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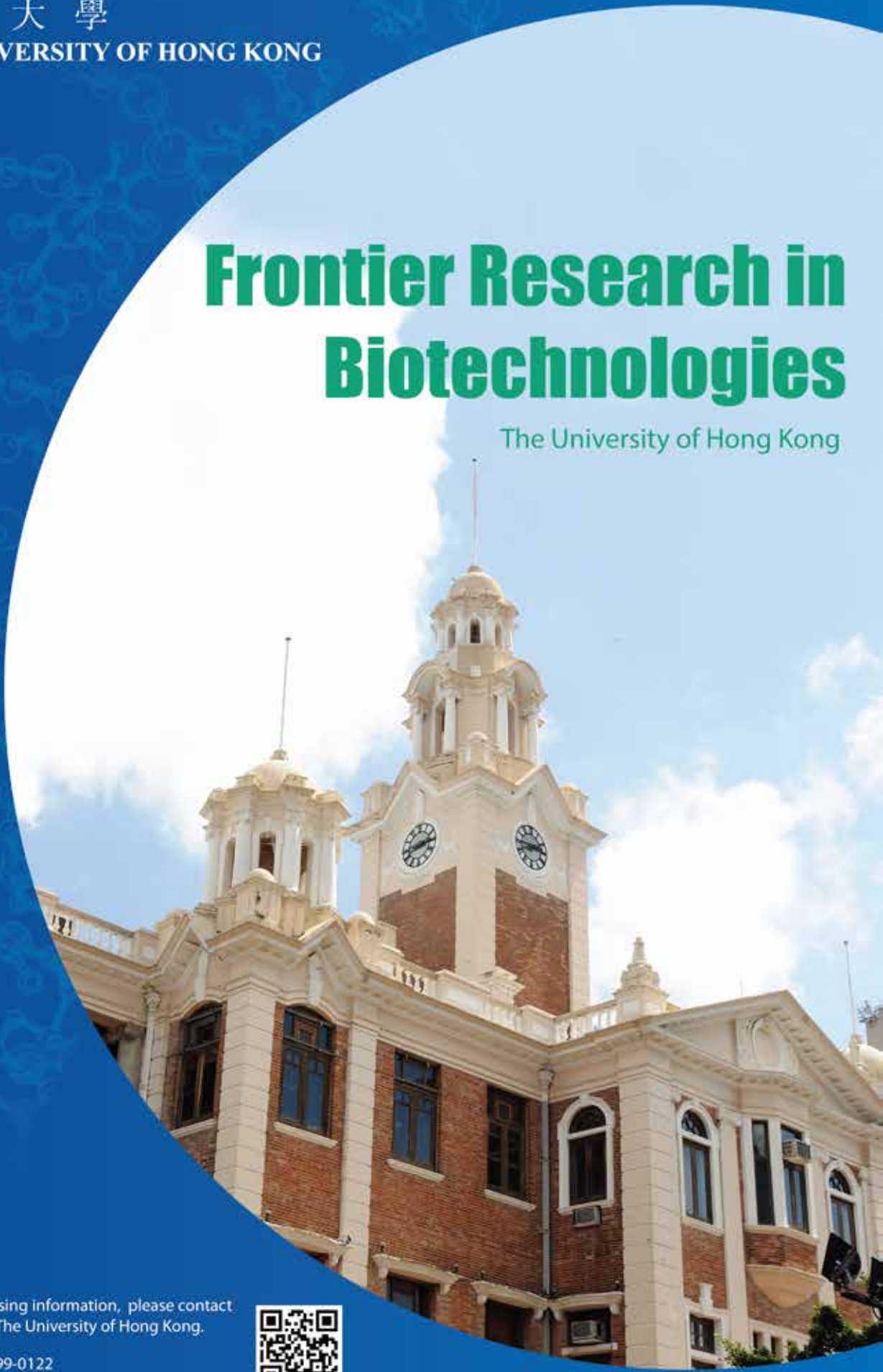
THE UNIVERSITY OF HONG KONG

Frontier Research in Biotechnologies

The University of Hong Kong



For further technical and licensing information, please contact Technology Transfer Office of The University of Hong Kong.

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About The University of Hong Kong

Being the first and foremost university in Hong Kong, The University of Hong Kong ("HKU") is an institution with a long and distinguished academic heritage, in addition to an international reputation for forward-looking pioneering research. HKU is consistently ranked among the very best in Asia by QS and Times Higher Education.

About Technology Transfer Office

The Technology Transfer Office (TTO) of HKU was established in 2006. TTO manages the use of the intellectual property assets of HKU by providing patenting, licensing, and other commercialization support to our researchers. Acting as the bridge linking HKU to society in the arena of technology commercialization, TTO helps industries and businesses to access HKU's powerhouse of knowledge, innovation, and expertise through close collaboration. One of our key aims is to bring the University's inventions and research know-how to the wider world through technology transfer, so that they can be used for public benefit.

Some highlights of our biotechnology inventions that are available for licensing are described in the following pages.

Table of Contents

Arsenol® (Arsenic Trioxide Oral Solution)

US Granted Patent No. 7,521,071
JP Granted Patent No. 4786341

Arsenol® is a clear solution of arsenic trioxide in water-for-oral- administration. It is indicated in the treatment of acute promyelocytic leukemia (APL), which is characterized by t[15;17] translocation or PML-RARα gene expression. Patients can be treated at initial presentation, for maintenance, or at disease relapse. Arsenol® is the first locally produced, registered, patented prescription drug in Hong Kong.

I: Development of Oral Arsenic Trioxide (Arsenol®)

- The formulation of oral arsenic trioxide was developed by Prof. Kumana and Prof. Kwong in Department of Medicine, The University of Hong Kong.
- The pharmacokinetic study showed that the arsenic bioavailability via oral route is comparable with the i.v. route.

II: Efficacy and Safety of Arsenol®

Therapeutic efficacy and safety of Arsenol® use in APL treatment has been investigated in clinical studies in Hong Kong with at least 200 clinical cases.

Table 1: Patient demographics for two main clinical studies

No.	Patient Status	Dosage and duration	Patient number	Median age
1	Relapsed APL (R1 or R2)	10 mg/day; Oral therapy until remission	12	33 years (13-65 years)
2	in CR1	10 mg/day; Maintenance 76 2 weeks every 2 months for 2 years 1 As_2O_3 (n=20) 2 As_2O_3 and ATRA (n=19) 3 As_2O_3, ATRA and ascorbic acid (n=37)	76	44 years (16-83 years)

Table 2: Results of the two clinical studies

No.	CR rate	Time to CR (median)	Relapse rate	Median time to relapse
1	100%	33 days	1/12 (8%)	10 months
2	N/A	N/A	8/76 (11%)	18 months

The 3-year leukemia-free-survival, event-free survival, and overall-survival rates for all three Arsenol® regimens combined in the study No.2 were 88%, 84%, and 91%, respectively.

III: Granted or Filed Patents of Arsenol®

Name of invention	Patent number / Application number	Status
Formulation of Oral Compositions Comprising Arsenic Trioxide and Methods of Use Thereof	US No. 7,521,071	Granted
	JP No. 4786341	Granted
	EP No. 3753241.3	Filed
	CN No. 201310136319.2	Filed
Method for Inhibiting Cancer Using Arsenic Trioxide (Cyclin D1)	US No. 8,906,422	Granted
Method for Inhibiting Cancer Using Arsenic Trioxide (Interleukin-6)	US No. 11/871,057	Filed
Compositions and Methods for Treating Rheumatoid Arthritis	US No. 12/781,970	Filed
The Use of Arsenic Trioxide to Suppress Rheumatoid Arthritis Activity	CN No. 201080021634.5	Filed
	EP No. 10777291.5	Filed
	JP No. 2012-511124	Filed

IV: Outstanding characteristics of Oral Arsenic Trioxide Therapy

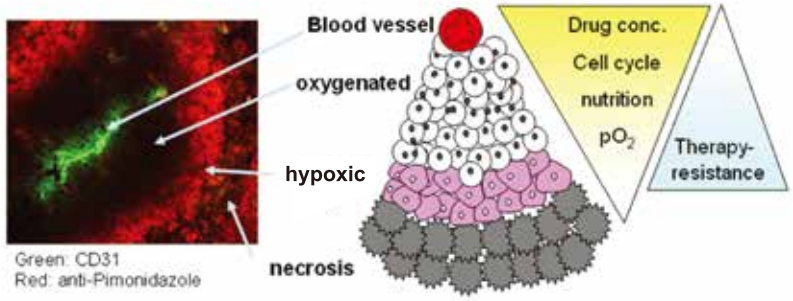
- No hospitalization and better quality of life
- Cost-effective
- Comparable arsenic bioavailability to arsenic trioxide intravenous injection
- High efficacy in APL treatment
- Good safety profile
- Fewer cardiac side effects compared to arsenic trioxide intravenous injection

Bio-Engineered Bacteria for Cancer Therapy

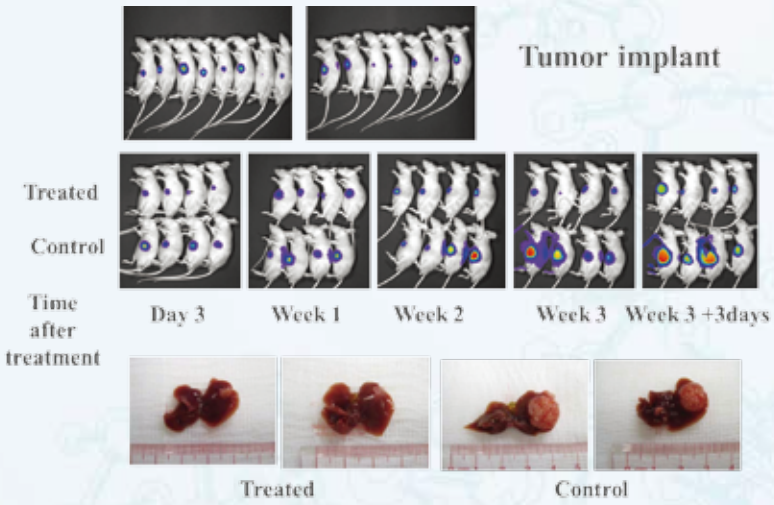
US Regular Application No. 13/871,716
CN Application (PCT) No. 201380023412.
EP Application (PCT) No. 13784697.8

By using technology of genetic engineering, genome recombineering, and synthetic biology, we reprogrammed Salmonella Typhimurium strain (YB1) into an "obligate" anaerobe without otherwise interfering with the function of the bacterium. This avoids the problem of infection in aerobic normal tissues, as the modified strain will lyse under these conditions. When in the hypoxic regions of a tumor, the bacterium can thrive and act as the wild type form as it is not compromised by an attenuation process.

Microenivironment of Solid Tumor



Advantages of Using synthetic biology method for cancer therapy



1. Make use of microenvironment of solid tumor
2. Identification of tumor type
3. Genetic diversity for engineering
4. Bacillus Calmette-Guerin (BCG) is the most effective method for bladder cancer therapy

Repression of tumor growth in nude mice model by YB1

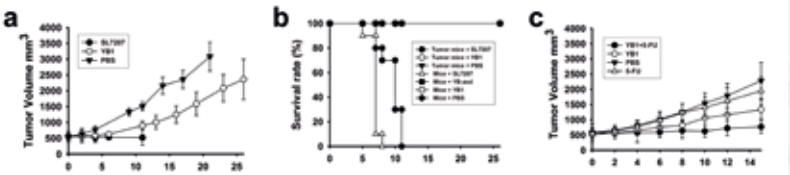


Fig3. (a) Tumor volume in nude mice injected with YB1, SL7207 or PBS (n=10, mean±sd). SL7207 treated nude mice died by day 11. (b) Survival chart for tumor free and tumor bearing nude mice treated with YB1, SL7207, YB-asd or PBS, respectively (n=10 each). (c) Tumor bearing nude mice were treated with YB1 or PBS (n=24 each). After three days, 5-FU was injected i.p. (60 mg/kg) to half the nude mice of each group (n=12) and repeated every three to four days for 2 weeks.

Key Features of HKU's YB1

1. Increasing bio-safety
(Repress bacteria accumulation in normal tissue)
2. Tumor targeting
3. Keep tumor repressing effect

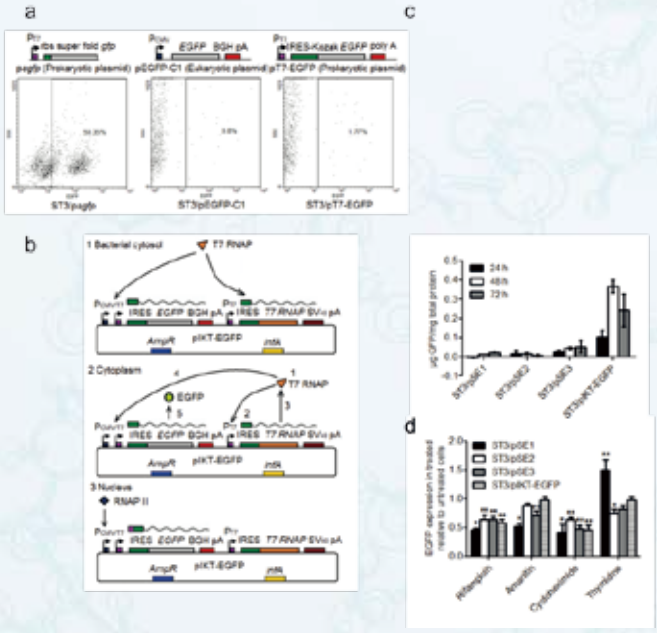
Combined Prokaryotic-Eukaryotic Delivery and Expression of Therapeutic Factors Through a Primed Autocatalytic Positive-Feedback Loop

US Regular Application No. 14/019,058 CN Application (PCT) No. PCT/CN2014/000282

Progress in bacterial therapy for cancer and infectious diseases is hampered by the absence of safe and efficient vectors. Sustained delivery and gene expression are critical for therapeutic efficacy. Here we develop a Salmonella typhimrium strain engineered to maintain and safely deliver a plasmid vector to target tissues. This vector is designed to allow dual transcription of therapeutic factors, such as cytotoxic proteins, short hairpin RNAs or combinations, in the nucleus or cytoplasm of eukaryotic cells, with this expression sustained by an autocatalytic positive-feedback loop. A mechanism to prime the system and maintain the plasmid in the bacterium are also provided. Application of this bacteria-vector system to immunocompetent mouse models caused tumour regression and prolonged survival, improving substantially on related methodologies. This innovative technology provides an effective and versatile vehicle for efficient inter-kingdom gene delivery that can be applied to cancer therapy and other purposes.

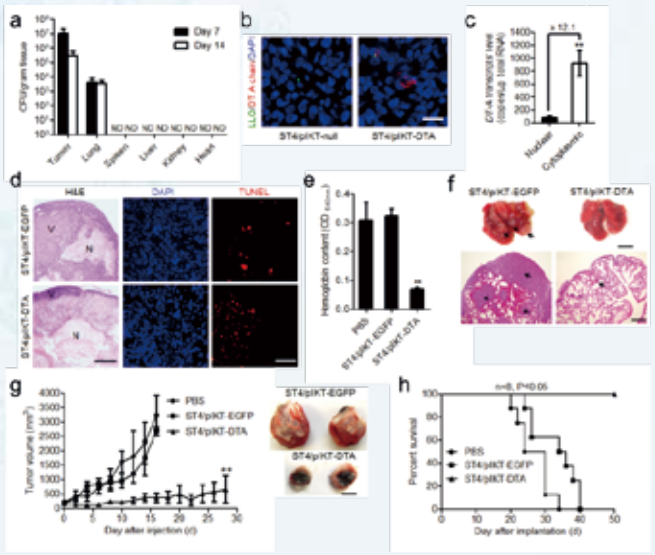
Development of a inter-kingdom dual expression system

The engineered *S. typhimurium* strain ST3 can incade eukaryotic cells, break the endosomal compartment and directly release protein, plasmid DNA and translation-competent mRNA into the cytosol, leading to the desired gene expression (a). Based on it, we developted a novel inter-kingdom dual expression (IKDE) plasmid system with a phage RNAP amplification circuit (b). Compared to plasmid DNA delivery and/or RNA delivery, ST3 carrying an IKDE system led to a more efficient transgene expression (c). After infection with strain ST3/plKT-EGFP, only prokaryotic transcritpion inhibitor (Rifampicin) and eukaryotic translation inhibitor (Cycloheximide), but not eukaryotic transcription inhibitor (Amanitin), significantly reduce EGFP expression in mannalian cells (d).



Potent therapeutic effects in the immunocompetent mice with highly aggressive tumor elicited by ST4-mediated expression of diphtheria toxin through on IKDE system

Tumor-targeting *Salmonella* strain ST4 was modified from ST3 by placing the essential gene asd with a tightly hypoxic regulated control. Aggressive 4T1 murine tumor cells were implanted into the mammart fat fad of immunocompetent BALB/c mice, which were subsequently injected with ST4/plKT-DTA. After 7 and 14 days post-injection, bacteria were only growing in primary tumors and metastatic nodules in the lung (a). After 2 weeks, the primary tumors were harvested. The intracellular presence of bacterial toxins (red) in the cytosol of ST4/plKT-DTA (green) infected cells was detected (b). Quantitative PCR showed that 92.7%±1.7% of the transcripts were driven by the T7 RNAP-based cytoplasmic expression system (c). In situ expression of the DT A chain caused a great proportion of necrotic areas and significant cell death, and it also significantly retarded angiogenesis in primary tumors as well as reduced pulmonary metastases (d-f). A single injection of ST4/plKT-DTA into mice bearing 4T1 tumors resulted in sustained tumor regression over 4 weeks and complete survival of mice (g-h).



Immunotherapeutic Targets Against Staphylococcus Aureus

US Provisional Application No. 62/093,752

The present scenario is that antibiotics are no answer to the multi-drug-resistant (MDR) pathogens infection problems. The more antibiotics used, the more MDR pathogens emerging. Therefore, vaccinations are better strategies to control MDR pathogen infections. The Research Team at the University of Hong Kong provide vaccine formulations and antibodies, and related methods, for the treatment and/or prevention of S. aureus infection. The present invention provides one or more S. aureus antigens for use in vaccine formulations, wherein two or more antigens act synergistically. Thus, the protection against S. aureus infection achieved by their combined administration exceeds that expected by mere addition of their individual protective efficacy. Further, the present invention provides vaccines which can protect against hematic spread, pneumonia and skin infection, and which may also elicit a protection antibody response. The invention also provides novel antibodies and antibody cocktails to treat S. aureus infection.

1. A model for developing 5 aureus vaccine

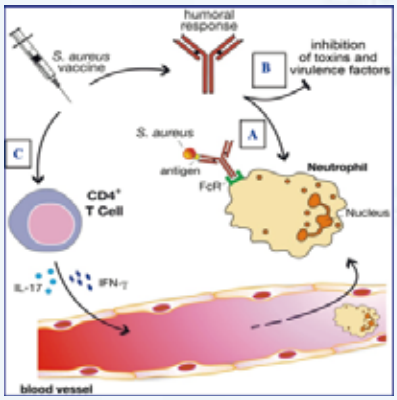


Fig 1. Vaccine efficacy shall be gained through three major immune responses:

A) Antibodies to mediate opsonophagocytosis;
B) Antibodies to directly inhibit bacterial viability and/or toxiclty
C) Cell-mediated immunity (Th17)

Any single immune response may not be sufficient to elicit protective effect against MRSA

2. The advantages of our S.aureus proto-type vaccine

- The previous vaccines or antibody are based on a single antigen, our invention provide a group antigens, including T cell (TH17) and B cell target, which two or more antigens act synergistically;
- The vaccine which can protect against hematic spread, pneumonla and skin infection, and which may also elicit a protection antibody response;
- The inventions not only provide a group of antigens for vaccine development, but also provide novel antibody cocktail to treat S.aureus infection.

The sustainability of the technical advantages

The vaccine antigen composition and antibody cocktail can not only develop human biological products, but also can develop dairy cow vaccine to control S. aureus infection.

MRSA is responsible for approximately 16,000 deaths annually in Europe and 19,000 in the US. MRSA infects an estimated 53 million people globally and costs more than $20 billion a year to treat (www.bellerophon-project.eu).

Moreover, there is an increasing public health concern over bovine mastitis because of the risk that treatment with antibiotics may lead to the entry of antibiotic resistant bacteria into the food chain. There are estimates that 80-100% of all herds have at least some S. aureus mastitis, with from 5 to 10% of cows infected.

Method And Compositions for Treating Cancer Using Probiotics

US Regular Application No. 14/460,732
PCT Application No. PCT/CN2014/084394

Hepatocellular carcinoma (HCC) is the fifth most prevalent cancer and the third leading cause of all cancer-related deaths in the world. Current standard treatment of HCC includes surgical treatment, local ablation therapy and chemotherapy but these standard treatments usually involve high risks, high costs and many negative side effects. Oral consumption of viable probiotics is one of the many alternative experimental cancer treatments reported in the literature. And there is substantial evidence that some probiotics can provide benefits by modulating immune functions, including modulating T helper cell response.

ProHep comprises of three probiotics compositions of which are heat-inactivated Lactobacillus acidophilus (Moro) Hansen and Mocqu (ATCC 53103), viable Escherichia coli Nissle 1917 and heat-inactivated VSL#3®. It has been found that pretreatment/ treatment of ProHep could reduce the tumor size of mice having subcutaneous tumor inoculation. Though the anti-cancer effects of probiotic groups were less potent than drug (cisplatin) treatment group, probiotics could be used as an alternative way for cancer treatment.

Figure A

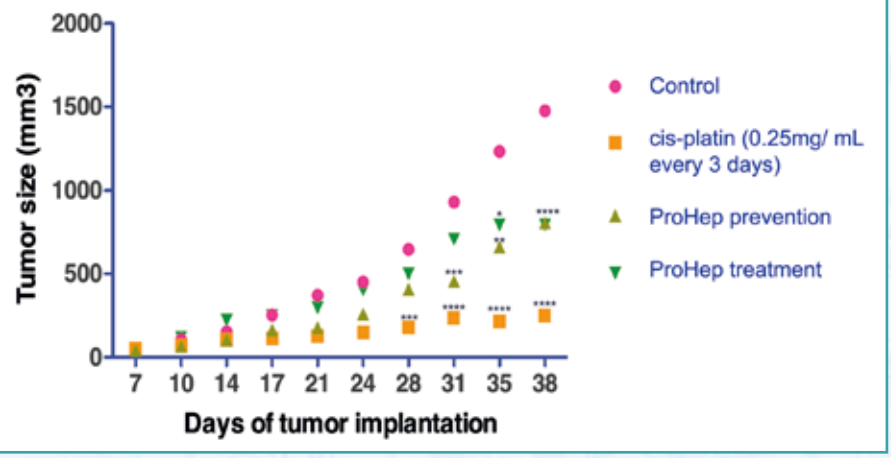


Figure B

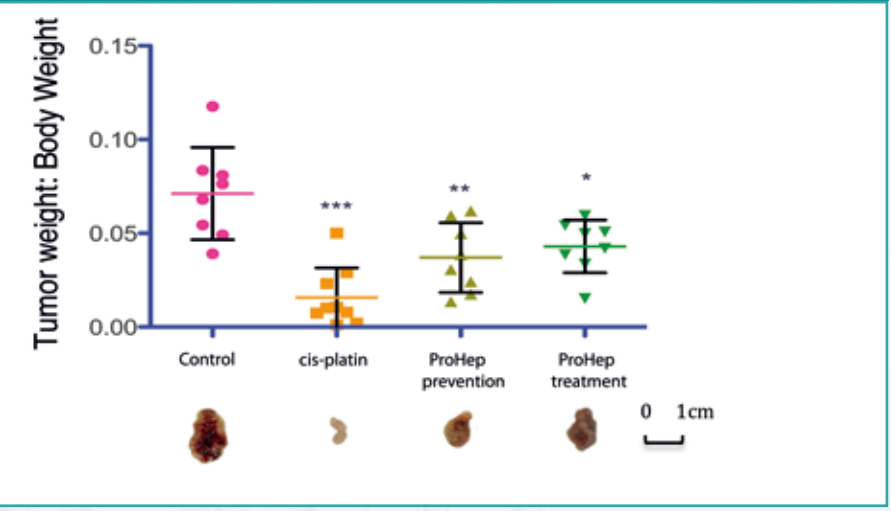
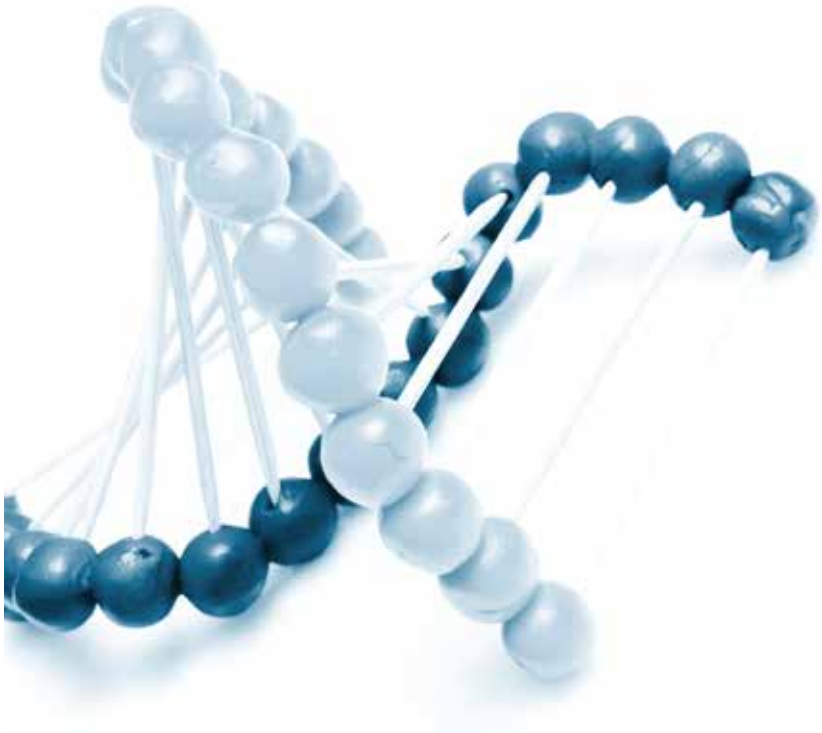


Figure shows graphs of A) tumor size and B) tumor weight in mice having subcutaneous Hepa1-6 tumor inoculation fed with a ProHep diet daily starting from either 1-week before (ProHep prevention) or at the same day (ProHep treatment) of tumor inoculation. Cisplatin was given as positive control every 3 days i.p.

Disease Diagnosis



Early diagnosis of severe diseases is essential to ensure most effective treatment in time. Cancers, diabetes, heart diseases and infectious diseases are all top killers around the world. Therefore diagnostic biomarkers and detection methods for these types of diseases are hot topics in this research field. Biomarkers are biological measures acting as indicators or predictors of the pathological processes or pharmacological responses to a treatment.

Nowadays, a number of gene and protein based biomarkers have already been used in patient care. Currently, scientists in HKU are active in identifying new biomarkers and developing novel diagnostic methods for various kinds of diseases.

Title	Patent application status
Cancer biomarkers	
Compositions and Methods for Prognosis and Therapy of Liver Cancer	Chinese Patent No. ZL200480029686.1 Hong Kong Standard Patent No. HK1098783 US Patent No. 8,076,077
Granulin-Epithelin Precursor (GEP) Overexpression as a Target for Diagnosis, Prognosis and Treatment of Hepatocellular Carcinoma (HCC)	Chinese Patent No. ZL200580013799.7 Chinese Patent No. ZL200780040670.4
Method for Predicting and Detecting Tumor Metastasis	US Patent No. 8,816,059
Cadherin-17 as Diagnostic Marker and Therapeutic Target for Liver Cancer	US Regular Application No. 12/569,386 PRC (PCT) Application No. 200980150076.X EP (PCT) Application No. 09818741.2
Gene Markers (Gene Markers Useful in the Diagnosis of Nasopharyngeal Cancer)	UK Application No. 1113887.2 PCT Application No. PCT/GB2012/051964 HKST (GB) Application No. 12107890.2
Use of Annexin A3 as a Diagnostic and Prognostic Biomarker and Therapeutic Target for Treating Hepatocellular Carcinoma	US Regular Application No. 14/485,206 PCT Application No. PCT/CN2014/089416
Method for Selecting Esophageal Squamous Cell Carcinoma Patients for Chemoradiation	PRC Application No. 201410436731.0
Diabetes biomarkers	
Use of Lipocalin-2 as a Diagnostic Marker and Therapeutic Target	US Patent No. 7,645,616
Methods and Compositions for Use of Neutrophil Elastase and Proteinase 3 as Diagnostic Biomarkers	US Provisional Application No. 62/004,969

Title	Patent application status
Cardiac disease biomarkers	
Lipocalin-2 as a Prognostic and Diagnostic Marker for Heart and Stroke Risks	US Patent No. 8,030,097 PRC (PCT) Application No. 200980116060.7 India (PCT) Application No. 8306/DELNP/2010 JP (PCT) Application No. 2011-506552 EP (PCT) Application No. 09737621.4
Diagnosis of infectious diseases	
Penicillium Marneffei Antigenic Protein	US Patent No. 5,973,131
Serum Biomarkers of Hepatitis B Virus Infected Liver and Methods for Detection Thereof	US Patent No. 7,257,365
A Novel Human Virus Causing Severe Acute Respiratory Syndrome (SARS) and Uses Thereof	Chinese Patent No. ZL200480007683.8 US Patent No. 7,375,202 US Patent No. 7,785,775 PRC Divisional Application No. 200910159269.3 US Patent No. 8,361,708
High-Throughput Diagnostic Assay for the Human Virus Causing Severe Acute Respiratory Syndrome	Chinese Patent No. ZL200480007680.4 US Patent No. 7,547,512
Diagnostic Assay for the Human Virus Causing Severe Acute Respiratory Syndrome (SARS)	Chinese Patent No. ZL200480007678.7 US Patent No. 7,267,942
Novel Human Virus Causing Respiratory Tract Infection and Uses Thereof	US Patent No. 7,553,944 US Patent No. 7,371,837 US Patent No. 8,092,994
Nucleic Acid Aptamers Against Plasmodium Lactate Dehydrogenase and Histidine-Rich Protein II and Uses Thereof for Malaria	US Regular Application No. 13/763,051 EP (PCT) Application No. 13747009.2 PRC (PCT) Application No. 201380008737.1
Diagnosis of other diseases	
Phox2B Polymorphisms as Hirschsprung's Disease Diagnostic Markers and Methods based thereon	US Patent No. 7,198,898
Protein Markers for Human Benign Prostatic Hyperplasia (BPH)	Chinese Patent No. ZL200480025775.9 UK Patent No. GB2418985
Biofunctional Magnetic Nanoparticles For Pathogen Detection	US Patent No. 7,754,444
Hepatitis B Variants with Reduced Sensitivity to Therapeutic Compounds, Their Detection and Uses Thereof	US Regular Application No. 12/384,132 PRC (PCT) Application No. 200980113181.6
Human Catechol-O-Methyltransferase (COMT) Assay	US Regular Application No. 12/555,529 Chinese Patent No. ZL200980138401.0 EP (PCT) Application No. 09815553.4

Fluorescent Probes

Fluorescent probes are widely used in biological assays and chemical analysis, which the probes bind to target molecules and give out fluorescence to be detected by different kinds of spectroscopic techniques. Probes are required to be highly sensitive and selective, more than that, reactivity, solubility, photophysical and photochemical properties are demanded to meet different scope of detection and determination.

Labeling is a convenient technique to do qualitative analysis. The below technologies are about detection of biomolecules or analyte in cells, with high sensitivity, selectivity and reactivity. HKU researches are striving hard to develop different fluorescent probes to detect different analyte with high sensitivity and selectivity.

Title	Patent application status
Fluorescent probes to detect chemical substances	
Reagents for Detection of Hypochlorous Acid	US Patent No. 7,858,598 EP Patent No. 2134724 Chinese Patent No. ZL200880014862.2
Diarylamine-based Fluorogenic Probes for Detection of Peroxynitrite	US Regular Application No. 13/754,499 PCT Application No. PCT/CN2013/071155 CN (PCT) Application No. 201380007241.2
Bistriflate-based Fluorogenic Probe for Detection of Superoxide	US Regular Application No. 14/597,408 PCT Application No. PCT/CN2015/000072
Diarylether-based fluorogenic probes for detection of hypochlorous acid	US Provisional Application No. 62/151,075
Fluorescent probes to detect biomolecules	
Metal chelation-based fluorescent probes for protein or other biomolecule labeling in cells	US Provisional Application No. 61/921,106 PCT Application No. PCT/EP2015/050063

Metal Complexes as Cancer Therapeutic Drugs

Cancer is a leading cause of death worldwide, causing 7 million deaths every year, and there are more than ten million newly diagnosed cancer cases yearly. Chemotherapy is a standard treatment for many types of cancers by using chemical substances to prevent the proliferation of cancer cells. However, chemotherapy targets all rapidly dividing cells and not specifically cancer cells, it causes a lot of side effects such as hair loss, low-blood cell counts, mouth and stomach ulcers, fatigue, weakened immune system, nausea and so on. Molecular targeted therapies have recently emerged as effective forms of cancer therapy, and as they are specifically designed to target cancer cells, the adverse effects on normal cells are very minimal when compared to cytotoxic chemotherapeutic drugs. Yet the cost of targeted therapy is extremely high that not many patients could afford it and targeted therapy would still be used in combination with chemo drugs.

The success of cisplatin to treat cancer has been drawn a lot of interested in developing platinum-based drugs. Anti-cancer metal medicine has been shown to have potent effect against tumor cells and it also has intrinsic advantages as the methods of preparation are simple and, hence, cost effective when compared to targeted therapy. HKU researchers investigated the efficacy of cancer therapeutic drugs while substantial studies are ongoing for pre-clinical stage.

Title	Patent application status
Anti-Cancer Phosphine Containing [AuIIIm(CNC)mL]n+ Complexes and Derivatives Thereof and Methods for Treating Cancer Using Such Compositions	US Patent no. 7,632,827
Hydroxy-Substituted Gold(III) Porphyrin Complexes as Histone Deacetylase Inhibitors	US Patent no. 8,563,712 EP Patent no. 2,493,897 PRC (PCT) Application No. 201080049811.0
Pharmaceutical Composition Containing Cyclometalated N-Heterocyclic Carbene Complexes For Cancer Treatment	US Patent no. 8,530,659 PRC (PCT) Patent no. CN ZL 201080049820 PCT Application No. PCT/CN2010/001705 EP (PCT) Application No. 10825938.3
A Method of Using Binuclear Gold(I) Compounds for Cancer Treatment	US Regular Application No. 14/070,096 PCT Application No. PCT/CN2013/086626
Novel Gold(III) Complexes Containing N-Heterocyclic Carbene Ligand, Synthesis and their Applications in Cancer Treatment and Thiol Detection	US Patent no. 8,828,984 PCT Application No. PCT/CN2013/001397

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