

Delivering on the Promise of RNAi Therapeutics



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Thomas Christély
Chief Operating Officer

Forward-Looking Statements



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- **Leader in the discovery, development and delivery of RNAi therapeutics**
 - RNAi offers a unique new class of drugs that overcomes hurdles of existing drugs
- **One of the sector's most comprehensive RNAi therapeutics platforms**
 - Proprietary siRNA structure (AtuRNAi) and delivery technologies (AtuPLEX, DACC, DBTC)
- **One of the industry's broadest RNAi clinical pipelines**
 - Five of the 13 siRNA clinical programs worldwide are based on Silence technology
 - > thereof 4 of the 5 Phase II studies worldwide
 - Clinical and pre-clinical pipeline in diverse therapeutic areas
 - Encouraging Phase I data on internal lead candidate Atu027 presented at ASCO 2011
- **Validating partnerships with leading global pharmaceutical companies**
 - AstraZeneca, Pfizer/Quark, Novartis/Quark and Dainippon Sumitomo
- **Broad intellectual property portfolio**
 - Issued patents covering aspects of delivery, siRNA-structures and -sequences
- **Listed on AIM (LSE) - operations in Berlin and London**

- **Silence Therapeutics AG (formerly Atugen AG) was founded in 1998 as spin-off from Ribozyme Pharmaceuticals (later renamed to Sirna Therapeutics)**
- **Developing delivery technologies for oligonucleotides since 1998**
- **First siRNA (AtuRNAi) patent application in 2002, US patent granted in Nov. 2008**
- **In 2005 reverse merger with SR Pharma plc (shell) listed on AIM, London**
- **Acquired US siRNA therapeutics company Intradigm Corp. in January 2010**
- **To date over £50m invested in RNAi platform**
- **Well funded following £5.9m fundraising in May 2011**

Silence siRNA Product Pipeline



	Products	Indications	Partners	Target	Delivery	Pre-Clinical	Phase I	Phase II	Target Tissue / Organ
Partnered programs	PF-4523655 (AtuRNAi)	Diabetic Macular Edema	Pfizer/Quark	RTP801	Naked siRNA				Local Delivery to the Eye
	PF-4523655 (AtuRNAi)	Age-related Macular Degen	Pfizer/Quark	RTP801	Naked siRNA				Local Delivery to the Eye
	QPI-1002 (AtuRNAi)	Prevention of Delayed Graft Function	Novartis/Quark	P53	Naked siRNA				Systemic Delivery to the Kidney
	QPI-1002 (AtuRNAi)	Acute Kidney Injury	Novartis/Quark	P53	Naked siRNA				Systemic Delivery to the Kidney
Internal programs	Atu027 (AtuRNAi)	GI & Lung & other cancers	Internal	PKN3	AtuPLEX				Systemic Delivery to Tumor Endothelium
	Atu134 (AtuRNAi)	Solid Tumors	Internal	CD31	AtuPLEX				Systemic Delivery to Tumor Endothelium
	Atu111 (AtuRNAi)	Acute Lung Injury	Internal	n.d.	DACC				Systemic Delivery to Lung Endothelium
	Atu195 (AtuRNAi)	Solid Tumors	Internal	n.d.	AtuPLEX				Systemic Delivery to Tumor Endothelium

Almost half of all ongoing siRNA clinical trials are based on Silence' AtuRNAi technology

Strong Validation Through Partnerships



- AstraZeneca - \$15M upfront payment with up to \$400M in milestones plus sales royalties for five targets (2007, extended 2010)
- AstraZeneca - Novel approaches to delivery of siRNA molecules (2008, extended 2010)



- Pfizer/Quark - Phase II products for diabetic macular edema and age-related macular degeneration; \$95m milestones plus royalties, \$6m received (2006). Next possible milestone \$4m on start of Phase III trials



- Novartis/Quark - Phase II products for acute renal failure and kidney transplantation; \$82m in milestones plus royalties, \$1m received (2010). Next milestone \$3-11m possible in 2012



- Dainippon Sumitomo - siRNA delivery collaboration, \$2m upfront (2009, expanded 2010)



- InteRNA - microRNA delivery collaboration (2011)

Strategic decision to increase BD resources



More deals generating non-dilutive funding to extend runway

“Blueprint For Life”

DNA



Transcription



“Message”

mRNA



**RNA
interference**

Translation



“Body’s Machines”

Protein



Small Molecules
Antibodies

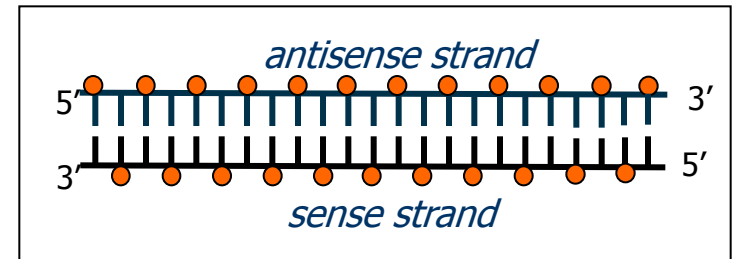
RNAi Therapeutics:

- New class of drugs based on a natural self-defense mechanism
- Recognised by the Nobel Prize to Fire and Mello in 2006
- Virtually all target genes can be addressed subject to functional delivery!
- No need to screen libraries of compounds/antibodies
- Faster pre-clinical development -> faster to market -> earlier revenues

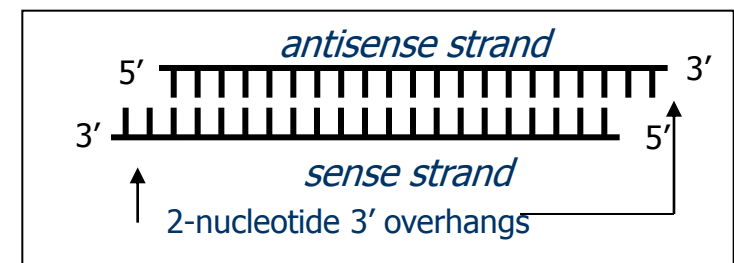
AtuRNAi: The De-Facto Standard

- **2'-O-Methylation offers greater stability and better tolerability**
 - No evidence of cytokine stimulation, activation of Toll-Like Receptors or toxic metabolites
 - Over 300 patients treated to date
- **Blunt-end strands show equivalent knock-down to overhangs**
- **Faster preclinical development**
 - Screening starts directly with modified siRNA
 - Same scale up process for all AtuRNAi products
 - Faster regulatory process expected as tox profile for AtuRNAi is known
- **Lower Cost of Goods**

Silence's AtuRNAi



Conventional siRNA



Silence' Functional Delivery Technologies Targeting Different Organs

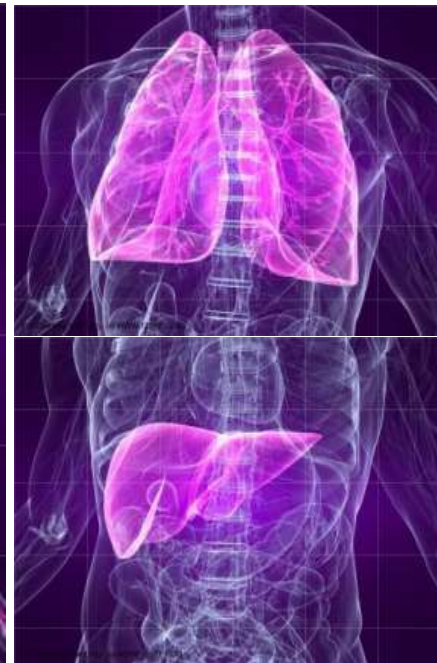


Silence develops delivery technologies for oligonucleotides since 1999

AtuPLEX

Validated broad delivery
to vascular endothelium

- Tumor & Metastasis
- Inflammation



DACC

Highly focused delivery to
lung endothelium

- Acute lung injury/ARDS
- Pulmonary Hypertension
- Infection & Inflammation

DBTC

Highly focused delivery to
liver parenchyma

- Hepatocellular carcinoma
- Ischemia Reperfusion Injury
- Fulminant Fibrosis

AtuPLEX

Validated broad delivery
to vascular endothelium

- Tumor & Metastasis
- Inflammation



Programm

1. Atu027 - PKN3 (Phase I trial ongoing)

- Key regulator during angiogenesis/lymphangiogenesis
- Major regulator of metastasis/motility during pathological processes

2. Atu134 - CD31 (PECAM-1)

- An endothelial target for the inhibition of cancer and metastasis

Atu027 Phase I: Clinical Update

Efficacy

- Stable disease observed in 9 out of 24 patients after treatment phase
- Efficacy and MOA in xenograft models (prostate, breast, lung, colon, pancreatic and other cancers)

PK

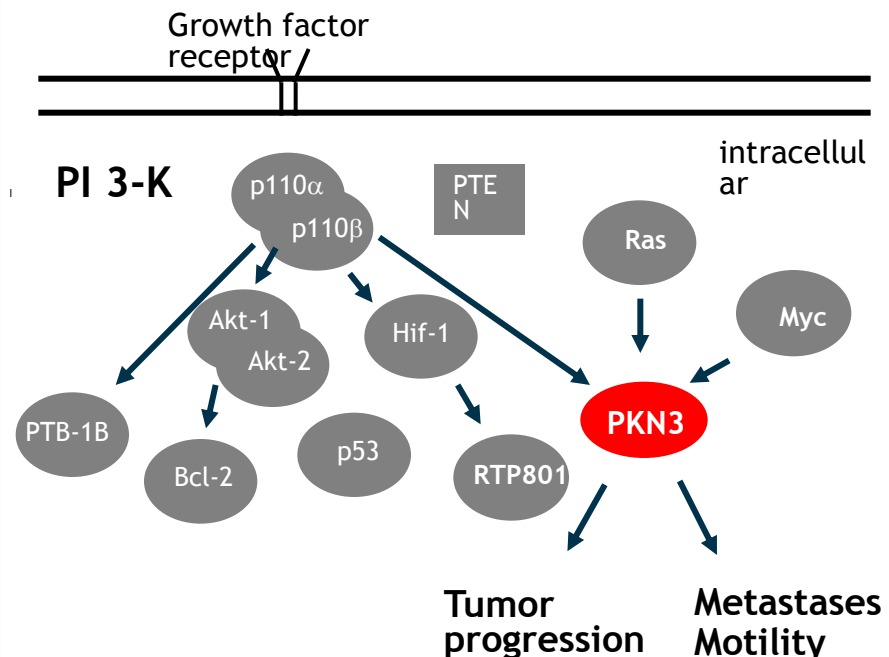
- Dose dependent PK in cynomolgus monkey correlates with PK profile in human

Safety

- No pre-medication with immunosuppressives
- 212 doses administered to 27 patients across 9 dose levels (out of 11 dose levels in total)
- Dose escalation still ongoing
- No dose limiting toxicities so far
- No dose-dependent trends in lab or clinical adverse effects
- 33 doses given to 1 patient incl. compassionate use

CMC

- Lyophilized formulation (shelve life >3 years)



PKN3 plays an important role in angiogenesis and cell motility, major processes leading to metastasis.

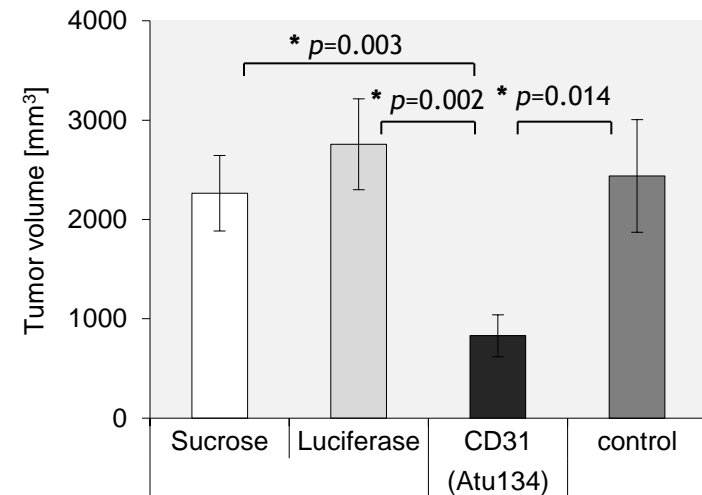
Inhibition of PKN3 leads to:

- reduced oxygen supply to tumour
- reduced tumour growth/metastases

Atu134: Strong Preclinical Efficacy Data

- Atu134 has demonstrated efficacy in a variety of preclinical cancer models
 - Orthotopic models
 - Ectopic models
- Atu134 has demonstrated strong efficacy against primary tumour
- Targets CD31 - well validated target
- GMP manufacturing commencing
- Preclinical toxicology testing due to start in 2012
- IND/IMPD filing expected in 2012
- Plan to partner during Phase I
 - target double digit royalty rate

*In preclinical studies
Atu134 significantly reduced
tumour growth*



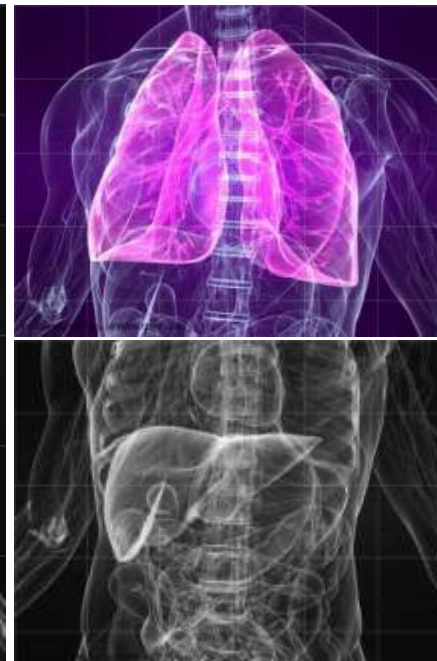
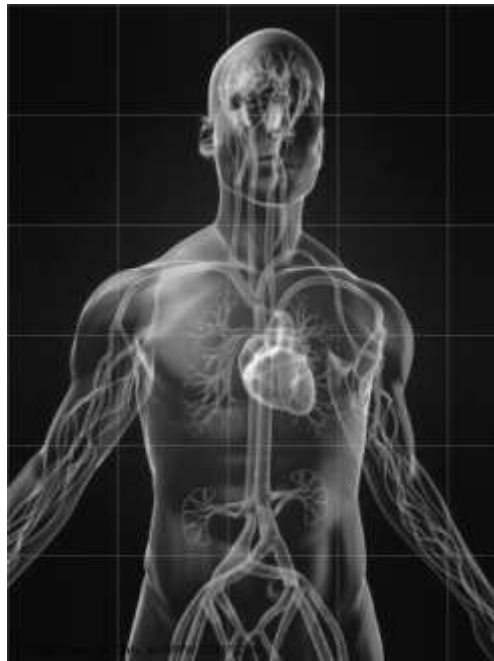
Breast (mammary fat pad)

DACC: Focused Delivery to the Lung

AtuPLEX

Validated broad delivery
to vascular endothelium

- Tumor & Metastasis
- Inflammation



DACC

Highly focused delivery to
lung endothelium

- Acute lung injury/ARDS
- Pulmonary Hypertension
- Infection & Inflammation

DBTC

Highly focused delivery to
liver parenchyma

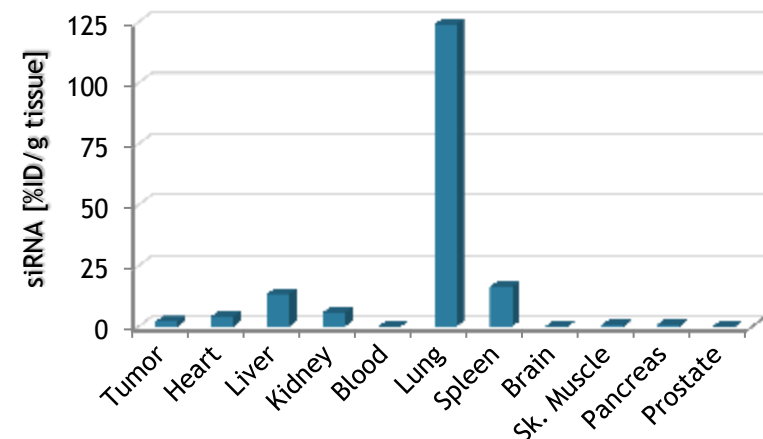
- Hepatocellular carcinoma
- Ischemia Reperfusion Injury
- Fulminant Fibrosis

DACC: Focused Delivery of siRNA for Acute Lung Injury and Other Lung Diseases

- **Acute lung injury (ALI)** is an area of high unmet medical need
- **Significant market opportunity**
 - Pneumonia is **2nd** highest cause of hospital admissions
 - Pneumonia treatment costs **\$8bn/yr** in US alone (mortality rate 12-30%)
 - ALI principle cause of mortality
- **Other potential applications.**
 - Pulmonary Hypertension
 - Infection & Inflammation
- DACC delivery system provides **highly focused delivery to lung** (see chart)
- DACC delivery system leads to **prolonged knock-down - more than 3 weeks**
 - potential for only one dose in ALI
- **Aim to partner in 2012**
 - target single digit royalty rate

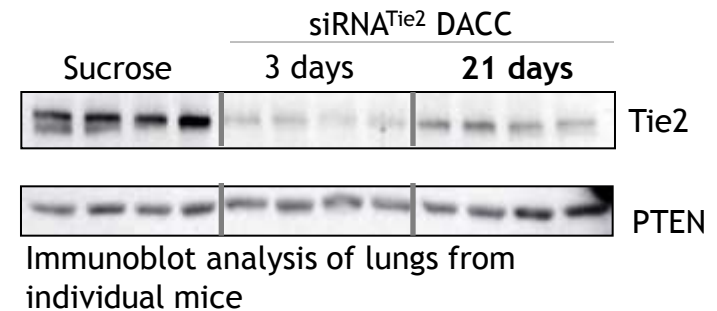
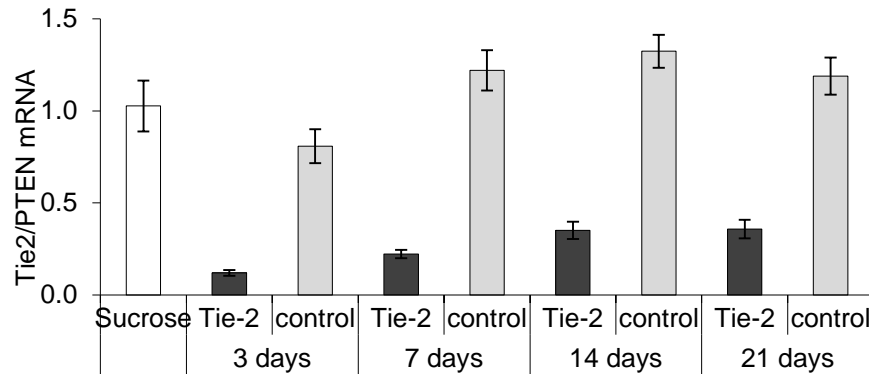


Organ distribution after delivery of siRNA with DACC

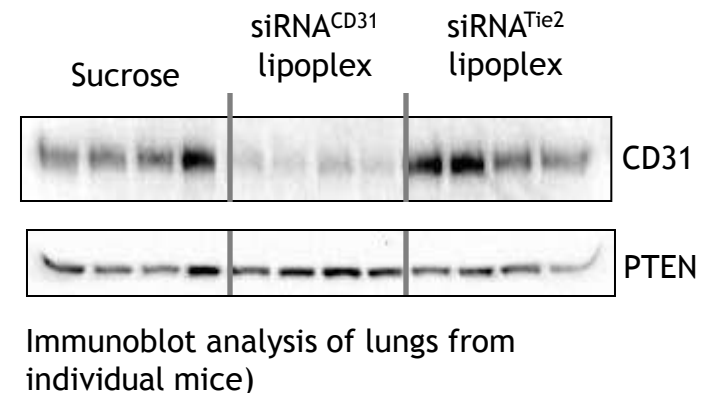
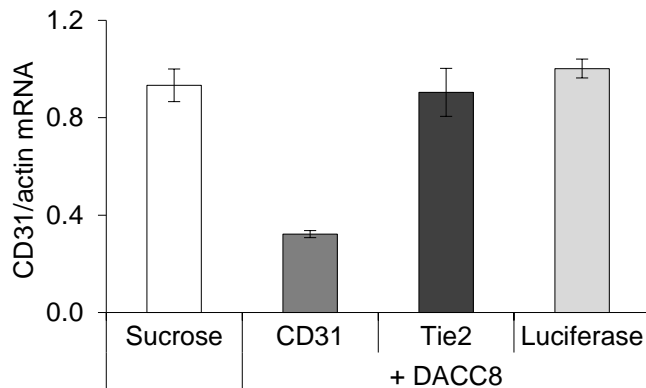


DACC: Long-Term Duration of mRNA and Protein Knockdown (> 21 Days)

Tie-2 mRNA knock-down after 1 single application with DACC



CD31 mRNA knock-down after 1 single application with DACC

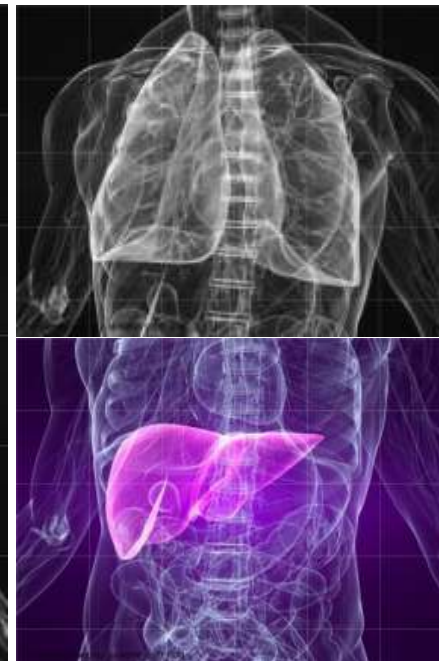
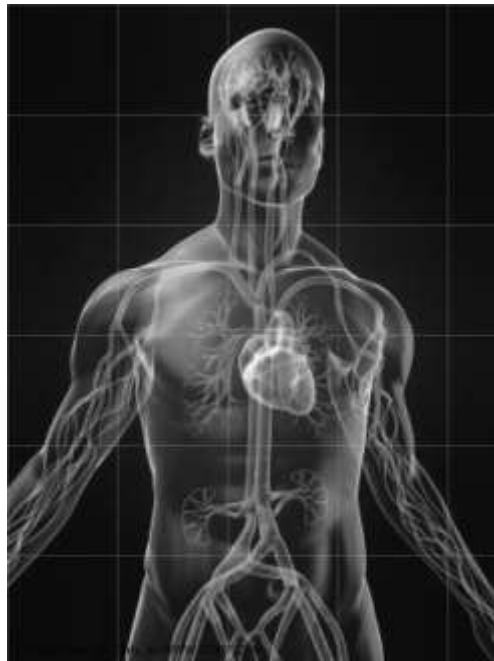


Targeting Different Organs

AtuPLEX

Validated broad delivery to vascular endothelium

- Tumor & Metastasis
- Inflammation



DACC

Highly focused delivery to lung endothelium

- Acute lung injury/ARDS
- Pulmonary Hypertension
- Infection & Inflammation

DBTC

Highly focused delivery to liver parenchyma

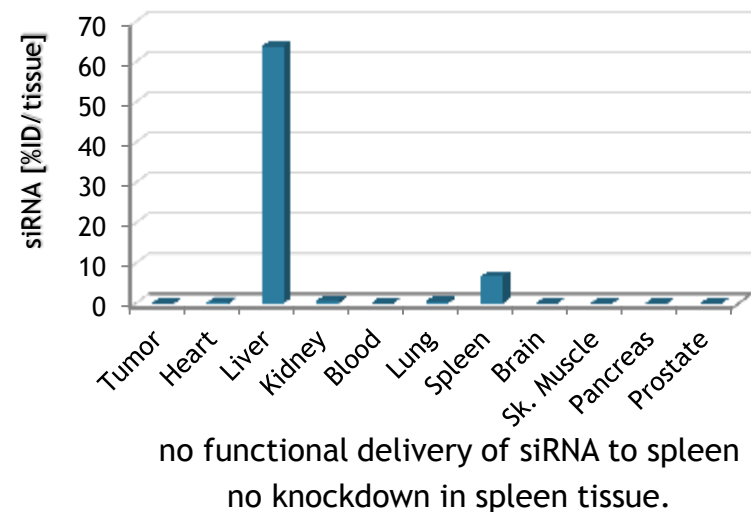
- Hepatocellular carcinoma
- Ischemia Reperfusion Injury
- Fulminant Fibrosis

DBTC: Targeting the Liver









- Proprietary lipid-based formulation targeting liver
- Significant market opportunities
 - Liver cancer
 - Ischemia reperfusion injury
 - Fibrosis
- DBTC delivers siRNAs primarily to liver (see chart)
- DTBC delivery system leads to persistent knock-down
 - Single dose knocks down gene expression for up to 1 week
- DTBC well tolerated
 - Dosed up to 8.3mg/kg



Organ distribution after delivery of siRNA with DBTC



- Out-license / co-develop internal candidates
 - e.g. Atu027 (in 2012), Atu111 (in 2012), Atu134 (TBD), Atu195 (TBD)
- Form new collaborative alliances with pharmaceutical partners (target-specific)
 - e.g. AstraZeneca and Dainippon Sumitomo
- Grant access to our proprietary technology platform (target-specific)
 - e.g. Quark/Pfizer and Quark/Novartis
- Collaborate with biotech partners
 - e.g. for co-development of miRNAs with Silence' delivery technologies

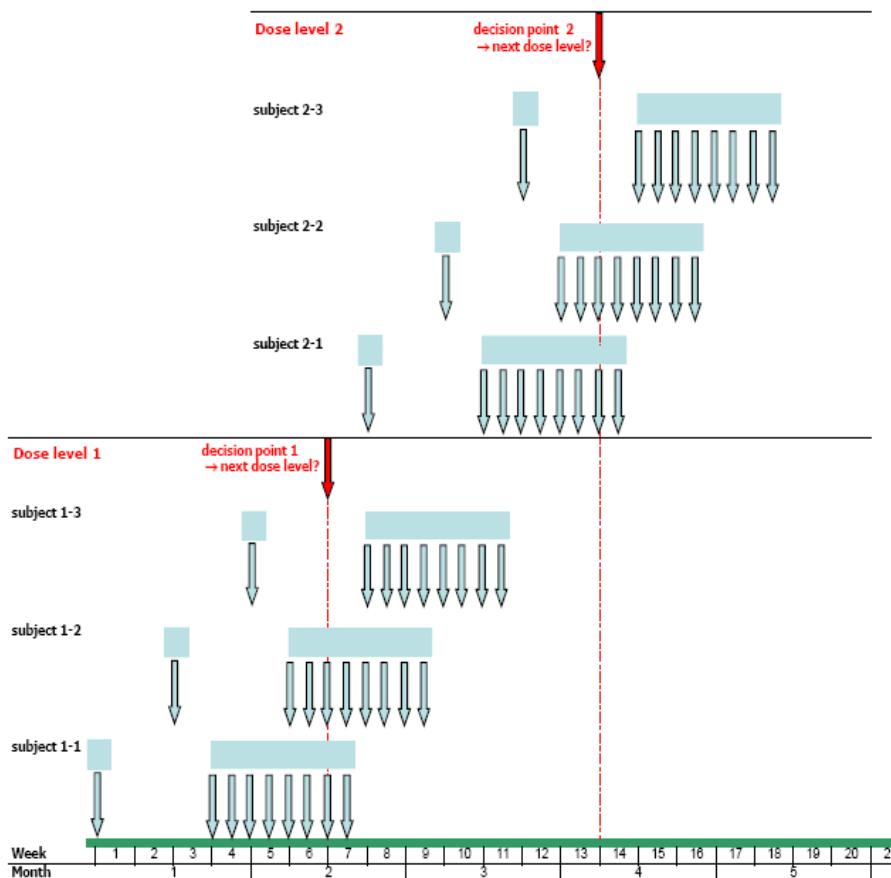
Update on progress of Atu027		Jan. 2011
Update on PF-'655 in diabetic macular oedema (DME)		Mar. 2011
Full year results for 2010		April 2011
Fundraising		May 2011
Present interim Phase I data of Atu027 at ASCO		June 2011
Completion of Phase II trial of PF-'655 in AMD (Pfizer/Quark)		July 2011
Sign new collaborations or extend existing collaborations		Sept. 2011
Further issuance of patents		2H11
Start of Phase IIb trial of PF-'655 in DME (Quark)		2H11
Start of Phase II trial of QPI-1002 in AKI (Quark/Novartis)		2H11
Completion of enrolment in Atu027 trial		1H12

APPENDIX

- Collaboration to deliver novel microRNAs against cancer
- InteRNA gains access to AtuPLEX™ for microRNAs
- InteRNA provides multiple microRNA drug candidates
- Silence receives
 - Upfront payment
 - Staged payments
- Research license only - financial terms for development milestones and commercial license not yet agreed
- Agreement further confirms AtuPLEX's value beyond delivery of siRNA



Schedule



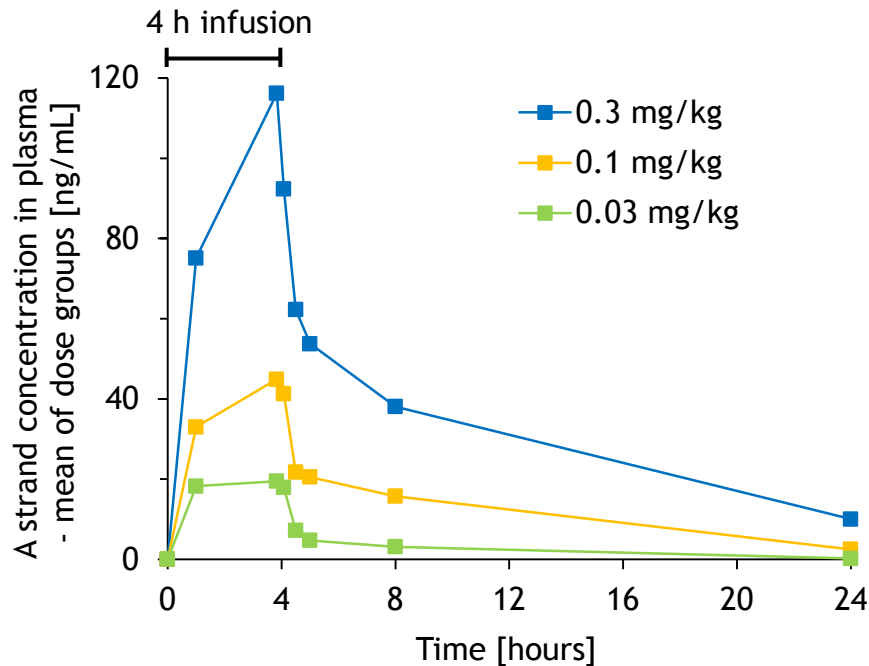
Dose levels

Dose level	Atu027 - Dose (mg/kg) (based on the siRNA content)
1 (starting dose)	0.001
2	0.003
3	0.009
4	0.018
5	0.036
6	0.072
7	0.120
8	0.180
9	0.253
10	0.336
11	0.447



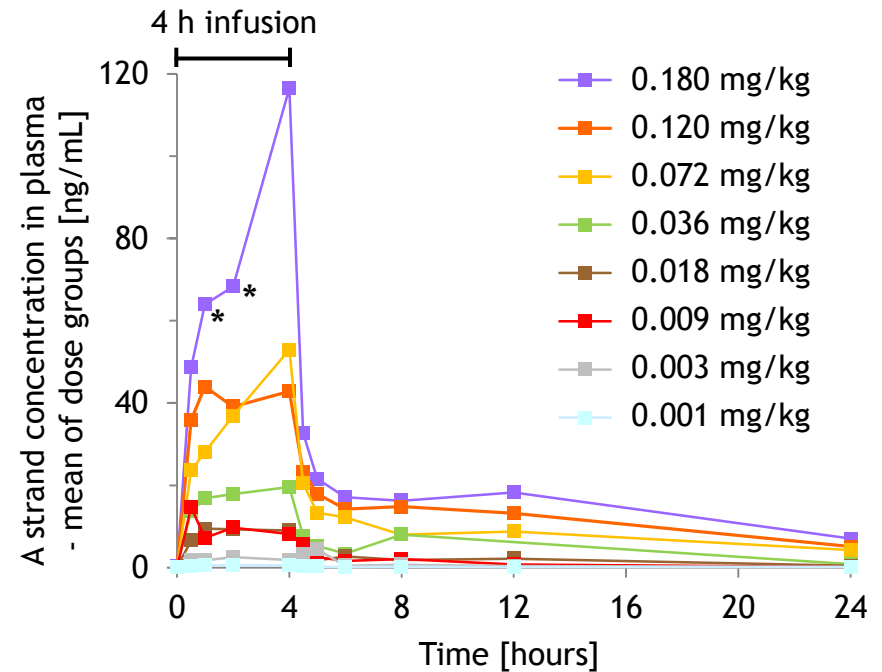
Atu027: Predictable Pharmacokinetics

Cynomolgus Monkey



In vitro: $IC_{50} \approx 1$ to 10 nM

Human



* Final/verified data pending

Predictable PK tells that Atu027 is behaving in humans as it did in pre-clinical models

Key Scientific Papers

The EMBO Journal (2004) 23, 3303–3313 | © 2004 European Molecular Biology Organization | All Rights Reserved 0261-4188/04
www.embojournal.org

THE
EMBO
JOURNAL

PKN3 is required for malignant prostate cell growth downstream of activated PI 3-kinase

Frauke Leenders¹, Kristin Möpert¹, Anett Schmiedeknecht¹, Ansgar Santel¹, Frank Czauderna¹, Manuela Aleku¹, Silke Penschuck^{1,3}, Sibylle Dames¹, Maria Sternberger¹, Thomas Röhl¹, Axel Wellmann², Wolfgang Arnold¹, Klaus Giese¹, Jörg Kaufmann¹ and Anke Klippel^{1,*}

¹Angen AG, Berlin, Germany and ²Pathologisches Institut der Unikliniken, Bonn, Germany

2004

Research Article

Structural variations and stabilising modifications of synthetic siRNAs in mammalian cells

Frank Czauderna, Melanie Fechtner, Sibylle Dames, Hüseyin Aygün¹, Anke Klippel, Gijbertus J. Pronk, Klaus Giese and Jörg Kaufmann¹

Angen AG, Otto Warburg Haus (No. 90), Robert-Rössle-Strasse 10, 13125 Berlin, Germany and ¹BioSpr Hanauer Landstrasse 526, 60386 Frankfurt, Germany

2003

Nucleic Acids Research, 2003, Vol. 31, No. 11 2705–2716
DOI: 10.1093/nar/gkg193

Atu027, a Liposomal Small Interfering RNA Formulation Targeting Protein Kinase N3, Inhibits Cancer Progression

Manuela Aleku¹, Petra Schulz¹, Oliver Keil¹, Ansgar Santel¹, Ute Schaeper¹, Britta Dieckhoff¹, Oliver Janke¹, Jens Endruschat¹, Birgit Durieux¹, Nadine Röder¹, Kathrin Löffler¹, Christian Lange¹, Melanie Fechtner¹, Kristin Möpert¹, Gerald Fisch¹, Sibylle Dames¹, Wolfgang Arnold¹, Karin Jochims¹, Klaus Giese¹, Bertram Wiedenmann², Arne Scholz² and Jörg Kaufmann¹

¹Silence Therapeutics AG, Medizinische Klinik mit Schwerpunkt Hepatologie und Gastroenterologie, Charité-Universitätsmedizin, Berlin, Germany and ²USON Consulting, Medlerstr. 2, Germany

2008

Cancer Therapy: Preclinical

Atu027 Prevents Pulmonary Metastasis in Experimental and Spontaneous Mouse Metastasis Models

Ansgar Santel, Manuela Aleku, Nadine Röder, Kristin Möpert, Birgit Durieux, Oliver Janke, Oliver Keil, Jens Endruschat, Sibylle Dames, Christian Lange, Mona Eisermann, Kathrin Löffler, Melanie Fechtner, Gerald Fisch, Christiane Vank, Ute Schaeper, Klaus Giese, and Jörg Kaufmann

2010



Gene Therapy (2006) 13, 1232–1234
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www.nature.com/gt

ORIGINAL ARTICLE

A novel siRNA-lipoplex technology for RNA interference in the mouse vascular endothelium

A Santel, M Aleku, O Keil, J Endruschat, V Esche, G Fisch, S Dames, K Löffler, M Fechtner, W Arnold, K Giese, A Klippel and J Kaufmann
Angen AG (SR Pharma plc subsidiary), Berlin, Germany

2006

Gene Therapy (2006) 13, 1265–1273
© 2006 Nature Publishing Group. All rights reserved 0969-7128/06 \$30.00
www.nature.com/gt

ORIGINAL ARTICLE

RNA interference in the mouse vascular endothelium by systemic administration of siRNA-lipoplexes for cancer therapy

A Santel, M Aleku, O Keil, J Endruschat, V Esche, B Durieux, K Löffler, M Fechtner, T Röhl, G Fisch, S Dames, W Arnold, K Giese, A Klippel and J Kaufmann
Angen AG (SR Pharma plc subsidiary), Berlin, Germany

2006

Microvascular Research 76 (2008) 31–41



Contents lists available at ScienceDirect

Microvascular Research

journal homepage: www.elsevier.com/locate/ymsvs



Regular Article

Intracellular localization of lipoplexed siRNA in vascular endothelial cells of different mouse tissues

Manuela Aleku, Gerald Fisch, Kristin Möpert, Oliver Keil, Wolfgang Arnold, Jörg Kaufmann, Ansgar Santel¹
Silence Therapeutics AG, 13325 Berlin, Germany

2008

Atu134 (CD31/PECAM-1): A well validated target

Gene Therapy (2006) 13, 1301–1370
© 2006 Nature Publishing Group All rights reserved 0969-7129/06 530.00
www.nature.com/gt

ORIGINAL ARTICLE

RNA interference in the mouse vascular endothelium by systemic administration of siRNA-lipoplexes for cancer therapy

A Santel, M Aleku, O Keil, J Endruschat, V Esche, B Durieux, K Löffler, M Fechtner, T Röhl, G Fisch, S Dames, W Arnold, K Giese, A Klippel and J Kaufmann
Atugen AG (SR Pharma plc subsidiary), Berlin, Germany



The American Journal of Pathology, Vol. 175, No. 2, August 2009
Vascular Biology, Atherosclerosis and Endothelium Biology

Angiogenesis in Platelet Endothelial Cell Adhesion Molecule-1-Null Mice

Geoyuan Cao, Melane L. Fehrenbach, James T. Williams, Jeffrey M. Finkelshteyn, Jing-Xu Zhu, and Horace M. DeLisser

Vascular endothelial platelet endothelial cell adhesion molecule 1 (PECAM-1) regulates advanced metastatic progression

Horace DeLisser^{a,1}, Yong Liu^{b,1}, Pierre-Yves Desprez^b, Ann Thor^c, Paraskevi Briasouli^b, Chakrapong Handumrongkul^b, Jonathon Wilfong^b, Garret Yount^b, Mehdi Nosrati^{d,2}, Sylvia Fong^{b,3}, Emma Shtivelman^{b,3}, Melane Fehrenbach^a, Gaoyuan Cao^a, Dan H. Moore^b, Shruti Nyack^b, Denny Liggitt^e, Mohammed Kashani-Sabet^{d,2}, and Robert Debs^{b,4}

18616–18621 | PNAS | October 26, 2010 | vol. 107 | no. 43

Antibody against murine PECAM-1 inhibits tumor angiogenesis in mice

Zhao Zhou¹, Melpo Christofidou-Solomidou¹, Cecilia Garlanda² & Horace M. DeLisser¹

¹Pulmonary and Critical Care Division, Department of Medicine, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania, USA; ²Mario Negri Institute for Pharmacological Research, Milan, Italy



Angiogenesis 3: 181–188, 1999.

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Delivering on the Promise of RNAi Therapeutics



Thank you