安徽乐金健康科技股份有限公司

关于与美国麻省总医院签订《合作研究协议》的补充公告

本公司及董事会全体成员保证公告内容真实、准确、完整，不存在虚假记载、 误导性陈述或重大遗漏。

安徽乐金健康科技股份有限公司（以下简称“公司”）于 2016 年 7 月 27 日披露了《关于与美国麻省总医院签订<合作研究协议>的公告》（公告编号 2016-066），应深圳证券交易所要求，现就此公告补充披露如下内容：

一、协议各方介绍：

1、甲方：安徽乐金健康科技股份有限公司

2、乙方：美国麻省总医院

美国麻省总医院，建立于 1811 年，是美国历史最悠久的三所医院之一，也是新英格兰地区建立最早、规模最大的医院，它是与哈佛医学院建立最早、规模最大的教学医院，里面具有世界一流的医学类博士、博士后人才，建立了多所全世界顶级技术的医学实验室，被誉为多项医学技术的领导者。麻省总医院在癌症、心血管、神经、脑血管、消化、风湿免疫、血液、内分泌等疾病临床治疗方面世界领先。医院拥有闻名全球的五大学科医疗中心，分别是：癌症中心、心脏中心、消化中心、移植中心以及血管中心，各中心汇集了众多权威专家，可为患者提供优质、高端的综合医疗服务。

美国麻省总医院网站地址：http://www.massgeneral.org/

二、合作团队主要成员介绍

1、王新慧博士（Wang X），1958 年出生，1982 年本科毕业于安徽医科大学，1999 年博士毕业于纽约医科大学，2012 年受聘为哈佛医学院暨麻省总院的外科肿瘤免疫学专家。王新慧博士（Wang X）获得专利如下表：

医院内部编号	获得日期	专利名称	专利号
1794	10/16/2008	FULLY HUMAN ANTIBODIES TO HIGH MOLECULAR WEIGHT-MELANOMA ASSOCIATED ANTIGEN AND USES THEREOF	61/106,055
1792	9/19/2008	MONOCLONAL ANTIBODIES FOR CSPG4 FOR THE DIAGNOSIS AND TREATMENT OF BASAL BREAST CARCINOMA	61/098,548
1792	9/18/2009	MONOCLONAL ANTIBODIES FOR CSPG4 FOR THE DIAGNOSIS AND TREATMENT OF BASAL BREAST CARCINOMA	2009293007
1794	10/15/2009	FULLY HUMAN ANTIBODIES TO HIGH MOLECULAR WEIGHT-MELANOMA ASSOCIATED ANTIGEN AND USES THEREOF	PCT/US2009/060903
1794	10/15/2009	FULLY HUMAN ANTIBODIES TO HIGH MOLECULAR WEIGHT-MELANOMA ASSOCIATED ANTIGEN AND USES THEREOF	2009305715
1792	9/18/2009	MONOCLONAL ANTIBODIES FOR CSPG4 FOR THE DIAGNOSIS AND TREATMENT OF BASAL BREAST CARCINOMA	PCT/US2009/057578
2181	6/16/2010	ANTIBODIES TO ENDOPLASMIN AND THEIR USE	61/355,516
2346	12/2/2010	DELAYING AND PREVENTING B-RAF INHIBITOR RESISTANCE	61/419,208
2343	5/27/2011	ANTIBODIES TO HLA-A2 ANTIGEN-MAGE-3271-279 PEPTIDE COMPLEX AND THEIR USES	61/491,118
1794	10/15/2009	FULLY HUMAN ANTIBODIES TO HIGH MOLECULAR WEIGHT-MELANOMA ASSOCIATED ANTIGEN AND USES THEREOF	2,737,597
1794	10/15/2009	FULLY HUMAN ANTIBODIES TO HIGH MOLECULAR WEIGHT-MELANOMA ASSOCIATED ANTIGEN AND USES THEREOF	9821279.8
1792	9/18/2009	MONOCLONAL ANTIBODIES FOR CSPG4 FOR THE DIAGNOSIS AND TREATMENT OF BASAL BREAST CARCINOMA	2,737,758
1792	9/18/2009	MONOCLONAL ANTIBODIES FOR CSPG4 FOR THE DIAGNOSIS AND TREATMENT OF BASAL BREAST CARCINOMA	9815308.3
1792	9/18/2009	MONOCLONAL ANTIBODIES FOR CSPG4 FOR THE DIAGNOSIS AND TREATMENT OF BASAL BREAST CARCINOMA	2011-528016
1792	3/16/2011	MONOCLONAL ANTIBODIES FOR CSPG4 FOR THE DIAGNOSIS AND TREATMENT OF BASAL BREAST CARCINOMA	13/119,428

1794	4/8/2011	FULLY HUMAN ANTIBODIES TO HIGH MOLECULAR WEIGHT-MELANOMA ASSOCIATED ANTIGEN AND USES THEREOF	13/123,489
1794	10/15/2009	FULLY HUMAN ANTIBODIES TO HIGH MOLECULAR WEIGHT-MELANOMA ASSOCIATED ANTIGEN AND USES THEREOF	2011-532263
2181	6/15/2011	ANTIBODIES TO ENDOPLASMIN AND THEIR USE	PCT/US2011/040580
2181	6/15/2011	ANTIBODIES TO ENDOPLASMIN AND THEIR USE	13/161,432
2346	12/1/2011	METHODS FOR TREATING A TUMOR USING AN ANTIBODY THAT SPECIFICALLY BINDS HMW-MAA	PCT/US2011/062943
2348	12/1/2011	METHODS FOR TREATING A TUMOR USING AN ANTIBODY THAT SPECIFICALLY BINDS GRP94	PCT/US2011/062946
2348	12/1/2011	METHODS FOR TREATING A TUMOR USING AN ANTIBODY THAT SPECIFICALLY BINDS GRP94	13/309,490
TBN	09/06/2012	University of Pittsburgh Invention Disclosure and Assignment Agreement- title EAF1 and EAF2 antibodies	Pitt Ref: 02877
00786-0886P01	04/04/2013	Combination Treatments with Sonic Hedgehog Inhibitors	MGH 22119
TBN	12/2014	CSPG4-specific human scFv SK5	USSN 62/143,456

2、Soldano Ferrone（Ferrone S）博士,意大利人，1991 博士毕业于米兰大学，2014 年受聘为哈佛医学院暨麻省总院外科和骨科教授。Soldano Ferrone 博士获得专利如下表：

医院内部编号	专利日期	专利名称	专利号
2346	12/2/2010	DELAYING AND PREVENTING B-RAF INHIBITOR RESISTANCE	61/419,208
2343	5/27/2011	ANTIBODIES TO HLA-A2 ANTIGEN-MAGE-3271-279 PEPTIDE COMPLEX AND THEIR USES	61/491,118
1792	3/16/2011	MONOCLONAL ANTIBODIES FOR CSPG4 FOR THE DIAGNOSIS AND TREATMENT OF BASAL BREAST CARCINOMA	13/119,428
1794	10/15/2009	FULLY HUMAN ANTIBODIES TO HIGH MOLECULAR WEIGHT-MELANOMA ASSOCIATED ANTIGEN AND USES THEREOF	2011-532263

2181	6/15/2011	ANTIBODIES TO ENDOPLASMIN AND THEIR USE	13/161,432
2346	12/1/2011	METHODS FOR TREATING A TUMOR USING AN ANTIBODY THAT SPECIFICALLY BINDS HMW-MAA	PCT/US2011/062943
2348	12/1/2011	METHODS FOR TREATING A TUMOR USING AN ANTIBODY THAT SPECIFICALLY BINDS GRP94	13/309,490
TBN	09/06/2012	UNIVERSITY OF PITTSBURGH INVENTION DISCLOSURE AND ASSIGNMENT AGREEMENT- TITLE EAF1 AND EAF2 ANTIBODIES	Pitt Ref: 02877

3、王新慧博士和 Soldano Ferrone 博士合作工作、研究课题 20 多年。 团队主要参考文献如下：

1. **Wang X, Ferrone S,** McPherson A. Crystal structure of an anti-anti-idiotype shows it to be self- complementary. J Mol Biol, 255:617-627, 1996. PMID: 8568901
2. **Wang X, Ferrone S**. HLA (A*0201) mimicry by anti-idiotypic monoclonal antibodies. J Immunol, 161:6705-6714, 1998. PMID: 9862700
3. **Wang X,** Noronha EJ, Kageshita T, **Ferrone S.** Characterization of human anti-high molecular weight-melanoma-associated antigen single-chain Fv fragments isolated from a phage display antibody library. Cancer Res, 58:2417-2425, 1998. PMID: 9622083
4. Noronha EJ, **Wang X,** Desai SA, Kageshita T, **Ferrone S**. Limited diversity of human scFv fragments isolated by panning a synthetic phage-display scFv library with cultured human melanoma cells. J Immunol, 161:2968-2976, 1998. PMID: 9743360
5. Ban N, Day J, **Wang X, Ferrone S**, McPherson A. Crystal structure of an anti-anti-idiotype shows it to be self- complementary. J Mol Biol, 255:617-627, 1996. PMID: 8568901
6. Noronha EJ, **Wang X,** Desai SA, Kageshita T, Ferrone S. Limited diversity of human scFv fragments isolated by panning a synthetic phage-display scFv library with cultured human melanoma cells. J Immunol, 161:2968-2976, 1998. PMID: 9743360
7. **Wang X,** Campoli M, Cho HS, Ogino T, Bandoh N, Shen J, Hur SY, Kageshita T, **Ferrone S.** A method to generate antigen-specific mAb capable of staining formalin-fixed, paraffin-embedded tissue sections. J Immunol Methods, 299:139-151, 2005. PMID: 15896802
8. **Wang X,** Ko EC, Peng L, Gillies SD, **Ferrone S.** Human high molecular weight melanoma associated antigen (HMW-MAA) mimicry by mouse anti-idiotypic (anti-id) mAb MK2-23: enhancement of immunogenicity of anti-id mAb MK2-23 by fusion with interleukin-2. Cancer Res, 65:6976-6983, 2005. PMID: 16061683
9. Anichini A, Mortarini R, Nonaka D, Molla A, Vegetti C, Montaldi E, **Wang X, Ferrone S**. Association of antigen processing machinery and HLA antigen phenotype of melanoma cells with survival in American Joint Committee on Cancer stage III and IV melanoma patients. Cancer Res, 66:6405-6411, 2006. PMID: 16778219

10. Luo W, Ko E, Hsu JC, **Wang X, Ferrone S**. Targeting melanoma cells with HMW-MAA-specific antibodies elicited by a peptide mimotope: functional effects. J Immunol, 176:6046-6054, 2006. PMID: 16670313
11. Luo W, **Wang X,** Kageshita T, Wakasugi S, Karpf AR, **Ferrone S**. Regulation of human high molecular weight-melanoma associated antigen (HMW-MAA) gene expression by promoter DNA methylation in human melanoma cells. Oncogene, 25:2873-2884, 2006. PMID: 16407841
12. Peng L, Ko E, Luo W, **Wang X,** Shrikant PA, **Ferrone S**. CD4-dependent potentiation of a high molecular weight-melanoma-associated antigen-specific CTL response elicited in HLA-A2/K^b transgenic mice. J Immunol, 176:2307-2315, 2006. PMID: 16455987
13. Raffaghello L, Nozza P, Morandi F, Camoriano M, **Wang X,** Garre ML, Cama A, Basso G, **Ferrone S**, Gambini C, Pistoia V. Expression and functional analysis of human leukocyte antigen class I antigen-processing machinery in medulloblastoma. Cancer Res, 67:5471-5478, 2007. PMID: 17545629
14. Tsuda N, Chang DZ, Mine T, Efferson C, García-Sastre A, **Wang X, Ferrone S**, Ioannides CG. Taxol increases the amount and T cell activating ability of self-immune stimulatory multimolecular complexes found in ovarian cancer cells. Cancer Res, 67:8378-8387, 2007. PMID: 17804754

该研究团队因其在单克隆抗体和肿瘤免疫逃逸机制的研究成果获得国际肿瘤免疫学领域的广泛认可，多次获得美国国立卫生研究院和美国国防部的科研经费。2010 年、2011 年、2012 年连续三年获得 university of Pittsburgh 的创新发明奖。根据团队的研究成果包括发现新的 3 阴乳腺癌靶点以及阻断放射治疗引起的乳癌肿瘤干细胞；针对 HLA 抗原和肿瘤相关抗原，已经研制出大量的单克隆抗体，包括抗 CSPG4 和细胞表面 GRP94 的抗体等，获得了多项与癌症靶向单克隆抗体相关的美国发明专利。目前，其将利用他们在嵌合抗原受体（CAR）主要成分-抗体领域的强大优势，研究团队致力于开展 CAR- T 细胞治疗实体瘤的研究及临床运用研究。美国麻省总医院王新慧团队介绍链接：http://www.massgeneral.org/research/researchlab.aspx?id=1565&display=team

三、研究课题详细描述：

1、拟利用不与正常组织，例如心脏、大脑和肺部发生交互反应的细胞表面特定 GRP94 靶向性 scFv 抗体，生成一个嵌合体抗原受体（CAR）转导的 T 细

胞靶细胞表面 GRP94。

2、测试工程 CAR 在人体 T 细胞中的表达水平。

3、测试一组癌细胞系，以及不同的原始和正常 PBMC 以及骨髓细胞。

4、评估工程 CAR- T 细胞在目标肿瘤细胞（一组肿瘤细胞）中的体外抑杀能力。

5、测试在存在靶细胞的情况下，CAR- T 细胞的体外 IFN-gamma 释放。

6、使用 CAR- T 细胞和正常细胞进行细胞杀伤和 IFN-gamma 释放试验。

7、测试 CAR 转导 T 细胞在老鼠原位异种移植模型系统中的体内抗瘤活性。

8、 为了改善 CAR- T 细胞的体内疗效，将设计并实施策略，抵消肿瘤细胞因肿瘤微环境诱导变化而产生的逃避机理。

四、风险提示：

1、本次签署的协议为合作研究协议，具体的实施进度存在不确定性。截止到目前为止，该研究成果尚未取得专利权，仍出于动物试验阶段，临床试验时间亦存在不确定性。

2、双方在未来的合作运营过程中可能存在一定的经营风险、合作风险、市场风险及政策风险等不确定因素，因此公司提请广大投资者注意投资风险。

特此公告。

安徽乐金健康科技股份有限公司

董事会

2016 年 8 月 1 日