Upstate Cancer Research Institute:
A Power House in Drug Development
in Central New York

Ziwei Huang, Ph.D.
Professor & Chairman, Department of Pharmacology
Director, Upstate Cancer Research Institute
State University of New York (SUNY)
Upstate Medical University
Syracuse, New York
Translating Basic Research to New Medicine: Integration of Pharmacology, Biology, and Medicine in Transdisciplinary Basic and Translational Research

Human Genome

Biology of Disease
Genetics and Genomics

Chemistry
Nanotechnology

Microarray (HTP Sciences)

Pharmacology

Protein Structures

Computer-aided Drug Design

Protein Targeted Drugs

New Medicine
Published in 2007
20 chapters by 70 leading experts and researchers from 25 universities, Institutes, and companies around the world in the fields of pharmacology, pharmaceutical chemistry, drug design, cancer biology, neuroscience, and translational medicine (Dennis Carson, UCSD; John Reed, Burnham; Paul Wender, Stanford; Andrew Hamilton, Yale; Joseph Sodroski, Harvard; Irwin Kuntz, UCSF, etc.)
Translational Research in Pharmacology: Connecting Basic Science with Clinical Medicine

**Cancer**
- Apoptosis: Bcl-2, Caspases, XIAP
- Angiogenesis: Eph-Ephrin
- Metastasis: Chemokine receptors

**Immune & Infectious Diseases**
- Immune Response: CD4, CD8, IgSF
- HIV infection: Chemokine receptors
- HCV-WNV-Dengue

**Neurodegeneration**
- Dementia: Chemokine receptors
- CNS injury repairs: Stem cell migration

**Cardiovascular Diseases**
- Stem cell-based regeneration
- APJ-Apelin; Wnt signaling

**Pharmacology**
- Cell Signaling
- Receptor-Ligand

**Translational Medicine**
- New Therapies
Pharmaceutical Discovery and Pharmacologic Research of Cancer

1. Cancer Apoptosis – Small molecule drugs targeting Bcl-2 and IAP (cancer and neurodegenerative diseases)

2. Cancer Metastasis – Small molecule and protein drugs targeting chemokine receptors (cancer, HIV, regenerative medicine for stroke, cardiac or brain injury)

Research Probes & Therapeutics Targeting Cancer Cell Apoptosis

Over 10 years of research on a novel Bcl-2 inhibitor HA14-1
The Bcl-2 Family

FADD

FADD

The IAP Family

XIAP
Survivin

Mitochondria

Caspase-8

Caspase-9

Apoptosome

Cytochrome c

Smac/DIABLO

Apaf-1

Procaspase-9

Bax
Bcl-2
Bcl-xL

Bad

CrmA

Caspase-3

Caspase-8

Apoptosis

Protein-protein Interactions in Programmed Cell Death

Huang, Chem. & Biol., 2002
Our Discovery of the First Reported Bcl-2 Inhibitor, HA14-1, by Structure-based Computer Screening

PNAS, 2000
FPA Method to Measure Binding of HA14-1 to Bcl-2 protein \textit{in vitro}

IC$_{50}$ = 9 \(\mu\text{M}\)

Cancer Res., 2000
PNAS, 2000
HA14-1 has a significant killing of primary AML.
Potential clinical application:
HA14-1 (5 uM) sensitizes HL-60/Bcl-2 cells to γ radiation (very low dose)

Prof. Jing An; Oncogene, 2007


Apoptosis pathways and drug targets

John C. Reed and Ziwei Huang
Research Probes and Therapeutics Targeting Viral Entry and Cell Movement Mediated by Chemokine Receptors

Synthetic Peptide Antagonist vs. Agonist of CXCR4
RCP168 & GG-DV1
Chemokines And Receptors Are Involved In Many Human Diseases

Adapted from A.E. Proudfoot, Nature | Immunology, 2:106-115, 2002
Mapping the locations of residues functionally important for SMM-chemokines, HIV-1 or SDF-1α on CXCR4 TM and ECL2 domains: Functional sites for SMM-chemokines and HIV-1 are distinct from those for SDF-1α

The locations of the TM residues required for SDF-1α binding are shown as white spots while those that are involved in HIV-1 coreceptor activity are shown as black spots.

Tian et al., J. Virology, 2005
Choi et al. J. Virology, 2005
A more complete picture of CXCR4-ligand interaction based on crystal structure determination of the ligand and molecular modeling and mutational study of the receptor.
Discovery of RCP168, a Novel CXCR4 Antagonist

X-ray crystal structure of RCP168 vs. native vMIP-II determined by Prof. Ziwei Huang’s laboratory
# Binding Affinity and Selectivity of SMM-Chemokines for CXCR4, CCR5 and CCR2

<table>
<thead>
<tr>
<th>Analog</th>
<th>CXCR4 Binding (nM)</th>
<th>CCR5 Binding (nM)</th>
<th>CCR2 Binding (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCP111</td>
<td>22</td>
<td>4</td>
<td>33</td>
</tr>
<tr>
<td>RCP112</td>
<td>&gt;2,700</td>
<td>146</td>
<td>104</td>
</tr>
<tr>
<td>RCP168</td>
<td>5</td>
<td>43</td>
<td>513</td>
</tr>
<tr>
<td>RCP169</td>
<td>141</td>
<td>&gt;2,700</td>
<td>&gt;2,700</td>
</tr>
<tr>
<td>RCP188</td>
<td>&gt;2,700</td>
<td>6</td>
<td>107</td>
</tr>
<tr>
<td>RCP189</td>
<td>&gt;2,700</td>
<td>106</td>
<td>&gt;2,700</td>
</tr>
</tbody>
</table>
Our SMM-Chemokine, RCP168 Compared With T20 Peptide, The Recently Approved Drug Targeting Viral gp41 Protein Mediated HIV-1 Entry

Data from Prof. Joseph Sodroski, Harvard Medical School
Discovery of CXCR4 agonists to promote stem cell migration to the injury sites for regenerative repairs of injuries in the brain and heart

in collaboration with Evan Snyder, Stuart Lipton (neurodegeneration), Mark Mercola (cardiovascular disease)
Two Distinct Functional (Binding Vs. Signaling) Pockets on CXCR4 Important for Antagonists and Agonists, Respectively

Our finding of distinctive binding and signaling pockets on CXCR4
Summary

1. Two representative examples of pharmacologic discovery and characterization of novel small molecules and engineered peptides as basic research tools and leads for chemical and biologic drugs

2. Similar strategies for pharmaceutical research targeting cancer, infectious diseases, and neurodegeneration
SUNY Upstate Cancer Research Institute

- Established in 2009; 60,000 s.f. space and 25 new faculty positions for future growth
- Currently > 120 PIs/faculty members from basic science and clinical departments of Upstate and other universities (Downstate, Albany, Buffalo, SU, Cornell, SUNY ESF)
- Five programs in: (1) cancer biology; (2) viral oncology; (3) structural/chemical biology & bioinformatics; (4) stem cell research; and (5) drug discovery & translational research
Upstate Cancer Research Institute

Ziwei Huang, Director

Administration Office

Internal Steering Committee

External Advisory Board

Cancer Research Programs

5 basic & clinical science programs

Each program headed by program leader(s)

Core Facilities

Drug Development Center

Education

Pre-doctoral (Ph.D. & M.D.) & postdoctoral training in cancer

Other University’s Core Facilities

Upstate Cancer Center
Scientific Advisory Board

Andrew Hamilton, Ph.D., Vice Chancellor, University of Oxford

Dennis Carson, M.D., Director of UCSD Cancer Center

Curt Civin, M.D., Director of Center for Stem Cell Biology and Regenerative Medicine, University of Maryland

Joseph Bertino, M.D., Associate Director and Chief Scientific Officer of the Cancer Institute of New Jersey

Said Sebti, Ph.D., Moffitt Cancer Center

Wayne Hendrickson, Ph.D., Columbia University and HHMI

Paul Wender, Ph.D., Stanford University
Oxford’s Vice Chancellor and scientific advisor Andrew Hamilton & business advisor Philip Schein at the advisory visit in January, 2011
Upstate Cancer Research Institute

- Grant funding
- Investment
- Donation

New faculty and students

Patients

Upstate Hospital
- New cures and diagnostics

Biotech Center
- New IPs, drugs and technologies
Attracting outstanding faculty from other renowned NCI designated cancer institutes/centers, bringing in multi million dollars in NIH grants

More than 7 new faculty in 2010, 3 from Pharmacology

1. Debasish Ghosh, Ph.D., Professor (Roswell Park Cancer Institute) – cancer structural biology and drug discovery

2. Jing An, M.D., Ph.D., Associate Professor (Cancer Center of the Burnham Institute, La Jolla) – cancer drug screening and cancer and stem cell biology

3. Juntao Luo, Ph.D., Assistant Professor (UC Davis Cancer Center) – cancer drug delivery and nanomedicine
Winning the American Cancer Society’s Institutional Research Grant (ACS IRG)

1. One of 14 cancer institutes/centers (such as UCSD and UCSF cancer centers) in the country to receive ACS IRG in 2010

2. Among a selected group of cancer institutes/centers in New York (such as Sloan Kettering and Roswell Park) that have or had ACS IRG
Chairs of the Department of Pharmacology

MARION S. DOOLEY 1919-1945

ALFRED FARAH 1953-1968

ALLAN D. BASS 1945-1953

IRWIN WEINER 1969-1988

JOSE JALIFE 1989-2008

ZIWEI HUANG 2009-
Center for Drug Discovery & Development

- 6 core laboratories headed by pharmacology faculty, ~ 15,000 S.F.
- 80 faculty members in the Center

Prof. Ziwei Huang
Drug Discovery

Prof. Debasish Ghosh
Structure Determination,

Associate Prof. Ying Huang
Target Discovery

Associate Prof. Jing An
Bioassay & Screening

Assistant Prof. Juntao Luo
Drug Delivery,

Assistant Prof. Golam Mohi
Preclinical Development
Highlights of the Current Research of the Center

Prof. Ziwei Huang
Comparison of a new CXCR4 inhibitor, RCP168 with T20 Peptide, an anti-HIV drug (J. Virol., 2007)

Prof. Debashis Ghosh
First crystal structure of aromatase and its complex with breast cancer drug (Nature, 2009)

Data from Prof. Joseph Sodroski, Harvard Medical School
Highlights of the Current Research of the Center

Prof. Jing An
Combinational therapy with a novel Bcl-2 inhibitor HA14-1 and low doses of gamma radiation (Oncogene, 2007)

Prof. Juntao Luo
Novel nanocarrier for cancer imaging and cancer treatment (Bioconjugate Chem., 2010)
Translating the Research Power of Upstate/Central New York to Clinical and Industrial Applications
Successful translation of a novel CD4 inhibitor to human clinical trials and commercialization

- CD4 inhibitor currently in a Phase II human clinical trial in cancer patients who have bone marrow transplantation for the prevention of Graft-Versus Host Disease (GVHD)
- Promising new therapy for patients with cancer, immune disorders or transplant rejection
Thank you!

Upstate Cancer Research Institute (CRI)
www.upstate.edu/CRI/

Department of Pharmacology
www.upstate.edu/pharm