CD70: TARGETING HEMATOLOGICAL MALIGNANCIES

Workshop, 8 December 2014

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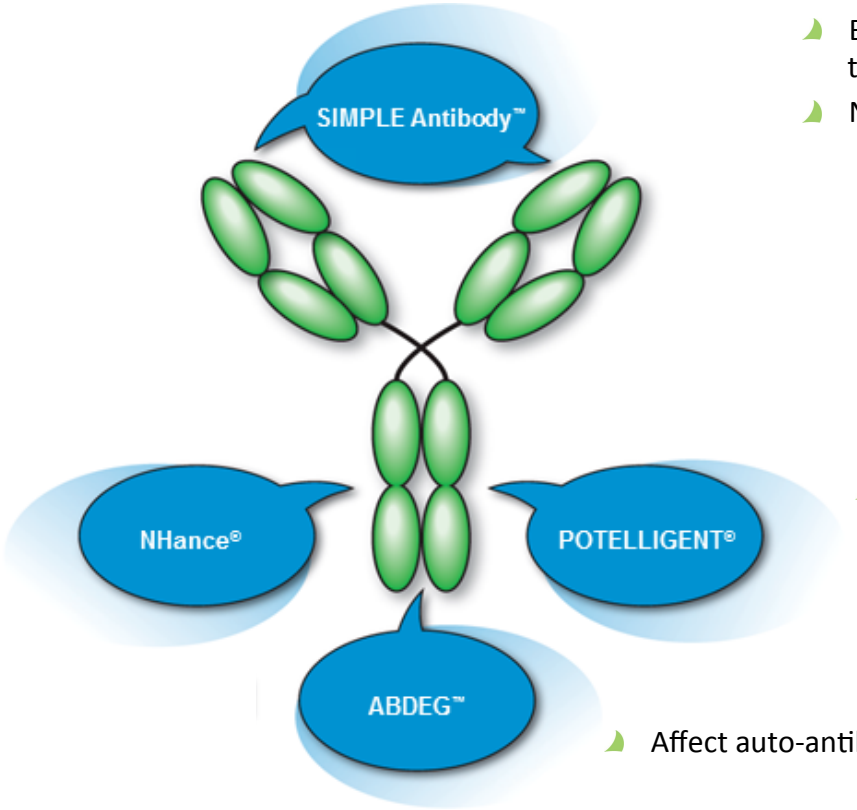
arGEN-X highlights

- Creating and developing therapeutic antibodies targeting **cancer & severe auto-immunity**
- Technology suite yields mAbs with **multiple modes of action** against **complex targets**
- Pipeline of **highly differentiated mAb** therapeutics
  - Demonstrated biological activity in early Phase 1 trials of ARGX-110 and ARGX-111
    - **ARGX-110 (oncology):** currently in Phase 1b expansion study; data expected in 2H 2015
    - **ARGX-111 (oncology):** currently in Phase 1 study with data expected in 2H 2015; partner post-Phase 1
  - Radically new mechanism of action to target crisis management in severe autoimmune disease
    - **ARGX-113 (auto-immune):** ongoing preclinical evaluation; CTA filing in 2015
- Development strategy leading to partnering for **major indications**
- **Strategic partnerships** with Shire, Bayer, Boehringer Ingelheim, Leukemia & Lymphoma Society
- **Solid cash position** (€58MM end July'14); no debt; runway thru 2017
  - Raised €42 mio in IPO (Euronext Bru: ARGX) on July 10, 2014

Suite of complementary antibody technology platforms

Therapeutic antibodies with multiple modes of action against complex targets

arGEN-X' technology suite



- Broad range of leads of therapeutic quality
- Novel & complex targets

- Extend half-life

- Boost cell killing

- Affect auto-antibody/disease target degradation

- **SIMPLE Antibody™: Unlock novel and complex targets**
- **NHance®, ABDEG™, POTELLIGENT®: Enhance SIMPLE Antibody™ leads**

Clinical stage pipeline of differentiated products

Drug Candidate	Indication	Pre-clinical	Phase 1	Phase 2	Ownership	Proposition
ARGX-110	Heme malignancies			LEUKEMIA & LYMPHOMA SOCIETY®	Wholly owned	Immune checkpoint (CD70) inhibitor Enhanced cell kill
ARGX-110	Solid tumors					
ARGX-110	Autoimmunity					
ARGX-111	Solid tumors Heme malignancies					Complete c-Met blocking Enhanced cell kill
ARGX-113	Autoimmunity					Potent FcRn blocking
ARGX-112	Atopic dermatitis					Complete IL22R blocking
Discovery	Autoimmunity Cancer	*multiple*				Novel, complex targets e.g. GARP
ARGX-109	Autoimmunity Cancer				Partnered	Potent IL-6 blocking Partnered with RuiYi
Shire	Undisclosed					Novel, complex targets
BAYER	Undisclosed					Novel, complex targets
Boehringer Ingelheim	Undisclosed					Novel, complex targets

CD70 biology in hematological malignancies

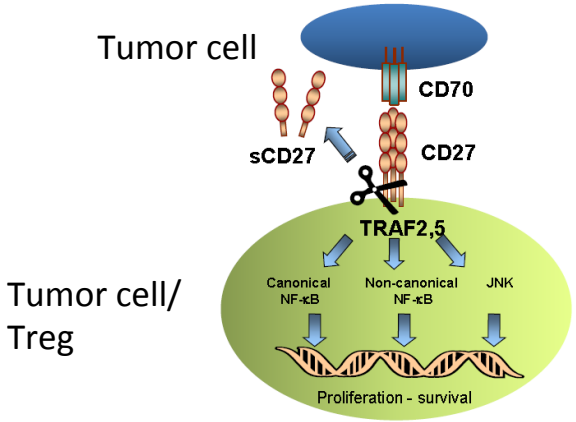
Hans de Haard, PhD, Prof.

Chief Scientific Officer, arGEN-X

CD70 is a promising target

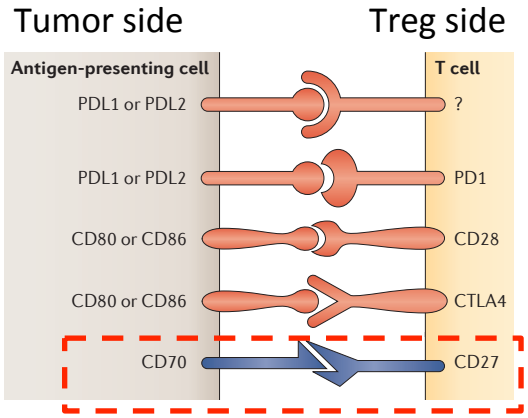
Involved in tumor growth, enables immune escape and is highly tumor specific

1. CD70 is a tumor/Treg growth signal



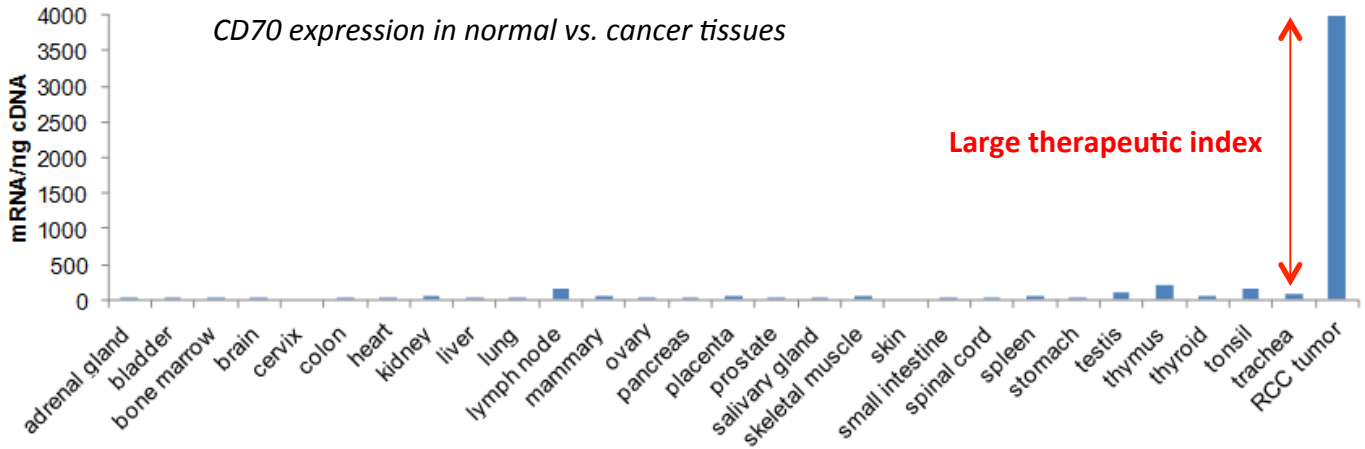
<u>Blocking</u> CD70 deprives tumor of growth signal

2. CD70 enables tumors to escape immune surveillance



<u>Blocking</u> CD70 deprives tumor of immune escape mechanism

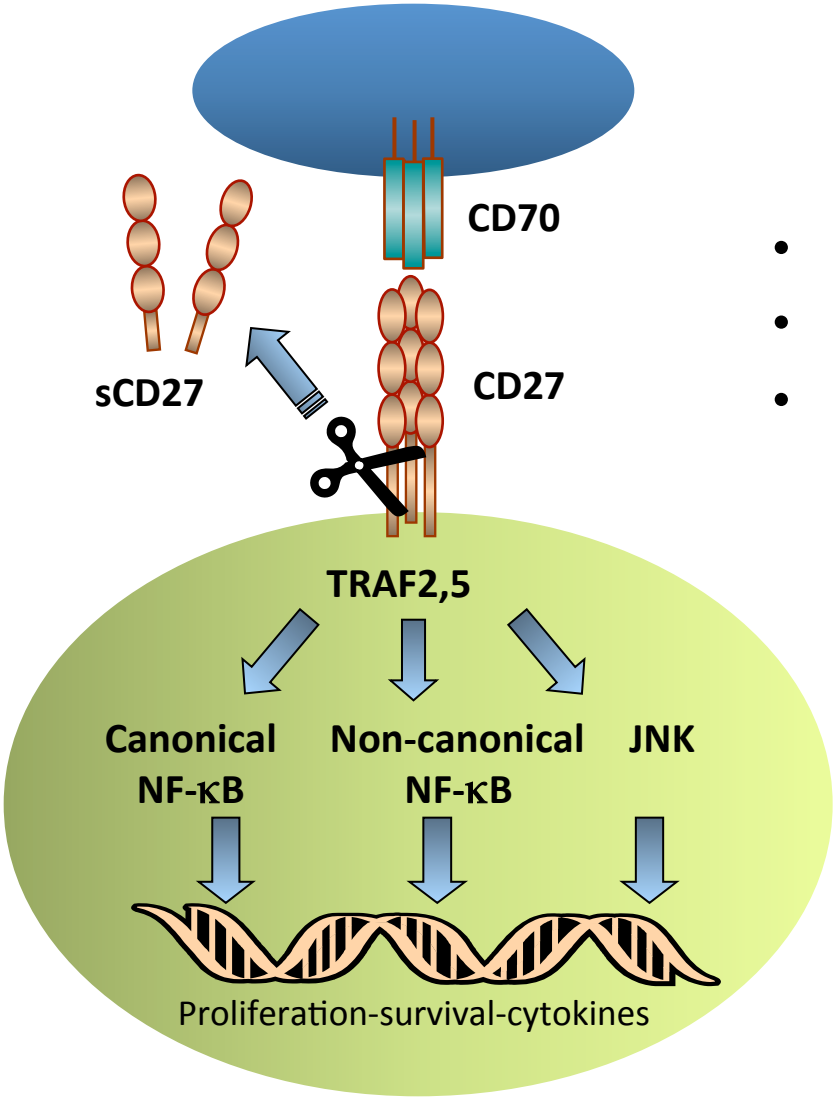
3. CD70 expression is highly tumor specific



<u>Killing</u> CD70+ cells should be safe

Pardoll 2012; Nolte, 2009 – adapted; Adapted from Adam 2006 ; Grewal 2008

CD70 signaling through CD27

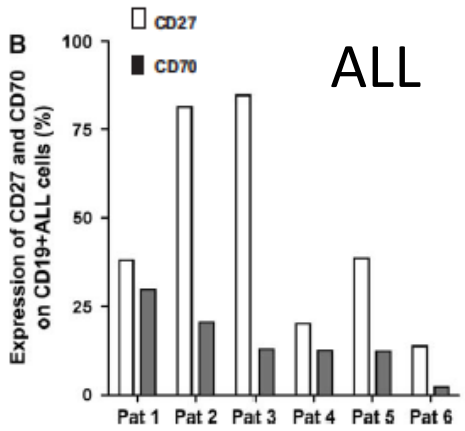


- Member of TNF family
- No signaling via CD70
- CD70 induces signaling of CD27 which results in shedding of sCD27

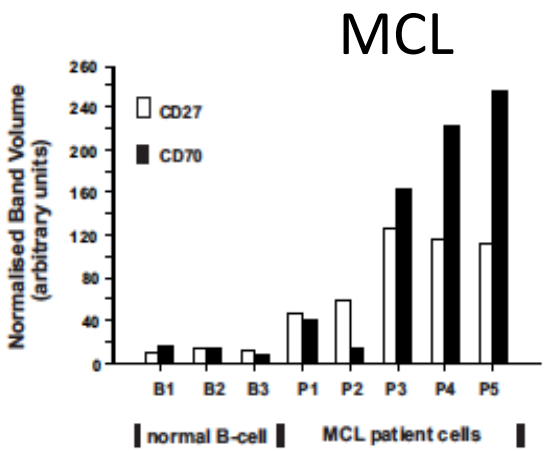
Immunol. Rev. (2009) ***229****: 216-231*

Co-expression of CD27 and CD70 in Lymphoma/Leukemia

Suggests existence of autocrine signaling loop



Exp Hematol. (2005) 33:1500-1507



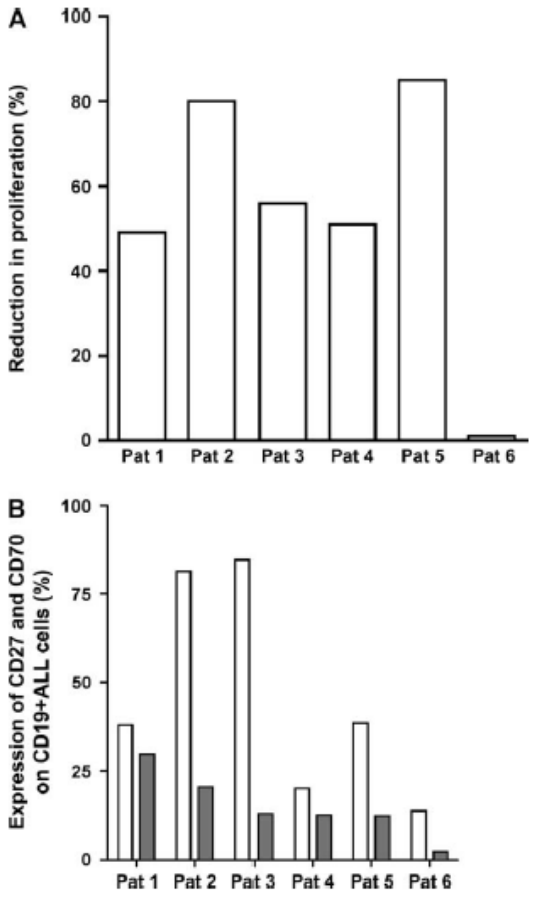
Mol. & Cell. Prot. (2009) 1501-1515

Type	CD70*	CD27*
Burkitt's lymphoma	+	+
CLL	+	+
Follicular lymphoma	+	+
MCL	+	+
LBCL	+	+
ALL	+	+
CML	+	+
T cell Lymphoma	+	+

*immunohistochemistry

Lymphomas abuse CD70/CD27 signaling pathway in lymphoid tissues

Role in tumor proliferation - ALL

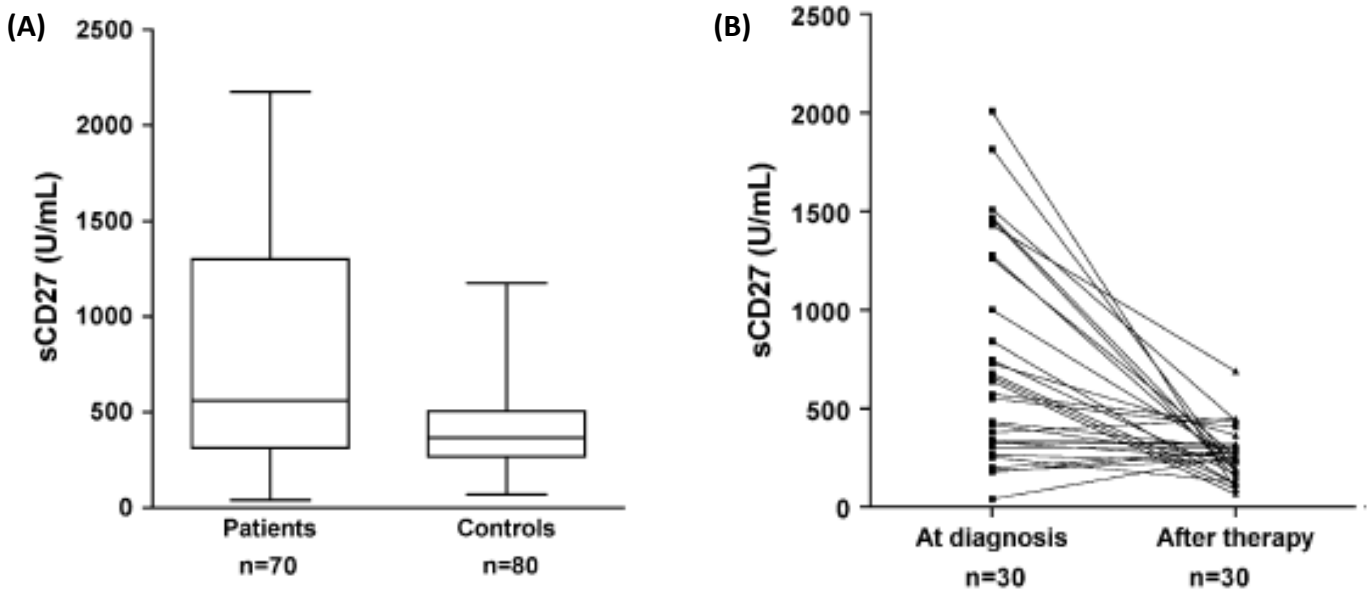


- Ligation of CD40L to CD40 on malignant cells in lymphoid tissues induces overexpression of CD70 (common in all types of lymphomas / leukemias)
- Patient-derived ALL cells isolated from bone marrow show autocrine CD70/CD27 signaling
- Anti-CD70 mAb blocks proliferation of patient-derived ALL cells **(Fig. A)**
- Degree of inhibition correlates with CD27 (open bars) and CD70 (closed bars) expression levels **(Fig. B)**

Exp. Hematol. (2005) ***33****: 1500 - 1507*

Elevated levels of sCD27 in ALL

Quantitative marker of active CD70-CD27 signaling



*Exp. Hematol. (2005) **33**:1500-1507*

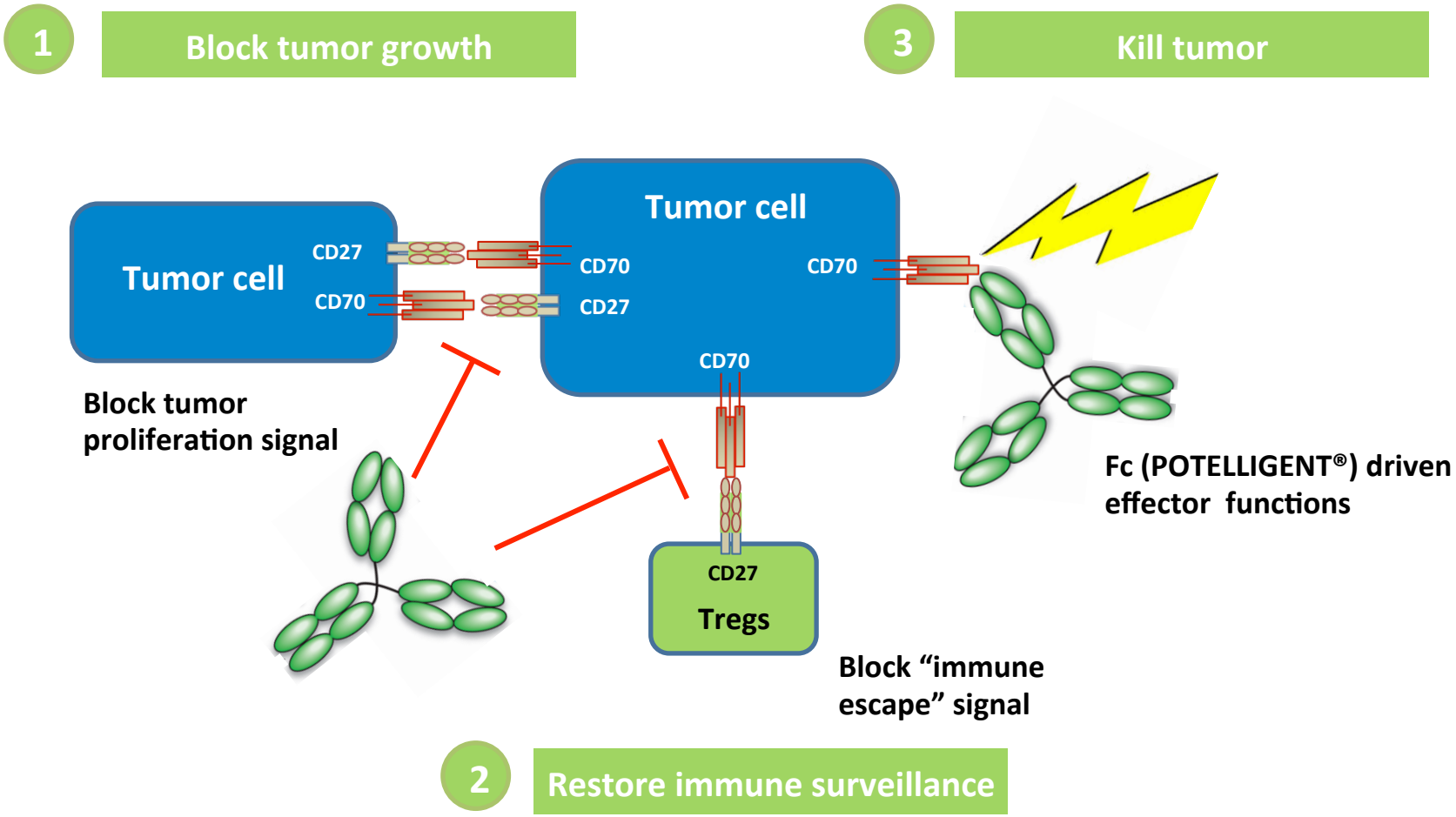
- Increased serum levels of sCD27 observed in ALL patients (**Fig. A**)
- Decrease of sCD27 levels correlates with successful treatment (**Fig. B**)

ARGX-110

Hans de Haard, PhD, Prof.

Chief Scientific Officer, arGEN-X

ARGX-110 targets CD70+ tumors via 3 modes of action



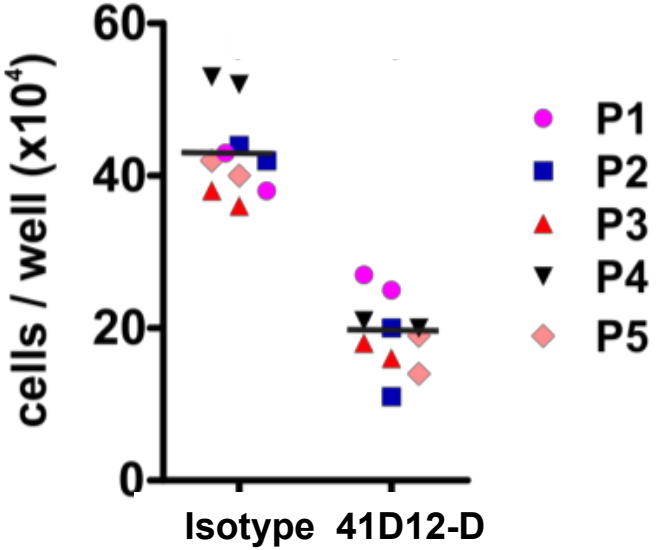
Silence et al., Mabs, 2014

1 ARGX-110 blocks growth of CD70^{+} tumor cells

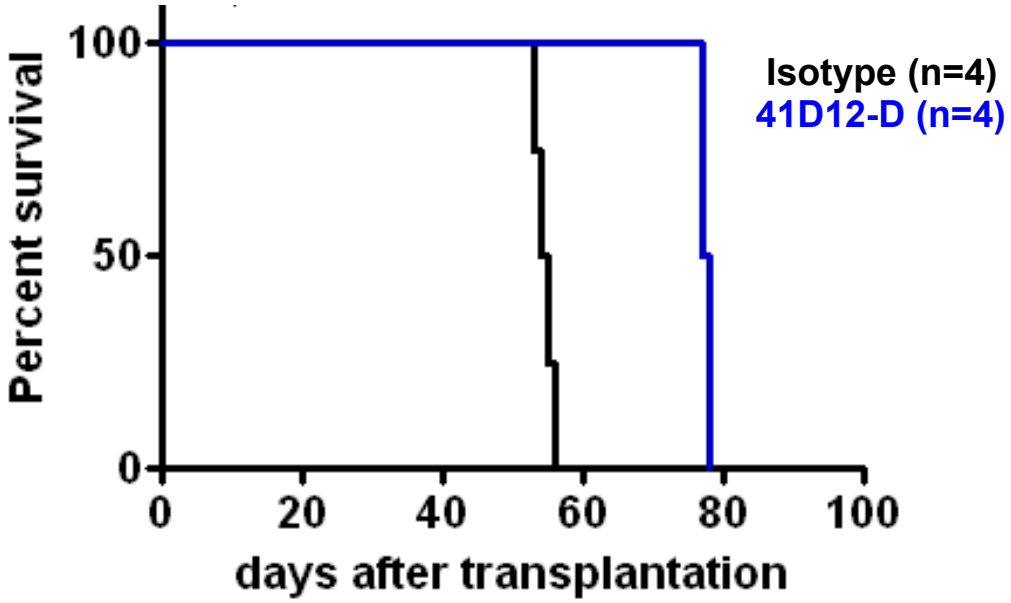
Inhibition of in vitro and in vivo proliferation of AML blasts

- 41D12-D blocks *in vitro* proliferation of blasts purified from newly diagnosed AML patients (left panel)
- Mouse xenograft model (right panel) using AML patient blasts
- Mice treated with 41D12-D
- 41D12-D has no effector functions: MOA is purely blocking

Blocking of proliferation of AML blasts



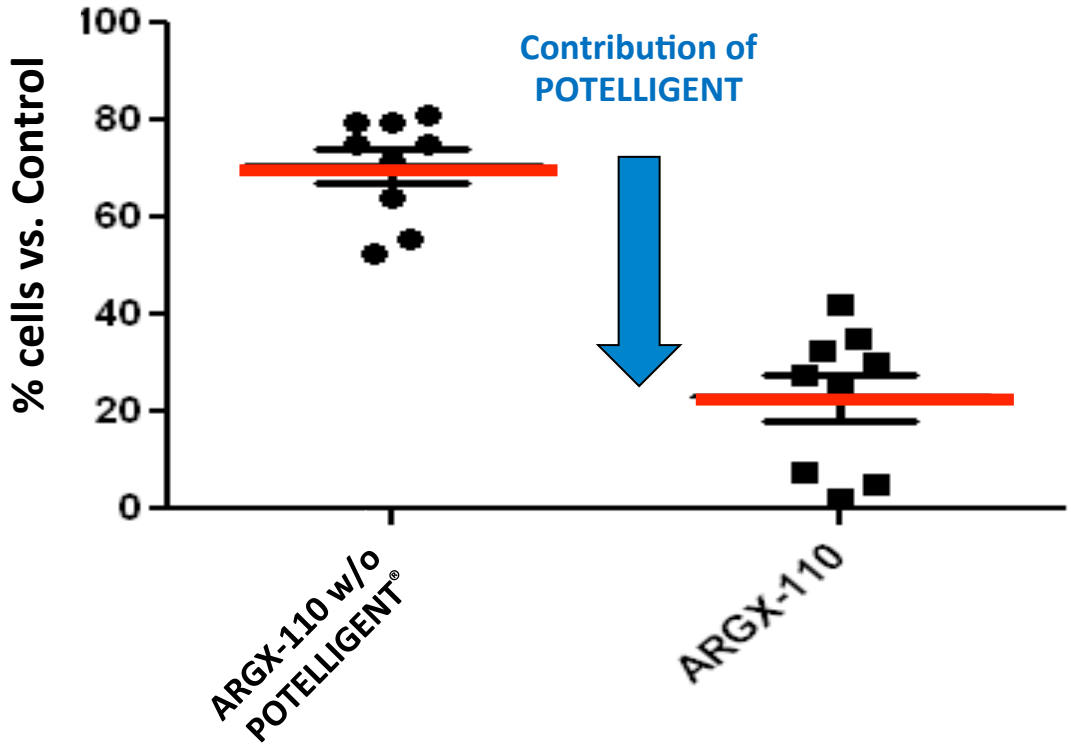
Prolonged survival in mouse Xenograft model



3 ARGX-110 kills CD70+ tumor cells via POTELLIGENT®

Effect of POTELLIGENT on AML patient blasts (n = 9)
(incubated with NK cells *in vitro*)

Each dot and corresponding square represent a patient



In house data, collaboration with prof. Ochsenbein (University of Bern, Switzerland)

CD70/CD27 signaling critical for Leukemic Stem Cell proliferation in CML

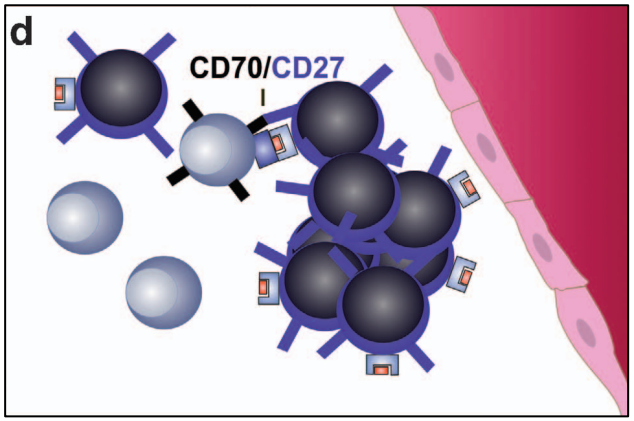
Cell Death and Differentiation (2014), 1–12

www.nature.com/cdd

Regulation of hematopoietic and leukemic stem cells by the immune system

C Riether[1,4], CM Schürch[1,2,4] and AF Ochsenbein*[,1,3]

- Leukemic stem cells responsible for disease initiation and maintenance
- CD27:CD70 induced proliferation in lymphoid tissues (Bone Marrow) leads to more differentiated malignant cells (see Figure)
- Leukemic stem cells can be resistant to drugs as demonstrated by Ochsenbein lab in CML for imatinib
- Combination treatment of ARGX-110 and imatinib eradicates Minimal Residual Disease in CML (manuscript submitted)



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aCD70/imatinib co-treatment eradicates human CD34^{+} CML stem/progenitor cells *in vitro* and *in vivo*

Carsten Riether, PhD

Tumor Immunology, Department of Clinical Research, University of Bern

CML

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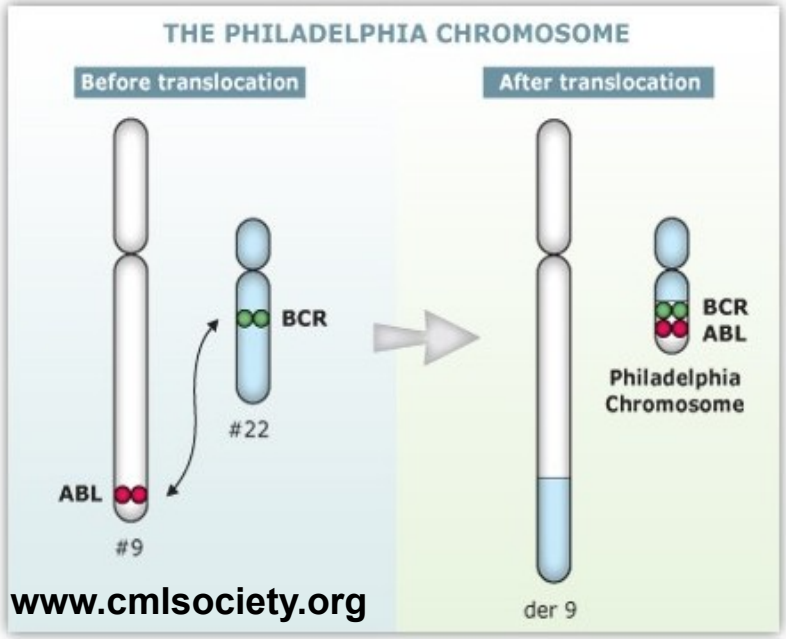
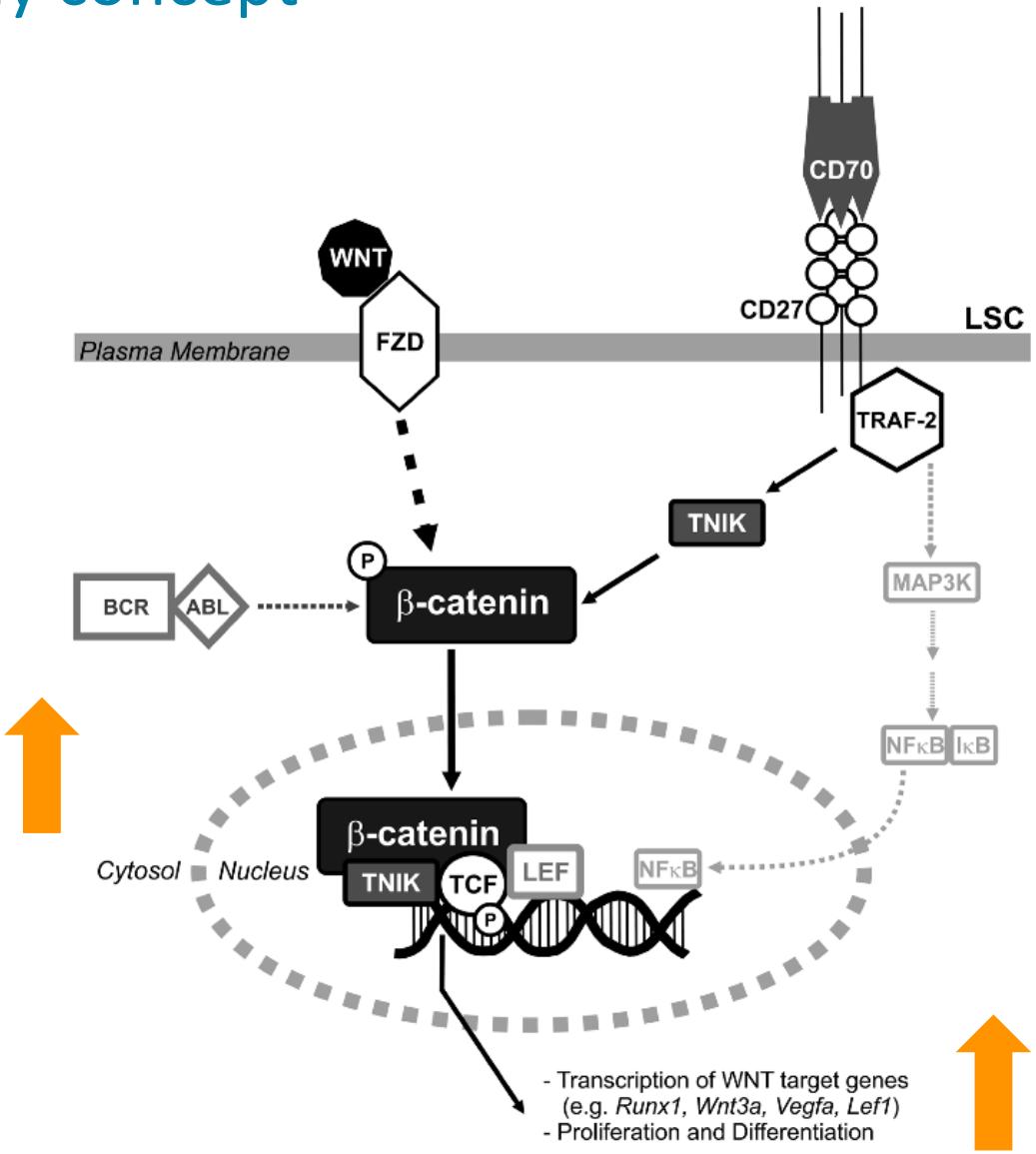
- Myeloproliferative neoplasm
- Transformation of hematopoietic stem cell
- 1-2 / 100‘000 / year, ~20% of adult leukemias
- Philadelphia chromosome (Ph‘, t9:22)
- Therapy:
  - targeted BCR-ABL1 inhibition (TKIs)
  - allogeneic BMT (curative)
- Problem:
  - leukemia stem cell (LSC)

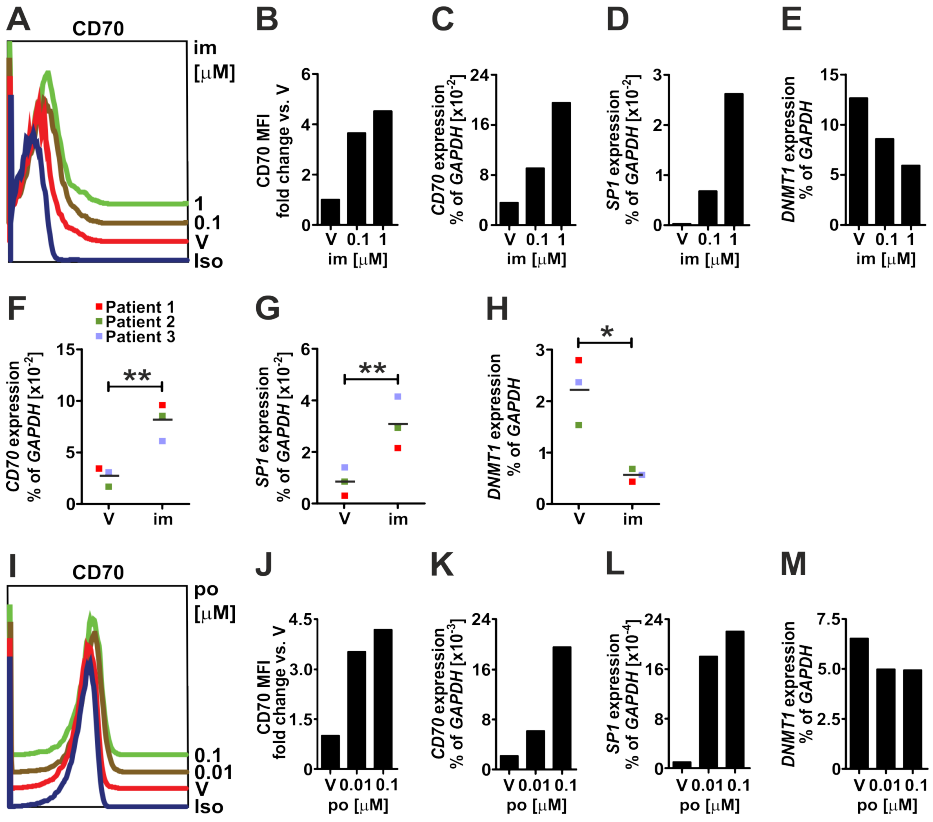


Study concept

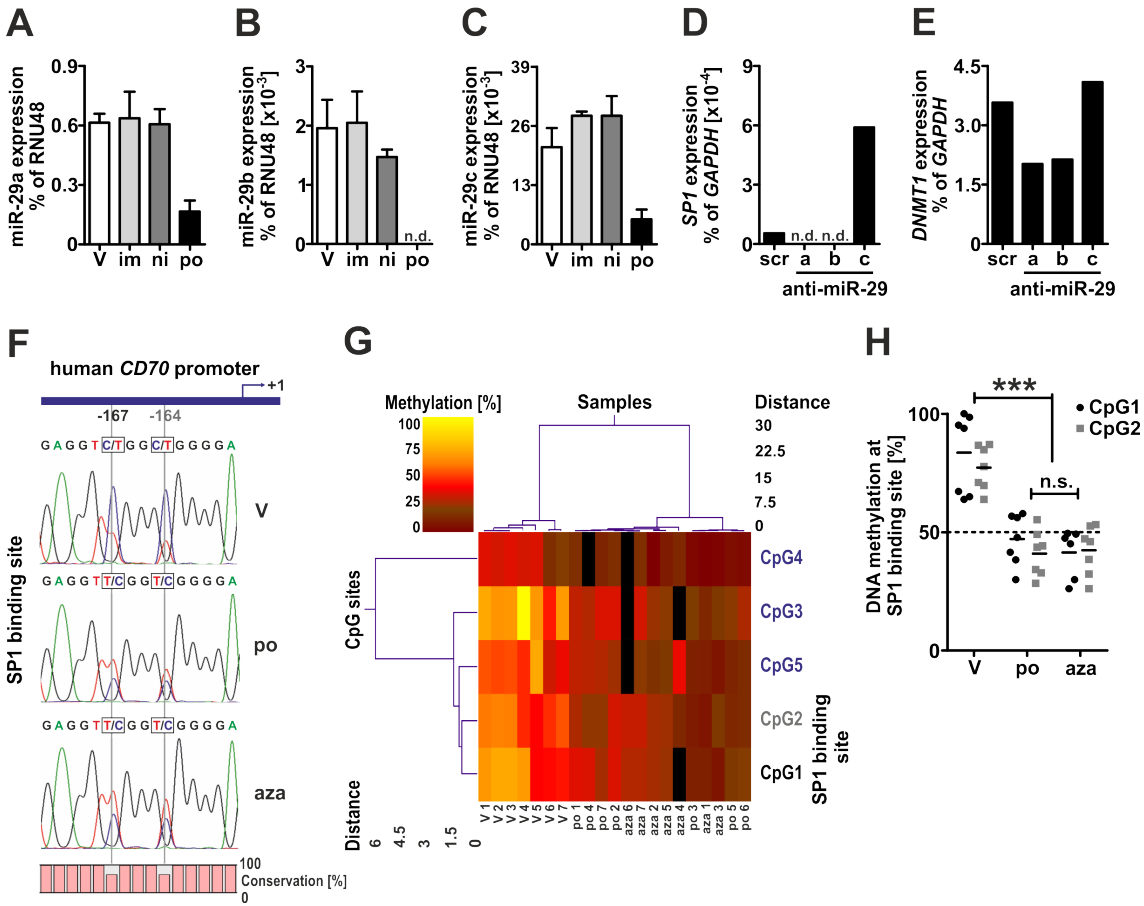


Schürch et al., *J Clin Invest*, 2012, 122(2):624-38.

TKI treatment induces CD70 expression in human leukemia cells



TKI treatment reduces miR-29 and induces DNA hypomethylation of CD70



Co-treatment eradicates human CD34$^+$ CML cells *in vivo*

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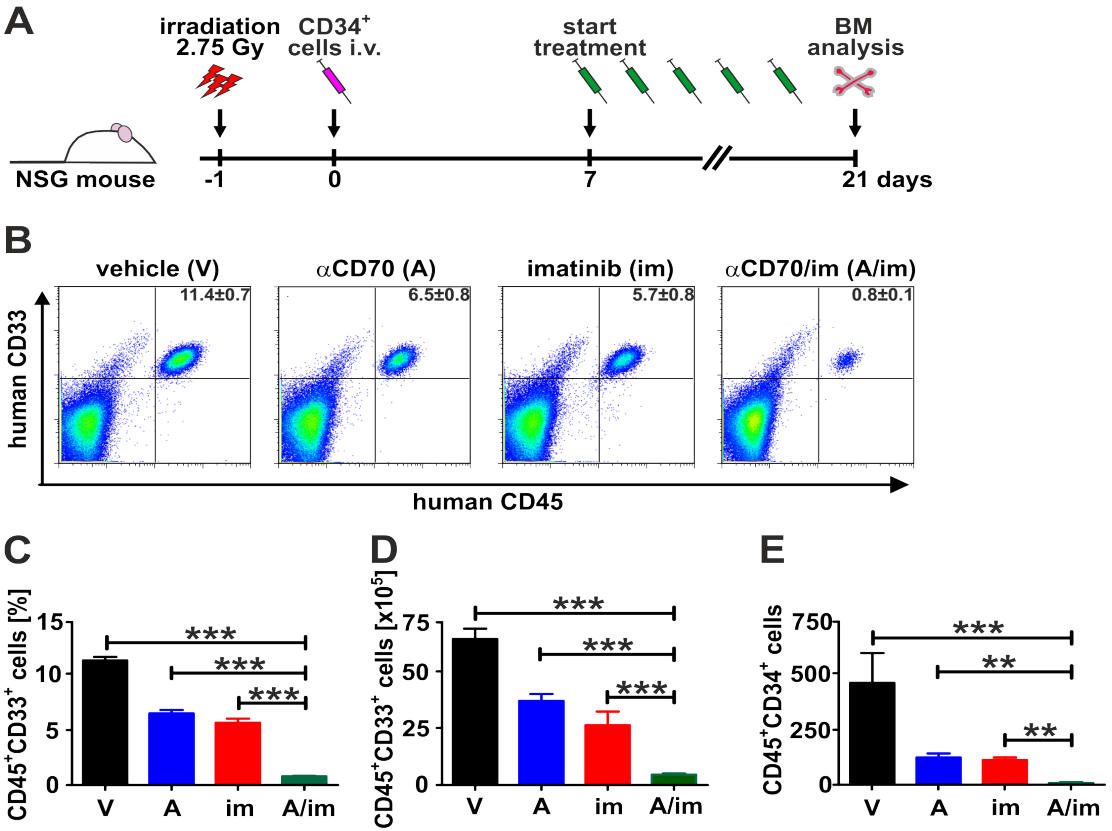
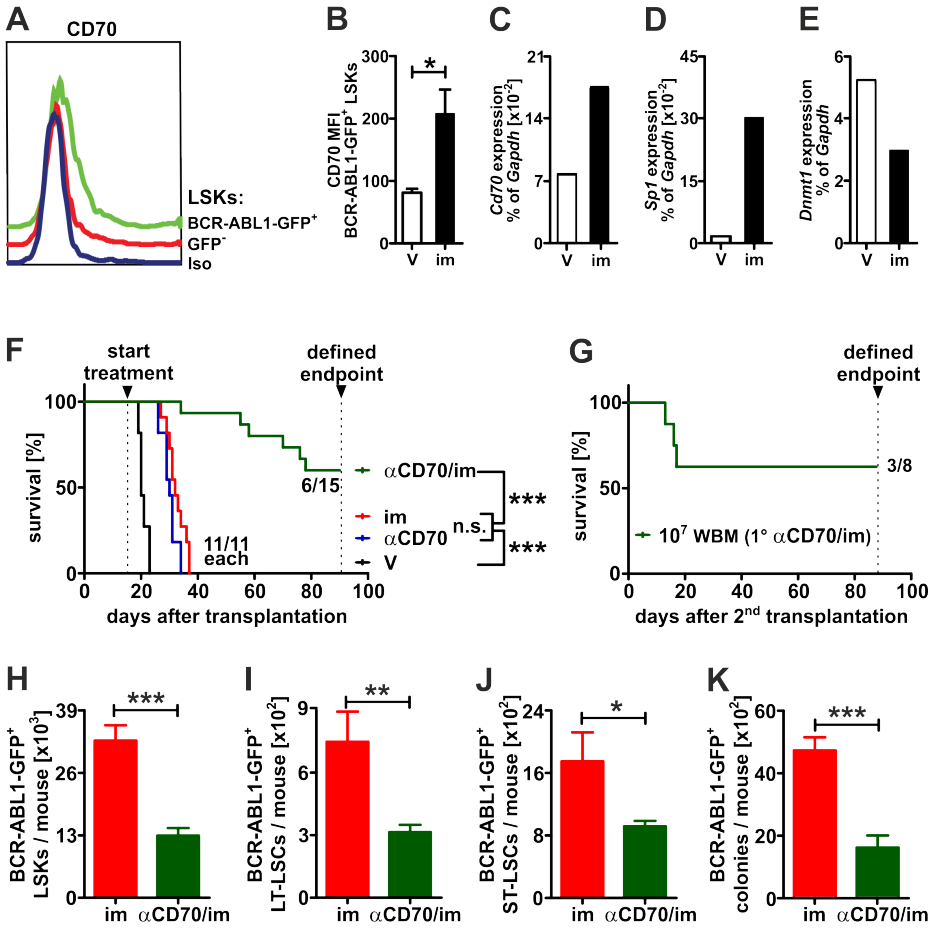
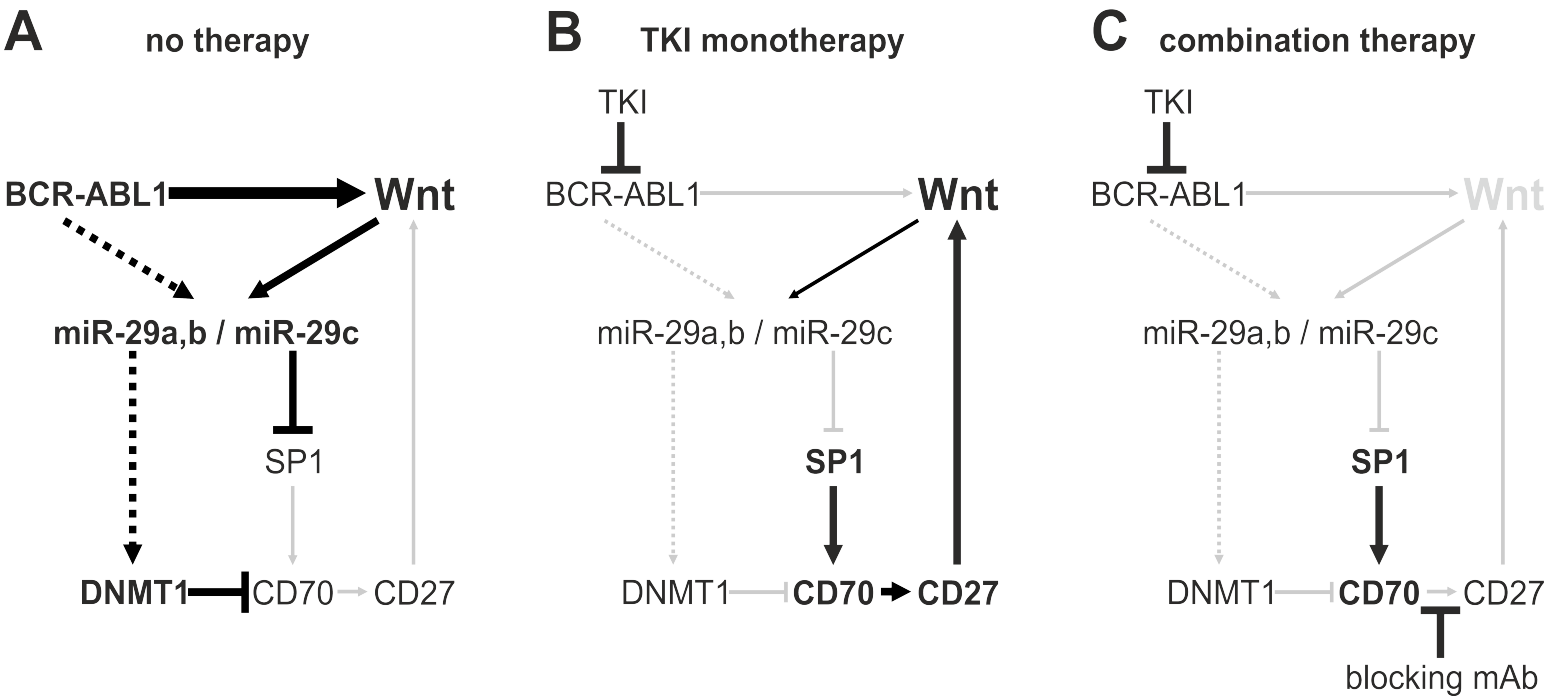


Combination therapy eliminates murine CML LSCs *in vivo*



Complementary pathway blockade



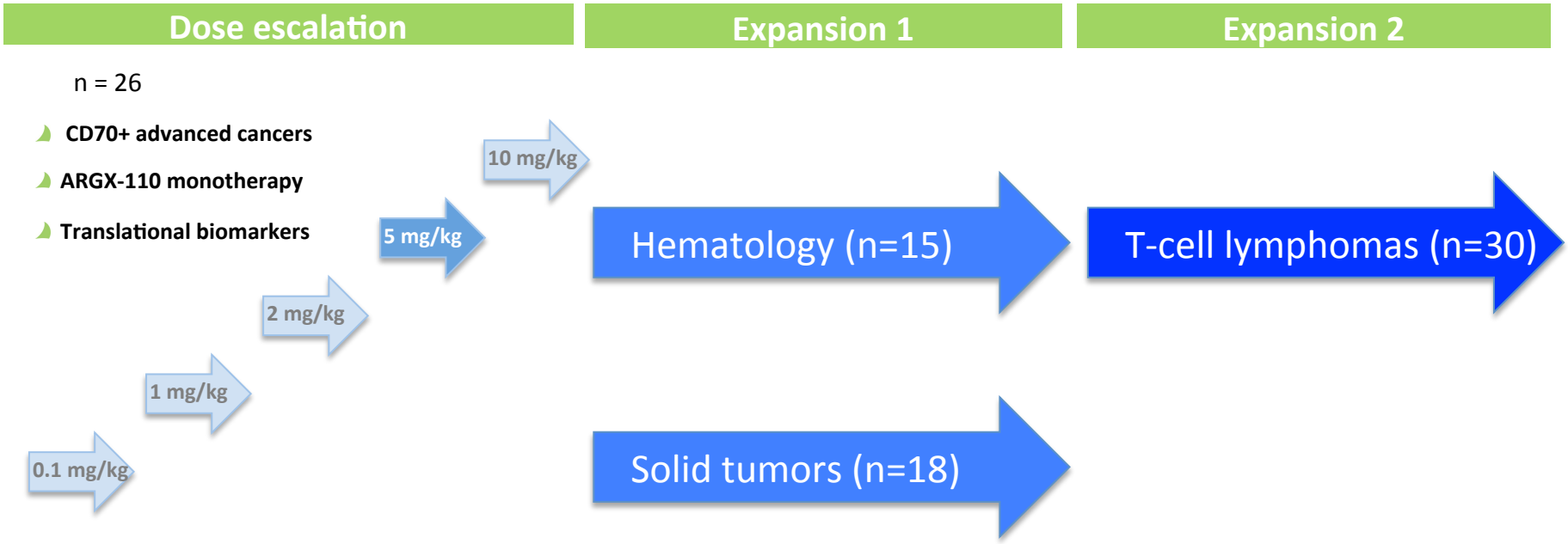
ARGX-110 Early Clinical Plan

Alain Thibault, MD

Chief Medical Officer, arGEN-X

ARGX-110: Phase 1 trial

Adaptive design leads to early focus on T-cell lymphomas



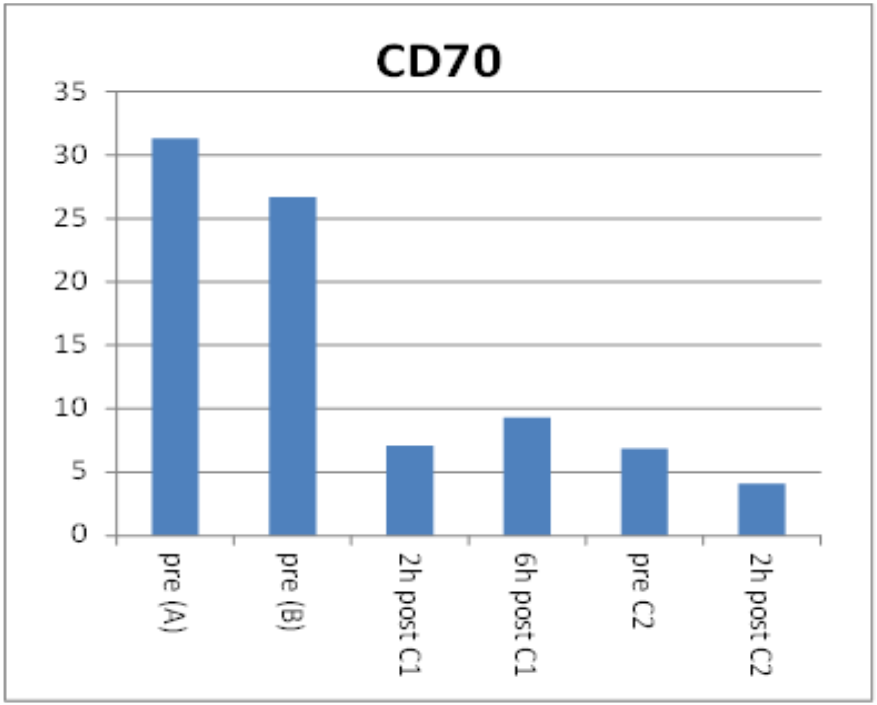
Take home

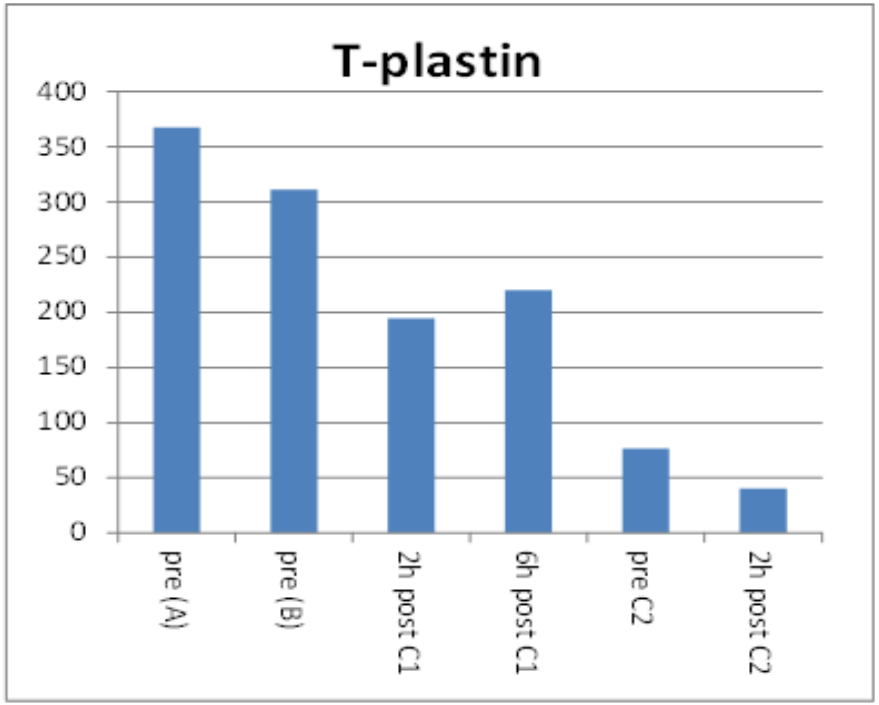
- ~ 50% of all comers are CD70+
- No dose-limiting toxicity or auto-immune related AEs: supports combination therapy
- Biological activity observed in T-cell lymphoma

ClinicalTrials.gov Identifier: NCT01813539

Indication rationale: Sézary syndrome

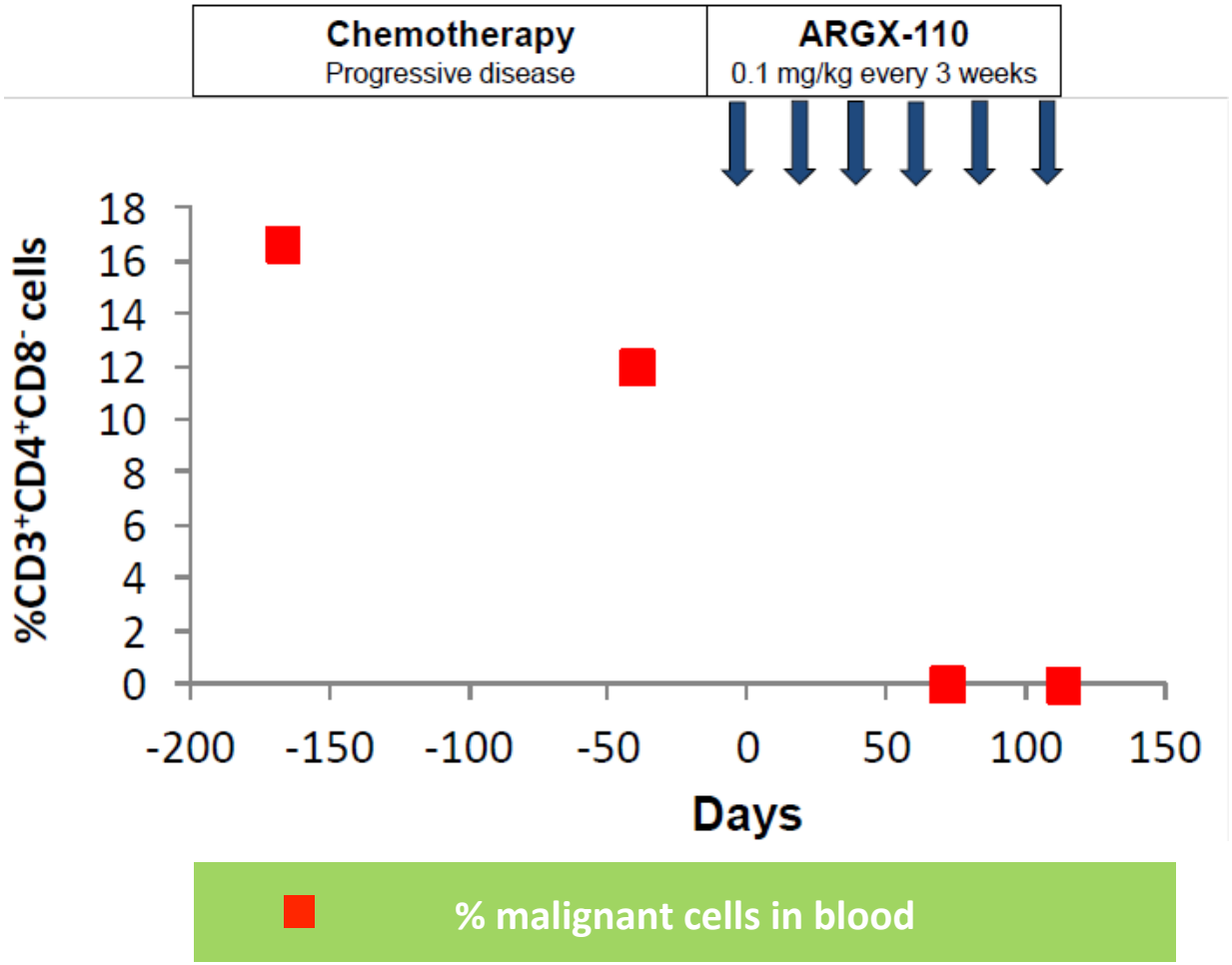
Comparative CD70 qPCR data vs. T-plastin gene specific for Sézary





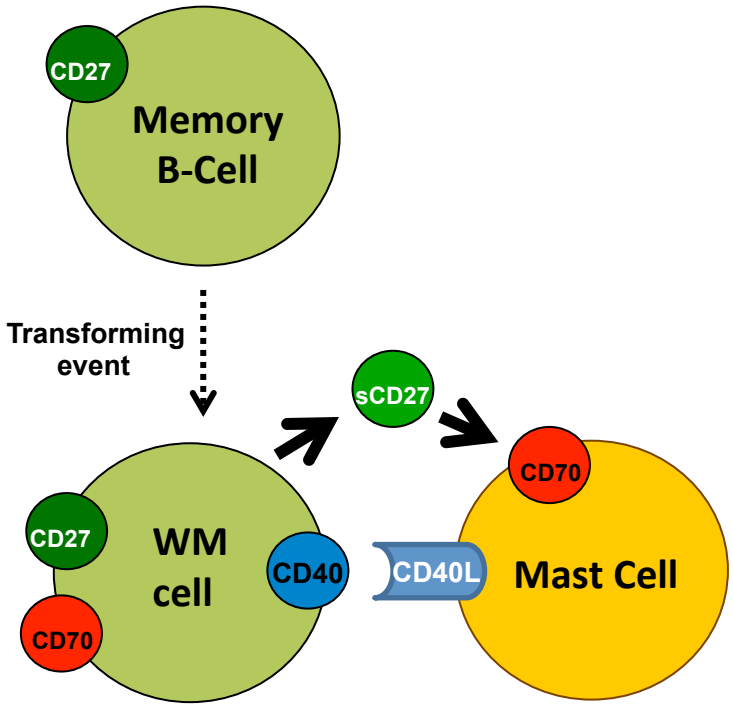
- Rapid depletion of circulating clone

Hematological CR in patient with Sézary Syndrome

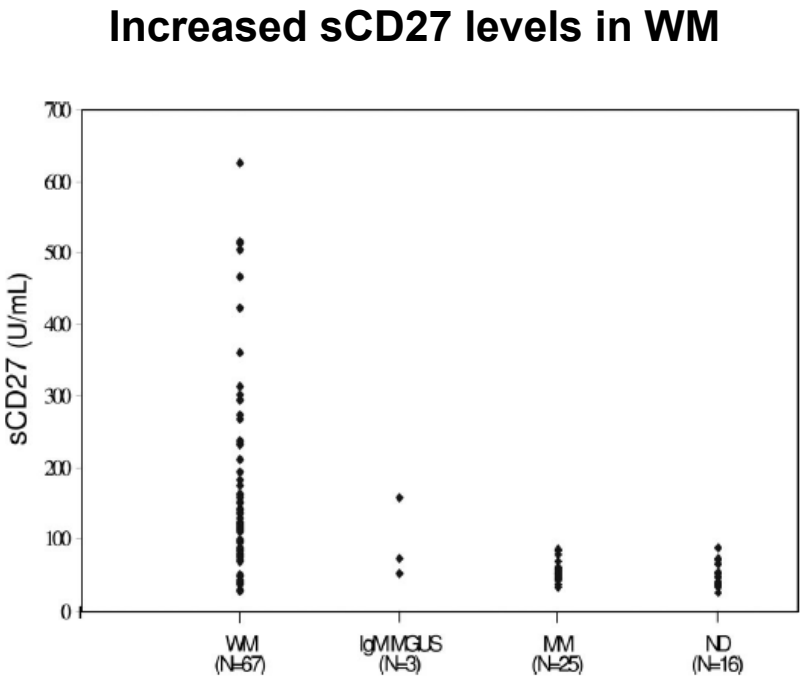


Indication rationale: Waldenström's Macroglobulinemia

CD70 involved in paracrine loop with bone marrow mast cells



*Ho, Blood **2008***



Indication	Phase	N	FPI
Waldenström's LEUKEMIA & LYMPHOMA SOCIETY®	1/2	30	1H 2015

arGEN-X Milestones

- **Progress ARGX-110**
  - Phase 2 monotherapy in Waldenström's - LLS collaboration
  - Phase 2 monotherapy in 2nd hematological indication
  - Phase 1 combination therapy in solid tumors
  - Phase 1 monotherapy in autoimmune disease
- **Progress ARGX-111**
  - Phase 1b monotherapy - establish safety and proof of mechanism
- **Progress ARGX-113**
  - Phase 1 in healthy volunteers
  - Plan for autoimmune indications
- **Advance and expand preclinical pipeline**
- **Access novel targets and technologies**

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