Biotech and early drug development in immunotherapy in China

M.D. Zhang Li,
Sun Yat-Sen University Cancer Center
2015-12-21 Singapore
Un-met needs for Development of Anti-Cancer Drug in China

300M cancer patients in China drive the big market of anti-Cancer Drugs

Anti-cancer drugs

Mono-Antibody drugs

http://m.biodiscover.com/news/industry/106268.html
Un-met needs for Development of Anti-Cancer Drug in China

Rituximab

http://m.biodiscover.com/news/industry/106268.html
Composition of different indication IND
Application in 2011 to 2012

Domestic IND
- Electrolyte, acid-base balance, nutriceutical and volume expanded drug
- Respiratory and antiallergic drugs
- Psychiatry drugs
- Anti-infection drugs
- Oncology drug
- Endocrinology drugs
- Dermatology and ophthalmology drugs
- Neurology drugs
- Reproductive drugs
- Surgical and other drugs
- Gastroenterology drugs

International, multicenter
- Oncology drug

- China Drug Review Annual Report
2014 IND Application in China

图4 2014年接收化药IND申请的治疗领域构成

- China Drug Review Annual Report
Application for Innovative Oncology drug

- **Domestic innovative Oncology drug application in 2008-2012** (Categories)

- All categories
- Small molecular targeted drugs
Immune Research in China

With the tremendous increase of funding from the National Natural Science Foundation of China, the Ministry of Science and Technology, the Ministry of Health, as well as regional governments in past years,

Between 2001 and 2011, the number of publications from China in the field of immunology rose from ranked fifteenth (in 2001–2005) to sixth (in 2006–2010).

X.T. Cao Nature Immunology 2008
Cancer Immunotherapy


2. Top Breakthrough of the Year 2013 in Science

3. Cancer immunotherapy methods include:
   - Immune checkpoint inhibitor antibody
   - Adoptive cell therapy (DC-CTL, TIL, TCR, CAR-T)
   - Cancer vaccines: peptide, protein, DNA
By controlling immune responses, immuno-Check point system can benefit the host by eliminating invading pathogens while not causing damage to host tissues.

In the traditional Chinese medicine theory, Yin (negative regulation) and Yang (positive regulation).
Immune checkpoint inhibitors in China

Ipilimumab
- Melanoma
- NSCLC
- SCLC

CTLA-4 inhibitor (Simcere Co)

PD-1 inhibitor
- BMS Checkmate 78
- Roche GO29436
- MSD Protocol 033

PD-1 inhibitor (Domestic)
- SHR1210 (Hengrui Pharm Co)
- BGB-A317 (BeiGene Co)
- JS001 (Junshi BioScie Co)
PD-L1 expression in tumor tissue samples and its correlation with recurrence free survival in NPC

Fang WF, Zhang L et al: Oncotarget 2014
LMP1 mediated the up-regulation of PD-L1 expression in EBV-infected human NPC cells

Fang WF, Zhang L et al: Oncotarget 2014
Two mechanisms of up-regulated PD-L1 expression on EBV positive nasopharyngeal carcinoma cells

Fang WF, Zhang L et al: Oncotarget 2014
Immune checkpoints Phase I trials in SYSUCC

• CheckMate 077: CHECK point pathway and nivolu MAb
clinical Trial Evaluation 077
  – A Phase 1/2, Open-Label Study of Nivolumab (BMS-936558) in
    Chinese Subjects with Previously Treated Advanced or Recurrent
    Solid Tumors

• CA 184247
  – A Phase 1 Dose Escalation Study of the Safety, Tolerability, and
    Pharmacokinetics of Ipilimumab in Chinese Subjects with Select
    Advanced Solid Tumors
Adoptive Cell Immunotherapy
A randomized, controlled trial of postoperative adjutant cytokine-induced killer cells immunotherapy after radical resection of hepatocellular carcinoma


Original article

A randomized controlled trial of postoperative tumor lysate-pulsed dendritic cells and cytokine-induced killer cells immunotherapy in patients with localized and locally advanced renal cell carcinoma

Chinese Medical Journal 2012;125(21):3771-3777

N=137

N=127
- **Personalized immunotherapy**

  *Use next-generation sequencing result to guide personalized therapy*

- Whole Exome Sequencing
- RNA-seq
- TumorCare Sequencing Panel

- **TumorCare Panel**
  - 622 genes selected from the important cancer pathway
  - 1053 panel genes number
  - 176 genes with therapy related alterations
  - 80 for Target therapy
  - 98 for Chemotherapy
  - 26 for other therapy
  - 255 genes with frequent savs in Cosmic
  - Genes with savs that appears in more than 10 samples in Cosmic

- **Oseq™-T Tumor Sequencing Panel**
  - measure 508 tumor-related genes
  - Test sensitivity of 88 different tumor drugs
Peptide Vaccine Development for Liver Tumor

**Experimental Design**
- Mutation discovery
  - Exome sequencing
  - MHC binding prediction
- Immunogenicity testing
  - Anti-tumor effects monitor
  - Mutation peptide screening
  - Immunize with peptide vaccine

**Exome Sequencing Result for Tumor Sample**
- Normal tissue
- Tumor tissue
- Hepa-16 cells
- C57BL/6 Mice
- SNVs
- Coding SNVs
- Nonsynonymous SNVs
- Predicted candidate neoantigen
  - 1343
  - 314
  - 102
  - 50

**Exome Sequencing Result**
- From outer to inner: Gene density, SNV, Transcript SNV, non synonymous coding SNV.

**Anti-tumor effect of predicted peptide GPR55**
- Control
- CFA
- GPR55

(Li et al., submitted 2015, BGI)
The repertoire of clonotypes continued to evolve over subsequent months of treatment. Overall survival was associated with maintenance of high-frequency clones at baseline.
The analytical pipeline in BGI - IMonitor

Wei Zhang et al., IMonitor: a robust pipeline for TCR and BCR repertoire analysis
doi: 10.1534/genetics.115.176735 Genetics
TCR repertoires of HCC patients are different from that of normal control.

Yinxin Han et al., Identification of characteristic TRB V usage in HBV-associated HCC by using differential expression profiling analysis, OncoImmunology Volume 4, Issue 8, 2015
Summary

- Big cancer patients pool drive the un-met needs for development of anti-Cancer drugs in China.

- Cancer immunotherapy will be more interesting treatment options for most solid tumor, especially for so-call: Chinese comment tumor type like liver cancer, esophageal cancer, gastric cancer, nasopharyngeal carcinoma

- Using new biotech like next-generation sequencing (NGS) result to guide personalized immunotherapy will be popular in the future.
THANK YOU!
Sun Yat-sen University Cancer Center