# Chemical Biology Platform, NCMM

http://www.med.uio.no/english/research/core-facilities/chemical-biology-screening/

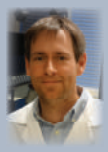
NORWAY

assay adaption screening site

OSLO

an official partner site of eu openscreen

## THE PEOPLE

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## THE PROJECTS

### *Targeting protein-protein interactions*

Regulating adrenergic $Ca^{2+}$ reabsorption into sarcoplasmic reticulum by targeting the AKAP18δ-PLB interaction in the heart

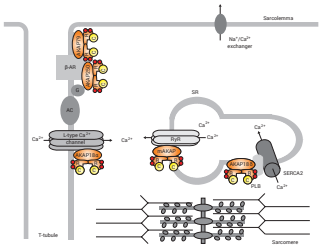
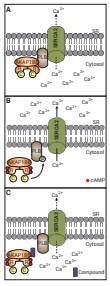


**Figure 1 . Schematic illustration of a cardiac myocyte and $Ca^{2+}$ handling.** Major components in the excitaion–contraction coupling in the myocyte are shown. The cycling of $Ca^{2+}$ is indicated by arrows and the different protein kinase A (PKA)–A-kinase anchoring protein (AKAP) complexes that provide adrenergic regulation of various components of the $Ca^{2+}$ handling machinery are indicated.
AC: Adenylyl cyclase; β-AR: β-adrenergic receptor; C: Catalytic subunit of PKA; mAKAP: Muscle-specifi cAKAP; PLB: Phospholamban; R: Regulatory subunit of PKA; RyR: Ryanodine receptor; SERCA: Sarcoplasmic reticulum $Ca^{2+}$-ATPase; SR: Sarcoplasmic reticulum; Red circle: cAMP.

*Lygren & Taskén 2008, Expert Opinion on Biological Therapy*



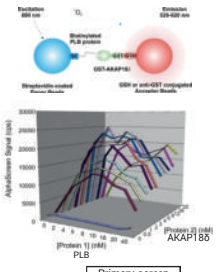


**Figure 2. AKAP18δ–PLB–sarcoplasmic reticulum $Ca^{2+}$-ATPase (SERCA)2 complex.** A. Resting situation, no adrenergic drive, low heart rate, SERCA2 inhibited by PLB with low ATP- and energy consumption. B. Adrenergic stimulation paces the heart, increased heart rate. SERCA2 released from PLB inhibition by PKA phosphorylation. Fast $Ca^{2+}$ reabsorption, high ATP- and energy consumption. C. Disruption of AKAP18δ–PLB complex prevents PKA phosphorylation and dissociation of PLB and thereby SERCA2 activation. Low ATP- and energy consumption.

Primary screen
79 000 comp.
51 hits

Secondary screen
344 comp.
62 hits

Cell assay
10 comp.

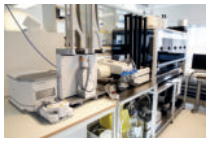
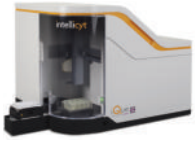
Tertiary screen
80 comp.

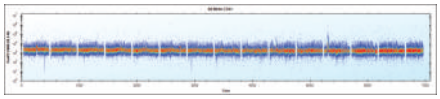
**45 compounds**

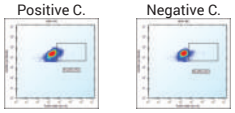
### *High-througput flow cytometry*

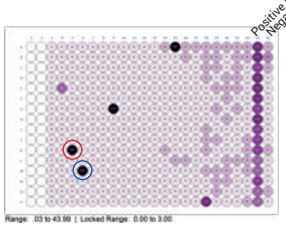
Analysis of FoxP3 expression on $CD4^+$ T cells

Fully automated sample preparation in 384-well format followed by sample analysis on the iQue screener PLUS.

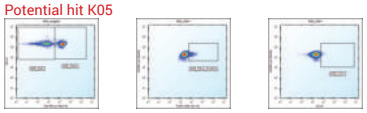





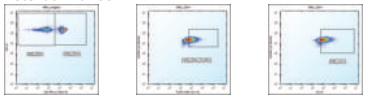



Potential hit K05



Potential hit K06



## THE HARDWARE

| | |
|---|---|
| ***liquid handling:*** | *Access Workstation with Echo550, Hamilton microlab star* |
| ***readers:*** | *BioTek Synergy Neo2, PerkinElmer EnVision, Molecular Devices FLIPR384, IntelliCyt iQue Screener PLUS, BD LSRFortessa* |
| ***assays:*** | *AlphaScreen, Lum, FI, FP, TRF, UV-visible Abs, $Ca^{2+}$-flux, HT flow cytometry* |
| ***compound storage:*** | *Roylan StoragePod (humidity controlled $N_2$ atmosphere)* |
| ***compound libraries:*** | *Enamine, ChemBridge, ChemDiv, Prestwick, Enzo Target/Pathway, SelleckChem Cancer/Kinase, Tocriscreen Mini, BioMol Kinase* |

## THE SOFTWARE

***software tools:***

- *Dotmatics Studies*
- *Dotmatics Vortex*
- *KNIME*
- *ChemAxon Instant JChem*
- *Prism Graphpad*

## THE OUTPUT


1. *Dukic et al. (2017) SLAS Discov.*
2. *Calejo & Taskén (2015) Front. Pharmacol.*
3. *Bach et al. (2014) Naunyn-Schmiedeberg's Arch Pharmacol.*
4. *Ellinger et al. (2014) Assay Drug Dev. Technol.*
5. *Vang et al. (2012) Nature Chem. Biol.*


***collaborations:*** *GSK, Seald AS, Rheumatech AS, Various groups from University / U. Hospital Oslo*

***networks:*** *NOR-OPENSCREEN, Nordic Chemical Biology Network*

***patents:*** *Taskén et al. WO 2013171332*

## THE FUTURE

***future plans:***
*expanding the compound collections attraction of international users*

***added value:***
*expertise in targetting protein-protein interactions and HT flow cytometry*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NCMM Centre for Molecular Medicine Norway
Nordic EMBL Partnership for Molecular Medicine