附件 7：

# 2027 年申请推免学生材料

姓　　名：刘星蕊

学　　号：22220601106

学　　院：医学部

专　　业：口腔医学

2026 年 9 月

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# 一、 个人申请表

## 江汉大学推免生资格申请表

填表日期　　年　月　日

<table>
<tr><td>姓名</td><td>刘星蕊</td><td>性别</td><td>女</td><td>身份证号</td><td colspan="3">420983200405140728</td><td rowspan="3"> </td></tr>
<tr><td>学号</td><td colspan="2">222210601106</td><td colspan="2">政治面貌</td><td colspan="3">中国共产党党员</td></tr>
<tr><td>学院（部）</td><td colspan="2">医学部</td><td colspan="2">专业</td><td colspan="3">口腔医学</td></tr>
<tr><td rowspan="2">成绩及排名</td><td>专业人数</td><td>42</td><td>加权平均成绩</td><td>91.63</td><td>加权平均成绩排名</td><td>1/42</td><td colspan="2" rowspan="2"></td></tr>
<tr><td>平均学分绩点</td><td>3.87</td><td colspan="2">外语水平（CET4、6或其他）</td><td colspan="3">CET6-607，CET4-594</td></tr>
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<tr><td colspan="2">拟选择接收学校</td><td colspan="7">1.　　2.　　3.</td></tr>
<tr><td colspan="2">拟选择接收专业</td><td colspan="7">1.　　2.　　3.</td></tr>
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|---|---|
| 本人申请 | 1. 思想政治表现：本人政治立场坚定，拥护中国共产党的领导，作为中共党员自觉以党员标准严格要求自己，认真学习党的理论知识，积极参加党组织生活，具有正确的世界观、人生观和价值观。在校期间获评优秀共青团员，主动参与班级和学院工作，团结同学，乐于助人。恪守医德医风，担任全国大学生口腔健康志愿宣讲活动宣讲员，累计开展宣讲十余场，受益群众近千人次。遵纪守法，无任何违法违纪行为；在协和医院实习期间严格遵守诊疗规范，尊重师长，关心患者。科研中秉持严谨求实态度，恪守学术诚信。<br>2. 学业情况：本人为江汉大学医学院口腔医学专业 2022 级本科生，学分绩点 3.87/4.00，专业排名 1/42。CET-4 成绩 594 分，CET-6 成绩 607 分。主修课程成绩优异，口腔正畸学 97 分、口腔种植学 94 分、口腔颌面外科学 94 分、口腔修复学 92 分、牙周病学 91 分。获校优秀学生标兵奖学金、校二等奖学金（2 次）。2026 年 7 月起在华中科技大学同济医学院附属协和医院口腔科实习，已完成正畸科轮转，系统观摩错胎畸形诊疗全流程，协助取模、口内拍照及病历整理。<br>3. 科研情况（含竞赛）：本人熟练掌握 R 语言（tidyverse、survival、ggplot2、WGCNA 等包）、GraphPad Prism 及 qPCR 实验操作与数据分析，具备 TCGA/GEO 数据库挖掘与科研绘图能力。以导师外第二作者发表论文一篇：《Identification of hub genes in breast cancer through genome-wide association and functional analyses of M2-like tumor-associated macrophages》（Gene & Protein in Disease, 2025, 4 (4)），负责多队列转录组数据质控、GEO 队列生存分析及核心图表复现。作为项目负责人主持全国大学生医学创新大赛省级优秀奖项目《嗜麦芽窄食单胞菌促进阿尔兹海默病进展的机制研究》（2025），统筹全流程设计，完成菌群测序数据挖掘与 qPCR 验证分析。作为核心成员参与校级学生科研重点项目《基于唾液酸相关基因的结肠癌分子分型及预后模型研究》（2024–2025），负责 TCGA/GEO 数据集清洗质控与差异表达分析。竞赛方面，获全国大学生医学创新大赛省级优秀成果奖、全国大学生英语竞赛国家级一等奖、"BETT 杯" 全国大学生英语阅读大赛国家级一等奖、CATTI 杯全国翻译大赛国家级三等奖、中西部外语翻译大赛国家级三等奖、湖北省翻译大赛省级二等奖。<br>4. 获奖情况：获国家级奖项 5 项：全国大学生英语竞赛（NECCS）一等奖、"BETT 杯" 全国大学生英语阅读大赛一等奖、CATTI 杯全国翻译大赛三等奖、中西部外语翻译大赛三等奖、《英语世界》杯全国大学生英语写作大赛优秀奖；省级奖项 3 项：湖北省翻译大赛二等奖、全国大学生医学创新大赛省级优秀成果奖及省级优秀奖；校级奖项包括优秀学生标兵奖学金、二等奖学金（2 次）、优秀共青团员；另获国际人才英语考试（中级）良好。<br><br>**本人确认以上信息正确，确保所提供的证明材料真实可信（证明材料另附）。**<br><br>本人签字：刘星悠<br><br>2026 年 9 月 5 日 |
| 学院（部）推免工作小组推荐意见 | 组长签字：　　学院（部）公章 |

## 二、 外语成绩单

# 全国大学英语四级考试
# 成绩报告单

CET®

姓　　名：刘星蕊
学　　校：江汉大学
院　　系：医学院
身份证号：420983200405140728

**笔　试**

准考证号：420200231101401
考试时间：2023年6月

| 总分 | 听力 (35%) | 阅读 (35%) | 写作和翻译 (30%) |
|---|---|---|---|
| 594 | 174 | 227 | 193 |

**口　试**

准考证号：--
考试时间：--

| 成绩 | -- |
|---|---|

成绩报告单编号：231142020002695

教育部教育考试院
证书专用章

校验码：Z2M7 TRW9 XRX8 7BIC

# 全国大学英语六级考试(CET6)成绩详情

姓　　名：刘星蕊

证件号码：420983200405140728

学　　校：江汉大学

**笔试成绩**

准考证号：420200261206409

总　　分：**607**

听　　力：**184**

阅　　读：**237**

写作和翻译：**186**

**口试成绩**

准考证号：--

成　　绩：--

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成绩报告单编号：261242020003401

考生姓名：刘星蕊

身份证号：420983200405140728

考试级别：医学英语水平考试三级

考试时间：2025年11月29日

准考证号：3142012550004

考试成绩：92

申请成绩复核

## 三、 体质测试成绩证明

刘星蕊

及格

学号: 222210601106

体测状态: 正常 体测说明: 暂无

刘星蕊

及格

学号: 222210601106

体测状态: 正常 体测说明: 暂无

刘星蕊

良好

学号: 222210601106

体测状态: 正常 体测说明: 暂无

刘星蕊

及格

学号: 222210601106

体测状态: 正常 体测说明: 暂无

# 四、 代表性论文

注：本人为导师外第二作者，已标亮

ACCSCIENCE PUBLISHING

Gene & Protein in Disease

ORIGINAL RESEARCH ARTICLE

## Identification of hub genes in breast cancer through genome-wide association and functional analyses of M2-like tumor-associated macrophages

**Guang Yang[1]*, Zhaorui Hao[2], Xingrui Liu[2], and Zixi Tang[2]**

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### Abstract

Breast cancer remains a leading cause of cancer-related mortality among women, and immunosuppressive M2-like tumor-associated macrophages (TAMs) contribute to tumor progression and poor prognosis. This study investigated M2-like TAMs to identify key genes promoting breast cancer progression. Using weighted gene co-expression network analysis (WGCNA), which leveraged the opposing prognostic roles of M1/M2 macrophages, we identified 3,127 M2-associated module genes. Intersection with up-regulated differentially expressed genes from GSE42568 and the Cancer Genome Atlas Breast Invasive Carcinoma dataset yielded 85 pivotal genes. Functional enrichment analyses using Gene Ontology and Kyoto Encyclopedia of Genes and Genomes pathways linked these genes to tight junctions, Rap1 signaling, and PI3K–Akt pathways. Protein–protein interaction network analysis via CytoNCA and degree algorithms prioritized four significantly up-regulated hub genes: *FOXA1*, *AGR2*, *MUC1*, and *ERBB3*. A nomogram model demonstrated their prognostic value, while receiver operator characteristic analysis confirmed its diagnostic utility in distinguishing tumor from normal tissue. Hub gene expression positively correlated with the infiltration of mast cells, M2 macrophages, $CD4^+$ T cells, monocytes, B cells, and dendritic cells. Pan-cancer analysis revealed breast cancer-specific overexpression of *FOXA1* and *ERBB3*. Mendelian randomization using fixed-effect inverse variance weighting indicated causal associations between elevated expression of *FOXA1*, *MUC1*, and *ERBB3* ($\beta>0$) and increased breast cancer risk. Drug sensitivity analysis using the Genomics of Drug Sensitivity in Cancer database identified associations between lapatinib sensitivity and expression of *FOXA1*, *ERBB3*, and *MUC1*. This WGCNA-based approach defines *FOXA1*, *AGR2*, *MUC1*, and *ERBB3* as M2-like TAM-related hub genes with diagnostic, prognostic, and therapeutic relevance for breast cancer, particularly in informing drug sensitivity strategies.

***Keywords:*** Breast invasive carcinoma; M2-like tumor-associated macrophages; Hub genes; Mendelian randomization; Genomics of drug sensitivity

***Corresponding author:**
Guang Yang
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### 1. Introduction

Breast cancer is one of the most common malignant tumors worldwide, and it seriously endangers the life and health of women.[1] Although improvements in health awareness

and early diagnosis technologies have contributed to better prognoses, the 5-year survival rate for metastatic breast cancer remains <30%.[2] The hidden onset, recurrence and metastasis, poor prognosis, and lack of effective early diagnostic markers pose great challenges to the diagnosis and treatment of breast cancer. Therefore, there is an urgent need to identify new molecular biomarkers and therapeutic targets for breast cancer.

Bone marrow-derived cells that penetrate tumor tissues or aggregate in the solid tumor microenvironment (TME) are known as tumor-associated macrophages (TAMs).[3] As an important component of the TME, TAMs influence tumor growth, angiogenesis, immune regulation, metastasis, and chemotherapy resistance.[4,5] Under the influence of cytokines in the TME, macrophages differentiate into M1-like and M2-like phenotypes. M1-like macrophages are generally considered tumor-killing macrophages and primarily exert anti-tumor and immune-promoting functions. In contrast, M2-like macrophages are immunosuppressive and promote tumor progression.[6] Therefore, it is necessary to characterize the molecular features associated with M2-like macrophages and to determine the key regulatory factors involved in M2-like TAM polarization. With tumor progression, M1 macrophages gradually polarize into the M2 phenotype, and an increasing abundance of M2-like TAMs indicates poor prognosis, including in breast cancer.[7]

To provide new insights into the molecular characteristics of M2-like TAMs in breast invasive carcinoma (BRCA) patients, we identified groups with high and low M1 macrophage levels and groups with high and low M2 macrophage levels. Survival analysis showed a significant difference between M1-like and M2-like macrophages, and BRCA patients with low M2 and high M1 macrophage content had longer survival. Based on these survival differences, we conducted a series of analyses to identify biomarkers closely related to BRCA.

Mendelian randomization (MR) is a reliable analytical method widely used in recent years to infer potential causality between etiological factors and disease outcomes. MR uses genetic variants strongly associated with exposure factors as instrumental variables to deduce causal relationships between exposures (etiology) and outcomes (diseases). Typically, single-nucleotide polymorphisms (SNPs) are used as instrumental variables to assess causal relationships between exposure factors and outcomes.[8,9]

In this study, we first identified differentially expressed genes (DEGs) between normal and breast tumor tissues from The Cancer Genome Atlas BRCA (TCGA-BRCA) and GSE42568 datasets, respectively. Next, we screened pivotal module genes most positively related to M2 macrophages in BRCA using weighted gene co-expression network analysis (WGCNA), which substantially narrowed the range of hub genes. We then identified four hub genes, namely *FOXA1*, *AGR2*, *ERBB3*, and *MUC1*, as potential markers through protein–protein interaction (PPI) network analysis, which may contribute to BRCA and further elucidate the underlying mechanisms of breast cancer-associated risk genes. Finally, the expression patterns of these four hub genes in breast cancer and their causal relationships with BRCA were explored through functional enrichment, pan-cancer, and MR analyses. Meanwhile, drug sensitivity and $IC_{50}$ associations for drugs targeting these hub genes were evaluated using the Genomics of Drug Sensitivity in Cancer (GDSC) database.

## 2. Materials and methods

### 2.1. Source data and preprocessing

A total of 1,226 cases with RNA-seq transcriptome profiling (High-Throughput Sequencing–Fragments Per Kilobase of transcript per Million mapped reads [HTSeq-FPKM]) and clinical information from TCGA-BRCA were obtained from the Genomic Data Commons TCGA data portal (https://portal.gdc.cancer.gov/). Two GEO cohorts (GSE42568, GSE58812) were downloaded from the Gene Expression Omnibus (https://www.ncbi.nlm.nih.gov/geo/). Patients without survival information and RNA-sequencing data were excluded from the analysis. The FPKM values were transformed to TPM (transcripts per million) values for subsequent analyses.[10,11]

### 2.2. Macrophage-related survival analyses

The CIBERSORT algorithm computationally infers (deconvolves) the relative proportions of specific cell types within a mixed bulk tissue sample based on its gene expression profile. In essence, CIBERSORT applies a known reference signature to deconvolute bulk RNA expression data from complex tissues, thereby inferring their cellular composition. The relative abundance of macrophages in each sample from TCGA-BRCA and GSE58812 was calculated using the CIBERSORT algorithm[12] (perm ≥100, QN=TRUE). Kaplan–Meier survival analysis was performed using the R "survival" package to evaluate whether BRCA patient survival was correlated with M1 or M2 macrophage content. The "surv_cutpoint" function in the "survminer" package was used to determine the optimal cut-off values for high- and low-content M1 and M2 macrophage groups and to assess survival differences between the high- and low-M1 or high- and low-M2 groups.

### 2.3. DEGs identification

Identifying DEGs between normal and tumor tissues can uncover molecular drivers of cancer by pinpointing genes with significantly altered expression. Transcriptome data were obtained from the TCGA-BRCA cohort (1,113 tumor and 113 normal samples) and the GSE42568 dataset (104 tumor and 17 normal samples). All data were processed in R (version 4.3.1), including normalization and batch-effect correction. The R "limma" package was used for DEGs analysis. Volcano plots and heatmaps were generated using the "ggplot2" and "pheatmap" packages, respectively. DEGs were selected based on |log2FoldChange| > 1 and adjusted $p<0.05$.[13]

### 2.4. Acquisition of pivotal genes associated with M2-like macrophages in breast cancer

The WGCNA allows identification of highly correlated gene modules associated with diseases and can reveal candidate biomarkers and therapeutic targets; it has been widely applied in various biological fields, such as cancer research.[14] BRCA samples were grouped according to M1-like or M2-like macrophage levels, and TCGA-BRCA expression data were analyzed using the R "WGCNA" package to identify genes associated with M2-like macrophages. Samples were first clustered to evaluate overall sample relevance. The soft-thresholding power β was selected according to the minimum power required to achieve a high scale-free topology fitting index, and the minimum module size was set to 60 genes. The module most strongly associated with M2-like macrophages was identified through module–trait correlation analysis. The genes within this module were intersected with up-regulated DEGs between BRCA and normal tissues to obtain M2-like TAM-related genes. These intersecting genes were considered candidate pivotal genes for BRCA pathogenesis. Functional enrichment analysis using Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene Ontology (GO) was performed to better understand the potential biological processes and pathways involved in BRCA.[15]

### 2.5. Screening of hub genes in the PPI network

STRING (https://string-db.org) was used to predict and visualize the PPI network with a required minimum interaction score of 0.400 (medium confidence). Key genes in the PPI network were ranked using the "CytoNCA" toolkit and the degree algorithm in Cytoscape software (www.cytoscape.org). The top 10 genes were displayed, and the hub genes most strongly associated with BRCA were selected for subsequent analysis.

### 2.6. Nomogram scoring model construction

We used a nomogram scoring model to predict the risk of BRCA using the "rms" and "rmda" packages.[16,17] The risk of disease was predicted based on the risk score of hub genes. We then used the "ROC" package to construct receiver operator characteristic (ROC) curves to verify the predictive validity of the hub genes. The area under the ROC curve (AUC) was used to represent accuracy. If the AUC was between 0.8 and 1.0, it indicated excellent prediction accuracy.

### 2.7. Correlation, Gene Set Enrichment Analysis, and pan-cancer analysis

The correlation between hub gene expression and immune cell infiltration was evaluated using the CIBERSORT algorithm. Gene Set Enrichment Analysis (GSEA) was performed to identify functional pathways associated with hub genes. Pan-cancer analysis was then conducted to determine whether these M2-like TAM-associated hub genes were more highly expressed in BRCA than in other tumors.

### 2.8. Mendelian randomization study

Two-sample MR was used to evaluate the causal relationship between hub genes (exposures) and breast cancer risk (outcome) using SNPs as instrumental variables. From genome-wide association study (GWAS) data for the hub genes, we extracted SNPs strongly associated at genome-wide significance ($p<5 \times 10^{-6}$) to ensure independence of instrumental variables and exclude linkage disequilibrium effects.[18-20] The genetic distance was set to 10,000 kb, and the linkage disequilibrium parameter ($r^2$) threshold to 0.01. GWAS data included 89,677 individuals, comprising 42,892 controls and 46,785 cases of European ancestry. MR analysis was performed using the "TwoSampleMR" package, and MR-Egger regression, weighted median, fixed-effects inverse variance weighting (IVW), simple mode, and weighted mode were used to assess the relationship between hub gene levels and breast cancer risk. MR-Egger was used for sensitivity analysis. The intercept term in the causal estimation was assessed, and MR-Egger regression was used to evaluate directional pleiotropy. In addition, the IVW method and MR-Egger regression were applied to detect heterogeneity between individual genetic variation estimates.

### 2.9. Drug sensitivity analysis

The GDSC database (https://www.cancerrxgene.org/) contains more than 1,000 human cancer cell lines, 265 drug response datasets, and over 17,000 genomic markers. We

collected mRNA expression levels of hub genes and $IC_{50}$ for 265 drugs across 51 BRCA-related cell lines and combined mRNA expression and drug susceptibility data. Pearson correlation analysis ($p$<0.03) was used to determine the correlation between hub gene mRNA expression and drug $IC_{50}$ values, and to investigate whether hub gene expression was associated with drug sensitivity or resistance. The databases used in this study and their download links are listed in Table S1.

### 2.10. Statistical analysis

Survival differences between groups were evaluated using Kaplan–Meier curves and log-rank tests. Correlation coefficients were calculated using Pearson correlation analysis. Statistical analysis was performed using R software (version 4.3.1), and values are represented as mean ± standard deviation. $p$<0.05 was considered statistically significant.

## 3. Results

### 3.1. Screening M2-like TAM-related candidate hub genes

To elucidate the relationship between macrophages and BRCA prognosis, the proportions of M1 and M2 macrophages in TCGA-BRCA samples were estimated using the CIBERSORT algorithm. BRCA patients were then divided into high- and low-content M1 or M2 macrophage groups, respectively. Kaplan–Meier survival analysis showed a significant difference between the high-content and low-content M1 macrophage groups ($p$=0.032; Figure 1A). Furthermore, a more pronounced survival difference was observed between the high-content and low-content M2 macrophage groups, with patients in the high-content M2 macrophage group showing worse prognosis than those in the low-content group ($p$<0.001; Figure 1B). These results indicated that the prognostic effects of M1 and M2 macrophages were opposite, and that M2 macrophages played a more pivotal role in BRCA prognosis than M1 macrophages. Analysis of the GSE58812 datasets confirmed these results (Figure S1A–B).

Based on these observations, WGCNA was performed to identify the key module related to M2 macrophages, and the soft-threshold power β = 5 (scale-free $R^2$ = 0.92) was selected to construct a scale-free network. As shown in Figure 1C, the green module was positively correlated with M2 macrophages and negatively correlated with M1 macrophages. A total of 3,127 genes in the green module were selected for downstream analysis. In addition, 2,098 DEGs (935 up-regulated and 1,163 down-regulated) were identified in GSE42568 (Figure 1D), and 2,753 DEGs (1,078 up-regulated and 1,675 down-regulated) were identified in TCGA-BRCA (Figure 1E). Finally, 85 overlapping genes were identified by intersecting WGCNA-derived M2-like TAM-related genes with up-regulated DEGs associated with BRCA, and were considered candidate hub genes potentially involved in BRCA development and progression (Figure 1F).

### 3.2. GO and KEGG pathway enrichment analysis

The GO and KEGG analyses were conducted to further explore the potential roles of the 85 candidate hub genes. GO analysis showed that these overlapping genes were mainly enriched in cellular components such as the bicellular tight junction, tight junction, and apical junction complex (Figure 2A). KEGG pathway analysis indicated enrichment in tight junction, Ras-associated protein 1 (Rap1) signaling pathway, and phosphatidylinositol 3-kinase (PI3K)–Akt signaling pathway (Figure 2B). The Rap1 and PI3K–Akt signaling pathways are well known to be associated with proliferation, invasion, and metastasis in cancer, whereas the relationship between tight junctions and tumors has been less frequently reported. Breast cancer is a complex and heterogeneous disease, and proper adhesion between adjacent epithelial cells is essential for maintaining normal epithelial tissue structure and function. Increasing evidence suggests that dysregulation of cell–cell adhesion is associated with many cancers. One study has suggested that tight junctions may be involved in the development or progression of breast cancer.[21]

### 3.3. PPI network analysis of hub genes

The PPI network of candidate hub genes was constructed using the STRING online tool (Figure 2C). The top 10 up-regulated genes in breast cancer were then identified and visualized using the "CytoNCA" toolkit and degree algorithm. The genes *FOXA1*, *AGR2*, *MUC1*, *ERBB3*, *TFF1*, *EZR*, *GATA3*, *FGFR3*, *SPDEF* and *AGR3* were ranked (Figure 2D). A deeper red color indicated a higher relevance score and greater importance in BRCA. *FOXA1*, *AGR2*, *MUC1*, and *ERBB3* were the most prominent hub genes.

### 3.4. Construction of a nomogram model and receiver operator characteristic diagnostic curve

A nomogram model was constructed to predict BRCA risk (Figure 3A). Higher scores indicated higher disease risk. In the examples shown in Figure 3A, a total score of 100 for the four hub genes corresponds to a breast cancer risk exceeding 90%. Calibration analysis verified the reliability of the nomogram model (Figure 3B). ROC curves were then generated for the four hub genes (*FOXA1*, *AGR2*, *MUC1*, and *ERBB3*) to assess predictive performance; the AUC values were 0.877, 0.907, 0.865, and 0.930, respectively.

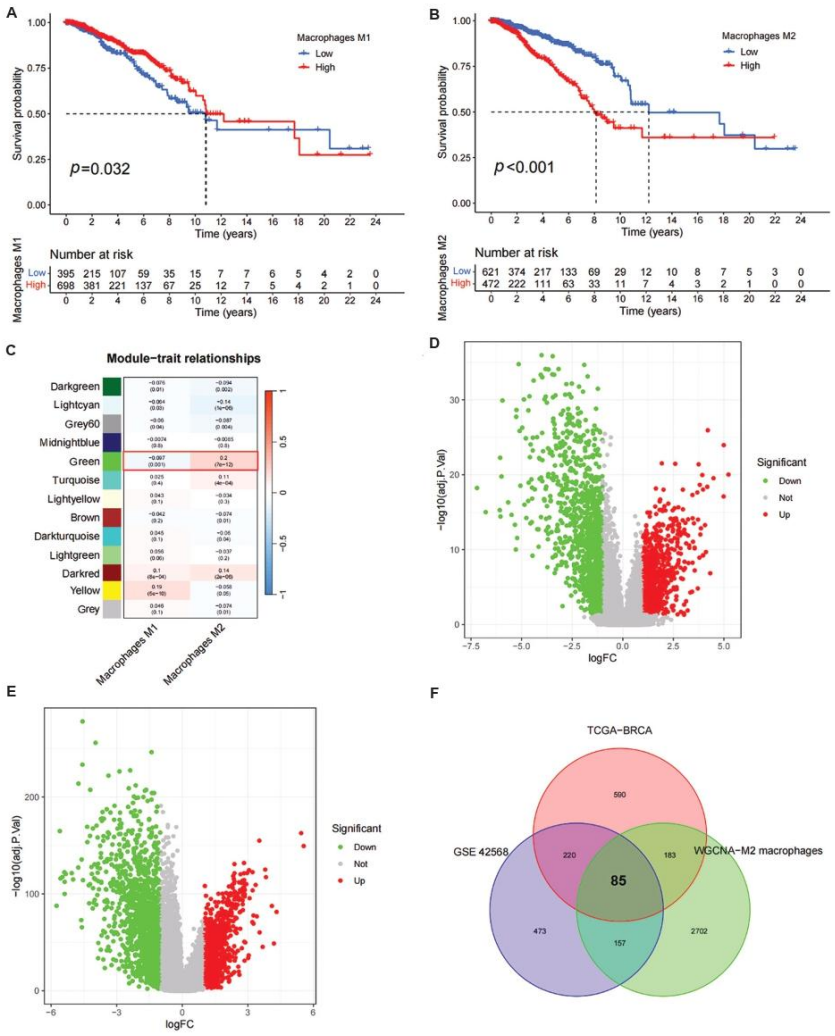


**Figure 1.** Survival analysis and screening of M2-like tumor-associated macrophage-related candidate hub genes. (A) Kaplan–Meier survival curves comparing high-content and low-content M1 macrophage groups. (B) Worse prognosis in the high-content M2 macrophage group. (C) Correlation analysis of modules and traits, with the green module most strongly associated with M2 macrophages. (D) Volcano plot of differentially expressed genes (DEGs) between normal and tumor tissues in GSE42568. Note: Red dots indicate up-regulated genes, green dots indicate down-regulated genes, and gray dots indicate nonsignificant genes. (E) Volcano plot of DEGs between normal and tumor tissues in TCGA-BRCA. (F) Venn diagram showing the intersection of weighted gene co-expression network analysis-derived M2-like TAM-related genes and up-regulated DEGs.
Notes: Red dots indicate up-regulated genes, green dots indicate down-regulated genes, and gray dots indicate nonsignificant genes.

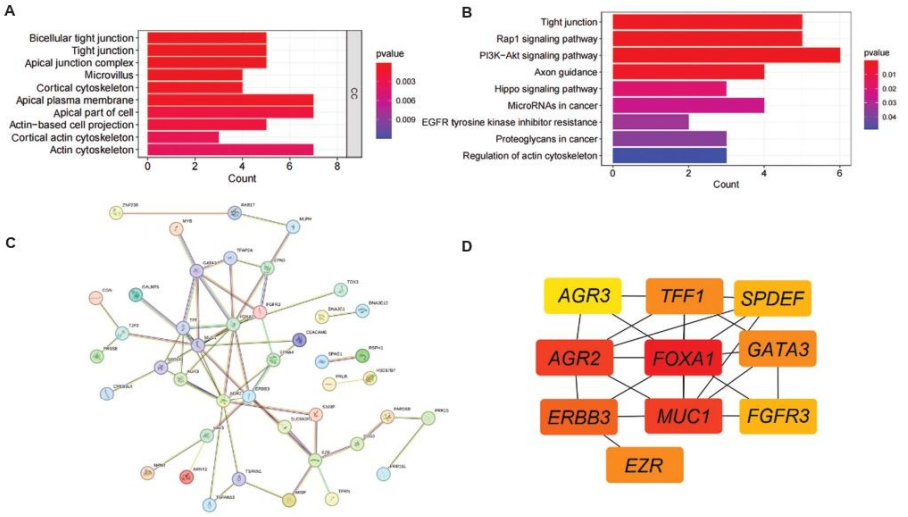


**Figure 2.** Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG), and protein–protein interaction (PPI) network analysis. (A) GO enrichment analysis of candidate hub genes. (B) KEGG pathway analysis of candidate hub genes. (C) PPI network of overlapping hub genes. (D) Core genes identified by the degree algorithm.

These results demonstrated that all four hub genes could effectively differentiate breast cancer from normal tissues (Figure 3C).

### 3.5. Functional analysis of M2-like tumor-associated macrophage-related hub genes

According to the correlation analysis between the four hub genes and M2-like macrophages, three of the four hub genes were closely related to M2-like macrophages. Among them, *FOXA1* and *ERBB3* showed the strongest correlations (Figure 4A). In the TCGA datasets, high *FOXA1* expression was associated with shorter overall survival (Figure 4B). In contrast, high *AGR2* expression was associated with better survival compared to low *AGR2* expression (Figure 4C).

Expression differences of the four hub genes between normal and breast tumor tissues were analyzed using TCGA-BRCA, and all four hub genes were significantly up-regulated in breast tumor tissues compared with normal tissues (Figure 4D). GSEA analysis showed that *FOXA1*, *AGR2*, and *ERBB3* were mainly enriched in tumor-related pathways, such as complement and coagulation cascades,[22] colorectal cancer, mTOR signaling pathway, and prostate cancer (Table 1). Complement and coagulation cascades are important components of the immune system. Platelets in the TME can promote tumor cell invasion and metastasis by activating the coagulation cascade.

In the pan-cancer analysis, the four hub genes were highly expressed in most tumor types, with particularly high expression of *FOXA1* and *ERBB3* in breast tumors (Figure S2A-D). Moreover, expression of the four hub genes was positively associated with age over 65 years in BRCA clinical data (Figure S2E-H).

Next, the relationship between hub gene expression and the TME was evaluated. CIBERSORT analysis showed that the four hub genes were significantly correlated with infiltration of immune cells, such as mast cells, M2 macrophages, $CD4^+$ T cells, monocytes, B cells, and dendritic cells (Figure S3A-D). In addition, *FOXA1*, *ERBB3*, and *AGR2* showed stronger correlations with M2 macrophages, consistent with the analysis shown in Figure 4A. Expression of all four hub genes was positively correlated with M2-like macrophage infiltration in BRCA, whereas the opposite pattern was observed for M1-like macrophage infiltration (Figure S4A-H).

### 3.6. Hub genes causally associated with the risk of invasive carcinoma

We assessed the causal association between the four hub genes and breast cancer. The SNPs associated with these

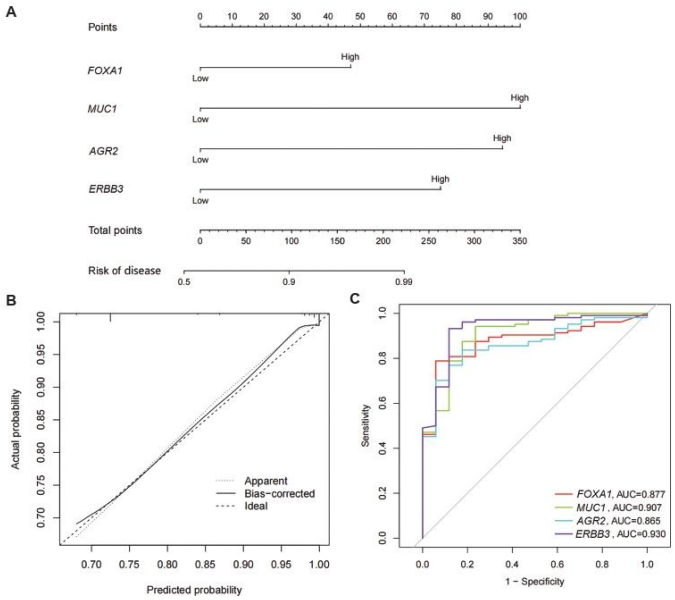


**Figure 3.** Nomogram model and receiver operator characteristic (ROC) curve analysis. (A) Nomogram model of four hub genes. (B) Calibration curve validating model performance. (C) ROC curves evaluating the predictive efficacy of each hub gene.
Abbreviation: AUC: Area under the ROC curve.

genes met the criteria for strong instrumental variables ($p<5\times10^{-6}$). Using the fixed-effects IVW method, we found that all four hub genes were associated with breast cancer risk (Table 2). A β-value greater than zero indicates that the exposure factor is a risk factor, and the risk of disease increases with increasing exposure. Except for *AGR2*, the expression of *FOXA1*, *ERBB3*, and *MUC1* was positively correlated with the occurrence of breast tumors ($\beta > 0$), which was consistent with the prognostic analysis results (Figure 4C). A strong causal association between *FOXA1* and breast cancer was observed (Figure 5A). The combined effect estimate of all SNPs was greater than zero, indicating that *FOXA1* is a risk factor and that breast cancer risk increases with higher *FOXA1* expression (Figure 5B). The weighted median and weighted mode methods also supported the results of the fixed-effects IVW method. The *FOXA1* funnel plot showed approximate symmetry around the central axis (Figure 5C), and no evidence of horizontal pleiotropy was observed at the MR-Egger intercept, indicating that pleiotropy did not bias the causal effect. In the leave-one-out analysis, MR analysis was repeated after removing each SNP, and the overall effect estimates remained consistent with the main result, indicating the robustness of the causal inference (Figure 5D).

### 3.7. Drug sensitivity analysis

To investigate whether the four hub genes influence drug sensitivity or resistance during chemotherapy, we integrated drug $IC_{50}$ and gene expression data from GDSC BRCA cell lines (Table 3). Through this analysis, drugs most strongly correlated with the hub genes were identified.

The results showed that the $IC_{50}$ values of A-443654, lapatinib, KIN001-102, CP724714, and ZSTK474 were negatively correlated with *FOXA1* expression, whereas the $IC_{50}$ values of pyrimethamine and BX-795 were positively correlated with *FOXA1* expression, according to Pearson correlation analysis (Figure 6A). The $IC_{50}$ values of lapatinib, A-770041, sorafenib, roscovitine, A-443654, MS-275, and paclitaxel were negatively correlated with *ERBB3* expression, indicating that *ERBB3* expression sensitizes cells to these drugs (Figure 6B). The $IC_{50}$ values of saracatinib, imatinib,

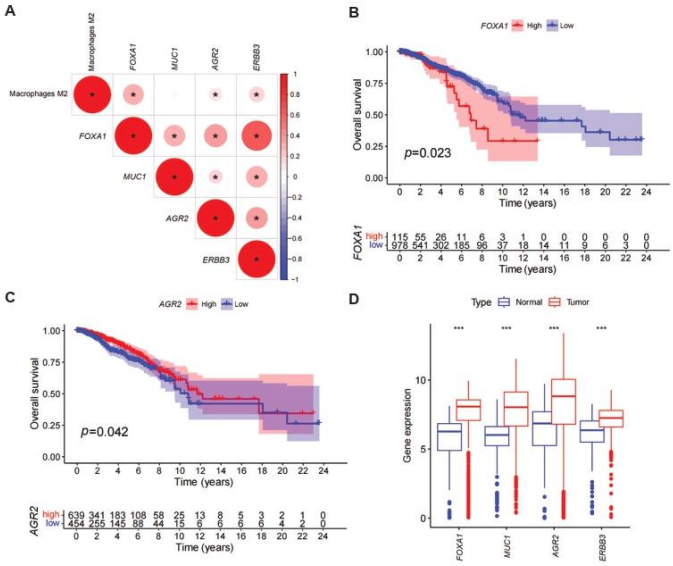


**Figure 4.** Correlation and survival analysis of M2-like tumor-associated macrophage-related hub genes. (A) Correlation between the four hub genes and M2-like macrophages. (B) Overall survival of TCGA-BRCA patients with high versus low *FOXA1* expression (Kaplan–Meier analysis). (C) Overall survival of TCGA-BRCA patients with high versus low *AGR2* expression (Kaplan–Meier analysis). (D) Expression of the four hub genes in normal versus breast tumor tissues.
Notes: Red: tumor samples; blue: normal samples. *$p<0.05$, **$p<0.01$ and ***$p<0.001$.

BMS-509744, and lapatinib were negatively correlated with *MUC1* expression, whereas olaparib, YK-4-279 were positively correlated with *MUC1* expression (Figure 6C). The $IC_{50}$ values of KIN001-102, CP724714, ZSTK474, and Afatinib showed a negative correlation with *AGR2* expression. Conversely, TAE684, XMD8-85, AZ628, and Pyrimethamine exhibited a positive correlation (Figure 6D).

Interestingly, the expression of *FOXA1*, *ERBB3*, and *MUC1* was associated with increased sensitivity to lapatinib. Lapatinib was approved by the United States Food and Drug Administration in 2007 as a treatment for human epidermal growth factor receptor-2 (HER2)-positive advanced breast cancer. These findings suggest that combined expression of *FOXA1*, *ERBB3*, and *MUC1* may represent a potential marker for lapatinib responsiveness in clinical breast cancer patients.

In contrast, *AGR2* expression was closely related to resistance of TAE684, XMD8-85, AZ628, and pyrimethamine, indicating that higher *AGR2* expression may be linked to increased drug resistance when $p<0.03$.

## 4. Discussion

Metastatic breast cancer responds less effectively to immunotherapy than primary tumors, although certain immune-oncology targets, macrophages, and angiogenic features show preserved expression.[23] Stage IV (metastatic) breast cancer is treatable but not curable, and treatment goals include prolonging survival and improving quality of life.[24] Immunotherapy is a potentially effective approach for controlling tumor growth in patients with stage IV breast cancer.[25] Although encouraging immunotherapy outcomes have been reported in some clinical trials, several challenges remain. Therefore, personalized immunotherapy is considered a potential complementary therapy for breast cancer, particularly in combination with chemotherapy.[26] Considering that existing studies have proved the importance of TAMs in BRCA immunotherapy[27], we examined the reliability of M2-like TAMs as biomarkers and predictors of tumorigenesis, based on the significant prognostic differences observed between M1 and M2 macrophages in patients with breast cancer.

**Table 1. Gene set enrichment analysis of four hub genes**

| Gene | KEGG pathway | Enrichment score | *p*-value |
|---|---|---|---|
| FOXA1 | GLYCOSYLPHOSPHATIDYLINOSITOL_GPI_ANCHOR_BIOSYNTHESIS | 0.64890 | 0.00064 |
| | COMPLEMENT_AND_COAGULATION_CASCADES | 0.46633 | 0.00027 |
| | VALINE_LEUCINE_AND_ISOLEUCINE_DEGRADATION | 0.51269 | 0.00147 |
| | NUCLEOTIDE_EXCISION_REPAIR | 0.49271 | 0.00267 |
| | PROTEIN_EXPORT | 0.57175 | 0.00729 |
| AGR2 | COMPLEMENT_AND_COAGULATION_CASCADES | 0.44045 | 0.00459 |
| | GLYCOSYLPHOSPHATIDYLINOSITOL_GPI_ANCHOR_BIOSYNTHESIS | 0.59598 | 0.02040 |
| | PRIMARY_IMMUNODEFICIENCY | –0.60826 | 0.02514 |
| | SPLICEOSOME | 0.32993 | 0.02020 |
| ERBB3 | PROSTATE_CANCER | 0.42079 | 0.00012 |
| | MTOR_SIGNALING_PATHWAY | 0.50957 | 0.00023 |
| | GLYCOSYLPHOSPHATIDYLINOSITOL_GPI_ANCHOR_BIOSYNTHESIS | 0.67080 | 0.00039 |
| | COLORECTAL_CANCER | 0.42077 | 0.00204 |
| | RNA_DEGRADATION | 0.44905 | 0.00061 |
| MUC1 | VALINE_LEUCINE_AND_ISOLEUCINE_DEGRADATION | 0.54677 | 0.00018 |
| | FATTY_ACID_METABOLISM | 0.51296 | 0.00144 |
| | CIRCADIAN_RHYTHM_MAMMAL | 0.69052 | 0.00805 |
| | GLYCOSYLPHOSPHATIDYLINOSITOL_GPI_ANCHOR_BIOSYNTHESIS | 0.51112 | 0.01853 |
| | GALACTOSE_METABOLISM | 0.48660 | 0.03024 |

Abbreviation: KEGG: Kyoto Encyclopedia of Genes and Genomes.

**Table 2. Results of Mendelian randomization (MR) analysis**

| Gene | Exposure | Outcome | Method | nSNPs | β-value | *p*-value |
|---|---|---|---|---|---|---|
| FOXA1 | prot-a-2611 | Breast cancer id: ebi-a-GCST007236 | MR-Egger | 26 | 0.1462 | 0.9402 |
| | | | Weighted median | 26 | 0.9526 | $5.54\times10^{-11}$ |
| | | | Inverse variance weighted (fixed effects) | 26 | 0.6474 | $5.44\times10^{-265}$ |
| | | | Simple mode | 26 | 0.4266 | 0.1621 |
| | | | Weighted mode | 26 | 0.5861 | $9.18\times10^{-7}$ |
| MUC1 | prot-a-1967 | Breast cancer id: ebi-a-GCST007236 | MR-Egger | 16 | 4.6470 | 0.0002 |
| | | | Weighted median | 16 | 1.8530 | $4.25\times10^{-18}$ |
| | | | Inverse variance weighted (fixed effects) | 16 | 0.7446 | 0 |
| | | | Simple mode | 16 | 1.6230 | 0.0040 |
| | | | Weighted mode | 16 | 1.6600 | $6.72\times10^{-10}$ |
| AGR2 | prot-a-58 | Breast cancer id: ebi-a-GCST007236 | MR-Egger | 10 | −1.3710 | 0.6640 |
| | | | Weighted median | 10 | −0.6746 | $7.32\times10^{-5}$ |
| | | | Inverse variance weighted (fixed effects) | 10 | −0.4915 | $6.48\times10^{-53}$ |
| | | | Simple mode | 10 | −1.6350 | 0.0004 |
| | | | Weighted mode | 10 | −0.6215 | 0.0061 |
| ERBB3 | prot-c-2617_56_35 | Breast cancer id: ebi-a-GCST007236 | MR-Egger | 3 | 1.4770 | 0.9365 |
| | | | Weighted median | 3 | 0.3960 | $2.55\times10^{-6}$ |
| | | | Inverse variance weighted (fixed effects) | 3 | 0.03712 | $1.93\times10^{-78}$ |
| | | | Simple mode | 3 | 0.3527 | 0.0267 |
| | | | Weighted mode | 3 | 0.3025 | 0.0229 |

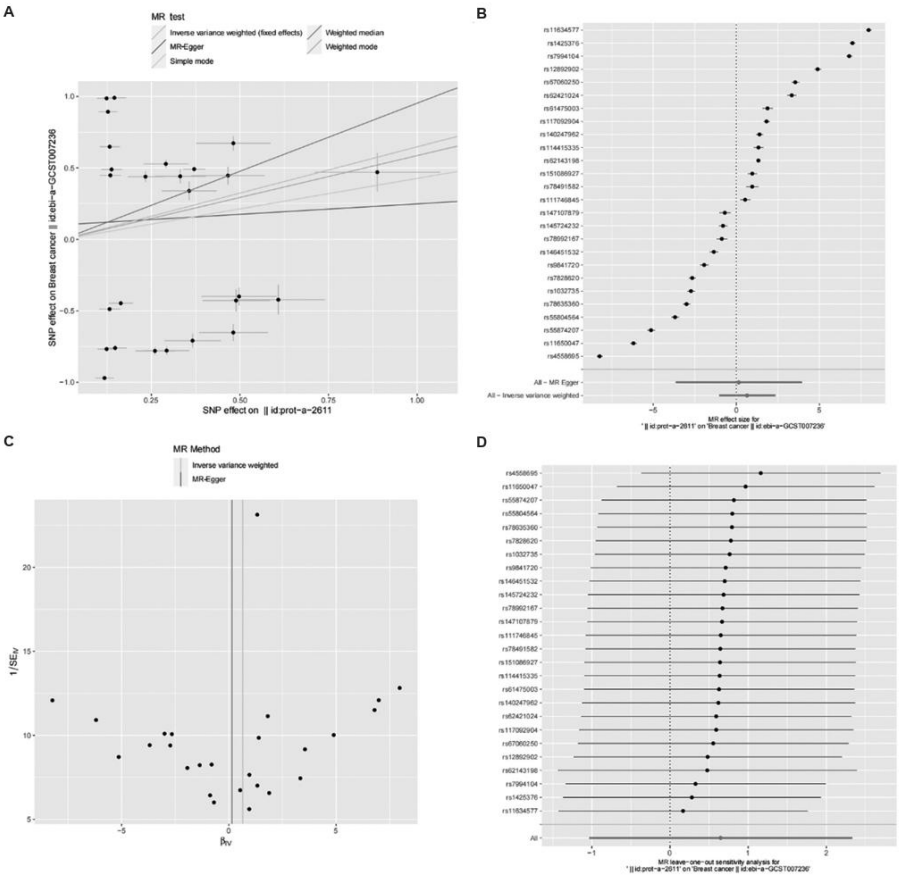


**Figure 5.** Mendelian randomization (MR) analysis of *FOXA1*. (A) Scatter plot showing the causal effect of *FOXA1* on breast cancer risk. (B) Forest plot showing the causal effect of individual single nucleatide polymorphism (SNP) on breast cancer risk. (C) Funnel plots assessing heterogeneity of MR estimates. (D) Leave-one-out plot evaluating the influence of individual SNPs on the causal estimate.

Tumor-associated macrophages are one of the most abundant immune cell populations in the TME.[28] M2-like TAMs are associated not only with poor prognosis in multiple cancers but also with the establishment of immunosuppressive TME.[27-30] M2-like macrophages secrete anti-inflammatory cytokines and growth factors and promote angiogenesis, supporting tumor cell proliferation.[31-33] Therefore, TAMs represent a promising therapeutic target, and identifying TAM-specific markers is critical. A TAM-related gene signature in breast cancer has been reported to be highly enriched in aggressive breast cancer subtypes,[34] and an M2-macrophage-related prognostic model has been developed in pancreatic ductal adenocarcinoma.[35] However, studies specifically investigating M2-like TAM-related hub genes in breast cancer remain limited.

To identify potential biomarkers for predicting prognosis in BRCA, we applied WGCNA and differential expression

**Table 3. Results of drug sensitivity analysis**

| Gene | Drug | Pearson correlation coefficient | *p*-value |
|---|---|---|---|
| FOXA1 | A-443654 | −0.502 | 0.00736 |
| | Lapatinib | −0.488 | 0.00883 |
| | KIN001-102 | −0.419 | 0.02051 |
| | CP724714 | −0.414 | 0.02173 |
| | ZSTK474 | −0.391 | 0.02821 |
| | Pyrimethamine | 0.634 | 0.02205 |
| | BX-795 | 0.616 | 0.02705 |
| ERBB3 | Lapatinib | −0.633 | 0.00420 |
| | A-770041 | −0.589 | 0.00724 |
| | Sorafenib | −0.530 | 0.01437 |
| | Roscovitine | −0.493 | 0.02152 |
| | A-443654 | −0.490 | 0.02222 |
| | MS-275 | −0.474 | 0.02627 |
| | Paclitaxel | −0.473 | 0.02655 |
| MUC1 | Saracatinib | −0.708 | $2.11\times10^{-5}$ |
| | Imatinib | −0.402 | 0.01027 |
| | BMS-509744 | −0.347 | 0.02361 |
| | Lapatinib | −0.334 | 0.02839 |
| | Olaparib | 0.491 | 0.01859 |
| | YK 4-279 | 0.481 | 0.02153 |
| AGR2 | TAE684 | 0.709 | 0.00735 |
| | XMD8-85 | 0.68 | 0.01109 |
| | KIN001-102 | −0.355 | 0.01299 |
| | CP724714 | −0.314 | 0.02230 |
| | AZ628 | 0.625 | 0.02303 |
| | Pyrimethamine | 0.613 | 0.02678 |
| | ZSTK474 | −0.291 | 0.02974 |
| | Afatinib | −0.291 | 0.02974 |

analysis to identify M2-like TAM-related hub genes. Firstly, we validated that the high M2-like TAM content was significantly associated with poorer prognosis in both the TCGA-BRCA and GSE58812 cohorts. Patients with high M2-like TAM content had significantly worse survival than those with low M2-like TAM content, indicating that M2-like TAMs are closely related to poor prognosis in BRCA. We then identified 85 candidate hub genes by intersecting M2-like macrophage modula genes with DEGs in BRCA. Next, four hub genes of breast cancer, including *FOXA1*, *ERBB3*, *AGR2*, and *MUC1*, were screened using the STRING and Cytoscape platforms. The nomogram model integrating these genes performed well in predicting breast cancer, and ROC curves confirmed that the four hub genes effectively distinguished breast cancer from normal tissues.

Functional analysis in TCGA-BRCA confirmed that the four hub genes were more highly expressed in tumors than in normal tissue, and high *FOXA1* expression was significantly associated with poor prognosis. GSEA analysis demonstrated that *FOXA1*, *AGR2*, and *ERBB3* were closely related to tumor-related pathways and functions. In pan-cancer analysis, these four hub genes were highly expressed in breast cancer patients over 65 years old. A study of 92 women over 65 years old reported that 77 women (83.6%) had malignant breast disease.[36] Mutations in *FOXA1* have been reported as a hallmark of estrogen receptor-positive (ER+) breast cancer.[37] *FOXA1* overexpression may be a prognostic factor for treatment resistance and a viable target for immunotherapy and chemotherapy sensitization in ER+ luminal breast cancer.[38] The positive correlation between *FOXA1* expression and M2 macrophage infiltration further supports its association with poorer prognosis. Previous research has also shown that *MUC1* can up-regulate M2 macrophage infiltration, and the cytoplasmic domain of *MUC1* plays an important role in promoting postpartum mammary tumors, suggesting a potential strategy for postpartum breast cancer prevention and treatment.[39]

We then explored the causal relationship between the expression levels of the four hub genes (*FOXA1*, *AGR2*, *MUC1*, and *ERBB3*) and breast cancer risk using two-sample MR based on large-scale GWAS data. This MR analysis suggested that *FOXA1*, *MUC1*, and *ERBB3* may be causally associated with increased breast cancer risk. MR reduces systematic bias caused by observational studies, such as confounding and reverse causality, in prospective randomized controlled trials.[40] To ensure that SNPs were not related to confounding factors between the four hub genes and breast cancer, only participants of the European ancestry were included. In addition, MR-Egger regression with an intercept term showed no evidence of directional pleiotropy, supporting the robustness of the causal inference.[41]

Finally, we explored whether hub gene expression influenced sensitivity or resistance to anticancer drugs based on the relationship between drug $IC_{50}$ values and gene expression. *FOXA1*, *MUC1*, and *ERBB3* expression were associated with increased sensitivity to lapatinib. Lapatinib is a HER-2 tyrosine kinase inhibitor used clinically, often in combination with capecitabine, for the treatment of advanced or metastatic breast cancer. The findings may assist in supporting the clinical application of lapatinib.

While this study is constrained by its *in silico* nature, its primary value lies in guiding future translational research. The absence of wet-laboratory validation is not an endpoint but a starting point, identifying the most promising candidates

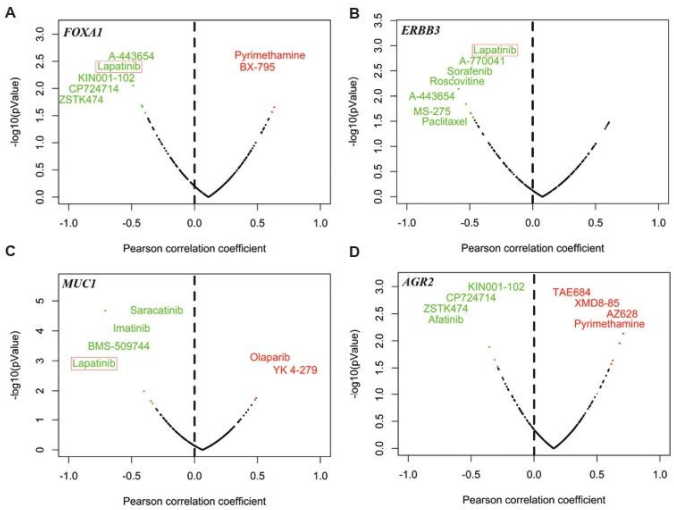


**Figure 6.** Pearson correlation analysis between hub gene mRNA expression and drug $IC_{50}$ values. (A) *FOXA1*, (B) *ERBB3*, (C) *MUC1*, (D) *AGR2*.
Notes: Green indicates a negative correlation between drug $IC_{50}$ and gene expression; red indicates a positive correlation.

for subsequent experimental investigation. Our integrated analysis serves as a filter, moving beyond correlation to suggest causality via MR and linking gene expression to clinically relevant drug responses. The genes identified here (*FOXA1*, *ERBB3*, *MUC1*) present a compelling rationale for future studies exploring their functional roles in modulating the tumor immune microenvironment and response to therapy, particularly to agents such as lapatinib. Thus, rather than a limitation, the computational design of this work represents a strength, offering a cost-effective basis to guide resource-intensive laboratory and clinical research toward the most viable targets.

## 5. Conclusion

Our study identified four M2-like TAM-related hub genes for predicting prognosis in breast cancer. These findings may contribute to improving prognostic assessment in breast cancer, and these genes may serve as potential biomarkers for clinical outcomes and immune responses.

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## Conflict of interest

The authors declare that they have no competing interests.

## Author contributions

*Conceptualization:* Guang Yang
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## Ethics approval and consent to participate

Not applicable.

## Consent for publication

Not applicable.

## Availability of data

All data were available in the TCGA database (https://portal.gdc.cancer.gov/), GEO database (https://www.ncbi.nlm.nih.gov/geo/), and GDSC database (https://www.cancerrxgene.org/). Questions regarding data can be directed to the corresponding author.

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# 五、 竞赛项目获奖材料

证 书

为表彰第十一届全国大学生医学创新大赛暨“一带一路”国际竞赛基础临床赛道中南部赛区复赛优秀成果奖（省级）获得者，特颁发此证书。

获奖项目：嗜麦芽窄食单胞菌促进阿尔茨海默病进展的机制研究

奖励等级：优秀奖

获奖团队：刘星蕊，白晶，陈嘉婵，向禹涵，贾梦雨

指导教师：夏亦元

所在高校：江汉大学

高等学校大学生医学创新竞赛委员会

2025年8月

证书编号：CUMITC2025A1886

No. 231107231002

# 2023年全国大学生英语竞赛(NECCS)

## 2023 National English Competition for College Students

# 获 奖 证 书

## CERTIFICATE OF AWARD

刘星蕊 同学：

你在2023年全国大学生英语竞赛(NECCS)中，成绩优异，荣获 C 类一等奖。

特发此证，以示表彰。

You have obtained the ***First Prize*** for Type C in 2023 National English Competition for College Students.

This certificate of commendation is hereby awarded to you as an encouragement.

国际英语外语教师协会
中国英语外语教师协会
二〇二三年六月二日

IATEFL · TEFL China

高等学校大学外语教学研究会
二〇二三年六月二日

College English Teaching & Research Association of China

第三届“BETT杯”

# 全国大学生英语阅读大赛

# 荣誉证书

江汉大学（单位） 刘星蕊（选手）

在第三届“BETT杯”全国大学生英语阅读大赛决赛中表现突出，荣获：

## 全国一等奖

特颁此证，以兹鼓励。

证书编号：FLRB2411D3009235　　查询网址：www.bett.org.cn

中国城市商业网点建设管理联合会
国际商务交流与外语研究分会
二〇二五年三月

证书编号:0420230612E0201053079

# 获奖证书

姓　　名：刘星蕊

证件号码：420983200405140728

荣获 2023年 CATTI 杯全国翻译大赛

初赛　大学非专业A组　中英（笔译）

三等奖

主办单位：

全国翻译专业学位研究生教育指导委员会

中国外文局翻译院

实施单位：

中国外文局全国翻译专业资格（水平）考试项目管理中心

2023 年 6 月 20 日

证书查询网址：http://www.catticenter.com/CattiCup/zhengshu

国际人才英语考试
English Test for International Communication

刘星蕊 参加 2022 年 11 月 12 日 国际人才英语考试（中级），成绩 良好，特发此证。

This is to certify that LIU XINGRUI has been awarded Pass with Merit in the English Test for International Communication (Intermediate) on 12 November, 2022.

身份证件号：
ID Number: 420983200405140728

证书编号：
Certificate Number: GC02B22110000508

| 口头沟通 Oral Communication | 书面沟通 Written Communication | 总分 Overall Score |
|---|---|---|
| 229 | 190 | 210 |

经国际人才英语考试（简称国才考试）评价、认定，该证书持有者在一般国际交流与工作场合中，具备 良好 的运用英语开展工作的能力。

国才考试是北京外国语大学中国外语测评中心研发的英语沟通能力认证体系，考题取自真实、典型的职场情境，重点考查口头沟通和书面沟通能力，包括国际视野与协商合作能力、跨文化理解与表达能力、分析问题与解决问题的能力三个维度，为用人单位选拔具有全球胜任力的国际化人才。

国才考试（中级）的任务设置为：解说数据、回复留言、报告信息、专题发言；会议纪要、研判材料、撰写提要、撰写邮件。

北京外国语大学
中国外语测评中心

证书编号：cwctic04598

获奖证书

刘星蕊

在2023年第九届中西部外语翻译大赛 决赛 中，荣获【非英语专业笔译组】

全国三等奖

特发此证，以资鼓励！

四川省翻译协会 二〇二三年十二月
广西翻译协会 二〇二三年十二月
河南省翻译协会 二〇二三年十二月
河北省翻译协会 二〇二三年十二月
甘肃省翻译工作者协会 二〇二三年十二月
宁夏翻译协会 二〇二三年十二月
安徽省翻译协会 二〇二三年十二月
重庆翻译协会 二〇二三年十二月
哈尔滨市翻译协会 二〇二三年十二月
山西省翻译协会 二〇二三年十二月
贵州省翻译协会 二〇二三年十二月
深圳市翻译协会 二〇二三年十二月
陕西省翻译协会 二〇二三年十二月
上海市科技翻译学会 二〇二三年十二月

湖北省翻译大赛
TRANSLATION & INTERPRETING CONTEST OF HUBEI PROVINCE

# 获奖证书
CERTIFICATE

刘星蕊 在第29届湖北省翻译大赛 笔译（非专业英语A组） 初赛中荣获 二等奖 。

特发此证，以资鼓励！

就读学校：江汉大学

参赛考点：江汉大学

（扫码查询证书有效性）

湖北省翻译工作者协会

证书编号：2201011618

二零二二年十二月三十日

英语世界™
The World of English

# 2024年第四届
# 《英语世界》杯全国大学生英语写作大赛

# 荣誉证书

CERTIFICATE OF HONOR

**刘星蕊**

**江汉大学**

在2024年第四届《英语世界》杯全国大学生英语写作大赛中，表现突出，成绩优异，荣获：

## 本科生组 优秀奖

特颁此证，以资鼓励！

《英语世界》编辑部

2025年2月

证书编号：YYSJ2404967

## 六、 社会服务类材料

证书编号：DM0320240400008008

# 证 书

**刘星蕊：**

您在2023年全国大学生口腔健康志愿宣讲活动中，圆满完成宣讲任务，为志愿服务作出贡献。

特发此证，以资鼓励。

团中央青年志愿者行动指导中心　　中国青年志愿者协会秘书处

2023年03月