

*Translating academic research into early stage drug
discovery projects*

Sheraz Gul
European ScreeningPort
Hamburg, Germany

1- PHARMACEUTICAL INNOVATION

2- EXAMPLES OF RESPONSES FROM BIG PHARMA, ACADEMIA AND OTHER INITIATIVES

3- CASE STUDY: CELL-BASED ASSAY FOR KINASE

Pharmaceutical innovation

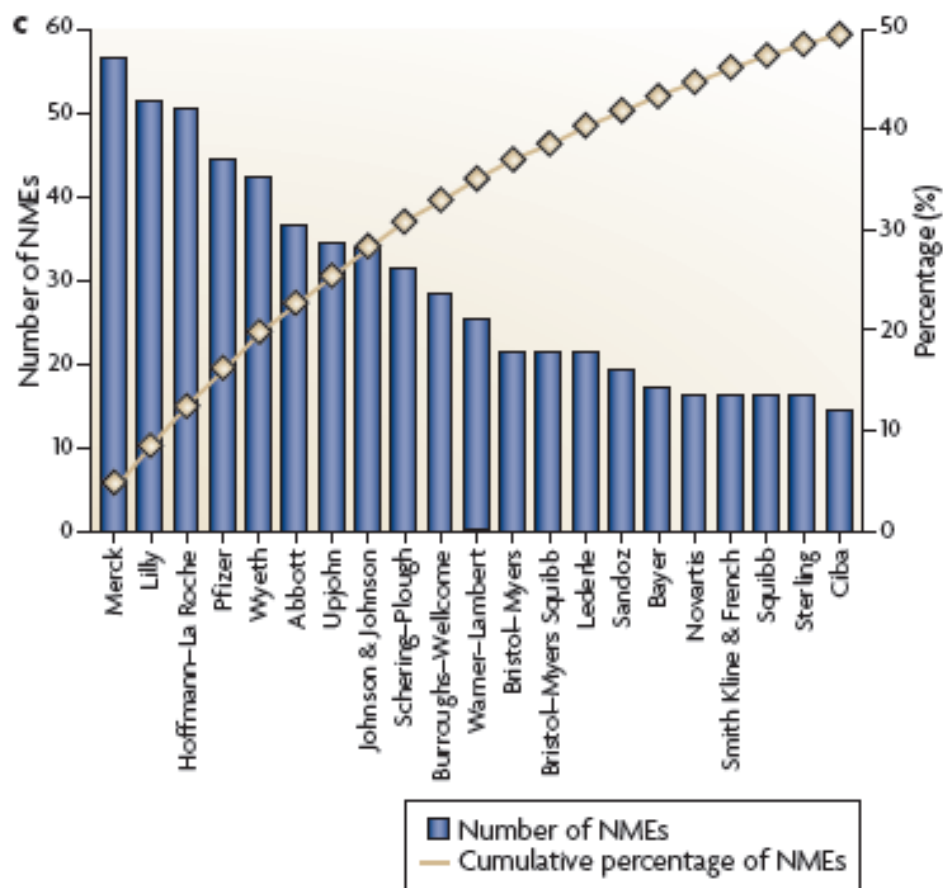


Figure 1 | Origins of new drugs.

c | 21 companies have produced half of all the NMEs that have been approved since 1950, although half of these companies no longer exist.

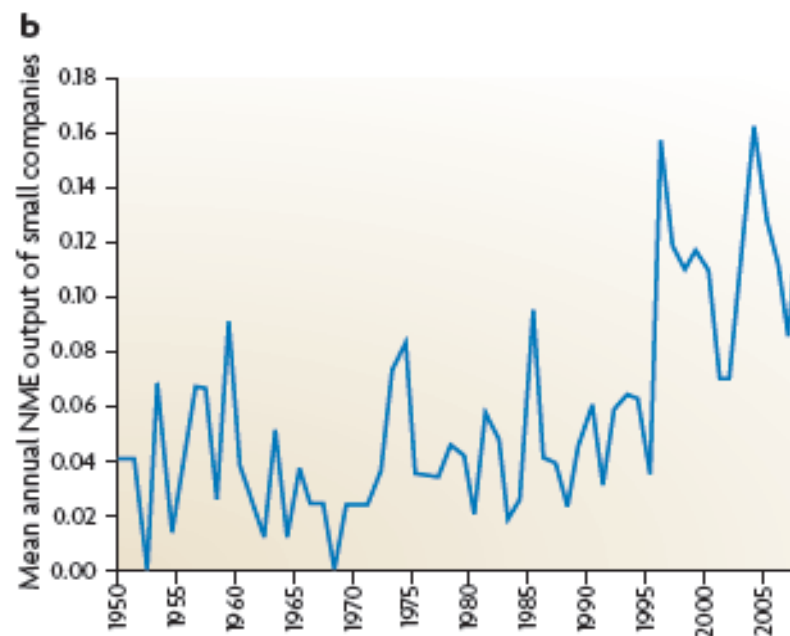


Figure 4 | Is bigger better?

b | Mean annual NME output for small companies.

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Indianapolis,
Indiana 46285, USA.*

Lessons from 60 years of
pharmaceutical innovation

Bernard Munos

NATURE REVIEWS | DRUG DISCOVERY

VOLUME 8 | DECEMBER 2009 | 959

Pharmaceutical innovation

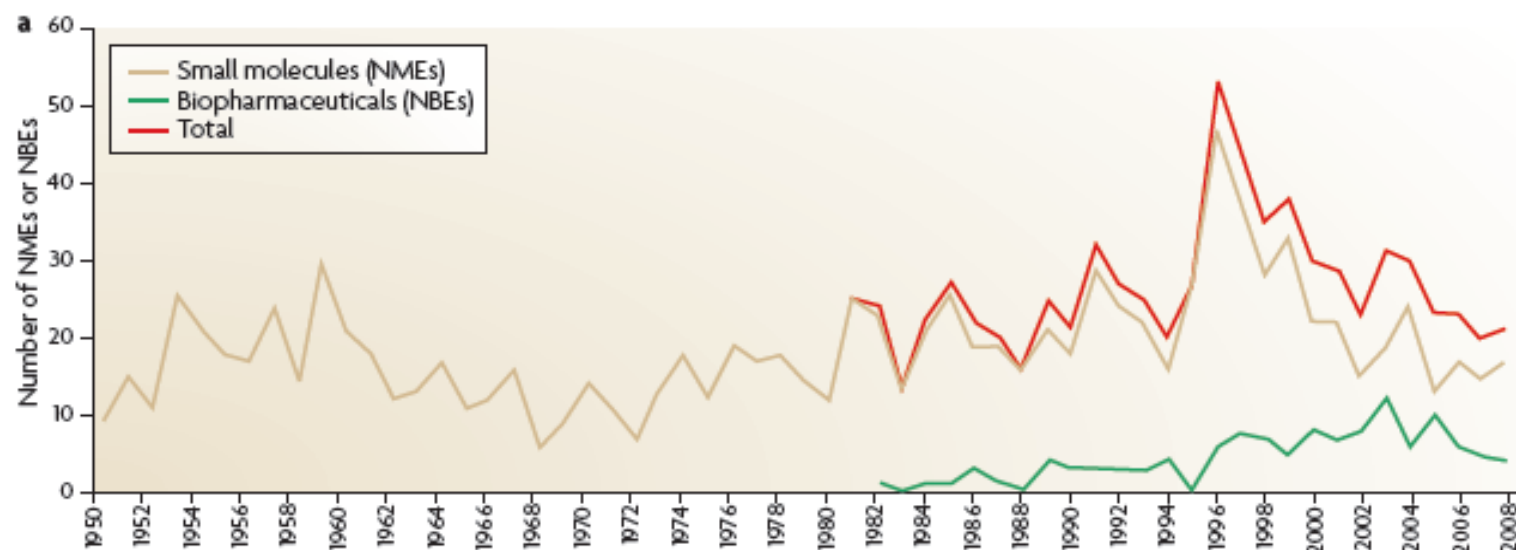


Figure 1 | **Origins of new drugs. a** | Timeline of approvals of new molecular entities (NMEs) and new biological entities (NBEs) by the US Food and Drug Administration (FDA) between 1950 and 2008.

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Lessons from 60 years of
pharmaceutical innovation

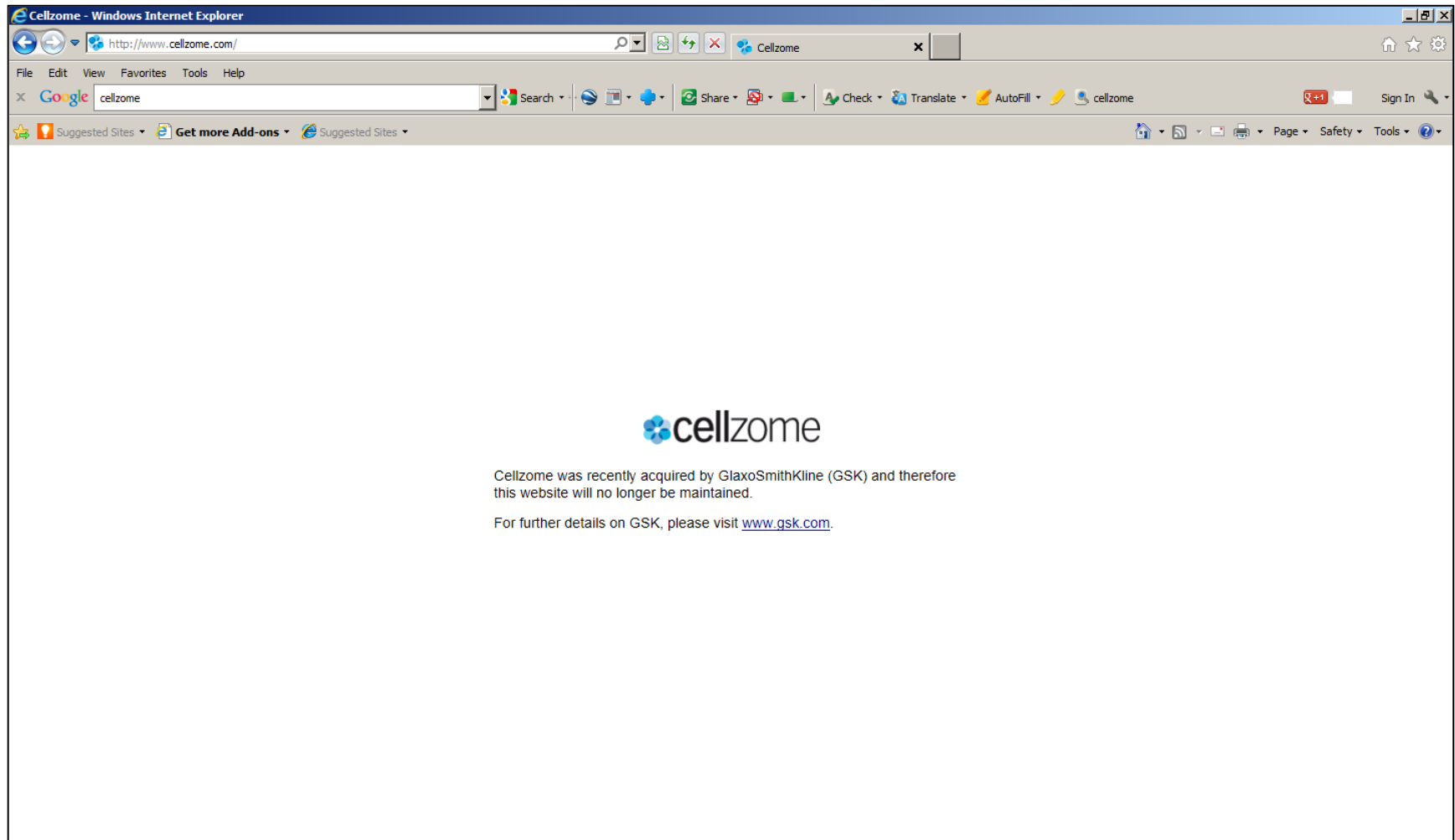
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Examples of responses from Big
Pharma, Academia and other initiatives

Response from Big Pharma (M&A)



Response from Big Pharma (Alliances)

PRESS RELEASE



Sanofi Provides an Update on its Research & Development Pipeline

Paris, France – January 8, 2013 – Sanofi (EURONEXT: SAN and NYSE: SNY) today will provide an update on its Research & Development (R&D) pipeline with Dr. Elias Zerhouni, President, Global Research and Development, presenting at the JP Morgan Healthcare Conference in San Francisco, California.

Portfolio update

- **SAR236553** (collaboration with Regeneron), a subcutaneously administered, fully-human antibody, is being evaluated for its impact on lowering low-density lipoprotein cholesterol (LDL-C) by targeting PCSK9. In November, Sanofi and Regeneron announced that the ODYSSEY OUTCOMES trial, a Phase III cardiovascular outcomes trial with SAR236553 started to recruit patients. This study will enroll approximately 18,000 patients, who recently suffered an acute coronary syndrome. With the start of this study, eleven Phase III trials are now recruiting hypercholesterolemic patients not at goal for LDL-C and mainly at high cardiovascular risk, a population estimated at 21 million people globally.
- **SAR231893** (collaboration with Regeneron), an anti IL-4R α monoclonal antibody with dual IL-4/IL-13 cytokine antagonism, will enter Phase IIb in mid-2013 in asthma and atopic dermatitis following positive proof of concept data for both indications. These data will be submitted for presentation at medical conferences in 2013.

GlaxoSmithKline Product development pipeline 2013

February 2013

Product development pipeline

February 2013

Option-based alliances with third parties that include assets in Phase I or later development:

| Company | Disease Area | Phase |
|-------------------------------------|--|--------|
| Cancer Research UK | cancer | I |
| ChemoCentryx | inflammatory disease | II* |
| Dynavax Technologies | cutaneous & systemic lupus erythematosus | II |
| ISIS Pharmaceuticals | transthyretin-mediated amyloidosis | IV/III |
| OncoMed Pharmaceuticals | oncology | I** |
| Prosenza Therapeutics | neuroscience | II |
| Ranbaxy Laboratories | respiratory | II |
| Telethon Institute for Gene Therapy | stem cell gene therapy | II** |
| Affiris | Alzheimer's disease treatment vaccine | II |

* CCX168

** Two assets

Response from Big Pharma (Alliances)

Final version: 14 October 2010

**PRESS
RELEASE**



Issued: TBC

GSK, Fondazione Telethon and Fondazione San Raffaele to collaborate on gene therapy for rare diseases

GlaxoSmithKline PLC (GSK), Fondazione Telethon and Fondazione San Raffaele today announced a new strategic alliance to research and develop novel treatments to address rare genetic disorders, using gene therapy carried out on stem cells taken from the patient's bone marrow (ex vivo). The alliance capitalises on research performed at the San Raffaele Telethon Institute for Gene Therapy (HSR-TIGET), a joint venture between Fondazione Telethon and Fondazione San Raffaele established since 1995.

Fondazione Telethon will receive an upfront 10 million euro payment from GSK and is eligible to receive further payments upon successful completion of a number of predetermined development milestones.

ADA-SCID is an autosomal recessive inherited disorder. Around 14 children in EU and 12 children in the US are born each year with the condition. A bone marrow transplant from a matched donor is currently the best treatment option available to patients. Unfortunately suitable bone marrow donors cannot always be found for all patients. In some cases, patients are treated with enzyme replacement therapy (ERT) but this requires frequent injections and is not a cure.

Molecular Libraries Program (USA)

NEWS FEATURE

National prescription for drug development

Vowing to reengineer drug discovery, NIH bets big with a new translational research center. Meredith Wadman reports.


Box 1 Molecular Libraries Program gets the axe

Table 1 MLP funding

| Year | Funding (\$ millions) |
|------|-----------------------|
| 2004 | 31,572 |
| 2005 | 66,611 |
| 2006 | 96,952 |
| 2007 | 114,734 |
| 2008 | 117,939 |
| 2009 | 112,337 |
| 2010 | 113,241 |
| 2011 | 103,234 |
| 2012 | 91,750 |
| 2013 | 34,075 |
| 2014 | 0 |

Admittedly, the program has critics. Christopher Lipinski, a scientific advisor to Melior Discovery in Exton, Pennsylvania, and a medicinal chemist at Pfizer until he left the company in 2002, says that the NIH paid rock-bottom prices to build the compound library in the early years of the program, and came up with “pretty wretched compounds. So in my opinion there was a lot of time and money squandered, wasted in the early time period. That’s the bad part. The good part is that the NIH learned from the mistakes and largely corrected them,” he says.

Molecular Libraries Program output



Welcome to the
Molecular Libraries Program
Pathways to Discovery

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News & Events

January 28, 2011

A probe project executed by the Scripps Research Institute (TSRI), a funded center of the NIH Common Fund Molecular Libraries and Imaging Program (MLP), has become the program's first to yield a drug candidate tested in humans. The initial probe compound resulting from the MLP efforts, an agonist of the sphingosine-1-phosphate receptor 1 (S1P1) and related molecules, was further developed outside of the MLP by TSRI and Receptos Inc., eventually resulting in [administration to the first human subject](#) in an FDA approved Phase 1 clinical safety study being undertaken by Receptos Inc. The clinical study has been initiated as a potential treatment for multiple sclerosis.

Multiple sclerosis ([MS](#)) is a neurodegenerative disease that affects the central nervous system (brain and spinal cord). Patients with MS suffer damages to myelin, the material that surrounds and insulates nerve cells. There are approximately 250,000 to 350,000 people in the United States with [MS diagnosed by a physician](#). MS is currently believed to be an immune-mediated disorder. Sphingosine-1-phosphate (S1P) is a phospholipid released by platelets, mast and other cells. S1P stimulates at least five different G-protein coupled receptors (GPCRs), called the S1P receptor subtypes 1-5 (S1P1-5). These GPCRs mediate a number of biological responses. S1P1 plays a key role in the immune system, regulating lymphocyte egress from lymphoid tissues into the circulation. It is believed that S1P1 agonists induce T-cell sequestration in lymph nodes, diminishing their ability to reach distant sites and contribute to MS pathology, including inflammation and demyelination.

NIH NCATS initiative



National Center
for Advancing
Translational Sciences

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PRESIDENT ANNOUNCES FISCAL YEAR 2014 BUDGET

The request includes \$665,688,000 for NCATS.

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RESEARCH HIGHLIGHTS


Clinical and Translational Science
Learn more about clinical and translational science activities at NCATS.

Rare Disease Research and Therapeutics
Learn more about rare disease research and therapeutics efforts at NCATS.

Re-engineering Translational Sciences
Preclinical translational research is the bridge between basic research and human medicine.

NCATS-Supported Programs
Learn more about each of the programs that NCATS supports.

Director's Message



A message from Christopher P. Austin, M.D., director of NCATS.

Funding & Notices

- Notice of Participation of NCATS in RFA-HL-14-012
- Small Market Awards: SBIR Phase IIB Competing Renewals for Heart, Lung, Blood and Sleep Technologies with Small Commercial Markets (R44)
- More Funding & Notices...

News & Events

- Innovative Health Coalition Creates Model for Community Health • University of California, San Francisco
- UCLA Fast-Tracking Autism Research • Examiner.com
- Alzheimer's Researchers Creating "Designer Tracker" to Quantify Elusive Brain Protein, Provide Earlier Diagnosis •

Frequently Asked Questions

- Collaborating with NCATS
- BRIDGs
- TRND
- Tissue Chips
- Therapeutics Discovery
- Rare Diseases
- Neglected Diseases

Response from the EU



Innovative Medicines Initiative

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THE INNOVATIVE MEDICINES INITIATIVE

The Innovative Medicines Initiative (IMI) is Europe's largest public-private initiative aiming to speed up the development of better and safer medicines for patients.

IMI supports collaborative research projects and builds networks of industrial and academic experts in order to boost pharmaceutical innovation in Europe.

IMI is a joint undertaking between the European Union and the pharmaceutical industry association EFPIA.

ANTIMICROBIAL RESISTANCE CALL LAUNCHED

IMI has launched its Call for proposals on antimicrobial resistance.

The **deadline** for submitting Expressions of Interest is **9 July 2012**.

[more](#) 

IMI NEWSFLASH



09/07/2012 : Sign up for IMI's webinars on the 7th Call clinical effectiveness topic on 20 July and 2 August
<http://t.co/AmRuPumg>

06/07/2012 : Evaluation of Stage 1 of IMI's 5th Call conducted 'professionally and fairly', Independent Observers state: <http://t.co/SM45s980>

05/07/2012 : Check out the new video on on-course, Europe's most comprehensive biomedical R&D postgrad course portal <http://t.co/ts1AF2I9>

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Response from the EU

□ Introduction



EU Lead Factory

- open otherwise safeguarded library assets to other Pharma and Public partners
- provide industry-like HTS platform to public projects – *focus on value generation*
- generate 'qualified hits' to be refined towards leads for drug development or tool compounds for target research
- combine pharma and academic expertises to develop differentiated novel chemistry for lead discovery
- provide novel type of platform to foster public-private partnerships around early drug discovery programs
- generate knowledge base to guide future library design activities

2

European Lead Factory

The EFPIA Contributors

Johnson & Johnson

ucb Pharma

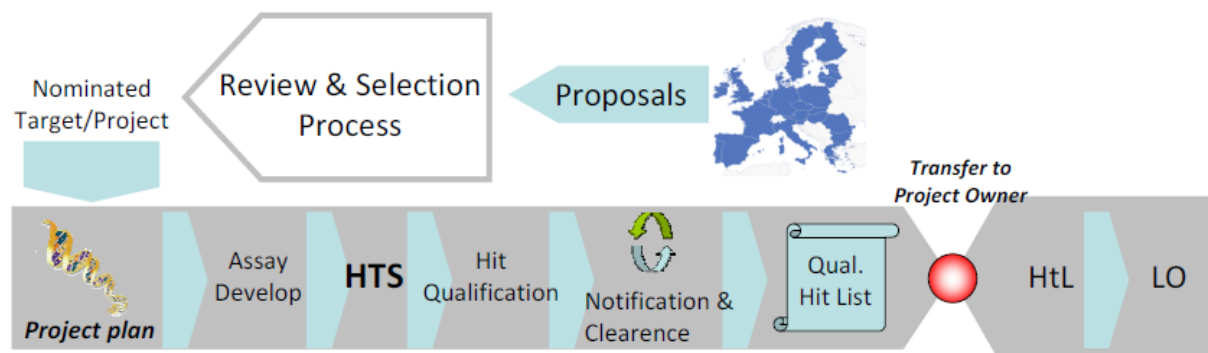
MERCK
SERONO

AstraZeneca

SANOFI

Lundbeck

Bayer



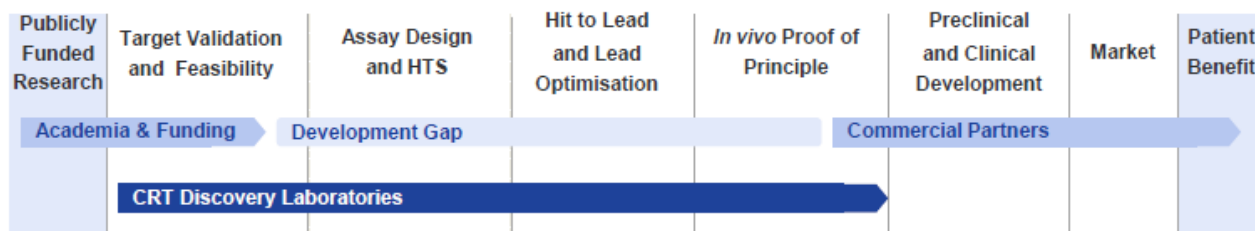
- **75-80 million EURO** EFPIA 'in kind contribution'
 - 6 x 50.000 compounds
 - EFPIA HTS project work
 - support and management
 - early partnering of public projects

Response from UK Academia (CR-UK)

Role of the CRT-DL


- To develop (and de-risk) to *in vivo* proof of principle stage
 - Partner at this stage
 - Maximise number of projects developed
- HTS, pharmacology, medicinal chemistry, crystallography; project validation function
 - Focus on industry experience and skills to prosecute a maturing portfolio
- Select “novel” targets as priority from CR-UK funded and other academic research
 - Collaborations worldwide with leading academic research groups
 - Discovery alliances with industry (AstraZeneca and Cephalon)
- Fully integrated part of CR-UK long-term Drug Discovery Strategy

CRT bridges the gap between academia and Industry




A word cloud of various cancer drugs, including: Taceva/erlotinib, Taxol/docetaxel, Avastin/bevacizumab, Nolvadex/tamoxifen, Tomudex/raltitrexed, Doxil/doxorubicin, Zoladex/goserelin, Erivedge/vismodegib, Eloxatin/oxaliplatin, Leukeran/chlorambucil, Gemzar/gemcitabine, Paraplatin/carboplatin, Zelboraf/vemurafenib, Rituxan/rituximab, Temodar/temozolomide, Myleran/busulphan, Herceptin/trastuzumab, Alkeran/melphalan, Arimidex/anastrozole, Zytiga/abiraterone, Cisplatin, Aromasin/exemestane, Iressa/gefitinib, Femara/letrozole, and many others.

Response from UK Academia (Dundee)



DDU Drug Discovery Unit
College of Life Sciences
University of Dundee
Novel targets and platforms | Fighting neglected diseases



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« 1 2 3 4 5 6 7 8 9 »

INITIATIVES

The Dundee Drug Discovery Unit has two major initiatives, neglected tropical diseases and innovative targets and pathways. [Major Initiatives](#)

CAPABILITIES

The DDU is a fully operational and integrated drug discovery team with the full range of disciplines needed for drug discovery. [Capabilities](#)

Drug Discovery Pipeline

See how our pipeline of molecular targets in both the neglected tropical diseases initiative and the innovative targets and pathways initiative. [Click here to view the Drug Discovery Unit film.](#)


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THE LEADERSHIP & MANAGEMENT AWARDS 2012
SHORTLISTED
KNOWLEDGE EXCHANGE/ TRANSFER INITIATIVE OF THE YEAR

Response from German Academia (LDC)



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News

Max Planck Innovation

Technology Fields

Technology Transfer

Success Stories


- Searching for Potential Drug Candidates**
- The Long Road to the Pharmacy Shelf
- Genes and their metabolites
- Connecting Science and Business
- Steel for the Cars of Tomorrow

SEARCHING FOR POTENTIAL DRUG CANDIDATES

Searching for Potential Drug Candidates

The Max Planck Society operates a center in Dortmund to make better use of the enormous potential of basic research in the area of drug discovery, and to bridge the gap between basic research and industrial product development. In this way, it aims to ensure that innovative ideas don't fall by the wayside before being given an opportunity to come to fruition.

Text: Marcus Anhäuser



The location is the outskirts of the German city of Dortmund. The days of coal mining and shaft towers are long gone here in the southwest. A number of research institutes, the Technical University, and the University of Applied Sciences have all cropped up on a campus called the "Technology Center." Since the mid-1980s, around 280 small and large companies involved in the electronics, microtechnology and nanotechnology sectors have also found a home on the campus near the academies – visible proof of the structural change that has been driving the region for decades. Similar to the companies that can often be found in the technology parks of any major city, 26 of these operations generate their revenues in the life sciences: bio-IT, analysis technology and medical technology.

Analytical challenges: Poured into specimen jars, potential drug candidates are subjected to elaborate testing at the... [\[more\]](#)

© Lead Discovery Center

In November 2008, however, a new company unlike any other anywhere in Germany opened its doors on the first and second floors of the Biomedicine Center: the Lead Discovery Center, or LDC. It was founded by Max Planck Innovation, the Max Planck Society's technology transfer company. Any assumption that this is likely just another Max Planck Institute is mistaken: "It is an independent company," explains Matthias Stein-Gerlach, Patent and Licensing Manager at Max Planck Innovation.

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RELATED LINKS

[The Long Road to the Pharmacy Shelf](#)

European ScreeningPort (SME)

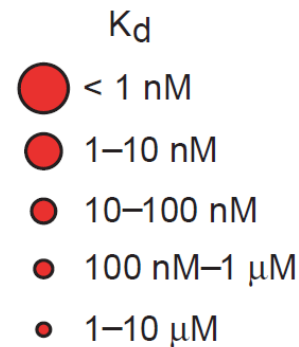
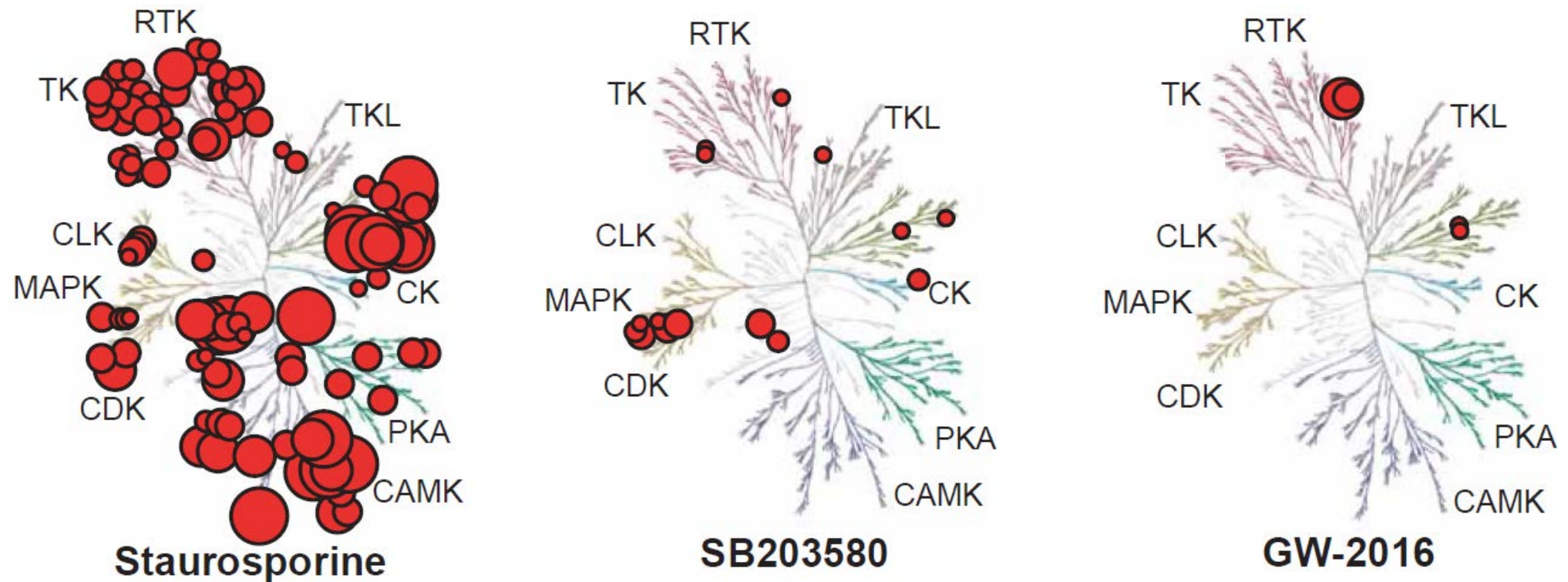
Public/Private Partnership based in Hamburg established in 2008

- apply academic research to industrialized drug R&D
- exploit established infrastructure at a central node
- assess druggability of targets for drug discovery
- generate preliminary IP for academic partners
- increase collaboration and transfer of skills



Case study:
Cell-based assay for kinase

Fabian et al, 2005: specific kinase inhibitors



NIK phosphorylates IKK- α

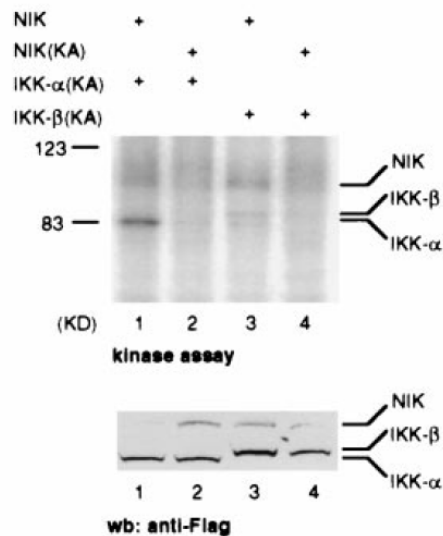
Proc. Natl. Acad. Sci. USA
Vol. 95, pp. 3792–3797, March 1998
Immunology

NF- κ B-inducing kinase activates IKK- α by phosphorylation of Ser-176

LEI LING, ZHAODAN CAO, AND DAVID V. GOEDEL*

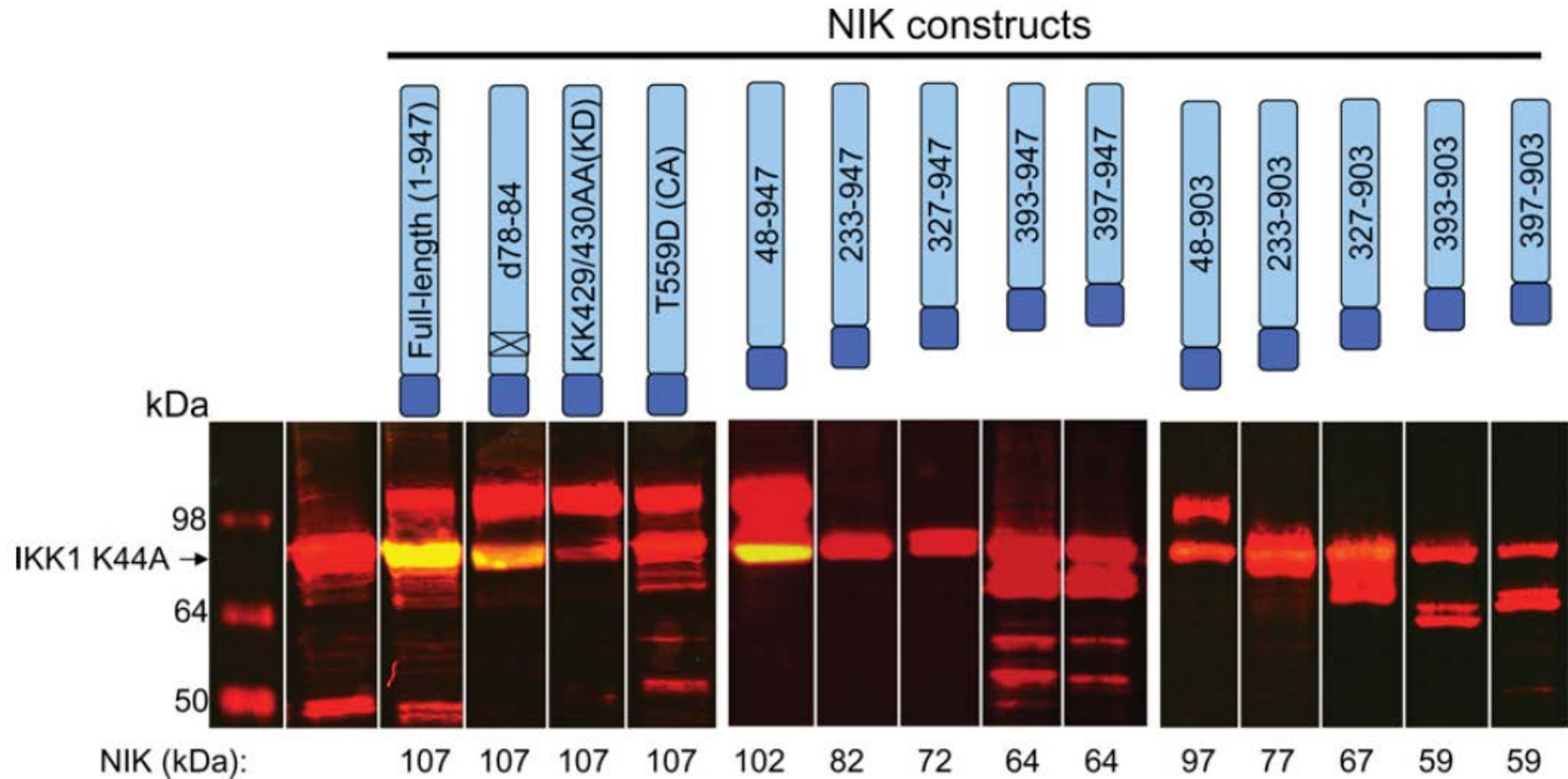
Tularik, Inc., Two Corporate Drive, South San Francisco, CA 94080

Contributed by David V. Goeddel, January 29, 1998

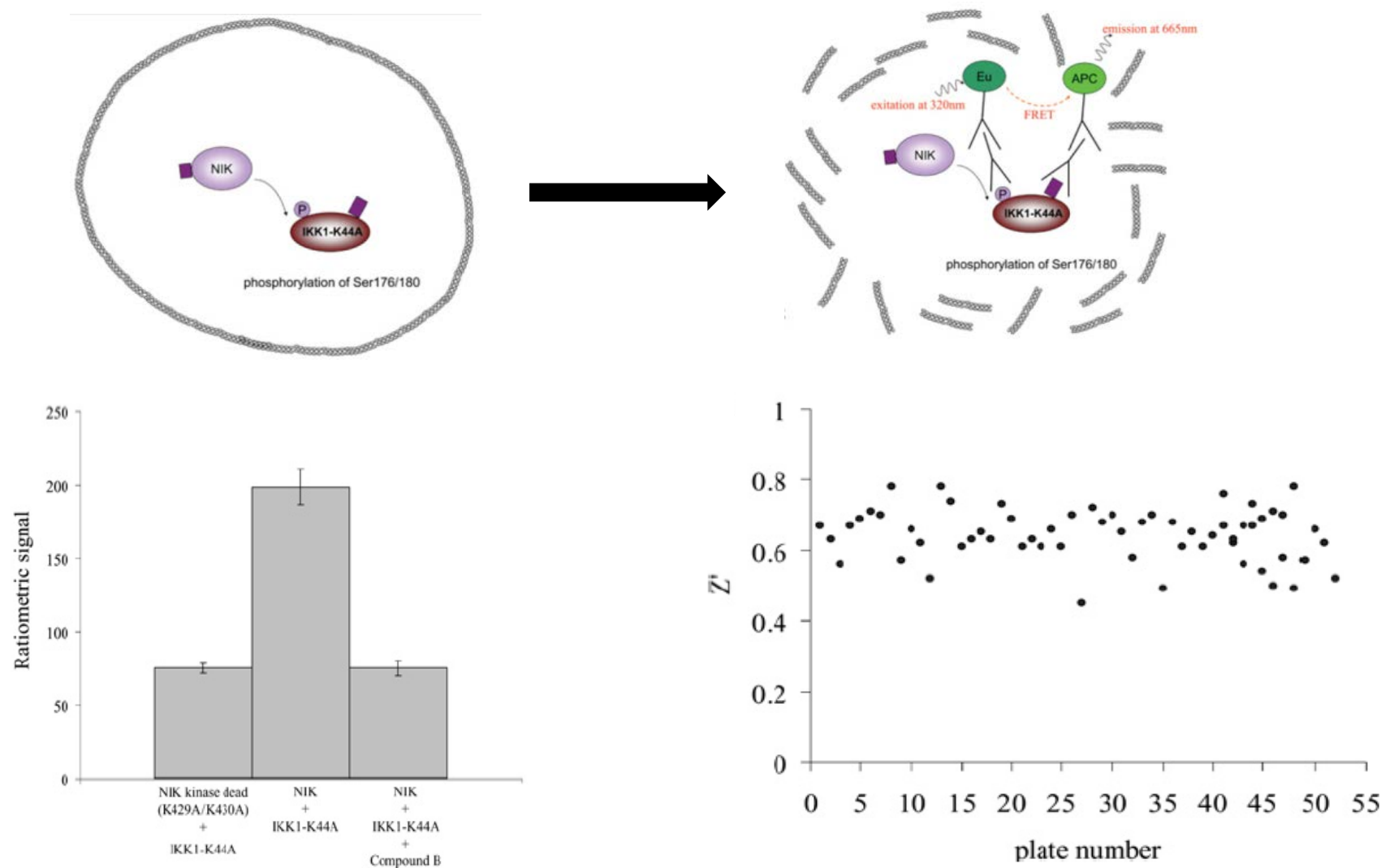


Phosphorylation of IKK- α (KA) and IKK- β (KA) by NIK. 293 cells were transiently transfected with expression plasmids encoding FLAG epitope-tagged wild-type NIK, IKK- α (KA), or IKK- β (KA). Purified proteins were incubated with [γ - 32 P]ATP, resolved by SDS/PAGE, and analyzed by autoradiography. The amounts of proteins used in the reactions were determined by immunoblotting (wb) with anti-FLAG polyclonal antibodies (*Lower*). The positions of IKK- α , IKK- β , and NIK are indicated.

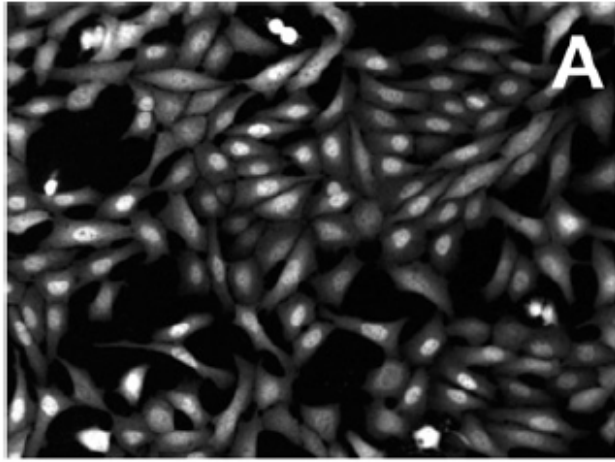
Full-length NIK phosphorylates IKK- α



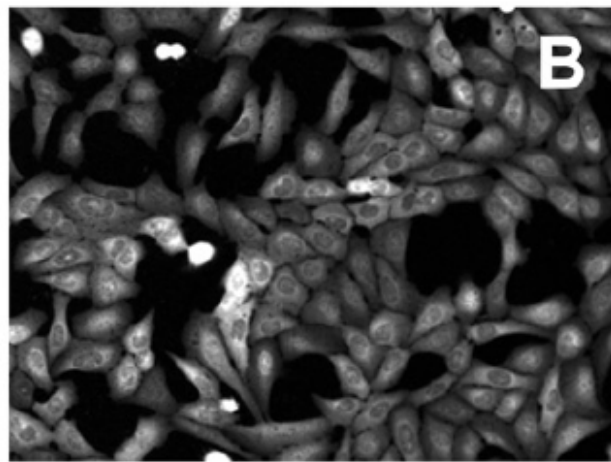
TR-FRET Insect cell-based assay for NIK



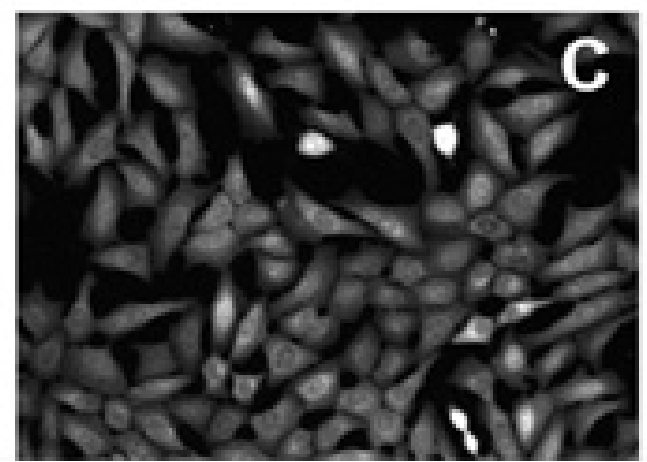
Use of HCS after cell-based NIK inhibitor screen



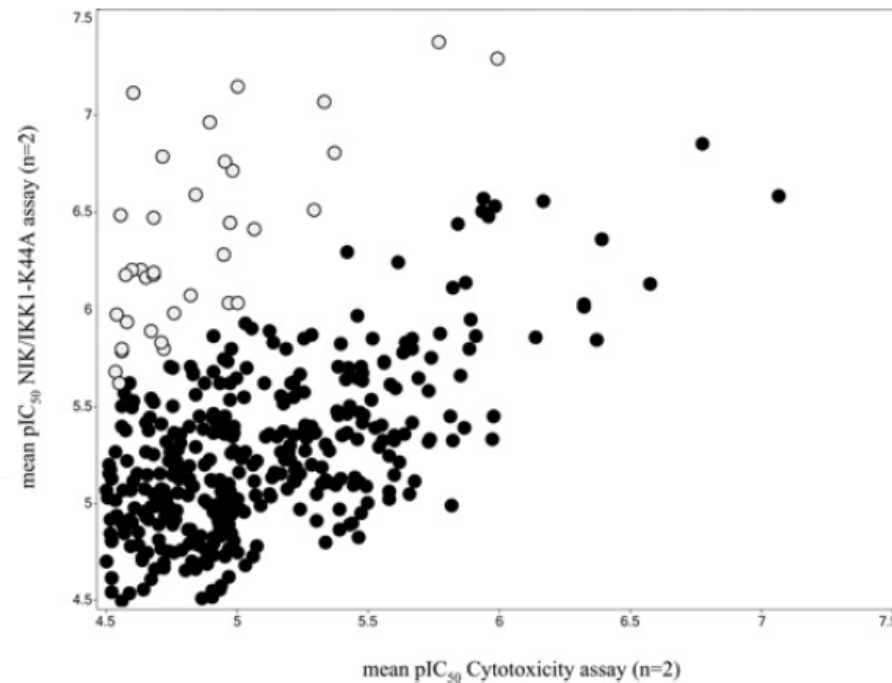
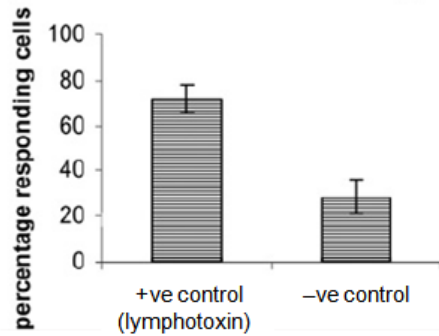
+ve control (lymphotoxin)



–ve control



Hit from cell-based screen



HEK cell-based assay for NIK

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



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Published:

Mohammed Kashem from Boehringer to Speak on the "Unexpected Off-Target Activity of Hits Identified Using a Cell-Based Kinase Assay" at 8th Protein Kinases in Drug Discovery Mtg on July 8-9, Boston

Cell-based assays can identify small molecule kinase inhibitors that may be undetectable by a biochemical assay run under less physiological conditions. Mohammed's team developed a robust cell-based assay, based on the work of Hassan et al. (Biochem. J., 2009, 419, 65-73), that measures in Sf9 insect cells the phosphorylation of a kinase-dead mutein of IKKα (IKKα-K44A) by full-length NIK (NFκB-inducing kinase) using anti-phospho- IKKα/β (Ser176/Ser180) antibody-based HTRF format. This presentation will review the results of these experiments and the lessons learned for cell-based kinase assays, offering the most current understanding of cell-based kinase assay that measures direct phosphorylation of its downstream substrate. Discussion topics also include how reduced assay signal may not be due to inhibition of cellular phosphoryl transfer activity, considerations that should be made when selecting the counter-screen to rule out false positives, and comparison of potencies of a select set of compounds in multiple NIK assays/formats.



**8TH PROTEIN KINASES
IN DRUG DISCOVERY**

JULY 8 - 9, 2013 • BOSTON, MA

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Leonard S. Schleifer, M.D., Ph.D.

Founder, President, and Chief Executive Officer

Leonard S. Schleifer, M.D., Ph.D., founded the Company in 1988, has been a Director and its President and Chief Executive Officer since its inception, and served as Chairman of the Board from 1990 through 1994. From 1984 to 1988 he was Assistant Professor at the Cornell University Medical College in the Departments of Neurology and Neurobiology. Dr. Schleifer received his M.D. and Ph.D. in Pharmacology from the University of Virginia. Dr. Schleifer is a licensed physician and is certified in neurology by the American Board of Psychiatry and Neurology.



George D. Yancopoulos, M.D., Ph.D.

Founding Scientist, President, Regeneron Laboratories & Chief Scientific Officer

George D. Yancopoulos, M.D., Ph.D., joined the Company in 1989 as its Founding Scientist and is currently President, Regeneron Laboratories and Chief Scientific Officer. He received his M.D. and Ph.D. from Columbia University. Dr. Yancopoulos was the 11th most highly cited scientist in the world in the 1990s, and in 2004 he was elected to be a member of the National Academy of Sciences. Dr. Yancopoulos is principal inventor and developer of Regeneron's three FDA-approved drugs - including EYLEA®, ZALTRAP®, and ARCALYST® - as well as of its foundation technologies including the TRAP technology, VelociGene®, and VelocImmune®.



1988

Regeneron is founded in New York City

[\[Less\]](#)

Leonard S. Schleifer, M.D., Ph.D., a young neurologist and assistant professor at Cornell University Medical College, establishes the company based on the principle that dedication to strong science would lead to important new medicines. His two co-founders are nationally-known scientists Drs. Alfred Gilman, Len's Ph.D. thesis advisor at the University of Virginia, and Dr. Eric Shooter. Drs. Gilman and Shooter recruit other leading scientists to join the company's scientific advisory board to help guide the young company. Two of those scientists, Dr. Joseph Goldstein and Dr. Michael Brown, shared a Nobel Prize in 1985, and Dr. Gilman would go on to win a Nobel in 1994. The company is named Regeneron because of the intention to focus on the use of gene technology to regenerate neurons. The first \$1 million is raised from Merrill Lynch Venture Capital, Inc.

🔊 [Len Schleifer discusses his motivation for starting the company](#)

🔊 [Len Schleifer describes how Regeneron raised its first \\$1 million](#)

🔊 [Len Schleifer explains how Regeneron got its name](#)

1990

Regeneron publishes first paper in Science, on cloning a novel neurotrophic factor, which becomes the most highly cited neurobiology paper of the year

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The Company quickly established itself as one of the top research groups in the industry, as Yancopoulos and his team publish a featured article in Science magazine on the cloning of a novel neurotrophic factor (Maisonpierre et al., 1990).

Company collaborates with Amgen to develop neurotrophic factors brain-derived neurotrophic factor (BDNF) & neurotrophin-3 (NT-3)

Regeneron launches an "Orphan Receptor" Program, which lays foundation for future Traps and Growth Factor efforts

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Efforts begin with cloning of receptors for neurotrophic factors (e.g. Davis et al., 1991; Squinto et al., 1991; Glass et al., 1992) and lead to examples in which orphan receptors are used to identify their unknown growth factor partners (Davis et al., 1994; Stitt et al., 1995; Davis et al., 1996; Glass et al., 1996; Maisonpierre et al., 1997; Shrivastava et al., 1997; Valenzuela et al., 1999). Neil Stahl, Aris Economides, Yancopoulos and their colleagues take the lessons they learn from these efforts to begin to devise the Traps approach that leads to the IL-1 Trap and the VEGF Trap.

1991

Regeneron goes public on the Nasdaq Stock Market

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On the heels of the Amgen collaboration and riding a wave of interest in biotechnology companies, Regeneron stock begins trading under the symbol REGN. The IPO raises \$91.6 million for Regeneron.

2011

Regeneron files for regulatory approval of EYLEA® (aflibercept) Injection in February, receives FDA approval in November, and immediately makes the drug available in the U.S.

Regeneron also announces positive Phase 3 results for EYLEA and ARCALYST in second indications and for ZALTRAP® (ziv-aflibercept) Injection for Intravenous Infusion. Regulatory application for ZALTRAP is submitted to the EMA.

The IL-6R antibody, now called sarilumab, enters Phase 3 development, and positive Phase 2 data are announced for the REGN727 (PCSK9) program. By year end, Regeneron employs approximately 1,700 full time employees.

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