SPEXIS

Macrocycle Therapeutics for Oncology & Rare Disease

August 2024

Non-Confidential

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Spexis AG (SIX:SPEX)

Life-Changing Macrocycle Therapeutics for Rare Disease & Oncology Patients

Macrocycle focus:

- Extensive macrocycle platform with both peptidic & non-peptidic libraries
- 20+ years leadership in fully synthetic macrocycle chemistry enabling unparalleled flexibility & optimizability of macrocycle-conjugates
- 3 in-house macrocycle products taken into clinical thus far, two through P3
- Significant radioconjugate & drug conjugate potential

Balixafortide:

- Best-in-class CXCR4i
- 8 clinical trials in >500 subjects to date
- **Now under P1b/2a development for pancreatic cancer**

Inhaled Murepavadin:

- Novel OMPTA-antibiotic
- 9 i.v. clinical trials in ~290 subjects to date
- **Positive P1 CF trial data reported in Jan 2023**

Lonodelestat:

- Best-in-class neutrophil elastase inhibitor
- **Phase 2 ready**

Excellent value growth potential:

- Assets highly de-risked
- Multiple clinical shots-on-goal
- Cutting-edge macrocycle platform
- **Strong PoC data generated on macrocycle drug conjugate (MDC) & macrocycle radio-conjugate (MRC) as next-gen alternative to ADCs**

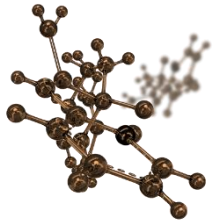
IMI – Innovative Medicines Initiative (EU research initiative)

The Spexis Story:

~20 Years & $400M Invested in Developing & Validating World-Class Macrocycle Libraries & Products

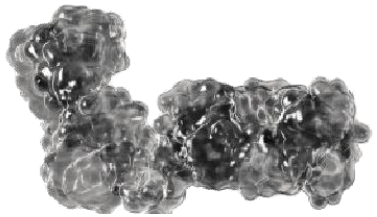
Most therapeutics are either:

Small Molecules



~90% of drugs
Potent but inflexible

Biologics



e.g. vaccines, antibodies
Difficult to scale, modify

SPEXIS

100 – 500 molecular weight
Small Molecules

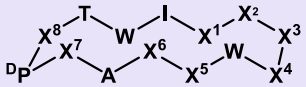
10k – 200k molecular weight
Biologics

Macrocycles possess advantages of BOTH classes:

- **Can hit difficult drug targets** inside & outside cells
- Unique drug-like profiles: favorable PK/PD, oral bioavailability, good stability & cell permeability

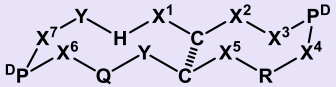
Example Spexis Macrocycles
500 - 2'000 MW

Thanatins



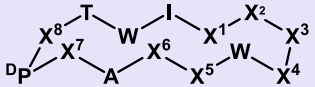
Acquired by
CARB-X
basilea PHARMACEUTICA

Balixafortide



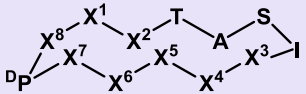
P3 Trial, licensed by
FOSUN PHARMA

Murepavadin



P3 Trial
CYSTIC FIBROSIS FOUNDATION
imi innovative medicines initiative

Lonodelestat



P2-ready

Pharma Interest in Macrocycles is Increasing:

Spexis is Uniquely Positioned to Take Advantage

News

https://doi.org/10.1038/d41573-023-00152-3

Macrocycle drugs serve up new opportunities

mid-sized cyclic peptides and stapled peptide therapeutics.

Drug developers expect that the cyclic structure of these molecules can confer medicinal chemistry pay-offs – offering the exquisite potency and selectivity of antibodies, with the dosing and target space opportunities of small molecules. Medicinal chemists are already embracing the 'beyond Rule of 5' space, and macrocycles show just how far they can bend these guidelines.

"Looking at the structure, it's amazing

nature reviews drug discovery

Volume 22 | October 2023 | 771–773 | 771

nature reviews
2023

Merck & Co. signs $220M macrocyclic peptide deal after hailing 'next wave of drug discovery'

By James Waldron · Jan 23, 2024 9:00am

Startup Orbis Medicines Launches With €26M for Next-Generation Peptide Drugs

Orbis Medicines is developing macrocyclic peptides that address a wider range of targets and can be taken as oral pills. Novo Holdings and Forbion are backing the startup, which is based on research from the scientific co-founder of peptide drug developer Bicycle Therapeutics.

By FRANK VINLUAN

Post a comment / Feb 29, 2024 at 5:00 PM

Genentech sees more potential in peptides, signs $1B biobucks deal with PeptiDream

By James Waldron · Sep 20, 2023 7:14am

Spexis Pipeline: Robust, Late-Stage, De-Risked, Validated

Potential for Significant Near-Term Value Generation

	Program	Research	Preclinical	Phase 1	Phase 2	Phase 3	Partnership / Funding
Oncology/ Rare Disease	**Balixafortide**	Pancreatic ductal adenocarcinoma (PDAC)					FOSUN PHARMA
Neutrophil Elastase Inhibition	**Lonodelestat**	Multiple respiratory indications					CYSTIC FIBROSIS FOUNDATION; imi innovative medicines initiative
Cystic Fibrosis & nCFBE	**Murepavadin IV**	Potential in priority AMR indications					
	Murepavadin Inhaled	nCFBE					
Macrocycle platform	Anti-infective program (CARB-X sponsored), acq by Basilea Macrocycle-Drug Conjugates (MDCs) Macrocycle-Radio Conjugates (MRCs)						CARB-X Combating Antibiotic-Resistant Bacteria; basilea PHARMACEUTICA

CF – cystic fibrosis; nCFBE – non-CF bronchiectasis

Spexis Macrocycles:
Validated Clinically & Via Partnerships

- **PEMFinder®:** Highly diverse & well-characterized bioactive **peptide** library **(~30k)**
- **MacroFinder®:** Scaffold-rich **small molecule-like** macrocycle library **(~20k)**
- **25 yrs & >$400M R&D investment to date**

Compound (aa)	Indication	Target family	Stage	Partner
Balixafortide (16)	Oncology	GPCR; CXCR4	P3	FOSUN PHARMA
Murepavadin (14)	Antibiotic	b-barrel protein	P1 completed	CYSTIC FIBROSIS FOUNDATION; imi innovative medicines initiative
Lonodelestat (13)	CF; NCFB	Serine protease	P1 completed	
Thanatin analogues	Antibiotic	b-barrel protein	Preclinical	basilea PHARMACEUTICA; CARB-X
SPX6926/7174 (6)	Oncology	GPCR; CXC-CK	Preclinical	
SPX7200/7178 (16)	Conf.	GPCR	Preclinical	
SPX7085/7172 (6)	Oncology	GPCR; chemokine	Preclinical	

Spexis' Macrocycles

Validated on Many Target Classes

- **PEMFinder®:** Highly diverse & well-characterized bioactive **peptide** library **(~30k)**
- **MacroFinder®:** Scaffold-rich **small molecule-like** library **(~20k)**

Target Family List Screened for PEMFinder/Macrofinder:

1. **GPCRs:** CXCR4 [1][2]; CXCR7[3]; CCR10[4]; FPR1[5] (there is published material for all of them); others
2. **Enzymes:** Serine proteases: human Neutrophil elastase (HNE)[1]; Cathepsin G; Tryptase; others. Cystein proteases: Caspase 1
3. **β-Barrel proteins (Gram-negatives):** BamA[6]; LptD/E[7]; LptA [8]
4. **LRPs (low-density lipoprotein receptors)**
5. **Checkpoint inhibitors**
6. **Integrins**
7. **Receptor tyrosine kinases**

Refs. [1] A. Luther et al. Curr. Opin. Chem. Biol. 2017, 38 :45-51 ; Review; [2] S. J. DeMarco et al. Bioorg. Med.Chem. 2006, 14, 8396-8404; [3] A. K. Azab et al. Blood 2014, 124, 1905-1914; [4] F. Daubeuf et al. Resp. Res. 2025, 16:77; [5] Q. Zhang et al. Nature, 2010, 484, 104-107; [6] A. Luther et al. Nature 2019, 576, 452-458; [7] N. Srinivas et al. Science 2010, 327, 1010-1013; [8] M. Schuster et al. Sci. Adv. 2023, 9, eadg 3683

Spexis vs Macrocycle Competitors

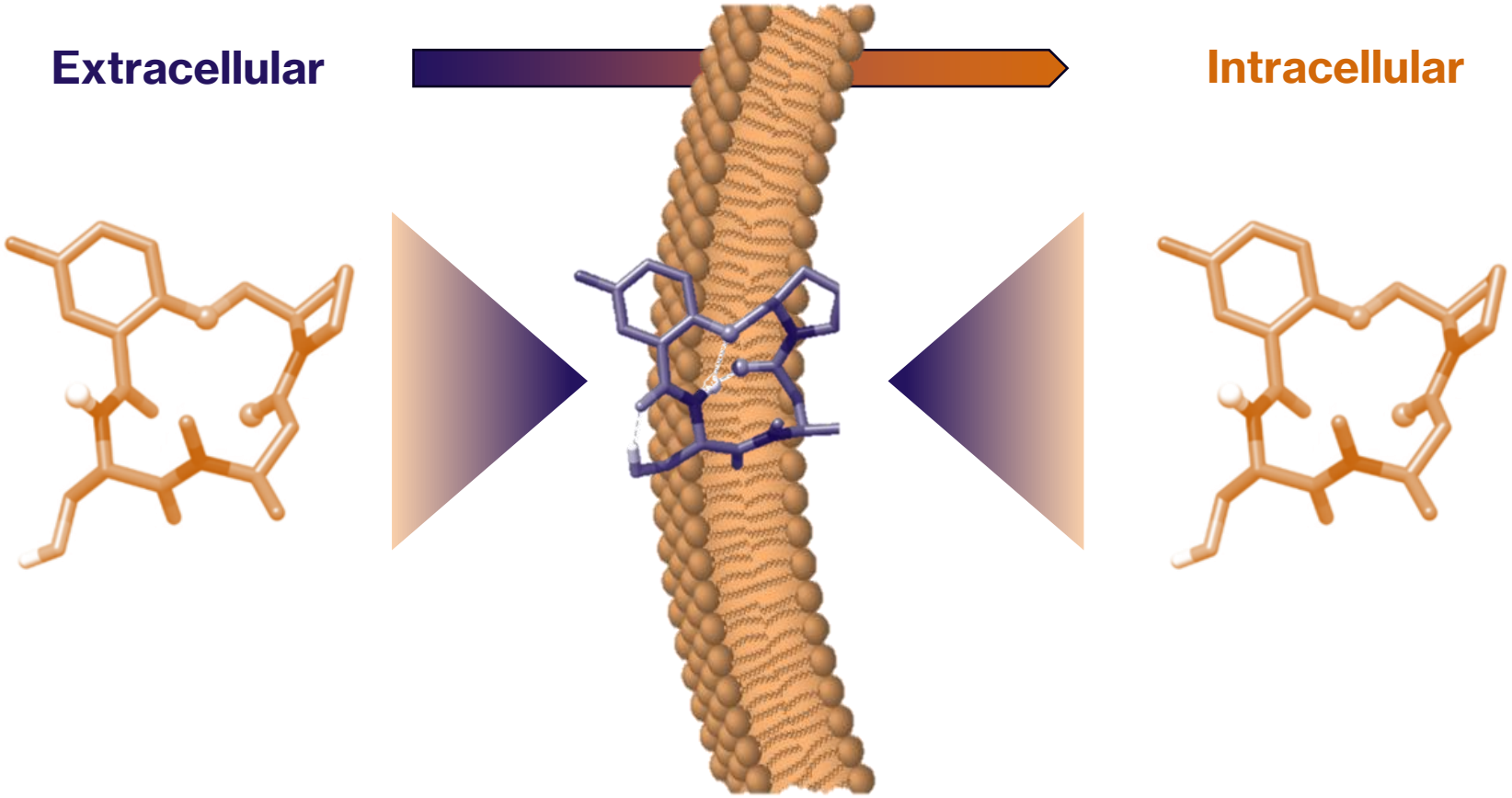
- Spexis is not the only company pursuing macrocycle-conjugation approaches but a**ll macrocycles are not created equal**
- Modern macrocycles are engineered by either biosynthetic or fully synthetic chemistry-based approaches
- Competitive MDC programs largely use biosynthesis

PeptiDream MERCK bicycle therapeutics

- For engineering drug conjugates, **fully synthetic chemistry has critical advantages**
  - Biosynthetic hits often very hydrophobic, large macrocyclic peptides with limited optimization potential (low cell permeability & limited oral bioavailability)
  - **Synthetic chemistry enables smaller, more optimizable hits**
- Spexis has **25+ years experience** in macrocycle synthetic chemistry, with multiple macrocyclic clinical candidates advanced through P3 trials

Library Scaffolds Designed w/ Conformational Chimerism

That Significantly Enhances Intracellular Receptor Targeting

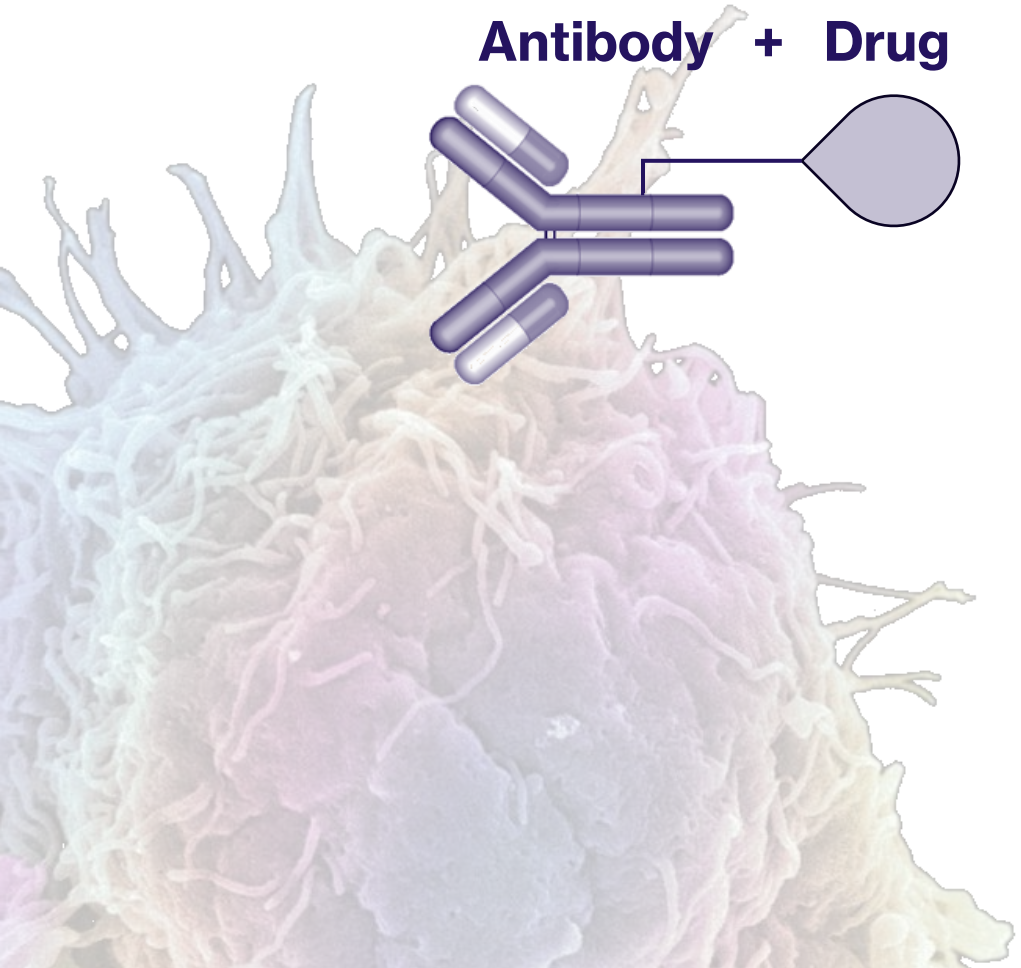


Chimeric macrocycles have demonstrated oral bioavailability: F >25%

Macrocycle-Drug Conjugates (“MDCs”)
Macrocycle-Radioconjugates (“MRCs”)

Antibody-Drug Conjugates (ADCs):

Massive Recent Partnering Activity Despite Limitations



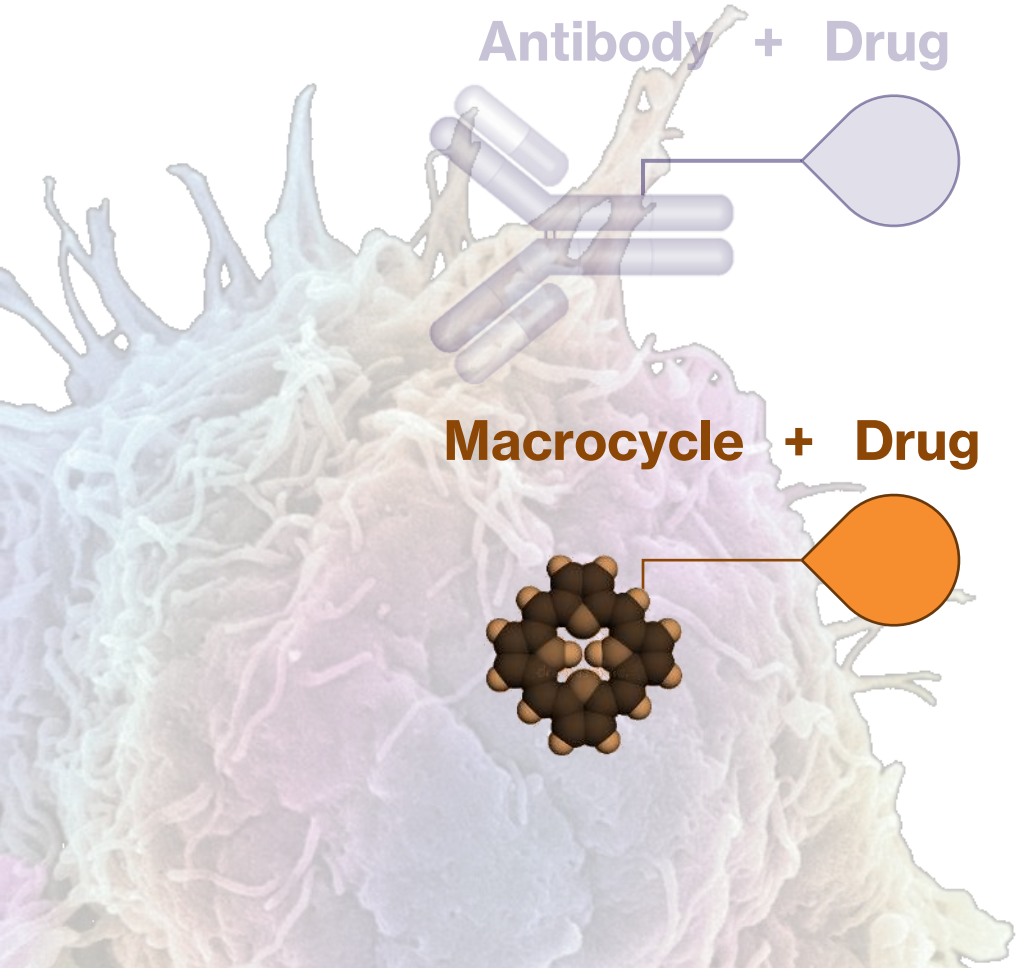
- ADCs join anti-cancer drugs to targeting antibodies for better specificity
- 20+ ADCs approved, most in last 5 yrs
- Already ~$10B market, growing 10% YoY

BUT

- Antibodies are large, complicated proteins
- Poor tumor penetration (1%)
- Off-target toxicity common (AEs)
- Difficult to engineer, produce, scale

Our Macrocycle Drug Conjugates ("MDCs")

High Specificity for Difficult Targets (Including GPCRs)

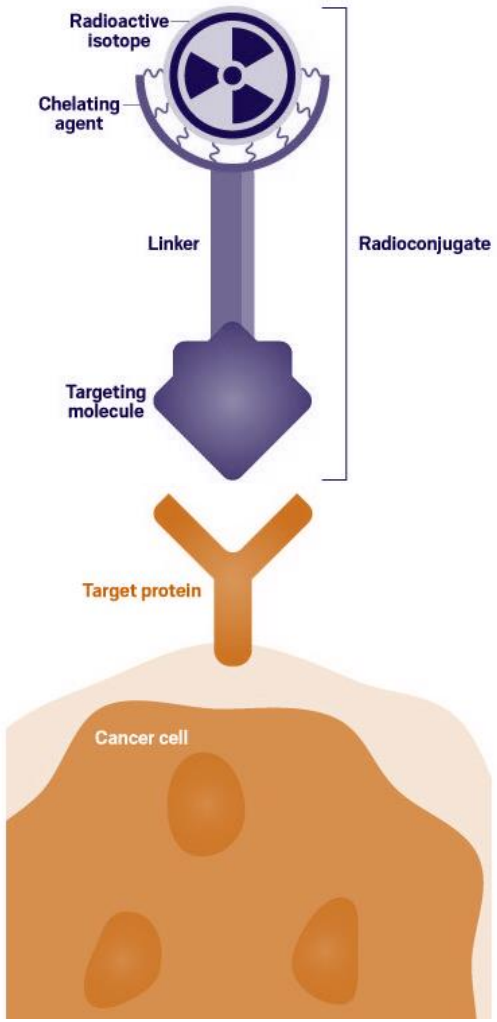


- Targeting advantage over antibodies & competitive biosynthetic macrocycles
- Drug-like, cell permeable, & orally bioavailable
- **Broad payload flexibility:**
  - Cytotoxic drugs
  - Macrocycle-radio conjugates ("MRCs")
  - Protein degraders
- Vs ADCs, MDCs will have:
  - Better tissue penetration
  - More efficient internalization
  - Designable with synthetic chemistry
  - Far better stability in solution & in vivo
- **PoC study data available under CDA**

Spexis Macrocycle Radio Conjugates ("MRCs"):

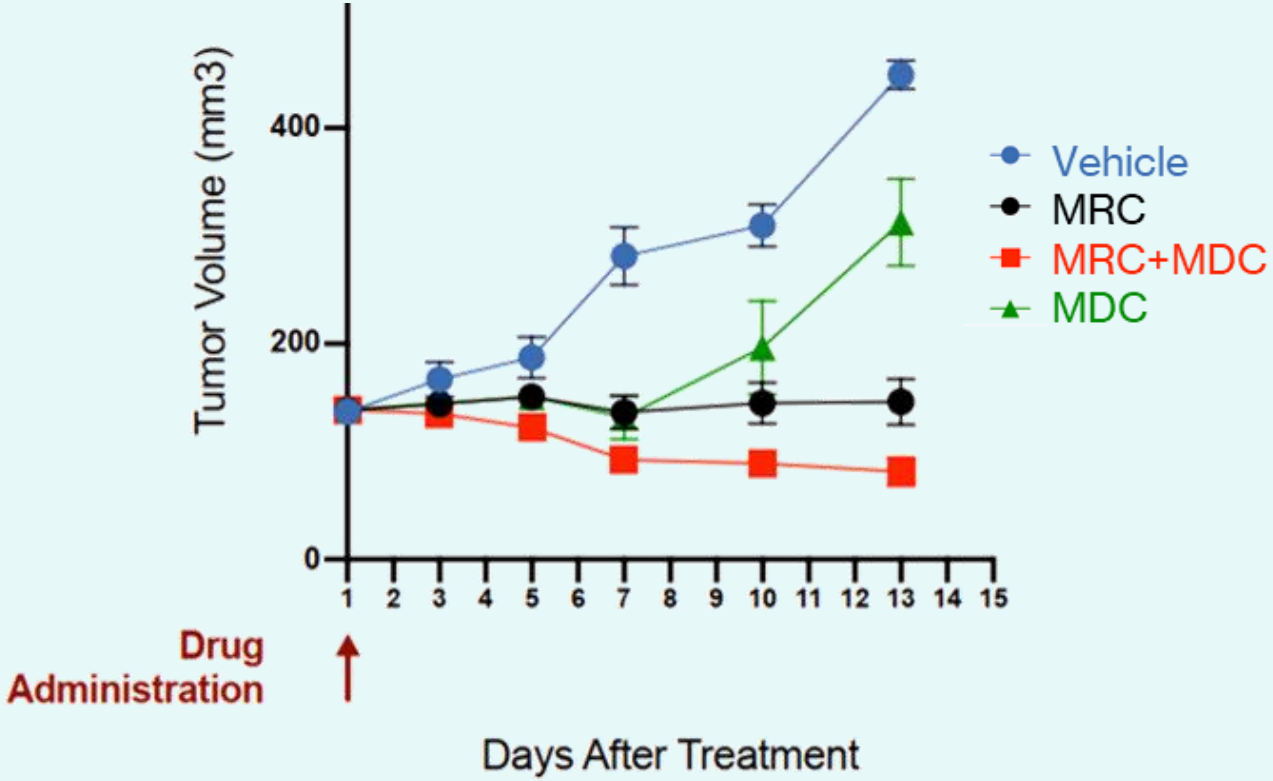
An Advance in Radio-Conjugation

- Most current radio-conjugates: antibodies as targeting elements
- Therefore suffer from same limitations seen in ADCs:
  - Off-target effects from radiation potentially oncogenic
  - Limited penetration/internalization: radiotherapy delivered intracellularly potentially boost therapeutic effect
  - Potential for immunogenicity and slow pharmacokinetics
- Spexis macrocycle library offers validated, highly-optimizable targeting elements, flexibility for different binders
- **PoC study data available under CDA**



Anonymized Efficacy Study: Synergistic Effect w/ MDC + MRC

MDC & MRC PoC Study Results



- Performed in gold-standard mouse model
- Both MDC & MRC alone reduced tumor growth compared to vehicle
- Combination therapy led to reduction in tumor volume
- Additional experiments, details shareable under CDA

MDCs/MRCs vs Other Targeted Therapies

MDCs/MRCs find "sweet spot" between specificity of drug-conjugates and stability + reach of macrocycles

	ADCs	MDCs/MRCs	Single-Agent Macrocycles	RDCs / PDCs
Clinically Validated	++	+	++	++ / -
Off-target AEs	**High**	Lower	Low	**High** / Low
Tumor Penetration	Low	**High**	**High**	Low
Tumor Specificity	**High**	**High**	Low	**High**
Production Difficulty	**High**	Lower	Low	Low / **High**
Scalability	Difficult	**Easier**	**Easy**	Difficult
In Vivo Stability	Low	**Better**	**High**	**Better**

ADCS: antibody-drug conjugates
MDCs: macrocycle-drug conjugates
MRCs: macrocycle-radioconjugates
RDCs: radio-drug conjugates
PDCs: peptide-drug conjugates

Key MDC/MRC Validation To Date & Next Steps

- Highly-characterized Spexis macrocycle conjugated to well-validated drug payload demonstrated proof-of-MDC-principle in two gold-standard animal models
- Macrocycle-radioconjugate (MRC) PoC study results also available
- Validated binding & killing of cancer cells *in vitro*
- Promising 1 hr tumor uptake *in vivo* (~8% I/D g)
- Plasma stable linkers conjugated to well-validated cancer-specific drug
- **IP strategy & status:**
  - Novel structures & binding mode
  - Proprietary linkers & conjugation methods
  - Non-patented trade secrets

Significant Spexis R&D Infrastructure:

Proven & Partner-Ready

- ~4000 m2 of lab space
- State-of-the art equipment & labs to support up to ~100 researchers
  - Acquisition cost >CHF 7M
  - Notable equipment includes:
    - 3 mass spectrometers
    - 2 microplate handlers
    - 5 peptide synthesizers
    - Full air handling & safety setups
    - Centrifuges, sample prep equipment
  - Full equipment list available
- Scientific leadership w/ 25+ years in macrocycle drug discovery, preclinical & clinical development

Balixafortide

Balixafortide: Potent CXCR4 inhibitor

Applicable to wide range of oncology and rare disease indications

Balixafortide

- Potent, highly selective blocker of CXCR4
- CXCR4 involved in tumor growth, metastasis and a variety of rare diseases

Clinical proof of concept established

- >500 patients in 8 clinical trials
- Phase 3 study in advanced HER-2 negative breast cancer did not achieve primary endpoint due to dosing & trial design issues

Good safety and tolerability profile

- Well tolerated by i.v. route of administration
- No limiting safety events identified at top dose given (5.5mg/kg)
- Shown to overcome SoC drug resistance
- Compatible with combination therapies

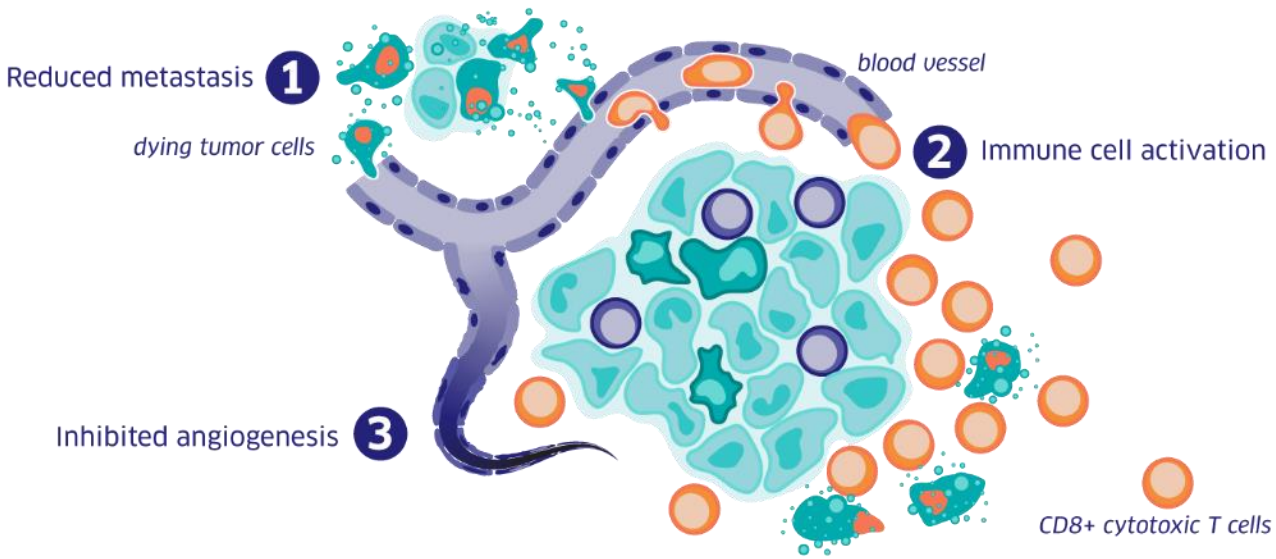
Pursuing new indications

- **Encouraging results of BLX + anti-PD1 in multiple animal models of pancreatic ductal adenocarcinoma (PDAC)**
- Also extensively profiled in animal models of stem cell mobilization, cancer, inflammatory and rare disease

Summary of CXCR4i Mechanisms

Anti-PD1

Balixafortide



CXCR4 Inhibition Results in:

1. Reduced Metastasis:

- Fewer tumor cells into the circulation, fewer metastases
- Inhibition of epithelial-to-mesenchymal transition
- Reduction of tumor stemness

2. Immune suppression › Immune cell activation:

- Reduction of immunosuppressive cells (e.g., Treg, MDSC, cancer-associated fibroblasts)
- Increase of tumor-eliminating cytotoxic T cells

3. Inhibited angiogenesis:

- Smaller and less blood vessels in the tumor leading to reduction of tumor blood supply
- Preventing entry of endothelial progenitor cells and differentiation

Pancreatic Cancer

Multi-Billion $ Indication w/ High Unmet Need

3rd leading cancer death (US)
Projected **2nd** by 2030[1]

~500k annual diagnoses ww[2]

~470k annual deaths ww[2]

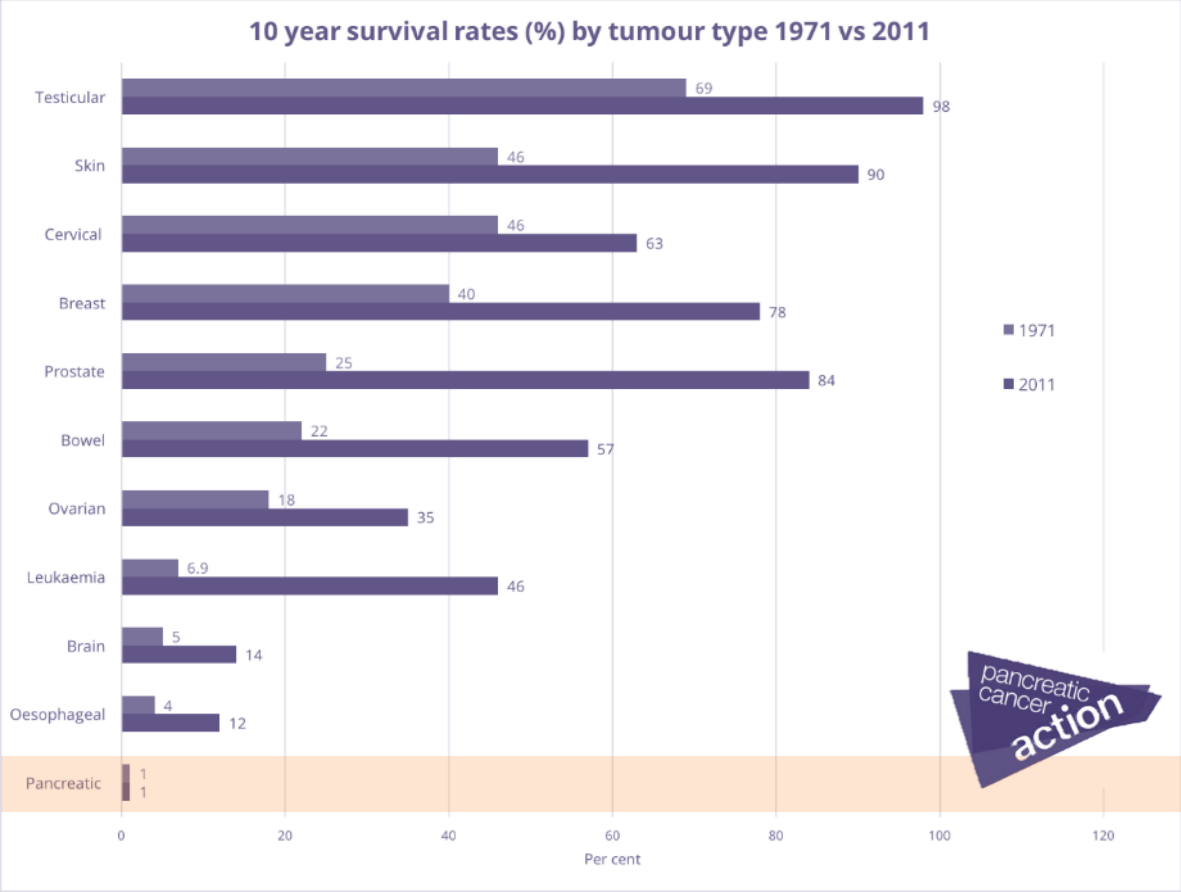
6% 5-yr survival for pancreatic ductal adenocarcinoma (PDAC)[4]

USD 6.85 Billion
projected market by 2029[3]

[1] Rahib L et. al, Estimated Projection of US Cancer Incidence and Death to 2040. *JAMA Netw Open*. 2021;
[2] World J Gastroenterol., Irena Ilic et al., 2022 Aug 28; 28(32): 4698–4715
[3] https://www.globenewswire.com/en/news-release/2023/02/20/2611273/0/en/Pancreatic-Cancer-Treatment-Market-Exhibits-15-7-CAGR-to-Hit-USD-6-85-Billion-by-2029.html
[4] Yushifumi Noda et al., Medical Imaging, 22, Article number: 23 (2022)

PDAC Patients Are Being Left Behind

In last 40 years, 10yr survival rates have dramatically improved for every cancer except pancreatic



Recently approved therapies (e.g. Abraxane) have increased 5-year survival only slightly (~12%)

[1] pancreaticcanceraction.org

Potential for Anti-PD1 in PDAC

Anti-PD1

Balixafortide

- PD-1 inhibitors have been most successful class of immuno-oncology agents
- Blocks mechanism by which many cancer cells suppress immune response

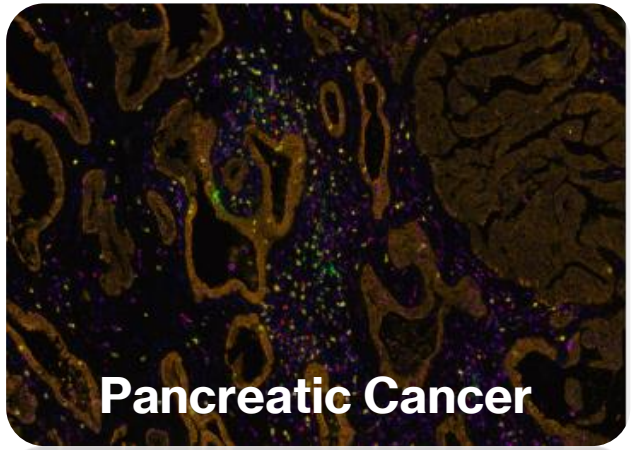
KEYTRUDA® (pembrolizumab) Injection 100 mg	2022 Revenues: **~$20.9B**	Approvals in melanoma, NSCLC, HNSCC, cHL, PMBCL, others
OPDIVO® (nivolumab)	2022 Revenues: **~$8.2**	Approvals in melanoma, NSCLC, KC, LC, CRC, melanoma, others
LIBTAYO® (cemiplimab-rwlc) Injection 350 mg	2022 Revenues: **~$445M**	Approvals in NSCLC, CSCC, BCC, others

- However, PD-1 inhibitors alone have not shown significant survival benefits in PDAC

[1] doi: 10.1016/B978-0-12-411638-2.00002-1

Immune Checkpoint Inhibitors (ICIs) Bring Survival Benefits,

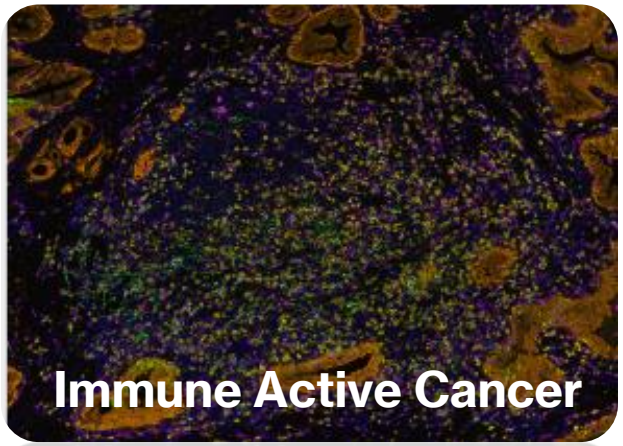
But Much Less Effective in PDAC to Date



⇦ PDAC has:

- Lower PD-1/PDL-1 expression (green)
- Lower CD8 expression (yellow)
- More FOXP3+ Treg cells (red)

Osipov Lab pending publication



Additional Issues with ICIs in PDAC[1]:

- PDAC is immunologically “cold” cancer: less T-cell infiltration, which ICI needs
- PDAC creates highly immunosuppressive tumor microenvironment (TME)
- PDAC often has dense stromal tissue barrier, acts as physical barrier

[1] doi: 10.1186/s12964-021-00789-w

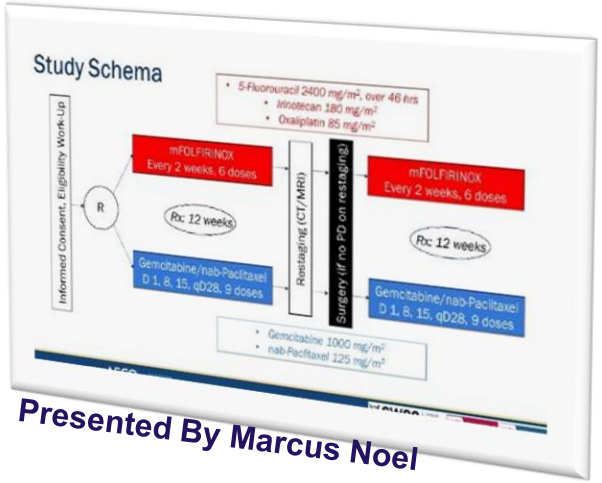
Potential for Anti-PD1 in PDAC

Anti-PD1

Balixafortide

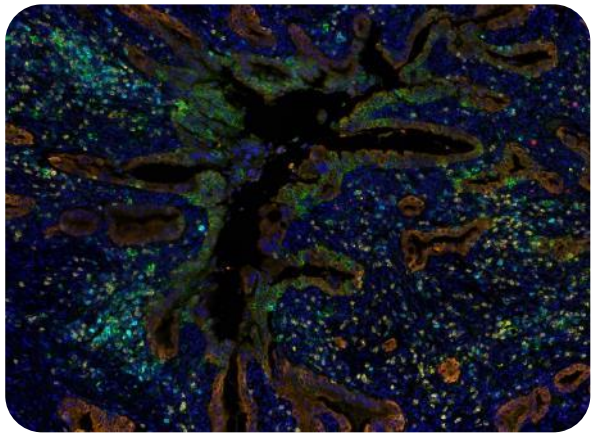
- However, recent studies suggest PDAC mutates to use PD-1 in response to chemotherapy

SWOG S1505: Results of Perioperative Chemotherapy with mFOLFIRINOX vs Gemcitabine/nab-Paclitaxel for Resectable Pancreatic Ductal Adenocarcinoma



Presented By Marcus Noel

- PD-L1 induction observed on tumor epithelium following neoadjuvant chemotherapy



Multiplex immunofluorescence staining of PDACs following neoadjuvant geme/abrax. CD 8 Yellow; FOXP3 Red; CD68 Magenta; PD-1 Cyan; PD-L1 Green; Keratin Orange; DAPI. Note that PD-L1 expression (in green) on tumor epithelium was induced following neoadjuvant chemotherapy

[1] doi: 10.1016/B978-0-12-411638-2.00002-1

Rationale for Balixafortide in PDAC

Anti-PD1

Balixafortide

- CXCR4 is an alpha-chemokine receptor specific for stromal-derived-factor-1 (SDF-1)
- CXCR4 overexpressed in 23 different solid tumor types, including pancreas[1]
- Data to date shows:
  - PDAC patient CXCR4 expression negatively correlates with overall survival
  - Exceptional responders to PDAC chemotherapy have lower CXCR4 expression
  - CXCR4 inhibition potentiates Anti-PD-1 therapies in animal models
- Hypothesis given above:
  CXCR4 could enable ICI treatment in PDAC

[1] doi: 10.1016/B978-0-12-411638-2.00002-1

Senior Leadership Team:
Significant Experience w/ Similar Value-Building

JEFF WAGER
Chair & CEO

- 30+ years VC, i-banking & CEO experience
- MSP (Havard VC fund): 30+ portfolio companies/$1B capital raised
- Spin-outs: Targacept (from RJR), Biocritica (Xigris®/Lilly), Artisan (from Asahi), others
- Co-founded Grupo Biotoscana SL: PE-backed, LATAM specialty pharma: $240M rev, $1B IPO
- Co-founded Spexis end-2021 via reverse-merger

CARL-ÅKE CARLSSON
New Board Member

- At Alpharma & Xellia: 5 company/product acquisitions ranging from $50m to $300m
- Acquired/integrated 2 US sterile injectable facilities
- CF domain: built leading supplier of CMS API globally, invested/chaired Pharmaero
- Led Xellia from an anti-infective API company to global specialty pharma company

MURIEL FLEMING
Chief Admin Officer & Acting CFO

- 14yrs experience supporting rapid organizational growth through M&A, Fundraising and Change Management
- Led global business integration (personnel, synergies & team build) thru Amgen's 2013 $10.4bn acquisition of Onyx Pharmaceuticals (US HQ, Swiss and UK branch) & AB InBev's 2016 £78.4bn acquisition of SABMiller (200 products, 70,000 employees in over 75 countries)

KHADIJA SCHWACH
Head of Corp Strat/BD

- 30 yrs leadership experience: previously Global head BD & M&A Life Sciences at PMI leading ~$2.5B in acquisitions (incl inhaled Tx Vectura, Otitopic)
- Created & integrated VecturaFertin Pharma for the life sciences arm of PMI. Established/grew sales & marketing ops in US & China from ground up
- Previously DSM Pharma, Head of BD at Novozymes

DANIEL OBRECHT
Acting CSO

- Key figure in macrocycle chemistry & drug development
- Polyphor Co-founder (1996-2021)
- Ex-head, Roche combinatorial chemistry
- 11 years @ Roche Basel Central Research Laboratories
- 68 publications & 35 patents, incl key patents on PEM & Spexis products incl balixafortide, murepavadin, etc

GONCALO BERNARDES
Head, Chem Bio

- Prof. of Translational Chem, University of Cambridge, 25-member lab, 2nd lab at IMM
- >$7.5M research funding (Royal Society URF/ERC)
- >150 publications (e.g., Science, Nature, Nature Chemistry, Nature Communications)
- Senior Fellow @ Flagship Pioneering, 2 cofoundings
- Took ADC product from bench to clinic through P2

Spexis Executive Management
& Board of Directors

Jeff Wager, MD CEO & Chairman	**30 yrs VC & CEO leadership;** **>$2.5B in value created since 2000**	GBT, artisanpharma, Zambon, Apeiron, Medical Science Partners
Muriel Fleming CAO & Acting CFO	14yrs experience supporting rapid organizational growth through M&A, Fundraising	AMGEN, ABInBev
Daniel Obrecht, PhD Acting CSO	Key figure in history of macrocycle chemistry & drug development	POLYPHOR, Roche
Goncalo Bernardes, PhD Head of Chemical Biology	Leading chemical biology researcher & successful company founder	University of Cambridge, MM, Flagship Pioneering
Dennis Ausiello, MD Vice Chair of the Board	**17yrs Physician-in-Chief, MGH** **8 yrs lead director of the Pfizer board**	Seres Therapeutics, Alnylam Pharmaceuticals, Pfizer, MGH, Massachusetts General Hospital
Kuno Sommer, PhD Director	Former CEO, Berna Biotech (acq. by J&J) Chairman Bachem, Sunstar, Targimmune, more	BACHEM, kenta biotech, Sunstar, TargImmune Therapeutics
Robert Clarke, PhD Director	20+ yrs inhaled R & D and CEO experience	KINASET THERAPEUTICS, pulmatrix, Alkermes
Dan Hartman, MD Director	25+yrs R & D leadership; Head of $2B Gates malaria R & D portfolio	Bill & Melinda Gates foundation, deCODE genetics, Pfizer, Lilly
Bernard Bollag, MBA Director	Senior finance executive across corporate finance & capital markets	syngenta, UNISYS, HomeSun Power from Partnership

SPEXIS

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