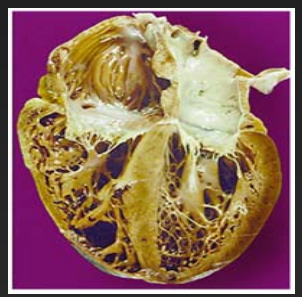
MAINTAINING A HEALTHY HEART - WHAT CAN THE UNIVERSITY PRESCRIBE?

Gavin Brooks
Professor of Cardiovascular Research
AMS, The University of Reading

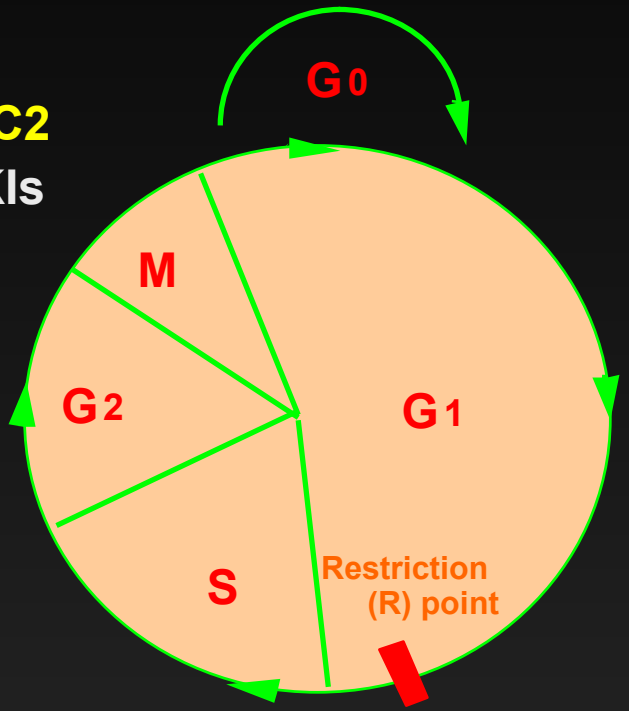
AGEnet Research Workshop
3rd December 2003



OVERVIEW

- The mammalian cell cycle
- Targeting the cell cycle machinery for the treatment of cardiovascular disease
  - heart failure
  - heart attack (myocardial infarction; MI)
- Establishing the Reading School of Pharmacy

THE MAMMALIAN CELL CYCLE



Cyclin B/CDC2
CIP/KIP CDKIs

Cyclin A/CDC2
CIP/KIP CDKIs

Cyclin A/CDK2
CIP/KIP CDKIs

Cyclin D/CDK4/6
INK4 and CIP/KIP CDKIs

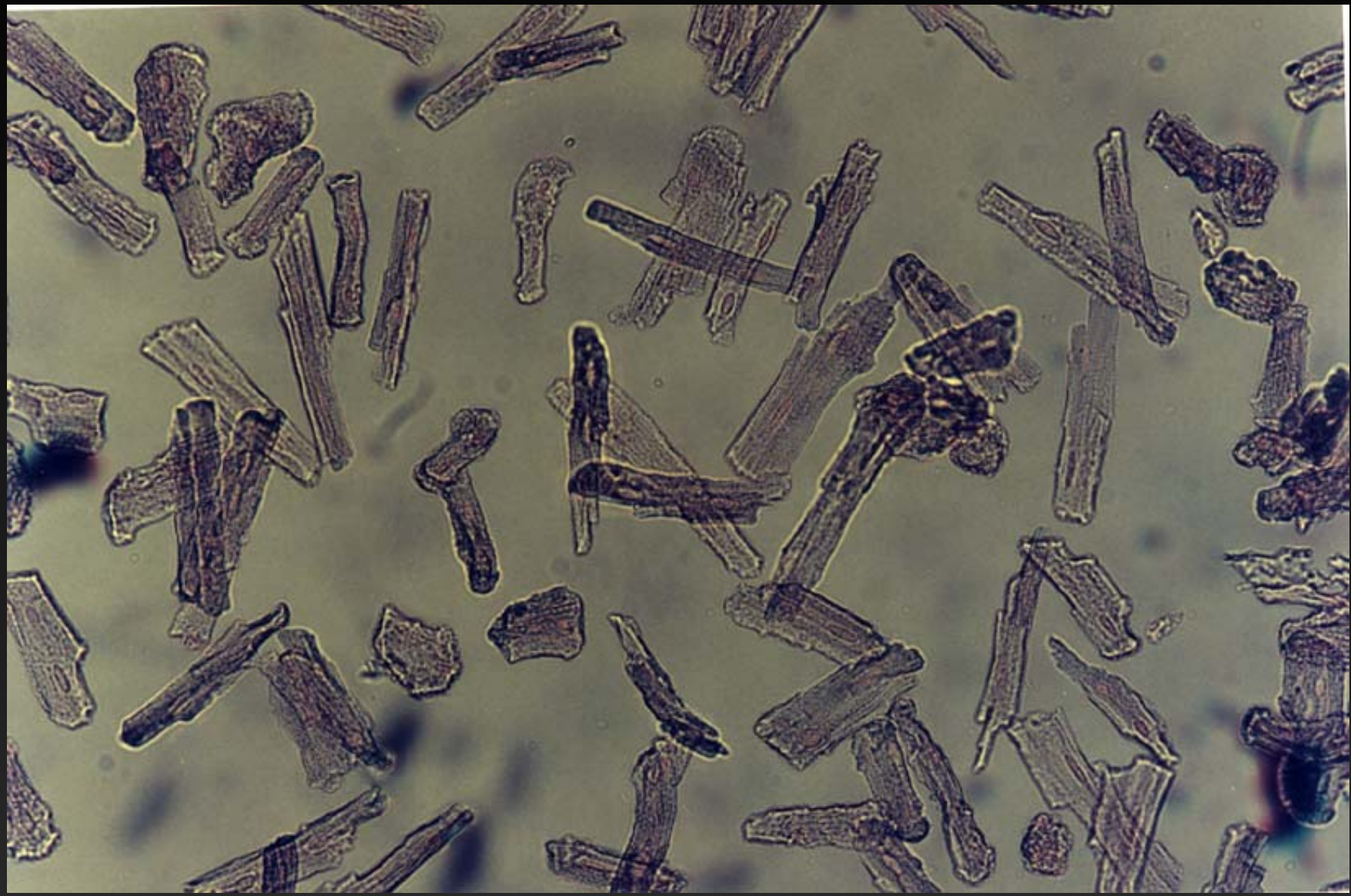
Cyclin E/CDK2
CIP/KIP CDKIs

From: Brooks & La Thangue (1999) *Drug Discovery Today* **4:** 455-464

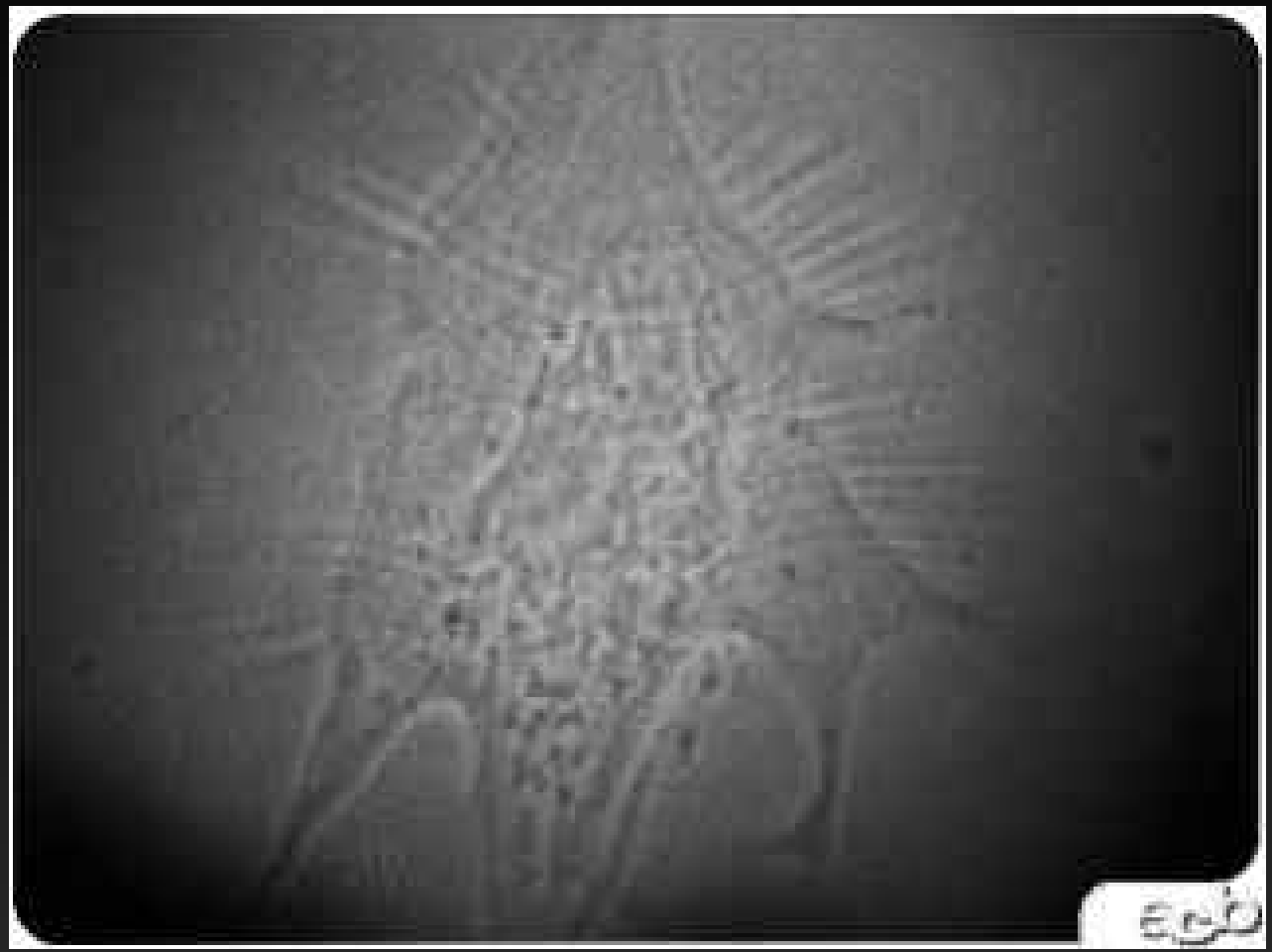
THE CELL CYCLE AS A TARGET IN HEART MUSCLE CELLS (CARDIAC MYOCYTES)

- Inhibition/regression of myocyte hypertrophy (HF)
- Regeneration of cardiac myocytes (MI)

ADULT CARDIAC MYOCYTES

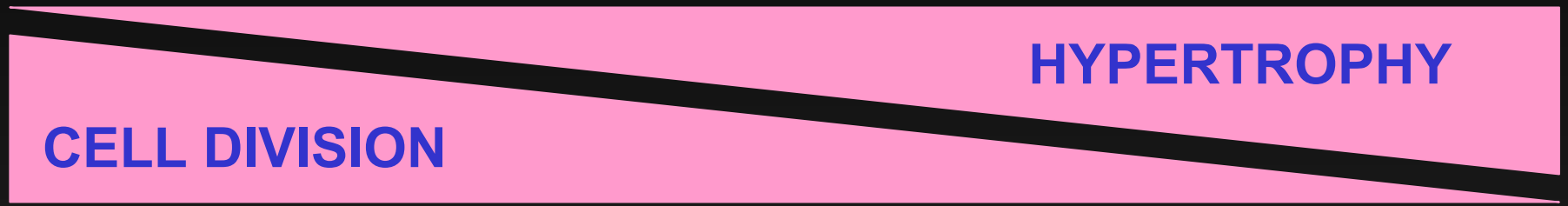


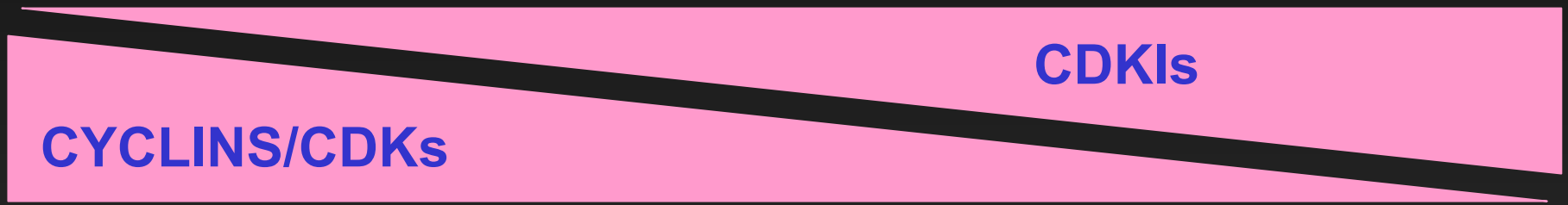
ISOLATED CARDIAC MYOCYTES RETAIN THE ABILITY TO BEAT



CHANGES IN MYOCYTE GROWTH DURING HEART DEVELOPMENT

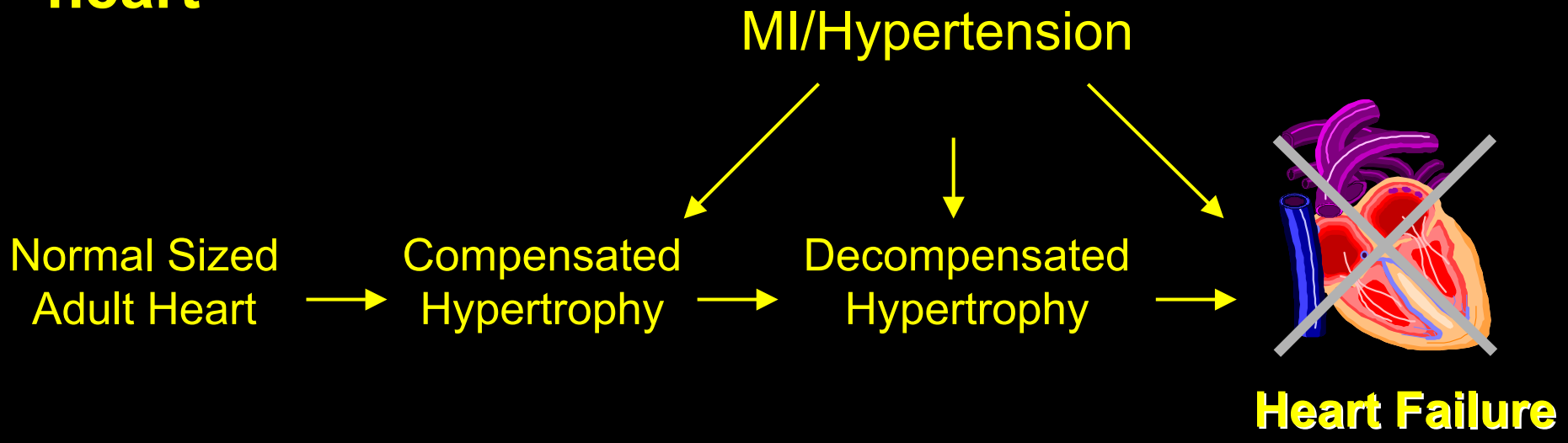
FETAL → NEONATAL → ADULT



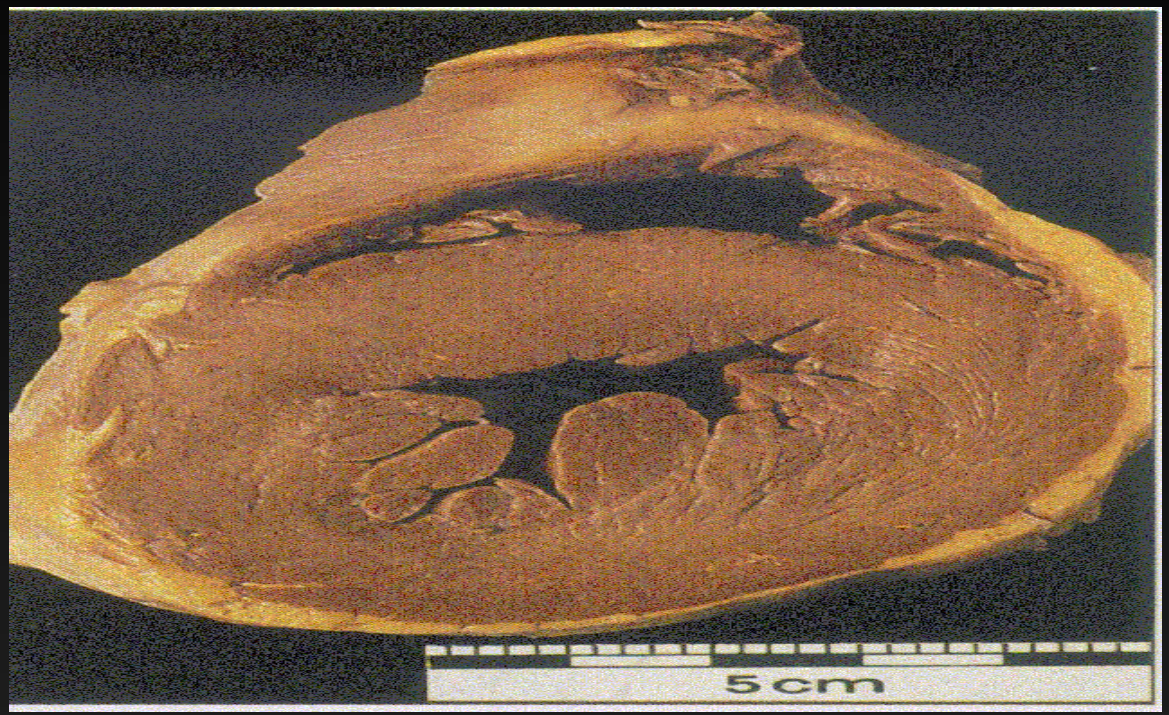


CARDIAC HYPERTROPHY

- **Haemodynamic overload as a result of MI or hypertension maintains a high work load on the heart**



HUMAN HEART FAILURE

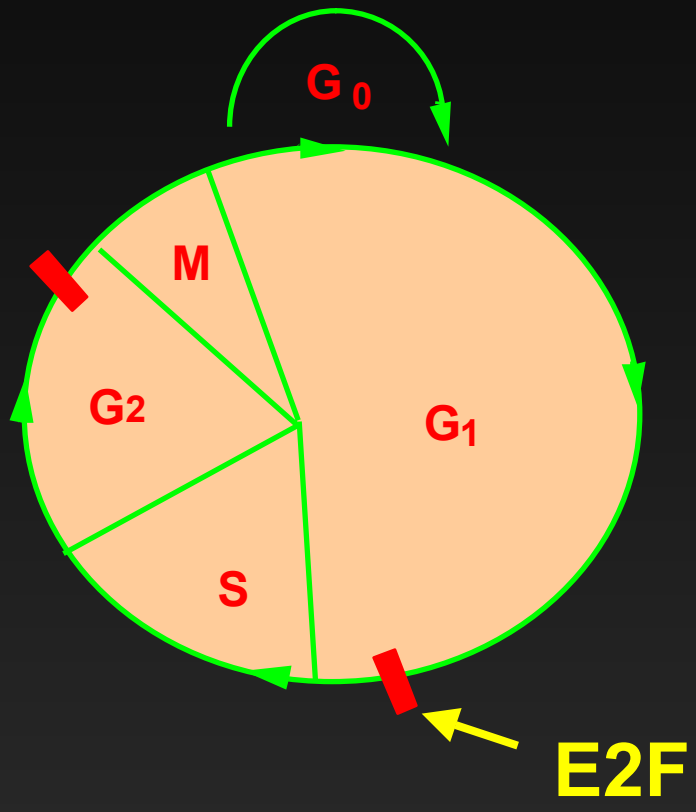


- CV diseases (HF, angina, CHD, stroke) responsible for 12 million deaths worldwide/yr
- CVD responsible for up to 50% of deaths in developed/ developing countries

THE CELL CYCLE AS A TARGET IN CARDIAC MYOCYTES

- **Inhibition/regression of LVH (HF)**
- Regeneration of cardiac myocytes (MI)

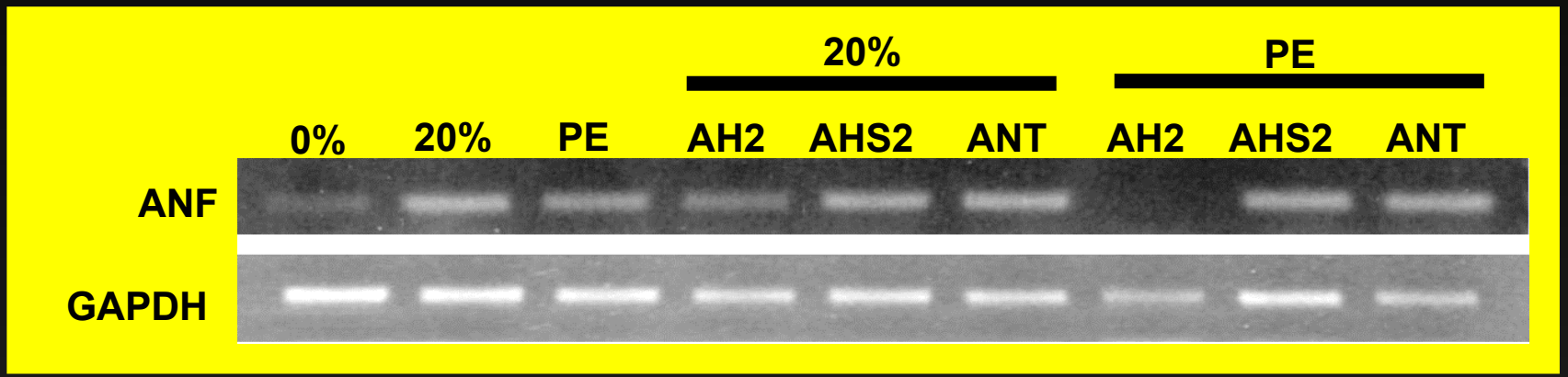
STRATEGIES FOR LIMITING DECOMPENSATED HYPERTROPHY - Targeting E2F



INHIBITING E2F-DP BINDING WITH PEPTIDES

- E2F needs to associate with DP in order to bind to DNA and transcribe genes

INHIBITION OF E2F ABROGATES THE DEVELOPMENT OF HYPERTROPHY



(Vara *et al* J.Biol.Chem. 2003)

THE CELL CYCLE AS A TARGET IN CARDIAC MYOCYTES

- Inhibition/regression of LVH (HF)
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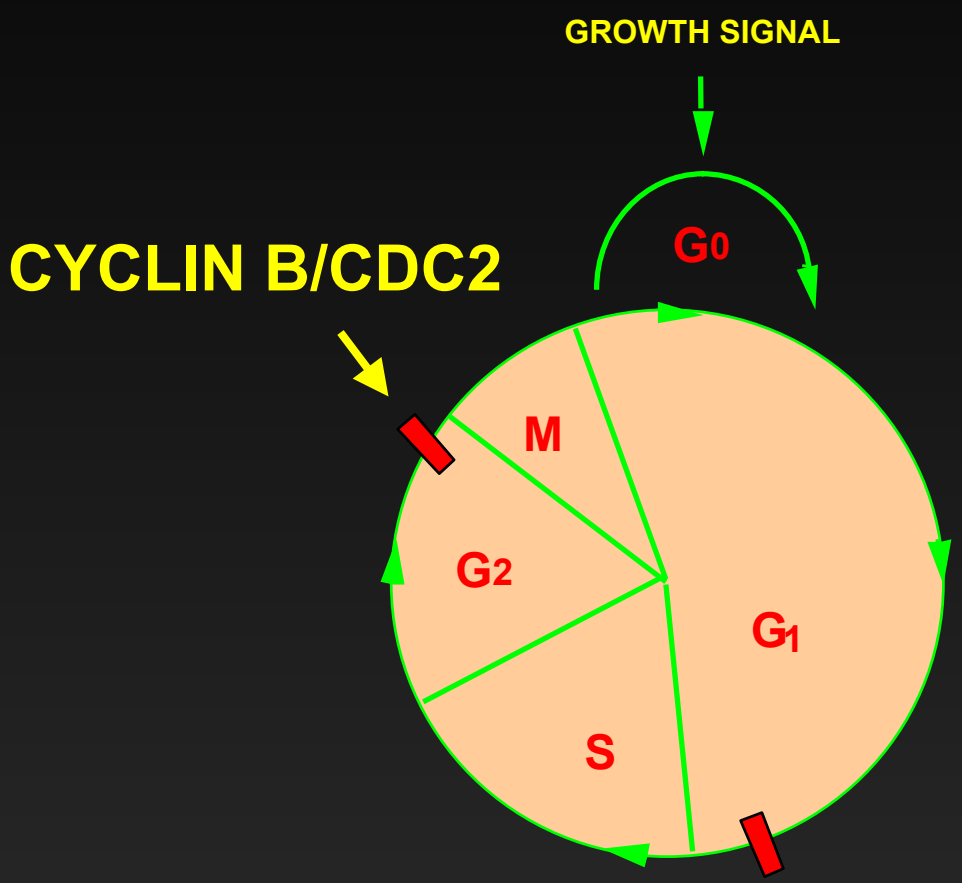
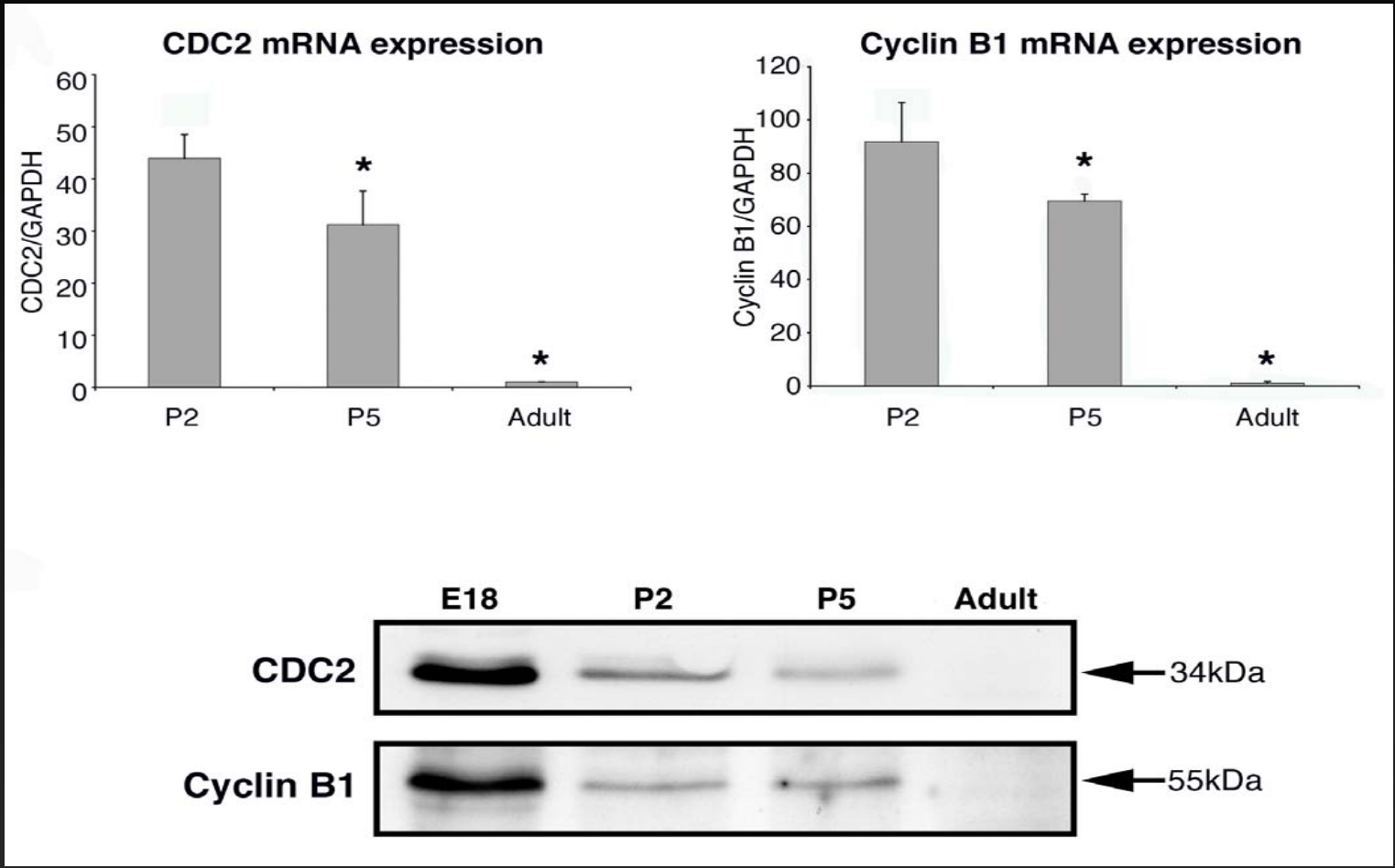
CYCLIN B AND CDC2 REGULATE CELL DIVISION



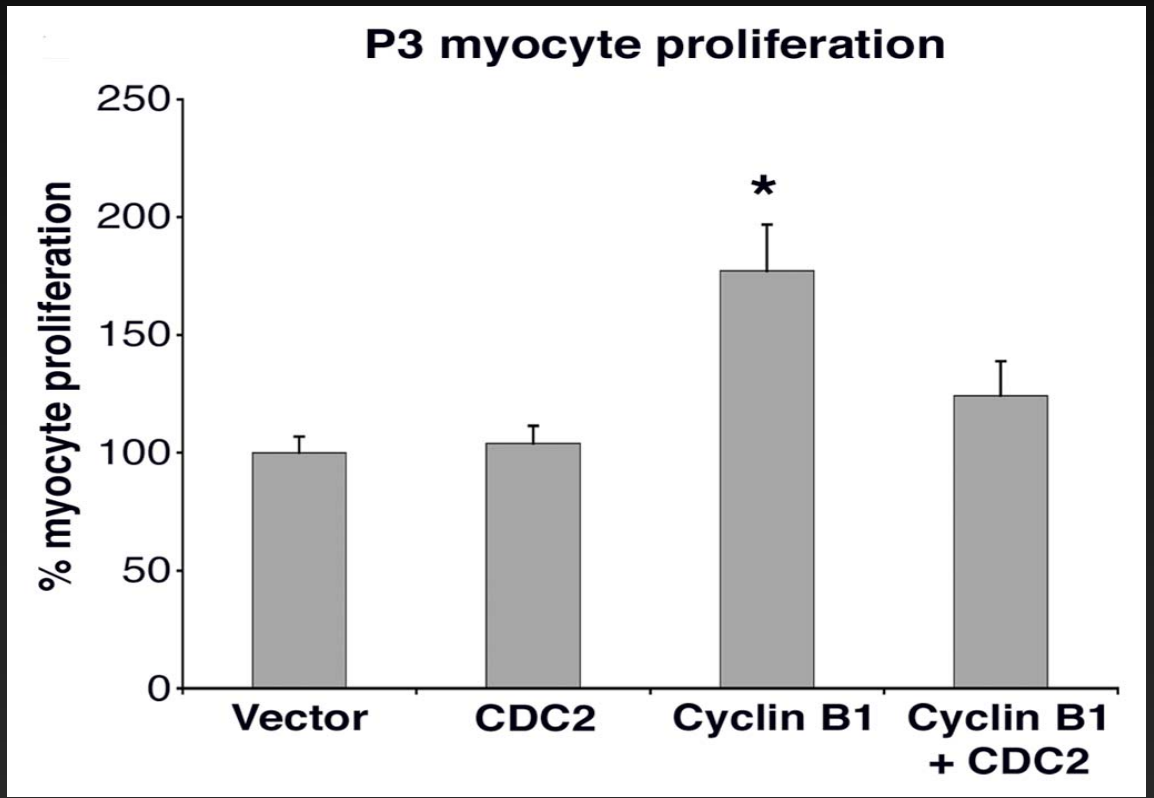
EXPRESSION OF CYCLIN B1:CDC2 DECREASES DURING MYOCYTE DEVELOPMENT



(From Bicknell and Brooks, Circulation 2002)

OVEREXPRESSION OF CYCLIN B1 INCREASES PROLIFERATION OF P3 MYOCYTES

- Transfection of cyclin B1 and/or CDC2 in P3 neonatal myocytes
- Myocytes were counted 72 hours post-transfection



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SUMMARY & CONCLUSIONS

- **Alterations in the cell cycle machinery occur during cardiac myocyte development and hypertrophy**

- **Targeting the cell cycle machinery in cardiovascular cells might offer an alternative/ adjunct to current therapies**
  - myocyte regeneration (CDK/cyclin/CDKI activities)
  - reduce/regress hypertrophic growth in heart failure (E2F inhibitors; CDKIs)
  - inhibit VSMC proliferation in restenosis/in-stent stenosis (E2F inhibitors; T-type Ca channel blockers)

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The Rayne Institute

Jian-Mei Li

Linda McLatchie

Michael Shattock

heart research
NATIONAL HEART RESEARCH FUND

British Heart Foundation

ESTABLISHING A SCHOOL OF PHARMACY AT THE UNIVERSITY OF READING

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- The UoR wishes to expand its primary healthcare interests

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- To increase the University's involvement with local industry and the population. Many graduates are likely to contribute to the local community by remaining in the area once qualified.

WHAT CONSTITUTES AN MPHARM DEGREE?

- Pharmacy Practice
- Pharmaceutics
- Pharmacology
- Pharmaceutical Chemistry
- Pharmacognosy

THE PROCEDURE FOR QUALIFYING AS A PHARMACIST

- 4 year MPharm
- 12 months Pre-registration training
- Pass RPSGB Registration Examination
- CPD
- Annual fee

PLANNING FOR THE RSOP

- Pharmacy Planning Group
- External Consultants
- Board of Studies for Pharmacy
- Pharmacy Advisory Board
- Other Committees (Infrastructure, student recruitment, post-graduate education etc.)

RPSGB ACCREDITATION PROCESS

Multi-stage process leading to Accreditation of MPharm degree

Stage 1 - visit by small Society team to evaluate suitability of Institution

Stage 2 - consideration by the RPSGB of the Business Plan

Stage 3 - consideration of MPharm curriculum

Full Accreditation not obtained until first cohort graduates (2009)

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- Shortfall in pre-registration year places

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- Source of Pharmacy undergraduates for placement/vacation work