Fragment Screening simplified
Frag Xtal Screen

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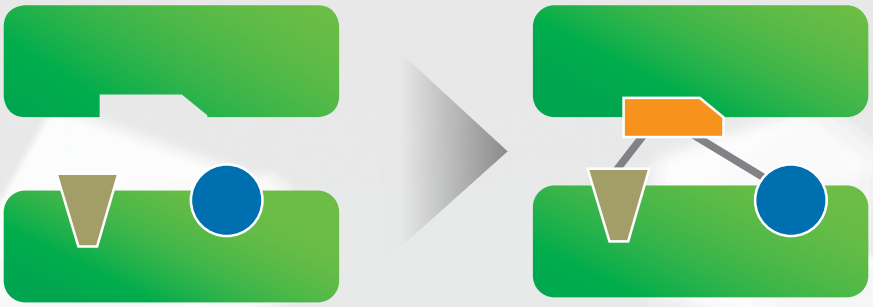
Building Blocks of Life

In drug discovery, often small molecules ("fragments") are screened for efficient binding* to a specific protein target. Due to their small size, fragments can be chemically evolved or linked to each other, finally yielding a desired high-affinity lead structure[1] (Fig. 1).



Fragments with millimolar affinity but high efficiency*

Nanomolar lead structure

Figure 1

Fragment-based lead discovery takes advantage of fragment evolution and linking. Small individual fragments with inherently low affinity but high efficiency are grown according to the structural model. The efficient binding of the fragments results in a nanomolar lead structure.*

Cat. No.	Amount
X-FS-101	96 fragments (2 x 50 nmol each)

The Frag Xtal Screen...

- ...consists of 96 fragments covering a large chemical space, selected by the groups of Gerhard Klebe (University of Marburg) and Manfred Weiss (BESSY II) based on
  - » a priori validation through compound selection from PDBeChem entries[5]
  - » proven capability of fragments to bind to proteins[2,5]
  - » validation with aspartic protease endothiapepsin (EP), hit rate 10 %[2]
- ...allows crystal soaking with fragment concentrations > 90 mM resulting in functional mapping of the entire target and identification of multiple binding sites
- ...avoids losing potential hits that are not identified by prescreening methods[3,4]

Assuming practical skills in transferring crystals and cryocooling, **96 distinct fragments can be screened within one week**.

The new Frag Xtal Screen is based on the approach "Crystallography first": X-ray crystallography shows not only whether a fragment binds to the protein but also where and how the binding occurs.

* binding efficiency = high binding energy/molecular mass

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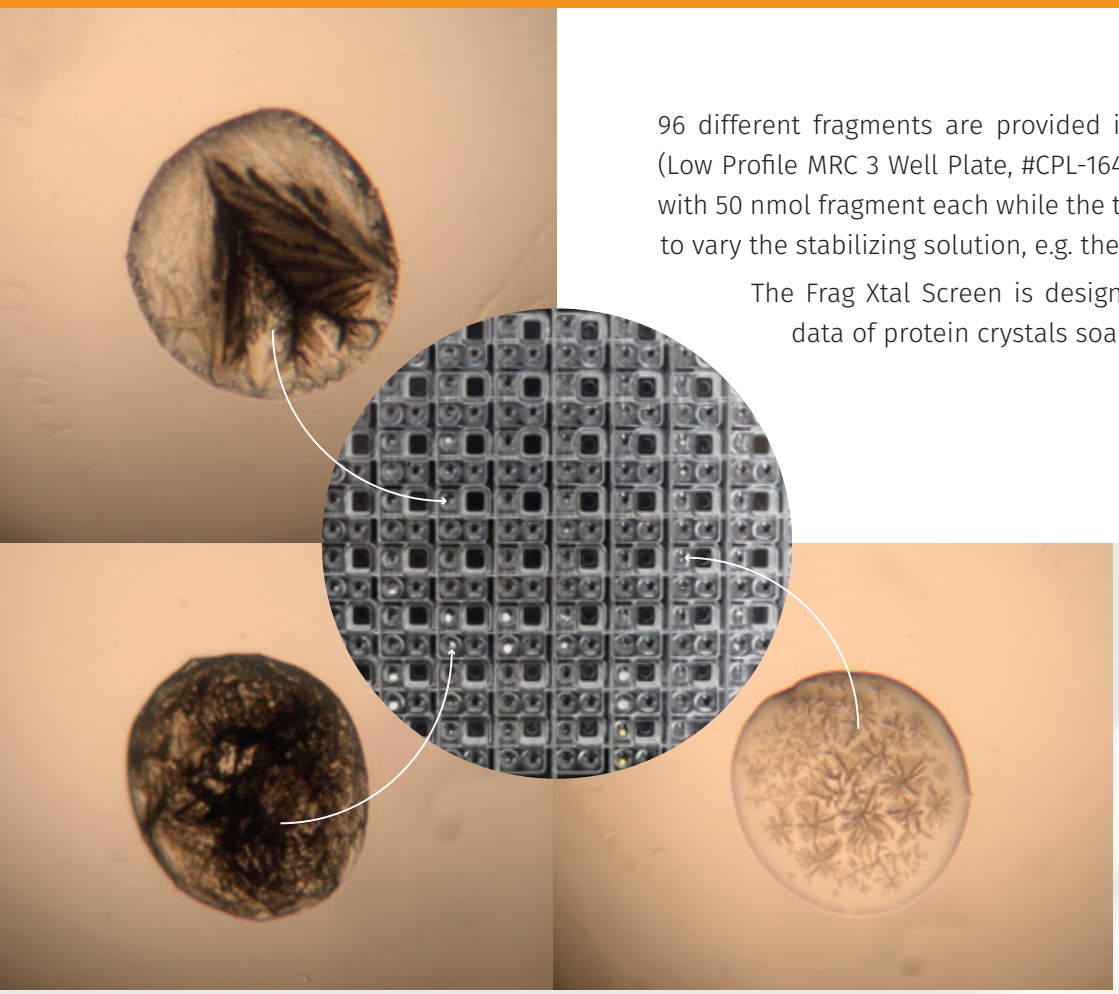

96 different fragments are provided in a 3 Well Crystallization Plate (Low Profile MRC 3 Well Plate, #CPL-164). Two protein wells are spotted with 50 nmol fragment each while the third one is kept free. This allows to vary the stabilizing solution, e.g. the DMSO content.

The Frag Xtal Screen is designed to directly collect structural data of protein crystals soaked with 96 different fragments.

The Frag Xtal Screen was developed in cooperation with the HZB MX-group at BESSY II (AG Weiss) and the Institute of Pharmaceutical Chemistry, University of Marburg (AG Klebe).

Short Fragment Soaking Protocol:

Step	Action
1)	Remove foil carefully
2)	Add 30 µL crystallization buffer to the reservoir (manually or by robot)
3)	Add 0.5 µL crystallization buffer on dried fragments (manually or by robot)
4)	Add 1–2 crystals per drop
5)	Seal the plate & incubate 1–48 h
6)	Fish & cryo-cool at least one crystal per condition

Online catalog
Frag Xtal Screen at ↘

References:

[1] Rees *et al.* (2004) Fragment-based lead discovery *Nat. Rev. Drug Discov.* **3:**660.
[2] Huschmann *et al.* (2016) Structures of endothiapepsin-fragment complexes from crystallographic fragment screening using a novel, diverse and affordable 96-compound fragment library. *Acta Cryst F* **72:**346.
[3] Schiebel *et al.* (2016) Six Biophysical Screening Methods Miss a Large Proportion of Crystallographic Discovered Fragment Hits: A Case Study. *ACS Chem. Biol.* **11:**1693.
[4] Schiebel *et al.* (2015) One Question, Multiple Answers: Biochemical and Biophysical Screening Methods Retrieve Deviating Fragment Hit Lists. *ChemMedChem* **10:**1511.
[5] www.ebi.ac.uk/pdbe-srv/pdbechem

Jena Bioscience GmbH
Loebstedter Str. 71
07749 Jena
Germany

Phone +49 (0)3641-62 85 000
Fax +49 (0)3641-62 85 100
info@jenabioscience.com
www.jenabioscience.com

IFTA AG
Certified QMS and EMS according to
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Crystallography