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CENTRE FOR
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11 July 2019

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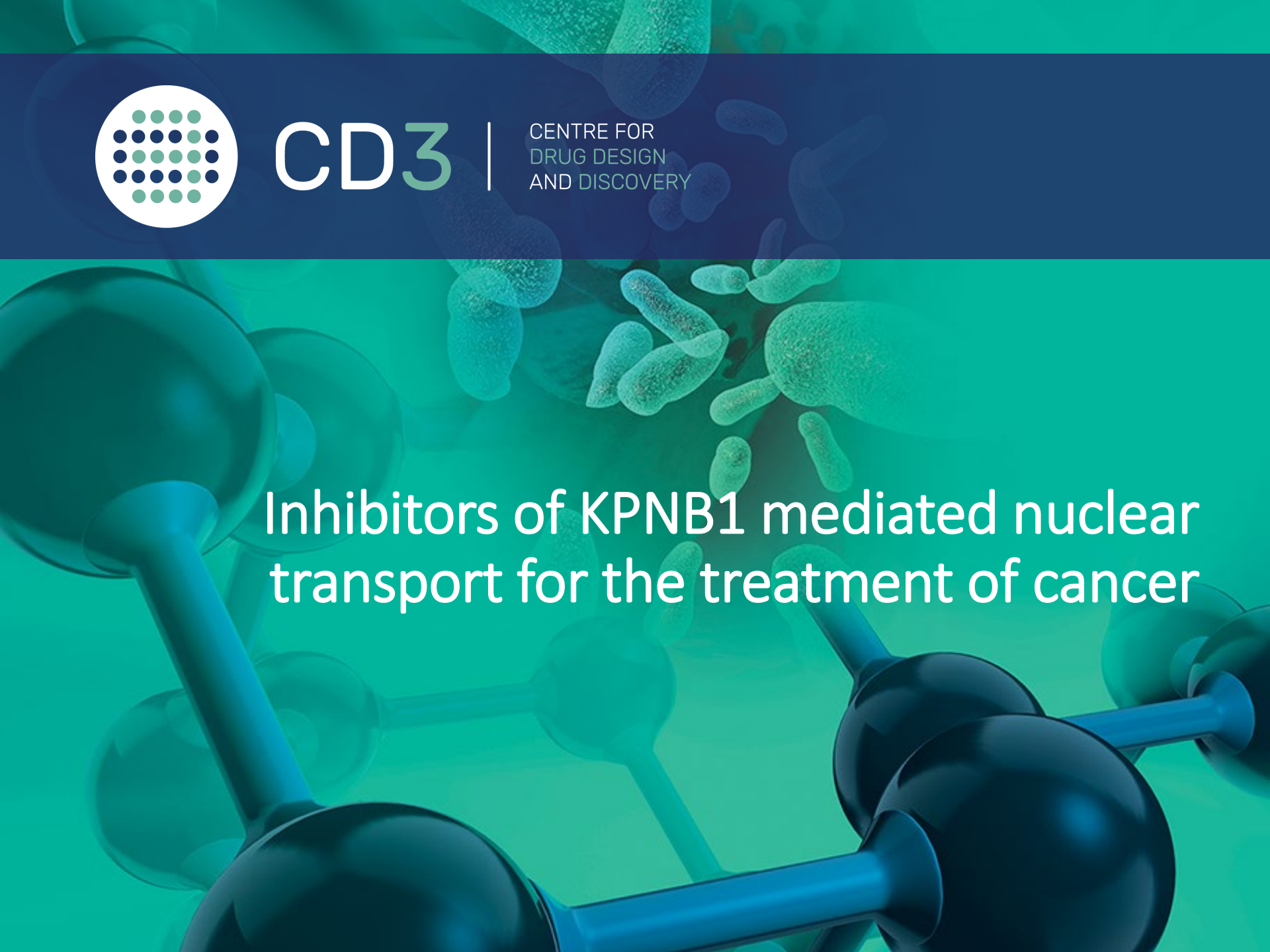
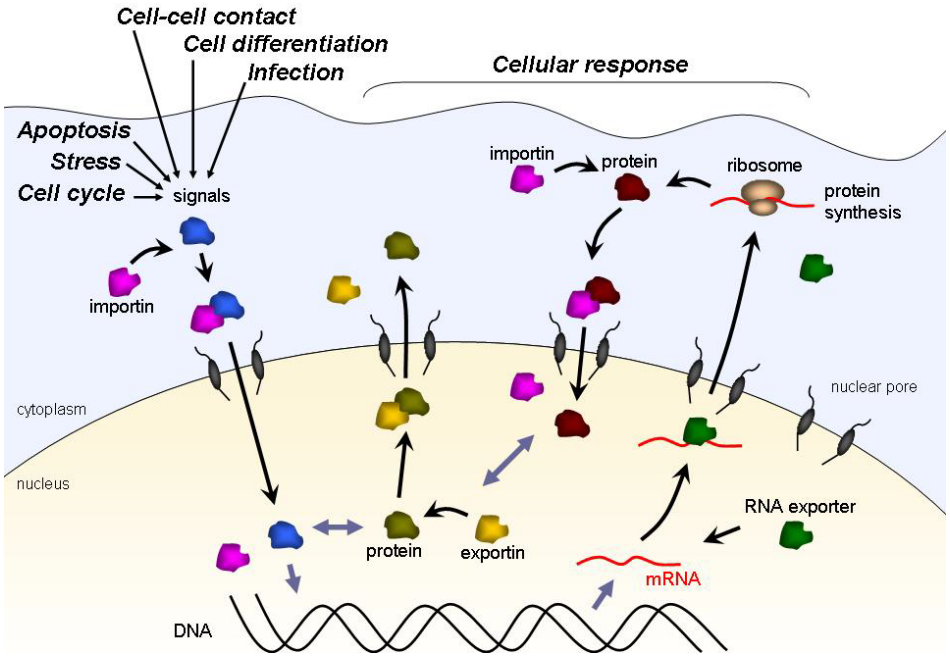
Inhibitors of KPNB1 mediated nuclear transport for the treatment of cancer



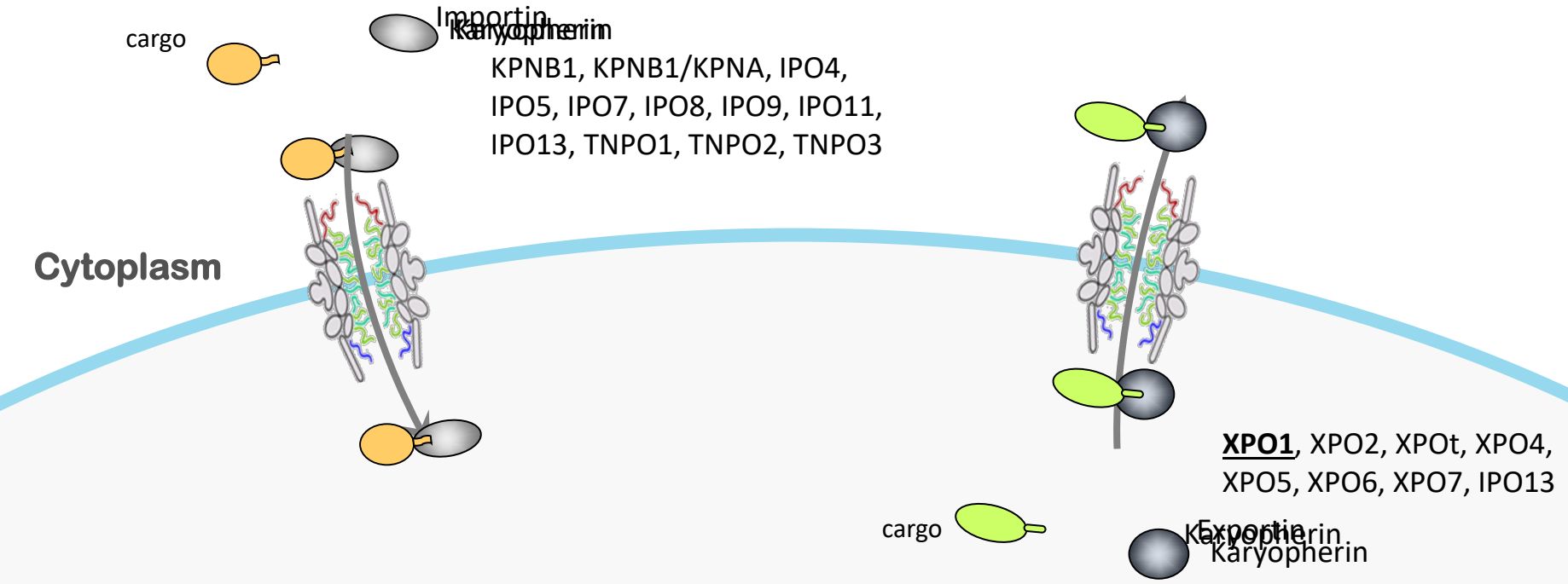
What is nuclear-cytoplasmic transport?

- Correct nuclear-cytoplasmic transport across the nuclear membrane is key to normal cell function
- Several proteins transported between nucleus and cytoplasm display aberrant subcellular localisation upon disease



What is nuclear-cytoplasmic transport

- Nuclear-cytoplasmic is mediated by soluble carrier proteins (karyopherins)



State-of-the-art in cancer

- Elevated expression of diverse importins and exportins (KPNA2, KPNB1, XPO1, XPO2) has been documented in many different cancer cells

- Down-regulation of KPNA2, KPNB1 and XPO1 inhibits cancer cell proliferation (van der Watt *et al*., *Int J Cancer* (2009); Noetzel *et al*., *Oncogene* (2012); Huang *et al*., *Cell Death and Dis* (2013); Angus *et al*., *Carcinogenesis* (2014))

- Silencing of Ran induces apoptosis in lung and breast cancer cells and down-regulates Mcl-1 (Yuen *et al*. 2012)

- First validation of XPO1 inhibition by small-molecule inhibitors show high promise
  - **KPT-330 (Selinexor)**

Selinexor: FDA Approved July 3rd 2019

Karyopharm Therapeutics

KU LEUVEN

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Home > News > FDA approves new cancer drug associated with KU Leuven discovery

FDA APPROVES NEW CANCER DRUG ASSOCIATED WITH KU LEUVEN DISCOVERY

The Food and Drug Administration in the United States of America has approved XPOVIOTM (also known as selinexor), a medicine for patients with relapsed refractory multiple myeloma, a type of bone marrow cancer. Around 230,000 people worldwide suffer from this rare disease. Selinexor was developed by Karyopharm Therapeutics Inc. based on inhibitors discovered at KU Leuven.

Multiple myeloma is a cancer of plasma cells. Plasma cells are white blood cells that produce antibodies to defend the body against infections. The disease usually occurs in people over 60 years old. There are several treatment options to control the cancer and prolong the life of patients, but multiple myeloma is as of yet incurable.

Myeloma patients with disease that is refractory to the most effective, currently available treatment options typically have a life expectancy of just three to five months. Results from a clinical trial demonstrated that patients with highly refractory multiple myeloma who were treated with oral selinexor lived over eight months, on average. Patients who responded to selinexor lived, on average, over fifteen months.

Selinexor inhibits Exportin 1 (XPO1 or CRM1), a protein that is responsible for the transport of other proteins from the cell nucleus to the surrounding cytoplasm. These include proteins that suppress the growth of tumors. If these proteins are not present in the cell nucleus, they cannot perform their function. Inhibitors of XPO1 restore the localization of these tumor suppressing proteins, causing cancer cells to regress.

Professor Dirk Daelemans discovered XPO1 inhibitors in collaboration with Professor Christophe Pannecouque, both working at the Laboratory of Virology and Chemotherapy at the Rega Institute, and with Professor Wim Dehaen of the Department of Chemistry, and in 2011 signed a collaboration agreement with Karyopharm Therapeutics, which was developing XPO1 inhibitors.

"We discovered these inhibitors while studying the transport of viral genetic material of HIV in infected cells", explains Professor Daelemans. "Inhibiting XPO1 turned out to be less appropriate for the treatment of HIV infections, but it is of use for cancer. This is an excellent example of how we can use our knowledge about viruses in the treatment of other life-threatening diseases. Selinexor is the first drug of its kind to be approved by the FDA. We are very happy about the collaboration with Karyopharm and the tremendous amount of work they have done to develop this medicine. Many patients can now be helped as a result of their work."

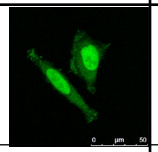
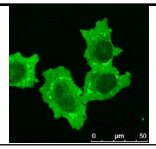
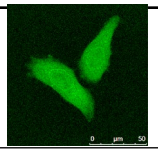
iKAP
Targeting nucelo-cytoplasmic transport - import

Discovery and validation of novel therapeutic **targets** in nuclear transport pathway

Drug discovery:
development of **compounds** with *in vivo* proof-of-concept

Identification and validation of **biomarkers**
for patient selection

Overview of phenotypic hit series

	Series 21	Series 22
Phenotype KPNA2-mNeongreen 		
Best EC_{50} KPNA2-mNeonGreen	• 2 µM	• 0.2 µM
MedChem - SAR	• Multiple active compounds within series • Activity requires "warhead"	
Biophysical characterization	• **Direct impact on KPNB1 (TSA, MST)** • **Covalent binding**	• No direct impact on KPNA2/KPNB1 detected
Cargo translocation	• Affects known KPNB1/KPNA2 cargos, e.g. cMYC, RelA, Smad2 • KPNB1 interactome	• Effect on KPNB1/KPNA2 cargos
Selectivity KPNAs	• Multiple KPNA's (NOT KPNA7)	• Mainly KPNA2 & KPNA7
Other Karyoph	• No impact on TNPO1, XPO1	• No impact on TNPO1, XPO1
Phenotype	• **Broad anti-cancer**	• No anti-cancer or anti-viral activity • No cellular toxicity • **Selective impact on Th17 dependent B-cell activation -**
Other	• robust activity vs. cytotoxicity window	• Probe cpd synthesized • Target identification ongoing

Phenotypic importin cargo assay (hTERT)

- IPO7 cargo assay: hTERT (telomerase)
  - Nuclear hTERT essential for unlimited replicative life-span, a hallmark of multiple cancers
  - Mutational activation of hTERT in several solid cancers, not expressed in normal cells
  - Direct targeting of hTERT with small molecules not tractable (1 oligo in clinical development)
  - Nuclear translocation assay developed and miniaturised
  - Pilot screen ongoing