Drug Discovery and Repurposing
Forming Partnerships

CTSI – Drug Development Collaborative Workshop

Clinical and Translational Science Institute

Our vision

To create a borderless, complementary and synergistic research environment in southeast Wisconsin to translate discoveries into better health for our citizens while simultaneously providing comprehensive educational and training programs to develop the next generation of clinical and translational researchers.

Nucleating Workshops

Exploring the Metabolic Syndrome:
Basic Mechanisms, Clinical Implications and Community Impact
Wednesday, February 9, 2011

Rehabilitation Research Workshop
Wednesday, May 26, 2010
12:00 – 4:00 pm Marquette University

CTSI-Cancer Center Workshop

Future Directions & Opportunities for Cancer-related Research Collaboration
Friday, December 16, 2011
CTSI Pilot Grant Award Program

Funding totals

<table>
<thead>
<tr>
<th>Year</th>
<th>Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>$287,158</td>
</tr>
<tr>
<td>2010</td>
<td>$380,000</td>
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<tr>
<td>2011</td>
<td>$576,000</td>
</tr>
<tr>
<td>2012</td>
<td>$679,000</td>
</tr>
</tbody>
</table>

2012 Pilot Awards: Convergence of Disciplines

- Medicine
- Biomedical Informatics
- Rehabilitation
- Psychology
- Economics
- Nursing
- Dentistry
- Public Health
- Computer Science
- Business
- Physical Therapy
- Exercise Science
- Biomedical Engineering
- Genetics
- Physics
- Chemistry
- Mechanical Engineering
- Psychiatry

Participants - Institution/Organization

Number of Participants: 20 organizations

Participants: 125 participants
### New NIH/NCATS Pilot Program - “Discovering New Therapeutic Uses for Existing Molecules Initiative”

- Designed to develop partnerships between pharmaceutical companies and the biomedical research community to advance therapeutic development
- NCATS has partnered initially with Pfizer Inc., AstraZeneca and Eli Lilly and Company
- The pilot program matches researchers with a selection of 20 molecular compounds to test ideas for new therapeutic uses to identify promising new treatments for patients
- In Fiscal Year 2013, for the initial pilot phase, NCATS will provide up to $20M to fund two- to three-year staged, cooperative agreement research grants
In Preparation for NIH Funding Opportunities

What are our strengths and needs for drug:

• Repurposing
• Discovery

Michael J. Barratt, PhD

• Dr. Barratt earned his degree in Biochemistry from Exeter College, Oxford University and obtained his PhD in Molecular Sciences from King’s College, London
• Dr. Barratt is currently the Program Coordinator on an international team of scientists led by Dr. Jeffrey Gordon at Washington University in St Louis to investigate new ways to diagnose, treat and prevent malnutrition in infants and children
• Previously Dr. Barratt served as Senior Director of Pfizer’s Indications Discovery Unit; Senior Director, Academic & External Alliances and Senior Director, Molecular Pharmacology for Pfizer R&D
• Dr. Barratt is co-editor and contributing author for the first book on Drug Repositioning, entitled Drug Repositioning – Bringing New Life to Shelved Assets and Existing Drugs (Wiley, May 2012)

Drug Repositioning: Forging Academic-Industry Partnerships

Michael J. Barratt, PhD.
CTSI – Drug Development Collaborative Workshop
May 31, 2012
Presentation outline:
- Why are drugs failing?
- Drug repositioning: the business case
- How the pharmaceutical industry is approaching repositioning
- Next Generation Industry-Academic Partnerships
  - Drug repositioning: a unique opportunity for risk sharing partnerships with academia and other not-for-profits
  - Orphan Diseases: a growing opportunity for industry-academia partnerships
- Lessons learned
  - Opportunities & Challenges

Drug candidates (New Medical Entities, NME) are failing at an alarming rate – 95% of NMEs entering Phase 1 do not make it to market.

- Principal reasons for failure (% of total Phase failures)\(^1\):
  - Safety, toleration in Phase 1 (~40%)
  - Efficacy/differentiation in Phase 2 & 3 (~60%)

- Loss in NME productivity and Pharma revenue highlighted by fact that 3 in every 4 US prescriptions in 2010 were for generic drugs

\(^1\)CMR International, a Thomson Reuters Business. 2010 Global R&D Performance Metrics Program

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Indication</th>
<th>Company</th>
<th>Status when Terminated</th>
<th>Reason for Termination</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVE-5530</td>
<td>Hypercholesterolemia</td>
<td>Sanofi-A</td>
<td>Phase III</td>
<td>Lack of efficacy</td>
</tr>
<tr>
<td>Axitinib</td>
<td>Pancreatic cancer</td>
<td>Pfizer</td>
<td>Phase III</td>
<td>Lack of efficacy</td>
</tr>
<tr>
<td>Candesartan cilexetil</td>
<td>Diabetic retinopathy</td>
<td>Takeda</td>
<td>Phase III</td>
<td>Lack of efficacy</td>
</tr>
<tr>
<td>Dexvanlafaxine succinate</td>
<td>Fibromyalgia</td>
<td>Wyeth</td>
<td>Phase III</td>
<td>Lack of efficacy</td>
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<tr>
<td>Dirucotide</td>
<td>Multiple sclerosis</td>
<td>Lilly/BioMS</td>
<td>Phase III</td>
<td>Lack of efficacy</td>
</tr>
<tr>
<td>DTP-HepB-Hib</td>
<td>Diphtheria, tetanus, Hep B, Hib</td>
<td>Sanofi-A</td>
<td>Phase III</td>
<td>Reallocation of resources</td>
</tr>
<tr>
<td>Esreboxetine</td>
<td>Fibromyalgia</td>
<td>Pfizer</td>
<td>Phase III</td>
<td>Lack of superiority over existing drugs</td>
</tr>
<tr>
<td>Imagabalin</td>
<td>Anxiety</td>
<td>Pfizer</td>
<td>Phase III</td>
<td>Lack of superiority over existing drugs</td>
</tr>
<tr>
<td>Liprotamase</td>
<td>Cystic fibrosis</td>
<td>Altus</td>
<td>Phase III</td>
<td>Reprioritisation of portfolio</td>
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<tr>
<td>Mepolizumab</td>
<td>Hypereosinophilic syndrome</td>
<td>GSK</td>
<td>MAA Filed</td>
<td>Insufficient Benefit-Risk</td>
</tr>
<tr>
<td>Resatorvid</td>
<td>Sepsis (TLR4 inhibitor)</td>
<td>Takeda</td>
<td>Phase III</td>
<td>Lack of Efficacy</td>
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<tr>
<td>Rosiglitazone</td>
<td>Alzheimer’s</td>
<td>GSK</td>
<td>Phase III</td>
<td>Lack of efficacy</td>
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<tr>
<td>Saredutant</td>
<td>Depression</td>
<td>Sanofi-A</td>
<td>Phase III</td>
<td>Negative study in combination with escitalopram</td>
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<tr>
<td>Sarpogrelate</td>
<td>Prevention of recurrent stroke</td>
<td>Mitsubishi Tanabe</td>
<td>Phase III</td>
<td>Lack of efficacy</td>
</tr>
<tr>
<td>Tanezumab</td>
<td>OA pain</td>
<td>Pfizer</td>
<td>Phase III</td>
<td>Safety – exacerbation of symptoms</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>NSCLC</td>
<td>AZ</td>
<td>NDA / MAA Filed</td>
<td>No survival advantage</td>
</tr>
</tbody>
</table>
• Why reposition (repurpose/reprofile)*?
  
  1. Saves time and money on early stage discovery, preclinical studies & safety/toleration
     - De novo drug discovery project from start to completion of Phase 1 (first-in-human) takes 5-7 years and $10M-50M

*Refers to marketed drugs or candidates terminated after Phase 1

• Why reposition?
  
  2. Approval rates are 3x higher!

  Development Success Rates for NMEs and Repurposed Candidates (2004-2009)

  - Starting Phase 2: 15%
  - Starting Phase 3: 50%
  - First submission to market: 90-95%
  - First approval to market: 90%

  Bayer – Common Mechanisms Research Group
  • Numerous others

  - Entrepreneurial, outward-looking

• Industry Approaches to Repositioning
  
  - ‘Opportunistic’, case-by-case:
    • Pfizer, Sildenafil - ED
    • Celgene, Thalidomide – ENL, MM
    • Merck, Finasteride – Male Pattern Baldness
    • Numerous others

  - ‘Systematic’, portfolio wide, dedicated groups:
    • Pfizer - Indications Discovery Unit
    • Novartis - New Indications Discovery Unit
    • Bayer – Common Mechanisms Research Group
    • AstraZeneca – New Opportunities iMED
    • Entrepreneurial, outward-looking
• Next Generation Industry-Academic Partnerships in Drug Repositioning

• Premise
  - There are many ideas outside Pharma to harness
  - Lack of budget/inefficiencies in building internal R&D capacity

• Mutual Benefits
  - Access to proprietary Pharma data and compounds
  - Academic investigators with access to unique patient populations & disease knowledge can inform new uses or treatment populations for existing biopharmaceuticals
  - RFPs will lead to novel ideas & collaborations aligned with both the academic investigator and Pharma interests
  - This results in new projects for Pharma and a means to prosecute them
  - Conduit for investigators to access broader Pharma resources (e.g. PK/PD, formulation etc.) and a means to get potential therapies into their patients quicker
  - Potentially enhanced competitiveness for subsequent NIH grant funding

• Examples:
  - Pfizer/ Washington University in St. Louis ~ 500 clinical compounds for repurposing
  - GSK ‘Pharma in Partnership’ program - Academic Discovery Performance Unit
    Academic researchers can either:
    - Propose novel ideas to evaluate the therapeutic potential of a range of GSK early clinical stage assets ('indication challenges')
    - Propose novel therapeutic candidates and are seeking a partner for further development
  - AstraZeneca/ UK Medical Research Council – 22 compounds for repurposing
  - Lilly ‘Open Innovation Drug Discovery’ program:
    – External researchers submit molecules for consideration by Lilly scientists for screening in specific phenotypic & target based assays.
    – TargetD2 Screening Panel: 6 target based assays
    – Tuberculosis screening module
    – If the submitted molecule is of interest, the company may enter into an in-licensing or collaboration agreement.
  - Bayer Healthcare ‘Grants4Targets’ initiative with academia
    – Focus on novel target validation and new clinical biomarkers
    – Oncology, cardiology, hematology, and gynecology
  - Pfizer Centers for Therapeutic Innovation/ UCSF, UCSD, BU + 7 NYC Research Hospitals – collaboration to discover develop biologic candidates from early research to Proof-of-Mechanism in humans
    – Access to funding, proprietary phage-display libraries, peptide libraries and associated technologies for rapidly generating antibodies & other modalities to be used as probes against the novel targets flagged by university researchers
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• NCATS NIH Industry Pilot Program: Discovering New Therapeutic Uses for Existing Molecules
  – Funds research to explore new uses for proprietary Agents from Pharma across a wide range of human diseases
  – Pfizer, Eli Lilly and AstraZeneca currently signed up
  – 20 Agents in the ‘pool’, all have human safety data (Ph1 or higher)
  – $20M funding in Fiscal 2013
  – CRA templates developed, covering IP/publication provisions, e.g.
    • Two-way non-exclusive, royalty free, worldwide license for use of IP for Research & Educational purposes
    • Pharma retains commercial rights to Pharma Inventions
    • Joint inventions/Academic Medical Center (AMC) Inventions: Pharma likely to have exclusive first option to acquire commercial license
    • Recognition of the importance of publication to the Academic Investigator
    • 30-60 day period for review of publications by Pharma, to enable patent filings (as needed) or restrict Confidential Information

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• Orphan Diseases – A Growing Opportunity for Industry-Academia Partnership?
  – US definition: Includes ‘Rare Diseases’ (<200,000 patients in the US - Rare Disease Act 2002) and also non-rare diseases ‘for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug (Orphan Drug Act, 1983)
  – Historically neglected by Pharma due to perceived lack of commercial return
  – Academics, foundations and Biotechs have driven disease understanding, patient advocacy and drug development
  – Orphan Drug Act designed to incentivize Pharma involvement
    • Clinical trial tax incentives
    • Fast track approval status; waived filing fees
    • Longer marketing exclusivity:
      – NCE = 5 years
      – New indication = 3 years
      – Orphan drug = 7 years

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• Orphan Diseases Act – Is it working?
  – Today there are > 800 orphan disease designations listed in the FDA database
  – Orphan drugs as proportion of total US approved:
    • 1998 - 1%, (10% from big Pharma in 2008-0)
    • 2009-2010 = 20%, 26% of these from big Pharma
  – Can be used as a strategy to expand into other indications and increase revenues
    • Imatinib – first-CML, now approved for 7 orphan disease ($4.65B in sales)
    • Epoetin alfa – anemia in chronic renal failure -> anemia associated with chemotherapy
    • Botulinum toxin A – hyperhidrosis -> wrinkles, spasms, dystonias
    • Rituximab – non Hodgkin’s lymphoma -> other B cell neoplasms, refractory RA
    • Infliximab – Crohn’s -> psoriasis, RA, UC
  – Increasingly attractive in ‘post-blockbuster’ era, especially with more biotherapeutics that enable premium pricing and longer market exclusivity (12 years)
  – Increasing emphasis on rare disease R&D in Pharma
    • Genentech acquire Genzyme
    • Pfizer, GSK establish rare diseases units

TRND, Partnership for Cures, Patient Advocacy Groups (PAGs) & Industry-Academic Alliances

- **Therapeutics for Rare & Neglected Diseases (TRND)**
  - NCRR project that acts as an incubator and catalyzes the development of new drugs for rare and neglected diseases. TRND stimulates drug discovery and development research collaborations among federal and academic scientists, nonprofit organizations, and pharmaceutical and biotechnology companies working on rare and neglected diseases.
  - More than a dozen active programs
- **Partnership for Cures, Patient Impact Initiative (PII) generates, selects and manages Rediscovery Research™ projects (24 currently funded)**
- **More than a dozen active programs**
- **Leukemia and Lymphoma Society (LLS) Therapeutic Acceleration Program (TAP)**
  - Capitalize on research advances LLS funded academic investigators
  - Catalyze Pharma/biotech interest in blood cancer therapies
  - Seek to lower regulatory and clinical development hurdles
- **MJFF – Repositioning drugs for PD – Call for proposals 2011**
  - $3M to fund successful repositioning proposals from both academia & industry
- **PKD Foundation – Accelerating Treatment for Patients (ATP)**
  - Disease Insight (Academia) – list of candidate targets/mechanisms
  - Existing compounds - Pharma
  - CRO - generate preclinical efficacy packages (harmonized models)
  - Pharma/biotech develops drug

Frequently Encountered Challenges at the Industry-Academia Interface

- Misalignment of interests
  - Focus on developing a drug vs. basic research
  - Lack of appreciation for cost/complexity/attrition in drug development
  - Value of asset – most of the cost & risk is in the clinical development, not the initial discovery
- Organizational dynamics/ change in industry
  - People and programs change – lack of continuity
    - Individual goals of context, relationships
    - Projects terminate for non-scientific reasons
  - Whole groups therapeutic areas change
  - Venture capital approach may offer alternative strategy (more control?) although this entails its own challenges!

Summary

- Reduced R&D productivity and variety of external pressures (regulatory, pricing, generics) are forcing Pharma to evolve
  - Leaner internal R&D groups, doing more with less (e.g. repurposing)
  - Extending focus from ‘mass market’ indications into Orphan indications & rare diseases
  - More work done ‘outside’ company walls
  - Opening the ‘doors’ through partnerships and alliances that would have not been entertained 5-10 years ago
- High degree of Pharma interest in ‘translationally-minded’ groups with access to unique patient populations & expertise
- PAGs are an excellent resource to link patients, academics, industry and regulators
### Industry considerations that can impact new indications/collaboration

<table>
<thead>
<tr>
<th>Opportunities</th>
<th>Challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong IP position (NCE/NBE)</td>
<td>Open IND needed to minimize risk of safety findings that could impact primary indication</td>
</tr>
<tr>
<td>Can leverage primary project team resources – cost &amp; time savings</td>
<td>High likelihood of attrition for efficacy &amp;/or safety pre-POC</td>
</tr>
<tr>
<td>Programs that have cleared Phase 1 and demonstrated human pharmacology represent excellent discovery opportunities to test novel targets</td>
<td>Access to old data packages and regulatory standards may require additional lic or PK studies</td>
</tr>
</tbody>
</table>
| Programs that have cleared Phase 1 and demonstrated human pharmacology provide improved probability of success in second indication (assuming hypothesis is valid & "on target") | Loss of patient equivalency - require validation on less robust (e.g. formulation/methods  
| (POC = Clinical Proof of Concept)                                           | models that allow direct comparison                                                                    |

### Structure-Based Drug Discovery

**Francis Peterson, PhD**

**Medical College of Wisconsin**

#### Projects and collaborations

- **Structure-based inhibition of chemokine activity**
  - Yu Chen – University of South Florida
  - Brian Schochet – University of California – San Francisco
  - Sam Hwang – Medical College of Wisconsin
  - Mike Dwinell – Medical College of Wisconsin

- **Small molecule agonists of the abiotic stress response in plants**
  - Sean Cutler – University of California - Riverside

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*POC = Clinical Proof of Concept*
**in silico screening for CXCL12 inhibitors**

Select 5 compounds for experimental validation

- Top 25 Hits

<table>
<thead>
<tr>
<th>ZINC ID</th>
<th>Compound Name</th>
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<tr>
<td>C02139869</td>
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<tr>
<td>C02567724</td>
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<td>C23443351</td>
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<td>C01667741</td>
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<tr>
<td>C02385849</td>
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</table>

**ZINC 310454 binds with micromolar affinity**

- in silico docking of ZINC 310454 to the CXCL12 sY21 binding pocket

**NMR structure of CXCL12:inhibitor complex**

- in silico model of the 310454:CXCL12 complex
  - ZINC ID 310454
  - Binds CXCL12
  - Blocks Ca**-flux

**References**

Veldkamp, CT et al., (2010) JACS

**In silico** screening for CXCL12 inhibitors

In silico screening of compounds from the ZINC virtual compound library.

ZINC 310454 binds with micromolar affinity

ZINC ID 310454

- Binds CXCL12
- Blocks Ca**-flux

NMR structure of CXCL12:inhibitor complex

NMR structure of the 310454:CXCL12 complex

Veldkamp, CT et al., (2010) JACS
NMR spectroscopy

- Biomolecular NMR facility
  - Established in 2001 by Biochem Dept.
  - Located in HRC basement
- State-of-the-art NMR equipment
  - Bruker Avance III 500 MHz
  - Bruker Avance II 600 MHz
  - Bruker DRX 600 MHz
  - All equipped with TXI or TCI [1H, 13C, 15N] cryoprobe
- Resource for biomolecular structure and dynamics
  - 3D structure determination
  - Target validation/binding site mapping
  - Structure-based ligand screening and K_d determination
  - Structure-activity relationship (SAR) by NMR

LEAP liquid handling robot

- Automated sample preparation for small molecule screening
- Located in TBRC 2nd floor

SampleJet

- Automated NMR sample changer
- Accommodates 500+ samples
- Delivery June of 2012

Protein Crystallography

- Macromolecular X-ray crystallography facility
  - Established in 1985 by Department of Biochemistry
  - Located in TBRC 2nd floor
- State-of-the-art robotic crystal screening
  - Hamilton Star for preparing crystallization screening buffers
  - Art Robbins Phoenix for nanoliter-scale 96-well screens
  - Art Robbins CrysCam for automated crystal imaging
  - Low vibration incubators and cold room for crystal growth
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**Protein Crystallography**

- 4th generation Rigaku X-ray diffractometer
  - MicroMax 007 X-ray generator
  - X-stream crystal cryocooler
  - R-AXIS IV++ image plate detector system

- Synchrotron access: Advanced Photon Source
  - LS-CAT membership since 2009 (MCW, Marquette and UWM; Brian Volkman, consortium leader); provides >35 days of shared beam time/yr
  - One fully tunable beamline and two fixed wavelength beamlines with MAR Mosaic CCD detectors

**Ligand/inhibitor screening**

- Flexstation 3 multimode microplate reader
  - 96/384-well plate based, with 8- or 16-channel automated pipettor
  - Fluorescence, FP, absorbance, luminescence
  - Optimized for use with FLPR calcium-sensitive dye for time-resolved fluorescence detection of intracellular Ca^{2+}
  - Measure IC_{50}, EC_{50} of agonists and antagonists

- Isothermal titration calorimetry
  - Microcal VP-ITC
  - Precise, direct measurement of ligand binding thermodynamics (K_d, ΔG, ΔH, ΔS, stoichiometry)

- Surface Plasmon Resonance
  - Biacore 3000 instrument
  - Real-time detection of ligand binding kinetics
  - Measure on/off rate constants, K_d, K_i

**Other shared biophysical instrumentation**

- Aviv spectropolarimeter (CD spectroscopy)
- PTI fluorescence spectrometer
- Applied Biosystems Voyager DE Pro MALDI MS

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**Summary**

1. **Resources Available**
   - NMR spectroscopy
   - Protein crystallography
   - Ligand/inhibitor screening

2. **Collaborations needed**
   - Medicinal chemistry

3. **Contact Information**
   - Francis Peterson
   - Medical College of Wisconsin
   - Department of Biochemistry
   - (414) 955-5777
   - fpeterso@mcw.edu
Preclinical Disease Models

John D. Imig, PhD
Department of Pharmacology & Toxicology
Medical College of Wisconsin

How to Decide on Preclinical Disease Models

- The Big Four:
  - Cancer / Cardiovascular / Neuroscience / Infectious Disease
- Time & Costs for Animal Models
- Measurements Required
- Clinical Applicability
- Market Size

First Steps

- Target identification
- Chemical compound / Antibody / Peptoid
- What is next?
The leap from test tubes and cell culture to animals

- Dosage
- Route of Administration
- Prevention versus Intervention
- Acute versus Chronic

Soluble epoxide hydrolase inhibitory (sEHi) activity:
sEHi activity was determined using PHOME assay.

Vascular reactivity: in coronary arteries using wire myograph.

Dosage: 3 mg/d or 10 mg/kg/d
Total amount = 120 mg
Route: i.p. osmotic pump
Intervention

Dosage: 1 mg/d or ~3 mg/kg/d
Total amount = 84 mg
Route: drinking water 25 mg/L
Prevention

Important Verification
- Plasma
- Urine
- Tissue / Brain Barrier
- Drug Metabolites

CDU
Plasma = 23 ng/ml
Metabolites: CDHU & CIUDA

AUDA
Plasma = 10 ng/ml
Urine = 38 ng/dl
Brain = 2 µmol/g
Metabolite: AUBA
The Unexpected - measurements that led to design of a new compound

How to Decide on Preclinical Disease Models
• The Big Four:
  – Cancer / Cardiovascular / Neuroscience / Infectious Disease
• Time & Costs for Animal Models
  • Market Size

Clinical vs. Experimental Measurements in Preclinical Disease Models
• Plasma, Urine, Imaging, Genetics, Histology,
  • Other clinical diagnostics based on disease
Pharmacology Drug Discovery Center

1. Our Capabilities today
   - Expert advise & assistance with moving from test tube & cell based studies to animal models of disease
   - Expert advice & assistance with preclinical animal models of disease
   - Conduct non-GLP pharmacokinetic & toxicity studies

2. Resources Available
   - Mass spectrometry facility
   - FLIPR-2 System – High throughput screening
   - Roche X-Celligence System – Screening cell functions
   - Building chemical synthesis facility

3. Collaborations needed

4. Contact Information
   a) 414-955-4785
   b) jdimig@mcw.edu
   c) http://www.mcw.edu/pharmacology/DrugDiscoveryCenter.htm

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Medicinal Chemistry and Lead Optimization

Subtype Selective GABA Ligands as Potential Therapeutic Agents

James M. Cook
Department of Chemistry & Biochemistry
University of Wisconsin-Milwaukee

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Diazepam

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### Action at BzR / GABA<sub>α</sub> Subtypes

<table>
<thead>
<tr>
<th>Subunit</th>
<th>Associated Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>α&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Sedation, ataxia anterograde amnesia, anticonvulsant (some), addiction (some)</td>
</tr>
<tr>
<td>α&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Anxiolytic; anticonvulsant (some); hypnotic (EEG) at higher doses; maybe some muscle relaxation at higher doses</td>
</tr>
<tr>
<td>α&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Anxiolytic (some); maybe some muscle relaxation at higher doses</td>
</tr>
<tr>
<td>α&lt;sub&gt;5&lt;/sub&gt;</td>
<td>Memory/Cognition; (Maybe memory component of anxiety?)</td>
</tr>
<tr>
<td>α&lt;sub&gt;6&lt;/sub&gt;</td>
<td>Diazepam-insensitive sites</td>
</tr>
</tbody>
</table>

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**GABA / BzR Chloride Ion Complex**

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**Unified Pharmacophore/Receptor Model for the Benzodiazepine Receptor**

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Binding Affinities of Ro15-4513 Analogs at BzR Subtypes (α1, α2, α3, α5, α6)

<table>
<thead>
<tr>
<th>Ligand</th>
<th>R1</th>
<th>R2</th>
<th>Kᵢ (nM)</th>
<th>α1</th>
<th>α2</th>
<th>α3</th>
<th>α5</th>
<th>α6</th>
<th>α1/α5</th>
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<tbody>
<tr>
<td>Ro15-4513</td>
<td>Et</td>
<td>H</td>
<td>-</td>
<td>3.3</td>
<td>3.5</td>
<td>3.5</td>
<td>3.0</td>
<td>3.6</td>
<td>13.7</td>
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<td>1</td>
<td>Et</td>
<td>H</td>
<td>-</td>
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<td>2</td>
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<td>4</td>
<td>t-Bu</td>
<td>H</td>
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<td>2.01</td>
<td>55.6</td>
<td>78.5</td>
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<tr>
<td>5</td>
<td>t-Bu</td>
<td>H</td>
<td>-</td>
<td>25.9</td>
<td>26.3</td>
<td>16.7</td>
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<td>5.4</td>
<td>67.3</td>
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<td>6</td>
<td>Et</td>
<td>H</td>
<td>-</td>
<td>3.75</td>
<td>7.2</td>
<td>4.14</td>
<td>1.11</td>
<td>44.3</td>
<td>3.4</td>
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<td>7</td>
<td>t-Bu</td>
<td>t-Bu</td>
<td>-</td>
<td>9.3</td>
<td>10</td>
<td>10</td>
<td>11</td>
<td>10</td>
<td>5.5</td>
</tr>
<tr>
<td>8</td>
<td>Et</td>
<td>H</td>
<td>-</td>
<td>5.9</td>
<td>11</td>
<td>10</td>
<td>11</td>
<td>142</td>
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<tr>
<td>9</td>
<td>Et</td>
<td>t-Bu</td>
<td>-</td>
<td>11</td>
<td>17</td>
<td>12</td>
<td>2.1</td>
<td>269</td>
<td>5.2</td>
</tr>
</tbody>
</table>

XHe-II-053 Analogs Designed by Molecular Modeling as Potential Non-Sedating Anxiolytics

Diazepam (Pink) and QH-II-066 (Black) Aligned in the Pharmacophore
Diminished Spinal Inhibition Causes Pain

Blockade of inhibitory neurotransmitters induces
- hyperalgesia
- allodynia (touch-evoked pain)
- spontaneous activity of dorsal horn neurons (spontaneous pain)

Early pharmacological data by Yaksh et al. and others have shown that pharmacological blockade of spinal GABAergic and glycinergic inhibition induces hyperalgesia (increased sensitivity to painful stimuli) and allodynia (painful sensation of stimuli which are normally not sensed as painful) in animals. More recent electrophysiological work has, in addition, shown that the blockade of glycine and GABA receptors disinhibits polysynaptic connections from touch sensitive fibers to normally pain-specific projection neurons and induces spontaneous activity in these cells. Blocking dorsal spinal glycine and GABA receptors therefore mimics many symptoms characteristic of chronic pain in humans.

HZ166: Comparison with Gabapentin-Side Effects

HZ166: Neuropathic and Inflammatory Pain
Data for HZ-166 from DiLio, Zeilhofer, Cook et al., submitted; for L-838,417 is from Knabl et al., Nature 2008, the dpz data are unpublished (diazepam and L838,417 have been tested in rats, HZ166 data was obtained in mice). Design was identical all experiments.

**HZ166: No Tolerance Development Against Analgesia**

<table>
<thead>
<tr>
<th>CCI</th>
<th>drug of vehicle (7-15)</th>
<th>test drug</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- HZ-166
- MO
- DZP
- L-838,417

# Disease Applications of α-Subunit Selective Compounds

- **PWZ-029**
- **SH-053-2'-F-CH**
- XHe-III-74
- CMD-45

**Patch clamp data from oocytes**

- Effective gap junctions for Alzheimer's disease
- Effective responses for Schizophrenia

The Cook Group
Our Capabilities: Pharmacophore modeling; QSAR; organic synthesis; natural products chemistry; neurochemistry

Resources Available: Development of ligand binding strategies and synthetic pathways; structural and functional compound analysis

Collaborations needed: Translational partnerships in neuro-psychiatric and infectious disease areas

Contact Information: J.M. Cook, PhD
UWM, Department of Chemistry & Biochemistry
PO Box 413, Milwaukee, WI 53201-0413
Email: capncook@uwm.edu
Telephone: 414-416-4400

Medicinal Chemistry and Lead Optimization

High-Throughput Screening
Assay Development

Alexander “Leggy” Arnold, PhD
Department of Chemistry & Biochemistry

Protein
Assay Development
Small Molecule Modulator
High Throughput Screening
Target ➔ Hit ➔ Drug
Arnold group
1. Develop assay
2. Optimize assay
3. Miniaturize assay

Detection:
1. Fluorescence
2. Luminescence
3. Radioactivity (scintillation)
4. Absorbance
5. Light scattering

Tecan M1000 (Quad4 Monochromator)

Direct labeling
1. Small fluorescence molecule
2. Isotope

Fusion protein
1. Fluorescent protein
2. Enzyme (luciferase, peroxidase, phosphatase, …..)
3. Affinity Tag (HIS, GST, FLAG, …..)
4. Epitope Tag (c-myc, …..)

Indirect labeling
1. Antibody
2. Affinity Tag

Labeled assay
### Label-free assay

1. Light scattering
2. Acoustic waves
3. Current (Amp)

### Assay optimization

1. Plate selection
2. Volume
3. Buffer composition (buffer type, pH, additives, ...)
4. Order of addition
5. Concentrations
6. Incubation times
7. Temperature
8. DMSO

Assay optimization results:
- **BAD Assay**: Z factor = 0.023
- **GOOD Assay**: Z factor = 0.72
Assay miniaturization

Edge effect vs. Row effect

High throughput screening

Hardware
1. Automation
2. Timing
3. Integration
4. Temperature

Consumables
1. Plates
2. Small molecule libraries (target libraries or full deck)
3. Large quantities of bio-molecules or cells

High throughput screening libraries

Target libraries (10-30K)
1. Kinases
2. GPCRs
3. Ion channels
4. Nuclear Receptors
5. Proteases

Activity targeted libraries
1. Cancer
2. Antibacterial
3. Antiviral
4. Analgesic
5. CNS

Based on 2D fingerprint similarity methodology (Tanimoto coefficient)

Full Deck (200-600k)
Diverse compounds (available in top 20 universities and institutes)
High throughput screening

Data analysis
1. Significant hits
2. False positives/negatives
3. Selection

Data Mining
1. Common pharmacophore
2. Promiscuous compounds
3. Drug-like compounds

Confirmation
1. Secondary Assays
2. Functional Assays

Our Capabilities

1. Intellectual:
   • Assay Design/Development
   • Assay Troubleshooting
   • Where and How to apply for screening
   • Support for Screening Campaign

2. Structural:
   • Instrumentation
   • Screening of small compound libraries
   • MedChem Advice
   • Virtual screening, docking, pharmacophore modeling and data analysis
   • Pre-clinical ADMET

Collaboration needed

1. Intellectual:
   • MD perspective
   • Animal protocols
   • Animal models

2. Structural:
   • In vivo toxicity
   • In vivo ADME
   • In vivo functional assays
   • Disease animal models

Our research

Small molecule modulation of VDR-mediated signal transduction

Cancer
Autoimmune Diseases
Metabolic Diseases
Drug Rescuing and Repurposing
*Teaching old drugs new tricks*

Behnam Ghasemzadeh
Department of Biomedical Sciences
Marquette University

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**Drug Development: Cost & Time**

- **Drug Discovery**: ~3 years
- **Preclinical**: ~3 years
- **Clinical Trials**: ~3 years
- **NDA Submission & FDA Review**: ~3 years

Total Time: 10 - 15 years
Total Cost: $500 million to $2 billion

---

**Drug Development: Success Rate**

Alternatives for conventional drug development

- Merging and acquisition of smaller companies

<table>
<thead>
<tr>
<th>Company</th>
<th>2011 market cap (US$ billion)</th>
<th>2011 rating</th>
<th>2012 rating</th>
<th>Major mergers or acquisitions since 2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer</td>
<td>170</td>
<td>1</td>
<td>4</td>
<td>Purchase of Wyeth</td>
</tr>
<tr>
<td>Novartis</td>
<td>135</td>
<td>2</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td>130</td>
<td>4</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Roche</td>
<td>120</td>
<td>5</td>
<td>2</td>
<td>Purchase of Genentech</td>
</tr>
<tr>
<td>Merck</td>
<td>114</td>
<td>2</td>
<td>2</td>
<td>Purchase of Schering-Plough</td>
</tr>
<tr>
<td>Gilead</td>
<td>97</td>
<td>1</td>
<td>5</td>
<td>Acquisition of Anthera, Genzyme</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>85</td>
<td>5</td>
<td>10</td>
<td>Purchase of Idenix</td>
</tr>
<tr>
<td>Alexion</td>
<td>55</td>
<td>2</td>
<td>8</td>
<td>Purchase of Lively</td>
</tr>
<tr>
<td>Biogen</td>
<td>51</td>
<td>3</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Bharat Mylan</td>
<td>40</td>
<td>1</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Erylux</td>
<td>30</td>
<td>2</td>
<td>4</td>
<td>-</td>
</tr>
</tbody>
</table>


Drug Repositioning

- Drug Rescuing
  - Development of abandoned drugs for new diseases

- Drug Repurposing
  - Development of FDA-approved drugs for new diseases

Examples of Abandoned/Repurposed Drugs

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade name (original Indication)</th>
<th>Trade Name (Repositioned Indication)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib</td>
<td>Celebrex, Osteoarthritis/Rheumatoid arthritis (Pfizer)</td>
<td>Celebrex, Adenomatous Polyposis, Colon &amp; Breast Cancer (Pfizer)</td>
</tr>
<tr>
<td>Minoxidil</td>
<td>N/A, Hypertension (Pharmacia &amp; Upjohn)</td>
<td>Rogaine, hair loss (Pfizer)</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Tegretol, Epilepsy (Johnson &amp; Johnson)</td>
<td>Topamax, epilepsy (Johnson &amp; Johnson)</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Xylocaine, local anesthetic (AstraZeneca)</td>
<td>Xylocaine, local anesthetic (AstraZeneca)</td>
</tr>
<tr>
<td>Imipramine</td>
<td>N/A, Depression (GlaxoSmithKline)</td>
<td>N/A, Depression (GlaxoSmithKline)</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Prozac, Depression ($ Lilly)</td>
<td>Sarafem, Premenstrual Dysphoria ($ Lilly)</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>Cymbalta, Depression ($ Lilly)</td>
<td>Cymbalta, Depression ($ Lilly)</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>N/A, Cancer (Academia)</td>
<td>AZT, HIV infection (Gilead/Wellcome)</td>
</tr>
</tbody>
</table>
National Center for Advancing Translational Sciences

- Promoting and facilitation of translational research
- A major focus on rescuing and repurposing drug molecules
- Initiated a collaborative program between pharmaceutical industry and researchers
- Industry participants are: AstraZeneca, Eli Lilly, and Pfizer
- In fiscal year 2013, $20 million will be provided to support this research program

Advantages

- **The patient perspective**
  - Time is of the essence
- **The business case**
  - Reduced risk of failure
  - Reduced development cost
- **The patent perspective**
  - Use-patent protection
  - Patient Stratification
- **The case for innovation**
  - Insight into disease mechanism

Legal Issues

- Can a use-patent be obtained and how valuable will it be?
- What is the effect of the diminished patent life for the drug?
- The off-label use of the drug.
- Will the patent have relevance if a drug is already a generic?
- Is such use-patent IP monetizable?
Schizophrenia – the Disease

- Symptoms emerge in mid-20s
- Life-long disorder
- Requires chronic treatment
- Disease has 3 categories of symptoms:
  - **Positive symptoms**: treated with current drugs, but with significant side effects: ~75% stop medication
  - **Negative symptoms**: not effectively treated with current drugs
  - **Cognitive symptoms**: not effectively treated with current drugs

Lifelong Behavioral Symptoms of Schizophrenia

- **Positive Symptoms**:
  - Delusions
  - Hallucinations
  - Thought Disorder
  - Movement disorders

- **Typical Antipsychotics**:
  - Haldol, Prolixin, Thorazine, Sparine

- **Atypical Antipsychotics**:
  - Risperidol, Zyprexa, Seroquel, Abilify

- **Negative Symptoms**:
  - Loss of interest
  - Loss of emotion
  - Loss of motivation
  - Social withdrawal
  - Neglecting Hygiene

AV115: rescued Alzheimer’s drug; treats cognitive & negative symptoms of Schizophrenia

- **Cognitive Symptoms**:
  - Faulty Information Processing
  - Attention deficits
  - Memory deficits
The Opportunity

- **AviMed’s product:**
  - A rescued drug (AVI115) to treat Schizophrenia symptoms
  - Treatment for an unmet medical need
  - Global Market: > $20 billion/year

- **AviMed’s Opportunity:**
  - **Social impact:** unmet need in the treatment of Schizophrenia
  - **Demsked investment:** Tested through Phase II for Alzheimer’s: proven human safety record; no known side effects
  - **Product differentiation:** Treats symptoms not treated by current medications
  - **Minimal competition:** AviMed owns use-patent (pending) on AVI115: no off-label competition

Business Overview and Strategy

- **AviMed’s product:**
  - A rescued drug (AVI115) to treat Schizophrenia

- **AviMed’s Road Map:**
  - Repeat preclinical studies
  - IND approval
  - Enter Phase I trials
  - Complete Phase Ila
  - License for further development (Phase Iib & III)

---

[Chemical structures and images]
Acute Administration of Phencyclidine:
Behavioral animal model of Schizophrenia

1. Forced Delayed Alternation Task (T-maze)
   Examines function of working memory: memory/cognitive function

2. Social Interaction
   Examines social behavior: negative symptom

3. Prepulse Inhibition
   Examines sensory gating processing, a cognitive function

Blockade of KCNQ channels reverses the PCP-induced deficit in working memory, a memory and cognitive effect.

<table>
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<tr>
<th>Condition</th>
<th>Correct Choices</th>
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<td>Sal/Sal</td>
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<tr>
<td>Sal/PCP</td>
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<tr>
<td>XE991/Sal</td>
<td>3.0</td>
</tr>
<tr>
<td>XE991/PCP</td>
<td>3.0</td>
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</table>

Blockade of KCNQ channels reverses the PCP-induced reduction in social interaction, a negative symptom.

<table>
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<th>Condition</th>
<th>Interaction Time (sec)</th>
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<tr>
<td>XE991/Sal</td>
<td>4.0</td>
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<tr>
<td>Sal/PCP</td>
<td>4.0</td>
</tr>
<tr>
<td>XE991/PCP</td>
<td>4.0</td>
</tr>
</tbody>
</table>
Drug Rescuing and Repurposing

A new strategy for drug development:

- Diminished risk
- Reduced cost
- Faster to market

Effective Treatments for the Patients

Structure-based Drug Design:
Technologies & Applications

Daniel Sem, Ph.D.
Associate Professor of Pharmaceutical Sciences

Director of the CSD
Acting Director of Technology Transfer and IP
Concordia University, School of Pharmacy
FBDD: Fragment-based Drug Design
NMR-guided Fragment Assembly:
Application to Kinases (p38α; arthritis)

Chemical & Biological.

Issued patents:
Sem, Pellecchia (2005) US 6,979,531;
Sem et al. (2010) US 7,653,490

Need good science and ⇒ Business strategy ⇒ Licensing; BD ⇒ Business model ⇒ IP strategy

BioWorld

Developed SAR by NMR:

Combinatorial FBDD using a privileged scaffold
Application to oxidoreductases - ID

Privileged scaffold

Privileged scaffold = rhodanine (similar to thiazolidinedione)


Human liver proteins (antitarget)
Malate dehydrogenase, mitochondrial precursor
Fructose-bisphosphate aldolase B (Liver-type aldolase)
Aldehyde dehydrogenase, mitochondrial precursor
Glutamate dehydrogenase 1, mitochondrial precursor
Retinal dehydrogenase 1 (Aldehyde dehydr. 1 family member A1)
10-formyltetrahydrofolate dehydrogenase (Aldehyde dehydr. 1 family member L1)

Elute proteome w/ scaffold
Identify scaffold-binding proteins with LC-MS

Chemically tune (add fragments to) privileged scaffold to avoid "anti-target" binding

Proteome-wide assay for drug binding (polypharmacology)

Application to existing drugs: off target sources of toxicity & new uses (repurposing)

Rhodanine is related to the thiazolidinedione (TZD) diabetes drugs; cardiotoxicity mechanism?

TZD (glitazone)

Docking to identify inhibitors – drug leads – using protein structure

Application to the M. tb thioredoxin system - protects against oxidative killing by macrophages

Need:

⇒ Protein 3D structure(s)
⇒ Library of compounds to dock
⇒ Assay to verify binding
⇒ 11,000 cpds. docked
⇒ NMR binding assay verifies binding location
⇒ Goal = uncompetitive inhibition; interface binding

Structure-Based Drug Design (SBDD) using protein = Docking

To identify Dusp5 ligands (vascular anomalies)

Ligand-based SBDD: search of FDA-approved drugs
(Match shape & electronic properties of 1st hit; repurposing)

Education – Connecting students & drug discovery researchers

Taking the SMART Team concept to the next level: 3D animations & molecular landscapes
Ensure our in-house library (11,000) is “drug-like” and diverse, for SBDD (protein).

Design a drug library for repurposing (SBDD; ligand).

Design a “fragment library” for FBDD.

Existing methods**

Remove potential for toxicity (ex. Ames test).

Synthetic accessibility.

Chemical fragment library:

Ensure our in-house library (11,000) is “drug-like” and diverse, for SBDD (protein).

Design a drug library for repurposing (SBDD; ligand).

Design a “fragment library” for FBDD.

Existing methods**

Remove potential for toxicity (ex. Ames test).

Synthetic accessibility.

Pathway with multiple toxicology endpoints.

Pharmacological screening.

CSD3 Core Capability

Libraries:

- Drug fragment
- Repurposing (200+)
- Screening (11,000)

Draft MOU being refined: the result of two brainstorming sessions; task force from CML, CUW, MCW, MU, UWM has prepared multiple drafts.

Help us finish it: come to roundtable!

Our Mission: To provide the post-discovery resources needed to develop drugs to the clinical stage, with focus on new chemical entities and repurposing of existing drugs. This is to be accomplished by bringing together academic and industrial partners with synergistic expertise, and to train the next generation of scientists to continue in the effort.

Towards this goal, we will produce more R&D funding, startup companies, and jobs in the innovation and application of drug discovery, development & manufacturing technology.
1. **Capabilities:** FBDD w/NMR; SBDD (ligand + protein)
2. **Resources:** various chemical libraries; NMR screening
3. **Collaborations needed:** anyone with a protein drug target—especially in cardiovascular, ID, CNS—needing a drug lead & looking to join forces on grant submissions
4. **CSD**³ services (csdd.org) – can write into proposals
5. **Bridge to Cures** – come to the roundtable!
6. **Contact Information:** 262-243-2778; daniel.sem@cuw.edu

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**CTSI – Drug Development Collaborative Workshop**

**Summary**

Novel Drug Formulations

Dr. Abhay S. Chauhan

*Director of Pharmaceutical Nanotechnology*

College of Pharmacy, Concordia University, Mequon, WI

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**Novel Drug Delivery Systems**

**NDDS- Features!**

- Drug

<table>
<thead>
<tr>
<th>Drug Release Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fast</td>
</tr>
<tr>
<td>• Sustained</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Absorption/Release site</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Stomach</td>
</tr>
<tr>
<td>• Small Intestine</td>
</tr>
<tr>
<td>• Colon</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Targeting Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Passive</td>
</tr>
<tr>
<td>• Active</td>
</tr>
</tbody>
</table>

**Stimuli-Responsive**

- pH
- Temperature
- Pathological conditions

**Drug Stability**

- Multi-Tasking

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38
Classification of NDDS
- Design
- Route of Administration
- Type of Drug molecule
- Patient Compliance

Controlled Release Tablet
- Pulmonary delivery
- Ophthalmic delivery
- Nasal Delivery
- Colon Delivery
- Transdermal Drug Delivery

Liposomes
- Vesicular structures based on lipid bilayers surrounding aqueous compartments
- Better efficacy and less toxicity
- Disadvantage: Rapid clearance by RES primarily liver, spleen, and kidney

Micelles

Pulsatile Drug Delivery System
- Drug release programmed by external stimuli like magnetism, ultrasound, and irradiation

Responsive Drug Delivery System
- Drug release is controlled by change in temperature, pH, inflammation

Intelligent Drug Delivery System
- Remote Intelligent Drug Delivery System (RDDS)
  - RDDS device with inbuilt sensors to monitor biomarkers of a patient's symptoms, pulse rate, or blood oxygen levels.
  - Wireless control will help to control the medication.
**Nanotechnology**
- Core: Small molecules, Nanoparticles, metals, Other dendrimers, Polymers, latexes
- Dendrimer:
  - Precise
  - Polymeric
  - Nanostructures
- Spherical 3-D Architecture: Surface Groups
  - Hydrophilic: Cationic, Anionic, & Neutral
  - Hydrophobic: aliphatic & aromatic
  - Combinations of surface groups
  - Number doubles or triples per generation
- Interiors Branching: Robust, covalent framework, Connects core to surface groups, Internal functional groups
- Void Spaces: Room for molecular cargo
- Size Range: 1 to 10 nm (typically)
- Improve Drug Solubilisation
- Improve Pharmacokinetics
- Targeted Delivery
- Reduce Toxicity
- Extend Patent Life

**Solubility Enhancement**
- Dissolution Rates
  - Aqueous solubility
  - Nanosuspension
  - Oil Solubility
- Controlled Release
- Stabilization

**Protein/peptide delivery**
- Protein/peptide becoming major contributor in the current therapy
  - Poor oral bioavailability
  - Protein denaturation in the digestive system
  - Acid hydrolysis in the stomach and enzymatic degradation
  - Poor adsorption due to size, polar/charge distribution

**Gene delivery**
- Success at in-vitro level
- FDA has not yet approved any human gene therapy product for sale

**Extending Half-Life**
- Maximum Tolerated Dose
Dendrimer Mediated Transdermal Drug Delivery

In vivo Magnetic Resonance Imaging

Nano-Drug: Anti-Inflammatory Dendrimer

1. Capabilities:
   • To develop formulations of new chemical entity, such as small drug molecules, protein, biologics towards clinical application.
   • Nanotechnology based drug delivery.

2. Resources Available
   • Intellectual capital to bring drug molecules from bench to bedside.
   • Dendrimer nanotechnology

3. Collaborations needed
   • To apply nanotechnology for treatment of various diseases such as cancer, neurological, cardiovascular, infectious, pediatric, blood, eye, diabetes, kidney, dental, aging, toxicity management, emergency, rare disease and virtually any disease condition...

4. Contact Information
   • Dr. Abhay S. Chauhan
   • 262 243-2786 (office); Email: abhay.chauhan@cuw.edu

Clinical Trials

James P. Thomas, M.D., Ph.D.
Associate Director for Clinical Investigation: MCW Cancer Center
Why Are Clinical Trials Important?

- Clinical trials translate results of basic scientific research into better ways to prevent, diagnose, or treat disease.
- The more people that take part, the faster we can:
  - Answer critical research questions
  - Find better treatments and ways to prevent disease
- Only 3 percent of U.S. adults with cancer participate in clinical trials.

Types of Clinical Trials

- Treatment trials
- Prevention trials
- Early-detection trials/screening trials
- Diagnostic trials
- Quality-of-life studies/supportive care studies
MCW Neoadjuvant Pancreas Trial

- Resectable or borderline resectable patients
- All patients are biopsied prior to starting treatment and sample sent for IHC, mRNA,
  - SPARC
  - ERCC
  - RRM1
  - hENT
  - TYMS
- Therapy determined by molecular profile
- Chemotherapy → chemoradiation therapy → Surgery
- Chemotherapy options
  - Gem/nab
  - FOLFRINOX
  - Gem/cape
  - Gem/Oxali
  - FOLFIRI

MCW Cancer Clinical Trials Office

Vision
To promote the conduct of cancer clinical trials in a methodologically sound, safe, compliant, expedient and cost-effective manner so that cutting edge technologies are available to the patients we serve and the state of the art is advanced

Services
- Trial design, activation, coordination & management
- Data collection and management
- Adverse event monitoring and reporting
- Regulatory support and compliance monitoring
- Development of trial budgets
- Contract negotiations
- Invoicing & revenue tracking

Clinical Trial Management Software
Phase I Trials

These trials are conducted to evaluate the safety of chemical or biological agents or other types of interventions, e.g., new radiation therapy techniques. They involve relatively small numbers of subjects to determine whether an intervention causes a harmful effect. Generally, these trials are conducted in patients with advanced cancer that cannot be treated effectively with standard (usual) treatments or for which no standard treatment exists.

Cancer Translational Research Unit

- Basic laboratory research has led to a number of important new targets in the war on cancer.
- A dedicated unit to perform first-in-man cancer treatment trials will make these promising treatments available to our patients sooner.
- Formation of this unit will also expedite new treatments developed on campus by our cancer research faculty.
- The Cancer TRU represents a unique opportunity for our clinicians, nursing staff and patients to engage in the development of important new therapies.
- Dedicated Senior Nursing staff experienced in administering investigational agents, who will be involved in the development and evaluation of research protocols.
- A facility that can accommodate the collection, processing, storage and shipping of research related samples such as plasma for pharmacokinetics.

Serum Creatinine

First PKD Incubation
Clinical Trials Summary

- The process of transitioning novel ideas into new clinical is a complex, time-consuming, expensive process.
- Infrastructure within the CTSI and the medical campus to assist investigators in the clinical trials process is rapidly expanding.

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Diagnostic and Therapeutic Biotech Targets Based on Greatest Unmet Clinical Needs

Elizabeth R. Jacobs, MD, MBA
Medical College of Wisconsin

Rapid screening tools for point of care use in Global Health

Global Health Perspective: 3 most important infectious diseases are HIV, TB, Malaria

- POC diagnostics for HIV used for screening, initial diagnosis, staging, treatment monitoring, and early infant diagnosis (NAAT or protein based).
- Over-the-counter self-testing options for HIV and CD4 counts
- Multiplexed platforms that allow for simultaneous detection of infections associated with HIV (Hep B and Hep C)
- But TB diagnostics are far behind!

Reference lab
Conventional NAAT
Clinical/decentralized lab
Newer NAAT-cartridge based
POC Handheld devices

Pai NP, Discovery Medicine 1-18-12
Rapid screening tools and diagnostics that provide new information: USA

4 Point-of-Care Technologies Research Networks (NIH Biotech & Bioengineering):
- Neurotechnologies
- Sexually Transmitted Diseases
- Global Health
- Disaster Readiness

Neurotechnologies: Examples: Rapid bedside screening for infectious meningitis or encephalitis, blood tests, urinalysis, imaging, non-invasive sensors, spinal fluid to diagnose stroke or other neurologic disorders.

Our methods for non-invasive diagnosis of Alzheimer's are poor. CNS amyloid or protein deposits identified by SPECT aid in the diagnosis of neurodegenerative disease.

Diagnostic innovations to provide new functional information

Example: new means to detect oxidoreductive state

Background: we have almost no tools to identify the potential of tissue to produce ATP in real time, but this information is more closely related to the subsequent fate of the tissue than other information.

Dr. Mahsa Ranji (UW Milwaukee) has developed the capacity to measure the oxidoreductive state of lung in real time in vivo.

This information can assist surgeons in identifying viable from non-viable tissue intra-operatively.

New therapeutics for infectious diseases

Development of new antibiotics is prohibitively expensive, so has slowed.

But NAATs to detect all common bacteria, viruses, parasites AND resistance patterns to antimicrobials are in progress.

Vaccines are incompletely effective and needed to protect from chronic colonization. Interventions to enhance (or dampen) innate immunity to counter chronic infections are in the pipeline.

TLR (Toll-like receptor) ligands as adjuvants for vaccines for chronic infections such as gram negative bacteria.
Innovations to improve the toxic to therapeutic ratio

- Lung cancer has poor prognosis; <10% survive 5 years.
- Radiation helps, but toxicity to healthy tissue limits total radiation dose.
- Micrometastasis in tumor tissue is hypoxic relative to that in healthy tissue.
- Radiosensitizers concentrated in hypoxic tissue focus killing effect of radiation on tumor relative to surrounding healthy tissue.

Xiaohua Peng PhD, UW Milwaukee

Other examples: cancer chemotherapy directed by genetics or targeted to tumor by antibody conjugates, immunotherapy, metastasis detection or control.

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Low Molecular Weight Drug-like Molecules to Treat Chronic Diseases

Small drug-like molecules have been developed to target G-protein coupled receptors, ion channels, enzymes and other targets.

Oxidative stress impairs HDL function.

D-4F is an apoA-1 mimic with powerful anti-inflammatory and antioxidant properties.

Oxidative stress

HDL cholesterol

K.A. Pitchford, MCW

Targeting oxidative stress may treat:
- Rheumatoid arthritis
- Pulmonary diseases
- Sickle cell disease
- Hypercholesterolemia systemic sclerosis

New methods of drug delivery (e.g. inhalational route)

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Small Molecule Therapy for Neurodegenerative Diseases

**Huntington’s Disease**: autosomal dominant movement disorder leading to dementia and death. No treatment.

Affects 30,000 persons in US, with potential to impact 200,000 more.

An expanded run of tandem CAG triplets at the 5 prime-end of the gene – glutamine residues and neurotoxic protein.

Non-coding small RNAs (22 nucleotide base pairs) offer a potential therapeutic approach of post-transcriptional gene silencing modifying mRNA stability or translation.

More RNA targeted to expanded CAG, SNPs in HD cells or mutant transgenes decreases neurotoxicity and improves symptoms in HD mice.

New agents to target obesity

More than one-third of U.S. adults (35.7%) and approximately 17% (or 12.5 million) of children and adolescents aged 2—19 years are obese.

Valentino, Lin, Waldman. Nature 87(6), 2010

Success rates of the best therapies for obesity over 1 year are under 10%.

Complications of obesity include diabetes, joint disease, cardiovascular disease, asthma, etc.

Interventions that improve the therapeutic potential with limited toxicity is welcome.

Summary: how to do it

Identify a problem /condition that:
• adversely impacts a large number of individuals
• responds poorly to existing diagnostics or therapies
• causes significant suffering or functional loss
• is chronic – job security!

Identify a solution that:
• provides a faster, cheaper or more convenient diagnosis
• offers more efficacious therapy or better delivery system
• focuses on new diagnostic or therapeutic target(s)
• improves toxic to therapeutic ratio

Diagnostic or therapeutic advances require interdisciplinary collaboration!

A leader sees solutions where others see problems. A visionary sees solutions before others knew problems existed.

Availability of and Access to CTSI Resources

Rachel F. Schiffman, PhD, RN, FAAN
University of Wisconsin - Milwaukee
CTSI Vision – Borderless Research Metropolis

Create a borderless, synergistic biomedical research enterprise that will accelerate the translation of research discoveries into new and improved medical treatments.

CTSI Resources – Online Community

- Starting Point: https://ctsi.mcw.edu/

CTSI Resources – Key Functions

Clinical & Translational Research Support Office (CTRSO)
Entry point and central integrator of the wide array of infrastructure, services and research grant opportunities available to the investigators to support Clinical and Translational Research.
CTRSO Contacts:

- MCW → Michael Dunn
- MU → Jeanne Hossenlopp
- MSOE → Thomas Bray
- UWM → Rachel Schiffman

Pilot and Collaborative Grants
Use designated resources of the partnering institutions to promulgate Clinical and Translational Research in a cohesive manner and to foster interdisciplinary collaborations among the participating institutions.

CTSI Resources – Key Functions

- Clinical and Translational Pilot Grants for collaborative teams of researchers
- Core support for facilities conducting research in novel methodologies
- Infrastructure support for services that promote clinical and translational research
- Support for the enhancement of technology transfer services and expertise
- Co-funding grant opportunities with A Healthier Wisconsin, Biomedical Technology Alliance, partnering institutions and others
Regulatory Knowledge and Support

- IRB, IACUC, and HIPAA, etc. coordination among the institutions
- Research Ethics

Participant and Clinical Interactions Resources (PCIR)

Provides a coordinated structure through Translational Research Units (TRUs) to support collaborative multi- and interdisciplinary Clinical and Translational research at MCW, its partner institutions and in the community.

Translational Technology and Resources (TTR)

Encouraging efficient use of existing technology cores, integrating isolated technology resources into core structures, providing technical assistance to core users, and by developing technology training programs for fellows, faculty, and staff.
CTSI Resources – Key Functions

Biomedical Informatics
• Support the collection and management of data from CTSI supported protocols;
• Provide infrastructure to support efficient identification of potential collaborators among the partner institutions.

Biostatistics / Epidemiology Research Design
• Statistical support to investigators on study design, data management, data entry, scannable form development, statistical software usage and analysis.
• Collaboration on the development of Institutional Review Board (IRB) proposals, federal and private grant proposals and Clinical & Translational Science Institute (CTSI) proposals and assistance in using national databases to study important health issues.
• Continuing education in statistical design and statistical methods for clinical and basic science investigators.

Community Engagement
Productively engage researchers and community participants in partnerships that move research bi-directionally from bench and bedside, to the community and back. Identify and overcome obstacles to community involvement.
CTSI Resources – Key Functions

**Education, Training, Mentoring**
To offer a coordinated continuum of clinical/translational research education and training opportunities for diverse individuals at varied stages of research career development.

CTSI Resources – Key Functions

**Evaluation and Tracking**
- Track and evaluate the degree to which the CTSI aims are achieved
- Provide regular reports to CTSI leadership
- Participate in the planning, design and conduct of the national NIH/NCRR program evaluation and provide information consistent with the national evaluation goals

CTSI Resources – Back to the Website!
CTSI Resources – Back to the Website!

Our Clinical and Translational Investigators!
Hopefully many of you are or will be counted among us.

Thanks to: Dr. Arthur Hefti and Dr. Ted Kotchen of the Office of Expanding Regional Collaborations and the planning committee for this workshop.