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Potency assay development

Cell-based therapy for cartilage repair



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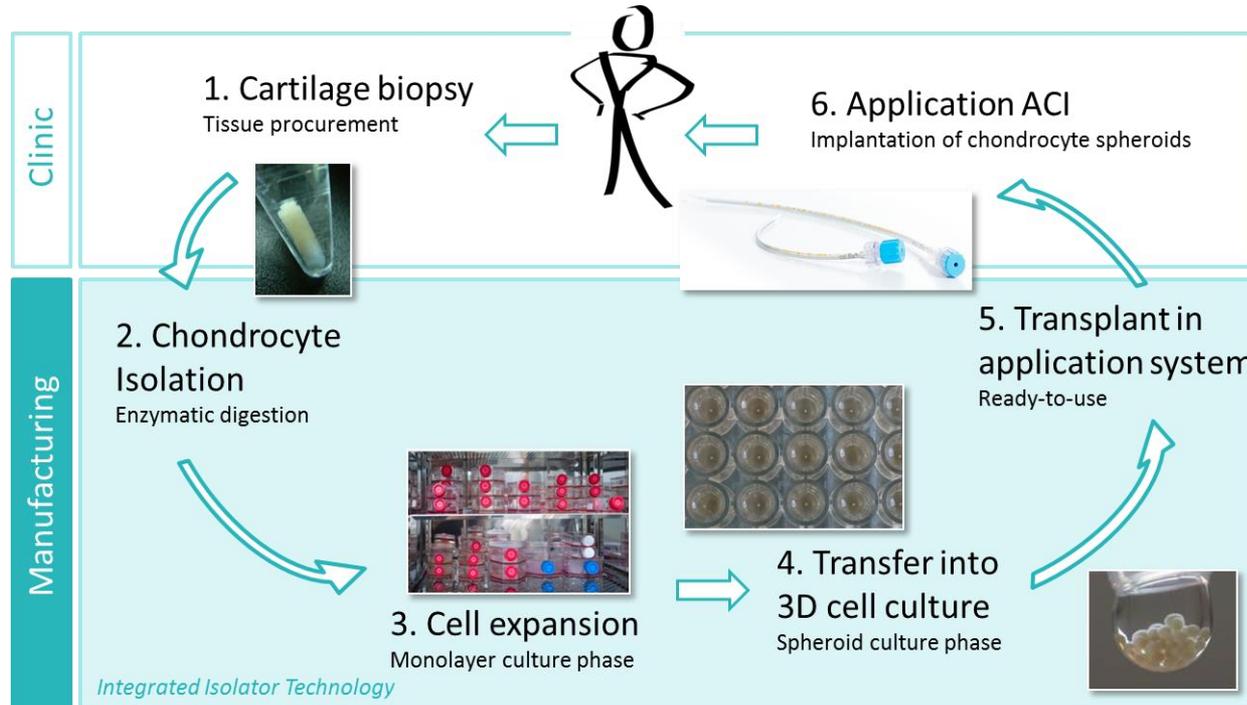
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Cell-based therapy for cartilage repair

Autogenous chondrocyte implantation



Integrated Isolator Technology

Aseptic manufacturing – from starting material to final product



Treatment of cartilage lesions

Application by arthroscopy



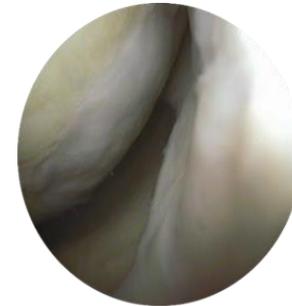
Cartilage
lesion



Application
by
arthroscopy



Chondrocyte
spheroids adhere
to the defect



Follow-up
after treatment
(13 months)

CMC development

Development of ,manufacturing design' and product-specific tests



Manufacturing process

- Cell cultivation times
- Cell expansion

Product Quality

- Surface, colour
- Cell number and viability
- Genetic stable cells
- Dose

Product Specifications

- Microbiological safety tests (Eu. Ph.)
- Identity
- Impurity
- **Potency**

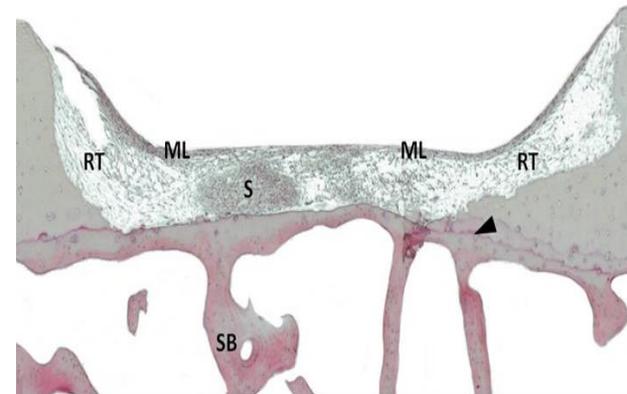
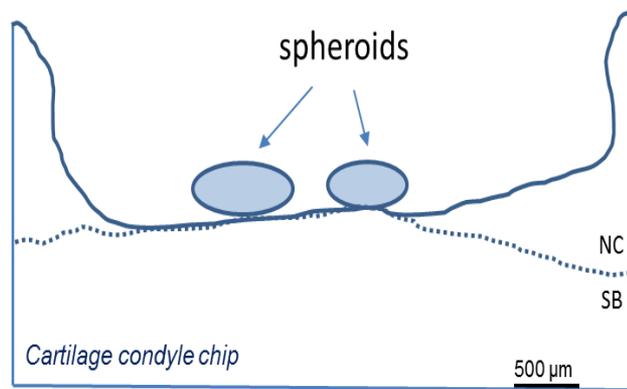
Potency test requirements

Challenges for autologous cell-based ATMPs

- Product-specific test
- Regulatory requirements ICH 6QB guidelines
 - Quantitative measure of the biological activity of the final product
 - Reflects the intended function/efficacy of the product
 - Critical quality attribute linked to product efficacy
- Small sample size
- Fast release test
 - Short shelf-life
 - For every single batch=individual patient

Development of a potency assay

Human cartilage condyle chip assay



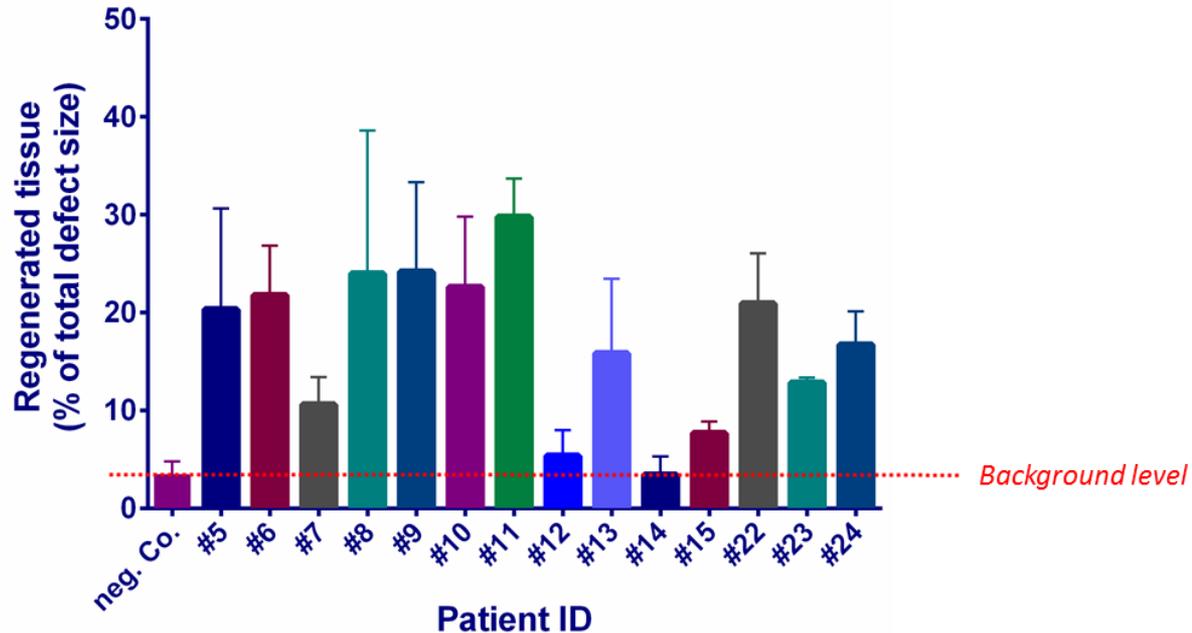
NC – native cartilage
ML – multilayer
RT – regenerated tissue
S – spheroid
SB, subchondral bone

- Simulation of clinical application
- Co-culture cartilage with defect and chondrocyte spheroids (product)
- Quantitative measurement of new tissue formation, *ex vivo*

Bartz et al., 2016 (Journal of Translational Medicine)

Potency assay

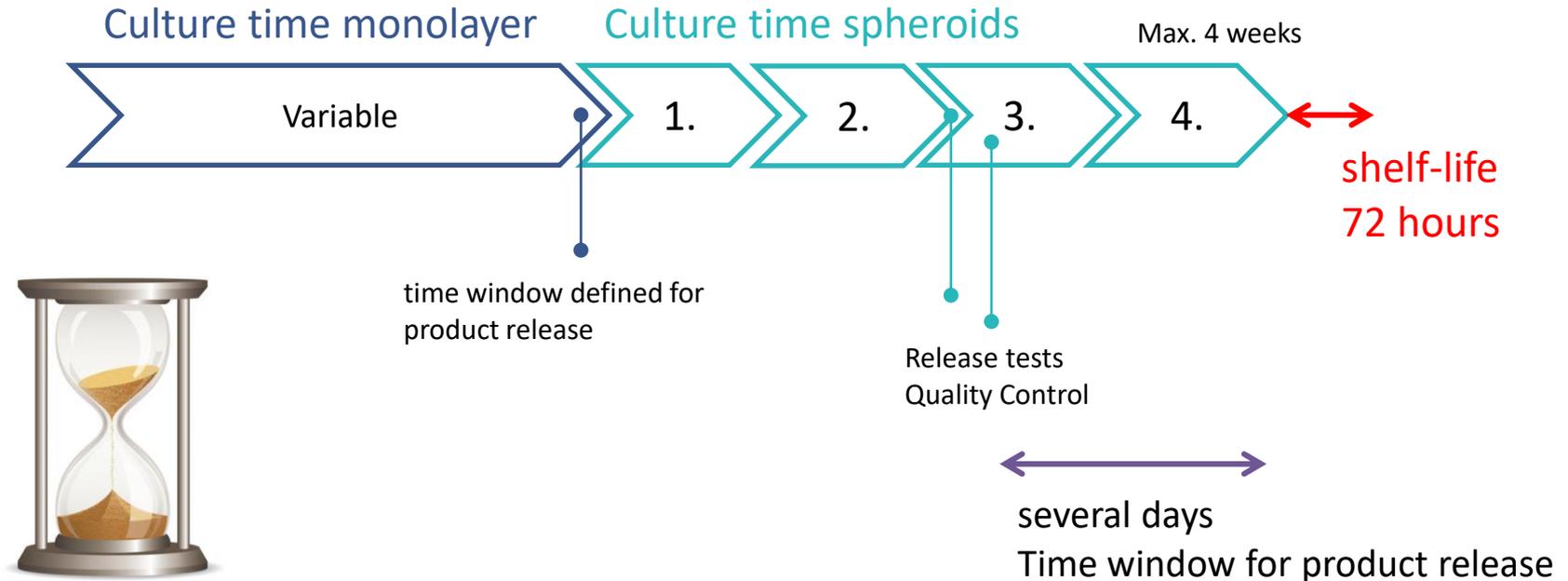
Quantification of tissue formation, *ex vivo*



Bartz et al., 2016 (Journal of Translational Medicine)

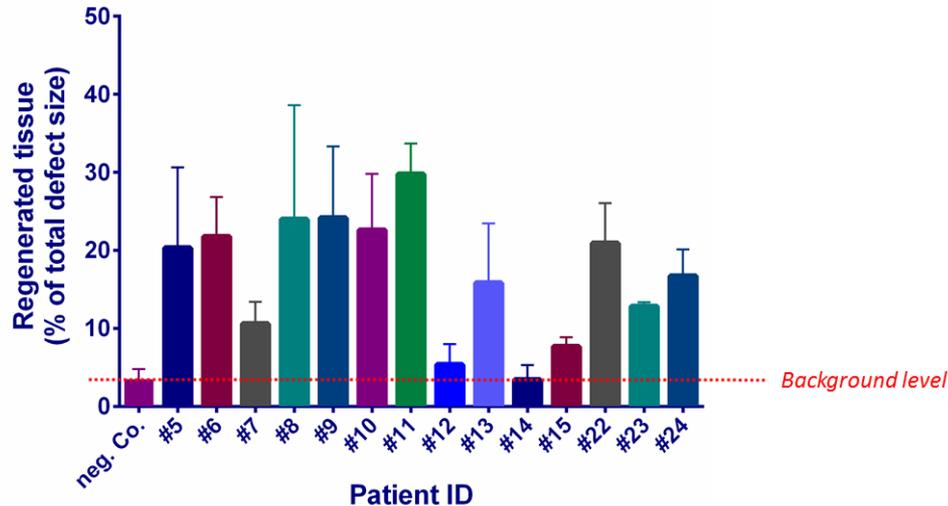
Potency assay

Challenges for autologous cell-based ATMPs



Potency assay

Batch-dependent regeneration potential



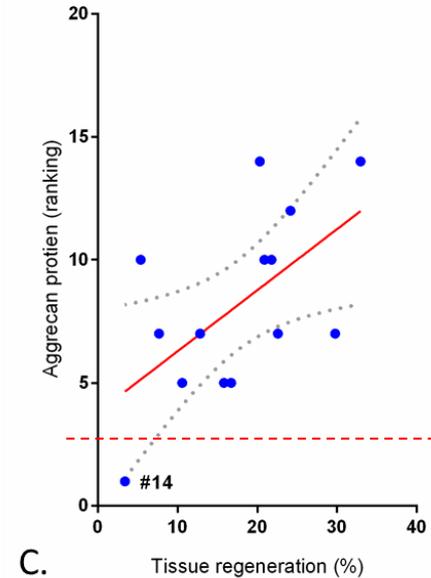
1. Quantify level of tissue formation=potency
 - Batch-specific
 2. Link regeneration potential to a biological marker
 - Screen expression levels of chondrogenic markers
 - Identify marker with predictive ability
- Set up a surrogate potency assay using qPCR

Bartz et al., 2016 (Journal of Translational Medicine)

Surrogate potency assay

Develop a fast release test for potency

- Correlation between ACAN levels and capacity of the spheroids to form new tissue
- Basis for a QC release test
- Release parameter: ACAN mRNA levels
- Method validation ICH Q2 (R1)
 - accuracy, sensitivity, precision, and specificity



Bartz et al., 2016 (Journal of Translational Medicine)

Validation of the release test for potency

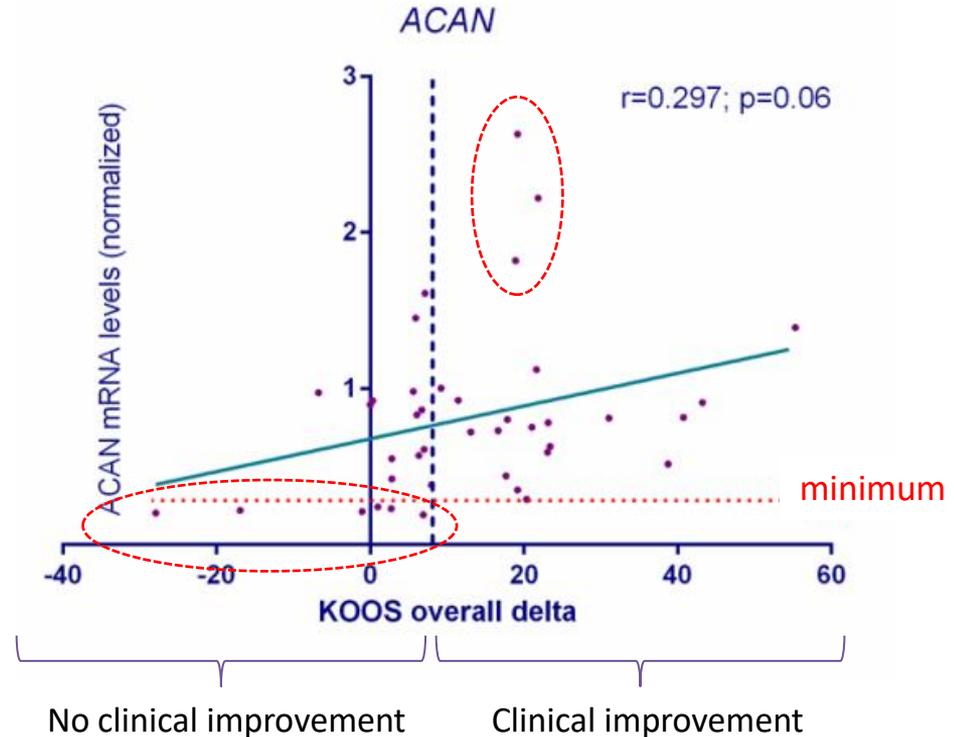
Justification of acceptance limit

- Assessment of spheroid batches used in Phase II+III clinical trials
 - ACAN mRNA levels
 - Clinical improvement (KOOS>8)
- Not statistically significant
- **Lowest ACAN levels**: no clinical improvement

Product specification

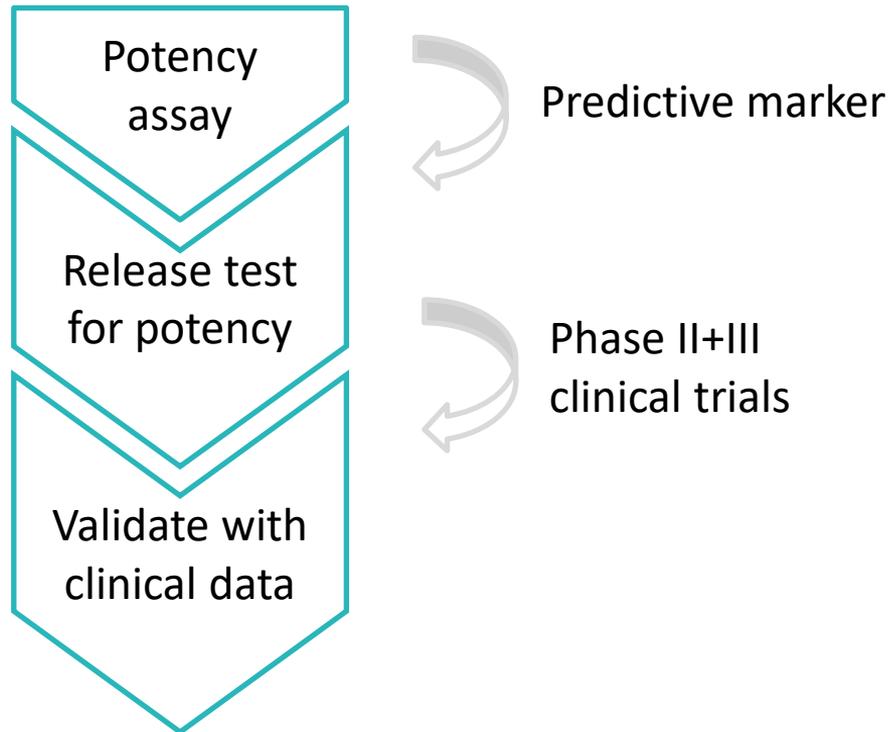
Minimal ACAN level justified by clinical outcome

(Re-validation using 2-year follow up data)



Summary

Establish a fast release test for potency



- not suitable as a release test
- Surrogate potency assay, fast release test based on qPCR
- Validation phase: justify acceptance limit for potency using clinical data

Acknowledgements

Potency Assay R&D

Former colleagues Dr. J. Smink, C. Bartz, M. Meixner, Dr. C. Bulwin
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Regulatory processes

Dr. C. Kaps + RA team
Dr. C. Eschen



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Intro

Dr. Giuletta Roël

- Universität Utrecht (Biologie, MSc), Hubrecht Institute, Utrecht NL (Doktorarbeit Entwicklungsbiologie)
 - Zell- und Molekularbiologin, seit 5 Jahren Biotechnologie- / Biopharmazieindustrie
 - Wissenschaftliche, von Fachleuten begutachtete (peer-reviewed) Publikationen in Fachzeitschriften
 - Tierstudien (z.B. Maus, Zebrafisch, Krallenfrosch), entwicklungsbiologische Wirkmechanismen

- CO.DON AG: Entwicklung von CMC Prozesse (Entwicklung Herstell- und Qualitätskontrollprozesse)
 - Entwickelte das Konzept für den Wirksamkeitstest bei der Sphäroidtechnologie (Spherox)
 - Optimierte den Herstellprozess unter Berücksichtigung der Sicherheit und Wirksamkeit für die Sphäroidtechnologie
 - Klinische Validierung aller Herstellparameter, auch der Biomarker und Spezifikationen in der Sphäroidtechnologie
 - Dokumentation und Interpretation von präklinischen Forschungsdaten für die Zulassung des Arzneimittels Spherox