CriPec® Nanomedicines for Superior Therapeutic Performance

Dr. Cristianne Rijcken, founder and CSO

8 April 2018

Introduction

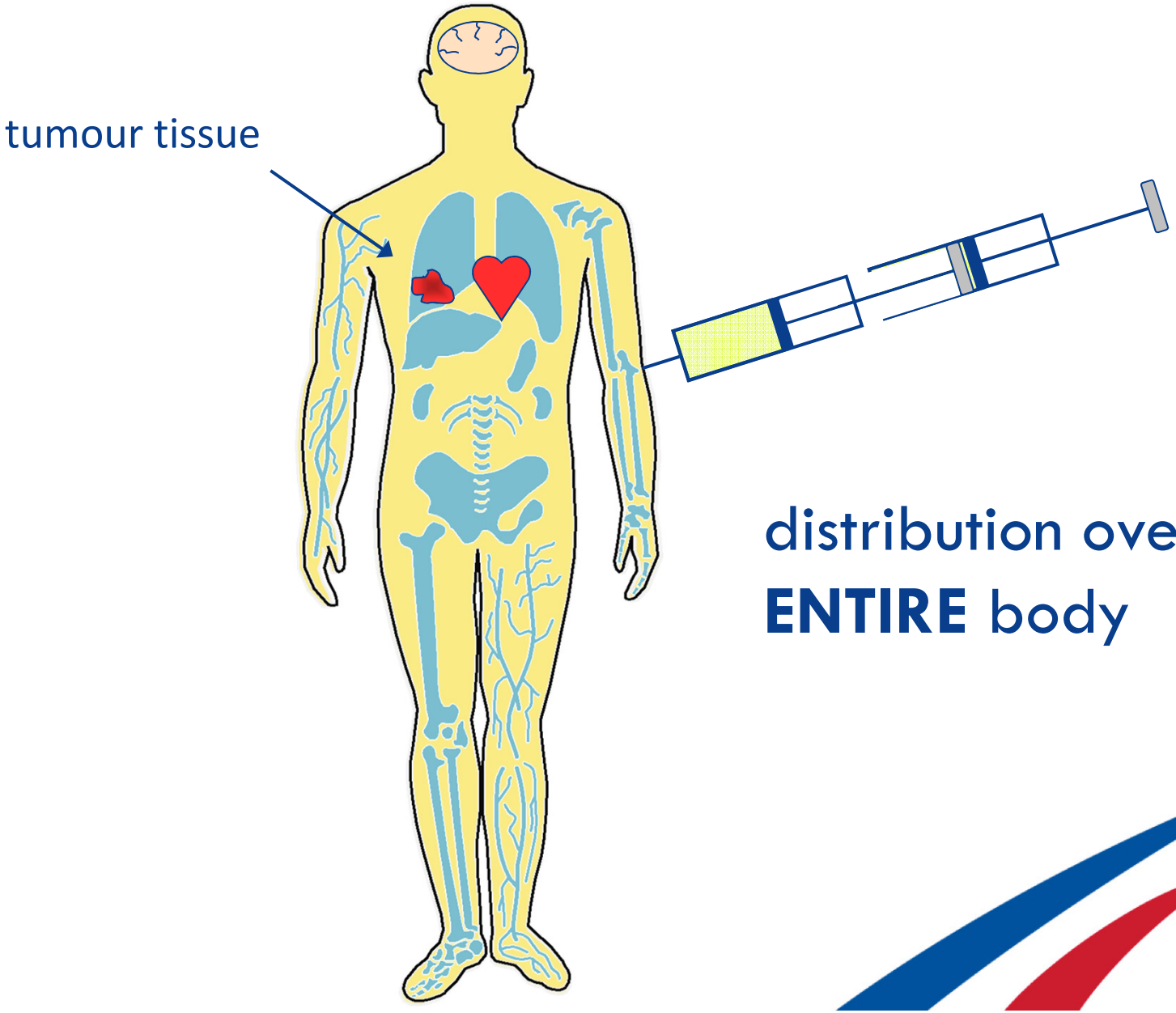
- Pharmaceutical company developing nanomedicines
- Founded in April 2011 in Utrecht
- Since October 2013 located in Maastricht

Experienced Management

- Dr. Joost Holthuis (CEO and co-founder, former CEO/founder of OctoPlus)
- Dr. Cristianne Rijcken (CSO and founder)
- Dr. Jeroen Tonnaer (CBO, former Executive Director, Worldwide Licensing, Merck Sharp & Dohme)
- Dr. Istvan Udvaros (Former Medical & Project Director Oncology at SGS Clinical Research)

Antitumour Drugs

Cristal Therapeutics



distribution over
ENTIRE body

Current Need in Oncology

Toxicity of chemotherapeutics to healthy cells

⇨ side effects ⇨ restrict dose ⇨ therapeutic effect ⇩

⇨ **Risk-benefit ratio is to be improved**

Solution: Entrapment drugs in nanoparticles

From Finding To Spinoff

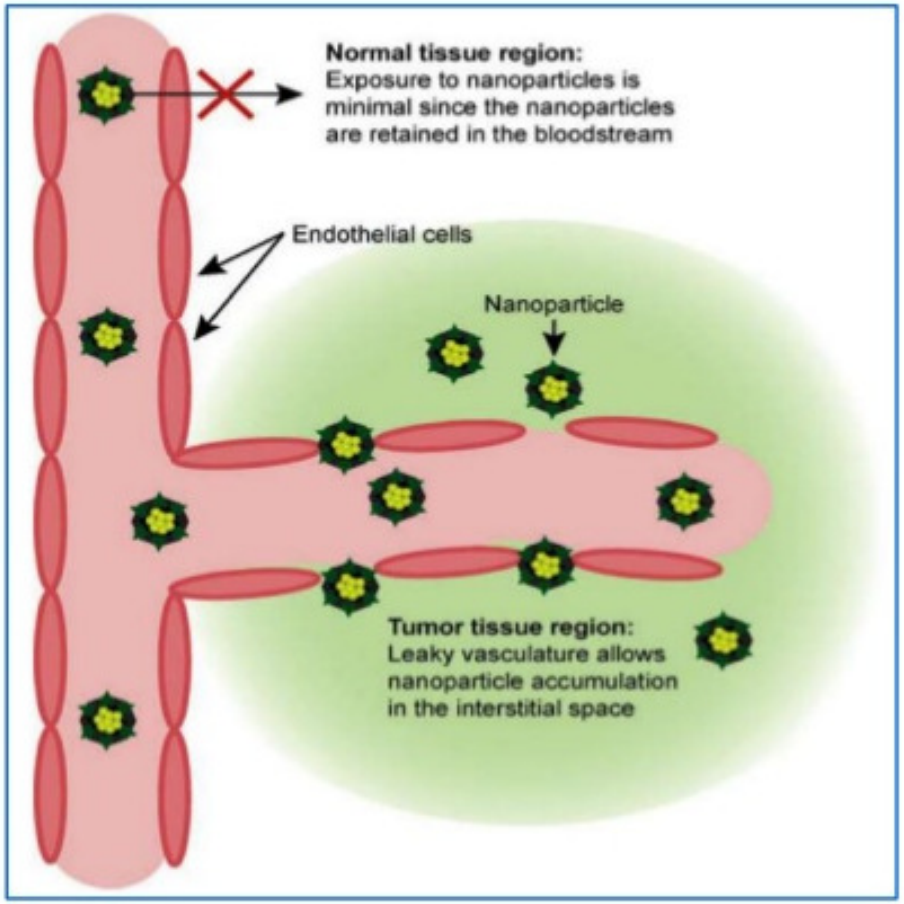
Start PhD
2003

Thesis
2007

Grants & awards
2007 - 2011

Establishment Cristal
Delivery B.V.
11-4-2011

CriPec® Nanoparticles in Oncology

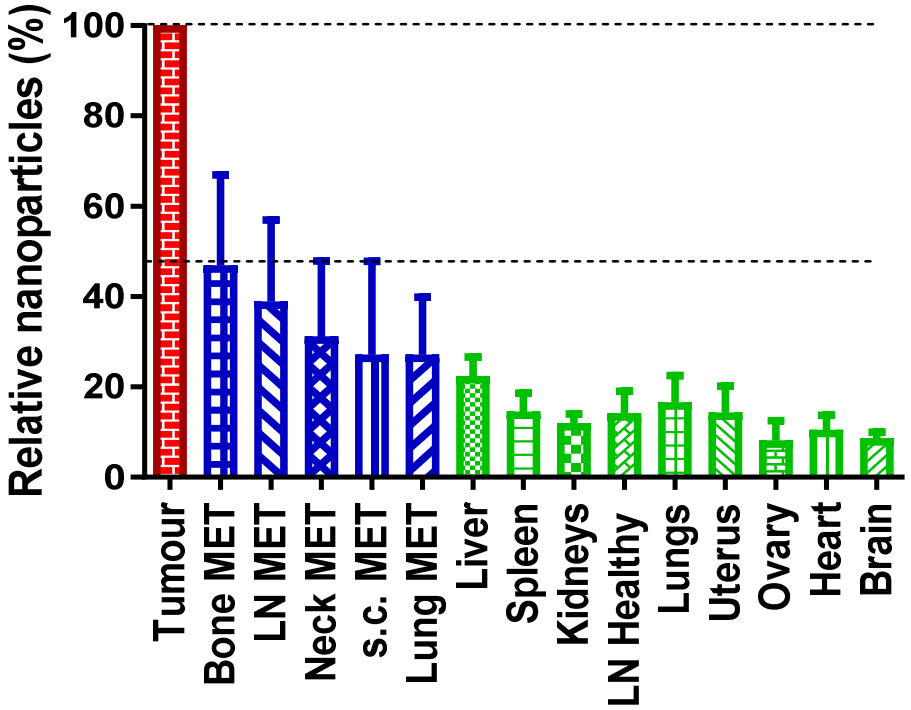


EPR: enhanced permeability and retention

- **Increased therapeutic index** via entrapment of drug in CriPec® nanoparticles
- Enhanced accumulation of CriPec® nanoparticles in tumour tissue, followed by sustained release in time = **increased efficacy**
- Drug is inactive as long as entrapped in CriPec® nanoparticle; less drug exposure to normal tissue = **improved safety**

CriPec® EPR Tumour Targeting

Biodistribution metastasising breast cancer in mice



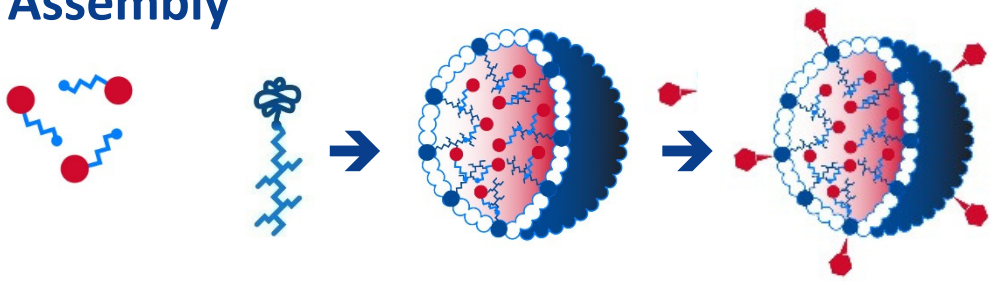
Accumulation upon i.v. administration of CriPec® nanoparticles:

- Significant uptake in primary tumour, metastases and metastasized lymph nodes
- Modest uptake in normal lymph nodes, bladder, lung and kidney

Advantages CriPec® Platform

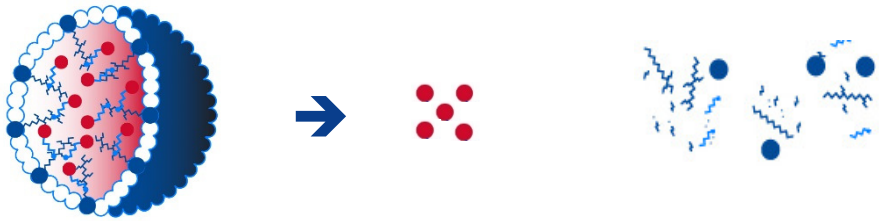
Rational design & ease of manufacturing

Assembly



Drug-Linker Polymer CriPec® Nanoparticle Targeted CriPec®

Release and Degradation



Nanoparticle Released Drug Degraded Polymers

- **Tailor made nanoparticle size between 30 to 100 nm (PDI< 0.2)**
- **Tuneable release covalently bound drug (hours till days)**
- **1 Step conjugation targeting ligand (small molecule - full antibody)**
- **Plug and Play development of new CriPec® product (≈3 m)**
- **2-3 Step manufacturing process already at clinical scale (40 L)**
- **Robust GMP manufacturing applicable for multiple products**

PATENT PROTECTED BY 6 PATENT FAMILIES

Pipeline

	Discovery	Preclinical	Phase 1a	Phase 1b	Phase 2	Milestones
Proprietary programs - Oncology						
CriPec® docetaxel						
Product development						**Ph2 – Q4 2018**
Distribution and uptake						**Ph1b – Q4 2018**
CriPec® oligonucleotides						**Preclin – Q3 2018**
CriPec® DUO						**Preclin – Q2 2018**
Proprietary programs - Inflammation						
CriPec® dexamethasone						**Seeking Partner**
Partnered programs						
3 Non-disclosed partnerships						

Business Model

Partnering-outlicensing

CriPec® proprietary products

- CriPec® docetaxel; preferably after phase 2
- Preclinical stage CriPec® dexamethasone; now available, PoC complete

CriPec® platform

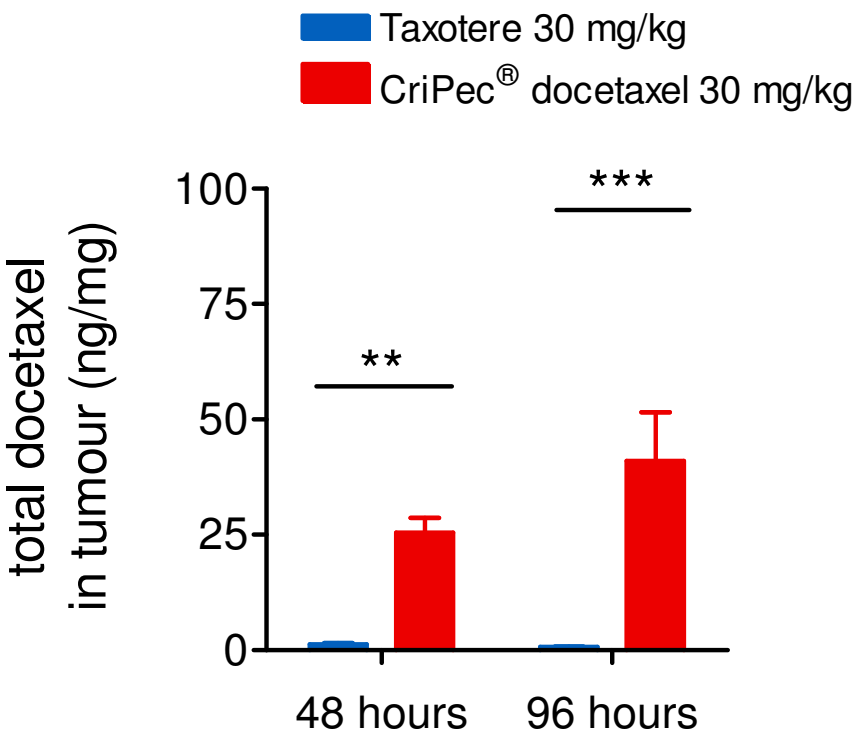
- Co-development opportunities available with partners products
  - CriPec® immuno-oncology (small molecules)
  - CriPec® oligonucleotides
  - CriPec® DUO (combination of 2 different compounds)
- Opportunities available for a range of disease indications, including inflammation, cardiovascular, liver…

Cristal Therapeutics

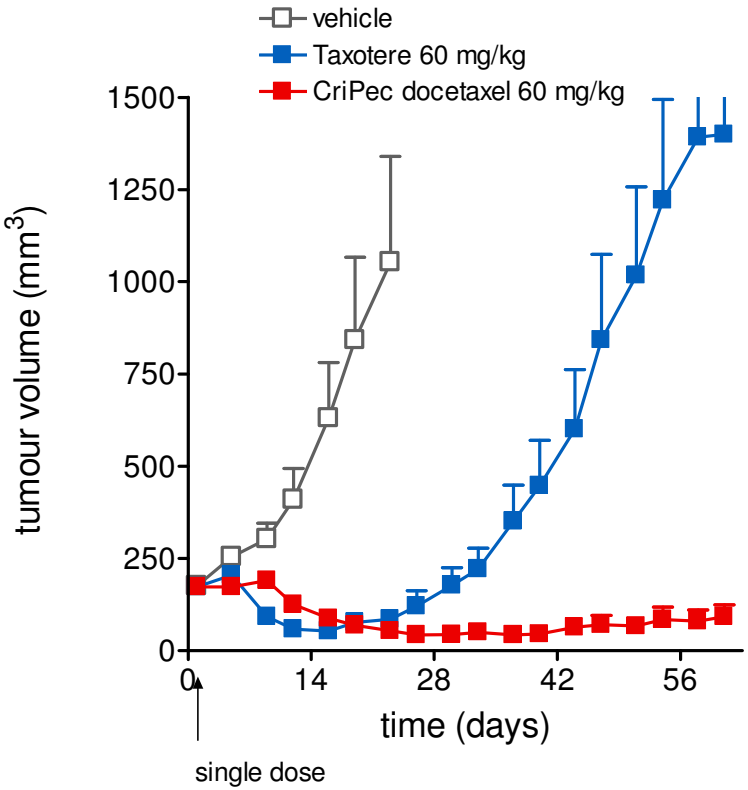
CriPec® docetaxel

Preclinical Uptake & Efficacy

MDA-MB-231 breast xenograft



single i.v. injection to s.c. MDA-MB-231 xenograft in nude mice (n = 3 ±SD)



single i.v. injection to s.c. MDA-MB-231 xenografts in nude mice (n=8 ±SD)

Hu et al, Biomaterials, 53 (2015) p370-378

Competitive Pharmacokinetics

Phase 1a

Parameter	Total docetaxel (mean)*				
	CriPec DTX 60 mg/m2	**CriPec DTX 80 mg/m2**	Taxotere 100 mg/m2	BIND-014 60 mg/m2	CRLX301 75 mg/m2
Cmax (mcg/ml)	**24.8**	**34.0**	3.7	24.9	38.4
AUC (mcg*h/ml)	**794**	**1266**	4.6	219	312
t ½ (hours)	**31.7**	**34.8**	11.1	6.3	n.d.
Vd (L/m2)	**3.3**	**3.4**	66	7.8	2.2

Taxotere reference data from SMPC
BIND-014 data from ASCO 2015, CRLX301 data from ASCO 2016
**Total docetaxel = docetaxel entrapped in or bound to nanoparticle matrix + released docetaxel*
**Total CriPec docetaxel mean calculated from cycle 1 and cycle 2 (n=3 total)*

Phase 1a Conclusions

- Unique pharmacokinetic and safety profile
- Significant reduction in certain dose limiting toxicities

  → clinical evidence for altered tissue distribution of CriPec® docetaxel

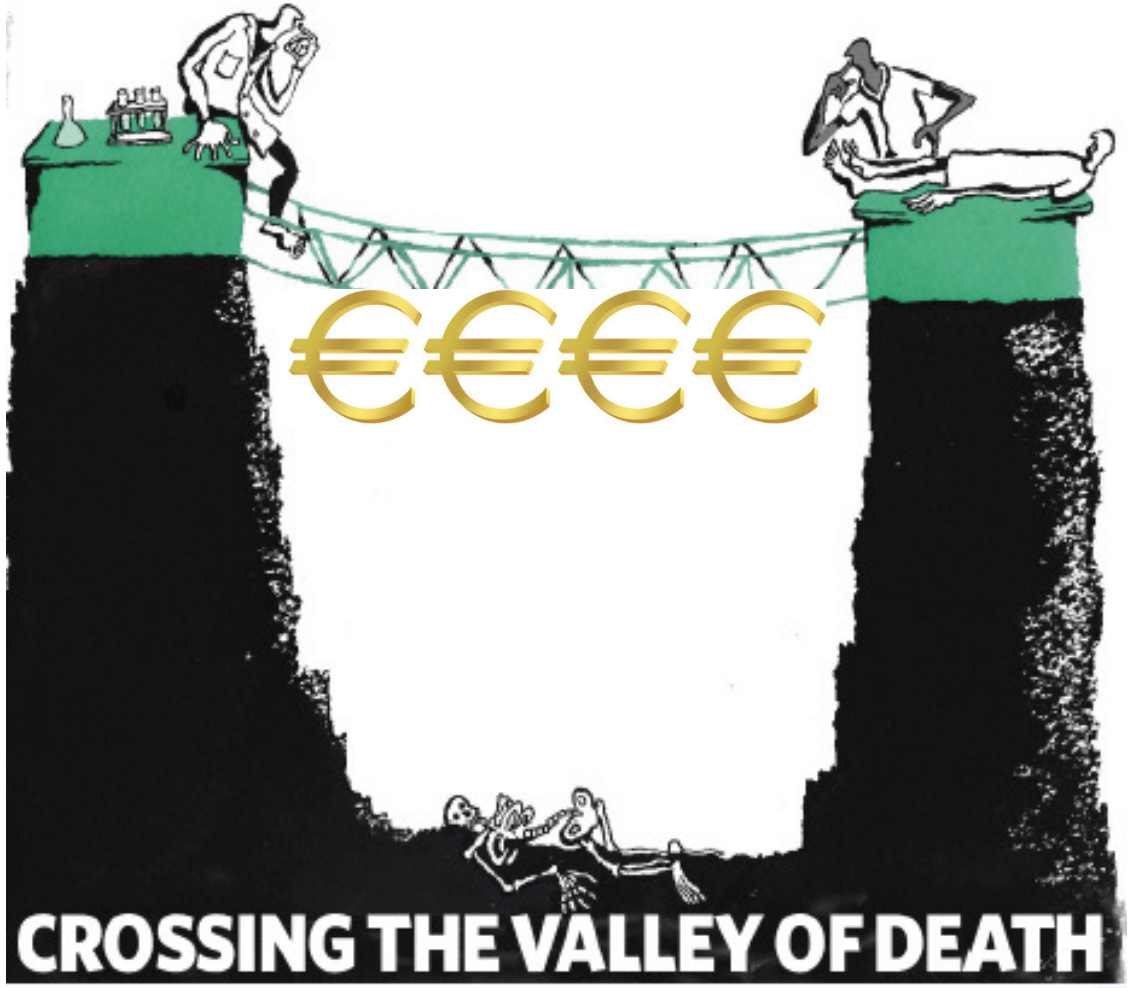
- Encouraging signs of target response

- Ongoing trials to determine
  - dose and dose frequency for follow-up trials
  - tumour uptake in actual patient setting

Financing

Pharmaceutical Startup

From bench to bedside



Company Financing

- Early stage
  - Founders
  - Friends, Family and Fools (FFF)

- Later stage
  - Professional investors
  - Grants and loans *(as an extra)*

Grants Require Often

- Collaborations, incl. academics *(timelines difficult to control)*
- Complex IP contracts
- Topic should be within scope of proposals
- Mainly research, not industrial development
- Timelines not matching with own schedules
- …

GRANTS ARE EXCELLENT – BUT NOT BASIS OF A PRODUCT COMPANY

Venture Capital (VC)

My Practical Experience

- < 1% of offered plans is funded, based on
  - Trust in management
  - Product status & opportunities
- Often heard arguments not to invest:
  - Too early
  - Not within scope
  - Already invested in similar company
  - Fundraising themselves
- Contribute with money AND knowledge to create significant value

A deal is truly closed if the money is on YOUR account

VC: Focus on Exit – Value Creation

Value inflection points for Cristal Therapeutics:

- Proprietary product in clinical evaluation
- Validation of flexible, broadly applicable platform
- Manufacturability with robust outcome
- Feasibility and development studies with partners → validating deals with pharma companies

Pharmaceutical Startup

From bench to bedside

Cristal Therapeutics raises €12.8 million in new financing round to advance novel medicines against cancer using its CriPec® nanotech platform

Posted on 19 January 2017 by cristaltherapeutics

Highlights

Proprietary Platform	CriPec® enables the rational design of highly competitive nanomedicines with a superior therapeutic performance
Blockbuster Product Candidate	CriPec® docetaxel has preclinically superior efficacy and tolerability as compared to Taxotere. Clinical phase 1a yielded excellent PK and safety results
Broad Applicability	CriPec® can be applied to small molecules, peptides and oligonucleotides, and combinations thereof. CriPec® nanoparticles can be combined with targeting ligands
Business Model	The business model is based on own product development, co-development and license agreements
Management Team	Experienced management team, supported by strong supervisory and scientific advisory board
Financial Position	Well financed; over € 19 M VC funding raised, plus over € 10 M non-dilutive financing

Cristal Therapeutics

THANK YOU!

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www.cristaltherapeutics.com