FCCDC

Fox Chase Chemical Diversity Center, Inc.

Drug Discovery Research Collaborator

Translating biomedical research into commercial opportunities

Pennsylvania Biotechnology Center
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January, 2017

Non-Confidential Summary of Collaboration and Service Offering

Fox Chase Chemical Diversity Center, Inc., (FCCDC) founded in 2008, is an emerging biotechnology company located in **Doylestown, PA** whose mission is to advance our clients' basic scientific discoveries by providing value-added early drug discovery and medicinal chemistry research support for the translation of viable preclinical drug and diagnostic candidates prior to eventual entry into human clinical trials. Our goal is to partner with suitable biomedical research collaborators on their selected projects or as their company's proprietary medicinal chemistry research service. We bring a unique and highly experienced team of internal scientists and collaborative external partners in order to leverage cutting edge scientific advances. The staff at FCCDC has over 220 years of drug discovery experience, drawing from a diverse background of pharmaceutical and biotech companies including Johnson & Johnson, Wyeth and Merck. FCCDC has fully functional, onsite medicinal chemistry laboratories with our own 300-MHz NMR (2), LC/MS (4), microwave reactors (2), and Gilson semi-prep HPLC (4) for compound and library purification and analysis. Importantly, and a distinguishing factor relative to other possible providers, FCCDC has onsite, free access to a >21,000 member onsite chemical inventory of reagents and starting materials, which are bar-coded, computer searchable, and segregated according to chemical class.

As the basis for our internal technology platform, we have the ability to empower research programs at multiple stages of their development: provide insight into probe molecule identification and synthesis, *in silico* identification of custom and commercial high throughput screening libraries, perform hit triage, hit to lead medicinal chemistry, and lead optimization. Importantly, we also prepare or assist in preparation of intellectual property documents. We seek to improve efficiencies in early drug discovery by quickly derisking the overall process using modern methods and wisdom regarding drug suitability and compound library evaluation.

For further information, visit our website (www.fc-cdci.com) and/or contact Allen Reitz, Ph.D. (CEO, AReitz@fc-cdci.com), Richard Scott, Ph.D. (VP Research, RScott@fc-cdci.com), or Jay Wrobel, Ph.D. (VP Academic Relations, JWrobel@fc-cdci.com).

Collaboration Options

- Multi-FTE research platform (medicinal chemistry participation on multiple projects from client proprietary chemistry or biology platform)
- FTE based hit to lead: proof of concept studies
- FTE based lead optimization to preclinical drug candidate
- NIH/DOD small business grants (SBIRs, STTRs) or basic research grants (R01, U01)
- Foundation grants (e.g., Wellcome Trust)
- VC or Angel investor based on a specific disease indication

Project Goals and Deliverables

- Molecular probes to better elucidate molecular target and understand potential therapeutic applications.
- Preclinical drug candidates from advanced screening hits
- Scale up of drug candidates, probes and chemical intermediates.
- Suitable ADME/PK properties: identify ADME/PK needs, design studies, select suitable CRO partner and interpret delivered data. Use the data in lead optimization, if warranted.
- Drug-like screening library (>7000 compounds) available for client screening assays.
- Triage of the client screening (HTS) hits, i.e., prioritizing and binning hits into potential series, eliminating poor hits that have unwanted, toxic functional groups, or are promiscuous, thereby finding the best starting points for a drug discovery program.
- Guide preclinical drug candidates though the IND enabling process.
- Intellectual property management and protection of the chemical matter.
- Assist client in preparation/execution of external documents/presentations in their pursuit of funding opportunities (public or private).

Scientific and Support Staff

Current staffing: 22 total, with 19 bench scientists, 13 Ph.D.-level, 7 M.S./M.Sc., 2 B.A.

- Synthesis Support and NCE Criteria.
  - New chemical entity (NCE) output at >100 compounds/person/year.
  - NCE purity goal of >95% as assessed by NMR, LC/MS.
  - Design molecules with industry standard *in silico* drug-like properties, devoid of unwanted functional groups.
  - Multiseat licenses for SciFinder (structure/reaction searching) and Chem Axon (internal compound database, *in silico* calculations).
- Biology and Pharmacology (onsite, Ph.D.-level experienced biologist).
  - Cytotoxicity screening using multiple cell lines.
  - Red blood cell hemolysis assays.
  - Bacterial MICs
  - Antifungal MICs

FCCDC Equipment and Infrastructure

5,500 ft^2 laboratory space; 3,000 ft^2 office space.

2 NMRs: Varian Mercury Plus 300-MHz Inova NMRs with multinuclear capability (^{1}H, ^{13}C, ^{31}P, ^{18}F).

HPLC/MS:
- Two Micromass ZQ Mass Spec. with Waters 2695 HPLC systems with 996 diode array detector.
- Two Thermo-Finnegan Surveyor Plus HPLC with MSQ Plus Mass Spec.
- Shimadzu Prominence and Agilent 1100 HPLCs.

Chromatography:
- Four Gilson 215 semi-prep HPLC systems, multi-wavelength, automated fraction collection.
- Three Teledyne Isco CombiFlash Rf, automated chromatography system.
- Three Isco Combiflash Sg 100c, personal chromatography systems.

Evaporation:
- Genevac EZ2 Evaporation System.
- Two FTS Systems Flexi-dry Lyophilyzer.
- 15 Rotavapors with vacuum pumps (Buchi, Heidolph).
- 2 VWR Sheldon 1400E Vacuum Ovens with Edwards oil pumps.

Hydrogenation: Three Parr 3911 Shaker hydrogenators.

Reaction:
- Two Biotage Initiator microwave synthesizer with 60 position autosampler.
- Innova platform shakers, model 2000.
- Six J-Kem Gemini-2 dual temperature controllers with teflon-coated thermocouples.
- >30 Ika Magnetic Stirrer/Hotplates.

BL2 Biological Lab and tissue culture lab:
- Baker SG400 and Labconco A2 Class II biological safety cabinets.
- ABI Prism 7000 Sequence Detection System.
- New Brunswick Environmental incubator shaker and incubator.
- Biotek Synergy 2 Multi-Detection Microplate Reader.
- Molecular Devices SpectraMax 190 microplate reader.
- Titertek Multidrop.
- Labomed iVU 1500 Microscope.
- Fisher and VWR Carbon dioxide incubators..

Storage, Miscellaneous:
- Four Justrite 45 Gallon Flammable Safety Cabinets.
- Four Refrigerator/Freezers, Frigidaire, GE, Revco.

Full Access to Pennsylvania Drug Discovery Institute (PDDI) Resources Onsite:
Reagent Collection: >20,000 reagents (>800 boronic acids), bar coded, searchable database

Therapeutic Area Experience

CNS (neurology, psychiatry cognitive disorders), Antiinfectives (antibacterial, antiviral, and antifungal), Cardiovascular (atherosclerosis, hyperlipidemia), Inflammation and Immunology, Metabolic Disorders (diabetes, diabetic complications, obesity), Oncology. *Targets*: GPCRs, Ion Channels, Kinases, Nuclear Hormone Receptors, Proteases, Protein-Protein interaction, Phenotypic Screening.

Our Drug Discovery / Medicinal Chemistry Processes

- *Chemical hit evaluation*
  - Confirmation of activity, structure and purity
  - Remove promiscuous inhibitors or aggregators
- *Hit to chemical lead by improving drug-like characteristics via iterative SAR processes*
  - Prepare small focused libraries or individual compounds
  - Improve *in vitro* potency and selectivity over similar protein targets
    - Assays in-house for antimicrobial and antifungal targets
    - Capability to develop additional in vitro biological assays
  - Improve physiochemical properties such as aqueous solubility, logP and tPSA
  - Monitor and reduce early toxicity liabilities
    - Cytotoxicity in relevant cell lines and RBC hemolysis
  - Early assessment of PK profile
  - Early assessments of efficacy in disease models
  - Incorporate *in-silico* computational and structure-based design
    - Molecular modeling: pharmacophore design and docking
    - Physiochemical design for drug-likeness and toxicity derisking: Rule of 5, Ligand Efficiency (LE), Ligand-Lipophilicity Efficiency (LipE)
    - Iterative X-ray crystallography (where applicable)
- *Choose chemical lead and optimize to preclinical drug candidate*
  - Lead status based on industry standard criteria and reviewed by consultants
  - Ensure patentability
  - Continue standard SAR optimization practices but focus on:
    - Minimize P450 cyp inhibition, cyp induction, efflux potential, plasma protein binding, and off target activities (e.g. hERG Ames)
    - Optimize solubility in aqueous vehicles, microsomal stability in multiple species, permeability and PK profile in multiple species
  - Obtain efficacy and potency target goals in animal disease models
  - Evaluate toxicity in cell and animal models

Grants Administration Conducted Onsite

Our senior staff has extensive experience in extramural grant application and administration. We can help identify appropriate grants, prepare and submit applications, ensure compliance and obtain funding from a variety of federal, state and private funding sources. Our onsite CFO and her staff file and administer all of our grants and contracts. We are audited by an external CPA firm on an annual basis.

Intellectual Property Management

This is a very important service that we provide our collaborators. Generally new composition of matter and/or known chemicals resulting in novel method of treatment will be produced during execution of research projects. Our company is flexible with respect to achieving mutually acceptable terms and conditions of an appropriate IP management agreement. We determine inventorship of intellectual property generated during the performance of the research in accordance with U.S. patent law, and ownership and commercialization of the IP will governed in accordance with the IP management agreement being entered into by and between the parties. Our staff has extensive pharmaceutical intellectual property experience with >200 issued U.S. patents and are well versed in the mechanics and opportunities afforded by patent filing and prosecution. Thus we can be directly involved in the preparation of draft documents which would be finalized and filed by our registered patent agent below. We follow all good laboratory practices regarding confidentiality and the keeping of laboratory notebooks, which are counter-signed and witnessed monthly using an automated reminder system. Our spectral data is stored electronically on a server, with a second back-up server also used to ensure records retention. We use the ACD software to prepare spectral data write-ups, which saves a great deal of time in the preparation of patent applications. We use SciFinder with a company license to explore novelty both with regard to freedom to operate and the potential for the creation of new composition of matter intellectual property. We can work with any patent attorney or registered patent agents in the preparation of new patent applications.

Current Legal counsel:

- We work with multiple legal firms.
- **Registered patent agent:** Benjamin E. Blass, Ph.D.

Leadership

Allen B. Reitz, Ph.D. (Founder, Chief Executive Officer): >35 years of demonstrated accomplishment as a medicinal chemist in the pharmaceutical industry, including nearly 26 years with Johnson & Johnson. At J & J he led the medicinal chemistry research effort in the area of the diseases of the central nervous system for both psychiatry and neurology at the Spring House, Pennsylvania Facility for most of his time there. He is co-inventor as well as Team Leader, in most cases, for seven compounds that have entered human clinical trials. He has >140 scientific publications and 60 issued U.S. patents, and is Editor-in-Chief of the journal *Current Topics in Medicinal Chemistry*. He is also Adjunct Professor at Drexel University College of Medicine, and has an Executive Masters in Technology Management from the University of Pennsylvania (Wharton). Dr. Reitz is also co-founder and CEO of ALS Biopharma, LLC, focusing on the neurological condition of amyotrophic lateral sclerosis.

Kathleen Czupich, M.B.A., (Chief Financial Officer): > 22 years of experience in business development. Prior to joining FCCDC Ms. Czupich was the Chief Financial Officer of the PA Biotechnology Center, Institute for Hepatitis and Virus Research and the Hepatitis B Foundation and was point of contact for all NIH grants and other government funding totaling more than $5 million. Ms. Czupich holds a B.S. degree in Accounting from the Pennsylvania State University and an M.B.A from Lehigh University, Bethlehem, PA. She is experienced in indirect cost requirements and negotiation. Ms. Czupich managed the financial and administrative aspects of a $7.9 million grant to construct the PBC and the resulting building project totaling more than $14 million. She was also instrumental in the negotiation, financing and purchase of the adjacent building, expanding the PBC to 115,000 square feet.

Richard W. Scott, Ph.D. (Vice President, Research): 36 years in the pharmaceutical industry and has broad experience in several disciplines including anti-infectives, acute coronary care, neurobiology and animal model development. He began his career at E.I. Dupont deNemours and then moved to Cephalon where he held positions of increasing responsibility leading to Vice President of Neurobiology. In 2002, he co-founded PolyMedix, and led the research team responsible for the identification and selection of two clinical compounds. He is an author on >70 peer-reviewed journal articles and book chapters and inventor on 16 U.S. patents.

Jay E. Wrobel, Ph.D. (Vice President, Academic Relations): 33 years as a medicinal chemist in the pharmaceutical industry, 27 years at Wyeth (later Pfizer), with his last position as Senior Director of Medicinal Chemistry at the Collegeville, PA facility. At Wyeth he mentored and guided the efforts of 31 Ph.D./MS medicinal chemists and worked successfully with outside alliance partners. He was directly involved in bringing forward nine development track candidates (Phase 0 and beyond) in a variety of therapeutic areas. He has co-authored 74 scientific publications and is an inventor on 78 issued U.S. patents.

Garry Smith, Ph.D. (Director of Chemistry): 23 years of experience in pharmaceutical drug discovery research with broad experience including 10 years in medicinal chemistry at Merck Research Labs and over 8 years at contract research organizations managing synthetic chemistry, eADME and toxicology teams of up to 30 Ph.D./MS. level scientists. Dr. Smith has extensive experience in project management, target validation, hit triage, hit-to-lead and lead optimization medicinal chemistry, and eADME profiling. He has made significant contributions in multiple therapeutic areas: oncology, neurology, cardiovascular and osteoporosis. He has 30 scientific publications and 8 issued U.S.patents.

Selected Recent Publications

Gregg, R. A.; Hicks, C.; Nayak, S. U.; Tallarida, C. S.; Nucero, P.; Smith, G. R.; Reitz, A. B.; Rawls, S. M. Synthetic cathinone MDPV downregulates glutamate transporter subtype 1 (GLT-1) and produces rewarding and locomotor-activating effects that are reduced by a GLT-1 activator. *Neuropharmacology*, **2016** *108*, 111-118.

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Vouga, A.;Gregg, R. A.;Haidery, M.;Ramnath, A.; Al-Hassani, H. K.;Tallarida, C. S.; Grizzanti, D.; Raffa, R. B.;Smith, G. R.;Reitz, A. B.;Rawls, S. M. Stereochemistry and neuropharmacology of a 'bath salt' cathinone: S-enantiomer of mephedrone reduces cocaine-induced reward and withdrawal in invertebrates. *Neuropharmacology* **2015**, *91*, 109-16.

Rubin, H.; Selwood, T.; Yano, T.; Weaver, D. G.; Loughran, H. M.; Costanzo, M. J.; Scott, R. W.; Wrobel, J. E.; Freeman, K. B.; Reitz, A. B. *Acinetobacter baumannii* OxPhos inhibitors as selective anti-infective agents. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 378-383.

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Pelletier, J. C.; Velvadapu, V.; McDonnell, M. E.; Wrobel, J. E.; Reitz, A. B. Intramolecular rearrangement of α-amino acid amide derivatives of 2-aminobenzothiazoles. *Tetrahedron Lett.* **2014**, *55*, 4193-4195.

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