2019 Scientific Retreat
FRIDAY, APRIL 26, 2019
DISCOVERY WORLD PAVILION

TURNING CANCER DISCOVERIES INTO TREATMENTS

Brian F. Volkman, PhD

Together, Taking on Cancer’s Toughest Challenges
mcw.edu/departments/cancer-center @MCWCancerCenter
SFI in Protein Foundry, LLC, manufacturer of recombinant proteins for research use

Inventor on multiple issued and pending patents on engineered proteins as potential therapeutic agents

mcw.edu/departments/cancer-center   @MCWCancerCenter
DISCOVERY AND DEVELOPMENTAL THERAPEUTIC PROGRAM

DDT = OPPORTUNITY

CANCER COLLABORATIVE
mcw.edu/departments/cancer-center @MCWCancerCenter
DRUG DISCOVERY AND DEVELOPMENT

1. DISCOVERY

IDEA

2. DEVELOPMENT

CLINICAL TRIALS
Once a disease target is identified, drugs are designed and tested. Both public and privately funded research are involved.

PHASE I

PHASE II

PHASE III

TRANSLATIONAL RESEARCH

3. DELIVERY

REGULATORY APPROVAL
Human trials are completed, FDA approval. Industry is responsible for bringing a drug to market. Safety and evaluation continue after approvals.

PATIENT CARE

mcw.edu/departments/cancer-center  @MCWCancerCenter
Together, Taking on Cancer’s Toughest Challenges

2019 Scientific Retreat

DRUG DISCOVERY AND DEVELOPMENT

1. DISCOVERY

MCW excels at basic science research

MCW excels at basic science research

IDEA

TARGET VALIDATION

TARGET IDENTIFICATION

TRANSLATIONAL RESEARCH

mcw.edu/departments/cancer-center  @MCWCancerCenter
Together, Taking on Cancer’s Toughest Challenges

2019 Scientific Retreat

MCW excels at basic science research.

Blake Hill, Francis Peterson, Davin Jensen, Brian Smith, Brian Volkman, Dan Sprague, Mike Olp, John Egner, Liza Lanum, Sarah Rolli

mcw.edu/departments/cancer-center  @MCWCancerCenter
Signaling by Fyn-ADAP via the Carma1–Bcl-10–MAP3K7 signalosome exclusively regulates inflammatory cytokine production in NK cells

Kamalakannan Rajasekaran1, Pawan Kumar1, Kristina M Schuld1, Erik J Peterson2, Bart Vanhaesebroeck3, Vishva Dixit4, Monica S Thakar1,5 & Subramaniam Malarkannan1,6,7

Inflammation is a critical component of the immune response. However, acute or chronic inflammation can be highly destructive. Uncontrolled inflammation forms the basis for allergy, asthma and various autoimmune disorders. Here we identified a signaling pathway that was exclusively responsible for the production of inflammatory cytokines but not for cytotoxicity. Recognition of tumor cells expressing the NK cell-activatory ligands H60 or CD137L by mouse natural killer (NK) cells led to efficient cytotoxicity and the production of inflammatory cytokines. Both of these effector functions required the kinases Lck, Fyn and PI(3)K (subunits p85α and p110α) and the signaling protein PLC-γ2. However, a complex of Fyn and the adaptor ADAP exclusively regulated the production of inflammatory cytokines but not cytotoxicity in NK cells. That unique function of ADAP required a Carma1–Bcl-10–MAP3K7 signaling axis. Our results have identified molecules that can be targeted to regulate inflammation without compromising NK cell cytotoxicity.

NATURE IMMUNOLOGY  VOLUME 14  NUMBER 11  NOVEMBER 2013

mcw.edu/departments/cancer-center  @MCWCancerCenter
TARGET IDENTIFICATION – FYN SH2

Subramaniam Malarkannan, PhD
MCWCC Cancer Biology Program
Together, Taking on Cancer’s Toughest Challenges

2019 Scientific Retreat

mcw.edu/departments/cancer-center @MCWCancerCenter
TARGET VALIDATION – FYN SH2

Computational solvent mapping identifies ligand binding hot spots
Fyn SH2 for NMR screening of chemical fragment libraries

mcw.edu/departments/cancer-center   @MCWCancerCenter
MCW INVESTMENTS IN DRUG DISCOVERY CAPABILITIES
MCW INVESTMENTS IN DRUG DISCOVERY CAPABILITIES

mcw.edu/departments/cancer-center   @MCWCancerCenter
DRUG DISCOVERY AND DEVELOPMENT

1. DISCOVERY

IDEA

TARGET IDENTIFICATION

TRANSLATIONAL RESEARCH

TARGET VALIDATION

2019 Scientific Retreat
mcw.edu/departments/cancer-center  @MCWCancerCenter
DRUG DISCOVERY AND DEVELOPMENT

Together, Taking on Cancer’s Toughest Challenges

2019 Scientific Retreat

mcw.edu/departments/cancer-center @MCWCancerCenter
DRUG DISCOVERY AND DEVELOPMENT

1. DISCOVERY  LINK  2. DEVELOPMENT

CHALLENGE: Promising new drug candidates are stranded

TRANSLATIONAL RESEARCH

CLINICAL TRIALS

PHASE I  PHASE II  PHASE III

mcw.edu/departments/cancer-center  @MCWCancerCenter
Goal: first-in-human clinical trials at MCW with MCW-derived discoveries

Inception: Formed in 2017, led by Bill Clarke, MCW’s first Director of Research Commercialization

Portfolio approach:
• Identify MCW-derived discoveries with therapeutic potential
• Meet with PIs to assess commercial promise, identify gaps in preclinical development
• Facilitate next steps toward IND
STRATEGICALLY MANAGED PORTFOLIO

Translational Portfolio

- All Compounds
  - Calendar
  - FRC Chairs

Kanban - Potential

Cancer Related, High...
- L12 dimer (CXCL12)
  - ADMET (Drug A...)
    - Metabolism
  - NDA
    - Not started
- INDICATION/DIS...
- Multiple myeloma, blo...
- PRIORITY SCORI...

Cancer Related, Low...
- CRR9
  - ADMET (Drug A...)
    - Absorption
- INDICATION/DIS...
- Cancer
  - PRIORITY SCORI...
  - DESCRIPTION

Cancer Related, None...
- ADMET (Drug A...)
  - Absorption
- NDA
  - Not started
- INDICATION/DIS...
- Renal protection - can...
- PORTFOLIO
  - PRIORITY SCORI...
<table>
<thead>
<tr>
<th>Description</th>
<th>Priority Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD19/20</td>
<td>10</td>
</tr>
<tr>
<td>Stopping Tyrosine Kinase CML</td>
<td>3</td>
</tr>
<tr>
<td>Targeting Pancreatic Cancer</td>
<td>10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Priority Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Description</th>
<th>Priority Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucosidase II inhibitors</td>
<td>3</td>
</tr>
<tr>
<td>PBRM1 BD2 inhibitors</td>
<td></td>
</tr>
<tr>
<td>Fyn inhibitors</td>
<td></td>
</tr>
<tr>
<td>Drp1 inhibitors</td>
<td></td>
</tr>
<tr>
<td>NAMPT inhibitors</td>
<td></td>
</tr>
<tr>
<td>Lif</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Priority Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Priority Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Description</th>
<th>Priority Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Role of Interleukin 23 GVHD</td>
<td>3</td>
</tr>
<tr>
<td>Genetic Mapping of Breast Cancer Risk</td>
<td>3</td>
</tr>
</tbody>
</table>

5 records | 11 records | 7 records
MC WD3: STRATEGICALLY MANAGED PORTFOLIO

**Target** | **Cancer Indication**
--- | ---
Honokiol | Head and Neck
Hippo | Breast
Mortalin | Thyroid
CRR9 | Pancreatic
p38G | Pancreatic and Colon
Glucosidase II | Breast
MitoMetformin | Pancreatic and Colon
PBRM1 | Gall bladder and Breast
Fyn | Leukemias
Drp1 | Breast and Testicular
NAMPT | Breast and Esophageal
Lif | Ovarian, Lung, Melanoma
K-Ras | Lung, Pancreas, Colon
Fis1 | Breast, Pancreas, Esophageal

**MCWD3 Members**
- Bill Clarke (OTD)
- Blake Hill
- John Imig
- Mike Dwinell
- Nita Salzman
- Ravit Boger
- Jim Thomas
- Ben George
- Paul Ornstein
- Matt Lasokowski
- Brian Volkman

2019 Scientific Retreat

Together, Taking on Cancer’s Toughest Challenges

mcw.edu/departments/cancer-center @MCWCancerCenter
Together, Taking on Cancer's Toughest Challenges

2019 Scientific Retreat

MC WD3: STRATEGICALLY MANAGED PORTFOLIO

MCWD3 Members
Bill Clarke (OTD)
Blake Hill
John Imig
Mike Dwinell
Nita Salzman
Ravit Boger
Jim Thomas
Ben George
Paul Ornstein
Brian Volkman
Matt Lasokowski

mcw.edu/departments/cancer-center   @MCWCancerCenter

Murphy, PM (2001) NEJM 345, 833-835.
CXCR4: VALIDATED TARGET FOR METASTATIC CANCER

Together, Taking on Cancer’s Toughest Challenges

2019 Scientific Retreat

Murphy, PM (2001) *NEJM* 345, 833-835.

CXCR4: VALIDATED TARGET FOR METASTATIC CANCER

ORIGINAL ARTICLE

Silencing of epithelial CXCL12 expression by DNA hypermethylation promotes colonic carcinoma metastasis

MK Wendt¹, PA Johanesen¹, N Kang-Decker², DG Binion³, V Shah² and MB Dwinell¹

¹Department of Microbiology and Molecular Genetics, Medical College of Wisconsin, Milwaukee, WI, USA; ²GI Research Unit, Department of Medicine, Mayo Clinic Foundation, Rochester, MN, USA and ³Department of Medicine, Medical College of Wisconsin, Milwaukee, WI, USA

Cellular metastasis is the most detrimental step in carcinoma disease progression, yet the mechanisms that regulate this process are poorly understood. CXCL12 and its receptor CXCR4 are co-expressed in several tissues

Introduction

Chemokines are small chemotactic cytokines, which direct cellular migration through receptor specific
EPIGENETIC REGULATION OF CHEMOKINE EXPRESSION

in development. Disruption of either gene causes embryonic lethality due to similar defects. Post-natally, CXCL12 signaling has a wide range of effects on CXCR4-expressing cells, including the directed migration of leukocytes, lymphocytes and hematopoietic stem cells. Recently, this signaling axis has also been described as an important regulator of directed carcinoma cell metastasis. We show herein that while CXCR4 expression remains consistent, constitutive colonic epithelial expression of CXCL12 is silenced by DNA hypermethylation in primary colorectal carcinomas as well as colorectal carcinoma-derived cell lines. Inhibition of DNA methyltransferase (Dnmt) enzymes with 5-aza-2’-deoxycytidine or genetic ablation of both Dnmt1 and Dnmt3b prevented promoter methylation and restored CXCL12 expression. Re-expression of functional, endogenous CXCL12 in colorectal carcinoma cells dramatically reduced metastatic tumor formation in mice, as well as foci formation in soft agar. Decreased metastasis was correlated with increased caspase activity in cells re-expressing CXCL12. These data constitute the unique observation that silencing CXCL12 within colonic carcinoma cells greatly enhances their metastatic potential.

Oncogene (2006) 25, 4986–4997. doi:10.1038/sj.onc.1209505; homoeostatic chemokine–chemokine receptor pair CXCL12 and CXCR4 is widely expressed throughout the body (Bleul et al., 1996). CXCL12, formerly known as stromal cell-derived factor-1, is an alpha type 7.8 kDa CXC chemokine (Shirozu et al., 1995). Originally described as a growth factor for bone marrow developing B cells (Nagasawa et al., 1994), CXCL12 was subsequently characterized as a chemoattractant for T cells and monocytes (Bleul et al., 1996). Genetic ablation of CXCR4 or CXCL12 results in embryonic lethality (Nagasawa et al., 1996). Similar embryonic defects in either of those chemokine receptor or chemokine gene-deficient animals has revealed roles for CXCR4–CXCL12 signaling in cardiovascular, neuronal and hematopoietic stem cell development as well as gastrointestinal vascularization (Tachibana et al., 1998; Zou et al., 1998). Previous studies by our group have established a role for CXCL12 and CXCR4 in gut vascularization, a key process in mucosal immunity and homeostasis (Heidemann et al., 2004).

In addition to endothelial expression, the cells of the human colonic epithelium also express both CXCL12 and CXCR4 (Dwinell et al., 1999; Jordan et al., 1999; Agace et al., 2000). Moreover, using an in vitro wound
CXCR4 INDUCES DIMERIZATION OF ITS LIGAND CXCL12


mcw.edu/departments/cancer-center  @MCWCancerCenter
CXCL12 L36C/A65C

**IC$_{50}$ ~ 5 nM**

THP-1 cells

Veldkamp, CT et al (2008)
Science Signaling 1:RA4
TRANSLATIONAL OPPORTUNITY: AN ENGINEERED PROTEIN THAT BLOCKS CANCER METASTASIS

MCW technology #1548

Liver metastases

Pancreatic cancer

Melanoma: lung metastases

Day 0
untreated

Day 21
L12 dimer treated


mcw.edu/departments/cancer-center @MCWCancerCenter
TRANSLATIONAL OPPORTUNITY: An Engineered Protein That Blocks Cancer Metastasis

1. DISCOVERY

2. DEVELOPMENT

CLINICAL TRIALS

MCW technology #1548

mcw.edu/departments/cancer-center   @MCWCancerCenter
TRANSLATIONAL OPPORTUNITY: AN ENGINEERED PROTEIN THAT BLOCKS CANCER METASTASIS

1. DISCOVERY

IDEA

TRANSLATIONAL RESEARCH

PRECLINICAL DEVELOPMENT

CLINICAL TRIALS

Licensed to biopharma company

Licensed to biopharma company

PROPEL promising therapeutic leads

2. DEVELOPMENT

PHASE I

PHASE II

PHASE III

mcw.edu/departments/cancer-center @MCWCancerCenter
BUILD

LINK

PROPEL
DDT = OPPORTUNITY

BUILD on established expertise and recent institutional investments

LINK discovery research and preclinical development

PROPEL MCW-invented therapies to the clinic
BUILD on established expertise and recent institutional investments
LINK discovery research and preclinical development
PROPEL MCW-invented therapies to the clinic

THANK YOU!