FROM BASIC RESEARCH TO PRODUCT - EXAMPLES OF FRAUNHOFER RESEARCH PROJECTS

Fraunhofer
IME

Dr. Sheraz Gul

AGENDA

Background to Fraunhofer Institute

Assay selection in pre-clinical drug discovery

Development of the collaborative COST Action ADME-Tox assay panel

Target Validation in CVD drug research

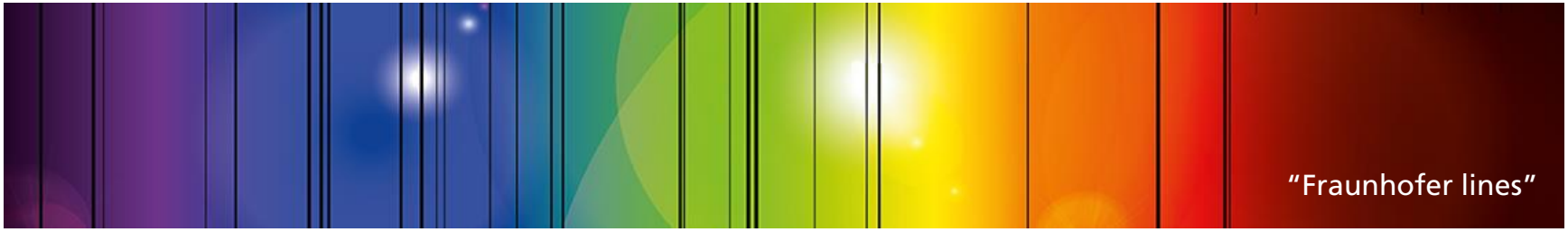
Genetic age test

Tools to de-risk drug research projects

Background to Fraunhofer Institute

Fraunhofer-Gesellschaft, the largest organisation for applied research in Europe

- 66 institutes and research units
- Nearly 24,000 staff
- More than €2 billion annual research budget. Of this sum, around 1.7 billion euros is generated through contract research
  - Roughly two thirds of this sum is generated through contract research on behalf of industry and publicly funded research projects
  - Roughly one third is contributed by the German federal and Länder governments in the form of base funding

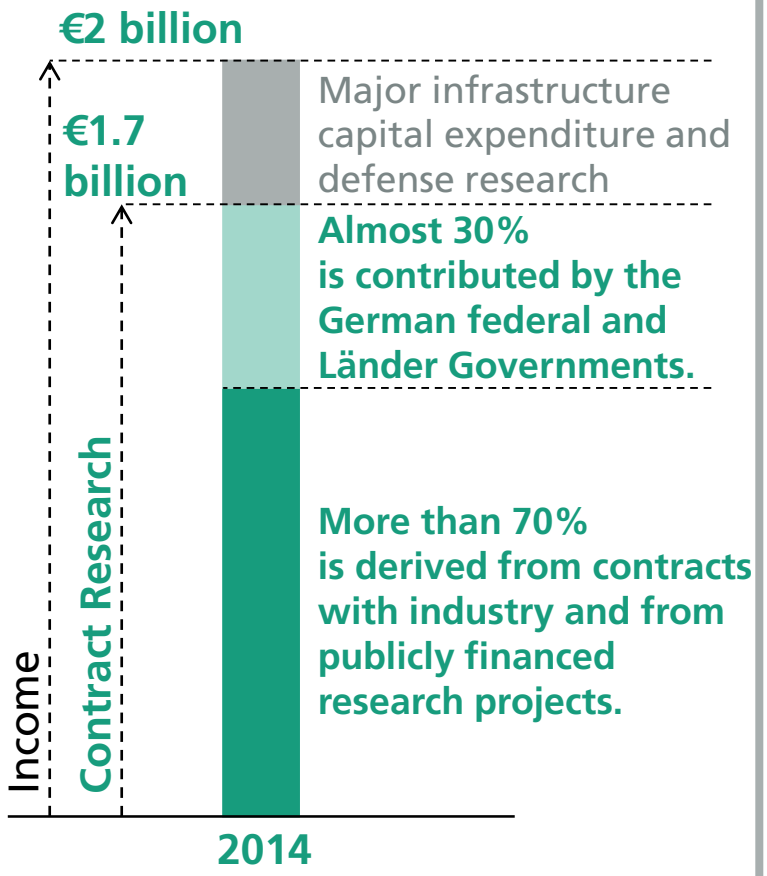


The Fraunhofer-Gesellschaft at a glance

The Fraunhofer-Gesellschaft undertakes applied research of direct utility to private and public enterprise and of wide benefit to society.

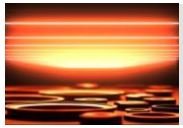
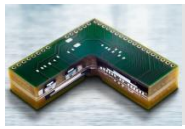
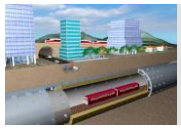
Nearly **24,000** staff

66 institutes and research units

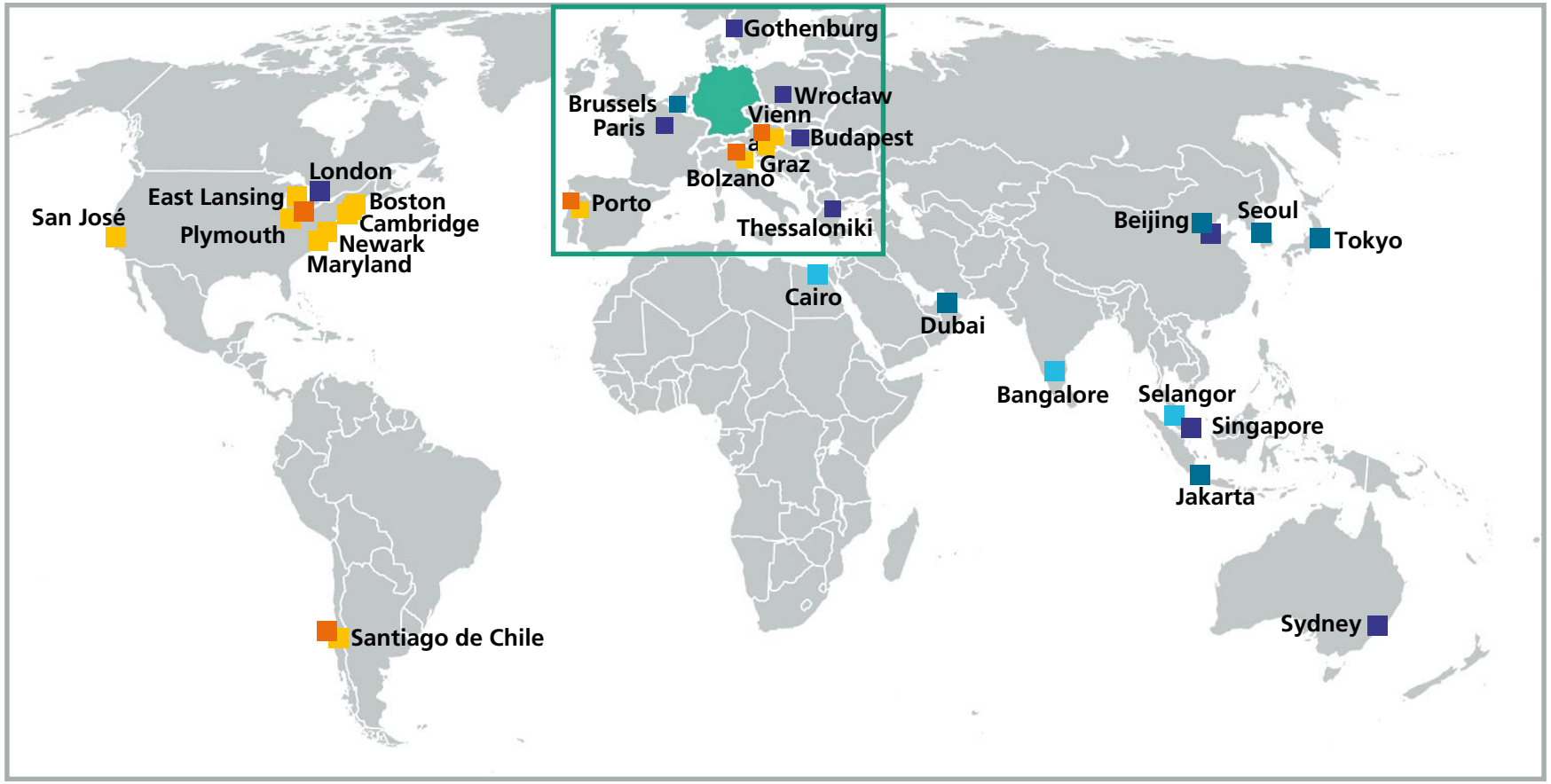


Fraunhofer IME

FRAUNHOFER GROUPS

	ICT	AISEC, ESK, FIT, FKIE, FOKUS, IAIS, IAO, IDMT, IESE, IGD, IOSB, ISST, ITWM, IVI, MEVIS, SCAI, SIT Associated members: HHI, IIS
	Life Sciences	EMB, IBMT, IGB, IME, ITEM, IVV, IZI
	Light & Surfaces	FEP, ILT, IOF, IPM, IST, IWS
	Microelectronics	EMFT, ENAS, FHR, HHI, IAF, IIS, IISB, IMS, IPMS, ISIT, IZM Associated members : ESK, FOKUS, IDMT, IKTS, IZFP
	Production	IFF, IML, IPA, IPK, IPT, IWU, UMSICHT
	Defense & Security	EMI, FHR, FKIE, IAF, ICT, INT, IOSB Associated members: HHI, IIS, ISI
	Materials & Components	EMI, IAP, IBP, ICT, IFAM, IKTS, ISC, ISE, ISI, IWM, IZFP, LBF, WKI Associated members: IGB, ITWM

Fraunhofer Worldwide



- Fraunhofer subsidiary
- Fraunhofer center
- Fraunhofer project center / strategic cooperation
- Fraunhofer representative office
- Fraunhofer senior advisor

Fraunhofer IME

Fraunhofer Molecular Biology and Applied Ecology (IME)
critical mass with 600 employees

National

International

Applied Ecology Division
Schmallenberg (1959)

Molecular Biology Division
Aachen (2000)

Center for Molecular Biotechnology
Newark, USA (2001)

Bioresources
Gießen (2009)

Biopolymers
Münster (2010)

TMP
Frankfurt (2012)

ScreeningPort
Hamburg (2014)

Center for Systems Biotechnology
Santiago, Chile (2010)

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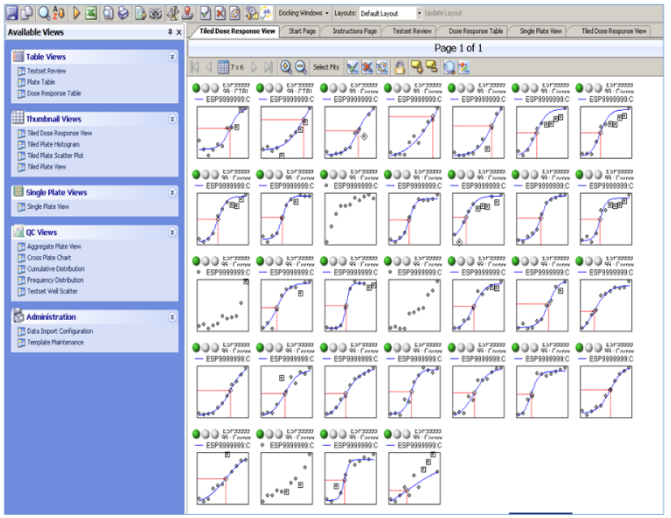
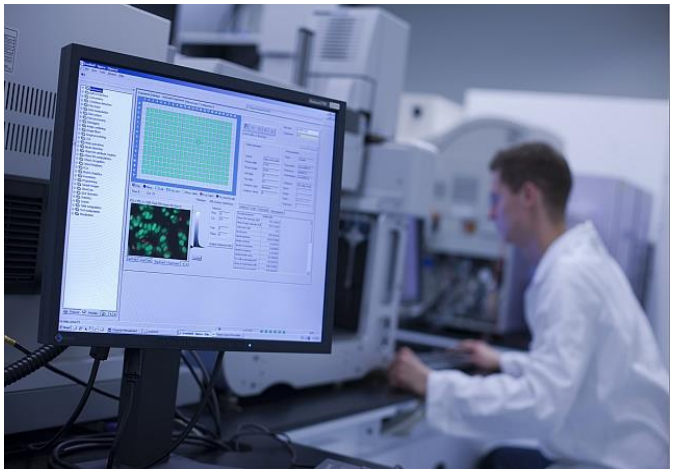
CAPABILITIES OF THE FRAUNHOFER-IME SCREENINGPORT





Fraunhofer IME

Assay selection in pre-clinical drug discovery (kinase)

NIK PHOSPHORYLATES IKK-α

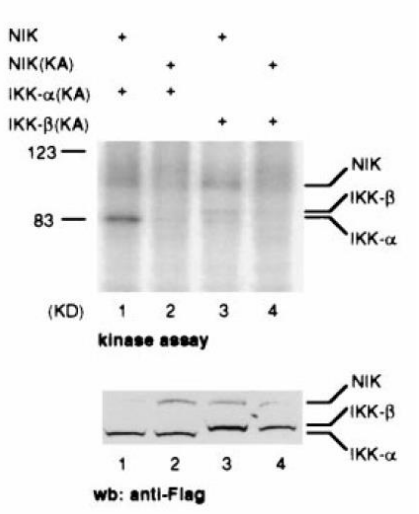
Proc. Natl. Acad. Sci. USA
Vol. 95, pp. 3792–3797, March 1998
Immunology

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

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

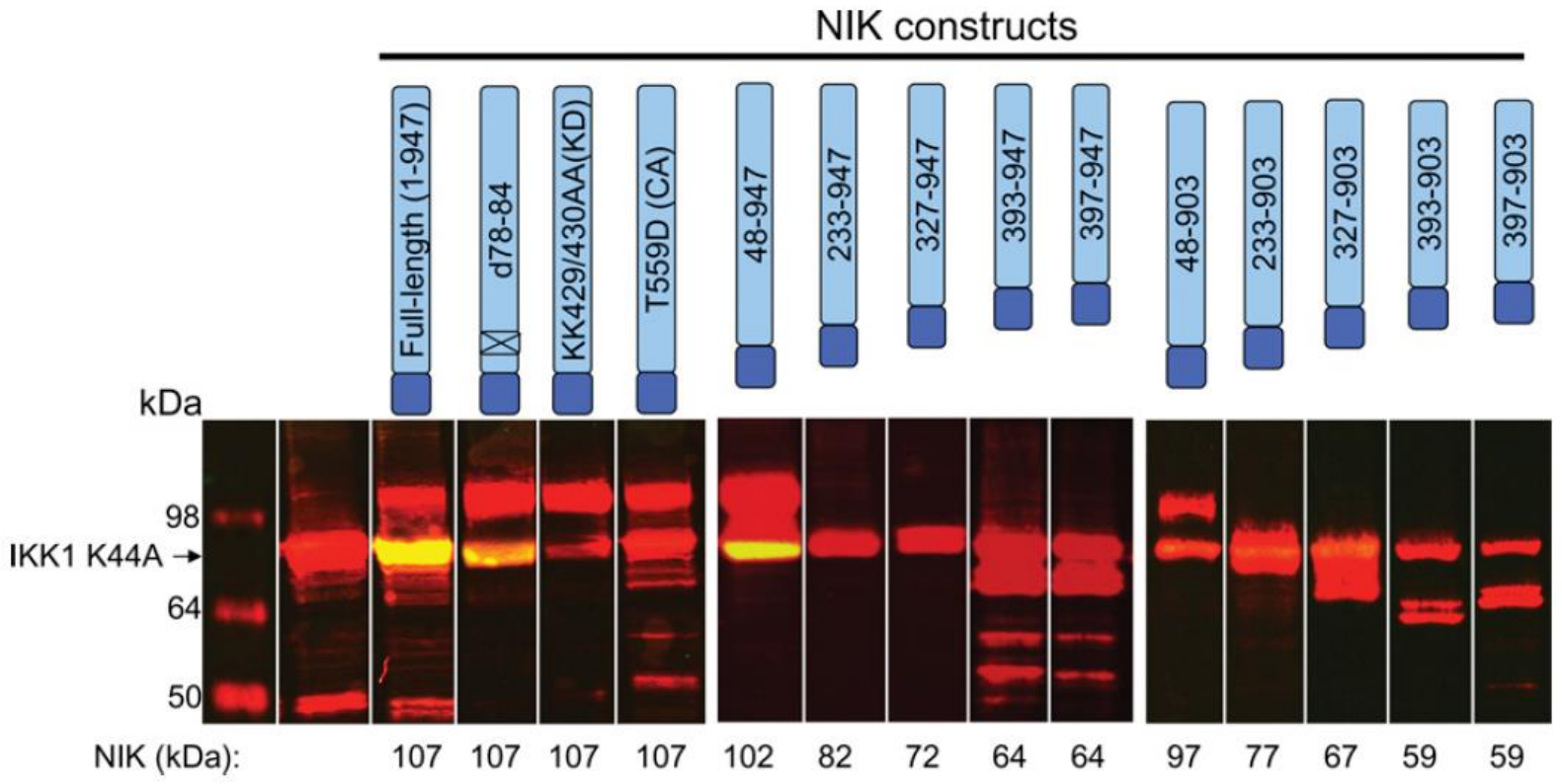
Tularik, Inc., Two Corporate Drive, South San Francisco, CA 94080

Contributed by David V. Goeddel, January 29, 1998



determined by immunoblotting (wb) with anti-FLAG polyclonal antibodies (*Lower*). The positions of IKK-α, IKK-β, and NIK are indicated. (*B*) 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.

CELL-BASED NIK ASSAY



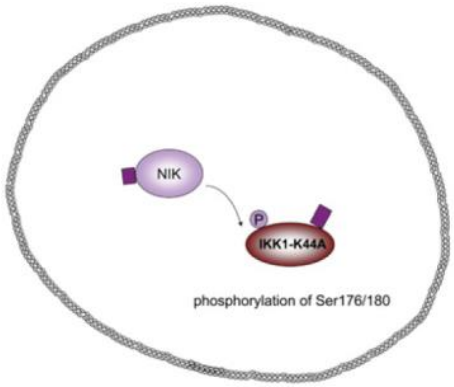
BJ www.biochemj.org
Biochem. J. (2009) 419, 65–73 (Printed in Great Britain) doi:10.1042/BJ20081646
65

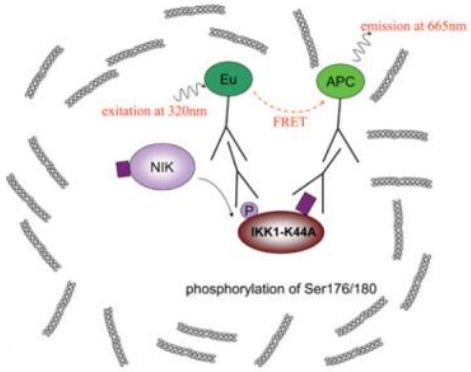
Development of an insect-cell-based assay for detection of kinase inhibition using NF-κB-inducing kinase as a paradigm

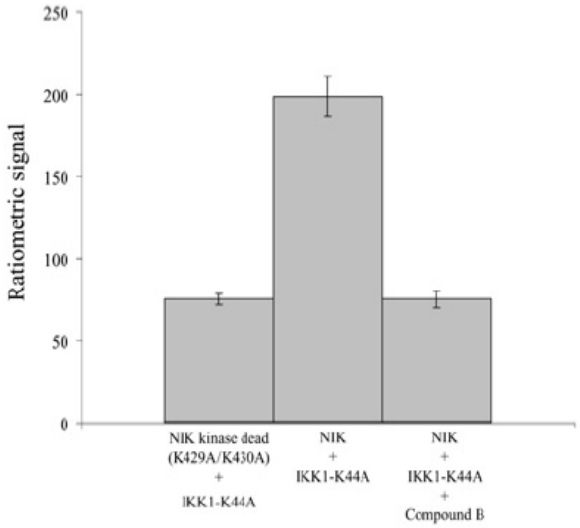
Namir J. HASSAN*†‡, Sheraz GUL*†, Fiona FLETT*, Edward HOLLINGSWORTH*, Angela A. DUNNE†, Amanda J. EMMONS†, Jonathan P. HUTCHINSON*, Martin J. HIBBS*, Susan DYOS‡, Jeremy D. KITSON§, Emma HILEY*, Martin RÜDIGER*, David G. TEW*, David J. POWELL* and Mary A. MORSE‖

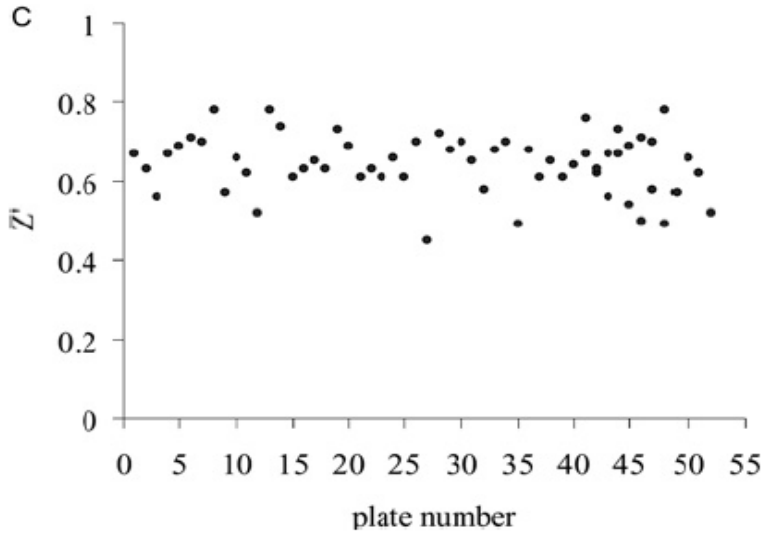
Fraunhofer IME

INSECT CELL-BASED ASSAY FOR NIK









BJ www.biochemj.org

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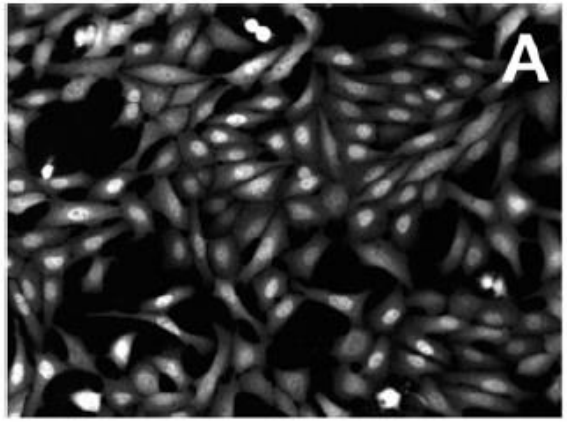
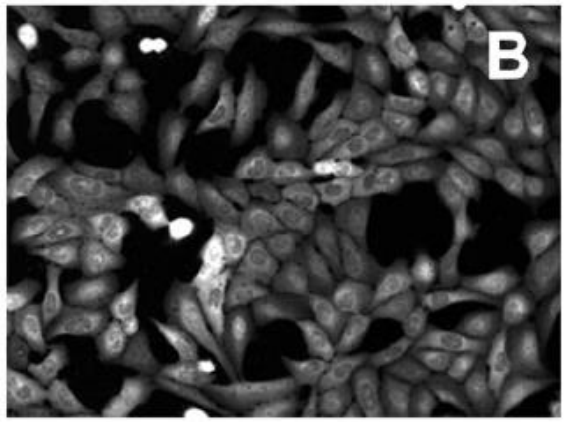
Fraunhofer IME

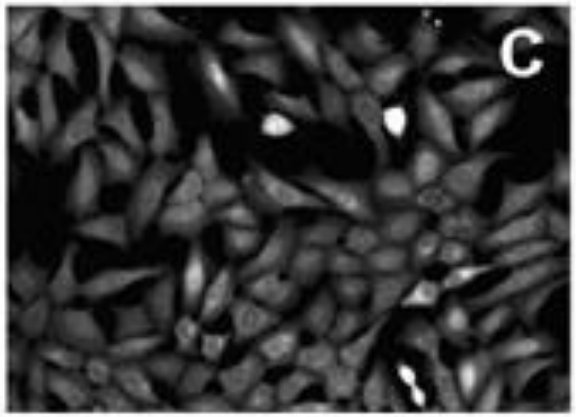
USE OF HCS AFTER CELL-BASED NIK INHIBITOR SCREEN



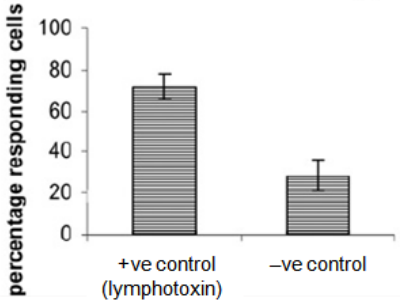
+ve control (lymphotoxin)

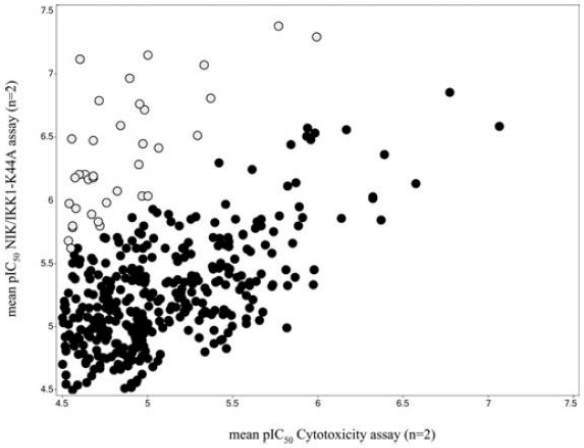


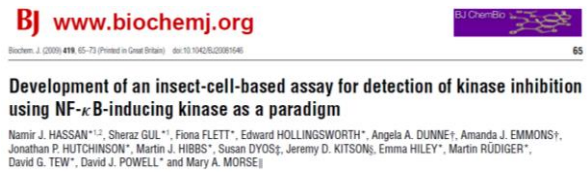
–ve control



Hit from cell-based screen






BJ www.biochemj.org

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Fraunhofer IME

Development of the collaborative COST Action ADME-Tox assay panel

INITIAL COST ACTION INVOLVEMENT

cost

EUROPEAN COOPERATION IN SCIENCE AND TECHNOLOGY

www.cost.eu/cmst

COST Action CM0801.

New drugs for neglected diseases

2008 | 2012

Objectives

- The Action will pave the way for the development of novel drugs to treat neglected diseases such as African sleeping sickness, Chagas' disease and Leishmaniasis.
- Related approaches of molecular genetics, biochemistry, medicinal chemistry, crystallography and bioinformatics will be coordinated and complemented with industrial experience.
- Established genomes are used to identify drug targets essential to the parasites but absent or different in the host, since inhibitors thereof hold promise as safe and efficacious therapeutics.
- Validated drug targets will serve as tools in drug discovery processes using complementary strategies: i) high-throughput screening; ii) in silico screening of virtual libraries; iii) lead optimization; and iv) structure-based inhibitor design.
- Promising compounds will be tested in established infection models for all the diseases to choose the most attractive candidates for preclinical and clinical development.

Main Achievements

- Trypanothione synthetase (TryS) previously demonstrated to be essential by inverse genetics was chemically validated as drug target in *Trypanosoma* and *Leishmania* spp.
- First TryS inhibitors comprising several new scaffolds showed promising *in vitro* activity.
- New target were validated and characterized (GPx-type tryparedoxin peroxidase; glyceraldehyde 3-phosphate dehydrogenase ; pteridine reductase; glucose-6-phosphate dehydrogenase; myristoyl transferase; others) and successfully used for inhibitor screening or design.
- Chemical scaffolds established in other fields of anti-infective therapy are being explored. i.e. anti-leishmanial quinolines (tafenoquine) and trypanocidal fluorinated artemisins.
- A monograph on 'Drug for trypanosomatid diseases' is in progress.

Chemistry and Molecular Sciences and Technologies (CMST)

Participating countries

BE, BG, CH, FI, FR, DE, EL, ES, IL, IT, LT, LV, NL, NO, PL, PT, SE, SI, UK, AU, SD, UY.

Contact details

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Prof. Leopold Flohé
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D-39106 Magdeburg Germany
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Science Officer
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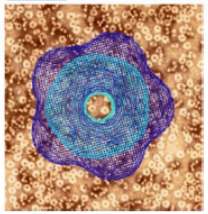
COST Office
lucia.forzi@cost.eu

Website
www.costcm0801.org/CM0801/Welcome.html



Tryparedoxin peroxidase interacting with 10 tryparedoxin molecules

COST is supported by the EU RTD Framework Programme

ESF provides the COST Office through a European Commission contract

COST

European Cooperation in the field of Scientific and Technical Research
- COST -

Brussels, 22 November 2013

COST 052/13

MEMORANDUM OF UNDERSTANDING

Subject : Memorandum of Understanding for the implementation of a European Concerted Research Action designated as COST Action CM1307: Targeted chemotherapy towards diseases caused by endoparasites

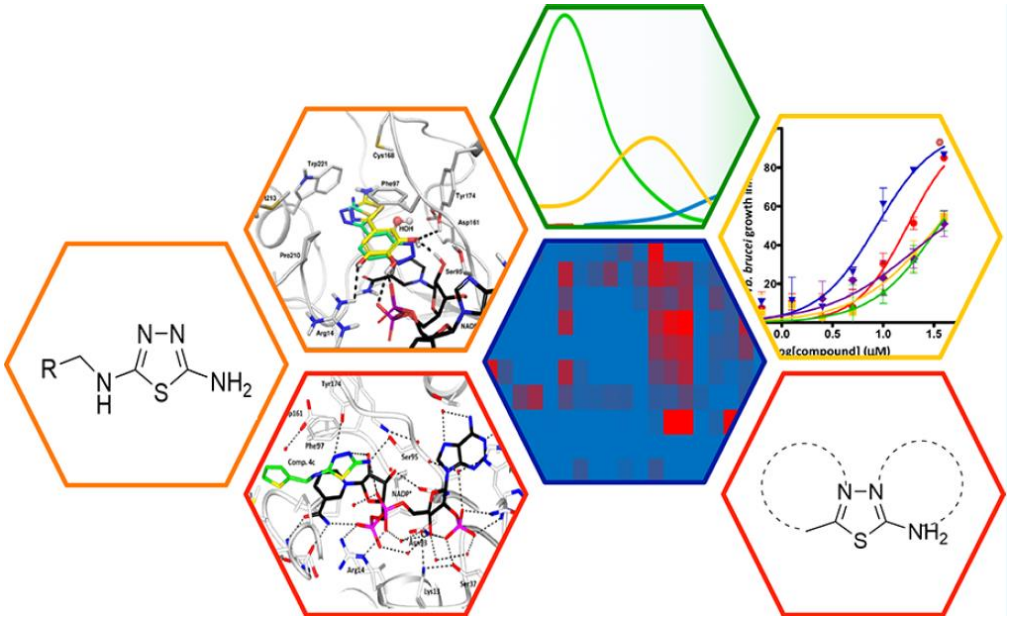
Delegations will find attached the Memorandum of Understanding for COST Action CM1307 as approved by the COST Committee of Senior Officials (CSO) at its 188th meeting on 14 November 2013

Fraunhofer IME

EU-FP7 Project: Delivering Lead molecules

New Medicines for Trypanosomatidic Infections

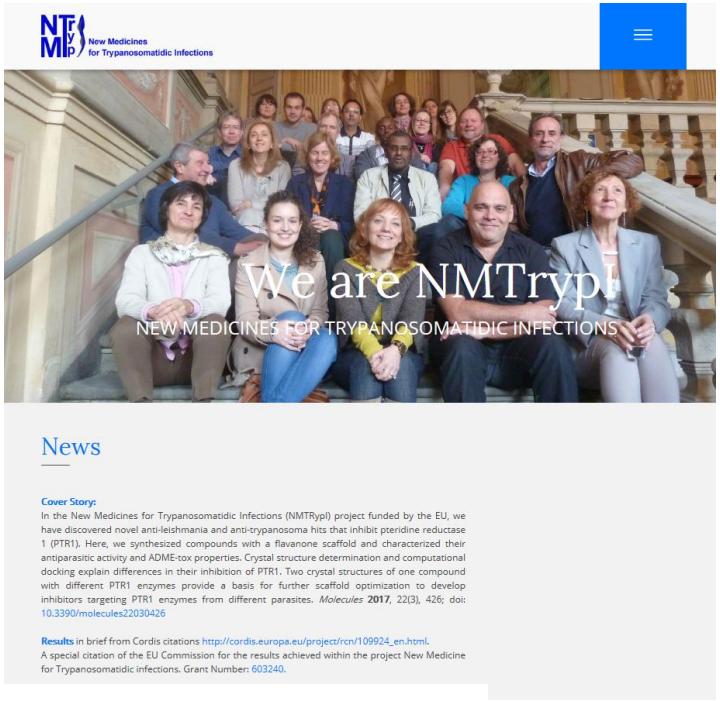
- World Health Organization: neglected tropical diseases afflict >1 billion people
- Parasitic infections caused by trypanosomatids represent a major challenge
- human African trypanosomiasis (African sleeping sickness) caused by *T. brucei*
- *T. brucei* pteridine reductase Drug Discovery effort

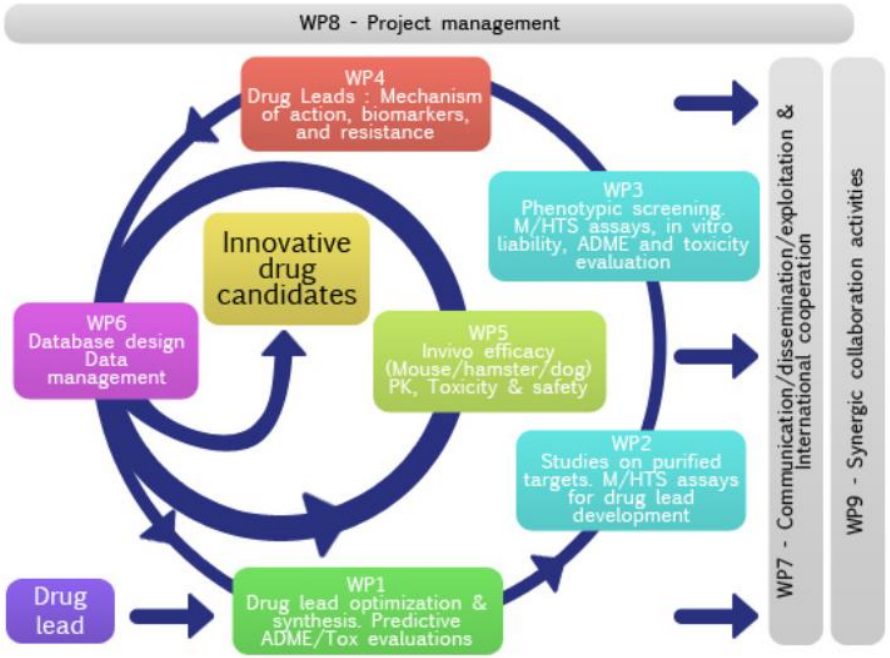


Fraunhofer IME

NMTRYPI CONSORTIUM

New Medicines for Trypanosomatidic Infections





GOVERNANCE | WP1 | WP2 | **WP3** | WP4 | WP5 | WP6 | WP7

WP3: Phenotypic screening. M/HTS assays, ADME-Tox evaluation.

WP3 concerns the development of functional screening through cellular testing.

Natural compound mixtures are tested first on sensitive parasites and then the optimal mixture tested against relevant drug resistant strains. Only the selected mixtures from the dereplication process will be purified, and compound isolated and characterized. Final ranking and selection of the leads identified with related molecular and biological properties will be provided based on TDLP criteria.

Decisions on compounds progression towards WP3 and WP5 or feed-back to WP1 for further chemical modification will be taken

WP3 leader: Dr. Sheraz Gul, Fraunhofer IME-SP

Main outcomes of WP3:

- Development of functional screening parasite testing.
- Development of compatible assays for targets, their use in screening against natural products.
- Ranking of compounds for further progression based on activities of compound properties to include suitable secondary assays and in vitro ADME-Tox data.

Fraunhofer IME

DELIVERING A LEAD MOLECULE

NTrypMed New Medicines for Trypanosomatidic Infections

Journal of Medicinal Chemistry

Article

pubs.acs.org/jmc

Profiling of Flavonol Derivatives for the Development of Antitrypanosomatidic Drugs

Chiara Borsari,[†,+] Rosaria Luciani,[†,+] Cecilia Pozzi,[‡,+] Ina Poehner,[§,+] Stefan Henrich,[§] Matteo Trande,[†] Anabela Cordeiro-da-Silva,[∥] Nuno Santarem,[∥] Catarina Baptista,[∥] Annalisa Tait,[†] Flavio Di Pisa,[‡] Lucia Dello Iacono,[‡] Giacomo Landi,[‡] Sheraz Gul,[⊥] Markus Wolf,[⊥] Maria Kuzikov,[⊥] Bernhard Ellinger,[⊥] Jeanette Reinshagen,[⊥] Gesa Witt,[⊥] Philip Gribbon,[⊥] Manfred Kohler,[⊥] Oliver Keminer,[⊥] Birte Behrens,[⊥] Luca Costantino,[†] Paloma Tejera Nevado,[◆] Eugenia Bifeld,[◆] Julia Eick,[◆] Joachim Clos,[◆] Juan Torrado,[#] María D. Jiménez-Antón,[#,¶1] María J. Corral,[#,¶1] José Mª Alunda,[#,¶1] Federica Pellati,[†] Rebecca C. Wade,[§,▽,○] Stefania Ferrari,[*,†] Stefano Mangani,[*,‡] and Maria Paola Costi[*,†]

[†]Department of Life Sciences, University of Modena and Reggio Emilia, Via G. Campi 103, 41125 Modena, Italy

[‡]Department of Biotechnology, Chemistry and Pharmacy, University of Siena, Via Aldo Moro 2, 53100 Siena, Italy

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[⊥]Fraunhofer Institute for Molecular Biology and Applied Ecology-ScreeningPort, Schnackenburgallee 114 D-22525, Hamburg, Germany

[#]Complutense University of Madrid, 28040 Madrid, Spain

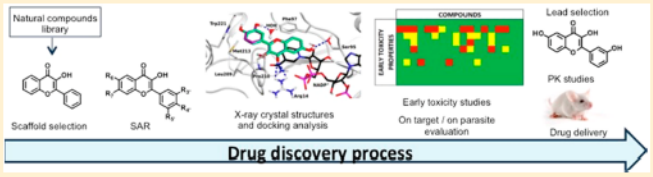
[▽]Center for Molecular Biology (ZMBH), DKFZ-ZMBH Alliance, Heidelberg University, 69120 Heidelberg, Germany

[○]Interdisciplinary Center for Scientific Computing (IWR), Heidelberg University,69120 Heidelberg, Germany

[◆]Bernhard Nocht Institute for Tropical Medicine, D-20359 Hamburg, Germany

[¶1]Instituto de Investigación Hospital 12 de Octubre, 28041 Madrid, Spain

Supporting Information



ABSTRACT: Flavonoids represent a potential source of new antitrypanosomatidic leads. Starting from a library of natural products, we combined target-based screening on pteridine reductase 1 with phenotypic screening on *Trypanosoma brucei* for hit identification. Flavonols were identified as hits, and a library of 16 derivatives was synthesized. Twelve compounds showed EC_{50} values against *T. brucei* below 10 μM. Four X-ray crystal structures and docking studies explained the observed structure−activity relationships. Compound **2** (3,6-dihydroxy-2-(3-hydroxyphenyl)-4*H*-chromen-4-one) was selected for pharmacokinetic studies. Encapsulation of compound **2** in PLGA nanoparticles or cyclodextrins resulted in lower in vitro toxicity when compared to the free compound. Combination studies with methotrexate revealed that compound **13** (3-hydroxy-6-methoxy-2-(4-methoxyphenyl)-4*H*-chromen-4-one) has the highest synergistic effect at concentration of 1.3 μM, 11.7-fold dose reduction index and no toxicity toward host cells. Our results provide the basis for further chemical modifications aimed at identifying novel antitrypanosomatidic agents showing higher potency toward PTR1 and increased metabolic stability.

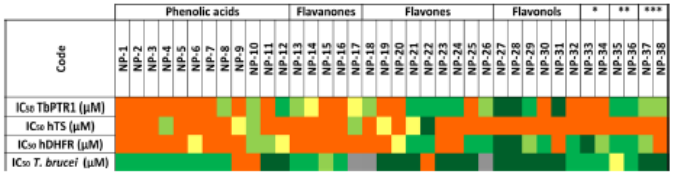


Figure 1. Activity profile of the 38 phytochemicals screened against *Tb*PTR1, hTS, and hDHFR and against the *T. brucei* parasite. The IC_{50} is indicated by the color: dark-green, 0−30 μM; green, 31−90 μM; light-green, 90−150 μM; yellow, 151−250 μM; red, >250 μM; gray, not tested. *, Catechins; **, triterpenes; ***, anthraquinones.

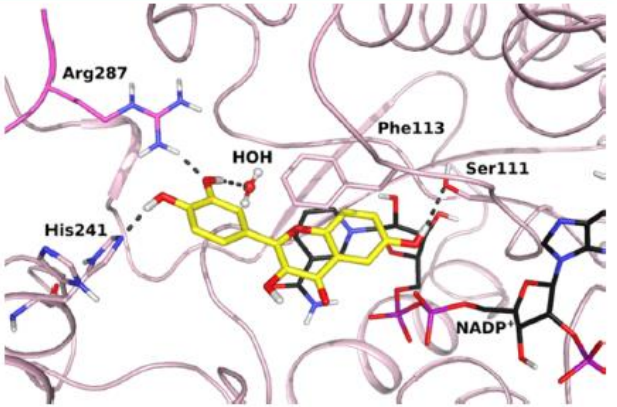


Figure 7. Superimposition of the crystal structure of *Lm*PTR1 (PDB ID 1E92) in cartoon representation and interacting residues in sticks representation. Chains A and D (containing Arg287) are colored in pale-pink and magenta, respectively) and the best predicted receptor conformation obtained in the induced-fit docking study starting from this crystal structure (His241 in H-bonding contact to compound 7) in complex with NADPH/$NADP^+$ (in sticks, black carbons) and compound 7 (in sticks, yellow carbons). A conserved water molecule is shown in ball-and-stick representation. Hydrogen bonds are indicated by dark-gray dotted lines.

Fraunhofer IME

NEW NMTRYPI PAPER – ADME-TOX PANEL FOCUS

New Medicines for Trypanosomatidic Infections

ASC Original Research

Accelerating Drug Discovery Efforts for Trypanosomatidic Infections Using an Integrated Transnational Academic Drug Discovery Platform

SLAS Discovery
1–16
© 2019 Society for Laboratory Automation and Screening
DOI: 10.1177/2472555218823171
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SAGE

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Abstract

According to the World Health Organization, more than 1 billion people are at risk of or are affected by neglected tropical diseases. Examples of such diseases include trypanosomiasis, which causes sleeping sickness; leishmaniasis; and Chagas disease, all of which are prevalent in Africa, South America, and India. Our aim within the New Medicines for Trypanosomatidic Infections project was to use (1) synthetic and natural product libraries, (2) screening, and (3) a preclinical absorption, distribution, metabolism, and excretion–toxicity (ADME-Tox) profiling platform to identify compounds that can enter the trypanosomatidic drug discovery value chain. The synthetic compound libraries originated from multiple scaffolds with known antiparasitic activity and natural products from the Hypha Discovery MycoDiverse natural products library. Our focus was first to employ target-based screening to identify inhibitors of the protozoan *Trypanosoma brucei* pteridine reductase 1 (*Tb*PTR1) and second to use a *Trypanosoma brucei* phenotypic assay that made use of the *T. brucei brucei* parasite to identify compounds that inhibited cell growth and caused death. Some of the compounds underwent structure-activity relationship expansion and, when appropriate, were evaluated in a preclinical ADME-Tox assay panel. This preclinical platform has led to the identification of multiple compound series, some of which have progressed in the trypanosomatidic drug discovery value chain to lead-like compounds as well as validated hits.

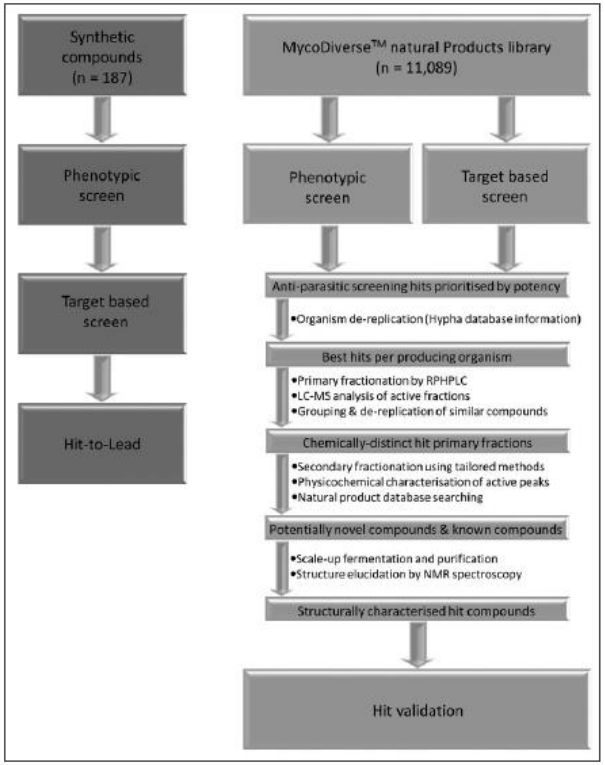


Figure 1. Overall workflow of the screening of synthetic compounds and natural products in the *Tb*PTR1 target-based assay and *Trypanosoma brucei* phenotypic assay. Synthetic compounds (derivatives of 2′-hydroxy chalcones, thiadiazole, and iltefosine from structure-based and ligand-based drug discovery programs) and natural products (MycoDiverse natural products library) were screened in the *Tb*PTR1 target-based assay and *T. brucei* phenotypic assay. The most promising compounds were subsequently evaluated in an absorption, distribution, metabolism, and excretion–toxicity assay panel. The synthetic compound libraries yielded multiple compound series that met the lead criteria. The MycoDiverse natural products screen yielded 40 hits from the *T. brucei* phenotypic assay and seven hits from the *Tb*PTR1 target-based assay.

Fraunhofer IME

THE ADME-TOX PANEL DELIVERABLES

- Compound Solubility Studies
- Cytotoxicity Assay
- Cytochrome (CYP) P450 Inhibition Assay
- HDAC Assay
- Aurora B Kinase Assay
- *h*ERG Cardiotoxicity Assay
- Mitochondrial Toxicity Assay

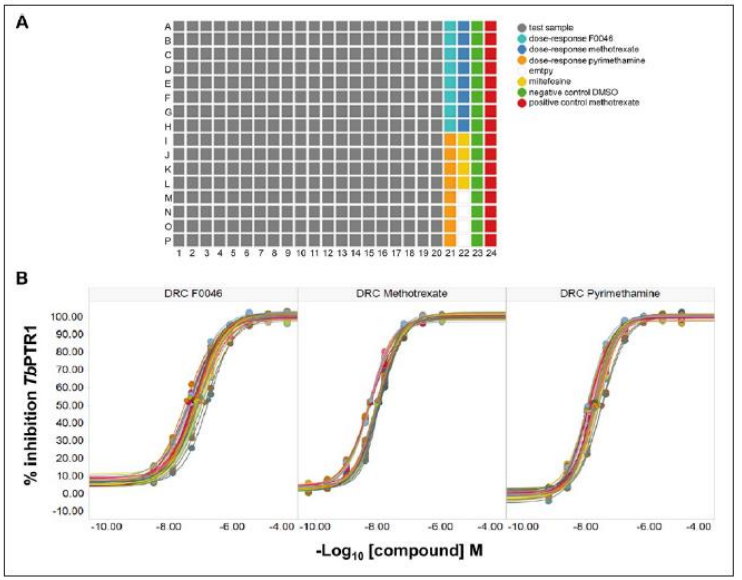


Figure 3. (**A**) Layout of samples and controls in assay plates for the *Tb*PTR1 target-based screen against the MycoDiverse natural products library. (**B**) Dose-response curves and average IC_{50} values across all 34 assay plates for each reference compound were for methotrexate 8.6 ± 2.3 nM, F0046 73 ± 27 nM, and pyrimethamine 16.7 ± 5.0 nM. Standard deviations are within ±10% of the values.

Compound class	Quantity	Hit validation	Hit-to-Lead
Triazole-linked privileged conjugates	18 compounds		
Aryl thiosemicarbazones	28 compounds		
Crassiflorone derivatives	9 compounds		
Thiadiazole derivatives	57 compounds		
Chroman-4-one derivatives	3 compounds		
Chalcone derivatives	13 compounds		
Flavonol derivatives	16 compounds		
Miltefosine analogues	52 compounds		
Natural products MycoDiverse™ library	11,089 mixtures		

Target Validation in CVD drug research

TARGET SELECTION

Discovery	Cases	Controls
European studies		
PROCARDIS	5,720[a]	4,381[b]
HPS (GWAS)	2,704	2,887[c]
South Asian studies		
PROMIS	4,255	4,098
LOLIPOP	2,741	3,696
TOTAL	**15,420**	**15,062**

59 SNPs selected for replication →

Replication	Cases	Controls
European studies		
HPS (non-GWAS)	9,248	7,692[d]
COROGENE	2,172	1,579
ISIS	1,971	1,434
SHEEP/SCARF	1,533	1,893
PROCARDIS TDTs	1,143	1,143
GISSI-P	979	452
AMC-PAS	597	1,285
THISEAS	406	879
South Asian studies		
PROMIS	2,092	1,728
INTERHEART	1,267	1,100
TOTAL	**21,408**	**19,185**

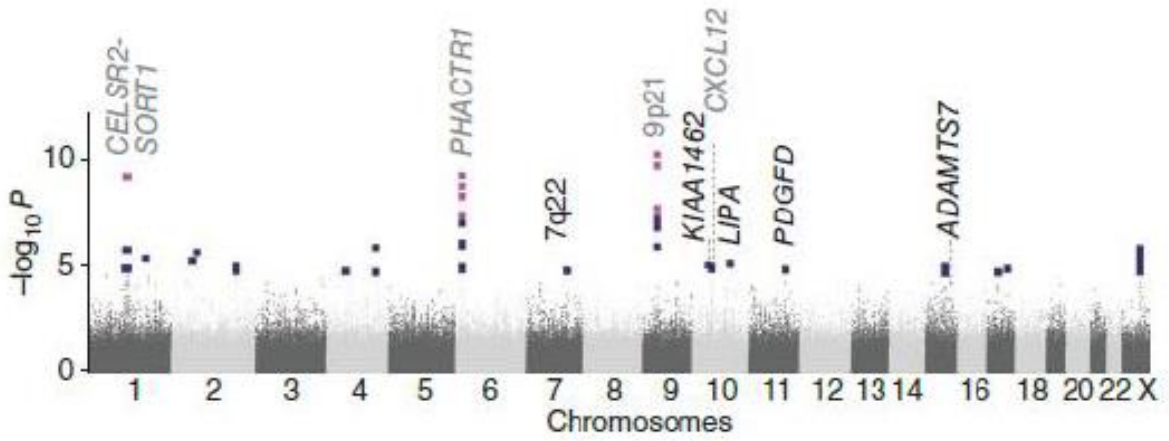
LETTERS

nature genetics

A genome-wide association study in Europeans and South Asians identifies five new loci for coronary artery disease

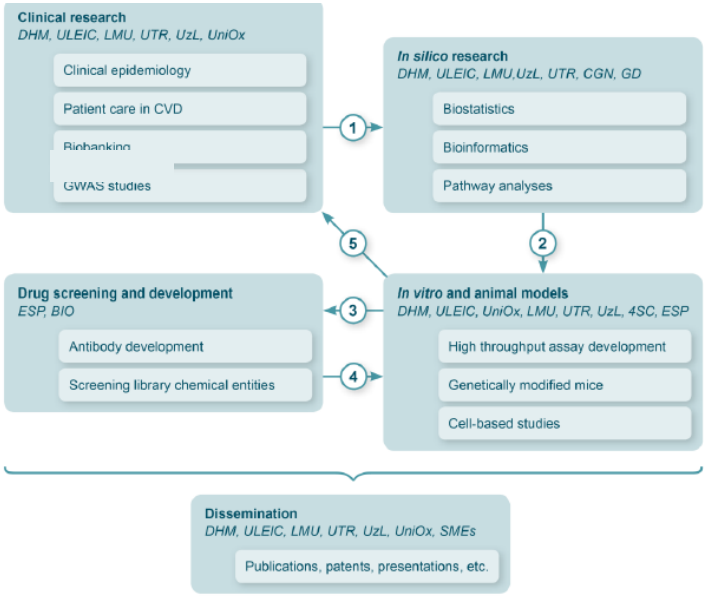
The Coronary Artery Disease (C4D) Genetics Consortium*

Genome-wide association studies have identified 11 common variants convincingly associated with coronary artery disease (CAD)[1–7], a modest number considering the apparent heritability of CAD[8]. All of these variants have been discovered in European populations. We report a meta-analysis of four large genome-wide association studies of CAD, with ~575,000 genotyped SNPs in a discovery dataset comprising 15,420 individuals with CAD (cases) (8,424 Europeans and 6,996 South Asians) and 15,062 controls. There was little evidence for ancestry-specific associations, supporting the use of combined analyses. Replication in an independent sample of 21,408 cases and 19,185 controls identified five loci newly associated with CAD ($P < 5 \times 10^{-8}$ in the combined discovery and replication analysis): *LIPA* on 10q23, *PDGFD* on 11q22, *ADAMTS7-MORF4L1* on 15q25, a gene rich locus on 7q22 and *KIAA1462* on 10p11. The CAD-associated SNP in the *PDGFD* locus showed tissue-specific cis expression quantitative trait locus effects. These findings implicate new pathways for CAD susceptibility.



CVgenes@target Project

- Coronary artery disease (CAD) – a leading cause of death in Europe
- >40 CAD genomic risk loci have been identified
- CVgenes@target project: bringing together expertise to validate CAD targets



- Project completed with further funding secured for progressing ADAMTS-7

Fraunhofer IME

BLOCKCAD

Forschung fördern

Fördermaßnahme

Volkskrankheiten

Targetvalidierung für die pharmazeutische Wirkstoffentwicklung

Eine der wichtigsten Grundlagen für die Wirkstofffindung ist die Wahl des Ansatzpunktes (englisch Target) für den neuen Arzneistoff, sei es, um eine menschliche Körperfunktion zu modulieren oder einen infektiösen Erreger anzugreifen.

Veröffentlichung der Bekanntmachung:	2017
Förderzeitraum:	2018 - 2020
Gesamte Fördersumme:	
Anzahl der Projekte:	12 Verbund- und Einzelprojekte

1. Ziele der Förderrichtlinie

Die weltweite Zunahme von Volkskrankheiten und Mehrfacherkrankungen, sowie der kontinuierliche Anstieg von Antibiotikaresistenzen und nosokomialen Infektionen bedrohen in zunehmenden Maß unsere Gesundheit. In diesem Zusammenhang stellt der starke Rückgang von neu zugelassenen Arzneimitteln, insbesondere im Bereich der Antiinfektiva, eine immense Herausforderung für das globale Gesundheitssystem dar.

FÖRDERUNG UND PROJEKTE

Suche

Verbünde

- Victori
- PyrBac
- GPS-TBT
- GOT-IT
- EnVision
- ComboMIR
- CONNEXIN
- CANCER
- BlockCAD
- AKAP18-PKA

Inhibition von ADAMTS7 zur Prävention und Therapie der Koronaren Herzkrankheit (BlockCAD)

Die Atherosklerose, bei der es durch die pathologische Einlagerung von Fetten in Blutgefäße zu deren Verhärtung und Verengung (Restenose) kommt, ist eine Ursache für das Auftreten von koronarer Herzkrankheit (KHK) und Schlaganfall. Diese Folgeerkrankungen zählen zu den führenden Todesursachen in Europa. Eine mögliche Behandlung einer solchen Gefäßverengung erfolgt durch das Einsetzen von röhrenförmigen Prothesen (Stents), die betroffene Gefäße offen halten sollen. Das *ADAMTS7*-Gen wurde als genetischer Risikofaktor für KHK identifiziert. In experimentellen Modellen konnte ein Zusammenhang zwischen der überschießenden Bildung der inneren Schicht der Blutgefäße (Intima) nach Implantation von Koronarstents mit der Expression von *ADAMTS7* festgestellt werden. Diese Gewebsveränderungen können bei der Verwendung von Stents auftreten, was weitere Ablagerungen in die Gefäßwand und damit deren Verengung fördert. Bisher sind etablierte präventive und therapeutische Maßnahmen auf die Reduktion von Risikofaktoren oder die nicht selektive Hemmung dieser pathophysiologischen Prozesse ausgerichtet, bei der keine spezifischen Genprodukte adressiert werden.

Das Ziel dieses Projekts ist es, mit ADAMTS7 einen der KHK und Restenose zugrunde liegenden genetischen Faktor als therapeutisches Target zu validieren. Die Verbundpartner werden dabei *in vitro* und *in vivo* Modelle anwenden. Die Nutzung von Strukturanalysen, spezifischen Biomarkern und klinischen Patientenproben sollen ein besseres Verständnis der biologischen Zusammenhänge gewährleisten. Das langfristige Ziel ist die Entwicklung von neuen, effizienten Behandlungsmethoden für KHK mit besserer Wirksamkeit und verminderten Nebenwirkungen. Die Entwicklung einer neuen Generation von Stents, die beispielsweise ADAMTS7-Antikörper oder kleine inhibierende Moleküle zur Modulation von ADAMTS7 freisetzen, wäre eine denkbare Therapieoption für die verbesserte Behandlung der Restenose.

TEILPROJEKTE

In vitro- und in vivo-Untersuchung einer ADAMTS7-Inhibition in der Prävention und Therapie der Koronaren Herzkrankheit

Förderkennzeichen:	16GW0198K
Gesamte Fördersumme:	428.032 EUR
Förderzeitraum:	2018 - 2019
Projektleitung:	Prof. Dr. Heribert Schunkert
Adresse:	Deutsches Herzzentrum München - Klinik an der Technischen Universität München - Klinik für Herz- und Kreislauferkrankungen Lazarettstr. 36 80636 München

Identifizierung kleiner Moleküle und Produktion spezifischer Antikörper zur Inhibition der Funktion von ADAMTS7 bei der Entwicklung der Koronaren Herzkrankheit

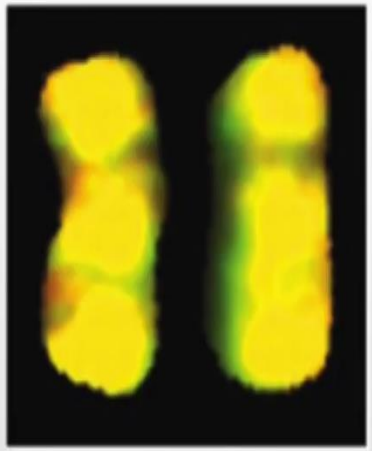
Förderkennzeichen:	16GW0199
Gesamte Fördersumme:	408.493 EUR
Förderzeitraum:	2018 - 2019
Projektleitung:	Dr. Philip Gribbon
Adresse:	Fraunhofer-Institut für Molekularbiologie und Angewandte Oekologie (IME) Schnackenburgallee 114 22525 Hamburg

Fraunhofer IME

Genetic age test

Age related epigenetic modifications in twins

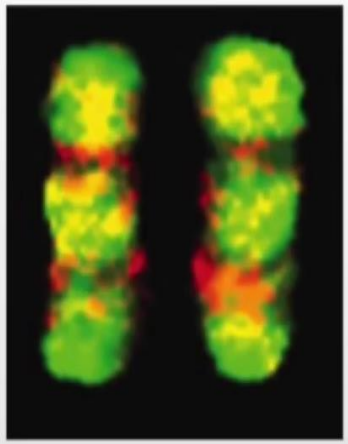
- identical twins begin life with similar epigenomes
- epigenetic tags of one twin are labelled green, and red for the other
- yellow areas indicate shared epigenetic tags



chromosomes of three year old identical twins

3 yrs. old

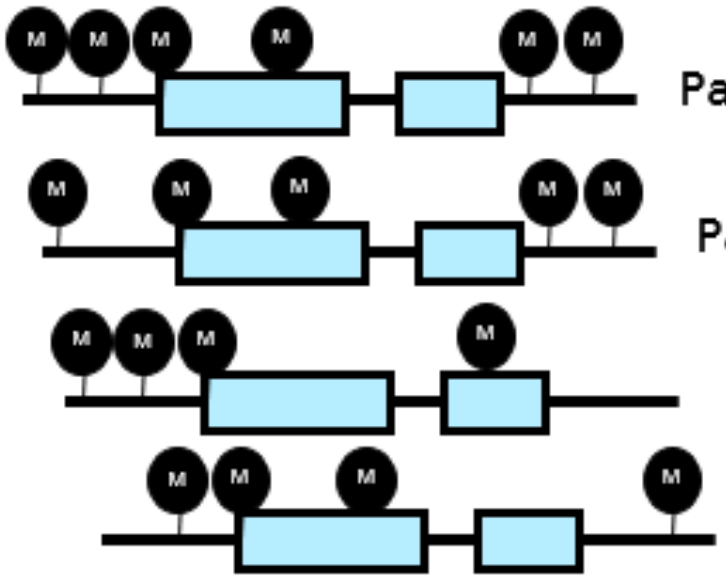
- over time environmental influences differ
- yellow regions indicate shared epigenetic tags
- epigenome of twins has diverged



chromosomes of fifty year old identical twins

50 yrs. old

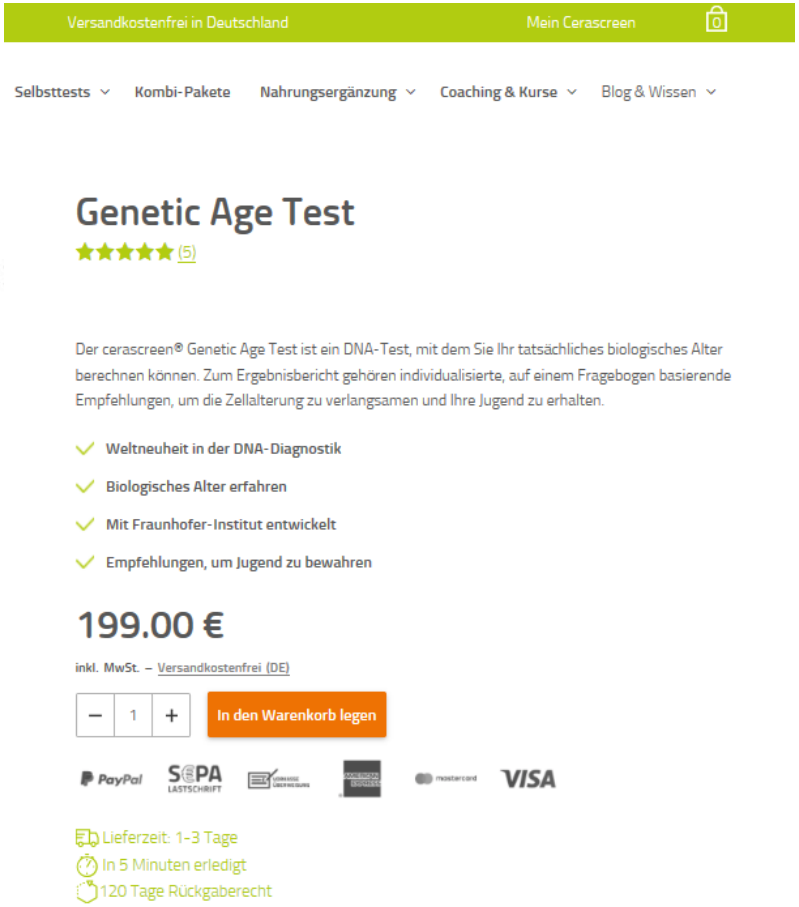
Methylation pattern analysis



	Natural Age	Predicted Age
Pat A	45	44
Pat B	35	36
Pat C	18	19
Pat D	20	21

M Methylation sites and associated levels

PRODUCT LAUNCHED IN 2018



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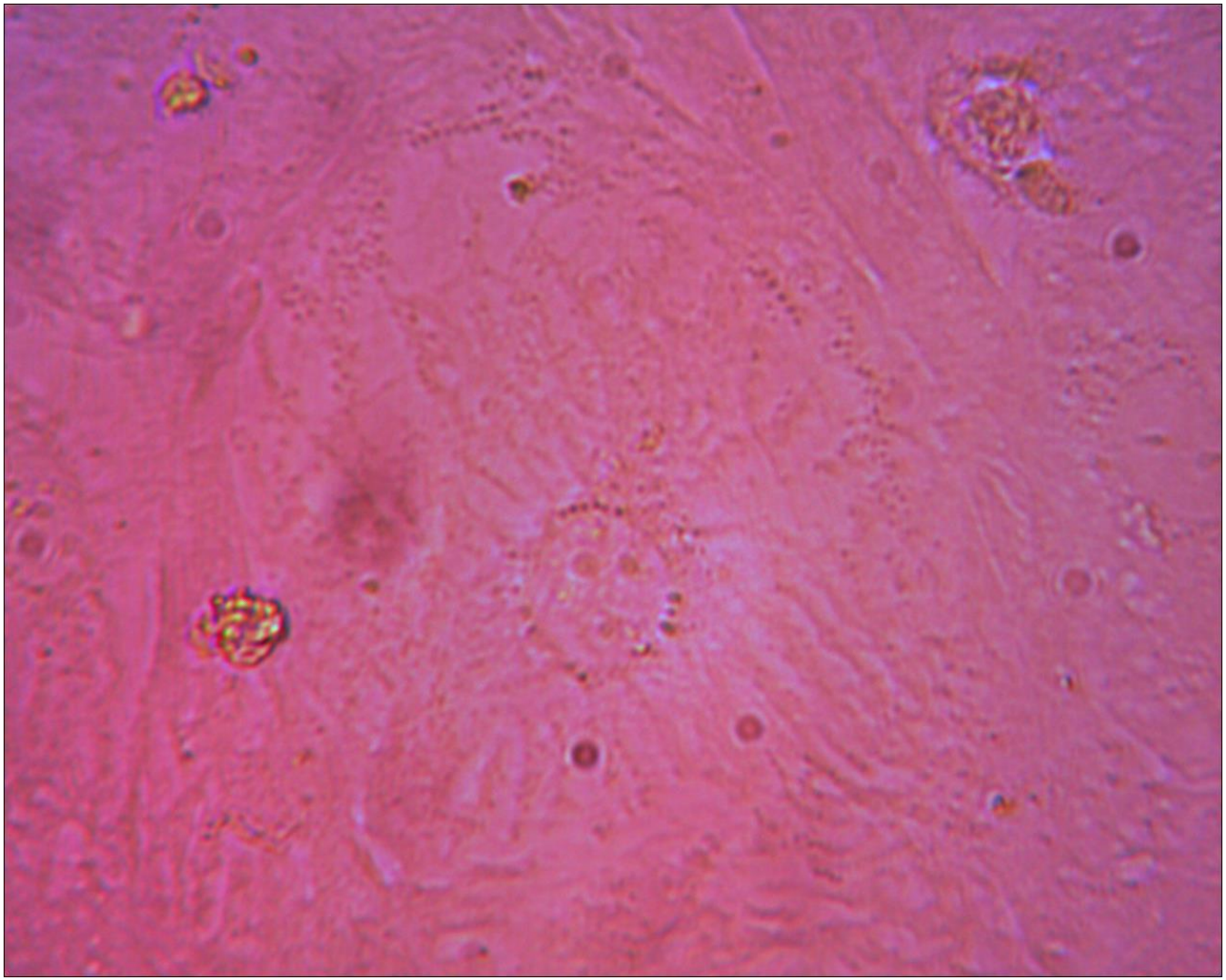
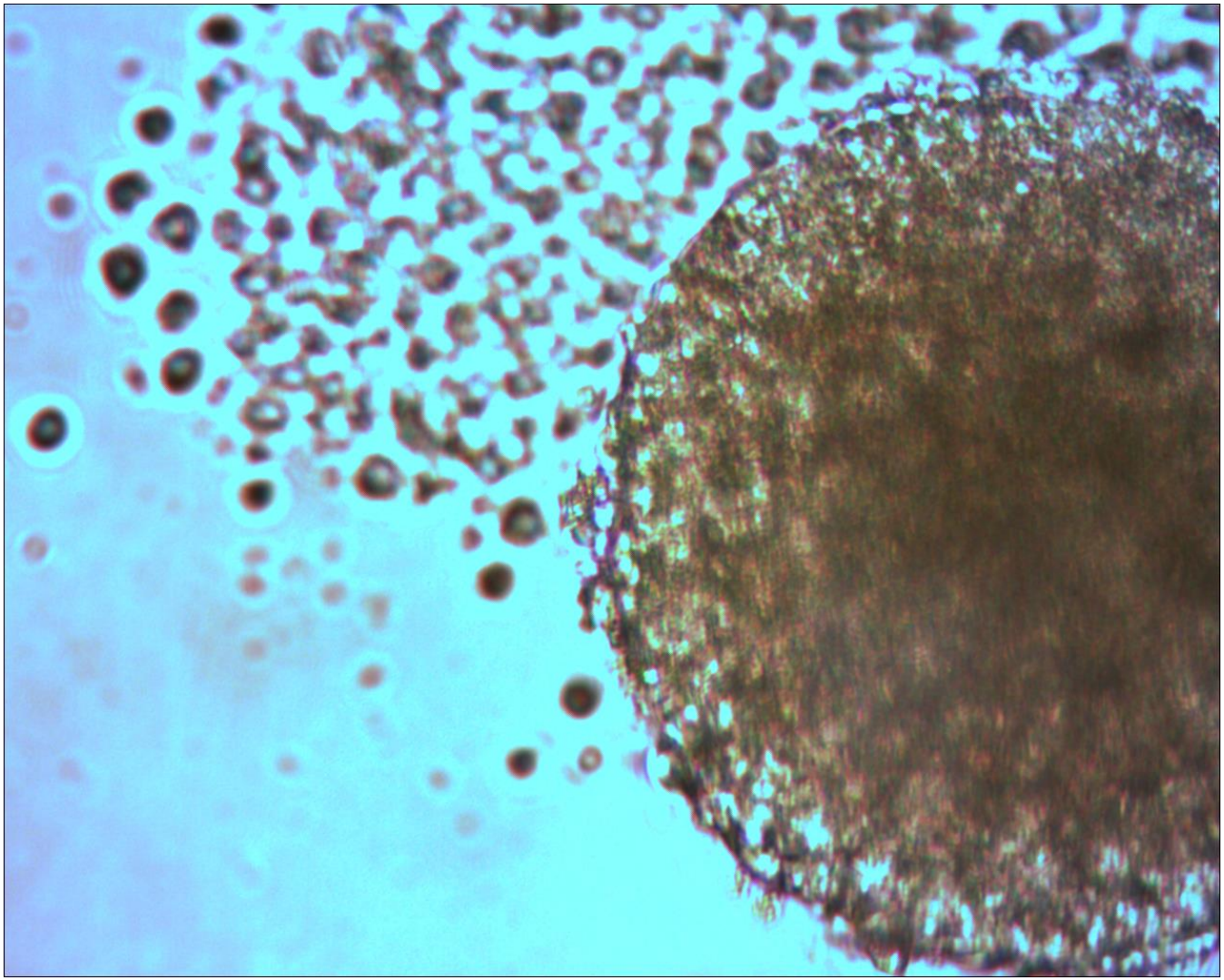
Tools to de-risk drug research projects

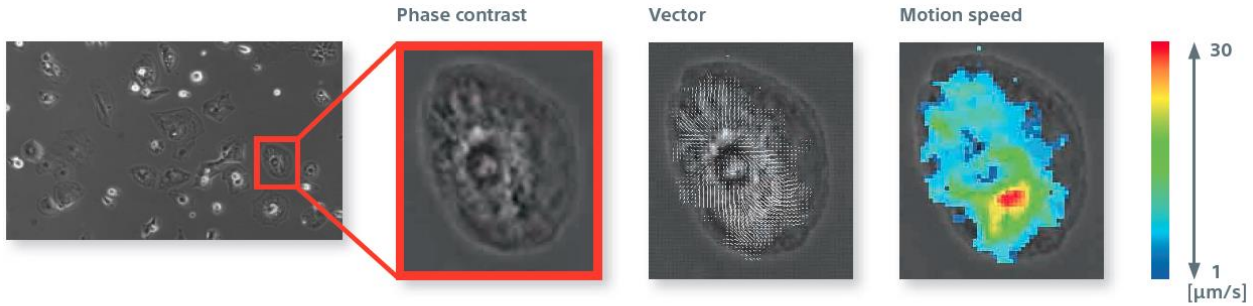
Cardiomyocytes in culture (2D)

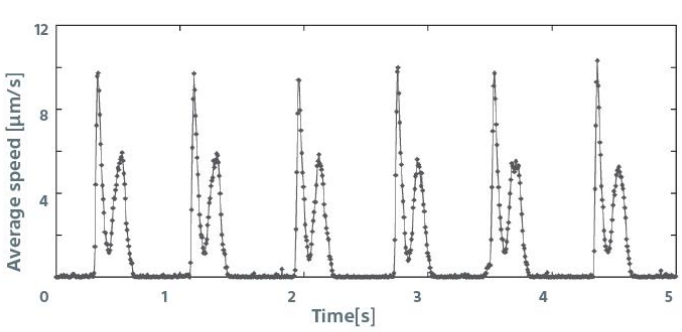


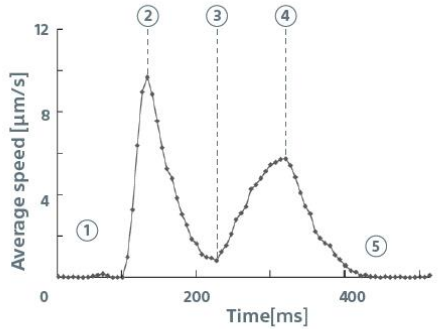
Cardiomyocytes in culture (3D)

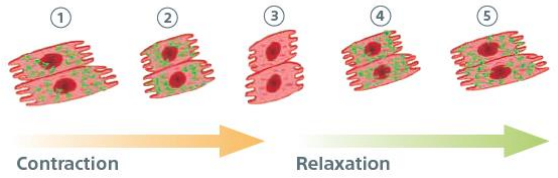


CELL MOTION IMAGING (SONY SI8000)



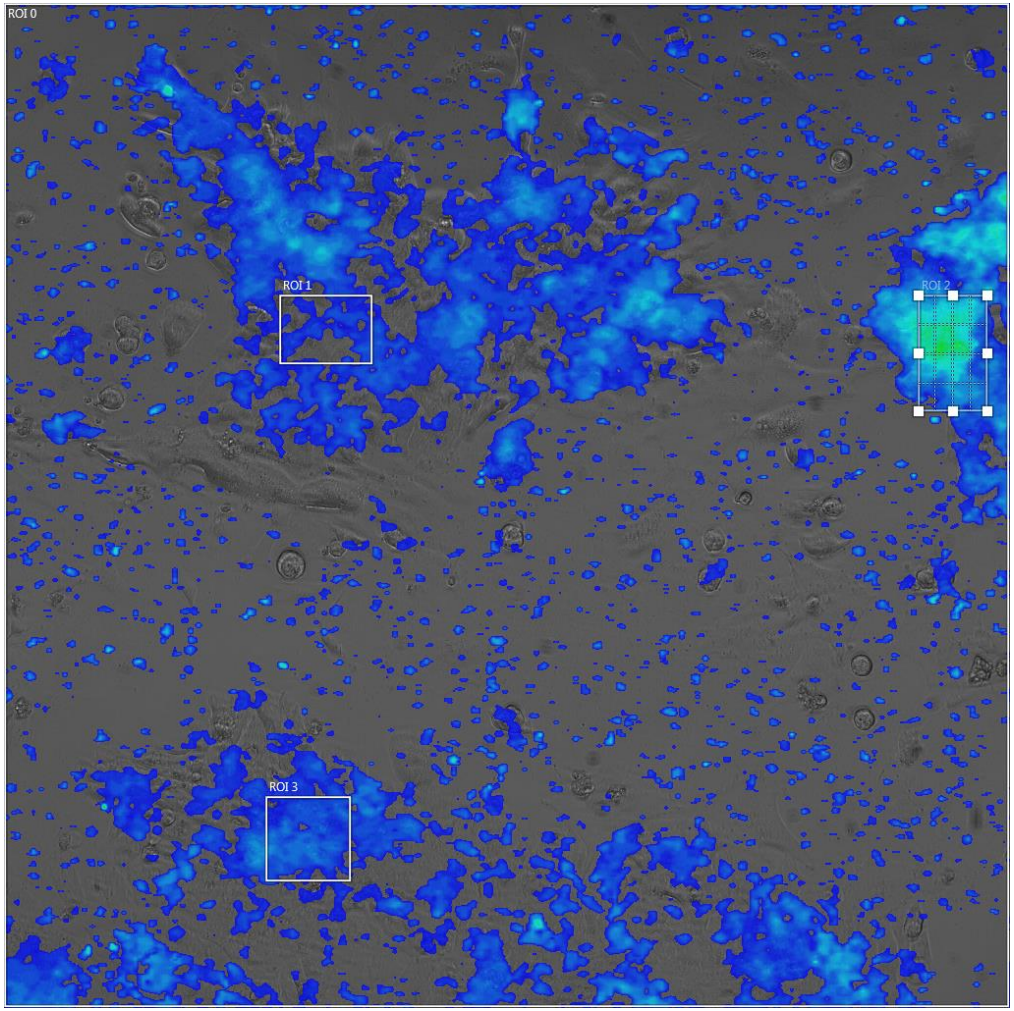






Fraunhofer IME

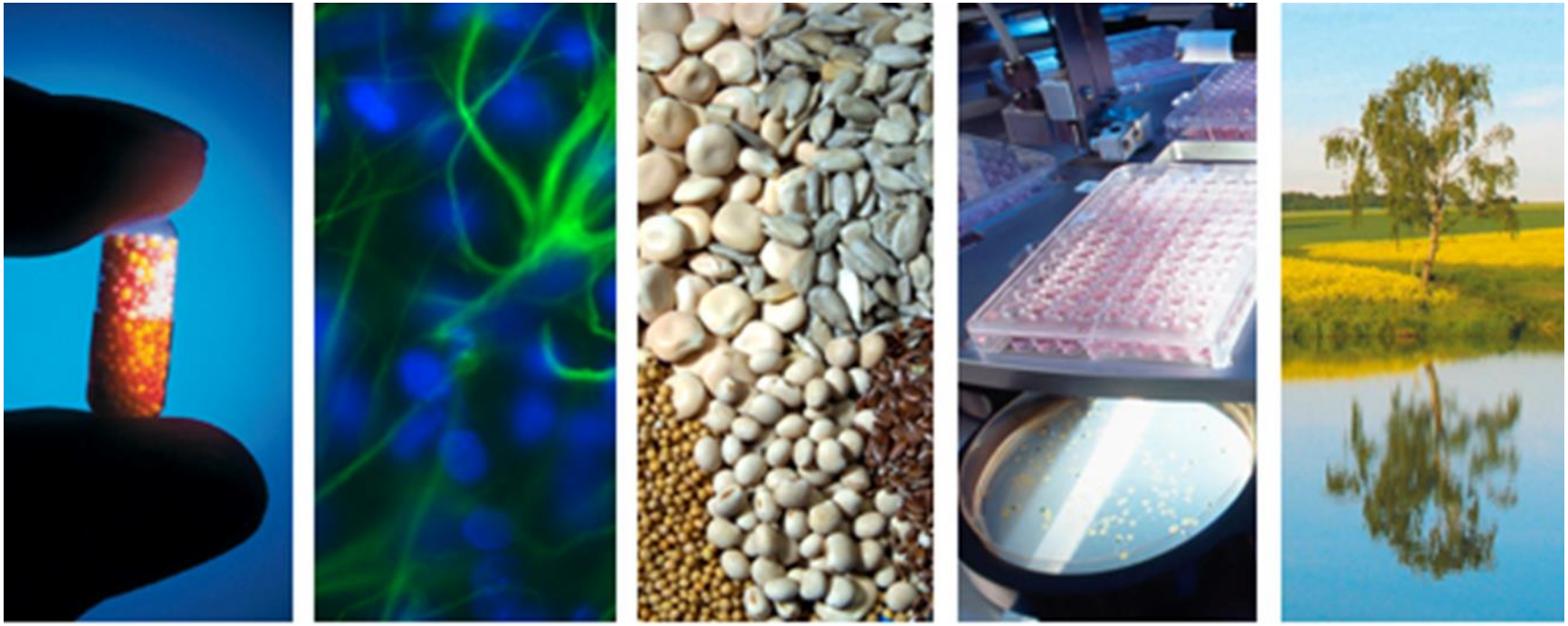
Example cardiomyocyte images & analysis (SONY SI8000)



The Minimum Information About a Bioactive Entity (MIABE)

- Molecule properties
  - Primary name, structure, salt, prodrug
- Molecule production
  - Synthesis, purity
- Physicochemical properties
  - M_r, water solubility, logP
- *In-vitro* cell-free assay and cellular assay
  - Primary target, cell types, SOPs
- Whole-organism studies
  - Animal studies, plant studies, fungal studies, disease models, dosing route, dosing schedule, toxicological observations, drug–drug interactions
- Pharmacokinetic studies
  - Absorption, protein binding, dosing route, dosing schedule, half-life, V_{max}, volume of distribution, bioavailability, metabolism, metabolites, excretion

From the Idea to the Product – Life Science at Fraunhofer



Thank you very much for your attention

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NMTRYPI

COST Actions (CM0801, CM1307, TD0905 & CM1406)

Fraunhofer IME