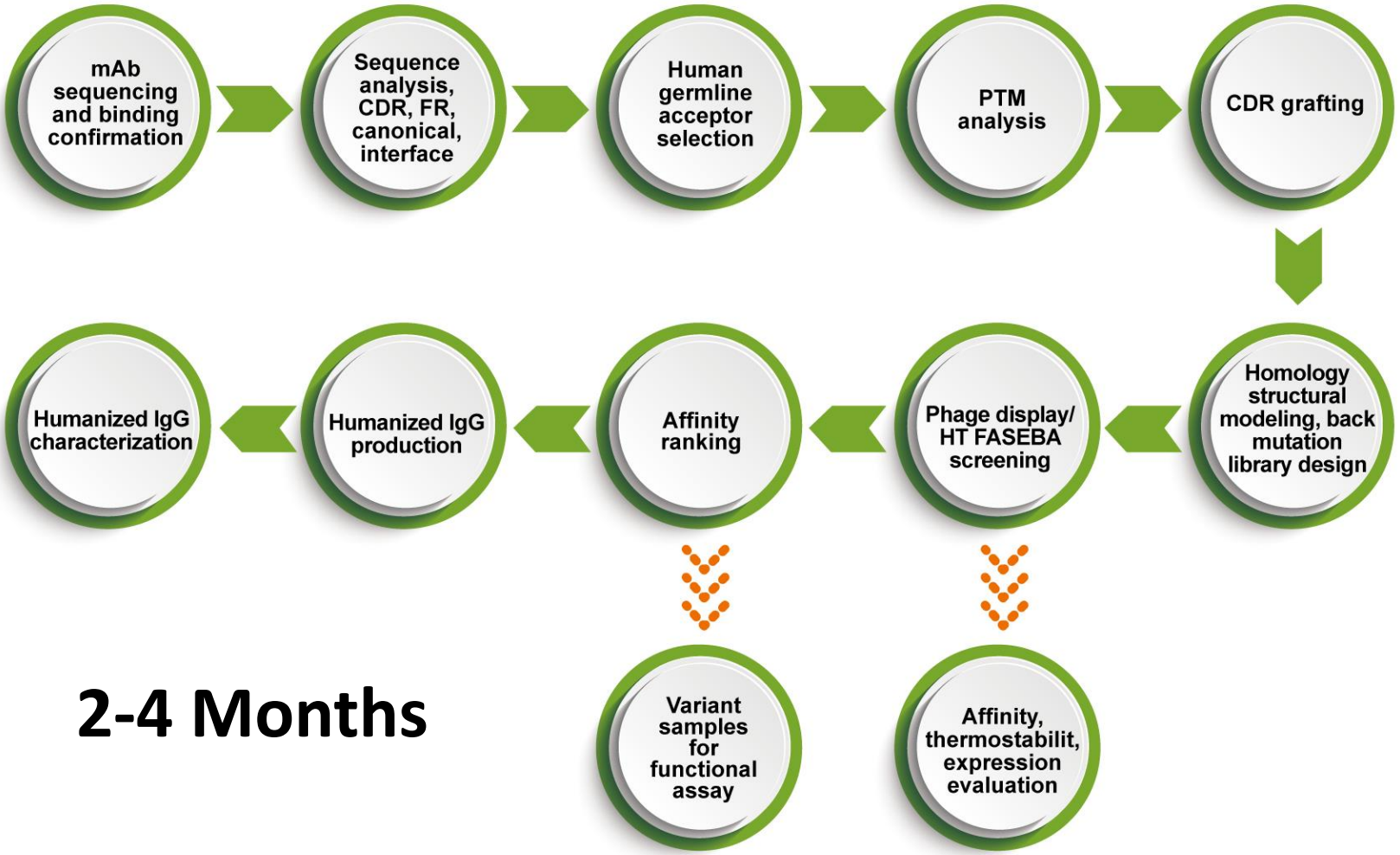
Ab Lead Optimization

Ab Lead Optimization

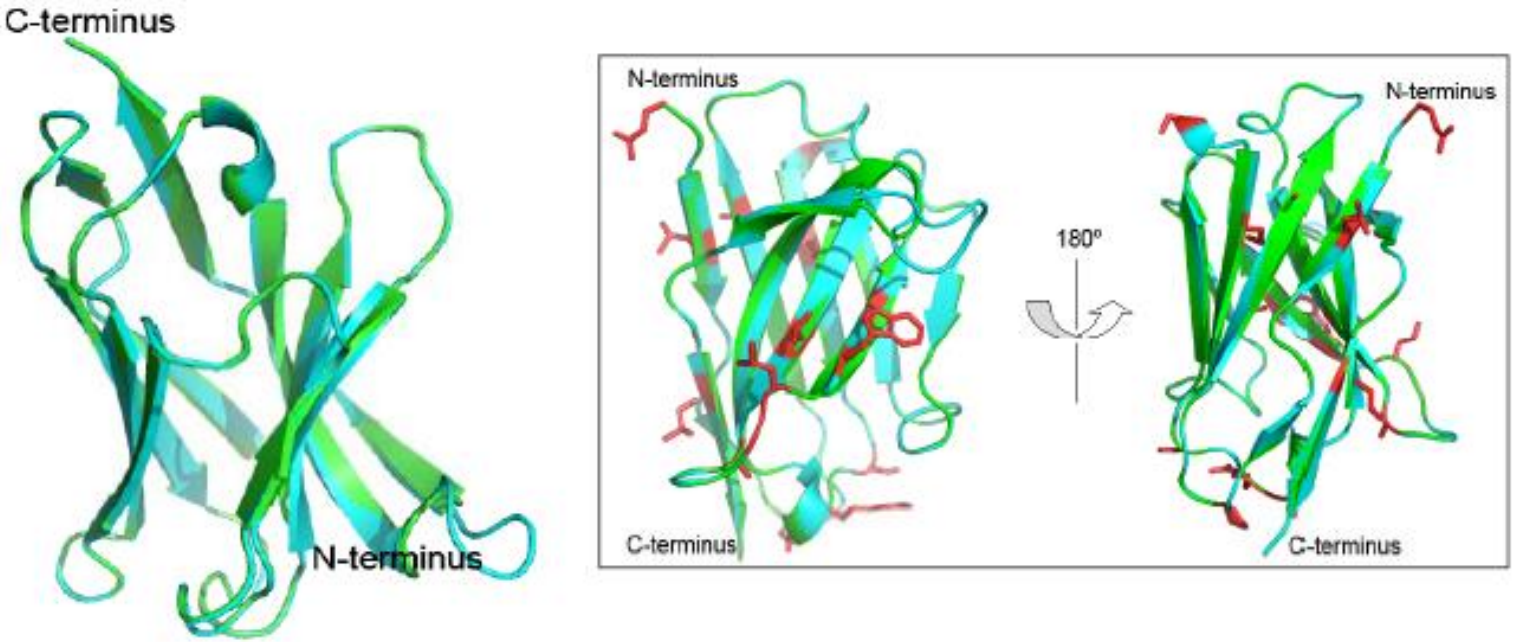


Antibody Humanization



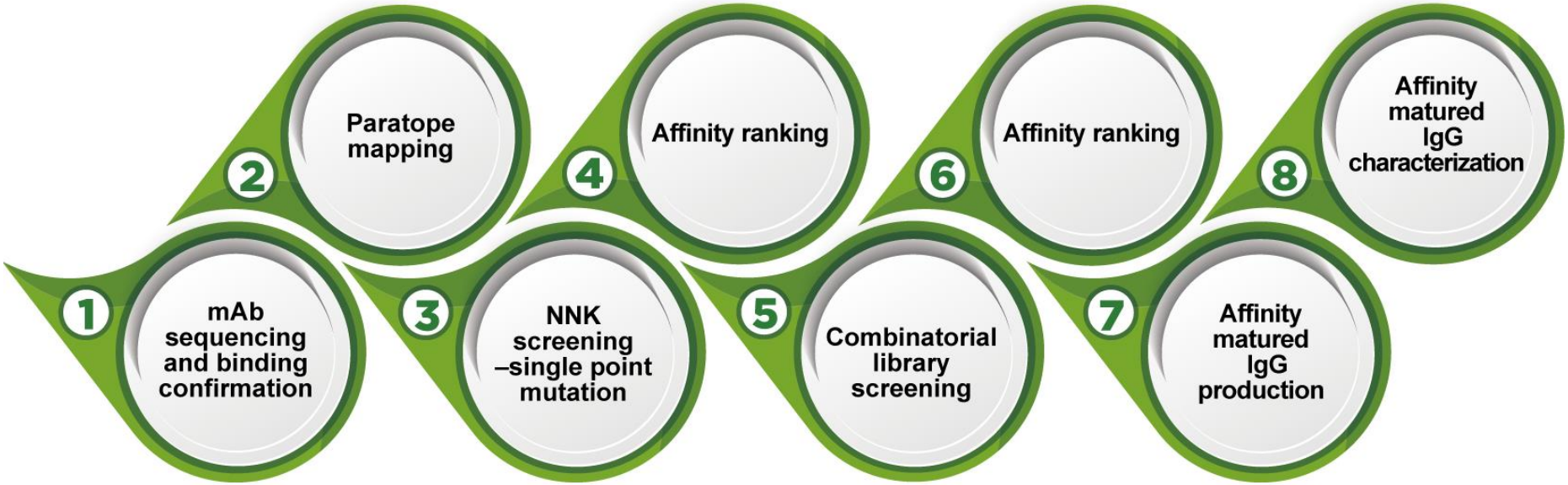
2-4 Months

Case Study:
Humanization of An Anti-cytokine sdAb



- **Homology Structure Modeling**: high sequence homology (71%), sdAb (cyan) and human acceptor (green)
- **Back Mutation**: 16 framework residues (red) were different, of which 5 positions were modeled to be potentially critical for antigen binding (close to CDRs) and putative back mutations performed

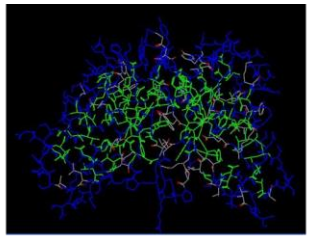
Affinity Maturation by HTS

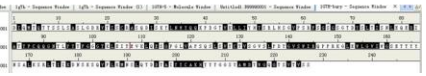


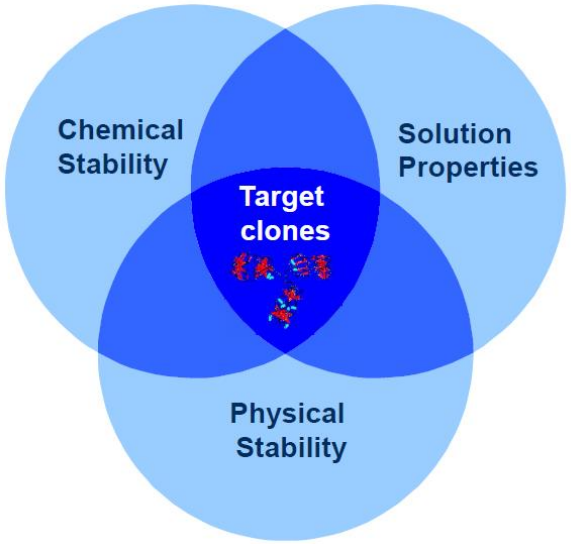
4-5 Months

Developability Assessment---Tools

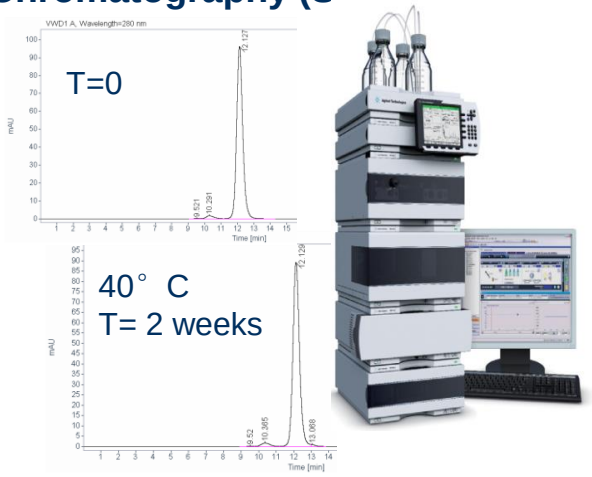
In Silico homology modeling







Size Exclusion Chromatography (SEC)



Agilent HPLC/UHPLC 1200/1260/1290

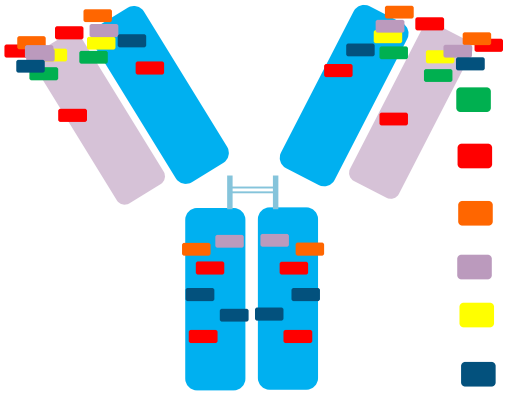
Peptide mapping and LC-MS analysis

SCIEX TripleTOF™ 4600

CE-SDS

Sciex P/ACE™ MDQ Plus

Potential PTMs in antibody



Fragmentation
Deamidation
Isomerization
N-Glycosylation
Free-thiol
Oxidation

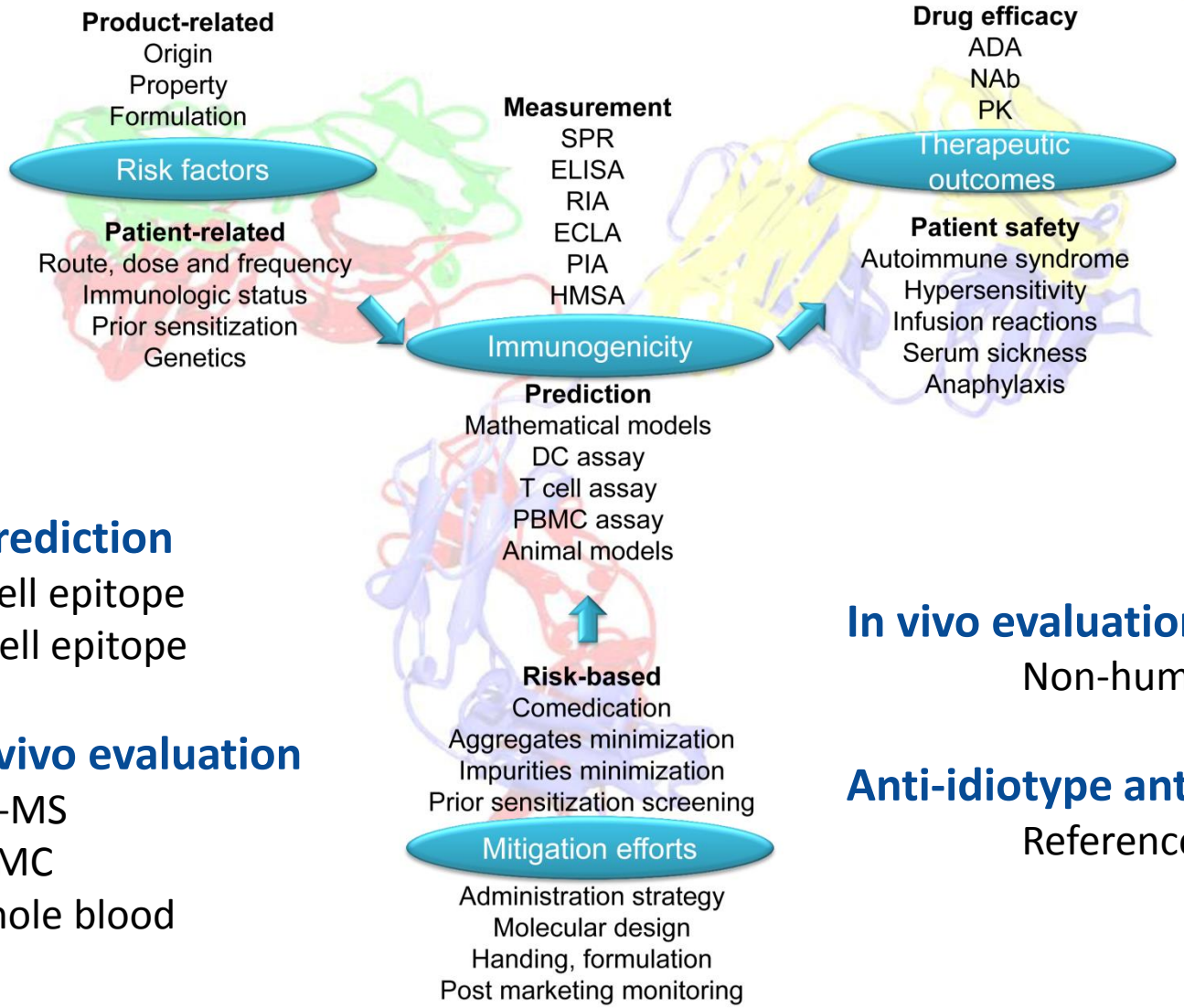
SPR capture assay

Biacore T200/8K

Developability Assessment---Methods

Category	Item	Description	Solution
Biophysical characterization and improvement	**Thermostability**	1. Incubate at 40 degrees up to 4 weeks, aliquots are analyzed by SEC-HPLC or ELISA. 2. Incubate at gradient temp. up to 70 degrees 20 min, aliquots are analyzed by SEC-HPLC or ELISA. 3. DSC	1.Optimizing hydrophobic core and charge cluster residues 2. Optimizing conserved residues 3. Removing hydrophobic surface residues
	Aggregation	Analyzed by SEC-HPLC	
	Freeze and thaw stability	Up to five freeze and thaw cycles, aliquots are analyzed by SEC-HPLC	
	Biomatrix stability	Analyzed by ELISA (serum, plasma)	Optimizing Ab through high throughput screening
	Expression and Solubility improvement	Analyzed by ELISA or SEC-HPLC	Removing/ reducing hydrophobic surface residues
Developability assessment (PTM hotspots identification and removal)	**Asparagine Deamidation**	1. Validated via peptide mapping followed by LC-MS/MS, 2. Binding analysis by SPR or FACS 3. SEC-HPLC	Optimized Ab through antibody engineering should retain the same affinity and activity as reference Ab
	Aspartate isomerization		
	Tryptophan oxidation		
	Hydrolysis		
	N-glycosylation		

Immunogenicity Assessment



In sicilico prediction

T cell epitope
B cell epitope

In vitro/ex vivo evaluation

DC-MS
PBMC
Whole blood

In vivo evaluation

Non-human primates

Anti-idiotype antibodies

Reference Ab

Liusong Yin, 2015, J. Immunology Research

Summary

Strategies of Constructing bsAb

- Symmetric IgG
- Asymmetric IgG
- Antibody Conjugation
- No Fc fragment
- Fc fusion protein

SMAB

- Single Domain antibody fused to monoclonal antibody
- “Being Natural”: Good Developability & Safety

Ab Lead Optimization is a combination of bioinformatics, antibody engineering & HTP screening and evaluation

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Summary of bsAb

bsAb: Meet Unmet Medical Needs

- **What we expect in Bispecific Antibody: 1+1>2**
  - Better response rate
  - More durable response
  - Better tolerability

- **Developing a SMAB needs to consider:**
  - Synergy of Target Biology
  - Efficacy, Developability & Safety of bsAb format

GenScript SMAB

A **Bispecific/Multi-Valent** & **Open-Access** Platform

Biosuperiority over monotherapy or combination treatment with novel MOA

"**Being Natural**": Good Developability & Low Immunogenicity

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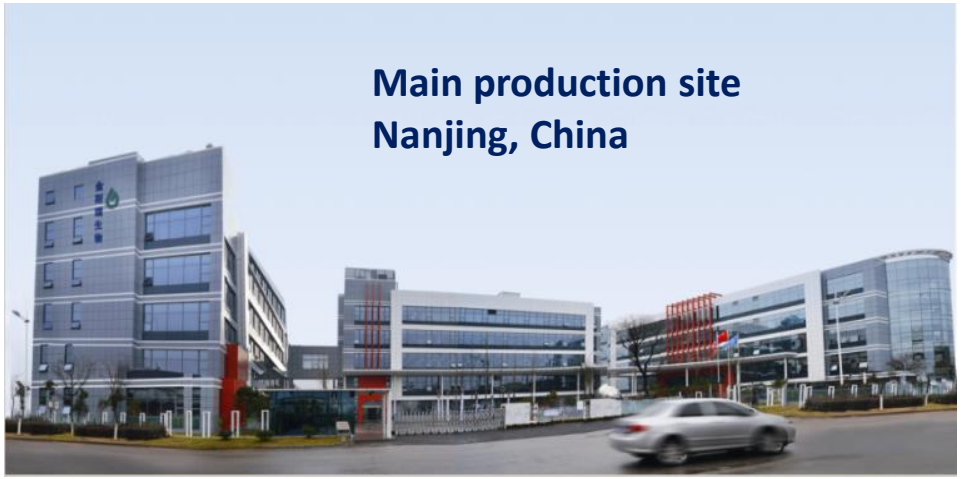
About GenScript

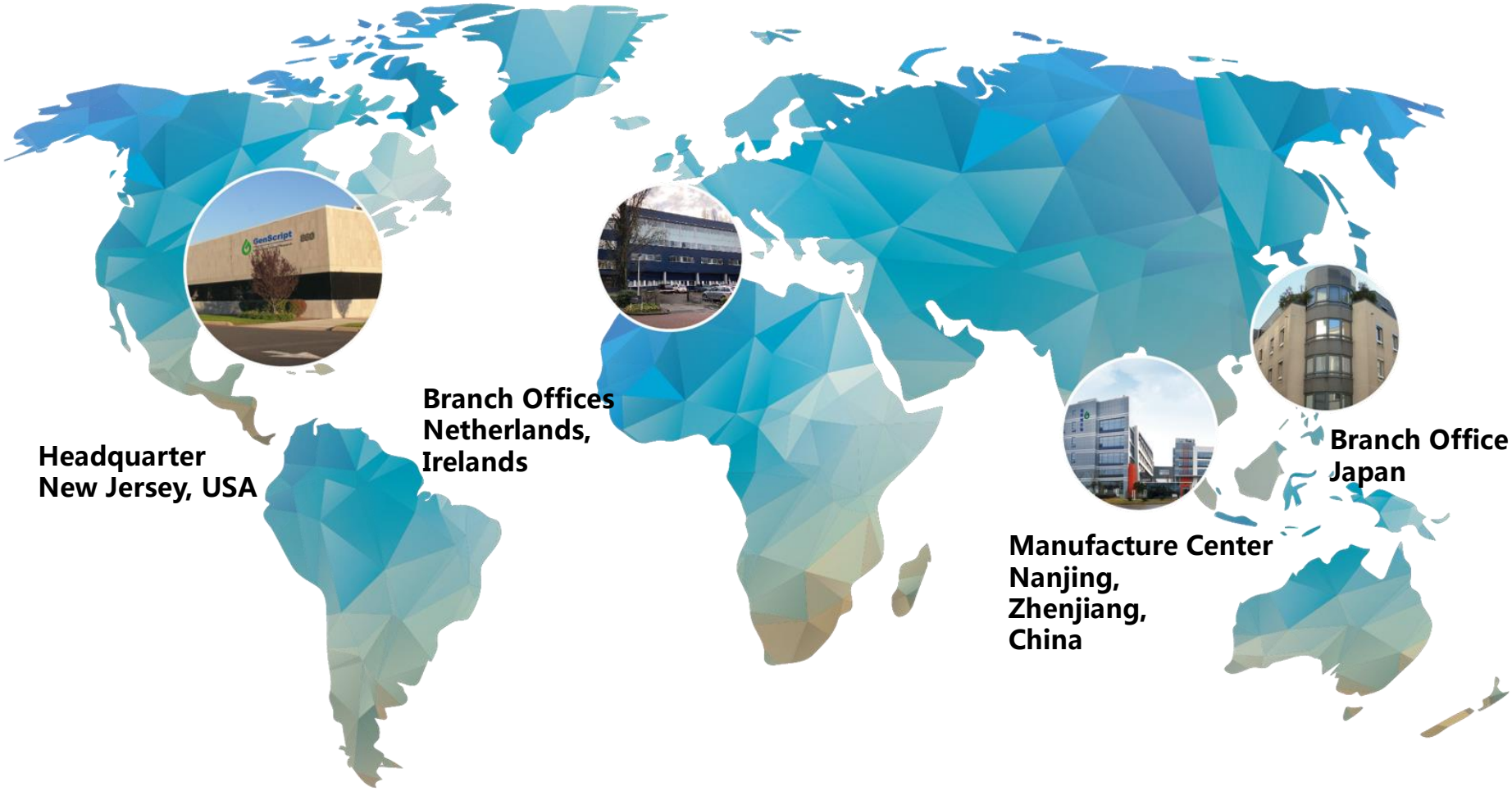
GenScript, A Global Bio-CRO

- Founded in 2002
- Publicly traded at Hong Kong Stock Exchange (HKG:01548)
- 2000+ employees
- No.1 in gene synthesis
- One of fastest growing Bio-CRO in China
- Offering one-stop service and specialized in Antibody discovery & development

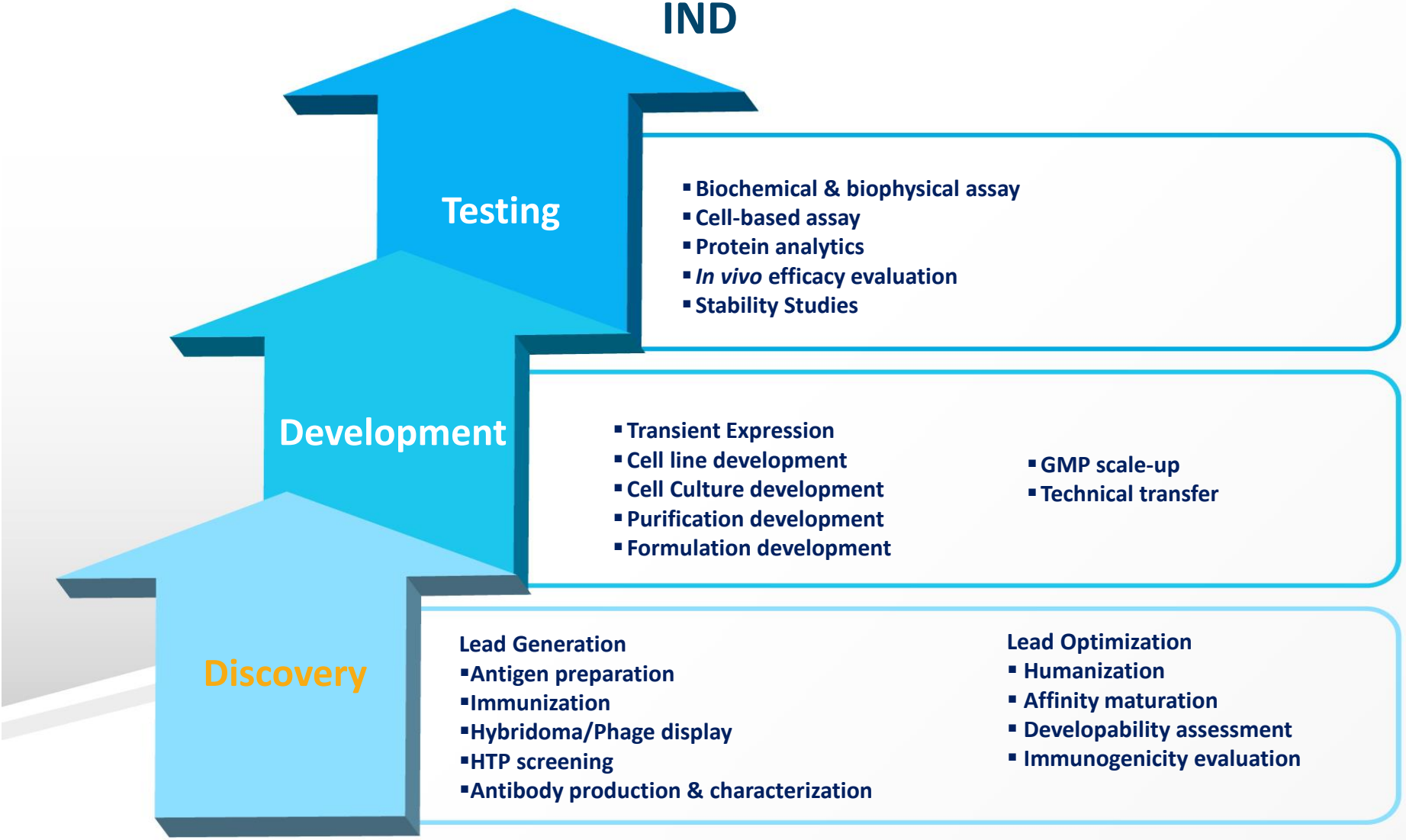
- **Local technical support**
- 24-hour customer service
- Fast global logistics
- Competitive pricing
- Stringent IP protection



Global Presence



Your Partner from Target to IND



- Biochemical & biophysical assay
- Cell-based assay
- Protein analytics
- *In vivo* efficacy evaluation
- Stability Studies

- Transient Expression
- Cell line development
- Cell Culture development
- Purification development
- Formulation development
- GMP scale-up
- Technical transfer

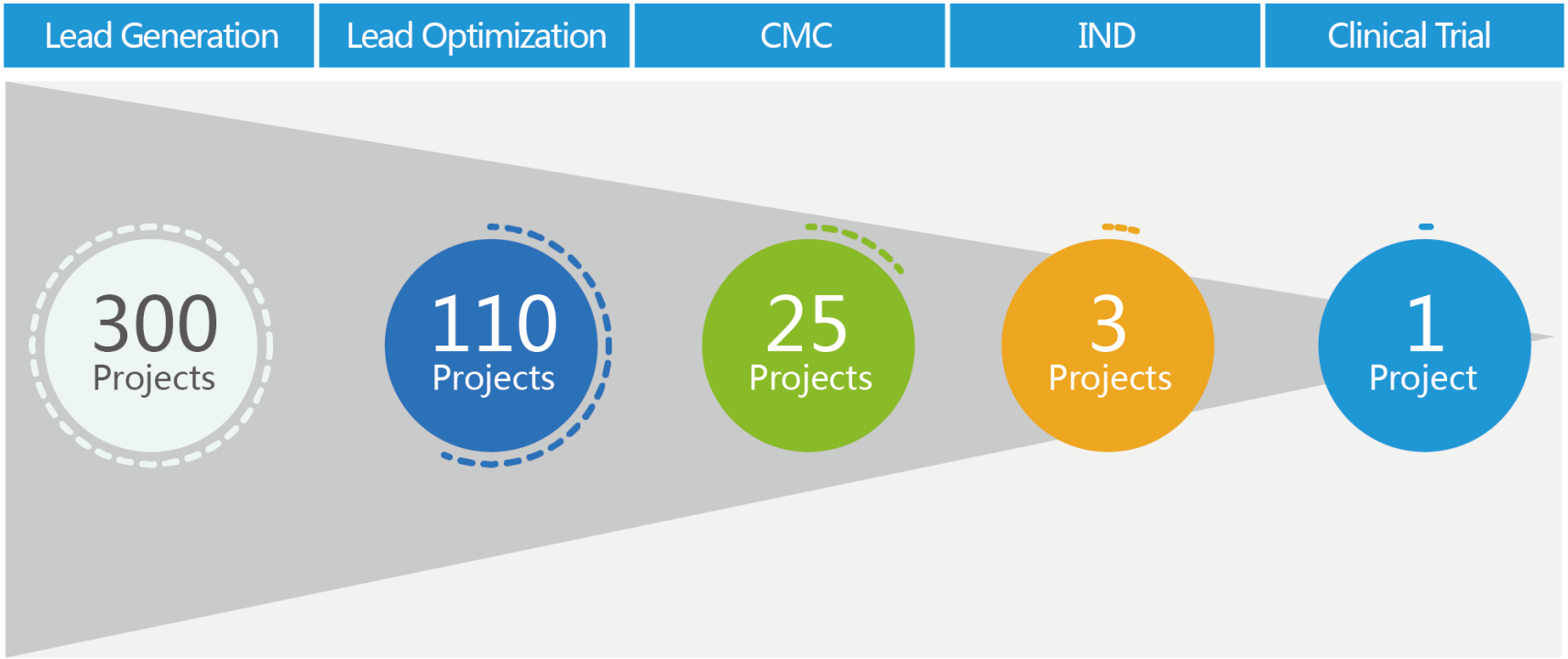
Lead Generation
- Antigen preparation
- Immunization
- Hybridoma/Phage display
- HTP screening
- Antibody production & characterization

Lead Optimization
- Humanization
- Affinity maturation
- Developability assessment
- Immunogenicity evaluation

Track Records

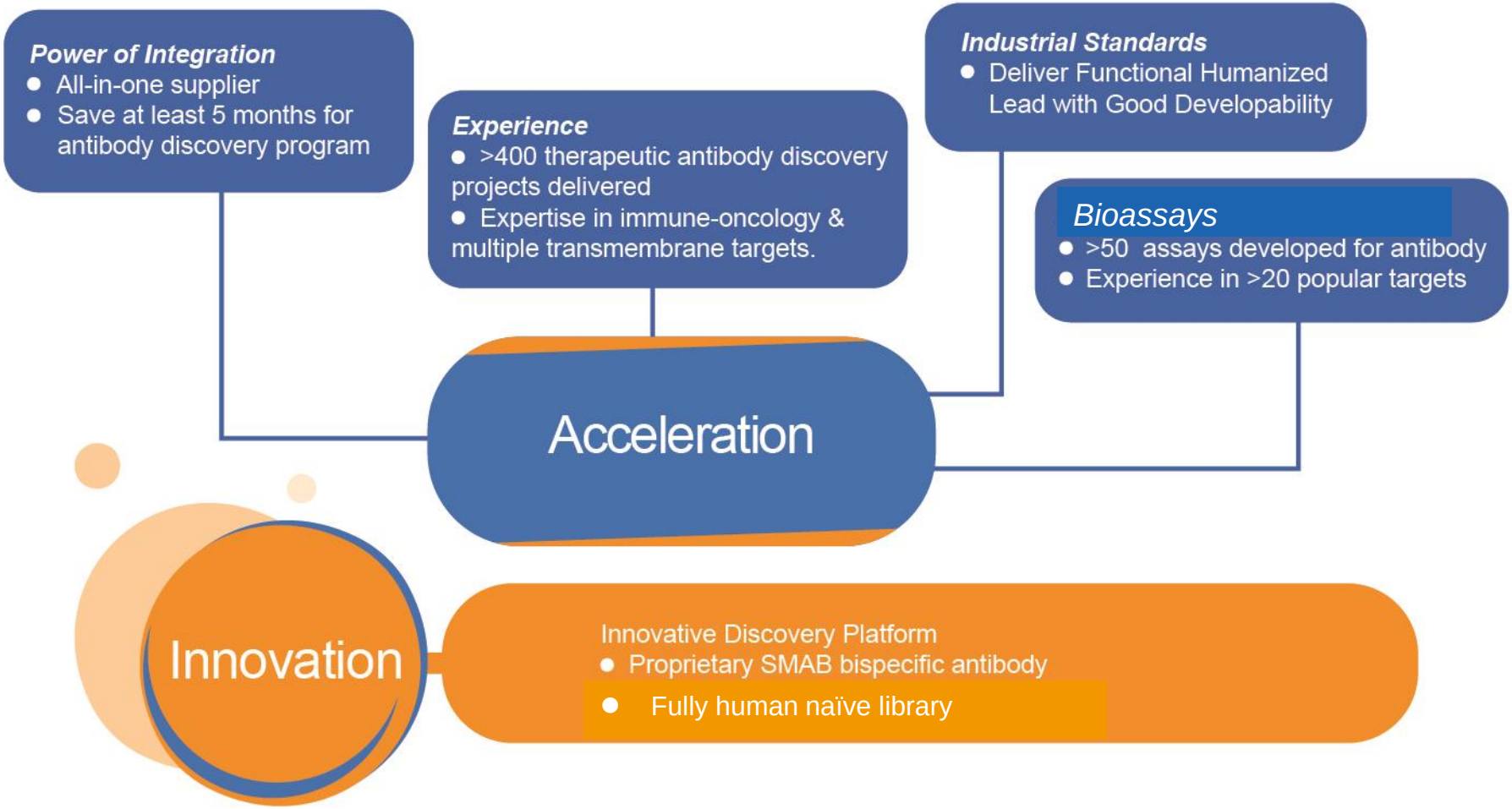
By Dec, 2017

- GenScript has delivered more than **300** antibody lead generation projects.
- GenScript has delivered **110** antibody lead optimization projects.
- GenScript has delivered **25** biologics CMC projects.
- **3** of them were moved forward to IND filing stage by end of 2017, with **1** approved for clinical trial

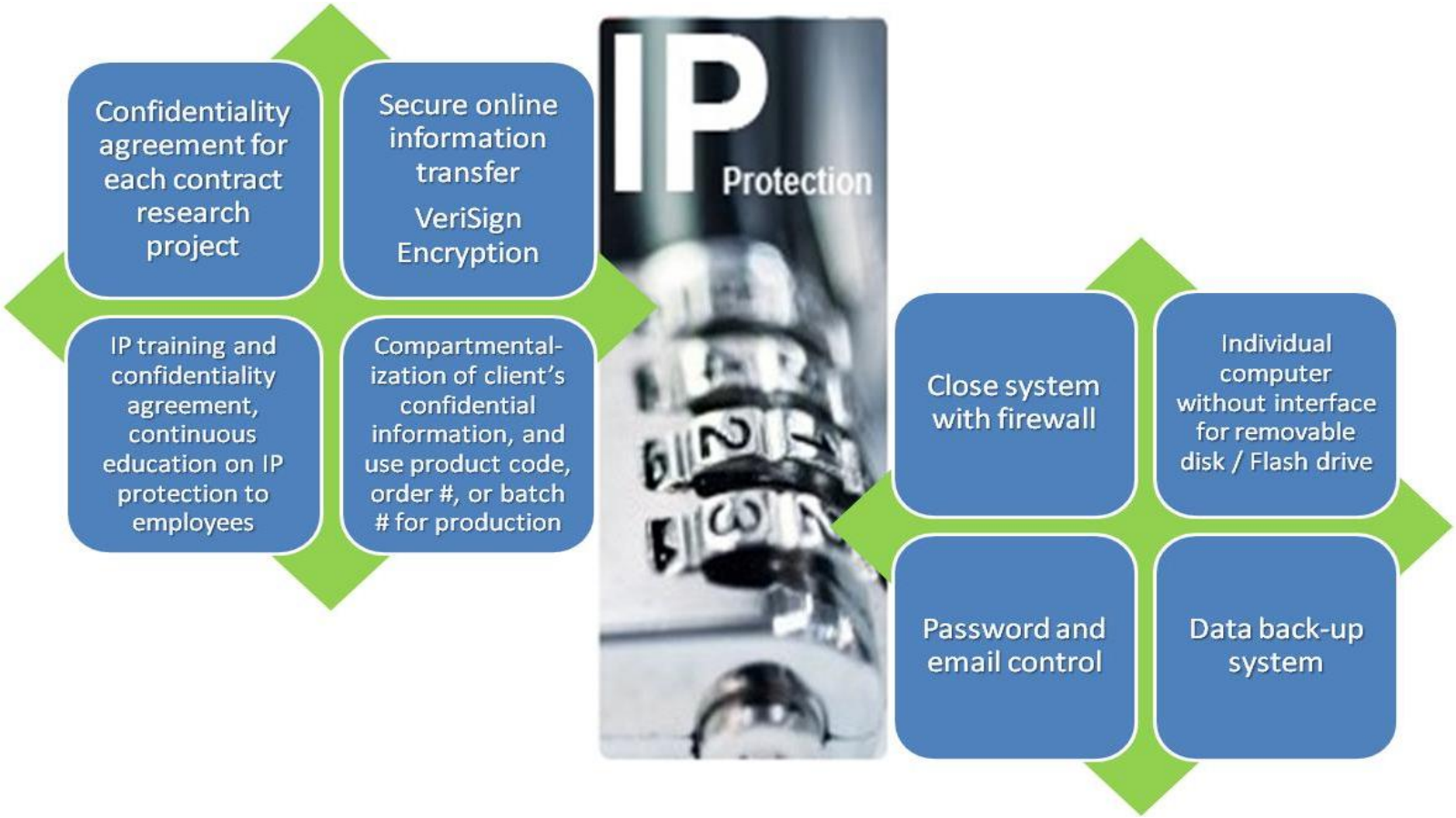


Accelerate Drug Discovery with Innovation

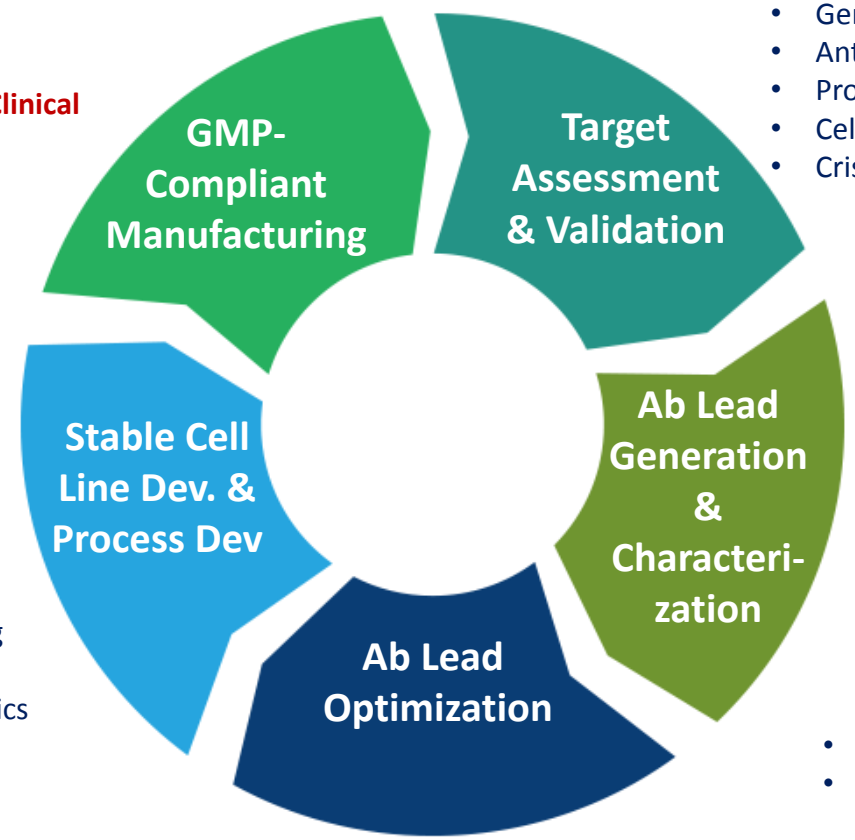
GenScript



IP Protection



One-Stop Solution from Target to IND



3 INDs & 1 in Clinical trial

- Gene & Peptide synthesis
- Antibody production
- Protein production
- Cell line engineering
- Crispr KO/KI engineering

- Hybridoma development
- Phage display
- Ab screening & characterization

300+ therapeutic antibody leads generation

- Stable cell line generation
- Process development
- Small- to mid-scale Production
- Research Cell Banking (RCB)
- Bioanalytics & Analytics

25+ cell line & process development projects delivered

- Humanization
- Developability assessment & optimization
- Affinity maturation

110+ humanization projects delivered

GenScript
Make Research Easy

Thank you!

Expertise, Flexibility, Solutions