

Bispecific Antibody: The Next Generation Therapeutics



GenScript
July, 2018

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Overview of Antibody Therapeutics



Bispecific Antibody



SMAB Case Study



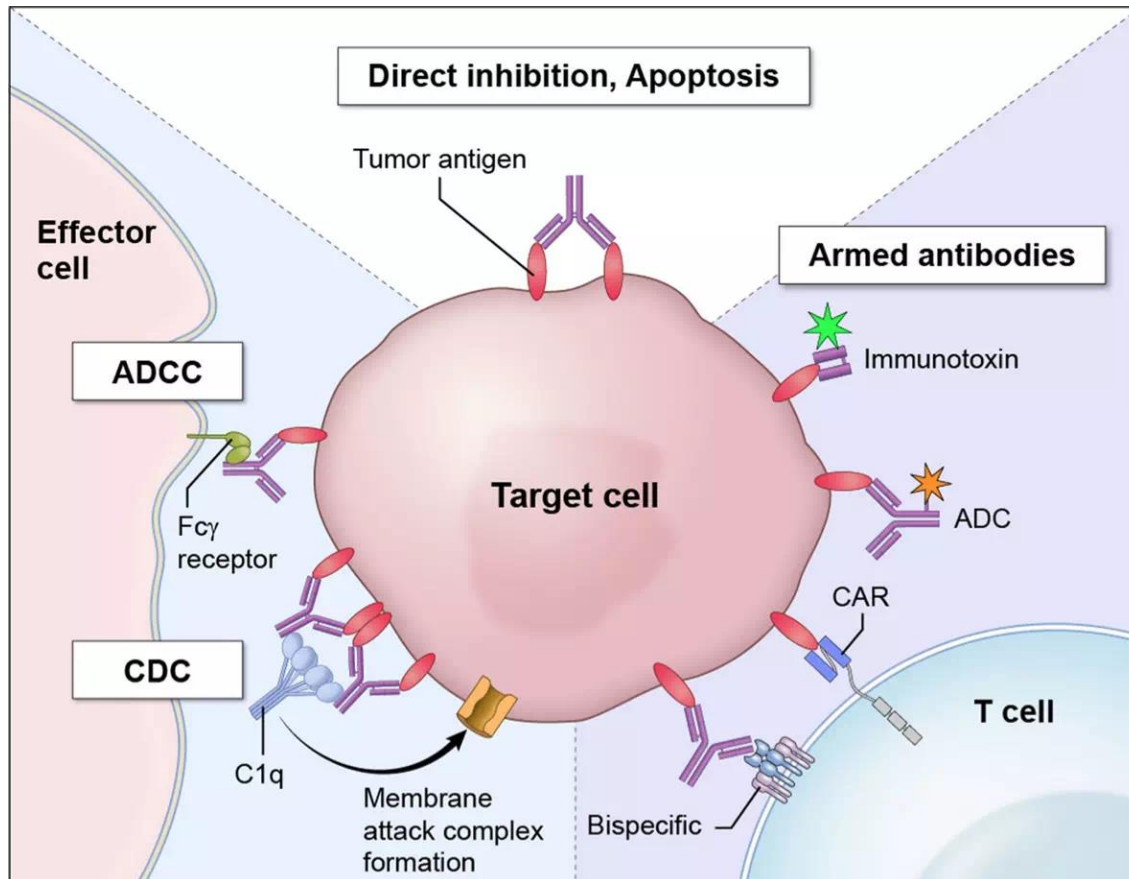
Summary



About GenScript

Overview of Antibody Therapeutics





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



DUPIXENT™
(dupilumab)



KYMRIAH™
(tisagenlecleucel) Suspension for IV infusion



HEMLIBRA™
emicizumab-kxwh | ISO
injection for subcutaneous use

Novel, First-in-Class Mechanisms
2017 FDA Approvals
As of Dec 1, 2017



IDHIFA®
(enasidenib) tablets
100mg • 50mg



Mepsevii™
(vestronidase alfa-vjbk)
injection, for intravenous use



Brineura™
(cerliponase alfa)



PREVYMIS™
(letermovir)
240 mg, 480 mg tablets
injection 20 mg/mL



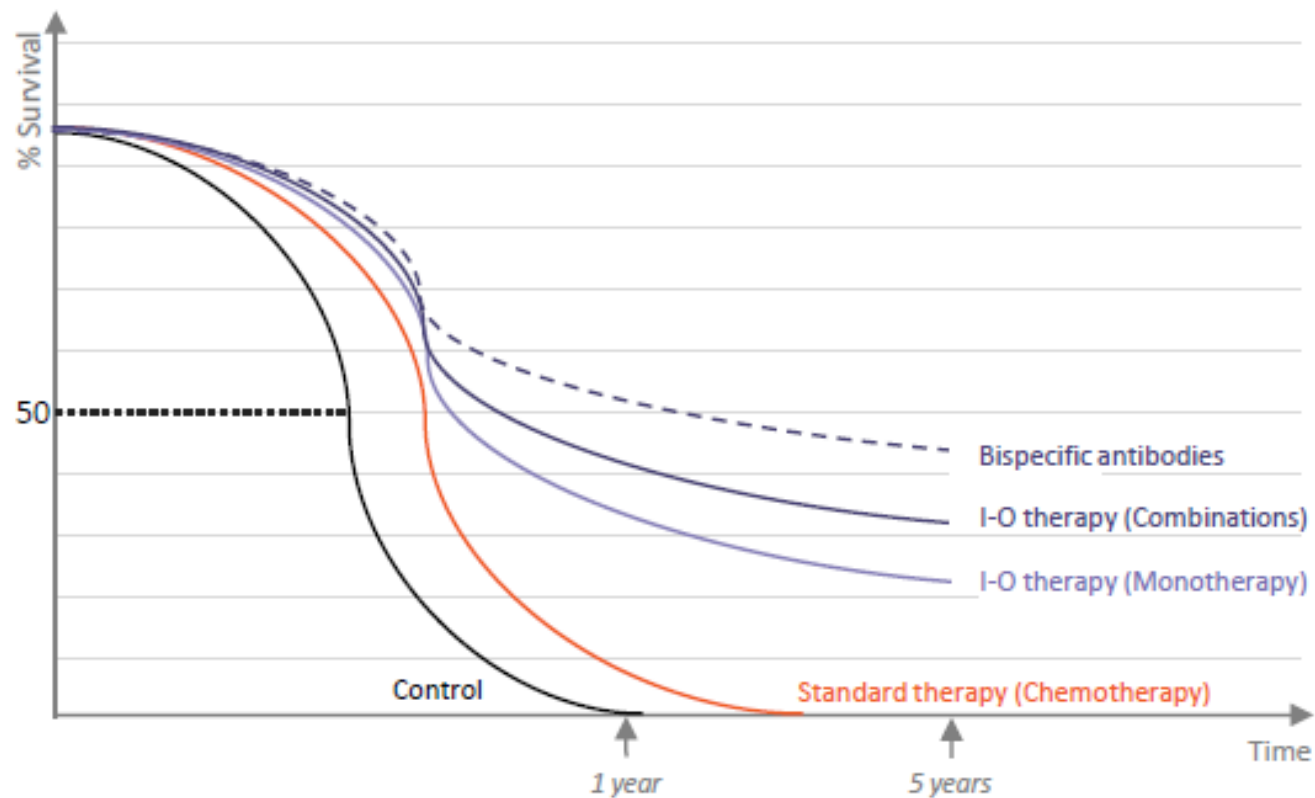
XERMELO®
(telotristat ethyl) tablets, 250 mg

Enzyme

Antibody

CAR-T

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



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 3/4 adverse effects with combination treatment

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**

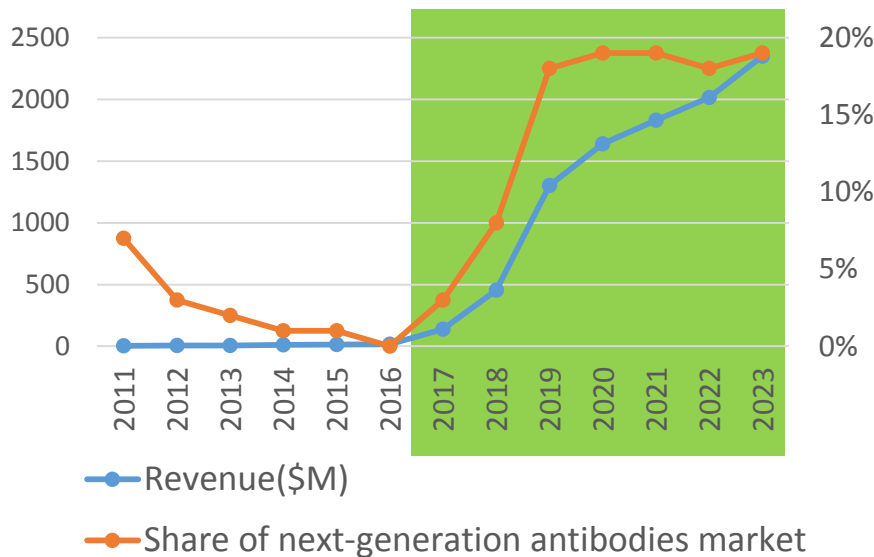
- Low off-target binding may reduce side effects

Controlling **Price**

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

Impressive bsAb Market

Bispecific Antibody 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
 - Blinatumomab: CD3+CD19
 - Emicizumab: factor IX+ factor X

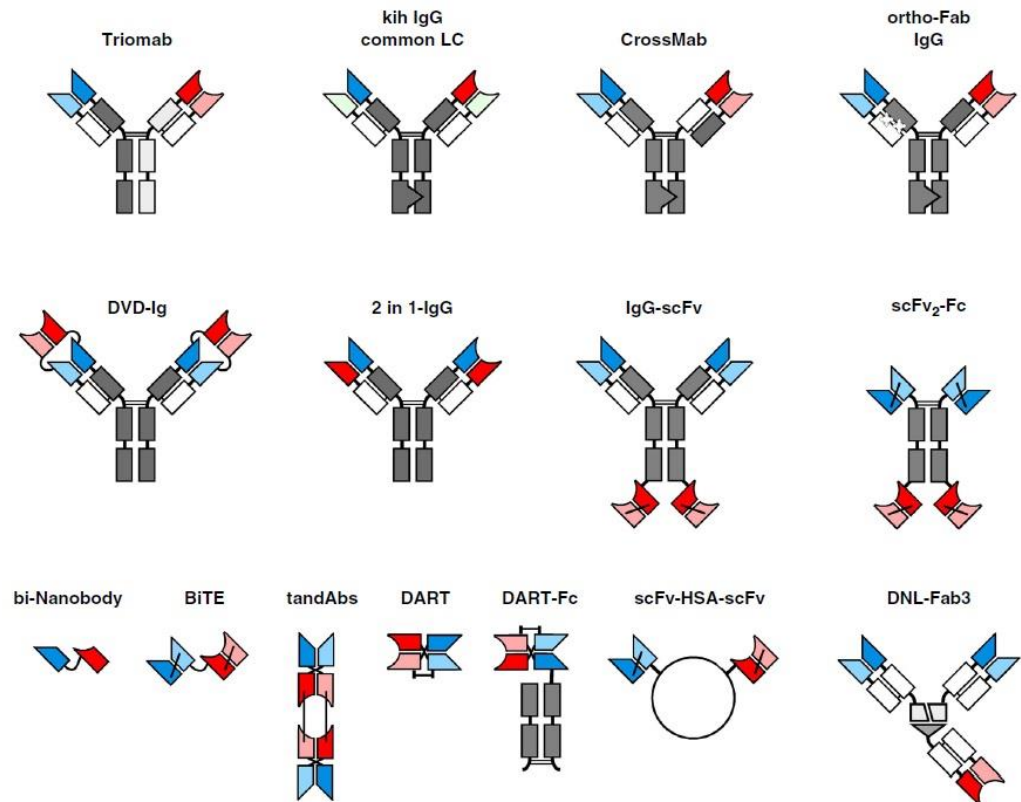
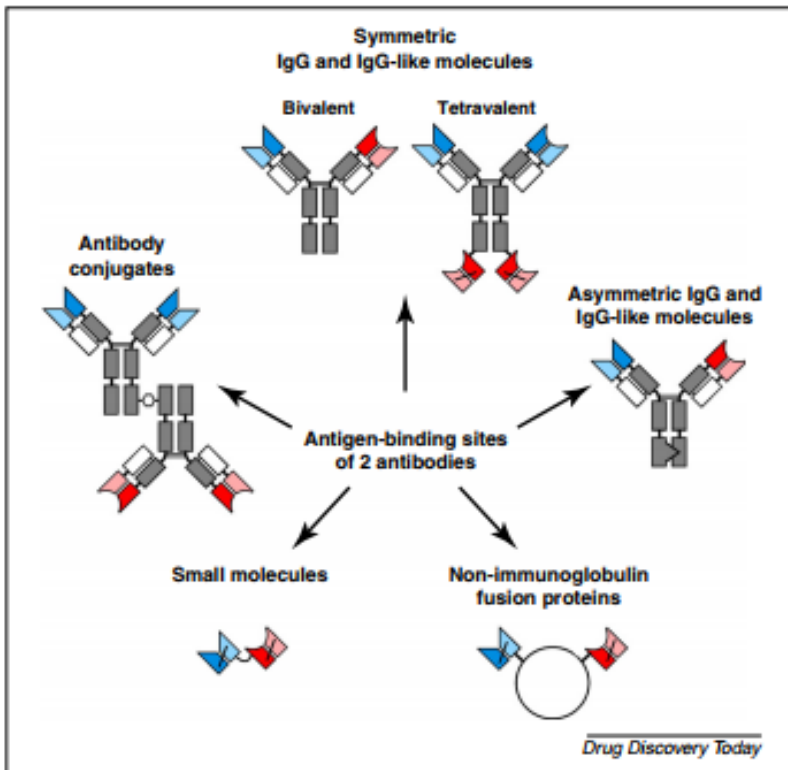
Target Combination & MOA of bsAb

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	/

Bispecific Antibody Platforms



Strategies of Constructing bsAb

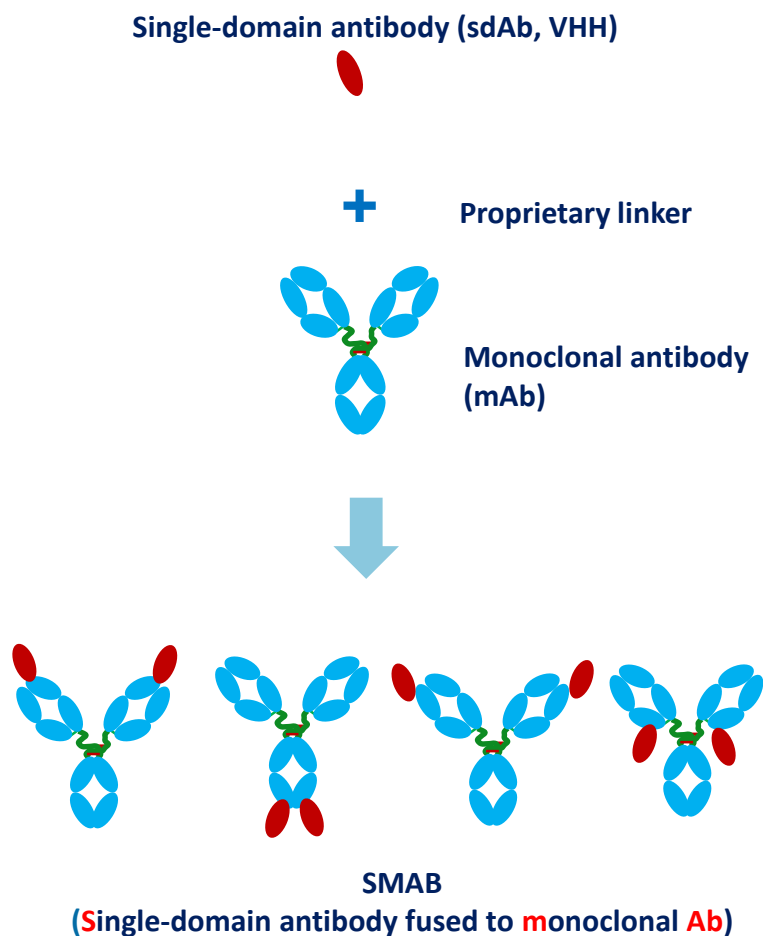


Immunogenicity

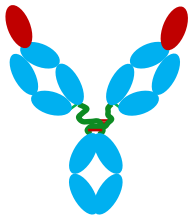
- Unnatural format

Manufacture problems

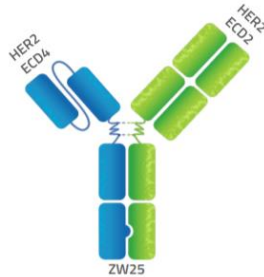
- Product instability
- Low expression level
- Complex purification process



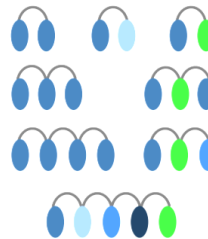
- **Symmetric structure without Fc engineering** (2 chains, intracellular assembly, no mismatch)
- **Single-step processing to yield pure product** (Protein A purification)
- **Developability comparable to conventional mAbs**
- **High yield** (same as mAb, gram level in cell line dev.)
- **High concentration 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



GenScript SMAB



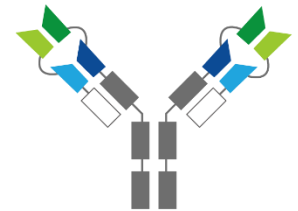
Zymeworks
Asymmetric bispecific Ab



Ablynx
Nanobody



GenMab
Duobody

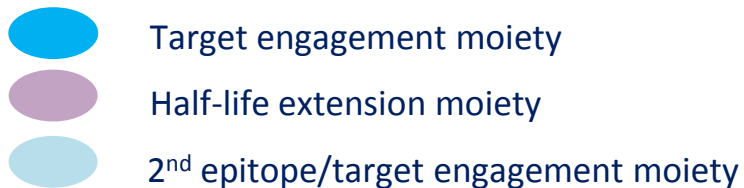
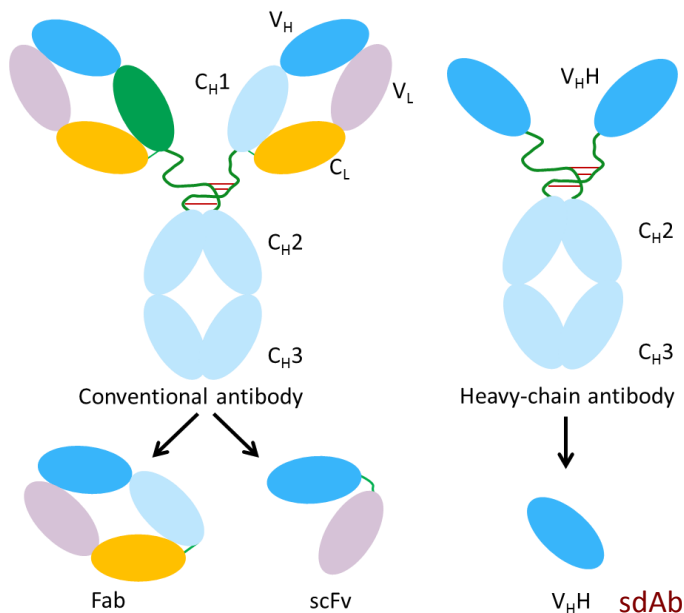


Abbvie
DVD-Ig

SMAB

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

Why sdAbs?



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

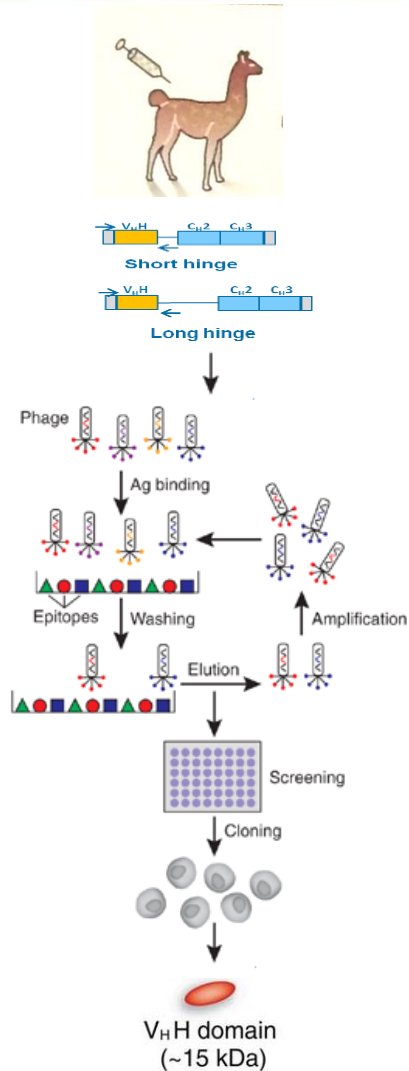
- Expressible in yeast or microbial systems
- Economy in production

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

Hybridoma technology

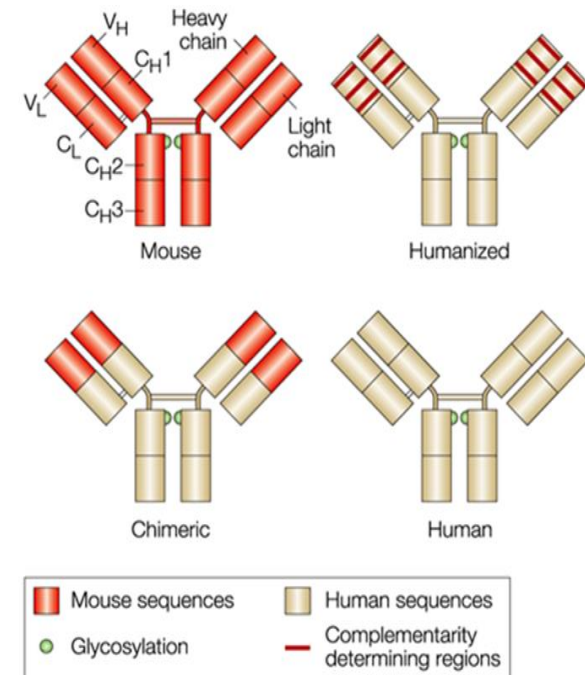
- Hybridoma with human transgenic mice/rats
>>>> **Human antibody** (*Medarex, Abgenix, Regeneron, OMT, Kymab, Trianni, Harbour*)
- Hybridoma with B-cells from immunized human body
>>>> *Human antibody*
- Hybridoma with rodent system
>>>> **Humanized antibody**

Library technology

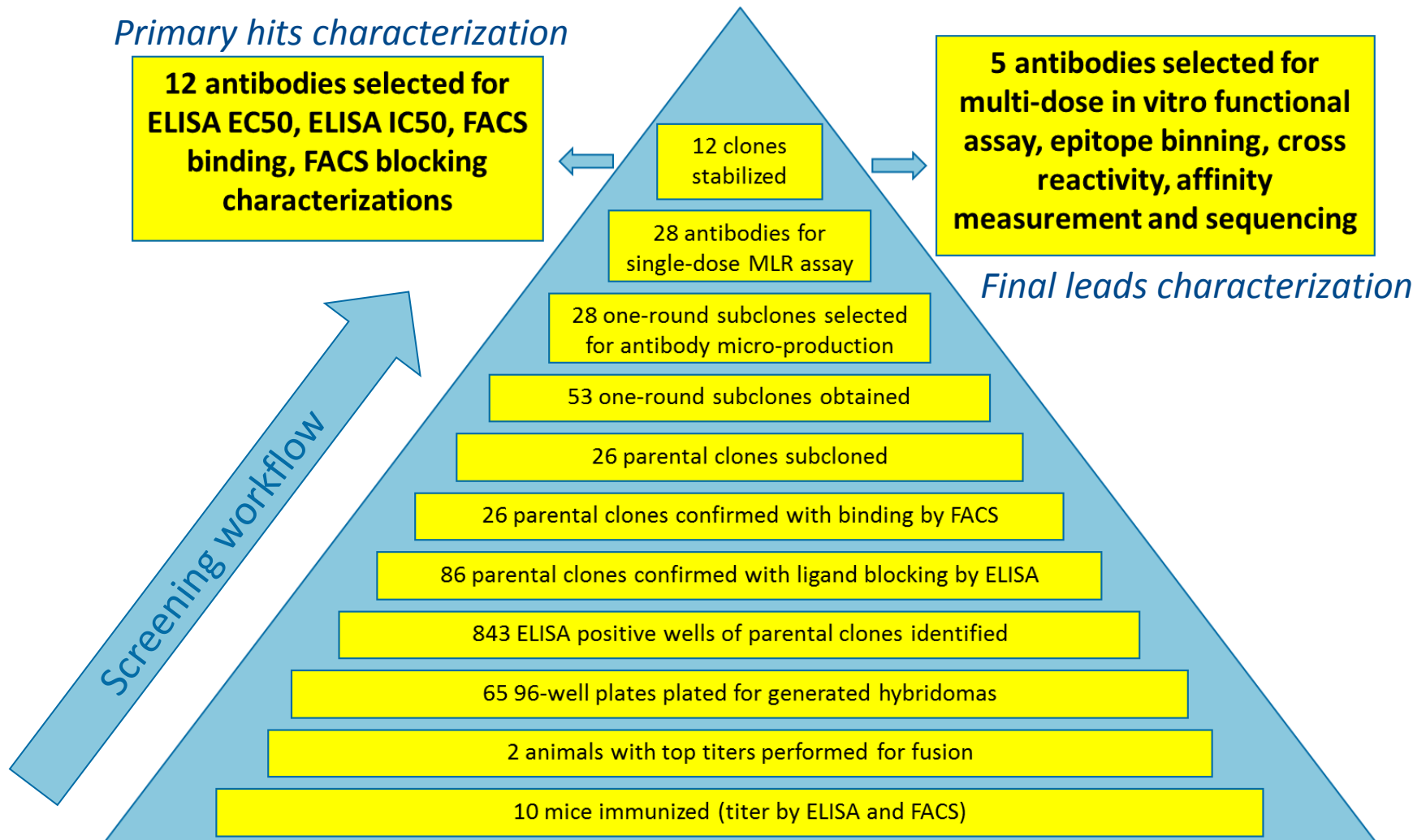
- Phage / Yeast / Ribosome display**
>>>> **Human/Humanized antibody**

Other technologies (single B cell)

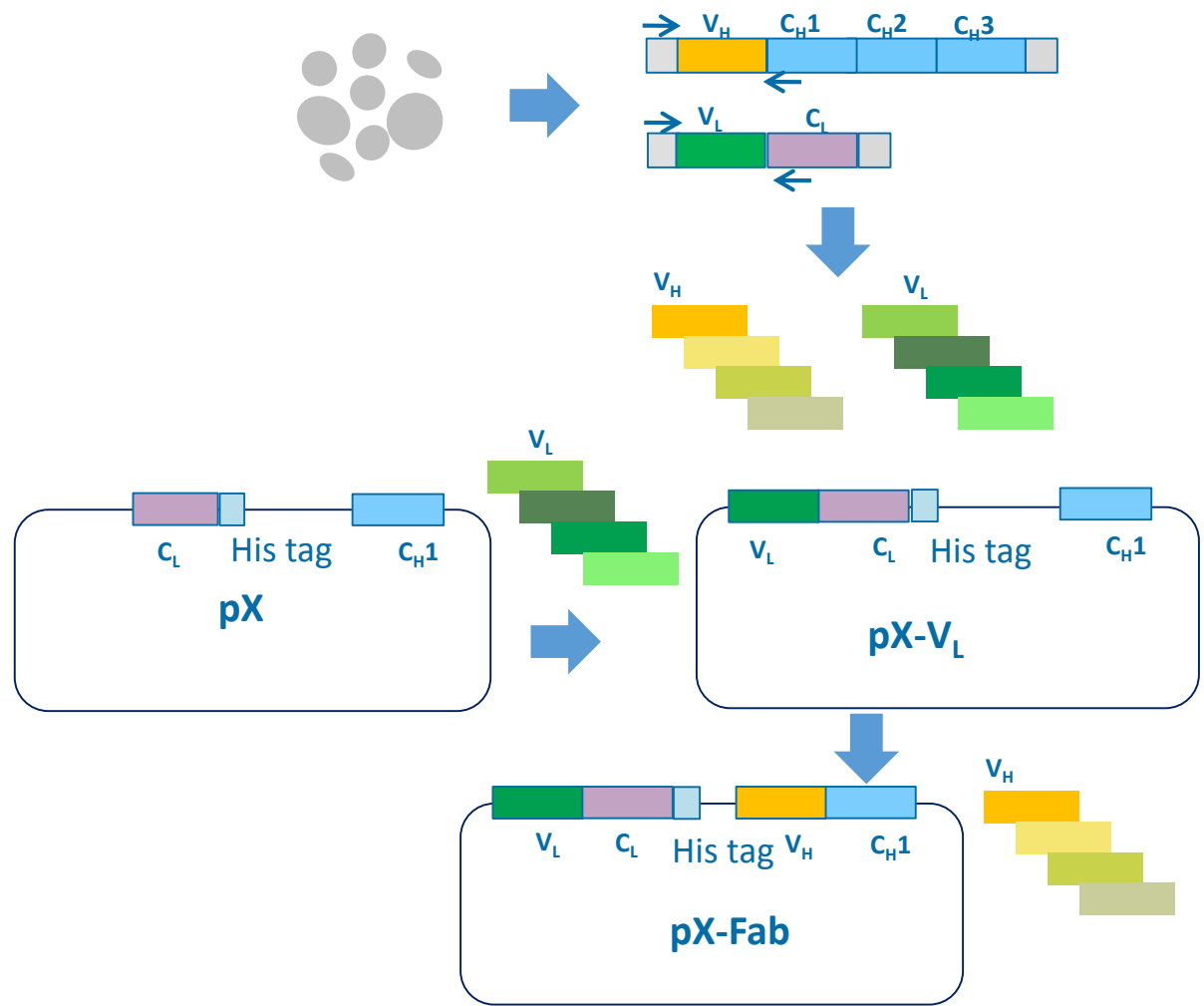
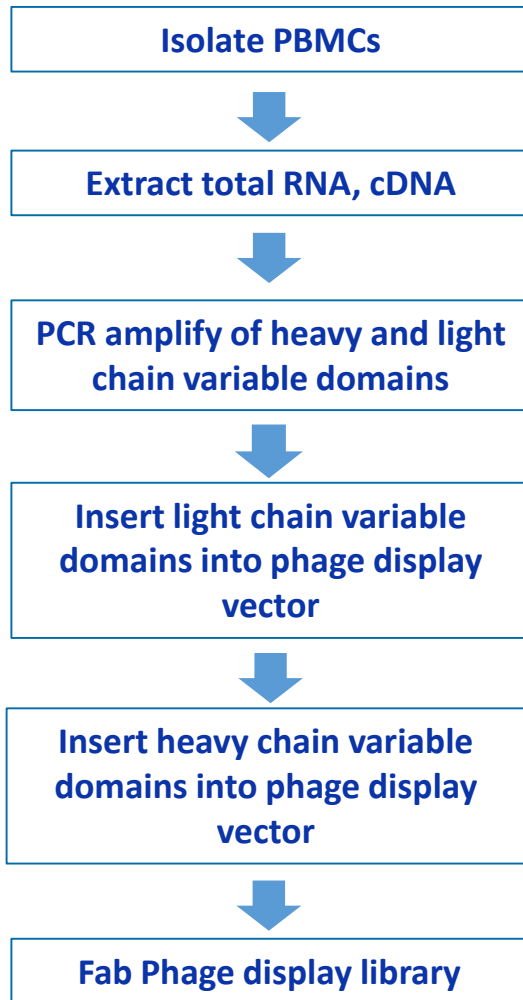
- SLAM technology
>>>> *Humanized antibody*
- Next generation antibody sequencing
>>>> *Human/Humanized antibody*



Nature Reviews | Cancer



Fully Human Naïve Fab Library



Comparison of Ab Lead Generation Technologies

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

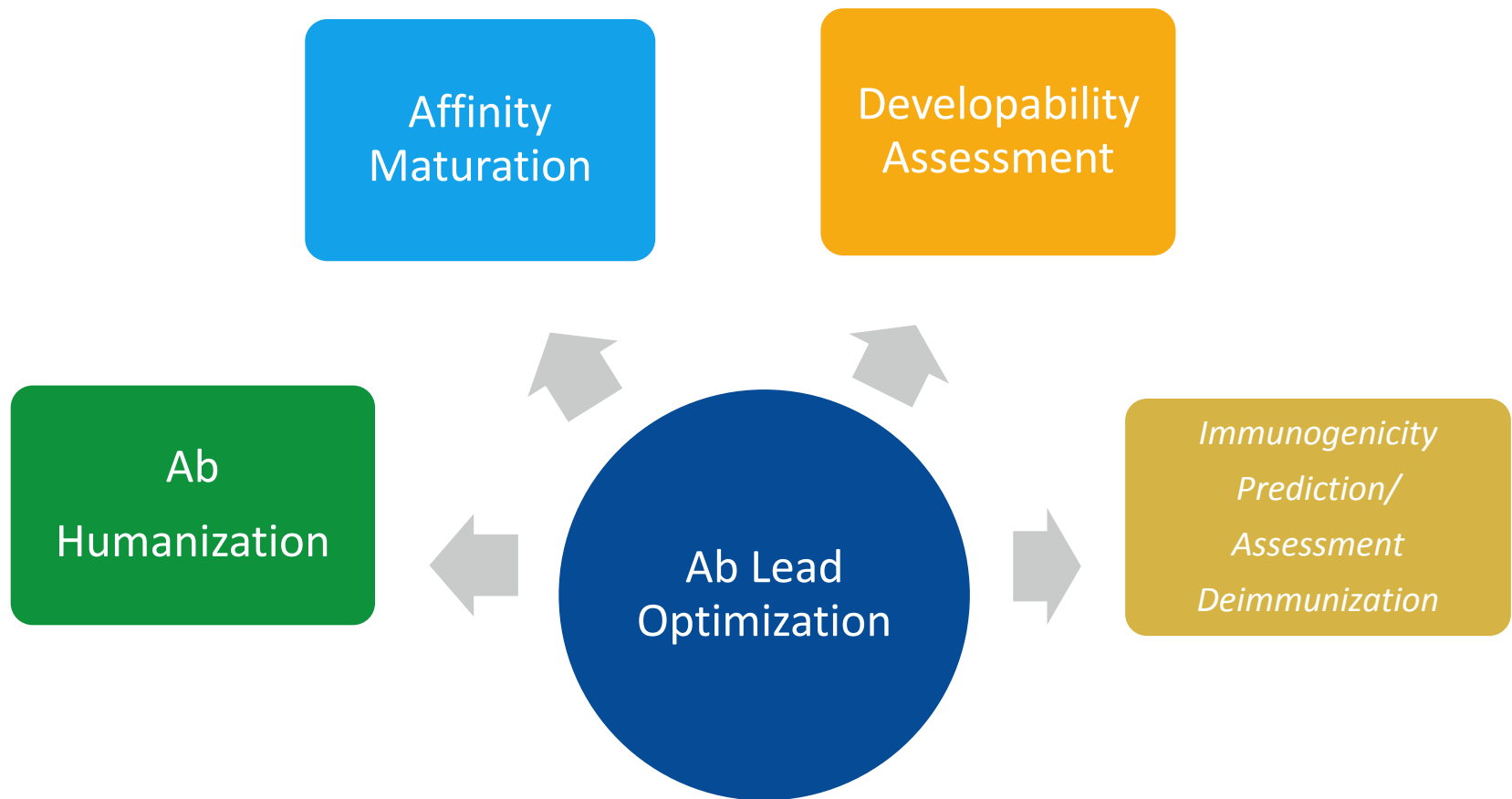
- Pros
 - Fast
 - Large library
 - No immune tolerance issue
- Cons
 - Developability issue
 - Specificity issue
 - Difficult to apply to certain targets(e.g. GPCR, ion channel)
 - Usually need affinity maturation

B cell cloning

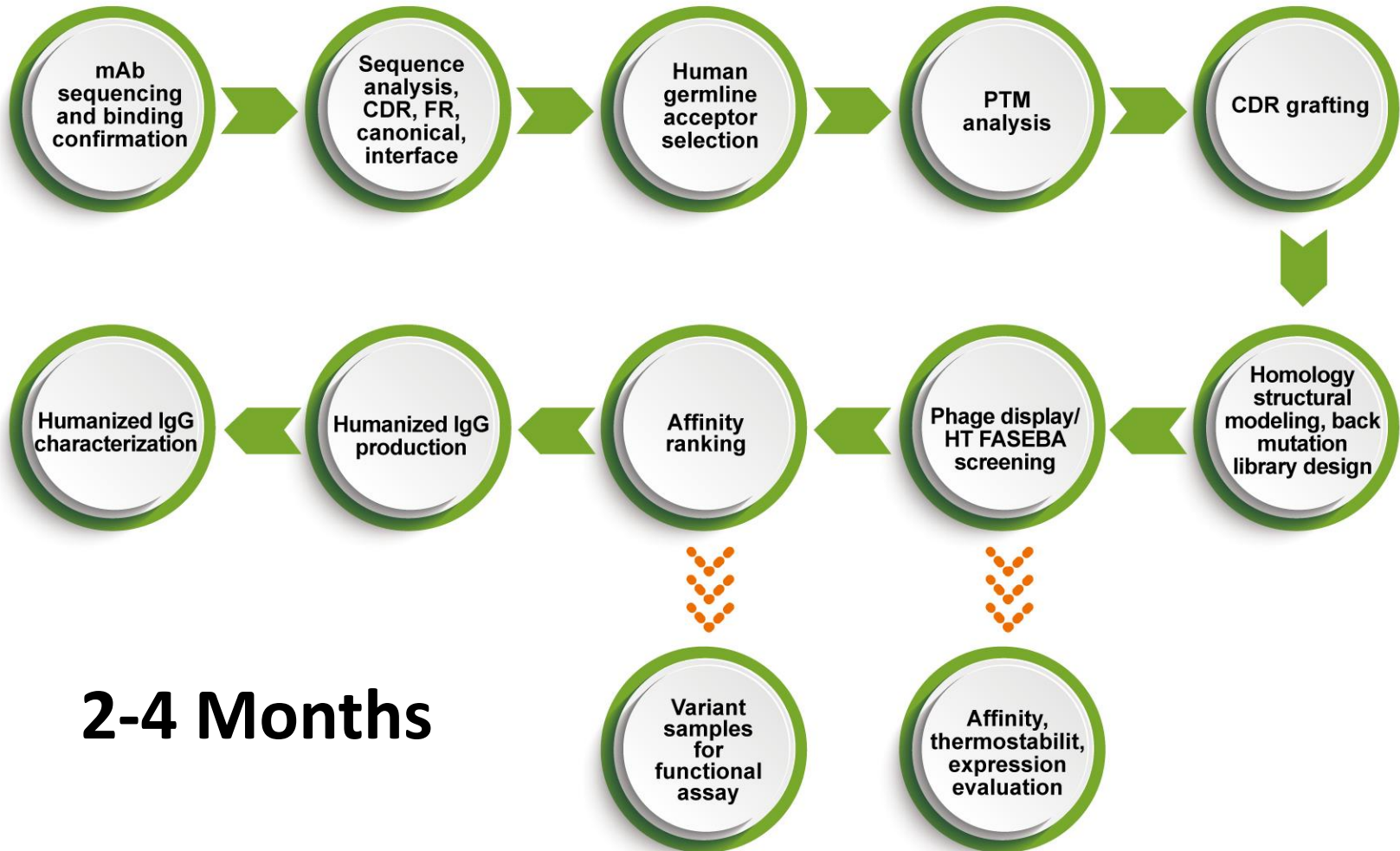
- Pros
 - Fully human
 - Natural occurring
- Cons
 - Limited to infectious diseases
 - Application to other disease area is uncertain
 - Difficult to identify target

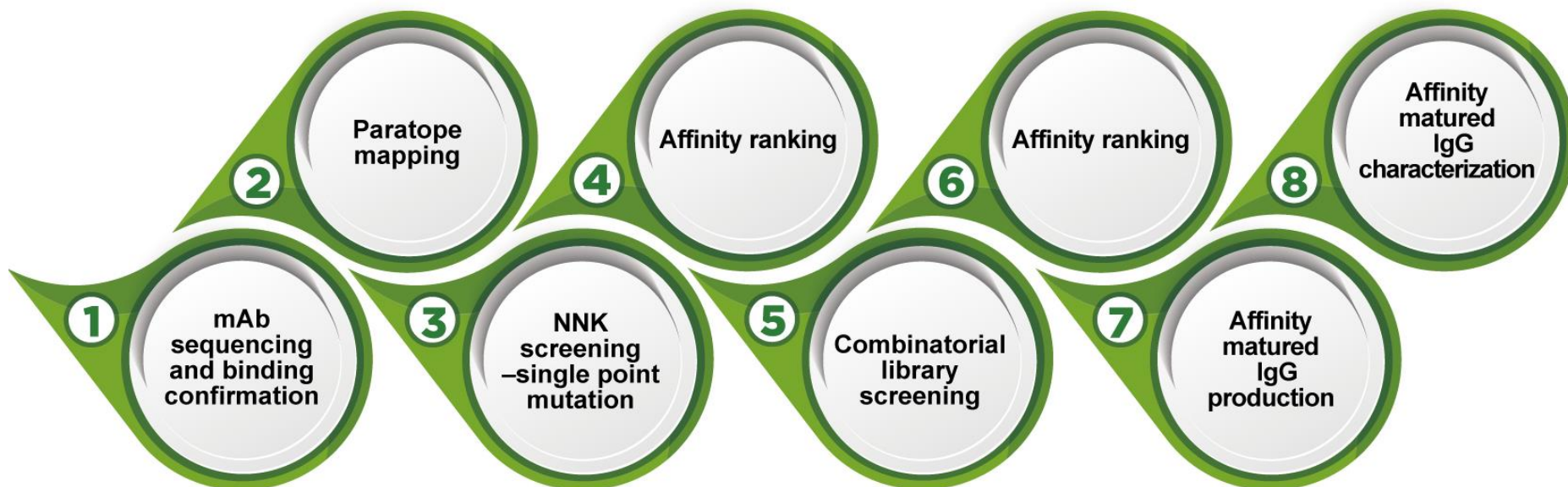
Ab Lead Optimization





Antibody Humanization

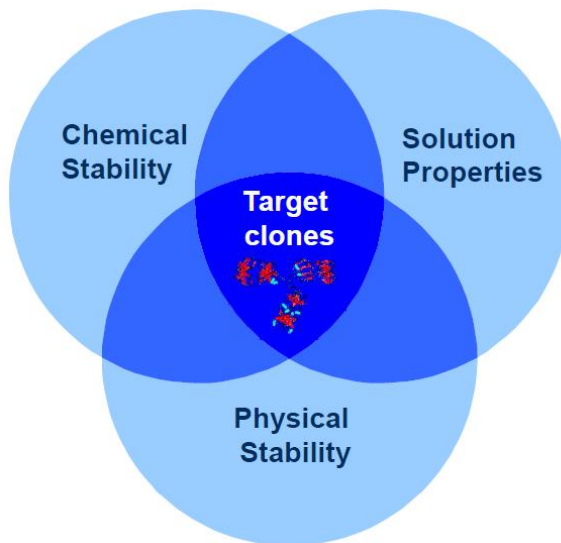
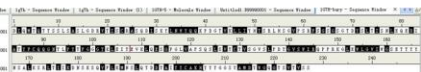
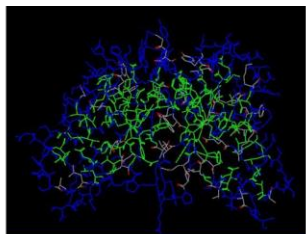




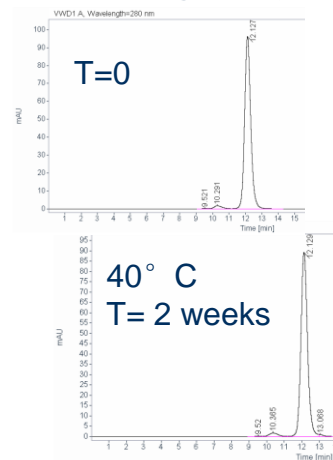
4-5 Months

Developability Assessment---Tools

In Silico homology modeling



Size Exclusion Chromatography (SEC)



Agilent HPLC/UHPLC
1200/1260/1290

Peptide mapping and LC-MS analysis



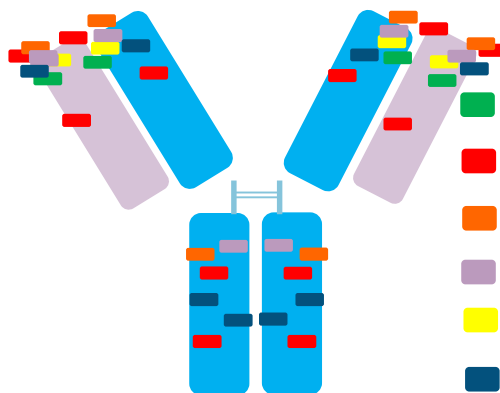
SCIEX TripleTOF™ 4600

CE-SDS



Sciex P/ACE™ MDQ Plus

Potential PTMs in antibody

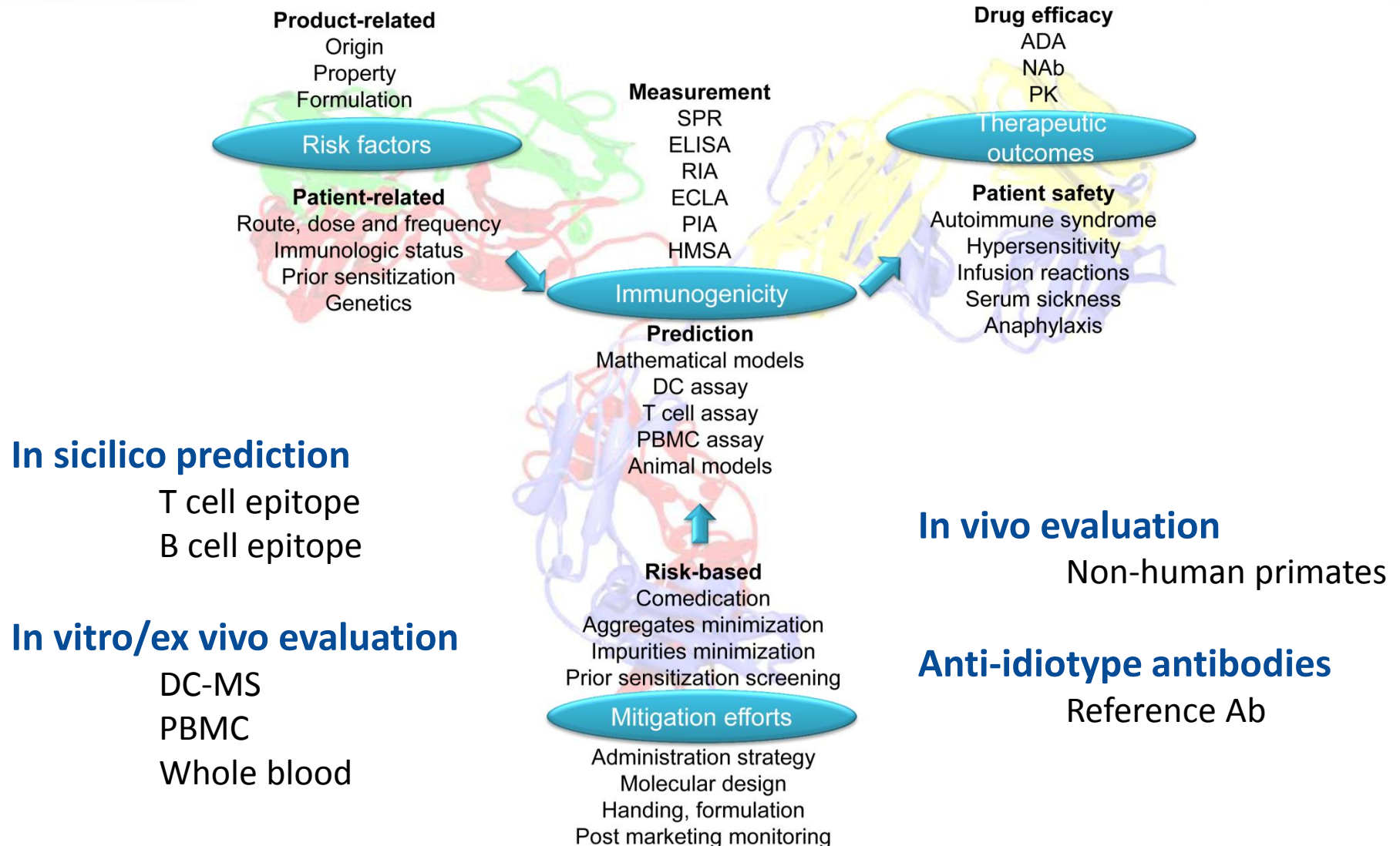


- Fragmentation
- Deamidation
- Isomerization
- N-Glycosylation
- Free-thiol
- Oxidation

SPR capture assay



Biacore T200/8K



Strategies of Constructing bsAb

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

SMAB

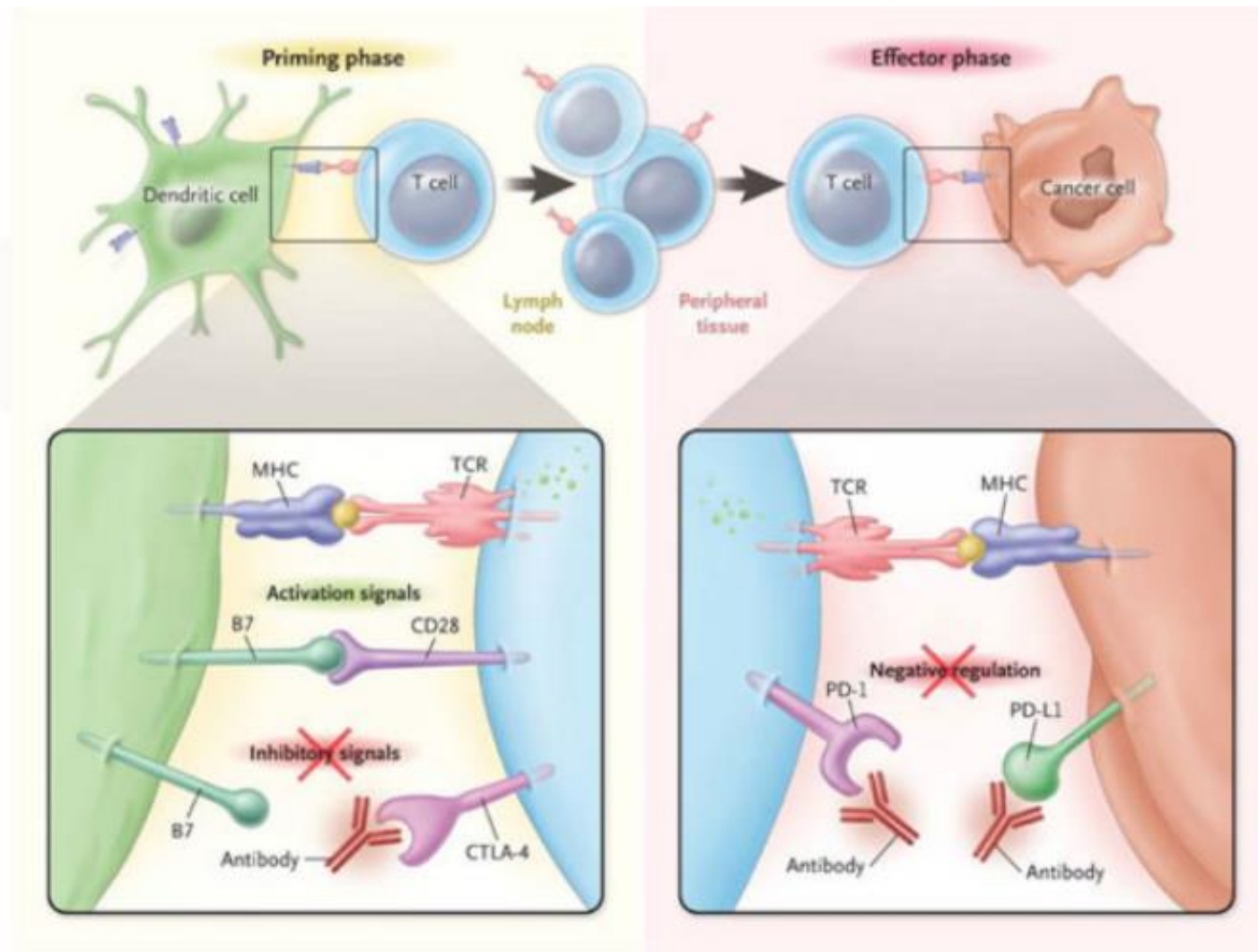
- Single Domain antibody fused to monoclonal antibody
- “Being Natural”: Good Developability & Safety

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

SMAB Case Study

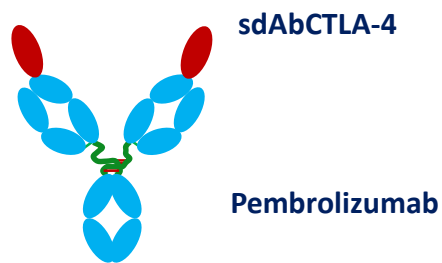


MOA of PD1+CTLA-4



Case Study:

PC101 (mAbPD-1 X sdAbCTLA-4)



PC101
hulgG4Pro (S228P)

Sample	K _D (nM)*	
	human PD-1-EC-His	human CTLA-4-EC-His
Pembrolizumab	4.7	/
sdAbCTLA-4-Fc**	/	4.5

*Determined by SPR

**Cross-reacts with cynomolgus CTLA-4

In vitro properties of PC101

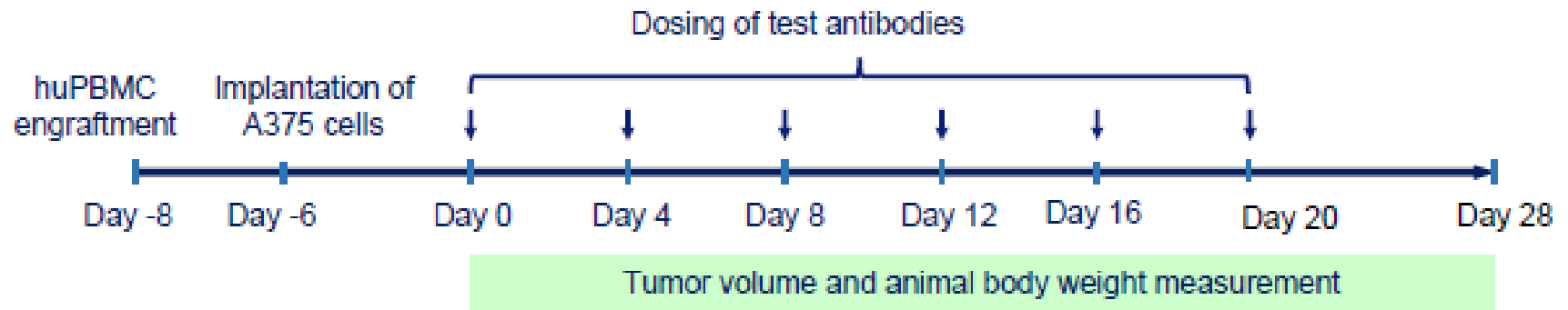
		PC101	mAbPD-1(γ4)	sdAbCTLA4(γ4)
Affinity(nM)	Human PD-1	2.5	4.7	/
	Human CTLA-4	2.6	/	4.5
Cell binding EC ₅₀ (nM)	Human PD-1	1.0	0.78	/
	Human CTLA-4	5.8	/	6.8
Ligand competition IC ₅₀ (nM)	Human PD-1	0.58	0.41	/
	Human CTLA-4	13.3	/	6.3
Functional assay EC ₅₀ (nM)	Human PD-1	2.2	1.59	/
	Human CTLA-4	10.8	/	14.1

Developability Parameters	Value
Transient expression in CHO cells	> 50 mg/L
Purity (one-step protein A)	94.02% (by HPLC)
Thermostability (T _m , melting point)	70.8 °C (by DSC)
Aggregation onset temperature	70.0 °C
Solubility	> 200 mg/ml
Tissue cross-reactivity *	Negative
Non-specific binding**	Negative
Stability	> 93.3% monomer after 5-time freeze-thaw

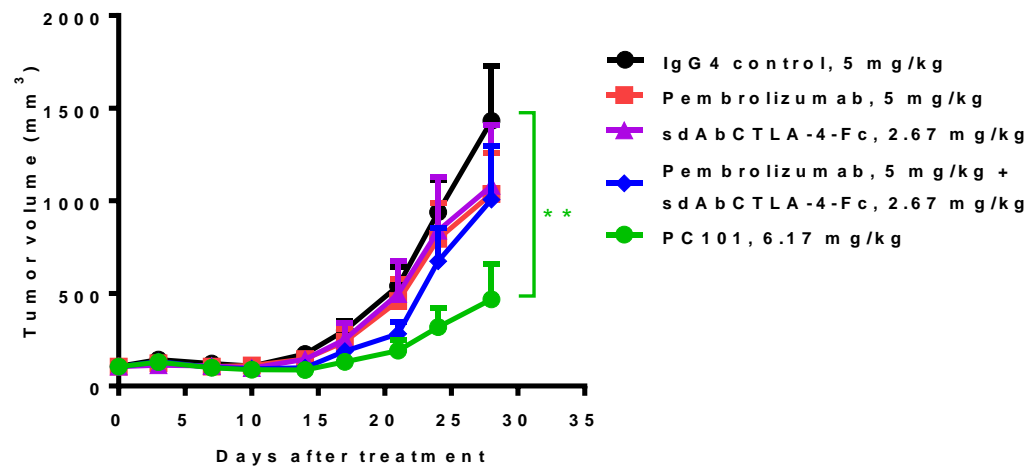
* Frozen tissues: lymph nodes, thyroid (adj.), gallbladder, appendix, and great saphenous vein

** Cells: HEK 293T

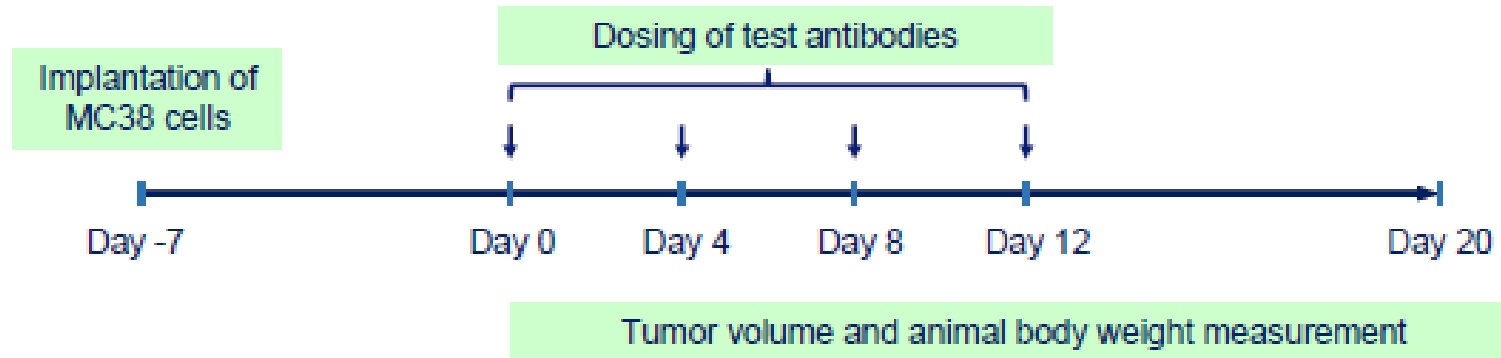
Synergistic *in vivo* activity of PC101



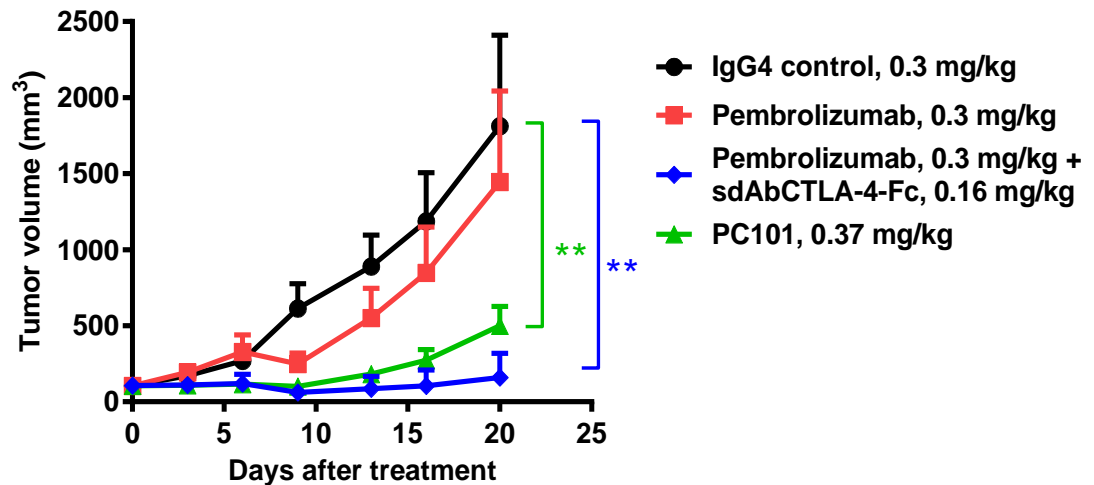
**Activity of PC101
in A375
melanoma model
with huPBMC
engraftment**



Synergistic *in vivo* activity of PC101-cont'd GenScript



Activity of PC101 in MC38 syngeneic tumor model with hPD-1 and hCTLA-4 double knock-in mice



- PC101 SMAB was determined to retain the *in vitro* potency of parental monoclonal and single-domain antibodies
- Results of preliminary developability assessment supports PC101 as a candidate for development
- PC101 was demonstrated with *in vivo* efficacy superior to the monotherapy, and equal or better efficacy compared with combo therapy

Summary of bsAb



- **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

A Bispecific/Multi-Valent & Open-Access Platform

Biosuperiority over monotherapy or combination treatment with novel MOA

“Being Natural”: Good Developability & Low Immunogenicity

About GenScript



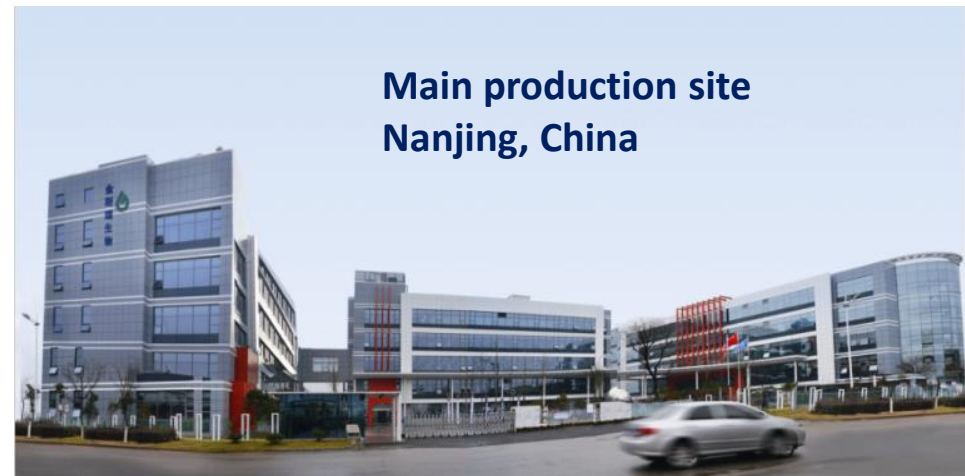
GenScript, A Global Bio-CRO



**Global headquarters
Piscataway, New Jersey, USA**

- 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**

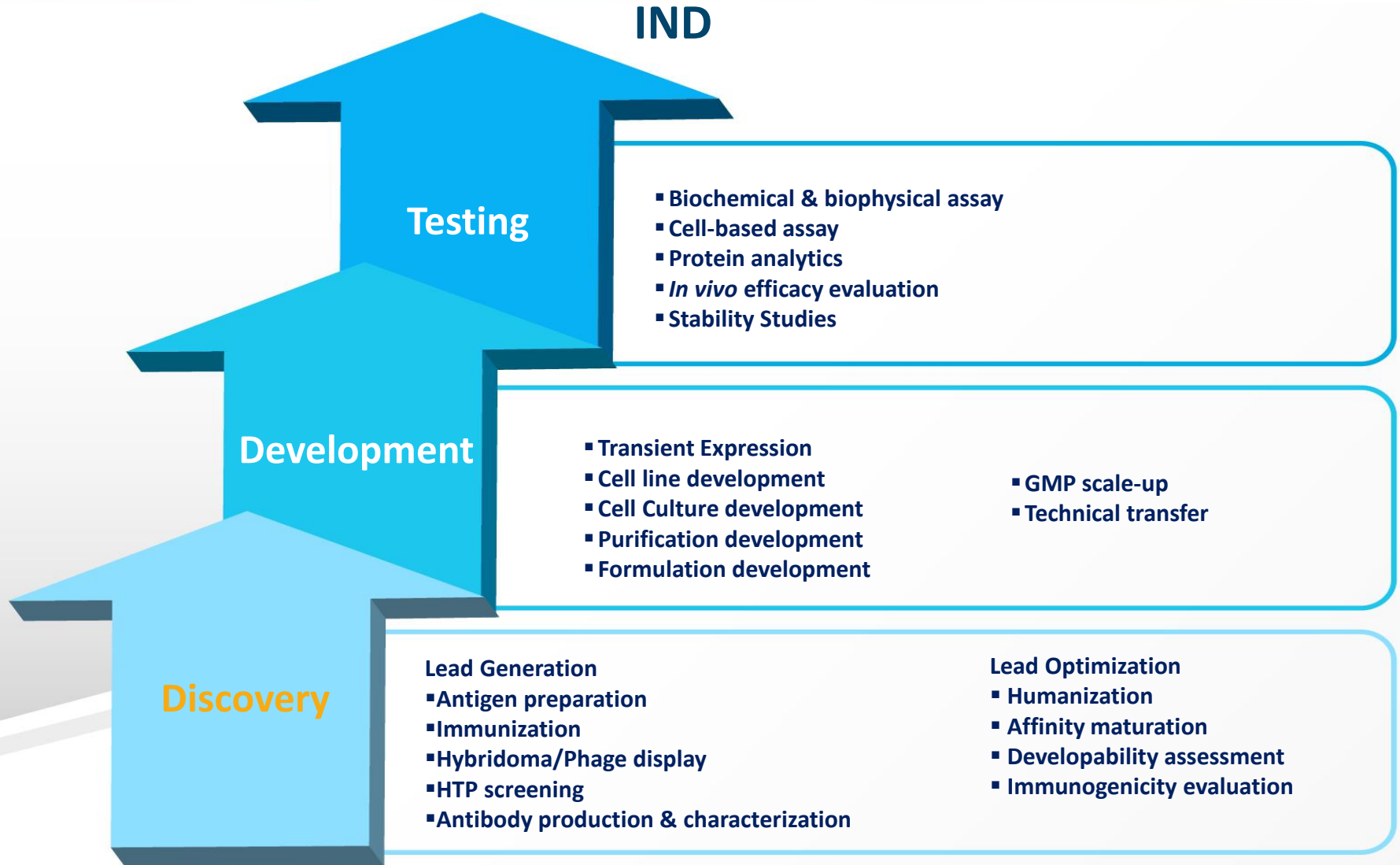
- **Local technical support**
- 24-hour customer service
- Fast global logistics
- Competitive pricing
- Stringent IP protection



**Main production site
Nanjing, China**

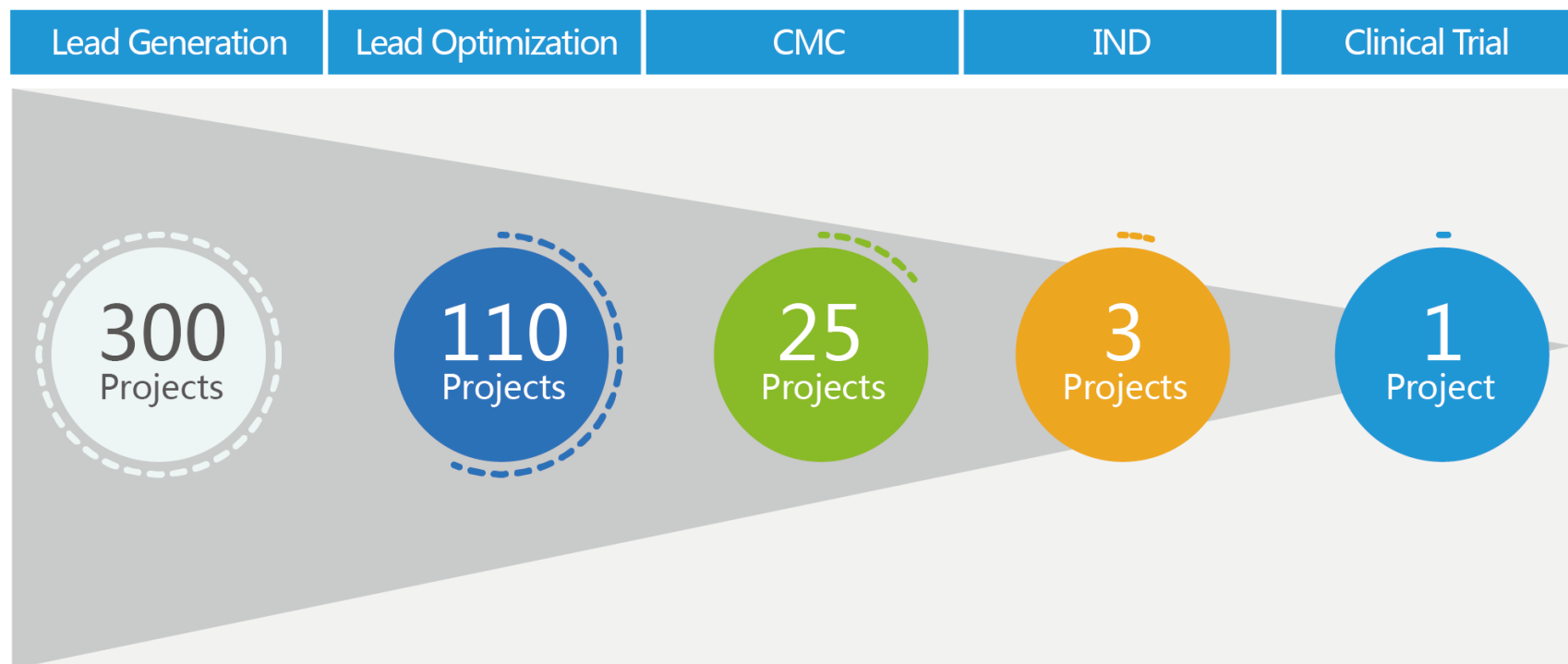


Your Partner from Target to IND

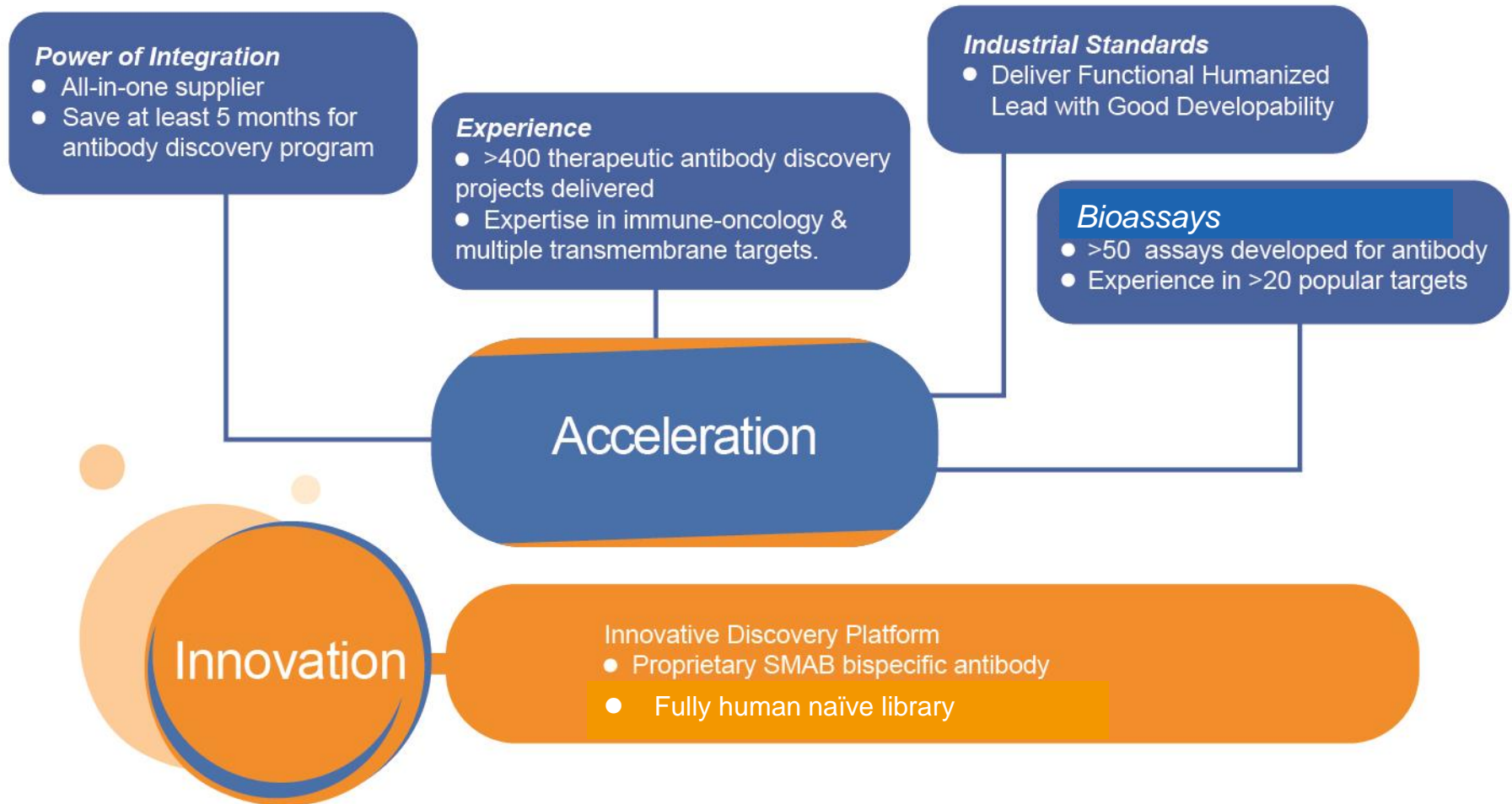


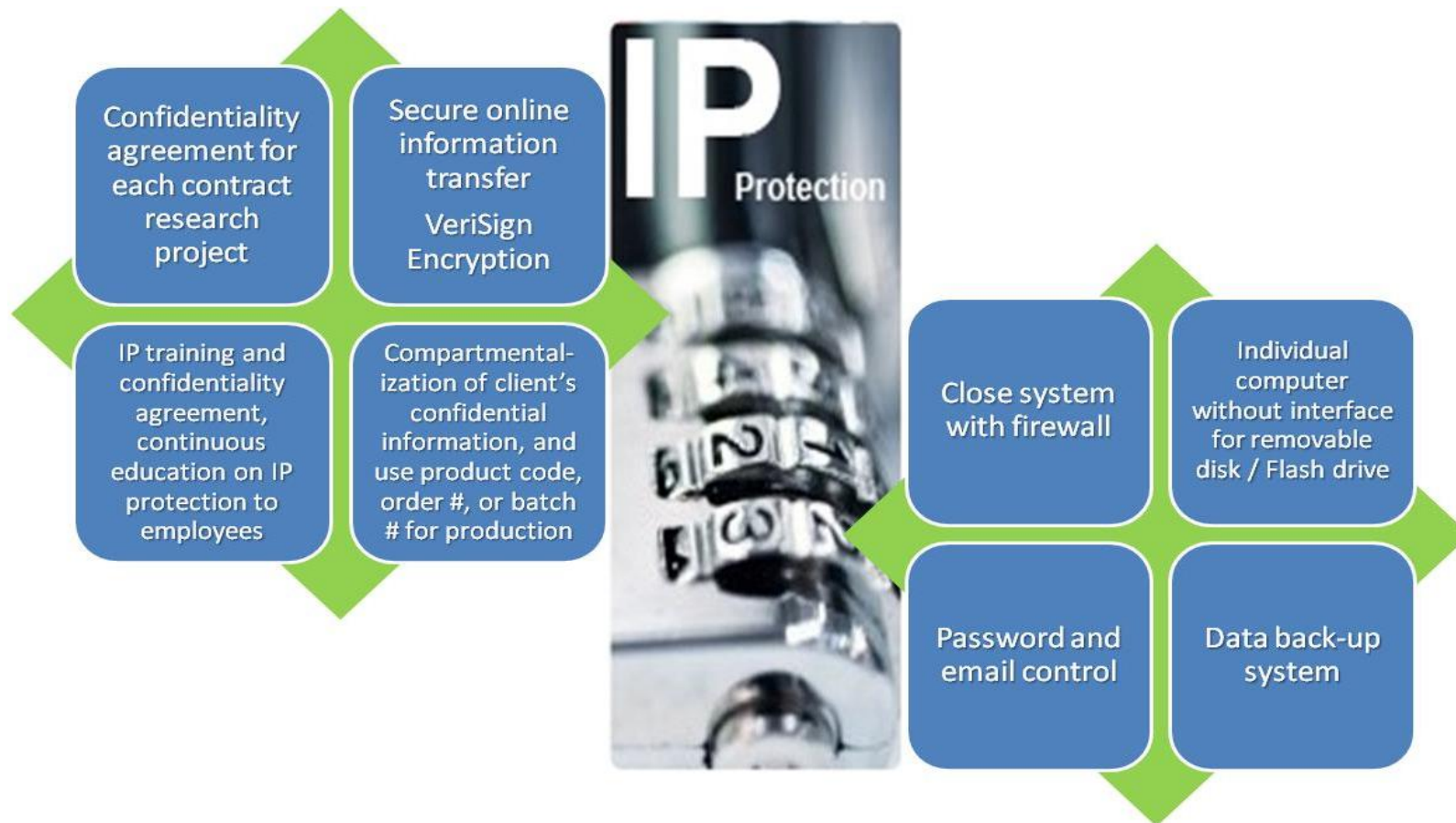
By Dec, 2017

- 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

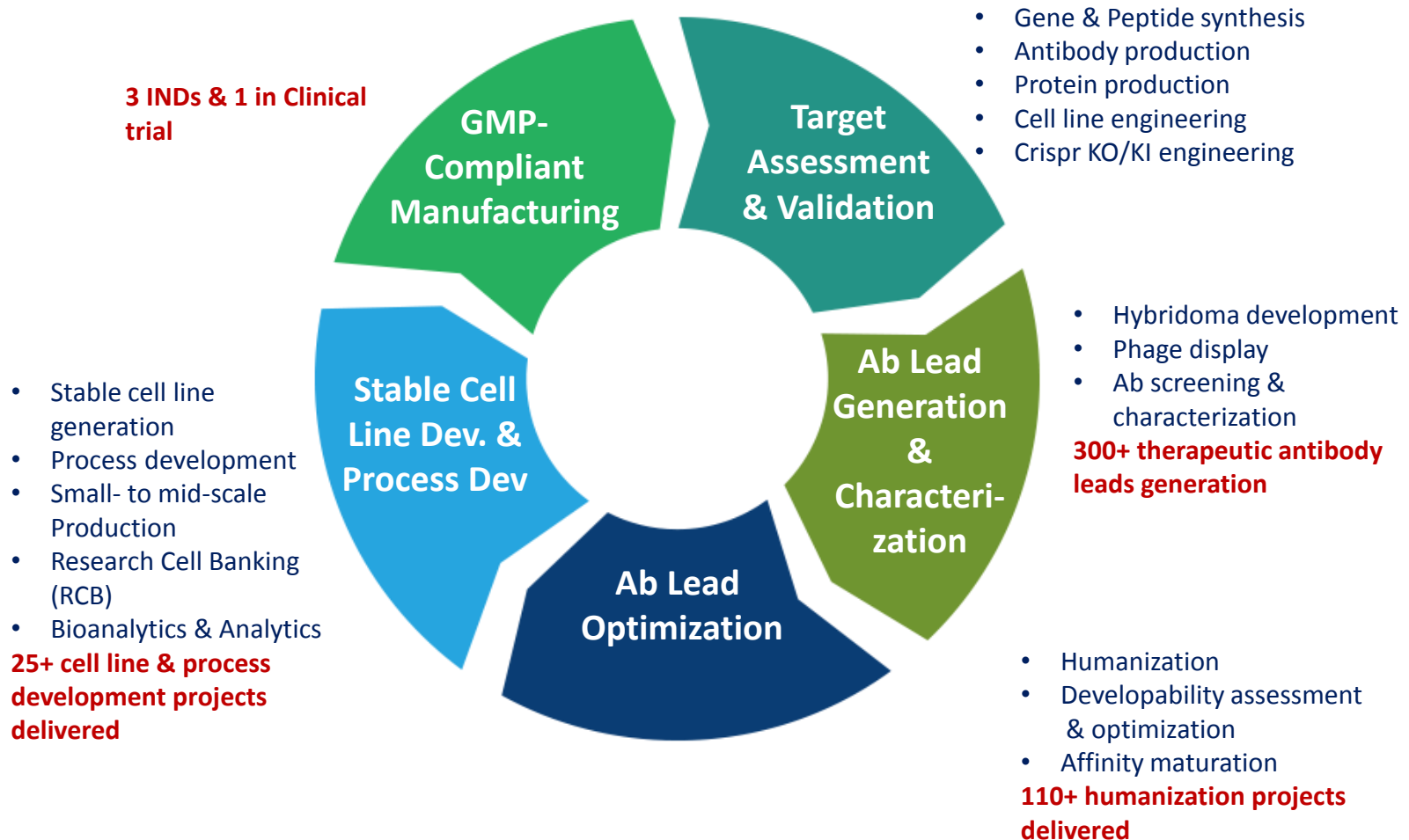


Accelerate Drug Discovery with Innovation GenScript





One-Stop Solution from Target to IND



Thank you!

Expertise, Flexibility, Solutions

