Imperial College London

A Platform For The Design of Optimal Personalised Treatment For Acute Myeloid Leukaemia (AML)

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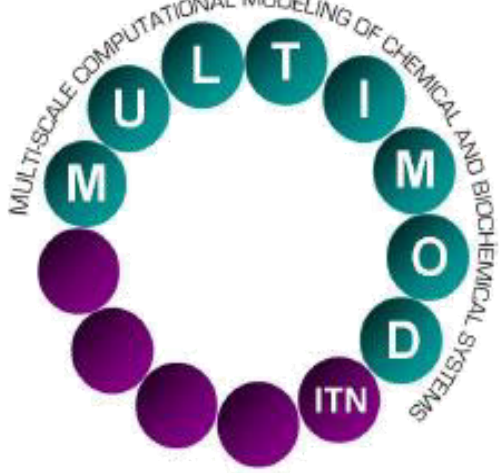
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Key words: chemotherapy optimization, cell cycle models, cyclin, 3D scaffold, AML, pharmacokinetics, pharmacodynamics
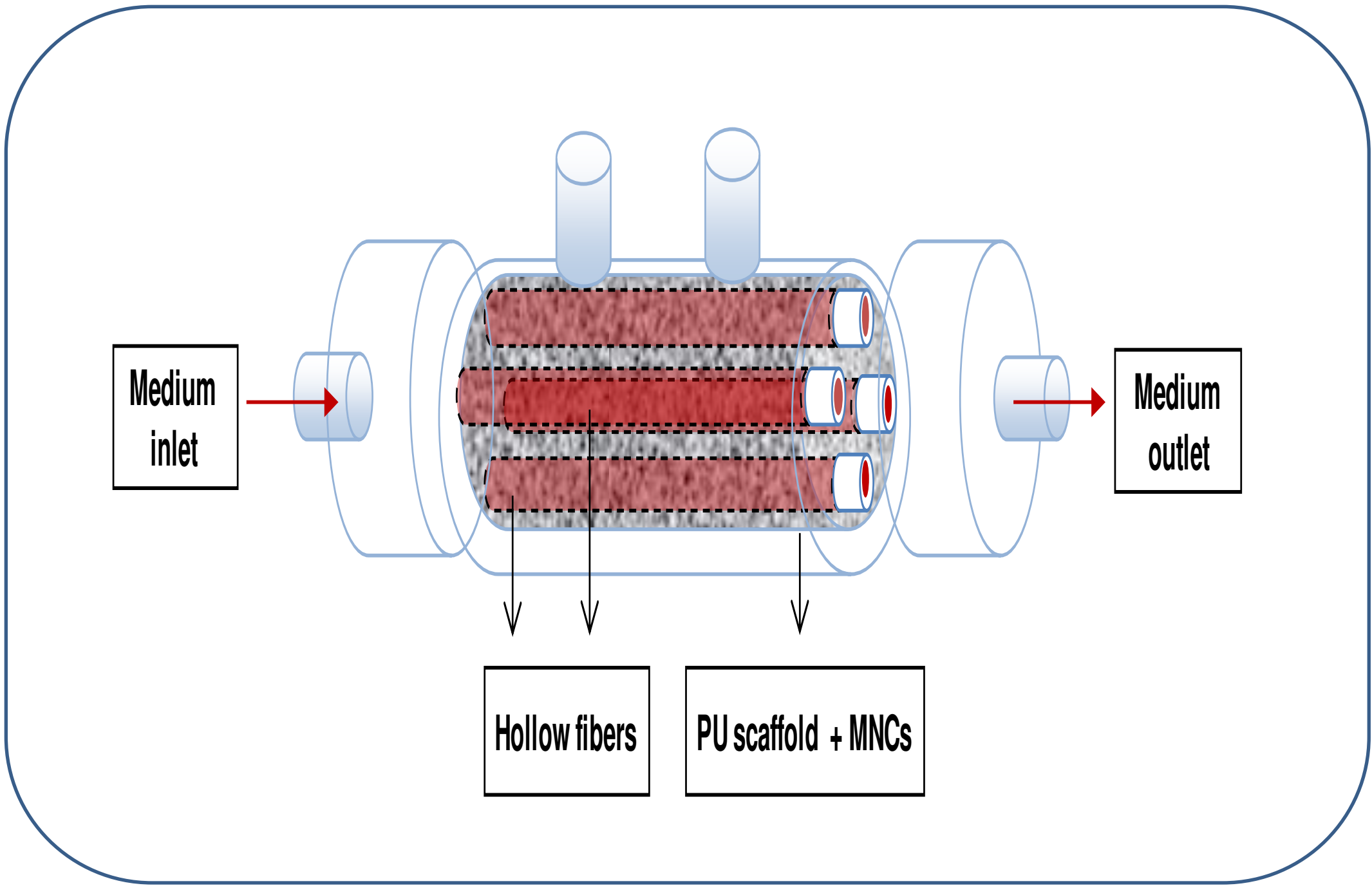
erc MOBILE

MULTIMOD ITN

Northwick Park Hospital, Leukaemia Research Fund

RICHARD THOMAS Leukaemia Fund

NHS National Institute for Health Research

BioBlood Platform

In Vitro Platform

Medium inlet — Medium outlet

Hollow fibers | PU scaffold + MNCs

Development of a platform for the in vitro biomimicry of Acute Myeloid Leukaemia

PATIENT → PATIENT SPECIFIC BIOMIMICRY CELL CULTURE → 3D-scaffolding system / Bioreactor → Optimization
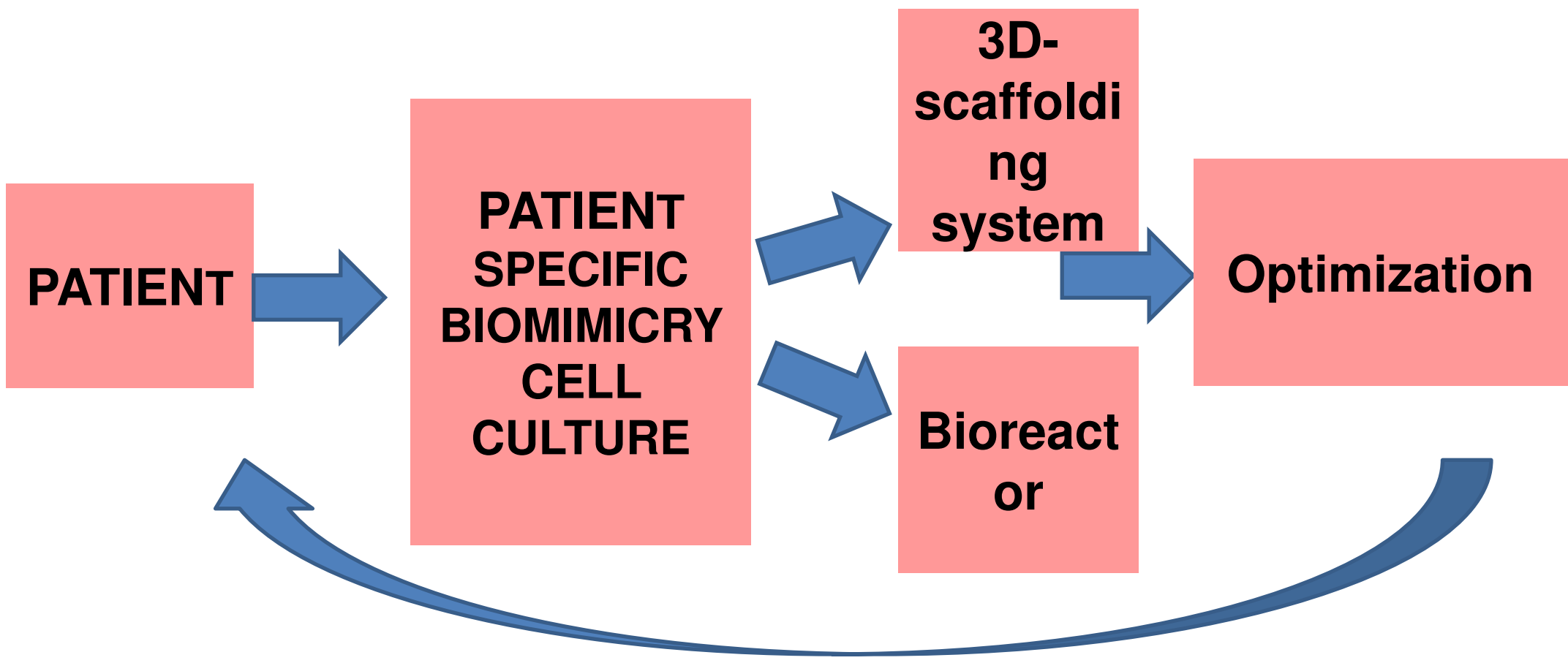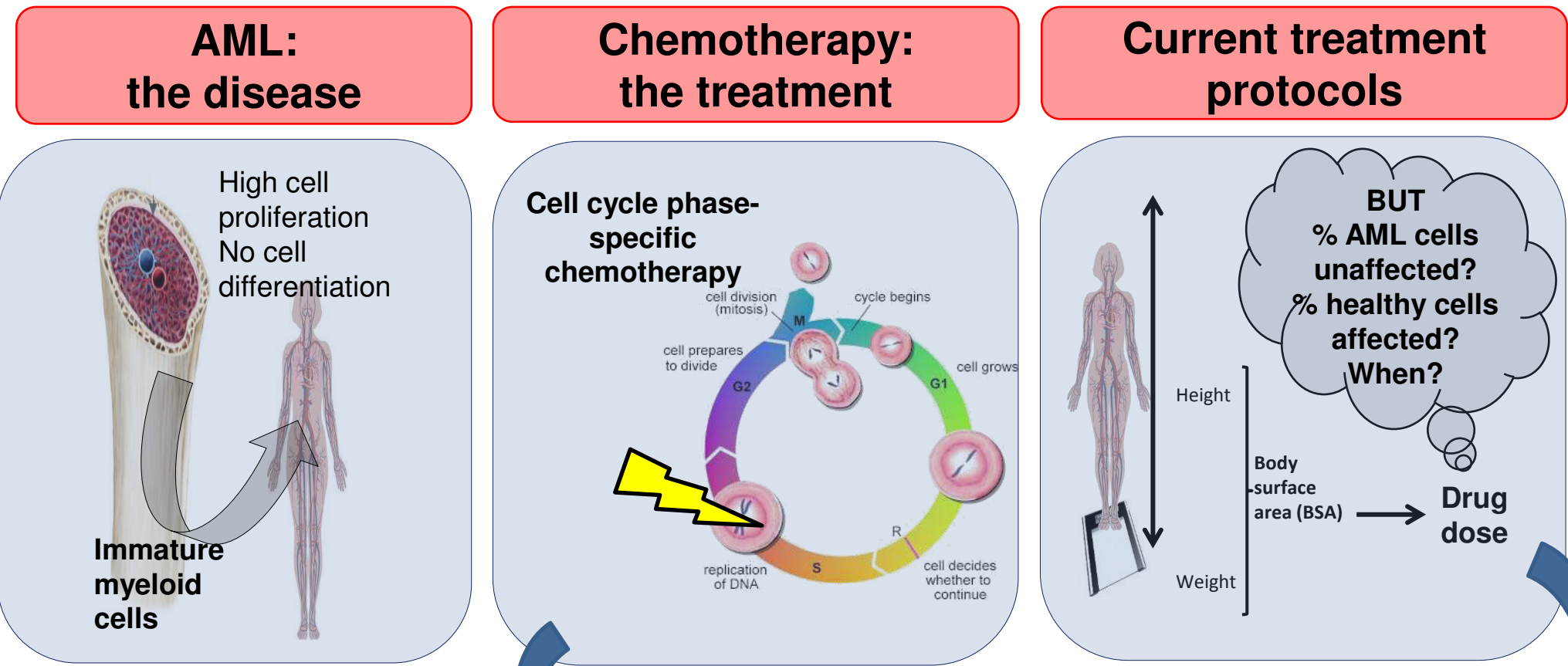
- Design of a **bioreactor** for laboratory cultivation of Acute Myeloid Leukaemia (AML).

- Optimization of the cultivation conditions in the bioreactor (reactor structural characteristics and environmental parameters).

- Application of environmental stress factors in a 3D-scaffolding system as well as in the developed bioreactor:
  Oxidative Stress
  (in vitro biomimicry of **hypoxia**)
  Starvation Stress
  (in vitro biomimicry of **hypoglycaemia** & **hyperglycaemia**).
  Heat Stress
  (in vitro biomimicry of **hyperthermia** & **hypothermia**).

- From **in vitro to in silico**: Data obtained in the in vitro platform will be an appropriate input towards the development and optimization of a mathematical tool for personalized chemotherapy.

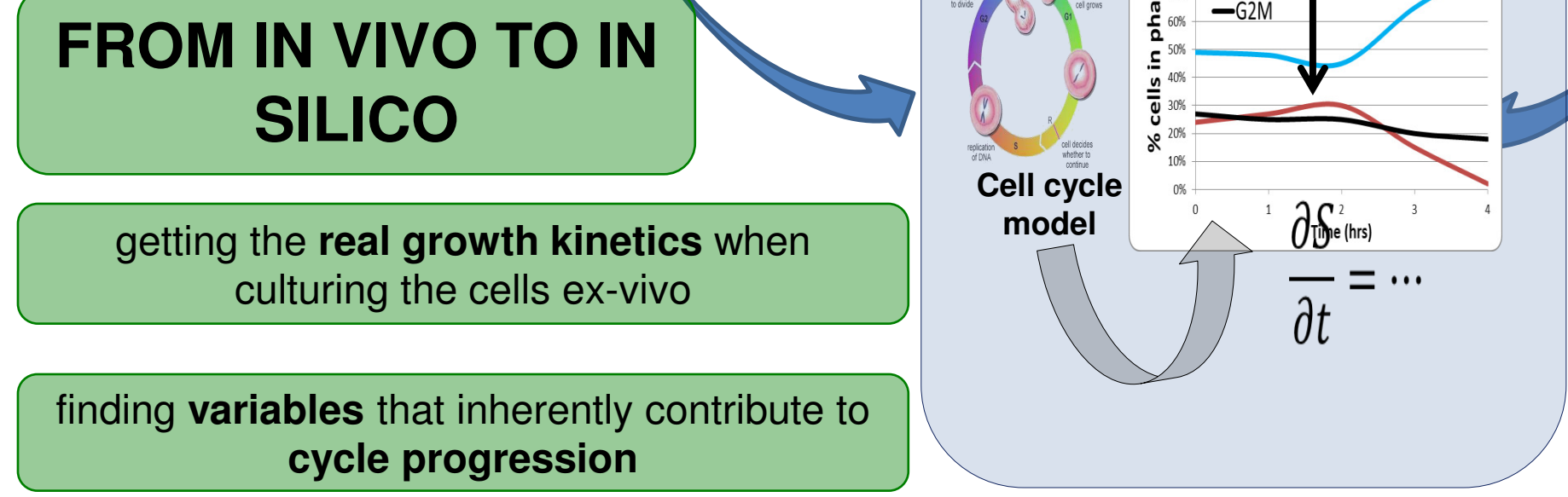---

Patient-specific Cell Cycle Characterisation
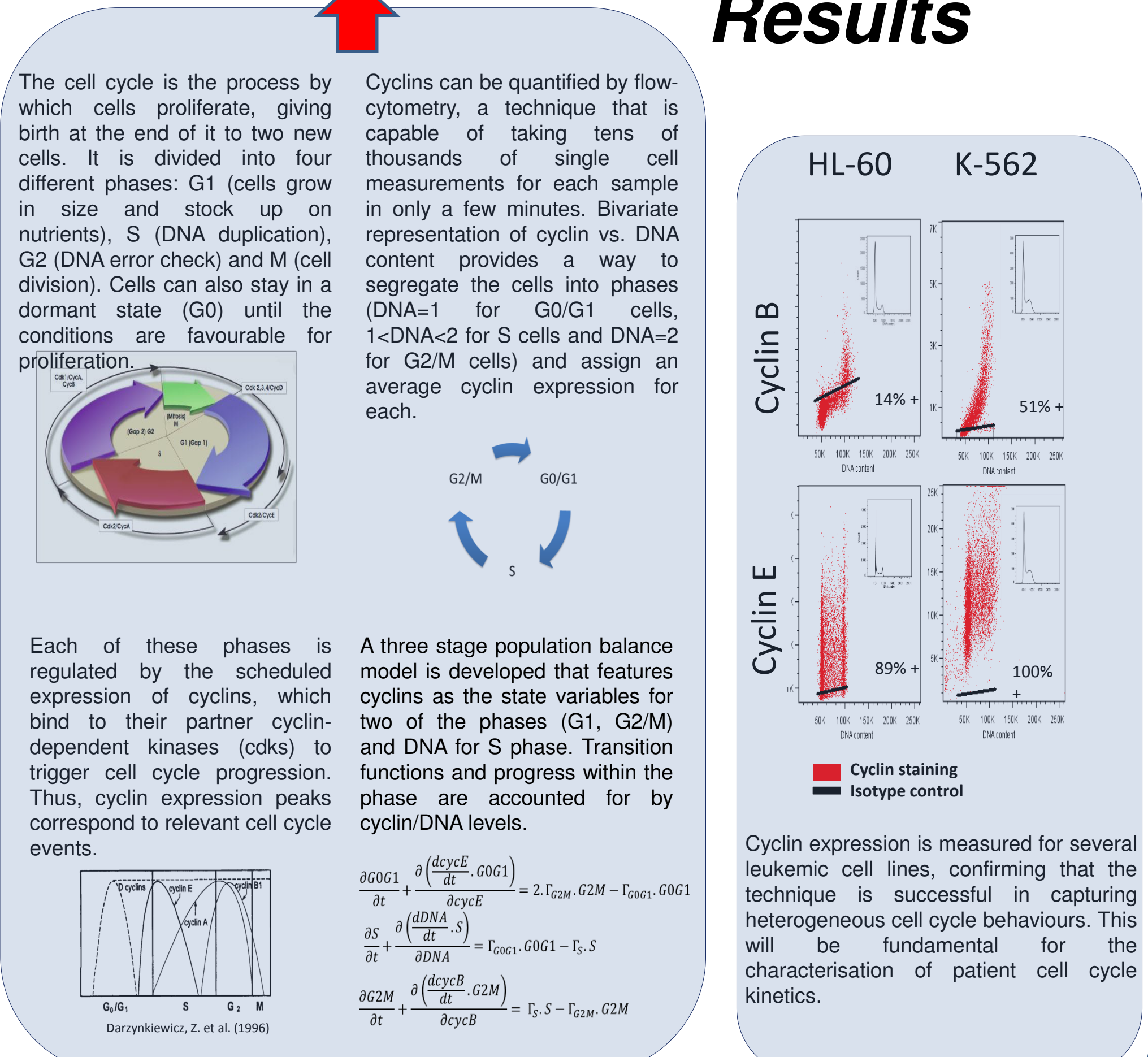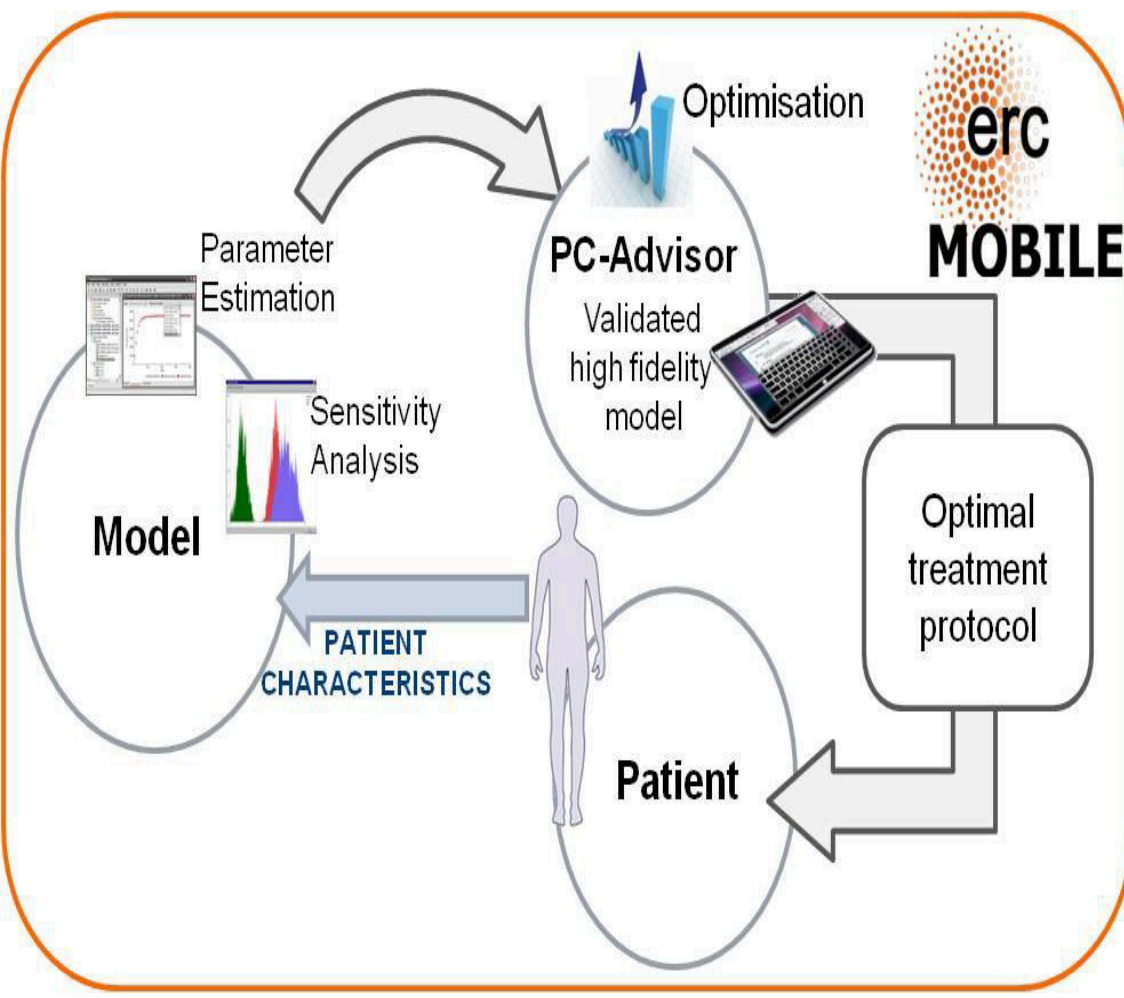
In vitro/In silico cell cycle platform

drug

GROWTH KINETICS

3D ex-vivo cell culture

CYCLIN PROFILES (PHASE PROGRESS INDICATORS)

Cell cycle model

cycle begins / cell to divide / cell grows / replication of DNA

G1, G0, S, G2, M

Patient sample

Motivation

AML: the disease	Chemotherapy: the treatment	Current treatment protocols
High cell proliferation No cell differentiation — Immature myeloid cells	Cell cycle phase-specific chemotherapy	BUT % AML cells unaffected? % healthy cells affected? When? — Height / Body surface area (BSA) / Weight → Drug dose

Approach

Proposed treatment protocols

FROM IN VIVO TO IN SILICO

getting the **real growth kinetics** when culturing the cells ex-vivo

finding **variables** that inherently contribute to **cycle progression**

Cell cycle model

$$\frac{\partial S}{\partial t} = \dots$$

chemotherapy

% cells in phase — G1/G0, S, G2/M

Results

The cell cycle is the process by which cells proliferate, giving birth at the end of it to two new cells. It is divided into four different phases: G1 (cells grow in size and stock up on nutrients), S (DNA duplication), G2 (DNA error check) and M (cell division). Cells can also stay in a dormant state (G0) until the conditions are favourable for proliferation.

Cyclins can be quantified by flow-cytometry, a technique that is capable of taking tens of thousands of single cell measurements for each sample in only a few minutes. Bivariate representation of cyclin vs. DNA content provides a way to segregate the cells into phases (DNA=1 for G0/G1 cells, 1<DNA<2 for S cells and DNA=2 for G2/M cells) and assign an average cyclin expression for each.

Each of these phases is regulated by the scheduled expression of cyclins, which bind to their partner cyclin-dependent kinases (cdks) to trigger cell cycle progression. Thus, cyclin expression peaks correspond to relevant cell cycle events.

A three stage population balance model is developed that features cyclins as the state variables for two of the phases (G1, G2/M) and DNA for S phase. Transition functions and progress within the phase are accounted for by cyclin/DNA levels.

$$\frac{\partial G0G1}{\partial t} = \frac{\partial (\frac{dcycE}{dt} \cdot G0G1)}{\partial cycE} = 2 \cdot \Gamma_{G2M} \cdot G2M - \Gamma_{G0G1} \cdot G0G1$$

$$\frac{\partial S}{\partial t} = \frac{\partial (\frac{dDNA \cdot S}{dt})}{\partial DNA} = \Gamma_{G0G1} \cdot G0G1 - \Gamma_S \cdot S$$

$$\frac{\partial G2M}{\partial t} = \frac{\partial (\frac{dcycB}{dt} \cdot G2M)}{\partial cycB} = \Gamma_S \cdot S - \Gamma_{G2M} \cdot G2M$$

Darzynkiewicz, Z. et al. (1996)

HL-60   K-562

Cyclin B: 14% / 51%

G2/M   G0/G1

S

Cyclin E: 89% / 100%

Cyclin staining
Isotype control

Cyclin expression is measured for several leukemic cell lines, confirming that the technique is successful in capturing heterogeneous cell cycle behaviours. This will be fundamental for the characterisation of patient cell cycle kinetics.

Output: Automated Optimal Protocols

Intelligent computer model-based system for drug delivery

Parameter Estimation / Sensitivity Analysis / Model / PATIENT CHARACTERISTICS / Optimisation / PC-Advisor Validated high fidelity model / erc MOBILE / Optimal treatment protocol / Patient

Derivation of a high-fidelity model for further application of an intelligent computer model-based system for drug delivery of chemotherapy to ensure:

- Reliable and fast calculation of the **optimal drug dosage**
- Flexibility to **adapt to changing patient characteristics**,
- **Safety of the patient**,
- Reduced side-effects by optimising the drug infusion rates

Framework for optimal tailor-made chemotherapy protocols

Treatment inflow — Box 1

Inflow → Blood drug Metabolism → Outflow
Outflow → Organ (i) → Inflow
Outflow → Kidney drug Metabolism → Inflow / Drug Excretion

Decision Box
if cancer cells > 0 **and**, normal cells > toxicity level
Optimise and suggest drug dose (u)
Otherwise **stop** until recovery of normal tissue   Box 5

Drug Concentration profile   Box 2

Cell Cycle
Normal Cells Population
Cancer Cells Population   Box 4

Pharmacodynamic Model
Dead_cancer=f(C)
Dead_normal=f(C)   Box 3

- **gPROMS Model Builder** (gPROMS, 2003) for derivation and validation of a high-fidelity model for the bahaviour of leukaemic and normal population under chemotherapy based on first-principle laws
- **gOPT** (gPROMS, 2003) for the calculation of the optimal treatment protocol for a specific patient case study (patient and disease characteristics)
- **Close-the-loop:** Validation of optimal treatment protocols through

In vitro chemotherapy application on the bioreactor disease sample

gPROMS, 2003, Introductory user's guide, release 2.2, Process Systems Enterprise Limited, London, U.K