XXIII РОССИЙСКИЙ НАЦИОНАЛЬНЫЙ КОНГРЕСС «ЧЕЛОВЕК И ЛЕКАРСТВО»

IN SILICO TECHNOLOGIES IN DEVELOPMENT OF INHIBITORS FOR MST1 – THE KEY REGULATOR OF BETA CELL APOPTOSIS AND DYSFUNCTION IN DIABETES

PRINCIPLE INVESTIGATORS IN THE CONSORTIUM:

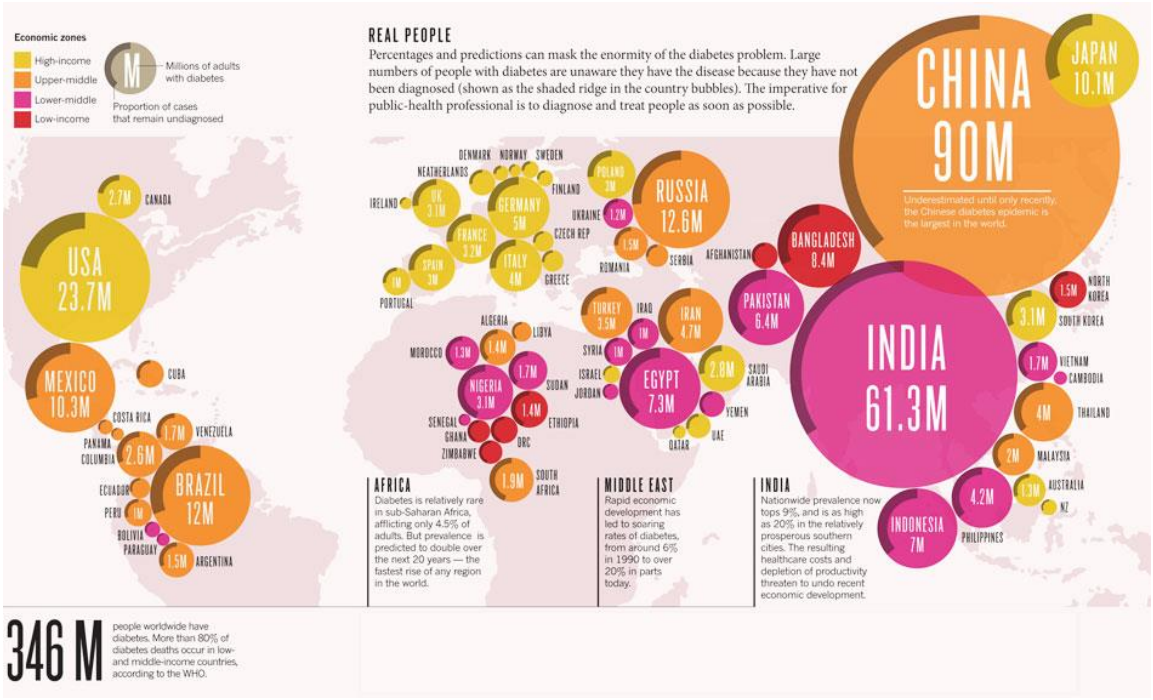
- **Dr. Elena Fedorova**, VVS Lab, Russia
- **Dr. Xiang-Guo Li**, Turku University Hospital and University of Turku, Finland
- **Professor Mark Johnson**, Åbo Akademi University, Finland
- **Karina Patz**, St. Petersburg Chemical Pharmaceutical Academy, Russia

Moscow, 2016

Diabetes in numbers

International Diabetes Federation

THE ECONOMIC COSTS OF DIABETES MAY EXCEED THE REVENUES FROM ECONOMIC GROWTH ALL COUNTRIES IN THE WORLD



Scully. Nature 485, S2–S3, 2012

MST1, PDX1 & diabetes

MST1 or Mammalian Sterile 20-like-1 (or STK4)

- Serine/threonine protein kinase
- Key component of Hippo complex → Pro-apoptotic
- Phosphorylates/inactivates PDX1 in the beta cells

PDX1 or Pancreatic and Duodenal Homeobox-1

- Insulin promoter factor 1
- Needed for beta cell maturation
- MST1 phosphorylation → Impaired insulin secretion

Block MST1 with inhibitors to treat diabetes

nature medicine

VOLUME 20 | NUMBER 4 | APRIL 2014

MST1 is a key regulator of beta cell apoptosis and dysfunction in diabetes

Amin Ardestani[1], Federico Paroni[1,6], Zahra Azizi[1,6], Supreet Kaur[1,6], Vrushali Khobragade[1], Ting Yuan[1], Thomas Frogne[2], Wufan Tao[3], Jose Oberholzer[4], Francois Pattou[5], Julie Kerr Conte[5] & Kathrin Maedler[1]

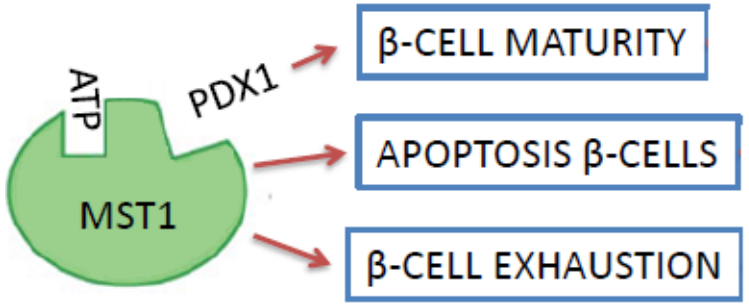
PDX1 involvement in diabetes
MST1 kinase regulates PDX1

N Engl J Med. 2001 Sep 27;345(13):971-80.

Molecular mechanisms and clinical pathophysiology of maturity-onset diabetes of the young.

Fajans SS[1], Bell GI, Polonsky KS.

- PDX1 activates multiple genes associated with glucose metabolism, including insulin, and PDX1 mutations are associated with development of diabetes in childhood



Nat Med. 2014 Apr;20(4):385-97. doi: 10.1038/nm.3482. Epub 2014 Mar 16.

MST1 is a key regulator of beta cell apoptosis and dysfunction in diabetes.

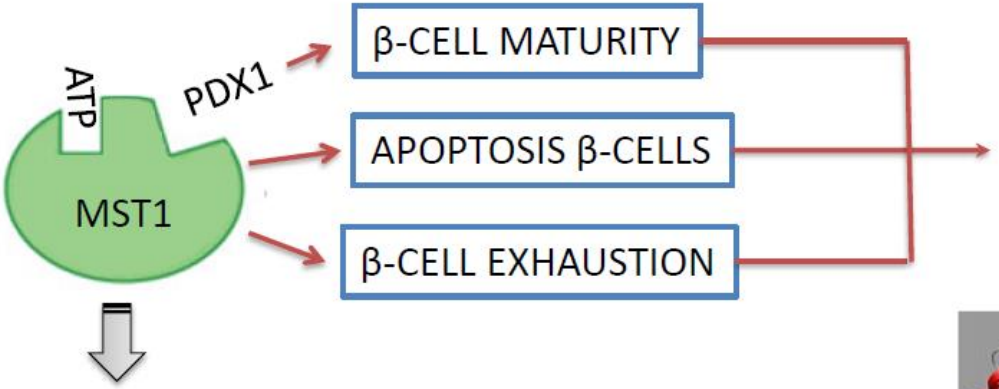
Ardestani A[1], Paroni F[2], Azizi Z[2], Kaur S[2], Khobragade V[1], Yuan T[1], Frogne T[3], Tao W[4], Oberholzer J[5], Pattou F[6], Kerr Conte J[6], Maedler K[1].

- MST1 is a key mediator of beta cell apoptosis and dysfunction, and MST1 depletion completely restores normoglycemia and prevents diabetes progression.

The goals

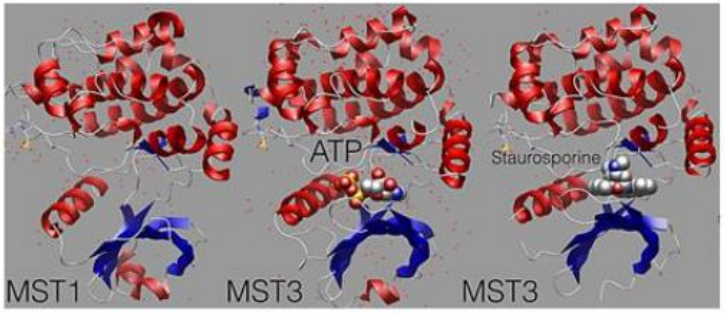
- 1. Stop phosphorylation of the PDX1 protein
- WHY?
  - Leads to beta cell apoptosis
  - ∴ Improving outcome in diabetes
- 2. Produce an in vivo tracer of beta cell health
- WHY?
  - Signal level of tissue damage
  - Report on efficacy of therapy

Solution

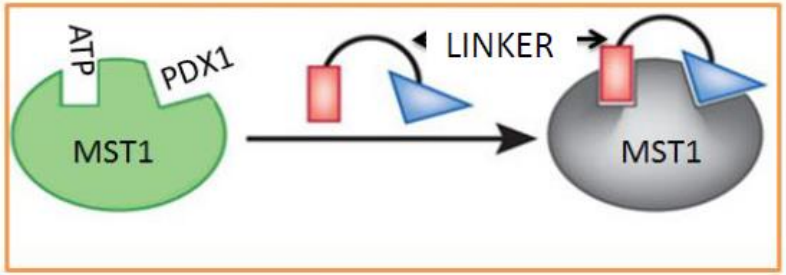


DIABETES
TYPE 1, TYPE 2, MODY

OBJECTIVE: To restore the function of β-cells



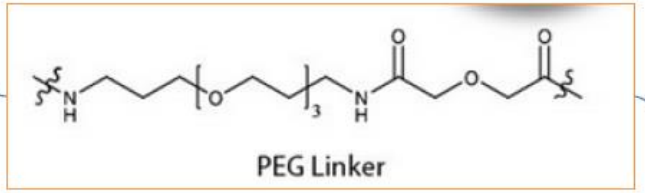
BIVALENT INHIBITOR



AFFINITY (ATP) + SELECTIVITY (PDX1)

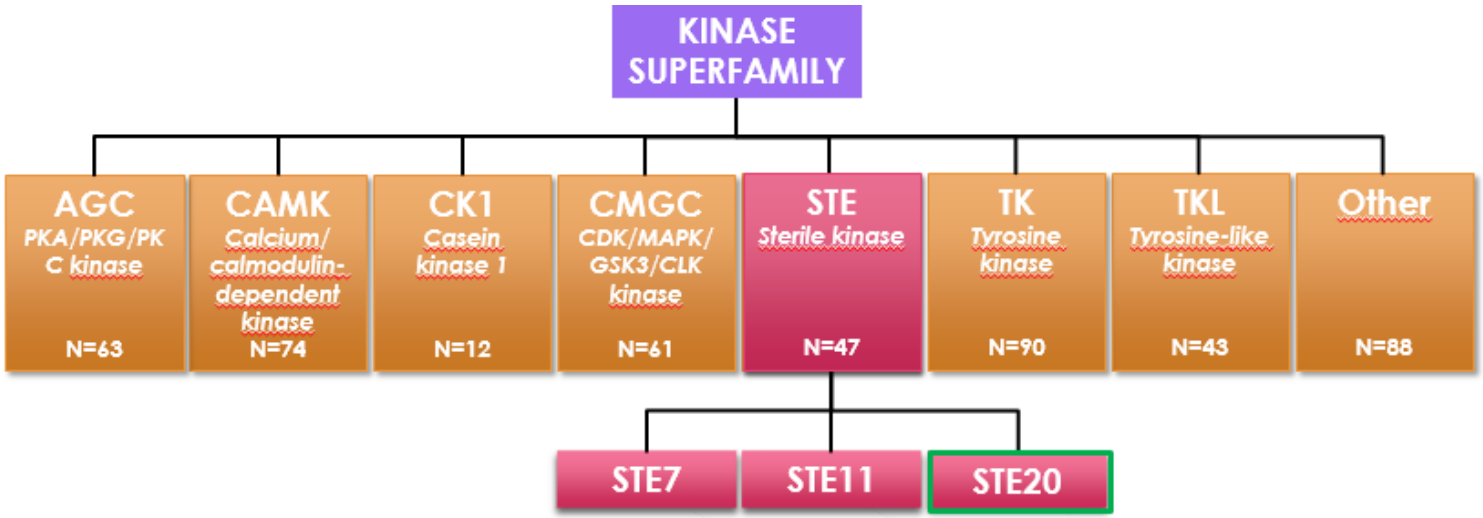
SOLUTION: Prototype of inhibitor

SMALL MOLECULAR COMPOUNDS

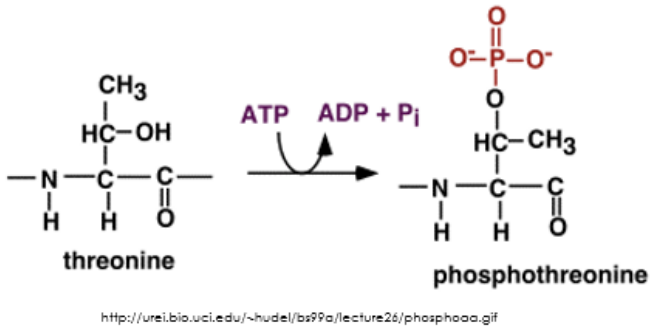


PEPTIDE SEQUENCES

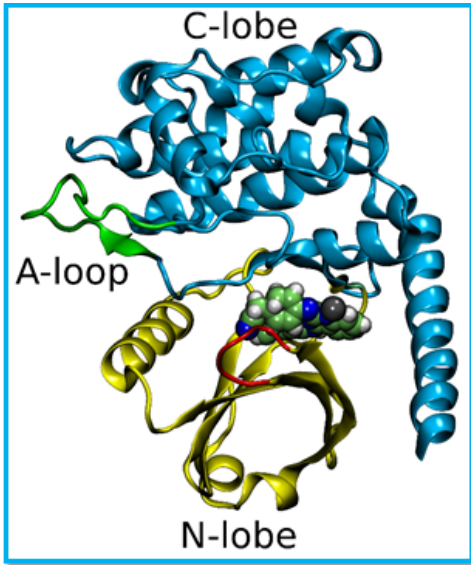
A lot of kinases…
MST1 kinase domain structure



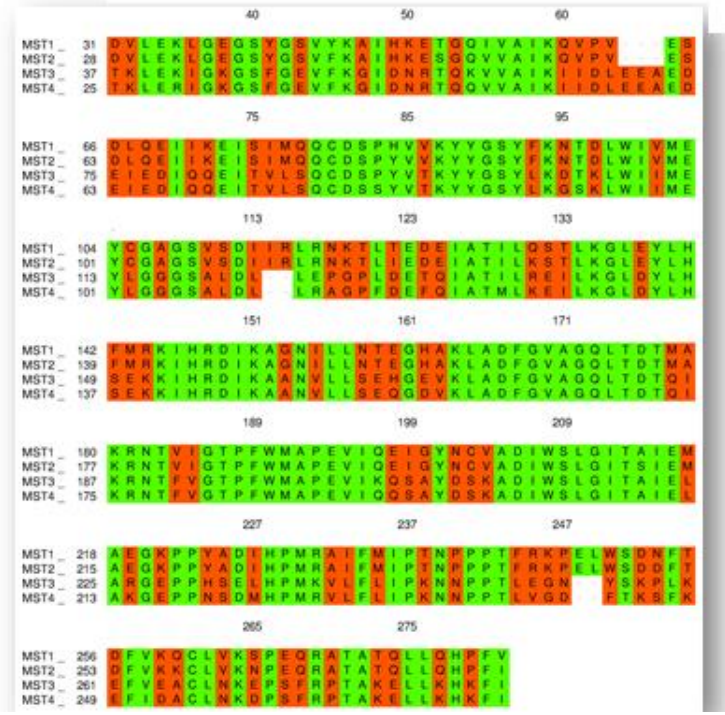
- Bi-lobed kinase domain: N- and C-terminal lobes
- ATP/Mg^{2+} complex is bound in a cleft
- Activation loop (or A-loop) phosphorylated → Activity



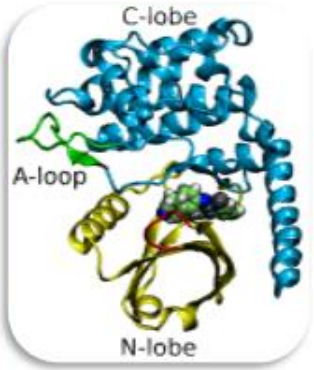
http://urei.bio.uci.edu/~hudel/bs99a/lecture26/phosphoaa.gif



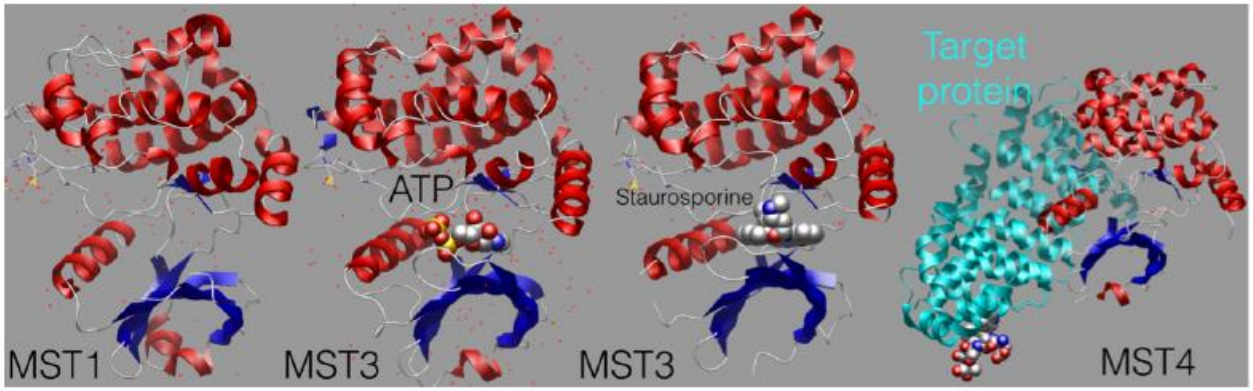
Kinase domain sequence



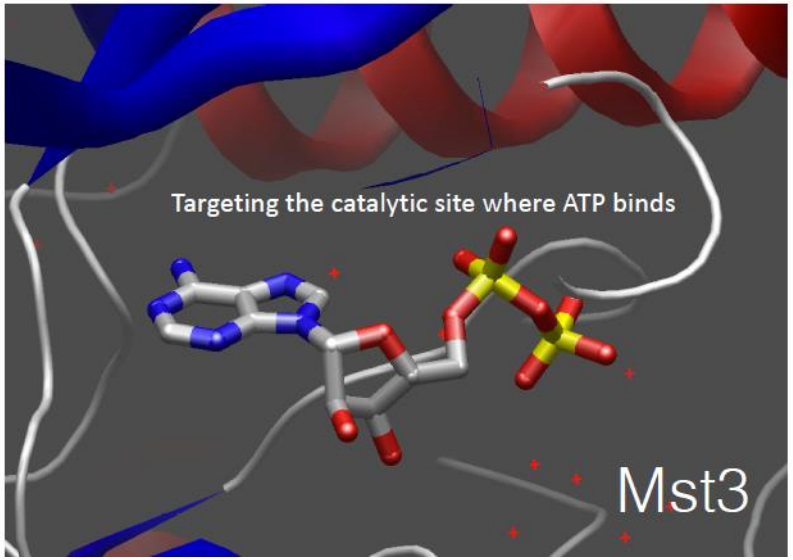
	MST1	MST2	MST3	MST4
MST1		96%	57%	56%
MST2	96%		58%	58%
MST3	57%	58%		88%
MST4	56%	58%	88%	



Obvious attack on ATP binding site
Obvious, but very challenging

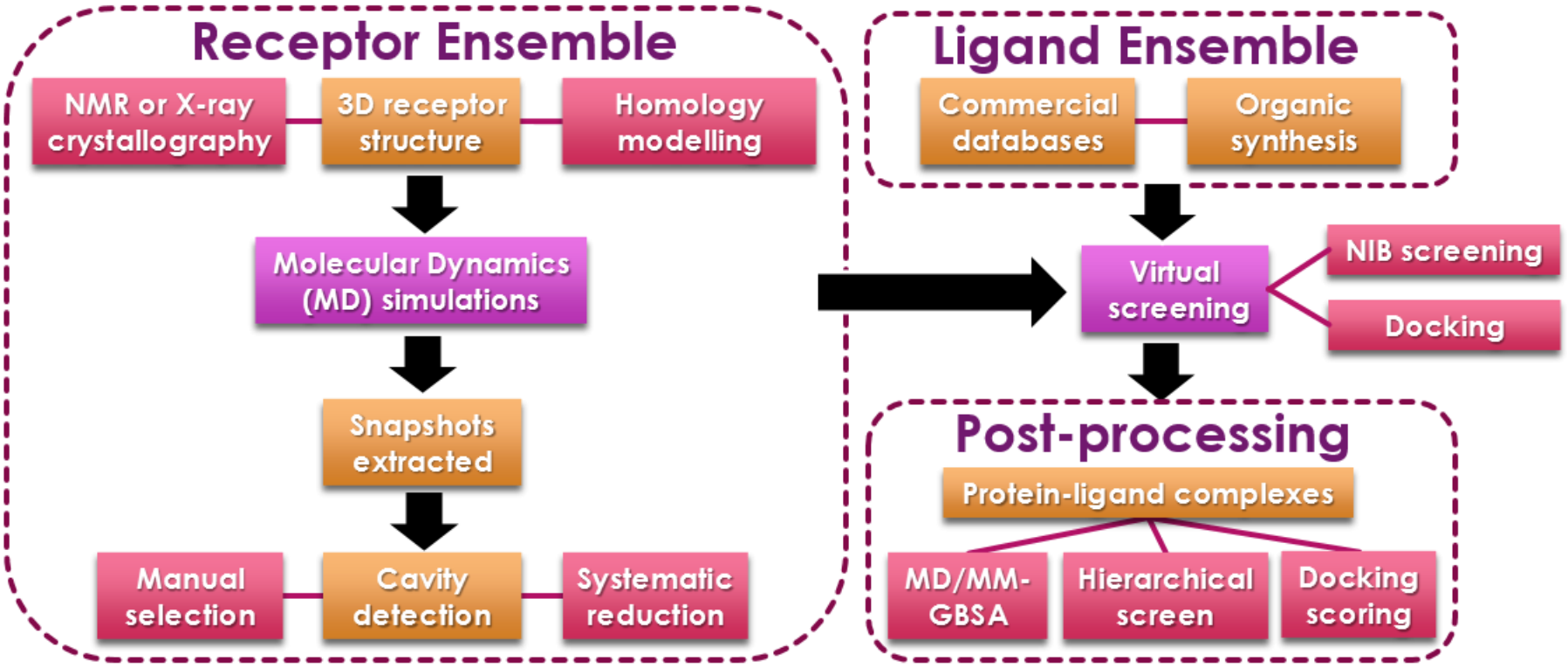


Have excellent three-dimensional structural data on kinase domains, but only the homeobox domain of PDX1 is known at this time

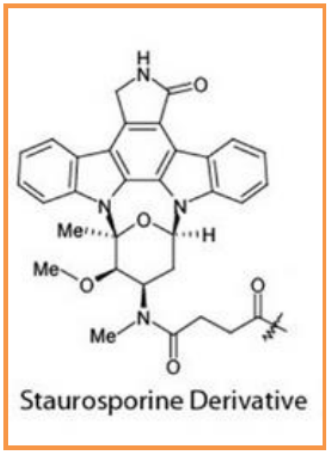


- L/I and L/C variation extends across many kinase families
- High selectivity nearly impossible?
- Seek other strategies, too

Ensemble-based virtual screening

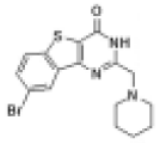


GUSAR - GENERAL UNRESTRICTED STRUCTURE ACTIVITY RELATIONSHIPS



$^{pred}IC_{50}$(Staurosporine)=2,5*10^{-6}

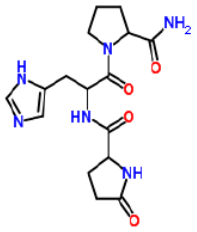
inhibit the target by 40%



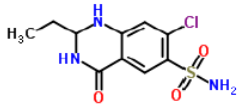
1*10^{-9}

In vitro test
ADP-Glo™ assay kits for MST1

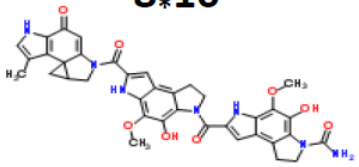
$^{pred}IC_{50}$



5,6*10^{-7}



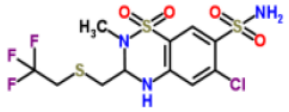
8*10^{-7}



7*10^{-6}

R^2=0,77

% of inhibition MST1



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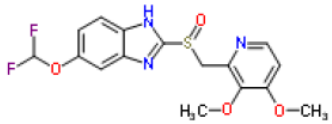

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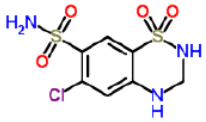
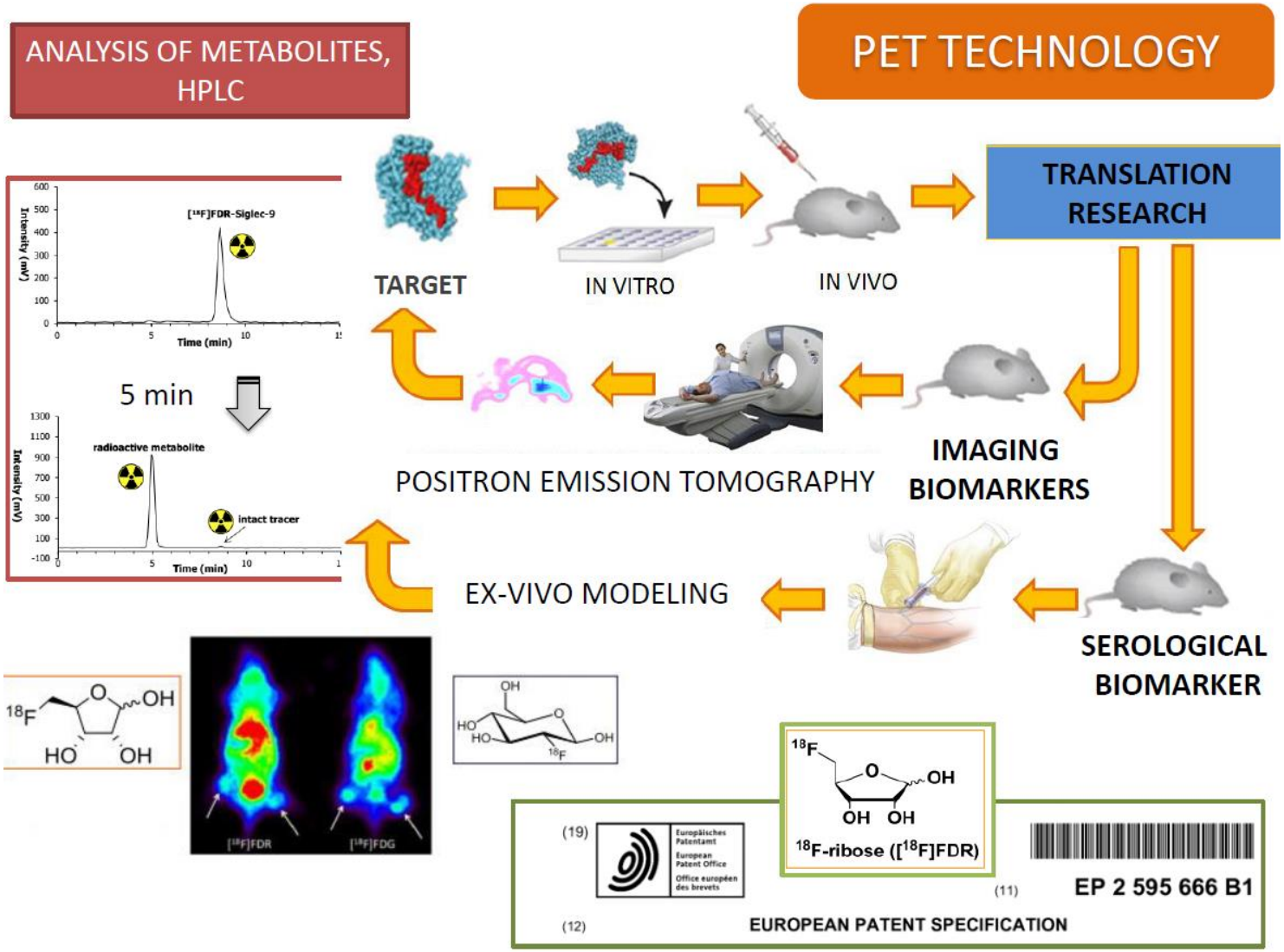


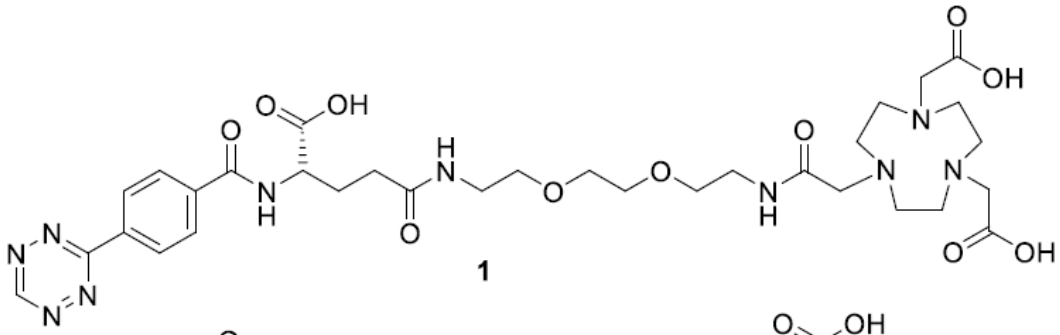
63

R^2=0,85

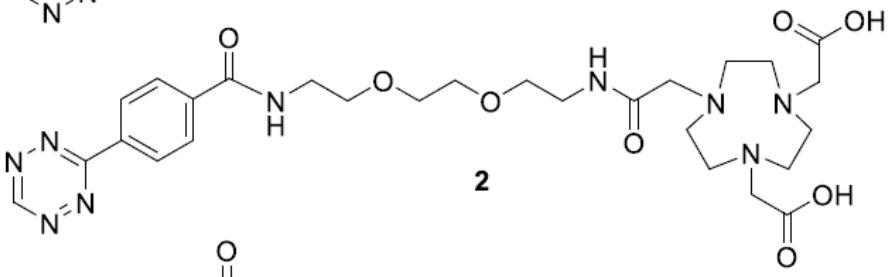
Positron emission tomography



Precursors and linkers for radiolabeling of peptides



1



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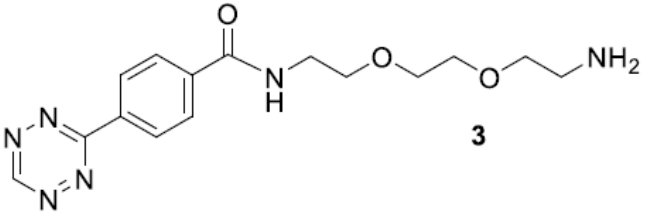

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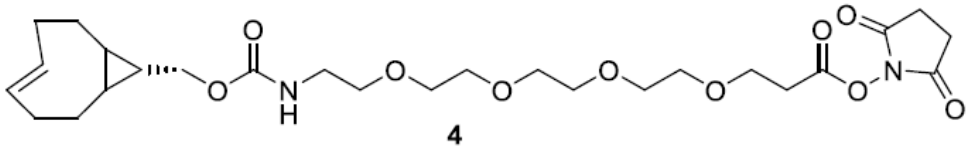

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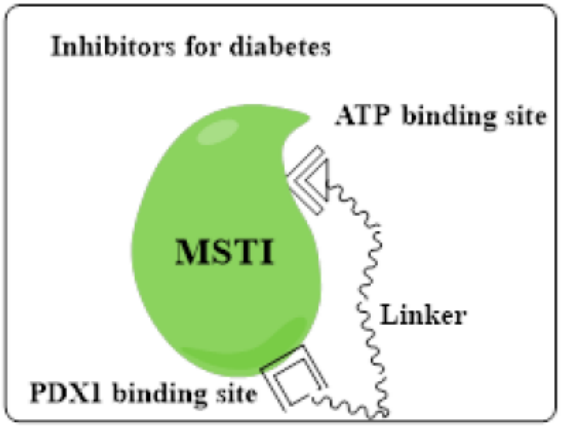

Other targets are appearing…

Diabetes. 2015 Oct;64(10):3475-84. doi: 10.2337/db15-0376. Epub 2015 Jun 17.

Diabetes Susceptibility Genes Pdx1 and Clec16a Function in a Pathway Regulating Mitophagy in β-Cells.

Soleimanpour SA[1], Ferrari AM[2], Raum JC[2], Groff DN[2], Yang J[2], Kaufman BA[3], Stoffers DA[4].

- Restoring Clec16a led to normalisation of mitochondrial trafficking

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Thank you for your attention!

Fedorova Elena
elena.vic.fedorova@gmail.com