诺诚健华2021研发日

科学驱动创新

Opening Remarks

诺诚健华
科学驱动创新

Co-Founder, Chairwoman and CEO

- 20+ years of experience in research and development and company management in the pharmaceutical industry
- Former CEO and CSO of BioDuro, a PPD Company
- Former Chair of Early Development Team, Cardiovascular Diseases at Merck US
- Post-doc Fellow at The Howard Hughes Medical Institute
- Ph.D. in Molecular Biology from Purdue University
- The 17th President of the Sino-American Pharmaceutical Professional Association (SAPA)

崔霁松博士
Dr. Jasmine Cui

Vision: Global Biopharmaceutical Leader that Develops and Delivers Innovative Therapies for Patients Worldwide

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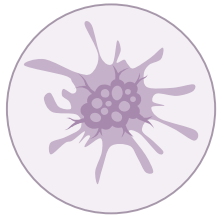
- Experienced **founding and management teams** with track record of success
- Fully integrated **biopharmaceutical platform** with strong in-house R&D capabilities
- **Worldwide rights** to all product candidates
- Strategically focused pipeline of potential **first/best-in-class** therapies

Autoimmune   Oncology

Our Therapeutic Focus

Corporate History and Milestones

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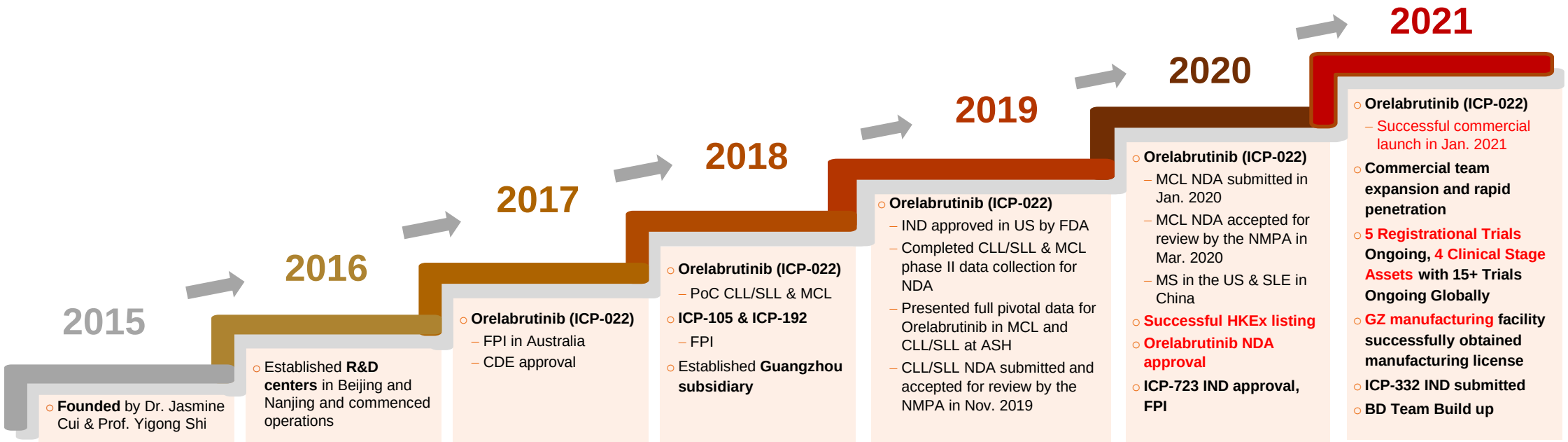
Support from top tier investors

Jan 2018
Series C round financing of **US$55.0MM**

Nov 2018
Commenced **Series D** rounds financing of **US$180.5MM**

Mar 2020
Initial Public Offering (IPO) at HKEx, raised **US$300+MM**

Feb 2021
Follow-on raised approximately US$393 MM



Our 3-5 Years Growth Objectives

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2015

IPO 2020

- NDA submitted for Orelabrutinib
- 3 clinical stage assets
- 3-5 pre-clinical assets
- Strong capabilities in R and D
- ~250 employees

2023-2025

- Significant pipeline expansion
  - 3-5 commercial products
  - 5-10 clinical stage assets
  - >10 products in pre-clinic
- Hematology market leader
- Strong solid tumor and autoimmune franchises
- Mature platform in R, D, M & C
- 3000-5000 employees

Today's Agenda

- Clinical Development Overview by Dr. Sean Zhang
- Liquid Tumor Clinical Development by Mr. Alan Zhu
- Solid Tumor Clinical Development by Dr. Renbin Zhao
- Autoimmune Disease Clinical Development by Dr. Carrie Zhou
- Translational Research Development by Dr. Jason Zhang

- BD Strategy by Dr. Manish Tandon/Ms. Gina Song

- Target Selection Strategy by Dr. Richard Liu (Small Molecule)
- Target Selection Strategy by Dr. Davy Ouyang (Large Molecule)
- Medicinal Chemistry Strategy by Dr. Xiangyang Chen

- Commercial Insights for R&D by Dr. Zhichao Si

- Q&A and Summary

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Overview of Clinical Development

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Chief Medical Officer

- Over 30 years of experience in clinical practice, and global clinical development of new drugs
- Former CEO and Board Member of Hengrui Therapeutics Inc
- Former Senior Director of Clinical Development at GSK
- Fellow of American College of Clinical Pharmacology (FCP)

张向阳博士
Dr. Sean Zhang

Our Clinical Development Strategy

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Our Therapeutic Area Focus

- Liquid Tumors
- Solid Tumors
- Autoimmune Diseases

In Addition to Expanding Orelabrutinib Indications in Liquid Tumors and Autoimmune Disease, We Will Aggressively Advance Other Clinical Stage Candidates Globally

- ICP-192 pan-FGFR
- ICP-723 pan-TRK

Strong Commitment to Global Innovative Drug Development

- To develop best-in-class or first-in-class drugs with differentiation points
- To meet the significant unmet medical needs

Product Pipeline – Liquid Tumors

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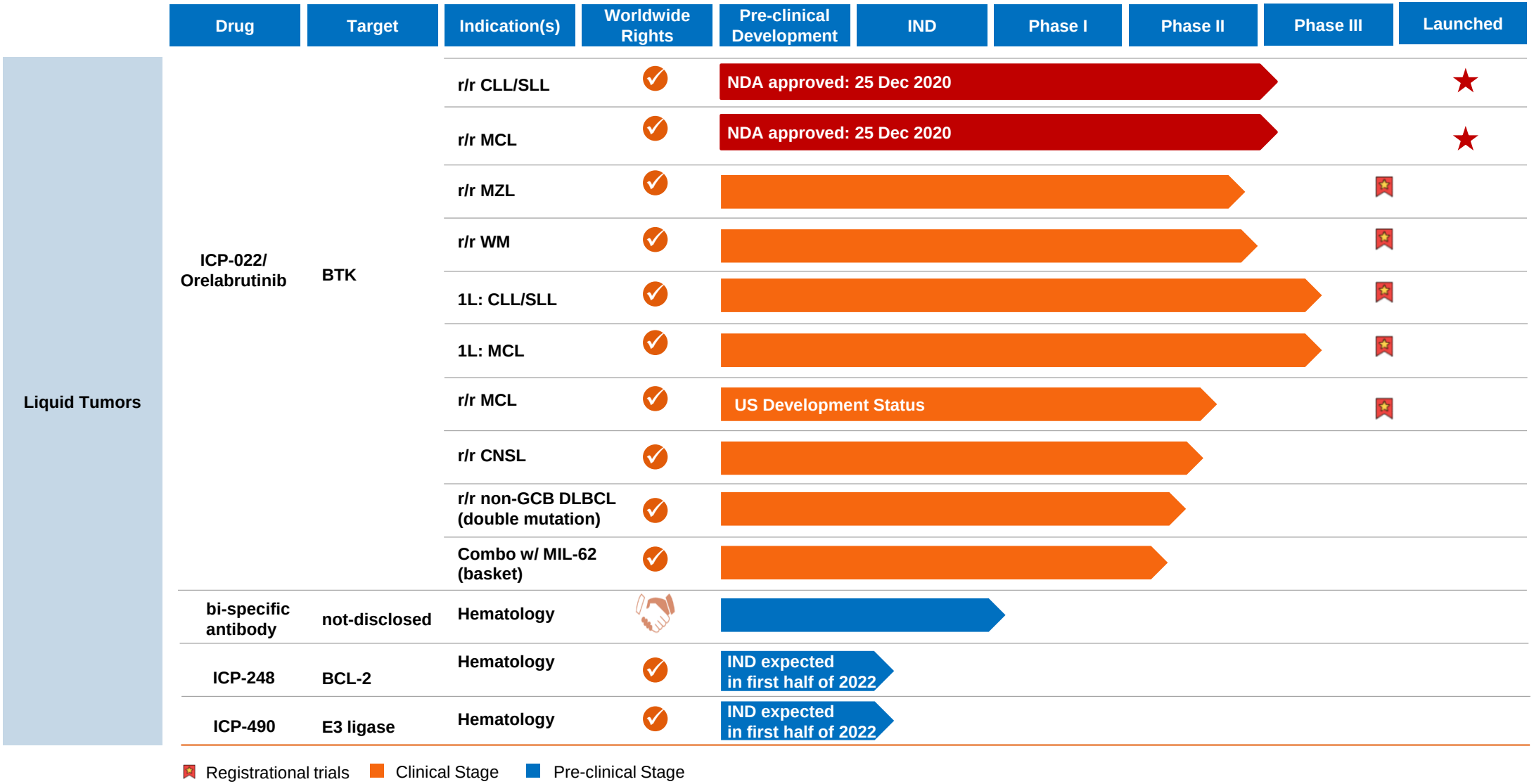

Product Pipeline – Solid Tumors and Autoimmune Diseases

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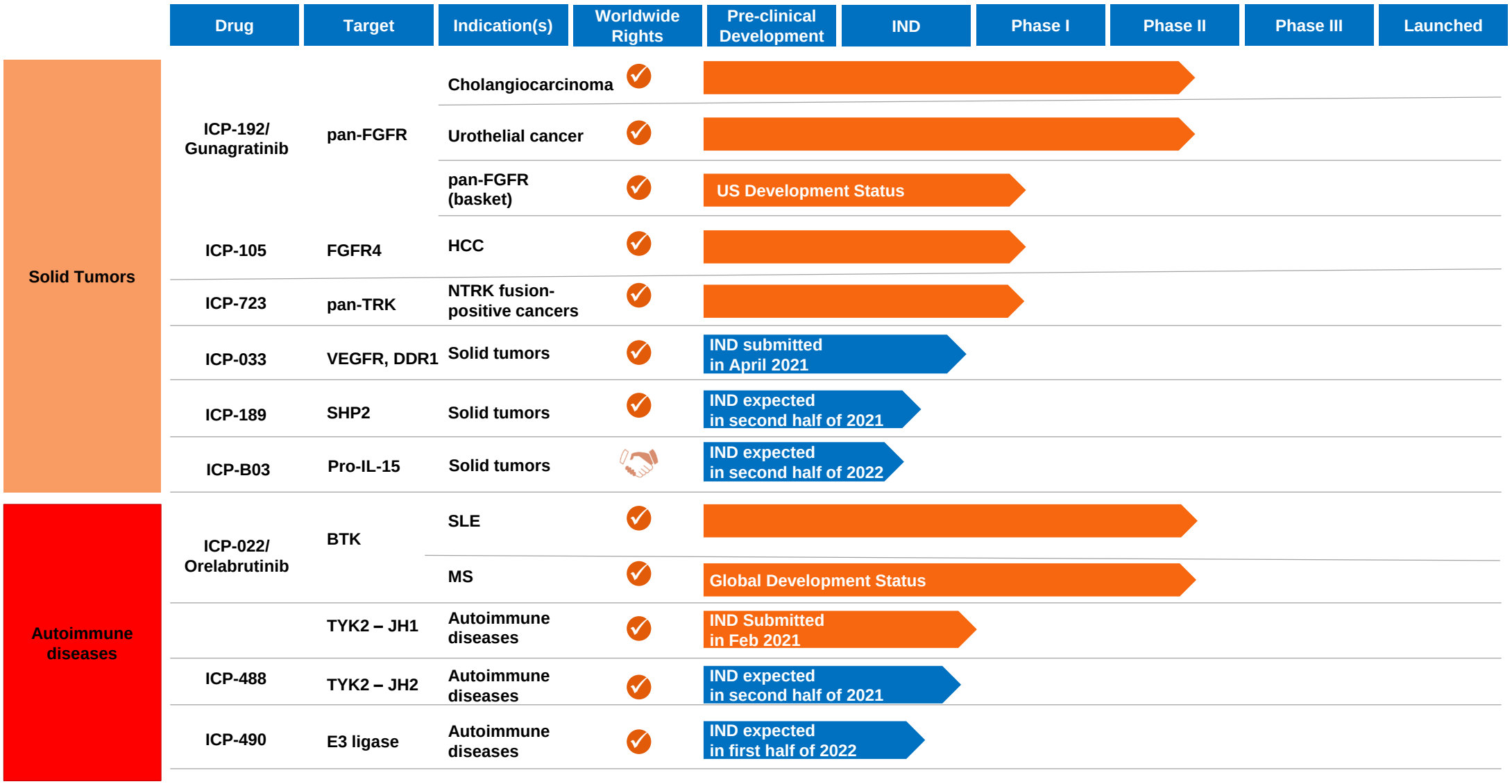

Experienced Development Team with Seamless Study Execution

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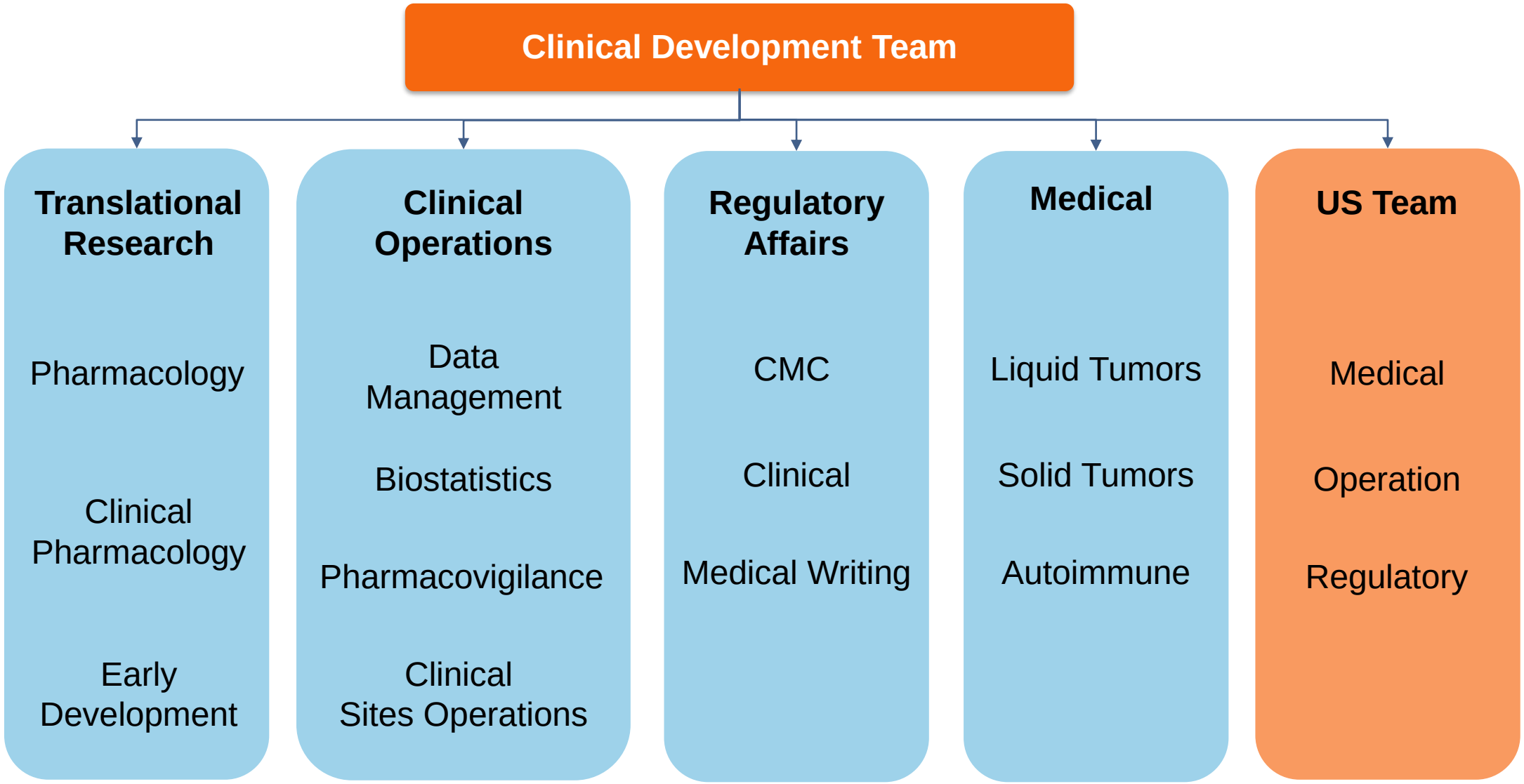

Strong Commitment to Global Innovative Drug Development

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Our Goal

- To build a global platform to support company's clinical development and market expansion worldwide

Our Approaches

- Leverage the clinical data generated from China and ex-China to expedite clinical development process and market application
- Reach out to global medical communities including liquid tumors, solid tumors and auto-immune KOLs to better understand clinical needs and adjust our clinical development strategy accordingly
- Build-up relationship with key drug development partners including relevant CROs for smooth study execution

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Orelabrutinib Clinical Development in B Cell Malignancies

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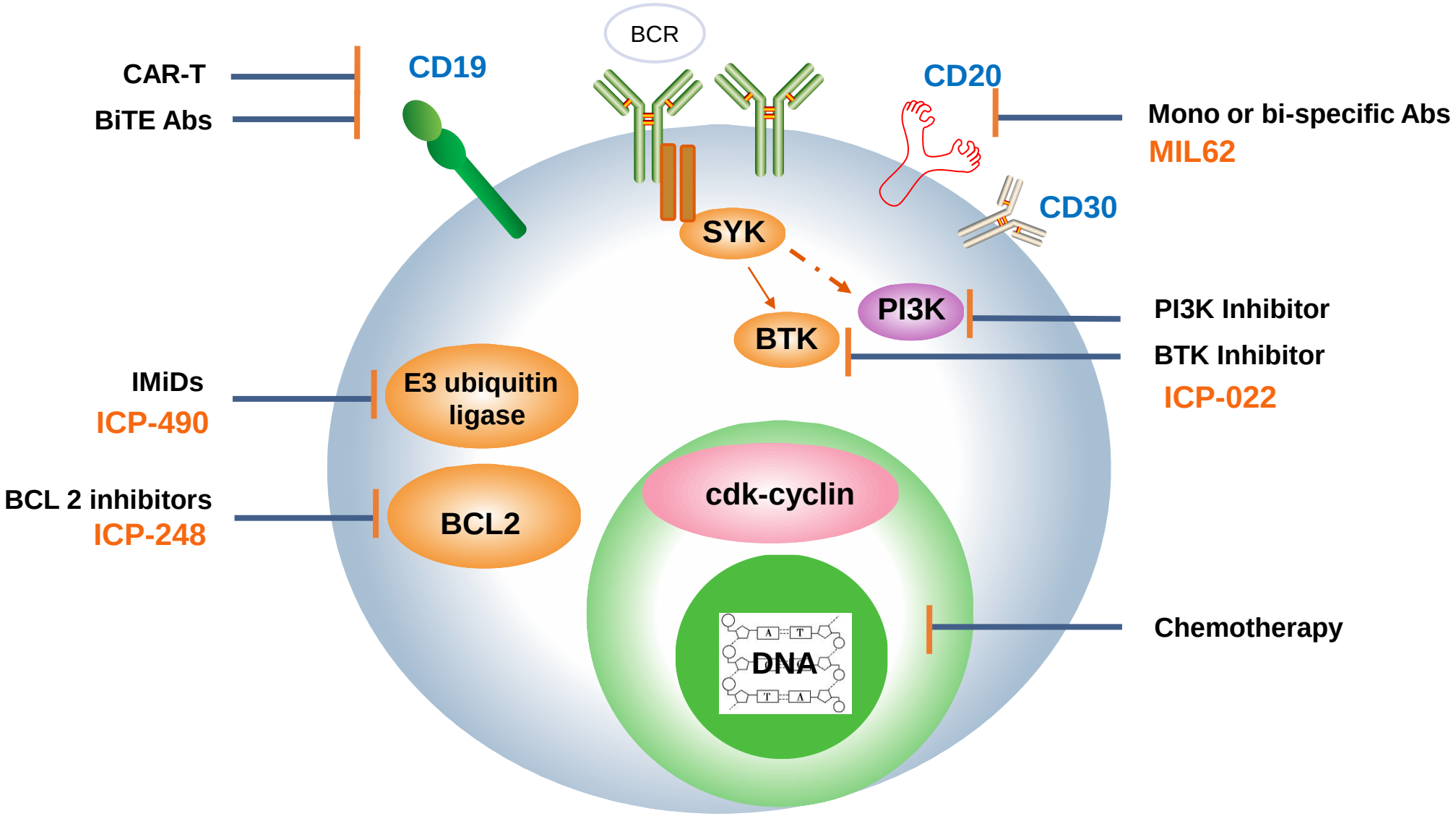
Senior Director of Medical Research

- More than 20 years of clinical research experience
- Former Medical Director at Chipscreen, Bettapharma, BMS
- Oncologist at Zhejiang Cancer Hospital

朱华强先生
Mr. Alan Zhu

Target Therapies in B-Cell Malignancies



NHL Treatment Landscape

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New target and Novel Therapies

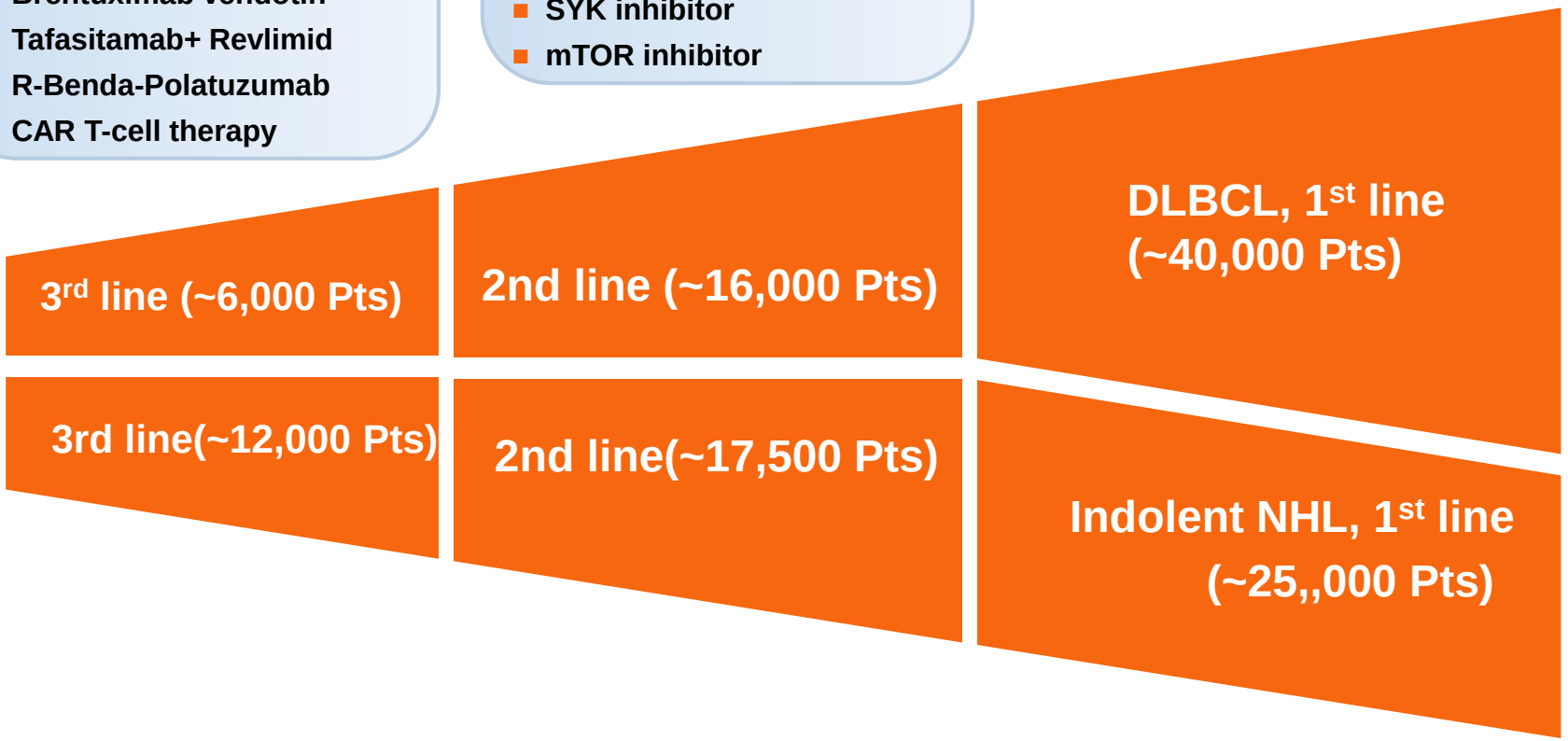
- R-Bendamustine
- R-GemOx, R-GDP
- Revlimid + R (R2)
- Brentuximab vendotin
- Tafasitamab+ Revlimid
- R-Benda-Polatuzumab
- CAR T-cell therapy

Target therapies/Combo therapies

- R-GemOx, R-GDP
- BTK inhibitor ± R
- BCL-2 inhibitor ± R
- PI3K Inhibitor
- EZH2 inhibitor
- SYK inhibitor
- mTOR inhibitor

Traditional Chemoimmunotherapy

- RCHOP
- REPOCH
- RCVP
- BR



Ambition in DLBCL

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Explore r/r DLBCL indication opportunity

MIL62+Orela (in B NHL)

Completed dose escalation
Expansion cohort

- r/r DLBCL
- r/r MCL, FL …
- Phase II study in r/r DLBCL
- Primary endpoint: ORR
- Planning CDE communication in 2021

Bispecific antibody

IND expected 2H2021
Cooperated with Keymed Biosciences Inc

Biomarker enrichment strategies

Orelabrutinib r/r DLBCL

r/r DLBCL with MYD88+ & CD79b+

- Single arm, phase 2 study
- Primary endpoint: ORR

Orela combo in DLBCL

Explore front line treatment for DLBCL

MIL62: Humanized type II anti CD20+ monoclonal Antibody
Beijing Mabworks Biotech Co.Ltd

CLL: Orelabrutinib Backbone Strategy

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r/r CLL/SLL: Best BTKi

Orelabrutinib Mono

- High CR rate: 21.3%
- Durable response: median DOR not reached @ 25.5 mo
- Well tolerated: Few off-target toxicities

Approved by NMPA

Treatment naive CLL/SLL: To be first choice

Orelabrutinib Mono

- Phase III study Orelabrutinib vs Chlorambucil Plus Rituximab

Explore Limited-Duration Therapy

Orelabrutinib Combo Therapy

- IIT
- MRD guided treatment, MRD primary endpoint
- Pilot study for Phase III design

Developing innovative therapies, with limited duration of treatment

- MIL62
- BCL-2 inhibitor

MCL: Orelabrutinib Moving Toward The First Line Setting

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r/r MCL: Best-in-class BTKi

Orelabrutinib Mono

- High ORR: 87.9%
- Durable response: median DOR not reached @ 16.4 mo
- Well tolerated: Few off-target toxicities

Approved by NMPA

Treatment naive MCL: To be first choice

Orelabrutinib Combo

- Phase III study Orelabrutinib+RCHOP vs RCHOP

More to explore in frontline therapy

Developing chemo free regimens

- MIL62
- BCL-2 inhibitor

Clinical Development For The Treatment of Other B Cell Malignancies

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r/r WM: to be the best choice

Orelabrutinib Mono

- Phase 2 study endorsed by CDE as registration trial
- Completed recruitment at the end of 2020
- NDA filing 2022

r/r MZL: to be the best choice

Orelabrutinib Mono

- Phase 2 study endorsed by CDE as registration trial
- Plan to complete recruitment in 2021

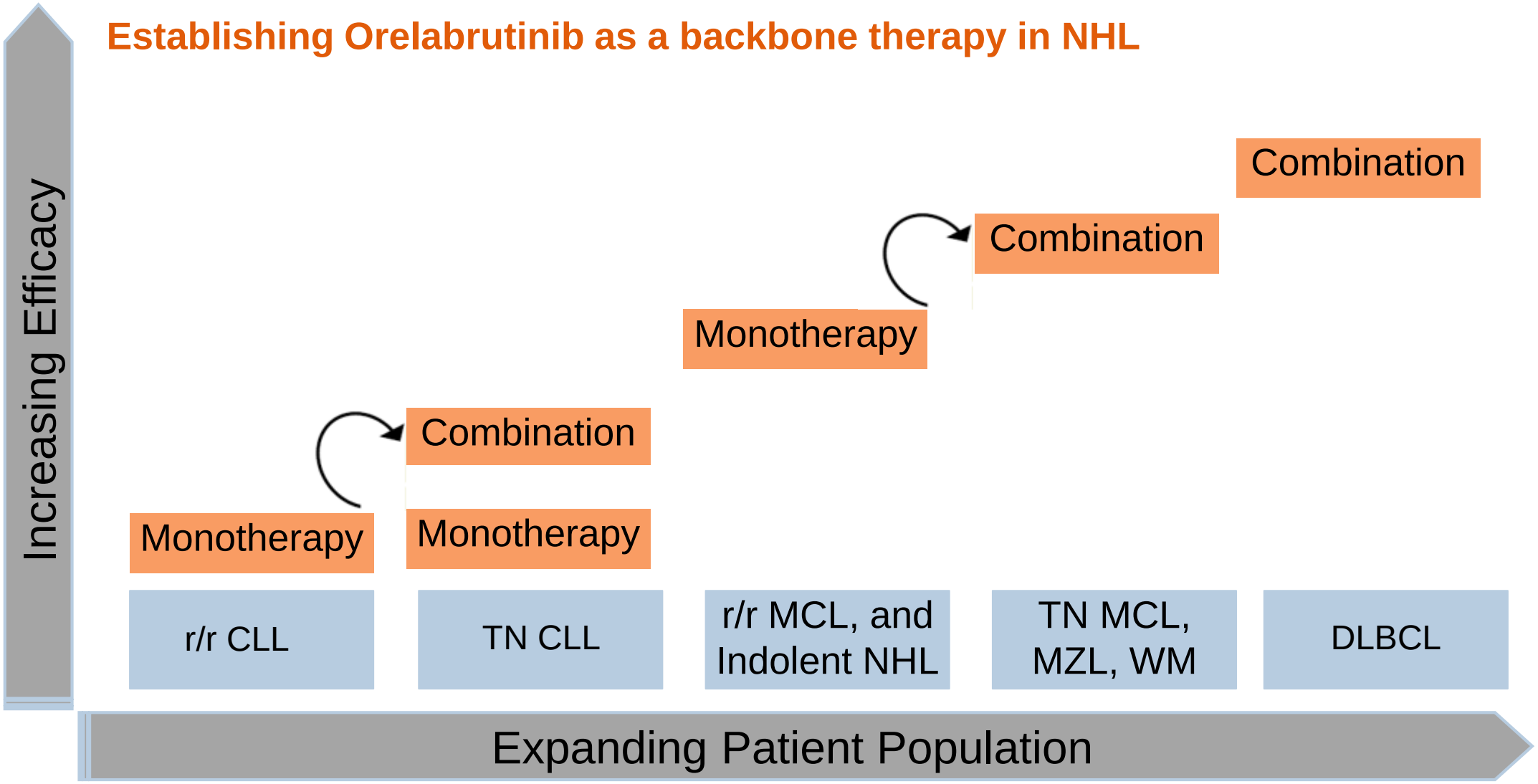
r/r PCNSL/SCNSL

Orelabrutinib Mono

- Phase 2 study of two cohorts with starting dose of 150mg QD
- Discussing with CDE about phase 2 registrational trial

Orelabrutinib Expanding in NHL

Establishing Orelabrutinib as a backbone therapy in NHL



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Research and Pipeline in Solid Tumor

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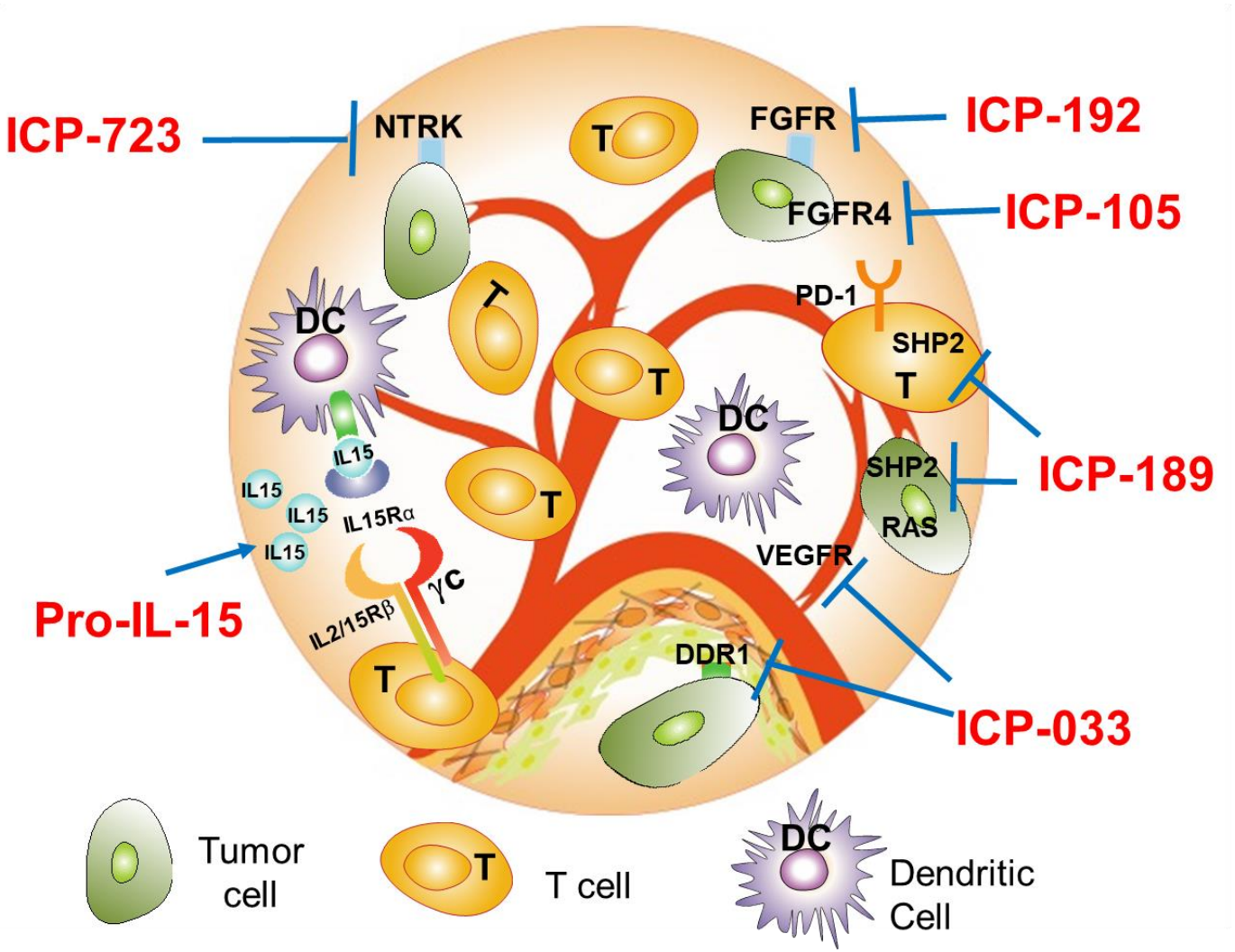
VP of Clinical Development and Regulatory Affairs

- More than 20 years of drug discovery experience
- Former Director of Discovery Biology at BioDuro, a PPD company
- Former Principal Scientist at J&J
- Ph.D. from Johns Hopkins School of Medicine

赵仁滨博士
Dr. Renbin Zhao

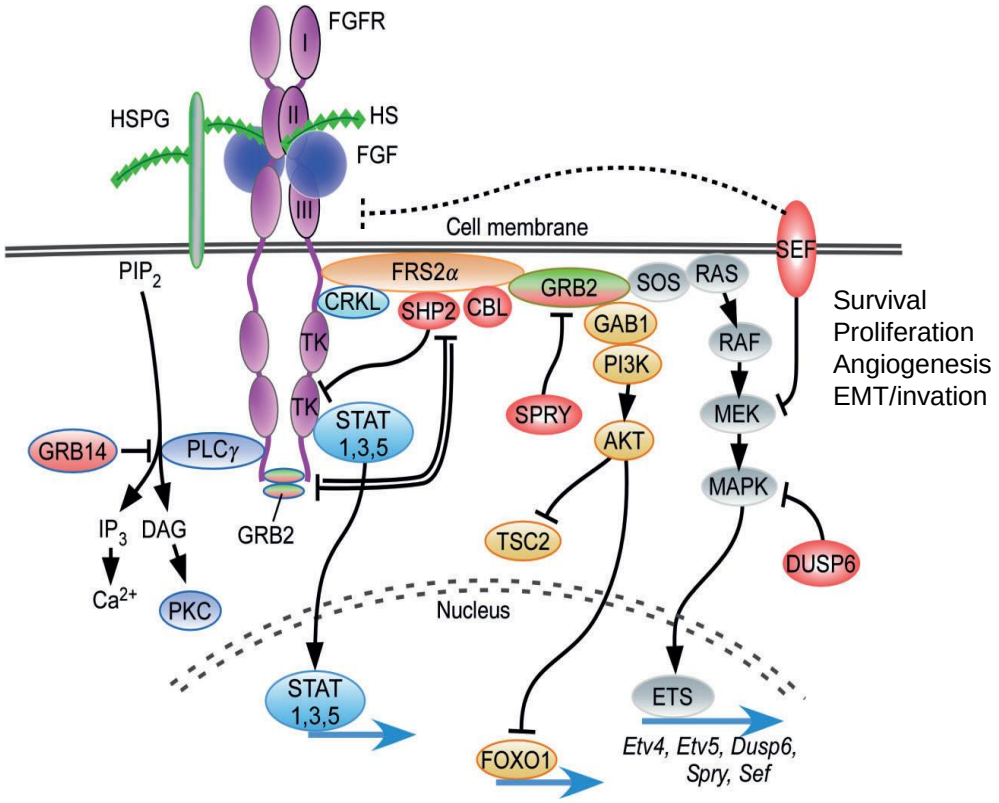
Solid Tumor Pipeline



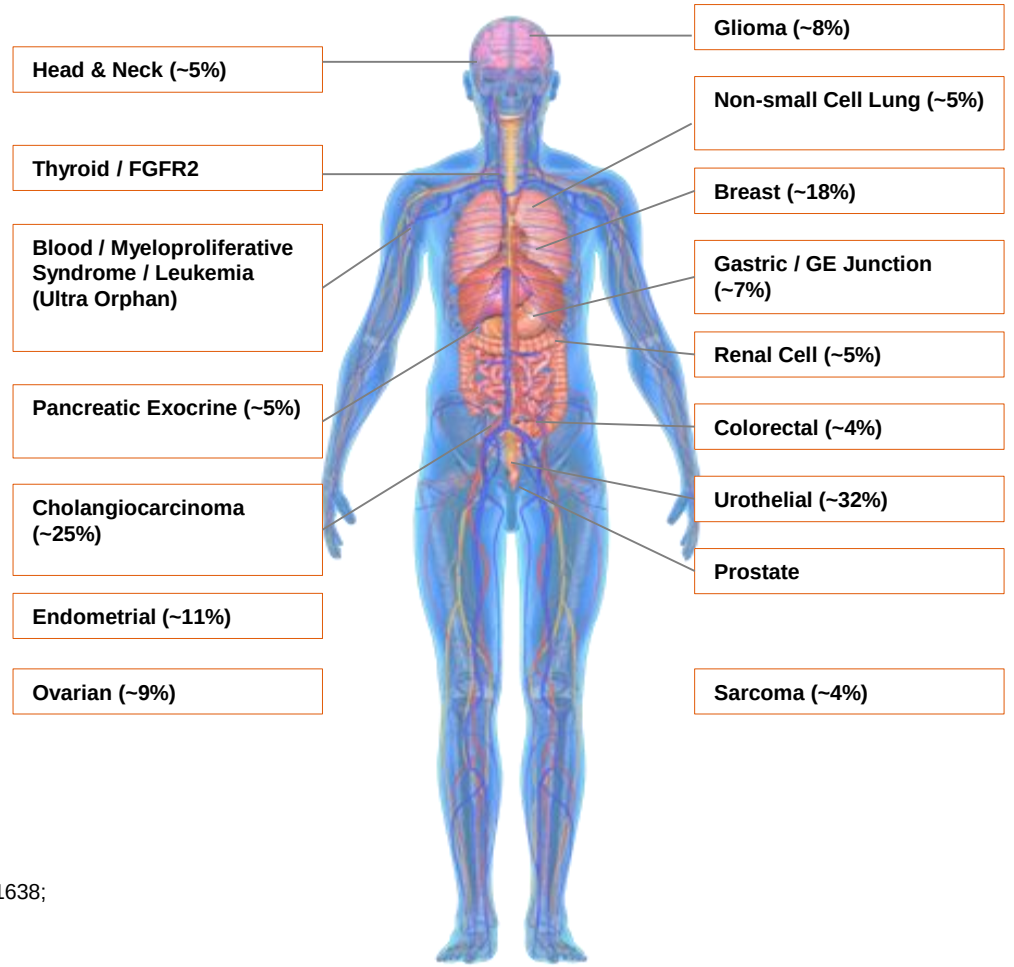
- **Target therapy (ICP-192, ICP-723, ICP-189, ICP-105)**
  - Excellent target selectivity
  - Biomarker driven precision medicine
- **Immuno-Oncology (ICP-189, Pro-IL-15)**
  - Depleting tumorigenic TAM, activating T cells by targeting SHP2.
  - Tumor activated IL-15 to activate T cell
  - Turn cold tumor to hot
- **Anti-Angiogenesis (ICP-033)**
  - VEGFR: a validated target for multiple solid tumors
  - DDR for tumor invasion
- **Combo strategy**
  - PD-1 and ICP-189
  - Target therapies with IO
  - ICP-033 with target therapy or IO

FGFR: A Target for Multiple Solid Tumors

Mechanisms of oncogenic FGFR signal



Frequency of All Currently Known FGFR 1, 2, 3 and 4 Aberrations



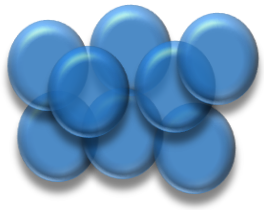
Note:

Wiley Interdiscip Rev Dev Biol. 2015 May-Jun;4(3):215-66.

Helsten et al., Clin Cancer Res 2016 (22), 257-267; FGFR2 fusions in iCCA: Graham et al. Hum Pathol 2014 (45), 1630-1638;

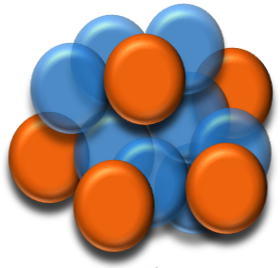
Jain et al. JCO Precis Oncol 2018 (2) 1-12; Frost & Sullivan analysis

Next-Generation pan-FGFR Inhibitor Overcomes Acquired Resistance to First-Generation FGFR TKIs



FGFR Alterations

First-generation FGFR inhibitor



FGFR Alterations

FGFR2	FGFR3	
V564F/I/M	V555M	Gatekeeper
N549H/K	N540K	
E565A		
L617M	L608V	
K641R		
K659M	K650E	
....	...	

FGFR Resistant mutations

First-Generation FGFRi

Erdafitinib (JNJ-42756493)
Pemigatinib (INCB54828)
Rogaratinib (BAY1163877)
Infigratinib (BGJ398)
Derazantinib (ARQ087)

Reversible/ ATP-Competitive

Second-Generation FGFRi

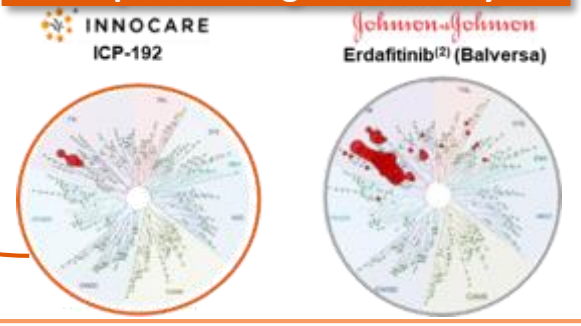
ICP-192

Irreversible/ Covalent

Overcome Acquired Resistant

Biochemical assay	IC_{50} (nM)	
	BGJ398	ICP-192
FGFR2 (N549H)	8.15	1.84
FGFR2 (V564I)	55.60	3.14

Improved Target Selectivity



ICP-192: Potential Best-in-Class Pan-FGFR Inhibitor

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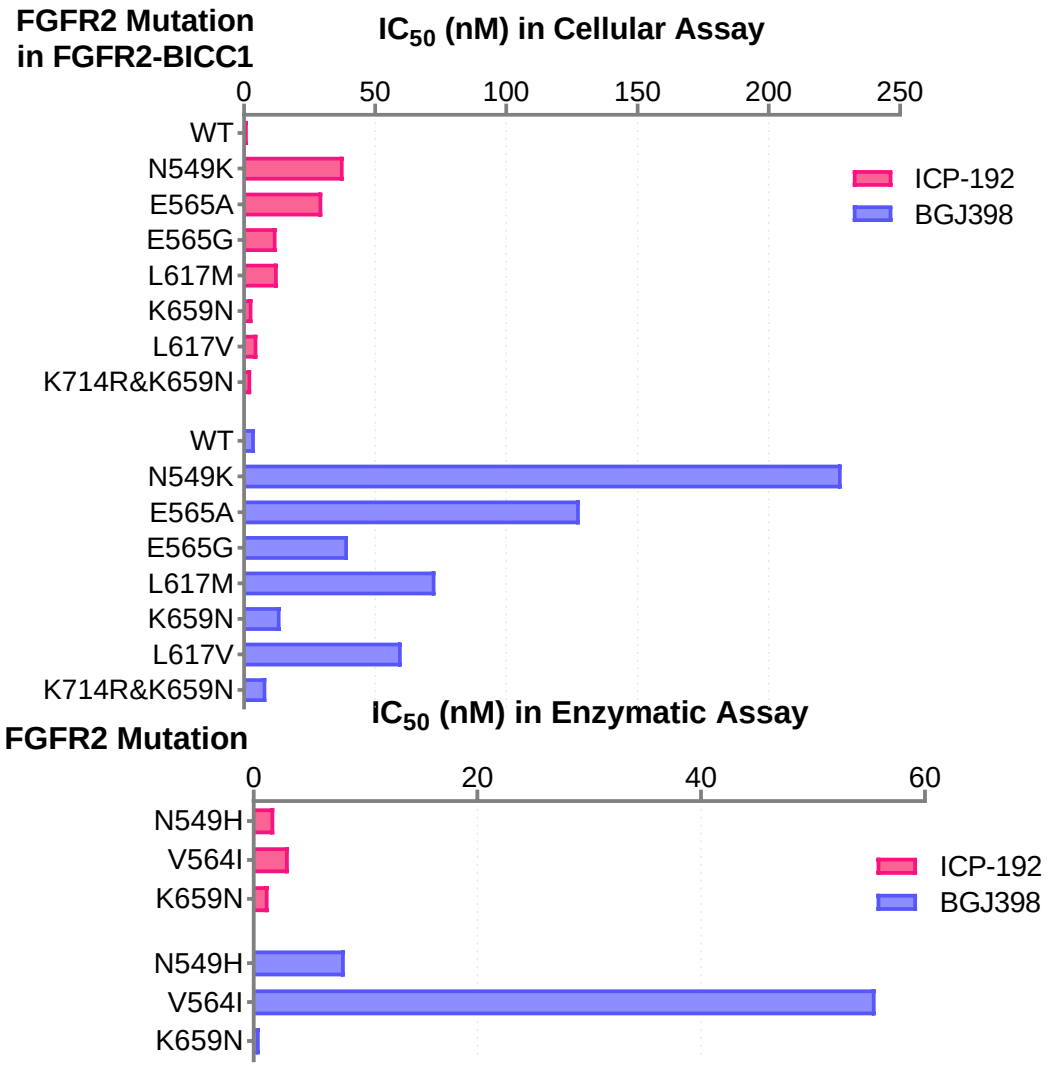
Overcomes Acquired Resistance to other FGFR Inhibitor



ICP-CL-00301: Preliminary Data Overview

Phase 1a
Dose Escalation Study
Advanced solid tumor patients (n=22)

16 mg QD PO	3 Pts
14 mg QD PO	4 Pts
12 mg QD PO	4 Pts
10 mg QD PO	3 Pts
8 mg QD PO	5 Pts
4 mg QD PO	1 Pt
2 mg QD PO	2 Pts

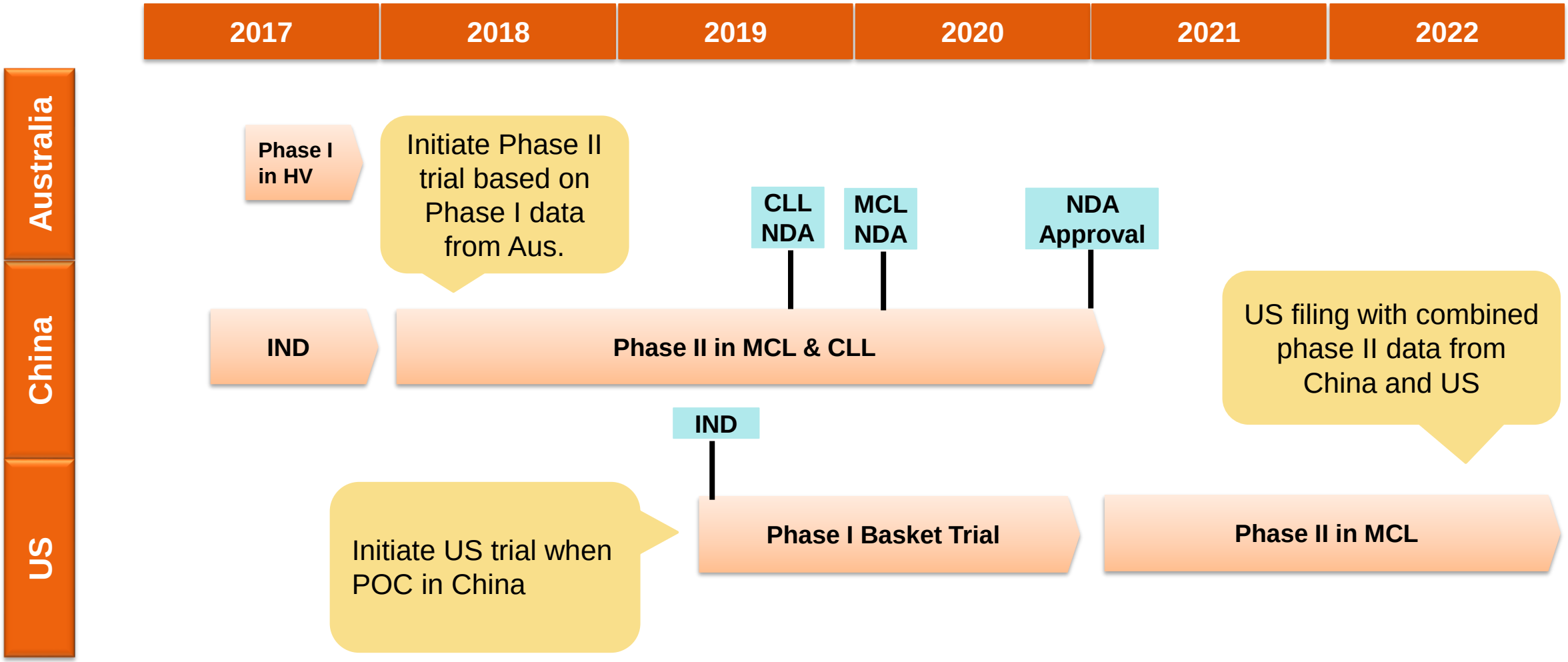
RP2D

Phase 2a
Dose Expansion Study

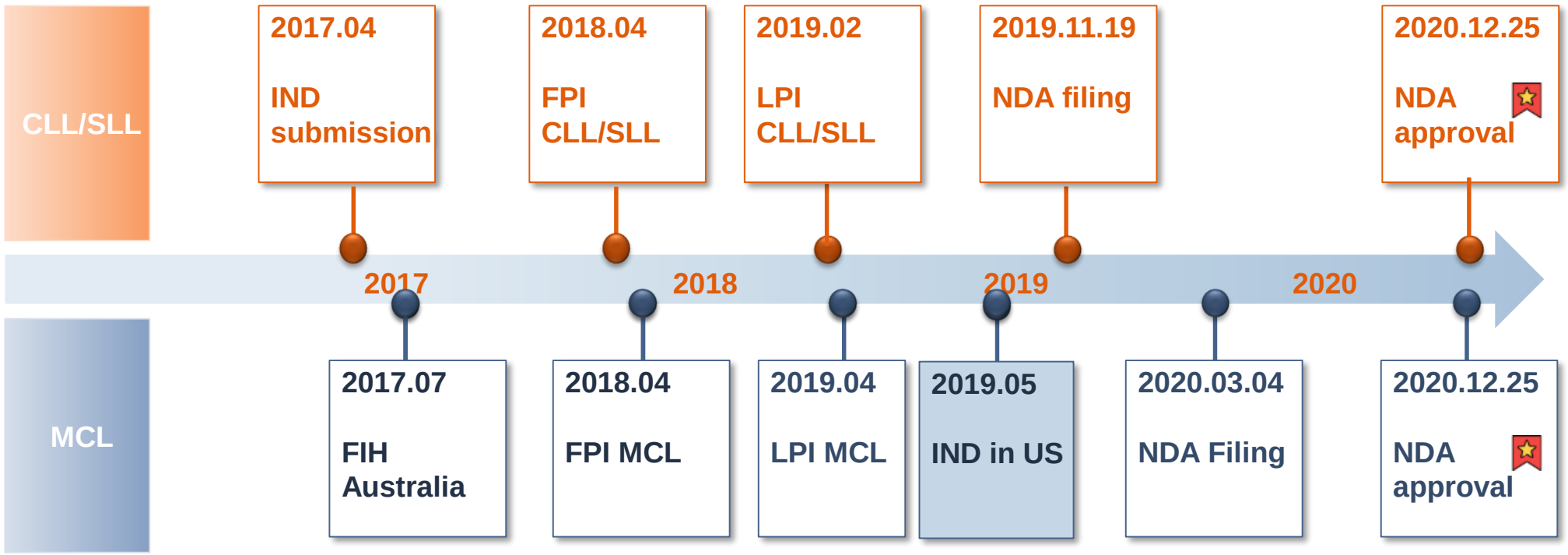
ICP-CL-301
iCCA (harboring FGFR2 fusion/rearrangement)
No: of patients: 15

	Patients with FGF/FGFR alterations
Total patients, n	30
Evaluable patients, n	12
CR, n	1 (8.3%)
PR, n	3 (25%)
ORR, n	4 (33.3%)
SD, n	7 (53.8%)
DCR, %	91.7

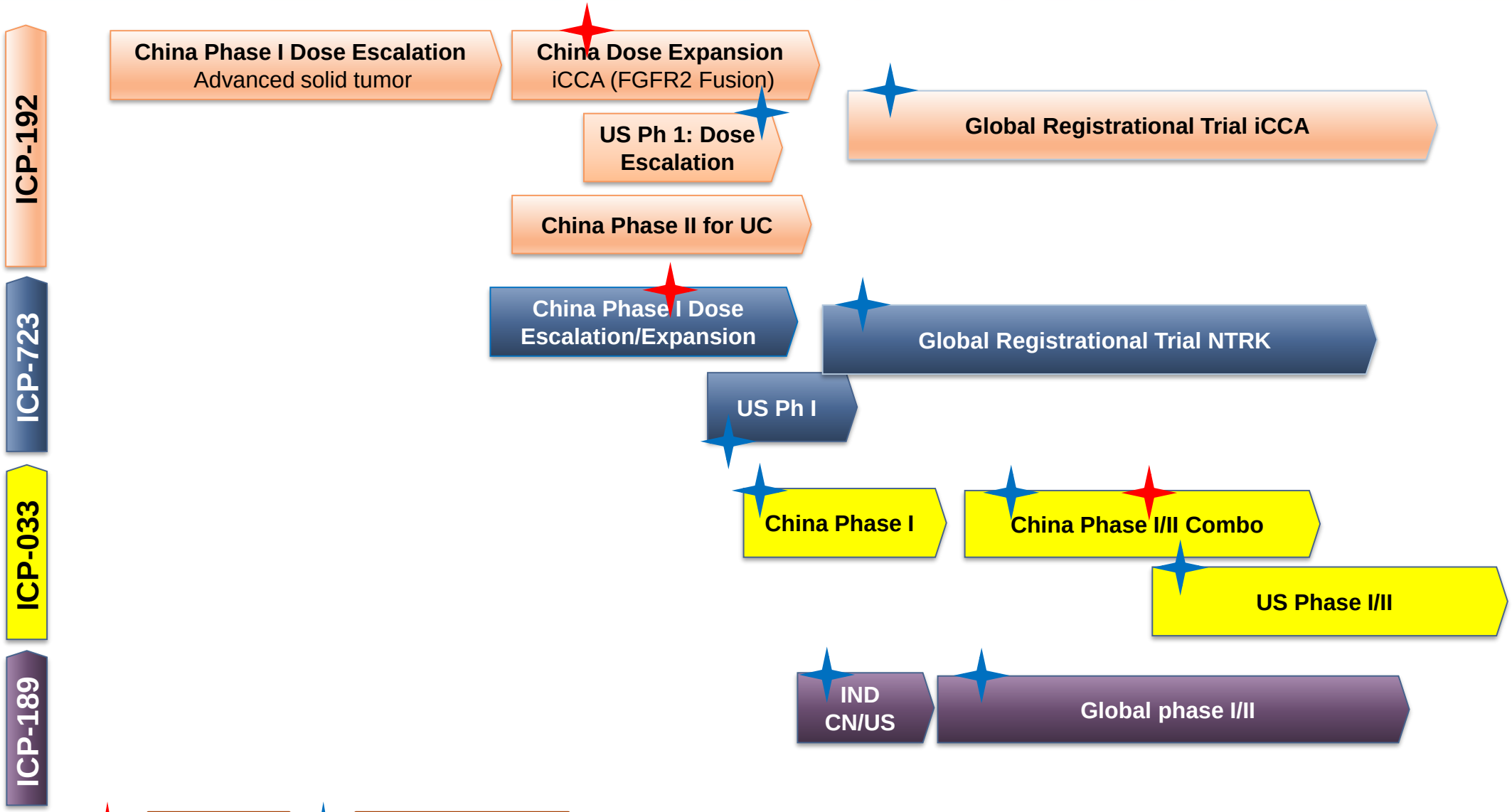
Accelerated Registration Strategy for Orelabrutinib



Highly Effective Clinical Development Team



Clinical Development Plan for Solid Tumor



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Autoimmune Disease Clinical Development

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Executive Medical Director

- More than 15 years of new drug clincial development experience
- Former Non-oncology Medical Head of Hansoh
- Former Asia Medical Direcotr of Takeda (Immuology, Neuroscience and CVM)
- Ph.D. of Nephrology
- Master of Surgery
- Master of Science in Pharmaceutical Medicine

周伟博士
Dr. Carrie Zhou

Autoimmune Pipeline and Disease Area Expansion Strategy

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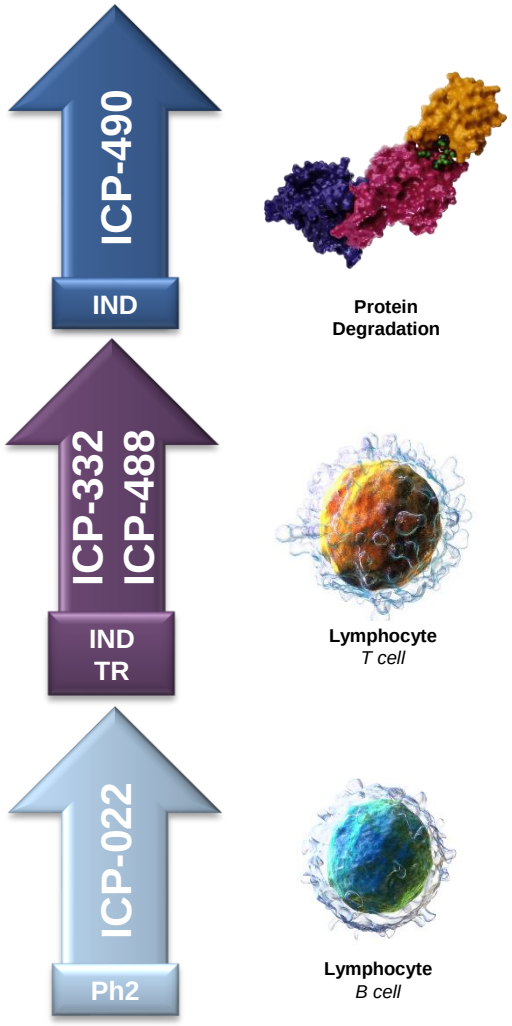


Nephrology

Gastroenterology

Dermatology

Hematology

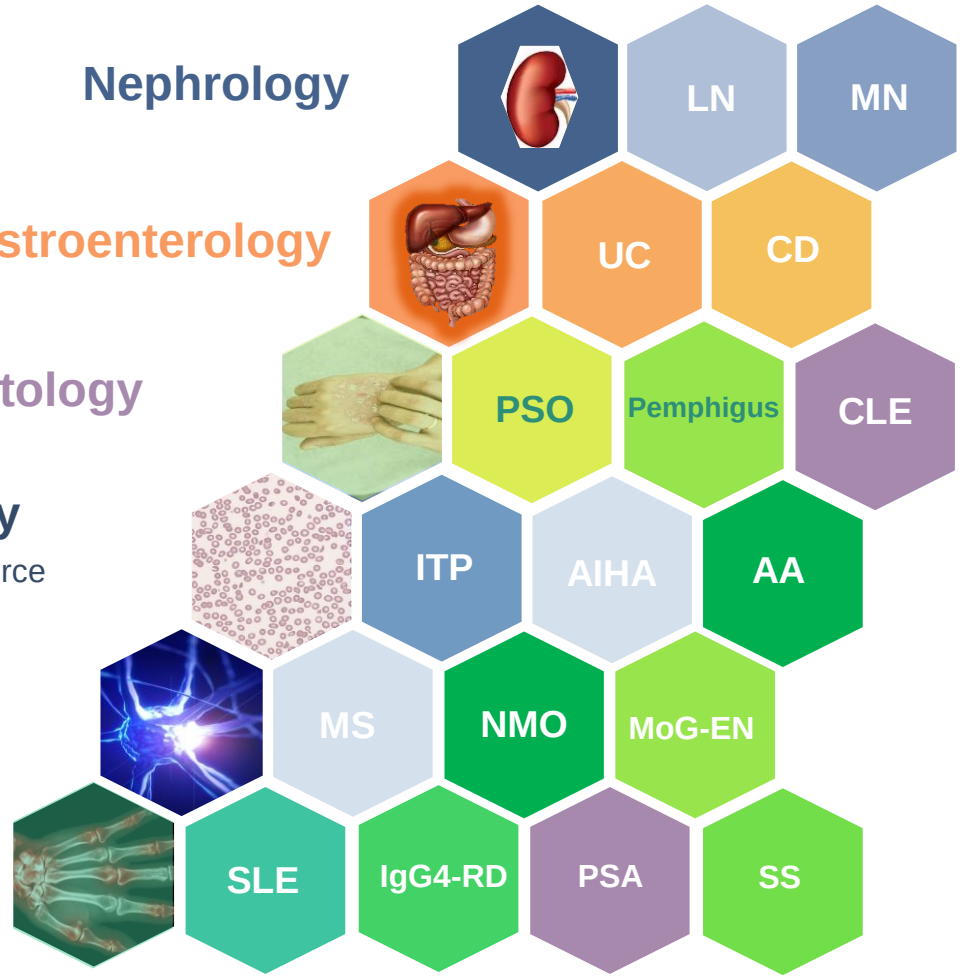
✓ Integrated Resource

Neurology

✓ Central and peripheral dual mechanism

Rheumatology

✓ Multiple compounds with multiple mechanism



AA: Aplastic Anemia
AIHA: Autoimmunehemolytic Anemia
CD: Crohn's Disease

CLE: Cutaneous Lupus Erythematosus
IgG4 RD: Immunoglobulin G4-related disease
ITP: Immune thrombocytopenic purpura

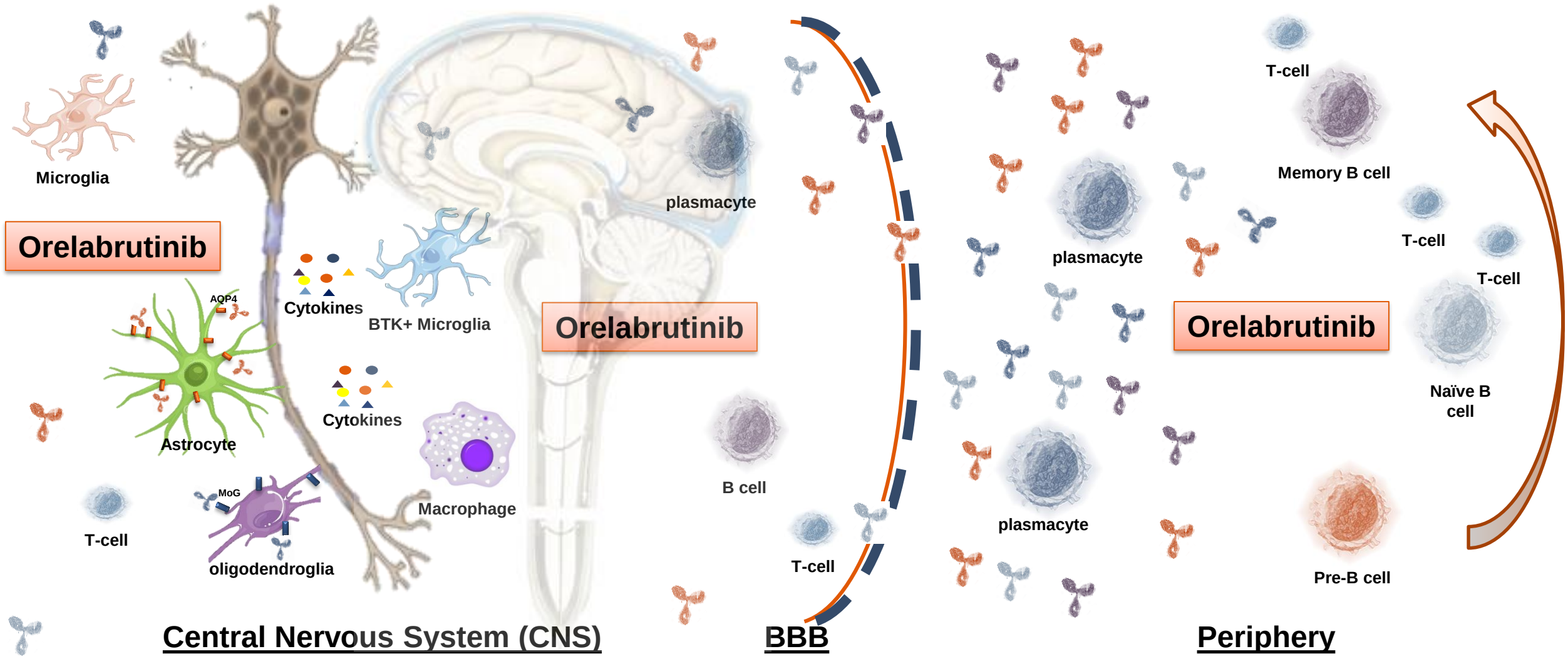
LN: Lupus Nephritis
MN: Membranous Nephropathy
MoG-EN: MOG encephalomyelitis

MS: Multiple Sclerosis
NMO: Neuromyelitis optica
PsA: Psoriatic Arthritis

PsO: Psoriasis
SLE: Systemic Lupus Erythematosus
SS: Sjogren syndrome

TR: Translational Research
UC: Ulcerative Colitis

Orelabrutinib Has Potential to Act in Both CNS and Periphery for Demyelinating Diseases



Orelabrutnib's BBB Penetration and Microglia's Role in MS Disease Progression

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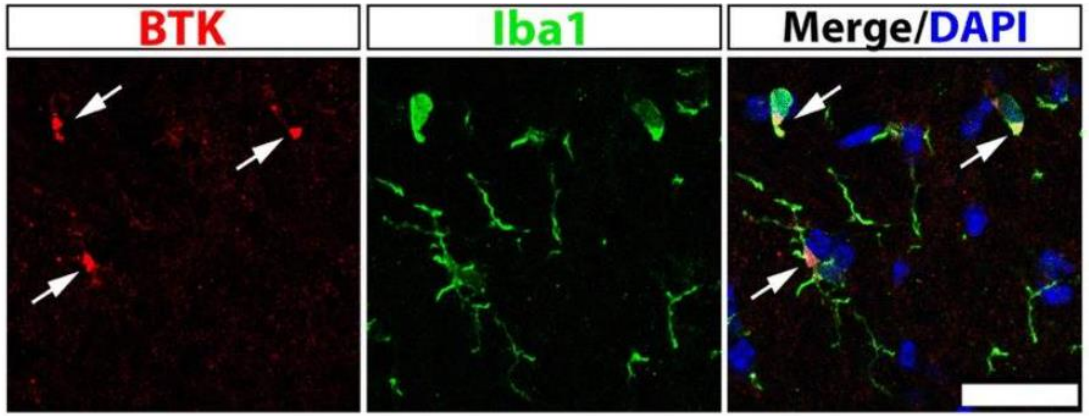
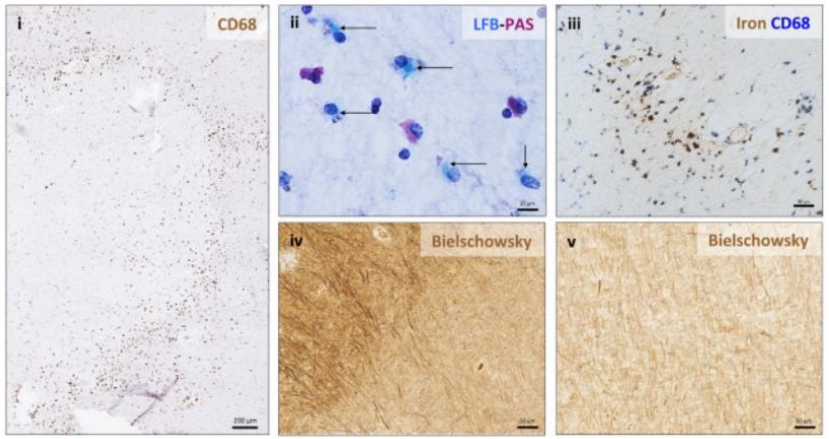
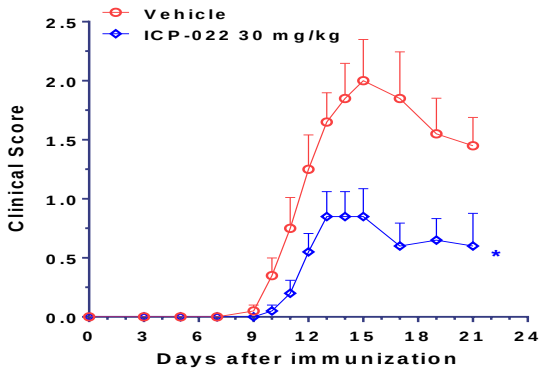
Representative confocal microscopy images of BTK immunoreactivity in Iba1-positive microglia in brains of wild-type mice[1]



Microglia are increased in the MS lesion rim[2]



Robust Pre-clinical Efficacy Profile



EAE model

Orelabrutinib's BTK pathway inhibition coupled with PK profile and BBB penetration presents a promising option for treating MS

BTK Inhibitor	Enzymatic IC_{50} (nM)	Cellular IC_{50} (nM)	Dose	CSF, 2 h (ng/mL)	CSF/ Cellular IC_{50}	C_{max} (ng/mL)	AUC (hr*ng/mL)
Orelabrutinib	1.6	3.4	150 mg	20.1	14x	1279	7000
Evobrutinib	8.9	N.A.	75 mg	N.A.	N.A.	252	345
SAR442168	~1.5	~0.4-0.7	120 mg	1.87	2.6-4.7x	~30	~80

Note:

[1] Keaney J et *al J Neuroimmune Pharmacol*. 2019; 14(3): 448–461.
[2] Absinta et al *J Clin Invest*. 2016 Jul 1; 126(7): 2597–2609.

This slide is compiled from different clinical studies at different time point, with difference in trial design and patient population. No head to head trilas have been conducted. Not published data, maybe inaccurate.

Concentration: ng/ml

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Translational Research

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Senior Director of Pharmacology and Translational Research

- More than 10 years of drug discovery experience
- Former Director of Biomarker Development at QIAGEN
- Former Associate Director at WuXi AppTec
- Ph.D. in Pharmacology from Tsinghua University
- Postdoctoral research fellow at University of Pittsburgh

张斌博士
Dr. Jason Zhang

Translational Medicine/Research

Translational Medicine/Research

- Target Selection
- Compound Design
- **Pharmacology: Potency/Efficacy**
- **DMPK/ADME Evaluation**
- **Toxicology**

Preclinical Discovery & Development

Clinical Development

- **Early Clinical Develop. → POC**
  - **–Safety/Tolerability**
  - **–Efficacy/Biomarker**
  - **–PK/PD**
- Late Clinical Development

Basic Research

Clinical Practice

- Basic Research Breakthrough **(Bench)**
- New Basic Research

- Clinical Application **(Bed)**
- Unmet Medical Needs

Biomarker-Driven Translational Research

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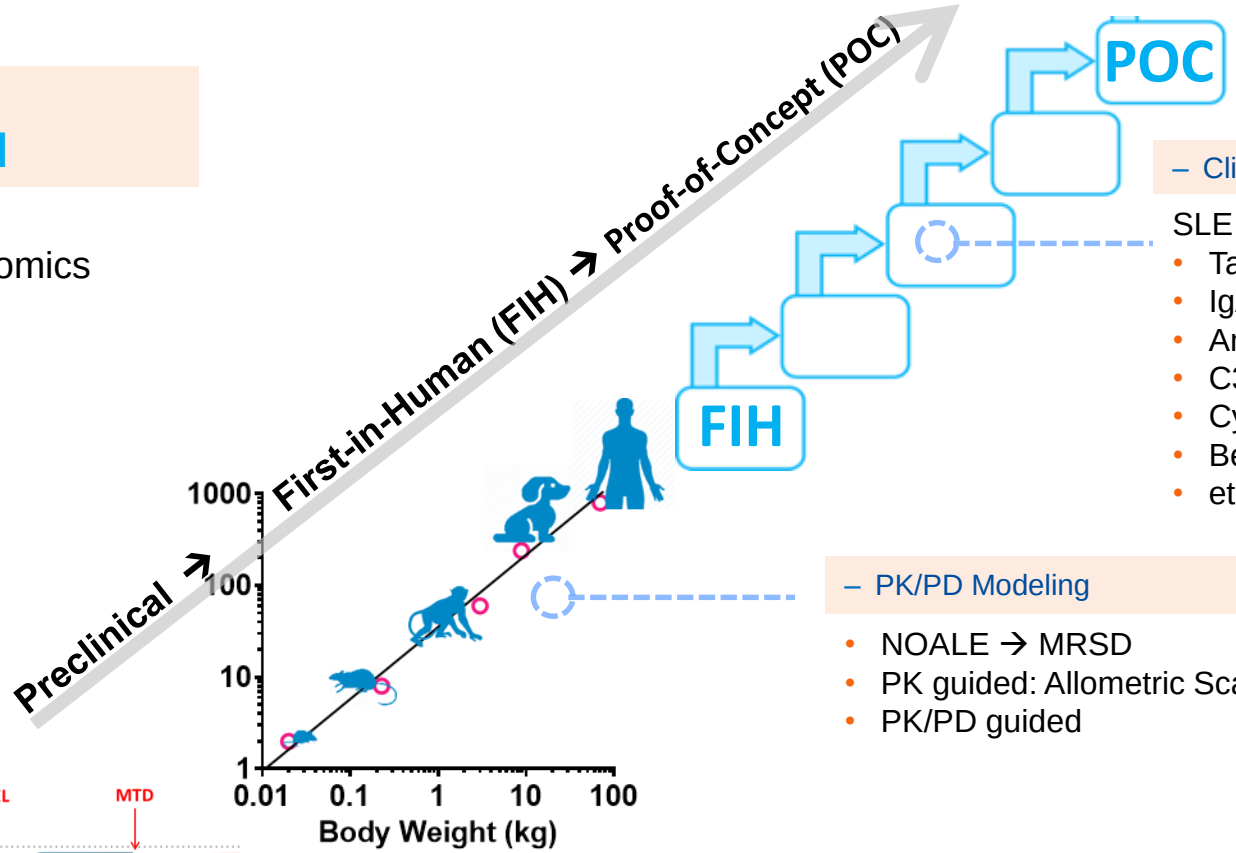
– Translational Research:
Preclinical → Clinical

- Biomarker
- Biology/Genetics and Genomics
- Pharmacology/Toxicology
- Pharmacokinetics (PK)
- Clinical Pharmacology



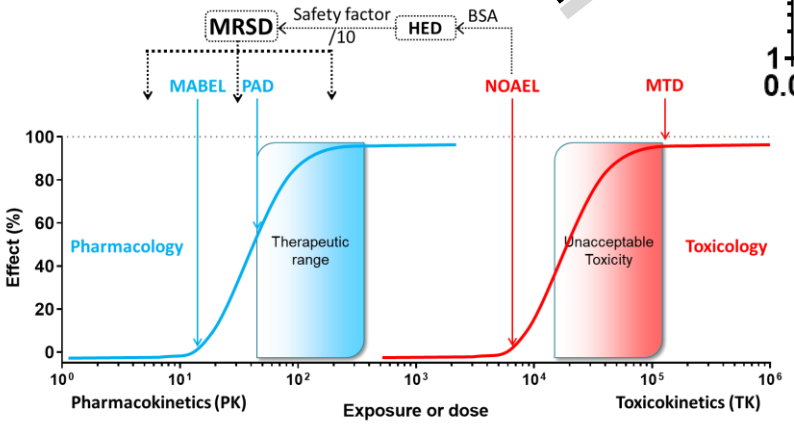
– Clinical Efficacy/Safety Biomarkers, PK/PD

SLE
- Target occupancy
- IgA, IgM, and IgG
- Anti-dsDNA
- C3 and C4 levels
- Cytokine: IFN-α, IL-6
- Beffs/ Bregs
- etc.

MS
- MRI imaging
- TBNK
- IgA, IgM, and IgG
- Neurofilament light chain (NfL)

– PK/PD Modeling

- NOALE → MRSD
- PK guided: Allometric Scaling etc
- PK/PD guided



– In Vitro Pharmacology

- Signaling pathways

– In Vivo Models

- RA: CIA model
- SLE: MRL/lpr model
- MS: EAE model
- Pso: IL-23-induced model

– Preclinical Biomarkers, PK/PD

- Target occupancy
- Imaging
- Cytokines: TNF-α, IL-6, IFN-γ etc.

Preclinical → First-in-Human (FIH)

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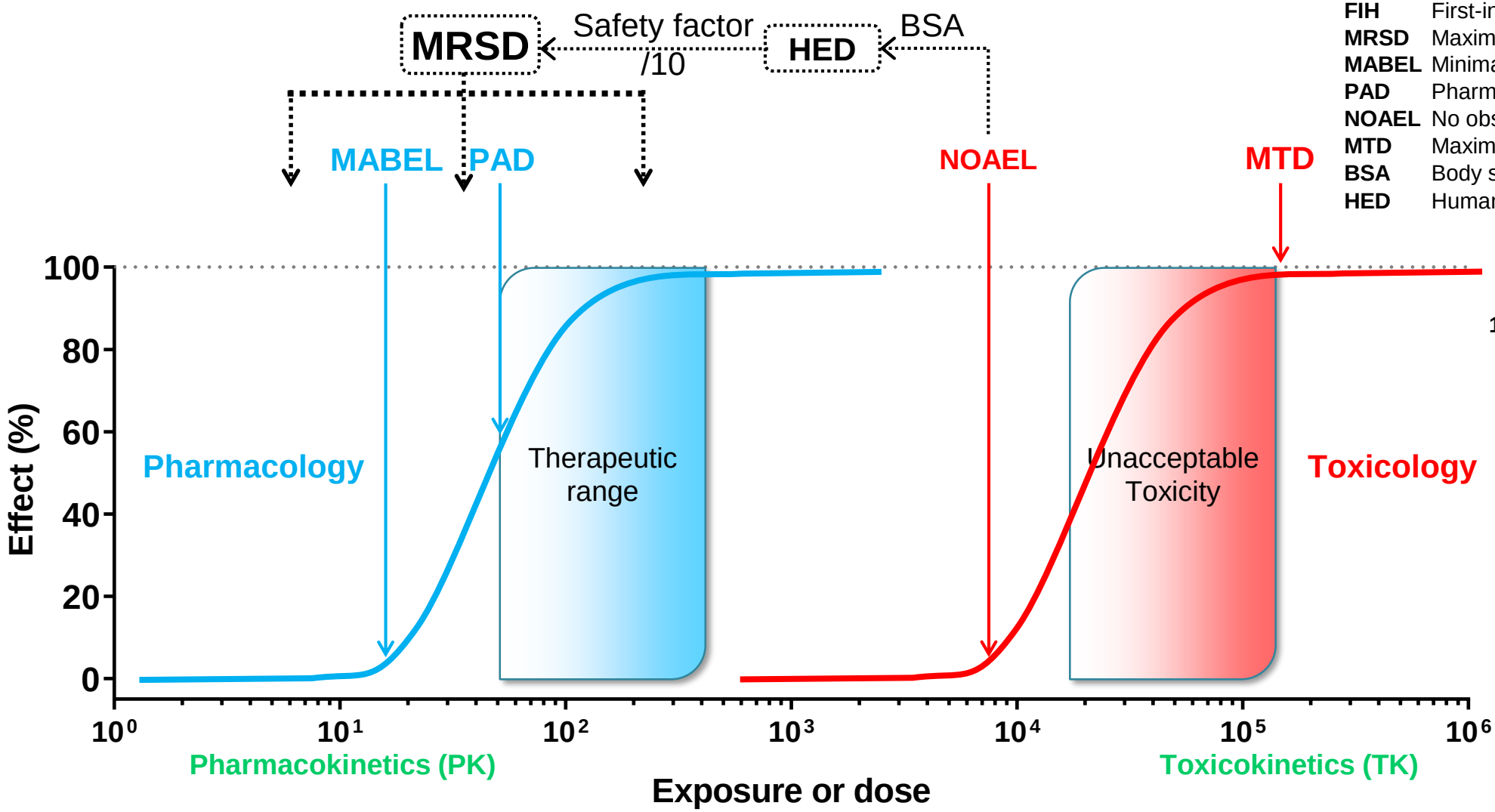
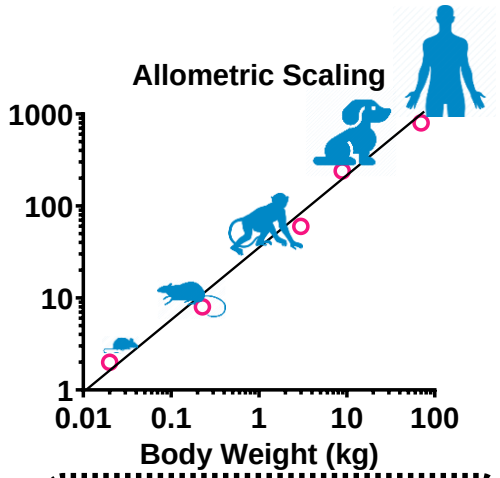
科学驱动创新

FIH	First-in-human
MRSD	Maximum recommended starting dose
MABEL	Minimal anticipated biological effect level
PAD	Pharmacologically active dose
NOAEL	No observed adverse effects level
MTD	Maximum tolerated dose
BSA	Body surface area
HED	Human equivalent dose





- PK-guided: AS, IVIVE, PBPK
- PK/PD-guided

Internal Research Capability

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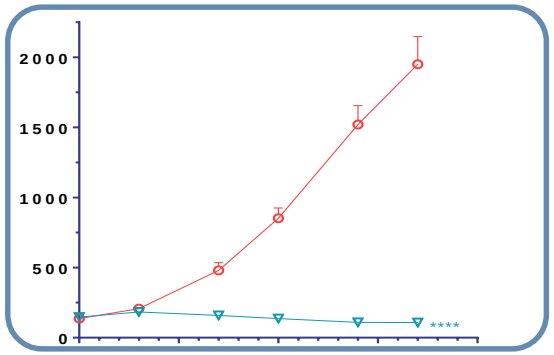
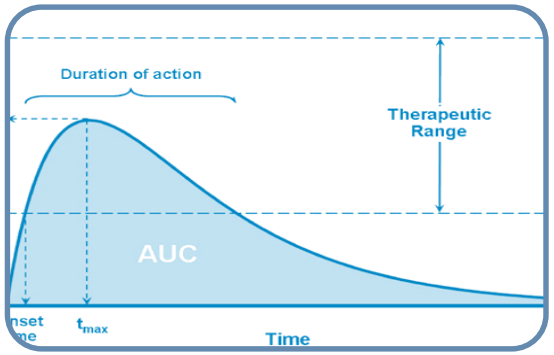
科学驱动创新





Compound

> 500 Pharmacology Studies

1. In Vitro & In Vivo
2. Oncology Models
3. AID Model

> 400 DMPK/ADME Studies

	Validation of Analytical Methods
A	In Vitro Permeability
	PK in Mouse/Rat/Dog/Monkey
D	Plasma Protein Binding
	Tissue Distribution in Rats
	CYP450 phenotyping
M	In Vitro Metabolites in LMs
	In Vivo Metabolites in Rats
E	Excretion in Rats/Dogs
DDI	CYP450 inhibition, induction
	Transporter substrate, inhibition

> 40 Toxicology Studies

1. Acute Tox
2. Chronic Tox
   1). Mouse
   2). Rat
   3). Dog
   4). Monkey
3. TK

- **PCC**
- **IND**

FIH → Proof-of-Concept (POC)/NDA
Changing Landscape of Early Phase Clinical Trials

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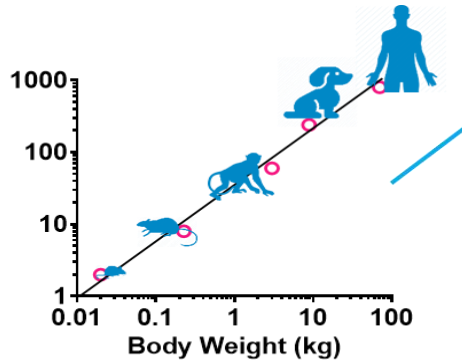
科学驱动创新

"One drug fit all"

Stratified – Personalized – Precision Medicine

Pre-Clinical



○PK-guided
○PK/PD-guided

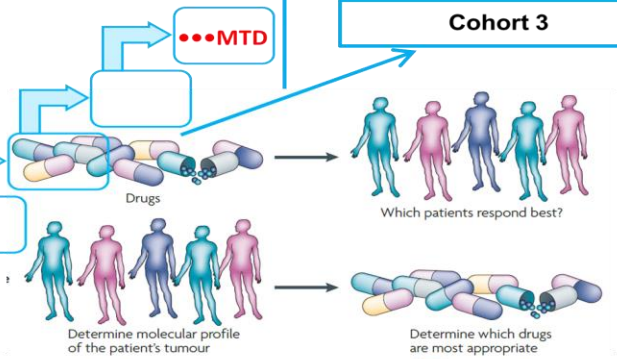
Combined Phase I + II → Accelerated Approval

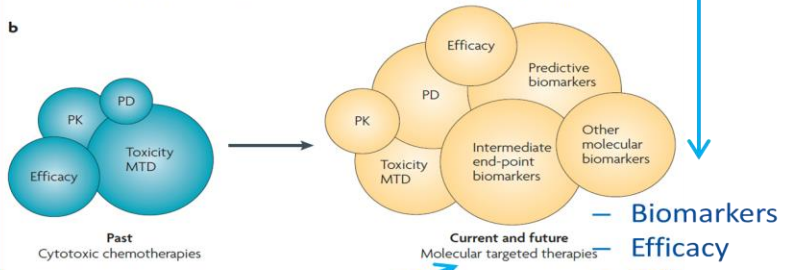
FIH

●●●MTD

Cohort 1
Cohort 2
Cohort 3

Registration
注册研究





- Biomarkers
- Efficacy
- Safety
- PK/PD

- Safety (DLT/MTD)
- PK/PD
- Efficacy

First-in-class

Best-in-class

- Right patient
- Right dose
- Right time
- Right drug

ICP-723: Next-Generation pan-TRK TKIs Address On-Target Resistance to Early-Generation TRKi

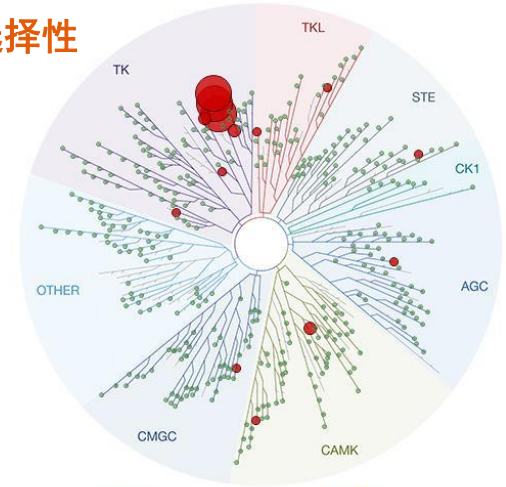
诺诚健华 科学驱动创新

In Vitro: Kinase Inhibition Overcome Resistance

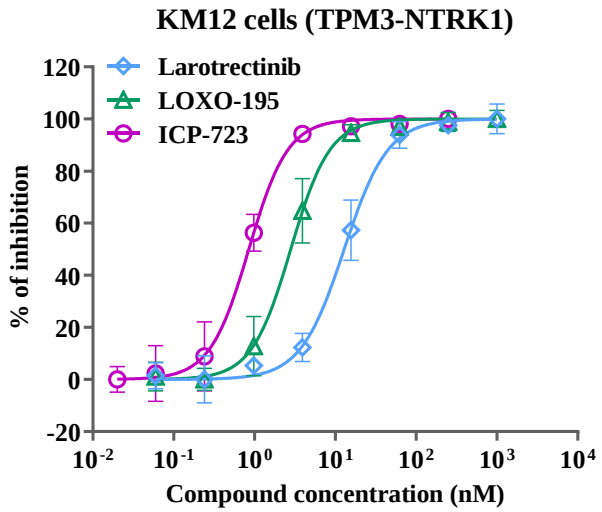
- **高活性** 第一代 →→ 第二代→→ 更优的第二代

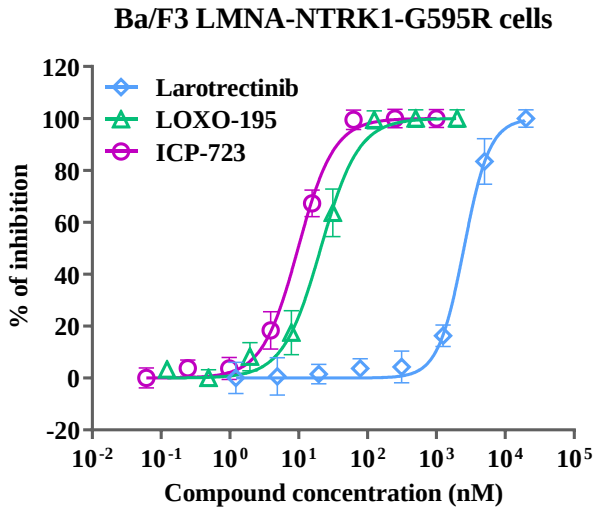
激酶/I C_{50} (nM)	Larotrectinib (拉罗替尼)	LOXO-195	ICP-723
TRKA	1.30	0.72	0.98
TRKB	0.63	0.21	0.12
TRKC	0.30	0.18	0.15
TRKA G595R (耐药突变)	88.4	0.56	0.31
TRKA G667C (耐药突变)	29.9	4.74	0.55

- **高选择性**

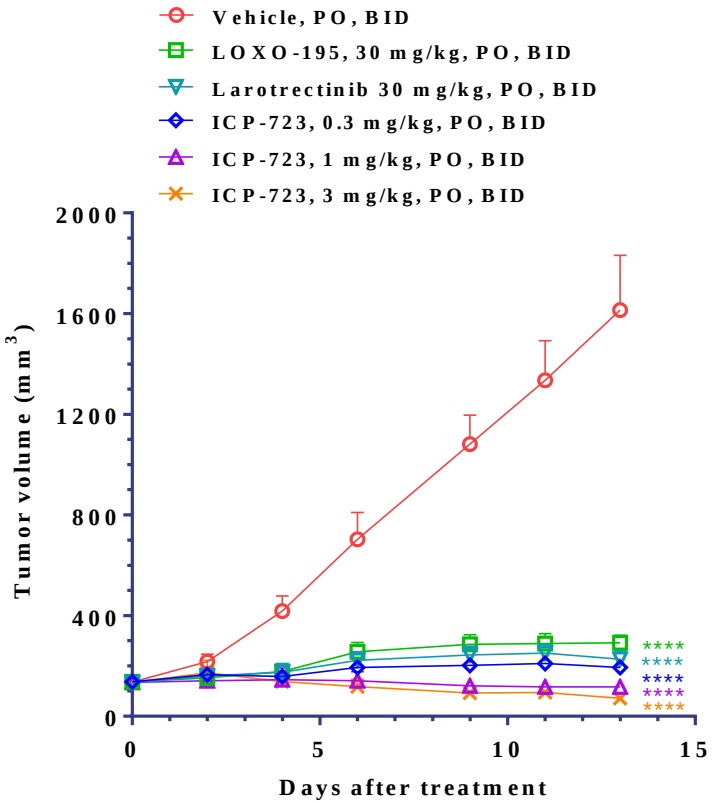


In Vitro: Anti-proliferation Overcome Resistance

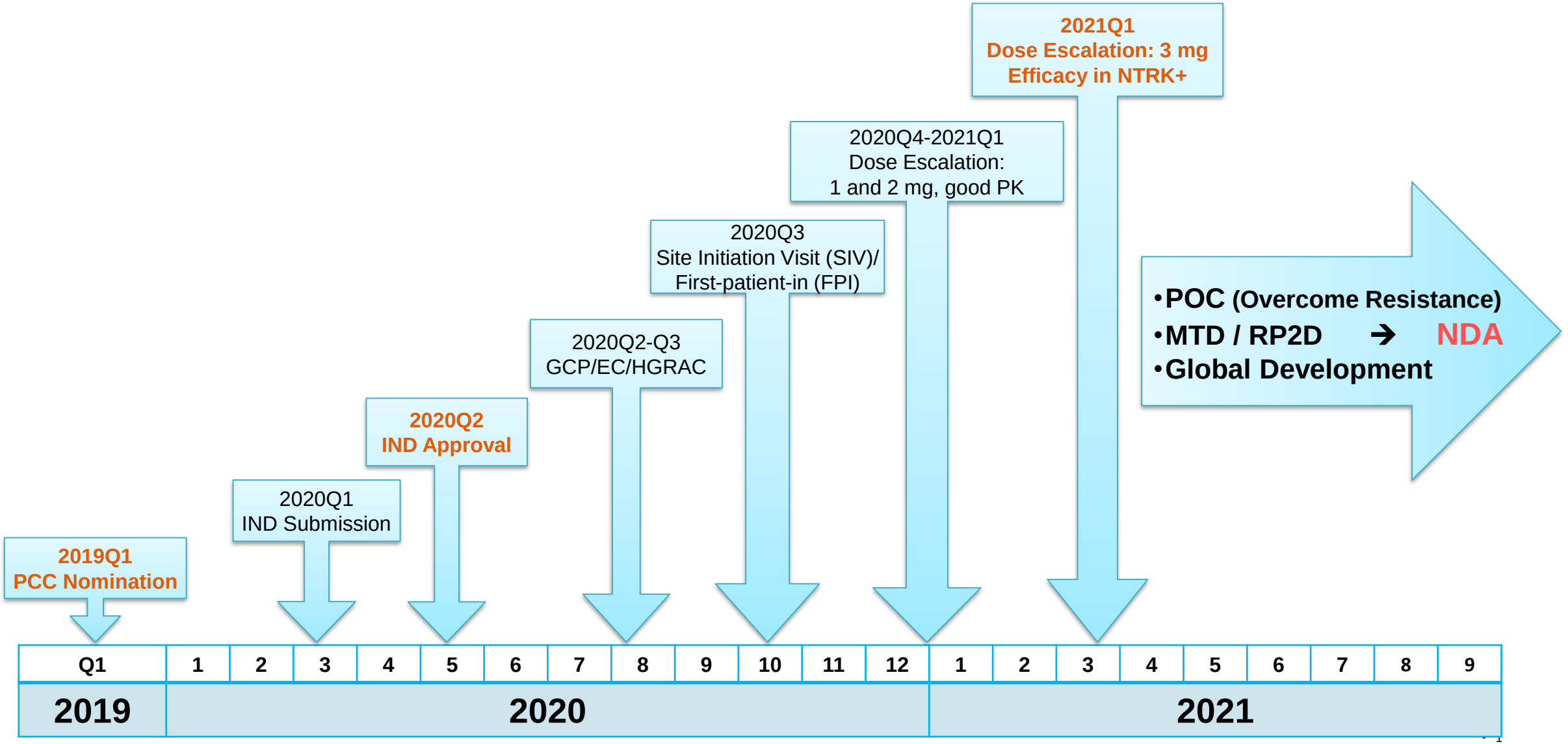




In Vivo Anti-Tumor Efficacy 10-100X Increase

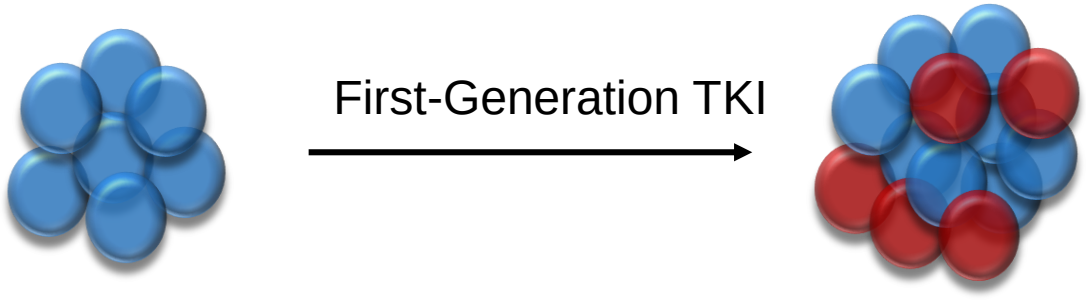


ICP-723: PCC → IND → FIH → POC Process



Next-Generation pan-TRK TKIs ICP-723 (Best-in-class)

Can Address On-Target Resistance to Early-Generation TRK TKIs



First-Generation Drug	Second-Generation Drug
Larotrectinib	**Selitrectinib** (LOXO-195) Selective TRK inhibitor
Entrectinib	**Repotrectinib** (TPX-0005) TRK/ROS1 inhibitor

ICP-723

Superior Second-Generation

Drilon. Cancer Discov. 2017;7:963. Drilon. Cancer Discov. 2018;8:1227.

CNS Penetration → Treatment of CNS Lymphoma (CNSL) → Treatment of Multiple Sclerosis (MS)

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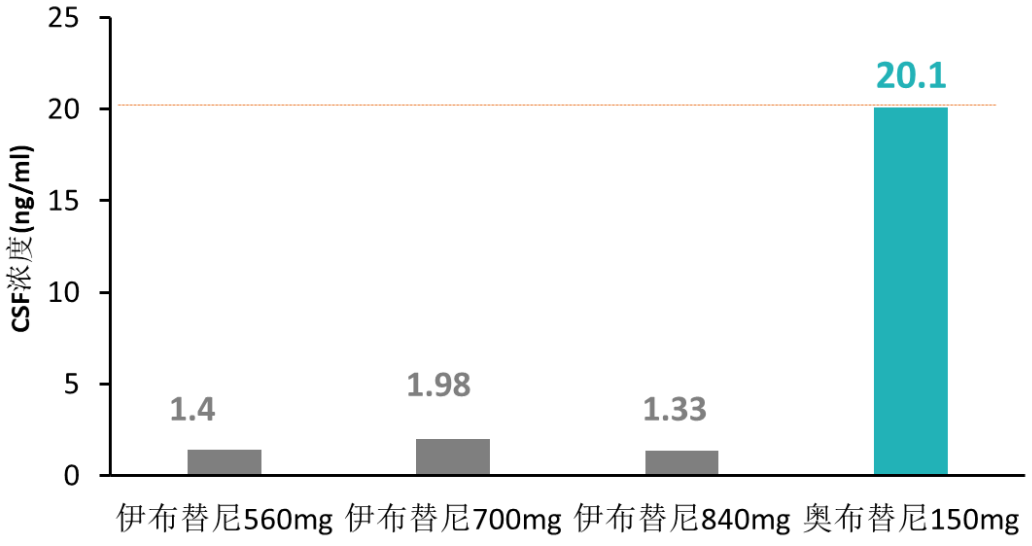
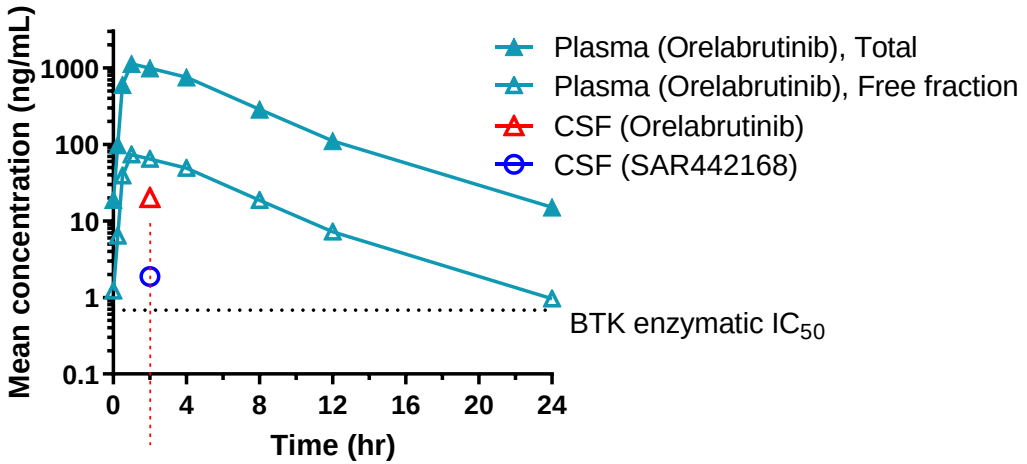
vs. Ibrutinib

- 奥布替尼150mg剂量下的CSF浓度显著高于伊布替尼560mg、700mg和840mg，CSF浓度分别为：20.1 vs. 1.4 vs. 1.98 vs. 1.33ng/ml



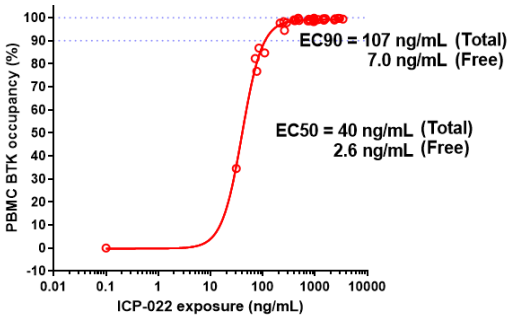
Michail S. Lionakis et al. Cancer Cell 31, 833–843

vs. SAR442168 (Sanofi)

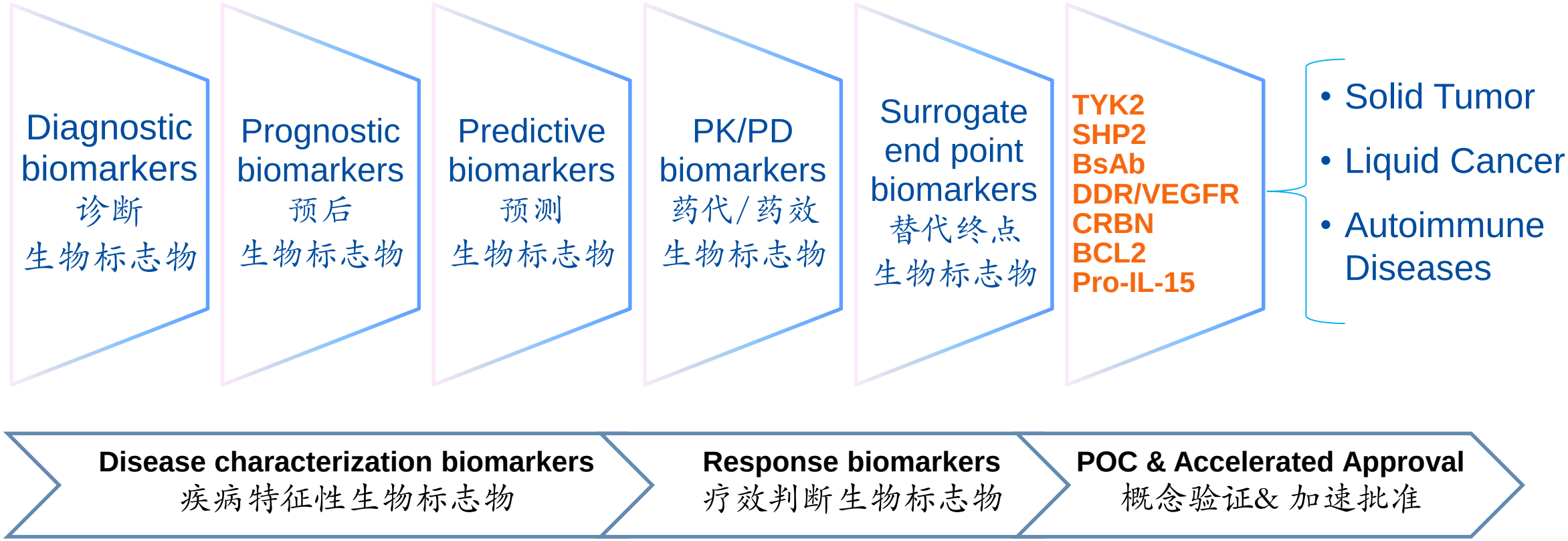


CSF, 2 h: 20.1 ng/mL > EC90 (7.0 ng/mL, Free fraction) (Free)

Exposure-Response Relationship Between C_{max} and BTK Occupancy at 24 hrs after Single Dose



Biomarker-Driven Translational Research to Advance the Pipeline



Note: Kelloff GJ, Sigman CC. Cancer biomarkers: selecting the right drug for the right patient. Nat Rev Drug Discov. 2012; 11(3): 201-14.

诺诚健华2021研发日

科学驱动创新

Business Development Strategy

诺诚健华
科学驱动创新

Vice President of Business Development

- Over 20 years of experience in the biotechnology space spanning business development, M&A and drug development
- Former Vice President of business development, alliance management, new product planning and intellectual property at ArQule
- Ph.D. in Organic Chemistry from Brown University
- MBA from Questrom School of Business at Boston University

Manish Tandon博士
Dr. Manish Tandon

Director of Business Development

- More than 10 years in finance and healthcare industries
- Former director of business development at Simcere Pharmaceuticals, VP of investment banking at RBS
- B.S./M.S. in Biochemistry from Tsinghua University
- M.B.A from UC Berkeley

宋歌女士
Ms. Gina Song

Pursuing Both Short-Term and Long Term Value Generating Corporate Development Strategy via Outlicensing and Inlicensing Assets

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科学驱动创新

Inlicensing

- Focus on oncology late stage (with proof-of-concept) assets especially heme-onc drugs to support our clinical development as well as commercial strategy
- Focus on assets that can be synergistic with our current pipeline program
- Broaden scope of our pipeline by adding new agents that target mechanisms not addressed by our current pipeline assets
- Start seeking promising novel early stage targets to fuel an innovative pipeline over the long term

Outlicensing

- Highly focused on maximizing clinical potential and commercial opportunity of Orelabrutinib
- Current strategy is to partner ex-China rights of pipeline assets with clinical proof of concept
- Partner selection is based on capabilities to fully develop and maximize the commercial value in indications ex-China

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Target Selection Strategy – Small Molecule

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科学驱动创新

Vice President of Biology and Procurement

- More than 20 years of drug discovery experience in Immunology
- Former Senior Director of Discovery Biology at BioDuro, a PPD company
- Former Senior Principle Scientist at BMS
- Ph.D. from University of Arkansas, USA

刘瑞勤博士
Dr. Richard Liu

Building a Coherent and Synergistic Portfolio

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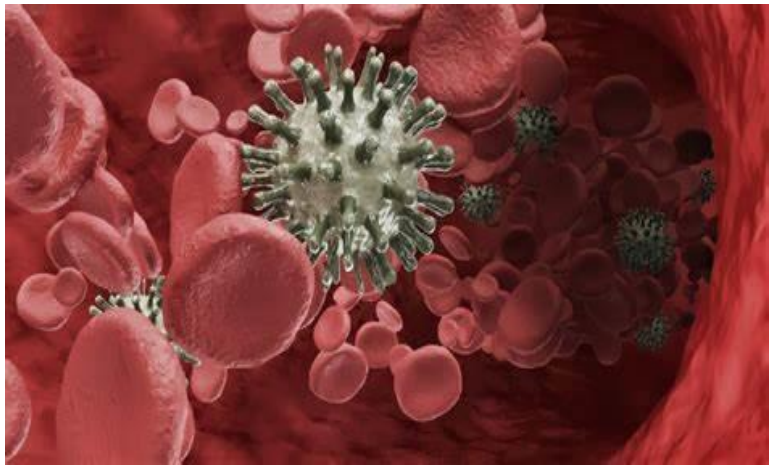
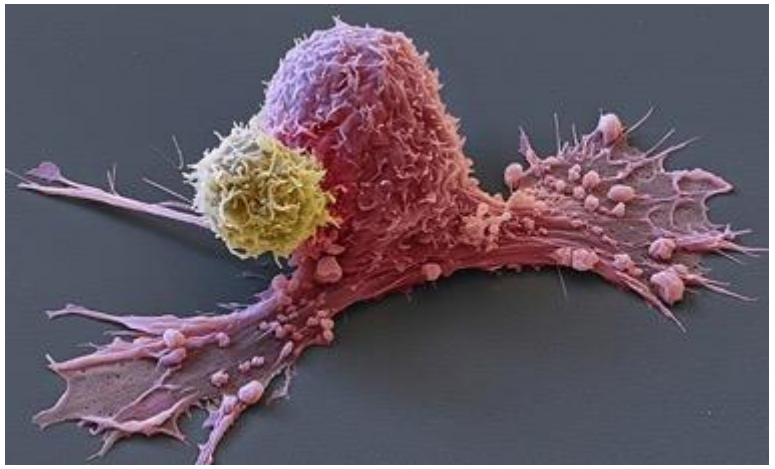
科学驱动创新

Blood Malignancies



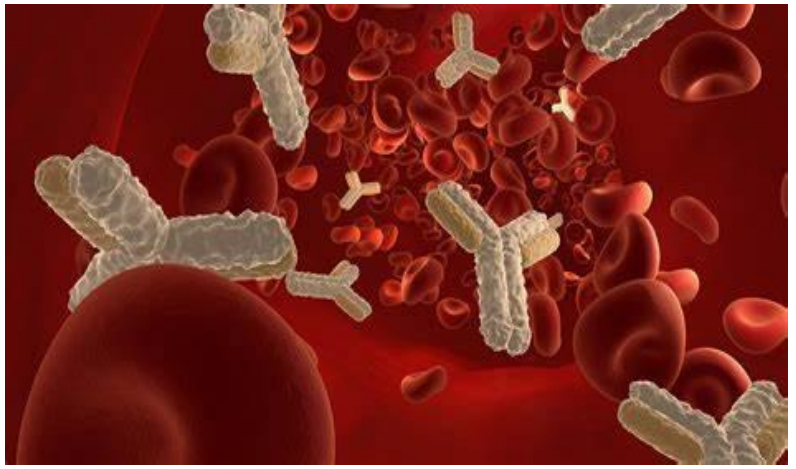
BTK
E3 Ligase
BCL-2
TYK2

Solid Tumors



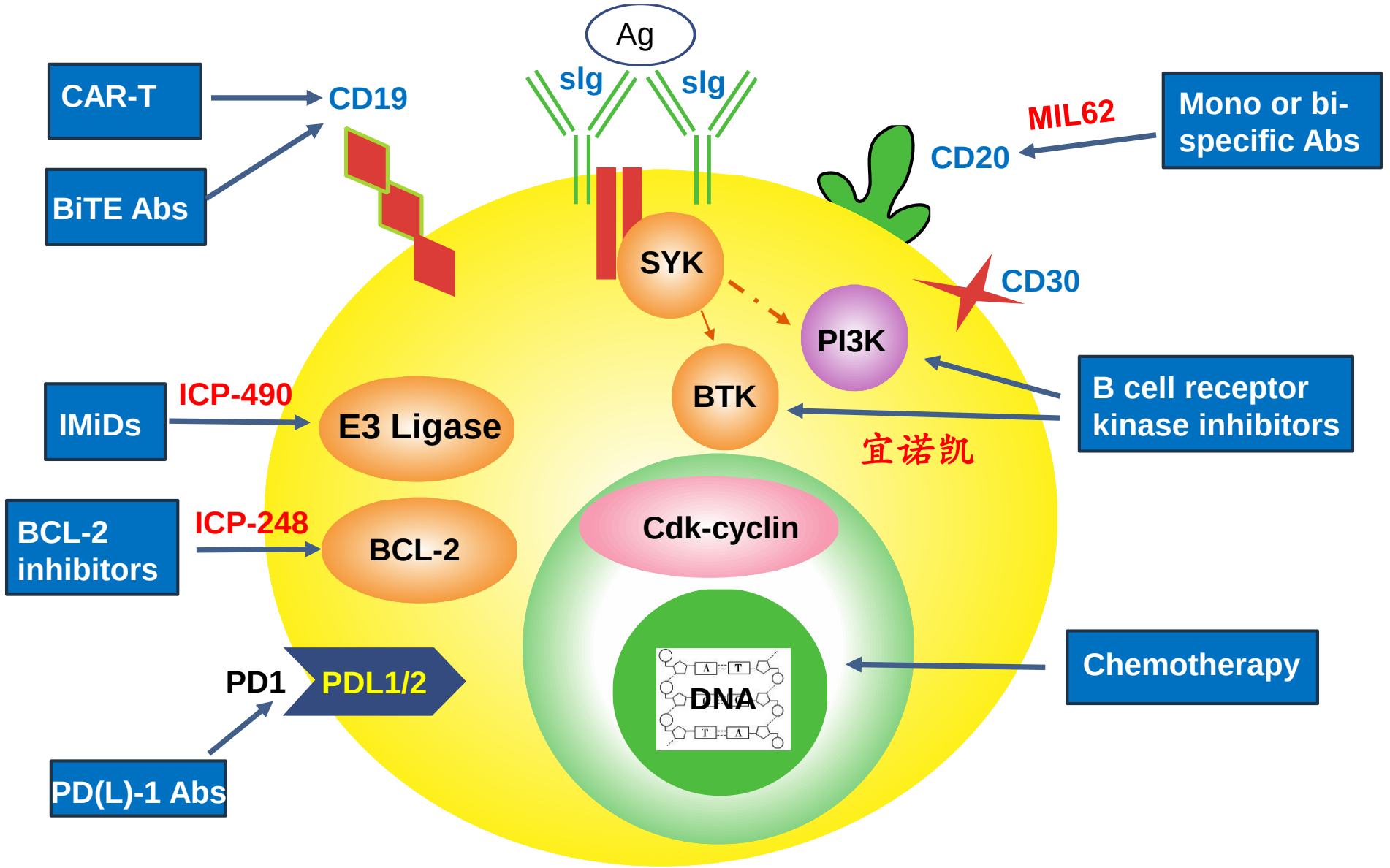
FGFR
NTRK
DDR1/VEGFR
SHP2

Autoimmune Diseases



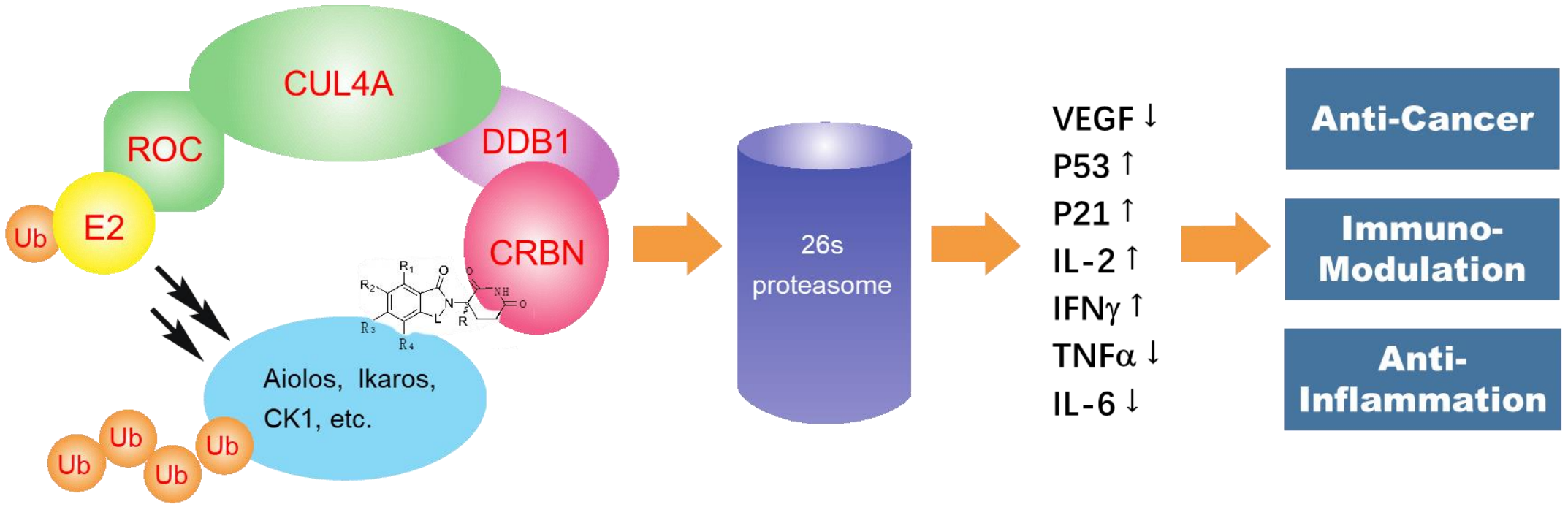
BTK
TYK2
E3 Ligase
Gut-Restricted JAKs

Maximizing MoA Coverage in the Hematological Space



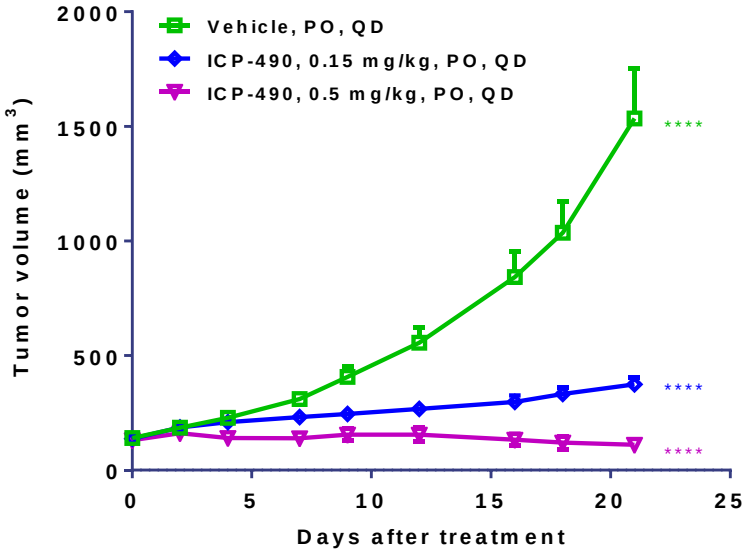
- BTK
- CD20
- BCL-2
- E3 Ligase

ICP-490 Acts as a Cereblon E3 Ligase Modulator in Protein Homeostasis for Various Therapeutic Applications

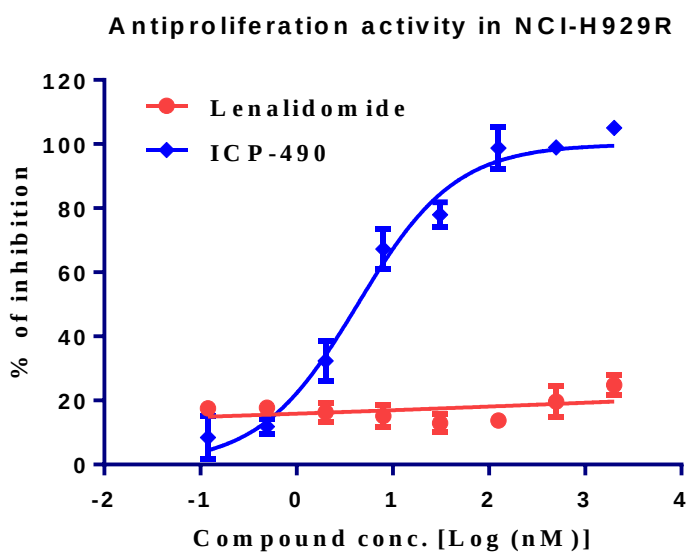


- IC_{50} 0.06 nM in an antiproliferation cellular assay
- IC_{50} 0.38 nM in an immune PBMC assay
- IC_{50} 0.02 nM in a MOA assay examining certain transcription factor degradation

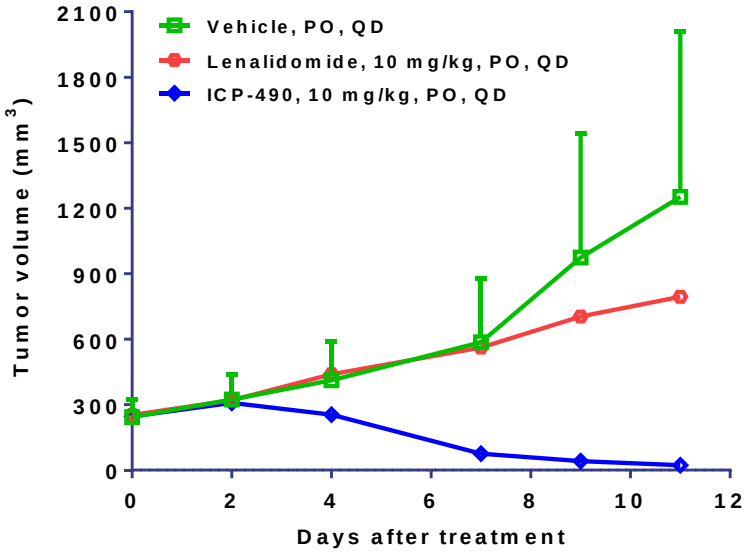
ICP-490 Has the Potential to Become the Next Generation Lenalidomide for the Treatment of Blood Malignancies



Effect of ICP-490 in the MM.1S xenograft model



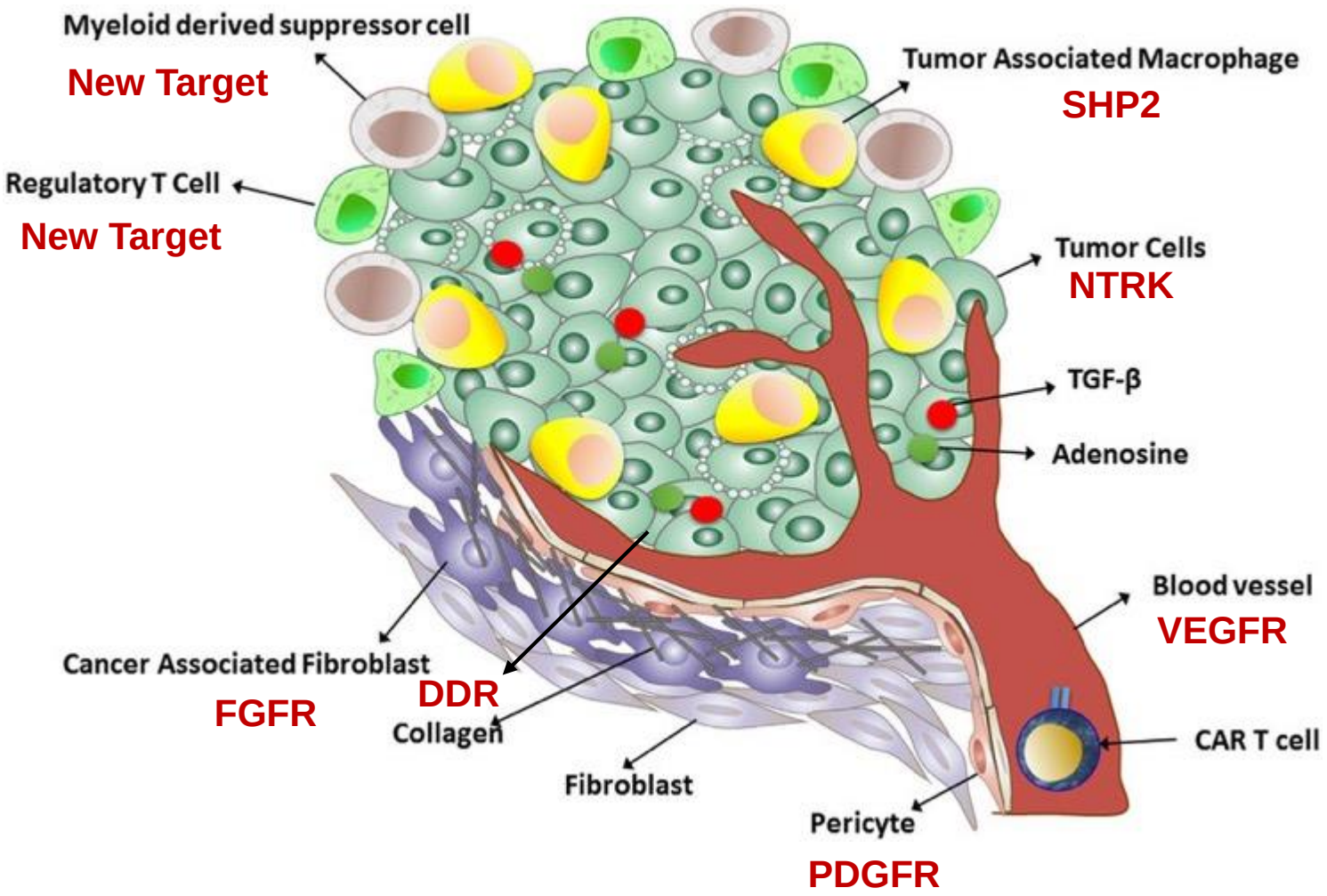
Effect of ICP-490 against proliferation in NCI-H929-R cells



Effect of ICP-490 in the NCI-H929-R xenograft model

ICP-490 is efficacious in the lenalidomide-resistant H929-R xenograft model

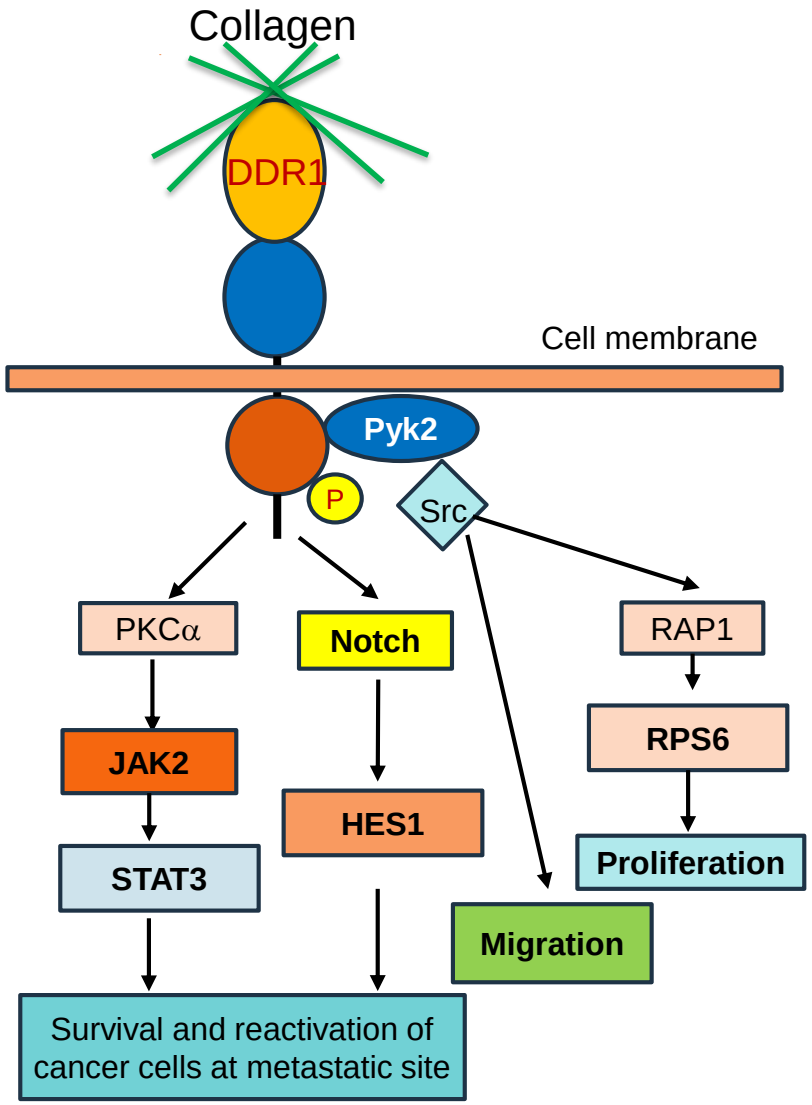
Focusing on Tumor Microenvironment Modulation to Target China-Prevalent Solid Tumors



- Modulation of the tumor microenvironment matrix
- Regulatory T cell modulation
- Modulation of myeloid derived suppressor cells
- Tumor associated macrophage polarization

Note：Front Immunol. 2017 Dec 22;8:1850

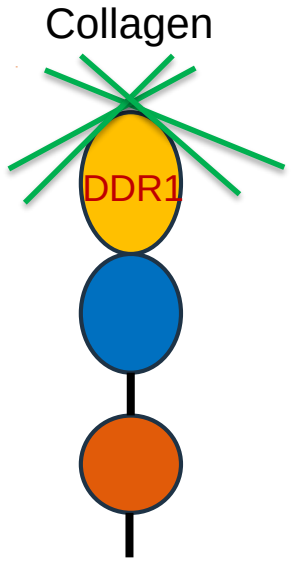
DDR1 Regulates Cancer Cell Differentiation and Invasion



ICP-033 in DU145 cancer cell clone formation assay

Collagen stimulation control

Collagen stimulation with 1 μM ICP-033

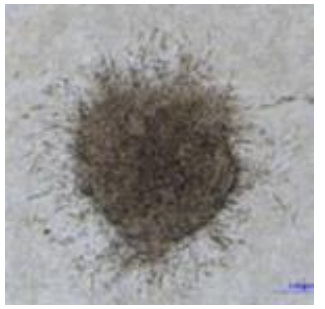


Induction of MMPs

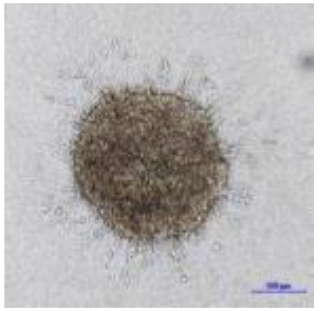
Matrix degradation

Invasion and tumor progression

ICP-033 in collagen-stimulated SK-OV-3 cancer cell invasion assay



Collagen stimulation control



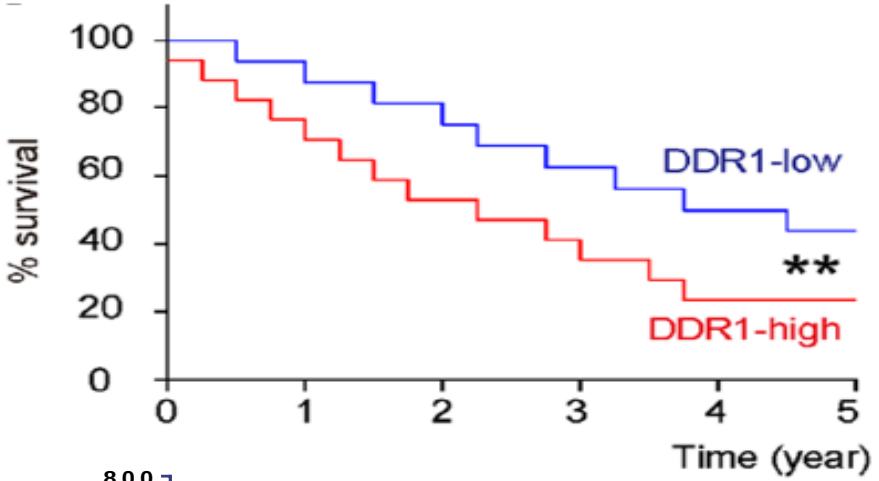
Collagen stimulation with 16 nM ICP-033

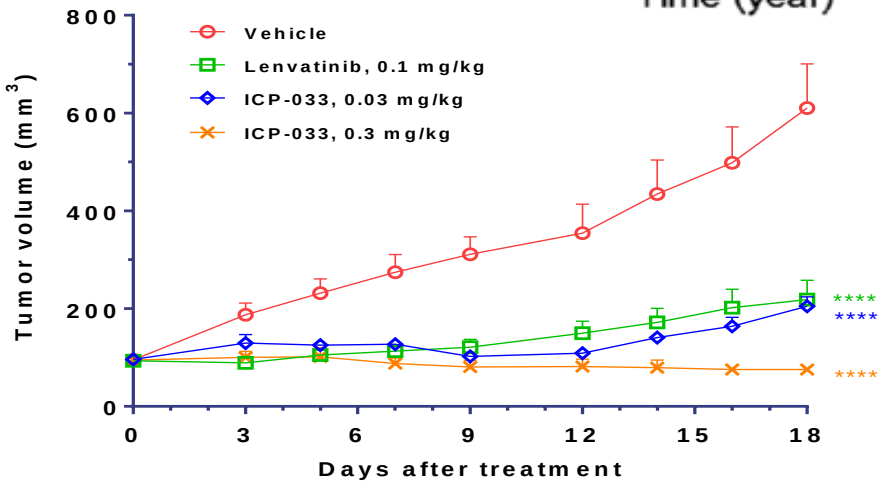
Note: CELL ADHESION & MIGRATION 2018, VOL. 12, NO. 4, 315–323

Targeting DDR1 Provides New Therapeutic Opportunities for the Treatment of Solid Tumors

诺诚健华 科学驱动创新

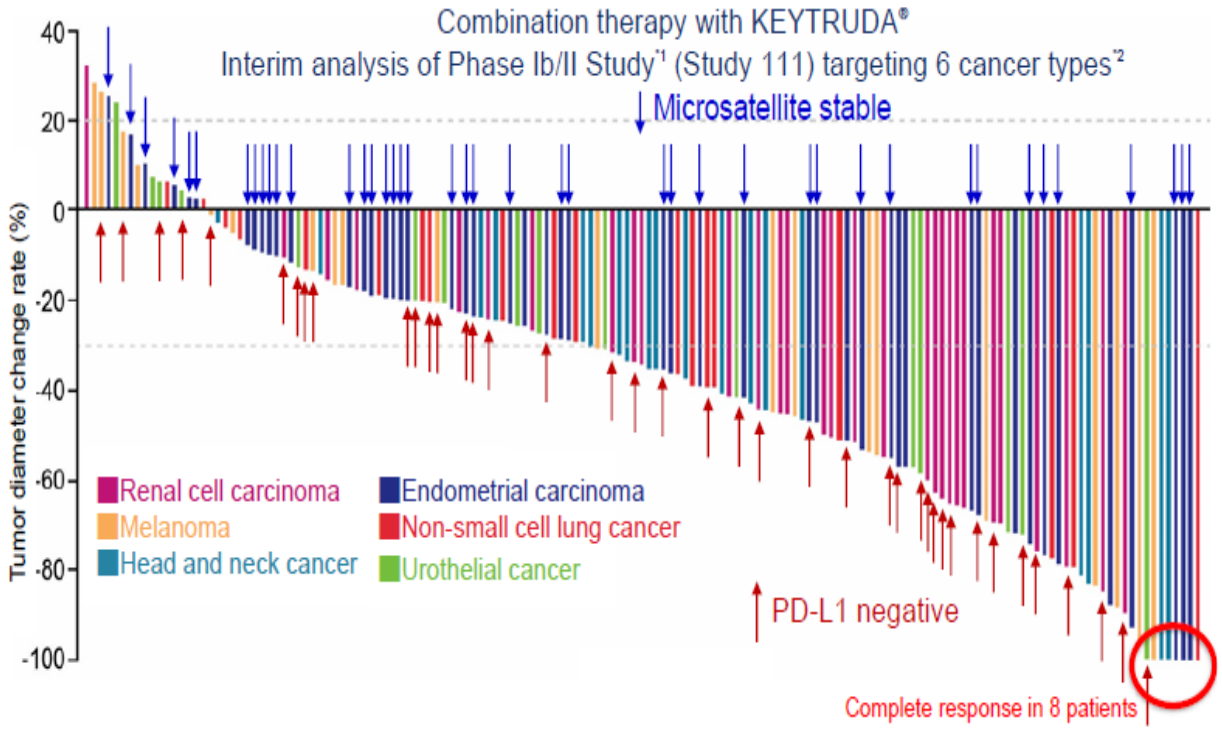
Kaplan-Meier Plot of 44 Bladder Cancer Patients All Diagnosed Stage IV and Followed for 5 Years*





Effect of ICP-033 in the DU145 prostate cancer xenograft model

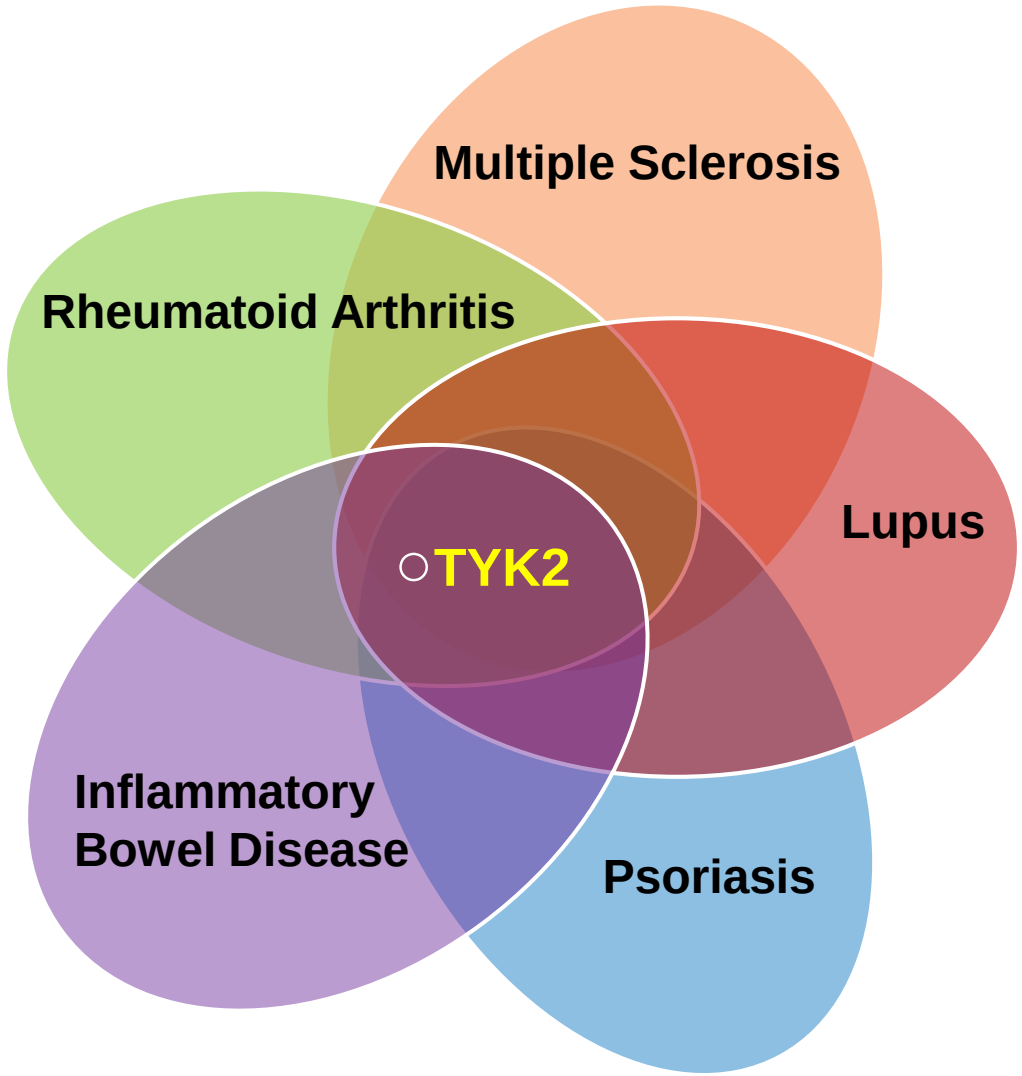
Lenvatinib's Immunomodulatory Effect Potentially Enhances the Efficacy of IO Treatment



ICP-033 has the potential to surpass lenvatinib due to additional DDR1 inhibition in combination with PD-1 antibodies for the treatment of various solid tumors prevalent in China

* Am J Transl Res 2017;9(5):2500-2507

TYK2: The Current Focus of the Autoimmune Space with the Potential to Produce Blockbuster Drugs for Multiple Indications

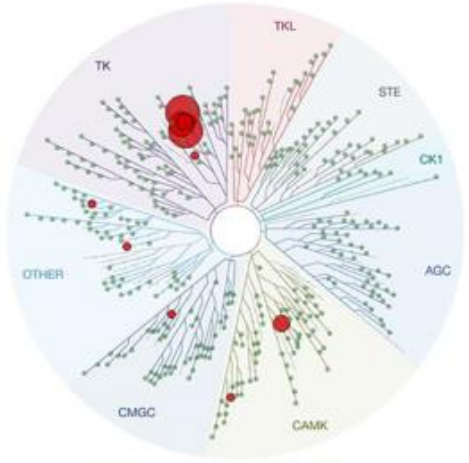


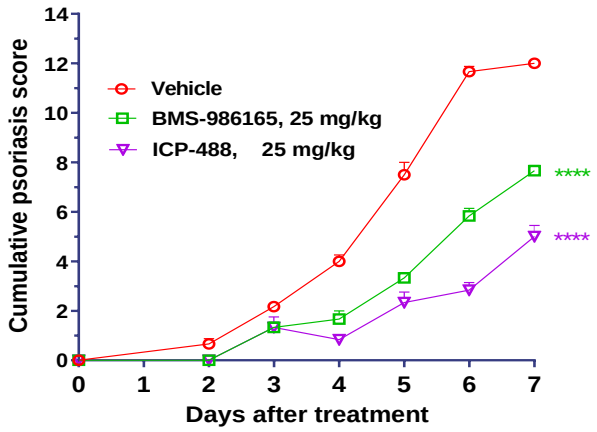
- Resides in drug-rich JAK family
- Regulates signaling of IL-23, IL-12, and type I IFN, contributing to the pathogenesis of various autoimmune diseases
- Approved JAK inhibitors demonstrate encouraging efficacy but raise serious safety concerns
- Developing a TYK2 inhibitor while minimizing safety issues presents a plausible strategy

ICP-332 and ICP-488 Bind to the JH1 or JH2 Domain of TYK2 with Excellent Selectivity over JAKs

诺诚健华 科学驱动创新

ICP-332 KINOME Map

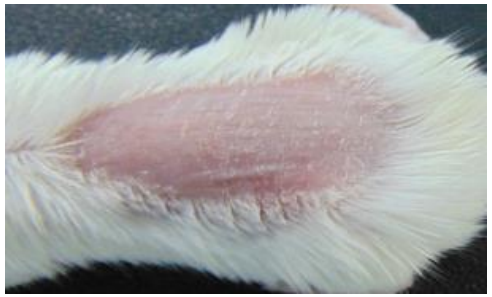




Imiquimod-induced psoriasis model

- **ICP-332, targeting the catalytic site**
  - IC_{50} of 0.5 nM against TYK2
  - 40X less active against JAK1
  - 400X less active against JAK2
  - 2000X less active against JAK3

Psoriasis model



Treated with ICP-332

- **ICP-488, targeting the allosteric site**
  - IC50 of 13 nM in the NK92 cell assay
  - Favorable PK/safety profile
  - Efficacious in multiple disease models with the potential to become the best-in-class molecule

Target Selection Strategy

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- Portfolio fit
  - Within the immuno-oncology space focusing on Tregs and MDSCs
  - Potential for either mono- or combo-therapy
  - Priority for the treatment of China-prevalent solid tumors
  - Unmet medical needs in the autoimmune disease area
- Increased initiative for first-in-class discovery
- Science-driven decisions with target/disease-specific biomarkers to evaluate therapeutic efficacy
- A well-balanced strategy in full phase, early phase, and exploratory phase programs for sustainable success

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Positioning Biologic Pipeline

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VP of Biology

- More than 15 years of drug discovery experience
- Former VP of Scientific Research & Innovation at Crown Bioscience
- Former Asso. Principal Scientist at Merck
- Ph.D. in Cancer Biology from the University of Hong Kong

欧阳雪松博士
Dr. Davy Ouyang

Overall Strategy for Building a Biologic Pipeline

- **Quick wins through crossover synergies with our small molecule programs**
  - Combination of Orelabrutinib and antibody drugs to own hematology oncology space (CD20, CD19, bi-specifics)
  - Potential combo partners for other small molecule programs (PD-1/PD-L1 etc.)
- **Highly focused biologic programs in Immuno-oncology space through collaborations**
  - Unique cytokine-based therapeutics with high potency and improved safety profiles.
  - First-in-class antibody-based therapeutics tackling immune-suppressive TME.
- **End-to-end biologic discovery and development capability**

Crossover Synergies with Small Molecule Programs

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Develop biologic compounds through business development to boost the value of Orelabrutinib & other small molecule programs.

- **Combination of Orelabrutinib and antibody drugs to own hematology oncology space**
  - Combo of Orelabrutinib & MIL62 (CD20 antibody) for B-Cell NHL (r/r DLBCL, r/r MCL, FL etc.)
  - Combo of Orelabrutinib & CD20/CD3 bi-specific antibody for r/r DLBCL
  - Translational research to rationalize the combo benefit by demonstrating direct tumor killing synergies & enhanced ADCC/ADCP function.
- **Identify potential combo partners for other small molecule programs**
  - ICP-490 (CRBN IMiD): Next generation IMiD activating T/NK cells, inducing type I cytokines (i.e. IL2, GM-CSF, TNFα, IFNγ), enhancing ADCC. Many combination options.
  - ICP-189 (SHP2): Depleting pro-tumorigenic TAM, activating T cells. Combo with PD1 antibody or other ICIs.
  - ICP-033 (TKI): multi-kinase inhibitor. Combo with PD1/PD-L1 antibody.
  - New undisclosed target: activating T cells. Combo with PD1 antibody.

Highly Focused Near Term Target Selection Strategy

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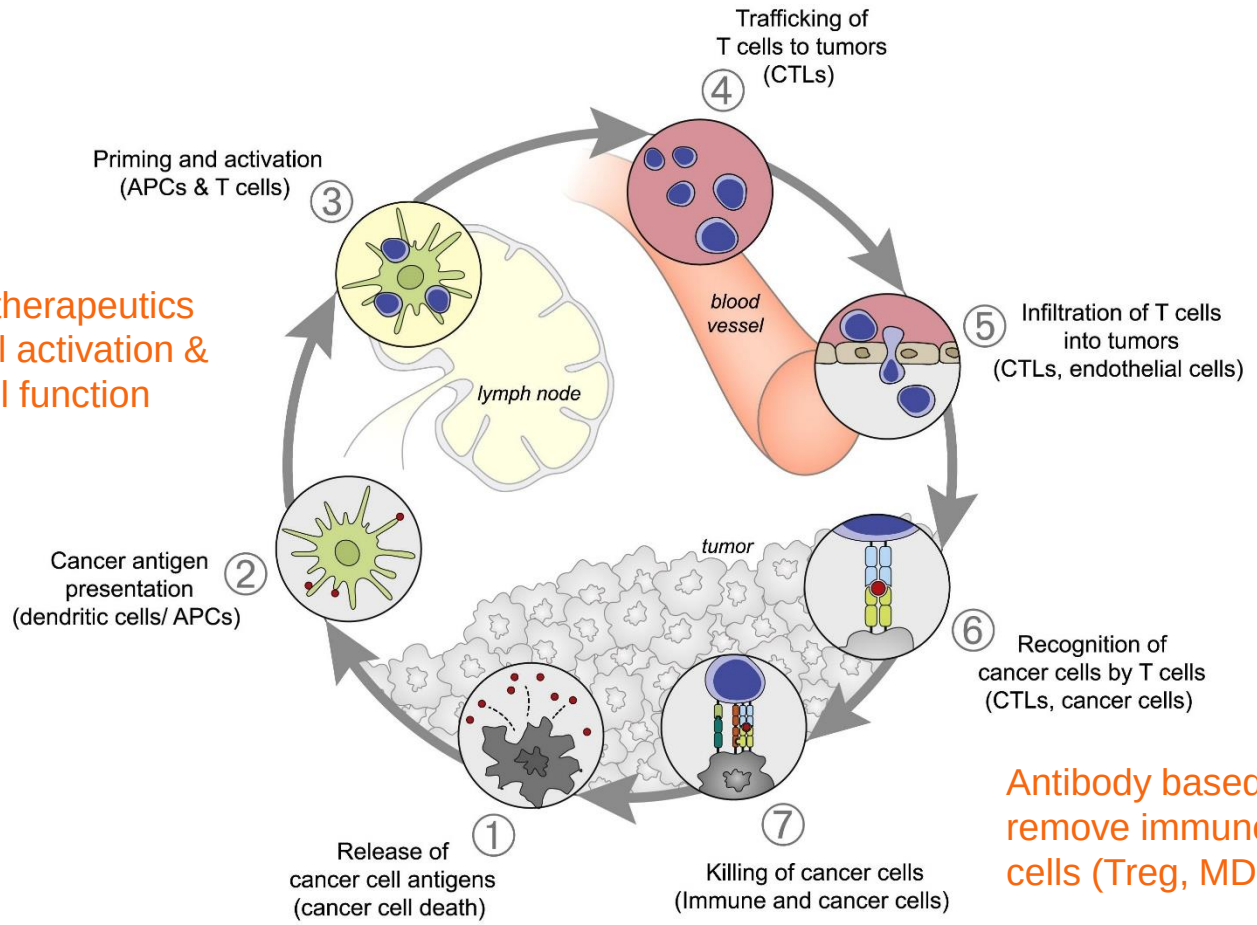
The Cancer-Immunity Cycle



Cytokine based therapeutics to enhance T cell activation & other effector cell function

Antibody based therapeutics to remove immune suppressive cells (Treg, MDSC, TAM etc.)

Note：Adapted from Chen & Mellman, Immunity 39,3-11:2013

Cytokine Based Immuno-Oncology Therapeutics

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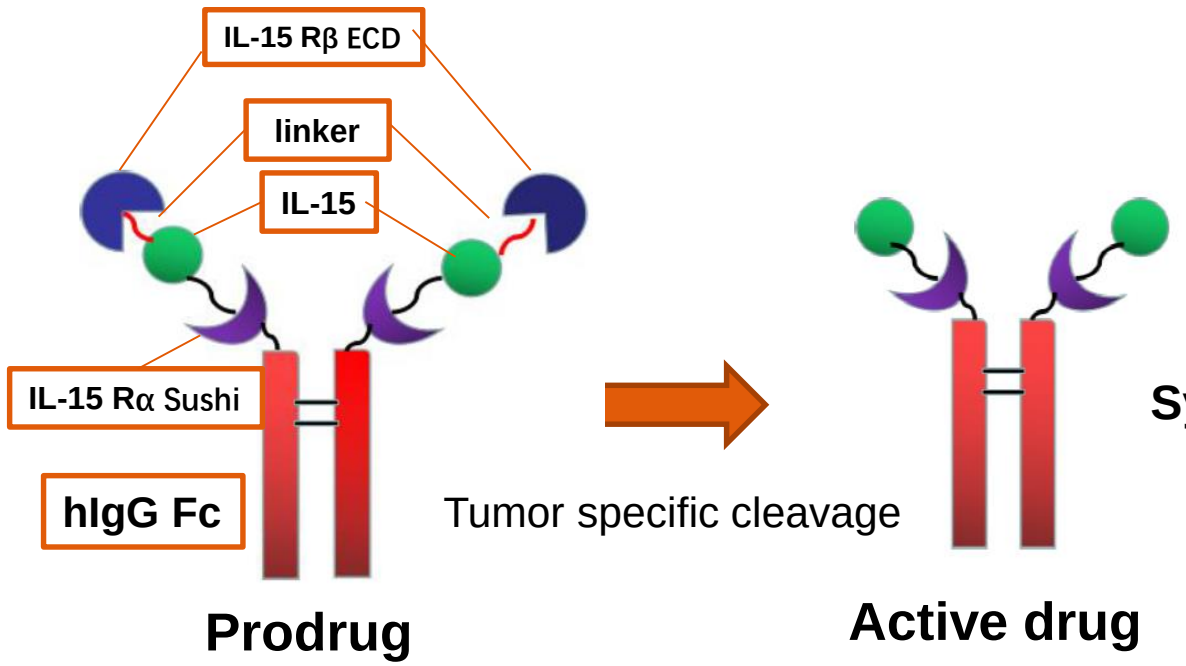
IL-2 and IL-15 therapeutics in clinical trials

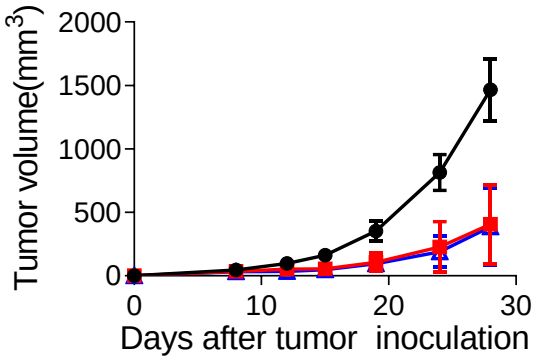
Drug Name	Company	Properties	Indications/Phase
IL-2 therapeutics			
NKTR-214	Nektar/BMS	IL-2, with 6 cleavable PEG groups	Melanoma, RCC, Bladder/ Phase III
ALKS-4230	Alkermes	Circularly permuted IL2v-IL-2Rα fusion protein	HNSCC / Phase II
THOR-707	Sanofi/Synthorx	IL-2, with 1 non-cleavable PEG groups	Solid tumor/ Phase I/II
RG6279	Roche	IL-2v-PD1 mAb fusion protein	Solid tumor/ Phase I
CUE-101	Cue Biopharma	IL-2-HLA complex – HPV16E7 fusion protein	HNSCC / Phase I
IL-15 therapeutics			
ALT-803	Nantworks	Mutated IL-15/Sushi fused IgG1	Bladder, NSCLC, MCC / Phase II
BJ-001	BJ Bioscience	Tumor targeting RGD-Fc IL-15Rα-IL-15	Solid tumor/ Phase I
CYP0150	Telix Pharma	Tumor targeting GD2-IL15-IL15Rα	Solid tumor/ Phase I
NIZ985	Novaryis AG	IL-15-IL-15Rα	Solid tumor/ Phase I
NKTR-255	Nektar	PEG-conjugated IL-15	Multiple Myeloma/ Phase I
SHR-1501	Jiangsu Hengrui	IL-15-IL-15Rα	Advanced tumors/ Phase I
XmAb24306	Roche	IL-15-IL-15Rα fused to bispecific XmAb Fc	Solid tumor/ Phase I
KD033	Kadmon	PDL1 mAb linked to IL-15/Sushi	Solid tumor/Phase I

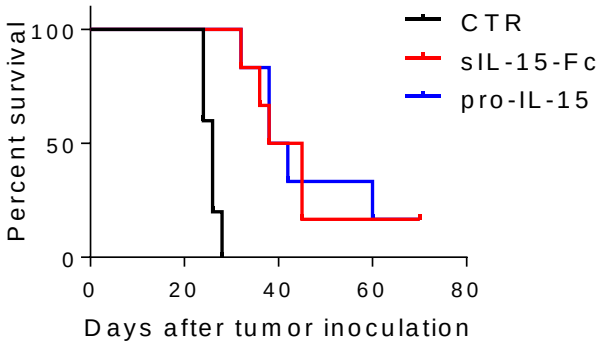
- 1st generation of cytokine therapeutics approved in the 90's didn't make effective anti-tumor drugs
- New generation of engineered cytokines become very attractive combination partners with ICIs and CAR-T therapies
- Unique characteristics of IL-15 vs. IL-2
- Common limitations: Poor PK & dose-limiting toxicity

Pro-IL-15 – A Prodrug Specifically Activated in Tumor Microenvironment (TME) with Much Improved Safety Profiles

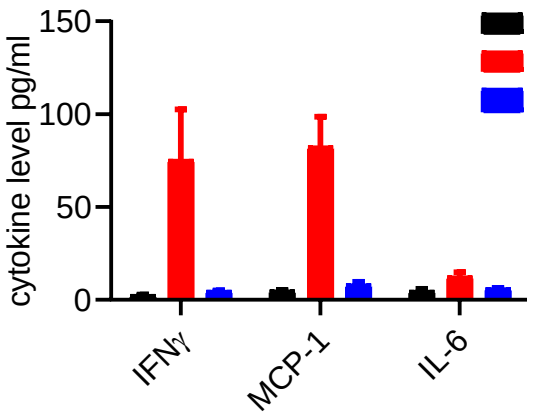


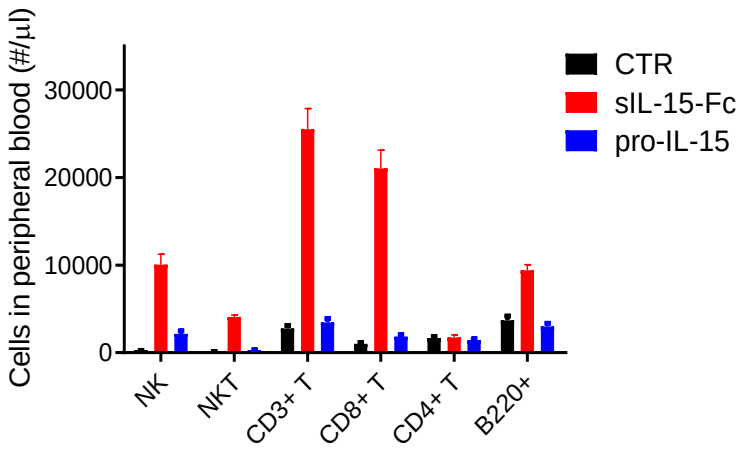
Efficacy assessment of pro-IL-15 & constitutive active drug





Systemic immune responses led by pro-IL-15 & active drug





Regulatory T Cells Mediated Immunosuppression & Targeting Opportunities

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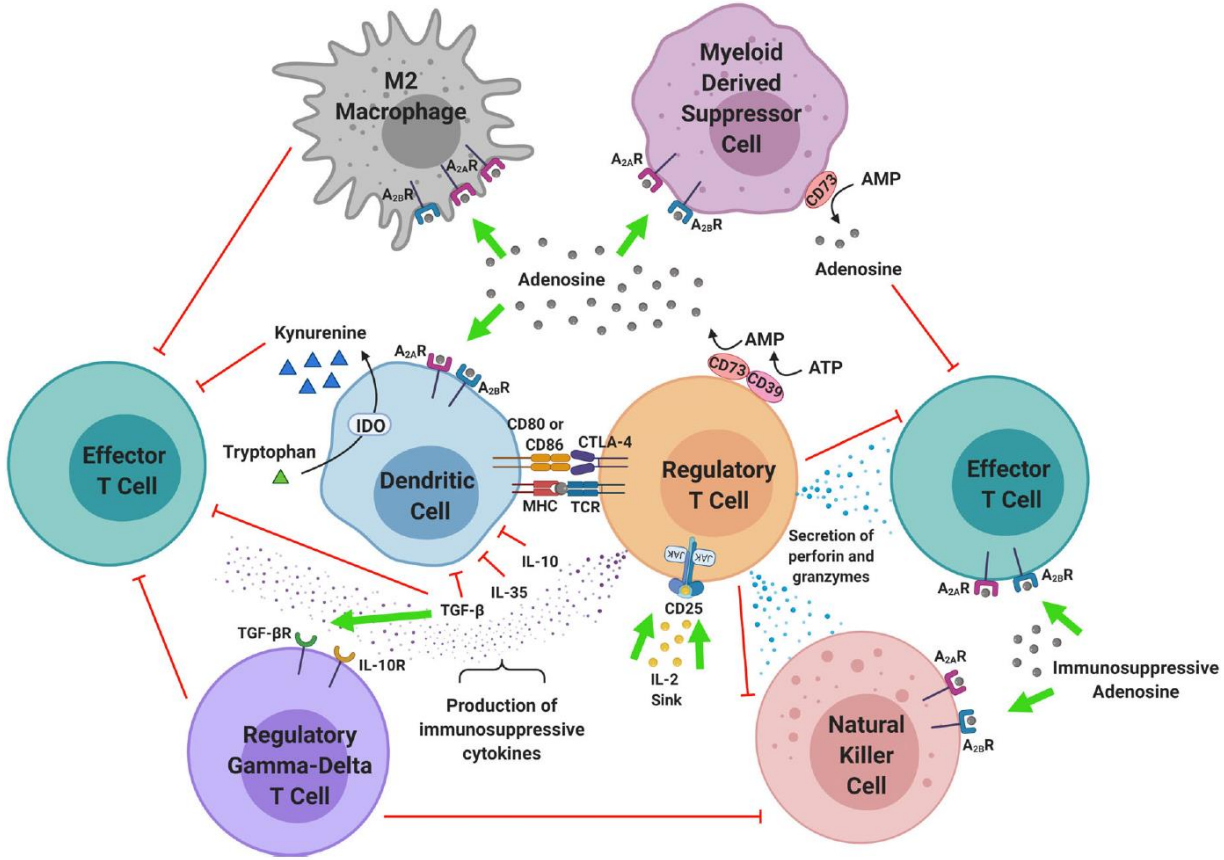
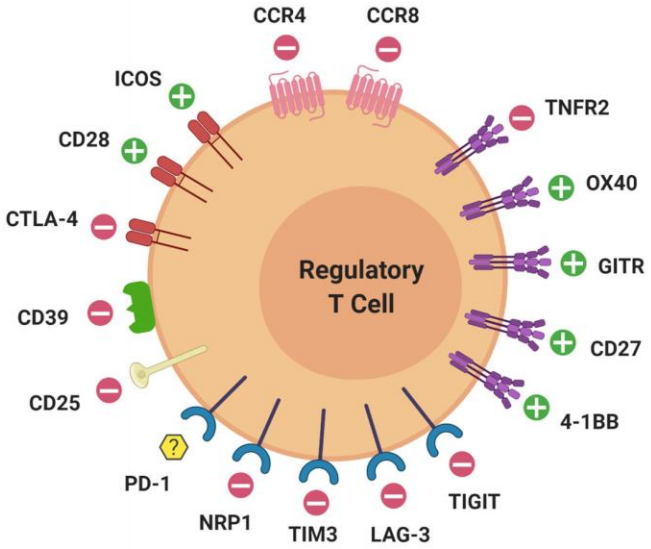
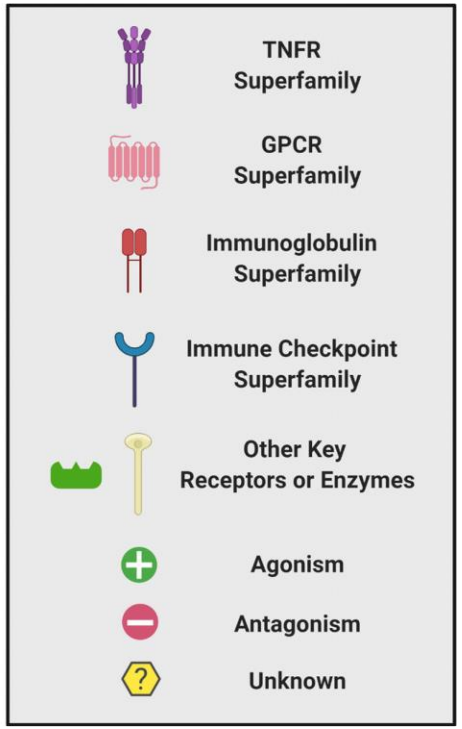
Regulatory T cells play vital immunosuppression roles to support tumorigenicity.



Adapted from Dees et al., Eur J Immunol, 51:280;2021

Potential therapeutic approaches to target regulatory T cells.





Undisclosed First-in-class Antibody Program to Inhibit Treg Differentiation and Recruitment to TME

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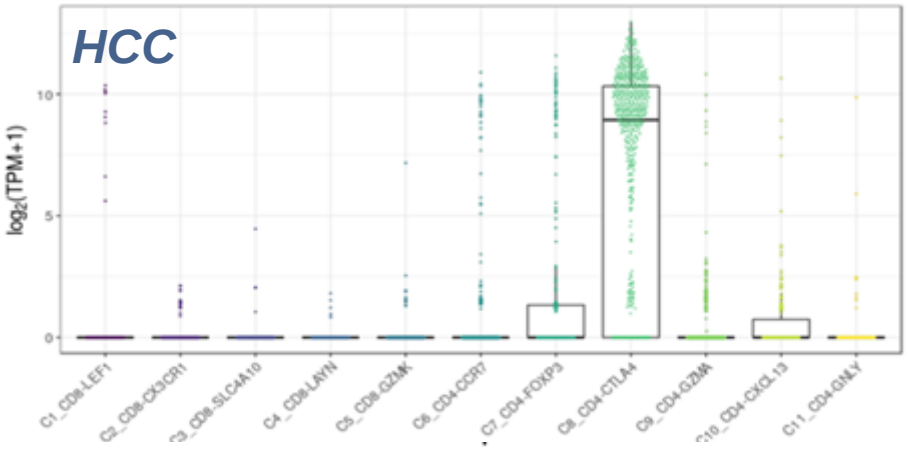
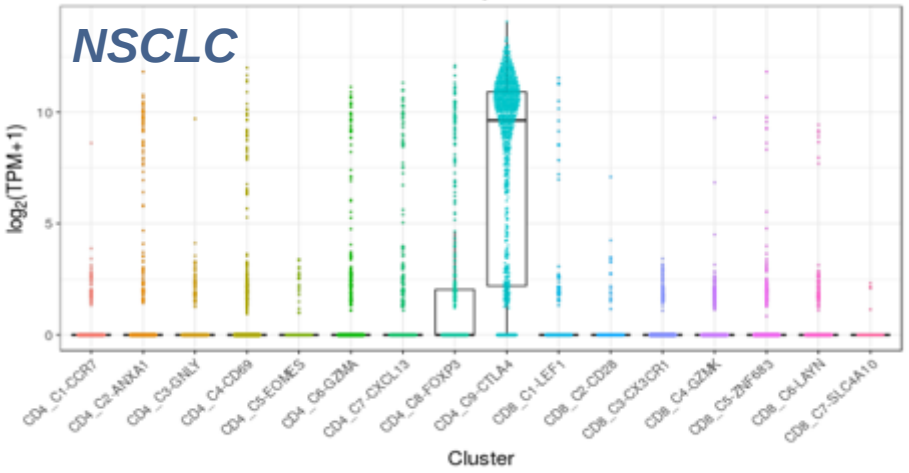
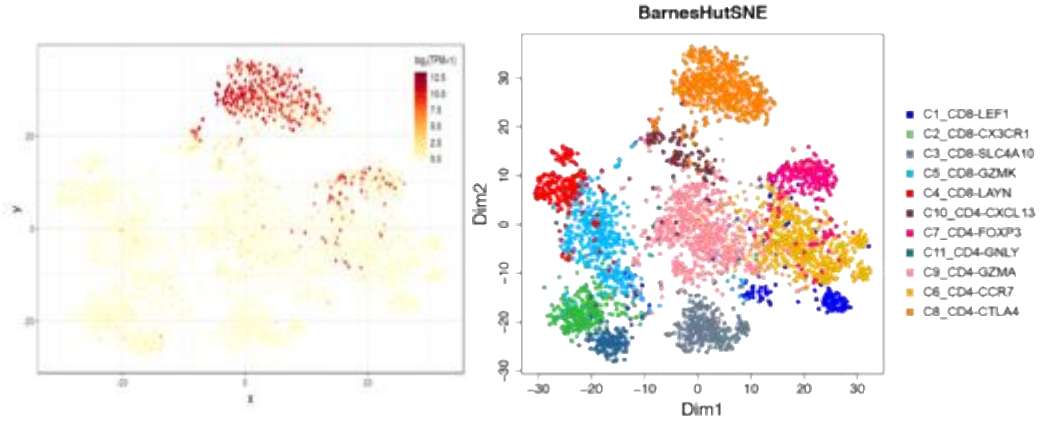
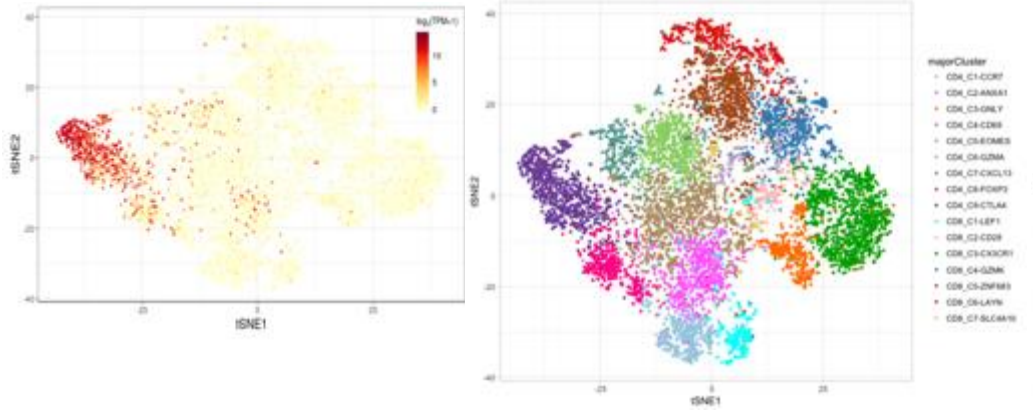
Proprietary single cell sequencing data revealed expression of the target in a distinct cluster of CD4 population in various tumors

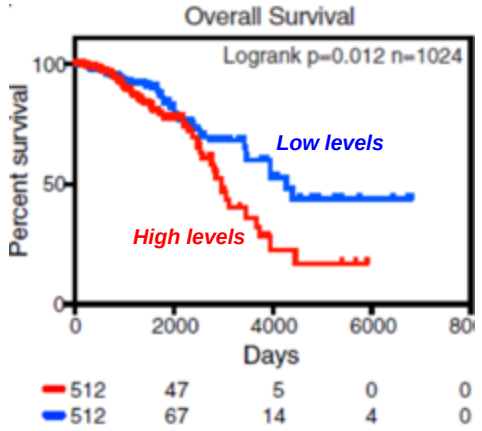




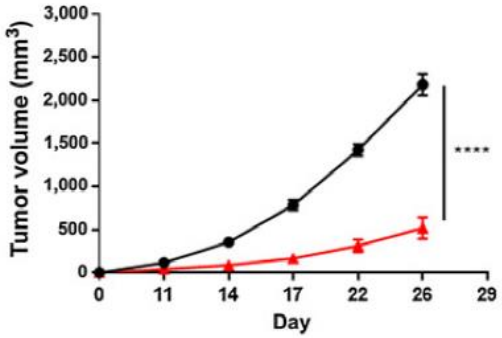




High expression is associated with poor overall survival



Mouse surrogate antibody treatment led to significant tumor growth inhibition



Building End-to-End Biologic Discovery and Development Capability

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- Scientifically rationalized and clinical biomarker driven target identification (Single cell sequencing & Data mining)
- Structure biology assisted antigen design
- Proprietary phage library, mono-specific & multi-specific mAb platform
- In silico druggability & immunogenicity analysis; humanization, affinity maturation.
- Full spectrum functional assays & pharmacology capability
- Proprietary CHOK1 cell line and expression vector
- CMC capability

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Small Molecule Design

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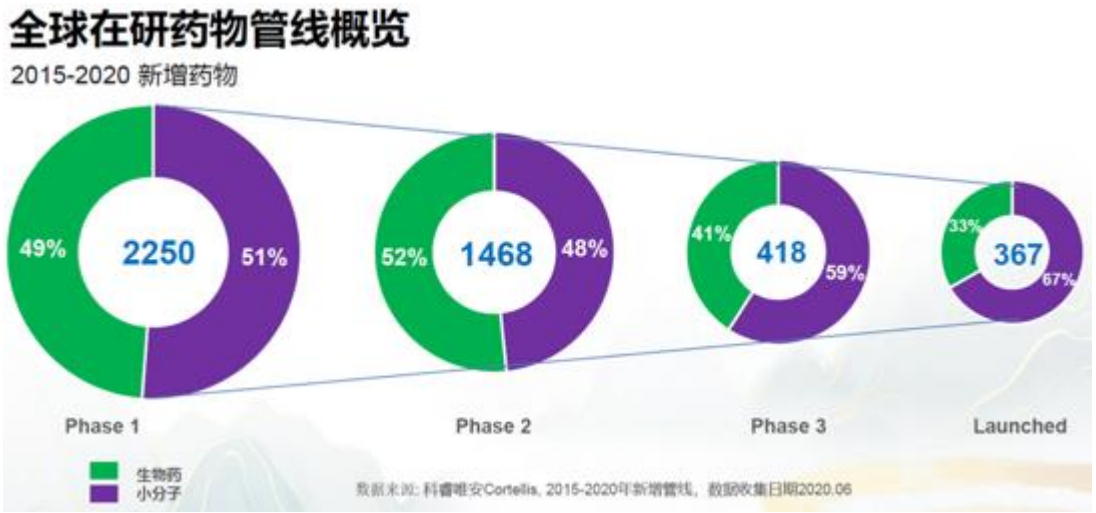
Chief Technology Officer

- More than 20 years of drug discovery experience
- Former Executive Director of Medicinal Chemistry at BioDuro, a PPD company
- Former Principal Scientist at Pfizer
- Ph.D. in Organic Chemistry at Emory University

陈向阳博士
Dr. Xiangyang Chen

“Small Molecules Continue to Drive Drug Innovation in 2020” – From American Chemical Society

- Small, synthetic molecules remain remarkably prevalent in both development pipelines and on the market
  - Advantages of small molecules: oral, on targets in/out-side cell (CNS), differentiable, non-immunogenic, etc.
  - It’s almost impossible to imagine just how many small molecules are out there
  - They’re relatively easy to make, scalable, and profitable



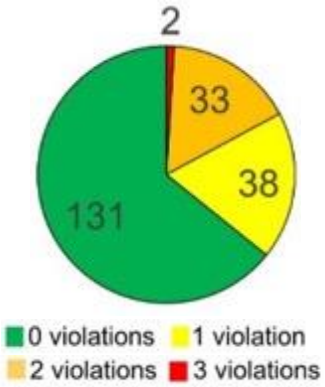
*From Cortellis’ presentation

Finding a Drug Candidate – Right Balance

Chemical space is huge

- 10^{63} possible stable molecules (MW<500)
- $10^{20\text{-}24}$ synthesizable structures
- ~2000 approved small molecule drugs

Ro5 violations 2010-2019 (oral drugs)

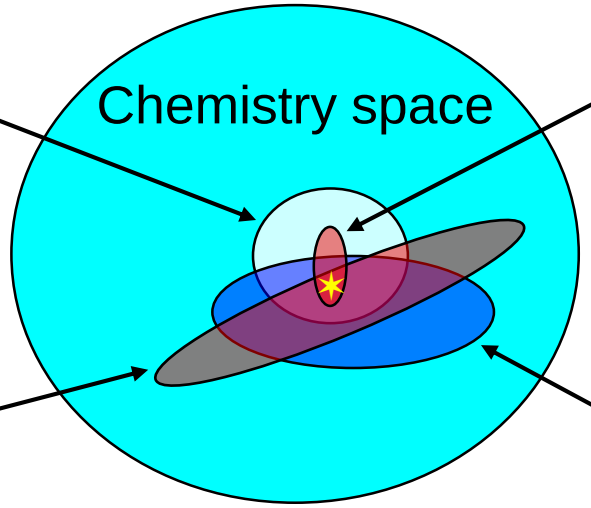


Gene family activity
"compatible space"

- Maximize interactions

Single target activity
"compatible space"

- Explore unique bindings



Safety
"compatible space"

- Avoid troublesome groups/motifs

ADME
"compatible space"

- Manipulate key structural attributes

Note: *The picture taken from RSC CICAG/RSC BMCS 20 Years of the Rule of Five Meeting, Sygnature Discovery, BioCity, Nottingham, UK and J. Med. Chem. 2021, 64, 2312-2338.

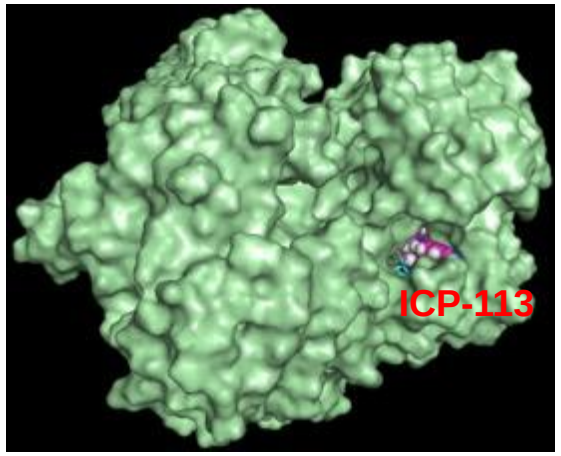
The Chemical Research @ InnoCare

- Apply our expertise in medicinal chemistry and structure-based drug design to discover novel NCEs with different chemical modalities and modes of action
  - Approach: structure understanding, template selection, multi-parameter optimization
  - Chemical modality: molecules in Ro5, beyond Ro5, macrocycles
  - Mode of action

<u>Binding site</u>
- Active
- Allosteric
- Molecular glue

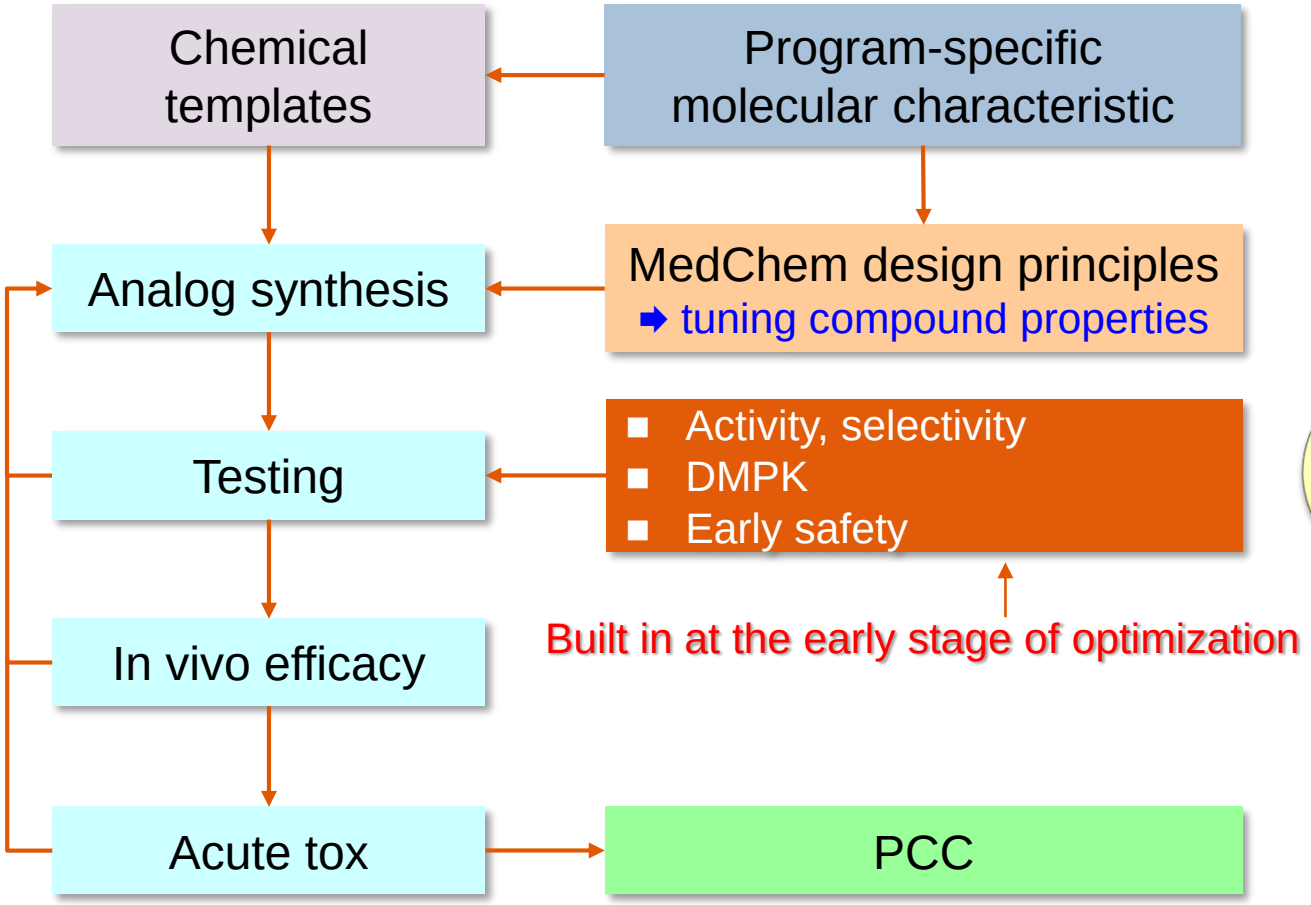
<u>Binding mode</u>
- Reversible
- Irreversible
- Protein degradation

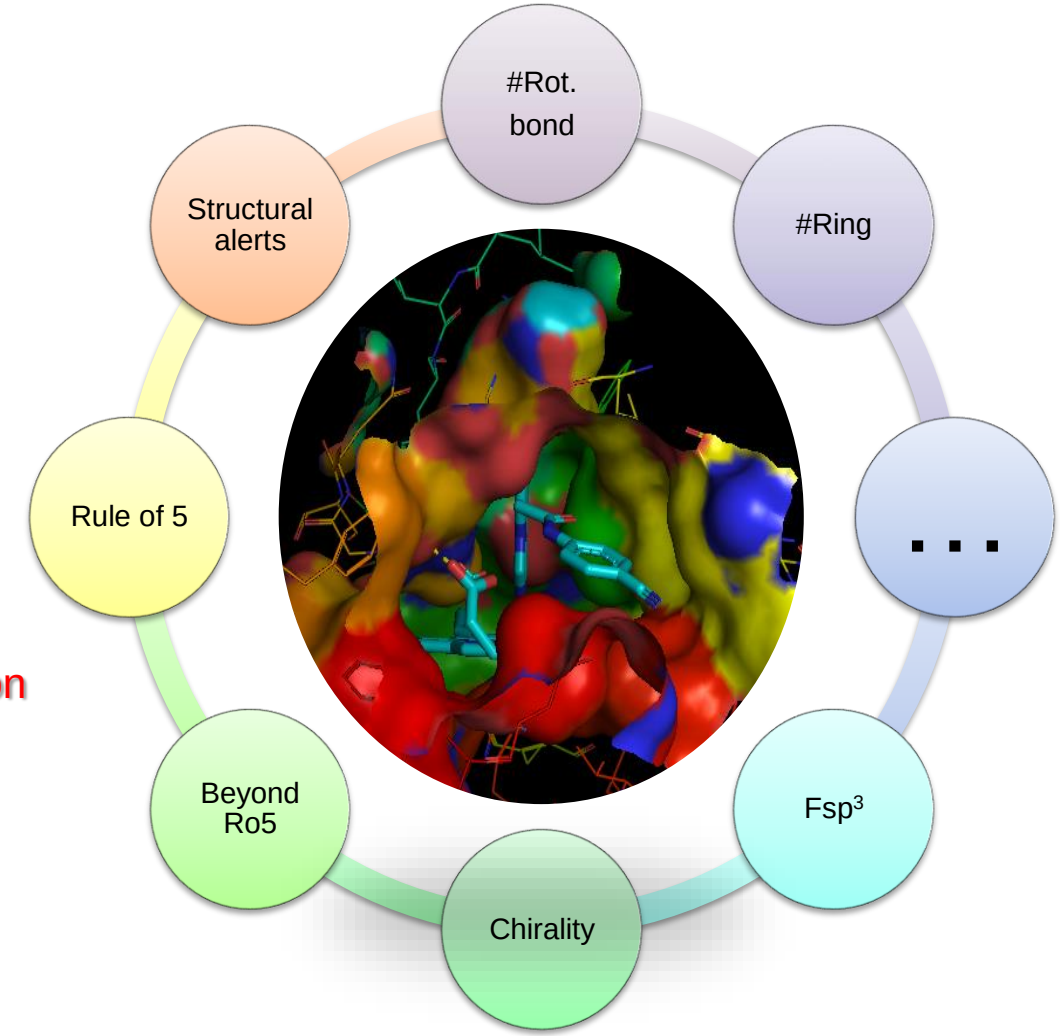
<u>Tissue-specific</u>



- Tackle different classes of the disease target: kinase, phosphatase, PPI, protein degradation, etc.

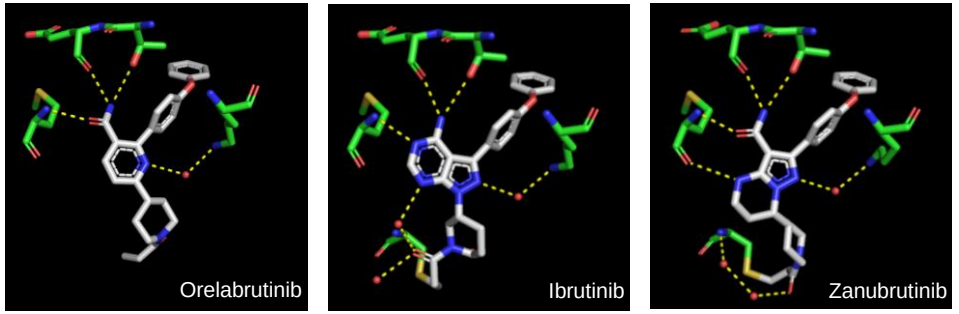
Discovery Process

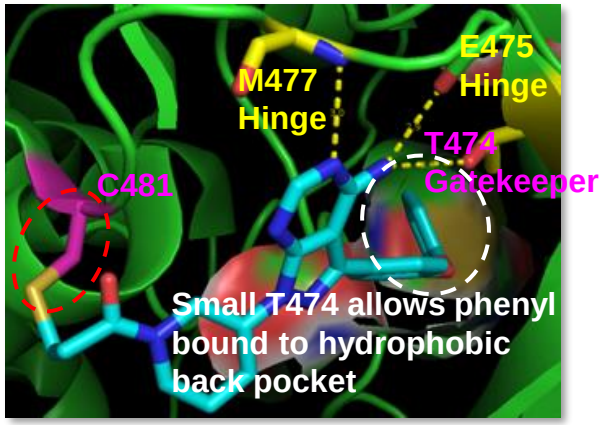




BTK: Orelabrutinib

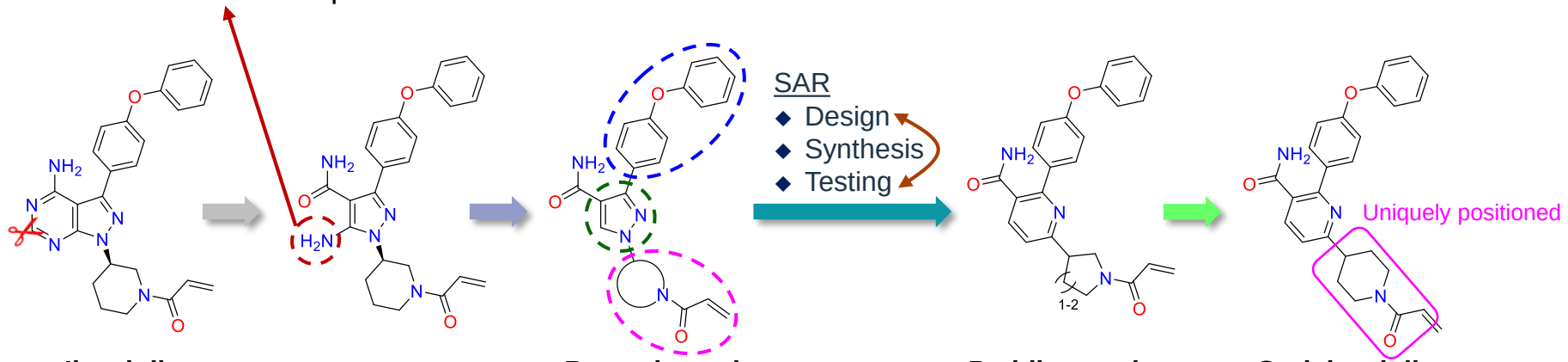
- High kinase selectivity for oncology and autoimmune diseases
- Covalent inhibition
- Compound characteristic: C_{max} driven (high C_{max}, moderate CL)





→ Stick close to lead
→ Make subtle changes

HBD
- Interacts with more kinases
- Affects absorption



Ibrutinib
Potent
Moderate CL
Kinase selectivity: not optimal

Pyrazole analog
Potent
High CL
IP: novel

Pyridine analog
Moderate potency
IP: novel

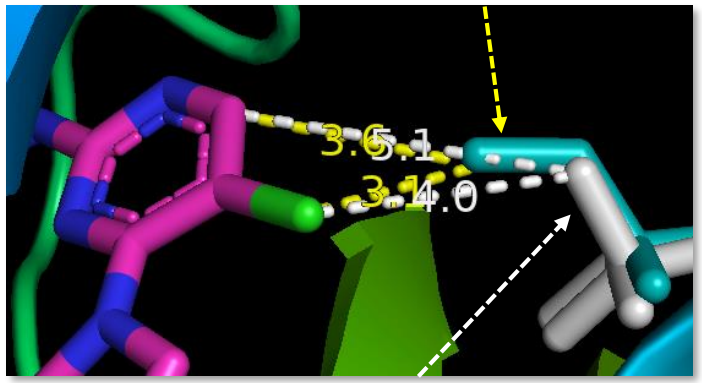
Orelabrutinib
Potent
Moderate CL
High Cmax
Kinase selectivity: superior
IP : novel
No chiral center

TYK2: ICP-332 & ICP-488

- Current JAK drugs are selective, but not specific
- High selectivity vs. JAK2
- Compound characteristic: AUC driven (low CL)

Achieving selectivity of ICP-332

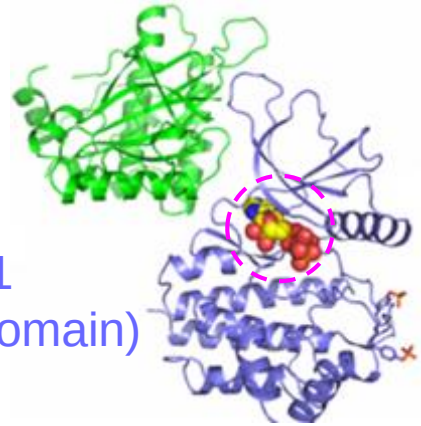
TYK2 - Ile960



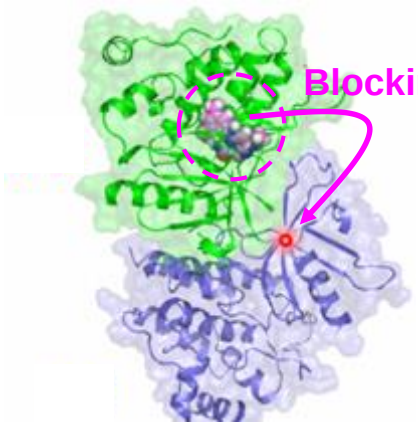
JAK2 - Val911

JH2
(pseudokinase domain)

JH1
(kinase domain)



Active site binding



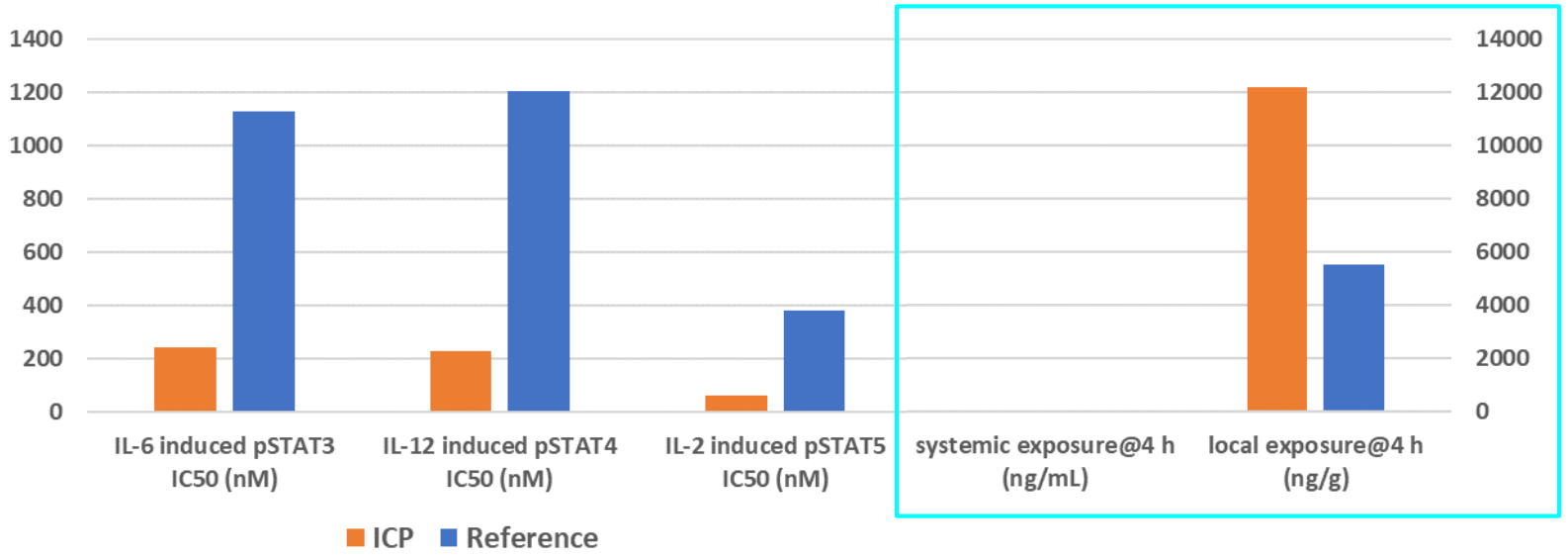
Allosteric site binding

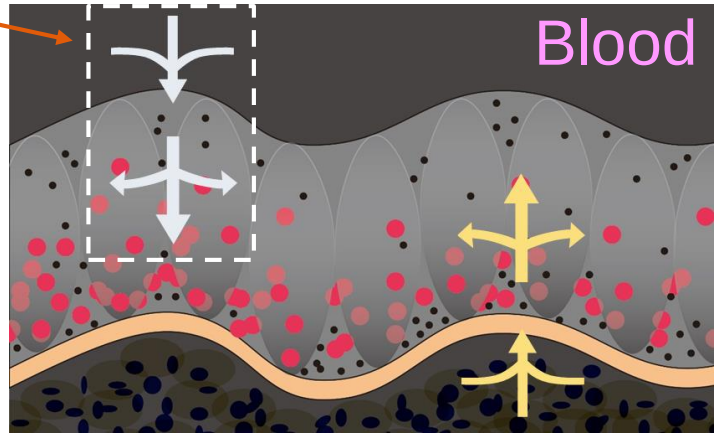
Inhibitor	IC_{50} (nM)	IC_{50} (nM) @1 mM ATP			
	TYK2 JH2	TYK2 JH1	JAK1	JAK2	JAK3
ICP-332	2319	0.5	19	191	930
ICP-488	5	>10,000			

Note: *The picture taken from Lombardo, SAPA Symposium 2020.

JAK Inhibition for Local Treatment

- Tissue specific inhibition
  - High tissue exposure ➡ maximal activity at the inflammation site
  - Low systemic exposure ➡ minimize AEs
- Potent pan-JAK activity
- Compound characteristic: High CL and/or low permeability





SHP2: ICP-189

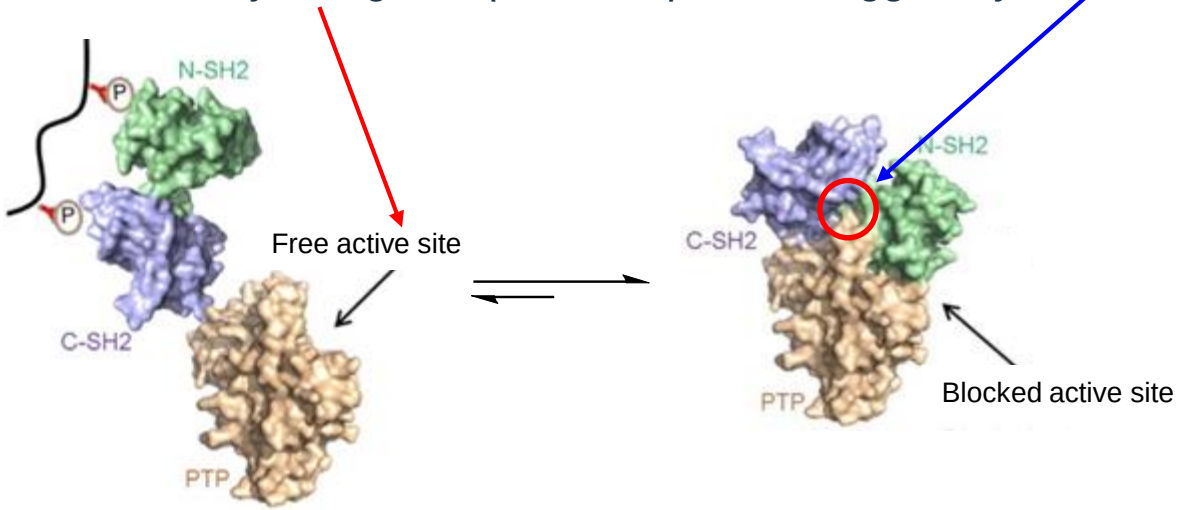
- Protein phosphatase: difficulty to target
- Taking a molecular glue approach to stabilize inactive conformation
- Compound characteristic: AUC driven (low CL)

Unfriendly catalytic pocket:

- High sequence homology ➡ poor selectivity
- Positively charged ➡ poor compound druggability

Molecular glue:

- In central tunnel formed at the interface of three domains
- Stabilizes inactive form ➡ inhibits phosphatase activity



Active conformation

Auto-inhibited conformation

ICP-189
✓Ro5 (HBD = 2)
Potent
Selective againist phosphatases
Excellent PK
No hERG@3 uM

TNO-155
Ro5 (HBD = 6)

RMC-4630
Ro5 (HBD = 5)

*The picture taken from JMC 2016, 59, 7773-7782.

Chemistry Perspective

- Continue what we do best
- May expend into new chemical modalities/MOAs
  - PROTACs
  - ADC
  - Small molecules targeting RNA or RNA-protein complex
- Utilize new technologies
  - AI

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Commercial Insight for R&D

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Function Head of Marketing

- 14 years of pharmaceutical experience with cross-functional position in Bayer, Novartis, J&J and Hengrui
- 3.5 years overseas work experience
- Imbruvica launch in China and several blockbuster oncology products management
- Neurosurgeon in Shandong Provincial Hospital

司志超博士
Dr. Zhichao Si

R&D and Commercialization

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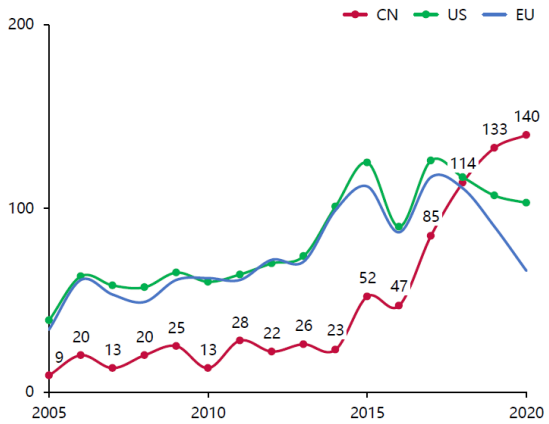
R&D is crucial to commercial success



- Clinical trial volume in China has exceeded US since 2018
- Innovative drug will empower market as essential competence

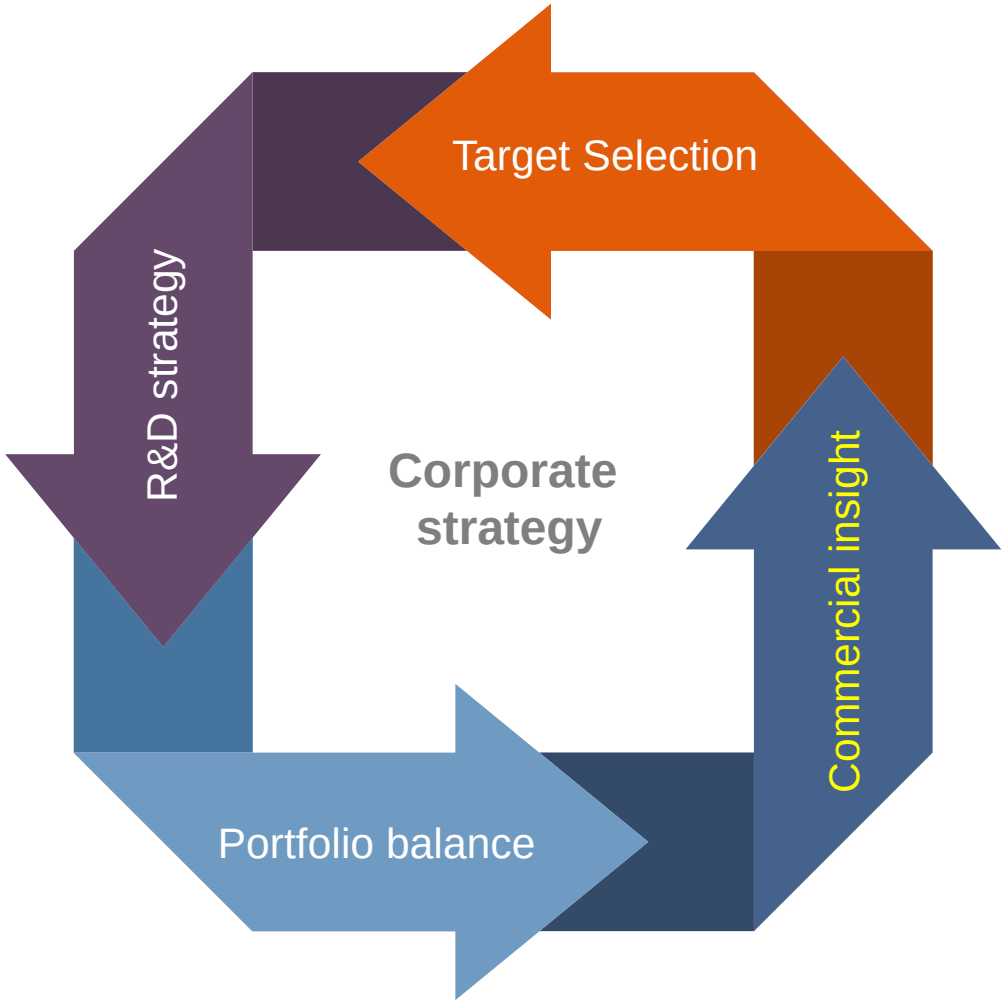
R&D innovation deeply changed the commercial model

- More swift update of new drugs/MOA
- Lifecycle management due to faster next generation approval

Commercial insights vice versa contribute to R&D thinking

- Rapidly changing competitive landscape
- Effort to understand and reflect the needs from stakeholders

Commercial Insights Incorporated into Corporate Strategy



Target population & market size

Who is it intended for? Which disease area? Which patients and where?

Key stakeholders opinions

Why will it be prescribed? Why will it be paid for?

The competitive landscape

How is it different from the product/MOA what is already there or will be?

Product value profile

Does it show promising efficacy? How is the safety profile? Stability? Route of Administration? Dosing Frequency?

Commercial Insights Vice Versa Contribute to R&D Thinking

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Commercial insights contribute to R&D strategy

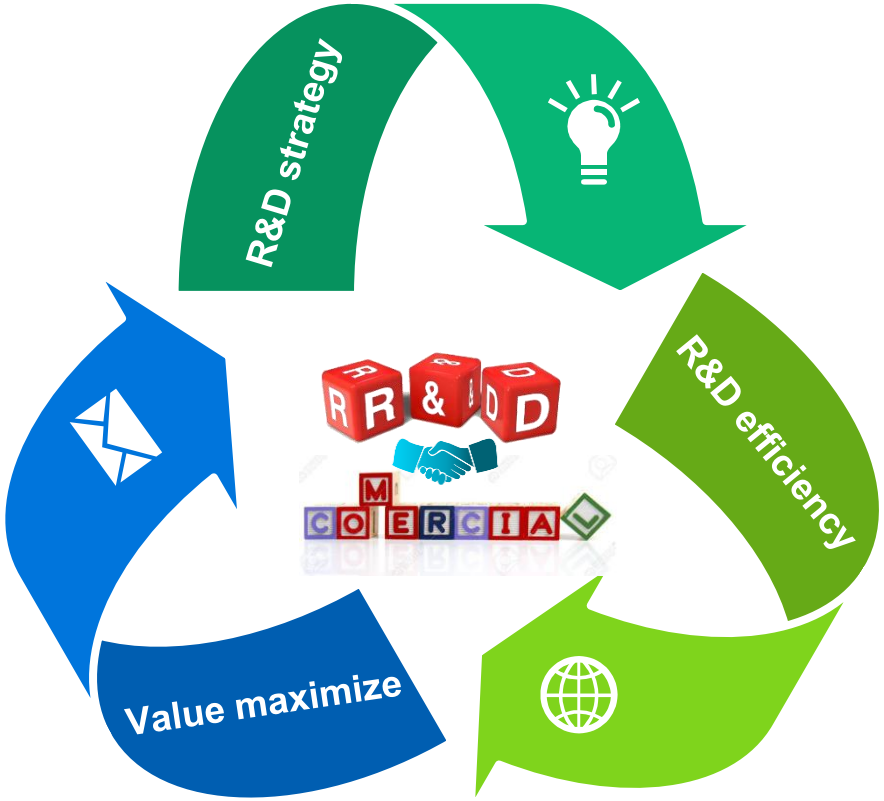
- Selecting for success in the therapeutic area: from "Target product profile“ to "**Target value profile**”

Commercial effort to improve R&D efficiency

- Improve efficiency by leveraging post-market activities and insights

From R&D to R&D & Commercialization

- R&D and commercial functions co-enables companies to make better informed **portfolio decisions, serve patients, and achieve higher returns**



Commercial Insights Contribute to R&D Strategy

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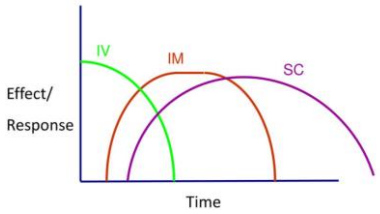
Customer insights to be incorporated into R&D strategy

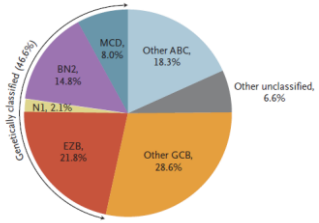
- **Insight:** Physician pay special attention on quick onset which can also release patient concern

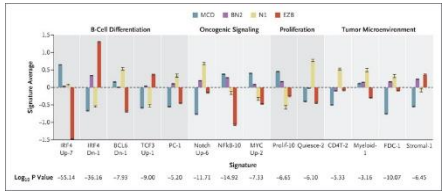


Impact on R&D strategy

- To put “fast onset and quickly release disease burden” as one of consideration when design new drug
- To smartly design a trial with emphasize the “fast onset” info and data

- **Insight :** DLBCL subtype has higher unmet medical need while might have better response to BTK inhibitor





R&D action to respond

- To quickly initiate a registration trial to target relevant DLBCL subtype with combo regimen which could support DLBCL indication extension

Commercial Insights Contribute to R&D Strategy

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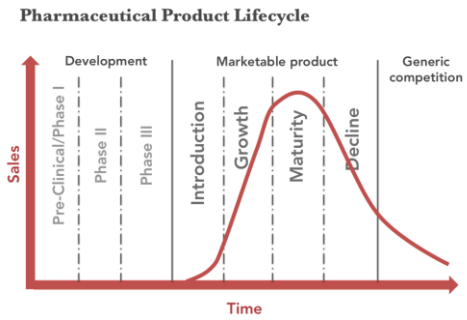
How long will it take to develop?

Speed is everything to prolong lifecycle

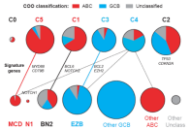


Time to Availability

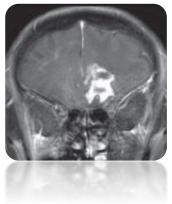
The starting point of lifecycle is decided by “first in class” approval other than the regulatory approval of “best in class” approval:

Commercial to support R&D efficiency?

Improve efficiency by leveraging post-market insights



- Targeting of patient population and TA which could be on “**fast track**”



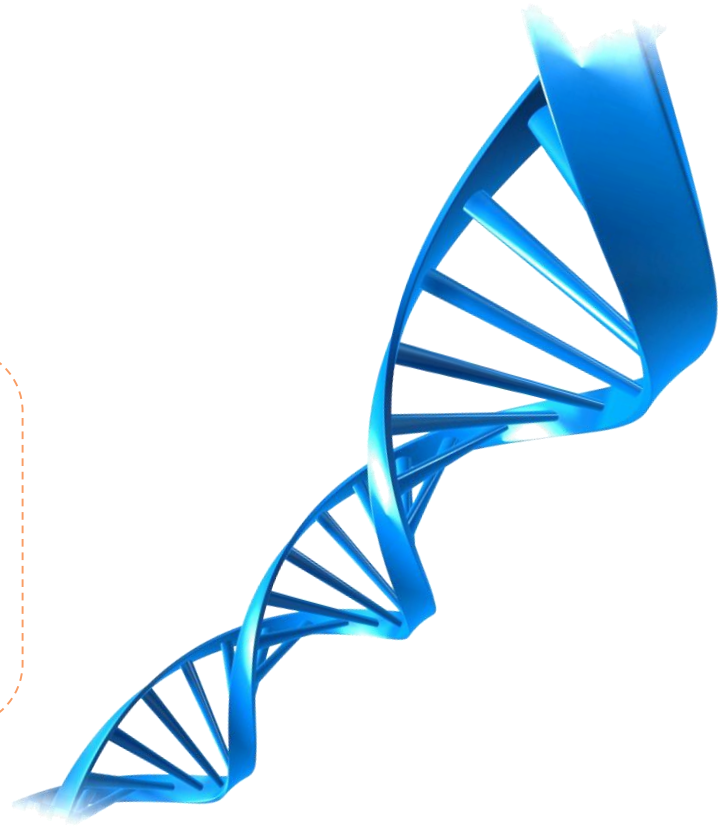
- To **pre-prove the concept** by understanding clinical practice information which could be supportive for registration study

- Provide KOL feedback and insights to contribute to **improve enrolment plan**

First in class OR **Best in class** AND **Fastest in class**

Paring R&D &C to Maximize the Value of Portfolio Assets

- Aim to develop efficacious, innovative drugs for a wide range/focused therapeutics
- Aim to regulatory approval
- View to enrich company pipeline



- Aim to seek for market focused product and 'value added' evidence to differentiate
- Aim to deliver a high-value portfolio to the market
- View to quickly respond to market and stakeholder needs

R&D and commercial functions co-enable companies to **make better informed portfolio decisions, serve patients**, and **achieve higher returns**

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