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MULTIPLE MYELOMA – TRANSFORMING THE APPROACH TO AN INCURABLE DISEASE
MULTIPLE MYELOMA IS A MAJOR CLINICAL PROBLEM AT MCW...AND GLOBALLY

**Definition:** Multiple Myeloma (MM) is a blood cancer derived from immunoglobulin-producing plasma cells that reside in the bone marrow and cause CRAB symptoms: hyperCalcemia, Renal failure, Anemia and Bone loss.

**Public health relevance:** MM is the 2nd most common blood cancer in the US. Accounts for approximately 1% of all cancers but 2% of all cancer deaths. Estimated 30,000 new cases in US in 2017 and 14,000 deaths.

**MCW:**
~300 new patients per year with plasma cell malignancies (in Wisconsin ~600 new cases p.a. and 200 deaths).
Circa 130 BMTs for myeloma annually; i.e., 45% of all HSC transplants.
Milwaukee area features high proportion of African American patients with myeloma. Addressing disparities in care and innovation is therefore an institutional priority.
1. **Multiple Myeloma Incidence: By Age Group and Race/Ethnicity**

2. - Prevalence of MGUS in African American (AA) patients 2-3 times higher than in Caucasian American (CA) patients.
- Earlier age of onset (~4 yrs) in AA patients and higher prevalence of IgA MGUS, a high-risk progression subtype.
IMPROVE ACCRUAL OF AA PATIENTS IN CLINICAL TRIALS FOR MYELOMA

- Underrepresentation of minorities results in data deficit, which poses a threat to external validity of trial results.

- External validity of a clinical trial (well designed, carried out and analyzed and thus internally valid) indicates whether results are applicable to affected populations at large.

- Meta-analysis of 51 clinical trials including 4,853 patients. Ideal O-to-E ratio is 1.
We evaluate the 7p15.3 risk allele with support of a supplemental NCI R01 award.

More strongly associated with MM in AA compared to CA patients.

C risk allele leads to elevated CDCA7L expression (eQTL analysis) – a prognosticator of poor OS, particularly for Blacks.

Our project relies on a variety of preclinical experimental model systems: HMCLs, Human-in-mouse xenografts, Mouse-in-mouse allografts, and GEMMs.
DESIGN AND TESTING OF NOVEL MYELOMA IMMUNOTHERAPIES

- Four (4) ongoing cellular therapy trials for myeloma
- PI: Dr. P. Hari, HemOnc, DOM, MCW
- Based on the experience of the MCW trial of first-in-human dual targeted CD20 and CD19 CAR-T cells for NHL, we are now proceeding with bispecific CD19 and BCMA targeted CAR-T cell therapies for myeloma.
- Preclinical support provided by the Bryon Johnson and Siegfried Janz Labs

[Diagram showing myeloma cell and CAR-T cell with CD19 and BCMA targets]
DEVELOPING COMPANION DIAGNOSTICS FOR NOVEL MYELOMA TREATMENTS

- Developing new methods for predicting cytotoxic immune responses in the post-ASCT bone marrow TME of myeloma

- Proteolytic cleavage of versican (VCAN) is associated with lack of immune response to myeloma

- Clinical project initiated by Dr. Binod Dhakal in collaboration with UW Madison

- Next step: Ancillary project led by Dhakal for BMT CTN 1401 MM Vaccine Study is approved.

- MCW is the highest accruing site.

Dhakal B et al. Leuk Lymphoma 8:1-5, 2019
DISCOVERING NEW MOLECULAR TARGETS FOR MYELOMA TREATMENT

- Surface antigen discovery program in collaboration with the Jeff Medin Lab and mass spec core directed by Rebekah Gundry
- Relies on myeloma cell membrane protein capture and characterization

Workflow diagram

Waas et al., J Proteome Res 18(4):1644, 2019
Fujinaka et al., Methods Mol Biol 1722:57, 2018
Haverland et al., Proteomics 17(19), 2017
DISCOVERING NEW MOLECULAR TARGETS…
CONT'D: COMPARATIVE ONCOGENOMICS

Multiple myeloma

Plasma cell tumors from GEMMs of human myeloma

Late stage MM & Fast mouse tumors

Early stage MM & Slow mouse tumors

Candidate myeloma genes such as:

hnRNPA1
5R01CA214246
PI: A. Lichtenstein, UCLA

FOXM1
2R01CA151354
PI: S. Janz, MCW

Park et al., BMC Genomics 2007; 8:302
Tompkins et al., PLoSOne 2013; 8(10):e76889
The transcription factor forkhead box M1 (FOXM1) is a validated oncoprotein in solid cancers, but its role in malignant plasma cell tumors such as multiple myeloma (MM) is unknown. We analyzed publicly available MM data sets and found that overexpression of FOXM1 prognosticates inferior outcome in a subset (~15%) of newly diagnosed cases, particularly patients with high-risk disease based on global gene expression changes. Follow-up studies using human myeloma cell lines (HMCLs) as the principal experimental model system demonstrated that enforced expression of FOXM1 increased growth, survival and clonogenicity of myeloma cells, whereas knockdown of FOXM1 abolished these features. In agreement with that, constitutive upregulation of FOXM1 promoted HMCL xenografts in laboratory mice, whereas inducible knockdown of FOXM1 led to growth inhibition. Expression of cyclin-dependent kinase 6 (CDK6) and NIMA-related kinase 2 (NEK2) was coregulated with FOXM1 in both HMCLs and myeloma patient samples, suggesting interaction of these three genes in a genetic network that may lend itself to targeting with small-drug inhibitors for new approaches to myeloma therapy and prevention. These results establish FOXM1 as high-risk myeloma gene and provide support for the design and testing of FOXM1-targeted therapies specifically for the FOXM1High subset of myeloma.

Gu et al., Leukemia 30(4):873-882, 2016
FOXM1 IS FURTHER UPREGULATED IN RELAPSED MYELOMA (rMM)

A

Log$_2$ FOXM1 gene expression units

Myeloma: Baseline | Relapse
---|---
Cases: 52 | 52
Present: 9 | 20
Absent: 43 | 32

$p = 0.05$

B

Proportion of patients with myeloma

Months from relapse

OS

Low: 52 | 20 | 6 | 3
High: 8 | 0

$p < 10^{-3}$

Gu et al., Blood Cancer J. 8(2):22, 2018
FOXM1 EXPRESSION IS ASSOCIATED WITH MYELOMA CELL PROLIFERATION, AN ADVERSE PROGNOSTICATOR OF OUTCOME

Gu et al., Blood Cancer J. 8(2):22, 2018

<table>
<thead>
<tr>
<th></th>
<th>nMM (n = 712)</th>
<th>rMM (n = 82)</th>
</tr>
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<tbody>
<tr>
<td>Log₂ FOXM1 expression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GPI: Lo Int Hi</td>
<td>272 360 80</td>
<td>14 46 22</td>
</tr>
<tr>
<td>Cases:</td>
<td>0 30 54</td>
<td>0 9 18</td>
</tr>
<tr>
<td>Present:</td>
<td>272 330 26</td>
<td>14 37 4</td>
</tr>
</tbody>
</table>

A

B

[Image of data and graphs]

[Image of FOXM1 and Ki67 staining]
Targeting CDK4/6 may re-sensitize FOXM1\textsuperscript{High} myeloma to chemotherapy

- Enforced expression of FOXM1 leads to diminished drug sensitivity of myeloma \textit{in vitro} and \textit{in vivo}
- FOXM1 engages the CDK4/6-Rb-E2F pathway, a regulator of myeloma senescence

Gu et al., BMC Cancer 18(1):1152, 2018
Clinical trial of CDK4/6-targeted therapies for patients with FOXM1^{High} myeloma at MCW?
Together, Taking on Cancer's Toughest Challenges

2019 Scientific Retreat

ROBUST ONGOING MCWCC TRIAL PROGRAM FOR MYELOMA

Phase 1: n = 9
Phase 2: n = 6
Phase 3: n = 4

Improving clinical care for all, including minority myeloma patients!
If you want to go fast, go alone.

If you want to go far, go together.

– African Proverb

ACKNOWLEDGEMENTS

Collaborators
Frank Zhan, Univ of Iowa
Guido Tricot, UAMS
Hartmut Goldschmidt, Germany
Dirk Hose, Germany
Brian Van Ness, UoMinnesota
Ye Yang, Nanjing, China

Others
Myeloma Care
Binod Dhakal
Anita D’Souza
Saurabh Chhabra
Parameswaran Hari
Schuett Foundation
Janz Lab
Fumou Sun & Yan Cheng
Michael Pisano & Krista Lingle Mullen

CANCER COLLABORATIVE

MEDICAL COLLEGE OF WISCONSIN CANCER CENTER

National Cancer Institute at the National Institutes of Health

Multiple Myeloma Research Foundation