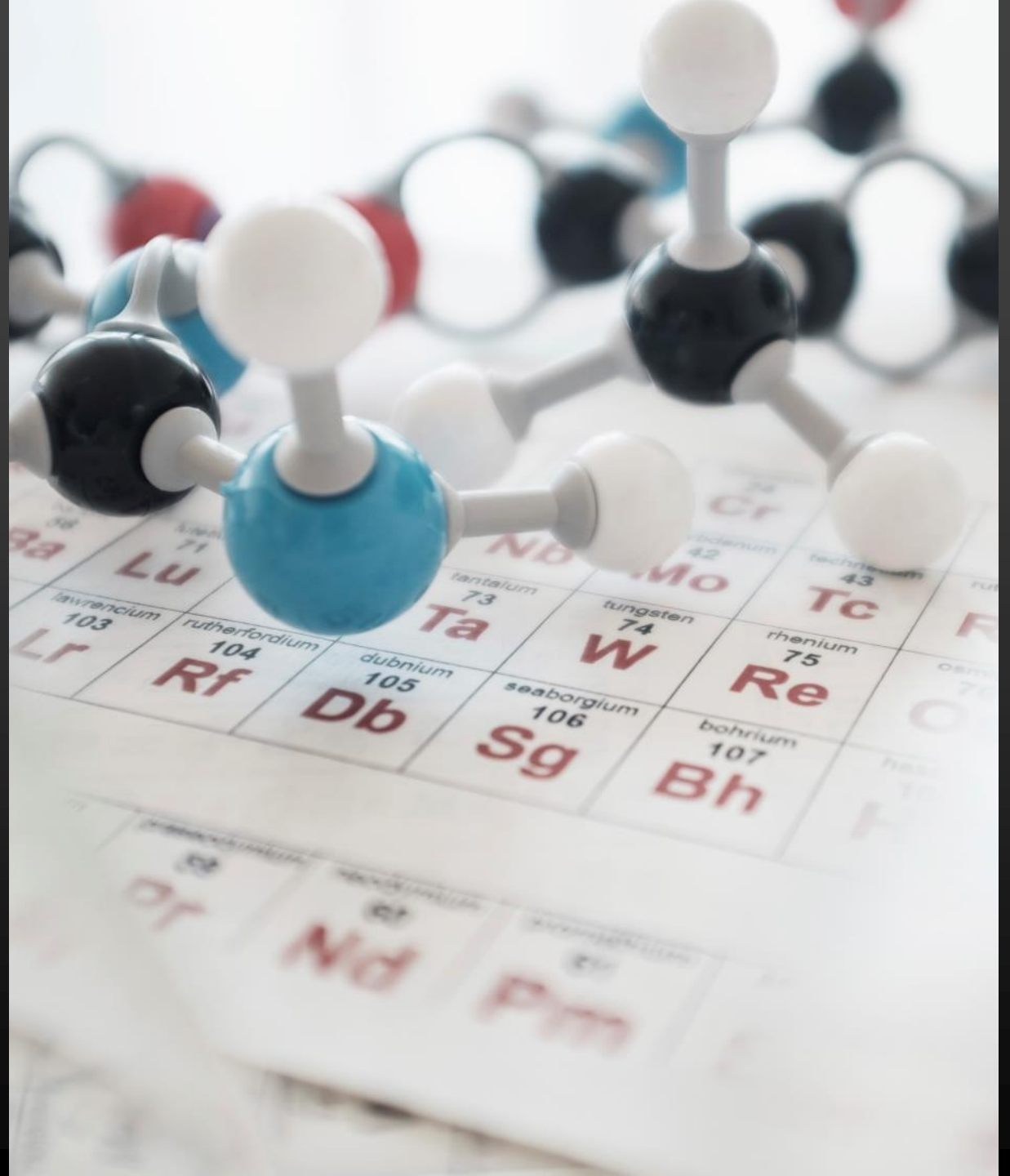
BRIGHT ROCK PATH LLC

www.brightrockpath.com

Core expertise, capabilities, and services at BRP

- *Consulting services in drug discovery*
- *... from early stages to clinics*

Oct 2020



About the company

Founded in September 2018

Bright Rock Path, LLC (BRP) provides consulting and advising services to entities ranging from start-up to large companies, CROs, academic groups, nonprofit patient, and government research agencies in support of their internal drug discovery programs.

Providing consulting services in pharmaceutical sciences

BRP offers services in foremost areas of the drug discovery (early-stage to clinical). BRP also provides consultancy to fill temporary skillset gaps.

Arizona LLC

While residing in the USA, BRP reaches globally and across multiple time zones.

About the founder

Marcel Patek, PhD

https://www.linkedin.com/in/marcelpatek/

- Over 20 years of experience in small molecule and peptide drug discovery across multiple therapeutic areas from target identification to clinical evaluation
- Skills include medicinal chemistry, drug disposition (ADME), analytical chemistry, computational chemistry and structure-based drug design, combinatorial technologies, and project management
- A strong track record of innovation and scientific contributions, including 17 issued patents and 34 publications

Led the Chemistry, Analytical, and Compound Logistics groups in support of drug discovery programs at Sanofi and Icagen, Inc. (2007 - 2018).

A wealth of expertise gained as a drug discovery scientist and manager in biotech and large pharmaceutical companies

Extensive experience in integrated drug discovery, multiple disease areas, target classes, and bioactive chemotypes

Embracing multi-disciplinary approaches to the discovery of new medicines with a focus on hit to lead and lead to clinical candidate

BRP: value proposition

Expertise @BRP

- Access to invaluable breadth and depth of knowledge in multiple disciplines
- Scalable capacity through established network of experts
- Project management of global research projects

Innovative Ideas

- Providing new insights, concepts, and ideas while always seeking a practical and timely implementation

Drug Discovery

- From hit identification to lead optimization to clinical candidate
- Practical understanding and expertise in integrating principal activities (building a screening collection, compound registration, sample storage, QC, physico-chemical properties, ADME, in vitro assays, hit/lead/candidate optimization)

Best fit for

- **Small biotech** companies seeking **pharma-grade expertise** in Medicinal Chemistry and drug discovery
- **Academic groups** developing and expanding their programs and grant support in drug discovery
- Drug discovery recommendations and strategy implementation in a **large pharma environment**
- **CROs** establishing or advancing integrated drug discovery services

Supported drug discovery activities I

Hits to leads to candidates

- Series expansion and multi-parametric optimization
- Identifying SAR for primary activity, selectivity, and solubility
- Identifying tractable scaffold candidates for lead selection
- IP driven SAR, re-scaffolding, synthesis
- ADME, PK, and acute toxicities of chemical classes
- Structure optimization based on Metabolite ID results

Structure-based design

- *in silico* quantum mechanical predictions of stereoelectronic properties
- Binding site analysis
- Chemoinformatics
- Compound design based on pharmacophore model
- Target-ligand docking and ligand conformational preferences
- Compound optimization based on *in silico* hypotheses

Analytical chemistry

- Advise in setting up quality control and method development
- Guidance in setting up and interpreting kinetic solubility and logD data
- Interpretation of follow up on chemical stability results
- Process integration
- Data processing using Python programming language in open source Jupyter notebook

Supported drug discovery activities II

Planning

- Case studies, white papers, topic reports
- Tool compounds
- Screening and hit identification
- Active series exploration
- Research and small business grant applications in drug discovery
- Outsourcing chemistry, DMPK at the US or international CROs

Compound libraries

- Library design, format selection, virtual collections
- Target family biased vs. diverse sets
- FDA-approved drugs, pharmacologically active compounds
- An established network for compound sourcing and custom synthesis
- Hit follow-up arrays (commercial, custom)
- Chemotype tractability, IP space

Methods and processes

- Solid-phase synthesis
- Peptide chemistry
- Combinatorial and high throughput chemistry
- Compound purification and archival
- Quality control and physico-chemical properties
- Integration of disciplines

Medicinal Chemistry

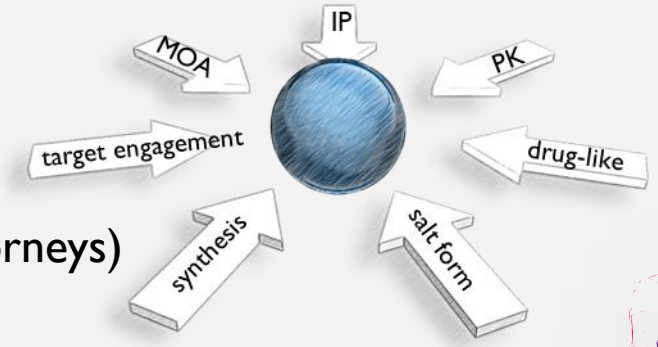
Managing, guiding, and collaborating with clients through the drug discovery process

- ✓ **Hit identification** (starting from high-throughput screening, fragment, virtual screening data)
- ✓ Hit confirmation and validation (hit triage)
- ✓ Series/singleton expansion (fragment, SAR)
- ✓ Fast multi-parametric optimization
- ✓ CRO sourcing, management

Mw	clogP	HB-D	HB-A	Lipinski	clogD_7.4	NHOH	PSA_7.4	RotB	TPSA	SMILES_formula
355.4	2.7	1	5	OK	2.1	1	55.2	5	54.0	)=C1)C(=O)NC1=
391.9	-1.7	1	5	OK	2.1	1	55.2	5	54.0	].COC1=CC(=CC(O
379.3	3.3	1	3	OK	0.9	1	42.8	7	41.6	=C(Br)C2=C(C=CC
246.2	1.7	4	5	OK	2.5	4	103.7	2	98.0	cc(O)cc2O)c(O)c
307.4	2.2	2	4	OK	1.5	2	47.0	4	45.8	C1)NC1=CC=C2O

- ✓ *in silico* structure-based design and prediction of physico-chemical properties
- ✓ Bioisosteric replacements

- ✓ **Hit to lead to clinical candidate progression**
- ✓ eADME, potency, and structure modifications
- ✓ Structure optimization within predicted and experimental properties
- ✓ IP (work with patent attorneys)
- ✓ Synthesis routes



SAR progression: process (what)

Managing, guiding, and collaborating with clients through the steps of compound optimization

- **Hit confirmation and exploration**
  - design and selection of hit/backup series/singletons
  - design of close analogs as positive and negative controls
  - assessment and structural changes to improve physico-chemical properties
  - correlation of potency and selectivity with chemical structure

- **SAR expansion**
  - identification of molecular features responsible for steep changes in SAR
  - identification of main drivers of SAR (potency, selectivity, solubility, ADME)
  - multi-parametric optimization (potency, solubility, logD, microsomal stability, passive cell membrane permeability, CYP inhibition, hERG channel inhibition)
  - re-scaffolding, swapping chemotype periphery, tuning polarity and predicted *in silico* properties

- **Lead optimization**
  - structure-based design (x-ray or pharmacophore models)
  - building into new IP space
  - selectivity panels, anti-targets (outsourcing)
  - interpretation of ADME, physico-chemical properties, PK and PD results
  - toxicology screens & panels

SAR progression: methodology (how)

Managing, guiding, and collaborating with clients to optimize series by recommending the most effective methods

- **Hit confirmation and exploration**
  - set up of rapid analoging – parallel synthesis, combinatorial chemistry
  - devising solution-phase and/or solid-phase methods
  - scaffold/reagent sourcing

- **SAR expansion**
  - design following lead-likeness, ligand efficiency, lipophilic efficiency
  - optimization of structural features (hydrogen bonding, molecular symmetry, polarity, lipophilicity, solubility)
  - optimization of properties enabling reliable *in vitro* and *in vivo* assays (cell membrane penetration, chemical stability, fluorescent properties, labeling)
  - guided by ADME properties (e.g., $T_{1/2}$ in liver microsomes, hepatocyte clearance, CYP inhibition & induction, protein binding)

- **Lead optimization**
  - solving issues with poor cross-target selectivity, cardiotoxicity, cell toxicity, and drug-drug interaction
  - formulating plans for scale up at CROs for PK, PD, tox studies
  - patent space assessment
  - recommendations for backup series

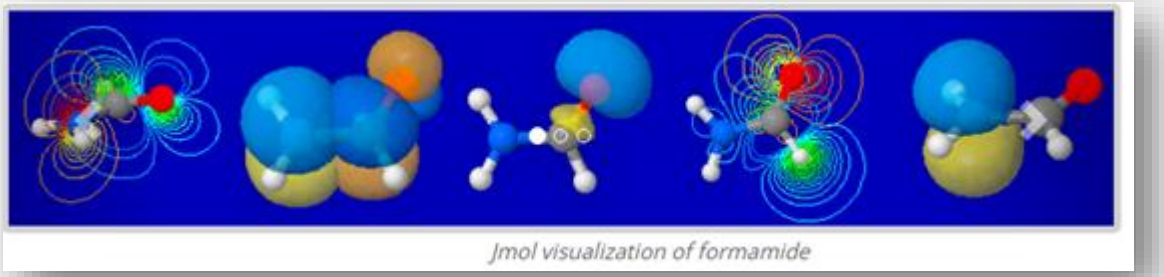
Computational chemistry capabilities

Calculation of approximate electronic structures and molecular properties [MedChem]

Conformational preferences, electrostatic potential and properties, pKa, polarization, dipole interactions, halogen bonding, π-stacking, hydrogen bonding, evaluation of docking results, understanding stereoelectronic features of functional groups

Open source quantum chemical software that provides a wide variety of methods using state-of-the-art numerical methods and algorithms. PSI4

Natural bond orbital (NBO) analysis, scripts and software



Jmol visualization of formamide

nbo.marcelpatek.com

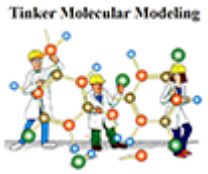
Density functional theory (DFT)

Frequently used density functionals:

- B3LYP: global-hybrid GGA (general geometry, HOMO-LUMO gap, optical properties, fast)
- ωB97X-D: long-range (LR) separated and dispersion-corrected hybrid GGA, (geometry, ~2x slower)
- M06-2X: global hybrid meta-GGA functional (tautomers, non-covalent energies, ~3x slower)
- ωB97X-V: LR separated and dispersion-corrected hybrid GGA (non-covalent interactions, isomerization, conformations, ~7x slower)

Typical basis sets:

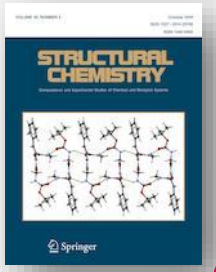
- 6-31G(d) (geometry)
- 6-311+G(2df,2p) (properties)
- (aug)-cc-pVDZ (properties)



Tinker

Tinker 8 - complete and general (free) package for molecular mechanics and dynamics. Adopted OPLS-AA, MM3, and AMOEBA force-fields for small molecules and proteins.

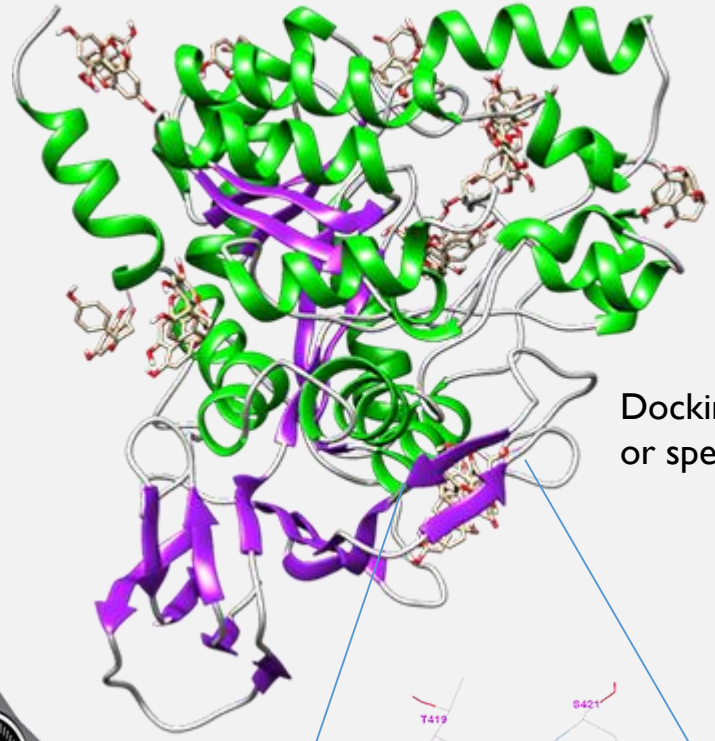
Gaussian 09 - commercial, general purpose computational chemistry software package.



Manzetti S., Patek M. **The accurate wavefunction of the active space of the rhenium dimer resolved using the ab initio Brückner coupled-cluster method.** *Structural Chemistry*, **2016**:1-10

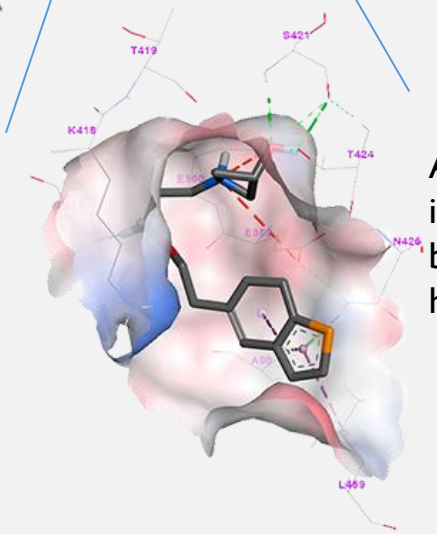
Structure-based design

- ❑ Visual inspection and prioritization of docked geometries
- ❑ *Forcefield* constrains based on QM calculations
- ❑ Target-ligand docking
- ❑ Ligand conformational preferences
- ❑ Binding site analysis
- ❑ Compound design (SAR)



Docking to multiple or specific sites

Scalable CPU & GPU computing on Amazon AWS



Analysis of key interactions and building binding hypotheses

Software and local PC environment:

- AutoDock Vina (open source), Smina, PyRx
- Integrative Modeling Platform toolkit (open source)
- Discovery Studio Visualizer (free, Biovia, 2019)
- OpenBabel (open source)
- Python scripts

Intel i7-8700 CPU @ 3.70 GHz (12 cores)
Nvidia GeForce GTX 1080 GPU (8 GB GDDR5X, 2560 CUDA cores)
Windows 10 and Linux OS

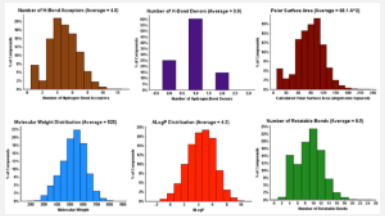
Chemoinformatics

- Similarity search using fingerprints (virtual screening) on various ZINC and CHEMBL datasets - fragments, drug-like molecules (3.2 M) ⇨ hit expansion
- Similarity (SMARTS) search within sets of bioactive (annotated) compounds (CHEMBL, PubChem) ⇨ finding bioactive analogs
- Multiple queries in CHEMBL database (bioactivity, assays, target, (sub)structure, approved drugs).
- Search for compounds with patent families using SureChembl queries
- Target prediction based on Naïve Bayesian CHEMBL model ⇨ cross-target selectivity prediction
- Generation of multiple molecular descriptors (RDKit, Mordred) ⇨ drug-likeness, Lipinski, lead-likeness
- Prediction of logD (lipophilicity) and other properties using ChemAxon engine and internal ML methods
- Data processing in Python-based Jupyter notebooks ensuring research reproducibility
- Machine learning enabled by DeepChem and RDKit for prediction of compound properties (e.g., solubility, logD, toxicity)

scalable at Google colab

Design of screening collections

Strong background and hands-on experience in creating screening collections through rigorous processes



Library design

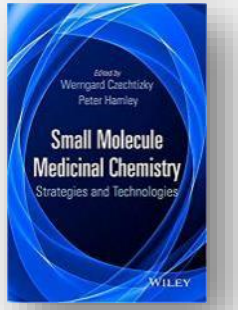
- Virtual library design
- IP assessment
- Drug-like properties
- Building block reactivity
- Format selection
- Diversity, target class bias
- Commercial libraries

Library development and synthesis

- Protocol optimization
- Building block replacement
- Building around new IP space
- Solid-phase synthesis
- Solution-phase synthesis
- Concept to product project management

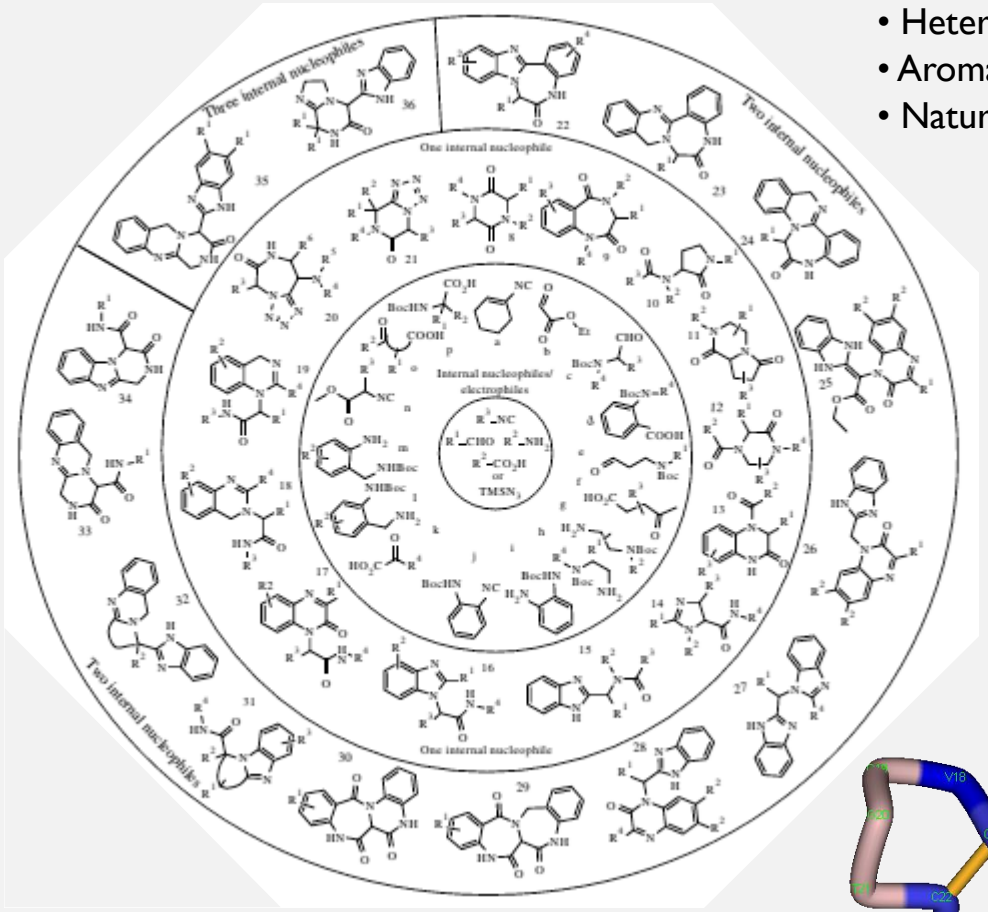
Library archival

- Library formatting
- Automated purification
- Product analysis
- Compound storage (vials, plates)



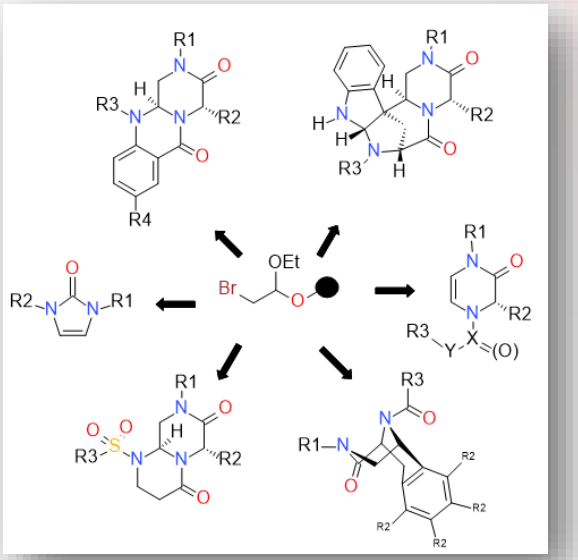
Patek M, Smrcina M, Wegrzyniak E, Nikolaev V, Mariscal A. **Solid-Phase Combinatorial Chemistry**. In: Czechtizky W, Hamley P, eds. *Small Molecule Medicinal Chemistry: Strategies and Technologies*. John Wiley&Sons; **2015**:103-143

From small molecules to small proteins



- Alicyclics
- Heterocycles
- Aromatic functions
- Natural product-like

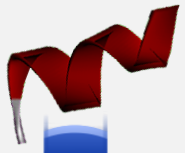
Small Molecules



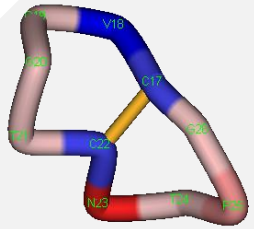
An example of versatile approach to diverse peptidomimetics.

Peptidomimetics

peptides, macrocyles

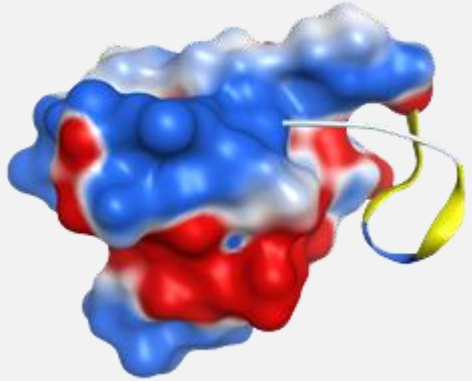


Helical peptides



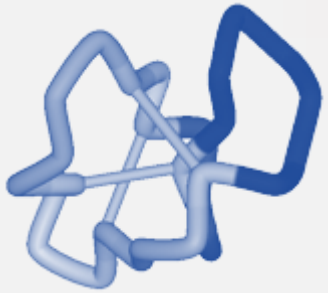
Macrocyclic peptides

Synthetic circular mini-proteins with grafted epitopes



Peptide chemistry

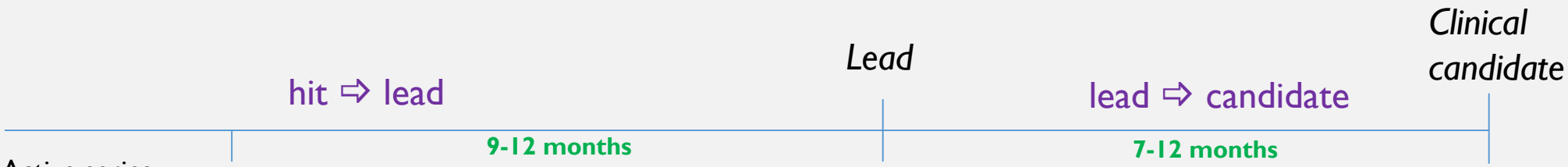
- An early practitioner of one-bead-one compound "split-mix" technology (Selectide Corp.)
  - combinatorial peptide libraries (100K-2M)
  - controlled release from resin beads for multiple assays
  - QC, peptide sequencing of coding tags
- Extensive experience in solid-phase synthesis of peptides and amide bond-containing molecules
- Experience with releasable linkers allowing orthogonal cleavage of solid-phase bound molecules
- Sort & combine synthesis of peptide arrays
- Synthesis of folded peptides/mini-proteins and synthetic grafting of peptide epitopes (includes knottin family, cyclotides), native chemical ligation protocols *
- Peptide design – potency, proteolytic stability, half-life modulation
- Peptide purification and storage
- Peptide conjugation and labeling



* Li, Y. C., Rodewald, L. W., Hoppmann, C., Wong, E. T., Lebreton, S., Safar, P., Patek, M., Wang, L., Wertman, K. F., Wahl, G. M. A **Versatile Platform to Analyze Low-Affinity and Transient Protein-Protein Interactions in Living Cells in Real Time**. *Cell Rep.* **2014**, *9* (5), 1946–1958

Hit to lead to candidate guidelines

... support clients all the way from the hit identification to clinical candidate



Active series
(hit) expansion

series optimization

lead optimization

hit ⇨ select series qualification ⇨ SAR, ADMET, selectivity

- LC-MS purity
- Potency, selectivity, IP
- cLogD,
- Kinetic solubility
- Microsomal stability
- CYP inhibition

lead series (+backup)

- Potency, selectivity, IP
- Cellular, animal activity (key compounds)
- cLogD, PAMPA
- Kinetic solubility
- Microsomal stability, CYP inhibition
- Clearance hepatocytes (key representatives)
- MetID (key representatives)
- HERG, Caco-2, PK (key representatives)
- logBB (key representatives)
- PK (lead, snapshot)

- Potency, selectivity, IP
- Cellular, animal activity (key compounds)
- Hepatic microsomal clearance in four species – mice, rats, dogs, cynomolgus monkeys, and half-life data, Clint (intrinsic clearance)
- Degradation of compounds by plasma enzymes (e.g., amide hydrolysis on selected compounds)
- IC50 data on competitive CYP inhibition on the 7 CYPs required by the FDA
- CYP induction in several CYP isoenzymes (e.g., 3A4, 1A2, 2B6)
- PK (Cl_{int}, $T_{1/2}$, AUC, F%), PPB, logBB
- Metabolite ID in human/rat hepatocytes to identify key metabolic hot-spots
- Mitochondrial toxicity to assess drug-induced mitochondrial dysfunction and cell toxicity
- hERG channel inhibition cardio-safety
- Mini-Ames evaluation of genotoxicity
- in vitro MNT

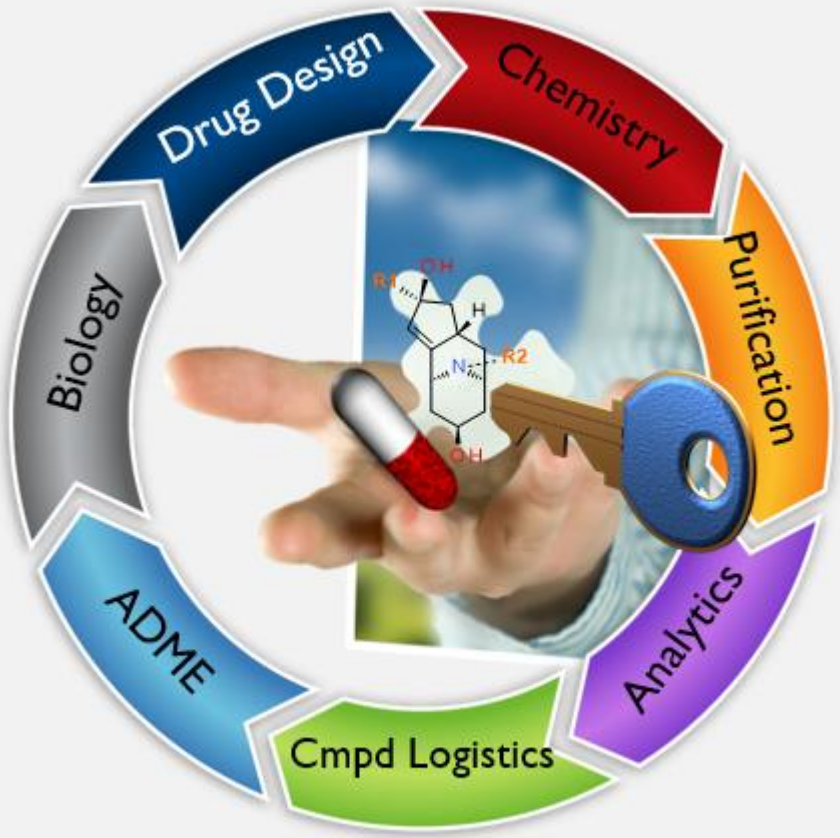
chemistry optimization:

- $T_{1/2}$
- Cl_{int}
- F(%)
- C_{max}
- PD
- (phototox)
- toxicity
- cardio safety

ADME support of the hit to lead to candidate optimization

Process and discipline integration

Consulting and guiding clients to adopt integrated approaches to drug discovery



Familiarity with rigorous processes

Compound progression flow

Tight integration of key functions

Instrumentation and modular setup

IT infrastructure

Industry level processes

BRP clients

Regulonix

Regulonix

"Non-opioid drugs for chronic pain to attack a global health epidemic." The approach pursued by Regulonix primarily modulates trafficking of the Nav1.7 sodium channel through a protein called CRMP2, or collapsing response mediator protein 2. Scientists and founders of Regulonix have invented and are developing a new class of non-opioid compounds to treat pain.

COLLEGE OF MEDICINE TUCSON
Pharmacology

University of Arizona

Support of academic research groups with a focus on the design of new therapeutics and understanding of the effects of compounds on disease state.

- Providing expert insights into drug discovery.
- Advice and input into experimental design.
- Input into grant applications and scientific papers.

Center for Innovation in Brain Science

Center for Innovation in Brain Science

Supporting the research and development of new therapies for ALS by targeting protein-RNA and protein-protein interactions. These difficult to target complexes are dysregulated in Amyotrophic Lateral Sclerosis (ALS), Alzheimer's Disease (AD) as well as rare neurodegenerative diseases, such as PCH1B.

ProteinQure
computational drug design

ProteinQure

Designing computational R&D tools to perform in silico drug design. The group at ProteinQure is leveraging quantum computing, quantum alghorithms, molecular simulations, and reinforcement learning to engineer novel therapeutic solutions.

Recent publications

- Perez-Miller, S.; Patek, M.; Khanna, R.; Moutal, A. **In silico identification of potential inhibitors of the interaction between neuropilin receptor 1 and SARS-CoV-2 Spike protein**. ACS Chem. Neurosci. (submitted 2020).
- Khanna, R.; Moutal, A.; Perez-Miller, S.; Chefdeville, A.; Boinon, L.; Patek, M. **Druggability of CRMP2 for Neurodegenerative Diseases.** ACS Chem. Neurosci. **2020**, 11 (17), 2492-2505. Link
- Cai, S.; Tuohy, P.; Ma, C.; Kitamura, N.; Gomez, K.; Zhou, Y.; Ran, D.; Bellampalli, S. S.; Yu, J.; Luo, S.; Dorame, A.; Ngan Pham, N. Y.; Molnar, G.; Streicher, J. M.; Patek, M.; Perez-Miller, S.; Moutal, A.; Wang, J.; Khanna, R. A **Modulator of the Low-Voltage Activated T-Type Calcium Channel That Reverses HIV Glycoprotein 120-, Paclitaxel-, and Spinal Nerve Ligation-Induced Peripheral Neuropathies.** *Pain* ***2020,*** *161 (11), 2551-2570.* Link
- Zhou, Y.; Cai, S.; Moutal, A.; Yu, J.; Madura, C.; Shan, Z., Ngan Pham N.; Serafini, M.; Dorame, A.; Scott, D.; Francois-Moutal, L.; Perez-Miller, S.; Patek, M.; Khanna, M.; Khanna, R. **The natural flavonoid Naringenin elicits analgesia through inhibition of NaV1.8 sodium and voltage-gated calcium channels, independent of actions on collapsin response mediator protein 2 (CRMP2).** *ACS Chem Neurosci* **2019**, 10 (12), 4834-4846. Link
- Shan, Z., Cai, S., Yu, J., Zhang, Z., Vallecillo, T.G.M., Serafini, M.J., Thomas, A.M., Pham, N.Y.N., Bellampalli, S.S., Moutal, A., Zhou, Y., Xu, G-B., Xu, Y-M., Luo, S., Patek, M., Streicher, J.M., Gunatilaka, L.A.A., Khanna, R. **Reversal of Peripheral Neuropathic Pain by the Small-Molecule Natural Product Physalin F via Block of CaV2.3 (R-Type) and CaV2.2 (N-Type) Voltage-Gated Calcium Channels.** *ACS Chem Neurosci* **2019**, *10* (6), 2939–2955. https://doi.org/10.1021/acschemneuro.9b00166
- Manzetti S., Patek M. **The accurate wavefunction of the active space of the rhenium dimer resolved using the ab initio Brückner coupled-cluster method.** *Structural Chemistry*, **2016**:1-10. http://dx.doi.org/10.1007/s11224-015-0726-1
- Patek M, Smrcina M, Wegrzyniak E, Nikolaev V, Mariscal A. **Solid-Phase Combinatorial Chemistry**. In: Czechtizky W, Hamley P, eds. *Small Molecule Medicinal Chemistry: Strategies and Technologies*. John Wiley&Sons; **2015**:103-143. https://doi.org/10.1002/9781118771723.ch5
- Li, Y. C., Rodewald, L. W., Hoppmann, C.; Wong, E. T., Lebreton, S., Safar, P., Patek, M., Wang, L., Wertman, K. F., Wahl, G. M. A **Versatile Platform to Analyze Low-Affinity and Transient Protein-Protein Interactions in Living Cells in Real Time**. *Cell Rep.* **2014**, *9* (5), 1946–1958. Link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www.brightrockpath.com
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mpatek@brightrockpath.com
+1-520-329-7809