Learn about new opportunities for moving solutions from the lab to the patient.

The event will be held from 9 a.m. to noon and feature:

**Allan Brasier** (9-9:30 a.m.)
Senior Associate Dean of the School of Medicine and Public Health, and Executive Director of the Institute for Clinical and Translational Research (ICTR).

**Jon Young** (9:30-10:30 a.m.)
Head of WARF Therapeutics - a new initiative to advance pharmaceuticals closer to patients.

**Thursday, February 21, 2019**

Discovery Building | 330 N. Orchard St., Madison

PLUS a panel of campus experts with deep pharma development experience. (11-Noon)

- **Jennifer Golden**, Assistant professor in the School of Pharmacy and associate director of the Medicinal Chemistry Center
- **Doug McNeel**, Professor in the Department of Medicine and scientific founder and chief medical officer of Madison Vaccines Inc.
- **Luigi Pugielli**, Professor in the Department of Medicine
WARF Therapeutics and Institute for Clinical and Translational Research to Provide Discovery and Translational Support

**Target Discovery**
- UW & MIR PIs
- Novel biological target
- Therapeutic hypothesis
- Rigorous target validation

**Preclinical Drug Discovery**
- Preclinical Drug Discovery Experts
- Small Molecule Design & Optimization
- Project Management
- Novel Intellectual Property (IP)

**Drug Development**
- Pharma/Biotech Partners
  - Clinical Trials
  - NDA

**Institute for Clinical and Translational Research (ICTR)**
- Preclinical research support

**Institute for Clinical and Translational Research (ICTR)**
- Clinical research support
Trends and Opportunities in Medicinal Chemistry/ Drug Discovery at UW

Allan R Brasier MD
Executive Director, ICTR
Senior Associate Dean Clinical and Translational Research
Email: abrasier@wisc.edu
Goals for Today

• Establish a community of practice
• Introduce ICTR and its translational research mission
• Identify trends in academics and industry in medicinal chemistry
• Discuss pathways where medicinal chemistry can advance academic research programs
• Resources/opportunities in academic partnerships (UW, NIH)
• Opportunities for industry partnerships
• Challenges
Institute for Clinical and Translational Research (ICTR)

ICTR is a unique partnership between UW Schools & Colleges (Medicine & Public Health, Pharmacy, Nursing, Veterinary Medicine, Engineering) and Marshfield Clinic

Our Mission is to discover, translate, and disseminate innovations in health and health care.

We are one of 63 Academic Health Centers with a Clinical and Translational Sciences Award (CTSA).

The National CTSA network
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<tr>
<td><strong>Basic Science Research</strong>&lt;br&gt;Preclinical and animal studies&lt;br&gt;Defining mechanisms, targets and lead molecules</td>
<td><strong>Translation to Humans</strong>&lt;br&gt;Proof of concept&lt;br&gt;Phase 1 clinical trials&lt;br&gt;New methods of diagnosis, treatment and prevention</td>
<td><strong>Translation to Patients</strong>&lt;br&gt;Phase 2 clinical trials&lt;br&gt;Controlled studies leading to effective care</td>
<td><strong>Translation to Practice</strong>&lt;br&gt;Phase 4 clinical trials&lt;br&gt;Population-level outcomes research&lt;br&gt;Delivery of recommended and timely care to the right patient</td>
<td><strong>Translation to Community</strong>&lt;br&gt;True benefit to society</td>
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**Translation from basic science to human studies**

**Translation of new data into the clinic and health decision making**
Why is translational research a focus?

- Of 101 promising discoveries with clear clinical potential, only five resulted in interventions with licensed clinical use 20 years later.

Pharmaceutical development is slow, inefficient and expensive.
- New drug development takes more than a decade
- More than 95% of drugs fail in development; 50% of drugs fail in phase II
- Costs for new drugs are $2.5B from phase I testing to licensing
Current Trends in Academia

Accelerated by the

- NIH Molecular Libraries program,
- Changes in Industrial R&D investment, and
- Growth of translational research centers- CTSA programs, SPARK, UPenns Institute for Translational Medicine, UCSF QB3, etc.

Academia has evolved from its traditional role of target identification/validation to substantial small molecule expertise-screening and innovating new probes that can inform therapeutics development
10 year outcome- innovations in small molecule probes
• 375 probes for exploring biology
• Fluorescence polarization high throughput assays
• Multiplexed small molecule screens
• Feasibility for complex targets
Provided new therapeutic pathways

Schreiber, 2015; *Cell* **161**:1252
Pharmaceutical industry trends

- Productivity “crisis” – only 1 in 10 drugs entering the clinic are approved, despite increased investment
  - Regulatory complexity
  - Cost of clinical trials
  - Internal processes favoring industrialization
- Investment in regional science hubs - GSK Tres Cantos, Pfizer Center for Therapeutic Innovation, SAGE bionetworks
- Greater emphasis on target validation originating from academia- and greater emphasis on deep understanding of disease/drug targets- motivates partnerships
Medicinal chemistry for biological targets

Medicinal chemistry can provide tools for deep understanding of interesting molecules (biological targets):
• to perturb function in complex systems;
• to image activity of the target;
• to identify “lead compounds” to advance to therapeutics

Pathways for development:

Aims
• Generalizable knowledge
• Publish/grants
• Intellectual property
• Clinical applications
The Drug Development Pipeline

TARGET DISCOVERY -> TARGET VALIDATION -> LEAD ID/ OPTIMIZATION -> PRECLINICAL STUDIES -> PHASE I-III -> REGULATORY APPROVAL

ICTR and UW Resources

Institute for Clinical and Translational Research
UNIVERSITY OF WISCONSIN–MADISON
UW Drug Discovery and Development Resources

- **UW Office of Campus Research Cores (OVCRGE)** – searchable database of approximately 114 Cores; 559 Resources; and 430 Services. **Director:** Isabelle Girard; research.wisc.edu/research-cores

- **Waisman Biomanufacturing** – GMP production of biologics for human clinical trials, plasmid DNA, recombinant proteins, cell therapeutics, viral vectors and vaccines, aseptic filling. **Managing Director:** Carl Ross; gmpbio.org

- **Wisconsin Center for NanoBioSystems (WisCNano)** promotes collaborative research efforts in nanomedicine. **Faculty Contacts:** Seungpyo Hong, Glen Kwon, Lingjun Li, and Sandro Mecozzi; pharmacy.wisc.edu/wiscnano

- **Zeeh Pharmaceutical Experiment Station** – expertise in formulation characterization, drug delivery, and stability evaluation. **Facility Director:** Ed Elder pharmacy.wisc.edu/zstation
UW Carbone Cancer Center (UWCCC) Drug Development Core (DDC)

- **Small Molecule Screening Facility (SMSF)** – libraries totaling more than 400,000 compounds, along with computational expertise for modeling of drug-target interactions. **Facility Manager:** Gene Ananiev

- **Cancer Pharmacology Lab** – development and conduct of bioanalytical assays to support pre-clinical experiments and human clinical trials. **Facility Contact:** Gene Ananiev

- **Medicinal Chemistry Center (MCC)** – example services include synthesis of lead and probe molecules for target ID, hit-to-lead optimization, and library construction. **Facility Manager:** John Feltenberger

- **Faculty Leaders:** Michael Hoffmann, Weiping Tang and Ron Burnette

[link] cancer.wisc.edu/research/ddc
National Center for Advancing Translational Sciences (NCATS) Resources

• **Division of Pre-Clinical Innovation (DPI)** - plans, conducts and uses both internal and contract resources to advance collaborative research projects across the pre-clinical phases of the translational science spectrum. [ncats.nih.gov/preclinical](ncats.nih.gov/preclinical)

• **Therapeutics for Rare and Neglected Diseases (TRND)** – clinical and pre-clinical resources for rare disease research. [ncats.nih.gov/trnd](ncats.nih.gov/trnd)

• **Assay Development and Screening Technology (ADST)** – development of innovative assay designs and chemical library screening methods. [ncats.nih.gov/preclinical/drugdev/assay](ncats.nih.gov/preclinical/drugdev/assay)

• **New Therapeutic Uses** program – discovering new therapeutic uses for existing molecules [ncats.nih.gov/ntu](ncats.nih.gov/ntu)

• **Core Technologies at NCATS** - resources such as automation, compound management, analytical chemistry and informatics. [ncats.nih.gov/preclinical/core](ncats.nih.gov/preclinical/core)
Academic Drug Development Resources

TART DISCOVERY
TARGET VALIDATION
LEAD ID/ OPTIMIZATION
PRECLINICAL STUDIES
PHASE I-III
REGULATORY APPROVAL

UW Departments
Wisc Nano
CCC-SMSF/Pharmacology
ICTR Clinical Research Unit
CCC-DDC
IND/IDE consulting (preclinical – approval)

Local (UW)
Med Chem Center
Zeeh Pharm
Waisman Bio

NIH Assay/Development
NIH New Therapeutics Uses
Rare Diseases

NIH/NCATS
NHLBI SMARTTT
Why consider partnerships?

Partnerships can bring substantial new insight, resources and technology to a translational problem.

Type of partnership may depend on the long term goals

• Academic biology/medicinal chemistry partnerships can lead to probes, drugs or imaging reagents to advance mechanistic studies;

• Industrial partnerships can lead to viable drug development. Academia can play a key role in providing understanding of disease mechanism, industry can provide expertise in drug development.
Industry- academic partnerships

- Most drug development projects fail due to lack of efficacy—e.g. insufficient understanding of the biological target and its role in disease.

- Academic research can provide a unique role in biological target validation—industry is recognizing importance of in-depth understanding of mechanism.

Cook et al, 2014; Nature Reviews 13:419
Reasons for lack of clinical efficacy

- Target linkage to disease not established or no validated models available: 40 (18%)
- Dose limited by compound characteristics or tissue exposure not established: 29 (13%)
- Indication selected does not fit strongest preclinical evidence: 20 (9%)
- Evidence from previous phase not robust enough: 11 (5%)

Percentage of all reported reasons (total number of projects: 28)

Cook et al, 2014; Nature Reviews 13:419
AZ-5 “Rs” of drug development

Focus on quality of target and understanding of its role in disease may reduce the efficacy failures

Right target
- Strong link between target and disease
- Differentiated efficacy
- Available and predictive biomarkers

Right tissue
- Adequate bioavailability and tissue exposure
- Definition of PD biomarkers
- Clear understanding of preclinical and clinical PK/PD
- Understanding of drug–drug interactions

Right safety
- Differentiated and clear safety margins
- Understanding of secondary pharmacology risk
- Understanding of reactive metabolites, genotoxicity, drug–drug interactions
- Understanding of target liability

Right patients
- Identification of the most responsive patient population
- Definition of risk–benefit for given population

Right commercial potential
- Differentiated value proposition versus future standard of care
- Focus on market access, payer and provider
- Personalized health-care strategy, including diagnostic and biomarkers

Cook et al, 2014; *Nature Reviews* 13:419
Challenges in academic-industry partnerships

Differences in motivations:
• Intellectual protection: Pressure to publish vs maintaining proprietary knowledge

Differences in experimental analysis
• Data reproducibility: 70% of academic discoveries cannot be reproduced in independent industry labs.

We need more efficient models for Technology Transfer, managing conflict of interest
ICTR Strategic Partnership in Precision Medicine Program

- In partnership with the SMPH Human Proteomics Program (HPP) we are seeking collaborations with established clinical and translational research programs to apply multi-omics profiling to identify biomarkers of therapeutic response.

Programs in Target Validation- under development

ictr.wisc.edu
Acknowledgments

• Rob Hagan, ICTR-Office of Therapeutics Discovery & Development (OTDD)
• Laura Hogan, ICTR-Science Editing
• Jennifer Golden, School of Pharmacy and Med. Chem. Center
• Laura Heisler, Dir. of Programming (WARF)
WARF Therapeutics: A Vision for Translation of UW-Madison & Morgridge Institute for Research Discoveries

Jonathan R. Young
Head of WARF Therapeutics
My Scientific Journey

Education
- B.S. Chemistry from the University of Minnesota-Duluth
- Ph.D. from Michigan State University under Assistant Professor John Stille
- Merck and NIH Post-doctoral fellow at University of Wisconsin-Madison with Professor Steven Burke

Industry experience
- Merck Research Laboratories, Director (19 years)
- Celgene, Director (4 years)
- Regulus Therapeutics, Vice President (1 year)
- Head of WARF Therapeutics
>20 Years of Medicinal Chemistry in Pharma and Biotech

- >50 Publications & patents

- 8 Clinical candidates
  - GPCR, Kinases
  - CNS, oncology, hematology, autoimmune, obesity

- Experienced in small molecule, PROTAC, RNA drug modalities
And in my spare time…

“Glacial Trail 50 mile” trail race in Greenbush Wisconsin

“Reach the Beach” relay race with the Merck Running club
Pillars of WARF Therapeutics: Invest - Develop - Partner

- **Mission:** To partner with UW and MIR Principal Investigators (PIs) interested in translational research, invest to discover & develop novel drug like molecules that modulate validated targets and improve human disease, and partner with bio-centric companies to develop and commercialize.

- **WARF Therapeutics:** A team of industry trained “Drug Hunters” with expertise in navigating the pre-clinical drug discovery space.

- **Aspirational Goals & Benefits:**
  - Continue the UW legacy & deliver novel medicines to patients with unmet medical needs
  - Revenue stream for PIs, UW, and WARF
WARF Therapeutics Wants to Connect With You (Early & Often)!

- If you are doing disease related research including validating targets & developing therapeutic translational hypotheses, please contact me!
  - Phenotypic programs

- Working with WARF Therapeutics is optional

- Goals need to be mutually aligned

Jonathan Young
Head of WARF Therapeutics
jyoung@warf.org
608-960-9850
https://www.warf.org/therapeutics
The WARF Therapeutics Difference

- Establishing Drug Discovery capabilities adjacent to a world class academic center to advance validated targets to licensable assets

- Industry Drug Hunter professionals:
  - will implement industry-standard processes to increase probability of technical success
  - with knowledge of compound profile / data package that pharma expects
  - with demonstrated track records of success

- Committed funding from WARF
Outline

❖ Introduction

❖ WARF Therapeutics
  ▪ WARF Therapeutics Virtual Laboratory: Bridging the Gap
  ▪ 5R philosophy: industry tested portfolio management framework
  ▪ Working with WARF Therapeutics: Program submission
    ▪ Example submission: JAK2 for myeloproliferative disorders

❖ How to collaborate and contact WARF Therapeutics
**Overview of Drug Discovery**

**WARF Therapeutics Optimal Patent Strategy**

**Target Discovery**

- **1-2 years**
  - **Target ID**
  - **Target Validation**
    - A. Novel Target

**Preclinical Drug Discovery**

- **1-2 years**
  - **Compound Screening**
  - **Hit to Lead ID**
    - B. 100’s of Small Molecule Screening hits

**Drug Development**

- **2-4 years**
  - **Lead Optimization**
  - **Development Candidate**
    - C. Novel composition of matter

- **5-8 years**
  - **IND**
  - **Tox**
  - **Phase I-II**
  - **Phase III**
  - **FDA Approval**

**Proposed Sequence of events:**

1. Pre-disclosure meetings (no paperwork required)
2. Disclose to WARF after completion of Target ID/Validation
3. WARF Therapeutics will invest in Preclinical Drug Discovery
4. Late Lead Optimization (LO) ideal time to file patent application
# Independent Pharma Models Not Sustainable

<table>
<thead>
<tr>
<th>Target Discovery</th>
<th>Preclinical Drug Discovery</th>
<th>Drug Development</th>
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</table>

- Independent Pharma Model
Collaborative Pharma Models: What Role does Academia Play?

- Collaborative: Pharma Drug Discovery & Development Model

- Majority of early discoveries occur in academic labs

- Issues:
  1. Cannot patent a target
  2. Pharma will not license an early stage target
  3. After publication pharma obtains information without a license
  4. Pharma requires a de-risked asset

Annual Reviews of Pharmacology and Toxicology 2019, 59, 15
Collaborative Pharma Models: What Role does Academia Play?

- Collaborative: Pharma Drug Discovery & Development Model

- Collaborative: Pharma Development Model

- How can Academia cross the “Valley of Death”?
Collaborative: Academia Pharma Development Model

Target Discovery  Preclinical Drug Discovery  Drug Development

Potential Licensable Asset  Early Lead- Late Lead- Development Candidate

Solution: Build drug discovery capabilities adjacent to academic centers

Investing in research, making a difference.
WARF Therapeutics Virtual Laboratory: Bridging the Gap between Novel UW Discoveries & Bio-Pharma

**Target Discovery UW & MIR PIs**
- Novel biological target
- Therapeutic hypothesis
- Rigorous target validation

**Preclinical Drug Discovery**
- Preclinical Drug Discovery Experts
- Small Molecule Design & Optimization
- Project Management
- Novel Intellectual Property (IP)

**Drug Development Pharma/Biotech Partners**
- IND Tox
- Clinical Trials
- NDA

**Institute for Clinical and Translational Research (ICTR)**
- Preclinical research support

**Sanford Burnham Prebys Research Institute**
- Risk/reward sharing partner
- Early Discovery
- MSA signed

**Pharmaron/Wuxi CRO**
- Flexible resource (FFS)
- Late Discovery
- MSA signed

**High Potential Licensable Assets**
- Novel Hits
- Early Leads
- Late Leads
- Clinical Candidate

Investing in research, making a difference.

Jonathan Young - January 2019
Incentives for UW PIs: Invest - Develop - Partner

- **Partnering** (collaboration) and **investment** will move validated targets to a high value **developed** chemical asset

- Potential for NIH grant funding (near-term) and **inventor or innovator shares** (long-term) if licensed

- Opportunity to work with industry trained Drug Hunters and BD professionals

- Relieve patient suffering and cure disease
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❖ How to collaborate and contact WARF Therapeutics
FDA Approvals Declined During Despite Increased R&D Spending

- Late stage attrition rates increased over this time period
Lessons learned from the fate of AstraZeneca's drug pipeline: a five-dimensional framework
Nature Reviews Drug Discovery 2014, 13, 4
"Disciplined approach to drug discovery and early development"
Science Translational Medicine 2016, 8 (349), 1
"Understanding drug targets: no such thing as bad news"
Drug Discovery Today, 2018, 23, 1925

75% of Program Failures Attributed to Insufficient Knowledge of Target

New Portfolio Strategy: Invest early in basic biology, prioritize opportunities that have the highest degree of validation, a solid therapeutic hypothesis, deemed to be safe, and will be differentiated from the standard of care.

Potential Impact: New portfolio strategy combined with a high quality chemical asset will yield a licensable asset
FDA Approvals as an Industry Have Increased Which is “Correlated” With New Industry Strategies
Industry “Lessons” Influence WARF Therapeutics Portfolio Selection and Management Process

- The Right Target
  - Strong link (human genetics) between target & disease
  - Strong Target Validation
  - Available & predictive biomarkers

- The Right Tissue
  - Adequate drug exposure in tissue of interest
  - Defined PD biomarkers
  - Clear understanding of PK/PD/functional relationships

- The Right Safety
  - Understanding ALL on-target modulation effects (TI)

- The Right Patients
  - Know how to identify and stratify patients

- The Right Commercial Potential
  - Differentiated versus standard of care (SOC)
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    - Example submission: JAK2 for myeloproliferative disorders

- How to collaborate and contact WARF Therapeutics
Message to PIs: Interact with WARF Therapeutics Early & Often

- Pre-submission: PI and WARF Therapeutics to have regular meetings
  - Review program data, identify gaps, plan next steps

- Submission Process to WARF Therapeutics (after Target Validation)
  1. PI submits IDR & “Program Nomination Form”
  2. Formal presentation made to Scientific Advisory Board
  3. Program Decision & Prioritization
     - If Program accepted
       - Develop work plan, Go / No Go decisions, timelines
       - Discuss and agree on public disclosure/publication plan
       - Determine model, allocate resources
     - If Program not accepted
       - Provide feedback & rationale
       - Suggest experiments that could increase chance of acceptance

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“Activating mutation in the tyrosine kinase JAK2 in polycythemia vera, essential thrombocythemia, and myeloid metaplasia with myelofibrosis”
Gilliland, Levine et al, Cancer Cell, 2005, 7, 387.

“Acquired mutation in the tyrosine kinase JAK2 in human myeloproliferative disorders”

“Gain of function mutation of JAK2 in Myeloproliferative Disorders”

“A unique clonal JAK2 mutation leading to constitutive signaling causes polycythemia vera”

“The JAK2V617F tyrosine kinase mutation in myelofibrosis with myeloid metaplasia: lineage specificity and clinical correlates”

**Polycythemia vera** - Increased red blood cell (RBC) production, thickening of blood, splenomegaly, risk of clotting & stroke
**JAK Biology and Their Key Role in Hematopoiesis**

- JAK isoforms include JAK 1, 2, 3, and TYK2
- Non receptor tyrosine kinases involved in signal transduction
- JAK-STAT pathway is critical for proliferation and differentiation in hematopoietic lineages
**Program Nomination Form:**
*Executive Summary*

**Name/Department of Principal Investigator:** Jonathan Young, Merck-Boston

**Target and Therapeutic Indication:** JAK2 for MPD’s

**Date of Submission (Month/day/year):** 2005

<table>
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<th>The Right</th>
<th>Information Requested and to be filled in from Principal Investigator (PI), WARF Therapeutics, or Consultant</th>
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</table>
| **Target** | 1. JAK2\textsuperscript{V617F} activating mutation found in high proportion of patients with MPD (~90% in PCV, ~50% with ET and PMF)  
2. In vitro gain of function (GOF) JAK2\textsuperscript{V617F} led to constitutively activated EPO-JAK2 pathway (p-JAK2 and p-STAT5); responsive to JAK inhibition  
3. In vivo GOF recapitulated a polycythemia vera phenotype: increased hematocrit (hct), red cell mass, splenomegaly |
| **Tissue** | 1. Jak kinases are expressed ubiquitously including bone marrow, peripheral blood, spleen  
2. Potential proximal (target engagement) biomarkers include p-JAK2, p-STAT5, or circulating JAK2\textsuperscript{V617F} allele  
3. Functional biomarkers include erythroid progenitors/reticulocytes (early readout), hct (later time point readout), spleen size |
| **Safety** | 1. Prolonged “on-target” inhibition of EPO-JAK2 signaling could lead to anemia or thrombocytopenia  
2. Pan-JAK inhibition could lead immunosuppression and increased risk of infection |
| **Patients** | 1. Patients can be stratified primarily by the WHO classification and diagnostic criteria  
2. JAK2 mutational status could have utility |
| **Commercial Potential** | 1. PCV: Standard of care (phlebotomy, aspirin, hydroxyurea) extends median survival from 18 months to >15 years. Key question for regulators is what are acceptable registration endpoints? Do you need to demonstrate a survival advantage? Could phlebotomy independence be used?  
2. PMF: bone marrow transplant is potentially curative, not all patients meet the requirement, survival 18-36 months |
| **Modality** | 1. **Small molecule**  
2. Ideally, the compound will be highly selective for JAK2 over other isoforms and preferably mutant selective |
The Right Target: JAK2\textsuperscript{V617F} Leads to Constitutive Pathway Activation and EPO Independent Growth

- JAK2\textsuperscript{wt} cells require EPO for activation
- JAK2\textsuperscript{V617F} cells constitutively activated
- BaF/3 cells (JAK2\textsuperscript{wt}) require EPO for growth
- BaF/3 cells (JAK2\textsuperscript{V617F}) growth EPO independent

The Right Target: Knockout of JAK2 in Patient-Derived Cells Reduces Erythroid Colony Expansion

- Erythroid colonies from PCV patient-derived cells expand spontaneous in an EPO independent manner
- JAK2 siRNA reduces erythroid colonies in PCV cells and in normal cells under EPO stimulation
- In summary, data supports key role of JAK2 in MPD and compelling in vitro Target Validation

The Right Target: GOF Studies in Mice Led to Clinical PCV Phenotype

Harvest bone marrow from WT donor mouse after 5-FU treatment

Transduce with retrovirus

Transplant into lethally irradiated WT recipients

Gilliland, Levine et al, Cancer Cell, 2005, 7, 387.

- JAK2 V617F Mutant led to increased:
  1. erythroid progenitors
  2. Hematocrit
  3. Spleen weight

- In vivo Target Validation achieved

![Graph showing relative values of CD71+ TER119+ in Spleen, Spleen BLI, Spleen Weight, and Hematocrit for Vehicle and Normal B6 groups.](image-url)
Evolution and Profile of Development Candidate 4 for MPD

- Compound 4 is a potent dual (JAK2/TYK2) inhibitor
- Potent inhibition of pSTAT5 in cells and in mice
- Drug exposure suitable for in vivo testing

<table>
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<tr>
<th>Enzymatic Selectivity</th>
<th>Cellular Selectivity</th>
<th>Acute PK/PD Assay Establishes Target Engagement Correlation</th>
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<tbody>
<tr>
<td>JAK2&lt;sup&gt;WT&lt;/sup&gt; IC&lt;sub&gt;50&lt;/sub&gt; (nM)</td>
<td>pSTAT5&lt;sup&gt;V617F&lt;/sup&gt; (HEL) IC&lt;sub&gt;50&lt;/sub&gt; (nM)</td>
<td>(C&lt;sub&gt;tot&lt;/sub&gt;) pSTAT5&lt;sup&gt;WT&lt;/sup&gt; IC&lt;sub&gt;50&lt;/sub&gt; (nM)</td>
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<tr>
<td>Fold-selectivity JAK1</td>
<td></td>
<td>(C&lt;sub&gt;unb&lt;/sub&gt;) pSTAT5&lt;sup&gt;WT&lt;/sup&gt; IC&lt;sub&gt;50&lt;/sub&gt; (nM)</td>
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<tr>
<td>Fold-selectivity JAK3</td>
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<td>In vivo PK/PD</td>
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<td>Fold-selectivity TYK2</td>
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<td>Acute PK/PD IC&lt;sub&gt;50&lt;/sub&gt;</td>
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<td>0.08</td>
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<td>3000</td>
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In vivo PK/PD

- IC<sub>50</sub> for pSTAT5<sup>WT</sup>

In vivo PK/PD Assay Establishes Target Engagement Correlation

- 9 mpk
- 18 mpk
- 36 mpk

Reference:
3 Days Dosing / 4 Day Holiday of Compound 4 Was Safe & Efficacious

- 3 Days dosing required to eliminate mutant allele (efficacy)
- 3 days dosing eliminated NK cells (safety)
- 4 day recovery repopulated NK cells
- *Compound 4 was chosen as clinical candidate*
WARF Therapeutics Wants to Collaborate with You!

- WARF Therapeutics will focus investment in your novel well-validated targets, that possess a strong therapeutic hypothesis, in areas of high unmet medical need

- WARF Therapeutics will be a virtual drug discovery laboratory adjacent to the world class UW campus
  - drug hunters & business development professionals
  - 5R portfolio management framework
  - key opinion & advisory board leaders

- Committed funding from WARF
Acknowledgements

— Allen, Lori
— Balistreri, Becky
— Baranczyk, Shauna
— Burmania, Jeanine
— Cagan, Leigh
— Carson, Joshua
— DeTienne, Andy
— Diaz, Rafael
— Fuller, Jacqueline
— Heisler, Laura
— Mayfield, James
— Nagel, John
— Najdowski, Chris
— O’Connor, Matt
— Werner, Beth
— Yasiri Moe, Jeanan
— Younger, Sally
Thank you all for attending!

Happy to answer any questions!
WARF Therapeutics Wants to Connect With You (Early & Often)!

- If you are doing disease related research including validating targets & developing therapeutic translational hypotheses, please contact me (or I may call you first) to set up a time to discuss your science!

Jonathan Young  
Head of WARF Therapeutics  
jyoung@warf.org  
608-960-9850  
https://www.warf.org/therapeutics
WARF Therapeutics Virtual Laboratory: Bridging the Gap between Novel UW Discoveries & Bio-Pharma

**Target Discovery UW & MIR PIs**
- Novel biological target
- Therapeutic hypothesis
- Rigorous target validation

**Preclinical Drug Discovery**
- Preclinical Drug Discovery Experts
- Small Molecule Design & Optimization

**Drug Development Pharma/Biotech Partners**
- IND Tox
- Clinical Trials
- NDA

**Sanford Burnham Prebys Research Institute**
- Risk/reward sharing partner
- Early Discovery
- MSA signed

**Pharmaron/Wuxi CRO**
- Flexible resource (FFS)
- Late Discovery
- MSA signed

**Institute for Clinical and Translational Research (ICTR)**
- Preclinical research support

**High Potential Licensable Assets**
- Novel Hits
- Early Leads

**Licenschable Assets**
- Late Leads
- Clinical Candidate

Investing in research, making a difference.

Jonathan Young - January 2019 35
Overview of the Drug Discovery Process & Timelines

Target Discovery
- Target ID
- Target Validation
- Compound Screening
- Hit to Lead ID
- Lead Optimization
- Development Candidate

Preclinical Drug Discovery
- IND
- Tox
- Phase I-II
- Phase III

Drug Development
- FDA Approval

Timeline:
- Target Discovery: 1-2 years
- Preclinical Drug Discovery: 1-2 years
- Drug Development: 2-4 years
- Drug Development: 5-8 years
Definition of Target Validation

**Target Validation:** the process of physiologically, pathologically, and pharmacologically evaluating a biomolecule. Might be performed at the molecular, cellular, or whole animal level.
**Innovator**: Individuals (or teams) that proposed a program that was accepted into WARF Therapeutics portfolio

**Inventor**: Simply stated, “inventorship is who conceived the invention.”
- Most patent filings in support of WARF Therapeutics will be composition of matter applications
- Inventorship is a legal determination made by patent attorneys

**Incentives for UW PI’s**
- Innovator or inventor shares will be given to UW PI’s when milestone or royalty income is realized
- Innovator and Inventor Shares Are Equivalent
Historically, Academia and Industry are incentivized differently
- Academicians: driven and evaluated by grants and publications
  - Rewarded to disclose data
- Pharma-Industry: driven to generate & protect proprietary information
  - Strong business case for strategic data disclosure
  - Early disclosures could diminish competitive advantage & invite competition

How do we balance these competing forces?
- Working with Warf Therapeutics is optional
- PI’s with translational research goals are a good fit
- Disclosure timelines will be discussed and agreed to prior to collaboration initiation and reviewed periodically

Are there alternative mechanisms to reward/incentivize PI participation?
- Potential grant funding with academic CRO
- Warf Therapeutics Inventor or Innovator shares
Potential Research Models for WARF Therapeutics Programs

- **Contract Research Organization (CRO) Model**
  - Medicinal chemistry, in vitro and in vivo assays executed at CRO
  - Data is transparently shared with the PI
  - PI involvement in drug discovery phase is encouraged but not required

- **Academic CRO Shared Risk Model**
  - Shared investments, decision rights, and milestone/royalties
  - Grant proposals to *generate funding for both UW and CRO*
  - Potential timeline delays

- **Biotech/Pharma Shared Risk Model**
  - Benefits could include:
    - Securing development partner early
    - Access to compound collection, screening capabilities and/or other resources
    - Expertise in specific drug modalities (mRNA, Protac, biologics)
Risk-Sharing Partnership Ideal for WARF Therapeutics Virtual Laboratory

<table>
<thead>
<tr>
<th>Drug Discovery Capabilities</th>
<th>Intellectual Contributions</th>
<th>Investment</th>
<th>Joint Development</th>
<th>Fee for Service</th>
<th>Build to Buy/License</th>
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**Identify Actives**
- Identification of Actives
- Confirmation of Hits
- Identification of Chemical leads

**Strengths**
- Proven expertise in “early” DD, working with academic PI’s

**Ideal Fit for WARF Therapeutics**
- Portfolio Partnership with Sanford Burnham Prebys: ideal for Early Drug Discovery (contracts pending)
- Partner with CRO for “flexible resourcing” & Late Drug Discovery needs (contracts pending)
- Strive to secure an early Biotech / Pharma partnership for select programs
Program Nomination Form: Executive Summary

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<thead>
<tr>
<th>The Right</th>
<th>Information Requested and to be filled in from Principal Investigator (PI), WARF Therapeutics, or Consultant</th>
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<tbody>
<tr>
<td>Target</td>
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<td>Tissue</td>
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<td>Commercial Potential</td>
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<tr>
<td>Molecule (Modality)</td>
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Name/Department of Principal Investigator:
Target and Therapeutic Indication:
Date of Submission (Month/day/year):
<table>
<thead>
<tr>
<th>The Right</th>
<th>Information Requested and to be filled in from Principal investigator (PI), WARF Therapeutics, or Consultant</th>
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| **Target** | 1. Specify the target  
2. Specify the intended or potential disease(s) and the therapeutic hypothesis  
3. Provide the existing (and/or planned) target validation data: for example target modulation-function relationships with either CRISPR, siRNA, or small molecule pharmacological modulation (in vitro and/or in vivo), human genetic-disease data |
| **Tissue** | 1. Specify which tissues where the target is expressed  
2. Specify which tissue is the intended target  
3. What potential target engagement and/or functional biomarkers and if these assays currently exist, would need to be developed or validated? |
| **Safety** | 1. Specify known target related pharmacology that could impact the therapeutic index in patients  
2. Specify proteins with high sequence homology |
| **Patients** | 1. Specify what patients would be targeted for this drug  
2. How would patients be identified or stratified? |
| **Commercial Potential** | 1. Specify what is the Standard of Care (SOC) for this disease  
2. How will a drug for this target differentiate versus SOC  
3. Specify the competitive landscape for this target or indication? |
| **Molecule (Modality)** | 1. Specify the preferred modality (small molecule, PROTAC, anti-sense, siRNA) |

Instructional template available for download from WARF Therapeutic website.
<table>
<thead>
<tr>
<th>Advisory Board Members</th>
<th>Governance Board Members</th>
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<tbody>
<tr>
<td>Deepak Dalvie PhD (Sr. Director Celgene, Pfizer)</td>
<td>Howard Bailey, MD (Director, Carbone Cancer Center)</td>
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<tr>
<td>Mark Deeg MD/PhD (CMO, Eli Lilly)</td>
<td>Gordon Brunner (WARF Trustee; CTO P&amp;G)</td>
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<tr>
<td>Chris Dinsmore PhD (VP FORMA; Executive Director, Merck)</td>
<td>Deborah Keller (WARF Trustee; CEO Covance)</td>
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<td>Paul Secrist PhD (VP LifeMine Therapeutics, AstraZeneca, Merck)</td>
<td>Richard Moss, PhD (Senior Associate Dean, SMPH)</td>
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<td>Steven Swanson, PhD (Dean, School of Pharmacy)</td>
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