FCTDI

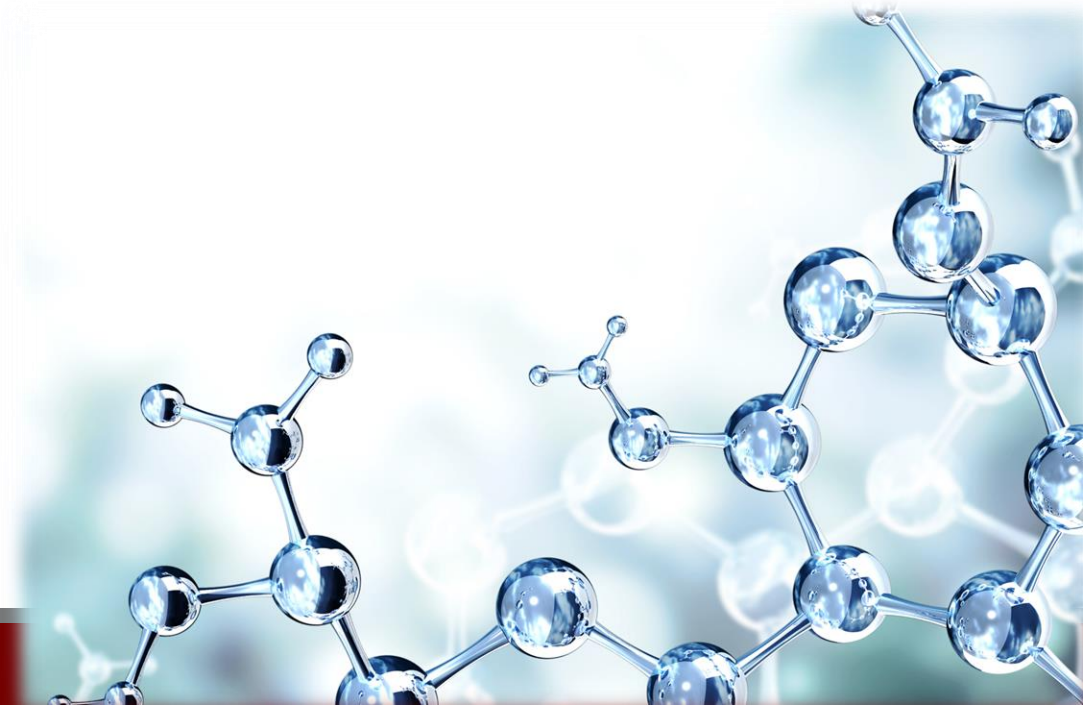
FCTDI: History, Capabilities and Experience

3805 Old Easton Rd.

Doylestown, PA 18902

October, 2023

www.fctdi.com



History

Originally named Fox Chase Chemical Diversity Center, Inc. (FCCDC) as the early focus was on medicinal chemistry

Renamed **Fox Chase Therapeutics Discovery, Inc. (FCTDI)** to highlight the addition of pharmacology and biochemistry and to emphasize the overall goal of discovering new small-molecule therapeutics to treat human disease

Founded in 2008 and received a Small Business Innovation Research (SBIR) grant in 2009 awarded in collaboration with a researcher at the Fox Chase Cancer Center, but is not affiliated with the Fox Chase Cancer Center in any way

Has received 28 Phase I and 12 Phase II SBIRs/STTRs, Department of Defense funding, support from three private foundations, investment support, and sponsored research funding

Total of >$45M in non-dilutive federal research funding

Prepared >15,600 New Chemical Entities (NCEs) as probe and drug candidates

Three compounds have advanced into human clinical trials together with collaboration partners

Leadership Team

Allen B. Reitz, Ph.D.
Chief Executive Officer and Founder

- Ph.D. in Chemistry, UC San Diego
- Executive Master's, Univ. of Pennsylvania
- Worked at Johnson & Johnson for 26 yrs
- Nine compounds in human clinical trials including mazapertine and troriluzole
- Co-authored 180 scientific publications, inventor on 79 issued US patents

Kathleen Czupich, M.B.A.
Chief Financial Officer

- >25 yrs of demonstrated accomplishment in the medical research industry in M&A, valuations and due diligence.
- M.B.A. from Lehigh University
- Managed financial and administrative aspects of >$50+ Million in federal grants mainly from the NIH

Jay E. Wrobel, Ph.D.
Vice President, Academic Relations

- At Wyeth, directly involved in bringing forward nine development track candidates (phase 0 and beyond) in a variety of therapeutic areas
- PI or Key Personnel on 17 SBIR/STTR funded grants
- 79 publications, inventor on 84 patents

Richard W. Scott, Ph.D.
Vice President, Research

- Ph.D., Microbiology, University of Pennsylvania
- 38 years in the pharmaceutical industry
- Extensive leadership in multiple disciplines including anti-infectives and neurobiology
- >69 peer reviewed publications, 17 US patents

Jeffrey C. Pelletier, Ph.D.
Director of Chemistry

- >35 years of experience in Medicinal Chemistry
- Experience in Big Pharma (Wyeth), Biotech and Academia
- Been with FCTDI for >10 years
- Coinventor of troriluzole
- >100 patents and publications

Katie B. Freeman, Ph.D.
Director of Biology

- PhD in Microbiology, University of Virginia
- >25 years experience in Pharma and Biotech
- Developed multiple in vitro assays on varied platforms to support SAR and compound mechanism of action studies
- >25 papers, inventor on 7 US patents.

Experience

Partial list of therapeutic area and target classes studied

- Oncology, Diabetes and Obesity, Inflammation and Immunology
- Anti-infectives (antibacterial, antiviral, antifungal)
- Central nervous system, neurology and psychiatry
- Ion channels (K, Na, Ca, nAChRs)
- GPCRs (integrins, $a_v b_3$, 5-HT, dopamine, adrenergic)
- Kinases (Raf, p38, DAPK, tryptase)
- Prodrugs and soft drugs

>315 Years of combined industrial experience

- Big Pharma (JNJ, Merck, GSK, Pfizer/Wyeth, DuPont)
- Biotech (Poymedix, Lexicon, Symphony, Alsgen, Tetralogic)
- 13 PhD-level scientific staff

Laboratories

Location: The Pennsylvania Biotechnology Center

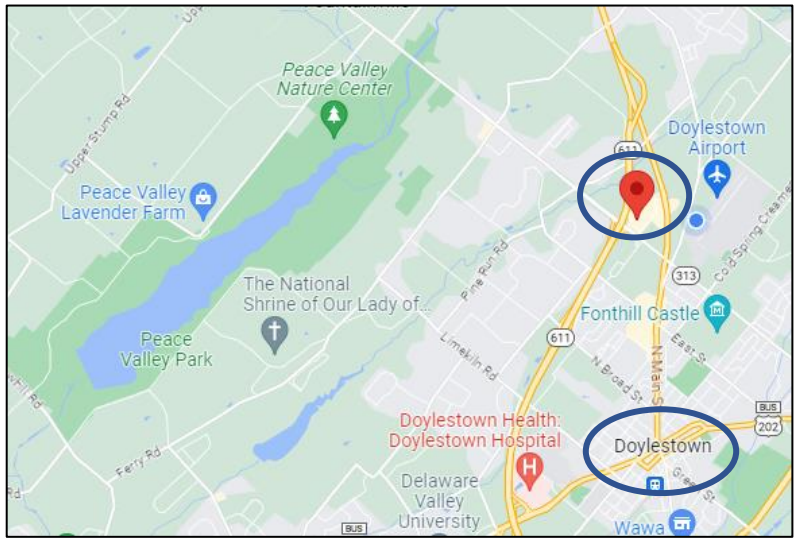
Doylestown, PA, north of Philadelphia

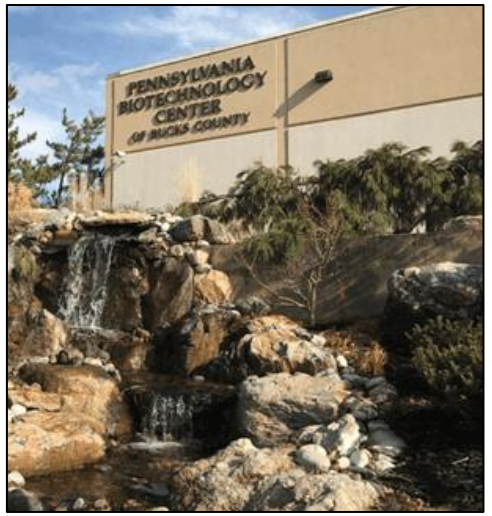
11,000 ft^2 combined laboratory and office space

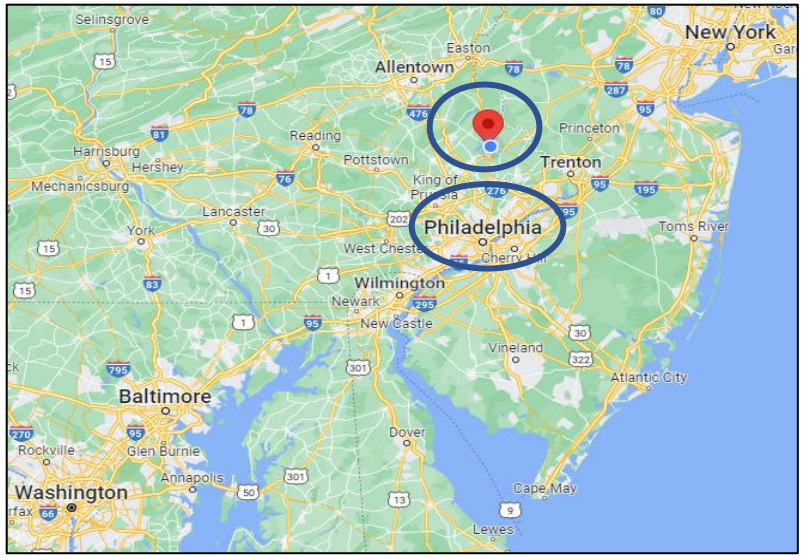
Fully outfitted with room to grow

Partial list of onsite resources and instrumentation

- 400-MHz 1H NMR, multinuclear probe, 2D capabilities
- Four Micromass ZQ Mass Spectrometers, Waters HPLC systems
- Wyatt DynaPro NanoStar Dynamic Light Scattering (DLS) instrument
- J-810 Jasco Circular Dichroism (CD) instrument
- IDA ElectraSyn 2.0 apparatus for electrochemical reactions
- Two microwave synthesis units
- >34,000 Reagents and starting materials including >2,000 boronic acids
- BSL2 pharmacology laboratories
- Cytation 5 with Biospa DAPI, TR, GRP 4 - 60 X objective
- BioRad Opus 384 Real-Time PCR Detection System
- Nikon Eclipse (TE 2000) microscope with image analysis software





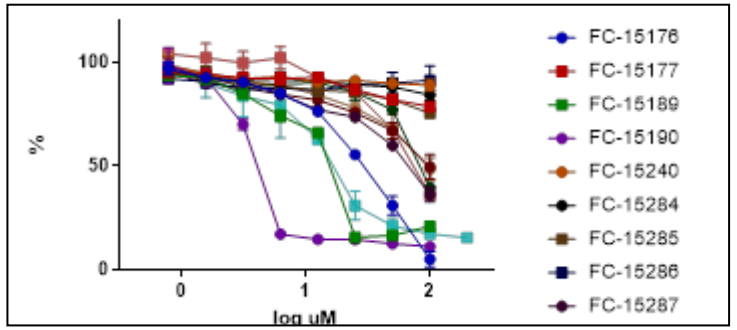


Drug Discovery Innovation via Iteration

Onsite: ~36,000 reagents and starting materials
Schrodinger software (AI, machine learning)
Competitive landscape and IP analysis

Researchers working together
FC has prepared >15,600 registered NCEs

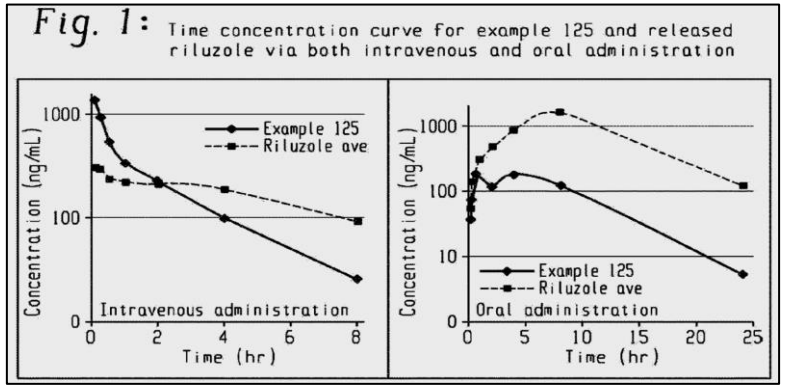
Primary biochemical assay(s)
Cytotoxicity testing (therapeutic index)
Cloning and expression of relevant proteins



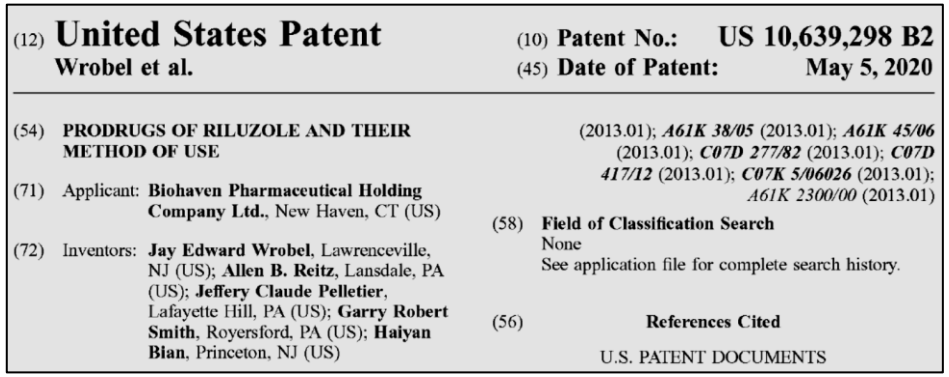
Secondary functional assay(s) in cells
Use of patient-derived stem cells as needed

- IND Enabling studies, multiple species
- Identification and collaboration with suitable development partners
- Clinical trials, NDA, commercialization, treatment of disease

ADME testing: hERG, Cyps, plasma protein binding, metabolic stability (m,r,d,nhp,h)
Pharmacokinetics testing (m,r,d,nhp if needed)



Patent applications and prosecution support



(12) **United States Patent**
Wrobel et al.

(10) **Patent No.: US 10,639,298 B2**
(45) **Date of Patent: May 5, 2020**

(54) **PRODRUGS OF RILUZOLE AND THEIR METHOD OF USE**

(71) Applicant: **Biohaven Pharmaceutical Holding Company Ltd.**, New Haven, CT (US)

(72) Inventors: **Jay Edward Wrobel**, Lawrenceville, NJ (US); **Allen B. Reitz**, Lansdale, PA (US); **Jeffery Claude Pelletier**, Lafayette Hill, PA (US); **Garry Robert Smith**, Royersford, PA (US); **Haiyan Bian**, Princeton, NJ (US)

(2013.01); *A61K 38/05* (2013.01); *A61K 45/06* (2013.01); *C07D 277/82* (2013.01); *C07D 417/12* (2013.01); *C07K 5/06026* (2013.01); *A61K 2300/00* (2013.01)

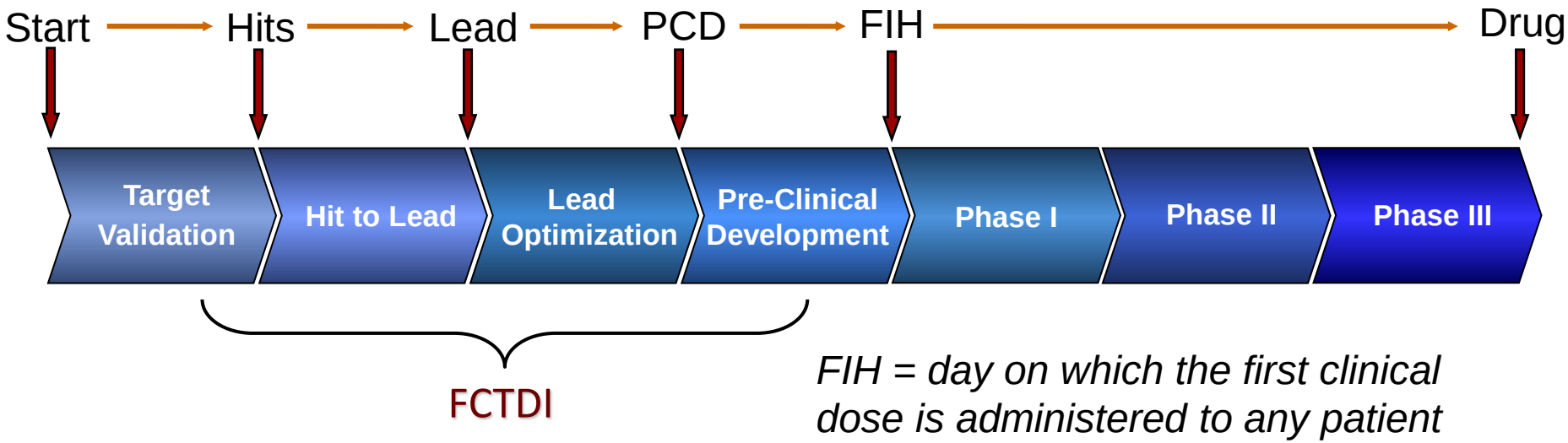
(58) **Field of Classification Search**
None
See application file for complete search history.

(56) **References Cited**
U.S. PATENT DOCUMENTS

Patent containing troriluzole for which an NDA has been filed

See www.fctdi.com for case stories, list of issued U.S. patents and publications

Drug Discovery Research Continuum



FCTDI is a value-added early-stage drug discovery partner focusing on

- unmet medical need
- new commercial opportunities
- creation of new intellectual property
- innovative pharmacology

SAR Development in Target Validation

Structure Activity Relationship (SAR) analysis to validate a proposed new molecular target to treat human disease

Hits and probes are obtained from computational prescreening, compound library screening, *in silico* design, literature precedent, and considerations of structural diversity

Preparation of smaller focused libraries or bifunctional conjugates to understand the relation of structure to function early on

Example:

Synthesis, Stereochemical Analysis, and Derivatization of Myricanol Provide New Probes That Promote Autophagic Tau Clearance

Mackenzie D. Martin,[†] Laurent Calcul,[‡] Courtney Smith,[‡] Umesh K. Jinwal,[†] Sarah N. Fontaine,[†] April Darling,[†] Kent Seeley,[‡] Lukasz Wojtas,[‡] Malathi Narayan,[†] Jason E. Gestwicki,[§] Garry R. Smith,[∥] Allen B. Reitz,[∥] Bill J. Baker,[*,‡] and Chad A. Dickey[*,‡,†,⊥]

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Supporting Information

ABSTRACT: We previously discovered that one specific scalemic preparation of myricanol (**1**), a constituent of *Myrica cerifera* (bayberry/southern wax myrtle) root bark, could lower the levels of the microtubule-associated protein tau (MAPT). The significance is that tau accumulates in a number of neurodegenerative diseases, the most common being Alzheimer's disease (AD). Herein, a new synthetic route to prepare myricanol using a suitable boronic acid pinacol ester intermediate is reported. An X-ray crystal structure of the isolated myricanol (**1**) was obtained and showed a co-crystal consisting of (+)-aR,11S-myricanol (**2**) and (−)-aS,11R-myricanol (**3**) coformers. Surprisingly, **3**, obtained from chiral separation from **1**, reduced tau levels in both cultured cells and *ex vivo* brain slices from a mouse model of tauopathy at reasonable mid-to-low micromolar potency, whereas **2** did not. SILAC proteomics and cell assays revealed that **3** promoted tau degradation through an autophagic mechanism, which was in contrast to that of other tau-lowering compounds previously identified by our group. During the course of structure−activity relationship (SAR) development, we prepared compound **13** by acid-catalyzed dehydration of **1**. **13** had undergone an unexpected structural rearrangement through the isomyricanol substitution pattern (*e.g.*, **16**), as verified by X-ray structural analysis. Compound **13** displayed robust tau-lowering activity, and, importantly, its enantiomers reduced tau levels similarly. Therefore, the semisynthetic analogue **13** provides a foundation for further development as a tau-lowering agent without its SAR being based on chirality.

Aberrant accumulation of the microtubule-associated protein tau is implicated in ~20 neurodegenerative disorders, collectively termed tauopathies, including chronic traumatic encephalopathy (CTE), Alzheimer's disease (AD), frontal temporal dementia linked to chromosome 17 (FTDP-17), Parkinson's disease, and Pick's disease.[1,2] Some of these diseases can be caused by mutations in the MAPT gene that result in amino acid substitution in critical microtubule-interacting domains.[3] Tauopathies may also result from a cascade of pathological events, such as amyloid β aggregation, leading to microtubule destabilization and the hyperphosphorylation of tau.[4] Tau hyperphosphorylation induces the formation of toxic

had mixed results in the clinic, but none of these inhibitors has been reduced to practice.[8,9] Immunotherapy is another strategy that is being extensively investigated to treat tauopathies. Both active and passive immunotherapy approaches can successfully remove pathological forms of tau in mouse models,[7] but passive immunization holds more promise in the clinic because of its higher selectivity for discrete tau species and greater administrative control in the event of autoimmune reactions. However, even this strategy has some safety concerns since phosphorylated tau species are found in normal as well as AD brains.[10] Nevertheless, clinical trials using passive immunization with antibodies targeting tau are ongoing. Another strategy being

SAR Development in Hit to Lead

Preparation of relatively-large number of related chemical analogs

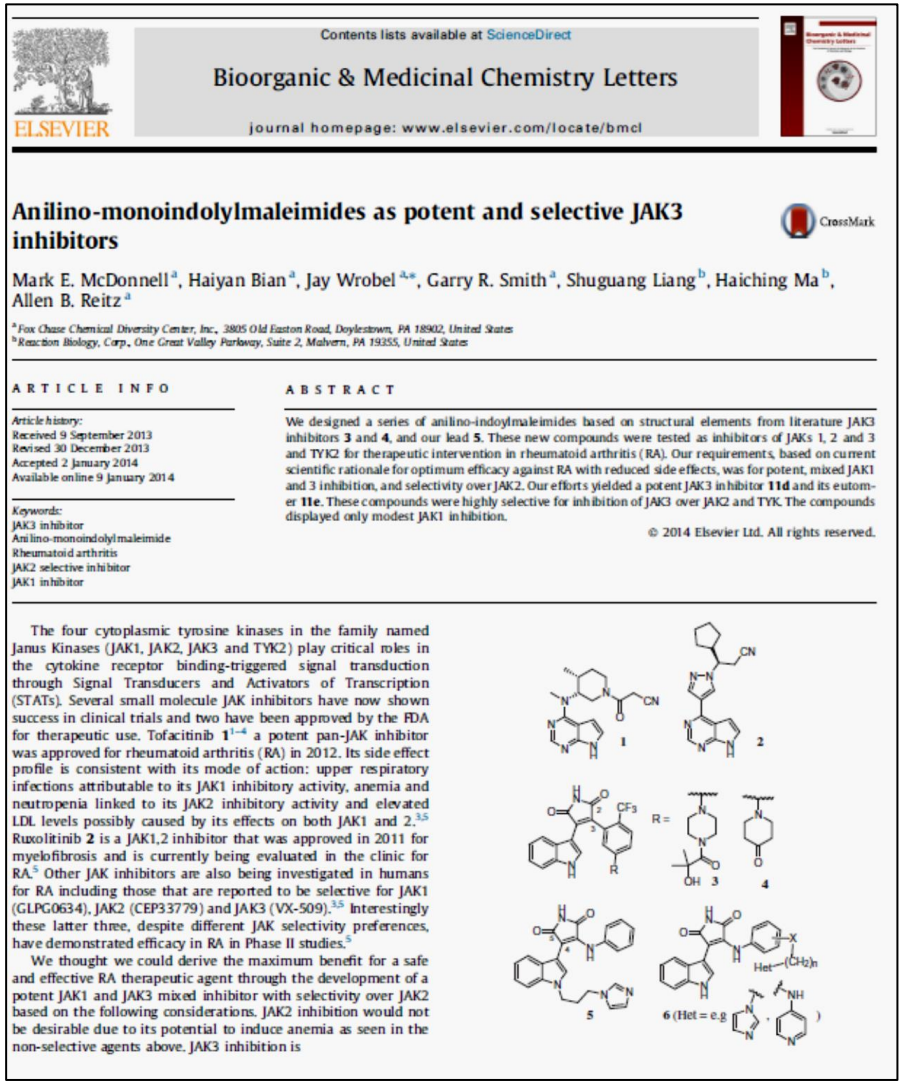
Factors to consider:

- Activity of hits
- Ease of synthesis
- IP position, and
- Assay throughput

Improve potency of hits as the SAR is established and understood

Initial understanding of metabolic stability from standard in vitro assays

Example:



Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Anilino-monoindolylmaleimides as potent and selective JAK3 inhibitors

Mark E. McDonnell[a], Haiyan Bian[a], Jay Wrobel[a,*], Garry R. Smith[a], Shuguang Liang[b], Haiching Ma[b], Allen B. Reitz[a]

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JAK3 inhibitor
Anilino-monoindolylmaleimide
Rheumatoid arthritis
JAK2 selective inhibitor
JAK1 inhibitor

ABSTRACT

We designed a series of anilino-indoylmaleimides based on structural elements from literature JAK3 inhibitors **3** and **4**, and our lead **5**. These new compounds were tested as inhibitors of JAKs 1, 2 and 3 and TYK2 for therapeutic intervention in rheumatoid arthritis (RA). Our requirements, based on current scientific rationale for optimum efficacy against RA with reduced side effects, was for potent, mixed JAK1 and 3 inhibition, and selectivity over JAK2. Our efforts yielded a potent JAK3 inhibitor **11d** and its eutomer **11e**. These compounds were highly selective for inhibition of JAK3 over JAK2 and TYK. The compounds displayed only modest JAK1 inhibition.

The four cytoplasmic tyrosine kinases in the family named Janus Kinases (JAK1, JAK2, JAK3 and TYK2) play critical roles in the cytokine receptor binding-triggered signal transduction through Signal Transducers and Activators of Transcription (STATs). Several small molecule JAK inhibitors have now shown success in clinical trials and two have been approved by the FDA for therapeutic use. Tofacitinib **1**[1–4] a potent pan-JAK inhibitor was approved for rheumatoid arthritis (RA) in 2012. Its side effect profile is consistent with its mode of action: upper respiratory infections attributable to its JAK1 inhibitory activity, anemia and neutropenia linked to its JAK2 inhibitory activity and elevated LDL levels possibly caused by its effects on both JAK1 and 2.[3,5] Ruxolitinib **2** is a JAK1,2 inhibitor that was approved in 2011 for myelofibrosis and is currently being evaluated in the clinic for RA.[5] Other JAK inhibitors are also being investigated in humans for RA including those that are reported to be selective for JAK1 (GLPG0634), JAK2 (CEP33779) and JAK3 (VX-509).[3,5] Interestingly these latter three, despite different JAK selectivity preferences, have demonstrated efficacy in RA in Phase II studies.[5]

We thought we could derive the maximum benefit for a safe and effective RA therapeutic agent through the development of a potent JAK1 and JAK3 mixed inhibitor with selectivity over JAK2 based on the following considerations. JAK2 inhibition would not be desirable due to its potential to induce anemia as seen in the non-selective agents above. JAK3 inhibition is

SAR Development in Lead Optimization

Preparation of focused libraries based on validated leads

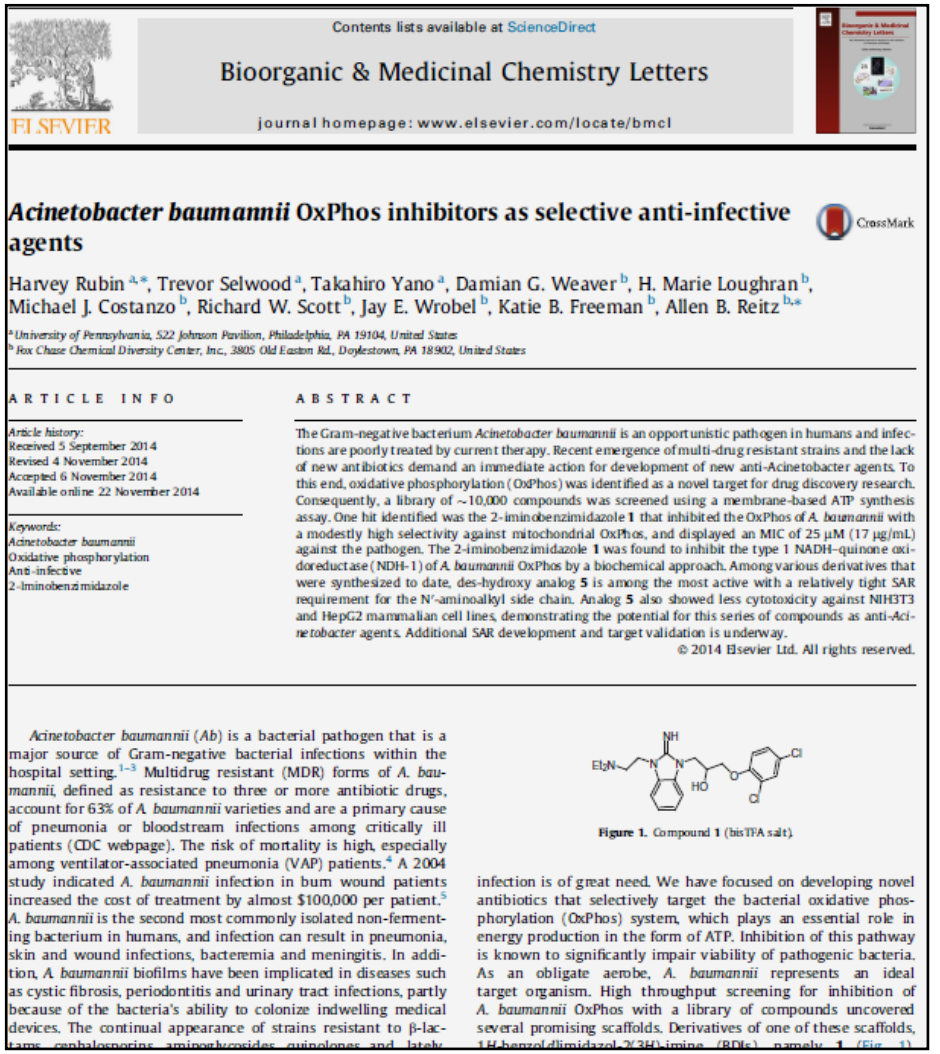
Absorption Distribution Metabolism Excretion (ADME) characterization

- Microsome and hepatocyte stability (human plus other species)
- Cyp 3A4, 2D6, etc.: drug-drug interactions
- Transporters: Caco-2, PAMPA, P-gP
- Plasma protein binding (human plus other species)
- Salt screening and formulations development

Off-target screening, including hERG, GPCRs, ion channels + others

Pharmacokinetics: T_{max}, $t_{1/2}$, C_{max}, %F; mice first, then rats and dogs

Example:



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Acinetobacter baumannii OxPhos inhibitors as selective anti-infective agents

Harvey Rubin [a,*], Trevor Selwood [a], Takahiro Yano [a], Damian G. Weaver [b], H. Marie Loughran [b], Michael J. Costanzo [b], Richard W. Scott [b], Jay E. Wrobel [b], Katie B. Freeman [b], Allen B. Reitz [b,*]

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Acinetobacter baumannii
Oxidative phosphorylation
Anti-infective
2-Iminobenzimidazole

ABSTRACT

The Gram-negative bacterium *Acinetobacter baumannii* is an opportunistic pathogen in humans and infections are poorly treated by current therapy. Recent emergence of multi-drug resistant strains and the lack of new antibiotics demand an immediate action for development of new anti-Acinetobacter agents. To this end, oxidative phosphorylation (OxPhos) was identified as a novel target for drug discovery research. Consequently, a library of ~10,000 compounds was screened using a membrane-based ATP synthesis assay. One hit identified was the 2-iminobenzimidazole **1** that inhibited the OxPhos of *A. baumannii* with a modestly high selectivity against mitochondrial OxPhos, and displayed an MIC of 25 μM (17 μg/mL) against the pathogen. The 2-iminobenzimidazole **1** was found to inhibit the type 1 NADH–quinone oxidoreductase (NDH-1) of *A. baumannii* OxPhos by a biochemical approach. Among various derivatives that were synthesized to date, des-hydroxy analog **5** is among the most active with a relatively tight SAR requirement for the N′-aminoalkyl side chain. Analog **5** also showed less cytotoxicity against NIH3T3 and HepG2 mammalian cell lines, demonstrating the potential for this series of compounds as anti-*Acinetobacter* agents. Additional SAR development and target validation is underway.

Acinetobacter baumannii (*Ab*) is a bacterial pathogen that is a major source of Gram-negative bacterial infections within the hospital setting.[1–3] Multidrug resistant (MDR) forms of *A. baumannii*, defined as resistance to three or more antibiotic drugs, account for 63% of *A. baumannii* varieties and are a primary cause of pneumonia or bloodstream infections among critically ill patients (CDC webpage). The risk of mortality is high, especially among ventilator-associated pneumonia (VAP) patients.[4] A 2004 study indicated *A. baumannii* infection in burn wound patients increased the cost of treatment by almost $100,000 per patient.[5] *A. baumannii* is the second most commonly isolated non-fermenting bacterium in humans, and infection can result in pneumonia, skin and wound infections, bacteremia and meningitis. In addition, *A. baumannii* biofilms have been implicated in diseases such as cystic fibrosis, periodontitis and urinary tract infections, partly because of the bacteria's ability to colonize indwelling medical devices. The continual appearance of strains resistant to β-lactams, cephalosporins, aminoglycosides, quinolones and lately

Figure 1. Compound **1** (bisTFA salt).

infection is of great need. We have focused on developing novel antibiotics that selectively target the bacterial oxidative phosphorylation (OxPhos) system, which plays an essential role in energy production in the form of ATP. Inhibition of this pathway is known to significantly impair viability of pathogenic bacteria. As an obligate aerobe, *A. baumannii* represents an ideal target organism. High throughput screening for inhibition of *A. baumannii* OxPhos with a library of compounds uncovered several promising scaffolds. Derivatives of one of these scaffolds, 1*H*-benzo[*d*]imidazol-2(3*H*)-imine (BDIs), namely **1** (Fig. 1)

FCTDI Computational Chemistry, Structural Biology

Computational methods are employed throughout the entire process

Pharmacophore SAR development and computational docking to targets

Software used: Schrodinger, ChemAxon, DataWarrior, ACD

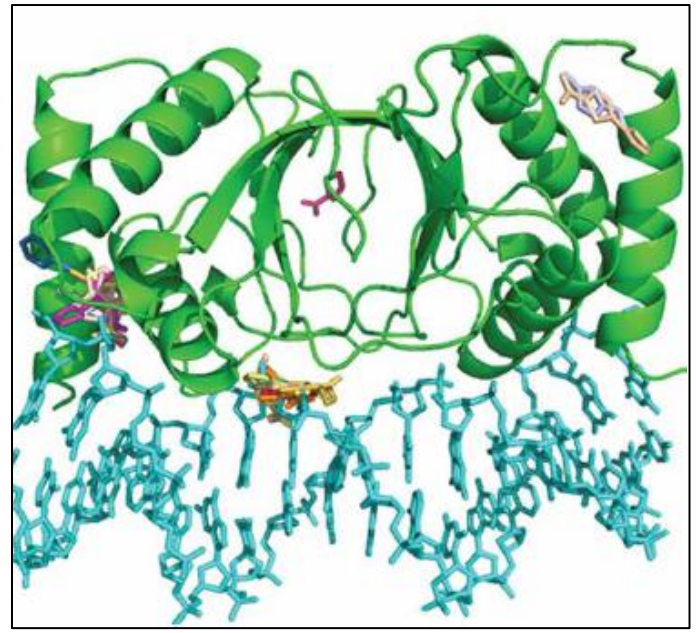
Use of drug-likeness metrics including ligand efficiency (LiPE)

Fragment-based drug discovery

Prodrug and soft drug approaches

X-ray and cryo-EM with collaborators

Example:



X-ray structure of an inhibitor of Epstein Barr Nuclear Antigen EBNA1 co-crystalized with the protein: FCTDI collaboration with The Wistar Institute (Messick et al., Sci. Transl. Med. 11, eaau5612, 2019).

Creation of New Intellectual Property

Freedom to operate and competitive landscape analysis

Industry-standard archiving of notebooks and data

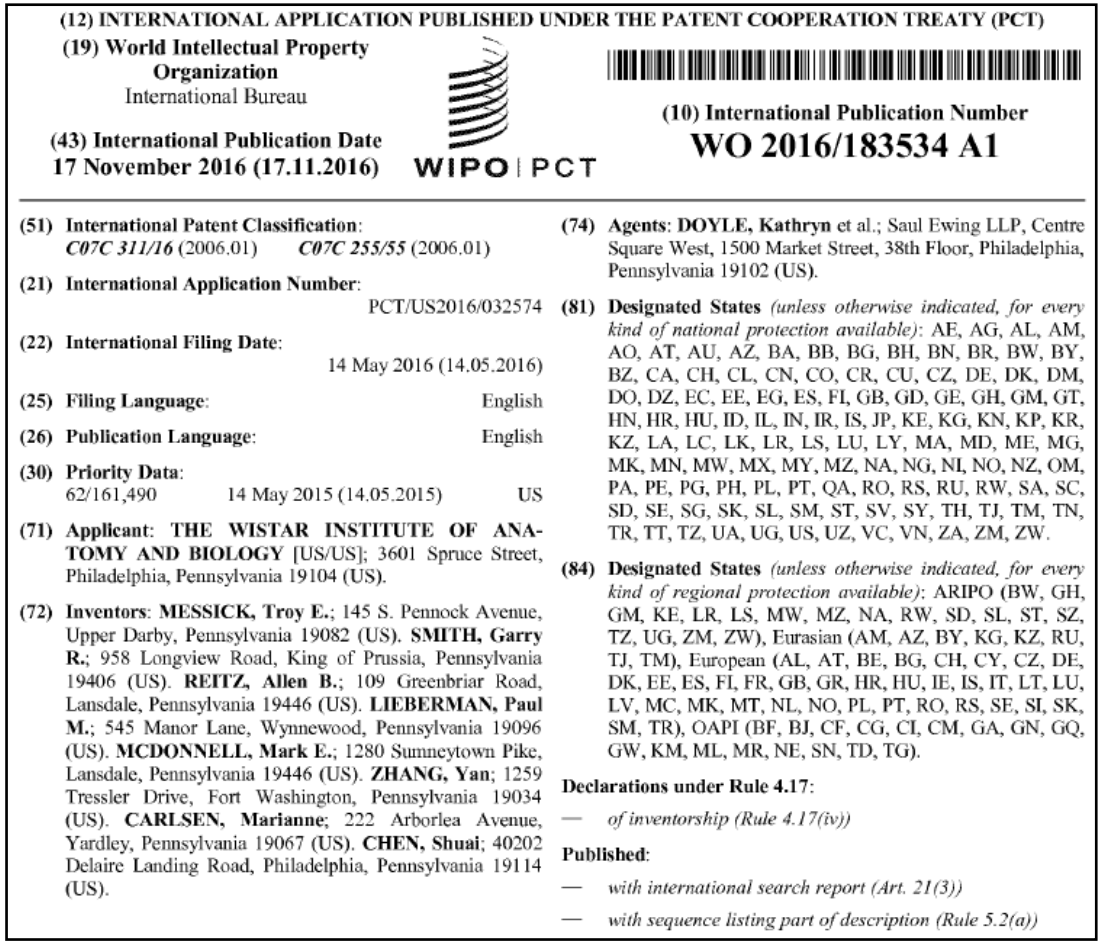
Back-up computer systems to prevent loss of data

Writing of applications with collaborators as appropriate

Assisting in patent prosecution as needed

>20 Issued U.S. patents total

Example:



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(25) Filing Language: English

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(30) Priority Data:
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(74) Agents: **DOYLE, Kathryn** et al.; Saul Ewing LLP, Centre Square West, 1500 Market Street, 38th Floor, Philadelphia, Pennsylvania 19102 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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Declarations under Rule 4.17:
— *of inventorship (Rule 4.17(iv))*

Published:
— *with international search report (Art. 21(3))*
— *with sequence listing part of description (Rule 5.2(a))*

FCTDI Financial Management Practices and Controls

FCTDI Financial Management. FCTDI receives funds from the National Institutes of Health. As such, it is required to conduct an annual audit subject to GASB standards (standards set by the Government Accounting Standards Board). FCTDI submits its annual audit to the NIH as part of its yearly compliance checklist. FCTDI's audit includes a review and opinion on the company's internal control policies. Its internal control policies ensure tight control over resources, while also compartmentalizing activities into different funds in order to clarify how resources are directed to various funded programs. FCTDI management utilizes financial information subject to Its internal controls to monitor for organizational efficiency, resource allocation, profitability and fraud prevention.

FCTDI Monitors Results with Timely Financial Reporting. FCTDI monitors financial results monthly versus budget and adjusts project spending as indicated based upon the scientific justification for the work, the funding that is available, and the economic rationale as determined by cost/benefit analysis.

FCTDI Maintains Compliance with National Institutes of Health Grant Policy Statement. As an NIH grant recipient, FCTDI continually monitors changes to the NIH Grant policy Statement and incorporates those changes into its policies and internal controls. FCTDI actively monitors and prevents undue conflicts of interest. FCTDI also maintains a federally negotiated indirect cost rate with Indirect Cost Branch of the Division of Financial Advisory Services (DFAS).

Three NCEs in Human Clinical Trials

Troriluzole. FCTDI has worked with **Biohaven Pharmaceuticals** since 2015 to advance prodrugs of riluzole including third-generation prodrug troriluzole which is actively transported by virtue of having a tripeptide moiety. Troriluzole was acquired by Biohaven Pharmaceuticals and is under clinical evaluation for the treatment of **spinocerebellar ataxia** and **obsessive compulsive disorders** and related conditions. It is described in US 10,485,791 (Nov. 26, 2019), US 10,639,298 (May 5, 2020),US 10,905,681 (Feb. 2, 2021) and US 11,052,070 (Jul. 6, 2021) with FCTDI staff listed as inventors.

VK-2019. FCTDI has performed collaborative research with **The Wistar Institute** since 2010 to advance small inhibitors of Epstein Barr Nuclear Antigen EBNA1 for the treatment of cancer. This work was supported by two rounds of funding from the Wellcome Trust for a total amount of >$11M. Lead VK-2019 is in human clinical trials for the treatment of **nasopharyngeal carcinoma** at Stanford University and is included in US 10,442,763 (Oct. 15,2019) and US 10,981, 867 (Apr. 20, 2021), both entitled “EBNA1 inhibitors and methods using same,” listing FCTDI and Wistar staff as inventors.

OLX-07010. As part of a collaborative research project, FCTDI has worked with **Oligomerix, Inc**. since early 2015 to discover new small molecules that inhibit aggregation of the protein tau for the treatment of **Alzheimer’s disease** and related disorders. From this work OLX-07010 was selected and advanced through preclinical development to First-in-Human clinical dosing on Feb.2, 2023. OLX-07010 is included in US 12,306,075 (Apr. 19, 2022) “Benzofuran, benzothiophene, and indole analogs that inhibit the formation of tau oligomers and their method of use” that lists FCTDI and Oligomerix staff as inventors.