Selected success stories from Switzerland in clinical research

Christoph Driessen, M.D.
Department Oncology/Hematology
Clinical Trials Unit
St. Gallen
I. Ask a relevant question

II. Have a clear, innovative scientific idea

III. Address competently with adequate methods

IV. Come to a result that leads into the future (sound, valid), communicate the result
Success in clinical research, defined as ..

- **scientific citations?**
  > 3500 citations in peer review journals
  h-Index 34

- **competitive research funding?**
  CHF 5.8 Mio 2006-2016

- **improving treatment options for patients?**
  Nelfinavir in Multiple Myeloma
... scientific focus: Multiple Myeloma

- most prevalent blood/lymph cancer
- remitting-relapsing, average survival 5-7 years
- proteasome inhibitors (PI): cornerstone of therapy
- PI-resistance: common, mean survival 6 months
- no approved drug for PI-resistant Multiple Myeloma
- activity of next generation drugs 20-30%
- costs of next generation drugs ca. 10 000 CHF/mo
Goal:

find a therapy for patients with PI-refractory Multiple Myeloma (MM)

Strategy:

1. understand biology of PI refractory MM
2. identify therapeutic concept in vitro
3. test concept in the clinic
understand biology

Activity patterns of proteasome subunits reflect bortezomib sensitivity of hem malignancies and are variable in primary human leukemia cells

M Kraus, T Rückrich, M Reich, J Gogel, A Beck, W Kammer, C Berkers, D Burg, H Overkleeft, H Ova and C Driessen

1The Department of Medicine II, University of Tübingen, Tübingen, Germany; 2The Department of Medicine IV, University of Tübingen, Tübingen, Germany; 3ZBIT/Proteomics, University of Tübingen, Tübingen, Germany; 4Division of Cellular Biochemistry, The Netherlands Cancer Institute, Amsterdam, The Netherlands and 5Department of Chemistry, Leiden University, Leiden, The Netherlands

Characterization of the ubiquitin–proteasome system in bortezomib-adapted cells

T Rückrich, M Kraus, J Gogel, A Beck, H Ova, M Verdoes, HS Overkleeft, H Kalbacher

1Department of Medicine II, University of Tübingen, Tübingen, Germany; 2ZKM GmbH, Heilbronn, Germany; 3Biologics, The Netherlands Cancer Institute, Amsterdam, The Netherlands; 4Institute of Chemistry, Leiden, The Netherlands; 5Interfaculty Institute of Biochemistry, University of Tübingen; 6Department of Oncology and Hematology, Cantonal Hospital St Gallen, St Gallen, Switzerland

Proteasome inhibitor-adapted myeloma cells are largely independent from proteasome activity and show complex proteomic changes, in particular in redox and energy metabolism

GP Soriano, I Besse, N Li, M Kraus, A Besse, N Meeuwenhoek, J Baden, B Everts, H den Dulk, HS Overkleeft, BI Florea and C Driessen
SCTO Symposium 2016

UPR «load»
- Biosynthese
- «poor redox»
- Energiemangel
- Mutationen
- Aneuploidie

UPR «capacity»
- Proteinabbau
- Chaperone
- ER-Größe
- «stringend redox»

normal cell

MM cell

Degree of UPR activation

XBP-low MM
therapeutic concept in vitro

Ritonavir induces endoplasmic reticulum stress and sensitizes sarcoma cells toward bortezomib-induced apoptosis

Marianne Kraus,1 Elke Malenke,1
Jeanette Gogel,1 Holger Müller,1
Thomas Rückrich,1 Herman Overkleeft,2
Huib Ovaar,3 Ewa Koscielnik,4
Jörg Thomas Hartmann,1 and Christoph Driessen1,5

bortezomib-resistant cells to bortezomib-induced apoptosis. Ritonavir may therefore be tested clinically to improve the sensitivity of solid malignancies toward bortezomib treatment. [Biol Cancer Ther 2008;7(7):1940–8]

Introduction

Nelfinavir augments proteasome inhibition by bortezomib in myeloma cells and overcomes bortezomib and carfilzomib resistance

M Kraus1, J Bader1, H Overkleeft2 and C Driessen1

Ritonavir, nelfinavir, saquinavir and lopinavir induce proteotoxic stress in acute myeloid leukemia cells and sensitize them for proteasome inhibitor treatment at low micromolar drug concentrations

Marianne Kraus1, Hendrik Müller-Ide2, Thomas Rückrich1, Jürgen Bader1, Herman Overkleeft2, Christoph Driessen1,5

1 Department of Pathology and Hematology, Canton Hospital, St. Gallen, Switzerland
2 Department of Medicine D, University of Tübingen, Germany
3 Leiden Institute of Chemistry, University of Leiden, The Netherlands

Nelfinavir: HIV drug
- oral drug
- low toxicity
- safe
- Induces UPR in mice
- Mammalian target unknown
Phase I

Phase I-study: bortezomib + nelfinavir

Cycle 1*, 2 and 3 (optionally 4-7)
- DL 0: 2 x 1250 mg/d
- DL 1: 2 x 1875 mg/d
- DL 2: 2 x 2500 mg/d

Nelfinavir*: p.o., d 1 to 14
Bortezomib 1.3 mg/m² i.v., d 1, 4, 8, 11

Week
-1* 1 2 3
PK/PD**
PK1, PK2, PK3, PK4

*Cycle 1 only: Run-in phase nelfinavir days -7 to -1 (=week -1)

Paraprotein response
Patients with bortezomib-refractory MM

Table 3. Patients with bortezomib-refractory multiple myeloma treated in the extension cohort of the trial. Overview of the disease characteristics, response to prior therapies, number of treatment cycles and response achieved on an individual patient basis.

Patient | Age | PS | Cyto-genetics | Prior lines of therapy | Refractory to last therapy | Bortezomib-resistant* within last 12 months | LEN-resistant | Cycles administered | Best response | Cycle where best response was reached | % paraprotein change after 2 cycles, relative to a baseline | Reason for termination
--- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | ---
13 | 66 | 2 | UN | 9 | Yes | No* | Yes | 3 | 7 | PR | -59 | Completed
14 | 52 | 1 | t(4;14) | 4 | Yes | Yes | Yes | 4 | PR | 2 | -61 | PD
16 | 77 | 1 | UN | 7 | Yes | Yes | Yes | 2 | MR | 1 | -28 | Pat. decision
17 | 70 | 2 | del 1p | 2 | Yes | Yes | Yes | 2 | PD | 1 | +35 | PD
18 | 63 | 1 | UN | 8 | Yes | Yes | Yes | 7 | PR | 7 | -58 | Completed
19 | 72 | 1 | UN | 4 | Yes | Yes | Yes | 5 | MR | 3 | -32 | Completed

*Per protocol. *Bortezomib-refractory >12 months before inclusion. Patient therefore per protocol received bortezomib monotherapy in cycle 1.showed progressive disease, and received bortezomib + nelfinavir from cycle 2 onwards. *Interrupted trial medication due to a peripheral oesophagus and surgical intervention, and experienced disease progression before resuming trial medication. UN = unknown.

Driesen C et al., Haematologica 2016 Volume 101(3):346-355
Phase II

Fortune, phase II study, SAKK 39/13

bortezomib/dexamethasone + nelfinavir in bortezomib-refractory MM

Pre-Planned interim analysis after 10/34 patients: PR in 7 of 9 evaluable patients

Accrual complete, final results summer 2016

Orphan drug designation «Nelfinavir-Driessen» for myeloma by Swissmedic (02/16)
success factor: translational lab

- basic science training: early, basic, full
- not parallel to clinical training
- establish independent, competitive lab research
- international «collaborative» lab science network

- 3 years MD thesis experimental immunology, summa cum laude
- 2.5 years postDoc Harvard University, Protease Biology, Immunology
- 1 year establishing lab laboratory-research only, DFG-funded
- 3 years clinic + lab building «Nachwuchsforschergruppe» (1 PhD, 1 Tech)
- 15 years collaboration Inst. of Organic Chemistry, Leiden, NL
success factor: clinical education

- clinical training: full, focused, time ≠ clinical expertise
- institutional support, fast track curriculum
- mentor?
- establish area of own scientific clinical expertise

- General Oncology 18 mo. before PostDoc
- ICU Medicine 1 year after postdoc
- «Innere Medizin» 2004 minimum time
- Habilitation Innere Medizin 2005
- Oncology/Hematology 2006 full clinical training program
- Oberarzt 2006 Myeloma, AML
- Associate Professor 2008
success factor: clinical research

- clinical research education: strategy, statistics, regulatory
- reliable time ressource
- multicenter Network
- clinical research infrastructure
- industry-independent funding

- Pharmaceutical Medicine European Course for Pharmaceutical medicine (ECPM), 2007-2009
- 30-50% research time
- SCTO, SAKK, PG Leukemia, Lymphoma, New Drugs
- Clinical Research Department Oncology KSSG, head 2006-2008
- CTU KSSG, founded 2008, head
- SNF, Oncosuisse, foundations, Gateway/rising tide award 2013
success factor: personality

- genuine, persistent interest in science
- creative and strategic
- able to prioritize and organize
- writing skills
- willing to postpone clinical career and to invest heavily in education
- social/family environment able and willing to support the dual challenge clinics/research
Most important

- select the right persons
- early training at high level in all areas
- built up scientific track record early
- Mentor
- protected time
- competitive infrastructure (lab, clinical research)
- funding independent from industry
- funding by scientific (quality) criteria
«Research Cycle»

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