

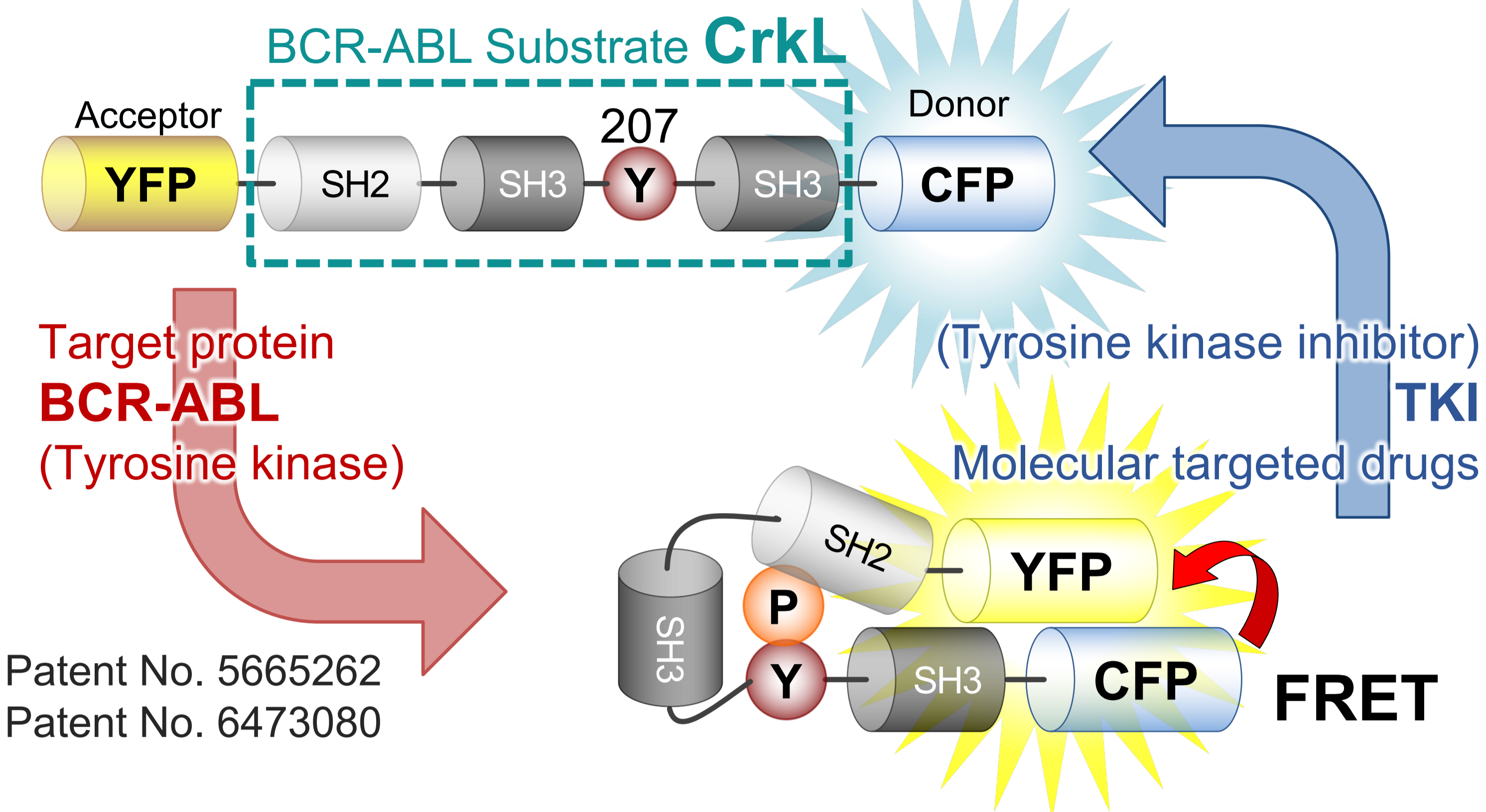
Opto-diagnostics

✓At the level of single living cells

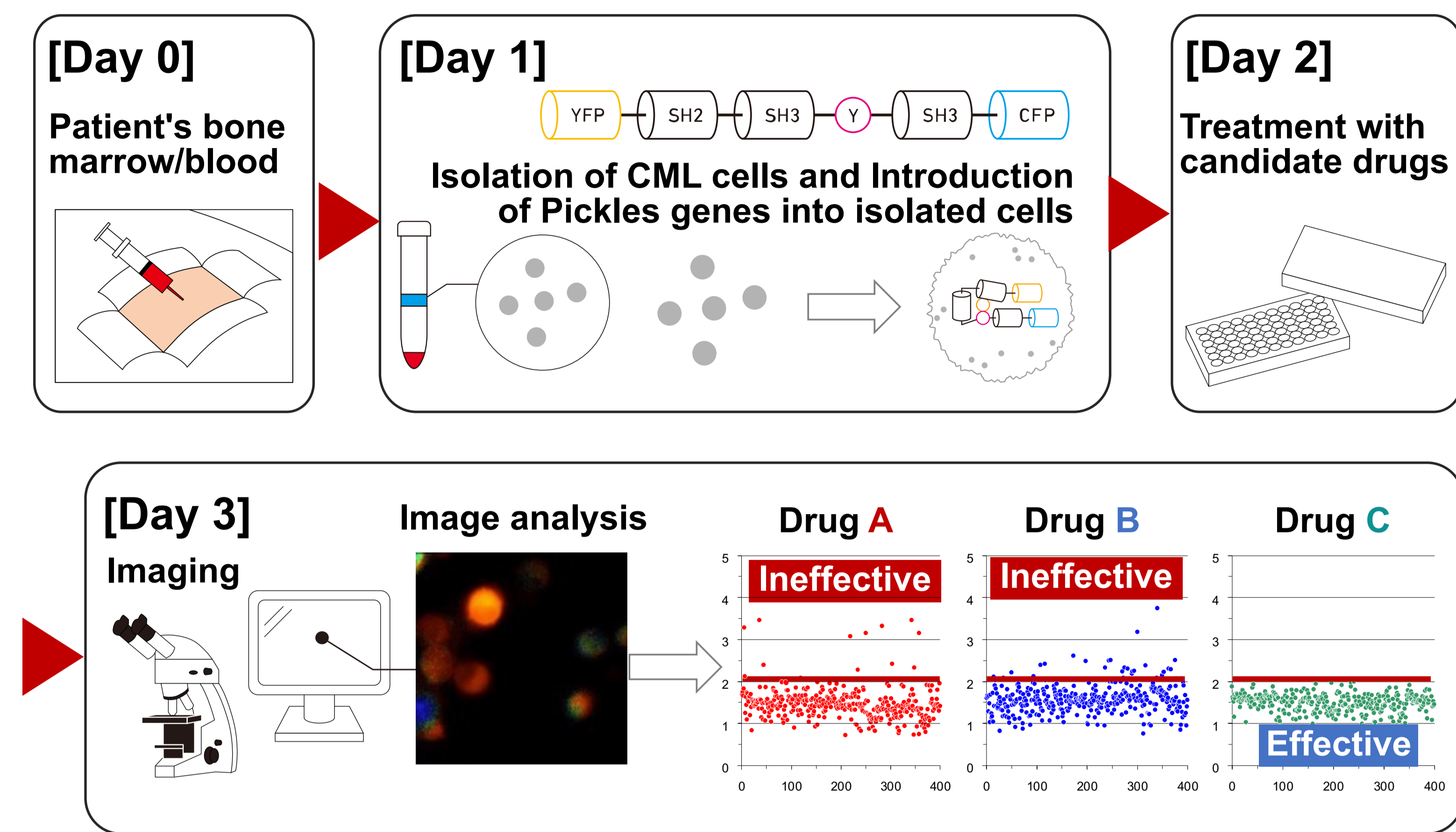
✓Directly measure the activity of driver gene products (the points of action for molecular targeted drugs)

○ Succeeded in drug sensitivity test (clinical study) for chronic myelogenous leukemia (CML)

- Opto-diagnostics "Pickles": A biosensor for BCR-ABL, the driver gene product of CML, dedicated to tyrosine kinase activity measurement



○ Drug Sensitivity Testing Process

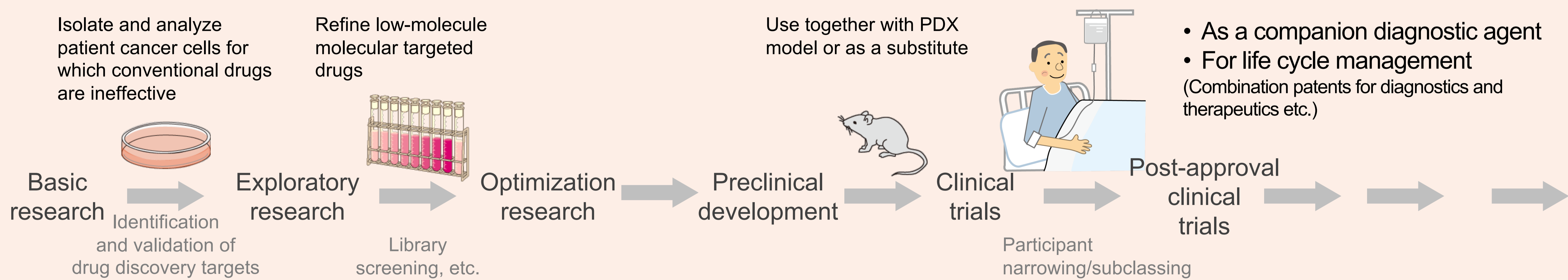


○ Drug sensitivity testing results -Determination of drug sensitivity prior to administration

| Year of implementation | Specimen | Subject | Result | Number of cases | Clinical Research (Papers) |
|------------------------|-------------------------------|---|---|-----------------|----------------------------------|
| 2006 to 2010 | Bone marrow/ Peripheral blood | Chronic phase CML 6, Blast phase CML 2, Ph ¹ -positive ALL 2, AML1 | 8 of 11 cases (72.7%) | 11 | (5) |
| 2011-2012 | Peripheral blood | Imatinib resistant/intolerant CML | 13 of 16 cases (81.3%) | 20 | Corporate collaborative research |
| 2011-2013 | Bone marrow | Untreated chronic phase CML (Underwent first-line treatment with Dasatinib) | Correlates with MR4 achievement at 6 months ($p = 0.004$) and with MR4.5 achievement at 12 months ($p = 0.012$) | 62 | IMIDAS (3) |
| 2011-2014 | Bone marrow | Untreated chronic phase CML (Underwent first-line treatment with Nilotinib) | Correlated with MR4 achievement at 12 months ($p = 0.037$) (Patients with Nilotinib dose intensity > 76.4%) | 42 | EsoFANTA (2) |
| 2023- | Bone marrow | Accelerated phase CML1 (TKI resistant) Untreated chronic phase CML 2 | Consistent with the clinical picture | 3 | - |
| Total | | | | 135 | |

○ Utilization of "Opto-diagnostics" as a Drug Discovery Platform

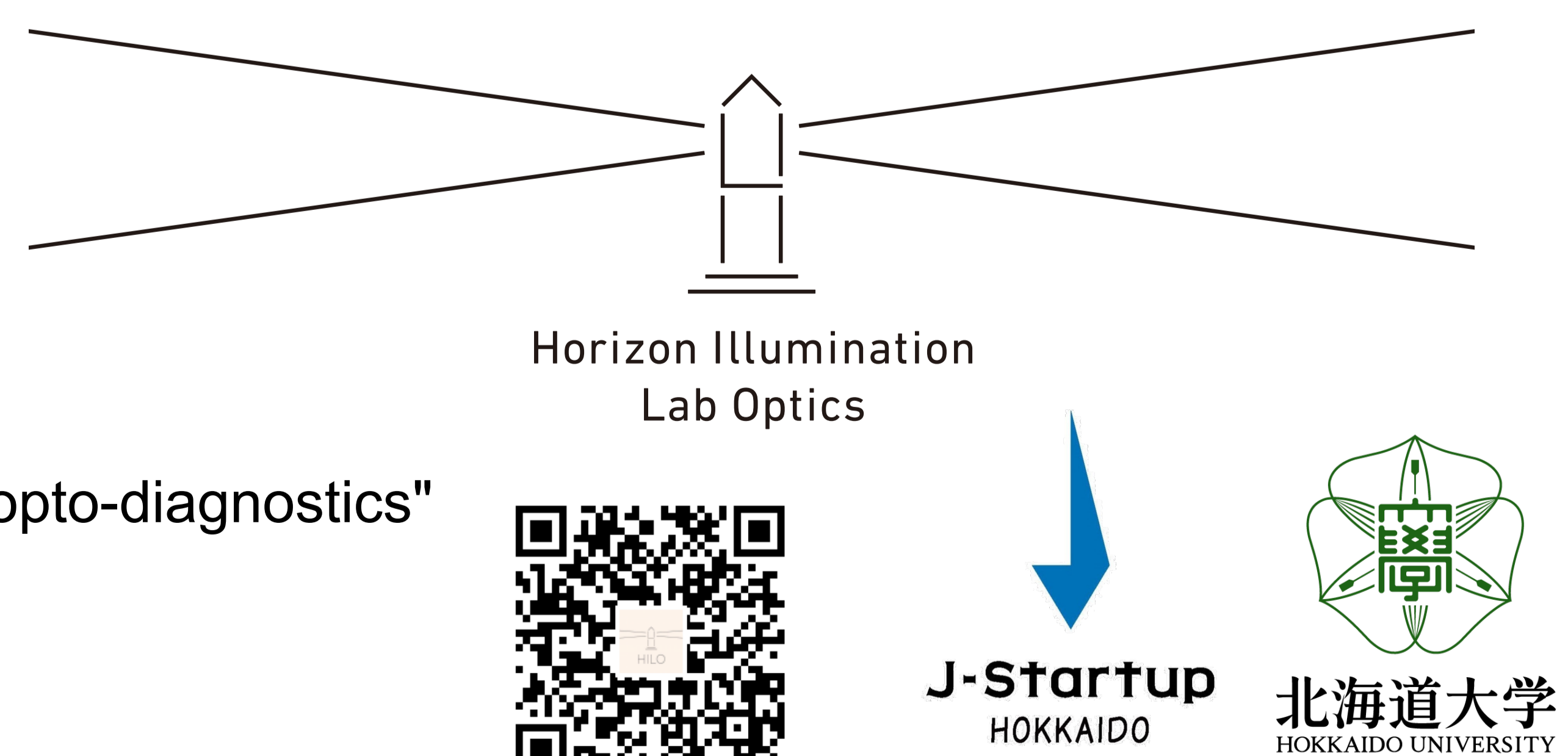
- With Pickles as a prototype, any kinase activity can be measured by substituting the substrate CrkL → Expandable for the drug sensitivity determination for any molecular targeted drug! (Owned knowhow)
- Applicable in various stages of drug discovery and development



○ Company Profile

We aim to create a society in which imaging technology can bring light to every patient's future and enable them to face the challenges of their treatment with peace of mind.

- Established: August 5, 2021 (Capital: JPY22.5 million)
- Business Overview: Development of opto-diagnostics, the fluorescence imaging technology from Hokkaido University Faculty of Medicine, to measure the efficacy of molecularly targeted drugs at the single-cell level. Providing services to determine the efficacy of drugs for each patient even before the start of treatment, etc.
- Future Outlook: (1) Regulatory approval (inclusion in insurance coverage) of "opto-diagnostics" (2) Expansion to all regions and all cancers (3) Provision of drug discovery platform to companies
- Website: <https://www.horizonillumination.co.jp/>



○ Papers

1. Localization of BCR-ABL to stress granules contributes to its oncogenic function. Kashiwagi S, et al, *Cell Struct Funct* **44**: 195, 2019
2. Clinical efficacy and safety of first-line nilotinib therapy and evaluation of the clinical utility of the FRET-based drug sensitivity test. Kondo T, et al, *Int J Hematol* **110**: 482, 2019
3. Pre-treatment evaluation of FRET-based drug sensitivity test for patients with CML treated with dasatinib. Kondo T, et al, *Cancer Sci* **109**: 2256, 2018
4. Improved FRET biosensor for the measurement of BCR-ABL activity in chronic myeloid leukemia cells. Horiguchi, M. et al, *Cell Struct Funct* **42**: 15-26, 2017
5. A novel FRET-based biosensor for the measurement of BCR-ABL activity and its response to drugs in living cells. Mizutani, T. et al, *Clin Cancer Res* **16**: 3964, 2010