全球生物药研发的挑战与机会：BsAb and TsAb

Challenges and Opportunities of Global Bio-Therapeutic Industry: BsAb and TsAb

周新华博士

嘉和生物药业有限公司创始人/总裁/首席科学家

2020年9月20日

弗戈制药论坛 江苏泰州

目录

治疗性生物药的开发

成本是最大的问题！(生物类似药与创新药)

靶点验证后的药物开发费用：

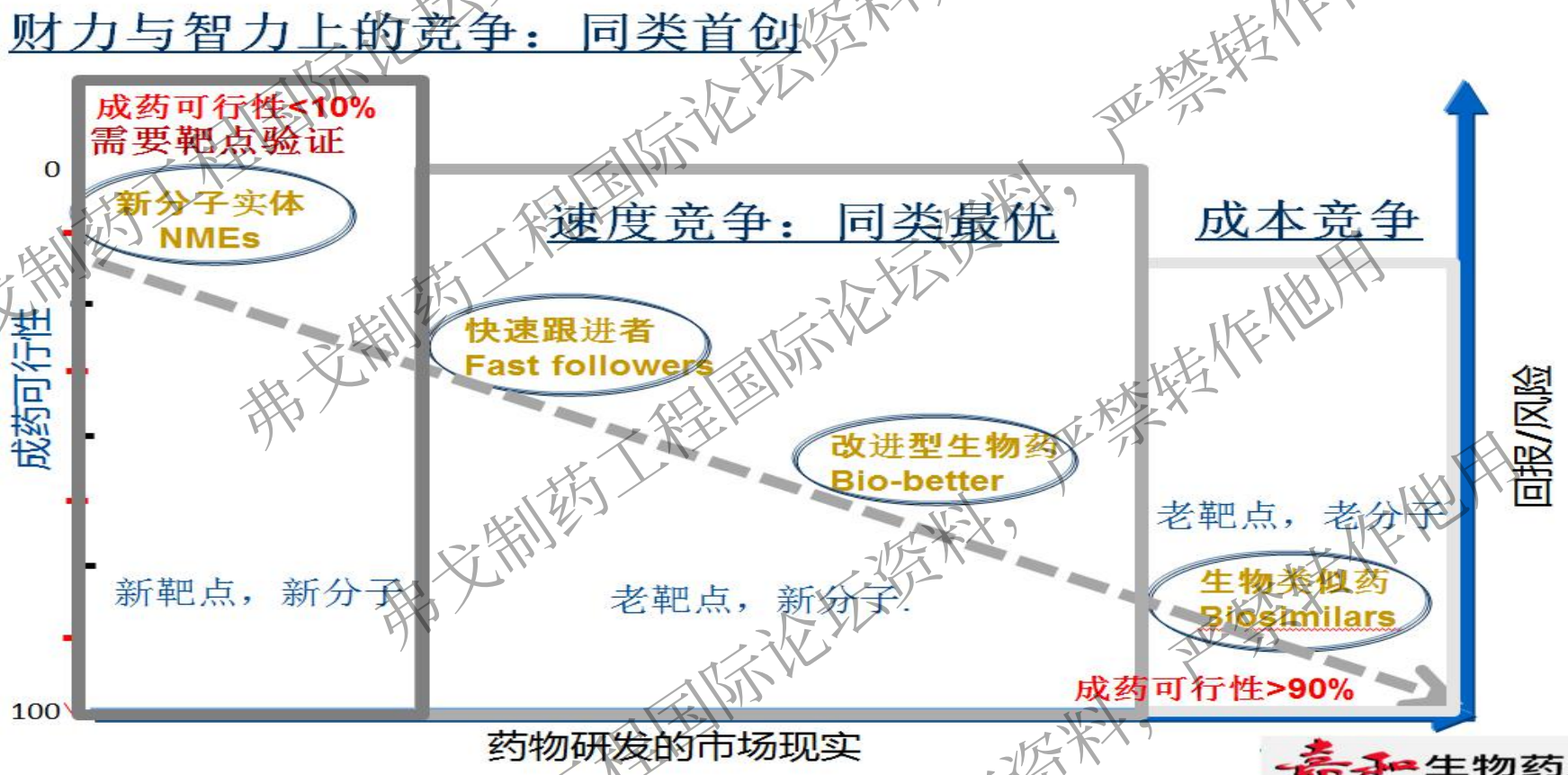
分子设计研发.
工艺和CMC

10%成本投入 10%成本投入

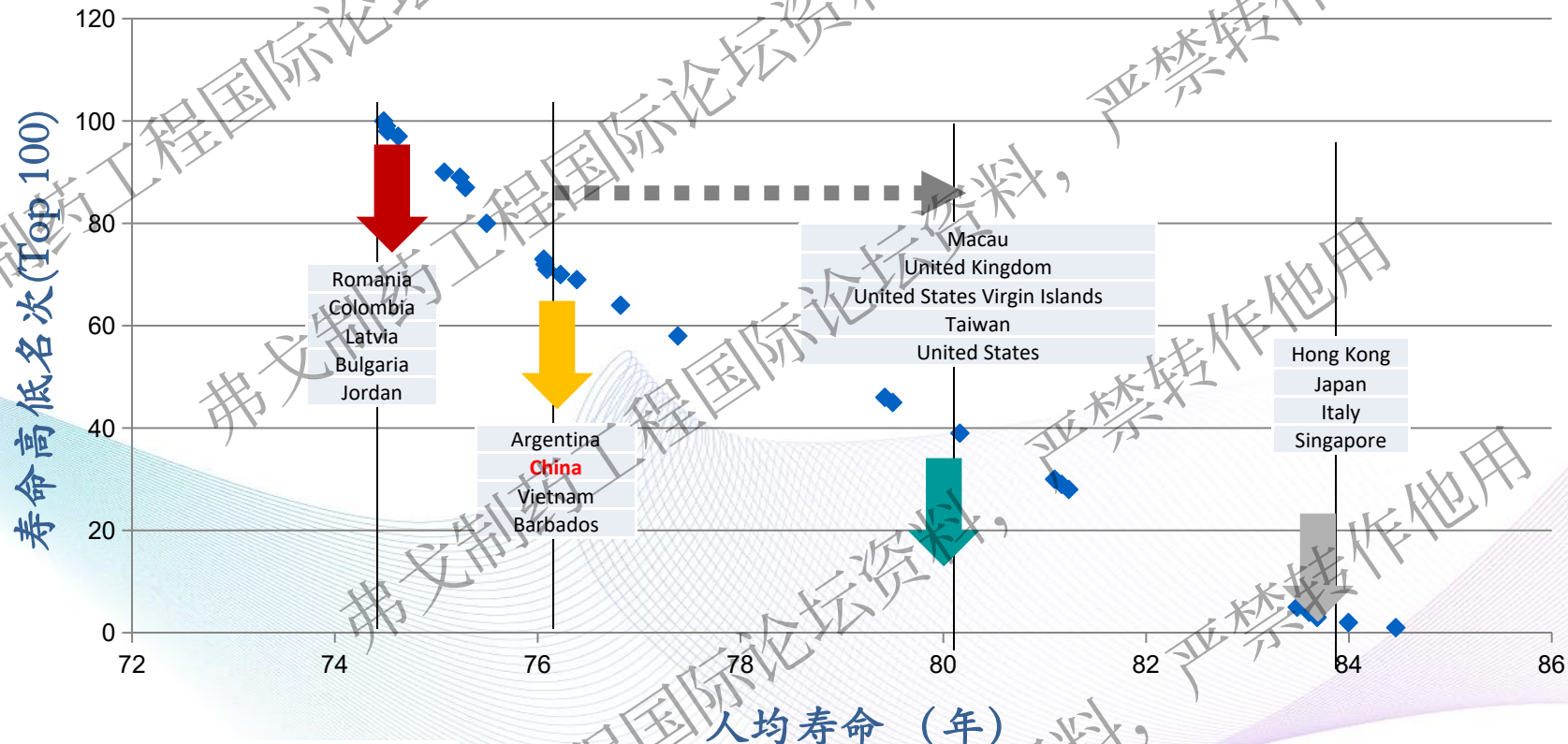
临床研究，病人和剂量的选择以及临床终点的设计
以探索药品在人体上***PK, PD/脱靶率***
进一步确定药物的安全性和效能

80%成本成本，且带有不确定性

新药、生物类似药还是其他



全球人均寿命最高的100个国家

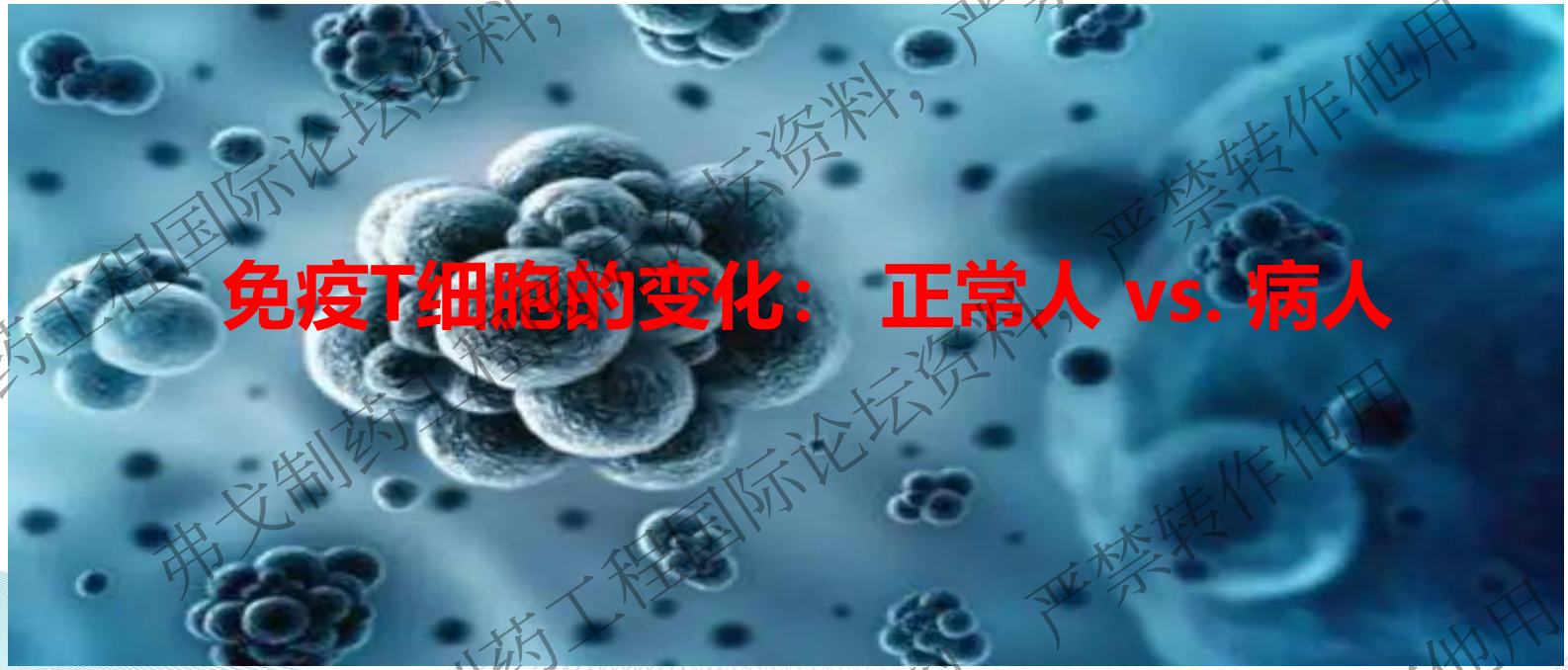


绝大多数癌症5年内将变成慢性病

1. 以单克隆抗体为主的单药或者与小分子的联合免疫疗法是第一战线的主力军

2. 以单克隆抗体为主的，加上融瘤病毒；或者以单克隆抗体为主的，加上个性化的肿瘤疫苗将是绝大多数癌症5年内将变成慢性病的终结章

癌症发生率 P=(abc)/D　癌症主要是老年性的，多突变点的，与免疫能力密切相关疾病；个别案例有遗传因素，也有环境因素



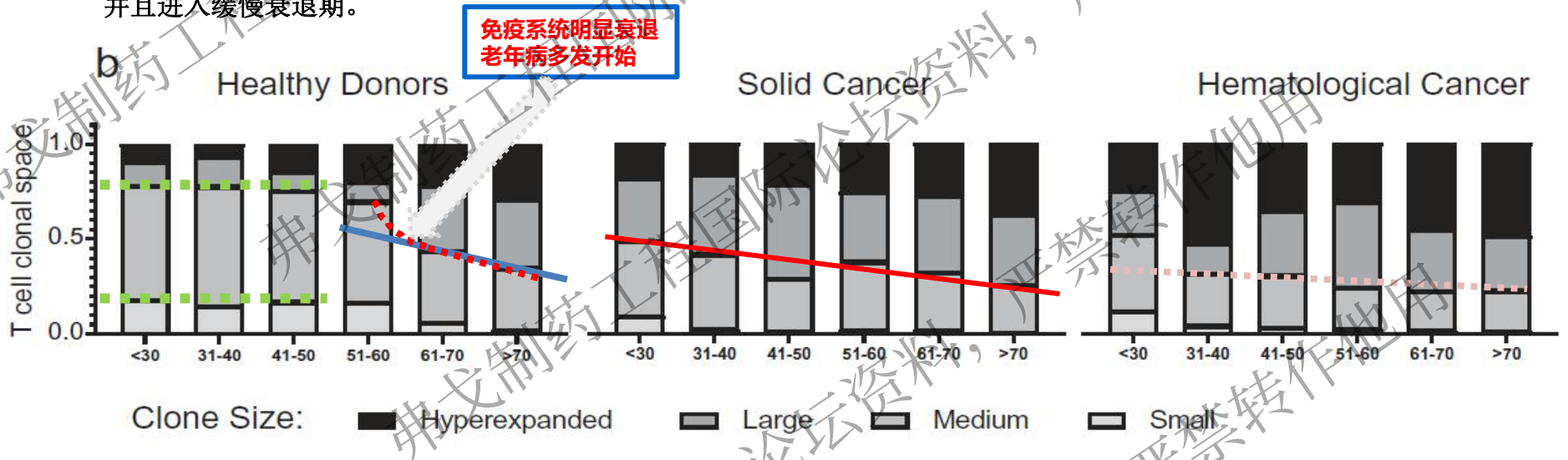
2019年,德国马丁路德大学的Donjete Simnicaa教授和德国汉堡-埃彭多夫大学医学中心的Nuray Akyüzb教授及其团队利用**NGS测序技术**对346份健康人和癌症患者的免疫T细胞受体(TCR)曲线图进行了研究和分析，形成了目前为止最大的**T细胞免疫系统数据库**，含有大约880万的TCR数据集。

To cite this article: Donjete Simnica, Nuray Akyüz, Simon Schliffke, Malte Mohme, Lisa v. Wenserski, Thorben Mährle, Lorenzo F. Fanchi, Katrin Lamszus & Mascha Binder (2019): T cell receptor next-generation sequencing reveals cancer-associated repertoire metrics and reconstitution after chemotherapy in patients with hematological and solid tumors, OncoImmunology,

正常人的T cells 在年轻至50岁基本保持正常水平，51岁开始衰退；发现明显的衰退在61岁-70岁，而70岁后处于年轻时T cells 水平的一半，并且进入缓慢衰退期。

实体瘤病人的T cells 在30岁后就处于正常人年轻时T cells 水平的一半，并且其缓慢衰退期直到大于70岁。

血液瘤病人的T cells 在年轻至30岁时的T cells水平好于实体瘤病人；31岁以后的T cells 水平的衰退相似与实体瘤病人。

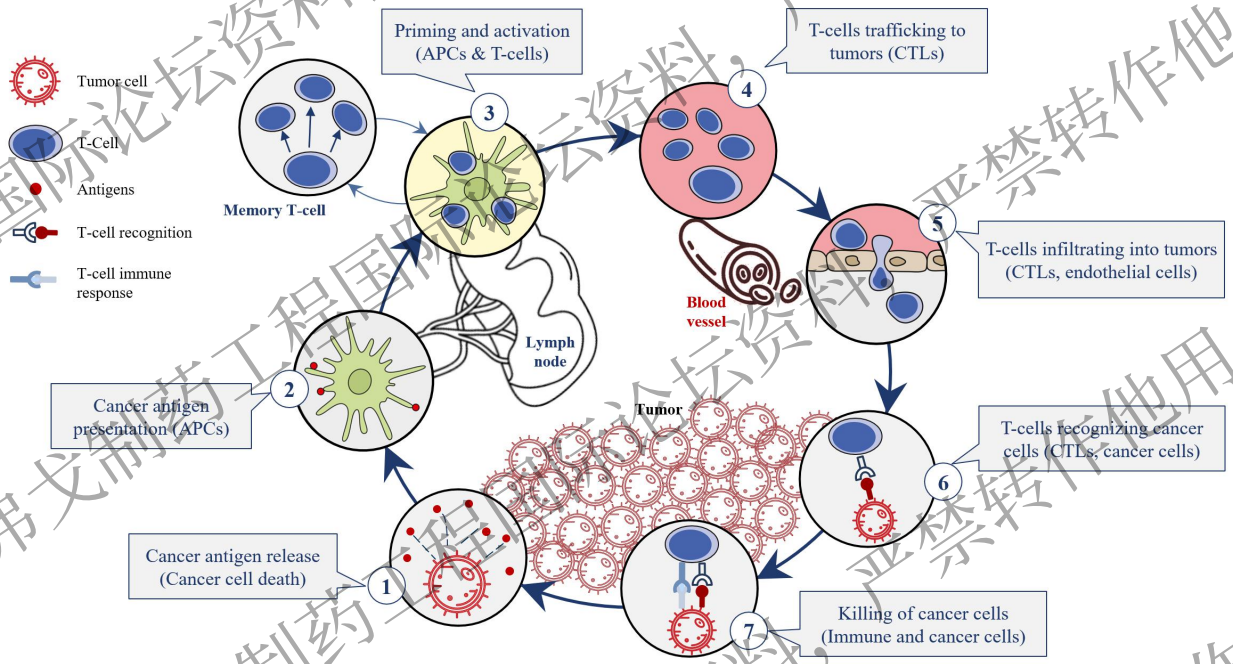


肿瘤免疫治疗通路

尽管2014年后，首个PD-1抗体药物上市以来，这类检查点抑制剂免疫疗法**获批的适应症创造了肿瘤医疗史上绝无仅有的奇迹：**恶性黑色素瘤、非小细胞肺癌、肾细胞癌、霍奇金淋巴瘤、头颈癌、膀胱癌、肝癌以及胃癌等多种恶性癌症。代表性药物Keytruda (pembrolizumab)更是成为了“广谱抗癌药”。但事实上，**这种免疫疗法并不是适合每一个人，临床试验表明，只有约20-40%的患者能够从中获益。**

正常情况下，T细胞中的“刹车”是为了阻止它们攻击自身组织的，但癌细胞通常会通过激活T细胞中的“刹车”来逃避免疫系统的追踪。**检查点抑制剂药物通过切断这些“刹车”，则可以“唤醒”免疫系统，对癌细胞发起攻击，并成功地消除了大约20 - 40 %的黑色素瘤和某些其他癌症类型患者的恶性肿瘤。**

其中最好的情况是，处于亢奋状态的T细胞能够持续存在，时刻监控以防止癌症的复发。但事实并非如此，**大多数患者体内的T细胞仍然处于休眠状态，任由癌细胞随意扩散，也就是我们所说的“刹车”失灵。所以如何引导T细胞找到目标的DC (树突状细胞)的聚集变得非常重要。**



输入异体NK cells for 1, killing tumor cells and 2, provide T cells **提供车辆**

释放新抗原：融瘤病毒，个性化肿瘤疫苗，靶向治疗 for activation of immune system **加油**

PD-1抗体释放刹车，CTLA-4抗体通过清除Treg进一步 **释放刹车**

肿瘤由急性病变成慢性病 **Patients life > 5 yrs**

最近发现表明由NK细胞分泌被称为FLT3LG的特异性免疫信号蛋白或细胞因子的表达与SDCs的存在紧密相关。因此NK细胞不仅仅具有杀死癌细胞能力，同时可以聚集SDCs DC (树突状细胞)从而导致提高T细胞活力。

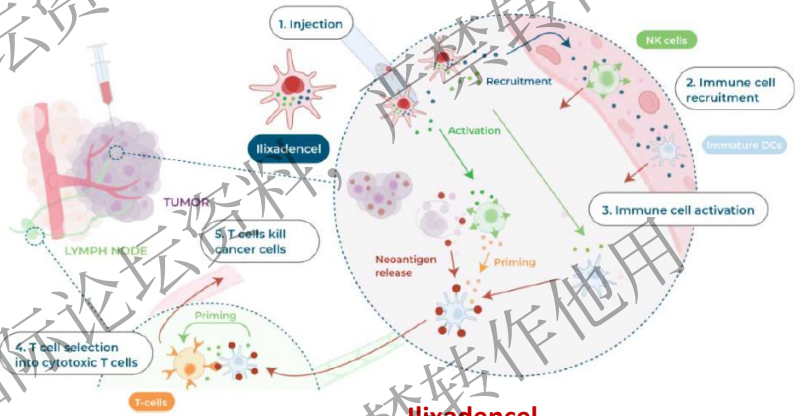
融瘤病毒或者个性化肿瘤疫苗可以协助释放新抗原，加强T/B细胞的免疫应答能力；加上检查点抑制剂药物（PD-1释放刹车，CTLA-4通过清除Treg进一步释放刹车）通过切断这些“刹车”，有效“唤醒”免疫系统，对癌细胞发起攻击。

Nature Medicine 2018, Kevin C. Barry et al & Matthew F Krummel

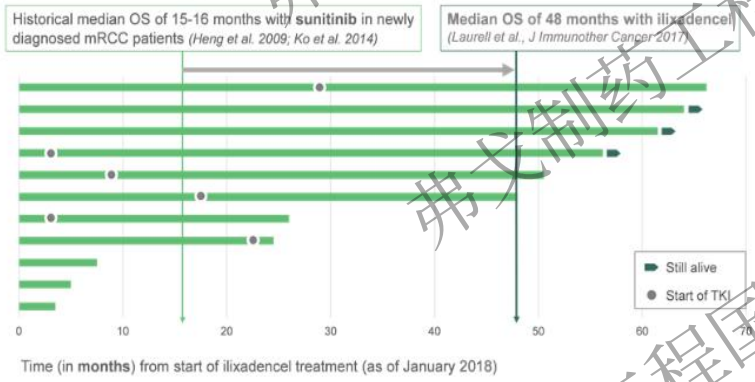
免疫治疗的“王牌”之一-实体肿瘤个体化疫苗

(Treos Bio Reports Positive Final Results of Phase I/II Off-The-Shelf CRC Cancer Immunotherapy in 2020 ASCO Poster Presentation)

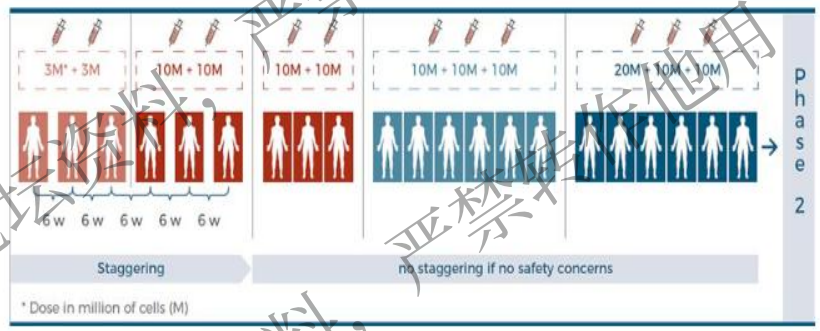
1. 肺癌 (CIMAvax-EGF, Atalante 1, NEO-PV-01, DCVAC/LuC)
2. 乳腺癌 (梅奥诊所, VRP-HER2, NeuVax)
3. 结直肠癌(Oncovax, PolyPEPI1018)
4. 脑瘤 (Survax, AV-GBM-1, DCVax-L, NeoVax)
5. 肾癌 (Ilixadencel, Rocapuldencel-T)
6. 黑色素瘤 (mRNA-4157)
7. 卵巢癌 (OCDC, DCVAC/OvCa)
8. 胰腺癌(GVAX)



I/II期试验结果显示，晚期肾癌患者的总生存期是历史对照组的3倍以上！



Ilixadencel



六种癌症类型，包括肾癌、肝癌、胃肠道间质瘤、头颈部肿瘤、非小细胞肺癌和胃癌

新型生物药的挑战与机会

类别	验证时间	研发速度	费用	成药可行性	竞争关键
针对新靶点的新型抗体药或小分子药	8-10 年	慢	高	不可控	成药可行性
针对肿瘤治疗的免疫检查点的新型抗体药或小分子药	≥10 年	慢	高	不可控	成药可行性
双特异性抗体	≥ 2-5年	OK	中	OK	协同效应 剂量和毒性
免疫细胞疗法 (CART or NK)	≥1-3年	快	低	可控	治疗窗口 剂量及毒性 可以用相似化学的双靶点抗体取代
肿瘤疫苗	≥1-3年	快	低	可控	靶向对PD-1抗体或其他疗法无效的肿瘤

优秀靶点连续开发的非成功案例

验证后优秀靶点：CD20, Her2, CTLA-4, PD-1, VEGFr, RANK-L…. ILxxxx

1. Case Study: CD20 Rituximab by IEDC/Genentech, Obinutuzumab (GA101) by Genentech, Chimeric mAb vs. Fully humanized mAb
2. Case Study: PCSK9 vs. pH-dependent mAb
3. Case Study: Herceptin, TD-M1 and Pertuzumab (Still not there yet)
4. CTLA-4 mAb: Tocixity
5. PD-1 mAb: Keytruda, Optival and others (Distinguished indications such as CRC…)

单克隆抗体的问题和双(多)靶点抗体的机会

1. **TARGET**: Very few of good targets left for oncology study
2. **NATURE** of mAb THERAPEUTICS: Low toxicity and high dosage
3. **COST**: High cost for manufacturing
4. **BIC**: Hard to pickup so-called Best in class

1. TARGET: 绕开单克隆抗体对已经验证过的优秀靶点的惨烈竞争
2. **For the first time mAb therapeutics can be designed, engineered and developed based on the theory of Quantitative Pharmacology**
3. NATURE of mAb THERAPEUTICS: 争取在生物学方面做到1+1>2,包括药效和毒性
4. COST: 尽量降低生产成本
5. **BIC: 有合适的方法筛选到BIC**
6. **Subcu. (subcutaneous) Injection Possibility** (vol. <1ml/per injection when the dosage is 50 mg/dose or less).

因此，BsAb/TsAb是抗体药物的升级换代

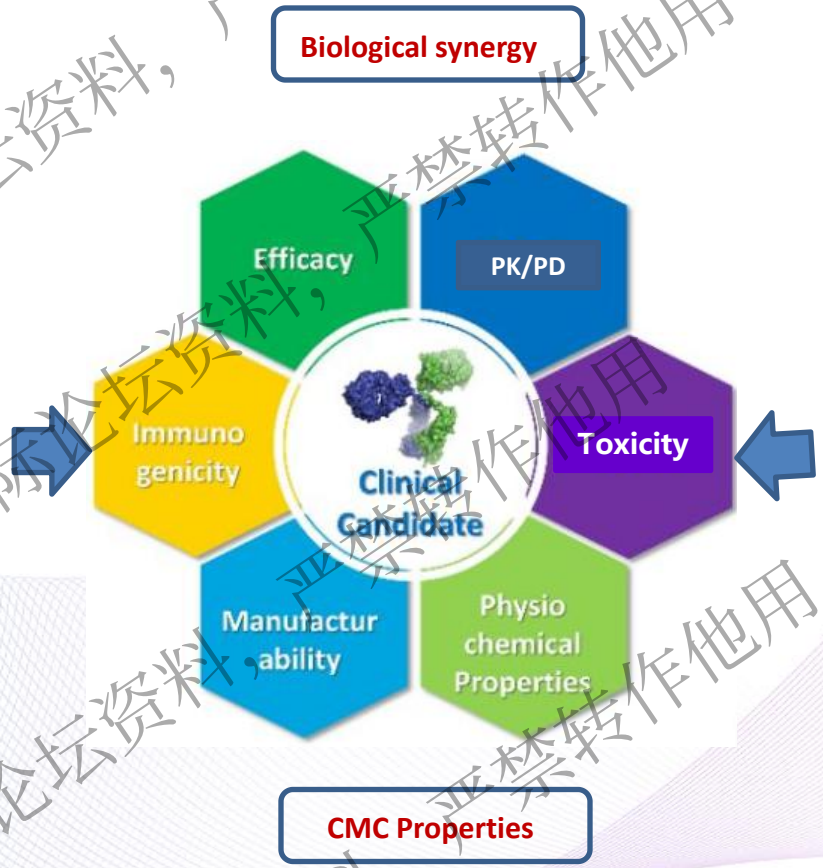
Four Critical Desires for Bispecific mAbs

1. Biological synergy (low dose)
2. Reduced toxicity (dosing flexibility)
3. Very minimal CMC issues
4. Less worries about immunogenicity issues after a long time treatment

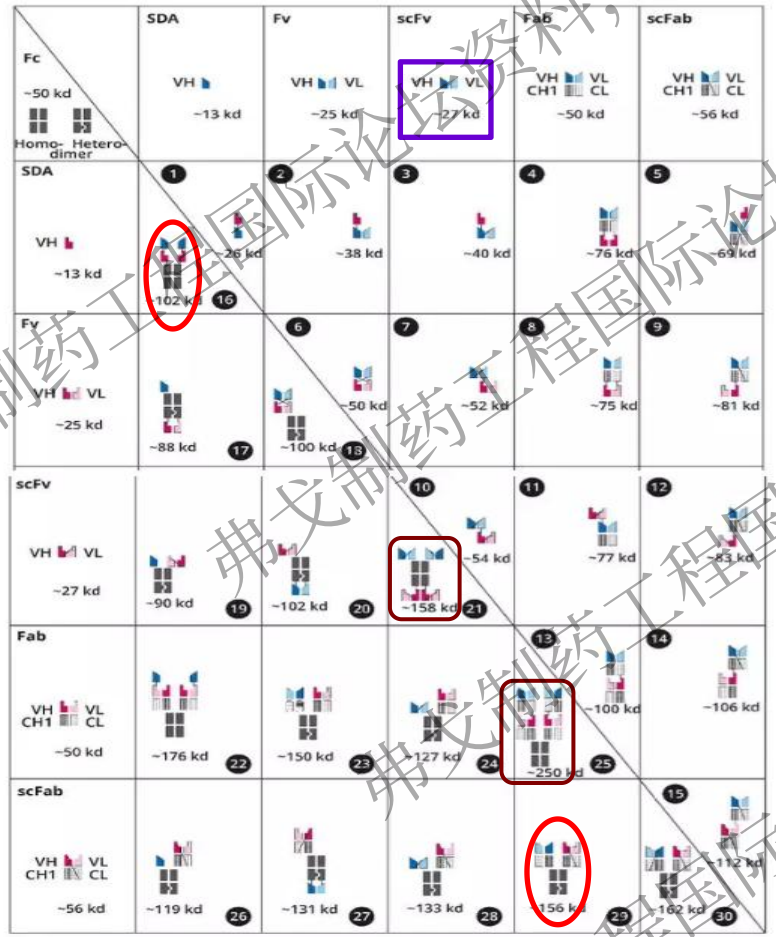
Select a right molecule：选择一个可以进入临床研究的理想双抗分子需要满足四个主要要素，包括1，生物学协同性，2，毒性，3，可生产性，4，免疫原性。其中生物学协同性包括对理想的临床疗效及合理的药代动力学的考量；可生产性主要包括Physicochemical-理化特性和Manufacturability-生产性的考量。

然而，目前很多抗体在研发阶段并未完全遵从或忽视上述关键考量，挑战之处是与生物功能相关的指标（如有效性、安全性、PK/PD和免疫原性）和可开发性指标（如表达水平、可溶性、稳定性、粘度等）往往并不完全相关，有时甚至相互矛盾。

因此，如何选择一个理想的双抗分子需要全局考量，这对后期临床开发的成功至关重要，需在早期发现和开发阶段被给予更多重视。



Antibody Therapeutics, 2020, Vol. 3, No. 1 ***18–62.*** **Siwei Nie et al**



结构分类

对于形式繁多的双抗分子可以按照五大类抗原结合域（SDA，Fv，ScFv，Fab，ScFab）组成的双抗分子根据其是否含有Fc片段一共分为30类。

下面5种类型抗体片段是构建双抗分子最为重要的模块：

1）SDA（single domain antibody）：单域抗体，也称为VHH，是指只含有抗体重链可变区结构；

2）Fv：包含两个肽链，重链可变区VH和轻链可变区VL；

3）ScFv：同样包含重链可变区VH和轻链可变区VL，但是通过linker的形式将VH和VL链接在一起成为单一肽链；

4）Fab：含有两个肽链，一个是重链可变区VH和恒定区CH，另一个含有轻链可变区VL和恒定区CL；

5）ScFab：通过linker将Fab的两个肽链连接起来。

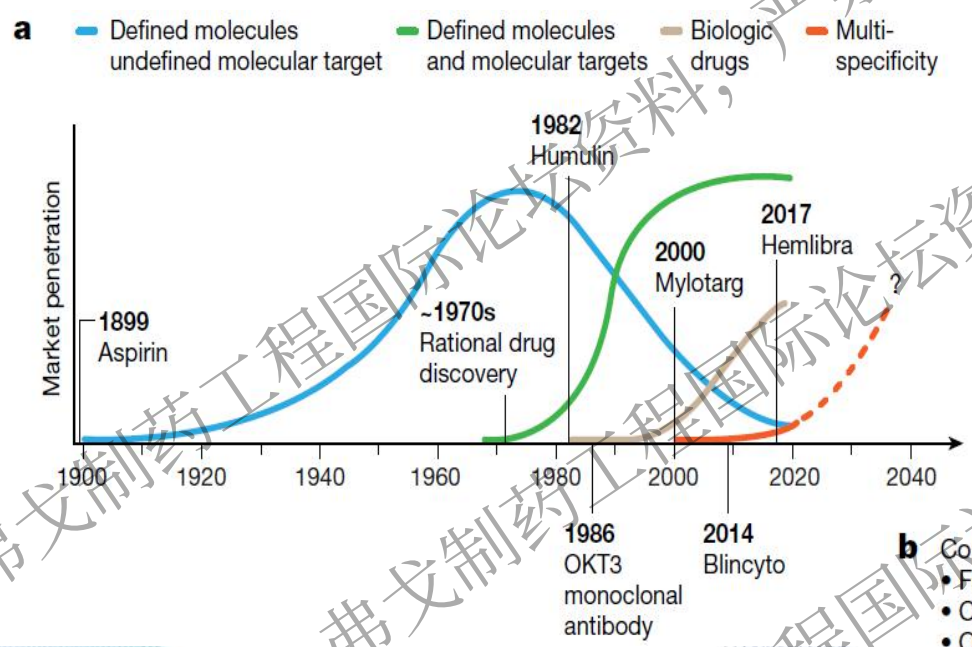
双抗分子形式上的多样性是由其功能和应用上的不同需求所决定的。根据不同的目的， TPP (Target Product Profile)有所不同，主要根据双抗分子的大小、结构域的组合、与抗原结合的亲和力和价位、以及其结构上的灵活性等因素进行选择和设计。

Antibody Therapeutics, 2020, Vol. 3, No. 1 ***18–62.*** **Siwei Nie et al**

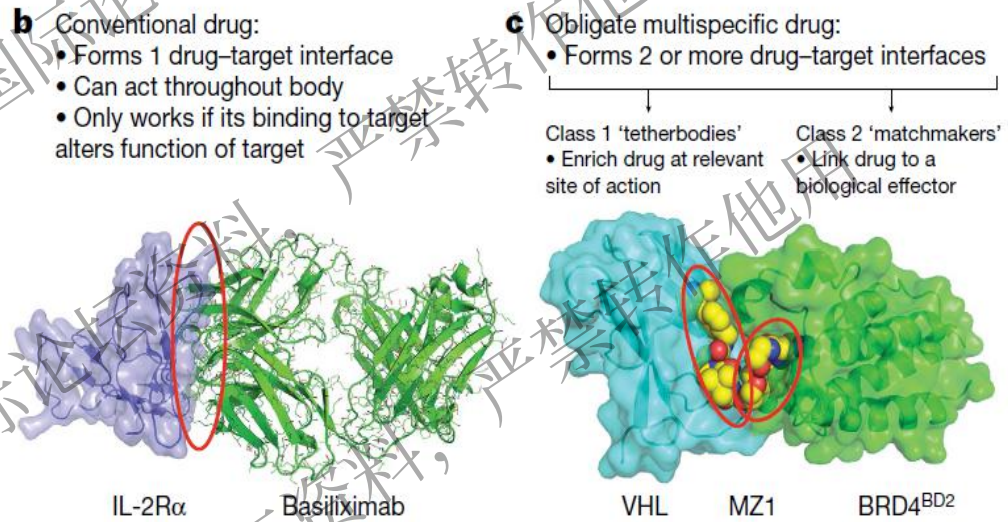
2020年4月15日，美国艺术与科学院院士、美国国家科学院院士、Amgen Research高级副总裁、PROTACs技术创始人之一的**Raymond J. Deshaies**教授针对制药行业当前的最热门话题“**多特异性药物**（multi-specific drug）”，在**Nature**杂志上发表题为**Multispecific drugs herald a new era of biopharmaceutical innovation**的独家综述。该综述**简述了现代制药业发展历程，重点对带来第四次制药业革命的多特异性药物进行了全面详实的阐述，并对多特异性药物将来的发展指出方向，也强调了可能存在的挑战。**

现代生物医药工业发迹于上世纪初，以神药阿司匹林等为标志，此后催生了一大批造福人类的现代药物。直至自上世纪70年代，药物开发都主要依赖于经典的经验药学，此后出现了两个成功的变革创新的浪潮：一个是70年代的理性药物设计方法学，另一个是80年代的基于重组蛋白的治疗药物。

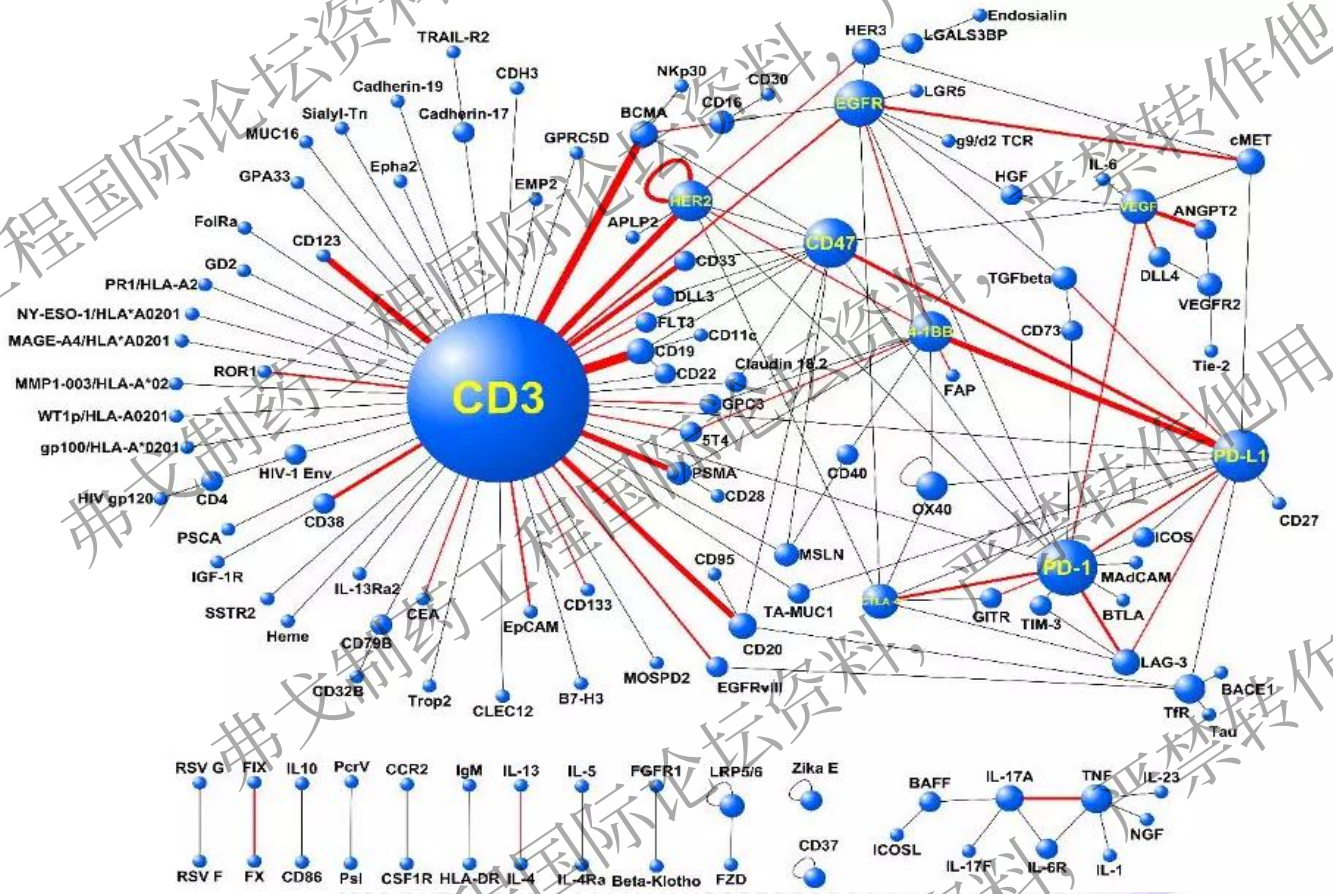
近年来，多特异性药物崭露头角，造就了新一波浪潮。这些具有前瞻意义的多特异性分子的成功开发让科学家不得不重新思考如何开展靶向性药物的研究和应用。在该综述中，Raymond概述了两类主要的多特异性药物：一种能够在特定位置发挥作用，而另一种则是将治疗药物与生物效应器进行偶联。以前的药物设计普遍要求药物分子与靶标进行结合并对其进行调节，而**第二类多特异性药物则完全脱离了这个约束，使得理论上可以靶向任何蛋白，尤其是那些过去被认为不可成药（undruggable）的靶点。**

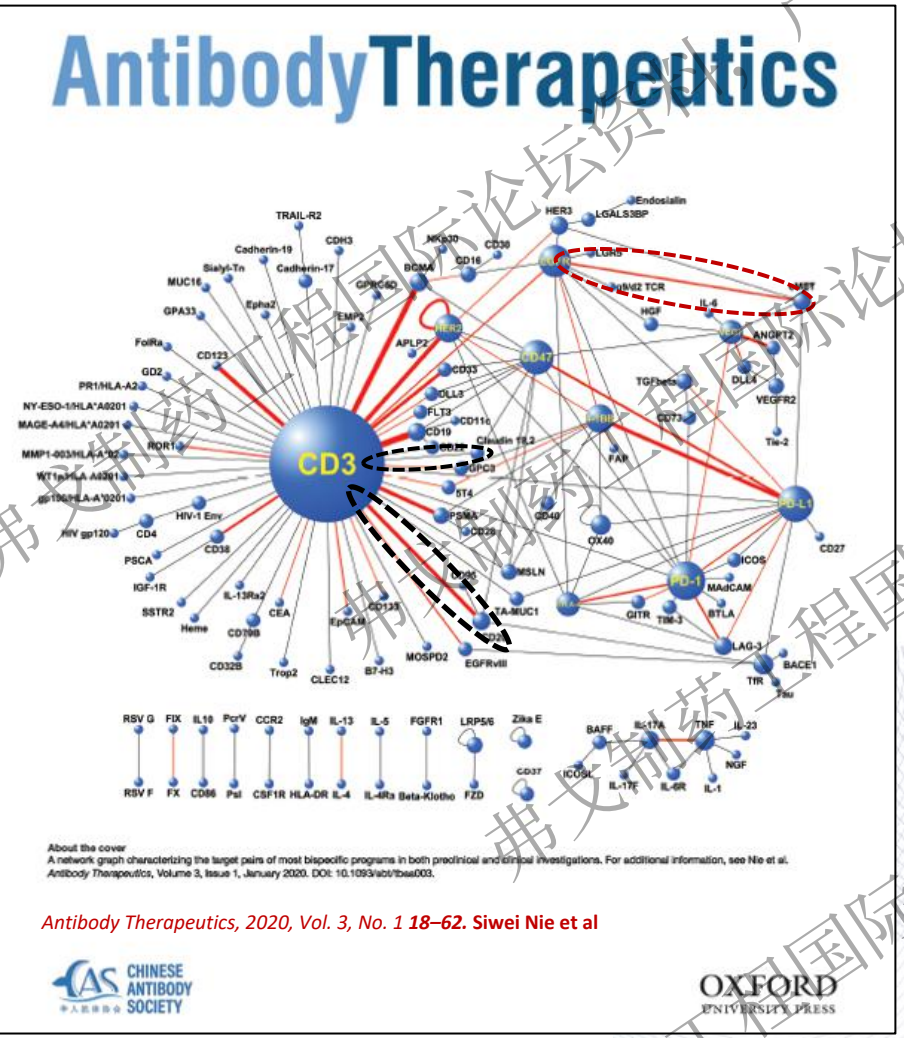


a, The biopharmaceutical industry began at the end of the nineteenth century, roughly coincident with the marketing of aspirin by Bayer. A merger of chemistry and pharmacology yielded defined therapeutic molecules (wave 1). This alliance held sway until the 1970s, when it began to decline with the ascendancy of target-centric rational drug discovery (wave 2). Recombinant proteins, which have become the biggest-selling drugs, emerged in the early 1980s (wave 3). We are now at the start of the fourth major wave of molecular therapeutic agents, which comprises multi specific (as opposed to monospecific) drugs.



b, A typical 1T1D biologic drug with a single drug–target interface (circled in red)120. **c**, Obligate multi specific drugs comprise two major categories: tetherbodies and matchmakers. The matchmaker drug MZ1 (yellow) is shown; this drug forms two interfaces, both of which are circled in red. The first interface contacts the effector, ubiquitin ligase subunit VHL (cyan), and the second interface contacts the target, the bromodomain 2 of BRD4 (BRD4BD2) (green)121.


CD3
TRAIL-R2
Cadherin-19
CDH3
Cadherin-17
Sialyl-Tn
MUC16
Epha2
GPA33
EMP2
FolRa
CD123
GD2
PR1/HLA-A2
NY-ESO-1/HLA*A0201
MAGE-A4/HLA*A0201
ROR1
MMP1-003/HLA-A*02
WT1p/HLA-A0201
gp100/HLA-A*0201
HIV-1 Env
HIV gp120
CD4
CD38
PSCA
IGF-1R
SSTR2
Heme
IL-13Ra2
CEA
CD79B
CD32B
Trop2
CD133
EpCAM
CLEC12
B7-H3
MOSPD2
EGFRvIII
CD20
TA-MUC1
MSLN
CD95
PSMA
CD28
5T4
CD19
CD22
CD33
DLL3
FLT3
CD11c
GPC3
Claudin 18.2
APLP2
HER2
GPRC5D
BCMA
NKp30
CD30
CD16
HER3
Endosialin
LGALS3BP
EGFR
LGR5
g9/d2 TCR
cMET
HGF
IL-6
VEGF
ANGPT2
DLL4
VEGFR2
Tie-2
CD47
TGFbeta
4-1BB
CD73
FAP
CD40
OX40
PD-L1
CD27
ICOS
PD-1
MAdCAM
BTLA
LAG-3
GITR
TIM-3
BACE1
TfR
Tau
RSV G
FIX
IL10
PcrV
CCR2
IgM
IL-13
IL-5
FGFR1
LRP5/6
Zika E
CD37
RSV F
FX
CD86
Psl
CSF1R
HLA-DR
IL-4
IL-4Ra
Beta-Klotho
FZD
BAFF
IL-17A
TNF
IL-23
NGF
ICOSL
IL-17F
IL-6R
IL-1



Antibody Therapeutics, 2020, Vol. 3, No. 1 ***18–62.*** **Siwei Nie et al**

CHINESE ANTIBODY SOCIETY

OXFORD UNIVERSITY PRESS

根据双抗或双功能蛋白的治疗领域将其分为抗肿瘤、针对自身免疫系统疾病、以及针对其他疾病的三大类。

抗肿瘤双抗

根据Cortellis数据库分析，目前双抗管线以抗肿瘤产品居多，在119种处于临床阶段和176种处于临床前的双抗项目中，分别有99个和153个项目是针对肿瘤领域。作者根据生物学机理将抗肿瘤双抗项目进一步分为以下五类：

1）**抗血管生成**（Anti-angiogenesis）：血管生成促进肿瘤的生长，促进其恶化、扩散和转移，抗血管生成在抗肿瘤中的作用已经被广泛应用。双抗分子能同时阻断两个，甚至多个血管生成的通路，例如VEGF、VEGFR2、DLL4以及ANGPT2，来增强抗血管生成的效果。

2）**抗肿瘤生成**（Anti-tumorigenesis）：靶向致癌受体也是被广泛使用的抗肿瘤手段之一。在这类双抗项目中，大部分靶点为HER2、HER3、EGFR、cMet、以及LRP5/6等。

3）**增强抗肿瘤免疫**（Enhancing tumor immunity）：肿瘤免疫治疗旨在提高病人自身抗肿瘤免疫反应，这主要可以通过增强T细胞辅助激活信号（即“踩油门”），例如4-1BB、OX40等；或阻断T细胞反应抑制信号（即“松刹车”），例如临床上取得巨大成就的抗CTLA4和抗PD1/PD-L1治疗。虽然如此，也只有10-30%的病人能受益于PD-1/CTLA4抗体治疗。通过同时阻断两个不同的T细胞反应抑制信号，双抗项目能进一步提高“松刹车”的效果。相较于“松刹车”，“踩油门”的肿瘤免疫治疗开发由于其安全性或疗效等问题一直没有突破性的进展。双抗分子可以通过其巧妙的设计，达到在局部肿瘤部位特异性地激活免疫共刺激信号，从而在提高病人抗肿瘤免疫反应的同时降低这类治疗中伴随的副作用。目前临床前和临床期分别有10种和19种这类双抗分子在研。

4）**调节肿瘤微环境**（Modulating tumor microenvironment (TME)）：为了逃逸免疫系统监控，肿瘤可以通过表达免疫抑制分子（如TGFβ、CD73）和招募免疫抑制细胞，来抑制肿瘤微环境中的免疫细胞的功能和增殖。有部分双抗和双功能蛋白被开发用于克服肿瘤微环境中的免疫抑制作用。

5）**靶向肿瘤细胞的清除**（Depletion of target cells）：这个类型体现了目前绝大多数在研双抗的生物学机制，即通过介导效应细胞或者通过Fc介导的ADCC、ADCP以及CDC等功能，直接靶向肿瘤细胞达到清除的目的。

抗炎双抗

自身免疫系统疾病是双抗第二大应用领域，目前分别有10个及12个双抗项目处于临床及临床前阶段。这些双抗项目大部分都是通过同时中和多个促炎因子的功能来达到比单抗更好的抑制炎症反应的功效。在研的这类双抗有：IL-1α x IL-1β、IL-17 x IL-13、IL-4 x IL-13和BAFF x IL-17等。

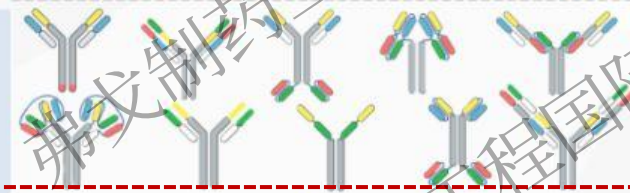
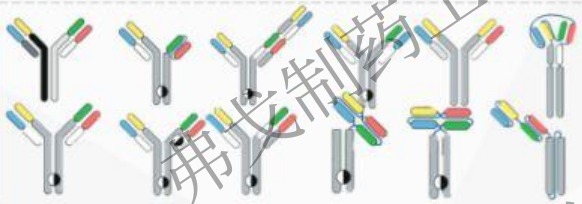
用于治疗其他疾病的双抗

例如血友病、眼部疾病、神经疾病、红斑狼疮，感染性疾病和糖尿病等领域均有双抗或双功能蛋白在进行研究和开发。

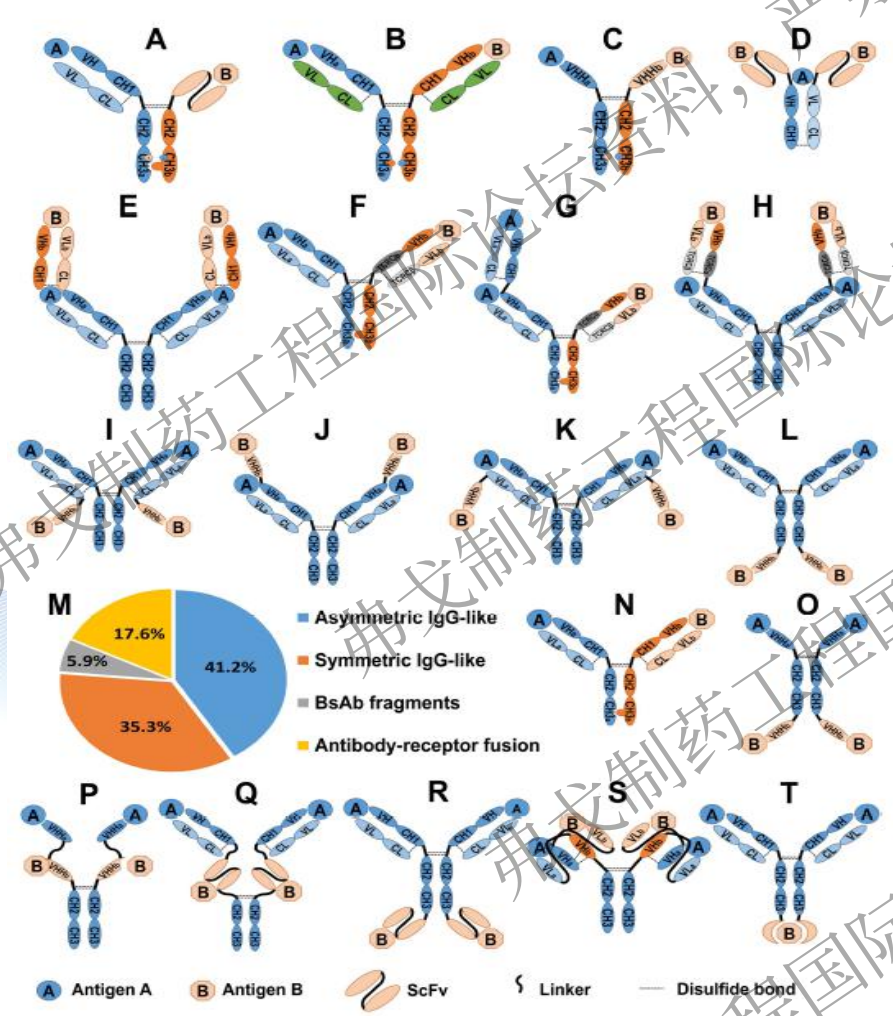
双特异性抗体技术平台按结构分为三类，不对称结构具有明显优势

医药魔方 PHARMCUBE

多样化的双抗结构类型

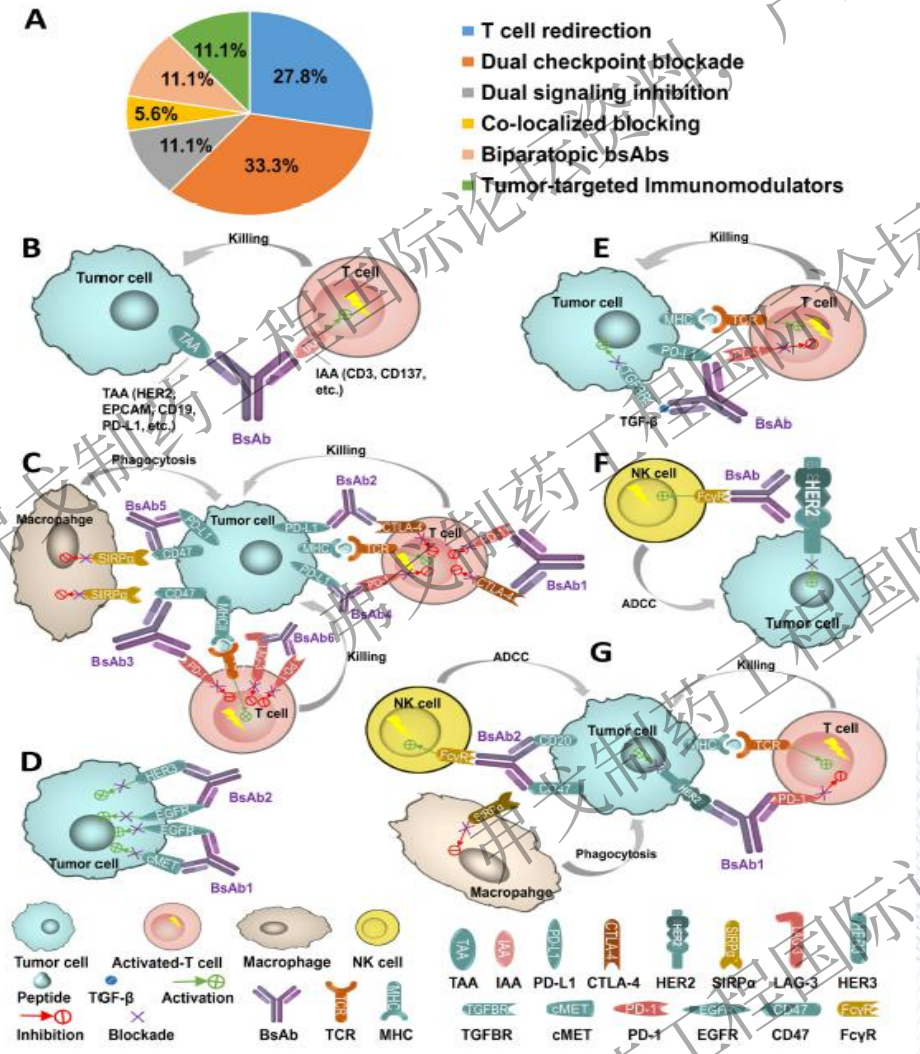
	主要结构	优点	缺点	上市举例
非IgG样		• 结构简单 • 临床给药量低，不到普通抗体用量的十分之一 • 免疫原性弱	• 缺点半衰期短（仅2个小时） • 结构不稳定，表达量低，工艺困难	• Blinatumomab，应用Tandem scFV及BiTE技术平台，2014年Amgen上市，急性淋巴细胞白血病
对称IgG样		• 近似天然IgG的结构及稳定性 • 工艺成熟，表达量高	• 空间双特异结合作用有限	
不对称IgG样		• 解决了knob-into-hole技术在common light chain方面的技术瓶颈 • 实现了肿瘤抗原的双价结合和CD3的单价结合，能够在结合肿瘤抗原时减小CD3抗体带来的毒性	• 技术路线长，设计和工艺难度较高	• Catumaxiomab应用Triomab asyme 1+1（Rat-mouse hybrid IgG）平台，2009年费-卡上市（于2017年撤市），恶性腹水 • Emicizumab应用Hetero H，cL IgG技术平台，2017年罗氏上市，血友病

资料来源：Bispecific antibodies: a mechanistic review of the pipeline, Nature Reviews, 2019; 医药魔方研究与分析



J Zhang, J Yi, P Zhou *Antibody Therapeutics, 2020, Vol. 3, No. 2* **126–145**

The bsAbs developed by Chinese biopharmaceutical companies in different formats. The structure diagrams of YBODY®, CRIBTM, ITabTM, FIT-IgTM,WuXiBodyTM, and SMABTM are illustrated. (**A**) YBODY® composites three segments including a Fab, scFv, and Fc region, wherein the Fab targets tumor-associated antigen (TAA), scFv to IAA, and heterodimeric Fc is stabilized by KiHs and a salt bridge. (**B**) and (**C**) In CRIBTM platform, the charge network among various Fc bonds is manipulated to increase the formation of heterodimers. (**D**) In ITabTM, a Fab domain binds to CD3 and two scFv domains bind to tumor surface antigen to form an immune synapse to recruit and activate T cells at the tumor site. (**E**) In tetravalent FIT-IgTM technology, two parental antibodies are combined into one single molecule, where the Fab A is structurally fused to Fab B in tandem at its N-terminus. (**F, G,** and **H**) In WuXiBodyTM**,** TCR C/C pair, (where TCR C and TCR C represent the and chains of human TCR constant region, respectively), is used to substitute the first constant domain of the heavy chain (CH1) and the constant domain of the or light chain (CL) of one of the two Fabs, while maintaining the variable regions of heavy chain (VH) and light chain(VL) pair (VH/VL) of this Fab and the whole structure of the other Fab to be their native forms. WuXiBody can be assembled by 1 or 2 of the different Fabs connected with each Fc of a heterodimer or a homodimer to provide 1 + 1 asymmetric bivalent (**F**), 2 + 1 asymmetric trivalent (**G**) and 2 + 2 symmetric tetravalent (**H**) bispecific antibodies (bsAbs), respectively. (**I–L**) In SMABTM, a VHH is fused to the C-terminal end of each light chain (**I**), or to the N-terminal end of each HC (**J**), or to the N-terminal end of each light chain (**K**), or to the C-terminal end of each HC (**L**) to provide 2 + 2 symmetric tetravalent bsAbs. (M) 17 of 20 bsAbs, which are currently under clinical trials in China have disclosed their structural formats, among which include seven asymmetric IgG-like bsAbs (7 of 17, 41.2%), six symmetric IgG-like bsAb (6 of 17, 35.3%), one bispecific fragment (1 of 17, 5.9%), and three antibody-receptor fusion proteins (3 of 17, 17.6%). Asymmetric IgG-like structure can be sub-classified as scFv-Fab IgG (**A**), hetero-H+ common LC IgG (**B**), hetero-VHH (**C**), and Duobody (**N**). Symmetric IgG-like structure can be sub-classified as (Fab)2-IGG (E), VHH-Fc-VHH (**O**), tandem VHHs-Fc (**P**), (Fab)2-(scFv)2-Fc (**Q**) where the two identical scFvs target antigen A and two Fabs target antigen B, and IgG-(scFv)2 (**R**); bispecific fragments structure involved scFv(s) and Fab(s) (**D**), and an antibody-receptor fusion protein (**S**) consisting a whole monoclonal antibody connected on its two C-terminal of HCs with the ex-cellular domain of the receptor.



MOAs of 18 bsAbs in Chinese clinical trials. (**A**) Among the 18 bsAbs, five of which are by T-cell redirection (5 of 18, 27.8%), six by dual-checkpoints blockade (6 of 18, 33.3%), two by dual signaling inhibitions (2 of 18, 11.1%), one by co-localized blocking (1 of 18, 5.6%), two by biparatopic bsAbs (2 of 18, 11.1%), and two by tumor-targeted immunomodulators (2 of 18, 11.1%). (**B**) T-cell redirection refers to bridge T cells and tumor cells by binding to both a TAA and IAA and redirecting the cytotoxic activity of effector T cells to attack specifically to the tumor cells. Represent projects in using the MOA include M802 (HER2 × CD3, by YZYBio), M701 (EPCAM × CD3, by YZYBio), A-319 (CD19 × CD3, by Generon), K193 (CD19 × CD3, by Lvzhu), and ES101 (PD-L1 × CD137, by Elpiscience). (**C**) Dual checkpoints blockade is by two-checkpoint blockers integrated into one antibody to inhibit two immune checkpoints simultaneously. AK104 (PD-1 × CTLA-4, by Akeso), KN046 (PD-L1 × CTLA-4, by Alphamab), IBI318 (PD-1 × PD-L1, by Innovent), HX009 (PD-1 × CD47, by HanxBio), IBI322 (PD-L1 × CD47, by Innovent), andMGD013 (PD-1 × LAG-3) are six of these examples. (**D**) Dual signaling inhibitions are to target two different receptors for preventing the receptors from phosphorylation and/or from the activation of both receptor-mediated signaling pathways to inhibit tumor proliferation. EMB-01 (EGFR × c-MET, by Epimab) and SI-B001 (HER3 × EGFR, by Biokin) are two of these typical bsAbs. (**E**) Co-localized blocking is by inhibiting two or more tumor cell intrinsic and extrinsic pathways to raise the possibility of superior antitumor activity compared with the monotherapy. SHR-1701 (PD-L1 × TGF-, by Hengrui) is one of such bsAbs. (**F**) Biparatopic bsAbs are by binding to two different epitopes of the same antigen or same receptor to enhance the antigen–antibody affinity and to improve the drug efficacy. Both KN026 (HER2 × HER2, by Alphamab) and MBS301 (HER2 × HER2, by Mabworks) bind to the D2 and D4 subdomains of HER2. (**G**) Tumor-targeted immunomodulators are designed for binding to both one TAA(e.g.HER2, CD20) to inhibit TAAsignaling pathway and one immunomodulating receptor (e.g. PD-1, CD47) to regulate the immune system to attack the tumors. IBI315 (HER2 × PD-1, by Innovent) and IMM0306 (CD20 × CD47, by ImmuneOnco) utilize such MOAs.

J Zhang, J Yi, P Zhou, *Antibody Therapeutics, 2020, Vol. 3, No. 2* **126–145**

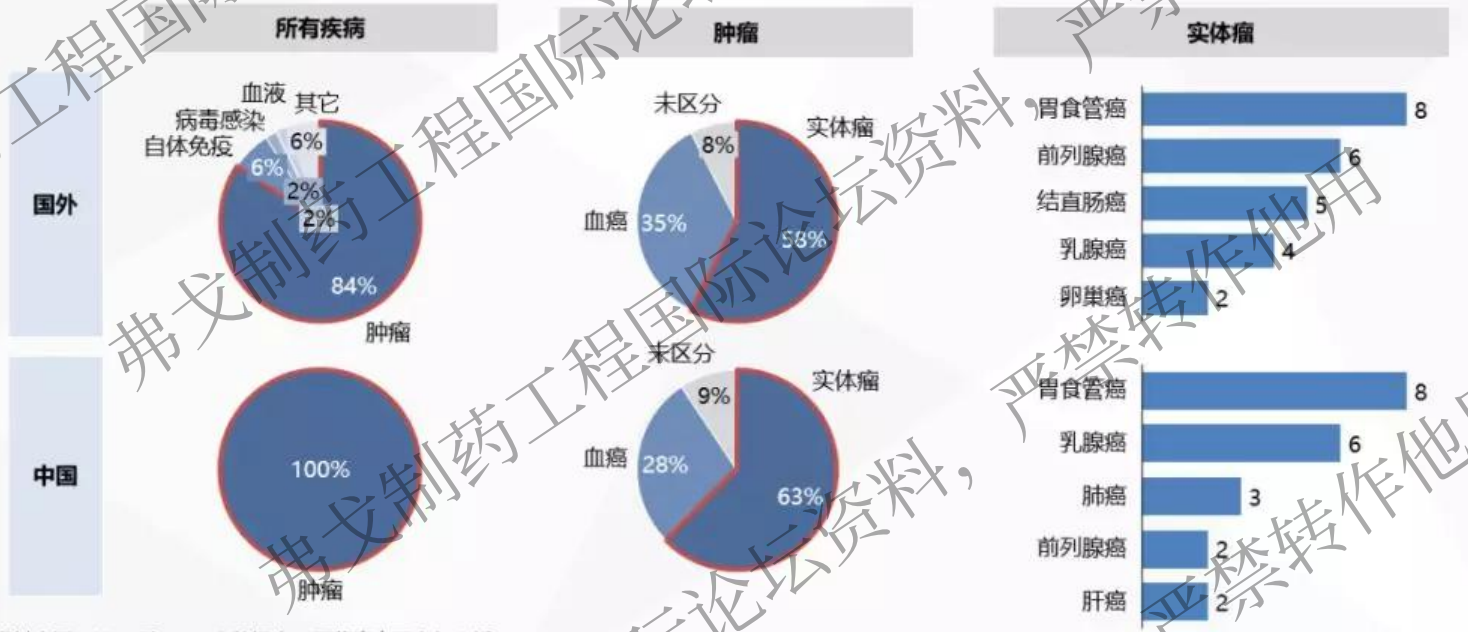
Bispecific antibody patents from Chinese applications granted by the United States Patent and Trademark Office

Identifier	Drug	Company	Targets	BsAb format and platform	Indication	Phase
CTR20171194	M802	YZYBio	HER2 × CD3	scFv-Fab IgG; YBODY	HER2-positive advanced solid tumor	I
CTR20181212	M701	YZYBio	EpCAM × CD3	scFv-Fab IgG; YBODY	Malignant ascites	I
CTR20182027	AK104	Akeso	PD-1 × CTLA-4	IgG-(scFv)2; Tetrabody	Advanced solid tumor and advanced or metastatic gastric adenocarcinoma or gastroesophageal junction adenocarcinoma	Ib/II
CTR20190205	A-319	Generon	CD19 × CD3	$(scFv)_2$-Fab; ITAB	Refractory or relapsed B cell lymphoma	I
CTR20190853	KN026	Alphamab	HER2 × HER2	Hetero H, common LC IgG; CRIB	Advanced gastric and gastroesophageal junction carcinoma with overexpression and low expression of HER2	II
CTR20182404 CTR20181823	SHR-1701	Hengrui Advanced malignant solid tumor	PDL1 × TGFβ	Antibody-receptor fusion	Metastatic castration resistant prostate cancer	I
CTR20181760	MBS301	Mabworks	HER2 × HER2	Duobody	HER2 high expression of locally advanced, inflammatory or early breast cancer, metastatic breast cancer, metastatic gastric cancer, etc.	I
CTR20190427	KN046	Alphamab	PD-L1 × CTLA-4	Hetero VHH-Fc; CRIB	Advanced unresectable or metastatic esophageal squamous cell carcinoma	II
CTR20190197					Triple negative breast cancer	II
CTR20190195					Non-small-cell lung cancer	II
CTR20181996					Chinese advanced solid tumor and lymphoma subjects	I
CTR20190241	EMB-01	Epimab	EGFR × c-MET	$F(ab)_2$-IgG; FIT-Ig	Advanced/metastatic solid tumors, including but not limited to non-small-cell lung cancer, colorectal cancer (no RAS-positive mutation), gastric cancer, liver cancer, and other solid tumors	I
CTR20190340	IBI318	Innovent	PD-1 × PD-L1	Duobody	Advanced malignant tumor	I
CTR20190888	ES101	Elpiscience	PD-L1 × CD137	Tandem VHH-Fc	Advanced solid tumor	I
CTR20191955	K193	Lvzhu	CD19 × CD3	$F(ab)_2$-$(scFv)_2$-Fc	B-cell lymphoma	I
CTR20191677	IBI315	Innovent	HER2 × PD-1	Duobody	Advanced malignant tumor	I
CTR20192612	IMM0306	ImmuneOnco	CD47 × CD20	Antibody-receptor fusion	Lymphoma	I
CTR20192299	HX009	HanxBio	CD47 × PD-1	Antibody-receptor fusion	Malignant tumors such as liver cancer, stomach cancer, and colorectal cancer	I
CTR20200502	SI-B001	Biokin	HER3 × EGFR	IgG-$(scFv)_2$	Locally advanced or metastatic epithelial tumor, including esophageal squamous cell carcinoma, lung squamous cell carcinoma, triple negative breast cancer, head and neck squamous cell carcinoma, colorectal cancer, etc.	I
CTR20200175	IBI322	Innovent	PD-L1 × CD47	Not available	Solid tumors and hematological tumors	I
CTR20200549	MGD013	ZLAB	PD-1/× LAG-3	DART	Advanced liver cancer (including hepatocellular carcinoma and intrahepatic cholangiocarcinoma)	I
CTR20200289					Advanced gastric adenocarcinoma or adenocarcinoma at the gastroesophageal junction with previous treatment failed	I
CXSL1900112	SI-B003	Biokin	Undisclosed	Not available	Undisclosed	IND
CXSL1900131	KD6001	Kanda	Undisclosed	Not available	Advanced malignant tumor	IND
CXSL1900150	PM8001	Biotheus	Undisclosed	Not available	Advanced solid tumor	I

J Zhang, J Yi, P Zhou *Antibody Therapeutics, 2020, Vol. 3, No. 2* **126–145**

全球双抗疾病分布较广泛，肿瘤占比高，而中国都为肿瘤

全球双特异性抗体数量疾病领域分布（只包括进入临床的，数据截止2020-2-28）



资料来源：NextPharma®数据库；医药魔方研究与分析

PD1/PDL和HER2是全球双抗热门靶点，国内HER2布局最多

医药魔方 PHARMCUBE

全球双特异性抗体数量单靶点分布（只包括进入临床的，数据截止2020-2-28）

研发阶段：批准上市 III期临床 II/III期临床 II期临床 I/II期临床 I期临床 xx 中国进入临床的双抗数量

资料来源：NextPharma®数据库；医药魔方研究与分析

国外双特异性抗体领先企业

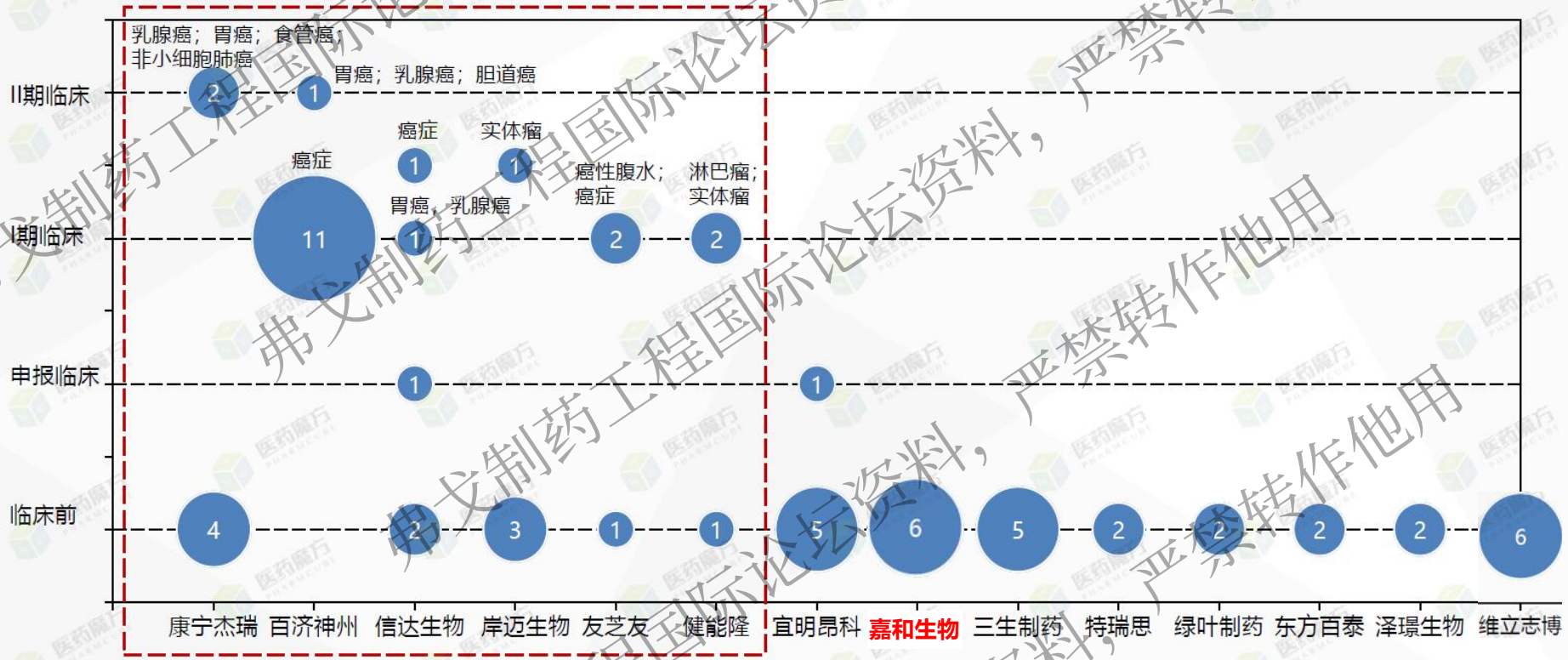
双特异性抗体研发领先企业
只统计进入临床阶段的产品，数据截止2020-2-28

资料来源：NextPharma®数据库；医药魔方研究与分析

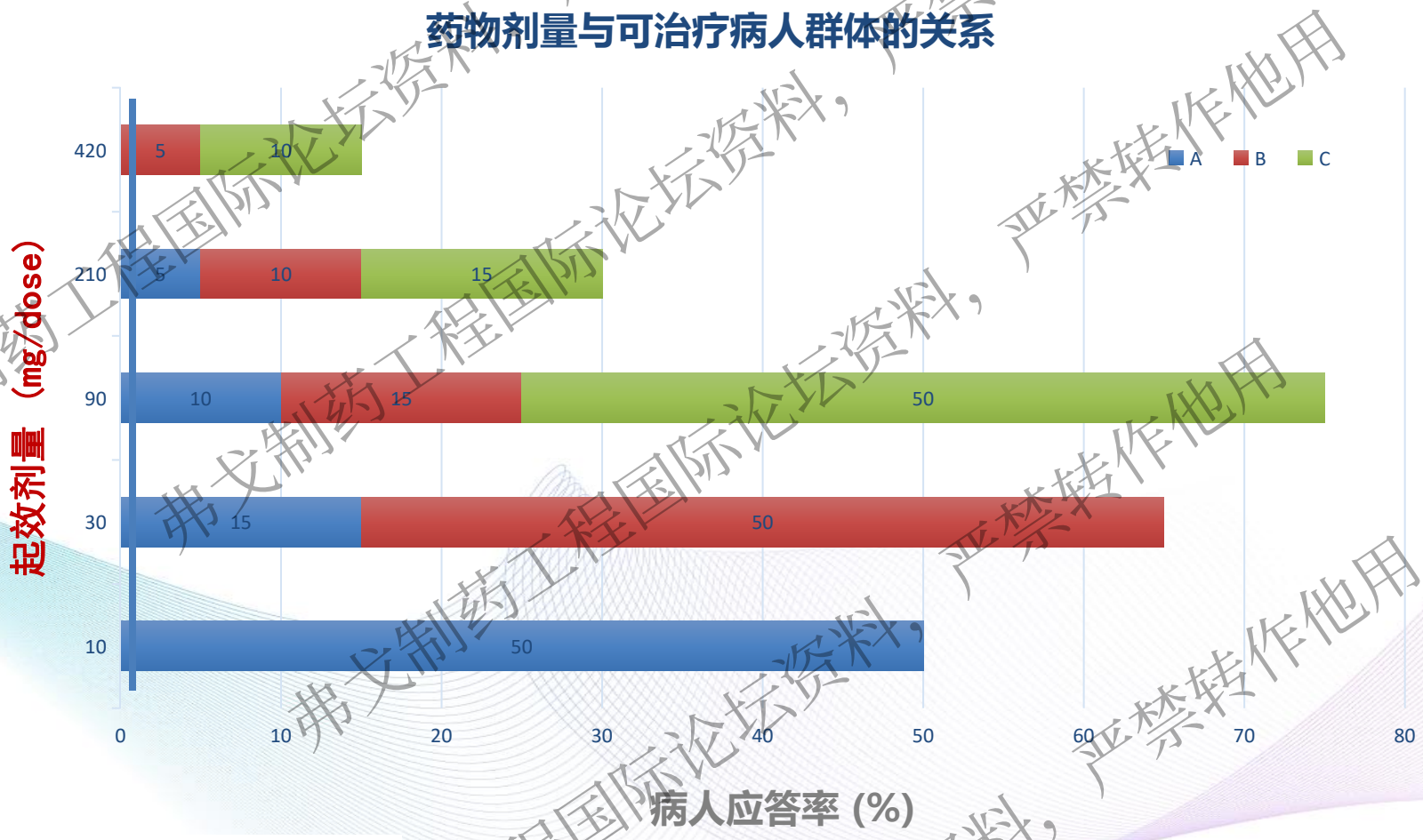
中国双特异性抗体代表企业

中国双特异性抗体研发领先企业（数据截止2020-2-28）

气泡大小：在研双抗数量



资料来源： NextPharma®数据库；医药魔方研究与分析



结语

新药研发包括生物药是非常冗长和高失败率的行业，特别是在资本严冬的最近几年，中国生物制药行业已经进入白热化竞争状态。在资本不确定的情况下，**尽快在竞争红海中找到蓝海，特别是PD-1抗体联合治疗的大适应症的选择上，高效率敢于破釜沉舟，尽快执行，才能让其他先加入的企业困在沙滩上；**有差异化（适应症）老靶点新分子可能是在药物价格持续下降的今天是最佳选择。

能够胜出细胞治疗产品如双靶点或者三靶点抗体可能是有效的选择；但是如何在药物安全性中定义出有明显差异的药物有效性是在其临床研究中一个关键考虑。

Together we can do better!