Allosterische AGC Kinase-Inhibitoren - erhöhte Spezifizität und verbessertes Nebenwirkungsprofil

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PSites Pharma GmbH,
Medizinische Klinik I, Universitätsklinikum Frankfurt
Theodor-Stern-Kai 7, 60590 Frankfurt, Germany

*PS*ites – Summary

PSites Pharma is a spin-off of the Research Group PhosphoSites of the University Frankfurt who made the key scientific discoveries and developments in the allosteric kinase modulation field since 2001.

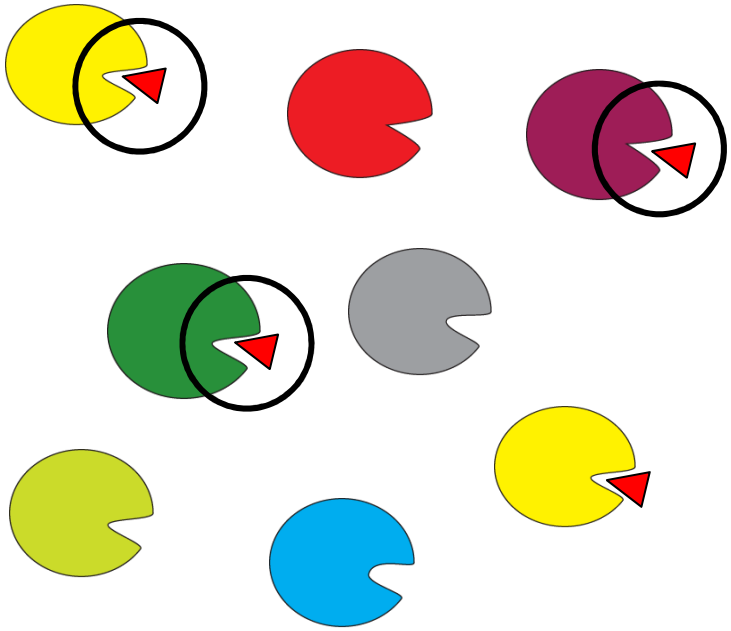
Based on the discovery of an additional, allosteric, non-ATP-competitive regulatory binding site, PSites developed the platform technology to produce the next generation of much more specific protein kinase activators and inhibitors.

First leads on selected targets show promising results in mice and have outstanding pharmcological prosperities.

PSites develops clinical candidates and INDs for own targets and client targets and out-licenses them to pharmaceutical partners.

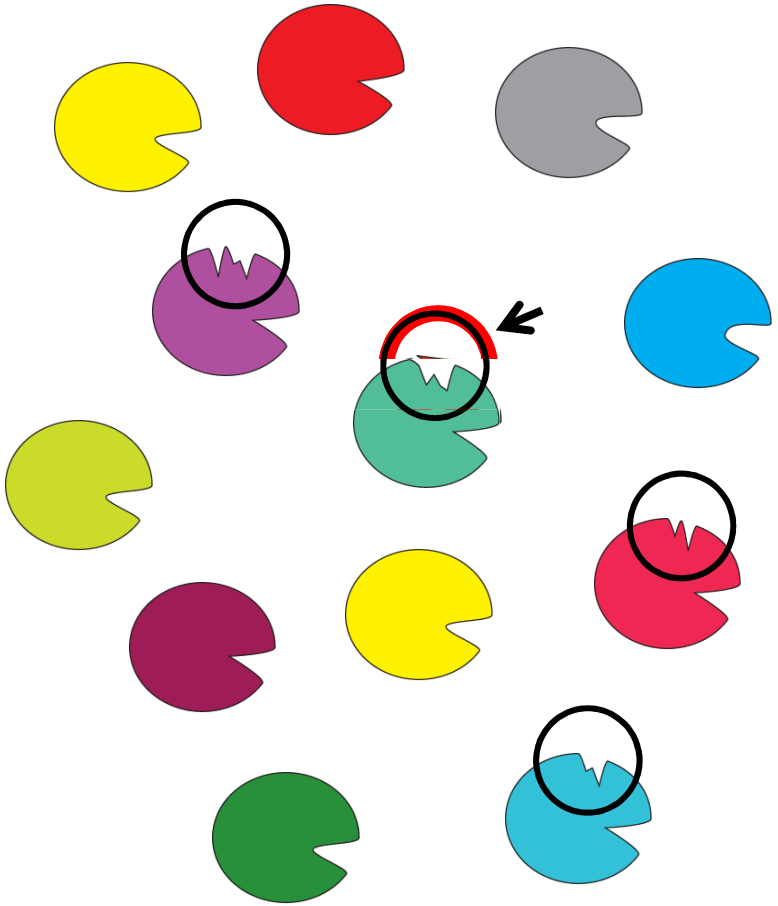
*PS*ites – Medical Need and Technology

- 20-30% of new drug development programs in the pharmaceutical industry are directed against „Protein kinases“.
- Protein kinases are validated drug targets, but todays drugs have drawbacks ...
- The drawback: a very conserved drug-binding site that triggers side-effects.

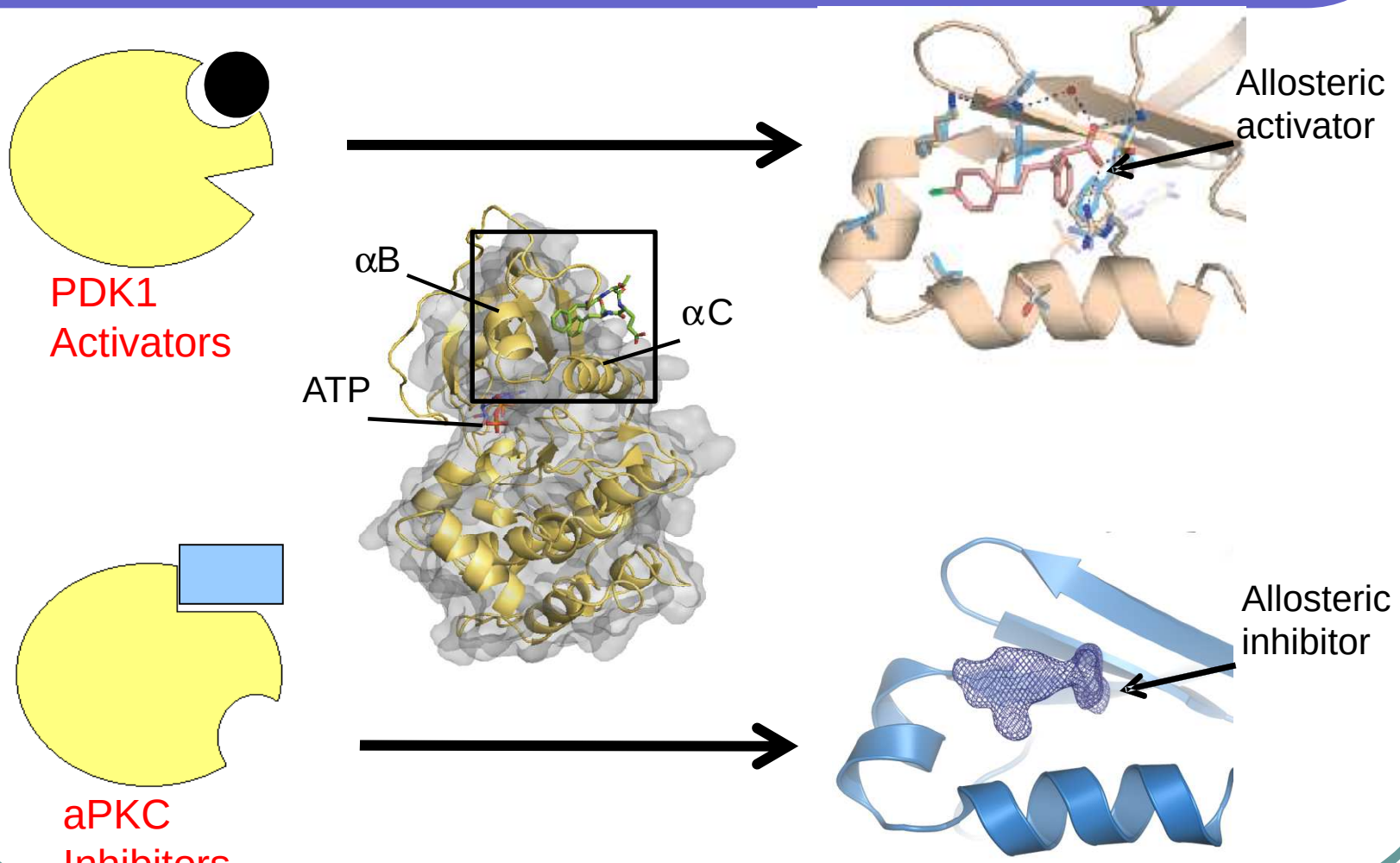


*PS*ites – Technology and Innovation

- One group of protein kinases AGC kinases, have a second pocket (PIF-pocket).
- By rational drug design we develop small compounds that bind to the PIF-pocket: allosteric activators and allosteric inhibitors.
- These compounds are more selective and allow the development of drugs with much less adverse side effects.
- Our technology can be applied on at least 60 protein kinases, with indications against cancer, diabetes, inflammation, autoimmune etc.

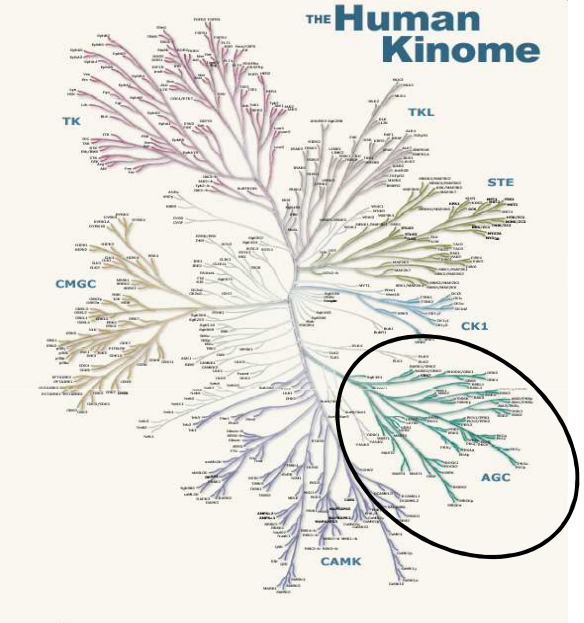


*PS*ites– Technology
Activators and Inhibitors



The technology can complement current client programs

*PS*ites– Technology + USP: The platform for AGC-Kinases



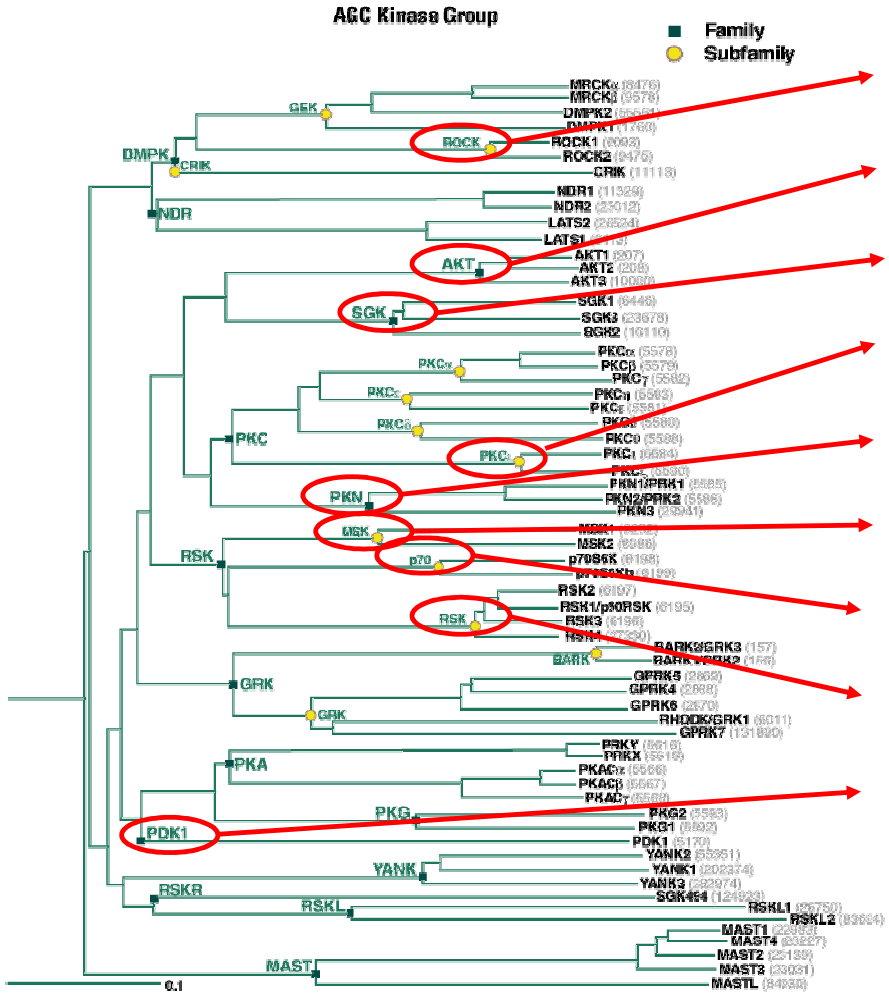
- We develop small molecules, i.e. allosteric activators and allosteric inhibitors that bind to the PIF-pocket of different AGC-Kinases.
- First PS-compounds for aPKCs are active in cellular and animal models of lung cancer without measurable side effects.
- PS-Platform and know-how enable us to develop drugs to other AGC-Kinases.

- **Focused library of compounds**
- **Screening platforms**
- **Crystallography platform**
- **know-how**

	PDK1	S6K	PKCz	SGK	RSK	PRK2	PKB	PKA	Aurora
PS X411	ACT	-	-	-	-	-	-	-	-
PS X841	-	INH	-	-	-	-	-	-	-
PS X906	-	-	-	INH	-	-	-	-	-
PS X454	-	-	INH	-	-	-	-	-	-
PS X434	-	-	INH	-	-	ACT	-	-	-
PS X191	-	-	-	-	ACT	-	-	-	-
PS X016	-	-	-	-	-	INH	-	-	-
PS XS066	INH	-	-	-	-	-	-	-	-
PS XS407		-	-	-	-	-	-	-	INH

AGC= protein kinase A, G, and C families (PKA, PKC, PKG).

*PS*ites - AGC kinases: **various validated drug targets**



ROCK, atherosclerosis and vascular disease

PKB / Akt, cancer; PKBb/Akt2 activators- diabetes

SGK, lowering of blood pressure

aPKC, cancer: eg lung cancer

PKN / PRK, cancer (eg prostate), HCV

MSK, activator – autoimmune disorders (eg rheumatoid arthritis)

p70S6K / S6K, diabetes, obesity

p90RSK / RSK, cancer, epithelial cancers (eg pancreatic cancer)

PDK1, cancer

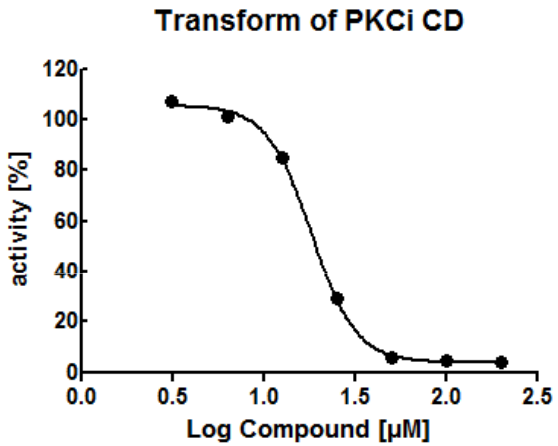
*PS*ites - 1. Target: **PKCiota**

- aPKCiota is a validated target against diverse cancers against non-small cell lung cancer (NSCLC), ovarian cancer and pancreatic cancer (work by Prof. Alan Fields (Mayoclinic) for over 12 years).
- The atypical PKCiota isoform, is overexpressed in different types of cancers.
- It resides in a chromosome location that is frequently amplified in human cancers (e.g. 70% of lung squamous cell carcinoma, 70% of ovarian cancers of serous subtype).
- Recent work shows that it is required for KrasG12D tumor formation in vivo and for cancer stem cells.

*PS*ites - Status: PKCiota-Inhibitor lead

indications: lung +prostate cancer

Example: Lead compound **PSX234**



Highly selective in vitro:
The effect of PSX234 was tested in more than 50 different kinases (in-house and outsource). One other AGC kinase and one non-AGC kinase are inhibited in vitro.

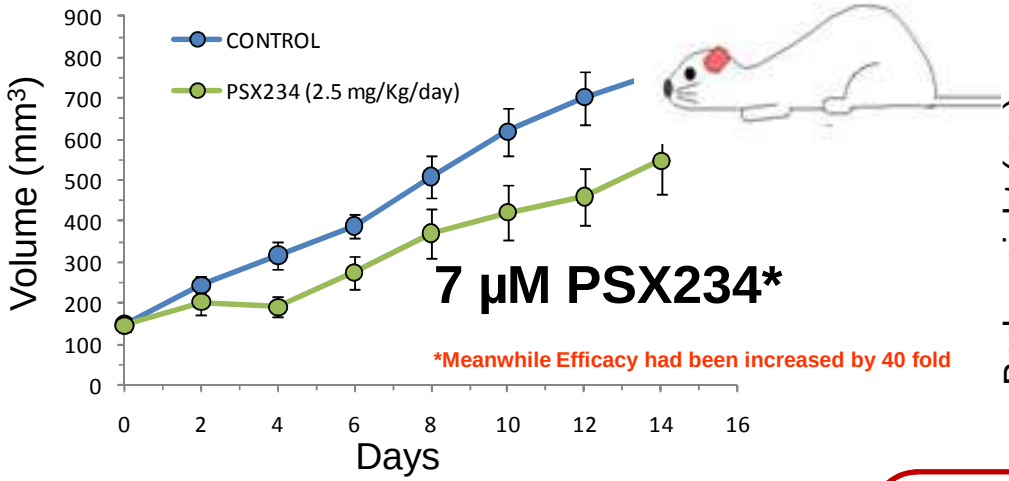
Selectivity for aPKCs:
PKCs iota and zeta (**IC_{50} 10-20 µM**)

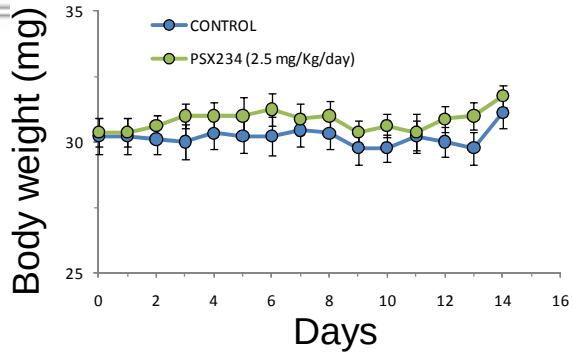
(PKCalpha; PKCbeta2; PKCiota; PKCdelta, all IC_{50} values > 100µM)

Highly selective in vivo. Yeast Selectivity assay:
PKC1 is required for the CWI pathway. Knock-out of PKC1 is lethal, but can be rescued by the expression of the constitutively active form of BCK1 (BCK1-20).

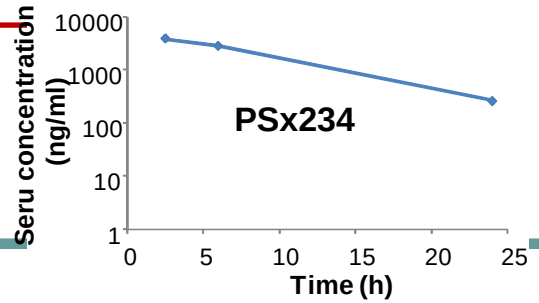
PSX234 inhibits yeast growth and the effect is rescued by BCK1-20, indicating that the toxicity in yeast is due to its target PKC1.

PSX234- promising in vivo data





The antitumor efficacy of PSX234:
PSX234 reduced tumor growth by 28.1% (P=0.0027), as expected from suboptimal concentration of PSX234 in serum



NoToxic effect observed:
No differences in the weight of the vital organs and in their histological characteristics at the end of the study

Preliminary Pharmacokinetics:

Pharmacokinetic experiments revealed that PSX234 has outstanding general pharmacokinetic properties

Allosteric Kinase-Inhibitors at one glance

- **Next generation of protein kinase inhibitors**
- **Superior specificity**
- **Specificity also allows safe small molecule activators**
- **60+ kinase targets available (cancer, inflammatory, anti-infectiva etc.)**
- **Technology extensible outside of AGC-Kinases (Aurora and others)**
- **Fresh IP for the allosteric regulatory binding site**
- **Combinations of classic ATP competitive and allosteric, non-ATP competitive compounds will enhance life cycles and improve long term efficacy**

Contact: **Psites Pharma GmbH**
Dr. Rolf Witte, CEO
Mobile: +49 172 924 8355
E-mail: rolf.witte@psites.de
www.psites.de