# ARIC Manuscript Proposal Form

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Publication Committee Review Date: **_09/17/24**
ARIC Manuscript Proposal Number: **# 4535**

**1.a. Full Title**: The Association Between Plasma IGFBP7 and Cancer Incidence, Cancer Mortality, and All-Cause Mortality

**b. Abbreviated Title (Length 26 characters): IGFBP7 and Cancer**

**2. Writing Group [please provide a middle initial if available; EX: Adam L Williams]:**
Writing group members: Vernon A Burk, Michael N Pollak, Josef Coresh, Corrine E Joshu, Elizabeth A Platz, and other interested ARIC investigators

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __VB___ **[please confirm with your initials electronically or in writing]**

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**ARIC author** to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (The ARIC author should be involved enough in ARIC to be able to point the lead author to appropriate ancillary study PIs and to be able to search ARIC manuscript proposals if the lead author doesn't have the access needed to do such a search).


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**3. Timeline**: 1 year

**4. Rationale**:

We aim to investigate the association between insulin-like growth factor-binding protein 7 (IGFBP7), which is also known as IGFBP-rg1, MAC25, AGM, TAF, PSF, and FSTL2, in relation to cancer incidence, cancer mortality, all-cause mortality, and all-cause mortality other than heart failure.

Based on protein sequence homology to other binding proteins, IGFBP7 was predicted to bind IGF-1, and prevent IGF-1 from signaling through its receptor (IGF-1R). This purported function is cancer important because plasma IGF-1 is robustly positively associated with epithelial cancers, including prostate, breast, and colorectal cancer (1-3). Based on these promising findings, drugs blocking IGF-1R were developed and tested in phase 3 clinical trials for the treatment of breast cancer. Counter to the hypothesis, these drugs were not effective (4). For example, a trial (Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging And moLecular Analysis 2 (I-SPY2)) that randomized women with breast cancer to neoadjuvant chemotherapy plus an anti-IGF-1R drug (a targeted antibody) versus chemotherapy alone did not document a notable benefit, including within subgroups of levels of tumor expression (from RNA seq) of IGF-family members (5). Tumor IGFBP7 expression was not considered in that analysis. However, post-hoc analysis of the trial tumor expression data, discovered that participants with higher IGFBP7-expressing tumors were resistant to the anti-IGF-1R drug, while tumors with lower IGFBP7 expressing tumors were responsive to the drug (unpublished manuscript: Godina C, Pollak MN, Jernström H, 2024: “Low tumor IGFBP7 expression predicts complete pathological response of breast cancer patients to IGF-1R targeting with ganitumab”). IGFBP7 has been shown to be able to bind directly to IGF-1R (6), with higher affinity than it binds IGF-1. Thus, Godina et al. hypothesized that IGFBP7 competes with the anti-IGF-1R drug for binding to the IGF-1 receptor.

However, Gondina et al. also found that risk of progression to metastasis was higher in tumors with higher IGFBP7 expression independent of treatment arm in that same post-hoc analysis, suggesting that IGFBP7 may be an agonist for IGF-1R. While the function(s) of IGFBP7 when bound to IGF-1R is not well characterized, other studies have reported positive associations between tumor IGFBP7 expression (7) and breast cancer progression, and preoperative circulating IGFBP7 levels when the tumor was positive for membrane IGF-1R and breast cancer recurrence (8).

While circulating levels of IGF-1 and other members of the IGF family have been extensively studied in relation to cancer risk (1-3), IGFBP7 has not. IGFBP7 is a secreted protein that is

detectable in blood. In small studies, insulin resistance (9), and alcohol drinking (10) were associated with higher blood IGFBP7. In ARIC, IGFBP7 is available in the SomaScan panel along with many of the other members of the IGF-family. Previously, a discovery study in ARIC that evaluated the association between 4,877 plasma proteins and heart failure risk, IGFBP7 was among the top hits after considering multiple testing(11),supporting the feasibility of studying this plasma protein with cancer incidence and mortality, and all-cause mortality (with and without death from heart failure) in ARIC.

At this time, the mechanism by which IGFBP7 may influence cancer risk is not certain. Here we propose a number of aims that are designed to inform the need for additional mechanistic experiments and for conducting future epidemiologic studies of this protein in cancer etiology (e.g., etiologically relevant window for measurement of levels).

## 5. Main Hypothesis/Study Aim:

Aim 1: To discover whether plasma IGFBP7 RFU is associated with the risk of:

a. Cancer incidence, including common cancer sites (prostate, breast, lung, colorectal)
b. Cancer mortality, including common cancer sites (prostate, breast, lung, colorectal)
c. All-cause mortality, including after censoring for incident heart failure

Main Hypothesis: IGFBP7, a secreted protein, is associated with a higher risk of cancer, independent of age.

Aim 2: To determine the within-person correlation in IGFBP7 at 3 time points (Visits 2, 3, 5) over the long-term

Aim 3: To determine the strength of association between IGFBP7 and cancer incidence, cancer mortality, and all-cause mortality with time since blood draw

Aim 4: To identify which plasma proteins across all of those measured in the SomaLogic protein paneling are correlated with plasma RFU levels of IGFBP7, including members of the IGF family

Aim 5: To identify which common cancer and other chronic disease risk factors (e.g., diabetes, BMI) are associated with plasma RFU levels of IGFBP7

## 6. Design and analysis - please address the following aspects:

### a) inclusion/exclusion

Exclusions:

- Did not consent to studies on outcomes beyond CVD or industry studies
- Do not have SomaScan data available at V2, V3, and V5
- Had a history of cancer before V2 (prevalent)

- Not Black or White

**b) study design**

Prospective cohort design

Follow-up from V2 to 12/31/2015 (cancer incidence analysis) or 12/31/2020 (mortality analyses)

**c) outcome and other variables of interest with specific reference to the time of their collection**

Exposure:
- IGFBP7 from the SomaScan at V2, V3, and V5

Outcomes after V2:
- Incident cancer
- Cancer mortality
- All-cause mortality
- All-cause mortality after censoring heart failure-related deaths

For cancer incidence and cancer mortality analyses, we will use the following cancer case files (common and/or known IGF associations):
- All solid cancers
- Prostate cancer
- Lung and bronchus cancer
- Breast cancer
- Colorectal cancer
- Pancreatic cancer
- Liver cancer

Covariates (at each plasma protein visit):
- Age
- Race
- Field Center
- Sex
- Smoking Status
- Packyears
- BMI
- Diabetes Status (diagnosed, undiagnosed, at-risk, normoglycemic)
- Cholesterol Levels
- Hormone replacement therapy (women)
- Physical activity (meeting guidelines)
- Height
- Alcohol drinking status
- Ethanol intake
- eGFR
- SomaScan proteomic panel, including IGF-family proteins

**d) summary of data analysis**

We will exclude participants without appropriate consent for this study on proteins and cancer. Aim 1: We will perform Cox proportional hazards regression models to determine whether plasma IGFBP7 RFU is associated with the risk of incident cancer, cancer mortality, and all-cause mortality. We will adjust for age, sex, categories of race and field center, and common cancer risk/protective factors, most of which are shared risk factors with all cause mortality (e.g., smoking, obesity). Where appropriate, we will explore whether the associations differ by age, sex, and race and we will test for interaction using a likelihood ratio test, if necessary. Additionally, we will perform model diagnostics of the Cox proportional hazards assumption for the IGFBP7 by time, and if violation is identified, we will include an interaction term in the model.

Aim 2: Because the biological variability in IGFBP7 has not been described over a long period of time, we will produce scatter plots to identify intra-individual variability in plasma IGFBP7 RFU at 3 time points: V2, V3, and V5. We will calculate ICCs.

Aim 3: We will repeat Aim 1 stratifying by time since blood draw.

Aim 4: We will use Spearman's rank correlation analyses to identify which plasma proteins across the SomaLogic panel are correlated with IGFBP7, especially other IGF-family proteins.

Aim 5: We will use linear regression with IGFBP7 as the outcome to determine the association between common risk/protective for cancer and other chronic disease risk factors (e.g., diabetes, BMI) are associated with plasma RFU levels of IGFBP7. We will adjust for age, sex, and categories of race and field center.

All analyses will be conducted in SAS and/or R.

**e) Any anticipated methodologic limitations or challenges if present**

1. Sample size for some cancers may be too small to study.
2. Prior work has not used the SomaScan platform. We confirmed that IGF-1 is associated with breast cancer risk in ARIC using this platform. We confirmed that IGFBP7 measured by SomaScan is correlated with other proteomics platforms.
3. IGFBP7 appears to have may functions and is likely correlated with many other proteins. We will attempt to assess correlations and adjust for any moderate to highly correlated proteins to address confounding.
4. Our collaborator (Dr. Pollak) reports that plasma levels of IGFBP7 do not appear to have strong genetic instruments (unlike IGF-1) and thus, we will not be able to address causation using Mendelian randomization.

**f) Will the author need Limited data to complete the proposed manuscript? ☐ Yes, Limited data is needed (Provide a brief (2-3 sentences) justification for requesting PHI data) . ☐ No, De-identified data will be sufficient.**

*Please note, Limited dataset access is strict and rarely provided. Limited data includes identifiable information such as dates (birthdays, visit dates, etc.). CMS, Genomic, Geocoded,

Proteomics/Somalogic, and other -omic data all fall under the limited data category. De-identified data does not include dates. All dates are date adjusted to "Days since Visit 1".

This study will use the SomaLogic data.

**7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? (Non-ARIC analysis means that the authors are not regarded as ARIC investigators and the "ARIC author" is essentially just a facilitator rather than an integral part of the writing group.)** ☐ **Yes** ☒ **No**

**b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ?** ☐ **Yes** ☐ **No**
(The file ICTDER is distributed to ARIC PIs annually, and contains the responses to consent updates related to stored sample use for research.)

**8.a. Will the DNA data be used in this manuscript?** ☐ **Yes** ☒ **No**

**8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the current derived consent file ICTDER05 must be used to exclude those with value RES_DNA = "No use/storage DNA"?** ☐ **Yes** ☐ **No**

**9. The lead author or the "sponsoring" ARIC author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status.** ARIC Investigators have access to the publications lists under the Study Members Area of the website at: https://aric.cscc.unc.edu/aric9/proposalsearch [ARIC Website□Publications□Proposal Search]

☒ Yes ☐ No

**10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?**
MS# 4519 Discovering plasma proteins associated with common solid cancer incidence in ARIC

**11.a. Is this manuscript proposal associated with any ARIC ancillary studies or does it use current [or ongoing] ancillary study data (this includes ACHIEVE)?** ☒ **Yes** ☐ **No → Skip to question 12**

**11.b. If yes to 11.a., is the proposal**
☒ **A. primarily the result of an ancillary study**

☐ **B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables)**

**11.c. If yes to 11.a., list number* __**

2017.27 Proteomic longitudinal ARIC study: SOMAscan of multiple visits
2011.07 Enhancing ARIC Infrastructure to Yield a New Cancer Epidemiology Cohort
1995.04 Cancer Study

*ancillary studies are listed by number
https://aric.cscc.unc.edu/aric9/researchers/ancillary_studies/approved_ancillary_studies [ARIC Website□Ancillary Studies□Approved Ancillary Studies]

**12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.**

**12b. The NIH instituted a Public Access Policy in April, 2008** which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PubMed Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in https://aric.cscc.unc.edu/aric9/publications/policies_forms_and_guidelines [ARIC Website□Publications□Publication Policies, Forms, and Guidelines]. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

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