Academia/Industry Cross-Fertilization through Translational Research

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Before we start…

anrt
association nationale
recherche technologie

Students
Boost your future with a diploma-based first job

Companies
Boost your performance by recruiting a PhD student

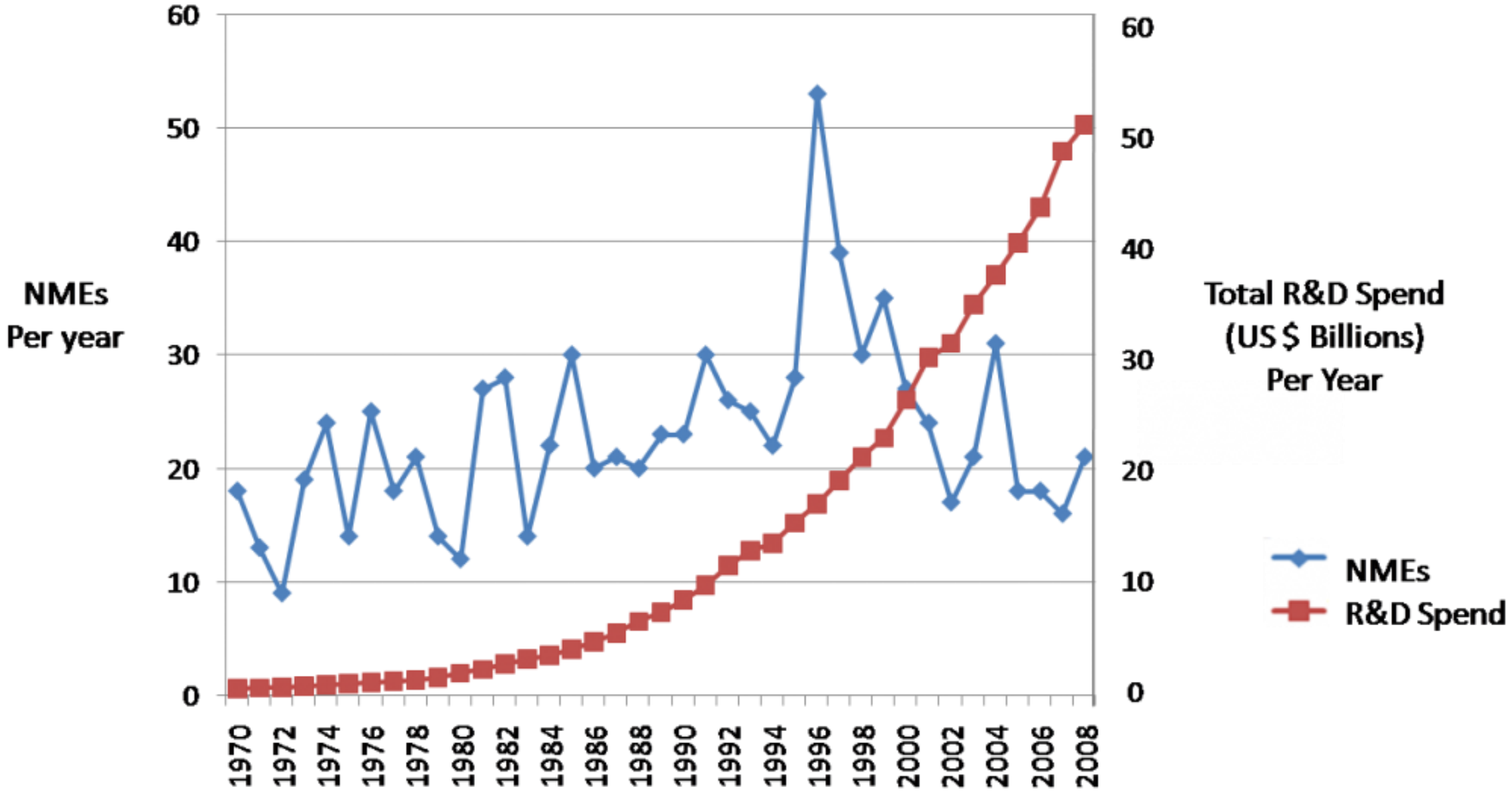
Laboratories
Boost your research with a CIFRE

→ CIFRE industrial fellowship: a WIN-WIN-WIN deal!

Presentation Outline

- **Current challenges in the Pharma industry and how to fill the innovation gap.**
- **Translational Research & its role in public-private partnerships**
- **Define the strengths of academia & industry in drug research and development**
- **The Scripps Research Institute's (TSRI) approach to Translational Research**
- **The NIH's Roadmap Initiative and its role in catalyzing translational research in the US**
- **Four examples of Industry/Academia collaborations performed at Scripps boosted through Translational Research**

Current Challenges in Drug Discovery

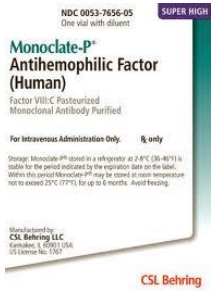


→ *How do we fill the innovation gap?*

How do we fill the Innovation Gap?

→ *with Translational Research!*

Scripps' Industrial Partnerships



Research Collaborations

NOVARTIS

Pfizer

Lilly

Bristol-Myers Squibb

SANDOZ

Johnson & Johnson
PHARMACEUTICAL RESEARCH & DEVELOPMENT, L.L.C.

PPG

envoy THERAPEUTICS

SIGMA-ALDRICH

Technology Licensing

Compound	Therapeutic Area	Company	Phase I	Phase II	Phase III	NDA
Late Stage Products						
Cilengitide	Oncology	Merck Serono				
ch14.18	Oncology	United Therapeutics				
Other CAT Products						
Tralokinumab	Respiratory	MedImmune/AstraZeneca				
CAM-3001	Inflammation	MedImmune/AstraZeneca				
Rozrolimupab	Cardiovascular	Symphogen				
GC-1008	Multiple Areas	Genzyme				
TB-403	Opthamology	BioInvent				
BI-505	Oncology	BioInvent				
MT-203	Inflammation	Micromet				
Bertilimumab	Allergy	iCo Therapeutics				
CovX Products						
CVX-060	Oncology	Pfizer				
CVX-096	Diabetes	Pfizer				
Sangamo Products						
SB-728	HIV	Sangamo				
SB-313	Oncology	Sangamo				
Click Chemistry Products						
Solithromycin	Antibiotic	Cempra				
AZ-01	Autoimmune	Allozyne				
Ambrx Products						
ARX-201	Growth Deficiency	Ambrx				
ARX-424	Autoimmune	Ambrx				
Other Early Stage Products						
IC-14	Respiratory	Implicit				
CTL-04	Oncology	J&J				
ALT-801	Oncology	Altor				
RPC-1063	Autoimmune	Receptos				
Shok-Pak	Organ Failure	InflammaGen				
RG-2833	Friedreich's Ataxia	Repligen				
HSC-835	Oncology	Novartis				
3K3A-APC	Cardiovascular	ZZ Biotech				

Startups/Spinouts

Ember THERAPEUTICS

ACTIVX Biosciences

ABIDE THERAPEUTICS

Ambrx

CovX

receptos

OPTIMER PHARMACEUTICALS, INC.

aTyr Pharma

ACHAOGEN

EPIC SCIENCES

syrrx

FoldRx

Zyngenia

Defining the strengths of Industry and Academia in Drug R&D

Academia

Tackle rare and neglected diseases

Define new understandings of existing disease targets/pathways

Discover New Technologies

Create innovative new chemical entities

Novel Targets, Assays, Entities & Technologies

Industry

Define applications of novel discoveries and technologies

Convert discoveries into clinical applications

Bring safe medicines to patients

Requirements:
Goals align with faculty
& funded by sponsors
Publications = Public

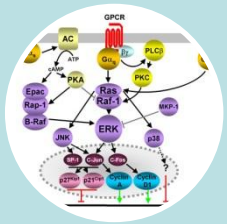
Requirements:
Goals align with shareholders
& funded by sales
Intellectual Property=Secret

→ Academia and Industry share common goals

How do we make Professor Calculus and Superman reach these common goals together?

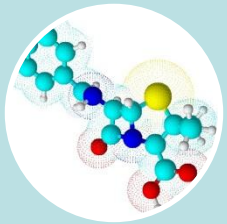
Scripps Florida's Translational Research Institute

Scripps Florida's Translational Research Institute

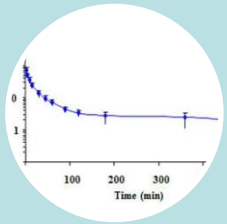


Discovery Biology

Lead Identification



Medicinal Chemistry



DMPK

Animal Studies

Translational Research Institute (TRI)

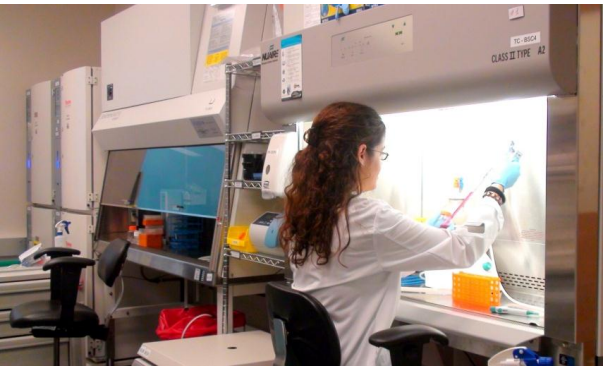
Novel or Neglected target

The Translational Research Institute offers:

- **Biotech-type organization**
- **A 50/50 blend of faculty from the industry and the academia**
- **A common language**
- **Drug Discovery Resources**
- **Pharma/Biotech expertise**
- **Advanced equipment and technologies**

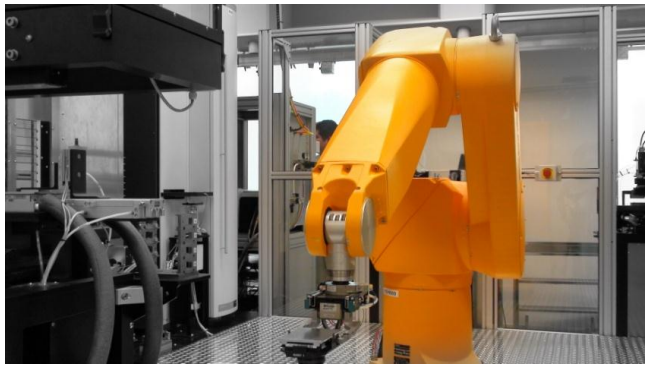
Drug Candidate

The uHTS/Lead Identification Group @ Scripps Florida



Assay Development Lab

"From test tube to plate"
protein expression/purification
>60 mammalian cell lines
insect cells
bacteria, yeast
Batch transfection
Frozen, assay-ready cells
Small organisms



GNF Systems uHTS Platform

>250,000 tests /day
1,536 well format
Homogenous & Heterogeneous Assays
FLINT, FP, TR-FRET, Lumi, Abs., FLIPR...
High Content Screening

Compound Management

> 1MScreening Repository:
~640K Proprietary to Scripps
~370K Public Domain (NIH)
~100K Private Collaborations
comprising both small molecules and natural products

- **The "Lead ID" facility occupies >6100 ft^2 of laboratory space**
- **20 FTEs: cell /molecular biologists, biochemists, microbiologists, software programmers, engineers, cheminformaticists, compound managers**
- **Access to >50 Medicinal Chemists, DMPK, Pharmacology @ Scripps FL**
- **Engaged in both private & NIH-funded HTS collaborations**

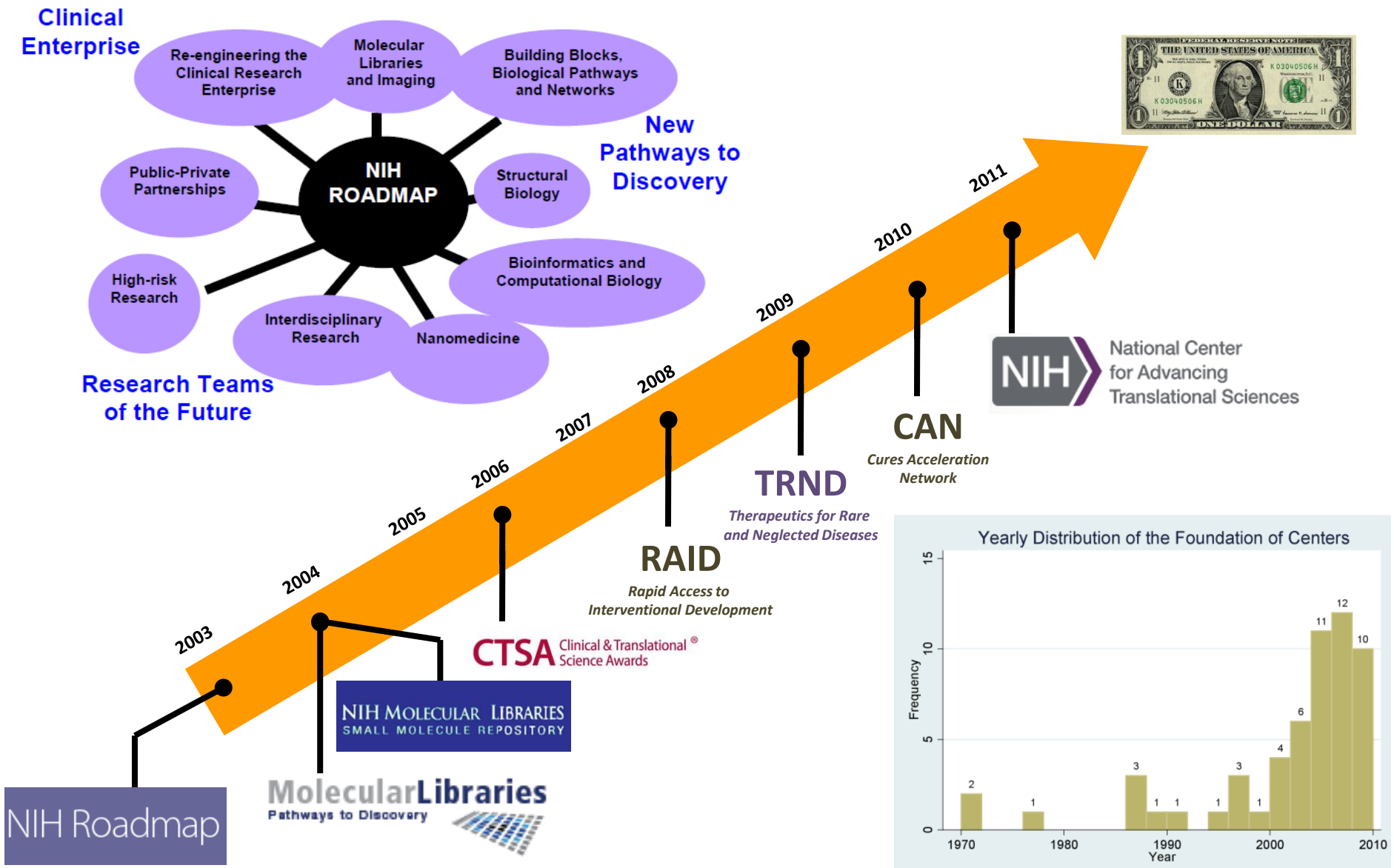
→ "industrial-grade" expertise and equipment , as well as workflows, timelines, and QC standards makes us credible interlocutors for the pharma industry

The Role of the NIH in catalyzing Translational Research

"It is the responsibility of those of us involved in today's biomedical research enterprise to translate the remarkable scientific innovations we are witnessing into health gains for the nation"

Elias Zerhouni, MD
Director, NIH
NEJM 2005

The Role of the NIH in catalyzing Translational Research



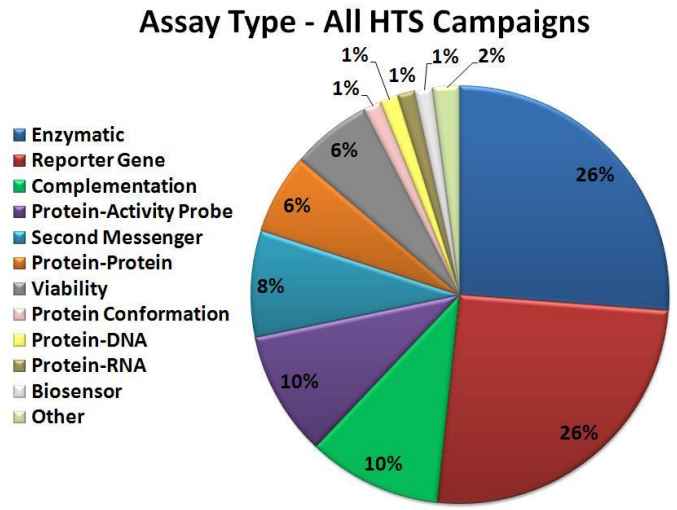
Frye et al. Nat. Rev. Drug Disc., 10:2011

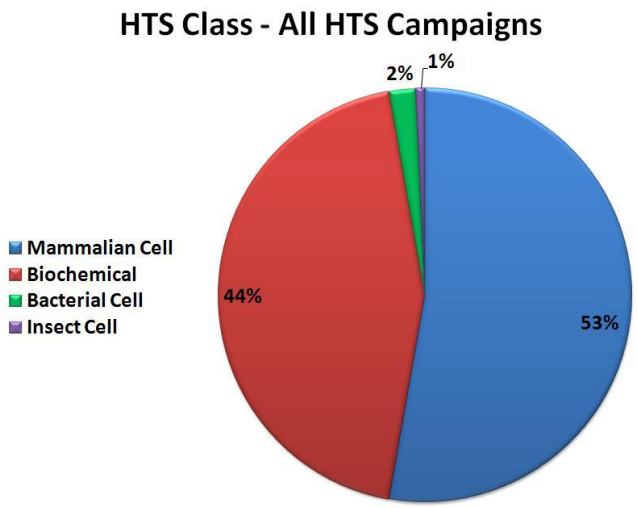
The Molecular Libraries Probe Production Center Network (MLPCN)

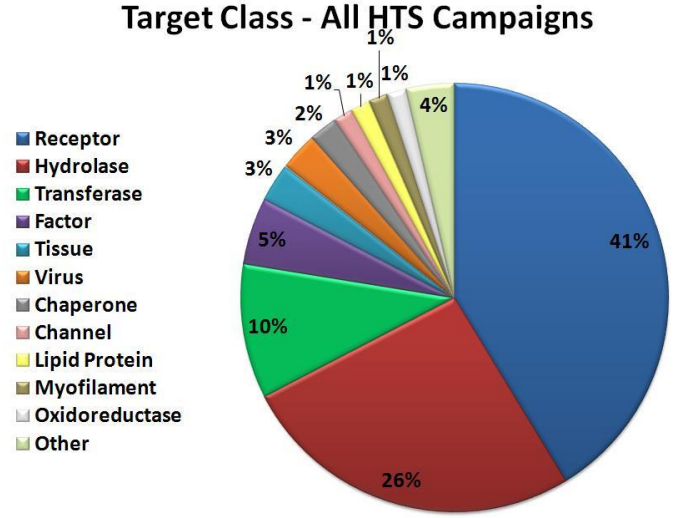
- **Part of NIH's "roadmap initiative" for biomedical research in the 21st century**
- **Grants for assay development and/or HTS**
- **Peer-reviewed process**
- **Open to academia, government, non-profit and industry**
- **Screening centers provide assay development, HTS, DMPK and medicinal chemistry support A/R**
- **All results are publicly available through NCBI's PubChem website**
- **Each center has a copy of the same library (360K, still growing)**
- **Production phase:**
  - **10 specialized centers**
  - **4 comprehensive centers 25 targets/year/center**

MLPCN @ Scripps: a retrospective of the past 6 years

- $89 million over 6 years
- >150 targets
- 71 chemical probes
- >1,300 PubChem reports
- 141 publications
- 4,155 citations





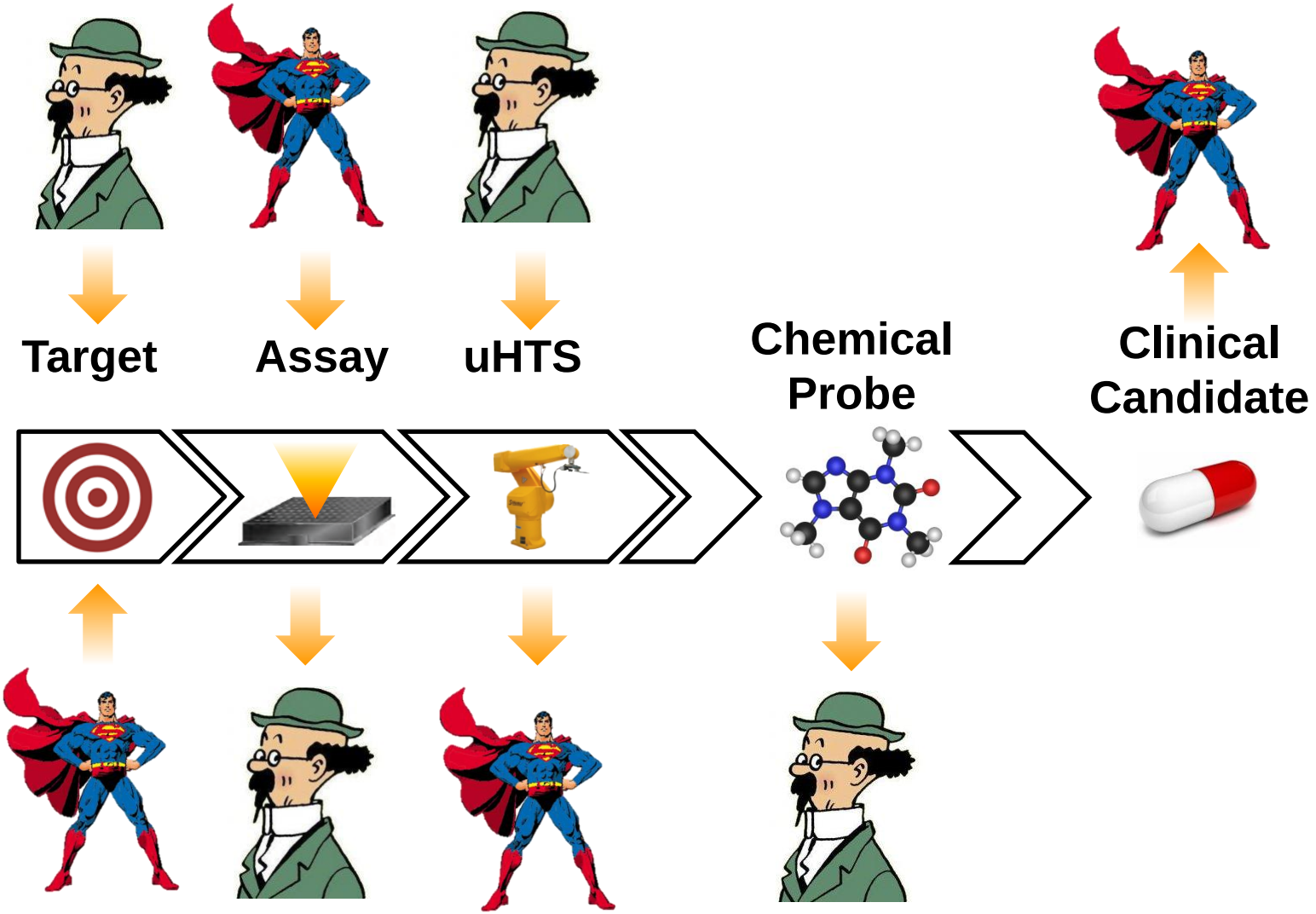


An interactive table that details all our public domain HTS collaborations can be found at:
http://hts.florida.scripps.edu/index.php/our-capabilities/hts-campaigns/pipeline.html

4 examples of Academia/Industry partnerships

Therapeutic area	Target	Target Class	Assay Technology	Academic Partner	Industrial Partner
Infectious Diseases	HCV-CORE	Viral protein	HTRF	Scripps FL Boston University	Pfizer
Cancer	SF-1	NHR	Luciferase Reporter	Scripps FL - CNRS	Orphagen + Biotech 'X'
Autoimmune Disorders	S1P1	GPCR	BLA	Scripps LJ	Receptos
CNS	x	x	x	Scripps FL	Envoy Therapeutics

Academia/Industry Cross-Fertilization

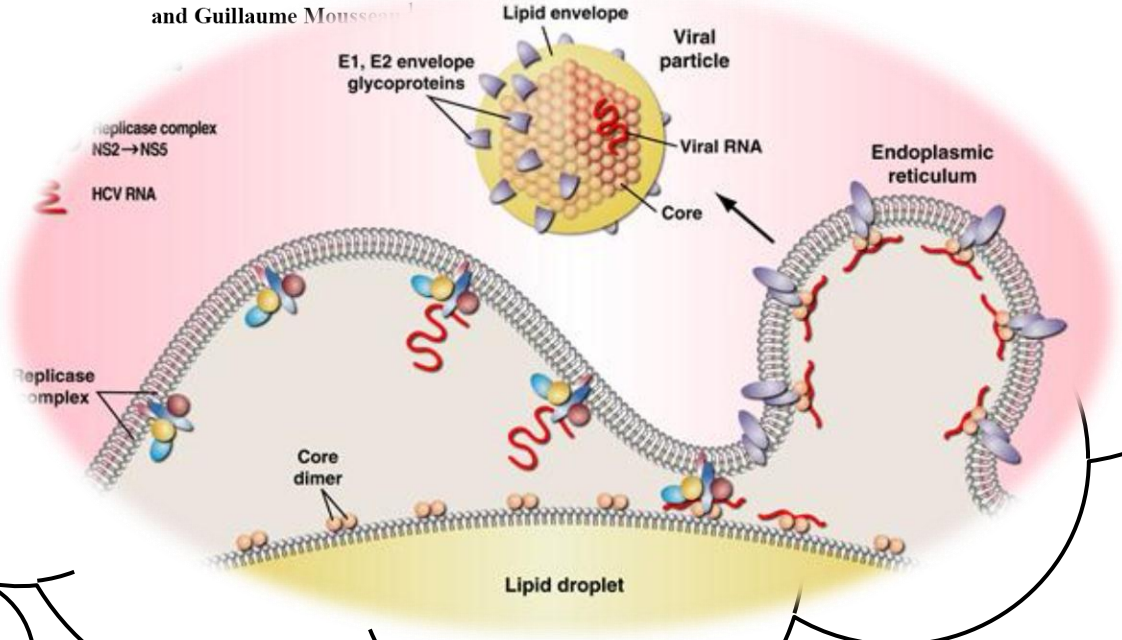


Example #1: HCV-CORE

Review

Core as a Novel Viral Target for Hepatitis C Drugs

Arthur Donny Strosberg [1,*], Smitha Kota [1], Virginia Takahashi [1], John K. Snyder [2] and Guillaume Mousseau [1]

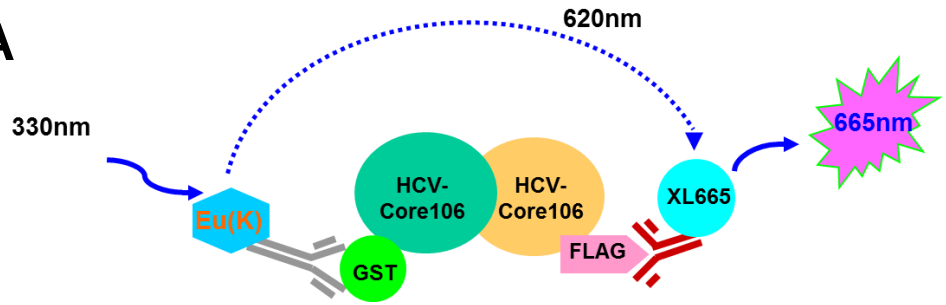


Donny Strosberg

A Time-Resolved Fluorescence–Resonance Energy Transfer Assay for Identifying Inhibitors of Hepatitis C Virus Core Dimerization

Smitha Kota,[1] Louis Scampavia,[2] Timothy Spicer,[2] Aaron B. Beeler,[3]
Virginia Takahashi,[1] John K. Snyder,[3] John A. Porco Jr.,[3]
Peter Hodder,[2] and Arthur Donny Strosberg[1]

A



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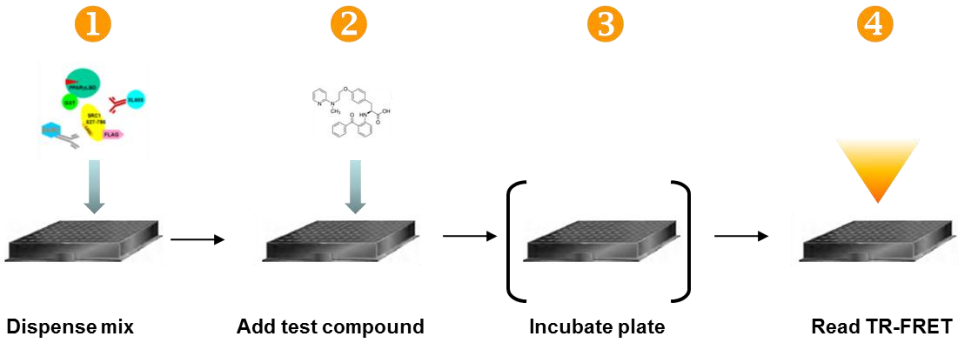
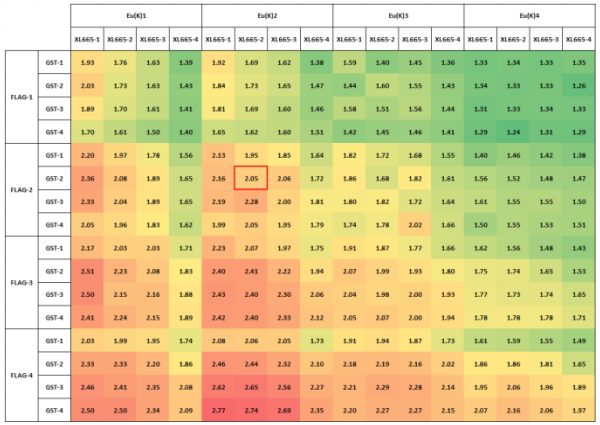
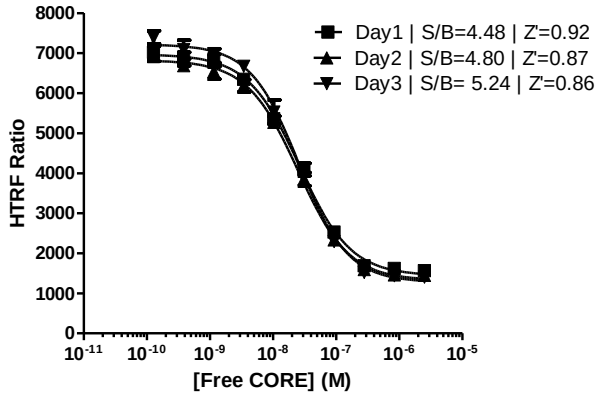


C



D



P-230

The identification of novel small molecule inhibitors of the hepatitis C virus core protein.

AntiVirals

Paul Targett-Adams[1], Jared Milbank[1], Helen Waller[1], Francois Bertelli[2], Smitha Kota[3], Donny Strosberg[3], Chris Pickford[1], Tanya Parkinson[1], Manos Perros[1].

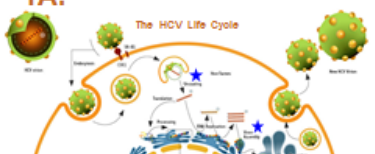
SandwichResearch

[1] Pfizer Antivirals Research Unit, Pfizer PGRD Laboratories, Sandwich, UK, CT13 9NJ; [2]Pfizer HTS Centre of Emphasis, Pfizer PGRD Laboratories, Sandwich, UK, CT13 9NJ; [3]The Scripps Research Institute, 130 Scripps Way, Jupiter, Florida 33458, USA.

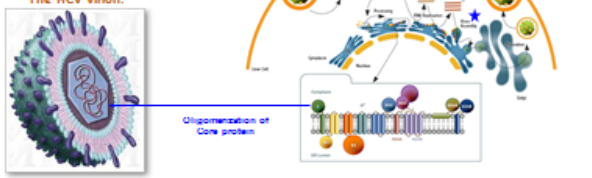
Summary: Hepatitis C virus (HCV) is a global health problem. Treatment with interferon and ribavirin is the current standard of care; however, it is not universally effective and is associated with considerable side effects. Consequently, there's an urgent unmet medical need for directed, well-tolerated antiviral medicines to combat the growing burden of HCV infection. The first generation of specific anti-HCV medicines are likely to be small-molecules targeting the virus-encoded enzymatic gene products. However, preliminary *in vitro* and *in vivo* data indicate the emergence of compound-resistant HCV quasi-species are likely to be a considerable complication. To improve our chances of successfully developing new medicines to treat HCV-infected patients, the Antivirals Research Unit is seeking to identify small-molecule inhibitors of core protein; a non-enzymatic HCV gene product. Core protein is the major structural component of the virus and is essential for productive infection; no virus is produced in its absence. Core oligomerizes around the RNA genome of the virus to form a protein shell (capsid), which protects the virus genome. The HCV core protein programme is a result of collaboration with The Scripps Research Institute, where a novel *in vitro* assay for core protein dimerization was developed. The assay was transferred to Pfizer and screened against a compound library composed of >2 million small molecules. Currently, we are progressing through the screening cascade and have identified a panel of compounds, which inhibit dimerization of the core protein *in vitro* and display no adverse effects in cell culture. Preliminary findings demonstrate a subset of this compound panel exhibits antiviral activity in the HCVcc virus-infectivity assay with low micromolar IC_{50}s. These data suggest inhibition of the core-core interaction *in vitro* can translate into antiviral activity in HCV-infected tissue culture cells and provides confidence in targeting core protein oligomerization as a mechanism for potential therapeutic intervention.

1. Introduction:

1A.



1B.

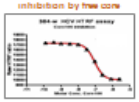


1A: Aspects of the HCV life cycle potentially susceptible to small molecule-mediated inhibition of core protein, namely, virion uncoating and assembly (★).

1B: Oligomerization of HCV core protein is required to form the virus capsid, which serves to protect the RNA genome.

1C.

1D.

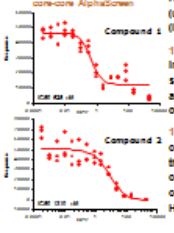


1C: HTRF energy transfer assay designed to recreate the capacity for HCV core protein to self assemble *in vitro*. Assay measures the interaction between GST-core108 and FLAG-core108.

1D: Inhibition of the core-core HTRF assay by free (untagged) core108 protein (IC_{50} 80nM).

1E.

1F.



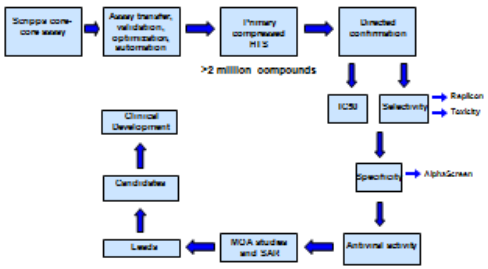
1E: AlphaScreen core-core interaction assay used as a selectivity counter-screen and for follow-up screening of HTS hits.

1F: Example of inhibition of core-core interaction using the AlphaScreen assay and 2 compounds identified as core-core inhibitors in the HTRF HTS.

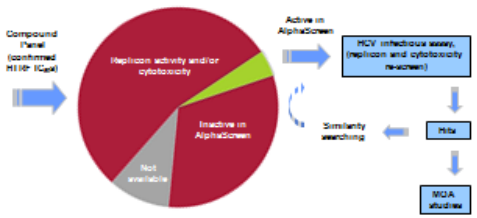
2. Screening:

2A: Over 2 million compounds were screened in a compressed format against the core-core HTRF assay. The primary screen generated 67,000 hits of which 8000 were confirmed at single concentration and 933 of those exhibited dose responses and passed lead filters.

2A. Screening Cascade:



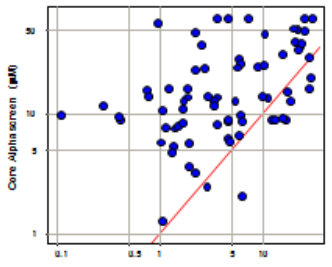
2B. Selectivity/Specificity Screening:



2B: 80% of the compound panel, which was composed of confirmed hits from the *in vitro* core-core HTRF interaction assay, exhibited cytotoxicity or off-target effects as judged by activities in cytotoxicity and/or HCV subgenomic replicon assays. 6% of the compound panel were active in the AlphaScreen selectivity assay and displayed no activity in the cell-based assays; these compounds were progressed to the HCVcc assay to identify molecules with antiviral activity. Similarity searching was used to identify series of compounds with antiviral activity.

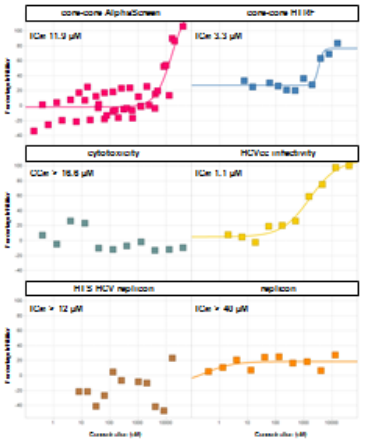
3. Follow-up:

3A. Core-Core interaction assays: Alphascreen versus HTRF



3A: Approximately 86% of compounds, confirmed as hits in the HTS HTRF core-core interaction assay, were also active in the AlphaScreen core-core selectivity screen. The scatter plot above describes the activity of a selection of compounds in both assays. Generally, compounds appeared more active in the HTRF assay compared to the AlphaScreen assay; a feature presumably related to the different assay technologies.

3B. Activity of a representative HTS hit in the different screening assays.

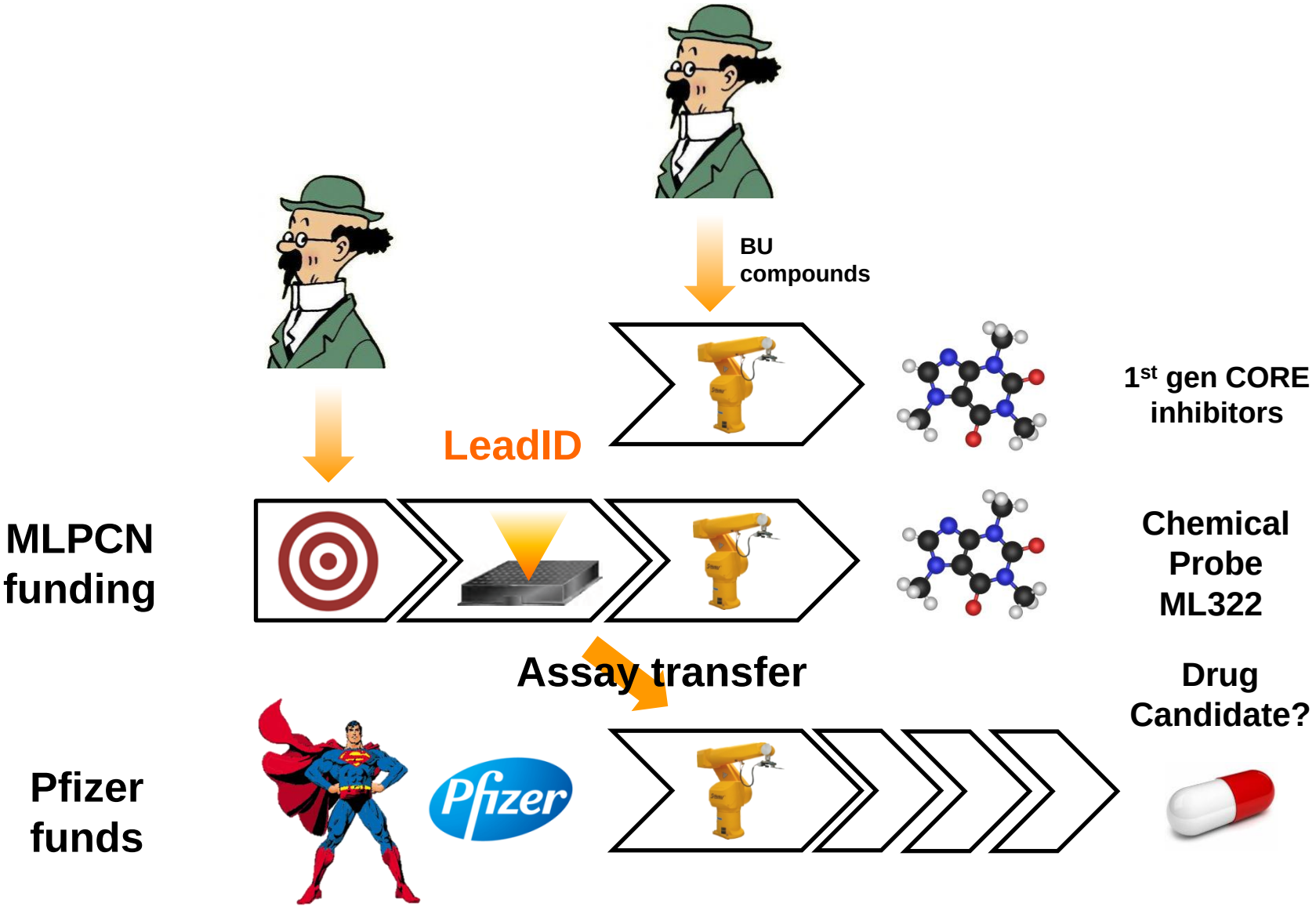


3B: Assay profiles of a representative anti-HCV core compound: Active in both *in vitro* core-core interaction assays (AlphaScreen and HTRF; IC_{50}s of 11.9 and 3.3 μM respectively), no apparent cellular toxicity (CC_{50} of over 16.6 μM), no off-target effects on HCV RNA replication (inactive in HCV subgenomic replicon assays), and active in the JFH-1 HCVcc infectivity assay (IC_{50} of 1.1 μM).

4. Conclusions:

Oligomerization of the HCV core protein has potential as a new target for the development of future therapies directed against HCV. Consequently, we have screened the Pfizer compound library for small molecule inhibitors of the core-core interaction and have identified compounds that inhibit the interaction *in vitro* as evidenced by activity in the primary HTRF assay, and the AlphaScreen selectivity assay. To rule out any off-target effects or cellular toxicity, the core actives were screened in replicon and W3T-1 toxicity assays. 'Core-targeting' compounds, inactive in the cell-based selectivity screens were tested for antiviral activity in the HCVcc assay. A subset of the core actives inhibited HCV infectivity with low micromolar IC_{50}s. Thus, inhibitors of the *in vitro* core-core interaction assay have the capacity to inhibit HCV infectivity in tissue culture cells, providing confidence that oligomerization of core protein represents a mechanism amenable to drug targeting.

Example #1: Summary

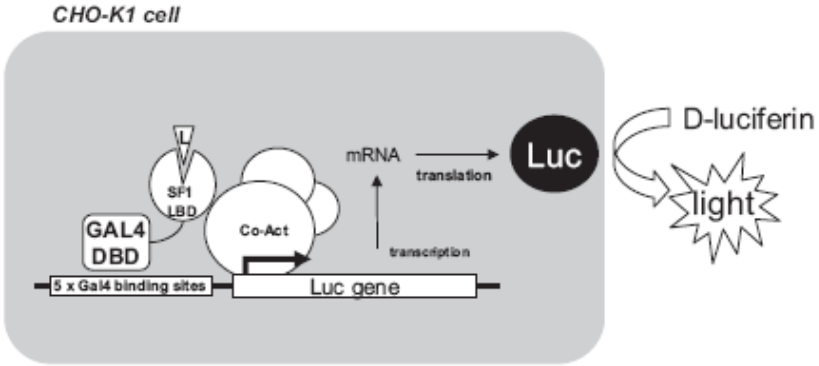


Example #2: SF-1 | Background

- **RO1 screening proposal submitted by Orphagen Pharmaceuticals**
- **SF-1 belongs to the nuclear hormone receptor (NHR) superfamily (druggable)**
- **Functional ligands are still unknown = orphan receptor**
- **SF-1 expression levels are higher in patients with Childhood Adrenocortical Tumors (ACTs)**
- **ACTs constitute a rare, yet very aggressive and poorly understood type of pediatric cancer**

Example #2: SF-1 | Lead Identification

A



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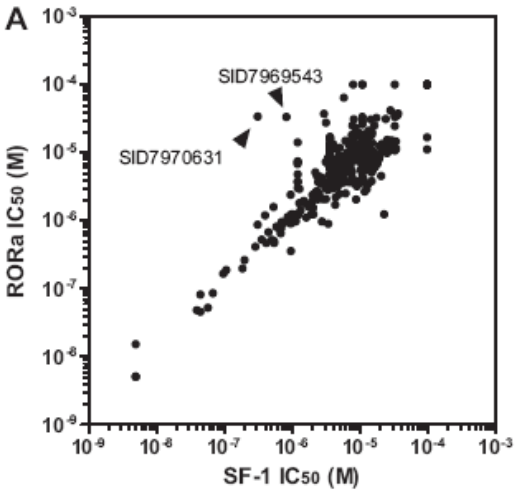

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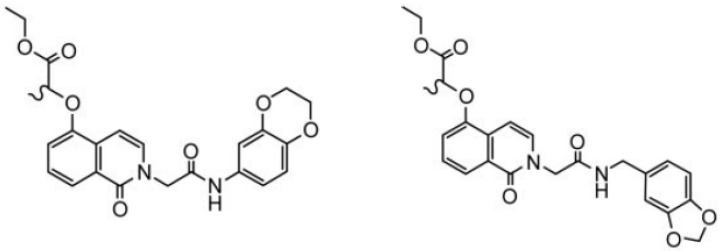


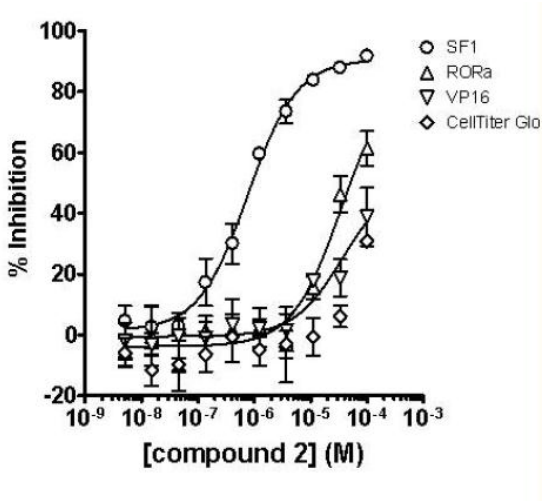
	SID7969543		SID7970631	
	Inhibition (Cytotoxicity)	IC_{50} (CC_{50})	Inhibition (Cytotoxicity)	IC_{50} (CC_{50})
	%	*nM*	%	*nM*
Gal4-fusion assays				
SF-1	84 ± 2	760 ± 102	80 ± 2	255 ± 63
ROR-α	16 ± 4	>33,333	20 ± 13	>33,333
VP16	18 ± 2	>33,333	−48 ± 21	>33,333
SFRE promoter assays with full-length proteins				
SF-1	136 ± 4	30 ± 15	126 ± 3	16 ± 7
LRH-1	0 ± 3	N.A.	−9 ± 9	N.A.
Cytotoxicity assay				
Cytotoxicity	-1 ± 6	>99,000	19 ± 1	>33,333

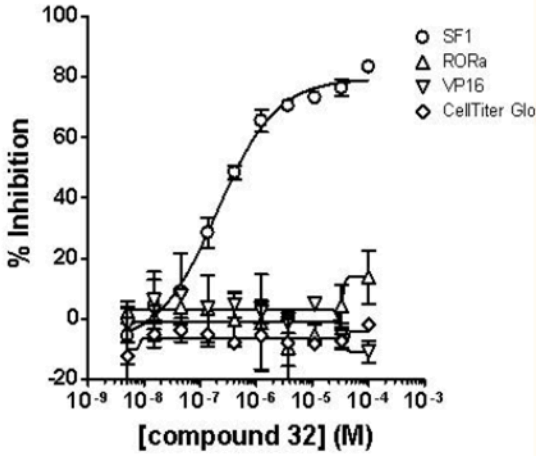
N.A., not applicable, because compound did not reach 50% inhibition; N.T., not tested.

→ a transient transfection cell-based screen led to the identification of 2 selective compounds

Madoux et al., Mol Pharm 2008

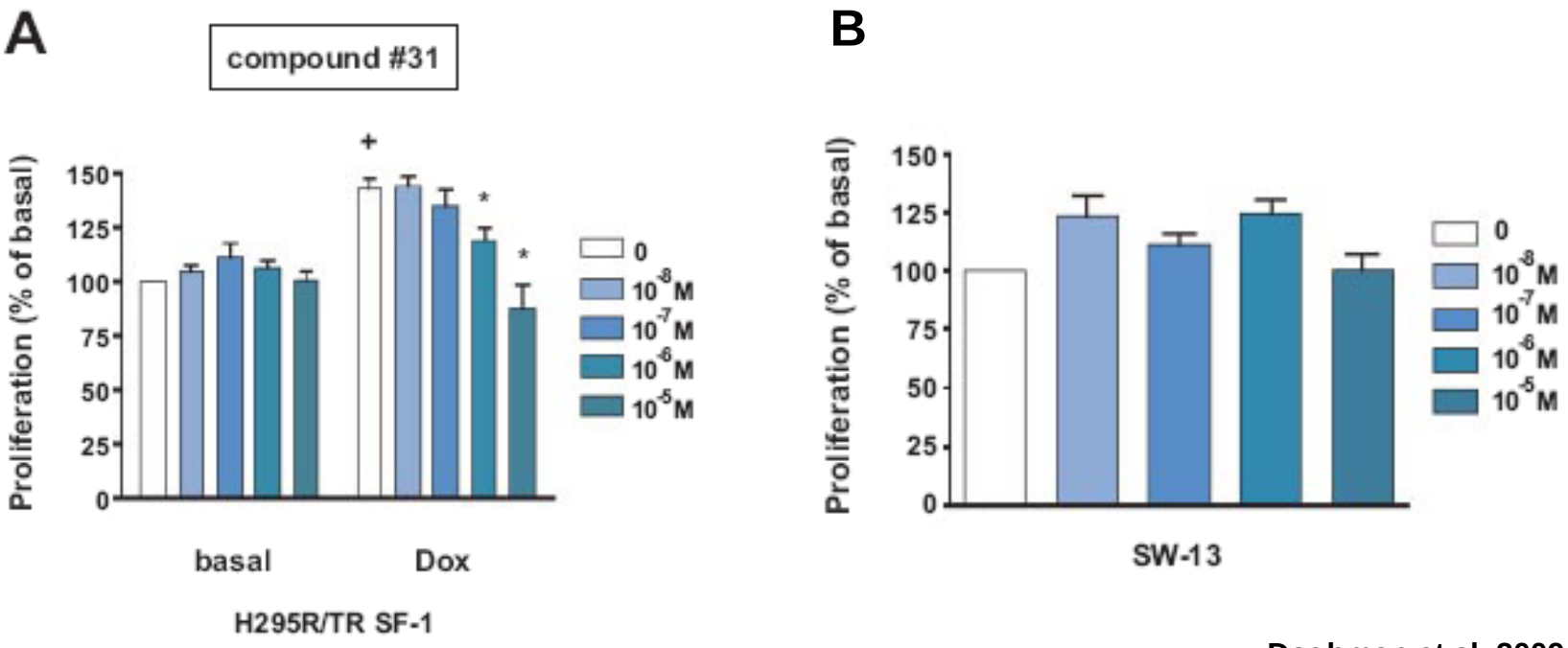
Example #2: SF-1 | Lead Optimization





Roth et al., Bioorg. Med. Chem. Lett. 2008

→a SAR-based chemistry optimization effort based on ≈50 analogs led to the generation of compounds exhibiting improved potency and a cleaner activity profile in the counterscreen assays



Doghman et al. 2009

→Compounds of the Isoquinolinone family inhibit adrenocortical cell proliferation in a SF-1 dependent

Example #2: summary

- Target
- Assays

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- Screening Results
- Probe Report

Orphagen

- Proof of concept
- Titration Results (1-year embargo)
- Chemical Probe
- Publications

PubMed

PubChem

Example #2: initiation of a virtuous cycle

Enzo Lalli

cnrs

PubMed

PubChem

Biotech “X”

grant Application for DAX-1

- Collaboration
- Probe Characterization
- Publications

NHR “X”

NIH

National Institutes of Health

MLPCN funding

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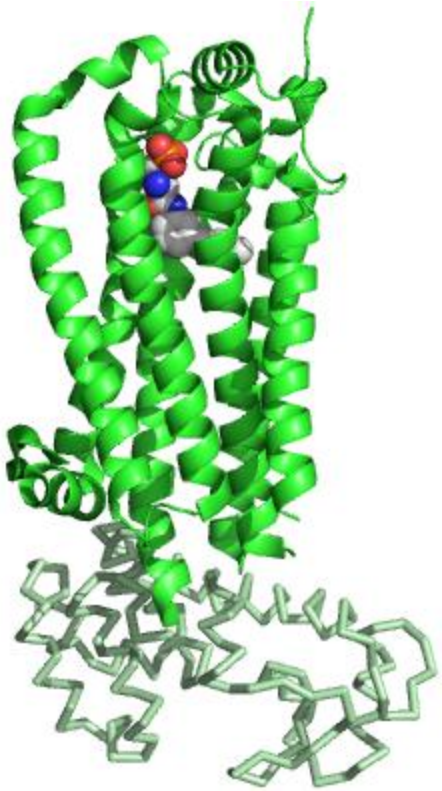
- Non-MLPCN funding

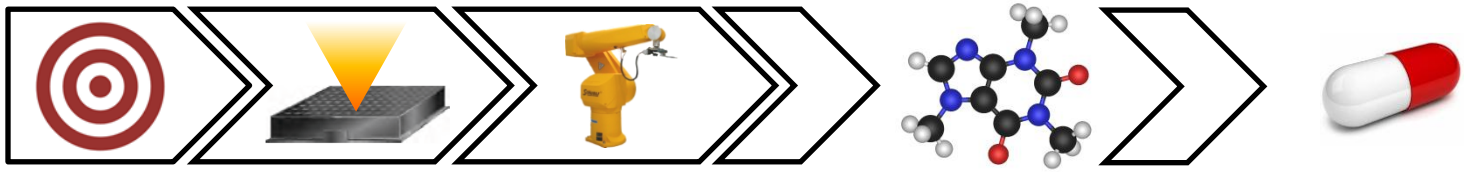
Example #3: S1P1 modulator



- **The sphingosine-1-phosphate (S1P)-driven signaling regulates fundamental biological functions, including cell proliferation, angiogenesis, endothelial cell chemotaxis, immune cell trafficking and mitogenesis.**
- **S1P1 receptor (S1P1-R) agonists can be used as immunosuppressants.**
- **S1P1R agonists can be used to treat autoimmune disorders such as relapsing–remitting multiple sclerosis**

Example #3: S1P1 modulator

Target → Assay → uHTS → Chemical Probe → Clinical Candidate



Hugh Rosen

receptos

Receptos Doses First Patient in Phase 2/3 Trial for RPC1063 in Multiple Sclerosis

SAN DIEGO, CA, October 22, 2012 – Receptos, Inc., announced today that its selective sphingosine-1- phosphate receptor 1 (S1P1) modulator, RPC1063, has been administered to the first patient in a Phase 2/3 study. RPC01-201, a Phase 2/3 placebo-controlled (Phase 2) and active comparator-controlled (Phase 3) trial, is the first of two planned pivotal studies for RPC1063 in the indication of relapsing multiple sclerosis (RMS).

Example #4: Collaboration with Envoy

Created a portfolio of CNS targets using their proprietary bacTRAP technology

Envoy and Scripps Add Three Drug Screening Programs

Envoy Therapeutics, Inc., a recently-formed drug discovery company, today announced that it has expanded its research collaboration with The Scripps Research Institute aimed at identifying new drugs for neurological and psychiatric diseases. Augmenting the collaboration Envoy and Scripps commenced in July focused on improved treatments for Parkinson's disease, scientists at the two organizations will carry out three additional drug discovery programs over the coming year. These programs will employ Scripps-Florida's high-throughput screening capabilities to discover compounds that modulate target proteins identified by Envoy.

Example #4: Collaboration with Envoy

Takeda buys Envoy for $140m

7 November 2012 Andrew Turley

Japanese drug maker Takeda has struck a $140 million (£88 million) deal to buy privately owned US drug discovery company Envoy.

The move gives Takeda access to Envoy's 'BacTrap' technology for labeling and extracting the protein-making components of specific types of cells. The technique is particularly useful in the brain, so its acquisition will strengthen Takeda's potential in the central nervous system drugs market.

Takeda plans to continue operating Envoy in Jupiter, Florida, until March 2013 and then transfer the majority of the Envoy scientific staff and management team to Takeda in San Diego, California.

Envoy was established in 2009 and now employs 21 people. Takeda invested in the company in October 2009 through its corporate investment wing, Takeda Ventures.

Example #4: Collaboration with Envoy

GENNewsHighlights More »

Mar 13, 2013

Takeda Expands Envoy-Scripps Collaboration

The Scripps Research Institute (TSRI) and the Takeda Pharmaceutical Company are expanding an initial collaboration launched in 2010 between scientists on the Florida campus of TSRI and Envoy Therapeutics, one that reportedly led to several breakthroughs in identifying potential new compounds for neurological and psychiatric diseases, to search for new drug targets for a variety of diseases. Envoy was acquired by Takeda Pharmaceuticals last November to obtain access to Envoy's CNS drug pipeline.

"We originally came to Jupiter because of Scripps Florida and are thrilled that the potential of our original collaboration has been realized," Stephen Hitchcock, svp, drug discovery at Envoy said. "Now we're moving into new therapeutic areas with different biological targets. The first step is to find small molecules that can validate those targets—and Scripps Florida is amongst the very best places to do that."

Takeda will be utilizing Scripps Florida's high-throughput screening facility, which is part of its larger translational research infrastructure. The facility reportedly has expertise in transforming slow, labor-intensive biological and biochemical bench-top experiments into high-throughput screening experiments ("screens"). Fully automated robotic screening platforms can then test more than 650,000 drug-like compounds for pharmacologic activity. After completion of the screens, the facility uses other technologies to support the development of clinically relevant compounds.

Takeda isn't just working with Scripps to develop new drugs: in February, they announced a partnership with Resolve Therapeutics to develop compounds for the treatment of lupus and other autoimmune diseases. Takeda will help fund continued development of Resolve's lead compound RSLV-132 through an initial payment of $8 million to Resolve and will pay Resolve an option exercise fee, plus the potential for additional development milestones totaling $247 million. Resolve is also eligible to receive royalties on product sales.

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Summary

- **Academia and Industry have complementary talents in Drug Discovery**
- **Ensuring parties speak the same language, align their goals and understand their differences are key to a successful collaboration**
- **A dedicated infrastructure and personnel (Translational Research Institute) helps interfacing between industry and academia**
- **A vision/ignition spark is needed: the US federal government (NIH) has played an integral role in the creation and implementation of translational research in academia in general and at Scripps in particular**
- **Successful collaborations exist in a variety of different forms. Be creative!**
- **Innovative targets, risky strategies, as well as rare and neglected diseases are excellent starting points for a successful collaboration**
- **Discoveries from either the Industry or Academia can fertilize the other, and vice-versa (virtuous cycle)**

In memoriam

Founder/Co-Founder of several biotechnology companies including:

- **HepCCo LLC.**
- **BioRelix (2005)**
- **Eventus DX (Lab Discoveries) (2005)**
- **Ocean Ridge BioSciences (2005)**
- **Symansis (2002)**
- **Axxima (1998)**
- **Hybrigenics (1998)**
- **Small Molecule Therapeutics (1997)**
- **Peptide ImmunoLigands (1996)**
- **Neurotech SA (1995)**
- **Pharmaceutical Peptides Inc./Praecis (1994)**
- **Vetigen (1992)**
- **Ideon/Incyte Inc. (1989/1991)**
- **AES-Chemunex (Chemunex SA) (1984)**

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